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# PSYCHIATRY

Third Edition

Volume 1

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# PSYCHIATRY
## THIRD EDITION

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# Contents

Color plates appear between pages 244 and 245 and between pages 2356 and 2357

## Volume 1


**List of Contributors** xxxi

**Preface to this Edition** xxxix

**Preface to the First Edition** xli

**Preface to the Second Edition** xliii

Section I **Approaches to the Patient** 1

*Section Editor: Robert J. Ursano*

Chapter 1 **Listening to the Patient** 3

*Paul C. Mohl*

Listening: The Key Skill in Psychiatry 3

The Primary Tools: Words, Analogies, Metaphors, Similes, and Symbols 4

How Does One Hear Words in This Way? 5

Listening as More Than Hearing 5

Common Blocks to Effective Listening 6

Crucial Attitudes That Enable Effective Listening 8

Theoretical Perspectives on Listening 10

Using Oneself in Listening 11

To Be Found: The Psychological Product of Being Heard 12

Listening to Oneself to Listen Better 13

Listening in Special Clinical Situations 15

Growing and Maturing as a Listener 16

Chapter 2 **Physician–Patient Relationship** 20

*Amy M. Ursano, Stephen M. Sonnenberg, Robert J. Ursano*

The Placebo Effect 20

Roles and Motivations 21

Modern Medicine and the Physician–Patient Relationship 21

Attachment Theory and the Physician–Patient Relationship 22

Formation of the Physician–Patient Relationship 22

Research on the Physician–Patient Relationship 26

Special Issues in the Physician–Patient Relationship 28

The Physician–Patient Relationship in Specific Populations of Patients 29

Conclusion 31

Chapter 3 **The Psychiatric Interview: Settings and Techniques** 33

*Edward K. Silberman, Kenneth Certa, Abigail Kay*

Goals of the Psychiatric Interview 33

The Psychiatric Database 37

Conduct of the Interview 41

Special Problems in Interviewing 47

Chapter 4 **The Cultural Context of Clinical Assessment** 54

*Laurence J. Kirmayer, Cécile Rousseau, G. Eric Jarvis, Jaswant Guzder*

Introduction: The Cultural Matrix of Psychiatry 54

What is Culture? 54

Culture and Gender 56

The Cultural Formulation 57

Cultural Competence 60

Conclusion: The Limits of Culture 64

Chapter 5 **Professional Ethics and Boundaries** 67

*Richard S. Epstein, Ahmed Okasha*

Introduction 67

Ethical Behavior and Its Relationship to the Professional Attitude 67

The Coherent Treatment Frame and the Role of Therapeutic Boundaries in Effective Psychiatric Treatment **71**
Boundary Violations **71**
Components of the Coherent Psychiatric Frame **73**
Summary **78**

Chapter 6 **Legal Issues in Psychiatric Practice 81**
*David M. Benedek, Thomas A. Grieger*

Introduction **81**
Categories of Legal Issues in Psychiatry **81**
Civil Issues: Patient's Rights **82**
Civil Issues: Doctor–Patient Relationship **84**
Criminal Issues: Competency and Insanity **88**
Other Criminal Issues: Diminished Capacity and Mitigating Factors **91**
Conclusion **92**

**Section II A Developmental Perspective on Normal Domains of Mental and Behavioral Functions 95**
*Section Editor: David A. Mrazek*

Chapter 7 **A Psychiatric Perspective on Human Development 97**
*David A. Mrazek*

Biological Development Genetic Considerations **98**
Neurological Considerations **98**
Endocrinological Considerations **99**
Cognitive Development **100**
Emotional Development **101**
Social Development **102**
Moral Development **102**
Developmental Psychopathology Risk and Protective Factors **104**
High-Risk Periods for Psychopathology **106**
Interlineal Decalage **106**
The Psychiatrist as a Developmentalist **107**

Chapter 8 **Infant Development: The First 3 Years of Life 109**
*Charles H. Zeanah, Brian Stafford, Neil W. Boris, Michael Scheeringa*

Theories and Models of Development and the First 3 Years of Life **109**
Lines of Development and Their Discontinuities **113**
Risk and Protective Factors **127**
Illustrative Risk Conditions **128**
Conclusion **131**

Chapter 9 **Preschool Development 135**
*Robert B. Clyman*

Historic Considerations **135**
Conceptual Framework **136**
Lines of Development **136**
Risk and Protective Factors **146**
Developmental Psychopathology **147**

Chapter 10 **School-Age Development 150**
*Theodore Shapiro, Dima Amso*

Conceptual Framework **151**
Biological Development **151**
Cognitive Development **152**
Emotional Development **153**
Sociocultural Development **154**
Moral Development **155**
Risk and Protective Factors **157**
Developmental Psychopathology **157**

Chapter 11 **Adolescent Development 161**
*Kenneth E. Towbin, John E. Showalter*

Historical Perspectives **162**
Conceptual Framework **163**
Biological Development **163**
Brain Development **168**
Cognitive Development **168**
Emotional Development **172**
Social Development **172**
Risk Factors, Protective Factors, and Gene–Environment Interactions **175**
Conclusion **178**

Chapter 12 **Adult Development 181**
*William R. Beardslee, George Vaillant*

Towards a Conceptual Framework **181**
Developmental and Cohort Effects **184**
Risk Factors, Protective Factors, and Resilience **185**
Young Adulthood as a Distinct Developmental Stage **186**
An Integrated Model for Adult Development **187**

Developmental Formulations of Adulthood **188**
Eriksonian Model of Adult Development **189**
Grief **192**
Transitions and Developmental Crises **192**
The Enduring Importance of Identity Formation **192**
Conclusions: Adult Development—an Ever-Evolving Field **193**

Chapter 13 **Late Life 196**
*David Bienenfeld*

Late-Life Development **196**
Cognitive Changes **197**
Sensory Changes **199**
Lifestyle **200**
Sexuality **201**

**Foundations 203–486**

Chapter 14 **A Brief History of Psychiatry 205**
*Michael H. Stone*

Ancient Times **205**
Beginnings of a Methodological Approach to Mental Phenomena **206**
Roman, Greek, and Other Influences in Early Christian Times **207**
Post-Roman and Medieval Times **207**
16th Century: The Beginnings of Modern Psychiatry **208**
17th Century: Slow Progress in Description and Empiricism **209**
18th Century **210**
19th Century **213**
20th Century **220**
Conclusion **231**

**Section III Neuroscientific Foundations of Psychiatry 243**
*Section Editors: Eric R. Kandel and H. Jonathan Polan*

Chapter 15 **Are there Biological Commonalities among Different Psychiatric Disorders? 245**
*Christopher Pittenger, Amit Etkin*

Introduction **245**
Diseases of the Mind and Diseases of the Brain **246**
Specific Biological Commonalities Among Disorders **246**
Beyond Gross Anatomical Similarities: Functional Circuitry in Psychiatric Disease **247**
The Ventral Striatum and Mechanisms of Reward **248**
Dysregulation of Reward in Disorders of the Ventral Striatum **249**
The Dorsal Striatum and the Automation of the Routine **249**
Maladaptive Habits in Disorders of the Dorsal Striatum **250**
Prefrontal Cortex: Attention and Behavioral Flexibility **250**
Attentional Deficits in Disorders of the Prefrontal Cortex **251**
Prefrontal Cortex: "Deliberate" Versus "Implicit" Emotion Regulation Strategies **251**
Dysfunctional Emotion Regulation in Disorders of the Prefrontal Cortex **252**
Conclusion **253**

Chapter 16 **Genetic Epidemiology and Molecular Genetics of Psychiatric Disorders 257**
*Kathleen R. Merikangas, Maria Karayiorgou*

Introduction **257**

***Genetic Epidemiology of Mental Disorders* 258**
*Kathleen R. Merikangas*

Genetic Epidemiology **258**
Genetic Epidemiology of Mental Disorders **259**
Future Applications of Genetic Epidemiology **262**

***Identification of Genes Underlying Mental Disorders* 264**
*Maria Karayiorgou*

Linkage Studies **264**
Association Studies **264**
Application of Linkage and Association Studies in Psychiatry **264**
Systematic Follow-Up of Linkage Signals **265**
Candidate Gene Approaches **266**
Fine Mapping of Genomic Rearrangements **267**
Iterative Human and Mouse Genetic Approaches **268**
Genetic Studies of Endophenotypes **269**
*Future Directions of Gene Discovery* **269**

Gene Discovery Via Genome-Wide Association Studies **269**
In-Depth Probing of Gene−Gene Interactions **269**
Implications for Understanding Disease Pathophysiology and for Improving Treatment **270**

Chapter 17 **Modeling Psychiatric Disorders in Experimental Animals 275**
*Trevor W. Robbins, Holly M. Moore*

Introduction **275**
Defining Phenotypes and Establishing Validity in Animal Models **277**
Dissecting Cognitive and Behavioral Endophenotypes from Complex Mental Disorders **278**
Using Neuropathological or Pharmacological Phenotypes to Test Etiologic and Pathogenic Hypotheses of Psychopathology **281**
"A Priori" Modeling Genetic, Environmental and Experiential Etiologies in Psychiatric Disorders **284**
Conclusions **286**

Chapter 18 **The Scientific Basis of Psychotherapy 289**
*Steven Roose, Arnold M. Cooper, Peter Fonagy*

The Scientific Basis of Psychotherapy **289**
Principles of Psychoanalysis: The Contribution of Freud **289**
Psychoanalysis after Freud **290**
Studies on the Effectiveness of Psychotherapies: Overall Efficacy of Treatment **292**
Biological and Neuroimaging Studies of Psychotherapy **295**
Conclusion **297**

Chapter 19 **The Neurobiology of Schizophrenia 301**
*William V. Bobo, Judith L. Rapoport, Anissa Abi-Dargham, Hossein Fatemi, Herbert Y. Meltzer*

Introduction **301**
Neurodevelopmental Concept **302**
Electrophysiological Abnormalities **311**
Conclusion **312**

Chapter 20 **Neurobiology of Anxiety Disorders 317**
*Michael J. Meaney, Joseph E. LeDoux, Michael L. Liebowitz*

Overview **317**
History and Clinical Picture of Anxiety Disorders **318**
Genetic Contributions to Anxiety Disorders **320**
Animal Models of Anxiety **321**
Pathophysiology of Anxiety Disorders **326**
Emotional Regulation: Role for the mPFC **326**
Therapeutic Targets: The Neurobiology of Coping **327**
Vulnerability for Anxiety Disorders **328**
Developmental Origins of Vulnerability for Anxiety Disorders **328**
Familial Transmission of Risk: Effects of Genes, Environment, and Their Interaction **329**
Conclusions **332**

Chapter 21 **Neurobiologic Foundations of Mood Disorders 339**
*Ronald Duman, H. Jonathan Polan, Alan Schatzberg*

Nomenclature **339**
Genetics **340**
Pathogenic Mechanisms **343**
Intracellular Signal Transduction Pathways and Growth Factors **346**
Conclusion **350**

Chapter 22 **Pathophysiology of Addiction 354**
*George F. Koob, Denise Kandel, Nora D. Volkow*

Clinical Picture **354**
Patterns of Substance Use and Substance Use Disorders **358**
Impact of Substance Use Disorders **360**
Vulnerability **363**
Neuropharmacology of Drug Intoxication and Reward **364**
Substance Dependence (Addiction) **367**

Chapter 23 **Neuroscience of Autism 379**
*David G. Amaral, John L. R. Rubenstein, Sally J. Rogers*

Introduction **379**
Diagnosis and Behavioral Features **380**
Medical and Other Comorbid Features **381**
Developmental and Genetic Mechanisms Implicated in the Etiology of Autism **382**
Neuropathology **385**

Functional Neuroimaging **386**
Behavioral Treatment **387**
Other Treatments **388**
Conclusions **388**

Chapter 24 **Neurodegeneration and Dementia 393**
*John Hardy, Scott A. Small*

Introduction **393**
Alzheimer's Disease **394**
Frontal Temporal Dementia **396**
Lewy Body Dementia **398**
Prion Diseases **398**
Conclusions **399**

**Section IV Psychological and Social Scientific Foundations of Psychiatry 401**
*Section Editor: Paulette M. Gillig*

Chapter 25 **Psychiatric Epidemiology 403**
*Philip S. Wang, Mauricio Tohen, Evelyn J. Bromet, Jules Angst, Ronald C. Kessler*

Overview **403**
The Scope of Inquiry in Psychiatric Epidemiology **404**
Epidemiological Methods **405**
Types of Epidemiological Studies **407**
Threats to Validity in Epidemiological Studies **409**
Examples of Psychiatric Epidemiological Studies **410**
The National Comorbidity Survey-Replication (NCS-R) **418**
Future Directions **423**

Chapter 26 **Cognitive Psychology 433**
*Geraldine Downey, Jamil Zaki, Kathy R. Berenson*

Introduction **433**
Historical Review of the Cognitive Framework **433**
Overview of Core Cognitive Processes **434**
Conclusions: Modularity and Integration **448**

Chapter 27 **Social Psychology 454**
*Howard Tennen, Paulette M. Gillig*

Introduction **454**
Attributional Style and Vulnerability to Depression **455**
Finding Benefits and Experiencing Growth Through Adversity **456**
Self-Report Depression Rating Scales: A Social Psychological Perspective **457**
The Cognitive Approach to the Self: The Multidimensional Social Self **459**
Cognitive Continuity: Self-Verification Theory **459**
Summary **461**

Chapter 28 **Psychoanalytic Theories 464**
*Patrick J. Haggard, Andrew C. Furman, Steven T. Levy, Jonathan E. Dunn, Robert M. Galatzer-Levy, Sybil A. Ginsburg, Lawrence B. Inderbitzen, Mark E. James, Arnold D. Richards, Ralph E. Roughton, Beth Seelig, Henry F. Smith*

Development and Major Concepts **464**
Other Psychoanalytic Perspectives **473**
Conclusion and the Future **480**
Glossary of Psychoanalytic Terms **482**

**Section V Manifestations and Assessments of Psychiatric Illness 487**
*Section Editor: Andrew E. Skodol*

Chapter 29 **Psychopathology Across the Life Span 489**
*Andrew E. Skodol, Donna S. Bender*

Continuity, Persistence, and Progression Across the Life Cycle **489**
Stress-Diathesis Model of Psychopathology **490**
Resilience **490**
Pathoplastic Effects of Age **490**
Problems of Childhood **490**
Problems of Adolescence **499**
Problems of Early Adulthood **503**
Problems of Middle Adult Life **510**
Problems of Late Life **512**
Conclusion **516**

Chapter 30 **Clinical Evaluation and Treatment Planning: A Multimodal Approach 525**
*Francine Cournos, David A. Lowenthal, Deborah L. Cabaniss*

Psychiatric Interview **525**
Physical Examination **530**
Neurological Examination **532**
Psychological and Neuropsychological Testing **532**

Laboratory Assessments **533**
Special Assessment Techniques **538**
Treatment Planning **540**
Conclusion **545**

Chapter 31 **The Initial Psychiatric Evaluation of Children and Adolescents 546**
*Christina G. Weston, William M. Klykylo*

Elements of the Psychiatric Evaluation **546**
Psychological Evaluation **549**
Laboratory Assessment **553**
Outcome of the Evaluation **553**
Conclusion **554**

Chapter 32 **Neuropsychological Assessment and Neurophysiological Evaluation 556**
*Larry J. Seidman, Gerard E. Bruder, Anthony J. Giuliano*

Overview **556**
Assessment of Brain Dysfunction by Neuropsychological Testing **557**
Neuropsychological Examination Compared with Other Examinations **557**
Types of Referral Questions in Psychiatry **559**
Differential Diagnosis **559**
Characterization of Adaptive Strengths and Weaknesses and Treatment Planning **560**
Assessment of Change Over Time **560**
The Flexible, Hypothesis-Testing Approach to Assessment **561**
Limitations of Reliability and Validity **563**
Neurophysiological Assessment **564**
Summary **566**

Chapter 33 **Brain Imaging in Psychiatry 570**
*Douglas S. Lehrer, Darin D. Dougherty, Scott L. Rauch*

Introduction **570**
Structural Imaging Modalities **570**
Functional Imaging Modalities **573**
In Vivo Neurochemical Research: Molecular Imaging **577**
Other Imaging Technologies **578**
Clinical Use of Imaging in Psychiatric Populations **579**
Summary **580**

Chapter 34 **Consciousness, Orientation, and Memory 582**
*Keith H. Claypoole, Richard D. Sanders*

Nature of Consciousness **582**
Levels of Consciousness **582**
Qualitative Changes in Consciousness **584**
Memory **584**
Intelligence **588**
Clinical Evaluation **590**
Conclusion **592**

Chapter 35 **Alterations of Speech, Thought, Perception, and Self-Experience 595**
*Ralph E. Hoffman, Thomas H. McGlashan, Douglas S. Lehrer*

Disorders of Speech **595**
Disorders of Thought **598**
Perceptual Disturbances **601**
Disorders of Identity and Will **602**
Conclusion **604**

Chapter 36 **Emotions 605**
*Robert Kohn, Martin B. Keller*

Behavioral, Neurological, and Cognitive Components of Emotion **605**
Assessment of Mood and Affect in the Clinical Interview **608**
Emotional Expression of Anxiety **609**
Emotional Expression of Depression **613**
Emotional Expression of Euphoria **617**
Emotional Expression of Apathy **617**
Emotional Expression of Hostility, Anger, and Rage **617**
Disturbances of Affect Incongruent with Mood **618**
Conclusion **618**

Chapter 37 **Physical Signs and Symptoms 621**
*Philip R. Muskin, Elsa G. E. Mirasol*

Evaluation of Physical Signs and Symptoms **622**
Physical Manifestations of Anxiety **622**
Physical Manifestations of Mood Disorders **624**
Physical Disorders Causing Secondary Mental Symptoms **625**
Intoxication and Withdrawal **626**
Agitation **626**

Physical Symptoms without Known Etiology **627**
Factitious Symptoms **630**
Conclusion **631**

Chapter 38 **Behavior and Adaptive Functioning 633**
*Susan C. Vaughan, John M. Oldham*

Personality Style **633**
Domains of Functioning **639**
Assessing Behavior and Adaptive Functioning in the Clinical Interview **641**
Problematic Patterns of Behavior **642**
Conclusion **646**

Chapter 39 **Culture and Psychiatric Diagnosis 648**
*Juan E. Mezzich, Roberto Lewis-Fernández, Maria Angeles Ruiperez*

Introduction **648**
Specific Cultural Considerations **649**
The Case of Culture-Bound Syndromes and Idioms of Distress **654**
Conclusion **656**

**Section VI** **Disorders 659**
*Section Editor: Michael B. First*

Chapter 40 **Psychiatric Classification 661**
*Michael B. First*

Introduction **661**
Goals of a Classification System **661**
Approaches to Classification **661**
History of the DSM Classification System **663**
DSM-IV Overview **666**
DSM-IV Multiaxial System **666**
DSM-IV Classification and Diagnostic Codes **667**
Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence **673**
Delirium, Dementia, Amnestic Disorder, and Other Cognitive Disorders **674**
Mental Disorders due to a General Medical Condition Not Elsewhere Classified **674**
Substance-Related Disorders **674**
Schizophrenia and Other Psychotic Disorders **674**
Mood Disorders **675**
Anxiety Disorders **675**
Somatoform Disorders **675**
Factitious Disorders **675**
Dissociative Disorders **675**
Sexual and Gender Identity Disorders **675**
Eating Disorders **675**
Sleep Disorders **676**
Impulse-Control Disorders Not Elsewhere Classified **676**
Adjustment Disorders **676**
Personality Disorders **676**
Other Conditions That May Be a Focus of Clinical Attention **676**
Appendix Categories **677**

Chapter 41 **Diagnostic Classification in Infancy and Early Childhood 679**
*Stanley I. Greenspan, Serena Wieder*

An Interdisciplinary Approach to Classification **680**
The Need for a Comprehensive Multidimensional Developmental Approach **680**
Multidimensional Classification Based on the DIR Model **681**
Unique Features of the ICDL-DMIC Multiaxial System **681**
Selecting a Primary Diagnosis **682**
Clinical Thresholds for Diagnosis **682**
Axis I: Primary Diagnosis **683**
Conclusion **688**

Chapter 42 **Childhood Disorders: Intellectual Disability 689**
*Kerim M. Munir, Sandra L. Friedman, Maija L. Wilska, Ludwik S. Szymanski*

Introduction **689**
*Intellectual Disability* **689**
Concept of Intellectual Disability **689**
Definitions of Intellectual Disability and Its Scientific Evolution **690**
Patterns of Comorbidity **692**
Etiology and Pathophysiology of Intellectual Disability **694**
Course and Natural History of Intellectual Disability **708**
Habilitation and Treatment Approaches to Intellectual Disability **709**
Prevention of Intellectual Disability **713**
*Mental Disorders in Persons with Intellectual Disability* **714**

Prevalence of Psychopathology in Persons with Intellectual Disability **714**
Intellectual Disability and Behavioral Patterns **715**
Diagnosis of Mental Disorders in Persons with Intellectual Disability **717**
Diagnosis of Specific Mental Disorders **723**
Forensic and Legal Issues in Intellectual Disability **731**
Overall Goals of Psychiatric Treatment of Persons with Intellectual Disability **732**
Pharmacotherapy **733**
Psychosocial Interventions **740**
Psychiatrist–Patient Relationship: Models of Delivery of Psychiatric Services **741**
Conclusion **741**

Chapter 43 **Childhood Disorders: Learning and Motor Skills Disorders 747**
*Larry B. Silver*

Definitions **747**
Diagnosis **748**
The Educational Curriculum and Diagnosis **751**
Differential Diagnosis **752**
The Cortical Disorders **756**
Social Problems **756**
Differences in Developmental, Gender, and Cultural Presentations **757**
Etiology **757**
Treatment **758**
Summary **761**
Special Considerations in the Doctor–Patient Relationship **762**
Comparison of DSM IV/ICD-10 Diagnostic Criteria **762**

Chapter 44 **Childhood Disorders: Communication Disorders 765**
*William M. Klykylo*

Introduction **765**
Expressive and Mixed Expressive-Receptive Language Disorders **765**
Demographic and Cultural Issues in Treatment **773**
Phonological Disorder **773**
Stuttering **774**
Communication Disorder Not Otherwise Specified **776**

Chapter 45 **Childhood Disorders: The Pervasive Developmental Disorders 779**
*James McPartland, Ami Klin, Alexander Westphal, Fred R. Volkmar*

Introduction **779**
Autistic Disorder **779**
Asperger's Disorder **791**
Childhood Disintegrative Disorder **795**
Rett's Disorder **796**
Pervasive Developmental Disorder—Not Otherwise Specified **799**
Summary **800**

Chapter 46 **Childhood Disorders: Attention-Deficit and Disruptive Behavior Disorders 804**
*Jeffrey H. Newcorn, Iliyan Ivanov, Vanshdeep Sharma, Kurt Schulz, Jeffrey M. Halperin*

Introduction **804**
Diagnosis **804**
Attention-Deficit/Hyperactivity Disorder **805**
Etiology and Pathophysiology **813**
Treatment **817**
Conclusions **826**

Chapter 47 **Childhood Disorders: Feeding and Related Disorders of Infancy or Early Childhood 830**
*Rachel J. Bryant-Waugh, Emma H. C. Piepenstock*

Introduction **830**
*Feeding Disorder of Infancy or Early Childhood* **831**
Diagnosis **831**
Assessment **833**
Epidemiology **834**
Comorbidity **834**
Course **835**
Differential Diagnosis **835**
Etiology and Pathophysiology **835**
Treatment **836**
*Rumination Disorder* **839**
Diagnosis **839**
Assessment **840**
Epidemiology **840**
Course **840**
Differential Diagnosis **840**
Etiology and Pathophysiology **841**
Treatment **841**

*Pica* **842**
Diagnosis **842**
Assessment **843**
Epidemiology **843**
Comorbidity **843**
Course **843**
Differential Diagnosis **843**
Etiology and Pathophysiology **844**
Treatment **844**

Chapter 48 **Childhood Disorders: Tic Disorders 847**
*Matt W. Specht, Courtney Pierce Keeton, John T. Walkup*

Diagnosis **847**
Epidemiology **850**
Etiology and Pathophysiology **852**
Treatment **856**
Treatment of Co-occurring Psychiatric Disorders in TD **861**
Treatment-Refractory Cases **862**
Conclusion **864**

Chapter 49 **Childhood Disorders: Elimination Disorders and Childhood Anxiety Disorders 868**
*Christopher P. Lucas, David Shaffer*

Enuresis **868**
Encopresis **875**
Other Disorders Specific to Children and Adolescents **879**
SAD **879**
Selective Mutism **883**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **885**

Chapter 50 **Stereotyped Movement and Reactive Attachment Disorder 889**
*Morgan Feilbelman, Charles H. Zeanah*

*Stereotyped Movement Disorder* **889**
Diagnosis **889**
Assessment **889**
Epidemiology **890**
Comorbidity **890**
Etiology and Pathophysiology **890**
Treatment **891**
*Reactive Attachment Disorder* **892**
Diagnosis **892**
Assessment **893**
Epidemiology **893**
Comorbidity **893**
Course **893**
Differential Diagnosis **894**
Etiology **894**
Treatment **895**

Chapter 51 **Dementia, Delirium, and Other Cognitive Disorders 897**
*Robert L. Frierson*

Dementia **898**
Degenerative Causes of Dementia **902**
Infectious Causes of Dementia **911**
Dementia due to Head Trauma **914**
Substance-Induced Persisting Dementia **915**
Dementia due to Other General Medical Conditions **916**
Delirium **917**
Amnestic Disorders **924**

Chapter 52 **Mental Disorders Due to a General Medical Condition 931**
*David P. Moore*

Introduction **931**
Psychotic Disorder Due to a General Medical Condition **932**
Mood Disorder Due to a General Medical Condition **935**
Anxiety Disorder Due to a General Medical Condition with Panic Attacks or with Generalized Anxiety **940**
Mental Conditions Due to a General Medical Disorder Not Elsewhere Classified **942**
Personality Change Due to a General Medical Condition **944**
Mental Disorder Not Otherwise Specified Due to a General Medical Condition **947**

Chapter 53 **General Approaches to Substance and Polydrug Use Disorders 957**
*Thomas R. Kosten*

Definition **957**
Diagnosis and Assessment **959**
Epidemiology **963**
Course and Natural History **964**
Etiology and Pathophysiology **964**
Standard Treatments **967**
Special Treatment Features **968**

Other Substance Use Disorders: Anabolic Steroids and Nitrites **969**

Chapter 54 **Substance Abuse: Alcohol Use Disorders 971**
*Thomas F. Babor, Carlos A. Hernandez-Avila, Jane A. Ungemack*

Definition **971**
Etiology and Pathophysiology **971**
Assessment and Differential Diagnosis **974**
Epidemiology and Comorbidity **983**
Course and Natural History **988**
Treatment **988**
Conclusion **999**

Chapter 55 **Substance Abuse: Amphetamine Use Disorders 1005**
*Kevin A. Sevarino*

Diagnosis **1006**
Epidemiology **1008**
Etiology **1011**
Treatment **1012**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1014**

Chapter 56 **Substance Abuse: Caffeine Use Disorders 1019**
*Roland R. Griffiths, Chad J. Reissig*

Introduction **1019**
Caffeine Intoxication **1019**
Caffeine Withdrawal **1024**
Caffeine Dependence **1029**
Caffeine-Induced Anxiety Disorder **1033**
Caffeine-Induced Sleep Disorder **1035**
Conclusion **1037**

Chapter 57 **Substance Abuse: Cannabis-Related Disorders 1041**
*Benjamin R. Nordstrom, Frances R. Levin*

Introduction **1041**
Epidemiology of Cannabis Abuse and Dependence **1041**
Endocannabinoid System **1043**
Treatment of Cannabis Related Disorders **1047**
Pharmacotherapy in Cannabis Self Administration or Intoxication **1053**
Conclusion **1055**

Chapter 58 **Substance Abuse: Cocaine Use Disorders 1058**
*Jennifer R. Baker, Charles Y. Jin, Elinore F. McCance-Katz*

Introduction **1058**
Epidemiology **1058**
Course and Natural History **1060**
Etiology and Pathophysiology **1061**
Diagnosis of Cocaine Use Disorders **1062**
Treatment of Cocaine Use Disorders **1066**
Assessment and Treatment Overview **1067**
Cocaine Use Disorders: Clinical Course **1067**
Overview of Treatment for Cocaine Use Disorders **1068**
Pharmacotherapies for Cocaine Use Disorders **1072**
Common Problems in Management **1077**
Psychiatric Comorbidity **1079**
Comorbid Mood Disorders or Attention Deficit Hyperactivity Disorder **1079**
Antisocial Personality Disorder **1080**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1081**

Chapter 59 **Substance Abuse: Phencyclidine Use Disorders 1090**
*Daniel C. Javitt*

Epidemiology **1090**
Etiology and Pathophysiology **1092**
Diagnosis and Differential Diagnosis **1093**
Assessment **1095**
Standard Approach to Treatment **1096**
Special Features Influencing Treatment **1097**

Chapter 60 **Substance Abuse: Hallucinogen- and MDMA-Related Disorders 1100**
*Rif S. El-Mallakh, John H. Halpern, Henry D. Abraham*

Introduction **1100**
Ethnobotanical Hallucinogens **1100**
Synthetic Hallucinogens **1102**
Human Experimentation with Hallucinogens **1102**
MDMA (Ecstasy) **1102**
Hallucinogen Intoxication **1103**
Hallucinogen Abuse **1107**
LSD-Related Psychotic Disorders **1108**

Hallucinogen Persisting Perception Disorder (HPPD) **1110**
MDMA **1113**

Chapter 61 **Substance Abuse: Inhalant-Related Disorders 1127**
*Charles W. Sharp, Neil Rosenberg, Fred Beauvais*

Introduction **1127**
Substances Inhaled **1127**
Inhalant Use Disorders **1130**
Inhalant-Induced Disorders **1131**
Psychiatric Disturbances Associated with Organic Solvent Abuse **1132**
Etiology and Pathophysiology **1132**
Clinical Manifestations After Chronic Inhalant Abuse **1133**
Treatment **1140**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1142**
A Tribute to Dr. Neil Rosenberg **1142**

Chapter 62 **Substance Abuse: Nicotine Dependence 1149**
*Douglas Ziedonis, Marc L. Steinberg, Susan J. Fiester, Cezar Cimpeanu*

Diagnosis **1149**
Definition and Diagnostic Features **1149**
Assessment **1150**
Epidemiology **1151**
Comorbidity Patterns **1152**
Course **1153**
Differential Diagnosis **1153**
Differences in Developmental, Gender, and Cultural Presentation **1153**
Etiology and Pathophysiology **1153**
Treatment **1155**
Treatment Benefits **1157**
Somatic Treatments **1157**
Psychosocial Treatments **1160**
Brief or Minimal Medical Professional-Delivered Interventions/Advice **1160**
Combined Psychosocial and Psychopharmacological Therapies **1162**
Problems in Management **1162**
Special Considerations in Treatment **1163**

Chapter 63 **Substance Abuse: Opioid Use Disorders 1169**
*George E. Woody, Paul J. Fudala*

Introduction **1169**
Opioid-Related Disorders **1169**
Epidemiology of Opioid Abuse and Dependence **1170**
Etiology and Pathophysiology of Opioid-Related Disorders **1170**
Clinical Picture of Opioid-Related Disorders **1171**
Assessment and Clinical Picture **1172**
Course and Natural History of Opioid Dependence **1175**
Treatment **1175**

Chapter 64 **Substance Abuse: Sedative, Hypnotic, or Anxiolytic Use Disorders 1186**
*Donald R. Wesson, David E. Smith, Walter Ling, Sanjay Sabnani*

Introduction **1186**
Sedative–Hypnotic Related Disorders **1186**
Sedative–Hypnotics and GABA Receptors **1187**
Abuse and Abuse Potential **1188**
Withdrawal Syndrome **1192**
Evaluation and Diagnosis **1194**
Treatment **1195**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1198**

Chapter 65 **Schizophrenia and Other Psychoses 1201**
*Jayendra K. Patel, Debra A. Pinals, Alan Breier*

Historical Overview **1201**
Diagnosis **1203**
Epidemiology **1207**
Etiology **1211**
Clinical Manifestations and Phenomenology **1230**
Differential Diagnosis **1233**
Course of Illness **1239**
Other Psychotic Disorders **1265**
Schizoaffective Disorder **1265**
Brief Psychotic Disorder **1268**
Schizophreniform Disorder **1270**
Shared Psychotic Disorder **1276**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1278**

Chapter 66 **Mood Disorders: Depression 1283**
*Heinz Grunze, Cornelius Schüle, David Casey, Thomas C. Baghai*

Diagnosis **1283**

Assessment **1284**
Epidemiology **1285**
Comorbidity Patterns **1286**
Course and Subgroups **1289**
Differential Diagnosis **1291**
Etiology and Pathophysiology **1294**
Treatment **1301**

## Volume 2

**List of Contributors xxxi**
**Preface to this Edition xxxix**
**Preface to the First Edition xli**
**Preface to the Second Edition xliii**

**Section VI Disorders (*Continued*) 1333**
*Section Editor: Michael B. First*

Chapter 67 **Mood Disorders: Bipolar (Manic–Depressive) Disorders 1335**
*Mark S. Bauer*

Introduction **1335**
Diagnosis **1336**
Etiology and Pathophysiology **1348**
Treatment **1354**

Chapter 68 **Mood Disorders: Premenstrual Dysphoric Disorder 1379**
*Teri Pearlstein*

Definition and Diagnostic Features **1379**
Differential Diagnosis **1380**
Course **1381**
Epidemiology **1381**
Etiology and Pathophysiology **1382**
Treatment **1383**
Conclusion **1387**

Chapter 69 **Anxiety Disorders: Panic Disorder With and Without Agoraphobia 1392**
*Gordon J. G. Asmundson, Steven Taylor*

Introduction **1392**
Diagnosis **1393**
Etiology and Pathophysiology **1399**
Treatment **1402**
Comparison of DSM-IV-TR and International Classification of Diseases, Tenth Revision (ICD-10) Diagnostic Criteria **1406**

Chapter 70 **Anxiety Disorders: Social and Specific Phobias 1409**
*Randi E. McCabe, Martin M. Antony*

Introduction **1409**
Diagnosis **1410**
Definition and Diagnostic Features **1410**
Assessment **1413**
Epidemiology **1414**
Comorbidity Patterns **1415**
Course **1416**
Differential Diagnosis **1416**
Differences in Developmental, Gender, and Cultural Presentations **1418**
Etiology and Pathophysiology **1421**
Genetic Factors **1421**
Neurobiological Factors **1422**
Psychological and Social/Environmental Factors **1423**
Treatment **1426**
Treatment Goals **1427**
Somatic Treatments **1427**
Psychosocial Treatments **1429**
Treatment Refractory Patients **1432**
Special Factors Influencing Treatment **1434**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1436**

Chapter 71 **Anxiety Disorders: Obsessive–Compulsive Disorder 1443**
*Michele T. Pato, Ayman Fanous, Jane L. Eisen, Katharine A. Phillips*

Definition and Diagnostic Features **1443**
Epidemiology **1448**
Comorbidity **1449**
Differential Diagnosis **1451**
Etiology and Pathophysiology **1454**
Treatment Goals **1457**
Conclusion **1467**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1467**

Chapter 72 **Anxiety Disorders: Traumatic Stress Disorders 1472**
*Amanda M. Flood, Jonathan R. T. Davidson, Jean C. Beckham*

*Posttraumatic Stress Disorder* **1472**
Diagnosis **1472**
Assessment **1474**

Epidemiology **1475**
Comorbidity Patterns **1475**
Course **1475**
Differential Diagnosis **1475**
Differences in Developmental, Gender, and Cultural Presentations **1476**
Etiology and Pathophysiology **1476**
Treatment **1479**
Summary of Treatment **1485**
Issues in the Doctor–Patient Relationship **1485**
*Acute Stress Disorder* **1485**
Diagnosis **1485**
Assessment **1485**
Epidemiology **1486**
Course **1487**
Differential Diagnosis **1487**
Etiology and Pathophysiology **1487**
Treatment **1487**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1489**

Chapter 73 **Anxiety Disorders: Generalized Anxiety Disorder 1494**
*Amy E. Lawrence, Timothy A. Brown*

Diagnosis **1494**
Assessment **1495**
Epidemiology **1497**
Etiology and Pathophysiology **1500**
Treatment **1502**
Summary **1506**

Chapter 74 **Somatoform Disorders 1510**
*Sean H. Yutzy, Brooke S. Parish*

Introduction **1510**
Differential Diagnosis **1511**
Differentiation Among the Various Somatoform Disorders **1513**
Epidemiology **1513**
Treatment **1513**
*Somatization Disorder* **1513**
Definition and Diagnostic Features **1513**
Epidemiology **1518**
Course **1518**
Differential Diagnosis **1518**
Etiology and Pathophysiology **1521**
Treatment **1521**
*Undifferentiated Somatoform Disorder* **1523**
Definition and Diagnostic Features **1523**
Epidemiology **1524**
Course **1524**
Differential Diagnosis **1524**
Etiology and Pathophysiology **1524**
Treatment **1525**
*Conversion Disorder* **1525**
Definition and Diagnostic Features **1525**
Epidemiology **1527**
Course **1527**
Differential Diagnosis **1527**
Etiology and Pathophysiology **1528**
Treatment **1529**
*Pain Disorder* **1530**
Definition and Diagnostic Features **1530**
Epidemiology **1531**
Course **1532**
Differential Diagnosis **1532**
Etiology and Pathophysiology **1533**
Treatment **1533**
*Hypochondriasis* **1535**
Definition and Diagnostic Features **1535**
Epidemiology **1536**
Course **1536**
Differential Diagnosis **1536**
Etiology and Pathophysiology **1537**
Treatment **1537**
*Body Dysmorphic Disorder* **1538**
Definition and Diagnostic Features **1538**
Epidemiology **1539**
Course **1540**
Differential Diagnosis **1540**
Etiology and Pathophysiology **1541**
Treatment **1541**
*Somatoform Disorder NOS* **1542**
Definition and Diagnostic Features **1542**
Differential Diagnosis **1543**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1544**
Conclusion **1543**

Chapter 75 **Factitious Disorders 1548**
*Anne M. Fleming, Stuart J. Eisendrath*

Introduction **1548**
*Factitious Disorder* **1549**
Diagnosis **1549**
Assessment **1551**

Epidemiology **1551**
Comorbidity Patterns **1551**
Course **1552**
Differential Diagnosis **1552**
Etiology and Pathophysiology **1552**
Treatment **1553**
*Factitious Disorder by Proxy* **1554**
Diagnosis **1554**
Assessment **1555**
Epidemiology **1555**
Comorbidity Patterns **1555**
Course **1555**
Differential Diagnosis **1555**
Etiology and Pathophysiology **1555**
Treatment **1555**
Summary **1556**

Chapter 76 **Dissociative Disorders 1558**
*José R. Maldonado, David Spiegel*

Development of the Concept **1558**
Epidemiology **1559**
Diagnostic Criteria and Treatment **1560**
Treatment **1567**
Theoretical and Research Issues: Models and Mechanisms of Dissociation **1573**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1574**
Conclusion **1574**

Chapter 77 **Sexual Disorders 1578**
*Stephen B. Levine*

Preface **1578**
The Components of Sexuality **1579**
Sexual Development Through the Life Cycle **1580**
*The Sexual Dysfunctions* **1580**
Significance of Sexual Dysfunction **1580**
DSM-IV-TR Diagnoses **1580**
Epidemiology **1580**
Sexual Equilibrium **1581**
The Nature of Sexual Desire **1581**
The Problems of Sexual Arousal **1586**
Problems with Orgasm **1589**
Sexual Pain Disorders **1592**
Sexual Dysfunction Not Otherwise Specified **1594**
*Gender Identity Disorders* **1594**
Extremely Feminine Young Boys **1594**
Masculine Girls: Tomboys **1595**
The Subjectivity of a Well-Developed Gender Disorder **1595**
Diagnostic Criteria of Gender Identity Disorder **1596**
Diagnostic Criteria of GIDNOS **1597**
The Relationship of GIDs to Orientation **1598**
Treatment Options for the GIDs **1598**
*The Paraphilias* **1600**
Three General Characteristics of the Paraphilias **1600**
Speculations About the Underlying Problem **1601**
The Specific Paraphilias **1602**
Treatment **1604**
*Sexual Disorder Not Otherwise Specified* **1606**
The Doctor–Patient Relationship and Sexual Disorders **1606**
*Final Thoughts* **1606**
Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria **1606**

Chapter 78 **Eating Disorders 1609**
*B. Timothy Walsh*

Introduction **1609**
*Anorexia Nervosa* **1609**
Diagnosis **1609**
Etiology and Pathophysiology **1615**
Treatment **1616**
*Bulimia Nervosa* **1618**
Definition and Diagnostic Features **1618**
Etiology and Pathophysiology **1620**
Treatment **1621**
*Binge-Eating Disorder* **1623**
Diagnosis **1623**
Etiology and Pathophysiology **1624**
Treatment **1624**

Chapter 79 **Sleep and Sleep–Wake Disorders 1626**
*Milton Erman, Sonia Ancoli-Israel*

*Phenomenology and Organization of Sleep* **1626**
Physiological Regulation of Sleep and Wakefulness **1626**
Normal Age-Related Changes in Sleep and Wakefulness **1628**
Neurophysiology and Neurochemistry of Sleep **1629**

*Sleep Disorders* **1629**
General Approach to the Patient with a Sleep Disorder **1630**
Role of the Sleep Laboratory in Clinical Sleep Disorders **1631**
Chronic Insomnia **1632**
General Approaches to the Clinical Management of Sleep Disorders in Psychiatric Patients **1637**
Hypersomnia **1638**
Breathing Related Sleep Disturbances (BRSD) **1641**
Circadian Rhythm Sleep Disorder (Sleep–Wake Schedule Disorders) **1643**
Shift Work Sleep Disorder **1645**
Jet Lag **1645**
PLMS and Restless Legs Syndrome (RLS) **1646**
Parasomnias **1647**
Sleep Disorders Due To a General Medical Condition **1650**
Substance-Induced Sleep Disorder **1651**
Comparison of DSM-IV-TR /ICD-10 Diagnostic Criteria **1656**

Chapter 80 **Impulse-Control Disorders 1658**
*Daphne Simeon, Heather Berlin*

Introduction **1658**
Intermittent Explosive Disorder **1661**
Kleptomania **1668**
Pyromania and Fire Setting Behavior **1674**
Pathological Gambling **1678**
Trichotillomania **1687**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1695**

Chapter 81 **Adjustment Disorders 1702**
*James J. Strain, Kim Klipstein, Jeffrey H. Newcorn*

Definition **1702**
Epidemiology **1705**
Etiology **1706**
Diagnosis and Differential Diagnosis **1707**
Course and Natural History **1709**
Treatment **1710**
Refractory Patients and Nonresponse to Initial Treatment **1713**
Conclusion **1713**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1714**

Chapter 82 **Personality Disorders 1718**
*Thomas A. Widiger, Stephanie N. Mullins-Sweatt*

Personality Disorder **1718**
Paranoid Personality Disorder **1724**
Schizoid Personality Disorder **1726**
Schizotypal Personality Disorder **1728**
Antisocial Personality Disorder **1730**
Borderline Personality Disorder **1733**
Histrionic Personality Disorder **1735**
Narcissistic Personality Disorder **1737**
Avoidant Personality Disorder **1740**
Dependent Personality Disorder **1742**
Obsessive-Compulsive Personality Disorder **1744**
Personality Disorder, Not Otherwise Specified **1746**

Chapter 83 **Psychological Factors Affecting Medical Condition 1754**
*James L. Levenson*

Definition **1754**
Assessment and Diagnosis **1755**
Differential Diagnosis **1757**
Epidemiology and Comorbidity **1757**
Course **1758**
Etiology and Pathophysiology **1758**
Treatment **1758**

Chapter 84 **Medication-Induced Movement Disorders 1773**
*Thomas W. Meeks, Dilip V. Jeste*

Introduction **1773**
Historical Background **1773**
Classification **1773**
Informed Consent/Medicolegal Issues **1774**
*Acute Neuroleptic-Induced Movement Disorders* **1774**
Neuroleptic-Induced Acute Dystonia **1774**
Neuroleptic-Induced Parkinsonism **1776**
Neuroleptic-Induced Acute Akathisia **1779**
*Prophylactic Anticholinergic Medication: Pros and Cons* **1780**
*Neuroleptic-Induced Tardive Movement Disorders* **1781**
Neuroleptic-Induced Tardive Dyskinesia **1781**
Other Tardive Movement Disorders **1785**

*Other Neuroleptic-Induced Disorders* **1785**
Neuroleptic Malignant Syndrome **1785**
Medication-Induced Postural Tremor **1788**
Comparison of DSM-IV/ICD-10 Diagnostic Criteria **1790**

Chapter 85 **Relational Problem Related to a Mental Disorder or General Medical Condition 1794**
*Martha C. Tompson, David J. Miklowitz, John F. Clarkin*

Introduction **1794**
Definition **1794**
Constructs and Manifestations of Relational Problems **1795**
Diagnosis of Relational Disorders **1800**
Assessment of Relational Disorders **1801**
Epidemiology of Relational Disorders **1802**
Treatment **1803**
Summary **1806**

## Treatments 1815–2462

Chapter 86 **Organization and Economics of Mental Health Treatment 1817**
*Michael F. Hogan, Ann K. Morrison*

Introduction **1817**
Historical Trends and Forces in Mental Health **1818**
The Economics of Mental Health **1834**
Managed Mental Health Care in the Public Sector **1841**
Defining and Improving the Quality of Mental Health Care **1844**
Prospects for the Future **1846**

**Section VII Psychotherapeutic and Psychosocial Treatments 1849**
*Section Editors: William H. Sledge and Bruce J. Rounsaville*

Chapter 87 **Individual Psychoanalytic Psychotherapy 1851**
*Jerald Kay, Rena L. Kay*

What Is Psychotherapy? **1851**
Expressive–Supportive Continuum **1852**
Theory of Psychoanalytic Psychotherapy **1853**
How Does Psychoanalytic Psychotherapy Work? **1857**
How Does Psychoanalytic Psychotherapy Differ from Psychoanalysis? **1860**
Tasks of the Psychoanalytic Psychotherapist **1860**
Indications for Psychoanalytic Psychotherapy **1862**
Contraindications to Psychoanalytic Psychotherapy **1862**
Supportive Psychoanalytic Psychotherapy **1863**
Gender Issues in Psychotherapy **1864**
Ethnocultural Issues in Psychotherapy **1864**
Is Psychoanalytic Psychotherapy Effective? **1866**
Long-Term versus Brief Psychotherapies **1869**
Disconnection between Psychotherapy Practice and Research **1869**
Toward a Neurobiology of Psychotherapy **1869**
Conclusion **1870**

Chapter 88 **Interpersonal Psychotherapy 1875**
*John C. Markowitz*

Introduction **1875**
Background **1876**
Conducting IPT **1876**
Research Findings: IPT for Mood Disorders **1879**
IPT for Nonmood Disorders **1883**
Summary **1884**
Training **1885**
The Future **1885**

Chapter 89 **Brief Psychotherapies 1889**
*Mantosh J. Dewan, Brett N. Steenbarger, Roger P. Greenberg*

A Short History Of Brief Therapy **1889**
Psychodynamic Therapy Issues, Outcomes and Comparisons **1891**
Efficacy of Brief Psychodynamic Psychotherapy: The Evidence **1891**
Models of Brief Psychotherapy **1893**
Factors Common to the Brief Therapies **1898**
Patient Inclusion Criteria **1898**
Focal Aims **1899**
Therapist and Patient Activity **1899**
Sequencing of Change **1900**
Conclusion **1900**

Chapter 90 **Group Psychotherapy 1904**
*Walter N. Stone*

History **1904**
Group Therapy Theory **1904**
Group Dynamics and Group Development **1906**
Therapeutic Factors **1908**
The Practice of Group Therapy **1909**
Therapist's Role **1911**
Initiating Treatment **1911**
Treatment Course **1912**
Special Treatment Considerations **1913**
Alternative Treatment Formats **1914**
Treatment Failures **1917**
Research **1917**
Training **1918**
The Future **1918**

Chapter 91 **Cognitive and Behavioral Therapies 1920**
*Edward S. Friedman, Michael E. Thase, Jesse H. Wright*

Cognitive Model **1920**
Behavioral Model **1923**
Cognitive and Behavioral Treatment Strategies **1924**
Behavioral Techniques **1930**
Formulation of Treatment **1933**
Efficacy of CBT **1936**
Conclusion **1940**

Chapter 92 **Family Therapy 1948**
*James L. Griffith, Lois Slovik*

Introduction **1948**
Psychodynamic Family Therapy **1949**
Structural Family Therapy **1950**
Strategic Family Therapy **1951**
Cognitive–Behavioral Family Therapy **1952**
The Postmodern Family Therapies **1953**
From Family Therapy to Family Psychiatry **1955**
Family Psychoeducation **1955**
Family Resilience **1956**
Reducing Caregiver Burden in Chronic Disorders **1957**
Family-Centered Treatment in International Mental Health **1958**
Summary **1959**
Appendix I: Psychodynamic Family Therapy **1959**

Chapter 93 **Couples Therapy 1963**
*Eva Ritvo, Ira D. Glick, Ellen Berman*

Introduction **1963**
Definition: What Is "Couples Therapy?" **1963**
Coupling and the life cycle **1964**
Couples Function and Dysfunction **1966**
Evaluation of the Couple **1968**
Indications and Contraindications for Couples Therapy **1970**
Treatment **1970**
Effectiveness and Efficacy of Couples Therapy **1972**
Special Considerations for Couples Therapy **1973**
Sexuality and the Treatment of Sexual Dysfunction **1974**
Conclusion **1980**

Chapter 94 **Hypnosis 1982**
*José R. Maldonado, David Spiegel*

Historical Background **1982**
Myth Dispelled: What Hypnosis Is and What It Is Not **1985**
Hypnotizability Scales **1986**
Hypnotizability and Psychiatric Disorders **1988**
Applications of Hypnosis **1991**
Neurophysiological Correlates of Hypnosis **2008**
Enhancing Hypnotizability **2013**
Conclusion **2013**

Chapter 95 **Behavioral Medicine 2027**
*Lisa Maria E. Frantsve, William H. Sledge, Robert D. Kerns, Paul Desan*

Historical Foundations of Behavioral Medicine **2028**
The Beginning of Behavioral Medicine **2029**
Theoretical Foundations within Behavioral Medicine **2030**
Selected Health Issues within Behavioral Medicine **2032**
The Practice of Behavioral Medicine **2039**
The Application of Behavioral Medicine: A Case of Chronic Pain **2041**
Summary and Conclusions **2043**

Chapter 96 **Psychosocial Rehabilitation 2047**
*Alan S. Bellack*

Psychosocial Rehabilitation **2047**
Issues in the Design of Psychosocial Interventions **2048**
Timing and Duration of Treatment **2048**
Individual Differences in Treatment Needs **2048**
The Role of the Person **2049**
Impairments in Information Processing **2050**
Adoption of a Compensatory Model **2051**
Rehabilitation Strategies **2051**
Social Skills Training **2051**
Cognitive Rehabilitation **2053**
Vocational Rehabilitation **2054**
Summary and Conclusions **2055**

Chapter 97 **Psychiatric Rehabilitation for Achieving Successful Community Living for Adults with Psychiatric Disabilities 2059**
*Phyllis Solomon, Sara W. Cullen*

Defining Adults with Psychiatric Disabilities **2059**
Prevalance Estimates Of Psychiatric Disability **2060**
Defining Psychiatric Rehabilitation **2061**
Development of Psychiatric Rehabilitation **2061**
Principles and Service Elements of Psychiatric Rehabilitation **2062**
Examples of Psychiatric Rehabilitation Practices **2062**
Recovery and Rehabilitation **2065**
Psychotherapeutic Evidence-Based Practices **2067**
Conclusion **2080**

Chapter 98 **Advocacy, Self-Help, and Consumer-Operated Services 2083**
*Harriet P. Lefley*

Introduction **2083**
Conceptual Distinctions **2083**
Citizen and Family Advocacy Movements **2085**
Citizen Advocacy Organizations **2086**
Stakeholder (Family and Consumer) Organizatons **2086**
Consumer Self-Help and Advocacy Organizations **2088**
Government Roles in Consumer Empowerment **2090**
Service Development by Family and Consumer Groups **2091**
Relations of Professionals and Self-Help Groups **2092**
Consumerism and a New Recovery Orientation in Mental Health Care **2093**
Conclusions **2093**

**Section VIII Pharmacological and Brain Stimulation Treatments 2097**
*Section Editor: Steven P. Roose*

Chapter 99 **General Principles of Pharmacologic Therapy 2099**
*Zahinoor Ismail, Bruce G. Pollock*

Introduction **2099**
Pharmacokinetics **2099**
Pharmacodynamics **2105**
Safety and Efficacy **2107**
Summary **2109**

Chapter 100 **Psychopharmacology: Ethnic and Cultural Perspectives 2112**
*Keh-Ming Lin, Chia-Hui Chen, Shu-Han Yu, Margaret T. Lin, Michael W. Smith*

Dispelling the "Color-Blind" Approach **2112**
The Cultural Context of Psychopharmacotherapy **2113**
Clinicians' Attitudes **2113**
Adherence **2113**
Expectation ("Placebo") Effects **2114**
The Concomitant Use of Alternative/Indigenous Treatment and Healing Methods **2115**
Biological Diversity and Its Consequence in Psychotropic Responses **2115**
Genetic Polymorphism of Genes Encoding "Drug-Metabolizing Enzymes" **2116**
Factors Affecting the Expression of Drug-Metabolizing Enzymes **2117**
Genetic Polymorphism of Genes Encoding Receptors, Transporters, or Other Therapeutic Targets **2119**
Genetic Polymorphism of Other Genes Affecting Pharmacological Responses **2119**
Summary and Future Research Directions **2120**

Chapter 101 **Antidepressants 2123**
*Robert J. Boland, Martin B. Keller*

Theoretical Basis for Treatment **2123**
The Basis for Determining Efficacy **2128**
The Formulation of Treatment **2131**
Initiation of Treatment **2143**
Phases of Treatment **2147**
Conclusions **2151**

Chapter 102 **Antipsychotic Drugs 2161**
*Seiya Miyamoto, David B. Merrill, Jeffrey A. Lieberman, W. Wolfgang Fleischacker, Stephen R. Marder*

Introduction **2161**
History of Antipsychotic Drug Development **2161**
Mechanism of Action of Antipsychotic Agents **2162**
Pharmacology of Antipsychotic Agents **2166**
Conditions Treated with Antipsychotic Medications **2170**
Effects of Antipsychotic Agents on Symptoms of Schizophrenia **2174**
Treatment of Different Phases of Schizophrenia **2177**
Use of Plasma Levels of Antipsychotic Drugs **2183**
Drug Interactions and Antipsychotic Agents **2183**
Antipsychotic Medications and Pregnancy **2183**
Adverse Effects **2184**
Future Directions in Antipsychotic Drug Research and Treatment **2192**
Conclusions **2193**

Chapter 103 **Mood Stabilizers 2202**
*David J. Muzina, David E. Kemp, Joseph R. Calabrese*

Introduction **2202**
Defining Mood Stabilizers **2202**
Mood Stabilizers for Acute Mania **2203**
Mood Stabilizers for Acute Bipolar Depression **2210**
Mood Stabilizers for Maintenance Treatment of Bipolar Disorder **2214**
Mood Stabilizers for Rapid Cycling Bipolar Disorder (RCBD) **2218**
Redefining Mood Stabilizers **2219**
Conclusion **2219**

Chapter 104 **Anxiolytic Drugs 2223**
*Deidre M. Edwards, Kathryn L. Hale, Rachel E. Maddux, Mark Hyman Rapaport*

Introduction **2223**
A General Approach to Using Medication with Anxious Patients **2223**
Antidepressant Medication **2224**
Benzodiazepine Medication **2225**
Buspirone **2225**
Beta-Blocker Medication **2226**
Anticonvulsant Medication **2226**
Antipsychotic Medication **2226**
Generalized Anxiety Disorder **2228**
Social Anxiety Disorder **2233**
Panic Disorder **2236**
Posttraumatic Stress Disorder **2240**
Obsessive–Compulsive Disorder **2244**
Future Directions **2248**
Conclusion **2248**

Chapter 105 **Pharmacologic Treatment of Insomnia 2254**
*David N. Neubauer*

Introduction **2254**
Sleep–Wake Cycle Regulation **2254**
Historical Overview **2255**
FDA-Approved Insomnia Treatment Medications **2255**
Prescription Medication Off-Label Use **2258**
OTC Medications **2260**
Complementary and Alternative Substances **2261**
Insomnia in Psychiatric Patients **2261**
Summary or Conclusions **2262**

Chapter 106 **Stimulants 2264**
*Natalya Paykina, Laurence L. Greenhill, Kelly N. Fahl, J. Craig Nelson*

***Treatment of Children with Disruptive Behavior Disorders* 2264**
*Natalya Paykina, Laurence L. Greenhill, Kelly N. Fahl*

Medications **2264**
Pharmacology **2266**
Indications and a Review of Efficacy Data in Children **2269**
Side Effects **2276**
Clinical Use **2279**

*Treatment of Adult Depression* **2284**
*J. Craig Nelson*

Acute Effects **2284**
Chronic Effects **2284**
Studies in Medically III and Geriatric Patients **2285**
Stimulants in Late Life Depression **2285**
Stimulant Augmentation in Depression **2285**
Acceleration of Response with Stimulants **2286**
Dextroamphetamine vs. Methylphenidate **2286**
Side Effects and Safety **2286**
Abuse Potential **2287**
Modafinil for Depression **2287**
Conclusions **2287**

Chapter 107 **Cognitive Enhancers and Treatments for Alzheimer's Disease 2294**
*Roy Yaari, Pierre N. Tariot, Lon S. Schneider*

History and Background **2294**
Regulatory and Methodological Issues **2294**
Etiopathology and Implications for Treatment **2295**
Treatment Paradigms **2296**
Summary **2312**

Chapter 108 **Complementary and Alternative Treatments in Psychiatry 2318**
*Richard P. Brown, Patricia L. Gerbarg, Philip R. Muskin*

Mood Disorders **2319**
Anxiety Disorders **2326**
Hormones for Anxiety Disorders and Insomnia **2332**
Cognitive Enhancement **2335**
How to Use CAM Treatments Safely and Effectively **2343**
Summary **2344**

Chapter 109 **Brain Stimulation in Psychiatry 2354**
*Stefan Rowny, Sarah H. Lisanby*

Introduction **2354**
Brain Stimulation: A Unique Family of Neuromodulation Interventions **2354**
Applications of Brain Stimulation in Psychiatry **2358**
Brain Stimulation Tools in Psychiatry **2358**
Conclusions and Future Directions **2368**

Chapter 110 **Pharmacologic Management of Treatment-Resistant Unipolar Depression 2372**
*Patrick J. McGrath, Jeffrey M. Miller*

Introduction **2372**
Evaluation of the Patient **2375**
Medication Management **2378**
Switching Antidepressants **2380**
Augmentation **2382**
Combination Antidepressant Strategies **2384**
Novel Agents **2384**
Proposed Algorithm for Treatment **2384**
General Principles of Management **2384**
Indications for Brain Stimulation Treatment **2386**
Limitations of Current and Likely Research **2386**

Chapter 111 **Pharmacological Treatment of Substance Abuse Disorders 2390**
*Wilfrid Noel Raby, Frances R. Levin, Edward V. Nunes*

Pharmacological Mechanisms of Treatment for Substance Use Disorders **2390**
Alcohol **2392**
Opiates **2397**
Nicotine Dependence **2407**
Stimulants: Cocaine and Amphetamines **2410**
Marijuana and Cannabinoids **2411**
Summary **2412**

Chapter 112 **Pharmacologic Issues During Pregnancy 2417**
*Kimberly A. Yonkers, Margaret Spinelli*

Introduction **2417**
Stress, Mood, and Adverse Birth Outcomes **2417**
In Utero Exposure to Antidepressants and Birth Outcomes **2418**
Psychotherapy **2421**
Pharmacotherapy During Lactation **2423**
Management Recommendations **2425**
Summary **2426**

Chapter 113 **Combined Treatment with Medications and Psychotherapy 2430**
*Bret R. Rutherford, Deborah L. Cabaniss, Steven P. Roose*

History of Combined Treatments **2430**
Evidence for Combined Treatments **2431**
Technical Considerations in Doing Combined Treatment **2439**
Conclusions **2444**

Chapter 114 **Patient Compliance 2447**
*Stephanie A. Riolo, Christina G. Weston*

Introduction **2447**
Definition: "Compliance" versus "Adherence" **2447**
Treatment Refusal **2448**
Overview of Theoretical Models **2448**
Prevalence of Medication Noncompliance **2449**
Patterns of Medication Noncompliance **2449**
Measurement of Medication Compliance **2450**
Risk Factors for Noncompliance **2451**
Specific Patient Populations **2455**
Intervention Strategies **2457**
Conclusions **2459**

**Section IX Special Populations and Settings 2463**
*Section Editor: Michelle B. Riba*

Chapter 115 **Managing Psychological Consequences in Disaster Populations 2465**
*Derrick A. Hamaoka, David M. Benedek, Robert J. Ursano*

Disaster Psychiatry **2465**
Conclusion **2474**

Chapter 116 **Management of the Suicidal Patient 2478**
*Glenn A. Melvin, Kelly Posner, Barbara H. Stanley, Maria A. Oquendo*

Introduction **2478**
What is Suicidal Ideation and Behavior? **2478**
Scope of The Problem of Suicidal Behavior: Mortality and Morbidity **2478**
Risk and Protective Factors **2479**
Demographic Risk and Protective Factors **2479**
Employment **2480**
Clinical Risk and Protective Factors **2480**
Management of the Suicidal Patient **2482**
Treatment **2483**
Legal and Ethical Issues **2486**
Conclusions **2486**

Chapter 117 **Restraints and Seclusion 2491**
*Wanda K. Mohr, Kevin Ann Huckshorn, Kim J. Masters*

Controversies Regarding Restraint and Seclusion **2491**
State of Research **2491**
The Legal Rights of Psychiatric Patients **2493**
The State of Education **2493**
Conclusion **2494**

Chapter 118 **Psychosomatic Medicine 2496**
*James L. Levenson*

Introduction **2496**
History **2496**
International Developments in Psychosomatic Medicine **2497**
Psychosomatic Medicine as a Scholarly Discipline **2497**
The Clinical Practice of Psychosomatic Medicine **2498**
Psychiatric Diagnosis in the Medically Ill **2498**
Psychosomatic Aspects of Cardiovascular Disease **2499**
Psychosomatic Aspects of Cancer **2501**
Psychosomatic Aspects of Endocrine Disorders **2503**
Conclusion **2505**

Chapter 119 **Psychiatric Conditions in Women during Reproductive Transitions 2507**
*Helen G. Kim, Nancy Raymond, Susan G. Kornstein*

Pregnancy **2507**
Postpartum Psychiatric Illness **2509**
Menopause **2511**
Conclusion **2513**

Chapter 120 **Death and Bereavement 2516**
*M. Katherine Shear*

Introduction **2516**

Death and Dying **2516**
Bereavement and Grief **2519**

Chapter 121 **Serving People Who Have Mental Illness and Homelessness 2526**
*Hunter L. McQuistion, Alan D. Felix, Judith Samuels*

Background: The Evolution of Services **2526**
The Stages of Care **2530**
Administration, Academics, and Advocacy **2534**

Chapter 122 **Gender Identity and Sexual Orientation 2538**
*Robert P. Cabaj*

Definitions and Concepts **2538**
History of Homosexuality and Psychiatry **2539**
Biology, Genetics, and Cultural Perspectives on Homosexuality and Bisexuality **2540**
Developmental Issues Facing Most Gay, Lesbian, and Bisexual People **2541**
Psychotherapy: Special Considerations **2542**
Gender Identity and Transgender Issues **2546**

Chapter 123 **Management of the Patient in Geriatric Psychiatry 2549**
*David A. Casey*

Introduction **2549**
Approach to the Patient **2549**
Management of Dementia **2551**
Management of Behavioral Disturbance in Dementia **2554**
Etiology of Behavioral Disturbance **2554**
Management of Depression in the Elderly **2557**
Conclusion **2560**

Chapter 124 **Management of Victims of Torture 2563**
*Marianne C. Kastrup, James M. Jaranson*

Introduction **2563**
Medical Aspects of Torture **2565**
Identifying Consequences of Torture and Need for Treatment **2566**
General Therapeutic Considerations **2568**
Treatment Interventions **2570**
Organization of Care **2572**
Specific Populations and Issues **2572**
Conclusions **2574**

Chapter 125 **Psychiatric Management of Victims of Physical and Sexual Abuse and Rape 2576**
*Donna E. Stewart, Simone N. Vigod*

Introduction **2576**
Epidemiology **2577**
Management—Acute Presentations of Physical or Sexual Abuse and Rape **2578**
Long-Term Mental Health Sequelae of Physical and Sexual Abuse and Rape **2584**
Management Considerations for Long-Term Psychiatric Sequelae of Physical and Sexual Abuse and Rape **2586**
Conclusions **2591**

Chapter 126 **Correctional Psychiatry 2593**
*Erik J. Roskes*

Epidemiology of Mental Illness in Correctional Populations **2593**
Criminal Justice/Mental Health Collaborative Interventions **2595**
Legal Considerations **2596**
Mental Health Care in the Correctional Setting **2596**
Special Topics and Challenges in the Correctional Setting **2598**
Conclusion **2600**

Chapter 127 **Treatment of Violent Behavior 2602**
*Fabian M. Saleh, John P. Fedoroff, Adekunle G. Ahmed, Debra A. Pinals*

Introduction **2602**
Assessment of Violence Risk in Clinical Settings **2602**
Classification of Violence **2603**
Link Between Anger and Aggression **2603**
Clinical Factors Associated with Violence **2603**
Violence, Physiology, and Biology **2605**
Treatment of Aggression **2608**
Conclusions **2612**

**Appendix I** **Appendix I**

Chapter 128 **Research Methodology and Statistics 2619**
*Daniel S. Weiss*

Introduction **2619**
Issues of Design **2619**
Designs and Threats to Validity **2620**
Power and Statistical Inference **2622**
Issues of Measurement **2624**
Standard Statistical Techniques **2626**
Basic Statistical Parameters **2626**
Univariate Approaches **2627**
Multivariate Approaches **2628**
Conclusion **2633**

**INDEX I**

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# *Preface to this Edition*

Time and science march on, and thus, a new edition of *Psychiatry* is now before you. The advances in our field continue at a rapid pace, with an ongoing transformation of our understanding of brain and mental functioning, and the development of ever more sophisticated treatments. We continue to feel tremendous gratitude to our colleagues, whose acceptance of *Psychiatry* has led to it becoming a leading reference text around the world.

This edition is marked not only by extensive revision of all chapters, and by the addition of many new chapters, but also by a major restructuring of the book. Where before there were seven major sections, there are now nine, reflecting both the expansion of our knowledge base, and what we believe will be a more useful organization of the material.

With all the revising and restructuring though, our philosophical preference continues to emphasize an integrative approach to both understanding psychopathology and providing treatment. And, as always, we hold to the view that the context of our understanding and intervention remains the therapeutic alliance we develop and maintain with our patients.

You will also see that we have expanded our panel of editors, reflecting both the breadth of the field, and the increasingly international scope of our work. Our two new editors are Michael First, MD and Mario Maj, MD. Professor Michael First in New York is an internationally known psychiatrist in the area of diagnostic classification, and one of the leaders in the development of the DSM-IV and DSM-IV-TR. Professor Mario Maj is chair of psychiatry at the University of Naples, Italy, an internationally known scholar in several areas, and incoming president of the World Psychiatric Association.

*Psychiatry's* success and international acceptance reflects the outstanding contributions of several hundred of the most eminent and scholarly group of colleagues with whom one could ever hope to work. As always, their diligence and commitment to excellence made the work of the section editors and editors much easier than one might imagine. Great thanks go to all the authors and section editors, who deserve the highest accolades for the quality of this work.

Thanks also go to all those at Wiley–Blackwell involved in the publication of this work. Special thanks go to Joan Marsh, Andrew Spong, Layla Paggetti, Jill Hawthorne, and Kerry Powell for their commitment to the project. None of the editors could have accomplished their work without the devoted assistance of their home-based secretaries and assistants, all of whom have our thanks.

Most importantly, special thanks go to our families, who, once again, tolerated hours of our reviewing manuscripts and correcting proofs, hours which otherwise would have been spent with them.

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# *Preface to the First Edition*

This is an exciting time in the field of psychiatry. Scientific progress has expanded the diagnostic and therapeutic capabilities of psychiatry at the same time that psychiatry has begun to play a larger role in the delivery of care to a wider population, both in mental health and in primary care settings. Psychiatry at the end of the 20th century plays an important role among the medical specialties.

The physician-patient relationship provides the framework for quality psychiatric practice. The skilled clinician must acquire a breadth and depth of knowledge and skills in the conduct of the clinical interaction with the patient. To succeed in this relationship, the psychiatrist must have an understanding of normal developmental processes across the life cycle (physiological, psychological, and social) and how these processes are manifested in behavior and mental functions. The psychiatrist must also be expert in the identification and evaluation of the signs and symptoms of abnormal behavior and mental processes and be able to classify them among the defined clinical syndromes that constitute the psychiatric nosology.

To arrive at a meaningful clinical assessment, one must understand the etiology and pathophysiology of the illness along with the contributions of the patient's individual environmental and sociocultural experiences. Furthermore, the psychiatrist must have a command of the range of therapeutic options for any given condition, including comparative benefits and risks, and must weigh the special factors that can influence the course of treatment such as medical comorbidity and constitutional, sociocultural, and situational factors.

The view of psychiatric practice just described forms the framework for *Psychiatry.* Section I, Approaches to the Patient, describes the importance of therapeutic listening and the development of the skills and knowledge necessary to assess and manage the interpersonal context in which psychiatric treatment occurs. Section II, A Developmental Perspective on Normal Domains of Mental and Behavioral Function, provides a review of normal development from a variety of perspectives across the life cycle. Section III, Scientific Foundations of Psychiatry, follows with a review of the scientific knowledge on which our understanding of behavior and mental functions, as well as psychopathology, is based.

Because we believe that good clinical practice must be based on comprehensive and sophisticated clinical assessment, Section IV, Manifestations of Psychiatric Illness, provides a detailed review of clinical assessment. What logically follows in Section V, which constitutes the heart of Psychiatry, is the discussion of psychiatric disorders. This section, which follows the nosology of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, differs from that found in other textbooks by the depth of the discussion of the clinical management of patients with each of these disorders. Unlike other texts, we have included substantial information on practical management; descriptions of common problems in management, including the treatment of refractory conditions; and discussions of typical issues that arise in the physician-patient relationship as treatment progresses.

The chapters in Section VI, Therapeutics, reflect our view that psychiatrists must be knowledgeable about a wide range of treatment options that include both somatic and psychotherapeutic interventions. The final section of the book, Section VII, Special Clinical Settings and Problems, reflects our belief that the sociocultural context within which the patient lives is a central aspect of the treatment process. Thus, we have included discussions of legal issues, reimbursement systems, ethical standards, the role of peer support and consumer advocacy, and the development of innovative non-hospital-based treatment programs.

Because no one should practice psychiatry without an appreciation of how the current knowledge base and treatment modalities have evolved historically, Appendix I, A Brief History of Psychiatry, provides a highly readable and scholarly review of the history of modern psychiatry. Because lifelong learning and the acquisition of new knowledge and skills are essential to optimal clinical practice, Appendix II, Research Methodology and Statistics, and Appendix III, Continued Professional Development, provide valuable information needed to assess the scientific worth of newly published literature in the field.

In a book with the depth and breadth of *Psychiatry*, a number of editorial decisions had to be made regarding the inclusion or omission of specific material and how information should be organized and presented. To make Psychiatry "user friendly," we have liberally used tables, charts, and illustrations to highlight key information. For example, clinical vignettes throughout the text are highlighted by a standard graphic element. Thus, an individual wishing to focus on the clinical aspects of psychiatry can do so by searching for the clinical vignettes located throughout the book. Whenever possible, we have used diagnostic and treatment decision trees to help both the novice and the experienced clinician arrive at a more rational method for making these clinical decisions. This reinforces the emphasis on clinical management issues in the section on

disorders (Section V). Also, each chapter is extensively referenced so that the interested reader can use the information from any chapter for further exploration of a topic.

For hundreds of years, modern medicine has struggled to understand the interactions of the mind and body. A review of medical history of the last several centuries reveals that this problem was resolved in Western cultures by splitting the functions of the mind and the body. In recent decades, as a result of substantial research advances, this approach has begun to change. We come down clearly on the side of those who believe that such a split not only is undesirable but also does not reflect the true state of human life. Thus, we have made every possible attempt to integrate the information in this book within a biopsychosocial framework. Along with the emergence of neurobiology as a discipline, social psychiatry has evolved in recent decades as we have become more aware that the unique social and cultural background of each individual patient can influence the development and manifestations of illness, the physician-patient relationship, the response to treatment, and long-term management. Rather than relegate these issues to a specific chapter, we have chosen to integrate them throughout the entire book.

We envision that *Psychiatry* will have multiple uses. Clinicians at all levels of experience, from the medical student who wishes a quick review to the experienced clinician who wishes to delve into a particular psychiatric topic, will find that the structure and format of *Psychiatry* are conducive to meeting a variety of needs. Health care professionals in other fields of medicine who must recognize or treat psychiatric illness will also find much useful information here.

*Psychiatry* is the centerpiece of a series of works that will provide a comprehensive program for psychiatric learning. Companion texts will include a review and self-assessment referenced to *Psychiatry*, a behavioral sciences text for medical students that offers a distillation of key information that every physician in training must have, a pocket guide for ready reference in the clinical setting, and a book that focuses on the pharmacological aspects of psychiatric practice.

*Psychiatry* has been enriched by the contributions of literally hundreds of individuals. Our section editors did an outstanding job both in helping to select chapter authors and in developing the specific format and content of each section. Although editing a multiple-authored text such as *Psychiatry* is a complex and challenging task, our work was made considerably easier by the uniform excellence of our authors' chapters and the diligence of our section editors in helping to mold first drafts into final products.

In addition to the scholarly aspects of the text, a work of this magnitude cannot be produced without the strong and ongoing support of a large number of individuals re-sponsible for its production. Each of us has had experience in editing other books, but never have we received such sustained and outstanding editorial support. Particular thanks go to Judy Fletcher, who approached Allan Tasman with her original idea for this book. Judy's accomplishments include not only successfully nurturing *Psychiatry* to fruition but also nurturing a baby daughter in the process. Judy was unfailingly available and helpful to us. Once the material reached the production stage, Les Hoeltzel, our developmental editor, did yeoman's work. A master of persuasion, Les shepherded the manuscripts through the production process into a finished textbook. Joanie Milnes, in Les' office, was consistently helpful and available.

Joan Lucas, in Allan Tasman's office, deserves our everlasting gratitude for her ability to keep track of hundreds of details and thousands of pages of manuscript and to maintain contact among three editors, seven section editors, and more than 100 chapter authors. Her level of organizational skill is matched only by her diplomatic skill in teasing delayed material from reluctant authors. Judy Yanko, in Jerry Kay's office, was also invaluable in sustaining our efforts. Maureen Ward, in Jeff Lieberman's office in New York (before he moved to North Carolina), efficiently and patiently coaxed, catalogued, and transferred dozens of chapters during the course of this project.

Most important, this work could not have been accomplished without strong support and encouragement from our families. With understanding and good humor, our spouses and children endured many hours of evening and weekend time devoted to work on *Psychiatry* that in other circumstances would have been devoted to them.

ALLAN TASMAN, MD

JERALD KAY, MD

JEFFREY A. LIEBERMAN, MD

# *Preface to the Second Edition*

When we undertook the development of the first edition of *Psychiatry*, our goal was to produce the highest quality textbook of general psychiatry; one that would provide a valuable resource to mental health clinicians, trainees, and students in a scholarly yet creative and accessible format. We have been very gratified by the response to the first edition of this textbook from colleagues, students, and reviewers who have found our book to be a comprehensive and valued reference. As we have watched the book's acceptance in both academic and clinical psychiatry settings, we have also been mindful of the march of science and the expanding knowledge base in our field. Thus, it became clear to us that between the successful reception of the first edition and the accelerated rate of scientific progress in psychiatry and neuroscience, it was time to plan for a second edition.

While this new edition maintains the same basic structure and philosophy on which the first edition was based, some significant changes have also been made. We maintain the emphasis on approaching the patient, and his/her diagnosis and treatment, from a biopsychosocial perspective, informed by an understanding of normal and pathological development, and complemented by an in-depth knowledge of the structure and function of the central nervous system. Moreover, we retain the focus on the centrality of the doctor–patient relationship in understanding our patients.

Because global scientific and medical communications are ever improving, we have expanded the book's scope to make it more international in its perspective. We have increased the emphasis on understanding how the cultural and ethnic background of our patients influences human development, disease expression and the nature of the doctor–patient relationship, and we have expanded our discussion of diagnostic and treatment variations around the world. Such additions are reflected by contributions from new authors and editors, with additional chapters, and new material within chapters. Additionally, the second edition contains 20 new chapters and extensive revisions of all chapters, reflecting all relevant clinical and scientific developments that have occurred since the first edition. With the benefit of an accelerated production process, we have been able to include many of the most important advances and references from 2002.

Once again, *Psychiatry* has benefited from the contributions of an incredibly scholarly and eminent group of authors and editors. The daunting task of producing this work was facilitated by their diligence and scholarship.

The publication of the second edition marks a new relationship with John Wiley & Sons, Ltd. Many individuals at Wiley have devoted themselves to helping produce and market the highest quality work, in particular Charlotte Brabants, Layla Paggetti, Amelia Bennett, and Andrew Spong. Charlotte, our editor, has been enthusiastic about the potential for the second edition since our first conversation, and that enthusiasm, paired with her skill and perseverance, has played an important role in bringing this work to fruition. Amelia has done sterling work to ensure that this edition has been produced with the highest standards of quality and on schedule. Just as with the first edition, we have also had tremendous help in our home institutions. Joan Lucas in Allan Tasman's office, Edward Depp in Jerry Kay's office, and Janice Linn and Tim McElwee in Jeff Lieberman's office all deserve credit for the quality and timeliness of this edition.

As before, this work could not have been completed without strong support and encouragement from our families. Though most of our children are now away from home, those remaining at home, and our spouses, deserve our thanks for their understanding as we took time to produce this work, time which otherwise would have been devoted to them.

ALLAN TASMAN, MD

JERALD KAY, MD

JEFFREY A. LIEBERMAN, MD

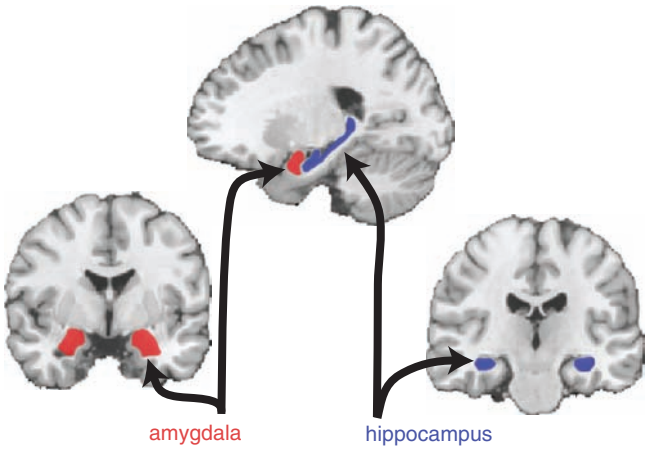



**Figure 15–1** *Location and relationship of the human hippocampus and amygdala. As described in the text, the hippocampus has an important role in memory formation and stress modulation. Hippocampal dysfunction is implicated in numerous psychiatric disorders, including major depressive disorder, PTSD, schizophrenia, and dementia. The amygdala, which we do not treat in detail in this chapter but which is discussed at length elsewhere in this textbook, is involved in both negative and positive emotion, and is implicated clinically in mood and anxiety disorders.*

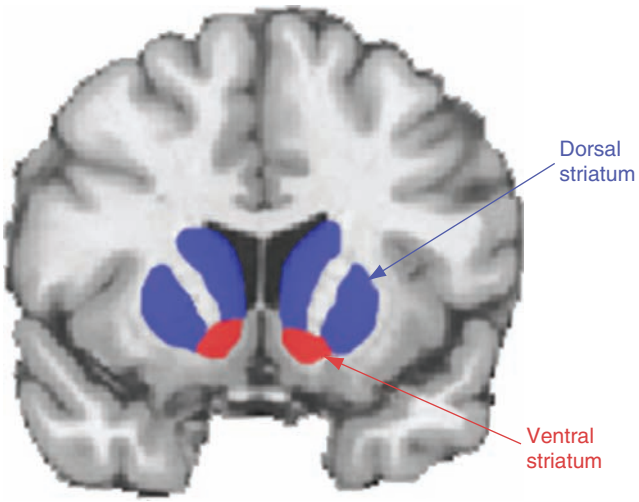



**Figure 15–2** *Anatomy of the human dorsal and ventral striatum, which are major input nuclei of the basal ganglia. As described in the text, the ventral striatum is implicated in reward and reinforced learning; dysregulation of ventral striatal function is implicated in addiction, schizophrenia, depression, and other disorders. The dorsal striatum functions both in motor control and in the acquisition and performance of automated learned behaviors, including habits; its dysfunction is implicated in OCD, drug addiction, and other disorders.*

Plate I

*Psychiatry, Third Edition.* Edited by Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First and Mario Maj.
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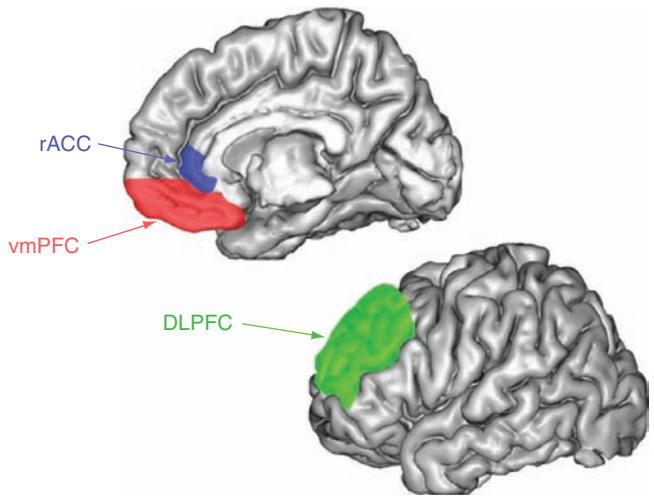



**Figure 15–3** *Neuroanatomy of the frontal cortical structures described in the text. The rostral anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC) have roles in emotion regulation, especially in the absence of an explicit attempt to regulate emotional processing. The dorsolateral prefrontal cortex (DLPFC) is critical for working memory and executive function and for deliberate forms of emotion regulation. As described in the text, functional perturbation of these structures and of their functional interrelationships is implicated in numerous psychiatric disorders, including schizophrenia, PTSD, and depression.*

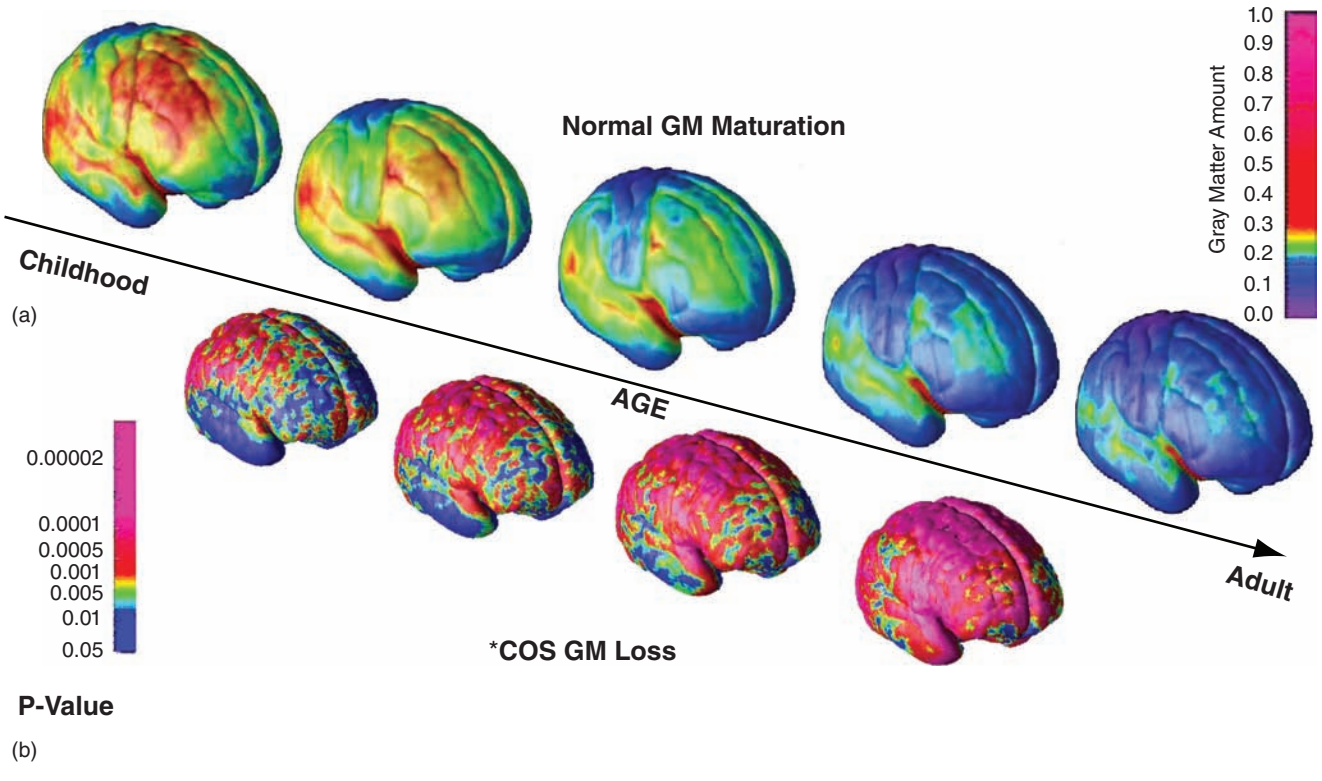



**Figure 19–2** *Gray matter maturation for healthy and schizophrenic children and adolescents. Comparison of the patterns of cortical gray matter (GM) loss in childhood onset schizophrenia (COS) (between ages 12 to 16) to that seen in normal cortical maturation (between ages 4 to 22). A.Right lateral view of the dynamic sequences of cortical GM maturation in healthy children between ages 4 and 22 (n=13; 54 scans; upper panel) rescanned every 2 years. Scale bar shows GM amount at each of the 65,536 cortical points across the entire cortex represented using a color scale (Red to Pink—More GM; Blue—GM Loss). Cortical GM maturation appears to progress in a "back to front" (parieto-temporal) manner (Gogtay et al. 2004). B. Right lateral view of the dynamic sequence of cortical GM maturation in COS between ages 12 to 16 compared with ages and sex matched healthy controls (n=12, 36 scans in each group), where children are rescanned every 2 years. Dynamic maps represent p-values for the difference in GM amount between COS and controls at each of the 65,536 cortical points, and p-values are represented using a color scale (that is Pink p<0.00002). Cortical GM loss in COS also appears to follow in a "back to front" direction on the lateral surface, thus suggesting that the COS pattern is an exaggeration of the normal GM maturation (Thompson et al. 2001). Data on childhood onset schizophrenia only, ages 12 to 16. International Psychopharmacology Algorithm Project (IPAP) Schizophrenia Algorithm (updated 17 March 2006). Available online at: www.ipap.org.*

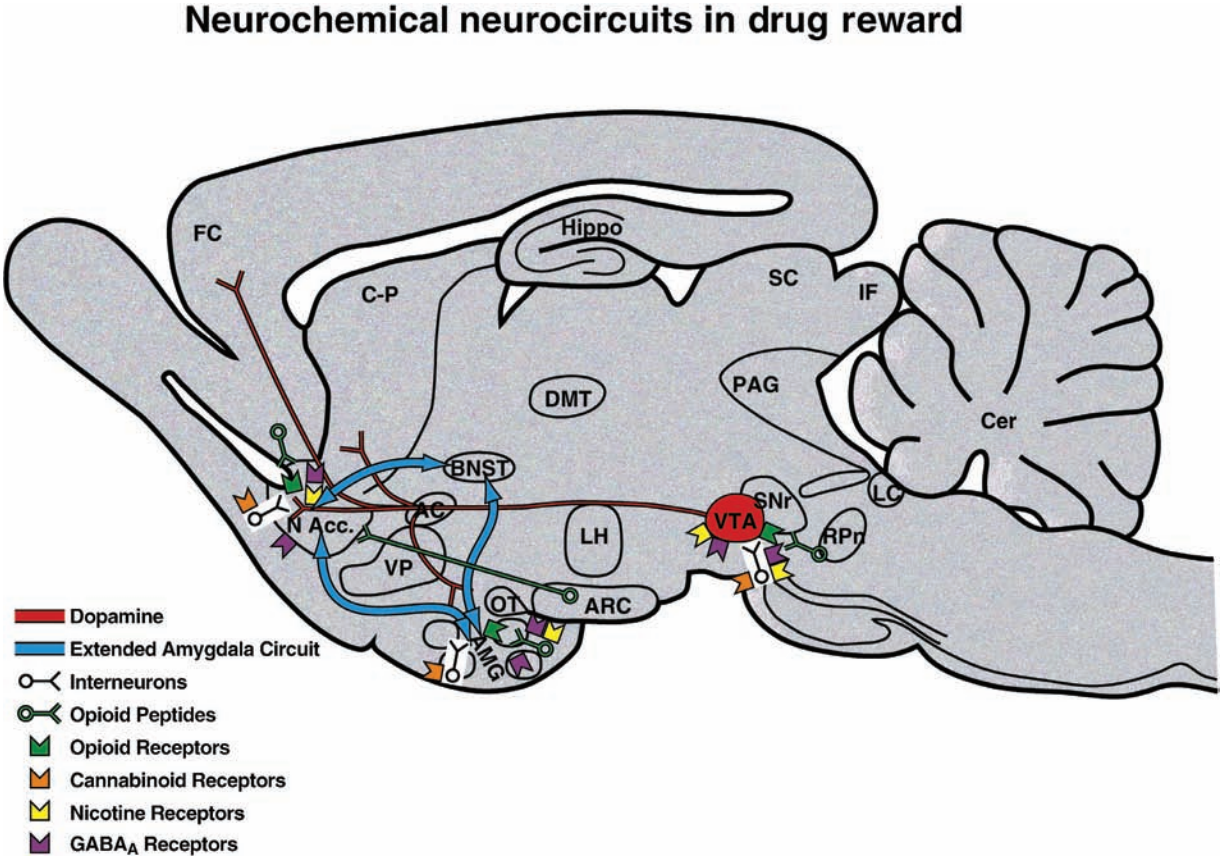



**Figure 22–7** *Sagittal section through a representative rodent brain illustrating the pathways and receptor systems implicated in the acute reinforcing actions of drugs of abuse. Cocaine and amphetamines activate the release of dopamine in the nucleus accumbens and amygdala via direct actions on dopamine terminals. Opioids activate opioid receptors in the ventral tegmental area, nucleus accumbens, and amygdala via direct actions on interneurons. Opioids facilitate the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens, but also are hypothesized to activate the elements independent of the dopamine system. Alcohol activates γ-aminobutyric acid-A ($GABA_A$) receptors in the ventral tegmental area, nucleus accumbens, and amygdala via either direct actions at the $GABA_A$ receptor or through indirect release of GABA. Alcohol is hypothesized to facilitate the release of opioid peptides in the ventral tegmental area, nucleus accumbens, and central nucleus of the amygdala. Alcohol facilitates the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens. Nicotine activates nicotinic acetylcholine receptors in the ventral tegmental area, nucleus accumbens, and amygdala, either directly or indirectly, via actions on interneurons. Nicotine also may activate opioid peptide release in the nucleus accumbens or amygdala independent of the dopamine system. Cannabinoids activate cannabinoid $CB_1$ receptors in the ventral tegmental area, nucleus accumbens, and amygdala via direct actions on interneurons. Cannabinoids facilitate the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens, but also are hypothesized to activate the elements independent of the dopamine system. Endogenous cannabinoids may interact with postsynaptic elements in the nucleus accumbens involving dopamine and/or opioid peptide systems. The blue arrows represent the interactions within the extended amygdala system hypothesized to have a key role in psychostimulant reinforcement. AC: anterior commissure; AMG: amygdala; ARC: arcuate nucleus; BNST: bed nucleus of the stria terminalis; Cer: cerebellum; C-P: caudate-putamen; DMT: dorsomedial thalamus; FC: frontal cortex; Hippo: hippocampus; IF: inferior colliculus; LC: locus coeruleus; LH; lateral hypothalamus; N Acc.: nucleus accumbens; OT: olfactory tract; PAG: periaqueductal gray; RPn: reticular pontine nucleus; SC: superior colliculus; SNr: substantia nigra pars reticulata; VP: ventral pallidum; VTA: ventral tegmental area. (Taken with permission from Koob 2005.)*

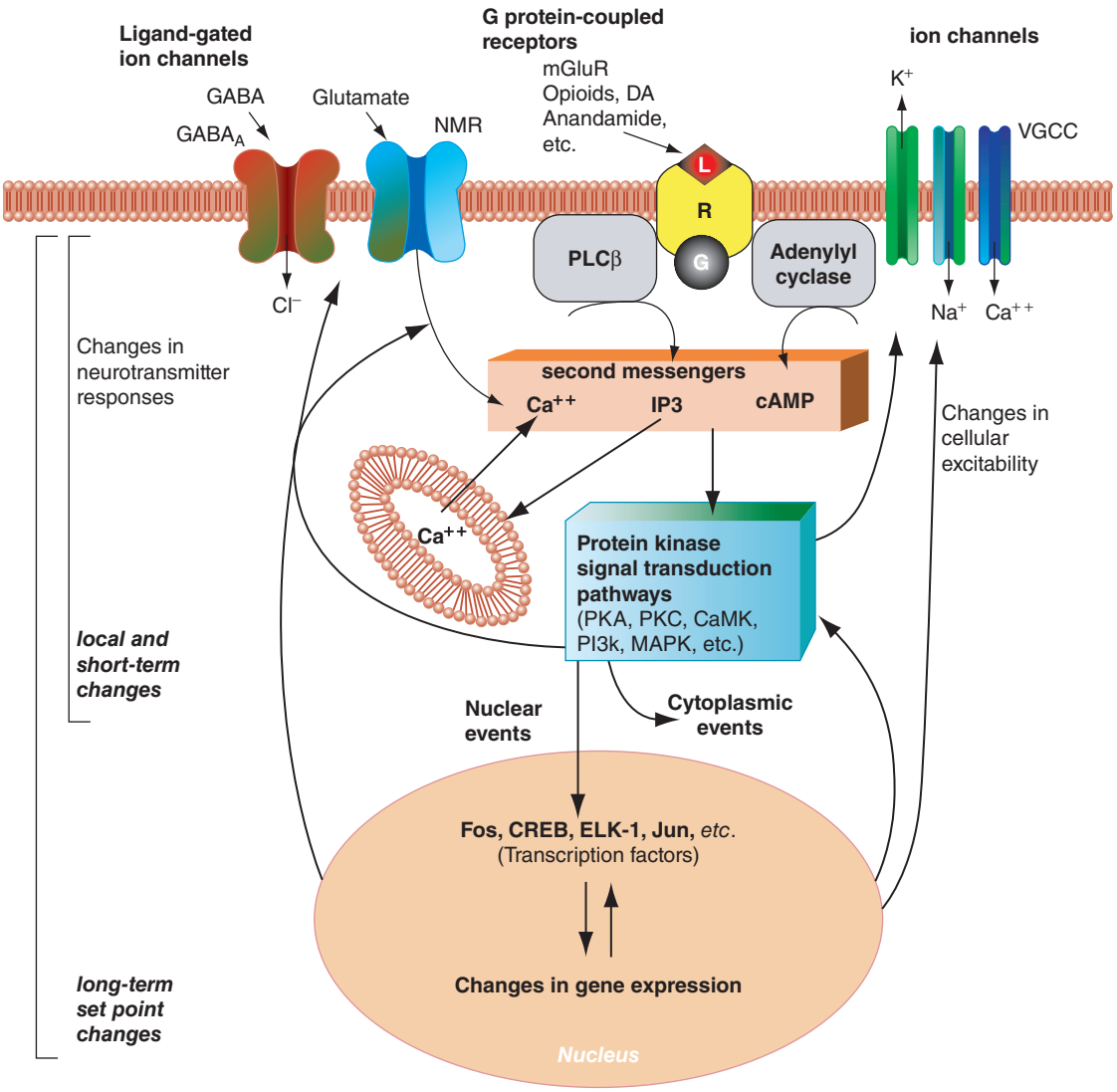



**Figure 22–10** *Molecular mechanisms of neuroadaptation.* Cocaine *and* amphetamines, *as indirect sympathomimetics, stimulate the release of dopamine which acts at G protein-coupled receptors, specifically $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$. These receptors modulate the levels of second-messengers like cyclic adenosine monophosphate (cAMP) and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Such protein kinases affect the functions of proteins located in the cytoplasm, plasma membrane, and nucleus. Among membrane proteins affected are ligand-gated and voltage-gated ion channels (VGCC). $G_i$ and $G_o$ proteins also can regulate potassium and calcium channels directly through their βγ subunits. Protein kinase transduction pathways also affect the activities of transcription factors. Some of these factors, like cAMP response element binding protein (CREB), are regulated posttranslationally by phosphorylation; others, like Fos, are regulated transcriptionally; still others, like Jun, are regulated both posttranslationally and/or transcriptionally. While membrane and cytoplasmic changes may be only local (e.g., dendritic domains or synaptic boutons), changes in the activity of transcription factors may result in long-term functional changes. These may include changes in gene expression of proteins involved in signal transduction and/or neurotransmission, resulting in altered neuronal responses. For example, chronic exposure to psychostimulants has been reported to increase the levels of protein kinase A (PKA) and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Chronic exposure to psychostimulants also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the nucleus accumbens by chronic cocaine treatment. Chronic cocaine induces a transition from Fos induction to the induction of the much longer lasting Fos-related antigens (Fras) such as ΔFosB.* Opioids, *by acting on neurotransmitter systems, affect the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Examples of ligand-gated ion channels such as the γ-aminobutyric acid-A ($GABA_A$) and glutamate* N*-methyl-D-aspartate (NMDA) receptor (NMR) and G protein-coupled receptors such as opioid, dopamine (DA), or the cannabinoid $CB_1$ receptors, among others, are shown. These receptors modulate the levels of second messengers like cAMP and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Chronic exposure to opioids has been reported to increase levels of protein kinase A and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Chronic exposure to opioids also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the nucleus accumbens and increased in the locus coeruleus by chronic morphine treatment, while chronic opioid exposure activates FRAs such as ΔFosB.* Alcohol, *by acting on neurotransmitter systems, affects the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Examples of ligand-gated ion channels such as the $GABA_A$ and the NMDA receptor and G protein-coupled receptors such as opioid, dopamine, or the cannabinoid $CB_1$ receptors, among others, are shown. The latter also is activated by endogenous cannabinoids such as anandamide. These receptors modulate the levels of second messengers such as cAMP and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Such protein kinases affect the functions of proteins located in the*

*(Continued)*

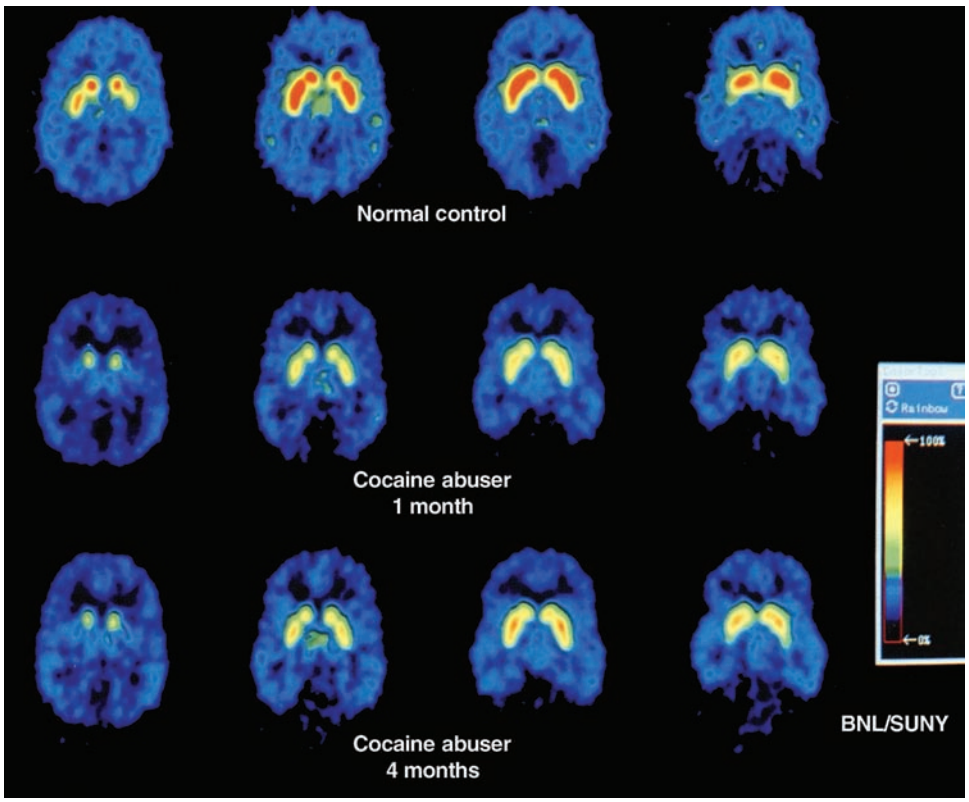



**Figure 22–8** *[$^{18}$F]N-methylspiroperidol images in a normal control and in a cocaine abuser tested 1 month and 4 months after last cocaine use. The images correspond to the four sequential planes where the basal ganglia are located. The color scale has been normalized to the injected dose. Notice the lower uptake of the tracer in the cocaine abuser compared to the normal control. Notice also the persistence of the decreased uptake even after 4 months of cocaine discontinuation. BNL: Brookhaven National Laboratory; SUNY: State University of New York. (Taken with permission from John Wiley and Sons Inc. 1993.)*

**Figure 22–10** *(Continued from facing page)*

*cytoplasm, plasma membrane, and nucleus. Among membrane proteins affected are ligand-gated and VGCCs. Alcohol, for instance, has been proposed to affect the $GABA_A$ response via protein kinase C (PKC) phosphorylation. $G_i$ and $G_o$ proteins also can regulate potassium and calcium channels directly through their βγ subunits. Chronic exposure to alcohol has been reported to increase levels of protein kinase A and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Moreover, chronic ethanol induces differential changes in subunit composition in the $GABA_A$ and glutamate inotropic receptors and increases the expression of VGCCs. Chronic exposure to alcohol also alters the expression of transcription factors themselves. CREB expression, for instance, is increased in the nucleus accumbens and decreased in the amygdala by chronic alcohol treatment. Chronic alcohol induces a transition from Fos induction to the induction of the longer lasting FRAs.* Nicotine *acts directly on ligand-gated ion channels. These receptors modulate the levels of $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Chronic exposure to nicotine has been reported to increase the levels of protein kinase A in the nucleus accumbens. Chronic exposure to nicotine also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the amygdala and prefrontal cortex and increased in the nucleus accumbens and ventral tegmental area.* $\Delta^9$-tetrahydrocannabinol, *by acting on neurotransmitter systems, affects the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Cannabinoids act on a G protein-coupled receptor, the cannabinoid $CB_1$ receptor. The $CB_1$ receptor also is activated by endogenous cannabinoids such as anandamide. This receptor modulates (inhibits) the levels of second messengers like cAMP and $Ca^{2+}$, which in turn regulates the activity of protein kinase transducers. Chronic exposure to $\Delta^9$-tetrahydrocannabinol also alters the expression of transcription factors themselves. PLCB, phospholipase CB; IP3, inositol triphosphate; CaMK, calmodulin-dependent protein kinase; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; ELK-1, endothelin-l-specific-like gene-l transcription factor. (Modified with permission from Koob et al. 1998.)*

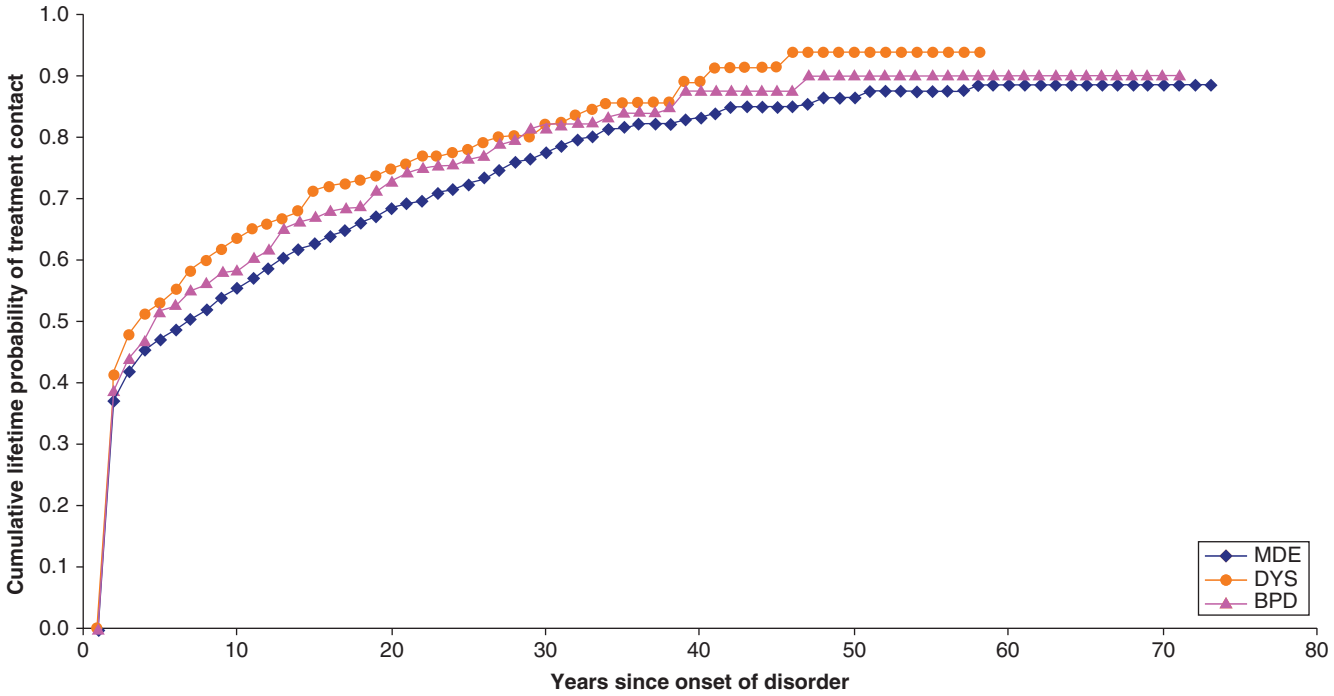



**Figure 25–4** *Cumulative lifetime probability of treatment contact for mood disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 0.7$, $p = .718$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: major depressive disorder (MDE), 88.1%; dysthymia (DYS), 94.2%; bipolar disorder (BPD) I and II, 90.2%.*

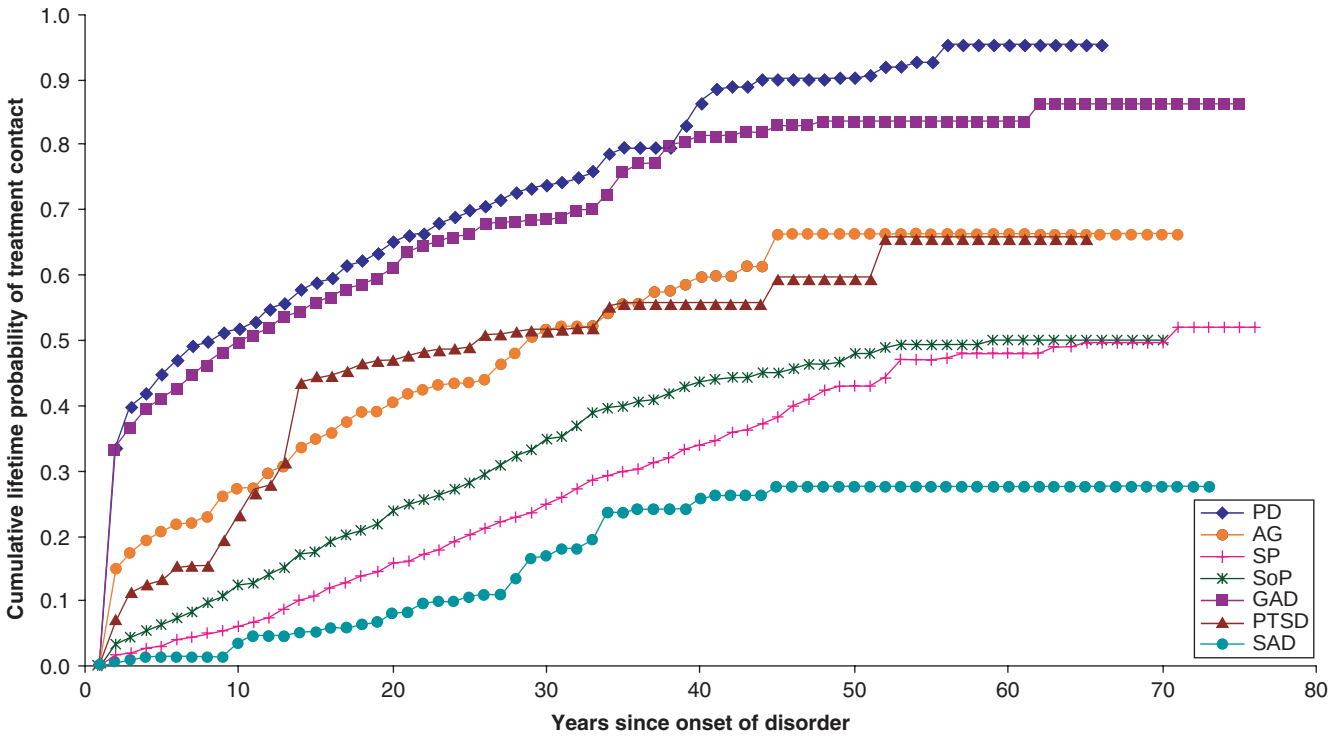



**Figure 25–5** *Cumulative lifetime probability of treatment contact for anxiety disorders from year of onset*[1]. *Significance of differences among curves: $x^2_4 = 242.4$, $p < .001$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: panic disorder (PD), 95.3%; agoraphobia without panic (AG), 66.5%; specific phobia (SP), 50.1%; social phobia (SoP), 74.0%; generalized anxiety disorder (GAD), 86.1%; posttraumatic stress disorder (PTSD), 65.3%; separation anxiety disorder (SAD), 27.3%.*

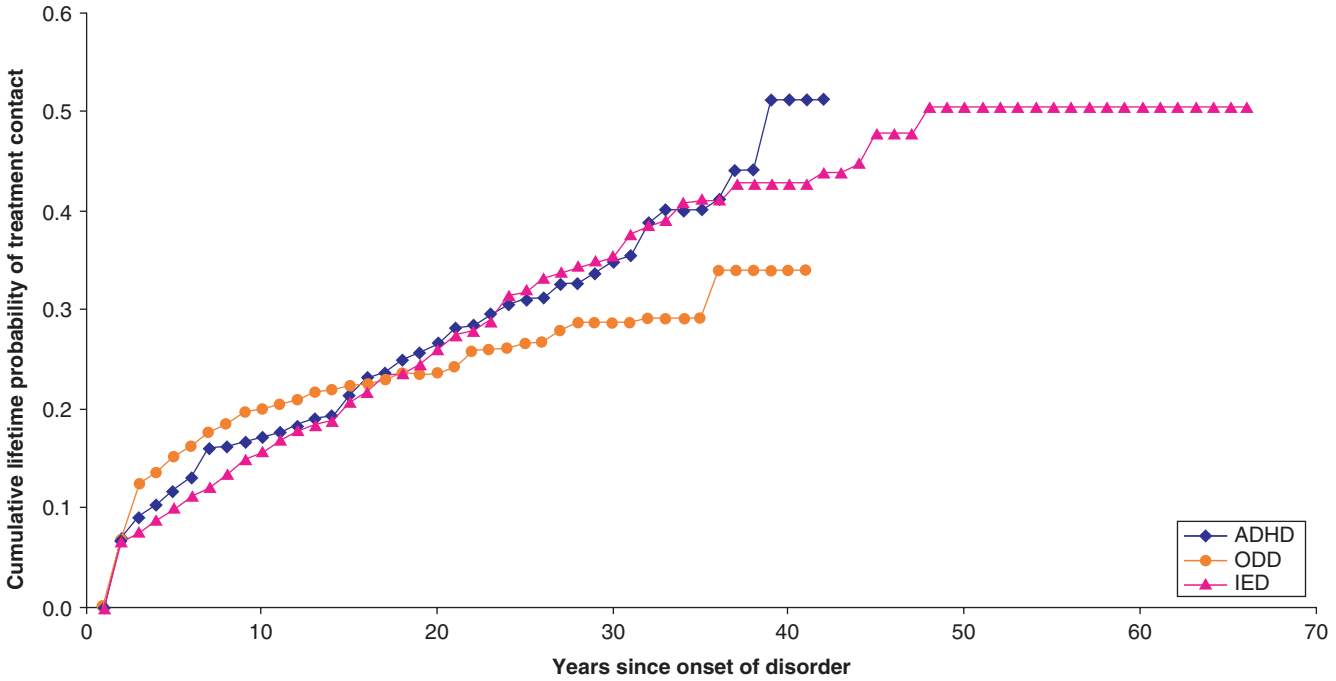



**Figure 25–6** *Cumulative lifetime probability of treatment contact for impulse-control disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 6.0$, $p = .050$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: attention-deficit/hyperactivity disorder (ADHD), 51.8%; oppositional defiant disorder (ODD), 33.9%; intermittent explosive disorder (IED), 50.4%.*

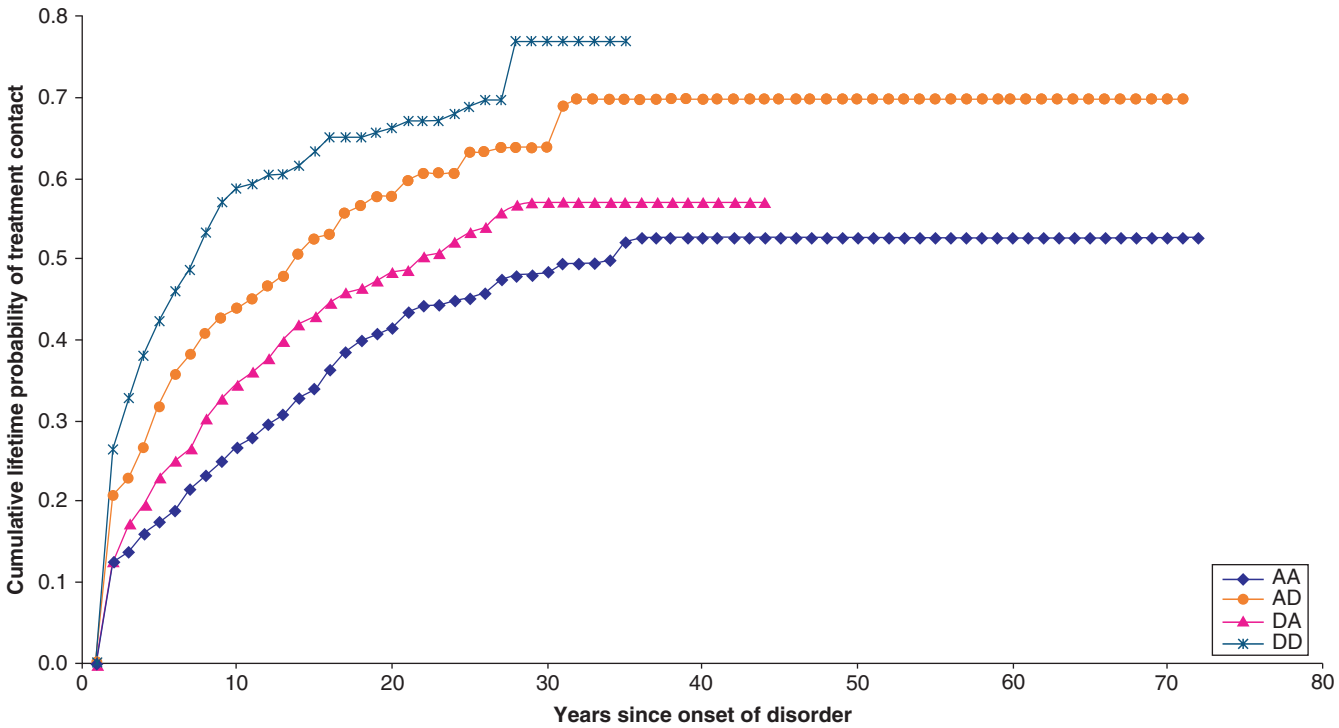



**Figure 25–7** *Cumulative lifetime probability of treatment contact for substance disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 44.8$, $p < .001$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: alcohol abuse (AA), 52.7%; alcohol dependence (AD), 69.8%; drug abuse (DA), 57.0%; drug dependence (DD), 76.9%.*

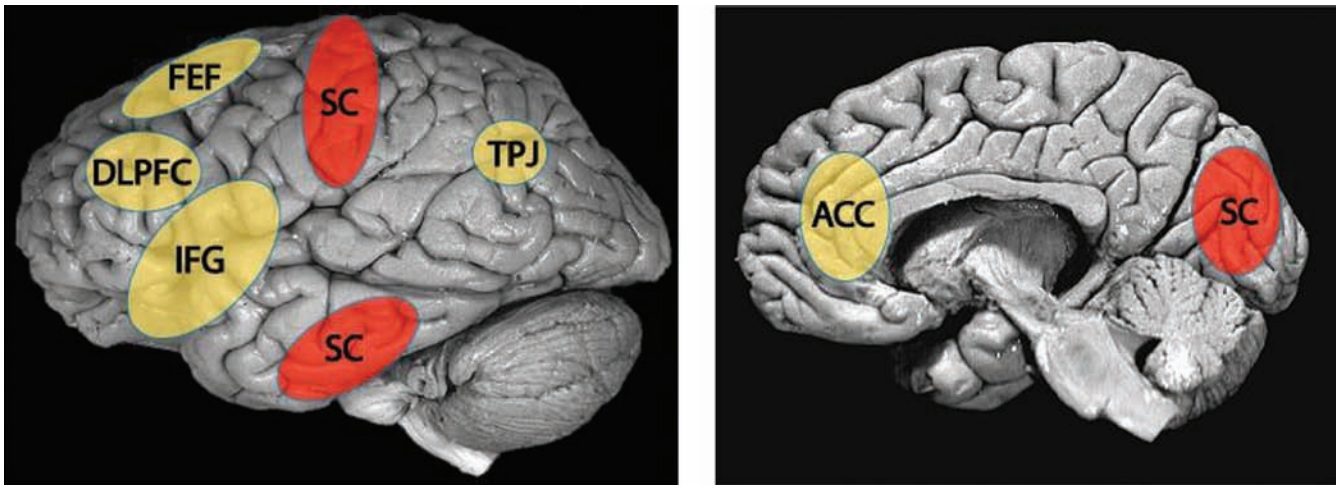



**Figure 26–1** *Some of the brain regions and cognitive processes involved in attentional deployment and executive function. Regions in red are targeted by regions in yellow, according to the theory of Miller and Cohen (2001), as well as others. Note that regions that are not shown would not be visible from the surface because they are located subcortically. FEF, frontal eye fields; TPJ, temporal parietal junction; IFG, inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; SC, sensory cortices.*

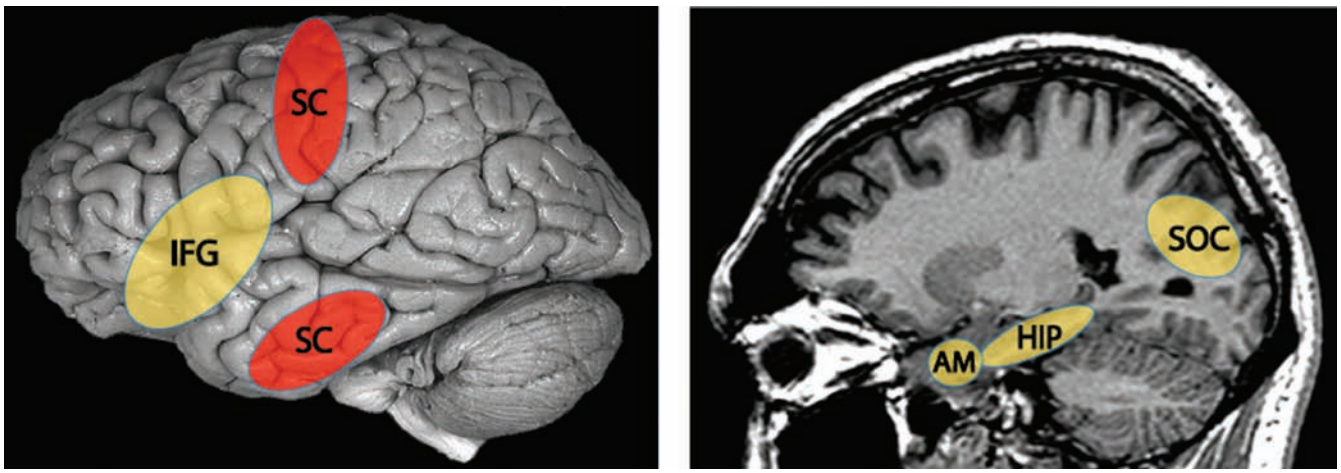



**Figure 26–2** *Some of the brain regions and cognitive processes involved in the encoding, binding, and retrieval of explicit and implicit memory. IFG, inferior frontal gyrus; HIP, hippocampus; AM, amygdala; SOC, superior occipital cortex.*

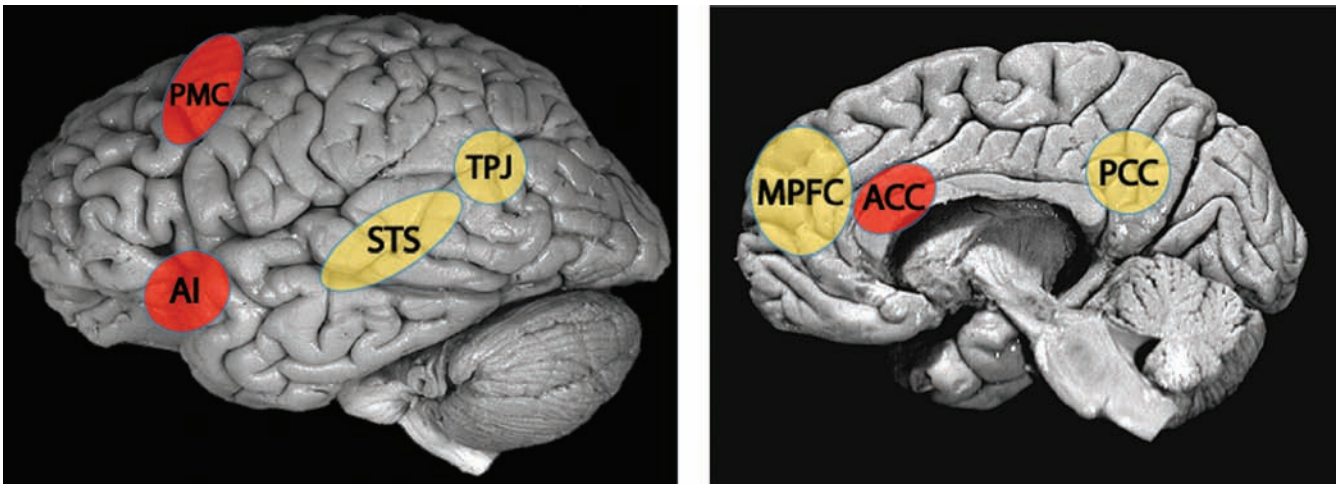



**Figure 26–3** *Some of the brain regions and cognitive processes involved in uniquely social cognition. Regions in red are predominantly involved in shared representations, and regions in yellow are predominantly involved in cognitive attribution and perspective taking, though this is by no means a definitive division of labor. Note that the anterior insula, while presented on the surface of the cortex, is underneath the cortex. MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; TPJ, temporoparietal junction; STS, superior temporal sulcus; ACC, anterior cingulate cortex; AI, anterior insula; PMC, premotor cortex.*

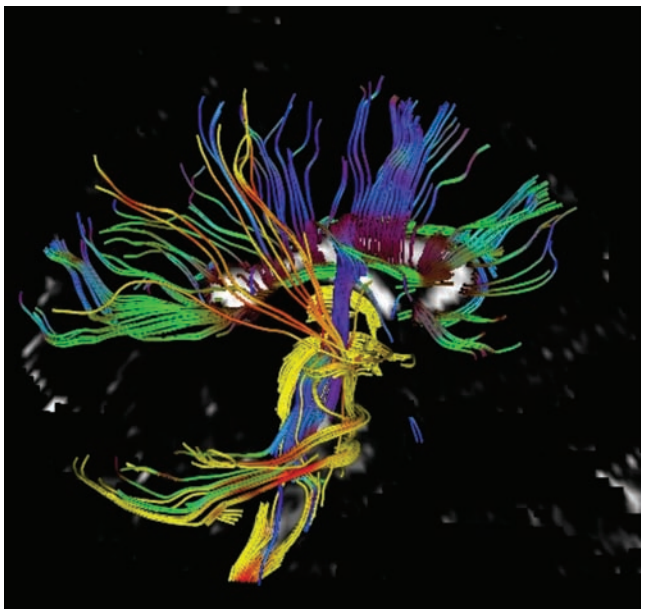


**Figure 33–3** *Diffusion tensor tractography image demonstrating major white matter tracts in the human brain. © Wallace-Kettering Neuroscience Institute*

Plate IX

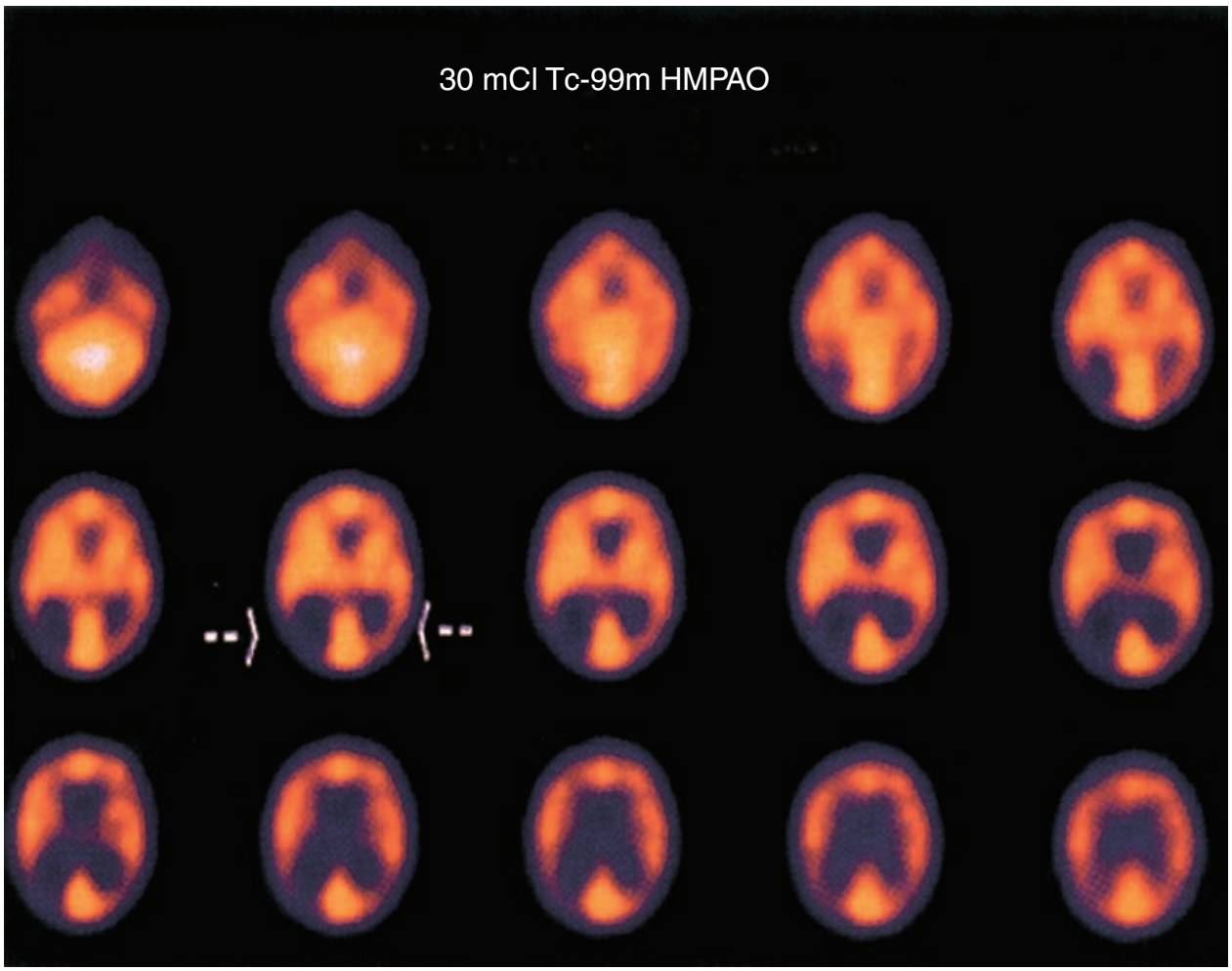



**Figure 33–6** *Illustration of the methodology for PET activation studies using blood flow tracers such as $^{15}O$-carbon dioxide or $^{15}O$-water. A series of scans are acquired in activated and control states and are subtracted to produce a different image. A statistical test is applied to the data to determine which changes in the difference image are statistically significant. This example shows the robust response to a hemifield stimulation of the visual system with a reversing checkerboard pattern using $^{15}O$-water as the tracer. The activated area in the visual cortex can clearly be seen, even prior to substraction. © Academic Press*

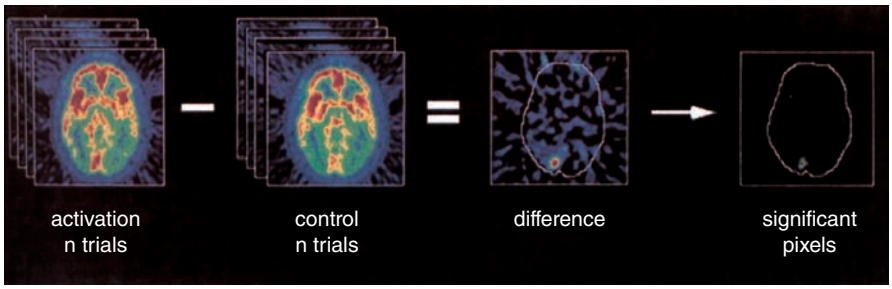



**Figure 33–7** *Serial axial HMPAO SPECT images from an individual with Binswanger's disease. HMPAO SPECT measures cerebral blood flow which is tightly coupled to neuronal activity. Note that there is generalized decrease in cortical activity compared with cerebellum. Additionally, small marked focal defects are seen in the cortex (arrowheads). © Mosby*

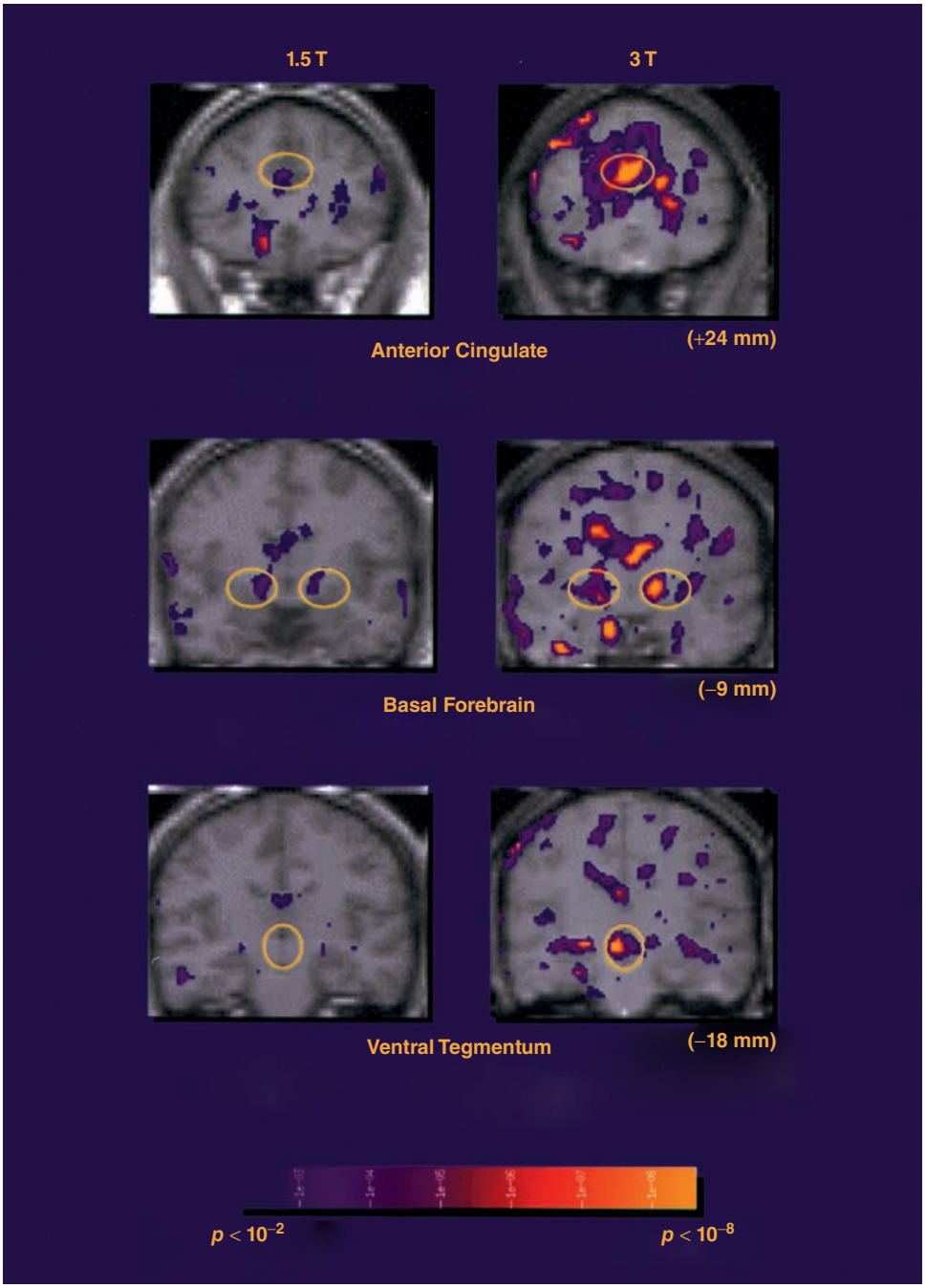



**Figure 33–8** *fMRI activation study where subjects were given either intravenous cocaine or saline at different times. When the saline condition is subtracted from the cocaine condition (see Figure 33–6 for activation study overview), statistically significant activation associated with administration of cocaine was demonstrated in regions associated with the reward circuitry of the brain. Also note that when this study is conducted using a 3 Tesla (unit used to quantitate the strength of a magnetic field) MR scanner, the findings are much more robust than when using a less powerful 1.5 Tesla MR scanner.*

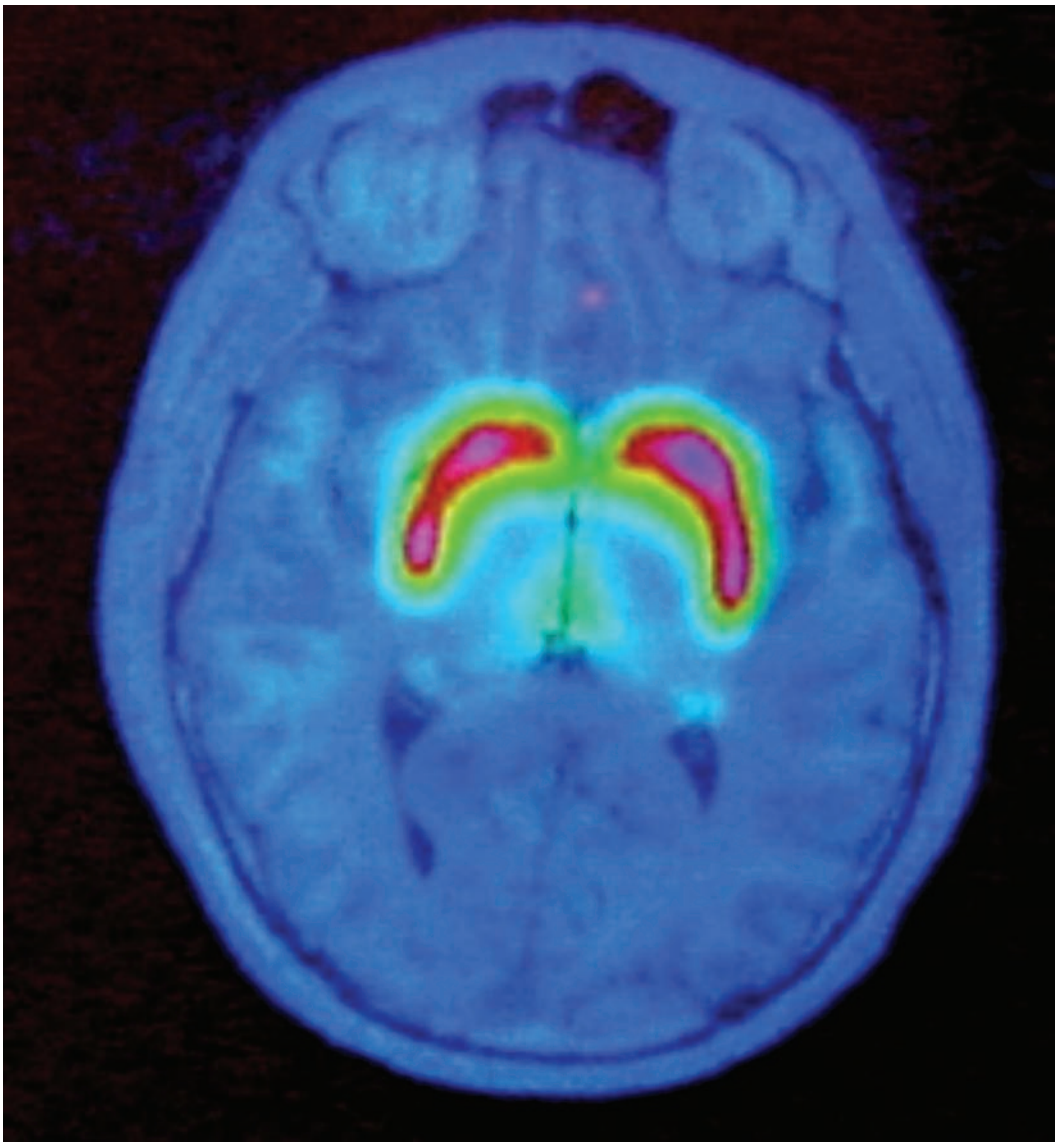


**Figure 33–9** *Molecular imaging. $^{18}$F-Fallypride is a dopamine receptor radioligand with high affinity for $D_2$ and $D_3$ dopamine receptors. The highest concentration of binding is seen in the dorsal striatum (caudate and putamen), followed by the thalamus and temporal and prefrontal cortices.*

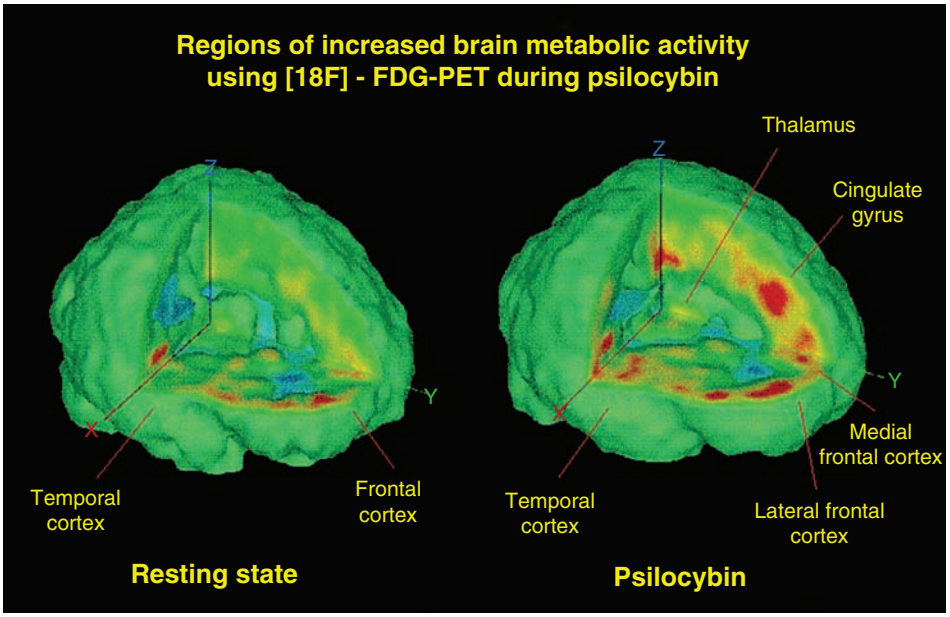
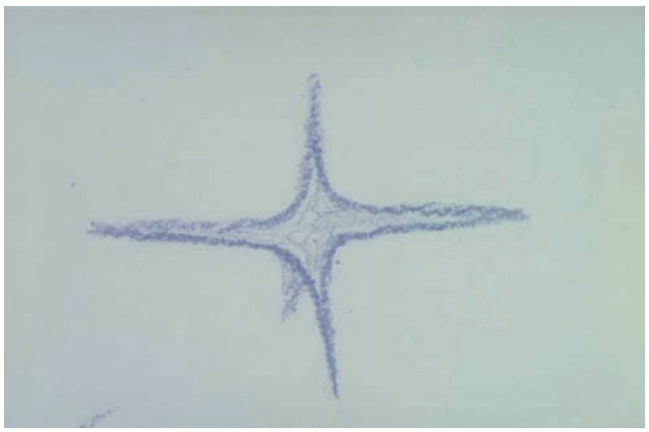
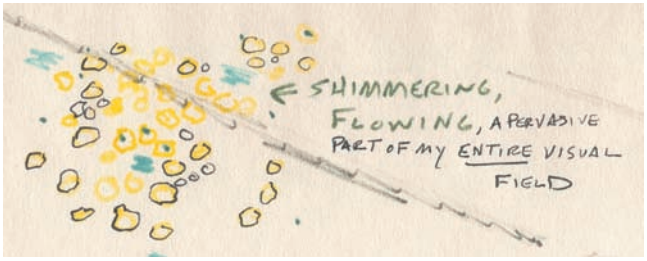



**Figure 60–5** *$^{18}$F-deoxyglucose positron emission tomography of health volunteers before and after the administration of psilocybin. In addition to a global increase in brain metabolic activity, note the increase in activation in the anterior cingulated and lateral and medial frontal cortex, and the medial temporal cortex. Metabolic activation correlated with the intensity of subjective symptoms. (Source: Adapted with permission from Hermle L, Spitzer M, and Gouzoulis E (1994) Arylalkanamine-induced 1 effects in normal volunteers: On the significance of research in hallucinogenic agents for psychiatry. In Fifty Years of LSD: Current Status and Perspectives of Hallucinogens, Pletscher A and Ladewig D (eds). Parthenon, New York, USA. Also, Vollenweider FX, Leenders KL, Scharfetter C, et al. (1997) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16, 257–272.)*



A



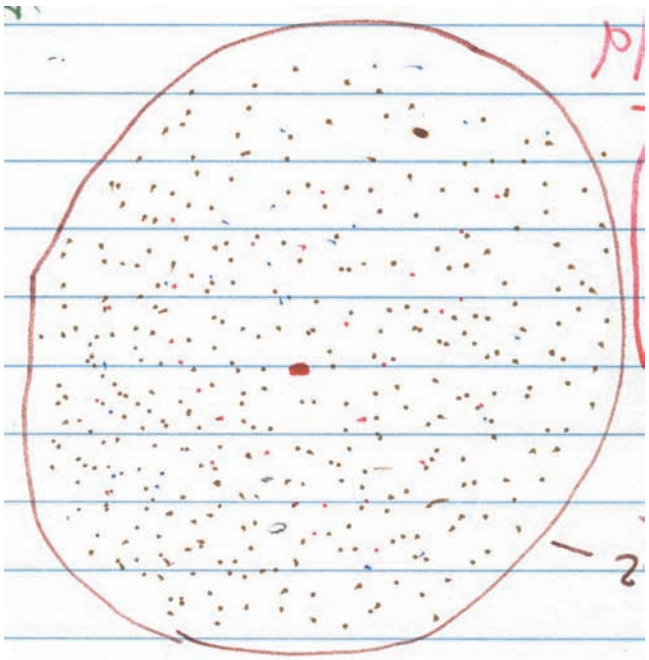

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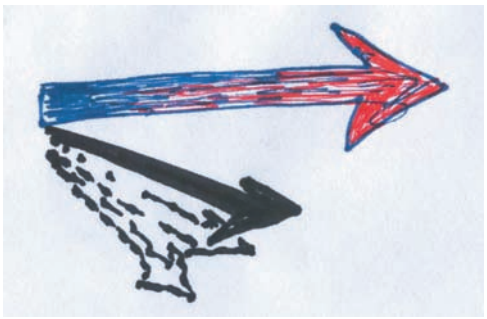
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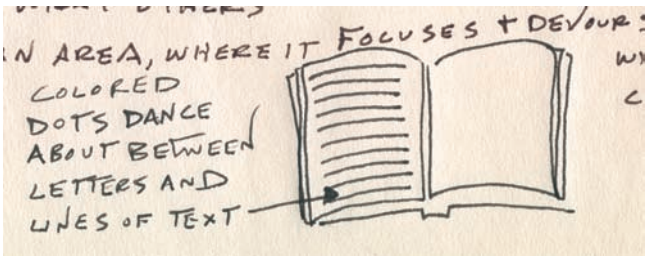



**Figure 60–6 a–f** *Drawings of hallucinations by patients with hallucinogen persisting perception disorder. These drawings of visual symptoms were made by actively symptomatic patients in a drug-free condition. Such imagery occurred to the patients on a daily basis. No patient was psychotic. Each knew that the visual disturbances were "not real." Image (A) the perception of flashes of light; (B) seeing countless dots moving in the air; (C) geometric shapes moving in swirling pattern; (D) pareidolia, in which the patient saw faces in the veneer of wood; (E) the trailing of afterimages as an arrow moved through the patient's visual field; (F) difficulty reading caused by moving afterimages of letters appearing on the paper suggesting an acquired dyslexia.*

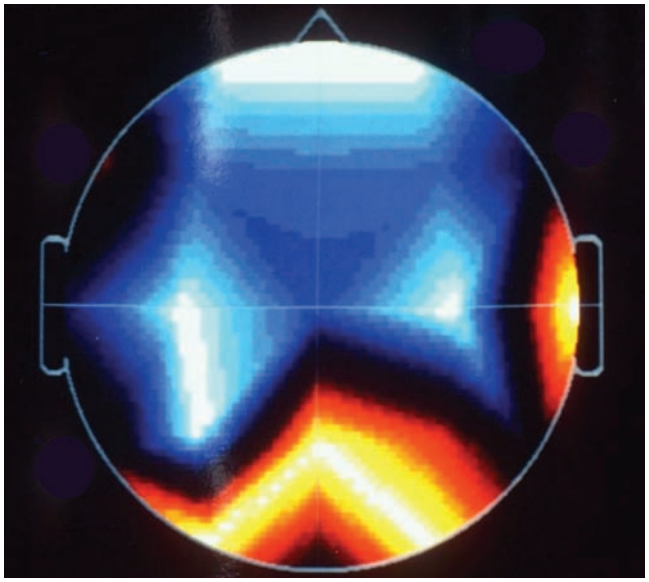


**Figure 60–8** *Increased EEG coherence in HPPD subjects between occipital electrodes. Thirty-eight actively symptomatic HPPD subjects and 33 controls were tested for electrical coherence, a measure of cortical coupling, between adjacent electrode pairs in the eyes open and closed states. The figure is a T-statistics Significance Probability Map of group differences in t-scores derived from mean coherence values at each pixel. Coherence is measured from the OZ electrode at 6 Hz. The view is top down, with the nose at the top. Increased coherence, denoted by a color gray scale, is increased occipitally denoted in white, and in the right temporal electrodes, in the HPPD sample with eyes closed, when visual hallucinations are reported to be more vivid. A global reduction in coherence is seen in HPPD between occipital and more distant electrodes, when compared to controls. (See the original publication for actual color values.) (Source: Reprinted with permission from Abraham HD and Duffy FH (2001) EEG coherence in post-LSD visual hallucinations. Journal of Psychiatric Research 107, 151–163 Copyright Elsevier (2001).)*

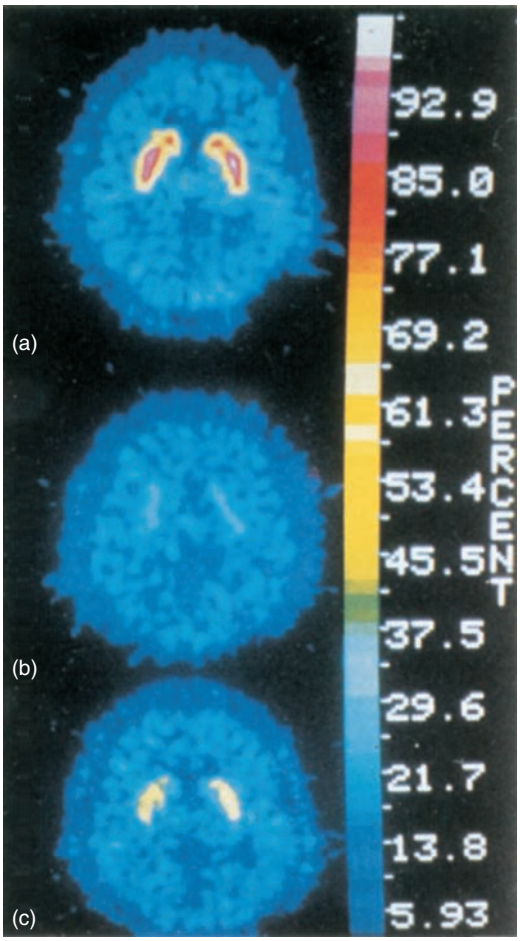



**Figure 65–7** *[$^{11}$C]Raclopride labeling of $D_2$ receptors in the striatum. (a) Medication-free healthy control subject. (b) Patient treated with 4 mg of haloperidol. (c) Patient treated with 500 mg of clozapine. (Source: Farde et al. (1988) Central $D_2$-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatr 45, 71–76. Copyright 1988 American Medical Association.)*

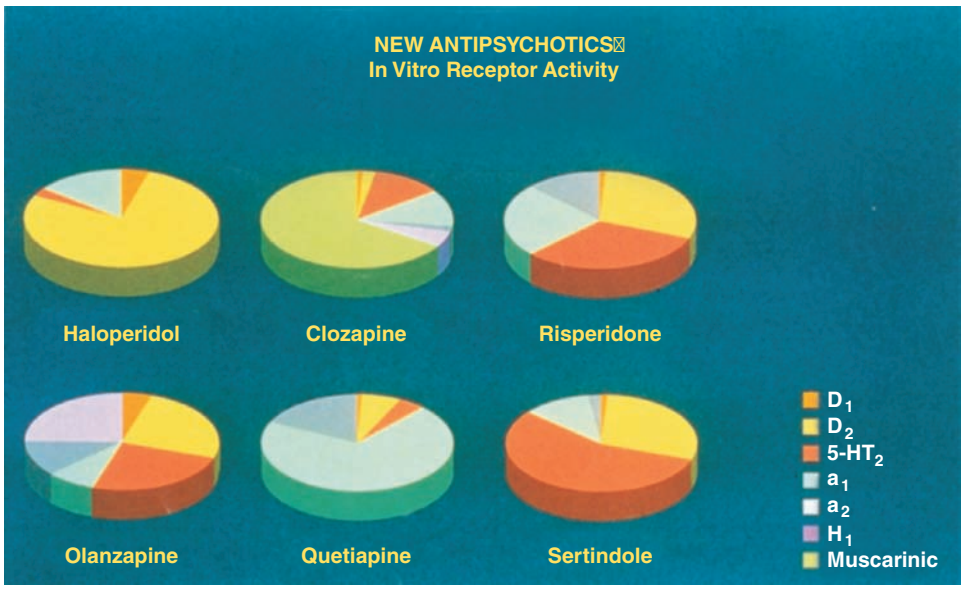



**Figure 65–10** In vitro *receptor affinity of new antipsychotic agents.*

Plate XVI

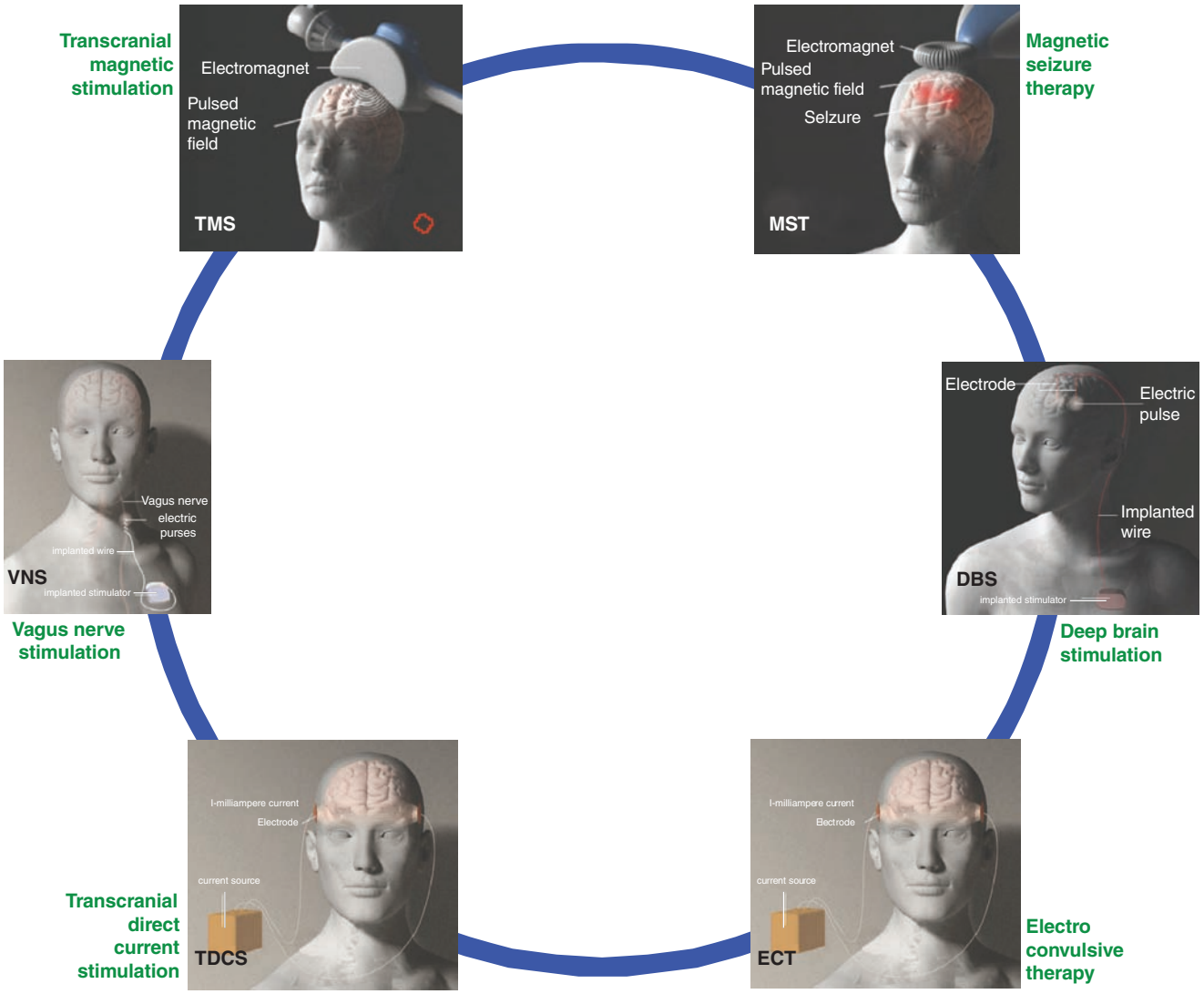



**Figure 109–1** *Brain stimulation tools.*

Plate XVII

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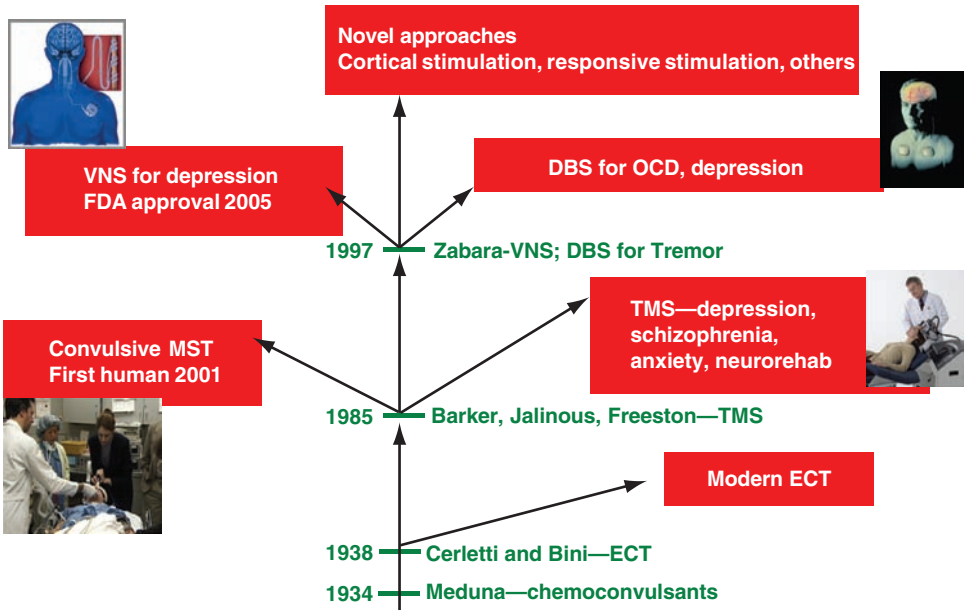



**Figure 109–2** *Evolution of brain stimulation in psychiatry.*

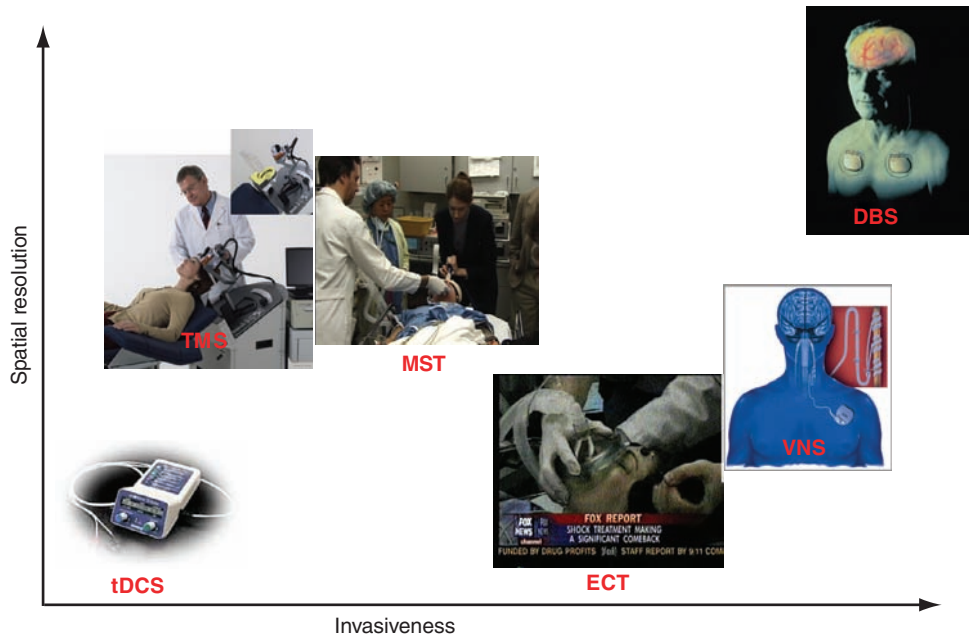



**Figure 109–4** *Brain stimulation landscape.*

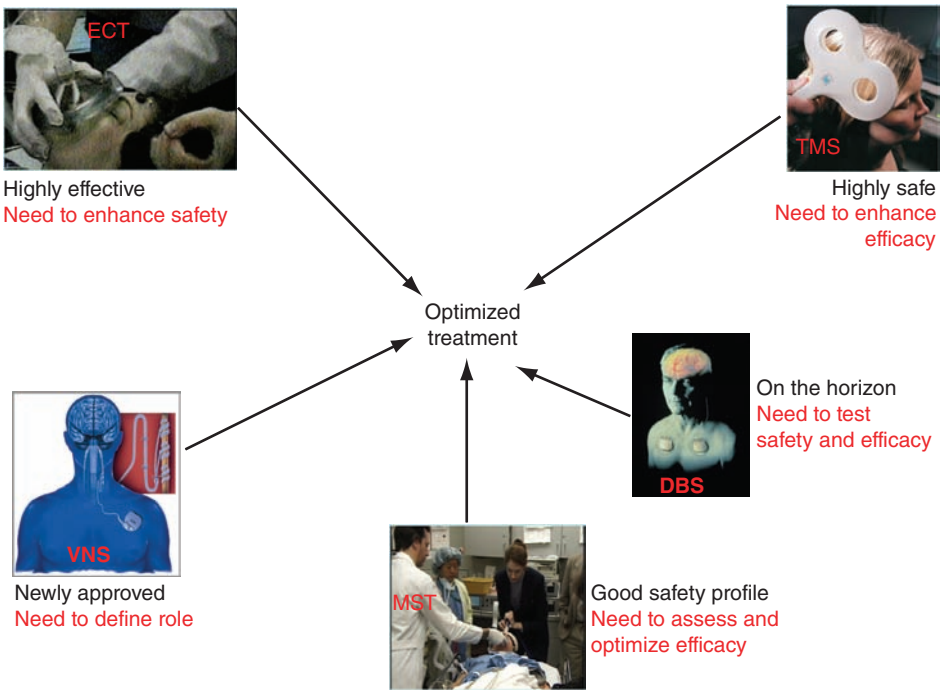
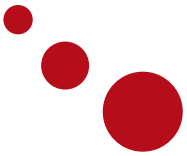



**Figure 109–11** *State of the evidence.*



SECTION I

Robert J. Ursano, Section Editor

# *Approaches to the Patient*

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CHAPTER 1

# Listening to the Patient

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## Listening: The Key Skill in Psychiatry

It was Freud who raised the technique of psychiatric examination—listening—to an expert level unexplored in earlier eras. Binswanger (1963) said of the period prior to Freud: "psychiatric 'auscultation' and 'percussion' was performed as if through the patient's shirt with so much of his essence remaining covered or muffled that layers of meaning remained unpeeled away or unexamined."

This metaphor and parallel to the cardiac examination is worth considering as we ask if listening will remain a central part of psychiatric examination. The explosion of biomedical knowledge has radically altered our evolving view and practice of the doctor–patient relationship. Physicians of an earlier generation were taught that the diagnosis is made at the bedside; that is, the history and physical examination are paramount. Laboratory and imaging examinations were seen as confirmatory exercises. As our technologies have blossomed, the bedside and/or consultation room examinations have evolved into the method whereby the physician determines what tests to run, and the tests are often viewed as making the diagnosis. A cardiologist colleague expresses the opinion that, given the growing availability of noninvasive tests—echocardiograms, for example—he is not sure that this is a bad thing (Hillis 2001, personal communication). This alteration of the core doctor–patient relationship has been exacerbated by the advent of the electronic medical record. It is not unusual for the patient to carry on a conversation with his/her physician as the doctor scans a computer screen.

So can one imagine a time in the not-too-distant future when the psychiatrist's task will be to identify that the patient is psychotic and then order some benign brain imaging study that will identify the patient's exact disorder?

Perhaps so, but will that obviate the need for the psychiatrist's special kind of listening? Indeed, there are those who claim that psychiatrists should no longer be considered experts in the doctor–patient relationship (expertise derived from unique training in listening skills) but experts in the brain (Nestler 1999, personal communication). On the other hand, the psychiatrist will always be charged with finding ways to relate effectively to those who cannot relate to anyone else. The treatment of individuals whose illnesses are expressed through disturbances of thinking, feeling, perceiving, and behaving will always demand special expertise in establishing a therapeutic relationship—that is dependent on special expertise in listening. As if to underline this point, teaching listening continues to be prominently emphasized in many psychiatry training programs irrespective of their emphases (Nuzzarello and Birndorf 2004). And the need to be listened to has led to the development of websites offering listening and training in the art (Yen 2006, Parekh 2006). Further, the field continues to turn out books on psychiatric interviewing and the art of listening regularly (Poole and Higgo 2006, Mackinnon et al. 2006).

**Clinical Vignette 1**

A 28-year-old white married man suffering from paranoid schizophrenia and obsessive–compulsive disorder did extremely well in the hospital, where his medication had been changed to clozapine with good effects. But he rapidly deteriorated on his return home. It was clear that the ward milieu had been a crucial part of his improvement, so partial hospitalization was recommended. The patient demurred, saying that he did not want to be a "burden." The psychiatrist explored this with the patient and his wife. Beyond the obvious "burdens" of cost and travel arrangements, the psychiatrist detected the patient's striving to be autonomously responsible for handling his illness. By conveying a deep respect for that wish, and then educating the already insightful patient about the realities of "bearing schizophrenia," the psychiatrist was able to help the patient accept the needed level of care.

Traditionally, this kind of listening has been called "listening with the third ear" (Reik 1954). Other efforts to label this difficult-to-describe process have developed other terms: the interpretive stance, interpersonal sensitivity, the narrative perspective (McHugh and Slavney 1986). All psychiatrists, regardless of theoretical stance, must learn this skill and struggle with how it is to be defined and taught. Biological or phenomenological psychiatrists listen for subtle expressions of symptomatology; cognitive–behavioral psychiatrists listen for distortions, irrational assumptions,

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or global inferences; psychodynamic psychiatrists listen for hints at unconscious conflicts; behaviorists listen for covert patterns of anxiety and stimulus associations; family systems psychiatrists listen for hidden family myths and structures. Another way to conceptualize this process, drawn from the empirical literature (Truax 1963), involves nonspecific factors crucial to outcome in all forms of psychiatric treatment: empathy, noncontingent positive regard, and therapist authenticity.

However one labels and defines the process of therapeutic listening, it requires sensitivity to the storyteller, integrating a patient orientation with a disease focus. The listener's intent is to uncover what is wrong, to put a label on it. Simultaneously, the listener is on a journey to discover who the patient is, employing tools of asking, looking, testing, and clarifying. The patient is invited to collaborate as an active informer. Listening work takes time, concentration, imagination, a sense of humor, and an attitude that places the patient as hero of his or her own life story. Key listening skills are listed in Table 1–1.

**Table 1–1 Key Listening Skills**

| | |
|---|---|
| Hearing | Connotative meanings of words |
| | Idiosyncratic uses of language |
| | Figures of speech that tell a deeper story |
| | Voice tones and modulation (e.g., hard edge, voice cracking) |
| | Stream of associations |
| Seeing | Posture |
| | Gestures |
| | Facial expressions (e.g., eyes watering, jaw clenched) |
| | Other outward expressions of emotion |
| Comparing | Noting what is omitted |
| | Dissonances between modes of expression |
| Intuiting | Attending to one's own internal reactions |
| Reflecting | Thinking it all through outside the immediate pressure to respond during the interview |

The enduring art of psychiatry involves guiding the depressed patient, for example, to tell his or her story of loss in addition to having him or her name, describe, and quantify symptoms of depression. The listener, in hearing the story, experiences the world and the patient from the patient's point of view, helping carry the burden of loss, lightening and transforming the load. In hearing the sufferer, the depression itself is lifted and relieved. Listening is healing as well as diagnostic. If done well, the listener becomes a better disease diagnostician. The best listeners hear both the patient and the disease clearly, and regard every encounter as potentially therapeutic.

## The Primary Tools: Words, Analogies, Metaphors, Similes, and Symbols

To listen and understand requires that the language used between speaker and hearer be shared—that meanings of words and phrases are commonly held. Common language is the predominant factor in the social organization of humanity (Chomsky 1972) and is probably the single most important key to the establishment of an active listener/engaged storyteller dyad that the helping alliance (Johansson and Eklund 2006) represents. The Sapir–Whorf hypothesis suggests that what we are able to think is limited/determined by the language in which we are working (Carroll and Whorf 1956, Sapir 2000). More recent evolutionary thinking about language suggests that it is a crucial mechanism for maintaining social organization (Dunbar 2004). That is, what people are disposed to speak of in normal ordinary speech are their relationships and their implications.

**Clinical Vignette 2**

A psychiatric consultant was asked to see a 48-year-old man on a coronary care unit for chest pain deemed "functional" by the cardiologist who had asked the patient if his chest pain was "crushing." The patient said no. A variety of other routine tests were also negative. The psychiatrist asked the patient to describe his pain. He said, "It's like a truck sitting on my chest, squeezing it down." The psychiatrist promptly recommended additional tests that confirmed the diagnosis of myocardial infarction. The cardiologist may have been tempted to label the patient a "bad historian," but the most likely culprit of this potentially fatal misunderstanding lies in the connotative meanings each ascribed to the word "crushing" or to other variances in metaphorical communication.

**Clinical Vignette 3**

A psychiatrist had been treating a 35-year-old man with a narcissistic personality and dysthymic disorder for 2 years. Given the brutality and deprivation of the patient's childhood, the clinician was persistently puzzled by the patient's remarkable psychological strengths. He possessed capacities for empathy, self-observation, and modulation of intense rage that were unusual, given his background. During a session the patient, in telling a childhood story, began, "When I was a little fella . . . " It struck the psychiatrist that the patient always said "little fella" when referring to himself as a boy, and that this was fairly distinctive phraseology. Almost all other patients will say, "When I was young/a kid/a girl (boy)/in school," designate an age, etc. On inquiry about this, the patient immediately identified "The Andy Griffith Show" as the source. This revealed a secret identification with the characters of the TV show, and a model that said to a young boy, "There are other ways to be a man than what you see around you." Making this long-standing covert identification fully conscious was transformative for the patient.

Patients are storytellers primarily about their important relationships, who have the hope of being heard and understood (Edelson 1993). Their hearers are physicians who expect to listen actively and to be with the patient at a new level of understanding. Because all human beings listen to many different people every day, we tend to think of listening as an automatic ongoing process, yet this sort of active listening remains one of the central skills in clinical psychiatry. It underpins all other skills in diagnosis, alliance building, and communication. In all medical examinations, the patient is telling a story only she or he has experienced. The physician must glean the salient information and then use it in

appropriate ways. Inevitably, even when language is common, there are differences in meaning, based on differences in gender, age, culture, religion, socioeconomic class (SES), race, region of upbringing, nationality, and mother tongue, as well as idiosyncrasies of individual history. These differences are particularly important to keep in mind in the use of analogies, similes, and metaphors. Figures of speech, in which one thing is held representational of another, are very important windows to the inner world of the patient. Differences in meanings attached to figures of speech can complicate their use. In psychodynamic assessment and psychotherapeutic treatment, these subtleties of language become the self-conscious focus of the psychiatrist, yet failure to hear such idiosyncratic distinctions can affect simple medical diagnosis as well.

In psychotherapy, the special meanings of words become the central focus of the treatment.

## How Does One Hear Words in This Way?

The preceding clinical vignettes, once described, sound straightforward. Yet, to listen in this way the clinician must acquire specific yet challenging skills and attitudes. It is extremely difficult to put into words the listening processes embodied in these examples and those to follow, yet that is what this chapter must attempt to do.

Students, when observing experienced psychiatrists interviewing patients, often express a sense of wonder such as: "How did she know to ask that?" "Why did the patient open up with him but not with me?" "What made the diagnosis so clear in that interview and not in all the others?" The student may respond with a sense of awe, a feeling of ineptitude and doubt, or even a reaction of disparagement that the process seems so indefinable and inexact. The key is the clinician's ability to listen. Without a refined capacity to hear deeply, the chapters on other aspects of interviewing in this textbook are of little use. But it is neither mystical nor magical nor indefinable; such skills are the product of hard work, much thought, intense supervision, and extensive in-depth exposure to many different kinds of patients.

Psychiatrists, more than any other physicians, must simultaneously listen symptomatically and narratively/experientially. They must also have access to a variety of theoretical perspectives that inform their listening, including behavioral, interpersonal, cognitive, sociocultural, and systems theories. Symptomatic listening is traditional medical history taking in which the focus is on the presence or absence of a particular symptom, the most overt content level of an interview. Narrative–experiential listening is based on the idea that all humans are constantly interpreting their experiences, attributing meaning to them, and weaving a story of their lives with themselves as the central character. This process goes on continuously, both consciously and unconsciously, as a running conversation within each of us. The conversation is between parts of ourselves and between ourselves and what Freud called "internalized objects," important people in our lives whose images, sayings, and attitudes become permanently laid down in our memories. This conversation and commentary on our lives includes personal history, repetitive behaviors, learned assumptions about the world, and interpersonal roles. These are, in turn, the products of individual background, cultural norms and values, national identifications, spiritual meanings, and family system forces. In diagnosing most medical ailments, attention to the complex meanings of words is not crucial (Clinical Vignette 2 is an exception); in psychiatry it is central.

Clinical Vignette 4

A 46-year-old man was referred to a psychiatrist from a drug study. The patient had both major depression and dysthymic disorder since a business failure 2 years earlier. His primary symptoms were increased sleep, decreased mood, libido, energy, and interests. After no improvement during the "blind" portion of the study, he had continued to show little response once the code was broken, and he was treated with two different active antidepressant medications. He was referred for psychotherapy and further antidepressant trials. The therapy progressed slowly with only episodic improvement. One day, the patient reported that his wife had been teasing him about how, during his afternoon nap, his snoring could be heard over the noise of a vacuum cleaner. The psychiatrist immediately asked additional questions, eventually obtained sleep polysomnography, and, after appropriate treatment for sleep apnea, the patient's depression improved dramatically.

Three factors were present that enabled the psychiatrist in this vignette to identify an unusual diagnosis that had been missed by three other excellent clinicians, using detailed structured interviews that, extremely inclusive in their symptom reviews. First, the psychiatrist had to have available in mind many symptoms and syndromes. Second, he was in a curious mode. In fact, this clinician had a gnawing sense that something was missing in his understanding of the patient. There is a saying in American medicine designed to focus students on the need to consider common illnesses first: when you hear hoofbeats don't look for zebras. This psychiatrist's mind was open to seeing a "zebra" despite the ongoing assumption that the weekly "hoofbeats" represented the everyday "horse" of clinical depression. Finally, he heard the patient's story in multiple, flexible ways, including the possibility that a symptom may be embedded in it, so that a match could be noticed between a detail of the story and a symptom. Eureka! The zebra could be seen though it had been there weekly for months.

Looking back at Clinical Vignette 3, we see the same phenomenon of a detail leaping out as a significant piece of missing information that dramatically influences the treatment process. This requires a cognitive template (symptoms and syndromes; developmental, systemic, and personality theories; awareness of cultural perspectives), a searching inquisitive stance, and flexible processing of the data. If one is able to internalize the skills listed in Table 1–1, the listener begins to automatically hear multiple meanings in the words.

## Listening as More Than Hearing

Listening and hearing are often equated. However, listening involves not only hearing and understanding the speaker's words, but attending to inflection, metaphor, imagery, sequence of associations, and interesting linguistic selections. It also involves seeing—movement, gestures, facial expressions, subtle changes in these—and constantly comparing what is said with what is seen, looking for dissonances, and comparing what is being said and seen with what was previously communicated and observed. Further, it is essential to

be aware of what might have been said but was not, or how things might have been expressed but were not. This is where clues to idiosyncratic meanings and associations are often discovered. Sometimes, the most important meanings are embedded in what is conspicuous by its absence.

It was Darwin (1955) who first observed that there appears to be a biogrammar of primary emotions that all humans share and express in predictable, fixed action patterns. The meaning of a smile or nod of the head is universal across disparate cultures. This insight was lost until the late 1960s when several researchers from different fields (Tiger and Fox 1971, Tomkins and McCarter 1964) returned to it and provided empirical support for it. LeDoux (1996) has been a leader in identifying the neurobiological substrate for primary emotions. Brothers (1989), using this work and her own experiments with primates, developed a hypothesis about the biology of empathy based on seeing as well as hearing. Both she and Damasio (1994) have identified the amygdala and the inferior temporal lobe gyrus as the neurobiological substrate for recognition of and empathy for others and their emotional states. Further research has identified that these parts of the brain are, on the one hand, prededicated to recognizing certain gestures, facial expressions, and so on, but require effective maternal–infant interaction in order to do so (Schore 2001). More recently, the discovery of mirror neurons has added to our grasp of the neurobiology of effective listening (Harris 2007).

Clinical Vignette 5

A 38-year-old Hispanic construction worker presented himself to a small-town emergency department in the Southwest, complaining of pain on walking, actually described in Spanish-accented English as "a little pain." His voice was tight, his face was drawn, and his physical demeanor was burdened and hesitant. His response to the invitation to walk was met by a labored attempt to walk without favor to his painful limb. A physician could have discharged him from the emergency department with a small prescription of ibuprofen. The careful physician in the emergency department responded to the powerful visual message that he was in pain, was beaten down by it, and had suffered long before coming in. This recognition came first to the physician as an intuition that this man was somehow more sick than he made himself sound. A radiograph of the femur revealed a lytic lesion that later proved to be metastatic renal cell carcinoma. To hear the unspoken, one had to be keenly aware of the patient's tone and how he looked, and to keep in mind, too, the cultural taboos forbidding him to give in to pain or to appear to need help.

All of this is synthesized in the listener as a "sense" or intuition as to what the speaker is saying at multiple levels. These mechanisms probably underlie Freud's observation that the unconscious of the analyst listens to the unconscious of the patient. As has been implied, not only must one affirmatively "hear" all that a patient is communicating, but one must also overcome a variety of potential blocks to effective listening.

## Common Blocks to Effective Listening

Many factors influence the ability to listen. Psychiatrists come to the patient as the product of their own life experiences. Does the listener tune in to what he or she hears in a more attentive way if the listener and the patient share characteristics? What blocks to listening (Table 1–2) are posed by differences in sex, age, religion, SES, race, culture, or nationality (Kleinman 2001, Comas-Diaz and Jacobsen 1991, Kochman 1991)? What blind spots may be induced by superficial similarities in different personal meanings attributed to the same cultural symbol? The act of listening is inevitably influenced by similarities and differences between the psychiatrist and the patient.

**Table 1–2 Blocks to Effective Listening**

| | |
|---|---|
| Patient–psychiatrist dissimilarities | Race |
| | Sex |
| | Culture |
| | Religion |
| | Regional dialect |
| | Individual differences |
| | Socioeconomic class |
| Superficial similarities | May lead to incorrect assumptions of shared meanings |
| Countertransference | Psychiatrist fails to hear or reacts inappropriately to content reminiscent of own unresolved conflicts |
| External forces | Managed care setting |
| | Emergency department |
| | Control-oriented inpatient unit |
| Attitudes | Need for control |
| | Psychiatrist having a bad day |

Would a woman have reported the snoring in Clinical Vignette 4 or might she have been too embarrassed? Would she have reported it more readily to a woman psychiatrist? What about the image in Clinical Vignette 2 of a truck sitting on one's chest? How gender, class and culture bound is it? Would "The Andy Griffith Show," in Clinical Vignette 3, have the same impact on a young African-American boy as on a Caucasian ? How widely is "The Andy Griffith Show" available; in which cultures would that model of family structure seem relevant? Suppose the psychiatrist in Vignette 3 was not a television viewer or had arrived in the US long after the show had aired?

Clinical Vignette 6

A 45-year-old successful attorney suffering from anxiety and mild depression faced multiple sources of turmoil in his family, including with his spouse. When asked what he valued about the members of his family, he listed many aspects: his long-standing with for the "American Dream" of a white picket fence house, the importance to his career, the responsibility for seeing his children thrive, etc. What he never mentioned was his own need for intimacy and friendship from his wife. When this was pointed out, a whole new area of the patient's life became exposed. He had never observed intimacy between his mother and father, never sought it for himself, never even imagined it as an important dimension of life.

It is likely that different experiences based on gender fostered this misunderstanding. How many women easily

identify with the stereotyped role of the barnyard rooster? How many men readily identify with the role of a prostitute? These are but two examples of the myriad meanings our gender may incline us toward. Although metaphor is a powerful tool in listening to the patient, cultural barriers pose potential blocks to understanding.

**Clinical Vignette 7**

A female patient came to see her male psychiatrist for their biweekly session. Having just been given new duties on her job, she came in excitedly and began sharing with her therapist how happy she was to have been chosen by her male supervisor to help him with a very important project at their office. The session continued with the theme of the patient's pride in having been recognized for her attributes, talents, and hard work. At the next session, she said that she had become embarrassed after the previous session at the thought that she had been "strutting her stuff." The therapist reflected back to her the thought that she sounded like a rooster strutting his stuff, connecting her embarrassment at having revealed that she strove for the recognition and power of men in her company, and that she, in fact, envied the position of her supervisor. The patient objected to the comparison of a rooster, and likened it more to feeling like a woman of the streets strutting her stuff. She stated that she felt like a prostitute being used by her supervisor. The psychiatrist was off the mark by missing the opportunity to point out in the analogous way that the patient's source of embarrassment was in being used, not so much in being envious of the male position.

**Clinical Vignette 8**

A 36-year-old black woman complained to her therapist (of the same language, race, and socioeconomic class) that her husband was a snake, meaning that he was no good, treacherous, a hidden danger. The therapist, understanding this commonly held definition of a snake, reflected back to the patient pertinent, supportive feedback concerning the care and caution the patient was exercising in divorce dealings with the husband.

In contrast, a 36-year-old Chinese woman, fluent in English, living in her adopted country for 15 years and assimilated to Western culture, represented her husband to her Caucasian, native-born psychiatrist as being like a dragon. The therapist, without checking on the meaning of the word "dragon" with her patient, assumed it connoted danger, one of malicious intent, and oppression. The patient, however, was using "dragon" as a metaphor for her husband—the fierce, watchful guardian of the family—in keeping with the ancient Chinese folklore in which the dragon is stationed at the gates of the lord's castle to guard and protect it from evil and danger.

Subtle regional variations may produce similar problems in listening and understanding.

Psychiatrists discern meaning in that which they hear through filters of their own—cultural backgrounds, life experiences, feelings, the day's events, their physical sense of themselves, nationality, sex roles, religious systems, and intrapsychic conflicts. Filters can serve as blocks or magnifiers if certain elements of what is being said resonate within the psychiatrist. When the filters block, we call it countertransference or insensitivity. When they magnify, we call it empathy or sensitivity. One may observe a theme for a long time repeated with different tones, embellishment, inflection, or context before what is meant comes to mind. The "little fella" example in Clinical Vignette 3 illustrates a message that had been communicated in many ways and times in exactly the same language before the psychiatrist "got it." On discovering a significant meaning that had been signaled before in many ways, the psychiatrist often has the experience, "How could I have been so stupid? It's been staring me in the face for months!"

Managed care and the manner in which national health systems are administered can alter our ability to be transforming listeners. The limitation on visits and time alloted and forms tediously filled out can be blocks to listening to the patient. With these time limits and other "third-party payer" considerations (i.e., need for a billable diagnostic code from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV-TR] or the *International Classification of Diseases*, 10th Revision [ICD-10]), the psychiatrist, as a careful listener, must heed the external pressures influencing the approach to the patient. Many benefits packages provide coverage only for relief of symptoms, restoration of minimal function, acute problem solving, and shoring up of defenses. In various countries, health care systems have come up with a variety of constraints in efforts to deal with the cost of care. This pressures listening toward a different purpose, approximating the crisis intervention model of the emergency room or the narrow medical model. Responding to this, the psychiatrist might use checklists, inventories, and scales for objectifying the severity of illness and response to treatment: the ear is tuned only to measurable and observable signs of responses to therapy and biologic intervention.

**Clinical Vignette 9**

In a family session, a psychiatrist from the South referred to the mother of her patient as "your mama," intending a meaning of warmth and respect. The patient instantly became enraged at the use of such an offensive term toward her mother. Although being treated in Texas, the patient and her family had recently moved from a large city in New Jersey. The use of the term "mama" among working class Italians in that area was looked upon with derision among people of Irish descent, the group to which the patient was ethnically connected. The patient had used the term "mother" to refer to her mother, a term the psychiatrist had heard with a degree of coolness attached. What she knew of her patient's relationship with her mother did not fit in with a word like mother, hence almost out of awareness she switched terms leading to a response of indignation and outrage from the patient.

With emphasis on here and now symptoms, will the patient be lost in the encounter? In the emergency department, emphasis is on symptom relief, assurance of capacities to keep oneself safe, restoration of minimal function, acute problem solving, and shoring up of defenses. Special attention is paid to identifying particular stressors. What can be done quickly to change stressors that threw the patient's world into a state of disequilibrium? At least in the

emergency room the careful listener may have 3–6 hours, as opposed to 3–6 sessions with the patient in a health maintenance organization or preferred provider contract. If one is fortunate and good at being an active listener–bargainer, the seeds of change can be planted in hopes of allowing growth between emergency department visits.

## Crucial Attitudes That Enable Effective Listening

The first step in developing good listening skills involves coming to grips with the importance of inner experience in psychiatric treatment and diagnosis. The DSM-IV-TR (American Psychiatric Association 1994) and ICD-10 (World Health Organization 1992) have been enormous advances in reliability and accuracy of diagnosis, but their emphasis on seemingly observable phenomena has allowed the willing user to forget the importance of inner experience even in such basic diagnoses as major depressive disorder. Consider the symptom "depressed mood most of the day" or "markedly diminished interest or pleasure" or even "decrease or increase in appetite." These are entirely subjective symptoms. Simply reporting depression is usually not sufficient to convince a psychiatrist that a diagnosis of depression is warranted. In fact, the vast majority of psychiatric patients are so demoralized by their illnesses that they often announce depression as their first complaint. Further, there are a significant number of patients who do not acknowledge depression yet are so diagnosed. The clinician might well comment, "Sitting with him makes me feel very sad."

The psychiatrist must listen to much more than the patient's overt behavior. There are qualities in the communication, including the inner experiences induced in the listener that should be attended to. The experienced clinician listens to the words, watches the behavior, engages in and notices the ongoing interaction, allows himself/herself to experience his/her own inner reactions to the process, and *never forgets that depression and almost all other psychiatric symptoms are largely private experiences*. The behavior and interactions are useful insofar as they assist the psychiatrist in inferring the patient's inner experience.

Therefore, to convince a clinician that a patient is depressed, not only must the patient say she/he is depressed, but the observable behavior must also convey it (sad-looking face, sighing, unexpressive intonations, etc.); the interaction with the interviewer must convey depressive qualities (sense of neediness, sadness induced in the interviewer, beseeching qualities expressed, etc.). In the absence of both of these, other diagnoses should be considered, but in the presence of such qualities, depression needs to remain in the differential diagnosis.

Even when we make statements about brain function with regard to a particular patient, we use this kind of listening, generally, by making at least two inferences. We first listen to and observe the patient and then infer some aspect of the patient's private experience. Then, if we possess sufficient scientific knowledge, we make a second inference to a disturbance in neurochemistry, neurophysiology, or neuroanatomy. When psychiatrists prescribe antidepressant medication, they have inferred from words, moved into inner experiences, and come to a conclusion that there is likely a dysregulation of serotonin or norepinephrine in the patient's brain.

As one moves toward treatment from diagnosis, the content of inner experience inferred may change to more varied states of feelings, needs, and conflicts, but the fundamental process of listening remains the same. The psychiatrist listens for the meaning of all behavior, to the ongoing interpersonal relationship the patient attempts to establish, and to inner experiences as well.

Despite the technological advances in medicine in general and their growing presence in psychiatry, securing or eliciting a history remains the first and central skill for all physicians. Even in the most basic of medical situations, the patient tries to communicate a set of private experiences (how does one describe the qualities of pain or discomfort?) that the physician must infer and sort into possible syndromes and diagnoses. In psychiatry, this process is multiplied, as indicated in Figure 1–1. William Styron (1990), a prizewinning novelist, went to extraordinary lengths in his eloquent attempt to convey the "searing internal mental pain" that he experienced when suffering from a major depression.

Silvano Arieti (1967) hypothesized that cognitive development produces changes over time in the inner experience of various affects. Does a person with borderline personality disorder experience "anxiety" in the same qualitative and quantitative manner in which a neurotic person does? What is the relationship between sadness and guilt and the empty experiences of depression? This perspective underlies the principle articulated in text after text on interviewing that emphasizes the importance of establishing rapport in the process of history taking. It is easy for the psychiatrist to attribute to the patient what she/he would have meant and what most people might have meant in using a particular word or phrase. The sense in the narrator that the listener is truly present, connected, and with the patient enormously enhances the accuracy of the story reported.

Words that have been used to describe this process of constant attention to and inference of inner experience by the listener include interest, empathy (Rogers 1951, Kohut 1991, Truax 1963), attentiveness, and noncontingent positive regard (Truax 1963). However, these are words that may say less than they seem to. It is the constant inquisitive awareness on the listener's part that she/he is trying to grasp the private inner experience of the patient, and the storyteller's sense of this stance by the psychiatrist that impels the ever more revealing process of history taking. This quality of listening produces what we call rapport, without which psychiatric histories become spotty, superficial, and even suspect. There are no bad historians, only patients who have not yet found the right listener.

In treatment, we even find empirical data to support this perspective. The two most powerful predictors of outcome in any form of psychotherapy are empathy and the therapeutic alliance (Horvath and Luborsky 1993, Greenson 1978). This has been shown again and again in study after study for dynamic therapy, cognitive therapy, behavior therapy, and even medication management (Elkin et al. 1989). This led some researchers and theorists to propose that the power of psychotherapy can be understood solely as a remoralization phenomenon based on support and empathy (Frank 1973, Omer and London 1989). The truth of this can be seen in the remarkable therapeutic success of the Clinical Management Cell of the National Institutes

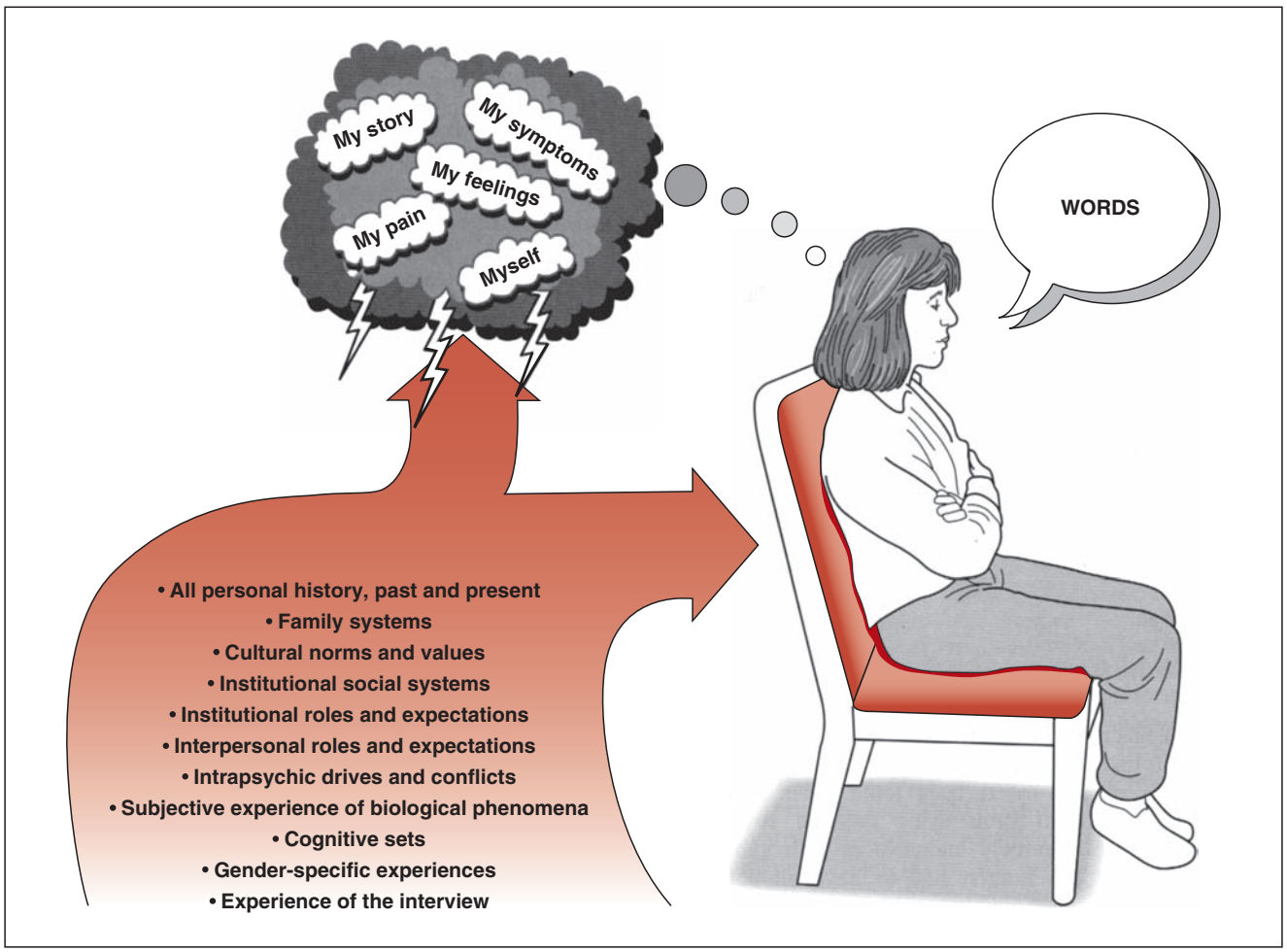



**Figure 1–1** *Finding the patient.*

of Mental Health Collaborative Study on the Treatment of Major Depression. Although the Clinical Management Cell was not as effective as the cells that included specific drugs or specific psychotherapeutic interventions, 35% of patients with moderate to severe major depressive disorder improved significantly with carefully structured supportive clinical management alone (Elkin et al. 1989).

Helpful psychiatric listening requires a complicated attitude toward control and power in the interview (see Table 1–3). The psychiatrist invites the patient/storyteller to collaborate as an active informer. He is invited, too, to question and observe himself. This attitude toward history taking remains the principal tool of general clinical medicine, even in this day of questionnaires and checklists as one arrives at the doctor's office. The checklists may focus the interviewer but not obviate the need to explore the key symptoms. However, as Freud pointed out, these methods of active uncovering are more complex in the psychic realm. The use of the patient as a voluntary reporter requires that the investigator keep in mind the unconscious and its power over the patient and listener. Can the patient be a reliable objective witness of himself or his symptoms? Can the listener hold in mind his own set of filters, meanings, and distortions as he hears? The listener translates for himself and his patient the patient's articulation of his experience of himself and his inner world into our definition of symptoms, syndromes, and differential diagnoses.

**Table 1–3 Attitudes Important to Listening**

| |
|---|
| The centrality of *inner experience* |
| There are no bad historians |
| The answer is always inside the patient |
| Control and power are shared in the interview |
| It is OK to feel confused and uncertain |
| Objective truth is never as simple as it seems |
| Listen to yourself, too |
| Everything you hear is modified by the patient's filters |
| Everything you hear is modified by your own filters |
| There will always be another opportunity to hear more clearly |

Objective–descriptive examiners are like detectives closing in on disease. The psychiatric detective enters the inquiry with an attitude of unknowing and suspends prior opinion. The techniques of listening invoke a wondering and a wandering with the patient. Periods of head scratching and exclamations of "I'm confused," or "I don't understand," or "That's awful!" or "Tell me more" allow the listener to follow or to point the way for the dyad. Finally, clear and precise descriptions are held up for scrutiny, with the hope that a diagnostic label or new information about the patient's suffering and emotional pain is revealed.

It is embarking on the history taking journey together–free of judgments, opinions, criticism, or preconceived notions–that underpins rapport. Good listening requires a complex understanding of what objective truth is and how it may be found. The effective psychiatrist must eschew the traditional medical role in interviewing and tolerate a collaborative, at times meandering, direction in which control is at best shared and sometimes wholly with the patient. The psychiatrist constantly asks: What is being said? Why is it being said at this moment? What is the meaning of what is being said? In what context is all this emerging? What does that tell me about the meaning and what does it reflect about the doctor–patient relationship?

## Theoretical Perspectives on Listening

Listening is the effort or work of placing the therapist where the patient is ("lives"). Greenson (1978) would call it "going along with"; Rogers (1951) "centering on the client." Greenson would add that it is better to be deceived going along with the patient than to reject him/her prematurely and have the door slammed to the patient's inner world. Personal beliefs and values are suspended in service of the discovery of the true self. Harry Stack Sullivan (1953), the father of interpersonal psychiatry, would remind us to heed those shrewd, small questions: "What is he up to?" "Where is he taking us?" Every human being has a preferred interpersonal stance, a set of relationships and transactions with which she or he is most comfortable and feels most gratified. The problem is that for most psychiatric patients they do not work well.

Beyond attitudes that enable or prevent listening there is a role for specific knowledge. It is important to develop a cognitive structure or theoretical framework and use it with rigor and discipline in the service of patients so that psychiatrists can employ more than global "feelings" or "hunches." In striving to grasp the inner experience of any other human being, one must know what it is to be human; one must have an idea of what is inside any person. This provides a framework for understanding what the patient—who would not be a patient if he fully understood what was inside of him—is struggling to communicate. Personality theory is absolutely crucial to this process.

Whether we acknowledge it or not, every one of us has a theory of personality (in the age of porous boundaries between psychology and biology, we should speak of a psychobiological theory of human experience) that we apply in social or clinical situations. These theories become part of the template alluded to earlier that allow certain words, stories, actions, and cues from the patient to jump out with profound meaning to the psychiatrist. There is no substitute for a thorough knowledge of many theories of human functioning and a well-disciplined synthesis and internal set of rules to decide which theories to use in what situations.

Different theoretical positions offer slightly different and often complementary perspectives on listening (Table 1–4). The basic tools of therapeutic power and diagnostic acumen spring from the following:

1. Freud's associative methods (Brill 1938) and ego psychology (Freud 1946), in which one listens for the associative trends and conflicts.
2. Melanie Klein's (1975) and Harry Stack Sullivan's (1953) object relations theory. The former discovered the story through inner world exploration and recognized the introjected persons of the past living within the patient's mind, comprising the person's psychic structure; the latter discovered the knowing through the interpersonal experience of the therapeutic dyad (Greenberg and Mitchell 1983).
3. Binswanger's (1963) understanding of the condition of empathy, in which the listener gives up his or her own position for that of the storyteller.
4. Kohut's (1991) self psychology, which emphasizes the use of vicarious introspection to reflect (mirror) back to the patient what is being understood. This mirroring engenders in the storyteller a special sense of being "found," that is, of being known, recognized, affirmed, and heard. This feeling of being heard helps to undo the sense of aloneness so common in psychiatric patients.

**Table 1–4 Theoretical Perspectives on Listening**

| Theory | Focus of Attention | Listening Stance |
|---|---|---|
| Ego psychology | Stream of associations | Neutral, hovering attention |
| Object relations | Introjects (internalized images of others within the patient) | Neutral, hovering attention |
| Interpersonal | What relationship is the patient attempting to construct? | Participant observer |
| Existential | Feelings, affect | Empathic identification with the patient |
| Self psychology | Sense of self from others | Empathic mirroring and affirmation |
| Patient centered | Content control by patient | Noncontingent positive regard, empathy |
| Cognitive | Hidden assumptions and distortions | Benign expert |
| Behavioral | Behavioral contingencies | Benign expert |
| Family systems | Complex forces maneuvering each member | Neutral intruder who forces imbalance in the system |

Each of the great schools of psychotherapy places the psychiatrist in a somewhat different relationship to the patient. This may even be reflected in the physical placement of the therapist in relation to the patient. In a classical psychoanalytic stance, the therapist, traditionally unseen behind the patient, assumes an active, hovering attention. Existential analysts seek to experience the patient's position and place themselves close to and facing the patient. The interpersonal psychiatrist stresses a collaborative dialogue with shared control; it stresses the need for each participant to act within that interpersonal social field.

In the object relations stance, the listener keeps in mind the "other people in the room" with him and the storyteller; the patient's introjects, constantly part of the patient's

internal conversation and thus influencing the dialogue of the therapeutic dyad. In connecting with the patient, the listener is also tuned in to the fact that parts and fragments of him or her are being internalized by the patient. The listener becomes another person in the room of the patient's life experience, within and outside the therapeutic hour. Cognitive and behavioral psychiatrists are kindly experts, listening attentively and subtly for hidden assumptions, distortions, and connections. The family systems psychiatrist sits midway among the pressures and forces emanating from each individual, seeking to affect the system so that all must adapt differently.

Referring again to Clinical Vignette 3, we can see the different theoretical models of the listening process in the discovery of the meaning of "little fella." Freud's model is that the psychiatrist had listened repeatedly to a specific association and inquired of its meaning. Object relations theorists would note that the clinician had discovered a previously unidentified, powerful introject. The interpersonal psychiatrist would see the shared exploration of this idiosyncratic manner of describing one's youth; the patient had been trying to take the therapist to "The Andy Griffith Show," attempting to induce the clinician to share the experience of imagining having Andy Griffith as a father.

Existentialists would note how the psychiatrist was changed dramatically by the patient's repeated use of this phrase and then altered even more profoundly by the memory of Andy Griffith, "the consummate good father" in the patient's words. The therapist could never see the patient in quite the same way again, and the patient sensed it immediately. And Kohut would note the mirroring quality of the psychiatrist's interpreting the meaning of this important memory. This would be mirroring at its most powerful, affirming the patient's important differences from his family, helping him to consolidate the memories. The behavioral psychiatrist would note the reciprocal inhibition that had gone on, with Andy Griffith soothing the phobic anxieties in a brutal family.

A cognitive psychiatrist would wonder whether the patient's depression resulted from a hidden assumption that anything less than the idyllic images of television was not good enough. The family systems psychiatrist would help the patient see that he had manipulated the forces at work on him and actually changed the definition of his family.

The ways and tools of listening also change, according to the purpose, the nature of the therapeutic dyad. The ways of listening also change depending upon whether or not the psychiatrist is preoccupied or inattentive. The medical model psychiatrist listens for signs and symptoms. The analyst listens for the truth often clothed in fantasy and metaphor. The existentialist listens for feeling, and the interpersonal theorist listens for the shared experiences engendered by the interaction. Regardless of the theoretical stance and regardless of the mental tension between the medical model's need to know symptoms and signs and the humanistic psychiatrist's listening to know the sufferer, the essence of therapeutic listening is the suspension of judgment before any presentation of the story and the storyteller. The listener is asked to clarify and classify the inner world of the storyteller at the same time he is experiencing it—no small feat!

## Using Oneself in Listening

Understanding transference and countertransference is crucial to effective listening. Tomkins, LeDoux, Damasio, and Brothers have given us a basic science, biological perspective on this process. However one defines these terms, whatever one's theoretical stance about these issues, Harry Stack Sullivan (1969) had it right when he said that schizophrenics are more human than anything else. To know ourselves is to begin to know our patients more deeply. There are many ways to achieve this. Personal therapy is one. Ongoing life experience is another. Supervision that emphasizes one's emotional reactions to patients is still a third. Once we have started on the road to achieving this understanding by therapy, supervision, or life experience, continued listening to our patients, who teach us about ourselves and others, becomes a lifelong method of growth.

To know oneself is to be aware that there are certain common human needs, wishes, fears, feelings, and reactions. Every person must deal in some way with attachment, dependence, authority, autonomy, selfhood, values and ideals, remembered others, work, love, hate, envy and loss. It is unlikely that the psychiatrist can comprehend the patient without his own self-awareness. Thus, Figure 1–1 should really look like Figure 1–2. The most psychotic patient in the world is still struggling with these universal human functions.

Clinical Vignette 10

An army private was brought to the emergency room in Germany by his friends, having threatened to commit suicide while holding a gun to his head. He was desperate, disorganized, impulsive, enraged, pacing, and talking almost incoherently. Gradually, primarily through his friends, the story emerged that his first sergeant had recently made a decision for the entire unit that had a particularly adverse effect on the patient. He was a fairly primitive character who relied on his wife for a sense of stability and coherence in his life. The sergeant's decision was to send the entire unit into the field for over a month just at the time the patient's wife was about to arrive, after a long delay, from the US. After piecing together this story, the psychiatrist said to the patient, "It's not yourself you want to kill, it's your first sergeant!" The patient at first giggled a little, then gradually broke out into a belly laugh that echoed throughout the emergency room. It was clear that, having recognized the true object of his anger, a coherence was restored that enabled him to feel his rage without the impulse to act on it. The psychiatrist then enlisted the friends in a plan to support the patient through the month and to arrange regular phone contact with the wife as she set up their new home in Germany. No medication was necessary. Hospitalization was averted, and a request for humanitarian dispensation, which would have compromised the patient in the eyes of both his peers and superiors, was avoided as well. And, with luck, the young man had an opportunity to grow emotionally as well.

In this case, the psychiatrist was able to connect with a patient's inner experience in a manner that had a fairly dramatic impact on the clinical course. That is the goal of listening. The art is hearing the patient's inner experience and then addressing it empathically, enabling the patient to

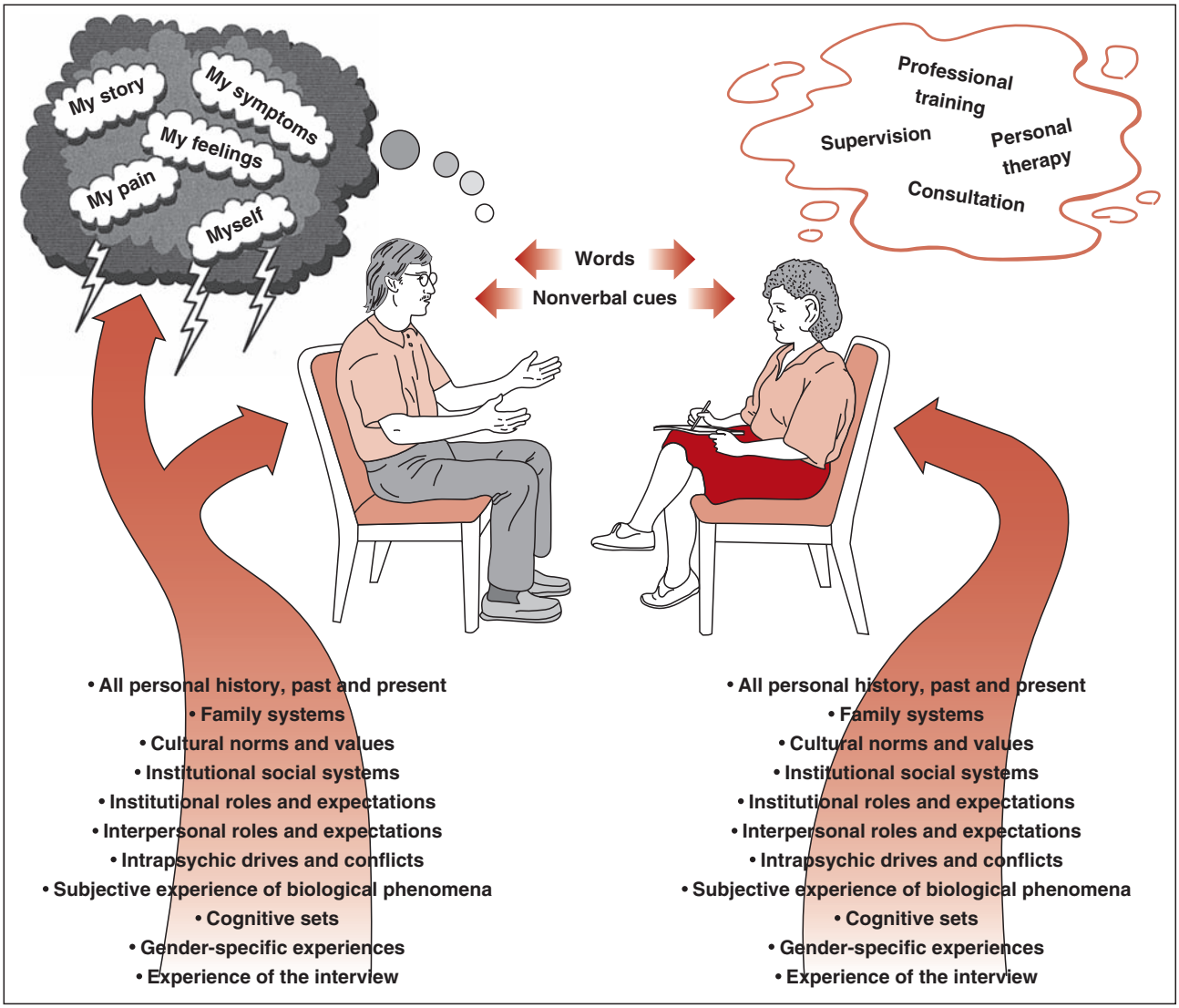



**Figure 1–2** *The therapeutic dyad.*

feel heard and affirmed. There are no rules about this, and at any given point in a clinical encounter there are many ways to accomplish it. There are also many ways to respond that are unhelpful and even retraumatizing. The skilled psychiatrist, just as she/he never forgets that it is the patient's inner experience that is to be heard, also never stops struggling to find just the right words, gestures, expressions, and inflections that say to a patient, "you have been understood." The most clever diagnostician or insightful interpreter who cannot "connect" with the patient in this manner will miss valuable information. This issue has been addressed by writers who have pointed out how little understood are the concepts of support and empathy (Peteet 1982).

Being human is also to be a creature of habit and pattern in linguistic, interpersonal, and emotional realms. The skilled psychiatrist listens with this ever in mind. What we see in the interview, what we hear in interactions, may be presumed to be repetitions of many other events. The content may vary, but the form, motive, process, and evolution are generally universal for any given individual. This, too, is part of listening. To know what is fundamentally human, to have a well-synthesized rigorous theory, and to hear the person's unique but repetitive ways of experiencing are the essence of listening. These skills "find" the patient in all his/her humanity, but then the psychiatrist must find the right communication that allows the patient to feel "found."

## To Be Found: The Psychological Product of Being Heard

Psychiatric patients may be lonely, isolated, demoralized, and desperate, regardless of the specific diagnosis. They have lost themselves and their primary relationships, if they ever had any. Stanley Jackson (1992) makes the point that before anything else can happen, they must be found, and feel found. They can only be found within the context of their own specific histories, cultures, religions, genders, social contexts, and so on. There is nothing more healing than that experience of being found by another. The earliest expression of this need is in infancy and we refer to it as the need for attachment. Referring to middle childhood, Harry Stack Sullivan spoke of the importance of the pal or buddy. Kohut spoke of the lifelong need for *self-objects*.

In lay terms, it is often subsumed under the need for love, security, and acceptance. Psychiatric patients have lost or never had this experience. However obnoxious or destructive or desperate their overt behavior, it is the psychiatrist's job to seek and find the patient. That is the purpose of listening.

If we look back to Clinical Vignette 3, wherein the phrase "little fella" bespoke such deep and important unverbalized meaning, the patient's reaction to the memory and recognition by the psychiatrist was dramatic. He had always known he was different in some indefinable ways from his family. That difference had been both a source of pride and pain to him at various developmental stages. However, the recognition of the specific source, its meaning, and its constant presence in his life created a whole new sense of himself. He had been found by his psychiatrist, who echoed the discovery, and he had found an entire piece of himself that he had enacted for years, yet which had been disconnected from any integrated sense of himself.

Sometimes objectifying and defining the disease/disorder enables the person to feel found. One of the most challenging patients to hear and experience is the acting out, self-destructive, demanding person with borderline personality disorder. Even as the prior sentence conveys, psychiatrists often experience the diagnosis as who the patient is rather than what she suffers. The following case conveys how one third-year resident was able to hear such a patient, and in his listening to her introduce the idea that the symptoms were not her but her disorder.

Clinical Vignette 11

A young man with paranoid schizophrenia had been admitted in 1979 to the hospital following a near lethal attack on his father. When asked about this incident, he became frankly delusional, speaking of the Arab–Israeli conflict, the preciousness of Jerusalem, how the Israelis must defend it at all costs. Unspoken was his conviction that he was like the Israelis, with the entire world attacking and threatening him. He believed his father had threatened and attacked him when, in fact, his father had done little more than seek to be closer, more comforting, and advising with the patient. The psychiatrist understood the patient to be speaking of that core of selfhood that we all possess, which, when threatened, creates a sense of vulnerability and panic, a disintegrating anxiety unlike any other. The psychiatrist spoke to the patient of Anwar Sadat's visit to Jerusalem and engaged him in a discussion of how that had gone, what the outcome had been, had the threat been lessened or increased. The patient, although still delusional, visibly relaxed and began to speak much more directly about his own sense of vulnerability and uncertainty over his personal integrity and its ability to withstand any closeness. He still required neuroleptic medication for his illness; however, his violent thoughts and behaviors reduced dramatically. He was able to begin interacting with his father, and his behavior on the ward changed as well.

Gender can play a significant role in the experience of feeling found. Some individuals feel that it is easier to connect with a person of the same sex, and others, with someone of the opposite sex. Clinical Vignette 6 is an excellent example of this. In these days of significant change in and sensitivity to sex roles, a misinterpretation such as that early in treatment could result in a permanent rupture in the alliance. Psychiatrists vary in their sensitivity to the different sexes. Some may do better with those who have chosen more traditional roles, and others may be more sensitive to those who have adopted more modern roles.

We now know that just as there is a neurobiological basis for empathy and countertransference, there is a similar biological basis for the power of listening to heal, to lift psychological burdens, to remoralize, and to provide emotional regulation to patients who feel out of control in their rage, despair, terror, or other feelings (Table 1–5). Attachment and social support are psychobiological processes that provide necessary physiological regulation to human beings. This has been shown by the work of Hofer (1996), Cobb (1976), Meaney (2001), Nemeroff (Heim and Nemeroff 2001), and many others. Additional work of Paul Ekman (1992) supports the notion of the patient's capacity to perceive empathy through the powerful nonverbal, universally understood communication of facial expressions. His research in basic human emotions sets forth the idea of their understanding across cultures and ages. It further supports the provocative idea that facial expressions of the listener may generate autonomic and central nervous system changes not only within the listener but within the one being heard, and vice versa. Indeed, the evidence is growing that new experiences in clinical interactions create learning and new memories, which are associated with changes in both brain structure and function (Kandel 1999, Gabbard 2000, Mohl 1987, Liggan and Kay 1999, Siegel 2006). When we listen in this way, we are intervening not only in a psychological manner to connect, heal, and share burdens but also in a neurobiological fashion to regulate, modulate, and restore functioning. When patients feel found, they are responding to this psychobiological process.

**Table 1–5 The Basic Sciences of Listening**

| |
|---|
| Neurobiology of primary affects |
| Universality of certain affective expressions |
| Neurobiology of empathy |
| Biological need for interpersonal regulation |
| Psychobiology of attachment |
| Biological impact of social support |
| Environmental impact on central nervous system structure and function |

## Listening to Oneself to Listen Better

To hold in mind what has been said and heard after a session and between sessions is the most powerful and active tool of listening. It is a crucial step often overlooked by students and those new at listening. It is necessary to hear our patients in our thoughts during the in-between times in order to pull together repetitive patterns of thinking, behaving, and feeling, giving us the closest idea of how patients experience themselves and their world. In addition, many of our traumatized patients have not had the experience of being held in mind, of being remembered, and their needs being thought of by significant others. These key experiences of childhood affirm the young person's psychological being. It is important to distinguish this kind of "relistening" to the patient—an important part of the psychiatrist's ongoing

processing and reprocessing of what has been heard and experienced—from what some may leap to call countertransference. One way of identifying this distinction would be to differentiate listening to oneself as one reviews in one's mind the patient's story versus becoming preoccupied and stuck with one's thoughts and feelings about a particular aspect of a patient.

Clinical Vignette 12

He was working the midnight Friday to 11 a.m. Saturday shift in a Psychiatric Emergency Room. The patient was a 26-year-old woman brought in by ambulance after overdosing on sertraline following an argument with her boyfriend. She had been partying with him and became enraged at the attention he was paying to the date of a friend who was accompanying them. After being cleared medically, the patient was transferred to psychiatry for crisis intervention. It was about 4 a.m. when she arrived. She was crying and screaming for the psychiatric staff to release her. In the emergency department she had grabbed a suture scissors attached to the uniform of the charge nurse. The report was given to the psychiatric resident that she had been a "management problem" in the medicine ER.

The psychiatrist sat wearily and listened to the patient tell her story with tears, shouts, and expletives sputtered through clenched teeth. She stated that she did not remember ever being happy, that she frequently had thoughts of suicide, and that she had overdosed twice before, following a divorce from her first husband at the age of 19 and then 8 months prior to this episode when she had been fired from a job for arguing with her supervisor. Her parents had kept her 6-year-old and 7-year-old sons since her divorce. She was currently working as a file clerk and living with her boyfriend of 2 months. She stated that she felt like there was a cold ice cube stuck in her chest as she watched her boyfriend flirting with the other woman. She acknowledged that she felt empty and utterly alone even in the crowded bar. She created an unpleasant scene and they continued to argue until they got home. Then he had laughed at her and left, stating that he would come back when she had cooled down.

The resident sat quietly and listened. He looked dreary. The night had been a busy one. She looked at him and complained, "Don't let me and my problems bore you!" He looked at her and said, "Quite the contrary. I've been thinking as you speak that I know what disorder you suffer from." With that statement, he pulled out the DSM-IV-TR and read with her the description of the symptoms and signs of borderline personality disorder. She had been in therapy off and on since she was 16 years old. No one had ever shared with her the name of the diagnosis but instead had responded to her as if the disorder was the definition of who she was. In his listening, he was able to hear her symptoms as a disorder and not the person. And in his ability to separate the two, he was able to allow her to distance herself from the symptoms, too, and see herself in a new light with her first inkling of her own personhood.

As the verbal interaction with the patient occurs, psychiatrists may find themselves expressing thoughts and feeling in ways that may be quite different from their usual repertoire. The following case is an example.

This sort of listening to oneself in order to understand the patient requires a good working knowledge of projective identification (Ogden 1979). Projective identification, first defined by Melanie Klein, describes a defense mechanism in which the patient, in an effort to master intolerably terrifying emotions, unconsciously seeks to engender them in the therapist and to identify with the psychiatrist's ability to tolerate and handle the feelings.

Clinical Vignette 13

A second-year resident, rotating through an inpatient unit that serves the psychiatric needs of very severely ill psychotic patients with multiple admissions, dual diagnoses, homelessness, criminal records, significant histories of medical noncompliance, and, in some, unremitting psychosis, was particularly struggling with a 33-year-old white woman admitted for the 11th time since age 19. The patient invariably stopped medications shortly after discharge, never kept follow-up appointments, and ended up on the streets psychotic and high on crack cocaine. She would then be involuntarily committed for restabilization. And so the cycle would repeat itself. The resident would see the patient on daily rounds. The patient's litany was the same day after day: "I'm not sick. I don't need to be here. I don't need medicines." And regularly she refused doses.

The resident spoke often of her patient to other residents in her class and often found herself ruminating about the patient's abject lostness. She began her regular supervision hours either frustrated or feeling hopeless that anything would change with this patient because the patient flatly refused to acknowledge her disorder. The patient's level of denial was of psychotic proportions. Shortly after a particularly difficult encounter with the patient concerning her refusal to take an evening dose of haloperidol, the resident came to supervision with the report that she had awakened terrorized by dreaming the night before that she had been diagnosed with schizophrenia. She had been intensely affected by overwhelming pain, confusion, and despair as she heard the diagnosis in her dream. "IT CAN'T BE!!!" she screamed, waking herself with a shaking start. "I'M NOT SICK!! I DON'T NEED TO BE HERE!! I DON'T NEED MEDICINE!!!" The words of her patient echoed in her mind as her own echoed in her ears. She had taken the patient's story and words home with her and kept them in mind at an unconscious level to be brought up in her dream, the ultimate identification with the patient. How more intensely can one be empathic with her patient than to dream as if she is experiencing the same horrifying reality? The patient and resident continued to struggle, but after the dream the resident was able to approach the patient and her story from a position of understanding the patient's need to maintain a lack of awareness or absence of insight. To acknowledge the presence of the disorder was more than the patient's already fragmented ego could bear. And now the resident "heard" it.

Clinical Vignette 14

A 45-year-old divorced white woman, being followed for bipolar disorder and borderline personality traits and stable for several years on lithium, was in weekly psychotherapy. During the prior weekend she had moved into another apartment closer to her work. On the day of the move, she overslept and woke up with a start. The admonition to herself as she awoke was, "You lazy bitch!

You can never manage on your own." She had earlier, as a child, experienced a mother who was needy, engulfing, punishing, hostile, critical, and dependent upon the patient. Her therapist, having some knowledge of the patient and her background, said, "Your mother is still with you. It was she in your head continuing to bombard you with derogatory statements." The same patient was often 10 or 15 minutes late for sessions, and her therapist found herself irritated at the patient's habitual tardiness. To her own surprise and enlightenment, the therapist also found herself thinking, "What a chaotic woman! She'll never manage to be here on time." She, too, had heard the voice of her patient's mother. In the next session she wondered with her patient if she found herself wishing to place her therapist in the position of her mother, wanting at once to be engulfed and punished.

Clinical Vignette 15

A psychiatrist was treating a 40-year-old man who was in the process of recognizing his own primary homosexual orientation. In the course of treatment he became enraged, suicidal, and homicidal. After one session, the psychiatrist, while driving home, experienced the fantasy that when he got home he would find his patient already there, having taken the psychiatrist's family hostage. The psychiatrist became increasingly terrified, even outright paranoid that this fantasy might actually come to pass. The patient was a computer expert who had indeed discovered the unlisted phone number and address of his therapist. But the psychiatrist realized that this fantasy was far out of keeping with his own usual way of feeling and the patient's way of behaving and viewing him. On arriving home to discover his family quite safe, the psychiatrist called the patient and scheduled him as his first for appointment the following morning. When the patient arrived, the psychiatrist said, "You know, I think I'm only now beginning to appreciate just how terrified and desperate all of this makes you." The patient slumped down into his chair, heaved a sigh, and said, "Thank God!"

## Listening in Special Clinical Situations

### Children

Listening to younger children often involves inviting them to play and then engaging them in describing what is happening in the play action. The psychiatrist pays careful attention to the child's feelings. These feelings are usually attributed to a doll, puppet, or other humanized toy. So if a child describes a stuffed animal as being scared, the psychiatrist may say, "I wonder if you, too, are scared when…" or "That sounds like you when…." The following case is an example.

### Geriatric Patients

Working with the elderly poses its own special challenges. These challenges include not only the unique developmental issues they face but also the difficulty in verbalizing a lifetime of experience and feelings and, commonly, a disparity in age and life experience between the clinician and the patient.

It is challenging to elicit the elements of a story, especially when they span generations. The elderly are often stoic. In the face of losses that mark the closing years of life, denial becomes a healthy tool allowing one to accept declining abilities and the loss of loved ones. The psychiatrist must appreciate that grief and depression can often be similar in some respects.

Clinical Vignette 16

A 4-year-old boy was brought in for psychiatric evaluation. He and his father had come upon a very serious automobile accident. One person had been thrown from the car and was lying clearly visible on the pavement with arms and legs positioned in grotesque angles, gaping head wound, obviously dead. The child's father was an off duty police officer who stopped to assist in the extraction of two other people trapped in the car. The father kept a careful eye on the youngster who was left in the car. The child observed the scene for about 30 minutes until others arrived on the scene and his dad was able to leave. That night and for days to come, the child preoccupied himself with his toy cars that he repetitiously rammed into each other. He was awakened by nightmares three times in the ensuing weeks. During his evaluation in the play therapy room he engaged in ramming toy cars together. In addition, he tossed dolls about and arranged their limbs haphazardly. As he was encouraged to put some words to his action, he spoke of being frightened of the dead body and of being afraid to be by himself. He was afraid of the possibility of being hurt himself. He came in for three more play sessions, which went much the same way. His preoccupation with ramming cars at home diminished and disappeared as did the nightmares. The content of his play was used to help him put words and labels on his scare.

### Chronically Mentally Ill

Listening to the chronically mentally ill can be especially challenging, too. The unique choice of words characteristic of many who have a thought disorder requires that the physician search for their meanings and those of phrases that may be peculiar and truly eccentric. Clinical Vignettes 1, 10, and 12 are examples of this important challenge for the psychiatric listener.

Clinical Vignette 17

A psychiatrist was asked to examine an 87-year-old white man whom the family believed to be depressed. They stated that he was becoming increasingly detached and disinterested in the goings-on around him. When seen, he was cooperative and compliant, but he stated that he did not believe he needed to be evaluated. The patient had faced multiple losses over the past few years. After retiring at the age of 65, he had developed the habit of meeting male friends at a coffee shop each morning at 7 a.m. Now, all but he and one other were dead, and the other was in a nursing home with the cognitive deficits of primary dementia of the Alzheimer's type, preventing his friend from recognizing him when visiting. The patient's wife had died 15 years before after many years of marriage. He had missed her terribly at first but then after a year or so he got on with his life. Several years later, he suffered a retinal detachment that impaired his vision to the point that he was no longer able to drive himself to get about as he once had. What he missed most was the independence of going

*(continues)*

Clinical Vignette 17 *continued*

places when it suited him, rather than relying on his son or grandson to accommodate him within their busy schedules. He had taken to watching televised church services rather than trouble his son to drive him to church. His mind remained sharp, he said, but his body was wearing out, and all the people with whom he had shared a common history had died. His answers were "fine" and "all right" when questions of quality of sleep and mood were asked—despite the fact that he had experienced significant nocturia. When questioned about his ability to experience joy, he retorted, "Would you be?" His youngest sister had died the year prior to the evaluation. She was 76 years old and had been on home oxygen for the last 18 months of her life for end-stage chronic obstructive pulmonary disease. He had been particularly close to her because she had been only 3 years old when their mother had died. He had been her caretaker all her life.

Although he denied feelings of guilt, he said that it "wasn't right" that he had outlived the youngest member of his family. His family said that he had taken her death especially hard and was tearful and angry. The focus of his anger during the final stages of her illness was at the young doctors whom he perceived as having given up on her. After her death, it fell to him to dispose of her accumulated possessions as she had no children and her husband had preceded her in death many years before. At first he said that he couldn't face the task. Finally, some 2 months later, he was able to close her estate. During that period of time, he had significant sleep disturbance, reduced energy, and his family often experienced him as crotchety and complaining. They and the patient attributed it to mourning her loss. However, recently he was emotionally detached, not very interested in life around him, and they found it particularly alarming that he had said to his son that he was "ready to die." What did all this mean? Was he depressed? Was he physically ill, creating the sense of apathy and disinterest? Was he grieving? He was not suicidal. He did not suffer negative thoughts about his own personhood. He was not having thoughts that he had let anyone down. Together, he and the psychiatrist decided that he was indeed grieving. This time, he was grieving for his own decline and imminent death. He, in fact, was in the final acceptance phase of that process. In a family meeting, in the discussions about the feelings of each member of the family, it became apparent that he was facing the end of life, which evoked many emotions in those who loved him.

Clinical Vignette 18

A young man with schizotypal personality disorder and obsessive–compulsive disorder presented for months using adjectives describing himself as "broken and fragmented." Only after listening carefully, not aided by the expected or normal affect of a depressed person, was the psychiatrist able to discern that his patient was clinically depressed but did not have the usual words to say it or was unable to discuss it.

Chronically psychiatrically disabled patients may have a unique way of presenting their inner world experiences. Sometimes the link to the outer world is not so apparent. The psychiatrist is regularly challenged with making sense of the meanings of the content and changes in intensity or frequency of the psychotic symptoms.

### Physically Ill Patients

In consultations with a colleague in a medical or surgical specialty one is evaluating a patient who has a chronic or acute physical illness. The psychiatrist must listen to the story of the patient but also keep in mind the story as reflected via the hospital records and medical and nursing staff. Then the psychiatrist serves as the liaison not only between psychiatry and other medical colleagues, but also between the patient and his caregivers.

Clinical Vignette 19

A 32-year-old black woman who had multiple hospitalizations for schizophrenia and lived with her mother was seen in the community psychiatric center for routine medication follow-up. Her psychiatrist found her to have an increase in the frequency of auditory hallucinations, especially ones of a derogatory nature. The voices were tormenting her with the ideas that she was not good, that she should die, that she was worthless and unloved. Her psychiatrist heard her say that she had wrecked her mother's car 2 weeks previously. The streets had been wet and the tires worn. She had slid into the rear of a car that had come to an abrupt stop ahead of her on a freeway. Although her mother had not been critical or judgmental, the patient felt overwhelming guilt as she watched her mother struggle to arrange transportation for herself each day to and from work.

## Growing and Maturing as a Listener

Transference/countertransference influence not only relationships in traditional psychotherapy but also interactions between all physicians and patients; it is omnipresent as a filter or reverberator of that which is heard. Even the most experienced of listeners are not always aware of the ways in which their patients' stories are impacted by countertransference. Patients come, too, with tendencies and predispositions to experience the listener, the other person in the therapeutic dyad, in a familiar but distorted fashion. The patient may idealize and adapt to interpretations. She/he may be hostile and distrustful, identifying the psychiatrist unconsciously with one who has been rejecting in the past. Listening to the "flow of consciousness," the psychiatrist discerns a thread of continuity and purposefulness in the patient's communications. As the psychiatrist becomes more familiar with his patient, he discovers the connections between threads and the meaning becomes apparent. This awareness may come as a sign and symptom, fantasy, feeling, or fact.

There is an increasing recognition that to be a healing listener one must be able to bear the burden of hearing what is told. Like the patient, we fear what might be said. A patient's story may be one of rage in response to early childhood attachment ruptures or abuse, of sadness as losses are remembered, or of terror in response to disorganization during psychotic breaks. The patient's stories invariably evoke anger, shame, guilt, abject helplessness, or sexual feelings within the listener. These feelings, unless attended to, appreciated, and understood will block the listening that is essential for healing to take place. Every insight is colored by what the listener

has known. The psychiatrist comes with his own experiences and the experiences he has had with others. To listen in the manner we are describing here is another way of truly experiencing the world. The experiences include the imaginings of how it must be to be 87 years old as a patient when one is a 35-year-old doctor just finishing residency, to be female when one is male, to be a child again, to grow up African-American in a small white suburb of a large city, to be an immigrant in a new country, to be Middle Eastern when one is Western European, and so on. One comes to know by listening with imagination, allowing the words of the patient to resonate with one's own experiences or with what one has come to know through hearing with imagination the stories of others or listening to the thoughts or insights of supervisors.

**Clinical Vignette 20**

A 35-year-old woman was hospitalized for complications of a pancreas/kidney transplant that was completed 20 months previously. Prior to surgery she had been on dialysis for over a year awaiting a tissue match for transplantation. That year she had been forced to take a leave of absence from her job as a social worker with a local child and adolescent community center. At the time of this hospitalization, she had been back at work for only 8 months when she developed a urinary tract infection that did not respond to several antibiotics. Her renal function was deteriorating and her doctors found her to be paranoid, hostile, and labile. Her physicians dreaded going into her room each morning and began distancing themselves from her.

Psychiatric consultation was sought following a particularly difficult interaction between the patient and her charge nurse, the leader of the transplant team, and the infectious disease expert. She was hostile, blaming, agitated, circumstantial, refused further medications, and pulled out her intravenous lines. The consultation requested assistance in hospital management.

When interviewed, the patient was lying quietly in bed but visibly stiffened when the psychiatrist introduced herself. She very quickly exhibited the symptoms described in the consultation. This patient had struggled with juvenile onset diabetes since the age of 9. Despite the fact that she consistently complied with diet and insulin, control of blood sugars had always been difficult. As complication after complication occurred, she often developed the belief that her physicians thought that she was a "bad" patient. And now, the hope that her life would normalize to the point that she could carry on with her career was dashed. She felt misunderstood and alone in her struggle with long-term, chronic illness. The psychiatrist resonated with the story emotionally and listened for ways to address symptoms from a biological standpoint as well. The patient felt reassured that someone was there to appreciate the tragic turn that her life had taken.

The best psychiatrists continue all their professional lives to learn how to listen better. This may be thought of not only as a matter of mastering countertransference but also of self education. One must learn to recognize when there are impasses in the treatment and to seek education, from a colleague or, perhaps, even from the patient. Consider these two examples.

How can the psychiatrist's demeanor convey to the patient that he is safe to tell his story, that the listener is one who can be trusted to be with him, to worry with him, and serve as a helper? Much is written about the demeanor of the psychiatrist. The air, deportment, manner, or bearing is one of quiet anticipation—to receive that which the patient has come to tell and share in the telling. Signals of anticipation and curiosity may be conveyed by such statements as "I've thought about what you said last time," "How do you feel about . . . ?" "What if . . . ?"

**Clinical Vignette 21**

A Jewish resident was treating an 8-year-old Catholic boy who came in one day and mentioned offhandedly that he was about to go to his first confession. The psychiatric resident made no particular note of the issue and kept on listening to the boy's play and its themes. He noted that guilt, which had been an ongoing theme, was prominent again. When he presented the session in supervision the supervisor wondered about the connection. It emerged that there was a large gulf between the therapist and the boy. Jewish concepts of sin and atonement are different from Christian ones, and the rituals surrounding them have rather different intentions and ideas of resolution. The resident had missed the opportunity to explore the young boy's first introduction, within his religious context, to the belief in a forgiving God, a potentially important step in helping the child to resolve his ongoing struggles with guilt over his own greedy impulses.

**Clinical Vignette 22**

A psychiatrist began treating a Nigerian native who was suffering from posttraumatic stress disorder after being assaulted at work. After several sessions, the psychiatrist felt a sense of being at a loss in terms of what the patient was expecting out of their work and how the therapist was being seen by the patient. He then took several sessions to inquire of the patient about his tribe, its structure, family roles, definitions of healing, ideas of illness and wellness, etc. After this exploration, the psychiatrist adopted a different stance with the patient, heard the patient's communications very differently, and the therapy proceeded much more smoothly and comfortably to a successful conclusion.

Efforts of clarification often serve as bridges between sessions and communicate that the listener is committed to a fuller understanding of the patient. Patients have the need to experience the psychiatrist as empathic. Empathy describes the feeling one has in hearing a story that causes one to conjure up or imagine how it would have been to actually have had an experience oneself. How does one integrate all this so that it is automatic but not deadened by automaticity? How does the psychiatrist continue to hear the "same old thing" with freshness and renewal? How does one encourage the patient with consistency, clarity, and assurance in the face of uncertainty and occasional confusion? Not by assurance that everything will be all right when things might probably not be. Not by attempting to talk the patient into seeing things the clinician's way but rather by the psychiatrist's having the capacity to hear things his patient's way, from the patient's perspective.

Psychiatry is one of those rare disciplines where the experience of listening over and over again allows the listener

to grow in their capacities to hear and to heal. Hopefully, we get better and better as the years advance, become smoother, and develop a style that blends with our personality and training. We are renewed by the shared experiences with our patients.

Clinical Vignette 23

A Psychiatrist with 22 years of experience had recognized during his residency and early career that although he could effectively care for schizophrenic patients in a variety of settings, but when he attempted to follow them as outpatients, invariably they dropped out of treatment. The psychiatrist assumed that this must reflect some block he had based on having been partly raised by a relative with schizophrenia. Though the psychiatrist had engaged in his own therapy and done much soul-searching on the subject, the clinical limitation continued and the clinician simply accepted that this would be a group of patients he would have to refer for ongoing outpatient care.

However, after many years of experience, the psychiatrist decided to try once more. He began following a young man with paranoid schizophrenia who was on a complicated psychopharmacologic regimen. The course was stormy with periodic hospitalizations, but reasonably successful for several years until the patient began to have suicidal ideation and to call the psychiatrist after hours, something that had not been part of the clinical picture. The clinician found himself becoming very agitated and angry to the point where he realized his judgment might be distorted. He arranged hospitalization one weekend evening and resolved to work with the hospitalist then next day to transfer the patient to someone better equipped to meet his needs. That night, the psychiatrist had a dream. All he could recall was that his relative with schizophrenia was in it, and he awoke with the most profound feeling of helplessness he had ever experienced.

With the careerlong block now clarified, the psychiatrist approached the patient very differently and has continued to treat him successfully for 5 further years, comfortable at long last with his role as sharing the burden of this extraordinary illness with the patient.

To hear stories of the human condition reminds the psychiatrist that he, too, is human. There is time to make discoveries in the patient's stories from previous times, and maybe in previous patients. Patients will always endeavor to tell their stories. The psychiatrist continues to grow by being the perpetual student, always with the ear for the lesson, the remarkable life stories of his patients.

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CHAPTER 2

# Physician–Patient Relationship

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For centuries, healers had little understanding of disease and lacked the technologies we now know are necessary for the treatment and cure of many diseases. Physicians had few medications, and surgery was only a last resort. In fact, the most important tool for healing was the relationship between the physician and the patient. Interpersonal relationships have a powerful influence on both morbidity and mortality (House et al. 1988). Social connectedness enhances health in both direct and indirect ways: directly regulating many biological functions, decreasing anxiety, providing opportunities for new information, and fostering alternative behaviors (Hofer 1984). We know little about the basic mechanisms by which interpersonal relationships, and the physician–patient relationship in particular, operate (Ursano and Fullerton 1991). However, clinical wisdom holds that both the reality-based elements of the physician–patient relationship—in modern times referred to as the working alliance or the therapeutic alliance (Greenson 1965, Zetzel 1956)—and the fantasy-based elements of that relationship affect the patient's pain, suffering, and recovery from illness.

Physicians learned through trial and error to interact with their patients in ways that relieved pain and promoted health (Frank 1971). Often the physician's only interventions were reassuring patients, providing knowledge about the patient's disease, and accepting the patient's feelings of distress as normal. In this way, physicians increased patient's expectations of improvement and maximized their hope for the future. Although these interventions, based on wisdom and intuition, are no longer the only tools available to the physician, they continue to be an important part of the physician's and particularly the psychiatrist's therapeutic armamentarium.

The physician–patient relationship is also a source of information for the physician. The way the patient relates to the physician can help the physician understand the problems the patient is experiencing in her or his interpersonal relationships. The nature of the physician–patient relationship can also provide information about relationships in the patient's childhood family, in which interpersonal patterns are first learned. With this information, the physician can better understand the patient's experience, promote cooperation between the patient and those who care for her or him, and teach the patient new behavioral strategies in an empathic manner, understanding the patient's subjective perspective, that is, the patient's feelings, thoughts, and behaviors.

## The Placebo Effect

The nonspecific aspects of cure are often thought to be mystical or mysterious. In fact, in biological studies they are recognized as the placebo effect. Oddly, these effects of interpersonal relationships are both one of the prized and one of the most denigrated aspects of all of medicine. Yet, as clinicians, we all strive to alleviate our patients' pain and suffering and return them to health as soon as possible with whatever tools may help. Many well-designed studies show that 20–30% of subjects respond to the placebo condition. Recent studies show that analgesic placebo has similar neural mechanisms to opioid analgesia (Petrovic et al. 2002). The expectation of symptom improvement has been thought to play a critical role in the placebo effect and has been associated with increased endogenous striatal dopamine release in Parkinson's disease and increased endogenous opioid transmission in placebo analgesia. Neuroimaging studies such as functional magnetic imaging and positron emission tomography suggests that expectations of improvement are associated with the frontal cortical areas, especially the dorsolateral prefrontal, orbitofrontal and anterior cingulated cortices, as well as with the ventral striatum (Lidstone and Stoessl 2007). The problem with placebos is not whether they work but that we do not understand fully how they work and, therefore, we do not have control over their effects. As a physician, one strives to maximize one's interpersonal healing effects and, in this way as well as with other healing tools, increase the chances of our patients' relief from pain and of recovery.

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## Roles and Motivations

The physician–patient relationship includes specific roles and motivations. These form the core ingredients of the healing process. In its most generic form the physician–patient relationship is defined by the coming together of an expert and a help seeker to identify, understand, and solve the problems of the help seeker. The help seeker (in modern terms, the patient) is motivated by the desire and hope for assistance and relief from pain (Sullivan 1954). A physician is required to have a genuine interest in people and a desire to help (Lidz 1983). Simply stated, "the secret of the care of the patient is in caring for the patient" (Peabody 1927). Caring about and paying attention to a patient's suffering can yield remarkable therapeutic dividends. More than one attending physician has been reminded of this when a patient deferred making a treatment decision until he or she was able to consult with "my doctor," who turned out to be the medical student. Interestingly, the doctor–patient relationship has evolved over the ages from a paternalistic model of interaction to one that is more balanced, collaborative, and patient centered (Kaba and Sooriakumaran 2007). This approach has been described as one where "the physician tries to enter the patient's world, to see the illness through the patient's eyes" (McWhinney 1989).

The relationship between the physician and the patient is essential to the healing of many patients, perhaps particularly so for many psychiatric patients. The physician who can skillfully recognize the patient's half-hidden comment that he or she has not been taking the prescribed medication, perhaps hidden because of feelings of shame, anger, or denial, is better able to ensure long-term compliance with medication as well as to motivate the patient to stay in treatment. Regardless of the type of treatment—medication management, biofeedback, hospitalization, or psychotherapy—the relationship with the physician is critical to therapeutic outcome.

## Modern Medicine and the Physician–Patient Relationship

Modern medicine emphasizes a specific role for the physician in the relationship with the patient. In many Western countries, the patient comes for help with a specific problem, the doctor's office staff secures permission from a third-party payer for the doctor to conduct a particular treatment, a prescribed intervention, which will take a specified amount of time. Decades ago, when the doctor was neighbor, advisor, and friend to the patient and was routinely invited to important family events in the patient's life such as weddings of children, and when doctors routinely cared for more than one generation of the same family, the physician typically assumed that he or she would be a source of strength and assistance to the patient throughout the cycle of life. This meant more than curing a specific disease or relieving a specific pain.

Although today's patients may not consciously expect that the physician's influence and healing powers will take many forms in a complex interpersonal relationship, human nature is still the same, and patients still want from their doctors many nonspecific forms of emotional support which can promote a sense of well-being and better health. Though modern doctors may feel a great deal of time pressure to see many patients each day and to narrowly focus their healing efforts, the physician must also be sensitive to the many needs of patients, who believe that the physician is possessed of wisdom and understanding. Sensitivity to such desires and needs will promote effective and ultimately efficient medical care in all specialties, with all patients. A view that such patients are unusually needy and demanding will not serve the cause of effective medical care.

In today's technology-driven medicine, the importance and complexity of the physician–patient interaction are often overlooked. The amount of information the medical student or resident must learn frequently takes precedence over learning the fine points of helping the patient relax sufficiently to provide a thorough history or to allow the physician to palpate a painful abdomen. Talking with patients and understanding the intricacies of the physician–patient relationship may be given little formal attention in the medical school curriculum. Even so, medical students, residents, and staff physicians recognize, often with awe, the skill of the senior physician who uncovers the lost piece of history, motivates the patient who had given up hope, or is able to talk to the distressed family without increasing their sense of hopelessness or fear. Systematic review of randomized clinical trials and analytic studies of physician patient communication have demonstrated a positive influence of quality communication on health outcomes (Teutsch 2003). Frequent use of computers, telemedicine, and email as regular means of communicating with and relating to patients complicates the physician–patient relationship even further. Issues of confidentiality, trust, boundaries, and expectations of physician availability can affect the quality of the working relationship (Pearce and Trumble 2006, Spielberg 1998).

Finally, in today's mobile and geographically evermore united world, the importance of recognizing the needs of patients from parts of the world other than that of the physician's is a challenge to the practitioner. The physician must be open to the limitations of his or her knowledge of the expectations, beliefs, and likely behavior of patients from different cultures, nations, religions, and ethnic and socioeconomic backgrounds. The physician must recognize this challenge and, one hopes, embrace it with enthusiasm. It can make the practice of medicine a more exciting experience.

Clinical Vignette 1

A 20-year-old female patient suffered a painful athletic injury. She was unsure exactly how her injury had occurred, but she did recall falling on her shoulder on the tennis court while running after a sharply hit ball. She went to the physician fearing that she had damaged her collarbone. When she was informed that there was no fracture, that her pain was due to a bruised muscle and would go away with ice, heat, and aspirin, she immediately felt better. Not only was she relieved but also her perception and experience of the pain actually changed: "It doesn't seem to hurt as much now."

Clinical vignettes described throughout this chapter illustrate that the physician–patient relationship is composed of both the reality-based component (the working alliance or therapeutic alliance) and the fantasy-based component (the transference) derived from the patient's patterns of interpersonal behavior learned in childhood. Either or both of these may maximize or limit the patient's sense of reassurance, available information, feelings of comfort, and sense of hope (Meissner 1996). In this way, the nonspecific

Clinical Vignette 2

Somewhat different was the situation of a 30-year-old male patient who developed chronic pain after an athletic injury. The patient had to convince himself to visit the physician. He felt he was being a "baby" to complain. One week after the injury, he went to his family physician who perfunctorily prescribed a strong painkiller and offered a follow-up appointment a month later. He left feeling that he had been a nuisance. The following week was a particularly bad one for the patient; the pain was severe. But the patient stopped taking the prescribed medication, did not keep the follow-up appointment, and never returned for help. This patient continued to experience pain, unnecessarily, for years. In large part, this was because the physician offered no hope; therefore follow-up care, including physical therapy and alternative medications, could not be provided.

Clinical Vignette 3

A 45-year-old single man was hospitalized for treatment of a bleeding ulcer. The patient had no past history of ulcers. Despite reassurance, he continued to feel hopeless. A psychiatric consultant was called to evaluate the patient. She found him to be needy, but could not understand why he was so pessimistic. The psychiatrist recognized the importance to this patient of showing interest in him, showing concern for his condition, and spending time with him. The patient's response was noteworthy; he clearly enjoyed the psychiatrist's company but seemed unusually sad when their times together ended. The psychiatrist asked the patient if this was a correct perception and, if so, why it was the case. The patient responded that the psychiatrist reminded him of his mother. Further inquiry revealed that the patient's mother had died several years ago of colon cancer. The psychiatrist inquired about the symptoms the mother had during her terminal illness. The symptoms were similar to the patient's symptoms: bleeding in the digestive tract and gastrointestinal pain.

The psychiatrist then understood the complex process through which the patient was feeling inordinately pessimistic. Transference was evident in his experience of each departure as an unconscious reminder of the loss of his mother. The patient's identification with his mother (as part of managing her death) was also the source of his unspoken expectation that he, too, was dying of colon cancer. It was the pattern of the relationship between the psychiatrist and the patient, the sadness shown whenever the psychiatrist left, that provided the information necessary to help the patient. Increasing the patient's understanding of his medical condition, specifically how it was different from his mother's, relieved his emotional pain, and he began on the road to recovery.

curative aspects of the physician–patient relationship may be enhanced or diminished.

## Attachment Theory and the Physician–Patient Relationship

Attachment theory has been thought to play a significant role in the physician–patient relationship. It postulates that the innate need to form strong attachments to early caregivers is a basic component of human nature and is important in the formation and maintenance of relationships, in developing a sense of security and ultimately in survival (Thompson and Ciechanowski 2003). On the basis of the early experience of the responsiveness and accessibility of caregivers, a person develops expectations of the likely behavior of others and also one's own style of relating to people throughout one's life (d'Elia 2001). A doctor responsive to a patient's verbal and nonverbal needs may be seen as a supplementary attachment figure. Attachment theory has been widely applied to the physician–patient relationship in those with chronic medical illness and also in the palliative care setting (Tan et al. 2005).

Insecure attachment styles (dismissing, preoccupied, and fearful) have been shown to affect the physician–patient relationship and medical treatment outcomes. Ciechanowski et al. 2001 evaluated 367 patients with type 1 and type 2 diabetes in a health maintenance organization's primary-care setting. Those with dismissing attachment styles tend to undervalue the need for relationships, to minimize symptoms and to be overly self-reliant. They found that these patients had significantly worse glucose control than those with a preoccupied or secure attachment. The patients with dismissing attachment style were also more likely to have poorer glucose control and higher glycosylated hemoglobin levels. They were less likely to take oral hypoglycemics and monitor their blood glucose. Overall, the quality of their doctor–patient relationships was poorer and within this group those that rated the quality of the communication with their provider as poor had higher glycosylated hemoglobin levels compared to those who rated the communication as good.

An additional study by Ciechanowski et al. (2004) examined the influence of patient attachment style on self-care and outcomes through a population-based mail survey. They collected data on 4095 patients with diabetes from nine different primary-care clinics and found that dismissing attachment styles were associated with significantly lower levels of exercise, foot care, and higher rates of smoking and that these associations were mediated through the doctor–patient relationship.

## Formation of the Physician–Patient Relationship

### Assessment and Evaluation

The physician–patient relationship develops during the assessment and evaluation of the patient. The patient observes the thoroughness and sensitivity with which the physician collects information, performs the physical examination, and explains needed tests. At each step, the physician's clarification of the treatment goals and interventions either builds up the patient's expectation of help and feelings of safety or creates increasing distress and disease for the patient. In many aspects and, in particular, in the physician's compassion and patience, he/she is like a good teacher, establishing the context in which learning and growth may occur and anxiety decrease (Banner and Cannon 1997). Alertness to the patient's fears and misunderstandings of the evaluation process can minimize unnecessary disruptions of the relationship and provide information on the patient's previous experiences with medical care and important authority figures. These past experiences form the patient's present expectations of either help or disappointment (Smith and Thompson 1993) (Table 2–1).

**Table 2–1 Mechanisms for the Formation of the Physician–Patient Relationship**

| |
|---|
| Assessment and evaluation process |
| Development of physician–patient rapport |
| Therapeutic or working alliance |
| Transference |
| Countertransference |
| Defense mechanisms |
| Patient's mental status |

## Rapport

Early in the relationship between a psychiatrist and a patient, the patient requests help with his or her pain, uncertainty, or discomfort. The psychiatrist initiates the "contract" of the relationship by acknowledging the patient's pain and offering help. In this action, the psychiatrist has recognized the patient's ill health and acknowledged the need for and possibility of removing the disease or illness. In this first stage of the development of rapport, the way of relating between the physician and the patient, the physician–patient relationship has begun to organize the interactions. Through the physician's and the patient's shared recognition of the patient's pain, the basis for rapport—a comfortable pattern of working together—is established.

The psychiatrist's ability to empathize, to understand in feeling terms every patient's subjective experience, is important to the development of rapport. Empathy is particularly important in complex interpersonal behavioral problems in which the environment (family, friends, schools, caretakers) may wish to expel the patient, and the patient has therefore lost hope. Suicidal patients, adolescents involved in intense family conflicts, and patients in conflict with their medical caregivers can often be convinced to cooperate with the evaluation only when the psychiatrist has shown accurate empathy early in the first meeting with the patient. When the physician acknowledges the patient's pain, the patient feels less alone and inevitably more hopeful (Marziali and Alexander 1991). This rapport establishes a set of principles of and expectations for the physician–patient interaction. On this basic building block, more elaborate goals and responsibilities of the patient can be developed.

Clinical Vignette 4

A young man sought treatment for ill-defined reasons: he was dissatisfied with his work, his social life, and his relationship with his parents. He was unable to say how he thought the psychiatrist could help him, but he knew he was experiencing emotional pain: he felt sadness, anxiety, inhibition, and loss of a lust for living. He wanted help. The psychiatrist noted the patient's tentative style and heard him describe his ambivalence toward his controlling and directing father. With this in mind, the psychiatrist articulated the patient's wish for help and recognized with him his confusion about what was troubling him. She suggested that through discussion they might define together what he was looking for and how she might help him. This description of the evaluation process as a joint process of discovery established a rapport based on shared work that removed the patient's fears of control and allowed him to feel heard, supported, and involved in the process of regaining his health.

## The Therapeutic or Working Alliance

For a patient to trust and work closely with a physician, it is essential that there be a reality-based relationship outside the conflicted ones for which the patient is seeking help (Friedman 1969, Rawn 1991). With more disturbed patients, considerable skill is required of the physician to reach this reality-based part of the patient and decrease the patient's fears and expectations of attack or humiliation. Even for healthy patients, the physician must bridge the gap between the patient and the physician that is always present because of their different backgrounds and perceptions of the world. This gap is an expectable result of differences between the physician's and the patient's culture, gender, ethnic background, socioeconomic class, religion, age, or role in the physician–patient relationship. The experienced physician makes communication across the gap seem effortless, using a different "language" for each patient. The student often sees this as an art rather than as a skill to be learned.

The therapeutic alliance is extremely important in times of crisis such as suicidality, hospitalization, and aggressive behavior. But it is also the basis of agreement about appointments, fees, and treatment requirements. In psychiatric patients, this core component of the physician–patient relationship can be disturbed and requires careful tending. Frequently, the psychiatrist may feel that he or she is "threading a needle" to reach and maintain the therapeutic alliance while not activating the more disturbed elements of the patient's patterns of interpersonal relating.

The therapeutic or working alliance must endure in spite of what may, at times, be intense, irrational, delusional, characterologic, or transference-based feelings of love and hate. The working alliance must outweigh or counterbalance the distorted components of the relationship. It must provide a stable base for the patient and the physician when the patient's feelings or behaviors may impair reflection and cooperation. The working alliance embodies the mutual responsibilities both physician and patient have accepted to restore the patient's health. Likewise, the working alliance must be strong enough to ensure that the treatment goes forward even when both members of the dyad may doubt that it can. The alliance requires a basic trust by the patient that the physician is working in his or her best interests, despite how the patient may feel at a given moment. Patients must be taught to be partners in the healing process and to recognize that the physician is a committed partner in that process as well. The development of common goals fosters the physician and patient seeing themselves as having reciprocal responsibilities: the physician to work in a physician-like fashion to promote healing; the patient to participate actively in formulating and supporting the treatment plan, "trying on" more adaptive behaviors in the chosen mode of treatment, and taking responsibility for his or her actions to the extent possible (Ursano and Silberman 1988). The relationship must be able to tolerate periodic review of progress toward these goals—both successes and failures.

Important to the reality-based relationship with the patient is the physician's ability to recognize and acknowledge the limitations of her or his knowledge and to work collaboratively with other physicians. When this happens, patients are most often appreciative, not critical, and experience a strengthening of the alliance because of the physician's commitment to finding an answer. When a patient loses

confidence in the physician, it is often because of unacknowledged shortcomings in the physician's skills. The patient may lose motivation to maintain the alliance and seek help elsewhere. Alternatively, the patient may seek no help.

## Transference and Countertransference

Transference is the tendency we all have to see someone in the present as being like an important figure from our past (Freud 1958). This process occurs outside our conscious awareness; it is probably a basic means used by the brain to make sense of current experience by seeing the past in the present and limiting the input of new information. Transference is more common in settings that provoke anxiety and provide few cues to how to behave—conditions typical of a hospital. Transference influences the patient's behavior and can distort the physician–patient relationship, for good or ill (Adler 1980).

Although transference is a distortion of the present reality, it is usually built around a kernel of reality that can make it difficult for the inexperienced clinician to recognize rather than react to the transference. The transference can be the elaboration of an accurate observation into the "total" explanation or the major evidence of some expected harm or loss. Often the physician may recognize transference by the pressure she or he feels to respond in a particular manner to the patient; for example, always to stay longer or not abruptly leave the patient (Sandler et al. 1973).

Transference is ubiquitous. It is a part of day-to-day experience, although its operation is outside conscious awareness. Recognizing transference in the physician–patient relationship can aid the physician in understanding the patient's deeply held expectations of help, shame, injury, or abandonment that derive from childhood experiences.

Transference reactions, of course, are not confined to the patient; the physician also superimposes the past on the present. This is called countertransference, the physician's transference to the patient (Table 2–2). Reich observed that the psychotherapist "must be aware of what the material does to him, before he does something with the material" (Reich 1977). The emotional responses evoked by a patient may provide the physician with some sense of who the patient is, how he relates to others, what his internal world is like and what a relationship with this patient may involve (Ivey 2006). Countertransference usually takes one of two forms: concordant countertransference, in which one empathizes with the patient's position; or complementary countertransference, in which one empathizes with an important figure from the patient's past (Racker 1968). For example, concordant countertransference would be evident if a patient were describing an argument with his or her boss, and the psychiatrist, perhaps after a disagreement with the psychiatrist's own supervisor and without having collected detailed information from the patient, felt, "Oh yeah, what a terrible boss." Similarly, complementary countertransference would be evident if the same psychiatrist felt, "This person (the patient) does not work very hard, no wonder the boss is dissatisfied," and felt angry with the patient as well. Paying close attention to our personal reactions while refraining from immediate action can inform us in an experiential manner about subtle aspects of the patient's behavior that we may overlook or not appreciate. In the preceding example, the psychiatrist with the concordant countertransference might be identifying with the patient's subtle need to fight with authority. The psychiatrist with the complementary countertransference might have identified with the patient's boss, seeing only the patient's more passive wishes.

Countertransference occurs in all "sizes and shapes," more or less mixed with the physician's past but often greatly influencing the physician–patient relationship. The wish to save or rescue a patient is commonly experienced and indicates a need to look for countertransference responses. When a patient is seriously ill, such as with cancer, we may increasingly want to treat the patient more aggressively, with procedures that may hold little hope, create substantial pain, and perhaps even be against the patient's wishes. The physician's feelings of loss of a valued person (in the present and as a reminder of the past) or feelings of failure (loss of the physician's own power and ability) can often fuel such reactions. More subtle factors, such as the effects of being overworked, can result in unrecognized feelings of deprivation leading to unspoken wishes for a patient to quit treatment. When these feelings appear in subtle countertransference reactions, such as being late to appointments, becoming tired in an hour, or being unable to recall previous material, they can have powerful effects on the patient's wish to continue treatment.

Major developmental events in physicians' lives can also influence their perceptions of their patients. When a psychiatrist is expecting the birth of a child, she or he may be overly sensitive to or ignore the concerns of a patient worried about a significant illness in the patient's child. Similarly, a physician with a dying parent or spouse may be unable to empathize with a patient's concerns about loss of a job, feeling that it is trivial.

**Table 2–2** Types of Countertransference

| | |
|---|---|
| Concordant countertransference | The physician experiences and empathizes with *the patient's* emotional experience and perception of reality |
| Complementary countertransference | The physician experiences and empathizes with the emotional experience and perception of reality of *an important person from the patient's life* |

Clinical Vignette 5

A psychiatrist was called to evaluate an agitated older adult resident of a nursing home. After she had interviewed the energetic, sad, and anxious patient, the psychiatrist found herself unexpectedly sad, confused, and unsure about what to do. This was not a new case for the psychiatrist, who had treated many similar cases. In considering her response, her thoughts turned to her grandmother with whom she had lived when she was 8 years old, and who had been displaced from her residence and moved to a nursing home in another city by well-meaning children who wanted her near them. After the move, her grandmother had become depressed and disoriented and died 3 months later. The psychiatrist recalled feeling confused at the time of her grandmother's death, wondering why she had died when she had just moved to an attractive new home. Recalling her confusion, the psychiatrist could think more clearly about her present

patient and wondered if the patient might be depressed. She talked further with the nurses and found symptoms of depression in addition to the nighttime agitation. This new information altered her decision on the type of medication to begin with and the need for psychotherapy in addition to medication.

## Defense Mechanisms

All people, including patients, employ mechanisms of defense to protect themselves from the painful awareness of feelings and memories that can provoke overwhelming anxiety. Defense mechanisms are specific cognitive processes: ways of thinking that the mind employs to avoid painful feelings (Freud 1966). They are often characteristic of a person and form a style of cognition (Shapiro 1965). Common defense mechanisms include projection, repression, displacement, intellectualization, humor, suppression, and altruism (Table 2–3).

**Table 2–3** Common Defense Mechanisms

| Healthier Defenses | More Primitive Defenses |
|---|---|
| Sublimation | Splitting |
| Humor | Projection |
| Repression | Projective identification |
| Displacement | Omnipotence |
| Intellectualization | Devaluing |
| Reaction formation | Primitive idealization |
| Reversal | Denial |
| Identification with the aggressor | Conversion |
| Asceticism | Avoidance |
| Altruism | |
| Isolation of affect | |

Defense mechanisms may be more or less mature depending on the degree of distortion of reality and interpersonal disruption they lead to. This patterning of feelings, thoughts, and behaviors by defense mechanisms is involuntary and arises in response to perceptions of psychic danger (Vaillant 1992). The patient's characteristic defense mechanisms, the cognitive processes used to lower anxiety and unpleasant feelings, can greatly affect the physician–patient relationship. Defense mechanisms operate all the time; however, in times of high anxiety, such as in a hospital or during a life crisis, patients may become much less flexible in the defenses they use and may revert to using less mature defenses.

Clinical Vignettes 6 and 7 are examples of defense mechanisms (conversion and avoidance or repression) affecting the treatment relationship. In Vignette 6, the conversion reaction that resulted in the paralysis expressed both the patient's anger and his conflict over what to do. In Vignette 7, the physician knew that the forgetting was neither intentional nor conscious but was directed at denying the need for treatment. In these cases, recognizing the defenses was important to knowing how to relate to the patient (Clinical Vignette 6) and avoid a countertransference reaction of anger at the patient for lack of compliance (Clinical Vignette 7).

Clinical Vignette 6

A 36-year-old army first sergeant was hospitalized for the evaluation of acute paralysis of his right hand. When the results of a neurological workup revealed no evidence of organic pathology, psychiatric consultation was obtained. The patient denied any past psychiatric history or significant alcohol or other substance abuse. He described a healthy family support system but then hesitated, saying, "You know, Doc, there's one thing I just haven't been able to talk about with anyone." He proceeded to speak of the extreme pressure he was feeling on the job, where he had found out that his boss (the company commander) was behaving unethically. The patient stated, "I feel like I'm between a rock and a hard place—if I report it, I'm being disloyal to my boss, but if I don't, I'm betraying my soldiers and the army." After further elaborating his feelings of anger and disgust toward his boss, the patient asked to terminate the interview but agreed to talk with the psychiatrist again in the morning.

Returning the next morning, the psychiatrist was greeted by the patient, who was brushing his teeth, using his right hand. "Hey, Doc, I'm good to go!" The patient then described what happened the evening before. "I was telling my wife about how I've got to get out of here and get back to work, because, after all, I'm the commander's right-hand man. And you know what, Doc? My hand started to work! Get me out of here, I'm not crazy after all!" The patient then reviewed the process, aided by the psychiatrist, and was able to further his understanding of the link between his conflicted rage toward his boss and how it was expressed symbolically as an involuntary physical paralysis of his right hand. He resolved: "I'm gonna do the right thing. I got to live with myself," and planned to report the commander's misconduct on return to work. He was discharged from the hospital later that day, having regained full use of his hand.

Clinical Vignette 7

A 20-year-old man came for consultation because of uncertainty about his career. He soon revealed that he felt profoundly sad, hopeless, helpless, and even suicidal. He had a family history of depression. The physician and patient agreed to employ antidepressant medication aggressively. Yet over a period of several weeks the patient did not improve. When the physician asked why that might be happening, the patient revealed that he had frequently forgotten to take the prescribed medication and had forgotten to tell the physician that this was the case during two meetings. The physician explored the reasons for this, and together the physician and the patient learned that the patient felt ashamed of having been diagnosed as depressed and of having been considered to require medication. He felt he was not his own master and had experienced this as a severe blow to his self-esteem. Taking the medication was a reminder of this "flaw." Hearing himself say this and feeling the physician's empathic support, the patient recognized the irrationality of his behavior and felt relieved. In addition, the physician now understood better the intensity of the patient's feelings and changed the prescription to once-a-day dosage at bedtime to decrease the patient's sense of shame and increase compliance with the treatment.

## Mental Status of the Patient

The patient's mental status is a major determinant of the formation and nature of the relationship with the physician. A young, healthy patient with an acute disorder has different needs and expectations than a somewhat older person who comes for help with a condition that has been present for a number of years. Both differ from the older adult who comes to the physician expecting that the future will be filled with physical and emotional losses.

It can be seen when comparing these two clinical vignettes (8 and 9) that the mental status of the patient helps define the nature of the physician–patient relationship, though in both cases the treatment relationship was of relatively brief duration and ended successfully.

Clinical Vignette 8

A 25-year-old recent law school graduate came to a psychiatrist following a romantic disappointment. He reported that he was very sad because his girlfriend had chosen to move to a different city, which he believed foretold the end of their relationship. He added that he had been having trouble sleeping for several weeks, and was worried because his exhaustion was causing problems in his ability to perform his work. When the physician took a careful history, he learned that this young man had led a successful life, and that his social and sexual development had been quite unremarkable. He had had good friends and close friendships, and several girlfriends in his life. He said he would miss his girlfriend, but that he never intended to marry her. The doctor indicated to her patient that sometimes, after such a disappointment, it was quite common for there to be a period of anxiety and that his sadness was a good sign, showing that he had a good capacity to attach and mourn the loss of a close friend. The psychiatrist also suggested that the patient may be more angry with the girlfriend than he had recognized, with which the patient agreed. The doctor prescribed a mild sleep medication, suggesting it may not even be required, and scheduled a follow-up appointment in a month. When the patient returned, he reported that he had used only two of the sleeping pills and had thrown the rest away. He did not want to schedule another appointment; he expressed gratitude to the psychiatrist and they parted company.

Clinical Vignette 9

A 70-year-old widowed lawyer was vigorous, active, financially comfortable, with many friends and professional associates. She explained to the psychiatrist that the last year had, however, been very difficult for her. Six months before, her husband of 45 years had died after a 2-year struggle with congestive heart failure. She now found herself seriously depressed, despite her active life. She was thinking actively about giving up her law practice, though she was very involved in several ongoing cases, which she had previously found interesting and which held the promise of significant financial reward. She went on to say that she had no appetite. She was chronically sleep deprived and was losing interest in her friends, children, and grandchildren. When taking a careful history, the psychiatrist also learned that this patient had suffered from a serious depression 35 years earlier, when she lost a pregnancy, and that this depression lasted for a year. It eventually resolved after she took a tricyclic antidepressant and engaged in brief, insight-oriented psychotherapy. In that therapy, her relationship with her own depressed mother had been discussed. With all this information, the psychiatrist suggested she and her patient meet weekly and that the treatment include a pharmacological intervention to help with the patient's current depression. This treatment ended successfully 1 year later.

The patient's mental status in this case (Clinical Vignette 10) was the focus of and major factor in the structure of a long psychotherapy that greatly assisted the rehabilitation of interpersonal skills and the understanding of his cognitive limitations and newly changed cognition. The ability to work with an empathic listener while confronting limitations and feelings of shame and embarrassment is a special opportunity of the well-formed doctor–patient relationship.

Clinical Vignette 10

A 40-year-old man came to a psychiatrist with a long history of emotional difficulties. He had been a healthy and happy college student when he developed a skin abscess, which caused a septicemia and a brain infection. After this, his entire life changed. Although college was quite challenging, he was able to finish it, but had difficulty concentrating, his judgment was poor, his impulse control impaired. He had difficulty remembering words, and he realized that his previously adequate social skills had been lost. Where once he had been charming and known for his sense of humor, now he was dull and in many ways boring. Yet there was more to him than that, and he longed for an opportunity to speak with an understanding listener in the hope that through such a relationship he might be able to make constructive changes in his life. He knew what had been lost, he wanted to understand his limitations better, and he wanted to be able to function well enough to keep a job. A more remote goal was to have a long-term relationship with a woman. His consulting psychiatrist knew that were she to take on this patient it would be for the long haul. Fortunately, there were no financial barriers to treatment, and the pair worked together on a weekly basis for many years. In the course of that treatment, the patient came to understand the social situations that made him anxious and the way his emotional states of mind influenced changes in his cognitive function. He developed the ability to work and love more effectively; he met a woman who was kind and loving. The psychiatrist was invited to his wedding. She attended the religious service but quietly left the reception after congratulating her patient and his wife. By that time, years into the physician–patient relationship, the patient saw his physician as a wise observer, an advisor, and a trusted friend. To the physician, her patient was a happy reminder of how much a person can strive to improve his life, and a rich source of learning about the interaction of emotion, cognitive function, and behavior.

## Research on the Physician–Patient Relationship

Research examining the physician–patient relationship has focused primarily on studies of psychotherapy. In general,

the research confirms what clinicians have long recognized: the physician–patient relationship is central to behavioral change in nearly all treatment modalities (Martin et al. 2000). The therapeutic alliance has been and continues to be the most studied aspect of the psychotherapy process (Orlinsky et al. 1994). A relatively large body of research has consistently documented that the quality of the therapeutic alliance correlates positively with therapeutic change across a variety of treatment modalities and clinical issues (Castonguay et al. 2006). Pioneered by Roger's (1957) view of the therapeutic relationship as providing "necessary and sufficient conditions" of change, psychotherapy process outcome studies have focused both on identifying the effects of particular components of the therapeutic alliance and on identifying the effects of the alliance on outcome (Orlinsky et al. 1994). The literature seems to also indicate that alliance quality correlates positively with some patient characteristics (psychological mindedness, expectation for change, quality of relationships) and negatively with others (e.g., avoidance, interpersonal difficulties, depressogenic cognitions) (Constantino et al. 2002) Research also suggests that certain qualities of the therapist are positively associated with quality alliances (warmth, flexibility, accurate interpretation) while other characteristics may be associated with difficulties with the alliance (rigidity, criticalness, inappropriate self-disclosure) (Ackerman and Hilsenroth 2003). Current research focuses on the patient's affective relationship to the therapist, the patient's capacity to work purposefully in therapy, the therapist's empathic ability, and their mutual agreement on the goals and tasks of therapy (Gaston 1990, Horvath and Luborsky 1993).

Psychotherapy outcome research has used meta-analysis to attain efficient and maximally objective integrative summaries of existing studies (Strube and Hartman 1983). Early studies focused on determining the extent of the benefit associated with psychotherapy in the existing literature as a whole, compared the outcomes of different treatments, and examined the impact of methodological features of studies on the reported effectiveness of treatments. Smith and colleagues (1980) found an average effect size of 0.85 standard deviation units for 475 studies comparing treated and untreated groups. This means that, after treatment, the average treated person was better off than 85% of the untreated sample.

Subsequent meta-analytic reviews of specific disorders likewise have yielded promising results. For depression, five meta-analytic reviews totaling 133 studies showed effect sizes ranging from 0.65 to 2.15 standard deviation units. For agoraphobia, three meta-analytic reviews totaling 95 studies showed effect sizes ranging from 1.2 to 2.10 units. For obsessive–compulsive disorder, two meta-analytic reviews totaling 43 studies showed effect sizes ranging from 1.34 to 1.37 units (Lambert and Bergin 1994).

Orlinsky and colleagues 1994 used meta-analysis for more than 2,300 findings on process outcome from approximately 300 psychotherapy studies conducted between 1950 and 1992. They concluded that the strongest evidence supports the importance of the therapeutic alliance to outcome, with more than 1,000 significant findings. The relationship of outcome to therapeutic alliance is particularly strong when the alliance is measured from the patient's perspective; for example, it is perhaps more important that the patient feels understood and valued than that the therapist thinks this is so. What therapists do, when they do it, and whether they are genuine in doing it all matter to patients, as does the level of the patient's emotional involvement in the process (Orlinsky et al. 1994). From the perspective of the therapeutic alliance, the therapist contributes to helping the patient achieve a favorable outcome mainly through empathic, affirmative, collaborative, and self-congruent engagement with the patient (Lambert and Bergin 1994).

Although there are many therapies, each with its own theoretical basis and specific techniques, there is only modest evidence to suggest the superiority of one school or technique over another. Common factors, which include the therapeutic alliance, loom large as the major mediators of treatment outcome. Research on specific techniques and research on common factors, however, are not necessarily in opposition (Docherty 1985). A growing number of researchers and clinicians assert that research cannot hope to separate the unique contributions of techniques and common factors to outcome. In this view, techniques are interpersonal and gain their meaning from the particular interaction of the individuals involved (Butler and Strupp 1986, Karasu 1986, Norcross and Goldfried 1992). Studies are needed to investigate the change processes associated with each of the various psychotherapeutic approaches, so as to determine which are common to all and which are unique (Goldfried 1991). Joyce et al. examined meta-analytic reviews of the effectiveness of psychotherapy, the movement to identify empirically supported treatments and research on the "common factor" or "contextual" models of psychotherapy. The studies supported two conclusions: (1) psychotherapy is superior to the absence of treatment and (2) different approaches to psychotherapy showed equivalent results. "Considerable evidence supports the importance of common factors as mechanisms of change; at present however, this relationship is predominantly correlational" (Joyce et al. 2006). Further research is needed to clarify these relationships. A converging of psychotherapeutic techniques from various perspectives will require a new understanding of our psychotherapeutic interventions as well as a rethinking of our methods of teaching, practicing and researching these.

Based on the existing evidence, the therapeutic alliance accounts for much, if not most, of the gains that result from therapy. This confirms the importance of the alliance for change. Further study is needed of the therapeutic alliance in treatment settings other than psychotherapy. In the interim, the data support the notion that physicians may enhance clinical outcomes by intentionally incorporating the components of the therapeutic alliance into their relationships with patients (Lambert and Bergin 1994).

Researchers have long debated the meaning of the term alliance in psychotherapy research and many note the limitations of the research secondary to a lack of a "consensual definition of the construct" (Hovarth 2006). Some maintain that the concept of alliance is limited to the more psychodynamically informed psychotherapies. However, others assert that the therapeutic alliance is a universal concept that exists in all treatments regardless of the extent to which it is explicitly formulated theoretically (Meissner 2006). Meissner even conceptualizes the alliance in broader terms than are typically used in research including elements of the therapist's empathy and neutrality. Others such as

Safran and Muran (2006) propose the alliance should comprise shifts in the quality of the therapeutic relationship at the conscious and unconscious level. It is clear that "greater specificity in identifying the alliance, as part of larger, common therapeutic relationship and within particular theoretical orientations, respectively is an essential step in future work" (Samstag 2006).

Other future directions of research may include a more careful study of the therapeutic processes in which the alliance does not develop or in which it ruptures. In this way, we may better understand the way in which alliance affects outcome (Castonguay et al. 2006). Crits-Christoph et al. (2006) write of the importance of examining for reverse causation, which is the concept that the alliance does not cause the outcome but instead early improvement in therapy creates a positive alliance. Additionally, research needs to examine the possibility of third variables such as patient personality style that might influence both alliance and treatment outcome (Crits-Christoph et al. 2006).

## Special Issues in the Physician–Patient Relationship

### Phase of Treatment

The treatment phase—early, middle, or late (Table 2–4)—affects the structure of the physician–patient relationship in terms of both the issues to be addressed and the task to be accomplished by the physician and the patient. The early stage of treatment involves developing a rapport, forming shared initial goals, and initiating the working alliance. Education of the patient is important to the success of the physician–patient relationship in this stage, so that the patient learns what he or she can expect. In the middle stage of treatment, the physician and patient continuously refine their shared goals, and various interventions are tried. While this takes place, transference and countertransference are likely to emerge. How these are recognized and managed is critical to whether the relationship continues and is therapeutic.

**Table 2–4** Key Features of Treatment Phases

| |
|---|
| Early: developing rapport, forming shared initial goals, initiating the working alliance |
| Middle: refining shared goal, using a variety of trial interventions |
| Late: assessing outcome, resolving presenting problems, planning for future |

In the later phase of treatment, the assessment of the outcome and plans for the future are the primary focus. The physician and the patient discuss the end of their relationship in a process known as termination. Successes and disappointments associated with the treatment are reviewed. The physician must be willing to acknowledge the patient's disappointments, as well as recognize her or his own disappointments in the treatment. The therapeutic alliance is strengthened in this stage when the physician accepts expressions of the patient's disappointments, encourages such expressions when they are not forthcoming, and prepares the patient for the future. Such preparations include orienting the patient as to when he or she might seek further treatment (Ursano and Silberman 2002). Solidifying the physician–patient relationship at the end of the treatment can be critical to the patient's self-esteem and willingness to return if symptoms reappear (Table 2–5).

**Table 2–5** Factors Affecting the Physician–Patient Relationship

| |
|---|
| Phases of treatment: early, middle, late |
| Treatment setting |
| Transition between inpatient and outpatient treatment |
| Managed care |
| Health and illness of the physician |

As a part of the termination process the physician and the patient must review what has been learned, discuss what changes have taken place in the patient and the patient's life, and acknowledge together the sadness and joy of their leave-taking. The termination involves a mourning process even when treatment has been brief or unpleasant. Of course, when the physician–patient relationship has been rewarding, and both physician and patient are satisfied with what they have accomplished, mourning is more intense and often characterized by a bittersweet sadness.

### Treatment Settings

The physician–patient relationship takes place in a variety of treatment settings. These include the private office, community clinic, emergency room, inpatient psychiatric ward, teaching hospital clinic, and general hospital ward. Psychiatrists treating patients in a private office may find that the relative privacy of this setting enhances the early establishment of trust related to confidentiality. In addition, the psychiatrist's personality is more evident in the private office where personal factors influencing choice of decor, room arrangement, and location play a role. However, in contrast to the hospital or community setting, the private office generally lacks other evidence of the physician's competence and humanness. In hospital and community settings, when a colleague greets the physician and the patient in the hall, or the physician receives a call for a consultation by a colleague or for a meeting, it indicates to the patient that the physician is qualified, skilled, and humane.

On the other hand, therapeutic work conducted in the community clinic, emergency room, and general hospital ward often requires the psychiatrist and patient to adapt rapidly to meeting one another, assessing the problem, establishing treatment goals, and ensuring the appropriate interventions and follow-up. The importance of protecting the patient's needs for time, predictability, and structure can run counter to the demands of a busy service and unexpected clinical and administrative requirements. The psychiatrist must stay alert to the patient's perspective but not all interruptions can be avoided. The patient can be informed and accommodated as much as possible, and any feelings of hurt, disappointment, or anger can be listened for by the physician and responded to empathically. At times, patients, particularly those with borderline personality disorder, may require transfer to another psychiatrist whose schedule can accommodate the patient's exquisite needs for stability.

The boundaries of confidentiality are necessarily extended in hospital and community settings to include

consultation with other physicians, nursing staff, and often family members (Wise and Rundell 2002). Particular attention must always be given to the patient's need for and right to respect and privacy. Regardless of the setting, patients receiving medication must be fully informed about the potential risks and benefits of and alternatives to the recommended pharmacological treatment (Kessler 1991). Patients must be educated about the risks and benefits of receiving prescribed treatment and of not receiving treatment. This is an important component of maintaining the physician–patient relationship. Patients who are informed about and involved in decisions about medication respect the physician's role and interest in their welfare. Psychiatrists must also pay particular attention to the meaning a patient attaches to any prescribed medication, particularly when the time comes to alter or discontinue its use (Ursano et al. 1991).

### Transition Between Inpatient and Outpatient Treatment

Many psychiatric treatments include the sheltered environment of a hospital for at least some time. The purpose of this environment is to provide the patient with a safe refuge, a moratorium during which stressors are reduced, supportive assistance is provided, and an inner equilibrium is reestablished in the mind and life of the patient. In this situation, the patient is temporarily relieved of some elements of personal responsibility, at least, compared with what is expected of that person in the community. This difference is reflected in the relationship between physician and patient. The change from inpatient to outpatient therapy involves the resumption of a greater degree of autonomy by the patient in the physician–patient dyad. The physician must actively encourage this separation and its hope for the future. This transition is delicate for any therapeutic pair.

So, too, is the extremely delicate situation that occurs when the patient must switch physicians for any reason. This often occurs when a patient leaves the hospital and begins outpatient work with a new therapist. It may also occur in a teaching hospital clinic in which residents rotate annually. Discussing with the patient the skills and abilities of the receiving physician can alleviate much anxiety and foster the new physician–patient relationship. The knowledge that the receiving physician is known and respected by the present physician is a powerful endorsement. In difficult cases, in which the strength of the therapeutic alliance is critical to the stability of the patient, as is seen in some psychotic disorders and with some patients with borderline personality disorder, it may be helpful to hold a joint meeting before the transfer. At this meeting, both the new and the old physicians should be present; the patient can be scheduled for an appointment with the new physician in the same week.

### Managed Care

Managed care, broadly defined as any care of patients that is not determined solely by the provider, currently focuses on the economic aspects of delivering medical care, with little attention thus far to its potential effects on the physician–patient relationship (Goodman et al. 1992). Discontinuity of care and the creation of unrealistic expectations on the part of patients have been raised as likely deleterious effects on that relationship (Emanuel and Brett 1993). Other issues that can affect the physician–patient relationship include the erosion of confidentiality, shrinkage of the types of reimbursable services, and diminished autonomy of the patient and the physician in medical decision-making. Additionally, many managed care systems dictate a split treatment model, with the psychiatrist prescribing psychopharmacologic treatment and a separate clinician providing psychotherapy. In such a system, there are complicated challenges faced both by clinicians and patients. With neither party in complete control of decisions, the physician–patient relationship can become increasingly adversarial and subservient to external issues such as cost, quality of life, political expediency, and social efficiency (Siegler 1993).

Psychiatrists can best serve their patients by continuing to conduct thorough diagnostic assessments covering the biological, psychological, and social aspects of the patients' conditions to determine the most effective plan for treatment (Engel 1980). This plan should be openly shared with the patient regardless of whether economic considerations render it infeasible. The psychiatrist and patient may then work together to make the best of what is possible, both aware of the societal and individual factors influencing their actions. (For a more detailed discussion of this topic, see Chapter 5.)

### Health and Illness of the Physician

Psychiatrists, like all people, become ill, and the illness can affect their ability to work effectively. Reactions of denial, projection, and hopelessness, to name but a few of the possibilities, can distort the psychiatrist's vision of the patient. The psychiatrist may be blinded to the patients' suffering, or see it as if it were his or her own or, worse yet, as a hopeless situation. In some instances, a physician who is ill must leave a practice temporarily or permanently, and in that situation therapy enters a late phase in which termination must take place. In some cases, when the onset of illness is devastating, this can be impossible; in other cases termination may have to be rapid. Sometimes, such as when the physician dies suddenly, colleagues must step in to conduct the termination of therapy or the patient's transfer and transition to another physician (Lasky 1990, Simon 1990).

Another situation that may impact the doctor–patient relationship occurs with the pregnancy of the physician. Patient's issues about fertility, parenting, loss may arise. Careful discussion and preparation for any planned or anticipated leave may be helpful as well. Referral to a covering physician during this time is helpful.

Depression and grief can also impair the physician's ability to make use of accurate empathy and medical decision-making. It is important for physicians to stay alert to these influences and seek clinical supervision or consultation to ensure accurate decision-making and a consistent physician–patient relationship. A thoughtful colleague who recognizes the role of depression and grief in the life course can assist in any treatment that is needed and also help to provide a necessary period of clinical supervision or consultation.

## The Physician–Patient Relationship in Specific Populations of Patients

### Cross-Cultural and Ethnic Issues

Addressing cross-cultural issues such as race, ethnicity, religion, and gender is vital to the establishment and

maintenance of an effective physician–patient relationship (see Chapter 4). Psychiatry, as practised in the US, generally represents the value orientation of the American middle-class family, emphasizing individualism, scientific rationale, free expression of speech, and tolerance of dissent (Kinzie 1978). Accordingly, therapists may unconsciously make value judgments stemming from their personal cultural perspective without adequate appreciation for the diversity of normal behavior (Ursano and Fullerton 1991). For example, assertiveness may be seen as manipulativeness, stoicism as passivity, religious ritual as compulsion, competence as dominance, unselfishness as masochism, charm as seductiveness, lack of concern with appearance as depression, family orientation as dependency, and homosexuality as perversion. Even similarities in background may create misunderstanding, in that both physician and patient may make unjustified assumptions or fail to explore certain behaviors or symptoms because the reasons for them seem self-evident. Failure to clarify cultural assumptions, whether stemming from differences or similarities in background, may impede the establishment of a trusting therapeutic alliance, making effective treatment unlikely (Cheng and Lo 1991).

Every individual is inevitably like everyone else, like someone else, and like no one else (Kluckhohn and Murray 1953). Thus, every physician–patient relationship involves the individuals, their unique past, and their interpersonal histories (Gabbard 2000). Maintaining a thoughtful awareness of and appreciation for the influence of cross-cultural issues can enrich and empower the physician–patient relationship.

When psychiatrists work with a patient who belongs to or identifies with a particular ethnic or minority group, they are well advised to learn about the culture of the patient and use caution in making assumptions based on stereotypical or popular beliefs. This is true even when the psychiatrist has the same ethnic or minority group background. Other significant cross-cultural factors include gender, sexual orientation, physical appearance, religious background, and personal experience (Comas-Diaz and Jacobsen 1991). Often, asking the patient how an event would be seen or understood from their country or cultural perspective can place the physician in the role of interested and helpful learner that the patient will appreciate.

Ethnicity, culture, and race can stir deep unconscious feelings in many individuals. These feelings may surface as projections in the physician–patient relationship. The physician must strive to understand what it is like to live in the patient's world, no matter how different its patterns or values may be from those of the physician's world. Maintaining therapeutic neutrality may be difficult and, in some cases, may require the physician to seek consultation (Kleinman 1991).

## Children, Adolescents, and Families

Establishing an effective physician–patient relationship with children, adolescents, and families is one of the most challenging and rewarding tasks in the practice of psychiatry. Rather than being treated as "little adults," children and adolescents must be approached with an appreciation for their age-appropriate developmental tasks and needs. When physicians treat this population, they must establish a trusting relationship with both the patient and the parents. Preadolescent children face the psychosocial developmental tasks of establishing trust, autonomy, initiative, and achievement. By understanding the facets of normal childhood development, physicians may help parents understand the nature of their child's disturbance and work within the family system to establish effective mechanisms for coping and recovery (Angold 2000, Erikson 1950).

Adolescent patients, facing the task of establishing an individual identity, pose particular challenges to the physician–patient relationship. Adolescents *can be* particularly sensitive to any signals from the physician that their powers of decision, their intelligence, or their perceptions are being ignored. The critical time for engagement with the adolescent is often in the first session, sometimes even in the first few minutes (Katz 1990). Defiance, detachment, and aggression may be anticipated and defused with a steady therapeutic presence grounded in consistent boundaries and open acknowledgment of the adolescent patient's distress (Colson et al. 1991).

In working with families, physicians in general and psychiatrists in particular must clearly address questions and concerns regarding all aspects of treatment and convey respectful compassion for all members. The therapeutic alliance, or "joining" with the family and patient, requires developing enough of a family consensus that treatment is worth the struggle involved. Taking sides and engaging with individual and family power struggles can be particularly destructive to the physician–patient relationship in families. Rather, it is the physician's ability to relate to the family as a multifaceted organism, massively interconnected, transcending the sum of its parts, that often allows treatment to progress and, in the best scenarios, allows for growth and understanding to occur (Fleck 1985, Ziegler 1999).

## Terminally Ill Patients

Terminally ill patients share concerns related to the end of the life cycle. Elderly patients at all levels of health face the developmental task of integrating the various threads of their life into a figurative tapestry that reflects their lifelong feelings, thoughts, values, goals, beliefs, experiences, and relationships and places them into a meaningful perspective. Patients newly diagnosed with a terminal illness such as metastatic cancer or acquired immunodeficiency syndrome may be particularly overwhelmed and initially unable to deal with the demands of their illness, especially if the patient is a younger adult or child. Psychiatrists may enhance the terminally ill patient's ability to cope by addressing issues related to medical treatment, pharmacotherapy, psychotherapy, involvement of significant others, legal matters, and institutional care (Lederberg and Holland 2000). Patients struggling with spiritual or religious concerns may benefit from a religious consultation, a resource that is frequently unused.

Countertransference feelings ranging from fear to helplessness to rage to despair can assist the therapist greatly in maintaining the physician–patient relationship and ensuring appropriate care. Physicians working with patients with acquired immunodeficiency syndrome must frequently confront their own feelings and attitudes toward homosexuality (McKusick 1988). Issues commonly encountered with disabled patients include inaccurate assumptions about their ability to function fully in all areas of human activity, including sex and vocation. Terminally ill patients may evoke reactions of unwarranted pessimism, thwarting the

physician's ability to help the patient maximize hope for the quality of whatever time may remain. Patients and their family members often look to their physician for guidance.

### Physicians, Important Persons, and Relatives

Treating other physicians, important persons, and personal relatives poses significant risks that must be actively addressed within the physician–patient relationship. Patients who are physicians are frequently expected to assume greater responsibility for their care and, if there is evidence of poor compliance, to "know better." Relinquishing control and acknowledging dependency run counter to the professional development of most physicians, who are accustomed to caring for others and may fear becoming a burden. Furthermore, they may refrain from asking pertinent questions to avoid further embarrassment and humiliation (Lederberg and Holland 2000).

Patients who are important persons or personal relatives pose similar challenges. With these patients and with other physicians, the treating physician may feel insecure and under increased pressure to perform flawlessly. Psychiatrists risk losing their usual assessment benchmarks when making exceptions to standard practice habits in recognition of a patient's special status. Difficult transferential issues for the physician include managing self-esteem, overidentification with the patient, ethical boundaries, and the potential dilemmas arising from ruptured treatment. Professional identification, awe of celebrity, and personal attachment exert tremendous pressures that can tax even the most seasoned psychiatrist in maintaining a healthy relationship with the patient. The psychiatrist may consult with uninvolved peers and, especially in the case of patients who are relatives, arrange for timely referrals to ensure appropriate treatment (Bridges 1993).

## Conclusion

The physician–patient relationship is essential to the healing process and is the foundation on which an effective treatment plan may be negotiated, integrating the best of what medical technology and human caring can provide. The centrality of this relationship is particularly true for psychiatric physicians and their patients. In the psychiatrist–patient relationship, empathy, compassion, and hope frequently serve as the major means of alleviating pain and enhancing active participation in all treatment interventions: biological, psychological, and social.

The development of the physician–patient relationship depends on skilled assessment, the development of rapport through empathy, a strong therapeutic alliance, and the effective understanding of transference, countertransference, and defense mechanisms. Current research findings support the purposeful use of common therapy factors, of which the therapeutic alliance is the most powerful, to enhance clinical outcome.

The development of the physician–patient relationship is influenced by numerous factors, including the phase of treatment, the treatment setting, transitions between inpatient and outpatient care, managed care, and changes in the physician's health. The astute physician is attuned to the needs and characteristics of specific populations of patients, adopting the therapeutic approach that most effectively bridges the gap between physician and patient and leads to a healing relationship.

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CHAPTER 3

# The Psychiatric Interview: Settings and Techniques

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The interview is the principal means of assessment in clinical psychiatry. Despite major advances in neuroimaging and neurochemistry, there are no laboratory procedures as informative as observing, listening to, and interacting with the patient, and none as yet are more than supplementary to the information gathered by the psychiatric interview. This chapter deals with the interview as a means of assessing the patient and developing an initial treatment plan in clinical situations.

Psychiatric interviews are analogous to the history and physical in a general medical assessment, and they share the major features of other types of medical interviews (Mackinnon and Yudofsky 1986); they systematically survey subjective and objective aspects of illness and generate a differential diagnosis and plan for further evaluation and treatment. They differ from other medical interviews in the wide range of biological and psychosocial data, which they must take into account, and in their attention to the emotional reactions of the patient and the process of interaction between the patient and the interviewer. The nature of the interaction is informative diagnostically and is a means of building rapport and eliciting the patient's cooperation, which is especially important in psychiatry (Reiser and Schroder 1980). The style and content of a psychiatric interview are necessarily shaped by the interviewer's theory of psychopathology (Lazare 1973). Thus, a biological theory of illness leads to an emphasis on signs, symptoms, and course of illness; a psychodynamic theory dictates a focus on motivations, attitudes, feelings, and personal interactions; a behavioral viewpoint looks at antecedents and consequences of symptoms or maladaptive behaviors. In past times, when these and other theories competed for theoretical primacy, an interviewer might have viewed exploration from a particular single perspective as adequate. However, modern psychiatry views these perspectives as complementary rather than mutually exclusive and recognizes the contributions of biological, intrapsychic, social, and environmental factors to human behavior and its disorders (Leigh and Reiser 1992b). The interviewer, therefore, faces the task of understanding each of these dimensions, adequately surveying them in the interview, and making informed judgments about their relative importance and treatment implications (Shea 1990).

The written psychiatric database, the mental organization which the interviewer maintains during the interview, and the structure of the interview itself may differ considerably from one another. The written psychiatric database is an orderly exposition of information gathered in the interview, presented in a relatively fixed format. The mental organization of the interviewer consists of questions and tentative hypotheses. It evolves flexibly over the course of the interview and is determined by the goals of the interview and emerging information that indicates needed areas of focus (Lazare 1976).

The third structure is that of the interview itself. While guided by general principles of interviewing, this structure is the most flexible of the three, being determined not only by the purpose of the interview and the type of problem that the patient presents, but also by the patient's mode of communication and style of interaction with the interviewer. Thus, the interviewer must hold his/her own structure in mind while responding flexibly to the patient.

## Goals of the Psychiatric Interview

The interviewer may be thought of as seeking the answers to several basic questions about the patient and the presenting problems (American Psychiatric Association 2006). These questions provide the mental framework of the interview (although not its explicit form). They begin by triaging the patient's problem into broad categories of type and severity

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**Table 3–1 Issues to be Addressed in a Psychiatric Assessment**

| Question | Implications |
|---|---|
| Does the patient have a psychiatric disorder? | Need for treatment |
| How severe is the disorder? | Need for hospitalization<br>Need for structure or assistance in daily life<br>Ability to function in major life roles |
| Are there abnormalities of brain function? | Degree of dysfunction of major mental processes, such as perception, cognition, communication, regulation of mood, and affect<br>Responsivity of symptoms to environmental and motivational features<br>Responsivity of symptoms to biological treatment |
| What is the diagnosis? | Description of the illness<br>prognosis and treatment response |
| What is the patient's baseline level of functioning? | Determination of onset of illness<br>State versus trait pathology<br>Goals for treatment<br>Capacity for treatment |
| What environmental issues contribute to the disorder? | Prediction of conditions that may trigger future episodes of illness<br>Need for focus on precipitating stressors<br>Prevention of future episodes through amelioration of environmental stressors and/or increased environmental/social support |
| What biological factors contribute to the disorder? | Need for biological therapy<br>Place of biological factors in explanation of illness presented to the patient<br>Focus on biological factors as part of on going therapy |
| What psychological factors contribute to the disorder? | Responsivity of the symptoms to motivational, interpersonal, and reinforcement factors<br>Need to deal with psychological or interpersonal issues in therapy |
| What is the patient's motivation and capacity for treatment? | Decision to treat<br>Choice of treatment |

and progress to inquiry about details in each salient area. Table 3–1 presents the questions that the interview addresses and the implications of each for understanding and treating the patient.

The answers to the questions in Table 3–1 are presented here in greater detail.

## Does the Patient Have a Psychiatric Disorder?

This is the most basic question which the psychiatrist is called upon to answer and determines whether or not there is any need for further psychiatric assessment or treatment.

## How Severe Is the Illness?

The answer to this question determines the necessary level of treatment, ranging from hospitalization with close observation to infrequent outpatient visits. The main determinants of severity are dangerousness to self and others and impairment in ability to care for oneself and function in social and occupational roles.

## What Is the Diagnosis?

In psychiatry, as in the rest of medicine, descriptive information about signs, symptoms, and course over time is used to assign a diagnosis to the presenting problem. Not all psychiatric diagnoses have well-established validity, but most convey knowledge of prognosis, comorbidity, treatment response, occurrence in family members, or associated biological or psychological findings (Tischler 1987). Even in the case of poorly understood entities, our present system of diagnosis using specific criteria maximizes uniformity in the description and naming of psychiatric disorders.

One important implication of diagnoses is whether there may be reduced plasticity of brain functioning due to anatomical or physiological abnormalities. Symptoms, deficits, and behaviors that stem from such abnormalities vary less in response to environmental and motivational factors than those behaviors that arise in the context of normal brain function. For example, mood swings in a patient with bipolar disorder, a condition for which there is strong evidence of a biological–genetic etiology, typically recur at regular time intervals, often independently of the patient's life situation. By contrast, mood swings in a patient with narcissistic personality disorder are much more likely to be triggered by interactions with other people. Furthermore, when brain function is impaired, biological treatments are more likely to be necessary, and verbal, interpersonal, or environmental interventions are less likely to be sufficient. Thus, the likelihood of altered brain function has major implications for understanding and treating the patient's problems.

Although the question of brain abnormalities is basic to psychiatric triaging, we do not yet have a clear-cut biological etiology for any disorder outside of those historically classified as "organic." Standard laboratory studies (such as brain imaging or electroencephalography) are not generally diagnostic of psychopathology; however, there is research-based evidence of altered brain function in many psychiatric disorders. Table 3–2 presents an overview of the current state of knowledge of brain abnormalities in psychiatric disorders, along with known responses to biological and psychosocial treatments.

## What Is the Patient's Baseline Level of Functioning?

Determining what the patient has been like in his/her best or most usual state is a vital part of the assessment. This information allows the interviewer to gauge when the patient became ill, and how he/she is different when ill versus well. Environmental, biological, and psychological factors that contribute to low baseline levels of functioning may also predispose a patient to the development of psychiatric disorders. Thus, information about baseline functioning provides clues about the patient's areas of vulnerability to future illness as well as his/her capacity to benefit from treatment. It is also an important guide to realistic goals and expectations for such treatment. Table 3–3 presents major components of functioning with examples of elements of each.

## What Environmental Factors Contribute to the Disorder?

Environmental contributions to the presenting problem are factors external to the patient. They may be acute events that precipitate illness or long-standing factors that increase

**Table 3–2 Brain Dysfunction in Psychiatric Disorders**

| Disorder | Evidence for Brain Dysfunction | Response to Biological Treatments | Response to Psychosocial Treatments |
|---|---|---|---|
| Delirium, dementia, amnestic, and cognitive disorders (Leigh and Reiser 1992a, Lipowski 1984, Lishman 1998, Popkin 1994) | Well established | Reversible causes respond to appropriate treatment, neuroleptics, anxiolytics, antidepressants, lithium, and anticonvulsants. Beta blockers may be helpful | Environmental support and supportive psychotherapy may be helpful |
| Schizophrenia (Bellack and Mueser 1993, Carpenter and Buchanan 1994, Davis 1975, Kotrla and Weinberger 1995, Sensky et al. 2000, Sullivan 2005) | Strong evidence | Most respond to antipsychotics; antidepressants, mood stabilizers, and anxiolytics may be helpful adjunctively | Environmental support, supportive psychotherapy, cognitive–behavioral therapy, family therapy, and skills training are helpful |
| Delusional disorder (Maber 1992, Manschreck 1996) | Little evidence—few studies | Poor to fair response to psychotics | Poor response to psychotherapy |
| Schizoaffective disorder (Keck et al. 1996, Kendler 1991, Winokur et al. 1996) | Evidence for relationship to schizophrenia and mood disorders | Most respond to combinations of antipsychotics, antidepressants, mood stabilizers, carbamazepine, and electroconvulsive therapy (ECT) | Not well established. Similar range of treatments as for schizophrenia may be helpful |
| Brief psychotic disorder (Jorgensen et al. 1996, Susser et al. 1995) | Little evidence—few studies | Not well established | Environmental support and supportive psychotherapy helpful |
| Bipolar disorder (Goodwin and Jamison 1990, Janowsky et al. 1974, Tsuang and Faraone 1990) | Strong evidence | Most respond to lithium, antidepressants, anticonvulsants, neuroleptics, or ECT | Supportive and educative psychotherapy and family therapy helpful |
| Major depressive disorder (Broestedt 2003, Elkin et al. 1989, Siever and Davis 1985, Thase and Howland 1995) | Evidence suggestive—considerable heterogeneity | Often responds to antidepressants or ECT | Less severe cases respond to cognitive, interpersonal, and psychodynamic psychotherapy |
| Panic disorder (Barlow 1988, Barlow et al. 2000, Goddard and Charney 1997, Milrod et al. 2000) | Evidence suggestive | Most respond to anxiolytics or antidepressants | Variable. Cognitive–behavioral therapy more effective than psychodynamic |
| Generalized anxiety disorder (Blazer et al. 1991) | Little evidence | Variable. Anxiolytics may be helpful | Variable. Psychodynamic, or cognitive–behavioral psychotherapies are often helpful |
| Simple phobia (Fyer et al. 1990, Marks 1987) | Little evidence | Medications not usually helpful | Most respond to behavioral therapy |
| Posttraumatic stress disorder (Heim et al. 2000, Katz et al. 1996, Marks et al. 1998) | Evidence suggestive | Variable. Antidepressants and mood stabilizers may be helpful | Psychotherapy with exploratory, supportive, and behavioral features usually helpful |
| Obsessive–compulsive disorder (Abramowitz 1997, Baxter 1992, Insel 1992) | Evidence suggestive | Most respond to selective serotonin reuptake inhibitors | Rituals but not obsessive thoughts respond to behavioral therapy |
| Somatization disorder (Cloninger et al. 1986, Min and Lee 1997) | Preliminary evidence | Poor. Medication for comorbid depression or anxiety may help | Poor. Supportive psychotherapy may help |
| Conversion disorder (Ford and Foulks 1985, Lazare 1981) | None known | Amytal interview may help; otherwise not indicated | Most respond to psychotherapy with exploratory, expressive, and behavioral features. May remit spontaneously |
| Hypochondriasis (Ford 1995, Kellner 1987) | None known | No direct response. Medications may help for treatment of comorbid depression and anxiety | Variable. Supportive–educative psychotherapy may be helpful |
| Dissociative disorders (Brenner and Marmer 1998, Kluft and Fine 1993) | None known | No direct response. Medications may help for treatment of comorbid depression and anxiety | Variable. Many respond to expressive–exploratory psychotherapy |
| Alcoholism (Merlett 1998, Prescott and Kendler 1999) | Strong evidence in subgroups | No well-demonstrated direct effects. Opiate antagonists may be helpful | Group and individual psychotherapies most common treatment modalities. Response variable, relapse high |

*(continues)*

**Table 3–2 Brain Dysfunction in Psychiatric Disorders** *continued*

| Disorder | Evidence for Brain Dysfunction | Response to Biological Treatments | Response to Psychosocial Treatments |
|---|---|---|---|
| Psychoactive substance use disorders (Banmohl and Jaffe 1995, Nesse and Berridge 1997) | Little evidence—some subgroups | No well-demonstrated direct effects | Group and individual psychotherapies most common treatment modalities. Response variable, relapse high |
| Sexual disorder (LoPiccolo 1985, Marshall and Barbaree 1990) | May be due to metabolic disorders; otherwise little evidence | Medications for underlying medical conditions may be necessary. Antiandrogens or serotonergic antidepressants may be helpful for paraphilias | Sexual dysfunctions often respond to behavior therapy. Couples therapy or exploratory therapy may also be helpful |
| Eating disorders (Halmi 1992, Johnson and Connors 1987) | Evidence suggestive | Antidepressants may help ameliorate symptoms | Expressive exploration, family, and behavioral therapy often helpful |
| Adjustment disorders (Andreasen and Hoevk 1982, Greenberg et al. 1995) | None known | Medications may alleviate symptoms of anxiety or depression | Supportive psychotherapy often helpful |
| Personality disorders: Cluster A (Kendler et al. 1984, Siever et al. 1991) | Evidence for relationship of schizotypal personality to schizophreni; otherwise none known | Schizotypal patients may improve on antipsychotic medication; otherwise not indicated | Poor. Supportive psychotherapy may help |
| Personality disorders: Cluster B (Bateman and Fonagy 2001, Coccaro and Kavoussi 1997, Tarnepolsky and Berlowitz 1987, Zuckerman 1996) | Evidence suggestive for antisocial and borderline personalities; otherwise none known | Antidepressants, antipsychotics, or mood stabilizers may help for borderline personality; otherwise not indicated | Poor in antisocial personality. Variable in borderline, narcissistic, and histrionic personalities |
| Personality disorders: Cluster C (Cloninger 1987, Cloninger et al. 1993, Millon 1996) | None known | No direct response. Medications may help with comorbid anxiety and depression | Most common treatment for these disorders. Response variable |

general vulnerability. Loss, change, and traumatic events are very common acute precipitants (Paykel 1978). Long-standing environmental stressors may predispose the patient to the development of illness and may also worsen the outlook for recovery.

It is important to identify adverse environmental influences that can be modified and to help the patient or family make necessary changes. For example, a patient with recurrent paranoid psychosis needed yearly hospitalization as long as she worked in an office with many other people. Once she was helped to find work that she could do in her own home, she no longer suffered severe relapses. However, even irreversible precipitants, such as death of a loved one, must be identified and dealt with in the treatment plan.

## What Biological Factors Contribute to the Disorder?

Biological factors may contribute to psychiatric disorders directly by their effects on the central nervous system and indirectly through the effects of pain, disability, or social stigma. Thus, biological factors must be assessed through both the psychiatric history and diagnosis, and the general medical history.

Biological factors affecting the central nervous system may be genetic, prenatal, perinatal, or postnatal. There is strong evidence of genetic contributions to schizophrenia, bipolar disorder, and alcoholism, among others (Carpenter and Buchanan 1994, Jorgensen et al. 1996, Kluft and Fine 1993, Sullivan 2005). Conditions such as maternal substance abuse or intrauterine infections may affect fetal brain development; birth complications may cause cerebral hypoxia with resultant brain damage. In postnatal life, the entire range of diseases that affect the brain may alter mental function and behavior, as may exposure to toxins at work, in the environment, and through substance abuse. In addition, medical conditions that do not directly affect brain functioning may have profound effects on the patient's state of mind and behavior.

**Clinical Vignette 1**

A 30-year-old married woman suffers from chronic low mood and lack of enjoyment of life. She is highly dependent on her husband for practical and emotional support, although she frequently flies into rages at him, feeling that he is cold and uncaring. She has had a series of secretarial jobs which she begins enthusiastically, but soon comes to feel that her employers are highly critical and belittling, whereupon she resigns. Her friendships are limited to people with whom she can have very special, exclusive relationships. She deals poorly with change or loss, which frequently triggers episodes of acute dysfunction. When a friend is not sufficiently available to her, she feels betrayed and worthless, her mood plummets, she becomes lethargic, has eating binges, and is unable to work or pursue her usual routine for up to weeks at a time.

**Table 3–3 Assessment of Baseline Functioning**

| Component | Examples |
|---|---|
| Level of symptoms | Depression<br>Anxiety obsessions and compulsions<br>Delusion<br>Hallucinations<br>Impulsive behaviors |
| Interpersonal relations | Sexual relationships and marriage<br>Quality and longevity of friendships<br>Capacity for intimacy and commitment |
| Work adjustment | Employment history<br>Level of responsibility<br>Functioning in nonpaid roles, e.g., homemaker and parent<br>Satisfaction with work life |
| Leisure activities | Hobbies and interests<br>Group and social activities<br>Travel<br>Ability to take pleasure in nonwork activities |
| Ego functions | Talents, skills, and intelligence<br>Ability to cope and reality testing<br>Control over affects and behaviors<br>Ability to formulate and carry through plans<br>Stable sense of self and others<br>Capacity for self-observation |

Clinical Vignette 2

A patient functions well in a responsible job and has had a long-standing, stable marriage. However, he is driven by the need to be liked and accepted by all who know him, and has a deep-seated, but not conscious, belief that he must continually fulfill the wishes of others in order to accomplish this. At the same time, he has a chronic feeling of powerlessness and an unarticulated wish to be able to say no. At times of increased demands by family members or coworkers, he develops flu-like symptoms and stays home from work "recuperating," relieved of responsibility for fulfilling the expectations of others.

Clinical Vignette 3

A young woman became acutely depressed upon receiving her acceptance to medical school. She was the oldest of four children and had been expected to assume a major caretaking role with her younger siblings. Her mother, a busy physician, wished for her daughter to have a similar career. To the patient, entering medical school meant accepting a lifelong role as a caretaker and forever relinquishing her own wishes to be taken care of.

Biological factors may both predispose to and precipitate episodes of illness. Thus, a patient with a genetic vulnerability to schizophrenic illness may have an episode of acute psychosis precipitated by heavy cocaine use. Similarly, a patient with borderline low intellectual capacity due to hypoxia at birth may have marginal ability to care for himself; an accident resulting in a fractured arm might overwhelm this person's coping capacity and precipitate a severe adjustment disorder.

### What Psychological Factors Contribute to the Disorder?

Psychological factors are mental traits that the patient brings to life situations. While they interact with social and environmental factors, they are intrinsic to the individual, and not readily changed by outside influences.

Psychological factors predisposing to illness include both general and focal deficits in coping adaptability. General deficits encompass the entire range of ego functioning, including poor reality testing, rigid or maladaptive psychological defense mechanisms, low ability to tolerate and contain affects, impulsivity, poorly formed or unstable sense of self, low self-esteem, and hostile, distant, or dependent relationships with others (Valliant 1977). Patients with such deficits generally meet diagnostic criteria for one or more personality disorders and are at increased risk for episodes of acute psychiatric illness. An example of general deficits in psychological functioning is illustrated by the following case.

Focal psychological issues may also contribute to mental disorders. These issues, which typically involve conflicts between opposing motivations, may affect the patient in certain specific areas of function or life situations, leaving other broad areas of function intact (Nemiah 1961a). Such conflicts are most likely to cause maladaptive behaviors or symptoms when the patient is not clearly aware of them.

The meaning of an event in the context of the patient's life course is another focal issue that may contribute to illness.

### What Is the Patient's Motivation and Capacity for Treatment?

Whatever the physician's view of the presenting problem, the patient's wishes and capacities are a major determinant of treatment choice (Lazare et al. 1975). Some patients seek relief of symptoms; some wish to change their behavior or the nature of their relationships; some want to understand themselves better. Patients may wish to talk or to receive medication or instructions.

The patient's capacity for treatment must also be considered in the treatment plan. For example, a patient with schizophrenia may agree to medication but be too disorganized to take it reliably without help. Suitability for exploratory psychotherapy depends upon such factors as the ability to observe oneself, tolerate unpleasant affects, and establish and maintain a working relationship with the treater (Strupp and Binder 1984). Such factors must be evaluated in the interview.

## The Psychiatric Database

The body of information to be gathered from the interview may be termed the psychiatric database (Tables 3–2 to 3–4). It is a variable set of data: either very specific or general, mainly limited to the present state or focused on early life, dominated by neurological questions or inquiry into relationships. To avoid setting the impossible task of learning everything about every patient, one must consider certain factors that modify the required database.

Whose questions are to be answered—the patient's concern about himself, a family or friend's concern about him, another physician's diagnostic dilemma, a civil authority's need to safeguard the public, or a research protocol

**Table 3–4 Core Database**

| Identifying Data | Chief Complaint | History of Present Illness |
|---|---|---|
| Name<br>Age/date of birth<br>Next of kin | Reason for consultation | Major symptoms<br>Time course<br>Stressors<br>Change in functioning<br>Current medical problems and treatment |
| **Past Psychiatric History** | **Past Medical History** | **Family History** |
| Any previous psychiatric treatment<br>History of suicide attempts<br>Functioning problems secondary to psychiatric symptoms<br>Alcohol/drug abuse | Ever hospitalized<br>Surgery<br>Medications | Psychiatric illness |
| **Personal History** | **Mental Status** | |
| Educational level<br>Ever married/committed relationship<br>Work history<br>Means of support<br>Living situation | Appearance<br>Attitude<br>Affect<br>Behavior<br>Speech<br>Thought process<br>Thought content<br>Perception<br>Cognition<br>Insight<br>Judgment | |

requirement? Who will have access to the data gathered and under what circumstances? What is the setting of the interview? Priorities in an emergency room differ from those in an office setting (Meyers and Stein 2000). Is the interview to be the first session of a psychotherapy regimen, or is it a one-time-only evaluation? What is the nature of the pathology? For example, negative responses regarding the presence of major psychotic symptoms, coupled with a history of good occupational function, will generally preclude a detailed inventory of psychotic features. A missed orientation or memory question will require careful cognitive testing. Patients with personality disorder symptoms warrant careful attention to the history of significant relationships (Nurnberg et al. 1991), work history, and the feelings evoked in the interviewer during the evaluation process. The database should be expanded in areas of diagnostic concern to support or rule out particular syndromes. The amount and nature of the data obtained is also, of necessity limited, by the patient's ability to communicate and his cooperativeness.

## Database Components

### Identifying Data

This information establishes the patient's identity, especially for the purpose of obtaining past history from other contacts, when necessary, as well as to fix his/her position in society. The patient's name should be recorded, along with any nickname or alternative names he/she may have been known by in the past. This is important for women who might have been treated previously under a maiden name, or a patient who has had legal entanglements and so has adopted aliases.

Date of birth, or at least age, and race are other essential parts of every person's database. A number of different classifications for race exist, as well as different terms and controversies (Porter 1993). In the United States and Canada, the categories of white, black (or African-American), Asian, Native American, and others are generally accepted. The additional modifier of ethnicity, especially Hispanic/non-Hispanic, is becoming more widely used. If a patient is a member of a particular subculture based on ethnicity, country of origin, or religious affiliation, it may be noted here.

A traditional part of the identifying data is a reference to the patient's civil status: single, married, separated, divorced, or widowed. The evolution of relationship patterns over the last two decades, with less frequent formalization of relationships, has made classification more difficult (Ishii-Kuntz and Tallman 1991), especially in the case of homosexual patients, whose relationships may have different degrees of recognition and terms depending upon the particular jurisdiction.

The patient's social security number (or other national ID number) can be a very useful bit of data when seeking information from other institutions. It is sometimes set aside for particular protection due to the danger of identity theft.

In most cases, it is assumed that the informant (supplier of the history) is the patient. If other sources are used, and especially if the patient is not the primary informant, this should be noted at the beginning of the database.

### Chief Complaint

The chief complaint is the patient's responses to the question, "What brings you to see me/to the hospital today?" or some variant. It is usually quoted verbatim, placed within quotation marks, and should be no more than one or two sentences.

Even if the patient is very disorganized or hostile, quoting his response can give an immediate sense of where the patient is as the interview begins. If the patient responds with an expletive, or a totally irrelevant remark, the reader of the database is immediately informed about how the rest of the information may be distorted. In such cases, or if the patient gives no response, a brief statement of how the patient came to be evaluated should be made and enclosed in parentheses.

### History of the Present Illness

**Minimum Essential Database.** The present illness history should begin with a brief description of the major symptoms that brought the patient to psychiatric attention. The most troubling symptoms should be detailed initially; later, a more thorough review will be stated. At a minimum, the approximate time since the patient was last at his/her baseline level of functioning, and in what way he/she is different from that now, should be described, along with any known stressors, the sequence of symptom development, and the beneficial or deleterious effects of interventions, included.

How far back in a patient's history to go, especially when he/she has chronic psychiatric illness, is sometimes problematic. In patients who have required repeated hospitalization, a summary of events since last discharge (if within 6 months) or last stable baseline is indicated. It is rare that more than 6 months of history be included in the

history of the present illness, and detailed history is more commonly given on the past month.

**Expanded Database.** A more expanded description of the history of the present illness would include events in a patient's life at the onset of symptoms, as well as exactly how the symptoms have affected the patient's occupational functioning and important relationships. Any concurrent medical illness symptoms, medication usage (and particularly changes), alterations in the sleep–wake cycle, appetite disturbances, and eating patterns should be noted; significant negative findings should also be remarked upon.

## Past Psychiatric History

**Minimum Essential Database.** Most of the major psychiatric illnesses are chronic in nature. For this reason, often patients have had previous episodes of illness with or without treatment. New onset of symptoms, without any previous psychiatric history, becomes increasingly important with advancing age in terms of diagnostic categories to be considered. At a minimum, the presence or absence of past psychiatric symptomatology should be recorded, along with psychiatric interventions taken and the result of such interventions. An explicit statement about past suicide and homicide attempts should be included.

**Expanded Database.** A more detailed history would include names and places of psychiatric treatment, dosages of medications used, and time course of response. The type of psychotherapy, the patient's feelings about former therapists, his/her compliance with treatment as well as circumstances of termination are also important. Note what the patient has learned about the biological and psychological factors predisposing him/her to illness, and whether there were precipitating events.

## Past Medical History

**Minimum Essential Database.** In any clinical assessment, it is important to know how a patient's general health status has been. In particular, any current medical illness and treatment should be noted (Slaby and Andrew 1987), along with any major past illness requiring hospitalization. Previous endocrine or neurological illness are of particular pertinence (Flomenbaum and Altman 1985).

**Expanded Database.** An expanded database could well include significant childhood illnesses, how these were handled by the patient and his/her family, and therefore the degree to which the patient was able to develop a sense of comfort and security about his/her physical well-being. Illnesses later in life should be assessed for the degree of regression produced. The amount of time a patient has had to take off work, how well he/she was able to follow a regimen of medical care, and his/her relationship with the family physician or treating specialist can all be useful in predicting future response to treatment. A careful past medical history can also at times bring to light a suicide attempt, substance abuse, or dangerously careless behavior, which might not be obtained any other way.

## Family History

**Minimum Essential Database.** Given the evidence for familial, genetic factors in so many psychiatric conditions, noting the presence of mental illness in biological relatives of the patient is a necessary part of any database (Hammen et al. 1987). It is important to specify during questioning the degree of family to be considered—usually to the second degree: aunts, uncles, cousins, and grandparents, as well as parents, siblings, and children.

**Expanded Database.** A history of familial medical illness is a useful part of an expanded database. A genogram (pedigree), including known family members with dates and causes of death and other known chronic illnesses, is helpful. Questioning about causes of death will also occasionally bring out hidden psychiatric illness, for example, sudden, unexpected deaths that were likely suicides or illness secondary to substance abuse.

## Personal History

**Minimum Essential Database.** Recording the story of a person's life can be a daunting undertaking and is often where a database can expand dramatically. At a minimum, this part of the history should include where a patient was born and raised, and in what circumstances—intact family, number of siblings, and degree of material comfort. Note how far the patient went in school, how he/she did there, and what his/her occupational functioning has been. If he/she is not working, why not? Has the patient ever been involved in criminal activity, and with what consequences? Has the patient ever married or been involved in a committed relationship? Are there any children? What is his/her current source of support? Does he/she live alone or with someone? Has he/she ever used alcohol or other drugs to excess and is there current use? Has he/she ever been physically or sexually abused or been the victim of some other trauma?

**Expanded Database.** An expanded database can include a great deal of material beginning even prior to the patient's conception. What follows is an outline of the kind of data that may be gathered, along with an organizational framework.

### *Family of Origin*

Were parents married or in committed relationships?
Personality and significant events in life of mother, father, or other significant caregiver.
Siblings: How many? Their ages, significant life events, personality, and relationship to patient.
Who else shared the household with the family?

### *Prenatal and Perinatal*

Was the pregnancy planned? Quality of prenatal care; mother's and father's response to pregnancy.
Illness, medication or substance abuse, smoking, and trauma during pregnancy; labor—induced or spontaneous?
Week's gestation, difficulty of delivery, vaginal or caesarean section.
Presence of jaundice at birth, birth weight, and Apgar score.
Baby went home with mother or stayed on in hospital.

### *Early Childhood*

Developmental milestones: smiling, sitting, standing, walking, talking, and type of feeding—food allergies or intolerance.

Consistency of caregiving: interruptions by illness and birth of siblings.
Reaction to weaning, toilet training, and maternal separation.
Earliest memories: problematic behavior (tantrums, bed-wetting, hair-pulling, or nail-biting).
Temperament (shy, overactive, outgoing, and fussy).
Sleep problems: insomnia, nightmares, enuresis, and parasomnias.

### *Later Childhood*

Early school experiences: evidence of separation anxiety.
Behavioral problems at home or school: firesetting, bed-wetting, aggressiveness toward others, cruelty to animals, and nightmares.
Developmental milestones: learning to read and write.
Relationships with other children and family: any loss or trauma.
Reaction to illness.

### *Adolescence*

School performance: ever in special classes?
Athletic abilities and participation in sports.
Evidence of gender identity concerns: overly "feminine" or "masculine" in appearance/behavior, or perception by peers.
Ever run away? Able to be left alone and assume responsibility.
Age onset of puberty (menarche or nocturnal emissions) and reaction to puberty.

### *Identity*

Sexual preference and gender identity and religious affiliation (same as parents?).
Career goals: ethnic identification.

### *Sexual History*

Early sexual teaching: earliest sexual experiences, experience of being sexually abused, and attitudes toward sexual behavior.
Dating history and precautions taken to prevent sexually transmitted diseases and/or pregnancy.
Episodes of impotence and reaction.
Masturbating patterns and fantasies.
Preoccupation with particular sexual practices, current sexual functioning, length of significant relationships, and ages of partners.

### *Adulthood*

Age at which left home and level of educational attainments.
Employment history, relationships with supervisors and peers at work, and reasons for job change.
History of significant relationships, including duration, typical roles in relationships, and patterns of conflict: marital history, legal entanglements and criminal history, both covert and detected, ever victim or perpetrator of violence.
Major medical illness as adult.
Participation in community affairs.
Financial status: own or rent home and stability of living situation.
Ever on disability or public assistance?
Current family structure, reaction to losses of missing members (parents and siblings), if applicable.
Substance abuse history.

## Mental Status Examination

It can be helpful to conceptualize the recording of the mental status examination as a progression. One begins with a snapshot: what can be gained from a cursory visual examination, without any movement or interaction—appearance and affect. Next, motion is added: behavior. Then comes sound: the patient's speech, though initially only as sound. The ideas being expressed come next: the thought process and content, perception, cognition, insight, and judgment. Table 3–5 gives a summary of areas to be commented on, along with common terms.

At every level of the mental status examination, preference should be given for explicit description over jargon. Stating that a patient is delusional is less helpful than describing the patient as believing that his/her neighbors are pumping poisonous gases into his/her bedroom while the patient sleeps.

**Table 3–5 Mental Status Examination**

| |
|---|
| **Appearance** |
| Level of consciousness (alert, hypervigilant, somnolent, or stuporous) |
| Dress (casual, appropriate for weather, eccentric, careless, or disheveled) |
| Grooming (style of hair, degree of makeup, shaven/unshaven, clean, and malodorous) |
| Idiosyncracies—tattoos (professional or amateur), prominent scars, or religious emblems |
| **Attitude** |
| Cooperative, hostile, evasive, threatening, or obsequious |
| **Affect** |
| Range (restricted, expansive, blunted, or flat) |
| Appropriateness to items discussed |
| Stability (labile or shallow) |
| Quality (silly or anxious) |
| **Mood** |
| Response to question: "How are you feeling/How's your mood been?" |
| **Behavior** |
| Psychomotor agitation or retardation |
| **Speech** |
| Rate (rapid, slowed, pressured, or hard to interrupt) |
| Volume (loud, soft, monotone, highly inflected, or dramatic) |
| Quality (neologisms, fluent, or idiosyncratic) |
| **Thought Process** |
| Goal directed, disorganized, loose associations, tangential, circumstantial, or flight of ideas |
| **Thought Content** |
| Major preoccupations, ideas of reference, or delusions (grandiose, paranoid, bizarre, state exactly what it is the patient appears to believe) |
| Thought broadcasting, insertion, or withdrawal |
| Suicidal or homicidal ideation. Plan and intent to carry out ideas |

*(continues)*

**Table 3–5 Mental Status Examination** *continued*

| |
|---|
| **Perception** |
| Illusions and hallucinations—type (auditory, visual, olfactory, tactile, or gustatory), evidence (patient spontaneous report, answer to interviewer question, or observation of patient attending or responding to nonexistent external stimuli) |
| Patient's beliefs about hallucinatory phenomenon—(do they seem to originate from the outside or inside, how many voices, what gender, talking to patient or to other voices, or are they keeping up constant commentary on the patient) |
| **Cognition** |
| Orientation: time, place, person, and situation |
| Memory: number of remembered objects, digit span, presidents backward, and recent events |
| Concentration: serial 7's, world spelled backward |
| Abstraction: proverb interpretation—what would someone mean by "the grass is always greener on the other side of the fence" ("Get off my back.") |
| Similarities: (How are these things alike—apple–orange, table–chair, eye–ear, and praise–punishment?) |
| Computation: number of digits successfully added or subtracted and ability to calculate change |
| (How many quarters are in $1.50? If you bought a loaf of bread for 89 cents and gave the cashier a dollar, what change would you get back?) |
| **Insight** |
| Knows something is wrong, that he/she is ill, that illness is psychiatric; understands ways in which illness disrupts function |
| **Judgment** |
| Response to standard questions (If you found a sealed, addressed, stamped letter, what would you do? If you smelled smoke in a crowded theater?) |
| Evidence from behavior prior to and during interview (Was the patient caring for himself/herself properly, handling business affairs well? Does the behavior during the interview match his/her stated goals—e.g., if he/she wishes to be thought to be in control, is he/she keeping the voice down and movement in check?) |

## Conduct of the Interview

### Factors Which Affect the Interview

A skillful interview will not necessarily yield all the relevant information but will make the most of the opportunities in a clinical situation, given the limitations that both the patient and the interviewer bring. Factors that influence the development of an alliance and the amount that can be learned in the interview include the following:

#### The Patient's Physical or Emotional Distress

Patients who are in acute distress either from physical discomfort or from emotional factors, such as severe depression or anxiety, will be limited in their motivation and ability to interact with the interviewer. The interviewer may be able to enhance communication by addressing the patient's discomfort in a supportive manner. However, he/she must also recognize times when the patient's discomfort necessitates a more limited interview.

#### The Cognitive Capacities of the Patient

Patients who are demented, retarded, disorganized, thought disordered, amnesic, aphasic, or otherwise impaired in intellectual or cognitive capacity have biologically based deficits that limit the amount of information they can convey.

#### The Emotionally Based Biases of the Patient

Patients bring to the interview a wide variety of preconceptions, expectations, and tendencies toward distortion, which influence how they view and relate to the interviewer. Such biases are commonly referred to as *transference* because they frequently can be understood as arising from interactions with important figures in childhood, such as parents, which then color perceptions of others during adult life (Nemiah 1961b). Transferential biases may be positive or negative. Thus, even before the start of the interview, one patient may be primed to view the doctor as a wise and kindly healer, while another will be predisposed to see him/her as an exploitative charlatan. Clearly, such biases affect the amount of openness and trust that the patient brings to the interview and the quality of information he/she provides.

#### The Emotionally Based Biases of the Interviewer

The interviewer, like the patient, may have feelings stirred up by the interaction. The interviewer's emotional reactions to the patient can be an invaluable asset in assessment if he/she can be conscious of them and reflect on their causes. For example, an interviewer finds himself/herself becoming increasingly annoyed at a highly polite patient. On reflection, he/she realizes that the politeness serves to rebuff his/her attempts to establish a warmer, more spontaneous relationship, and is a manifestation of the patient's underlying hostile attitude.

When the interviewer is unable to monitor and examine his/her emotional reactions, they are more likely to impede rather than enhance understanding of the patient. This is most likely to happen when emotional reactions are driven more by the interviewer's own biases than by the patient's behavior. Such reactions are referred to as the interviewer's *countertransference* (Mackinnon and Michels 2006). In the example cited in the previous paragraph, the interviewer might inaccurately perceive a polite patient as rigid and hostile due to unconscious biases (countertransference) based on his/her relationship with his/her own rigidly polite parent. The entire range of countertransferential interviewer attitudes toward the patient, from aversion to infatuation, might similarly bias judgment.

#### Situational Factors

Patients' attitudes toward the interview will be strongly influenced by the situation in which the consultation arises. Some patients decide for themselves that they need treatment, while others come reluctantly, under pressure from others. Patients who are being evaluated for disability or in connection with a lawsuit may feel a need to prove that they are ill, while those being evaluated for civil commitment or at the insistence of family members may need to prove that they are well. Similarly, a patient's past history of relationships with psychiatrists or with health professionals in general is likely to color his/her attitude toward the interviewer.

The interviewer may also be affected by situational factors. For example, pressure of time in a busy emergency service may influence the interviewer to omit important areas of inquiry and reach premature closure; the experience of a recent patient suicide may bias the interviewer toward overestimation of risk in someone with suicidal thoughts.

As with countertransference reactions, it is important for the interviewer to minimize distortions due to situational factors by being as aware of them as possible.

### Racial, Ethnic, and Cultural Factors

The degree of racial, ethnic, cultural, and socioeconomic similarity between the patient and the interviewer can influence the course and outcome of the interview in many ways. It may affect the level of rapport between patient and interviewer, the way both view the demands of the situation, the way they interpret each other's verbal and nonverbal communications, and the meaning the interviewer assigns to the patient's statements and behaviors (Gaw 1993). Not only racial or cultural prejudice but also well-intentioned ignorance can interfere with communication and accurate assessment.

Some cultures, for example, place a higher value on politeness and respect for authority than does Western culture. A patient from such a background might be reluctant to correct or disagree with the interviewer's statements even when they are erroneous. The interviewer might not suspect that he/she was hearing distorted information or conversely, might see the patient as pathologically inhibited or unemotional. Many non-Western cultures place a higher value on family solidarity than on individuality (Barrett 2006). Pressing a patient from such a culture to report angry feelings toward family members might raise his/her anxiety, decrease rapport with the interviewer, and produce defensive distortions in the material.

## General Features of Psychiatric Interviews

### Setting

The ideal interview setting is one that provides a pleasant atmosphere and is reasonably comfortable, private, and free from outside distractions. Such a setting not only provides the physical necessities for an interview but also conveys to the patient that he/she will be well cared for and safe. Providing such a setting may pose special problems in certain interviewing situations. For example, it may be necessary to interview highly agitated patients in the presence of security personnel; interviewers on medical–surgical units must pay special attention to the patient's comfort and privacy.

### Verbal Communication

Verbal communication may be straightforward imparting of information: "Every year around November, I begin to lose interest in everything and my energy gets very low." However, patients may convey information indirectly through metaphor or use words for noninformational purposes, such as to express or contain emotions or to create an impact on the interviewer.

In metaphorical language, one idea is represented by another with which it shares some features. For example, when asked how she gets along with her daughter-in-law, a woman replies, "I can never visit their house because she always likes to keep the thermostat down. It's never as warm as I need." Such a reply suggests that the woman may not feel "warmly" accepted and welcomed by her son's wife. Metaphor may also use the body to represent ideas or feelings. A man who proved to meet the diagnostic criteria for major depressive disorder described his mood as "OK" but complained that his life was being ruined by constant aching in his chest for which the doctors could find no cause. In this instance, the pain of depression was experienced and described metaphorically as a somatic symptom.

Language may be used to express emotions directly ("I'm afraid of you and I don't want to talk to you"), but more often is used indirectly by influencing the process of the interview (Bernstein and Berstein 1985). Patients may shift topics, make offhand remarks or jokes, ask questions, and compliment or belittle the interviewer as a way of expressing feelings. The process of the interview frequently expresses the patient's feelings about his/her immediate situation or interaction with the interviewer (Malan 1995). For example, a woman being evaluated for depression and anxiety suddenly said, "I was just wondering doctor, do you have any children?" The further course of the interview revealed that she was terrified of being committed to a hospital and abandoned. The question was an attempt to establish whether the interviewer was a good parent and therefore safe as a caretaker for her.

Language may also be used in the service of psychological defense mechanisms to contain rather than express emotions (Freud 1946). For example, a young man with generalized anxiety was asked whether he was sexually active. He replied by talking at length about how all the women he knew at college were either unappealing or attached to other men. Further discussion revealed that he developed severe symptoms of anxiety whenever he was with a woman to whom he felt sexually attracted. His initial reply represented an automatic, verbal mechanism (in this case, a rationalization) for keeping the anxiety out of awareness.

Another form of process communication is the use of language to make an impact on the interviewer (Casement 1985). A statement such as "if you can't help me I'm going to kill myself" might convey suicidal intent, but may also serve to stir up feelings of concern and involvement in the interviewer. Similarly, the patient who says, "Dr. X really understood me, but he was much older and more experienced than you are," may be feeling vulnerable and ashamed, and unconsciously trying to induce similar feelings in the interviewer. When language is used in this way, the interviewer's subjective reaction may be the best clue to the underlying feelings and motivations of the patient.

### Nonverbal Communication

Emotions and attitudes are communicated nonverbally through facial expressions, gestures, body position, movements of the hands, arms, legs, and feet, interpersonal distance, dress and grooming, and speech prosody (Knapp 1978). Some nonverbal communications such as gestures are almost always conscious and deliberate, while others often occur automatically outside one's awareness. The latter type are particularly important to observe during an interview because they may convey messages entirely separate from or even contradictory to what is being said.

Facial expression, body position, tone of voice, and speech emphasis are universal in the way they convey meaning (Ekman et al. 1972). The interviewer will automatically decode these signals but may ignore the message due to countertransference or social pressure from the patient. For example, a patient may say, "I feel very comfortable with you, doctor," but sit stiffly upright and maintain a rigidly fixed smile, conveying a strong nonverbal message of

tension and mistrust. The nonverbal message may be missed if, for example, the interviewer has a strong need to be liked by the patient. Another patient denies angry feelings while sitting with a tightly clenched fist. The interviewer may unconsciously collude with the patient's need to avoid his/her anger by ignoring the body language.

As with any medical examination, observation of nonverbal behavior may provide important diagnostic information. For example, a leaden body posture may indicate depression, movements of the foot may arise from anxiety or tardive dyskinesia, and sudden turning of the head and eyes may suggest hallucinations.

Nonverbal communication proceeds in both directions, and the nonverbal messages of the interviewer are likely to have a considerable effect on the patient. Thus, the interviewer who sits back in his/her chair and looks down at his/her notes communicates less interest and involvement than one who sits upright and makes eye contact. Similarly, an interviewer who gives a weak handshake and sits behind a desk or far across the room from the patient will communicate a sense of distance, which may interfere with establishing rapport. It is important that the interviewer be aware of his/her own nonverbal messages and adapt them to the needs of the patient.

### Listening and Observation

The complexity of communication in the psychiatric interview is mirrored by the complexity of listening (Luborsky 1984). The interviewer must remain open to literal and metaphorical messages from the patient, the impact the patient is trying to make, and the degree to which nonverbal communication complements or contradicts what is being said. Doing this optimally requires that the interviewer also be able to listen to his/her own mental processes throughout the interview, including both thoughts and emotional reactions. Listening of this kind depends upon having a certain level of comfort, confidence, and space to reflect and may be very difficult when the patient is hostile, agitated, demanding, or putting pressure on the interviewer in any other way. With such patients, it may take many interviews to do enough good listening to gain an adequate understanding of the case.

Another important issue in listening is maintaining a proper balance between forming judgments and remaining open to new information and new hypotheses. On the one hand, one approaches the interview with knowledge of diagnostic classifications, psychological mechanisms, behavioral patterns, social forces, and other factors that shape one's understanding of the patient. The interviewer hears the material with an ear to fitting the information into these preformed patterns and categories. On the other hand, the interviewer must remain open to hearing and seeing things that extend or modify his/her judgments about the patient. At times the interviewer may listen narrowly to confirm a hypothesis, while at others he/she may listen more openly, with relatively little preconception. Thus, listening must be structured enough to generate a formulation but open enough to avoid premature judgments.

### Attitude and Behavior of the Interviewer

The optimal attitude of the interviewer is one of interest, concern, and intention to help the patient. While the interviewer must be tactful and thoughtful about what he/she says, this should not preclude behaving with natural warmth and spontaneity. Indeed, these qualities may be needed to support patients through a stressful interview process. Similarly, the interviewer must try to use natural, commonly understood language and avoid jargon or technical terms. The interviewer must communicate his/her intention to keep the patient as safe as possible, whatever the circumstances. Thus, while one must at times set limits on the behavior of an agitated, threatening, or abusive patient, one should never be attacking or rejecting.

Empathy is an important quality in psychiatric interviewing. While sympathy is an expression of agreement or support for another, empathy entails putting oneself in another's place and experiencing his/her state of mind. Empathy comprises both one's experiencing of another person's mental state and the expression of that understanding to the other person (Barrett-Lennard 1981). For example, in listening to a man talk about the death of his wife, the interviewer may allow himself/herself to resonate empathetically with the patient's feelings of loneliness and desolation. Based on this resonance, he/she might respond, "After a loss like that, it feels as if the world is completely empty."

As a mode of listening, empathy is an important way of understanding the patient; as a mode of response, it is important in building rapport and alliance. Patients who feel great emotional distance from the interviewer may make empathic understanding difficult or impossible. Thus, the interviewer's inability to empathize may itself be a clue to the patient's state of mind.

## Structure of the Interview

The overall structure of the psychiatric interview is generally one of reconnaissance and detailed inquiry (Sullivan 1970). In reconnaissance phases, the interviewer inquires about broad areas of symptomatology, functioning, or life course: "Have you ever had long periods when you felt very low in mood?" "How have you been getting along at work?" "Tell me what you did between high school and when you got married." In responding to such questions, patients give the interviewer leads, which then must be pursued with more detailed questioning. Leads may include references to symptoms, difficulty in functioning, interpersonal problems, ideas, states of feeling, or stressful life events. Each such lead raises questions about the nature of the underlying problem, and the interviewer must attempt to gather enough detailed information to answer these questions. Reliance on yes or no "gate questions" to rule out areas of pathology has been shown to increase the risk of missing important information. This risk may be minimized by asking about important areas in several ways (Barber et al. 2001).

In general, the initial reconnaissance consists of asking how the patient comes to treatment at this particular time. This is done by asking an open-ended question, such as "what brings you to see me today?" or "how did you come to be in the hospital right now?" A well-organized and cooperative patient may spontaneously provide most of the needed information, with little intervention from the interviewer. However, the patient may reveal deficits in thought process, memory, or ability to communicate, which dictate more structured and narrowly focused questioning.

The patient's emotional state and attitude may also impede a smooth flow of information. For example, if the

patient shows evidence of anxiety, hostility, suspiciousness, or indifference, the interviewer must first build a working alliance before trying to collect information. This usually requires acknowledging the emotions that the patient presents, helping the patient to express his/her feelings and related thoughts, and discussing these concerns in an accepting and empathic manner (Strean 1985). As new areas of content open up, the interviewer must continue to attend to the patient's reactions, both verbal and nonverbal, and to identify and address resistance to open communication.

Setting an appropriate level of structure is an important aspect of psychiatric interviewing. Psychiatric patients may spontaneously report a low number of symptoms, and initial diagnostic impressions may be misleading (Herran et al. 2001). Over the past two decades, a variety of structured interview formats have been developed for psychiatric assessment (Spitzer et al. 1978, Wiens 1990). In these interviews, the organization, content areas, and, to varying degrees, wording of the questions are standardized; vague, overly complex, leading or biased, and judgmental questions are eliminated, as is variability in the attention given to different areas of content. The major benefits of such interviews are that they ensure complete coverage of the specified areas and greatly increase the reliability of information gathered and diagnostic judgments. In addition, formats that completely specify the wording of questions can be administered by less highly trained interviewers or even as patient self-reports.

The disadvantages of highly structured interviews are that they diminish the ability to respond flexibly to the patient and preclude exploration of any areas not specified in the format (Groth-Marnat 2003). They are therefore used to best advantage for interviews with focused goals. For example, such interviews may aim to survey certain DSM-IV-TR Axis I disorders, assess the type and degree of substance abuse, or delineate the psychological and behavioral consequences of a traumatic event. They are less useful in a general psychiatric assessment where the scope and focus of the interview cannot be preordained.

In the usual clinical situation, while the interviewer may have a standardized general plan of approach, he/she must adapt the degree of structure to the individual patient. Open-ended, nondirective questions derive from the psychoanalytic tradition. They are most useful for eliciting and following emotionally salient themes in the patient's life story and interpersonal history. Focused, highly structured questioning derives from the medical/descriptive tradition and is most useful for delineating the scope and evolution of pathological signs and symptoms. In general, one uses the least amount of structure needed to maintain a good flow of communication and cover the necessary topic areas.

## Phases of the Interview

The typical interview comprises an opening, middle, and closing phase. In the opening phase, the interviewer and patient are introduced, and the purposes and procedures of the interview are set. It is generally useful for the interviewer to begin by summarizing what he/she already knows about the patient and proceeding to the patient's own account of the situation. For example, the interviewer may say, "Dr. Smith has told me that you have had several episodes of depression in the past, and now you may be going into another one," or "I understand that you were brought in by the police because you were threatening people on the street. What do you think is happening with you?" or "when we spoke on the phone you said you thought your marriage was in trouble. What has been going wrong?" Such an approach orients the patient and sets a collaborative tone.

The opening phase may also include clarification of what the patient hopes to get from the consultation. Patients may sometimes state this explicitly, but often do not, and the interviewer should not assume that his/her goals are the same as the patient's (Lazare et al. 1975). A question such as "how were you hoping I could help you with the problem you have told me about?" invites the patient to formulate and express his/her request and avoids situations in which the patient and interviewer work at cross-purposes. The interviewer must also be explicit about his/her own goals and the extent to which they fit with the patient's expectations. This is especially important when the interests of a third party, such as an employer, a family member, or a court of law, is involved.

The middle phase of the interview consists of assessing the major issues in the case and filling in enough detail to answer the salient questions and construct a working formulation. Most of the work of determining the relative importance of biological, psychological, environmental, and sociocultural contributions to the problem is done during this phase. The patient's attitudes and transferential perceptions are also monitored during this phase, so that the interviewer can recognize and address barriers to communication and collaboration.

When appropriate, formal aspects of the mental status examination are performed during the middle phase of the interview. While most of the mental status evaluation is accomplished simply by observing the patient, certain components such as cognitive testing and review of psychotic symptoms may not fit smoothly into the rest of the interview. These are generally best covered toward the end of the interview, after the issues of greatest importance to the patient have been discussed and rapport has been established. A brief explanation that the interviewer has a few standard questions he/she needs to cover before the end of the interview serves as a bridge and minimizes the awkwardness of asking questions that may seem incongruous or pejorative.

In general, note-taking during an assessment interview is helpful to the interviewer and not disruptive of rapport with the patient. Notes should be limited to brief recording of factual material, such as dates, durations, symptom lists, important events, and past treatments, which might be difficult to keep in memory accurately. The interviewer must take care not to become so involved in taking notes as to lose touch with the patient. It is especially important to maintain a posture of attentive listening when the patient is talking about emotionally intense or meaningful issues. When done with interpersonal sensitivity, note-taking during an assessment interview may actually enhance rapport by communicating that what the patient says is important and worth remembering. This is to be distinguished from note-taking during psychotherapy sessions, which is more likely to diminish the treater's ability to listen and respond flexibly.

In the third or closing phase of the interview, the interviewer shares his/her conclusions with the patient, makes treatment recommendations, and elicits reactions. In situations where the assessment runs longer than one session, the interviewer may sum up what has been covered in the

interview and what needs to be done in subsequent sessions. Communications of this kind serve several purposes. They allow the patient to correct or add to the salient facts as understood by the interviewer. They contribute to the patient's feeling of having gotten something from the interview. They are also the first step in initiating the treatment process because they present a provisional understanding of the problem and a plan for dealing with it. All treatment plans must be negotiated with the patient, including discussion of mutual goals, expected benefits, liabilities, limitations, and alternatives, if any. In many cases, such negotiations extend beyond the initial interview and may constitute the first phase of treatment.

## Dimensions of Interviewing Techniques

Although many systems have been suggested for classifying interview techniques (Elliott et al. 1987), it is convenient to think about four major dimensions of interviewing style: degree of directiveness, degree of emotional support, degree of fact versus feeling orientation, and degree of feedback to the patient. The interviewer must seek a balance among these dimensions to best cover the needed topics, build rapport, and arrive at a plan of treatment.

### Directiveness

Directiveness in the interview ensures that the necessary areas of information are covered and supplies whatever cognitive support the patient needs in discussing them. Table 3–6 provides interventions that are low, moderate, and high in directiveness.

Low-directive interventions request information in the broadest, most open-ended way and do not go beyond the material supplied by the patient. Moderately directive interventions are narrower in focus and may extend beyond what

**Table 3–6 Degrees of Directiveness in the Interviewer**

| Directiveness | Intervention | Examples |
|---|---|---|
| Low | Open-ended questions | "What brings you to the hospital?"<br>"Tell me about your current situation in life." |
| Low | Repetition | Patient: "Last night I suddenly started to feel so terrible I was afraid I was going to die."<br>Interviewer: "You were afraid you were going to die." |
| Low | Restatement | Patient: "Nobody is on my side anymore—even my family is out to get me."<br>Interviewer: "So it seems as if everyone has turned against you." |
| Low | Summarization | "To review what we have been discussing, over the last month you've been very low in mood, you felt overwhelmed even by small chores, and you no longer want to see any of your friends." |
| Low | Clarification | "You told me that it 'upsets' you to have to say no. It seems that when you say no to your boss your feeling is fear, but when you say no to your children you feel guilty." |
| Low | Nonverbal acknowledgment | "Uh-huh"; nodding of head |
| Low | Attentive listening | In talking about the recent death of his wife, the patient became tearful and hesitant in speech. The interviewer remains silent, but attentive, allowing the patient time to express himself. |
| Moderate | Broad-focus questions | "What do you notice about yourself lately that is different from usual?" "What is it about your job that you find stressful?" |
| Moderate | Use of examples | "Sometimes illness seems to be triggered by something that happens, like a change in finances or living situation, or losing someone who's close to you. Has anything like that been happening to you?" |
| Moderate | Confrontation | "You told me you got a 'terrible' evaluation at work, but in 9 of 10 categories your rating was actually excellent."<br>"You don't feel the medicine does you any good, but whenever you've stopped it you've had to go back into the hospital. How do you account for that?" |
| Moderate | Interpretation | "Part of the tension between you and your wife is that you forget things she tells you. Perhaps this is what you do when you are angry at her." |
| High | Narrow-focus questions | "Do you have trouble getting to sleep or staying asleep?<br>"How much alcohol do you drink in a week?" |
| High | Question repetition | Interviewer: "How has your daily routine changed in the last month?"<br>Patient: "I used to like to read, but now I don't anymore. My husband thinks I would feel better if I pushed myself to keep busy, but I tell him that this dizziness makes it impossible for me to do anything. I don't know what to think anymore."<br>Interviewer: "How else has your routine changed lately?" |
| High | Redirection | Patient: "I've always thought that my father's personality caused a lot of my troubles in life."<br>Interviewer: "I'd like to hear more of your thoughts about that, but first I need to get a clearer picture of what's been happening with you lately. When did you decide to make the appointment with me?" |
| High | Change of topics | "You mentioned before that your brother had similar problems to yours. Can you tell me how many brothers and sisters you have, and if they've had any emotional problems?"<br>"We've been talking about your marriage, but now I'd like to know something about your work." |
| High | Change of topics | "You mentioned before that your brother had similar problems to yours. Can you tell me how many brothers and sisters you have, and if they've had any emotional problems?"<br>"We've been talking about your marriage, but now I'd like to know something about your work." |
| High | Limit-setting | "I'm going to have to interrupt you because there are a few more things we need to cover in the time left."<br>"I know you feel restless, but I have to ask you to try to stay in your chair and concentrate on what we're talking about." |

the patient himself/herself has said. For example, confrontation makes the patient aware of paradoxes or inconsistencies in the material and requests him/her to resolve them; interpretation requests the patient to consider explanations or connections that had not previously occurred to him/her. Highly directive interventions aim to focus and restrict the patient's content or behavior. Such interventions include yes–no or symptom-checklist-type questions and requests for the patient to modify behaviors that impede the progress of the interview.

## Supportiveness

Patients vary considerably in the degree of emotional and cognitive support they need in the interview. Table 3–7 provides examples of emotionally supportive interventions. Each such intervention supports the patient's sense of security and self-esteem. While some patients may come to the interview feeling safe and confident, others have considerable anxiety about being criticized, ridiculed, rejected, taken advantage of, or attacked (literally so in the case of some psychotic patients).

Overt manifestations of insecurity range widely, from fearful demeanor and tremulousness to requests for reassurance to haughty contemptuousness. The interview's task is to identify such anxiety when it arises and respond in a manner that conveys empathic understanding, acceptance, and positive regard.

Obstructive interventions are one that (usually unintentionally) impede the flow of information and diminish rapport. Table 3–8 gives common examples of such interventions. Compound or vague questions are often confusing to the patient and may produce ambiguous or unclear answers. Biased or judgmental questions suggest what answer the interviewer wants to hear or that he/she does not approve of what the patient is saying. "Why" questions often sound critical or invite rationalizations. "How" questions better serve the purposes of the interview. ("How did you come to change jobs?" rather than "why did you change jobs?") Other interventions are obstructive because they disregard the patient's feeling state or what he/she is trying to say. Paradoxically, this may include premature reassurance or advice.

**Table 3–7 Supportive Interventions**

| Intervention | Examples |
|---|---|
| Encouragement | Patient: "I'm not sure I'm making any sense today doctor."<br>Interviewer: "You're doing very well at describing the troubles you've been having." |
| Approval | "You did the right thing by coming in for an appointment."<br>"You've been doing your best to keep going under very difficult circumstances." |
| Reassurance | "What you are telling me about may seem very strange to you, but many people have had similar experiences."<br>"You feel like you will be sick forever, but with treatment you have a very good chance of feeling better soon." |
| Acknowledgment of affect | "You look very sad when you talk about your brother."<br>"I have the impression that my question made you angry." |
| Empathic statements | "When your boyfriend doesn't call you, you feel completely helpless and unloved."<br>"It seems unfair for you to get sick so many times while others remain well." |
| Nonverbal communication | Smiling, firm handshake, attentive body posture, and gentle touch on shoulder. |
| Avoidance of affect-laden material | Interviewer elects to defer discussion or probing of topics that arouse intense feelings of anxiety, shame, or anger. |

**Table 3–8 Obstructive Interventions**

| Intervention | Examples |
|---|---|
| Suggestive or biased questions | "You haven't been feeling suicidal, have you?"<br>"You've had six jobs in the last 2 yr I guess none of them held your interest." |
| Judgmental questions or statements | "How long have you been behaving so selfishly?"<br>"What you've told me is typical of delusional thinking." |
| "Why" questions | "Why can't you sit still?"<br>"Why do you keep choosing men who can't make a commitment to you?" |
| Ignoring the patient's leads | Patient: "I'm afraid I'm going to fall apart."<br>Interviewer: "Have you had any odd experiences, such as hearing voices?"<br>Patient: "No, but I just feel as though I can't cope and I wanted to talk to someone about it."<br>Interviewer: "Has your sleep pattern or appetite changed?"<br>Patient: "Well, I don't sleep as well as I used to, but it's getting through the days that's the hardest."<br>Interviewer: Have you had any suicidal thought?" etc. |
| Crowding the patient with questions | Patient: "I just can't get it out of my mind that this cancer of mine is a punishment of some kind because I …"<br>Interviewer: "Have you been in a low mood or been tearful?" |
| Compound questions | "Have you ever heard voices or thought that other people were out to harm you?" |
| Vague questions | "Do you feel socially self-conscious a lot?"<br>"How much trouble do you have with your memory?" |
| Minimization or dismissal | Patient: "I don't seem to be able to enjoy my life as much as I think I should."<br>Interviewer: "You're doing well at your job and have a nice family—you're probably just feeling some minor stress." |
| Premature advice or reassurance | Patient: "I've been having terrible headaches and I forget a lot of things. There's nothing wrong with my brain, is there?"<br>Interviewer: "Headaches and forgetfulness are very common and are probably due to some minor cause in your case."<br>Patient: "I've started to have thoughts that I married the wrong man and I should leave my husband."<br>Interviewer: "Maybe the two of you ought to take some time away together." |
| Nonverbal questions | Sitting at a distance, yawning, looking at watch, fidgeting, frowning, and rolling of eyes. |

When given before the interviewer has explored and understood the issue, this has the effect of cutting off feelings and coming to a premature closure.

### Fact versus Feeling Orientation

Interviews differ in the degree to which they focus on factual–objective versus feeling–meaning oriented material. Tables 3–9 and 3–10 provide examples of interventions of both types. The interviewer must determine what the salient issues are in a given case and develop the focus accordingly. For example, at one extreme, the principal task in assessing a cyclically occurring mood disorder might be to delineate precisely the symptoms, time course, and treatment response of the illness. At the other end of the spectrum might be a patient with a circumscribed difficulty in living, such as the inability to achieve an intimate, lasting love relationship. In such a case, the interviewer may focus not only on the facts of the patient's interactions with others but also on the feelings, fantasies, and thoughts associated with such relationships.

### Feedback

Interviews differ in how much the interviewer conveys to the patient of his/her own thoughts, feelings, conclusions, and recommendations. Table 3–11 presents common types of feedback from the interviewer. Judicious statements about the interviewer's ongoing thoughts and feelings can be used to pose questions or make clarifications or interpretations while enhancing rapport and trust. Communication of factual information, formulations of the problem, and treatment recommendations are the foundations of joint treatment planning with the patient. Responding to questions and giving advice may serve an educational purpose, as well as enhancing the alliance. When responding to requests for advice or information, the interviewer must first take care to be sure of what is being asked, and for what reason.

There are little systematic data on the superiority of one clinical interviewing style over another, but what there are suggest that many styles can be used effectively. Rutter et al. have investigated this question in a series of naturalistic and experimental studies of interviews of parents in a child psychiatry clinic (Cox et al. 1981, 1988, Rutter et al. 1981). The major findings of these studies are as follows:

1. Active, structured techniques are no better than nondirective styles in eliciting positive findings (i.e., areas of pathology). However, active techniques are better in eliciting more detailed and thorough information in areas where pathology is found and are also better at delineating areas without pathology.
2. An active, fact-gathering style does not prevent the interviewer from effectively eliciting emotional reactions from informants.
3. Use of open questions, direct requests for feelings, interpretations of feelings, and expressions of sympathy are associated with greater expression of emotions by informants.
4. Less activity on the interviewer's part is associated with more informant talkativeness and spontaneous emotional expression. Less directive techniques also tend to produce more emotional responses at times when they are not specifically requested. Conversely, more active styles of asking about feelings may be more effective for informants who are low in spontaneous emotional expression.
5. In summary, techniques that actively elicit both facts and emotions are likely to produce the richest, most detailed database. When skillfully used, these do not impair the doctor–patient relationship.

**Table 3–9 Fact-Oriented Interventions in the Psychiatric Interview**

| Intervention | Examples |
|---|---|
| Questions about symptoms | "Do the voices seem to come from within your own head or from outside?"<br>"When did you first begin to check your door lock many times before going out?" |
| Questions about behavior | "What do you do when you fly into a rage—do you yell, hit the furniture, or hit people?"<br>"Since you've had your pain, how is your daily routine different than it used to be?" |
| Questions about events | "What was the next thing you did after you took the overdose of medication?"<br>"What led up to your decision to move out of your parents' home?" |
| Request for biographical data | "Who lived with you when you were growing up?"<br>"How many times have you been in a psychiatric hospital?"<br>"Tell me about your close relationships with women." |
| Requests for medical data | "What medicines do you take?"<br>"What conditions do you see a doctor for?" |

**Table 3–10 Feeling-Oriented Interventions in the Psychiatric Interview**

| Intervention | Examples |
|---|---|
| Questions about feelings in specific situations | "Some people might have been angry in the situation you told me about. Did you feel that way?"<br>"How did you feel when your doctor told you that you had a heart attack?"<br>"I've noticed your voice got much quieter when you answered my last question. What were you feeling just then?" |
| Questions or comments about emotional themes or patterns | "Growing up, you never felt like you measured up to your mother's expectations. Do you feel that same way in your marriage?" |
| Questions or comments about the personal meaning of events | "You are concerned about becoming enraged at your daughter. When she disregards your wishes, what do you feel that means about you as a parent?" |

## Special Problems in Interviewing

### The Delusional Patient

Clinical Vignette 4

A 26-year-old man presented to the emergency department seeking a safe haven from "the mob." He was convinced that he was being set up to be killed, as evidenced by the sequence of license plate numbers of the cars that had passed him on the way to work. He had initially gone to a police station, which had referred him to the hospital.

**Table 3–11 Feedback in the Psychiatric Interview**

| Intervention | Examples |
|---|---|
| Sharing of ongoing thoughts | "As you were talking I began to wonder if you had ever lost anyone very close to you."<br>"As I hear your story it occurs to me that you've been an outsider every place you've lived in." |
| Sharing of subjective reactions | "What you are saying makes me feel quite sad."<br>"You've told me how you left treatment with your last psychiatrist, but I still feel a bit confused about what happened."<br>"I notice I'm feeling somewhat tense right now and I wonder if you might be feeling it too." |
| Imparting of information | "About 75% of people with your condition respond well to medication."<br>"The tendency to develop the kind of symptoms you have described runs in families, and probably is inherited." |
| Proposing a formulation | "I think the immediate cause of your depression and insomnia is your heavy drinking."<br>"When you are under stress you tend not to think clearly and to develop unrealistic fears. It seems as though your present stress comes from the way you and your family are getting along at home." |
| Making treatment recommendations | "In order for you to keep safe and begin treatment I think it would be best to go into the hospital for a while."<br>"Medication should help you get out of your depression much faster. When you are feeling better, it would be a good idea for us to try to understand how you got so isolated from your friends and family." |
| Advice | "It might be better not to decide about changing jobs until you're feeling back to your regular self." |
| Response to questions | Patient: "What type of psychiatrist are you, doctor?"<br>Interviewer: "I'm a general psychiatrist who uses medication and psychotherapy. I also have a special interest in anxiety disorder."<br>Patient: "Have you ever seen another patient like me?"<br>Interviewer: "I can answer your question better if you tell me what there is about you that I might have never seen before."<br>Patient: "Do you think I'm a terrible person?"<br>Interviewer: "I don't think you are terrible, but I wonder what you think about yourself that you would ask me that." |

Psychotic patients often present with a variety of delusions—fixed, false beliefs that are not consistent with their cultural milieu. Delusions may be persecutory, grandiose, or a variety of other types. Conducting an interview with a patient who is not in touch with reality can be unsettling: often the patient is aware that what he/she is saying is odd and may seek reassurances that he/she is believed.

The interviewer must walk a fine line between giving what reassurance he/she can, while at the same time not validating the delusions. Often the question "do you believe me?" can be interpreted as "will you help me?" The clinician should not simply agree with a patient's bizarre belief system. He or she might instead express genuine surprise at the ideas presented (a surprise which the patient likely shares, thus enhancing a sense of common purpose) and question if the patient is sure of this or how does he/she know for certain. If pressed, a reasonable response could be "it seems unlikely," with an offer to work with the patient to discover the truth. It may also be helpful to agree with the affect but not with the facts. Thus, one might say, "You don't feel safe out there right now."

It is also important to keep in mind that delusions are by definition unresponsive to logical argument. Whatever psychological or neurobiological purpose they serve will not be easily abandoned. The interviewer risks any chance of alliance, with almost no chance of benefit, by trying to persuade a patient he/she is mistaken. In the case described earlier in this section, if the interviewer sought to convince the patient that he/she was not the object of a potential murder; it is quite possible that the patient would begin to suspect that the interviewer was himself/herself a part of the conspiracy.

## The Violent, Agitated Patient

Clinical Vignette 5

A 48-year-old woman with a history of alcohol dependence is in her second postoperative day. Her physician is called after she assaulted the nurse who came to check her vital signs. The patient was being restrained by security personnel when the physician arrived. She was screaming, "They're coming to kill me. I have to get out," and was trying to bite the hands of those restraining her.

Agitation is a sign of many different types of mental disorders as well as a part of normal temperament variation. Extreme degrees, leading to violence, are a common reason for psychiatric as well as legal interventions. The clinical interview requires, first of all, that a safe environment be established. No helpful intervention can be made in an atmosphere of fear and uncertainty. Adequate resources such as additional people, physical restraint, seclusion, or distance must be used in order to obtain an appropriate assessment (Marder 2006).

In conducting an interview with an unpredictable or potentially violent person, it is appropriate to make the patient aware of one's concern that he/she might be unable to control himself/herself and find out if the patient agrees. If he/she does, then the patient and interviewer together must ensure a safe environment. Most potentially, violent people fear the violence as much as anyone and are relieved by efforts to help them maintain control—even with the use of four-point leather restraints (though this must always be the last resort, used only when all else fails).

If a patient is unable to agree with needed measures, and the potential for violence mandates their use, the intervention should proceed in an orderly manner. Explanation should be given to the patient concurrently, including exactly what will be done, the reason for it, assurance of the patient's safety, and what behavioral requirements there are for the cessation of the intervention.

Sometimes patients will refuse to conduct an interview after safety measures have been instituted. They will insist that the interview-room door not be left open, that security personnel leave, that they be permitted out of a seclusion room, or that restraints be removed. Assuming that the initial decision for such intervention was appropriate, it is useful to remind the patient that a valid assessment is the quickest way to achieve what he/she wishes. No one should accept an unsafe situation as part of a bargain to get questions answered.

## The Hostile Patient

Clinical Vignette 6

A 15-year-old girl is brought to the office by her mother because of illicit drugs found in her room. The patient slouches in a chair and tells the interviewer, "I don't like you and I don't like this place. My mother's the one with the problem, talk to her."

A therapeutic alliance is the sine qua non of most interviews. Without an agreed basis on which to work, anything an interviewer says can be interpreted as intrusive and provoke an angry response. Overt hostility must be acknowledged right at the outset, or the patient may perceive further things to feel hostile about. Pointing out the incongruity of the anger, once it is acknowledged, can be the next step; after all, the clinician presumably is conducting an evaluation in the service of the patient.

An understanding of the true object of the patient's anger, such as her mother in the case above (or more precisely, what the mother represents), can be helpful, especially if the clinician can define a boundary between this object and himself/herself: "I'd like to be of help to you; your mother will have to wait."

Clearly, responding to hostile provocation with hostility has no place in an interview. Ignoring it, or being too accommodating to provocative acts, can have deleterious effects as well, by breaking the usual interview frame of two people working together to solve the problems of one of them.

## The Depressed Patient

Clinical Vignette 7

A 70-year-old man is brought for evaluation by his children. Since his wife's death 8 months ago, he has lost 30 pounds. The children report that he leaves his home only when they strongly encourage him, and that he has stopped joining in conversation.

Talking to a profoundly depressed patient can sap the energy of the interviewer. The patient will often have the classic symptom of prolonged latency of response; it can be difficult to avoid repeating the question, suggesting responses, or simply changing the line of inquiry. An occasional rephrasing or seeking to find out if the patient understands the question is all the interviewer can do. A great deal of patience is required when conducting an evaluation of someone very depressed.

Another difficult aspect of dealing with a very depressed person is the emotional drain. The pessimism, hopelessness, and helplessness of these patients can be somewhat infectious. Those who express existential despair (lamenting the human condition) or who have suffered a painful loss that the interviewer might tend to identify with (e.g., the death of a child) can evoke an empathic response of shared pain or futility. It is important to recognize this as another element of the diagnosis and reflect a bit of it back to the patient to aid in rapport-building but keep oneself well centered.

Crying is a frequently encountered affect in the interview of a depressed patient, which is sometimes problematic. Especially when the patient's first priority is expressing the depth of his emotion, it may be difficult to get needed information. At times, the patient must be told of this difficulty and the importance of completing the assessment in a timely manner in order to reduce his/her pain.

When the widower insists that life is meaningless now that he is old and alone, the interviewer must be careful to detect the nihilism of depression and to educate the patient about this process.

## The Confused Patient

Clinical Vignette 8

A 76-year-old woman is brought by her family for evaluation after she was found wandering in the streets surrounding her home. She has had a progressive decline in her memory and ability to care for herself, and her family is concerned that she might need to be placed in a nursing home. The patient has become combative at times when caretakers are brought into the home to assist her, because she believes they are trying to rob her.

Assessing a patient with cognitive loss requires a ratcheting down of expectations for historical data and the realization that the going will be slow. Most patients who are confused will not be able to respond to open-ended questions reliably; the unstructured stimulus requires too much secondary processing on the patient's part. Instead, simple yes–no questions, of no more than about 10 words, are likely to yield the most reliable responses.

Patients with memory problems will also need to be frequently reoriented to their surroundings as well as to the task at hand. It is helpful to query the patient about his/her current situation at times and provide the reassurance of his being in a treatment situation dedicated to his/her welfare.

The mental health status exam of the confused patient deserves special attention. It is important that the patient's performance be characterized precisely: both the requested task and the patient's response should be included. The format of most standard tests—serial 7's, remembering three objects, presidents backward, digit span, spelling *world* backward—does not require explication; it is important, though, to describe exactly how the patient responded to which test rather than just a notation of poor memory or concentration.

With confused patients, more than any other, the setting of the interview can markedly affect the results. Patients with impaired cognitive processing are very susceptible to extraneous distractions—the capacity to focus attention is often lost. As much as possible, stimuli other than the interviewer should be at a minimum. When outside forces interfere, they should be noted as part of the database; this includes physical aspects of patient comfort, such as uncomfortable positioning in restraints or pain from underlying medical illness.

## The Seductive Patient

**Clinical Vignette 9**

A woman in her 30s is referred by another patient for an evaluation for anxiety and work inhibition. She describes a series of unhappy relationships and then begins to discuss what she knows of the interviewer's personal life, by way of comparison. She announces, "Jill was right—you are very easy to talk to. What am I going to do when I fall in love with you? I guess that's easy—the real question is, what are you going to do?"

Psychiatric assessment requires that the interviewer display a degree of emotional openness and support that can stimulate a powerful longing in some patients. Few aphrodisiacs can compare in potency to the sincere, nonjudgmental interest from another person, especially one in a position of relative power. In particular, patients who have been sexually abused as children, or those who have been unable to achieve close relationships, will sometimes find the interview an invitation to greater intimacy.

At one level, the management of this problem is straightforward. The patient is reminded of the limits of the situation, what role he/she and the interviewer have, and the inviolable boundaries that apply. However, it is important to set limits in a way that does not imply reproach. A good clinician will try to foster an atmosphere wherein the patient can feel comfortable sharing anything, including such deeply personal things as sexual attraction. Therefore, the interviewer must maintain the boundary between expression of sexual feelings and acting on them.

The interviewer's own emotional reaction to the patient, including at times sexual attraction (or repulsion), can play a part in how he/she responds to seductiveness. An awareness that the patient is usually responding more to what he/she needs to see or hear (i.e., to transferential perceptions), rather than to the actual person of the interviewer, can help keep the interaction in perspective.

Seductiveness on an initial interview, such as described above, is rare. It may signify a frontal lobe dysfunction or hypomania, or a misunderstanding of the clinical situation. Pointing out this misunderstanding is an effective way of management. "My understanding is that your're here for help with some things that are troubling you. Helping as your therapist is something I can do, but that is a specifically limited relationship."

## Cultural Disparity

Significant cultural, religious, ethnic, racial, language, and other differences between the patient and the interviewer

**Clinical Vignette 10**

A man in his 20s is brought to the emergency room by his male lover/partner for treatment of self-inflicted wrist cuts. These had occurred during a violent fight between the two. The patient refused to be evaluated by a male psychiatric resident unless he first answered a long list of questions about his attitudes toward gays.

create at least three major problems, which are closely related: the basic problem of obtaining information, the interpretation of information in the appropriate cultural context, and finally the establishment of necessary rapport. The information-gathering problem is obvious when the patient literally speaks a different language, but it can be just as problematic, or even more so, when the patient belongs to a subculture with idiosyncratic word usage, nuances, values, and styles of interaction.

The use of an interpreter deserves special mention. Whenever possible, an unbiased third party should be used rather than a family member. The interpreter must be explicitly instructed to interpret verbatim, as much as possible, except perhaps in the fortuitous circumstances where the interpreter is also a clinician. The purpose of the interview, how long it will last, and of course the need to respect confidentiality should all be explained. Confidentiality is especially important when dealing with members of small minority groups, because the likelihood of common business or social ties is high.

Membership in subcultures creates problems for understanding "peculiarities" of word choice and concept. Assessment for delusional beliefs in particular must take the patient's background into account; a delusion cannot be diagnosed if the belief is shared by a significant percentage of the patient's peers. The degree of emotional expressiveness, guardedness in the presence of others, the amount of eye contact, the rate and tone of speech are all cultural variables. Consultation with other members of the culture will help to set the norm against which the patient must be evaluated.

The final issue, and the one described in the last example, is the degree of comfort a patient can have with an "outsider." The wish to be understood, to be accepted, and to be valued are part of the human condition and are at work in nearly every interview. When there are cultural discrepancies between the patient and the clinician, fears of being misunderstood can be overwhelming. It is the interviewer's responsibility to reassure the patient of his/her commitment to understanding the patient as best as possible and to take what steps he/she can to minimize the chance of distortion.

## The Deceitful Patient

**Clinical Vignette 11**

A man in his 50s presents to a hospital emergency room complaining of memory loss after having fallen down. A work up for mental status change is begun, until the patient is recognized by a resident who had seen him while moonlighting in another hospital. His complaint of memory loss had mysteriously vanished after spending the night and eating breakfast in the emergency room.

One of the basic expectations of the doctor–patient relationship is honesty. Patients come in asking for help and are expected to give whatever information is required honestly. One of the formative events of any clinician's professional development is the dawn of awareness that sometimes patients lie, either by omitting important parts of the history or by actually fabricating symptoms.

There are many different reasons for the deception. Most commonly, the patient has a different agenda, which he/she feels must be kept hidden from the interviewer and which is often directed toward achieving the secondary gains of illness. At times, the patient hides symptoms because of his/her own fear of them or because of his/her fear of what treatment might be required. A patient who is mistrustful of the medical establishment may be unwilling to share important information, believing that the patient himself/herself is the best judge of what care he/she needs, and will couch the patient's replies in the way he/she thinks will best achieve his/her own ends.

In addition to consciously lying to achieve secondary gain (known as malingering), there is another scenario in which patients speak falsely. Factitious disorder, or Munchausen's syndrome, is an example of a patient making false statements about himself/herself and his/her disease. These are usually elaborate tales of illness, often accompanied by hidden actions to bolster the story or even to induce sometimes life-threatening symptoms. In this circumstance, there is no secondary gain; the motivation appears to be simply to gain the patient role and all the benefits that entail, and fool medical caregivers in order to satisfy deeper psychological needs.

Both of these types of deceit, malingering and factitious, must be distinguished from situations in which the patient is unaware that he/she is giving misinformation. Patients with conversion disorder experience neurological symptoms purely on a psychological basis and may be unable to speak, walk, or see with no organic defect. These patients are not being deceitful; they truly cannot function and will not until their illness is treated.

## Telepsychiatry

Modern audiovisual telecommunication offers the possibility of bringing psychiatric services to patients who otherwise would have no access to them. Advantages of telepsychiatry over telephonic communication are the enhanced "social presence" provided by the visual modality and the chance to observe nonverbal forms of communication. At the same time, the procedure still has technical limitations that may degrade the visual image and contribute to a depersonalized quality in the interview. Research has shown that, in terms of quantity of usable visual cues and patient satisfaction, telepsychiatry interviews are better than those conducted over the telephone, but not as good as in-person interviews (Ball et al. 1995, Gammon et al. 1998).

Experience in telepsychiatry suggests the following guidelines to enhance the effectiveness of the interview (Hilty et al. 2002):

1. The interviewer should practice with staff before attempting a telepsychiatry interview with a patient.
2. The interviewer must pay extra attention to his/her own and the patient's nonverbal communication. In the present case, attention to facial expression, body posture, and body mobility would be especially important.
3. The setup should provide far-end camera control, so that the interviewer can refocus or zoom the camera as needed.
4. The interviewer should learn to avoid rapid movements, which will transmit with poor quality.
5. The equipment should use as high a bandwidth Internet connection as possible (preferably, at least 384K) to maximize clarity and avoid movement artifacts (Yoshino et al. 2001).

Clinical Vignette 12

The patient is a 71-year-old woman living on a farm in a rural area. She has been seen by her primary care physician with increasing frequency over the past 3 months for complaints of fatigue, chest pain, and dyspepsia. Repeated medical evaluations have turned up no significant pathology, and her physician has referred her to be evaluated for depression. There is no psychiatrist in the area, and the patient cannot drive long distances. However, the local medical clinic has a telemedicine setup that is linked to a branch of the state medical school. A psychiatric interview using this audiovisual equipment has been scheduled.

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CHAPTER 4

# The Cultural Context of Clinical Assessment

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## Introduction: The Cultural Matrix of Psychiatry

Although it has long been recognized that the mode of expressing psychological distress and behavioral disturbances varies with cultural beliefs and practices, a growing body of evidence shows that the effects of culture are more far-reaching. Research has clearly demonstrated that the causes, course, and outcome of major psychiatric disorders are influenced by cultural factors (Kleinman 1988, Kirmayer 2001, Leff 2001, López and Guarnaccia 2000). For example, international studies by the World Health Organization have provided compelling evidence that the prognosis for schizophrenia is better in some developing countries than it is in England or the US (Jablensky et al. 1994, Craig et al. 1997). Wide variations in the prevalence of many psychiatric disorders across geographic regions and ethnocultural groups have been documented with current standardized epidemiological survey methods (Canino et al. 1997, Kirmayer and Groleau 2001). In addition, social and cultural factors are major determinants of the use of health care services and alternative sources of help (Rogler and Cortes 1993).

For all these reasons, a careful assessment of the cultural context of psychiatric problems must form a central part of any clinical evaluation (GAP 2002). Beyond this, culturally based attitudes and assumptions govern the perspectives that both patient and clinician bring to the clinical encounter. Lack of awareness of important differences can undermine the development of a therapeutic alliance, and the negotiation and delivery of effective treatment.

The changing demography of North America has made the recognition and response to cultural diversity increasingly important in psychiatric practice (GAP 2002, Gaw 1993, Lim 2006). The US and Canada have always been the countries of immigrants, but earlier waves of migration involved people from European backgrounds who shared many commonalities. In the US, the overarching ideology took for granted that these newcomers would gradually become just like all other Americans through a process of cultural assimilation (Portes and Rumbaut 1996, Susser and Patterson 2001). However, sociological research has shown a high degree of retention of ethnic culture with the persistence of religious practices, family life cycle rituals, and ethnic enclaves in many cities. Added to this is the recognition of the importance of maintaining and renewing ethnocultural identity to combat the legacy of racial discrimination against African Americans, Native American people, and other groups. This has led to rethinking of the notion of assimilation to take into account other modes of acculturation including the development of multiple cultural identities.

More recent waves of global migration from south to north and east to west have brought together new mixes of people with greater differences in their cultural assumptions with corresponding challenges for intercultural clinical work. Although the US maintains a dominant social ethos and "mainstream" culture, the country is moving rapidly toward a composition of a majority of minorities. This is also reflected in the changing demography of the profession of psychiatry itself.

These changes, along with larger forces of globalization, have encouraged a fresh look at culture in every area of psychiatry. In clinical practice, "cultural competence" has become the rubric under which to advance a broad range of skills and perspectives pertinent to working with a culturally diverse clinical population (GAP 2002). In the sections that follow, we will summarize some of the concepts and approaches that can inform the culturally competent clinical practice.

## What is Culture?

There is a famous saying to the effect that "we don't know who discovered water but it wasn't the fish." So it is with

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culture: we are immersed in our own cultural worlds from birth, and consequently, our culture is largely implicit and unexamined. Just as we are unconscious of many of our own motivations and patterns of thought and behavior until they are reflected back to us by others, so too we are unconscious of our cultural background knowledge and assumptions. Bringing the cultural unconscious to light may be more difficult than facing the individual unconscious because institutions and others around us may reinforce our assumptions and resist any attempt to question them. Our explicit appreciation of culture usually comes from intercultural encounters, which make us suddenly aware of culture through difference. More formally, anthropological research comparing different cultures allows us to see the tacit assumptions of our own worldviews. There is no substitute for this sort of systematic reflection on cultural difference, which should extend to the critical analysis of the construction of psychiatric knowledge (Lock and Gordon 1988, Young 1995).

Older views of culture were based on ethnographic studies of relatively isolated, small-scale societies. Many accounts tended to assume that cultures were finely balanced systems and that, as a result, everything was for a purpose and had an adaptive function for the group (if not always for the individual). The outsider was thus cautioned not to pass judgment on cultural differences or to see pathology where there was a simple difference. This is still a wiser advice. However, it is clear that cultures are not homeostatic systems in a steady state or equilibrium but are constantly shifting and evolving systems. They may be driven by conflict and create maladaptive circumstances, not only for disadvantaged individuals, but for specific groups or even the whole society. Thus, while refraining from prejudging specific cultural values or practices, the clinician must nevertheless consider that every culture encompasses practices that may help or hinder patients, and aggravate or ameliorate any given type of psychopathology. Each society tends to cultivate blind spots around the specific forms of social suffering that it produces (Kleinman et al. 1997). Openness, respect, and capacity for collective self-criticism are thus key elements of any transcultural clinical encounter.

At the same time, anthropologists have come to recognize the high level of individual variability within even small cultural groups, and the active ways in which individuals and groups make use of a variety of forms of knowledge to fashion an identity and a viable way of living. In urban settings where many cultures meet, individuals have a wide range of options available, and can position themselves both within and against any given ethnocultural identity or way of life. This has led the anthropologists to rethink the notion of culture or even to suggest that it has outlived its usefulness.

Indeed, the modern world includes forms of electronic communication and rapid transportation that have begun to weave the whole globe together in new ways. This results in the intermixing of cultural worlds and the creation of new ethnocultural groups and individuals with multiple or hybrid identities. Many people now see themselves as transnational, with networks of affiliation and support that span great distances. The mental health implications of these new forms of identity and community have been little explored, and will be an increasingly important issue for psychiatry in the years to come (Bibeau 1997, Kirmayer and Minas 2000).

As this brief discussion makes clear, the notion of culture covers a broad territory. It is useful precisely because of this breadth, but to apply it to clinical practice we need to make some further specifications and distinctions. In the North American context, it is useful to distinguish notions of race, ethnicity, and social class from culture.

Race is a term used to mark off groups within and between societies. Racial distinctions generally reflect a few superficial physical characteristics and hence have little correlation with clinically relevant genetic variation. The boundaries of any racial group are socially defined and have no biological reality (Graves 2001). Race is usually ascribed by others and cannot be readily changed or discarded unless larger social criteria change. Race is significant as a social category that is employed in racist and discriminatory practices. Racism is clinically important because of its demonstrable effects on mental and physical health, individual and collective self-esteem, and health service utilization(Hollar 2001, Smedley, Sith and Nelson 2003). The painful history of slavery and racial discrimination in the American society makes it difficult for people to talk readily about their experiences of racism, and so the clinician needs to work at becoming clear, sensitive, and open to discussing the impact of racism on patients' lives, as well as its inevitable expressions in his or her own thinking (Pinderhughes 1989).

Ethnicity refers to the collective identity of a group based on common heritage, which may include language, religion, geographic origin, and specific cultural practices. Ethnic identity is often constructed vis-à-vis others and a dominant society. Hence, it is sometimes assumed that "foreigners" or minorities have ethnicity while the dominant group (e.g., Americans of British or Northern European extraction) does not. This obscures the fact that everyone may become aware of an ethnic identity in the right context (in China, an American clearly has a distinct ethnicity). Ethnicity may be chosen or ascribed by others. For example, the US census defined five ethnoracial blocs: White, African American, Hispanic, Asian American and Pacific Islander, and American Indian and Alaska Native. These are heterogeneous categories variously based on race, language, geographic origin, and ethnicity. Although the categories are fictive, they have acquired practical and political reality because they have been used to present epidemiological findings and define health-service needs (Hollinger 1995). Nevertheless, the clinician must recognize that to meet the patient on a common ground requires a much more fine-grained notion of ethnocultural identity than afforded by these crude categories.

Finally, social class reflects the fact that most societies are economically stratified and individuals' opportunities, mobility, lifestyle, and response to illness are heavily constrained by their economic position. Issues of poverty, unemployment, powerlessness, and marginalization may overshadow cultural factors as causes of illness and influences on identity and help-seeking behavior. Violence is a particularly striking example in North American society of the overlap of exclusion, poverty, discrimination, and intergenerational transmission of trauma.

The notion of culture is sometimes extended to speak of various subcultures or the cultures of professions. In this sense, we can speak of the cultures of biomedicine and of

psychiatry. Each of these systems of knowledge includes a wide range of behavioral norms and institutional practices that may be familiar to clinicians but novel and confusing to patients. However, familiar cultural notions of self and personhood underwrite these technical domains, which therefore serve to reinforce larger cultural ideologies (Lock and Gordon 1988). This becomes clear when we consider alternative systems of medicine such as traditional Chinese medicine or Indian Ayurveda, which are based on different notions of the person (ethnopsychology), the body (ethnophysiology), different roles for patient and healer, and, indeed, different epistemologies (Leslie and Young 1992). Even the understanding and practice of biomedicine may differ across countries; so the clinician should not assume that familiar terms always refer to the same practice.

## Culture and Gender

Gender refers to the ways in which cultures differentiate and define roles based on biological sex or reproductive functions. Because of this link with physical aspects of sex, there is a tendency to view gender differences as biologically given. However, while some distinctions may be closely related to the physiological differences between males and females, most are assigned to the sexes on the basis of specific cultural beliefs and social organization (Comas-Diaz and Greene 1994).

Men and women do have some fundamentally different experiences of their bodies, of their social worlds, and of the life course. It has been suggested that women are more in touch with their bodies because of the experiences of menstruation, childbearing, childbirth, breast-feeding, and menopause. These differences may be as substantial as any between disparate cultures. At the same time, there is much evidence that these bodily grounded experiences vary substantially across cultures. For example, anthropologist Margaret Lock (1993) has shown that Japanese women report fewer bodily symptoms of menopause and do not think of the end of menstruation as a distinctive "change of life" in the same terms as many women in North America.

There are also important gender differences in styles of emotional expression, symptom experience, and help-seeking. In epidemiological surveys in the US, women tend to report more somatic symptoms as well as more emotional distress, and they are more likely to seek help for psychological or interpersonal problems. However, the gender difference in symptom reporting varies significantly cross-nationally (Piccinelli and Simon 1997).

In North America, important differences have been documented in male and female styles of conversation that are relevant to the clinical context (Tannen 1994). In general, women tend to give more frequent acknowledgments that they are listening to a speaker. They may give signs of assent simply to indicate that they are following the conversation. Men tend to be more taciturn and, if they signal assent, it usually means that they actually agree with the speaker. These differences in communication style may lead to systematic misunderstandings between men and women that are further aggravated by cultural differences in gender roles and etiquette. This may occur in clinical settings where rules for gender appropriate behavior and interaction between men and women may be misinterpreted as evidence of individual personality traits or psychopathology(as illustrated in the Clinical Vignette 1).

**Clinical Vignette 1**

When an ultraorthodox Jewish family arrives for their consultation, the female psychiatrist, who is dressed in a short skirt, welcomes them offering her hand to the father in greeting. He is confused and offended, avoids eye contact, and is reluctant to proceed with the session. The female doctor's style of dress and friendly handshake were viewed as disrespectful or as indicating her lack of familiarity with norms of conduct with observant orthodox families.

In many societies, gender is associated with marked differences in power and social status. For example, in patriarchal societies, men have specific power and privileges that give them a measure of control over the lives of women. This is often coupled with responsibilities for maintaining family honor and well-being. In recent years, the North American society has espoused social and political equality in gender roles. From this egalitarian point of view, patriarchal families may seem oppressive to women. However, women may accept and participate in cultural definitions of their roles that appear restrictive by North American cultural norms but make family life meaningful. Any judgment as to whether a given family's relationships are oppressive or pathological must not only take into account social norms and practices but also explore the meaning of issues and events for the individuals involved. A common dilemma in assessment occurs in clinical interviews when women show culturally prescribed deference in the presence of their husbands or male kinfolk. (Clinical Vignette 2).

**Clinical Vignette 2**

A 29-year-old East Indian woman, in the US for six months, presents with symptoms of depression and posttraumatic stress disorder (PTSD). Throughout the initial evaluation, the patient looks away from the male psychiatrist, never making an eye contact. The interviewer is concerned that he may have offended the woman in some way. The female interpreter explains that the patient is showing respect by not looking directly at a male in authority.

Differences in cultural definitions of gender roles may become sources of conflict after migration. Culturally prescribed patterns of marriage and child bearing may be central to the social status, identity, and self-esteem of men and women even when they are not given the same importance in the dominant culture. For example, for women

**Clinical Vignette 3**

A 28-year-old woman from South Asia has an arranged marriage with an older man from the same religious community, who has lived all his life in the US. The couple has been unable to conceive for five years and is in the midst of extensive infertility treatments. The husband complains that she is paranoid and does not want to work or go out of the house. The woman tearfully relates that she feels depressed and ashamed because of her predicament, and fears that her marriage will end if she cannot bear children.

from some backgrounds, a socially valued identity may be strongly linked to childbearing and infertility may precipitate a crisis both for the individual and the extended family. As seen in Clinical Vignette 3, this may express itself not only in symptoms of demoralization and depression but in intense concern about one's social standing with others in the community.

## The Cultural Formulation

In an effort to address the cultural dimensions of clinical assessment, DSM-IV-TR introduced an outline for a cultural formulation (Table 4–1). This outline covers the major areas that a clinician should explore in a comprehensive evaluation. These are integrated in a formulation that helps to account for symptomatology, diagnosis, prognosis, and appropriate treatment (Lewis-Fernandez and Diaz 2002). The cultural formulation may go well beyond the DSM-IV-TR categories to consider many sorts of problems and predicaments relevant to the patient's well-being.

**Table 4–1 DSM-IV-TR Outline for the Cultural Formulation**

- Identity of the individual
- Explanations of the illness
- Psychosocial environment and levels of functioning
- Relationship between the individual and the clinician
- Overall assessment with implications for diagnosis and care

*Source:* American Psychiatric Association 1994, pp 843–849.

The cultural formulation is merely intended as a checklist or reminder to encourage the clinician to perform the needed exploration and integration of a broad range of relevant social and cultural information. Clearly, cultural considerations may apply to every aspect of the clinical assessment and interview, and must not be used only as an afterthought to the standard psychiatric interview.

### Ethnocultural Identity

The first dimension of the cultural formulation involves ethnocultural identity. This includes the individual's ethnic or cultural reference groups and the position of these groups vis-à-vis the larger society. Certain groups have a specific ethnocultural identity ascribed to them by others; this may have an impact on individuals' everyday experience and narratives of identity whether or not they are explicitly aware of it.

In a world of mass migration and intermingling of people over generations, identity is very often hybrid, multiple, and fluid (Bibeau 1997). For immigrant and ethnic minorities, it is important to understand the degree of involvement with both the culture of origin and the host culture. Ethnic identity may be situational and may shift with social context. The ethnocultural and religious groups with which the patient identifies the most may depend on who asks the question and in what context. For example, whether someone self-identifies as Canadian, West Indian, or Trinidadian may depend on the perceived identity of the interviewer and the setting where the interview takes place.

Language is central to identity for many people and has a profound effect on clinical encounters. Individuals who speak multiple languages, learned at different stages in their life, may have different memories, effects, and interpersonal schemas associated with the use of each language. Languages may be associated with developmentally important relationships and tied to specific areas of conflict or mastery. Personal and political allegiances within the family and community may be expressed through choice of language.

Language is the medium through which experience is articulated; hence, the assessment of higher cognitive functions, complex emotions, and experiential symptoms of pathology all depend on the clinician's access to the patient's language. Patient's who are hobbled in a second language may be misjudged as less intelligent or competent than they actually are; wishing to avoid such bias, clinicians may be overly generous in their assessment and miss significant problems or pathology.

Even where patients have a moderate level of facility in the clinician's preferred language, they may not express themselves fully in a second language so that important details are not conveyed. The use of a second language not only affects doctor–patient communication, but also influences individuals' ability to reflect about themselves. When the patients are forced to formulate their problems in a language in which they are not proficient, they may be less creative and effective as problem solvers. When patients are able to use their own best language, their accounts of experience become much richer, more complex, and nuanced; their thinking is subtler; they can express a wider range of affections and engage in playful therapeutic exchanges.

Multilingual people sometimes report that they feel and think differently when using a second language. This is partly due to the cognitive effort of having to find words in a language in which one is not totally fluent. Since each language favors certain modes of expression and ways of thinking, bilingual speakers may report that they feel like a different person in their other language. It follows that aspects of history and experience of a patient can be less accessible in a clinical evaluation if patients are not able to express themselves in the appropriate language. Of course, use of a second language may also afford the patient some distance from intense emotions and painful memories and so assist in coping and affect regulation. Careful attention to spontaneous or strategic shifts in the use of language in a multilingual assessment can provide the clinician with important information about areas of conflicts and strengths. This often requires the use of a trained interpreter, as discussed in a later section of this chapter.

Religion is another key marker of identity. For many individuals and communities, it may structure the moral world more strongly than ethnic or national identity. The term "spirituality" has gained currency to acknowledge the fact that many individuals maintain deeply held personal beliefs about God, the meaning of life, and what happens after death without being formally affiliated with one religion or another. Religious affiliation is also a frequent source of discrimination.

Despite the ubiquity of religious and spiritual experience, it is frequently neglected during routine psychiatric evaluation. A thorough cultural formulation requires consideration of the patient's religion and spirituality. Areas to cover include religious identity, the role of religion in the family of origin, current religious practices (attendance at services, public and private rituals), motivation for religious

behavior (i.e., religious orientation), and specific beliefs of the individual and of his family and community

## Illness Explanations and Help-Seeking

The second major dimension of the cultural formulation concerns the cultural explanations of symptoms and illness. Cultures provide systems of diagnosis and treatment of illness and affliction that may influence patients' experience of illness and help-seeking behavior. People label and interpret their distress based on these systems of knowledge, which they share with others around them. Much research in medical anthropology has developed the idea of explanatory models, which may include accounts of causality, mechanism or process, course, appropriate treatment, expected outcome, and consequences. Not all of this knowledge is related directly to personal experience—much of it resides in cultural knowledge and practices carried on by others. Hence, understanding the cultural meanings of symptoms and behavior may require interviews with other people in the patient's family, entourage, or community. (Kirmayer, et al. 2004,Philips, et al. 2002)

**Table 4–2** **Explanatory Model Interview** (Kleinman et al. 1978)

1. What do you call your problem?
2. What causes your problem?
3. Why do you think it started when it did?
4. How does it work?
5. What is going on in your body?
6. What kind of treatment do you think would be the best for this problem?
7. How has this problem affected your life?
8. What frightens or concerns you most about this problem or treatment?

Table 4–2 provides questions for eliciting patients' explanatory models. These questions should be modified based on the patient's responses. For example, the origins of problems may be located not in the body but in the workings of the mind, the family, the community, the realms of ancestors or spirits, or in mythological accounts which explain the social and moral order.

In many cases, particularly with acute illness, patients may not have well-developed explanatory models. Instead, they reason by analogy on the basis of past experiences of their own or other prominent prototypes encountered in family, friends, or mass media. Once an explanatory model is evoked in conversation, patients may give formulaic accounts that accord with that cultural model or script. Therefore, to obtain more complete information about the cognitive and social factors that are actually influencing the patients' illness experience and behavior, it is useful to begin with an open-ended interview that simply aims to reconstruct the events surrounding the symptoms and the patient's illness experience (Groleau, Young and Kirmayer 2007). This will reveal idiosyncratic temporal patterns of contiguity and association that may not fit any explicit cultural model. Following this, the clinician can ask about prototypes (Have you ever had anything like this before? Has anyone you know ever had anything like this before?). This will uncover salient models of illness that may shape illness experience and be used to reason analogically about the current episode. Finally, it is important to inquire into explicit cultural models using the sorts of questions devised for the explanatory model interview.

The ethnomedical systems described in anthropological texts are often idealized and complex portraits pieced together by working with cultural experts. In clinical practice, patients usually have only partial or fragmentary knowledge of the traditional explanations and treatment for their problem. Depending on the knowledge and attitudes of family and kin, and on the availability of practitioners of traditional medical systems, patients may be influenced by larger cultural systems to which they themselves do not fully subscribe. Eliciting these illness interpretations may require a high level of trust and rapport, particularly when they are viewed negatively (e.g., as "backward" or "superstitious") or have led to conflicts with other professionals in the health care system. In many cases, people employ multiple interpretive systems that link their symptoms to salient life events and issues. This is particularly the case with serious, chronic, or disabling conditions that often receive explanation in moral, spiritual, or religious terms, as seen in Clinical Vignette 4.

In everyday life, people use culturally prescribed idioms to discuss their problems. These cultural idioms of distress cut across specific diagnostic categories. They may be used to talk about ordinary problems as well as to shape the expression of distress associated with major psychiatric disorders. For example, many cultures have notions of "nerves" (in Spanish, *nervios*), which signal emotional distress that may range from being mildly upset with life events to disabling anxiety or psychosis. Appendix I of DSM-IV-TR provides a list of some common idioms of distress. The same appendix also lists some well-described culture-bound syndromes, culturally distinctive clusters of symptoms that may be of pathological significance. Many culture-specific terms, however, do not refer to syndromes or idioms of distress but are actually symptoms or illness attributions that reference folk models of causality (Groleau and Kirmayer 2004). For example, *susto,* a term used in Central and South America, attributes a wide range of bodily symptoms and diseases (including infectious diseases and congenital malformations) to the damaging effects of sudden fright.

Clinical Vignette 4

A family from Nigeria consults for developmental delay in their 4-year-old son. Problems had become evident when they attempted to integrate the child into a preschool program. The child presents a classical profile of pervasive developmental disorder. The parents comment that their family doctor raised the possibility of autism but that they did not consider that what he described applied to their son. They explain that the migration process, when the child was 2 years old, had hindered his acquisition of speech and social activities. After a few sessions it becomes apparent that the child's difficulties had already been recognized in Nigeria but were attributed by both the maternal and the paternal lineage to sorcery on the other side of the family because they were in conflict.

Many cultural idioms of distress use bodily metaphors for experience. In seeking medical help, patients usually try to present the sort of problems they believe the clinician is competent to treat. Consequently, in biomedical settings patients tend to emphasize physical symptoms. This pattern of clinical presentation combined with the wide currency of somatic idioms of distress has led to a characterization of many ethnocultural groups as prone to somatize their distress (Kirmayer 2001). The social stigma commonly associated with psychiatric symptoms and disorders, as well as with substance abuse, antisocial behavior, and various other behaviors, may also prevent patients from acknowledging such problems and events. However, with clear communication and a respectful stance, the clinician may be able to build sufficient trust over time for patients to disclose shameful or potentially stigmatizing information.

Similarly, people commonly use multiple remedies or consult various healers for their symptoms, and may be reluctant to disclose treatments that they think the clinician will not understand or accept. They may also omit mention of preparations they view as "natural" or as foods and, hence, not included under the rubric of medications or drugs. Commonly used remedies like ginseng, St. John's Wort, and *gingko biloba* have significant effects on pharmacokinetics and drug metabolism and are, therefore, important for their potential impact on physiology as well as their role in patients' belief systems and a sense of control over their illness. A nonjudgmental inquiry by the clinician will enable patients to more freely discuss their use of traditional and alternative treatments.

## Psychosocial Environment and Levels of Functioning

Cultural factors have a dual influence on the psychosocial environment: They determine life circumstances and, at the same time, provide interpretations of their meaning and significance for the individual. This dual effect of culture means that the clinician must explore both events and their personal and cultural meanings to understand the impact of the social environment.

There are wide cultural variations in the composition and functioning of families including the variety of people living together in a household (not always identical to the family or kin); person who is considered close or distant kin; hierarchy, power structure, and economic arrangements; age and gender roles; organization of household activities and routines; styles of expression of emotion and distress; body practices (arrangements and procedures for sleeping, eating, washing, dressing, recreation, and use of physical remedies for ailments); conflict management strategies; and the relationship of family to larger social networks and communities.

Social support must be assessed with attention to cultural configurations of the family and community. Extended multigenerational families, tightly knit religious and ethnocultural communities, and transnational networks, all may provide specific forms of instrumental and emotional support. Often these supports are inextricably intertwined with interpersonal obligations and demands that may constitute burdens for the individual. This complex relationship of burden and support may have crucial implications for clinical interventions. In some cases, these burdens or conflicts within the family may constitute crucial clinical problems in their own right as seen in Clinical Vignette 5.

Clinical Vignette 5

A woman from South Asia appears to have a severe depression with vegetative symptoms and persistent suicidal ideation. She does not respond to trials of several antidepressant medications. On reassessment with a clinician who speaks her language, she reveals that her husband has an unpaid debt of honor to her daughter's husband's family, and she is suffering from the ongoing feud, which has barred her from seeing her daughter and grandchildren. When this is addressed in a series of family therapy sessions, her "depression" lifts dramatically.

Similarly, levels of functioning and disability must be assessed against culturally determined notions of social roles and values. It is important to recognize that the clinician's priority may not be the most important issue for patients or their families.

In addition to these general cultural considerations, certain social situations present specific stressors with which the clinician must become familiar. All immigrants and refugees have arrived in the host country after a migration experience. For some, migration is a personal choice taken in the hopes of bettering personal and family prospects; for others, the experience is borne out of extreme difficulty and is only taken under threat of harm or death. Many new arrivals face bleak job prospects, are isolated from family and cultural institutions, and have an uphill battle as they adapt to a new language and unfamiliar social rules and obligations. Furthermore, the path that some immigrants take prior to arriving at their final destination is often lengthy, circuitous, and costly, in addition to being dangerous. It is crucial, therefore, to take into account the migration experience when evaluating immigrants and refugees. Questions must be carefully phrased and asked in a judicious manner, as not all patients will be ready to discuss their reasons for leaving their homeland. Important points to cover include the premigration lifestyle of the patient, the context of migration, the experience of migration, the postmigration experience, and the "aftermath" of migration, or the long-term adjustment and acculturation to the host society (Beiser 1999).

The stress experienced by refugees may include the confusion and disorientation of unplanned flight and exile; loss of social status, wealth, security, and community; and worry about the safety of family left behind and still in peril. Refugee claimants or asylum-seekers usually face a stressful period of uncertainty while waiting to have their status determined. The refugee-review process itself may be traumatic because it often occurs in an adversarial atmosphere that questions the veracity of the refugee's story even as it foregrounds traumatic memory (Silove et al. 2000). Individuals who have endured war-related trauma, torture, or other forms of organized violence have special needs to insure the safety of the clinical setting and relationship (Silove 1999). In some instances, they may experience routine hospital or clinical procedures as threatening and this can undermine the clinical encounter and aggravate their condition (Clinical Vignette 6).

Clinical Vignette 6

A 35-year-old professional from Peru visited the emergency room (ER) because of high fever caused by pneumonia. While waiting to be seen, he suddenly became agitated and fled the hospital, breaking through the parking lot barrier. After his arrest, the judge ordered a psychiatric assessment. The patient explained that on seeing the medical instruments in the ER, he was reminded of his torture in Peru and felt convinced that he was back there and that his life was in danger. The combined effects of fever and reminders of the trauma had triggered a dissociative episode.

The growing number of undocumented people in North America also presents ethical and pragmatic challenges to the medical profession. These illegal immigrants and families may have particular mental health needs, which are largely unrecognized because there is almost no funded research or services to address them.

## Clinician–Patient Relationship

The roles of healer, helper, and physician differ across cultural contexts, and patients may have correspondingly different expectations of their relationship with clinicians, including the duration, level of disclosure (Savin and Martinez 2006), formality, and emphasis on technical competence. These expectations often need to be explored, with opportunities for patients and clinicians to negotiate or explain the limitations of the roles they are able and willing to adopt. Once these differing perspectives are made explicit, a culturally appropriate and professionally acceptable relationship and working alliance can be negotiated.

Clinicians must become aware of their own ethnocultural background and identity, and reflect on how it is perceived by patients from their own and different backgrounds. The terms "cultural transference" and "cultural counter transference" have been used to acknowledge that both patient and clinician may have fantasies and responses to the other that are based on earlier relationships with others from that culture or on culturally rooted associations to the other, rather than to strictly personal characteristics (Adams 1996, Comas-Diaz and Jacobsen 1991). The history of racism, colonialism, and discrimination in a society inevitably affects the clinical encounter. As illustrated in Clinical Vignete 7, acknowledging the impact of these issues in the patient's life may be necessary to establish trust and rapport.

Clinical Vignette 7

Sent by her 8-year-old son's school, a university-educated woman from Somalia consults for the conduct problems of her son, who is not responding to stimulant medication for attention deficit hyperactivity disorder prescribed by a pediatrician. She is obviously reticent about the assessment process. The white clinician explicitly addresses the difficulty of being a black, veiled woman in North America because of the strong prejudices against both Islam and Africa. The woman visibly relaxes and begins to explain that she feels that she is being treated as though she is intellectually handicapped or as a child by the school. They use a loud voice and simplistic formulations when they speak to her, and she finds this very humiliating. Later in the interview, after further strengthening of the alliance with the clinician, she discloses the war trauma to which the boy was exposed.

## Overall Assessment

The aim of cultural assessment is to integrate all of the pertinent elements of the cultural context of the patient's identity, illness, and social context in a formulation that can guide diagnosis and treatment (Hays 2001, Tseng and Streltzer 1997). Factors associated with one aspect of the formulation may have an impact that cuts across many dimensions of illness experience and behavior. The salient aspects of culture vary across cases and may reflect issues in the dominant society as much as any intrinsic characteristics of the patient's ethnocultural group.

For example, cultural notions of race and racism may profoundly affect every aspect of the cultural formulation (Pinderhughes 1989, Patel et al. 2000, GAP 2002). Racial categories may impose a disvalued identity on the patient; this may be resisted by reconstructing identity in a fashion that imbues one's background with dignity and "cultural capital" (Comas-Diaz and Greene 1994, Kareem and Littlewood 1992). Race may figure in explanations of the nature of illness. For example, some native people have come to view alcoholism, diabetes, and other conditions as "white man's illnesses," which they suffer in large numbers precisely because of the history of colonization and racist practices. High blood pressure among African Americans has been linked to the stresses of racial prejudice and related economic and educational disparities (Dressler et al. 1998). Institutionalized racism may have a powerful impact on the level of stress and social support for individuals, families, and communities, which may fracture or unite around this issue. The legacy of racism may define the clinician–patient relationship, where it may influence the transference and undermine rapport.

## Cultural Competence

Recent years have seen the development of professional standards for training and quality assurance in cultural competence (Lopez 1997, Sue 1998). This term stands for a range of approaches aimed at improving the delivery of appropriate services to a culturally diverse population. Cultural competence may involve both culture-specific and generic strategies to address a range of practical issues in intercultural work (Lim 2006, Okpaku 1998). This includes the clinician's ability to elicit cultural information during the clinical encounter (Table 4-3), to understand how different cultural worlds of patients and their families influence the course of the illness, and to develop a treatment plan that empowers the patient by acknowledging cultural knowledge and resources while allowing appropriate psychiatric intervention. As Clinical Vignette 8 illustrates, accepting a place for culturally based interventions can facilitate psychiatric treatment.

Specific cultural competence has to do with knowledge and skills pertaining to a single cultural group, which may include history, language, etiquette, styles of child-rearing, emotional expression, and interpersonal interaction, as well as cultural explanations of illness and specific modalities of healing. Often, it is assumed that specific cultural competence

**Table 4–3 Strategies to Elicit Cultural Information**

- Present an open, friendly face of the institution (have the diversity of the community represented within the diversity of the institution, with attention to not simply reproducing the class structure of the society in the institutional hierarchy).
- Make explicit the clinician's position and identity, explain goals and methods, and use self-disclosure appropriately.
- Ask for clarification of unfamiliar terms or key terms that may be mistakenly assumed to be familiar.
- Ask for detailed description of practices related to health, illness, and coping.
- Have the patient compare situation with previous events, or experiences of others from similar backgrounds.
- Interview other family members and patient's entourage to obtain normative framework, and identify consensus and conflicting perspectives.
- Consult knowledgeable clinicians, culture-brokers, interpreters, anthropologists, and ethnographic literature.

Clinical Vignette 8

A 16-year-old girl from Haiti presents with disorganized schizophrenia, which began around age 14. Her family has not been compliant with the treatment, and this had led to several hospitalizations of the patient in a dehydrated state. During the third hospitalization, the clinical team decide to explore the family's interpretation of the illness. A grandaunt insists on sending the girl to Haiti for a traditional diagnosis. The traditional healer indicates that the problem is due to an ancestor's spirit in the mother's family and that for this reason, it will be a prolonged illness. This explanation helps to restore cohesion in the extended family by rallying people around the patient, and her family receiving much support. The traditional interpretation and treatment has broken the family sense of shame and isolation, and promoted an alliance with the medical team and the acceptance of antipsychotic medication.

is assured when there is an ethnic match between clinician and patient (e.g., a Hispanic clinician treating a client from the same background). However, ethnic matching without explicit training in models of culture and intercultural interaction may not be sufficient to insure that clinicians become aware of their tacit cultural knowledge or biases and apply their cultural skills in a clinically effective manner.

Ethnic matching can occur at the level of the individual, the technique, the institution, or any combination of these levels (Weinfeld 1999). At the level of the individual, it may be easier to establish rapport when clinician and patient share a common background. However, there is a risk that some issues may be left unexplored because they are taken for granted, or are awkward to approach. There is also difficulty when the patient's expectations of a fellow community member are not met because the clinician applies the rules and limits dictated by professional training. This may include expectations of receiving special treatment, of being cured quickly, of becoming friends, or of intervening inappropriately on behalf of other family or community members.

In many cases, however, ethnic matching is only crude or approximate. For example, the term *Hispanic* covers a broad territory with many cultural, educational, and social class differences that transcend language (Arcia et al. 2002). Indeed, there is enormous intracultural variation and no single person carries comprehensive knowledge of his own cultural background, and so there is always the need to explore local meanings with patients.

In the course of professional training, clinicians may distance themselves from their own culture of origin and become reluctant or unable to use (or understand the impact of) their tacit cultural knowledge in their clinical work. Clinicians from ethnic minority backgrounds may resent being pigeon-holed and expected to work predominately with a specific ethnocultural group. Patients may have complex reactions to meeting a clinician from the same background. These issues require attention and sensitive exploration just as much as the feelings evoked by meeting someone from a different background.

At the level of technique, the clinician familiar with a specific ethnocultural group learns to modify his or her approach to take advantage of culturally supported coping strategies. For example, religious practices, family and community supports, and appeals to specific cultural values may all provide useful strategies for symptom management and improved functioning. Traditional diagnostic and treatment methods may be used in concert with conventional psychiatric treatments. The clinician may use his or her own person differently in recognition of cultural notions of healing relationships, adopting a more authoritative stance, making selective use of self-disclosure, or participating in symbolic social exchanges with patients and their extended families to establish trust and credibility.

At the level of institutions, ethnic match is represented in the organization of the clinical service, which should reflect the composition of the community it serves (Kareem and Littlewood 1992). This is not merely a matter of hiring practices but also involves creating structures that allow a measure of community feedback and control of the service institution. When people feel a sense of ownership in an institution, they will evince a higher level of trust and utilization. It is important, therefore, for clinicians to understand how the institutional setting in which they are working is seen by specific ethnocultural communities.

Increasingly, clinicians work in settings where there is great cultural diversity that precludes reaching a high level of specific competence for any one group. Changes in migration patterns and new waves of immigrants and refugees lead to corresponding changes in patient populations. For all these reasons, it is crucial to supplement specific cultural competence with more generic competence that is based on a broad theoretical understanding of culture and ethnicity. Generic cultural competence abstracts general principles from specific examples of cultural differences. The core of generic competence resides in clinicians' understanding of their own cultural background and assumptions, some of which are related to ethnicity and religion, and many of which are derived from professional training and the context of practice. Appreciating the wide range of cultural variation in gender roles, family structures, developmental trajectories, explanations of health and illness, and responses to adversity allows the clinician to ask appropriate questions about areas that would otherwise be taken for granted. The culturally competent clinician has a keen sense of what he or she does not know, and has a solid respect for difference.

While empathy and respectful interest allow the clinician to gradually come to know another's world, the clinician must tolerate the ambiguity and uncertainty that comes with not knowing. In the end, patients are the experts in their own experiential worlds, and cultural context must reconstructed simultaneously from the inside out (through the patient's experience) and from the outside in (through an appreciation of the social matrix in which the patient is embedded).

The wide range of specific and generic skills needed for competent intercultural work means that most clinicians will find it helpful to work in multidisciplinary teams that contain cultural diversity that reflects the patient population. A variety of models for such team work have been developed (Kareem and Littlewood, Kirmayer et al. 2003).

## Working with Interpreters and Culture Brokers

A key skill, which has not been addressed in many training programs, concerns as to how to work with interpreters (Table 4–4). In the absence of familiarity with this technique and quality assurance standards insisting on appropriate use of interpreters, many clinicians simply try to avoid the situation, relying on patients' sometimes-limited command of the clinician's language. This is unfortunate, and may lead to errors in diagnosis and management as well as the failure to engage and help many patients (Karliner et al. 2007).

There are several models of working with interpreters (Westermeyer 1989). Medical interpreters have adopted a code of ethics and model of working that owes much to forensic and political interpreting. Their goal is to provide accurate, complete, and literal translation of the statements of patient and physician. This model tends to portray the interpreter as providing a transparent window or conduit of communication between clinician and patient. In this approach, the clinician addresses the patient directly as though the interpreter is not present. The interpreter may speak in first person for the patient and for the clinician alternately. The model assumes that it is possible to achieve complete and accurate translation of messages in both directions, and treats the interpersonal triad of doctor–interpreter–patient as if it was a dyad. To do so assumes that the interpreter does not have an independent relationship with patient or clinician. Of course, this is certainly not the case in any clinical encounter that goes on for a time or involves repeated meetings. Indeed, at the level of transference, it is never the case because the mere presence of another person immediately evokes distinctive thoughts, feelings, and fantasies. Then too, the presence of the interpreter inevitably changes a dyad into a triadic social system with its own complex interpersonal dynamics. These dynamics are complicated by the ethnocultural background of the interpreter and his or her own cultural assumptions.

The very idea of literal translation is also problematic. Across languages, the words and phrases with similar denotation often have different sets of connotations. Every translation, therefore, is an interpretation that emphasizes some potential meanings while muting or eliding others. Interpreters tend to smooth out fragmentary, complete, or incoherent statements, and so may mask thought disorder or other idiosyncrasies of speech with diagnostic relevance. The clinician needs to understand the choice of alternatives made by the interpreter in order to appreciate the connotations of the patient's words and to convey his or her own nuanced meanings. These requirements place much higher demands on interpreting in mental health than in other medical or legal settings.

**Table 4–4 Guidelines for Working with Interpreters and Culture-Brokers**

*Before the Interview*
- Explain the goals of the interview to the interpreter
- Clarify the roles of interpreter and clinician, and the conduct of the interview
- Discuss the interpreter's social position in the country of origin and local community as it may influence the relationship with the patient
- Explain the need for literal translation in the mental status examination (e.g., to ascertain thought disorder, emotional range and appropriateness, and suicidality)
- Ask for feedback when something is hard to translate
- Discuss etiquette and cultural expectations

*During the Interview*
- Arrange seating (usually in a triangle)
- Introduce yourself and the interpreter
- Discuss confidentiality and ask for patient consent to have this interpreter
- Look at and speak to the patient; use direct speech ("you" instead of "s/he")
- Use clear statements in everyday language
- Slow down your pace; speak in short units
- Do not interrupt interpreter
- Clarify ambiguous responses (verbal or nonverbal)
- Ask patient for feedback to insure that crucial information has been communicated and to ask questions or express concerns that have not been addressed

*After the Interview*
- Debrief the interpreter to address any of their own emotional reactions and concerns
- Discuss the process of the interview, any significant communication that was not translated, including paralanguage
- Assess the patient's degree of openness or disclosure
- Consider translation difficulties and misunderstandings
- Plan future interviews
- Work with the same interpreter/culture-broker for the same scase whenever possible

A slightly different model views the interpreter as a "go-between." In this approach, the interpreter takes turns interacting with clinician and patient to clarify what is being said and to find a means of conveying it. This model acknowledges the interpreter as an active intermediary and allows the interpreter some autonomy. The sequential dyadic interaction puts greater time and distance between clinician and patient. This demands that the interpreter has a high degree of clinical knowledge and interpersonal skill, which is possible when the interpreter has been trained as a clinician. Taking this autonomy further, the interpreter may be viewed as a cotherapist. In this approach, the interpreter with clinical skills develops his or her own working alliance with the patient. The interpreter may respond independently to the patient and initiate interventions. This sometimes happens because of language barriers, when patients may contact the interpreter to ask for help with practical issues.

Given the complexities of interpreting, we prefer to view the interpreter as a culture-broker who works to provide both the patient and the clinician with the cultural context

needed to understand each other's meanings. To do this, the interpreter must understand something of the perspectives, cultural background, and social positions of both patient and clinician, and appreciate the goals of the clinical task. Based on this knowledge, the culture-broker can enhance patient and clinician understanding of each other, and can help negotiate compromises when there are widely divergent understandings of a problem and its solutions.

Despite increasing recognition of the importance of adequate interpretation, many clinicians or institutions use lay interpreters who are directly available at no cost, usually family members (even children) or other workers within the institution. Except in emergency situations, this practice should be avoided both because it exerts a strong censorship on what may be disclosed in the encounter and because it may damage relationships that are very important to the patient by transgressing social and familial boundaries.

Both interpreters and culture-brokers need training to perform competently, and clinicians need training, in turn, to work with these allied professionals. The clinician must take a systemic approach, understanding the other people in the room as part of an interactional system. Clinicians must also understand the interpreter's position in the larger community. Some of this training can go on when clinicians have an opportunity to work repeatedly with the same interpreters, who thus become part of a treatment team. A culture broker with clinical skills can use their identity and intimate knowledge of the patient's culture to position themselves in ways that foster communication and a strong therapeutic alliance (Clinical Vignette 9).

Clinical Vignette 9

A 42-year-old man from the Congo is referred for psychiatric consultation because of the concern that he is depressed following chemotherapy for leukemia. The patient lies in bed staring out of the window and complaining of poor appetite, headache, and fatigue. At first, he says little to the Euro-Canadian interviewer. After a few minutes of stilted conversation, the culture-broker, a psychologist from Central Africa, stands at the foot of the bed and delivers a lecture full of exhortations to the patient. He explains that the doctor has come to help, urges the patient to cooperate with the doctor, and insists that he must try to get better. After this intervention, the patient speaks more openly, clarifying that his fatigue and poor appetite are not due to depression or the lingering effects of chemotherapy, but stem from the absence of appropriate African food in his diet and the fear that he will die an improper death, far from home. His symptoms improve markedly once suitable food is arranged by contacting some supportive members of his cultural community.

## Culture and the Stigma of Mental Illness

Stigma refers "to an attribute that is deeply discrediting" that marks the person as different from others and "of a less desirable kind" (Goffman 1963). Stigmatization occurs through processes of labeling, stereotyping, separation, status loss, and discrimination in a situation of differential power that allows one group of individuals to negatively label and devalue another (Link and Phelan 2001). Any socially marked characteristic of individuals can be used to assign stigma, including age, gender, physical appearance, behavior, national origins, accent, illness, or disability. It is thus not uncommon for individuals to suffer multiple forms of stigma that may interact in complex ways.

While most theories of stigma emphasize the psychological processes of stereotyping and social exclusion, social structural models show how some forms of prejudice and discrimination arise at the institutional level and reflect larger social, economic, political, and historical forces (Corrigan 2004). Examples of structural discrimination include legislation that restricts the rights of the mentally ill or media representations of negative stereotypes of people with mental illness (e.g., as dangerous or unpredictable).

Cultural explanations for psychiatric disorders, particularly causal attributions for symptoms or behaviors, influence whether stigma is attached to an individual with a particular disorder. Psychiatric labeling itself provides a particular interpretation of illness, and may be a major source of stigma. The meaning of the label depends on wider cultural systems of meaning. For example, initial hopes that giving biological explanations for mental disorders would reduce stigma have proved overly optimistic (Angermeyer and Matschinger 2005). In many cultures, the notion that an illness is biological means that it is intrinsic to the person and probably hereditary. This then leads to great stigmatization of the afflicted person, as well as their siblings and family who may find their prospects for marriage and social status significantly reduced. Fear of stigma by patients or other family members may be a major obstacle to help-seeking and treatment adherence. These considerations point to the importance of carefully assessing the potentially stigmatizing meanings of symptoms, behaviors, diagnostic labels, and treatment interventions. This assessment should extend beyond the patient to include attention to the meanings of the illness to others since they are the ultimate sources of stigma and social exclusion or acceptance and integration.

In most developing countries, psychiatry is associated only with the most severe chronic disorders and involves asylum treatment (Cohen 1988, Desjarlais, et al. 1995). Psychiatric disorders are highly stigmatized and the diagnosis of a family member may have negative effects on the social position of siblings and others. In contrast, common disorders like depression and anxiety are more likely to be understood as problems in living or sociomoral dilemmas that are not appropriate to be brought to a doctor or health professional (Kirmayer 1989). This is illustrated in Clinical Vignette 10.

Several issues touched upon in the interview may explain Mr. A.'s decision to not follow through with crisis intervention. He attributed the cause of his symptoms to his marital separation and, therefore, thought that an appropriate solution would be an intervention to help him to regain control over his situation by convincing his wife to rejoin the marriage. He did not see how "just talking" to a psychiatrist could solve his problem. Beyond this pragmatic focus on his social predicament, cultural factors may have played a role in Mr. A.'s reluctance to follow through on psychiatric treatment for his depression.

Clinical Vignette 10

Mr. A., a 32-year-old man from Trinidad, presented to the ER with insomnia, poor concentration, tearfulness, decreased energy and appetite, loss of interest in his usual activities, feelings of hopelessness about the future, and ruminations about his current predicament. His symptoms began when his wife left the marriage six months earlier. He came to the hospital ER stating that he could no longer wait for an upcoming appointment with his family physician because the symptoms had begun to affect his ability to work. The psychiatric consultant to the ER explained the symptoms to Mr. A. as indications of an episode of major depression secondary to his recent life events. He was offered medication and psychotherapy, and was referred to the crisis intervention service. However, he did not keep this appointment and did not respond to the follow-up letters from the team.

In Trinidad in the 1980s, the depression and demoralization felt by a man who had been betrayed or abandoned by an unfaithful wife might be understood as a problem of *tabanka*, an indigenous concept of reactive depression (Littlewood 1985). While the signs of tabanka may include the typical vegetative symptoms of depression, it has specific social meaning. Tabanka tends to elicit ridicule rather than solicitous concern from others, since the affected man is seen as "weak of mind" and his suffering a sign of embarrassing vulnerability or subordination to another. As a result, it is humiliating to seek outside help for this predicament—one is expected to overcome it alone. Also, psychiatric services in Trinidad are primarily associated with the treatment of severe psychotic disorders. For Mr. A. then, seeing a psychiatrist for the distress caused by his wife leaving him poses the threat of ridicule and damage to his reputation or social standing, as well as aggravating his feelings of loss of control. It is possible that a strategy in the ER consultation based on identifying these issues and mobilizing appropriate social support would work better than a referral for treatment of his depressed "state of mind."

This case illustrates multiple barriers to delivery of mental health care: the stigma associated with psychiatric diagnosis and treatment, the conflict between specific cultural understandings of problems and biomedical theories, and the difficulty in offering services in a form that makes cultural sense and will enhance the individual's social standing and functioning. Responding to these barriers begins before the clinical encounter and continues through the diagnostic assessment and the whole course of treatment. The process of framing and labeling patients' problems must be done in a collaborative fashion that takes into account the social meanings and dilemmas posed by a particular diagnosis.

## Conclusion: The Limits of Culture

The cultural formulation and the basic strategies of cultural competence represent useful initial approaches to exploring clinically relevant dimensions of patients' cultural backgrounds. However, to apply these tools successfully, the clinician must avoid some biases implicit in psychiatric assessment and in the concept of culture itself.

Psychiatric diagnosis tends to be individual-centered, locating problems inside the individual, in their psychology, or neurophysiology. Cultural psychiatry, in agreement with family theory and therapy, recognizes that many problems are systemic and reside in interpersonal interactions or social contexts.

In cultural formulation, culture tends to appear as something distinctive of patients who come from ethnocultural minorities, migrants, or indigenous peoples. The clinician too has a culture that is distinctive from the patients' point of view. Indeed, culture also constitutes the larger social matrix in which the clinical encounter is embedded. The cultural critique of psychiatric theory and practice are important correctives to this view of culture as something only possessed by the "other."

Talk of culture tends to reify and essentialize it as a fixed set of traits or characteristics shared by all members of a group. However, there is enormous diversity and individual variation within any cultural group, and many divergent perspectives. The integrated whole of culture then appears to be a fiction or idealization. Contemporary anthropologists have argued for entirely dispensing with the notion of culture or else viewing it as an abstraction for a shifting set of perspectives, discourses, and resources used by individuals and groups to construct and position socially viable selves (Kirmayer 2006). This perspective recognizes that cultures are flexible frameworks that provide both opportunities and constraints but do not wholly determine the trajectories of individual lives.

With these caveats in mind, the clinician can apply the cultural formulation by approaching each case as unique, with a focus on the social and cultural context of the behavior and experience of the identified patient and his or her family (Kleinman and Benson 2006). Cultural competence involves using one's knowledge of culture, language, and etiquette as modes of inquiry rather than as a priori answers to the dilemmas of a specific case. With the help of cultural experts, the clinician can appreciate the range of variation in a cultural group and its significance for individuals and the community. In this way, it is possible to recognize when culture is a camouflage for problems at other levels and when it itself is constitutive of problems. In assessment, the aim is to formulate cultural dynamics as part of a comprehensive process model of pathology. This can then be used to design interventions to address the most flexible or accessible level of the individual, family, or social system. Whenever possible, clinical interventions should mobilize and work with the family and ethnocultural community, who will have their own strategies and resources for problem solving and coping with adversity.

Cultural competence is based on respect for and interest in difference. It requires that clinicians become familiar with and comfortable talking about cultural differences rather than attempting to "treat everyone the same" in a misguided sense of "color blindness" or "neutrality"; lack of recognition of important differences results in ethnocentrism, seeing the world strictly from one's own cultural point of view. Instead, the clinician must learn to decenter, to encounter the other on a more equal footing that allows questioning the cultural assumptions built into psychiatric practice. The language of competence is comfortable for clinicians because it suggests that we can add to our skills to

master another domain of expertise. But cultural competence goes well beyond refining our technical approaches, to demand that we examine our place, as individuals and practitioners, in the larger social and historical contexts that shape our relationships with patients.

Mainstream care cannot respond adequately to the needs of a diverse population unless it gives explicit attention to cultural issues. The ethnocultural diversity of mental health professionals represents an invaluable resource. Training programs must recognize this and make it safe for clinicians to explore their own ethnocultural background and assumptions as a path to more sensitive and responsive work with others.

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CHAPTER 5

# Professional Ethics and Boundaries

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## Introduction

In the last several decades, advances in psychiatry have made it possible to treat mental disorders that were previously unamenable to successful intervention. There has been a dark side to this progress, however, because futuristic anticipation of subduing disease and forcing nature to surrender up her secrets, has led many practitioners to outrun their headlights. Like technical sorcerers of science-fiction confusing promise with reality, we are in danger of being lulled into an intellectual arrogance that can cause us to forget what it means to be professionals. One manifestation of this process has been the defensive reliance by clinicians on reductionistic explanations for complex and multi-determined disorders, combined with a neglect of the important role of trust and empathy as a curative factor in treating mental disorders.

A bewildering potpourri of treatment options and methods for financing health care present psychiatrists with other sources of confusion. Patients' health and safety often depend upon our ability to make rapid clinical decisions regarding diagnosis, and to utilize an optimal psychotherapeutic or psychopharmacologic approach. The psychiatrist's dilemma is similarly compounded by conflicts between the cost-determined restrictions of managed care, versus the sacred promise to advocate primarily for patients' welfare.

Building a cooperative and trusting relationship with patients has always been an essential factor enabling clinicians to foster the healing process. In ancient times, when there were few specific remedies available, physicians relied on a highly integrative view of the sick person. For example, ancient Egyptian medicine did not make a special distinction between soma and psyche in considering physical and mental disorders, and therefore attached no special stigma to the mentally ill (Okasha and Okasha 2000). Similarly, the rabbinic sage and physician, Moses Maimonides (1135–1204 A.D.) (1944), relying on scriptural and clinical wisdom, taught that both physical and mental illness resulted from imbalances in somatic and mental processes, and that physical health and mental health are interdependent (Gorman 2001).

In most instances, modern technology augments but cannot substitute for a trusting doctor–patient relationship. Patients seeking medical care must suspend ordinary social distance and critical judgment if they are to allow physicians to enter their physical and psychological space. While neither the law nor medical ethics relieve patients from taking an active responsibility for treatment outcome (American Medical Association 1993), society places a greater burden upon the healer—a mandate to act with the special care and vigilance expected of a fiduciary (Frank and Frank 1991), (Simon 1987) or of a Common Carrier (Epstein 1994, pp 59–61), as a precondition for granting licenses to practice.

As we review in this chapter, the ability to sustain a professional attitude, and to practice within a set of coherent boundaries, forms the foundation of proper psychiatric treatment, regardless of theoretic orientation or treatment modality. An understanding of psychiatric ethics plays a vital role in the psychiatrist's ability to keep proper boundaries because these values provide a stable beacon in the cognitively perplexing fog that so often pervades the treatment situation.

## Ethical Behavior and Its Relationship to the Professional Attitude

The term professional derives from medieval times, when scholastics were expected to "profess" their belief in a doctrine (Dyer 1988 p 17). In modern times, a professional is expected to be a learned person who has acquired special knowledge of a subject that is of vital importance for the welfare of the community. Having expertise is not enough, however. A professional is also obliged to adhere to certain societal responsibilities that are founded upon a code of ethical behavior, and an attitude of service to those in need. A professional commitment to ethical behavior and service must take precedence over monetary compensation (Dyer 1988, p 16). All physicians, including psychiatrists, are

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bound by such a covenant—a sacred vow to place patient well-being before other considerations (Webb 1986).

## General Principles of Medical Ethics

In western tradition, the canon of medical ethics derives primarily from the teachings of Hippocrates, a Greek physician from the Island of Cos, who practiced Medicine in 5th century B.C.E. Hippocrates' Oath is the predominant pledge recited at the graduation exercises at American medical schools (Dickstein et al. 1991), and contains three of the six core principles of modern medical ethics, including beneficence, non-malfeasance, and confidentiality:

> I will follow that system of regimen which according to my ability and judgement, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous … With purity and holiness I will pass my life and practice my Art … Into whatever houses I enter, I will go into them for the benefit of the sick, and will abstain from every voluntary act of mischief and corruption; and, further, from the seduction of females or males, of freemen and slaves. Whatever, in connection with my professional practice or not, in connection with it, I see or hear, in the life of men, which ought not to be spoken of abroad, I will not divulge, as reckoning that all such should be kept secret (Hippocrates 1929).

The other three general principles of medical ethics include autonomy, justice, and veracity (see Table 5–1 for a description and summary of all six ethical principles (Epstein 1994, p 20).

**Table 5–1 Six Basic Principles of Medical Ethics***

| Principle | Description |
|---|---|
| Beneficence | Applying one's abilities solely for the patient's well-being |
| Non-malfeasance | Avoiding harm to a patient |
| Autonomy | Respect for a patient's independence |
| Justice | Avoiding prejudicial bias based on idiosyncrasies of the patient's background, behavior, or station in life |
| Confidentiality | Respect for the patient's privacy |
| Veracity | Truthfulness with oneself and one's patients |

*Adapted from Epstein (1994).

## Psychiatric Ethics

Radden (2002) reasoned that the emotionally charged interpersonal process that often plays such a key role in psychiatric treatment, necessitates a unique and generally more stringent ethical system than the basic principles of medical ethics. Psychiatric patients are especially vulnerable during treatment, to such extent that the ethical character of the psychiatrist has a unique and powerful potential to help or to harm our patients. By working to enhance their own positive character traits, psychiatrists improve their potential to be able to be helpful. Positive character virtues that are likely to enhance the effectiveness mental health professionals include compassion, humility, fidelity, trustworthiness, respect for confidentiality, veracity, prudence, warmth, sensitivity, perseverance, patience, and generosity (Radden 2002).

In keeping with its status as a medical specialty organization, the American Psychiatric Association (APA) (American Psychiatric Association 1973) adopted the American Medical Association's (AMA) Principles of Medical Ethics as the underlying basis of its canon of ethics. APA solved the problem of psychiatry's unique requirements by adding special annotations applicable to psychiatric practice, to the AMA Principles of Medical Ethics.

The APA has produced six revisions of these annotations. The seven sections of the AMA principles are summarized in Table 5–2. Table 5–3 summarizes some of the salient APA ethical annotations for psychiatrists (American Psychiatric Association 1993).

**Table 5–2 Summary of the Principles of Ethics of AMA**

| Section | Statement of Principle |
|---|---|
| Preamble | The medical profession's ethical standards are designed primarily for the well-being of patients. As professionals physicians are required to acknowledge a responsibility to patients, to society, to self, and to their colleagues. |
| Section I | Dedication to competent, compassionate care. Respect for human dignity. |
| Section II | Obligation to deal honestly with patients and colleagues and to expose physicians who are incompetent or fraudulent. |
| Section III | Respect for the law. Obligation to seek changes in laws harmful to patient care. |
| Section IV | Respect for the rights of patients, and colleagues. Within legal constraints, preservation of confidentiality. |
| Section V | Commitment to continued education, sharing of relevant knowledge, and obtaining necessary consultation. |
| Section VI | Except in emergency, freedom to decide whom to treat, with whom to associate, and the setting in which one serves. |
| Section VII | Acknowledge the responsibility to contribute to improving the community. |

*Source*: American Psychiatric Association (1993).

**Table 5–3 Summary of Selected Ethical Principles for Psychiatrists**

| Principle | Annotations |
|---|---|
| Competent care | The psychiatrist must scrutinize the effect of his/her conduct on the boundaries of the treatment relationship |
| Honest dealing | Sex with a current or former patient is unethical. Information given by patients should not be exploited. Contractual arrangements should be explicit. Fee splitting is unethical |
| Confidentiality | Restraint in release of information to third parties. Adequate disguise of case presentations |
| Respecting colleagues | Disclosure of lack of confidentiality in non-treatment situations. Sex with students or supervisees may be unethical |

*Source*: American Psychiatric Association (1993).

## International Guidelines Psychiatric Ethics

The World Psychiatric Association (WPA) (World Psychiatric Association 1999–2002), (World Psychiatric Association Ethical Statements 2000) developed and approved ethical guidelines, starting with the Declaration of Hawaii in 1977, galvanized by concerns about the abuse of Psychiatry. A long process of investigation within the domain of professional ethics, provided the foundation for the Declaration of Madrid that was endorsed by the General Assembly of the World Psychiatric Association in 1996. In its final form, the Declaration of Madrid included seven general guidelines that focused on the aims of psychiatry (World Psychiatric Association 1999–2002; World Psychiatric Association Ethical Statements, 2000). They are summarized as follows:

**Summary of Ethical Principles in the Declaration of Madrid**

1. Psychiatry's concern should be to provide the best treatment and rehabilitation for persons with mental disorders, consistent with scientific knowledge, ethical principles, and with the least possible restriction on the freedom of the patient.
2. Psychiatrists have a duty to keep abreast of scientific developments. Psychiatrists trained in research should seek to advance the frontiers of knowledge.
3. The psychiatrist–patient relationship must be based on mutual trust and respect, and should allow the patient make free and informed decisions. The psychiatrist has a duty to accept the patient as a partner in the therapy and to empower the patient with necessary information for rational treatment decisions.
4. Psychiatrists should consult with families of incapacitated patients to safeguard the human dignity and the legal rights of the patient. Treatment should not be given against the patient's will, unless withholding treatment would endanger the life of the patient or others. Treatment must always be in the best interest of the patient.
5. Psychiatrists performing assessments, especially when retained by a third party, have a duty to inform the person being examined about the purpose of the intervention, the use of the findings, and the possible repercussions of the assessment.
6. Unless there is a threat of serious harm to the patient or other persons, psychiatrists should keep all patient information in confidence, and use such information only for the purpose of helping the patient. Psychiatrists are prohibited from making use of such information for personal, financial or academic benefits.
7. It is unethical to conduct research that is not in accordance with the canons of science. Research activities should be approved by an appropriate and ethically constituted oversight committee. Because of the vulnerability of psychiatric patients, extra caution and strict ethical standards should be employed to safeguard patients' autonomy, patients' mental and physical integrity, and the selection of population groups.

An appendix in the Declaration of Madrid includes additional guidelines on specific ethical issues in psychiatry, including the following (World Psychiatric Association 1999–2000; World Psychiatric Association Ethical Statements 2000):

- **WPA Guidelines on Euthanasia**

The physician's role first and foremost, is to promote health, reduce suffering and protect life. The psychiatrist, whose patients may include those who are severely incapacitated or incompetent to reach an informal decision, should be particularly careful about actions that could lead to the death of individuals who cannot protect themselves because of disability, and should be vigilant to the possibility that a patient's views could be distorted by mental illness such as depression. In such situations, the psychiatrist's role is to treat the illness.

- **WPA Guidelines on Torture**

A psychiatrist should not take part in any process of mental or physical torture, even when authorities attempt to force their involvement in such acts. Furthermore, a psychiatrist should not participate under any circumstances in legally authorized executions, nor participate in assessments of competency to be executed.

- **WPA Guidelines on Sex Selection**

It is unethical for a psychiatrist to participate in decisions to terminate pregnancy for the purpose of sex selection.

- **WPA Guidelines on Organ Transplantation**

Psychiatrists should seek to protect their patients and help them exercise self-determination to the fullest extent possible. The role of the psychiatrist is to clarify the issues surrounding organ donations and to deal with the religious, cultural, social, and family factors to ensure that informed and proper decisions be made by all concerned.

- **WPA Guidelines on Genetic Research and Counseling in Psychiatric Patients**

Psychiatrists participating in genetic research should be mindful that the ramifications of genetic information are not limited to the individual subject or patient, but can lead to far reaching repercussions and consequences that can have a negative and disruptive effect on the larger family or community. Psychiatrists are ethically obligated to observe proper practice, avoid the risks associated with premature disclosure, misinterpretations, or misuse of genetic information, and should never advise a pregnant woman with mental disorders to get an abortion based on the medical or genetic basis of their mental illness. They should not refer patients to genetic testing unless there are satisfactory levels of quality assurance and adequate genetic counseling available to the patient.

Further guidelines on the relationship between psychiatrists and the media, ethnic discrimination, ethic cleansing, and genetic research and counseling were endorsed by the WPA General Assembly in 1999:

- **WPA Guidelines on Ethnic Discrimination and Ethnic Cleansing**

The Madrid Declaration defines ethnic discrimination as basically racist, as it fails to accept diversity and humanity's common heritage. In its most malignant form, ethnic cleansing is a crime against humanity. In this regard,

psychiatrists should not discriminate nor help to discriminate against patients on ethnic grounds, nor be involved in any activity that promotes ethnic cleansing.

• **WPA Guidelines on Psychiatrists Addressing the Media**
It is important that psychiatrists use the media in an affirmative way for a variety of goals that promote good mental health care such as advocating for the destigmatization of mental disorder and mental patients. In all their interactions with the media, psychiatrists are obliged to advocate for the mentally ill and to maintain the dignity of the profession. Psychiatrists should be mindful of the effect of their statements on the public perception of the profession and patients, and abstain from making statements or undertaking public activities that may be demeaning to either. Patients' confidentiality should be maintained, and the sensationalization of mental illness should be avoided. Regarding the disclosure of research findings, psychiatrists should cautious to report only results that are generally accepted by experts, and to convey the presentation of such results in a way that serves patients' welfare and dignity.

## Ethical Principles Applicable to Forensic Psychiatrists

A controversy exists regarding the ethical duties of forensic psychiatrists in settings where the sole and explicitly stated function of the psychiatrist is to conduct an examination of an individual for the purpose of providing a report or testimony during legal proceedings. According to Arboleda-Florez (2006), one point of view, sometimes termed the "English position," considers forensic psychiatry to be just another medical specialty, in which case the psychiatrist is fully bound by the principles of medical ethics. Another point of view, known as the "American position," argues that a forensic psychiatric examination is conducted under the aegis of a legal process and is not a medical procedure. Prior to the forensic interview, the examinee is informed that the sole purpose of the examination is to report psychiatric findings to a third party, usually some type of legal or administrative forum. According to the latter position, no treatment relationship is ever established, and the sole ethical obligation of the forensic psychiatrist is to seek and report the truth in the interest of serving justice for the common good of the community. As stated by Appelbaum (1999), the forensic psychiatrist does not establish a physician–patient relationship with the examinee, and is therefore bound primarily by the ethical principle of justice, and not the pursuit of health. He cautioned that attempts to maintain a semblance of the physician–patient relationship and its ethical requirements during forensic psychiatric examinations would lead to role confusion for both parties and difficulties with dual agency.

Gaughwin (2004) reviewed the relationship between federal court rules in Australia, and Practice Guideline No. 9 of the Royal Australian and New Zealand College of Psychiatrists. He cited Practice Guideline No. 9:2.3, that states that the psychiatrist must strive for honesty and objectivity regardless of who retained the psychiatrist, and that the psychiatrist should take care not to act in the role of an advocate in reporting. Thus, even if the psychiatrist feels strong empathy for the distress of the individual being examined, in accepting the role as a forensic expert, the psychiatrist must be prepared for the potential that his or her opinion might be adverse to the wishes of the examinee, and may be very different than the role that would be taken if the examinee was a patient in treatment with the examiner.

Sarkar and Adhead (2002) outlined some of the ethical complexities inherent in the forensic psychiatrist's role. Despite the fact that medical experts are legally immune with regard the content of their testimony in a judicial forum, the professional expectations placed on psychiatrists as health care professionals by judges, juries, and litigants is such that they could still be held to account for their conduct in a forensic examination or report, particularly if they were negligent in the manner by which they conducted their examination.

Tarboda and Abdalla-Filho (2002) concluded that improvement is needed in developing coherent ethical guidelines for forensic psychiatrists in their role as experts who report or testify in a third-party forum. Issues they cited included concern about experts who appear to sell their opinions like "hired guns," and the need for experts to guard against incomplete and biased testimony arising from unconscious identification with the side that retained the examiner's services.

Forensic psychiatrists should be aware that an examination by a skilled psychiatrist can have a powerful emotional effect on the examinee, even if unintended. This effect is engendered by the subtle vulnerabilities mediated by a relaxation of defenses on the part of the examinee, and can occur despite the examinee having been informed that the interview is solely for legal testimony and not for treatment. Lowering of psychological defenses is particularly likely to occur with examinees that have experienced previous psychiatric treatment. Such individuals have often developed embedded feelings of trust that lead them to view psychiatrists in general, as friendly and benevolent individuals whose primary goal is to help them feel better. For this reason, forensic psychiatrists should endeavor assiduously not only to maintain a respectful and professional demeanor during forensic examinations, but to be particularly alert to any tendency to exploit an examinee's tendency to transform the exam into a treatment session, or to use the authoritative aura of psychiatrist to shame or trick the examinee during the exam much like a cross-examining attorney might try to impeach an adverse witness during a trial. These caveats are especially important in situations where the forensic psychiatrist has been hired by a party taking a position adverse to the examinee's legal claims.

In situations where it is possible to do so, examiner bias is likely to be reduced if the forensic psychiatrist obtains a retainer fee in advance. This reduces the financial threat of withheld payment if the expert's opinion turns out to be adverse to the side that retained the expert. The examiner's desire to satisfy the hiring attorney or agency in order to be retained for future cases is another potential source of bias. This bias is best handled by striving for integrity rather than trying to please the retaining party. Other sources of bias occur when a psychiatrist takes on a dual role by attempting to take a forensic examinee into treatment, or alternatively by endeavoring to testify as a forensic expert with a current patient who is in ongoing treatment with the psychiatrist (Epstein 1994, Chapter 7; see also Subsection "Avoiding Dual Relationships" below).

Forensic psychiatrists should strive for honesty and objectivity by conducting a meticulous and thorough examination. This examination should, if possible, include interviews with other persons who have collateral knowledge of the examinee or of other factual information pertinent to the case, as well as full review of all available medical and legal documents. During the interviews with the examinee, interviews with collateral informants, and in the formulation of expert psychiatric opinions, the psychiatrist should take a skeptical mental stance and try to avoid prematurely jumping to conclusions. Instead, the expert should weigh the entire realm of logical possible alternatives that could explain the clinical findings as they unfold during the evaluation process. In this way, the forensic psychiatrist's ultimate opinion is refined in the crucible of an internal adversarial dialogue in a way that is likely to reduce bias and increase objectivity.

## The Coherent Treatment Frame and the Role of Therapeutic Boundaries in Effective Psychiatric Treatment

The "frame" of a social interaction was defined by Goffman (1974), as consisting of the spoken and unspoken expectations defining meaning and involvement in a given situation. For example, patients seek out psychiatrists based on a tacit assumption that the doctor is a reliable and experienced clinician who has the ability to assist them in finding relief for distress. However, many patients tend to frame their treatment in pathological ways. For example, some will attempt to pressure the psychiatrist into the role of a magical wizard who will confer unconditional love and pleasure. Whatever method the patient employs to frame the relationship, any abrupt disappointment or rupture of these unspoken expectations often results in intense and disruptive feelings of mortification and betrayal. A sudden breach of a social frame can lead to the dissolution of one's sense of meaning and connection, and is often accompanied by intense feelings of shame. By examining verbal and behavioral responses following violations of the treatment frame, Langs (1984–85) was able to document that patients usually perceive the offending therapist as an unreliable and mentally unstable person–someone seeking perverse pleasure at another person's expense.

The psychiatrist's task is to provide a coherent therapeutic frame within which to contain the patient's illness. The psychiatrist's frame makes it secure to proceed with the specific therapeutic modality, just as the surgical suite provides a safe environment for operative techniques. The treatment frame enables the patient to maintain a feeling of trust and connectedness while learning to deal with the unrealistic nature of his/her expectations. The frame is comprised of various boundary factors that include acting in a reliable way; showing respect for the patient's autonomy by explaining the potential risks and benefits of the treatment method; maintaining confidentiality; avoiding exploitation of the patient's sexual feelings; and resisting the patient's manipulative efforts by explaining the maladaptive nature of such behavior (Epstein 1994, Simon 1992).

Frank and Frank (1991) conducted an extensive review of the literature concerning psychotherapy outcome. They determined that there were four basic factors common to all successful psychotherapies (see Table 5–4), and that treatment efficacy relied upon the ability of the therapist to form a structured, mutually trusting, confidential, and emotionally arousing relationship. Their findings sustain the argument that maintaining a coherent treatment frame is an essential part of all psychiatric treatment, regardless of the therapeutic paradigm being employed. These issues are important whether the patient is being treated solely with psychotropic medication management, cognitive/behavioral therapy, or psychoanalysis.

**Table 5–4 Factors Common to All Successful Psychotherapy**

| | |
|---|---|
| Inspiring trust | The therapist establishes an emotionally arousing, trusting, and confidential relationship |
| Coherent structure | A structured setting is formed that is associated with the healing process |
| Rationale explained | A reasoned treatment method is offered that plausibly explains the patient's problems |
| Cooperative engagement | Therapist and patient actively work together in the program. Both believe it will work |

*Source*: Frank and Frank (1991).

## Boundary Violations

Psychiatric treatment cannot be conducted without doctor and patient entering into each other's space, just as it is impossible to perform a bloodless laparotomy. Gutheil and Gabbard (1993) termed such incursions occurring during the therapeutic process as "boundary crossings." They defined boundary violations as "boundary crossings" that cause injury to the patient. However, it is not always easy to be sure of the consequences of such a "crossing," since harmful effects may be delayed or concealed. Many patients are unable to articulate their sense of injury because the psychiatrist's aberrant behavior may appear so similar to exploitation they have experienced in previous pathological relationships. For example, patients who were sexually abused in childhood are more likely to acquiesce to an amorous advance by a psychiatrist, and to avoid complaining about feeling used, because they fear the threat of the psychiatrist's rejection and retaliation. Certain non-sexual boundary crossings such as conflicts of interest might seem harmless on the surface, but can interfere with patients' ability to feel safe in their psychiatrist's care, and will diminish their chances for optimal recovery. In this context, a boundary violation can be defined as any infringement that interferes with the primary goal of providing care, or causes harm to the patient, the therapist, or the therapy itself (Epstein 1994, p 2).

Prior to the 1970s, open discussion of the topic of psychiatrist−patient sex was virtually taboo, and considered "too hot to handle" as a subject for publication in scientific journals (Dahlberg 1970). Professional societies demonstrated an inconsistent and ambiguous attitude of "amused tolerance" (Pope and Bouhoutsos 1986, p 161) towards mental health practitioners engaging in sexual behavior with their patients.

The public has become increasingly interested in the subject of psychiatric boundary violations in the past 25 years, particularly those involving sexual exploitation. State licensing boards, professional ethics committees, and civil juries are much more likely to mete out strong sanctions

against violators than ever before. These attitudinal changes have taken place in spite of the fact that popular movies continue to romanticize the idea of psychiatrist–patient sexuality, and almost always seem oblivious to the horrendous feelings of shame, betrayal, and devastation that patients experience when these things happen to them in real life.

One reason for the public's intolerance of sexual involvement between psychiatrists and patients has resulted in part from the increasing empowerment of the victims of incest, rape, and spousal abuse, and a better understanding of the psychological sequelae that follow mental trauma such as posttraumatic stress disorder (PTSD). In addition, psychiatric patients have become more willing to expose unethical or exploitative behavior on the part of clinicians, particularly, when it involves sexual activity. This trend has been augmented by the fact that courts and professional licensing bodies are now more inclined to render sanctions for injuries that are solely psychological in nature.

Quantitative estimates of the frequency of sexual boundary violations among mental health professionals derive from survey studies conducted over the last 20 years (Pope and Bouhoutsos 1986, Kardener et al. 1973, Perry 1976, Holroyd and Brodsky 1977, Gartrell et al. 1986, Borys and Pope 1989, Schoener 1990). A review of these studies shows that from 5.5–13.7% of male mental-health clinicians admit to engaging in sexual activity with patients. Epstein (1994, pp 207–208) calculated a crude weighted average from Schoener's (1990) comprehensive review of survey studies reporting frequency of sexual violations by clinicians' gender. From ten studies involving a total of 5,816 respondents (excluding a large survey of nurses) an average of 7.4% of male and 2.3% of female clinicians admitted to engaging in sexual behavior with patients. These data suggest that male clinicians are about three times more likely to admit they have become sexually involved with patients. Although more recent studies suggest that sexual exploitation by mental health practitioners might be occurring less frequently, increasing media reports of severe sanctions taken against offending therapists has probably diminished the validity of self-report questionnaires.

Studies of non-sexual violations suggest that many mental health clinicians still have serious problems maintaining professional boundaries with patients, (Borys and Pope 1989; Epstein et al. 1992). Epstein et al. (1992) queried 532 psychiatrists practicing in the United States about their behavior with patients within a prior 2-year period, using the Exploitation Index (EI) developed by Epstein and Simon (1990). They found that 19% of respondents reported engaging in a personal relationship with patients after treatment was terminated, 17% told patients the personal details of their life in order to impress them, and 17% joined in activities with patients to deceive a third party such as an insurance company (see Table 5–5, reviewing the frequency of non-sexual boundary violations among respondents in this study). Xiangyi and Tiebang (2001) surveyed mental health clinicians in China using a Chinese translation of the EI. They found a rate of endorsement of boundary violations that was similar to the findings in the US study, although there were distinct variations in the pattern of certain responses that the authors attributed to cultural differences between the two populations.

Simon (1989) emphasized that when clinicians engage in non-sexual infringements of the treatment relationship, it is often a prelude to subsequent sexual behavior. Sexual involvement with patients often starts with excessive personal disclosure, accepting and giving gifts, requesting favors, and meeting patients outside of the office setting. Like a seduction, the behavior escalates over time until it culminates in sexual contact (Simon 1989).

**Table 5–5 Summary of Survey Results of Non-Sexual Boundary Violations Among 532 Psychiatrists**

| Behavior | Engaging in Behavior (%) |
|---|---|
| Using touch (exclusive of handshake) | 45 |
| Treating relatives or friends | 32 |
| Personal relationships post-termination | 19 |
| Personal disclosure | 17 |
| Colluding with patient against third party | 17 |
| Influencing patient for political causes | 10 |
| Using patient communication for financial gain | 7 |

*Source*: Epstein et al. (1992).

Regardless of the specific type of infringement involved, there are common elements to all boundary violations. Peterson (1992) argued that such activity emanated from a disturbed and disconnected relationship. She suggested four basic behavioral themes in this regard, including efforts on the part of the clinician to reverse roles with the patient, to intimidate the patient to maintain secrecy, to place the patient in a double-bind, and to indulge professional privilege. Indulgence of privilege is often accompanied by a sense of entitlement on the clinician's part, such that he/she regards the patient as a wholly owned subsidiary.

Epstein (1994, pp 89–110) outlined the progression of boundary violations as they originate from dysregulation in the clinician's personal ego boundaries. Circumstances impairing the clinician's ability to cope with patients and their problems may include deficient knowledge, general stress, mental disorder, or a treatment induced regression. These factors may lead the clinician to employ maladaptive intrapsychic or behavioral coping mechanisms that manifest in the form of therapeutic boundary violations. Other general factors common to all boundary violations include a slippage of the original purpose of the treatment (Epstein 1994, pp 97–98), pseudo-eclecticism (Epstein and Janowsky 1969), a narcissistic sense of specialness (Epstein 1994, pp 107–110, Epstein and Simon 1990), and efforts to de-professionalize the relationship by fostering an atmosphere of "pseudo-equality" between clinician and patient (Peterson 1992).

The double-binding messages that exploitive clinicians employ often represent a way for them to project their own disavowed feelings of shame and inadequacy onto vulnerable patients. For example, a therapist may deceive a patient suffering from low self-esteem and sexual dysfunction by encouraging her to have sex with him. He may rationalize:

> You have told me that you feel unattractive and inadequate as a woman. Since therapy is supposed to help you with your problems, I will help show you how attractive and effective you are as a woman by having sex with you.

Psychotherapy and erotic behavior can both be construed as sub-categories of the superordinate class of "Activities that help people feel better" (Epstein 1994, p 102). In the example above, the exploitive therapist blurs the logical boundaries between the two sub-categories, and fails to inform the patient that sexual behavior with him is likely to be harmful to her. Blurring of logical categories is an essential aspect of double-binding messages. Patients who are subjected to such reasoning are often in a dependent and cognitively regressed state, and are unable to understand the logical absurdity of the double bind. They fear that if they refuse to comply with the therapist's suggestions, they will be rejected for failing to cooperate with the therapist.

It is important to place the burgeoning literature on boundary violations in its social context. An aroused public has been exposed to recurring reports of psychiatrists and other mental health professionals, who have been disciplined or sued for behavior such as sexual involvement with patients and spouses of patients; using information learned in patients' psychotherapy sessions to gain inside data on financial investments; and accepting large bequests from elderly patients. Each new scandal serves to erode society's trust in the integrity of psychiatry as a profession, and makes it more difficult for the mentally ill to obtain needed treatment. Compounding this problem is the fact that many of these well-publicized reports of boundary violations involved highly trained psychiatrists who were leaders in their field, and who served as important role-models for students in professional training.

As has occurred many times before in history, societal changes tend to overshoot the mark, leading some observers to caution against an hysterical "witch hunt" against suspected offenders. Slovenko (1991) cautioned that the current climate has become ripe for an increasing number of false accusations to be made against innocent clinicians. Gutheil (1992) has documented such cases, and provided guidelines for proper forensic psychiatric evaluation following allegations of sexual misconduct.

## Components of the Coherent Psychiatric Frame

The purpose of the therapeutic frame is to protect the patient's safety and to promote recovery. It is the therapist's responsibility to structure the frame through word and deed. Langs (1984–85) stressed that a healthy and secure therapeutic environment is predicated on reducing variability and uncertainty in the treatment setting as much as possible. Table 5–6 summarizes the major boundary factors comprising the coherent treatment frame. Careful attention to these boundary issues can assist treating psychiatrists to communicate defining messages that strengthen the differentiation of role and identity between patient and practitioner.

The diversity of opinion regarding optimal methods of treatment for specific psychiatric disorders makes it very difficult to devise a set of specific guidelines that are appropriate for psychiatrists adhering to a wide spectrum of theoretical orientations. Dyer (1988; pp 45–57) emphasized how problematic it is to define a comprehensive ethical system, whether it is based on a set of specific rules (deontological ethics), on a list of values and goals (teleological ethics), or from consideration of the emotional and practical consequences of a given course of action (consequentialist ethics). A parallel dilemma exists when it comes to defining psychiatric boundaries.

**Table 5–6 Major Boundary Issues Contributing to the Formation of a Coherent Treatment Frame**

| Boundary Issue | Function and Purpose | Implicit Message to Patient |
|---|---|---|
| Stability | Consistency as to time, place, location, parties involved, and treatment method | "The doctor is reliable. This treatment can contain my irrationality." |
| Avoiding dual relationships | Utmost fidelity to the primary purpose of helping the patient | "The doctor focuses his/her attention on my problem, and is not sidetracked." |
| Neutrality and promoting patient autonomy | Avoiding abuse of power, and promoting the patient's independence | "The doctor values my ideas and encourages me to exercise choices." |
| Non-collusive Compensation | Scrupulous and forthright terms of remuneration for the clinician | "Aside from the payment, I don't have to gratify the doctor."- |
| Confidentiality | To protect the patient's privilege of keeping his/her communications secret | "My thoughts and feelings belong to me, not to the doctor." |
| Anonymity | Avoids seductiveness and role reversal | "This is a place to bring my issues, not a forum for the doctor's personal problems." |
| Abstinence | Encourages verbalization rather than action in dealing with feelings and conflicts | "There is a big difference between wishes and reality." |
| Preserving the clinician's safety and self-respect | Discourages the patient's destructive behavior, sets a good role-model for establishing healthy self-esteem | "It is possible to have a close relationship without someone getting hurt." |

For this reason, guidelines for psychiatrists should enhance patient safety, foster adherence to established clinical principles, and help to avoid specific consequences that are detrimental to either patient or practitioner. Such an approach is consistent with an intensifying interest in reducing preventable medical error. In his seminal work on human error, Reason (1990, p 69) outlined three major types of performance as a way to address the sources of preventable human error. These categories include rule-based performance, skill-based performance, and knowledge-based performance. As an example, Reason described how the use of inadvisable rules leads to rare but preventable collisions at sea, citing studies reporting how experienced maritime

pilots expose themselves and others to unnecessary and potentially serious risk by allowing their own vessel to navigate too closely to adjacent ships even when there is plenty of sea room to avoid such proximity:

> The confidences these and other experienced operators have in their ability to get themselves out of trouble can maintain inadvisable rule behavior. This is particularly so when a high value is attached to recovery skills and where the deliberate courting of a moderate degree of risk is seen as a necessary way of keeping these skills sharp.

With regard to rule-based procedures for reducing error in psychiatric practice, each boundary issue can be examined from the point of view of clearly indicated procedures, relatively risky procedures, and contraindicated procedures (Epstein 1994 pp 113–117). In the ensuing discussion of components of the psychiatric frame, lists of these various types of procedures are adapted from Epstein's earlier work on boundaries (Epstein 1994, pp 119–236).

Riskier procedures that fall into the "gray zone" are not necessarily unethical or unsound. However, psychiatrists engaging in such activity should be aware of the circumstances under which they increase or reduce the chance for injury either to the patient or themselves. For example, under most conditions, it is probably unwise to attempt psychiatric treatment of one's next-door neighbor. Nevertheless, practitioners living in remote areas, or working in confined ethnic communities, might as a matter of practicality, be forced to treat such a patient for whom no reasonable alternative exists. The hazard of no treatment may outweigh other factors in the situation. However, the fact that psychiatrists sometimes must treat patients under risky circumstances does not mean they should disregard the increased hazard they are assuming, or forget about optimal treatment standards, just as the exigencies of battlefield surgery do not obviate the need to strive for aseptic technique.

Psychiatrists should safeguard against any semblance of inappropriate behavior, even if the activity can be justified as seemingly harmless. For example, seeking social activities with patients outside of the treatment setting can be interpreted by patients or their family members as seductive. Gutheil and Gabbard (1993) have emphasized that the very appearance of undue familiarity with a patient, may in and of itself, hamper successful defense against false allegations of professional wrongdoing.

## Stability

Configuring a stable and consistent treatment setting is analogous to the "holding environment" provided by parents in early childhood (Winnicott 1960). Patients with psychiatric illnesses will find it very difficult to entrust their lives to a psychiatrist whom they perceive to be unreliable. Indicated measures regarding stability include formulating an agreement with the patient for a treatment regimen that will take place according to a specific method and schedule; encouraging truthful disclosure and cooperation; establishing a commitment to beginning and ending sessions on time; discouraging interruptions during treatment sessions; offering advanced notice as to when the psychiatrist will be absent; providing for coverage by another practitioner when the psychiatrist is off duty; maintaining coherent therapeutic demeanor; and maintaining relative consistency as to who participates in the treatment situation.

It is generally unwise for a psychiatrist to disparage a patient's complaints about issues like the doctor's tardiness in starting sessions, or to become defensive when explaining the meaning of the patient's distress about such complaints. Many psychiatrists experience patients' demands for consistency as a form of control and imprisonment. Out of anger, they may react to these patients as if their wishes for reliability and concern were infantile and irrational:

> Your complaints about my lateness are a reflection of your need to control me.

The psychiatrist's tardiness might in fact be creating tremendous anxiety because it reminds the patients of parents who never took their feelings into account.

## Avoiding Dual Relationships

Psychiatrists should avoid treatment situations that place them in a conflict between therapeutic responsibility to patients and third parties. Examples of dual relationships in psychiatric practice include clinicians treating their own relatives and friends; the same therapist employing concurrent family and individual therapy paradigms with a given patient; and clinicians testifying as forensic witnesses for current psychotherapy patients. Although it is very common practice (Epstein et al. 1992), accepting psychotherapy patients referred by one's current or former patients embraces certain risks that must be considered (Pope and Vetter 1992). For example, a current patient might refer an attractive friend for therapy as a way of either seducing the therapist or sabotaging the treatment (Langs 1973, pp 60–62).

Role conflicts are quite widespread (Pope and Vetter 1992) and interfere with the practitioner's single-mindedness of purpose as a healer. Chodoff (1993, pp 457–459) placed special emphasis on this issue by arguing that advocating for the needs of the mental illness was one of psychiatry's primary societal responsibilities. By eroding public trust, dual relationships interfere with the ability of psychiatrists to carry out their vital functions in the community.

The burgeoning expansion of prepaid care in the US over the last two decades has provoked concern about a new source of role-conflict for psychiatrists. Managed care has been espoused as an important modality to reduce unnecessary treatment by encouraging preventive care, and to promote cost-consciousness among physicians (Fries et al. 1993). Stephen Appelbaum (1992) argued that psychotherapists practicing under the old fee-for-service model were more inclined to provide unnecessarily prolonged treatment than those working under an organizational system that prevented direct monetary involvement between patient and practitioner.

On the other hand, increasing coverage of the population of the US under a system of managed care has generated serious concerns regarding potential conflicts-of-interest (McKenzie 1990, pp 113–126). This disquietude is particularly noticeable in the field of psychiatry. Many managed care organizations (MCOs) have severely restricted the number of psychiatrists within a given community allowed to serve on their treatment panels. Patients' access to their

regular treating practitioner has been further limited, even when the doctor is allowed to enroll on the panel.

For example, under the rules of some MCOs, a psychiatrist might be prevented from maintaining continuity of care for outpatients needing hospitalization. During their hospital stay, such patients must be attended by a preselected group of psychiatrists who conduct all hospital treatment for the plan.

Although there are little scientific data to support the contention that restricted managed care panels are necessary for lowering costs, it is important that both patients and clinicians be informed as to the hazard such a system of care entails. Since participation on a panel is often contingent on cost-efficiency profiles, psychiatrists who derive a significant portion of their income from a given MCOs are discouraged from advocating for patients needing more expensive care. In addition, some managed care organizations refuse to pay for integrated treatment by psychiatrists for mentally ill patients enrolled in their panel. These MCOs insist instead on a split treatment model in which the patient obtains psychotherapy from a social worker or psychologist, and is allowed only brief medication management visits with a psychiatrist. Psychiatrists attempting to do medication management under this model often have little contact with the psychotherapist, are very restricted in the frequency and duration of visits with the patient, and are thereby limited in making overall clinical decisions that might become necessary. Such a situation creates an ethical bind for the psychiatrist in which the medical responsibility is not accompanied by a commensurate degree of authority to direct the treatment process.

In the face of reports of physicians claiming they were terminated from managed care contracts because they protested treatment denials, fear of retaliation for patient advocacy has mounted (McCormick 1994). Judge Atlas (1993) has suggested that psychiatrists who fail to give informed consent regarding the risks to the patient of their role conflicts would be exposing themselves to civil damages in the event of an adverse outcome. Although the extent of the legal duty to disclose risks factors under managed care is unresolved, Appelbaum (1993) proposed that mental health clinicians inform beginning patients that payment for treatment under managed care might be stopped before the patient feels ready to terminate.

Limitations as to who may serve on a managed care panel and what functions the clinician may perform, are other factors that have strong potential for creating disruption in the continuity of care. For example, Westermeyer (1991) described seven case histories in which psychiatric patients treated under managed care committed suicide or suffered serious clinical deterioration. Clinically uninformed managed care practices appeared to serve as critical aggravating factors for each of these patients. In the cases of two individuals who killed themselves, the employer had switched contracts to different managed care companies, and the patients were forced to transfer to new clinicians. These disruptions appeared to play an important role in the patients' suicides.

Although more research is required to evaluate the full ramifications of managed care on psychiatric populations, recent studies suggest that some groups face adverse outcomes under this system. For example, Rogers et al. (1993) found that on an average, patients with depression who were treated by psychiatrists under pre-paid treatment plans acquired new limitations in their physical or day-to-day functioning over a 2-year period, while those treated in the traditional fee-for-service setting did not.

## Autonomy and Neutrality

Freud (1912, 1913) recommended that psychoanalysts adhere to a position of neutrality with their patients by refraining from the temptation to take sides in the patient's internal conflicts or life problems . This advice has relevance for all psychiatric treatment, insofar as it espouses the idea that practitioners should maintain profound respect for their patients' autonomy and individuality. This is a fundamental therapeutic stance that fosters independence, growth, and self-esteem. It reinforces the idea that the clinician believes the patient to be the owner of his or her body, life, and problems. The patient receives the following message:

> The doctor tries to help by assisting me to learn about myself, not by trying to take control of me.

Patient autonomy has not always been accorded its current importance in the hierarchy of priorities in medical practice in the United States. According to Blackhall et al. (1995), in 1961, 90% of physicians in the United States did not inform their patients of a diagnosis of cancer. By 1979, 97% of American physicians made it their policy to inform patients with cancer of their diagnosis (Blackhall et al. 1995). This change appears to be the result of physicians assuming less of a paternalistic attitude, and becoming more enlightened and respectful of patients' right to participate in medical decisions. In some parts of the world, similar changes have occurred in clinical practice with mentally ill patients.

Cultural, ethnic, and probably sociodemographic factors strongly shape attitudes regarding patient autonomy and informed consent. In some cultures, a higher value may be placed on the harmonious functioning in the interlocking pattern of family relationships than on the autonomy of individual family members. For example, according to Okasha (2000) patients reared in some cultures may not wish to continue treatment with a physician who is not sensitive regarding the importance of involving the family directly in communications about the patient's illness. The psychiatrist should diligently explore the role that cultural and family relationships play in the patient's healthy mental functioning, and be guided primarily by the patient's communications about their degree of comfort or conflict with these family relationships. Psychiatrists should be considerate and respectful of cultural differences between themselves and their patients, and be particularly cautious about interpreting those differences as a pathological process.

In addition to being mindful of cultural issues, indicated ways of encouraging autonomy include encouraging informed consent by outlining the potential benefits, risks, and alternatives for a proposed treatment approach; explaining the rationale for the treatment; and fostering the patient's participation in the treatment process. Paradoxically, acutely suicidal patients often require the psychiatrist to assume temporary responsibility for their safety. In most cases this serves to augment the patient's sense of autonomy through a coherent modeling process (Bratter 1975), since true independence is impossible without self-governance.

Clinical actions that may interfere with the patient's autonomy include advice regarding non-urgent major life decisions; attempting to exert undue influence on issues unrelated to the patient's health; reluctance to allow patients to terminate treatment; seeking gratification by exerting power over patients; and using power over patients as a form of retaliation.

## Coherent and Non-Collusive Compenation

Although there are rewards to be obtained from working in an interesting and creative profession, this is best applied to one's collective professional endeavors. With a specific patient, monetary compensation is the only gratification psychiatrists should realistically expect (Epstein and Simon 1990). When compensation is direct, there should be a set fee, and the patient should be responsible for the scheduled appointment time. When compensation is indirect or salaried, the psychiatrist must avoid colluding either with the patient against the party paying for the treatment, or with the third party against the patient (see the above Subsection "Avoiding Dual Relationships"). Whatever method is being used for paying for mental health treatment, a coherent and non-collusive arrangement imparts the message to the patient:

> The doctor has needs of his/her own, but they are limited to a salary or fee. Aside from financial obligations, I don't have to please, gratify, or nurture my doctor.

The practice of charging for missed appointments under the traditional fee for service paradigm is often misunderstood by patients, because their experience with physicians in other branches of medicine has usually been that they were charged on a fee-for-procedure basis, rather than fee-for-time. Charging for missed appointments is justifiable from an ethical standpoint as long as the rationale is clearly explained to the patient at the beginning of the treatment, and the patient agrees to it. In addition, no attempt should be made to hide the fact of billing for missed appointments from third party payers. Some states have an absolute prohibition against billing for missed appointments under entitlement programs such as Medicaid and Medicare (Epstein 1994, p 169). Within certain guidelines, it is permissible to bill the patient (but not Medicare) for missed appointments under the Medicare program (Epstein 1994, pp 169–170). Readers are cautioned that regulations regarding Medicaid and Medicare are subject to periodic legislative revisions, and may vary according to jurisdiction.

Generally risky compensation arrangements include working for a treatment organization one perceives to be financially exploitive; accepting inexpensive gifts from patients especially when such gifts are not part of a culturally expected mode of behavior; bartering goods or services in return for treatment; referring patients for treatments or procedures in which one has a proprietary financial interest; and neglecting the patient's failure to adhere to the original agreement regarding payment of fees. Certain practices are absolutely contraindicated and likely to be destructive, including fraudulent billing; accepting expensive gifts; fee-splitting; colluding with the patient or third party; and use of financial insider information.

## Confidentiality

It is essential that psychiatrists treat their patients' communications as privileged. This means that patients alone retain the right to reveal information about themselves. The advent of managed care has raised even greater concern about the privacy of patients' personal communications with their psychiatrists because of the potential for an increasing number of persons connected with the MCOs to have access to material from patients' files. Psychiatrists should caution their patient about the potential limitations to confidentiality, and be prepared to explore the consequences of these exceptions. For example, if a patient is raising his/her mental health as an issue in litigation, some or all communications to a psychiatrist could be legally discoverable. Coherent boundaries with regard to confidentiality send the message to the patient:

> My thoughts and feelings belong to me. The doctor does not treat them as if they belong to him/her.

Indicated means of preserving confidentiality include obtaining proper authorization from patients before releasing information; explaining the need for confidentiality with parents of children and adolescents; and involving all participants in family and group psychotherapy in agreements about confidentiality. Problematic activities that may endanger confidentiality include stray communications with concerned relatives of patients in individual psychotherapy where there is not a prior expectation on the patient's part about discussions with relatives; discussion of privileged information with the psychiatrist's own family members; releasing information about deceased patients; and failure to properly disguise case presentations.

## Anonymity

Many psychiatrists associate the principle of relative anonymity with Freud's advice to psychoanalysts (Freud 1912):

> The doctor should be opaque to his patients and, like a mirror, should show them nothing but what is shown to him.

Freud argued that it was dangerous for psychoanalysts to expose their own mental problems or intimate life details in a spurious attempt to place themselves on an "equal footing" with patients (Freud 1912, pp 117–118). The merit of this recommendation extends beyond its origin in psychoanalytic technique to a fundamental boundary issue applicable to all forms of psychiatric treatment. It serves as a reminder to both patient and clinician of the professional purpose of the relationship. Avoiding unnecessary personal disclosure to patients protects both patient and practitioner from a reversal of roles–one of the critical themes recurring in boundary violations in general (Peterson 1992). Many patients experience excessive self-disclosure by the psychiatrist as seductive, and it has been frequently observed to be a precursor to subsequent sexual involvement (Schoener and Gonsiorek 1990, p 403). By maintaining a policy of relative anonymity, the patient receives the following message about the treatment:

> This a place where I can bring my issues. The doctor doesn't burden me with his/her stuff.

The psychiatrist should not construe the principle of anonymity to justify a demeamor that is aloof or distant. This can be very traumatic for some patients. To the contrary, when a patient insistently requests personal information about the psychiatrist that are not pertinent to the logistical and administrative aspects of treatment (e.g., whether the doctor planning to retire in the near future), the opportunity arises for the psychiatrist to become more engaged with the patient by explaining the reasons why personal revelations are likely to be damaging to the therapeutic process. It also presents an opening to ask the patient the reasons for their wanting to know the information, and enables one to explore with the patients their previous experiences of having emotionally important things hidden from them, or conversely, the occurrence of developmentally inappropriate disclosures made by early caregivers.

Certain forms of self-disclosure are indicated in the course of work with psychiatric patients, including apprising patients regarding the clinician's qualifications and treatment methods as part of informed consent; discussing reality factors about the psychiatrist's health status or intentions regarding retirement that will impact on the patient's treatment decisions; and using "reality checks" to help patients contain disturbed and frightening fantasies.

## Abstinence

Abstinence means that psychiatrists should discourage direct forms of pleasure such as touching or sexuality in the course of their interactions with patients. In the therapeutic relationship, the patient's ability to consent to sexual activity with the psychiatrist is vitiated by the knowledge the latter possesses over the patient, and by the power differential that vests the psychiatrist with special authority.

For patients, actual gratification from the psychiatrist is best confined to realistic goals for recovery and emotional growth. Psychiatrists should limit themselves to the pleasure of getting paid for a job well done, and for the opportunity to participate in an interesting and creative profession. Although steadfast application of this boundary can be quite frustrating for both doctor and patient, it pays excellent dividends in the long run by encouraging autonomy and a more mature way of dealing with impulses. The rule of abstinence as a therapeutic boundary has an analogous function to the incest taboo as a social organizer. In all known human cultures, the incest taboo has survival value because during childhood development, it serves to strengthen the sense of individuality and personal boundaries so necessary for growth, independence, and social responsibility (Parker 1976).

From a practical standpoint, psychiatrists can strengthen their patients' boundaries in this regard by resisting behaviors such as physical touching, accepting gifts, socialization outside of treatment, and sexual involvement. The patient receives the following messages from a clinician who is able to properly adhere to this principle:

> The doctor is more interested in my health than his/her own gratification and doesn't try to take possession of me. I am learning that I can have wishes that needn't result in action.

There are occasions when psychiatrists are obligated to employ physical procedures such as taking blood pressures, checking for extrapyramidal symptoms, restraining dangerous patients, or administering electroconvulsive therapy (ECT). Indeed, clinical touching of patients is considered an integral part of the physician–patient relationship because of its important role in physical examination and therapeutic procedures. Even though psychiatrists are physicians, they are obligated to use much more restraint in this regard than is expected of colleagues in other branches of Medicine. It is probably too invasive for the same physician on a protracted basis, to simultaneously intrude both into the patient's psychological and physical spaces.

Other risky forms of gratification include embracing or kissing patients; eating and drinking with patients; socializing with patients outside of the therapy setting; and failure to understand and resolve recurrent or obsessive sexual fantasies about a patient. Engaging in sexual behavior with current or former patients is contraindicated because it is almost invariably destructive, even though the damage may not be immediately manifested.

The APA (APA 1993) took a principled and unequivocal stand regarding sexual activity between psychiatrists and their current or former patients:

> Additionally, the inherent inequality in the doctor−patient relationship may lead to exploitation of the patient. Sexual activity with a current or former patient is unethical.

The APA's position is in agreement with the principles espoused in the Hippocratic oath, which clearly mandates that a physician approach a patient "for the benefit of the sick, and abstain from every voluntary act of mischief and corruption; and, further, from the seduction of females or males, of freemen and slaves."

Despite the ancient basis of this proscription, and convincing evidence in our times of the damaging effects of sexual relationships between therapists and former patients (Epstein 1994, pp 218–220; Luepker 1990; Brown et al. 1992) some authors have raised legal and theoretical challenges to the permanent prohibition contained in the APA guidelines (Appelbaum and Jorgenson 1991). While refraining from calling for a repeal of APA's ethical proscription against sex with former patients, Malmquist and Notman (2001) argued that legal misapplications of imprecise and unproven concepts of transference and countertransference have exposed therapists who enter post-termination sexual liaisons with their patients to inappropriate legal liability.

Research examining the causation and prevention of human error has provided neurocognitive evidence supporting the ancient wisdom of Hippocrates' injunction. Skilled performance is subject to potentially calamitous error when experts fail to follow empirically derived safety guidelines, or lack an adequate knowledge base upon which to initiate critical interventions (Reason 1990). Skillful performance in conducting medical procedures is acquired from overlearned behavior that enables an expert to undertake complex cognitive and behavioral operations in a smooth and rapid fashion. Performance skills whose success depends on over-learned and automatic processes rely primarily on the procedural memory system (Cabeza and Nyberg 2000). The Hippocratic mandate of approaching the patient solely for their benefit and to avoid mischief, is a prime example of

an over-learned automatically embedded error protection message acquired through years of medical training. Anything that interferes with such an intensively elaborated internal safeguard endangers patients' well-being.

Whether they realize it or not, psychiatrists who justify the permissibility of post- termination sexual relationships are sabotaging their own over-learned commitment to act primarily in their patient's best interest, and are exposing their patient to a biased and error prone treatment. This self-permissive attitude would make a psychiatrist more prone to engage in seductive grooming of a patient during the treatment process in anticipation of termination. In addition, biased by this attitude, a psychiatrist is likely to avoid making any communication to the patient that would discourage a subsequent romantic post-termination liaison (Epstein 2002). While a psychiatrist might consciously deny that this attitude is a violation of the Hippocratic dictum, in actual cases where psychiatrists have engaged in post-termination sex with patients, their pre-termination subliminal thinking ran like this:

> I'm treating this patient only for her/(his) benefit. Like Hippocrates, I will abstain from every voluntary act of mischief and corruption and further, from seduction. However after I cure this very attractive patient, I will keep his/(her) phone number and after a respectable period of time, it will be a different matter, and we will see what will happen.

Note that this reasoning represents a form of dissociative thinking based on a primitive wish for inappropriate gratification with a patient that magically disavows the connection between post-treatment behavior and pre-treatment reality. All psychiatric treatment is based on the assumption that a psychiatrist's interventions by means of positive attitudes, words, deeds, and medical interventions will have a lasting beneficial effect on the patient after the treatment has ended. There is no realistic escape from the fact that the reverse is also true, namely that inappropriate attitudes, words, deeds, and interventions are likely to have a lasting harmful effect on the patient after the treatment has ended.

For the reasons outlined above, psychiatrists should adhere to the dictum of *"once a patient, always a patient."* The vast majority of our patients suffer from chronic struggles. It is not uncommon for patients who have terminated from treatment to return to the same psychiatrist for further assistance, sometimes several decades later. Any attitude or behavior that could predispose the psychiatrist to ignore this clinical reality will increase the risk of serious harm to the patient and the treatment process.

### Self-respect and Self-protection

It is essential that psychiatrists protect themselves from being exploited by patients. This principle is necessary to protect clinicians and patients alike. Many patients seeking treatment have endured abusive relationships in which being victimized became the price for maintaining human connectedness. For such patients, efforts to exploit the psychiatrist may be an action-question that inquires:

> Must one of us be injured in order for us to have a close relationship?

By setting a proper role model for self-respect, and self-caretaking, the psychiatrist imparts the following message to the patient:

> Relationships need not be structured on the basis that one or both parties must be exploited. If I as the doctor allow you to hurt me, I am setting a poor role model.

Psychiatrists should attempt to discuss the meaning of any exploitive behavior on the patient's part as soon as possible. With unstable or impulsive patients who are prone to acting out, confrontation should be timed to maximize safety. For example, it would be more prudent to interpret the manipulative aspects of a patient's suicidal behavior after the patient is admitted to a hospital. If a patient makes a sudden physical overture such as attempting a sexually provocative embrace, it must be dealt with the same urgency as a physical assault. The psychiatrist should inform the patient that such behavior is inconsistent with coherent treatment (Epstein 1994, pp 228–231; 58). It is generally risky to allow repeated exceptions such as last-minute prolongation of sessions or repeated lateness in paying fees; excessive intrusion into the psychiatrist's personal space in the form of regular and frequent late night phone calls or taking items from the office.

Certain psychiatrists find themselves avoiding confrontation with an exploitive patient out of fear of the latter's narcissistic rage. This is an indication of an escalating situation that may lead to further boundary violations either by the patient or the psychiatrist. A useful explanation of this behavior is provided in Gabbard's (1994) description of a sub-group of clinicians who become sexually involved with patients as part of a self-defeating pattern of behavior he termed "masochistic surrender." These practitioners are unable to defend against being tormented by certain highly demanding patients. They succumb to the patient's importunings, sometimes while in a dissociated state, even though they may know their behavior is wrong. Gabbard (1994) argued that the aberrant behavior of these clinicians is rooted in an impaired ability to cope with their own aggressive feelings, resulting in their feeling that it would be sadistic to set limits on the patient.

## Summary

The ethical and boundary issues discussed in this chapter were designed to stimulate a better understanding of an extremely thorny topic, rather than to provide an exhaustive compendium.

Table 5–7 summarizes selected indicators of potential boundary violations, along with remedial responses clinicians might employ to deal with these situations. A burgeoning literature regarding the psychological characteristics of clinicians who have problems with maintaining proper boundaries (Epstein 1994, Gutheil and Gabbard, 1993, Epstein and Simon 1990, Schoener and Gonsiorek 1990, Gabbard 1994, Twemlow and Gabbard 1989, Gabbard 1991, Geis et al. 1985) provides useful guidance in this regard.

The difficulties psychiatrists may encounter in keeping boundaries derive from many sources. In the past, professional training programs have not addressed this issue systematically. Recent proposals to bolster the study of ethics and boundaries in medical school and residency programs (Roman and Kay 1997, Kay and Roman 1999), will help to remediate this problem. It behooves psychiatrists to determine whether they have suffered deficiencies in training

**Table 5–7 Indicators of Potential Boundary Violations with Suggested Remedial Responses**

| Indicator | Suggested Remedial Response for Clinician |
|---|---|
| Clinician is frequently tardy starting sessions | Avoid criticizing patient for complaining about lateness. Re-examine reasons for tardiness in light of patients' need for a stable treatment frame |
| Clinician changes the treatment paradigm in "midstream," i.e., switching from individual therapy with Mr. A to couples therapy with Mr. A and his wife | Avoid dual relationships that may interfere with primary loyalty to the first patient. If dual relationships cannot be avoided, explain risks to patient(s) according to the principle of informed consent |
| Clinician frequently advises patients on matters not related to treatment process | Consider if this is a general pattern of need for control in one's non-clinical relationships. If so, consider ways to help patient to make his/her own decisions |
| Clinician often relates to patient as if he/she were a personal friend | Listen for signs that the patient feels burdened. Acknowledge pattern of role reversal and importance of clinician's fiduciary obligations to patient |
| Clinician feels overly resentful about having to keep boundaries because they feel too constraining and spoil the "fun" and creativity of being a therapist | Remember that therapy can often be difficult, burdensome, and frustrating work, and that boundaries are necessary for the patient's safety |
| Clinician accepts gifts from patient | Try to explore patient's motive for the gift. Consider refusing the gift by explaining that it might interfere with the effectiveness of treatment. Be prepared to work with patient's and one's own feelings of shame in this regard |
| Clinician seeks contact with patient outside of therapy setting | Avoid such contact, and explain the reason to patients. In settings where social contact is likely, discuss problems and options with the patient in advance |
| Clinician is unable to confront patients who are late paying fees, remove items from the office, repeatedly try to prolong sessions, or torment therapist with insatiable demands | Listen to the content of patient's communications and dreams regarding people injuring one another. Explore fear of one's own anger, the patient's anger, or of setting limits |
| Clinician often tries to impress patients with personal Information about him/herself | Refrain from further disclosure and examine one's possible motives. Consider how such activity might relate to sexual feelings to patient or need to control patient |
| Clinician becomes sexually preoccupied with patient. For example, feels a pleasurable sense of excitement or longing when thinking of patient or anticipating his/her visit | Consider that one's sexual feelings may portend the re-enactment of an actual or symbolic incestuous scenario from the patient's past. Remember that incestuous behavior or its symbolic equivalent infantilizes the victim. Obtain supervision and/or personal psychotherapy if sexual preoccupations continue unabated |

or adverse role-modeling during the course of their professional development, and whether their own emotional problems significantly interfere with maintaining coherent professional boundaries.

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CHAPTER

# 6 Legal Issues in Psychiatric Practice

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## Introduction

Our society values individual freedom, autonomy, and privacy. Sometimes a patient's individual interests or stated desires may be at odds with those of society. Questions such as whether to pursue involuntary hospitalization for a severely ill patient, how to manage a patient who refuses appropriate medical treatment, or whether to divulge information about a potentially dangerous patient to police may arise in these circumstances. *Mental health law* encompasses the efforts of courts, legislatures, and regulatory agencies to resolve the questions and conflicts that arise between patients, clinicians, and the state (i.e., society). Since issues pertaining to legal aspects of patient care arise for all clinicians, an understanding of the clinical-legal tensions that arise in psychiatry and of the legal regulations governing the field is necessary for effective practice.

The subspecialty of forensic psychiatry focuses specifically on issues at the medico–legal interface. However, the role of the forensic psychiatrist differs from that of the practicing clinician in several key aspects. In most circumstances, the forensic psychiatrist owes his *agency* to—or works for—a third party (e.g., the court system) rather than a patient. Most often, the *purpose* of the forensic psychiatric evaluation is to assess for the presence of a condition or impairment and to aid third-party decision makers in an adversarial or adjudicative proceedings (e.g., in determining competence, reaching a verdict, or in assigning a disability rating) rather than to provide treatment. Because agency and purpose in forensic evaluations differ, the *degree of diagnostic certainty required* for such assessments may also differ. The forensic evaluator, as compared to a clinician in a traditional doctor–patient relationship, may require a greater reliance on objective findings in an effort to establish "historical truth" as the basis for action. The clinician may be more inclined to base clinical decisions on the "narrative truth" elicited from the subjective reports of a patient's experiences (Cohen 2003).

This chapter will provide an overview and organizational framework for understanding the law as it is applied to the practice of clinical psychiatry. For the interested clinician, a number of textbooks provide more detailed discussions of the practice of forensic psychiatry (Gutheil and Appelbaum 2000, Lande and Armitage 1997, Rosner 2003, Simon and Gold 2004).

## Categories of Legal Issues in Psychiatry

Table 6–1 outlines categories into which legal issues in psychiatric practice may be divided. Legal issues surrounding mental illness and treatment may be broadly divided into two groups: *civil issues* and *criminal issues.* Civil issues may be further subdivided into patient's rights issues including involuntary hospitalization or treatment refusal and doctor–patient issues such as patient–therapist privilege, confidentiality and malpractice. Criminal issues tend to focus on competency to stand trial and criminal responsibility (i.e., whether a person accused of a crime should be held responsible and punished or should be found not guilty by reason in insanity). Behaviors or psychiatric conditions of persons alleging a crime or having been victimized may also be matters for the court's consideration. Other issues such as the degree to which psychiatric illness may potentially contribute to repeat offenses or alter punishment determination may also be considered criminal issues.

**Table 6–1 Categories of Legal Issues in Psychiatry**

| Civil Issues | Criminal Issues |
|---|---|
| Patients' rights<br>• Involuntary hospitalization/ civil commitment<br>• Treatment refusal | Competency |
| Disability/fitness evaluations | Criminal responsibility |
| Child custody evaluation | Other trial related<br>• Diminished capacity<br>• Mitigating factors<br>• Aggravating factors<br>• Witness reliability<br>• Victim impact<br>• Child/adolescent |
| Doctor–patient<br>• Confidentiality<br>• Informed consent<br>• Malpractice | Juvenile waiver |
| | Child witness reliability |
| | Victim impact |

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## Civil Issues: Patient's Rights

### Involuntary Hospitalization

In the United States, an individual may be involuntarily hospitalized for psychiatric reasons only if certain legal criteria are met. Therefore, clinicians do not actually commit patients. The psychiatrist often initiates commitment proceedings by certifying that a mental illness requiring hospitalization exists and that a patient is refusing voluntary hospitalization. A legal decision-making body is thereby petitioned to order hospitalization. The decision as to whether a patient is actually involuntarily hospitalized ultimately rests with the courts—or in some states quasijudicial boards. Although the statutory language for involuntary hospitalization (civil commitment) varies from state to state, three principles serve as the basis for all commitment laws. The individual must be

- mentally ill, and
- dangerous to self or others, or
- unable to provide for his or her own basic needs (i.e., "gravely disabled").

In most statutes, the term mentally ill is not clearly defined but requires the petitioner (e.g., the psychiatrist) to state the psychiatric problem necessitating hospitalization. In some states, additional criteria such as an overt act of violence toward self or others or damage to property within a specified period of time, or the absence of available less restrictive treatment alternatives, must also be established before an individual is hospitalized against his or her expressed desires. Most states allow for a period ranging from 1 to 20 days of emergency hospitalization for the purposes of providing immediate crisis intervention and completing a more detailed evaluation. All states require periodic reassessment of the need for continued involuntary hospitalization (Gutheil and Appelbaum 2000).

When persons are involuntarily hospitalized, they generally maintain their rights to manage their own financial matters, to communicate with others via phone or mail, and to receive personal visitors. They also have rights to privacy including space to secure valuables, private bathing and toilet facilities, and personal space. These rights are typically statutorily quantified. In most states, the right of psychiatric inpatients (including those involuntarily committed) to refuse therapy and/or medication is also preserved. Involuntarily hospitalized patients require a separate judicial proceeding to establish incompetence to manage finances before a guardian can be appointed or to establish incompetence to make medical decisions before involuntary medications may be ordered.

Patients' rights in hospital settings may be restricted by the clinical judgment of treating professionals in consideration of both the patient's interests and the rights and safety of other persons within the hospital. Involuntary hospitalization, even when accomplished entirely in the patient's best interests, represents an extreme curtailment of civil liberty. Disputes over violations of patient's rights in such situations are inevitable. In many jurisdictions, a civil rights officer or ombudsman is mandated to assist in resolving these disputes. Occasionally, patients or their ombudsmen allege that a psychiatrist has failed to act in good faith or adhere to statutory requirements in petitioning for commitment. Lawsuits may be brought under the theories of wrongful imprisonment, malicious prosecution, or abuse of authority (Simon 2002). Fortunately, most states grant immunity from liability for psychiatrists exercising reasonable professional judgment when initiating commitment. However, a psychiatrist may be successfully sued if evidence exists of willful or blatant failure to adhere to commitment procedures. Psychiatrists must therefore be aware of specific regulatory guidance surrounding commitment wherever they practice.

### The Psychiatrist's Role in Hospitalization Decisions

In most cases, the decision for psychiatric hospitalization represents the culmination of a collaborative dialogue between the clinician and his patient. The decision is made by the patient after a thorough discussion of the reasons for the physician's recommendation for hospitalization, the risks, benefits, and alternatives to hospital treatment. This dialogue also allows for the clinician's assessment of the patient's ability to understand the ideas discussed, manipulate information, and come to a rational decision. Thus, most hospitalizations occur with the *informed consent* of a patient capable of making treatment decisions (including whether or not to be admitted to the hospital). The idea that physicians must obtain and document informed consent before initiating any form of treatment is a universally recognized principle of medical practice and failure to do so frequently underlies malpractice claims (see below).

In situations where involuntary hospitalization is sought, it is impossible to obtain informed consent. Typically, an individual is brought to emergency clinical attention by a law enforcement official because the individual was acting in a bizarre manner, or was demonstrating or threatening behavior dangerous to self or others. The psychiatrist is asked to assess the individual and make a decision about disposition in situations when an individual does not demonstrate a capacity to rationally discuss psychiatric treatment options or hospitalization. If the psychiatrist believes the person to be mentally ill, dangerous, and/or gravely disabled, the appropriate legal body (e.g., the hospitalization magistrate court) is provided with appropriate documentation, and a commitment order is sought. Generally, reasonable clinical judgment dictates erring on the side of safety rather than allowing a potentially dangerous individual to leave the emergency room. Similarly, when a voluntarily admitted patient requests hospital discharge but is believed to present an ongoing danger to self or others, a court order for continued (involuntary) hospitalization may also be sought. Most states require that a clinician other than the primary treatment provider must certify mental illness, dangerousness, and/or grave disability under these circumstances.

During the deinstitutionalization movement of the 1970s, the courts increasingly took over the authority to determine whether commitment was legally appropriate. The majority of states began to adopt outpatient commitment statutes under which persons could be required by the courts to receive treatment in community settings. Some critics have argued that dangerousness criteria required for commitment, if met, cannot be satisfied by outpatient care and also that relaxation of this requirement may allow

for abusive violation of civil liberties (Mulvey et al. 1987). Others have argued that without sufficient community resources, and in the context of a preserved right to refuse specific treatment, outpatient commitment is ineffective in establishing safety to the individual or community (Munetz et al. 2000, Stein and Diamond 2000). As states continue to adopt and refine their outpatient commitment regulations, psychiatrists must pay increased attention to their potential roles in determining which patients may be appropriate for outpatient commitment and to the challenges associated with caring for patients in this status and in such settings.

## Competency and Treatment Refusal

As noted above, for most patients including those hospitalized involuntarily, the right to refuse specific treatment is preserved. This is not the case for persons legally declared incompetent to make medical treatment decisions. All physicians routinely assess their patients' abilities to make medical decisions as they obtain informed consent for treatment or procedures. Typically, caregivers assess their patients' abilities to make treatment decisions implicitly rather than through an explicit process. Psychiatric consultation tends to be requested only when questions arise surrounding a patient's decision making such as when a patient refuses an important diagnostic or therapeutic procedure, or refuses physician-recommended medication(s). In these situations, a psychiatrist may be asked to determine whether the patient is competent to make treatment decisions.

As with involuntary hospitalization, "competency" is a legal determination, rather than a medical one. All persons are presumed competent unless they have been explicitly declared legally incompetent by the appropriate court. This rule holds for even the most severely psychotic or demented patients. While a determination of incompetence is a legal one, in practice the judicial system relies heavily on medical expert testimony in making such determinations. Therefore, psychiatrists should be comfortable with processes used to assess the extent to which a patient's *capacity* to make a particular decision may be impaired. Capacity—or functional impairment—is a clinical rather than legal determination.

Decision-making capacity and competence are task specific. Patients may be competent (e.g., demonstrate the capacity) to make some medical decisions but not others depending on the complexity and consequences of the medical decision and the complexity of the medical information the patient must understand. Since there is no single legal standard for competency, appropriate criteria for assessing decision-making capacity may vary from jurisdiction to jurisdiction. Beyond clinical judgment about the complexity of the medical decision and relevant clinical information, basic principles underlying legal determinations of medical competency have been identified by Grisso and Appelbaum (1998). These concepts provide a framework for the clinical assessment of medical-decision-making capacity. They are summarized in Table 6–2.

All courts have accepted the notion that patients who are unable to communicate a choice are not competent to make medical decisions. Therefore, a comatose patient, or a psychotically paranoid patient refusing to speak to all clinicians, would be declared incompetent to make treatment decisions. More than merely communicating a decision, most courts have determined that a patient's stated decision must be sufficiently stable to be considered evidence of competence. A patient's decisions need not be fixed (e.g., a patient may change his mind upon further consideration). However, inconsistent responses of an amnestic or severely demented patient responding to a repeated question without consideration of the facts recently presented or who appears to be forgetting his previous responses would not be considered evidence of competence.

**Table 6–2 Factors in the Determination of Medical Competency (See Grisso and Appelbaum 1998)**

| Elements of Competency to Make Medical Decisions |
|---|
| • The ability of the patient to communicate a choice |
| • The ability of the patient to understand the relevant facts |
| • The ability of the patient to appreciate his own particular circumstances and apply the facts to his particular case |
| • The ability of the patient to rationally manipulate data in reaching a decision |

The degree to which a patient understands the relevant facts may be discerned from the questions he or she asks during the informed consent process. The patient's ability to paraphrase information presented or to ask questions about potential benefits, risks, and side effects that are reasonable derivations from the information provided by the clinician suggest understanding. A determination that a patient does not understand relevant information requires more clinical judgment than a determination of the patient's ability to communicate a choice. However, the idea that a patient cannot give informed consent if he does not understand the facts presented is also widely accepted by the courts.

Determining the ability of a patient to appreciate how the facts apply to his particular case and the ability to rationally manipulate data require an even higher level of clinical judgment. These capacities relate to insight (or the extent to which insight is diminished as a result of psychiatric illness) and to higher cognitive processes such as prioritizing and balancing probabilities. A severely depressed, newly diagnosed HIV patient may be able to understand that antiretroviral therapies are life prolonging. He may even understand that the vast majority of persons will respond. But he may, as a result of depression-related hopelessness, believe that the medications will not be able to help him. An assessment of the facts of treatment distorted by depression might also impair the patient's ability to weigh the benefits of treatment over the risks of side effects.

While most courts recognize understanding of the relevant facts and ability to communicate a choice as sufficient standards for competence, psychiatrists should, in their assessments of decision-making capacity, comment on the patient's abilities to apply the relevant facts to his or her particular case and the ability to rationally manipulate data. The psychiatrist should focus on signs that demonstrate that the patient is (or is not) applying the facts to his or her own situation (e.g., weighing the expected side effects of a treatment in association with his or her own social and occupational priorities), considering and balancing alternatives, and prioritizing. The clinician may not base determination on the extent the patient's ultimate decision corresponds to clinical recommendations.

Except in emergencies, patients lacking medical-decision-making capacity need an authorized representative

or court-appointed guardian to make treatment decisions. The time and cost of formal legal proceedings for an adjudication of incompetence may be daunting for many families, and may delay appropriate treatment. Some states allow for legally authorized proxy consent of the next of kin when a patient is *thought to be* incompetent. All states allow for the establishment of a durable power of attorney, which allows for patients' next of kin to consent when a patient becomes incompetent. Some states have passed health-care proxy laws creating documents similar to durable power of attorneys but limited to health-care decisions. Since consent options vary from state to state, psychiatrists should be aware of the options available to patients and their families in the jurisdictions they reside (see Table 6–3).

**Table 6–3 Medical Decision Making for Incompetent Persons**

| Consent Options for Patients Lacking Medical-Decision-Making Capacity |
|---|
| • Proxy (next of kin) |
| • Patient-appointed health-care decision maker |
| • Advance directives (living will, durable power of attorney) |
| • Legal determination of incompetence and court-appointed guardian |
| • Hospital committees or external treatment review committees |
| • Substituted judgment of the court (e.g., medical decision made by the court) |

## Civil Issues: Doctor–Patient Relationship

### Informed Consent

The legal doctrine of *informed consent* requires that physicians obtain informed consent before initiating any treatment or procedure. According to this doctrine, three elements must be satisfied for a patient's consent to be considered valid. Consent must be

- competent
- informed, and
- voluntary.

By requiring patients to demonstrate the capacity to make medical decisions and physicians to fully disclose information about likely and severe risks or side effects, benefits, and alternatives and to answer patient questions, the informed consent doctrine facilitates patients becoming partners in medical treatment decisions. That consent is voluntary means that a physician may not manipulate the patient by introducing information that might undermine the patient's ability to understand potential outcomes (e.g., by exaggerating potential outcomes of the offered treatment, risks of not accepting the treatment, or declining provision of further care if a specific treatment is refused).

As with medication therapies, informed consent is required for electroconvulsive therapy (ECT). Many states require signed, written consent forms for this treatment. Informed consent must include a discussion of the risks of anesthesia as well as the ECT itself (to include memory loss). Most states require that consent must be obtained from the courts when competency is in question, and in Illinois, the courts have specifically ruled that guardians cannot consent to ECT for their wards and that parents may not consent for their adolescent children without judicial review (In re Branning 1996, Matter of A.M.P. 1999).

The ethical guidelines of both the American Psychiatric Association and American Psychological Association require that informed consent be obtained prior to the initiation of psychotherapy (American Psychological Association 2002, American Psychiatric Association 1998). The extent to which it is obtained and documented in clinical practice has not been well studied. This practice is made more challenging by uncertainties about the relative risks and benefits of specific psychotherapies for various and at times comorbid psychiatric diagnoses. The courts have recently awarded considerable damages in "recovered memory" litigation (Beahrs and Gutheil 2001) related to the potential consequences of recollection of childhood events of questionable veracity. In the case of *Oscheroff v. Chestnut Lodge*, the plaintiff sued after spending a year in a hospital receiving only psychoanalytic treatment for severe depression. The case was settled out of court, leaving open the question of psychotherapist liability for failure to disclose the alternative forms of psychotherapy or the potential use of medications (Malcolm 1986).

There are several exceptions to the requirement of informed consent. In emergency situations where the patient experiences an acute threat to life requiring immediate medical attention, consent is implied when the patient is unable to communicate a choice (e.g., unconscious). Circumstances and options when the patient is incompetent are addressed elsewhere in this chapter. A competent patient may also decline being informed of all facts relating to a medical decision (*waiver*) and a physician may choose to withhold full disclosure if disclosure would seriously worsen a patient's condition or impede rational decision making (*therapeutic privilege*). In situations where a psychiatrist asserts an exception to informed consent, his reasoning should be clearly documented in the medical record.

### Consent to the Treatment of Minors

Historically, the law has considered minors—children under the age of 18—incompetent to make medical decisions. In the last half-century various states have authorized children aged 13 through 18 varying degrees of autonomy in some medical decision making. More than one third of the states (and the District of Columbia) grant some minors the authority to consent to outpatient mental health services. Most of these states impose age restrictions and preclude medication use for minors who obtain services without parental notification or consent. The majority of states also allow minors to obtain counseling services for substance-use related problems without parental consent. Emergency evaluation of minor students by psychiatrists working in schools is permissible in most states. However, parental consent for initiating and ongoing treatment is generally required. When parents are divorced or separated, informed consent for treatment must be obtained from the parent with legal custody. Emancipated minors—those legally determined to be capable of living on their own and managing their own affairs—are considered competent to make their own medical decisions. Some states recognize "mature minors" as those capable of appreciating the nature and consequences of medical treatment without requiring emancipated status. Psychiatrists evaluating or treating minors

must be knowledgeable of the specific laws regarding consent to the treatment of minors in the states in which they practice. Exceptions to the doctrine of parental consent or parental notification exist in most jurisdictions for mental health counseling, substance abuse counseling, and sexually transmitted disease (STD) testing. Some states waive parental consent for the treatment of STDs and more than half allow for contraceptive services, prenatal and delivery services without parental consent (Schlam and Wood 2000). While psychiatrists do not provide all of these services, knowledge of the state regulations in these areas may facilitate initial psychiatric assessment and psychotherapeutic intervention in minors seeking assistance from mental health professionals surrounding these issues.

## Confidentiality and Privilege

One hallmark of the doctor–patient relationship is confidentiality—the obligation of a physician to keep patient communications spoken or written in confidence undisclosed to outside parties without authorization. The ethical codes of various medical and mental health professional organizations (including the American Medical Association, the American Psychiatric Association, and the American Psychological Association) all recognize this patient right and expectation in their ethical codes. Moreover, all 50 states and the District of Columbia have included confidentiality provisions in professional licensure laws or other statutes. Confidentiality is considered an element of the fundamental right to privacy, derived from various guarantees in the Constitution.

The psychiatrist has a duty to safeguard patients' disclosures once the doctor–patient relationship has been established. However, the obligation is not absolute. There are circumstances where breaching confidentiality is both ethically permissible and legally required (see Table 6–4). Patients may waive confidentially. Such waivers may be necessary for participation in managed care settings. Patients routinely authorize disclosure to employers or insurance companies to obtain benefits. All states and the District of Columbia require that physicians report certain infectious diseases, child abuse or suspicion of child abuse. These reports may necessitate a breach of confidentiality. Some states have similar reporting requirements for elder abuse. Most states either require or permit physician disclosure of patient confidences when these relate to behavior potentially harmful to a third party. The laws detailing specific situations where a psychiatrist may have either a *duty to warn* or a *duty to protect*, as articulated in the 1976 California Supreme Court's *Tarasoff* decisions vary from state to state (Tarasoff v. Regents of the University of California 1976). The degree of discretion a psychiatrist has in discharging these so-called Tarasoff duties (either through warning a potential victim, by notifying the police, or other means) varies by jurisdiction. Some states require that a physician take steps to warn a potential victim, others to notify police, or to secure hospitalization of the potentially dangerous patient. Other states permit a physician to exercise clinical judgment as to which if any of these steps are taken (Kachigian and Felthous 2004, Herbert et al. 2002).

**Table 6–4 Exceptions to Confidentiality**

| Exceptions to Confidentiality |
|---|
| • Patient requests the release of information to a third party |
| • Duty to protect (e.g., to warn police or potential victim) |
| • Emergencies |
| • Mandatory reporting statutes (e.g., child abuse) |
| • Court-ordered evaluations |
| • Patient initiates litigation (e.g., in defense of malpractice) |

Testimonial privilege is sometimes confused with confidentiality. As noted above, confidentiality is an ethical obligation of the physician, which is abrogated in certain situations. Privilege is a statutorily defined rule of evidence that permits the holder of the privilege (the patient or his representative) to prevent the holder of confidential information from disclosing this information in a legal or administrative proceeding. Confidentiality and privilege are compared and contrasted in Table 6–5. While there is no specific constitutional "right to privacy" the language of the 1st, 4th, 5th, and 14th amendments have been interpreted by the courts to support the existence of a constitutionally derived right to privacy. It is noteworthy that while only 42 states recognize a specific physician–patient privilege, all 50 recognize a specific patient–psychotherapist privilege. A psychiatrist is considered a psychotherapist in all of these statutes.

**Table 6–5 Confidentiality and Privilege**

| Confidentiality | Privilege |
|---|---|
| Patient statements, medical issues not to be discussed with third parties | Patient statements not to be admitted in court or judicial proceedings |
| Physician holds responsibility | Patient holds the right |
| Established by ethical guidelines; supported by Hippocratic oath | Established via case law and statute; supported by "right" to privacy* |
| Legal exceptions created by statute where physician must breach | Legal exceptions created by statute where physician must breach |
| Patient may voluntarily waive | Patient may voluntarily waive |

*Inferred from the 1st, 4th, 5th, and 14th amendments to the US Constitution.

## Malpractice

Psychiatric malpractice occurs when negligence in the conduct of one's professional duties results in injury to a patient. Negligence may result by acts of commission (e.g., doing something one should not) or acts of omission (e.g., failing to do something one should) on the part of a psychiatrist with a duty to care for a patient. *Tort* law—the body of law pertaining to noncriminal wrongdoing—specifies procedures and standards for *plaintiffs* (patients or their families) seeking remedy for physician negligence.

The exact language of the legal standard of care to which psychiatrists are held varies from state to state but generally requires that a psychiatrist must exercise the "the care and skill customarily exercised by a similarly prudent (or qualified) psychiatrist". To prove malpractice, the plaintiff must establish by a preponderance of evidence that (1) a doctor–patient relationship existed that created a *duty* of care, (2) the doctor's care was a *deviation* from the legal standard, (3) that the patient was *damaged*, and (4) that the

deviation *directly caused* the damage. Direct causation is the phrase articulating the idea that damage would not have occurred *but for* the action (or omission) of the psychiatrist. These four elements are often referred to as the "four D's" of medical malpractice (Table 6–6). In the courtroom, experts (often forensic psychiatrists) representing the psychiatrist and the plaintiff testify as to whether the plaintiff's psychiatrist deviated from the standard of care based on a discussion of relevant textbooks and journals, practice guidelines, and the ethical and practices guidance of professional organizations (Simon 2005).

**Table 6–6 The "Four D's" of Medical Malpractice**

| The "Four D's" of Malpractice |
|---|
| • Dereliction of |
| • Duty |
| • Directly causing |
| • Damage |

In civil liability cases, the plaintiff need only establish the "four D's" of malpractice by a preponderance of evidence, meaning that it is "more likely than not" that duty, deviation, damage, and direct causation occurred in the specific case. This level of proof is much less rigorous than either the "clear and convincing evidence" standard used in commitment proceedings (discussed above) or the "beyond a reasonable doubt" standard of criminal trials (see Table 6–7). However, unless each of the four elements is established as being more likely than not, there is no physician liability. For example, if a patient is harmed as a result of a medication side effect, but a psychiatrist exercises and documents appropriate care in making a diagnosis, considering treatment alternatives, obtaining informed consent, and monitoring treatment then malpractice has not occurred.

**Table 6–7 Standards for Level of Proof in Legal Proceedings**

| Standards for Proof | Level of Certainty |
|---|---|
| Beyond a reasonable doubt (criminal cases) | Greater than 90% |
| Clear and convincing evidence (civil commitment determinations) | Greater than 50%; less than 90% |
| Preponderance of the evidence (civil cases) | Greater than 50% |

Although it is estimated that 50–65% of all physicians will experience at least one malpractice lawsuit during their careers, psychiatrists tend to be sued less often than other physicians. One reason is that by virtue of the treatments they provide psychiatrists are less likely to kill or maim a patient. Also, psychiatric care may focus more on the development of the doctor–patient relationship and often on the development of long-term care relationships than other specialties. Both patients and families view such relationships as demonstrative of the concerned and dedicated care provider doing his or her best for the patient. Lawsuits tend to occur when bad outcomes are associated with bad feelings about the physician on the part of the plaintiff.

Patient suicide is one of the most frequent outcomes associated with psychiatrist lawsuits. Suicides occurring in hospitalized patients often result in litigation, since one purpose of hospitalization is to provide close monitoring and a safe environment for patients with suicidal ideation. In a hospital environment, psychiatrists are assumed to have greater control of their patients' actions. In such situations, malpractice is more likely to be established when physicians, nurses, or other medical staff members fail to adhere to hospital or Joint Commission on Accreditation of Health Care Organizations policies and regulations regarding the monitoring of suicidal patients.

"No-suicide contracts" have been used by clinicians under the mistaken belief that these will protect them from liability. There is no evidence that a "no-suicide contract" reduces suicide, litigation, or adverse legal outcomes (Kroll 2000, Simon 1999a). Such contracts may create a barrier to patient communication or to the development of therapeutic alliance and may inappropriately diminish vigilance for suicidal potential (Miller et al. 1998). These contracts cannot be considered an adequate measure for protecting patients or physicians.

The courts have recognized that current medical knowledge does not fully allow for the prediction of suicidal behavior—particularly in less restrictive (e.g., outpatient) settings. Consequently, outpatient psychiatrists are somewhat less likely to be sued when patients commit suicide. However, routinely assessing for risk of suicide, monitoring changes in risk, and providing treatment informed by ongoing risk assessment are considered part of the standard of psychiatric care in both inpatient and outpatient settings (Simon 1999a). The courts have generally held that suicide should be prevented if it *reasonably foreseeable*, suggesting that a psychiatric risk assessment should be reasonable (e.g., include an examination for known risk factors such as history of suicide attempts, depression, anxiety, psychosis, recent socioeconomic or interpersonal loss, possession of firearms and substance abuse). Management plans should also be altered to reflect changing risk factors. Psychiatrists should carefully document and periodically update suicide risk assessment in their patients as well as interventions aimed at mitigating the risk.

Clinical Vignette 1

**Alleged Psychiatric Malpractice**

A businessman refers his 23-year-old stepdaughter to a psychiatrist, explaining: "I told her she could only come to work in my office if she got her act together, stopped partying so much, stopped acting so down and out every time things didn't go her way, and acted more responsibly." At the initial evaluation, the woman relates a lengthy history of low self-esteem, intermittent episodes of depression accompanied by neurovegetative symptoms, a history of deliberate self-injurious cutting behaviors when particularly feeling "overwhelmed by my life," and of suicide attempts (via combinations of medication and alcohol overdoses), and related psychiatric hospitalizations. She notes that she has neither attempted suicide, nor been hospitalized since her mother remarried 8 months ago.

At the time of the evaluation, she denies depressed mood or neurovegetative symptoms of depression explaining, "the only good thing my last doctor did was start me

on paroxetine and I think that's helped, but she reports increasing anxiety since starting work for my stepdad, since he expects me to work on odd hours and my boyfriend doesn't seem to like it when I can't be at his beck and call." Her affect is labile during the interview, but she does not appear anxious and she denies significant anxiety except surrounding her boyfriend "who means everything to me." She denies current suicidal ideation, but reports increased urges to cut herself when her boyfriend (of four weeks) threatens to terminate the relationship. He has done this twice in the last two weeks, but they have reconciled on each occasion. The woman also reports weekly binge alcohol use with her boyfriend, but denies alcohol-related legal or occupational difficulties. She notes, "I drink a lot less then my real father, and unlike him, I don't abuse anyone when I'm loaded."

The psychiatrist obtains informed consent to begin individual psychotherapy and group dialectical behavior therapy with the patient and to continue the paroxetine started by the patient's family physician. He recommends that she consider specific treatment aimed at reducing her alcohol use and provides information on Alcoholics Anonymous and phone numbers for local AA meetings. The patient declines participation noting, "I've got enough on my plate with my appointments with you, this DBT group thing, work, and my boyfriend."

Two weeks later, the patient is killed in a single vehicle alcohol-related motor vehicle accident. The police investigation reveals that on the night of her death, after her boyfriend broke up with her at a local bar, the woman fled in tears. Her former boyfriend notes that her last words to him were, "If this is goodbye it is my last goodbye. Life isn't worth it." The police determine the accident to have been a suicide. The businessman sues the psychiatrist for failure to sufficiently treat the patient's depression.

At the trial, the psychiatrist produced medical record documentation of his thorough diagnostic evaluation, his diagnostic assessment (including a risk assessment for suicide) and his efforts to target modifiable risk factors for self-injury. These included continued treatment and monitoring for depressive symptoms, addressing anxiety-provoking situations and behaviors in therapy, and continued efforts to enroll the patient in alcohol-specific treatments. The psychiatrist had addressed the issues of the potential for acute mood and behavioral changes precipitated by workplace or social stressors with the patient; the medical records indicated that he had provided the patient with his emergency phone number as well as the number for 24-hour emergency coverage associated with his practice. The records indicate that the patient had agreed to utilize these numbers if she believed she needed help between appointments.

The psychiatrist's lawyer obtained expert testimony acknowledging the standard of care for comorbid depression, borderline personality disorder, and alcohol abuse, and the effort the psychiatrist had taken to anticipate the potential for self-harm. The expert also identifies the intervening variable (the boyfriend's decision to break off the relationship) as one over which the psychiatrist had no control. The psychiatrist's lawyer argues that no deviation from the standard of care occurred, that the relationship break-up precipitated the suicide, thus there was neither "deviation" nor "direct causation." The defense was successful, and the jury determined that no malpractice occurred.

## Liability for Supervising Other Professionals

Psychiatrists may interact with a variety of other mental health professionals in providing care for a given patient and may have different levels of responsibility for the care provided by others. In broad terms, a psychiatrist may supervise other clinicians, may collaborate with others in treatment, or he may be asked by another professional to provide consultation.

When a psychiatrist supervises another therapist, the supervisor gives active guidance and professional direction and retains responsibility for patient care. The legal doctrine of *respondeat superior*—"let the master answer for the deeds of his servant"—provides the basis for the assumption of liability by the supervising psychiatrist in malpractice cases involving the care provided by those whom he supervises. When a psychiatrist provides consultation, guidance provided may be accepted or declined by the professional seeking consultation. Therefore, the consulting psychiatrist is not considered to have assumed responsibility for the patient's care.

Frequently, the relationship between the psychiatrist and nonphysician therapist takes the form of collaboration. Here, the responsibility for patient care is shared between the two clinicians in accordance with the professional qualifications and limitations of their respective professions. It is important to recognize the degree of ongoing communication between collaborators necessary to provide most effective care and continued clarity amongst patient and collaborators regarding the boundaries of responsibility. The American Psychiatric Association's professional guidelines require that patients be fully informed of the nature of the relationship between the psychiatrist and others interacting in care and that the responsibilities of psychiatrist and other therapists be delineated to the patient. The guidelines indicate that both the psychiatrist and collaborating therapist are responsible for periodic reassessment of the appropriateness of the continued collaboration for patient care, and for notifying the patient if the collaboration is terminated (American Psychiatric Association 1980).

## Physician–Patient Boundary Violations

The professional ethical code of the American Psychiatric Association explicitly states that a psychiatrist should not have sexual contact with current or former patients (American Psychiatric Association 1998). Accordingly, sexual activity between a psychiatrist and a patient or former patient has become a relatively common cause for malpractice litigation. In addition to monetary damages, psychiatrists face reprimand or expulsion from professional organizations and suspension or revocation of their medical license for such deviations from the standard of care. Many states have adopted statutes specifically related to patient–therapist sexual misconduct, facilitating either criminal prosecution or civil litigation (Simon 1999b). Other malpractice claims experienced by psychiatrists may involve incorrect treatment (e.g., failure to appropriately evaluate, diagnose, prescribe treatment, monitor or supervise care), improper commitment, breach of confidentiality, slander, and libel. Such claims (e.g., incorrect treatment) may arise in the context of physician–patient boundary violations or under unrelated circumstances.

## Disability and Fitness Evaluations

In conducting complete psychiatric evaluations for the purpose of treatment, clinicians must evaluate the degree of

distress and/or social or occupational impairment attributable to mental disorder symptoms in order to determine the severity of illness, and to establish a baseline for monitoring the utility of clinical interventions. In contrast, when conducting evaluations for workers compensation and the Social Security Administration, psychiatrists are called upon to determine psychiatric *disability*. Federal statutes define impairment as essentially any physical or mental disorder, defect, illness, loss or condition affecting organ systems (including the nervous system). However, disability is defined as the extent to which impairment limits or precludes a person's ability to meet important psychosocial or occupational demands. Specifically, disability determination requires

1. a physical or mental impairment that substantially limits one or more of the major life activities of such individual,
2. a record of such an impairment, or
3. being regarded as having such an impairment (Americans with Disabilities Act 1990).

Workers compensation, paid for disability occurring in the workplace, is a remedy based on the worker's prior salary and degree and duration of disability. As an alternative to litigation, states have developed mandatory insurance programs into which employers pay to provide coverage for workplace-related injuries. States vary in their implementation of workers compensation programs. In most there are no awards for pain and suffering (as might occur in civil litigation) but compensation is provided for physical trauma causing mental injury, mental injury causing physical deficits, and mental stress causing mental deficits. Social Security disability—for persons who contribute to the fund while working—was established in 1956. Supplemental Security Income was established as a federal matching payment for state benefit programs in 1972.

In litigation and in determination of medical disability benefits, it is the degree of disability (not the specific diagnosis or mere presence of impairment as defined above) that determines the amount of damages or monetary award. In the military active duty and Veteran's Administration Medical Care systems, clinicians must often make assessments of disability and determine whether disability is related to military service. Various regulations guide the conduct of disability examinations for military members (Ritchie et al. 2006). In workers compensation and tort actions, causation is a necessary factor in the determination of monetary award. Social Security disability focuses more precisely on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders without concern for causation. The Social Security Disability Reform Act of 1984 mandates medical improvement prior to termination of payments so documentation of treatment and course of symptoms is important in ongoing Social Security disability evaluations. The American Medical Association has published guidelines for the conduct of disability determinations, which parallel processes recommended by the Social Security Administration (American Medical Association 2004).

While treating physicians may be placed in the role of completing disability evaluations, they must be conducted in the context of other evaluations completed at the request of third parties. The physician must strive for objective determination of degree of impairment based on complete review of relevant medical records and other collateral information as well as specific reports from the patient quantifying the degree to which symptoms impede work or other life demands. Adjudicators of disability benefit from specific examples of barriers to work function created by psychiatric conditions. Examples might include avoidance of occupationally required situations that trigger reexperiencing phenomena and anxiety in persons with posttraumatic stress disorder.

In other situations, an individual may wish to maintain employment but may claim a need for accommodations under the provisions of the Americans with Disabilities Act or an employer or licensing board may question whether a person is able to work safely after accommodations are made. Psychiatrists are often asked to provide such input for police, fire, and rescue workers, and also for other physicians (McNaught and Schofield 1998, Rostow and Davis 2004). These evaluations are often called "fitness evaluations, return-to-work evaluations," or "fitness for duty evaluations." While patients and employers may request such evaluations from treating physicians (out of convenience or a belief that the treating physician may know best the patient's degree of impairment) it may be difficult or inappropriate for clinicians to shift from therapist to disability evaluator. The differences in purpose, agency, and degree of medical certainty required in these different roles may warrant an independent medical examination conducted by a nontreating physician (American Academy of Psychiatry and the Law 2005, Simon and Wettstein 1997). Any disability or fitness for duty evaluation should be performed in the context of a specific question or questions (e.g., are there occupation-specific requirements and work environments precluded by impairment?), and include comprehensive medical and psychiatric evaluation and mental status evaluation, review of medical records, and collateral information from third parties such coworkers and employers (Anfang and Wall 2006).

## Criminal Issues: Competency and Insanity

In contrast to the civil issues outlined above, practicing psychiatrists interact much less frequently with the criminal law system. In the tradition of common law and in subsequent case law and statutes, the basic elements of any crime are (1) commission of the criminal act itself termed *actus reus* or "guilty act" and (2) the mental level of intent or desire to commit the criminal act, termed *mens rea*, or "guilty mind." In criminal proceedings the state (or government) must prove, by the most rigorous "beyond a reasonable doubt" level, that the defendant committed the criminal act with the requisite mental intent to do so in order to convict a person of a crime. Therefore a person's mental state at the time of an alleged offense may play a critical role in determining whether he or she is found guilty or acquitted, sentenced to prison or hospitalized. The US Supreme Court has also established that before any defendant can be prosecuted he must understand the charges against him and must have sufficient mental capacity to assist counsel with the defense. While clinical psychiatric practice allows for varying degrees of diagnostic uncertainty, a variety of treatment options, and flexibility in determining care plans, the courts have

adopted much more stringent criteria for determining whether mental state precludes prosecution or should be grounds for acquittal. Because of the societal value placed on civil liberty, the courts have held that safeguards such as the high standard of proof of guilt and more precise determinations of mental state are necessary in decisions that may result in the most severe curtailments of liberty such as imprisonment or execution.

## Competency to Stand Trial

In a 1960 decision, the US Supreme Court established the standard for competency to stand trial in criminal prosecutions. The court noted that "the test must be whether he (the defendant) has sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding–and whether he has a rational as well as factual understanding of the proceedings against him" (Dusky v. United States 1960). The ruling articulated the idea that competency refers to a defendant's current mental capacity (e.g., at the time of the court proceeding rather than at the time of the alleged offense). Consequently, a defendant's competency may be called into question at any point during criminal proceedings if mental capacity deteriorates. Subsequent court decisions have concluded that this standard applies not only to the process of standing trial, but also to decisions such as waiving the right to counsel, or to entering a plea of guilt or innocence (Godinez v. Moran 1993). The lack of explicit quantification of the terms *sufficient* or *reasonable degree* within this standard allows for considerable range of interpretation of this standard, and the courts rely on the input of mental health experts in making such determinations.

The determination of competency (or incompetence) to stand trial does not hinge on a specific psychiatric diagnosis or even the presence of a psychiatric diagnosis. Rather, it is based on assessment of the defendant's capacity to understand criminal proceedings. Questions or checklists identifying the defendant's understanding of the roles and functions of witnesses, prosecuting attorneys, judge and jury, knowledge of potential outcomes (e.g., guilty vs. not guilty, potential punishments), defendant rights with regard to counsel, testifying and hearing the testimony of others against him, and the role defense counsel and his interaction with defense counsel are of practical importance in clinical assessment (Grisso 1986). The Supreme Court has determined that incompetent persons may not be held indefinitely merely for the purpose of restoring competence (Jackson v. Indiana 1972). In cases where the forensic evaluator believes that a defendant may be incompetent to stand trial, diagnostic and prognostic information may be useful to the court in its determination of the likelihood of competence being restored through treatment.

When questions about a defendant's competency to proceed arise at any point prior to or within a criminal trial, the court (as provided by statutory language varying from state to state) may order a clinical assessment of competency. The court may appoint experts to conduct the evaluation and testify in the subsequent competency hearing. Such input is usually provided by a forensic psychiatrist, who relies on clinical experience and specific training in competency assessment as well as various standardized instruments in making determinations for the state. When incompetence is determined to be potentially restorable through treatment (e.g., for a psychiatric illness) a defendant may be ordered to specific state facilities for the purpose of restoring competence.

All states have legislation governing the periodic review of persons held for restoration of competence to ensure that such involuntary hospitalization is not continued indefinitely. Statutes allow for the initiation of civil commitment procedures for incompetent persons that pose imminent threat of danger to self or others upon release.

The Supreme Court has articulated a prohibition against executing inmates who become incompetent (Ford v. Wainwright 1986) in states where capital punishment is permissible. While the judicial requirement for competency to participate in criminal proceedings is generally viewed as morally and ethically prudent, considerable controversy exists surrounding the issue of clinical efforts to restore competency (or even evaluate competency) of persons potentially facing capital punishment (Bonnie 1990, Rosner et al. 1991). Critics view physician participation in restoration of competency for the purpose of execution as contradictory to the Hippocratic imperative to "first, do no harm" (Appelbaum 1990). Many states have crafted legislation bifurcating capital trials into distinct guilt/innocence and sentencing phases, allowing the judge or jury to hear evidence regarding mitigating factors (e.g., mental illness) or aggravating factors (including future dangerousness) in determining a sentence (Showalter and Bonnie 1984). Clinicians asked by attorneys or the courts to become involved in such determinations may choose to defer to forensic psychiatrists, but at a minimum should seek forensic consultation before proceeding with such requests.

## Criminal Responsibility and the Insanity Defense

Since our legal tradition and common law dictate that a person may only be convicted if it is proven that he performed the criminal act and did so with the requisite "guilty mind," it follows that a competent defendant may seek acquittal for lack of requisite *mens rea*. The insanity defense is an assertion that the defendant did not possess a "blameworthy" state of mind at the time of the criminal act. Like competency, insanity is a legal construct rather than a clinical entity. Unlike competency, insanity refers to the defendant's mental state at the time of the alleged offense. Our society values autonomy—the freedom to make choices—and consequently holds dearly the idea of accountability for one's choices and behaviors. Societal emphasis on personal accountability is perhaps one reason the insanity defense is among the most controversial concepts in western jurisprudence. In the United States, the legal standard for insanity has been modified in various jurisdictions in recent years and remains variable across states. Since the insanity standard reflects our society's changing views on the balance between personal accountability and scientific determinism, a review of the evolution of the standard is informative.

Until the 1950s the test of insanity articulated in the 1843 British trial of Daniel M'Naghten for the murder of Prime Minister Robert Peel's secretary served as the standard for insanity in most states. In this trial, lawyers established that M'Naghten was under the delusional belief that the Pope and Prime Minister were conspiring against him.

A parliamentary inquiry after his acquittal resulted in the following guidance:

> to establish a defense on the ground of insanity it must be proved that, at the time of the committing of the act, the accused was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or, if he did know it, that he did not know what he was doing was wrong. (Queen v. M'Naghten 1843)

The basic principle underlying the insanity defense articulated in M'Naghten was that of a strictly cognitive test for insanity; that is

1. the presence of a mental disorder or "defect of mind" and
2. a lack of comprehension of the nature or wrongfulness of the act (e.g., "as to not know the nature and quality . . . or what he was doing was wrong") (Ray 1871).

This standard served as the model for most US jurisdictions through the first half of the 20th century. It was criticized by clinicians and legal authorities with increasing understanding that psychiatric illness might impair a person's ability to apply knowledge—even if he or she satisfied a strict cognitive test of knowing right from wrong. Beginning in the 1950s, states adapted standards incorporating a volitional prong allowing for insanity acquittal if the defendant's behavior was determined to be the "product" of a mental disease or defect (Durham v. United States 1954). This concept evolved into interpretations allowing for acquittal if the mental disease or defect resulted in "an irresistible impulse to perform the criminal act" (Weinberg 1957), or "substantially impair(ed) behavioral controls" (McDonald v. United States 1962). The American Law Institute (ALI) test that formed the basis for laws in many jurisdictions stated: "A person is not responsible for criminal conduct if, at the time of such conduct, as a result of mental disease or defect he or she lacks substantial capacity to appreciate the criminality (wrongfulness) of his or her conduct *or* to conform his or her conduct to the requirements of the law" (Model Penal Code 1962). In the 1980s a societal reemphasis on law, order, and discipline (in reaction to the permissiveness of the 1960s and 1970s) was accompanied by recognition of limits of present day science in defining human behavior. Recognition of limits of scientific and medical expertise in determining whether a mental disorder resulted in the inability to refrain from criminal behavior led to revision and modification of these more inclusive standards in many jurisdictions.

Public outrage at the insanity acquittal of John Hinckley after his attempt to assassinate President Reagan precipitated the passage of the Comprehensive Crime Control Act of 1984. The act provides that for persons prosecuted in federal courts, the insanity defense may be asserted only when "the defendant, as a result of severe mental disease or defect was unable to appreciate the nature and quality or the wrongfulness of his acts." The act also states: "Mental disease or defect does not otherwise constitute a defense." This stringent standard eliminates any defense based on a volitional standard for insanity. Finally, the act states that the burden of proof is shifted to the defense. The defense must establish, by "clear and convincing evidence" that mental disease or defect rendered the defendant incapable of appreciating the nature and quality or wrongfulness of his acts, rather than requiring the state to prove (beyond a reasonable doubt) that a defendant was sane (Comprehensive Crime Control Act 1984). While the level and burden of proof vary from jurisdiction to jurisdiction, most states have followed the federal lead in adopting more restrictive standards.

Regardless of jurisdiction, the trier (judge or jury) relies on expert psychiatric testimony in deciding insanity defense cases. Court-ordered evaluations of criminal responsibility (or sanity) are most often conducted by forensic psychiatrists. As in the case with competency determinations functional capacity, rather specific diagnosis, is the threshold determination. In criminal responsibility evaluations, the examiner seeks to establish the mental state of the defendant at the time of the alleged offense. Clinical interview and diagnostic evaluations are augmented by review of related medical records, police and investigative reports, and collateral interviews of witnesses (those who may have seen the alleged criminal act, as well as those who had opportunity to interact with the defendant in the weeks, days, hours or minutes before and after the criminal acts).

Psychiatrists in clinical practice are generally concerned with a patient's perceptions of his or her interactions with others and with the environment or the patient's subjective experiences. Clinicians may rely on collateral information when they believe the patient may be particularly unreliable and safety is an issue. In contrast, the forensic evaluator is asked to determine the "actual" or objective mental state of the defendant at the time of the alleged criminal act or acts. This objective mental sate is a component of the "historical truth," which the forensic evaluator seeks to reconstruct. Persons being evaluated for criminal responsibility are frequently ordered into evaluation (rather than voluntarily

**Table 6–8 Evolution of Standards for Criminal Responsibility**

| Standard | Criteria |
|---|---|
| M'Naghten rule (cognitive test) | • Presence of a mental disorder or "defect" and<br>• Lack of comprehension of the nature and quality of the act, or<br>• Lack of knowledge of the wrongfulness of the act |
| Durham (product) rule (volitional test) | • Insanity acquittal if defendant's behavior was "product" of a mental disease or defect |
| ALI—American Law Institute (cognitive or volitional tests) | • Presence of mental disease or defect and<br>• Lack of capacity to appreciate criminality, or<br>• Lack of capacity to conform conduct to requirements of law |
| Comprehensive Crime Control Act 1984 (eliminated volitional test) | • Presence of mental disease or defect and<br>• Inability to appreciate nature and quality of wrongfulness of acts<br>• Burden of proof shifted to defense |

seeking treatment) and may not inherently trust the evaluator. They may be motivated by the prospect of avoiding criminal prosecution to deliberately embellish or feign symptoms. In forensic psychiatry, particular effort is made to corroborate reports of the defendant and to assess for malingering during clinical interview and through psychological testing. While decisions to initiate treatment in clinical settings may (with informed consent) be based on "the working diagnosis" or the most likely diagnosis based on patient report and physical findings, expert opinion regarding diagnosis, competence, and criminal responsibility in forensic evaluations must be based on "a reasonable degree of medical certainty." Reasonable medical certainly is not clearly defined in any jurisdiction, but the concept incorporates a threshold level of scientific and objective basis for diagnosis and opinions and that will withstand cross-examination by other experts in the courtroom setting. Table 6–8 summarizes the evolution of the insanity standard.

Clinical Vignette 2

A 38-year-old single man with a history of chronic schizophrenia lives with his grandmother. He is not allowed to live with his parents because of past frequent threats he had made toward them. His aggressive behaviors toward his parents were based on his delusional belief that they were not his real parents, but conspirators in a plot to use his brain for "government mind control research." He was often noncompliant with medications because he believed that they were dissolving his brain. During one period of medication noncompliance he becomes increasingly confused and concludes that his grandmother must also be a conspirator and secretly putting chemicals into his food or injecting them while he was asleep. He waits for her to go to bed. Once she is asleep he enters her room and beats her repeatedly in the head with a baseball bat until she is dead. He then wraps her body in a blanket and conceals it in the trunk of a car parked in the garage. He destroys the bed linen and remakes the bed. When his parents repeatedly telephone during the next few days he does not answer the calls. They ultimately summon the police who, after and extensive interrogation and search, discover the body.

Upon the advice of his attorney, the man enters a plea of not guilty be reason of insanity. He is evaluated by a forensic psychiatrist appointed by the state who renders the opinion that the man is competent to understand the charges and assist in his defense. The defense attorney argues that because of the severe and chronic nature of his client's psychotic illness he could not have possibly understood the wrongfulness of his acts—or if he did, he did not have the capacity to plan the murder and should only be found guilty of the lesser included offense of manslaughter. Forensic psychiatrists hired by the prosecution and by the defense testify with opposing views about the man's capacity to appreciate the wrongfulness of his acts or to form a specific intent.

During his closing arguments, the prosecuting attorney asks the jury for a finding of guilt for the charge of premeditated murder. He urges them to use their own common sense to understand that taking the bat into the room and striking a woman repeatedly in the head could have no explanation other than for the purpose of killing her or inflicting grievous injury. He further argues that one can infer from the actions following the killing (changing the bed linen, hiding the body, and refusing to answer the telephone) that the man was clearly aware at that time that he had committed a wrongful act.

The judge then instructed the jury on the current standard for mental responsibility for criminal acts. The jury concluded that the man was aware of the wrongfulness of the act at the time he committed it and the jury returned a verdict of guilty for the charge of premeditated murder. During the sentencing phase of the trial, the defense was able to enter evidence regarding the severity of illness, potential of improvement with ongoing supervised treatment, and risk for future acts of violence. After extensive deliberation the jury recommended a sentence of 20 years imprisonment rather than possible maximum sentence of life in prison without the opportunity of parole.

## Other Criminal Issues: Diminished Capacity and Mitigating Factors

### Diminished Capacity and Mitigating Factors

In some circumstances, the law acknowledges the concept that mental disease or defect may alter the mental capacity of a defendant without completely eliminating appreciation for the nature, quality or wrongfulness of one's actions as required by the insanity defense. Certain offenses, termed *specific intent* crimes require proof of a more stringent *mens rea* than appreciating wrongfulness. For example, the definition of Assault with Intent to Commit Homicide requires the defendant to have acted with the "purpose of killing or committing grave bodily harm" in most jurisdictions. Forensic psychiatrists, in such cases, may testify as to whether clinical evidence suggests that a defendant's mental disease or defect contributed to actions for which the defendant could not have formed such specific intent. If a mental disease or defect precludes the specific intent of a crime, the defendant is acquitted of that crime, but may be convicted of a lesser crime such as manslaughter (Morse 1984, Melton et al. 1987). Since the law presumes that a person's intent may be inferred from his actions, it is particularly challenging for defense attorneys to assert the defense of diminished capacity without expert psychiatric testimony. Various jurisdictions have placed limits on whether expert testimony regarding diminished capacity is permissible (Lande and Armitage 1997, Slovenko 1995). As with questions of criminal responsibility, the forensic psychiatrist must evaluate objective evidence of disease state at the time of the offense based on clinical evaluation, record review, crime scene evidence (e.g., investigative summaries and witness accounts) as well as other collateral sources of information.

Other criminal defenses may also benefit from the input of a forensic psychiatrist. Defendants may be acquitted if they can establish that alleged criminal behavior resulted from an *automatism*—an act occurring in a state of mental unconsciousness or dissociation without purpose or intention. Acts occurring in the context of somnambulism, involuntary movement disorders or seizure disorders, prescription medications side effects, and hypoglycemic states are examples of situations where psychiatric testimony may inform the court and result in acquittal (Low et al. 1982, Devinsky and Bear 1984). Most jurisdictions do not recognize alcohol or illicit drug intoxication as an automatism defense as such intoxication is generally considered a voluntary act.

However, alcoholism and acute intoxication may be considered as determinants of degree of mental capacity for specific intent crimes (Granacher 2004, Merikengas 2004).

The existence of treatable mental disorders, including substance use disorders, and a defendant's motivation for treatment may also be introduced as factors for consideration in sentencing proceedings (evidence of mitigation or extenuation). The same may be said for various other psychiatric disorders and syndromes for which symptoms are less clearly defined or do not rise to a level necessitating a finding of incompetence or insanity. Examples include "battered woman syndrome," "battered child syndrome," "rape trauma syndrome," culture-bound syndromes, and posttraumatic reactions (Ibn-Tamas v. United States 1979, Sacks 1994, Gallin 1994, Simon 1995). Sentencing proceedings allow for testimony (subject to cross-examination) about a range of issues including the defendant's psychosocial and developmental environments, lack of access to treatment, and psychiatric prognostic factors for rehabilitation. Accordingly, forensic psychiatrists and treating psychiatrists are often frequently called upon by defense and prosecuting attorneys to inform the judge or jury in the sentencing phase of criminal trials. In situations where a general psychiatrist is asked to participate in such proceedings, it is prudent to consult with a forensic psychiatrist to explore the strengths and weaknesses of any arguments that the court may hear and prepare for the cross-examinational scrutiny that testimony may receive in an unfamiliar adversarial process.

## Children and Adolescents

Child psychiatrists often become involved in child custody evaluations (Waller and Daniel 2005, Ackerman and Kane 2002), but they may also be involved in court-ordered assessments of delinquent behavior and consideration for child criminal cases to be waived into the adult criminal justice system. They may be called to participate as witnesses in adult criminal trials involving child or adolescent victims. They may be asked to testify regarding the reliability of child testimony or the psychiatric impact of criminal victimization in the cases of sexual assault or other traumatic exposures (Schetky and Benedek 2002). Although school shootings and other forms of school-related child and adolescent violence are relatively rare, the treatment and management of youths considered at risk for school violence is increasingly a focus for mental health professionals consulting to school systems. Clinicians must recognize the limits of confidentiality when others may be in danger, the limits and conditions of potential treatment (e.g., with or without appropriate support from the family and other school-based resources) and the complications created by competing interests. Pending legal charges against the patient, custody disputes between parents, or potential placement in special education programs or institutions must be considered. For the forensic evaluator, these challenges may also impede comprehensive risk assessment. Both clinical assessment and forensic assessment require comprehensive psychiatric and mental status evaluation, review of collateral information, synthesis of information from a variety of other persons (family members, peers, teachers, school counselors, and law enforcement personnel), and careful documentation (Murakami et al. 2006). Structured assessment tools developed specifically for violence risk assessment may augment clinical and forensic evaluations (Grisso et al. 2001, Catchpole and Gretton 2003). Child psychiatrists participating in such proceedings may also find it prudent to avail themselves to consultation from a growing number of child forensic psychiatrists.

## Correctional Psychiatry

There are roughly one million incarcerated adults within the United States at any given time. As many as 20% of inmates in jails and prisons may suffer from serious mental illness (American Psychiatric Association 2000). While less than 5% of those incarcerated in U.S. jails and prisons are women, an estimated one third to two thirds of this group require mental health treatment (Lewis 2006). High rates of major depression, posttraumatic stress disorder, substance dependence, and antisocial personality disorder are present in prison populations (Jordan et al. 1996). In recent years, considerable attention has been devoted to the development of appropriate mental health services and programs for the incarcerated population with a particular emphasis on early assessment and suicide prevention (National Commission on Correctional Health Care 1996, American Psychiatric Association 2000, Metzner and Dvoskin 2004, Scott and Gerbasi 2005). The development of programs and policies that ensure appropriate allocation of available services, address the complex comorbidity observed in many prisoners, and facilitate continued treatment after release are areas of active research.

Although forensically trained psychiatrists often work in correctional settings, the majority of prison psychiatrists, psychologists, and social workers in jails and prisons do not have specific forensic training. Work in these often under-resourced and potentially dangerous environments may be particularly challenging. Increasingly, prisoners who are either unable or unwilling to follow institutional rules are placed in disciplinary segregation (solitary confinement or "lockdown") as a means of punishment, to promote institutional safety, or both. It is widely believed that placement of seriously mentally ill offenders in such environment will result in clinical deterioration and is clinically contraindicated. However, the long-term effects of such segregation on more healthy inmates, the delivery of appropriate therapeutic interventions to prisoners who are placed in segregation units, and the degree to which confinement, social isolation, and relative sensory deprivation must be limited to prevent long-term psychological harm are less clear. Input from appropriately trained and forensically experienced mental health professionals into the disciplinary process with correctional institutions may clinically inform the disciplinary process and enhance safety in correctional institutions (Metzner and Dvoskin 2006).

## Conclusion

The practicing psychiatrist is more appropriately concerned with the nuances of clinical presentation, diagnosis, and therapeutic intervention than the forensic aspects of mental health and legal proceedings. The standards for determination of competency, criminal responsibility and the objective analysis of mitigative or exculpatory factors in criminal proceedings fall more squarely within the scope of practice of the forensic psychiatrist. Regardless of interest, clinical psychiatrists must interface with the legal system in situations

where patients may be dangerous to self or others, or do not demonstrate the capacity to provide informed consent for treatment. Psychiatrists are involved in malpractice litigation less frequently than most other physicians, but they are at particular risk in the aftermath of suicide or as a result of boundary violations. Familiarity with state laws and regulations regarding involuntary commitment, duty to warn, and standards of care is important for all psychiatrists. Consultation with forensic psychiatrists may be helpful in issues related to dangerousness assessment, civil commitment, or potential Tarasoff obligations. Consultation will also help prepare nonforensic psychiatrists for courtroom testimony on civil or criminal proceedings.

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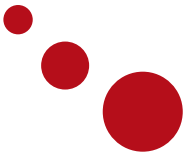
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SECTION

# II

David A. Mrazek, Section Editor

# *A Developmental Perspective on Normal Domains of Mental and Behavioral Functions*

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CHAPTER 7

# A Psychiatric Perspective on Human Development

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The miracle of human development has always fascinated physicians. Psychiatrists and pediatricians have formally studied developmental processes and have used the knowledge gained from these investigations to create more effective strategies for care of patients. With the evolution of the specialty of geriatrics, interest in the developmental changes that occur after having achieved full maturation has further expanded the scope of investigations. With better understanding of the changes that predictably occur in the last half of life, it has become possible to link more effectively early precursors of illnesses to the later expression of developmental delays and deviations.

There are two classical approaches to the study of human development: the stage model and the longitudinal lines of development model. Each has distinct advantages and disadvantages. The more traditional approach is to examine each stage of development. Consequently, the unfolding of the many new capabilities of the infant is reviewed chronologically so that the child as a whole can be better understood. Thinking about development as a series of stages is a particularly useful approach for clinicians and therefore is the primary strategy used to organize this section on human development. There are six chapters that chronologically address the development of (1) infants, (2) preschool children, (3) school-age children, (4) adolescents, (5) adults, and (6) older adults. The reader can turn to each of these chapters and come away with a clear understanding of the developmental changes that occur during each of these stages. Furthermore, the special risks associated with each period of development that are relevant to the onset of psychiatric illness are reviewed.

An alternative strategy used to teach development is to choose a particular aspect of human development and track it from birth until death. This is a helpful strategy for understanding the process of development and is useful for researchers who are searching for the antecedents of characteristics that occur during later developmental periods. However, the accurate charting of these lines of development has proven to be difficult. Clearly, it is not feasible for a single investigator to study the extensive changes that occur over the lifespan. Longitudinal studies that span at least 10 years are usually conducted by a series of principal investigators who work sequentially in order to achieve continuity. Consequently, most investigators become specialists in narrow age ranges of the developmental process and must work collaboratively with colleagues to link together the transitions from infancy to childhood or adolescence to the adult years.

In this chapter, an overview of five prominent lines of human development is presented so that the reader can quickly obtain a sense of the timetable of normal development. These are (1) biological development, (2) cognitive development, (3) emotional development, (4) social development, and (5) moral development.

In addition, a longitudinal review of periods of development that are associated with an increased risk of specific psychiatric disturbances is provided.

There has been a scientific preoccupation with defining the relative contributions of genetic endowment and environmental experience on the course of human development. While early behavioralists took the extreme view that children could be shaped almost exclusively by their environments, contemporary evidence supports the view that genes and experience interact in a transactional manner that leads to the unique development of an individual. The study of environmental contributions has steadily improved through the application of more careful methods of assessment and an appreciation of the value of examining the many components of the early experience of children.

However, the most explosive advances in the understanding of human development have been made, as specific gene variations have been identified and linked to physical and behavioral outcomes. In the past decade, the pace of new gene discovery has increased exponentially as a consequence of the success of the Human Genome Project. It is now estimated that human beings have less than 30,000 genes. Determining the precise number has been elusive, as

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it has been necessary to gradually understand that human genes are more complex than the genes of simpler organisms. Specifically, many human genes produce multiple proteins. We are now learning about the degrees of genomic variability that exist between individuals, as well as beginning to understand how genes interact with each other and how they are regulated by the environment. A key focus of new research is the discovery of how the passage of time and the gradual maturation of the individual affect the expression of genes that have remained silent but potentially ominous from the beginning of fetal development. Future studies of cohorts of infants who are at known genetic risk of a trait or illness may well identify environmental factors associated with both the expression and the suppression of gene expression.

The concept of studying development longitudinally has its origin in the lives described by Plutarch and popularized by Shakespeare. In many ways, biographers strive to examine the origins of adult traits through consideration of the early experiences of their particular subject. This tradition was adopted by psychoanalysts who searched for the origins of psychopathology through the exposition of a "genetic formulation." The choice of the word "genetic" to describe a conceptual formulation that was created by the experience of the individual is certainly ironic. Nonetheless, this focus on the influence of early experience on development may well have been a foreshadowing of the importance of intense early experience on gene expression. In all likelihood, the genetic formulations of the future will focus on how experience regulates gene expression at the molecular level.

The concept of parallel yet interacting lines of development was popularized by Anna Freud (1946) who created a classical monograph that articulated nine lines of development that were well described through adolescence. Although some of these conceptual lines have been abandoned, the overarching principle of a line of development has proven to have heuristic value. Other developmentalists have built on her model to create parallel developmental lines extending into adulthood. Erikson (1963) further elaborated the evolution of domains of function in the creation of his epigenetic stage model. His paradigm continues to have a strong influence on psychiatric theory, as is well illustrated by the work of Vaillant (1977).

Although lines of development are attractive conceptually, they are deceptively simplistic representations of the complex evolution of personality. The concept of "decalage" was put forward by Piaget (1952) to refer to a disengagement in the normal evolution of the parallel development of specific cognitive abilities. However, decalage is equally salient in the conceptualization of major distortions in emotional or social development. In this chapter, five broad lines of development are reviewed as they evolve over the course of the lifespan. Developmental timelines for each line of development are included. In the following chapters, there is a more detailed discussion of these timelines, as well as a discussion of the interactions that are typical within each stage of development and the stage-specific risk factors.

## Biological Development Genetic Considerations

The genes that an individual possesses contain all of the information required to define the individual. Some genes have strong penetrance and express themselves in virtually all environments. This is the traditional view of the influence of genes, which, if taken literally, leads to the erroneous conclusion that any genetic influence is immutable. It is now clear that many genes have only partial penetrance and that there are both physical and emotional environmental factors associated with the expression of these genes.

In considering the biological development of an individual, it is apparent that single genes that control such critical functions as physical growth have a high degree of penetrance in a wide range of environments. For example, while malnutrition, maltreatment, and medications can retard growth, genes have a powerful impact on adult height. This is demonstrated by the observation that monozygotic twins are nearly identical in adult height. Interestingly, the same is not true of weight, which suggests that a wider range of environmental factors lead to adult variation in weight. In monozygotic twin pairs, adult weight can vary by more than 20%, although the majority of twins are actually much closer in size.

A timeline of biological development over the course of the lifespan is presented in Figure 7–1.

## Neurological Considerations

Brain growth is one of the most basic indicators of neurological development. The brain is already at approximately one-third of its adult size at birth, and it grows rapidly, reaching 60% of its adult weight by approximately 1 year and 90% of its adult weight by 5 years of age. The final 10% of growth occurs during the next 10 years with attainment of full weight by 16 years of age. The processes of myelinization, synapse proliferation, and synaptic pruning occur in the course of the lifespan, but they are particularly active in the first years of life when the functional structure of the brain is becoming defined. Maximum synaptic density is reached at different development time points in different brain regions. Maximum density in the auditory cortex is achieved by 3 months, whereas maximum density in the middle frontal gyrus is not reached until 15 months of age (Huttenlocher and Dabholkar 1997). After this point, the density of dendritic spines generally decreases as glucose metabolism becomes fully developed. The establishment of biological rhythms occurs in early infancy, as sleep becomes more organized and of shorter nocturnal duration. A stable pattern of temperament cannot be documented in the first months of life, but temperament gradually becomes established during the second year. During the preschool period, individual neurons and neural networks are preferentially preserved if they receive stimulation. Motor skills emerge as a reflection of the underlying neuronal development of the central nervous system.

By the age of 7 years, considerable sensory integration has occurred. Handedness has been clearly established, and brain plasticity has decreased. By 10 years of age, limitations in the ability to learn to speak an unaccented second language reflect further changes in the development of the motor linguistic pathways. In the years of adolescence, full brain weight is achieved, but myelinization continues well into the fourth decade. By the end of the fifth decade, there is often evidence of the beginning of decline in specific neuronal functions, with vision and memory being particularly vulnerable. However, integrative capacities may reach a peak during the later decades.

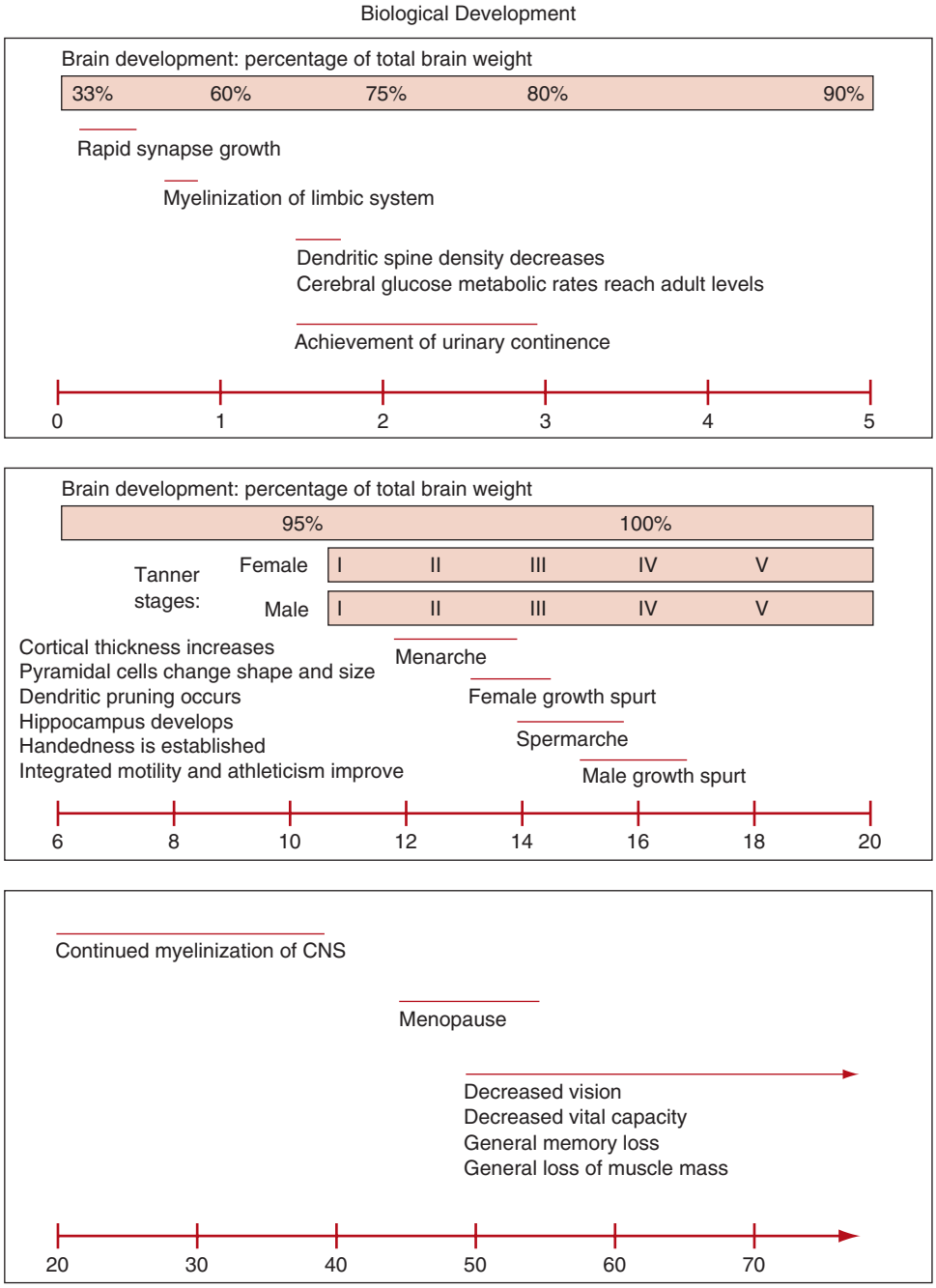



**Figure 7–1** *Timeline (in years) of biological development across the lifespan.*

## Endocrinological Considerations

While interesting changes in hormonal development occur in the first years of life, dramatic changes in both physical and emotional functions are triggered by the hormonal shifts associated with puberty that characterize the adolescent years. In girls, estradiol and progesterone production results in the onset of breast development, followed by the onset of pubic hair growth and vaginal elongation. Axillary hair subsequently develops during stage 3 of pubic hair development. Although there is wide variability in different cultural environments, menarche is usually attained 2 years after the onset of breast development and has been reported to occur at an average of 12.8 years of age in population studies (Zacharias et al. 1976). In boys, puberty begins when rising levels of pituitary hormone result in enlargement of the testes and subsequent increases in circulating testosterone. Spermatogenesis occurs after testicular enlargement at approximately 14 years of age. Pubic hair development is triggered by adrenal androgens and occurs in five stages during the course of about 2.5 years. Facial hair tends to develop between 14 and 15 years of age.

Growth hormone and gonadal hormones are both necessary to initiate the adolescent growth spurt. This occurs earlier in girls, usually during Tanner's breast stages 2 and 3, whereas in boys it does not occur until stage 4 of genital development. Both an acceleration of bone growth and a maturation of the skeletal structure as reflected by increased bone density and closing of epiphyses occur during this process.

Sexual function peaks early in the adult years in men, but there is only a gradual decline in sexual function as measured

by frequency of orgasm from 20 to 70 years. Women have consistent sexual functioning throughout the childbearing years and frequently become more orgasmic in their 30s. However, decreases in estrogen levels associated with menopause usually occur between 45 and 54 years of age. Men have no comparable menopausal change in hormonal levels.

## Cognitive Development

The study of cognitive development provides a perspective on the evolution of the capacity to think. Increased cognitive abilities are an integral component required for the onset of language. Changes in thinking ultimately shape the course of emotional, social, and moral development. Recent investigations of the relation of brain development to cognitive development have attempted to attribute specific developmental changes in central nervous system function, with the achievement of new cognitive abilities (Casey et al. 2000, Anderson 2001).

However, the acquisition of mental abilities has been charted as an independent sequence of mental accomplishments. Piaget established the field of cognitive development, and his stage theory of the evolution of cognitive processes has dominated this field (Piaget and Inhelder 1969). Although specific aspects of his four primary stages have been modified by subsequent empirical experiments as well as by the development of a greater appreciation of the role of emotions and context in the utilization of cognitive abilities, his careful observations and deductions have provided the framework on which much of our knowledge of cognitive development has been built. In contrast, Vygotsky (1978) provided a model of early cognitive development that placed greater importance on the influence of culture- and language-mediated guidance by adults.

Piaget introduced the concept of "schemas" that he defined as units of cognition. He further described processes that result in schema modification, which begin in infancy as a child assimilates new information and accommodates to novel stimuli. A particularly important Piagetian concept has been that of a decalage within cognitive development, which refers to an unevenness in cognitive development. For example, a child may demonstrate cognitive abilities at the concrete operational stage of development with regard to conservation of volume and at the same time retain preoperational forms of thinking such as persistent egocentrism. Such an unevenness can also be seen across lines of development.

Even newborns have the ability to learn through making associations between different states or experiences. There is evidence that cognitive "prewiring" exists, which allows for the perceptual capacities of infants that are necessary to seek stimulation and interaction with adult caregivers. A key capacity required for these early cognitions is recognition of the invariant features of perceptual stimuli coupled with the ability to translate these invariant features across sensory modalities. For example, infants can differentiate the human voice from other sounds innately without "learning" the complex characteristics of the structure and pitch of speech.

By 2–3 weeks of age, cross-modal fluency is demonstrated by the ability of infants to imitate facial expression. This requires the recognition of a visual schema of a facial expression to be linked with a proprioceptive tactile schema of producing a facial expression. By 3 months of age, infants can be classically conditioned, and their interest in stimuli led Piaget to suggest that this was a period dominated by attempts to make "interesting spectacles last" (Piaget and Inhelder 1969).

By 6 months of age, associations between "means" and "ends" have been demonstrated. This is followed by object permanence, which evolves during the second half of the first year. During the second year, infants can infer cause after observing an effect as well as anticipate effects after producing a causal action. A corollary of this new ability is that they are now able to correctly sequence past events.

By the third year of life, children enter the preoperational stage. This form of thinking is more similar to adult cognition, but it incorporates magical explanations and is marked by a tendency to focus on one perceptual attribute at a time. Idiosyncratic cosmological theories are common and are usually dominated by transductive reasoning, which attributes causality based exclusively on temporal or spatial juxtaposition. Throughout the preschool period, attention span and memory are limited while pretend play and fanciful thinking are common. Not surprisingly, children having imaginary friends and talking pets characterize this cognitive period. The preoperational stage is also the time during which explosive language development occurs. This development appears to be made possible by a genetically determined capacity for language. However, language development is clearly enhanced by experiential support and parental communication that is sensitive to the child's ability to process new words and grammatical structure.

By the age of 6 or 7 years, children begin to use operational thinking. The child who has attained concrete operational thought has the ability to conserve both volume and quantity, as well as being able to appreciate the reversibility of events and ideas. A shift from an egocentric perspective results in a new capacity to appreciate the perspective of others. These new cognitive skills demonstrate an ability to engage in logical dialogue and to develop an appreciation of more complex causal sequences. These new cognitive abilities are clearly required for a child to benefit from the grade school curriculum.

Adolescence results in the development of a new processing capacity that involves the manipulation of ideas and concepts. Furthermore, the informational fund of knowledge is dramatically expanded and serves as a referent for verification of new data that are assimilated. A final major transition is possible with the development of the ability to reflect on cognition as a process. This is referred to as the development of a metacognitive capacity. Achievement of this capacity allows adolescents to understand and empathize with the divergent perspectives of others to a greater degree than was previously possible. This capacity is necessary for recursive thinking, which involves an awareness that others can think about the domain of the adolescent's own thought. These cognitive skills represent the transition into the final stage of cognitive ability, which is referred to as the use of formal operations. One capacity characteristic of this stage is the ability to understand complex combinatorial systems that require a well-developed sense of reversibilities that include inversion, reciprocity, and symmetry. New levels of problem solving are achieved that include the ability to recognize a core problem or core isomorph within a more complex new problem. The adult with formal operational

ability can recognize a previously successful solution and use this knowledge to develop a parallel innovative solution to the complex problem. However, many adults remain at the stage of concrete operations and never develop these capacities.

A timeline of cognitive development during the course of the lifespan is presented in Figure 7–2.

## Emotional Development

The emotional state of the newborn is largely assessed by facial expression and accompanying vocalizations. However, the communicative capacity of young infants has become increasingly well appreciated. In the first weeks of life, contentment and distress have been reliably monitored (Lewis 1994). These primary emotions further differentiate during the first months of life. By 7–9 months, a transition occurs, which is based on the earliest attainment of intersubjectivity. At this point, infants begin to understand that their own inner experiences and feelings can be appreciated by other individuals (Trevarthen 1979, Emde 1984). This leads to the possibility of developing affect attunement as parents match their own behavior with the behavior of their infant, while experiencing shared internal feeling states. An infant pouting to elicit a parental response evidences the instrumental use of emotions. Social referencing is usually evident by 12 months of age, when infants turn to examine their mothers' facial expressions at times when they are confronted with potentially fearful situations or objects (Klinnert 1984).

In the second year of life, the rapprochement crisis occurs, as infants become aware of their separateness from

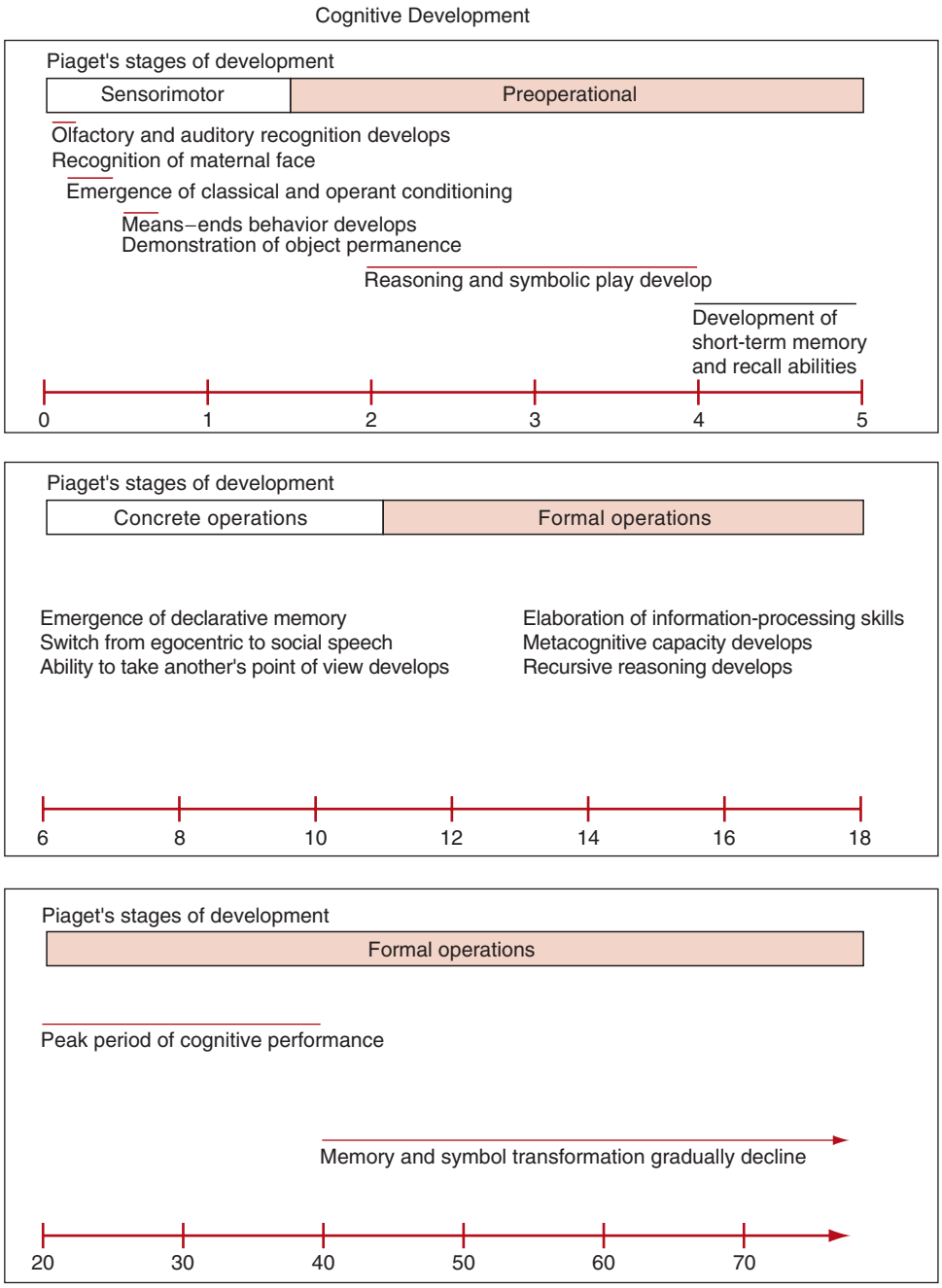



**Figure 7–2** *Timeline (in years) of cognitive development across the lifespan.*

their primary attachment figure and the limitations of their control on her/his behavior. After the infant has attained self-cognition, new, more complex emotions of embarrassment and envy emerge that further evolve to feelings of shame, pride, and then guilt by the end of the second year. Object constancy, or the ability to reduce anxiety in response to the separation from the primary caretaker, reflects the association of an emotional state with the memory of the sense of internal security provided by the attachment figure.

During the preschool years, children begin to learn the nature of the relationship between emotions and behaviors. They begin to understand the culturally defined rules associated with affect expression and consequently begin to mask their emotions. This is also the period when the Oedipus impulses are most evident, and children must deal with both their conscious attraction to the parent of the opposite sex and their fear of potential retaliation from the same-sex parent.

As children move into the school years, they experience the full range of adult emotions, although there is at least a qualitative sense that during the prepubertal period there is less intense expression of affect. Although sadness is easily recognized from the second year of life, prolonged periods of depressed affect are rare during this period. However, temperamental styles tend to emerge, and, specifically, behavioral inhibition can become more clearly appreciated within the context of increasing social and educational demands (Kagan et al. 1989).

In adolescence, emotions are more intensely displayed, and there is an emergence of a greater incidence of affective disorder and anxiety. Similarly, there is a dramatic increase in suicidal behavior that is in part associated with cognitive ability. At this point, there is a greater reflection on aspects of existential crisis, which can be experienced from more complex vantage points.

A perspective on the evolution of defense mechanisms as regulators of affect suggests that a hierarchy of more sophisticated and effective defensive strategies emerge throughout adolescence and adulthood (Vaillant 1993). A timeline of emotional development during the course of the lifespan is presented in Figure 7–3.

## Social Development

It has become widely appreciated that infants are socially interactive from the first days of life. The strong tie that parents feel for their infants has been referred to as the parent–infant bond. Between 7 and 9 months of age, infants develop separation protest and a negative reaction to the approach of a stranger. During the second half of the first year, the attachment of the infant to his or her parents evolves. The primary role of the attachment figure is the provision of a secure base from which the infant can begin to explore a wider social environment (Ainsworth et al. 1978). It is within the context of the attachment relationship that the first Eriksonian state of "basic trust" is achieved.

By 18 months, play begins to be more directed toward peers, but this does not become the predominant form of play until the third year. Along with the striving toward autonomy that characterizes Erikson's second stage, there emerge more negative affective interactions within the context of the attachment relationship. This phenomenon is widely recognized within the popular culture as the arrival of the "terrible twos." However, the quality of the attachment relationship earlier in life has been shown to predict better preschool social adaptation and a stronger sense of self-worth. Included in it is the observation that patterns of social dominance become established during the third year of life and that insecure, attached preschoolers exhibit more conflict and aggression in the establishment of their social status. These early social strivings are compatible with Erikson's third stage, which has as its central developmental objective the achievement of initiative within the context of potential failure and guilt.

Gender differences emerge by 2 years of age. Boys are more aggressive and tend to play with toys that can be manipulated. Girls prefer doll play and artwork. By the end of the third year, gender preference in play has emerged, and the preference is to play with children of the same sex. This preference remains throughout childhood. Associative play, which refers to play that involves other children and the sharing of toys but does not include the adopting of roles or working toward a common goal, becomes more prominent during the preschool years. Cooperative play also emerges along with a strong tendency to include elements of pretend play into the cooperative sequences. The cultural context begins to shape the nature of social interaction even at these earliest stages of development.

During the school years, the role of peers in shaping social behavior becomes predominant. Small groups form, and the concept of clubs becomes important. Shared activities, including the collection of baseball cards or doll clothes, are a common and important characteristic of this period. Sharing secrets and making shared rules also serve as organizing social parameters. Social humor develops, and appearance and clothing become an important social signaling system. It is a time of practicing and developing athletic, artistic, and social skills that are associated with Erikson's fourth stage of achievement of industry within the context of a sense of potential interpersonal inferiority.

In adolescence and throughout the adult years, social and sexual relationships play a complex and powerful role in shaping experience. With the onset of strong sexual impulses and increasing academic and social demands in adolescence, the role of peer influences in shaping both prosocial and deviant behaviors becomes powerful. Adolescence is the period during which Erikson described the central objective to be the establishment of an individual identity, and there has been wide acceptance of this sense of self occurring within the context of the social and cultural experience. The roles of adulthood are complex and focused on the most basic issues of marriage, parenting, working, and ultimately dealing with death. A timeline of social development during the course of the lifespan is shown in Figure 7–4.

## Moral Development

The newborn infant lives in an interactive world, but one that is free of moral directives or structure. However, by the second year of life, the emergence of "moral emotions" such as embarrassment, shame, and guilt demonstrates that the beginning of a code of moral behavior, in the most primitive sense, is being established. By 36 months, most children demonstrate the internalization of parental standards even when their parents are not available to provide

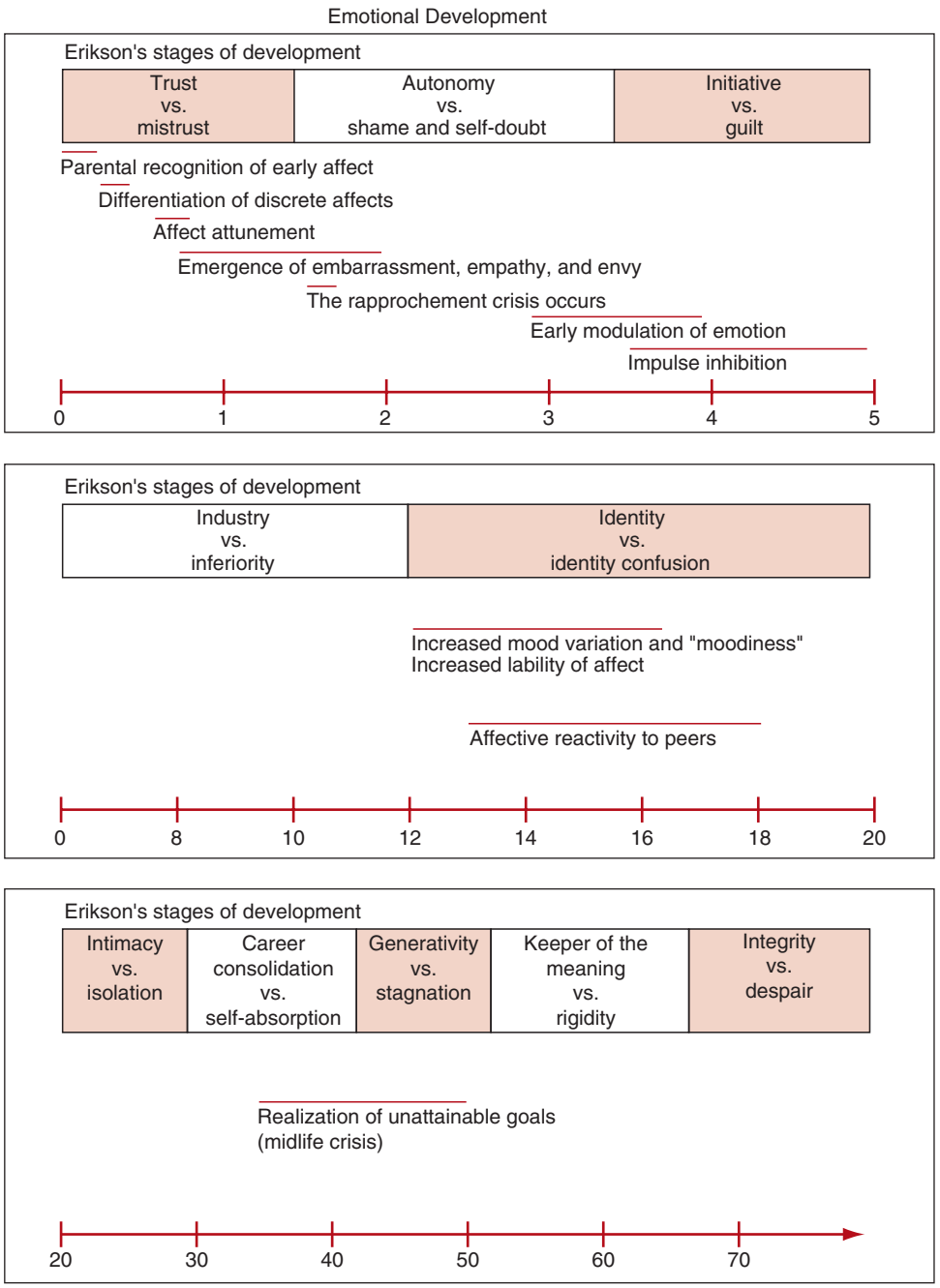



**Figure 7–3** *Timeline (in years) of emotional development across the lifespan.*

cues or reinforcement. The importance of emotions in the early evolution of moral behavior during the preschool years is particularly important and represents a distinct departure from the more traditional perspective that moral development does not occur until the establishment of concrete operation.

During the school years, the importance of rules and adhering to them become well defined. The moral code tends to be one of absolutes with strong consequences for transgressors. Extreme examples of children turning their parents into authorities because of political resistance provide a sobering perspective on the strength of the convictions of some children. However, for most boys and girls during this period, interpersonal relationships with peers or siblings are a consideration in the determination of "chosen outcomes" when situational paradigms designed to clarify moral priorities are presented (Smetana and Asquith 1994).

The later evolution of moral principles is a complex process. With the development of abstract reasoning, adolescents progress through Kohlberg's (1964) stages of conventional morality, which entail meeting the expectations of others (stage 3) and subsequently accepting the maintenance of societal norms and rules as an appropriate standard (stage 4). These stages do not progress in a strictly sequential manner. Stages 5 and 6, which ultimately lead to the conviction that moral principles of justice should supersede those of human-made laws, have not been easily codified either, given the influence of complex emotions on behavior and the well-documented moral inconsistencies that occur over the course of adult development (Gibbs 1979).

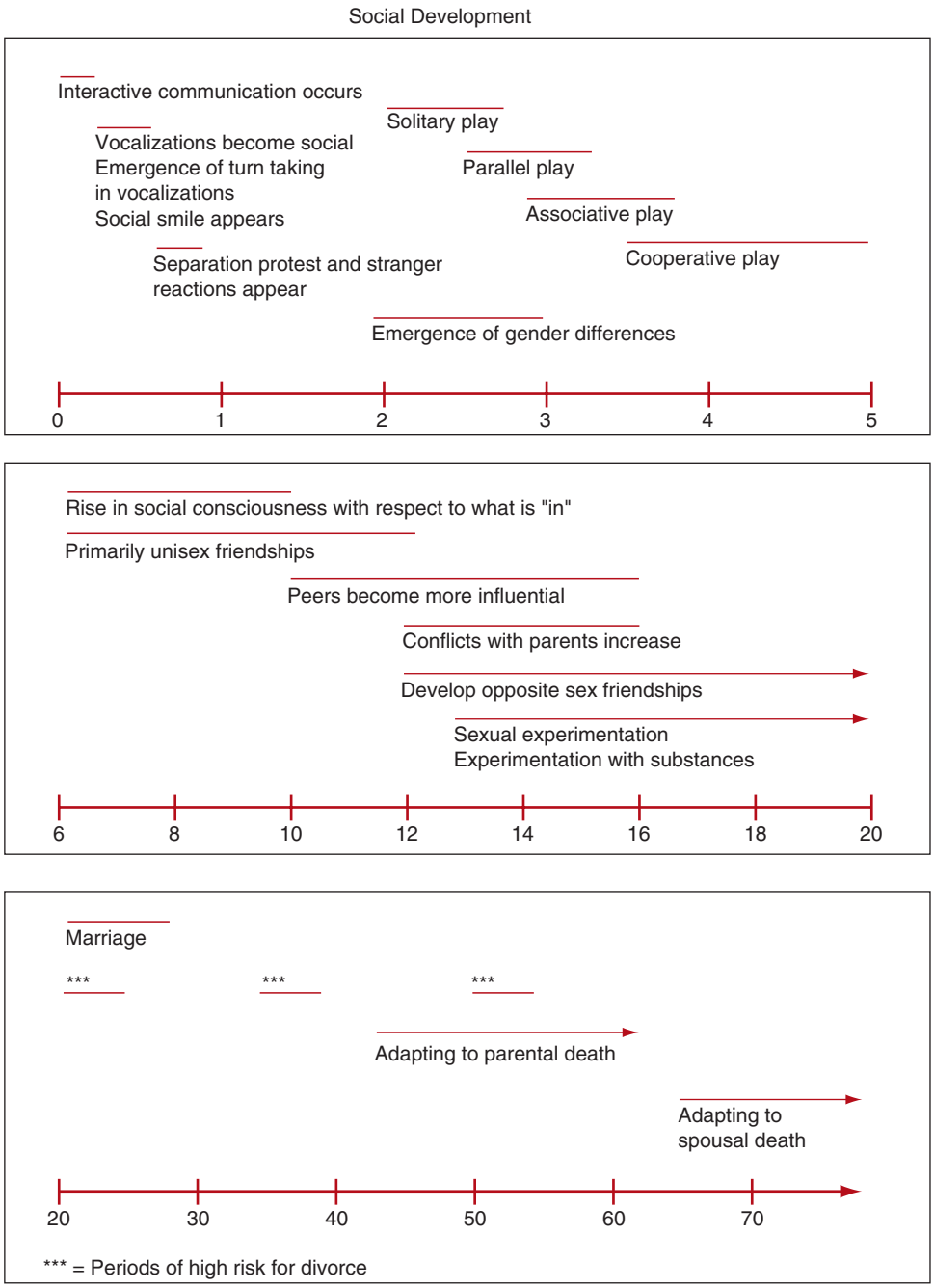



**Figure 7–4** *Timeline (in years) of social development across the lifespan.*

A timeline of moral development during the course of the lifespan is presented in Figure 7–5.

## Developmental Psychopathology Risk and Protective Factors

The risk and protective factor model is a paradigm that facilitates the understanding of developmental deviations. It can be applied at any stage of development. In the chapters that follow, the stage-specific considerations that are relevant to infants, toddlers, children, adolescents, and adults are addressed. Risk factors have been divided into three large categories: those at the level of the individual, the family, and the community.

The first category of risk factors is defined at the level of the individual. Both physical and emotional considerations are relevant. Examples include atypical genetic polymorphisms, deficits in perception, and high levels of generalized anxiety. Variable possibilities for adaptation exist, but for a trait or condition to be considered a risk factor there must be a demonstrated increase in the probability of subsequent emotional or behavioral disorder associated with the factor. Furthermore, the pathogenesis of early environmental stressors has been shown to be variable in individuals who have different degrees of genetic vulnerability. This has been demonstrated using developmental analyses of two longitudinal cohorts of children. Variation in the serotonin transporter gene (e.g., SLC6A4) has been linked to depression (Caspi et al. 2003) and variations in the monoamine oxidase A gene (e.g. MAOA) have been linked to a range of behavioral problems (Caspi et al. 2002, Kim-Cohen et al., 2006).

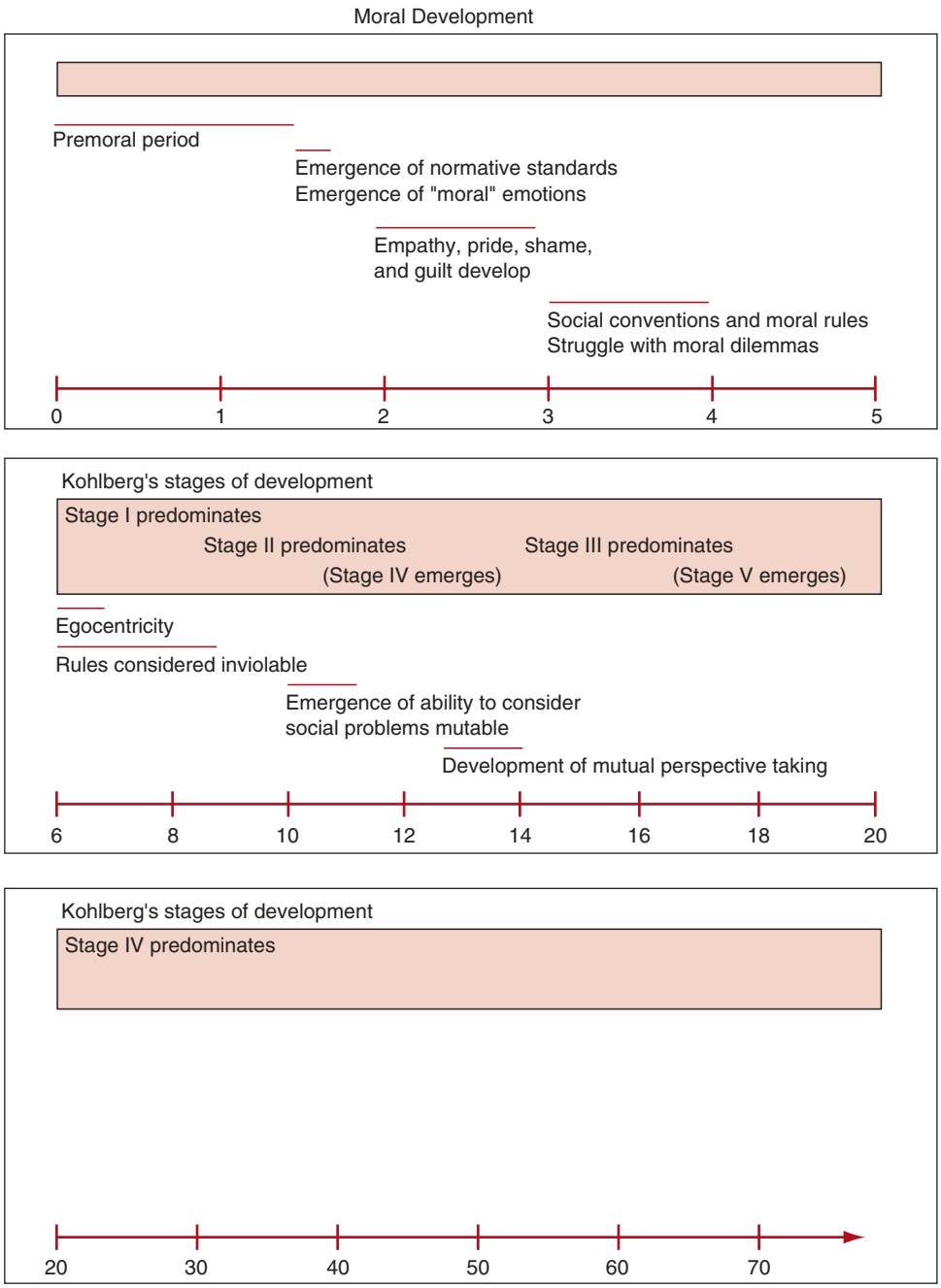



**Figure 7–5** *Timeline (in years) of moral development across the lifespan.*

Of particular interest, these studies suggest a gene–environment interaction (Rutter et al. 2006) and the possibility that environmental risk factors such as the use of cannabis can have a differential effect in children with different genetic vulnerabilities (Caspi et al. 2005).

The second category of risk factors is conceptualized at the level of the family. One of the classic examples of a familial risk factor is a parent with a serious mental illness. It is difficult to define the mechanism by which this risk is transmitted. Each parent provides exactly one-half to their genome of the child. However, parents are also in a powerful position to shape the early environment of their children. The full range of family risk factors is quite broad and extends beyond the influence of single individuals within the family to include the impact of family dynamics, which influence the development of the child. For example, a scapegoated child in a family environment who tolerates overt child maltreatment is at particularly high risk of developing psychopathology. While for many years it has been appreciated that unhappy parental separation is a major risk factor for children and even young adolescents, it has only been in recent years that vulnerability to separation has been demonstrated to be partially heritable (O'Connor et al. 2003).

The third category of risk factors is defined at the level of the community. Discrimination based on ethnic or racial status falls into this group of risk factors, as does social disadvantage. Although there is little controversy regarding the negative consequences of discrimination and poverty, the quantification of this risk has been problematic. Community

risk factors rarely occur in the absence of individual and familial risk factors, making it difficult to fully understand their specific influence.

One strategy that has been used to determine the overall risk for developmental psychopathology is to add up the specific factors that a child must deal with, creating an adversity index. This has been accomplished for young children (Sameroff 1986) as well as applied to risk factors occurring later in development (Rutter 1985a, 1985b). Most individuals can cope with a small number of risk factors, particularly if protective factors are also present. However, under the weight of multiple risk factors, most individuals begin to show signs of disturbance. Sophisticated research designs have been developed to estimate relative contributions (Topolski et al. 1997). Curiously, the quantitative effects of protective factors have been less extensively studied, although investigations into the life course of resilient individuals provide some understanding of these factors (Mrazek and Mrazek 1987).

Resilient children represent one of the most fascinating opportunities to understand the mechanisms by which risk and protective factors interact. The study of the children of mothers with schizophrenia or bipolar disorder has been an area of investigation that is of particular interest to psychiatrists. Perhaps this is because these children have been perceived to have had both a high risk for the inheritance of genes that confer poor adaptive skills and the misfortune of having a parent with impaired capacities for sensitive responses to their early developmental needs. While twin studies have suggested that resiliency may be in part heritable (Kim-Cohen et al. 2004), what is striking is that some of these children turn out to be productive and happy adults despite what appear to be overwhelming odds.

A timeline of the development of psychopathology during the course of the lifespan is presented in Figure 7–6.

## High-Risk Periods for Psychopathology

Psychiatrists who treat children and adolescents are particularly aware of the precursors and onset of psychiatric illnesses. Two examples of age-specific vulnerabilities are discussed, but Figure 7–6 gives an overview of the periods of most probable onset for many of the major psychiatric disorders. The first example is autism, which is unusual in both its invariant early onset and its striking presentation. The second is suicide, which is particularly interesting because of episodic periods of particularly high risk during the developmental course.

Autism is a disease of early onset, which has been shown to have a strong genetic basis. Nevertheless, the role of the environment in affecting the onset of autism is still striking, as demonstrated by the quite dramatic variability in the symptom presentations and ultimate adaptations of monozygotic twins. Autistic children appear normal at birth. During their first months of life, they begin to develop severe deficits in their capacity to form relationships and communicate with others. Once fully expressed, autism has a devastating impact on the subsequent development of afflicted children. What is perhaps most striking is the inevitability of early expression, as there are no examples of onset later in childhood or adolescence.

Suicide provides a sharp contrast to autism. Suicide is highly associated with mental disorder in general and affective disorder in particular. It has also been shown to be moderately heritable. Whereas the onset of suicidal thoughts does occur in rare cases in the preschool period, the capacity to commit suicide increases with age. After puberty, the rate of suicide increases nearly 10-fold. The underlying explanation for this dramatic increase is complex and involves consideration of risk factors at the level of the individual, family, and community. However, the ultimate life course pattern is striking, as there is a second dramatic increase in suicidality in the later years of life. The explanation for this second increase usually focuses on the increase in medical problems of the elderly, but the multiple emotional losses of these years also provide a vulnerable context for depression and despair.

## Interlineal Decalage

Piaget (1969) defined uneven developmental progress of specific cognitive abilities as a decalage. Psychiatrists must often help patients deal with a decalage across lines of development. Although the chapters in this section are largely devoted to the explanation of normal development, there has been a systematic effort to illustrate how deviations in development may lead to the onset of developmental psychopathology. Normality can be defined as a multilineal progression of development without a decalage, or unevenness of progress, across any of the primary domains of function. Normal children learn to think, to make friends, to deal with intense affects, and to honor the customs of their society. Problems occur when development is uneven. The patterns of these interlineal decalages are varied, and their complexity is, in large part, one of the persistent areas of fascination for psychiatrists. To illustrate this process, two straightforward decalages are discussed. Finally, a more complex example of a severe arrest in development is presented.

Cognitive delays can result in a decalage in which a teenager has the mental capacity of a second grader, while having the sexual urges and emotional swings of a normal adolescent in high school. The cognitive ability of such a teenager may not be perceived as abnormal in the context of a protected classroom. However, within the general population, he/she will be clearly labeled as deviant and will be at high risk of experiences that will place him/her in jeopardy for negative social and academic outcomes. Beyond the obvious limitations in achievement that must be dealt with, there are also emotional risks to be considered if intellectual limitations cannot be placed within a context that protects such an adolescent from ridicule and humiliation.

Emotional delays provide a similar potential for a variety of decalages. A child who is cognitively normal or even precocious may remain emotionally immature. The decalage can be widened if intensive academic effort and subsequent successes become the predominant strategy that the child develops for dealing with social awkwardness or peer rejection. Temper tantrums that were expected in the early years become less easily tolerated in the child "genius" who repeatedly demands to have family and social events orchestrated on her or his terms. In more severe cases, frustration and despair may interfere with adaptation in the same way that they do in the child who is cognitively delayed.

If a domain of function becomes arrested, the decalage becomes more severe. In these cases, overt psychopathology

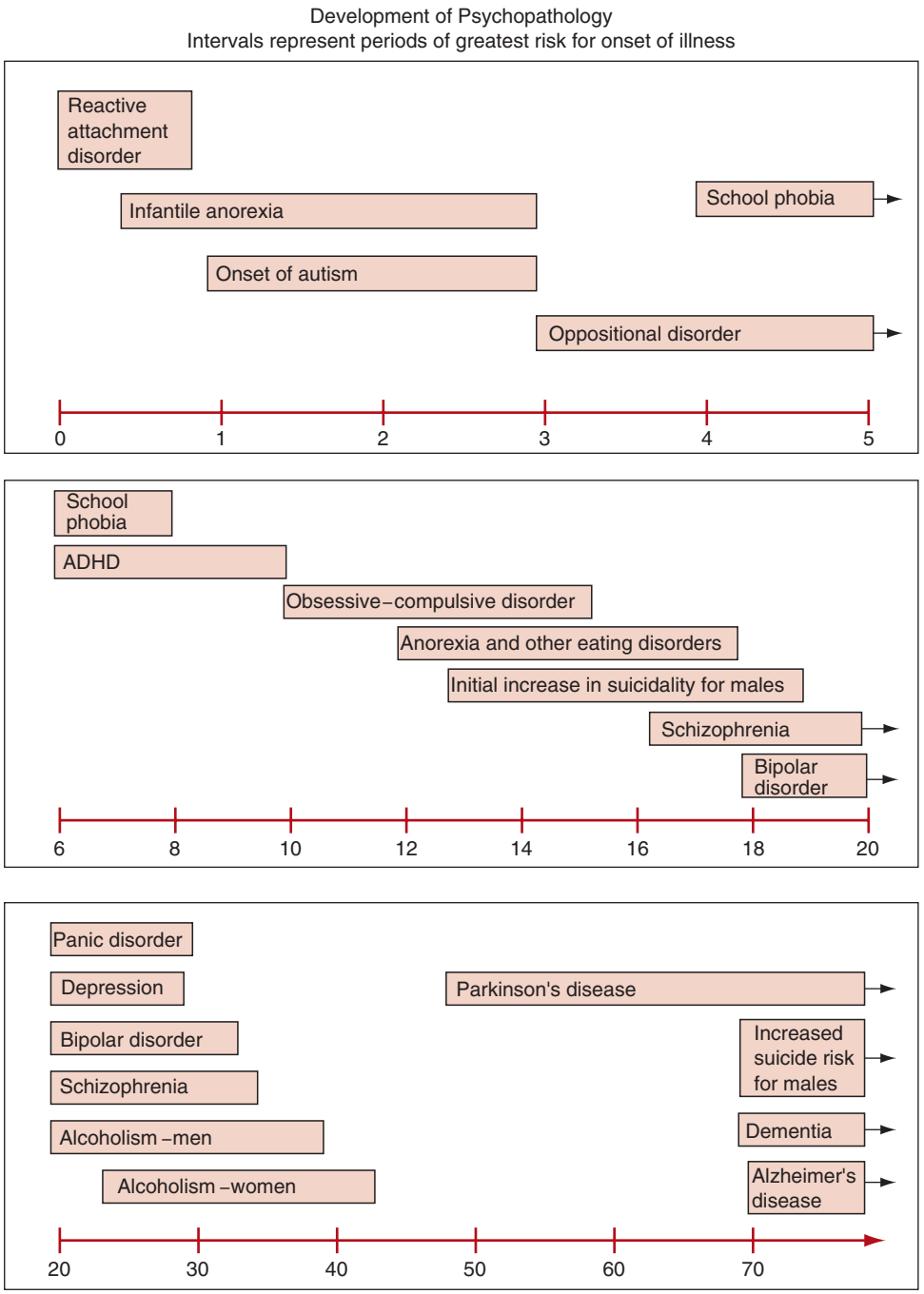



**Figure 7–6** *Timeline (in years) showing the development of psychopathology across the lifespan.*

often results. A clear example is the development of conduct disorder and, subsequently, antisocial personality disorder. In these individuals, physical, cognitive, and social developments appear to be progressing well, but a specific deficit in the development of moral judgment occurs. In some cases, the deficit is best described as the persistence of an immature sense of right and wrong, but in other adolescents there is a deviant development of amorality that is abnormal at any stage of development. Given the resistance of adults with antisocial personality disorder to current treatments, there is a strong case for focusing on the origins of this developmental decalage with the expectation that earlier intervention may be more effective.

## The Psychiatrist as a Developmentalist

All psychiatrists inevitably become students of development. The life histories of their patients demand developmental formulations to achieve a sense of understanding of the origins of the presenting symptoms and disturbing behaviors that bring the patients to psychiatric treatment. Perhaps one of the most poignant examples is Huntington's chorea. The gene that causes this disease has been identified, and it is possible to know accurately whether an infant is destined to struggle with the symptoms of this crippling disability for many decades in the future. Yet it is the life experiences of this individual that shape many of the coping strategies that determine the ultimate outcomes of these future struggles.

Anticipating the challenges of later life and understanding the origins of the strengths and weaknesses of each patient are at the core of the therapeutic process, whether it involves influencing the balance of the central neurotransmitters or identifying and supporting available community resources.

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CHAPTER 8

# Infant Development: The First 3 Years of Life

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For most clinicians treating individuals suffering from psychiatric disorders, early development is of great interest. How did the disorder begin? Were there early biological or psychosocial risk factors that could have led to early identification of the disorder or even its prevention? Is there anything unique or more important about events occurring in the first 3 years of life compared with other years of development with regard to the ontogenesis of psychiatric disorders? More broadly, how do patterns of behavioral adaptation follow particular developmental trajectories, and what factors are most influential with regard to establishing those trajectories?

Many factors may contribute to clinicians' interest in early development, and new knowledge from research on infant development in the past 35 years has afforded greater insight into clinical issues. Theories of development, which guided the teaching of clinicians for many years, have been supplemented, revised, and in some instances supplanted by data from scientifically rigorous investigations in developmental and cognitive psychology, ethology, neurobiology, chronobiology, behavioral genetics, neuroimaging, and linguistics. Greater collaboration among researchers, clinicians, and theoreticians from these diverse disciplines has led to exploration of increasingly rich, interesting, and pressing clinical questions. Researchers who study infants are now attempting to characterize and measure formerly unapproachable constructs such as relationships and the dimensions of subjective experiences. These developments have made possible new insights in the realm of infant development, while also enriching our understanding of clinically relevant issues.

In this chapter, we present a broad overview of research on infant development relevant to clinical work on infancy and later phases of life. First, we briefly describe influential theories and models of development. Then we trace various lines of development through the first 3 years of life. Next, we consider various risk and protective factors as they affect infant development. Finally, we consider selective examples of psychiatric disorders that occur in infancy to illustrate clinical application of developmental findings. Three overarching points are emphasized throughout. First, infants are active participants in their development, and individual differences in their characteristics and capacities have important implications for how infants are experienced by their caregivers. Second, the caregiving environment is the crucible within which individual differences in development in the first 3 years of life are shaped, preparing infants for transition to the broader influences of the preschool years and beyond. Finally, development occurs within the enabling or limiting multiple dynamic contexts of biology, relationships, culture, and technology.

## Theories and Models of Development and the First 3 Years of Life

### Theories of Development

Theories are important to the study of development for a number of reasons. They organize and prioritize large

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**Table 8–1 Developmental Theories and the First 3 Years of Life**

| Theorist | Type and Focus of Theory | Stages or Phases |
|---|---|---|
| Sigmund Freud (1940) | Psychoanalytic drive theory (psychosexual stages) | Oral (birth–18 months) Anal (18–36 months) |
| Jean Piaget (1952) | Cognitive | Sensory–motor intelligence (first 2 years)<br>Modification of reflexes (birth–1 month)<br>Primary circular reactions (1–4 months)<br>Secondary circular reactions (4–10 months)<br>Coordination of secondary schemas (10–12 months)<br>Tertiary circular reactions (12–18 months)<br>Representational thinking (18–24 months)<br>Preoperational intelligence (2–6 years) |
| Erik Erikson (1951) | Psychoanalytic theory (psychosocial stages) | Trust vs. mistrust (birth–18 months)<br>Autonomy vs. shame or doubt (18–36 months) |
| Margaret Mahler (1975) | Psychoanalytic theory (separation and individuation) | Autistic phase (birth–2 months)<br>Symbiosis (2–4 or 5 months)<br>Differentiation (4 or 5–8 or 9 months)<br>Practicing<br>Early practicing (8 or 9–12 months)<br>Practicing proper (12–18 months)<br>Rapprochement (18–24 months)<br>On the way to object constancy (24–36 months) |
| John Bowlby (1969, 1973, 1980) | Attachment theory | Phase of limited discrimination (birth–2 months)<br>Phase of limited preference (2–7 months)<br>Phase of focused attachment and secure base (7–24 months)<br>Phase of goal-corrected partnership (24–36 months) |
| Daniel Stern (1985) | Psychoanalytic theory (sense of self-development) | Sense of emergent self (birth–2 months)<br>Sense of core self (2–3 months)<br>Sense of subjective self (7–9 months)<br>Sense of verbal self (18–20 months) |

amounts of data regarding infant development, indicating which are the most salient and why. Often, they also explain the importance of the early years for subsequent development, indicating how developmental issues are related to broader issues of the lifespan. Generally, they move from beyond mere descriptions of behavior and attempt to explain why individuals are motivated to behave in certain ways at certain times. Finally, they may generate meaningful and testable hypotheses for empirical research.

On the other hand, theories also have inherent liabilities. The root word for theory is "*themai*" meaning "to behold," and so theories are framed from a particular point of view, often with specific agendas. A selective focus on one theory may obscure others of equal or greater value. Theories also inevitably lead to oversimplification of complex processes and events. They may create biases that affect how we interpret observations and how we make inferences from these observations. The history of psychology is filled with examples of adherence to a particular point of view, making it impossible to see disconfirming information. All of these factors urge us to be cautious about the uncritical use of theories to understand development. We believe that a useful theory is one which is developmental, integrative, contextualist, constructionist, and perspectivist in nature, discounting its own absolute claim to truth and integrating as many relevant approaches as possible. An integrative developmental theory accounts for the dynamic interactions of biology (including neuroanatomy, genetics, neurotransmitters, etc.), relationships (including parental, sibling, peer, and wider social groups), culture (including cultural norms for individual and collective development), and technology (including medication, informatics, etc.) (Wilber 2000).

Table 8–1 presents a brief summary of some of the major theories of development as they pertain to the first 3 years of life. Although others could have been selected,

**Table 8–1 Developmental Theories and the First 3 Years of Life *continued***

| Focus and Features | Strengths | Weaknesses |
|---|---|---|
| Attempted to describe the unfolding of innate drives, whose objects progressed from oral to anal during first 3 years of life | Most sophisticated and comprehensive theory of human behavior ever developed. Accounts for the irrational component of behavior through construct of unconscious, which has been widely accepted. Clinically useful and generative; linked to important treatment concepts and techniques | No systematic evidence for fixation-regression model. Constructs not well operationalized and as a result many of its major premises are untestable. Exclusive focus on aggression and libido as motivators of behavior to the exclusion of other seminal constructs. Derived in large part from reconstructive method and from populations of patients. Mechanistic view of person motivated by tension reduction |
| Concerned with how infants construct, organize, and transform information | Most comprehensive theory of cognition ever proposed. Based on observable behaviors and replicated cross-culturally. Describes qualitative differences in how children think | Considerable evidence of uneven performance based on task and contextual factors. Evidence of sophisticated cognitive endowment in newborns that the theory cannot account for, especially in regard to cross-modal fluency and memory. Minimized social and familial contributions to cognition |
| Accepted Freud's drive model but placed developmental issues in a social context | Places Freud's intrapsychic metapsychology in a social context and introduces issues that are more obviously salient than psychosexual stages (trust instead of orality) | Stages imply qualitative changes that are not always supported by data. Theory ties clinical issues to particular stages of development. There are few efforts at validation of first two stages, and clinical implications are not well articulated |
| Also accepted drive model but focused on emergence of psychological self, which she believed was not differentiated until the later part of the second year of life | Deals with fundamental human dilemma of how to be with others and how to be alone. Developed in part from observing normal infants. Moved psychoanalysis to a focus on self-development | Presupposes what it purports to demonstrate that psychological birth gradually unfolds during first 2 years of life. Accepts fixation-regression. Logical inconsistencies. Derived in part from study of deviant behavior |
| Described the development of attachment, a biologically endowed motivational system responsible for maintaining felt security | Careful attention to observable behavior. Has inspired more research than any other developmental theory. Describes how individual continuity occurs within model of developmental change. Major premises confirmed in cultures around the world. Places emotional intimacy as centerpiece of interpersonal relatedness | Limited to one domain of infant–parent relationships. Overstates importance of early separations. Minimal attention to individual differences in infants as contributors to attachment |
| Concerned with how the infant subjectively experiences the world; senses of self continue to function throughout the life span once they are formed | Clear focus on subjective experience of infants in relationships. Abandoned stages in favor of model in which new capacities are added rather than effacing away older capacities. Freed clinical issues from being tied to particular stages in development. Derived primarily from empirical studies of development | Clinical implications not well developed. Does not account for fantasies and distortions by infants |

those presented have been most influential with regard to clinical practice and research on early development. As noted in Table 8–1, the theories vary with regard to their particular focus of development, although most use stages to describe periods of discontinuity.

## Models of Development

Whereas theories of development describe the evolution of particular issues such as cognition, aggression, attachment, or the sense of self, models of development are more concerned with the process by which development proceeds. How do individuals change or remain the same over time? What drives both continuities and discontinuities in development?

Although it is common to suggest that we are now beyond nature–nurture conflicts, this ancient debate actually continues in every aspect of science concerned with human development. Although most extreme positions in the debate have been eliminated, the weight that different clinicians, investigators, and theorists give to environmental or to genetic influences varies enormously.

The field of behavioral genetics has made some important and even surprising contributions to this debate. Studies of twins and adopted siblings are able to determine the proportion of variance in various outcomes explained by genes, by shared environment, and by nonshared environment. Shared environment includes all aspects of environmental contributions that two individuals in the same family have in common, such as social class, family warmth, and neighborhood. Nonshared environment refers to the aspects of environmental contributions that are unique and nonredundant for an individual, such as unique aspects of relationships with parents, peer relationships, and unexpectable life events. There is considerable evidence to suggest that for the broad areas of intellectual capacities, personality traits, and many types of psychopathology nonshared environmental contributors are more important than previously recognized. For

example, heritability estimates of separation-anxiety in boys range from 0 to 19%, with the major factor being nonshared environmental factors (Topolski et al. 1997). What matters most for a particular infant's development is not the general characteristics of family size, income, or warmth, but instead the particular ways in which the family relates to that child.

Despite these contributions, behavioral genetic formulations are limited to explaining proportions of variance in relation to a particular outcome. They say nothing of the actual gene–environment transactions that underlie development. It now appears that gene–environment transactions are extraordinarily complex, with genes switching on and off at various points in development, often in response to various environmental perturbations (Sameroff 1997). Research associated with the human genome project may begin to fill in some of these important gaps in our understanding of developmental processes. It appears that many psychiatric syndromes do not exhibit simple Mendelian genetics, but rather poly- or oligogenic inheritance, incomplete penetrance, variable phenotypical expression, or genetic heterogeneity (State et al. 1997). It may also be that the genetic factors contributing to many psychiatric disorders will be "normal variants" of genes, with a particular combination of alleles needed to confer susceptibility to a disorder. This is not unlike the contribution of environmental risk factors discussed later in this chapter.

## Transactional Model

Linear biological models suggest that insults at an early age might be expected to lead to adverse outcomes. This suggests that we should look for biological markers in infancy for subsequent emotional, behavioral, and cognitive disabilities. Nevertheless, longitudinal studies of child development suggest that biological risk factors considered alone are not strongly predictive of outcomes. Sameroff (1997) cited one study in which the importance of 169 biomedical and behavioral variables assessed in infancy was examined in relation to cognitive outcome of over 25,000 children 4 years later (Broman et al. 1975). Although only 11 of the 169 variables involved family factors, parental social class and mother's educational level were more predictive of outcome than all biological risk factors combined.

These and related results have led to the creation of linear environmental models of development. Here the idea is that the child's outcome is shaped by the quality of the caregiving environment. There is, in fact, abundant evidence that the environment contributes powerfully to the infant's outcome. Nevertheless, ample data also indicate that early adverse environments are not linked in straightforward ways with poor outcomes (Rutter 1989). For example, the Kauai Longitudinal Study followed children at high clinical risk from the age of 2 years through adulthood and found considerable variety and complexity of interactions among environmental factors (Werner 1993). Similar results from other studies suggest that linear environmental models are as inadequate as linear biological models.

Sameroff and Chandler (1975) proposed the transactional model of development in which genetic and environmental regulators of an individual's behavior transact continually over time, mutually influencing one another. In fact, Sameroff (1997) has posited that much as the genotype acts as the biological regulator of infants' behavior, the environtype acts as the social regulator of infants' behavior. For infants, the environtype comprises the cultural, familial, and parental characteristics that regulate infants' experiences and opportunities. This model describes individuals transacting continually with genotypic and environtypic regulators over time. Behavior at any point in time is a result of the dynamic interplay of genotype, environtype, and individual.

The transactional model is currently the most widely accepted description of the developmental process. It appears to account reasonably well for most developmental outcomes that have been studied except for those that follow the extremes of biological insults, such as certain chromosomal disorders or extreme environmental adversities, such as intense deprivation. Still, the transactional model does not give predictive weight to any particular set of risk or protective factors, and the search for more precise predictive models continues.

## Cultural Context of Development

One of the most important contexts for development is that of culture, which influences not only the developmental process but also the variables we choose to study it. There is increasing recognition within the behavioral sciences that in a country as culturally diverse as the US, we must face the challenges of better understanding, interpreting, and appreciating cultural diversity as it affects developmental processes. Cultural theorists also remind us of the important influences of culture and technology (Lewis 2000).

Culture refers, as stated above, to a shared system of beliefs, attitudes, and values that characterize a particular social group who share a common history and heritage. Culture includes the worldview of the group and describes normative assumptions that provide individuals within the group with a frame of reference for developing their own values and beliefs. Culture is crucial to understanding development, because one of the major means of transmitting cultural meanings, assumptions, and values is from caregivers to children during child-rearing (Berg 2000). From these descriptions, culture appears to stand as a static cultural construct, when, in fact, it is also dynamic and coevolves within the broader cultural context, especially in these days of simplified individual and technological transportation.

Sameroff and Fiese (2000) have emphasized the role of the cultural code in regulating development through processes of socialization and education. They believe that culture sets the broad developmental agenda for child-rearing, with individual differences apparent within the broad framework. A number of investigators of cultural influences on development provide support for these assertions.

Garcia-Coll and Meyer (1993) have drawn several conclusions from their overview of some of the major research findings from investigations of cultural differences and similarities in child-rearing and their implications for infant development. First, despite enormous differences in child-rearing techniques around the world, parents are motivated to do what is best for their children. Second, despite differences in child-rearing, there is remarkable consistency of some aspects of development across cultures, such as attaining communicative, intellectual, and social competence, although the meanings of what is competent may differ considerably. Third, the timing, content, and expression of developmental processes vary widely across different

cultures. Finally, there appears to be a universality of gender differences in cultures around the world, with boys being more aggressive and girls being more nurturing.

This raises the question of what other universals exist with regard to development across different cultures. LeVine (1977) suggested that there exists a universal hierarchy of parental goals that guide child-rearing behavior. At the most basic level, parents are concerned about developing children's capacities for self-maintenance as adults. At the next level, parents are concerned about developing children's capacities for economic self-maintenance as adults. Finally, parents are concerned with developing their children's cultural values. There is a developmental sequence implied in this model, in which the first goal takes precedence over the other two and is the first major concern of parents in the child's first years of life.

The application of cultural universals may well be limited, at least beyond the broad outline provided by LeVine. What may be more important from the clinical perspective is identifying within-cultural deviance from the broadly accepted norms, with less regard for the content of the norms themselves.

## Conceptual Framework

To describe the details of psychological development within the first 3 years of life, we selected the following lines of development with regard to their continuities, discontinuities, and content. These lines are biological–neurological, referring primarily to the brain and central nervous system development and temperament; cognitive, referring to individual changes in intellectual capacity and modes of thinking; emotional, including the differentiation of discrete affects and emotional expression; communicative, referring to understanding of and use of preverbal and verbal modes of communication; and social, referring to all aspects of relatedness and affiliative behavior with others. Discussing these lines separately has some heuristic value, although all the lines of development are interwoven and interdependent such that changes in one resonate through the others.

Rather than discussing each line of development in succession from the birth to 3 years, we review findings relevant to each of the developmental lines within the four different periods. These epochs are defined by three major periods of qualitative reorganization or discontinuity in infancy: 2–3 months, 7–9 months, and 18–20 months. (Table 8–2 summarizes emerging patterns of behavior at different points during the first 52 weeks of life.) These epochs describe different periods of qualitative change in biological, cognitive, emotional, communicative, and social development in which new capacities for experiencing and relating emerge and are different in kind, rather than amount, from earlier capacities. Thus, development between these points consists primarily of quantitative changes, whereas development across these points results in qualitative changes. See Figures 8–1 to 8–4 for a summary of these developmental transitions.

It is important to acknowledge that the transition points can also be overemphasized. By focusing on these major transition points, their importance may be exaggerated at the expense of more minor transitions that are salient for some particular domain of development at a particular point in time. Nevertheless, there is considerable evidence that these specific developmental transitions include observable changes in cognitive, emotional, communicative, and social development (Stern 1985).

# Lines of Development and Their Discontinuities

## First 2 Months of Life

The first 2 months of life were once considered a period of psychological inactivity or at least incomprehensibilty. William James (1890), for example, considered the newborn to be a "blooming, buzzing confusion." In the conceptualizations of learning theorists, the newborn was a passive recipient of external influences, a tabula rasa or blank slate, on which the environment drew particular characteristics. Following Freud's ideas about a stimulus barrier, which was postulated to protect a young infant from potentially overwhelming environmental input, Mahler et al. (1975) described the first 2 months of life as the relatively "autistic" phase of development.

All of these views of the first 2 months of life have been challenged by creative and careful experimental work that began in the late 1960s and 1970s. From this work has emerged a new view of the human infant as a perceiving, remembering, organizing, regulating, and communicating individual. Nevertheless, the first 2 months may be thought of as a period of stabilization for infants as they adjust to postnatal life. During this period of stabilization, infants do not undergo major transitions or reorganizations but appear to consolidate prenatal changes in neurological and psychological development.

### Biological–Neurological Development

Although birth is a dramatic transition, change at the level of neuroanatomy and neurophysiology is much less striking. Brain growth and specialization, which began in fetal life, continue after birth; in some areas more sophisticated associative pathways continue to develop for many years. Cell migration is completed by the sixth prenatal month, and cell differentiation follows. Over the course of development, cells develop axons and dendrites, make abundant synapses, lose connections (synapse pruning), and become myelinated. Synaptogenesis, pruning, and myelination have variable courses of development, depending on what part of the brain is developing. Overall, the structural development of the brain is completed largely before birth. However, the functional development of the brain is made possible by the selective strengthening and pruning of synapses and circuits through experience with the environment (Nelson and Bosquet 2000). During the first 2 months of life, however, changes in these domains are generally quantitative rather than qualitative and are due to the growth of synapses rather than the birth of new neurons. Positron emission tomography (PET) scan studies of glucose metabolism are fairly consistent with the highest degree of activity in primary sensory and motor cortex, thalamus, brain stem, and cerebellar vermis, and a relatively high level of metabolism in the cingulate cortex, amygdala, hippocampus, and basal ganglia, with a relative paucity of metabolism over most of the cerebral cortex (Chugani 1994). These findings are consistent with the relatively limited behavioral repertoire of newborns with intrinsic brain stem reflexes and limited visual–motor integration.

On the other hand, growing physiological stability becomes apparent within a few days after birth. In this case, interaction with the environment facilitates the rhythmic

**Table 8–2 Emerging Patterns of Behavior During the First Year of Life**

| | |
|---|---|
| | Neonatal Period (First 4 Weeks) |
| Prone: | Lies in flexed attitude; turns head from side to side; head sags on ventral suspension |
| Supine: | Generally flexed and a little stiff |
| Visual: | May fixate face or light in line of vision; "doll's-eye" movement of eyes on turning of the body |
| Reflex: | Moro's response active; stepping and placing reflexes; grasp reflex active |
| Social: | Visual preference for human face |
| | At 4 Weeks |
| Prone: | Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension |
| Supine: | Tonic neck posture predominates; supple and relaxed; head lags on pull to sitting position |
| Visual: | Watches person; follows moving object |
| Social: | Body movements in cadence with voice of other in social contact; beginning to smile |
| | At 8 Weeks |
| Prone: | Raises head slightly farther; head sustained in plane of body on ventral suspension |
| Supine: | Tonic neck posture predominates; head lags in pull to sitting position |
| Visual: | Follows moving object 180 degrees |
| Social: | Smiles on social contact; listens to voice and coos |
| | At 12 Weeks |
| Prone: | Lifts head and chest, arms extended; head above plane of body on ventral suspension |
| Supine: | Tonic neck posture predominates; reaches toward and misses objects; waves at toy |
| Sitting: | Head lag partially compensated on pull to sitting position; early head control with bobbing motion; back rounded |
| Reflex: | Typical Moro's response has not persisted; makes defensive movements or selective withdrawal reactions |
| Social: | Sustained social contact; listens to music; says "aah, ngah" |
| | At 16 Weeks |
| Prone: | Lifts head and chest, head in approximately vertical axis; legs extended |
| Supine: | Symmetrical posture predominates, hands in midline; reaches and grasps objects and brings them to mouth |
| Sitting: | No head lag on pull to sitting position; head steady, tipped forward; enjoys sitting with full truncal support |
| Standing: | When held erect, pushes with feet |
| Adaptive: | Sees pellet, but makes no move to it |
| Social: | Laughs out loud; may show displeasure if social contact is broken; excited at sight of food |
| | At 28 Weeks |
| Prone: | Rolls over; pivots; crawls or creep-crawls (Knobloch) |
| Sitting: | Sits briefly, with support of pelvis; leans forward on hands; back rounded |
| Standing: | May support most of weight; bounces actively |
| Adaptive: | Reaches out for and grasps large object; *transfers* objects from hand to hand; grasp uses radial palm; rakes at pellet |
| Language: | Polysyllabic vowel sounds formed |
| Social: | Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact |
| | At 40 Weeks |
| Sitting: | Sits up alone and indefinitely without support, back straight |
| Standing: | Pulls to standing position; "cruises" or walks holding on to furniture |
| Motor: | Creeps or crawls |
| Adaptive: | Grasps objects with *thumb and forefinger*; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person |
| Language: | Repetitive consonant sounds (mama, dada) |
| Social: | Responds to sound of name; plays peek-a-boo or pat-a-cake; waves goodbye |
| | At 52 Weeks (1 Year) |
| Motor: | Walks with one hand held (48 weeks); rises independently, takes several steps (Knobloch) |
| Adaptive: | Picks up pellet with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture |
| Language: | A few words besides mama, dada |
| Social: | Plays simple ball game; makes postural adjustment to dressing |

*Source*: Behrman RE (ed) (1992) Nelson Textbook of Pediatrics, 14th edition. WB Saunders, Philadelphia, PA, USA, p 41, with permission from Elsevier.

organization of behavior (Anders and Zeanah 1985). Feeding is the first regularly recurring postnatal temporal event, and a cycle of behavioral and physiological regularity becomes organized around the interval between feedings. Notably, human infants seem able to adjust their rhythms to cycle lengths varying from 1 to 6 hours to accommodate cultural differences in feeding practices.

Other components of young infants' rhythmically organized behaviors are circadian rhythms (diurnal cycles) and ultradian rhythms (faster periodic functions such as heart and respiratory rates). Although circadian rhythms are generated endogenously, they are regulated by exogenous cycles, especially light–dark, temperature, and social cues. Environmental cues impose period and phase control on rhythmicity through a process called "entrainment" (Anders and Zeanah 1985). The pacemaker or oscillators regulating ultradian rhythms are less well understood, but study of recurrent physiological patterns temporally in

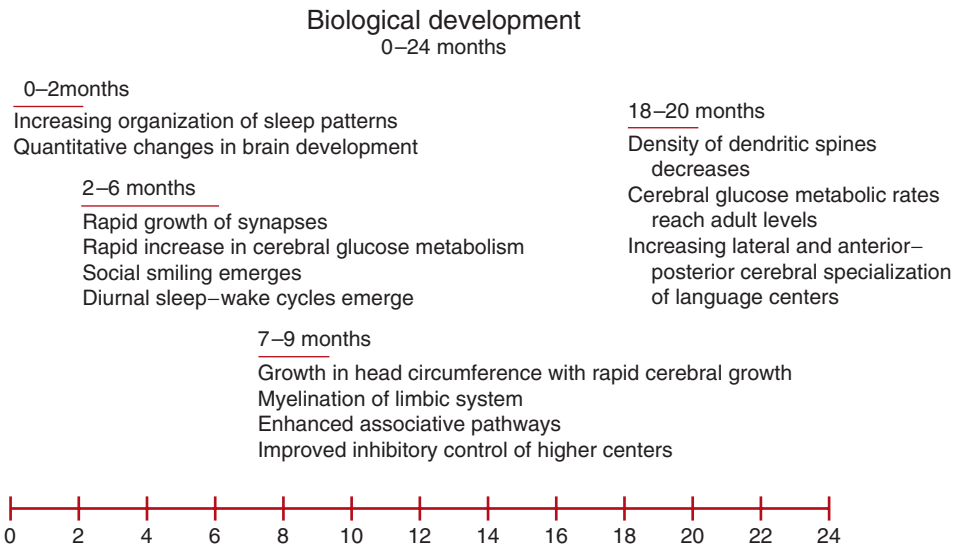



**Figure 8–1** *Biological development during the first 2 years of life.*

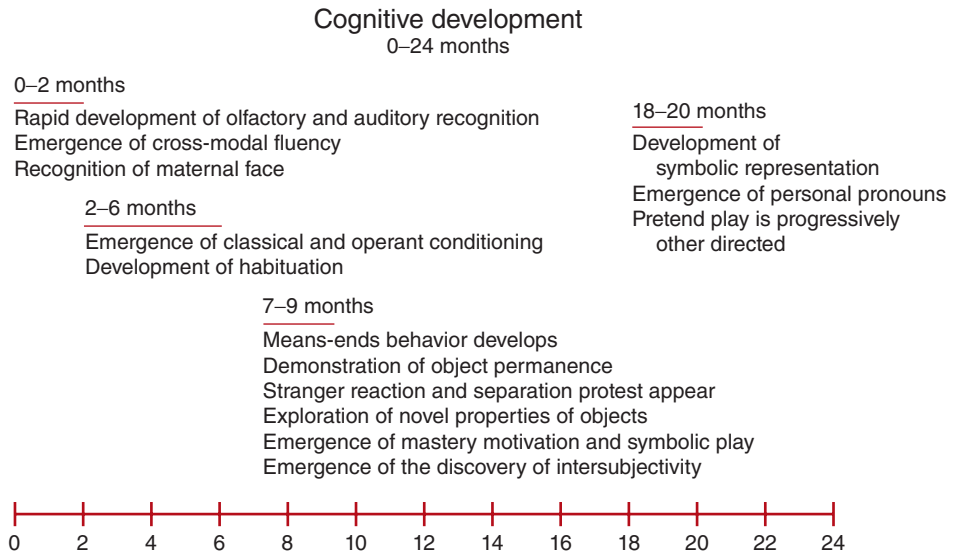



**Figure 8–2** *Cognitive development during the first 2 years of life.*

phase with one another has led to interest in infants' states of consciousness and arousal.

The newborn's day and night are spent shifting between six states of arousal, listed in Table 8–3. At first, there is little stability in the duration of these states, although from birth there is some order in the direction of transitions between them. Compared with the two sleep states, which occupy two-thirds of the newborn's day, the awake states are particularly unstable in the first few weeks, although they become progressively better organized and more sustained during the second month of life (Anders et al. 1983).

Dyadic interaction—reciprocal behavior between infant and caretaker,—although once considered minimal or superfluous during this period of development—is probably of significant importance in regulating development of neural mechanisms that modulate and control central nervous system arousal. Caregivers regulate the newborn's behavioral, neurochemical, autonomic, and hormonal functions through different aspects of the relationship, such as the provision of nutrition, warmth, sensory stimulation, and especially rhythmical responsiveness (Anders and Zeanah 1985).

Rhythmicity is a behavioral referent to hypothesized differences in the central nervous system that are often referred to as "temperament." All major theories of temperament suggest that temperamental dispositions are rooted in biological differences (Goldsmith et al. 1987). Although individual differences in newborns have been widely demonstrated, there is only modest convergence of measures of temperament (Goldsmith et al. 1987). In other words, meaningful differences in temperament appear to be difficult to ascertain within the first 2 months of life (Woroby 1986). This is not surprising given that behavioral genetics research comparing monozygotic and dizygotic twins has demonstrated virtually no genetic contributions to temperament in newborns (Riese 1990).

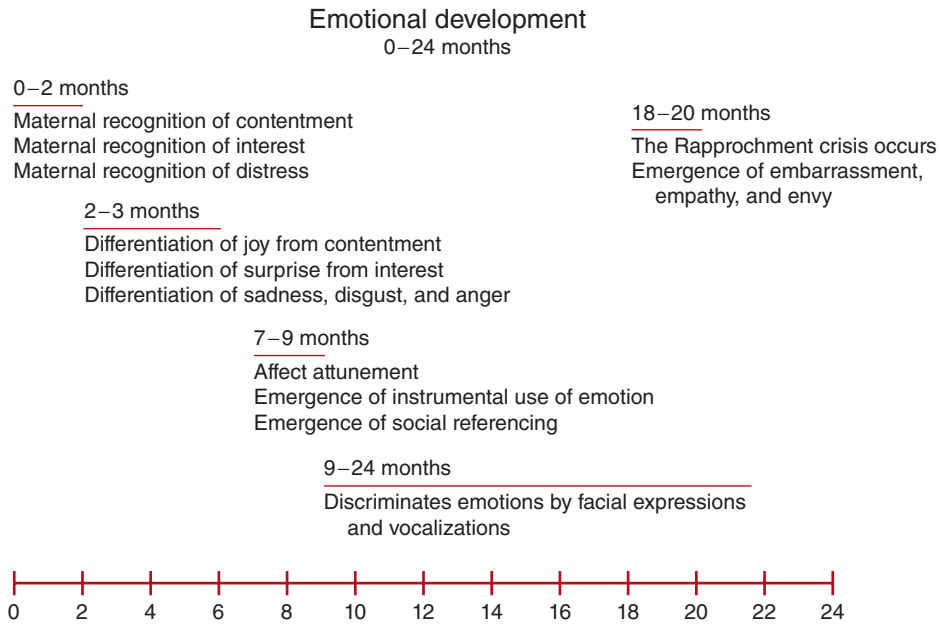



**Figure 8–3** *Emotional development during the first 2 years of life.*

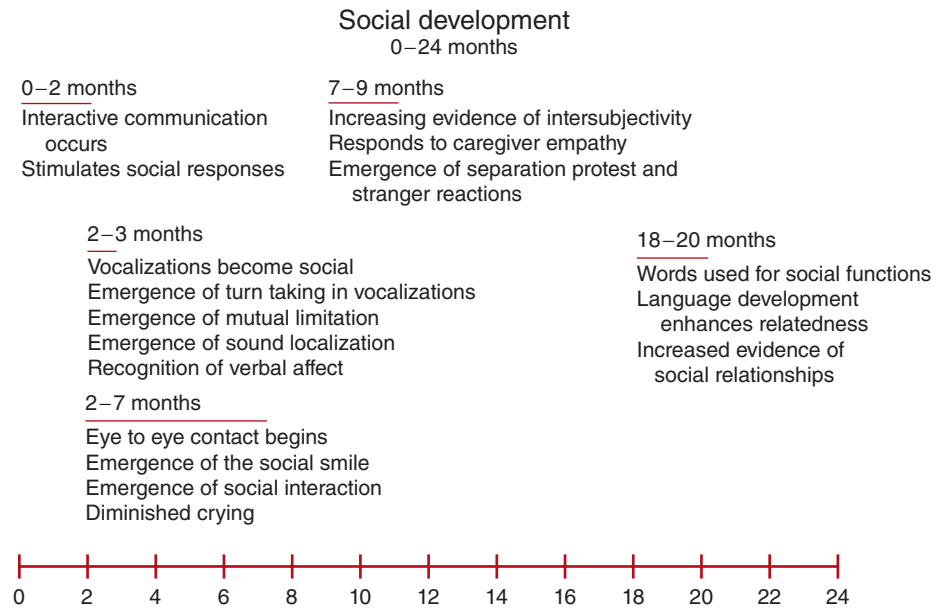



**Figure 8–4** *Social development during the first 2 years of life.*

## Cognitive Development

The human infant has a remarkable ability to learn through perception, discrimination, and indication of preference. Newborns (and even third-trimester fetuses) can be conditioned to auditory stimuli successfully and reliably. Infants at birth seem to prefer female voices, but they also "work" by nonnutritive sucking to recordings of their mothers' voices in preference to another woman. DeCasper and Spence (1986) reported that when mothers read Dr Seuss' *The Cat in the Hat* to their fetuses once a day during the last 6 weeks of pregnancy, newborns found that story much more familiar (as detected by patterns of nonnutritive sucking) than another story also read by their mothers soon after birth. This suggests that fetuses' early preference for their own mothers' voices may have developed as a result of hearing them *in utero*.

Early recognition in the olfactory domain also indicates newborn recognition of the mother. MacFarlane (1975) demonstrated that 6-day-old infants reliably discriminated the smell of their mothers' milk. When the breast pad of a 6-day-old nursing infant's mother and the pad of another lactating woman were placed on either side of an infant's head, the infant turned preferentially toward the mother's pad. In addition, 4-day-old infants can discriminate between their mothers' amniotic fluid, colostrum, and milk, and show a preference for amniotic fluid and colostrum on day 2 and milk on day 4 (Marlier et al. 1998). These behaviors may contribute

**Table 8–3 Newborn States of Arousal**

| States of Arousal | Characteristics |
|---|---|
| Quiet sleep | Regular respirations, limited movements |
| Active sleep | Rapid eye movements, irregular respirations, large muscle paralysis |
| | Most common state in newborn period |
| Drowsy | Transitional state between sleep states and waking states |
| Quiet alert | Sustained gaze, limited movements, maximal alertness |
| | Limited in first few weeks |
| Active alert | Active movements, mild distress occasionally |
| Crying | Unable to attend to other stimuli |

importantly to parents' beliefs that their infants recognize them.

In addition to the capacity for rapid learning, research has documented that human newborns are born with a sophisticated biological endowment that Stern (1985) has called their "prewired knowledge" of the world. This knowledge consists of curious perceptual capacities enabling them to seek stimulation actively, to regulate their environment, and to interact with adult caregivers. At the core of these capacities is a remarkable ability to detect the invariant features of perceptual stimuli and to translate the invariant features across different sensory modalities.

Gaze fixation and visual following of the face, as documented by Fantz (1964), demonstrate that infants possess an unlearned preference for visual stimuli that conform to the characteristics of the human face. By 1 month of age, infants demonstrate by differential looking times that they can distinguish the features of their mothers' face from that of an unfamiliar woman.

A similar case holds for auditory stimuli. Infants are born not only with a preference for the human voice but also with a preference for voices in the usual pitch ranges of females rather than males. Infants are able to recognize innately that speech is a special class of acoustic signal and that language is composed of discrete units (Eimas and Miller 1992). This is quite important because it would take several lifetimes to learn through trial and error how to distinguish between speech and nonspeech sounds.

Even more sophisticated forms of prewired knowledge are referred to as intermodal matching or cross-modal fluency. Meltzoff and Moore (1977) first described the ability of 2 to 3-week-old infants to imitate human facial expressions. This capacity requires that infants match a visual schema of the facial expression with the proprioceptive–tactile schema of the act of producing the facial expression. This visual–proprioceptive cross-modal translation has been replicated in infants of 36 hours old (Field et al. 1982). In another study, 1-month-old infants were given either a smooth or rough pacifier. When shown both pacifiers, infants looked preferentially at the pacifier they had mouthed but had never seen before (Meltzoff and Borton 1979). This tactile–visual matching seems to be innate rather than learned, although the debate still lingers (Maurer et al. 1999). Finally, infants are able to match the intensity of events across modalities. For example, infants can indicate that a light of a certain brightness is comparable to a sound of certain loudness (Lewkowicz and Turkewitz 1980). Visual–tactile matching is facilitated preferentially by two-dimensional rather than three-dimensional representations (Strert and Molina 1993). Four-month infants are also capable of matching faces and voices when presented with an adult's or child's face or voice (Bahrick et al. 1998). Stern has emphasized the importance of cross-modal fluency for interactional synchrony and for early self–other differentiation in human infants.

Although there has been great interest in the innate knowledge and learning capacities of newborns, it is important to remember that demonstrations of these capacities require setting up careful experimental conditions and conducting frequent trials that generate only a small amount of usable data. In fact, newborns have important limitations in their cognitive capacities, which become substantially more sophisticated beyond the first 2 months of life.

For experience to be significant in the development of individual infants, they must have some ability to form representations of experience that they carry forward. Developmental research on memory has demonstrated that infants, from birth, are capable of perceiving and recalling experiences in the form of behavioral, perceptual, emotional, and somatosensory modes, although remembering does not involve any subjective sense of recall (Bauer 1996). This implicit memory does not require conscious processing during encoding or retreival (Squire et al. 1993). Implicit memory must rely on brain structures present and functioning at birth, such as the amygdala, basal ganglia, motor, and perceptual cortices. As already described, the infant's mind is able to detect similarities and differences across experiences and modalities, and thus has a process for making generalizations. These generalizations represent the sum of what the infant has experienced and also determine the infant's anticipations of what will come next (Siegel 2001).

These memories or representations are encoded not in the temporal cortex but in the neural circuits directly involved in behavior, emotion, and image. We will elaborate further on these processes in subsequent sections.

## Emotional Development

Most observers agree that newborns exhibit two major forms of emotional expression: distress and contentment. Nevertheless, Lewis (1994) has pointed out that the expression of interest also seems to be present at birth. He has proposed a model of differentiation of emotional expressions in which the three major emotional states, contentment, interest, and distress, are present in the first 2 months of life and later differentiate into more specific emotional states. All of the studies of early emotions rely on infants' emotional experience based on facial expressions of emotion and crying; still, most investigators believe that facial expressions are reasonable indices of emotional experience (Lewis 1994).

## Communicative Development

Biological, cognitive, and emotional development in infants during the first 2 months have implications for the infants' communicative behaviors. A wide variety of spontaneous behaviors in the neonate, including diffuse motility, crying, smiling, startles, and mouthing movements, guarantee that the infant has an impact in the environment. The recurrence

of these behaviors during the different states of sleep and wakefulness provides periodic opportunities to relate to significant others. As infants become better organized and more rhythmically regulated during the first 2 months, they also probably exert a more systematic impact on caregivers, who are highly attuned to interpreting who their infants are and what their infants' behavior means (Zeanah and Anders 1987). In fact, interaction with adult caregivers is frequently initiated by infants through enactment of simple, recurring behaviors that stimulate affiliative responses by adult caregivers.

Infants prefer human faces and voices to inanimate objects or to nonspeech sounds. Long before language symbols are available to infants, they are communicating interactively through crying, quieting, cuddling, looking, and occasional vocalizations. Caregivers, whose attributional processes are highly attuned to infant behaviors, respond to these communications and imbue them with elaborate meanings (Zeanah and Anders 1987).

### Social Development

Infants are wonderful projective stimuli. They elicit interest and responses from caregivers, who unconsciously change their behaviors to optimize interaction with the infants (Stern 1985). Facial expressions are exaggerated in time and space. Speech is modified by amplified syntax, short length of utterance, nonsense sounds, and transformations of consonants (i.e., motherese). Vocal pitch is exaggerated and sound intensity is varied more dramatically when caregivers communicate with infants than when they speak with adults. The speed of speech is generally slowed down, with brief eruptions of speeded-up utterances. Gaze is maintained by adult caregivers with infants for much longer periods than with adults. These changes in adult behavior are testimony to the socially evocative power of human infants.

Klaus and Kennell (1976) first popularized the term "bonding" to describe the parents' emotional ties to their newborn infants. Observations of newborns provide underpinnings of the argument that the first few hours after birth constituted a "sensitive period" for facilitating parental attachment to their children. These observations include the following: (1) a newborn left on its mother's abdomen will crawl to her breast, turn its head, find the nipple, and begin suckling within the first hour of life (Varendi et al. 1994); (2) a mother's ability to thermoregulate the baby's body temperature is as efficient as a high-tech heating device (Christensson et al. 1992); and (3) an infant cries less on its mother's chest than being dried, wrapped, and placed in a bassinet (Christensson et al. 1995). Providing or preventing an opportunity for parents to have intimate physical contact with their newborns has putative long-term effects on the parent–infant relationship. Although their assertions contributed to a useful demedicalization of the childbirth experience, they probably overstated the importance of the immediate period after birth and oversimplified attachment by dichotomizing it as present or absent. Early contact between parents and their newborns should be regarded as potentially helpful rather than essential.

Several studies have investigated the onset of parents' reported feelings of affection for their infants, although methodological problems make generalization difficult. There appear to be wide variations in onset of affection from the first trimester of pregnancy to several weeks after birth. The clinical significance of these findings is not established, although it is clear that most of the US mothers report feeling as if they love and have a relationship with their infants within the first several weeks after birth (Zeanah et al. 1990). There is also preliminary evidence that breast-feeding may facilitate these feelings, perhaps mediated by the release of oxytocin after the mother's breast is stimulated by the infant's lips (Nissen et al. 1992).

### Summary of Development in the First 2 Months

In contrast to earlier theories of development that held that the human newborn was disorganized, passive, reactive, or withdrawn, research on newborn behavior suggests a radically different view. Biological, cognitive, communicative, emotional, and social capacities, which are functionally integrated, enable infants to seek stimulation actively and to regulate their own behavior through interactions with the environment. The psychobiological endowment of infants at birth includes prewired knowledge of the world, such as cross-modal fluency, as well as a remarkable ability to detect and to remember invariant aspects of experiences. These capacities make the infant in the first 2 months of life a far more sophisticated social partner than most widely quoted developmental theories have recognized.

## 2- to 3-Month Transition

The first significant developmental transition occurs at about 2 to 3 months of age. A significant convergence of researchers, theoreticians, and clinicians have noted dramatic qualitative changes in infants that occur at this time. Stern (1985) has pointed out that parents also frequently remark about the qualitative change that occurs at this time because their infants become more focused, better organized, more communicative, and more enjoyable social partners.

### Biological–Neurological Development

Development of the central nervous system at the time of the 2- to 3-month transition is beginning to be studied. Brain growth which continues at a rapid pace after birth, results from growth of neurons and their connections. Growth of synapses in the cortex enters its most rapid phase from about 2 to 6 months of age. Again, synaptogenesis appears in association with functional development. For example, synapse formation in the auditory cortex precedes synaptic formation in Wernicke's area, which, in turn, precedes formation in Broca's area (Huttenlocher 1999). Midbrain–cortical visual pathways become myelinated at this time (Ceaser 1993).

Functional changes in the brain are also apparent after this transition at 2 months. Local rates of glucose metabolism, as determined by PET, are believed to represent an important window into brain functioning. Maturation of patterns of glucose metabolism is apparent for the first time in large parietal, occipital, and temporal areas after the 2- to 3-month transition (Chugani 1994), coinciding with improved visuospatial and visuomotor integration, the disappearance or reorganization of brainstem reflex behaviors, and evidence of increasing cortical contribution to the Electroencephalogram (EEG). In addition, electrophysiological research corroborates functional changes (Emde et al. 1976). Although we have not yet moved beyond global correlations between developments at the level of brain

functioning and newly appearing behavioral capacities, this is an area in which rapid progress may be anticipated within the next few years. At present, a host of changes in infant behavior and capacities at 2 to 3 months of age have biological correlates that are only partially elucidated.

One of the hallmarks of the 2- to 3-month transition is the social smile. Interestingly, evidence suggests significant genetic contributions to the onset of social smiling. Onset of social smiling is better predicted by the date of the last menstrual period than by the time elapsed since birth (Hofer 1981). Furthermore, monozygotic twins are more concordant for onset of social smiling than are dizygotic twins (Freedman 1974).

Another important maturational development for most infants is that the diurnal organization of sleep–wake cycles begins to appear at this time (Anders et al. 1983, 1985). Infants begin spending more of their time sleeping at night and having longer periods of wakefulness during daylight hours, probably as a result of maturation of internal pacemakers (Anders and Zeanah 1985).

Most investigators believe that after the 2- to 3-month transition, behaviors reflecting temperamental dispositions are apparent. All of the major theories of temperament endorse the idea that temperament is rooted in biological differences (Goldsmith et al. 1987). The most influential view has been that of Thomas et al. (1968) in the New York Longitudinal Study. They viewed temperament as a child's behavioral style, the "how" of behavior as opposed to its content or motivation, and they included dimensions such as activity level, intensity of emotional expression, adaptability to changes in routine, and the tendency to appraoch or avoid in novel situations.

A major advance in temperament research in the past two decades has been increased emphasis on behavioral assessment of temperament rather than parental report. Perhaps the most widely used laboratory assessment for tapping a broad range of temperamental dispositions for infants in this age range is the Laboratory Temperament Assessment Battery (Lab-TAB) procedure (Goldsmith et al. 1987). This allows for operationalization and standardized assessment of a number of important domains, including assessments of attention, inhibitory control, and positive and negative expression of emotions, among others.

Following the 2- to 3-month transition, temperamental differences begin to emerge more clearly than they had in the first two months (Rothbart 1981, Rothbart and Derryberry 1981). Rothbart's model of temperament derives from current empirical work in neuroscience, particularly the work of Davis (1992) and LeDoux (1987), to describe the neural systems involved in temperamental "fear." Also, she has used the neuroscience work of Posner (Posner and Peterson 1990), Tucker (Tucker et al. 1995) and others to describe the neural systems relevant to the development of attentional and cognitive systems involved in the regulation of fear, as well as describing constructs such as surgency (preferring high-intensity stimulation, extraverted, active, positive affect), negative affectivity (disposed towards anxious or irritable behavior), and effortful control (well regulated attention, prefers low-intense stimulation), and orienting sensitivity. One of the unique aspects of Rothbart's model is that temperament is not only a biological given present at birth but also as a developing individual difference that emerges across the period of early childhood. Individual differences in reactivity and in the processes involved in the control of such reactivity both fall under the purview of temperament (Rothbart and Bates 1998).

## Cognitive Development

At 2 to 3 months after birth, infants develop greatly enhanced cognitive capacities across a number of different types of learning. Infants demonstrate enhanced classical conditioning, operant conditioning, and habituation at about this time. In general, infants become more interested in a wider range of the world around them. Piaget (1952) designated this period of focus as that of secondary circular reactions as the infant behaves to make interesting spectacles last.

## Emotional Development

Further elaboration and development of the basic emotions of contentment, distress, and interest, which may be reliably observed in the first 2 months of life, begin after the transition at 2 to 3 months. By the time infants have reached 6 months of age, they exhibit a differentiation of contentment into joy and contentment, of interest into surprise and interest, and of distress into sadness, disgust, and anger (Lewis 1994).

Lewis (1994) has provided a timetable for the emergence of discrete emotional expression. Joy appears soon after the 2- to 3-month transition and is often elicited by familiar faces, voices, or events. Sadness appears at about the same time and has been reliably elicited in middle-class US infants when their mothers stop interacting with them. Disgust appears for the first time also, often in the context of an unpleasant new taste. As with the ability to demonstrate emotions, infants also acquire the ability to perceive emotions in a developmental fashion, relying initially on multimodally presented information, and then shifting to vocal recognition, and then to facial expressions alone (Walker-Andrews 1997). Context also determines the infants' ability to recognize emotions, with infants as young as 3.5 months able to recognize happy and sad expressions in their own mothers but not in unfamiliar women (Kahana-Kalman and Walker-Andrews 2001).

Anger is clearly evident somewhat late, perhaps between 4 and 6 months of age, although it has been demonstrated as early as 2 months in specially designed experimental situations (Lewis et al. 1990). Because it includes a response designed to overcome some obstacle to a goal, the emergence of anger must be closely tied to the cognitive capacity needed to appreciate the relationship of a means to an end (Lewis 1994). This suggests that at least a limited form of means-end differentiation must be available to human infants even before 7 months of age.

During this period, the infant is also learning strategies from caretakers about regulating emotion. Emotion-regulation, defined as an individual's attempt to monitor, evaluate, and modify their internal emotional reactions (Thompson 1994), and emotion-related behavior regulation (Eisenberg 1997), defined as the modulation of the overt expression of emotion, serve as regulatory attempts to monitor internal, emotional states and external, emotional displays in a goal-directed attempt to regulate response. Because of the relational context of emotion expression in early infancy, emotional regulation at this point in time is both a within-the-infant and a relational property.

## Communicative Development

Communicative behavior of infants changes after the 2- to 3-month transition. Infant vocalizations become more clearly social as infants begin to react to vocalizations from others and to coo responsively. Patterns of turn-taking in vocalizations begin to appear at this time, suggesting far greater appreciation by infants of the behavior of their interactive partners.

Expressive communication at 2 to 3 months includes production of several different vowel sounds (e.g., ah, eh, uh) as well as some simple mutual imitation. Coos, squeals, and screams appear at about 2 months, followed by consonants at 4−6 months, as infants begin to babble (canonical babbling) using repetitive syllable sequences, such as da-da-da (McCormick 1984).

Advances in receptive language are apparent after the 2- to 3-month transition, as well. In addition to the enhanced ability to take into account the behavior of others, infants begin to localize the source of voice sounds and noisemakers. They attend and respond differently to different affects in caregivers, such as anger and playfulness (McCormick 1984). At this early age, the infants' perceptual abilities for speech are impressive. They can already recognize the same speech sound when spoken by different speakers and at different rates (Jusczyk 1999).

These enhanced receptive and expressive communicative capacities are central components of a blossoming of social behavior that appears concurrently. Essentially, these changes in communicative behavior make possible a qualitative advance in infants' abilities as social partners.

## Social Development

Enhanced eye-to-eye contact, diminished crying, more sustained wakefulness, periods of quiet alertness, and blossoming of the social smile all contribute to a sense of the infant as a more playful and engaging social partner after the 2- to 3-month transition. Therefore, it is not surprising that a great deal of attention has been paid to infants' social behavior in the period from 2 to 7 months. Individual differences in infant–parent interactive behaviors, as measured by features such as matching emotional states, synchrony, reciprocity, and turn taking, have been related to infants' cognitive competence (Barnard et al. 1989), emotion regulation (Lyons-Ruth and Zeanah 1993), language development (McCormick 1984), and sense of self (Stern 1985).

Infants who are interacting with their caregivers between 2 and 7 months engage in alternating periods of engagement and disengagement, or time-outs. The interactive pattern of a dyad may be thought of as a mutual feedback system in which each partner's behavior affects the other's in ongoing transactions over time (Beebe et al. 1985, Cohn and Tronick 1988). Infants are more likely to respond to changes in their mothers' behaviors if mothers are more responsive to changes in their behavior (Cohn and Tronick 1988) and able to interpret their infants' emotions accurately.

What sustains play periods or social interaction for infants at this age is maintaining the level of stimulation within some optimal range. If caregivers provide too little feedback, infants lose interest and turn their attention elsewhere. If caregivers are too stimulating, infants avert their gaze or otherwise interrupt or even terminate the interaction until the stimulation is reduced to a level that they can tolerate.

Although much of the literature on infant–parent interaction has emphasized matching affective states, infants and their caregivers actually spend little time in matching states, even when observed in situations designed to maximize opportunities for interaction. This observation led Tronick and Cohn (1989) to speculate that infants' coping strategies are challenged by their efforts to effect repair of mismatching affective states and interactive errors. These efforts would then stimulate efforts to attain reparation and effectance. Some studies have demonstrated links between individual differences in infants' emotion regulation efforts at this age and subsequent development. For example, infants who used more positive efforts to elicit responsiveness from their mothers (when the mothers had been instructed to refrain from responding) were more likely to be securely attached at 1 year of age (Cohn et al. 1991). Not surprisingly, infants who were more positive also had mothers who were more sensitive in their caregiving responses (Kogan and Carter 1996).

Depressed mothers often are unable to match positive affective displays with their infants. Presumably, this leads their infants to display more negative and less positive affect (Cohn et al. 1986). In addition, this pattern generalizes to nondepressed strangers (Field et al. 1988), but not to nondepressed fathers (Hossain et al. 1994). Infants of depressed mothers also demonstrate atypical right frontal brain electrical activity, known as right frontal EEG asymmetry, as early as 1 month of age (Dawson et al. 1999, Jones et al. 1997).

Repeated patterns of social interaction are remembered and even anticipated by infants between 2 and 7 months. If mothers are instructed not to respond to infant displays by keeping their faces "still," infants exhibit negative affect and behavioral dysregulation (Cohn and Tronick 1988). These early interactions also seem to be internalized by the infants and lead to later positive reciprocity. An observation of maternal sensitivity behavior at 3 months correlated with infants' positive mood, social and play behavior, and visual contact. These findings were replicated at 12 months. Statistical analysis showed that infant behavior at 3 months of age contributed to later maternal sensitive behavior (Kivijärvi et al. 2001) The nature of these early social expectations is believed to have great importance in influencing the way infants anticipate and experience intimacy in later relationships (Stern 1985).

## Summary of the 2- to 3-Month Transition

Dramatic changes in developmental capacities across a number of domains appear between 2 and 3 months after birth, changing both infants' behavior and the behavior of caregiving adults. All of these changes enhance infants' appeal to others as a more responsive and enjoyable social partner. The nature of caregivers' responsiveness to infants is associated with relationship characteristics that probably have far-reaching implications for infant development. Infants' efforts at adaptation within the goal-correcting system of interaction with their primary caregivers provide an early feel for what it is like to be with another in an intimate relationship.

## 7- to 9-Month Transition

At 7 to 9 months, another major developmental transition occurs. This has been one of the best studied transitions from biological, cognitive, communicative, and socioemotional perspectives. Emde (1984) has termed this shift the "onset of focused attachment," and Stern (1985) has termed it "the discovery of intersubjectivity." Both of these conceptualizations call attention to the enhanced importance of subjective experience for infants that develops at this time.

### Biological–Neurological Development

Evidence for changes in brain development at this time is extensive. As Fischer and Rose (1994) have pointed out, these include changes in electroencephalographic frequency, power, and coherence; changes in patterns of glucose metabolism documented throughout PET techniques; and a spurt in head circumference and brain growth (Bell and Fox 1992, Chugani and Phelps 1986, Epstein 1974, Fischer 1987). Increased glucose requirements also coincide with the expansion of dendritic fields and the increased capillary density observed in the frontal cortex during this time (Diemer 1968, Schade and van Groeginen 1961). Research also has demonstrated that selected portions of the limbic system are myelinated at this time (Ceaser 1993). These documented changes are all compatible with a hypothesized qualitative change in central nervous system functioning that may be associated with other qualitative changes in motor, cognitive, emotional, and social domains of development.

Fischer and Rose (1994) have suggested that biological changes along with other developmental advances at these times must include connections between the frontal cortex and other regions because more sophisticated cognitive and communicative skills require coordination of components, which is a frontal region activity. In keeping with this reasoning, a new rise in glucose metabolism in the frontal lobes occurs at the time of the 7- to 9-month transition (Chugani 1994). Also, Bell and Fox (1992) demonstrated that both EEG frequency and coherence change at this time of transition, implying that they reflect improved inhibitory control of the prefrontal cortex and enhanced associative pathway links. Having more sophisticated coordination of pathways probably makes possible the qualitatively different behavioral advances that are apparent at this time.

With regard to temperament, individual differences in the second half of the first year and first half of the second year may be a bit more stable than in the first 6 months of life, although the absence of an agreed-upon "gold standard" assessment procedure has limited interpretability of findings. The general trend is for parental convergence about temperamental differences to increase during this time, although lack of convergence between parental report and observer ratings of temperament remains a formidable challenge (Seifer et al. 1994).

### Cognitive Development

In the cognitive realm, dramatic advances are apparent. Infants are now able to use one scheme as a means of obtaining another scheme that is the desired goal. For example, infants know that that they can pull a string to reach an attractive toy to which the string is attached. This means-end behavior is the prototype of all later problem-solving behavior. In addition, infants demonstrate object permanence; that is, infants purposefully remove a cloth covering a hidden object that seems to have disappeared under it. This suggests that infants possess an enhanced ability to retain a mental image of the absent object.

This enhanced capacity has been used to explain the development of stranger reaction and separation protest, which appear for the first time after the 7- to 9-month transition. Infants begin to protest separations from their primary caregivers and react with increased wariness or outright distress when approached by unfamiliar adults.

Also, in the cognitive realm, infants begin for the first time to explore novel properties of objects and to pursue novelty for its own sake. The notions of causality advance, and infants at this age develop a clearer understanding of the independence of objects and that these objects carry with them their own properties. Infants also begin to experiment with different ways of accomplishing goals when their efforts are thwarted (Piaget 1952).

A tendency for infants to explore the unfamiliar and to attempt to master challenges through repeated practice appears in the latter part of the first year and has been termed "mastery motivation." Mastery behaviors are believed to reflect an innate motivational system in human infants. As assessed in the laboratory, mastery has been shown to be stable over months and to be predictive of subsequent cognitive performance (Messer et al. 1986). In addition, mastery behavior is related to maternal feedback and control at 24 months (Kelley et al. 2000). Mastery appears to represent early indicators of competence, although most efforts to capture these behaviors in the laboratory have been focused on cognitive rather than social competence.

Progress toward symbolic or pretend play begins to emerge after the 7- to 9-month transition, although true pretend play does not appear until after the 18- to 20-month transition. Whereas before 9 months, infants' play with toys consists largely of banging, mouthing, or visually inspecting them, by about 12 months functional play appears. At this age, infants may hold a telephone receiver properly, then let it go, or hug a baby doll. Over the course of the next 6 months, other-directed play generally increases until true pretend play emerges.

Perhaps the most important cognitive development in terms of its social and emotional implications for the infant is the discovery of intersubjectivity (Trevarthen 1979). This refers to a variety of changes in infant behavior that seem to indicate that infants now understand that their own inner experience, that is, their thoughts, feelings, and desires, can be appreciated by and shared with others. The ability to share thoughts and feelings with others represents a monumental discovery for infants, with far-reaching implications for the development of empathy and the subjective experience of intimacy.

### Emotional Development

One of the more important clinical and developmental phenomena that intersubjectivity makes possible is "affect attunement" (Stern 1985). Affect attunement between mother and infant involves an emotional interchange in which the mother matches her behavior to the infant's behavior. This matching is not imitative; rather, it involves some aspect of an internal feeling state that is shared. Single occurrences

of affect attunement appear at 2 to 4 months and become more common than imitation by 6 months, and eventually the dominant mode of relating by 8 months (Jonsson et al. 2001). Affect attunement appears to be an essential ingredient of empathy, intimacy, mirroring, and other clinical phenomena.

Emotions begin to be used instrumentally for the first time after the 7- to 9-month transition (Emde 1984). Smiling and pouting expressions mark infants' efforts to get their own way. For the first time, anger is often purposefully directed toward another person. Parental report studies have suggested that parents as well as observers note that infants begin to use affects as a means to an end toward the latter half of the first year (Klinnert et al. 1983).

Infants also begin to detect and share affective states with their social partners. Social referencing describes infants' use of cues from others to resolve affective uncertainty (Moses et al. 2001). If a mother and her 1-year-old are in a playroom and a noisy and flashing robot advances toward the infant, the infant looks at the mother's face. If the mother smiles encouragingly, the child is likely to smile and to perhaps approach the robot. If the mother looks frightened, on the other hand, the infant is likely to cry or approach the caregiver for comfort. Infants are just as likely to reference their fathers as their mothers (Hirshberg and Svejda 1990), and they also adapt different strategies with each parent (Bridges and Grolnick 1998). There is additional evidence that infants also use fearful maternal vocalizations even when unaccompanied by matching facial features (Mumme et al. 1996).

Mahler et al. (1975) suggested that exuberance and joy are the dominant emotions around 1 year of age, noting that infants at this age also demonstrate a relative imperviousness to frustration. These observations have not yet been subjected to any attempt at empirical confirmation.

## Communicative Development

The importance of intersubjectivity for communicative development cannot be overstated. After the 7- to 9-month transition, infants begin to behave not only as if they understand others but also as if they anticipate that others will understand them. Infants younger than 7 months may reach for desired objects, but they do not check back to the caregiver's face in an appeal for help. After 9 months, infants behave as if they attribute to the other person comprehension of their own intention and the capacity to satisfy their intention. This builds on their capacity of parsing dynamic actions into initiation and completion of events (Baldwin et al. 2001).

The emergence of intentional communication is one of the hallmarks of the 7- to 9-month transition, with major implications for the infant's new appreciation of both self and other. In contrast to Mahler et al. (1975), who viewed infants at this age as only beginning to emerge from symbiotic unity with their mothers, Stern (1985) has argued convincingly that it is only after infants develop intersubjectivity that they can even conceive of the kind of unity that Mahler presupposes to be present at birth.

Advances in symbolic functioning after the 7- to 9-month transition also have communicative implications. Infants understand by 8 to 10 months that a word is agreed upon to designate a specific object, a specific phonetic form for a specific object. By 1 year of age, infants may have an expressive vocabulary of a few words, although gestural communication dominates in interactions until the latter part of the second year (McCormick 1984). Language development does not occur in isolation, it requires effort and engagement (Bloom 1998). For example, maternal responsiveness at age 9 and 13 months predicted the timing of children's achieving language milestones over and above children's observed behaviors (Tamis-LeMonda et al. 2001).

Previous exposure to language also affects how language continues to be perceived. For example, newborns and toddlers less than 8 months of age can discriminate among all the phonetic units used in the world's languages regardless of the language environment in which they will be raised. However, previous exposure to a specific language affects future perception of linguistic phonemes. At 7 months of age, Japanese infants equally discriminate between American English "r" and "l," but by 10 months of age, they have lost this ability (Kuhl 1999). Also, at 6 months of age, infants do not show preference for native speakers or native stress patterns, while they do so at 9 months of age.

## Social Development

Of course, biological, cognitive, emotional, and communicative developments at the 7- to 9-month transition have major implications for infants' social development. Stern (1985) has emphasized that what infants discover at the 7- to 9-month transition is that their own inner subjective experiences may be shared with someone else. Intentional communications via gestures that convey "I want a cookie," affective sharing that conveys "This is exciting!" or joint referencing that conveys "Look at this toy" are all evidence of that intersubjectivity. When this occurs, interpersonal relatedness has moved in part from overt actions and responses to internal subjective states lying behind the actual behaviors. Stern (1985) has emphasized that infants not only feel different to others but also experience others differently. At this point, infants not only experience caregiver empathy through overt behavioral responses but also directly experience the subjective empathic process of which these responses are only a part.

There is also another monumentally important social development at this time—the infant "falls in love." Although the attachment relationship between the caregiver and the infant begins to develop at birth, it becomes increasingly focused during the latter half of the first year. Attachment describes a tendency for human infants to seek comfort, support, nurturance and protection from one or more discriminated caregivers. The tendency for selective seeking of comfort is not apparent at birth, however. Following a period of sociability and comfort with a wide range of adult caregivers during the first 6 months, two new infant behaviors appear: stranger wariness and separation protest, both at about 7 to 9 months of age. Stranger wariness describes an apparent discomfort with unfamiliar adults and selectively turning to those they know and trust for comfort. Separation protest refers to the infant's new tendency to protest separation from familiar caregivers. Although individual differences in the intensity and expression of these behaviors is clear, they may be considered virtually ubiquitous. When these behaviors appear, the infant is said to be attached to one or more caregivers.

Under species-typical rearing conditions, all infants become attached to caregivers. Research has demonstrated clearly that the quality of infants' attachments to one or more caregivers is predictive of subsequent psychosocial adaptation. By the time the infant is 1 year old, the quality of the attachment relationship to a particular caregiver can be measured categorically. A laboratory procedure known as the Strange Situation Procedure (SSP) involves observing how 11month transition to 20-month old infants organize their behavior around attachment figures when they are mildly stressed by being in a strange room, encountering an unfamiliar adult, and being left briefly by their attachment figure (Ainsworth et al. 1978). The most important parts of the procedure from the standpoint of classifying the infant's attachment relationship are the two reunion episodes between infant and caregiver after separation. Qualitatively different patterns of infant to caregiver attachment have, as assessed by the (SSP), have been replicated in studies conducted throughout the world. These patterns include secure attachment, and several forms of insecure attachment, including avoidant, resistant, and disorganized attachment. Table 8–4 provides a list and description of infant attachment patterns.

Caregivers support infant attachment through two forms of emotional and behavioral responses. Secure base behaviors by the caregivers support the infant's moving out into the world to explore. Safe haven behaviors by the caregivers support the infant's need to return for comfort, support, and nurturance. Securely attached infants demonstrate a fluid and responsive balance between these two tendencies. Later in development, this balance between exploration and attachment becomes a balance between the individuals' need to balance independent functioning with a need to rely on others.

Infants who lack a coherent strategy of emotional and behavioral regulation during reunion episodes are classified as disorganized. Caregiving behavior predictive of this classification is characterized as being either frightened or frightening. That is, the caregiver behaves in ways that make the infant feel afraid of or fearful about the caregiver's emotional well-being. In addition, broader indices of caregivers' disrupted affective communication with their young children, including high levels of expressed emotion, have been linked to disorganized attachment in young children.

Attachment classifications are not within-child traits (as temperament is believed to be); instead, these classifications summarize salient features of the relationship pattern between an infant and a particular caregiver. The clearest evidence for this is that infants' attachment classifications with different caregivers may be different (Fox et al. 1991). Moreover, Steele and associates (1993) identified differential characteristics in mothers and in fathers prenatally that were predictive of mother–infant and father–infant attachment measured more than a year later.

Secure attachment is perhaps best considered as a protective factor against the development of psychopathology. For example, infants classified as securely attached to their primary caregivers at 12 and 18 months are more developing more favorably emotionally and behaviorally in preschool, school age, and adolescence (Weinfield et al. 2000). At present, one of the best indicators in infancy of later adaptation is the security of the infant's attachment classification to the primary caregiver as measured by the Strange Situation Procedure.

In terms of risk for psychopathology, the strongest links have been demonstrated between disorganized attachment and psychopathology rather than any other types of insecure attachment. Disorganized attachment has been demonstrated to predict a variety of externalizing and internalizing problems concurrently and in later childhood and adolescence. Still, attachment relationship experiences are more clearly related to psychopathology when considered in the context of other risk factors. What is far less clear, are the mechanisms involved linking attachment relationship experiences and psychopathology.

After 7 to 9 months of age, almost all infants will demonstrate discriminated attachments to one or more trusted adults. For infants raised in extremely adverse caregiving environments, however, such as in severely neglectful homes or in institutions, attachment may be seriously compromised or even absent (Zeanah et al. 2004, Zeanah et al. 2005). Reactive Attachment Disorder (RAD) describes a constellation of aberrant attachment behaviors and other social behavioral anomalies that are believed to result from social neglect and deprivation. Two clinical patterns have been described: an emotionally withdrawn/ inhibited pattern and an indiscrimately social/disinhibited pattern. In the

**Table 8–4 Patterns of Attachment**

| Characteristics | Secure Pattern | Avoidant Pattern | Resistant Pattern | Disorganized Pattern |
|---|---|---|---|---|
| Distress | Open display of distress and need for comfort | Inhibited display of distress | Exaggerated display of distress | Odd or contradictory display of distress |
| Soothing | Effective soothing; positive greeting | No soothing; avoidance instead of greeting | Ineffective soothing; no positive greeting because of distress | Ineffective soothing; usually no positive greeting; often odd or ambivalent greeting |
| Anger | Little angry behavior | Displaced anger | Angry, resistant behaviors | No predictable pattern |
| Stress | Low cortisol secretion | High cortisol secretion | No cortisol data | No cortisol data |
| Strategy for obtaining comfort | Coherent strategy of seeking comfort directly when needed | Coherent strategy of minimizing distress by displaced attention | Coherent strategy of exaggerating distress to mobilize caregiver | Incoherent strategy or significant lapse in organization of strategy |
| Parental characteristics | Sensitive, emotionally available caregiving; balanced perspective on childhood relationship experiences | Emotionally restricted caregiving; dismissing of painful relationship experiences and their effects | Inconsistent caregiving; unintegrated emotional response to relationship experiences | No data on caregiving; unresolved losses or traumatic childhood experiences |

emotionally withdrawn/inhibited pattern the child exhibits limited or absent initiation or response to social interactions with caregivers and aberrant social behaviors, such as inhibited, hypervigilant, or highly ambivalent reactions. This type seems to be equivalent to the absence of a discriminated attachment figure. In the indiscriminate pattern, the child exhibits lack of expected selectivity in seeking comfort, support and nurturance, with lack of social reticence with unfamiliar adults and a willingness to "go off" with strangers. This pattern often remains even after the child develops one or more discriminated attachments.

### Summary of the 7- to 9-month Transition

Infants emerge from this period of developmental transformation quite differently than when they entered it—in cognitive, communicative, emotional, and social terms. After the 7- to 9-month transition, infants act as if they understand that their thoughts, feelings, and actions can be understood by another person, and they have strong preferences for caregivers with whom they have established relationships. The dual capacities for intersubjectivity and focused attachment underlie the specific changes in capacities that develop at this time. These changes continue to develop and to be refined throughout the next year, but their appearance for the first time after the 7- to 9-month transition makes infants at this age qualitatively different social experiencers and agents (Stern 1985). Under usual circumstances, after 7 to 9 months, infants have developed a strong preference for turning to a relatively small number of caregiving adults for nurturance and comfort. By having their caregiver function as a secure base from which to explore their environment and other relationships, and a safe haven to which they can return during periods of stress, they can use more sophisticated motor capacities for independent locomotion to explore the world exuberantly.

## 18- to 20-Month Transition

The final transition period of major reorganization in infancy occurs at age 18- to 20-months. Although this transition is marked dramatically by the appearance of language, it is actually the qualitative change in symbolic representation that underlies the child's remarkable advances in language, cognition, affect, and social functioning at this age. These advances predate the evolution of infants' moral development, which burgeons after the 18- to 20-month transition. After this transition, much of what follows in the third year involves further elaboration, refinement, and consolidation of the functions that emerge during the transition.

### Biological–Neurological Development

Much remains to be learned about specific dimensions of brain development at 18 months and about the relationships between this development and changes in behavior at this time. Evidence suggests that there are important associations between changes in central nervous system structure and function and the spurt in capacities noted to appear in other domains of development across the period of reorganization.

One of the important spurts of brain growth in the first 2 years of life occurs at about 10 to 20 months and is due to myelination and to synaptic growth and pruning. Density of dendritic spines, which represent sites of synaptic contact, decreases postnatally and almost reaches adult levels by 21 months of age (Huttenlocher 1994). Myelination of structures associated with language occurs at this time (Ceasar 1993). Associated behavioral changes need to be studied in relation to these anatomical developments.

Functional changes are apparent as well. Although local cerebral metabolic rates for glucose in infants qualitatively resemble those of adults by 1 year of age, they typically reach levels comparable to those of adults in the second year (Chugani 1994).

Discontinuities in event-related potentials between 13 and 20 months have been documented in association with processing of language. Specifically, by studying differential responses of brain electrical activity to comprehended unknown words, investigators have demonstrated that different parts of the brain are involved in language comprehension (Mills et al. 1994). Whereas diffuse patterns of activity were widely distributed over the anterior and posterior parts of both hemispheres before 18 months, by 20 months they had become more localized to temporal and parietal regions of the left hemisphere.

These data suggest increasing lateral and anterior–posterior specialization of brain systems responsible for language comprehension at the 18- to 20-month transition. In fact, individual differences in language competence have been associated with the degree of specialization of brain function (Mills et al. 1994).

In the realm of temperament, behavioral inhibition is a trait that has been reliably identified after the 18- to 20-month transition. Kagan et al. (1987) have suggested that behavioral inhibition to the unfamiliar characterizes about 10% of middle-class white 2-year-olds and is counterbalanced by a roughly equal number of children deemed uninhibited. Descriptively, uninhibited infants strongly avoid novel stimuli. Kagan et al. (1987) have suggested that despite the poles of inhibited and uninhibited, behavioral responsivity in the face of novelty does not represent a continuum. Instead, they believe that behaviorally inhibited children represent a qualitatively different group. In support of this assertion, they have demonstrated stability of the trait for 4 years and associated it with physiological activation of the hypothalamic–pituitary–adrenal axis, the reticular activating system, and the sympathetic arm of the autonomic nervous system (Kagan et al. ). In addition, infants who remained continuously inhibited displayed right frontal asymmetry as early as 9 months of age (Fox et al. 2001), which in turn, is especially predictive of social wariness at age 4 years (Henderson et al. 2001). Behavioral inhibition is associated with increased incidence of social withdrawal and internalizing behaviors in early and middle childhood and possibly predisposes to anxiety disorders in adolescence. A number of studies have shown that inhibited children are more likely than their uninhibited peers to display symptoms of anxiety (Biederman et al. 1993, Hirshfeld et al. 1992, Schwartz et al. ). Thus, behavioral inhibition is a heritable trait that is mediated through central and peripheral nervous systems and predisposes infants to anxious and inhibited behavior in a variety of novel contexts.

### Cognitive Development

A qualitative advance in symbolic representation at 18 to 20 months is believed to be the central cognitive development occurring at this time. More sophisticated symbolic

representation makes possible significant advances in infants' understanding of causality, including the ability to infer causes based on observed effects and to anticipate effects based on their actions. They are also able to remember specific past events and sequences even when no sign of the event or sequence remains. This capacity allows the infant access to two versions of the same reality: a representation of the original act as performed by the other and a representation of their own anticipated performance of the act. This seems to require some representation of the self as on objective entity.

In fact, Lewis and Brooks-Gunn (1979) and Kagan (1981) have provided evidence of the emergence of an objective self at 18 months. Experimental studies have demonstrated toddlers' clear facial recognition of themselves in mirrors, in still photographs, and in videotapes. In addition, self-awareness has been demonstrated by self-descriptive utterances, by a variety of gestural directives, and by emotional reactions to success or failure. Personal pronouns begin to be used at this time. Gender identity appears to consolidate at this point, although it is not until about age 5 years that children attain gender constancy wherein they recognize gender is an immutable characteristic of the individual (Gouze and Nadelman 1980).

A further dramatic implication of symbolic representation occurs in the realm of pretend play. Whereas younger toddlers' play is generally self-directed, by the time a child is 18 months, the play has become progressively more other directed and is more sustained. True pretend play emerges at this time and becomes progressively richer and more complex. The importance of all these advances is that infants can, for the first time, entertain and maintain a formed wish of how they would like reality to be, even if this is different from fact (Stern 1985). Internal experience of social interactions now includes wishes that involve past memories, present realities, and expectations of the future.

The gains of symbolic representation continue to be extended and refined after 18 months. By about two years of age children begin to compare themselves to various evaluative standards, such as "I am small" or "I am pretty." Children move into Piaget's preoperational stage in the third year of life. By this time, they have advanced sufficiently that we may consider the ways in which their thinking differs from that of adults. Piaget's work reminds us, for instance, that children's judgments are limited by their perceptions of objects and events and that they have difficulty attending to more than one perceptual attribute at a time (Piaget 1952). Furthermore, egocentrism describes children's difficulty viewing events in another perspective than their own. Similarly, toddlers at this age may have some difficulty differentiating between subjective experiences and objective reality. Piaget also noted that toddlers use transductive reasoning in which events are believed to be causally related merely by temporal or spatial juxtaposition.

The development of a toddler's ability to recall experiences of the day and the way the self should look require a memory with more elaborate processes than implicit memory. Paralleling the maturation of the medial temporal lobe and the orbitofrontal cortex, this ability allows the child to have the internal sensation that "I am remembering something about 'me'." This ability also requires the increased ability to sequence (possibly a hippocampal function). This nonimplicit or explicit memory can be divided into memory for facts (semantic memory), also known as noetic knowledge, and facts about the self (episodic memory), also known as autonoetic knowledge. There is preliminary neuroimaging evidence that these types of memory are functionally quite distinct (Wheeler et al. 1997).

## Emotional Development

Emotional development at 18 months has been less carefully studied than cognitive or language development. The observational studies of Mahler suggest that exuberance and ebullience of the previous 6 months change as infants become more irritable, more somber, and more clingy. Mahler et al. (1975) view this as evidence of the rapprochement crisis in which toddlers are seen for the first time aware of their own relative powerlessness and ineffectiveness. Stern (1985) has noted that the somberness and irritability of this period derive from the toddlers' sense of verbal estrangement from their own experience (Stern 1985). That is, their well-developed sense of their own subjective experiences as lived cannot yet be adequately represented by language, leading to observable frustration and emotional turmoil. Nevertheless, it should be pointed out that there have not been systematic investigations validating the observations on which Mahler's and Stern's explanations are based, although this remains an important area for future research.

Some of the most important work on emotional development at this transition is that of Lewis et al. (1989) on the emergence of self-conscious emotions, including the emotions of embarrassment, empathy, and envy. They appear not to emerge until the toddler demonstrates self recognition at about 18 months. Lewis (1994) also asserts that the cognitive development of comparing one's behavior to an evaluative standard, which probably appears at around 24 months of age, is required for the development of self-conscious evaluative emotions such as guilt, pride, and shame.

Attachment relationships between young children and their caregivers are transformed following the 18- to 20- month transition. The appearance of expressive language, and the enhanced capacity of young children to be aware of the other's perspective, means that young children must learn to negotiate in order to have their needs met. In attachment terms, the secure base function of parents allows the child to interact more independently with peers and other adults. The safe haven function provides support for the child following separations. In the third year of life, young children are gradually able to sustain relationships in absence of frequent contacts but they still need emotional availability and reasonably frequent contact (especially verbal). Extended separations from primary attachment figures remain risky for the young child's well being.

## Moral Development

Emde et al. (Emde and Buchsbaum 1990, Emde et al. 1988) have considered the implications of cognitive and emotional advances at the 18- to 20-month transition for the development of morality. Toddlers at this age are able to generate and monitor their attainment of their goals much more competently than before. They are also able to construct value labels and normative standards based on the evaluation of others (Kagan 1981) and to react with distress to violations of these standards, including broken toys and disapproved-of behaviors (Lyons-Ruth and Zeanah 1993).

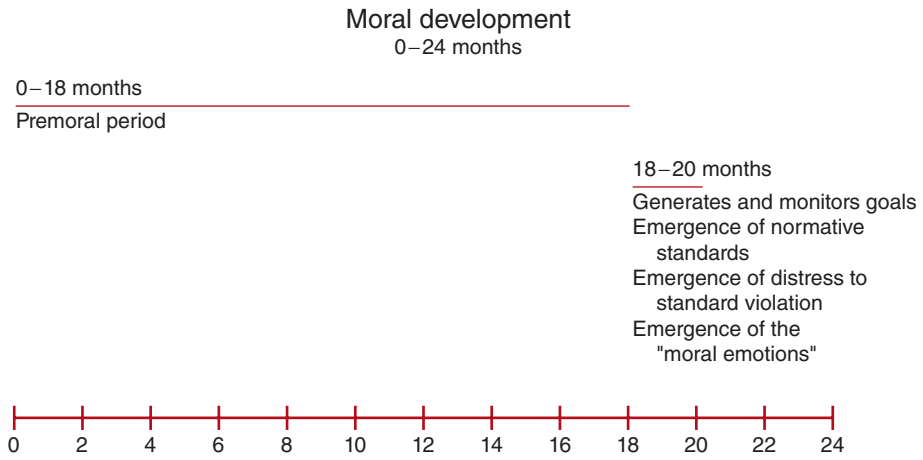



**Figure 8–5** *Moral development during the first 2 years of life.*

The emergence of the "moral emotions" of embarrassment, empathy, pride, envy, shame, and guilt at this age are core accompaniments of these various cognitive manifestations of moral development. These emotions have important implications for the infant's subjective experience of morality (Figure 8–5).

By about 24 months of age, infants begin to demonstrate an internalization of parental standards in the presence of parents, although consistent demonstrations of this in their parents' absence probably do not occur until at least 36 months of age (Emde et al. 1988). Of course, different parental styles are associated with important individual differences in moral development. Considerable evidence in the US families suggests that power-assertive strategies by parents are associated with an increase in children's defiant behavior, whereas reasoning and negotiating on the part of the parent facilitate internalization of the parent's standards (Lyons-Ruth and Zeanah 1993). Committed compliance, a child's eager embrace of the parental agenda rather than situational compliance, a demonstration of compliance that lacks sincere commitment to parental agenda, has been demonstrated in children as evidence of internalization of parental standards; as committed compliance was observed in situations where the child was alone, whereas situational compliance was not (Kochanska et al. 2001).

## Communicative Development

Language makes possible a dramatic advance in the infant's capacity for relatedness with others. Considerable variability in language production is so common that it is difficult to describe modal patterns. At 18 months, the US toddlers have a median expressive vocabulary of 50 words with a range of less than 10 for those at the 10th percentile to more than 200 words for those at the 90th percentile. Toddlers use word-initial or partial information to understand fluent speech, and the more words they know predicts their accuracy and speed in identifying these words, demonstrating incremental speed processing even before entering the vocabulary spurt (Fernald et al. 2001). Short-term stability in expressive language is high, but the long-term implications of differences at this age are largely unknown (Fenson et al. 1994).

Toddlers use words for a variety of different social functions between 18 and 24 months. Although language comprehension generally precedes production, Bretherton and Bates (1979) found that the magnitude of the gap varied considerably from child to child. New evidence suggests that some infants produce word utterances before they understand the meaning of the utterances, so that comprehension of a particular word does not always precede production of that word.

By age 24 months, the US toddler has a median expressive vocabulary of about 200 words with a range of less than 50 for those at the 10th percentile to more than 500 words for those at the 90th percentile (Fenson et al. 1994). They begin to combine two or more words and to recognize that the combination means more than either word can convey in isolation. Nevertheless, toddlers' comprehension remains heavily dependent on social cues, as most parents who attempt to have their 2-year-olds "talk to grandma" on the telephone can attest. As toddlers' language learning progresses, they begin to realize that different forms of messages have different effects on different listeners. Two and 3-year-olds are beginning to infer what listeners know and do not know because they ask significantly more questions when interacting with adults instead of peers, simplify their speech when talking to younger children, and whine almost exclusively in the presence of their parents.

To summarize, all infants progress from cooing to canonical babbling to words to two-word utterances and eventually to meaningful speech. The progression of this development is conserved; however, the timing of each stage is dependent on biological and especially on environmental influences, especially the amount of direct and engaging speech the child is exposed to. As the child begins to develop more proficiency in the realm of his environmental language, his ability to perceive, discriminate, and reproduce nonnative speech begins to decline. Stern (1985) has pointed out that a toddler is on the way to being able to narrate his or her own life stories. This carries with it numerous possibilities for changing one's view of oneself. What toddlers tell in stories about themselves and how they tell these stories probably have crucial developmental implications.

## Social Development

Symbolic representation permits the child to appreciate social relationships more. Most theories of development have emphasized conflicts between toddlers and their

caregivers because of an increasing move by infants toward autonomy. Interestingly, however, as famous as the "terrible twos" are, there have been no investigations that have addressed the question of difficult behavior in 2-year-olds and whether or not it differs systematically from difficult behavior in 1- or 3-year-olds. A number of contextual factors are probably important, and it is plausible that different infants and toddlers are perceived as more or less challenging at different ages by different parents. As one example, Crockenberg (1987) found that adolescent mothers who had both experienced rejection in childhood and received little support from partners after the birth of their infants were more likely to be angry and punitive with their toddlers; toddlers, in turn, were angry and noncompliant and distanced themselves from their mothers.

In the third year of life, toddlers become far more aware of their relation to others in group and are more sensitive to being included or excluded. Along with increasing independence, toddlers develop a sense of personal space and possession (Emde 1984). At this age, toddlers are able to perceive their own self-efficacy (Bandura 1981). Social relationships, especially attachment relationships, become increasingly important referents for children's self-appraisal. Sroufe and Matas (Matas et al. 1978) showed that 2-year-old children with secure attachments to their primary caregivers showed more competent autonomous functioning in stressful problem-solving situations. In preschool years, securely attached infants were more socially competent and more ego-resilient than anxiously attached infants (Arend et al. 1979, Waters et al. 1979).

With peers, children begin to move from having little to do with others to engaging in complex and mutually cooperative play. In naturalistic observations of interactive play, parallel play (in which children played in proximity but without interaction) emerged at around 18 months but did not become common until the end of the second year. Episodes of fleeting contact, which contained a clear invitation to interaction but were not sustained beyond one- or two-step exchanges, also emerged as early as 18 months but were more common in the third year (Whiteside et al. 1976).

Dominance hierarchies appear in the third year, presumably as means of controlling aggression. Aggressive interchanges in children's groups occur almost exclusively among members who are quite close to one another in the hiearchy. This implies, of course, that children are able to detect and respond to subtle social cues about relationships. Troy and Sroufe (1987) demonstrated the behavioral manifestation of such detection by studying patterns of victim–victimizer in pairs of preschool children. They found, as predicted, that children with a history of secure attachment in infancy were neither victims nor victimizers, whereas children with a history of avoidant attachment were always engaged in victim–victimizer interactions when paired with another insecurely attached child.

### Summary of the 18- to 20-Month Transition

Infants change profoundly during the 18- to 20-month transition. New biological developments appear to make possible significant advances in symbolic representation, which are in turn associated with dramatic cognitive, emotional, communicative, and social advances. Infants are substantially more verbal, both in understanding others' directives to them and in making their own intentions apparent to others, and this affects both their emotional experience and their social relatedness. Stern (1985) has emphasized that the changes at 18 to 20 months also introduce a new sense of self, the verbal self, in which individuals experience both the power and the limitations of language for expressing their most important ideas and feelings.

After all of these dramatic changes, infants consolidate and enhance their new capacities during the third year of life as they prepare to move into wider social spheres of peer and teacher influences in the preschool years. By the time children reach their third birthday they have a sophisticated repertoire of skills for communicating and experiencing relationships. Qualitative features of their caregiving context during the first 3 years of life shape their expectations of relationships as they move into the broader social world.

## Risk and Protective Factors

Throughout this review of development, we have set aside the biological and environmental factors that may adversely affect infant development and eventually lead to dysfunction. Given the greater understanding of development that is now available, it is important to address how maladaptive patterns appear and how they influence lines of development. A central focus of the research in developmental psychopathology is on describing the processes of adaptive and maladaptive development and the mechanisms by which risk and protective factors influence developmental processes. The impressive cognitive and social competence of infants and the important biobehavioral shifts during this period of rapid developmental change support the notion that infancy is a critical time to study these mechanisms. Furthermore, the emphasis on longitudinal study of these mechanisms has major implications for prevention of mental disorders, and infancy has long been recognized as an important time for initiating preventive efforts (Mrazek and Haggerty 1994).

Research in developmental psychopathology has been influenced by increasingly sophisticated models of development designed to capture the complex interrelationships between biological, interpersonal, and wider social factors. Given this complexity, it is not surprising that research on how risk and protective factors affect development has rarely supported the notion that the transmission of risk is specific and linear in nature (Seifer et al. 1992). For example, maternal depression is related not just to an increased incidence of childhood depression but also to a host of other less specific outcomes (Beardslee et al. 1983). Furthermore, multiple risk conditions from different domains (e.g., biological, psychological, or social) may occur simultaneously and may, in turn, be exacerbated or ameliorated by the care the infant receives (Seifer et al. 1992, Sroufe and Rutter 1984). This has led to the important observation that the total number of risk conditions affecting an infant may be more predictive of competence in later life than exposure to any single specific risk factor (Sameroff et al. 1987). Again this is similar to genetic contributions toward risk.

Rutter (1987) has suggested that the field must move toward understanding protective processes as well as documenting mechanism by which risk conditions operate.

Indeed, a risk condition that sets off a negative chain reaction in one infant may immunize another against future developmental deviance merely by allowing the infant to overcome that condition (Rutter 1987). In this case, the presence of other risk conditions or of critical protective factors in the infant or environment is likely to account for the difference in outcome.

## Illustrative Risk Conditions

Defining what constitutes a risk factor or condition is somewhat arbitrary, and many risk factors have been postulated. Nevertheless, the four illustrative areas that are reviewed in this section and summarized in Table (8–5) have been studied extensively. Most studies document effects on broad outcomes of groups of infants and families exposed to a given risk condition, and the results of these investigations provide only limited information about a particular infant and its family. We move from a discussion of broader social risk conditions toward more biological risk conditions, with the important caveat that risk conditions only rarely occur in isolation.

### Poverty

Poverty has long been recognized as a powerful risk condition with myriad developmental implications. Its effects are considered to be largely nonspecific and may be mediated through many associated factors (e.g., teenage parenting, poor education) that are more common in families that are economically disadvantaged. In fact, poverty is probably best understood as a risk condition that is an aggregate of many separate risk factors. An approach to considering this topic has centered on breaking down poverty into its component parts, allowing the researcher to attempt to tease apart the critical specific factors that are most related to outcomes of interest.

Poverty is defined in the US by household income; currently, the cutoff is $18,100 per year for a family of four. Approximately two-thirds of poor infants are supported by welfare and the same number live in mother-only families (National Center for Children in Poverty 1990). Of the 700,000 poor children younger than 2 years in the US, 40% live in inner cities and 30% live in rural areas. More than one half of the parents of these children have not completed high school, and approximately one half of all mothers in poverty began parenting in their teenage years.

There are biological risk factors associated with poverty, some of which exert influences before birth and contribute to high neonatal and postneonatal mortality indices in this country. From a lack of prenatal care, poor peripartum nutritional status, high rates of prenatal drug and alcohol exposure, and lack of familial support infants born into poverty often face early hurdles. These problems may be compounded by the higher rates of lead intoxication and iron deficiency in poor infants compared with infants raised in more economically advantaged homes. Each of these variables has been shown via well-designed studies to have similar effects on cognitive function in infants; together, they may have synergistic effects that are severe. Finally, rates of hospitalization are higher and lengths of stay longer for poor infants, suggesting a diminished access to preventive medical care.

These biological factors may be ameliorated or exacerbated by a host of psychological and social factors. As with biological risk, there are group differences in the prevalence and severity of the different component factors given later. Although they may be more common in poor families, none are exclusive to poor families, and the clinician is left having to screen for these problems in each individual case.

The most devastating effects of poverty may be on the family, including factors such as parenting style, responsiveness, and resulting family cohesiveness (Rutter 1985). There has been some research focused on parenting style and its relationship to poverty. On the whole, data collected regarding caregiving environments in families faced with poverty suggest that infants may compete for parental attention against many instrumental factors to which parents must attend. Furthermore, there appears to be an overall pattern of reduced or inconsistent attentiveness to infants in these settings, often because of the parents' own history of inadequate nurturance (Halpern 1993). Not uncommonly, the consequences of this intergenerational transmission of parenting vulnerability include hostile, intrusive interactions by the time of toddlerhood (Lyons-Ruth et al. 1989). These interactions appear to be associated with the increased incidence of anxious and disorganized attachment in samples with low socioeconomic status (Lyons-Ruth et al. 1989, Zeanah et al. 1995) and may interact with other factors to predict insecure attachment across time in low-income families (Egeland and Farber 1984).

The consequences of insecure and/or disorganized attachment have been addressed in longitudinal research.

**Table 8–5 Developmental Risk Factors**

| Risk Factor | Biological Effect | Psychological Effect | Social Effect |
|---|---|---|---|
| Poverty | Malnutrition | Attachment problems | Family dysfunction, environmental threat |
| Child maltreatment | Trauma effects, failure to thrive | Disturbed affective responsiveness, poor social interaction, attachment problems | Risk for depression and suicide as well as antisocial behavior and conduct disorder |
| Maternal substance abuse | Impaired prenatal central nervous system development | Inconsistent and unpredictable parenting, attachment problems | Family dysfunction |
| Premature birth and serious illness in infancy | Delayed or disrupted central nervous system development, increased developmental disorders | Increased parental stress | Environmental destabilization |

These patterns are predictive of subsequent behavioral problems, impulse control problems, low self-esteem, disordered peer relations, and poor cognitive performance (Troy and Sroufe 1987, Lewis et al. 1984, Easterbrooks and Goldberg 1990, Cassidy 1988, Jacobsen et al. 1994). These associations are suggestive of the seeds of disruptive behavior disorders, and longitudinal studies suggest that socioeconomic status is a powerful predictor of, among other things, conduct disorder in children (Kolvin et al. 1988, Offord et al. 1986). The rates of disorder appear to be linked to high-delinquency neighborhoods where children are exposed to high rates of adult criminal behavior, substance abuse, and child maltreatment (Rutter and Giller 1983). Here, the association of poverty with other risk factors for antisocial behavior may represent the final link in a chain reaction begun by poor perinatal nutrition, insufficient maternal responsiveness, and insecure or disorganized attachment.

In fact, it is the accumulation of biological, psychological, and/or social risk factors that account for the association of poverty with numerous adverse outcomes in childhood. Each of these factors appears to exert nonspecific effects, so that the exact mechanisms by which they are related to outcome are difficult to untangle and often inconsistent in different individuals. The clinician is faced with putting the individual puzzle together for each infant to reduce the toll of these complex effects on eventual outcome.

## Child Maltreatment

Child maltreatment is another broad risk condition related in its etiology to complex interactions between separate risk factors and in its outcome to a variety of possible effects on young children. Physical abuse is the leading cause of death in children younger than 1 year in the US. In 2000, more than 1,000,000 children younger than 3 years were abused and/or neglected. These cases amount for more than two-thirds of child victims in the US (National Child Abuse and Neglect Data System 1992). The first year of life has the highest incidence of maltreatment in all the years from birth to age 18 years, and more than two-thirds of child victims of physical abuse are younger than 6 years (Schmitt and Krugman 1992). The so-called shaken infant syndrome is particularly devastating and is associated with high morbidity and mortality. Intracranial hemorrhages (typically in the subdural space) and retinal detachment that result, along with intra-abdominal injuries, account for most cases of death and disability related to physical abuse in this age group (Waller et al. 1989).

Another common presentation of child maltreatment in infancy is the syndrome of failure to thrive. As many as 35% of all cases of failure to thrive are considered to be due to parental neglect, and it is estimated that 5 to 10% of all children who fail to thrive have also been physically abused (Schmitt and Krugman 1992). Because severe malnutrition in the first 6 months of life may have permanent neurologic sequelae, failure to thrive may be associated with significant morbidity in a minority of cases.

Although there appear to be associations between child maltreatment and poverty, unemployment, child disability, parental psychopathology, parental substance abuse, parental history of child maltreatment, and parental antisocial behavior, none of these conditions alone or in combination are either necessary or sufficient to predict abuse. Attempts to reconcile these facts have led to models designed to understand child maltreatment in the family and in the wider social contexts in which it occurs. In these contexts and influenced by any or all of the associated factors previously given, some parents may withdraw from their children, resulting in neglect; others may strike out at their children leading to emotional and physical abuse: still others may use children for their own sexual gratification. Frequently, different forms of maltreatment exist together in a given family, and there is some evidence that simply witnessing abuse of a sibling or violence between parents may be harmful to children (Hinshaw-Fuselier et al. 1999).

Researchers studying the outcomes related to child maltreatment are similarly challenged to integrate numerous coexisting factors. For infants whose capacities to remember and integrate abusive experiences are different from older children, these issues are doubly complex. The limited data gathered prospectively regarding the effects of child maltreatment on the psychological functioning of infants and toddlers suggest problems in multiple domains of functioning. First, infants who have been abused have disturbed patterns of affective responsiveness (Gaensbauer and Mrazek 1981). Second, they tend to exhibit high levels of anger, especially in interactions with peers during toddlerhood, leading to disturbed patterns of social interactive behavior (George and Main 1979, Main and George 1985).

These problems probably reflect the higher levels of insecure and disorganized patterns of attachment in abused and neglected infants (Schneider-Rosen and Cicchetti 1984, Pianta et al. 1989, Carlson et al. 1989). They also demonstrate early disorders in self-representation (Toth et al. 1997). Finally, they may also be the seeds of subsequent psychiatric disorders linked to abuse in infancy and childhood.

Child maltreatment in infancy is a serious problem in the US and results in significant morbidity and mortality. Some of the morbidity may be apparent in early childhood as an abnormal pattern of social relatedness, and there may be significant long-term sequelae including the possibility of major psychiatric disorders in adulthood.

## Maternal Substance Abuse

Substance abuse has long been recognized as a major public health problem in the US. Statistics indicating that each year between 100,000 and 375,000 women give birth to infants prenatally exposed to illicit drugs (not including alcohol and nicotine) have generated mounting public interest in this problem (US General Accounting Office 1990). In particular, the rising incidence of crack cocaine use among pregnant women has led to increased research in this area, in part because of the concern regarding direct toxic effects on infants and possible long-term developmental effects.

The tendency for pregnant substance abusers to use more than one drug, and the large number of pre- and postnatal risk factors associated with substance abuse have complicated research in this area. There is no evidence that simple models linking prenatal drug exposure directly to any specific developmental outcome are valid. Instead, as with other broad risk conditions, the interplay among individual biological and psychosocial risk factors must be accounted for in determining the ultimate effect of prenatal drug exposure on infant outcome.

Several important issues in the prenatal period are related to abuse of drugs by pregnant women. First, the drug-using lifestyle is often associated with inadequate nutrition, which may itself affect fetal growth. Second, this problem may be exacerbated by the tendency for substance-abusing women not to receive adequate prenatal care. Third, the issue of timing, dose, and duration of drug exposure is almost never controlled for in studies in this area, although these factors may be critical in determining possible structural effects on the developing central nervous system. Because these issues are difficult to account for even in the most well-designed studies, the relative effects of drug exposure itself remain obscured. Even the effects of alcohol, long known to have direct effects on the developing neurons as evidenced by fetal alcohol syndrome, appear to be modified by factors unrelated to dosage of exposure (Abel and Sokol 1987, Sampson et al. 1989).

There are also numerous postnatal factors associated with what has been called the culture of drug abuse that may independently affect infant outcome. First, drug abuse appears to be more common among women living in poverty, especially in the inner cities. Second, there appears to be high rates of parental psychopathology associated with substance abuse during pregnancy. Third, caregiving environments for infants whose mothers abuse drugs may be marked by disorganization, with infants often being exposed to multiple caregivers. Thus, there may be direct and indirect contributors to the high rates of insecure and disorganized attachment in infants prenatally exposed to drugs (Rodning et al. 1990).

Reports in the media of early research on the effects of prenatal exposure to drugs raised public concern that a generation of "crack infants" would be irreparably damaged, despite the fact that studies were often retrospective and did not control for many prenatal and postnatal associated risk factors. Prospective studies are now under way that attempt to account for drug-associated environmental risk factors while also delineating possible specific neurobehavioral effects. Neurobehavioral effects are understood to be physiological effects on the developing nervous system that may have behavioral manifestations, such as difficulty with state regulation in the neonatal period. The infant's ability to manage these effects is seen to be partly determined by his or her interactions with the environment, which may serve to heighten or lessen these behavior patterns and their physiological triggers. As yet, there is no consistent picture of what these neurobehavioral effects might even be in the neonatal period, nor are there data on how these effects might be transformed over time (Lester and Tronick 1994). Some early studies that simultaneously track the long-term impact of teratogenic insult due to prenatal alcohol and drug exposure, and the confounding developmental risks associated with being reared by alcohol and/or drug abusing parents do find direct, mediator, and moderator effects (Jacobson and Jacobson 2001). Main effects mean that one can detect the direct pharmacological effects of drug exposure on long-term child development after controlling for potential confounds. These have been demonstrated for alcohol on cognition and behavior related to prenatal exposure. Main effects on global cognitive development have not been found for cocaine exposure. However, direct effects have been demonstrated on narrow-band information processing tests and subtle behavioral assessments of attention and arousal regulation.

Infants prenatally exposed to drugs and to a collection of these associated risk factors are at high risk for adverse developmental outcome. As with many of the broad risk conditions, this outcome is best predicted by analysis of the number and severity of individual risk factors affecting the infant's proximal environment and the infant's neurobehavioral profile.

## Premature Stress and Serious Illness in Infancy

Premature birth and serious medical illness in infancy represent obvious biological risk factors that may significantly influence infant outcome. Given the wide variability in the causes and limitations of severe medical conditions and premature birth, it is probably the interplay of aggregates of risk factors that may eventually lead to negative outcomes. Interestingly, even with great variability in biological risk factors in preterm infants, psychosocial and especially family factors are most predictive of outcome (Sameroff 1997).

Approximately 3% of births in the US show evidence of major malformations and about 1% of children born weigh less than 1,500 g (Kalter and Warkany 1983a, 1983b, Pharoah and Alberman 1990). This means that approximately 135,000 infants per year are at heightened risk for major developmental problems. However, these numbers do not account for many of the children who eventually suffer from developmental disorders; in fact, developmental disorders occur in 3 of every 1,000 children, a majority of which are not diagnosed until after 2 years of age. Most of these developmental disorders have a primarily biological basis (e.g., chromosomal abnormalities, inadequate fetal blood supply, infections), although 10% are idiopathic (Kopp and Kaler 1989).

Understanding the developmental pathways for children born biologically compromised is complicated by the fact that there are a wide range of degrees of compromise even within types of disorders. This makes outcome research difficult because the groups studied may not be comparable. Furthermore, rates of biological compromise are not equally spread across socioeconomic strata or family composition. For instance, the rate of low birth weight (less than 2,500 g) for healthy white women aged 20 to 30 years is 3%, whereas it is as high as 9% for minority teenagers of low socioeconomic status, a higher proportion of whom are single (National Center for Health Statistics 1987). Although these rates are different primarily because of prenatal psychosocial determinants, these factors define the infant's postnatal environment as well. As for every infant, the particulars of the proximal environment of the medically compromised infant are powerful determinants of long-term functioning. There must also be some consideration regarding experiences, common in this group of infants, that are of relevance for later development. For instance, the number, length, and timing of hospitalizations in infancy and toddlerhood may affect development significantly (Quinton and Rutter 1976).

Research suggests that the etiology of medical compromise in infancy is likely to be less important than the severity of the compromise and the context in which it occurs. A seriously ill infant burdens parents in many ways,

both direct and indirect. The stress of caring for the infant may affect marital and family relationships. It may also awaken feelings of shame and guilt in caretakers, thereby further compromising the formation of a stable early relationship. There are often significant financial and social burdens that compound these effects and may further destabilize the infant's proximal environment. Finally, the specific manifestations of the infant's medical status (e.g., increased irritability resulting from neurological injury) may influence caregiver's responses.

These problems, common in families dealing with an ill infant, may themselves be potentiated or diminished by associated nonspecific factors such as socioeconomic status or social support. Hence, the context in which the stressors occur helps determine how these stressors affect a given infant and its family. Fortunately, intervention with parents of premature and seriously ill infants often helps to avert a negative chain reaction of parental stressors affecting the infant's caregiving environment and may improve eventual outcome (Minde 1993).

Like other broad risk conditions, prematurity and serious medical illness in infancy have direct biological effects that may be modified by associated psychological and social factors impinging on the infant's environment.

## Conclusion

The field of developmental psychopathology and the study of risk and protective factors have provided a framework for understanding critical determinants of infant and family functioning and outcome. Poverty, child maltreatment, maternal drug abuse, and serious illness in infancy represent important high-risk conditions. Their eventual effects are determined largely by the associated risk conditions with which they cluster. The mechanisms by which these risk factors exert their main, mediating, and moderating effects are not well understood and may be different for different infants. Still, risk assessment has important clinical implications and future research will better identify these mechanisms. Better delineation of risk and protective factors may lead to better understanding of clinical disorders of infancy and beyond.

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CHAPTER

# 9 Preschool Development

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> Maturation is a useful concept, but in reality there is only development.
>
> *(Spitz et al. 1970)*

Maturation is a useful concept, but in reality there is only development (Spitz et al. 1970). The preschool period is a time of remarkable development. Toddlers who are "into everything" and require constant parental supervision become kindergartners who can play alone or with peers for extended lengths of time. The 2-year-old who struggles to put two words together in order to communicate a simple desire, turns into a 5-year-old who can tell complex, richly embellished stories. Toddlers who have just mastered the ability to recall information become preschoolers who surprise their parents when they remember events that happened 6 to 12 months earlier, events the parents themselves may have forgotten. In this chapter, development from the beginning of the third year of life until the child enters the first grade is systematically reviewed. The preschool period encompasses rapid growth in all developmental domains, including biological, cognitive, linguistic, emotional, and moral development. Each of these areas and sociocultural influences is addressed. A brief introduction to the field is followed by a discussion of a conceptual framework for considering a range of developmental issues in the preschool period. The chapter concludes with a description of risk and protective factors and a developmental perspective on the ontogeny of psychopathology in this age group.

## Historic Considerations

The designation of the preschool period as a unique developmental epoch is relatively modern. Many observers of young children consider the preschool period to be a critical time during which children develop the skills that are necessary to move from the safe haven of the home into the broader social world of school. Historically, psychoanalytic thinkers helped to focus our attention on the importance of early childhood for the future life of the child. Currently, thinking about the preschool years has been influenced by the increase in infant and toddler daycare, as an increasing number of women have moved into the out-of-home work force. Our understanding of development, as of all areas in social science, is embedded in a historical context.

Sigmund Freud (1953) emphasized the role of young children's thoughts and feelings in influencing their subsequent development, focusing on the child's oedipal fantasies. He left the field with a rich legacy of interest in children's individuality and the importance of understanding the meaning of events to children. His daughter, Anna Freud (1965), developed the important concept of developmental lines through her observations of children. She examined the unfolding of different domains of development, much as Piaget (1952) did in his fascinating explication of the cognitive growth of preschoolers. Erik Erikson (1959) further directed our study to the prominent developmental themes of each age period, emphasizing the development of autonomy for toddlers and initiative for preschoolers. He also broadened psychoanalytic interest from the intrapsychic to the world of actual social relationships, anticipating an important focus of current empirical research.

Whereas psychodynamic clinicians have derived their hypotheses about child development predominantly from clinical experience with children and adults, modern developmental psychology requires that observations be subjected to the rigor of empirical research. Developmental studies, as in much of psychiatry, continue to struggle with integrating clinical and empirical insights. Researchers, such as Sroufe (1983), have extended studies of parent–infant attachment to the preschool period, demonstrating both continuities and discontinuities in attachment status through time, as well as delineating some of the negative correlates of insecure attachment. Cicchetti (1989) has examined how normative and at-risk populations of children negotiate stage-salient developmental tasks either adaptively or maladaptively, shedding light on both normal development and the origins of some forms of psychopathology. Broader social influences on children's linguistic (Bruner 1983) and social

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developments (Dunn 1988) are increasingly being studied within cultural context.

## Conceptual Framework

As children progress from infancy through the preschool years, they attempt to master specific developmental issues and to acquire certain skills. For example, with the advent of walking at the end of the first year of life, children begin to grapple with autonomy issues. However, these issues are not resolved completely within any single developmental period, but they continue to be important throughout the life span (Stern 1985). More or less successful resolution of stage-specific issues leads to healthier or less successful adaptation for the child. Children who do not master stage-specific issues will not inevitably develop psychopathology, but they are at increased risk of subsequent developmental failures and the development of certain psychiatric disorders. This is particularly noticeable when the individual subsequently encounters the same issue in a different developmental form, such as when young physicians once again confront autonomy issues when they complete their long years of training and move into practice. It is often overlooked that this process is frequently positive, offering new opportunities for growth. Each new developmental stage enables the individual to rework past traumas, resolve problematical issues, and master new skills. This positive perspective emphasizes children's potential resilience to trauma and loss, an important area for future research.

Developments within different functional domains do not necessarily progress in concert. A child may be more advanced cognitively than socially. Lines of development are not parallel lines. They interact, supporting or inhibiting growth in other domains, such as when a 3-year-old who has not yet developed much language has difficulty in communicating needs and regulating frustration. Examples of developmental milestones in the preschool period for different developmental domains appear in Table 9–1.

Much of early development occurs within the context of the parent–child relationship. Parents tune in to the skills their young child has and the skills the child needs to acquire in order to move forward to the next phase of growth. Parents who structure their child's learning so that they provide most of what the child needs are helping the child acquire the next level of skill. Vygotsky (1978, 1986) referred to this as working in the "zone of proximal development." An example would be a parent helping a youngster with a puzzle by orienting the piece so that the child can see where it fits in the puzzle. Another example would be a parent watching a child struggle with the temptation to reach for a forbidden cookie and reminding the child not to take it. By reminding the child of the restriction, the parent helps the child to resist the temptation. Scaffolding the child's development, as this is called, requires that parents provide assistance when needed but do not provide unneeded help.

Modern models of development emphasize that not only do parents influence their children but also children influence their parents. Children within the same family are born with different temperaments, and parents often remark on how different their children are. Over time, children and parents influence each other, mutually affecting the child's developmental trajectory. This is referred to as a transactional model of development. As children grow older, the influences of teachers, peers, and other adults become more important. More recently, we are beginning to understand how genetic influences contribute to these processes. Genes become activated at different times in development. Further understanding of these processes may well result in a major reorganization of our thinking about development in this age group.

These transactional processes result in both continuities and discontinuities in development. For example, there is substantial continuity in aggressive behavior from the preschool to the school-age period. But a happy infant can become a detached autistic 3-year-old, reflecting a major discontinuity in development. Given this overall model of development in the preschool period, the development of different domains will be examined.

## Lines of Development

### Biological Development

The field of behavioral genetics is changing the way we think about child development. Behavioral genetics research not only has demonstrated that there are genetic influences on children's development but also has provided the best evidence that environmental influences affect children. By conducting studies of monozygotic and dizygotic twins or of adopted children, researchers can begin to tease apart the genetic and environmental influences on children's cognitive, emotional, and social development.

This research has led to a number of surprising findings that are relevant for our understanding of the preschool period. First, parents have different effects on different children. This is referred to as the effects of the "nonshared environment" (Plomin and Daniels 1987). In understanding children's development, we must focus on how each parent influences each child separately. It becomes more important to examine not the nurturing parent but how this nurturing parent shapes the development of each child individually. Second, genetic influences vary with age. For example, although environmental influences explain significant variability in IQ in childhood, this is no longer true in adolescence (Loehlin et al. 1989). Third, nongenetic factors appear to interact with genetic factors in the development of most psychiatric disorders (Plomin 1994). An exception is autism. Concordance for developing autism is 65 for monozygotic but only 10 for dizygotic twins, indicating a powerful genetic influence for an illness that was initially thought to result entirely from environmental factors (Rutter et al. 1993). Understanding the factors that lead to the expression of genes that carry risk for psychopathology, particularly if the expression of the genes occurs before the first manifestation of the disorder, would contribute substantially to our ability to intervene with infants and young children to prevent psychiatric disorders.

A central principle of neural development is that while brain maturation influences children's behavior, environmental experience also influences neurobiological development. This is evident when we consider brain development. By 18 weeks of gestational age, nearly all cortical neurons have formed and migrated to their neural destination (Sidman and Rakic 1973). However, at birth, the average infant brain is only one-third the weight of the adult brain. There is an important brain growth spurt approximately

**Table 9–1 Emerging Patterns of Behavior from 1 to 5 Years of Age***

| | |
|---|---|
| | 15 months |
| Motor: | Walks alone; crawls up stairs |
| Adaptive: | Makes tower of three cubes; makes a line with crayon; inserts pellet in bottle |
| Language: | Jargon; follows simple commands; may name a familiar object (ball) |
| Social: | Indicates some desires or needs by pointing; hugs parents |
| | 18 months |
| Motor: | Runs stiffly; sits on small chair; walks up stairs with one hand held; explores drawers and waste baskets |
| Adaptive: | Makes a tower of four cubes; imitates scribbling; imitates vertical stroke; dumps pellet from bottle |
| Language: | 10 words (average); names pictures; identifies one or more parts of body |
| Social: | Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with pucker |
| | 24 months |
| Motor: | Runs well; walks up and down stairs, one step at a time; opens doors; climbs on furniture; jumps |
| Adaptive: | Tower of seven cubes (six at 21 months); circular scribbling; imitates horizontal stroke; folds paper once imitatively |
| Language: | Puts three words together (subject, verb, and object) |
| Social: | Handles spoon well; often tells immediate experiences; helps to undress; listens to stories with pictures |
| | 30 months |
| Motor: | Goes up stairs alternating feet |
| Adaptive: | Tower of nine cubes; makes vertical and horizontal strokes but generally does not join them to make a cross; imitates circular stroke, forming closed figure |
| Language: | Refers to self by pronoun "I"; knows full name |
| Social: | Helps put things away; pretends in play |
| | 36 months |
| Motor: | Rides tricycle; stands momentarily on one foot |
| Adaptive: | Tower of 10 cubes; imitates construction of "bridge" of three cubes; copies a circle; imitates a cross |
| Language: | Knows age and sex; counts three objects correctly; repeats three numbers or a sentence of six syllables |
| Social: | Plays simple games (in "parallel" with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands |
| | 48 months |
| Motor: | Hops on one foot; throws ball overhand; uses scissors to cut out pictures; climbs well |
| Adaptive: | Copies bridge from model; imitates construction of "gate" of five cubes; copies cross and square; draws a man with two to four parts besides head; names longer of two lines |
| Language: | Counts four pennies accurately; tells a story |
| Social: | Plays with several children with beginning of social interaction and role-playing; goes to toilet alone |
| | 60 months |
| Motor: | Skips |
| Adaptive: | Draws triangle from copy; names heavier of two weights |
| Language: | Names four colors; repeats sentence of 10 syllables; counts 10 pennies correctly |
| Social: | Dresses and undresses; asks questions about meaning of words; domestic role-playing |

*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 5 years, the Stanford-Binet, Wechsler-Bellevue, and other scales offer the most precise estimates of developmental level. In order to have their greatest value, they should be administered only by an experienced and qualified person.

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at the age of 4 years, and by the age of 5 years, brains of children weigh 90% as much as the brains of adults (Lowery 1986). Much of this increase in size is due to the growth of neurons and their connections. However, increases in brain mass do not tell the most important story.

Another important principle of neurobiological development is that synaptic connections strengthen in response to experience. Activation of both individual neurons and neural networks in response to stimulation increases their likelihood of surviving. This is an important mechanism for the influence of environmental experience on brain development (Changeux and Danchin 1976).

Different brain systems develop at different rates, much as different functional systems develop at different rates. Synaptic density in the frontal cortex peaks at 1 year and pruning of synapses begins by 7 years of life (Huttenlocher 1979). This process occurs earlier in the human visual cortex, where synaptic density peaks at 6 months. Loss of synapses is under way by 1 year of life.

Functional evidence reveals that the brain's capacity for plasticity varies with age. Young children can recover

language functions after the dominant hemisphere is damaged (Dennis and Whitaker 1976). However, after the age of 8 years, progress is limited, suggesting that language is represented bilaterally in young children but that it may be represented unilaterally by the early school years (Woods and Teuber 1978). The development of new brain imaging tools is providing a new method for studying the relationship between brain structure and function.

Motor development progresses rapidly during the preschool years (Berger 1994). This is particularly true of the development of gross motor skills involving large body movements such as jumping and running. Whereas toddlers are often awkward in their gross motor movements, most American kindergartners can throw and catch a ball and ride a tricycle. Fine motor skills are more difficult for preschoolers to master. Their limited muscular control, patience, judgment, and short and stubby fingers make it difficult for them to draw or cut food with a knife and fork. Parents who provide a sensitive scaffold for their children, accurately judging their children's abilities and helping them to master the next level of skill, facilitate their children mastering these skills.

The age at which children acquire bowel and bladder control varies among individuals within the normal range. Bowel control is established between 20 and 30 months. Daytime bladder control is acquired in the third year of life, and nighttime control develops between 3.5 and 4 years of age.

Activity level peaks in the third year of life and then decreases (Eaton and Yu 1989). Individual differences in activity level reflect the influences of both nature and nurture. Genetic influences are reflected in the observation that monozygotic twins are more equal in their activity levels than are dizygotic twins (Saudino and Eaton 1994). However, children's activity levels are quite influenced by context (e.g., children are often more fidgety when they are expected to sit quietly, as in school), and cultural expectations influence their level of activity as well. As is true for most developmental domains, genetic, familial, and cultural influences together shape children's activity levels.

A time line of biological development from age 20 months to 5 years is presented in Figure 9–1.

## Cognitive Development

Piaget (1952) believed that the idiosyncratic and, at times, humorous ideas of preschoolers were not random thoughts. Rather, they reflect the activity of inquiring young minds operating according to a unique set of rules. He referred to these rules as the preoperational stage of reasoning. The transition from the sensorimotor to the preoperational stage at 18–24 months is marked by the development of the capacity for symbolic representation. The 2-year-old can store representations of objects in memory, even when not perceiving the objects. This enables the child to recall information. The child in the preoperational stage is capable of symbolic reasoning and symbolic play. A 3-year-old rides a broom as if it were a horse or pretends that a block is a car and races it around the room. These cognitive abilities lead to a fascination with pretend play, which continues until it yields to the school-age child's interest in games, sports, and hobbies.

Parents often take delight in the magical thinking of young children. Piaget's classification of these idiosyncratic modes of reasoning is valuable as a way of characterizing the children's thought processes. "Animism" refers to endowing inanimate objects with the qualities of living things. For example, young children may say that the sun shines "because it wants to." "Artificialism" is the belief that all things are made for our use. The child who states that day turns into night because people need to sleep is demonstrating artificialism. "Centration" is the child's tendency to focus on only one aspect of a problem at a time. Young children can identify two rows of five identical objects as being of equal length (Figure 9–2). Yet, if one of the rows is spread out, 3- and 4-year-old children say that the longer row has more objects, centrating on the length of the row (see Figure 9–2). This experiment also indicates that preschoolers are unable to *conserve* number; the number of items is not conserved across a transformation. Development of this ability heralds the onset of the operational stage of thinking at about 7 years of age.

Although Piaget noticed that young children had difficulty distinguishing surface appearances from underlying realities, careful research has now documented preschoolers' growing abilities to distinguish reality from appearance. Whereas 3-year-olds have difficulty knowing that a stone

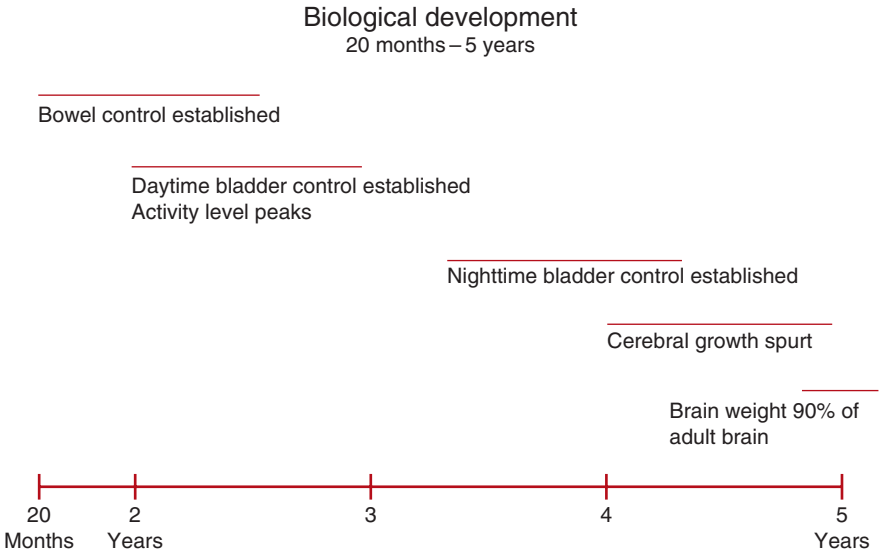



**Figure 9–1** *Biological development during the preschool years (20 months to 5 years).*

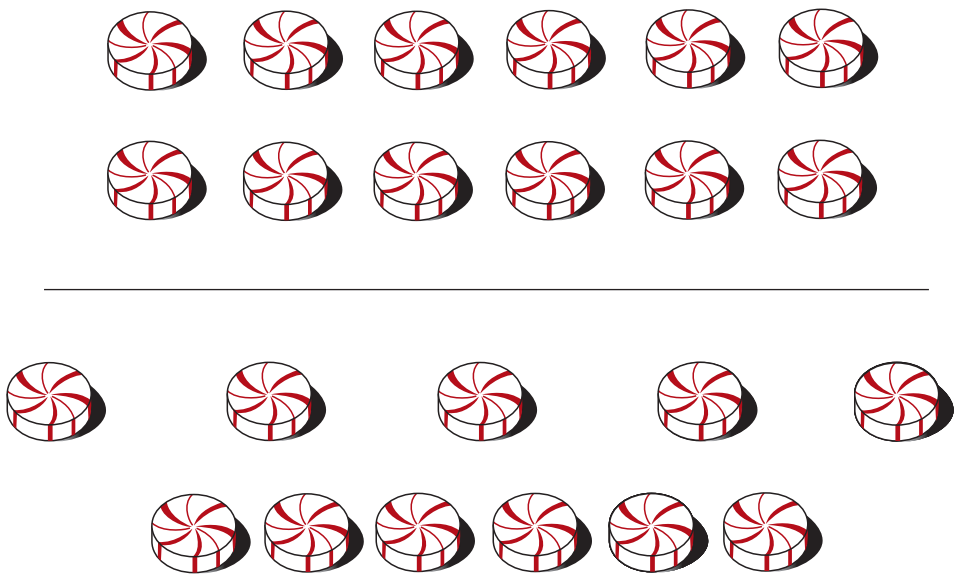


**Figure 9–2** *Piaget's experiment on the conservation of numbers. When shown the arrangement of candies in the top two rows and asked whether one line has more or both lines are the same, the 4- or 5-year-old generally answers that both lines contain the same number of candies. Using the same candies, those in the lower row were pushed closer together and one candy was removed from the upper row, but the line was spread out so that it was longer. The child has watched this operation and has been told that he or she may eat the candies in the line that contains more. Even preoperational children, who can count, insist that the longer line has more, although they have gone through the exercise of counting off the candies in each line. [Reproduced from Craig GJ. Human Development, 6/e, \C 1992, p. 266, with permission of Prentice-Hall, Upper Saddle River, NJ.]*

that is painted to look like an egg is not an egg, older preschoolers readily discriminate the two (Flavell et al. 1983). This is known as the appearance–reality distinction.

An important extension of this research has been studies on children's theory of mind. Theory of mind is the term used to describe the understanding of beliefs, desires, motivations, and emotions as mental states that are ascribed to one's self and others. This understanding is important for children, as they seek to make sense of their social environments, predict how others will behave, and develop richer and more complex relationships (Wellman 1990). The traditional experiment for theory of mind development is to have a child and an adult confederate observe that an object is hidden in one place. The confederate then exits the room, and the child observes the experimenter hide the object in another place. The child is then asked where the confederate thinks the object is. Typically, 3-year-olds incorrectly base their answer on where the object *actually is* rather than where the confederate *thinks it is.* Most 4-year-olds do not make this mistake, understanding that the confederate has a false belief about where the object is (Wimmer and Perner 1983). This and other evidence about preschoolers' growing understanding about their own and others' mental states suggest that at approximately 4 years of life there is a radical shift in young children's understanding of the mind (Gopnik 1993, Wellman and Bartsch 1988, Wimmer and Weichbold 1994). Interestingly, autistic children do not seem to make this shift in their thinking. Older children with autism do not pass the false-belief task, even when their mental capacities exceed those of normal 4-year-olds (Charman and Baron-Cohen 1995). By not making the belief–reality distinction, these children demonstrate that they lack an essential instrument for interacting with others. Piaget described preschoolers as egocentric, indicating that they have difficulty taking the perspective of others. This claim derived from a famous experiment using a three-dimensional model of three distinct mountains. Preschoolers are unable to report which mountain is in front of the other mountains on imagining the model from different angles. Such results do not demonstrate that young children are egocentric in all ways. For example, empathy requires the adoption of another's perspective, and the development of empathy and prosocial behavior can be demonstrated in young children.

Problems with the Piagetian view of egocentrism reflect a more general problem with Piagetian stage theory. At the heart of the theory is the claim that all thinking in one age period is characterized by certain principles, which can be elucidated by observing children's performance on specific tasks. However, the performance of young children is sensitive to even small contextual influences. For examples, when more familiar materials are used to assess children, they perform better.

Attempts to characterize both adults' and children's cognitive abilities have focused on how information is processed. This approach emphasizes children's limited information-processing capacities. For example, preschoolers have limited attention spans. They approach tasks in an unsystematic fashion, not focusing on the most relevant features of the task. Their short-term memory capacity is limited (Case and Khanna 1981). However, when information is presented more slowly and the child already has some background in the area, performance improves, again demonstrating young children's sensitivity to the contextual demands of the task.

Although children in the preoperational period can recall some information, their abilities remain quite limited at this age. However, their memory is more similar to the memory of adults than was previously thought. Preschool children have a good capacity to form generalized event memories, or scripts, of commonly occurring events. These knowledge structures are general templates that represent the expected events in a familiar routine. Children as young as 3 years old can report what typically happens during familiar events or routines. These structures are quite important, as they organize young children's memories. For example, children use them to make inferences about what happened when recalling an event. If asked to retell a story that they have just been told, young children tell it as if certain commonly occurring events occurred, even if they never happened in the story (Nelson and Gruendel 1981). Preschoolers may be more able to recall generalized memories than specific memories of events, known as episodic memories

(Nelson 1986). Like adults, memories of the past enable children to anticipate future events. Similarly, memory supports preschoolers' growing ability to establish goals, to outline a plan of behavior to reach those goals, and to sustain the effort to accomplish those goals.

The development of scripts supports the development of transference expectations. Transference expectations reflect the child's experience or fantasy of how adults act toward them. Children whose parents neglect and ignore their emotional needs may come to believe that adults, in general, will behave in this way toward them. Transference expectations form in response to the normative needs of children to understand their world and to anticipate future events, whether those events are nap time in school or emotionally charged issues such as whether parents act helpfully or punitively toward them (Bretherton 1985, Clyman 1991).

These cognitive abilities also support the development of talents for telling stories and engaging in imaginative play. They permit children to explore what Bruner (1986) has termed "possible worlds." Children develop imaginary friends, play dress up, and create stories with doll figures. This forms the basis for play therapy. With the support and insight of the play therapist, children can try out more successful solutions to problematical situations or reenact traumatic events, tolerating the disturbing emotions that the events evoke within the safety of the therapeutic relationship. The ability to make narratives of experience helps the child make sense of emotions and relationships. The ability to tell coherent narratives about important issues and events in their lives is an important developmental achievement.

Understanding cognitive development is helpful for both parents and psychiatrists. Although young children are no longer in the sensorimotor stage, in which all reasoning occurs within the context of direct sensory experience, it is often quite helpful to teach them with concrete examples. When explaining a surgical procedure to a young child, a picture is worth more than a thousand words. A sound clinical strategy is to have the child draw a picture of what he or she thinks is wrong. The picture provides a clear view of the child's understanding of the illness. Preschoolers normatively have a short attention span, substantial distractibility, and an unsystematic approach to tasks. It is, therefore, difficult to establish the level of disturbance required to diagnose attention-deficit/hyperactivity disorder in preschoolers.

A time line of cognitive development from age 20 months to 5 years is presented in Figure 9–3.

## Language Development

Language acquisition is an enormous accomplishment. Children are exposed to complex utterances and must induce the multiplicity of grammatical rules that permit them to understand and converse in their language. Chomsky (1975) has argued that language development is genetically driven by the formation of specific mental capacities, which he termed the language acquisition device (LAD). His view suggests a strong separation between language and cognition,

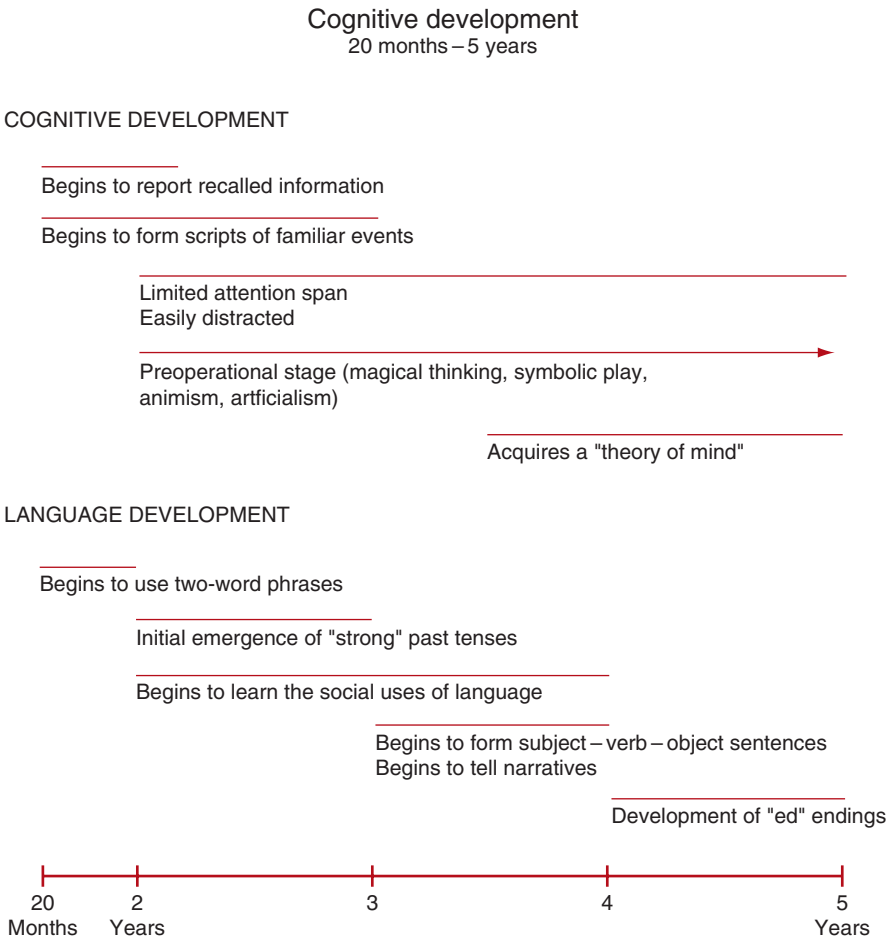



**Figure 9–3** *Cognitive development during the preschool years (20 months to 5 years).*

and it downplays the role of social processes in language development. Others, such as Bruner (1983), have argued that adults scaffold language input for children. For Bruner, the process of learning language is a shared rather than an individual achievement. Bruner has suggested that language development requires not only a LAD but a LASS as well—a language acquisition support structure—the social environment that supports the child's growing linguistic abilities.

Linguistic development can be separated into four domains: sounds (phonology), words, methods of combining words (grammar), and sociocultural roles that language serves. Preschoolers are actively acquiring the capacity to pronounce different sounds, which becomes apparent when one compares how 3- and 4-year-olds talk. However, the capacity to form different sounds develops at different rates in this age group.

It is remarkable that children learn the meaning of individual words by listening to how they are used and trying to use them themselves. They tend to learn simpler forms first. A 2-year-old can say "no," but at 3 years he can say "nobody" and "nothing." Language learning is an active process, and children make mistakes. Toddlers engage regularly in overextension when they use a word, as if it refers to more than it actually does. They might say "daddy" to refer to all men. Another example of overextension occurred when a 5½-year-old, in describing the relative merits of two toy tanks, said that he or she liked one better because it was "gunnier." Preschoolers also engage in underextension when they restrict the meaning of a word. An example would be using "animal" to refer only to certain familiar mammals, such as cats and dogs, but not fish. Children by 2–3 years of age learn strong past-tense endings (such as "brought" or "sang"), because these endings are common and useful. They learn these verb forms before they learn to apply "ed" as a suffix to form the past tense for standard verbs, as in "teased." The development of "ed" endings, which occurs at about the age of 4 years, leads them to switch to overgeneralized versions of verbs that take a strong past-tense ending (they say "bringed" and "singed"). By the end of the preschool period, most young children have sorted out the rules and use these verb forms correctly.

Why do we learn to say "I will let you play" but not "I will allow you play"? Children must learn to use grammar to organize words into sentences so that they can communicate their ideas and wishes. Toddlers begin the third year of life in the two-word phase. They are able to form propositions, typically by bringing a subject together with a verb or object: "Me cookie" or "Rover come." By the age of 3 years, children can form subject–verb–object sentences. Later, they develop the capacity for narrative. As Bruner and others have indicated, the linguistic environment supports language learning in children. Parents speak to their infants slowly in simple statements, using small vocabularies (Snow 1972). This use of "motherese" occurs across languages and social classes (Shatz and Gelman 1973). However, children learn grammar primarily through exposure to examples of correct syntax. It is uncommon for parents to correct their children's grammar. Strikingly, when they do, children usually ignore them. There are gender differences in language input as well. Mothers talk more to daughters, and girls are more advanced than boys in their language development.

Preschoolers acquire substantial knowledge of the social uses of language. Two-year-olds begin to understand that "Is the door shut?" is often an indirect command and not a question (Shatz 1978). Four-year-olds can take into account who their listener is when speaking. They alter their speech and use motherese when they speak with children who are younger than themselves (Shatz and Gelman 1973). Young children learn an impressive volume of language rules during the preschool years.

## Emotional Development

Regulation of emotion is a principal developmental task of the preschool years (Maccoby 1980). An emotionally competent 6-year-old can regulate multiple emotions in diverse contexts. An increased capacity for regulation of emotion enables the child to make the transition from the normative dependency and supervision in the home to the broader social world of the school, where greater emotion regulation and self-regulation are expected (Kopp 1989).

Earlier views conceptualized emotions as principally disorganizing behaviors. However, emotions also act as adaptive organizers of behavior. When confronted with a frightening stimulus, a child's fear organizes a fight-or-flight response. On seeing a novel, loud toy that can elicit either fear or pleasure, infants use adults' expressions of emotion to guide their behavior. They are more likely to approach the toy if the adult smiles and flee from it if the adult shows fear (Klinnert et al. 1986). This is known as social referencing, and it indicates that emotions can serve functional roles, organizing children's behavior. Emotion regulation has been characterized as having two component processes. First, children appraise the meaning of the stimulus within the context of their values and goals. Most emotions are elicited through appraisal processes. A leaping tiger induces fear because it can imminently inflict harm. Second, children modulate the behavioral expression of the emotion. Many of the skills that are used to interpret events, elicit emotions, modulate expression, and organize behavior develop in the preschool period.

Central to the social cognitive skills that underlie appraisal processes is a growing ability to think about emotions and relationships. At the end of infancy, toddlers can discriminate emotions by facial expression (Haviland and Lelwica 1987) and differences in vocalizations (Fernald 1992). Their knowledge of the situational elicitors of emotion increases (Denham 1986). They understand that individuals' desires and beliefs affect the emotions they feel in different situations (Wellman and Woolley 1990). Children understand that people are happy if they expect to obtain a goal, even if they are incorrect in their belief that they will obtain that goal (Harris et al. 1989). They can evaluate the intent of others (Dodge et al. 1986), and they increasingly understand the relationship between emotion and behavior (Denham et al. 1994). These skills support children's ability to interpret accurately the meaning of events, as emotions are elicited during their day-to-day life.

There are substantial advances in the capacity of preschool children to modulate the expression of emotion. They become better able to modulate their emotional arousal, and preschoolers develop increasingly sophisticated coping strategies to regulate the expression of emotions. They are able to use parents and teachers to organize their emotional responses to disconcerting events. Young children learn to abide by culturally defined rules of emotional expression,

which includes learning to mask emotional expression in certain situations. For example, if 3- to 4-year-olds are promised a gift but are given one they do not want, they inhibit their display of disappointment if the adult who gave them the toy is present but they express their disappointment if they are alone (Cole 1986).

The interrelationship between cognitive and emotional development is apparent in preschoolers' growing ability to modulate their expression of emotions. Preschoolers develop a capacity to inhibit and delay behavioral plans (Mischel 1983, Gottman 1986), begin to use problem solving in a reflective and planful manner, act in accordance with internalized standards when not in the caregiver's presence, and develop a sense of personal responsibility for their own actions (Kopp 1989). The role of neural development in these processes, particularly in the frontal lobes, remains an important area of investigation.

One of the most important advances in emotion modulation skills is the ability to use symbolization, language (Cicchetti 1989, Greenberg et al. 1991), and narrative (Buchsbaum and Emde 1990) to express emotions. By the age of 3 years, children can communicate about past, current, and future emotions (Bretherton et al. 1986). However, there are large individual differences in this domain. In a naturalistic, home-based study, 3-year-olds varied from almost never talking about their feelings to talking about them every 2 minutes with their mothers (Dunn et al. 1991). Peers and siblings also play an important role in the development of emotion language. One study found that although children who were 2 years 9 months old talked more with their mothers about their feelings, by 3 years 11 months they talked more with their older siblings. Interestingly, the children were more likely to comment on their siblings' feelings than their mothers' feelings, suggesting that siblings provide an opportunity for learning about others' emotions that may be less available to only children (Brown and Dunn 1992).

As indicated, preschoolers are able to tell coherent narratives or stories about their experiences. This not only enables them to organize their understanding of the meaning of events but also supports their expressing it in language rather than in action. Play therapy is helpful to children in part because it promotes the development of these skills. This is particularly noticeable when young children learn to put angry feelings into words instead of acting aggressively.

One of the central principles of emotional development is that it occurs within the context of relationships. Children's primary caregivers are always critical in their emotional development. Interest in how young children develop emotionally within the context of the parent–child relationship has developed primarily from psychoanalytic observations. These investigations have focused on preschoolers' progressive physical and intrapsychic separation from their parents. Children are increasingly able to tolerate being at both a physical and a psychological distance from their parents for longer lengths of time. Winnicott (1958) described this as the ability to be alone. Mahler and colleagues (1975) characterized this process as the fourth subphase of separation individuation, which they described with the unusual phrase "on the way to libidinal object constancy." Object refers to the people to whom the individual is relating, in contrast to the index child or subject. Object constancy refers to the ability to calm oneself, self-soothe, and reduce and tolerate anxiety in response to separation from the primary caregiver. Object constancy has been thought to depend on the 2-year-old's capacity to recall an image of the caregiver as soothing, even when the caregiver is absent. However, object constancy is not an act of memory but is an emotional skill that builds on the child's growing capacity for recall (Clyman 1991). Difficulties in acquiring object constancy in the presence of disorganizing anxiety has been linked to patients with borderline personality disorder (Kernberg 1975).

Object constancy is believed to be facilitated by achieving a sense of "basic trust" (Erikson 1950) that the infant develops from emotionally sensitive and competent caregiving. Bowlby (1969) characterized this process as the development of a secure attachment to the caregiver. In the preschool period, attachment researchers have focused on the development of internal working models of the attachment relationship, an idea that derives from the work of psychoanalytic object relations theorists (Klein 1948, Fairburn 1954). The hypothesis is that children construct a mental model involving emotions, memories, and sets of expectations of how their caregivers act toward them. Are they warm and nurturing, responding helpfully when the child is hurt, or harsh and punitive? Internal working models may develop from young children's ability to form scripts of repeatedly occurring events (Bretherton 1985, Clyman 1991, Main et al. 1985). These expectations become a frame, or internal context, within which children appraise the meaning of events. These appraisals then elicit the children's emotional reactions, organizing their behavior. For example, a child who expects his/her father's frustration to turn into abusive anger may feel anger or fear and then hide. A number of competing hypotheses address the development of internal working models of relationships (Buchsbaum et al. 1993).

The notion of the Oedipus complex is related to these ideas. In its simplest form, the oedipal hypothesis postulates that young children emotionally and sexually desire the parent of the opposite sex and are angry at the parent of the same sex, with whom they perceive themselves in competition for the opposite-sex parent but also fear retribution from this parent. The Oedipus complex involves developing a set of feelings and ideas about one's parents and how they feel and are likely to act. Like internal working models of relationships, these ideas and feelings acknowledge the preschooler's ability to form expectations about others' actions, which then organize preschoolers' emotions and behavior. Whereas internal working models are thought to be constructed from actual experiences, oedipal thoughts were believed to develop from the child's internal fantasies. Furthermore, the theory of the Oedipus complex involves hypotheses about the specific content of those fantasies, such as fear of the parent of the opposite sex. Mental structures become critical in the lives of preschoolers, as they are intimately involved in personality formation.

A time line of emotional development from the age of 20 months to 5 years is presented in Figure 9–4.

## Sociocultural Influences

Much of children's socialization occurs within the context of the parent–child relationship. Vygotsky (1978, 1986) described how parents scaffold their children's development in the zone of proximal development. Parents influence their children's development predominantly through

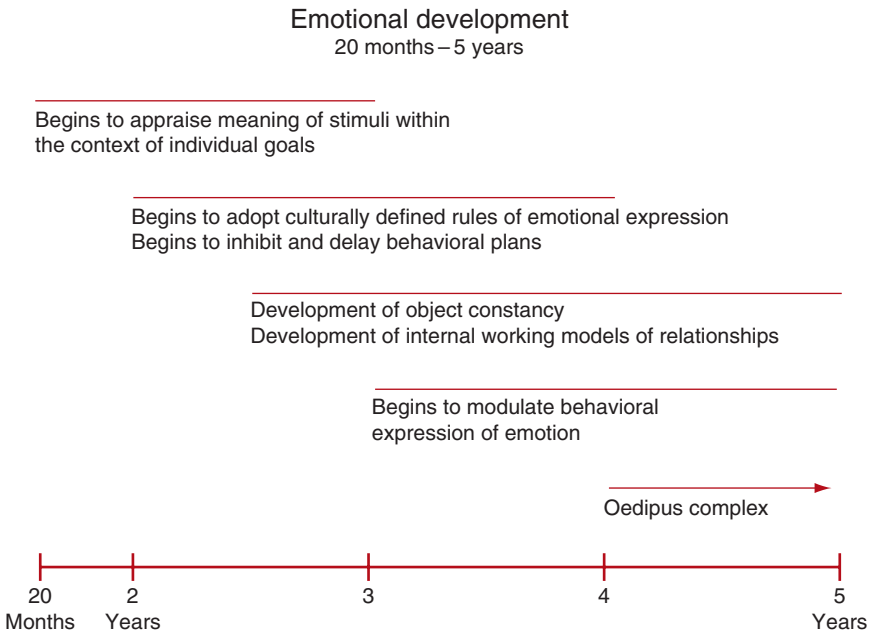



**Figure 9–4** *Emotional development during the preschool years (20 months to 5 years).*

their moment-to-moment, day-to-day interactions with their children. They express delight in their toddlers' growing motoric abilities, supporting the development of pride and self-esteem. They offer them choices when appropriate, supporting their toddlers' sense of themselves as agents who can have a positive impact on their environment. They teach them social mores as well as moral rules, promoting prosocial behavior and attenuating aggressive behavior. They talk with the toddlers, recalling events of the day, and read stories, encouraging the development of language. They support their enjoyment of imaginative, pretend play, which enhances symbolic thinking and social understanding. They take pleasure in their children's developing ability to play with peers, supporting a healthy separation from the parents, and their developing autonomy. Above all, children learn about healthy, reciprocal relationships by loving and being loved by their parents.

Baumrind (1971) has delineated four general styles of parenting (Table 9–2). The authoritarian style parent is demanding, is controlling, and makes frequent use of threats and punishment. This parenting style correlates with having children who are moody, irritable, aggressive, and at higher risk of developing disruptive behavior disorders. Indifferent parents set few limits, engage in less monitoring of their children's behavior, and often appear detached. Their children tend to be demanding, tend to be less compliant, and have poorer interpersonal skills with peers. The permissive style parent is loving, is emotionally available, tends to set few limits, and is accepting and encouraging. The children are often impulsive and have behavioral problems. The authoritative parenting style is characterized as caring, emotionally available, setting appropriate limits, and maintaining structure and reasonable expectations for the children. The children in turn are more independent, have better social skills, and are more self-confident.

Siblings and peers become increasingly important to young children during the preschool years. Preschoolers tend to spend more time with peers and less time with adults than toddlers. In turn, siblings and their peers influence the development of social and cognitive skills in their younger brothers and sisters (Lamb 1988). Children who compete with siblings for toys or for their parents' attention may be more motivated to decipher what others think and feel, which may support the development of social cognitive skills (Berger 1994). These skills can then be used either to please or to annoy their siblings (Dunn 1988). An interesting finding in this area is that, although young children are more likely to be rivalrous with their siblings than with unrelated peers, they are also more likely to be more cooperative and nurturing with their siblings than with other children (Berger 1994).

There are sex differences in the development of children's peer relationships that are evident by the age of 2 years. Boys are more aggressive, more likely to engage in

**Table 9–2 Parenting Styles**

| Style | Characteristics | Clinical Correlation in Children |
|---|---|---|
| Authoritarian | Demanding, controlling, threatening, and punishing | Moodiness, irritability, aggressivity, and risk of development of behavior disorders |
| Indifferent | Sets few limits, little monitoring of behavior, and detachment | Demanding, less compliant, and poor peer relationships |
| Permissive | Loving, emotionally available, sets few limits, accepting, and encouraging | Impulsivity and behavior problems |
| Authoritative | Caring, emotionally available, appropriate limit setting, maintains structure, and reasonable expectations | Independent, stronger social skills, and confident |

rough-and-tumble play, and more apt to play with objects that can be manipulated, such as blocks or trucks. Girls often prefer doll play, dress up, and artwork. However, children of both sexes engage in both types of play. Children in all cultures prefer to play with same-sex partners, which is known as gender segregation. These preferences are evident by 33 months and increase during the school years. There is a long history of debate over whether sex differences primarily reflect the influence of nature or nurture. Observations of parents clearly document differences in their behavior toward children of different sexes. However, the degree to which these differential parental behaviors occur in response to genetic variation rather than in response to cultural demands to shape early behavior remains unclear.

Much of children's cognitive and social learning occurs through play. Preschoolers progress through four stages of play: solitary play, in which children play alone; parallel play, in which children play side by side but limit their interactions; associative play, in which children share toys but do not adopt roles or cooperate to reach a goal; and cooperative play, in which the latter features become prominent (Parten 1932). Solitary and parallel plays decrease and associative and cooperative plays increase during the preschool years. However, children continue to engage in all forms of play. In the preschool years, children increasingly enjoy pretend play, which allows them to try out new roles and experiences and master difficult feelings. By the beginning of elementary school, children become more interested in rule-governed games, which support the growth of collaborative problem solving.

Daycare has become an important caregiving environment for young children. This has raised questions about its influence on children's development. Some studies suggest that children may be less likely to develop secure attachments to their parents if they have more experience in daycare. However, children may also develop secure attachments to their daycare providers. Intellectual and linguistic development may actually improve for middle-class children cared for in good daycare centers (Clarke-Stewart 1984). These children tend to be more self-sufficient and less dependent on their parents. Findings are mixed on other variables: children may be more knowledgeable about and more comfortable in social situations, yet they may be less compliant and more aggressive than children not exposed to daycare (Cole and Cole 1989). These studies suggest that the quality of the daycare is the critical variable. Larger daycare centers are less likely to let children initiate activities, and they tend to emphasize rules to maintain order. Teachers may be less likely to be sensitive to the individual needs of children (LeVine 1980).

There has been increasing recognition of the importance of cultural influences on children's development. Children develop within a culture, acquiring many of its expectations and patterns outside their awareness. The meaning of their behavior can then be understood only within the context of those cultural patterns and norms. For example, when children are evaluated for depression, we must understand whether the child's culture values concealing or expressing emotion. Children who learn not to express emotion may be seen as having a flat facial affect, which can be misinterpreted as reflecting depression. It is essential to understand the functional meaning of a behavior as it is understood within the child's culture.

These issues have become more prominent as we have increasingly appreciated the cultural and class bias in previous developmental studies. Most studies of child development, including those reviewed in this chapter, have focused predominantly on middle-class, white families. This has made it difficult to know what is universal and what is culture specific in children's development. This is critical because research indicates that cultural variability is prevalent in children's development. Another example is the cross-cultural differences in siblings' roles. Many non-Western, nonindustrialized cultures encourage children to be important caregivers for their younger siblings (Weisner 1982). Parents' use of praise (Whiting and Whiting 1975) and children's attention-seeking behavior (LeVine 1977, 1980) show marked cross-cultural variation. Many cultures do not value independence and assertiveness in children to the extent that they are valued in the majority American culture, instead emphasizing caretaking and mutual responsibility (Whiting and Child 1953). These differences may have an important impact on children's social development.

A time line of social development from age 20 months to 5 years is presented in Figure 9–5.

## Moral Development

Why do children learn to behave in accordance with societal standards? It is not simply a matter of learning social mores and moral rules. Some children know what is expected of them but are not motivated to comply. Other children want to follow their parents' directives, but they find themselves becoming angry and aggressive and then regretting their destructive actions. These observations illustrate the complexity of the cognitive, emotional, and motivational

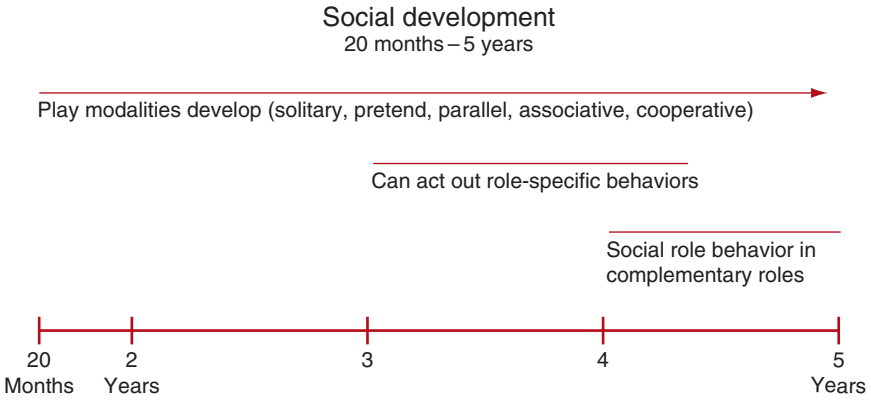



**Figure 9–5** *Social development during the preschool years (20 months to 5 years).*

processes involved in moral behavior. Central to these processes is the principle that moral development, like emotional development in general, occurs within the context of relationships. Parents influence the moral development of their children through their moment-to-moment interactions with them. They communicate their expectations both explicitly and implicitly. They model acceptable behavior, both self-consciously and without forethought. They help their children to regulate their anger and aggression and to act prosocially, learning to share their toys and to act fairly with their friends. Children internalize their parents' expectations within the context of a loving relationship with them.

The value of a broad perspective in understanding moral development has been articulated. This view emphasizes the central role that emotions play in organizing moral behavior, the early development of moral motives and behavior in the infant and toddler years, the importance of shared experience with others in internalizing moral emotions and values, and the role of nonconscious information processing in moral behavior (Emde et al. 1991). This view stands in contrast to the historically important views of Piaget (1952) and Kohlberg (1982), who argued that moral development begins with the acquisition of perspective taking, with the onset of concrete operations at about the age of 7 years.

The development of moral emotions is a critical process for children's moral development. In the first years of life, infants express the basic or Darwinian emotions, which include anger, happiness, sadness, fear, surprise, and disgust. These emotions appear to be neurobiologically hard wired, are tied to characteristic facial expressions of emotion, and appear across cultures (Ekman 1971). Beginning in the second year of life and continuing through the preschool years, the moral emotions of empathy, pride, shame, and guilt develop. Unlike the basic emotions, they do not all have characteristic facial expressions, are more internal yet appear to develop from shared experience, and arise either in situations of conflict or in response to internalized standards. Like all emotions, they play functional roles in motivating and organizing children's behavior. Only when they are particularly intense are they likely to disorganize or dysregulate children's behavior.

Toddlers show anxiety when internalized standards are violated, such as when they are presented with a flawed toy or doll (Kagan 1981). This emotion signals a violation of a norm. Empathy also develops quite early. Infants in the first year of life cry in response to another's distress. By the end of the second year of life, toddlers comfort others who are hurt or crying, patting them gently or bringing them a favorite blanket (Zahn-Waxler et al. 1979). This finding was critical in focusing research attention on early moral development (Radke-Yarrow et al. 1983). Empathy, like pride, is important in the acquisition of the "do's" of moral development (Emde et al. 1988). Although parents (and researchers) tend to focus on the "don'ts," that is, children's misbehavior, children often act in accordance with parental and societal standards without a sense of struggle or conflict. Early games involving turn taking and reciprocity, such as an infant and an adult handing a shiny toy back and forth, may set the stage for sharing and early prosocial behavior. Empathy can motivate children's prosocial behavior in the absence of conflict. A twin study has demonstrated that both empathic concern and prosocial behavior are under some genetic control, although to different degrees at different ages (Zahn-Waxler et al. 1992). This should not surprise us, because altruistic behavior may increase the likelihood that a social group reproduces, therefore increasing the probability that altruism is selected for in evolution (Wilson 1975). This view stresses the role empathy plays as a critical mediator of early moral development.

Pride also develops early in childhood. Like embarrassment, shame, and guilt, it evokes a relationship with a significant other who has set a standard that the child has internalized. Pride involves pleasure over meeting that standard and may be expressed with one's head held high, a puffed-up posture, and a puffed-up feeling. Young children are excited and proud when they experience themselves as agents who can have an important effect on people and events in their world (Erikson 1950). In contrast, shame and embarrassment evoke an image of the significant other casting a disapproving look, and the child wishes that he or she could escape from being seen. Shame and embarrassment are remarkably visual emotions. Guilt is an auditory emotion in that we readily evoke the significant other's disapproving voice. Guilt appears later than the other moral emotions, although it may develop from earlier reparative behaviors (Zahn-Waxler and Kochanska 1990). Whereas guilt appears to be invoked when a child feels that an act was bad, shame appears to arise when it is the self that is evaluated negatively (Lewis 1992).

Moral emotions evoke a sense of shared experience with important others that are central to the process of moral internalization. By the end of the first year of life, children engage in social referencing, looking to an adult when they are uncertain and modifying their behavior depending on the adult's emotional response. This interpersonal emotional signaling is transformed into internal emotional signaling with the development of moral emotions. Moral emotions alert us to possible or actual rule violations, invoking an auditory or visual representation of the significant other's emotional response.

The acquisition of moral and social rules also develops from shared experience. Young toddlers who are repeatedly told not to approach a stove become older toddlers who utter "no" or "hot" to themselves when they walk near it. However, rule internalization is quite tentative at this age, and toddlers typically regulate their behavior "under the watchful eyes of the caregiver" (Emde et al. 1988). It is not until later that they learn to withstand temptation by themselves without direct adult support. But there is developmental continuity in these processes from quite an early age.

The acquisition of regulatory rules often occurs outside conscious awareness (Clyman 1991). Just as children learn to use grammatical rules before they learn in school how to articulate those rules, young children learn to behave in accordance with parental and cultural standards before they can articulate, or are even conscious of, those standards. Indeed, a child can acquire moral and social rules even if adults never verbalize them to the child. Much of psychological research is directed at articulating the rules that govern human behavior, even though individuals are not conscious of those rules. This is particularly true for moral and social standards.

As the child moves directly into the preschool period, social cognitive processes become increasingly important

in mediating development in the moral sphere. Young children are increasingly able to appraise the meaning of others' behavior and to interpret social cues. They develop an understanding that others have feelings and intentions. This is referred to as acquiring a theory of mind, realizing that others have thoughts, feelings, and desires as we do. Children also begin to deceive others in the preschool years, perhaps because they understand that others can hold beliefs that are not true. Ironically, this is a developmental achievement (Hay 1994).

Preschoolers begin to justify their prosocial actions. In response to teacher's directives, they explain that one should obey authority figures or indicate that they fear punishment. However, when justifying prosocial behavior toward friends or peers, they refer to their relationships with them or comment on their needs (Eisenberg et al. 1985). By the end of the third year of life, children can distinguish between social conventions (e.g., not to place your elbows on the table) and moral rules (e.g., not to hurt others), and they know that moral violations are considered more serious (Smetana and Braeges 1990).

Children also develop more sophisticated strategies for coping with temptation. Mischel (1983) and Flavell (1985) offered preschool children a choice of an immediate reward or a more desirable prize after some delay. Few young preschoolers spontaneously develop delay strategies. However, when the researchers provided the children with strategies, such as trying to distract themselves, they were able to use them to resist the temptation. Similarly, parents teach their children to regulate temptation within the zone of proximal development.

The development of preschoolers' capacity for narrative permits them to talk about moral events and to consider alternative outcomes. Moral themes are frequent in young children's doll play. Children as young as 3 years old can struggle with simple moral dilemmas, if presented to them in an age-appropriate form (Buchsbaum and Emde 1990). They struggle, for example, with whether they should help an injured peer even if it means disobeying a parental directive. There may be substantial variations in how children resolve moral dilemmas, depending on their caregiving environment (Buchsbaum et al. 1993).

Psychoanalysts have focused on the oedipal narrative as central to moral development. In this view, the resolution of this conflict leads the child to internalize the same-sex parent's standards and ideals, resulting in the formation of the superego. The Oedipus complex builds on preschool children's ability to narrate experience, think about other's feelings, experience guilt, and entertain alternative possible worlds. Whether the Oedipus complex is central to moral development and personality formation continues to be debated both within and outside psychoanalytic circles (Kohut 1977). We know, however, that the traditional psychoanalytic view did not adequately address females' experiences or moral development before the age of 4 years and that it overemphasized the role of fear of retribution and guilt without adequately appreciating the part played by empathy and reciprocity in young children's moral development.

A time line of moral development from age 20 months to 5 years is presented in Figure 9–6.

## Risk and Protective Factors

Modern theories of developmental psychopathology suggest that psychiatric disorders develop from the interaction of risk and protective factors in development. Children with more risk factors and fewer protective factors are more likely to develop psychiatric disorders. Risk and protective factors operate at multiple levels of influence. There can be child factors such as prematurity or attentional problems, genetic factors such as functional polymorphisms, nongenetic biological factors such as closed head injuries, parental influences such as maltreatment, family influences such as the protective value of growing up with caring grandparents or other concerned adults, community influences such as the availability of treatment services, and societal influences such as the current prevalence and toleration of violence in America.

These risk and protective factors can influence all domains of children's development. For example, children who are maltreated are more likely to have language delays and to be angry and aggressive. These risks interact with the

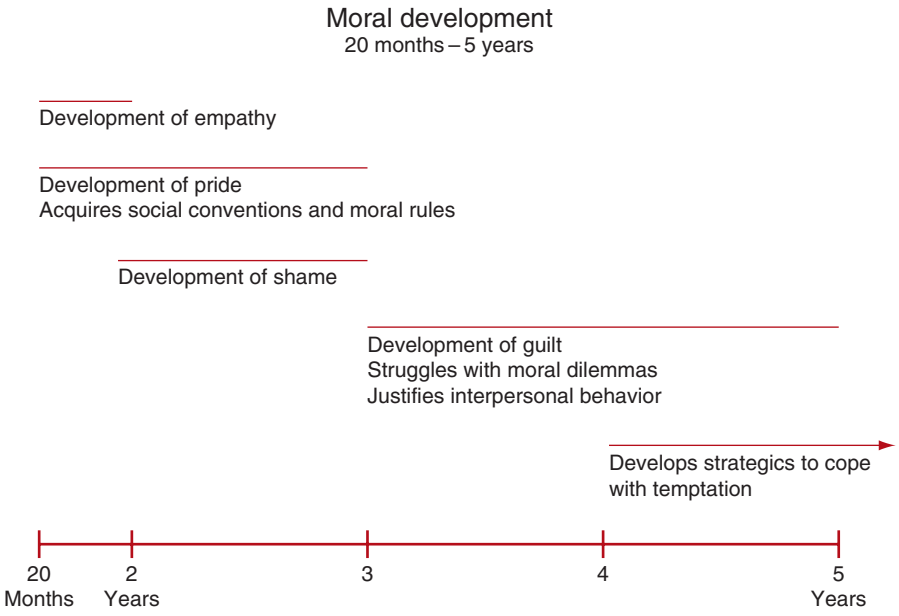



**Figure 9–6** *Moral development during the preschool years (20 months to 5 years).*

availability of community services, such as early intervention programs. Preschoolers may be particularly sensitive to the influence of risk and protective factors because development is so rapid in this period. Their influence is best understood within the broader context of developmental psychopathology.

## Developmental Psychopathology

Developmental psychopathology posits that the ontogeny of psychiatric disorders can best be examined within the context of normal development (Cicchetti 1989, Sroufe and Rutter 1984). For example, the meaning of temper tantrums can be understood only if we know the age of the child. Temper tantrums in a 2-year-old have a different meaning than a tantrum in a 10-year-old. Atypical development provides an "experiment in nature" (Bronfenbrenner 1979) that illuminates our understanding of normal development. Just as the normal functioning of the islets of Langerhans was determined by studying diabetic patients, we can learn about normal development by studying psychopathological variations.

Multivariate, transactional models are used to understand the reciprocal influence that the child and the caregiving environment have on each other over time. The balance of risk and protective factors is critical in influencing the child's outcome. Risk is considered probabilistically. Inability to master developmental tasks at one age places the child at increased risk of subsequent developmental difficulties. But later developmental challenges offer new opportunities for emotional growth. Outcomes are often evaluated as healthier or less optimal adaptations to exigent conditions, both environmental and genetic. Psychopathology is often evaluated dimensionally, examining, for example, more or less aggression, emphasizing the continuities between normal and atypical development. This view stands in contrast to the biomedical, categorical perspective that characterizes psychiatric diagnoses. The perspective of developmental psychopathology can be illustrated with an example.

The disruptive behavior disorders, including attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder, are the most common reasons for presentation to child psychiatric clinics (Robins 1991). Disruptive behavior is particularly common in the preschool period. However, judging whether oppositional and aggressive behavior reflects a psychiatric disorder is often difficult in preschoolers, because some defiant and aggressive behavior is normative in this age group, as children struggle to define themselves, separate from parents, and modulate their strong emotions.

There is growing evidence of continuity in disruptive behavior patterns from preschool to later childhood. Examining 3-year-olds with disruptive behavior problems, Richman and colleague (1982) found that the problems persisted, both at home and in school, at the age of 8 years. However, stability of behavior problems was associated with a range of risk factors operating at multiple levels of influence, including family factors (marital conflict, maternal depression, and punitive child-rearing styles) and social factors (including poor housing and financial difficulties). Child factors are important as well. Children with early language difficulties are subsequently at risk of both emotional and behavioral disorders (Stevenson et al. 1985). Early disruptive behavior is associated with other outcomes, such as internalizing disorders, reading difficulties, and low school achievement (Stevenson et al. 1985, Campbell 1990). Severe behavior problems in preschoolers can also predict multiple difficulties into adolescence (Lerner et al. 1985). Protective factors operate as well. For example, stable family functioning can prevent early temperamental difficulties from developing into later behavioral disorders.

Research has focused explicitly on the development of aggression and has shed light not only on the normative development of aggression but also on the development of pathological aggression and ways to prevent it. Historically, studies of violent individuals began with adolescents and followed them to adulthood. This led researchers to conclude that aggression peaked during late adolescence and young adulthood and decreased afterwards. This view also reflected the dominance at that time of social learning theory (Patterson 1982), which held that the children who would become violent later in life learned to be aggressive in childhood (Trembley 2004).

More recent longitudinal studies, begun with toddlers, have changed our view and reached two major conclusions. The first conclusion is that aggression peaks between 2 and 4 years of age, not late in adolescence or early adulthood (Trembley 2002, Côté et al. 2006). The second conclusion is that children typically fall into three major groups. For example, a nationally representative Canadian study of 10,000 children from 2 to 11 years of age found that about one-third of the children were essentially never aggressive across this age span, one-half were occasionally aggressive as toddlers and preschoolers but their aggression decreased until they were not aggressive by the age of 11 years, and one-sixth were already highly aggressive by the age of 2 years and remained so until they were 11 years old (Côté et al. 2006). These studies have dramatically changed our understanding of the normative development of aggression, have helped shift prevention efforts to focus on infants and toddlers, and have suggested that a major prevention strategy is to help young children regulate their anger and aggression, in contrast to the social learning approach of helping children to not learn to be aggressive from their parents (Patterson 1982).

Developmental psychopathology models continually confront us with the complexity of the development of preschool-age children. Both those who are at risk and those who are developing well provide insights into what young children can do, what they can learn, what they can feel, and what they can understand.

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CHAPTER

# 10 School-Age Development

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The age span discussed in this chapter is 6 years to pubescence. Demarcating this period as school age is an artifact of the public school system. However, research supports the concept that this period of childhood is a discrete stage in which new skills and neurodevelopmental capacities evolve. Freud (1905) discussed this phase of development as the result of the resolution of the Oedipus complex and noted subsequent reorganizations in behavior. Piaget (1929) emphasized that in this period the child achieves a new stage of operational thinking associated with new capacities for learning. He provided a detailed description of the concrete operations that bridge the preoperational stage and the later advent of abstract operations. This period has been characterized by different labels that reflect their theoretical origins. Freud referred to this period as "latency" to designate that early infantile sexuality is repressed and remains latent until puberty. Erikson (1963) called it the "age of industry," signifying the tendency of children during this stage to be persistent and task oriented. Sullivan (1940) simply referred to it as the "juvenile era," offering an explanation of the consolidation of early attachments and the bridge into adolescence.

Each of these models is based on the concept that there is a discontinuity from toddlerhood. Thomas and Chess (1977) argued that this period should simply be called "middle childhood," with the warning that more specific names represent the strong biases of theories. Some of these perspectives indicate continuities from early childhood into adulthood. Werner (1957) provided an alternative perspective of discontinuity and hierarchical reorganization, indicating that new functions emerge that are not easily derived from prior stages. Shapiro and Perry (1976) argued that the behaviors that become apparent during the period of middle childhood cannot be clearly foretold from the epigenetic sequences of the prior lives of children. Indeed, this is a period marked by a greater capacity and consequent opportunity to learn. These achievements have sufficient consistency across cultures to be considered a maturational discontinuity. These new capacities have been recognized repeatedly by new social roles as well as new cognitive capacities. Drawing on Spitz (1965), Emde and colleagues (1976) developed the concept of biodevelopmental shifts, based on a maturational succession of organizers that evolve in average expectable environments.

Puberty marks the end of this period and is associated with the onset of adolescent behaviors that are shaped by cultural expectations. However, puberty is not equivalent to adolescence, despite the reality that adolescence is often initiated by various social and religious rituals that presuppose biological maturity.

Middle childhood has been divided into early and late stages. In schools, the curriculum of pre-fourth graders focuses on reading and writing before the introduction of integrative studies such as social sciences and literature. Gesell and Ilg (1949) have provided the best behavioral descriptions of normal American school-age children. These studies began in the 1930s but are still valid. They wrote, "There is a kind of quieting down at seven. Six-year-olds tended to produce brash reactions and bursts of activities. The 7-year-old goes into lengthy periods of calmness and self-absorption." They further remarked, "At home, as at school, the child's personal social behavior shows an increasing awareness of both self and of others. He is more companionable. . . . He is not a good loser. He tattletales. If a playground situation grows too complex and things go badly, the 7-year-old runs home with a more or less righteous declaration, 'I am quitting.' Let us be duly grateful for his germinating righteousness. It is evident that the 7-year-old is developing an ethical sense." Concerning 8-year-olds, Gesell and Ilg continued, "Eight is more a person by adult standards and in terms of adult–child relationships. One converses with an 8-year-old with lessening condescension. . . . There are three traits that characterize the dynamics of his behavior: speediness, expansiveness, evaluativeness. The 9-year-old is no longer a mere child, nor is he yet a youth. Nine is an intermediate age in the middle zone which lies between the kindergarten and the junior high school teens."

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Within 4 years, there is a significant behavioral reorganization. There is a growing preoccupation with self, but also an increased interest in peer relationships. An expanded moral and social orientation helps the child first to bridge the preschool period with the new period and later to move into adolescence. Thus, middle childhood can be understood as a bridge as well as a stage in its own right. Moreover, it is a time in the life of a child when he/she is gathering the tools that will lead to a more adaptive adolescence.

## Conceptual Framework

The concept of lines of development outlined throughout this section provides a means of considering development in a dimensional manner. Anna Freud (1965) defined conceptual developmental lines (Figure 10–1) moving from egocentricity to companionship, from body tyranny to mastery over one's body, and from dependency to independence. All of these transitions represent examples of the tasks that are partly accomplished during middle childhood. There are times when some functions and skills lag behind others, and yet we can recognize a child who is passing through middle childhood.

Children of 6 and 7 years have long been believed to have achieved the capacity for some degree of independent action. In our culture, children remain dependent well into adolescence, but it is recognized that 6- and 7-year-olds are able to attend school and learn the basic skills that are necessary for his/her education and adaptation. Preschool and kindergarten currently provide early socialization experiences that previously occurred within the family. Preschool gatherings are preparatory for "real" schoolwork. Kohlberg and Gilligan (1971) commented that all cultures recognize "two great stages of transformation and development": one is at 5–7 years and the other is in adolescence.

The Roman Catholic Church considered the age of 7 years to be the age of reason (Aries and Baldick 1962) and recommended that first communion should appropriately take place then. Similarly, the early English kings determined that the age 7 years was significant for common law. Children younger than age 7 years were believed to be incapable not only of criminal intent but also of taking an oath to testify in a courtroom. At 7 years, boys were apprenticed as tradesmen and artisans to learn specific skills (Pinchbeck and Hewitt 1969).

During the industrial revolution, 7-year-olds were employed as laborers in factories. Because of their size they were often given positions as chimney sweeps or mine crawlers, which placed them at increased risk of a variety of industrial diseases and physical abuse. In the USA, the child labor laws were among the first laws to protect children. These laws were later expanded to curtail abusive practices involving adult laborers.

Freud looked at postoedipal latency as a major step in the development of the rules of civilized behavior (Shapiro 1977). Freud was presaged by Diderot and St. Augustine regarding the moral development of children. Diderot (1966) wrote, "If the little savage were left to himself, preserving all his foolishness and adding to all the small sense of a child in the cradle the violent passions of a man of thirty, he would strangle his father and lie with his mother." Augustine earlier wrote, "If babies are innocent, it is not for lack of will to do harm, but for lack of strength" (Rudnytsky and Spitz 1994).

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**Figure 10–1** *Developmental lines. [Adapted from Freud A (1981).]*

The Oedipus complex provides a basic human formula containing the permutations of the experiences of the developing child directed toward the first two important objects of dependence—mother and father. Freud's (1926) hierarchy of anxieties or danger signals includes the threat of castration as a mental deterrent to the wishes of this period and leads to repression of the constellations that are again revived in postadolescent children. Bornstein (1951) suggested that there is "a persistent denial of the struggle against the breakthrough of instinctual impulses" during the early period. Former lively desires are repressed and the latency child directs energy to the accomplishment of age-appropriate tasks.

There is sufficient variation in the course of middle childhood to lead some observers to question the capacity of the theory-driven model to explain the phenomena encountered. Longitudinal studies that traverse latency suggest a more linear developmental course (Thomas and Chess 1972, Offer and Offer 1975, Hauser et al. 1991). With the emergence of industriousness, an increase in number and kinds of relationships, and the importance of belonging to peer groups, five emergent patterns of development have been described. The first is characterized by a steady developmental progression through this period (Offer and Offer 1975, Neubauer and Flapan 1976). A second group has behavioral difficulties early in life, which are resolved during middle childhood. A third group presents with early behavior problems and develops new problems in middle childhood that are associated with new stressors. A fourth group has early behavioral problems that persist into middle childhood. A fifth group demonstrates entirely new problems in middle childhood.

A more specific group of children known as *difficult children* was distinguished by Chess and Thomas (1984). Difficult children express early behaviors that are correlated with later school problems, social difficulties, and psychiatric disorders. They show slower adaptability to new situations and intense negative reactions to stimuli.

Persistent difficulties from preschool through latency were first described in a London epidemiological study (Richman et al. 1982). Polysymptomatic 3-year-olds were found to show persistent trouble when they were followed up at 7 and 9 years of age. However, early epidemiological studies demonstrated that, with advancing age, there is a decrease in the prevalence of behavior disorders in middle-class school-age children (LaPouse and Monk 1959, McFarland et al. 1954). Later longitudinal data drawn from the Duneden studies show some persistent continuities (Caspi et al. 2003).

## Biological Development

Early biologically oriented investigations described the gradual cephalocaudad maturation and intersensory integration of the developing child with specific documentation of the discontinuities that seem to occur at ages 6 and 7 years. Many investigators showed the increasing regularity of mature

performance on a variety of visual–motor and neuroperceptual tests by the age 7 years (Piaget 1929, 1948, Pinchbeck and Hewitt 1969, McFarland et al. 1954, Pollock and Goldfarb 1957, Pollock and Gordon 1960). Seven-year-olds appreciate two simultaneous stimuli and can make more complex visual–motor and intersensory integrations. Seven-year-olds can also have established handedness, eyedness, and footedness, and haptic–auditory and auditory–visual integrations are more reliable (Birch and Lefford 1967). Motility is better integrated, motor sequencing behaviors are performed more accurately and smoothly, and athletic prowess emerges. Delays in some of these achievements have been called soft neurological or nonfocal neurological signs. If three or more signs are present in children older than 7 years, associations with psychopathology have been demonstrated (Hertzig 1982).

Magnetic resonance technologies, magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), are techniques for capturing features of brain development. Understanding the development of pathways underlying cognition, the experiences (experience-dependent learning) that alter them, and the patterns of physical development (maturation) that support them, should guide the study of both typical and atypical school-age development.

Studies have shown that cortical maturation corresponds to milestones in cognitive development (e.g., Gogtay et al. 2004, Sowell et al. 2004). Motor and sensory systems supporting primary functions are earliest to mature. Temporal and parietal association cortices involved in basic language skills and spatial attention follow and are the last to mature. Higher-order association areas, such as the prefrontal and lateral temporal cortices, modulate basic attention, and language processes (Gogtay et al. 2004, Sowell et al. 2004). Structural MRI studies show that loss of cortical gray matter occurs earliest in the primary sensorimotor areas and latest in the dorsolateral prefrontal cortex (Gogtay et al. 2004, Reiss et al. 1996). Shaw and colleagues (2006) report a shift in the correlation between IQ and cortical thickness with development. Specifically, the correlation is negative in early childhood but becomes positive in late childhood and beyond. The level of intelligence was found to be associated with the trajectory of cortical development in frontal regions. While grey matter decreases in a U-shaped fashion with age, white matter volume and density increase linearly (Giedd et al. 1999, Gogtay et al. 2004, Jernigan et al. 1991). These changes reflect, at least in part, ongoing myelination of axons, which enhances neuronal conduction and communication and may play a role in speed of processing.

Maturational changes in childhood have also been observed in subcortical regions that project to association cortex. Developmental changes have been demonstrated in parts of the basal ganglia, possibly reflecting the gradual elimination of certain connections and strengthening of others (Sowell et al. 1999, Gogtay et al. 2004). Studies have shown that the maturation of this circuitry has important implications for cognitive development and specifically cognitive control. The ability to suppress inappropriate thoughts or actions in order to select goal-appropriate alternatives, termed cognitive control, develops over the first two decades of life. A series of imaging studies of cognitive control indicate that children recruit larger and more diffuse prefrontal regions when performing these cognitive tasks than adults do (Brown et al. 2005, Durtson et al. 2006). This is consistent with more diffuse patterns of frontal activation in children relative to adults found in behavioral verbal fluency tasks (Gaillard et al. 2000).

Current "go–no go" paradigms, based on earlier studies designed to show how language can regulate behavior in a more articulated fashion, continue to show the gradual ability of children to become more proficient at following verbal instructions as they move from kindergarten toward puberty (Luria 1961). Tasks relating to attentional disposition have also been used to show the gradual approximation of adult reaction-time patterns during the 6–12-year-old span (Fan et al. 2002). Attentional tasks include orienting, alerting, and executing functions. Each of these tasks results in the activation of discrete brain areas and specific networks. Any distracter from the cue can increase reaction times if the distracter cannot be inhibited as nonsalient. In accord with the general rule of greater specificity and greater capacity to eliminate noise in favor of signal, school-age children become progressively better able to accurately respond, and the brain activations concurrently approach adult levels as the children mature (Posner 2001).

The time line in Figure 10–2 presents biological development from age 6 to 12 years.

## Cognitive Development

Piaget raised the question of what cognitive mechanisms underlie children's reasoning. His followers were able to achieve a new understanding of invariant sequences in cognitive development. These observations of basic developmental sequencing have been repeatedly demonstrated.

The initial cognitive sensory–motor organization of the child evolves to the preoperational stage after the child attains object permanence. However, it is not until about age 7 years that concrete operations are achieved, permitting children to effectively learn and utilize school instruction.

A number of significant transformations become possible with operational intelligence. There is a shift from egocentrism to being able to take another person's vantage point. An examiner can ask what the room would look like from the perspective of another. There is a shift to conservation of material volume and quantity and a shift to reversible operations. At this point, children can begin to understand that their speech and language are useful for social aims and story telling rather than simply for conveying desires and wishes.

The formal capacity for taking the vantage point of another on a perceptual task suggests a newfound possibility for perspective taking in emotion and empathy as well as achieving a firmer theory of mind. Up to age 7 years, simple repetition or monologues are possible. However, preschool children do not have true topic maintenance. Explanations are often noncausal and are cast in a mere sequential juxtaposition of desires, wishes, or events. Preoperational children use the word "because" nonconsequentially. By contrast, the concrete operational child can produce causal sequences. The child can now make predictions about relationships or about past–future relationships. In anticipation of going on a trip, the child can say, "When we get to Grandma's home, we'll go to the room that she has for us, and we'll put our toys away, and then we can go downstairs and have dinner, and then you can tuck me into the new

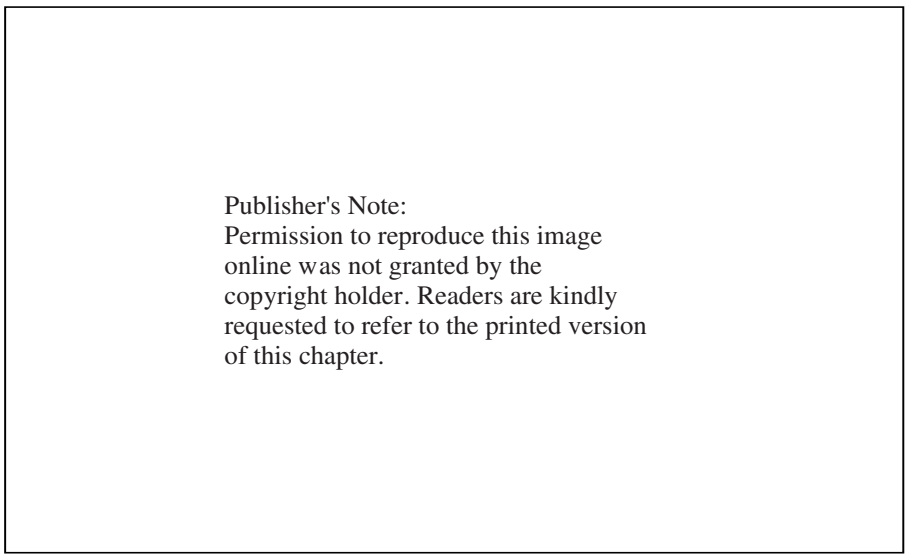



**Figure 10–2** *Biological development in the school-age child (6–12 years).*

bed." This sequence suggests that memories are operative and based on past experiences. Forward-looking adaptive discussion is possible.

The child of this age can understand that transformations of form can take place even though there is a constant material basis in reality. Thus, toys called "transformers" are based on the idea that a basic material module can be changed by manipulation of its parts. Noticing that the actors in a theater are actually children or adults who take on parts and then return to their former roles as ordinary persons is a feature of conservation. This conservation of person is also demonstrated materially. For example, colored liquid in a shallow pitcher is conserved as the same quantity when it is poured into a tall tubular pitcher, as are a row of coins whether spread out or piled together. These achievements indicate that there are shifts in the child's mental strategies available to assimilate new tasks in formal elementary education and logic. These new strategies permit comprehension and production of sequential relationships in story lines and also the integration of stories into larger generalized categories above and beyond the immediate task orientation.

An alternative to the Piagetian perspective, that is focus on a uniform change in children's problem-solving skills at each stage, is one that examines the set of strategies children use for problem solving, as well as the changes this strategy undergoes with development. Trial-by-trial analyses have shown a great deal of variability in the approaches of children to problems of arithmetic, spelling, and moral reasoning, which are the classical domains that have given rise to stage theories (Siegler et al. 1996). For example, trial-by-trial analysis of the performance of 5-year-olds in a number conservation task showed that they make judgments on the basis of not only the relative length of the rows, but also the type of transformation made, and the results of counting (Siegler 1995). The influence of this cognitive variability on the process of learning is largely determined by the efficiency of strategy selection. The school-age period has been the major focus of research on the adaptiveness of the strategy that children choose. An adaptive approach might be to use a fast strategy when speed is contextually important and the slower backup strategy when accuracy is emphasized. Age and experience are accompanied by acquisition of new strategies, changes in use of existing strategies, improvements in execution of strategies, and more adaptive choices between strategies (Lemaire and Siegler 1995). Generalization of strategies to new problems is a slow process, specifically in cases when other effective strategies exist (Kuhn et al. 1992, Siegler and Jenkins 1989).

Neopiagetians have challenged the strict sequential notions that mark the original model of Piaget. However, they do not take issue with the idea of the constant set of transformations and the increasing capacity for new mental strategies and varying forms of logical integration that are characteristic of this period. Kendler and Kendler (1962) showed that children of age 7 years can solve particular cognitive experimental sequences that demonstrate that they now use integrative reasoning, insight, and inferential behavior. White (1965) offered a comprehensive summary of the discontinuity and developmental achievements of middle childhood, recommending that the hierarchical arrangement that was suggested by Werner (1957) on theoretical grounds was valid. These new cognitive strategies are also geared toward change in language representation. White described the new capacity to maintain a constant orientation toward an invariant dimension even though the surroundings are varied. These new modes are not simply epigenetic in their organization based on cumulative achievements; they are indeed new skills based on new integrative cognitive structures.

The time line in Figure 10–3 presents cognitive development from age 6 to 12 years.

## Emotional Development

If we look at emotions as native dispositions represented by the seven emotions of Darwin, we observe that the emotional life of infants and toddlers is reciprocally modulated in relation to the caretaking environment by feedback behaviors defined as *social referencing* (Klinnert et al. 1986). Mahler and associates (1975) described the checking

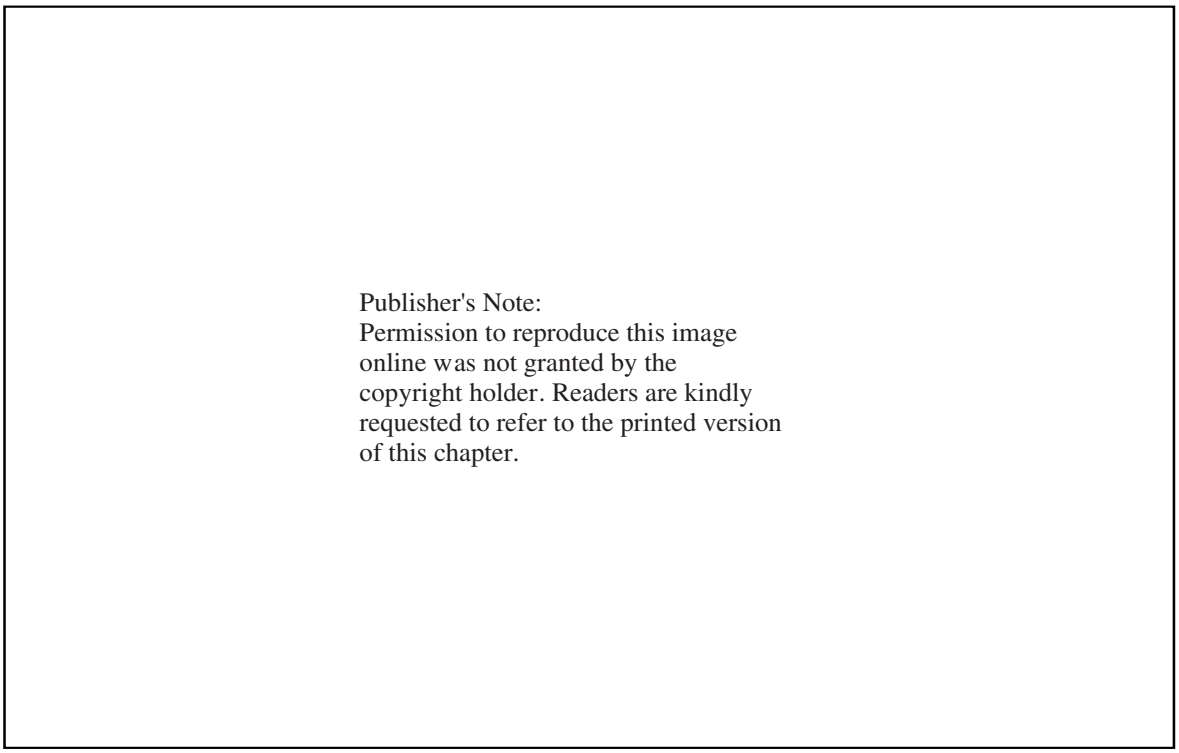



**Figure 10–3** *Cognitive development in the school-age child (6–12 years).*

and "refueling" that take place during development in 2–3-year-olds. Two lines of investigation address the precursors to emotional development in latency, which are significant. One pertains to the follow-up studies on security of attachment at 18 months using the strange situation paradigm of Ainsworth et al. (1978). The other line of research concerns temperamental variation in early childhood and its predictive value for emotional modulation and expression during middle childhood. Sroufe and Fleeson (1984) showed that by the time securely attached children are 8, 9, and 10 years old, they are more socially adaptive and have better peer interactions (Sroufe et al. 1999). However, the earlier measure does not guarantee good outcome, as there are many significant transactional social and familial factors that mitigate development.

The work of Chess and Thomas (1984) has already been cited with regard to the continuities and discontinuities that they found in the difficult child. Such continuities only account for a small amount of the variance of later outcome.

Although epidemiological studies show that depression is not highly prevalent in middle childhood, it is now clear that major depressive disorders do occur (Puig-Antich and Rabinovich 1986, Kovacs 1989). There is a rising rate of emotional disorders in early adolescence, followed by a steep, continuing rise of incidence of these disorders into late adolescence. Kagan et al. (1989) showed that early behavioral and emotional inhibition often evolves in middle childhood as anxiety disorders that match parental anxiety and may reflect a genetic origin. This method of tracking the extremes from early childhood suggests a useful research strategy for the study of the genetic determinants of behavior.

The modulation of emotions by new cognitive structures was thought to occur as a result of a signal of anxiety triggered by perceived dangers concerning bodily harm. This was thought at times to take the form of behavioral separation anxiety (Freud 1926). In the later forms, school avoidance and school reluctance may be the major features of manifest anxiety seen in the clinic (Shapiro and Jegede 1973). The idea that the modal latency-age child is more emotionally contained than the exuberant preschooler has not been found across cultures, just as the postulated diminution of sexuality was shown to be culturally bound (Ford and Beach 1951). These findings notwithstanding, Ramsey (1943) found that rates of masturbation in boys rose from 10% at age 7 years to more than 80% at age 13 years.

There are also suggestions that development provides a trigger for gene expression at various times in childhood. Thus, it may not be only the condition of changing dependency that is central to the emergence of mood disorders. Support for the discontinuity model is provided by the observation that children with the earliest expression of major depression seem to have a different course from those with a later onset (Kovacs 1989). It is during this period of middle childhood that peer socialization takes on new significance, becoming an additional boost to feelings of approval and self-esteem. At a biological level, the progressive maturity of the dorsolateral frontal cortex places the brain under the most forceful modulating effect, guaranteeing less impulsivity.

## Sociocultural Development

Erikson (1963) provided an epigenetic model that maintains that prior stages have strong influences on the later stages of development. His model contrasts with discontinuity

models insofar, as traversing a stage-phase boundary does not permit the developing child to leave behind the "faults" that characterized a prior stage. By contrast, the discontinuity model offers the possibility for reorganizations without the necessary continuing major impact of earlier dynamisms. Sociocultural behavior of middle childhood has been described most extensively for middle-class US culture, although some poor and inner-city populations have been studied. Many behaviors of middle childhood can be construed as new aspects of the socialization process that is fostered by schools, community involvement, and the gradual distancing from the family.

Children of this age form clubs that mimic parental social groups. The "natural club" of the school-age child borrows from larger societal forms, but, unlike the Cub Scouts or Brownies, it does not accept the rules offered by adult structures. The rules are provided by a new oligarchy of strong-minded children experimenting with leadership, demanding many CEOs and fewer workers.

Secrets and collecting are important. The tendency to collect everything from bottle caps to baseball and Pokeman cards has led to widespread advertising that stimulates peer pressure. More sports-minded children can become devoted to collecting enormous cadres of statistics regarding their favorite sport. Children who may not perform as well in athletics often turn to collecting. If you cannot hit home runs, you can at least have at your fingertips the names and records of baseball heroes to impress your peers. The traditional image of the child emptying pockets stocked with pieces of string, small stones, keys, and other personal treasures is typical of this period. Stamp collecting and coin collecting have their origins and fascinations during this period and lead to increased knowledge that parallels and enhances the learning of geology, geography, and history. Newer collections based on current fads bring the child into his/her peer culture. Devotion to particular forms of attire also becomes clearly delineated at this point, as social consciousness rises with respect to what is "in" and what is "gross." Children may also become rather cruel toward each other with regard to teasing or "tacky" name-calling. Particular styles of dress become associated with idealized figures and are treasured with regard to early crushes and devotions that become paramount in adolescence.

The concept of a joke can be appreciated in a new way during middle childhood, as "knock–knock" jokes are replaced by more pointed stories with clear punch lines. The school-age child can be reduced to hysterical laughter by bathroom humor. Explicit virtuoso performances of burps or flatus are exceedingly popular. The titter that is created by these demonstrations sometimes evolves into belly laughs that adults find silly or inappropriate.

Mastery of the body is also a prominent theme during latency. A latency-age child may shoot baskets or practice the piano for hours. Boys may endlessly grease and pound a new baseball glove to make the perfect pocket. Girls of this age are likely to dance or exercise for hours on end.

The unisex friendships of this period lead to a number of avoidant practices that emerge in groups. The frequent culturally determined "cooties," a mythical contagious disease that comes from touching a person of the opposite sex, serve the function of maintaining a safe sexual distance. The notion of contamination by those who are sexually active and the reaction formation of expressing disgust at the thought of kissing and turning away from romantic scenes in films are prominent behaviors during this period. The tendency to establish same-sex groupings becomes more pronounced at ages 7 and 8 years.

Shame serves as another social regulator. Any suggestion of romantic attachment or interest in someone of the opposite sex may raise titters among latency children, with embarrassment as a deterrent. During this time, boys and girls are trained to "one-up" each other, with the threat of potential humiliation. Skill at sports, dance, or other physical prowess often leads to increased socialization and enhanced self-esteem and competence during middle childhood. Peers have little tolerance of boys who deviate from clear gender role play. Anthropological investigations show that most cultures provide rituals that accompany the transition to adult male status and that preparation for these rituals begins during middle childhood (Gilmore 1990).

Anthropologists also have indicated that in cultures other than middle-class US culture and also within ghetto cultures, sexuality is not dormant. Variations in latency are determined by aspects of permission and prohibition within each culture. Erikson (1963) described the variations in Native American and urban US cultures. Maccoby (1990) conducted studies modifying our notion of the latent period in middle-class US samples. Nonetheless, although some cultures do not appear to show a latency, most take some notice of prepubertal status, because it is during the next phase that most of the rites and privileges of young adulthood are bestowed by ceremonial or ritual behaviors, permitting children to enter into adult practices. It is a time when respect for parents and larger cultural institutions begins to be solidified.

## Moral Development

Moral development may be looked at as an independent line that describes the capacity of the child to act in accord with conscience and moral imperatives rather than egocentric values. The belief that the superego was formed as a residue of identifications and drive resolution at the end of the oedipal stage has been modified by new evidence of internal control in accord with the development of moral injunction during the preschool years (Buchsbaum and Emde 1990). Nonetheless, the internalized "oughts" and "shoulds" of the latency period represent a new cognitive advance and a new capacity to contain emotions that sometimes lead to conflict and/or exceedingly rigid moral restraint. It is a period when an 8-year-old can turn on his or her father for the slightest moral infraction for the sake of obeying the code. It is a time when children receiving religious education chide their parents for not following the rules and not attending church. Latency-age children frequently recognize parental hypocrisy preceding the more widely recognized phenomenon of adolescent protest. There is a tendency for good and bad to take on absolute valence that allows little room for shades of gray.

Gilligan (1982) has found in naturalistic observations that the quality of mercy that was involved in human interactions and concern for interaction is more characteristic of girls than of boys. Boys in contrast tend to seek blind justice.

Piaget (1948) studied how children use varying systems of rules. He observed boys playing a game of marbles and,

feigning ignorance, asking how the game worked. He concluded that there were stages in the acquisition of moral judgments. From 4 to 7 years, children appear egocentric because they are not able to take another's perspective. They follow a fluctuating set of rules that is governed by inner dictates. From 7 to 11 years, rules are followed more carefully. Only at 11 or 12 years are absolute rules scrupulously demanded in rule-governed games. He also found that 5–9-year-old children believe that rules are inviolable, originating in some obscure absolute authority. However, 10- or 11-year-old children question this and show the ability to consider social contracts mutable. Piaget similarly studied ethical questions, showing that younger children believe that if something bad is done, punishment must follow. In contrast, older children take motivation into account, asking what the individual meant to do. Children's sense of fairness also begins to evolve during this time, and the idea of "it isn't fair" emerges. Colby et al. (1983) and Colby and Kohlberg (1987) used Piagetian techniques to study the response to moral dilemmas at various ages.

The six stages of moral development described by Kohlberg were believed to have an invariable sequence, mimicking Piaget's scheme (Table 10–1). The first two stages were called preconventional morality. The vast majority of 10-year-olds were found to be at this level. The first stage is egocentric, with the rights of others being irrelevant. Action at this stage is deferred to avoid punishment. The second-stage child acknowledges that other people have interests too, but the child's own interest prevails at this level. Conventional morality, stage 3, involves being good by living up to what people generally expect of one. By stage 4, the child is oriented toward maintaining the social norm. At postconventional morality, a child may consider questions from both a moral and a legal point of view, even acknowledging that there might be conflict. At stage 6, there is consideration of a universal moral principle of justice that may override human law. Walker (1989) found some support for Kohlberg's sequencing of stages but not for the existence of significant differences between the sexes. Smetana and colleagues (1991) studied third, sixth, and ninth graders and found little support for Gilligan's differential between boys and girls, commenting that there were few sex differences between interpersonal considerations and issues of justice, while the precursors of moral judgment are already present in 3-year-olds; according to Buchsbaum and Emde (1990), there is a consolidation of moral rules during latency marked by excessive rigidity, which becomes more broadly conceived in light of reason and the human condition as adolescence proceeds.

**Table 10–1 Kohlberg's Stages of Moral Development**

| | | |
|---|---|---|
| Preconventional: | Stage 1 | Children at this stage are egocentric and experience difficulty with perspective taking when considering moral dilemmas. Motives and intentions are ignored when judging the goodness or badness of a behavior. |
| Emphasis on avoiding punishments and getting rewards | Might makes right (punishment and obedience orientation) | |
| | Stage 2<br>Look out for number one (instrumental and relativist orientation) | Recognition that others have different points of view occurs at this stage, but this understanding is still somewhat limited. Action is viewed as right if it satisfies one's needs. The reason to be nice to people is that they will also be nice to you. |
| Conventional: | Stage 3<br>"Good girl" and "nice boy" | Approval is more important than any specific reward. The individual has newly acquired abilities for mutual perspective taking. In this stage, a person can anticipate what another person is feeling and knows that other people also have this ability. |
| Emphasis on social rules and conformity to social norms | | |
| | Stage 4<br>Law and order | The individual can now take into consideration societal laws when deciding a course of action. A behavior is considered right if it involves obeying rules established by authority. |
| Postconventional: | Stage 5 | Rules are regarded as more flexible, with the aim of furthering human values. They are not absolute. This stage emphasizes fair procedures for interpreting and changing the law when the law is destructive or unethical. Ethics are considered when evaluating laws. |
| Emphasis on moral principles and values | Social contract, legalistic | |
| | Stage 6<br>Universal ethical principles | At this stage, there is the recognition that some principles and values (i.e., "life is sacred") transcend laws and that some moral obligations are valid for humanity. |

*Source*: Kohlberg L (1964) "Children's Statements Illustrating Developmental Stages an Two Aspects of Morality" In Review of Child Development Research, Reprinted with permission. Russell Sage Foundation, New York, USA pp. 383–432.

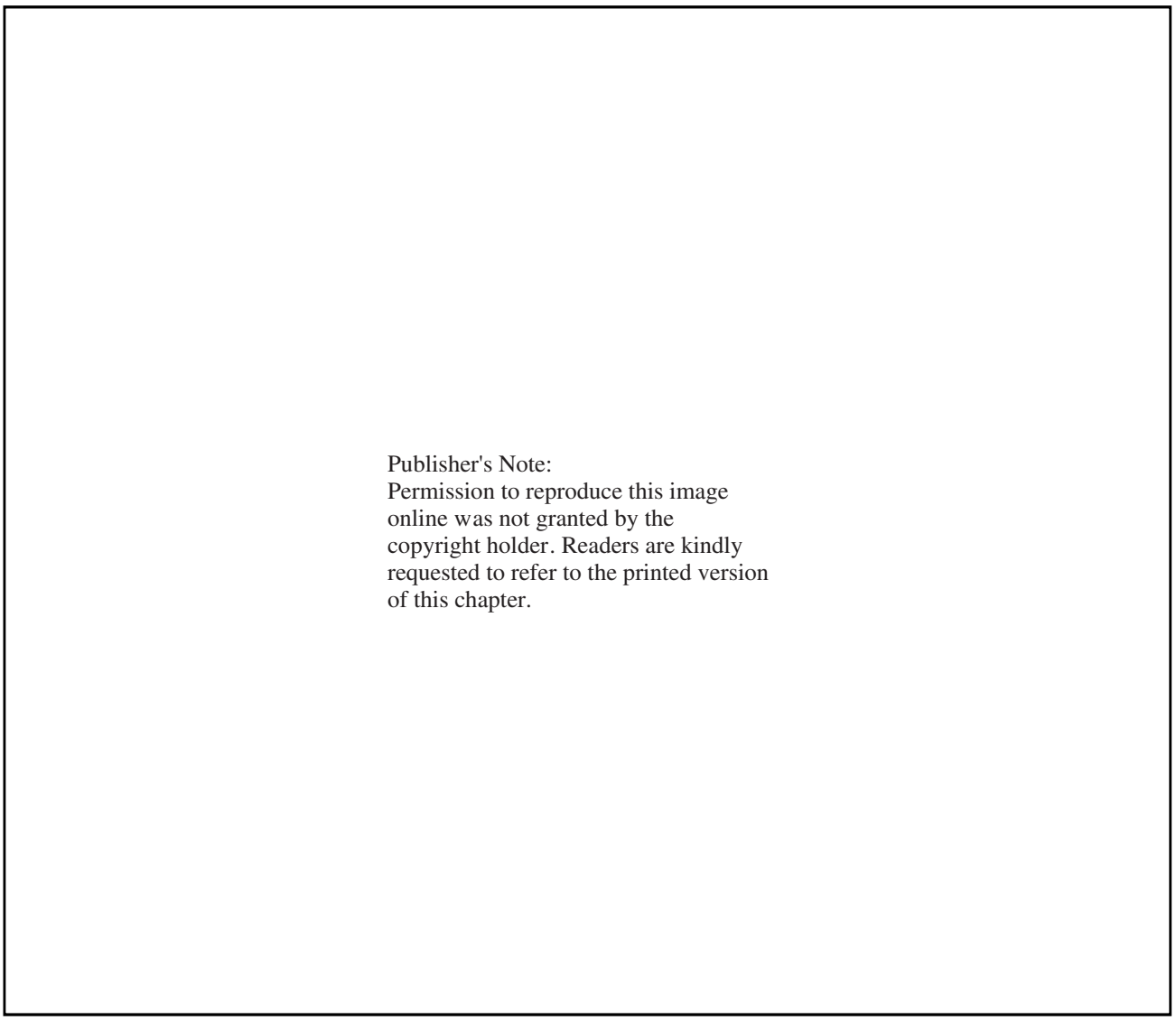



**Figure 10–5** *Moral development in the school-age child (6–12 years).*

Figures 10–4, 10–5, and 10–6 present time lines for emotional, moral, and social development in 6–12-year-olds.

## Risk and Protective Factors

During the school-age years, the prevalence of psychiatric disorders begins to rise. Prepubertal depression is associated with a worse prognosis (Kovacs 1989). Attention-deficit hyperactivity/disorder increases in prevalence as school demands increase. Separation disorders emerge as schooling away from home becomes mandatory (Shapiro and Jegede 1973). Children who are prone to conduct disorders show their symptoms more prominently when new demands of school are introduced. The onset of psychopathology is linked to "turning on" genes. This process must be understood within the context of risk and protective factors. Sameroff and Chandler (1975) examined the notion of a continuum of reproductive casualty and found that social influences become more significant among the factors that account for the expression of disorder. If problems related to early biological hazards are considered, the school-age child's problems are better accounted for on the basis of sociofamilial factors than perinatal insult. Specifically, the status of growing up in extreme poverty, in a single-parent family, and being subjected to child abuse is more highly associated with the onset of psychopathology than the occurrence of early anoxia, prematurity, or complications of delivery. Early positive influences must also be considered. For example, programs such as Head Start seem to have protective influences later in development (Consortium for Longitudinal Studies 1983).

## Developmental Psychopathology

The middle years are marked by a new availability of skills and coping mechanisms, permitting children to expand

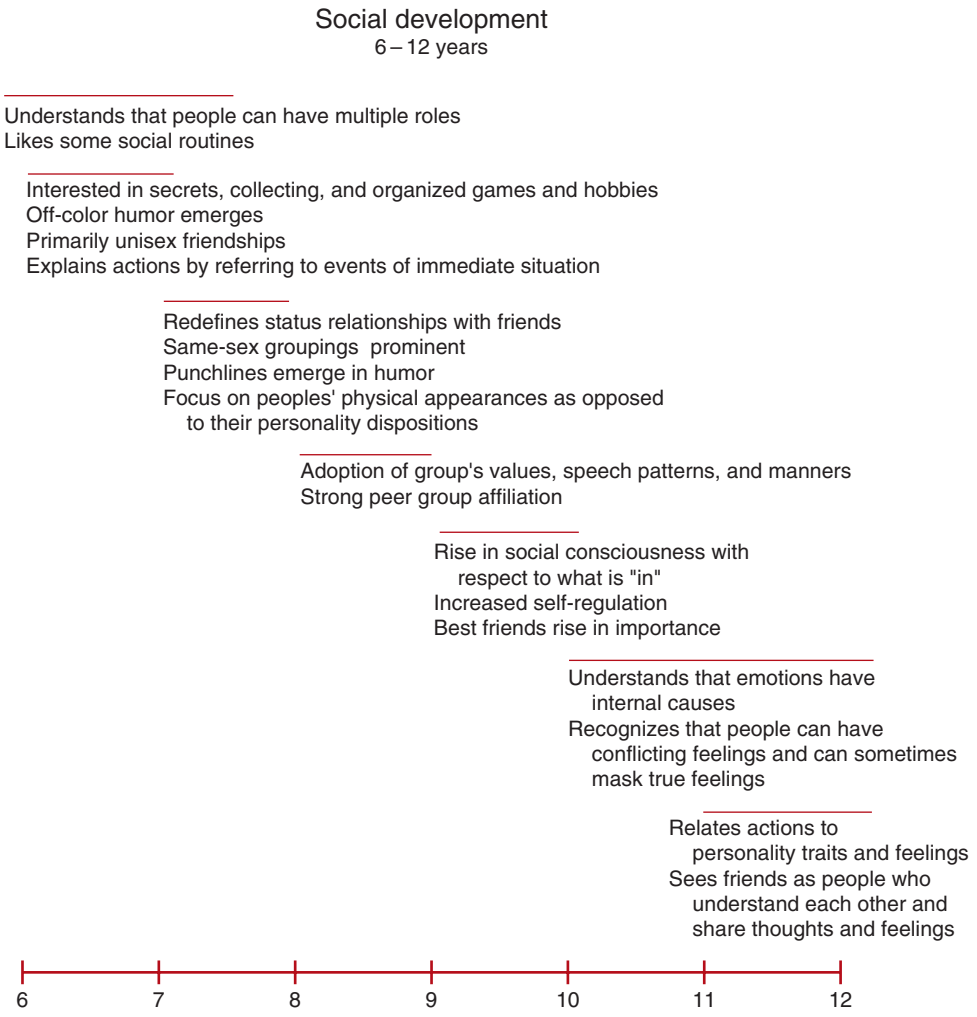



**Figure 10–6** *Social development in the school-age child (6–12 years).*

their achievements when appropriate support systems are available. The emergence of psychopathology can be understood from the perspective of factors that enhance or inhibit these new roles or skills. It is widely accepted that developmental psychopathology is the result of multiple causes (Cicchetti and Cohen, 1995). The origins of psychopathology are best understood by examinations of both successful and unsuccessful adaptations, always maintaining that psychopathology occurs in the developing organism. Anxiety disorders are of the most prevalent form of *emotional* psychopathology in school-age children (Costello et al. 2003, Ford et al. 2003). Many *cognitive* childhood disorders have at their core some deficit in the suppression of inappropriate thoughts or behaviors.

There are factors that predispose children to developing anxiety disorders and others that are protective. Neuroticism, behavioral inhibition, and disgust sensitivity are genetically based factors thought to play a role in the pathogenesis of childhood anxiety disorders (Muris 2006). Experiential factors include negative life events and family dynamics (Dadds and Roth 2001). Indeed, early attachment relationships have been shown to influence the pathogenesis of childhood anxiety disorders. Effortful control has been cited as a protective factor. This is defined as the ability to effectively regulate thoughts and behavior for goal-appropriate action. Interestingly, several disorders that emerge during the school-age years are characterized by disruptions in this effortful control.

Children with attention deficit hyperactivity disorder have problems with attentional focus, distractibility, and impulsivity (Barkley 1997, Casey et al. 1997a, 1997b, Trommer et al. 1991). In Tourette syndrome, children have difficulty suppressing either movements or vocalizations (Leckman et al. 1987). Obsessive compulsive disorder is described as an inability to suppress intrusive thoughts or behaviors, and in childhood-onset schizophrenia children cannot control attending to inappropriate thoughts and information (Asarnow et al. 1995). While the specifics of the disorders are different, all share an inability to override irrelevant thoughts or behaviors, and all have been shown to involve the basal ganglia and the prefrontal cortex, which is known to be maturing during middle childhood.

The tasks and challenges of the school-age period represent an amalgam of cognitive and emotional maturation. Developmental course can be enriched or impoverished by the environment. Success in mastering environmental challenges during the school years provides an important foundation for the challenges of adolescence.

Sexual dimorphism supported by the strong effect of societal norms is at its height in this period. Postpubertal

sexual behaviors are cultivated during latency. As Erikson (1963) noted, this is a period of industry in which tools for the intellectual work to come are forged, but prepubatal fantasy and sexual role definition are also silently cultivated. Thus, areas such as sexual role, identity, and partner choice are significantly influenced by the prior period of latency.

### Clinical Vignette 1

This case demonstrates the interplay between biological predispositions and current stressors, which permits the expression of emergent pathological conditions in the middle school years. Josh was a vulnerable infant who had suffered seizures and had a restrictive temperament. His mother's panic and his parents' separation augmented his rising anxiety. Unfortunately, his anxiety was aggravated by the anxiety that his mother experienced.

### Clinical Vignette 2

Josh, a 7-year-old boy, was in second grade for about 1 month when he had a mild febrile illness that kept him at home for 2 days. Because the next day was Friday and his mother was at home for the day, she permitted Josh to recover over the long weekend. He and his 5-year-old brother Kevin played well. His mother seemed quite pleased that the three of them had these days to spend together.

On Monday morning, Josh did not want to go to school. He protested that his stomach and head hurt. He also said that he was worried that his mother would be hurt at her job. His mother worried that Josh was ill again and decided to stay home with him. Within 40 minutes, Josh seemed content and happy, but he was reluctant to let his mother out of his sight. However, he promised that he would go to school in the morning. The next day he was again reluctant to go to school and wept bitterly as his mother became increasingly anxious and angry. This pattern continued each morning throughout the week. Consequently, his mother was advised to obtain a child psychiatric consultation.

The development history revealed that Josh's mother separated from his father when he was 5 years old. Although his father had been conscientious in his visitation, there had been an altercation about child support between his parents and unpleasant accusations had been exchanged. Josh overheard these arguments and became progressively worried about his mother and his own safety. Josh's mother had suffered from panic anxiety for many years. She found it difficult to maintain social relationships and was generally fearful about her children when she became anxious about their safety.

Josh was a normal full-term infant, but he had developed an elevated bilirubin level that required ultraviolet light treatment. He had two febrile seizures before he was 18 months old and was temporarily given phenobarbital. He had frequent otitis media and was described a "slow to warm up" child with a cautious restrictive temperament. His motor and language landmarks were all well within normal limits, but when he began kindergarten, he took longer to get used to the daily separations than his peers. Otherwise, he was a bright, imaginative youngster who did well in one-on-one interactions.

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CHAPTER

# 11 Adolescent Development

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Adolescence is the developmental phase that spans the transition from relatively complete childlike reliance on parents to nearly complete self-reliance for the management of one's own life (Kett 1997). Although the term adolescence did not have its current meaning before the middle of the nineteenth century, young people have always had to make the transition from being considered dependent children to being regarded as independent adults. This transition occurs in almost all societies. Although the Bible, St. Augustine, and Shakespeare have commented on the joys, dangers, and sorrows of this transition period, it has been studied only in this century (Hall 1882). In premodern times, the passage to adulthood was demarcated by a puberty rite. Before enacting the rite, one was a child; after completing it, one was an adult. This ritual was far more explicit than it is today. The contemporary steps include a variety of experiences such as first communion, bar mitzvah and bat mitzvah, paying the full cost for social events and being granted certain privileges such as driving legally, consuming alcohol, voting, and performing military service.

It appears that different societies have different time frames for this transition, and even the same society is likely to modify the steps and ages over time. The clearer and narrower a society is in its definition of and expectations for adulthood, the more smoothly the child passes through adolescence. Greater freedom fosters greater latitude for the young person and generates greater confusion about what constitutes an adult to the individual, his or her parents, and society.

The changes during adolescence span physical, psychological, and emotional domains. Near the time of puberty, there is a sudden increase in the size of hands and feet, height, body hair, and genitalia. Boys experience a voice change and an increase in muscle mass; girls develop breasts and begin menstruation. Thinking also changes. Particularly for boys, sexual thoughts become more common, explicit, and intrusive, and there is an upsurge of aggressive feelings and urges. However, the timing of these changes is highly variable.

Girls typically enter puberty about 2 years earlier than boys, but for both sexes the age of onset of puberty is highly variable. Some girls begin their growth spurt as early as age 9 or 10 years and are physically adults 4 or 5 years before late-developing boys even begin their pubertal changes. Consequently, one contribution to the emotional chaos of this age group stems from the widely divergent physical and emotional development of its members. A seventh- or eighth-grade classroom is filled with ever-changing strangers, and teachers must cope with the diversity of physical and emotional maturity within the constraints of the same curriculum, textbooks, sports matches, and social events. Not only is there a disparity in appearance among students, but how individual students feel about themselves is often in flux as well. It is not unusual for a young adolescent to feel and behave maturely and independently in one context and then childishly and dependently in another.

It is useful to divide adolescence into three overlapping biopsychosocial phases (Table 11–1) that are epigenetic in that each leads to the next. However, there are wide variations among individuals with regard to the age at onset and duration of each phase. On average, girls precede boys into each phase. Early adolescence typically begins near the end of grade school or the beginning of middle school. This phase is characterized by a growth spurt, beginning development of secondary sex characteristics, greater social separation from parents and family, and greater affinity with peers. These shifts are often manifested by changes in attitude, clothing, and hairstyle. It is common for adolescents and their parents to harbor doubts about whether the changes in body and thought are normal, and reassurance is often sought from the family physician or pediatrician about these fears. Masturbation begins or becomes more frequent, and although there may be strong romantic crushes on older and unobtainable persons, the peer group

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**Table 11–1 Phases of Adolescence**

| Phase | Age (Years) | Characteristic |
|---|---|---|
| Early | 11–13 | Growth spurt, development of secondary sex characteristics, beginning of social separation from parents and family, and greater affinity with peers |
| Middle | 14–16 | Consolidation of sense of self, increased sexual experimentation, and decreased sense of threat from adults |
| Late | 17–19 | Concerns about entering adult life—work, independence, and intimacy |

remains predominantly unisexual. Concerns about possible homosexuality are common, especially for boys.

Midadolescence typically occurs during the middle teenage years, and sexual experimentation between teenagers usually begins at this time. As the individual gains a more consolidated and surer sense of himself or herself, there are more serenity and less uncertainty about sexual orientation. Late adolescence, which typically takes place during the late teens, is a time of assuming adult responsibilities and perspectives rather than focusing on earlier conflicts related to dependency. This requires decisions about school, work, leaving home, and romantic relationships and commitments.

**Table 11–2 Ideal Task Accomplishment to Attain Adolescence**

- Disengagement from parents along with ability to make decisions about one's life
- Value system respecting self and others
- Solid employment, possibly beginning a vocation
- Fixed sexual identity
- Long-term sexual relationship

Table 11–2 shows a set of tasks that are accomplished by psychologically healthy adults (Schowalter 1995). These tasks are seldom fully completed by the end of the teenage years or even in the early 20s but represent key development objectives for this period.

## Historical Perspectives

Kett (1977) claimed that "every generation of intellectuals since 1820 has been convinced that an acceleration of the velocity of social change has disrupted traditional harmony and has had a calamitous effect on youth," but it seems clear that the industrial revolution of the late nineteenth century was crucial for the structuring of adolescence as we now know it. Earlier, teenagers had been expected to perform tasks that required strong backs, good endurance, a willingness to work for little pay, and little experience. Machines became the ideal substitute for this workforce, and in the late nineteenth century, there was a diminishing need for teenagers in the workplace. This displacement continues and has had important economic ramifications for society and personal implications for adolescents and their parents. Before the twenty-first century, children in this country were usually considered an asset for the family. In a mainly agricultural society, they helped around the house and out in the fields. Usually, formal education was available only for boys in the upper classes. Apprenticeships granted to teenagers who were not required for family work provided the opportunity for these boys to learn trades other than those of their fathers.

Kett believed that adolescence as a developmental phase was "invented" by the American psychologist G. Stanley Hall, who influenced the public's opinion of teenagers. Struck by the religiosity of many young people, Hall (1882) stated that religious conversions are most dramatic for persons in their second decade of life.

Hall theorized that religious awakening and sexual awakening had many similarities and that through maturation they both began at about the same time. He conceived of adolescence as a "new start" or recapitulation of an earlier age. Some psychoanalysts proposed similar theories about the possibility of experiential traits being passed genetically (Kett 1977). Hall (1904) focused on the importance of biological heritage and minimized social factors. When the Boy Scouts began in the USA in 1910, its leaders were influenced by Hall's anthropomorphic notions. For example, it was believed that adolescents should be in the outdoors because this was how young people traditionally learned to look after themselves and to become independent.

Hall's theory, which stressed recapitulation and biological inevitability, was reassuring to parents and educators because it explained teenage behavior without attributing blame. Adolescence was just a difficult time. Kett noted that although Hall originally conceived the age of adolescence as extending into the early 20s, his educator followers shifted the time frame of adolescence to be coincidental with secondary school. Eventually, adolescence became synonymous with the years between the end of primary school and the leaving of school in the middle to late teens, although this is artificially too brief.

Sigmund Freud (1953) in *Three Essays on the Theory of Sexuality* declared that puberty was not when sexuality emerged. Rather, humans experience an active and varied array of sexual wishes and feelings from the time of infancy. Freud believed puberty was the time when the genital zone attained primacy. He proposed that this occurred when the earlier oral, anal, and phallic sexual instincts come under the sway of the reproductive function. Psychoanalysts have debated the preeminent importance of the first 3 years of life, the oedipal period of about ages 4–6 years, and the period of adolescence for adult development.

Anna Freud (1946) in *The Ego and the Mechanisms of Defence* focused on the adolescent years. She described the mind's defense mechanisms and highlighted their use for adaptation during adolescence.

Blos (1962) stressed that the two primary and interacting developmental themes for adolescents are the revival of the Oedipus complex and the need to disengage from the close childhood-based ties to parents. Blos proposed that a major problem arises when the adolescent withdraws emotionally from the parents and from the parents' values. This leaves the adolescent bereft of accustomed moral underpinnings just at the time when sexual and aggressive fantasies and urges are greatest.

Psychoanalysts emphasized that adolescence was a time of *Sturm und Drang*—storm and stress. By the 1960s

and 1970s, research began to indicate that emotional upheaval was not necessary for a successful transition from childhood to adulthood. Offer (1969) and colleagues (Offer et al. 1989) studied high school students in Chicago and reported that a large majority displayed relatively little turmoil. Although these youngsters became more attached to and influenced by peers, they were still most powerfully influenced by their parents. Rutter and colleagues (1976) reported on studies demonstrating that major turmoil during adolescence was not a developmental necessity. Rutter believed that adolescents often feel more misery than is noticed by parents and other adults but that the degree of turmoil and its psychiatric importance had been exaggerated in earlier clinical reports. This view opened the way to a more modern, empirically driven view of cognitive and emotional development during adolescence.

## Conceptual Framework

The conceptual framework draws on concepts of continuity and linkage. The sections of this chapter consider biological, cognitive, social, and moral development as separate pathways, but each has its inception in childhood and merges imperceptibly into adulthood. Thus, development can be viewed as a continuous process that begins with the absolute helplessness and dependency of an infant and proceeds toward the capacity to fulfill one's own requirements and to effect propagation of the species. At any one point there is continuity, connections with the previous and succeeding points on this continuum. For example, adolescents' first experiences with members of the opposite sex are influenced by prior experiences with same-sex relationships in childhood and in turn may affect later decisions about their adult choice of a sexual partner.

Moreover, this continuum is composed of a number of simultaneous developmental events that occur at different levels in different domains (Figure 11–1). These events and domains are said to be linked. That is, they are related to one another and influence one another but are not epigenetically dependent on one another. At any one moment, an individual may be more mature in one domain than in another. Yet the interplay of these domains affects overall development in a fundamental way. For illustration, one domain, such as heightened motor skills, may interact with a separate domain, such as enhanced cognitive abilities, resulting in improved athletic performance. Increased strength and reflex speed do not activate the ability to perceive weaknesses and form a strategy for defeating an opponent. However, when they are combined, the player may be more victorious on the field. Subsequent varsity success may affect self-image and peer social status.

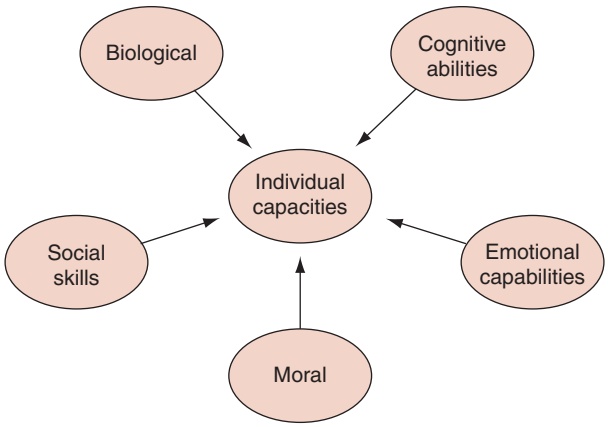



**Figure 11–1** *Interplay of developmental domains.*

At each arbitrarily defined phase there are tasks, responsibilities, and pressures that are particularly characteristic of that time. Across individuals, no matter how different the sources of these demands and pressures may be, the conflicts of a particular developmental phase are remarkably similar. Thus, it has been argued that adolescence recapitulates the struggles of toddlerhood, but at a different level (Blos 1962). One similarity between these two developmental phases is the conflict between wishes for self-sufficiency and the recognition that one's capacities are not yet at a level that permits these strivings to be fulfilled. However, major differences exist. The limitations of adolescence are derived from much broader realms than those of the toddler. The immediate source of limitations on strivings for adulthood may be physical, familial, cultural, or social. Moreover, the pressures on adolescents stem from both internal and external sources. Examples of internal sources are sexual urges and capacities, longings for self-sufficiency, awareness of new capabilities, and feelings of dependency and uncertainty. Some examples of external sources are the tacit requirements for being a responsible member of society, expanded parental expectations, and more intense and complex peer pressures that exert demands to "fit in."

The negotiation of these conflicting pressures is determined by the interplay of biological, social, familial, cultural, and psychological factors. Although there is continuity in some of these domains, there are also discontinuous events. Falling ill with a chronic viral disease, suffering a traumatic physical injury, experiencing war, living in a period of economic decline, or experiencing sudden parental death may not be related to what has come before but certainly influences what follows. Models of development cannot take these more random events into account, but the factors that influence successful accommodation to them are probably rooted in the same elements that promote optimal adaptation to the predictable conflicts of development. There is a bias in the assumption that these unpredictable events typically exert an adverse effect on development. Positive developmental consequences of unpredictable events are also possible.

## Biological Development

Adolescence is related but not identical to puberty. Puberty is a biological event, whereas adolescence is a period designated by society. The biological changes of puberty may predate or may not have occurred by the age that society has designated as the definition of adulthood. Puberty originates from the Latin *puber*, which refers to "being of marriageable age." This linguistic link implies an emerging capacity for reproduction. There is a prominent implication of the primacy of biological capacities in the understanding of this stage of development. These biological changes are both the most rapid and the most striking of the physical changes that the body experiences after infancy. By the end of this stage of development, the body has reached adult stature and sexual appearance. Biological changes include

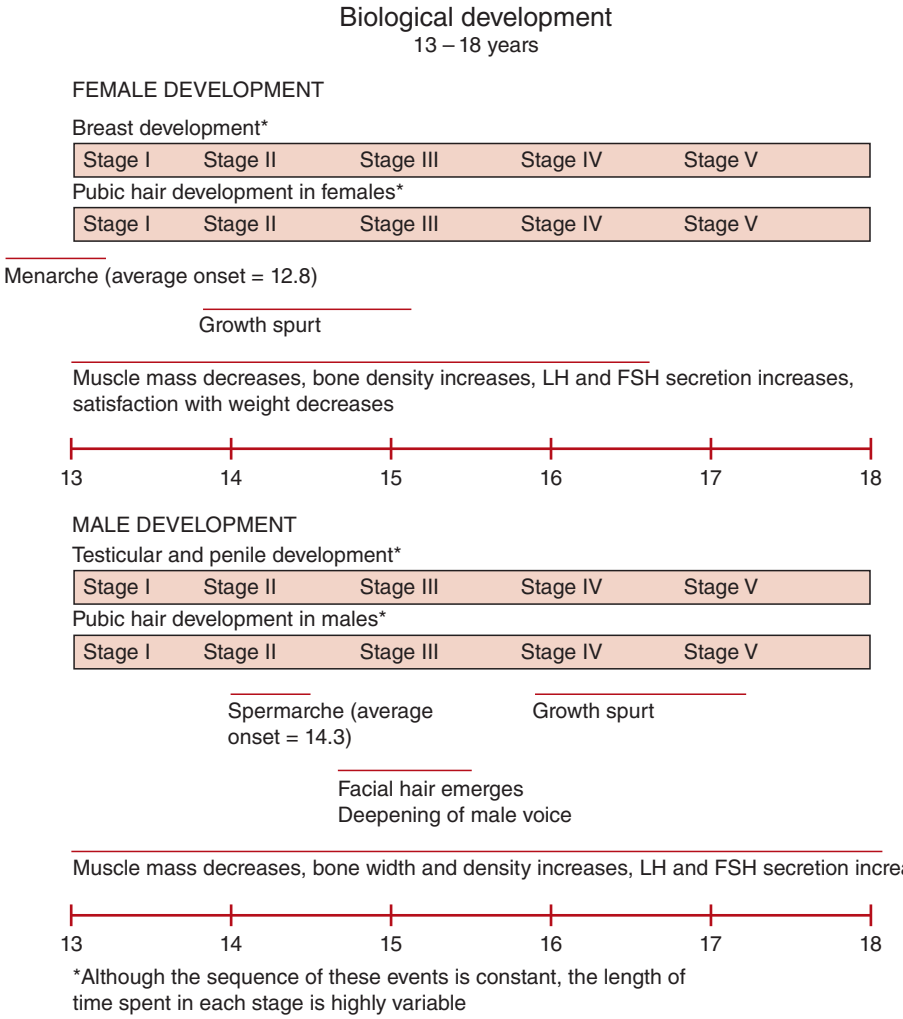



**Figure 11–2** *Biological development during the adolescent period (age 13–18 years).*

maturation of sexual organs and capacities, cardiovascular function, body composition, height, and weight. A time line of biological development from age 13 to 18 years is presented in Figure 11–2.

The development of secondary sex characteristics in both sexes has been well documented (Marshall and Tanner 1969, 1970). Although photographs imply that staging development is an objective process that be accomplished with great accuracy, one should understand that breast or testicular growth are continuous and placement into each stage is subjective (Sun et al. 2005).

Marshall and Tanner (1969) suggested five stages of pubic hair development (pubarche). In both sexes, stage I has no pubic hair. The chain of events leading to pubic and axillary hair growth (adrenarche) is separate from production of gonadal steroids, and this accounts for some children developing hair growth prior to breast budding or testicular enlargement. Thus, pubic hair stages may lag behind breast stages in girls (Figure 11–3) and genital development in boys (Figure 11–7). Andrenarche begins with production of dehydroepiandrosterone sulfate (DHEA-S) in the adrenal zona reticularis beginning at the age of 6 years and peaking at the age of 25 years (Achus and Rainey, 2004). The mechanism for the onset of these events remains obscure, but circulating levels of insulin (Slyper 2006), leptin (Garcia-Mayor et al. 1997), and ACTH may be important (Taha et al. 2005), as well as inhibition of 3β-hydroxysteriod dehydrogenase (Gell et al. 1998). Circulating DHEA-S is converted locally to testosterone and dihydrotestosterone in apocrine glands, leading to body odor, and hair follicles, giving way to production of coarser hair in the axillae and pubic region (Achus and Rainey, 2004).

In girls, stage II hair development is characterized by straight or only slightly curly hair that has little pigmentation and primarily appears on the labia (Figure 11–5). These changes arise at an average age of 9.4–10.6 years—recent figures reflecting earlier onset than the previous 11.9 years (see Figure 11–6) (Sun et al. 2002). Stage III shows the characteristically dark curly hair that spreads from the labia over the mons. By this time, the mons itself has gained in size as a result of increased fat deposition. Stage IV shows the entire mons overspread by thick dark pubic hair that does not yet extend as far as the medial aspect of the thigh. Stage V shows the typical adult distribution, which includes the areas of the medial thigh (see Table 11–3 and Figure 11–5). In girls, axillary hair develops during the later portions of stage III or during stage IV and appears at an average age of 13.2 years (Wheeler 1991).

Male pubic hair development, under control of adrenal androgens (see Figure 11–5), may not be synchronous with genital development (Marshall and Tanner 1969). Stage II is characterized by sparse growth of slightly pigmented

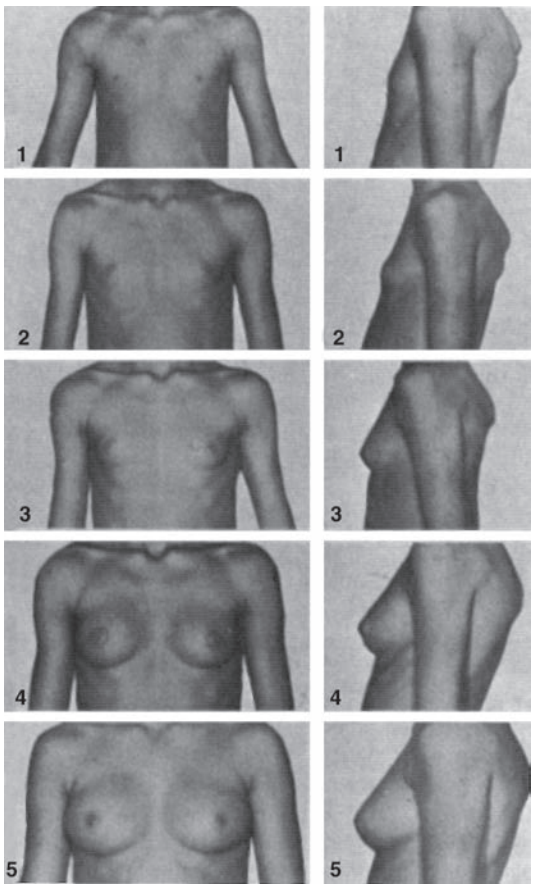



**Figure 11–3** *Sex maturity ratings of breast changes in adolescent girls. [Courtesy of Tanner JM, MD, Institute of Child Health, Department of Growth and Development, University of London, London, UK.]*

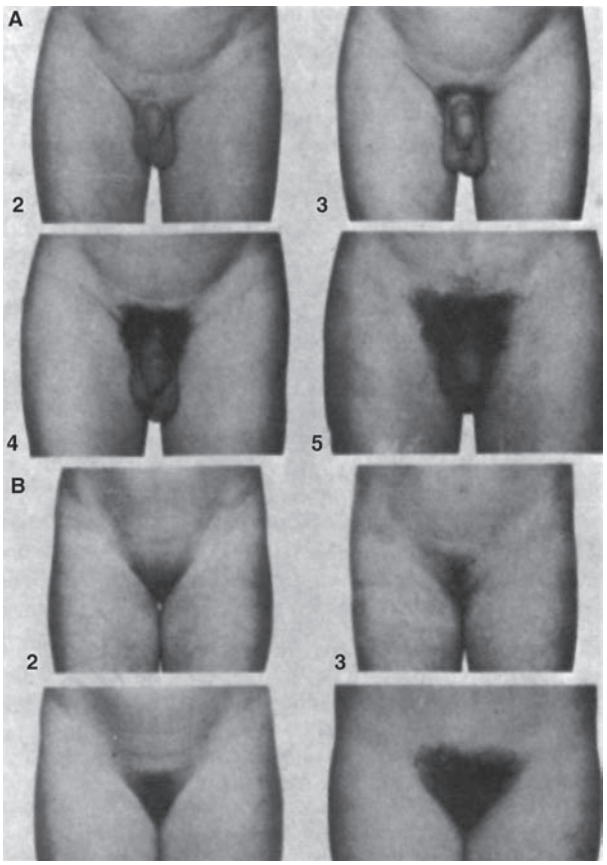



**Figure 11–5** *Sex maturity ratings of pubic hair changes in adolescent boys and girls. [Courtesy of Tanner JM, MD, Institute of Child Health, Department of Growth and Development, University of London, London, UK.]*

straight hair primarily at the base of the penis. Stage III corresponds to hair that is dark, curly, and distributed over the mons. Stage IV hair is spread over the mons but does not reach the medial aspect of the thigh. In stage V, hair growth has reached the adult distribution (Table 11–4). For boys, the average time from the emergence of the first pubic hair to reaching the adult pattern is 2.7 years (Wheeler 1991).

In girls, roughly 50% will have thelarche and pubarche at the same time (Biro et al. 2003). In a study of white females, among the other 50%, 60% had the onset of puberty with the appearance of thelarche, and 40% had the onset with pubarche (Biro et al. 2003). Whether one exhibited the thelarche or pubarche pattern was not associated with differences in the age of onset of menarche. However, those who showed thelarche before pubarche exhibited higher body

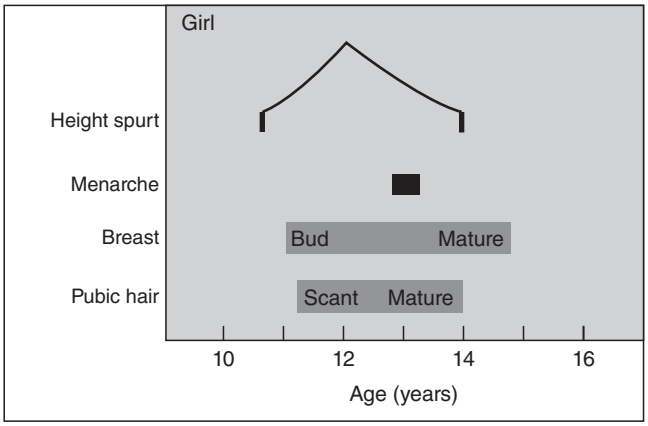



**Figure 11–4** *Temporal sequence of events for the "average" girl during puberty. [Reproduced from Rebar (1991) and Tanner (1974).]*

**Table 11–3 Classification of Sex Maturity Stages in Girls**

| Sex Maturity Rating Stage | Pubic Hair | Breasts |
|---|---|---|
| I | Preadolescent | Preadolescent |
| II | Sparse, lightly pigmented, straight, medial border of labia | Breast and papilla elevated as small mound; areolar diameter increased |
| III | Darker, beginning to curl, increased amount | Breast and areola enlarged, no contour separation |
| IV | Coarse, curly, abundant but amount less than in adult | Areola and papilla form secondary mound |
| V | Adult feminine triangle, spread to medial surface of thighs | Mature; nipple projects, areola part of general breast contour |

*Source*: Data from Tanner (1962). With permission from Blackwell Publishing, UK.

**Table 11–4 Classification of Sex Maturity Stages in Boys**

| Sex Maturity Rating Stage | Pubic Hair | Penis | Testes |
|---|---|---|---|
| I | None | Preadolescent | Preadolescent |
| II | Scanty, long, slightly pigmented | Slight enlargement | Enlarged scrotum, pink texture altered |
| III | Darker, starts to curl, small amount | Longer | Larger |
| IV | Resembles adult type, but less in quantity; coarse, curly | Larger; glans and breadth increased in size | Larger, scrotum dark |
| V | Adult distribution, spread to medial surface of thighs | Adult size | Adult size |

*Source*: Data from Tanner (1962). With permission from Blackwell Publishing, UK.

mass indices (BMIs) and proportion of body fat (Biro et al. 2003). They also showed greater risk of obesity in adult life (Garn et al. 1986). Before these observable changes, ovarian secretion of estradiol and progesterone produces an increase in vaginal length and cytological transformation of the cells in the vaginal lining (Wheeler 1991).

Breast development (Figure 11–3) follows a predictable sequence under the influence of ovarian estradiol and progesterone production. Asymmetrical growth is common (Marshall and Tanner 1969). The average age for the onset of breast development (thelarche) has required revision with more comprehensive epidemiological methods (Sun et al. 2002). A previous figure was 11.2 years, but the age of thelarche has declined and newer estimates recognize considerable racial and individual variation (Sun et al. 2002). A more accurate estimate for phase II is probably 9.5–10.4 years old (Sun et al. 2002) (Figure 11–6). Stage I consists of only a raised papilla. In stage II a breast bud is visible, with enlargement of the areola. In stage III, there is an enlarged breast without separation of the contours between the areola and the breast itself. Stage IV is defined by further enlargement and projection of the areola and papilla to form a secondary mound above the level of the breast. In stage V, there is an adult breast contour with elevation of the papilla only (Table 11–3; see Figure 11–3).

Typically, within 2 years of the onset of breast development menarche is attained (see Figure 11–4) (Zacharias and coworkers 1976). The average age for menarche is 12.4 years (Sun et al. 2005, Chumlea et al. 2003), and the range is 10–14 years. This is influenced by race. On average, onset is earliest in non-Hispanic blacks, slightly later in Hispanic girls, and latest in non-Hispanic whites. Across all races, 10% of girls will have onset of menses by an average age of 11.1 years and 90% will have menarche by 13.8 years of age (Chumlea et al. 2003). After menarche, from 2 to as long as 5 years, menstrual cycles are typically anovulatory (Wheeler

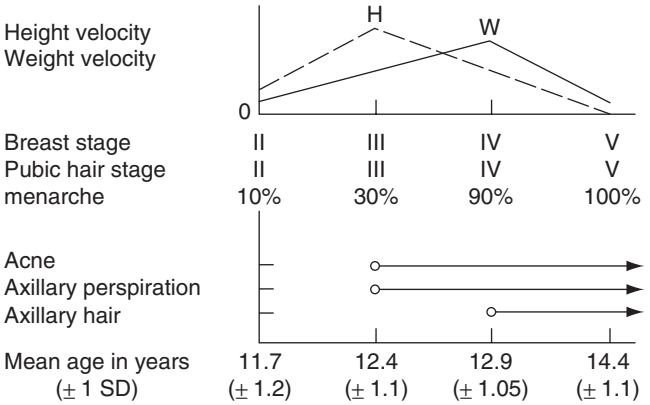



**Figure 11–6** *Sequence of maturational events in girls. [Reproduced from Marshall and Tanner (1969). With permission from BMJ Publishing Group]*

1991). The sequence of maturational events in girls is shown in Figure 11–6.

In nearly all boys, the onset of puberty begins with testicular enlargement. Enlargement is a consequence of cellular proliferation of the seminiferous tubules caused by rising levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Odell 1995). Prepubertal testes respond to a variety of tropic substances with production of testosterone. The appearance of sustained increases in levels of circulating testosterone lags behind measures of testicular volume, implying separate mechanisms in the induction of testosterone secretion by Leydig's cells and the proliferation of seminiferous tubules. Spermatogenesis occurs after the increase in testicular volume. Obtaining an estimate for spermarche has proved difficult, as it may be based on the average age of conscious ejaculation or presence of sperm in urine samples. Different methods yield very different results, leaving the age of onset uncertain. The reported average age of spermarche is 14.3 years (Wheeler 1991).

The stages of male genital development are based on testicular size and penile length and are associated with increases in serum testosterone levels (Marshall and Tanner 1970) (Figure 11–5). Stage I is characterized by testicular

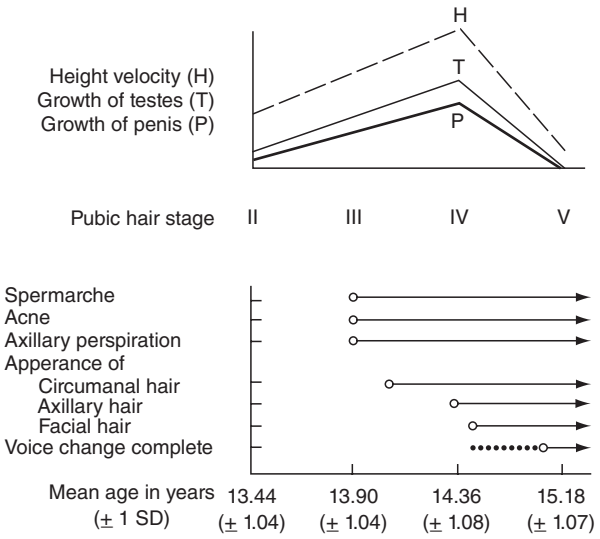



**Figure 11–7** *Sequence of maturational events in boys. [Reproduced from Marshall and Tanner (1969). With permission from BMJ Publishing Group]*

length less than 2.0 cm. Stage II is defined by testicular length between 2.5 and 3.2 cm and is usually associated with scrotal thinning. Stage III reflects growth of the penis and lengthening of the testis to between 3.3 and 4.0 cm. Stage IV is characterized by lengthening of the penis and testicular enlargement to 4.1–4.9 cm in length, with darkening of the scrotum. Stage V corresponds to adult testicular size (greater than 5 cm). Usually, the left testicle hangs lower in the scrotum and the right testicle is larger (Odell 1995). In boys, onset of pubic hair growth ranges from age 8.3 to 12.8 years (Sun et al. 2002, Lee et al. 2001).

Male axillary and facial hair growth is affected by testosterone and is not tightly linked to the appearance of other sexual features. The typical adult pattern of facial hair occurs within 2 years of Tanner's stage II pubic hair development (Wheeler 1991). Male facial hair emerges at an average age of 14.9 years at the lateral aspects of the lip and moves medially (Lee 1980). Chin hair usually appears last. The deepening of the male voice is a consequence of enlargement of the larynx and thickening of the vocal chords. These changes are under the control of testosterone and its metabolites and correspond to the male growth spurt. The sequence of maturational events in boys is shown in Figure 11–7.

Puberty changes the distribution of muscle, fat, and water in the body. In girls, muscle mass continues to develop until menarche and then declines. In boys, muscle mass, which is under androgenic stimulation, develops throughout adolescence and is accompanied by increases in bone density. In girls, fat distribution continues throughout puberty and by the end of puberty lean body stores of fat are double those of boys. In boys, intracellular water increases during puberty to 39%, whereas in girls it decreases to 29% (Wheeler 1991).

A variety of factors affect the onset of puberty, including, but not limited to, genetic endowment, adequate nutrition, and general health status, as well as environmental factors such as altitude, and physiological factors such as prolonged heavy exercise. There may also be an association between deprivation of exposure to light and earlier onset of puberty. Girls who are blind from birth or who reside in extreme latitudes where there is little light for protracted periods may have earlier onset of puberty on average (Cardinali and Vacas 1984). The importance of nutrition for the onset of menarche is highlighted by data that suggest that menarche in America now occurs more than a year earlier than it did in the mid-nineteenth century (Wheeler 1991, Brook and Hindmarsh 1992).

Long before body changes appear, there are gradual increases in levels of circulating FSH and LH, which are produced in response to secretion of gonadotropin-releasing hormone (GnRH) (or leutinizing releasing hormone (LHRH)) into the portal pituitary circulation. GnRH is secreted in a nocturnal circadian rhythm in pulses (Grumbach 2002). Throughout childhood, GnRH, LH, and FSH follow a steady nocturnal pulsatile pattern (Boyar 1978). As adolescence approaches, the rate and amount of secretion of GnRH increase and the pattern changes to day and night pulses (Boyar 1978). The switch that produces increasing LHRH pulse frequency and amplitude appears to be "turned on" by inhibition of gamma aminobutyric acid (GABA) and increased release of glutamate leading to activation of *N*-methyl-D,L aspartate (NMDA) receptors (Grumbach et al. 2002). As much as 2 years before increases in circulating gonadotropins, circulating adrenal androgenic hormones—dehydroepiandrosterone and 17-ketosteroid—increase in both sexes. As puberty nears, LH and FSH levels increase sharply. LH in boys increases the secretion of testosterone, which reaches adult levels within a year.

Both growth hormone (GH) and gonadal hormones are needed to initiate and sustain the adolescent growth spurt. GH is one of the most important influences on height and may be excreted at significantly higher levels in taller children than in their smaller peers during childhood (Brook and Hindmarsh 1992). The secretion of GH is under the control of GH-releasing hormone and somatostatin. In addition, estrogen, thyroxin, and glucocorticoids affect GH secretion. The timing of GH spikes is dependent on diminishing levels of somatostatin, and the amplitude of the GH spikes is directly related to GH-releasing hormone levels. GH-releasing hormone also appears to have a role in facilitating GH gene transcription.

The adolescent growth spurt depends on GH levels. Throughout childhood, GH levels are similar in both sexes. Under the influence of rising levels of gonadal steroids and GH, the growth spurt appears earlier in female development. The female growth spurt typically occurs during breast stages II and III, whereas the male growth spurt occurs during genital stage IV (Wheeler 1991, Odell 1995, Brook and Hindmarsh 1992). The circadian timing of GH secretion is the same in both sexes, but the magnitude of the GH spike is greater in boys.

There are changes in body proportions as well as composition during adolescence. The relationship between the shoulders and hips changes depending on sex. In boys the shoulders increase in comparison with the hips, whereas the hips widen relative to the shoulders in girls. Similarly, the relationship between leg and trunk lengths changes. In boys the lengthening of the femur is greater in proportion to overall bone growth than it is in girls. This leads to longer legs in boys. Growth of the bones of the face also affects appearance between childhood and adulthood. Mandibular length increases and the frontal sinuses evolve. This results in the protrusion of the jaw, a more upright alignment of the incisors, and creation of a brow ridge. The nose extends downward and forward to a greater extent as well (Wheeler 1991).

It is common for adolescents to worry about their health and whether they will be "normal" adults. The broad range of height and sexual maturity seen at any one time during adolescence can be a source of concern, particularly for those who are "late bloomers." Both sexes worry about being too tall or short. A boy or girl whose "growth spurt" is very early or late can be reassured that this timing does not influence eventual height (Abbassi 1998, Gasser et al. 2001). Generally, pubertal growth accounts for 17 to 19% of adult height. It also appears that late-maturing individuals have longer legs than those who mature early, although significant overall height differences are not observed (Gasser et al. 2001). Genetic endowment (i.e., parental height) remains the greatest single determinant of height in well-nourished individuals and accounts for approximately 55% of the variance (Harrap et al. 2000). Moreover, there are indications that the genetic mechanisms underlying height are coming into focus. One contribution may relate to polymorphisms of CYP19,

which metabolizes aromatic substances such as androgen to estrogen. Since estrogen influences when the epiphyses close and the growth of long bones, the efficiency of androgen metabolism could play a role in determining height. Ellis and coworkers (2001) studied the interplay between the Y chromosome and CYP19 sites and reported that these sites have additive effects on height in males.

The physical changes of puberty and adolescence produce a wide variety of psychological effects. These changes affect the way others look at adolescents and how adolescents view themselves. The rate and timing of these physical changes have a powerful effect on later psychological, social, and emotional development. The individual may be thrust into roles or responsibilities prematurely or, conversely, may be denied access to privileges. The influence of hormones on the behavior of adolescents has also come to be questioned. "Raging" hormones continue to be advanced as an explanation for teenage behaviors. However, many studies show inconsistent or modest correlations between hormone levels and types of adolescent behavior (Hill 1993).

## Brain Development

By the 1980s, it was known that brain myelination proceeds throughout childhood and adolescence accompanied by synaptic pruning, the reduction in exuberant synaptic connections seen in the neonatal period (Huttenlocher 1979, 1990). These findings emerged from anatomical studies of postmortem brains and were followed by PET studies in the 1990s (Chugani et al. 1987). However, the patterns and timing of these brain changes and implications for cognitive functioning are becoming clearer (Sowell et al. 2002). Casey and coworkers (1997) investigated increasing skills in attentional processes and related these to brain growth through adolescence using structural MRI. They suggested that the time table for various developmental changes might be different in different brain regions. In one study, they reported that the right anterior cingulate gyrus grew more than surrounding areas of the cerebrum and related to increasing attentional skills (Casey et al. 1997). Subsequent structural and functional MRI (fMRI) investigations have revealed a pattern of myelination and pruning that proceeds from posterior to anterior and inferior to superior regions (Sowell 2002).

Between childhood and adolescence, whole brain volume increases about 9–12%, and this is noted to be roughly equal in the cerebrum and cerebellum (Giedd et al. 1999, Sowell 2002). Cerebral spinal fluid increases by nearly 100% during the period from late childhood through adolescence (Sowell et al. 2003). Overall, throughout childhood and adolescence these larger volumes appear to arise from increases in white matter. During childhood there is a general, modest increase in gray matter that reaches its peak in adolescence and is followed by a cortical region-specific reduction in volume (Giedd et al. 1999). This has been interpreted to reflect progressive white matter myelination and synaptic pruning in gray matter. There are both sex and cortical region differences in the timing of these changes; earlier maturation usually is seen in females and volumes peak first in the parietal, then in the frontal, and finally in the temporal lobes (Lenroot and Giedd 2006, De Bellis et al. 2001). Male brains are roughly 7% larger than female brains (Giedd et al. 1999, Sowell et al. 2003, De Bellis et al. 2001). Giedd and coworkers (1999) and Lenroot and Giedd (2006) reported that parietal gray matter reached maximum volume in males at 11.8 years and in females at 10.2 years. Boys reached the maximum volume in the frontal lobes at 12.4 years and girls at 10.2 years. In the temporal lobes, the pattern was reversed—boys peaked at 16.2 years and girls at 16.7 years. More remains to be learned about the amount of these changes in different regions; there are some data to suggest that the greatest changes arise in frontal and parietal regions (Sowell et al. 1999, 2002). Sowell and coworkers (2003) reported on gray matter density changes from mid-childhood to adulthood. They observed a linear decline in parietal and frontal gray matter density from age 7 to 78 years. However, in the left posterior temporal region, subserving language functions, density continued to increase up to age 30 years before beginning to deteriorate (Sowell et al. 2003).

Development of some subcortical gray matter structures also appears to show sex-specific patterns of growth. The amygdala appears to increase during adolescence in males and is associated with a greater number of androgen receptors (Lenroot and Giedd 2006). Conversely, females display continued growth and enlargement of the hippocampus, a structure with a higher density of estrogen receptors (Lenroot and Giedd 2006). The data on sex differences in growth of white matter are inconsistent. One of the largest longitudinal studies has not observed sex differences in white matter development (Lenroot and Giedd 2006), but others have (De Bellis et al. 2001). There is general agreement that increasing size in white matter regions is seen throughout adolescence (Lenroot and Giedd 2006), and this is particularly true of the corpus callosum. In an extension of their studies of brain development, Sowell and coworkers ((2007) replicated finding of greater brain mass in males than in females and that males had larger brains in every region. However, there were significant sex differences in the thickness of the cortex in specific regions. The greatest differences were observed in right inferior parietal and posterior temporal regions, where females exhibited nearly 0.5–0.6 mm greater cortical thickness (Sowell et al. 2007). These differences were apparent by early childhood and were also noted in adults (Sowell et al. 2007). The implication of these differences is less clear; greater thickness may reflect greater synaptic connectivity or decreased synaptic pruning (Sowell et al. 2007).

The mechanism by which sex differences affect gray matter growth is open to speculation. It may be that synaptogenesis and pruning are influenced by sex hormones (Giedd et al. 1999). De Bellis and coworkers (2001) point to work suggesting that estradiol increases synaptogenesis and decreases pruning, while testosterone may promote myelination.

These findings are exciting because they link the development during adolescence of specific cognitive skills such as organizing information, conceptualization, perspective taking, and social perception to structural changes in frontal cortical and subcortical structures (Sowell et al. 2001). With further study, we may illuminate the circuitry and brain regions subserving these functions and learn about how they are influenced by experience, hormonal events, and genetic expression.

## Cognitive Development

The child's cognitive apparatus undergoes dramatic transformations throughout adolescence. This maturation of the child's capacity for thinking and memory is as significant

as the physical changes that unfold throughout this time. The transformation itself is mediated by the emergence of novel cognitive skills that allow the manipulation of ideas and permit the adolescent to assimilate more highly complex information. The adolescent's informational catalog expands, allowing the verification of new facts. Among the most important developments is the emergence of the ability to reflect on cognition itself; this is referred to as the development of metacognitive capacity, facilitating both understanding and empathy (Flavell 1981).

Piaget's theories (Gelman and Baillargeon 1983) provide a fundamental starting point for understanding childhood cognitive development (Flavell et al. 1993) despite problems in the staging of skills at certain developmental times. Most of Piaget's descriptions and sequences of skills have proved to be valid, but consensus is lacking on whether the skills aggregate or can be demarcated in a manner that supports Piagetian developmental stages (Flavell et al. 1993).

A major contribution of Piaget was the description of the ways in which the child's conscious mind is transformed and recasts itself from an efficient but heavily subjective and relatively concrete memory and organizational tool into an exquisite "conceptual processor" during preadolescence and adolescence. But contemporary theory has suggested that there are limitations that must be acknowledged when trying to generalize from the capacities of preoperational and operational stages. It may be that there are some skills that come "online" at one phase of development but do not readily generalize to other functions as Piaget suggested. Logical skills in particular may display the least generalization. "Conditional reasoning begins to appear in elementary school years or earlier, but remains incomplete and imperfectly used even in adulthood. Truly abstract thought is a rarity and, if it appears in the adult at all, seems to be dependent on specialized training" (Mandler 1983).

In comparison with its developmental forerunners, the processing skill of the adolescent is capable of much higher levels of abstracting and conceptualizing. This higher-level processing capacity is linked closely to abilities to grasp novel attributes and perceive critical elements. As a result, concepts can now be manipulated as things in free-standing objects that may be uncoupled from actual experience. With this ability, critical elements can be applied across situations or subtracted out of a logical string of assumptions. Similarly, novel attributes can be generalized to other problems. Consequently, the adolescent begins to understand and apply concepts in imaginative ways outside the circumstances in which they were first learned or even without having observed them firsthand. When actions are under consideration, the more powerful processing skill permits the adolescent to imagine the outcome of a theoretical or conceptualized intervention without actually having experienced the situation or needing to perform the action directly. The adolescent acquires far greater capacities for comparing outcomes and imagining emotional consequences and, as a result, acquires far greater abilities to understand, integrate, and relate experiences and ideas.

For Piaget and Inhelder (1969), logical reasoning is "a transformation of thought that permits the handling of hypotheses and reasoning with regard to propositions removed from concrete and present observation." It is this ability that undergoes rapid growth just before and during adolescence. These mechanisms equip the child with additional cognitive abilities such as a combinatorial system, an ability to understand combinations of objects, an acquisition of new propositional combinations, and an appreciation of reversibilities like inversion, reciprocity, and symmetry (Inhelder and Piaget 1958).

Consequently, adolescents are able to understand, organize, and relate information in new ways. As Flavell and coworkers (1993) have described, adolescents are able to entertain ideas about possible alternatives that are not immediately in front of them. Adolescents readily grasp possibilities that are beyond the realm of reality or that may contradict all previous assumptions they have held. In addition, novel problem-solving methods become available. Deductions can be made from hypotheses that are no longer fashioned exclusively from facts that are known or apparent. Adolescents can conceive of outcomes from mental experiments that are based on concepts alone. Abstract ideas can be entertained. The consequences of living under the simultaneous coexistence of two competing value systems, neither one of which the adolescent has ever known, can be imagined and explored. Such skills extend beyond an ability to imagine or the creativity of manipulating these ideas; they are based on an ability to think beyond one's self and one's subjective experience.

Adolescents can understand the relationships between objects outside subjective experience. Adolescents learn to work from "intrapropositional versus interpropositional knowledge" (Inhelder and Piaget 1958). "Formal operational thinkers understand that logical arguments have a disembodied and passionless life of their own, at least in principle. Concrete–operational thinkers have enough trouble seeing what logically follows from credible premises, let alone from premises that actually contradict one's knowledge, beliefs, or values" (Flavell et al. 1993).

These ideas formed the foundations of cognitive sciences for adolescence throughout the 1960s and 1970s. But during the past decade, there has been an elaboration and expansion of Piaget's concepts, and they have been interwoven with discoveries from other lines of inquiry. Information-processing theory and the concept of metacognition have been major contributions to these modifications of traditional Piagetian views.

Information-processing theory posits alternative explanations for several of the most basic tenets that underlie Piaget's constructs of cognitive development at this stage. A key acquisition of the adolescent in Piaget's schema of this period is the ability to understand abstract theoretical concepts. He proposed that greater logical skills were at the core of this competence (Piaget and Inhelder 1969). However, an inviting alternative hypothesis from information theory suggests that the success of the adolescent, compared with the child in this arena, has less to do with logic than with experience and knowledge. Information theory suggests that the amount of knowledge possessed by the individual influences both learning efficiency and techniques. The developmental difference between children and adolescents stems from the latter's "ability to access and flexibly use competencies they are known to possess. Development consists in part of going from the context-dependent state where resources are welded to the original learning situation to a *relatively* context-independent state where the learner extends the ways in which

initially highly constrained knowledge and procedures are used" (Brown et al. 1983). The hypothesis draws from observations of problem-solving techniques used by children and adolescents. In a series of studies, younger children appeared to reason through new problems one at a time. On the other hand, the more experienced adolescents or adults were able to (1) more readily distill the critical features of the new problem and (2) recognize how the new problem resembled other more familiar problems (Lovett and Flavell 1990).

Three mechanisms by which this efficiency occurs have been suggested: (1) more thorough processing of information, (2) greater capacity to transfer different learning strategies from one kind of problem solving to new problems, and (3) greater familiarity with the problems and solutions (Sternberg and Powell 1983). The higher success of the more experienced individual when presented with a novel problem does not appear to be attributable to more refined logic skills. One line of development through childhood to adulthood involves improvement in the completeness with which data are scanned and processed with increasing age (Sternberg and Powell 1983). Children tend to overlook or prematurely cease scanning information compared with adolescents.

A second factor influencing efficiency may be that more experienced solvers possess a better ability to withstand the confusion of new vocabulary, unfamiliar subjects, or new ideas (Chi et al. 1981) and to place the problem in the context of what they know. This ability to place the problem in the context of other knowledge is called transfer processing (Sternberg and Powell 1983). "Transfer components are processes involved in carrying over retained information from one situational context to another" (Sternberg and Powell 1983). One factor promoting facility with transfer skills is experience. "Novices tend to use key words in the problem format when they are asked to sort problems into types; in contrast, experts generally sort on the basis of underlying conceptual identities" (Brown et al. 1983). Information theory suggests that when the common elements of a problem can be discerned, the access to knowledge about this type of problem is greater and an approach to its solution is more likely to be found.

Familiarity with the type of problem is another important advantage of experience (Glaser and Chi 1988). With greater experience and knowledge, an individual is more likely to recognize a familiar pattern—a so-called problem *isomorph*—within the new problem (Brown 1982). Experience increases the individual's ability to recognize the pattern and to transfer knowledge of the solution from a similar problem to the new one. The techniques of problem solving also change as a result of this knowledge. Instead of working through to find the solution each time, the more experienced individual relies on familiar strategies, rote learning, and analogy. If the isomorph is discerned, the method is applied and the solution can be recalled; the answer to the new problem follows by analogy.

Metacognition, as used by Brown and Flavell and their coworkers, refers to "any knowledge or cognitive activity that takes as its objects, or regulates, any aspect of any cognitive enterprise." In other theories, metacognition is encompassed in the wider category of executive control or processes (Flavell et al. 1993, Brown et al. 1983, Sternberg and Powell 1983). The ability to think about thinking means that the adolescent can consider her or his own thinking styles, aptitudes, and limitations. Moreover, this reflective capacity can be applied to understanding others. A deeper appreciation of the way others think and how their thinking influences their behavior reaches the grasp of the adolescent.

A typical school-age child who is asked to reason out the behaviors involved in an interpersonal exchange between two others is inclined to draw on only the interactions that were perceivable at the time—in the here and now. Such a child has only a rudimentary capacity to understand what prior experiences may have contributed to the thoughts or feelings that influenced the exchange.

Unlike the younger child, the adolescent with metacognitive skills understands something about the act of thinking and the antecedents of feelings. The adolescent thinks about the perceivable elements of the exchange—the overt proximal emotional and environmental factors—but also understands that thought and perception may be influenced by a host of internal events that lie beyond what is visible. The modal adolescent is aware of a wider array of internal states, subjective motives, and unique historical forces; adolescents know that each person possesses an inner life and a past that impinge on current behavior and thought. Thus, the adolescent is aware that people have unique histories that affect their assumptions and perceptions and influence their thinking and actions. Adolescents also know that thinking itself can be influenced by fatigue or emotion. This permits typical adolescents to compare their observations with knowledge of behaviors or influences that are foreign to their subjective experience.

Some elements of metacognition begin to appear in childhood and are relatively well established in the later part of childhood. One component of metacognition that commences in childhood but is extended considerably throughout adolescence is cognitive monitoring (Flavell 1981). In one study, two groups of children, one of school-age children and another of preschoolers, were asked to memorize a small series of simple items and decide for themselves when they were ready to recall them from memory (Flavell et al. 1970). The younger children were significantly less prepared despite their claims of readiness; the older children were considerably more competent. Tasks such as this hinge on an ability to understand one's own thinking or gauge one's own learning ability. In adolescence, the ability to reflect on thinking moves to a higher level. This next level, which relies on the so-called recursive reasoning, permits one to reflect on another's thinking about oneself. The capacity to "think about your thoughts about my thoughts and so on" (Flavell 1988) is an important cognitive and developmental milestone. On reaching it, the adolescent acquires a greater understanding of thought and behavior.

The applications of recursive thinking have educational and interpersonal relevance. In literature, they permit the more developed adolescent to imagine what the protagonist would think about how the antagonist would regard the protagonist's thoughts. This sort of "mind game" is the basis for a variety of theatrical intrigues. For example, character A attempts to outthink or "psych out" character B by anticipating what B would predict of A's line of reasoning. A may even attempt to lead B in a certain direction, anticipating that this would encourage B's presumption. A then exploits B's predictability. A acts in a different way than B has assumed in order to gain the advantage of surprise.

It is no coincidence that this ability to conceive of ways in which peers, parents, and authority figures think about how one is thinking is associated with a time of immense social self-consciousness and preoccupation for the adolescent. In interpersonal endeavors, recursive thinking permits adolescents to imagine misunderstandings and distortions that may arise between themselves and their friends and thus respond in ways that repair mistakes. They can imagine the reactions that would follow from what others think about them. Conversely, these abilities can be used to tease or manipulate others at a more sophisticated level of destructiveness. These skills may also be applied to test taking and essay assignments, in which the student thinks about the instructor's thoughts about her or his likely responses to the question.

In summary, a number of salient features distinguish the cognitive development of adolescents. The capacity to grasp conceptual underpinnings and to manipulate them as objects themselves appears consistently across nearly all theories of cognitive development and might be regarded the most significant. Information theory departs from the traditional Piagetian reliance on development in logic skills during this phase. It asserts that larger foundations of information and better skills in discerning the isomorphic features shared by new and familiar problems are critical. In addition, more thorough scanning skills, flexible use of learning strategies, and control or monitoring of information processing appear to be important (Sternberg and Powell 1983). Development of metacognitive skills has emerged as a vital developmental activity during adolescence, based on studies of knowledge transfer and executive function processes (Flavell et al. 1993).

Executive functions are a hypothetical set of cognitive skills that guide goal-directed activity (Anderson 2001, Shallice and Burgess 1991). They often refer to inhibition of prepotent responses, working memory, attention, goal setting, mental flexibility, and organization. There is evidence that many of these executive functions rapidly develop during childhood and remain relatively stable or increase during adolescence (Anderson 2001, Adleman et al. 2002). Two exceptions are sharp increases in attentional control and processing speed seen in midadolescence (Anderson et al. 2001) and smaller but significant increases in goal-setting skills in early adolescence (Anderson et al. 2001). Active investigations now focus on the links between enhanced executive skills and fMRI findings of increasing frontal lobe myelination during adolescence. The increasing volume of the anterior cingulate and dorsolateral prefrontal cortex during adolescence are particularly remarkable, as these regions are thought to play an important role in attention and inhibitory functions (Casey et al. 2000). Similarly, in a study from childhood through adulthood of the Stroop task, which is linked to cognitive interference skills, Adleman and coworkers (2002) noted increases in activation in left lateral prefrontal and left anterior cingulate activity with age and skill performance.

A growing body of literature suggests that changes in brain function from infancy to adulthood may be about specific regions but also about *interactions* between regions (Johnson 2001, 2003). Johnson (2001) has described the older, maturational view as considering functions based on the development of specific brain regions. Increasingly this idea has been augmented by encompassing neural circuitry—the relationship and organization of circuits *between* regions. Two subtypes of interaction emerge from this view. In one, the reinforcement of interactions between regions increases the efficiency, organization, and number of connections between them (Johnson 2001). In the other, the skill-learning view (Johnson 2001, 2003), a specific brain regions might be recruited for learning a function. As the skill becomes honed and routine, its location and activation shift so that it eventually resides elsewhere (Johnson 2001).

A time line of cognitive development from age 13 to 18 years is presented in Figure 11–8.

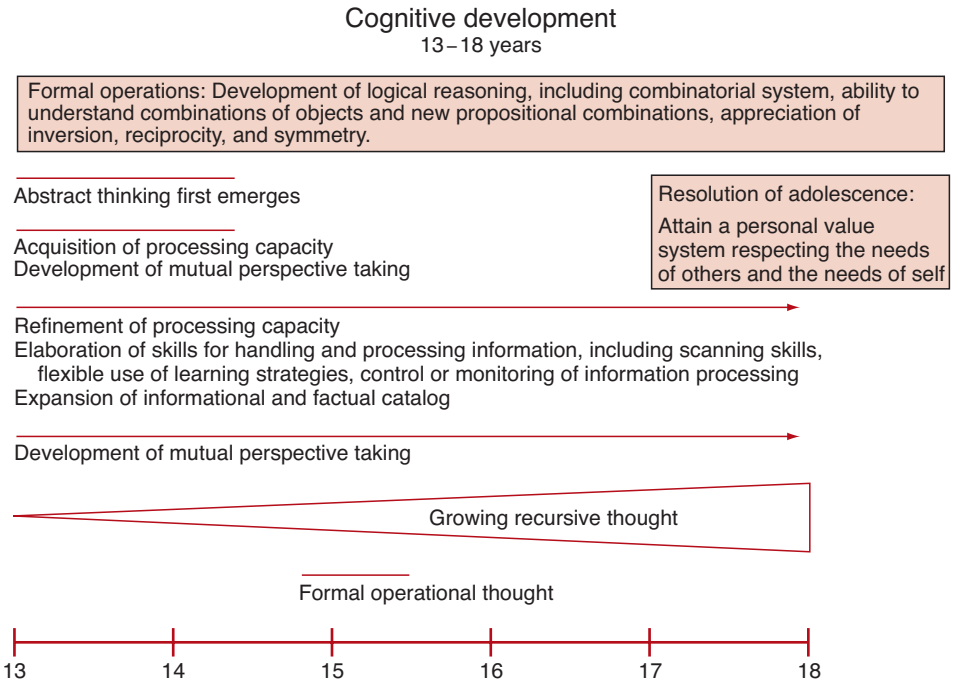



**Figure 11–8** *Cognitive development during the adolescent period (age 13–18 years).*

## Emotional Development

During adolescence, emotional development is advanced and shaped by experience and cognitive maturation. The emotional life of children in middle childhood can be characterized as relatively concrete, instantaneous, and circumstantial. They have access to a wide array of emotions, can distinguish subtle gradients of difference, and can identify these emotions in others as readily as in themselves. They worry about how others think of them and display empathy for their friends. However, a deeper appreciation of others' sentiments is limited by the school-age child's ability to understand the mental lives and motives of others who have a different sense of time, experience, and memory. In contrast, adolescents are capable of perceiving a range of events from an individual's distant history that may be influential at the present time. They can reason that events well outside their shared experience with an individual might be strongly influential, and they can reason backward from the sequence of events and emotions to speculate on motives or feelings that might be at work. Capacities for abstraction permit adolescents to consider factors outside their own immediate emotional experience. Consequently, adolescents are more emotionally interactive than at any previous period of development.

Emotions can be more thoroughly understood and explored within the context of the various cognitive changes that occur during adolescence. Emotions in adolescence exert an increasingly important role in guiding behavior. They become a sustaining motivation for behaviors and mediate the adolescent's relationship with peers and family.

There are differences of opinion about whether adolescents are actually more emotional than school-age children. Psychoanalytic theory proposes that emotionality arises as a consequence of efforts by the ego to integrate conflicts between wishes or drives and social demands. The theory suggests that these developmental conflicts achieve a comfortable equilibrium during the latency years before puberty and are remnants of what was incompletely resolved in toddlerhood. The intrusion of the biological drives of adolescence is believed to upset this equilibrium and force the conflict to resurface in a new way and at a different level. Just as in toddlerhood, the child is confronted with internal pressures that must be brought into alignment with social and familial demands. The social demands on adolescents have different objects and aims, but the task of accommodation remains much the same. Similarly, the outlets available for managing the conflict in adolescence are more diverse and are influenced by more mature cognitive and physical capacities.

Psychoanalytic theory proposes that this conflict is not only typical of adolescence but is inevitable in the developmental process. Consequently, a lack of overt conflict should be viewed as atypical. "Convenient as this may be, it signifies a delay of normal development and, as such, is a sign to be taken seriously. These are children who have built up excessive defenses against their drive activities and are now crippled by the results which act as barriers against the normal maturational processes of phase development" (Freud 1958).

Empirical investigations do not support this hypothesized increase in emotionality (Larson and Lampman-Petraitis 1989). Direct sampling of adolescents revealed no greater quantity of emotional feeling than is found among children in the preteenage period. In addition, research on nonclinical populations does not support the concept of a disruption of the equilibrium from middle childhood. Investigation suggests that emotional tone remains quite stable from middle childhood through adolescence. Moreover, the stability of these measures was observed across several different cultures (Offer et al. 1981). Overall, the empirical investigations offer little support for the idea that adolescence is a period of emotional turmoil, just as there is minimal support for the concept of a normative period of intense conflict between parents and adolescents.

One way to reconcile the difference between the clinical observations and the research findings is to observe the quantitative increase in emotional disorders arising during this time. A variety of studies support the premise that anxiety and depression rise steeply, particularly among girls, during adolescence (Buhrmester 1990). Clinicians are in the position of treating adolescents with these disorders and are thus at risk of erroneously generalizing their experience to the entire population. "Office epidemiology" may be quite an accurate reflection of incidence trends of psychopathology but is inappropriate when generalized or applied as prevalence in the nonclinical population.

Another way to reconcile these different perspectives draws on studies of the means by which adolescents resolve conflict compared with the methods used by younger children. The cognitive set of adolescents promotes seeking advice and looking to peers for sympathy. There are cultural and sexual differences in the quantities of and conventions surrounding these exchanges (Seiffge-Krenke 1990). However, whatever culture is being considered, there are differences in the amounts of discussion and intimate exchange that occur in adolescence, compared with earlier periods of development (Buhrmester 1990). Thus, emotional expression and discussion about conflict may increase in adolescence and lead to the distorted perception that the actual amount of turmoil has increased. This is analogous to the incorrect presumption of increasing crime rates that follows the expanded availability of police. The ease of reporting decreases barriers to detection and rates appear to rise. Thus, although the emotional life of adolescents is more complex and more interpersonal than that of younger children, it does not appear that the developmental changes of adolescence are in themselves sources of increased emotionality.

A time line of emotional development from age 13 to 18 years is presented in Figure 11–9.

## Social Development

Unlike the relatively clear biological criteria defining puberty, the demarcation of adolescence is variable because it is basically designated by society; that is, society determines the criteria for adolescence. At times there are social pressures that dictate whether a larger or a smaller proportion of the teenage population are considered to be adults. For example, when the economy is depressed, teenagers competing with adults for jobs are an economic threat. Conversely, when there is a war, the demand for military personnel defines that it is appropriate for strong and vigorous teenagers to become soldiers. Enright and colleagues (1987), taking a developmentalist's perspective, studied this bias by tracing articles published in the *Journal of Genetic Psychology* from 1890 through 1945. This span encompassed two periods of

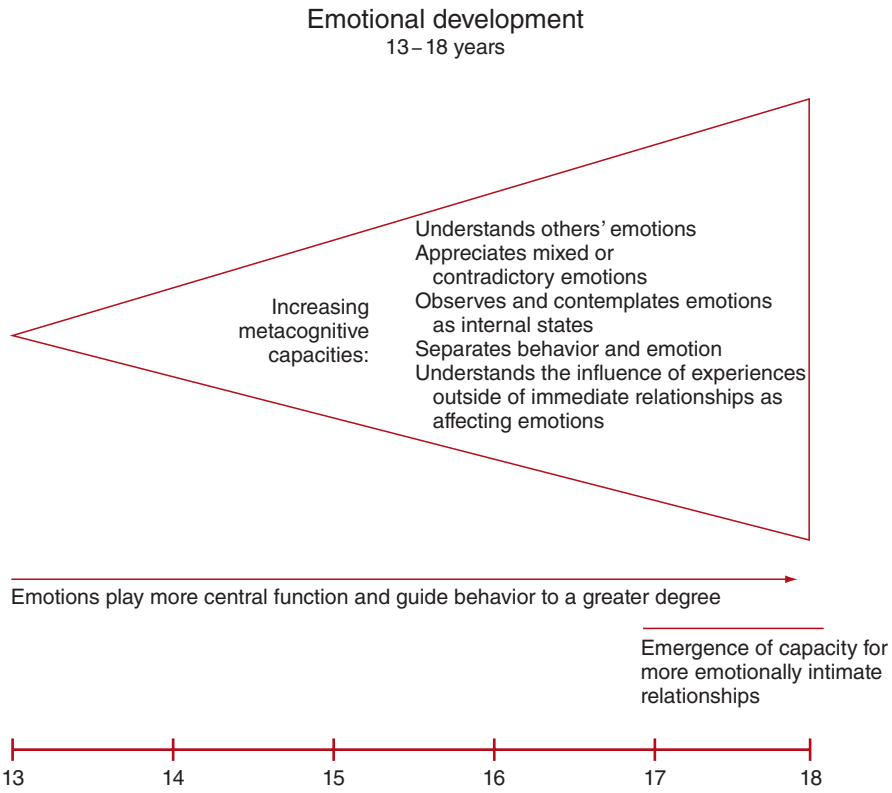



**Figure 11–9** *Emotional development during the adolescent period (age 13–18 years).*

depression and both world wars. The research focused specifically on the attributes assigned to teenagers during these four periods. Through the two depressions, youth tended to be described as relatively childlike and immature, obviously still needing time before becoming adults. During the two wars, youth were more often described as mature and developmentally ready to fight for their country.

Two examples illustrate how the perception of the maturity of teenagers changed in the twentieth century. The first was in response to the Great Depression, when, in 1938, the Congress passed the first federal child labor laws to protect adults, many of whom had families to support. The second was during the Vietnam War. The age of legal maturity at that time was defined as 21 years, but soldiers were drafted at age 18 years. The media made much of the fact that the government forced 18-year-olds to fight (and die) for 3 years before they were allowed to buy alcohol legally or vote. In response, the Congress lowered the age of majority to 18 years. Since then, there has been mounting concern about teenagers' deaths caused by drunken driving. Therefore, although the voting age and age of entry into military service have remained at 18 years, states have raised the legal age for drinking alcohol to 21. The latter was strongly encouraged when federal dollars for state highway projects became dependent on the state's drinking age being 21. Highway funds will also be cut for states that by 2004 do not use 0.08 as the blood alcohol standard for drunk driving. A new approach by states that is gaining popularity is the "graduated" driver license based on set periods of time and the absence of violations. For example, the youth first obtains a license that requires the presence of a licensed adult. With a level-two license, the young person can drive alone from 5 AM to 9 PM, and, thereafter, a full license is granted. Some data show that this approach can cut down the number of youth crashes (Foss et al. 2001).

Just as state and national policies affect a teenager who is considered to have reached adulthood, so do more local and personal pressures such as family and ethnic expectations. These may favor a teenager's being regarded as an adult earlier or later than another youth of the same age.

Poverty is an important factor that influences crucial aspects of life such as nutrition, health care, housing, recreation, and education. Other factors such as race or ethnicity can also affect many facets of life. For example, minority adolescents are much more likely to be raised by a single parent. This in turn is associated with a higher likelihood of poverty, less education, increased drug use, and, for a woman, raising a child as a single parent. Similarly, African-American and Hispanic youth have been shown to be at greater risks of certain injuries and illnesses. Although homicide rates have fallen since the early 1990s, the greatest risk for African-American adolescents, particularly male adolescents, is that of being murdered. The homicide rate for 15–20-year-old black males is more than six times that for white males and twice the rate for Hispanic males (Centers for Disease Control and Prevention 2001). According to the National Commission on Children, "teenage boys of all races are more likely to die from gunshot wounds than from all natural causes combined" (National Center for Health Statistics 1988).

Suicide rates are higher for white than for African-American teenagers (Centers for Disease Control and Prevention 2001). This ratio, however, has remained relatively stable, compared with the widening racial gap for homicides. As with homicides, firearms have become increasingly popular for committing suicide.

Age at onset and type of sexual experiences are associated with social and ethnic background. The family is the first and foremost conveyor of culture. A child's expectations for sexual activity stem mostly from parent or parents, relatives, and neighbors. African-American adolescents of both sexes are more likely than their Hispanic or other white peers to have had sexual intercourse at each age through the teens (Mott and Haurin 1988). Although education and economic variables are influential in the timing of first sexual experiences, timing is also powerfully molded by what is considered normative (Furstenberg et al. 1987). Early sexual activity in turn is linked to early pregnancy and to a greater likelihood of contracting sexually transmitted diseases. Condom and other contraceptive use is more common as adolescents become older. Self-esteem and sexual activity are linked to the adolescents' personal beliefs (Miller et al. 1987). If the teenager believes that sexual experience is a positive activity, abstinence lowers self-esteem and participation raises it. The teenager develops a mental value about sexual activity through his or her experiences during the first 12 years of life.

Early sexual experience is not only a social issue, but also a serious health risk. All sexually transmitted diseases are more common among poor and minority teenagers than in any other groups. There has been an increase in sexually transmitted diseases in adolescents. A national risk surveillance survey of high school students in 1999 gave an update of the behavior patterns and how they did or did not vary from a similar survey in 1991 (Centers for Disease Control and Prevention 2000). Significant ($p < 0.05$) increases were found in the use of marijuana and cocaine. By the same token, condom use was up, along with seat belt and bicycle helmet use. Physical fighting, carrying a gun or other weapon, and sexual promiscuity were all significantly down. Human immunodeficiency virus (HIV), other sexually transmitted diseases, and unwanted pregnancies correlated with age at time of first sexual intercourse and frequency of intercourse. Half of the high school students had intercourse. The racial percentages for black, Hispanic, and white students were 71.2%, 54.1%, and 45.1% respectively.

Although the acquired immunodeficiency syndrome (AIDS) is seldom diagnosed during the teenage years, it is often at this time that HIV infection is contracted. AIDS does not occur until 7, 10, or more years after infection. In a study of African-American young people, aged 9–15 years, rates of foreplay even among the 35% who were sexually active were quite low, but among those who were sexually active, 24% of boys and 35% of girls had anal intercourse, a strong risk factor for HIV infection (Stanton et al. 1994). Only about 60% of these youngsters reported that they used a condom during their last intercourse. In 1989, 92% of births to African-American adolescent mothers occurred outside marriage. Pregnant adolescents are more likely than other mothers to deliver low-birth-weight infants, who in turn are more likely than average-sized infants to have developmental delays.

Early sexual activity, alcohol and other drug use, early pregnancy, and sexually transmitted diseases are all intercorrelated (Elster and Kuznets 1994). They all embody risk taking and increase the likelihood of injury, disease, and further poverty. An estimated 25% of 10–17-year-olds engage in behaviors that create a serious danger to themselves or others (Dryfoos 1990). Drug and alcohol use correlates with decreased use of condoms. Drug use may reduce sexual inhibitions, and sexual favors may be sought in exchange for drugs or money for drugs. Transmission of HIV arises from unprotected sexual intercourse or the injection of drugs.

Parents often feel unappreciated by teenagers or envious of the increasing beauty, strength, or intelligence of their offspring. Giving up control over their children may also represent to parents that they are aging and less needed. The ability to exchange points of view can moderate this conflict. Extremes can be destructive; too few parental rules can be just as much a problem as too many. When parents are absent psychologically, teenagers may increase their misbehavior to learn what limits exist. If there are no parental limits, social limits become salient.

Brion-Meisels and Selman (1984) have described an invariant sequence of five stages of moral perspectives. Selman's third stage usually comes just before or during preadolescence and permits the child to put her or his viewpoint aside and take the perspective of another person. The fourth stage occurs in the early teens and includes mutual perspective taking, the ability to take the perspective of a neutral third-party observer. Obviously, the ability to accomplish these stages is related to intelligence and the quality of social morality displayed by parents and mentors to the adolescent throughout childhood. This sequence of moral stages cannot be accelerated, but it can be slowed or stopped.

Conflicts between teenagers and their parents typically intensify about the time of puberty and begin to subside after secondary sexual characteristics become evident (Hill 1993). Most parent–child quarrels begin over minor issues and do not escalate. Baumrind (1971) has classified parental discipline into authoritarian, authoritative, and permissive types. Permissiveness is characterized by too few rules, whereas authoritarian parenting is quite strict and does not balance punishment with praise for positive behaviors. The authoritative approach includes consistency, firmness, and a warmth for the adolescent as well as reinforcement of his or her mature responses (Baumrind 1971). Authoritative parenting appears to be associated with the acquisition of positive social attributes (Hill 1987). It is also remarkable that the overall incidence of family abuse and neglect is, if anything, higher for adolescents than it is for younger children (Council on Scientific Affairs 1993).

Peers become more influential as a child enters adolescence, and peer pressure can be socially positive or negative. Children seem most susceptible to peer pressure in early adolescence, and this begins to lessen after age 13 or 14 years (Hill 1993). Most early teenagers believe that their parents are not objective enough to help them resolve doubts about parental values and viewpoints. To a large extent, during early adolescence, the peer group comes to represent the stamp of normality and an assurance of acceptance. Typically, adolescents who have many friends possess high self-esteem. Friends may change their individual behaviors to conform to the group, or groups may be formed because of shared peer interests. Both processes probably occur (Kandel 1978). Teenagers often quit groups that are not sufficiently homogeneous or have unacceptable expectations.

It is common for parental abuse or neglect to push adolescents into associations with adverse peer influences. Boys seem more influenced by group pressures toward antisocial

behavior, but otherwise the relationships between gender and group conformity do not show consistent findings. Under peer pressure, cigarette and alcohol use may rise (Fisher and Bauman 1988), but so may school grades (Epstein 1983). Not all groups or group members are equal. Some group members are more influential than others, and some groups are more demanding of members. Peer groups in early adolescence tend to be rather narrow, same-gender cliques, but they become mixed gender, larger, and more loosely structured by later adolescence. Adolescents who cannot make friends usually manifest emotional, social, and academic problems. Their self-esteem tends to be low. Peer acceptance and support are less available to these individuals (East et al. 1987).

Schools are where adolescents typically spend most of the time that they are not at home. Doing poorly in school and dropping out of school are highly correlated with having behavioral, social, and legal problems (Rutter 1983). According to the Educational Testing Service, which is responsible for testing aptitude for admission to college, fewer than half of American 17-year-olds have the skills and basic knowledge required for college or for many entry-level jobs (Applebee et al. 1989). About one in eight adolescents drops out of school. Four of five prison inmates are high school dropouts (Committee for Economic Development 1991), who are nearly twice as likely as high school graduates to be unemployed (US Congress, Office of Technology Assessment 1990). For adolescents from families and neighborhoods that have powerful antisocial tendencies, school offers one possible way to learn other values and other paths to being successful. Friendships, skills, and mentoring are all positive attributes that can be obtained through school.

The decision to drop out of high school carries with it potential risks that are seldom foreseen by the teenagers themselves. Part-time work during high school may be positive or negative, depending on the experiences provided and whether or not educational and social opportunities are critically curtailed. Part-time work for more than 15–20 hours per week usually undermines basic education (William 1988).

The standardized age of 21 years for legal drinking did in the 1990s correlate with a number of positive public health statistics. A later age for the onset of drinking is associated not only with less fighting throughout a male's life (Hingson et al. 2001), but also with fewer pregnancies and sexually transmitted diseases.

A paradox of independence is produced for youth who attend college, live away from home, and have their parents help pay for it all. The young person living away from home is legally an adult but remains financially unemancipated. Graduate or professional school further prolongs the interval between adolescence and adulthood. Some young people cannot tolerate this protracted period of dependency and either quit school or stop taking money to achieve financial liberation from their parents.

A time line of social development from age 13 to 18 years is presented in Figure 11–10.

## Risk Factors, Protective Factors, and Gene–Environment Interactions

The epidemiology of serious psychiatric disorders points to adolescence as a time of increased risk. It has

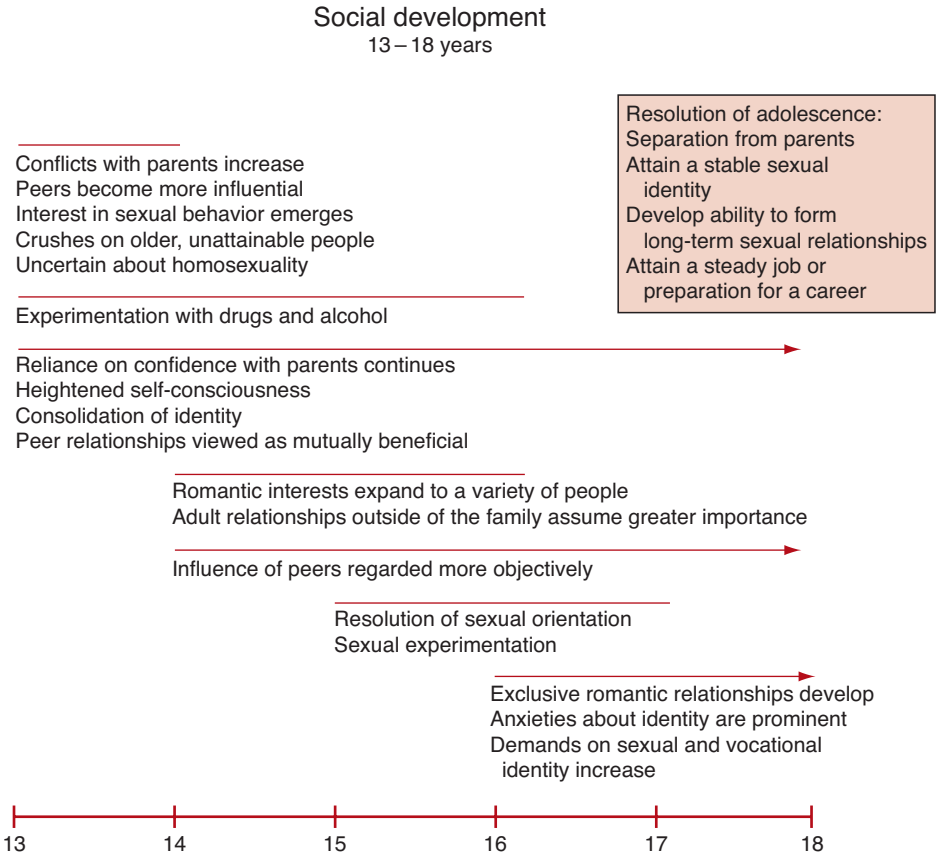



**Figure 11–10** *Social development during the adolescent period (age 13–18 years).*

been established that incidence rates for depression (Angold 1988, Joyce et al. 1990), bipolar affective disorder (Akiskal et al. 1985), panic disorder (von Korff et al. 1985), obsessive-compulsive disorder (Rasmussen and Eisen 1992), anorexia nervosa (Lucas et al. 1991), bulimia nervosa (Kendler et al. 1991), substance abuse (Compton et al. 2007), antisocial behavior (Rutter and Giller 1983), and schizophrenia (Angermeyer and Kuhn 1988) either peak or display a major increase during adolescence. Why adolescence should be the developmental period of greatest risk for so many chronic psychiatric disorders remains unclear. At one point it was thought that the total number of stressors or the quantity of adversity might account for the appearance of disorders. Sameroff (1989) noted, "except at the extremes of biological deviation, it is the number rather than the nature of risk factors that is the best determinant of outcome." Examples of individual biological vulnerabilities were male sex, low birth weight, mental retardation, and prenatal exposure to large amounts of alcohol. However, a modern view points to the specific interplay of biological, familial, social, and cultural forces in the emergence of serious disorders. Only recently have we begun to appreciate the mechanisms behind some of these interactions.

Studies in the last decade showing specific *gene–environment interactions* have transformed our understanding of risk and protective factors across development and opened a rich avenue for further investigation (Moffitt et al. 2005). These efforts have substantially affected our understanding of the mechanisms by which one's genes and environment shape development and lead to disorders. Rutter and coworkers (2006) trace the history of thinking about this interplay of genes, environment, and psychopathology. Rutter and coworkers (2006) emphasize how our view of genes as solely and inevitably determining an outcome has modified to one of genes as relative risk factors. In this sense, susceptibility genes are "part of multifactorial causation and not any direct genetic effect….In most cases, the susceptibilities are dimensional, rather than categorical" (Rutter et al. 2006). The expression of a genetic sequence is profoundly affected by accessory chemical reactions that may in turn be switched on by events. Several premier examples have surfaced showing that these epigenetic factors—environmental influences on gene expression—play a fundamental role in the development of psychopathology.

Examples of gene–environment interaction are the effect of early maltreatment in combination with polymorphisms of the promoter region coding for monoamine oxidase A (MAO-A) leading to antisocial behavior and violence (Caspi et al. 2002, Kim-Cohen et al. 2006) and the effect of life stress in combination with functional polymorphisms in the promoter region of the serotonin transporter gene on the onset of depression (Caspi et al. 2003, Eley et al. 2004).

MAO-A, an enzyme coded by a gene on the X chromosome, metabolizes catecholamines including norepinepherine (NE), dopamine (DA), and serotonin (5-HT) in brain. Caspi and coworkers (2002) were aware of findings from animal and human research that weak MAO-A is associated with aggression and that maltreatment in childhood may lead to antisocial behavior and to persistent elevations of 5-HT, DA, and NE. They sought to learn how MAO-A deficiency and early maltreatment might be linked. To do this, the investigators genotyped 1037 boys who had been characterized and followed for more than 23 years as part of an epidemiological sample in a longitudinal study of child growth and development. A strength of choosing an epidemiological sample is that there were a range of early-life experiences among the boys—8% were identified as having experienced "severe" maltreatment, 28% "probable" maltreatment, and 64% no maltreatment. The investigators grouped the sample according to high and low MAO-A activity (63% and 37% of the cohort, respectively). Only boys were chosen because their single copy of the X chromosome allows for a simpler, dichotomous classification of MAO-A activity (high or low). Females possess two copies of the gene and MAO-A activity may be low, medium, or high. The sample of boys was reviewed for presence of DSM-IV diagnoses of conduct disorder, antisocial symptoms, and criminal convictions for violent crimes. Among adolescent boys who suffered probable or severe maltreatment *and* had low MAO-A activity, presence of a DSM-IV diagnosis of conduct disorder was nearly three times more likely than among those with no maltreatment (the odds ratio (OR) was 2.8, 95% confidence interval (CI): 1.42–5.74). However, among boys with high MAO-A, the effect of maltreatment was much smaller and failed to reach significance. (OR 1.54, 95% CI: 0.89–2.68). ORs for measures of antisocial behavior, conviction for violent offenses, and self-reports of violent behavior produced similar results. Thus, having both early maltreatment and low MAO-A substantially increased the risk of conduct disorder and violence later in life. In contrast, having either high MAO-A or an early life free of maltreatment conferred some measure of protection against the emergence of these antisocial behaviors.

Caspi and coworkers (2003) also examined the relationship between stressful life events and polymorphisms of the serotonin transporter (HTT) gene. The role of serotonin in depression is suggested by findings of abnormalities in serotonin physiology and the effectiveness of medications targeting serotonin dynamics. The serotonin transporter is the major mechanism for clearing serotonin from the synaptic cleft and is also the site of activity for selective serotonin reuptake inhibitor (SSRI) medications. The transcription of proteins for HTTP is under the control of a gene, termed the HTT-linked polymorphic region (HTTLPR), on chromosome 17 (17.11.1-q12), and the efficacy of SSRIs has been linked to alleles of this controller gene (Serretti et al. 2007). There are several alleles of the HTTLPR region, including at least a long "l" version that is efficient and short "s" allele that is inefficient in transcribing the HTT protein. The investigators were aware of the extensive work suggesting a relationship between depression and low activity of HTT. As before, Caspi and coworkers (2003) drew from the Dunedin Longitudinal study and ascertained 847 Caucasian, 26-year-old individuals, of whom 17% were homozygous for the "s" allele, 51% were heterozygous, and 31% were homozygous for the "l" version, distributed similarly in both sexes. The participants were then asked to rate presence of stressful life events since age 21 years and individuals were grouped according to the number of adverse events. The cohort was then assessed for the presence of DSM-IV major depression in the past year, and 17% met criteria for depression, 58% of whom were female. When analyses of the effect of recent stressful life events were performed *excluding* those with a history of depression prior to age 21 years, being "s/s" or "s/l" significantly predicted major depression and

did not predict depression in "l/l" individuals. Among those who reported suffering four or more stressful life events, 10% had at least one copy of the "s" allele yet they accounted for 25% of all the cases of depression, and one-third of those with an "s" allele became depressed—nearly twice the rate of those who were l/l (Caspi et al. 2003).

These methods reveal why lower levels of analysis failed to find effects. Looking at disorders using only genetic data, or using only data on earlier environmental exposure, or only the developmental period when the disorder had it onset would never illuminate these mechanisms. Gene–environment interactions require the integration of our knowledge of gene action, the neurophysiology of disorders, genetic influences on the receptors and substrates behind that physiology, and how epigenetic events can influence genetic expression.

A great deal remains to be learned about the nature of environmental stressors and how they affect the individual. The potency of any particular stressor appears to vary with age and sex. Boys appear more vulnerable to both physical and psychosocial stressors from the prenatal period to about age 10 years; girls grow more vulnerable to stressors during their teens (Mrazek and Haggerty 1994). Similarly, maternal inattention during childhood plus residence in high-crime neighborhoods in adolescence appear to associate with substance abuse in adolescence (Cohen et al. 1990).

Temperamental features are also relevant. The combination of difficult temperament and parental psychopathology appears to produce a particularly malignant prognosis (Rutter and Quinton 1984). A variety of parental and familial attributes have been proposed to influence the onset of child and adolescent psychiatric illness. Examples that have been advanced include high levels of parental personality disorder and depression, expressed emotion, unavailability of mother, marital discord, and low degree of family cohesion. Hill (1993) suggested that "early puberty, authoritarian or permissive parenting, family disruption, large impersonal schools, and the availability of a negative peer culture" are important. In addition, Hill (1993) notes "a low level of parental monitoring of the adolescent's behavior [is] a risk factor for involvement with antisocial peers" (also Patterson 1986, Patterson and Stouthamer-Loeber 1984). Similarly, temperamental factors can moderate the course of illness (Zanarini et al. 2006).

*Goodness of fit* is another concept from temperament research that is relevant for adolescent development and risk. Chess and Thomas (1984) defined goodness of fit as that which "results when the environmental expectations, demands, and opportunities are consonant with the individual's temperament and other characteristics so that he can master them effectively." Conversely, *poorness of fit* occurs "when the environmental demands are excessive for the individual's capacities, so that excessive stress and an unhealthy developmental course may be the result" (Chess and Thomas 1984). In this paradigm, stress accompanies developmental progress even when the fit between parent and child is good. The difference between good fit and poor fit is the degree to which parents provide support, modulation, and buffering so that stress and demands are no greater than the child's capacities to assimilate them (Chess and Thomas 1984). When adolescents possess biological vulnerabilities and there is a poor fit between them and their parents, the risks of a poor adaptation and maximal expression of the vulnerability are increased. "Goodness of fit" has been taken to new levels of sophistication and specificity as Fox and coworkers (2005) showed an interaction between short "s" alleles and low levels of social support in the family predicting social inhibition.

A further elaboration of this risk paradigm, for adolescents, is to consider how personality traits can be reinforced or reduced by the responses that they evoke from the wider community. Scarr and McCartney (1983) proposed a reinforcing loop that reverberates between the individual, home, and extrafamilial environment. They suggested that genes affect the children's and adolescents' behaviors which in turn select or shape the experiences that individuals have outside the family milieu. The loop is completed when these extrafamilial experiences further encourage the same genetic traits (Scarr and McCartney 1983). This model implies that when worried parents report that their adolescent is associating with "bad company," their concern should not be dismissed. It appears that such affiliations are an influential, separate variable that is associated with delinquency and social adjustment problems later (Kandel 1978). Conversely, involvement with prosocial activities such as the school science club, athletics, a violin quartet, or community volunteer organizations reinforces an adolescent's socially adaptive behavior. This paradigm also underscores that adolescents' behaviors affect their parents' behaviors. For example, teenagers' behaviors affect parental self-esteem. Self-esteem can be enhanced through pride or lowered through shame, and these changes in turn influence the parent's actions toward the teenager.

Rutter (1979) has suggested that certain family factors raise the likelihood of adolescents having greater difficulty coping with their impulses and with the rules of society. He cited severe marital discord, large family size with physical or psychological overcrowding, maternal mental disorder, and paternal antisocial behavior as examples of these family risk factors. Furthermore, attending impoverished schools, living in dangerous neighborhoods, and becoming involved in social welfare or correctional institutions such as foster or residential care and juvenile detention facilities add to overall emotional stress. These stressors further jeopardize the adolescent because, typically, they emerge in the context of preexisting biological and psychological risk factors.

A common misunderstanding of the way in which genes influence psychiatric illness is a deterministic view that biology is everything and immutable. One lesson that emerges from these more recent specific gene–environment models is that environmental interventions can moderate or neutralize genetic vulnerability. Thus, research on the mechanisms of disorders opens the way to learn about interventions that might be protective (Rapee et al. 2002, 2005, Mrazek and Haggerty 1994). There is less research on protective factors than on risk factors. One might consider protective factors to be the obverse of risk factors, but this would be an oversimplification. Clearly, physical health, normal or high IQ, and economic advantage play a role. Having above-average intelligence influences school success and facilitates problem solving. Garmezy (1986) stressed three categories of protective factors: "(1) personality dispositions in the child, (2) a supportive family milieu, and (3) an external support system that encourages and reinforces a child's coping efforts and

strengthens these by reinforcing the child's positive values." Garmezy suggested that such adolescents (and children) were more successful in eliciting helping responses from adults and making use of their support. In a similar way, they may also be more successful in making relationships with peers and responding to the support peers offer (Rutter 1989). Such skills increase the chances of parents, peers, and teachers being available to support and guide decisions and challenges that would be difficult to face alone. Better-quality advice and chances to consider the entire set of possible alternatives also increase the likelihood of a favorable outcome. O'Grady and Metz (1987) submitted that adolescents who feel in charge of their lives and know how to obtain help are highly resilient, even when otherwise at risk. The Kauai Longitudinal Study has also reported that the ability to find and use an external support system is a significant protective factor for adolescents who were otherwise considered in jeopardy (Werner and Smith 1992). To this one might add that specific genes capable of counteracting earlier risks can also be triggered by events.

There are suggestions that sex differences may be relevant to resilience too. Girls appear to possess a wider range of coping skills than boys, particularly in forming relationships (Seiffge-Krenke 1990). The community is also a source of protection for adolescents. Scouting or youth clubs, school extracurricular activities, and church involvement provide safe activities for teenagers to acquire friends, find supportive adults, and develop new competencies.

## Conclusion

Increasing attention to adolescent development in the past decade has resulted in substantial changes in our understanding of social, familial, cognitive, and biological characteristics of this period. A great deal is still outside our understanding, and tenacious myths about adolescents persist (Offer and Schonert-Reichl 1992). However, new findings place adolescent development into greater harmony with the principles of the preceding developmental epochs. The revised view of these changes during adolescence suggests that they are paradoxically dramatic and yet remarkably similar to those of antecedent periods and much less tumultuous than was once presumed. It is intellectually reassuring to be able to place normal adolescence within the context of the constitutional and experiential past. Increasingly, adolescence emerges as a time in which innate capacities are extended under the influence or guidance of secure familial, cultural, and social supports. Noxious forces from the past and in the present oppose these changes, and their cumulative impact may be greater during this time than at others. It is more accurate to view adolescence as a time much influenced by innate biology and the preceding risk and protective factors, rather than a major metamorphosis triggered by unpredictable interactions between hormones, peer pressures, and the increased separation from parents.

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CHAPTER

# 12 Adult Development

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The study of adult development is evolving within the context of new empirical investigations. Rich theoretical conceptualizations (Kegan 1982), psychologically informed biographies (Erikson 1963), and empirical cohort-based research (Vaillant 2002) have all contributed to the knowledge base. Although these data have limitations in terms of a lack of specific focus on the experience of different cultural and ethnic groups within this country across time, especially those who have relatively recently immigrated to this country, and an overemphasis on male development, enough evidence has accumulated to suggest well-founded conceptualizations of adult development.

## Towards a Conceptual Framework

The central thesis of this chapter is that development occurs in multiple dimensions throughout the course of adulthood. Moreover, adult development is influenced by a wide array of factors including the historical context or times in which individuals live, their economic circumstances, cultural patterns, close intimate relationships, genetic and constitutional factors and history of medical illness, adverse life circumstances, and also positive life circumstances. First, current biological perspectives on adult development are reviewed. Next, the importance of a developmental perspective for understanding serious psychopathology and resiliency is discussed. Last, theoretical perspectives of developmental stages in adulthood are discussed within the context of three longitudinal empirical studies.

This chapter takes place in the context of a rapidly expanding knowledge base about development in general as is evident from other chapters in this volume. Central to understanding development is the core construct of developmental plasticity which emphasizes the capacity of the developing child to flexibly adapt to biological and environmental challenges, be they low birth weight, injury, or medical illness (National Institute of Mental Health 1998). In contrast to earlier genetic theories emphasizing determinism, the growing awareness of how profoundly the environment influences gene expression in a multitude of ways further emphasizes the plasticity of development (Eisenberg 1995). Such a construct emphasizes that at many different points across the life span, individuals can change and grow in response to new challenges. Equally important has been the broadening awareness of the importance of the ecological context, as Uri Bronfenbrenner has emphasized (Bronfenbrenner 1979), in which the child is raised and how attention to various levels in such context can have a positive influence both on children's development and on adults' development across the life span. The very structure of a child's brain across development is profoundly influenced by environmental factors and many of these are susceptible to intervention (Board on Children, Youth and Families 2000, National Scientific Council on the Developing Child 2005). Just as understanding the scientific basis of child development provides the foundation for effective prevention efforts in childhood, so does understanding the multiple influences within a biopsychosocial framework on adult development provide the foundation through which to develop appropriate preventive interventions and clinical approaches. Correspondingly, there is an emphasis on the need to develop programs at multiple levels including throughout adulthood those that foster effective development (Institute of Medicine 1994).

This chapter builds naturally on the preceding review of developmental stages from infancy through adolescence and relies on the integrative framework of Erik Erikson as its organizing principle. Broadly, adult development represents a continued assimilation (the process by which a person takes in and makes sense of material from the environment) and accommodation (a person's response to changing circumstances within the environment) to both the external world and inner life. Adult development occurs in response to a series of predictable and unpredictable challenges. Such development follows a probable but not invariant sequence as each stage builds on what has gone before. Adult development, although sequential, is not invariably tied to specific ages. For example, puberty in girls may normally occur at age 10 years or at age 16 years. If puberty does not occur, the vicissitudes of menopause will not occur either. Most adults reach puberty, but other stages of adult development may not be attained. Under ideal circumstances, adult development can be conceptualized as an ever-widening social radius.

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## Challenges in Studying Adult Development

Five factors render our understanding of adult development difficult. First, there must be a recognition that adult development does, in fact, occur. For example, the concept is more accepted in the United States than in much of Europe. Second, longitudinal studies must be understood within the context of cohort effects, cultural characteristics, and historical biases. Third, the observer must maintain a constancy in perspective while documenting development in other matters. Fourth, the duration of empirical longitudinal studies that span the entire range of adult development will, by definition, exceed the productive life of a single researcher. Finally, there is increasing awareness of the need for cultural competence and cultural humility in understanding diverse cultures that profoundly influence both child and adult development within this country and in the larger world (Rogler 1989). It is particularly difficult to incorporate these perspectives in longitudinal studies as many different groups are highly mobile both within a country or in moving between countries whether in urban or rural areas and are difficult to follow over time. Just as understanding how to effectively render culturally competent care is just beginning within medicine and psychiatry, so is understanding the influences of different cultural and ethnic backgrounds on development in individuals over decades (U.S. Department of Health and Human Services 1999).

The most challenging of these issues is that development in adulthood occurs over a much longer time interval than earlier developmental phases. The specific stages of childhood described in earlier chapters may span only one or two years, which renders their detailed documentation much more feasible.

One of the more recent evolutions in the study of adult development is directly relevant, that is, the recognition that both late adolescence and early adulthood constitute a distinct phase of adult development different biologically and in terms of expectations than development from the mid-20s on.

Although the current emphasis on diagnosis within psychiatry has allowed for progress in the study of cross-sectional psychopathology, diagnostic systems have only minimally incorporated developmental principles and, consequently, have obscured the developmental variation that characterizes some disorders (Munir and Beardslee 1999). For example, the diagnostic criteria used to establish depression are identical for children and adults despite the fact that a depressed 8-year-old presents with different symptoms than a depressed 80-year-old, because of differences in psychological, linguistic, and neurological maturation. Also, some anxiety disorders that begin in childhood have been shown to evolve into a major depressive disorder later in life. The genotype remains constant, but the phenotype changes with development. Finally, many schizophrenics chronic and "incurable" at 35 would not meet diagnostic criteria for the disorder at 65.

An additional cause for difficulty in the study of adult development is the fact that individuals are greatly affected by the era in which they live. The profound changes in family structure in the United States in the 20th century provide contemporary illustration. In 1960, 5% of all births occurred to unmarried mothers; by 1988, this figure had risen to 26%. Furthermore, in 1910, only 1% of children experienced parental divorce. In 1993, almost 50% of all children experienced parental divorce during childhood and lived in a single-parent family for at least five years (Carnegie Task Force 1994).

There has been a significant increase in children raised in poverty, and young parents with young children have disproportionately fewer resources. Between 1971 and 1991, although the number of children younger than 6 years old increased by less than 10%, the number of children who were poor increased by 60%. When poverty and single parenthood are combined, the situation becomes even more difficult. Only 8% of children in homes with two parents live in poverty while 32% of children who reside in single parent homes do (McLanahan et al. 2005). When additional risk factors are added, the situation is even more difficult (Foege 1998). Finally, there have been significant economic changes over the last three decades with a widening gap between the rich and poor and the concentration of wealth, particularly, among a relatively small percentage of individuals and families. At the same time, poverty in old age has decreased. These factors have a profound implication for the mental health and development of adults and children.

## Transactional Model

A transactional model facilitates the understanding of developmental evolution. The interactions between constitutional and genetic predispositions in an individual, the effects of early childhood experience and caregiving, and the individual's interaction with broader society reciprocally affect outcome for a long time period. Although initial transactional models primarily emphasized the influence of factors on the developing child and young adult, more recent models have stressed that the patterns of influence are mutual (Cicchetti and Toth 1995, Sameroff 1989, Sameroff et al. 1998). Endogenous characteristics that develop within a child, adolescent, or adult (e.g., puberty or schizophrenia) can have a profound impact on the environment of the family. As yet, such transactional models, for the most part, have not been able to include longitudinal perspectives on the role cultural variation plays in influencing developmental transactions and different pathways of adult development.

Finally, the need for utilizing caution when considering the certainty of prediction in adult development is demonstrated by empirical studies. Discontinuities are not uncommon in studies of adult development (Rutter 1993, Vaillant 1977) and simple linear developmental lines are often difficult to discern.

In most studies, there are clear correlations between certain childhood and adult characteristics such as intelligence or endomorphy, but these consistencies are less evident as the complexity of the characteristic increases. For example, schizoid children rarely grow up to be schizophrenic adults. In contrast, children with profound mental retardation or autism experience lifelong effects from these conditions. In populations of healthy individuals, the discontinuities are particularly evident and emphasize the degree of change that adults undergo over time. One reason for these changes is the gradual penetrance in adult life of genetic predispositions (e.g., Huntington's disease, alcoholism, and bipolar disorder). Identical twins are often more similar in personality at age 60 years than they were at age 10 (Bouchard et al. 1990).

Knowledge of adult development has evolved from four sources: (1) theoretical conceptualizations of development, (2) detailed studies of individual lives, (3) empirical examinations of discrete phenomena over time, and (4) most rarely, studies that have attempted to integrate conceptual theoretical frameworks with empirical data. The synthesis of these results provides a heuristic overall framework.

## Biological Perspective

A developmental perspective is useful in understanding the biological changes of adulthood (Figure 12–1). Most individuals pass through puberty. For a majority, this leads in turn to the achievement of independent living, sexual intimacy and procreation. By the age of 65 years, an individual has undergone many biological developmental transformations that are quite independent from the decrements of function that result strictly from the aging process. The adaptive responses to the penetrance of genetically controlled diseases such as bipolar depression or alcoholism vary with age and the course of the illness. The biological bases for these differences are less well understood than the equally important environmental forces that affect the individual. Careful longitudinal and cross-sectional studies are required to differentiate genetically determined developmental changes from those that are environmentally determined. For example, although epiphyseal closure is genetically determined, it occurs at puberty, and the onset of puberty is powerfully affected by environmental factors. The languages one speaks are entirely environmentally determined and can be acquired at any age. However, the accent that characterizes speech becomes fixed within a biologically determined period, usually at about the age of 14 years.

Myelinization of the central nervous system continues to occur until the fifth decade (Benes et al. 1994). This may offer a partial explanation for why simple cognitive operations, such as memory and symbol transformation, decline after the second decade, but more complex cognitive operations such as sociational skills continue to improve until the end of the third decade. Continued brain development may explain why sensitivity to simple sensations such as night vision usually peaks at about age 10 years, but reaction time peaks at age 20. Similarly, appreciation of spatial transformations is usually best at age 30 years, whereas the ability to delay gratification probably peaks after age 40. Whereas records for sprinting are held by 20-year-olds, those for long distance races are held by 30-year-olds. Mathematicians and physicists often do their best work before 35 years of age, but philosophers and playwrights often create their finest works after this age. In general, peak cognitive performance usually occurs between the ages of 10 and 40 years and then begins to decline. However, skills of one type often develop to compensate for losses in other areas. For example, 50-year-olds have dramatically better driving records than do 20-year-olds. In contrast, suicide becomes an increasingly high risk with increasing age.

There are predictable developmental changes in Stage 4 and rapid-eye-movement sleep (Roffwarg et al. 1966), electroencephalograms (Woodruff 1978), extrapyramidal symptoms, and brain neurochemistry (Weinberger 1987), but the significance of these changes is not known. For example, extrapyramidal symptoms after administration of neuroleptic agents at age 20 years are quite different from those at age 60 and appear unrelated to brain impairment. The initial manifestations of the gene responsible for Huntington's disease vary with age.

In the locus caeruleus between ages 40 and 60 years, tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of norepinephrine, declines while the activity of monoamine oxidase, the rate-limiting factor for the breakdown of norepinephrine, increases. These changes suggest that the activity of the locus caeruleus may be significantly attenuated in the middle years (Roose and Perdes 1989).

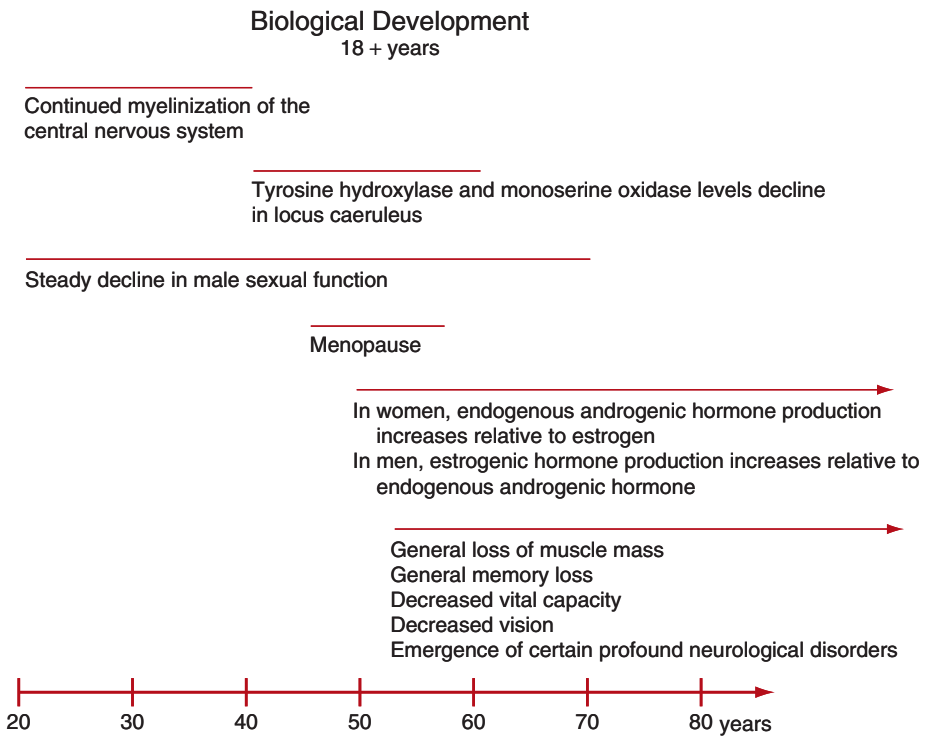



**Figure 12–1** *Biological development from age 18 years through adulthood.*

In terms of adult development, it is important not to confuse healthy aging with the results of injury and disease. After age 55 years, there is a considerable decline in a variety of biological functions, including a general loss of muscle mass, loss of memory, decreased vital capacity, and diminished vision, as well as the emergence of certain profound neurological disorders such as Alzheimer's disease. In some elderly persons, these deficits may reflect disease rather than developmental decline. Some octogenarians can carry out almost every cognitive and physical function as well as an average 40-year-old despite some loss of abilities in memory and flexibility. In addition, the cross-sectional evidence suggesting that general intelligence declines between ages 20 and 70 years is probably an artifact of cohort effects on educational opportunities as opposed to biological processes. Prospective studies do not support such declines in general intelligence (Schaie and Parham 1977).

During puberty, predictable shifts occur in sex hormones that are known to affect cerebral functioning. Particularly in women, changes in the reproductive system are marked during the years of adulthood. In early adulthood, most women menstruate and are able to bear children. Between the ages of 45 and 54 years, a series of endocrine changes accompany menopause, including changes in the balance and production of female hormones. After age 50 years in women, endogenous androgenic hormone production increases relative to estrogens. Although wide individual differences exist, these hormonal changes may facilitate a shift toward increased female dominance that occurs within some couples after the age of 50 years (Guttman 1977). For men, no single biological change occurs, but there is considerable evidence of decline in testosterone production and sexual functioning.

The relative importance of sexual life compared with other facets of intimacy can increase at any point between 15 and 65 years of age. Although there is a steady decline in male sexual function from ages 20 to 70 years in terms of the mean number of orgasms per week, this is not true for women. Studies have shown that women become increasingly orgasmic with age in their third and fourth decade.

The importance of a developmental perspective in dealing with fundamental psychopathology has been illustrated by using schizophrenia (Weinberger 1987). The psychopathology of schizophrenia can best be explained by a developmental hypothesis that acknowledges the underlying brain abnormalities that are present long before the disorder of schizophrenia appears in young adulthood. During childhood and adolescence, the individual with these biological abnormalities appears developmentally normal. It is in early adulthood that predictable stressors may place high demands on these vulnerabilities, which leads to the expression of symptoms. In a somewhat different model, the hypothesis has been advanced that schizophrenia emerges in adolescence due to the excessive pruning of neuronal structures in adolescence (see Chapter 19).

Similarly, studies of Parkinson's disease suggest that both the general symptoms and the monoamine oxidase concentration in the globus pallidus change depending on the age at onset of the disease (Robinson et al. 1977). Various metabolic diseases and brain disorders (e.g., traumas, tumors, and injuries resulting from war) are similarly affected by age at onset. The same underlying structural abnormality may lead to different symptoms depending on the developmental stage of the individual. In short, the manifestations of disorders of the nervous system are heavily influenced by the developmental level of the adult.

## Developmental and Cohort Effects

The importance of a developmental perspective is emphasized by studies of substance abuse and addiction across the life span. Secular trends have a strong impact on drug use. Different drugs have been "in fashion" during different decades. Consequently, it is important to separate social trends and cohort effects from more universal patterns of adult development. Despite these difficulties, there is substantial evidence that adults at different life stages use drugs for different reasons. In adolescence and young adulthood, drugs are often used for novelty and excitement. In middle life, drug abuse is more likely to be linked to social and family rituals. Finally, drug abuse is often the result of an effort to produce calm and to reduce the anxiety-producing effects of novelty and change in late life (Arnett 2000).

Typically, most stimulant drug use occurs before the age of 20 years. Specifically, inhalants, such as glue (in glue sniffing) and tobacco (in cigarette smoking), are among the first drugs to be abused. These rapid-acting agents are more likely to produce dependence in young adults. Furthermore, by adjusting their behavioral repertoire, young adults often use alcohol and barbiturates in ways that create excitation. In contrast, the peak use of sedative drugs occurs after age 45 years when these drugs are used not to party but to calm (Figure 12–2). Cessation of illegal drug use by adults in midlife appears linked to emotional maturation, which allows for greater tolerance of depression and the replacement of drugs with intimate relationships (Vaillant 1996).

More generally, there is a developmental pattern to the onset of different psychiatric disorders. Antisocial behavior is more common in adolescents, schizophrenic symptoms in young adulthood, and affective disorder in middle life (Weinberger 1987). There is evidence that the 12-month prevalence of psychiatric disorders declines across early adulthood. Tanner et al. found declines in 12-month prevalence of anxiety and substance use disorders over the third decade of life in a community sample. In contrast, the rate of depression during a lifetime increased from 8.8% at age 21 to 31% at age 30 emphasizing the need to look at different disorders across different developmental epochs and heightening a focus on the internalizing conditions in early and mid adulthood.

Elder illustrated a cohort effect on adult development by examining individuals who grew up during the Great Depression (Elder 1990). In a prospective study of children at the Institute of Human Development at Berkeley, California, USA, he demonstrated the differential effects of World War II and the Great Depression by following a 1920s cohort and a 1930s cohort from birth into adulthood. In the 1920s cohort, boys grew up to be more successful and competent, whereas girls fared relatively poorly. Conversely, in the 1930s birth cohort, the boys did less well than the girls. Purportedly, financial privation affected prepubertal children differently from adolescents.

Elder provided a cohort-based explanation that considered a variety of social, economic, and psychological

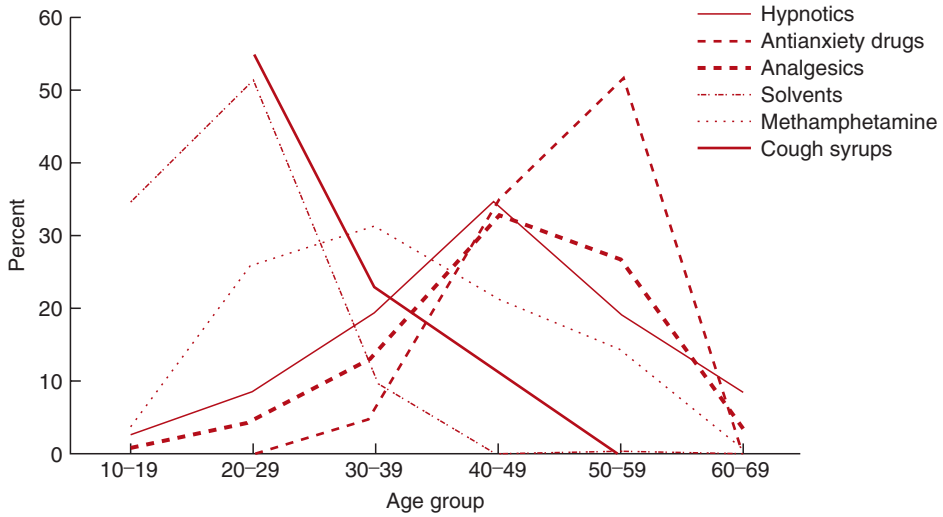



**Figure 12–2** *Age distribution of psychiatric patients with substance use disorder. (Source: Fukui S, Watanabe N, Iyo M, et al (1998) An Epidemiological Survey of Drug Dependence. 1987 Report of Studies of Etiological Factors and Pathological Conditions of Drug Dependence. Ministry of Health and Welfare, Tokyo, pp. 169–182.)*

factors. For example, because of paternal unemployment, the boys in the 1920s cohort were forced to enter adulthood earlier. Therefore, they left home at a younger age and avoided some of the family problems created by the unemployment of their fathers. Ninety percent of these men served in the armed services in World War II, which offered them a moratorium and allowed them to extend their adolescence and to take advantage of the GI bill. In contrast, the girls remained dependent on their families during adolescence, and their self-esteem was negatively affected by their relative poverty during high school. These girls married at a young age and tended to drop out of work.

In contrast, the boys in the 1930s cohort were unable to avoid the emotional impact of the Great Depression. Effectively, many did not have a father during boyhood. In adolescence, they "lost" their mothers to war-related jobs and grew up with lower aspirations. Although 70% of these men served in the Korean War, this experience did not offer them the moratorium or the financial benefits available to World War II veterans. The girls in this cohort fared better perhaps because it was easier for a girl to be less well dressed in grade school than in high school. These girls also tended to provide comfort to their stressed mothers.

A study of depression also emphasizes the importance of the cohort effect. There is increasing evidence that cohorts born in subsequent decades in this country and in Europe during the twentieth century have increasingly higher rates of depression and an earlier onset of symptoms (Institute of Medicine 1994). However, a developmental perspective is also necessary for understanding the onset of depression. It is now accepted that the onset of depression often occurs in adolescence (Sameroff 1989) after the onset of puberty and that early onset prior to puberty may represent a more severe form of depression (Weissman et al. 1987a).

## Risk Factors, Protective Factors, and Resilience

Some developmental challenges that occur during adulthood, such as child-rearing, are also risk factors for the onset of affective disorder. Studies show that mothers who have several children younger than the age of 6 years and who lack adequate social and financial support are at particularly high risk for the onset of major depressive disorder (Weissman et al. 1987b). Evidence has accumulated that multiple risk factors occurring together including poverty, exposure to violence, social isolation, and lack of access to resources along with depression, place individuals in families at high risk for depression and other negative outcomes (Institute of Medicine 1994).

Several studies of children at high risk for depression have followed these children into adulthood. Quite high rates of depression in their offspring have been reported and continue to increase as these young people age (Weissman et al. 1999). Thus, a developmental perspective on the emergence of difficulties in adulthood should include identifying individuals who experienced disorders in childhood and those at high risk for disorder. Also, it is now clear that grandparents' illness as well as parents' illness contribute to the multigenerational transmission of depression (Weissman et al. 2005). Thus, consideration of risks across several generations is needed. At the same time, evidence has accumulated that grandparents can be an important resource for both children and young adults as they develop and mature. Understanding both risks and protective factors across development will continue to evolve.

Resilient individuals do well despite being at high risk for negative outcomes. There is convergent evidence identifying a set of factors that contribute to resilience. In seminal work on resilience, Garmezy et al. (1984) have proposed broad categories of such protective factors, including self-esteem, positive social orientation, family cohesion, and availability of an external support system. Luthar et al. (2000) have produced a useful review and conceptual framework for understanding resilience. Understanding resilience is one essential component of developing effective preventive intervention strategies. Such strategies often aim to encourage those resilient characteristics identified in unusually resilient individuals in the entire group at risk.

In adulthood, resilience depends on the ability to find, use, and internalize social supports. Throughout the life span, maturity of ego defense is an important characteristic of resilience. The specificity of stressors appears to be less important than the relative number of risk and protective factors. This suggests that the number of

protective factors minus the number of risk factors provides a crude but useful index for predicting outcome. Luck, the timing of the stressor, and the individual's fundamental sense of self-esteem and self-efficacy also affect outcome (Vaillant 1993).

Data from a number of ongoing longitudinal studies illustrate the different facets of resilience over time. Werner and Smith (1992) conducted a 30-year study on the island of Kauai and followed up infants from different cultural backgrounds into adulthood. Many were at high psychosocial risk because of family dysfunction and poverty, but approximately one fifth of these high-risk youngsters demonstrated good adult adjustment. The protective factors were categorized as those within the child, within the family, and within the environment.

In terms of factors related to the individual child, the absence of distress in early life and good sleeping and eating habits were important protective factors. Similarly, being affectionate (for girls), being active (for boys), the absence of behavior problems at age 10 years, and the presence of high intelligence were associated with good adult outcomes. Other studies have confirmed the importance of positive temperament, above-average intelligence, and sociability (Werner and Smith 1992, Rutter 1985). The presence of a close and caring relationship with at least one parent or other caregiver during early childhood has been shown to enhance resiliency (Werner and Smith 1992, Werner and Smith 1982). More recently, attention has focused not just on the achievement of resilience at a particular stage but on the mechanisms by which adolescence and adults become resilient and on the processes which underlie such resilience (Luthar et al. 2000). Just as risk factors interact across time, so does the presence of protective factors acting in combination with one another.

Research also emphasizes the importance of the ecological framework or multiple layers of influence from family, neighborhood, community, and even social policy in determining resilient or non-resilient outcomes at a particular developmental stage (Bronfenbrenner 1979).

Within the family, high educational level of the opposite -sex parent and warm relationships with both parents proved important. The presence of rules and structures in the household strongly supported adolescent development, as did having mothers who worked. Families with four or fewer children and with at least a 2-year interval between children were also protective (Werner and Smith 1992).

In terms of protective factors within the community, relationships outside the family and external support systems such as churches, youth groups, schools, and recreational activities were important (Bronfenbrenner 1979, Jones and Offord 1989, Werner 1989). Good secondary schools also had a positive effect (Werner 1989, Rutter et al. 1970).

In adulthood, second-chance opportunities occurring at major life transitions were protective. These included marriage or entry into a long-term relationship, the birth of a child, finding a supportive employer, entering the military service, or joining a church group (Werner and Smith 1992, Jones and Offord 1989). More generally, two kinds of protective factors in adulthood have been identified: those that arise from social supports and personality attributes that affect the ability of an individual to master stress (O'Grady and Metz 1987). Also, the capacity for self-reflection and self-understanding is an important component of resilience in adolescents and adults facing adversity (Beardslee 1989). Moreover, understanding these protective factors have important and direct preventive intervention implications, for example, making certain that there are second change opportunities for all groups in the population around transitions or encouraging the capacity for self-reflection and self-understanding through appropriate preventive intervention strategies.

## Young Adulthood as a Distinct Developmental Stage

The Study of Young Adulthood has advanced the conceptualization of resilience considerably (Masten et al. 2004) and has focused particularly on the transition to young adulthood as a possible time for the emergence of strengths. There is increasing awareness that the transition to adulthood is a distinct developmental stage and presents both challenges for young adults moving through this phase and opportunities, in particular, a chance to develop new relationships and identifications (Arnett 2006). Much less attention has focused on the transition to adulthood in youth growing up in contexts of adversity.

Arnett first used the terms "emerging adulthood" to indicate the period 18−25 years which included exploration and growth and was distinct from both adolescence and early adulthood (Arnett 2000). He further (Tanner 2006) indicated defining elements as explorations of identity in the areas of love and work, being self-focused, and explorations of possibilities and opportunities to pursue. In Tanner's conceptualization (Tanner 2006), there is "a recentering of relationships," in particular, family relationships. Accomplishment of this stage is often quite heterogeneous. For many young adults, there is a considerable freedom without strict requirements for their behaviors (Gladstone et al. 2006). Others have also advanced the view that the transition to adulthood is important and, in fact, this generation is different than the past in being less unified and, for some, in carrying higher aspirations. American society has also delayed expectations which, in turn, has led to a prolonged developmental phase.

Shanahan (2000) has observed that within the individual's life, there is a greater change and more variety in social roles in young adulthood than at any other time. Correspondingly, there seems to be a decrease in mental health problems for some groups of young adults (Tanner et al. 2007). Several psychologists have observed that the experience of transition to adulthood occurs in a balance between autonomy and relatedness (Best et al. 1997, Eccles et al. 2003). The health of emerging adults is tied to their families (Gladstone et al. 2006, Kaimal 2007).

Fuligni and Pedersen (2002) have argued that remaining related to parents is a key task of emerging adulthood and may indeed set the stage for later caregiving. They found that responsible behavior towards family members increased following high school and, more generally, relationships with family members increased.

In a study of 205 individuals tracked into early adulthood, Roisman et al. (2004) demonstrated the predictive connections between three tasks of late adolescence and young adulthood: academic attainment, quality of friendships, and absence of disruptive conduct symptoms.

They also examined two domains that they hypothesized emerge during this area: romantic competence and work competence. Romantic competence means being able to function effectively in an intimate relationship. Work competence means accomplishing appropriate tasks in the area of work. In following these individuals until age 30 and combining reports from the participants, the parents, and clinical ratings by judges, they found that the salient tasks from age 20 predicted within domains success ten years later with one exception that both conduct and academic competence at 20 predicted absence of conduct problems and rule abiding behavior at 30. They also looked at resources and resilience in the transition to young adulthood, again combining multiple domains as had the earlier Werner and Smith work. They found that success in both early and young adulthood related to core resources that were present in childhood, namely, higher IQ, good parenting quality and socioeconomic status and also a set of within person adaptive resources that included the capacity to be planful, to have motivation for the future, to have a sense of autonomy and coping skills, and also the presence of adult support. This work suggests important domains for possible preventive interventions for youth at high risk across this developmental transition. It also illustrates the continuity between childhood and early adulthood. These investigators plan to follow these young people into middle adulthood which will further our understanding of this important stage.

Changes in the demographics have also influenced this stage of young adulthood (Tanner et al. 2007). In 1970, the median age of males and females at the time of marriage was 22.8 and 20.3, respectively, whereas today, it is 26.8 and 25.1, respectively. This has profound implications for development. Similarly, in 1970, the proportion of high school graduates who enrolled in college was about 51.8%. This increased to 63.3% in 2000. Moreover, the transition of youth into the workforce has become much longer and more unstable. The demand for service jobs outweighs the need for jobs in manufacturing. Certain areas like highly technological endeavors have seen the increase and also highlighted the need for a more educated workforce. All of this has contributed to a change in adult role with a greater focus on obtaining additional education. Part of the amount of formal education and the delay has led Arnett (2000) to formulate the concept of emerging adulthood as described previously. In some ways, identity formation in Eriksonian terms may be viewed as being prolonged and much more the task of young adulthood. Arnett has also added that in addition to tasks of love and work, another goal is the attainment of an appropriate enduring worldview.

Another important characteristic of contemporary emerging adulthood is the rapid pace of change and a set of challenges not well described in previous epochs. One of the interesting challenges in work on the study of adult development in the future will be to see how these new changes influence outcomes. Robert Blom (National Research Council and Institute of Medicine 2006) of Johns Hopkins recently described a set of firsts for America's youth and young adults. Specifically, Blom posits that today's youth will be the first generation to:

- understand terrorism as a domestic issue,
- will be called upon to compete fully in a global economy
- live through instantaneous communication that is available throughout the world,
- who will spend a portion of childhood in a single parent household,
- have the threat of AIDS over their entire lives, and
- have watched an entire American city destroyed, that is, New Orleans in the wake of Katrina.

Blom's point is not at all that prior generations did not face difficult or even more difficult challenges but that the nature of these challenges will shape the experience of young people. How these particular events singly or occurring together will have an influence on this generation's development remains to be investigated, but there is no doubt that these events will influence the course of development. As one example, how will the various kinds of much more rapid technologically supported communication, such as instant messaging and e-mail, influence the development of intimate relationships? This is a question that has yet to be answered but one with important implications for understanding both development and the influence of communication and relationships on development. Another is does the widespread use of instantaneous communication devices by children and adolescents affect their overall physical and mental development either positively or negatively in significant ways?

Our emphasis in the preceding section on the importance of the emergence of young adulthood speaks to the addition of this distinct stage to the creation of developmental schemas. Furthermore, it is important to recognize that while the current generation is the first to experience these new challenges, the trajectories of development of all generations are influenced.

## An Integrated Model for Adult Development

The best model for understanding development is one that integrates clearly defined behavioral tasks and functions in the external world, such as having friends, with innate and developing capacities within the individual, such as coping skills. Vaillant and Vaillant (1981) studied a sample of adolescent boys until age 50 years. These boys had been at risk because of poverty and recent immigrant status. They found the most important predictor of success to be "competence." Clausen (1993) similarly described "planful competence" as a core integrative construct that predicted successful adult outcome. Competence reflected the presence of regular part-time work, performance of household chores, participation in extracurricular activities, good school grades relative to IQ, and ability to plan.

In the study by Vaillant and Vaillant (1981), competence measured what the individuals did, not what they reported about their feelings. Examination of adult outcomes in objective behavioral terms led to three important findings. First, the capacity to work in early adolescence was strongly correlated with good mental health in midlife. Second, the boys who were most successful in adolescence in terms of competence were much more likely to be successful in adulthood, in terms of both their paid jobs and their capacity to have relationships with others. Third, the presence of positive attributes in the family environment was more predictive of outcome than was the presence of negative attributes. Similarly, the positive presence of

planful competence outweighed the presence of negative factors.

The complex interactions between risk factors and protective factors and the emergence of resilience over time are illustrated in a different way by two investigations conducted in London. The study by Quinton and Rutter (1988) of difficulties in parenting provides an illustration of complex development transitions. This study followed up a group of girls who had been placed in residential or group homes as youngsters. Those girls who, after leaving the residential home, entered positive family environments were more likely to make positive decisions later in life, such as in the selection of a supportive spouse. They also developed better parenting skills. Similarly, those who had good school experiences were more likely to demonstrate planning in terms of career choice and marriage partners. On the other hand, the youngsters who did not have positive family experiences tended to marry quickly and to make poor choices in life. These women more frequently divorced and displayed difficulties in parenting their own children. Thus, the capacity to plan emerged as crucially important in making choices about marriage partners. This, in turn, was strongly related to success in child rearing.

Brown and Harris (1989) demonstrated that a complex interactional model of risk and protective factors was associated with the onset of depression in a group of women living in London. They found that the absence of close confiding relationships in adulthood coupled with the presence of unusual stresses preceded depression in women. Focusing on earlier events, Rutter (1981) demonstrated that it was the loss of care for the child and the degree of the disruption in the child's life after the death of a parent that predicted a negative outcome rather than parental loss per se.

## Developmental Formulations of Adulthood

Most theorists believe that development involves an increase in cognitive and affective differentiation that leads to a greater capacity to relate to the environment. The observations by Piaget (1932) of the dual processes of assimilation and accommodation and the invariate sequence of stages in the development of intelligence have supported this fundamental belief. He also described the stages in the development of intelligence and the cognitive structures or schemas that underlie the learning paradigm. Individuals progress from one cognitive stage to the next through periods of disequilibrium. The process of equilibration involves coming into balance in the new phase.

Piaget's approach has been applied in adults to moral development (Piaget 1932), the development of self-understanding (Damon and Hart 1982), and the development of interpersonal understanding (Selman 1980). Kohlberg (1973) delineated six stages of moral development: Stage 1, a premoral level with a punishment and obedience orientation; Stage 2, a naive and straightforward hedonism; Stage 3, a level involving conforming to avoid disapproval; Stage 4, a level entailing conforming to avoid criticism by legitimate authorities in the development of guilt; Stage 5, morality of contract in which there is an agreement to maintain and respect impartial laws; and Stage 6, morality of individual principles in which the individual conforms to avoid self-condemnation. Processes similar to those described by Piaget were hypothesized to occur in the development of each stage. Although these stages of moral development provide some support for a stage sequential perspective, this work has been criticized for not addressing gender-specific differences.

A second model, based on the principles of ego psychology, is compatible both with the developmental frameworks presented in this chapter and with the work of Loevinger (1976). This model attempts to describe and characterize inner states, processes, and functions that manifest themselves in a wide array of behavioral situations that correspond to behavioral functioning. Ego defenses and ego maturation are viewed as critical organizing constructs across the life span. This formulation of the ego proposes a mediating function in the inner life that facilitates the completion of complex behavior tasks. In psychoanalytic terms, the ego resolves conflicting impulses and, in contemporary terms, it performs executive and organizing functions such as focusing attention.

Differences in ego functioning explain the mechanism by which individuals cope with conflict or stress. Longitudinal studies of development have found conceptualizations of increasing capacities of the ego and maturing defensive structure to be useful (Vaillant 1993, Haan 1977). Vaillant's work illustrates a heuristic framework of ego development parallel to shifts in diagnostic domains. Ratings of defenses were based on both objective behaviors and awareness of inner states (Rutter 1993, Vaillant 1993). The "immature" defenses, which are common to character disorders, include denial through fantasy, dissociation, projection, passive aggression, hypochondriasis, and acting out. There is also a set of "neurotic" defenses including intellectualization (isolation,

**Table 12–1 Contrasting Ways of Altering the Conscious Representation of a Conflict**

| Defense | DSM-III Phenomenological Diagnosis* | |
|---|---|---|
| No defense | 309.9 | Adjustment reaction with atypical features |
| Psychotic defense | | |
| Denial | 298.8 | Brief reactive psychosis |
| Immature defenses | | |
| Projection | 301.0 | Paranoid personality disorder |
| Passive aggression | 300.4 | Dysthymic disorder |
| Acting out | 301.7 | Antisocial personality disorder |
| Fantasy | 301.2 | Schizoid personality disorder |
| Neurotic (intermediate) defenses | | |
| Dissociation | 300.15 | Atypical dissociative disorder |
| Displacement | 300.29 | Simple phobia |
| Isolation (or intellectualization) | 300.3 | Obsessive-compulsive disorder |
| Repression | 300.02 | Generalized anxiety disorder |
| Reaction formation | — | |
| Mature defenses | — | |
| Suppression | — | |
| Sublimation | — | |
| Altruism | — | |

*Diagnosis assumes that conscious representation of the conflict was carried to pathological extremes and that the other criteria for the diagnosis were met. DSM-III, Diagnostic and Statistical Manual of Mental Disorders, Third Edition.

*Source*: Data from Vaillant GE (1993) The Wisdom of the Ego. Harvard University Press, Cambridge, MA, USA.

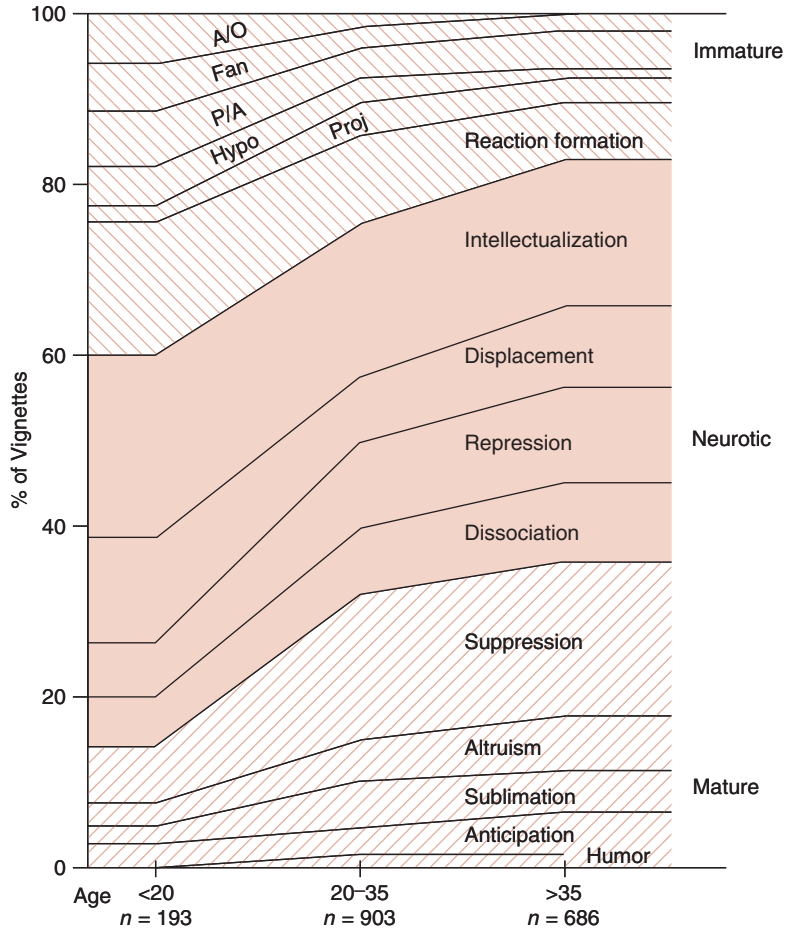



**Figure 12–3** *Shifts in distribution of defensive vignettes shown by 95 subjects at adolescence, young adulthood, and middle age (A/O: acting out; Fan: fantasy; P/A: passive aggression; Hypo: hypochondriasis; Proj: projection). (Source: Vaillant GE (1976) Natural history of male psychological health, Archives of General Psychiatry 33, 535–545. Copyright 1976 American Medical Association.*

undoing, and rationalization), repression, displacement (including phobias and conversions), reaction formation, and disassociation (neurotic denial and counterphobia (Weinberger 1987) (Table 12–1).

Finally, there are "mature" defenses such as altruism, sublimation, suppression, anticipation, and humor. These defenses are particularly relevant to the adulthood stage because many of them are thought to appear only in late adolescence or adulthood. Altruism entails doing for others as one would have done for oneself. The person engaging in altruistic behavior is at least partially gratified, and such behavior contributes to self-efficacy. Sublimation allows the expression of intense emotion without either adverse consequences or loss of pleasure. Suppression involves the semiconscious decision to postpone paying attention to a particular inner impulse. Anticipation involves realistic and effective planning for the future rather than denying and incorporates thinking and planning about affective issues as well as cognitive ones. All of the mature defenses integrate sources of conflict and thus do not involve characteristic modes of self-deception. Unlike other defenses, mature defenses allow subjects to experience themselves, their relationships, their ideas, and their feelings fully and without ignoring important parts of either external reality or their internal lives.

The relative maturity of defenses was ascertained by comparing the proportion of an individual's mature defenses with the proportion of her or his immature defenses. Two major findings emerged. Immature defenses were negatively correlated with good adjustment and positively correlated with psychopathology. The reverse was true for mature defenses. They were associated with health, whether health was defined as the presence of successful objective life adjustment, the absence of psychopathology, or the achievement of subjective satisfaction. Men characterized by passivity, pessimism, self-doubt, fear of sex, and dependence were more likely to use immature defenses. In general, adolescents also utilized immature defenses, whereas adults in middle life typically used mature defenses. Between the ages of 15 and 45 years, there was a gradual evolution in both of the longitudinal samples from the use of immature defenses to the use of mature defenses (Vaillant 1993, Haan 1977). Figure 12–3 provides a graphical representation of changes in the use of defenses over time. As with Kohlberg's data, such evidence strongly suggests a maturational process that occurs during the course of adulthood.

## Eriksonian Model of Adult Development

Whether there are stages that characterize adult development in the same way that there are stages in childhood and adolescence development is unlikely. Nevertheless, adults manifest a developmental sequence of task mastery illustrated by Erikson's model that has been found to be useful (Erikson 1956, Havinghurst 1972). These tasks have the advantage of being less ethnocentric than either an individual-centered stage sequential model

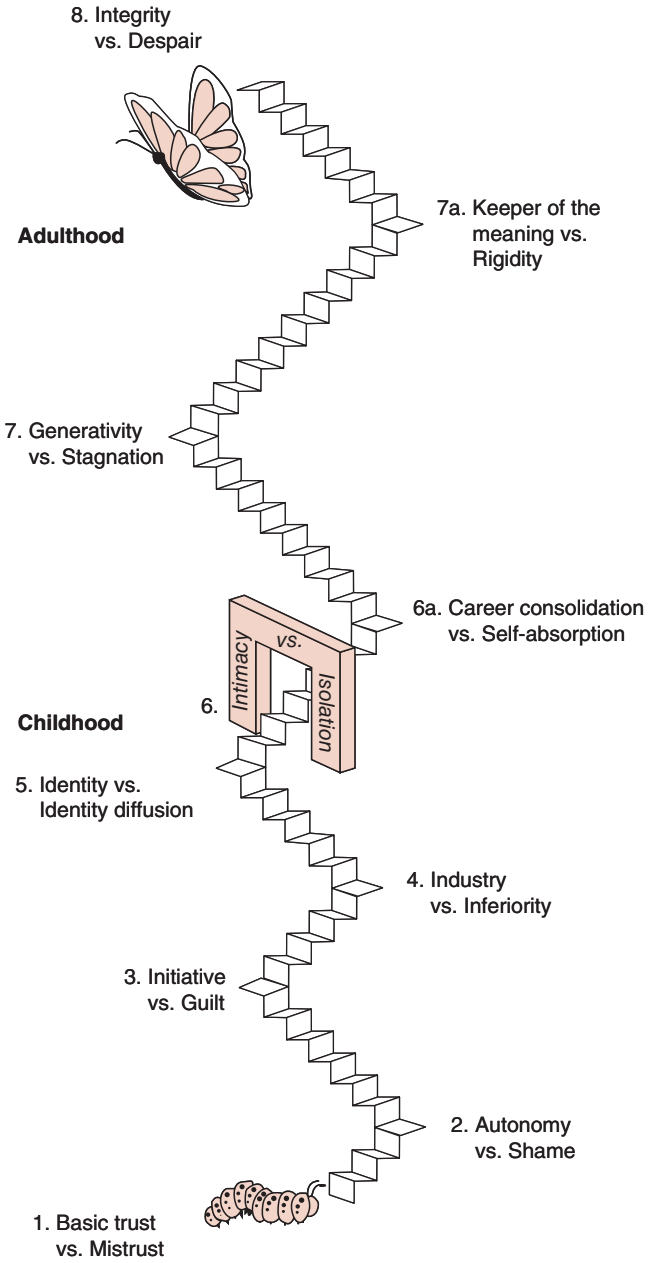



**Figure 12–4** *A model of adult development. This is essentially Erik Erikson's model of the adult life cycle with the addition of Stages 6a and 7a. (Source: Modified and reprinted by permission of the publisher from Vaillant GE (1993) The Wisdom of the Ego. Harvard University Press, Cambridge, MA, USA. Copyright 1993 The President and Fellows of Harvard College.)*

or a defense-centered model. Erikson's model suggests that a term such as Havinghurst's developmental task is a more appropriate construct than stage of development (Havinghurst 1972). A modification of Erikson's model of the adult life cycle is presented in Figure 12–4 as a series of expanding ripples. This model depicts the growing adult's ego capacity to master and feel at ease in an increasingly complex social radius. The spiral depicted in Figure 12–4 contains two stages, career consolidation (Stage 6a) and keeper of the meaning (Stage 7a), that have been added to Erikson's original eight stages.

The key to understanding the sequential nature of adult ego development lies in the appreciation of both the relative complexity and the inner threat of the tasks and commitments that must be mastered. The twin anxieties of young adulthood involve the abilities to commit to one person and to commit to one job without sacrificing autonomy. Older adults, having mastered these tasks, may serve as mentors in the process.

There is correspondence between the accomplishment of tasks in the external world, such as maintaining a long-term intimate relationship, and ego development. This framework is valuable not only for organizing the unfolding of development in normal individuals but also for providing a useful framework for understanding how psychopathology may affect development at different stages.

In the empirical studies, those individuals who achieved generativity almost always had also evolved to stages of identity formation, achievement of intimacy, and career consolidation. This proved true both for men and for women (Vaillant 1993).

Erikson's task of identity versus identity diffusion, Stage 5, reflects mastering the last task of childhood which is the sustained separation from social, residential, economic, and ideological dependence on one's family of origin. Such separation derives as much from the identification and internalization of important childhood figures as it does from the ability to master modern life. Identity is not just a product of egocentricity, of running away from home, or of marrying to escape the family. There is a world of difference between the instrumental act of running away from home and the developmental task of knowing where one's family's values end and one's own values begin.

Men and women who fail to reach a sense of identity do not achieve independence from their family of origin, or they remain dependent on institutions (Stage 5). In middle life, such individuals remain dependent on others and never commit themselves either to occupational specialization or to sustained intimate friendships. Many individuals diagnosed as having schizophrenia with stable community adjustment fall in this category.

Mastery of the task of intimacy versus isolation (Stage 6) serves as the gateway to adult development. Intimacy is defined as living with another person in an interdependent, committed, and intimate fashion for years. Although marriage, heterosexuality, and orgasm are not necessarily criteria for intimacy, intimacy is initially achieved most often with a spouse. Adolescents and adults with pervasive developmental disorders are usually incapable of close mutual interdependence. For many young adults, mastery of interpersonal intimacy is a major focus of psychotherapeutic treatment.

The creation of a stage between intimacy and generativity reflects the importance of achieving a stable career identity. The construction of this stage distinguishes the development of identity within one's family of origin from the development of identity within the world of work. The internalized (usually familial) mentors important to achieving identity are rarely the same as the (rarely familial) mentors important to achieving an identity in the world of work. This task has been described as career consolidation, which involves the achievement of vocational identity that, like intimacy, reflects reciprocity. Put differently, the task of career consolidation is often accomplished after the achievement of intimacy but is characterized by commitment,

compensation, contentment, and competence. In behavioral terms, this task involves making a clear, specialized career identification as measured by personal satisfaction and appreciation by others. These four concepts distinguish a career from a job. Career consolidation involves the transformation of preoccupation with self into a specialized role valued by both self and society. Just as the task of intimacy includes the mastery of attachment, so mastery of this task involves the modulation of anger.

One of the tasks of mature adult development is to compensate for societal imperatives rather than to accommodate to them. The study by Broverman et al. (1972) showed that both men and women attributed a specific cluster of traits including independence, rationality, and self-direction to the ideal man, independent of their level of education. Both sexes attributed a different cluster of traits such as warmth, emotional expressiveness, and relatedness to the ideal woman. Prospective studies suggest that by midlife a major developmental task for women is to achieve the traits of independence, rationality, and self-direction (Vaillant 1977, Guttman 1977). Similarly, it becomes equally enriching for men in midlife to achieve warmth, emotional expressiveness, and relatedness (Rogler 1989, Guttman 1977).

Selfless generativity (Stage 7) reflects a clear capacity to care for and guide the next generation. Generativity means assuming sustained responsibility for building the community and for the growth, well-being, and leadership of others. It can entail serving as a consultant, guide, mentor, or coach to young adults in the society. In Figure 12–4, we have split off certain facets of Erikson's concept of generativity and relabeled them as Stage 7a, keepers of the meaning. Generativity and its virtue, care, require taking care of one person rather than another (Erikson 1963). Keeper of the meaning and its virtue, wisdom, involve a nonpartisan and less personal approach to others. Thus, the tasks of a generative coach or partisan parent of adolescent children are vastly different from the tasks of a Supreme Court judge or chair of a historical society.

The generative individual cares for others in a direct, future-oriented relationship such as teacher cares for a student. In contrast, the keeper of the meaning speaks for past cultural achievements and guides groups, organizations, and bodies of people toward the preservation of traditions. Care and justice, as Gilligan (1977) underscored, have always been different dimensions of development. However, the term wisdom is preferable to justice, for it is less value-laden and, hopefully, synthesizes care and justice.

The final state, integrity, may be compared to putting a garden to bed for the winter. Life-review facilitates coming to terms and accepting the past. Planning legacies involves appreciation that families, like gardens, go on living after one's death. At the end of life, spiritual life may deepen and include more of humanity than one's earlier faith tradition.

Further empirical justification for Erikson's model has been provided by data from three different major longitudinal studies of adults: (1) the Grant Foundation study of Harvard men (Vaillant 2002), (2) the core city study of the men in Boston enrolled in the early 1930s (Vaillant and Vaillant 1981), and (3) the Terman study of gifted women in California (Vaillant 2002, Oden 1968, Sears 1984). Individuals in these studies mastered these tasks sequentially in a manner relatively independent of social class and education. Individuals who did not master earlier tasks (such as intimacy) were much less likely to master later stages (such as generativity) (Garmezy et al. 1984).

There are several heuristic advantages to depicting Erikson's model in Figure 12–4 as a spiral rather than simple staircase. First, this representation underscores that during adult life, individuals evolve rather than merely grow. Second, the spiral conveys the concept that with maturational change, past progress is not lost. Third, the model suggests that as in climbing a spiral staircase, failure to attain one landing makes it unlikely that one will attain the next. Fourth, the left and right sides of the model reflect the rhythmic changes in malleability of character that occur during the life span. The oedipal years (Stage 3), adolescence (Stage 5), midlife (Stage 7), and old age (Stage 8) are often times of personal change and instability. These periods of life often involve reworking ascribed identity and questioning conventional morality. They are times of heightened introceptiveness, affective lability, and fresh instinctual conflict.

On the right side of the spiral, the life periods of autonomy, industry, career consolidation, and keeper of the meaning are represented. During these periods, individuals are preoccupied with the preservation of sameness and autonomy and are involved in following and maintaining rules. Such individuals are more likely to be concerned with absorbing, observing, and promulgating the past traditions than with reworking their culture. During the life span there appears to be an oscillation with a still longer amplitude than the journey depicted in the spiral staircase model. At some point in life, there are suddenly more yesterdays than tomorrows. At this point one seemingly retraces the stairs one has climbed. If the steps from infancy through childhood to adolescence lead sequentially to mastering one's body, one's external environment, and, finally, one's emotions, then from age 40 years to senescence the steps lead in the reverse direction. Like the adolescent, the 40-year-old in crisis struggles with feelings; like the 10-year-old, the 60-year-old struggles to resist the changing times; and the 80-year-old, like the toddler, is preoccupied with an unruly, unsteady body. Neugarten (1964) has written that if 40-year-olds "see the environment as one that rewards boldness and risk-taking, 60 year-olds seem to see the environment as complex and dangerous, no longer to be reformed in line with one's own wishes and to see the self as conforming and accommodating to outer world demands."

Another area of importance is a growing awareness that parenting itself can have a very positive developmental influence on adults who are parents (Beardslee 2003). While most formulations, as Erickson does, acknowledge raising children as one of the important tasks of generativity and relating to one's own children and other young people is needed in later stages, much more attention needs to be focused on understanding how parenting can positively influence development. As one example, evidence has accumulated that for parents who are depressed, a preventive intervention approach which incorporates a focus on effective parenting and fostering resilience in their children has considerable merit (Beardslee et al. 2003, Beardslee et al., in press).

## Grief

Although it is believed that as one ages, one becomes more accepting of death, increases in age also increase the likelihood of experiencing the loss of a loved one or a family member. Bereavement, or grief, usually occurs after such a loss. Uncomplicated grief is believed to proceed through a series of anticipated stages (Schulz 1978). The initial stage, which occurs during the first few weeks after the loss, is characterized by feelings of shock and disbelief. The second or intermediate phase takes place during the first year after the loss; it is distinguished both by feelings of loneliness and by thoughts about the death, why it happened, and how it could have been prevented. Usually by the beginning of the second year after the loss, the individual begins the recovery phase; during this time the individual begins to seek out social situations and moves on with life (Dworetzky 1995, National Institute of Mental Health 1988). Lehman et al. (1987) pointed out that little is known about the actual duration of grief, and in their studies of parents and spouses who were experiencing unexpected loss, grief often continued to be experienced many years after the loss.

Unexpected or sudden deaths often result in more severe and long-lasting periods of grief than those that were anticipated (Lehman et al. 1987, Parkes and Weiss 1983, Stroebe and Stroebe 1987). Death of one's spouse, regardless of the nature of the death, can have a significant impact on the health of the individual, with it "not being uncommon for the remaining spouse to become seriously ill or to die within two years (Dworetzky 1995, Stroebe and Stroebe 1987)." A gender difference in the period of greatest risk has been observed, with widowers being at increased risk for the first year after loss and widows during the first 3 months (Mellstrom et al. 1982). Widowers who remarry appear to have lower mortality rates than those who do not (Helsing et al. 1982).

The effects of loss do not appear to lessen with increased age. Lesher and Bergey (1988) found that the loss of a child resulted in a number of negative effects in elderly bereaved mothers. These mothers experienced high levels of "psychological distress" as well as changes in "health, functional activities, family cohesion and psychological well being." The authors pointed out that not only does the loss of a child have an impact on the older individual's sense of life order, but it may also have a strong impact on the quality of their life. This can be due to the assistance that the child could have provided or to the decreased contact with their deceased child's spouse and/or children that can result.

As individuals pass from childhood through adolescence and into early adulthood, most have developed a belief that death is irreversible, final, and inevitable (Dworetzky 1995). Kubler-Ross (1969) has identified five stages that occur when individuals are confronted with death: (1) denial and isolation, (2) anger, (3) bargaining, (4) depression, and (5) acceptance. These stages are useful in understanding the experience of dying, but it should be noted that they do not necessarily occur in a particular order and that all stages may not be experienced by every individual. For example, an individual's response to death may be influenced by their age: those of a younger age may be more likely than older persons to experience stages of denial and anger (Pattison 1977).

## Transitions and Developmental Crises

Several investigators prefer to chart adult development in terms of transitions and developmental crises. In some sense, transitions are a by-product of normal development. Certainly, the process of adult development is more than the achievement of chronological landmarks such as one's graduation, first job, marriage, and first child. Development creates transitions, and transitions then influence development.

The crises associated with transitions often have more to do with three nondevelopmental factors than they do with the process of development. The first factor is psychopathology. For example, individuals who have a particularly troubled adolescence are also likely to have a particularly troubled middle life. Similarly, a tendency to serious depression makes almost any change a crisis. However, community studies of people during adolescence and middle age suggest that such assumptions of inevitable developmental crisis are unwarranted (Farrell and Rosenberg 1981, Offer and Offer 1986).

The second factor associated with crisis during developmental transitions involves poorly culturally mediated changes in role. For example, an uncelebrated retirement or a perfunctory civil marriage ceremony may lead to greater instability of adjustment and to later crises. Nonindustrialized cultures frequently ritualize adolescence, menopause, and old age more effectively than do modern industrialized cultures. Smooth transitions appear to be facilitated by cultural, ritual, and sacramental celebrations.

The third factor associated with the crises of life transitions occurs when the transitions take place outside of the appropriate temporal sequence. Widowhood is a greater developmental crisis at 40 than at 80. Menopause may be a crisis at 30 years of age but a welcome fact of life at 50. In contrast, the death of a child is always a crisis because it runs counter to the expectations of adult development.

## The Enduring Importance of Identity Formation

In reflection on the course of development, several points deserve emphasis. The first is that within the various Eriksonian stages, an emphasis on identity formation and identity is the key to each stage. A firm sense of personal identity is a critical achievement of adult development. This identity can change as the individual grows and develops, but identity nonetheless provides both an internal anchor and a stable way of relating to others in the world. Erikson emphasized that the adolescent process of identity formation ends only when an individual develops a new kind of identification and, indeed, long-term commitments both to others and to work. Furthermore, before an identity is formed, there is often a psychosocial moratorium during which an individual postpones making life choices. Erikson emphasized the dynamic interaction between the inner sense of self and the manner in which individuals have responded to and dealt with those around them. In simple terms, youngsters evolve from being dependent on their parents and going to school to maintaining jobs of their own, functioning independently, and developing close intimate relationships. In broader terms, mastering the task entails mastering internal conflicts so as to be able to engage in working and loving. Erikson emphasized that identity

formation is not simply an internal process of selecting identification during childhood but a process through which others often "through sub-societies identify the young individual (Erikson 1956)."

### Clinical Implications

From a clinical perspective, it is well worth determining the fundamental identity of the person under consideration and where along the various stages of adult development the individual falls. A second consideration is how the individual deals with her or his own children. The stages of adult development are closely tied to functions related to child rearing. In the stage of career consolidation, one component is the need for the provision of adequate resources to raise a family. One area that needs much more attention is how being a parent can actually foster the growth of maturity and development in adults and that for many adults, the most meaningful and generative relationships they have is with their children. Moreover, a focus on parenting and being successful as a parent can be very helpful to adults who face unusual risks because of experiencing multiples of adversities or major mental illness (Beardslee et al. 2003, Beardslee and Knitzer 2003). In the later stages, characterized by generativity, individuals proceed from being concerned mainly with their own children to becoming concerned about broader issues such as the next generation in general. This occurs as their own children become parents and as people of the next generation assume leadership positions and become mentors and teachers. The penultimate stage, keeper of the meaning, includes being a wise grandparent or, in figurative terms, embodying family wisdom and cultural wisdom.

Mastery and integrity, the last stage of life, is often facilitated by the clinician or hospice worker, being attuned to the need for life review, guided as to biography and a chance to examine one's deeper spirituality.

Understanding what the normative developmental tasks that children of different ages face and how well they are accomplishing them compared to their peers are important components of evaluation for children and adolescents. This also applies to the evaluation of adults. Thus, for example, a crucial normative developmental task for young adults is mastering intimacy with others, or for older adults, becoming generative. Evaluating patients on how they are accomplishing these tasks in the context of the difficulties they present for care is important. Also, how individuals have successfully accomplished the challenges of prior developmental stages is likely to have a profound effect on how they master or do not master subsequent stages.

### Preventive Intervention Implications

Over the last two decades, there has been a remarkable increase in the quantity and quality of evidence-based preventive interventions for children, youth, parents, and adults. The basic building block for developing effective preventive interventions is a knowledge of human development across the lifespan. The evolving study of adult development provides a rich groundwork in which to consider mounting effective preventive interventions. For example, Phyllis Silverman (1986) has devised an innovative widow-to-widow intervention program based on the understanding of the stages of grief outlined by Kubler-Ross (1969) and the vital role of close social relationships in coping with grief. Rick Price et al. (1992) have developed an innovative job retraining program, initially for workers in Michigan who had lost their jobs, that has shown long-term effects on reemployment and also on mental health dimensions in providing what may be deemed a second chance opportunity in adulthood. These are two examples of effective preventive interventions being built both on an understanding of adult development and on the challenges presented by a particular crisis.

Recent reports have emphasized the need for more evidence-based preventions (Institute of Medicine 1994, National Advisory Mental Health Council 2001). A number of registries of effective preventive interventions across the lifespan have been developed. In the future, one of the most promising areas in the study of adult development will be to link advances to the development of new and effective preventive interventions. In this, it will be particularly important to consider adults in their own developmental trajectories and adults in their roles as parents. There is a consensus across preventive intervention efforts that strength-based approaches are best; hence, the need for understanding healthy development from a nonpathological point of view. There is equally an awareness that family strengthening interventions have great power (Beardslee and Knitzer 2003), which inherently take advantage of the two generational opportunities. Finally, undoubtedly, on multiple levels as our understanding of developmental plasticity evolves, there will be new opportunities for effective preventive interventions across the lifespan of adulthood.

## Conclusions: Adult Development—an Ever-Evolving Field

Another major emphasis of this chapter is that the study of adult development is an evolving field. At present, there are various competing ways of thinking about development. Combining knowledge of the inner life with observable behaviors can be effectively organized around the framework of ego psychology. Broad domains for inquiry have been identified that are likely to remain robust in the future. These include the importance of measurement of observable behaviors, the necessity of a stage sequential approach, and awareness of qualities within individuals, such as ego identity, that acquire stability over time but can also evolve. These are the building blocks that must be incorporated into any reasonable formulation of adulthood. Although development does take place during adulthood, simple cross-sectional approaches will not lead to the uncovering of developmental processes. This is because the time frames in which adult development occur are so large that it is not possible to see them in short periods.

One of the crucial areas for further study in the future is the way adult development proceeds differently within different cultural groups, either within this country or elsewhere. Cross-national comparisons on the influences of living in a particular country on adult development are also important. Finally, the powerful influences of moving from one culture to another, of immigration legal or illegal, of displacement for economic or other factors, need to be much more fully integrated into the study of adult development.

The growing awareness of the profound influences of gender, culture, and historical context are likely to yield

important new insights about the development of adults. Also, as more complete integrative models are developed about pathways to healthy adult development, these will provide vital information for the development of preventive interventions for individuals at risk either because of familial factors or environmental factors such as exposure to violence or poverty, or because of the particular challenges posed by a stage of adult development.

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CHAPTER

# 13 Late Life

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## Late-Life Development

### Life-Span Theory

Erik Erikson's epigenetic framework of adult development was a groundbreaking model and, as elaborated in Chapter 7, it still forms the framework for much of the contemporary perspective on lifelong psychological development. Erikson labeled the final task of development as the attainment of integrity, which he defined as "the acceptance of one's own and only life cycle as something that had to be and that, by necessity, permitted of no substitutions" (Erikson 1963, p. 268). This Zen-like balance between responsibility and acceptance does seem to mark those who age most wisely and peacefully, but it is no easy achievement.

There are several characteristics of the epigenetic framework that highlight the particular difficulties of late-life development. First, the "life cycle" is no cycle at all. A unique task for the elderly is the acceptance of the finitude of life and the inevitability, even proximity of death. Second, none of the preceding stages is resolved completely in one direction or the other; every adult has some elements of mistrust and some degree of shame and doubt. Not only do these partial resolutions accumulate over years, but also the crises most relevant to earlier phases in life never go away completely. Issues of industry and intimacy persist and recur. As a result, the oldest individuals must use partially developed capacities to juggle a range of challenges. Finally, the successful resolution of the Eriksonian stages requires a supportive environment. Trust is not possible for an infant who is not fed; intimacy can only be achieved with the cooperation of a willing and able partner. In late life, the physical and social environment is not particularly friendly. Physical decline, interpersonal isolation, and societal rejection make the achievement of integrity particularly challenging. Yet, the vast majority of elders achieve satisfaction and fulfillment; despair and distress afflict only a minority (Bienenfeld 1990, Hamarat et al. 2002, Vanderhorst and McLaren 2005).

### Coping, Defenses, and Adaptation

One of the most consistent findings in investigations of adult development is that personality traits remain stable across the life span. Mentally healthy elders (i.e., the majority) retain a full repertoire of coping resources. What changes with age is the pattern of adaptive mechanisms used (Costa et al. 1987, Hamarat et al. 2002).

In Chapter 7, the maturing profile of defense mechanisms through adulthood is described. In healthy aging, mechanisms such as acting out and denial are progressively abandoned, and defenses such as sublimation, altruism, and humor are increasingly brought to bear (Vaillant 1977). Defense mechanisms, by Vaillant's description and by their very definition, are mostly unconscious. They frame the perception and meaning of life events and determine their emotional impact; they may further influence a person's response.

Coping mechanisms refer more specifically to predominantly conscious ways in which individuals react to stressors. Coping mechanisms may be either problem focused or emotion focused. Problem-focused coping aims to change the stressful situation; it is directed outside the self. Emotion-focused coping changes the meaning and impact of the situation; it is directed internally. When comparing coping profiles across age cohorts, it is usually found that older groups use less escapism and avoidance than younger ones, but equal levels of problem-solving maneuvers. More precisely, however, coping mechanisms are selected in the contest of particular stressors. When a situation cannot be changed, emotion-focused coping is certain to be more effective. In old age, when increasingly many problems are unchangeable, emotion-focused coping is both more widely used than in younger cohorts and correlated with more effective psychological results. Patterns of coping with successful maturity are thus quite compatible with the patterns of mature defenses in healthy aging (Whitty 2003).

One of the stressors of old age is the proximity of death. Elders report that time passes more quickly for them. This perspective shapes the goals of coping and defense. With increasing age, there is less motivation to expand one's horizons and accumulate broader experiences, and more motivation to derive meaning from what is available. Thus, coping mechanisms shift away from attempts to reverse a shrinking world of contact and toward increasing the depth and meaning of those relationships that are available (Carstensen et al. 2003). Abraham Maslow (1943) described an ascending hierarchy of needs that motivate human beings (Figure 13–1). Once the most basic level is satisfied, one aims for the next level. For most of adulthood, the progression is

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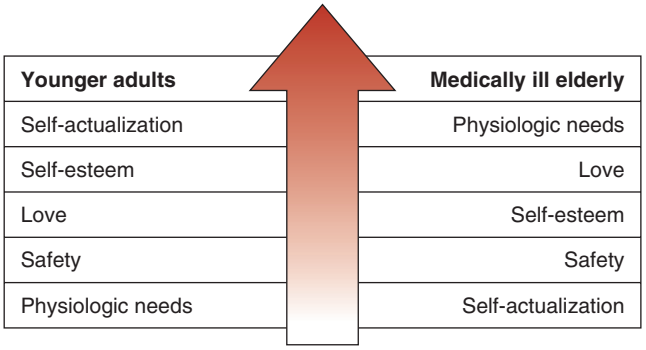



**Figure 13–1** *Changes in hierarchy of needs. (*Source: *Majersik 2005 with pemission from S. Karger AG, Basel.)*

from physiological needs to safety, to love, to self-esteem, and then to self-actualization. In late life, however, acceptance of unchangeable physiological realities forces a distortion of the hierarchy. For geriatric medical patients, the progression begins with self-actualization and then progresses to safety, to self-esteem, to love, and only in the end to physiological needs (Majersik 2005).

## Reminiscence

Among the adaptive tools particular to later years is reminiscence. While more common with increasing years, reminiscence is not universal and does not seem to represent a biologically based drive (Coleman 2005, Webster 1999). Like other adaptive mechanisms, it is employed for particular purposes. Among the purposes that it can serve are as follows:

- boredom reduction
- death preparation
- identity maintenance
- problem solving
- vehicle for conversation
- intimacy maintenance
- old bitterness revival
- teaching and information for those who will follow (Webster 1999).

In general, with increasing years reminiscence is used more for intimacy maintenance and less for bitterness revival. This pattern is consistent with the thrust toward increasing the depth and meaning of relationships noted above. The level of death preparation motivating reminiscence is proportional to life satisfaction (Webster 1999). Those who engage in more obsessive styles of reminiscence and focus on bitterness revival and boredom reduction demonstrate much lower levels of life satisfaction (Coleman 2005).

# Cognitive Changes

Popular media often portray elders as doddering, forgetful, and amusing. There are real changes in cognitive function with age, but they are more complex than the cartoon image of confused Uncle George. In all of the following discussions, it should be noted that within-group differences in cognitive function increase with age and that two normal 80-year-olds may differ from each other more than the average 80-year-old differs from the average 40-year-old (Grégoire 2001).

Aging affects processing, learning, memory, and intelligence. Processing is the translation of stimuli into usable neural signals. Learning is the acquisition of skills and information. Memory is the storage and retrieval of that information. Intelligence is the capacity to manipulate and apply available knowledge (Bienenfeld 1990).

## Processing and Learning

The most predictable age-related finding in the realm of cognition is a reduction in processing speed (Spar and LaRue 2006). A representative test of processing speed presents pairs of letter sets and asks subjects to indicate whether the two sets are identical. Subjects are scored by the number of correct matches in a fixed time (Wood et al. 2005). Older groups perform much worse than younger ones on such tasks.

Because learning requires the retention of data into a small "compartment" of memory for just a few seconds before further processing, the reduction in processing speed effectively limits the capacity of this store, leading to a cascade of memory deficits downstream. Executive function is defined as the system of control over virtually all other cognitive functions. It includes planning, abstraction, cognitive flexibility, recognizing rules, selecting relevant information, initiating appropriate actions, and inhibiting inappropriate actions. It is typically measured by tools such as card-sorting tests and abstract associations tests. This function declines in late life, but executive losses are directly proportional to processing speed, and not to age (Crawford et al. 2000, Rabbitt and Lowe 2000). Not only pure memory but also a wide variety of functional capacities, including activities of daily living, driving, and mobility, diminish as a function of processing speed (Wood et al. 2005).

Additionally, older individuals are more vulnerable to distraction when trying to learn information than are younger ones. When groups are given items to learn, the difference between learning with and without distractions increases significantly in later life (Grégoire 2001, Spar and LaRue 2006). When randomly selected, groups of older individuals are much less likely to use mnemonic techniques to learn and retain information than are their younger counterparts. This difference may be a cohort effect; that is, people currently in their 80s had less reason to learn and employ such techniques because they had far fewer lists of things to memorize than did cohorts born half a century later. When taught mnemonic techniques, older people improve their scores on memory tests, but not as much as do younger groups taught the same techniques. Older groups tend not to apply the techniques as consistently or correctly as younger ones. Part of this deficit is a further result of diminished processing speed, which impairs the ability to learn and retain the techniques, but part is also due to a reduced ability to adopt the associations required to make the techniques work. The latter limitation is a function of neural plasticity, which is elaborated below (Jones et al. 2006).

## Memory

Memory is not a singular function, and its parts are variably affected by aging. Immediate (or short-term) memory holds a small amount of information, the size of about seven digits, for a few seconds (Figure 13–2). In general, the capacity of this store is not affected by age, but processing speed and vulnerability to distraction play a significant role in making it less efficient. Working memory allows one to manipulate the data from immediate memory and process

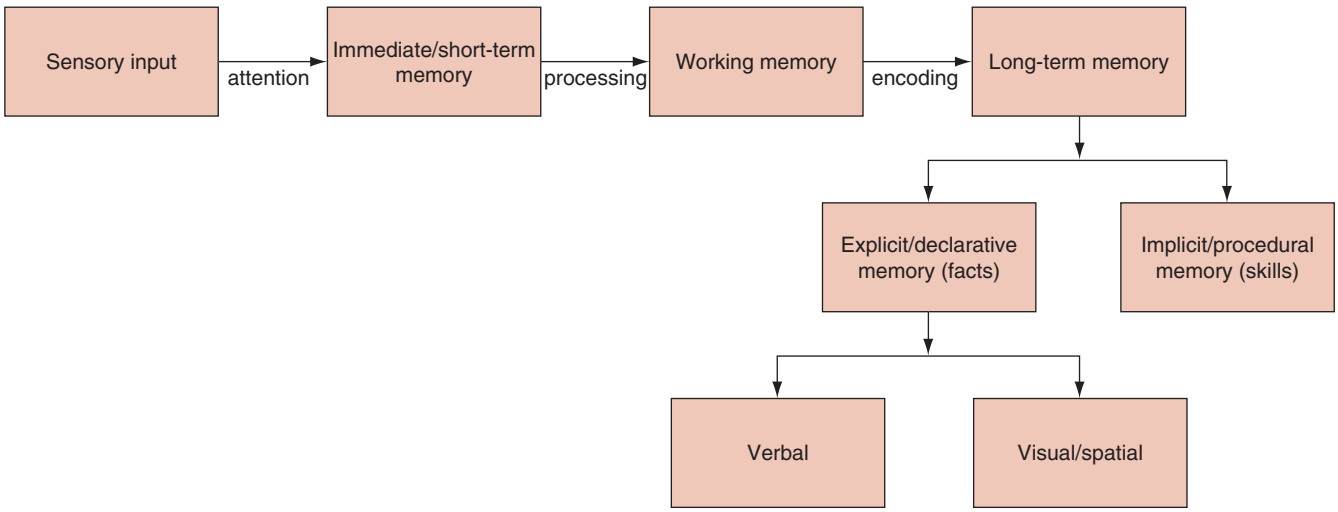



**Figure 13–2** *Compartments and processes of memory.* (Source: *Craik 2006, Shaw 2006, Spar and LaRue 2006.*)

it for further storage. Its capacity is directly affected by diminished processing speed with increasing years. Working memory encodes data for long-term storage. Because of the learning deficits described above, it declines moderately with age, though its total storage capacity is stable. Remote or long-term memory is more variably affected by aging. Information put into long-term store appears to remain intact, but retrieval mechanisms may become less efficient. New information put into long-term memory is similarly filed less efficiently, making subsequent retrieval unreliable (Craik 2006). Elements of personal history are least vulnerable to long-term memory effects of aging (Spar and LaRue 2006).

Verbal memory consistently declines with age. Spatial memory, as measured by location of pieces on a chessboard or objects on a map or in the real environment, also becomes less effective with age. Pure visual memory, however, as measured by recollection of geometric shapes, appears much less vulnerable (Shaw 2006). Explicit memory, as evidenced in pure verbal recall, is more severely affected by aging than is implicit memory, which drives learned motor tasks (Spar and LaRue 2006).

## Intelligence

The most long-accepted model for describing and explaining the effects of aging on intelligence is Horn and Cattell's (1966) model of fluid and crystallized intelligence. Crystallized intelligence is the accumulated body of knowledge about one's world and the skills used to function in it. Fluid intelligence includes the "processes of reasoning in the immediate situation in tasks requiring abstracting, concept formation and attainment, and the perception and education of relations" (Horn and Cattell 1966). When common intelligence instruments, such as the Wechsler Adult Intelligence Scale, are measured grossly against age, the results are inconsistent and unrevealing. When subsets of the scales are separated, verbal scores, which reflect crystallized intelligence, remain stable and even increase modestly. Subsets that require novel thinking and manipulation of knowledge, reflected in performance scores, decline gradually from early adulthood; these functions are representative of fluid intelligence. Since crystallized intelligence is the product of experience, and fluid intelligence depends on neural factors that decline with age, the model is useful and consistent (Bienenfeld 1990, Grégoire 2001). Yet, there are details that require a more nuanced view of intelligence in late life.

Age-related diminution of processing speed, along with increased distractibility, expectably reduces the capacity of working memory. As a result, there is a reduced capacity to hold all the information needed to solve an immediate problem in reasoning. In the face of this effect, inductive reasoning (the ability to draw general conclusions from specific instances) and deductive reasoning (the ability to draw specific conclusions from general rules) decline proportionately and are reflected in measures of fluid intelligence. Reduction of scores on tasks such as digit-symbol substitution depends much more directly on visual processing speed than on pure visual memory (Grégoire 2001). Executive function, which is similarly affected by reduced processing speed, is more significant for the spatial and organizational tasks of fluid intelligence than it is for the verbal and explicit capacities defined in crystallized intelligence (Shaw 2006). In intelligence, even more than in measures of pure memory, within-group variability increases dramatically with increasing age of the cohorts (Grégoire 2001).

## Plasticity

The neural substrate of memory and intelligence is affected in many ways by aging. The concept that captures its effects most effectively is the notion of plasticity. Functional imaging of the brain allows investigators to identify the neural correlates of many of the changes described above. When groups of younger and older adults are taught a visual mnemonic technique, younger groups tend to improve more than the older ones. Both positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) demonstrate that younger people who learn the mnemonics show increased activity in the left dorsolateral prefrontal cortex, while older groups, both those who show improvement and those who do not, fail do display this increase in activity. Activity in the more posterior occipitoparietal area correlated with improved function on this visually intensive technique, in both young and old subjects. Similarly, activity in the medial temporal lobe is associated with associative and paired learning. Mnemonic techniques would have to

use this area to be effective. Older learners whose memory capacity improved with the mnemonics showed enhanced medial temporal activity—less so than younger participants, but much more than older ones who failed to learn the techniques (Jones et al. 2006). In sum, the brain structures that are required for the acquisition of memory-enhancing functions become less able to do so with increasing age, in a pattern that exceeds the effects of reduced processing speed alone.

Many of the declines in cognitive function described above seem to be less dramatic in individuals of higher educational achievement. Common wisdom holds that continued intellectual engagement in late life is somehow protective against loss of memory and intellect. More specifically, higher levels of education are associated with less severe declines in verbal scores on intelligence tests, but measures of fluid intelligence seem equally vulnerable regardless of education (Compton et al. 2003). Processing speed is not at all protected by higher levels of education. Rather, better educated elders are able to compensate for inevitable reductions in capacity by mobilizing other intellectual resources, which are better developed as a product of education (Compton et al. 2000).

Functional brain imaging is consistent with the psychometric findings. In tasks of verbal recall, young adults will remember details as well as the essence of a story. Older adults become more likely to omit details but retain the meaning. PET and fMRI show that younger adults tend to localize activity for such tasks, but with increasing age, the cortical representations become more diffuse. This effect may represent either compensation by recruiting or else a dedifferentiation. Dedifferentiation is comparable to the intellectual patterns of younger children who may identify all pets as "doggy" or all vehicles as "car" (Craik 2006).

## Sensory Changes

Just as healthy development depends on a base of sound cognition, so do memory and intelligence require reliable sensory input. Sensation and discrimination are affected by age and put their stamp on many manifestations of mental function. As with cognition, the effects of aging are both more specific and more subtle than the images portrayed by conventional wisdom A summary of sensory changes with aging is presented in Table 13–1.

### Vision

*Presbyopia* is the term applied to aging-related diminution in the flexibility and clarity of the lens. As a result, near vision is compromised and activities such as reading and sewing become more difficult. Additionally, glare becomes a problem, affecting the ability to see faces of people who are lit from behind and to drive at night. Spots and floaters increase with age and, although they are inherently harmless, can be a source of subjective distress. Cataract, glaucoma, and macular degeneration are not normal at any age, but become more common with increasing years and significantly affect functional capacity and mental well-being (Pennsylvania Optometric Association 2006).

Of Americans over age 70, almost one in five is blind in one or both eyes (Crews and Campbell 2004). Many more have significant visual impairment than complete blindness. Vision loss is frustrating and aggravating. It diminishes one's sense of psychological security and ability to communicate (O'Donnell 2005). Compared with visually intact elders, those with impaired vision report less engagement in leisure activities and social function, poorer capacity for instrumental activities of daily living (IADL), impaired mobility, and increased levels of medical utilization, hip fractures, mortality, depression, and family stress (Crews and Campbell 2004). In most studies, prevalence of depression in visually impaired elders is about twice the rate in visually intact age cohorts. Loss of valued activities such as reading and driving is discouraging. The effort required to undertake IADL is often sufficient to reduce motivation and functional independence (O'Donnell 2005). And even in the absence of blindness, changes in visual acuity are proportionately reflected in most measures of cognition, including verbal learning, executive function, processing speed, and cognitive flexibility (Valentijn et al. 2005).

### Hearing

*Presbycusis* is the term applied broadly to all age-associated hearing loss. About 40% of Americans over 65 have some hearing loss, compared with 10% across all ages. Some of this loss is due to reduced flexibility in the ossicles that conduct sound, but more is the result of the loss of hair cells in the cochlea. This loss is most extreme in the cells that detect high-frequency sounds, and it gradually progresses to lower frequency cells. Additionally, temporal resolution of sound signals decreases with age, as does "spectral resolution," the ability to discriminate pitch.

These changes have functional significance. Loss of acuity for high-pitched sounds in speech (such as the voiceless consonants f, k, p, s, t, and ch) makes it hard for people to understand speech; indeed, most complain of difficulty understanding long before they complain of inability to hear. As the frequency spectrum becomes compressed, speech loses some of its musicality and becomes more monotonous; attention may require more effort. Many important signals, such as alarms, turn signals, and gas leaks, are of high frequency and may be inaudible to some elders.

Temporal resolution of sound is the basis for localization, as the brain compares the difference in timing of signals coming from the two ears to determine the source of the sound. As temporal auditory resolution declines with age, so does the capacity for sound localization. This circumstance can be dangerous and can also be frustrating in social environments. Similarly, resolution of sound spectra normally allows one to filter out background noise. Reduction of this capacity with age makes it harder to recognize alarms or discriminate speech in noisy settings (Gates 2005, Wingfield 2005).

Hearing loss is associated with social isolation and depression. Hearing-impaired elders are more susceptible to falls and stroke and demonstrate diminished mobility. They have difficulty sustaining social participation. Further, hearing loss is associated with increased incidence of dementia and accelerated cognitive decline in those who have dementia (Crews and Campbell 2004). The extra effort needed to discriminate and process speech places increased demands on cognitive resources, leaving less available for encoding signals into memory (Wingfield 2005).

Much hearing loss, due to both aging and disease, is correctible. But of all those who could benefit from hearing aids, only 20% ever purchase them; of those, about one in three either abandon or underuse their aids (Gates 2005).

**Table 13–1 Aging and Sensory Function**

| | Age-Related Changes | Functional Implications |
|---|---|---|
| Vision | Diminished flexibility of lens<br>Diminished clarity of lens<br>Vulnerability to glaucoma, cataract, and macular degeneration | Impaired near vision<br>Impaired night vision<br>Increased glare |
| Hearing | Reduced flexibility of ossicles<br>Loss of cochlear hair cells<br>Diminished temporal resolution<br>Diminished spectral resolution | Impaired ability to comprehend speech<br>Loss of ability to perceive high-frequency sounds<br>Perceived monotony of speech<br>Impaired ability to discriminate sounds in noisy environment<br>Impaired ability to localize sounds |
| Touch | Diminished spatial discrimination<br>Increased tactile threshold | Poorer capacity and increased effort for fine movement |
| Taste/smell | Disproportionate loss of salt and bitter taste buds<br>Loss of olfactory cells<br>Need for dentures and adhesives | Distorted smells and tastes<br>Diminished sensitivity to smell and taste |

*Sources*: Gates (2005), Pennsylvania Optometric Association (2006), Rawson (2003), Stevens et al. (2003), Wingfield (2005), and Wysocki (2006).

## Smell and Taste

Most of what is experienced as "taste" is in fact a combination of signals from taste buds on the tongue and olfactory receptors in the nose. Both types of cells die off with age. On the tongue, salt and bitter taste buds are lost out of proportion to sour and sweet ones, resulting in a change in perceived flavors of particular foods with age (Rawson 2003). Olfactory cells are lost much more severely and smell is affected more than taste by aging (Wysocki 2006). In addition to cell loss, there are age-related changes in receptor proteins and ion channels. The presence of dentures and adhesives alters taste and smell. Reductions in these acuities are noted early in Alzheimer and Parkinson diseases, which are age-related illnesses.

Not only does the sense of smell become generally diminished, but there is a reduced ability to discriminate smells, as this sense is more crudely tuned to specific aromas. A significant functional effect of these changes is that food loses some of its appeal and selection of foods becomes less varied. Nutritional balance may become compromised (Rawson 2003).

## Touch

The threshold for tactile sensation rises dramatically with age. The ability to distinguish separate touches, measured by the minimum distance necessary to discriminate, weakens with age. Both of these effects are more marked peripherally than centrally (e.g., more in the finger than on the abdomen). As a corollary, hand strength drops, as do pinch force and precision. Functionally, the result is poorer capacity and increased effort required for fine movements, such as buttoning and eating (Ranganathan et al. 2001, Stevens et al. 2003).

## Lifestyle

Physical and psychological changes outlined so far do not all occur as inevitable consequences of aging. Personal choices and behaviors can have a substantive influence. Smoking is an obvious example. It accelerates many age-related physical changes, and resulting smoking-related illness and disability contribute to a vulnerability to depression and reduction in perceived quality of life. By aggravating vascular deterioration, it increases susceptibility to cerebrovascular disorders and is associated with higher rates of both vascular and Alzheimer dementias. Cessation of smoking yields benefits at all ages, including senescence (Flicker et al. 2006, Taylor et al. 2004).

## Diet

Age brings undesirable changes in metabolism, with detrimental effects on cognition and mood. The prevalence of diabetes increases with age and usually comes in the context of the *metabolic syndrome* (including obesity, hypercholesterolemia, and hypertension). Diffusion of glucose through the extracellular fluid diminishes and with it the delivery of the brain's sole source of energy. With elevated glucose levels, more proteins become glycosylated, negatively affecting signal transduction in the brain. The metabolic syndrome is accompanied by more reactive oxygen species, leading to diffuse neural damage. In the presence of insulin resistance, there are elevated levels of both glucose and insulin, leading to inflammatory damage to brain cells and vasculature. Further, insulin normally plays a positive role in memory, synaptic transmission, neurogenesis, and the clearing of beta-amyloid, a pathogenic protein involved in Alzheimer disease. The relative weakness of these effects in insulin resistance, and in later stages of diabetes where absolute insulin levels drop, contributes to further brain vulnerability.

Impaired glycemic control is most directly associated with explicit and episodic memory, as well as other functions of the hippocampus and nearby structures. Individuals with Type II diabetes are more susceptible to Alzheimer disease. Diabetes at all ages is correlated with disproportionate rates of depression (Hendrickx et al. 2005).

All these negative metabolic effects can be slowed with lifestyle changes. Proper choice of diet, pharmacologic control of diabetes, and exercise can have salutary effects. Diets low in high-glycemic-index carbohydrates positively affect glucose levels and the risk of metabolic syndrome. Avoidance of saturated fats can also help reduce the risk of cerebrovascular deterioration. Oral hypoglycemics may stabilize memory function early in Alzheimer dementia (Hendrickx et al. 2005).

The role of specific nutrients is less clear. Reductions in dietary homocysteine and vitamin B12 are common in old age and associated with impaired cognition. However, poor cognition may lead to poor food choices, which are then reflected in lower levels of homocysteine and vitamin B12. Evidence that omega-3 fatty acids may retard cognitive and physical deterioration is inconclusive. Supplemental antioxidants such as vitamin E are popular, but their efficacy in affecting mental or physical changes is unproven (Flicker et al. 2006).

## Exercise

The Centers for Disease Control and Prevention (CDC) has outlined minimal recommendations for physical activity by older adults, stipulating they engage in at least 30 minutes of moderately intense physical activity at least 5 days and preferably 7 days per week. These exercise sessions should include both cardiorespiratory and strength programs (Centers for Disease Control and Prevention 2006). Exercise of moderate intensity is the equivalent of at least brisk walking. However, this goal is rarely achieved. Overall, fewer than one in ten persons over age 64 meet the CDC recommendations. Fully two thirds of persons in this age group, and 90% of those age 85 or older, are "inactive," which is defined as performing less than one 30-minute episode per week (Taylor et al. 2004).

Lack of exercise contributes to the metabolic problems described above (Hendrickx et al. 2005). Muscle weakness is directly reflected in the frequency of falls, which often precipitate a cycle of functional, cognitive, and affective decline. Osteopenia increases the risk of fracture with resulting immobility and dependency.

The capacity to engage in physical activity is not inherently affected by aging, and the benefits are significant. Physical activity improves endothelial relaxation, compensating for some of the effects of age on cerebrovascular function. Resistance training in particular improves strength, flexibility reaction time, and bone density, with a reduction in the incidence of falls and fractures (Taylor et al. 2004).

More directly, people who exercise the most are the least susceptible to depression (even in studies that negate the effect that exercise reduces depression). In those who are already depressed, physical exercise achieves measurable antidepressant effect. In persons with cardiac and pulmonary disease, it reduces levels of anxiety. The subjective sense of psychological well-being is also strongly correlated with physical activity.

Physical (especially aerobic) fitness is associated with improved performance of executive tests of cognitive function, and rates of cognitive decline vary inversely with the intensity of routine exercise. Individuals with high levels of physical activity suffer reduced risk of dementia in general and Alzheimer disease in specific (Flicker et al. 2006, Taylor et al. 2004).

## Sexuality

Physical changes in the reproductive system are numerous and significant, but their effects on sexual function and satisfaction are much less profound than is popularly imagined. Most adults retain a high degree of interest in sex regardless of age and, in the absence of prohibitive illness, achieve considerable satisfaction.

In healthy men, levels of testosterone do not decline measurably even in late life, and levels of sexual desire at age 70 are as much as 90% as high as they are in younger years. However, there is some attenuation of elements of sexual function. With age, men experience fewer morning erections. Their penile sensitivity declines, and they are less likely to achieve erection without direct physical stimulation. Erections may be less firm, and full rigidity may only be achieved seconds before ejaculation.

Further, a number of age-related illnesses can affect sexual abilities in old age. Hypertension and diabetes are leading causes of erectile dysfunction (ED); half of older diabetic men experience ED. The same vascular pathology underlying coronary artery disease is often manifest in penile vascular disease. Many medications prescribed to elders can inhibit desire and function, most particularly serotonergic antidepressants and dopamine-blocking antipsychotics.

Yet, overall, of men over age 70, more than 75% engage in sex at least once a month, and one third do so at least weekly. The best predictors of a man's level of sexual activity and satisfaction in old age are his own health, his level of sexual function in younger years, and the health and interest of his partner (Metz and Miner 1998).

In women, the loss of estrogen is responsible for most physical changes. The vaginal epithelium flattens, becoming more vulnerable to bacterial infection and vaginitis. There is atrophy of the *labia majora*, a loss of fat and subcutaneous tissue from the *mons pubis*, a reduction in vaginal secretions and a loss of elasticity in the vaginal barrel. All these changes can make vaginal intercourse uncomfortable. Functionally, the excitement phase takes longer to achieve and the plateau phase of the sexual response cycle is prolonged. Capacity for orgasm is retained, although the number and intensity of vaginal contractions is reduced (Table 13–2).

Medical conditions such as arthritis and hemorrhoids, along with surgical procedures to the hips and abdomen, may be causes of dyspareunia. As in men, medications including especially antidepressants and antipsychotics can affect desire and function (Gelfand 2000). The loss of reproductive capacity at menopause may cause some women to see themselves as less desirable and secondarily reduce their own levels of sexual desire. Similarly, those who perceive graying hair and aging skin as unattractive may stop seeing themselves as sexual beings (Kingsberg 2000).

**Table 13–2 Sexual Changes with Aging**

| | Men | Women |
|---|---|---|
| Hormones | No change in testosterone | Decline/loss of estrogen |
| Genital function | Fewer morning erections<br>Diminished penile sensitivity<br>Erection requires direct stimulation | Drying of vaginal vault<br>Flattening of vaginal epithelium<br>Atrophy of labia and vaginal barrel<br>Longer time to excitement<br>Diminished intensity of orgasm |
| Illnesses affecting sexual function | Hypertension<br>Diabetes | Arthritis<br>Hemorrhoids |

*Sources*: Gelfand (2000), Kingsberg (2000), and Metz and Miner (1998).

Because women outlive men, there are fewer unattached men than single women among the elderly, and this cohort tends to engage in sex only as part of a stable relationship. As a result, men engage in much more sexual activity in their later years than do women. Nonetheless, diminished levels of activity in both sexes are not accompanied by any loss of enjoyment.

Older people find ways other than vaginal intercourse to achieve sexual satisfaction, including masturbation, cuddling, and fondling. Negative attitudes about sex learned in younger years may impair one's ability to enjoy sex later. In general, the level of sexual activity in late life is directly proportional to the levels achieved at younger ages. Age-related changes in sexual activity are more in the realm of types of activities than in amount, interest, or enjoyment (Deacon et al. 1995).

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# FOUNDATIONS

## *A Brief History of Psychiatry*

## ***Section III***

## ***Section IV***

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CHAPTER

# 14 A Brief History of Psychiatry

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## Ancient Times

As human beings we are inescapably social animals, dependent on the group for our welfare and survival. Perhaps unique among species, we are also aware that our lives are of finite duration. This double consciousness—of our interrelatedness and our ultimate death—shapes our behavior and our personalities. Since prehistoric times, the bulk of persons within the human community have noticed that some fraction of their number behave or think or show emotion in ways that differ markedly from the rest of the group—ways that are odd or maladaptive or, in extreme cases, dangerous to the welfare of the persons themselves or to the group at large. It was this fraction that became the domain of the early "healers of the mind"—most of whom, in this long era far distant in time from the days of organized medicine, were wise elders or religious adepts. Their collective wisdom and recommendations to those who were of "troubled soul" constitute the forerunners of psychiatry, whose Greek roots convey this very notion: healing the soul.

Long before the age of reliable psychodiagnosis (at most, the past 200 years of our million-year history), a primitive vocabulary developed to label the odd and disturbing people within the body social: terms like *wild* or *eccentric* or *mad*. The first word in Homer's *Iliad*—*manis* or "wrath"—is the origin of our word mania; Homer used it to describe the overpowering rage of Achilles when he felt that he was cheated of his "prize" (the captive girl Briseis). In time, people who were wild, eccentric, or mad were called insane (whose Latin roots convey merely "not healthy"), especially if their behavior was so aberrant as to make living within their own families intolerable.

It is impossible to pinpoint a date for the first example of a psychotherapeutic intervention by some wise person (within or outside the realm of religion). Suffice it to say that this primordial intervention, whatever form it took, must have antedated by many thousands of years the example I am about to relate, which occurred 2,500 years ago, or about 2 millennia before we can speak of anything like organized psychiatry. This story has become part of standard Buddhist teachings and, although cast in the form of a parable, seems to reflect an actual event in the life of the Buddha, between the 5th and 6th centuries bc:

> The young wife of a wealthy family, Kisagohtami by name, suffered the death of her only son, and in the aftermath, lost her mind. She would grasp his cold body in her arms and go about wandering in the streets, asking here and there whether there were someone who could restore her "sick" child. The townspeople, having no idea what to do for this crazed soul, would gaze sorrowfully at her and walk on past. However, a devotee of the Buddha, who could not help noticing the woman as she walked nearby, suggested to Kisagohtami that she go with her child to the abode of the Buddha in Gionshohja. Straightaway, the woman took herself to the Buddha, carrying the child in her arms. The Buddha, calmly surveying her situation, said to her: "Woman, to restore this child it will require seeds of the poppy. Go then into the town and obtain four or five grains of poppy. These poppy seeds must come from the house of only such persons who have never been touched by Death." So the crazed mother went out into the town asking for poppy seeds. The seeds themselves were easy to find—though not from the house of someone whom Death had never touched, for there were no such houses. At last, unable to obtain the seeds from such a house, she returned to the abode of the Buddha. There, in the company of his calm figure, she began to realize the inner meaning of the Buddha's words. As though awakening from a dream, her mind was restored, and she buried the cold body of the child in a grave. After she did this, she returned to the abode of the Buddha and became his disciple. (*Source: Bukkyoh Seiten*, pp 186–188; my translation from Japanese.)

What is remarkable about this example is the extraordinary sensitivity of the "therapist" (here, Siddhartha

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Gautama, who became the Buddha, the Enlightened One)—not only to the plight of his distraught "patient" in her "brief psychotic episode" after the death of her infant, but as shown by his instantly finding a way to help her save face. Rather than shaming her by pointing out the obvious, the Buddha gave her an exercise, whose completion was most likely to be accompanied by satori, enlightenment (today we would speak of it as insight). Out of his wisdom and compassion he devised a gentle trickery by which she, in effect, cured herself.

In speaking of the soul, our ancestors often divided the concept into various compartments: the intellect, the emotions, the perceptions, and the passions. The soul was in the hands of the Gods; its explication, a matter for priests and philosophers. For the ancient Hindus and Egyptians and Israelites alike, madness, as a derangement of the soul, was a manifestation of the divine or "possessed." Persons we might consider psychotic were often thought to be possessed by demons ("evil spirits"). In about 1000 BC, as an example, King Saul had grown envious of David after David's reputation had outstripped his after he killed Goliath. Saul tried to kill David (1 Samuel 18:11), an urge described as having arisen out of the "evil spirit which came upon Saul." Later, when his army was defeated by the Philistines, Saul committed suicide. A little earlier, David feigned madness when captured by the forces of the Gath king Achish, who, because he would not kill an insane man, promptly released David. Elsewhere, we encounter Hannah, the mother of king Samuel; she was for years depressed, tearful, and bitter because she was unable to conceive. When she eventually did, she became arrogant and grandiose. The prophets Jeremiah and Ezekiel were both fanatical social critics and truth sayers. Ezekiel went so far as to follow God's command (as he heard it) to eat bread made with "dung that cometh out of man" in sight of the Israelites, whom God had wanted to humiliate for their sins. What can we say of these Biblical figures? Was Saul manic–depressive? Was Hannah dysthymic? Were Jeremiah and Ezekiel paranoid? We do not know enough about their personal histories or about the culture of their time and place to situate them confidently within this or that category of our diagnostic manual. Certainly in a culture in which it is normal to hear God's voice, this does not constitute a hallucination. All these figures stood out from the average enough to have the biblical authors give us these few details about their emotional life. Which were supernormal, which were like our schizophrenics, which had mild personality disturbances or "neuroses," we cannot say.

## Beginnings of a Methodological Approach to Mental Phenomena

In Hinduism and its 6th-century offshoot, Buddhism, mind and body were not conceptually separate. Mind was seen as an *aggregate of causes and conditions*, something composed of atoms that come together for a time, destined to fly apart later on and insert themselves in other objects or creatures. This atomistic view is also noted in the works of certain Greek philosophers, such as Eratosthenes: it does not lend itself to a theory of mind built on notions of stability, let alone compartmentalization into categories of normal and abnormal types. About 500 BC, before the era of Hippocrates, the Hindu physician Sushruta began to picture mental illness as something distinct from possession by demons; he thought that the causative factors were strong emotions and passions.

Plato (427–347 BC) embraced a dualistic theory in which mind and matter were separable. "Mind" overlapped conceptually with "soul" and was divided into a rational soul (immortal, divine, and located in the brain) and an irrational soul (in the chest, near the heart, the seat of anger, and the abdomen, the seat of the "lower passions"). The forms of "madness" consisted of melancholia, mania, and dementia, which occurred when the irrational soul became decoupled from the rational—something that happened when there was a maldistribution of the *chymoi* or humors that reached the irrational soul.

Plato's pupil Aristotle (384–322 BC) viewed the brain's function as one of condensing vapors that emanated from the heart. This notion still held sway in the 18th century, when *alienists* (as mental specialists were then called) like Purcell and Pommé spoke of the vapors as responsible for nervous states, especially hysteria.

Aristotle's pupil Theophrastus (370–285 BC) developed a rudimentary characterology in which he gave brief sketches of some 30 traits. Many of these read like the "items" of our current personality disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Theophrastus' characters included, for example, *mempsimoria* ("querulousness") and *apistia* ("distrustfulness"), elements of what we would call *paranoid* personality.

Hippocrates (460–377 BC), a contemporary of Plato and, unlike the aforementioned philosophers, a physician, was primarily a systematizer. His theories were oriented toward anatomy, physiology, and temperament. Variations in the four humors—earth, air, fire, and water—were held accountable for fears, shame, grief, and other mental states, including positive ones like pleasure. Phlegm was equated with the water element; the froth that accumulates during a grand mal seizure Hippocrates took as evidence for "excess phlegm." In this, as in other mental conditions, he ignored the nerves in favor of the blood vessels. Based on what he saw of the body's remarkable recuperative powers, Hippocrates' prescription for treatment relied heavily on the idea of giving nature a chance, that is, not interfering with the body's ability to heal itself. As for the frenzied state called hysteria, Hippocrates endorsed the then prevailing notion that hysteria affected only women and that it resulted from the womb (Greek *hyster*) traveling periodically to the brain. His recommended cure was the same as Pinel's in the 1790s: early marriage (suggesting that ancient as well as early modern physicians saw a connection between hysteria and sexual frustration).

The philosopher Epicurus (342–270 BC) spoke of both rational and irrational emotions, recognizing that in many instances fear, grief, or anger might be justified by circumstances and thus "rational." Epicurus and his followers represent a humanistic attitude, emphasizing the individual, in contrast to the biological orientation of Hippocrates, a distinction we see repeated over and over in the ensuing centuries. The Epicurean school preferred "moderate discourse" in persuading patients to change their irrational ideas, although sometimes it was recognized that more outspoken language was required to divert a patient from some destructive path.

At the beginning of the Common Era we find what is arguably the first example of self-mutilation; in the New Testament there is mention (Mark 5: i–xi) of a hermit "possessed of an unclean spirit" who was always "crying and cutting himself with stones." Jesus cured the man by ordering the evil spirit to depart from him, here continuing the Old Testament tradition of picturing mental aberration as a matter of good versus evil, related to the world of spirits rather than to the realm of medicine.

At the end of the 1st century AD Artemidorus of Ephesus compiled a *Dream Book*, outlining some 130 common dream symbols (e.g., hair, teeth, ants) and their alleged meaning. This approach remained the popularly accepted way of understanding dreams until Freud's *Traumdeutung* in 1899.

## Roman, Greek, and Other Influences in Early Christian Times

The Roman encyclopedist Celsus, a contemporary of Christ, accepted humoral theory, adding that the humors flowed more freely during springtime—hence the frequency, as he viewed it, of melancholia and insanity during this season. His recommendations for treatment varied from mild to harsh: melancholy might be relieved by soft music, yet in cases of visions, of either the depressed or hilarious (manic) type; Celsus thought that the best approach was "torture, starvation, fetters, or flogging" (methods that hardly fell out of favor over the next 1,800 years).

A generation later, Aretaeus of Cappadocia expressed the opinion that melancholia and mania were different forms of the same malady, a modern conception reminiscent of Falret and Baillarger (*folie circulaire, folie à double forme*) in the 1850s. He favored descriptive trait words over "humoral" language, speaking of certain persons as "irritable, violent, and given to joy" rather than simply "manic."

The standard Roman nosology consisted mostly of Latinized terms from the Greek: *furor* (for mania), *vesania* (similar to paranoia), *amentia* (for those born without good intellectual function), *dementia* (for those who lost intellectual function later), and *stultitia* (for idiocy). Melancholia was retained without Latinization.

Bulimia was recognized as a mental condition around this time; it is mentioned in the Talmud as a valid excuse for eating during the holy fast day of Yom Kippur. The word had appeared earlier in the works of Aristotle.

Social and personal, as opposed to biological, causes of mental illness were acknowledged by Caelius Aurelianus (2nd century AD): abuse of wine, head injury, superstition, excessive preoccupation with glory, or money. Yet he accepted the superstitions of his time, such as that of the incubi, demons who, as their name suggests, lay upon women and seduced them during sleep. This belief, fostered by the sexual repression of the early Church, persisted through the 18th century. Through Aurelianus' works we know of Soranus (100 AD), a physician in the humanist tradition, who inveighed against the use of restraints (1,700 years before Pinel!) and who placed suicidal patients on the first floor of a hospital so that any jump from their windows would not be fatal.

Medicine in the second half of the 2nd century was dominated by Galen, born in 131 AD in what is now Turkey. An eclectic writer, he asserted that the seat of the soul was in the nerve centers, that the brain was the center of psychic functions, and that sensation was the foundation of all our faculties—hearing, vision, and so forth. Galen spoke of four temperaments, each related to one of the "four elements," and to a body fluid in which each element was supposedly concentrated.

| Temperament | Element | Body Fluid |
|---|---|---|
| Melancholic | Earth | Black bile |
| Sanguine or manic | Air | Blood |
| Choleric | Fire | Yellow bile |
| Phlegmatic | Water | Phlegm or lymph |

Galen ascribed hysteria to engorgement or "suffocation" of the womb, rather than to its traveling to the brain.

## Post-Roman and Medieval Times

The millennium from the fall of Rome in the 5th century spans the so-called Dark Ages and the medieval period. Galen's teachings were kept alive via transmission to Persia, then to the court of Harun al-Rashid in Baghdad. Greek medical learning reentered Europe in the 11th century, thanks to translations of a compendium by the Arabic physician Avicenna.

The philosophy of the early Christian church was in part a reaction against the anarchic sexuality and corruption of the Greco–Roman world. The early Christians took pride in sexual abstinence and in sparseness of diet, signs of self-denial, and a higher morality. Gradually, faith became more important than logic; mental abnormalities were once again understood mainly as manifestations of evil and deviltry. Belief in evil spirits, ghosts, incubi, and succubi (female versions of incubi) replaced reliance on science and observation. Sexual repression, particularly intense among the celibate clergy and nuns, sometimes exploded into "hysteric" crises, taking such forms as bouts of fasting, showing the stigmata, self-mortification, or chaotic behavior.

In areas of Europe where the Moors made their conquests, however, the rational and humane treatment of the mentally ill championed by the Greeks was now introduced by Arabic physicians and scholars. Ibn-Rhazes (860–930), for example, kept a separate wing in his hospital for the care of the insane. Similar humane institutions were established in Moorish Spain. A contemporary of Rhazes, Unhammad, developed a classification that included, besides melancholia and mania, delirium, persecutory psychosis (*kutrib*), and lovesickness (*ishk*).

The neoplatonist Avicenna (980–1037) was both an encyclopedist of medicine and a master clinician. He once diagnosed depression related to lovesickness in the nephew of the king in Avicenna's native Persia: by feeling a quickening of the young man's pulse as a townsman recited in the doctor's presence the various quarters and streets and houses in the city, Avicenna was able to demonstrate that the man was pining for a woman from such-and-such a house on a certain street. Although deeply mortified, the man admitted Avicenna was correct. The king, on hearing of the doctor's finding, quickly approved the marriage (the woman, although related, was only a cousin), and the man's depression at once lifted.

In the Arabic world, many of the common people still believed in spirits, called *jinns* (the origin of our genie), who were blamed for provoking mental disturbances. Arabic

scholars, such as Avenzoar and Averrhoes of the 12th century, rejected this notion, although their rejection had to be worded delicately so as not to offend the populace. The Jewish physicians and moralists of this age were less at the mercy of these superstitions. Maimonides (1135–1204), born in Spain, spent most of his life at Saladin's court in Cairo, where he wrote extensively on the soul, on his *Guide to the Perplexed*, and on ideal behavior. For the last he relied heavily on Aristotelian conceptions of the golden mean: good deeds, for example, are those that are equibalanced, maintaining the mean between two bad extremes—the too much and the too little.

In 13th-century Spain there were groups of Christian and Jewish mystics in touch with one another, each influencing the other. A figure of importance, albeit indirect, for psychiatry was Avraham Abulafia of Saragossa, who developed a technique called *k'fitzah* ("skipping"), where one trained oneself to skip from one thought to another, by way of escaping the mundane, rational world, to gain access to the spiritual world of God. Centuries later, this tradition was to serve as the stimulus for Freud's psychoanalytic technique of free association, although with a different goal in mind.

What may be understood as the origins of community psychiatry took place around this time in the small town of Gheel in Belgium. It was there that an Irish princess repaired, so the legend has it, after her flight (during the 7th century) from the incestuous advances of her father. Saint Nymphna, as she became known, took holy orders and cured several persons of "demonic possession." A 12th-century church was built in Gheel honoring her and became a refuge for the insane. In recent centuries, the townspeople have taken in as boarders chronic mental patients who are well enough to sustain extramural life. Esquirol, who visited Gheel in 1822, held up the town and its people as a model of humane concern for the mentally ill, a reputation it enjoys to this day.

Many examples of "fasting girls" became well known in the 13th century, including Princess Margit of Hungary (for whom Budapest's Margitsziget, Isle of Margaret, is named), and the Venerable Lukardis, the German nun who became the first to show the stigmata. The Church eventually discouraged this kind of self-mortification, although the tendency toward anorexia nervosa, especially in adolescent women, has persisted in the West, reflecting similar "dynamics" related to fears about adult sexuality.

The 13th century also witnessed the struggle between the reactionary inclinations of the Church and the burgeoning rational and scientific spirit of the professors, whose number and influence were on the rise, owing to the construction of many universities throughout Europe. Progress toward a more rational view of the mentally ill was severely impaired for many decades after the Great Plague of 1347–1348, when Europe lost a third of its population. Not understanding the cause of the disaster, a rat-borne bacillus, people blamed the Devil, the Jews, or their own "sinfulness" (the flagellants of Hungary exemplifying the last). Also blamed were the one group of creatures whose efforts could have slowed down the Plague, cats, many of whom were caught and destroyed as though they were the embodiments of the Devil. More important, many women were also singled out as witches, held responsible through their supposedly wicked dealings for the ever-mounting death toll. Yet even in this dark time a few forward steps were made in the care of the insane: the first asylum in Europe was built in Hamburg (1375), followed by others in Valencia (1410) and in London (the Bethlehem Hospital, known then and now as "Bedlam," from which the popular word for chaos derives).

The confrontation between dogmatism and scholarship continued during the tumultuous 15th century. The conquest of Constantinople by Mehmet II in 1453 led to a flight of Christian scholars westward, bringing with them Greek and Latin learning and helping to usher in the Renaissance. Meantime the widespread sale of indulgences by the Western Church, to defray the expenses of the Crusades (beginning in the 11th century), alienated many of the faithful and became one of the root causes of the Protestant Reformation. The continued witch hunting and preoccupation with heresy, especially in the Spanish court of Ferdinand and Isabella, led to persecution of the new Christians (the *conversos* who had converted from Judaism after the persecutions of 1391 and who were now fully assimilated Christians). Pope Innocent VIII empowered his Inquisitors to punish those who strayed from the true belief; 3 years later in 1487 the Dominican monks Kraemer and Sprenger published their guidebook for the Inquisition, the *Witches' Hammer*, asserting that "all wickedness is but little to the wickedness of a woman." Ferdinand and Isabella gave the Inquisition a free hand in persecuting those whom it deemed heretics: witches, Moors, Jews, and new Christians (falsely accused of "Judaizing") alike. The importance to psychiatry of these events was significant. Because of the expulsion, extermination, and denigration of these groups, psychiatry practitioners and those who embodied the scientific spirit fled southwest Europe and headed for more tolerant, usually Protestant-dominated areas. The history of psychiatry from the 16th century until recent times became recentered in Germany, Switzerland, Great Britain, France, and the Low Countries.

## 16th Century: The Beginnings of Modern Psychiatry

The year 1492 marks a kind of turning point in history. In this year, some 40 years after Gutenberg's printing press, Ferdinand expelled the Moors from Spain and Columbus discovered America; it was also the birth year of the converso scholar Juan Luis Vives, whom many consider the founder of modern psychiatry.

In his greatest work, *De Anima et Vita* of 1538, Vives demystified the concept of soul, stating simply that the soul is itself the author and moving force behind our functions, drawing its energy from no divine or external source, only from within the body. He spoke of its various compartments, the five senses, and its capacities: intelligence, memory, recall, talent, thought, and will. These capacities are echoed centuries later in Heinz Hartmann's notion of the conflict-free ego sphere in his psychoanalytic treatise of 1950. Vives also described the positive and negative emotions: pleasure, sympathy, and joy versus anger, hatred, envy, shame, and arrogance. Vives also championed the idea of his predecessor, Pico della Mirandola (1463–1494), that humans are not mere puppets on the strings of God but have free will and can determine (and are responsible for) their own fate and their own ideals, which can be realized only through education. Vives' monistic concepts—soul as abstraction of what the brain does (the issue of what it is, if anything, he left to religion)—prefigure the objections to dualism raised by the

early biological psychiatrists such as Griesinger in the 19th century, marking Vives as quite modern.

The Swiss physician Paracelsus (1493–1541) was an outspoken opponent of the witch burners and also denounced Galen and Avicenna as hopelessly old-fashioned. Paracelsus saw mind and body as inseparably intertwined and was one of the first to employ the concept of an unconscious (in relation to people's often being unaware of the motives behind their behavior).

Even more of a maverick and polymath was Paracelsus' contemporary, the Milanese physician Cardanus. In line with the then popular pseudoscience of *physiognomy*, he published a book purporting to diagnose all different character types according to the lines of the forehead (metoposcopia).

The most outstanding physician of the second half of the 16th century, in relation to psychiatry, was the Dutch-born Johann Weyer. A careful observer and thoroughgoing rationalist, he debunked the *Witches' Hammer* in his magnum opus *De Praestigiis Daemonum (The Deceptions of the Devil* 1564*)*. Later he wrote a tract on the "disease of anger," calling anger the "most fertile mother of numberless evils, converting the nature of man into that of a savage beast." He also debunked a case of "prolonged fasting" in a young girl by inviting her to his home, where her actions could be closely watched. When she thought no one was looking, she stole food and beer from the pantry, thus establishing herself as a case of factitious anorexia.

Toward the end of the century, Rudolf Goekel, in a treatise on how to improve humankind, used the term *psychology* for the first time. In Spain, Juan Huarte y Navarro wrote of his theory of what we would call *eugenics*: how to improve the nature of one's offspring by having the expectant mother eat a diet in which the four elements of the ancient Greeks (here in the form of cheese, whey, butterfat, and honey) are perfectly "balanced."

*Physiognomy* (diagnosis by the shape of the head), which we can take as the forerunner of biological psychiatry had another ardent exponent Giovanni della Porta (1545–1615), who asserted that a man whose face resembles that of a lion has a "leonine" (brave, fearless) personality; those who look like goats are sexually lubricious, and so on.

One of the first premodern classifiers of mental illness was the Swiss Felix Plater (1536–1614); he used the term *alienation*, which became the norm for the next 200 years. He ascribed mental disease to brain damage, especially if the brain was "excessively dry"—an allusion to the still widely accepted humoral theory. Treatment was also dictated by this theory; Plater recommended the use of purgatives, as though these would rid the body of an excess of the offending humor (black bile).

Apropos the "black bile" of melancholy, the book on this subject by England's Timothy Bright (1551–1615) is noteworthy for having influenced Shakespeare (who made many references to melancholia but none to mania) (Bright 1613).

## 17th Century: Slow Progress in Description and Empiricism

Although the humoral terms persisted (as they do to this day), progress in anatomy (e.g., the dissections of Vesalius) led to further weakening of Galenic notions. Rationalism and empiricism gained ground, albeit slowly. Syphilis was introduced into Europe around 1500, and cases of general paresis were noted increasingly, although the underlying cause remained obscure until late in the 19th century.

In France, Charles LePois (1565–1633) not only disclaimed any connection between hysteria and the uterus but also stated that men could develop hysteria as well, a point that was not well received when Freud said as much 250 years later.

Writing on lovesickness, Jacques Ferrand also fought against tradition, asserting that the heart was not the organ of love; rather, the trouble results from the derangement of the brain, where the imagination has become depraved. Melancholy in this case had nothing to do with black bile but (as with Avicenna's young patient) with unrequited love.

Philosophers and physicians were at pains to enumerate and categorize the emotions in a rational way. Expanding on Plato's observation that lust is the most powerful passion, the French theologian Senault created a catalog of 11 passions including love, hatred, desire, despair, anger, and hope.

François Bayle contributed to the understanding of "supposed" witchery and hysteria, drawing attention to the phenomenon of contagion, to explain how a susceptible person near a hysterical person may also become hysterical.

The most important figure in 17th-century French psychiatry was not a physician but the deductive-rationalist philosopher René Descartes (1596–1650). Separating the basic from the complex passions, Descartes (1650) identified six that were irreducible: admiration (in the sense of noticing with surprise), love, hate, sorrow, joy, and desire. A complex emotion like jealousy was composed of desire (for the love object), sorrow (at the loss of this person), and hate (toward the rival). Descartes reasoned that, because it had no bilateral representation and was solitary, the pineal gland must be the center of the soul. In Cartesian dualism, soul and body were of different natures. This argument was to go through many forms over the next 3 centuries, and continues currently as controversies about the relationship of mind to brain.

In Germany, Johann-Caspar Westphal wrote on the immense power of the imagination, which he thought was sufficient to account for the phenomenon of witchcraft, hitherto ascribed to the Devil.

The first English physician to write of women accused of witchery as unfortunate persons suffering from some medical condition was Edward Jorden, whose book (1603) spoke of hysterical "fits" that might occur with remarkable regularity: monthly, yearly, or weekly.

Another case of factitious illness, similar to Weyer's, was described by Richard Baddeley (1586–1670), that of a boy whom Baddeley eventually spotted mixing ink with his urine by way of simulating disease. Meantime, Richard Sibbs, a Cambridge theologian, wrote in 1636 about inner conflict, in a manner reminiscent of later psychoanalytic theory: persons who felt tormented between the desire to do what is socially acceptable and the desire to do what is wrong.

The most widely known English book of the 17th century relevant to psychiatry also comes from a theologian, the dean of divinity at Oxford, Richard Burton, whose *Anatomy of Melancholy* was published in 1621. Interspersed with the encyclopedic references to every aspect of melancholy is a running commentary on Burton's own case of this affliction (the chief features of which were an inordinate sense of wrongdoing and guilt, despite the exemplary, blameless life

that the scholar actually led). For treatment, Burton advocated a form of psychotherapy consisting of revealing one's troubles to a trusted friend. In addition, healthy diet, vacations in the country, and various medicaments (e.g., aloes, hellebore) were deemed effective.

One of 17th-century England's most prominent physicians was Thomas Sydenham (of the eponymous chorea). Like most physicians of his age in Christian Europe, he wrote in Latin and on all medical topics, not just those related to the mind. For apart from the few who worked in asylums, there were as yet none who devoted themselves solely to psychiatry. Sydenham used the term hysteria to connote severe mental disorders in general and thought that there was a similarity between hysteria and hypochondriasis (both of which he believed arose from "irregular motions of the animal spirits").

The great Thomas Willis (1621–1675), of the brain vasculature's circle of Willis, originated the term *neurology* and also spoke of the study of the corporeal soul as *psychology*. A founder of biological psychiatry, Willis implicated the nerves, not the blood vessels, as the realm in which the disturbances lay. He likened hysteria to a "fit" of simply lesser severity than an epileptic convulsion. Like LePois, Willis was aware that hysteria could be found "in women of all ages and classes, and even in men." In contrast to Burton's mild measures, Willis recommended, when faced with "madness," restraints, beatings, bloodlettings, and other harsh treatments. In his 1672 treatise *De Anima Brutorum*, we find what is probably one of the earliest descriptions of schizophrenia: adolescents who, although once clever and graceful, become dull, foolish, and insipid; although once intelligent and quick to learn, become enfeebled and listless. This resembles our negative signs; Willis made no mention of the positive signs, like delusions, but we must remember that the clinical picture of an illness such as schizophrenia is culture dependent and is described differently, depending on the era, in accordance with what physicians of the time noticed or thought was important.

Cartesian dualism and the human-as-machine model had many opponents; among them was Lord Chief Justice Matthew Hale, who argued (in 1677) that human perception, memory, and fantasy cannot be reduced to "modification of matter or the natural motion thereof." He believed in the influence of the moon on mental states (the term *lunacy* derives from this view) and thus was a forerunner of Richard Mead (18th century). He also put forward the notion of temporary insanity, noting that certain women denounced as witches were "at the height of their distemper at the full moon." The justifiability of the concept is still being debated in our day and is related to the equally controversial issue of diminished capacity.

Besides the feigned fasting of Weyer's case, there were true cases as well. Richard Morton (1637–1698), physician to King James II, has credit for the earliest description (in an 18-year-old girl with wasting, amenorrhea, and hyperactivity), which he called a consumptive disorder. The term *anorexia nervosa* was not coined until William Gull's treatise in the 1860s.

Despite the ascendancy of rationalism and empiricism in England, belief in magic and the miraculous hardly disappeared. Effecting cures of various diseases by the queen's touch or by the laying on of hands was widely practiced. Outstanding in this regard was Valentine Greatraks (1628–1683), a devout Protestant soldier in Oliver Cromwell's army. In 1649 he began to feel himself possessed of the benevolent power to cure others by his touch. Patients flocked to him by the hundreds, mostly with palsies and headaches, but others with "possession," hysteria, and other mental disorders. Greatraks' touch depended for its efficacy on his faith in himself and on his patients' faith in him, which constitute a testimonial to the powers of suggestion, faith, hope, and the body's natural self-healing tendencies. Both reason and imagination, sound medical tradition but also faith, have their place. A healer like Greatraks reminds us that medicine, in its effort to be wholly scientific, cannot afford to shun the humanistic and the mysterious.

The themes of reason and imagination are clearly intertwined in the great treatise of Francis Bacon (1561–1626), *The Advancement and Proficience of Learning (1640)*. Through his encouragement of physiological experiment and careful description, Bacon helped psychology gain respect as a solid science. His division of mind into two major components, reason and imagination, resonates well with current interest in the functions mediated by the dominant and nondominant cerebral hemispheres: logical thought and emotional thought, respectively. Bacon also distinguished himself through his humanism: his insistence on compassionate care of suffering patients and his acceptance of euthanasia.

In Italy at this time, Curtius Marinello also made mention of imagination and reason, both faculties being adversely affected in melancholy. The latter was still viewed in humoral terms in Italy and Spain; the by-now-old-fashioned treatment of purging and bloodletting persisted. Tomaso Garzoni was an advocate of mental patients' being housed in hospitals rather than being penned up in prison-like stronghouses. Even so, his remarks about patients have a contemptuous ring all too common in this era, when the insane were often stockaded in places (as in Vienna's Narrenturm or Fools' Tower) where the public could gawk at them as a kind of entertainment. The best-known Italian alienist of the 17th century was Paolo Zacchia (1584–1659), physician to Pope Innocent X. His 1630 compendium on medicolegal questions establishes him as the founder of forensic psychiatry. Zacchia held that certain persons who committed murder could be medically "insane" (in our sense of *psychotic*, since the term was not purely a legal one as in our day) yet legally sane, hence responsible for their actions.

## 18th Century

Although by the 18th century everyone recognized the vastness and the roundness of our planet, the world of psychiatry was for all intents and purposes confined to a tiny square, 14° of latitude or longitude on a side, from Edinburgh to Florence and from London to Berlin. With few exceptions, the chief figures in history during this period came almost entirely from the realms of the Protestant Reformation. Aside from Mesmer and Pinel, their names would be unknown except to specialists in the history of our field. We might, to be generous, include the Wild Boy of Aveyron, the feral child treated by Pinel's pupil, Itard, although the boy (about whom a movie was made some years ago) is much more famous than his doctor.

The 18th century is considered the *Age of Enlightenment* and was peopled by such prominent scientists, writers,

and philosophers as Voltaire, Rousseau, Newton, Hume, Kant, Moses Mendelssohn, Hegel, Benjamin Franklin, and Goethe. Even in that small square of northwest Europe where the enlightenment shone most brightly, conditions for the institutionalized mentally ill were mostly woeful. Wings for the incurable patients were added in 1730 to London's Bethlem/Maudsley Hospital (built in 1676), but their quarters were still shabby. Many were still in chains, both there and at Paris' Salpêtrière, until the century's end. Bloodletting, emetics, and purges remained the "treatment of choice" almost everywhere; the taxonomy remained brief, composed of *mania, melancholy, paranoia, dementia, idiocy, epilepsy*, and little else.

## Germany, Switzerland, and Holland

In the early years of 18th-century Germany, the most influential contributor to the history of psychiatry was Georg Stahl (1660–1734). Strongly opposed to the mechanistic theories of Descartes and Willis, Stahl contended that mind and matter were unified and that the soul was not a spirit peculiar to humankind but a force characteristic of all living beings. For Stahl, mental illness stemmed from a derailment of this life force, such as if one were caught up in a mood or idea that was contrary to the proper direction of the life force. He advocated specific psychological treatment for the mentally ill, as opposed to then popular physical measures (e.g., purges). Stahl's interest in the psyche helped set the stage for the German romanticist movement of the early 1800s, with its intense concern for the individual patient.

Although Goeckel used the word *psychology* earlier, the German writer Christian Wolff is commonly given credit for coining the term because he used it in a way closer to contemporary usage, that is, as a label for particular studies connected with the mind. His important monographs were *Psychologia Empirica* (1732) and *Psychologia Rationalis* (1734). Wolff spoke of psychology and philosophy as interrelated subjects; it was only later in the 19th century that the two disciplines became more separate, psychology now more allied with physiology and experimental methods.

In Holland, Hermann Boerhaave, whose medical opinions were expressed in almost 1,500 *Aphorisms* (1728), still ascribed to humoral theory. He saw mania and melancholy as different phases of the same condition. To cure melancholy, he recommended taking patients by surprise and immersing them in water, a kind of primitive shock therapy.

Closer to modern shock therapy was the method employed by Leopold Auenbrugger (1722–1809), the originator of auscultation. He described cures of mania via camphor (1776), thus anticipating Meduna's cure by 150 years—Auenbrugger's work having simply been forgotten in the long interim.

Equally forgotten is the work of Friedrich Scheidemantel, who deserves credit as the founder of psychosomatic medicine. In his 1787 book *The Passions as Curative Agents*, he spoke of the harmful effects of the negative emotions (e.g., hate, envy, anger), recommending the positive emotions of joy and laughter as the antidote. In his view, many physical ailments, including colic and women's disorders, were susceptible to cure if one could help the patient to feel joy.

In Switzerland the clergyman Johann Lavater (1741–1801) wrote extensively on physiognomy, specifically, on the personality characteristics supposedly related to subtle differences in measurements of the head. His work constitutes the bridge from della Porta and Cardanus to Gall and Spurzheim in the next century.

Toward the end of the 18th century, interest shifted in Germany from empiricism to focus on individual persons and their histories, ushering in the period of romanticism. The first book containing lengthy biographies of individual mental patients, for example, was published in 1796 by Christian Heinrich Spiess: *Biographien der Wahnsinningen* (Biographies of the Insane).

## France

The spirit of the Age of Enlightenment in France was embellished by its two most famous philosophers, Rousseau and Voltaire. Rousseau spoke of our "lost unity with Nature" and on the value of emotion over reason (which placed him in the vanguard of the romantic movement). Voltaire, at once devout yet opposed to organized religion, stood for empiricism and liberal humanism. Their contemporary Condillac espoused materialism, believing that inert matter, if it could somehow be endowed with sensation, might acquire the intelligence of the human mind.

The Lausanne physician Tissot, interested in the connections between physiology and emotion, had ideas about dreams that foreshadowed Freud; dreams carried forward the preoccupations of the day, and nocturnal emissions happened as a result of unfulfilled sexual desires. He saw hysteria as the baleful result of sexual abstinence.

Of the two most famous persons in 18th-century French psychiatry, one was actually an émigré from Austria: Franz Mesmer (1734–1815). Charismatic healer and maverick, Mesmer came to believe in a "universal magnetic fluid" that permeated the universe and had healing powers that could supposedly be harnessed to cure diseases (including mental ones) (Mesmer 1799). Chased out of Vienna because he was accused of touching in a sexual way a young woman whose blindness he cured, he went to Paris. There he gathered around him many devoted disciples, to whom he taught his method. This method consisted of placing the patient in an oaken bucket and of concentrating the "animal magnetism" on the patient via a wand. This practice stirred the ire of the medical establishment, who accused him of charlatanry. To examine the matter, Louis XVI commissioned the great scientists of the day (including Lavoisier and Benjamin Franklin), whose report was submitted in 1784. The conclusion was that the effects of mesmeric treatment were due to the power of the imagination; there was no invisible magnetic fluid. This in no way deterred his disciples, Deslon, Desleuze, Bergasse, and the Marquis de Puységur. The marquis put mesmeric treatment on a more acceptable footing by showing that one did not need the bucket and the wand; it sufficed to rely on the power of suggestion. This improvement was a step on the way to hypnosis, which was perfected in the 19th century. Mesmer and his followers worked chiefly with ambulatory patients suffering from a variety of physical and "nervous" ailments. In the early 1800s, mesmerists often saw their patients five times a week for an hour each, an intensity of individual therapy that may be seen as a foretaste of the psychoanalytic method, with its similar schedule and concentration on one individual.

Although some have proposed Vives (and others, Johann Weyer) as the founder of modern psychiatry, the majority would choose Philippe Pinel, who is in any case much more known to contemporary psychiatrists. Director at various times of two Parisian psychiatric hospitals (the Bicêtre for men, the Salpêtrière for women), Pinel rejected humoral theory and the outmoded treatments it spawned, asserting that mental illness was caused either by hereditary factors or by "intolerable passions," such as fear, anger, hatred, grief, or elation. Pinel strongly urged removal of the chains from psychiatric inpatients, although he was not the first to do so (Arab and Spanish physicians were doing this in the 15th century). Pinel's suggestions for treatment were based on rational considerations and direct observation. He advocated a nonviolent approach to violent patients; for example, if many staff members quietly approach such patients they see that they are outnumbered and quiet down without anyone having to touch or hurt them. For severe menstrual pain Pinel recommended early marriage and frequent pregnancy, which may strike us as quaint or even "chauvinistic" but which had the advantage of being effective.

Pinel's diagnostic schema, although simple, was an advance over earlier nosologies. He spoke of melancholy, mania without delusion, mania with delusion, dementia, and idiotism. He also described hysteria, anorexia, bulimia, hypochondriasis, and (as *folie du doute*) what we recognize as obsessive–compulsive disorder. The latter could at times take the form of a compulsion to murder, akin to the forensic concept of irresistible urge. Here, Pinel cited the case of a missionary who immolated his children, ostensibly to guarantee them eternal life in heaven.

Pinel's pupil Jean-Marc Itard brought a compassion and humanism similar to his teacher's to his work with the mentally retarded. Physician to an institute for the deaf–mute, in 1799 Itard heard of a feral child wandering the woods of Aveyron. Not quite Rousseau's noble savage, the boy was dirty, unclad, insensitive to heat or cold, and inarticulate except for animal-like grunts. Itard undertook to rehabilitate him, despite the warnings of Pinel, who, with uncharitable candor (and unfortunate accuracy), declared the boy a congenital idiot. Itard took the boy into his home for 2 years. There, guided by the principles of Condillac and by his own naive optimism, Itard succeeded in making the boy tractable, sensitive to changes in temperature, and capable of understanding much of what was said to him. However, the boy never learned to say more than two words: milk and God. Itard's humane attitudes and his techniques were passed on to his pupil, Séguin, who became the leading figure in the treatment of the retarded in the 19th century.

## England and Scotland

Among the major forces of the Age of Enlightenment in Britain were the works of Isaac Newton and David Hume. Hume sought to bring the experimental methods employed by Newton to the study of the mind. Hume's skepticism was manifest in his assertion that mind is not something given us in perception; hence the concept of self is an abstraction, the product of our imagination.

In the early years of the 18th century, the Scottish physician George Cheyne became the first to devote a book to a description of his own nervous disorder: the *English Malady* (1733). No true confessional, the book merely deals with the melancholy, anxiety, and biliousness that affected him for many years. Also, he extended himself an indirect compliment, stating that "Fools, weak or stupid persons are seldom troubled with Vapours or Lowness of Spirits"; rather, these are the afflictions of the highly intelligent.

Richard Mead (1673–1754), a highly respected physician in his day, is noteworthy for two theories he elaborated. One concerned his observation of a certain tubercular patient: as she became delirious, her physical condition improved; when the latter deteriorated again, her mind cleared. Speculating that the body seemed not able to harbor both kinds of illness at once, he thought perhaps giving a mentally ill patient a physical disease on purpose might cure the patient. This theory surfaced again in the 20th century in relation to epilepsy and schizophrenia, which became the (false) rationale for modern shock therapy. Mead also wrote on the influence of the sun and moon on the body, chiefly as concerned menstrual disorders but also various diseases in men that broke out at the full moon. Impressed by this theory, Mesmer plagiarized from Mead in writing his medical school thesis and, as we saw, developed his own theory about extraterrestrial forces affecting the body.

The first extensive text devoted solely to psychiatric conditions was that of William Battie, his *Treatise on Madness* (1758). As director of Bethlehem Hospital in 1742, he found the conditions there so dreadful as to inspire him to build a new hospital (St. Lukes) in 1751. He distinguished between internal and external causes of insanity (the latter related to damage of the brain) and was probably the first to teach psychiatry as a medical school topic in England.

The Scottish neurologist Robert Whytt (1714–1766) worked mostly with the milder mental conditions (in effect, the neuroses): the hysterical, hypochondriacal, and neurasthenic. The last was the term for "nervous exhaustion," which he thought was caused by different motilities of the nerves. Women were especially vulnerable, he believed, because their nerves were "more motile" than men's. For similar reasons he thought that women were "more subject to violent passions."

Charles Moore (1743–1811), a vicar from Kent, wrote a lengthy monograph on suicide, one of the first of its kind. As predisposing factors, he enumerated melancholy, liquor, and a "deplorable want of composure and equanimity of temper," which Moore thought was endemic among the English. As a cleric, he regarded suicide as an offense against God and society and had some acid remarks about the *Sorrows of Young Werther* (which sparked a wave of suicides in Europe): "a pernicious publication, first broached in Germany by one Goethe."

Toward the century's end, John Ferriar (1761–1815) wrote on apparitions, asserting that a "morbid disposition of the brain" might produce the impression of having seen ghosts or specters, even in the absence of delirium or insanity. He originated the term *hysterical conversion*, in which a distant organ acted abnormally, as if out of sympathy with the affected organ, a concept revived by Freud a century later.

## Italy

In Florence, Vicenzo Chiarugi (1759–1820) was renowned for his humane treatment of the insane and for his opposition to physical restraints. Regarding the latter, he antedated Pinel by a few years, although priority is not so important here

as the fact that the Enlightenment spurred social reforms in many places at once, independent of one another. Chiarugi became director of the Hospital of Bonifacio (1788) shortly after the appearance of his three-volume work on insanity, *Delle Pazzia in Genere ed in Specie*. Chiarugi believed that insanity was a consequence of deterioration of the brain and attached great importance to postmortem examination of the brain. As for his humanistic approach, he wrote concerning the duties of his hospital staff: "It is a superior moral duty and medical obligation to respect the mentally ill patient as a person." His comment serves as a fitting prelude to the emerging movement of romanticism, with its emphasis on the particular histories and sufferings of individual psychiatric patients.

## 19th Century

In the 19th century, psychiatry began to assume a form with which we, at the beginning of the 21st century, can identify. The term *psychiatry* itself was used for the first time in the early 1800s. *Psychosis* took the place of lunacy and insanity—the latter serving mostly as a forensic label. Psychiatry became a recognized branch of medicine, taught in all medical schools. The persecution of witches became a rarity. Psychiatrists concerned themselves increasingly with the mildly ill, not just with hospitalized psychotic patients. The sanitaria were much improved, as was the care of the retarded. America came into the picture at mid-century, helped in part by the steamboat and the railroad, facilitating the exchange of ideas of practitioners within each country and across the ocean.

### German-Speaking Countries

For roughly the first half of the 19th century, German philosophy was preoccupied with the irrational, the strivings of the individual, and the wish to return to nature. It is this attitudinal shift that became known as *romanticism*. The focus in psychiatry was on dreams, sexuality, and hidden desires (for which the term *unconscious* came into use). Schopenhauer's will, to which reason and knowledge were subservient, resembles, in the language of Freud, the concepts of libido and unconscious.

One of the most important contributors in the romantic period was Johann Reil (1759–1813). Reil originated the term *psychiatry*. Reil (1803) spoke of a basic feeling of being and experience, the *Gemeingefuehl*, similar to our sense of identity, loss of which was associated with psychosis. Reil was among the first to employ occupational therapy, as well as music and drama therapy, as ways of reeducating patients to develop more adaptive ways of coping.

Other figures of the romantic period include Carl Carus, Ernst von Feuchtersleben, and Eduard Beneke. Carus saw the unconscious as the "fundamental biological force," one part of which remained forever inaccessible. Von Feuchtersleben viewed psychotherapy as a reeducative process for helping patients untangle the problems resulting from their disordered personality. In opposition to Descartes, he saw mind and body as one. For Beneke, abnormal ideas could become translated into bodily reactions—establishing him as a psychosomaticist. Ethics derived from natural law because humans are creatures of nature, our ethics therefore an expression of our need to get along with our fellow humans.

A forerunner of the psychoanalytic movement (although never credited as such), Johann Heinroth (1773–1843) developed a theory of mind embodying a tripartite structure: the instinctual forces, consciousness (*Bewusstsein* or *das Ich*), and the *Ueber-uns* (that which is "over us") (Heinroth 1818). Besides anticipating Freud's 1923 division of mind into id, ego, and superego, Heinroth introduced the notion of internal conflict, for example, that between sin and conscience. He stressed the need to treat patients according to their individual qualities and symptoms, utilizing kindness and warmth with some, firmness with others.

Anxiety secondary to sexual unfulfillment was recognized by Karl Ideler, director of Berlin's Charity Hospital. In 1841 he published a book containing lengthy biographies of 11 patients, the first such book by a psychiatrist.

Beginning in the 1840s, the pendulum swung toward the side of biological or experimental psychiatry. Gustav Fechner (1801–1887) studied the relationship between the intensity of external stimuli and the strength of the corresponding sensation. He enunciated a pleasure principle and introduced the concept of repetition, later reworked by Freud as the repetition compulsion: the tendency to repeat earlier patterns, especially ones involving traumatic experiences.

The most important figure in this new epoch was Wilhelm Griesinger (1817–1868), whom many consider the founder of biological psychiatry. For Griesinger, mental disease was somatic disease, a decidedly monistic position. Neuropathology and psychiatry were one and the same field. He gave great importance to temperament, always commenting on each patient's temperament (e.g., *sanguine-ocholeric*) in a case description. Impressed by Calmeil, who showed the connection between general paresis and a certain brain pathology, Griesinger (1871) concluded that all mental disease must stem from abnormalities of brain cells; there were no "functional" disorders.

Other biologically oriented physicians of this era include Theodore Meynert, Karl Wernicke, PE Flechsig, and Wilhelm Wundt. Meynert outlined different layers of the cerebral cortex according to cell type, Wernicke developed a theory of associations based on cerebral histology, Flechsig helped define projection and association areas in the cortex and distinguished motor from sensory aphasias, and Wundt studied the phenomenon of psychological associations.

In the second half of the century, the towering figure of biological psychiatry was Emil Kraepelin (1855–1926) (Figure 14–1). A student of Wundt and Flechsig, he was also inspired by Morel's 1852 treatise on *démence précoce*, concerning intellectual deterioration beginning in adolescence. A great systematizer and diagnostic "lumper," Kraepelin unified nosology among the psychoses, placing catatonic, hebephrenic, and the various paranoid conditions under the rubric *dementia praecox* (Kraepelin 1909–1915). Kahlbaum (1874) had earlier described *catatonia*; his pupil, Hecker, *hebephrenia*. Kraepelin assigned the task of finding the histological abnormalities he assumed patients with praecox exhibited to Alois Alzheimer. Although Alzheimer was unsuccessful in that task, he did discover characteristic lesions in certain cases of senile dementia, the eponymous Alzheimer's disease. Kraepelin also described subtle or borderline forms of the major psychoses, particularly the abnormal temperaments associated with manic–depression: (hypo)manic, depressive, irritable, and cyclothymic. Because of Kraepelin's emphasis on precision and objective

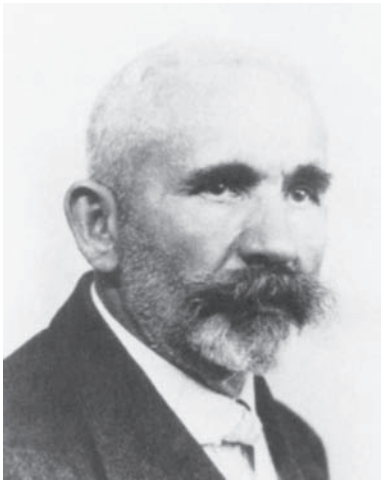


**Figure 14–1** *Emil Kraepelin 1855–1926. (Source: Courtesy of Stock Montage, Inc. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright(c) 1997 Michael H Stone, M.D., p 81.)*

diagnostic criteria, current editions of the DSM are considered neo-Kraepelinian.

Toward the turn of the century the works of Krafft-Ebing and Emminghaus appeared. Krafft-Ebing described a broad range of sexual disorders including the *paraphilias*; Emminghaus put child psychiatry on a separate footing, noting that disorders in children were often incommensurate with those typical of adults.

In the history of psychiatry the only name to become a household word is that of Sigmund Freud. Born in Pribor (Czechoslovakia) in 1856, he moved with his family to Vienna when he was 3 years old. In 1876 as a student of Bruecke, Freud joined his mentor in the search for neurophysiological substrates for psychological processes. During the next phase of his work, with Meynert (1882–1886) he became codiscoverer of the anesthetic properties of cocaine. In 1886 he studied hypnosis and hysteria under Charcot in Paris. Impressed by the power of hypnosis to relieve hysterical symptoms, he returned to Vienna and formed a friendship with Josef Breuer, who was sympathetic to the new methods. In 1893 Breuer and Freud published a paper on the psychic mechanisms of hysteria, a transitional work between hypnotherapy and psychoanalysis proper. Discovery that the unconscious could be mined through free association with even better effect than by hypnosis came in 1895. Although he never relinquished his interest in neurology, Freud realized that the science of the day could not supply the answers to the questions he was posing. His writing turned more psychological and remained so to the end. His most enduring work is his *Traumdeutung*, the *Interpretation of Dreams* (1899, but printed as 1900). The meaning of dreams could be plumbed via free association, unlocking hidden conflicts between different agencies of the mind (usually related to forbidden sexual wishes and the dictates of conscience). Making the unconscious conscious within the context of the transference relationship with the analyst was the key to the psychoanalytic cure for the various psychoneuroses: milder conditions such as phobic, obsessive, hysteric, or depressive character disorders. Freud believed that psychotic patients were unable to form a transference and were thus not amenable to the analytical method. In time psychoanalysis became both a new psychology (for understanding how the mind works) and a new therapy for the psychoneuroses. In 1923 Freud proposed a tripartite model of mind: the instincts constituting the id portion, the conscience constituting the superego, and with the ego as the reality-based agency that mediated between them. By the time of Freud's death in 1939, there were psychoanalytic institutes for training and treatment throughout Middle and Western Europe and in the US. Although many of Freud's assumptions have had to be revised or discarded, there remains a strong foundation having to do with the hidden motivations that direct people's behavior. Before Freud, case descriptions of patients lacked details about childhood fantasies and traumatic experiences, rendering those accounts arid and unsatisfying. It was Freud's return to the attention on the individual that lent to his psychology its richness and fascination. One might speak of his having ushered in a new period of German romanticism, which in the late 20th century has been largely pushed aside by the renewed interest in biological psychiatry; the same evolution we saw unfold in the 19th century.

## France

In France, psychiatry evolved in a fashion almost opposite to that of Germany: the emphasis during the first half-century was on biological aspects; during the second half there was less "neurologizing" and more attention to individuals.

In 1803 the philosopher Pierre Maine de Biran outlined three types of memory, using a classification that strikes us as modern: mechanical or habit memory, sensitive memory (dealing with the recollection of sensations and emotions), and representative memory (long term, associative). Another philosopher, P.J.G. Cabanis, in a work devoted to sensation (1802), also outlined various instincts, subserving self-preservation, movement, and nutrition. He noted a similarity between madness and dreaming and agreed with Pinel that "imbeciles often have a diminution in their brain size that accounts for their limitation"—an appealing notion at the time because it seemed so scientific.

Along similar lines the pseudoscience of *phrenology* (Figure 14–2) became enormously popular, stimulated by the publications of Franz Gall and Caspar Spurzheim, who claimed to be able to predict personality from the shape of the head (as though the latter reflected the brain's "37 organs"—for reverence, conscientiousness, amativeness, acquisitiveness, and so on). Misguided though these efforts were, they led the way to more serious research on brain mapping a generation later.

Serious work was already being done in the area of general paresis by Calmeil (1826) and Antoine Bayle, who discovered a link between certain forms of meningitis and the disorder that would later be identified as neurosyphilis, when in 1913 Noguchi demonstrated the responsible spirochete—the whole sequence of discoveries constituting a triumph of biological psychiatry.

The most famous French psychiatrist of this era was Jean-Etienne Esquirol (1772–1840). A disciple of Pinel, he made contributions to descriptive psychiatry, originated the term *hallucination*, and with his colleague Guillaume Ferrus helped bring about law reforms in 1838 that led to improvements in asylums. Esquirol's nosology recognized

1. Organ of destructiveness
2. Organ of amativeness
3. Organ of philoprogenitiveness
4. Organ of adhesiveness
5. Organ of inhabitiveness
6. Organ of combativeness
7. Organ of secretiveness
8. Organ of acquisitiveness
9. Organ of constructiveness
10. Organ of cautiousness
11. Organ of love of approbation
12. Organ of self-esteem
13. Organ of benevolence
14. Organ of reverence
15. Organ of firmness
16. Organ of conscientiousness
17. Organ of hope
18. Organ of marvellousness
19. Organ of ideality
20. Organ of mirthfulness or gayness
21. Organ of imitation
22. Organ of individuality
23. Organ of configuration
24. Organ of size
25. Organ of weight and resistance
26. Organ of coloring
27. Organ of locality
28. Organ of order
29. Organ of calculation
30. Organ of eventuality
31. Organ of time
32. Organ of tune
33. Organ of language
34. Organ of comparison
35. Organ of causality

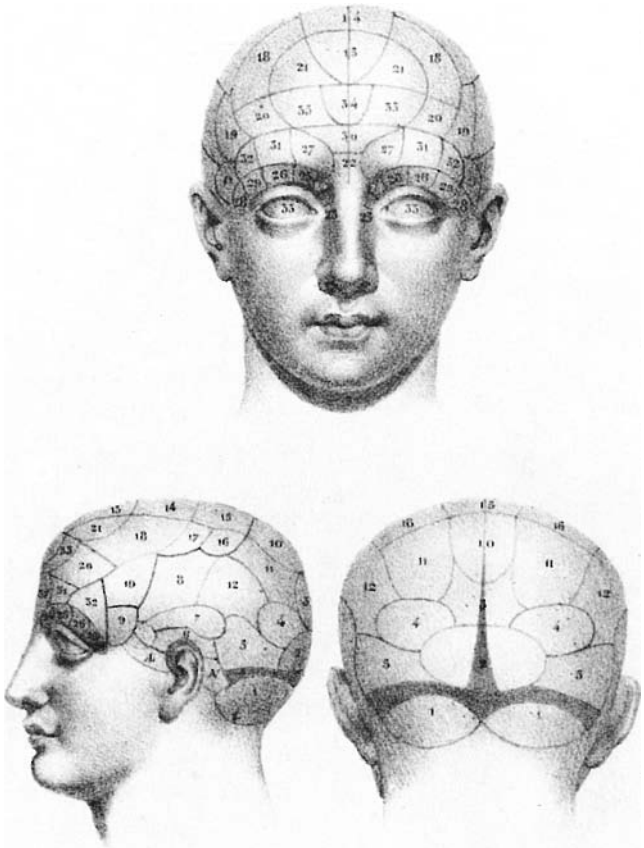


**Figure 14–2** *A phrenological map of the head, as depicted by Theodore Poupin, based on the works of Gall, Spurzheim, and Lavater. Each of the 35 regions was considered a separate "organ," controlling a different characteristic of the personality or the mind. (Source: Poupin T [1837]. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright (c)1997 Michael H Stone, M.D., p 89.)*

*délire général* (all-encompassing psychosis), *délire partielle* (which later became *monomanie*, delusions in just one area), and *affaiblissement intellectuelle*. Among the many *délires partielles* were kleptomania and pyromania, terms still in use; his term for psychotic depression, *lypémanie* ("grief-madness"), never enjoyed wide use (Figure 14–3). In his important 1838 textbook Esquirol also addressed the issue of suicide and provided some statistics on methods used and rates in various communities.

Apropos hallucinations, Brierre de Boismont in his 1845 monograph on the subject mentioned that ecstasy, especially religious ecstasy, predisposed to hallucinations, as in the case of the 18th-century visionary, Emmanuel Swedenborg. Such persons need not be considered mentally ill. He alludes also to the hallucinations of Jeanne D'Arc who, at about age 12 years, heard a voice from the sky tell her, "Jeanne, it is you whom the Lord of the Heavens has chosen to restore the kingdom of France and to be the help and support of King Charles." A similar point was made by another French alienist, Louis-Rufin Szafkowski who, in his 1849 book on hallucinations, distinguishes between hallucinations of reason versus hallucinations of madness. The former type was applicable not only to Jeanne D'Arc, but also to Luther (who envisioned the Devil standing in front of him) and Mahomet, whom the author regarded as a supranormal man given to voices he ascribed to the angel Gabriel, dictating to Mahomet what was to become the *Koran*. Such phenomena were understood by these French alienists as in keeping with the culture of the times in which these great figures lived.

At mid-century, Jean-Pierre Falret and J. Baillarger each proposed that mania and melancholy were two forms of the same process, to which Falret gave the name *folie circulaire* and Baillarger *folie à double forme*. The two entered an acrimonious dispute over priority and over which was the more accurate term; both deserve credit for clarifying the nature of what we now call Bipolar Disorder, DSM-IV-TR.

J. Moreau de Tours, a pupil of Esquirol, described the effects of hashish, likening the altered mental state to the dream state. Benedict Morel wrote a general text on mental illness in 1852, in which he described, under the title *démence précoce* (the inspiration for Kraepelin's dementia praecox), the deterioration of the intellect in certain adolescents. Morel attributed the condition to hereditary "degeneration"; the fathers, he thought, were often alcoholic (Morel 1860).

A number of French alienists gave attention to forensic matters. Persons given to outbursts of homicidal or suicidal behaviors in an impulsive manner, yet without seeming engulfed in madness, were described under the heading of *monomanie homicide*. Some of the cases mentioned by Dagonet in his 1862 psychiatric textbook resemble our current "psychopaths," in that the patients showed no regret or remorse, and were calm and without fear when they committed murder. Yet they differed from the cold psychopath, in that they stayed near the corpse, and confessed readily



**Figure 14–3** *A woman suffering from lypemania, or severe depression. (Source: Esquirol J-E [1838]. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright © 1997 Michael H Stone, M.D., p 91.)*

to the magistrates, condemning the acts they had just carried out. One such man, in a fit of jealousy over rejection by a woman, tried first to commit suicide. He then contemplated killing the woman, so that he would be caught and executed. Later, horrified by that idea, he planned to kill a prostitute, regarding prostitutes as symbols of the source of his anguish and sexual frustration. We nowadays confront such patients usually in the forensic hospital: persons who have assaulted or murdered under the influence of strong passion or despair—seriously depressed, but not psychotic. Other examples where psychiatry and the law intersect, and which were addressed by mid-19th-century psychiatry, concern brain damage from "general paralysis" (tertiary syphilis), mental retardation, erotomania, and religious delusions. The subject of infanticide was taken up by two French authors, Ambroise Tardieu (1868) and Paul Brouardel (1897). The majority of Tardieu's cases concerned young unmarried women who suffocated their newborns (in what we now call *neonaticide*), fathered all too often by the master of the house where they had been employed as maidservants.

Other important French contributors include Paul Broca, who outlined the "speech area" in the cerebrum; Briquet, in whose 1859 treatise on hysteria Briquet's syndrome is described (multiple somatic complaints for which no physical cause can be found); Edouard Séguin (1866), who instituted humane reforms in the care of the retarded (substituting coaxing and kindness for corporal punishment); Henri Le Grand du Saulle, whose 1866 descriptions of obsessive–compulsive disorder (*folie du doute*) are unparalleled in detail; and Georges Gilles de la Tourette of the eponymous Tourette's disorder (tics and compulsive scatologia).

A source of inspiration for Freud's landmark treatise on dream interpretation was a most unusual book by a French aristocrat, Hervé de Saint-Denys (1867), who felt he could direct the content of his dreams by conscious effort before going to sleep. To this end he kept a diary of many of his dreams—something that almost no one had done before. Saint-Denys pictured dreams as an amalgam of images derived from the brain's vast scrapbook of visual memories stemming from the whole course of one's life. He understood something of the phenomenology of dreams, but little of their psychology. Consider this example from Part 3 of his book: "I saw a young woman dressed in an old-fashioned style, playing with pieces of red-hot metal—which in no way injured her. Whenever she touched them, long tongues of flame remained momentarily at the edges of her fingers. When she rubbed her hands against one another, a shower of sparks scattered noisily from them." Viewed through the Freudian prism the dream seems full of allusions to sex and passion. However, the author provides us with no associations. It was a mark of Freud's genius to realize that dreams could be unraveled and understood only through the associations of the dreamer—associations that are unique to each person, and not to be decoded via the popular dream "dictionaries" of his day.

It was from the great neurologist Jean-Martin Charcot (1825–1893) that Freud learned about hypnosis and hysteria. Freud then studied with the famous hypnotherapists in Nancy, Liébault, and Bernheim. Charcot also influenced the experimental psychologist Théodule Ribot, who envisioned a continuum between normal and abnormal personality (a term he used in 1885). Influenced also by Darwin, Ribot wrote on the importance of heredity in determining personality.

## England, Scotland, and Ireland

In Great Britain there was little attention to the individual throughout the 19th century. Much more consideration was given to topics like taxonomy, heredity, and asylum reform (including the use of nonrestraint). Many of the prominent physicians and alienists trained or taught in Scotland. Edinburgh's William Cullen introduced the term *neurosis* as a general term for nonfebrile conditions of the brain and nervous system. Only later did it become (an equally vague) term for mild characterological disorders amenable to psychoanalysis. Joseph Cox, also from Scotland, was the first in Britain to study medicine with the avowed purpose of

working with the mentally ill. He devised a rotating chair by which patients were swung (and frightened), so as (literally) to drive out disturbing thoughts and emotions. William Hallaran in Ireland also advocated "swinging" but along with it occupational therapy and brief stays in the hospital.

One of the early systematizers was Thomas Arnold, a pupil of Cullen, who enumerated many varieties of "insanity" that fit well with our concept of personality disorders. Similar to our terms schizoid, paranoid, histrionic, and narcissistic, for example, were Arnold's descriptors *misanthropic, suspicious, amorous*, and *arrogant*.

The nonrestraint movement gained ground in England, spurred by such men as William Tuke (1813), the Quaker tea merchant who founded the York Retreat, and John Conolly (1830), who removed restraints at the Hanwell Asylum.

John Haslam (1766–1844) stands out for his excellent descriptions of both general paresis and what would later be called *schizophrenia*, while he was medical director of Bethlem Hospital. In 1810 he published the first book devoted to a single case of insanity—persecutory paranoid in form—concerning a man who thought that there was an "infernal machine" controlling his life and subjecting him to all manner of excruciating tortures. The case resembled the "influencing machine" patient described by Viktor Tausk in the 1920s.

The originator of the term *moral insanity* was James Prichard (1786–1848), the director of several hospitals in England. A systematizer like Arnold, he followed Heinroth's division of mental life into thought, affect, and behavior. Aberrations of feeling he spoke of as examples of moral insanity, using "moral" in the French sense (*morale*) of one's spirits or general mood. Some of the cases he described under this heading did show the lack of compassion we associate with the psychopath (in contemporary parlance), although mostly Prichard was referring to cases of affective disorder (Prichard 1835).

A few years later William Browne, superintendent of the Montrose Asylum in Edinburgh, spoke of delinquency and moral insanity in the same breath. A great reformer of asylums, Browne emphasized kindness toward the patients and involving them in useful occupations. Although he was visited by Dorothea Dix in 1855, he was no admirer of America: "The fact cannot be overlooked," he said, "that the source of the population which has been flowing to America has been impure and poisoned."

Modern research on hemispheric asymmetry seems to have been anticipated in the work of Arthur Wigan (1785–1847). Based on autopsy findings of patients with lesions in one hemisphere, he postulated that the two hemispheres amount in effect to two separate brains: one "superior in its rational powers," the other presiding over the irrational.

The first to use the term *hypnosis* was the Scottish physician James Braid (1795–1860). Intrigued with mesmerism after a lecture in 1841, he became an effective hypnotizer, curing many of the milder nervous afflictions but incurring the wrath of the medical establishment (Braid 1843). The tremendous enthusiasm generated by Braid and other Mesmerians led to the publication of an important journal, *The Zoist* (1843–1856), whose 13 volumes contain numerous testimonials to the efficacy of the mesmeric/hypnotic method in the cure of such conditions as blindness, deafness, delirium, epilepsy, headache, hysteria, palsy, rheumatism, and ulcers.

The medicolegal consequences of insanity were reexamined by Forbes Winslow (1810–1874) in a book appearing in the same year (1843) as the famous M'Naghten case. Legal insanity was defined in that case as a state wherein a perpetrator is unable, because of mental disease, to recognize the nature of the act or that it is wrong. This has remained a standard throughout much of the Anglo-American community.

The work of Charles Darwin (1809–1882), the most well-known man of science in 19th-century England, stimulated psychiatric research along two fronts: one concerning adaptation and heredity (the latter study helped immeasurably by Darwin's contemporary Gregor Mendel), the other emotions. The two areas are interrelated: our facial and bodily expressions, treated in Darwin's 1872 essay, all have their survival value; they help us gauge the friendly from the hostile stranger, they elicit sympathy when others show grief, and so on. Both psychogenetics and behavioral theory and therapy received much of their impetus from Darwin's discoveries.

Darwin's cousin, Sir Francis Galton, published a book in 1869 (based on an earlier article endorsed by Darwin), *Hereditary Genius.* Standardized intelligence tests not yet having been created, he drew up his own bell curve, concluding that a small percentage of the population were either geniuses or idiots. His avowed purpose was to contribute to the eventual betterment of humankind through eugenics. (Owing to the atrocities by the Nazis under the aegis of eugenics, the whole field has fallen into disrepute.)

Two prominent figures at the century's close were Henry Maudsley and John Hughlings Jackson. Maudsley saw mental disease as organic brain disease. He wrote on the "insanity of early life," 20 years before Emminghaus' monograph, and was aware that dreams partake of "ancestral modes of thought" in which imagination gains ascendancy over reason. Hughlings Jackson, inspired by Darwin's work on evolution, spoke of the nervous system as organized, via evolution, from the most to the least organized and from the most to the least complex. For example, the highest, cortical centers are least organized at birth, becoming more so throughout life.

## United States

Although the US is now the major source of new knowledge in the mental health disciplines, at the debut of the 19th century it was just beginning to make its presence felt.

Philadelphia's Benjamin Rush (1745–1813) (Figure 14–4), the first US psychiatrist of prominence, assumed directorship of the Pennsylvania Hospital in 1787. Still adhering to the theory that abnormalities of the cerebral vasculature underlay mental disease, Rush thought that mania represented inflammation of those vessels. He coined many diagnostic terms: *manicula*, for mild manic disorders; *tristemania*, for depressive states; and even *home-phobia*, for men who preferred the tavern to the home. His suggestions for treatment were paradoxical; he favored removal of the chains, yet also recommended barbaric measures like dunking under water and total immobilization in the tranquilizing chair (see Figure 14–5).

The first psychiatric book published in the US was a reprint of an English work, *A View of the Nervous Temperament*, by Thomas Trotter (1760–1832). Trained in Edinburgh, Trotter wrote his medical thesis on alcoholism, which he considered a disease rather than merely degeneracy. As a

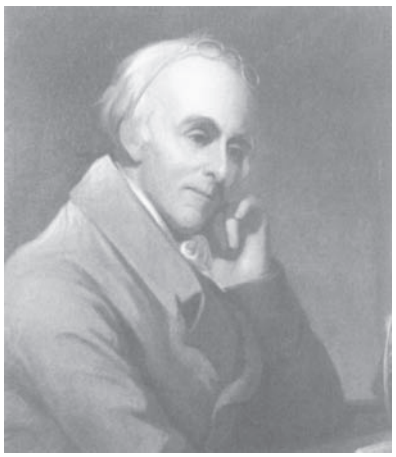


**Figure 14–4** *Benjamin Rush, 1745–1813. (Source: Courtesy of Independence National Historical Park Collection. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H. Stone, M.D., p 120.)*



**Figure 14–5** *Rush's "Tranquilizer," which enforced the most complete restraint of a patient ever devised. (Source: Hunter R and Macalpine I [1963], p 671. Reprinted with permission. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H Stone, M.D., p 121.)*

remedy he urged immediate cessation of drinking. As to the causes of mental illness, Trotter inculpated tea, coffee, overwork, reading trashy novels, and, worst of all, stage drama, which "communicates such poison as has no antidote on the shelves of the apothecary."

The first meeting of what was to become the APA took place on October 16, 1844 in Philadelphia. The most well known in our time of the 13 founders are Samuel Woodward (one of the founders of the Hartford Retreat), Thomas Kirkbride, Amariah Brigham, Isaac Ray, Pliny Earle, and Luther Bell. Brigham was the first editor of the *American Journal of Insanity* (in 1844), forerunner of the A*merican Journal of Psychiatry.*

Isaac Ray, director of Butler Hospital in Providence, was the most admired psychiatrist at mid-century. His 1839 treatise *Medical Jurisprudence of Insanity* was the most important US work on forensic psychiatry. He favored restraint, arguing that Europeans, even when insane, were more obedient than Americans.

The most dramatic psychiatric case was that of Phineas Gage, a Vermont railroad worker through whose skull a 3-foot tamping rod passed during a blasting powder accident (see Figure 14–6). Although Gage miraculously survived, he underwent a marked personality change, becoming fitful, irreverent, and rude, whereas he had been temperate and shrewd beforehand. It has been shown that the lesion was in the ventral and medial sectors of the frontal lobes, which appear to subserve social decisions and moral choices.

The 19th-century American relevant to the history of psychiatry who comes closest to being a household word was not a psychiatrist but a Boston schoolmistress turned reformer: Dorothea Lynde Dix. A woman who had struggled with her own serious depression, she had deep compassion for the mentally ill, although she was 39 years old before she actually witnessed the wretched conditions of the asylums. She then addressed the state legislature, at first in Massachusetts, later in other states, and also in Scotland and England (where she met Samuel Tuke, son of the founder of the York Retreat). Her oratory and her zeal (she was not above portraying the conditions in the hospitals as a little worse than they were to maximize her impact) led both to improvements in existing facilities and to the construction of dozens more. Here is a brief excerpt from her remarks in 1848 to the assembly in North Carolina (where a hospital named after her exists to this day):

> In the Providence of God, I am the voice of the maniac whose piercing cries from the dreary dungeons of your jails penetrate not—your Halls of Legislation. I am the hope of the poor crazed beings who pine in the cells, and stalls and cages, and waste-rooms of your poor-houses. I am the Revelation of hundreds of wailing, suffering creatures, hidden in your private dwellings, and in pens and cabins—shut out from all healing influences, from all mind-restoring cares.

One of the men who "caught the fever" from Dix's impassioned pleas was Thomas Kirkbride, who became the guiding spirit of model hospital building in the 1870s.

Several important contributions in the latter half of the century came from neurologists. Silas Weir Mitchell, besides writing *Diseases of the Nervous System, Especially in Women* (1881), described a case of "double personality" (1889). The patient, Mary Reynolds, had moved to Pennsylvania from England as a child. Although melancholic and avoidant ordinarily, absorbed in Bible reading all day long, at age 18 years she began having "hysterical attacks," after which she lost all memory of her past, even how to speak, such that she had to be taught language from the beginning.

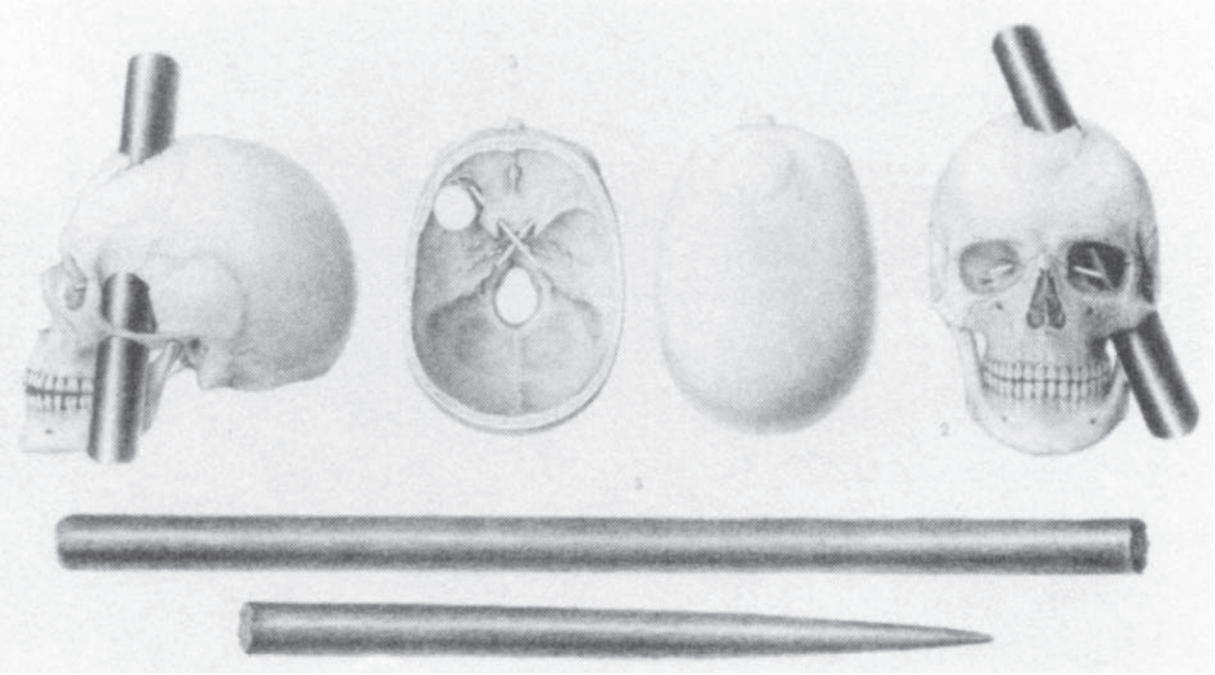
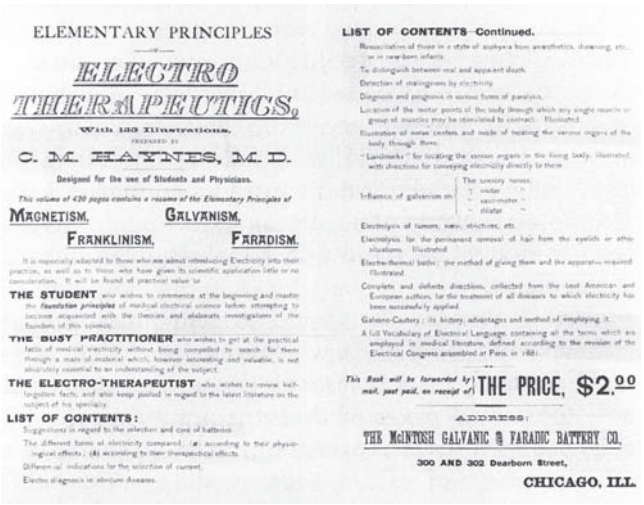


**Figure 14–6** *The skull of the railroad worker, Phineas Gage, through which an iron bar passed in a nonfatal, yet personality-altering, accident involving blasting powder. (Source: Bigelow H [1850]. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H Stone, M.D., p 124.)*

In this state she was prankish and cheerful. A few months later, after a prolonged sleep, her former self would reappear. These switches recurred regularly till age 36 years, when she remained in her cheerful, buoyant state till her death at age 61 years. There is no evidence as to whether she had been an abuse victim, as is so regularly the case with patients with multiple personalities in our era.

The other neurologist, George Beard, achieved greater fame, if less respect, than Mitchell, for his somatic treatment based on electricity. Beard introduced the term *neurasthenia*, similar to Whytt's nervous exhaustion. He began using electricity to provide a "tonic" for depressed, lethargic patients, chiefly in the form of faradic stimulation. Soon faradic machines were sold and used all over the US, as a cure for a whole dictionary of disorders from ataxia to paralysis (see Figure 14–7). Although in reality no more than mechanical "snake oil," electrical treatment kept alive the tradition of biological or somatic psychiatry, which would soon become the respectable branch it is today.


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**Figure 14–7** *Advertisement at the end of Beard's book, illustrating that anyone with the $2 to purchase Dr. Haynes' text could present himself as an electrotherapist. (Source: Beard GM [1875]. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H Stone, M.D., p 130.)*

## Other Countries

Immensely famous in late 19th-century Europe, Cesare Lombroso, professor of anthropology in Torino, wrote extensively on physiognomy and on hereditary genius. Convinced that there was a strong correlation between certain facial configurations and criminal tendencies, Lombroso amassed a vast collection of etchings of various criminals, who looked unusually mean, hostile, and untrustworthy. This lent to his work great popularity, because it pleased the "moral majority" of his day to think that criminals looked different from respectable people. Meanwhile, Lombroso's other thesis—that genius was akin to madness—was also pleasing to ordinary people, as though the distance that separated them from brilliance also separated them from insanity. With his colleague, Guglielmo Ferrero, Lombroso also devoted attention to female criminals (1893). In their compendium they provided data on weight, height, facial beauty or the lack of it—on large numbers of female offenders (many of whom were prostitutes), along with data of normal women "controls." The differences in the two groups strike us as at most—minor, and often, quite biased. Yet the meticulousness of their approach set the tone for the methodical examination in the years to come—of variables of much greater importance and of a less prejudicial nature—in the domain of research on the criminal mind.

The great Spanish neurohistologist, Ramon y Cajal, contributed importantly to psychiatry by placing on a firmer scientific footing the inextricable linkage between brain and "mind." His pioneering work (Ramon y Cajal 1889) paved the way to the research on the synaptic cleft and on the various neurotransmitters, as carried out in the 1960s and beyond by Hornykiewicz, Schildkraut, Kety, Solomon Snyder, and others.

In Russia, work that was to lead to behaviorism and behavioral therapy was being carried out on conditioned reflexes, first by Ivan Sechenov and then by his more famous pupil Ivan Petrovich Pavlov (1849–1936). Both men held that psychological acts were merely the final expression of external stimuli impinging on our sense organs. Pavlov showed that repetitive learning could be used to create conditioned reflexes, built on the organism's unconditioned reflexes. In his famous experiments (for which Pavlov won the Nobel Prize), a dog learned to salivate to the sound of a bell, if the bells were rung simultaneously with the presentation of food (Pavlov 1898).

## 20th Century

As the 20th century drew to a close, we began to see trends that were less readily apparent a generation ago. The century's two halves were dramatically different, in psychiatry as in everything else. At mid-century, World War II had just ended and had just ushered in the atomic age. Afterward the world found itself on the steep slope of the S curve of population. Jet travel, television, fax machines, and now e-mail have enhanced communication beyond the wildest dreams of our grandparents. Psychiatry is now truly worldwide. Although there are many countries with few psychiatrists, there are few countries with no psychiatrists. The term *international*, as applied to psychiatric meetings, used to be a conceit indulged by the few Americans, British, French, and Swiss who actually attended. Now participants may come from 30 or 40 countries, representing all six continents. Excellent and original work is being done in so many places that a proper history of psychiatry's last half-century would be a multiauthored production only a little less voluminous than the *Oxford English Dictionary*.

## The Early Years

In 1903 Alfred Binet published his important study on intelligence: produced with the help of his colleague T. Simon, the famous Binet–Simon test appeared in 1905, permitting greater precision and meaningfulness than were possible in Galton's day. Pierre Janet (1851–1947) emerged as a key figure in descriptive psychiatry; among his numerous books were one on *idées fixes* and others on obsessions, religious mania, hysteria, and personality (Janet 1890). Treatment, for Janet, consisted in helping patients express "fixed ideas" hitherto locked in their "subconscious."

In 1905 Freud published his landmark *Three Theories of Sexuality*, in which he discussed the sexuality of children and the (as he saw it) inverse relationship between the neuroses and the perversions (see Figure 14–8). The case of "Little Hans", a 5-year-old boy whose Oedipus complex was resolved via Freud's discussions with the father, also appeared. In 1909 Freud lectured at Clark University in Worcester, accompanied by Jung and Ferenczi, introducing psychoanalysis to American shores.



**Figure 14–8** *Sigmund Freud in 1909. (Source: Courtesy of The Warder Collection. Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H Stone, M.D., p 140.)*

Adler coined the term *inferiority complex* in his 1907 book explicating his theory that the crucial dynamic behind human behavior was the wish for power.

In Russia, Vladimir Bechterev developed his psychoreflexology (in the tradition of Pavlov) and effected cures of alcoholism with aversive conditioning.

A former mental patient, Clifford Beers, wrote a book, *A Mind That Found Itself* (1909), describing his (manic) psychosis and recovery—despite the degrading circumstances of his hospitalization. He lectured widely afterward and was instrumental in effecting salutary changes in mental hospitals.

Shortly before Eugen Bleuler's epoch-making monograph on the "group of schizophrenias," a work that unified under one rubric the many varieties of delusional syndromes then recognized, Sérieux and Capgras published their exhaustive treatise on the paranoid syndromes: *Les Folies Raisonnantes* (1909). Some of their examples were to be subsumed under the heading of "Capgras' Syndrome"—in which the patient insists that the person in front of him (a mother or wife, e.g.) is not "really" that person, but an impostor dressed up to resemble the person in question. In one of their clinical examples, a woman with what we would call paranoid schizophrenia would examine minutely the letters she received in the hospital from her family. She made interpretations based on the vagaries of punctuation and spelling. When her brother wrote, for example, "We are eager for your recovery," she insisted that the period ("point" in French) at the end of the sentence was bigger than ordinary, and therefore signified: "Nous ne désirons *point* ta guérison." ("We don't want you to get better at all.")

The decade of the 1910s saw a break in Freud's relations with Adler (because of his overemphasis on the power motif) and with Jung (because of his preoccupation with mystical themes of a collective unconscious). Karl Abraham,

who remained loyal, wrote on the oral, anal, and genital character types adumbrated in Freud's developmental track. Freud's papers dealt with the unconscious homosexual themes in paranoia (the Schreber case), grief reactions (mourning and melancholia), and obsessional neurosis (the "Wolf Man"). Alfonse Maeder and Poul Bjerre took issue with Freud's dictum that schizophrenic patients could not form a transference or benefit from psychoanalysis; both men reported on psychoanalytic "cures" of patients they considered schizophrenic (1911).

The Hungarian lay analyst Melanie Klein (1882–1960), after working with Ferenczi and Abraham, moved to England, where she set up a psychoanalytic group in opposition to that of Anna Freud and Ernest Jones. Klein's interest was in early object relations and the analysis of children. Her theories are interpersonal, focused on the first few (preoedipal) years of life, and are weighted far toward the psychological (while ignoring heredity and constitution). Klein's theories concerning developmental stages in infancy, which she characterized as the *paranoid–schizoid position*, and a later *depressive position*, have been influential in the works of later psychoanalytic theoreticians, including Otto Kernberg, and more recently, Nancy McWilliams, who speak of the therapeutic progress one hopes to achieve with, for example, paranoid patients, as exemplifying the passage from less to more mature positions, as Klein had outlined.

In the US Isador Coriat, another enthusiast for the analytical treatment of individuals with schizophrenia, founded the American Psychoanalytic Institute.

John Watson (1878–1958) founded behaviorism (1913), which stressed the observable rather than the unconscious. He saw phobias as arising out of early conditioning, curable by desensitization. His work influenced other behaviorists, Thorndike and Skinner.

In Zurich Eugen Bleuler became director of the Bürghölzli clinic, where he worked intensively with patients with dementia praecox, which he was soon to rename schizophrenia in his 1911 monograph in which he outlined the "four A's" of its diagnosis: autism, associational loosening, ambivalence, and affect inappropriateness. His criteria were broader than those of Kraepelin and lent a more hopeful outlook to prognosis. Many of his "good outcome" patients with schizophrenia (including the composer Robert Schumann) would be considered bipolar according to current diagnostic standards.

In Germany, Julius von Wagner-Jauregg (1857–1940) introduced malaria therapy for syphilis, on the grounds that luetic patients who became febrile with an infection seemed to get better. There is no actual evidence that this was so, yet he was awarded the Nobel Prize in 1927. Elsewhere in Germany, Ernst Ruedin published data on the siblings of patients with dementia praecox in what was the first scientific report on the inheritance of schizophrenia (his figures suggested a model based on two recessive genes). His data also suggested the genetic independence of schizophrenia and manic–depression.

In the 1920s Ernst Kretschmer proposed that the major psychoses were associated with certain body conformations; he thought that individuals with schizophrenia were leptosomes (thin) and those with manic–depression pyknic (fat). Kurt Schneider (1887–1967) enumerated some 11 "first-rank symptoms" of schizophrenia, such as thought broadcast and thought insertion (Schneider 1932). Assumed to be pathognomonic of schizophrenia, these signs were later shown to occur in other psychoses as well. Schneider also outlined a schema of personality types, similar to those of DSM but with different wording (e.g., fanatic for paranoid, anankastic for obsessive). In 1921 Hermann Rorschach published his inkblot test for revealing psychodynamics, which laid the foundation for a whole subspecialty of psychology (cf. Rorschach 1932).

Psychoanalysis flourished in the 1920s, having become firmly established in the US and Western Europe. Freud published his key paper "Inhibition, Symptoms and Anxiety" (1923), in which he enunciated his tripartite theory of mind: id, ego, and superego, with anxiety serving as a signal of impending threat to one's psychological welfare. Ernest Jones became editor of the *International Journal of Psychoanalysis*. Sandor Ferenczi, Freud's closest collaborator, was concerned primarily with clinical issues and put his faith in the emotional reliving of the "infantile neurosis" as the curative factor. Like Melanie Klein, he saw the mother as of equal if not greater importance than the father in a child's early development. Melanie Klein originated play therapy; Jung wrote on personality types, including the extravert and the introvert. Wilhelm Reich, Freud's brash and brilliant protégé in the early 1920s, published important monographs on sexual function, on impulse-ridden characters, and on character types in general. However, after the latter book (1929) he became paranoid and delusional, lost favor with the orthodox analytical community, and eventually came to the US, where he fashioned "orgone boxes" to capture what he imagined was healing "orgone energy" from the sky, with which to cure cancer and other diseases.

After leaving Zurich to come to the US, Adolph Meyer (1866–1950) exerted enormous influence here, primarily through his lectures (he wrote little). He opposed Kraepelin as too one sidedly biological, proposing instead a psychobiological theory, in which all data, the psychological as well as the biological, must be taken into account in understanding any patient. He spoke of reaction types rather than of diseases. A schizophrenic "reaction" might arise out of adverse hereditary factors yet could also arise out of a combination of other adverse environmental factors. This seemed a more hope-inspiring view at the time and dominated US psychiatry until the last generation.

There were advances in group therapy, thanks to the work of Jacob Levi Moreno, who introduced psychodrama as a way of dramatizing and relieving neurotic conflicts, and also of Samuel Slavson, who popularized group therapy for both children and adults.

Morton Prince (1854–1929) is remembered for his detailed account of a multiple personality with "alters": Sally Beauchamp, whose main self was playful and angry, and her two alters, fearful and suggestible, respectively.

The Hungarian psychiatrist Ladislaus von Meduna used camphor to induce seizures in patients with schizophrenia (on the false theory that schizophrenia and epilepsy could not occur in the same patient). In Italy, Ugo Cerletti collaborated with L. Bini in developing electroshock therapy for use with schizophrenic and manic–depressive patients. Psychoanalysts who worked with schizophrenic patients were beginning to realize that more active, supportive interventions were necessary; Gustav Bychowski, Gregory Zilboorg,

and Kurt Eissler were at the forefront of this movement. Leland Hinsie in New York advocated for such patients an approach emphasizing reeducation and removal from the stressful environment.

The first twin study on the inheritance of schizophrenia was carried out in Munich by H. Luxenburger (1928). He found a concordance rate among monozygotic twins of 67%.

In the area of forensics, the most notable contribution was that of August Aichhorn (1878–1949), who set up a model reformatory for delinquent adolescents. His famous book *Wayward Youth* (1925) reflects his beliefs in the efficacy of warmth and understanding, along with a demonstration of the superiority of a value system based on honesty. In the years that followed, many centers were built on this model.

## The Middle (Including the War) Years

The topic of personality received considerable attention during the 1930s. Gordon Allport and Henry Odbert, psychologists at Harvard, combed the unabridged dictionary and came up with 18,000 trait words. Later investigators drew on this list in condensing the many adjectives into more manageable lists of personality factors, which might number 20 or 30 or 60. In Sweden, Henrik Sjöbring broke personality down into a small number of crucial dimensions: validity, solidity, and stability. Cyclothymic patients, for example, he considered "substable."

In the area of psychoanalysis, Freud's eldest daughter, Anna Freud, made notable contributions in both child psychiatry and the elucidation of defense mechanisms. Her *Ego and the Mechanism of Defense* (1936) has become a classical work. Once Hitler assumed power in 1933 the situation for Jews deteriorated rapidly. Psychoanalysts, many of whom were of Jewish origin, fled Germany, settling mostly in England and the US. Among them were Sandor Rado, founder of the Columbia Psychoanalytic Institute; Ernst Simmel, director of the Los Angeles Psychoanalytic Association; Edith Jacobson, a major theoretician who came to New York; Helene Deutsch, who wrote extensively on female psychology and on the "as-if character"; and Franz Alexander, who, after emigrating from Budapest to Chicago, wrote on psychosomatic medicine and also on the history of psychiatry. Alexander's interest in finding correlations between certain somatic diseases and their presumed psychological precursors inspired Flanders Dunbar (and in Argentina, Angel Garma) to look for such patterns in conditions like ulcer, colitis, and asthma. Gastric ulcer, it was thought, occurred in persons who had introjected a demanding, hypercritical mother (who literally gnawed at one's insides). It remained for Arthur Mirsky to show how simplistic such theories were. He postulated that, in the case of ulcer, hereditary gastric hypersecretion of pepsinogen was the more valid causative agent in ulcer development. We now see the etiology of the putative psychosomatic condition as more "somatic" than ever: the bacillus *Heliobacter pylori* is present in about 2/3 of the cases; other contributing factors include smoking, alcohol, and having close relatives with ulcer.

Karen Horney (1885–1952) immigrated to the US where she founded an analytical institute built around her theoretical position, namely that the source of neurotic conflict was primarily cultural. She objected to the biological substrate in orthodox psychoanalytic theory. Freud himself was turning his attention to cultural issues during the last years of his life (he died in 1939). Among his last works were *Civilization and Its Discontents* and *Moses and Monotheism.*

Side by side with orthodox psychoanalytic groups in the US, alternative movements took hold; the most influential was the school founded by Harry Stack Sullivan (1892–1949), a "home-grown" analyst (Sullivan was born in upstate New York). His approach was interpersonal; he emphasized the personhood of the analyst, not just that of the patient, and was keenly alive to the impact of the analyst's feelings on the patient and vice versa. Sullivan worked primarily with hospitalized patients with schizophrenia, whose difficulties in relating are particularly severe and who often engender strong countertransference feelings in their therapists. Analysts who devoted themselves to this work after the war years—Frieda Fromm-Reichmann, Lyman Wynne, and Harold Searles—adopted Sullivan's interpersonal approach, developing along the way profound insight into the inner workings of the schizophrenic mindset. As a curative method, however, their approach produced only modest results at best. It must be remembered that before the phenothiazines came into wide use (about 1960), intensive analytically oriented therapy was often the best psychiatry could offer in the treatment of schizophrenia.

In opposition to psychoanalytic psychology, the behaviorist was also gaining prominence, in the 1930s and 1940s. The chief exponent was Burrhus Frederick Skinner (1938), for whom the neuroses could be understood simply as sets of learned behaviors, acquired through conditioning, which happened to be maladaptive for the individual—behaviors that could be unlearned through various techniques for deconditioning.

Other approaches to the treatment of schizophrenia at mid-century included the use of insulin coma, pioneered by Manfred Sakel (1900–1957). Because of difficulties in administration and questions about its scientific rationale, the method was no longer in vogue 20 years later.

Atypical psychoses were also recognized. In 1933 Jacob Kasanin coined the term *schizoaffective* to designate a form of psychosis in which there was a mixture of cognitive and affective symptoms and a clear precipitant (and a better prognosis than is typical of schizophrenia).

The heritability factor in schizophrenia was revised upward in strength by Franz Kallmann, who estimated a monozygotic concordance at 86%. Eliot Slater in England found a monozygotic concordance rate of 68%. Later estimates have been lower (in the range of 40%), and the impression is that Kallmann was studying a group of particularly severely ill schizophrenic patients for whom the higher, but not truly representative, figure might have been justified.

The US physiologist Walter Cannon (1881–1945) demonstrated the effects of intense emotional states—rage and fear—on the endocrine system, specifically that under severe stress the adrenal glands become activated. His work, supplemented by that of J. Papez on the limbic system, helped put psychosomatic medicine on a firmer footing by showing a link between emotional and physiological states.

In 1935 Leo Kanner published the first textbook on child psychiatry in English. Kanner is also known for his theory that childhood autism, with its aloofness and uncommunicativeness, resulted from maternal "coldness." It happened that the first cases he confronted were the children of women

with PhDs in his own department. He assumed the mothers, being bright and career oriented, were somehow aloof from their children. In fact, they were quite devoted mothers; subsequent study showed that autism was the expression of biological factors (as was recognized by Lauretta Bender) and had nothing to do with cold mothers. A little later, mothers would come under fire again, as "schizophrenogenic" mothers who create schizophrenia by giving their children double messages. This equally specious theory nevertheless dominated the field until the 1970s and unnecessarily stigmatized many mothers of schizophrenic children. It was not long after Kanner's book that the Viennese physician Hans Asperger published a paper in 1944, describing several children with an autistic-like syndrome, consisting of normal intelligence, but marked deficiencies in social and communication skills, failure to develop peer relationships, and often a preoccupation with restricted patterns of interest. Fifty years were to elapse before the syndrome was included, as an autistic-spectrum disorder, in DSM-IV-TR.

W.H. Sheldon continued the work of Kretschmer on correlations between body type and psychological type. He depicted three extremes of habitus: the (thin) ectomorph, the (fat) endomorph, and the (muscular, beefy) mesomorph. Sheldon concluded that schizophrenic patients were often ectomorphic and delinquents or gynandromorphic (having features of both sexes). In 1995 it was revealed that Sheldon made thousands of nude photographs of first-year college students. Some of these men and women went on to achieve great prominence. The negatives were traced—and shredded—along with Sheldon's not totally incorrect but much overblown theory.

In 1948 Alfred Kinsey published his large-scale survey of the sexual habits and practices of US men, showing, among other things, that about 6% of men were fixedly homosexual. Although the study was not representative of the population and was methodologically flawed, it provided figures that were more realistic than were the assumptions held by the public beforehand.

David Wechsler, at New York's Bellevue Hospital, developed an intelligence test (the Wechsler–Bellevue IQ test) considered more reliable than the earlier Binet–Simon test. Hans Eysenck in England created a system for evaluating personality based on three broad factors: neuroticism, extraversion, and psychoticism. The factors are used dimensionally; each person is assessed as belonging somewhere along these three axes, according to their responses to a standardized questionnaire.

In Switzerland, Jean Piaget made important contributions throughout the 1940s and 1950s to our understanding of normal intellectual development, outlining four phases of increasingly sophisticated thought processes in children. The progression Piaget outlined went from a sensory–motor stage (in which a child learns about surrounding space), through stages in which verbal symbols are learned and objects become classified according to similarities, to a stage of formal operations (in early adolescence) in which adult logic is utilized.

What is probably the most widely utilized test of personality, the Minnesota Multiphasic Personality Inventory, was developed by S.R. Hathaway and J.C. McKinley in 1940. This self-report instrument, with its 10-dimensional scales, generates a profile covering all major aspects of personality, with abnormalities emerging as high points on one or more of the scales.

Among psychoanalysts, interest in borderline conditions was growing when it was noticed that certain patients, although considered amenable to analytical treatment at first, failed to improve no matter how prolonged the analysis. Adolph Stern gave a workable, if loose, definition of the term *borderline* in 1938 (relying on such attributes as inability to withstand ordinary stresses and paranoid mechanisms). Melitta Schmideberg (the daughter of Melanie Klein) characterized these patients as stably unstable, referring to their ego weakness and to the predictable quality that their lives always seemed to be in a state of crisis. Borderline, for the analysts of this generation, meant two things: on the border between analyzability and nonanalyzability and also in the borderland between normality and schizophrenia (in the broad, Bleulerian way this was defined in that era). Meantime the Scottish analyst W. Ronald Fairbairn was proposing a modification of Freud's instinct-based psychology with one based on object relations. The latter focused on the early mother–infant bond and its abnormalities rather than on the triangular oedipal situation and thus had greater explanatory power vis-à-vis borderline patients (whose primitive mental mechanisms bespoke an earlier set of abnormalities). Wilfred Bion (1897–1979), a Kleinian analyst, evolved a theory of group function, based on his experience with soldiers in two world wars, that underlined the importance of three basic assumptions—dependency, fight–flight, and coupling—that tend to dominate the reactions of people in groups (whether in small groups or in society at large).

In the realm of clinical neuroscience, the Portuguese neurologist Egaz Moniz (1874–1955) achieved fame through his development of lobotomy, the inspiration for which came from his belief that obsessive and melancholic patients suffered from recurring thoughts that might reflect the presence of reverberating circuits in the frontal lobe centers for consciousness. Lobotomy, by interrupting these pathways, ought to bring relief. Moniz used the procedure for schizophrenic patients as well. Although lobotomy has fallen out of favor (except in the cases of intractable obsessive–compulsive disorder), its initial apparent success was enough to earn Moniz a Nobel Prize. Less drastic measures for dealing with schizophrenic patients in this prephenothiazine era would include the extremely confrontational brand of psychoanalysis advocated by John Rosen. His *Direct Analysis* (1947) relied on blunt, repugnant interpretations ("What you really want is to suck your father's dick!") geared to jangle the patient out of backward torpor into greater perkiness and activity (which unfortunately wore off after a few weeks). Far more effective and humane were the techniques developed by Frieda Fromm-Reichmann, the much admired analyst at Chesnut Lodge near Baltimore, who was the beloved therapist of Hannah Green, author of *I Never Promised You a Rose Garden*. Fromm-Reichmann wrote her *Principles of Intensive Psychotherapy*, containing sound advice for the humanistic interpersonal approach to working with schizophrenic patients, including advice on how to work productively with the inevitable countertransference feelings elicited by extremely ill patients.

In biological psychiatry a great advance in the late 1940s was the discovery by the Australian researcher J.F.J. Cade of the calming effects of lithium salts. Mogens

Schou in Denmark and Ronald Fieve in New York pioneered the use of lithium for manic–depressive psychosis. Great advances were made in neural science by John Eccles, who probed single neurons with microelectrodes to study synaptic transmission—which then enhanced our understanding of the interactions among the myriad neurons that make up the nervous systems, whether of the humble Aplysia (as studied later by Kandel and Schwartz [1985]) or of man. Eccles' first major study, *The Neurophysiological Basis of Mind*, was published in 1953.

Contributors to child psychiatry in this era include Margaret Ribble, who observed the destructive effects on infants of severe maternal neglect (the result might be a failure to thrive and wasting away, called *marasmus*), and David Levy, who wrote on the effects of maternal overprotectiveness (which might lead to excessive dependency). Adelaide Johnson published her landmark paper on the superego lacuna (1949) concerning juvenile delinquents who act out the gap, or lacuna, in the conscience of one or another parent.

Among the major accomplishments of the 1950s was the publication of the first edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I). This represented the first attempt to provide operational definitions of the various mental disorders. Meyerian in its approach, DSM-I used the term *reaction type*—as in the diagnosis "schizophrenic reaction, paranoid type." In New York, the Hungarian analyst Sandor Rado broke away from the New York Psychoanalytic Institute to found the Columbia Institute. Rado stressed the importance of better adaptation to one's interpersonal world and also acknowledged the role of heredity in schizophrenia, proposing the term *schizotype* for the phenotype of the genetic factor(s) underlying the illness. Other influential analysts of this period include Robert Knight (for his work on borderline conditions), Edith Jacobson (a theoretician who also recognized the hereditary factor in certain cases of severe depression), Donald Winnicott (who described the transitional object), Annie Reich (former wife of Wilhelm Reich; she wrote extensively on countertransference), Heinz Hartmann (who pioneered ego psychology and the notion of a conflict-free ego sphere, embracing memory, language perception, and mathematical reasoning), and Eric Homburger Erikson (for his famous elucidation of life stages spanning not just the first 6 years of life but continuing throughout the life cycle). Nathan Ackerman applied analytical principles to the field of family therapy, of which he was essentially the founder.

Alcoholics Anonymous was founded in 1935 in Akron, Ohio, by "Bill" Wilson, but the organization's growth did not reach worldwide proportions until the 1950s. By then the 12-step program, the model for all subsequent 12-step programs for combating other addictive behaviors was recognized as the most effective approach to the control of alcoholism and to the maintenance of sobriety.

Recognition of the impact of certain (especially "VIP") patients on hospital staff was the subject of important work in the 1950s by Thomas Main in London and by A.H. Stanton and M.S. Schwartz in Boston. Their publications led to greater efficacy on the part of hospital staff in dealing with narcissistically "entitled" and otherwise difficult patients.

For a time, the term *pseudoneurotic schizophrenia*, coined by Paul Hoch and Philip Polatin in New York, was a popular label for borderline patients who exhibited many different neurotic signs at once (obsessions, depression, phobia, chaotic sexuality). Most of these patients, it was later recognized, were not even in the penumbra of "true" schizophrenia but either suffered affective disorders or had been traumatized physically or sexually in their early years.

While these modest changes were taking place in the diagnosis and therapy of schizophrenia, a revolution was taking place in psychobiology. In 1951 Henri Laborit was using chlorpromazine in anesthesia and thought it might have applications in psychiatry. His French colleagues Joseph Hamon and, shortly thereafter, Jean Delay and Pierre Deniker used this agent successfully with psychotic patients. This was the birth of the tranquilizer era, to be followed almost immediately by the discovery of the monoamine oxidase and tricyclic antidepressants. I.J. Selikoff and J. Delay reported in 1952 on the use of iproniazid (Marsilid), R. Kuhn in 1957 on the use of imipramine (Tofranil). In 1960 L.H. Sternbach reported on the antianxiety properties of chlordiazepoxide (Librium). Methylphenidate (Ritalin) was found to be useful for children with attention-deficit/hyperactivity disorder and was studied extensively by Paul Wender. Ironically, the era of effective and specific medications for most of the severe psychiatric disorders was also the era of inappropriate experimentation with "model psychosis" drugs like lysergic acid diethylamide and with rampant abuse of illicit psychoactive agents like marijuana, methamphetamine (Methedrine), cocaine, and peyote, resulting in a worldwide plague that has not abated. Psychiatrists have had to familiarize themselves with the diagnosis and treatment of the self-induced paranoid and other psychoses, along with the conventional, idiopathic psychoses.

In the forensic area Hervey Cleckley gave a detailed picture of the psychopath, in the modern sense of the glib, remorseless antisocial person of the "con man" type, in his famous monograph the *Mask of Sanity* (1952). Cleckley devised a scale for diagnosing psychopathy, which was revised in the 1980s by Robert Hare of Vancouver and shown to have utility as a prognostic gauge in forensic work.

## Advances in the 1960s

In the US and in many Western countries, the 1960s were characterized by what Christopher Lasch called the culture of narcissism. Development of better contraceptive devices (the "pill") contributed to greater freedom for women, including the freedom to have fewer children and to pursue a career. The divorce rate increased steeply, leading to a destabilization of family life and the customary supports for children and adolescents. These changes in turn contributed to a heightening of the suicide rate, especially in young men, such that the high-risk age for suicide, which used to be in the sixth decade of life, is now in the third decade.

The improvements in psychopharmacology during the 1950s led to massive deinstitutionalization of the psychiatric hospitals, especially in the US—a mixed blessing, because many mental patients were now able to live extramurally and even take their place in the work sphere, but the still chronically (although now less floridly delusional) ill often drifted into homelessness.

In psychoanalysis the British Independent Group (Michael Balint, Donald Winnicott, Charles Rycroft) studied the object-relational abnormalities in borderline patients.

John Frosch in New York concentrated on the abnormalities in the sense, feeling, and testing of reality in patients with a psychotic character (similar to the borderline). Otto Kernberg, then director at the Menninger Clinic, published his landmark analysis (1967) of borderline personality organization, as a level of function between the neurotic and psychotic levels and characterized by an enfeebled identity sense yet with adequate reality-testing capacity. His recommendations for the treatment of borderline patients centered on the integration of their tendency toward splitting (seeing themselves and others as alternately all good and all bad). In London, Joseph Sandler, a major analytical theoretician, clarified diagnostic issues relevant to obsessive disorders, showing that there were two distinct entities: the characterological obsessive (similar to the current obsessive personality disorder) and the true obsessional picture (our obsessive–compulsive disorder).

The second edition of DSM was published in 1968, and its contents were brought more in line with the British and continental *International Classification of Diseases* by way of enhancing international communication and research.

The sheer volume of knowledge in the various psychiatric subspecialties had by now increased to the point at which no one or two psychiatrists could write a complete textbook, derived solely from their areas of expertise. Lawrence Kolb in the US, D.K. Henderson and R.D. Gillespie in England, and Nils Retterstol in Norway were among the last to offer such works. From now on multiauthored texts guided by a few editors became the norm: Arieti's *Handbook*, Kaplan and Sadock's textbook, and later those of Robert Michels or of Stuart Yudofsky or the current one, edited by Tasman, Kay, Lieberman, First and Maj.

The 1960s also marked the transition between old conceptions about homosexuality, such as espoused by Irving Bieber, and newer theories, championed by Robert Spitzer. Bieber saw homosexuality as an illness (the prevailing view among psychoanalysts), engendered by aloof fathers and seductive, overinvolved mothers. Spitzer, Richard Friedman, and others argued that homosexuality represented simply a different sexual orientation within our species, determined largely on biological and constitutional grounds, not a pathological condition caused by this or that family pattern. The latter view prevailed (although politically correct, it also happened to be scientifically correct) and led to the demedicalization of homosexuality (i.e., it was no longer listed in DSM as a pathological condition). Meantime, the tendency of some heterosexual men with sexual inadequacies to fear being homosexual was described by Lionel Ovesey, under the heading "pseudohomosexuality."

Behavioral therapy was gaining ground in the 1960s, thanks to the research of Isaac Marks in England and Ben Wolpe in the US. Aaron Beck in Philadelphia was another pioneer in this field. All made major contributions to the therapy of phobic conditions, anxiety disorders, and depression, showing that the clinical efficacy was as great as and often greater than that of psychoanalysis and took less time and expense.

The intensive, analytically oriented psychotherapy of schizophrenia, honed by the skills of Harold Searles, Silvano Arieti, Marguerite Sechehaye in Zurich, Racamier in Paris, and Margaret Little and Herbert Rosenfeld in England, was now challenged by a new generation of investigators who saw no superiority in outcome of this method, compared with supportive therapy plus the neuroleptic drugs. At the vanguard of the new movement was Philip May in California, whose 1969 book, despite its shortcomings (May's patients were poorly educated and were treated only by residents in training over just a few months rather than years), set the therapy of schizophrenia on a new track. Henceforth, the emphasis would be on medications, rehabilitative measures, and social skills training.

Spurred by the discovery of the rapid eye movement phase of sleep and its connection to dreaming (by E. Aserinsky and N. Kleitman in 1953), researchers (such as Howard Roffwarg, W.C. Dement, and Ernest Hartmann) began to reappraise Freudian concepts of dream function. It seemed closer to the truth to think of dreams as a problem-solving mechanism (engrafted onto a common mammalian phenomenon), rather than as the "guardian of sleep" or "expression of wish fulfillment" as Freud had postulated.

In the field of affective disorders, controversy continued over whether manic–depressive psychosis was one condition or an umbrella term for two. Jules Angst in Zurich and George Winokur and Paula Clayton in the US concluded that it made better sense to speak of two forms: bipolar and unipolar depressed. There is a greater tendency for ill relatives of bipolar individuals to have bipolar disorder and vice versa.

More sophisticated twin studies in the 1960s, especially by Einar Kringlen in Norway, pointed to a heritability figure for schizophrenia of about 40%. This is not to be interpreted as meaning that schizophrenia is genetically based in only 4 cases of 10, but rather that, as Lucille Erlenmeyer-Kimling in New York suggested, the idiopathic cases are always genetically based but the phenotype (the clinically obvious case) does not always develop, sometimes because of low genetic liability, favorable modifying influences, or other reasons.

Not all manic patients respond to lithium, so it was a pleasant discovery in the 1960s (once again by a French investigator, Lambert, with his colleagues, Carraz and Carbel [1966]) that valproic acid, ordinarily used as an anticonvulsant, also had antimanic properties.

Wigan's hunch of the 1840s having been long forgotten, it was not until the 1960s that real progress was made in understanding the roles of the two cerebral hemispheres. Much of the work was done by R.W. Sperry, Michael Gazzaniga, and Joseph Bogen. Besides showing that the dominant hemisphere (usually the left) mediates sequential, logical thought and arithmetical reasoning and the nondominant visual–spatial tasks, comprehension of emotions, and jokes, this research also proved relevant to the problem of dyslexia. Some individuals with dyslexia, for example, were, as Martha Denckla observed, right handed and right footed but left eye dominant, and perhaps more vulnerable as a result to confusion in learning to read.

The barriers to recognition of physical and sexual abuse of children were finally breached in the 1960s. Arthur Green in New York and other physicians had the courage to follow up on their suspicions in the cities' emergency departments and documented how often children's burns and broken bones had been inflicted by their parents and caretakers. It became clear that incest was not something that happened now and again in Greek plays but happened here and often.

Solid epidemiological data on the topic were beginning to accumulate, although the best studies (such as that of Diana Russell in San Francisco) were not to be completed until the 1980s.

The characteristics of children and adolescents at high risk for schizophrenia and manic–depressive illness were mapped out by a number of researchers in the 1960s: Sarnoff Mednick, Seymour Kety, David Rosenthal, and Paul Wender, all relying on the Danish adoption records; L. Erlenmeyer-Kimling, concentrating on schizophrenia; and Ella Pozanansky, Dennis Cantwell, and Clarice Kestenbaum, concentrating on affective disorders. These studies helped identify the "soft" signs of the major conditions before they acquired their full form in adult life.

The displacements and losses suffered by millions of persons during World War II stimulated research on the effects of separation and death of loved ones on small children. Outstanding among these investigations were the works of John Bowlby in England, who identified three stages in the grief reaction: initial protest, despair, and finally detachment. The first volume of his trilogy, *Attachment, Separation*, and *Loss*, appeared in 1969.

Biologists such as Austria's Konrad Lorenz and Irenäus Eibl-Eibesfeldt in Germany opened up a field of great relevance to psychiatry: ethology (the study of species, including our own). These investigators drew attention to the innate, preprogrammed patterns that underlay many of the approach–avoidance and sexual behaviors in animals and humans. Using motion photography, Nikolaas Tinbergen focused on human gestures, including the unconscious tendency of men to straighten their ties and pull in their stomachs when introduced to an attractive woman—apparently to create a more "masculine" image.

Inspired by emerging ethological data, Jane Sherfey reworked Freudian theory of male and female sexuality in her monumental integrative monograph of 1966. She argued that neither sex is programmed biologically for monogamous marital life; rather, our mating system (emphasizing monogamy, kinship ties, inheritance laws, and so forth) grew out of compelling survival needs as we ceased to be nomadic hunter–gatherers and developed agriculture and geographically stable communities.

## Recent Trends

Progress in psychiatry has been so enormous in the past 25 years that it would be no exaggeration to say that more has been written, and more knowledge has been accumulated, during this period than in the preceding 2,500 years. This chapter is devoted to the history of psychiatry, yet history inevitably blends into current events seamlessly and without a clear boundary. For reasons of space and because the past quarter-century has more the feel of current events than of history (at least to those old enough to have been in the field more than 25 years), it has been chosen to present, relative to this period, simply the highlights (Table 14–1). Table 14–1 lists some of the more important advances or trends, along with (where pertinent) the main authors or initiators of these developments. Before moving to these highlights, we must single out a most important highlight: the awarding of the Nobel Prize for medicine in 2000 to the Columbia University professor, Eric Kandel, for his work on memory mechanisms in humans as well as in other animals—the outgrowth of his research on the small invertebrate, Aplysia.

The exponential growth of new information in articles and books in our field, even since the last edition of *Psychiatry* in 2003, has meant that the path from "current events" to what feels like "history" is even shorter than it was from the first to the second edition.

Since the time when the second edition was in preparation, for example, the "atypical" antipsychotics, such as risperidone, olanzapine, aripiprazole, and their close cousins, have become "typical"; the older medications—chlorpromazine, haloperidol, fluphenazine, etc.—are either used less than before or else have fallen into desuetude. In the domain of bipolar illness, there is now an expanded array of antimanic medications, including lamotrigine, which has offered an effective alternative to lithium in the control especially of those bipolar persons prone to episodes of depression.

Thanks to the new and developing field of pharmacogenomics, we have begun to increase our understanding of the genetic variability to the efficacy and also to the toxicity of various psychopharmacological agents—a point made by Julie Johnson in the first issue of the *American Journal of PharmacoGenomics* (2001). From this research, it has been learned that there tend to be differential responses to lithium and neuroleptics in Asian-American, as compared with Caucasian patients. This may relate to differences in the activity of CYP2D6 and CYP2C enzymes in the two groups. Similarly, Black patients may require smaller doses of tricyclic and serotonin reuptake blocking antidepressants than would be needed in Caucasian patients, to achieve similar antidepressant responses. Further research concerning group differences may lead to better selection and dosages of psychotropic drugs at the onset of a condition, with less need than in the past for empirical, time-consuming trial-and-error choices.

In the field of personality disorders, many experts have drawn increasing attention to the need for adding a dimensional, as opposed to merely categorical, perspective to the array of disorders. John Livesley, John Oldham, Thomas Widiger, Robert Cloninger, among others, have championed this approach, and have devised new dimensional schemata for amplifying the next edition of the DSM in its section on personality. Perhaps this amounts to pouring old wine in new bottles, inasmuch as the MMPI devised by Hathaway and McKinley in 1940, and widely used ever since, embodies a dimensional view of personality, acknowledging that people each show *varying degrees* of the conventional and arbitrarily chosen "categories" of personality.

Very much in vogue over the past few years are elaborate *manuals* for different types of psychotherapy. Thus, Marsha Linehan and her colleagues have compiled a manual for the proper carrying out of dialectic behavior therapy (DBT); Kernberg, and his coworkers have published a manual of guidelines for conducting transference-focused psychotherapy (TFP); Bateman and Fonagy have recently published (2004) an encyclopedic work on borderline personality disorder, containing within it a manual for their mentalization-based treatment for borderline patients. Arnold Winston and his colleagues (including Henry Pinsker, who had published a similar work in 1997) have written guidelines for *supportive* psychotherapy. Manuals of this sort have the advantage of contributing to

**Table 14–1** Developments in Psychiatry: 1970–1995

| Taxonomy, Diagnosis, Biometrics | Investigator | Year |
|---|---|---|
| Objectifiable diagnostic criteria | J. Feighner | 1972 |
| Research diagnostic criteria | R. Spitzer | 1975 |
| Distinctions between schizophrenia and manic–depressive disorder | R. Kendell | 1975 |
| The Global Assessment Scale | J. Endicott | 1976 |
| Multiaxial inventory/personality | T. Millon | 1977 |
| The "atheroretic" DSM-III | R. Spitzer | 1980 |
| DSM-III, revised edition | R. Spitzer | 1987 |
| Classification of personality traits | A. Buss | 1987 |
| Personality Assessment Schedule | P. Tyrer | 1988 |
| Revised Psychopathy Checklist | R. Hare | 1990 |
| Comorbidity patterns in personality disorder | J. Oldham | 1992 |
| Japanese version of personality scale | M. Takeuchi | 1993 |
| DSM-IV-TR | A. Frances | 1994 |
| **Psychoanalysis** | | |
| Self psychology | H. Kohut | 1971 |
| Résumé of technique and practice | R. Greenson | 1970s |
| Borderline and narcissistic personalities: diagnosis and treatment | O. Kernberg | 1975 |
| Revision of terminology | R. Schaefer | 1976 |
| Theory of emotion as messages | H. Dahl | 1978 |
| Short-term dynamic therapy | H. Davanloo | 1980 |
| Psychology of aggression | A. Mitscherlich | 1982 |
| Explication of narcissism | A. Cooper | 1980s |
| Masochism and its treatment | R. Stolorow | 1988 |
| Rebirth of psychoanalysis in Eastern Europe | | 1989 |
| Reexamination of homosexuality | R. Friedman | 1990s |
| Description of malignant narcissism | O. Kernberg | 1992 |
| Psychoanalysis enters its 2nd century | R. Michels | 1994 |
| Self psychology in depression | J. Lang | 1995 |
| **Epidemiology** | | |
| Affective disorders | M. Weissman | 1970s |
| Incest (broadly defined) | D. Russell | 1986 |
| Physical violence in US families | M. Straus | 1990 |
| Adverse life events | C.K. Cross and R.M.A. Hirschfeld | 1986 |
| Personality disorders | K. Merikangas | 1986 |
| Personality disorders | T. Widiger | 1989 |
| Suicide | C. Ernst and J. Angst | 1992 |
| Impact of socioeconomic class | B. Dohrenwend | 1992 |
| All major conditions | M. Tsuang | 1995 |
| **Statistical methods** | | |
| The power of statistical analysis | J. Bartko (many contributors including J. Cohen and R. Fleiss) | 1988 |
| **General Psychiatry** | | |
| Human sexual response | W. Masters and V. Johnson | 1970s |
| Attention-deficit disorder | P. Wender | 1971 |
| Treatment of anorexia nervosa | H. Bruch | 1973 |
| Multiple personality: review | G. Greaves | 1980 |
| Multiple personality | R. Kluft, F. Putnam, and R. Loewenstein | 1980s |
| Dysthymia versus hyperthymia | H. Akiskal | 1980s |
| "Endogenomorphic" depression | D. Klein | 1980s |
| Premenstrual syndromes | R. Friedman | 1982 |

*(continues)*

**Table 14–1** Developments in Psychiatry: 1970–1995 *continued*

| | | |
|---|---|---|
| **General Psychiatry** | | |
| Father–daughter incest, effects of | J. Herman | 1981 |
| Brief therapy and personality styles | M. Horowitz | 1984 |
| Life events and personality | N. Seivewright | 1987 |
| Seasonal affective disorder | T. Wehr | 1989 |
| Coercive religious cults | M. Galanter | 1989 |
| Serotonin and obsessive–compulsive disorder | J. Rapoport | 1989 |
| Obsessive–compulsive disorder: theory and treatment | M. Jenike | 1990 |
| Compulsive–impulsive disorders | E. Hollander | 1990s |
| Bulimia: possible relation to incest | G. Waller | 1991 |
| Cognitive science and clinical disorders | D. Stein | 1992 |
| Aggressive behavior and cocaine | S. Yudofsky | 1993 |
| Treatment of hypochondriasis | B. Fallon | 1993 |
| Posttraumatic stress disorder: neurophysiological correlates | B. van der Kolk | 1990s |
| American Psychiatric Association *Compendium on Treatment of Psychiatric Disorders*. | | |
| First edition | B. Karasu, ed. | 1989 |
| Second edition | G. Gabbard, ed. | 1995 |
| **Hospital Psychiatry; Psychoses** | | |
| Ego function in schizophrenia: review of schizophrenia | L. Bellak | 1970s |
| Long-term outcome in schizophrenia | M. Bleuler | 1972 |
| Long-term outcome in the psychoses | M. Tsuang | 1975 |
| Vulnerability concept in schizophrenia | J. Zubin | 1977 |
| High expressed emotion in families with schizophrenia | C.E. Vaughn and J.P. Leff | 1976 |
| Long-term outcome in schizoaffective patients | J. Angst | 1980s |
| "Basic" (negative) symptoms in schizophrenia | G. Huber | 1980s |
| Education therapy for schizophrenic families | W. McFarlane | 1985 |
| Paranoid psychosis delineated | K. Kendler | 1985 |
| Long-term follow-up of schizophrenia | C. Harding | 1985 |
| Social skills training | R. Liberman | 1987 |
| Brief therapy for schizophrenia | M. Herz | 1980s |
| Manic–depressive illness: overview | F. Goodwin | 1990 |
| Low birth weight and schizophrenia | L. Rifkin | 1993 |
| General discussion of Alzheimer's disease | D. Masterman | 1995 |
| **Personality Disorders** | | |
| Objective criteria for borderline personality disorder | J. Gunderson | 1975 |
| Follow-up studies of borderline personality disorder | T. McGlashan | 1986 |
| Heredity versus environment influences | R. Plomin | 1987 |
| Pharmacotherapy for borderline patients | P. Soloff | 1986 |
| Biological (neurotransmitter) theory | R. Cloninger | 1986 |
| First International Congress | (Copenhagen) | 1988 |
| Dimensional versus categorical diagnoses | T. Widiger | 1988 |
| Impact of incest on borderline patients | M. Zanarini | 1989 |
| Schizoid, schizotypal, and paranoid personality disorders | L. Siever | 1989 |
| Personality as predictor of outcome | A. Andreoli | 1989 |
| Dimensions of personality | J. Livesley | 1990 |
| Impact of temperament | J. Strelau | 1991 |
| Therapy in borderline and narcissistic disorders | A. Higgitt | 1992 |
| Use of cognitive–behavioral techniques | M. Linehan | 1990s |
| Use of cognitive–behavioral techniques | D. Stein | 1990s |
| Use of cognitive–behavioral techniques | C. Padesky | 1995 |

*(continues)*

**Table 14–1** Developments in Psychiatry: 1970–1995 *continued*

| | | |
|---|---|---|
| **Psychopharmacology and Biological Treatment** | | |
| Unilateral electroconvulsive therapy for depression | L. Strömgren | 1973 |
| Carbamazepine for mania | T. Okuma | 1973 |
| Phototherapy for depression | M. Terman | 1989 |
| Selective serotonin reuptake inhibitors for obsessive–compulsive disorder and depression | R. Fontaine and G. Chouinard | 1980s |
| Pimozide for pathological jealousy | A. Byrne | 1989 |
| Drug treatment of personality disorder | G. Stein | 1992 |
| New antidepressants: pharmacology | B. Leonard | 1993 |
| Treatment of social anxiety | J. Gorman | 1990s |
| **Biological Psychiatry and Basic Sciences** | | |
| Smooth-pursuit eye movements in schizophrenia | P. Holzman | 1973 |
| Genetics of the psychoses | E. Gershon | 1975 |
| Genetics of the psychoses | L. Siever | 1984 |
| Neuroimaging: positron emission tomographic scan, regional cerebral blood flow, magnetic resonance imaging in psychoses, obsessive–compulsive disorder, and so on | N. Andreasen (plus many other investigators, e.g., T. Insel, P. Goldman Rakic, R. Gur) | 1980s |
| Evoked potentials in psychosis | C. Shagass | 1978 |
| Neurotransmitters (including endorphins) | S. Snyder | 1970s |
| Correlates of aggression | L. Valzelli | 1970s |
| Serotonin levels in suicide and aggression | M. Åsberg | 1980s |
| Genetics of schizophrenia | I. Gottesman | 1980s |
| Neurobiology of memory | E. Kandel | 1980s |
| Neurobiology of memory | (also M. Mishkin, L. Squire, Y. Dudai) | |
| Processing abnormalities in dyslexia | P. Tallal | 1980s |
| Psychobiology of suicidal behavior | J. Mann | 1986 |
| Neuronal group selection theory | G. Edelman | 1987 |
| Polysomnography in borderline patients | A. Akiskal | 1989 |
| Serotonin and impulsive aggression | E. Coccaro | 1989 |
| Hypofrontality in schizophrenia | D. Weinberger | 1989 |
| Cerebral structure in borderline patients | P. Lucas | 1989 |
| Frontal lesions in violent patients | R. Heinrichs | 1989 |
| Neural networks, connectionist theory | D. Rumelhart | 1990s |
| Psychobiological correlates of violence | A. Raine | 1990s |
| Genetic factor in antisocial adoptees | R. Cadoret | 1990 |
| Psychobiology of personality | M. Zuckerman | 1991 |
| Prenatal diethylstilbestrol and gender role | A. Ehrhardt | 1992 |
| Consciousness | F. Crick | 1992 |
| Genetic factor in female homosexuality | J. Bailey | 1993 |
| Regional cerebral blood flow in obsessive–compulsive disorder | S. Rauch | 1994 |
| Facial shape and female attractiveness | D. Perrett | 1994 |
| Serotonin pathways in obsessive–compulsive disorder | T. Insel | 1992 |
| Serotonin pathways in alcoholic offenders | M. Linnoila | 1995 |
| Language centers: sex differences | B. Shaywitz | 1995 |
| Right brain activity and recall or trauma | F. Schiffer | 1995 |
| **Psychology** | | |
| Normal moral stages | L. Kohlberg | 1976 |
| Rorschach for borderline patients | J. Kwawer | 1980 |
| Minds, brains, and programs | J. Searle | 1980 |
| Lexicon of personality traits | L. Goldberg | 1982 |
| Long-term stability of personality | P. Costa | 1986 |
| The Five-Factor Model reexamined | T. Widiger | 1992 |
| The moral sense | J. Wilson | 1993 |
| The Rorschach Inkblot Test in serial sexual homicide | R. Meloy | 1995 |

*(continues)*

**Table 14–1** Developments in Psychiatry: 1970–1995 *continued*

| | | |
|---|---|---|
| **Ethology** | | |
| Adaptive and survival strategies | R. Dawkins | 1976 |
| Sociobiological approach | E. Wilson | 1978 |
| Machiavellian intelligence | R. Byrne | 1988 |
| **Child Psychiatry** | | |
| High-risk studies of schizophrenia | N. Garmezy | 1974 |
| Autism versus childhood schizophrenia | M. Rutter | 1972 |
| Psychological birth of the infant | M. Mahler | 1975 |
| Suicide in children | C. Pfeffer | 1980s |
| The mother–infant bond | D. Stern | 1980s |
| Anorexia nervosa in adolescents | P. Jeammet | 1980s |
| The borderline child | K. Robson | 1983 |
| The history of child psychiatry | J. Noshpitz | 1995 |
| **Forensics** | | |
| Dangerousness | C. Webster | 1985 |
| Biological approaches to crime | S. Mednick | 1987 |
| Family violence | V. van Hasselt | 1988 |
| Criminal responsibility and addiction | S. Peele | 1990 |
| The insanity defense | A. Halpern | 1991 |
| Serial killers | C. Wilson | 1992 |
| The psychopathology of crime | A. Raine | 1993 |
| The psychology of psychopathic individuals | R. Hare | 1993 |
| Antisocial personalities | J. Coid | 1993 |
| Mental disorder and crime | S. Hodgins | 1993 |
| Personality of serial killers | M. Stone | 1994 |

the standardization of therapeutic techniques. In addition they facilitate research (including randomized controlled studies of contrasting methods) concerning the effectiveness of the different approaches, in hopes of creating a generation of psychotherapies that are empirically supported and "evidence based" (a term also very much in vogue currently). The new emphasis is not without its downside. There is now a tendency to derogate the psychoanalytic therapies partly because, by their very nature, it is inherently difficult to compress them into the evidence-based mould—as has been pointed out by Nancy McWilliams 2004 in her excellent guide to psychoanalytic psychotherapy. But this does not invalidate the utility of the analytic therapies, given the well-trained therapist and the amenable patient. Perhaps there is an analogy to chess. There are well thought-out theories, some very definite *don'ts* and some highly recommendable *do's* in chess, but in between a nearly infinite sea of choices that cannot be reduced to a manual, no matter how lengthy. So it is with psychotherapy.

Many have argued for an eclectic approach to the therapy of the more severe personality disorders, even while acknowledging that one must be grounded in a particular method—before incorporating and utilizing other techniques as the occasion may demand. John Livesley and John Gunderson have espoused this position, as have Judd and McGlashan (2004) in their outstanding treatise on the therapy of borderline patients.

One of the goals of the various psychotherapeutic approaches to the treatment of personality disorders, especially that of borderline personality disorder (BPD), is to help the patient advance from a state of insecure attachment (with its various subtypes: entangled, disorganized, and dismissive) to a state of secure attachment. This emphasis on attachment type and level, which is noticeable in much of the recent literature on therapy, derives from increasing attention to the work of earlier investigators in this field: John Bowlby in the 1950s, Mary Ainsworth in her work on assessing infant attachment in the 1970s, Mary Main, who with her colleagues developed scales for the assessment of adult attachment types, and in the last few years, Otto Kernberg and Peter Fonagy in their works on the treatment of BPD. And Sonkin and Dutton 2003 have even shown how the psychology of attachment and its abnormalities can be made applicable to their work with assaultive men.

An emerging field whose research has contributed both to our understanding of personality and to the treatment of its disorders is *evolutionary psychiatry*. Prominent investigators in this area include the following: Richard Dawkins; Anthony Stevens and John Price; Jerome Barkow, Leda Cosmides, and John Tooby; Joseph LeDoux; Michael McGuire and Alfonso Troisi; John Cartwright and Nancy Etcoff. Whereas conventional psychiatry focuses on the abnormal aspects of personality, that is, the disorders of personality, evolutionary psychiatry focuses on the adaptive aspects of the different personality configurations. Seen in this light, the "disorders" can be understood as exaggerations of tendencies that in less intense form serve valuable purposes in a social species like ours. In what is termed the evolutionarily stable state, a community will be divided into certain proportions of leaders, followers, meticulous workers, unconventional

"creative" types, extraverts, introverts, persons susceptible of guilt, persons with few scruples, and the like. Take these various types toward their extremes, and one sees the "disorders": the hypomanic, the schizoid, the obsessive–compulsive, the hysteric, the depressive, the antisocial, and all the rest. From the standpoint of *evolutionary "fitness"* (which relates, not to the success of the individual, but to the number of offspring left in the next generation), it can be seen that certain antisocial men impregnate a number of women, whom they then abandon—but whose DNA is sent into the next generation—even if the negligent father is subsequently killed at an early age in a barroom brawl. Survival needs universal in our species are emphasized in evolutionary psychiatry, such as that of *resource-holding power*. This relates to the ability to accumulate and retain valuable goods and relationships that will guarantee the survival of the individual and his or her offspring. Nancy Etcoff 2000 has written on the way in which feminine beauty serves this need: beauty, in evolutionary language, equates with the visual cues that signify symmetry (equated in turn with physical health) and fertility (youthful appearance, waist-to-hip circumference of about 0.7, dimpled cheeks that signal puberty). The sexual attractiveness associated with these features conduce to successful reproduction, hence evolutionary fitness.

Considerable strides have been made in the past few years in study of the brain via magnetic resonance imaging and related techniques. This is true even in the area of personality disorder, where Bremner has recently shown (2005) abnormalities in borderline patients. In women with borderline personality who had histories of early abuse, for example, decreased function was observed in the anterior cingulate and temporal cortex. Diminished anterior cingulate function, as Larry Siever's work suggests, is associated with a poorer "braking mechanism" giving rise to exaggerated reactions of fear, panic, or rage in response to key interpersonal stresses. The recent overview on neuroimaging by Dougherty et al. 2004 is a rich source of information about brain abnormalities in schizophrenia (viz., ventricular enlargement, medial temporal abnormalities, etc.), posttraumatic stress disorder (PTSD), and various cognitive disorders, including Alzheimer's disease.

Apropos Alzheimer's disease, recent research has identified a gene, in addition to the earlier identified Apolipoprotein-E4 gene, that is associated with the commoner, late-onset (after age 65) form of the disease. This gene, called *SORL1*, has been noted with greater than expected frequency in certain ethnic groups. Meantime, a chemical marker called FDDNP, when injected intravenously during positron emission tomography (PET) has been shown helpful in detecting the plaque and tangle deposits associated with the disease—when it is still in the subclinical stage. The discovery of more such genes that may be involved with Alzheimer's lends some hope of better diagnostic tests for spotting those at risk, and of better drugs to combat or forestall its devastating effects.

There has been renewed interest in the topic of empathy, particularly in relation to gender differences in brain structure and function. Simon Baron-Cohen and his colleagues, in a recent book (2003), entered this controversial area, making a number of interesting observations. Female-type brains appear, on average, better at empathizing and communicating; male-type brains, better at understanding and building systems. Asperger's syndrome, viewed in this context, emerges as an extreme type of the male brain: those who exemplify the syndrome seem uncannily good at analyzing complex systems, and uncannily handicapped at grasping emotions and at relating to the emotional nuances of those in their midst. At the end of the book is an empathy scale composed of 36 faces, each with a different emotional expression: the reader must choose among four possible descriptive adjectives. In general, women are shown to perform better in this test than men.

In the forensic arena research in the last few years, much attention has been devoted to the neurobiology of violence. Several excellent texts are available (Niehoff 1998, Volavka 2002). The focus in many related articles is on neurophysiological abnormalities in criminal psychopaths, about which Adrian Raine has been an important contributor (Raine et al. 2003, Yang et al. 2005). Psychopathy (especially in persons "unsuccessful"—in that they were caught) has been associated with diminished prefrontal gray matter. Psychopaths tend also to show an increase in callosal white matter—which Raine suggested might underlie atypical neurodevelopmental processes in psychopathy, including the affective and interpersonal deficits associated with this personality type. Decreased reactivity has also been noted in psychopaths during evoked potential studies of reactions to highly emotional words, which may account for the glibness of speech and facility in lying that are prominent characteristics of the psychopath. A crime that has been on the rise in recent years is that of *stalking*, whether of romantic partners (actual or imagined), celebrities, or persons in the workplace who have disappointed or dismissed an employee. Specialists who have written extensively on the taxonomy, nosology, treatment, and legal implications of stalking include Paul Mullen and Reid Meloy; some of their contributions are included in the compendium edited by Boon and Sheridan 2002. Stalking and attachment are interrelated topics, inasmuch as the stalkers are pathologically unable to detach themselves from the objects of their relentless pursuit. In an interesting footnote to the subject of *homicide*, including the murders of teachers and fellow students by adolescent school-shooters, and also *suicide* over the entire age range, a recent study from the Harvard School of Public Health has demonstrated that the states with the highest rates of household firearms (viz., Wyoming, Alaska, Montana) have significantly higher homicide rates than is noted in states, such as Massachusetts, where the gun ownership rate is at the lowest level for the US. This was particularly true of women who were killed by guns, since they are killed usually by current or former boyfriends or spouses, using guns that were already in the home.

## Conclusion

It is difficult to tell what age one has been living in until it has passed. We can easily see now the cultural influences that shaped Freud's thinking—about the roles of fathers and mothers, about women's "masochism," about "unconscious homosexual strivings" in paranoia—because we have the distance of a century to give us perspective. What about trends now? Certainly we can say that this is a time when, thanks in part to the computer, symptom-specific drugs, neuroimaging techniques, and rigorous statistical methodology, our interests have shifted toward the biological and

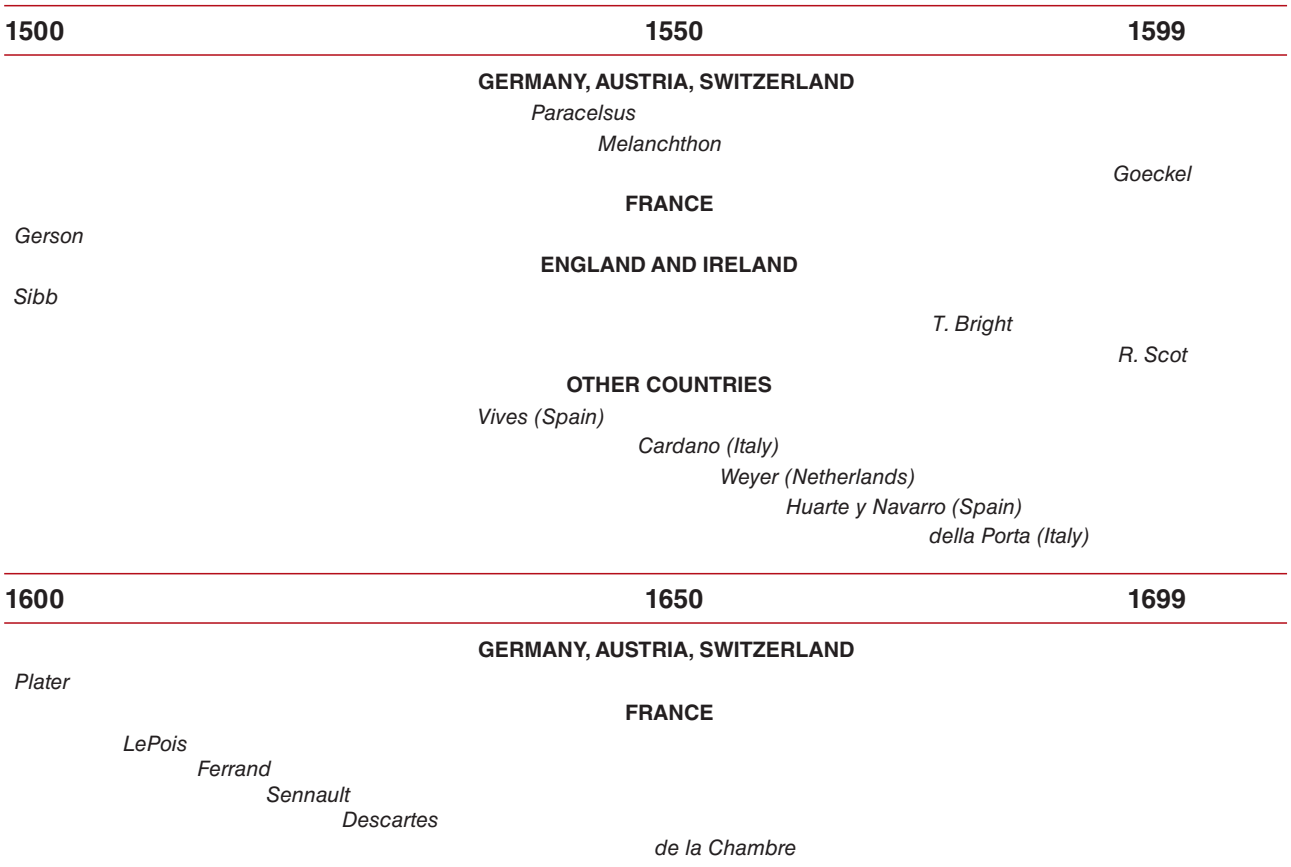
away from the individual. Psychiatrists often rely more on fluoxetine (Prozac) than on the spoken word. We have seen that a similar shift occurred in the 19th century.

There is no question that past generations of psychiatrists have witnessed exciting discoveries. (See Figures 14–9 and 14–10.) Some have been alluded to in Table 14–1; brain imaging has shown loss of tissue in associational areas of the cortex (hypofrontality) in chronic schizophrenia, abnormalities in basal ganglion pathways have been outlined in obsessive–compulsive disorder, abnormalities in autonomic nervous system function, and in "empathy centers" have been proposed as the key to psychopathic behavior, and Bessel van der Kolk's neuroimaging studies of traumatized persons (in whom Broca's language area does not "light up" when they concentrate on a painful memory) help explain the failure, in many cases of posttraumatic stress disorder, to remember in words. All these are a tribute to the triumph of biological psychiatry in the late 20th century.

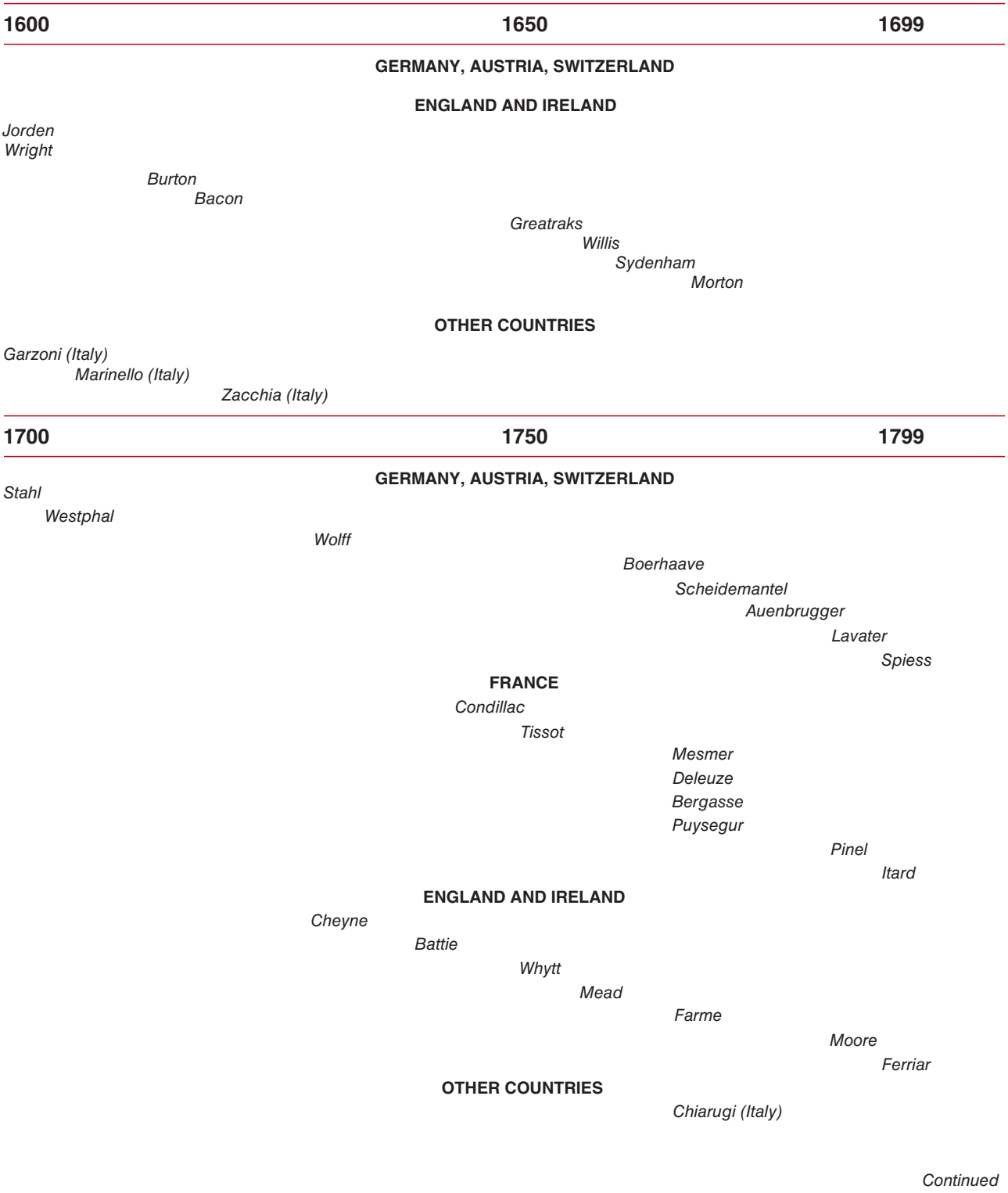
While this is happening, we hear even so biologically oriented a researcher as Robert Cloninger speak of having identified yet another key variable in personality: self-transcendence. Van der Kolk mentions, as a soft sign in posttraumatic stress disorder, loss of faith in the future and of trust in other people. These qualities are related to our humanness and to the unique qualities of individuals. This is what we do not hear when we listen only to Prozac. In a parallel fashion, a number of books have appeared on our moral sense and its biological, evolutionary roots: James Q. Wilson's *The Moral Sense* (1993), Matt Ridley's *The Red Queen: Sex and the Evolution of Human Nature* (1993), and Robert Wright's *The Moral Animal* (1993). Wilson reminds us that human society is held together by fine wires of sympathy, fairness, self-control, and duty, built into us through evolution because of their survival value in a communal animal. Psychiatry had for too long put these issues on the back burner. And our enthrallment with biology has begun to put human individuals, our one-at-a-time psychiatric patients, on the back burner. It should not surprise us, then, that in the current century, alongside the breathtaking strides of biological psychiatry—for they will continue—a new Ideler or Freud will emerge, redirecting our attention to the individual and to some new kind of verbal psychotherapy keyed to the needs and sufferings of 21st-century men and women.

## Timeline: 1500–1900

**The approximate years during which the major figures lived are indicated below and are listed for each major geographical area.**



## Timeline: 1500–1900 *Continued*




*Continued*

## Timeline: 1500–1900 *Continued*

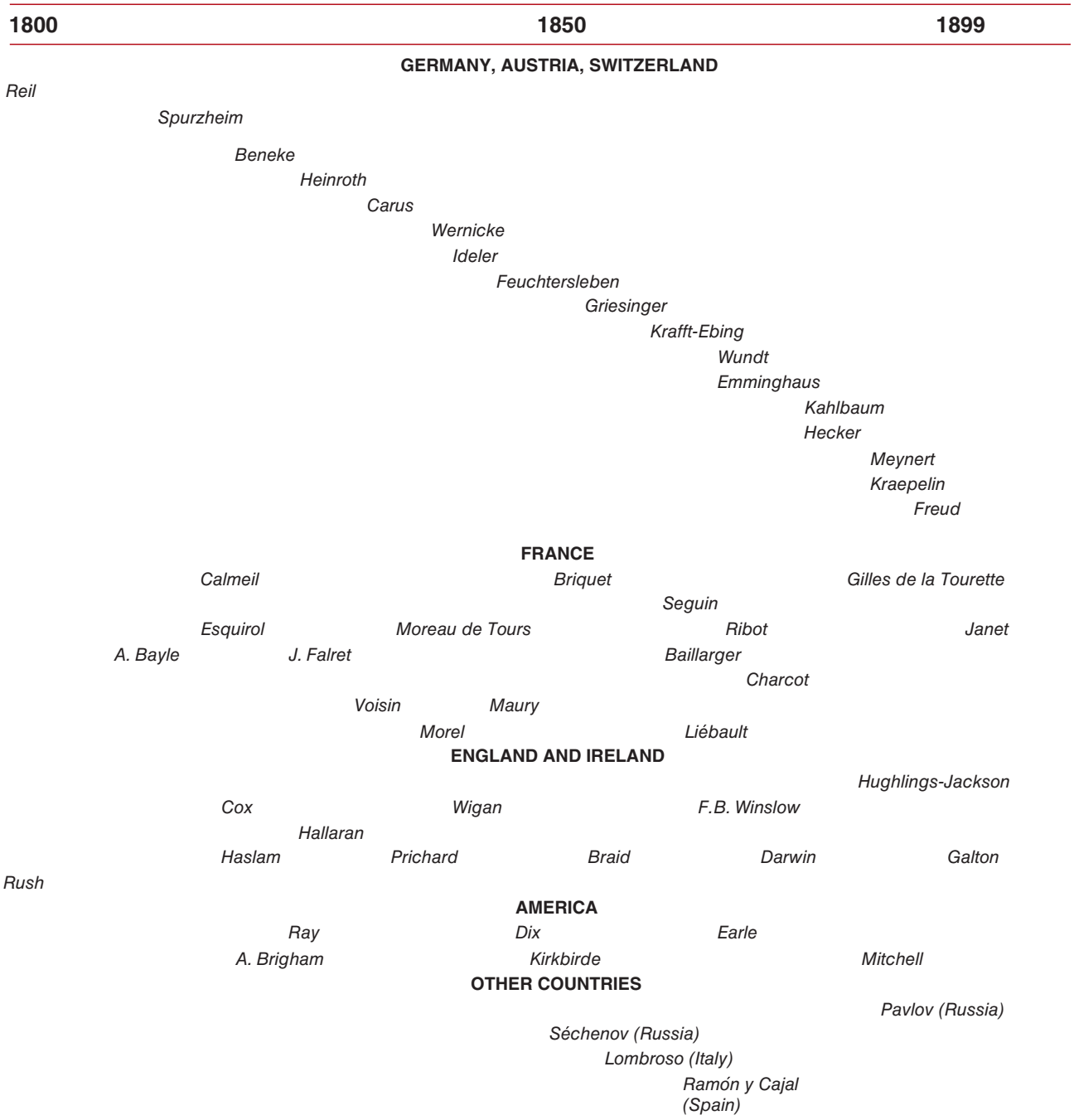



**Figure 14–9** *Timeline 1500–1900 (Source: Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H. Stone, M.D. Copyright 1997 Michael H. Stone, M.D., pp 435–438.)*

## Chronology of Historical Events and Persons: 15th–20th Centuries

*15th–16th Centuries*

1445 Gutenberg invents the printing press.
1453 Constantinople falls to Mehmet II.
1492 Columbus discovers America.
The beginning of the Spanish Inquisition; dominated by persecution, burnings, or expulsion of Jews and Moors.
1517 Luther (1483–1546) posts his 95 theses at Wittenberg, demanding discussion about the abuses of indulgences.
1520 Luther's efforts at reformation begin to succeed; Philip Melanchthon offers formulation of Luther 's doctrines.
1523 Lutherans in the Netherlands are persecuted by Charles V; heretics are burned in Brussels.
1531 In England, King Henry VIII (1509–1547) is recognized as head of the Anglican Church.
1534 Ignatius Loyola (1491–1556) founds the Jesuit order.
1535 English clergy deny authority of the Pope, but Sir Thomas More refuses to acknowledge the supremacy of the king and is executed for treason.
1536 Calvin (1509–1564) promulgates his Protestant doctrine in predestination to either salvation or damnation.
1542 Andreas Vesalius, Flemish anatomist, presents drawings of the anatomy of the human body.
1543 Copernicus, promulgator of heliocentrism, dies.
1553 Geneva becomes center of Protestant world; Calvinsim spreads to countries outside Switzerland.
1556 Holy Roman Emperor Charles V fails to win back Metz and Verdun from France and abdicates; this contributes to a gain in power for the nation state and to forfeiture of the dream of a universal Catholic empire.
1558 Birth of Queen Elizabeth (d. 1603), who retains concept of royal supremacy over the Church.
1562 Hugenot wars erupt in France; many Hugenots leave France following their defeat in 1593 by Cardinal Richelieu.
1564 Birth of Galileo.
1566 Calvinism becomes official church in the Netherlands.
1572 Twenty thousand Hugenots are massacred in France.
1588 The English destroy the Spanish armada.
Birth of Thomas Hobbes (d. 1679), English philosopher who asserts that "life is but motion," a reductionist theory that places no value on subjective experience.
1596 Birth of Descartes (d. 1650), who advocated rationalism and the deductive method, and asserted that nature and spirit are distinct ("dualism") and that the body, which is made up of particles that move like tiny machines, must be understood also in machine terms (thus uniting physics and biology).

*17th Century*

1600 Giordano Bruno is burnt at the stake for advocating heliocentrism and the concept of an infinite universe.
1601 Danish scientist Tycho Brahe, teacher of Kepler and architect of first astronomy observatory, dies.
1609 Emperor Rudolph II permits freedom of religion in Bohemia. Galileo studies the motion of falling bodies.
1618 The beginning of the Thirty Years War of religious conflict, culminating in the Peace of Westphalia, ushering in an era of greater religious tolerance and the secular state.
1619 William Harvey discovers the circulation system of the blood.
1620 Puritan separatists cross the Atlantic on the *Mayflower*.
1632 Birth of English philosopher John Locke (d. 1704), a senior figure in British empiricism who postulates that experience (ideas of sensation and reflection) form the basis of understanding. *Some* ideas (the "primary qualities"), however, come from an "all-knowing God." Locke believes that religion and morality are open to demonstration and proof, as is mathematics.
Birth of Spinoza, whose concept of oneness of thought and existence helps pave the way for the Enlightenment.
1633 The Catholic Church forces Galileo to recant his Copernican theory about the earth moving around the sun (which provokes Galileo to mutter under his breath, "*Eppure, si muove* [even so, it moves]").
1637 Descartes: analytic geometry.
1642 Death of Galileo; birth of Newton.
1644 John Milton writes "Areopagitica," arguing for freedom of the press.
1646 Birth of Leibniz, coinventor (with Newton) of the Calculus. The "Stubborn Child Law" is enacted by Puritans in the Massachusetts Bay Colony: Parents claiming a child was stubborn or rebellious could seek state reprimands, including execution.
1647 Birth of Pierre Bayle, philosopher of the French Enlightenment, who champions freedom of thought and religion.
1648 English civil war erupts as Oliver Cromwell demands end of allegiance to the king (Charles I), who wishes to reintroduce Catholicism in England.

## Chronology of Historical Events and Persons: 15th–20th Centuries *Continued*

1649 Charles I of England is beheaded; Cromwell assumes power; Charles II goes into exile.
1661 The monarchy in England is restored and Charles II is crowned as king.
1665 Newton invents the Calculus (as does Leibniz independently in 1672). Robert Hooke 's book on microscopy is published.
1690 John Locke's "An Essay Concerning Human Understanding" is published.
1694 Birth of Voltaire (d. 1778), French philosopher/essayist, who argued against the Church and the notion of faith.

*18th Century*

1704 Isaac Newton's "Opticks" demonstrates wave aspect of light.
1710 George Berkeley's essay, "A Treatise Concerning the Principles of Human Knowledge, " is published.
1711 Birth of David Hume, English skeptical philosopher, whose tendency to doubt all "certain" knowledge challenges and limits the assertions of the Enlightenment: Man is a *tabula rasa* at birth, upon whom experience impresses its symbols.
1712 Birth of Rousseau, Swiss/French philosopher, whose views that man was good by nature—corrupted because he does not allow himself to be guided by his feelings—places him in the next movement following the Enlightenment.
1714 German physicist Gabriel Fahrenheit's invention of the thermometer.
1724 Birth of Immanuel Kant in Prussia.
1728 Death of Cotton Mather, Massachusetts witch hunter.
1729 Death of German/Jewish philosopher, Moses Mendelssohn, grandfather of the composer; around this time there is greater tolerance in Germany toward the Jews.
1733 Birth of German physician and hypnotist, Anton Mesmer.
1735 Linnaeus, Swedish botanist, publishes his taxonomy of organic life.
1739 Hume's "A Treatise of Human Nature " is published.
1745 Birth of Benjamin Rush, Philadelphia physician/alienist.
1751 Assembling of the French *Encyclopedie* by Diderot and D'Alembert; contributors include La Mettrie, who asserts that man is a machine, and atheist materialist philosopher, Etienne Condillac; work is completed in 1777.
1752 Benjamin Franklin invents lightning conductor.
1761 Morgagni's work marks the beginning of pathological anatomy.
1770 Birth of German philosopher Friedrich Hegel.
In Kant's inaugural dissertation he asserts that we have a *priori* knowledge of space and time only because they are forms imposed by our own subjective experience, which also determines the schema of space and time, and gives rise to the distinction between things *as they are in themselves* and things as they are perceived by us, and to the distinction between experience and thought.
1770s Steam power, civil liberty, and free trade give rise to the Industrial Revolution, first in England, thence throughout the world.
1771 Galvani discovers electrical nature of nerve impulses.
1774 Goethe's publication of *The Sorrows of Young Werther* marks the beginning of German Romanticism and emphasis on the individual and the emotions (the novel also sets off a wave of suicides in Europe).
1775 Digitalis used by Withering for "dropsy."
James Watt 's invention of the steam engine.
1776 The American Revolution erupts.
1781 Kant's Critique of Pure Reason is published, whose ethic is based on the search for a supreme principle of morality, a "categorical imperative" (in practice, similar to the Golden Rule). Kant 's *idealism* represents a break with empiricism, whereby knowledge is tied to experience.
1784 Louis XVI commissions Lavoisier, Guillotin, Benjamin Franklin, and others to examine the merits of Mesmer 's claims.
1789 The storming of the Bastille and beginning of the French Revolution.
1790 Jews in France are granted civil liberties.
1796 English physician William Jenner synthesizes a vaccine against smallpox.
1798 English economist Thomas Malthus' "An Essay on the Principle of Population " is published.

*19th Century*

1800 Napoleon becomes First Consul and commissions a civil code to be drawn up: the "Napoleonic code."
1804 Napoleon is proclaimed emperor of France.
1807 Robert Fulton's paddle steamer navigates the Hudson River. Publication of Hegel 's *Phenomenology of the Mind*.
Arguably the most prominent philosopher in 19th-century Germany, influencing Marx and Engels, Hegel views history as progress toward *freedom*, conceived not as mere license, but as living self-consciously in a rationally organized community via the consent of the rational conscience of its members. Hegel writes in the spirit of German Romanticism, admiring skepticism, with its respect for freedom and reason (leading to the point where the "mind knows itself"). Hegel's prescription for reaching the ultimate goal is the *dialectic*: using reason to overcome the contradiction between thesis and antithesis, via finding the proper synthesis, again and again, until perfection is reached.

## Chronology of Historical Events and Persons: 15th–20th Centuries *Continued*

1808 Napoleon abolishes the Inquisition in Spain.
1809 Birth of English naturalist Charles Darwin.
1810 Height of Napoleon's powers; after divorcing Josephine, he marries Archduchess Maria Louise of Austria.
1811 Insanity due to porphyria of King George III of England. Charles Bell's *New Idea of the Anatomy of the Brain* is published.
1813 Birth of Søren Kierkegaard, Danish philosopher, the first existentialist.
1814 Abdication of Napoleon after a series of defeats; he is banished to the island of Elba.
1818 Birth of Karl Marx.
1819 Schopenhauer's *The World as Will and Representation* is published.
1821 Mary Baker Eddy, influenced by followers of Mesmer, founds the Church of Christ, Scientist, commonly known as Christian Science.
1822 Birth of Austrian botanist Gregor Mendel, founder of genetic science.
1823 English mathematician Charles Babbage invents the calculating machine, precursor of computer.
1827 Joseph Niepce, French chemist, develops photographs on a metal plate and 2 years later forms partnership with Louis Daguerre, French inventor; beginning of era of photography.
1829 Birth of F.A. Kekule, German chemist, who discovered (1865) ring shape of the benzene molecule.
1830 Poland revolts against Russia; defeated by the Russians in 1831. Birth of future Emperor Franz Joseph of Austria.
1831 Invention of chloroform as anesthetic; Faraday 's and Maxwell's work on electromagnetism; Charles Darwin sails as naturalist on H.M.S. *Beagle*. Death of Hegel.
1833 Karl Gauss, German mathematician and astronomer, devises electromagnetic telegraph with a 2-mile range.
1834 Birth of Dimitri Mendeleyev in Russia, discoverer of the periodic table in chemistry.
1837 Victoria becomes Queen of England for the next 64 years. During her reign England becomes the dominant world power, with territories in every continent, amounting to a fourth of the world's land mass; London becomes the world's greatest city. Samuel Morse invents the electric telegraph.
1838 Birth of the science of sociology, developed by French philosopher Auguste Comte.
Birth of Franz Brentano (d. 1917), German philosopher and founder of the phenomenological movement, emphasizes "directedness of intentionality" as a fundamental aspect of thought and consciousness that distinguishes the mental from the physical.
1840 Establishment of postage in Great Britain.
1842 American surgeon Crawford Long develops ether as anesthetic. Birth of William James, American physician, psychologist, philosopher. His famous Principles of Psychology was published in 1820.
1843 John Stuart Mill's System of Logic is published.
1844 Birth of German philosopher Friedrich Nietzsche.
1847 English mathematician G. Boole develops a mathematical analysis of logic. Births of Thomas Edison and Alexander Graham Bell, American inventors.
1848 Marx and Engels issue *The Communist Manifesto*.
1850 Helmholtz establishes speed of nervous impulse.
1852 First use of the term "evolution" (by Herbert Spencer).
1854 Boole's mathematical theories of probability.
Pope Pius IX declares doctrine of the Immaculate Conception of the Virgin Mary.
1857 General Guiseppi Garibaldi begins unification of Italy.
French chemist Louis Pasteur shows that fermentation contains living organisms (bacteria).
1859 Darwin's *The Origin of Species by Means of Natural Selection* is published.
Birth of Edmund Husserl, German philosopher and founder of phenomenology. Attempts to reconcile the subjective/psychological nature of mental life with its objective/logical content.
Birth of John Dewey, American philosopher/psychologist (d. 1952), who carries forward the work of William James and Charles Peirce.
1860 Abraham Lincoln is elected US president.
Fechner's *Psychophysics* is published.
1862 Bismarck becomes prime minister in Prussia.
1865 Mendel announces his laws of heredity.
1866 Alfred Noble invents dynamite.
1867 Austro–Hungarian dual monarchy is created.
1868 Shogunate abolished in Japan; Meiji, the reign of the emperor, is restored.

## Chronology of Historical Events and Persons: 15th–20th Centuries *Continued*

1869 Parliamentarian system is reintroduced in France.
John Stuart Mill's *The Subjection of Women* and Francis Galton's *Hereditary Genius* are published.
1870 Franco–Prussian war erupts, ending the next year with France ceding Alsace-Lorraine to Germany.
*Kulturkampf* against the Catholic Church in Prussia; doctrine of papal infallibility is enunciated at First Vatican Council.
1871 Darwin's *The Descent of Man* is published.
1873 A republic is proclaimed in Spain.
Development of color photography.
Wundt's *Physiological Psychology* is published.
1874 Society for the Prevention of Cruelty to Children is founded in New York.
1876 Alexander Graham Bell invents the telephone.
1877 Thomas Edison invents the phonograph.
1878 Victor Emmanuel, king of united Italy, dies, succeeded by Humberto I. In Germany, historian Treitschke beings radical anti-Semitic movement.
1879 Birth of Albert Einstein.
1880 Electric lights invented by Thomas Edison and Joseph Swan.
1881 Pogroms unleashed in Russia; many Jews emigrate to Western Europe and United States.
1882 Joseph Breuer, Viennese physician, uses hypnosis to treat hysteria.
1883 Nietzsche's *Thus Spake Zarathustra* is published. Nietzsche describes a "will to power" as the prime moving force in human nature; failure to win power breeds resentment. The so-called *Übermensch* (the "Over-Man") escapes this resentment not by bullying (as the Nazis supposed, later on) but by mastering his passions and embellishing his character with creativity. Also skeptical about objective notions of truth or fact and the supremacy of reason, Nietzsche 's views were a forerunner of "postmodern" deconstruction preference for a large variety of interpretations of a text, etc.
1885 Karl Benz, German inventor, invents the motor car.
1886 Krafft-Ebing's *Psychopathia Sexualis* is published.
1888 "Jack the Ripper" murders six prostitutes in London; he is never identified or captured.
1890 Bismarck is dismissed by Wilhelm II of unified Germany.
1893 Henry Ford builds his first car.
Breuer and Freud's first paper on hysteria treated by psychoanalysis is published.
1894 Auguste Marie Louis Lumiére, French inventor, builds first cinematograph, precursor of movies.
John Dewey becomes chairman of University of Chicago department of philosophy and psychology. A pragmatist, he opposes the formal, rigid educational practices of his time, arguing that the child is an active, inquisitive creature, whose education must be fostered by experience, supplemented by knowledge and acquisition of skills. Enquiry is seen as a self-corrective process by Dewey.
1895 First wave of Turkish massacres of Armenians, culminating in mass murder of Armenians in 1915.
Discovery of X-rays by German physicist Wilhelm Roentgen.
Persecution of Oscar Wilde for his homosexuality.
1896 French physicist Alexandre Becquerel discovers radioactivity, followed by the Curie 's discovery of radium and polonium (1898).
1897 English psychologist Havelock Ellis' Studies in the *Psychology of Sex* is published.
1899 Freud's *Interpretation of Dreams* is published (though with publication date of 1900).

*20th Century*

1900 Death of Nietzsche.
Max Planck formulates quantum theory of physics in Germany.
1901 The "Edwardian Era" begins as Edward VII succeeds Victoria. Italian physicist Guglielmo Marconi transmits messages via radio.
1903 The Wright brothers invent and fly an airplane.
1904 Marie Curie's "Research on Radioactive Substances" is published.
The Russo–Japanese war erupts.
1905 First workers' soviet formed in St. Petersburg, partly in reaction to Russia 's loss in the war with Japan; sailors mutiny on the battleship Potemkin.
Albert Einstein formulates his "Special Theory of Relativity" and the photon theory of light.
Birth of Jean Paul Sartre, existential novelist and philospher. Opposing psychoanalysis, Sartre argues against determinism and the notion of unconscious motivation, and in favor of "free will." Only humankind, with its capacity for subjectivity, has the possibility of stepping outside the chain of causality and of exercising freedom of choice.

## Chronology of Historical Events and Persons: 15th–20th Centuries *Continued*

1907 William James' *Pragmatism* in published, built upon the work of Charles Pierce (1839–1914). James' treatise denies the possibility of absolute truth in an ever-changing universe, absolute moral standards must be replaced by a system of values, taking into consideration the vicissitudes of human experience.
Women are given suffrage in Austria.
1909 Freud and Jung lecture in the US at Clark University.
Women are admitted to German universities.
1911 Fall of the Manchu dynasty in China; a republic is proclaimed.
1912 The *Titanic* sinks on her maiden voyage.
Lenin takes over editorship of *Pravda*.
Scottish physicist Charles Wilson detects electrons and protons in cloud chamber.
1913 Birth of Albert Camus, existential novelist, who emphasizes the individual, the experience of choice, the inability to comprehend the universe, with a consequent sense of the "absurdity of life."
Publication of Edmund Husserl's *Phenomenology* and Karl Jaspers' *General Psychopathology*.
1914 Outbreak of World War I.
English philosopher/mathematician Bertrand Russell's *Our Knowledge of the External World* is published.
1915 Einstein postulates his "General Theory of Relativity."
Margaret Sanger is jailed for writing *Family Limitation*, the first book on birth control (the following year she opens the first birth control clinic).
1917 The Russian Revolution erupts; Lenin becomes chief commissar.
1918 Influenza pandemic.
1920 World population is recorded at 1.8 billion; USA, 105 million.
Rorschach develops inkblot test in psychology.
1921 Bertrand Russell's *Analysis of Mind* and Wittgenstein's *Tractatus Logico-Philosophicus* are published.
Death of Prince Peter Kropotkin, Russian philosopher, who asserted that humans are social creatures who flourish best in small communities; he disapproved of the centralized state with its use of coercion.
American biologist Thomas Hunt Morgan presents his chromosome theory of heredity.
1923 Martin Buber's *I and Thou* are published.
1924 Death of Lenin; Stalin assumes power in USSR.
Publication of German Protestant theologian Karl Barth's *The World of God and the World of Man* assert that we cannot attain knowledge of God via use of reason; unlike traditional Calvinists, he did not believe in the possibility of redemption for everyone.
1925 Scottish inventor John L. Baird transmits images via television.
Physicists Werner Heisenberg and Neils Bohr develop quantum mechanics at atomic level.
Tennessee forbids sex education in schools; also in Tennessee, John Scopes is narrowly acquitted for teaching evolution in a public school.
1926 *Hitlerjugend* founded in Germany.
Joseph Goebbels appointed by Hitler as *Gauleiter* in Berlin.
Leon Trotsky expelled from Moscow.
Hirohito becomes emperor in Japan.
1927 Russian physiologist Ivan Pavlov's *Conditional Reflexes* is published.
Publication of *Being and Time* by German existentialist philosopher Martin Heidegger, who urges return to "authentic communion with independent nature"; he equates "being" with people's consciousness of their place in the world (their *Dasein*). His image was ultimately sullied by his championing of Nazi Germany.
1928 Scottish bacteriologist Alexander Fleming discovers penicillin.
1929 World economic crisis ushered in by Wall Street stock market "crash" on October 28th.
1932 Hitler gaining power in Germany; Nazis achieve plurality in the *Reichstag*.
Publication of French philosopher Henri Bergson's *The Two Sources of Morality and Religion*. An evolutionist who was hostile to materialism, Bergson views evolution not in Darwinian terms as driven by natural selection, but as propelled by a "creative life force" (the *élan vital*). Modern developments in evolution and neuroscience have discredited his views.
Nobel prizes awarded to Edgar Adrian and Sir Charles Scott Sherrington for their work on neurons.
1933 Hitler becomes chancellor and soon consolidates supreme power in Germany; the first concentration camps are erected.
The era of the Great Depression in the US (lasting throughout the 1930s).
1934 Publication of US anthropologist Ruth Benedict's *Patterns of Culture* and Rudolf Carnap's *Logical Syntax of Language*.
1939 Outbreak of World War II; flight of many Jews, including a large number of psychoanalysts, to England and the US.

## Chronology of Historical Events and Persons: 15th–20th Centuries *Continued*

| | |
|---|---|
| 1942 | First automatic computer is constructed in the US. |
| | Publication of German philosopher Hans Reichenbach's *Philosophic Foundations of Quantum Mechanics*, emphasizing considerations of probability rather than reductionism. |
| 1943 | Publication of French philosopher and novelist Jean Paul Sartre's *Being and Nothingness*, focusing on the structure of consciousness and emphasizing the capacity for choice as the essential feature of human nature. By virtue of our consciousness and intentionality, we are responsible for our choices. |
| 1945 | World War II ends with the defeat of Germany in May and Japan in August—the latter following the atomic bombing of Hiroshima and Nagasaki, ushering in the Atomic Age; discovery of the death camps in Poland and the full extent of the Holocaust: 8–10 million killed, including 6 million Jews from all over Europe. |
| | Approximate beginning of steep rise in world population. |
| 1947 | Culmination of "nonviolent" movement in independence of India. |
| 1949 | Communist takeover in China under Mao Zedong. |
| 1950 | Publication of American anthropologist Margaret Mead's *Social Anthropology*. |
| 1951 | Death of Wittgenstein, whose logical-positivist position opposes scientific (especially Freudian) reductionism and the then more accepted theory of consciousness as a manifestation of atomic and evolutionary processes peculiar to organisms with highly developed nervous systems. |
| 1953 | Death of Stalin and his succession by Krushchev in USSR; coronation of Queen Elizabeth II in England. |
| | E. Aserinsky and N. Kleitman discover rapid eye movement sleep and its connection to the dream state. |
| 1956 | Publication of British philosopher Alfred Ayer's *The Problem of Knowledge*, whose *Language, Truth and Logic* appeared in 1936, combining empiricism and the focus on logic as espoused by Bertrand Russell. |
| 1957 | Death of John von Neumann, US mathematician (noted for his theory of games and decision-making), whose work led to construction of newer, more powerful computers. |
| 1960 | American scientists develop the laser. |
| 1960s | Beginning of dramatic increase in abuse of illicit drugs in the US and Western Europe. |
| 1961 | First US space flight. |
| 1962 | Nobel Prizes awarded to James Watson and Francis Crick for discovery of the molecular structure of DNA. |
| 1963 | Assassination of President John F. Kennedy. |
| 1964 | US enters the Vietnam war (lasts until 1975). |
| | Social theorist Herbert Marcuse's book *One Dimensional Man* becomes the Bible of radical students. |
| | Death of US mathematician Norbert Wiener, creator of the field of "cybernetics." |
| 1968 | Period of student rebellions in the US and Western Europe; rise of the feminist movement; violent crime increases more than 50% since 1960. |
| 1969 | First manned landing on the moon. |
| 1973 | Women's rights advanced by Supreme Court's *Ros v. Wade* decision to permit abortions. |
| 1974 | Church attendance down to 40% weekly in the US from about 65% a decade earlier. |
| | Nixon resigns presidency in wake of Watergate scandal. |
| 1978 | Death of Austrian mathematician Kurt Gödel, who proves that pure mathematical reductionism does not work; he also opposes the view espoused by Alan Turing that all thinking is "computational." |
| 1980 | Death of Swiss developmental psychologist Jean Piaget. |
| 1980s | Rise of Japan and the other Pacific Rim countries as economic powers and important contributors to science. |
| 1981 | Identification of the AIDS virus (the epidemic may have begun circa 1977). |
| mid-1980s | Significant progress in neuroscience in the areas of memory (Kandell, Miskin, Squires-Wheeler), computer modeling of neuronal activities (Edelman, Rumelhart, McClelland), mathematical/philosophical approaches to the question of "computability" of the mind (Penrose, Searle, Minsky, the Churchlands), neuroimaging (Andreasen, the Gurs, the Shaywitzs), the circuitry underlying obsessive–compulsive disorder (Insel, Baxter, Kellner, Rubin), the nature of consciousness (Dennett). |
| 1986 | The Chernobyl nuclear-plant disaster erupts near Kiev. |
| 1987 | Gorbachev introduces *glasnost* (openness) and *perestroika* (restructuring) into the Russian political scene; becomes president of the USSR the following year. |
| 1989 | Collapse of the Communist regime in the USSR; beginning of fractionation into independent states, with democratically elected chiefs. |

**Figure 14–10** *Chronology of historical events and persons: 15th–20th centuries. (Source: Courtesy of WW Norton & Company; excerpt from Healing the Mind—A History of Psychiatry from Antiquity to the Present by Michael H Stone, M.D. Copyright 1997 Michael H Stone, M.D., pp 439–450.)*

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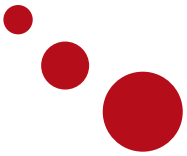
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SECTION III

Eric R. Kandel and H. Jonathan Polan, Section Editors

# *Neuroscientific Foundations of Psychiatry*

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CHAPTER

15

# Are there Biological Commonalities among Different Psychiatric Disorders?

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## Introduction

Psychiatric diagnosis is in a state of flux (Kupfer et al. 2002, Zachar and Kendler 2007). Recent editions of the standard manual of American psychiatric diagnosis, the *Diagnostic and Statistical Manual* (DSM), have espoused a neo-Kraeplinnean diagnostic framework, wherein disorders are divided into discrete, often mutually exclusive entities on the basis of their symptoms (American Psychiatric Association 1980, 1994). This theory-neutral framework has enhanced the precision of psychiatric diagnosis and thereby accelerated psychiatric research over the past 25 years. Recent data challenge this framework, however, by emphasizing common features among ostensibly discrete disorders.

The National Comorbidity Survey, which examined the epidemiology of psychiatric disease across the population, illustrates the challenges faced by the categorical diagnostic system laid out in DSM-III and DSM-IV-TR. A startling percentage of patients with one disorder were found to have one, two, or more additional diagnoses. Moreover, the number of diagnoses correlated highly with the severity of symptoms (Kessler et al. 1994). This may suggest that the sickest psychiatric patients have an underlying vulnerability or predisposition toward psychopathology, independent of the particular symptoms expressed and of the specific diagnosis they receive under our current system.

This picture of commonality among disorders more closely resembles the schema of Griesinger than that of Kraeplin. Griesinger proposed in the 19th century that there is a single protean psychiatric disorder (*Enheitpsychose*) whose expression in different patients is modulated by continuously variable traits. With the next edition of the DSM planned for 2010, an active debate is underway as to what form psychiatric nosology should take (Kupfer et al. 2002). One important perspective in this debate is that of the neurobiology of psychiatric disorders, which has been advancing at an accelerating rate. This conceptual debate—whether psychiatric disease is best conceptualized in terms of discrete entities or of overlapping continua—therefore motivates the central question of this chapter; namely, are there biological commonalities among different psychiatric disorders?

In this chapter, and by way of introduction to the more focused discussions that follow, we explore evidence for the thesis that disorders that we currently consider to be distinct entities often have overlapping or shared biological underpinnings. In the first section, we briefly explore the general relationship between brain and behavior, and thus between disorders of brain function and psychiatric disease. We then provide examples of epidemiological, clinical, neuropathological, and genetic evidence for biological commonalities among different disorders. Finally, we explore a cognitive neuroscience perspective on this question in more detail. In so doing, we discuss how an understanding of the normal functions of different brain circuits informs hypotheses about the consequences of their disruption in psychiatric disease, and therefore how dysregulation of the same brain circuits across different disorders can shed light on aspects of their overlapping symptomatology. Throughout, we focus largely on three major disorders—schizophrenia, major depressive disorder, and drug addiction—making reference to other conditions where appropriate. While this discussion only scratches the surface of the rich neurobiology of these structures and the larger networks in which they are embedded, it serves to illustrate the contributions of an advancing neurobiological knowledge-base to our understanding of psychiatric neurobiology, of diagnosis and, it is to be hoped, of treatment.

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## Diseases of the Mind and Diseases of the Brain

### Mind and Brain in Psychiatric Disease

Hippocrates first proposed a fundamental relationship between disordered behavior and disordered brain function. In the treatise on epilepsy entitled "On the Sacred Disease," Hippocrates decries those who would ascribe this behavioral malady to an extracorporeal cause: "They who first referred this malady to the gods appear to me to have been just such persons as the conjurors, purificators, mountebanks, and charlatans." Rather, he wrote that "the brain is the cause of this affliction, as it is of other very great disease" (Hippocrates 1952).

This correspondence has not always seemed obvious. Descartes' substance dualism formalized the intuitive divide between functions of the body and functions of the mind, a division that continues to color Western thinking about brain and behavior. A dualist perspective persisted in formal psychiatric diagnosis into the latter part of the 20th century in the form of the organic/nonorganic distinction that was present in DSM-III (American Psychiatric Association 1980, Spitzer et al. 1989). Indeed, research into psychiatrists' diagnostic practices and assignment of personal responsibility for symptoms of psychiatric disease reveals persistent dualist tendencies to this day (Miresco and Kirmayer 2006). However, the organic/nonorganic distinction was abandoned with DSM-IV in 1994 (American Psychiatric Association 1994), and by the end of the 20th century the equation of behavioral disorders with pathological brain states had become a fundamental tenet of psychiatry (Kandel 1998, Kendler 2005).

The simple statement that psychiatric disorders are brain disorders masks enormous complexity. Clear, unitary, causes of symptoms are rare in psychiatry. One example is found in the once common affliction known as *general paresis of the insane*. This condition, which was enormously common in the 19$^{th}$ and early 20th century, was a dreaded combination of psychosis, progressive dementia, and paralysis. In 1913 Noguchi and Moore discovered that general paresis results from tertiary syphilis, or chronic infection of the brain by the spirochete *Treponema pallidum*. When penicillin was found to kill the spirochete, general paresis became not only treatable but completely preventable if syphilis was treated early. This became a powerful paradigm of simple causation: a psychiatric entity, characterized by dramatic abnormalities in behavior and cognition, which was found to have a specifiable, straightforward biological cause, permitting a definitive new treatment.

Such single necessary and sufficient etiologic agents are, however, the exception in psychiatry. More often, multiple causal factors, each with a small effect, act in concert to produce disease. Moreover, the effects of causal factors may be described at multiple levels of scientific investigation. For example, in the case of major depressive disorder—an example to which we will return throughout this chapter—alterations have been reported in many different neurobiological processes. Genetic loci with a role in the vulnerability to major depression include regulators of monoaminergic neurotransmission as well as neurotrophic factors (Levinson 2006). Antidepressant drugs primarily act on the serotonergic and noradrenergic systems, but some antidepressant drugs also interact with receptors for the neuropeptides corticotropin-releasing factor and substance P, glucocorticoids, the NMDA glutamate receptor, and cholinergic receptors (Holtzheimer and Nemeroff 2006). Functional and structural imaging has implicated dysfunction in dorsolateral prefrontal cortex, orbitofrontal cortex, cingulate cortex, and hippocampus. Postmortem studies indicate alterations in the number of glia in multiple brain regions as well as changes in neuronal density and the size of neuronal cell bodies (Rajkowska 2003) and a reduction in subpopulations of interneurons (Rajkowska et al. 2007). The etiology and biology of a disorder in which so many diverse genetic mechanisms, neurochemical systems, brain regions, and cellular abnormalities have been implicated are likely to be complex and multifactorial. The daunting complexity of psychiatric disorders therefore raises this question: how may one meaningfully investigate biological commonalities between disorders?

### Endophenotypes in Psychiatry

One fruitful way to come to terms with this complexity is through the analysis of *endophenotypes*. An endophenotype is a measurable neurobiological or psychological parameter that meaningfully contributes to an aspect of a psychiatric disorder but is simpler, less heterogeneous, and more closely tied to measurable aspects of the underlying biology. The study of working memory as an endophenotype, for example, has contributed greatly to an understanding of cognitive dysfunction in schizophrenia—an example that will be explored in greater detail later in this chapter. Endophenotypes may also be shared across overtly distinct disorders, as illustrated by the presence of working memory impairments in schizophrenia, major depression and attention-deficit hyperactivity disorder (ADHD). Investigations focusing on endophenotypes may therefore help bridge the explanatory gap between ultimate etiologic causes, such as genetic or environmental variables, and resulting psychiatric phenomenology (Gottesman and Gould 2003) and thereby provide a handle on biological commonalities.

In the latter portion of this chapter, we explore psychiatric endophenotypes from a cognitive neuroscience perspective. The premise for our arguments is that certain discrete psychological functions are mediated through consistent, definable neural circuitry. Deficits in these psychological functions (i.e., endophenotypes) are therefore likely to be associated with abnormalities in the associated neural circuits. Furthermore, the presence of similar endophenotypes in otherwise disparate disorders predicts that related alterations may be observable in the same neural circuitry. This approach to understanding different psychiatric disorders provides a powerful framework in which to conceptualize mental illness; namely, as a set of conditions that come about due to different combinations of endophenotypes. Therefore, a larger category of illness, such as schizophrenia or depression, may be better "carved at its joints" along endophenotypic lines.

## Specific Biological Commonalities Among Disorders

As mentioned earlier, evidence for shared biological perturbations across different psychiatric disorders can be sought in many domains. Before exploring a cognitive neuroscience perspective, we first briefly describe other ways in which

different psychiatric disorders can be seen to have overlapping biological underpinnings.

## Genetic Commonalities

Specific alleles of certain genes have been associated with multiple psychiatric disorders. For example, a polymorphism in the promoter region of the serotonin reuptake transporter (SERT) gene, which influences the efficiency of removal of serotonin from synapses, has been associated with numerous psychiatric disorders, including depression, psychosomatic disorders, alcoholism, smoking, eating disorders, ADHD, and autism (reviewed in Serretti et al. 2006). Similarly, polymorphisms in the dopamine beta hydroxylase (DBH) gene, whose product is the last step in the synthesis of norepinephrine from dopamine, have been associated with schizophrenia, cocaine-induced paranoia, depression, ADHD, and alcoholism (reviewed in Cubells and Zabetian 2004). The association of the same genetic polymorphism with several different disorders directly suggests shared neurobiological underpinnings.

Possession of a disease-associated gene variant, however, rarely guarantees development of disease. Rather, the risk of developing disease often derives from interaction of genetic contributors with environmental factors (e.g., Caspi et al. 2003). This fact further complicates an understanding of shared mechanisms across psychiatric disorders, leading to complex causal webs (e.g., Kendler et al. 2002, 2006).

## Environmental Etiologies

Important nongenetic etiological factors can also contribute to different psychiatric conditions. For example, childhood stress, including abuse and parental loss, is an important etiological contributor to major depression (e.g., Kendler et al. 2002, 2006), posttraumatic stress disorder (PTSD) (e.g., Pine and Cohen 2002), and borderline personality disorder (e.g., Lieb et al. 2004). This overlap suggests that the neurobiological consequences of childhood stress may be relevant to all of these disorders. Numerous other examples of etiological factors shared among discrete psychiatric disorders can be found in this textbook, and others will doubtless come to light as our understanding of the etiology of neuropsychiatric disease grows.

## Neurochemical Commonalities

Disruptions in defined neurochemical systems can contribute to a variety of psychiatric disorders. For example, dysregulation of dopaminergic neurotransmission is found in schizophrenia, affective disorders, and substance abuse (e.g., Mann 2003, Frankle et al. 2005). Disruption of noradrenergic neurotransmission is implicated in anxiety disorders, affective disorders, suicide, substance abuse, and PTSD (e.g., Mann 2003). Serotonin dysregulation has been linked to affective disorders, anxiety, PTSD, and many other conditions (e.g., Mann 2003). Dysregulation of glutamatergic neurotransmission has been linked to depression (e.g., Kugaya and Sanacora 2005, Pittenger et al. 2007), obsessive—compulsive disorder (OCD) (Pittenger et al. 2006a), anxiety disorders (e.g., Simon and Gorman 2006), and drug addiction (Kalivas et al. 2005). The fact that dysregulation of these neurochemical systems can contribute to so many different psychiatric disorders points yet again to shared neurobiological substrates.

## Histopathological Similarities

The characterization of histopathological abnormalities in psychiatric disorders is still in its infancy. Gross anatomical abnormalities suggestive of underlying cellular change, such as enlarged ventricles and widened sulci in dementia and schizophrenia, have been well characterized for some time (e.g., Steen et al. 2006), but documentation of more specific pathological changes in the brains of individuals with major psychiatric disorders has been harder to come by. Nonetheless, it is becoming clear that here, too, overlapping histopathological changes can correspond to different neuropsychiatric disorders. For example, reduced numbers of glial cells in regions of cortex have been described in major depression (Rajkowska et al. 1999), bipolar disorder (Rajkowska et al. 2002), alcohol dependence (Miguel-Hidalgo et al. 2002), and schizophrenia (Rajkowska et al. 2002). Functional or structural disruption of GABAergic interneurons has been described in schizophrenia (Lewis et al. 2005), major depression (Rajkowska et al. 2007), and Tourette syndrome (Kalanithi et al. 2005).

## Gross Anatomical Changes

The involvement of the same neuroanatomical structures can point the way to overlapping biology between disorders. Structural imaging studies have revealed several such examples. For example, reduced hippocampal size has been observed in depression, PTSD, Alzheimer's dementia, and schizophrenia (e.g., Sapolsky 2000, Gilbertson et al. 2002, Steen et al. 2006).

# Beyond Gross Anatomical Similarities: Functional Circuitry in Psychiatric Disease

Mental functioning derives from the operation of large groups of neurons, organized into nuclei, brain regions, and neural circuits. Understanding brain function in terms of functional neural circuitry is the domain of cognitive neuroscience, an approach enabled in part by advances in functional neuroimaging over the past few decades. A cognitive neuroscience perspective allows for integration across other levels of analysis, reflecting the functional consequences of genetic, neurochemical, histopathological and gross anatomical alterations in more psychologically meaningful terms.

The hippocampus provides a useful introductory example (Figure 15–1). As noted above, reduced hippocampal size and other pathological changes have been noted in several neuropsychiatric diseases, including major depression, PTSD, and some forms of dementia. Functional characterization of the hippocampus, in human neuroimaging studies, lesion studies, and animal models, reveals that it contributes critically to the formation of memories for both facts and events (e.g., Scoville and Milner 1957, Tulving 2002, Squire et al. 2004). It would be predicted, then, that memory may be impaired in those disorders in which disruption of hippocampal function has been described. And, indeed, declarative memory is impaired—most obviously in dementias such as Alzheimer's disease, but also in major depression and PTSD (Sapolsky 2000). The hippocampus also has an important role in the regulation of the stress response, as orchestrated in part by the hypothalamus-pituitary—adrenal (HPA) axis. And indeed, HPA axis regulation and the stress response are dysregulated in major depression, PTSD, and some

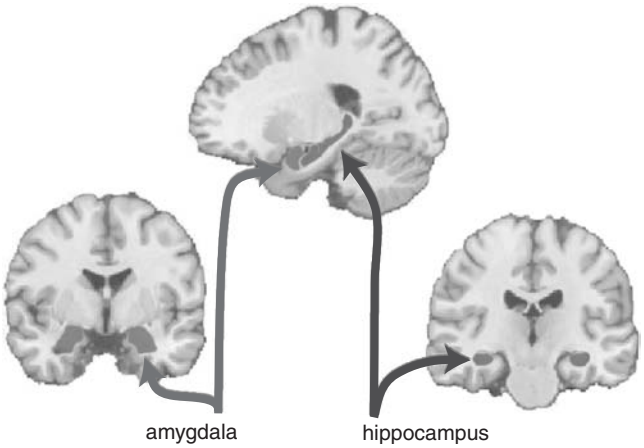



**Figure 15–1** *Location and relationship of the human hippocampus and amygdala. As described in the text, the hippocampus has an important role in memory formation and stress modulation. Hippocampal dysfunction is implicated in numerous psychiatric disorders, including major depressive disorder, PTSD, schizophrenia, and dementia. The amygdala, which we do not treat in detail in this chapter but which is discussed at length elsewhere in this textbook, is involved in both negative and positive emotion, and is implicated clinically in mood and anxiety disorders. (See Color Plate I)*

dementias (McEwen 2004). Hippocampal dysfunction represents an endophenotype of multiple disorders.

This neural circuitry perspective on the question posed in this chapter—whether disparate psychiatric disorders have shared neurobiological underpinnings—has particular advantages, beyond its cogency in individual cases, that motivate its further exploration. First, by its nature it is of heuristic value in understanding the relationships between specific brain functions and the phenomenology of psychiatric disease. Second, it motivates the study of brain biology by psychiatric clinicians. Third, it represents a fruitful guide to future research: when seeking neurobiological data on a poorly understood psychiatric disorder, it is useful to examine brain areas whose normal function is known to correspond to domains in which the disorder's symptomatology is expressed.

Finally, examination of circuits that are perturbed in different psychiatric disorders is likely to inform the rational categorization of psychiatric disease, and is therefore likely to contribute to the ongoing debate as to what form DSM-V nosology should take. This is true for either a categorical or dimensional conception of psychiatric disease. If two conditions are shown to correspond to qualitatively different functional perturbations of a defined brain circuit, with minimal overlap, then different categorical diagnoses may be appropriate—even if the conditions are phenomenologically similar. Such a discovery might help differentiate a complex syndrome, such as major depression, into meaningfully different subtypes. Conversely, if two conditions are found to be characterized by qualitatively similar perturbations of a particular underlying brain circuit, they might best be conceptualized as lying along a continuum—even if they present quite differently at the clinical level. This might be the case, for example, in psychotic depression, psychotic mania, and schizophrenia, which could contribute to a dimensional categorization of psychosis that transcends our current diagnostic system.

We spend the remainder of this chapter exploring this perspective on the shared biology of distinct psychiatric diseases. We focus on four particular circuits: the ventral striatum, the dorsal striatum, the anterior cingulate cortex, and the dorsolateral prefrontal cortex. While this treatment cannot be exhaustive, it demonstrates the utility of a cognitive neuroscience perspective and exhibits how commonalities between disorders at the level of brain circuitry can reveal relationships that may inform psychiatric diagnosis in the future.

## The Ventral Striatum and Mechanisms of Reward

As Freud famously emphasized, many of our actions are driven, directly or indirectly, by the quest for reward—food, sex, power, affiliation, acclaim. Investigation of the neurobiology of reward has revealed a central role for the ventral striatum, especially the nucleus accumbens, and related structures such as the orbitofrontal cortex and ventral tegmental area (VTA) in reward-driven behavior and reinforcement learning.

The striatum can be divided into at least two functionally distinct regions, the dorsal striatum (the caudate and putamen) and the ventral striatum (Figure 15–2; Haber 2005). The ventral striatum receives input from the orbital and medial frontal cortex, the hippocampus, the amygdala, and the thalamus. It also receives a prominent dopaminergic projection from the VTA, which has profound effects on motivational processing.

The cells of the VTA fire spikes, leading to phasic dopamine release in the nucleus accumbens, when an animal encounters an unexpected reinforcer—precisely the circumstances under which reinforced learning occurs (Schultz 2006). All addictive drugs also result in dopamine release in the nucleus accumbens (Wise and Rompre 1989, Hyman et al. 2006). Perturbations of the nucleus accumbens in experimental animals alter motivated behavior in response

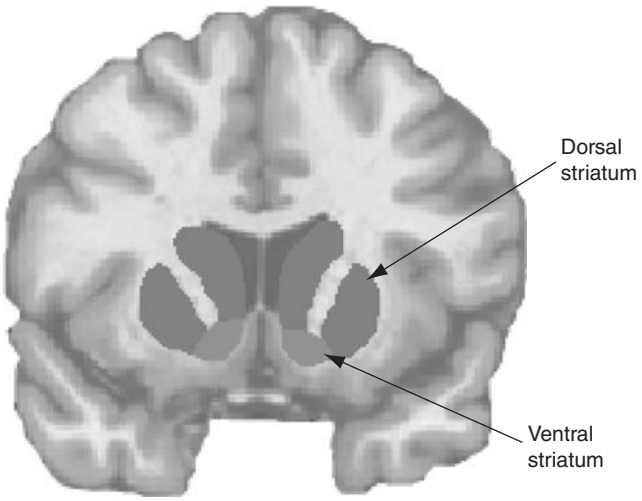



**Figure 15–2** *Anatomy of the human dorsal and ventral striatum, which are major input nuclei of the basal ganglia. As described in the text, the ventral striatum is implicated in reward and reinforced learning; dysregulation of ventral striatal function is implicated in addiction, schizophrenia, depression, and other disorders. The dorsal striatum functions both in motor control and in the acquisition and performance of automated learned behaviors, including habits; its dysfunction is implicated in OCD, drug addiction, and other disorders. (See Color Plate I)*

to drugs of abuse (e.g., Carlezon et al. 1998) and to naturally occurring reinforcers, including sex (e.g., Barrot et al. 2005), food (Georgescu et al. 2005), and emotional stimuli (Barrot et al. 2002). Similarly, the human ventral striatum, together with its orbitofrontal afferents, is central to the processing of reward expectation and response (McClure et al. 2004, Phan et al. 2002, Kringelbach 2005).

## Dysregulation of Reward in Disorders of the Ventral Striatum

### Drug Addiction

Dopamine release in the nucleus accumbens correlates with the "high" associated with consumption of drugs of abuse. Increased dopamine release in the orbitofrontal cortex, which projects to the accumbens, correlates with drug craving—the motivation to engage in behaviors aimed at procuring more of the abused substance (Volkow et al. 1997). In experimental animals, triggering of drug seeking by stress, drug-associated cues, or drug administration depends on activation of the accumbens by a glutamatergic projection from the prefrontal cortex (e.g., McFarland et al. 2003). Modulation of this circuitry is therefore likely to be important in future therapeutic strategies aimed at reducing relapse into drug use (reviewed by Kalivas and Volkow 2005).

Human and animal studies have demonstrated pathological changes in this prefrontal-accumbens circuitry after extended drug use. In cocaine users, dopamine release is attenuated in the ventral striatum, suggesting a compensatory response to chronic overstimulation (Volkow et al. 1997). Basal prefrontal metabolic activity is also reduced in drug addicts (reviewed in Kalivas and Volkow 2005). In animals, there are a variety of changes in the glutamatergic projection from the prefrontal cortex to the ventral striatum after chronic cocaine exposure (reviewed in Kalivas et al. 2005). Experimental manipulations in the nucleus accumbens can, in turn, alter animals' behavioral responses to cocaine and other drugs of abuse (e.g., Carlezon et al. 1998). The chronic functional alterations in the reward-regulating circuitry correspond to the profound dysregulation of reward that is one of the core features of the addicted state.

### Mood Disorders

Depression and mania are characterized by opposite abnormalities of motivation and reward. Anhedonia, the blunting of motivation and pleasure, is one of the cardinal symptoms of major depression. Several functional neuroimaging studies have suggested that hypometabolism of the ventral striatum may underlie these symptoms (Dunn et al. 2002). For example, in depressed subjects Epstein et al. (2006) found reduced ventral striatal activation to positively valenced words; this reduction correlated with the intensity of their anhedonia. Studies in animal models of depression likewise implicate ventral striatal function in aspects of a depression-like state (Nestler and Carlezon 2006). Convergent evidence, therefore, implicates dysfunction of the ventral striatum in the anhedonia of depression. This circuit-level understanding of the etiology of anhedonia has recently received a dramatic application and test, when Schlaepfer et al. used direct stimulation of the nucleus accumbens as a treatment for profoundly refractory major depression, with promising initial results (Schlaepfer et al. 2007).

Manic patients display the inverse of anhedonia (Hasler et al. 2006), such that reward-driven behaviors are heightened. Typically, manic patients are driven to pursue the most immediate and potent rewards, namely food, sex, social attention, money, and drugs of abuse. The role of the ventral striatal reward circuitry in bipolar disorder is poorly understood. However, structural and functional imaging studies of bipolar disorder indicate dysfunction in a circuit that includes the ventral striatum (reviewed in Blumberg et al. 2004, Strakowski et al. 2005). For example, reduced gray matter in both ventral striatum and the anterior cingulate cortex have been shown to be associated with genetic risk for bipolar disorder (McDonald et al. 2004). It is plausible that the hyperhedonic state of mania correlates with dysregulated overactivity of the ventral striatum and associated structures involved in reward and reinforcement—the opposite of the effect seen in major depression.

### Schizophrenia

Anhedonia is also a cardinal symptom of schizophrenia. Indeed, this negative symptomatology is often more chronic and more disabling than the more colorful, episodic positive symptoms of psychosis. Perturbation of ventral striatal function may contribute to this aspect of schizophrenia. All effective antipsychotics are antagonists at the D2 subclass of dopamine receptors (reviewed in Kapur et al. 2006), which are prominent throughout the striatum. The ventral striatum of schizophrenics shows a blunted response to rewarding stimuli, which correlates with negative symptoms (Juckel et al. 2006) and appears analogous to anhedonia in major depression (e.g., Epstein et al. 2006). The blunting of ventral striatal reactivity in both schizophrenia and major depression suggests important overlap between the underlying neurobiology of these syndromes.

## The Dorsal Striatum and the Automation of the Routine

Many everyday actions have an automatic character. When driving a new road, attention is fully engaged. We respond flexibly to events and cues; we note associations between them and form explicit memories of the process. This contrasts with the experience of driving an overlearned route, like a daily commute. When driving such a route, it is a common experience to suddenly find oneself at one's destination, having performed a complex series of behaviors without engaging much attention or forming any explicit memories at all. This automation of the routine is adaptive in that it frees attentional resources for other tasks, but it comes at a cost in behavioral flexibility. When engaged in a habitual pattern of responses, effort is required to deviate from the familiar pattern, as when one drives "on autopilot" to a familiar destination even when today's goal differs from the norm.

Several lines of evidence implicate a circuit including the dorsal portion of the striatum—the caudate nucleus and putamen—in the automation of routine, overlearned behaviors (Mishkin and Petri 1984, Packard and Knowlton 2002, Yin and Knowlton 2006). The caudate and putamen, which regulate multiple aspects of behavior including motor patterning, oculomotor control, and habit learning, receive projections from virtually the entire neocortex and several subnuclei of the thalamus, along with modulatory input from hippocampus and other structures. They, in

turn, project to other, deeper nuclei of the basal ganglia and, ultimately, back to neocortex via the thalamus (Haber 2005).

Neuroimaging implicates the human caudate in overlearned, automated behaviors. For example, following an overlearned route in virtual reality engages the caudate nucleus, while navigating a novel route engages the dorsal hippocampus (Hartley et al. 2003). The caudate is also engaged by nonspatial "probabilistic classification learning," a form of subconscious, or implicit, pattern recognition (Knowlton et al. 1996, Poldrack et al. 1999). Dorsal striatal function has also been implicated in implicit sequence-learning (e.g., Rauch et al. 1997) and certain motor-learning tasks (e.g., Gabrieli et al. 1997). Studies in rodents similarly support a role for the dorsal striatum in habit and related forms of procedural learning (e.g., Packard and McGaugh 1996, and Knowlton 2006, Pittenger et al. 2006b). Indeed, the pattern of striatal neuronal firing has been shown to shift during the learning of a striatum-dependent cue-driven simple navigation task (Jog et al. 1999).

## Maladaptive Habits in Disorders of the Dorsal Striatum

### Obsessive–Compulsive Disorder (OCD)

OCD is characterized by intrusive, anxiety-provoking, irrational thoughts, and compulsive behaviors that attempt to relieve the anxiety that attends them. The stereotyped and automatic character of these thoughts has the appearance of a habitual cognition gone awry, suggesting that dysregulation of the dorsal striatum might contribute to the underlying neurobiology of OCD. Indeed, a circuit consisting of the orbitofrontal cortex, the striatum, and the thalamus has consistently been shown to be hyperactive in patients with OCD, and this pathological activation is moderated in parallel with symptom improvement after treatment with either psychotherapy or pharmacotherapy (reviewed in Jenike 2004). Learning of a striatum-dependent implicit sequence-learning task (Deckersbach et al. 2002) and of an implicit card-learning task (Joel et al. 2005) are disrupted in OCD, suggesting that the function of the striatum in learning new automated behaviors are disrupted by this circuit-level dysregulation. Further work will be needed to investigate whether this disruption contributes to the rigid habit-like structure of some OCD symptomatology.

### Drug Addiction

Drug seeking is often initially motivated by the desire for pleasure or reward, and then at times by attempts to minimize the dysphoria of craving and withdrawal; as noted above, the ventral striatum and related circuitry play a major role in these phenomena. Later, with the development of true addiction, compulsive, habit-like behaviors develop—drug-associated behaviors that are executed automatically. These drug-associated behaviors, which are likely to derive from a subversion of the mechanisms of normal stimulus-response habit learning, are a particularly pernicious aspect of addiction, as they occur without conscious control and are resistant to extinction (Tiffany 1990, Robbins and Everitt 1999, Everitt and Robbins 2005). Automated drug-associated behaviors are likely to represent an important target in the development of novel treatments for addiction.

These observations predict dysregulation of the dorsal striatum in addicted states. Indeed, observations in animal models link compulsive drug-seeking behaviors to the dorsal striatum (Vanderschuren and Everitt 2004, Vanderschuren et al. 2005). In humans, cocaine dependence is associated with increased volume of the dorsal striatum (Jacobsen et al. 2001). Moreover, the dorsal striatum may have a particularly important role in drug seeking after abstinence in animals (Fuchs et al. 2006) and humans (Sinha et al. 2005).

The association of perturbed dorsal striatal function with maladaptive, habit-like behaviors in OCD and drug addiction suggests an important role for the habit-forming circuitry of the dorsal striatum in these and related forms of psychopathology. This points to a commonality between disorders that are widely separated in our current diagnostic system, and may point the way to the development of new therapies specifically aimed at the mechanisms of habit formation.

## Prefrontal Cortex: Attention and Behavioral Flexibility

The capacity for creative, context-responsive flexibility in behavioral responses—termed "top-down" cognitive control or executive functioning—is a function of the frontal lobes. The prefrontal cortex (PFC) is typically not required for the learning or performance of simple tasks. But when task demands change, the PFC is required for proper adjustments in behavior to maintain accuracy. This role for the PFC in cognitive control is seen in humans (Milner 1963), nonhuman primates (Dias et al. 1996), and even in rodents (Birrell and Brown 2000). More broadly, the PFC is responsible for maintaining an internal representation of current goals and modulating activity in brain regions responsible for perception or action in order to flexibly achieve these goals. In order to accomplish this, the PFC must be able to (1) maintain a representation of goals in the face of distraction (working memory), (2) update these representations as new information is received, through multiple sensory modalities, and (3) provide a feedback signal that can select the neural pathways appropriate for the current task context (Miller and Cohen 2001).

In humans, frontal cortical cognitive control mechanisms have been probed using a variety of behavioral tasks. Cognitive control tasks of various sorts recruit a consistent prefrontal network, which includes the dorsolateral PFC (DLPFC) (Duncan and Owen 2000) (see Figure 15–3). In the classic color-word Stroop task (Stroop 1935), for example, subjects have to name the ink color of a word whose meaning is either congruent (e.g., GREEN printed in green ink) or incongruent with the ink color (e.g., GREEN printed in red ink). Naming the ink color in an incongruent trial requires subjects to ignore word meaning. The conflict between the ink color and the incongruent word meaning slows reaction times and increases errors, a phenomenon known as the Stroop effect.

When subjects experience conflict on an incongruent Stroop trial, however, they also reflexively prepare for a subsequent incongruent trial. Consequently, reaction time becomes faster on the second of two consecutive incongruent trials. This anticipatory adjustment in cognitive control for the purpose of performance improvement has been linked to activation of the DLPFC (Kerns et al. 2004).

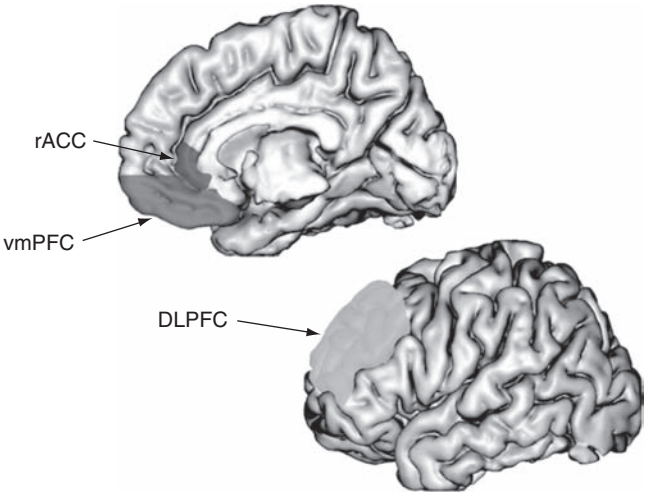



**Figure 15–3** *Neuroanatomy of the frontal cortical structures described in the text. The rostral anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC) have roles in emotion regulation, especially in the absence of an explicit attempt to regulate emotional processing. The dorsolateral prefrontal cortex (DLPFC) is critical for working memory and executive function and for deliberate forms of emotion regulation. As described in the text, functional perturbation of these structures and of their functional interrelationships is implicated in numerous psychiatric disorders, including schizophrenia, PTSD, and depression. (See Color Plate II)*

Consistent with this, subjects with frontal lobe lesions have difficulty dealing with color-word conflict and make more errors in the Stroop task (Vendrell et al. 1995). The DLPFC achieves this top-down cognitive control in part by enhancing the sensory representation of an object at the focus of attention (Egner and Hirsch 2005).

The capacity for increasing cognitive control to meet task demands, however, is not unlimited. This is illustrated by the *n*-back task, in which subjects must decide on each trial whether the current stimulus matches the one shown 1, 2, or 3 trials back. Doing so requires the sequential updating of working memory content, and maintenance of task goals in the face of increased working memory load. Frontal lobe lesions lead to more errors at greater working memory loads in this task (Muller et al. 2002). Activity in the DLPFC increases as task demands increase through the 0-, 1- and 2-back conditions (Callicott et al. 1999). As subjects' working memory capacities are exceeded at the more difficult 3-back condition, however, both subjects' performance and dorsolateral prefrontal activity decline relative to the 2-back condition.

## Attentional Deficits in Disorders of the Prefrontal Cortex

### Schizophrenia

Psychosis often dominates the initial presentation of schizophrenia. However, negative symptoms and cognitive dysfunction, including impairments in executive function and working memory, are more chronic, better predict poor outcome, and are not substantially helped by available pharmacotherapies (Harvey et al. 2004). Patients with schizophrenia typically perform worse than control subjects in many neuropsychological tests of frontal lobe function, and this deficit has been linked to greater disorganization of thought and speech (Kerns and Berenbaum 2002). It is of great interest, therefore, to examine prefrontal cortical function in schizophrenics during tasks that require elements of the cognitive control processes discussed above.

Neuroimaging studies of working memory have indeed found abnormal activation of DLPFC in these patients, but of inconsistent direction: while some studies have found hypoactivation in schizophrenics, others have found hyperactivation. This seeming inconsistency in the data led to debate about the nature of the neuropsychologically suggested "hypofrontality" of patients with schizophrenia.

A solution to this debate arose from the finding that activity in the DLPFC of healthy subjects decreases from its peak as working memory is stressed beyond its maximal capacity (Callicott et al. 1999). If the DLPFC of schizophrenic patients operates less efficiently than that of controls, patients may be found to hyperactivate this region as they strain to keep up with low working memory loads that control subjects can easily handle, and hypoactivate this region at higher working memory loads that exceed patients' working memory capacity, but not that of controls (Callicott et al. 2003b). In other words, whether relative hyper- or hypofrontality is found in imaging studies depends on the presence of performance differences between patients and controls. Unaffected siblings of schizophrenics, who carry some of the genetic load for the disease, were found to hyperactivate the DLPFC relative to performance-matched controls in a working memory task, consistent with reduced processing efficiency in this region (Callicott et al. 2003a).

### Depression

Patients with major depression also often display neurocognitive deficits consistent with frontal lobe dysfunction, though the deficits are generally not as severe as those seen in schizophrenia (reviewed in Rogers et al. 2004). Imaging studies of resting blood flow or metabolism have supported the view that cognitive control circuitry is perturbed in depression. A number of studies have noted DLPFC hypometabolism in depressed patients (Drevets 1999). These findings support an influential theory of depression, which suggests that hypofunction of the DLPFC and related prefrontal regions accounts for the cognitive symptoms of depression—problems with attention, concentration, and memory (Mayberg 2003). The relationship between these abnormalities and the central mood and motivational symptoms of depression, however, remains unclear.

Neuroimaging studies of activation during cognitive control tasks such as those discussed above have further suggested inefficiency of DLPFC activity in depressed patients. This is true both for the Stroop task (Wagner et al. 2006) and the *n*-back task (Harvey et al. 2005). These studies, however, suggest that while the DLPFC is inefficient in major depression, its capacity for increasing its activity to match task demands is not as easily overwhelmed as that of the DLPFC of schizophrenics.

## Prefrontal Cortex: "Deliberate" Versus "Implicit" Emotion Regulation Strategies

We are constantly exposed to a larger number of sensory stimuli than our sensory and cognitive resources can process. Representations of individual stimuli therefore compete

for attentional selection to determine which will be further processed, encoded in memory, or used for preparation for action; this is known as the biased competition model of attention. Emotionally salient stimuli are widely believed to have a special advantage in this competition, as evaluation of an emotional stimulus may be critical for predicting threat or reward. Because emotional stimuli nonetheless must compete for further processing, regulation of the effects of emotional stimuli is thought to occur through the same cognitive control process that selects between competing nonemotional stimulus representations.

Gross (2002) has proposed a framework for classifying different emotion regulation strategies. One important distinction is between "antecedent-focused" strategies, which aim to alter emotional responses before they begin, and "response-focused" strategies, which suppress emotional responses after they have been initiated. Antecedent-focused strategies include willful detachment, distraction, and cognitive reappraisal; response-focused strategies include voluntary suppression of positive or negative emotional reactions. Unstated within this framework is that an emotion regulation strategy may be "deliberate," requiring conscious top-down intentionality, or "implicit," engaging top-down regulation of emotional processes without requiring conscious intentionality.

Several recent neuroimaging studies of the neural circuitry associated with deliberate efforts at emotion regulation (Beauregard et al. 2001, Kalisch et al. 2005, Kalisch et al. 2006, Levesque et al. 2003, Ochsner et al. 2004) find that deliberate emotion regulation involves the DLPFC, which is associated with top-down cognitive control, regardless of whether an antecedent-focused or a response-focused strategy is being employed. This view of emotion regulation, moreover, suggests that in any disorder in which the DLPFC is dysfunctional, such as in schizophrenia and depression, one might expect deficits in deliberative forms of emotional regulation. Difficulty regulating emotion in this manner would be a specific instance of a more general cognitive control deficit.

A different picture emerges when one considers implicit forms of emotion regulation. Implicit emotion regulation is based on an individual's expectation or anticipation of emotional stimuli, but without the explicit goal of emotion regulation, and appears to be mediated by top-down regulation of limbic structures by the rostral (pregenual) portion of the anterior cingulate cortex (rACC) and adjacent ventromedial PFC (vmPFC) (see Figure 15–3). These regions have direct projections to regions involved in emotion, such as the amygdala and brain stem. Studies in the likely rodent homologs of these areas also suggest that these projections are inhibitory in nature (Quirk et al. 2003). Importantly, abnormalities in circuitry mediating implicit emotional regulation can be seen in emotional dysregulation disorders in which no dorsolateral prefrontal deficits are observed (Etkin and Wager 2007).

To frame implicit emotional regulation more clearly in the experimental methods employed by the cognitive control literature, Etkin et al. (2006) recently developed an emotional analog to the color-word Stroop task. They showed subjects images of fearful or happy facial expressions and asked them to identify the affect. Written across the faces were the words "fear" or "happy," which were either of the same affect (congruent) or of a different affect (incongruent) as the facial expression. As in the color-word Stroop task, subjects were to ignore the text but were unable to avoid involuntarily reading the word and extracting its meaning. The emotional meaning of the words thus led to direct conflict with interpretation of the facial affect. As a result, incongruent stimuli interfered with affect identification in all subjects.

Resolution of emotional conflict in this task activated the rACC, rather than the DLPFC. Rostral anterior cingulate activation was accompanied by a simultaneous and correlated reduction in amygdala activity. These results are consistent with a recent study of the extinction of conditioned fear responses, in which subjects evaluate and override expectations for aversive stimuli. Fear extinction involved increased activity in the rACC and vmPFC and decreased activity in the amygdala (Phelps et al. 2004). Likewise, rostral anterior cingulate activation has also been observed during placebo anxiety reduction, a process in which control over an emotional stimulus (an aversive picture) is recruited to diminish the effect of the emotional stimulus (Petrovic et al. 2005).

## Dysfunctional Emotion Regulation in Disorders of the Prefrontal Cortex

### Posttraumatic Stress Disorder (PTSD)

PTSD is characterized by prominent emotional dysregulation. Patients experience disproportionate arousal—often to stimuli processed outside of conscious awareness—and have exaggerated startle responses, vivid intrusive thoughts, and unbidden images in the form of flashbacks and nightmares related to past trauma (Ehlers and Clark 2000). Patients may go to great lengths to avoid physical or psychological trauma reminders, and may experience dissociative symptoms or emotional numbing. It has been suggested that PTSD is a disorder of excessive conditioned fear, triggered by a severe and often discrete traumatic event (Ehlers and Clark 2000). This view, however, appears to explain only some PTSD symptoms; in particular, it leaves out the symptoms of emotional dysregulation, such as dissociation, emotional numbing, and intrusive thoughts and images.

Neuroimaging studies have searched for markers of abnormal fear responses and abnormal emotion regulation. Amygdala hyperactivity in patients has been noted in a number of these studies (reviewed in Bremner 2004) and has been used to support an excessive fear conditioning model of PTSD. Significant inconsistencies exist in the neuroimaging literature, however, as a number of similar studies have reported no abnormality, or even hypoactivation, in the amygdala of patients with PTSD (Etkin and Wager 2007).

More consistently observed is hypoactivation within the rACC and vmPFC in patients with PTSD (Bremner et al. 2004). DLPFC deficits, in contrast, have not been reported. Moreover, data from other anxiety disorders in which excessive conditioned fear has been proposed to be an important mechanism—social anxiety disorder and specific phobia—suggest that rACC and ventromedial prefrontal hypoactivity is specific for PTSD (Rauch et al. 2003, Bremner et al. 2004, Shin et al. 2006, Etkin and Wager 2007). Thus, these data suggest that emotional dysregulation in PTSD is related to abnormalities in implicit forms of emotion regulation, which

involve the rACC and vmPFC, and spares more deliberate forms of emotion regulation that rely on DLPFC cognitive control mechanisms.

## Depression

Helen Mayberg has developed a model of depression (Mayberg 2003) in which the rACC serves as a regulator region, linking dorsal cognitive/attentional circuitry (dorsal anterior cingulate and DLPFC) with ventral emotional/vegetative circuitry (subgenual anterior cingulate, amygdala, brain stem, and hypothalamus). A number of studies have noted a positive correlation between the outcome of antidepressant treatment and pretreatment levels of rACC activity. A landmark PET study of the pharmacological treatment of unipolar depression, for example, found that resting activity in the rACC uniquely differentiated treatment responders from nonresponders (Mayberg et al. 1997); responders were hypermetabolic prior to treatment with respect to controls, while nonresponders were hypometabolic. Subsequent studies have found similar positive correlations between pretreatment rACC activity and outcome in response to paroxetine (Saxena et al. 2003), nortriptyline (Pizzagalli et al. 2001), venlafaxine (Davidson et al. 2003), and partial sleep deprivation (Wu et al. 1999). Importantly, these results generalize across widely varying neuroimaging methods, including resting FDG-PET (Mayberg et al. 1997, Saxena et al. 2003, Wu et al. 1999), fMRI activation to emotional stimuli (Davidson et al. 2003) and resting EEG (Pizzagalli et al. 2001). Consistent with the outcome-based studies above, an fMRI study of treatment-resistant depression found hypoactivity in the rostral rACC of patients in response to both positive and negative affective pictures (Kumari et al. 2003).

Together, these data suggest that certain treatment-resistant subtypes of depression involve hypofunction of the rACC. If the rostral anterior cingulate is critical for implicit emotional regulation, as suggested above, then its hypofunction may indicate poor capacity to modulate negative emotion. It is furthermore interesting to note that while consistent findings have been observed in the rACC, a comparable relationship between DLPFC activity and clinical outcome has not been observed. Thus, hypofunction of the rACC in patients who are less likely to respond to treatment may represent a neural marker of poor emotional coping resources. Patients who cannot draw on their implicit emotion regulatory reserves may benefit less from treatment.

## Conclusion

Our understanding of the neurobiological abnormalities underlying many psychiatric disorders is rudimentary. Nevertheless, it is becoming clear that the pathophysiology of different psychiatric syndromes results from overlapping perturbations in specific brain systems. This observation challenges current psychiatric diagnostic practices, based as they are on discrete categorical constructs.

We have explored one perspective on the shared neurobiological substrates of disparate psychiatric disorders in detail: that of cognitive neuroscience. Examination of the normal function of various brain regions and circuits, through human lesion and neuroimaging studies and in animal models, produces a progressively refined understanding of regional brain function under normal circumstances. Functional abnormalities in these brain regions or circuits across distinct psychiatric disorders demonstrate how perturbation of normal brain function relates to specific domains of psychiatric phenomenology and endophenotypes. Such a circuit-level understanding of a disorder can have dramatic implications, as illustrated by the recent interest in invasive neurosurgical techniques for directly modulating brain function—such as by deep brain stimulation—for otherwise refractory psychiatric disease (Mayberg et al. 2005, Greenberg et al. 2006, Schlaepfer et al. 2007).

We have illustrated these principles with several well-characterized neural circuits, and shown how dysfunction of individual functional circuits can contribute to aspects of multiple different psychiatric disorders. This is hardly a complete catalog of brain regions and functions with which such a cognitive neuroscience perspective could be illustrated, nor is our treatment of the circuits and functions that we have described in any way comprehensive. Our purpose has rather been illustrative—to give examples of the utility of a cognitive neuroscience perspective and how it supports the idea that distinct neuropsychiatric conditions have biological commonalities.

This fact has important implications. It reinforces the now obvious truth that psychiatry must, as it advances, be informed by neuroscience, and that an understanding of the normal function of the brain is essential to comprehending how its perturbation can lead to disease. This perspective also illustrates how understanding the underlying biological substrates of psychiatric conditions can inform how we classify psychiatric symptomatology. Likewise, a biological understanding impacts how we view the relationship, both etiological and phenomenological, between disorders that we have previously considered distinct under the symptom-based, categorical nosology of DSM-III and DSM-IV-TR.

Ultimately, the exploration of biological commonalities among different psychiatric disorders, and of endophenotypes that are shared by different disorders, may present a major challenge to our current categorical diagnostic system. When the same neural systems are perturbed in two disorders, what is it that makes them distinct? Conversely, when symptomatically different conditions share underlying etiological factors, whence derives the difference in symptomatic presentation? Future diagnostic systems will have to reflect both the degree of biological relatedness across disorders and the biological and phenomenological differences between syndromes. In the future, we may diagnose psychiatric illnesses on new axes of genetic, environmental, and neural systems levels of analysis, resulting in unexpected groupings of disorders into new categories, spectrums, and dimensions of psychopathology.

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CHAPTER

# 16 Genetic Epidemiology and Molecular Genetics of Psychiatric Disorders

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## Introduction

Advances in molecular and human genetics have led to the identification of nearly all of the genes underlying Mendelian diseases (i.e., those with clear-cut adherence to Mendelian law such as autosomal dominant, autosomal recessive, or X-linked). This progress has been revolutionary in terms of predicting disease risk (e.g., Huntington's disease (Langbehn et al. 2004)), and understanding pathogenesis (e.g., familial hemiplegic migraine (Joutel et al. 1993) and Alzheimer's disease (Hardy and Selkoe 2002)). The rapid success in identifying genes for Mendelian diseases generated the expectation that the same research strategies would eventually be successful in identifying genes for complex diseases, such as heart disease, obesity, cancer, diabetes and many common psychiatric conditions. However, the identification of genes for complex disorders has been more difficult, and few of the genes that have been identified through the candidate gene approach have withstood the test of replication (Altmuller et al. 2001, Ioannidis et al. 2001, Hirschhorn et al. 2002, Ott 2004a, Hirschhorn and Daly 2005).

The chief obstacles to identifying genes for complex diseases with the candidate gene approach include the lack of validity of phenotype characterization, biased sampling, inadequate controls, failure to correct for multiple tests, high false positive rate due to low a priori probability, use of an overly liberal alpha value, and the lack of adequate power of gene searching approaches (Todd 2006, Wacholder et al. 2000, 2004, Risch 2000).

Because of the failure to replicate of association studies of candidate genes, the genome-wide association method has been proposed as the most promising approach to gene identification in future studies of complex diseases (Botstein and Risch 2003, Hirschhorn and Daly 2005). The genome-wide association method that is based on a systematic search of equally spaced genetic markers across the genome with a comparison of cases to controls was demonstrated to have greater power than linkage (within family associations between genetic markers and disease) and association studies testing specified candidate genes between sibling pairs or between cases and controls (Risch and Merikangas 1996). The identification of a large set of common single nucleotide polymorphisms (SNPs) that capture much of the variation in the human genome and the advent of high throughput genotyping chips that can survey over 500,000 of these SNPs at a single pass, have enabled investigators to compare individual variation across large numbers of cases and controls. Whole genome association studies linking common SNPs, as well as copy number variations (CNVs) to vulnerability for complex disorders have become feasible. This approach has recently identified genes for macular degeneration (Klein et al. 2005, Edwards et al. 2005, Haines et al. 2005), and several other complex disorders including inflammatory bowel diseases (Duerr et al., 2006), diabetes (Field et al. 2007, Grant et al. 2006, Sladek et al. 2007, Groves et al. 2006), and prostate cancer (Freedman et al. 2006, Amundadottir et al. 2006). However, this approach has not yet led to gene identification for psychiatric disorders (Couzin and Kaiser 2007).

The first section of this chapter summarizes the background disciplines and approaches used to investigate genetic factors in mental disorders and reviews our current knowledge of the role of genetic epidemiology in mental disorders. The second section describes the approaches to gene identification and review the findings on specific genes

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underlying mental disorders. This review will focus on findings on schizophrenia and affective disorders, the two disorders that have been most widely investigated with the tools of both genetic epidemiology and molecular genetics.

# Genetic Epidemiology of Mental Disorders

Kathleen R. Merikangas

## Genetic Epidemiology

The substantial role of genetic factors underlying mental disorders was firmly established by the pioneering work of Rüdin, Böök, Sjögren, Angst, and Perris in Europe and Kallman, Heston, Rosenthal, Wender, and Kety in the US. Heston (1966) performed the first adoption study of schizophrenia, and found significantly higher rates of schizophrenia in adult offspring who had been adopted away from hospitalized schizophrenic mothers compared to offspring who had been adopted away from parents with no mental illness. The rates of schizophrenia in both groups approximated the rates expected in offspring who are reared by their biological parents. This result clearly implied that a substantial proportion of the increased risk of illness to biological offspring of schizophrenia mothers is independent of the rearing environment. Whether the mechanism of transmission of that risk was genetic or an effect of the prenatal environment could not be determined by this study. Heston's result was confirmed and extended by Rosenthal, Wender, and Kety in a series of publications beginning in 1968 that used a much larger sample of adopted away offspring of schizophrenics in Denmark. These studies demonstrated unequivocally that a substantial portion of the risk for schizophrenia is accounted for by the presence of the disease in birth parents independent of the rearing environment (Kety et al. 1976, 1978). In a second study, half-siblings were studied (Kety 1987) in order to control for prenatal environment. These results indicated that genetics alone was responsible for a large proportion of the familial risk for schizophrenia.

During the latter decades of the last century, twin studies, which estimate the heritability of a disease by comparing the rates of concordance for the illness in monozygous versus dizygous twin pairs, became more common than adoption studies as a method of separating genetic from environmental risks for many psychiatric illnesses. At the same time, psychiatric genetics expanded from inpatient to outpatient settings, particularly in the US (Gershon and Cloninger 1994). With the introduction of epidemiologic research in psychiatry, systematic control groups were included in family studies and methods for incorporating population base rates and risk assessment were developed.

The field of genetic epidemiology examines the genetic and environmental causes of familial resemblance, and focuses on the role of genetic factors that enhance vulnerability or afford protection against disease. Genetic epidemiology employs traditional epidemiologic study designs to identify explanatory factors for aggregation in groups of relatives ranging from twins to migrant cohorts. Since epidemiology has developed sophisticated designs and analytic methods for identifying disease risk factors, these methods have been extended to include both genes and environmental factors as gene identification proceeds (MacMahon and Trichopoulos 1996, Kuller 1979). In general, study designs in genetic epidemiology either control for genetic background while letting the environment vary (e.g., migrant studies, half siblings, separated twins) or control for the environment while allowing variance in the genetic background (e.g., siblings, twins, adoptees'-non-biologic siblings). Investigations in genetic epidemiology are typically based on a combination of study designs including family, twin and adoption studies.

### Family Studies

Familial aggregation is traditionally the first source of evidence that genetic factors may play a role in a disorder. The common indicator of familial aggregation is the relative risk ratio, computed as the rate of disorder in families of affected persons divided by the corresponding rate in families of controls. The degree of genetic relatedness implies what proportion of genes is shared between a particular relative and an index family member or proband. First-degree relatives share 50% of their genes in common; second-degree relatives share 25% of their genes in common and third-degree relatives share 12.5% of their genes in common. Rates resemblance across first, second, and third degree relatives suggest possible patterns of genetic factors underlying a disorder. If familial resemblance is wholly attributable to genes, there should be a 50% decrement in disease risk with successive degrees of relationship from first to second to third. Likewise, diseases with strong genetic contributions tend to be characterized by 50% decrement in risk across successive generations. If the risk to second and third degree relatives decreases by more than 50% this suggests that either no single locus predominates in conferring disease risk, or that there may be a gene environment interaction or a more complex mode of gene transmission. This information can be used to derive estimates of familial recurrence risk within and across generations as a function of population prevalence. Specifically, the ratio of the rate of the disorder in relatives to a population-based rate ($\lambda$) is commonly used (Risch 1990). Whereas $\lambda$ tends to exceed 20 for most autosomal dominant diseases and those for which a single gene accounts for most of the risk, the range of values of $\lambda$ derived from family studies of many complex disorders tend to range from 2−5.

Besides suggesting possible patterns of genetic factors underlying disorders family studies may also provide evidence regarding etiologic or phenotypic heterogeneity. Phenotypic heterogeneity is suggested by variable expression of symptoms of the same underlying risk factors. On the other hand etiologic heterogeneity is demonstrated by common

manifestations of different etiologic factors between families. The family study method also permits assessment of associations between disorders by evaluating specific patterns of co-segregation of two or more disorders within families (Merikangas 1990).

### Twin Studies

Twin studies which compare concordance rates for monozygotic twins (who share the same genotype) with those of dizygotic twins (who share an average of 50% of their genes in common) hold environmental influences constant. They thus provide the most direct estimates of the genetic contribution to the etiology of a disease phenotype. A rough estimate of the genetic contribution to the risk for a disorder is calculated by doubling the difference between the concordance rates for monozygous and dizygous twin pairs. Modern genetic studies employ path analytic models to estimate the proportion of variance attributable to additive genes, common environment and unique environment. There are several other applications of the twin study design that may inform our understanding of the roles of genetic and environmental disease risk factors. (1) Twin studies provide information on the genetic and environmental sources of sex differences in a disease, (2) Environmental exposures may be identified through comparison of discordant monozygotic twins, (3) Twin studies can also be used to suggest the genetic mode of transmission of a disease by inspection of the adherence of the decrement in risk between monozygotic and dizygotic twins to the mendelian ratio of 50%, (4) Twin studies may contribute to enhancing the validity of a disease through inspection of the components of the phenotypes that are most heritable. The twin family design is one of the most powerful study designs in genetic epidemiology not only because it yields estimates of heritability but also because it permits evaluation of multigenerational patterns of expression of genetic and environmental risk factors. Recent updates of findings of twin studies of psychiatric disorders are available (e.g., Shih et al. 2004).

### Adoption Studies

Adoption studies have been the major source of evidence regarding the joint contribution of genetic and environmental factors to disease etiology. Adoption studies either compare the similarity between an adoptee and his or her biological versus adoptive relatives, or the similarity between biological relatives of affected adoptees with those of unaffected, or control adoptees. The latter approach is more powerful because the potentially confounding effect of environmental factors is eliminated. Similar to the familial recurrence risk, the genetic contribution in adoption studies is estimated by comparing the risk of disease to biological versus adoptive relatives. These estimates of risk are often adjusted for the sex, age, ethnicity and other potential factors that may confound the links between adoption status and an index disease.

With the recent trends towards selective adoption and the diminishing frequency of adoptions in the US, adoption studies will be less feasible in identifying genetic and environmental sources of disease etiology (National Adoption Information Clearinghouse 2007). However, the increased rate of reconstituted families comprised of both siblings and half siblings may offer a new opportunity to evaluate the role of genetic factors in the transmission of complex disorders. Genetic models predict that half siblings should have a 50% reduction in disease risk compared to that of full siblings. Deviations from this risk provide evidence for either polygenic transmission, gene-environment interaction or other complex modes of transmission.

### Migration Studies

Migrant studies are perhaps the most powerful study design to identify environmental and cultural risk factors. This study design has been used to study Asian immigrants to the US to demonstrate the strong environmental contributions to many forms of cancer and heart disease (Kolonel et al. 2004). One of the earliest controlled migrant studies evaluated rates of psychosis among Norwegian immigrants to Minnesota compared to native Minnesotans and native Norwegians (Lavik 1993). The study found a higher rate of psychosis among the immigrants compared to both the native Minnesotans and Norwegians. The results were ultimately attributed to a migration selection bias rather than an environmental exposure in the new culture. The application of migration studies to the identification of environmental factors is only valid if potential bias attributed to selection is considered.

## Genetic Epidemiology of Mental Disorders

The wealth of data from family, twin, and adoption studies of the major mental disorders exceeds that of all other chronic human diseases. The increased recognition of the role of biologic and genetic vulnerability factors for mental disorders has led to research with increasing methodologic sophistication that has spanned the second half of the 20th century (Gershon et al. 1989, Weissman et al. 1986). There are numerous comprehensive reviews of genetic research on specific disorders of interest as well as on psychiatric genetics in general (Merikangas and Swendsen 1996, Shih et al. 2004, Kendler 1995, Tandon and McGuffin 2002, Tsuang et al. 2003).

Table 16–1 presents a summary of the relative risks (i.e., proportion of affected among first-degree relatives of affected probands versus those of relatives of controls) derived from controlled family studies of selected psychiatric disorders. The risk ratios comparing the proportion of affected relatives of cases versus controls are greatest for schizophrenia and bipolar disorder; intermediate for substance dependence and subtypes of anxiety, particularly panic disorder; and lowest for major depression. The estimates of heritability (i.e., the proportion of variance

**Table 16–1 Risk Ratios and Heritability Estimates for Major Mental Disorders**

| Disorder | Risk Ratios | Heritability Estimates |
|---|---|---|
| Mood disorders | | |
| Bipolar disorder | 7–10 | 0.60–0.70 |
| Major depression | 2–3 | 0.28–0.40 |
| Anxiety | | |
| All | 4–6 | 0.30–0.40 |
| Panic disorder | 3–8 | 0.50–0.60 |
| Schizophrenia | 8–10 | 0.80–0.84 |
| Substance dependence | 4–8 | 0.30–0.50 |

attributable to genetic factors) are derived from twin studies, which compare rates of disorders in monozygotic and dizygotic twins. These findings reinforce the notion that genes play a major role in the extent to which mental disorders run in families. The heritability estimates for specific disorders shown in Table 16–1 are parallel to the risk ratios derived from family studies. Furthermore, adoption and half-sibling studies also support a genetic basis for the observed familial aggregation.

## Schizophrenia

More is known about the genetic basis of schizophrenia than perhaps any other psychiatric disorder, with genetically-informative studies stemming from early in the last century. There are numerous reviews of this extensive body of research (Zerbin-Rudin 1980, Gottesman 1994, Kendler and Diehl 1993, Sullivan et al. 2003). Despite wide differences in methods, samples and geographic locations, controlled family studies yield a remarkably similar average relative risk of 8.9 to first-degree relatives. The role of genetic factors in the familial aggregation of schizophrenia is demonstrated by the four-fold greater concordance rate of schizophrenia in monozygotic compared to dizygotic twins found in the twelve studies to date. The average heritability in liability to schizophrenia across 12 studies is 0.81 (Sullivan et al. 2003). Similarly, adoption studies using traditional paradigms and modern diagnostic criteria (if available) demonstrated that the average risk to first-degree relatives was 15.5% compared to 3.6% for controls, yielding a relative risk of 4.3.

Despite evidence regarding the importance of genetic risk factors for schizophrenia, the lack of expected mendelian risk ratios in the decrement in risk of schizophrenia as a function of genetic similarity suggests that schizophrenia is a genetically complex disorder (Risch 1990). Recent reviews of the genetic epidemiology of schizophrenia also converge in demonstrating the multifactorial etiology of this condition (Hallmayer 2000, Tsuang 2001, McGuffin 2004, Portin and Alanen 1997, Sullivan et al. 2003). The contribution of nonspecific environmental factors (i.e., multiple factors that may affect brain development) to schizophrenia's etiology is implied by the largest and most recent cross-fostering study that showed that adoptive family environment was associated with schizophrenia spectrum disorders among genetically vulnerable individuals (Tienari et al. 2004).

Another important clue about potential environmental risk factors is the increased risk for the development of schizophrenia among immigrants in several different countries including East African immigrants to Sweden (Selten et al. 2002), Surinamese immigrants to the Netherlands (Hanoeman et al. 2002), Afro-Caribbean immigrants to the UK (Cooper 2005), Finnish immigrants to Sweden (Leao et al. 2006), and European immigrants to Canada (Smith et al. 2006). Although selective migration may be one explanation, there is converging evidence that socially disrupted environments may trigger the onset of schizophrenia in susceptible individuals.

An increased incidence of numerous neurodevelopmental abnormalities among children at high risk for the development of schizophrenia based on having an affected parent compared to offspring of parents without schizophrenia (Owens and Johnstone 2006, Brewer et al. 2006) has led to a focus on early developmental factors in the etiology of schizophrenia. Some of the specific environmental risk factors currently under investigation include obstetric complications (Clarke et al. 2006), childhood trauma (Morgan and Fisher 2007), prenatal factors such as nutritional deficiencies (Ludvigsson et al. 2007), increased paternal age (Malaspina et al. 2002), family interactions (McGuffin 2004), maternal cytokines (Buka et al. 2001a), maternal infections (Buka et al. 2001b); gluten sensitivity (Kalaydjian et al. 2006), and cannabis use (Arseneault et al. 2002, Dean and Murray 2005). In summary, schizophrenia is now widely viewed as a neurodevelopmental disorder comprised of a confluence of vulnerability genes and environmental exposures (Dealberto 2007).

## Mood Disorders

Mood disorders are comprised of a heterogeneous group of syndromes, of which major depression and bipolar disorder (manic-depression) are major subtypes. Bipolar disorder is one of the most widely studied psychiatric disorders from a genetic perspective (Sullivan et al. 2000, Merikangas and Yu 2002). Both major depression and bipolar disorder have important genetic components. Controlled family studies show a five-fold risk to relatives of major depression, and greater than a ten-fold risk to first-degree relatives of bipolar patients. The concordance rate for bipolar monozygotic twins is over five times that of dizygotic twins, and twin concordance for depression shows less dramatic but still notable differences. A summary of five methodologically comparable twin studies of major depression yielded an average estimate of the heritability of major depression of 0.37, with the remainder nearly totally attributable to environmental factors unique to the individual (i.e., 0.63) (Sullivan et al. 2000). The relative risks based on the few existing adoption studies also confirm that the familial recurrence cannot be attributed solely to environmental factors (Merikangas and Yu 2002).

The aggregate adoption study data on mood disorders reveal a moderate increase in rates of mood disorders among the biologic compared to adoptive relatives of adoptees with mood disorders (Faraone et al. 1990). With respect to bipolar disorder, there is little evidence for differential risk among biologic compared to adoptive relatives of adoptees with bipolar disorder. However, the small numbers of bipolar adoptees who have been studied (i.e., less than 50) do not provide an adequate test of genetic and environmental influences. The most compelling finding from adoption studies, however, is the dramatic increase in completed suicide among biological relatives of mood disorder probands (Mendlewicz and Rainer 1977).

## Anxiety Disorders

At present, relatively few studies have examined anxiety disorders from the perspective of genetic epidemiology, and there is virtually no data from certain paradigms (such as adoption studies) (Carey and Gottesman 1981, Hettema et al. 2001). However, the existing research indicates that most anxiety disorders aggregate in families and several investigations have offered specific support for genetic etiology.

### Panic Disorder

Of the anxiety subtypes, panic disorder has the strongest degree of familial aggregation. A review of 13 family studies

of panic disorder by Gorwood et al. (1999) shows a sevenfold relative risk of panic among relatives of panic probands compared to controls. In addition, early onset panic, panic associated with childhood separation anxiety, and panic associated with respiratory symptoms have each been shown to have a higher familial loading than other varieties of panic disorder (Goldstein et al. 1997). Although there has been some inconsistency reported by twin studies of panic disorder, recent studies using contemporary diagnostic criteria show that panic disorder has the highest heritability of all anxiety disorders at 44% (Kendler et al. 2001).

### Phobic States

Though there are far fewer controlled family and twin studies of the other anxiety subtypes, all of the phobic states (i.e., specific phobia, agoraphobia) have also been shown to be familial (Fyer et al. 1995, Noyes et al. 1987, for review: see Merikangas and Angst 1995). The average relative risk of phobic disorders in the relatives of phobics is 3.1, with greater familial aggregation for the generalized subtype of social phobia. The heritability of phobias in twin studies is about 0.35% (Kendler et al. 1992).

### Generalized Anxiety Disorder

There is also evidence for both the familial aggregation and heritability of generalized anxiety disorder in a limited number of studies (Newman and Bland 2006). The average familial odds ratio is approximately 5 (Mendlewicz et al. 1993, Noyes et al. 1987) and the heritability is 0.32 among female twin pairs (Kendler et al. 1992).

### Obsessive–Compulsive Disorder

Controlled family studies of obsessive–compulsive disorder also reveal an elevated familial risk in probands with obsessive compulsive disorder compared to controls, with greater familial aggregation associated with early age of onset and obsessions rather than compulsions (Nestadt et al. 2000, Grabe et al. 2006, Pauls et al. 1995). However, twin studies of obsessive-compulsive disorder have yielded only weak evidence for heritability (Bellodi et al. 1992, Carey and Gottesman 1981, Lenane et al. 1990).

## Substance Use Disorders

A positive family history of a substance use disorder is a consistent and robust risk factor for substance use outcomes in first-degree relatives (for comprehensive reviews of alcoholism see Heath et al. 1997, 2001, Tsuang et al. 2001, Merikangas 2002). Controlled family studies of alcohol use disorder reveal a three-fold increased risk of alcoholism and two-fold increased risk of drug abuse among the relatives of probands with alcoholism as compared to those of controls. Both alcohol abuse and dependence appear to be familial among females, whereas only dependence aggregates among the relatives of males with alcohol dependence (Merikangas et al. 1998a).

Twin studies have demonstrated the contribution of both genetic and environmental risk factors to both alcoholism and drug abuse (Kendler et al. 1994). Heritability of alcoholism (narrowly defined) has been estimated at 59% by some researchers (Kendler et al. 2000), while the heritability of problem drinking (using broad definitions) has been estimated at 8−44% in females and 10−50% in males (Heath et al. 1997). Several adoption studies conducted in Scandinavia demonstrated the importance of genetic factors underlying alcoholism (Goodwin 1985, Sigvardsson et al. 1996). Adoption study paradigms have shown not only that a disturbed adoptive family environment interacts with a genetic predisposition for alcoholism to affect the risk for the disorder (Cutrona et al. 1994), but that the adoptive family environment can predict alcohol abuse or dependency independent from genetic vulnerability (Cadoret et al. 1995). A recent "quasi-adoption" study that investigated the association between the biologic family background (genetic factors), and a history of exposure to alcoholism during childhood (environmental factors) revealed greater effect of genetic risk factors among men than women, and common genetic and environmental risk factors contributing to alcohol dependence in both men and women (Light et al. 1996). The importance of environmental transmission of substance use disorders was demonstrated in a recent study of adoptive and step families (Newlin et al. 2000).

Although there has been less systematic research on the familial aggregation of drug use disorders, numerous family history studies and uncontrolled and controlled family studies have demonstrated that rates of substance use disorders are elevated among relatives of drug abusers compared to that of controls and population expectations (Bierut et al., 1998, Merikangas et al. 1998a). One controlled family study of drug use disorders using contemporary family study data (Merikangas et al. 1998b) showed an eight-fold increased risk of substance use disorders (opioids, cocaine, cannabis, and alcohol) among relatives of probands with drug disorders compared with relatives of psychiatric and normal controls. Family, twin, and adoption studies have also demonstrated common genetic and environmental factors that contribute to cannabis use disorders and other drug use disorders (Agrawal and Lynskey 2006.) The results of numerous twin studies of substance use disorders in general, as well as those of specific drugs have shown that there are genetic factors underlying drug abuse in general (Kendler et al. 1999), as well as unique genetic factors associated with specific drugs of abuse including nicotine and cannabis (Kendler and Prescott 1998a, 1998b; Kendler et al. 2000, Tsuang et al. 2001).

## Complex Patterns of Transmission

The application of advances in genomics to mental disorders is still limited by the complexity of the process through which genes exert their influence on mental disorders. There is substantial evidence that a lack of one-to-one correspondence between the genotype and phenotype exists for most of the major mental disorders. Phenomena such as *penetrance* (i.e., probability of phenotypic expression among individuals with susceptibility gene), *variable expressivity* (i.e., variation in clinical expression associated with a particular gene), *gene-environment interaction* (i.e., expression of genotype only in the presence of particular environmental exposures), *pleiotropy* (i.e., capacity of genes to manifest several different phenotypes simultaneously), *genetic heterogeneity* (i.e., different genes leading to indistinguishable phenotypes), *gene-environment correlation* (Dick et al. 2006) and *polygenic and oligogenic modes of inheritance* (i.e., simultaneous contributions of multiple genes rather than mendelian single gene models) are characteristic of the mental disorders, as they are of numerous

other complex disorders for which susceptibility genes have been identified (Risch 1990). Other complicated situations include mitochondrial inheritance, imprinting, and epigenetic phenomena (Guttmacher and Collins 2002).

The high magnitude of *comorbidity* and co-aggregation of index disorders with other major psychiatric disorders (i.e., bipolar disorder and alcoholism, major depression and anxiety disorders, schizophrenia and drug dependence), in part induced by the classification system, has been demonstrated in both clinical and community studies (Merikangas 1990, Merikangas et al. 1998a, Maier et al. 1993, Maier et al. 2002). For example, alcoholism, a well-established complication of bipolar illness, may mask the underlying features of bipolarity, leading to phenotypic misclassification in genetic studies (Merikangas et al. 2007). *Non-random mating* is also a common phenomenon in mental disorders that impedes evaluation of patterns of familial transmission (Merikangas 1982). Assortative mating is particularly pronounced for substance use disorders for which substance dependence among spouses of substance dependent probands may be as high as 90% (Galbaud du Fort et al. 1998). These phenomena serve to decrease the signal to noise ratio in defining the mental disorders for genetic studies. Studies that attempt to identify the impact of these phenomena on phenotypic expression in individuals and families will bring us closer to understanding the role of the underlying genes on the components of mental disorders.

## Future Applications of Genetic Epidemiology

The importance of epidemiology to the future of genetics has been described by numerous geneticists and epidemiologists who conclude that the best strategy for gene identification for complex disorders will ultimately involve large epidemiologic studies from diverse populations (Peltonen and McKusick 2001, Risch 2000, Khoury and Little 2000, Merikangas and Risch 2003). It is likely that population-based association studies will assume increasing importance in translating the results of genomics to public health. There are several reasons that population-based studies will be critical to the future of genetics. First, the prevalence of newly identified polymorphisms, whether SNPs or other variants, especially in particular population subgroups, is not known. Second, current knowledge of genes as risk factors is based nearly exclusively on clinical and non-systematic samples. Hence, the significance of the susceptibility alleles that have been identified for cancer, heart disease, diabetes, and so forth is unknown in the population at large. The next stage of research needs to move beyond samples of affected individuals to the general population in order to obtain estimates of the risk of specific polymorphisms for the population as a whole. Third, identification of risk profiles will require very large samples to assess the significance of vulnerability genes with relatively low expected population frequencies. Fourth, human genome epidemiology can provide information on the specificity, sensitivity, and impact of genetic tests (Khoury and Little 2000). Some of the areas where epidemiology can contribute to future genetic studies are described below.

### Samples

The shift from systematic large-scale family studies to linkage studies in psychiatry has led to the collection of families according to very specific sampling strategies (e.g., many affected relatives, affected sibling pairs, affected relatives on one side of the family only, availability of parents for study, etc.) in order to maximize the power of detecting genes according to the assumed model of familial transmission. Despite the increase in power for detecting genes, these sampling approaches have diminished the generalizability of the study findings, and contribute little else to the knowledge base if genes are not discovered. Future studies will attempt to collect both families and controls from representative samples of the population in order to enable estimation of population risk parameters, enhance generalizability and examine the specificity of endophenotypic transmission.

### Selection of Controls

The most serious problem in the design of association studies is the failure to select controls who are comparable to the cases on all factors except the disease of interest (Wacholder et al. 2000, Ott 2004b). Controls should be drawn from the same population as the cases, and must have the same probability of exposure (i.e., genes) as the cases. Controls should be selected to ensure the validity rather than representativeness of a study. Failure to equate cases and controls may lead to confounding (i.e., a spurious association due to an unmeasured factor that is associated with both the candidate gene and the disease). In genetic case-control studies, the most likely source of confounding is ethnicity because of differential gene and disease frequencies in different ethnic subgroups.

### Risk Estimation

Because genetic polymorphisms involved in complex diseases are likely to be non-deterministic (i.e., the marker neither predicts disease nor nondisease with certainty), traditional epidemiologic risk factor designs can be used to estimate their impact. As epidemiologists add genes to their risk equations, it is likely that the contradictory findings from studies that have generally employed solely environmental risk factors, such as diet, smoking, alcohol use, etc., will be resolved. Likewise, the studies that seek solely to identify genes will also continue to be inconsistent without considering the effects of nongenetic biologic parameters, as well as environmental factors that contribute to the diseases of interest.

There are several types of risk estimates that are used in public health. The most common is *relative risk*, defined as the magnitude of the association between an exposure and disease. It is independent of the prevalence of the exposure. The *absolute risk* is the overall probability of developing a disease in an individual or in a particular population (Gordis 2000). The *attributable risk* is the difference in the risk of the disease in those exposed to a particular risk factor compared to the background risk of a disease in a population (i.e., in the unexposed). The *population attributable risk* relates to the risk of a disease in a total population (exposed and unexposed) and indicates the amount the disease can be reduced in a population if an exposure is eliminated. The population attributable risk depends on the prevalence of the exposure, or in the case of genes, the gene frequency. Genetic attributable risk would indicate the proportion of a particular disease that would be eliminated if a particular gene or genes were not involved.

For example, the two vulnerability genes for Alzheimer's disease include the very rare, but *deterministic genes* $\beta$-amyloid precursor, presenilin-1, and –2, that signal a very high probability of the development of Alzheimer's disease, particularly at a young age, and the *susceptibility* gene apolipoprotein-E $\varepsilon$-4 (APOE $\varepsilon$4) (Tol et al. 1999). The apolipoprotein-E $\varepsilon$ 4 (APOE $\varepsilon$4) allele has been shown to increase the risk of Alzheimer's disease in a dose-dependent fashion. Using data from a large multiethnic sample collected by more than 40 research teams, Farrer et al. (1997) reported a 2.6−3.2 greater odds of Alzheimer's disease among those with one copy, and 14.9 odds of Alzheimer's disease among those with two copies of the APOE $\varepsilon$4 allele. Moreover, there was a significant protective effect among those with the $\varepsilon$2/$\varepsilon$3 genotype. As opposed to the deterministic mutations, the APOE $\varepsilon$ 4 allele has a very high population attributable risk because of its high frequency in the population. The APOE $\varepsilon$-4 allele is likely to interact with environmental risk and protective factors (Kivipelto et al. 2001, 2002). The population risk attributable to these mutations is quite low because of the very low population prevalence of disease associated with these alleles. This model of combination of several rare deterministic genes in a small subset of families and common genes with lower relative risk to individuals but high population attributable risk is likely to apply to many of the psychiatric disorders as well, and may in part explain some of the discrepancies in findings across studies to date.

## Use of Endophenotypes for Classification

Numerous studies have begun to deconstruct psychiatric phenotypes by their component features or subtypes, including bipolar disorder (Benazzi 2007, Angst 2007), general anxiety disorder (Angst et al. 2006), obsessive compulsive disorder (Eapen et al. 2006), schizophrenia (Braff et al. 2007, Gur et al. 2007), and panic disorder (Smoller and Tsuang 1998). Identification of phenotypic traits or markers, which are themselves heritable, and that may represent intermediate forms of expression between the output of underlying genes and the broader disease phenotype, have been termed "endophenotypes" (Gottesman and Gould 2003). Studies of the role of genetic factors involved in these systems may be more informative than studies of the aggregate psychiatric phenotypes since they may more closely represent expression of underlying biologic systems. To the extent that particular endophenotypes more clearly represent expression of genotypes, they may help to unravel the complexity of transmission of the mental disorders. For example, some of the endophenotypes that may underlie mood disorders include circadian rhythm, stress reactivity, and mood, sleep and appetite regulation (Lenox et al. 2002). However, before applying endophenotypes in gene identification studies, there should be evidence that the endophenotype has a stronger genetic signal than the broader phenotype. A recent meta- analysis of psychiatric endophenotypes (Flint and Munafo 2007) and a review of the genetic architecture of traits in model organisms do not provide evidence that endophenotypes are superior to current phenotypic disease definitions (Valdar et al. 2006).

## Identification of Environmental Factors

Once susceptibility genes have been identified, it will be important to identify environmental factors that operate either specifically or non-specifically on those with susceptibility to mental disorders in order to develop effective prevention and intervention efforts. Langholz et al. (1999) describe some of the world's prospective cohort studies that may serve as a basis for studies of gene-disease associations or gene-environment interactions. There is increasing evidence that gene-environment interaction will underlie many of the complex human diseases. Some examples include inborn errors of metabolism, individual variation in response to drugs (Nebert 1999), substance use disorders (Heath et al. 2001, Rose et al. 2000) and the protective influence of a deletion in the CCRS gene on exposure to HIV (Michael 1999).

However, few environmental exposures have been shown to have an etiologic role in mental disorders in prospective studies. Over the next decades, it will be important to identify and evaluate the effects of specific environmental factors on disease outcomes and to refine measurement of environmental exposures to evaluate specificity of effects. Study designs and statistical methods should focus increasingly on gene-environment interaction (Ottman 1990, Beaty 1997, Yang and Khoury 1997). Although numerous recent studies have reported gene-environment interaction between several genes that interact with nonspecific environmental exposures such as life stress, or childhood adversity and a range of outcomes including depression, cannabis dependence, and conduct disorder (Gillespie et al. 2005 Caspi et al. 2003), replication of these findings is still forthcoming (Ioannidis et al. 2001, Zammit and Owen 2006). Increased knowledge of the developmental pathways of emotion, cognition, and behavior will expand our ability to identify specific environmental factors such as infection, poor diet, prenatal environment, and early life experiences that interact with the genetic architecture of mood regulation and cognition (Meaney 2001).

## Impact of Genomics on Psychiatric Science and Practice

Progress in genomics has far outstripped advances in our understanding of psychiatric phenotypes, and the complexity of their etiologies, as well as our current ability to identify genetic and environmental risk factors. Therefore, despite the extraordinary technical advances and availability of rapidly expanding genetic databases, the application of psychiatric genetic research to understand diagnostic heterogeneity, course and/or treatment outcome is still limited due to the lack of consistent findings of genetic studies to date. However, increasing understanding of the complex mechanisms through which genes exert their influence over the next decade should enhance the clinical utility of psychiatric genetics.

The goal of genomics research is ultimately prevention, the cornerstone of public health. Gaining understanding of the significance of genetic risk factors and learning proper interpretation of their meaning for patients and their families will ultimately become part of clinical practice, and clinicians will become increasingly involved in helping patients to comprehend the meaning and potential impact of genetic risk for nonpsychiatric disorders as well. As our knowledge of the role of genes in mental disorders advances, it will be incumbent upon clinicians to become familiar with knowledge gleaned from genetic epidemiologic and genomics research.

In the meanwhile, recurrence risk estimates from family studies constitute the best available knowledge on which to predict the risk of the development of mental disorders.

# Identification of Genes Underlying Mental Disorders

Maria Karayiorgou

## Linkage Studies

The traditional approach for locating a disease gene in humans is *linkage analysis*, which tests the association between DNA polymorphic markers and affected status within families. After linkage is detected with an initial marker, many other markers nearby may also be examined. Markers showing the strongest correlation with disease in families are assumed to be closest to the disease locus.

Linkage analysis uses DNA sequences with high variability (i.e., polymorphisms) in order to increase the power to identify markers that are associated with a disease within families. Historically, different methodological approaches have been applied. Earlier linkage studies employed Restriction Fragment Length Polymorphisms (RFLP's) (Botstein et al. 1980), whereas subsequent studies examined short tandem repeat markers, or "microsatellites," (Weber et al. 1991) DNA sequences that show considerable variability among people but that have no functional consequences. More recently, linkage and association studies have examined SNPs (Risch and Merikangas 1996) to track diseases in families.

Markers in the candidate region identified by linkage analysis can be used to narrow the location of the disease gene through *linkage disequilibrium* (LD) *analysis.* LD is a population association between two alleles at different loci, and occurs when the same founder mutation exists in a large proportion of affected subjects in the population studied. Usually, the closer the marker is to the disease locus, the greater the proportion of affected subjects who carry the identical allele at the marker (Risch 2000). However, in measuring the strength of LD for a given marker, it is also important to select unaffected control subjects from the same population, because an allele shared among affected subjects may also be common in the general population and thus shared by chance rather than due to proximity to the disease locus (Risch 2000).

For complex human diseases, a simple mode of genetic inheritance is not apparent, and indeed, multiple contributing genetic loci are likely to be involved. Study designs that do not depend on the particular mode of inheritance are required for linkage analysis. Since affected relatives provide most of the information for such analyses, studies that focus on searching for increased sharing of marker alleles above chance expectation among affected relatives may be employed. The simplest of such studies involves *affected sibships*, where allele sharing in excess of 50% (the expectation when there is no linkage) is sought.

## Association Studies

Linkage analysis has not proven successful in identifying genes for most complex diseases, presumably because the effects of the underlying genes are not strong enough to be detected by linkage (Risch and Merikangas 1996). Therefore, genome-wide association studies have been offered as a more powerful approach. Completion of the human genome project has provided an unprecedented opportunity to identify the effect of gene variants on complex phenotypes, such as psychiatric disorders. Functional genomics technology involving microarrays and proteomics will provide added insights regarding gene function on the cellular level, improving our ability to predict phenotypic effects of genes at the organismic level (Risch 2000). The recently proposed project (known as the HapMap project) to develop a map of human haplotypes, or blocks of genes that may have been conserved in evolutionary history, has generated considerable enthusiasm for its potential to inform the genetic basis of complex disorders in the general population. There has been considerable discussion regarding the value of studying SNPs with functional significance versus non-coding or evenly spaced SNPs. Botstein and Risch (2003) propose that the initial work employ sequence-based association studies that focus on functional coding regions rather than a map based approach (Collins et al. 1997, Gabriel 2002) that relies solely on the location of haplotypes in order to maximize power and efficiency for detecting genes for complex human diseases.

Association studies generally examine candidate genes among affected individuals and unrelated unaffected controls. The same limitations that apply to case-control studies of other risk factors must also be considered in genetic case-control studies. The most serious problem in the design of association studies is the failure to select controls who are comparable to the cases on all factors except the disease of interest. Failure to equate cases and controls may lead to confounding (i.e., a spurious association due to an unmeasured factor that is associated with both the candidate gene and the disease). In genetic case-control studies, the most likely source of confounding is ethnicity because of differential gene and disease frequencies in different ethnic subgroups. Aside from confounding, association studies are particularly prone to false positive findings due to multiple testing without correction and the low prior probability of a gene-disease association (Wacholder et al. 2004). In addition, there is a strong publication bias against reports of negative association studies (Ioannidis et al. 2001). The former problem can be resolved in part by the use of much higher $\alpha$ levels (i.e., false positive error rates) in association studies (Wacholder et al. 2000).

## Application of Linkage and Association Studies in Psychiatry

Based on the dramatic advances in molecular genetics during the past 20 years as described above, there has been a

major shift in the focus of psychiatric genetic investigations during the past decade from elucidating patterns of familial transmission to localizing genes underlying mental disorders using linkage studies and association studies (McInnes and Freimer 1995). Although there remains controversy regarding what constitutes replications of genetic findings for several mental disorders, there are several recent promising findings in psychiatric genetics, and the outcome of several large genome wide association studies of mental disorders will soon be available. In addition, the increasing tendency for collaborative efforts on genetics studies within psychiatry may yield greater power to detect genes of small effect. In fact, the success of this approach has already been demonstrated as described above.

## Systematic Follow-Up of Linkage Signals

In schizophrenia, more than 20 genome-wide linkage scans aiming to localize genes have been reported thus far. Two meta-analyses have also taken place (Lewis et al. 2003, Badner and Gershon 2002). The goal of such meta-analyses is to examine the combined results of several genome-wide scans to clarify inconsistencies among individual studies and detect signals that may have been missed in individual studies (meta-analytic approaches tend to amplify signals that are weak but consistent among studies and attenuate ones that are strong but non-reproducible). The first meta-analysis study confirmed 8p, 13q, and 22q as valid linkage regions, likely containing one or more susceptibility gene. The second meta-analysis study (using a different statistical methodology) implicated 2p12–q22.1 (under stringent criteria), as well as loci at 5q, 3p, 11q, 2q, 1q, 22q, 8p, 6p, 20p, and 14q (under less stringent thresholds). It would appear that approximately ten regions of the genome are likely to contain schizophrenia susceptibility genes, although this is almost certainly an underestimate because (a) meta-analytic approaches tend to attenuate true strong signals that are population specific and (b) it is expected that many schizophrenia susceptibility genes will be undetectable by linkage studies. The ultimate validation of the linkage results will be the identification of the susceptibility genes themselves. For some of the loci described above, systematic fine-mapping efforts were undertaken. These systematic efforts employ genotyping of relatively large numbers of markers, including SNPs and LD assays in family-based or case-control samples and have resulted in the identification of strong positional candidate genes (Gogos and Gerber 2006, O'Tuathaigh et al. 2007). To date, at least 10 genes have been identified through systematic follow-up of linkage signals in schizophrenia (see Table 16–2 for a list of these genes, as well as their possible biological functions).

Similar to schizophrenia, previous linkage studies and meta-analyses have implicated several genomic loci in bipolar illness as well (Segurado et al. 2003). Dense mapping and search for a causative mutation in these loci is currently in progress but the results have not been as forthcoming as in schizophrenia. For example, Barden and colleagues (2006) examined over 3 candidate genes at 12q24.3 and found nominal association in bipolar families with a non-synonymous SNP at the *P2RX7* gene, a purinergic ligand-gated ion channel. This Gln460Arg polymorphism occurs at an amino acid that is conserved between humans and rodents and is located in the C-terminal domain of the receptor, known to be essential for normal P2RX7 function. Blair et al. (2006) examined 17 brain-expressed genes on 4p35 and found that

**Table 16–2 Schizophrenia and Bipolar Disorder Positional Candidate Genes: Chromosomal Locations and Potential Function***

| Gene Symbol | Locus | Function |
|---|---|---|
| | | **Schizophrenia** |
| *PRODH* | 22q11 | Metabolism of l-proline; potential indirect influence on glutamatergic transmission |
| *DTNBP1* | 6p22 | Member of dystrophin protein complex and biogenesis of lysosomal related organelle complex; potential pre-synaptic effects on glutamate release at excitatory synapses |
| *NRG1* | 8p12 | Broad involvement in neuronal development, survival and synaptic function |
| *G72* | 13q34 | Potential modulation of D-amino acid oxidase; potential mitochondrial function and morphology |
| *DISC1* | 1q42.1 | Multifunctional; possible involvement in cytoskeletal and centromere function and in cell membrane receptor localization and signal transduction |
| *CAPON* | 1q22 | Potential regulator of neuronal nitric oxide synthase association with PSD-95; implications for NMDA receptor coupled nitric oxide signaling |
| *ZDHHC8* | 22q11 | Palmitoylation of PSD-95 and other substrates, potential implications for synaptic architecture and plasticity |
| *TAAR6* | 6q23 | G-protein–coupled receptor for trace amines, potential role in neurotransmission |
| *EPN4* | 5q33 | Clathrin-mediated pit formation and endocytosis; potential role in reuptake and storage of neurotransmitters |
| *GABA(A) Receptors* | 5q34 | GABAergic transmission |
| *QKI* | 6q25 | RNA binding protein; role in myelination and neuronal development |
| *PCM1* | 8p22 | Centrosomal protein |
| | | **Bipolar Disorder** |
| *FAT* | 4q35 | Member of the cadherin family of cell-cell adhesion proteins |
| *P2RX7* | 12q24 | Purinergic ligand-gated ion channel. |

*In chronological order of appearance of the reports until August 2006.

the haplotype extending over the *FAT* gene, encoding a cadherin family protein, is associated with bipolar disorder in four independent sample sets. They also found that lithium treatment in mice down-regulates the *FAT* gene, and concluded that this gene confers a genetic risk for bipolar disorder.

Notably, several common regions have been implicated in linkage genome scans for bipolar illness and schizophrenia, which has led to the formulation of the hypothesis that the two disorders share some susceptibility genes. Indeed, the *G72* gene on chromosome 13q and the *DISC1* gene on chromosome 1q (Table 16–1) have been associated with genetic risk for both schizophrenia and bipolar illness.

Compared to schizophrenia and bipolar disorder, efforts to systematically identify positional susceptibility genes for other major and common psychiatric disorders, such as major depression, are lagging. This may be due to higher phenotypic or genetic heterogeneity or to the contribution of environmental factors that confounds the effort to identify genetic factors. Despite these potential limitations, the number of reports of large-scale linkage studies of depression is increasing. Implicated genomic regions include 1p36, 12q23.3-q24.11, 13q31.1-q31.3, 15q25.3-26.2, 3p12.3-q12.3 and 18q21.33-q22.2 and there is some evidence for convergence of linkage findings across studies, but more data are needed to permit meta-analysis (Levinson 2006). Interestingly, some of these regions overlap with those implicated in bipolar disorder and it was recently shown that the non-synonymous coding SNP in the *P2RX7* gene previously found to be associated with bipolar disorder (see above), was significantly associated with major depression as well (Lucae et al. 2006).

It should be emphasized that, even for the stronger genetic findings, it is too early to draw firm conclusions about their generalization among different samples and populations. Even for genes where association signals have been observed in several "replication" studies, a critical review of the literature would reveal issues with the extent of coverage of the implicated loci, consistency of the risk allele or risk haplotype across studies, or structure of the samples used in the original and replication studies. In addition, publication bias against negative reports can also provide a false picture of the overall available data. While these issues are relevant to all common, complex disorders, they are likely to be more pronounced in genetic studies of psychiatric disorders, which are confounded by a larger degree of phenotypic heterogeneity.

One way to evaluate the data and assess the degree of significance of the findings described above is to use a combination of criteria that include the degree of statistical significance, the reproducibility of the associations in independent samples, the identification of independent rare risk alleles and the consistent findings from animal model studies and endophenotype-based studies in humans. Based on these criteria, support for at least some of the genes shown in Table 16–2 (such as *PRODH, DTNBP1, NRG1, G72,* or *DISC1*) appears to be quite strong. However, a recent study evaluating the evidence supporting the dysbindin (*DTNBP1*) gene (Mutsuddi et al. 2006) is particularly didactic and has raised some important general concerns. *DTNBP1* was first identified as a putative schizophrenia-susceptibility gene in Irish pedigrees, with a report of association to common genetic variation (Gogos and Gerber 2006). As is the case with many genes in Table 16–2, several replication studies have claimed confirmation of an association to this gene in independent European samples, but the reported risk alleles and haplotypes appear to differ between studies. To facilitate evaluation of existing evidence of association for this gene, Mutsuddi et al. (2006) genotyped all associated SNPs reported in the original and replication studies in a reference control sample. Using this high-density reference map, they compared the putative disease-associated haplotype from each study and found that the original and replication studies are inconsistent with regard to the identity of the disease-associated haplotype at *DTNBP1*. The authors further demonstrated that, in all studies, the European-derived populations studied have haplotype patterns and frequencies that are consistent with HapMap samples (and each other), rendering it therefore unlikely that population differences are creating the inconsistency of the association studies. The authors concluded that evidence of association for *DTNBP1* is, at present, equivocal and unsatisfactory. This may also be applicable to other genes in Table 16–2 for which similar patterns of association were observed and unless a definition of replication, which is strict and precise is implemented, false positive findings may propagate and confuse the literature (Sullivan 2007).

## Candidate Gene Approaches

Genes are considered candidates for a psychiatric disorder based usually on their function (in the context of perceived deficits in disease pathophysiology) or genomic location (in the context of linkage signals or chromosomal abnormalities). Indeed, the most active area in molecular genetic research of psychiatric disorders is replication studies of previously reported candidate genes and analysis of related genes. As a result, the list of candidate genes is extensive and rapidly growing. Listing all the candidate genes is beyond the scope of this chapter, but a reasonably complete and regularly updated list of candidate genes can be found at http://geneticassociationdb.nih.gov Table 16–3 shows the genetic data for a small subset of candidate genes that are either located in the general vicinity of linkage signals or identified through multi-pronged candidate gene approaches that produced convergent genetic and biological evidence, or both (Gogos and Gerber 2006, O'Tuathaigh et al. 2007).

Despite the burgeoning nature of the candidate gene research most replication studies do not support the initial positive findings. There are several good reasons for that, some of them described by Freimer and Sabatti (2004). For example, "too much testing," that is, testing of many variants without the appropriate corrections for the number of performed tests, can lead to false positive findings, whereas "too little testing," that is, failure to test exhaustively the entire genetic variation in a given locus, can lead to false negative findings. Possibly the most important issue is that of the prior probability of association of a trait to a single candidate gene. If one makes the conservative simplifying assumption that the gene was picked at random from the approximate 30,000 genes in the genome, the prior probability that a given candidate gene is associated with a trait is approximately 1/30,000. Almost no candidate gene association study meets this threshold and usually,

**Table 16–3 Schizophrenia Functional and Positional Candidate Genes**

| Gene Symbol | Locus | Function |
|---|---|---|
| *COMT* | 22q11 | Metabolism of dopamine; regulation of extracellular dopamine levels in prefrontal cortex |
| *RGS4* | 1q23 | GTPase activator, which modulates signal transduction via dopamine, metabotropic glutamate and muscarinic receptors |
| *PPP3CC* | 8p21 | Gamma catalytic subunit of protein phosphatase, calcineurin; subunit-specific function unknown. Calcineurin is involved in synaptic plasticity and D1 receptor signaling |
| *AKT1* | 14q32 | Involved in neuronal development, synaptic plasticity and D2, NMDA and GABA receptor signaling |
| *GRM3* | 7q21 | Metabotropic glutamate receptor |
| *CHRNA7* | 15q13 | Alpha7 nicotinic receptor |
| *BDNF* | 11p14 | Multiple roles in CNS development and neurotransmission |

investigators implicitly assume that meaningful prior evidence guides the selection of a candidate gene (i.e., that the prior probability of association is higher than 1/30,000). However, for association studies, there is no form of prior evidence that can be readily quantified in a probability and therefore estimates of prior probability are inherently subjective. As a result, stringent cut-offs for gene association studies are not usually applied in the majority of genetic publications, so that many of even the most highly publicized results are probably false positives.

Nevertheless, a number of interesting candidate genes have emerged (Table 16–3) and intriguingly some of the most interesting candidates are located in the general vicinity of linkage signals. Although far from proven, the recurrent observation of clustering of candidate susceptibility genes could indicate that more than one gene could contribute to at least some of the linkage signals in psychiatric disorders. This is not surprising since linkage "peaks" are large, often spanning tens of millions of base pairs and hundreds of possible genes. Interestingly, recent efforts to fine-map Quantitative Trait Loci (QTL) peaks in simpler organisms (analogous to linkage peaks in human studies) have shown that often an apparently single QTL fractionates into multiple tightly linked QTLs. For example, Yalcin et al. (2004) have fine-mapped in the mouse a QTL shown to influence anxiety-related behaviors and found that it fractionates into three discrete peaks. Therefore, the task of fine-mapping specific susceptibility genes under linkage peaks in humans, where we have fewer and less powerful approaches than in model organisms, may be even more difficult than we have previously estimated. It is likely, for example, that some of the genes described in Table 16–2 may not account for the entire linkage signal and that linkage studies may have substantially underestimated the number of loci that are involved in any of the mental illnesses.

## Fine Mapping of Genomic Rearrangements

### Isolated *De Novo* and Familial Chromosomal Abnormalities

Both *de novo* and familial chromosomal abnormalities have been described in patients with psychiatric or neurological conditions, but only a small proportion of these have been studied at the molecular level. One example is that of a large Scottish family in which there is a highly significant co-segregation (LOD > 7) between major mental illness and the presence of a balanced translocation between chromosomes 1 and 11. The *DISC1* gene is directly disrupted by the chromosome 1 breakpoint (Millar et al. 2000) and subsequent supportive evidence for its involvement in schizophrenia and bipolar disorder has come from linkage and case–control association studies on karyotypically normal populations (Gogos and Gerber 2006, O'Tuathaigh et al. 2007).

It has been suggested that DISC1 is involved in neuronal development particularly within the cerebral cortex, and that loss of DISC1 function might underlie neurodevelopmental dysfunction in schizophrenia and other psychiatric disorders (Kamiya et al. 2005). Based on *in vitro* observations that phosphodiesterase 4B (PDE4B) and DISC1 physically interact, Millar et al. (2005) proposed an alternative model of DISC1 action involving regulation of cAMP signaling, a second messenger system known to modulate affect and cognition. Recently, Koike et al. (2006) attempted to mimic the effects of the chromosomal translocation observed in the Scottish family using a gene-targeting approach designed to generate a truncated *Disc1* transcript, and possibly protein. C57BL/6J mice carrying a debilitated *Disc1* allele demonstrated a deficit in spatial working memory performance, which is often affected in patients with schizophrenia and their unaffected relatives. This deficit was observed in both heterozygous and homozygous mutant mice, although neither showed any changes in locomotor activity or PrePulse Inhibition (PPI).

Analysis of further cytogenetic abnormalities in schizophrenic patients have identified additional genes, such as *PDE4B* (Millar et al. 2005), *NPAS3* (Kamnasaran et al. 2003), *GRIK4* (Pickard et al. 2006) and *GRIA3* (Gecz et al. 1999) as potential candidate genes, but in most of these cases convergence of supportive genetic evidence from karyotypically normal patient populations and from animal model studies is still lacking. Interestingly, mice bearing inactivating mutations in the genes encoding the NPAS1 and NPAS3 transcription factors have been shown to exhibit a spectrum of behavioral and neurochemical abnormalities and adult brain tissues from Npas3- and Npas1/Npas3-deficient mice exhibited a distinct reduction in reelin, a large, secreted protein whose expression has been reported to be attenuated in postmortem brain tissue of some patients with schizophrenia and other neuropsychiatric disorders (Erbel-Sieler et al. 2004, Brunskill et al. 2005).

## Copy Number Repeat Variations

CNVs are ≥1-kb DNA segments that are present in variable copy number in comparison to a reference genome. Recently, a detailed CNV map of the human genome has emerged (Redon et al. 2006, Sebat et al. 2004). Redon et al. (2006) analyzed 270 individuals from 4 distinct populations with ancestry in Europe, Asia, or Africa and described a total of 1,447 CNVs covering 12% of the total genome (~360 megabases of DNA). Though the vast majority of CNVs were found outside of coding sequences, thousands of putative functional segments of DNA fall within CNVs and 99% of them overlap with conserved non-coding sequences. In addition, at least 10% of disease-related genes in the Online Mendelian Inheritance in Man (OMIM) database are associated with CNVs. As this may be only a fraction of the number that will eventually be uncovered, the data suggest that CNVs may represent the greatest source of human genetic diversity.

The implications of these findings in the genetic basis of psychiatric disorders will become clear in the next few years. Psychiatric research already has one extensively studied example of a relatively rare CNV (the 22q11 microdeletion, Karayiorgou and Gogos 2004) and probing for additional more common CNVs may prove to be the next frontier in psychiatric genetics. Indeed, CNVs were found in the *PRODH*, *DISC1*, *CAPON*, *ETH*, and some of the other leading susceptibility genes described in Table 16–2.

## Iterative Human and Mouse Genetic Approaches

Mouse models of "susceptibility genes" hold considerable promise not only in understanding the function of a gene and its contribution to disease pathogenesis and pathophysiology, but also in additional gene discovery. In order to create accurate genetic mouse models of psychiatric disorders, the functional nature of any genetic variant associated with the disease must be taken into account (Arguello and Gogos 2006). Unfortunately, in the case of complex genetic disorders, the associated variants usually have no obvious effect on protein structure. Given this limitation, genetic mouse models have been limited, for the most part, to constitutive or conditional knock-outs, although a few mouse models have also appeared that actually attempt to mimic the functional outcomes of rare genetic variants associated with psychiatric disorders (Arguello and Gogos 2006).

Animal models of psychiatric disorders (including schizophrenia) are traditionally analyzed through behavioral assays, but mechanistic insights into the nature of the deficit under investigation cannot be achieved by behavioral assessment alone. Rather, a combined approach that begins at the behavioral level and culminates at the cellular and molecular levels is needed. Approaches at the molecular level have two important advantages. First, molecular functions of a gene are more likely to be evolutionarily conserved compared to any behavioral outcomes the gene may influence. Second, it is conceivable that the "closer" one probes to the primary deficit, the less likely it is that downstream compensatory mechanisms come into play and the more likely that any resulting functional consequences will be detectable. Molecular level approaches in particular can be used to identify (in a high-throughput fashion) changes in gene expression, protein levels, or post-translational modifications underlying the consequences of specific genetic disruptions, thus facilitating *in vivo* identification of physiologically relevant genes, gene pathways and cellular processes that either serve as direct targets, or interact with the disrupted pathways to modulate susceptibility to a given psychiatric disorder (Lai et al. 2006). Indeed, recent work in genetic mouse models suggests that some changes in gene expression induced by a mutation could be adaptive in nature and could reduce the penetrance of the primary mutation (Arguello and Gogos 2006). The involvement of these genetic pathways can be verified in follow-up human genetic studies.

The power of such iterative human and mouse genetic approaches was recently demonstrated in a series of studies designed to understand the dramatically enhanced risk for schizophrenia (20–30 fold increase) associated with a heterozygous microdeletion of chromosome 22q11.2 (22q11DS) (Paterlini et al. 2005). Next to having two schizophrenic parents or an identical twin with schizophrenia, a microdeletion in the q11.2 locus of chromosome 22 is the highest known risk factor, genetic or environmental, for schizophrenia (Karayiorgou and Gogos 2004). *PRODH* is a leading candidate gene from the 22q11.2 locus identified initially through human genetic studies in families afflicted with schizophrenia. It encodes a mitochondrial enzyme that metabolizes L-proline, a putative neuromodulatory amino acid that may influence glutamatergic transmission (Gogos and Gerber 2006, O'Tuathaigh et al. 2007). A *Prodh* mutant mouse strain that represents an accurate model of the functional consequences of susceptibility variants described for this gene has been established and shows many neurochemical and behavioral features relevant to schizophrenia. Specifically, *Prodh* deficiency caused increased cortical dopamine efflux in mutant mice following acute, systemic amphetamine (AMPH) administration. *Prodh*-deficient mice also show hypersensitivity to the locomotor effects of AMPH, abnormal PPI and deficits in associative learning. Deficits in a spatial working memory task emerged in *Prodh*-deficient, but not wild-type, mice only upon pharmacological inhibition of Comt, an enzyme involved in degradation of dopamine and encoded by a schizophrenia candidate gene also located within the 22q11 microdeletion locus, revealing a previously unsuspected interaction between these two genes. This interaction was also reflected at the transcriptional level, with levels of Comt transcript and protein upregulated in the frontal cortex of *Prodh*-deficient mice. This seems to represent a homeostatic response, whereby an increase in Comt expression is engaged to buffer excessive dopamine signaling in the frontal cortex of mice with a hypomorphic variant of the *Prodh* gene (Paterlini et al. 2005). Based on these observations it was speculated that individuals with schizophrenia who have a 22q11.2 deletion are at a particular disadvantage because they are deficient for both genes and perhaps unable to compensate efficiently, through COMT, for the cortical dopaminergic hyperactivity induced by PRODH deficiency. This may explain, at least partly, the high risk for schizophrenia associated with 22q11DS. Because the *COMT* gene comes into primarily two forms (O'Tuathaigh et al. 2007), one low activity (Met-COMT) and one high activity (Val-COMT), one expectation of this model is that hyperprolinemic 22q11DS subjects carrying the deletion on one chromosome and the Met-COMT low activity allele in their non-deleted copy are at higher risk for psychosis. Raux

et al. 2007 tested this prediction in a sample of 92 adult or adolescent subjects with 22q11DS. They found, as predicted from the mouse model, that hyperprolinemic 22q11DS subjects bearing the Met-COMT low activity allele are indeed at higher risk for psychosis. In addition to demonstrating the power of genetic mouse models, these findings produced by iterative human and mouse genetic approaches have important potential therapeutic consequences for subjects with 22q11 microdeletions and schizophrenia.

### Genetic Studies of Endophenotypes

In evaluating the significance of the genetic findings described thus far, with the exception of the 22q11 microdeletions, one is puzzled by the small odds ratios that have been assigned to any given association between individual genes and psychiatric illnesses. These range largely from 1.1 to 1.5, as shown in several meta-analyses of functional candidate gene association studies and early results from positional candidate genes (Kendler 2005). Given our expectation that the first set of effects detected in any research area tend to be the most robust, it is perhaps likely to expect that any additional genes that will be discovered for psychiatric disorders will have smaller average effects than the genes found thus far.

In that context, it is widely believed that use of endophenotypes holds promise in making the mapping of candidate genes for the complex phenotype more successful. By "endophenotypes" or "intermediate phenotypes" we usually refer to heritable quantitative traits that mediate the disease phenotype and can serve as biological markers (Gottesman and Gould 2003). The expectation is that use of endophenotypes can reduce the heterogeneity and largely subjective nature of a qualitative psychiatric diagnosis by utilizing traits that are quantitative, more objectively measured and, hopefully, simpler in their genetic architecture. There is also the common assumption that the effect sizes of genetic loci contributing to endophenotypes are larger than those contributing to disease susceptibility, thus increasing the chance that genetic linkage and association tests will detect them. As a result, the endophenotype concept emerged as a potential strategy for characterizing the neural systems affected by risk gene variants to elucidate quantitative, mechanistic aspects of brain function implicated in psychiatric disease. However, as described above, before proceeding with the application of endophenotypes in association studies of mental disorders, it will be important to demonstrate their superiority to current phenotypes for mental disorders (Flint and Munafo 2007, Valdar et al. 2006).

## FUTURE DIRECTIONS OF GENE DISCOVERY

### Gene Discovery Via Genome-Wide Association Studies

As described above, large-scale association studies using maps of anonymous and common SNPs have been promoted as the tool that will accelerate the discovery of genes related to common diseases (Maraganore et al. 2005, Herbert et al. 2006). This approach is not without limitations, however. For example it has, by design, low power to detect the effects of rare variants, which are poorly tagged by common SNPs. In addition, it remains unclear whether reproducible but small effect (OR < 1.25) common genetic variants potentially involved in complex psychiatric diseases will be readily detectable by such large-scale association testing approaches. Despite these and other statistical hurdles, genome-wide association studies, if appropriately performed and interpreted, promise to expand considerably our knowledge of the genetic basis of psychiatric disorders.

### In-Depth Probing of Gene–Gene Interactions

It is widely believed that genetic interactions among susceptibility genes (especially epistasis, a phenomenon whereby the effects of a given gene on a biological trait are masked or enhanced by one or more other gene) lie at the core of their complexity. By utilizing statistical models to risk of illness in various classes of relatives, Risch (1990) has suggested that gene-by-gene interactions are important in the etiology of schizophrenia. However, such interactions have been studied very little, primarily because twin and adoption studies, which would be normally employed, are very weak at detecting such effects (Neale et al. 1994). The biological basis of these epistatic interactions thus remains largely elusive in psychiatric disorders, but recent studies have provided some important relevant insights (Paterlini et al. 2005, Millar et al. 2005). The Paterlini et al. study, which is also described earlier, is particularly instructive because it indicates that patterns of genetic interactions that involve impaired synaptic function and impaired homeostasis or compensation (genomic buffering) might also account for the epistatic component of the genetic risk of psychiatric disorders in general. The Millar et al. study did not explicitly address the pattern of interaction at the organism level, but used the two-hybrid system to identify a molecular interaction between the products of two schizophrenia candidate genes, the DISC1 protein and (PDE4B) (Millar et al. 2005). Although the gene encoding for PDE4B is not included in the list of strong candidate genes outlined earlier, the authors showed it is disrupted by a balanced translocation in a subject diagnosed with schizophrenia and a relative with chronic psychiatric illness. The PDEs inactivate cAMP, a second messenger implicated in learning, memory, and mood. It was shown that DISC1 interacts with the UCR2 domain of PDE4B and that elevation of cellular cAMP leads to dissociation of PDE4B from DISC1 and an increase in PDE4B activity. The authors proposed a genetic interaction model whereby DISC1 sequesters PDE4B in resting cells and releases it in an activated state in response to elevated cAMP.

Statistical methods of analysis designed to probe epistasis are clearly of growing importance in the genetic dissection of complex disorders. Currently, a variety of methods exist to detect or control for the presence of epistasis. However, all the difficulties with association studies of the main effect of genes (such as low a priori probabilities and multiple testing) are further exacerbated in studying interactions. In addition, these methods are limited by the need for large sample sizes that ensure adequate power to detect gene interactions. An accumulating number of association studies have reported interactions, but none of these studies have yet been widely replicated. For example, Hennah et al. (2007) conditioned their sample of Finnish families for the presence of the Finnish tentative risk allele for *DISC1*, and re-analyzed their genome-wide scan data

of 443 markers based on this stratification. Two additional loci displayed evidence of linkage (lod > 3), and included a locus on 16p13, proximal to the gene encoding NDE1 that has been previously shown to bind DISC1. Although none of the observed linkages remained significant after multiple test correction through simulation, further analysis of *NDE1* revealed a suggestive association between variation in the *NDE1* gene and schizophrenia specific to females. This finding awaits replication, but overall it supports the concept that initial gene findings in multifactorial diseases will assist in the identification of other components of complex genetic etiology.

In general, direct biological inference from the results of statistical tests is very difficult because statistical interaction does not necessarily imply interaction at the biological level. In all, the degree to which statistical modeling can provide insights into the underlying disease mechanisms is likely to be limited, and might require prior knowledge of the underlying etiology. The question of true biological interaction remains of extreme importance in the field of complex psychiatric genetics, but might ultimately be better answered primarily via a combination of molecular and animal model-based approaches.

## Implications for Understanding Disease Pathophysiology and for Improving Treatment

What are the implications of the genetic findings obtained thus far for our understanding the disease pathophysiology? If we use schizophrenia as an example, there are two major pharmacological hypotheses regarding the pathophysiology of this disease—the dopaminergic and glutamatergic hypotheses (Seeman 1987, Coyle 1996). The two hypotheses are not incompatible as it is likely that primary changes in one system would lead to associated alterations in the other. Efforts for synthesis of the initial genetic findings in the context of specific neurotransmitter systems have been reported (for example, Moghaddam 2003). However, it might be premature at this point to claim that the existing genetic data support the critical involvement of one neurotransmitter system over another. For one thing, the genes identified thus far (see for example Tables 16–2 and 16–3) are involved in several neurotransmitter systems. For some of them (such as *PRODH, G72, DTNBP1, NRG1, ZDHHC8, CAPON*) there is variable degree of experimental evidence that they are involved in excitatory glutamatergic pathways, while for others, there is clear evidence of involvement in dopamine (*COMT, AKT1*), GABA (5q *GABA* receptor cluster, *AKT1*), or trace amine signaling (*TAAR6*). However, even for genes that primarily act via disruption of excitatory synaptic function, the final effect could be mediated by abnormal dopamine signaling. In addition, several of the hypotheses regarding the function of the candidate genes have not been sufficiently tested and may be inaccurate (for example the function of G72 as a DAO activator and modulator of NMDA signaling has been recently questioned). Finally, many of the genes appear to have pleiotropic effects that are not restricted to a particular type of synaptic transmission and involve several aspects of neuronal biology. Thus, it is too early to determine from the existing genetic evidence what neurotransmitter systems might be primarily affected in the disease. Indeed, at this juncture, it is equally probable that the cumulative effect of the risk variants will emerge from the pattern of expression and the pattern of interaction among these genes, and it could be restricted to specific brain regions, specific cell types, or both, rather than specific neurotransmitter systems. This spatial selectivity could underlie the differences and commonalities among common psychiatric disorders, as well as their distinction from other common and serious CNS conditions, such as mental retardation, or epilepsy that employ common neurotransmitter systems.

Understanding the function and the interactions among individual susceptibility genes could eventually lead to the design of highly effective targeted therapies for patients with fewer side effects. However, in simpler genetic conditions where knowledge of the genes and protein alterations is often available it has proven highly challenging to translate this genetic knowledge into creation of therapies. Although optimism should perhaps be tempered by this experience, it is conceivable that despite their more complex etiology, multifactorial disorders like schizophrenia may be more amenable to mechanism-based therapeutic intervention (Gogos and Gerber 2006): disease risk associated with common small effect genetic variations is usually very low, but because the risk alleles are so common, a low disease risk corresponds to a large population attributable risk (which means that if the population were monomorphic for the non-risk allele, the prevalence of the disease would be considerably lower). Thus, as noted before, directed therapies might only need to provide relatively modest modulation of appropriate molecular targets to reach an effective threshold in a large fraction of patients, in contrast to simple conditions, where compensation for more pronounced functional alterations might be required.

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CHAPTER

# 17 Modeling Psychiatric Disorders in Experimental Animals

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## Introduction

For the past 60 years, the predominant strategy for developing treatments for psychiatric disorders has depended on the discovery of a prototypical treatment through serendipity, or "trial and error" (Berton and Nestler 2006, Gould et al. 2004, Jacobsen 1986). Research efforts would then be focused on the neurobiological actions of the discovered treatment, with the goal of developing more effective and selective treatments. This method may continue to be useful as our ability to explore the actions of these drugs moves beyond the pharmacology of membrane receptors to intracellular processes (Gould et al. 2004). However, the strategy of understanding a disease through the neurobiology of a prototypical therapeutic drug ultimately reaches an asymptote. Moreover, this approach not only limits the discovery of novel treatments, but also has the broader impact of biasing research on the etiology of the disorder toward mechanisms related to existing drug treatments (Baumeister and Francis 2002). Importantly, this leaves a gap in the understanding of the etiology of the disorder and a significant proportion of patients untreated (Berton and Nestler 2006, Lieberman et al. 2005). A more viable strategy to the study of the neurobiological basis of a psychiatric disorder is to use clinical and epidemiological findings to develop animal models. The purpose of an animal model in psychiatric research is to simplify a problem that is otherwise intractable because of the many factors that need to be investigated to fully understand the disorder. The etiology and symptomotology of disorders such as schizophrenia, depression, and anxiety are complex. However, models of specific components of each of these disorders can be established in experimental animals and can accomplish four aims: (1) elucidate neurobehavioral and neurocognitive processes operating in the disorder, (2) examine candidate mechanisms of pathogenesis, (3) evaluate the plausibility of etiological hypotheses, and (4) identify molecular and neural-circuit targets for novel treatments.

Animal models work best when, as in certain neurological disorders, there is (1) a relatively well-defined syndrome to model as, for example, the cluster of identifiable neuropathological markers in Alzheimer's disease, or (2) a known etiology, such as the single gene mutations that occur in Huntington's disease or Rett's syndrome. In those cases for which causal genes have been discovered, scientists were able to identify a cardinal phenotype, and then select a family or isolated population in which the cardinal phenotype, even if complex, is highly stereotyped. The success of this strategy is exemplified in the discovery of genes for Huntington's disease and Rett's syndrome, where the genetic lesions discovered through linkage studies have proven to exist in the affected population as a whole, and have been proven in animal models to produce key aspects of the disorders (Hackam et al. 1999, Zoghbi 2005). However, even these clear-cut successful examples illustrate the complexities in understanding and treating a nervous system disorder, even with good animal models. More than a decade after confirming the disease-causing gene in Huntington's, the biological pathways leading from the gene to the diagnostic neuropathology, and the links between neuropathology and behavioral symptoms, remain under intense investigation (Landles and Bates 2004). Thus, although innovative animal research has revealed key aspects of the etiologies of neurological disorders such as Huntington's disease, in the course of recapitulating what was assumed to be the necessary and sufficient neuropathology, researchers have found that the pathogenesis

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of the neurobehavioral syndrome is more complex than anticipated.

Modeling psychiatric disorders is likely to be even more complex, given that there are almost certainly multiple *genetic*, *environmental*, and *experiential* factors that underlie the development of these disorders. At the level of genes, the weight of evidence suggests that schizophrenia, depression, and anxiety are *polygenic*: each gene confers a small proportion of risk to the population and the set of genes contributing to the disorder may not be the same from patient to patient (Norton et al. 2006). Indeed, the approach that identified the primary *causal* genes in Huntington's disease and Rett's syndrome, linkage analysis, has thus far identified *susceptibility* genes in schizophrenia. For example, a linkage study of a family in Scotland with a high incidence of psychotic disorders revealed a translocation of a region of human chromosome 1 containing the *Disc1* gene. Neurobiological studies of *Disc1* provide a high level of plausibility for the involvement of the gene in aspects of schizophrenia and depression (Hennah et al. 2006). However, unlike the *huntingtin* gene in Huntington's disease, *Disc1* abnormalities are not a common feature across schizophrenia patients (Norton et al. 2006). Thus, in discerning the genetic basis of these psychiatric disorders, we must deal with (1) genetic pleiotropy, the probability that one gene affects more than one trait, and (2) trait complexity: the fact that the traits underlying psychiatric disorders are disruptions of adaptive behaviors that are, in turn, modulated by multiple genes. This reality, combined with the large number of genes expressed in brain cells (55% of the genome) and the probabilities for biologically significant mutations in multiple loci within a gene, leads to the possibility that underlying even the most narrow classification of a mental illness "may lie a vast diversity of potential behavior-impairing mutations across the thousands of genes involved in brain development" (Keller and Miller 2006). Not surprisingly, links between specific genes and psychiatric illnesses are only now beginning to be delineated (Harrison and Weinberger 2005, Norton et al. 2006). Moreover, in contrast to some genes linked to Alzheimer's disease, the biological effects (e.g., effects on protein structure or function) of psychiatric disease-related genetic polymorphisms are, as yet, unknown (Harrison and Weinberger 2005). At the next level of complexity, susceptibility polymorphisms interact with environmental factors that impact on embryonic and postnatal development (Cannon et al. 2003). Lastly, the limitations or neural "biases" that are set by genetic or early-life factors interact with—and may limit—the experience of the person (i.e., learning), which, in turn, is essential for normal neural and behavioral maturation. In summary, three domains of etiologic factors, "genetic/epigenetic," "environmentally induced injury" and "experience" interact to determine risk for a psychiatric disorder. Figure 17–1 shows a model by which these factors interact to influence neural function, psychological processes, and behavior. We argue below that the best strategy for understanding how these etiologic factors lead to a psychiatric disease is to study the effects of these factors on neurocognitive and neuroaffective constructs, that is, the relationship between neural function and a cognitive or affective process. Animal models can be used to understand these processes, and that understanding can then be applied to the corresponding human behaviors.

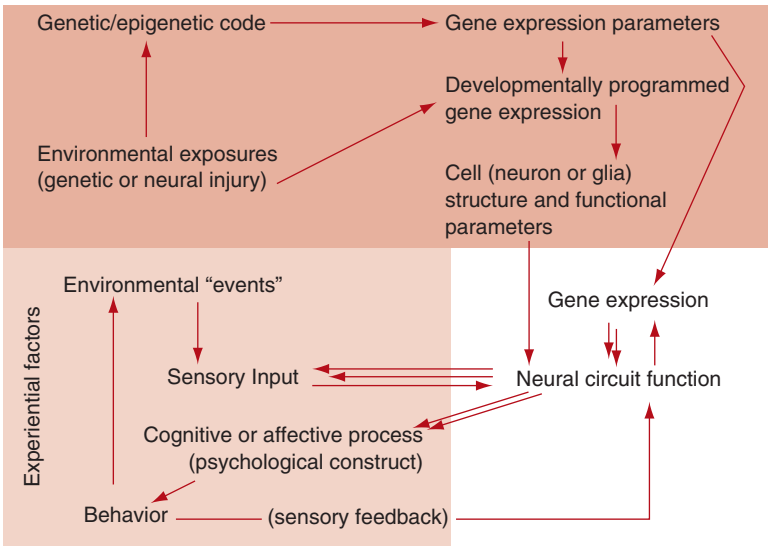



**Figure 17–1** *Three domains of etiologic factors in psychiatric disorders. Genetic/epigenetic factors are familial and pre- or neonatally programmed limits on gene expression. "Environmental exposures" cause permanent biochemical or physical injuries to the brain that may also limit gene expression or neural function. The experiential domain represents an iterative process involving the organism reacting to and acting on the environment. As shown in the "blue pathway," genetic code and early environmental exposures set limits on developmentally programmed gene expression, environmentally induced gene expression, and neural function. These limitations on neural-circuit function, in turn, limit and/or bias sensory input and/or cognitive or affective processes. The behavioral output from such a system is less adaptive. The "red pathway" shows the influence of experience on cognitive and affective processes. "Events" include stimuli and contingencies that promote or threaten individual survival or procreation. Skewed cognitive processing conferred by factors in the blue pathway may lead to maladaptive behavior and adverse outcomes. As a result, the process by which experience affects neural function and structure is altered. Thus, genetic and early environmental factors form limits that, in turn, alter the cumulative effects of experience on brain and behavior. Traditionally, "etiologic" animal models have been designed to measure the effects of manipulating factors in the blue pathway, whereas "psychopathology" models manipulated factors in the red pathway. Ultimately, however, the animal experiment should model the effect of a specific etiologic factor on (1) a cognitive or affective process known to be disrupted in a psychiatric disorder and (2) the operation of neural circuits hypothesized to mediate the psychological construct.*

## Defining Phenotypes and Establishing Validity in Animal Models

### Defining the Phenotype to be Modeled

Despite, or arguably *because of*, the complexity in modeling psychiatric disorders, it is essential to approach the goal of defining the phenotype to be modeled and establishing the model's validity using rational strategies that have been successful for neurological disorders (Lewandowski and Small 2005). The best of these strategies involve three steps: (1) to identify one or a set of cardinal phenotypes of the disease, (2) to operationalize each phenotype, (3) to test the effects of candidate genetic and environmental determinants of the disease on the cardinal phenotype(s). For disorders such as Alzheimer's disease, which shares behavioral phenotypes (e.g., memory deficits) with other etiologically distinct diseases (e.g., multi-infarct dementia), the most successful approach has been to relate the cardinal behavioral phenotype (e.g., memory deficits) to a neuropathological phenotype (e.g., decreased hippocampal blood volume or presence of plaques or neurofibrillary tangles), and then search for genetic variation associated with the neural phenotype (Lewandowski and Small 2005). The more precise the description of the behavioral and neuropathological phenotypes, the higher the probability is of discovering the underlying genetic basis. Thus, the success of this strategy depends on a robust operational definition of a neuropsychological or "neurocognitive" phenotype. This is a description of a behavioral abnormality that incorporates a knowledge of the neural circuits essential for the operation of the psychological processes underlying the affected behaviors (Chudasama and Robbins 2006, Everitt and Robbins 2005). Table 17–1 shows a number of affective and cognitive processes that are affected in psychiatric disorders such as schizophrenia, anxiety, and depression.

The definition of a "neuroaffective" or "neurocognitive" phenotype affected in a psychiatric disorder depends not only on the precise description of the psychological process involved, but also on an accurate characterization of the neuropathology correlated with the abnormal affective or cognitive function. These neural correlates are determined in vivo with structural and functional imaging (Davidson and Heinrichs 2003, Laruelle 2000) and electrophysiological methods (e.g., electroencephalography) (Braff et al. 2001, Shelley et al. 1999); they are also revealed through postmortem histopathological studies (Harrison 2004, Lewis 2002). In psychiatric disorders, the cardinal behavioral phenotypes are often not exhibited by experimental animals. However, there is now a significant amount known about the neuropathology associated with these disorders (Harrison 2004, Harrison and Gittins 2003, Lewis 2002). Thus, the above strategy can be used to examine biochemical mechanisms that might lead to an observed neuropathology (Harrison and Weinberger 2005, Lewandowski and Small 2005, Lewis 2002) and, in parallel, to determine how the experimentally-induced neuropathology impacts behavior (Chudasama and Robbins 2006, Everitt and Robbins 2005, Gimenez-Llort et al. 2007, Moore et al. 2006).

Although animal models have often been designed to understand symptoms of diseases (e.g., psychosis or anxiety), it may be more fruitful to study the determinants of an *endophenotype*. An "endophenotype" was defined by Gottesman and Gould (2003) as a heritable trait that underpins a mental disorder and is more closely associated with genetic factors than are the disorder's symptoms. Examples of candidate endophenotypes in psychiatric disorders might be neural processes that mediate reward learning, expectancies for aversive events, or goal-driven behavior. Such endophenotypes may contribute, respectively, to "surface" symptoms such as reduced motivation, avoidance behaviors, and disorganized speech observed in schizophrenia. However, although endophenotypes are essential for modeling genetic etiologies of disease, experiments aimed at understanding environmental regulation of neural activity and behavior are important for understanding the more "proximal" determinants of a psychiatric disorder or its symptoms. The combined knowledge gained from endophenotype-based models and models of environmental or pharmacological regulation of a phenotype will help us understand the spectrum of mechanisms underlying the manifestation of a psychiatric disorder.

### Forms of Validity

There are several forms of validity that can be achieved in an animal model. Although these concepts were most commonly applied in personality theory and standardized testing in humans, they are equally useful in developing effective animal models. Complete descriptions of forms of validity and their significance are provided in Robbins (2004). Here we briefly illustrate the usefulness of three key types of validity. *Construct validity* is arguably critical in the rational development of animal models of psychiatric disorders. In establishing construct validity, researchers draw on well-developed theories about psychological (e.g., emotional or cognitive) "constructs"—processes that cannot be measured directly. Experiments guided by these theories have produced a wealth of data in humans and experimental animals showing how such constructs affect behaviors. As an example, unlike body temperature, selective attention cannot be measured directly. However, based on a well-accepted operational definition of selective attention, we can infer that this process is modulating a behavior (e.g., identifying a friend's face) if the behavior is disrupted by adding irrelevant stimuli to the environment. The distinction between the overt behavior and the underlying psychological construct is important for at least two reasons. First, most generally, an overt behavior may be affected by different psychological processes at different times. Following the previous example, one may fail to identify a friend's face because the *memory* for the features of the face is inadequate or because one's ability to filter out the other faces in the crowd, that is, *selectively attend* to the relevant face, is impaired. The second reason, more directly relevant to animal models, is that while psychological constructs may operate similarly across species, the behaviors that can be quantified may be different. For example, loss of "executive control" over responding might be measured by inappropriate speech in a human, reaching in a nonhuman primate, or nose-poking in a rat. When possible, it is best to try to use similar behaviors (e.g., lever pressing). However, what is essential for psychological and neural construct validity is that the behavioral response of the experimental animal changes as a function of the same environmental and biological factors that

**Table 17–1** Psychological Constructs Affected in Psychiatric Disorders and Related Animal Models

| | Psychological Construct | Phenotype Affected in Psychiatric Disorders | Example of Animal Model |
|---|---|---|---|
| Affective | Processing of reward | Associating hedonic value with stimuli | Stimulus preference; conditioned place preference |
| | Avolition, incentive | Willingness to *pursue* (work for) items or events that person finds rewarding | Reinforcement ratio breakpoint; incentive/reward ratio tasks |
| | Social drive | Desire and intent to engage in social interaction | Approach and exploration of conspecifics; conditioned place preference for social stimuli; allogrooming |
| | Threat sensitivity | Fear/anxiety; maladaptive risk-taking | Conflict (approach–avoidance) paradigms<br>Resident/intruder paradigms<br>Forced swim or similar tests |
| | Passive coping | | Shock- or threat-induced freezing behavior |
| | Active coping | Withdrawal, immobility<br>Operating on threatening stimulus, escape, Displacement Behavior | Shock-induced behavioral activation |
| | Expression of affect | Production of movement that reflects emotion | No clear analogues (possibly vocalization) |
| Cognitive | Perception | Olfactory, visual or auditory discrimination | Olfactory, visual, or auditory discrimination |
| | Preattention | Stimulus-evoked responses in cortical EEG | Stimulus-evoked changes in field recordings or EEG; modulation of reflexes by "oddball" stimuli |
| | | Prepulse inhibition of startle | Prepulse inhibition of startle |
| | Sustained and selective attention | Signal detection as a function of time, space and distractors | Signal detection as a function of time, space and distractors, e.g., multiple-choice (bars or nose-poke locations) stimulus-detection reaction time tasks |
| | Executive control | Organizing and redirecting behavior around a goal<br>Changing attentional bias and responses according to optimize outcome (attentional set shifting) | Attentional set-shifting tasks; reversal of spatial or stimulus discriminations |
| | Working memory | Active maintenance of information for future use in computation or decision<br>Measured by tasks that vary "load" (the amount of information maintained in order to make correct choice) | Maze or operant-box-operated tasks in which load is varied or accumulates over trials |
| | Relational memory | Recall of relationships among elements of verbal passages or events | Recognition of spatial context (e.g., contextual fear conditioning); trace conditioning |
| | Execution of behavioral sequences | Maintaining unlearned or learned, goal-directed behavioral sequences | *Species specific: Nonsocial*<br>Food hoarding, self-grooming<br>*Species specific: Social*<br>Play, allogrooming, sexual behavior, maternal behavior<br>*Learned:* Ordinal-response operands |

are hypothesized or known to modulate the disease-related behavior in humans.

The *predictive validity* of the model is assessed by testing how the model responds to the treatments or factors known to improve or exacerbate the relevant symptoms of the disease. Finally, it is important to use complementary experimental methods and different target behaviors to test a hypothesized relationship between a neural phenotype and a psychological construct. Such an approach adds *convergent* and/or *discriminant* validity to the model.

## Dissecting Cognitive and Behavioral Endophenotypes from Complex Mental Disorders

The first step in identifying a neurocognitive phenotype in a psychiatric disorder is considering the psychological process or *construct* that might be most closely related to particular symptoms. A great advance in understanding basic cognitive functions in schizophrenia has been achieved, at least in part, using first monkeys and then rodents to explore the cellular basis of working memory in the prefrontal cortex and to study the parallel impairment in schizophrenia (see Goldman-Rakic 1998). Similarly, in the area of drug abuse, it is hard to reject the evidence that the simple operant paradigm of drug self-administration through intravenously implanted catheters in mice, rats, or monkeys is highly predictive of which drugs are likely to be abused in humans. In theoretical terms, there is considerable evidence that this self-administration behavior taps into a fundamental brain reinforcement mechanism that includes basal forebrain structures such as the ventral striatum (Everitt and Robbins 2005). There is, indeed, a case for considering drug self-administration behavior to be perhaps the most convincing and best validated of all animal models of neuropsychiatric

disorders (Le Moal et al. 2007). At the more controversial end of the spectrum, positive symptoms of schizophrenia such as hallucinations and delusions, or symptoms of depression and anxiety such as ruminations of low self worth, are often cited as examples of psychopathology which cannot have measurable equivalents in experimental animals. However, these assumptions may be premature, as is illustrated by the following examples of models of neurocognitive and neuroaffective phenotypes in these disorders.

## Modeling Neurocognitive Phenotypes in Schizophrenia: From Sensory Gating to Cognitive Flexibility

Core cognitive and behavioral phenotypes in schizophrenia have been identified primarily by "reformulating" the interpretation of symptoms to postulate cognitive processes that may underlie the symptoms. For example, delusions and disorganized behavior might both be reconceptualized as failures in the "reference" and "working memory" processes necessary to maintain goal-directed behavior. In addition, cognitive phenotypes have been revealed by using quantitative tests that were originally developed to understand normal cognition or test-specific cognitive abilities in nonpatient (often military) populations as predictors of job performance. Examples of these cognitive constructs and the key features of the rodent behavioral tasks that are used to measure them are presented in Table 17–1. A useful summary of the rodent behavioral tests used to test these constructs can also be found in Arguello and Gogos (2006). In the case of schizophrenia, it is important to note that specific cognitive deficits have been identified at nearly every stage of cognitive processing from perception to "executive function" and relational memory (see Table 17–1 for summary). This section reviews selected behavioral paradigms that have proven useful in modeling the pathogenesis of abnormalities occurring at the lowest and highest levels of cognition in schizophrenia.

### Modeling Perceptual and Preattentional Deficits in Schizophrenia

Stimulus "gating" refers to an alteration in the detection or response to the second of two stimuli. A deficit in this process is considered a core cognitive impairment in schizophrenia and may contribute to its clinical symptoms (Braff et al. 2001). Gating processes are "automatic" in that they are unconscious and require no effort. Physiologically, "sensory gating" is operationalized as a change in the amplitude of an electroencephalographically measured neural population response potential, for example, the N40 or P50 potentials, evoked by the second stimulus compared to the first. Another type of perceptual process impaired in schizophrenia is the so-called "oddball" task in which the EEG response to a discrepant stimulus in a series is a function not of its physical properties per se, but of its contrast with the expected stimulus. Given the very short-latency neural responses involved and the fact that they can be measured at the cortical surface, sensory gating is considered to be a very "early" event, occurring within the sensory thalamocortical systems. Deficits in "oddball" and sensory gating tasks are well replicated in schizophrenia and have been successfully modeled in nonhuman primate models following repeated administration of phencyclidine (Shelley et al. 1999) using nearly identical electrophysiological outcome measures. There is no a priori reason why similar models could not be employed in rodent models.

### Sensorimotor Gating and Latent Inhibition

Sensorimotor gating and latent inhibition are constructs that involve the influence of the automatic encoding of neutral stimuli on subsequent reflexive or learned behaviors. These constructs show a high level of homology across species, and the rodent models for both of them have elucidated the neural circuitry and pharmacology of antipsychotic drug (APD) effects.

Sensorimotor gating is the process by which a reflexive response to a stimulus is blunted by an almost immediately preceding, less salient (indeed, hardly detectable), surrogate stimulus. Prepulse inhibition (PPI) is a useful objective index of sensorimotor gating. PPI follows the same psychophysical principles and is mediated by similar neural circuits across many species, including humans, monkeys, and rodents (Geyer et al. 2001, Swerdlow et al. 2001). These features of PPI, along with the fact that it is reduced in schizophrenia patients, makes it an optimal paradigm for evaluating neuropathology or pharmacology relevant to schizophrenia. The utility of PPI in preclinical schizophrenia research has been extensively reviewed (Geyer et al. 2001, Swerdlow et al. 2001). PPI deficits are neither diagnostic for nor unique to schizophrenia. The main strength of the model has been its construct validity with regard to the neural circuits that are abnormal in schizophrenia and its predictive validity with respect to APDs (Geyer et al. 2001).

The acoustic startle reflex response is mediated by brainstem mechanisms, but PPI itself represents a top-down modulation of this circuitry by hippocampal-striatal circuitry that is homologous to circuits implicated in schizophrenia (Swerdlow et al. 2001). PPI can be disrupted by excessive limbic striatal dopamine transmission, a mechanism that has long been postulated to mediate psychotic symptoms in schizophrenia (Laruelle 2000). Accordingly, APDs that primarily block dopamine D2 (DRD2) receptors (the "typical" phenothiazine and butyrophenone APDs) reverse dopamine-agonist-induced PPI deficits. An important finding in preclinical schizophrenia research was that PPI deficits induced by the nondopaminergic psychotomimetic phencyclidine could be reversed by the atypical APD clozapine but not DRD2 antagonists. Although PPI can be sensitive to drugs that have no antipsychotic efficacy, this paradigm has been valuable in dissecting the pharmacology of "atypical" APDs in pharmaceutical development (Geyer et al. 2001, Hagan et al. 2005). The sensitivity of PPI to neurodevelopmental manipulations that produce schizophrenia-relevant histopathology or pathophysiology in limbic cortical circuits (Geyer et al. 1993, Lipska et al. 1995, Moore et al. 2006) is likely to open new views of the role of PPI in animal models of psychiatric disorders.

Latent inhibition (LI) was discovered by animal learning theorists; it is the process by which preexposure to a neutral stimulus (e.g., a tone or light) retards the formation of a Pavlovian association between that stimulus and an unconditioned (usually aversive) stimulus (US). Theoretically, through covert attention to the stimulus during the preexposure, the animal learns that the stimulus predicts the *absence* of a significant event. This contingency must then

be extinguished during the learning of the new contingency between the neutral stimulus with the aversive US (Weiner 2003). LI is mediated by limbic cortical and striatal regions, which exhibit pathologies that correlate with the positive symptoms of schizophrenia. Moreover, multiple clinical studies indicate that LI is disrupted during psychotic episodes and is restored during subchronic APD therapy. Like PPI, LI has been useful in predicting or categorizing pharmacotherapies in schizophrenia. However, its most important role in preclinical research may be as a model of the roles of the entorhinal cortex and specific striatal subregions in relatively automatic cognitive processes that, in turn, may disrupt the cognitive "switching" necessary to recognize and adapt to new environmental contingencies (Weiner 2003).

### Modeling Cognitive Flexibility, an Executive Function Disrupted in Schizophrenia

A test of cognitive flexibility, the ability to shift attention from one aspect of an object to another, used in the assessment of patients with frontal lobe damage is the Wisconsin Card Sort Test (WCST). The WCST and more parametric "response-rule-switching" tasks have been extremely useful challenge tests for schizophrenia patients. The patients show deficits in these tasks, and the recruitment of the frontal lobe by these tasks is abnormal in these patients, as shown by functional brain imaging. Thus, the neuropsychological tests of "executive function" have had a prominent role in the development of the idea of "hypofrontality" in schizophrenia (Weinberger et al. 1988). In the Cambridge Neuropsychological Test Automated Battery, the WCST has been reconfigured to produce a simpler suite of tasks, not only for humans but also for animals, that reflect the building blocks of this complex cognitive test. In short, two perceptual dimensions (e.g., shape and color) are defined and compound stimuli are formed by combining exemplars of the two dimensions. The subject is then trained to discriminate the dimensions on the basis of trial-and-error feedback, and learn which exemplar is correct. This discrimination may be reversed so that the alternative object is correct and the formerly correct stimulus wrong. When the subject has learned to discriminate and reverse this discrimination, new exemplars are introduced with the same dimension remaining relevant. This is called an intradimensional shift and requires the establishment of an attentional set, through "learning-to-learn." Eventually, having learned to form an overall set in this way, new exemplars are again introduced, and the subject is required to shift attention to the alternative dimension. This is called an "extradimensional shift" and is a core element of the WCST.

The neural basis of this set-shifting behavior has been studied in marmoset monkeys with fiber-sparing lesions of the lateral prefrontal cortex or orbitofrontal cortex. Strikingly, whereas reversal learning was impaired by lesions to the orbitofrontal cortex, extradimensional shifting was deficient following lesions to the lateral prefrontal cortex, thus demonstrating a "double dissociation" of the roles of these two prefrontal cortex regions in these different forms of shifting behavior (Dias et al. 1997). Understanding the basic functions of these two prefrontal cortex regions is a necessary prerequisite for understanding their contribution to cognitive deficits in neuropsychiatric disorders such as schizophrenia and to interpreting the effects of selective neurotransmitter manipulations on these aspects of cognitive performance. This experiment demonstrates the utility of the intradimensional/extradimensional test as a probe of prefrontal cortical function in experimental animals.

Subsequently, the intradimensional/extradimensional paradigm has been validated in studies of humans with frontal lobe lesions (Owen et al. 1991) and using functional magnetic resonance imaging (Hampshire and Owen 2006). This paradigm has now also been generalized to the rat (Birrell and Brown 2000) and to the mouse (Garner et al. 2006) using taste and texture as perceptual dimensions, but embodying the same principles of intradimensional and extradimensional shifting. Thus Birrell and Brown (2000) confirmed Dias et al. (1997) in demonstrating frontal correlates in the rat of different forms of behavioral shifting; this evidence is of theoretical importance in showing a form of functional homology between the primate and rodent brain, even for complex frontal cortex-mediated executive functions relevant to the cognitive deficits in schizophrenia. There has also been considerable work on the neurochemical substrates of this paradigm that are relevant for its use as a model of cognitive dysfunction in psychiatric disorders (Chudasama and Robbins 2006). Because the Cambridge Neuropsychological Test Automated Battery intradimensional/extradimensional test, using the same stimuli as used in monkeys, is sensitive to deficits in patients with schizophrenia (Pantelis et al. 1997), a vertical integration of findings in certain areas appears feasible across species and for human psychiatric disorders.

The positive symptoms such as hallucinations and delusions are regarded as some of the most difficult to model in animals. Although the models of basic cognitive processes such as sensorimotor gating and LI just discussed may be related at some level to psychosis, there is no a priori reason why hallucinations themselves cannot be modeled in animals. Clinicians use not only self-reports by patients to indicate the presence of hallucinations, but also behavioral observations that strongly suggest that a patient is responding to internal stimuli, such as speaking and gesticulating, as if in conversation with an unseen social partner. By analogy, a hallucination might be operationally defined in animals as a complex, voluntary behavioral sequence similar to operant- or stimulus-driven behavior, but that occurs in the absence of relevant stimuli or contingencies. Examples include the apparent manipulation of "imaginary" food objects or apparent aversive reaction to a nonexistent object, expressed by monkeys following chronic amphetamine or phencyclidine treatment (Lyon 1991). Similarly paranoid delusions, conceptualized as the attribution of inappropriate salience to stimuli (Kapur 2003), might be modeled in animals.

## Affective Constructs: The Approach–Avoidance Conflict in Anxiety and Depression

Threat detection, fear-related behaviors, reward processing, incentive, and social drive comprise an interactive cluster of "affective" constructs relevant to all psychiatric disorders (see Table 17–1), but especially anxiety and mood disorders. Animal models of affective constructs are designed by adapting ethological observations to the laboratory, and on quantifying behaviors that appear to be mediated by processes that correspond to human subjective affective states. A key

distinction is between states of fear and anxiety. Any animal, such as a rat or mouse, exposed to highly threatening stimuli, such as a cat, shows characteristic responses (Blanchard et al. 1997). In the immediate presence of the cat, the rat's defensive options depend on whether it can escape or not. If it can escape, then it will flee ("flight"), or if there is no route of escape, it may exhibit immobility, or "freezing" behavior, which deprives the predator of sensory cues needed to locate it. As a last resort, the rat may exhibit defensive aggression. Besides biting, the rat may vocalize, which serves a social function, that is, signaling the presence of danger to other rats. (It should be noted that vocalizations and other specific behaviors distinguish defensive aggressiveness from predatory behavior.) Collectively, all of these behavioral responses to the predator's immediate presence can be defined as fear. By contrast, "anxiety" might be defined as a process involving (1) the detection of unconditioned (e.g., odor) or learned cues that *predict* danger and (2) the physiological and behavioral responses to these cues, by which the animal can avoid the danger.

Another concept of anxiety involves conflict. In general, an animal's environment contains a mixture of oppositely valenced cues: appetitive (e.g., predictive of food, water, safety, or sex), neutral, and aversive (predictive of life-threatening or painful events) ones. The cognitive processing of and behavioral responses to these cues are governed by the animal's internal state (e.g., hunger) and the cues' salience or predictive power. Thus, in the wild, animals are continually in *conflict* between approach and avoidance tendencies. Since Freud, the conflict between desire and fear has been central to our concept of anxiety. The resolution of the conflict is highly influenced by the appraisal of stimulus-outcome contingencies. Many studies have now shown that a "threat-detecting" bias revealed in cognitive tasks predicts trait anxiety and/or diagnosis of an anxiety disorder (Chan et al. 1996). Moreover, continued avoidance behaviors limit the organism's engagement in incentive learning and positively reinforced behaviors, a diagnostic feature of depression.

Additional construct and etiologic validity for conflict tests can be found in environmental or developmental models of heightened anxiety. Specifically, peripubertal social isolation, a manipulation shown to be associated with anxiety in humans, produces anxiety-like profiles on conflict tests, as well as pathology in the cortico-limbic regulation of stress hormones in rodents (Serra et al. 2000). Other cross-species examples can be found in the inhibition of appetitive behaviors, including play or solicitation of the mother, in juvenile humans, monkeys or rats when confronted by a potentially threatening social stimulus (Hofer 1996, Kalin and Shelton 1998). A high tendency toward avoidance ("shyness") can be a juvenile behavioral trait marker for anxiety later in life (Muris 2006).

There are well-validated behavioral paradigms used to model conflict in rodents (Broekkamp and Jenck 1989). In some of these, the stimulus is designed to evoke both unconditioned appetitive and avoidance behaviors. Such models include (1) the light–dark shuttle box, in which the rodent's tendency to avoid open (e.g., well-lit) areas conflicts with a learned aversive association (foot shock) with the dark chamber; and novelty-suppressed feeding, in which the tendency to approach and consume a food bait is in conflict with the bait's location in the brightly lit center of a novel open field. In other tests, positively reinforced responses are suppressed by contingent punishment. These tests include the punished drinking test, in which licking from waterspout is punished by electric shocks, and the safety signal withdrawal operant paradigm, in which suppression of lever pressing for food is induced by the withdrawal of a conditioned signal for safety. Behaviors in other tests, such as locomotion in a novel open field, can certainly be modulated by conflict. However, the most interpretable tests are those in which the two conflicting "drives" are systematically manipulated. In the next section, we review basic studies on the pharmacology and neural circuitry underlying conflict behavior and fear and show that these models have provided strong validation of the primacy of this construct in anxiety.

## Using Neuropathological or Pharmacological Phenotypes to Test Etiologic and Pathogenic Hypotheses of Psychopathology

Ideally new animal models should drive translational research, which involves two strategies that are employed in parallel: (1) sorting human samples according to behavioral traits relevant to psychiatric disorders in order to investigate hypothesized neural systems or genetic differences that account for the behavioral effect, and conversely (2) disrupting candidate genes, neurotransmitter systems, or neural circuits in animals to determine their role in the animal's behavior that models the psychological processes impaired in a psychiatric disorder. For example, a study finding a correlation between a neural phenotype and a behavioral abnormality in humans would generate the hypothesis that the neural system is necessary for, or mediates, a specific psychological construct (i.e., function). That hypothesis would then be tested using animal models in which the neural system is directly manipulated (e.g., by lesions or pharmacological or genetic manipulation), and the effect on behaviors related to the psychological construct of interest is measured. Throughout this process, convergent and construct validity are important. If a number of complementary methods are used to manipulate the target neural system, and the results converge on a set of behavioral outcomes that are consistent with the theorized operation of the psychological construct, then convergent and construct validity have been established. This increases the probability that the neural target is important for the psychological process underlying the human symptom. In the next section, we provide examples from basic and translational research in anxiety and schizophrenia to illustrate this point.

## The Anatomy and Pharmacology of Conflict Behavior: An Example of "Full Reciprocal Translation" in Anxiety Research

Animal models of the neural substrates of fear and conflict behavior have been central to the search for pathogenic neural processes and molecules for anxiety disorders. The neural circuits necessary for anxiety-related (i.e., high avoidance) or fear behaviors in rodents center on the amygdala (Davis et al. 2001, LeDoux 1992) and correspond to the brain regions implicated in anxiety by functional neuroimaging studies (Strange et al. 2006). Consistent with the importance of the constructs of threat detection and avoidance in anxiety, predator threat in rodents leads to changes in

neurotransmission in the amygdala (Roseboom et al. 2007). Alterations in forebrain serotonin transmission also mediate fear and anxiety. For example, serotonin (5HT) reuptake inhibitors or agonists selective for the 5HT1A receptor modulate conflict behavior and are therapeutic as treatments for anxiety (Broekkamp and Jenck 1989). Genetic or developmental pharmacological manipulations of serotonin transmission in mice produce specific abnormalities in conflict behaviors, which suggests that these molecules modulate the bias toward avoidance or defense during the appraisal of ambiguous or mildly aversive situations (Ansorge et al. 2007, Gross and Hen 2004, Weisstaub et al. 2006). The data from gene expression mapping across specific brain regions and the effects of tissue-specific manipulations of gene expression on conflict behaviors have led to more specific hypotheses regarding serotonin transporter or receptor modulation of specific limbic and cortical circuits in anxiety (Plath et al. 2006, Weisstaub et al. 2006). One example of "fully reciprocal translation" in modeling the neurobiology of anxiety has been identification of genotypes that lead to more or less activity at the serotonin transporter. The genetic mouse models predicted that in humans the genotypes would have functional significance for cortico-limbic activity and the processing of the "aversiveness" of stimuli in the environment. This prediction was borne out by studies combining genotyping, functional imaging, and anxiety trait assessment in normal humans (Hariri and Holmes 2006).

## Models of Neuropathological and Pathophysiological Phenotypes in Schizophrenia

Animal behaviors that may bear little resemblance to the human behavior being modeled can nevertheless have construct validity in modeling the neural pathology of behavioral symptoms. Schizophrenia, used as an exemplar in this section, is diagnosed by positive (hallucinations and delusions) and negative (anhedonia, social withdrawal, alogia) symptoms, but also characterized by cognitive deficits (see Table 17–1). There is now a considerable literature on the correlations between symptom domains and neuropathology. Neurobehavioral hypotheses of schizophrenia under active investigation include (1) dopamine "imbalance" consisting of excessive or dysregulated striatal dopamine (DA) transmission (Kapur 2003, Laruelle 2000) coupled with deficient frontal cortical DA transmission (Abi-Dargham et al. 2003, Goldman-Rakic 1998) and (2) specific disruptions of glutamate- or GABA-mediated neurotransmission in cerebral cortex. These pathogenic processes are likely to be related. Indeed, animal models have shown that the pattern of spike activity of neurons projecting from the prefrontal cortex and hippocampus is determined by glutamatergic synaptic input from thalamic and other cortical regions and is tightly controlled by GABAergic interneurons (Gonzalez-Burgos et al. 2005, Klausberger et al. 2003). This cortical activity, in turn, regulates subcortical and cortical dopamine systems (Floresco et al. 2001, 2003) (Figure 17–2). In schizophrenia, activity in prefrontal cortex (PFC) and anterior medial temporal cortex (hippocampus and parahippocampal cortex: HIPP) are *dysregulated* by abnormal dopaminergic and GABAergic inputs onto the cortical projection neurons, and by alterations of synaptic structure and signal processing intrinsic to the projection neurons. This produces abnormal signaling from the PFC and HIPP to other cortical regions and to the striatum (STR). As described in Section "Modeling Neurocognitive Phenotypes in Schizophrenia," frontal and limbic (e.g., hippocampal and parahippocampal) cortico-striatal circuits, and their modulation by dopamine, mediate a number of important cognitive processes affected in schizophrenia and have been hypothesized to underlie the positive and negative symptoms of schizophrenia (Moore et al. 1999).

At the level of symptoms, psychotic symptoms have been found to correlate with excess metabolic activity in the HIPP (Harrison 2004, Schobel et al., in press) and increased DA transmission in STR (Laruelle 2000), whereas negative symptoms and cognitive deficits are associated with decreased metabolic activity in the PFC, decreased anterior temporal lobe size, and presumed decreases in cortical dopamine transmission (Abi-Dargham et al. 2003, Goldman-Rakic 1998, Sigmundsson et al. 2001). There is also substantial support for the hypothesis that these neural phenotypes arise from genetic and environmental factors

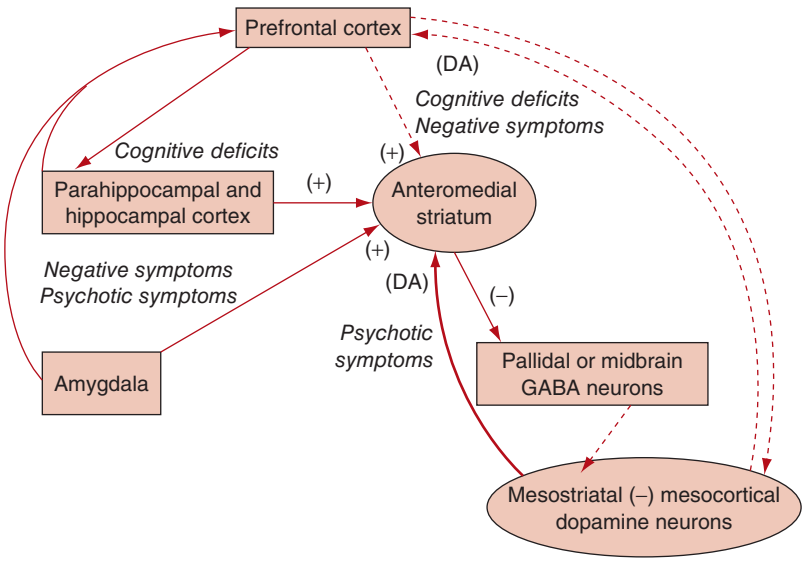



**Figure 17–2** *Abnormal cortical and subcortical circuits in schizophrenia. Yellow shading and thick, striped arrows indicate regions or circuits in which increased activity is associated with psychotic symptoms. Gray shading and dashed gray lines indicate structures or circuits in which decreased activity is associated with cognitive deficits and decreased affective behaviors (negative symptoms). Simple black lines show additional selected anatomical connections postulated to play a role in the disruption of cognitive and affective constructs in schizophrenia. See the text for description of psychological constructs mediated by these circuits.*

influencing brain development (Harrison and Weinberger 2005). Below we review examples of models in which the *relationships between* disease-relevant *neuropathology and key cognitive or affective constructs* in the disorder are characterized.

## The Cortical–Subcortical Dopamine Imbalance in Schizophrenia

Any model of schizophrenia has to take account of the fact that dopamine D2 receptor blockade is an effective treatment for the positive symptoms (Laruelle 2000). The dopaminergic neurons of the mesencephalon project to the frontal cortex, the hippocampus, and many subcortical regions (Gardner et al. 2000) (Figure 17–2). The most densely DA-innervated structure in the forebrain is the striatum. Several lines of evidence suggest that enhanced DA transmission in the striatum is an essential mechanism of psychosis. First, the efficacies of most APDs correlate with their affinity for D2-like receptors (Seeman and Seeman 1987). Second, abuse of DA-releasing drugs, especially amphetamine, can lead to schizophrenia-like paranoid delusions (Laruelle 2000). Most of these actions appear to depend on regulation of the mesolimbic dopaminergic system by limbic afferents from structures such as the basolateral amygdala and hippocampus (Moore et al. 1999). As described above and shown in Figure 17–2, excess limbic drive of subcortical DA may mediate psychosis. Thus data from animal models converge with human data to support the hypothesis that cortical or limbic "dysregulation" of striatal DA transmission may disrupt the evaluation of the significance of stimuli, and that this neurobehavioral pathology may contribute to hallucinations.

Reduced DAergic innervation of the frontal and temporal cortex has been observed in postmortem studies of schizophrenia. This may be one neuropathological underpinning of reduced functionality of the frontal cortex in this disorder (see Section "Modeling Neurocognitive Phenotypes in Schizophrenia"). The dopamine D1 receptor has long been associated with cognitive function such as working memory within the PFC, with both diminished and excessive D1 receptor stimulation disrupting functions such as working memory (Abi-Dargham et al. 2003, Goldman-Rakic 1998). This is consistent with a large amount of evidence in experimental animals that working memory and attentional functions depend upon the integrity of the prefrontal cortical DA system (Crofts et al. 2001, Goldman-Rakic 1998). The hypothesis is relevant to the parallel working memory deficits shown by monkeys with mesocortical dysfunction, and schizophrenics tested in delayed saccade and other procedures suitable for measuring working memory (Goldman-Rakic 1998, Park and Holzman 1992). It may also account for the deficits found in abstracting rules in the Cambridge Neuropsychological Test Automated Battery intradimensional/extradimensional task (Pantelis et al. 1997). Similar deficits in this task have been found in monkeys with mesocortical DA loss (Crofts et al. 2001). Consistent with these studies are studies in monkeys in which a down-regulation of cortical D1 receptors produced by chronic D2 antagonist administration (Castner et al. 2004) also impairs working memory. The apparent paradox of having *increased* subcortical DA function coupled with *reduced* cortical DA activity in schizophrenia has been modeled in experimental animals showing that selective lesions of the frontal cortical DA system increases the responsiveness of the striatal DA system (Boyce and Finlay 2005, Venator et al. 1999). An inverse relationship between prefrontal cortical activity and striatal DA function has also been shown in human imaging studies. Specifically, in schizophrenic patients performing the WCST during scanning, the task-related increase in blood flow in frontal cortex in frontal blood flow was reduced and this deficiency correlated with DOPA uptake, a presynaptic marker for DA, in the striatum (Meyer-Lindenberg et al. 2002). Combined, these studies predict that administration of drugs that selectively boost cortical DA D1 receptor function would improve cognitive functioning in schizophrenia.

An example of a bottom-up approach that tests the converse of the "cortical regulation of striatal dopamine" is a genetic model recently reported by Kellendonk et al. (2006). The tissue-specific mutation of the DA D2 receptor gene produces a reversible overexpression (by 15%) of striatal dopamine D2 receptors. This model approximates the excess D2 receptor binding observed in schizophrenic patients (Laruelle 2000). Overexpression of postsynaptic D2 receptors in the striatum throughout development leads to deficits in cognitive functions normally mediated in part by the PFC, and increased D1 receptor transduction in the PFC. Importantly, turning off the transgene in adulthood can normalize D2 receptor number, but reverses the D1 receptor abnormality in the cortex, resulting in abnormally low receptor functionality there. This finding is consistent with a neurodevelopmental role of D2 receptors in the pathogenesis of schizophrenia-relevant phenotypes, and with the data indicating that an optimal level of D1 receptor functionality in the frontal cortex is necessary for normal working memory. Similar to the "full reciprocity" described for the genetic models of anxiety described above, this mouse model has been used to predict a relationship between cognitive function and a functionally significant variant in the DA D2 receptor gene. Neuropsychological testing has provided evidence that this overactivity of the receptor is associated with cognitive deficits that are consistent with the cognitive impairments shown by the mouse model (Xu et al. 2007).

## Models of Abnormalities in Glutamatergic and GABAergic Synaptic Transmission in Cortical Circuits

The glutamate and GABA hypotheses overlap considerably with the mesocortical DA hypotheses in schizophrenia, deriving in part from evidence of malfunction of glutamatergic and GABAergic (Lewis and Moghaddam 2006) systems in cortical regions important in the regulation of dopamine systems (Moore et al. 1999).

The glutamate hypothesis is more precisely a hypothesis of NMDA receptor hypofunction. Evidence from both human and animal models has advanced this hypothesis. Abuse or experimental administration of the NMDA antagonist phencyclidine (PCP) or ketamine can produce a phenocopy of schizophrenic psychosis, including disorganization, depersonalization, and auditory hallucinations. The effects of PCP abuse can also mimic negative symptoms such as social withdrawal (Jentsch and Roth 1999). Schizophrenia patients are more sensitive than normal

subjects to the psychotogenic properties of phencyclidine. In humans ketamine also produces impaired prefrontal cortical function as evident in impaired "error prediction" signals measured by means of a frontal hemodynamic response in human volunteers. Moreover, these abnormalities in error signal predicted the degree of delusional phenomena experienced by normal volunteers experiencing higher doses of ketamine and the delusional scores on psychiatric scales in patients with schizophrenia (Corlett et al. 2006). These data illustrate how a concept arising from work on associative learning theory in animals and their instantiation of a pharmacological model of psychosis can lead to powerful new models and hypotheses about schizophrenia. Experimental animal models have shown that NMDA channel blockers (PCP, ketamine or MK-801) can, when given acutely or in a sensitization regimen, produce striatal DA hyperactivity (Balla et al. 2001). On the other hand, chronic PCP or MK-801 leads to decreased DA turnover in the PFC and is associated with deficits in tests of working memory or response inhibition (Jentsch and Roth 1999). More recently, the discovery of a number of susceptibility biological pathways has pointed to a primary defect at the glutamatergic synapse on the cortical pyramidal neuron (Harrison and Weinberger 2005). Thus it is likely that NMDA antagonists mimic a loss of calcium-mediated signaling at the glutamatergic synapse onto the cortical pyramidal neuron. This pathology is compounded by loss of normal regulation of the activity of these neurons by specific populations of GABAergic interneurons (Lewis and Moghaddam 2006).

### Modeling Neurodevelopmental Pathogenic Pathways

The convergent lines of evidence supporting the notion that schizophrenia is a neurodevelopmental disorder have been extensively reviewed; a recent literature search shows more than 200 review articles on this topic, a few of which are cited here (Cannon et al. 2003, Lewis et al. 2004, McGrath et al. 2003, Singh et al. 2004, Weinberger and Lipska 1995). This evidence has led to animal models of a schizophrenia-relevant form of abnormal brain development. These models are sometimes considered etiological; however, they do not all start by mimicking known etiologic factors. Rather, a subset of these models aim to mimic abnormal development of key cortico-striatal circuits as *pathogenic processes* upon which etiologic factors are likely to converge. Unlike distal etiologic factors, these processes are postulated to be more deterministic of proximal risk for symptomatology.

The hallmark studies in this field used focal lesions of the neonatal hippocampus and of adjacent structures known to be affected in schizophrenia (Lipska et al. 2003). Neonatal lesions of the ventral hippocampus lead to an increased behavioral responsiveness to dopamine agonists and stressors that evoke dopamine release in the striatum and limbic regions. These abnormalities emerge during or after puberty, similar to the age of emergence of psychosis in most schizophrenia patients. Neonatal lesioned rats also exhibit abnormal responses to glutamate receptor antagonists such as PCP and deficits in both working memory as well as in PPI, as might be expected in a model of schizophrenia. The implications are that abnormalities in the cortico-limbic systems projecting to the striatum lead secondarily to dysregulation of the ascending dopaminergic systems, perhaps involving a form of sensitization (Lipska et al. 2003).

Another example of "abnormal neurodevelopment models" includes gestational exposure to the nucleic acid methylator methylazoxymethanol acetate (MAM) (Flagstad et al. 2004, Moore et al. 2006, Talamini et al. 1999). Offspring of dams injected with MAM during gestation show structural changes in the hippocampus, perirhinal and entorhinal cortex, the most structurally affected cortical regions in schizophrenia (Moore et al. 2006, Talamini et al. 1999). More specifically, offspring of dams administered MAM at embryonic day (E) 17 exhibit a pattern of gross brain morphology and neurohistopathology that appears similar to what has been reported in schizophrenia. This pattern involves small-to-moderate reductions in cross-sectional thickness, with a disproportionate reduction in the hippocampus, increased neuronal density in the cerebral cortex, and reduced anterior thalamic size (Moore et al. 2006). Importantly, in addition to showing this neuropathological phenotype, MAM E17 offspring also show a postpubertal emergence of supersensitivity to DA-releasing drugs, several cognitive deficits relevant to schizophrenia (Moore et al. 2006), and show increased amphetamine-induced striatal dopamine efflux in adulthood (Flagstad et al. 2004). This shows that validation across neuropathological and neurocognitive phenotypes provide opportunity to examine potential neurophysiological and neurochemical mechanisms that may represent novel targets for pharmacogenomic treatment strategies.

To summarize, animal models have been used to test the plausibility of a number of neurobiological hypotheses regarding the pathogenesis of schizophrenia. Table 17–1 supplements this section by summarizing other important neuropathological phenotypes in schizophrenia that can be measured in experimental animals. Because the validity of experimental models is increased by the homology of the neurobehavioral relationships in the different species, it is becoming paramount to both "neurocognitive" (see Section "Dissecting Cognitive and Behavioral Endophenotypes from Complex Mental Disorders") and "etiologic" (see Section "'A Priori' Modeling Genetic, Environmental and Experiential Etiologies in Psychiatric Disorders") models of schizophrenia that assessments of neuropathology be included.

## "A Priori" Modeling Genetic, Environmental and Experiential Etiologies in Psychiatric Disorders

Just as cognitive and behavioral phenotypes in animals can be used to model the manifestations of psychiatric disease, manipulations of genetic or environmental factors can be used to identify possible etiologic pathways to the neuro- and psychopathologies relevant to psychiatric disorders. These manipulations model the three types of etiologic pathways defined in the introduction: genetic, environmental, and experiential.

### Exploring the Functional Significance of "Susceptibility Genes"

Susceptibility genes are identified through association or linkage studies. These studies identify genetic variants or rare mutations associated with increased risk for schizophrenia. A number of susceptibility genes have been identified in schizophrenia (Harrison and Weinberger 2005), anxiety (Hariri

and Holmes 2006), unipolar depression (Urani et al. 2005), and bipolar disorder (Carter 2007). The rodent models of these susceptibility genes usually serve at least one of two aims. The first is to elucidate biological processes regulated by the gene product that might overlap with hypothesized pathophysiology of the disorder. The second, more ambitious aim is to model the genetic variation that has been shown through linkage or association studies to increase the risk for the disorder. A thorough review of how current genetic mouse models are used with respect to these aims can be found in the reviews cited above. Particularly important for establishing etiologic and construct validity in these models is the nature of the genetic variants associated with a given disorder and whether the specific polymorphism or mutation can be reproduced in the genetic mouse model. For example, how does one model a gene allele that does not show sufficient penetrance to be expressed in a large number of cells, but if coincident with other gene variants or epigenetic factors, may contribute to risk? Such possible *epistasis* of effects has hardly been investigated thus far in rodent models. A final crucial factor to consider is the interaction of the genotype with possible environmental situations or triggers, which may help determine its expression.

The case for most susceptibility genes in psychiatric disorders, particularly schizophrenia, is that the effect, if any, of the risk alleles on the structure or quantity of protein is poorly understood. Moreover, a particular variant may not affect the gene in which it is embedded, but rather, may affect expression of a nearby or even relatively distal gene. In these cases, it is unlikely that a gene "knockout" will serve as an accurate model of the risk allele. Moreover, functional significance of a risk allele must be assessed as a function of brain development. Lastly, as with any manipulation made early in development, genetic mutations will have pleiotropic effects, that is, effects unrelated to the disorder of interest. Given this pleiotropy, it is necessary to control for several confounding factors in genetic models. These include the genetic background onto which a mutation is backcrossed, which will also affect behavior, and the "environment," that is, the laboratory procedures used to produce and test a genetic model. The emphasis hitherto on using the male gender for most analyses also has to be redressed, given the accumulating evidence for gender-specific genetic effects in psychiatric disorders. Despite the challenges, strategies for measuring neurocognitive constructs are being employed in an increasing number of genetic mouse models with possible relevance to schizophrenia (see Arguello and Gogos [2006] for a detailed review) and other psychiatric disorders (Hariri and Holmes 2006). Continued development of these models will reveal links between susceptibility genes and the neuro- and psychopathology of psychiatric disorders.

## Modeling Environmental Exposures as Risk Factors in Schizophrenia

Early exposures to environmental toxins or trauma have been shown to significantly increase the risk for cognitive and psychotic disorders. Particularly relevant to the etiology of schizophrenia are rodent models of maternal or paternal exposures or age. For example, nutritional deprivation of the dam during gestation, mimicking starvation or selective deprivation of nutrients such as protein or vitamin D, leads to persistent abnormalities in expression of developmentally regulated genes in the hippocampus, hippocampal neuron morphology, dysregulation of catecholamine systems, as well as PPI and social behavioral deficits in the offspring (Almeras et al. 2007, Debassio et al. 1994, Marichich et al. 1979, Palmer et al. 2004, Rehn et al. 2004). Similarly, the increased risk for schizophrenia in the offspring of women exposed to infection during pregnancy has led to rat models of the prenatal infection or immune activation (Zuckerman and Weiner 2003, 2005). Several studies show that viral infection and immune system manipulations during gestation result in cytochemical abnormalities in the cerebral cortex, as well as deficits in LI and responses to psychostimulants in the adult offspring (Shi et al. 2003, Zuckerman and Weiner 2003, 2005). Advanced paternal age as a risk factor for schizophrenia is a highly replicated finding (Malaspina 2001). While animal models of potential mechanisms of this effect, including de novo mutations and DNA methylation in germ cells, are well developed (Oakes et al. 2003, Walter et al. 2004), there are as yet few studies on schizophrenia-relevant behavioral phenotypes in the offspring (Auroux 1983). Parental exposures to toxins such as lead also increase the risk for schizophrenia in the offspring (Opler and Susser 2005). Teratologic models of these factors exist, but in general, do not adequately model neurocognitive or neuroaffective constructs.

## Experiential Factors in Etiologies of Psychiatric Disorders: Stress and "Maladaptive" Contingency Learning in Anxiety and Depression

Experiential contributions to psychopathology often invoke the construct of stress, defined by Selye (1956) as a challenge to homeostasis. This concept is often invoked in hypotheses regarding the cumulative effects of "life events," in the etiologies of mood disorders, and to a more limited extent, schizophrenia. Exposure to stress in experimental animals often entails experiences produced by a regimen of shock presentations, or the imposition of restraint or cold temperatures. However, much more subtle and realistic forms of stress have been employed to reflect the human situation. Social stressors have been much studied in nonhuman primates, but now are increasingly studied in rodent models; for example, early separation from the mother or peers, or both (Champagne and Meaney 2001, Dalley et al. 2002, Mineka and Suiomi 1978). Interest has also focused on situations where there is an important emphasis on the schedule of the stressors and whether they are controllable by the animal, which affects the animal's ability to marshal coping responses to mitigate the stress (Willner 1997).

### Early Experiences as Etiologic Factors in Adult Psychopathology

Models of early developmental experiences that contribute to the risk of adult psychopathology include maternal isolation in neonates or social isolation in weanlings. Prolonged or repeated isolation of rat pups from their mothers during the early postnatal period produces persistent and profound behavioral, neurochemical, and epigenetic effects (Champagne and Meaney 2001, Ellenbroek and Cools 2000, Holmes et al. 2005, Meaney et al. 2002). These include epigenetically programmed maternal and defensive behaviors, sensorimotor gating and cognitive deficits, enhanced

responsivity to psychostimulants, and altered behavioral responsivity to novel and aversive stimuli. These cognitive and behavioral phenotypes are likely mediated by persistent changes in the function of multiple neural circuits relevant to schizophrenia, anxiety, and depression, including in dopamine, norepinephrine and serotonin systems and the hippocampal-hypothalamic-pituitary-adrenal axis. Moreover, these interact with genotype (Ellenbroek and Cools 2000).

Whereas the perinatal stress manipulations are largely physiological in nature, social isolation of weanlings is arguably more analogous to a human psychological stressor. Social isolation leads to persistent deficits in preattentional and attentional processes, response inhibition, changes in sensitivity to reward, novelty, and psychostimulants. These behavioral phenotypes are accompanied by changes in forebrain dopamine and serotonin transmission (Dalley et al. 2002, Hall et al. 1998, 1999, Wilkinson et al. 1994). Taken together, studies of early postnatal or juvenile stressors indicate that forebrain serotonin and dopamine systems are exquisitely sensitive to early-life stress.

### Learned Helplessness as an Experiential Etiology in Depression

Learned helplessness is a form of learning that leads to coping behavior that, outside of the learning situation, is not adaptive. This paradigm exposes an animal to uncontrollable, unpredictable aversive events, which leads to a failure to learn avoidance or an escape response to that event even when it is avoidable or escapable (Seligman 1972). This failure to respond is interpreted as a state of helplessness, analogous to the sense of helplessness that is a core symptom of clinical depression (LoLordo 2001). Other phenotypes associated with learned helplessness, some of which are consistent with its status as a model of depression, include elevations in reinforcement threshold, impairments in appetitive behavior and body weight, and sleep disturbance. "Helplessness" can be counteracted by antidepressant treatments such as tricyclic drugs, MAO inhibitors, and electroconvulsive shock regimens, which strengthens its validity as a model of depression. Such antidepressant drugs are often screened using tests that include inescapable stress, such as the tail suspension test for mice and a forced swim test ("behavioral despair") for rats (Porsolt 2000).

## Conclusions

This chapter has illustrated the utility of animal models of psychiatric disorders in several ways. The examples, primarily models of schizophrenia, depression, and anxiety, illustrate strategies used to relate cognitive and affective processes affected in these diseases to relevant neuropathology. Animal models will be necessary to delineate disease-specific abnormalities in these systems. Importantly, animal models have heuristic value for developing new hypotheses about the nature and causation of mental disorders. Future modeling attempts should also advance the analysis of the clinical syndromes themselves, from the nosological, epidemiological and therapeutic, to the neurocognitive, pathophysiological and genetic/molecular domains. Ultimately, animal models will advance the understanding of how the multiple etiological factors for mental disorders lead to cognitive and affective phenotypes and their underlying neuronal pathology.

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CHAPTER

# 18 The Scientific Basis of Psychotherapy

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## The Scientific Basis of Psychotherapy

The insights that have come from neuroscience research during the past quarter century have begun to provide the opportunities for better understanding the relations of brain and mind. The demonstrated effectiveness of some manualized psychotherapies, preliminary understanding of how psychotherapy changes brain function, increasing demand for scientific study of psychotherapeutic effectiveness and neuroscience demonstrations of unconscious mental functioning have all contributed to renewed interest on the part of the psychodynamic and psychoanalytic communities in participating in neuroscience research. These studies will be important contributors in our continuing search for the neuroscientific basis of consciousness.

The term psychotherapy designates a broad category of treatments that derive from different theoretical orientations, and use a variety of techniques, durations, and frequencies, but have in common that their primary mode of action is verbal exchange between patient and therapist. Psychoanalysis was the first intentional psychotherapy. For many years, it was the only form of psychotherapy and thus it had a dominant influence on American psychiatry. Subsequently, other psychotherapies, for example, cognitive behavioral therapy (CBT), rational emotive therapy, gestalt therapy, client-centered therapy, interpersonal psychotherapy (IPT), and dialectical behavioral therapy (DBT), were developed. The therapeutic outcomes of some of these have now been far more systematically studied than psychoanalysis or its offshoot psychodynamic psychotherapy. Furthermore, whereas the theory and technique of psychoanalysis developed exclusively from the clinical situation, other forms of psychotherapy such as behavior therapy have their roots in laboratory models of animal learning. This chapter will review three dimensions of the scientific basis of psychotherapy; (1) an historical review of the development of psychoanalysis, the Freudian model of the mind, and the growing influence of developments in neuroscience on psychodynamic theory and technique, (2) a review of the evidence that psychotherapy is an effective treatment, and (3) the study of psychotherapy as a biological intervention.

## Principles of Psychoanalysis: The Contribution of Freud

In this section, the fraught early attempt of psychoanalysis to place psychotherapy on a scientific footing is reviewed critically to illustrate the difficulties all psychotherapies grapple with in this endeavor. In subsequent sections, recent but still very preliminary, efforts to investigate the neuroscience of psychotherapy are described. The methods of contemporary psychotherapy began at the end of the 19th century with the discoveries of Breuer and Freud (1955). Breuer and Freud, working with Anna O.; a patient who suffered from multiple disabling 'hysterical,' now called conversion symptoms, which are motor or sensory symptoms that have no neuroanatomic or physiologic cause. Breuer discovered that the recovery of 'forgotten' traumatic memories could be achieved by the simple but innovative technique of permitting his patient to talk at random, or free associate. The recovery of these memories led to symptomatic relief.

After a 15-year career as a researcher in neuroanatomy, Freud became a clinician out of financial need. Following Breuer's lead, Freud treated a number of patients and set out to understand the origins and complexity of the mental operations that he was observing.

Among Freud's most fundamental insights was that free association led to the origin of patients' fantasies and memories. Although the distinctions are not always clear, it is useful to differentiate the phenomena that Freud observed in the treatment situation from the explanatory hypotheses that he developed in his attempt to establish a theory of mind. Freud listened to adult patients' fantasies and memories, and their free associations to these fantasies and memories. From these, he inferred their origin in infancy or early childhood. He then constructed hypotheses to explain

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these observations and their putative developmental origins. Among these hypotheses, "Freud Introductory Lectures" (Freud 1963) were:

1. that infantile aggressive and sexual needs, desires, and attachments, and corresponding prohibitions holding these needs and relationships in check, proceed through development into childhood and adulthood.
2. that unresolved conflicts between these early needs and prohibitions, as well as early traumas, although not available to conscious recall, motivate adult behavior and cause symptom formation in mental illnesses. This process of motivation by unconscious mental content is called the 'dynamic unconscious' ("Three Essays on Sexuality," Freud 1953). Anxiety is the affect that signals the presence of an unresolved unconscious conflict.
3. that patients in psychotherapy reenact their earliest relationships in their relationship with the therapist—called the transference. Freud discovered that the transference and its interpretation by the analyst played a central role in the therapeutic process.
4. that the mental mechanism of repression operates to prevent conscious awareness of early conflicts over prohibited desires.
5. that the resolution of conflicts arising from the Oedipus complex, the child's triangulation of relations between its mother and father and himself (and a parallel complex in girls), plays a central role in directing development towards healthy or maladaptive outcomes.
6. that the patient's free association to memories, fantasies, and dreams, told to the therapist as they occurred, and the therapist's interpretation of these, was the most effective therapeutic method to bring repressed unconscious conflicts into consciousness, resolve them, and thereby relieve mental symptoms.

These observations and hypotheses were the foundation of a revolutionary new understanding of mental life and human behavior. Following the logic of basic research, Freud developed a mechanistic and reductionist "metapsychology," to provide a conceptual framework for the observations and hypotheses that he had formulated in the consulting room. These include the familiar concepts of libido, the source of mental energy and drives; the structural theory of the mind, which postulated the existence of the id, ego, and superego, which contain the unconscious drives and prohibitions; and the pleasure principle, a homeostatic mechanism that underlies all mental activity and aims at maximizing pleasure and minimizing unpleasure by reducing libidinal tension. Freud called both the new therapy and its metapsychological conceptualization psychoanalysis.

It was Freud's early hope that the structures and mechanisms that he postulated could be grounded in the anatomy and physiology of the brain. Stimulated by his own basic research on the nervous system, he attempted to construct a neuroscience-based description of psychic function—the "Project for a Scientific Psychology" (Freud 1966). However, he abandoned this project when he realized that the neurobiology of his time was inadequate for the complexity of mental function that he had described. Freud would have preferred a unitary mind–brain model, but the continued separation of mind and brain was a necessary strategy without better methods for investigating the brain. Freud (1912) said:

> Psychoanalysis has talked a lot about the accidental factors in etiology and little about the constitutional one; but that is only because it was able to contribute something fresh to the former, while, to begin with, it knew no more than was commonly known about the latter. We refuse to posit any contrast in principle between the two sets of etiological factors; on the contrary, we assume that the two sets regularly act jointly in bringing about the observed result. Endowment and Chance determine a man's fate–rarely or never one of these powers alone.

## Psychoanalysis after Freud

As the history of psychoanalytic theory and therapy unfolded, metapsychology, which Freud at one point referred to as "the witch" (Freud 1937) because it reified theoretical constructs without any basis in biology, became a larger part of psychoanalytic theory. The seemingly insurmountable gap between metapsychology and biololgy led to an attitude and conviction on the part of psychoanalysts that psychoanalysis was a self-sufficient realm of exploration, and efforts to introduce reductionist materialist concepts were generally rejected out of hand. Developments in neurobiology were either ignored, viewed as irrelevant, or actively rejected as representing sources of reductionist interference with the ongoing effort to understand mental function.

With neuroscience still in its infancy, psychoanalytic hubris went unchecked. With little objective evidence psychoanalysts claimed therapeutic success treating ulcerative colitis, peptic ulcer, rheumatoid arthritis, bipolar disorder, the varieties of depressive disorder, schizophrenia, and other disorders. The placebo effect, although well known, was ignored, and outcome studies, considered desirable, were generally dismissed as too difficult to undertake, ignored, or even regarded as irrelevant to psychoanalytic pursuits.

The confluence of three research areas radically altered this situation: (1) clinical psychopharmacology, (2) behavioral observation of infants and young children, and (3) basic neurobiologic animal models of memory and affect.

1. The discovery of chemical transmission in the brain in the 1940s and 1950s, accompanied and/of drugs that affect specific forms of chemical transmission mandated reassessment of the putative role of psychodynamic mechanisms in psychopathology and the nature of therapeutic action of psychoanalysis.
   Depressive mood, excessive anxiety, panic attacks, tics, so-called psychosomatic disorders, manic states, psychotic delusions and hallucinations, unstable forms of attachment all respond to medication to varying degrees. Although for each of these conditions psychodynamic mechanisms have been hypothesized, the relevance of such formulations varies from case to case. For some patients, a psychotherapeutic approach may provide them with insight and have some effectiveness, for others psychotropic medication is the treatment of

choice. Current research indicates that for some patients, a combination of medication and psychotherapy is still more effective. The psychodynamic community initially responded with hostility to the use of medications for anxiety and depression, claiming that removing symptoms prior to altering the underlying psychodynamic etiology would be counterproductive, leaving the patient with unresolvable conflicts that would continue to interfere with the pursuit of life goals. Clinical evidence quickly demonstrated that, to the contrary, symptom removal alone was highly beneficial. Without crippling symptoms of anxiety or depression, patients were often able to reorganize their intrapsychic functioning in healthy ways without much further assistance. Their enhanced self-esteem and renewed self-confidence permitted bolder and more creative responses to the outer world. The overwhelming evidence for the benefits of symptom removal per se eventually persuaded the psychoanalytic community that patients freed of overwhelming affective states were better able to explore their unconscious conflicts. Survey data today indicate that a large proportion of patients in psychoanalysis are also receiving some variety of psychotropic medication.

2. Beginning in the 1950s, John Bowlby, a psychoanalytically trained psychiatrist, set out an ethologically based theory of the attachment relationship between an infant and its mother, which complemented, and in many ways challenged, the psychoanalytic libido and structural theories. Attachment theory placed the infant's relationship with its mother on an equal footing with satisfaction of its basic physiological needs as a primary influence on development. At around the same time, Rene Spitz documented the profound deleterious effects on infant development of major disruptions in the attachment relationship that occurred in institutionalized infants, while Harry Harlow used an animal model (the rhesus monkey) to show how maternal separation experienced in infancy causes major lifelong impairments in psychological and social function. In the 1960s and 1970s, several investigators and theorists extended these findings. Mary Ainsworth tested Bowlby's theory in the laboratory with human infants and their mothers, and developed a standard observational evaluation of the quality of the infant's attachment relationship. This method has given rise to prospective studies of the effects of normal and disturbed attachments on a number of developmental outcomes and to correlational studies of infant attachment quality with maternal psychopathology. At about the same time, the psychoanalysts Margaret Mahler and Daniel Stern, and the psychologist Jerome Kagan used direct observations of mother infant interactions to reconceptualize the normal course of mental development as processes of acquiring individuality, intersubjectivity, and the ability to manage environmental novelty. Finally, basic researchers exemplified by Myron Hofer, Tom Insel, and Michael Meaney, have used rodent models to reveal how the mother regulates physiologic, neuroendocrine, and molecular biological processes of infant development. Together these advances have spawned a rich observationally-based research endeavor aimed at understanding the developmental origins of adult mental life and the environmental and innate determinants of deviant development leading to psychopathology. In the aggregate, these findings and concepts have permeated the current theory and practice of psychotherapy in general and psychoanalysis in particular through notions of attachment, affect attunement, and separation and individuation in the therapist patient relationship.
3. Learning and memory have now been understood at the cellular, molecular and genetic levels as processes of synaptic plasticity. Eric Kandel, the neurobiologist who pioneered this work in the relatively simple nervous system of the marine snail Aplysia and extended it to mice, is a psychiatrist with psychoanalytically based training. From the outset of his research, Kandel has been keenly aware of the significance of basic neurobiologic explanations of memory for the psychoanalytic endeavor, which holds memory to be the key to mental life and symptoms. On the heels of Kandel's work Joseph LeDoux, Michael Davis, and others using rodent models have worked out the circuitry and cell biology of learned fear and anxiety, which are also key symptoms in many mental disorders.

Kandel has been pivotal in trying to join the hypotheses of psychoanalysis and the findings of neuroscience (Kandel 1999a). To do so, he has had to oppose those who would prefer to abandon psychoanalysis in their pursuit of neuroscience as well as those who would abandon neuroscience in their adherence to a strict interpretation of psychoanalysis. Beginning in 1979, a series of papers by Kandel (1999b) forcefully argued that scientific reductionism should be applied to our understanding of how the mind arises from the brain. Kandel's own work demonstrates that a reductionistic understanding of neural processes can radically alter our conception of mental processes. He has extended this view by proposing that psychotherapy, which is a form of learning, must lead to detectable functional or structural alterations in the brain. Discovering the brain mechanisms of psychotherapy is thus seen as a deep problem whose answer must be sought through intellectual collaborations between biologically educated clinicians and clinically astute neurobiologists.

Referring to Kandel's work in 1983 with aplysia, Cooper (1985) said:

> The interaction of the environment and the adaptive responses of the organism can now be partially understood in terms of basic cellular neurobiology. The readiness with which an analyst attempts to affect the patient's self or his brain organization through a new relationship or medication has philosophical and ethical connotations, and in the current absence of specific indications for either or both treatments, the treatment choice will reflect individual bias.

In this paper, Cooper also said that most analytic treatment carries with it a strong implication that it is a major analytic task of the patient to accept responsibility for his actions. In the psychoanalytic view, this responsibility is nearly total. We are even responsible for incorrectly or

exaggeratedly holding ourselves responsible. It is our job to change our harsh superegos, and it is our job to do battle with unacceptable impulses. However, it now seems likely that there are patients with depressive, anxious, and dysphoric states for whom the usual psychodynamic view of responsibility seems inappropriate and who should not be held accountable for their difficulty in accepting separation from dependency objects, or at least they should not be held fully accountable.

## Studies on the Effectiveness of Psychotherapies: Overall Efficacy of Treatment

In practical terms, the scientific basis of psychotherapy must rest on a firm base of valid outcome research. Psychological therapy, perhaps best defined as "an interpersonal process designed to bring about modifications of feelings, cognitions, attitudes and behavior which have proved troublesome to the person who is seeking help from a trained professional" (Strupp 1978), now covers a very diverse set of activities which include at least six major approaches, each providing a model of human behavior as well as heuristic foci for interventions. These are as follows: (1) Psychodynamic psychotherapy, particularly concerned with how the experience of problematic internal states are encoded into relationship patterns that are evident in the person's life and in relation to the therapist, (2) Behavioral and cognitive–behavioral therapy, rooted in classical as well as social learning theory but which now incorporates traditionally psychoanalytic ideas such as the influence of early life on patterns of thought, defensive avoidance of painful ideas, notions of helplessness, cognitive distortions, and discrepancy between an ideal and perceived self, (3) Interpersonal psychotherapy, which is primarily concerned with current social relationships and takes general educational as well as pragmatic approaches to relationship problems, (4) Strategic or systemic psychotherapies focusing on the family or institutional context that generates the problem behavior rather than any particular individual within the system, (5) Supportive and experiential therapies which facilitate self-awareness and reject the mechanistic philosophies of psychodynamic, systemic and behavioral therapies, and (6) Group therapies, which are appropriate to all the previous five types of interventions but represent an approach their in own right. The psychology of the therapeutic group is both the focus and a vehicle of the intervention.

Although all of these models provide etiologic formulations, their evidence base is limited. The best way of comparing these treatments is by RCTs where variables likely to influence outcome are controlled, for example, therapist experience, treatment length, etc. Increasingly, studies also ensure that treatments are carried out in conformity with their theoretical description, for example ensuring that cognitive behavioral treatment does not include psychodynamic elements and vice versa. To meet this goal, certain treatments have been manualized, thus operationalizing and standardizing the core techniques of the therapy. Manualization allows (1) multiple therapists to be trained according to a standard that is backed by expert consensus and (2) reviewers to determine whether a treatment was delivered in a manner consistent with that standard. There are limitations to this approach, such as differences between the groups that occur despite randomization because of small sample sizes. Whereas the presence of an untreated control group would provide an ideal benchmark, it is not ethically viable to withhold treatment in cases other than the very short-term psychotherapies. Increasingly, there are studies that compare psychosocial interventions with medication or the addition of psychosocial interventions to pharmacological treatment. The criteria most often used to establish the evidence base of a therapeutic approach for a particular condition is the replication of good quality RCTs with an independent group of investigators testing the same manualized treatment with the same diagnostic group.

Since Hans Eysenck (1952) expressed doubts about the overall efficacy of psychotherapy, there have been several meta-analyses of the psychotherapy research literature (Wampold 2001), as well as narrative reviews (Roth and Fonagy 2005), of hundreds of studies. Most studies report a considerable effect size (0.50–0.85) when treatment is contrasted with no treatment but much of this effect may be attributable to placebo effects. The major meta-analyses of therapy outcome have been drawn from rigorously-controlled studies (random assignment, careful specification of patient population, use of a treatment manual, raters naïve to conditions, statistical power adequate to examine the null hypothesis, and replication by independent investigators).

Space does not permit a review of the empirical status of psychotherapy for all mental disorders (for a comprehensive recent review: Roth and Fonagy 2005). To illustrate the nature of the evidence base, we will consider only the two most prevalent Axis I disorders, anxiety and depression, and the most commonly investigated Axis II condition, borderline personality disorder (BPD).

The literature on RCTs clearly identifies cognitive, behavioral, and cognitive behavioral treatments as highly efficacious in the treatment of anxiety disorders. The best effect sizes have been reported for cognitive therapy for panic disorder (Clark et al. 1994, 1999), cognitive therapy for post-traumatic stress disorders (Ehlers and Clark 2003, Ehlers et al. 2005), cognitive therapy for social phobia (Clark et al. 2006, Clark et al. 2003), CBT for generalized anxiety disorder (Dugas et al. 2003, Ladouceur et al. 2000), exposure and response prevention for obsessive-compulsive disorder (OCD) (McLean et al. 2001, Whittal et al. 2005) and exposure for specific phobias (Ost et al. 2001, Ost et al. 1997). Many of these studies used unstructured supportive treatment as a control for receiving clinical attention, that is, a placebo control.

There are a few RCTs of psychodynamic therapies for anxiety (e.g., Milrod et al. 2007) but there are some notable trials for depression (e.g., Shapiro et al. 1995). The National Institutes of Mental Health's (NIMH) Treatment of Depression Collaborative Research Program (Elkin, 1994) is perhaps the most widely cited research program, which set a standard against which other studies could be judged. Patients were randomized to receive one of four interventions: cognitive–behavioral psychotherapy, IPT, imipramine plus clinical management (IMI–CM), or a placebo pill plus clinical management (PLA–CM). Clinical management consisted of a weekly meeting of 20–30 min to discuss medication, side effects, and the patient's clinical status and when necessary, provide support, encouragement, and advice. Thus, that both medication conditions (imipramine and placebo)

contained psychotherapeutic elements. Two hundred and thirty nine patients, all moderately to severely depressed, entered the trial at three sites. Patients were assessed before treatment and at 4, 8, 12, and 16 weeks and followed up at 6, 12, and 18 months. At termination of therapy (Elkin et al. 1989), patients who received IMI–CM had the lowest symptom scores, PLA–CM the highest, and the two psychotherapies intermediate. Although the magnitude of these differences was not large, those who received IMI–CM and IPT were significantly more likely to have recovered at 16 weeks than those who had received PLA–CM. There were no significant differences between the two psychotherapies or between psychotherapies and IMI–CM. For patients with less severe depression, PLA–CM, which could be considered a "minimal support" intervention, was as effective as the active therapies. At the 18-month follow-up, no more than 25% of patients in any of the groups were recovered and without relapse. This key finding suggests that treatment of depression, whether pharmacologic or psychotherapeutic, requires a minimum duration to alter the underlying neurobiology.

The studies with the most rigorous methods demonstrate the efficacy of IPT and CBT. In the single trial comparing dynamic-interpersonal therapy (IPT) and CBT, there was no difference in efficacy. This broad equivalence in outcomes between distinct psychotherapies is an important result, suggesting that depression responds to a range of psychotherapeutic technique. Many large-scale careful studies, such as the Helsinki study (Knekt and Lindofrds 2004), found no difference between therapies. For example, there was no difference between psychodynamic psychotherapy and solution-focused psychotherapy, a systemic therapy. Overall, the generally-observed effect size for the psychodynamic treatment of anxiety is hard to estimate, and for depression the outcome of psychodynamic psychotherapy is comparable to CBT, although both therapies have only small to medium effects in the long-term (Leichsenring et al. 2004). In no instance has psychodynamic therapy been shown to be superior to CBT. Most studies compare CBT with drug treatment, and the average effect size across 12 studies ($n$ = 1,200) for comparisons with drug treatment indicate that pharmacotherapy is just as effective (ES = 0.01 (95% CI = –0.1,0.13)). In a recent meta-analysis of short-term psychodynamic psychotherapy Abbass et al. (2007) analyzed 23 studies of 1,431 randomized patients with common mental disorders. These studies covered a range of patient groups including somatic, anxiety, and depressive patients, as well as those with social adjustment problems. Moderate effect sizes were obtained in most comparisons indicating significantly greater improvement in the treatment versus the control groups, which were generally maintained in medium and long-term follow-up. The findings indicated that short-term dynamic psychotherapy showed modest to moderate gains for a variety of patients, which were mostly sustained. There was, however, substantial heterogeneity and variability in treatment delivery and treatment quality indicating the need for larger studies of higher quality and with specific diagnoses.

For most Axis-I conditions, the largest number of RCTs use forms of CBT, with relatively good results. RCTs show that personality disorders are less amenable to CBT. Some studies of BPD show marginal effectiveness of CBT (Davidson et al. 2006a, Davidson et al. 2006b), and some even reported slight iatrogenic effects (Tyrer et al. 2004).

DBT, an outgrowth of CBT that was tailored for BPD, was shown to be highly effective in treating suicidality and self harm behaviors in borderline women, but not in treating depression (Linehan et al. 1991, Linehan et al. 2006). By contrast, a somewhat longer psychodynamic treatment yielded similar effect sizes for para-suicide, but also showed improvement for depression and anxiety (Bateman and Fonagy 1999, 2001). Head-to-head comparisons have yielded equivocal results. One 3-year treatment trial apparently favored a version of cognitive therapy over psychodynamic treatment (Giesen-Bloo et al. 2006), but another, better-controlled trial showed little difference between DBT, psychodynamic therapy and supportive psychotherapy (Clarkin et al. 2007).

RCTs are the gold standard in evidence-based medicine, but the results of these trials are often hard to apply in the context of a medical practice (Rothwell 2005). A major reason for this is that individuals participating in clinical trials will not always resemble the patients that a clinician would see in psychotherapy (see Westen and Morrison 2001). In general "research therapy" appears more effective than clinical practice (Weisz and Jensen 1999). This may relate to methodological issues—among them the use of focused and structured manualized treatments, careful attention to ensure therapist adherence to protocol, participants recruited by advertisement rather than through clinical services, are screened for strict diagnostic criteria and severity levels, and subject to exclusion criteria.

## Mechanisms of Psychotherapy

Outcome studies demonstrate that psychological treatments are effective, but which specific therapies are superior can only be addressed by "head to head" comparative trials.

A number of such studies have compared a wide of range of therapies, including psychodynamic, behavioral, cognitive, interpersonal, and client-centered methods. The results are surprisingly consistent: with notable exceptions (e.g., the superiority of CBT over IPT for the treatment of OCD and other anxiety disorders) research has failed to show that any one method is more potent than the others. For example, an ambitious comparison of transference focused psychotherapy, Dialectical Behavior Therapy (DBT) and supportive psychotherapy for BPD, showed little difference between these three forms of treatment after one year of therapy (Clarkin et al. 2007). In recent decades psychotherapy research has demonstrated repeatedly that a substantial proportion of the variability in therapeutic outcomes across trials is not well explained by differences between formally defined therapeutic procedures, differences between client groups, or (less well examined) the interaction between these two factors (e.g., Beutler et al. 2004, Beutler et al. 1994, Clarkin and Levy 2004, Garfield 1994). At the same time, controlled trials repeatedly demonstrate that the therapeutic relationship without theoretically coherent content is of little therapeutic value (Wampold 2001, Wampold et al. 2002), Thus, while the specific method applied does not generally correlate well with outcome, the consistent application of one method appears to be important.

In addition, no strong correlations have been found between outcome and the particular symptom that is

targeted by a specific type of therapy. For example, in a study of CBT, the extent of focus on 'parental issues', a theme generally viewed as more central to interpersonal or psychodynamic therapies, was positively associated with outcome (Hayes et al. 1996). In a study of psychodynamic psychotherapy process and outcome, Piper (Piper et al. 1991) found that in sicker patients for whom the therapeutic alliance is shaky, the use of transference interpretations was associated with worse outcome, not better. Another study found a negative association between the number of transference interpretations and therapy outcome, indicating that the overuse of this technique frequently regarded by clinicians as essential to therapeutic success, may even be iatrogenic (Connolly et al. 1999). It is possible that the commonalities among psychotherapies, the 'non-specific' elements, are the effective ingredients, rather than their specific differences.

Frank and Frank (Frank and Frank 1991) proposed that a nonspecific factor common to all successful therapies is the therapist's ability to instill their patients with hope. Yet a methodological review of child psychotherapy treatment studies between 1995 and 2004 (Jensen et al. 2005) found that recent research did not give adequate attention to nonspecific factors, including the effects of attention, positive regard and therapeutic alliance, as well as the effects of treatment dose, intensity, and actual processes mediating therapeutic change. One nonspecific component of all therapies that has been investigated is the quality of the therapist/patient relationship. Results revealed that a good relationship with one's therapist is a crucial factor in the treatment's outcome (Lambert 2004, Luborsky et al. 1988). Further, the therapeutic alliance is influenced by the quality of the therapist's and patient's attachment styles and quality of object relations, and in particular the therapist's attachment security (e.g., Black et al. 2005, Eames and Roth 2000, Hilliard et al. 2000, Pinsker-Aspen et al. 2007). It is plausible that therapists with a secure attachment style approach the therapeutic relationship with greater openness and optimism which might be more effective in instilling hope in the client. Particularly, strong associations have been found between pretreatment expectations and the observed quality of the therapeutic alliance (Dew and Bickman 2005, Gaudiano and Miller 2006, Meyer et al. 2002, Zuroff and Blatt 2006). Clearly this evidence suggests that a good therapist/patient relationship is central to psychotherapy's effectiveness.

## Therapist Factors in Therapy Outcome

Wampold (2001) points out that evidence for common factors highlights the importance of the therapist and his or her skill.

In Kim et al.'s (2006) analysis of the NIMH's Treatment of Depression Collaborative Research Project (NIMH TDCRP) dataset, 5–10% of the variance in outcomes was shown to be associated with therapists. In more naturalistic studies, the effects tend to be larger. Very large studies, with datasets of over 5,000 patients, consistently report large effects associated with therapists (Okiishi et al. 2006).

Therapist factors have been shown to be associated with the rate of improvement. For example, among 91 therapists treating nearly 2,000 patients, those therapists whose patients showed the most improvement had an average rate of improvement 10 times greater than the sample's mean rate (Okiishi et al. 2003). This is consistent with other studies using a growth curve approach, where as much as 17% of the variance in rates of patient improvement has appeared to be attributable to the therapist (Lutz et al. 2007).

Some therapists are better than others, but what contributes to that quality? Beutler et al. (Beutler et al. 2004; Beutler et al. 1994) reviewed studies of the impact of therapist characteristics on outcome. The therapist's age, gender, and ethnicity appear to have little or no impact on results, nor are there significant differences in outcome when therapist and client are matched on these variables. Assessment of the impact of therapist personality variables is limited, with some studies attempting post hoc atheoretical analysis, and others a more theory-driven approach, with no consistent or robust findings. There are indications that therapists with better levels of adjustment may have better outcomes, though there is inconsistency across studies.

Contrary to received wisdom, empirical findings suggest that the therapist's experience does not help to predict outcome. Attempts to show the effects of experience have no conclusive results (Beutler et al. 2004, Propst et al. 1994). Wierzbicki and Pekarik's (Wierzbicki and Pekarik 1993) meta-analysis of 125 studies found that there was no correlation between dropout rate and the therapist's experience in years or professional qualifications—although there is some evidence that experience becomes a more important predictor of outcome with patients who are more disturbed.

## Long-term Psychotherapy

Most psychoanalysts would consider that the aims and methods of short-term once-a-week psychotherapy are not comparable to a 'full analysis', or at least long-term psychodynamic psychotherapy involving more than one session per week usually for several years. What do we know about the value of intensive and long-term psychodynamic treatment and how do these results compare to short-term therapy? Here the evidence base becomes patchy and we cannot restrict the review to RCTs.

The Boston Psychotherapy Study (Stanton et al. 1984) compared long-term psychoanalytic therapy (two or more times a week) with supportive therapy for patients (once a week) with schizophrenia in a randomized controlled design. On the whole, patients who received psychoanalytic therapy fared no better than those who received supportive treatment. In a partial-hospital RCT (Bateman and Fonagy 1999, 2001) for BPD the psychodynamic arm of the treatment included therapy groups once a week plus individual therapy once or twice a week over an 18-month period. Compared with psychiatric treatment as usual, which consisted of less frequent visits to a psychiatrist and home visits by a nurse but no formal psychotherapy, showed the benefit of the psychodynamic therapy by 18 months, which continued over a further 18 months follow-up period. Another further controlled trial of intensive psychoanalytic treatment of children with chronically poorly controlled diabetes reported significant gains in diabetic control in the treated group relative to treatment as usual which was maintained at one year follow-up (Moran et al. 1991). Experimental single case studies carried out with the same population supported the causal relationship between interpretive work and improvement in diabetic control and physical growth (Fonagy and Moran 1991). The work of Chris Heinicke also suggests that

four or five sessions per week may generate more marked improvements in children with specific learning difficulties than a less intensive psychoanalytic intervention (Heinicke and Ramsey-Klee 1986).

The Stockholm Outcome of Psychotherapy and Psychoanalysis Project (Blomberg et al. 2001, Grant and Sandell 2004, Sandell et al. 2000) followed 756 individuals who received National Insurance-funded treatment for up to three years in psychoanalysis or psychoanalytic psychotherapy. The groups were matched on many clinical variables. Analysis four or five times a week had similar outcomes at termination when compared with one or two sessions per week of psychotherapy. During the follow-up period, psychotherapy patients did not change, but those who had had psychoanalysis continued to improve, almost to a point where their scores were indistinguishable from those obtained from a nonclinical Swedish sample (Sandel et al. 2002). While there are methodological problems with this study (e.g., lack of random assignment and an accelerated longitudinal design), the finding of a strong 'sleeper effect' restricted to the psychoanalytically treated group is unique.

The German Psychoanalytic Association carried out a major follow-up study ($n = 401$) of psychoanalytic treatments undertaken between 1990 and 1993 (Leuzinger-Bohleber et al. 2003, Leuzinger-Bohleber and Target 2002). Between 70 and 80 per cent of the patients (at an average of 6.5 years after the end of treatment) had achieved good and stable psychic changes. The evaluation of mental health costs showed fewer days' sick leave on the part of the patients during the 6.5 years after long-term psychoanalytic treatment. In the absence of pre-treatment measures, it is impossible to estimate the size of the treatment effect.

The Research Committee of the International Psychoanalytic Association recently prepared a comprehensive review of North American and European outcome studies of psychoanalytic treatment (Fonagy et al. 2002a,b). The committee concluded that existing studies failed to demonstrate the efficacy of psychoanalysis relative to either alternative treatment or active placebo (placebo that generates an expectation of change). Studies showed a range of methodological and design problems, including absence of intent to treat controls, heterogeneous patient groups, lack of random assignments, failure to use independently administered standardized measures of outcome, etc. Nevertheless, the report, which ran to several hundred pages and describes more than fifty studies, did contain data that would encourage the development and execution of methodologically rigorous outcome studies of psychoanalysis. Another overview (Gabbard et al. 2002) suggested that psychoanalytic treatments may be necessary when other treatments proved to be ineffective. This study concluded that psychoanalysis appears to be consistently helpful to patients with milder disorders and somewhat helpful to those with more severe disturbances. More controlled studies are necessary to confirm these impressions.

## Conclusions

Several conclusions can be drawn from the psychotherapy research literature. First, it appears evident that psychotherapy is effective in treating a wide variety of clinical conditions, with results often equal to those for drug-based treatments. Second, the affinity between patient and therapist (the so-called therapeutic alliance) may be a key factor in effective therapy. Third, although therapist skill is important in establishing this relationship, experience is not critical. Fourth, level of functioning and the ability to form a therapeutic alliance are better predictors of outcome than diagnosis. Fifth, evidence suggests that common factors and not specific techniques are crucial in therapy. Finally, it appears that most patients benefit from psychotherapy within the first six months of treatment, and that long-term therapy has no significant advantage over short-term therapy. However, psychodynamic psychotherapy may be associated with so-called 'sleeper effects' which means that the full benefit of therapy may not be evident until some months after the termination of the trial.

Research into psychotherapy will require further investigation to understand its mechanisms, especially into the therapeutic alliance, matching specific techniques with specific types or severity levels of problems, and the effect of dose and frequency of therapy.

## Biological and Neuroimaging Studies of Psychotherapy

Most of the initial studies have focused on the hypothalamic pituitary-adrenal axis (HPA), specifically cortisol levels. Increased HPA activity, as reflected by increased serum or salivary cortisol levels, is considered to be the physiological expression of stress and so the primary experimental paradigm was to determine if there is a reduction in cortisol levels following a psychotherapeutic intervention (Gaab et al. 2002).

Studies of patient cohorts with varying pathologies including bullying behavior (Nickel et al. 2006), spider phobias (Straube et al. 2005), post-traumatic stress disorder (Mason et al. 2002), and generalized anxiety disorder (Jockers-Scherübl et al. 2006) receiving varied interventions including family therapy, mindfulness training (Marcus et al. 2003), and CBT, have consistently reported decreased post-treatment cortisol levels compared to baseline following a psychotherapy intervention.

Other variables that have been studied include heart rate, which was decreased from baseline following CBT in women who were under the stress of in-vitro fertilization procedures (Facchinetti et al. 2003). EEG sleep measures were different at baseline in responders vs. nonresponders to IPT in a sample of depressed patients Buysse et al. 1992) suggesting that sleep physiology is a predictor of recovery, rather than an indicator of a specific action of the therapy. Most intriguingly, a recent study assessed nerve growth factor (NGF) in patients with generalized anxiety disorder before and after treatment with CBT (Jockers-Scherübl et al. 2006). NGF has neurotropic actions within the central and peripheral nervous system but there is accumulating evidence that it also has immuno–modulatory functions as well. Serum levels of NGF are raised in stressful situations. Perhaps somewhat contrary to expectations, patients who responded to CBT had increases in serum NGR compared to patients who did not respond. This has been interpreted as an indicator of better stress management post-treatment but is open to other interpretations.

The use of functional positron emission tomography (PET), Functional magnetic resonance imaging (fMRI), and

structural magnetic resonance imaging (MRI), to demonstrate the effects of psychotherapy is relatively new and still needs significant development. Nonetheless, this approach has the potential to reveal which brain regions and networks are responsible for specific psychopathologies, and which register the effects of psychotherapy (see reviews: Roffman et al. 2005, Linden 2006). As a treatment, psychotherapy focuses on learning, unlearning, mastery and control, and it results in new evaluations and behavioral responses to both internal and external stimuli. The use of imaging to study psychotherapy has taken three approaches: (1) the documentation of metabolic (PET) or structural (MRI) effects of psychotherapy alone or psychotherapy compared to medication treatment in anxiety and depressive disorders; (2) the use of fMRI to study responsiveness to charged stimuli before and after treatment, for example, exposure to spider images in patients with spider phobia; and (3) the use of imaging techniques to validate concepts that are central to dynamic psychotherapies, for example, the demonstration of unconscious affects.

The imaging studies to date demonstrating the effects of psychotherapy have methodological problems in common, including small sample sizes, the fact that comparator studies (medication vs. psychotherapy) are often not randomized, and that data analysis does not always compare responders to nonresponders.

The first studies of psychotherapy used $\{^{18}F\}$ fluorodeoxyglucose (FDG) PET to assess metabolic changes associated with CBT for the treatment of OCD (Baxter et al. 1992). Baseline studies of patients with OCD have reported increased activity in the right caudate and a significant correlation between caudate, orbital frontal cortex and thalamic activity (Baxter et al. 1987, 1988). In the studies of CBT, responders showed a decrease in right caudate activity and importantly the significant correlation between the caudate, thalamus and OFC was significantly attenuated. These effects were observed not only for CBT but also for fluoxetine treatment suggesting the important possibility that the effects of therapy on brain function depend on response, not on modality, even for those modalites as disparate as a psychological intervention and a drug (Baxter et al. 1992, Brody et al. 1998). The same finding of decreased activity in the right caudate after treatment with CBT was also reported in a second study of 22 patients with OCD using other methodologies to measure cerebral blood flow (Nakatani et al. 2003). In summary, though the studies are few and the numbers are small, there has been a surprisingly consistent finding of hyperactivity in the right caudate at baseline in particular with obsessive/compulsive disorder, and significant decrease in activity in this area in patients after psychotherapy and, in at least one study, after selective serotonin reuptake inhibitor (SSRI) medication treatment as well.

One study used MRI to determine whether there is a structural difference in the thalamus after 12 weeks' CBT in patients with OCD (Rosenberg et al. 2000). There was no change in thalamic volume, which is perhaps not surprising given the relatively brief time between baseline and post-treatment measurement. The documentation of structural brain changes may require either a longer time between baseline and post-treatment measurements and/or different imaging methodologies to detect meaningful but small changes in hypothesized regions of interest.

Three studies have compared psychotherapy to medication in patients with major depressive disorder, one study comparing IPT to venlafaxine using single photon emission computed tomography (SPECT) (Martin et al. 2001), one study comparing IPT to paroxetine using FDG PET (Brody et al. 2001), and one study comparing CBT to paroxetine also using FDG PET. (Goldapple et al. 2004) Perhaps due to the heterogeneity of most samples of patients meeting criteria for major depressive disorder and/or due to limitations in study design including small sample sizes, the findings of these studies have been inconsistent and at times contradictory. Nonetheless, Goldapple et al. proposed (Goldapple et al. 2004), a cogent theoretical model to explain the results of their study in which they compared paroxetine to CBT treatment for depression, namely that, in contrast to the findings of Baxter et al. described above, improvement can occur in different ways. In Goldapple et al.'s (2004) study, the two treatment modalities seemed to produce opposite changes in responders, specifically that in the pre-frontal cortex there was decreased activity after CBT but increased activity after paroxetine treatment, whereas in the limbic areas the reverse was reported, namely increased activity after cognitive behavioral treatment and decreased activity after paroxetine treatment. The hypothesis offered is that, at least in the case of depression, psychotherapy has a top–down effect, which means that cortical effects influence sub-cortical structures, whereas pharmacotherapy has a bottom-up effect, that is from limbic and sub-cortical areas through to the cortex. Pre-clinical studies of medications with antidepressant action have documented a series of effects, including aminergic reuptake inhibition, autoregulatory desensitization, and receptive remediative second-messenger and neurotropic signaling effects, which have been interpreted as a bottom-up chain of events. In clinical studies that have assessed functional changes in patients who have responded to antidepressant medication, the most consistently reported findings are changes in the frontal cortex involving the normalization of both frontal overactivity and under-activity, which may result from bottom-up effects such as those found in animal models. In contrast to the bottom-up effect of medications, the hypothesized mechanism by which CBT and other psychotherapies are effective in the treatment of depression is generally thought to involve directly modifying attention and memory functions involved in cognition and maladaptive processing of external and internal stimuli; this is thought primarily to be a top–down mechanism.

The second approach to exploring the impact of psychotherapy is to use fMRI to measure response to symptom provocation before and after treatment. There are two studies of patients with arachnophobia, in which the patients are shown standardized images of spiders both before and after treatment with CBT (Straube et al. 2005). There were significant decreases in activity post-treatment, but the localization of the decreased activity was somewhat different for the two treatment studies, with decreases in right dorsal lateral pre-frontal cortex vs. the insula and thalamus, respectively.

In the third approach, imaging techniques have been used to validate the brain correlates of unconscious processes, which are central to the theory and practice of psychoanalysis, but for which to date the evidence has been

limited to behavioral correlates and verbal communications in psychodynamic treatment. For example, a central tenet of psychodynamic theory is that unconscious affects are crucial determinants of behavior. In an innovative paradigm, Etkin et al. (2004) measured baseline anxiety in a group of normal subjects and then exposed them to a series of fearful faces. It is known that fearful faces will reliably stimulate activity in the amygdala, but the unique aspect of this experiment was that the faces were presented in two different ways, one that stimulates conscious activity and another that is registered without conscious awareness. The nonconscious processing was achieved through a procedure called backward masking, in which the fearful face is presented too briefly to be recorded consciously, and is then immediately followed by the presentation of a neutral image. If the subject reacts to the backward masked fearful face, this is interpreted as as an unconscious response. There was an increase in amygdala activity after the presentation of fearful faces, which correlated with the baseline trait anxiety scores. However, this was only found when the fearful faces were processed unconsciously. This method has the potential to test differential effects of a psychotherapy that targets conscious thoughts such as cognitive therapy vs. one that targets unconscious processes such as transference focused psychotherapy.

## Conclusion

For years, psychodynamic and psychoanalytic paradigms dominated the theory and practice of psychotherapy. The psychoanalytic community's initial rejection of empirical research was reversed by (1) the clearcut effectiveness of pharmacologic treatments, (2) observational research on normative and pathological infant and childhood behavior which forced a reexamination of fundamental concepts of development, and (3) the advent of powerful techniques for a reductionist neurobiology of complex mental functions such as learning, memory and affect. These advances have motivated new interest in psychotherapy and have spurred the development of methods for demonstrating the effectiveness of psychotherapy and ultimately for understanding its mechanisms of action at the levels of interpersonal, intrapsychic, and neural function. It is now accepted that any form of psychotherapy, including dynamic psychotherapy, must have its effectiveness established by rigorous clinical trials as a prerequisite for the investigation of its mechanisms of action. Furthermore, the study of the effects of psychotherapy offers a unique opportunity to illuminate the fundamental problem of the relationship between the mind and the brain.

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CHAPTER

# 19 The Neurobiology of Schizophrenia

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## Introduction

The key features of schizophrenia are psychotic, or so-called positive symptoms (especially delusions and hallucinations), negative symptoms, and cognitive dysfunction (see chapter on clinical manifestations of schizophrenia). These symptoms are often accompanied by fluctuating symptoms of affective and psychomotor dysregulation such as depression, anxiety, hostility, and agitation (Figure 19–1). These components of the disorder vary in their form, time of presentation, intensity, and course from patient to patient, often independently of each other. Treatments affect them differently. It is not yet clear if these three symptom clusters result from a single pathophysiological process or whether their underlying biological bases are distinct (Meltzer 1979, Kirkpatrick et al. 2001). New evidence indicates that neurobiological features are shared between bipolar disorder with psychotic features and schizophrenia—disorders that have been regarded as separate since the work of Emil Kraepelin (1856–1926, Adler and Strakowski 2003).

There is extensive evidence for the hypothesis that schizophrenia is a neurodevelopmental disorder, which continues to unfold throughout life. It is thought to result from genetic and environmental factors, and to lead to abnormalities in neural systems that are critical substrates for the assessment of sensory input, information processing and storage, and social interaction. As discussed in Chapter 14, genetic factors play a major causal role in schizophrenia, with multiple genes contributing to the pathogenesis and determining response to treatment. Epigenetic mechanisms bridge the gap between environment and the genetic predisposition (Petronis et al. 1999). Stressful life events, which activate the hypothalamic-pituitary–adrenal axis and stimulate the release of various brain neurotransmitters, especially dopamine and norepinephrine, are also thought to be a key factor in the etiology of schizophrenia (Phillips et al. 2006). Gender differences in schizophrenia (Patel et al. this volume) suggest a possible role for sex hormones in the etiology of schizophrenia. Environmental factors may include drugs of abuse such as cannabis, stimulants such as amphetamine, and psychotomimetic agents such as phencyclidine, which interact with the genetically determined vulnerability to trigger the disorder, usually in late adolescence and early adulthood, but also in childhood (Hambrecht and Hafner 2000, Millan 2005).

The neurobiology of schizophrenia includes both structural and functional abnormalities. The structural changes in the brains of patients with schizophrenia have been studied with classical neuropathological methods, and more recently, brain imaging (Jarskog et al. 2007). The pioneering work of Carlsson and Seeman focused on the role of dopamine in the pathophysiology of schizophrenia's psychotic symptoms. However, dopamine's role is now understood within the framework of other neurotransmitters, especially GABA, glutamate and serotonin, which regulate the activity of dopaminergic neurons and the response of neurons to dopamine in several regions of the brain including the prefrontal and anterior cingulate cortex, the medial temporal lobe, and the thalamus (Coyle 2006).

This chapter provides a broad overview of several of the advances in the understanding of the neurobiology of schizophrenia. Evidence for the neurodevelopmental hypothesis will be presented first. Abnormalities in key neurotransmitter systems and neural circuits will be considered. The use of intermediate phenotypes (endophenotypes), which are measurable traits that may be more proximal to the underlying genetic vulnerabilities, are also discussed.

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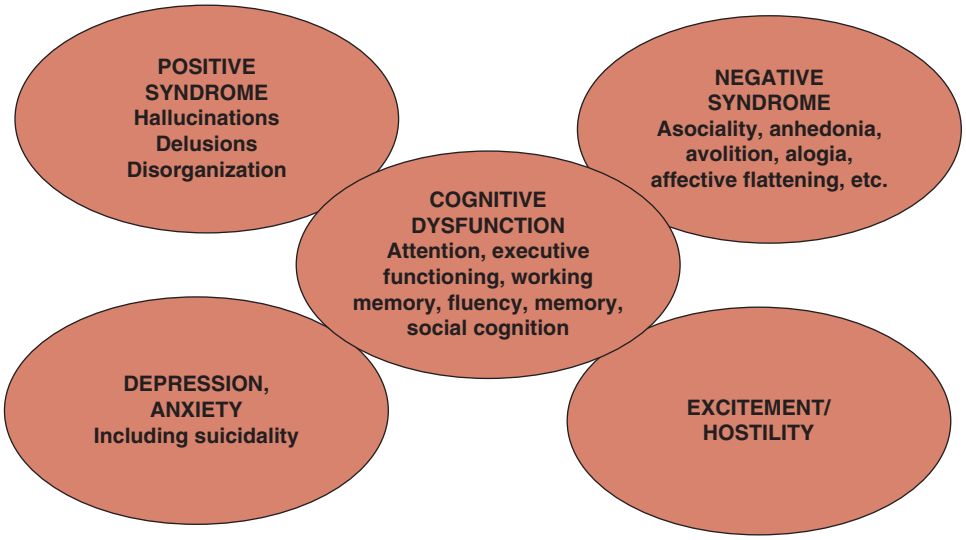



**Figure 19–1** *Psychopathological domains of schizophrenia.*

## Neurodevelopmental Concept

The neurodevelopmental model of schizophrenia posits that schizophrenia results from abnormalities in development that begins in utero and continues through infancy, adolescence, and young adulthood. The initial processes predate the onset of clinical symptoms, and are thought to be caused by a combination of genetic and environmental factors (Singh et al. 2004, Jarskog et al. 2007). Individuals who later develop schizophrenia have higher rates than healthy subjects of pre- or perinatal insults with minor physical anomalies, as well as minor deviations in motor, cognitive, and social development. There are at least two major epochs during which developmental brain insults are believed to heighten the risk of schizophrenia: (1) pre- and perinatal and (2) disturbances in brain maturation during late adolescence (Feinberg 1982, Mathalon et al. 2003). Initial postmortem studies appeared to support the early neurodevelopmental model, they reported abnormalities in neuronal migration and organization were fetal in origin (Jakob and Beckmann 1986, Akbarian et al. 1993). Subsequent and more reproducible observations of reduced neuronal size and arborization (Selemon and Goldman-Rakic 1999), which could have developed later in life, indicated that the pathophysiological processes involved in schizophrenia need not be restricted to the pre-or perinatal period. This is in agreement with brain imaging studies that reveal progressive changes for early onset as well as adult onset patients. Indeed, candidate genes for schizophrenia include some that are involved in neurodevelopment across different developmental periods, e.g., DISC-1, reelin, neuregulin-1, dysbindin-1, and AKT-1 (Arnold et al. 2005). Variability in the number and combination of mutations of these and other neurodevelopmental genes could provide the basis for the heterogeneity of schizophrenia.

### Pre- and Perinatal Risk

A large number of studies have found a relationship between obstetric complications (OCs) and the onset schizophrenia. The two main reasons for the interest in OCs are the availability of relevant data from objective and contemporaneous medical records and the specificity of the nature and timing of such events. A meta-analysis of population-based data found significant increases in three main categories of OCs: (1) complications of pregnancy such as bleeding, pre-eclampsia, diabetes, and rhesus blood group incompatibility; (2) abnormal fetal growth and development including low birth weight, congenital malformation, and small head circumference; and (3) complications of delivery, in particular, asphyxia, uterine atony, and emergency Cesarean section (Cannon et al. 2002a, 2002b). The increase in overall risk for schizophrenia conferred by such events seems genuine but small, with a pooled odds ratio for the effect of OCs on the subsequent development of schizophrenia about 2.0. The role of obstetric complications may be greater for individuals with greater impairment, or early onset (before age 18). Rather than being direct causal agents for schizophrenia, obstetrical events could be markers for some other neurodevelopmental or environmental factors, particularly since OCs are themselves multifactorial in origin. For example, low birth weight and small head circumference reflect retardation of fetal growth, but almost any factor affecting the fetus adversely will retard its growth.

Bleeding in pregnancy, pre-eclampsia, and delivery complications are thought to result in chronic hypoxia or acute asphyxia (Cannon et al. 2002a, 2002b). Cannon and co-workers (Rosso et al. 2000) argue that ischemic damage leads to neuronal loss in temporal brain regions such as the hippocampus, which are known to be involved in schizophrenia (see discussion of premorbid risk below) and are sensitive to hyoxic insults. The association between schizophrenia and serologically confirmed in utero influenza, rubella, and respiratory infections (Brown and Susser 2002) may reflect abnormal maternal immune response, consistent with the possible role of early infection. Several studies have reported elevation of pro-inflammatory cytokine levels (Ashdown et al. 2006).

### Premorbid Risk

Follow-back, cohort, and special population studies show that the premorbid history of patients with adult onset schizophrenia is replete with a variety of subtle

neurodevelopmental abnormalities beginning in childhood (Cannon et al. 2002a, 2002b).

### Early Developmental Delays/Skeletal Muscle and Motor Abnormalities

Children who went on to be diagnosed as having schizophrenia were found to have abnormal upper limb movements (Walker et al. 1994). Neuromotor abnormalities have been found to be, along with cognition, the most reproducible biological marker for schizophrenia in high-risk family studies (Owens and Johnstone 2006). Although they are not specific for schizophrenia, they do support the neurodevelopmental hypothesis. Two major British cohort studies, the National Survey of Health and Development and the National Child Development study, found delays in the speech and motor development of British children born during specified periods in 1946 and 1958, respectively. Such abnormalities were most obvious for motor milestones before the age of 2 years and for language development between the ages of 2 and 15 years. The increased risk was associated with deficits across several developmental domains, including achievement of age-appropriate motor, social, and intellectual milestones, perhaps reflecting some underlying general risk (Jones et al. 1994, Isohanni et al. 2004).

Retrospective and clinical studies show that speech and language deficits increase in frequency and severity with earlier age of onset (Hollis 1995). Finally, motor abnormalities appear to be trait markers for schizophrenia as they have been noted in both drug-free patients and in their unaffected first-degree relatives (McCreadie et al. 2003).

A variety of abnormalities in the morphology of skeletal muscle, the physiology of motor nerves, and subterminal motor nerve branching, as well as the loss of motor neuron units leading to increased size of surviving motor units, have been reliably reported in patients with schizophrenia and their first-degree relatives (Meltzer 1976, Goode et al. 1977, Flyckt et al. 2000).

### Social and Cognitive Development

A variety of studies including the British cohort studies mentioned above document poor peer relationships, social isolation, social anxiety, and a gender effect with boys being more disruptive and girls being more withdrawn. These studies again indicate increasing risk over a whole range of developmental measures suggesting some underlying general risk for psychosis rather than a threshold model (Jones et al. 1994).

General cognitive ability, assessed between the ages of 7 and 17 years either by formal cognitive tests or by using educational achievement as a proxy measure, is lower in preschizophrenic children compared to their healthy peers (reviewed in Rapoport et al. 2005). Decline in general intellectual function (between ages 4 and 7 years) and persistently low scores in cognitive testing during early childhood (between ages 3 and 11 years) show some specificity for schizophrenia and schizophrenia spectrum disorders, while emotional and social problems seem to be nonspecific indicators of a variety of different adult psychiatric outcomes (Cannon et al. 2002a, 2002b).

### Premorbid Psychopathology

Kim-Cohen et al. (2003) found a diversity of premorbid psychopathology in patients who went on to develop schizophrenia by including Diagnostic and Statistical Manual (DSM) diagnostic data in a prospective study of a representative birth cohort of 1037 individuals participating in the Dunedin Multidisciplinary Health and Development Study. In this study, 53% of individuals who were diagnosed as having schizophrenia or schizophreniform disorder (a schizophrenia-like syndrome that lasts 6 months or less) at age 26 had been evaluated at ages 11, 13, 15, 18, 21 years. Unlike mood and anxiety disorders, which were generally preceded by similar types of affective disorder in childhood, schizophreniform disorder (and subsequently schizophrenia) was preceded by an array of juvenile diagnoses including anxiety, depression, conduct disorder or oppositional defiant disorder, and attention deficit hyperactivity disorder. At age 11, nearly 15% of the sample reported some delusional or hallucinatory experience (Poulton et al. 2000). At 26, 25% of the group with the most prominent childhood psychotic symptoms was diagnosed with a schizophrenia-related psychotic illness using modified DSM-IV-TR criteria for schizophrenia and schizoaffective disorder designed to minimize misdiagnosis. By adulthood, 70% of these individuals developed schizophrenia-related symptoms that did not satisfy diagnostic criteria. This important finding contradicted the widely held belief that psychotic symptoms occurring in nonpsychotic children have little predictive power for the future development of schizophrenia. These data are also inconsistent with the concept that psychotic symptoms associated with schizophrenia are possible only when higher order association systems 'come on line' later in development.

### Premorbid Cognitive Impairment

Individuals at risk for schizophrenia have significant cognitive impairment before the onset of psychosis, especially memory and learning. Although most of these impairments seem nonspecific, they nevertheless support a neurodevelopmental hypothesis. The level of cognitive impairment is less than in the first episode of schizophrenia (Keefe et al. 2006, Owens and Johnstone 2006). Neurocognitive deficits appear to be an early predictor or risk for the development of schizophrenia or other psychotic disorders (Keefe et al. 2006).

## Brain Imaging Studies during Development

The developmental abnormalities discussed above are paralleled by developmental disturbances in brain development. Longitudinal studies in adult onset patients provide evidence for progressive changes in grey matter, including cortical atrophy, although the number of studies and sample sizes are small, and the follow-up periods are relatively short (DeLisi 1999, Mathalon et al. 2003, Shenton et al. 2001). These findings may reflect subtle abnormalities in brain plasticity that result from a continuing neuropathologic process or systemic physiological fluctuations. Pantelis et al. (2005) examined a group of individuals before and after the onset of psychosis and also reviewed other longitudinal studies. Longitudinal studies of first episode patients (mean age between 26 and 30 years) have provided evidence of increases in ventricular volume over a 2–4 year

period, and bilateral decreases in frontal lobe gray matter volume. Similar decline in frontal lobe volume and posterior superior temporal grey matter volume has also been reported in chronic schizophrenic patients (mean age 39 years) over a 4 year period (Mathalon et al. 2001). These findings suggest both early and late phases of brain tissue loss.

### Studies of Childhood Onset Schizophrenia (COS)

Variability in age of onset must be explained by any proposed etiology of schizophrenia. Patients with childhood onset schizophrenia generally have the most severe illnesses and exhibit a high rate (85%) of early developmental delays (Nicolson and Rapoport 1999). Nicolson and Rapoport found no increased obstetrical risk in those with an early age of onset.

Premorbid diagnoses for the childhood onset patients included high rates of anxiety disorders (57%) and pervasive developmental disorders (26%). There was no predictive specificity of these earlier diagnoses for schizophrenia, as elevated rates for these disorders were also seen in individuals with other adult psychiatric outcomes. These varied premorbid diagnoses most probably reflect the variability in the developmental phenotypes produced by the risk genes. Alternate hypotheses include locus heterogeneity, varied environmental stressors or toxins, and "noise" in the developmental system (Singh et al. 2004).

### Pediatric Brain Imaging Studies Relevant to Schizophrenia

In the last decade, there has been a concerted effort to obtain normative structural data for human brain growth across the understudied child and adolescent age period. The anatomic development of subcortical structures, including the amygdala, basal ganglia, and thalamus, has been shown to be relatively complete by late childhood, with cortical regions having substantially longer developmental trajectories. Grey matter volume increases in late childhood and decreases during puberty, following a consistent "back to front" pattern (Gogtay et al. 2004). Based on studies of primate and human cerebral cortical development, these volumetric changes are thought to reflect initial overproduction, followed by selective elimination and structural alterations of dendritic synapses (Zecevic et al. 1989, Huttenlocher and Dabholkar 1997). Medial aspects of the temporal lobe mature early while the lateral regions representing higher integrative areas are among the last to mature (Gogtay et al. 2004).

Anatomic MRI studies of childhood onset schizophrenia show grey matter reduction and ventricular enlargement typical of that seen in adults (Frazier et al. 1996a, 1996b). Longitudinal data from subjects with early onset schizophrenia show striking progressive changes. Thompson et al. (2001) reported that the earliest deficit was profound parietal grey matter loss, which then moved anterior into the temporal lobes, sensorimotor and dorsolateral prefrontal cortices, and frontal eye fields. This difference was diagnostically specific, as it is not seen in children with atypical and affective psychoses who were receiving the same medications. In the same cohort of patients, there was also progressive increase in ventricular and decrease in hippocampal volume (Giedd et al. 1999). As shown in Figure 19–2, these cortical changes appear to be exaggerations of the normal cortical development.

## Genetics and Developmental Neurobiology

The genetics of schizophrenia is covered in detail in Chapter 13 Merikangas and Karayiorgou . Only certain key neurodevelopmental aspects of the genetics of schizophrenia will be highlighted here. Converging data indicate that there are abnormalities in the brains of patients with schizophrenia related to synapse formation, stabilization, function, and elimination (Levitt 2005). These, in turn, are consistent with genetic pathways which have been identified in genome-wide association as well as candidate gene studies (Harrison and Weinberger 2005, Ross et al. 2006). As discussed below, risk genes for schizophrenia are associated with premorbid neurodevelopmental impairment and/or MRI abnormalities in the growth of brain grey and white matter. Finally, very early onset illness is associated with a 10% rate of cytogenetic abnormalities, a rate similar to that seen in autism (Rapoport et al. 2005).

### Gene Expression Throughout Development

Eukaryotic cells use a variety of post-transcriptional mechanisms to regulate gene expression. By developmentally regulated and tissue-specific alternative splicing, multiple protein forms can be produced from a single gene. It appears that many, if not most, genes act at more than one developmental period, with different levels of expression and even different sites in the brain most active at different developmental time points (see Rapoport et al. 2005). These expression patterns are now being studied for schizophrenia susceptibility genes (eg, for the 22q11 region; Maynard et al. 2003).

Knowledge of how the identified susceptibility genes for schizophrenia contribute to the disease's pathogenesis is in its early stages. Some of them have multiple roles in normal function during adulthood and development that could be relevant. For example, neuregulin (NRG1), one of the first known susceptibility genes for schizophrenia (Stefansson et al. 2002), is involved in neuronal migration and connectivity, cell signaling, and myelination (Corfas et al. 2004). Schizophrenia associated single nucleotide polymorphisms (SNPs) alter the mRNA transcript levels for at least two isoforms of NRG1, Type I and Type IV, suggesting that differential isoform expression accounts for the role of NRG1 in schizophrenia (Law et al. 2006). The NRG1 Type IV isoform is of particular interest because it is brain specific and is particularly abundant in the fetal brain. One of the schizophrenia risk SNPs is associated with differential activity of Type IV's upstream 5' promoter region (Tan et al. 2007). Other important candidate genes for schizophrenia, including DISC-1, reelin, and dysbindin-1, appear to have critical roles in both brain development and/or neural integrity. For instance, DISC-1, the expression of which is increased during neuronal development (Schurov et al. 2004), is believed to be involved in the regulation of neuronal migration and neuronal maturation, as well as modulation of synaptic transmission and plasticity (Porteous et al. 2006). Dysbindin appears to be a key regulator of glutamatergic transmission and prefrontal functioning, and may be important to the glutamatergic

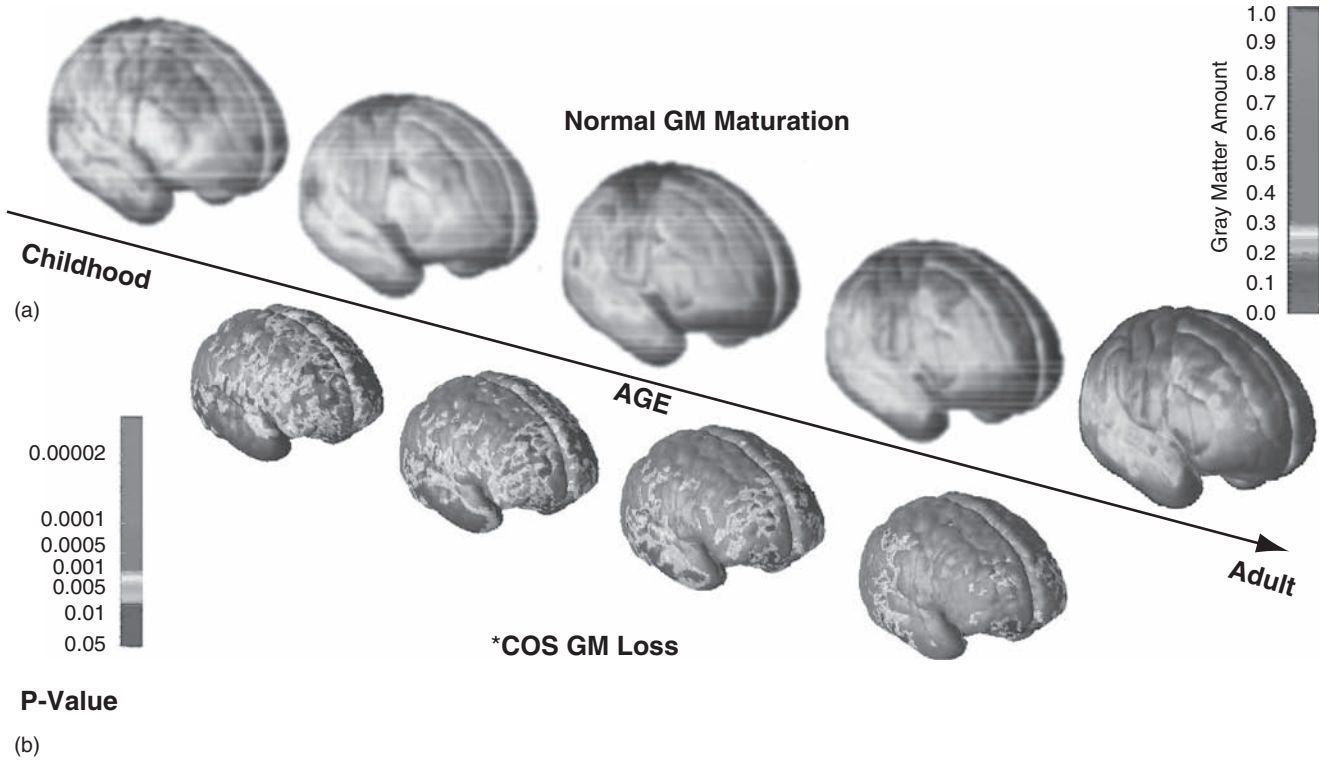



**Figure 19–2** *Gray matter maturation for healthy and schizophrenic children and adolescents. Comparison of the patterns of cortical gray matter (GM) loss in childhood onset schizophrenia (COS) (between ages 12 to 16) to that seen in normal cortical maturation (between ages 4 to 22). A.Right lateral view of the dynamic sequences of cortical GM maturation in healthy children between ages 4 and 22 (n=13; 54 scans; upper panel) rescanned every 2 years. Scale bar shows GM amount at each of the 65,536 cortical points across the entire cortex represented using a color scale (Red to Pink—More GM; Blue—GM Loss). Cortical GM maturation appears to progress in a "back to front" (parieto-temporal) manner (Gogtay et al. 2004). B. Right lateral view of the dynamic sequence of cortical GM maturation in COS between ages 12 to 16 compared with ages and sex matched healthy controls (n=12, 36 scans in each group), where children are rescanned every 2 years. Dynamic maps represent p-values for the difference in GM amount between COS and controls at each of the 65,536 cortical points, and p-values are represented using a color scale (that is Pink p<0.00002). Cortical GM loss in COS also appears to follow in a "back to front" direction on the lateral surface, thus suggesting that the COS pattern is an exaggeration of the normal GM maturation (Thompson et al. 2001). Data on childhood onset schizophrenia only, ages 12 to 16. International Psychopharmacology Algorithm Project (IPAP) Schizophrenia Algorithm (updated 17 March 2006). Available online at: www.ipap.org. (See Color Plate II)*

deficit which appears to occur in schizophrenia (Maier et al. 2006).

## Genetics and Endophenotypic Markers

Family, twin, and adoption studies involving schizophrenic patients have revealed high heritability, estimated at 80% (Cardno et al. 1999, Sullivan et al. 2003). This does not exclude a role for nongenetic factors: the concordance rate for schizophrenia in monozygotic twins is only 50% (Cardno et al. 1999). Nevertheless, there is now convincing evidence that a combination of risk genes contributes to the overall susceptibility to developing schizophrenia.

The search for schizophrenia's neurobiological basis has been slowed by the disorder's complex inheritance and clinical phenotype, as noted above. This has led to investigations of disease characteristics that are themselves heritable, more quantifiable than clinical symptoms, and presumed to be proximal to the disease's neurobiological causes. Because these characteristics, termed "endophenotypes," are themselves heritable and tend to be highly penetrant, they are also present in unaffected family members. Additional criteria for endophenotypes that have been proposed (Gottesman and Gould 2003) are that endophenotypes must (1) manifest as traits, i.e., features that persist independently of the presence or severity of disease symptoms, (2) cosegregate with the illness within families, and (3) occur at a higher rate among non-affected family members than that of the general population.

Several endophenotypes for schizophrenia have been proposed. One group of proposed endophenotypes are deficits of sensorimotor control and reflex inhibition. Specific sensorimotor control and inhibition phenomena that are impaired in schizophrenia include smooth pursuit eye movements, antisaccade eye movements, P50 auditory evoked responses, and pre-pulse inhibition. Approximately 50% of patients with schizophrenia have abnormalities in smooth pursuit eye movements, which are independent of the severity of psychotic symptoms, attentional state, or antipsychotic drug treatment (Lee and Williams 2000). A specific component of smooth pursuit eye movements, predictive pursuit, has high concordance within sibling pairs in which the proband has schizophrenia. This finding suggests that predictive pursuit eye movements represent a heritable neurobiologic trait related to risk for schizophrenia (Hong et al. 2006). The antisaccade task requires the subject to inhibit the reflexive saccadic pursuit of a target and direct her gaze to the mirror image opposite position. Both are impaired in individuals with schizophrenia

and their unaffected relatives (Calkins et al. 2004) and are thought to reflect dysfunctional interactions between areas of the frontal, temporal, or parietal cortices and the striatum.

Two indicators of sensorimotor gating, the P50 event-related potential (ERP) and pre-pulse inhibition (PPI), consistently demonstrate deficits of inhibition in schizophrenia. Inhibition of the P50 auditory ERP is deficient in patients with schizophrenia (Bramon et al. 2004) and unaffected relatives (Turetsky et al. 2007). In this paradigm, an auditory stimulus produces an evoked response after approximately 50 msec. The response to a second stimulus given 500 msec later is normally inhibited, as indicated by a reduced ERP. In schizophrenia the inhibition of the second response is absent, which is interpreted as an abnormality of a basic sensory gating mechanism that is associated with deficits of sustained attention and vigilance (reviewed in Martin and Freedman 2007). The PPI paradigm makes use of the eye blink startle reflex to a sudden loud tone. When a softer tone precedes the loud one, the startle response is inhibited, an effect that depends on the interaction of a cortico–striatal–pallidal–pontine circuit with the primary startle reflex. The inhibition of startle by the pre-pulse is impaired in both schizophrenics and their relatives (Kumari et al. 2005). PPI deficits have been related to clinical parameters in patients with schizophrenia including positive and negative symptoms and specific types of cognitive deficits (Geyer et al. 2001).

Another type of endophenotype for schizophrenia involves abnormalities in the detection of novel or discrepant sensory information. Patients with schizophrenia, compared to normal controls, show an attenuated response to another ERP, the P300 response to novel, unexpected, or emotionally laden stimuli (Ford 1999). This wave form, occurring 300 ms after the stimulus, represents a composite of temporally overlapping separate cortical responses that include aspects of directed attention, working memory, and the attribution of salience to the stimulus (Turetsky et al. 2007). Its reduced amplitude is a particularly robust physiologic phenomena in schizophrenia (Turetsky et al. 1998). There is also strong evidence that unaffected family members of schizophrenic individuals have decreased P300 amplitudes (Kimble et al. 2000, Weisbrod et al. 1999). In a related paradigm, mismatch negativity, a "novel" auditory stimulus is included in a series of uniform auditory stimuli. A normal response is the generation of a negative electroencephalographic signal, an effect that is blunted in patients with schizophrenia (Michie 2001). Like PPI, abnormalities in mismatch negativity have also been related to cognitive deficits in schizophrenia (Baldeweg et al. 2004).

## Cognitive Dysfunction

Deficits in cognitive functioning in schizophrenia are now viewed as core features of the disorder and are believed to directly reflect specific abnormalities in brain development or functioning. For example, working memory dysfunction in schizophrenia has been associated with reduced activation of dorsolateral prefrontal cortex (Levy and Goldman-Rakic 2000). The cognitive deficits also appear to have a greater impact on functional outcome than psychotic symptoms such as hallucinations and delusions (Green et al. 2000). The domains that are most impaired include attention, working memory, language skills, and executive functioning, with the greatest impairments in verbal learning and memory (Bowie and Harvey 2005). Although no specific cognitive deficits is pathognomonic of schizophrenia, spatial working memory in particular may be heritable (Cannon et al. 2000) and over-represented in relatives of schizophrenic patients (Myles-Worsley and Park 2002, Saperstein et al. 2006). Thus, the cognitive deficits characteristic of schizophrenia may qualify as an endophenotype for the illness.

The cognitive dysfunction in schizophrenia occurs independently of the severity of positive symptoms (Addington et al. 1991), and is only weakly correlated with negative symptoms (Buchanan et al. 1994, Harvey et al. 1996). Impairments in cognition persist even when psychotic symptoms remit, and are apparent even before the first onset of psychotic symptoms. Treatment with typical neuroleptic medications, on average, does not result in significant improvement of cognitive deficits in schizophrenia, whereas most studies suggest that atypical antipsychotics appear to exert a modest beneficial effect (Woodward et al. 2005) (although a recent multicenter comparison showed slight and approximately equal benefits to cognitive function for both atypicals and typicals (Keefe et al. 2007)). Conversely, while treatment with typical neuroleptics can worsen psychomotor performance for some patients, these drugs do not consistently appear to worsen cognitive performance; thus, cognitive impairment in schizophrenia is not caused by treatment with typical neuroleptic drugs (Hoff et al. 1999). As further evidence of this, neuropsychological function deficits have been identified among medication-naïve schizophrenic patients at the first break (Brickman et al. 2004).

The course of cognitive deficits has been examined in both cross-sectional and longitudinal studies. Deficits identified at baseline in these studies were stable over long-term follow up, with no clear evidence of declining cognitive function (Townsend and Norman 2004). Whereas attention, executive function, memory, and psychomotor speed have improved in some studies and declined in others, most studies suggest that impairments in cognitive functioning are stable and persist in spite of improvements in positive and negative symptoms.

## Neurochemical Abnormalities in Schizophrenia

### Dopamine

The identification of dopamine (DA) as a neurotransmitter and the ability of chlorpromazine to block DA receptors (Carlsson and Lindqvist 1963) led to the DA hypothesis of schizophrenia, which suggested that increased dopaminergic transmission was causally related to schizophrenia (Rossum 1966). This concept received strong support from (1) the extremely tight correlation between clinical doses of a wide range of antipsychotic drugs and their potency to block DA $D_2$ receptors (Seeman et al. 1975, Creese et al. 1976) and (2) studies confirming the psychotogenic effects of DA enhancing drugs such as amphetamine and methamphetamine (Meltzer and Stahl 1976). The mesolimbic dopaminergic pathway, with cell bodies in the ventral tegmentum, and terminals in the ventral striatum, which includes the nucleus

accumbens, the stria terminalis, and the extended amygdala, was viewed as the specific region of the brain that produced the positive symptoms, delusions and hallucinations (Meltzer and Stahl 1976). The nigrostriatal dopaminergic pathway includes projections from the substantia nigra pars compacta to the dorsal striatum and is involved in motor function. Typical antipsychotic drugs, of which haloperidol is the most commonly used, are thought to ameliorate the positive symptoms via the mesolimbic pathway but to cause extrapyramidal symptoms by their ability to block DA $D_2$ receptors in the dorsal striatum.

About one-third of patients with schizophrenia who are given amphetamine or methylphenidate, another indirect DA agonist develop a marked increase in psychotic symptoms, although some patients actually improve, particularly with regard to negative symptoms (Janowski et al. 1974, Meltzer and Stahl 1976, Lieberman et al. 1987). Marked and exaggerated decreases in [$^{11}$C] raclopride and [$^{123}$I] iodobenzamide (IBZM) binding in the striatum occur after acute amphetamine exposure in patients with schizophrenia relative to matched control subjects, indicating increased dopamine release (Abi-Dargham 2004). These effects have been demonstrated in first-break, drug naïve subjects, as well as those who have received antipsychotic drug treatment. The exaggerated DA response effects after amphetamine exposure were also shown to be greater in magnitude among schizophrenic patients who were experiencing a psychotic exacerbation compared with those who were clinically stable (Laruelle et al. 1999). Numerous efforts to directly identify excessive output of DA by patients with schizophrenia using cerebrospinal fluid or plasma levels of DA metabolites, homovanillac acid and dihydroxyphenylacetic acid, have produced equivocal results. On the post-synaptic side, PET and postmortem studies of $D_2$ receptor density in the striatum of patients with schizophrenia originally produced mixed results (Lauruelle 1998).

Imaging studies have also shown higher baseline occupancy of $D_2$ receptors in patients with schizophrenia who were experiencing an acute exacerbation of psychosis, relative to healthy control subjects. Moreover, recent PET scanning with increased resolution, which allows compartmentalization of the striatum, unexpectedly found that the increase in basal $D_2$ receptor occupancy is highest in the dorsal striatum. Since higher pretreatment synaptic dopamine levels predict a better response to atypical antipsychotic drug treatment, this suggests that the dorsal striatum may be as important for generating symptoms as the ventral striatum (Abi-Dargham et al. 2000). Together, these studies provide further support for striatal dopaminergic excess as a key component of the pathophysiology of particularly positive signs and symptoms in schizophrenia, as well as the importance of striatal DA $D_2$ receptor blockade in the pharmacological activities of antipsychotic drugs. All typical and most atypical antipsychotic drugs have significant $D_2$ antagonist or partial agonist effects at the central DA $D_2$ receptor. The importance of prefrontal DA transmission at $D_1$ receptors (the main DA receptor in the neocortex) for optimal PFC performance was an important step in moving beyond interest in the $D_2$ receptor and schizophrenia, despite the failure of $D_1$ antagonists to improve psychosis (Goldman-Rakic et al. 2000) and the finding that $D_1$ receptor affinity did not discriminate between typical and atypical antipsychotic drugs (Meltzer et al. 1989). The view that too little or too much cortical DA receptor stimulation can lead to impaired cognition has been particularly influential (Goldman-Rakic et al. 2000). Indeed, results from in vivo molecular imaging studies of $D_1$ receptor availability indicate a relationship between cognitive functioning and $D_1$ receptor levels in the prefrontal cortex in patients with schizophrenia, although, due to the use of a variety of ligands, the findings have been inconsistent (Abi-Dargham and Moore 2003).

Increasing awareness of the importance of enduring negative and cognitive symptoms in this illness, their independence from positive symptoms, and the inability of typical antipsychotic drugs to improve these symptoms, led to an appreciation of the severe limitations of the DA hypothesis. Clearly, increased dopaminergic activity in the limbic system was an insufficient basis for schizophrenia as a whole, and perhaps not even for psychosis, in that about one-third of all patients with schizophrenia fail to respond to typical antipsychotic drugs, regardless of dose. In addition, numerous types of preclinical and clinical data suggested that cognitive impairment and negative symptoms might arise from deficits in dopaminergic activity in the prefrontal cortex (PFC) (Meltzer and Stahl 1976, Davis et al. 1991, Knable and Weinberger 1997, Rao and Moller 1994). Eventually, a more nuanced hypothesis emerged: hyperactive subcortical mesolimbic projections (resulting in hyperstimulation of mesolimbic $D_2$ receptors and positive symptoms) and hypoactive mesocortical DA projections to the PFC (resulting in hypostimulation of $D_1$ receptors, negative symptoms, and cognitive impairment) supplanted the original formulation of the DA hypothesis (Davis et al. 1991). These hypotheses are based, in part, upon an appreciation of the evidence that prefrontal cortical dopaminergic activity, when diminished, may increase the activity of subcortical DA neurons which innervate the ventral striatum (Pycock et al. 1980, Jaskiw et al. 1990, Tzschentke 2001). There is some evidence of an association between low levels of homovanillic acid levels (HVA), the major metabolic byproduct of DA, and severity of negative symptoms and cognitive deficits (Davis et al. 1991). However, most of the evidence to date is indirect. Supporting evidence includes the observed changes in $D_1$ receptor levels in the PFC and the observation that atypical antipsychotic agents, which are believed to be more effective for treating cognitive dysfunction and negative symptoms than typical neuroleptics (Moller 2003, although see the recent CATIE study, Keefe et al. 2007), appear to increase DA release in the prefrontal cortex (Kuroki et al. 1999) and hippocampus (Chung et al. 2002). Direct evidence comes from immunohistochemical studies that show a decrease in the number of tyrosine hydroxylase positive terminals in the prefrontal cortex (Akil et al. 1999).

## Serotonin

A role for serotonin (5-hydroxytryptamine, 5-HT) in the etiology of schizophrenia was first postulated because of the structural similarity between 5-HT and the hallucinogenic drug, lysergic acid diethylamide (LSD; Gaddum 1954). LSD, as well as other hallucinogens such as mescaline and psilocybin were subsequently found to be 5-$HT_{2A}$ and 5-$HT_{2C}$ agonists. Stimulation of 5-$HT_{2A}$ receptors is predominantly responsible for the hallucinogenic effect of these agents (Gresch et al. 2002). Although these drugs produce mainly

visual hallucinations, which are far less common than auditory hallucinations in schizophrenia, the hypothesis of a role for 5HT in schizophrenia has proved useful. Genetic mutations of serotonin system genes, primarily those coding for 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, have been reported to be more common in patients with schizophrenia or linked to the action of atypical antipsychotic drugs (Reynolds et al. 2005, Norton and Owen 2005). The more tolerable side effects and possibly greater efficacy of the atypical antipsychotics, such as clozapine, compared to the typicals has been attributed to their relatively more potent antagonism of 5-$HT_{2A}$ than of $D_2$ receptors (Meltzer 1989, 1991). This pharmacologic profile prompted the development of "balanced" 5-$HT_{2A}$-$D_2$ antagonists as antipsychotics, e.g., risperidone, olanzapine, quetiapine, ziprasidone, and laurasidone.

The anatomic distribution and physiologic actions of 5HT receptors suggest what role these receptors play in the therapeutic effects of atypical antipsychotics. Excitatory 5-$HT_{2A}$ and inhibitory 5-$HT_{1A}$ receptors are located on glutamatergic pyramidal neurons and GABAergic interneurons in the cortex and hippocampus, which enables them to modulate glutamate release in the terminal regions of these neurons (Meltzer 1999, Millan 2000). 5-$HT_{2A}$ receptors are also located on the cell bodies of DA neurons in the ventral tegmentum and substantia nigra, while 5-$HT_{1A}$ receptors are also found on the cell bodies of 5-HT neurons in the raphe nuclei (reviewed by Meltzer et al. 2003). Clozapine and related atypical antipsychotic drugs combine high potency 5-$HT_{2A}$ receptor antagonism with relatively lower potency $D_2$ receptor blockade (Meltzer et al. 2003) and direct or indirect agonism of 5-$HT_{1A}$ (Ichikawa et al. 2002b). Aripiprazole, which substitutes partial $D_2$ receptor agonism for $D_2$ antagonism, is also a 5-$HT_{2A}$ antagonist and 5-$HT_{1A}$ partial agonist and, thus, fits the clozapine model fairly well. In preclinical models, atypical antipsychotic drugs, but not typical neuroleptics, are associated with increases in cortical DA efflux, an effect which is due, in part, to 5-$HT_{2A}$ antagonism combined with low $D_2$ receptor antagonism (Meltzer et al. 2003). It is hypothesized that the ability of atypical antipsychotic drugs to preserve or even enhance cortical DA release may be one mechanism by which these drugs may ameliorate negative symptoms and improve cognition. Because 5-HT exerts tonic inhibition of DA release via 5-$HT_{2A}$ heteroceptors located on DA cell bodies in the substantia nigra (Nocjar et al. 2002), the 5-$HT_{2A}$ receptor antagonism associated with most atypical antipsychotic drugs may release these cells from tonic inhibition by 5-HT. Such an effect may bring about relative preservation of dopaminergic tone in the nigrostriatal dopaminergic pathway, and limit the potential for EPS.

## Glutamate

Four main lines of evidence suggest a dysfunction of the glutamate system, and in particular *N*-methyl-D-aspartate (NMDA) receptor dysfunction, in schizophrenia. First, NMDA receptor antagonists such as phencyclidine (PCP) or ketamine have been shown to produce positive, negative, and cognitive symptoms in healthy individuals and exacerbate preexisting symptoms in patients with schizophrenia even after one single use (Javitt and Zukin 1991, Krystal et al. 1994). Alterations in certain neurophysiological measures, including N1 event-related potential and mismatch negativity generation, P50 gating, and pre-pulse inhibition (PPI) (discussed below), are among the most consistent and robust indices of brain dysfunction in schizophrenia and can be observed in humans after single administration of NMDA antagonists (Umbricht et al. 2000). Second, NMDA dysfunction can lead to the dopaminergic alterations observed in schizophrenia with imaging techniques: an acute challenge with ketamine can produce increased subcortical dopamine release (Kegeles et al. 2002) and chronic recreational use of ketamine leads to alterations in dorsolateral prefrontal cortical $D_1$ receptor density similar to that observed in schizophrenia (Narendran et al. 2005). Third, certain genes that have recently been associated with an increased risk for schizophrenia such as neuregulin 1, GRM3, and DISC-1, can influence the function of modulatory sites on the NMDA receptor or synaptic glutamate transmission (Hahn et al. 2006, Moghaddam 2003). For instance, the Type II metabotropic glutamate receptor encoded by GRM3 regulates the expression of glutamate transporters on glial cells, has a major influence on extracellular glutamate levels (Aronica et al. 2003). Fourth, postmortem studies have shown numerous alterations in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus of subjects with schizophrenia (Meador-Woodruff and Healy 2000). These studies overall lend strong support to the concept of broad alterations in NMDA transmission in schizophrenia and suggest these may lead to additional downstream effects on the actions of DA and GABA.

Some evidence links certain aspects of NMDA receptor-mediated dysfunction to DA or 5HT. Thus, haloperidol pretreatment reduced impairments in executive cognitive functions produced by ketamine infusion in normal volunteers, but not the psychosis, perceptual changes, negative symptoms, or euphoria (Krystal et al. 1999). Systemic administration of PCP and ketamine increase the efflux of 5-HT in the mPFC of rats. The atypical antipsychotics clozapine and olanzapine, as well as ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, and prazosin, an alpha1-adrenoceptor antagonist, but not the typical $D_2$ antagonist antipsychotic haloperidol, reversed the PCP- and ketamine-induced increase in 5-HT efflux. PCP-induced disruption of sensory gating was blocked by the selective 5-$HT_{2A}$ receptor antagonist, M100907, as well as clozapine (Javitt 2004). These findings implicate 5-HT in NMDA receptor hypofunction and again emphasize the importance of 5-HT receptor blockade in the action of the atypical antipsychotic drugs.

## GABA

A variety of abnormalities in indices of GABA neurotransmission have been reported in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia (Lewis et al. 2005). Postmortem studies have consistently shown reduced expression of the mRNA for the 67 kDa isoform of glutamic acid decarboxylase (GAD67), the rate-limiting enzyme in GABA synthesis, and its corresponding protein, in the DLPFC (Lewis et al. 2005, Akbarian and Huang 2006). GAD67 mRNA expression is undetectable in a subpopulation (about 25–30%) of GABA neurons in cortical layers 2–5 in the brains of patients with schizophrenia. These neurons are among the calcium-binding parvalbumin (PV)-containing GABA neurons in the DLPFC, which appear

to be important modulators of pyramidal cell firing and synchronization of overall cortical activity. The mRNA for the GABA transporter (GAT1) expression is also decreased in PV-positive chandelier interneurons. Together, these findings suggest that both the synthesis and re-uptake of GABA are reduced in a subset of DLPFC inhibitory neurons in schizophrenia (Lewis and Gonzalez-Burgos 2006).

Postmortem data indicate that the levels of the $GABA_A$ receptor $\alpha 2$ subunit in the DLPFC of patients with schizophrenia is more than double that of control subjects (Lewis et al. 2004). One interpretation of this observation is that $GABA_A$ receptors may be upregulated at pyramidal neuron axon initial segments in response to deficient GABA release from parvalbumin (PV)-containing chandelier neuron axon terminals. Recent data have shown that NMDA antagonists can produce the alterations that are observed in schizophrenia in GABA neurotransmission selective for PV-containing neurons. This observation suggests that, like dopamine dysregulation, GABA dysregulation can be a downstream effect of NMDA hypofunctioning (Lewis and Gonzalez-Burgos 2006).

### Acetylcholine (ACh)

ACh is involved in schizophrenia at multiple levels via both nicotinic receptors (nAChR), which are ionotropic and muscarinic receptors (mAChR), which are metabotropic. People with schizophrenia have abnormalities in the expression of central nervous system nicotinic receptors, and the alpha-7 and alpha-4 beta-2 nAChR are the nAChRs that have been most implicated. Deficits in P50 measures, discussed below, of auditory gating in schizophrenics and their first-degree relatives, are associated with alpha-7 subunit gene promoter polymorphisms. Decreased alpha-7 nicotinic receptor binding has been noted in the reticular nucleus of the thalamus, the hippocampus, and various regions of the cortex. P50 auditory gating has been linked to the chromosome 15q14 locus of the alpha-7 nicotinic acetylcholine receptor gene (CHRNA-7) (Freedman et al. 1997).

The muscarinic system has also been implicated in schizophrenia directly by postmortem findings of decrease in some subtypes (mostly $M_1$) in brain regions of patients with schizophrenia (DLPFC and hippocampus (Crook et al. 2001). These findings, coupled with indirect pharmacological data, support a role for the muscarinic system in the pathophysiology and treatment of cognitive symptoms (Raedler et al. 2006). Atypical antipsychotic drugs enhance the efflux of ACh in the cortex (Ichikawa et al. 2002a) and hippocampus (Chung et al. 2002). Muscarinic receptor agonists such as sabcomeline, xanomeline, and *N*-desmethylclozapine, the major metabolite of clozapine, are of considerable interest at the current time as novel treatments for psychosis as well as to improve cognition in schizophrenia (Weiner et al. 2004, Li et al. 2005).

## Pathology of the Plasma Membrane

Several abnormalities in phospholipids and other cellular membrane fatty acids have been found in patients with schizophrenia (Berger et al. 2006, Yao and Reddy 2003). Schizophrenia-associated abnormalities in receptor-mediated signaling of neurotransmitters may be secondary to membrane phospholipid dysfunction (du Bois et al. 2005). Certain membrane phospholipids, particularly arachidonic acid and docosahexaenoic acid, are critical secondary messengers involved in dopaminergic, serotonergic, glutamatergic, and cholinergic signal transduction (du Bois et al. 2005, Rana and Hokin 1990), particularly in response to environmental demands. Finally, arachidonic acid is also a secondary messenger in the signaling of several neurotrophic factors including brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (du Bois et al. 2005). Thus, phospholipids play an important role not only in cellular signaling, but also in neuronal growth and integrity during early neural development and beyond.

Clinically, abnormalities in antioxidant defense systems, which prevent formation of *OH, have been reported in both medicated and unmedicated patients with schizophrenia (Yao et al. 2001). Reduced levels of arachidonic acid and docosahexaenoic acid in erythrocytes have been associated with predominantly negative symptoms of schizophrenia, but were not associated with severity of positive symptoms (Glen et al. 1994). Specific membrane phospholipid dysfunction may come as a result of damage secondary to oxidative stress through the generation of free radicals (Yao et al. 2001). There is accumulating evidence for the involvement of free radical toxicity, free radical-induced mutations, and failure of antioxidant defense systems in the pathogenesis of schizophrenia that may be genetically determined (reviewed by Rao and Balachandran 2002, Yao et al. 2001). In one neurodegenerative model of schizophrenia, increased apoptosis may be triggered by increased oxidative stress, leading to progressive synaptic dysfunction and clinical deterioration over time (Margolis et al. 1994). Increased oxidative stress may lead to phospholipids peroxidation and generation of free radicals. In an experimental model of schizophrenia, mice exposed to NMDA antagonists showed an increase in the generation of hydroxyl free radicals (*OH), the primary biochemical species driving lipid peroxidation, in posterior cingulate and reterosplenial cortex (Zuo et al. 2007). In rats exposed to the NMDA antagonist, MK-801, increased levels of prefrontal malondialdehyde, an indicator of lipid peroxidation, were increased compared with control animals (Ozyurt et al. 2007).

Interestingly, administration of omega-3 essential fatty acids, which have been associated with a possible protective effect against lipid peroxidation, along with MK-801, resulted in significantly decreased levels of prefrontal malondialdehyde in rodents, compared with animals who were given MK-801 alone (Ozyurt et al. 2007), suggesting that omega-3 fatty acids and other antioxidants may have an adjunctive therapeutic or preventive role in schizophrenia (Mahadik et al. 2006). Clinical studies have demonstrated positive correlations between omega-3 essential fatty acids and improved clinical outcomes, though results are still preliminary (Werneke et al. 2006). Free-radical mediated lipid peroxidation has also been implicated in the adverse effects of antipsychotic drugs—namely, tardive dyskinesia (TD) and clozapine-induced agranulocytosis. For example, schizophrenic patients treated with antipsychotics who were also diagnosed with tardive dyskinesia had lower plasma levels of antioxidant enzymes compared with non-TD patients (Zhang et al. 2007). In addition, malondialdehyde levels were positively correlated with the severity of TD. Clozapine has been found to significantly increase production of reactive oxygen species and expression of pro-apoptotic

genes in neutrophils (Fehsel et al. 2005), suggesting that the well-known risk of agranulocytosis associated with clozapine treatment may be related to induction of oxidative stress in the context of increased pro-apoptotic gene expression.

## Neural Circuits

It is apparent that multiple key brain regions are implicated in the pathophysiology of schizophrenia, including the prefrontal cortex, limbic structures (namely, hippocampus and anterior cingulate gyrus), striatum, and thalamus. There have been various abnormalities in cellular architecture, neurochemical activity, and functional activity demonstrated for each brain area. These can be expected to affect connectivity and circuitry necessary for the normal processing and flow of information within and between these brain regions. For example, alterations in connectivity within the DLPFC can cause working memory impairment, while diminished or dysregulated pyramidal cell outputs to other brain regions, such as the striatum, will in turn produce abnormalities in mesolimbic and nigro-striatal dopaminergic function (Bunney and Bunney 2000). Since these key regions are interconnected by several neuronal circuits, alterations in one region are likely to affect one or more of the others, leading to alterations in the functions subserved by the circuit.

The cortico–striato–pallido–thalamo–cortical (CSPTC) pathways represent five parallel circuits that connect cortical and subcortical regions of brain that are involved in regulating cognition, impulse control, affect, motivation, and drive (Alexander et al. 1986). They consist of closed loops that, in general, start in a particular area of cortex, synapse first in the striatum, then in the globus pallidus/substantia nigra, followed by the thalamus, and finally back to the cortex. In schizophrenia, neuropathological and in vivo data point to impaired dorsolateral prefrontal cortex (DLPFC) function and disrupted connectivity between it and striatal as well as other components of the cortico–striatal–thalamo–cortical loop. For instance, in neuropathological studies of the DLPFC of subjects with schizophrenia, pyramidal neurons exhibit decreased soma size, dendritic length, and spine density. Multiple alterations related to GABAergic transmission within the DLPFC have also been reported. The thalamus in patients with schizophrenia appears to have decreased cell numbers and fewer projections to the DLPFC, consistent with structural neuroimaging studies which show reduction in thalamic volume (Clinton and Meador-Woodruff 2004).

Functional and molecular neuroimaging studies have documented abnormally reduced activity in DLPFC in patients with schizophrenia both at rest and during a variety of cognitive tasks, especially those that involve working memory and executive function. Prefrontal cortical activity at rest appears to be inversely related to severity of negative symptoms (Liddle et al. 1992). In addition, poor cognitive performance was associated with increased availability of cortical dopamine $D_1$ receptors as measured by PET, a possible result of $D_1$ receptor upregulation resulting from low prefrontal dopaminergic tone (Abi-Dargham et al. 2002). A link between DLPFC hypofunctioning and exaggerated striatal DA release has also been demonstrated. Thus, reduced DLPFC activation during a working memory task predicted increased striatal DA release in a cohort of schizophrenic subjects (Meyer-Lindenberg et al. 2002).

Exactly how problems with DLPFC outflow to underlying brain structures occur is a matter of active investigation. As previously discussed, there is evidence of cytoarchitectural disruption of pyramidal cells, the principal mode of excitatory cortical output, among patients with schizophrenia. The axon terminals of the chandelier class of GABA neurons form distinctive arrays, termed "cartridges," which provide inhibitory input exclusively to the axon initial segment of pyramidal cells. This enables them to regulate the excitatory output of pyramidal neurons and, consequently, to substantially affect the patterns of neuronal activity within the PFC. The relative density of the GABA membrane transporter, GAT-1, of chandelier neurons, but not other populations of GABA neurons, was decreased by 40% in the PFC of schizophrenic subjects compared with matched groups of normal control and nonschizophrenic psychiatric subjects (Woo et al. 1998). The chandelier neurons may be responsible for maintaining the synchronized firing of pyramidal neurons (Lewis et al. 1999). This type of synchronized firing oscillates in the gamma band range of ~30–80 Hz (Lewis et al. 2005). In the DLPFC, these gamma oscillations increase during tests of working memory (Lewis et al. 2005); thus, impairment of pyramidal firing synchronization in DLPFC secondary to malfunction of these GABAergic interneurons could contribute to deficits in working memory. In addition, these PV-containing GABAergic interneurons express NMDA and $D_1$ receptors in nonhuman primate brain; thus, GABAergic dysfunction and aberrant cortical pyramidal excitatory output may result from reduced excitatory glutamatergic (from other cortical pyramidal neurons) or dopaminergic input (from basal forebrain structures), or both. Cho et al. (2006) studied induced gamma-band activity during a cognitive task which requires cognitive control processes in association with prefrontal cortical activations in imaging studies. Electroencephalographic studies have demonstrated that the ability to generate greater gamma band coherence during talking is disrupted in patients with schizophrenia (Ford and Mathalon 2005). Patients with schizophrenia did not show the induced gamma band activity in prefrontal areas that normal controls did when increased cognitive control demands were needed. Disturbances in gamma-band activity in patients correlated with illness symptoms.

Dysfunction within the limbic system has also been implicated in the pathophysiology of schizophrenia. Based in part on its reciprocal connections with frontal cortex, the anterior cingulate cortex is involved in cognition (especially attention), affective control, motivation, and drive (Tamminga et al. 2000). Neuropathological studies have shown reduced density of GABAergic interneurons in anterior cingulate of patients with schizophrenia (Benes et al. 2001), while neuroimaging studies have found reduced functional activity of the anterior cingulate cortex both at rest and during cognitive challenge (Yucel et al. 2002, Heckers et al. 2004). There is also evidence of impaired hippocampal structure and functioning in schizophrenia. Specifically, many studies have reported subtle reductions in hippocampal volume in patients with schizophrenia, as well as in their first-degree relatives, compared with controls. There is also evidence of white matter changes and synaptic disorganization in the hippocampi of patients with schizophrenia and, thus, impaired connectivity

(Heckers and Goff 2002). Neuroimaging and electrophysiological data support a role for disrupted connectivity between frontal and temporal structures in schizophrenia (Friston and Frith 1995). In patients with schizophrenia, the normal reciprocal activation of prefrontal cortex and mesial temporal cortex is impaired during cognitive challenge as measured by PET (Dolan et al. 1999).

### Neuropathology and Structural Brain Changes

Pathological studies have documented cytoarchitectural abnormalities in both cortical and subcortical regions in postmortem schizophrenic brain, including reduced glial density and proliferation, loss of cortical gray matter volume, and white matter abnormalities including volume loss (Arnold 1999). These changes may be responsible, in part, for earlier observations of decreased cortical thickness and total brain weight associated with schizophrenia. As yet, there is no clear evidence of neuronal loss or other markers (e.g., reactive gliosis) that would suggest that schizophrenia is primarily a neurodegenerative disease (Halliday 2001). Other quantitative histopathological studies have, on the other hand, documented schizophrenia-associated reductions in dendritic spines and total dendritic length (collectively referred to as "neuropil"), as well as deficits in synaptic markers (e.g., synaptophysin, complexins) in cortical pyramidal neurons (Glantz and Lewis 2000, Pierri et al. 2001). Although they are of considerable interest, these subtle cytoarchitectural changes lack diagnostic specificity for schizophrenia. Findings from gene array studies have documented reduced expression of synaptic gene products, providing further evidence for schizophrenia-associated abnormalities in synaptic connectivity and transmission (Dean 2000).

Structural magnetic resonance imaging (MRI) and computerized tomography (CT) studies of individuals with schizophrenia have shown morphological alterations in nearly every brain region (Henn and Braus 1999). The most consistent findings include reduced whole brain volume, reduced prefrontal and medial temporal gray matter volume, reduced thalamic volume, and enlargement of lateral and third ventricles, relative to normal controls. Two findings, lateral and third ventricular enlargement and medial temporal lobe volume reduction, have been the most frequently replicated and have achieved significant meta-analytic effect sizes (Elkis et al. 1995, Honea et al. 2005, Shenton et al. 2001, Wright et al. 2000). Most of these morphological changes have been documented at the first episode of psychotic illness, and are thus not believed to occur as an artifact of antipsychotic drug treatment. Importantly, reduced temporal volume has been correlated with the severity of positive symptoms including auditory hallucinations and disordered thought (Onitsuka et al. 2004).

Several of these aforementioned structural abnormalities are present before the first onset of psychotic symptoms (Kumari and Cooke 2006), and may be progressive (Ho et al. 2003). The progressive course of structural changes with MRI may follow a similar trajectory to several of the neurocognitive changes reviewed earlier, and may also contribute to the deterioration in clinical course commonly observed in the treatment of schizophrenia. Specifically, further increases in ventricular volume identified in patients with schizophrenia were observed during longitudinal follow up (Ho et al. 2003). In addition, studies of first-episode schizophrenic patients have documented progressive loss of total cerebral gray matter volume, with pronounced loss occurring in frontal and superior temporal cortex (Gur et al. 1998).

White matter abnormalities have been found in structural neuroimaging studies, particularly diminished total white matter volume among patients with schizophrenia relative to normal controls (Walterfang et al. 2006). Specific volume reductions have been reported in white matter zones underlying frontal, temporal, partietal, and occipital cortices. The clinical significance of these findings and their response to antipsychotic drug treatment is relatively uncertain. A technology that is based on MRI, diffusion tensor imaging (DTI), has been used to measure abnormalities in the integrity of white matter tracts themselves. Disruptions in white matter tract integrity measured by DTI have been associated with deficits in both declarative memory and executive-type functioning among patients with schizophrenia (Kubicki et al. 2007). Schlosser et al. (2007) analyzed both fMRI (during a working memory task) and DTI data in 18 patients with schizophrenia and 18 controls. DTI analyses revealed reductions of fractional anisotropy (FA), an indicator of cerebral white matter integrity, in the right medial temporal lobe adjacent to the right parahippocampal gyrus. In addition, fMRI revealed prefrontal, superior parietal and occipital relative hypoactivation in patients versus controls. This was accounted for by reduced prefrontal activation during the encoding phase of the task, but not during maintenance or retrieval phases. This study also found a positive correlation in patients between frontal FA reduction and fMRI activation in regions in the prefrontal and occipital cortex. Thus, the combined use of fMRI and DTI demonstrated altered structure–function relationships in schizophrenia. They also suggest an important relationship between anatomical changes in a frontal-temporal anatomical circuit and functional alterations in the prefrontal cortex.

## Electrophysiological Abnormalities

### Functional Brain Imaging

Functional MRI (fMRI) studies of schizophrenia have measured regional cerebral blood flow (rCBF) as an index of metabolic activity in areas of interest at rest and while performing specific cognitive tasks. In general, no specific, consistent disease abnormalities in cortical activity, as estimated by rCBF, in the resting state, have been identified in patients with schizophrenia (Liddle et al. 1992). However, during active auditory hallucinations, rCBF is increased in several areas, including ventral striatum, medial temporal lobe, and superior or middle temporal gyrus (Kircher and Thienel 2005). This suggests that auditory hallucinations are perceived as real to patients because they occur in structures that mediate normal language.

Abnormalities in rCBF in patients with schizophrenia compared with normal controls have been reported during the performance of specific cognitive tasks. In particular, during working memory tasks, reduced frontal and DLPFC activation has been observed in patients with schizophrenia (Glahn et al. 2005). Deficits in DLPFC activation have also been reported among patients with schizophrenia during problem solving and other executive functioning tasks, while

deficits in activation of other regions of prefrontal cortex have been documented during tasks that require selection of responses based on emotional content and probability of reward. Poor prefrontal activation has also been demonstrated in a cohort of individuals who were in the prodromal stage of schizophrenia, providing further support for prefrontal cortical dysfunction as a core element of the disorder (Morey et al. 2005).

While patients with schizophrenia show diminished cortical activation during some cognitive tasks, they also appear to demonstrate normal or even enhanced DLPFC activation when performing other tasks, where performance is also impaired relative to healthy controls (Weinberger and Berman 1996). When performance of DLPFC-related cognitive tasks are equalized between patients with schizophrenia and healthy controls, patients with schizophrenia show a relative increase in cortical activation, suggesting that more DLPFC activation may be required for patients with schizophrenia for the same level of performance on a task. This decrease in cortical efficiency has been hypothesized as being a result of abnormal dopaminergic transmission (reviewed earlier), or impaired connectivity and synchronization with other brain regions (Heinz et al. 2003).

Abnormalities of cortical activation as measured by fMRI have been documented in other brain regions. Studies of memory and auditory processing have reported abnormal cortical responses, often in the form of overactivity, in medial and superior temporal lobes, including the hippocampus and parahippocampal gyrus (Davidson and Heinrichs 2003, Zakzanis et al. 2000). In particular, certain aspects of hippocampal-dependent memory functioning (encoding of new information and retrieval of previously stored information) are impaired in patients with schizophrenia. This observation has been paired with observed patterns of hippocampal hyperactivity at baseline along with impaired modulation of hippocampal activity during retrieval. Other regional changes in response to memory or executive function challenges have been reported in the striatum, thalamus, and cerebellum.

Many of the key results from fMRI studies reviewed above have been supported using other functional neuroimaging techniques. For example, PET has been successful in demonstrating increased glucose utilization in the temporal cortex during auditory hallucinations in patients with schizophrenia (Silbersweig et al. 1995). These results are consistent with those from fMRI studies already cited. Magnetic resonance spectroscopy (MRS) studies have also provided further evidence of prefrontal deficits in schizophrenia (Abbott and Bustillo 2006). Using 31P-MRS, increased membrane phospholipids degradation and impaired synthesis have both been reported in the frontal lobes of patients with schizophrenia, while 1H-MRS has been used to demonstrate increased levels of frontal lobe glutamine and glutamate which are reduced by treatment with atypical antipsychotic drugs. Finally, diffusion tensor imaging (DTI) studies have provided further evidence of white matter disorganization in frontal and temporal subcortical zones, as reviewed earlier. Specifically, both increased and decreased white matter bundle connectivity has been documented for patients with schizophrenia relative to normal controls, as well as in actively hallucinating patients relative to normal controls and patients who were not actively hallucinating (Hubl et al. 2004). These results provide further evidence of abnormalities in the coordination of neural activity between key brain regions, such as the prefrontal and temporal cortices.

## Conclusion

Even though we cannot claim to fully understand the etiology or pathophysiology of schizophrenia, there has been considerable progress in understanding its neurobiology during the past few decades. The major advances include the following findings: (1) multiple genes confer vulnerability to develop schizophrenia; among the candidate genes are those that regulate the development of the nervous system and the maintenance of synaptic integrity; (2) there is evidence for overlap between the genetic determinants of schizophrenia and bipolar disorder. As a result, genetic testing for vulnerability to develop schizophrenia or bipolar disorder may become possible; (3) the neurodevelopmental hypothesis bridges the gap between these risk genes and the schizophrenia phenotype. This hypothesis posits important roles for environmental factors, ranging from intrauterine events to adolescent stresses and neurodegenerative processes in the overall pathologic process; (4) there is now a consensus that there is a decrease in the neuropil of patients with schizophrenia but not neuronal loss in selected areas of the brain, including the prefrontal cortex; (5) abnormalities in GABAergic neurons have been consistently identified, even though this information has not yet translated into more effective or safer treatments for schizophrenia; (6) glutamatergic pyramidal neurons in the cortex and hippocampus, with strong serotonergic inputs which regulate their firing, have emerged as the most important candidates for causing the cognitive disturbance that is a hallmark of schizophrenia, even if it is not specific for it. Based largely on the strong similarity between some aspects of schizophrenia and the effects of NMDA receptor antagonists, glutamate is now considered perhaps the most relevant neurotransmitter for understanding the pathophysiology of the disorder.

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CHAPTER

# 20 Neurobiology of Anxiety Disorders

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Recent advances in basic and clinical research in the anxiety disorders converge on several areas: (1) critical distinguishing clinical features of these disorders, (2) the neurobiological basis of anxiety disorders in human populations, (3) animal studies that define cause–effect relations between neural function and anxiety or fear behaviors, and (4) studies of etiology that provide an increasingly clear understanding of the developmental trajectories that define vulnerability for anxiety disorders. Additionally, an emerging area of research is studies of behavior, cognitive function, and neural activity in clinical populations to define the clinically relevant effects of pharmacological and psychotherapeutic treatments. This chapter summarizes and synthesizes current research approaches to anxiety disorders and attempts to show the impact of this research on current trends in their diagnosis and treatment. Currently, there is increasing emphasis on relevant clinical dimensions, as opposed to more traditional categorical approaches, and an emerging view of anxiety as a set of cognitive–perceptual disorders that derives from alterations in neural systems critical for attentional processes and emotional regulation.

## Overview

The characterization of anxiety disorders in *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (DSM-IV) (American Psychiatric Association 1994) was based on the assumption that a number of disorders shared essential features in the domain of fear or anxiety that merited their inclusion in one overarching category. At the same time, DSM-IV emphasized that that these conditions differed sufficiently from one another that they deserved to be regarded as distinct disorders. Anxiety disorders are extremely common. The National Comorbidity Survey Replication (Kessler et al. 2005) found that almost 30% of adults in the US reportedly suffer from at least one of these conditions over the course of their lives.

Historically, anxiety disorders have been subdivided into two basic categories: (1) conditions that occur in response to aversive events (reactive states of anxiety) and (2) those conditions that are associated with the constant and unrealistic anticipation of danger. Another important and somewhat overlapping distinction common in clinical research is between a high level of anxiety that is stable over time (trait anxiety; Spielberger 1971) compared with those that characterize a short-term condition (state anxiety). As described in the following historical review, the diagnosis of anxiety disorders reflects these distinctions. The modern era of clinical research that more clearly describes specific and relevant symptoms of patient populations has led to the improved diagnostic categories in DSM-IV. Nevertheless this categorical approach remains limiting, due in part to the fact that the reactive and anticipatory anxiety, as well as the state and trait anxiety, are not nearly as distinguishable as once thought. For example, a panic attack represents a clear example of anticipation as well as contemporary state of anxiety. The repeated occurrence of panic attacks worsens subsequent attacks such that each attack is a product of the current state of anticipation associated with the reaction to previous attacks. The form of the disorder changes accordingly such that patients suffering repeated panic attacks will often develop severe agoraphobia. Moreover, panic attacks do not occur randomly in the population, and as described below in sections on vulnerability, panic disorder (PD) is a familial condition in which affected individuals show an enhanced, premorbid vulnerability that is often defined by what we would consider as increased trait anxiety. A similar interaction between premorbid vulnerability (trait) and the occurrence of trauma commonly defines patients with chronic posttraumatic stress disorder (PTSD) (see below).

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Similarly, clinical experience indicates that the severity of any form of anxiety disorder, including obsessive–compulsive disoder, will worsen in response to stress. Trait and state, reaction and anticipation are invariably linked and thus blur diagnostic distinctions.

Research in psychology, neuroscience, and clinical psychiatry and psychology has greatly advanced our understanding of anxiety disorders. Neuroimaging of human populations together with relevant animal models have led to remarkably a coherent description of the neural circuits that mediate the expression of fear-related emotional states. Studies of human and nonhuman subjects have led to an understanding of the developmental origins of vulnerability for anxiety disorders. Animal models suggest that vulnerability emerges as a function of gene–environment interactions occurring within cells in the neural circuits that underlie fear and anxiety. These are critically important advances. Thus, the ultimate treatment of individual patients, even those expressing a common set of symptoms, may be determined by etiology as well as a knowledge of the underlying patterns of neural activity. This may be equally true for psychotherapy and pharmacologically-based interventions (Etkin et al. 2005b).

## History and Clinical Picture of Anxiety Disorders

### History

Classifications of psychiatric disorders pertaining to anxiety that predated *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) (American Psychiatric Association 1980) were heavily influenced by psychoanalytic theory. *Diagnostic and Statistical Manual of Mental Disorders*, First Edition (DSM-I) (American Psychiatric Association 1952) included various anxiety states under "psychoneurotic disorders" and assumed that they were reactions to unconscious emotional conflict, with or without external provocation. In particular, in DSM-I, the disorders that were considered to be anxiety-related included "anxiety reaction," "phobic reaction," and "obsessive–compulsive reaction." In addition, normal personalities exposed to catastrophic trauma could suffer "reversible decompensations" that were labeled "gross stress reactions," a forerunner of what is now considered (PTSD). The consideration of anxiety disorders in *Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (DSM-II) (American Psychiatric Association 1968) did not significantly differ from DSM-I. This early stage, the development of diagnostic categories, reflected the broader challenge of dissociating between state (reactive) and trait (neurosis) conditions of anxiety. In the 1950s, 1960s and 1970s, several nonpsychoanalytic approaches began to suggest subdivisions of categories considered in DSM-I and DSM-II. In Britain, the behavior therapist Isaac Marks examined phenomenology, family history, and psychophysiology in his clinical population and subdivided phobic disorders, into agoraphobia, social phobia, and specific phobias (Marks and Gelder 1966). In the US, psychiatrist Donald Klein and colleagues found that patients with unexpected panic attacks often went on to develop a fear of having further panics (anticipatory anxiety) and a fear of traveling places where help was hard to obtain or rapid exit was difficult (e.g., agoraphobia) (Klein and Fink 1962). Klein distinguished this syndrome, which he called PD with or without agoraphobia, from more chronic, but less intense anxiety (which ultimately became generalized anxiety disorder (GAD)) on the basis of phenomenology, course of illness, and response to pharmacologic treatment. These advances reflected an initial improvement in diagnosis on the basis of more sophisticated clinical and pharmacological phenotyping.

These findings culminated in the DSM-III (American Psychiatric Association 1980) classification of anxiety, which fundamentally altered psychiatric nosology from an etiological one (based largely on psychoanalytic theory) to a set of descriptive categorical diagnoses (Mayes and Horowitz 2005). DSM-III contained for the first time an umbrella category of anxiety disorders and operational criteria for distinct anxiety disorders within it. The umbrella category had two main components: the phobic and the anxiety disorders ("neuroses"). The phobic disorders consisted of agoraphobia with or without panic attacks, social phobia and simple phobia. Agoraphobia was characterized as manifesting marked fear and avoidance of being alone or in public places from which escape might be difficult. This formulation is close to our current view. Social phobia, however, was narrowed from Marks' conception of fear and avoidance of performance or social situations to a conceptualization limited largely to performance anxiety, while more generalized interpersonal fear and avoidance was called avoidant personality disorder. The term simple phobia was reserved for persistent, irrational fears and avoidances of objects or situations that did not fit agoraphobia or social phobia.

In DSM-III, the anxiety states included PD, GAD, obsessive–compulsive disorder (OCD), and PTSD. The distinction between PD, characterized by unexpected, paroxysmal panic attacks, and more persistent but less intense emotional and physical anxiety symptoms of GAD. was initially spurred by Klein's pharmacological dissection of anxiety disorder. The distinction proved clinically significant and robust. It was therefore carried forward into *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (American Psychiatric Association 1987) and DSM-IV (American Psychiatric Association 1994) (see below), although recently there is evidence that GAD bears a closer relationship to major depression than to the anxiety disorders (Kendler et al. 2007). OCD, while recognized in earlier classifications, was given operational criteria for the first time. PTSD, foreshadowed by DSM-I's "gross stress reaction," was officially recognized and given operational criteria that included a "recognizable stressor that would evoke significant symptoms of distress in almost everyone" and features of avoidance and reexperiencing of the traumatic situation along with symptoms of hyperarousal and emotional numbing.

DSM-III-R's (American Psychiatric Association 1987) dissection of the anxiety disorders was not a major departure from DSM-III, but there were some notable changes. Widespread fear and avoidance of many interpersonal situations was recognized for the first time as an anxiety disorder, and included in social phobia together with the specifier "generalized type." In DSM-III, social phobia was limited to performance anxiety, and the more generalized interpersonal fears and avoidance were considered a manifestation of avoidant personality disorder. This change was important, because

research beginning in the late 1980s demonstrated that generalized social phobic symptoms were amenable to pharmacological (Liebowitz et al. 1992) and cognitive behavioral (Heimberg et al. 1990) treatments, which were less likely to be considered if practitioners thought affected patients were suffering from personality disorders. This success in treatment derived from research on the psychobiological basis of anxiety (see below). Other changes in DSM-III-R were the elevation of worry and apprehensive expectation from one of several possible symptoms of GAD to its defining feature, and increasing the minimum required duration for diagnosing that disorder from one to six months.

## Clinical Picture

The principal anxiety disorders included in DSM-IV are as follows: PD with or without Agoraphobia, Agoraphobia without history of PD, GAD, OCD, PTSD, Acute Stress Disorder, Social Anxiety Disorder (SAD) (Social Phobia), and the Specific Phobias. The major changes from DSM-III-R were dropping the terms anxiety and phobic neurosis, completing the nosology's transformation from a theoretical to a symptomatic base, and adding the condition of acute stress disorder for immediate overwhelming reactions to catastrophic trauma. Below, we briefly consider each of these anxiety disorders in terms of phenomenology, course of illness, prevalence, morbidity, comorbidity, and differential diagnosis.

### Panic Disorder and Agoraphobia

The key feature of PD is the recurrence of unexpected panic attacks. These episodes of severe anxiety seem unprecipitated, rise in intensity in seconds to minutes, and reach a crescendo marked by physical and emotional symptoms. These symptoms typically include rapid or pounding heart beat, shortness of breath, lightheadedness, dizziness, nausea and/or parasthesias, a fear of dying, losing control or going "crazy," and an urgent desire to flee. Individuals suffering such panic attacks are initially terrified by the experience, and begin to dread the possibility of having recurrences, which takes the form of an anticipatory anxiety. Affected individuals often become fearful and avoidant of going places where neither assistance nor escape are options should an attack occur; agoraphobia is also diagnosed when such an avoidance pattern becomes persistent and is a source of distress or disability.

PD has a usual onset in the late teens or 20s, although some cases begin decades later. The condition can be episodic or chronic. There are no proven precipitants, although endocrine changes like hypothyroidism or sudden separation from trusted figures may be triggering events in vulnerable individuals. Lifetime prevalence of PD with or without agoraphobia is 4.7%, and for agoraphobia without panic, the comparable figure is 1.4% (Kessler et al. 2005). PD can be highly distressing, and individuals who also become agoraphobic can be totally disabled and unable to travel anywhere if not accompanied by a trusted figure. Depression is a common sequela, sometimes with suicidality. Other anxiety disorders and substance abuse disorders are also common comorbid features. Differential diagnosis of PD includes cardiac arrythmias, pulmonary and gastrointestinal disorders, inner ear disturbance, SAD, specific phobias and generalized anxiety disorder.

### Generalized Anxiety Disorder (GAD)

According to DSM-IV the key features of GAD are excessive anxiety and uncontrollable worry over an extended period of time, with six months as a minimum. Associated symptoms include restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension and disturbed sleep. These symptoms suggest a dysfunctional activation of normal fear circuits. Indeed, the diagnosis is buttressed by results of neuroimaging studies that reveal increased activation of brain regions associated with fear (see below).

GAD tends to be a chronic condition, with waxing and waning symptoms dependent in part on current life circumstances. The lifetime prevalence rate for adults is 5.7% (Kessler et al. 2005). GAD can be disabling at times, but more often it interferes with a person's quality of life by reducing the ability to relax, be productive or optimistic. It is a risk factor for both affective and substance abuse disorders.

GAD is highly comorbid with other anxiety disorders, as well as major depressive disorder. In fact, GAD is a risk factor for major depressive episodes and appears to share a common genetic basis (see below). GAD patients are stressed by normal life conditions and lack more active coping skills, perhaps exacerbating the effect of stress on mood. The strong link between GAD and affective disorder may result in the shift of GAD into the affective disorders in DSM-V. Differential diagnosis of GAD includes depressive disorder, PD, OCD, dependence on sedative medication and substance abuse disorders.

### OCD

OCD is characterized by obsessions, which are repetitive intrusive thoughts that are highly anxiety-provoking, and compulsions, which are either mental or behavioral rituals or avoidances intended to alleviate the distress caused by the obsessions. Interestingly, animal studies suggest that such "displacement" behaviors actually do reduce hormonal indices of distress. The rituals of OCD are often normal behaviors, and thus a critical feature is the degree to which the rituals become excessive and interfere with normal function. Obsessions can take a variety of forms and shape the compulsive response. Unwanted thoughts about dirt, germs or contamination often lead to compulsive and extensive washing and bathing. Repetitive thoughts about whether a task was properly performed (locking the door, shutting off the stove or an electrical appliance) can lead to compulsive checking behavior. Intrusive thoughts about hurting oneself or others are usually associated with mental rituals that are aimed at neutralizing horrific images. Persistent doubting and uncertainty about whether something will be needed in the future makes it very hard to throw things away, leading to compulsive hoarding.

OCD can be crippling, making it hard to learn, hold a job or perform normal household tasks. It can arise in childhood, adolescence or young adulthood, and assume either an intermittent or chronic course. Lifetime prevalence appears to be 1.6% (Kessler et al. 2005). Because of morbidity and chronicity, OCD ranks high on the World Health Organization's list as a contributor to the overall burden of illness. OCD is also highly comorbid with depression, tic disorders and other anxiety disorders. Differential diagnosis for OCD

includes tic disorders, GAD, depression with ruminations, specific illness phobias, and schizophrenia.

### Post Traumatic Stress Disorder and Acute Stress Disorder

PTSD describes the severe emotional disturbance that follows exposure to a life-threatening or terrifying experience. The features of PTSD include elements of reexperiencing the traumatic event, avoiding conditions reminiscent of the trauma, a general numbing of emotional responsiveness, and symptoms of increased arousal. Reexperiencing can take the form of nightmares about the traumatic event, having frequent, unusually vivid, disturbing recollections, or flashbacks, that may include recurrent sensations as though the traumatic event was reoccurring. Trauma-related avoidance involves conscious suppression of thinking or talking about the event, avoiding reminders of the event, and the inability to recall aspects of the trauma. Emotional numbing can be manifest as a loss of interest in formerly meaningful life activities, feelings of detachment and estrangement from other people, a restricted range of affect, and pessimism about being able to achieve a normal life. Thus, chronic PTSD is often comorbid with depression. Increased arousal is apparent in symptoms of insomnia, irritability, difficulty concentrating, hypervigilance and increased startle response.

Current diagnosis of PTSD is linked to the occurrence of trauma. However, the distinction between acute and chronic PTSD is clinically important. PTSD symptoms immediately after severe trauma are common, but their prevalence diminishes with time. For example, over 90% of rape victims express acute PTSD one week after the event, whereas far fewer, about 40–50% of victims, still express a full PTSD state by 6–12 months later. Likewise, the frequency of PTSD symptoms declined in the victims of the 9/11 attacks. PTSD symptoms appear to abate as the victim begins to place the event into a specific spatial-temporal context, and becomes less affected by unprovoked recall, avoidance, and hypervigilance. The most relevant clinical state is chronic PTSD in which there is no decline in the frequency or severity of the PTSD symptoms. Thus, the clinical literature in PTSD has come to emphasize individual differences in vulnerability for PTSD (Brewin et al. 2000) and the process of recovery from trauma. Factors that predict recovery from acute PTSD include the magnitude of the initial reaction to the trauma, the current level of social support, persisting adversity, and the quality of early family life (see below).

PTSD has a lifetime prevalence of 6.8% (Kessler et al. 2005) and can follow a variety of terrible experiences such as physical or sexual abuse in childhood, rape, or armed robbery, exposure to violent combat in military service, or the experience of imprisonment and torture. Chronic PTSD is highly disabling and often leads to depression and substance abuse. Issues that sometimes complicate the diagnosis of PTSD are whether the stressor meets the necessary threshold, and the possibility of malingering in situations where compensation or benefit issues are involved.

Because PTSD, as defined by DSM-IV, requires that symptoms be present for at least a month, another category was needed for individuals who become highly symptomatic immediately after exposure to a severe trauma. Symptomatically, the criteria are similar to PTSD except that dissociative symptoms are more prominent. The differential diagnosis includes brief psychotic reactions, substance induced disorders and malingering. The condition is what Freud described as "traumatic neurosis."

### SAD (Social Phobia)

SAD is characterized by fear of social or performance situations in which a person is exposed to scrutiny by others, and dreads appearing foolish or inept. It is common, with a lifetime prevalence of 5–12% depending on the sensitivity of the criteria applied to the data (Kessler et al. 2005, Grant et al. 2005, Narrows et al. 2002). Most affected individuals avoid feared situations, but some endure with a high degree of distress. If the fear and avoidance involve only performance situations (public speaking, interviewing, artistic performances), the individual expresses a non-generalized form of the disorder. If the fears extend to common interpersonal situations such as meeting unfamiliar people, going to parties, talking with colleagues, etc, then the generalized form is diagnosed. For clinicians, SAD may be difficult to recognize, as it appears to represent the tail end of a normal distribution for some underlying trait, such as shyness or inhibition. This is especially true for children that commonly express increased fearfulness. SAD is commonly associated with a heightened response to evaluative social situations as well as to facial displays of emotion.

SAD begins early; the generalized form is often manifested in the high school years. While the non-generalized form can be disabling in particular instances, the generalized form is often so, interfering extensively with school, work and social life. Depression, substance abuse (particularly alcohol) disorders and other anxiety disorders are frequently comorbid, however, SAD usually begins first and may directly contribute to the comorbid conditions. Differential diagnosis includes schizoid personality disorder, agoraphobia, and chronic depressive conditions and shyness as a trait on the normal spectrum, which lack the distress and impairment of SAD. In the current nomenclature, avoidant personality disorder largely overlaps with the more severe form of SAD.

### Specific Phobia

Phobias involve marked and persistent fear that is excessive or unreasonable, cued by exposure to specific stimuli that usually and reliably provokes an immediate anxiety response. DSM-IV distinguishes animal, natural environment (heights, storms), blood-injection-injury, situational (enclosed places, elevators, airplanes) and other types based on the focus of fear. Specific phobias are usually more distressing than disabling, have a high lifetime prevalence of 12.5% (Kessler et al. 2005), can have an early age of onset, and are usually chronic. Other anxiety disorders may be comorbid. Differential diagnosis includes agoraphobia and SAD, PTSD, OCD, and hypochondriasis.

## Genetic Contributions to Anxiety Disorders

Estimates of heritability, that is, the proportion of risk contributed by genetic variation (including gene–environment interactions) are commonly derived from studies with monozygotic and dizygotic twins that share 100 and 50% of their genes, respectively. Heritability estimates for anxiety disorders range from 20–50% depending on disorder and

study. Four of five studies, including two large epidemiologically based samples found greater concordance for PDs in monozygotic versus dyzygotic twin pairs (Kendler et al. 2001, Skre et al. 1993, Scherrer et al. 2000, Torgersen et al. 2000, Andrews et al. 1990). A recent meta-analysis of the subset of these data that met strict methodologic criteria (3 twin, 5 family interview studies) estimated heritability of PD at approximately 48% (Hettema et al. 2001). Several twin studies reported moderate genetic heritability of a variety of irrational fears that are frequently the subject of social and specific phobias (Rose and Ditto 1983, Torgersen 1979). The only population based twin study of DSM-phobic disorders obtained moderate heritabilities for social phobia (51% and three subtypes of specific phobia: animal (47%), situational (46%) and blood injury (59%) (Kendler et al. 1999, Hettema et al. 2005). A series of analyses in two population-based twin samples indicate a modest genetic contribution (heritability 15%–30%) to risk for GAD (Kendler et al. 2006, Scherrer et al. 2000, Kendler 1996). Direct interview family studies indicate significantly elevated risk for GAD among first degree relatives of individuals with GAD (Noyes et al. 1987, Mendlewicz et al. 1993). Thus, there is considerable evidence for familial transmission of anxiety disorders that likely reflects a genetic predisposition.

Linkage and association studies can indicate respectively the involvement of a particular genomic region or allelic variant. Though there are some promising leads, specific liability genes have not been identified. The aggregation of these disorders in families is "complex" and does not follow typical Mendelian patterns (e.g., dominant, recessive). It seems likely that in addition to a large non-genetic contribution the heritable mechanisms that predispose to anxiety disorders will involve multiple genes as well as considerable heterogeneity within each DSM category. Of course genes encode for proteins, not disorders and thus there is a continuing discussion as to what is inherited: risk for a particular disorder, a general anxiety proneness that is shaped into a particular syndrome by subsequent environmental events or some combination of both scenarios. More recently it has been speculated that genetically based variation in certain neural circuits and their function (e.g., associational fear learning and extinction, memory consolidation; autonomic tone) may underlie a predisposition for anxiety disorders. Thus, studies have employed a candidate gene approach based on working models of the neurobiology of anxiety. Despite the apparent merits of this approach, the only well-replicated finding is the Val158Met polymorphism of the catechol-O-methyltransferase (COMT) gene on chromosome 22q. COMT catalyzes the degradation of dopamine in the prefrontal cortex, and the function of this region is critical across multiple anxiety disorders. Four studies (Hamilton et al. 2002, Woo et al. 2002, Domschke et al. 2004 and Rothe et al. 2006) report significant associations between PD and a COMT Val158Met polymorphism. It is not known if these associations reflect an involvement of COMT or another nearby gene that confers risk for PD. There are negative candidate gene studies attempting to link social anxiety to genes in the serotonin and dopamine systems (Stein et al. 1998, Kennedy et al. 2001). A recent small study ($N = 32$) of generalized social phobia patients found an association between serotonin transporter (5HTTLPR) genotype and social anxiety (Stein et al. 2006).

Research on the genetic basis of vulnerability for anxiety disorders is hampered by the overlap in diagnostic categories. One approach to this problem is that of a dimensional approach that emphasizes specific endophenotypes rather than diagnostic categories. This approach is buttressed by the findings from twin studies that relevant endophenotypes (e.g., fear conditioning, startle response) show different patterns of heritability (Siever et al. 2002). These direct measures of function are more likely to have specific neurobiological substrates that more clearly associate with specific genomic variants than do broader diagnostic categories that reflect mulitiple component processes. Thus, the future success of studies on the genetics of anxiety disorders will benefit from an improved knowledge of the neurobiology of relevant psychological and physiological processes that are emerging from studies of animal models.

## Animal Models of Anxiety

### Fear and Anxiety in Humans and Animals

In spite of their value, animal models of psychiatric conditions are limited by differences in the brains of humans and other animals that give rise to differences in mental and behavioral functions (Kalueff and Tuohimaa 2004). Humans' use of language and imagination to conceptualize and anticipate threats, even highly improbable or physically impossible threats, cannot be fully modeled in animals. It is therefore important to be clear about which components of human anxiety, or the vulnerability to anxiety, can be suitably studied using animal models. Fear and the cognitive processes that regulate the emotional state of fear are normal responses to threat or actual danger. In all animals, these events activate the brain's fear system, coordinating physiological adaptive responses that include behavioral responses (fight, flight, and self-protective immobility or freezing) and changes in autonomic and endocrine activity necessary to provide increased metabolic support. When the threat is posed by an immediately present or imminent stimulus, the emotional response of the organism is typically called a state of fear. When the activation of the fear system in the brain occurs in response to cognitive processes evoked by a perceived threat is not present or imminent, either because it is poorly defined or temporally remote (in the future), the emotional state is usually called anxiety. Thus, fear is a sensory-driven reaction of the fear system to threat, while anxiety occurs when the fear system is activated by cognitive processes that predict and appraise possible threats. The importance of this distinction is apparent in the various clinical states of anxiety, each of which is characterized by an enhanced apprehension of threat resulting in the activation of the fear system. However, anxiety disorders are characterized by cognitive processes that evoke a maladaptive level of activity within the fear system. In general, it is now believed that the source of the disorder lies within the cognitive processes and not within the fear system itself. Thus, as described in the section on the pathophysiology of anxiety disorders below, the critical brain regions that underlie anxiety disorders lie not within the neural structures directly responsible for the expression of fear, but rather in those regions that regulate the activity of the fear system, including in the prefrontal cortex, the amygdala and the hippocampus. Thus, anxiety disorders

reflect cognitive–perceptual dysfunction; the severity of the disorder is defined by the degree to which fear responses are activated. This is true even for PTSD which is caused by a clearly defined traumatic event, but the symptoms of which are manifestations of fear such as hypervigilance, enhanced startle, and avoidance that are activated by anticipation of a reoccurrence of the event. The fear system is activated by cognitive states that are direct reminders of the trauma (such as happens during during flashbacks and nightmares). GAD, characterized by a lower level of chronic activity in the fear system, is defined by the cognitive state of worrying about hypothetical or imagined situations and consequences. In each case, the overt symptoms of the anxiety disorder is manifested by, and its severity determined by, the maladaptive activation of the fear system. But the origin of the disorder lies in the neural structures that regulate the activity of the fear system. Thus, as discussed in the next sections, patients with anxiety disorders as well as those with an increased vulnerability for anxiety disorders exhibit an attentional bias towards threat.

People in states of fear often have conscious experiences, or feelings, that seem to define the state. However, as William James pointed out (James 1884), conscious feelings are often the outcomes of, rather than the essence of, underlying emotions. All animals, including simple single cell organisms, detect and respond to danger in ways that enhance survival, regardless of whether they consciously experience fear and anxiety (LeDoux 1996, 2000, Hofer 1992). Moreover, such responses can be conditioned, such that the probability or magnitude of the response reflects an anticipatory state. Such conditioned fear responses occur in *drosphila* and are therefore a phylogenetically well-conserved response to danger. Studies demonstrate that fear arousing stimuli can be presented to people in such a way as to elude conscious perception, but nevertheless engage the brain's fear system and elicit autonomic nervous system (ANS) responses (e.g., Ohman and Mineka 2001, Etkin et al. 2005a). These findings reveal that the fear system can be activated independent of conscious awareness, which therefore can be considered as distinct from the neural systems that underlay the cognitive regulation of the fear system.

The expression of fear involves similar circuits in humans and other mammals, including those that detect threat and regulate fear in the presence of threats (LeDoux 1996, 2000, Maren and Quirk 2004, Phelps and LeDoux 2005, Phelps 2004, Sotres-Bayon et al. 2004, Quirk and Beer 2006). Thus, in humans and rodents, the amygdala plays a key role in processing sensory cues associated with threat, while the medial prefrontal cortex (mPFC) is pivotal for the regulatory higher-order cognitive processes. The hippocampus is likely involved in processing spatial and temporal information essential for contextual learning about potential danger. Neuroimaging studies reveal clear evidence for dysfunction within all three neural systems in various forms of anxiety disorders (Dougherty et al. 2004, Liberzon and Martis 2006).

There are limitations to animal models. While the expression of fear responses is very similar in humans, primates and rodents, greater evidence for species differences emerge as we consider the cognitive processes that regulate the activation of the fear system. For example, while the rat shows a highly functional medial prefrontal system, this region is substantially more complex in humans. Nevertheless, whereas fear and the regulation of fear responses in humans reflect their unique cognitive capacities, the fundamental networks that process threats and initiate states of fear are similar in rodents. Thus, the discussion of animal models of fear and anxiety refers not to their subjective aspects, but to behavioral and/or physiological responses controlled by evolutionarily conserved networks that function unconsciously as well as to the cognitive processes that regulate the fear system. Studies with animal models that focus on the latter are those with the greatest relevance to anxiety disorders in humans.

## Animal Models of Fear, Anxiety, and Fear Conditioning

Perhaps the most common approach to modeling fear and anxiety in animals involves the use of behavioral tasks that elicit unequivocal signs of fear in normal animals. In many instances, the fear responses are directly comparable in humans and other animals. For example, studies with humans and other animals use startle paradigms that examine responses to sudden and potent stimuli (loud noises). These responses are the result of a direct and unconscious activation of the fear system. A startle response in the rat is defined by a motor response, flinching, that can be readily quantified; the louder and more sudden the noise, the greater the flinch. In humans, the same conditions elicit a startle response defined by an eye-blink as well as a flinching. Both responses can be quantified and used as a measure of the activation of the fear system. Likewise, both humans and rats show "fear-potentiated startle" in which the magnitude of the startle response is enhanced by the presentation of threatening stimuli. Thus, a light that was systematically paired with an electric shock presented prior to the loud noise enhances (or potentiates) the magnitude of the startle. This effect is apparent in both humans and rodents. The magnitude of the potentiation (the increase above the baseline startle condition) defines fear-potentiated startle, which can be interpreted as anxiety since it depends on the cognitive processes associated with prior learning about the light. States of apprehension also potentiate the startle response. Thus, in the rat (normally a nocturnal animal that shies away from daytime conditions), a loud noise presented to the animal in a brightly lit room evokes a greater startle response. In humans, conditions that simulate night, such as a dark room, potentiate startle. These conditions represent relevant models for anxiety disorders since both examine the influence of cognitive states that regulate the expression of fear responses.

Additional models of anxiety involve cognitive states, which normally emerge when animals are placed into novel settings, comparable to apprehension and uncertainty. Thus food-deprived animals provided food in a novel setting show a longer latencies to eat compared to animals given food in a familiar setting, a behavior called novelty-induced suppression of feeding; Bodnoff et al. 1989, Dulawa and Hen 2005). The novelty-induced delay in feeding is eliminated by prior treatment with an anxioltyic drug, which has no effect on eating in the familiar setting. Anxiolytic drugs also increase the willingness of rats or mice to explore brightly-lit novel areas. Importantly, while anxiolytic drugs have no effect on the expression of pure startle responses,

they effectively dampen fear- or light/dark-potentiation of a startle response (Davis 2006). This finding provides further pharmacological evidence for the distinction between the fear-system, which is resistant to anxiolytic medications, and the cognitive systems that regulate fear, which are sensitive to such compounds.

Fear or light/dark potentiated startle are seen in normal human subjects that show no evidence of anxiety disorders. Predictably, patients with anxiety disorders show exaggerated physiological responses to threats, such as increased responses of the ANS revealed by fear-potentiated startle responses (Morgan and LeDoux 1995, Roth 2005, Cornwell et al. 2006). Likewise, patients with anxiety disorders also show enhanced Pavlovian fear conditioning, which depends upon cognitive processing of stimuli that predict aversive events. Thus, novelty-induced fear, fear conditioning and potentiated-startle responses are considered here as models of anxiety processes. Animal models of these processes have the important advantage of a direct human equivalent. This has been invaluable in translating the findings from studies with rodents and primates to human clinical research, especially research using neuroimaging approaches (see below).

Since the expression of fear in behavioral models of anxiety is reduced by treatment with anti-anxiety medications (Gray 1982, File 1987, Blanchard et al. 2001), animal models of anxiety are used to screen drugs for their potential efficacy in relieving anxiety. Commonly drugs such as the benzodiazepines (BZs), which alleviate anxiety in humans, are effective in such animal models. Anxiolytic drugs thus reduce overt behavioral measures of fear, such as freezing, and also increase active coping behaviors such as exploration of the threatening stimuli if the danger is not direct and immediate (i.e., exploration and risk assessment). Microinjections of BZs into the amygdala are generally as effective as systemic application, consistent with the amygdala's central role in anxiety. The conflict tests, which create a conflict between a fear-evoking condition and a motivation to obtain a reward, are especially useful in the testing of novel anxiolytic agents (File 1987, McCown et al. 1983, Millan and Brocco 2003, Quintero et al. 1985). Anxiolytic drugs such as BZs and alcohol reduce anxiety in animal models and reduce situational anxiety in healthy people as well as in those with debilitating chronic anxiety.

Animal behavioral models have been the most direct means for exploring the neural circuits of fear and, importantly, for clinical translational studies of the cognitive processes that regulate the fear system, which are altered in anxiety disorders (Rosen and Schulkin 1998, Hariri et al. 2005, 2006, Cahill et al. 1999, LeDoux 1996, 2000). Pavlovian fear conditioning has been especially useful in characterizing the fear system at the level of circuits, cells and synapses, molecules and genes (LeDoux 2000, Rodrigues et al. 2004, Maren and Quirk 2004, Davis 2006). In fear conditioning, a neutral stimulus, the conditioned stimulus, such as a light or tone, is paired with an aversive unconditioned stimulus, such as a shock or loud noise. Through this process of association of the two stimuli, the conditioned stimulus comes to elicit aversive responses formerly elicited only with the unconditioned stimulus. Neural structures involved in fear conditioning converge within the amygdala (Fanselow and LeDoux 1999, LeDoux 2000). Behavioral processes by which organisms learn relationships between specific sensory signals (i.e., cued fear-conditioning) and contexts (i.e., contextual fear-conditioning) that predict danger engage multiple regions of the the amygdala, as well as the bed nucleus of the stria terminalis, an extension of the amygdala, the prefrontal cortex, and the hippocampus. Fear responses are regulated through outputs from the central nucleus of the amygdala (Davis 1998).

Efferents of the central nucleus of the amygdala and the bed nucleus of the stria terminalis include the parabrachial nucleus, producing an increase in respiratory rate, the lateral nucleus of the hypothalamus and midbrain sites that activate the sympathetic nervous system causing autonomic arousal and sympathetic discharge, and the reticular pontine nuclei that activate a startle response (Davis 1998, LeDoux 2000). Projections from the central nucleus of the amygdala to the periaqueductal gray region contribute to selected defensive behaviors such as freezing. The central nucleus of the amygdala is also a source of neuronal projections that release corticotrophin-releasing factor (CRF) and activate the noradrenergic neurons of the locus coeruleus (Van Bockstaele et al. 1998), which then influences cortical and hippocampal systems involved in attention and memory regulation. Such CRF effects may involve CRF projections to the bed nucleus of the stria terminalis (Davis 1998), which shows high expression of the relevant $CRF_1$ receptor. Increases in amygdala CRF and noradrenergic activity stimulate the release of CRF from the hypothalamic-paraventricular nucleus and thus activate the hypothalamic–pituitary–adrenal (HPA), or stress, axis (Gray and Bingham 1996). There is a compelling similarity between the downstream consequences of activation of the central nucleus of the amygdala/bed nucleus of the stria terminalis and the symptoms of anxiety disorders (Gorman et al. 2000). There is also evidence for relevant "bottom-up" effects. Thus, the output of these systems, including adrenal glucocorticoids as well as catecholamines of both central and peripheral origin, act on the amygdala to facilitate the recall of information associated with aversive events (Cahill and McGaugh 1998). The dynamic effects of catecholamines on reconsolidation of fear memories via $\beta$-adrenoreceptors in the amygdala (Debiec and LeDoux 2006) have spurred trials of $\beta$-blockers following trauma to prevent PTSD (Pitman and Delahanty 2005). Other means of disrupting consolidation or reconsolidation of trauma-based memories (Nader et al. 2000), such as glucocorticoid receptor inactivation during retrieval (Tronel and Alberini 2007), could lead to additional approaches to the prevention of PTSD in the future.

## Extinction and Safety Conditioning are Distinct Forms of Learning

Fear-conditioning represents a process whereby the individual's knowledge of the environment regulates the expression of an emotional state. In the case of cued fear-conditioning, this "knowledge" is derived from the learning that results from the pairing of the cue with an aversive event. Stimuli that reliably predict aversive events elicit a conditioned fear response that depends upon the activation of the lateral, basolateral and central nuclei of the amygdala and/or the bed nucleus of the stria terminalis. However, such conditioned fear responses diminish if the conditioned stimulus is no longer reliably followed by the aversive stimulus, a process called extinction. Extinction is an independent form of

learning (Rescorla and Heth 1975, Bouton and King 1983, Quirk et al. 2006), not simply the passive waning of a conditioned fear response or an erasure of the fear memory. Rather, it is an active inhibition of the response through subsequent acquisition of information concerning the conditioned stimulus (Bouton and Bolles 1979, Konorski 1967, Pavlov 1927). Extinction learning depends upon projections from the medial prefrontal cortex, notably the infralimbic cortex, to a population of inhibitory GABAergic neurons that inhibit the central nucleus of the amygdala (Morgan et al. 1993, Quirk et al. 2000, Rosenkranz et al. 2003). Thus, Quirk et al. (2003) found that stimulation within this region of the mPFC inhibits the activation of the central nucleus of the amygdala.

Interestingly, classic anxiolytics, such as the BZs, are amnesic agents that therefore block extinction learning (Bouton et al. 1990). These medications also reduce the efficacy of exposure therapy, underscoring that fact that extinction represents a form of new learning. Neuroscience research reveals that the neurotransmitter glutamate acting at the N-methyl-D-aspartate (NMDA) receptor is critically involved in multiple forms learning and memory (Bear 1996, Castellano et al. 2001, Morris et al. 1990, Newcomer and Krystal 2001). Blockade of the NMDA receptor with selective antagonists blocks extinction (Falls et al. 1992). Likewise, compounds that enhance NMDA receptor signaling increase the efficacy of extinction training in rats. One such compound is D-cycloserine does not bind to the NMDA receptor itself, but to the glycine receptor that positively regulates NMDA receptor activity. Preliminary studies with D-cycloserine in humans reveal a significantly enhanced effect of exposure therapy with acrophobics (Davis et al. 2006).

The induction of anxiety increases amygdala activity in healthy human volunteers (Phelps et al. 2001) and amygdala activity is seen in patients with a variety of anxiety disorders (Stein et al. 2002, Shin et al. 2005, Straube et al. 2005, Protopopescu et al. 2005). Predictably, studies using a variety of fear-inducing conditions reveal strong evidence for increased amygdala activation in patients with anxiety disorders (see Pathophysiology of Anxiety below). These studies also show evidence for the importance of structures like the hippocampus and prefrontal cortex that regulate activity within the amygdala and bed nucleus of the stria terminalis. Animals respond not only to new information concerning previously threatening stimuli, but also about environmental signals that predict that absence of threat; signals of safety. Safety signals are established in a novel context through repeated and explicit pairing of a conditioned stimulus with the absence of an aversive event. The aversive event occurs randomly when the conditioned stimulus is absent; thus the conditioned stimulus reliably predicts a respite from an otherwise menacing set of conditions. As animals learn safety signals their presentation is associated with decreased activity in the lateral nucleus of the amygdala (Rogan et al. 2005). The inhibition of amygdaloid activity appears in response to signals from the striatum and is thus distinct from extinction learning.

Extinction and safety conditioning form the basis for psychotherapeutic approaches to selected forms of anxiety. For example, phobias are commonly treated with "exposure therapy" that pairs the threatening stimulus with the absence of an aversive outcome. Likewise, an important psychotherapeutic approach in the treatment of PTSD involves the distinction between stimuli that predict a reoccurrence of the traumatic event from those that do not. Each of these approaches appears to involve brain regions that actively inhibit various regions of the amygdala and might be considered as a fundamental form of emotional regulation.

## Animal Models of Anxiety Disorders

The behavioral models described above subject animals to environmental conditions that reliably cause fear or anxiety. However, in humans anxiety disorders are not determined solely by exposure to aversive environmental conditions. For example, only a proportion of people exposed to a severe trauma will develop chronic PTSD, and chronic stress is a risk factor for affective disorders. Animal models are helping to account for individual differences in susceptibility and resilience to stress (Charney 2004), and have the potential to define causal relations between genomic variants or programmed environmental variations and risk of illness. Relevant behavioral manipulations in adult animals typically involve the induction of intense and/or chronic stress (Miller and McEwen 2006, Cohen and Zohar 2004), including immobilization, restraint, electric shock, and cold stress, as well as underwater trauma and predator exposure (Adamec et al. 2006, Korte and De Boer 2003, Morilak et al. 2005, Rau et al. 2005, Rittenhouse et al. 1992, Richter-Levin 1998, Cohen et al. 2004). Importantly, chronic stress alters subsequent performance on an anxiety test (elevated plus-maze) and produces hypertrophy of dendrites in the amygdala. The behavioral effects of chronic stress are usually blocked by concurrent treatment with an antidepressant drug. Chronic stress (or sustained treatment with glucocorticoids) also blocks synaptic plasticity in the hippocampus and produces dendritic atrophy in the mPFC (McEwen 1999, 2007). These effects are potentially associated with enhanced threat-induced activity in the amygdala, and, as described below (see Pathophysiology of anxiety disorders), hippocampal/mPFC dysfunction in humans, which is associated with increased vulnerability for anxiety disorders. Thus chronic stress might enhance the risk for anxiety through effects on the morphology of the neural circuit that regulates fear and anxiety.

The distinction between state and trait fear or anxiety is also important for animal models (Andreatini and Bacellar 2000, Lister 1990). State fear or anxiety is a transient condition elicited by a stimulus or situation. Trait fear/anxiety is an enduring condition that is independent of specific stimuli or contexts. When anxiety is measured in a behavioral task, does that task assess a state or a trait? That some models, especially in normal animals with limited genetic variability, assess state rather than trait anxiety is suggested by the relatively poor test-retest reliability of the elevated plus maze test, a task widely interpreted as an anxiety equivalent (Andreatini and Bacellar 2000). Behavioral models with rodents that incorporate relevant genomic variations are an important advance in overcoming this limitation. A number of genetic manipulations have been used to create lines of anxious animals. This has been done with selective breeding to enhance performance on anxiety tests (Aguilar et al. 2004, Escorihuela et al. 1997, 1999, Ferre et al. 1995, Pisula and Osinski 2000, Walker et al. 1989, Steimer and Driscoll

2003, Wehner et al. 1997, Paterson et al. 2001, Morilak et al. 2005, Brunelli and Hofer 2007) and with transgenic models (Gross and Hen 2004, Leonardo and Hen 2006, Sibille and Hen 2001, Heisler et al. 1998, Tecott et al. 1998, Tecott 2000, Low et al. 2000, Shumyatsky et al. 2005) that alter genes expressed in the brain and then assess performance on anxiety tests. Of course, these studies are also critical in defining relevant genomic targets within the fear/anxiety neural circuitry. In rodents, increased anxiety is associated with the activation of CRF1 receptors in the amygdala and the locus coeruleus that regulate noradrenaline release in corticolimbic regions. Thus, mice carrying a deletion of the gene for the CRF1 receptor show greatly reduced levels of anxiety-like behavior in a number of behavioral tests (Smith et al. 1998). The expression of fear in rodents is inhibited by serotonin activity in the hippocampus and amygdala, an effect that involves GABAergic transmission in the amygdala. Animals bearing a selective knockout of the 5-$HT_{1A}$ receptor or of selected subunits of the $GABA_A$ receptor show enhanced anxiety (Crestani et al. 2002, Gross et al. 2000).

Studies with animals bearing gene mutations provide a critical test of cause—effect relations between specific neural signals and behavioral phenotypes, and can serve as the basis for human clinical research. For example, studies with humans lend further support to the idea that alterations in the $GABA_A$/BZ receptor complex might form the basis for individual differences in vulnerability for anxiety disorders. Unmedicated patients with a history of PD show a significant decrease in labeling of the BZ receptor antagonist [$^{11}$C]flumazenil in the orbitoprefrontal cortex and amygdala/hippocampal region in PET studies (Malizia et al. 1998). The findings are consistent with those of pharmacological measures of reduced BZ receptor sensitivity in patients high in neuroticism (Glue et al. 1995), PD (Roy-Byrne et al. 1990, 1996), or generalized anxiety (Melo de Paula 1977, Oblowitz and Robins 1983). These findings are at least consistent with the idea that decreased BZ binding levels in critical sites, such as the amygdala, are related to increased vulnerability to anxiety disorders (Gorman et al. 2000).

These findings, together with the well-defined anxiolytic effects of BZ agonists, inspired studies on the molecular basis of $GABA_A$/BZ receptor function in rodents (McKernan and Whiting 1997). Predictably, behavioral responses to stress are inhibited by BZs, which exert their potent anxiolytic effect by enhancing GABA-mediated Cl- currents through $GABA_A$ receptors (McKernan and Whiting 1997, Mehta and Ticku 1988). BZ receptor agonists exert anxiolytic effects via their actions at a number of limbic areas, depending upon the test conditions. However, to date the evidence is perhaps strongest for BZ effects at the level of the basolateral complex of the amygdala, comprising the lateral, basal and anterior basal nuclei (Pitkanen et al. 1997), and the central nucleus of the amygdala. Direct administration of BZs into the basolateral or central regions of the amygdala yields an anxiolytic effect. Interestingly, dynamic variations in $GABA_A$ receptor function often occur as a result of allosteric modulation of the $GABA_A$ receptor including at the BZ site. These findings have led to a focus of investigation on the $\alpha$ and $\gamma$ subunits that form the BZ receptor. Point mutations in either subunit are sufficient to eliminate BZ receptor binding, and animals bearing a null mutation of the $\gamma 2$ subunit show a loss of BZ binding (Gunther et al. 1995) and increased fear-conditioned freezing as well as elevated reactivity to natural aversive stimuli (Crestani et al. 1999).

Althought exaggerated symptoms of fear and anxiety are central to all anxiety disorders, each has unique features. Some of the models described above have been targeted for specific disorders. For example, chronic stress, inescapable footshock, and underwater submersion have been used to mimic traumatic stress conditions, such as PTSD (Richter-Levin 1998, Adamec et al. 2004, Cohen et al. 2004, Matar et al. 2006, Pitman and Delhanty 2005, Servatius et al. 1995, Wakizono et al. 2007). PD has been modeled by treating animals with drugs that induce panic in human subjects, such as lactate (Shekhar et al. 1996) or doxapram (Sullivan et al. 2003), and then showing enhanced fear or anxiety in behavioral tests such as the open field, elevated plus-maze, a social interaction test, or fear conditioning. Stimulation of brain circuits (amygdala, hypothalamus) by drugs (Frankland et al. 1997, Sajdyk and Shekhar 1997, 2000, Sanders and Shekhar 1995, Sanders et al. 1995, Keim and Shekhar 1996) or electrical stimulation (Rosen et al. 1996, Rosen and Schulkin 1998) has been used to alter control of autonomic and behavioral responses to model PD (Sajdyk et al. 1999, Shekhar et al. 1999, 2003, Graeff et al. 1993). Models of OCD also exist (Korff and Harvey 2006).

## Amygdala Function and the Pathophysiology of Anxiety Disorders

### Emotional Processing and Amygdala Function

Studies of the association between attention regulation and anxiety reveal that adults with anxiety disorders exhibit enhanced vigilance and increased attention to threat, as evidenced by reaction times to fear-related words or pictures. As in other species, these effects in humans are attributed to activity of a neural circuit comprised of the amygdala, hippocampus and prefrontal cortex. In humans aversive stimuli activate the amygdala, which mediates immediate responses and learning and memory for these stimuli. Individual differences in trait anxiety predict the response of the amygdala to unconscious processing of threatening stimuli (Etkin et al. 2005a). Neuroimaging studies reveal increased amygdala activity during the acquisition phase of fear conditioning (LaBar et al. 1995, LaBar et al. 1998, Morris et al. 1998), and patients with amygdala damage show profound deficits in fear conditioning (Bechara et al. 1995, LaBar et al. 1998). In addition, the hippocampus is involved in processing spatial and temporal information related to threats as indicated by so-called "trace conditioning." In this paradigm, in which the US follows the CS after a delay, the hippocampus, amygdala, and anterior cingulate cortex are recruited (Buchel et al. 1999) and are critical in associating the threat with the predictive stimuli across temporal intervals. The hippocampus is also critical in the identification of stimuli and places as novel, and thus facilitates new learning. Activation of the amygdala is primary and thus individual differences in the degree of amygdaloid activation during fear conditioning predict the strength of a conditioned autonomic fear response (Furmark et al. 1997). Moreover, as in rodent models, hormones released in response to stress (catecholamines and glucocorticoids) facilitate the establishment of emotional memories in humans (Cahill and McGaugh

1998). These effects involve the activation of glucocorticoid and β-adrenergic receptors in the amygdala. Indeed, agents that block these receptor sites are considered promising areas for therapeutic development in clinical cases that involve traumatic memory (Tronel and Alerbini 2007).

Further evidence for the importance of the amygdala in emotional processing of sensory information emerges from studies in human populations with amygdala damage. Amygdala lesions in humans are associated with impairments in the recognition of fear and anger (Scott et al. 1997). Humans with such lesioins are more likely than controls to judge photographs of strangers as trustworthy and approachable (Adolphs et al. 1998). Patients with amygdala seizures, involving repeated excess activation of the amygdaloid complex commonly suffer from severe anxiety disorders (Picardi et al. 2007). In rodents, amygdaloid kindling, which replicates the seizure activity of these patients, dramatically increases anxiety (Kalynchuk et al. 2001).

## Pathophysiology of Anxiety Disorders

Anxious individuals of any age show an attentional bias to threat. Severe threat rivets attention in all people, whereas mildly to moderately threatening conditions are best for distinguishing individuals with increased trait anxiety or overt anxiety disorders (e.g., Grillon et al. 1999). Such conditions evoke highly focused attentional responses in anxious individuals, which are comparable to normal individuals' attentional response to serious threats. Neuroimaging studies, which are among the most powerful techniques for studying brain pathophysiology, reveal this attentional bias, which reflects the altered cognitive–perceptual processing of sensory information through the prefrontal–amygdala circuit. Attentional biases towards threat are associated with cognitive impairments, such as disruptions of working memory that occur as a function of the increased distractability associated with hypervigilance. Such effects are, in part, associated with catecholamine influences on prefrontal function (Birnbaum et al. 1999). Not surprisingly, there is considerable comorbidity between anxiety disorders and attentional-deficit disorder (ADD).

Images of human faces are the most common stimuli used in neuroimaging of human anxiety. Studies among adults suggest that SAD is associated with a heightened response in the amygdala both to complex evaluative social situations and to relatively simple stereotyped facial displays of emotion (Evans et al. 2007). One study also demonstrated enhanced fear conditioning to facial stimuli among adults with SAD, which was reflected in changes in the amygdala.

Several studies reported activation of the amygdala in response to facial expressions of fear or anger compared with neutral faces (Morris et al. 1996, Phillips et al. 1997, Stein et al. 2002) or unpleasant versus neutral pictures (Irwin et al. 1996). Predictably, there is neuroimaging evidence of increased amygdala activity in patients with a wide range of anxiety disorders (e.g., Breiter et al. 1996, Rauch et al. 1996). Social phobics seeing neutral faces show activation of the amygdala comparable to that observed in controls in response to aversive stimuli (Birbaumer et al. 1998). Similarly, children with anxiety disorders have increased amygdala activity compared with controls when viewing fearful versus neutral faces (Pine et al. 2005). Taken together, these studies indicate that the amygdala of anxiety disorder patients is more reactive to mildly aversive stimuli.

## Emotional Regulation: Role for the mPFC

Neuroimaging studies of PTSD patients that focused on combat-related exposure in veterans with PTSD (Rauch et al. 1996, Liberzon et al. 1999, Bremner et al. 1999) have found increased regional activation with measures of cerebral blood flow in the amygdala and decreased activation of the mPFC in response to trauma-related material versus neutral stimuli. Interestingly, an area that consistently shows "de-activation" is the mPFC area 25, which also shows anatomical alterations in depressed patients (Drevets et al. 1997). Not surprisingly there is considerable comorbidity between PTSD and depression. A script-driven imagery and PET study of Vietnam War veterans with or without PTSD showed rCBF decreases in the medial frontal gyrus for the traumatic versus neutral comparison in the PTSD group (Shin et al. 2004). Activity in the mPFC was inversely correlated with changes in the amygdala, which is consistent with the rodent model showing that the mPFC modulated amygdala activity and dampened fear conditioning. Differential activation of the amygdala in patients with PTSD is not limited to specifically trauma-related material. Thus, PTSD patients show increased amygdala responses to facial expressions of fear or anger (Shin et al. 2005). Importantly the magnitude of the response in the amygdala correlates negatively with activity in the dorsal region of the mPFC. Similarly, there is a negative correlation between activity in the ventral medial prefrontal cortex (vmPFC) and that of the amygdala following presentation of aversive pictures or emotional facial expressions (Urry et al. 2003, Kim et al. 2003).

Such patterns of neural activation also predict the magnitude of cortisol responses to stressors (Davidson 2004), which in turn reflects the magnitude of the perceived severity of the threat. Recall that glucocorticoids act on the amygdala to enhance the memory for the event. The negative correlation between activity in the mPFC and the amygdala also relates to cognitive processes during emotional learning and memory. Fear conditioning is an obvious example of an association that activates a negative emotion, and the ability to appropriately extinguish conditioned emotional responses is critical for affect regulation. Phelps et al. (2004) paired a visual stimulus with a mildly painful wrist shock. During the acquisition phase, activity in the amygdala predicted the magnitude of the conditioned emotional response. In the extinction phase, the visual stimulus was repeatedly presented without the US, which normally results in a suppression of the learned response. Following extinction, activity within the vmPFC predicted the magnitude of the conditioned emotional response.

Stimulation of the rodent analog of vmPFC inhibits responses in the amygdala (Quirk et al. 2003, Rosenkrantz et al. 2003). Across multiple species the mPFC has direct projections to the amygdala (Carmichael and Price 1995) as well as to the primary source of ascending serotonergic (dorsal raphé nucleus) and noradrenergic (locus coeruleus) projections. Amat et al. (2005) found that inactivation of an area of the mPFC that contains relevant descending projections eliminates the effect of perceived controllability on behavioral and neurochemical responses to stress. In the

rat, as in humans, the ability to actively control a stressor diminishes the adverse effects; uncontrollable stressors produce far more profound impairments on behavior and neural activity. Lesions of the mPFC rendered controllable stressors as potent as uncontrollable stressors, suggesting that the processing of the information related to the detection of controllability relies upon mPFC function, and likely on descending projections from the mPFC. Thus the diminished activation of regions such as the mPFC in patients with anxiety disorders might underlie an impaired capacity for a 'top-down' regulation of emotional states.

## Therapeutic Targets: The Neurobiology of Coping

Studies of blood flow and metabolism as well as functional magnetic resonance imaging (fMRI) reveal a common pattern of decreased activation of the prefrontal cortex, cingulate gyrus, and increased amygdala activity in patients with mood disorders (Davidson et al. 1999). Thus, amygdaloid dysfunction is associated with both anxiety and depression (Drevets et al. 1997) and negative affect is strongly correlated with amygdaloid activity in positron emission tomography (PET) scans, particularly in the right amygdala (Abercrombie et al. 1998, Michelgard et al. 2007). Thus, PET studies indicate that right amygdala blood flow is increased in PTSD patients (Rauch et al. 1996, Shin et al. 1997). Importantly, the reciprocal dysfunction in the prefrontal cortexand amygdala is at least partially normalized with successful treatment of the mood disorder (Goldapple et al. 2004). Likewise, Furmark et al. (2002) report that both medication (citalopram) and cognitive behavioral therapy reduce the activation of amygdala and hippocampus in anticipation of public speaking in patients with social phobia. The decrease in the activation of the amygdala predicts symptom severity one year later.

The results of neuroimaging studies converge with those examining the psychological processes that render individuals vulnerable for anxiety disorders. Active cognitive appraisal of emotionally disturbing stimuli and the evaluation of the emotional states associated with such events is a coping style that predicts a reduced risk for anxiety, as well as other forms of psychopathology. Appraisal involves the processing of information related to the stimuli as well as a reinterpretation of the accompanying emotional state that appears to reduce the emotional response and physiological arousal (Phan et al. 2004). Ochsner et al. (2002) used aversive pictures to scan subjects with fMRI and instructed them to attend (be aware of feelings elicited by the picture) or reappraise (reinterpret the picture so that it no longer elicits a negative emotional response). Attending alone was associated with increased emotional responses and increased activity in the amygdala, as well as regions of the PFC associated with processing aversive material. Reappraisal of highly negative scenes reduced emotional responses and increased activation of the dorsal and ventral lateral regions of the mPFC. As noted above, these regions are associated with inhibition of amygdala activity and thus vmPFC activation during reappraisal was inversely correlated with activity in the amygdala. Effective reappraisal associates with increased activation in mPFC regions implicated in working memory, cognitive control, and self-monitoring, and with decreased activation of medial orbital frontal cortex and amygdala, regions implicated in emotion processing. Using a similar paradigm, Phan et al. (2005) showed aversive pictures to subjects instructed to either respond normally or to actively suppress negative responses through reinterpretation of the material and affect. Successful reduction of negative affect was associated with increasing activation of mPFC and with decreasing activity in the nucleus accumbens and the amygdala, as well as with the intensity of negative affect. Likewise, using functional MRI Schaefer et al. (2002) demonstrated that when subjects were instructed to regulate their negative emotion voluntarily, there occurred a reliable bilateral decrease in amygdala activity that was correlated with the increased signal in the vmPFC (Urry et al. 2003).

Cognitive-based psychotherapeutic interventions that are clinically effective in treating a range of anxiety disorders focus on the issue of appraisal and affect regulation. Not surprisingly, these interventions are associated with alterations in the activity of the mPFC (Etkin et al. 2005a, Roffman et al. 2005, Mayberg 2007). Likewise, clinically effective pharmacological therapies target neural structures implicated in states of anxiety, especially the amygdala and its projections to the noradrenergic neurons of the locus coeruleus. Anxiety disorders are commonly associated with increased central and peripheral noradrenergic activity. Acute BZ treatment in the rat or human reduces fear and this effect is associated with BZ action at the level of the amygdala. The anxiolytic effect of the BZs in the rat can be achieved with direct infusion of the BZ into the amygdala and by the suppression of activity in the locus coeruleus. Selective serotonin reuptake inhibitor's (SSRI) target this same neural circuit. Coplan et al. (1997) showed that after 12 weeks of fluoxetine treatment, patients with panic who responded to treatment showed a decrease in plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of noradrenaline. This finding suggests that SSRIs decrease noradrenergic activity, and cardiovascular symptoms associated with panic attacks. The 5-HT projection to the locus coeruleus is inhibitory and SSRI treatment in the rat enhances serotonergic inhibition of basal and stimulated firing rates of locus coeruleus neurons (Blier 2001). Stutzmann and LeDoux (1999) showed that 5-HT modulates sensory input at the lateral nucleus of the amygdala, inhibiting excitatory inputs from glutamatergic thalamic and cortical pathways. The effect of 5-HT is mediated by the $GABA_A$ receptor, which is the principal pharmacological target of the BZs. Thus, the findings from clinical research further implicate the mPFC–amygdala connections in anxiety. As discussed above, there is evidence linking reduced GABAergic function in the amygdala to vulnerability for anxiety in humans. These findings suggest that states of increased anxiety are associated with a diminished capacity in mPFC structures that modulate activity in the amygdala and thereby regulate affect. Increased amygdaloid activity may well serve as a common neural substrate for alterations in the assessment of stimulus salience, conditioned emotional responses, and hypervigilance that define anxiety states.

Neuroimaging studies of individuals with affective disorders provide a biological basis for subgrouping patients on measures of neural activity that are proximal to the symptoms (Etkin et al. 2005b). Indeed, many in clinical psychology and psychiatry argue for such a subgrouping on the

basis of symptoms or specific traits rather than categorical approaches. Neuroimaging studies provide a complementary level of clinical analysis of both pathogenesis as well as treatment outcome. Thus, for example, pretreatment levels of activity in the rostral portion of the anterior cingulate predicted the treatment response to venlaflaxine in depression (Davidson et al. 2003). There is also evidence that neuroimaging may provide indications for differential treatment (Etkin et al. 2005b). Among OCD patients, pretreatment levels of activity in the orbitofrontal cortex predicted the response to psychotherapy versus pharmacotherapy (Brody et al. 1998). Moreover, complex affective disorders will likely show multiple etiologies even when the presentation of the current symptoms is similar (Etkin et al. 2005b). Etiology matters for treatment outcome. Thus, Nemeroff et al. (2003) showed that patients with major depression and a history of childhood trauma responded significantly better to cognitive psychotherapy than to an antidepressant medication; patients with major depression but no evidence of childhood trauma showed a better response to the medication. Such findings underscore the importance of etiology and a clear understanding of the intermediate phenotypes, including patterns of neural activity that define the premorbid vulnerability for anxiety disorders.

## Vulnerability for Anxiety Disorders

The question of vulnerability lies at the heart of research on anxiety disorders (Yehuda 2004). Surprisingly, not all humans subjected to even profound trauma develop PTSD (Ressnick et al. 1993, Shalev and Freedman 2005, Storr et al. 2007). A critical question concerns the traits that characterize individuals vulnerable for anxiety disorders, and the identity of the critical neural processes that define the high-risk state. Much of the initial clinical research compared patterns of neural morphology or patterns of activation in patient samples and controls. A limitation of such studies is the inability to directly relate alterations in neural activity to the onset of pathology. One example lies in the consistent finding that PTSD associates with decreased hippocampal volume (Bremner 2002). This relation is potentially critical for recovery from PTSD, since the hippocampus is crucial for contextual information. A major challenge following trauma is for the individual to place the event into an appropriate time and place such that memory for it and concomitant emotional responses are limited to situations that realistically predict repeated occurrence of the trauma. Hippocampal dysfunction could thus serve to impair recovery in PTSD. Moreover, hippocampal impairments could serve as a risk for chronic PTSD. However, the dilemma lies in the interpretation of correlational findings that relate hippocampal volume and PTSD. Do such findings suggest that decreased hippocampal volume might render individuals vulnerable for chronic PTSD, or does the chronic PTSD state result in decreased hippocampal volume (Sapolsky 1996). Gilbertson et al. (2002) directly addressed this issue and found that in PTSD subsequent to combat exposure was associated with reduced hippocampal volume by comparison to combat-exposed individuals without PTSD. However, the twins of these subjects, who never experienced combat, showed the same differences in hippocampal volume, suggesting that the differences in hippocampal volume are of developmental origin and define a state of increased vulnerability. A critical question concerns the nature of such an increased state of vulnerability for anxiety.

Studies of functional asymmetries in the mPFC provide a further understanding of the neural basis of emotional regulation and vulnerability for anxiety disorders (Davidson 2004). The processing of stimuli associated with negative emotional states activates regions in the right prefrontal cortexmore than on the left. Stimuli associated with positive emotions show the reverse pattern of activation (Davidson et al. 1990, Ahern and Schwartz 1985, Jones and Fox 1992). There are stable, individual differences in baseline prefrontal electroencephalogram (EEG) asymmetries that map onto those observed in emotional reactivity (Davidson 2004). Individuals with a relatively greater prefrontal activity in the right hemisphere show increased shyness, timidity and negative affect (Tomarken et al. 1992, Urry et al. 2004). Individuals with relatively greater prefrontal activity in the left hemisphere show more positive affect, increased sociability and are more likely to approach and explore novel conditions. An attentional bias is revealed in responses to films of positive versus negative content: Left-biased individuals are more responsive to the former, right-biased individuals respond more to the latter. Importantly, these findings suggest that altered activity within the right prefrontal cortexis associated not only with increased reactivity to aversive stimuli, but also with negative affect. Both, of course, are cardinal symptoms of anxiety disorders. Such individual differences are apparent in EEG studies with rhesus monkeys. Animals with increased activity in the right prefrontal cortex show elevated levels of CRF in cerebrospinal samples and increased basal cortisol levels (Kalin et al. 1998).

## Developmental Origins of Vulnerability for Anxiety Disorders

### Behavioral Inhibition

Support for the developmental perspective derives from studies of the longitudinal course and familial nature of anxiety disorders. Familial influences include heritable genetic variants, gene x–environment interactions and environmental effects. Childhood behavioral problems very commonly precede emotional problems in adults. Indeed, many adult anxiety disorders appear to have a childhood or adolescent onset (Kendler et al. 1992, Merikangas 2005) or, in the case of PTSD, predisposing factors stemming from early family life (Udwin et al. 2000). Predictably, research focuses on developmental precursors to endophenotypes that associate with anxiety disorders. Perhaps the most fruitful area is that of research on individual differences in cognitive and affective responses to mild threat in children, subsumed under the term "behavioral inhibition" (Kagan et al. 1987, Pérez-Edgar and Fox 2005). Behavioral inhibition first manifests in infants. It is characterized by increased physiologic reactivity and behavioral withdrawal in response to novelty, including to strangers, inanimate objects, or other forms of challenging situations (Kagan et al. 1987, Fox et al. 2001). Physiological manifestations of behavioral inhibition include low heart rate, variability, accelerated heart rate, increased HPA activity under basal and stimulated conditions, as well as an increased startle response. Among North Americans behaviorally inhibited individuals

comprise the 15% of the population that have the most shyness and timidity. Behavioral inhibition in infancy is a risk factor for anxiety in childhood or adolecence particularly for social phobia or SAD (Biederman et al. 2001).

Behaviorally inhibited infants show high levels of negative emotional states (Pérez-Edgar and Fox 2005), and are typically agitated and fearful in response to novelty. At later ages, behaviorally inhibited children are often wary in social situations and socially withdraw from unfamiliar peers. Maternal ratings of persistent shyness in childhood predict the development of anxiety disorders in adolescence (Prior et al. 2000).

Behaviorally inhibited children are hypervigilant and show an increased startle response, both common characteristics of adults with affective disorders. These children also show heightened fear in response to situations that noninhibited individuals experience as nonthreatening (Pérez-Edgar and Fox 2005). This distinction is comparable to the negative emotional bias that characterizes individuals with increased trait anxiety or with anxiety disorders. Indeed, there are impressive similarities in the defining features of behavioral inhibition and critical features of clinical anxiety (Pérez-Edgar and Fox 2005), including social withdrawal and an avoidant style of coping. Importantly, behavioral inhibition and clinical anxiety are both characterized by an increased attentional bias to threat-related stimuli (Lonigan et al. 2004). For example, when presented with ambiguous situations, young, socially anxious children perceive threat more quickly and report more negative feelings (Pérez-Edgar and Fox 2005). Behaviorally inhibited children show more negative cognitions and make lower estimates of their competency to cope with dangerous or stressful events (Pérez-Edgar and Fox 2005). This negative temperament is associated with enhanced amygdala activation in response to faces (Schwartz et al. 2003), which suggests that a neural "fear circuit" plays a role in this phenotype.

Individual differences in behavioral inhibition are apparent in early development, as are the asymmetries in mPFC activity discussed above (Davidson and Fox 1989). Thus, 10-month-old babies who cry in response to maternal separation are more likely to show greater right-sided prefrontal activation during a preceding resting baseline compared with those infants who did not cry. Rothbart and colleagues (Rothbart 2004) showed that infants prone to distress, suggesting increased behavioral inhibition, are less adept at shifting attention away from a distressing stimulus and have difficulty engaging in self-soothing activity. Such findings suggest an early developmental appearance of the problems with emotional regulation and patterns of neural activity that define an increased vulnerability for anxiety disorders. Dawson and colleagues (e.g., Dawson et al. 2003) showed that the offspring of depressed mothers show increased behavioral inhibition and greater baseline EEG activity in the right prefrontal cortex.

## Familial Transmission of Risk: Effects of Genes, Environment, and Their Interaction

These findings raise the obvious issue of the familial transmission of the neural substrates for behavioral inhibition. Indeed, children of parents with anxiety disorders are more likely to show extreme behavioral inhibition (Rosenbaum et al. 1991). Moreover, unaffected siblings of anxious adolescents also show significant levels of emotionality and shyness. Behavioral inhibition appears heritable, with estimates ranging from 0.40–0.70 in twin studies (Pérez-Edgar and Fox 2005). For example, one study (Smoller et al. 2003) links behavioral inhibition and an allelic variantion in gene for CRF. Auerbach et al. (2001) showed that variants of the 5-HT transporter gene are associated with negative temperament in infancy. The same allelic variation is associated with increased expression of the harm avoidance personality trait that includes increased fearfulness, shyness and timidity (Arbelle et al. 2003) as well as increased amygdala responses to emotional facial stimuli. These findings suggest that genomic variations might function in early development to regulate the development of neural systems that mediate emotional states. This idea is consistent with animal studies that reveal increased fearfulness in animals bearing a targeted disruption of the 5-$HT_{1A}$ receptor (Gross et al. 2000). Hen and colleagues (Gross et al. 2002) subsequently found that the critical period for the effect of the 5-$HT_{1A}$ knockout on anxiety-like behavior in adult animals was that of early development, when 5-HT actively regulates the growth and development of synaptic connections in regions such as the amygdala, hippocampus and mPFC. These regions are all major 5-HT targets.

These studies suggest that genomic inheritance describes, in part at least, the variance in behavioral inhibition across children. It is important to note, however, that estimates of heritability include the variation in traits associated with gene x environment interactions that might serve to modify the expression of behavioral inhibition over development. Thus, a critical issue concerns the stability of the traits that define behavioral inhibition (Fox et al. 2001). As young adults, children identified as behaviorally inhibited at two-years of age show greater activation of the amygdala in response to novel faces than do those that were characterized as behaviorally uninhibited as toddlers (Schwartz et al. 2003). Longitudinal studies report moderate stability (i.e., correlations of approximately $r = 0.25–0.60$) of behavioral inhibition from early to middle and late childhood through to early adulthood (Pérez-Edgar and Fox 2005). Stability is greater among extremely inhibited children. However, while the majority of adults with behavior problems initially developed signs of such problems as children, most behaviorally inhibited children do not develop anxiety disorders in later life. Such findings appear to reflect the importance of gene x environment interactions acting through development that determine cognitive-emotional outcomes. Fox and colleagues (Pérez-Edgar and Fox 2005) found that emotionally negative infants at 4 months of age are more likely to become less inhibited as toddlers when placed in nonparental care environments, such as daycare settings, for at least 10 hours per week. Family function, particularly parent-offspring interactions, also seems to be defined the developmental outcomes in behaviorally inhibited children. Rubin et al. (2002) found that behavioral inhibition at two predicted reluctance to interact with unfamiliar peers at four years of age only in mothers that were intrusive and critical. Hence parental style determines the developmental trajectory of behaviorally inhibited children. Bowlby (1960) associated anxiety with the quality of the mother-infant bond to the security of attachment and the fear of separation. Fleming (1988) found that the anxiety level of the mother was

the single best predictor of her level of responsivity to the infant: More anxious mothers were less responsive. These findings underscore the potential for intervention studies that target parental responses to more anxious or temperamental infants. Indeed, the clinical literature supports the idea that such interventions yield significant results in offsetting the lont-term risk for affective disorders (Belsky 1997).

These findings suggest that the developmental outcomes associated with behavioral inhibition in early life are modulated by environmental influences. This idea is consistent with findings from studies with nonhuman subjects that reveal direct effects of maternal care on neural systems that regulate fear. In humans, behavioral inhibition is associated with gene–environment interactions occurring in childhood (Fox et al. 2005), presumably through environmental regulation of genes the products of which later regulate activity in neural circuits associated with fear and anxiety.

Levine and colleagues showed that a behavioral manipulation in infancy, handling, which consists of daily brief separation from the mother over the first two postnatal weeks, leads to resistance to the behavioral and endocrine responses to stress in adulthood. For example, handled infant rats had reduced glucocorticoid responses to active avoidance learning (Weinberg and Levine 1977), and the altered HPA response bias was lifelong (Meaney et al. 1988) due to permanently increased hippocampal type II glucocorticoid receptor binding (Meaney et al. 1991). Interestingly, postnatal handling of infant rat pups alters the behavior of the mothers. These effects appear to mediate, in part, the influence of the handling on stress reactivity. Subsequent studies on the effects of maternal care have provided direct evidence for parental influences on the development of neural circuits that regulate fear and anxiety (Meaney 2001, Zhang et al. 2006).

In the rat, naturally occurring variations in maternal care stably alter the expression of genes in brain regions, such as the hippocampus, amygdala and prefrontal cortex, that regulate behavioral, autonomic and endocrine responses to stress (Cameron et al. 2005, Meaney 2001, Zhang et al. 2006). These studies focus on individual differences in maternal behavior in the absence of any experimental manipulation of the mother or her pups, particularly one specific maternal behavior in the rat, pup licking. By licking her pups the mother regulates the activity of their endocrine systems that strongly influence somatic growth. Thus, licking enhances the circulating levels of growth hormone (Schanberg et al. 1984) and suppresses the release of the catabolic glucocorticoids (Levine 1994). Considering the effects on somatic development, we might think of pup licking as a rudimentary form of "nurturance." And there are very stable, individual differences in the frequency with which rat mothers lick their offspring in early development. Importantly, these variations can directly 'program' gene expression. For example, the adult offspring of high mothers that show high levels of licking over the first week of postnatal life have increased expression of $GABA_A$ receptor subunits in the amygdala, which confers greater sensitivity to GABA as well as to BZs and their anxiolytic effects (Fries et al. 2004). Predictably these adult offspring show decreased fearfulness, reduced fear conditioning and more moderate noradrenaline responses to stress (Caldji et al. 1998, 2003). Such effects target the $\alpha 1$ and $\gamma 2$ subunits of the $GABA_A$ receptor, and selective knockdown of these subunits in mice results in increased fearfulness in response to novelty and enhanced conditioned emotional responses (e.g., Crestani et al. 1999). Recall that among human subjects, there is reduced sensitivity to BZs (which act at the $\alpha 1$ and $\gamma 2$ subunits of the $GABA_A$ receptor) among those with an increased vulnerability for anxiety disorders (see above).

The effects of maternal care in the rat on the $GABA_A$ receptor system and fear behavior are reversed with cross fostering, revealing a direct maternal effect on the development of the $GABA_A$ receptor system (Caldji et al. 2003). Moreover, these same variations in maternal care also directly alter the expression of genes that promote synaptic development of the hippocampus (Liu et al. 2000), and individual differences in hippocampal morphology are associated with vulnerability for anxiety disorders (Gilbertson et al. 2002). Finally, maternal care over the first week of life in the rat also regulates the expression CRF and CRF1 receptors in the amygdala and the locus coeruleus (Caldji et al. 1998). The offspring of low licking mothers show increased CRF activity and, predictably, enhanced noradrenaline release in response to threat.

The results of Gilbertson et al. (2002) suggest that the reduced hippocampal volume commonly reported among PTSD patients is developmental in origin. Rodent studies suggest parental effects. Thus, the neonatal rats exposed to prolonged periods of maternal separation show reduced expression of brain-derived neurotrophic factor (BDNF) in the hippocampus (Roceri et al. 2002). BDNF stimulates synaptic development in the rat hippocampus, and elsewhere in the developing brain. Studies of naturally occurring variations in maternal care in this species show that maternal licking increases BDNF expression in the hippocampus (Liu et al. 2000). As adults, the offspring of high licking mothers show enhanced hippocampal synaptic density (Liu et al. 2000, Bredy et al. 2004). These findings suggest that maternal care can directly regulate hippocampal development, and there is at least correlational evidence for such an effect in humans (Buss et al. 2007). Interestingly, the antidepressant medications, often effective in the treatment of certain anxiety disorders, increase hippocampal BDNF expression (Tanis et al. 2007).

These findings suggest that parental care can directly regulate the development of neural and molecular substrates that are involved in emotion. One question concerns the mechanism by which parental care in early life might stably alter gene expression in the offspring. Recent studies in the rat suggest an epigenetic mechanism, that is, functional modifications to the DNA that do not involve a change in sequence. Such modifications commonly involve alterations in the methylation status of cytosines lying within the promoter regions of genes. DNA methylation is commonly associated with the silencing of gene expression. A recent set of studies (Weaver et al. 2004, 2005, 2007) found that pup-licking by the mother alters the methylation state of a promoter for the glucocorticoid receptor in the hippocampus of the offspring. The offspring of high-licking mothers showed reduced methylation of the promoter and increased hippocampal glucocorticoid receptor expression. Such effects persist well into adulthood and are functionally relevant. The hippocampal glucocorticoid receptor inhibits CRF expression in the hypothalamus and thus regulates HPA responses

to stress. The adult offspring of high-licking mothers show reduced hypothalamic CRF activity and more modest HPA responses to stress than do animals reared by low licking mothers. These effects, including those on promoter methylation, are reversed with cross-fostering, revealing direct maternal effects.

These findings suggest that, in the rat at least, maternal care can program defensive responses to threat. Interestingly, chronic stress during gestation reduces postpartum pup licking such that stressed mothers are low-licking mothers (Champagne and Meaney 2006). This pattern of maternal care results in more anxious offspring (Champagne and Meaney 2006). Under certain conditions, such effects might in fact be adaptive. Among humans, behavioral inhibition predicts greater success among young males living in poor, high-crime environments (Farrington 1988, Haapasap and Tremblay 1994). Such fearful boys are considered less likely to participate in criminal activity. Such potentially adaptive patterns of development come at a cost that is reflected in the increased risk for anxiety disorders. Indeed, low socioeconomic status is a risk factor for anxiety disorders.

The findings with nonhuman species suggest that variations in the quality of early parental care are relevant for individual differences in emotional reactivity, even for low-risk populations. This conclusion is supported by data in children from Hane and Fox (2006), who used standardized coding systems to score variations in child care (i.e., low quality versus high quality maternal care behavior). Infants receiving low-quality maternal care showed more fearfulness, less positive joint attention, and greater right frontal EEG asymmetry than infants receiving high-quality care. Group differences in stress reactivity were not related to infant temperament. The results suggest that variations in parental care in human infants may influence the development of neural systems involved in behavioral inhibition. In children, a disorganized infant–parent attachment relationship is associated with increased salivary cortisol, suggestive of greater stress reactivity (Nachmias et al. 1996). Among adult humans, Pruessner et al. (2004) found that individuals who report having had low-quality relations with their parents show significantly more release of dopamine in the ventral striatum, as evidenced by reduction in [$^{11}$C]raclopride binding potential in PET scans, during a stressful event than individuals who report high-quality relations with their parents.

These finding suggest familial influences on the development of vulnerability for anxiety that are mediated by variations in parental care. More dramatic evidence for this effect emerges from studies of child maltreatment. Individuals abused in childhood are especially sensitive to facial expressions of anger, which is of course a very salient stimulus for children living in such harsh settings. Event-related potential (ERP) studies reveal that abused individuals, children or adults, show increased neural activity in response to angry faces; no such effect is apparent in response to happy or fearful faces. Interestingly, such individuals are likely to interpret anger in facial expressions that controls perceive as neutral. These findings reveal an increased sensitivity to social or interpersonal threat among abused individuals. Not surprisingly, abused individuals show an increased tendency for fear and social withdrawal (i.e., increased behavioral inhibition). Nevertheless, despite the very immediate and profound impact of parental abuse on the child, such experiences do not necessarily lead to psychopathology in adulthood. Studies of the risk for pathology among abused individuals reveal clear examples of the importance of gene–environment interactions. Thus, adult males who were abused as children are relatively protected from the development of antisocial personality by a functional polymorphism of the gene for monoamine oxidase that causes high expression of the enzyme.

As development progresses, environmental events more proximal to the onset of affective illness interact with other genes. Among individuals with the short allelic variant of the 5-HT transporter, which predicts an increased risk for anxiety (Lesch et al. 1996), major life stress in early adulthood results in a very substantial increase in depression (Caspi et al. 2003). Conversely among those carrying the long variant of the 5-HT transporter gene, adversity as a young adult had little effect on the probability of subsequent depression. In Rhesus monkeys (Suomi 1997), the peer rearing compared with the maternal rearing increases the stress reactivity. The Rhesus monkey shows a similar functional polymorphism in the 5-HT transporter gene promoter, and the effects of peer rearing on stress reactivity are substantially greater among animals with the short variant. Peer rearing has little effect among animals homozygous for the long allelic variant of the 5-HT transporter (Barr et al. 2004, Bennett et al. 2002).

The results presented above are often taken to reflect evidence for differences in vulnerability, and allelic variations at genomic sites such as the promoter region of the 5-HT transporter gene as "vulnerability genes." This may not be the most fruitful interpretation. Individuals bearing the short allelic variant of the 5-HT transporter promoter are certainly more affected by parental care with respect to measures of stress reactivity (Rhesus monkey) or affective illness (human). Hence the allelic variant confers greater susceptibility to environmental influences (with respect to these specific outcomes). This reasoning is consistent with studies in child development demonstrating differential susceptibility to parental care as a function of infant temperament (frequent distress, crying and agitation; Belsky 1997). Interestingly, parental care may exert an even greater influence on developmental outcomes in more vulnerable populations (Belsky 1997) such as emotionally reactive children. For example, positive parenting (positive affection and sensitivity to the child) compared with negative parenting (irritable and intrusive control of the child) had a significantly greater effect on behavioral inhibition in childhood among offspring that showed negative temperament in infancy (Belsky et al. 1998). Similarly, Kochanska (1997), and Feldman et al. (1999) found that parenting was a better predictor of measures of emotional development for more temperamentally difficult infants. Interestingly, there is also evidence that environmental conditions that influence the quality of parent – child relations have a larger effect on developmental outcomes in more temperamental infants. Thus, Crockenberg (1981) reports that the parental–social support was predictive, of infant attachment security but only in the case of highly irritable infants. Blair (2002) showed that an enriched rearing experience comprised of educational day care combined with home visiting and parent support over the child's first three years of life

affected social and emotional development among children who were highly negatively emotional infants, with no such treatment effect with other infants. These findings reflect an increased response to enriched environmental conditions among infants with negative temperament suggesting an increase in susceptibility to environmental variation, rather than merely greater vulnerability to adversity.

These findings provide an understanding of the nature of the gene–environment interactions that might define individual differences in vulnerability for anxiety disorders. Heritable genomic variations as well as the quality of maternal-fetal interactions in prenatal life predict behavioral inhibition in the child, and such individual differences in temperament are apparent in early infancy (Thomas and Chess 1977). Individual differences in behavioral inhibition are associated with patterns of neural activity that they themselves are related to increased vulnerability for anxiety disorders. However, while behavioral inhibition in early life is a risk for anxiety in later life, the majority of behaviorally inhibited children do not develop anxiety disorders. Variations in child care are likely a critical factor in determining the developmental outcomes associated with states of increased vulnerability. Thus, Rubin et al. (2002) showed that increased behavioral inhibition in infancy predicted fear of interacting with peers only if parents were highly intrusive and controlling. Such forms of parenting are, of course, a function of the parents' anxiety. It is precisely this level of complexity that reflects the consistent gene–environment interactions inherent in the familial origins of anxiety disorders.

## Conclusions

Recent clinical research has clarified the criteria for the diagnoses of the anxiety disorders, clearing the way for major advances in the understanding of the pathophysiology of specific anxiety disorders such as PTSD and social phobia. Important findings have come from human neuroimaging and genomic studies. Current neuroimaging research highlights the reciprocal roles of the prefrontal cortexand the amygdala in the pathogenesis of anxiety disorders. Underactivity of the PFC and overactivity of the amygdala biases adults and children to perceive stimuli as threats and to react to them fearfully, thus predisposing them to anxiety disorders. Linkage and association studies of candidate genes have suggested a significant association between PD and a functional COMT polymorphism, while large cohort studies have implicated the interactions of specific alleles for serotonin and catecholamine signaling, the serotonin transporter and monoamine oxidase genes respectively, with specific environmental stressors particularly childhood abuse and major life adversity as risk factors for affective dysregulation. Animal models using transgenic, molecular biological, and pharmacological methods have demonstrated that normal anxiety responses depend on the presence of the CRF1 receptor, while anxiety modulation requires on the integrity of the serotonin 1A and $GABA_A$ receptors. Extinction and safety conditioning are separate forms of learning that depend on specific projections to the amygdala from the mPFC and striatum, respectively, which have implications for the treatment of PTSD.

Variations in early development, both genetically based and due to environmental factors, predispose to anxiety disorders. Behavioral inhibition, a moderately heritable trait, is a marker in infants of risk for anxiety disorders in adolescence, but the quality of parenting these infants receive is a mediating variable. Animal models of maternal care have made strides in our understanding of how early environment can produce lifelong biases towards anxiety responses to stress versus adaptive coping. The first two postnatal weeks are a critical period during which serotonin 1A receptors establish normal anxiety-like behavior in the adult. High levels of maternal care in the form of pup licking delivered in the first postnatal week results in adult resistance to behavioral and endocrine manifestations of stress-induced anxiety. Pup licking increases the expression of hippocampal glucocorticoid receptors which places the HPA axis under tighter negative feedback control. The mechanism of this increased expression may be via epigenetic reduction of gene silencing of a promoter region of the glucocoricoid receptor in the hippocampus. These findings may inform future approaches to early intervention of prevention of anxiety disorders.

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CHAPTER

# 21 Neurobiologic Foundations of Mood Disorders

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In his classic paper, Mourning and Melancholia, Freud provided a vivid clinical description of what we now call major depression, as well as a pscyhodynamic formulation. Freud acknowledged that some forms of depression were biological in origin. The past 40 years have witnessed a major effort to understand the biology of depression and the major affective disorder, manic depression. This chapter highlights the history of biological approaches to mood disorders and then reviews recent advances in understanding the neurobiology of these complex disorders.

Perhaps the major development in the past decade has been a shift from a view of depression as a relatively straightforward disorder of monoaminergic function to a more nuanced view of multiple causal steps ranging from alterations in neuronal second messenger systems to dysregulation of growth factor, peptide, and transmitter systems. These approaches have led to the investigation of decreased activity of neurotrophins and neurogenesis in specific brain regions and to altered activity in novel circuits. In each of these areas, available technology has generated new findings, which have spurred new theories of etiology.

## Nomenclature

The modern era of biological research on affective disorders depended on the development of a reliable classification. Investigators in the United Kingdom and Germany took the lead in classifying depressions. Three major distinctions were made. The first distinguished endogenous from nonendogenous depression. Endogenous depression referred either to a depression that was not precipitated by external events or to depression with prominent biological symptoms akin to melancholia. Over time it was recognized that some patients developed severe melancholic depressions that were clearly precipitated, so that the diagnostic significance of external precipitation for major depression was dropped in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III). The second distinction was the qualifier psychotic versus nonpsychotic. Originally connoting severe or nonreversible, a psychotic affective disorder came to mean "characterized by delusions or hallucinations".

The last distinction separated unipolar depression from bipolar, or manic-depressive disorder. Emil Kraepelin, whose nosology of major psychiatric disorders anticipated DSM-III, saw severe recurrent unipolar depression as a form of manic-depressive illness. Over time, family history data and risk for mania in probands led to a distinction between the two disorders, which is reflected in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR). More recent interpretations of evidence from family studies, adoption studies, and susceptibility gene studies have blurred this distinction, suggesting that unipolar depression and bipolar disorder are on a continuum of major affective disorders. Some of this evidence for this view is discussed below.

Major depression today is characterized in DSM-IV-TR by the presence of five of nine possible symptoms that last for at least 2 weeks. These symptoms include low mood, decreased energy or agitation, impaired concentration, anhedonia, sleep disturbance, appetite disturbance, suicidal ideation, guilt, and diurnal variation. These were derived empirically and while reliable, their validity has not been demonstrated definitively. The syndrome of major depression can be further specified as melancholic, atypical, or severe and as with or without psychotic features. There

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are some data to support these differentiations; however, debate continues on the optimal subclassification of depressive disorders.

Two symptom clusters that are common in depression but that are not included as specific criteria for a major depressive episode are anxiety and chronic pain. Both are seen in some 45–75% of depressed patients but neither are core criteria. Anxiety was not included in part because there was an inherent bias in DSM-III and DSM-IV-TR to distinguish between anxiety and depressive disorders. However, these symptoms frequently co-occur. Pain was not included because at the time DSM-III and DSM-IV-TR were written there was little epidemiologic data to indicate how commonly it accompanied depression or whether the comorbidity that was seen in medical settings generalized to broader populations. Recent data indicate that chronic pain is common in depressive subjects in the community.

Bipolar disorder includes manic or hypomanic episodes alternating with depressive episodes, with periods of normal mood between episodes. The diagnostic criteria for a manic episode include a cluster of symptoms lasting at least one week: euphoric or irritable mood accompanied by psychomotor acceleration or agitation, impulsivity, hypersexuality, inflated self-esteem or grandiosity, pressured speech, which is rapid and difficult to interrupt, and flight of ideas, a stream of thoughts that are only loosely connected. The distinction between full-blown mania and so-called hypomania is one of degree. The depressive episodes of bipolar disorder are phenomenologically indistinguishable from unipolar depressions.

## Genetics

### Behavioral Genetics

#### Family, Twin, and Adoption Studies

Family, twin, and adoption studies provide inferential statistical evidence for genetic and/or environmental contributions to the etiologies of mood disorders. Family studies provided the initial evidence of the possibility of a genetic basis for mood disorders. Family studies demonstrated familial clustering among first-degree relatives for both unipolar and bipolar disorders. A review of family studies by McGuffin and Katz (1986) covered the findings for both. Bipolar disorder was found to have an average lifetime morbid risk among first-degree relatives of 8% compared to a base rate of 1% in the general population. For unipolar major depression the rates were nine and 3%, respectively. Family studies also revealed that first-degree relatives of bipolar depressed probands are more likely than persons in the general population to experience unipolar depression, whereas patients with unipolar depression are not at increased risk for bipolar depression. One interpretation of this asymmetry is that unipolar and bipolar depression may not be fully distinct diagnostic categories, but rather comprise a dimension on which unipolar depression is less severe than bipolar disorder.

Family studies have also served as initial tests of the validity of some of the subtypes of affective diagnoses discussed above. For example, family studies have not supported the reactive versus endogenous distinction. On the other hand early onset depression appears to be a more severe form of unipolar depression, if not a separate category, because when offspring of parents with early onset major depression (i.e., before age 20) are compared to offspring of parents with later onset major depression, the former are twice as likely as the latter to themselves suffer at some point from depression (Weissman et al. 1988). Some family studies of therapeutic response to medications have observed familial trends (Tsuang and Faraone 1990).

Family studies showing a correlation between genetic relatedness and disease risk cannot separate the contributions of genetic relatedness from that of shared environment. However, twin and adoption studies do address that distinction. Twin studies can be thought of as human experiments of nature in which the independent variable is the degree of genetic relatedness (mono- versus dizygous twins), while the environment is constant (under the so-called equal environments assumption, that the amount of shared environment within monozygous and dizygous twin pairs is the same). By contrast in adoption studies the environment varies. Twin studies estimate heritability of a disease by comparing the rate of concordance for a disease in monozygous versus same-sex dizygous twin pairs. The degree of shared environment is assumed to be unaffected by whether the twins are mono- or dizygous. An approximation of the disease's heritability is obtained by doubling the difference in concordance rates between the monozygous and diszygous samples.

Twin studies have provided strong evidence for a genetic contribution to the causation of both unipolar depression and bipolar disorder, with bipolar disorder tending to show higher heritability than unipolar depression. Such studies also indicate that genetic predispositions to mood disorders are generally higher when measured in samples of probands that have more severe cases, as indicated by hospitalization. Various studies have suggested heritabilities for bipolar disorder ranging from 64% (Allen 1976) to effectively 100% (Bertelsen et al. 1977), and in aggregate suggesting a heritability of about 80%. These same studies and two others of unipolar depressed hospitalized patients (McGuffin et al. 1996, Torgersen 1986) found monozygous twin concordances of about 40% and dizygous concordance rates ranging from 11–20%, suggesting a heritability up to 50%. Studies among population-based samples of twins, which include a majority of less severe cases of depression, generally reveal less heritability. Importantly. If concordance among monozygous twins for a disorder is less than 100%, there must be nongenetic components of the risk for that disorder. Thus, the twin studies of the major affective disorders suggest that there are important, though unspecified, environmental components to the pathogeneses of these disorders, especially unipolar depression.

Adoption studies have confirmed the twin-study evidence of a substantial genetic contribution to bipolar disorder. The so-called adoptees' study method separates genetic from environmental influences by comparing disease rates of adopted offspring of affected biological mothers and unaffected biological mothers. Another common design, the adoptees' family method, compares rates of the disease in the first-degree relatives of affected and unaffected adoptees. The rate of disease concordance of adoptive offspring with their biological relatives is used as an index of heritability, while the concordance of the adoptive offspring with their

adoptive relatives provides an estimate of the influence of shared environment. Mendelewicz and Rainer (1977) found that among adoptees with bipolar disorder versus control adoptees, 7% of biological parents of bipolar adoptees had bipolar disorder as opposed to none of the biological parents of the control adoptees. The rates of bipolar disorder in the adoptive parents of both groups did not differ substantially. Taken together, the data of this study are consistent with a predominant genetic contribution to bipolar disorder. The evidence for genetic contributions to unipolar depression from adoption studies is less clear-cut. However, the study by Mendelewicz and Rainer (1977) strengthens the impression from family studies for a genetic overlap between bipolar disorder and unipolar depression. Specifically, biological parents of bipolar adoptees had a rate of unipolar depression of 21% compared with 2% among the biological parents of control adoptees.

## Susceptibility Gene Discovery for Affective Disorders

Evidence from twin or adoption studies that a disorder is heritable implies the existence of genes that confer risk for that disorder. No common psychiatric disorder has been found by study of family pedigrees to follow simple single gene Mendelian inheritance patterns. Most psychiatric disorders are polygenic, that is, they result from the combined effects of variants of multiple genes each of which is responsible for a relatively small proportion of risk for the disorder. The identification of specific genes opens up the ability to directly investigate molecular mechanisms of psychiatric diseases leading from genotype through cell biology and neural circuitry to behavioral phenotype, paving the way for more effective and more specific treatments and perhaps preventions.

The techniques that are used to identify specific candidate susceptibility genes include cytogenetics, linkage analysis, positional cloning, and association studies. Studies testing the association of candidate genes with a disease of interest must have appropriate control samples. Generally the unaffected comparison group and the affected subjects should be drawn from the same ethnically homogeneous population to control for genetic background. If an association is found, the gene's role as a susceptibility gene for the disorder must be validated by replication in other populations.

Among the first susceptibility genes to be identified was that for the serotonin transporter, the protein responsible for the reuptake of the neurotransmitter serotonin at synapses. This protein is the target of the most commonly used antidepressant medications, the serotonin selective reuptake inhibitors. Studies have implicated polymorphisms in the promoter region and in an intron of this gene. A Croatian study compared patients with major depression with healthy controls on two polymorphic regions of the serotonin transporter gene, a 44-base pair insertion/deletion in the promoter region and a variable number of tandem repeats in the second intron (Bozina et al. 2006). In this study, the short allele of the polymorphism in intron 2 was associated with major depression.

The human genome project has facilitated the task of identifying susceptibily genes. Many studies exploit the mapping on the genome of thousands of single nucleotide polymorphisms (SNPs), which can be detected in the DNA of subjects and are used to pinpoint the location, and identity of the allele associated with the disease of interest. Thus, the number of genes implicated in the causation, severity, or treatment responsiveness of mood disorders has proliferated. Some of these have been identified by just one study, often in relatively homogeneous samples from one ethnic group or one country, and require replication for validation.

Using SNP technology, the gamma amino butyric acid (GABA) transmitter system has been studied for a possible role in the genetics of depression. From a population based twin sample, cases and controls were selected for having extreme high or low scores on a genetic factor representing major depression and several anxiety-disorder diagnoses (Hettema et al. 2006). This genetic risk factor was tested for its association with SNPs in the genes of two enzymes that synthesize GABA from glutamate, glutamic acid decarboxylase (GAD) 1 and 2. Several of the 6 SNPs tested in GAD1 were associated with the pathologies of interest and formed a common high-risk haplotype that was more frequent in cases than controls.

Another recent study investigated 21 SNPs in a family of genes for cyclic phosphodiesterase nucleotides, which hydrolyze the intracellular second messengers cAMP and cGMP (Wong et al. 2006). Because this degradation of these second messengers has the effect of downregulating the cell's response to extracellular signals such as neurotransmitters, hormones and growth factors, PDE genes were considered as depression susceptibility candidates. Polymorphisms in the gene for PDE11A in Mexican Americans were found to be associated with either the diagnosis of major depression or with antidepressant-induced remission from it. In addition a specific haplotype, GAACC, was found to be significantly associated with depression. Further SNPs in PDE9A and PDE1A were associated either with the diagnosis or with therapeutic response, respectively.

The angiotensin converting enzyme (ACE) gene has also been considered a potential candidate gene for depression for two reasons. First because of ACE's putative influence on the hypothalamic-pituitary-adrenal axis, which is hyperactive in a large proportion of patients with major depression, and second because this gene is known to be associated with cardiovascular disorders, which themselves are correlated with risk for major depression. Thirty-five SNPs in this gene were tested among patients with unipolar depression and controls (Baghai et al. 2006). Using an internal replication strategy, one SNP, rs4291, located in the gene's promoter region was found to be significantly associated with a diagnosis of depression. Furthermore, the T-allele of this SNP was associated with depression and the depressed T-allele carriers had both high ACE serum levels and hypothalamic–pituitary–adrenal (HPA) axis activity, suggesting that this allele could represent a common risk for both depression and cardiovascular disease.

In light of this finding, it may not be surprising that evidence for another susceptibility gene involved directly in the regulation of the HPA axis, the glucocoritcoid receptor, has been found. HPA axis dysfunction found in major depression may be due to impaired glucocorticoid signaling, perhaps mediated by the glucocorticoid receptor. The N363S and BCII polymorphisms are associated with glucocorticoid hypersensitivity whereas the ER22/23EK polymorphism is

correlated with resistance to glucocorticoids. Four hundred and ninety depressed inpatients and 496 healthy controls were genotyped and investigated for HPA axis function and response to antidepressant treatment (van Rossum et al. 2006). Significantly, more depressed patients than controls were homozygous for BCII or carried the ER22/23EK polymorphism. In addition, the ER22/23EK polymorphism was associated with faster response to treatment.

The P2RX7 gene is a purinergic adenosine triphosphate (ATP)-binding calcium channel expressed in certain brain neurons and microglial cells. This gene was considered to be a candidate risk gene for depression because of its location in a in a chromosomal region, chromosome 12q24.31, that had previously been found by linkage and association studies to be a susceptibility locus for mood disorders. German patients with major depression were compared with controls from the same population for the presence of 29 SNPs in or near the P2RX7 gene (Lucae et al. 2006). One nonsynonymous SNP within the coding region of the P2RX7 gene, rs2230912, was found to be significantly associated with major depression. This SNP alters the amino acid in the C-terminal cytosolic domain of the P2RX7 channel protein. Importantly, this same SNP had previously been found to be associated with the diagnosis of bipolar disorder, providing molecular evidence of the suggestions from family studies that unipolar major depression and bipolar disorder lie on a severity dimension of mood disorders.

Some studies have focused on the genetic predisposition for the comorbidity of depression and another illness. For example, the short variant of the functional polymorphism in the serotonin transporter linked promoter region (5-HTTLPR) was associated with post-stroke depression (Ramasubbu et al. 2006). Other studies have focused on genetic predispositions for specific clinical features of depression such as suicide and self-injurious behavior. One study, using DNA extracted from blood or frozen brain tissue, compared depressed patients who had completed suicide with depressed controls on the frequencies of two polymorphisms in the serotonin transporter gene. These polymorphisms are the same ones that were studied for an association with the diagnosis of depression in the Croatian sample discussed above (Bozina et al. 2006). Namely, a 44-base pair insertion/deletion in the promoter region, and a variable number of tandem repeats in intron 2, containing either 9, 10, or 12 copies of a 17-base pair element. Both of these polymorphisms affect the expression level of the gene. There was a significant association between completed suicide and the intron 2 variant containing 10 copies of the repeated element, which has lower expression than the 12 repeat allele (Lopez de Lara et al. 2006). Another study found that patients with depression who carry the T allele of G protein beta3 (GNbeta3) were more likely to engage in self-mutilating behaviors (Joyce et al. 2006), especially younger depressed patients.

Candidate genes chosen for investigation because of their plausibility for a functional role in bipolar disorder include some involved in neurotransmitter systems that regulate of mood states. Meta-analyses of studies of relatively small samples have yielded significant evidence for three such genes each with small effects: monoamine oxidase-A (MAO-A) (Preisig et al. 2000), an enzyme associated with the outer mitochondrial membrane and distributed widely in the brain, which metabolizes the neurotransmitters, norepinephrine (NE) and serotonin; catechol-O-methyl transferase (COMT) (Jones and Craddock 2001), the enzyme most responsible for the metabolic inactivation of the neurotransmitter dopamine in the prefrontal cortex; and the serotonin transporter (5-HTT) (Anguelova et al. 2003), which inactivates serotonin released into synapses by returning it to the presynaptic cell ending. The locus for the d-amino acid oxidase activator (DAOA) gene, originally reported to be in linkage disequilibrium for schizophrenia, has recently been found in U.S., German, and British samples to be in linkage disequilibrium with bipolar disorder (Chen et al. 2004, Schumacher et al. 2004, Williams et al. 2006). There is as yet no evidence for a functional or pathological mechanism; however, the gene for d-amino acid oxidase (DAO), which is activated by DAOA, lies in a region that has been implicated in recent genome scans, the 12q23 region (Ewald et al. 2002, Shink et al. 2005).

Finally, there is evidence for brain derived neurotrophic factor (BDNF) as a susceptibility gene. It affects multiple neural processes central to current hypotheses of mood disorders, that is, those involving loss of synaptic plasticity due to chronic stress and affects the actions of antidepressants (see below). In the developing brain BDNF is important in the growth and survival of certain types of neurons; it is involved in activity-dependent plasticity in the mature brain (Duman 1999). The gene for BDNF is located in the chromosomal region 11p13, which has been implicated in some linkage studies of bipolar disorder. A single SNP, which codes for an amino acid substitution of the amino acid valine to methionine in the pro-BDNF precursor molecule, could potentially be responsible for functionally important differences in the processing of BDNF itself. Three family association studies of Caucasian samples revealed a higher proportion of the valine (Val) allele in bipolar individuals (Sklar et al. 2002, Neves-Pereira et al. 2002, Geller et al. 2004). This association has not been found in other populations (Skibinska et al. 2004, Hong et al. 2003). One study found an association between the Val allele and rapid cycling within the bipolar group (Green et al. 2006).

## Gene Environment Interactions

As suggested above, the major affective disorders cannot be explained either by genetic susceptibility or environmental factors alone. Twin and adoption studies of mood disorders generally indicate higher heritabilities for bipolar disorder than for unipolar depression. The corollary of these findings is that environment may play a larger role in the causation of unipolar depression than bipolar disorder (Paykel 1994, Paykel 2003). Pending the conclusive demonstration of specific environmental risks in human depressive disorders, some animal models, discussed below, have begun investigating the possible mechanisms of candidate environmental insults that are suggested by human population and clinical studies. However, such studies cannot address a larger question, namely by what mechanisms do environmental insults precipitate depression in some people but not others. This question is addressed by interesting recent studies designed to detect interactions between specific candidate risk genes and specific candidate environmental insults in

mood disorders. This design has the potential to not only discover these kinds of interactions, but also to potentially reveal novel susceptibility genes that may act only under certain adverse environmental conditions and would otherwise remain unknown.

A functional variable number tandem repeats (VNTR) polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) produces short (s) and a long (l) sequence variants. The s variant is associated with lower transcription efficiency of the promoter than the l variant, resulting in less mRNA and protein (Lesch et al. 1996). Eight hundred forty-seven 26-year-olds in a New Zealand birth cohort were genotyped for the 5-HTTLPR s and l variants (Caspi et al. 2003). Fourteen kinds of serious stressful life events that occurred in the prior 5-year interval were determined by self-report. There were no differences across the genotypes in the number of stress events experienced. A standardized questionnaire based on DSM-IV-TR, and informant reports, were used to quantify depressive symptoms and detect the diagnosis of an episode of major depression in the year prior to the study. Statistical analyses revealed that the impact of life events on depressive symptoms and on the categorical diagnosis of major depression was significantly stronger in individuals carrying one or two copies of the s allele versus individuals who are homozygous for the lallele. A parallel finding applied to suicidal ideation or suicide attempts: that is, stressful life events predicted these symptoms in carriers of the s allele but not in l/l homozygotes.

One study extended this result to depression during adolescence: an interaction between the 5-HTTLPR polymorphism and environmental risk in was found for females (Eley et al. 2004). Studies with similar designs in samples of older individuals have not consistently replicated the effect (Wilhelm et al. 2006, Gillespie et al. 2005, Surtees et al. 2006). Thus the interaction may occur primarily in younger persons.

Each susceptibility gene discovered to date accounts for only a small proportion of the variance in the population for the occurrence of a mood disorder. Thus mood disorders may require the additive or interactive effects of multiple genes as well as the interactions of genes and environmental conditions. The gene by environment interaction design has been elaborated in more complex designs that can detect gene by gene as well as gene by environment interactions. For example, early maltreatment places children at risk for depression, yet some succumb to the disorder while others are resilient. A study tested whether gene by gene or gene by environment interactions may explain the differences and whether social support moderates the risk. One hundred nine abused children and 87 nonabused controls were genotyped for alleles in two genes implicated as susceptibility genes for depression: (1) the VNTR short variant of the 5-HTTLPR and (2) the BDNF Val66Met substitution, both discussed above. There was a significant three-way interaction between the 5-HTTLPR and BDNF genotypes and maltreatment. Children with both copies of the 5-HTTLPR s allele and the Met substitution for BDNF were most vulnerable to depression, but only if they were maltreated. There was also a significant four-way interaction in which social supports moderated the risk for depression.

### Gene Expression in Mood Disorders

The use of microarrays provides an approach for high throughput expression profiling of the entire human genome, offering the potential to identify genes whose altered expression could contribute to neuropsychiatric illnesses. However, the application of this approach to complex, heterogeneous tissue such as brain poses novel challenges for optimizing signal strength and achieving sufficient sensitivity to observe small changes. In addition, validating identified gene expression changes and elucidating the role of these genes in behavioral abnormalities poses further challenges. In spite of these problems, recent studies have begun to make progress in profiling gene expression changes in mood disorders.

Two studies have focused on subfamilies of genes that have been implicated in mood disorders based on preclinical and clinical work. The first of these demonstrates altered expression of genes in the fibroblast growth factor (FGF) family in postmortem tissue of depressed subjects relative to matched controls (Evans et al. 2004). This includes decreased expression of FGF-2 and FGF receptors 2 and 3 in regions of the prefrontal and cingulate cortices implicated in depression. These effects were observed in two separate cohorts of depressed subjects, providing evidence of the replicability of these effects. A role for FGF-2 in depression is also supported by preclinical studies demonstrating that the expression of this factor is increased by antidepressant treatment (Mallei et al. 2002) and more generally by evidence for a neurotrophic hypothesis of depression (see below).

A second paper from this group highlights altered expression of molecular components of the glutamate and GABA neurotransmitter systems (Choudary et al. 2005) in major depressive disorder and bipolar disorder. This study reports that the patients with major depression had decreased expression of genes in the prefrontal cortex that control synaptic and extrasynaptic levels of glutamate. Reduced expression of these genes, two types of glutamate transporters and an enzyme that converts glutamate to nontoxic glutamine could result in excessive levels of glutamate and, as a consequence, neurotoxic damage. The astroglial localization of these glutamate signaling regulators is vidence of glial cell involvement in depression and is consistent with reports of decreased neuroglia in depressed subjects (Ongur et al. 1998, Rajkowska et al. 1999, Cotter et al. 2001). This study also reports altered expression of several glutamate and GABA receptor subunits in major depression and bipolar disorder, and two GABA receptor subunits in patients with either diagnosis who had suicided. Additional studies will be needed to confirm these findings and further characterize the gene expression changes in depressed subjects, as well as studies to determine the functional significance of these changes.

## Pathogenic Mechanisms

### Transmitter Systems

The earliest approaches to the biology of depression revolved around (1) the function of neural monoamies, particularly the catecholamine; NE, or noradrenaline, and the indoleamine; serotonin and (2) neuroendocrine function, particularly the HPA axis, which is responsible for the synthesis and release of the stress hormone, cortisol. The

hypothesis that monoaminergic systems were dysfunctional in depression was first suggested by clinical pharmacologic observations, the so-called psychopharmacologic bridge, that: (1) the antihypertensive agent, reserpine, depleted monoaminergic stores and caused depression in some individuals, (2) monoamine oxidase inhibitors (MAOIs), which metabolize bioamines in neurons and were originally used to treat tuberculosis, were potent antidepressants, and (3) the tricyclic antidepressant (TCA), imipramine, blocked the reuptake of NE into presynaptic neurons and improved mood. Initially American researchers focused on the NE hypothesis (Bunney and Davis 1965, Schildkraut 1965, Schildkraut and Kety 1967) whereas British researchers favored an indoleamine hypothesis (Coppen 1968). Schildkraut 1965 and Schildkraut and Kety (1967) noted that a functional deficiency of NE appeared to be associated with depressive states and a functional excess of NE seemed to be associated with elation, implying a role for catecholamine transmission in the mechanisms of both depression and mania. Coppen's (1968) paper suggested parallel actions of serotonin. Early animal models and additional observations from clinical psychopharmacology bolstered these hypotheses. For example, in rats, stress caused alterations in behavior and in NE turnover, some of which were reversed by antidepressants. The introduction of the tricyclic and selective serotonin reuptake inhibitor (SSRI) classes of antidepressants, which inhibit the actions of the NE and serotonin transporter molecules, strengthened the psychopharmacologic bridge.

The spychopharmacologic bridge hypothesis received support from studies of cerebrospinal fluid in which levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) were noted to be decreased in depressed patients who later suicided especially by violent means. Altered transport activity in blood components and decreased binding for serotonin reuptake in depressed patients, using displacement of the serotonin reuptake inhibitors imipramine, a TCA, and paroxetine, an MAOI, was demonstrated. Delgado and Charney developed an elegant tryptophan depletion strategy. Depressed patients who had responded to SSRI antidepressants demonstrated relatively rapid relapse of symptoms when placed on a diet that was low in tryptophan, the serotonin precursor (Delgado et al. 1999). They similarly demonstrated that chemically inhibiting the biosynthesis of NE would precipitate relapse in patients who had responded to noradrenergic agents (Heninger et al. 1996).

However, the initial central amine hypothesis proved to be simplistic, as shown by a large body of research using indirect measures of NE and serotonin function beginning in the late 1970s. Because brain tissue levels of the central amines and their associated enzyme and transporter molecules could not be measured, biochemical indices of NE and serotonin function were measured in the periphery and were assumed to be proxies for brain central amine function. Such studies began to reveal the complexity of the role of central amines in major affective disorders. For example, urinary excretion of the NE metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG), viewed as an index of noreipnephrine turnover in the brain, was found to be lower in bipolar depression than in either unipolar depression or controls and was heterogeneous in unipolar depression (Schatzberg et al. 1982).

At the same time, abnormalities in the enzymes and transporter molecules that inactivate NE and serotonin in extracellular spaces and synaptic clefts were hypothesized to account for the altered function of these transmitters in mood disorders. Platelet MAO activity was used as a presumptive marker for the activity of brain MAO, which metabolizes both NE and serotonin. These studies showed intriguing but inconsistent differences between platelet MAO activity in unipolar depressives, bipolar depressives, and well controls (Edwards et al. 1978, Samson et al. 1985). A related hypothesis, based in part on animal lesion studies (McIntyre et al. 1984) and on correlations found in clinical samples, suggested that serotoninergic activity regulates the activity of the HPA axis. This was of interest because cortisol hypersecretion in some patients with endogenous depression (see below) was postulated as a pathogenic mechanism. Thus, the central amine hypofunction and HPA hyperfunction hypotheses were linked by the hypothesis that high MAO activity in depressed patients, which would suggest low serotoninergic activity, might be associated with hypersecretion of cortisol. Several studies found that platelet MAO activity had a positive correlation with nonsuppression of serum cortisol following administration of the synthetic glucocorticoid dexamethasone in major depression but not in bipolar depression (Schatzberg et al. 1983, Bagdy et al. 1986, Pandey et al. 1992).

Direct study of the aminergic neurotransmitter systems in postmortem brain tissue has been ongoing for several decades and since the 1990s has benefited from the use of modern, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), diagnoses established from premortem medical records or structured interviews of the next of kin. Reviewing postmortem studies of bipolar disorder, Vawter et al. (2000) concluded that NE turnover, as measured by the ratio of NE's main metabolite, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), to NE, may be increased in areas of the cortex and thalamus, while 5-hydoxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, and the serotonin transporter (5-HTT) may be reduced in the cortex. Membrane suspensions from postmortem tissues are used to test the functional levels of the aminergic neurotransmitter receptors. These receptors are coupled to G-proteins located on the cytoplasmic side of the cell membrane, which transduce the extracellular neurotransmitter signal into second messenger intracellular signals. When a neurotransmitter molecule binds to its receptor, the activated G-protein exchanges a guanine diphosphate (GDP) molecule for a guanine triphosphate (GTP). This process can be quantified by measuring the binding of a radiolabeled GTP analog to the G-protein. This method has demonstrated that in the frontal cortex presynaptic $\forall_{2A}$ autoreceptors, which decrease the release of NE, are four times more sensitive in suicide victims with mood disorders than those of controls (González-Maeso et al. 2002). Clearly investigating postmortem brain tissue provides the ability to study anatomic structures at very fine levels of resolution. Such studies must use age, gender, and postmortem interval-matched controls. However, important limitations include the availability of brains for sufficiently large sample sizes, the possible effects of various causes of death, including suicide, and whether an episode of the

affective disorder under study was current at the time of death.

Among the most exciting new methods for elucidating the pathophysiology of major affective disorders is neuroimaging. Positron emission tomography (PET) in conjunction with increasingly sensitive and specific radiolabeled ligands that directly measure MAO and serotonin transporter activity in the living brain are providing a new level of detail and complexity to our view of the role of the central amines in mood disorders. The density of MAO-A, the form of MAO that has high affinity for both serotonin and NE, was determined with PET using harmine labeled with carbon 11, a radioligand selective for MAO-A. High levels of MAO-A were found in medication-free patients with major depression compared to controls in each region that was tested: the prefrontal cortex, the anterior and posterior cingulate cortices, anterior temporal cortex, caudate and putamen, thalamus, midbrain, hippocampus, and parahippocampus (Meyer et al. 2006). The use of a new PET ligand for the serotonin transporter, carbon 11 labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB), has greatly improved selectivity and specificity for imaging the serotonin transporter (5-HTT). One group has investigated the role of 5-HTT in unipolar and bipolar depression. They first investigated unmedicated depressed bipolar disorder patients versus health controls: the depressed bipolars had high 5-HTT binding potential in the thalamus, dorsal cingulate cortex medial prefrontal cortex, and insula, but decreased 5-HTT binding in the brainstem at the level of the pontine raphe nuclei compared to healthy controls (Cannon et al. 2006). There were also differences between bipolar patients who had made suicide attempts compared to those who had not and to controls.

The same group compared 5-HTT binding potential in unmedicated depressed patients with unipolar versus bipolar disorder and well controls. They found both overlapping and distinct regions of increased 5-HTT binding potential in bipolar and unipolar depressed patients. Greater serotonin binding potential in the thalamus, insula and striatum was found in both unipolar and bipolar depressed patients compared to controls. By contrast, only the unipolar depressives had high 5-HTT binding in the vicinity of the periaqueductal gray compared to the other two groups, whereas only the depressed bipolar disorder patients had high 5-HTT binding potential in the vicinity of the pontine raphe nuclei (Cannon et al. 2007). These studies are beginning to permit the construction of a regional brain map of the serotonin system's role in depression. Development of similarly sensitive and specific radioligands for the in vivo study of the norepinephrine transporter in major affective disorders is obviously of considerable interest, but to date has not been successful (Severance et al. 2007).

## Neuroendocrine Systems: Role of the Hypothalamic Pituitary Adrenal Axis

The observation of a strong positive correlation between uniary MHPG and cortisol (Rosenbaum et al. 1983) established a coupling between the catecholamine and HPA axis function. Dysregulation of circadian rhythms of neurohormone and neuroendocrine secretion has been proposed as a mechanism of depression. Koenigsberg et al. (2004) found evidence that the coupling of the circadian rhythms for the secretion of NE, cortisol, and other neurohormones such as growth hormone and prolactin measured in serum, are phase advanced and possibly out of synchrony. Neuroendocrine approaches to mood disorders began with observations that stress in humans was associated with the release of cortisol from the adrenal cortex in parallel with the release of catecholamines from the adrenal medulla. In particular investigators began to describe abnormalities in the diurnal rhythm of the secretion of cortisol in major depression. Sachar's group demonstrated elevated pulses of cortisol in severely depressed patients particularly at night (1973). Some depressed patients were also found to lack the normal suppression of cortisol release after the administration of a synthetic glucocorticoid, dexamethasone, which works-via the hypothalamic-pituitary-adrenal axis feedback loop. Although nonsuppression of cortisol by dexamethasone is not a specific test for melancholia, at least two metanalyses have supported the observation that the test is highly abnormal in depressed patients with psychosis.

Cortisol release from the adrenal gland is stimulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn is controlled by corticotropin releasing hormone (CRH) produced in neurosecretory cells of the paraventricular nucleus of the hypothalamus and transported to the pituitary via a portal circulation. Investigators have demonstrated depressogenic effects of CRH in rats and monkeys. CRH levels have been reported to be elevated in depressed patients, while depressed patients have a blunted ACTH response to CRH in comparison to healthy controls.

The characterization of two brain receptors for cortisol was a further advance in understanding the role of the HPA axis in the pathogenesis of affective disorders. Mineralocorticoid receptors are high affinity receptors found largely in the hippocampus, whereas glucocorticoid receptors are low-affinity and distributed broadly throughout the brain. Mineralocorticoid receptor activity tends to maintain homeostasis by limiting the physiologic perturbation caused by a stressor, while glucocorticoid receptors contribute to recovery after the stress challenge (de Kloet and Derijk 2004). An imbalance of brain mineralocorticoid and glucocorticoid receptor activities is hypothesized to underlie HPA axis dysfunction and stress-related behaviors. Over activity of cortisol in the brain has been hypothesized to play a role in psychotic depression (Keller et al. 2006), with excess secretion of cortisol occurring during the evening nadir in psychotic depressed patients compared to nonpsychotic depressives and normal controls. Glucocorticoid synthesis inhibitors and antagonists of CRH and of glucocorticoid receptors are under active investigation as treatments for psychotic and nonpsychotic depression (Norman and Burrows 2007).

Genetics has opened up other new avenues to explore the HPA axis and its relationship to depression. Co-chaperone and chaperone proteins for the glucocorticoid receptor have been identified and SNPs for a co-chaperone have been reported to be associated with greater cortisol responses to dexamethasone-CRH challenge and to be associated with rapid antidepressant response as well as a greater prevalence of relapse. Similarly, genetic glucocorticoid receptor variations have also been identified and may have predictive value for medical illneses as well as depression.

## Intracellular Signal Transduction Pathways and Growth Factors

The actions of neurotransmitter and endocrine systems on neuronal function are mediated by regulation of complex intracellular signaling pathways. Elucidation of the alterations of these pathways in depression and the influence of antidepressant treatment on these pathways provides insights on the pathophysiology and treatment of mood disorders. This section highlights and discusses a few of the key signaling pathways, the cAMP response element binding (cAMP-CREB) and mitogen-activated protein (MAP) kinases pathways, that have been implicated in the mood disorders. These signaling cascades have also been implicated in learning and memory and are discussed in other chapters in this volume. Other pathways to consider include the phosphatidylinositol pathway and glycogen synthase kinase cascade, both of which have been implicated in the actions of mood stabilizing agents as well as antidepressants, (see Manji et al. 2001, Nestler et al. 2002, Coyle and Duman 2003, Einat and Manji 2006).

## Cyclic AMP–CREB Cascade

### Receptor Coupled cAMP Signaling System

The cAMP system is one of the earliest identified and characterized intracellular signaling pathways. This pathway is comprised of adenylyl cyclase, the enzyme that catalyzes the formation of the second messenger cAMP, and stimulatory and inhibitory G proteins, Gs and Gi, that couple to neurotransmitter receptors that either activate or inhibit formation of cAMP (Nestler and Duman 2006). There are several NE and 5-HT receptors that couple to the cAMP cascade, including stimulatory ($b_1$-adrenergic, 5-$HT_4$, 5-$HT_6$, and 5-$HT_7$) and inhibitory subtypes ($a_2$-adrenergic, 5-$HT_{1A}$, 5-$HT_{1B}$, and 5-$HT_{1D}$ to name a few). There are also several isoforms of adenylyl cyclase that differ in sensitivity to regulation by $Ca^{2+}$/calmodulin as well as in their ability to free another G protein subunit, Gb. The actions of cAMP are mediated by activation of cAMP-dependent protein kinase (PKA), which regulates many cellular proteins via phosphorylation. One of the key factors that underlies the actions of receptor coupled cAMP signaling on gene expression is the phosphorylation and activation of the transcription factor, CREB protein. The receptor coupled cAMP system has been the focus of depression research for over 25 years and this work has contributed to our understanding of the actions of antidepressant treatments.

### Regulation by of the cAMP-CREB Cascade by Antidepressant Treatment

Early studies reported that the ability of b-adrenergic receptors to stimulate cAMP formation is decreased by antidepressants, leading to the hypothesis that the actions of these treatments is mediated by desensitization of this receptor coupled second messenger system (Banerjee et al. 1977). However, subsequent studies of the intracellular components of this cascade demonstrate the opposite effect, that this pathway is up-regulated by antidepressants. This includes increased coupling of Gs-adenylyl cyclase, increased levels of PKA (Nestler et al. 1989, Perez et al. 1989), and increased levels of CREB (Nibuya et al. 1996, Thome et al. 2000). In addition to PKA, CREB is also regulated by other signaling pathways, including Ca2+/camodulin dependent PKAs and MAP-extracellular-signal-regulated kinase (MAP-ERK) signaling cascades, which also have been implicated in the actions of antidepressant treatment (see below, and review by Tardito et al. 2006).

These studies illustrate an important concept when interpreting neurotransmitter receptor data, particularly from in vitro studies but also in vivo receptor imaging studies. Although antidepressant treatments increase levels of b-adrenergic stimulation of cAMP formation, as would be expected when levels of NE are increased in response to blockade of reuptake or metabolism, sufficient numbers of receptor remain to stimulate cAMP formation in the presence of enhanced synaptic levels of neurotransmitter (see Duman 2004c). Another important concept resulting from this work is that persistent activation in response to chronic, but not acute, antidepressant treatment leads to up-regulation of the cAMP-PKA-CREB cascade. This represents a type of neural plasticity that contributes to the functional actions of antidepressant in animal models of depression and antidepressant response (see below).

Up-regulation of the cAMP-CREB cascade occurs with different classes of antidepressants, including both NE and 5-HT selective reuptake inhibitors (Nestler et al. 1989, Nibuya et al. 1996, Thome et al. 2000, Blom et al. 2002, Laifenfeld et al. 2005). In addition, these effects require chronic antidepressant treatment, consistent with the time course for the therapeutic action of antidepressants. Although it is difficult to determine the therapeutic relevance of these effects, there are several lines of evidence that support the hypothesis that up-regulation of the cAMP-CREB pathway contributes to a therapeutic response, and that disruption of this system could even contribute to depression. First, postmortem studies have found that levels of CREB are decreased in the brains of depressed subjects, and increased in subjects taking antidepressant medication at the time of death (Dowlatshahi et al. 1998, Yamada et al. 2003). Second, rolipram, a drug that activates the cAMP-CREB cascade by blocking the breakdown of cAMP, produces antidepressant effects in human subjects, as well as in animal models. Studies to test the action of the cAMP-CREB cascade in animal models of depression are discussed below as well as the consequences of these findings for drug development.

### Functional Consequences of Altered cAMP-CREB Signaling

To determine if up-regulation of cAMP-CREB signaling contributes to the actions of antidepressants, studies have been conducted using viral vectors and mutant mouse models. Viral expression of CREB in the hippocampus, the limbic brain structure where CREB is increased by antidepressant treatment, produces an antidepressant-like effect in the forced swim test (FST) and the learned helplessness (LH) paradigms (Chen et al. 2001a). These are referred to as behavioral despair models of depression that are responsive to antidepressant treatments (see below for discussion of behavioral models). In addition, overexpression of CREB in the amgydala, a region known to control fear and anxiety as well as emotion, also produces an antidepressant response in the LH paradigm in a state dependent fashion (Wallace et al. 2004). That is, when CREB is overexpressed in amygdala

after exposing animals to inescapable stress an antidepressant effect is observed, but when CREB is expressed before the inescapable stress it enhances the stress response and produces a pro-depressive effect. This is consistent with CREB acting as a mediator of neural plasticity and the ability of amygdala responses to be conditional based on the experiential state of the animal.

Studies of the nucleus accumbens, a target area of the mesolimbic dopamine system that controls motivation and reward, further demonstrate the region specific effects of CREB. Viral over-expression of CREB in this region produces pro-depressive effects in the FST, while expression of a dominant negative mutant of CREB in the nucleus accumbens produces an antidepressant response in the FST and LH paradigm (Pliakas et al. 2001, Newton et al. 2002). Studies of mutant mice carrying a null mutation of CREB exhibit a similar phenotype in the FST (Conti et al. 2002). Taken together, these data demonstrate that altered CREB expression or function influences behavioral models of depression in a region specific manner, consistent with the function of this transcription factor as a prime mediator of neural plasticity in a circuit and state dependent manner (see Carlezon et al. 2005, Blendy 2006).

Up-regulation of CREB indicates that there are target genes of this transcription factor that are regulated and that are directly involved in the function of antidepressants and the cAMP-CREB cascade. Several candidate genes that contain a cAMP response element (CRE), a promoter sequence that CREB binds to, have been examined, most notably the neurotrophic/growth factors BDNF and vascular endothelial growth factor (VEGF). These factors are up-regulated by antidepressant treatment and will be discussed in more detail below in the context of a neurotrophic hypothesis of depression. The induction of these genes demonstrates that antidepressant regulation of the cAMP-CREB cascade has functional consequences on gene transcription that could underlie, in part, the actions of these treatments.

### cAMP-CREB Cascade and Novel Therapeutic Agents

These studies raise the possibility of targeting the cAMP-CREB cascade for the treatment of depression and related mood disorders. There are several potential drug targets that can be considered, from receptors that stimulate this second messenger system, to adenylyl cyclase, PKA and CREB. Direct agonists of b-adrenergic or 5-HT receptors provide insufficient evidence to support the choice of one receptor subtype over another. There are very few examples of drugs acting at the level of PKAs or transcription factors. The most interesting and potentially useful stratety is to increase cAMP levels by blocking its degradation via inhibition of cAMP specific phosphodiesterase type IV (PDE4). Previous studies have demonstrated the feasibility of this approach. Rolipram, a selective inhibitor of PDE4, produces an antidepressant response in animal models of depression (Wachtel and Schneider 1986, Griebel et al. 1991, O'Donnell 1993, O'Donnell and Zhang 2004). Moreover, early clinical studies have demonstrated that rolipram administration has antidepressant efficacy in depressed subjects (Horowski and Sastre-Y-Hernandez 1985, Bobon et al. 1988, Fleischhacker et al. 1992). These positive actions of systemic rolipram administration indicates that the prevailing effect in the brain is an antidepressant response, not depressive as was found in some viral vector and mutant mouse models. However, there was some incidence of nausea in patients receiving rolipram, limiting the clinical utility of this agent.

Molecular cloning studies have renewed the interest in PDE4 as a target for drug development. These studies demonstrate that there are 4 different PDE4 isoforms, three of which are expressed in brain, PDE4A, 4B, and 4D, and all equally sensitive to rolipram. The 3 brain specific isoforms are differentially expressed in limbic structures, suggesting that one or more could mediate the antidepressant effects of rolipram, while another could underlie the unwanted side effects. Recent studies have demonstrated that PDE4A, PDE4B, and PDE4D are up-regulated in animal models and could thereby delay or counter the actions of antidepressants (Takahashi et al. 1999, Ye et al. 2000, D'Sa et al. 2004, Dlaboga et al. 2006). PDE4D is expressed in the area postrema, a region known to control emesis and could contribute to the nausea caused by rolipram (Takahashi et al. 1999). Studies are currently underway to directly test the role of each PDE4 isoform using mutant mice and to develop selective inhibitors of PDE4A, 4B, and 4D. Early studies demonstrate that PDE4D null mutant mice display an antidepressant profile in the FST, suggesting that this subtype could be involved in the actions of rolipram (Zhang et al. 2004). Further studies of PDE4A and PDE4B in this and other behavioral models will be needed to further identify the most important isoform target for the treatment of depression.

## Growth/Neurotrophic Factors in Depression and Antidepressant Actions

Several lines of evidence have contributed to a neurotrophic hypothesis of depression and antidepressant response, including data from basic and clinical studies. A brief review of neurotrophic/growth factor systems and signaling pathways will be discussed, followed by an overview of the data demonstrating the role of these factors in the pathophysiology and treatment of depression (Duman 2004a, Duman and Monteggia 2006).

### Neurotrophic/Growth Factor Systems

The nerve growth factor (NGF) family has been the focus of stress, depression and antidepressant studies, although recent work has also demonstrated a role for other growth factor systems, most notably insulin like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), and VEGF. The NGF family includes NGF, BNDF, neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). These factors were originally identified for their role in the development and survival of neurons, but it is now clear that members of the NGF family are expressed in the adult brain and continue to influence neuronal survival and protection, as well as many aspects of neuronal function, including neural plasticity and adult neurogenesis. IGF-1, VEGF, and FGF-2 are also differentially expressed in the adult brain and exert effects that overlap with NGF family members, as well as other functions.

### Neurotrophic/Growth Factor Signaling Cascades

The receptors for BDNF and other NGF family members have an extracellular binding domain and intracellular

tyrosine kinase domain. There are three receptors, TrkA, TrkB, and TrkC that bind with selectivity to NGF, BDNF, and NT-3/NT-4, respectively, although NT-3 can also bind to TrkB. Binding of a neurotrophic factor dimer to a receptor dimer is required for functional activation of the tyrosine kinase domain, leading to autophosphorylation and activation of multiple signal pathways. This includes the MAP or ERK kinase cascade, phosphatidyl inositol-3 kinase (PI-3K) and phospholipase Cg (PL-Cg) These pathways are activated by phosphorylation of or interaction with coupling proteins that link with effector/catalytic components of each. For the MAP kinase pathway, this includes phosphorylation of the adaptor protein Shc, which then couples with another adaptor protein Grb2, which in turn recruits the guanine nucleotide exchange protein Sos. This leads to loading of the membrane bound GTPase, Ras, which then recruits and activates Raf, the first kinase in the MAP pathway. Raf activates MEK that in turn phosphorylates and activates ERK. This leads to translocation of ERK to the nucleus where it regulates a number of transcription factors. ERK can also phosphorylate and activate RSK family kinases that can activate CREB.

Trk receptors also recruit and activate PI-3K via Shc and Grb2, leading to the activation of AKT, which has anti-apoptotic actions. Trk receptors directly phosphorylate and activate PLCg, leading to regulation of Ca2+ and PKA signaling pathways. All three of these pathways (MAP kinase, PI-3K, and PLCg) also serve as the major signaling cascades for other trophic factors implicated in depression (i.e., IGF-1, FGF-2, and VEGF).

## Atrophy and Cell Loss: Decreased Growth Factor Expression

Evidence from basic and clinical research studies have provided evidence of neuronal atrophy and cell loss in depression, supporting the possibility of altered neurotrophic and growth factor support in mood disorders. Basic research studies demonstrate that repeated stress causes atrophy of pyramidal neurons in the hippocampus and prefrontal cortex, characterized by a decrease in the number and length of apical dendrites (Wooley et al. 1990, Watanabe et al. 1992, Radley et al. 2004, McEwen 2005). Studies in rodent models have also demonstrated that stress decreases the proliferation of new neurons in the adult hippocampus and the number of glia in the adult prefrontal cortex (Gould et al. 1997, 1998, Czeh et al. 2001, Duman 2004b, Banasr et al. 2007). Decreased number of glia and size of neurons has also been reported in postmortem studies of depressed subjects (Ongur et al. 1998, Rajkowska et al. 1999, Cotter et al. 2001). This type of atrophy and cell loss could underlie the reduction in volume that is reported in the hippocampus and prefrontal cortex of depressed subjects (Bremner et al. 1995, Drevets et al. 1997, Sheline et al. 1999, 2001).

While the mechanisms underlying neuronal atrophy and cell loss are have not been fully determined, decreased neurotrophic factor support could play a role. Different types of acute and chronic stress, as well as physical, social and emotional stress decrease the expression of BDNF in the hippocampus and prefrontal cortex (Smith et al. 1995, Duman and Monteggia 2006). Other neurotrophic/growth factors are decreased by stress, including reduced levels of NGF (Ueyama et al. 1997) and VEGF (Heine et al. 2005). In addition, postmortem studies demonstrate that levels of BDNF, as well as B-Raf-ERK signaling, are decreased in suicidal depressed subjects (van Praag et al. 1999, Madsen et al. 2000, Malberg et al. 2000, Dwivedi et al. 2001, Nakagawa et al. 2002, Santarelli et al. 2003, Dwivedi et al. 2003, Duman 2004b, Karege et al. 2005, Dwivedi et al. 2006a, 2006b). Levels of BDNF in serum of depressed subjects are also decreased, which can be reversed with antidepressant treatment, providing a possible biomarker of depression and antidepressant response (Karege et al. 2002, Shimizu et al. 2003, Aydemir et al. 2004, Gervasoni et al. 2005, Karege et al. 2005). Taken together, these findings provide strong support for loss and/or dysregulation of trophic factor support in mood disorders.

## Antidepressant Treatment Increases Neurotrophic Factor Expression

In contrast to the effects of stress, antidepressant administration increases the expression of neurotrophic factors in limbic brain regions. Increased BDNF expression is observed with administration of different classes of antidepressants, including 5-HT and NE reuptake inhibitors, MAOIs, atypical antidepressants, and electroconvulsive therapy (ECT) (Nibuya et al. 1995, Nibuya et al. 1996, Duman and Monteggia 2006). It is notable that other treatments with antidepressant efficacy, also increase the expression of BDNF, including exercise, transcranial magnetic stimulation, AMPAkines, and NMDA receptor antagonists (see Duman and Monteggia 2006). Antidepressant treatment reverses the decrease observed with stress in animal models (Nibuya et al. 1995) and in postmortem brains of depressed subjects (Chen et al. 2001b). The actions of chemical antidepressants require repeated treatment, consistent with the time course for the therapeutic action of these agents. There are also negative reports, that antidepressant treatment does not increase the expression of BDNF, possibly due to uncontrolled (e.g., stress, activity) as well as controlled variables (e.g., dose, treatment time) (see Duman and Monteggia 2006). The regulation of ERK by chemical antidepressants has also been variable (Tiraboschi et al. 2004, Fumagalli et al. 2005), and additional studies will be needed to further characterize the regulation of this and other trophic factor signaling cascades by antidepressants.

In addition to BDNF, there are several other growth factors that are reported to be up-regulated by chronic antidepressant treatment, including VEGF (Newton et al. 2003, Warner-Schmidt and Duman 2007), IGF-1(Khawaja et al. 2004), and FGF-2 (Mallei et al. 2002). A postmortem microarray study has also found that the expression of FGF-2 is decreased in the brains of depressed subjects (Evans et al. 2004). The role of these factors in the neurogenic and behavioral actions of antidepressants is discussed in more detail below.

## Functional Consequences of Altered Neurotrophic Factors

To determine if the expression of BDNF in specific brain structures leads to functional effects related to the actions of stress and antidepressants, recombinant proteins and mutant mouse models have been tested. Infusions of BDNF into the midbrain, hippocampus, or lateral ventricles produce an antidepressant effect in behavioral models of depression and

antidepressant response, including the FST and LH paradigms (Siuciak et al. 1997, Shirayama et al. 2002, Hoshaw et al. 2005). Chemical inhibitors of the MAP-kinase cascade block these effects of BDNF (Shirayama et al. 2002), and also block the actions of antidepressant treatment (Duman et al. 2006). Infusions of either other trophic factors, including VEGF (Warner-Schmidt and Duman 2007) or IGF-1 (Hoshaw et al. 2005) also produce antidepressant effects in behavioral models. Studies of BDNF mutant mice also demonstrate that the actions of antidepressants are dependent on an intact BDNF system (Saarelainen et al. 2003, Monteggia et al. 2004). Similar effects have been observed in mice that express a dominant negative form of the BDNF receptor, TrkB (Saarelainen et al. 2003). However, it should also be noted that BDNF in the mesolimbic dopamine system is required for behavioral responses in a social defeat model (Berton and Nestler 2006).

Partial or complete deletion of BDNF or TrkB does not lead to a depressive phenotype in mouse models, indicating that loss of BDNF alone is not sufficient to produce a depressive response(MacQueen et al. 2001, Zorner et al. 2003, Chourbaji et al. 2004). However, when mice with a partial deletion of BDNF are exposed to stress a depressive phenotype is observed (Duman et al. 2006). A similar genotype x environment effect has been demonstrated for the short (S) allele of the 5-HT transporter in humans exposed to early life stress or trauma (Caspi et al. 2003) (see below), and a recent study has demonstrated that individuals carrying a met allele at position 66 of BDNF instead of a val allele, combined with the 5-HT S allele are susceptible to depression when exposed to early life trauma (Kaufman et al. 2006) (see below). This type of genetic disposition explains, in part, why certain individuals are vulnerable to stress exposure, while others experience stress but do not become depressed.

## Neurogenesis in the Adult Hippocampus

Despite earlier work, it is now clear that new neurons continue to be added to two specific regions of the brain, the hippocampus and olfactory bulbs, in adult animals and even in old age (Gould and Tanapat 1999, Gage 2000). New cell birth has been reported in a variety of animals, including birds, rodents, nonhuman primates, and in humans using brdu labeled brain tissue obtained postmortem from cancer patients (Eriksson et al. 1998). Moreover, the rate of new cell birth is influenced by a variety of stimuli, including those that increase it (e.g., antidepressants) and those that decrease it (stress, aging, drugs of abuse), suggesting that neurogenesis is a type of neural plasticity with consequences for neuronal function and behavior. Although studies to determine the functional significance of adult neurogenesis are technically demanding, some of the most convincing work has been done with respect to models of depression and antidepressant action.

### Opposing Actions of Stress and Antidepressant Treatment

These studies demonstrate that stress exposure decreases the proliferation of newborn neurons in the adult hippocampus of rodents and nonhuman primates (Gould et al. 1997, 1998, Czeh et al. 2001, Duman 2004b). Decreased neurogenesis is observed in response to different types of stress, including social subordination, predator odor, restraint, and chronic mild stress. In addition, administration of the adrenal-glucocorticoid that is active in rodents, corticosterone, decreases neurogenesis, indicating the actions of stress could occur via this stress-responsive steroid (Cameron et al. 1998).

In contrast, chronic antidepressant administration increases the proliferation of new neurons in the adult hippocampus. Increased neurogenesis is observed with different types of antidepressants, including 5-HT and NE selective reuptake inhibitors, MAOIs, rolipram, ECT, and exercise (van Praag et al. 1999, Madsen et al. 2000, Malberg et al. 2000, Nakagawa et al. 2002, Santarelli et al. 2003, Duman 2004b). The actions of antidepressant treatment require chronic administration, consistent with the time course for the therapeutic effects of antidepressants. In addition to increased neurogenesis in naïve animals, antidepressant administration also blocks the down-regulation of new cell birth that is caused by stress (Czeh et al. 2001, Malberg and Duman 2003, Alonso et al. 2004). Antidepressant administration increases the rate of cell proliferation, as well as the survival of newborn cells, and increases the number of mature neurons in the granule cell layer of the hippocampus (Malberg et al. 2000, Nakagawa et al. 2002).

### Functional Consequences of Altered Neurogenesis

The opposing actions of stress and antidepressants raise a question regarding the functional relevance of adult neurogenesis. At the very least, the consistent reports that stress decreases and that different classes of antidepressants increase adult neurogenesis indicate that this is a reliable marker of responses to these treatments. Indeed, increased neurogenesis is being used to test for novel antidepressant medications. It has been difficult to determine the functional significance of newborn neurons, because approaches to block cell proliferation specifically in the hippocampus have been technically difficult and limited.

However, significant progress has been made using a variety of approaches. In a landmark paper, Rene Hen's laboratory demonstrated that blocking antidepressant induction of adult neurogenesis, by either irradiation or in a mutant mouse model, completely blocked the actions of antidepressants in two behavioral models (Santarelli et al. 2003). Focused irradiation of the hippocampus kills dividing cells and thereby blocks cell proliferation; a null mutation of the 5-HT1A receptor blocks the induction of neurogenesis by SSRI antidepressants. When these animals were treated with an antidepressant, the expected behavioral responses in the novelty suppressed feeding and chronic unpredictable stress paradigms were completely blocked. Both of these models require chronic antidepressant treatment, consistent with the time frame required for differentiation and maturation of newborn neurons. However, the reduction in neurogenesis caused by irradiation alone did not cause a depressive phenotype in these models. Taken together the data demonstrate that induction of neurogenesis in the adult hippocampus is required for the behavioral actions of antidepressants, but that decreased neurogenesis alone is not sufficient to produce depression. Studies are currently underway in a number of laboratories to further test this hypothesis using transgenic mice that express cell cycle inhibitors in neural progenitor cells.

### Mechanisms Underlying Actions of Stress and Antidepressants

There has been some progress in identifying the mechanisms underlying the regulation of adult neurogenesis by stress and antidepressants. Administration of corticosterone also decreases neurogenesis, and this effect can be blocked by administration of an NMDA receptor antagonist (Cameron et al. 1998). In addition, recent studies demonstrate that infusion of an interleukin-1b antagonist blocks the down-regulation of adult neurogenesis caused by acute stress (Koo and Duman, personal communication). These studies demonstrate a complex interaction between adrenal steroids, glutamate neurotransmission, and cytokines in the actions of stress.

Studies of antidepressants have focused on the cAMP-CREB cascade and neurotrophic/growth factors. Activation of the cAMP-CREB cascade by rolipram increases adult neurogenesis, and up-regulation of this pathway could contribute to the actions of antidepressant treatment (Nakagawa et al. 2002). Studies of BDNF demonstrate that this neurotrophic factor plays a role in the survival, but not proliferation of newborn neurons resulting from antidepressant administration (Sairanen et al. 2005). A recent report demonstrates that VEGF plays an essential role antidepressant induction of neurogenesis (Warner-Schmidt and Duman 2007). Blockade of VEGF signaling blocks the induction of neurogenesis by different types of antidepressants, including 5-HT and NE reuptake inhibitors and ECT, and infusion of VEGF is sufficient to increase neurogenesis. In addition, this study demonstrated that blockade of VEGF signaling blocks the actions of antidepressants in both long-term models that require neurogenesis (i.e., novelty suppressed feeding and chronic unpredictable stress) as well as short-term models (i.e., FST and LH). These studies demonstrate that VEGF is an important mediator of the neurogenic actions, but indicate that VEGF also leads to more rapid effects, possibly at the level of synaptic activity and/or neural plasticity.

## Conclusion

The causes and mechanisms of mood disorders are beginning to be investigated at multiple levels of analysis. Research in humans and animal models is clarifying the roles of altered neuromodulator and neuroendocrine systems, and discovering the involvement of intracellular signialling cascades, nerve growth factors, and risk genes and their interactions with specific adverse environments, in the pathogenesis of unipolar and bipolar disorders. Susceptibility genes for bipolar disorder or unipolar depression are believed to include: (1) regulators of neurotransmitter function including glutamic acid decarboxylase1, monoamine oxidase A, catechol-O-methyl transferase, and the serotonin transporter, (2) regulators and participants in intracellular signaling including phosphodiesterase 11A and brain-derived nerve growth factor, and (3) components of the hypothalamic pituitary adrenal axis including the glucocorticoid receptor. The early putative mechanisms involving neuromodulator and neuroendocrine dysregulation have been extended and linked to the roles of intracellular cAMP-CREB and nerve growth factor family signaling cascades as well as hippocampal neurogenesis. These insights are leading to new hypotheses for candidate therapies.

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CHAPTER

# 22 Pathophysiology of Addiction

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## Clinical Picture

### What is Addiction?

Drug addiction, also referred to diagnostically as substance dependence (American Psychiatric Association 2000), is a chronically relapsing brain disorder characterized by: (1) compulsion to seek and take a given drug; (2) loss of control in limiting intake; and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when the drug is unavailable or access to it is prevented (Koob and Le Moal 1997).

We will also use *addiction* and *substance dependence* interchangeably throughout this text. Drug addiction is a *chronic* relapsing disorder (Meyer 1996), defined by presenting symptoms, etiology, and pathophysiology that moves from drug experimentation to abuse to addiction. The associated medical, social, and occupational difficulties that usually develop during the course of addiction do not disappear after detoxification because addictive drugs are thought to produce changes in brain pathways that endure long after the person stops taking them. These protracted brain changes and the associated personal and social difficulties put the detoxified patient at risk of relapse (O'Brien and McLellan 1996), a risk higher than 60% within the year that follows discharge (Finney and Moos 1992, Hubbard et al. 1997, McLellan and McKay 1998, McLellan et al. 2000). While much of the initial study of the neurobiology of drug addiction focused on the acute impact of drugs of abuse (comparing no drug use to drug use), the focus now is shifting to the study of chronic administration and the acute and long-term neuroadaptive changes in the brain that result in relapse. Cogent arguments have been made supporting the idea that addictions are similar in their chronic relapsing properties and limited efficacy of treatment to other chronic relapsing disorders such as diabetes, asthma, and hypertension (McLellan et al. 2000). The purpose of current neurobiologic drug abuse research is to understand the cellular and molecular mechanisms that mediate the transition from occasional, controlled drug use, to the loss of behavioral control over drug-seeking and drug-taking, and chronic addiction (Koob and Le Moal 1997).

The diagnostic criteria for substance use disorders, as specified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), cover two maladaptive patterns of substance use: (1) substance abuse and (2) substance dependence (addiction). Abuse is less severe than dependence and is diagnosed only if criteria for dependence are not met. The criteria for dependence have evolved over the past 30 years with a shift of emphasis from the necessary physiological criteria of tolerance and withdrawal to behavioral criteria for compulsive use. Tolerance and withdrawal form two of the seven potential criteria that need to be experienced within a 12-month period. The criteria for substance dependence outlined in the DSM-IV-TR closely resemble those outlined by the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) (World Health Organization 1992) (Table 22–1). In both systems, the specific withdrawal symptoms vary across drugs. As noted by Hughes (2006), generic criteria are based in part on shared genotype across different drugs, common underlying neurobiological processes, as well as by common behavioral correlates, such as antisocial syndromes (Compton et al. 2005a, Nelson et al. 1999). However, the assumption on which these criteria are based has been challenged, especially

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**Table 22–1 DSM-IV-TR and ICD-10 Diagnostic Criteria for *Alcohol and Drug Dependence***

| | DSM-IV-TR | ICD-10 |
|---|---|---|
| Clustering criterion | A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following occurring at any time in the same 12-month period: | A. Three or more of the following have been experienced or exhibited at some time during the previous year: |
| Tolerance | 1. Need for markedly increased amounts of a substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of the substance. | 1. Evidence of tolerance, such that increased doses are required in order to achieve effects originally produced by lower doses. |
| Withdrawal | 2. The characteristic withdrawal syndrome for a substance or use of a substance (or a closely related substance) to relieve or avoid withdrawal symptoms. | 2. A physiological withdrawal state when substance use has ceased or been reduced as evidenced by: the characteristic substance withdrawal syndrome, or use of substance (or a closely related substance) to relieve or avoid withdrawal symptoms. |
| Impaired control | 3. Persistent desire or one or more unsuccessful efforts to cut down or control substance use.<br>4. Substance used in larger amounts or over a longer period than the person intended. | 3. Difficulties in controlling substance use in terms of onset, termination, or levels of use. |
| Neglect of activities | 5. Important social, occupational, or recreational activities given up or reduced because of substance use. | 4. Progressive neglect of alternative pleasures or interests in favor of substance use; or |
| Time spent | 6. A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance used. | A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance use. |
| Inability to fulfill roles | None | None |
| Hazardous use | None | None |
| Continued use despite problems | 7. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use. | 5. Continued substance use despite clear evidence of overtly harmful physical or psychological consequences. |
| Compulsive use | None | 6. A strong desire or sense of compulsion to use substance. |
| Duration criterion | B. No duration criterion separately specified. However, several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g., "often," "persistent," "continued"). | B. No duration criterion separately specified. |
| Criterion for subtyping dependence | *With physiological dependence*: Evidence of tolerance or withdrawal (i.e., any of items A-1 or A-2 above are present).<br>*Without physiological dependence*: No evidence of tolerance or withdrawal (i.e., none of items A-1 or A-2 above are present). | None |

regarding nicotine dependence (Hughes 2006), and needs better empirical validation. Indeed, the number of criteria met by dependent users varies with the drug in question, the severity of the addiction, the stage of the addiction process, and the age of the user (Chung and Martin 2001). For instance, for alcohol, marijuana, cocaine, and heroin, the two most frequently mentioned criteria are *tolerance* (criterion #1) and *time spent using*, *procuring the drug* (criterion #5). *Withdrawal* (criterion #2) is mentioned much more frequently with respect to heroin than cocaine, and more frequently with respect to alcohol than cocaine, based on the National Survey on Drug Use and Health (NSDUH) 2005 (Substance Abuse and Mental Health Services Administration 2006). The DSM-IV-TR does not include withdrawal from cannabis as a criterion even though a cannabis withdrawal syndrome is now well-established (Budney et al. 2003).

Abuse is diagnosed if the person has not been diagnosed as being dependent, but engages in recurrent substance use during a 12-month period resulting in at least one of the four harmful consequences, including failure to fulfill major role obligations, hazardous use, legal problems, and continued use despite social or interpersonal problems caused by the substance (Table 22–2).

*Dependence* has multiple meanings. Particularly confusing has been the use of "physical dependence," which refers to the adaptations that occur with repeated exposure to drugs and that upon discontinuation result in symptoms of withdrawal that can be mild (such as mild fatigue with cocaine) or severe (vomiting, seizures with alcohol and heroin) and which are distinct from the adaptations that result in addiction. The changes and symptoms associated with physical dependence develop and resolve much faster than

**Table 22–2 DSM-IV-TR Diagnostic Criteria for *Drug Abuse***

| | DSM-IV |
|---|---|
| Criterion | A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring at any time in the same 12-month period: |
| Inability to fulfill roles | 1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use). |
| Hazardous use | 2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile when impaired by substance use). |
| Legal problems | 3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct). |
| Continued use despite problems | 4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by use of the substance (e.g., arguments with spouse about consequences of intoxication). |
| Exclusion criterion | B. The symptoms have never met the criteria for substance dependence for this class of substance. |

the symptoms associated with "addiction." Thus, an individual can become physically dependent on a drug without being addicted, and an individual can be addicted without suffering from physical dependence. Meeting the DSM-IV-TR criteria for *substance dependence* is much more than a manifestation of a withdrawal syndrome (physical dependence); rather it reflects an addictive state. In this chapter, we will refer to *substance dependence* as defined by the DSM-IV-TR. *Substance dependence*, *addiction*, and *alcoholism* will be held equivalent.

## Stages of the Addiction Cycle

From a psychiatric perspective, drug addiction has aspects of both impulse control and compulsive disorders. Impulse control disorders are characterized by three factors: (1) an increasing sense of tension or arousal before committing an impulsive act; (2) pleasure, gratification, or relief at the time of committing the act; and (3) regret, self-reproach, or guilt following the act (American Psychiatric Association 1994). In contrast, compulsive disorders are characterized by two factors: (1) anxiety and stress before committing a compulsive repetitive behavior; and 2) relief from the stress by performing the compulsive behavior. As an individual moves from an impulsive disorder to a mixed compulsive/impulsive disorder, there is a shift from positive to negative reinforcement driving the motivated behavior and increasing control by automated prepotent responses (Koob 2004) (Figure 22–1). As these arguments illustrate, drug addiction can best be conceptualized as a disorder that progresses from impulsivity to compulsivity in a cycle comprised of three stages: *preoccupation/anticipation*, *binge/intoxication*, and *withdrawal/ negative affect*. (Koob and Le Moal 1997) (Figure 22–2).

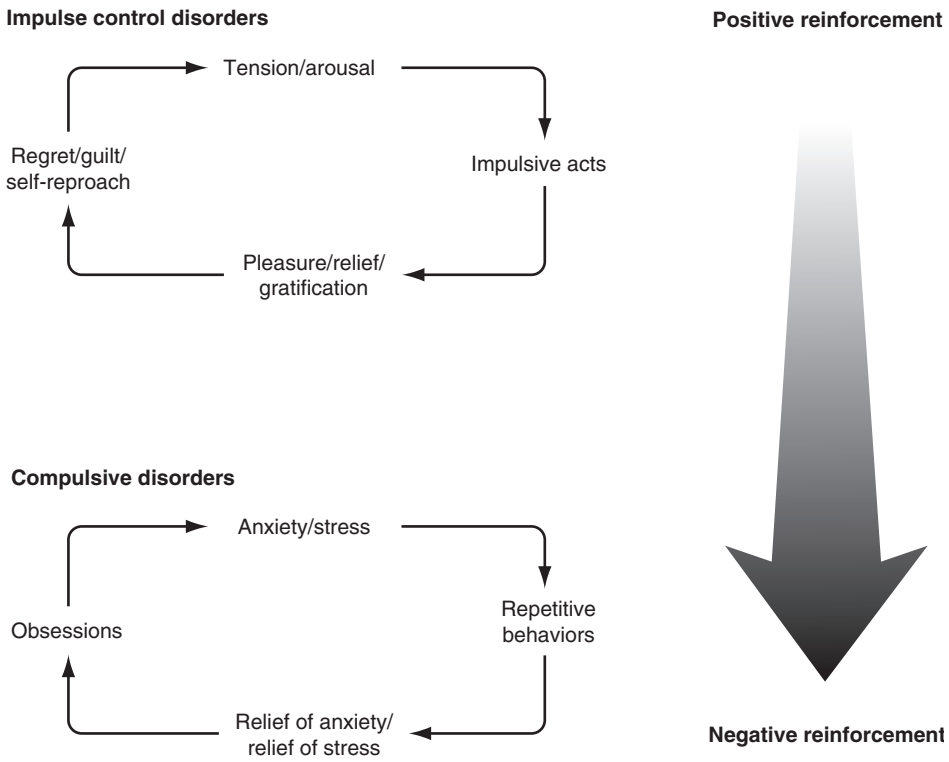



**Figure 22–1** *Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders, an increasing tension and arousal occurs before the impulsive act, with pleasure, gratification, or relief during the act. Following the act, there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (American Psychiatric Association 1994). Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders. (Taken with permission from Koob 2004.)*

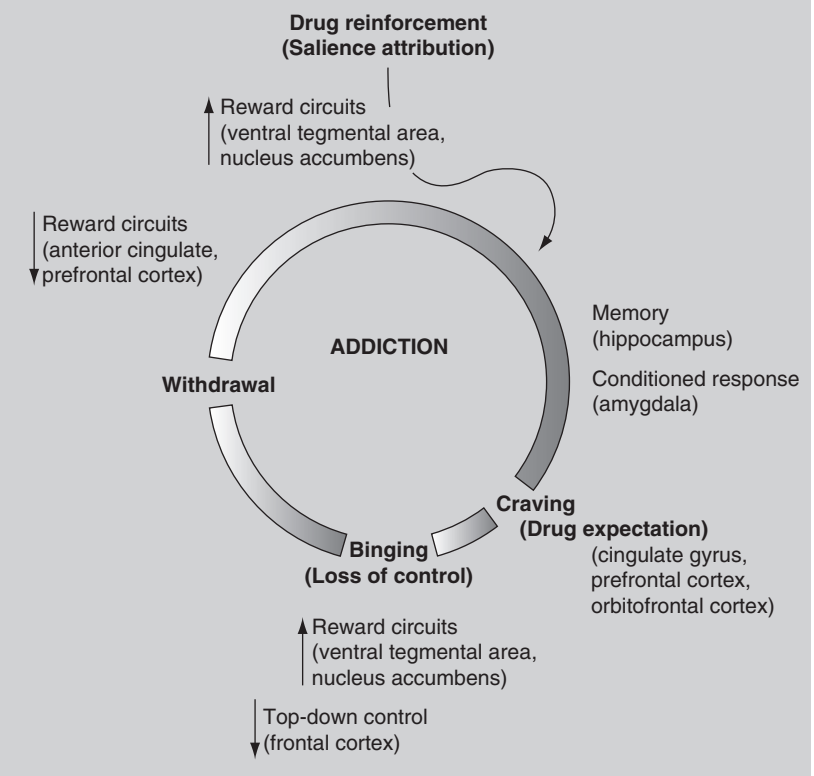



**Figure 22–2** *Integrative model of brain and behavior describing the Impaired Response Inhibition and Salience Attribution (I-RISA) syndrome of drug addiction (Goldstein and Volkow 2002). The mesolimbic dopamine circuit, which includes the nucleus accumbens, amygdala, and hippocampus, has been traditionally associated with the acute reinforcing effects of a drug and with the memory and conditioned responses that have been linked to craving. It is also likely to be involved in the emotional and motivational changes seen in drug abusers during withdrawal. The mesocortical dopamine circuit, which includes the prefrontal cortex, orbitofrontal cortex, and anterior cingulate, is likely to be involved in the conscious experience of drug intoxication, drug incentive salience, drug expectation/craving, and compulsive drug administration. Note the circular nature of this interaction: The attribution of salience to a given stimulus, which is a function of the orbitofrontal cortex, depends on the relative value of a reinforcer compared to simultaneously available reinforcers, which requires knowledge of the strength of the stimulus as a reinforcer, a function of the hippocampus and amygdala. Consumption of the drug in turn will further activate cortical circuits (orbitofrontal cortex and anterior cingulate) in proportion to the dopamine stimulation by favoring the target response and decreasing nontarget-related background activity. The activation of these interacting circuits may be indispensable for maintaining the compulsive drug administration observed during bingeing and to the vicious circle of addiction. (Reprinted with permission from the American Journal of Psychiatry, © American Psychiatric Association.)*

## Patterns of Addiction

Different drugs produce different patterns of addiction with emphasis on different components of the addiction cycle. Opioids are probably the classic drug of addiction. A pattern of drug-taking evolves, including an intense intoxication via the intravenous or smoking routes for heroin and oral or intravenous administration for opioid analgesics, the development of tolerance, escalation in intake and profound dysphoria, physical discomfort and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops that often precedes the somatic signs of withdrawal, and this preoccupation is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and internal and external states of stress. The drug must be obtained to avoid the severe dysphoria and discomfort during abstinence.

Addiction to alcohol follows a similar pattern, but the intoxication is less intense and the pattern of drug-taking is often characterized by binges of alcohol intake that can consist of daily episodes or prolonged days of heavy drinking. A binge is defined as five standard drinks for males and four standard drinks for females in a 2 h period or a blood alcohol level of 0.08%. Addiction to alcohol is characterized by a severe emotional and somatic withdrawal syndrome and intense craving for the drug that is often driven by negative emotional states, positive emotional states, and environmentally conditioned stimuli (stimuli that have been associated with drinking). Many alcoholics continue with such a *binge/withdrawal* pattern for extended periods, but some evolve into an opioid-like situation where they must have alcohol available at all times to avoid the consequences of abstinence.

Nicotine addiction contrasts with the above patterns in that nicotine has less of a *binge/intoxication* stage. Cigarette smokers who meet the criteria for substance dependence are likely to smoke throughout the waking hours and to experience negative emotional states with dysphoria, irritability, and intense craving during abstinence. The *binge/intoxication* stage forms a minor component of nicotine dependence where the pattern is highly titrated intake of the drug that does not interrupt daily activity and that is maintained throughout the day only to be interrupted during periods of sleep. Psychostimulants such as cocaine and amphetamines show a pattern that emphasizes the *binge/intoxication* stage. Such binges can last for hours or days and are often followed by a crash characterized by dysphoria, fatigue, and inactivity. Intense craving follows later, and is driven both

by environmental conditioned cues signifying availability of the drug and internal states often linked to negative emotional states and stress.

Marijuana dependence follows a pattern similar to opioids and tobacco. There is a significant intoxication stage, but as chronic use continues subjects begin to show chronic intoxication during waking hours. Withdrawal is characterized by dysphoria, irritability, and sleep disturbances. While less studied to date, the craving associated with marijuana (Heishman et al. 2001) is most likely linked both to environmental and internal states similar to those of other drugs of abuse. Significant differences in the pharmacokinetics of various drugs, which determine the duration of their pharmacological effects, account in part for the differences in their patterns of use. Thus, nicotine has a very short half-life, which requires frequent administration, whereas $\Delta^9$-tetrahydrocannabinol (THC) has a much longer half-life, which is why marijuana smokers do not need to smoke as many cigarettes as is the case for cigarette smokers.

### Development of Addiction: Self-Regulation and Self-Medication

Failure of self-regulation is thought to be at the root of major social pathologies and a key element in the development of addiction (Baumeister et al. 1994). Important self-regulation elements may be involved in the different stages of addiction as well as in other pathological behaviors such as compulsive gambling and binge eating. Self-regulation failures set up future failures to self-regulate, and ultimately lead to the chronic relapsing disorder considered as addiction (Baumeister et al. 1994).

From a self-medication perspective, two critical elements (disordered emotions and disordered self-care) and two contributory elements (disordered self-esteem and disordered relationships) have been identified and incorporated into a self-medication hypothesis. Here, individuals with substance use disorders are thought to take drugs as a "means to cope with painful and threatening emotions." In this conceptualization, addicted individuals experience states of subjective distress and suffering that may or may not be associated with conditions meeting the DSM-IV-TR criteria for a psychiatric diagnosis (American Psychiatric Association 1994).

Self-medication may be drug-specific in that individuals may prefer to use drugs that fit with the nature of the painful affective states that they are attempting to alleviate. For example, certain individuals may find that opiates are effective in reducing psychopathological states of violent anger and rageful feelings. Others, suffering from anhedonia, anergia, or lack of feelings, will prefer the activating properties of psychostimulants. Some individuals who are flooded in their feelings, or cut off from feelings, will welcome repeated moderate doses of alcohol or antidepressants to express feelings that they are not able to communicate. Thus, in some cases, the operative motive is to relieve painful feelings; in others, it is to control or express feelings (Khantzian, 1995, 1997, Khantzian and Wilson 1993). According to this view, each class of drugs can, in principle, serve as a specific antidote to specific dysphoric states and act as a "replacement for a defect in the psychological structure" of the individuals (Kohut 1971). The paradox of addiction, of course, is that by choosing drugs to self-medicate emotional pain, the drugs themselves will perpetuate it, by perpetuating a life revolving around drugs.

This psychodynamic approach integrates well with growing evidence for a critical role of dysregulated brain reward and stress systems in drug addiction from studies on the neurobiology of addiction using animal models (see sections that follow). However, from a neurobiological perspective, there is an additional insult to personality produced by the direct effects of the drugs themselves that perpetuate, and actually *create*, such character flaws (Koob 2003).

## Patterns of Substance Use and Substance Use Disorders

### Overall Prevalence

Modern epidemiological studies have distinguished three clinical patterns of drug use: (1) occasional, controlled or social use; (2) drug abuse and/or harmful use; and (3) drug dependence/addiction. A large number of individuals in the population engage in each of these behaviors. Four national surveys implemented since 2001 have measured substance use and substance use disorders in the US population: the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Grant et al. 2004c, Compton et al. 2005a, Conway et al. 2006), the National Comorbidity Survey Replication (NCS-R) (Kessler et al. 2005a, b), the NSDUH (Substance Abuse and Mental Health Services Administration, 2006), and the annual Monitoring the Future, which focuses on adolescents. (Johnston et al. 2007) These surveys have different strengths and weaknesses and generate somewhat different estimates of rates of substance use and substance use disorders (Compton et al. 2005a, Cottler 2007, Grant et al. 2007, Grucza et al. 2007, Kessler and Merikangas 2007). Prevalences based on the 2005 NSDUH are displayed in Table 22–3. In 2005, 46% (112 million) of the US population of 12 years or older were engaged in nonmedical or illicit drug use at some time in their lives. Of these, approximately 2.8% (6.8 million) experienced a DSM-IV-TR substance use disorder of an illicit drug in the last year, 0.9% experienced abuse, and 1.9% experienced dependence (SAMHSA 2006: Tables G.1., G.2, G.29, G.30; secondary analyses).

Eighty-three percent (202 million) of persons aged 12 years and over had ever drank alcohol, while 52% (126 million) had consumed alcohol within the last month (SAMHSA 2006: Table G.16). Of those who drank in the last year, 11% (18.6 million) met the criteria for DSM-IV-TR substance abuse or dependence on alcohol (SAMHSA 2006: Tables G.29, G.30). All said, 22.2 million Americans, 9% of the population aged 12 and older, experienced abuse or dependence on alcohol or an illicit drug within the prior 12 months; the same proportion did so among those aged 18 and older. This compares to 12-month prevalence of 9% for mood disorders or 11% for anxiety disorders in the population aged 18 and older (Grant et al. 2004b). In addition, 66% (161 million) of those aged 12 and over who had ever smoked cigarettes, and 35% (25.1 million) of those who smoked in the last year met the criteria for nicotine dependence in the last 30 days, as measured by the Nicotine Dependence Symptom Scale (NDSS) (Shiffman et al. 2004).

**Table 22–3** **Estimated Lifetime and Last Year Prevalence of *Nonmedical Substance Use*, *Substance Abuse*, and *Substance Dependence* among all Persons Aged 12 and over**

| | Total | | | | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % |
| *Alcohol*† | 83.0 | 66.6 | 11.4 | 4.9 | 86.3 | 70.3 | 14.7 | 6.0 | 79.9 | 63.2 | 7.9 | 3.7 |
| *Tobacco**,† | 70.6 | 35.1 | — | — | 78.3 | 42.6 | — | — | 63.4 | 28.1 | — | — |
| Cigarettes† | 66.3 | 29.2 | — | 35.3 | 71.2 | 32.2 | — | 34.1 | 61.7 | 26.4 | — | 36.7 |
| *Any Illicit Drug* | 46.1 | 14.4 | 18.8 | 12.9 | 50.9 | 16.9 | 20.2 | 13.0 | 41.7 | 12.2 | 17.0 | 12.7 |
| Cannabis | 40.1 | 10.4 | 15.3 | 9.7 | 45.0 | 13.1 | 16.8 | 10.3 | 35.4 | 8.0 | 13.0 | 8.7 |
| Cocaine | 13.8 | 2.3 | 27.8 | 20.4 | 17.2 | 2.9 | 25.0 | 16.7 | 10.3 | 1.6 | 32.8 | 26.9 |
| Hallucinogens | 13.9 | 1.6 | 9.9 | 3.9 | 17.1 | 2.0 | 9.9 | 3.7 | 10.4 | 1.0 | 9.8 | 4.5 |
| Analgesics | 13.4 | 4.9 | 13.2 | 9.6 | 15.6 | 5.3 | 13.0 | 9.1 | 11.5 | 4.4 | 13.5 | 10.1 |
| Inhalants | 9.4 | 0.9 | 9.3 | 2.2 | 12.4 | 1.0 | 10.9 | 2.0 | 6.2 | 0.8 | 7.3 | 2.5 |
| Tranquilizers | 8.7 | 2.2 | 8.2 | 4.6 | 9.5 | 2.3 | 8.9 | 4.6 | 7.8 | 2.0 | 7.5 | 4.6 |
| Stimulants | 7.8 | 1.1 | 14.3 | 9.9 | 8.7 | 1.2 | 12.0 | 6.8 | 6.8 | 1.1 | 16.5 | 13.0 |
| Sedatives | 3.7 | 0.3 | 12.6 | 6.9 | 4.5 | 0.3 | 9.6 | 5.3 | 2.9 | 0.3 | 15.5 | 8.5 |
| Heroin | 1.5 | 0.2 | 53.7 | 45.4 | 2.0 | 0.2 | 48.5 | 39.2 | 0.9 | 0.1 | 63.2 | 56.7 |

* Only dependence on cigarettes was ascertained.
† *Source*: NHS03710, 3713, 3718, 3733, 3743, 3744.

*Source*: Based on secondary analysis of the 2005 National Survery on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2006).

The proportion of individuals meeting the criteria for abuse or substance dependence on a given drug among those who used the drug varies greatly across drug classes. In 2005, the percentage of last year users with a substance use disorder was the highest for heroin, followed by cigarettes (nicotine) and cocaine (Table 22–3 and Figure 22–3). The percentages for the other drugs were much lower. The proportion of individuals with an alcohol-related disorder among those who consumed alcohol in the last year was among the lowest of any of the substances. However, because so many individuals consume alcohol, this percentage translates into a large number of affected individuals.

Considering all drugs in aggregate in 2005, only 12% of the population aged 12 and over had not experimented with any substance; 41% had experimented with all three major classes: alcohol, tobacco, and illicit drugs (based on 2005 NSDUH). Similarly, multiple substance use disorders tend to co-occur. In 2001–2002, 40% of individuals aged 18 and over in the population who met the criteria for abuse or dependence on one drug class also met the criteria for abuse or dependence on at least another drug; 12% met the criteria for abuse or dependence on two other substances. The highest comorbidity was between dependence on an illicit drug and dependence on alcohol or nicotine. 70% of those dependent on an illicit drug also were dependent on alcohol, and 69% were dependent on nicotine (secondary analysis of 2005 NESARC). Yet, only a minority of addicted individuals have been treated for their addiction (Compton et al. 2007).

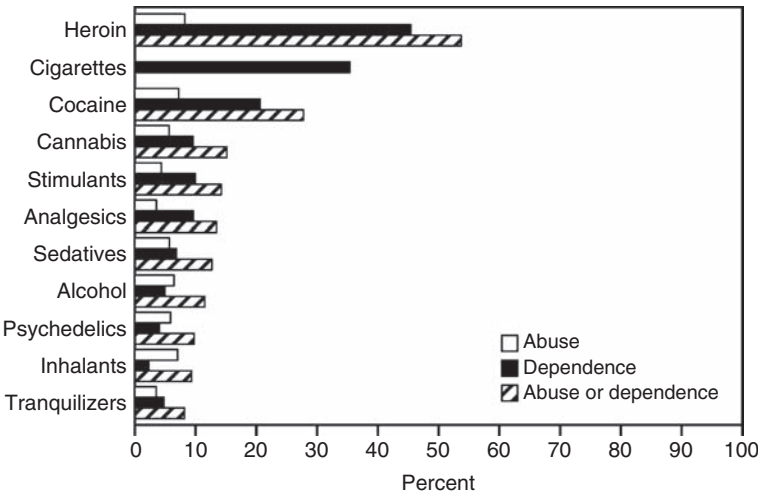



**Figure 22–3** *Rates of DSM-IV-TR substance use disorders among last year users 12+ years old (based on the 2005 NSDUH; Substance Abuse and Mental Health Services Administration 2006).*

## Developmental Stages of Involvement in Drugs

Not only are there regular patterns of co-occurrence of use, abuse, and dependence across drugs, but also there are regular sequences of progression from the use of one drug class to another. The existence of a developmental sequence of involvement in drugs is one of the best replicated findings in the epidemiology of drug use (Kandel 2002). Both in the United States and in other Western societies, a regular sequence and stages of progression have consistently been found. In this sequence, the use of cigarettes (nicotine) or alcohol precedes the use of marijuana (cannabis) and, in turn, the use of marijuana precedes the use of other illicit drugs. Very few individuals who have tried cocaine and heroin have not previously used marijuana, and the majority have used alcohol or cigarettes prior to their use of marijuana. Such behavioral regularities have given rise to the Gateway Hypothesis. However, in the 30 years since publication of the original observation (Kandel and Faust 1975), surprisingly, little progress has been made in addressing three fundamental questions that derive from the observation that the use of one class of drug is followed by the use of another class. We still do not know: (1) whether the use of the first class of drugs, such as nicotine, is a cause of the use of the second class, such as cocaine, or whether the sequence is determined exclusively by availability of the drug or other social factors; (2) what biological mechanisms underlie this progression in drug use; and (3) why early use during adolescence leads to more extensive and chronic use than later onset of drug use postadolescence. Ongoing work on animal models will help answer these questions.

## Prevalence Rates by Age, Gender, Race/Ethnicity

There are important differences in the prevalence of use and substance use disorders in different subgroups in the population.

### Age

Age differences in patterns of substance use are the most pronounced, and this is particularly evident in the use of illicit drugs. The highest rates of substance use occur among young adults 18–24 years old. At age 25, the rates for cigarettes and illicit drugs begin to decline steeply; whereas the rates for alcohol do not begin to decline until age 50 (Figure 22–4). Among users, the age-related patterns for dependence differ across drugs. For alcohol and illicit drugs, the rates of dependence among last year users peak at age 18–24 and decline gradually whereas for cigarettes they climb steadily through age 35–49, when they stabilize.

### Gender

Gender patterns for substance use differ from those for substance use disorders. For all substances, including the nonmedical use of psychotherapeutic drugs, males have consistently higher prevalences of use than females (Table 22–3). Among drug users, however, males have higher rates than females for alcohol, cannabis, inhalants, and tranquilizers; for all other drug classes, the rates of disorders among users are the same or higher among females. With regard to dependence specifically, the conditional rate of alcohol dependence is 60% higher among males than females; the rates of dependence on cocaine, stimulants, sedatives, and heroin are 40–90% higher among females than males.

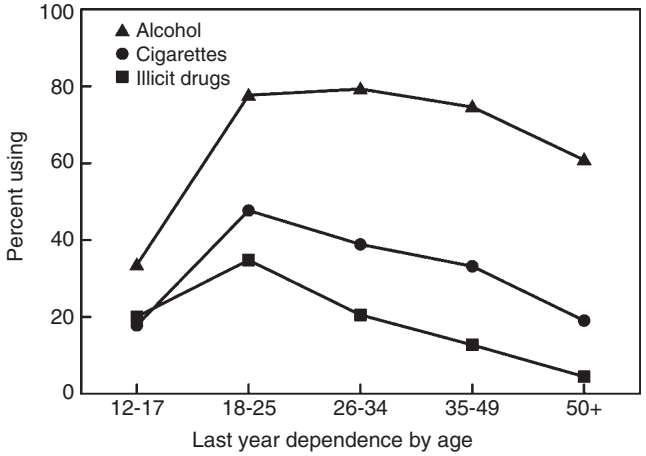



**Figure 22–4** *Prevalence of last year use of alcohol, cigarettes, and illicit drugs by age. (Taken with permission from Substance Abuse and Mental Health Services Administration 2006.)*

### Race/Ethnicity

There are striking race/ethnic differences in patterns of substance use and substance disorders in the population (Table 22–4). With the exception of heroin, the lifetime prevalence of use for each drug class is higher among non-Hispanic whites than non-Hispanic African-Americans or Hispanics, and especially Asians, who have the lowest rates of use of any group. However, the differences in rates of use between non-Hispanic whites and African-Americans reverse by the age of mid-30s (Kandel 2006). By contrast, except for cigarettes, analgesics, and tranquilizers, the rates of substance use disorders among users of each substance, and particularly dependence, are consistently higher among Non-Hispanic African-Americans than any other group; the rates are generally lowest among Asians.

# Impact of Substance Use Disorders

## Medical Consequences

Substance abuse and addiction contribute to various medical disorders, including pulmonary and cardiovascular disease, stroke, cancer, infectious diseases (HIV and hepatitis C), and mental disorders (i.e., anxiety disorder, depression, psychoses). Smoking is considered the number one preventable cause for morbidity and mortality worldwide. It is estimated that tobacco is responsible for five million deaths worldwide each year (Ezzati and Lopez 2003), a figure expected to rise to ten million deaths annually by 2020 (World Health Organization 1999). Though the most frequently recognized causal association is that between tobacco smoking and lung cancer, smoking also contributes to cancers of the mouth, throat, larynx, blood, stomach, pancreas, kidney, bladder, and cervix. Smoking also contributes to a wide variety of pulmonary diseases, most notably chronic obstructive pulmonary diseases and asthma.

The medical consequences of the use of drugs depend on their pharmacological effects, routes of administration,

**Table 22–4** Lifetime *Substance Use* and *Substance Abuse* or *Dependence* among Persons Aged 12 and over among Last Year Users by Race/Ethnicity

| | NonHispanic White | | | | NonHispanic African-American | | | | Hispanic | | | | Asian | | | | Other | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % | Used lifetime % | Used last year % | Dependence/Abuse among last year users % | Dependence among last year users % | Used lifetime % | Used last year % | Dependence/Abuse among Last Year Users % | Dependence Among Last Year Users % | Used Lifetime % | Used Last Year % | Dependence / Abuse Among Last Year Users % | Dependence Among Last Year |
| *Alcohol* | 87.0 | 70.7 | 11.1 | 4.4 | 75.3 | 55.9 | 11.5 | 6.0 | 75.7 | 60.6 | 13.5 | 6.6 | 63.3 | 51.6 | 6.8 | 2.9 | 80.5 | 61.2 | 18.6 | 9.1 |
| *Tobacco*[*] | 76.4 | 37.2 | — | — | 60.6 | 31.8 | — | — | 58.1 | 31.0 | — | — | 43.5 | 20.2 | — | — | 69.3 | 41.5 | — | — |
| Cigarettes | 72.0 | 30.3 | — | 40.2 | 55.5 | 27.1 | — | 29.0 | 54.6 | 28.0 | — | 16.9 | 39.9 | 17.9 | — | 20.6 | 64.9 | 36.5 | — | 31.1 |
| *Any Illicit Drug* | 48.8 | 14.6 | 18.1 | 12.8 | 45.5 | 16.4 | 23.4 | 15.4 | 37.5 | 13.7 | 17.2 | 10.5 | 28.4 | 6.8 | 17.1 | 10.0 | 51.9 | 18.4 | 26.3 | 17.7 |
| Cannabis | 43.4 | 10.7 | 14.1 | 8.9 | 39.7 | 12.6 | 19.7 | 13.1 | 29.0 | 8.9 | 16.8 | 9.6 | 18.3 | 4.0 | 14.7 | 9.6 | 44.5 | 14.3 | 20.2 | 12.4 |
| Cocaine | 15.2 | 2.4 | 26.0 | 19.9 | 10.4 | 2.0 | 47.9 | 33.7 | 11.7 | 1.9 | 24.2 | 13.1 | 4.0 | 0.5 | 4.6 | 4.6 | 13.8 | 3.3 | 25.5 | 20.0 |
| Hallucinogens | 16.1 | 1.7 | 8.5 | 3.4 | 6.5 | 0.9 | 13.7 | 6.2 | 9.0 | 1.2 | 14.0 | 6.9 | 5.2 | 0.6 | 21.9 | 3.3 | 19.1 | 2.7 | 13.3 | 2.0 |
| Analgesics | 14.6 | 5.1 | 13.6 | 10.6 | 10.0 | 3.8 | 12.8 | 5.2 | 11.8 | 4.7 | 8.3 | 5.2 | 8.8 | 2.6 | 11.9 | 10.2 | 17.1 | 5.6 | 26.3 | 20.0 |
| Inhalants | 10.8 | 0.9 | 7.8 | 1.7 | 4.1 | 0.8 | 9.8 | 5.9 | 7.2 | 1.1 | 15.5 | 2.2 | 3.6 | 0.5 | 2.6 | 0.0 | 10.6 | 1.4 | 12.9 | 3.5 |
| Tranquilizers | 10.2 | 2.7 | 8.4 | 4.7 | 4.2 | 0.6 | 7.6 | 0.9 | 5.9 | 1.7 | 8.0 | 5.3 | 4.1 | [†] | — | 2.8 | 9.2 | 1.6 | 9.1 | 6.9 |
| Stimulants | 9.3 | 1.4 | 14.4 | 10.0 | 2.7 | 0.4 | 22.4 | 17.9 | 4.9 | 1.1 | 13.2 | 7.6 | 3.3 | 0.4 | 0.0 | 0.0 | 9.4 | 1.4 | 11.8 | 11.8 |
| Sedatives | 4.4 | 0.3 | 9.2 | 4.1 | 1.6 | 0.2 | 23.8 | 23.8 | 2.0 | 0.3 | 20.7 | 9.7 | 2.1 | [†] | — | 0.0 | 3.7 | 0.3 | 55.5 | 43.9 |
| Heroin | 1.4 | 0.2 | 51.4 | 41.1 | 2.0 | 0.2 | 81.2 | 81.2 | 1.0 | 0.1 | 59.0 | 52.2 | [†] | [†] | — | 40.5 | 2.0 | 0.3 | 6.9 | 5.4 |

[*] Only dependence on cigarettes was ascertained.
[†] Fewer than 10 cases.

*Source*: Based on secondary analysis of the 2005 National Survery on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2006).

duration of use, and stage in a subject's life at which they are consumed. For example, alcohol is a recognized teratogen, and its use during pregnancy is associated with severe adverse developmental consequences to the offspring, including facial dysmorphology, growth retardation, and mental retardation. In addition, heavy drinking associated with thiamine deficiency can lead to Wernicke's Korsakoff syndrome (Day et al. 2004) characterized by neurological symptoms and severe anterograde amnesia with intact retrograde memory. The neurological syndrome is reversible, but the amnesia is irreversible and is associated with neuronal loss in temporal lobe structures, orbitofrontal cortices, and the hippocampus.

Smoking during pregnancy also contributes to significant morbidity. The Centers for Disease Control and Prevention (CDC) identifies smoking during pregnancy as the single-most preventable cause of illness and death among mothers and infants. Maternal smoking is thought to account for over 20% of all sudden infant death syndrome cases in the United States (Shah et al. 2006), and is linked to preterm birth (Kolas et al. 2000), intrauterine growth retardation, and small head circumference (Kallen 2001). Smoking during pregnancy also may account for up to 25% of externalizing behavioral disorders including conduct disorder (Williams et al. 1998), and attention deficit hyperactivity disorder (ADHD) (Linnet et al. 2005), and may increase the risk of smoking and nicotine dependence in offspring (Kandel et al. 1994, Buka et al. 2003).

Two other major complications of drug use are infectious diseases and brain damage. Injection of drugs such as heroin, cocaine, and methamphetamine accounts for more than a third of new AIDS cases and AIDS deaths in the United States. Drug intoxication also increases the likelihood of risky sexual behaviors, which contribute to the spread of HIV/AIDS, hepatitis B and C, and other sexually transmitted diseases.

Brain damage depends on the class of drug. A common mechanism of neurotoxicity results from vascular effects that can trigger ischemia to the nervous tissue. Thus, strokes have been associated with consumption of a wide variety of drugs, including cocaine, alcohol, methamphetamine, and nicotine. In addition, certain drugs target specific cell types such as serotonin neurons by ecstasy or dopamine cells by methamphetamine. Inhalants also have been linked with unique neurotoxic effects that target white matter tissue and peripheral nerves.

## Psychiatric Comorbidity

There is extensive comorbidity between addiction and mental illness, documented most recently by NESARC (Compton et al. 2005a, Conway et al. 2006, Grant et al. 2004b, c, d, Hasin et al. 2005). Psychiatric comorbidity is especially high for drug dependence on an illicit drug. In 2001–2002, 41% of individuals with a drug use disorder (abuse or dependence) had a mood disorder and 30% an anxiety disorder. Among those with dependence specifically, the rates were 50% higher, i.e., 62% and 47%, respectively (Conway et al. 2006). The associations between psychiatric disorders and substance dependence (as measured by odds ratios) are highly statistically significant for all substances

and all classes of psychiatric disorders (Table 22–5). The associations are somewhat higher for mood than anxiety disorders, and much higher—by a factor of two or three—for antisocial personality than mood or anxiety disorders. However, psychiatric comorbidity is almost the same with dependence on alcohol and nicotine, and lower for these two legal drugs and inhalants than for the remaining seven classes of illicit drugs that were considered. The associations between psychiatric disorders and dependence on the seven classes of illicit drugs are all extremely high, and lower for the legal drugs alcohol and nicotine, and for inhalants. In general, the substances with the lowest prevalences of dependence in the population have the highest rates of comorbidity with psychiatric disorders (Compton et al. 2005a, Conway et al. 2006). There are associations between specific disorders and specific drugs (Conway et al. 2006; Tables 4 and 5).

A particularly strong comorbidity exists between schizophrenia and nicotine use and dependence. Rates of smoking may be three to four times higher among schizophrenics than in the general population and higher than among individuals diagnosed with other psychiatric disorders (Dalack et al. 1998, Kumari and Postma 2005). This association may represent self-medication for the cognitive and negative symptoms prominent in schizophrenia, given the interaction of nicotine with dopaminergic and glutamatergic transmitter systems (Dalack et al. 1998, Kumari and Postma 2005).

As suggested by Compton et al. (2005a), the strong association with antisocial disorders across various substances suggests that there is an underlying comorbidity factor rather than substance-specific links. This has important implications regarding the potential commonality of selected mechanisms and genetic factors underlying substance use disorders and psychiatric disorders, especially antisocial personality disorders. Although rates of psychiatric disorders vary substantially across racial/ethnic groups, the association between alcohol dependence and drug dependence on illicit drugs with mood and anxiety disorders is similar among whites, African-Americans, Hispanics, and Asians, but not Native Americans (Smith et al. 2006).

These cross-sectional associations do not elucidate developmental processes underlying comorbidity, whether the mental illness was followed by drug dependence or whether drug dependence was followed by mental illness. For some cases, mental illness and addiction may co-occur independently (Grant et al. 2004a). For others, there might be a sequential relationship. The direction of causality between psychiatric disorders and dependence is ambiguous because both pathways of influence have been documented. For instance, among adolescents and young adults, depression and social anxiety predict the onset of smoking and nicotine dependence (Breslau et al. 2004, Karp et al. 2006, Kessler 2004), but prior smoking and nicotine dependence also predict depression, disruptive disorders, panic attacks and disorder, and agoraphobia (Breslau and Klein 1999, Breslau et al. 2004, Glassman 1993, Klungsøyr et al. 2006). The association between depression and smoking is probably reciprocal (Breslau et al. 1998), and may be determined by shared genetic or environmental factors. It is likely that different neurobiological factors are involved in comorbidity depending on its developmental course. When mental illness is followed by dependence on some types of drugs, comorbidity might reflect self-medication, as discussed earlier. However, when drug dependence is followed by mental illness it is possible that chronic drug exposure itself could lead to changes in the brain that would increase the risk for a mental illness, particularly in persons with genetic vulnerability. For example, the high prevalence of smoking after individuals become depressed could reflect the antidepressant effects of nicotine and of monoamine oxidase A and B inhibition by cigarette smoke (Fowler et al. 2003). On the other hand, the reported risk for depression with early drug abuse (Brook et al. 2002) could reflect neuroadaptations in monoamine systems that might make individuals more vulnerable to depression.

**Table 22–5 Lifetime Comorbidity (Odds Ratio) of Alcohol and Substance Use Dependence with Three Classes of Psychiatric Disorders among Persons Aged 18 and over in the United States**

| | Any Mood Disorder† Odds Ratio* | Any Anxiety Disorder† Odds Ratio* | Antisocial Personality Disorder‡ Odds Ratio* |
|---|---|---|---|
| Alcohol dependence | 3.3# | 2.7# | 7.8‡ |
| Nicotine dependence | 3.1# | 2.7# | 6.2# |
| *Any illicit drug dependence* | 7.1 | 4.9 | 16.7 |
| Sedatives | 9.0 | 7.4 | 20.9 |
| Tranquilizers | 10.7 | 7.8 | 23.0 |
| Opioids | 11.2 | 8.2 | 18.0 |
| Amphetamines | 7.5 | 5.3 | 17.1 |
| Hallucinogens | 11.6 | 6.5 | 18.3 |
| Marijuana | 6.5 | 5.0 | 18.7 |
| Cocaine | 7.1 | 4.3 | 15.1 |
| Inhalants | 4.1 | 2.6 | 18.7 |

* Unadjusted odds ratios.
† Conway et al., 2006: Tables 4 and 5.
‡ Compton et al., 2005a: Table 3.
#Secondary analysis of 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions.

*Source*: National Institute on Alcohol Abuse and Alcoholism, 2006.

## Vulnerability

### Developmental Factors: Adolescence as a Critical Exposure Period

Normal developmental processes may result in higher risk for drug use at certain stages of the life cycle than others. Epidemiological data on patterns of drug use as well as animal studies support the notion of critical development periods for drug behavior (Purves et al. 2001). Experimentation most often starts in adolescence, as does the process of addiction (Wagner and Anthony 2002), a period during which the brain is still undergoing significant developmental changes (Dahl and Spear 2004). The percentage of children exposed to a drug of abuse during adolescence is not negligible. *Monitoring the Future*, a national study of drug use among high school students, reported that in 2006, the lifetime rates of use among adolescents in the 8th, 10th, and 12th grades for alcohol were 41%, 62%, and 73%, respectively; for cigarettes, 25%, 36%, and 47%, respectively; and for illicit substances, 21%, 36%, and 48%, respectively (University of Michigan 2006). Although the effects of drugs of abuse during this stage of development have not been adequately investigated, initial exposure during adolescence is associated with more chronic use, more intensive use, and greater risk of dependence compared with initiation at older ages (Figure 22–5). For example, epidemiological studies have provided evidence of an increased likelihood for the development of a substance use disorder when cigarette smoking, drinking, or the use of illicit drugs start early during adolescence (Anthony and Petronis 1995, Hingson et al. 2006, Kandel 2003, Kandel and Chen 2000, Volkow 2006). Normal adolescent-specific behaviors (such as risk-taking, novelty-seeking, response to peer pressure) increase the propensity of experimenting with legal and illegal drugs (Spear 2000), which might reflect incomplete development of brain regions (e.g., myelination of frontal lobe regions) involved in the processes of executive control and motivation (Sowell et al. 2003). The importance of adolescence as a critical developmental risk period for drug involvement and substance dependence is supported by work on rodents, which documents the greater vulnerability of adolescents than of adults to a variety of drugs. For example, in rats, exposure to nicotine during the period corresponding to adolescence is associated with greater nicotine self-administration than first exposure in adulthood, a difference that persists when the adolescent rats reach adulthood (Levin et al. 2003). Adolescent rats appear to be more sensitive than adult rats to the rewarding actions of nicotine (Belluzzi et al. 2004) and to nicotine-induced alterations in nicotine receptors (Adriani et al. 2003) in cholinergic systems in the cerebral cortex, midbrain, and hippocampus (Abreu-Villaca et al. 2003). In addition, enhanced expression of plasticity-related genes following injection of nicotine in adolescents compared with adult rats has been observed throughout the brain, but especially the forebrain (Schochet et al. 2005). Similar vulnerabilities in adolescence have been reported for alcohol (Rezvani and Levin 2004, Slawecki and Roth 2004, Ristuccia and Spear 2005), amphetamines (McPherson and Lawrence 2006), and morphine (White and Holtzman 2005). Future research should clarify whether neurobiological changes cause greater vulnerability of adolescents than of adults to addiction to nicotine (Kandel and Chen 2000) and alcohol (Grant et al. 2001).

### Genetic Factors

It is estimated that 40–60% of the vulnerability to addiction is attributable to genetic factors (Uhl and Grow 2004). These factors play a less important role for initiation of substance abuse than dependence (Fowler et al. 2007, Lerman and Berrettini 2003). Multiple genes have been identified in animals as key to drug responses, and their modifications markedly affect drug self-administration (Laakso et al. 2002) (see below). In humans, several chromosomal regions have been linked to drug abuse, but only a few specific genes have been identified with polymorphisms (alleles) that either predispose to or protect from drug addiction (Uhl and Grow 2004). Some of these are polymorphisms that interfere with drug metabolism. For example, specific alleles for the genes that encode alcohol dehydrogenase ADH1B and acetaldehyde dehydrogenase ALDH2 (enzymes involved in the metabolism of alcohol) are reportedly protective against alcoholism (Chen et al. 1999). Similarly, polymorphisms in the genes for cytochrome P-450 2A6 and 2D6 (enzymes involved in nicotine and opioid metabolism, respectively) are reportedly protective against nicotine addiction (Rao et al. 2000) and codeine abuse (Kathiramalainathan et al. 2000).

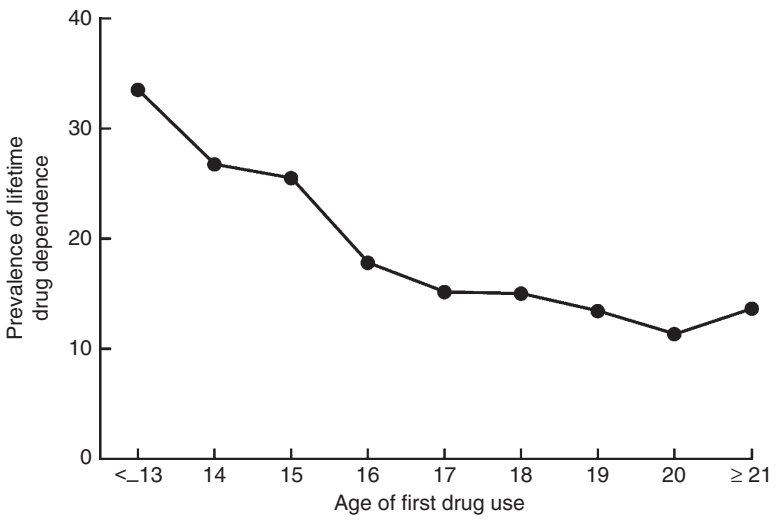



**Figure 22–5** *Prevalence of lifetime drug dependence by age at first drug use in the US population aged 18 and over in 1992. The prevalence of lifetime dependence decreased steeply with increasing age of onset of drug use. Overall, the prevalence of lifetime dependence among those who started using drugs under the age of 14 years was about 34%, dropping sharply to 15.1% for those initiating use at age 17, to about 14% among those initiating use at the age of 21 or older. (Taken with permission from Grant and Dawson 1998.)*

Some polymorphisms of genes that encode receptors that mediate drug effects have also been associated with a higher risk for addiction. For example, there is an association between alcoholism and the genes for the γ-aminobutyric acid-A ($GABA_A$) receptors, GABRG3 (Dick et al. 2004), GABRA2 (Edenberg et al. 2004), and nicotine dependence and the β3 nicotinic cholinergic receptor (Bierut et al. 2007). Dopamine $D_2$ receptor polymorphisms have been linked to a higher vulnerability to drug addiction, although some studies have failed to replicate this finding (Uhl 2004). Replication for many of the genetic findings in substance abuse and addiction is still pending.

### Environmental Factors (Adolescent Use and Vulnerability)

Environmental factors that have been consistently associated with the propensity to self-administer drugs include structural factors (such as low socioeconomic class), proximal factors (such as parental drug use and dependence, poor quality of parenting, parental depression, and peer influence), and more distal factors (such as drug availability, school, neighborhood characteristics, advertising, and the media) (Glantz and Hartel 1999, Hawkins et al. 1992, Petronis and Anthony 2000). Stress might be a common feature in a wide variety of environmental factors that increase the risk for drug abuse. The mechanisms responsible for stress-induced increases in vulnerability to drug use and to relapse in those addicted are not yet well-understood, but there is evidence that the stress-responsive neuropeptide corticotropin-releasing factor (CRF) is involved through its effects in the amygdala and the pituitary–adrenal axis (Koob 1999) (see below).

Imaging techniques now allow us to investigate how environmental factors affect the brain and how these, in turn, affect the behavioral responses to drugs of abuse. For example, in nonhuman primates, housing conditions and social status affects dopamine $D_2$ receptor expression in the brain, which in turn affects the propensity for cocaine self-administration (Morgan et al. 2002). Animals that achieve a dominant status in the group show increased levels of dopamine $D_2$ receptors and are reluctant to administer cocaine, whereas animals that are subordinate have lower dopamine $D_2$ receptor levels and readily administer cocaine. Animal studies have shown that increasing dopamine $D_2$ receptors in nucleus accumbens markedly decreases drug consumption (which has been demonstrated for alcohol) (Thanos et al. 2001), which could provide a mechanism by which a social stressor could modify the propensity to self-administer drugs.

### Gene–Environment Interaction

Ultimately, understanding the etiology of substance use and dependence will require the examination of interactions among genetic and environmental factors (Compton et al. 2005b). Advances in human genetics make it easier as well to identify environmental factors. We now can test in experimental animals as well as in people how a genetic risk will be modified by environmental factors and vice versa. Ottman (1996) first outlined five potential patterns of gene–environment interactions. The genotype produces or increases the expression of the environmental risk factor; the genotype exacerbates the effect of the risk factor; exposure to the risk factor exacerbates the effect of the genotype, without which there would be no effect; both the genotype and the risk factor are required to increase the risk; the genotype and the risk factor each affect risk, and their joint effects can be higher or lower than the effect of each alone (Hernandez and Blazer 2006: Figure 8.1, p. 166). One of the first demonstrations of a gene–environment interaction was the finding by Caspi et al. (2003) that the neurotransmitter-metabolizing enzyme monoamine oxidase A moderated the effect of childhood maltreatment on the development of conduct disorder, antisocial personality, and adult violent crime among boys. People with low monoamine oxidase A levels were more likely to develop such problems than those with high levels.

Very few empirical studies have yet identified gene–environment interactions with respect to substance dependence. Caspi et al. (2005) found that a functional polymorphism in the catechol-*O*-methyltransferase gene increased the risk that an adolescent who used cannabis would meet criteria for schizophreniform disorder at age 26. Another recent illustration is the finding that team sport participation buffered the effect of two genotypes that confer risk for smoking (the dopamine reuptake transporter SLC6A3 and the dopamine receptor DRD2) on the progression of adolescent smoking (Audrain-McGovern et al. 2006).

## Neuropharmacology of Drug Intoxication and Reward

### Animal Models

Much of the recent progress in understanding the neurobiology of addiction has been derived from the study of animal models. While no animal model of addiction fully emulates human addiction, animal models do permit investigation of specific elements of the process of drug addiction. Such elements can be defined by models of different stages of the addiction cycle, models of psychological constructs such as positive and negative reinforcement, and models of actual symptoms of addiction.

Animal models of reward are extensive and wellvalidated. Animals and humans will readily self-administer drugs in the nondependent state. Drugs of abuse have powerful reinforcing properties such that animals will perform many different tasks and procedures to obtain the drugs, even in the nondependent state. Drugs that are self-administered by animals correspond well with those that have high abuse potential in humans, and intravenous self-administration by animals is considered predictive of abuse potential (Collins et al. 1984). Intravenous self-administration of drugs such as cocaine, methamphetamine, heroin, and nicotine in rodents and primates produces a characteristic pattern of behavior that lends itself to neuropharmacological study (Figure 22–6). Using this procedure, the dose, cost of responding, and second-order schedules (working for a stimulus [cue] that then allows the reinforcer to be delivered), all can be manipulated to determine the value of the reward. Similar studies have been performed and validated with oral self-administration of alcohol as a reward where animals will work to obtain meaningful blood alcohol levels (Samson 1986).

Two other animal models have been used extensively to indirectly measure drug reward: conditioned place preference and brain reward thresholds. Conditioned place preference assesses the reinforcing efficacy of drugs using a

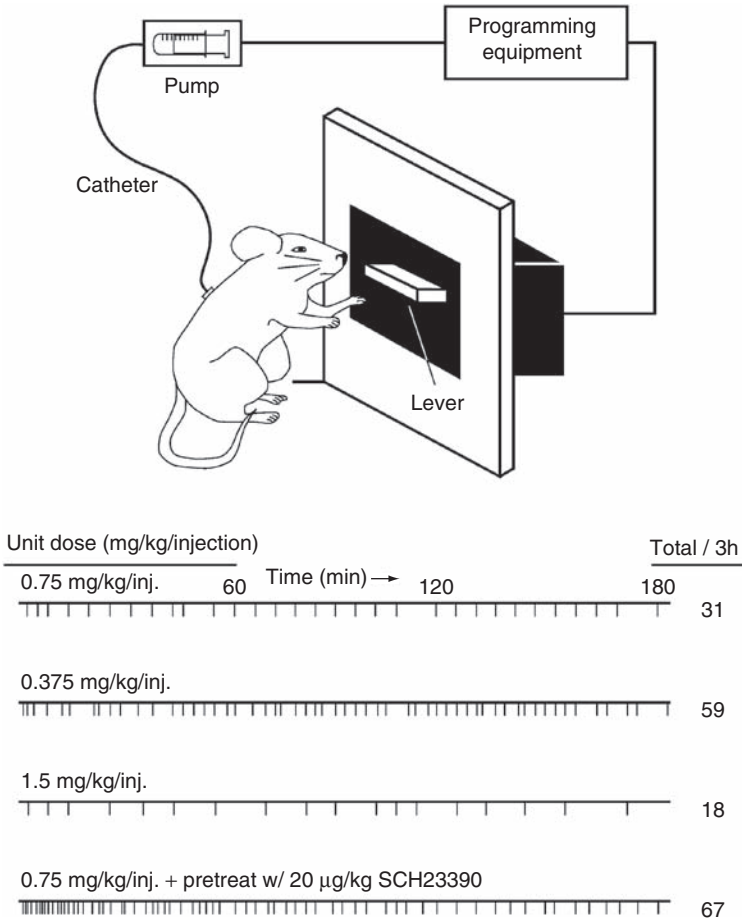



**Figure 22–6** *(a) Drawing describing the procedure for intravenous self-administration in the rat. (b) Event record and dose–response relationship relating the dose of cocaine to the number of infusions. Rats implanted with intravenous catheters and trained to self-administer cocaine with limited access (3 h/day) will show stable and regular drug intake over each daily session. No obvious tolerance or dependence develops. Rats are generally maintained on a low-requirement, fixed-ratio (FR) schedule for intravenous infusion of the drug, such as FR-1 or FR-5. In an FR-1 situation, one lever press is required to deliver an intravenous infusion of cocaine. In an FR-5 situation, five lever presses are required to deliver an infusion of cocaine. A special aspect of using an FR schedule is that the rats appear to regulate the amount of drug self-administered. Lowering the dose from the training level of 0.75 mg/kg/injection and pretreating the animal with dopamine $D_1$ receptor antagonist SCH23390 increase the number of self-administered infusions and vice versa. (Taken with permission from Caine et al. 1993.)*

classical or Pavlovian conditioning procedure. Here, animals experience two distinct neutral environments that are paired spatially and temporally with distinct drug or nondrug states, respectively. The animal is then given an opportunity to choose to enter and explore either environment, and the time spent in the drug-paired environment is considered an index of the drug's reward value. Animals typically exhibit a conditioned place preference for an environment associated with drugs that are self-administered by humans and avoid environments that induce aversive states (for conditioned place aversion, see below).

Lowering the threshold of brain stimulation reward also reliably measures drug reward. Animals will self-administer electrical stimulation to certain brain areas, notably the origins and projections of the medial forebrain bundle, and humans have described stimulation of these areas as pleasurable. The hypothesis derived from Olds and Milner and the subsequent body of work show that brain stimulation reward directly stimulates neuronal circuits that are activated by natural reinforcers thus tapping directly into the brain reward circuitry. Drugs of abuse decrease thresholds for brain reward, and there is good correspondence between the ability of drugs to decrease brain reward thresholds and their abuse potential (Kornetsky and Bain 1990).

## Types of Drugs

A key element of drug addiction is how the brain reward system changes with the development of addiction. Indeed, to understand how these systems change with the development of addiction, one must understand the neurobiological bases for acute drug reward. A principal focus of research on the neurobiology of the positive reinforcing effects of drugs of abuse has been to examine the origins and terminal areas of the mesocorticolimbic dopamine system, important in psychostimulant reward. This specific circuit has been broadened to include the many neural inputs and outputs that interact with the ventral tegmental area and the basal forebrain, and as such has been termed by some as the mesolimbic reward system (Figure 22–7).

Recently, specific components of the basal forebrain that have been identified with studies of drug reward have also focused on the "extended amygdala," which includes the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition zone in the medial (shell) part of the nucleus accumbens. As the neural circuits for the reinforcing effects of drugs of abuse has become better understood, so has the role of the neurotransmitters/neuromodulators involved. Four systems have been identified as having an important role in the acute reinforcing effects of drugs of abuse: the mesolimbic dopamine system, the opioid peptide system, the GABA system, and the endocannabinoid system (Table 22–6). While some have argued for a drug reward system in series with the mesolimbic dopamine system, others have argued that as one moves away from the psychostimulant drugs, such as cocaine and amphetamines, the importance of dopamine diminishes, and other neurochemical systems may have drug reward functions independent of dopamine in the extended amygdala.

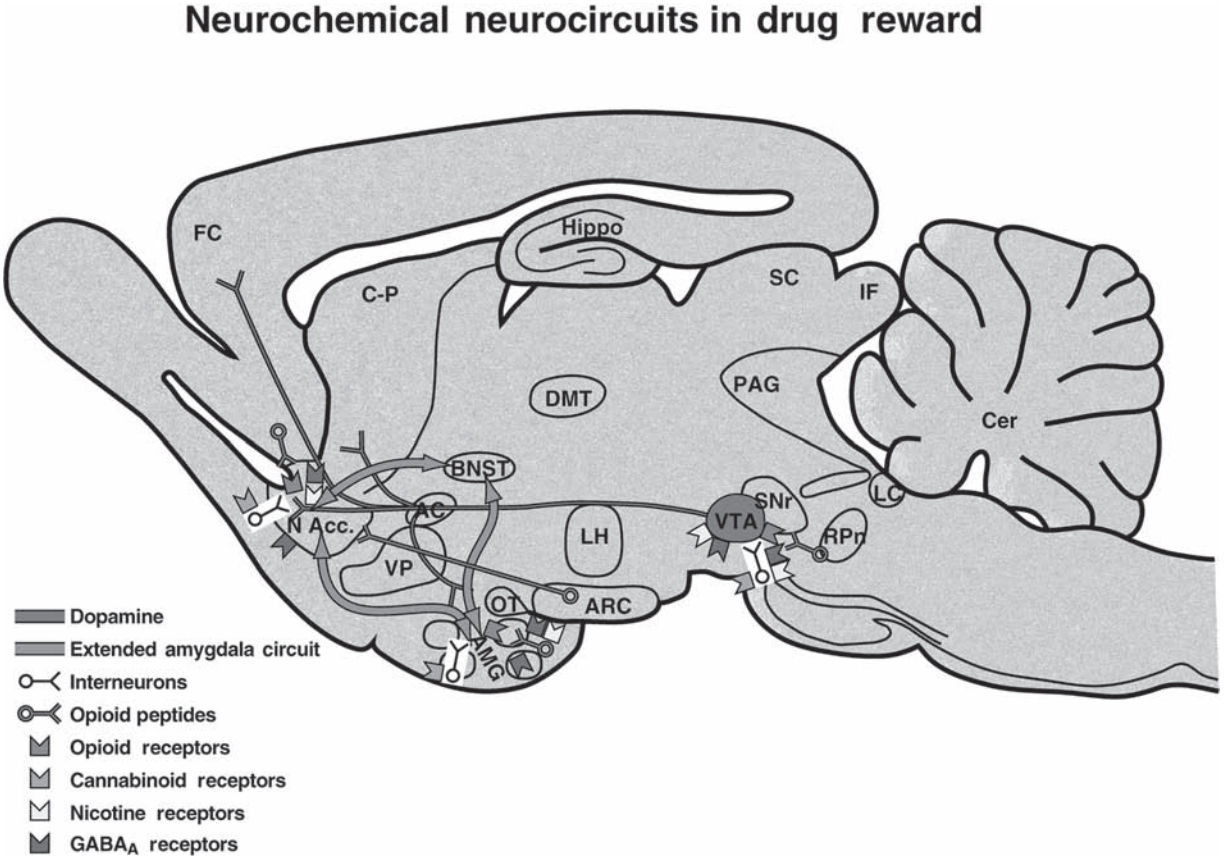



**Figure 22–7** *Sagittal section through a representative rodent brain illustrating the pathways and receptor systems implicated in the acute reinforcing actions of drugs of abuse. Cocaine and amphetamines activate the release of dopamine in the nucleus accumbens and amygdala via direct actions on dopamine terminals. Opioids activate opioid receptors in the ventral tegmental area, nucleus accumbens, and amygdala via direct actions on interneurons. Opioids facilitate the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens, but also are hypothesized to activate the elements independent of the dopamine system. Alcohol activates γ-aminobutyric acid-A (GABA$_A$) receptors in the ventral tegmental area, nucleus accumbens, and amygdala via either direct actions at the GABA$_A$ receptor or through indirect release of GABA. Alcohol is hypothesized to facilitate the release of opioid peptides in the ventral tegmental area, nucleus accumbens, and central nucleus of the amygdala. Alcohol facilitates the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens. Nicotine activates nicotinic acetylcholine receptors in the ventral tegmental area, nucleus accumbens, and amygdala, either directly or indirectly, via actions on interneurons. Nicotine also may activate opioid peptide release in the nucleus accumbens or amygdala independent of the dopamine system. Cannabinoids activate cannabinoid CB$_1$ receptors in the ventral tegmental area, nucleus accumbens, and amygdala via direct actions on interneurons. Cannabinoids facilitate the release of dopamine in the nucleus accumbens via an action either in the ventral tegmental area or the nucleus accumbens, but also are hypothesized to activate the elements independent of the dopamine system. Endogenous cannabinoids may interact with postsynaptic elements in the nucleus accumbens involving dopamine and/or opioid peptide systems. The blue arrows represent the interactions within the extended amygdala system hypothesized to have a key role in psychostimulant reinforcement. AC: anterior commissure; AMG: amygdala; ARC: arcuate nucleus; BNST: bed nucleus of the stria terminalis; Cer: cerebellum; C-P: caudate-putamen; DMT: dorsomedial thalamus; FC: frontal cortex; Hippo: hippocampus; IF: inferior colliculus; LC: locus coeruleus; LH; lateral hypothalamus; N Acc.: nucleus accumbens; OT: olfactory tract; PAG: periaqueductal gray; RPn: reticular pontine nucleus; SC: superior colliculus; SNr: substantia nigra pars reticulata; VP: ventral pallidum; VTA: ventral tegmental area. (Reproduced with permission from Koob 2005.) (See Color Plate III)*

## Stimulants

Early work on psychostimulants showed that destruction of the mesocorticolimbic dopamine system with a dopamine-specific neurotoxin blocked both the locomotor activation and rewarding effects of cocaine and methamphetamine (Roberts et al. 1980). Subsequent pharmacological studies revealed a key role for three of the five dopamine receptor subtypes ($D_1$, $D_2$, and $D_3$) and a localization of such effects to the medial parts of the nucleus accumbens (shell) and some activity in the central nucleus of the amygdala and bed nucleus of the stria terminalis (for review see Koob et al. 1998). Other neurochemical systems modulating the psychostimulant reward include serotonin and glucocorticoids.

## Nicotine

As with psychostimulants, blockade and destruction of the mesocorticolimbic dopamine system with dopamine-specific neurotoxins blocks the acute rewarding effects of nicotine, but the neuropharmacological action has been hypothesized to be via nicotinic receptor activation of dopamine release primarily in the ventral tegmental area but also presynaptically in the nucleus accumbens (Watkins et al. 2000). However, nicotine reward as measured by conditioned place preference appears to be independent of the mesocorticolimbic dopamine system (Laviolette et al. 2002). Other substrates implicated in nicotine reward include cholinergic inputs to the pedunculopontine nucleus (Yeomans and Baptista 1997). In the ventral tegmental area, different nicotine receptor

**Table 22–6 Neurobiological Substrates for the Acute Reinforcing Effects of Drugs of Abuse**

| Drug of Abuse | Neurotransmitter | Site |
|---|---|---|
| Cocaine and amphetamines | dopamine | nucleus accumbens amygdala |
| Opioids | γ-aminobutyric acid | nucleus accumbens |
| | opioid peptides | ventral tegmental area |
| | dopamine | |
| | endocannabinoids | |
| Nicotine | dopamine | nucleus accumbens |
| | γ-aminobutyric acid | ventral tegmental area |
| | opioid peptides | amygdala |
| $\Delta^9$-tetrahydrocannabinol | endocannabinoids | nucleus accumbens |
| | opioid peptides | ventral tegmental area |
| Alcohol | dopamine | nucleus accumbens |
| | dopamine | ventral tegmental area |
| | opioid peptides | amygdala |
| | γ-aminobutyric acid | |
| | glutamate | |
| | endocannabinoids | |

Taken with permission from Koob and Le Moal, 2006.

subtypes and other neurotransmitter modulation suggest that nicotine acts via desensitization of α4, β2 nicotinic receptors and activation of GABAergic interneurons with simultaneous activation of α7 nicotinic receptors (Kelley 2002). Finally, activation of opioid peptide systems via the μ opioid receptor may contribute to the acute rewarding effects of nicotine (Berrendero et al. 2002).

### Alcohol

Alcohol does not bind to a specific receptor but appears to activate ethanol receptive elements in hydrophilic pockets of proteins. Multiple neurotransmitter systems have been implicated in its rewarding effects, including GABA, opioid peptides, dopamine, serotonin, and glutamate. Systemic and local intracerebral administration of $GABA_A$ antagonists and opioid antagonists block the acute rewarding effects of alcohol; and the most sensitive site appears to be the central nucleus of the amygdala. In addition, dopamine antagonists, cannabinoid $CB_1$ antagonists, and serotonin antagonists (serotonin-3 receptor and serotonin reuptake blockers) all have been shown to block ethanol reward as measured by oral self-administration of pharmacological amounts of ethanol in nondependent animals (Koob 2003). Ethanol at low doses may act as a glutamate antagonist specifically at the *N*-methyl-D-aspartate (NMDA) receptor, and this antagonism may also contribute to the acute rewarding effects of ethanol (Hoffman et al. 1989).

### Cannabis

Neuropharmacological studies on cannabinoids have implicated both cannabinoid and opioid mechanisms. Opioid and cannabinoid $CB_1$ antagonists block intravenous self-administration of tetrahydrocannabinol (THC) in squirrel monkeys (Justinova et al. 2003). A role for the mesocorticolimbic dopamine system has been hypothesized based on indirect evidence that THC administration activates the release of dopamine in the shell of the nucleus accumbens similar to other drugs of abuse (Tanda et al. 1997).

### Opioids

The analgesic actions of opioids are due to direct inhibition of nociceptive activity throughout the neuraxis including ascending pathways from the dorsal horn of the spinal cord and pain control circuits that descend from the midbrain back to the dorsal horn (Mansour et al. 1995). Neuropharmacological studies of opioid reward in nondependent animals have revealed key roles for activation of opioid receptors in the ventral tegmental area, pedunculopontine nucleus, nucleus accumbens, and central nucleus of the amygdala, both dependent and independent of the mesocorticolimbic dopamine systems (Koob et al. 1998). The key opioid receptor subtype involved in the rewarding effects of opioids is the μ opioid receptor. Activation of the κ opioid receptor, while producing analgesia, actually produces aversive dysphoric reactions. One region of overlap of the neural substrates for the rewarding effects of opioids and the effects of opioids on pain modulation is the central nucleus of the amygdala.

### Hallucinogens and Inhalants

Data on hallucinogens and inhalants are limited to indirect measures of intoxication. Serotonin-2A antagonists block the drug discrimination stimulus effects of lysergic acid diethylamide (LSD) in animal studies (Gresch et al. 2007) and the psychedelic experience in humans (Glennon et al. 1984). Inhalants such as nitrous oxide produce analgesia that is blocked by opioid antagonists (Chen and Quock 1990), and self-administration of nitrous oxide is blocked by opioid antagonists (Wood et al. 1977). There is evidence of place preference to toluene in rats (Lee et al. 2004), which was blocked by administration of the GABA transaminase inhibitor γ-vinyl-GABA; however, little pharmacology is available on the mechanisms of action of toluene and other inhalants.

## Substance Dependence (Addiction)

### Animal Models

A large focus in animal studies has been on the synaptic sites and molecular mechanisms in the central nervous system on which drugs of abuse act initially to produce their rewarding effects (see above). Recently, however, a number of new animal studies have examined components

of the negative reinforcing effects of dependence and are beginning to explore how the nervous system adapts to drug use. In addition, there are models of craving involving drug-, cue- and stress-induced reinstatement of drug-seeking behavior. Finally, animal models have been designed to address the transition to addiction ranging from compulsive drug-taking, as measured by escalation in drug intake (Ahmed and Koob 1998), or drug-seeking despite negative or aversive consequences (Vanderschuren and Everitt 2004, Deroche-Gamonet et al. 2004). These models also have begun to address specific elements of the diagnostic criteria used by the American Psychiatric Association and the World Health Organization to define addiction or substance dependence (American Psychiatric Association 1994, World Health Organization 1992).

Rodents will increase self-administration of drugs during withdrawal from the dependent state (termed escalation) as measured both by increased self-administration of the drug and working harder to obtain the drug. Such increased self-administration in dependent animals has now been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol (Ahmed and Koob 1998, Kitamura et al. 2006, O'Dell and Koob 2007, Ahmed et al. 2000, Roberts et al. 2000). Equally compelling are studies showing drug-taking in the presence of aversive consequences in animals with extended access to the drug. Rats with extended access to cocaine did not suppress drug-seeking in the presence of an aversive conditioned stimulus, which has face validity for the DSM-IV-TR criteria of "continued substance use despite knowledge of having a persistent physical or psychological problem" (Vanderschuren and Everitt 2004).

Animal models of craving (preoccupation/anticipation stage) involve both the conditioned rewarding effects of drugs of abuse and measures of the conditioned aversive effects of dependence (Shippenberg and Koob 2002). Resistance to extinction has been used to measure the residual motivational properties of drugs by assessing the persistence of drug-seeking behavior in the absence of response-contingent drug availability. Other measures of craving examine the motivational properties of the drugs themselves, or cues paired with the drugs, after extinction. Drug-induced reinstatement first involves extinction, and then presentation of a priming injection of a drug. Latency to reinitiate responding, or the amount of responding on the previously extinguished lever are hypothesized to reflect the motivation for drug-seeking behavior. Similarly, drug-paired or drug-associated stimuli can reinitiate drug-seeking behavior (cue-induced reinstatement). Other measures of craving include second-order schedules where animals can be trained to work for a previously neutral stimulus that predicts drug availability.

From the aversive side, acute stressors can also reinitiate drug-seeking behavior in animals that have been extinguished, and this is called stress-induced reinstatement. Increased brain reward thresholds and increased anxiety-like behavior have been shown to persist after acute withdrawal in animals studies and have been hypothesized to reflect protracted abstinence. Finally, with opioids, conditioned withdrawal has been observed. Previously neutral stimuli paired with precipitated opioid withdrawal have been shown to produce place aversions and motivate increasing self-administration of opioids (Kenny et al. 2006).

## Brain Circuitry Neuroadaptations

### Reward Circuit

The reinforcing effects of drugs during intoxication set the initial stage that, if perpetuated, triggers the neuronal adaptations that result in addiction. Imaging studies in drug abusers as well as nondrug abusers have shown that drugs of abuse increase the extracellular concentration of dopamine in the striatum (where the nucleus accumbens is located) and that these increases are associated with their reinforcing effects. Subjects having the greatest increases in dopamine were the ones that perceived drug effects such as "high," "rush," or "euphoria" most intensely (Laruelle et al. 1995, Volkow et al. 1999b, Drevets et al. 2001). These studies also showed that the reinforcing effects appeared to be associated not only with the magnitude of the dopamine increase but also with the abruptness of the increase. Thus, for an equivalent increase in dopamine, the drug was perceived as reinforcing when it was injected intravenously, which leads to fast drug uptake in the brain and presumably very fast changes in dopamine concentration, but not when it was given orally (Volkow et al. 2001), which leads to a slow rate of brain uptake and presumably slow increases in dopamine concentration. The relation of the reinforcing effects of drugs to fast and large increases in dopamine concentration parallels the fast changes in dopamine concentration induced by phasic dopamine cell firing (fast burst firing >30 Hz) (Wightman and Robinson 2002), which mediates the salience of stimuli (Grace 2000). This contrasts with tonic dopamine cell firing (slow firing at frequencies of around 5 Hz) (Wightman and Robinson 2002), which maintains baseline steady-state dopamine levels, whose function is to set the overall responsiveness of the dopamine system. These findings have led to the hypothesis that by inducing changes in dopamine concentration that mimic, but exceed those produced by phasic dopamine cell firing, drugs of abuse overactivate the neuronal processes of saliency, accounting for their high reinforcing value.

However, increases in dopamine concentration during intoxication occur in both addicted and nonaddicted subjects, so this by itself cannot explain the process of addiction. Since drug addiction requires chronic drug administration, it seems likely that addiction results from the repeated perturbation of reward circuits (marked dopamine increases followed by dopamine decreases) and the consequent disruption of the circuits that it regulates (motivation/drive, memory/learning, and control). Indeed, imaging studies in drug-addicted subjects have consistently shown long-lasting decreases in the numbers of dopamine $D_2$ receptors in drug abusers when compared with controls (Volkow et al. 2002) (Figure 22–8). In addition, cocaine abusers also have decreased activity, as demonstrated by reduced dopamine release in response to a pharmacological challenge with a stimulant drug (Volkow et al. 1997). The decrease in the number of dopamine $D_2$ receptors, coupled with the decrease in dopaminergic activity, in the abusers could well result in a decreased sensitivity of reward circuits to stimulation by natural reinforcers. This decreased sensitivity would lead to decreased interest in ordinary environmental stimuli, possibly predisposing subjects to seek drug stimulation as a means to activate these reward circuits. Imaging studies provide evidence of disrupted sensitivity to natural reinforcers

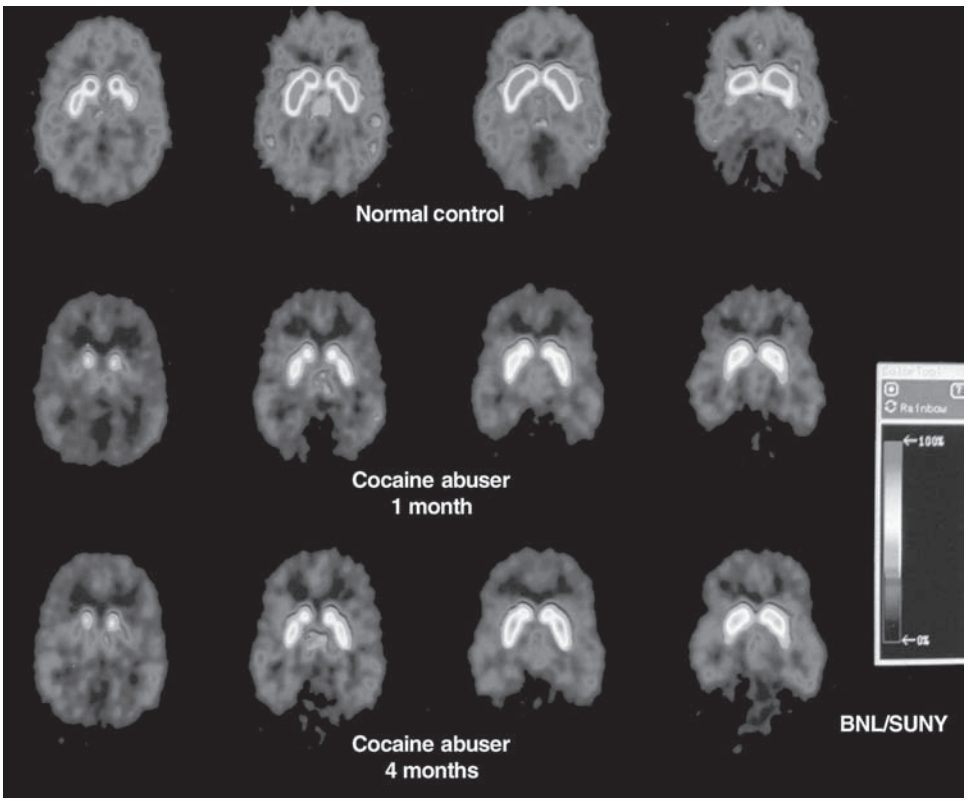



**Figure 22–8** *[$^{18}$F]N-methylspiroperidol images in a normal control and in a cocaine abuser tested 1 month and 4 months after last cocaine use. The images correspond to the four sequential planes where the basal ganglia are located. The color scale has been normalized to the injected dose. Notice the lower uptake of the tracer in the cocaine abuser compared to the normal control. Notice also the persistence of the decreased uptake even after 4 months of cocaine discontinuation. BNL: Brookhaven National Laboratory; SUNY: State University of New York. (Taken with permission from John Wiley and Sons Inc. 1993.) (See Color Plate V)*

in addiction. For example, in a study by Martin-Solch et al. (2001), the mesostriatal and mesocorticolimbic circuits of opiate addicts were not activated in response to natural reinforcers whereas they were in controls subjects. Similarly, in a second study by the same group, dopamine-regulated reward centers in tobacco smokers failed to activate in response to monetary reward. Interestingly, decreased sensitivity of reward circuits to acute alcohol administration has also been documented in cocaine abusers when compared to control subjects (Volkow et al. 2000). These findings suggest an overall reduction in the sensitivity of reward circuits in drug-addicted individuals not only to natural reinforcers but also possibly to drugs that are different from the drug to which they are addicted.

## Drive/Motivation Circuit

During addiction, the value of the drug as a reinforcer is hypothesized to be so much greater than that of any other natural reinforcer that natural reinforcers can no longer compete as viable alternatives, and the enhanced "saliency value" of the drug becomes fixed. This is in contrast to natural reinforcers for which the saliency is momentary and decreases with exposure to the reinforcer (Di Chiara 2002) or by the presentation of alternative, more appealing reinforcers. One of the areas of the brain involved in shifting the relative value of reinforcers is the orbitofrontal cortex (Schultz et al. 2000, Rolls 2000).

Imaging studies have provided evidence of disruption of the orbitofrontal cortex during addiction (reviewed in Volkow and Fowler 2000). The orbitofrontal cortex appears to be hypoactive in drug-addicted subjects tested during withdrawal (Volkow et al. 1992, Adinoff et al. 2001), which may reflect the lack of stimulation by salient stimuli during detoxification. In contrast, in active cocaine abusers, the orbitofrontal cortex has been shown to be hypermetabolic in proportion to the intensity of the craving experienced by the subjects (Volkow et al. 1991). Since increased orbitofrontal cortex activation has been associated with compulsive disorders (Insel 1992), activation of the orbitofrontal cortex in addicted subjects may contribute to the compulsive drug intake. Indeed, preclinical studies have shown that damage of the orbitofrontal cortex results in a behavioral compulsion to procure the reward even when it is no longer reinforcing (Volkow and Fowler 2000). This is consistent with the descriptions by drug addicts who claim that once they start taking the drug, they cannot stop even when the drug is no longer pleasurable. Exposure to the drug or drug-related stimuli in the withdrawal state reactivates the orbitofrontal cortex and may be responsible for the compulsive drug intake that ensues. Indeed, activation of the orbitofrontal cortex has been reported during drug intoxication in drug-addicted, but not in nondrug-addicted, subjects and the level of activation predicted the intensity of drug-induced craving (Volkow et al. 1999a, Brody et al. 2002). Similarly, activation of the orbitofrontal cortex has been reported during exposure to drug-related cues when these elicit craving. Since the orbitofrontal cortex also processes information associated with the prediction of reward (Schultz et al. 2000), its activation during cue-exposure could signal reward prediction, which could be perceived as craving by the addicted subject.

In detoxified drug abusers, the decreased activity in the orbitofrontal cortex is associated with reductions in the numbers of dopamine $D_2$ receptors in striatum (Volkow et al.

1993, 2001). Since dopamine $D_2$ receptors transmit reward signals into the orbitofrontal cortex, this association could be interpreted as a disruption of the orbitofrontal cortex, secondary to changes in striatal dopamine activity (such as lack of stimulation during withdrawal and enhanced stimulation with exposure to drugs or drug-related cues). However, since striatal–frontal connections are bidirectional, this association could also reflect the disruption of the orbitofrontal cortex, which then deregulates dopamine cell activity.

## Emotional Circuit

Addiction also involves a long-term, persistent plasticity in the activity of neural circuits mediating motivational systems that derives from recruitment of *antireward* systems that drive aversive states. *Antireward* is a concept developed based on the hypothesis that there are brain systems in place to limit reward (Koob and Le Moal 1997), an opponent process concept that forms a general feature of biological systems. The concept of an antireward system is derived from the hypothesis of not only a within-system neuroadaptation, such as a loss of dopamine function (see above), but also a between-system neuroadaptation to activation of the reward system at the neurocircuitry level. Here, a between-system neuroadaptation is a circuitry change where circuit B (antireward circuit) is activated by circuit A (reward circuit).

The *withdrawal/negative affect* stage defined above consists of key motivational elements such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia, and loss of motivation for natural rewards, and is characterized in animals by increases in reward thresholds during withdrawal from all major drugs of abuse. Significant plasticity occurs in the neurotransmitter circuits identified as critical for the acute reinforcing effects of drugs of abuse. In animal models of the transition to addiction, increases in brain reward threshold (decreased reward) occur that temporally precede and highly correlate with escalation in drug intake (Ahmed et al. 2002). During acute withdrawal, there is decreased activity of the reward systems as well as decreased opioid peptide, GABA, glutamate, and neuropeptide Y activity in elements of the extended amygdala and/or nucleus accumbens (see above).

However, as dependence and withdrawal develop, brain antireward systems such as corticotropin-releasing factor (CRF), norepinephrine, and dynorphin are recruited (Figure 22–9). For example, extracellular CRF in the extended amygdala is increased during acute withdrawal from drugs of abuse, and critically, CRF antagonists block excessive drug-taking during dependence (Koob 2003). These neurotransmitter systems are known to be activated during the development of excessive drug-taking as a between-system opponent process (see above), and this activation is manifest when the drug is removed (acute withdrawal and protracted abstinence). The observation that CRF receptor antagonists in the amygdala can block excessive drug intake associated with the development of dependence provides a compelling example of a key aspect of the plasticity of the extended amygdala in the development of addiction. Thus, antireward circuits are recruited as between-system neuroadaptations (Koob and Bloom 1988) during the development of addiction, producing

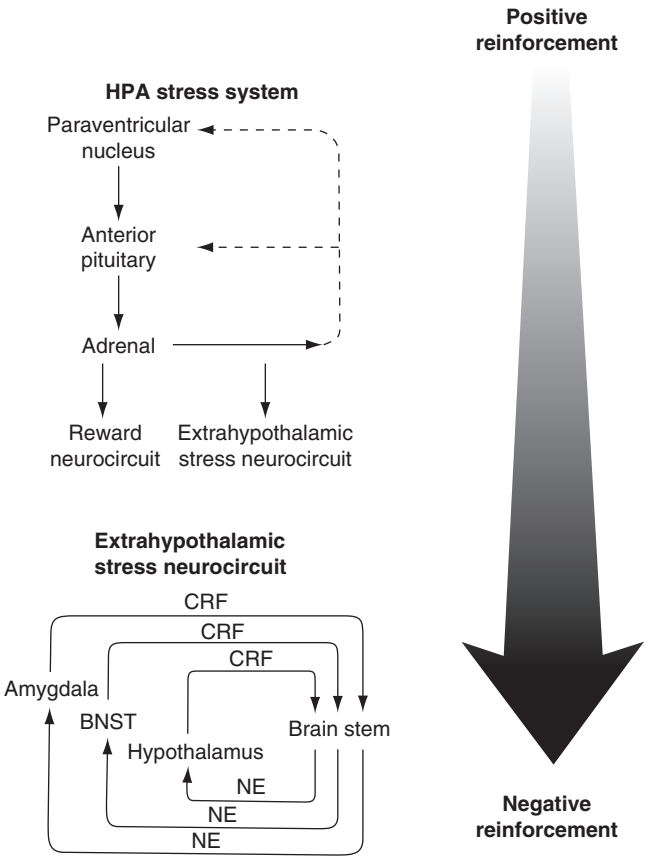



**Figure 22–9** *Hypothalamic-pituitary-adrenal (HPA) and brain stress circuits hypothesized to be recruited at different stages of the addiction cycle, as addiction moves from positive reinforcement to negative reinforcement (Aston-Jones and Harris 2004, Kreek and Koob 1998, Shaham et al. 2003). The top circuit refers to the HPA axis which (a) feeds back to regulate itself, (b) activates the brain reward neurocircuit, and (c) facilitates the extrahypothalamic stress neurocircuit. The bottom circuit refers to the brain stress circuits in feed-forward loops. Here, corticotropin-releasing factor (CRF) in the extended amygdala drives norepinephrine systems in the pons-medulla of the brain stem, which in turn drives CRF in the extended amygdala (see Koob 1999). (Adapted from Koob and Le Moal 2004.)*

aversive or stress-like states (Koob 2003, Nestler 2001, Aston-Jones et al. 1999). Within the motivational circuits of the extended amygdala, the combination of decreases in reward neurotransmitter function and recruitment of antireward systems provides a powerful source of negative reinforcement contributing to compulsive drug-seeking behavior and addiction. The development of the aversive emotional state that drives the negative reinforcement of addiction may also contribute to the critical problem in drug addiction of chronic relapse, where addicts return to compulsive drug-taking long after acute withdrawal (Koob and Le Moal 2005). Neurotransmitter/neuromodulator systems implicated in stress-induced relapse include CRF, glucocorticoids, and norepinephrine, suggesting reactivation of antireward systems during relapse (Piazza and Le Moal 1996, Shaham et al. 2000, See et al. 2003). Thus, the dysregulation of emotional processing may persist during protracted abstinence to set the tone for vulnerability to "craving" by activation of the drug-, cue-, and stress-induced reinstatement circuits, now augmented by a hypofunctioning prefrontal system (Le Moal 1995).

### Control/Executive Function Circuit

One of the most consistent findings from imaging studies is that of abnormalities in the prefrontal cortex including the anterior cingulate gyrus in drug-addicted subjects (reviewed in Goldstein and Volkow 2002). The prefrontal cortex is involved in decision-making and in inhibitory control (Royall et al. 2002). Thus, its disruption could lead to inadequate decisions that favor immediate rewards over delayed but more favorable responses. It could also account for the impaired control over the intake of the drug even when the addicted subject expresses the desire to refrain from taking the drug (Goldstein and Volkow 2002). Thus, one could expect that the disruptions of self-monitoring and decision-making processes that are observed in drug-addicted subjects (Bechara and Damasio 2002, Ernst et al. 2003) are in part related to disrupted prefrontal functions. Moreover, preclinical studies show that chronic administration of cocaine or amphetamine result in a significant increase in dendritic branching and in the density of dendritic spines in the prefrontal cortex (Robinson et al. 2001). These changes in synaptic connectivity could be involved in the changes in decision-making, judgment, and cognitive control that occur during addiction. Indeed, imaging studies have shown evidence of changes in prefrontal activation during a working memory task in smokers compared to ex-smokers (Ernst et al. 2001).

Disruption of the prefrontal cortex could lead to loss of self-directed/willed behavior in favor of automatic sensory-driven behavior. Moreover, the disruption of self-controlled behavior is likely to be exacerbated during drug intoxication from prefrontal disinhibition of the amygdala (Rosenkranz and Grace 2001). The disinhibition of prefrontal top-down control would release behaviors that are normally kept under close monitoring, and simulate stress-like reactions in which inhibitory control is suspended and stimulus-driven behavior is accentuated (Goldstein and Volkow 2002).

### Learning/Memory Circuit

The relevance of learning and memory in addiction is made evident by the pernicious effect that a place, a person, or a cue (that brings back memories of the drug) has on the addict who is trying to remain drug-free. These factors trigger an intense desire for the drug (craving) and, not infrequently, relapse. Multiple memory systems have been proposed in drug addiction including conditioned incentive learning (mediated in part by nucleus accumbens and amygdala), habit learning (mediated in part by the caudate and putamen), and declarative memory (mediated in part by the hippocampus) (White 1996). Through conditioned incentive learning, the neutral stimuli, coupled with the drug of abuse, acquire reinforcing properties and motivational salience even in the absence of the drug. Through habit learning, well-learned sequences of behavior are elicited automatically by the appropriate stimuli. Finally, declarative memory has been related to the learning of affective states in relationship to drug intake.

Memory circuits are likely to influence the effects of the drug during intoxication since they set the expectations of the drug effects in the addicted subject (Kirk et al. 1998). Activation of regions linked with memory has been reported during drug intoxication (Breiter et al. 1997, Stein et al. 1998) and during craving induced by drug exposure, video, or recall (Grant et al. 1996, Childress et al. 1999, Kilts et al. 2001, Wang et al. 1999). Also, studies in drug abusers during withdrawal have shown evidence of decreased $D_2$ receptor expression and decreased dopamine release in the dorsal striatum (Volkow et al. 1997). In animal studies, the drug-induced changes in the dorsal striatum are observed after longer drug exposures than those observed in the nucleus accumbens, and have been interpreted to reflect further progression into the addicted state (Letchworth et al. 2001). This is relevant since involvement of the dorsal striatum, which is a region associated with habit learning, indicates that in drug addiction the routine associated with drug consumption may be triggered automatically by exposure to the drug or drug-related cues (Ito et al. 2002).

## Molecular Neuroadaptations

The common neurocircuitry actions of drugs of abuse and the change in plasticity of these circuits (see above), have long been hypothesized to involve molecular neuroadaptations that either drive the weighting of the circuits or result from the changes in activity of the circuits or both (Figure 22–10). Repeated perturbation of intracellular signal transduction pathways may cause changes in neuronal function or nuclear function and altered rates of transcription of particular target genes. Altered expression of such genes would lead to presumably long-term altered activity of the neurons where such changes occur, and ultimately to changes in neural circuits in which those neurons operate.

### Transduction Factors

Signal transduction mechanisms are one of the key molecular changes following acute administration of drugs of abuse. Dopamine acutely activates and inhibits G-proteins via G*s* ($D_1$ family) and $G_i$ ($D_2$ family). Opioids produce their effects in target neurons via interactions with μ, δ, and κ classes of receptors, which are coupled via pertussis toxin-sensitive G-protein binding proteins and acutely inhibit adenylyl cyclase (Law et al. 2000).

Activation of opioid receptors also leads to recruitment of $G_i$ and related G proteins, which leads to the inhibition of adenylyl cyclase and of the cyclic adenosine monophosphate (cAMP) protein phosphorylation cascade (Gutstein and Akil 2001). Recruitment of $G_i$ also leads to activation of certain $K^+$ channels and inhibition of voltage-gated $Ca^{2+}$ channels, although the two actions occur to varying extents in different neuronal cell types. Both are inhibitory actions—more $K^+$ flows out of the cell and less $Ca^{2+}$ flows into the cell—that mediate some of the relatively rapid inhibitory effects of opioids on the electrical properties of their target neurons. Similarly, reductions in cellular $Ca^{2+}$ levels alter $Ca^{2+}$-dependent protein phosphorylation cascades. Altered activity of these protein phosphorylation cascades, which also can vary among different cell types, leads to the regulation of still additional ion channels which contribute further to the acute effects of the drug (Nestler 2004, Nestler and Malenka 2004).

However, chronic exposure to opioids increases adenylyl cyclase (Sharma et al. 1975, Collier and Francis 1975), leading to other perturbations in intracellular messenger pathways, including protein phosphorylation mechanisms. These perturbations eventually elicit changes in many other neural processes within target neurons (Nestler 2004, Nestler and

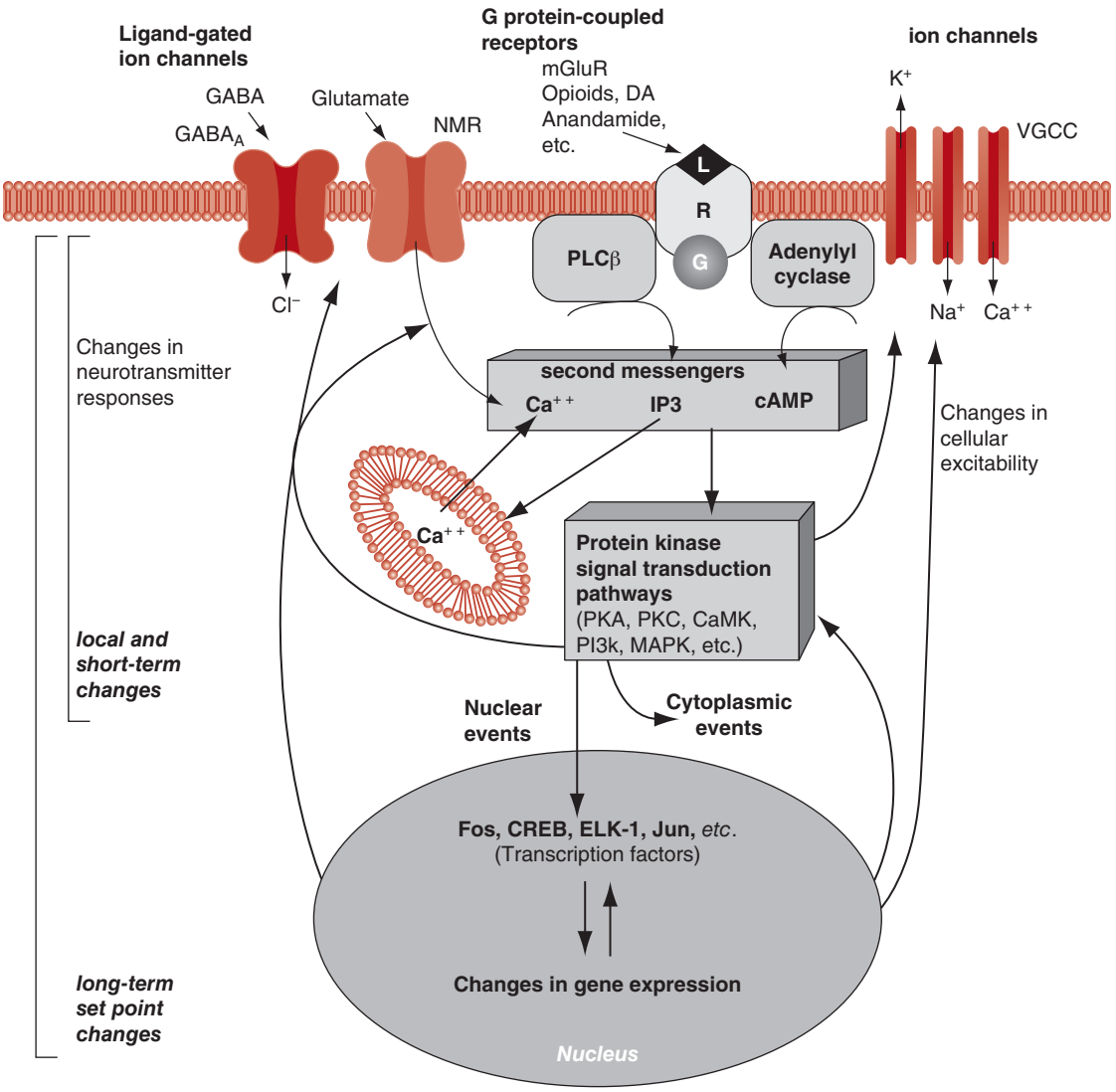



**Figure 22–10** *Molecular mechanisms of neuroadaptation.* Cocaine *and* amphetamines*, as indirect sympathomimetics, stimulate the release of dopamine which acts at G protein-coupled receptors, specifically $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$. These receptors modulate the levels of second-messengers like cyclic adenosine monophosphate (cAMP) and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Such protein kinases affect the functions of proteins located in the cytoplasm, plasma membrane, and nucleus. Among membrane proteins affected are ligand-gated and voltage-gated ion channels (VGCC). $G_i$ and $G_o$ proteins also can regulate potassium and calcium channels directly through their βγ subunits. Protein kinase transduction pathways also affect the activities of transcription factors. Some of these factors, like cAMP response element binding protein (CREB), are regulated posttranslationally by phosphorylation; others, like Fos, are regulated transcriptionally; still others, like Jun, are regulated both posttranslationally and/or transcriptionally. While membrane and cytoplasmic changes may be only local (e.g., dendritic domains or synaptic boutons), changes in the activity of transcription factors may result in long-term functional changes. These may include changes in gene expression of proteins involved in signal transduction and/or neurotransmission, resulting in altered neuronal responses. For example, chronic exposure to psychostimulants has been reported to increase the levels of protein kinase A (PKA) and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Chronic exposure to psychostimulants also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the nucleus accumbens by chronic cocaine treatment. Chronic cocaine induces a transition from Fos induction to the induction of the much longer lasting Fos-related antigens (Fras) such as ΔFosB.* Opioids*, by acting on neurotransmitter systems, affect the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Examples of ligand-gated ion channels such as the γ-aminobutyric acid-A ($GABA_A$) and glutamate* N*-methyl-D-aspartate (NMDA) receptor (NMR) and G protein-coupled receptors such as opioid, dopamine (DA), or the cannabinoid $CB_1$ receptors, among others, are shown. These receptors modulate the levels of second messengers like cAMP and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Chronic exposure to opioids has been reported to increase levels of protein kinase A and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Chronic exposure to opioids also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the nucleus accumbens and increased in the locus coeruleus by chronic morphine treatment, while chronic opioid exposure activates FRAs such as ΔFosB.* Alcohol*, by acting on neurotransmitter systems, affects the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Examples of ligand-gated ion channels such as the $GABA_A$ and the NMDA receptor and G protein-coupled receptors such as opioid, dopamine, or the cannabinoid $CB_1$ receptors, among others, are shown. The latter also is activated by endogenous cannabinoids such as anandamide. These receptors modulate the levels of second messengers such as cAMP and $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Such protein kinases affect the functions of proteins located in the cytoplasm, plasma membrane, and nucleus. Among membrane proteins affected are ligand-gated and VGCCs. Alcohol, for instance, has been proposed to affect the $GABA_A$ response via protein kinase C (PKC) phosphorylation. $G_i$ and $G_o$ proteins also can regulate potassium and calcium channels directly through their βγ subunits. Chronic exposure to alcohol has been reported to increase levels of protein kinase A and adenylyl cyclase in the nucleus accumbens and to decrease the levels of $G_{i\alpha}$. Moreover, chronic ethanol induces differential changes in subunit composition in the $GABA_A$ and*

Malenka 2004). Early studies involving the locus coeruleus showed upregulation of the cAMP pathway in locus coeruleus neurons (Nestler et al. 1993) and formed a molecular model of opioid neuroadaptation in the brain (Collier 1980, Nestler 1996, Sharma et al. 1975). This up-regulated cAMP pathway was hypothesized to contribute to the increase in the intrinsic electrical excitability of locus coeruleus neurons that underlies the cellular forms of tolerance and dependence exhibited by these neurons (Rasmussen et al 1990, Nestler 1996). Similar molecular elements show neuroplasticity in the brain motivational circuits, notably the nucleus accumbens. Heroin exposure also increased protein kinase A activity in the nucleus accumbens (Self et al. 1995), and increased cAMP response element (CRE)-regulated transcription also has been observed in the nucleus accumbens during opioid withdrawal (Shaw-Lutchman et al. 2002).

## Transcription Factors

Two transcription factors in particular have been implicated in the plasticity associated with addiction: cAMP response element binding protein (CREB) and ΔFosB. CREB regulates the transcription of genes that contain a CRE site within the regulatory regions and can be found ubiquitously in genes expressed in the central nervous system such as those encoding neuropeptides, synthetic enzymes for neurotransmitters, signaling proteins, and other transcription factors. CREB can be phosphorylated by protein kinase A and by protein kinases regulated by growth factors, putting it at a point of convergence for several intracellular messenger pathways that can regulate the expression of genes.

Much work in addiction has shown that chronic exposure to opiates, cocaine, and alcohol leads to activation of CREB in the nucleus accumbens and to deactivation of CREB in the central nucleus of the amygdala. The activation of CREB in the nucleus accumbens with psychostimulant drugs is linked to the symptoms of psychostimulant withdrawal, possibly through induction of the opioid peptide dynorphin which binds to k opioid receptors and has been hypothesized to represent a mechanism of motivational tolerance and dependence. These molecular adaptations decrease an individual's sensitivity to the rewarding effects of subsequent drug exposures (tolerance) and impair the reward pathway (dependence) so that after removal of the drug, the individual is left in an amotivational, dysphoric, or depressed-like state.

In contrast, decreased CREB phosphorylation has been observed in the central nucleus of the amygdala during alcohol withdrawal and has been linked to decreased neuropeptide Y function and consequently increased anxiety-like responses. Such molecular changes point to transduction mechanisms that could produce neurochemical changes in the neurocircuits outlined above and are critical for breaks with reward homeostasis in addiction.

Transcription factors can change gene expression and produce long-term changes in protein levels, and as a result, neuronal function (Nestler 2005). While acute administration of drugs of abuse can cause a rapid (within hours) activation of members of the Fos protein family, such as c-*fos*, FosB, Fra-1, and Fra-2 in the nucleus accumbens, other transcription factors, isoforms of ΔFosB, accumulate over longer periods of time (days) with repeated drug administration. Animals with activated ΔFosB have exaggerated sensitivity to the rewarding effects of drugs of abuse, and ΔFosB may be a sustained molecular "switch" that helps to initiate and maintain a state of addiction (Nestler 2005).

## Molecular Genetic Evidence

Genetic and molecular genetic animal models have provided some convergent support for the neuropharmacological substrates identified in neurocircuitry studies. High-alcohol-preferring rats have been bred that show high voluntary consumption of alcohol, increased anxiety-like responses, and numerous neuropharmacological phenotypes such as decreased dopaminergic activity and decreased neuropeptide Y activity. In an alcohol-preferring and -nonpreferring cross, a quantitative trait locus was identified on chromosome 4, a region to which the gene for neuropeptide Y has been mapped. In the inbred preferring and nonpreferring quantitative trait loci analyses, loci on chromosomes 3, 4, and 8 have been identified which correspond to loci near the genes for the dopamine $D_2$ and serotonin-1B receptors.

Gene knockout and transgenic knockin approaches have led to the ability to systematically inactivate the genes that control the expression of proteins that make up neurotransmitter and neuromodulator receptors and ligands in the central nervous system. Whereas these approaches do not guarantee that these genes are the ones that convey vulnerability in the human population, they provide viable candidates for exploring the genetic basis of endophenotypes associated with addiction.

Opioid-related gene knockout studies in mice have focused on knockout of the μ opioid receptor. Opiate (morphine) reinforcement as measured by conditioned place preference or self-administration is absent in μ knockout mice, and there is no development of somatic signs of dependence on morphine in these mice. Knockout of the μ opioid receptor also decreases nicotine reward, cannabinoid reward, and alcohol drinking in mice.

Knockout and neuropharmacological studies have implicated numerous neurotransmitter systems in ethanol preference, including opioid, dopamine, GABA, and serotonin. Novel modulatory effects on ethanol preference

*glutamate inotropic receptors and increases the expression of VGCCs. Chronic exposure to alcohol also alters the expression of transcription factors themselves. CREB expression, for instance, is increased in the nucleus accumbens and decreased in the amygdala by chronic alcohol treatment. Chronic alcohol induces a transition from Fos induction to the induction of the longer lasting FRAs.* Nicotine *acts directly on ligand-gated ion channels. These receptors modulate the levels of $Ca^{2+}$, which in turn regulate the activity of protein kinase transducers. Chronic exposure to nicotine has been reported to increase the levels of protein kinase A in the nucleus accumbens. Chronic exposure to nicotine also alters the expression of transcription factors themselves. CREB expression, for instance, is depressed in the amygdala and prefrontal cortex and increased in the nucleus accumbens and ventral tegmental area.* $\Delta^9$-tetrahydrocannabinol, *by acting on neurotransmitter systems, affects the phenotypic and functional properties of neurons through the general mechanisms outlined in the diagram. Cannabinoids act on a G protein-coupled receptor, the cannabinoid $CB_1$ receptor. The $CB_1$ receptor also is activated by endogenous cannabinoids such as anandamide. This receptor modulates (inhibits) the levels of second messengers like cAMP and $Ca^{2+}$, which in turn regulates the activity of protein kinase transducers. Chronic exposure to $\Delta^9$-tetrahydrocannabinol also alters the expression of transcription factors themselves. PLCB, phospholipase CB; IP3, inositol triphosphate; CaMK, calmodulin-dependent protein kinase; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; ELK-1, endothelin-l-specific-like gene-l transcription factor. (Modified with permission from Koob et al. 1998.) (See Color Plate IV)*

have been suggested by protein kinase and G-protein-activated inwardly rectifying $K^+$ channel knockout studies (Crabbe et al. 2006).

Selective deletion of the genes for expression of different dopamine receptor subtypes and the dopamine transporter has revealed significant effects on challenges with psychomotor stimulants. Dopamine $D_1$ receptor knockout mice show blunted responses to the locomotor-activating effects of cocaine and amphetamine and in their acquisition of intravenous cocaine self-administration compared to wildtype mice. $D_2$ knockout mice have severe motor deficits and blunted responses to psychostimulants and opiates, but the effects on psychostimulant reward are less consistent. Dopamine transporter knockout mice are dramatically hyperactive but also show a blunted response to psychostimulants. Although compensatory developmental factors must be taken into account, it is clear that $D_1$ and $D_2$ receptors and the dopamine transporter play important roles in the actions of psychomotor stimulants.

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CHAPTER

# 23 Neuroscience of Autism

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## Introduction

Autism as a specific syndrome was first described in the scientific literature in 1943 by Leo Kanner, a preeminent child psychiatrist at Johns Hopkins University (Kanner 1943). Drawing from his wealth of experience about early psychiatric and developmental disorders, he identified a set of common features of 11 children seen over a 5-year period that set them apart, and "…whose condition differ[ed] so markedly and uniquely from anything reported so far" (p. 217). His first paper described the presenting "fascinating peculiarities" of these 11 children, and his later papers followed their development over time.

Kanner described a range of individual differences in the language ability among the children, but also a set of core features, the most important of which was "the children's inability to relate themselves in an ordinary way to people and situations from the beginning of life" (p. 242). The parental phrases that he quoted: "happiest when left alone, acting as if people weren't there, oblivious to everything around him"—are phrases that parents in 2007 still use to describe their children during diagnostic evaluations.

Kanner (1971) followed nine of these 11 children into adulthood. There was some improvement in all symptoms during the school-aged period. Yet all of the individuals continued to lack normal social relations and only two adults were eventually employed, although still single and living with their parents.

Hans Asperger, a German pediatrician, wrote a paper in 1944 (Asperger 1944) that echoed many of Kanner's descriptions, although it was not available to English readers for a number of years. Asperger also used the term "autistic" to refer to his patients and also emphasized that impairment in social integration was primary to the disorder and lifelong, affecting the child's relations to the whole environment. Like Kanner, Asperger emphasized that this difference was present from early in life, and not a progressive event as seen in schizophrenia. He underscored the pervasive nature of the condition: "it totally colours affect, intellect, will, and action" (p. 39). However, Asperger described a degree of loquaciousness, intellectual ability in math and reading, and aggression and conduct problems. The latter do not figure prominently in Kanner's patients, perhaps due to differences in age and functioning levels of the two groups of patients. Unlike Kanner, Asperger also described an abnormal relation to objects, involving abnormal fixations, collections, and lengthy monologues about these special interests.

Both Kanner and Asperger commented on the individual differences and range of levels and outcomes seen in their patients and attributed this to biological variation in the condition. Both were also of the view that there was a strong genetic contribution. Kanner, in particular, foresaw that the incidence of autism would increase as the field learned how to differentiate it from other developmental and childhood psychiatric conditions.

## Epidemiology of Autism

The current rate of autism in the population has been a cause for marked concern and focused research from many different perspectives, including brain science, toxicology, education, and social policy. Prevalence estimates have increased in the past 15–20 years by more than 10-fold (Chakrabarti and Fombonne 2005) from a widely accepted figure of five cases per 10,000 to current estimates of one in 150 (Kuehn 2007) for autism spectrum disorders.

While some reasons for the change are understood, others are not, fueling both concern within the parent community and scientific interest in the biologies of autism. Some of the change is clearly artifactual, due to increased sensitivities in diagnosis (Fombonne 2005, Newschaffer et al. 2007) and the widening of diagnostic definitions. While definitions of autism 20 years ago reflected the more classic and severe presentation of the disorder, the current DSM-IV-TR classification system (American Psychiatric Association 2000) now includes both children who meet

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full criteria for autistic disorder (AD) and those who do not meet these stringent criteria and are classified instead with Asperger disorder, or the even less specified diagnosis of pervasive developmental disorder—not otherwise specified (PDD-NOS). A number of epidemiological studies have examined the prevalence of children diagnosed with PDD-NOS and found it to be higher than those with AD (Baker 2002, Yeargin-Allsopp et al. 2003, Chakrabarti and Fombonne 2005). Thus, including both of these diagnostic groups would more than double prevalence rates. Therefore, the group of persons now being counted in prevalence studies includes many who would not have been counted based on earlier diagnostic definitions of autism.

Social practices have also affected autistic spectrum disorder (ASD) screening and diagnosis. Due to public policies involving educational practices for children with ASD, more special education services and other types of supportive and habilitative services have become available. Such interventions often have diagnostic criteria for inclusion and thus have led to greatly increased use of differential assessments that identify autism, particularly in school-aged and younger children, when the symptoms are clearest. Greater diagnostic attention has likely identified many more cases (Chakrabarti and Fombonne 2005, Gurney et al. 2003).

A variety of biological causes have also been suggested to account for some of the increasing prevalence rates of autism spectrum disorders. Environmental exposures, particularly mercury exposure through vaccinations, dental procedures, and environmental contaminants; increased use of fertility treatments; interactions between immune abnormalities in mother or child and exposure to immune challenges in the uterine or postuterine environments; and air and environmental pollutants such as heavy metals and PCBs (Newschaffer et al. 2007) have increased significantly in the past decade. Most important, understanding the changing prevalence rates is frustratingly limited at this time by our lack of knowledge of the underlying biologies of autism.

## Diagnosis and Behavioral Features

### Core Behavioral Features of Autism

The first key features Kanner described were that his patients were oblivious to the social world, not unaware but uninterested. They ignored speech to such an extent that some were considered to be deaf, although none had a hearing impairment. The children ignored the comings and goings of their parents, the presence of strangers, and the presence of other children (Kanner 1943). Kanner described what is now considered to be the most severe form of a continuum of impairment in reciprocal social relatedness. Wing (1981) has suggested three main types of relatedness impairments in ASD: aloof (as Kanner described), passive (responsive to others' interactions but not initiating interactions themselves), and active but odd (clearly interested in social interaction but very unusual in the way they go about it).

Children demonstrate social reciprocity in a variety of ways, including patterns of eye gaze, shared emotional expressions, social body postures, and gestures. This capacity is present in human development from the first few months of life, in gestures such as raising arms up to be lifted, use of eye contact to communicate, and use of facial expressions directed to others to communicate feelings (Stern 1985, Trevarthen and Aitken 2001). These are all affected in autism across age and spectrum of ability levels (Hobson and Lee 1999, Wimpory et al. 2000).

A second key feature of autism involves abnormal development and use of language. This may involve abnormal rhythm, rate, and prosody of speech. A significant number of persons with autism do not acquire speech. This group typically does not develop an alternative communication system of gestures or icons without extensive instruction. Thus, this subgroup lacks verbal and nonverbal communicative behaviors.

For those who develop speech in the preschool period, speech appears less a system for sharing thoughts, feelings, desires, and experiences with others and more a system of naming objects. Children with autism rely much more heavily on repetition, or echolalia, for language learning than others. Development of sentences is typically delayed and marked by echolalia (repetition of other's sentences), with resulting pronoun confusion. More verbal children eventually master the syntactic rules, but for them language is very literal and they often have difficulty with metaphor, irony, and humor (Tager-Flusberg et al. 2005).

A lack of variation in daily behaviors is also characteristic of children with autism. They have a narrow range of activities and interests and devote large amounts of time to repetitive and ritualized behaviors. Motor stereotypies such as hand flapping, toe walking, finger movements, odd visual behaviors, repetitive words, or other vocalizations are also common. Rituals and routines may involve consistent patterns of grouping objects or insisting that household objects not be moved or changed. This feature was quite evident in Kanner's first patients (Kanner 1943), and these behaviors continue to be an important part of the diagnostic picture (DSM-IV-TR, American Psychiatric Association 2000).

Many children and adults with autism have unusual reactions to the sensory world. Kanner (1943) described these symptoms in many of his early cases. Feeding, an early difficulty for six of them to the point of requiring tube feeding, resolved in all. Many children with autism respond strongly to loud noises and moving objects, although they themselves could make just as loud noises without being upset. Fascination with moving objects, water, watching the wheels of cars and trains spin, elevator doors, and feeling textures may go hand in hand with severe aversions to clothing textures, food textures, certain sounds, and negative reactions to haircuts or hair washing. Sensory over- or under-responsiveness may be seen in any sensory domain, and in the same child. The adult autobiographical literature gives vivid descriptions of the degree of difficulty this symptom can cause in everyday life (Grandin 1992, Williams 1992).

### Current Diagnostic Definitions

In the United States, the diagnosis of ASD is made according to the DSM-IV-TR criteria. ASD, or pervasive developmental disorders (the DSM-IV-TR generic term for ASD), involves five diagnostic groups: AD, Asperger disorder, PDD-NOS, childhood disintegrative disorder, and Rett disorder.

The criteria for AD take precedence over all other diagnoses. The diagnostic criteria for AD involve demonstrating

a total of six or more of the listed symptoms, including two from the social communication category, one from language category, and one from the restricted and repetitive behaviors category. The DSM-IV-TR dictates that if a child meets criteria for AD, that diagnosis must be assigned. Diagnoses involving Asperger disorder and PDD-NOS should only be used for cases that fail to reach criteria for AD.

The two other diagnoses, Rett syndrome and childhood disintegrative disorder, are generally not currently considered part of the pervasive developmental disorder group. Rett syndrome is a single gene mutation involving the MECP2 gene. It affects mostly girls, is progressive in its course, and results in very severe intellectual impairment and profound disability in all areas of functioning over time. While the surface features of Rett syndrome may resemble AD at its early stages, it differs in many symptoms, in onset patterns, in course, and in response to treatment.

Childhood disintegrative disorder is a very rare condition in which a fairly rapid regression occurs, generally between the third and fifth years, in children previously developing typically. The regression is marked by a dramatic loss of language abilities, onset of motor abnormalities, severe anxiety, and profound changes in social engagement and activities. After an initial regression, the functioning level stabilizes, and after that point children appear indistinguishable from other children with fairly severe AD and intellectual deficits (Volkmar and Klin 2005).

## Diagnostic Practices, Tools, and Problems

The diagnosis of pervasive developmental disorder is made from three types of diagnostic procedures: a detailed history from parental interviews, parental description of current functioning in typical situations, and clinical observation and assessment of the child's behavior. Recent developments in assessment tools have made the diagnosis of autism much more reliable. In fact, the diagnosis of AD among experienced clinicians has the highest rate of inter-rater agreement and the most stability of any of the psychiatric diagnoses. However, as with any behavioral disorder, diagnostic agreement is strongest in the moderate range of symptoms. There is less inter-rater agreement at the mildest end of the pervasive developmental disorder spectrum, and in the end where very severe intellectual deficits are also present (Lord 2005).

Unlike most other psychiatric and developmental diagnoses, autism is diagnosed from infancy through adulthood, and in persons, which range from intellectual impairment to normal and to gifted intellects. This large range of functioning within autism results in very few tools that can discriminate autism at all ages and all functioning levels. Clinicians need to choose diagnostic instruments accurately that will best differentiate autism from other diagnostic conditions (Lord 2005). The most common tools for ascertaining pervasive developmental disorder participants in research studies include the autism diagnostic inventory (ADI-R), an experimenter-administered interview, the social communication questionnaire, a parent questionnaire with key questions from the ADI-R, the autism diagnostic observational scale (ADOS), an interactive semistructured interview with the child or adult being diagnosed, and the childhood autism rating scales (CARSs), an examiner behavior rating system completed after a developmental evaluation.

## Medical and Other Comorbid Features

As the prevalence of autism spectrum disorders has increased over the last two decades, parents, clinicians, and researchers have attended to a variety of common comorbid symptoms. Some of these were already described, at least in some form, by Kanner and Asperger.

### Seizures

While epilepsy has long been associated with autism spectrum disorders, the proportion of patients reported to demonstrate comorbid seizure disorder varies from 5% to 44% (Tuchman and Rapin 2002). A recent study (Hara 2007) carried out a follow-up of 135 patients with idiopathic autism. Of these, 33 of the follow-up group (25%) exhibited epileptic seizures, which had an onset between 8 and 26 years of age. Two types of seizure were observed: partial seizures with secondarily generalized seizure (in 61%) and generalized seizure. While 18% of the nonepileptic group exhibited epileptic discharges on EEG, 68% of the epileptic group revealed epileptiform EEG findings before the onset of epilepsy. Some studies have found an association between low IQ and the occurrence of epilepsy (Pavone et al. 2004) or low IQ and motor deficit and epilepsy (Tuchman et al. 1991). As in the Hara (2007) study, abnormal or epileptiform EEG is also observed in substantial numbers of individuals with autism who do not have seizures (Tuchman et al. 1991, Tuchman and Rapin 1997). While the presence of seizure disorder and its association with other aspects of autism may provide interesting clues to the underlying pathophysiology, it remains unclear to what extent epileptiform activity is a core attribute of autism spectrum disorders.

### Anxiety

In Kanner's (1943) original description of autism, he noted unusual fear or anxiety in several of his young patients. One child, Herbert, was "tremendously frightened by running water, gas burners, and many other things." He became upset by any change of an accustomed pattern. "If he notices change, he is very fussy and cries." Another child did a "good deal of worrying." He was upset because the moon did not always appear in the sky at night. He preferred to play alone and would get down from a play apparatus as soon as another child approached. Insistence on sameness leads children with autism to become greatly distressed when anything is broken or incomplete, and they demand consistency in the sequence of daily events. Kanner noted that although many individuals with autism learn to tolerate changes in routine and interactions with other people in their environment as adults, these interruptions cause a great deal of anxiety in young children with autism. Social interactions with other people are an unwelcome intrusion to the child with autism. When social interaction is forced upon the child, Kanner observed that the child, with a great deal of anxiety, will either ignore the person attempting to interact or quickly answer to end the intrusion. This aspect of autism, although consistently described by parents (Gurney et al. 2006) and included as a feature in the DSM-IV-TR, has not been extensively studied.

Muris and colleagues (1998) examined the presence of co-occurring anxiety symptoms in 44 children diagnosed with autism or pervasive developmental disorder. Using

parental report, they found that 84.1% of the children met criteria for at least one anxiety disorder. Gillott et al. (2001) compared high-functioning children with autism to two control groups including children with specific language impairment and normally developing children on measures of anxiety and social worry. Children with autism were found to be significantly more anxious on both indices.

### Gastrointestinal Disorders

Children with autism have a higher incidence of gastrointestinal (GI) problems than typically developing children or children with developmental delays (Valicenti-McDermott et al. 2006). GI problems are a common complaint of parents of children with autism and has been one of the factors that have prompted the use of complementary and alternative medicines (Harrington et al. 2006). A number of clinicians have emphasized the need to investigate GI problems, particularly in low-functioning children who are unable to communicate their distress and for whom alleviation of the GI condition may appreciably improve the quality of life.

### Autoimmune Disorders

Immune dysfunction may play an important role in a subset of pervasive developmental disorder cases (van Gent et al. 1997). Some patients with pervasive developmental disorder demonstrate abnormalities and/or deficits of immune system function leading to inappropriate or ineffective immune response to pathogen challenge (Ashwood and Van de Water 2004b). For example, children with autism or pervasive developmental disorder often have recurrent infections (Stern et al. 2005), peripheral immune abnormalities (Ashwood et al. 2003, Croonenberghs et al. 2002, Singh 1996), or neuroinflammatory responses in the central nervous system (CNS) (Vargas et al. 2005). In addition to general immune system dysfunction, recent evidence suggests that certain forms of autism are associated with an autoimmune condition (Ashwood and Van de Water 2004a, 2004b). Autoimmunity occurs when the immune system inappropriately identifies and reacts to "self" components. Antibodies produced during an autoimmune response play a critical role in the pathogenesis of several peripheral neurological diseases, including myasthenia gravis, Lambert–Eaton myasthenic syndrome, and neuromyotonia (Lang et al. 2003a, 2003b, Lang and Vincent 2003, Newsom-Davis et al. 2003, Scoppetta et al. 2003). Autoimmunity may also play a role in CNS diseases, notably psychological and neural disorders associated with streptococcus (PANDAS), which accounts for a subgroup of childhood-onset obsessive–compulsive disorders (OCD) and tic disorders (Snider and Swedo 2003). Several studies have also reported that autoimmune disorders are more common in family members of ASD patients compared to typically developing controls. Mothers and first-degree relatives of children with autism are more likely to have an autoimmune disorder (16% and 21%) than controls (2% and 4%) (Comi et al. 1999). Similar results were obtained in a study of autoimmune disorder frequency in families that have children with pervasive developmental disorders, including autism (Sweeten et al. 2003). A recent study of 308 children with ASD reported that regression in autism was significantly associated with a family history of autoimmune disorders (Richler et al. 2006).

Antibodies directed against CNS proteins have been found in the sera of autistic children. Targets of autoantibodies in pervasive developmental disorder patients include neuron–axon filament protein (Singh et al. 1997), myelin basic protein (Singh et al. 1993), serotonin receptor (Todd and Ciaranello 1985), cerebellar neurofilaments (Plioplys et al. 1994), nerve growth factor (Kozlovskaia et al. 2000), alpha-2-andrenergic binding sites (Cook et al. 1993b), and antibodies against the caudate nucleus (Singh and Rivas 2004).

Maternal antibodies to fetal brain tissue may also play a role in a subset of pervasive developmental disorder cases (Vincent et al. 2003). Antibodies from serum of mothers who have children with pervasive developmental disorder have been shown to react to antigens on lymphocytes from their affected children (Warren et al. 1990). Given that antigens expressed on lymphocytes are also found on cells of the CNS, these authors proposed that aberrant maternal immunity may be associated with the development of some cases of pervasive developmental disorder. In support of this, the presence of antibodies against brain tissue was recently identified in the serum of a mother whose child has autism (Dalton et al. 2003). Van de Water and colleagues have identified a common pattern of autoantibody production to fetal brain tissue in the serum of mothers who have two or more children with pervasive developmental disorder (Braunschweig et al., in press). Collectively, these studies suggest that an atypical maternal antibody response directed against the fetal brain during pregnancy may be present in a subset of pervasive developmental disorder cases.

## Developmental and Genetic Mechanisms Implicated in the Etiology of Autism

There is growing consensus that autism is caused by multiple mechanisms that derail development of the brain (Belmonte and Bourgeron 2006, Freitag 2007, Gupta and State 2007, Happe et al. 2006, Moldin and Rubenstein 2006, Moldin et al. 2006). In this section of the chapter, we address developmental and genetic mechanisms that are likely to participate in susceptibility to autism.

Autism affects boys roughly four-fold more often than girls, a key observation whose mechanism remains a mystery. Based on the concordance rates in monozygotic twins (~60–90%), roughly 10-fold higher than in dizygotic twins and siblings, autism is considered to be the most heritable of neuropsychiatric disorders (Bailey et al. 1995, Smalley et al. 1988). However, it is generally acknowledged that autism is genetically heterogeneous. While a small subset of cases are caused by X-linked, autosomal-dominant, autosomal-recessive, or chromosomal defects, researchers currently believe that many cases are due to more complex genetic mechanisms, including coinheritance of multiple alleles and/or epigenetic modifications (Freitag 2007, Gupta and State 2007). Furthermore, approximately 10% of sporadic cases of autism are associated with de novo copy number variations in either single genes or sets of genes; *de novo* copy number variations occurred in only ~2% of multiplex cases and 1% of controls (Sebat et al. 2007). The mechanisms that cause these copy number variations are unknown, but paternal age contributes to autism risk (Reichenberg et al. 2006); perhaps increasing age leads to the accumulation of these de novo germline mutations.

The clinical and neuroanatomical features provide boundary conditions for considering the genetic and developmental underpinnings of autism. Autism is probably caused by defects in neural systems that process social information, language, and sensorimotor integration. The components of the neural systems required for these complex behaviors are beginning to be understood, yet much work needs to be done. Neural system lesions can be localized or distributed (Rubenstein 2006). A localized lesion that weakens or disables one component of a circuit can impede the function of the entire circuit, generating a behavioral phenotype. This phenotype can likewise be generated by defects in another component of the same circuit. Thus, related behavioral syndromes can be generated by a variety of anatomical defects.

Distributed lesions can be caused by defects that are common to many regions of a given neural system, or to multiple neural systems. For instance, mutation of a gene that is broadly expressed, such as that causing fragile X mental retardation (FRAXA; FMR1), Rett syndrome (MeCP2), and tuberous sclerosis (TSC1&2), will disrupt neural function throughout the nervous system, weakening neural processes such as synaptic transmission or synaptic plasticity. Localized lesions are exemplified by mutation of genes that are expressed in neurons that share common features (such as neurotransmitter type or participation in a common circuit). For instance, members of the Dlx homeobox gene family (which encode transcription factors) are expressed during development of most forebrain GABAergic neurons, and some Dlx genes are expressed in mature forebrain GABAergic neurons (Cobos et al. 2005). Mutations that simultaneously block the function of pairs of mouse Dlx genes disrupt development of most forebrain GABAergic neurons (Anderson et al. 1997). This has the potential to disrupt the cortex–basal ganglia–thalamus–cortex circuit, through defects in cortical GABAergic local circuit neurons, basal ganglia GABAergic projection neurons, and the GABAergic thalamic reticular nucleus. Furthermore, individual Dlx genes (e.g., Dlx1) are required for function and survival of maturing cortical interneurons; loss of Dlx1 function can result in epilepsy (Cobos et al. 2005). Mutations in the Dlx genes have been detected in autistic individuals, although it is unknown whether these alleles contribute to the disorder (Hamilton et al. 2005).

Developmental defects can alter the connectivity between regions or the function within a given region and thereby derail neural systems. Interregional connectivity defects can be caused by alterations in axon pathfinding and synapse choice. It is not known whether these types of abnormalities are found in autism, although there is evidence for connectivity defects from functional imaging studies (Kana et al. 2006). Below, we briefly review salient information about genes whose functions are linked to autism. We have organized this information according to known functions of these genes, although many of these genes have functions that are not limited to their assigned categories.

## Signal Transduction

### Tuberous Sclerosis (TSC1&2) and PTEN

Children with TSC (autosomal dominant) have greatly increased rates of autism (25–50%), epilepsy, and mental retardation (Wiznitzer 2004). TSC1 (hamartin, 9q34) and TSC2 (tuberin, 16p13) encode GTPase-activating proteins that inhibit the activity of the small G-protein Rheb. TSC1/TSC2 are tumor suppressors by reducing activity of mTOR kinase (Inoki et al. 2005). mTOR promotes protein synthesis and other processes that increase cell growth.

TSC1/TSC2 are integral regulators of signal-transduction cascades downstream of signaling pathways that activate receptor tyrosine kinases (Inoki et al. 2005). These signals activate a family of phosphatidylinositol lipid kinases (phosphatidylinositol-3 kinases, PI3K) that in turn activate the serine-threonine kinase AKT, which then represses TSC1/TSC2 (Inoki et al. 2005). TSC1/TSC2 are also regulated by intracellular amino acid concentration and by the ATP/AMP ratio—the end product of this regulation is to promote appropriate levels of protein synthesis and cell size (Inoki et al. 2005).

While TSC patients develop focal CNS lesions (tubers), it is likely that the general function of TSC1&2 in most neurons underlies the autistic symptoms. For example, reduced TSC dosage in hippocampal pyramidal neurons results in increased size of the cell body and dendritic spines (Tavazoie et al. 2005). This is intriguing given the increased size of the brain in some children with autism.

Further clues that implicate this signaling cascade in autism come from the observation that some patients with mutations in the phosphatidylinositol phosphatase (PTEN; 10q23.31) have autism with macrocephaly (Butler et al. 2005). PTEN reduces activity of the PI3K pathway through dephosphorylation of phosphatidylinositol-tris-phosphate. Mice lacking CNS function of PTEN have increased signaling through the serine-threonine kinase AKT, TSC, and mTOR pathway (Kwon et al. 2006). These mutants have enlarged brains that are associated with increased dendritic and axonal arbors and increased dendritic spines and synapses. PTEN mutant mice also exhibit abnormal social behavior, further implicating this signaling pathway in autism (Kwon et al. 2006).

### Met Typrosine Kinase (MET)

MET encodes a receptor tyrosine kinase (7q31) that is an oncogene which mediates hepatocyte growth factor signaling. MET plays an important role in neuronal migration in the forebrain and cerebellum, as well as in immune and GI function. Mouse knockout mutants have reduced numbers of cortical interneurons and a hypoplastic cerebellum. Campbell et al. (2006) identified a common functional allele in the promoter region of the MET gene that is associated with autism.

### Control of Translation

#### *Fragile X (FRAXA; FMR1)*

Mutations that reduce expression (usually through CGG triplet expansion) of this X-linked gene (Xq27.3) cause mental retardation, and about 30% of these boys have autistic symptoms (Belmonte and Bourgeron 2006). In humans and mice, FMR1 mutants have dendritic spines that have an immature morphology (too long and thin). This may result from the fact that FMR1 encodes an RNA-binding protein whose functions include translation regulation in dendrites. Indeed, activation of metabotropic glutamate receptors

leads to FMR1-regulated protein synthesis in dendrites. This includes production of proteins, such as PSD-95, that participate in excitatory synaptic transmission (Bear et al. 2004, Todd et al. 2003). Thus, FMR1 functions at least in part through transducing excitatory synaptic signals into changes in the protein constituents that modify synaptic function and structure.

### Synapse Formation and Function

#### *Neuroligins (NLGN3 and NLGN4)*

Neuroligins encode plasma membrane proteins that are implicated in regulating synapse development through binding neurexin proteins (Varoqueaux et al. 2006). Specific combinations and splice forms of neuroligin/neurexin proteins can specify whether an excitatory or an inhibitory synapse will form (Chih et al. 2006). In rare cases of autism, mutations in two X-linked neuroligins (NLGN3 and NLGN4; Xq13 and Xp22.33, respectively) have been found (Jamain et al. 2003). Furthermore, a de novo deletion in *neurexin1* (NRX1) has recently been identified in a pair of affected siblings.

#### *SHANK3 (ProSAP2)*

SHANK3 (22q13.3) encodes a protein associated with the postsynaptic density of excitatory synapses and can promote dendritic spine maturation. Rare missense mutations in SHANK3 have been identified in autistic individuals (Durand et al. 2007). Furthermore, this region of chromosome 22 is a site of recurrent deletions in autism (Sebat et al. 2007).

### Neurotransmitters/Neuromodulators

#### *Oxytocin and Vasopressin Receptors (OXTR; AVPR1a)*

Oxytocin and vasopressin peptides are neuromodulators expressed by neurons in the hypothalamus and the amygdala. These neuropeptides have been implicated in the mediation of certain social behaviors (Young et al. 2005) and the receptors for oxytocin (OXTR; 3p25–p26) and arginine vasopressin 1a (AVPR1a; 12q14–15) are associated with autism (Wu et al. 2005, Yirmiya et al. 2006).

#### *Serotonin Transporter (SLC6A4)*

Serotonin has potent effects on many behavioral and developmental processes. One of the earliest biochemical indications that serotonin metabolism may be altered in autism was the finding of an increase in serum serotonin levels in approximately 30% of individuals with autism (Cook et al. 1993a). Although this is not a specific diagnostic finding, it increases the potential importance that some alleles of the serotonin transporter gene (SLC6A4, SERT; 17q11.2) might be associated with autism (Brune et al. 2006, Sutcliffe et al. 2005).

### Ion Channels

#### *Calcium and Sodium Ion Channels (CACNA1C, CACNA1H, SCN1A, and SCN2A)*

Missense mutations in the L-type (CACNA1C, Cav1.2; 12p13.3) and the T-type (CACNA1H, Cav3.2) calcium channels have been identified in rare cases of autism (Splawski et al. 2004, 2006). Similarly rare missense mutations have been identified in two sodium channel genes (SCN1A; 2q24; SCN2A; 2q23–q24.3) (Weiss et al. 2003).

## Metabolic Genes

### Phenylalanine Hydroxylase

Historically, the finding that autism is highly associated with phenylketonuria (PKU—hyperphenylalaninemia) was one of the turning points in establishing a biological etiology of autism (Cohen et al. 2005). There are several hundred alleles of phenylalanine hydroxylase (12q23.2) (www.pahdb.mcgill.ca), many of which can cause PKU in the homozygous phenotype. Interestingly, relatively little is known concerning the neuropathology of PKU-associated autism. And, the condition is now relatively rare due to neonatal screening and dietary treatment.

### D7-Dehydrocholesterol Reductase Smith–Lemli–Opitz

The Smith–Lemli–Opitz (SLO) gene encodes D7-dehydrocholesterol reductase (DHCR7; 11q12–q13); loss of function mutations causes accumulation of D7-dehydrocholesterol. This recessive disorder has broad developmental affects, including autism (Sikora et al. 2006). While SLO is a rare cause of autism, it demonstrates that the more general disruption of cholesterol metabolism, and related pathways, may be one component of the etiologic mechanisms.

### Regulation of Gene Expression

#### *Rett Syndrome (MeCP2)*

Rett syndrome is due to loss of function mutations of the methyl-CpG-binding protein 2 (MeCP2; Xq28) (Moretti and Zoghbi 2006). Girls with Rett syndrome commonly exhibit autistic symptoms; males generally die prenatally. Some mutations result in milder symptoms that include autism in both boys and girls. MeCP2 is a nuclear protein that binds to methylated CpG dinucleotides. It recruits a corepressor complex that is implicated in transcriptional repression. Mouse MeCP2 mutants show subtle increases and decreases in brain gene expression, including reduced ubiquitin protein ligase E3A (UBE3A) and b3 GABA A receptor (Gabrb3); these are imprinted genes in the Angelman's disease locus. Inheritance of a maternal duplication of this region (15q11.2–q13) is the most commonly associated chromosomal abnormality found in autism (Schanen 2006). MeCP2 mutants also show increased Dlx5 expression, variable effects on brain-derived neurotrophic factor expression, and RNA splicing defects (Moretti and Zoghbi 2006). MeCP2's association with autism highlights the possibility that epigenetic modifications of chromatin (e.g., cytosine methylation and histone methylation/acetylation) and parent of origin effects (imprinting) may have broader roles in the etiology of autism (Schanen 2006).

#### *Engrailed2 (EN2)*

Alleles of the En2 homeobox transcription factor (7q36), which regulates cerebellum development, is associated with autism in some studies (Benayed et al. 2005). Mouse mutants exhibit social deficits (Cheh et al. 2006).

### *Distal-less 2 & 5 (Dlx2 and Dlx5)*

Missense mutations of the Dlx2 (2q31.1) and Dlx5 (7q21.3) homeobox transcription factors have also been identified in autistic individuals (Hamilton et al. 2005). These genes regulate development of forebrain GABAergic neurons, and Dlx1 mutations lead to epilepsy in mice (Cobos et al. 2005).

## Summary

The array of genes that either cause or predispose to autism speaks to the diversity of genetic and epigenetic mechanisms that can cause this heterogeneous disorder. It seems likely that autism can be caused by an even larger number of genes—perhaps through combinatorial mechanisms involving coinheritance of multiple weak alleles and environmental factors that influence epigenetic state as well as brain development and function. Despite this complexity, some mechanistic themes are beginning to emerge:

1. Defects in molecular pathways that link synaptic and nonsynaptic signals with changes in protein synthesis that can modulate neural response properties (FRMR1, MET, NGLN3/4, PTEN, Shank3, and TSC1/2).
2. Defects in transcriptional regulation of neural genes (DLX2/5, EN2, and MeCP2).
3. Defects in neural excitatory state (CACNA1C, CACNA1H, SLC6A4, SCN1A, and SCN2A).
4. Defects in signals within specific neural circuits important for social behavior (AVPR1a; OXTR) (Belmonte and Bourgeron 2006, Hong et al. 2005, Levitt et al. 2004, Persico and Bourgeron 2006, Rubenstein and Merzenich 2003).

In the end, we will need to understand how these molecular lesions disrupt neural systems that process cognition and social behaviors. For instance, mutations that alter the balance of excitatory and inhibitory synapses in key brain regions may impede the ability to detect salient sensory signals above ambient noise (Levitt et al. 2004, Rubenstein and Merzenich 2003). Mutations in many of the genes described above cause epilepsy, which is a gross manifestation of dysregulated excitatory/inhibitory balance. One of the several questions raised by these genetic studies is whether certain brain regions or certain cell types are selectively affected in autism. To address this question, we turn next to an overview of the neuropathology of autism.

# Neuropathology

## Structural Magnetic Resonance Imaging Studies

While early computed axial tomography studies carried out on individuals with autism described abnormalities such as ventricular enlargement (Damasio et al. 1980), later studies determined that there were no consistent tomographic findings in children with classic autism (Prior et al. 1984). One of the most consistent findings from MRI studies (Brambilla et al. 2003, Piven et al. 1997, Sparks et al. 2002) is an increase in total cerebellar volume.

Other brain regions that have been found to be abnormal in autism include the cerebral cortex (although the salient portion of the cerebral cortex varies from study to study), medial temporal lobe structures such as the amygdala and hippocampus, and the corpus callosum. In a comprehensive review of the structural MRI studies through May 2003, Brambilla et al. 2003 concluded:

> …despite a growing number of quantitative MRI studies, few robust findings have been observed. Structural abnormalities involving total brain volume, the cerebellum and, recently, corpus callosum have been consistently replicated…. In order to overcome design limitations of the previous morphometric neuroimaging reports, future quantitative MRI studies should focus on identifying possible morphological brain markers including homogeneous groups of well characterized individuals with autism and healthy controls, matched for aged, gender, SES and IQ and should longitudinally investigating (sic) these groups (p. 567).

The notion that cortical development may be altered in autism arose initially from clinical observations indicating that the head circumference of children with autism is larger than general population controls. For example, Bailey et al. (1993) found that 37% of their subjects had a head circumference above the 97th percentile (macrocephalic), while Lainhart et al. (1997) found that 14% of autistic subjects had macrocephaly. Fombonne and colleagues (1999) conducted a meta-analysis of published literature and concluded that an average estimate of macrocephaly in autism was 20.6%. These data would suggest that large head and thus brain size might be a common, although by no means universal, feature of individuals with autism.

A number of studies have indicated that cortical development may be altered in autism. Piven et al. (1990) noted malformations of the cortex such as polymicrogyria, but these observations have not been replicated. Piven et al. (1995) were also the first to use a computer-aided assessment system to evaluate the cerebral cortex in adults with autism. They concluded that there were increases in the volumes of the temporal, parietal, and occipital lobes but not of the frontal lobes. Neither Aylward et al. (1999) nor Schumann et al. 2004 observed a difference in total brain volume.

Courchesne and colleagues have published a series of studies that demonstrate abnormal brain growth in autism (Carper and Courchesne 2005, Courchesne et al. 2001, 2003, Redcay and Courchesne 2005). They propose that the brains of children with autism are either of normal size or perhaps slightly smaller than typically developing children at birth. However, the cerebral cortex, and preferentially the frontal lobe, undergoes a rapid and precocious growth (relative to control children) during the first 2 years of life. Subsequently, brain growth plateaus and ultimately the volume of the brains of typically developing children catch up. Thus, in older children with autism, the brain is either the same size or even slightly smaller than typically developing subjects. Importantly, this finding has recently been replicated by the Piven laboratory (Hazlett et al. 2005). This study indicates that precocious brain growth may not begin until near the end of the first year of life and is clearly evident by the second year of life.

Beyond the cerebral cortex, other brain regions have also been found to have an abnormal brain development. Perhaps most striking is the amygdala, a region of the

temporal lobe that is involved in the detection of dangers in the environment and in modulating some forms of social interaction. Interestingly, the amygdala undergoes a very protracted development in boys (Giedd et al. 1996). It increases in size by nearly 40% between the ages of 8 and 18 years (Schumann et al. 2004). This is striking since the rest of the brain actually decreases in size during this same time period by about 10%. For boys who have been diagnosed with autism, the amygdala demonstrates precocious growth and has reached adult size by 8 years of age.

Many studies have gone beyond simply evaluating the volume of brain regions and have analytically broken the tissue down into compartments representing gray and white matters. There have been some indications that alterations in white matter volumes may actually be a more sensitive indicator of pathology in autism than grey matter differences (Carper and Courchesne 2005, Courchesne et al. 2001, 2003, Herbert 2005, Herbert et al. 2004). In fact, some have proposed that the enlarged brain volume that has been reported can be accounted for, in large part, by disproportionate increases in the volume of white matter. There are reports of greater white matter volumes in boys with autism aged 2–3 years, when compared to controls. Interestingly, this pattern was not found in adolescence, further supporting an abnormal early development. Other analyses of white matter have suggested that those compartments of white matter that develop latest (i.e., the radiate regions that mature late in the first year and into the second postnatal year and beyond) are of greater volume than the earlier maturing sagittal and bridging fibers (Herbert et al. 2003). Recent studies using diffusion tensor-weighted imaging of white matter indicate that in autism regionally specific disruptions of white matter integrity may persist into adulthood (Keller et al. 2007).

To summarize, despite the heterogeneity of findings, a few clear directions are emerging:

1. Autism is clearly not a disorder that affects a single brain region.
2. The kind of brain pathology in a particular individual may depend on the phenotypic characteristics of autism (e.g., presence versus lack of developmental delays) as well as comorbid features of the disorder (e.g., seizures versus no seizures).
3. Finally, the pathology of autism may not be apparent in the mature size and shape of the brain but in the time course of development of both the structure and the connections of the brain.

## Microscopic Neuropathology

There is no obvious lesion in the brains of individuals with autism. In fact, at first blush the brain looks remarkably normal. One consistent finding in autism has been the lower number of Purkinje cells in the cerebellum (Ritvo and Garber 1988). When using neural stains that mark cell bodies, there are noticeable gaps in the orderly arrays of Purkinje cells. Whether Purkinje cell loss is due to autism, epilepsy, or the co-occurrence of both disorders is not currently clear. It is also not clear whether loss of Purkinje cells is characteristic of autism or a more general finding in many neurodevelopmental disorders. Thus, cerebellar alterations have been reported in idiopathic mental retardation, Williams syndrome, and many other childhood disorders. There have also been a few reports of alterations of brainstem nuclei, such as the olivary complex, that is connected to the cerebellum (Bailey et al. 1998). These findings might inform the time frame of neural insults responsible for autism, but they are currently based on too few observations to be considered typical of autism.

The cerebral cortex has also been reported to be abnormal at a microscopic level in autism. There have been some published examples of migration defects such as ectopias (Bailey et al. 1998). It has also been proposed that the columnar organization of the cortex in autistic patients is abnormal (Casanova 2006, Casanova et al. 2002). These provocative findings are awaiting confirmation in larger studies using sophisticated quantitative strategies. Finally, the amygdala has been found to have fewer neurons in the mature brain (Schumann and Amaral 2006). Since this study was carried out with cases that did not have comorbid epilepsy, this could be a real component of autistic neuropathology.

## Functional Neuroimaging

Another approach to establishing which brain regions are most impacted by autism is the use of functional imaging. While this literature is growing rapidly and has provided important insights into the neural impairments of autism, it also applies only to the high-functioning segment of the population who can be compliant with the demands of the behavioral and imaging conditions. Many of the functional imaging studies have focused on brain regions thought to be involved in social function, such as the frontal lobe and amygdala, and on behaviors thought to be selectively impaired in autism, such as perception of social stimuli and theory of mind. Given that more than 400 papers have appeared in recent years dealing with functional imaging of individuals with autism, we only briefly highlight some findings related to the amygdala that, as described above, is clearly pathological in autism. For recent, more extensive reviews of fMRI in autism see Kana et al. (2006) and Just et al. (2007).

The amygdala has been the focus of a large number of functional imaging studies in autism prompted, in part, by the "Amygdala Theory of Autism" proposed by Baron-Cohen and colleagues (2000). Functional neuroimaging studies have indicated that individuals with an autism spectrum disorder show abnormal patterns of amygdala activation in response to social stimuli. High-functioning adults with autism or Asperger syndrome demonstrate deficits in the ability to infer the mental state of another person from viewing images of their eyes (Baron-Cohen et al. 1997). This task activates the amygdala and superior temporal gyrus in control subjects. In contrast, individuals with autism or Asperger syndrome activate the frontotemporal regions but not the amygdala when performing this task (Baron-Cohen et al. 1999). Pierce et al. (2001) found that the amygdala was activated when typically developing individuals viewed unfamiliar faces, but the amygdala was not activated in individuals with autism during this task. Children and adolescents with autism spectrum disorders show abnormal amygdala activation while matching faces by emotion and assigning a label to facial expressions (Wang et al. 2004). While children in the control group showed more amygdala activation when matching faces by emotion than assigning a verbal label, the children with autism spectrum disorders did not demonstrate this pattern of task-dependent amygdala modulation.

One caveat to interpreting findings from face processing studies is that subjects with autism are reluctant to make eye contact, and there is some controversy as to whether they are actually examining the face in a similar manner as controls (Davidson and Slagter 2000). In fact, when viewing faces, patients with autism show abnormal visual scan paths during eye-tracking studies, typically spending little time on the eyes (Klin et al. 2003, Pelphrey et al. 2002). Whether these findings represent active avoidance of the eye region, potentially involving the amygdala, or a more global lack of social interest or motivation is unclear. An emerging hypothesis is that the amygdala may play a role in mediating or directing visual attention to the eyes (Adolphs et al. 2005, Grelotti et al. 2005, Schultz 2005).

Research from typically developing children indicates that children who are physiologically aroused by a distressing film were more likely to avert their gaze from the stimulus. It is plausible that children with autism utilize a similar strategy of gaze aversion in response to arousing social stimuli. Given the amygdala's role in fear and anxiety, one would predict heightened amygdala activation during eye contact in persons with autism if they found the eye contact aversive. Dalton and colleagues (2005) found that the amount of time persons with autism spent looking at the eye region of the face was strongly positively correlated with amygdala activation, but this was not the case in control subjects. The autism subjects also showed greater left amygdala activation relative to controls in response to unfamiliar faces and greater right amygdala activation in response to both familiar and unfamiliar faces. This suggests a heightened emotional, or even fearful, response when autistic individuals look at another person's eyes, regardless of whether they are familiar or a stranger. Nacewicz et al. (2006) recently found that individuals with autism (8–25 years of age) who had a smaller amygdala were also slower to distinguish emotional from neutral expressions and showed least fixation on the eye regions of the face. These same individuals were also the most socially impaired in early childhood.

Recently, Ashwin et al. (2007) found that during the perception of fearful faces, Asperger syndrome patients showed less activation in the left amygdala relative to controls. However, these results may again be due to the abnormal way in which individuals with autism view faces. Spezio et al. (2007a, 2007b) confirmed that participants with autism show less fixation on the eyes and mouth, but also a greater tendency to saccade away from the eyes when information was present in those regions. This study provides insight into the aberrant manner in which people with autism view faces, which likely influences face processing and subsequent functional imaging study results. Additional studies would benefit from measuring the physiological responses associated with arousal and anxiety (i.e., increased heart rate, skin response, etc.) during face processing in individuals with autism.

## Behavioral Treatment

Early on in autism treatment two main treatment approaches dominated the literature: treatment based on a psychodynamic conceptualization of autism (e.g., Bettelheim 1967) and treatment based on the application of Skinnerian models of learning. The first empirically supported paper came from the latter tradition. In 1964, Wolf and colleagues (1964) published the first single subject design of the application of behavioral principles to the symptoms of a young child with autism. The treatment was carried out virtually all day, every day, for several years in an institutional setting. The child eventually returned to his/her home, with greatly improved behavior, language, adaptive, and cognitive abilities. The teaching procedures involve massed trial teaching, and many of the core approaches to teaching are still in use today (Leaf and McEachin 2001, Lovaas 1981).

The view that autism was a neurobiological disorder, championed by Bernard Rimland (1964), had fundamental effects on treatments. Gradually, autism became viewed as a developmental disorder, like mental retardation, for which rehabilitation (or, more exactly, habilitation) was the appropriate approach. Then, the passage of public law 94–142 in 1975 mandated appropriate free public education for all children with disabilities and cast tremendous responsibility on school districts for appropriate education and habilitative services.

### Main Intervention Approaches

Three main philosophies guided the development of interventions. One strategy involved the continued application of learning theory to reduce behavioral deficits and to decrease behavioral excesses (Wolf et al. 1964). These strategies, under the umbrella of applied behavior analysis, were applied in two basic forms. The first involved massed trials with high levels of adult control and direction of the teaching (Lovaas 1987, McEachin et al. 1993). A more naturalistic application of learning principles capitalized on children's own interests, preferences, and initiatives to assure high levels of motivation for learning. These approaches are best described in two well-known models: incidental teaching, first applied to autism by McGee et al. (1983, 1991), and pivotal response training, as developed by Schreibman and Koegel (Koegel et al. 1988, Schreibman and Pierce 1993, Williams et al. 1981).

A second main approach was the TEACCH model of intervention (Schopler et al. 1984, 1995). This capitalized on teaching by directing tasks to children's visual–spatial skills, focused on developing skills for independent work and independent functioning, minimized the need for ongoing social instruction and verbal instruction, used visual communication systems to supplement verbal instruction, built a great deal of repetition and routine into the organization of the teaching, and reduced the sensory complexity of the environment to maximize attention. This approach also focused on parents as primary deliverers of child interventions.

The third main approach focuses on autism as a developmental deficit. This approach takes as a premise that early compromises in social–communicative development have increasingly large downstream effects that impair the development of triadic relations (Meyer and Hobson 2004, Rogers and Pennington 1991, Sigman and Capps 1997). The developmental approaches have flourished and some of the better-known current models include Greenspan and Widers' floortime approach (Greenspan et al. 1997), Gutstein's relationship development intervention (Gutstien 2005), the Denver model (Rogers and Lewis 1989), and the SCERTS model (Prizant et al. 2006). These approaches strongly emphasize the quality of the relationship between child and teacher and child and parent, use a child-centered approach based on following children's interests and initiatives, and strongly emphasize progress in social communication skills.

A fourth treatment orientation focuses on the sensory and motor differences characteristic of autism. Some practitioners think that the sensory differences in autism are the primary impairments, with the social, communicative, and behavioral abnormalities resulting from the intense distress or confusion that the sensory impairments cause (reviewed in Baranek 2002). Occupational therapists have led the way in evolving treatments targeted at sensory deficits in autism.

### Treatment Delivery

Behavioral treatments may be delivered to change very targeted symptoms. Virtually all the main symptoms of autism have been demonstrated to be modifiable with targeted treatments (Schreibman 2005). Two very important attributes of this literature deserve mentioning. First, positive treatment outcomes for targeted skills have been documented across the entire age range and functioning range for persons with autism spectrum disorders. The second important point is that the techniques used have changed considerably over the years. The use of aversive consequences has largely disappeared, as the field has become more sophisticated in the application of reinforcement strategies (Carr et al. 2002, Horner et al. 2002, Howlin 1998, Lalli et al. 1995). It is now clear that autism is treatable.

The current science of early behavioral intervention in autism is targeting several main research questions: (1) Is "recovery" possible for more than an occasional child? (2) Are some treatments more effective than others? (3) What are the "active ingredients" of effective comprehensive treatments? (4) What child, family, programmatic, and environmental variables mediate and moderate early intervention outcomes? (5) Can we identify an aptitude by treatment interaction in autism that will allow us to know which subgroups of children with autism will respond best to which treatment approach or treatment elements?

We still have no randomized controlled trials that compare the best-known comprehensive approaches. The few randomized controlled trials that exist have consistently demonstrated that well-planned and carefully delivered treatments, both developmental and behavioral, improve children's functioning, particularly IQ and language abilities, compared to no treatment, both over the shorter term and over the longer term (Jocelyn et al. 1998, Smith et al. 2000). The fact that IQ and language are so responsive to high-quality treatment delivered in the preschool period is quite promising, since these are the best predictors of outcomes over time in autism (Howlin 2005). Given the findings from other models thus far, it is likely that a carefully planned intensive and comprehensive intervention with expert delivery will result in positive gains for children compared to a no-treatment condition.

Comprehensive intervention for older children occurs every day in classrooms across America, but these have not received the scrutiny of early intervention approaches. While some classrooms for older children also follow a very specific educational model, it is probably more often the case that public schools use a variety of teaching methods to teach the individual educational objectives that guide each child's special education in the public schools. Two areas of research in this group involve the development of social skills, especially for children with milder symptoms (Ozonoff and Miller 1995, Simpson et al. 1997, Wooten and Mesibov 1986), and the questions about inclusive education (Janney and Snell 1997, Kellegrew 1995, Simpson and Smith Myles 1993).

## Other Treatments

### Psychopharmacological Treatments

Given the lack of specific brain or neurotransmitter systems as a target for pharmacological treatment, currently there is no psychopharmacological treatment that is directed at the core symptoms of autism (Palermo and Curatolo 2004). The atypical antipsychotics (olanzapine, ziprasidone, quetiapine, and aripiprazole) have shown some efficacy in improving certain behavioral symptoms of AD such as aggressiveness, hyperactivity, and self-injurious behavior (Stachnik and Nunn-Thompson 2007). Weight gain and sedation are frequently reported adverse consequences of these treatments. Risperidone has become the first approved drug for treatment of autism. Previously risperidone was studied as off-label medication to treat autism because of its increased safety and efficacy over conventional neuroleptics. Risperidone can be used as a potentially safe and effective treatment for disruptive behavioral symptoms in children with autism (West and Waldrop 2006). The long-term use of these drugs in conjunction with the plethora of other alternative medications that are being used require additional analysis pertaining to safety (McCracken 2005).

### Complementary Alternative Medicine Treatments

It would be fair to say that in no area of developmental pediatric practice is there more controversy than in the selection of treatments for children with ASDs. An increasing number of complementary and alternative medical therapies are often tried because they are perceived as treating the cause of the children's symptoms (Levy and Hyman 2005). Current treatments range from various forms of restricted diet (Millward et al. 2004) to hyperbaric oxygen treatment (Rossignol 2007) to a variety of vitamin and mineral supplementations (Hanson et al. 2007). Secretin provides a good example of how an incidental perception of behavioral improvement following treatment leads to widespread clinical use despite little or no scientific rationale for the therapy. And even despite nearly unanimous negative results in placebo-controlled clinical trials (Esch and Carr 2004), there still remains substantial parental interest in attempts at using secretin as one potential therapy. In many respects, this speaks to the desperate need of parents and practitioners alike to obtain more scientifically based approaches to the therapy of both the core and the comorbid symptoms of autism.

## Conclusions

Autism is a spectrum disorder that is defined behaviorally as consisting of social and communication impairments and the presence of stereotyped behaviors and/or circumscribed interests. There is a general consensus that autism has a variety of etiologies that consist of different proportions of genetic and environmental contributions. While some 10% of autism cases are associated with a defined medical condition such as fragile X syndrome, the cause(s) of the remainder of idiopathic autism are currently unknown.

Various behavioral therapies based on the operant conditioning literature are valuable for eliminating unwanted behaviors and bolstering language, social interaction, and pragmatic life skills. Autism affects the development of several brain systems. The most common biological finding is precocious brain development of the cerebral cortex and amygdala. However, the neuropathology of autism is still at a very early stage of understanding and both additional structural MRI and postmortem studies are needed to better define the neural systems involved. Beyond the nervous system, there appears to be a variety of dysregulated functions in the immune system of some individuals with autism and some mothers of individuals with autism. Whether the immune dysregulation is a cause or effect of autism remains to be determined. Finally, autism is generally agreed to be a polygenic disorder, with multiple genes showing weak association. This may be a reflection of the fact that better phenotyping of autism subtypes is essential before fruitful genotyping can be accomplished.

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CHAPTER

# 24 Neurodegeneration and Dementia

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## Introduction

As a syndrome characterized by incapacitating cognitive decline, dementia is easy to define in general terms but difficult to pin down with categorical precision. Although recognized in ancient times, the term "dementia" was first introduced in 1789 by Phillipe Pinel, and indeed it was 19th century clinicians who first grappled with its defining features. Pinel's student Jean Esquirol, for example, divided the dementias into acute, chronic, and senile forms, and his characterization of senile dementia is a remarkably accurate description of what came to be known as Alzheimer's disease (AD). Senile dementia, he maintained, begins with "enfeeblement of memory" particularly the memory of recent events. Over time, dementia progressed to include difficulty in comprehension and attention and a diminishment of "will."

Recapitulating many of these earlier descriptions, in its current usage dementia requires three defining features. First, the decline should exist across multiple cognitive domains, typically including memory plus another domain such as language, visuospatial ability, or executive function; second, cognitive decline should emerge chronically, not acutely; and third, cognitive decline should be sufficiently profound to impair patient's day-to-day function. Accordingly, a syndrome that presents with impairments in a single cognitive domain is not dementia but rather defined according to its selective domain—for example, amnesia, aphasia, or attention deficit disorder. A syndrome that presents acutely might be labeled delirium, not dementia.

As with any attempt at developing a categorical definition, the difficulty is at the boundaries of the definition. Two points in particular have been most problematic and are still matters of debate. The first is the requirement that memory per se represent at least one of the impaired cognitive domains. For example, diseases that spare the medial temporal lobes might present early on with relative little memory dysfunction, but nevertheless target multiple cognitive domains and by all accounts are dementing illnesses. A second and perhaps more problematic point of debate is the requirement that the cognitive decline have a significant impact on daily function. Not only are functional deficits difficult to quantify, but early stages of many dementing illnesses cause subtle defects. Whether these defects actually impair a patient's function depends very much on the cognitive challenges of an individual's daily life.

With a greater understanding of the neuroanatomical correlates of cognition, and with techniques that can directly assess the functional integrity of these brain regions, an anatomical definition of dementia is beginning to supplant antiquated and categorically elusive definitions. Specifically, dementia can be defined as a progressive disorder that begins in one cortical region and over time spreads to involve multiple cognitively important sites. Beyond the advantage of relying on more objective measures, an anatomical definition of dementia is useful when attempting to distinguish among the different causes dementia. In principle, abnormalities in four general processes can cause dementia—infections (such as syphilis); "metabolic" deficiencies (such as B12 thyroid hormone deficiencies); structural lesions (such as neoplasm, hemorrhage, and stroke); and neurodegeneration. Diagnostic tests currently exist for the first three categories, but not for neurodegeneration. Furthermore, reflecting the diminished incidence of tertiary syphilis, the greater awareness and early treatment of vitamin and hormonal deficiencies, and the widespread availability of brain imaging, the vast majority of patients who present to a dementia clinic end up having neurodegeneration. In practice, therefore, distinguishing among the different types of neurodegeneration (Table 24–1) is the typical diagnostic dilemma facing the clinician. These disorders are different because they target separate regions of the brain, particularly early in the disease process, and therefore mapping the anatomical sites of dysfunction is currently the most effective method for accurately diagnosing the most common causes of dementia.

Importantly, since most neurodegenerative processes spread over time, mapping differential anatomical patterns is best achieved during the early phases of the disease. In contrast to other diseases, such as stroke for example, currently there are no definitive markers of regional disease

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**Table 24–1 Dominant Causes of Dementia in Later Life**

| Category of Disease | Key Examples | Key Tests |
|---|---|---|
| Toxic/metabolic | Hypothyroidism, B12 deficiency, drug toxicity, liver or kidney failure | B12, folate, thyroid function* |
| Inflammatory/infectious | Syphilis, Lyme disease, paraneoplastic syndromes, autoimmune, AIDS | RPR (rapid plasma regain)* |
| "Structural" lesions | Stroke, tumors, hematomas, hydrocephalus | Structural imaging tests such as CT or MRI |
| Neurodegenerative | Alzheimer's disease, frontal temporal degeneration, Lewy body dementia, Prion diseases, posterior cortical atrophy, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis | Neuropsychological tests, functional imaging† |

*Additional serologic or CSF studies when indicated.
†Additional genetic, serologic, or CSF studies when indicated.

caused by neurodegeneration. A patient's map of cortical dysfunction, therefore, usually emerges as a composite from three sources of information. A detailed history of symptoms and a careful exam, including cognitive testing, will typically offer first clues about affected sites. An extensive neuropsychological battery of tests will provide additional information in localizing the neurodegenerative lesions. Finally, information from brain imaging can sometimes contribute in mapping sites of dysfunction. As a general point, despite the justifiable enthusiasm engendered by brain imaging, the current diagnostic utility of these techniques is still under investigation. Currently, conventional MRI, typically ordered to rule out structural lesions, occasionally shows focal patterns of atrophy which can aide in the diagnostic process. Functional imaging techniques that map basal metabolic defects (e.g., positron emission tomography, which assesses basal glucose uptake or single-photon emission computerized tomography, which assesses basal blood flow) are sometimes ordered to help distinguish frontotemporal degeneration from AD.

Beyond its diagnostic value, a focus on the anatomy of neurodegeneration holds promise in expanding our understanding of underlying molecular mechanisms. To date, as discussed in the sections below, most molecular insight into neurodegeneration has come from a focus on protein aggregates (e.g., amyloid plaques, neurofibrillary tangles, or Lewy bodies) or from a focus on genetic polymorphisms that either cause disease or contribute to its risk. With the introduction of techniques capable of profiling gene expression levels, a focus on brain tissue itself is expected to offer additional molecular clues. To maximize the yield of this approach, it has therefore become imperative to first pinpoint the anatomical sites most vulnerable to a neurodegenerative process (Lewandowski and Small 2005).

Because of the forgoing discussion, in this chapter we will focus almost exclusively on neurodegenerative causes of dementia (Table 24–1). Instead of just offering a brief description of each item on this long list, we will provide an in-depth discussion on a select few. Those chosen reflect diseases that are most common and/or those in whom the greatest scientific discoveries have been made, highlighting general principles applicable to all neurodegeneration.

## Alzheimer's Disease

One hundred years ago, Alois Alzheimer examined the brain of Auguste D., a demented woman who began developing cognitive deficits in her late 40s, and thereby established that dementia can be associated with neurofibrillary tangles and amyloid plaques (Alzheimer 1907). In 1910, Emile Kraepelin defined "Alzheimer's disease" as a distinct dementing illness, which, he maintained, provided evidence that dementia can have an "organic" etiology. Yet, for decades thereafter, the major dementia of late life was either dismissed as the inevitable endstage of normal aging or else attributed to "cerebral atherosclerosis." Over 50 years would pass before investigators began appreciating that late-onset ("senile") dementia and early-onset ("presenile") AD are phenotypically indistinguishable under the microscope, prompting the unification of the disorders under the same name.

Nevertheless, despite a shared name and overlapping features, the early-onset and late-onset forms of AD are epidemiologically and etiologically distinct. The early-onset form is extremely rare and is caused by monogenic defects that follow an autosomal dominant pattern. Like other autosomal dominant diseases, early-onset AD has proven amenable to linkage analysis, and many pathogenic mutations have been isolated. In contrast, late-onset AD, which typically manifests after the sixth decade, accounts for over 95% of all cases and has a complex etiology. Like other complex disorders, the cause of late-onset AD has been difficult to pinpoint. Indeed, the late-onset form has historically been called "sporadic" AD to reflect the elusiveness of its etiology. Not only is late-onset disease the more common form of AD, but with increased longevity, late-onset AD has emerged as one of the most common disorders of the brain.

### Clinical Features and Anatomical Profile

Alzheimer's disease is, by far, the most common cause of dementia. Typically, AD follows a predictable cognitive course, which has mapped the disease's anatomical progression. At the gross anatomical level, AD begins by targeting the hippocampal formation, accounting for the fact that during its earliest stages AD presents with hippocampal-dependent memory decline—i.e., difficulty learning new names, place, or events. The hippocampal formation itself is made up of multiple subregions, and AD targets the pyramidal neurons of the entorhinal cortex and CA1 subfield, with relative preservation of the granule cells of the dentate gyrus. From the hippocampal formation, AD typically spreads in a serial fashion to involve other neocortical sites: Dysfunction in the temporal lobes causing language defects, dysfunction in the posterior parietal lobes causing visuospatial defects,

and finally, later in the disease, frontal lobe dysfunction, manifesting as defects in executive function and personality.

## Pathology and Pathogenesis

As first described by Alzheimer himself (1907), AD is characterized by two abnormal protein aggregates—extracellular amyloid plaques and intracellular neurofibrillary tangle. The molecular characterization of these aggregates was only established in the 1980s, when the appropriate biochemical and molecular tools became available.

Glenner and Wong (1984) first isolated amyloid plaques from the meningovasculature of patients with AD, and establishing that Aβ peptide is its core constituent. Then, in a succession of molecular discoveries, this peptide was found to be a cleaved product of the amyloid precursor protein (APP), and the enzymes that cleave APP were identified (Hardy and Selkoe 2002). Transgenically engineered mice, expressing mutations that lead to accelerated Aβ production and plaque deposition, have become an important extension of these discoveries, shedding light on the cell biology of amyloid processing and informing on its mechanisms of toxicity.

Two enzymatic steps liberate Aβ from APP. In the first, "β-cleavage" step, BACE (β-APP cleaving enzyme) cleaves APP at or near the N-terminus of the Aβ peptide. Then, in the second, or "β cleavage" step, the APP fragment is cleaved by the β-secretase, a multimeric complex thought to be made up of an essential quartet of transmembrane proteins—presenilin 1 (or 2), nicastrin, APH1, and PEN2. Amyloid plaques themselves are manufactured by Aβ peptide in an assembly line of chemical events. Single monomeric peptides bind together to form oligomeric strings, which bind to form fibrillar sheets, and multiple fibrils bind to form the backbone of the amyloid plaque ensnaring other macromolecules along the way. Thus, Aβ exists in different molecular species—monomers, oligomers, protofibrils, fibrils, and plaques. Operationally, these Aβ species can be dichotomized into monomers, oligomers, and protofibrils, which are soluble, versus fibrils and plaques, which are insoluble when exposed to conventional proteases. Not just a biophysical distinction, the soluble versus insoluble dichotomy have become important in the debate about Aβ neurotoxicity. Earlier cell culture studies suggested that the insoluble species of Aβ are toxic to neurons. One of the main contributions of transgenic mouse models of AD has been to correct this mistake, establishing that it is the soluble species of Aβ that in fact represent the key neurotoxin in the APP pathway.

With respect to neurofibrillary tangles, Tau had been identified as a protein involved in microtubule assembly (Weingarten et al. 1975). Its identification as the central component of the tangles was made through antigenic analysis (Brion et al. 1985), through protein purification methods (Grundke-Iqbal et al. 1986), and eventually through direct sequencing of the isolated pair helical filament peptides (Goedert et al. 1988). Tau protein in the tangles was shown to be highly phosphorylated which was widely believed to underlie its abnormal deposition. Of great importance in our understanding of the pathogenesis of tangles has been the dissection of the etiology of FTDP-17 (see below).

Elucidating the molecular pathways leading to the formation of amyloid plaques and neurofibrillary tangles, however, did not clarify a long-standing debate about whether the Aβ or tau pathway plays a pathogenic role in the disease process. This question was finally resolved when the genetic mutations that cause the early-onset form of the disease were identified (Goate et al. 1991). All the mutations were found to modify the metabolism of APP, with little affect on tau or neurofibrillary tangles, suggesting that the Aβ pathway is pathogenic in AD (Hardy and Selkoe 2002). Thus, although the monogenic early-onset form is extremely rare, this finding has clarified the pathogenic mechanism for all forms of the disease.

## Diagnosis and Treatment

When an elderly patient presents with dementia the clinical diagnosis of "probable" AD is made when (a) the history of the illness suggests a slowly progressive process that begins with hippocampal-dependent memory complaints; (b) other illness have been ruled out (i.e., blood tests to rule out B12 deficiency, hypothyroidism, and syphilis, and brain imaging to rule out large strokes, tumors, or bleeding); and (c) when neuropsychological testing identifies in addition to hippocampal dysfunction in other cognitive domains. Imaging studies can strengthen the diagnosis. Specifically, structural MRI might reveal localized atrophy in the medial temporal lobes; or functional imaging studies might reveal dominant hypometabolism in these posterior parietal lobes or medial temporal lobes. Currently, the diagnosis of "definite" AD can only be made when brain tissue is examined, showing a sufficient degree and distribution of amyloid plaques and neurofibrillary tangles.

During the earliest stages of the disease, when the disorder is restricted to the hippocampal formation, AD causes mild forgetfulness and, by definition, is in its predementia stage. Although its precise time course is undetermined, the predementia stage of AD can last many years. Currently, it is impossible to diagnose predementia AD with sufficient accuracy, hampered primarily by the fact that normal aging itself targets the hippocampal formation. With the anticipation that effective drugs will soon be developed, improving the diagnosis of predementia AD has become an important goal. Three diagnostic approaches are currently under investigation: chemical profiles of blood or CSF, cognitive profiles as assessed by neuropsychological testing, and imaging techniques that rely on indicators of neuronal dysfunction or neuronal loss, or indicators of amyloid plaques and neurofibrillary tangles.

Currently, three acetylcholinesterase inhibitors have been approved by the FDA for the treatment of AD dementia—donizapil (Aricept), rivastigmine (Excelon), and razadyne (Reminyl). Most recently, the glutamate receptor blocker memantine (Namenda) has also been approved. In the best case, these drugs slow disease progression, but do not halt its progression or reverse the disease process. Although large-scale studies have demonstrated that these drugs have a statistically significant effect over placebo, whether the effect is clinically meaningful remains a matter of debate. Put into historical context, these relatively safe drugs should be considered "first generation" pharmacological agents, offering therapeutic options whereas only a decade or so ago there were none. Although it is reasonable to consider these drugs for AD patients, it is widely acknowledged that drugs with greater efficacy are urgently needed.

## Genetics

Genetic analysis of families with AD showed that some families did show linkage to chromosome 21 markers (Goate et al. 1989), but that the disease was genetically heterogeneous (Schellenberg et al. 1988, St. George Hyslop et al. 1990). At this time, Levy et al. (1990) had shown that the Aβ was deposited in the blood vessel walls in hereditary cerebral hemorrhage with amyloidosis, Dutch type, (HCHWA-D) (Van Duinen et al. 1987): Van Broeckhoven et al. (1990) and Levy et al. (1990) showed that an APP mutation underpinned this disorder. With this background, focused sequencing of the APP gene in those Alzheimer families that showed evidence for genetic linkage to chromosome 21, identified APP mutations (Goate et al. 1991). The precise positions of these mutations showed that their most likely effect was to alter APP processing (Hardy 1992). More recently, APP duplications in families with a variant of AD have indeed been discovered (Rovelet-Lecrux et al. 2006) and this, together with the absence of AD in Down's syndrome who were trisomic distal of the APP locus (Prasher et al. 1998), clearly shows that APP overexpression can be a cause of the disease.

In general, families with APP mutations have a typical AD phenotype, although some mutations, including the APP duplications, have a phenotype reminiscent of HCHWA-D (Levy et al. 1990). The age of onset of cases with APP mutations is typically in the late 40s to mid-50s. Cases with APP mutations and Down's syndrome cases can have Lewy bodies (see below) as well as tangles (Lantos et al. 1994).

The majority of families with autosomal dominant AD did not have APP mutations. Schellenberg et al. identified linkage to chromosome 14 (1992) and Sherrington et al. (1995) identified presenilin 1 as the major locus underlying early-onset autosomal dominant disease. Genetic analysis had shown that a group of German families from Russia (the Volga Germans) did not show linkage to chromosome 14 markers, but rather showed linkage to chromosome 1 markers. A homologue of presenilin 1, presenilin 2, mapped to this region and was shown to underlie the remaining few cases of autosomal dominant disease (Levy-Lahad et al. 1995). In general, cases with presenilin 1 mutations also have typical AD with an age of onset in the late 30s to mid-40s though some cases present with spastic paraparesis and have unusual "cotton wool" plaques (Crook et al. 1998). Cases with presenilin 2 mutations also have features similar to typical AD, but the onset ages are more variable, even within a family (Bird et al. 1989). Cases with presenilin mutations also frequently have Lewy body pathology (Lippa et al. 1998) (see below).

Progress identifying risk genes for sporadic late-onset Alzheimer's has, not surprisingly, been slower. Corder et al. (1993) identified apolipoprotein E4 as a risk factor and another common variant, apoE2, as negatively associated with the disease. They appear to account for about a third of the population attributable risk for developing AD. However, the mechanism behind this association remains unclear, with most authorities suspecting a role in amyloid deposition (Holtzman 2004). Despite extensive work, no other genetic risk factors for late-onset disease have been validated (Bertram and Tanzi 2004)

## Frontal Temporal Dementia

Whereas in the past frontal temporal dementia (FTD) was used synonymously with Pick's disease, according to current nosology FTD encompasses multiple dementing illnesses, including corticobasal ganglionic degeneration (CBGD) and progressive supranuclear palsy (PSP). As implied by the name, FTD and its variants are unified anatomically by targeting the frontal and lateral temporal lobes, with notable sparing of the medial temporal lobes including the hippocampal formation. Furthermore, at the histological level, FTD and its variants are typically characterized by neuronal inclusions that stain positive for tau or ubiquitin.

### Clinical Features and Anatomical Profiles

FTD subtypes are organized according to whether the patient presents with personality and behavioral changes or whether the patient presents with language-predominant dysfunction. Anatomically, the first subtype, historically termed Pick's disease but currently called frontal variant FTD, targets the prefrontal cortices. In accordance with the functional roles served by the dorsolateral or the orbitofrontal regions of the prefrontal cortex, this subtype of FTD presents with a range of behavioral changes. When the orbitofrontal site is the primary target, patients present with disinhibition, poor impulse control, irritability, aggressiveness, violent outbursts, and mood swings. Dysfunction in the dorsolateral regions manifests with social withdrawal and apathy (often misdiagnosed as depression), loss of will (abulia), and loss of personal or social awareness. Of course, both prefrontal sites might be involved in inappropriate social behavior (i.e., sexual overtures or racially insensitive comments, urination in public, altercations, etc.) are common, as are stereotyped behavior, such as perseverative speech or activities. Changes in eating patterns or religious feelings, obsessive or compulsive behavior, delusions, and hypomania are also part of the syndrome.

After beginning in the prefrontal cortices, this subtype can spread anatomically. When spreading to involve the primary motor cortex or even the spinal cord, a clinical picture of motor neuron disease (MND) manifests. If spreading occurs to the midbrain and the tracts regulating eye movements, a clinical picture of supranuclear palsy (PSP) emerges.

The language subtype of FTD, called primary progressive aphasia (PPA), is further subdivided according to whether the aphasia is fluent or nonfluent. Progressive nonfluent aphasia begins in or around Broca's area in the frontal lobes, and occasionally will spread to the basal ganglia, in which case this subtype is called CBGD. The fluent aphasia subtype is called semantic dementia, because it is characterized by semantic paraphasias and forgetfulness primarily for words and word meanings. This subtype targets the left lateral temporal lobes.

### Pathological Features and Pathogenesis

The underlying histopathology of FTD is variable, with essentially three forms recognized so far, each of which can occur in the context of either familial or sporadic disease: the first is tau pathology, which manifests as tangles, wispy tau filaments or Pick bodies; the second is ubiquitin inclusions; and the third is neuronal loss in the absence of identified histopathology (Forman et al. 2006). These three pathological entities map onto different genetic entities, and while the view we present here may be over simplified, it allows a

convenient presentation of our knowledge in this complex area.

## Diagnosis and Treatment

When an elderly patient presents with dementia the clinical diagnosis of "probable" FTD is made when (a) the history of the illness suggests a slowly progressive process that begins with complaints that localize to anterior cortical sites; (b) other illness have been ruled out (i.e., blood tests to rule out B12 deficiency, hypothyroidism, and syphilis, and brain imaging to rule out large strokes, tumors, or bleeding); and (c) when neuropsychological testing suggests dominant dysfunction in the frontal lobe or anterior temporal lobe, and relative preservation in hippocampal-dependent tasks. Imaging studies can strengthen the diagnosis. Specifically, structural MRI might reveal localized atrophy in the frontal lobes or the anterior temporal lobes; or functional imaging studies might reveal dominant hypometabolism in these same brain regions. Currently, the diagnosis of "definite" FTD can only be made when brain tissue is examined, typically showing either/or tau-positive or ubiquitin-positive inclusions.

Clinical signs and symptoms can further speciate FTD into its different subtypes: Basal ganglia dysfunction suggests either CBGD or progressive supranuclear palsy; midbrain dysfunction, notably impairment in downward gaze suggests supranuclear palsy; upper or lower motor neuron dysfunction suggests FTD-MND (motor neuron disease); dysfunction to language areas suggests PPA or semantic dementia.

Currently, there are no drugs that are approved for treating the primary process in FTD. Symptomatic treatment is often used, such as neuroleptics or anxiolytics, to allay the behavior manifestations of the disease.

## Genetics

Several genetic linkages have been reported for which the precise genes have not been identified. In this chapter we will not discuss these, not least because, in the past, some of these genetic linkages have not been confirmed. With this background, we will discuss the three known genes, MAPT (tau), PGRN (progranulin), and CHMP2B because these correspond to the three pathologies: tau pathology, ubiquitin inclusions, and no distinctive histopathology (Hardy et al. 2006). However, there are certainly other genes to be found for these syndromes.

Wilhelmsen et al. (1994) identified linkage to chromosome 17 in a kindred with a dementing syndrome. Over the next few years, other kindreds, with very variable dementing phenotypes were described to ostensibly be linked to the same locus, and a 1996 consensus meeting (Foster et al. 1997) facilitated the description of this syndrome as FTDP-17. The linkage region contained the tau gene and Spillantini et al. (1998) pointed out that the majority of kindreds had variable tau pathology. In fact (and confusingly), the PGRN gene is only 1 Mb away from the MAPT gene and the exceptions to these statements turned out to have PGRN mutations (Baker et al. 2006).

Hutton et al. (1998) and Poorkaj et al. (1998) identified mutations in the MAPT gene that caused the syndrome. The known function of tau is to bind microtubules, and tau exists in two classes of isoforms: those with 3 microtubule binding domains, and those with 4. These classes of isoforms are generated by alternate splicing of exon 10. One set of mutations alters splicing control and causes only the 4 repeat isoforms to be generated and the other mutations are point mutations which either disrupt microtubules binding or initiate tau aggregation. In general, those mutations that affect splicing lead to the deposition of wispy filaments consisting of 4 repeat tau; those missense mutations that are in exon 10 lead to heavy deposits of only 4 repeat tau as typical neurofibrillary tangles; and those that are elsewhere in the protein (in exons 9, 11, 12, and 13) usually lead to deposition of typical neurofibrillary tangles consisting of both 3 and 4 repeat tau, although some of these latter lead to the deposition of 3 repeat tau as Pick bodies. Interestingly, two mutations have been found in exon 1 which had been postulated to play a role in the control of tau binding to microtubules and these lead to the deposition of 4 repeat tau tangles.

These general principles connect the genetics to the histopathology of the disorder, but there is presently little understanding of the relationship between the precise clinical features of the disease (which are very variable) and either the genetics or the pathology (though see below). By definition, FTDP-17 is an autosomal dominant disorder. However, its clinical and pathological features overlap with sporadic PSP, sporadic corticobasal degeneration and sporadic Pick's disease, and it is perhaps worth thinking of these diseases as being separated from FTDP-17 by an accident of nosology.

On close examination of the MAPT gene in Europeans, it was noted that there were two haplotype clades in this population: H1 and H2 (Baker et al. 1999). It is now known that these clades are separated because of a genomic inversion which prevent recombination between them (Stefansson et al. 2005). Only the H1 clade is present in non-Europeans. About 60% of Western Europeans are H1 homozygotes, but >95% of those who have either sporadic PSP or CBD are H1 homozygotes, indicating that MAPT is a risk factor locus for the disease (Baker et al. 1999), and suggesting that genetic variability in tau expression or splicing must underlie this association. In these diseases, the predominant tau species deposited is 4 repeat tau, and furthermore, more detailed analysis of the MAPT locus and tau expression has shown that the risk haplotype is associated with both slightly increased tau expression (~10%) and slightly increased production of the 4-repeat isoform (~20%) (Myers et al. 2006).

## Ubiquitin Inclusions: FTDP-17 without Tau Pathology

As noted above, a significant proportion of kindreds which showed linkage to chromosome 17 markers did not have mutations in the MAPT locus and these same cases did not have any tau pathology. These cases were first thought to have no distinctive pathology, but careful examination revealed that they had distinctive inclusions staining for ubiquitin, a class of proteins one of whose normal functions is to mediate the selective degradation of other proteins. More recently, careful biochemical analysis has revealed that the predominant protein in these inclusions is TDP-43, an RNA binding protein (Neumann et al. 2006).

For several years, the predominant notion was that these cases must have complex mutations at the MAPT locus: however, eventually, Baker et al. (2006) identified that the locus responsible for the cases without MAPT mutations was the progranulin gene (PGRN) which is about 1 Mb

centromeric of MAPT. The location of the two pathogenic loci, giving rise to indistinguishable clinical syndromes seems to be completely coincidental. All the pathogenic mutations in the PGRN gene described so far give rise to simple loss of function alleles making it clear that hemizygosity for the PGRN locus gives rise to the disease phenotype. The known function of the PGRN locus is as a growth factor in wound repair, making a plausible hypothesis that those who are hemizygous fail to respond adequately to minor head injuries: this suggestion is consistent with the observation that the disease is incompletely penetrant and that the clinical features are extremely variable.

The same pathology (ubiquitinated TDP-43 inclusions) is found in many ALS cases, though so far, no PGRN mutations have been found in such cases. The relationship between ALS and this form of dementia is presently an area of intense investigation.

### Dementia without Identified Histopathology

Gydesen et al. (1987) reported a large Danish family with a profound, late-onset dementia, which was later genetically linked to chromosome 3. Eventually, a complex splicing mutation in the endosomal sorting protein, CHMP2B was identified (Skibinski et al. 2005). However, no other convincingly pathogenic mutations have been found. It currently seems most likely that this mutation is indeed pathogenic, but that its pathogenicity is dependent on the unusual nature of the mutation, which adds a nonsense sequence to the C-terminal of the protein (Momeni et al. 2006).

## Lewy Body Dementia

As in the case of FTD, recent classification schemes have tried to "lump" rather than "split" disorders that are unified by having both dementia and Parkinsonism (bradykinesia, resting tremor, gait instability, rigidity) as their key clinical characteristics, and Lewy bodies in both the subcortex and neocortex as their histological characteristics. The term Lewy body dementia (LBD) is now commonly used to encompass both Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB).

### Clinical Features and Anatomical Profiles

A growing number of studies are suggesting that dysfunction of the posterior parietal and anterior occipital regions are the neocortical sites that best distinguish LBD from FTD and AD. This anatomical pattern has been implicated by functional imaging studies, showing hypometabolism in these regions, and neuropsychological studies that often uncover dominant dysfunction in visuospatial and visuoconstructive abilities. Furthermore, LBD patients often present with visual hallucinations as a primary and early symptom.

Both the PDD and DLB subtypes of LBD present with Parkinsonism, reflecting underlying dysfunction in the basal ganglia. The temporal profile in which neocortical and basal ganglia dysfunction emerge is a key feature distinguishing PDD and DLB. Specifically, in PDD the basal ganglia is targeted first followed by involvement of the neocortex, while in the DLB the temporal profile is reversed. Thus, patients with PDD are typically diagnosed first as having classic Parkinson's disease that then, over time, progress to develop dementia. In contrast, patients with DLB first present with dementia that then progress to develop extrapyramidal signs and symptoms.

Because of the delayed onset of dementia, PDD does not typically present a diagnostic dilemma. The same is not true for LBD, and so when presented with a patient with a primary diagnosis of dementia, diagnostic features have been proposed that aid in distinguishing LBD from AD or FTD. In addition, patients with long-standing AD can manifest Parkinsonism as well. So, together with evidence of relatively early Parkinsonism and visual hallucinations, patients with LBD typically have fluctuating cognition, and can have rapid eye movement sleep disorders, neuroleptic hypersensitivity, and reduced dopamine transporter activity assessed by neuroimaging.

### Diagnosis and Treatment

When a patient presents with dementia the clinical diagnosis of LBD is made when (a) the history of the illness suggests a slowly progressive process that begins with complaints that localize to the basal ganglia and posterior cortical sites; (b) other illness have been ruled out (i.e., blood tests to rule out B12 deficiency, hypothyroidism, and syphilis, and brain imaging to rule out large strokes, tumors, or bleeds); and (c) when neuropsychological testing suggests dominant dysfunction in posterior cortical sites, and relative preservation in hippocampal-dependent and frontal lobe-dependent tasks. Imaging studies can strengthen the diagnosis. Specifically, functional imaging studies might reveal dominant hypometabolism in the posterior cortical sites. Currently, the diagnosis of "definite" LBD can only be made when brain tissue is examined, typically showing Lewy bodies in the basal ganglia as well as in the neocortex.

Dopaminergic agents are typically effective in the extrapyramidal signs of PDD, but less so for DLB. Because of their hypersensitivity to neuroleptics, the use of this drug category for symptomatic treatment of hallucinations should be used with extreme caution.

### Genetics

Because DLB is an overlap disorder, its genetics are a complicated. For example, some AD cases with APP or presenilin mutations have Lewy bodies in addition to neuritic plaques and there is an association with the APOE4 allele as there is with AD. However, individuals with α-synuclein mutations can have a pure DLB (without plaques). However, this situation is most easily reconciled with the view that α-synuclein aggregation is the proximal reason for cell death in these diseases and this can be caused directly through α-synuclein mutations or overexpression, but that this process is potentiated by Aβ.

## Prion Diseases

Prion diseases are neurodegenerative disorders caused by the transmissible particles that contain a pathogenic isoform of the prior protein. The most common prionapathy is Creutzfeldt-Jakob disease (CJD), which is further subdivided based on modes of transmission: (a) sporadic CJD, whose etiologic basis remains unknown (thus "sporadic"; (b) familial CJD is an inherited form that follows an autosomal-dominant pattern of transmission; (c) iatrogenic CJD, which is typically caused in patients who received contaminated corneal transplants or injections of hormones

extracted from human pituitary glands, and in surgeons who are exposed to contaminated surgical instruments; and (d) variant CJD, which was first described in 1994, occurring in patients who have consumed cattle contaminated with bovine spongiform encephalopathy.

### Clinical Features and Anatomical Profiles

Anatomically, CJD targets subcortical structures including the basal ganglia and thalamus, as well as widespread involvement of the neocortical mantle, in particular the frontal lobes and posterior cortical sights including the occipital lobes, and the cerebellum. This accounts for the wide range of symptoms found in patients with CJD, including change in sleep, cognitive deficits, visual disturbance, and gait instability. Sporadic CJD, by far the most common form, typically presents after the fifth decade of life. Variant CJD is found in younger patients, and has the additional distinguishing feature of presenting with painful sensory symptoms and more florid psychiatric manifestations.

### Diagnosis and Treatment

Clinically, CJD is typically dissociated from other neurodegenerative processes by the rapidity of its progression (thus, it is often called a subacute, not achronic, encephalopathy), by the evidence of cortical, basal ganglionic, and cerebellar dysfunction, and by the appearance of stimulus-induced myocolonus. Ancillary tests include EEG, which can sometimes show characteristic abnormal biphasic and triphasic complexes; MRI which can sometimes show increased signal intensity in the basal ganglia; and CSF studies, with elevated levels of the 14-3-3 protein found in most cases. There is currently no treatment for this devastating disease, which typically kills patients within a couple of years of diagnosis.

### Pathological Features and Pathogenesis

Prion diseases, historically, were called the spongiform encephalopathies because of the characteristic spongy appearance of the pathological tissue. The histopathology can be very variable, from clearly defined plaques of the prion protein to very subtle deposition. The distribution of the deposition is also very variable, with the entire cortex and basal ganglia as well as cerebellum, all capable of having deposits and evidence of spongiform change.

While the mechanism of cell death in prion diseases still remains mysterious, the basic principles of disease initiation have become clear. The prion protein is at the center of the disease process and can exist as one of two forms: the "normal" form ($PrP^{c}$) and the pathologic form $PrP^{Sc}$) (Sc stands for scrapie, the prion disease of sheep) (Prusiner 2001). On interaction with $PrP^{Sc}$, $PrP^{c}$ is converted to $PrP^{Sc}$ by a templating mechanism. As the concentration of PrPSc increases, the pace of propagation accelerates. $PrP^{Sc}$ exists as several different variants and these correspond to the "strains" (Hill and Collinge 2004). Each of the strains (the number is unknown, but certainly of the order of a dozen) corresponds to a different structure: each has differing clinical effects and attacks different neuronal predilections. Bovine spongiform encepatholopathy/new variant CJD corresponds to a new strain of $PrP^{Sc}$ (Jackson and Collinge 2001). Part of the determinant of strain/$PrP^{Sc}$ structure is a common coding polymorphism, M129V. New variant, CJD, for example, cannot occur in someone with a V129 allele (Wadsworth et al. 2004).

With this background, many of the bizarre features of prion disease become easier to understand. Infectious/iatrogenic CJD occurs when the origin of the $PrP^{Sc}$ is in the contaminating material (whether it is food, or contaminated surgical instruments): hereditary prion disease occurs when there is a mutation in the prion gene, which makes a transition from $PrP^{c}$ to $PrP^{Sc}$ more likely and sporadic disease occurs, most plausibly, by a stochastic conversion from $PrP^{c}$ to $PrP^{Sc}$. In all cases, the more efficient the conversion from $PrP^{c}$ to $PrP^{Sc}$ the more efficient the disease process. Thus, prion gene homozygosity at codon 129 predisposes to sporadic disease and M129 homozygosity predisposes to new variant CJD (Wadsworth et al. 2004).

This simple explanation leaves many questions unanswered: the precise structural determinants and the number of strains is not clear. But perhaps most mysterious of all, is the reason that the prion gene has evolved to have such bizarre structural propagation properties is completely mysterious.

## Conclusions

As reviewed above, the last 10 years in particular have brought a revolution in our understanding of the initiating lesions in many of the dementia: we have clear outlines of some of the initial steps in their molecular pathogeneses. In general, however, we have almost no understanding of how the genetic lesions initiate the reasonably selective neuronal losses that distinguish the diseases: neuronal selectivity is still a black box into which we cannot yet peer. Finally, and most importantly, our improved molecular understanding has not helped us at all with mechanism therapies yet. To the extent we have therapies for these devastating disorders, we rely on transmitter-based therapies. We have to hope that the next 10 years will see some improvement in this regard.

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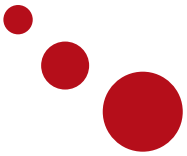
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SECTION IV

Paulette M. Gillig, Section Editor

# *Psychological and Social Scientific Foundations of Psychiatry*

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CHAPTER

# 25 Psychiatric Epidemiology

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## Overview

The President's New Freedom Commission in the United States and the Green Paper from the European Union have outlined key goals for reducing the burdens from mental disorders (President's New Freedom Commission on Mental Health 2003, Health and Consumer Protection Directorate General 2005). These have included increasing public awareness of the frequency and consequences of mental disorders, understanding and reducing stigma and disparities in mental health, as well as promoting early detection and timely receipt of high-quality treatment. Accomplishing all of these important goals will clearly rely heavily on contributions from the field of psychiatric epidemiology.

The discipline of psychiatric epidemiology is at its most basic level the study of the patterns of mental disorders, including how frequently disorders occur, how they are distributed in populations, and what are the associated risk factors. Psychiatric epidemiology also defines the time course of mental disorders including their onset, duration, and recurrence. This basic information is fundamental to the understanding of mental disorders and the development of effective intervention and prevention programs. Recently, the field has greatly expanded and now includes detailed examinations of the natural history of psychiatric disorders, genetic epidemiology, the relationships between physical and mental disorders, and studies of the use and outcomes of mental health treatments. This expansion has required significant advances and developments in psychiatric epidemiologic methods (Tsuang and Tohen 2002). This progress has also benefited from the continuing operation of doctoral and postdoctoral psychiatric epidemiology training programs in centers throughout the United States funded by the National Institute of Mental Health (NIMH).

Important characteristics that distinguish psychiatric epidemiological research from other clinical investigations are the inclusion of representative samples and the application of systematic methods for determining diagnosis or outcome. The specific type of sample and choice of mental health measure depend on the goal of the study. For studies aimed at establishing prevalence and incidence rates, the population-based survey is the optimal method. Complex sampling procedures have been developed to ensure random selection for both single-stage- and two-stage studies. For rare disorders, identified patients are usually ascertained from registries or a representative set of psychiatric treatment facilities. However, because only a minority of individuals with diagnosable disorders are ever treated for psychiatric problems within the mental health care system (Regier et al. 1993, Kessler et al. 1994, Wang et al. 2000), these sources may omit true case patients who do not present for treatment. Another source for epidemiological samples is an institution, such as a psychiatric hospital, general medical facility, school, or workplace. There has been particular interest recently in conducting psychiatric epidemiologic research in primary medical care settings, both because individuals with psychiatric disorders are relatively heavy utilizers of general medical services and because primary care providers are increasingly being given the responsibility of treating mental disorders (Schulberg 1991, Von Korff et al. 1992). Such studies have focused on the recognition and treatment of mental disorders and the specific patterns of health service use by patients with diagnosable psychiatric conditions (Wells et al. 1994, Coyne et al. 1995). In the past, defining "caseness" in psychiatric epidemiologic studies has been difficult. The lack of reliable and cost-efficient methods for making diagnoses has been a central impediment to conducting research that could yield even basic data on the occurrence of mental disorders. Earlier studies have employed case definitions ranging from scoring above a threshold on a general symptom inventory to

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receiving mental health services. The development of structured diagnostic interview schedules (DISs) tailored to clear, operationalized diagnostic criteria was the crucial element underlying the recent progress in psychiatric epidemiology. As a result of the development of structured DISs, the need to establish the prevalence of specific disorders was finally realized, at least within the limits of our current ability to operationalize mental disorders and within the constraints inherent in interview data (Fennig and Bromet 1992). Estimates suggest that approximately 12% of children (Institute of Medicine 1989) and 15% of adults (Regier et al. 1988) currently meet criteria for one or more mental disorders. More precise estimates will be possible as more sensitive diagnostic tools become available.

This chapter begins with a description of the scope of questions covered in psychiatric epidemiologic investigations. We then briefly cover the methodology that characterizes psychiatric epidemiological research, focusing on the strengths and limitations of different approaches particularly with respect to reliability and validity. This is followed by a discussion of examples of important psychiatric epidemiologic studies, including their findings and critical developments that made them possible. Finally, we conclude with a brief discussion of continued challenges to conducting psychiatric epidemiological research and the need for future developments.

## The Scope of Inquiry in Psychiatric Epidemiology

"Epidemiology" is derived from the Greek words *epidemos*, meaning "among the people," and is defined as the study of "the patterns of disease occurrence in human populations and of the factors that influence these patterns" (MacMahon and Pugh 1970). Because the ultimate goal of epidemiological research is to understand the cause of disease and prevent its occurrence, epidemiology is the backbone of public health. Among the earliest epidemiologic investigations is that of John Graunt (1939), who in 1662 used birth and mortality records collected by parish clerks to study variations in birth and death patterns by sex, urban-rural residence, and seasonality, in hopes that such data could provide clues toward understanding human disease. Early epidemiologic research also includes the work of John Snow (Snow 1936). Snow concluded that the London cholera outbreak of 1848 was associated with the discharge of fecal waste into the water supply, after observing that the mortality rate among residents served by a company whose source was from a heavily polluted part of the Thames River was eight to nine times higher than that of residents served by the other company whose water was drawn from a less contaminated part of the river. Importantly, Snow reduced the level of mortality by turning off the offending company's pump, thus demonstrating that prevention efforts can be highly successful even if the specific cause of a disease (in this case, a microorganism) is not known. The principles by which modern epidemiologic studies are now conducted, have largely emerged since the end of World War II (Rothman and Greenland 1998). With the establishment of such principles, large-scale epidemiologic studies on numerous diseases and conditions have proliferated. Results of these studies have had a profound impact on our understanding of diseases (e.g., cardiovascular disease), their risk factors (e.g., smoking), and on public health (e.g., highly successful primary prevention programs for infectious diseases such as poliomyelitis).

Important advances have also been made in psychiatric epidemiology, largely since World War II. To make such advances, investigators have had to overcome formidable problems that are fairly unique to the study of psychiatric disorders. Foremost among their achievements has been the development of the ability to define mental disorders reliably and efficiently. This accomplishment has, in turn, allowed investigators to conduct descriptive analyses that have yielded much-needed estimates of the incidence, prevalence, age at onset, and frequency of recurrence of mental disorders.

The ability to accurately categorize cases and noncases has also been essential for allowing psychiatric epidemiologists to progress from simple descriptive work establishing rates, to analytical research aimed at identifying risk factors as well as biological and psychosocial variables that modify the effects of these risk factors. Examples of promising areas in which there has been significant research activity include investigations of the genetic bases for psychiatric disorders (Risch and Merikangas 1996) and the modification of risk by environmental exposures, especially in the prenatal period (Neugebauer et al. 1999).Whereas traditional epidemiology has largely been concerned with the occurrence and causes of disease, clinical epidemiology has emerged as a closely related discipline which seeks to identify the occurrence and determinants of clinical outcomes from illnesses (Sackett et al. 1985, Weiss 1985). Clinical epidemiologic studies employ the same principles and methods of population-based epidemiology, but are usually conducted among clinical samples. Clinical epidemiologic investigations, such as the NIMH Collaborative Program on the Psychobiology of Depression (CPPD) and the Harvard–Brown Anxiety Research Program have provided important information on prognostic factors associated with the natural history of psychiatric disorders (Judd et al. 1998, Rogers et al. 1999). Other examples include two countywide longitudinal studies of first-admission psychosis (Beiser et al. 1989, Bromet et al. 1992), which included patients from all facilities in the respective geographical regions, a follow-up study of first-episode psychotic patients admitted to the McLean Hospital in Belmont, Massachusetts (Tohen et al. 1992), and the Avon Longitudinal Study of Parents and Children [ALSPAC], a prospective cohort study following 14,000 children and their mothers (Golding et al. 2001).

Psychopharmacoepidemiology has been an especially fast growing component of clinical epidemiologic inquiry (Wang et al. 2003), in part because psychotropic medications are now widely used in both general medical and psychiatric populations. Many psychopharmacoepidemiologic studies have consisted of descriptions of the patterns and predictors of psychiatric medication use (Wang et al. 2000, Olfson et al. 2002) as well as investigations of unanticipated hazards from psychiatric medications (Wang et al. 2001a, 2001b, 2001c, Wang et al. 2002a, 2002b).

Clinical epidemiologic research has also begun to evaluate the economic costs associated with mental disorders, both the direct costs for provision of mental health services as well as the indirect costs to society secondary to the disability caused by disorders. The WHO Global Burden of

Disease (GBD) study (Murray and Lopez 1996) identified mental disorders as among the most costly diseases in the world. For example, major depression was the single most burdensome disease in the world among individuals under 45 years of age. Another closely related area of inquiry is that of mental health services research. This discipline investigates the patterns of utilization of mental health services, unmet needs for treatment, barriers to help-seeking, the appropriateness and quality of treatments, and premature dropout from treatment (Wang et al. 2000, 2002, Kessler et al. 2001a, Edlund et al. 2002).

The accumulation of information on risk factors for mental disorders, their outcomes, and treatment has, in turn, led to another important line of inquiry in psychiatric epidemiology, namely, interventional research. In addition to efficacy trials of psychiatric treatments conducted under rigorously controlled conditions (Tohen et al. 2000, 2002), experimental studies have also begun to include effectiveness trials of "real-world" treatment strategies (Katon et al. 1995, 1996, Simon et al. 2000, Wells et al. 2000). Finally, the proliferation of effective but costly interventions, coupled with growing constraints on health care budgets, have also made it imperative to study not only the effectiveness of interventions but also their cost-effectiveness and cost-benefits. For this reason, economic analyses now frequently accompany efficacy and effectiveness trials of interventions (Schoenbaum et al. 2001).

## Epidemiological Methods

Conducting investigations across this broad scope of inquiry has required the development of rigorous psychiatric epidemiologic methods. The following section contains a brief description of some of the basic elements of this methodology.

### Measures of Disease Frequency

Epidemiological studies examine the incidence and prevalence rates of disorders in populations at risk and the factors associated with onset and recurrence. A rate is determined by the number of cases (the numerator) divided by the population at risk (the denominator).

#### Incidence

Incidence rates refer to new cases that arise in a healthy population during a fixed time. The most commonly applied incidence rate in psychiatric epidemiology is the cumulative incidence rate, also known as the incidence proportion (Selvin 1991), that is, the proportion of a population at risk that has a disease during a specified time. For example, we wished to determine the cumulative incidence rate of depressive and anxiety disorders in a sample of mothers of young children during the year after the accident at the Three Mile Island nuclear power plant. A total of 312 women with small children living within 10 miles of the plant were interviewed with the SADS-L (Bromet et al. 1982). Of them, 84 met research diagnostic criteria for major depression or generalized anxiety disorder *before* the accident. Forty-five cases occurred during the year after the accident, of which 26 were first-onset or incident cases. The 1-year cumulative incidence rate is, thus, 26 divided by 228 (the total sample less those with a prior history, or 312−84), or 11.4%.

Cumulative incidence is appropriate when a study has a fixed cohort design (i.e., when all of the members of the cohort are observed for the same time). However, when attrition occurs, the cumulative incidence rate is a less desirable measure. Individuals lost to follow-up who would have become case patients are excluded from the numerator, whereas the denominator, which is the total population, remains unchanged. Moreover, those who become lost to follow-up are often a biased subgroup of the original study population (Eaton et al. 1992). Therefore, cumulative incidence should be considered most reliable when there is a small loss to follow-up during the specified time. When loss to follow-up occurs or when the occurrence of a health outcome is measured in a dynamic cohort (i.e., when members of the cohort come in and out, different statistical adjustments must be employed) (Selvin 1991).

$$\text{Comulative incidence} = \frac{\text{number of new cases}}{\text{total population at risk}}$$

In epidemiology, incidence rate refers to the number of new cases occurring in a specified time period divided by the sum of time periods of the observation for all individuals in the population at risk, or person-time (Rothman and Greenland 1998). For example, suppose an investigator wishes to calculate the incidence rate of suicide in 100 patients with mania during the 5-year period after initial diagnosis. The numerator is the number of patients who committed suicide, and the denominator is 100 patients × 5 years, or 500 person-years. If five suicides occur, the incidence rate of suicide will be 5 divided by 500 person-years. The units of incidence rates are time$^{-1}$. Because the units and the numerical value of an incidence rate are difficult to interpret, incidence rates are usually compared with each other to obtain incidence rate ratios.

$$\text{Incidence rate} = \frac{\text{number of new cases}}{\text{person-years}}$$

#### Prevalence

Prevalence rates measure the proportion of individuals who have the disease at a specified point or period in time. Incidence refers only to new-onset cases, whereas prevalence includes all new, recurrent, or chronic cases in the numerator and the entire population, including those with a history of the disorder, in the denominator. The point prevalence rate is the proportion of a population affected by a disease at a given point in time. Period prevalence refers to the proportion of a population affected by a disease during a specified time period, such as 6 months, 1 year, or lifetime. Prevalence rates are influenced by the duration of a disease. For nonchronic disorders, such as major depression, the point prevalence is usually lower than the period prevalence. For chronic conditions, such as schizophrenia, the point prevalence and period prevalence are expected to be similar.

$$\text{Prevalence rate} = \frac{\text{number of cases}}{\text{total population at risk}}$$

In general, prevalence data are less useful than incidence data for etiological research. Prevalence is determined not just by factors that cause a disease but by factors secondary to the disease itself. On the other hand, prevalence measures

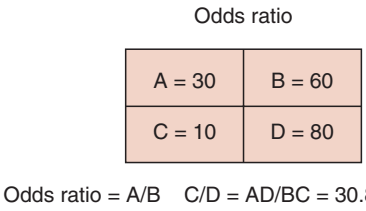



**Figure 25–1** *Calculation of relative risks using a ratio of the odds of exposure of case patients to that of control subjects.*

are useful in public health or service utilization situations. For instance, the geographical location and planning of specific services of a community mental health center are usually based on findings from prevalence studies.

### Measures of Association

Incidence rates can be used to calculate two types of effects. One is the attributable risk, or the absolute effect. The attributable risk is the difference between two incidence rates. This is most commonly used in comparing rates of exposed with nonexposed populations. For example, the Three Mile Island study included a sample of mothers of young children living near another nuclear power plant in Pennsylvania. The risk of depression and anxiety attributable to the Three Mile Island accident was the incidence rate in the exposed population (11.4%) minus that in the comparison population (3.2%), or 8.2%. The second type of effect is the relative risk, which is the ratio of the incidence rates of the exposed and unexposed groups. In the same example, the relative risk was 3.56%. In case-control studies, it is not possible to estimate incidence rates. Relative risks, however, can be calculated with an odds ratio, which is the ratio of the odds of exposure of the case patients to that of the control subjects (Figure 25–1).

## Instruments to Identify Cases

The lack of reliable and cost-efficient methods for making diagnoses has been a central impediment to conducting research that could yield even basic data on the occurrence of mental disorders. Earlier studies have employed case definitions ranging from scoring above a threshold on a general symptom inventory to receiving mental health services. The development of structured DISs tailored to clear, operationalized diagnostic criteria has been the crucial element underlying the recent progress in psychiatric epidemiology.

The history of development of uniform methods for eliciting and quantifying clinical information largely starts with the United States–United Kingdom project (Cooper et al. 1972), in which previously observed cross-national differences in the distributions of schizophrenia and affective disorders in hospitalized patients disappeared when consistent diagnostic procedures were administered. The feasibility and benefits of structured, or semistructured, interview schedules that could systematically elicit criteria for objectively defined disorders further became evident after the appearance and widespread use of instruments such as the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978), the companion interview for the Research Diagnostic Criteria (Spitzer et al. 1978). The SADS and the Research Diagnostic Criteria were originally developed for use by psychiatrists in the multisite Collaborative Study of the Psychobiology of Depression sponsored by the NIMH (Katz et al. 1979). Two community-based studies demonstrated that master's-level mental health professionals could successfully administer the lifetime version of the SADS (SADS-L) for epidemiological purposes (Weissman et al. 1978, Bromet et al. 1982). Other standardized psychiatric interviews that have been commonly used are the Present State Examination (Wing et al. 1974) and its successor, the Schedule for Clinical Assessment in Neuropsychiatry (Wing et al. 1990); the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1992); and the Diagnostic Interview for Genetic Studies developed by the NIMH-sponsored centers for genetic linkage research (Nurnberger et al. 1994). Puig-Antich et al. have also developed an instrument for use with children, the Kiddie-SADS, that has been modified for epidemiological studies (Orvaschel 1985).

Robins (Robins 1978) was among the first to advocate the development of fully structured DISs that could be administered in the community by non–mental health professionals or lay interviewers. Although some such instruments were developed before the introduction of the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition (DSM-III), the first widely used of this family of instruments is the DIS (Robins et al. 1981). The DIS was originally designed for the five-site Epidemiological Catchment Area (ECA) study of DSM-III disorders (Regier et al. 1984). Subsequent versions of the DIS incorporated revised DSM-III (DSM-III-R) as well as *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV-TR) criteria. In the field of children's mental health, fully structured DISs have also been designed, such as the DIS for Children (Costello et al. 1988, Jensen et al. 1995).

Another fully structured instrument is the Composite International Diagnostic Interview (CIDI), developed in collaboration with the World Health Organization (World Health Organization 1990) and NIMH (Wittchen et al. 1991). The CIDI was designed to be used with both DSM and International Classification of Diseases (ICD) diagnostic criteria and to be available in multiple languages. Since it first became available in 1990, the CIDI has been used in the National Comorbidity Survey (NCS) (Kessler et al. 1994), the National Comorbidity Survey Replication (NCS-R), as well as other major epidemiologic surveys in a number of countries (Wittchen et al. 1992, Bijl et al. 1998, Caraveo et al. 1998). The WHO created the International Consortium in Psychiatric Epidemiology (ICPE) in 1997, in part, to oversee and facilitate comparative analyses from such international surveys employing the CIDI (Kessler 1999). The currently ongoing WHO World Mental Health Survey (WMH) initiative, which involves surveys of the general population in over 30 countries throughout the world, also employs the CIDI (Kessler 2000).

## Psychometric Properties of Instruments

An instrument's sensitivity (proportion of those with true-positive results identified as such by the study instrument) and specificity (proportion of those with true-negative results identified as such by the study instrument) are one set of measures. For an instrument to be useful in epidemiology, it should have high sensitivity and, at least, moderately high specificity.

To identify cases accurately, an instrument used for case identification must be reliable and valid. Reliability refers to the reproducibility of a measure (i.e., the consistency of measurement regardless of the rater, the situation, or the time of administration). Interrater agreement is usually calculated with statistical methods, such as the kappa statistic, which control for chance agreement. Test–retest reliability, or temporal stability, is calculated with product-moment or intraclass correlation coefficients. Validity refers to whether a construct is measured accurately. This concept is more difficult to establish in psychiatry because there is generally no "gold standard" or biological marker for the disorders under study.

A number of studies assessing the reliability of the DIS have found it to vary depending on the diagnosis under consideration and to be better when the DIS is compared with itself in the hands of a physician (Helzer et al. 1985) than when it is compared with other semistructured diagnostic instruments (Anthony et al. 1985). Clinical reappraisal studies have documented acceptable to good concordance between most CIDI diagnoses and blind clinical reinterviews using the Structured Clinical Interview for DSM-IV-TR (SCID) as the validation standard (Spitzer et al. 1987, Kessler et al. 1998). Exceptions include mania (Kessler et al. 1997) and nonaffective psychosis (Kendler et al. 1996), both of which are overdiagnosed by the CIDI according to clinical reinterviews. Overdiagnosis of mania has been handled in the NCS by confining received CIDI diagnoses to the euphoric-grandiose subtype of mania, which was assessed with good validity. Overdiagnosis of nonaffective psychosis was addressed in the NCS by carrying out clinical reinterviews with all respondents who screened positive for nonaffective psychosis by the CIDI and basing final diagnoses on these clinical assessments rather than on the original CIDI classifications.

### Risk Factor Identification

Risk factors are characteristics whose presence increases the chances for development of a disease. A true risk factor must exist before a disease develops. For example, being male and having a family history of alcoholism are risk factors for the development of alcoholism (Merikangas 1990). When a variable cannot be definitively proved to predate the onset of a disorder, it is best conceptualized as a correlate. For example, although socioenvironmental factors, such as adverse life events and chronic strain, are statistically associated with the development of depressive disorders, they usually should be regarded as correlates because the causal sequence of these relationships is difficult to determine.

Psychiatric epidemiologists are increasingly turning their attention to the identification of modifiable risk factors for psychiatric illnesses. A major goal of such work is to shed light on information that can guide the development of successful interventions for primary and secondary prevention efforts.

## Types of Epidemiological Studies

In general, epidemiological studies are designed to find associations between exposures and health outcomes. A main concern in epidemiological studies is the selection of study groups on the basis of either disease status or exposure status. Epidemiological studies can be classified as (1) experimental, (2) quasi-experimental, and (3) nonexperimental or observational.

### Experimental Studies

The main distinction of experimental studies is that the investigator assigns the status of exposure or nonexposure to each subject. The assignment to the exposure group becomes part of the study protocol. Once subjects are assigned to exposed or nonexposed groups, they are observed for a time, and observations about changes in morbidity are recorded. The most common experimental design is the clinical trial, in which clinical populations are exposed to a specific treatment protocol to measure an outcome, usually resolution of symptoms. To ensure the integrity of a clinical trial, three main elements are necessary (Miettinen 1985): (1) randomization, to ensure comparability of the populations; (2) placebo, to ensure comparability of the effects; and (3) "blinding," to ensure comparability of information.

In randomization, subjects are randomly assigned (e.g., through a random number generator) to different exposure groups to attempt to ensure that subjects in each group have similar clinical and demographic characteristics. It is possible that with a small sample size, the groups may have different characteristics in spite of randomized allocation. If these characteristics are factors that could affect the outcome, they then need to be controlled for in subsequent analyses. Of course, in many cases, not all factors predicting a good or a poor outcome are known. Randomization should theoretically achieve a balance of unknown factors in the different groups.

Placebo groups are used to ensure that extraneous effects of a specified experimental treatment (such as extra attention from an examiner) do not alter or account for the experimental findings. A placebo controls for factors that may affect the outcome of the study independently of the exposure status. For example, if subjects in an open trial are aware of what medication they receive, this knowledge could bias their response to the treatment. Similarly, subjects who are aware of being in an untreated control group could respond over time in a biased fashion as a result of this knowledge. One goal in assigning patients at random to treatment or placebo control groups is to keep the subjects from being aware of whether or not they are receiving treatment. In a single-blind study, only the patient is unaware of the actual treatment. In a double-blind study, the investigator and the subject of investigation are unaware of treatment assignment. In a triple-blind study, the data analyst is also not informed of the meaning of the group assignment code.

### Quasi-Experimental Studies

Natural experiments that permit comparisons of two populations, one that receives an exposure and the other that does not, are referred to as quasi-experimental studies. Even though the investigator does not have full control over the exposures and environments, these designs still permit an understanding of the influence of different environmental constraints.

To be considered quasi-experimental, baseline data must have been collected before the exposure event. Without that requirement, the study is simply a retrospective observational study. For example, during the course of the

Three Mile Island investigation, widespread unemployment occurred at the Pennsylvania comparison site because of massive layoffs from a recession in the steel industry. Since data for the original Three Mile Island project had already also been collected at the comparison site, Penkower et al. (Penkower et al. 1988) were able to chart the long-term effects of husbands' layoff and to identify prior-event predictors from interview data obtained before the layoffs occurred.

## Nonexperimental Studies

Nonexperimental studies are divided into cross-sectional and longitudinal designs.

### Cross-Sectional Designs

Cross-sectional designs are typically employed in surveys aimed at providing data on the distribution of disorders in the population. Differences in rates by basic demographic data are also usually derived. In epidemiology, cross-sectional designs are usually best employed when causal hypotheses are not being tested. For example, when a community wants to investigate the distribution of an illness to decide on the need for psychiatric services, a cross-sectional survey is highly appropriate. Even though cross-sectional data may be limited in terms of the level of inference that can be drawn, such surveys must still assess a well-defined population at risk with reliable assessment tools to be epidemiologically useful. For example, surveys that are based on volunteers or instruments with no established psychometric utility are not regarded as using epidemiological methodology.

Cross-sectional studies include not only current symptoms but also retrospective data on age at onset of the disorder. With sophisticated statistical modeling techniques, it is possible to develop informed hypotheses about links between potential risk factors and disease. However, the true test of such hypotheses must be drawn from data obtained prospectively.

### Longitudinal Designs

Longitudinal designs are divided into case-control and cohort studies and are characterized by a time interval between cause and effect. In cross-sectional studies, there is no interval between exposure and illness, which are measured at the same point in time.

#### *Case-Control Studies*

In case-control studies, subjects are defined in terms of having (case patients) or not having (control patients) the disease of interest. The groups are compared in terms of history of exposure. In general, two types of control groups are used: hospital control groups and population control groups. The selection of the control group is a key point in terms of validity. Control subjects should be selected independently of exposure status. Case and control patients may be matched on different characteristics, the key issue being that control patients should represent those individuals who, if they had the disease, would be selected as case patients (Miettinen 1985). One of the most widely cited case-control studies focused on the role of stressful life events in the onset of depression (Paykel et al. 1969). In this study, women treated for depression were assessed about their previous life events, and a control group of nondepressed women were similarly assessed. Calculations were then made of the excess risk of depression associated with the occurrence of life events.

Among the strengths of case-control studies are their feasibility and relatively low cost. Case-control studies allow the evaluation of multiple hypotheses and are the ideal design for investigating rare diseases, such as anorexia nervosa. The primary limitation of case-control studies is potential recall bias, particularly in the control patients for whom there may be no corroborating record information. In addition, it is often difficult to obtain suitable data on rare exposures.

Case-control studies can assess whether a risk factor is more prevalent in case than in control patients but may not be able to establish the rate of disease after exposure to that risk factor. For the purpose of estimating the true rate of disease associated with an exposure, the prospective cohort study design is the preferable methodology.

#### *Cohort Studies*

In cohort studies, subjects are identified in terms of exposure or nonexposure status and are observed for a specified time to determine the presence or absence of a health outcome. Cohort studies are divided into prospective and retrospective. In prospective cohort studies, the exposure or nonexposure status is defined when the study is initiated. The subjects of investigation are followed up into the future to determine disease or nondisease status. In retrospective studies, the status of exposed or nonexposed is defined in the present. In prospective cohort studies, exposures of the present are evaluated; in retrospective cohort studies, exposures of the past are being evaluated. Cohort groups share the common exposure status and are observed to ascertain the presence or absence of a disease or outcome.

#### *Retrospective Cohort Studies*

A second retrospective design is the retrospective cohort study, in which subjects are identified from archival data collected many years previously and located in the present. In other words, exposure status is defined in the past, and illness status is defined in the present. A classic example of this type of design is a study entitled *Deviant Children Grown Up* (Robins 1966), in which 524 individuals who had been evaluated 30 years earlier in a child guidance clinic, along with demographically matched school-based control subjects, were assessed with respect to subsequent psychopathological processes and sociopathic behaviors. The data in the agency records served as predictor variables in the analysis. This design has the advantage of obtaining information in a timely and cost-effective manner. The primary disadvantage, however, is that the interval experiences are reconstructed for long periods and, in the absence of objective records, may be subject to considerable recall bias. Another disadvantage is that the samples themselves may not be representative of individuals with the exposure. Furthermore, some studies have reported considerable loss to follow-up through either mortality or mobility. For example, in a long-term "follow-back" study of patients from a clinic in Switzerland, Ciompi (1980) assessed only 289 of the original 1642 patients, or 18%.

#### *Prospective Cohort Studies*

In prospective cohort studies, subjects are identified in terms of exposure or nonexposure status and observed forward for

a specified interval to determine the presence or absence of a health outcome. Cohort studies are similar to an experimental study with the exception that exposure or nonexposure status is not assigned by the investigator. To illustrate, Solomon (1993) identified a sample of Israeli soldiers who fought in the war between Israel and Lebanon and soldiers who were not on active duty at the time. After the war, they were followed up for several years to determine the onset of long-term war-related mental disorders. The prevalence of subsequent psychiatric illness was significantly higher in the soldiers exposed to war than in soldiers not exposed.

The sources of cohort groups are variable. The most powerful type of cohort is the birth cohort drawn from the general population. Two British birth cohorts have been used to study a range of diseases, including schizophrenia (Crow and Done 1992). Another powerful source of a cohort is a community. In 1947, Essen-Moller began a longitudinal study of the 2550 inhabitants of Lundby, Sweden; the cohort was subsequently followed up for more than 25 years (Hagnell et al. 1982). Often, healthy cohorts are identified from specific settings, particularly universities and medical facilities. For example, a well-known study in American psychiatry is Vaillant's (Vaillant 1983) 40-year study of initially healthy Harvard University undergraduates. Another common population targeted for cohort research is an occupational group. To minimize bias in determining whether an occupational condition is associated with an adverse health outcome, members of occupational cohorts must be identified at the point of hire. Because most disorders occur infrequently, another cohort source frequently used in psychiatry is the offspring of mentally ill adults, such as children of individuals with alcoholism, children of individuals with schizophrenia, and children of depressed parents.

For comparison groups, a cohort study can use an internal subset of the population under study, by comparing exposed with unexposed members of the cohort, or an external comparison. A comparison cohort can be selected from a similarly defined population (e.g., mothers living near Three Mile Island were compared with mothers similarly sampled from around another nuclear power plant), or the cohort can be compared with the general population (e.g., symptoms among women living near Three Mile Island can be compared with norms established for the same measure for women of the same age).

The major strength of the cohort design is the possibility of estimating a temporal relationship between exposure and disease. With a cohort study, it is possible to study rare exposures and to evaluate multiple outcomes from a single exposure. The limitation of cohort studies is primarily one of feasibility because most such studies are expensive and involve study populations that are difficult to recruit and maintain for follow-up.

## Threats to Validity in Epidemiological Studies

An essential feature of epidemiological studies is a comparison of two groups in terms of presence or absence of exposure or presence or absence of disease. For the measurements to be comparable, the investigator should ensure absence of bias. Biases can be divided into three general types: selection bias, information or observation bias, and confounding bias.

### Selection Bias

Selection bias can arise when the sampling procedure is influenced a priori by the disease or the exposure. For example, studies of employed populations are limited by the "healthy worker effect" because disabled individuals or those who were adversely affected by aspects of the work environment will not be in the cohort (Monson 1980). The Three Mile Island investigation compared unionized nuclear power plant workers at Three Mile Island with workers at a comparable power plant in western Pennsylvania (Bromet et al. 1982). Because of union regulations, the workers at Three Mile Island could not transfer to a less stressful type of power plant without losing their seniority and benefits, but the comparison site employees could and did transfer. Thus, because of the bias introduced by the different union regulations, the two samples were not comparable.

Another example, referred to as self-selection bias, occurs when subjects who have been exposed to an event are more likely to participate in a study if they have the disease or prodromal stages of the disease under study. A similar type of selection bias can occur when subjects are solicited from newspaper or other similar advertisements. To illustrate, in a study of individuals who responded to an advertisement seeking healthy volunteers as control subjects in a mental health study, Halbreich et al. (Halbreich et al. 1989) reported that one-third had a history of diagnosable mental disorders. Selection bias can also occur when the mortality rate is elevated as a result of the exposure. Thus, concentration camp survivors or survivors of major earthquakes are not necessarily representative of individuals who underwent those stresses.

When an investigator suspects selection bias at the start of a study, it is usually difficult to isolate the source because it is often impossible to obtain sufficient information about the nonrespondents. As we will see later in the chapter, Kessler et al. (Kessler et al. 1994) conducted a special study of nonrespondents to the NCS and discovered that they had a higher rate of psychiatric illness than did the sample interviewed without special procedures. On the other hand, considerable detail has accumulated about individuals who drop out of longitudinal studies. Such individuals tend to be at both ends of the spectrum, that is, they have either the highest or the lowest degree of psychiatric illness. Each longitudinal study needs to include an analysis of the bias imposed by attrition.

### Information (Observation) Bias

In case-control studies, information bias occurs when the details about prior exposure are obtained in a noncomparable manner or are subject to poor recall. To minimize such bias in case-control studies, exposure data should be collected without knowledge of disease status. This procedure is known as blindness. However, because of selective recall, when the sole source of information is the affected individual, this type of bias sometimes presents insurmountable problems (see also Chapter 27) for a discussion of this phenomenon). For instance, in studies of life events and onset of depression, it is likely that subjects who present with the disease under study will have a more accurate recollection of life events than will individuals without depression. Subjects themselves may break the blind feature built into a study. In research on occupational lead exposure, an

attempt was made to keep the interviewers blind as to exposure status by putting all questions about employment at the end of the interview (Parkinson et al. 1986). However, the subjects frequently volunteered information about their jobs early in the interview. Another example comes from clinical trials in which raters can, sometimes, accurately guess which subjects are receiving placebo and which are not and, hence, bias the results about the drug's effects.

### Confounding Bias

Confounding bias results when a third factor that is a cause of the disease under study is also associated with the exposure. A confounding factor is a cause of the disease under study independent of its association with the exposure. For instance, if unemployment is considered a cause of suicidal behavior, and, at the same time, alcoholism is related to both unemployment and suicidal behavior, then alcoholism would be a confounding variable for a study designed to measure the association between unemployment and suicidal behavior. In such a study, the measure of association between unemployment and suicidal behavior should be adjusted by the presence or absence of alcoholism.

## Examples of Psychiatric Epidemiological Studies

Dohrenwend and Dohrenwend (1982) have divided the growth of psychiatric epidemiological research into three periods, or generations. This section describes the key studies and prevalence rates from each of these periods.

### First-Generation Research

The first-generation studies took place for the most part before World War II. These studies are characterized by their reliance on known cases, usually individuals in mental hospitals, to define mental illness. There were three extraordinary studies conducted during this time. The first was a prevalence study performed in 1885 in Massachusetts in which case patients were identified through key informants, such as general practitioners and clergy, and hospital records (Jarvis 1971). This study, the first known American prevalence study, identified 2632 "lunatics" and 1087 "idiots" in need of care.

The second landmark study in the history of psychiatric epidemiology was an etiological study of pellagra, a common disorder found in patients in mental hospitals. In the early 1920s, Goldberger et al. (Terris 1964) demonstrated with the case-control method that pellagra was associated with nutritional deficiency. Although no specific nutrient was identified, dietary changes were instituted that dramatically reduced the level of morbidity from this disease in institutional settings.

The third landmark study conducted before World War II was an ecological analysis of hospital patients, *Mental Disorders in Urban Areas* (Faris and Dunham 1939). This pioneering study examined the geographical distribution of all first-admission patients hospitalized between 1922 and 1934 in mental hospitals in Chicago. They found that the central area of the city, which had the greatest degree of social disorganization, had the highest rates of admissions for patients with schizophrenia (46% of all admissions). The rates decreased progressively with distance away from the center, reaching a low of 13% in the outermost area. This study became influential in mental health research because the investigators interpreted the results as indicating that adversity in the social environment played an etiological role in the occurrence of severe mental illness. Critics argued that downward social drift could have accounted for the high number of cases from the central urban area. Because the study used an ecological design, the data could not be used to test causal hypotheses about the relative role of personal versus environmental risk factors. Nevertheless, the debate about the causal contributions of these risk factors led to an extensive body of research on the contribution of social factors to the onset of mental illness.

In general, the median prevalence rate among the various first-generation studies relying on key informants and agency records was 3.6% (Dohrenwend and Dohrenwend 1982). Compared with findings from later studies, this design is generally believed to result in an underestimate of the true prevalence of mental disorders.

### Second-Generation Studies

World War II represented a turning point in psychiatric epidemiology (Weissman and Klerman 1978, Dohrenwend and Dohrenwend 1982). A number of events converged during this time. First, mental illness accounted for the largest proportion of men rejected for military service. The fact that such large numbers of (untreated) recruits failed the psychological screen emphasized that treated patients, who served as the foundation of previous prevalence estimates, represented the tip of the iceberg, albeit a biased one. Second, healthy men who fought in the war frequently suffered from combat stress reactions when faced with the overwhelming horrors of battle, indicating that stress can play an etiological role in the onset of mental disorders under some circumstances. Some of these individuals were subsequently discharged because of psychiatric illness (Grinker and Spiegel 1945). Also, psychologists in the armed forces developed the Neuropsychiatric Screening Adjunct, which became a forerunner of symptom questionnaires administered after the war.

In 1946, the Congress passed the National Mental Health Act (Public Law 79-487), enabling the creation in 1949 of the NIMH as a separate agency within the National Institutes of Health. This facilitated governmental support of training, prevention, and epidemiological research in mental health. The second-generation studies profited from this financial support. Growing conceptually out of the experiences of World War II that suggested a major role for stress in relation to mental disorders, these studies focused on early childhood and contemporaneous sources of stress believed to influence psychological well-being adversely.

In the early 1950s, three major studies were initiated to examine the prevalence of and risk factors associated with psychosomatic and affective symptoms in the general population, the Midtown Manhattan Study (Srole et al. 1962), the Nova Scotia Stirling County research (Leighton et al. 1963), and the University of Michigan's national survey of mental health (Gurin et al. 1960). These early representatives of the second-generation studies used lengthy symptom questionnaires, modified in large part from the Neuropsychiatric Screening Adjunct, which were directly administered to carefully selected samples of the population. The underlying assumption of these studies was that

mental illness existed along a unidimensional continuum of severity, and that impairment ratings by psychiatrists who reviewed the symptom questionnaires were appropriate and suitable reflections of true mental illness. This conceptualization of mental illness as existing along a continuum was congruent with the paradigm of social disruption as an etiological factor of psychiatric illness.

The common denominator of the early second-generation studies was the direct interview of all subjects with supplementation of data from other sources, such as medical or community records. The care and elegance of the data collection in the earlier studies are important to emphasize. For example, in the Stirling County study, 1010 adults were assessed initially by a lay interviewer using a structured questionnaire (Leighton et al. 1963). Further information was collected from general practitioners and psychiatrists practicing in the area. All of the information was evaluated by research psychiatrists using the DSM-I nosology. The prevalence of mental illness was estimated to be 20%. The Midtown Manhattan Study (Srole et al. 1962) used a similar methodology; social workers were hired to collect the interview data. On the basis of psychiatrists' ratings of impairment, this study reported that 23.4% of the sample was severely impaired.

In the late 1950s, Hollingshead and Redlich (Hollingshead and Redlich 1958) conducted a landmark study of the impact of social class on the treatment experiences of psychiatric patients, drawing on treated patients from the city of New Haven, Connecticut. Similar to the Chicago study of Faris and Dunham (Faris and Dunham 1939), major differences were found across socioeconomic strata. The most influential finding was that regardless of diagnosis, the type of therapy patients received varied according to their class of origin. Patients from the working and lower classes were more likely to be treated with electroconvulsive therapy or medications. In contrast, patients from the upper classes were mostly treated with psychotherapy. Researchers also found a higher treated prevalence for the lower social classes.

Later second-generation studies used abbreviated assessment methods empirically derived from the lengthy symptom inventories and eliminated the role of psychiatrists in case identification. These studies continued to focus on the role of social adversity in the occurrence of psychiatric symptoms. However, these studies have been criticized for not adequately assessing the full range of psychiatric symptoms, particularly those associated with psychosis, aggression, and substance use, and, hence, drawing biased conclusions about both rates and risk factors (such as female gender). Furthermore, although many such studies were longitudinal (e.g., the New Haven study of stressful life events and symptoms) (Myers et al. 1971), they were unable to disentangle cause and effect because they were not prospective (i.e., they did not start with a healthy cohort and detect whether or under what conditions the risk factors under observation led to new cases of individuals with high symptom counts). The primary limitation, however, was the assessment of symptoms rather than diagnosable-level disorder.

Nevertheless, it became clear that mental illness was a public health problem and that most individuals with significant symptoms never received psychiatric treatment. In part on the basis of these community studies, including the highly influential *Social Class and Mental Illness,* President Kennedy delivered a message to the Congress on mental illness and mental retardation in 1963 that set the stage for the Community Mental Health Centers Act.

## Third-Generation Studies

The methodology for the third-generation epidemiological studies reflected the view in American psychiatry in the early 1970s that mental illness could be delineated into discrete, operational categories. These changes in nosology were exemplified in the 1970s with the development of the Feighner criteria at Washington University in St. Louis (Robins and Guze 1970, Feighner et al. 1972) and culminated in the creation of DSM-III a decade later. By operationalizing diagnoses with specific criteria, it was possible to create structured diagnostic assessments to elicit the symptoms needed for these categories. Preliminary evidence about the utility of using diagnostic procedures in community samples was obtained in a third-wave follow-up of the New Haven study noted before. In this study, Weissman et al. (Weissman et al. 1978) successfully administered the SADS-L in a community population. This and other studies (Bromet et al. 1982) demonstrated that structured diagnostic instruments designed for clinical investigations could produce meaningful findings when administered in population-based studies.

The third-generation studies, thus, are characterized primarily by the use of structured diagnostic assessment procedures. In the next sections, we describe the largest third-generation studies, the ECA, the NCS, and NCS-R. Many other important investigations focusing on diagnosable mental disorders have also been conducted. These include (but are not limited to) the National Vietnam Veterans Readjustment Study (Kulka et al. 1990), the prevalence study of major depressive disorder and alcohol abuse or dependence in white-collar employees of Westinghouse Electric Corporation (Bromet et al. 1990), the prevalence and risk factor study of psychiatric disorders in an Israeli birth cohort (Dohrenwend et al. 1992, Levav et al. 1993), the social risk factor study of adults residing in metropolitan Toronto (Turner and Marino 1994), and the MacArthur Foundation's Midlife Development in the United States (MIDUS) survey (Wang et al. 2000). It is also important to note the progress in studying the epidemiology of children's disorders. Since Rutter's (Rutter et al. 1976) pioneering research of children living on the Isle of Wight and in an inner-city area of London, several community studies have been conducted using structured diagnostic assessment procedures. These studies have been conducted in several countries, including Canada (Ontario) (Offord et al. 1987), United States (New York State (Velez et al. 1989), Pittsburgh (Costello et al. 1988), Puerto Rico (Bird et al. 1988), New Zealand (Anderson et al. 1989), and France (Fombonne 1994). In a review of prevalence studies, Costello (1989) concluded that the rate of diagnosable mental disorders in children and adolescents may be as high as 18–20%.

### The Epidemiological Catchment Area Study

In response to the 1978 President's Commission on Mental Health report, NIMH sponsored the ECA project to determine the prevalence of mental disorders in specific sites and the proportion receiving mental health services (Regier et al. 1984). Parallel to the planning of the ECA study, the American Psychiatric Association published the DSM-III

(American Psychiatric Association 1980), which had clearly defined operational criteria that facilitated case definition. Thus, the concept of a case as a discrete entity that had been achieved in the late 1970s permitted the categorical determination of psychiatric caseness as opposed to the dimensional assessment of symptom impairment. As a prelude to the ECA, the NIMH cosponsored the development of the DIS (reviewed earlier).

### Design

The ECA study estimated the prevalence of mental disorders in designated catchment areas with at least 200,000 persons. Catchment areas were selected within New Haven, Connecticut; Baltimore, Maryland; Raleigh-Durham, North Carolina; St. Louis, Missouri; and Los Angeles, California. In each location, approximately 3000 individuals were assessed initially (Regier and Kaelber 1995). The sampling was not intended to provide national estimates; rather, the focus on specific geographical sites facilitated the project's goal of linking mental health assessments to service use information.

The basic design involved face-to-face baseline interviews with random samples of adults selected from the catchment areas, 6-month telephone follow-up interviews to obtain interim information on medical and psychiatric service use, and 1-year face-to-face interviews with the original sample. The initial response rate ranged from 68% (Los Angeles) to 79% (St. Louis and Durham) (Leaf et al. 1991). Overall, 12% of the original respondents were lost to or refused to participate in the follow-up interview. Eaton et al. (Eaton et al. 1989) reported that failure to be tracked was associated with being male, young, unmarried, and Hispanic; refusal to participate was associated with being older, married, and uneducated.

### Prevalence

Overall, 32.2% of the adults included in the five sites met criteria for one or more of the assessed mental disorders during their lifetime (Table 25–1 and Figure 25–2). Phobias and alcohol abuse and dependence were the most common mental disorders (Regier et al. 1988). The lifetime prevalence for phobia was 12.5%, and the 1-month prevalence was 6.2% (Tables 25–1 and 25–2). The rates for drug abuse and dependence were 5.9% for lifetime and 1.3% for 1-month prevalence (Tables 25–1 and 25–2).

The ECA study investigators did extensive analyses of the variation in prevalence rates by demographic characteristics. For lifetime diagnosis, 36% of men at some point suffered from an addictive or mental disorder, compared with 30% of women (Table 25–3 and Figure 25–3). As seen in Table 25–3 , some differences also emerged by age groups, with age groups younger than 30 and 30–44 years having the highest lifetime prevalence rates. Interestingly, individuals older than 65 years reported lower prevalence rates, suggesting a possible underreporting of symptoms in this age group (Robins et al. 1991). Furthermore, Regier and Kaelber (1995) suggested that it is possible that individuals with psychiatric disorders tend disproportionately to die prematurely. Table 25–3 also indicates that the rates overall are higher in African-Americans than in Whites and Hispanics, but this is confounded by social strata because rates are similar across ethnic groups when social class is controlled (Regier and Kaelber 1995). Similarly, individuals who did not complete high school had a higher prevalence of mental disorders than did those who graduated from high school (see Table 25–3). Lifetime prevalence rates were also associated with unemployment (especially in men) and with being separated or divorced (see Table 25–3).

**Table 25–1 Lifetime Prevalence Rate of Specific (DIS)–DSM-III Disorders***

| Disorder | Estimated Prevalence Rate (% Population) |
|---|---|
| Any DIS disorder covered | 32.2 |
| Any DIS disorder except cognitive impairment, personality disorder, and substance abuse | 19.6 |
| Substance use disorders | 16.4 |
| Alcohol abuse and dependence | 13.3 |
| Drug abuse and dependence | 5.9 |
| Schizophrenia and schizophreniform disorders | 1.5 |
| Affective disorders | 8.3 |
| Manic episode | 0.8 |
| Major depressive episode | 5.8 |
| Dysthymia | 3.3 |
| Anxiety disorders | 14.6 |
| Generalized anxiety disorder | 8.5 |
| Phobia | 12.5 |
| Panic | 1.6 |
| Obsessive—compulsive disorder | 2.5 |
| Somatization disorder | 0.1 |
| Personality disorder | |
| Antisocial personality | 2.5 |
| Cognitive impairment (severe) | 1.3 |

From Regier DA, Boyd JH, Burke JD Jr, et al. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives of General Psychiatry 45, 977–986. Copyright 1988, American Medical Association.

*Based on five ECA sites, standardized to the 1980 U.S. census.

The pooled 1-month prevalence rates for the five sites (see Table 25–2) was 15.4% for all ages for any DSM-III disorder. The age group 25–44 years had the highest overall rate of 17.3%. Although this age pattern was also true for women, men aged 18–24 years had the highest overall rate. This occurred because of the peak in rates of drug abuse and dependence in men in this age group. Anxiety disorders were most prevalent at 11.7% in women 25–44 years old, compared with only 4.7% for men in the same group. The overall prevalence for all affective disorders was 5.1%; the age group with the highest prevalence was women 25–44 years old.

### Incidence

Incidence rates were calculated based on the 12-month follow-up assessments of healthy individuals found during the initial assessments (Regier et al. 1993). Because some ECA respondents reported symptoms inconsistently across the two waves of interviews, Eaton et al. (Eaton et al. 1989) presented estimates adjusted for this unreliability for seven disorders (major depressive disorder, panic disorder, phobia, obsessive–compulsive disorder, drug abuse and dependence, alcohol abuse and dependence, and cognitive impairment). Overall, phobias had the highest incidence rate (4.0%);

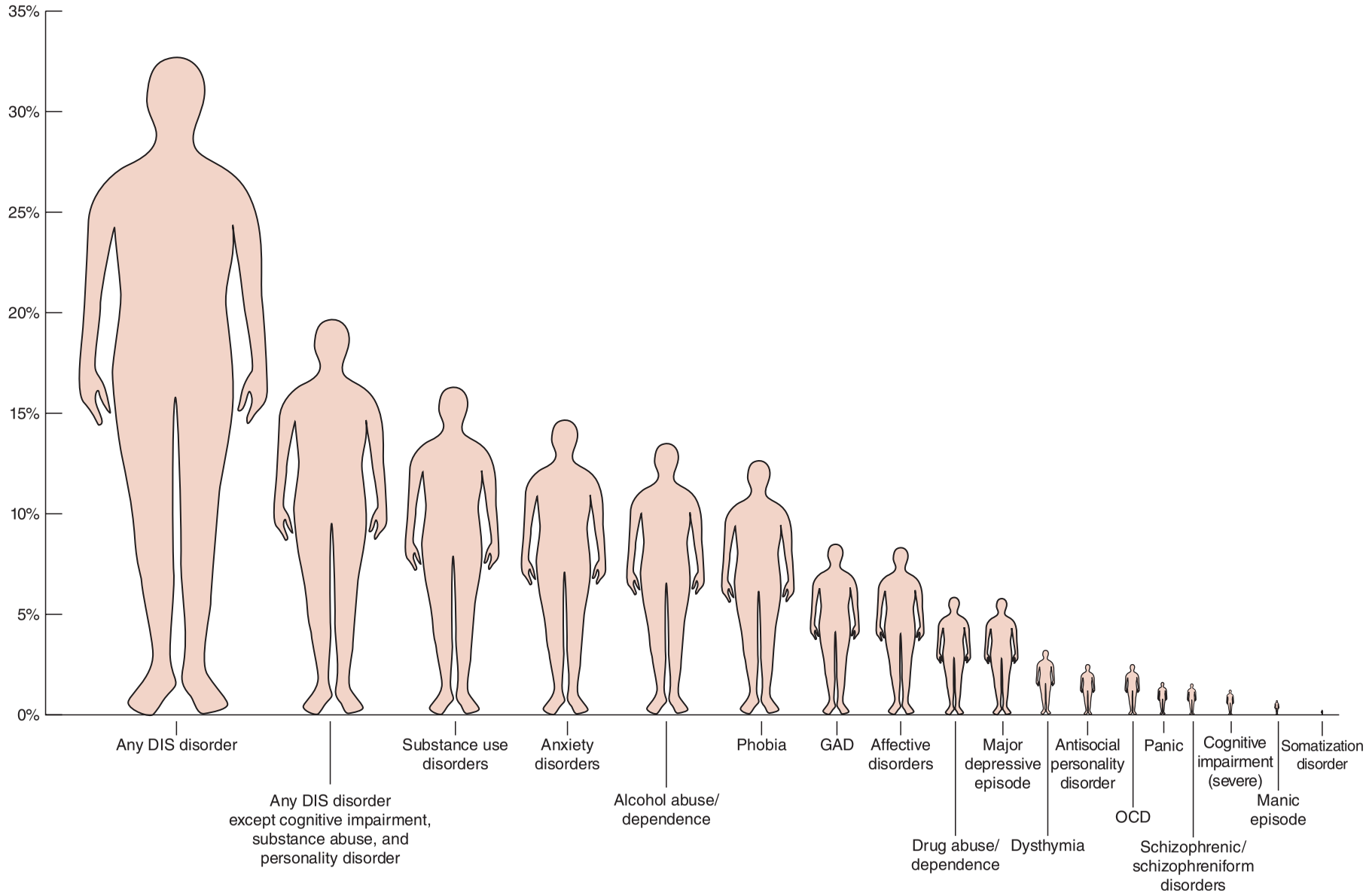



**Figure 25–2** *Estimated lifetime prevalence rates of a specific (DIS)–DSM-III disorder at five ECA sites. GAD, Generalized anxiety disorder; OCD, obsessive–compulsive disorder. [Reproduced from Regier DA, Boyd JH, Burke JD Jr., et al. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives of General Psychiatry 45, 977–986.]*

**Table 25–2 One-Month Prevalence Rate (%) of Specific (DIS)--DSM-III Disorders***

| | Any DIS Disorder | Any DIS Disorder Except Cognitive Impairment, Substance Use, and Antisocial Personality | Drug Abuse and Dependence | Schizophrenia | Schizophreniform Disorders | Anxiety Disorders | Phobia | Panic | Obsessive–Compulsive Disorder | Affective Disorders | Manic Episode | Manic-Depressive Episode | Dysthymia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Both Sexes | | | | | | | | | | | | | |
| All ages | 15.4 | 11.2 | 1.3 | 0.6 | 0.1 | 7.3 | 6.2 | 0.5 | 1.3 | 5.1 | 0.4 | 2.2 | 3.3 |
| 18–24 | 16.9 | 11.0 | 3.5 | 0.7 | 0.1 | 7.7 | 6.4 | 0.4 | 1.8 | 4.4 | 0.6 | 2.2 | 2.2 |
| 25–44 | 17.3 | 13.0 | 1.5 | 0.9 | 0.1 | 8.3 | 6.9 | 0.7 | 1.6 | 6.4 | 0.6 | 3.0 | 4.0 |
| 45–64 | 13.3 | 10.7 | 0.1 | 0.4 | 0.0 | 6.6 | 6.0 | 0.6 | 0.9 | 5.2 | 0.2 | 2.0 | 3.8 |
| 65+ | 12.3 | 7.4 | 0.0 | 0.1 | 0.0 | 5.5 | 4.8 | 0.1 | 0.8 | 2.5 | 0.0 | 0.7 | 1.8 |
| Men | | | | | | | | | | | | | |
| All ages | 14.0 | 7.6 | 1.8 | 0.6 | 0.1 | 4.7 | 3.8 | 0.3 | 1.1 | 3.5 | 0.3 | 1.6 | 2.2 |
| 18–24 | 16.5 | 8.4 | 4.8 | 0.7 | 0.2 | 4.9 | 3.6 | 0.4 | 1.7 | 3.4 | 0.4 | 1.5 | 2.2 |
| 25–44 | 15.4 | 8.2 | 2.3 | 0.8 | 0.1 | 4.7 | 3.5 | 0.3 | 1.2 | 4.5 | 0.5 | 2.2 | 2.8 |
| 45–64 | 11.9 | 7.5 | 0.1 | 0.6 | 0.1 | 5.1 | 4.8 | 0.5 | 0.6 | 3.1 | 0.2 | 1.2 | 2.0 |
| 65+ | 10.5 | 4.5 | 0.0 | 0.1 | 0.0 | 3.6 | 2.9 | 0.0 | 0.7 | 1.4 | 0.0 | 0.4 | 1.0 |
| Women | | | | | | | | | | | | | |
| All ages | 16.6 | 14.5 | 0.7 | 0.6 | 0.1 | 9.7 | 8.4 | 0.7 | 1.5 | 6.6 | 0.4 | 2.9 | 4.2 |
| 18–24 | 17.3 | 13.5 | 2.4 | 0.7 | 0.0 | 10.4 | 9.1 | 0.4 | 1.8 | 5.3 | 0.8 | 2.9 | 2.2 |
| 25–44 | 19.2 | 17.7 | 0.8 | 1.1 | 0.2 | 11.7 | 10.2 | 1.1 | 1.9 | 8.2 | 0.6 | 3.9 | 5.1 |
| 45–64 | 14.6 | 13.7 | 0.0 | 0.3 | 0.0 | 8.0 | 7.0 | 0.7 | 1.2 | 7.2 | 0.2 | 2.6 | 5.4 |
| 65+ | 13.6 | 9.4 | 0.0 | 0.1 | 0.0 | 6.8 | 6.1 | 0.2 | 0.9 | 3.3 | 0.0 | 0.9 | 2.3 |

From Regier DA, Boyd JH, Burke JD Jr., et al. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives of General Psychiatry 45, 977--986. Copyright 1988, American Medical Association.

*Based on five ECA sites.

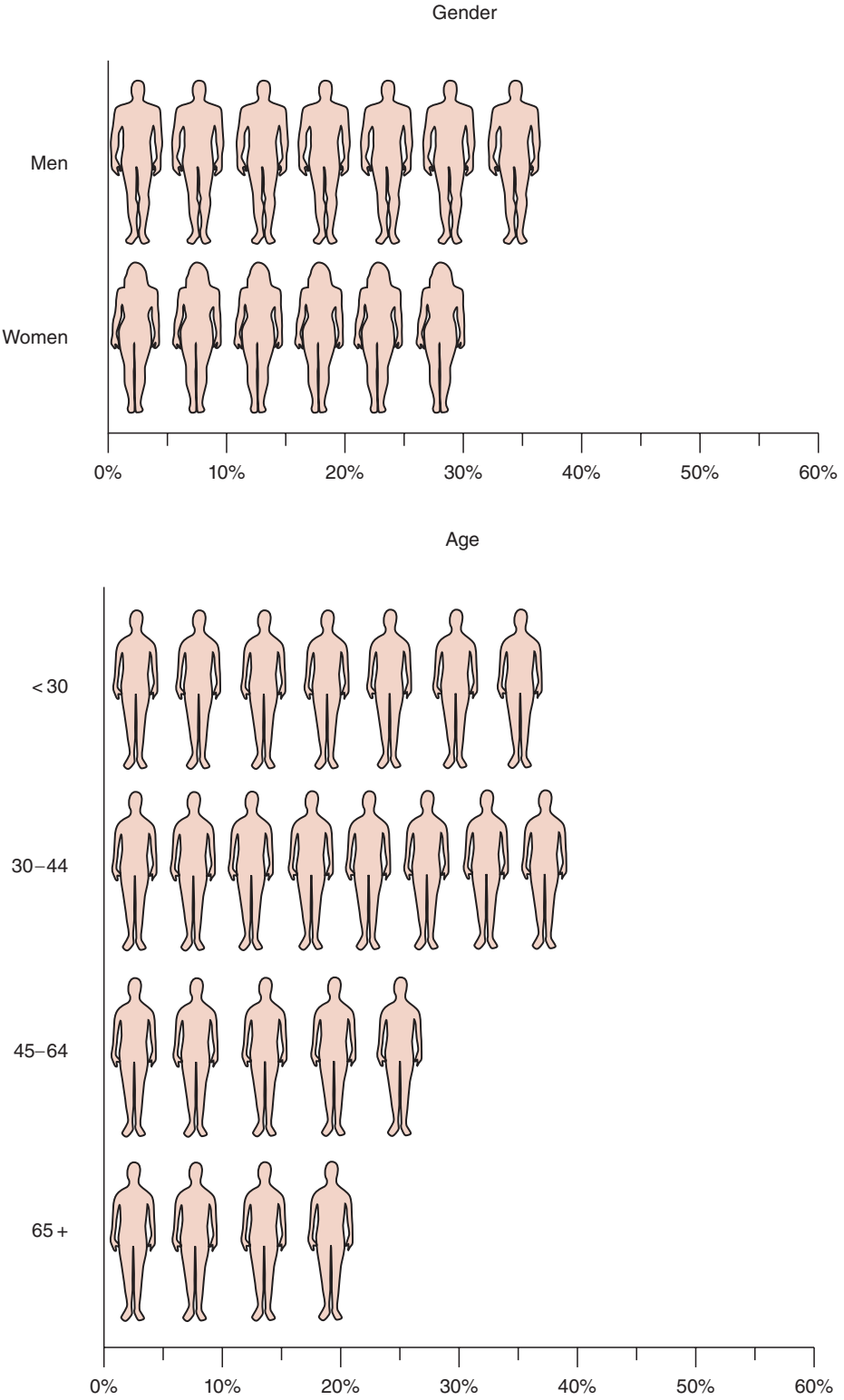



**Figure 25–3** *Estimated lifetime prevalence rates of any psychiatric disorder at five ECA sites. [Reproduced from Regier DA, Boyd JH, Burke JD Jr., et al. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives of General Psychiatry 45, 977–986.]*

panic disorder and obsessive–compulsive disorder had the lowest (0.6% and 0.7%, respectively). The female/male ratio for phobias was approximately 3:1. Women also had a higher rate of obsessive–compulsive disorder. The opposite was found for drug abuse and dependence, with men having a much higher 1-year incidence rate. Also, as expected, older age groups had virtually no new cases of drug abuse and dependence. Interestingly, the incidence of alcohol abuse and dependence was somewhat associated with age; a slight increase was found after the age of 60 years and even more after 75 years. For 1.6% with new onsets of major depressive disorder, women, especially those in their mid-40s, were at highest risk (female/male ratio was more than 2:1).

During the 1-year follow-up period, 6% of the total population had one or more new disorders (Regier et al.

**Table 25–3 Epidemiological Catchment Area Study Lifetime Prevalence Rate of any Psychiatric Disorder**

| | *N* | Lifetime Prevalence (%) |
|---|---|---|
| Total | 19640 | |
| Sex | | |
| Men | 8419 | 36 |
| Women | 11221 | 30 |
| Age (years) | | |
| 30–44 | 4650 | 39 |
| 45–64 | 4194 | 27 |
| 65+ | 5912 | 21 |
| Ethnicity | | |
| White | 13091 | 32 |
| Black | 4697 | 38 |
| Hispanic | 1606 | 33 |
| Education | | |
| Not completed high school | 8818 | 36 |
| High school or more | 10,565 | 30 |
| Occupational status of men (30–64 years) | | |
| Total | 3452 | 35 |
| Unemployed | 774 | 48 |
| Unskilled | 599 | 40 |
| Skilled or higher | 2061 | 30 |
| Rural/urban | | |
| Urban | 4694 | 34 |
| Rural | 2107 | 32 |
| Marital history | | |
| Married and never divorced or separated | 9216 | 24 |
| Single and never cohabited for 1 y | 3424 | 33 |
| Ever divorced or separated | 5906 | 44 |
| Unmarried and cohabited | 986 | 52 |

1993). Also, 5.7% of those with a history of a mental disorder suffered a relapse or a new condition in the 1-year period for a total of 12.3% of new cases in 1 year.

### *Institutionalized Sample*

The ECA investigators interviewed individuals institutionalized in psychiatric hospitals, halfway houses, nursing homes, and prisons. Not surprisingly, rates were much higher in these institutionalized populations. Estimates of lifetime prevalence of 65% and 1-year prevalence of 51% were reported (Regier and Kaelber 1995). Also, not surprisingly, the prevalence of different diagnoses varied depending on the type of the institution (Robins et al. 1991).

### *Use of Mental Health Services*

Although 28.1% of the sample had diagnosable mental or addictive disorders, only 14.7% (23 million) received care, indicating that a disproportionate number of individuals suffering from mental and addictive disorders did not receive treatment. Conversely, although 22% of respondents who had recently used a medical care facility met criteria for a DSM-III disorder, 17% of nonusers had a diagnosable illness (Kessler et al. 1987, Eaton et al. 1989, Narrow et al. 1993, Regier et al. 1993). The disorders making the greatest contribution were alcohol abuse and dependence in men and major depression in women. The ECA study found that 0.9% received inpatient treatment in a specialty mental and addictive disorders facility during a 1-year period. Among individuals with any DSM-III disorder who received mental health services, 28.5% sought treatment from either a mental health clinician or medical physician (see Table 25–4).

**Table 25–4 Epidemiological Catchment Area Study Mental Health Visits in Service Sector in 1 Year**

| Diagnosis | Proportion With Mental Health Visits (%) |
|---|---|
| Any DIS–DSM-III disorder | 28.5 |
| Any DIS–DSM-III disorder except substance abuse | 31.9 |
| Any mental disorder with comorbid substance use | 37.4 |
| Substance use disorder | 23.6 |
| Alcohol abuse and dependence | 22.0 |
| Drug abuse and dependence | 29.8 |
| Schizophrenia and schizophreniform disorders | 64.3 |
| Affective disorders | 45.7 |
| Manic episode | 60.9 |
| Major depressive episode | 53.9 |
| Dysthymia | 42.1 |
| Anxiety disorders | 32.7 |
| Phobia | 31.1 |
| Panic | 58.8 |
| Obsessive—compulsive disorder | 45.1 |
| Somatization disorder | 69.7 |
| Antisocial personality | 31.1 |
| Severe cognitive impairment | 17.0 |

From Regier DA, Narrow WE, Rae DS, et al. (1993) The de facto US mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Archives of General Psychiatry 50, 85–94.

### *Comorbidity of Mental and Substance Use Disorders*

The ECA study provided valuable data about the prevalence of comorbidity of alcohol and substance use disorders with mental disorders (Regier et al. 1988, 1990). Before the ECA study, most of the information about comorbidity came from populations in treatment settings. Since the early 1950s, it has repeatedly been found that patients in clinical settings typically present themselves for treatment because they have more than one disorder, a phenomenon first described by Berkson (1946). Thus, clinical populations provide a biased (and inflated) view of comorbidity.

The ECA study defined comorbidity as the occurrence of more than one disorder and did not require that the disorders overlap temporally. Up to 29% of individuals with a mental disorder suffer from a comorbid substance use disorder. Similarly, individuals with alcohol use disorder have twice the risk of having a comorbid mental disorder and more than five times the risk of having a comorbid drug use disorder. Of all mental disorders, antisocial personality disorder carried the highest risk of having a comorbid substance use disorder, 83.6%, which translates to nearly 30 times the odds of having a substance use disorder compared with the general population. Bipolar disorder had the next highest prevalence of substance use disorder (60.7%), and the odds of having a substance use disorder were 7.9 times higher than that of the general population. Interestingly, the rate of substance use disorder in respondents with bipolar disorder was higher than in those with major

depressive disorder or schizophrenia. Furthermore, 26.7% of respondents with bipolar I disorder had a comorbid drug dependence disorder. The cause for such high prevalence of substance use disorder comorbidity in patients with bipolar disorder remains unclear (Tohen 1994, Tohen and Goodwin 1995). Among individuals with alcohol use disorders, the most common comorbid mental disorder was anxiety disorder, with a prevalence of 19.4%. For individuals with drug use disorder, 22% suffered from a mental disorder. Again, anxiety disorder was the most prevalent with 28.3%.

In summary, findings from the ECA confirmed the widespread and impairing nature of mental disorders reported in the second-generation community studies described earlier. The methodologic rigor with which the ECA was conducted was instrumental at dispelling the disbelief and criticism of methodology that frequently accompanied second-generation studies. The rates in the five ECA sites confirmed the high prevalence of untreated mental disorder. ECA results, such as the finding that individuals with mental disorders were relatively more likely to use general medical services compared with those without disorders, raised provocative questions for a new generation of psychiatric epidemiologists.

## The National Comorbidity Survey

Because the ECA study was conducted in five specific sites, each selected because it contained unique population characteristics, the findings could not be readily extrapolated to the United States as a whole. Therefore, the NCS was designed to estimate the prevalence and comorbidity of psychiatric and substance use disorders in the mainland United States. The NCS was designed by Kessler et al. (Kessler et al. 1994) as the first population-based study administered to a nationally representative sample in the United States using a structured diagnostic interview. It built upon a history of conducting (second-generation) national studies of the prevalence of psychiatric symptoms in the United States at the University of Michigan. The NCS also built on the knowledge and experience of the ECA study. Among its many advantages, it uniformly included a set of demographic and psychosocial risk factors.

### *Design*

The NCS used a stratified probability sampling procedure and focused on individuals aged 15–54 years. It included only noninstitutionalized individuals in 48 states. A total of 8098 individuals were interviewed, which represented 82.6% of the targeted population. To understand the full impact of nonresponse, we reapproached a random sample of the initial refusers and gave them further incentives to participate in a short form of the original interview. These individuals were subsequently found to have elevated rates of psychiatric illness. Therefore, a nonresponse adjustment weight was included in the analysis.

Subjects were administered a modified version of the CIDI (World Health Organization 1990). The NCS obtained estimates of 14 DSM-III-R diagnoses, including alcohol abuse and dependence, antisocial personality disorder, drug abuse and dependence, dysthymia, generalized anxiety disorder, panic disorder, social phobia, agoraphobia, simple phobia, major depression, and nonaffective psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and atypical psychosis). In addition, to address the ECA finding that psychotic disorders had poor reliability and validity when assessed by nonclinicians (Anthony et al. 1985, Helzer et al. 1985), NCS individuals endorsing psychotic symptoms in the survey were reinterviewed by telephone by a clinician with the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1992).

### *Prevalence*

Table 25–5 presents the NCS 1-year and lifetime prevalence rates of the various psychiatric disorders. Lifetime prevalence rates are the proportion of individuals who ever experienced a disorder, and 1-year prevalence represents the proportion of individuals who experienced a disorder in the year before the interview. The lifetime prevalence for any DSM-III-R disorder was 48.7%, and the 12-month prevalence was 27.7%. When grouped by diagnostic category, the lifetime prevalence rates were 24.9% for anxiety disorders, 26.6% for substance abuse and dependence, and 19.3% for affective disorders. As expected, anxiety and affective disorders were more common in women, and substance abuse was more common in men.

### *Comorbidity*

An important focus of the NCS was the assessment of comorbidity. Interestingly, whereas 21% of the sample experienced only one disorder, 14% met criteria for three or more lifetime disorders. Furthermore, among individuals with a lifetime disorder, 53.9% had three or more lifetime disorders. Among individuals with a disorder occurring in the past 12 months, 58.9% experienced three or more disorders. The level of comorbidity was most dramatic for individuals with a severe disorder in the past 12 months, defined as active mania, nonaffective psychosis, or active disorder of other types that either resulted in hospitalization or created severe role impairment. In that subset of respondents, 89.5% had three or more disorders.

### *Risk Factors and Correlates*

The NCS also yielded important data on demographic correlates and potential risk factors for mental disorders. Several earlier patterns of association observed for gender and other characteristics were confirmed. For example, affective disorders occurring in the past 12 months were more frequent in 15- to 24-year-olds, Hispanics, respondents with the lowest income, and respondents who had not graduated from college. Anxiety disorders occurred more frequently in 15- to 24-year-olds, respondents in the three lower income categories (less than $70,000 per annum), and those without a college degree. Substance abuse was found less frequently in African-Americans and more frequently in 15- to 44-year-olds, respondents earning $0–19000 per annum, and non–college graduates. All of these risk factors were also associated with having three or more disorders. No significant results were found for region of the country where the respondent resided (e.g., the Midwest, Northeast, West, and South). However, although residing in a major metropolitan versus a rural area was not a risk factor for the individual disorders, respondents from major metropolitan areas were four times more likely than those from rural areas to have three or more disorders.

**Table 25–5 National Comorbidity Survey Lifetime and 12-Month Prevalence Rates (%)**

| Disorders | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | Lifetime Rate | 12-Month Rate | Lifetime Rate | 12-Month Rate | Lifetime Rate | 12-Month Rate |
| Affective disorders | | | | | | |
| Major depressive episode | 12.7 | 7.7 | 21.3 | 12.9 | 17.1 | 10.3 |
| Manic episode | 1.6 | 1.4 | 1.7 | 1.3 | 1.6 | 1.3 |
| Dysthymia | 4.8 | 2.1 | 8.0 | 3.0 | 6.4 | 2.5 |
| Anxiety disorders | | | | | | |
| Panic disorder | 2.0 | 1.3 | 5.0 | 3.2 | 3.5 | 2.3 |
| Agoraphobia without panic disorder | 3.5 | 1.7 | 7.0 | 3.8 | 5.3 | 2.8 |
| Social phobia | 11.1 | 6.6 | 15.5 | 9.1 | 13.3 | 7.9 |
| Simple phobia | 6.7 | 4.4 | 15.7 | 13.2 | 11.3 | 8.8 |
| Generalized anxiety disorder | 3.6 | 2.0 | 6.6 | 4.3 | 5.1 | 3.1 |
| Substance use disorders | | | | | | |
| Alcohol abuse without dependence | 12.5 | 3.4 | 6.4 | 1.6 | 9.4 | 2.5 |
| Alcohol dependence | 20.1 | 10.7 | 8.2 | 3.7 | 14.1 | 7.2 |
| Drug abuse without dependence | 5.4 | 1.3 | 3.5 | 0.3 | 4.4 | 0.8 |
| Drug dependence | 9.2 | 3.8 | 5.9 | 1.9 | 7.5 | 2.8 |
| Any substance abuse and dependence | 35.4 | 16.1 | 17.9 | 6.6 | 26.6 | 11.3 |
| Nonaffective psychosis* | 0.6 | 0.5 | 0.8 | 0.6 | 0.7 | 0.5 |
| Any National Comorbidity Survey disorder | 48.7 | 27.7 | 47.3 | 31.2 | 48.0 | 29.5 |

*Schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and atypical psychosis.

### *Use of Mental Health Services*

The NCS also examined the patterns of use of health services by the respondents. Only 40% of individuals with a mental disorder ever received professional care, and only 25% received their care in the mental health specialty sector. On the other hand, 60% of individuals with three or more comorbid disorders received professional help, 40% in the mental health specialty sector. Furthermore, one-third of persons with three or more comorbid disorders received professional help in the past year compared with only 20% of those with one disorder. These findings indicate that the use of health services is concentrated in the segment of the population with a high degree of comorbidity.

Subsequent analyses of service utilization in the NCS have shed light on the magnitude and potential determinants of important subcomponents of the problem of unmet needs for mental health treatment. For example, while only a minority with active major depression received any care in the prior year, an even smaller percentage (7%) received treatment that could be considered minimally adequate (Katz et al. 1998). Even among the extremely vulnerable and impaired population that met criteria for active Serious Mental Illness (SMI), only 40% received any treatment in the prior year (Kessler et al. 2001a) and only 15% received care that could be considered minimally adequate (Wang et al. 2002). Among NCS respondents with mental disorders who received treatment in the prior year, 19% dropped out prematurely (Edlund et al. 2002).

## The National Comorbidity Survey-Replication (NCS-R)

The rapid pace of change in the American mental health care system has made it imperative to reexamine the burdens from mental disorders and their care. Although new forms of treatment have been introduced and promoted, their efficacy and safety have been questioned as well (Food and Drug Administration; Eisenberg et al. 1993, 1998, Leucht et al. 1999, Kessler et al. 2001c, Olfson et al. 2002, Rosenthal et al. 2002, Schatzberg and Nemeroff 2004). Initiatives promoting awareness, detection, help-seeking, and best-practices for mental disorders have been launched but little is known concerning their impacts (Agency for Health Care Policy and Research 1993, Jacobs 1995, Katon et al. 1995, Hirschfeld et al. 1997, National Committee for Quality Assurance 1997, American Psychiatric Association 1998, 2000, 2002, 2004, Lehman and Steinwachs 1998, Wells et al. 2000, Katon et al. 2002). Likewise, effects of the many delivery system, financing, and mental health policy redesigns that have taken place are unclear (Williams 1998, Mechanic and McAlpine 1999, Sturm and Klap 1999, Williams et al. 1999, Weissman et al. 2000, Kessler et al. 2001a, Bender 2002). To shed light on these impacts and to provide up-to-date data on the current burdens from and care of mental disorders in the United States, the National Comorbidity Survey Replication (NCS-R) was undertaken between 2001 and 2003 as part of the larger WHO WMH Survey Initiative.

### Design

The NCS-R is a nationally representative household survey of respondents ages 18 and older in the coterminous United States (Kessler et al. 2004). Face-to-face interviews were carried out with 9282 respondents between February 2001 and April 2003. Part I included a core diagnostic assessment administered to all respondents. Part II assessed risk factors, correlates, service use, and additional disorders and was administered to all Part I respondents with lifetime disorders plus a probability subsample of other respondents.

The overall response rate was 70.9%. Diagnoses were made using Version 3.0 of the World Health Organization's (WHO) CIDI (Kessler and Ustun 2004), a fully structured lay-administered diagnostic interview that generates diagnoses according to the definitions and criteria of both the ICD-10 (World Health Organization 1991) and DSM-IV-TR (American Psychiatric Association 1994) diagnostic systems. Disorders included mood disorders (major depressive episode [MDE], dysthymia [DYS], and bipolar disorder I or II [BPD] studied together for increased statistical power), anxiety disorders (panic disorder [PD], agoraphobia without panic [AG], specific phobia [SP], social phobia [SoP], generalized anxiety disorder [GAD], posttraumatic stress disorder [PTSD], and separation anxiety disorder [SAD]), substance disorders (alcohol and drug abuse and dependence [AA, DA, AD, DD]), and impulse control disorders (intermittent explosive disorder [IED], oppositional defiant disorder [ODD], and attention-deficit/hyperactivity disorder [ADHD]). Blinded clinical reappraisals using the SCID (First et al. 2002) have shown generally good concordance between DSM-IV-TR diagnoses based on the CIDI and the SCID for anxiety, mood, and substance disorders (Haro et al. 2006).

## The Early Ages of Onset for Lifetime Mental Disorders

NCS-R estimates of the lifetime prevalence of mental disorders are broadly consistent with those found in previous community surveys in the United States (Kessler et al. 1994, 1998) in showing that half of the general population is afflicted by mental disorders at some time in their life. Similar to these earlier studies, anxiety and mood disorders are common classes with MDD, SP, SoP, and AA being the most prevalent individual disorders. What may be more surprising, given the paucity of prior lifetime data, is the frequency of impulse control disorders, which have a combined lifetime prevalence that is higher than for either mood disorders or substance disorders.

In addition to their high prevalences, mental disorders examined in the NCS-R are notable for their ages of onsets, which are concentrated in the first two decades of life with later-onset disorders largely occurring as temporally secondary comorbid conditions. Consistent with previous epidemiological surveys (Christie et al. 1988, WHO International Consortium in Psychiatric Epidemiology 2000), median ages of onset are earlier for anxiety disorders (age 11) and impulse-control disorders (age 11) than for substance (age 20) and mood disorders (age 30) (see Table 25–6). Such data reveal that mental disorders are uniquely burdensome in that they typically attack youth; almost all chronic physical disorders have conditional risks that increase with age, typically peaking in late middle or old age (Murray and Lopez 1996).

Taken together, the NCS-R findings on lifetime prevalence of mental disorders plus the enormous personal and societal burdens of these disorders, suggest that greater attention be paid to public health interventions that target the child and adolescent years. With appropriately balanced considerations of potential risks and benefits, focus is also needed on early interventions aimed at preventing progression of primary disorders and onset of comorbid disorders.

## Failure and Delays in Initial Help-Seeking

The NCS-R lifetime data on use of mental health services reveal large and underappreciated needs for mental health treatment in the United States. First, a large number of lifetime cases never seek help. Figures 25–4–25–7 present survival curves showing the proportion of cases with mood, anxiety, impulse-control, and substance disorders that will eventually make treatment contact. As revealed by these curves, failure to seek help is especially true for substance and impulse control disorders, where nearly half of all lifetime cases never make any treatment contact.

A second source of unmet need documented in the NCS-R lifetime data concerns pervasive delays in initial treatment contact. The proportion of cases that made treatment contact in the year of first onset of the disorder and the median delay among people who eventually made treatment contact after the year of first onset were estimated from survival curves and are presented in Table 25–7. Proportions of cases making treatment contact in the year of disorder onset range from highs of 37.4–41.6% for the mood disorders to lows of 1.0–3.4% for SP, SoP, and SAD. The median years of delay also differ greatly, from lows of 6–8 years for mood disorders to highs of 20–23 years for SP and SAD. These delays have not been a focus of previous research, as mental health services research has traditionally focused on treatment of current episodes for established cases (Joseph and Boeckh 1981, Leaf et al. 1985, 1986, 1988, Temkin-Greener and Clark 1988, Hu et al. 1991, Padgett et al. 1994). These NCS-R findings suggest that the focus needs to be expanded to address the speed of initial help-seeking since, even for disorders where eventual treatment is typical, long delays are pervasive.

## The Seriousness of 12-Month Disorders

The NCS-R results confirm that episodes of DSM-IV-TR disorders are highly prevalent during the prior year, affecting over one-quarter of Americans. Although many cases are mild, the prevalence of moderate and serious cases is still substantial, affecting 14.0% of the population. The 5.7% with a serious disorder is remarkably close to the estimated prevalence of Serious Mental Illness (SMI) defined by SAMHSA in the original NCS (Kessler et al. 1996). Consistent with prior studies (Bijl et al. 2003, Demyttenaere et al. 2004), mood disorders have the highest percentage of serious cases (45.0%) and anxiety disorders the lowest (22.8%) (see Table 25–8).

A striking finding from the NCS-R 12-month prevalence data is that more than 40% of cases in the prior year also have comorbid disorders. Patterns of bivariate comorbidity are broadly consistent with the ECA and original NCS in showing that the vast majority of disorders are positively correlated. Relative magnitudes of associations are also quite similar across the three surveys, with high rank-order correlations of odds-ratios among comorbid pairs in the NCS-R versus published odds-ratios (Kessler 1995) in both the NCS (.79) and the ECA (.57). These high levels of comorbidity among cases of 12-month disorders are concerning because NCS-R data also reveal that severity is strongly related to comorbidity. For example, the proportion of 12-month cases having a serious disorder was 9.6% of those with one diagnosis, 25.5% with two, and 49.9% with three or more diagnoses.

**Table 25–6 Ages at Selected Percentiles on the Standardized Age-of-Onset Distributions of DSM-IV-TR/WMH-CIDI Disorders With Projected Lifetime Risk at Age 75**

| | Projected Lifetime Risk at Age 75 | | Ages at Selected Age-of-Onset Percentiles | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | % | (*SE*) | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 99 |
| I. Anxiety disorders | | | | | | | | | | |
| Panic disorder | 6.0 | (0.3) | 6 | 10 | 16 | 24 | 40 | 51 | 63 | |
| Agoraphobia without panic | 1.6 | (0.2) | 6 | 7 | 13 | 20 | 33 | 48 | 51 | 54 |
| Specific phobia | 13.2 | (0.4) | 4 | 5 | 5 | 7 | 12 | 31 | 41 | 64 |
| Social phobia | 12.6 | (0.4) | 5 | 6 | 8 | 13 | 15 | 23 | 34 | 52 |
| Generalized anxiety disorder | 8.3 | (0.4) | 8 | 13 | 20 | 31 | 47 | 68 | 65 | |
| Posttraumatic stress disorder* | 8.7 | (0.6) | 6 | 9 | 15 | 23 | 39 | 53 | 61 | 71 |
| Obsessive--compulsive disorder† | 1.9 | (0.3) | 10 | 11 | 14 | 19 | 30 | 48 | 44 | 44 |
| Separation anxiety disorder‡ | 5.2 | (0.4) | 5 | 5 | 6 | 7 | 10 | 13 | 14 | 17 |
| Any anxiety disorder§ | 31.5 | (1.1) | 5 | 5 | 6 | 11 | 11 | 41 | 51 | 65 |
| II. Mood disorders | | | | | | | | | | |
| Major depressive disorder | 23.2 | (0.6) | 12 | 14 | 19 | 32 | 44 | 66 | 43 | |
| Dysthymia | 3.4 | (0.3) | 7 | 11 | 17 | 13 | 31 | 17 | 73 | |
| Bipolar I--II disorders | 5.1 | (0.3) | 11 | 13 | 17 | 25 | 20 | 07 | 75 | |
| Any mood disorder | 28.0 | (0.8) | 11 | 13 | 18 | 30 | 34 | 43 | 33 | |
| III. Impulse-control disorders | | | | | | | | | | |
| Oppositional-defiant disorder‡ | 8.5 | (0.7) | 5 | 6 | 8 | 13 | 34 | 67 | 78 | |
| Conduct disorder‡ | 9.5 | (0.8) | 6 | 7 | 10 | 13 | 35 | 77 | 78 | |
| Attention-deficit/hyperactivity disorder‡ | 8.1 | (0.6) | 5 | 6 | 7 | 7 | 8 | 11 | 16 | |
| Intermittent explosive disorder | 5.4 | (0.3) | 6 | 8 | 11 | 15 | 20 | 26 | 46 | |
| Any impulse-control disorder‡ | 25.4 | (1.1) | 5 | 6 | 7 | 11 | 15 | 83 | 36 | |
| IV. Substance disorders | | | | | | | | | | |
| Alcohol abuse* | 15.1 | (0.7) | 15 | 16 | 18 | 21 | 19 | 99 | 44 | |
| Alcohol dependence* | 6.5 | (0.4) | 16 | 17 | 19 | 23 | 31 | 41 | 55 | |
| Drug abuse* | 8.5 | (0.4) | 15 | 16 | 17 | 19 | 23 | 99 | 66 | |
| Drug dependence* | 3.4 | (0.3) | 15 | 16 | 18 | 21 | 28 | 61 | 19 | |
| Any substance use disorder§ | 16.3 | (0.6) | 15 | 16 | 18 | 20 | 27 | 71 | 14 | |
| V. Any disorder | | | | | | | | | | |
| Any§ | 50.8 | (1.2) | 5 | 5 | 7 | 14 | 24 | 42 | 51 | 64 |

*Posttraumatic stress disorder and substance disorders were assessed only in the Part II sample ($n$ = 5692).

†Obsessive–compulsive disorder was assessed only in a random one-third of the Part II sample ($n$ = 1808).

‡Separation anxiety disorder, oppositional defiant disorder, conduct disorder, attention-deficit/hyperactivity disorder, and any impulse-control disorder were assessed only among Part II respondents aged 18–44 years ($n$ = 3199).

§These summary measures were analyzed in the full Part II sample ($n$ = 5692). Obsessive-compulsive disorder, separation anxiety disorder, oppositional defiant disorder, conduct disorder, and attention-deficit/hyperactivity disorder were coded as absent among respondents who were not assessed for these disorders.

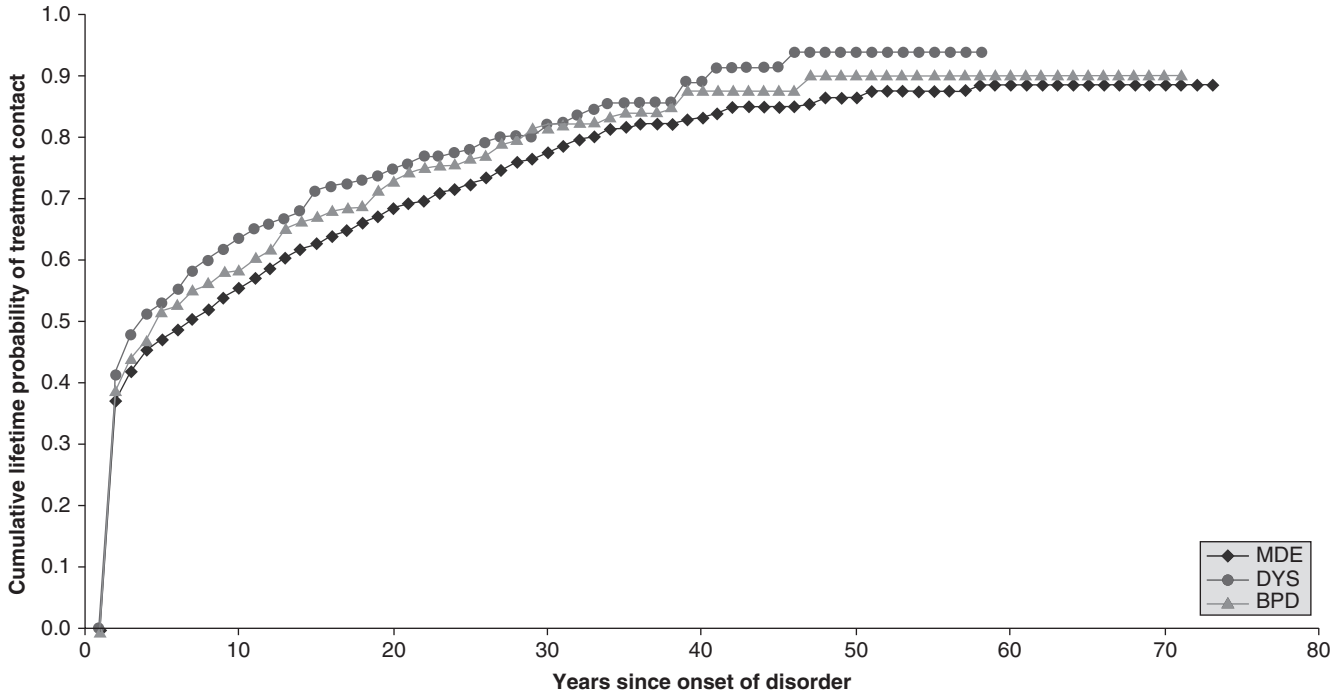



**Figure 25–4** *Cumulative lifetime probability of treatment contact for mood disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 0.7$, $p = .718$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: major depressive disorder (MDE), 88.1%; dysthymia (DYS), 94.2%; bipolar disorder (BPD) I and II, 90.2%. (See Color Plate VI)*

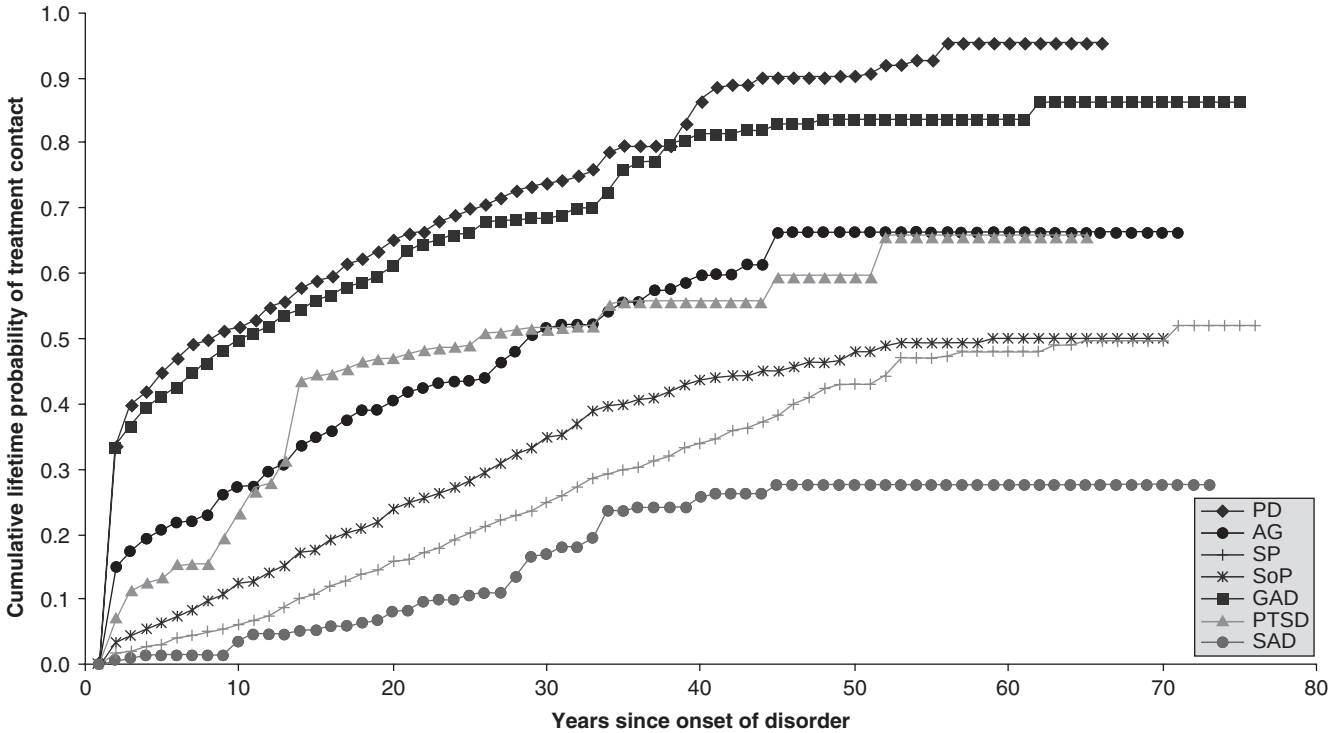



**Figure 25–5** *Cumulative lifetime probability of treatment contact for anxiety disorders from year of onset*[1]. *Significance of differences among curves: $x^2_4 = 242.4$, $p < .001$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: panic disorder (PD), 95.3%; agoraphobia without panic (AG), 66.5%; specific phobia (SP), 50.1%; social phobia (SoP), 74.0%; generalized anxiety disorder (GAD), 86.1%; posttraumatic stress disorder (PTSD), 65.3%; separation anxiety disorder (SAD), 27.3%. (See Color Plate VI)*

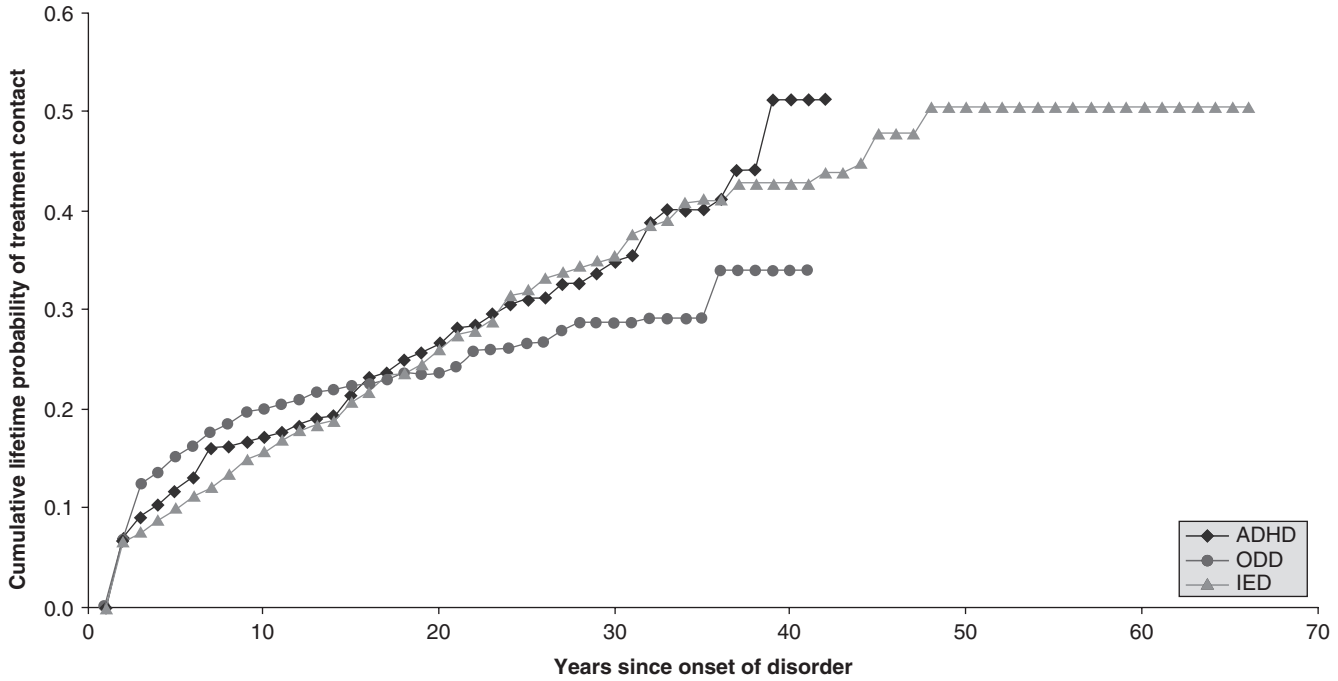



**Figure 25–6** *Cumulative lifetime probability of treatment contact for impulse-control disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 6.0$, $p = .050$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: attention-deficit/hyperactivity disorder (ADHD), 51.8%; oppositional defiant disorder (ODD), 33.9%; intermittent explosive disorder (IED), 50.4%. (See Color Plate VII)*

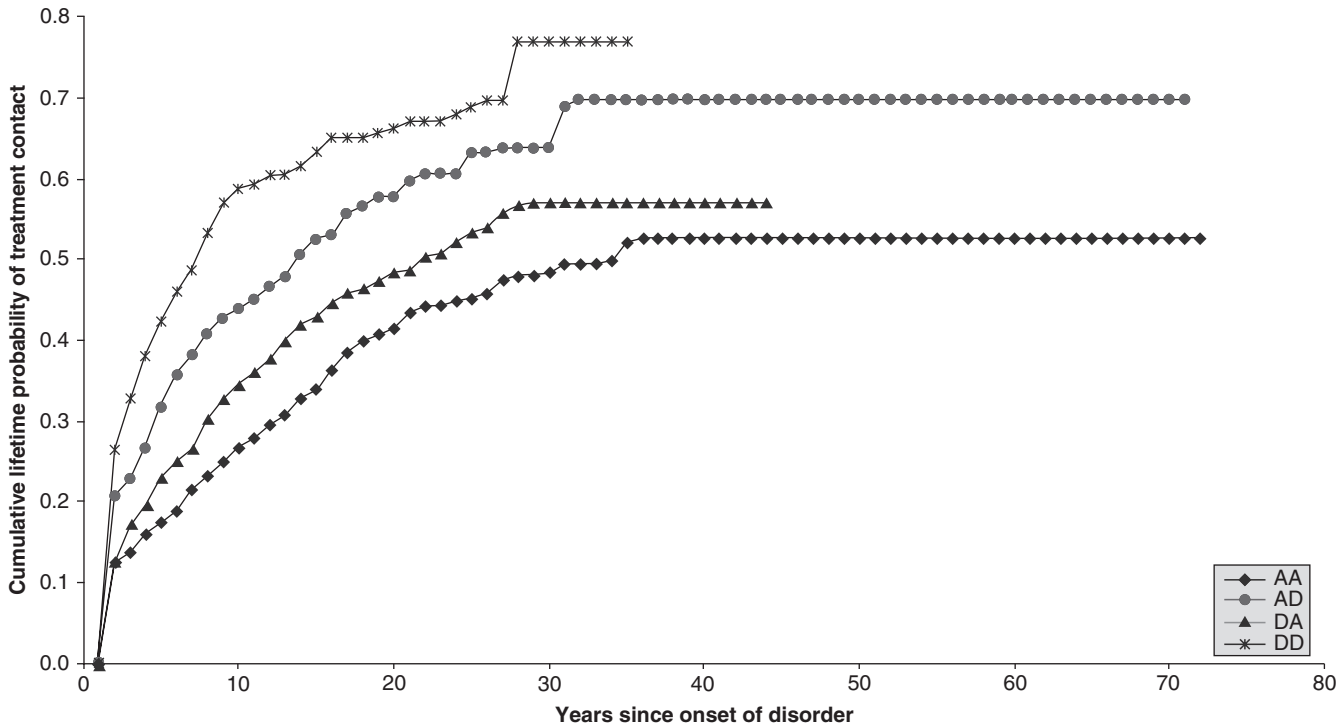



**Figure 25–7** *Cumulative lifetime probability of treatment contact for substance disorders from year of onset*[1]. *Significance of differences among curves: $x^2_2 = 44.8$, $p < .001$. [1]Based on survival analysis. The projected proportions of cases that will eventually make treatment contact for each disorder are estimated to be: alcohol abuse (AA), 52.7%; alcohol dependence (AD), 69.8%; drug abuse (DA), 57.0%; drug dependence (DD), 76.9%. (See Color Plate VII)*

**Table 25–7 Proportional Treatment Contact in the Year of Disorder Onset and Median Duration of Delay Among Cases That Subsequently Made Treatment Contact**

| | Treatment Contact Made in the Year of Onset (%) | Median Duration of Delay (Years)* | $n^{\dagger}$ |
|---|---|---|---|
| I. Anxiety disorders | | | |
| Panic disorder | 33.6 | 10 | 269 |
| Agoraphobia | 15.1 | 12 | 137 |
| Specific phobia | 1.6 | 20 | 720 |
| Social phobia | 3.4 | 16 | 694 |
| Generalized anxiety disorder | 33.3 | 9 | 444 |
| Posttraumatic stress disorder | 7.1 | 12 | 389 |
| Separation anxiety disorder | 1.0 | 23 | 234 |
| II. Mood disorders | | | |
| Major depressive episode | 37.4 | 8 | 1092 |
| Dysthymia | 41.6 | 7 | 229 |
| Bipolar I–II disorders | 39.1 | 6 | 224 |
| III. Impulse-control disorders | | | |
| Attention-deficit/hyperactivity disorder | 7.0 | 13 | 253 |
| Oppositional defiant disorder | 6.6 | 4 | 324 |
| Intermittent explosive disorder | 6.8 | 13 | 447 |
| IV. Substance disorders | | | |
| Alcohol abuse | 12.4 | 9 | 751 |
| Alcohol dependence | 20.7 | 6 | 307 |
| Drug abuse | 12.5 | 6 | 450 |
| Drug dependence | 26.5 | 5 | 174 |

*Projections based on time-to-contact survival curves in Figures 25–1–25–4.

†Weighted number of respondents with a lifetime history of the disorder.

## The Adequacy of Treatment for 12-Month Disorders

NCS-R findings on 12-month use of mental health services shed light on additional forms of poor mental health care in the United States, including underuse, poor quality regimens, use of unproven modalities, and suboptimal allocation of services. On one hand, only 41.1% of those with 12-month DSM-IV-TR disorders used mental health services in the prior year. Among those receiving services, many go outside of health care sectors; for example, complementary-alternative treatments account for 32% of all mental health visits despite a paucity of data supporting their efficacy (Eisenberg et al. 1993, 1998, Weaver 1995, Kessler et al. 2001b, 2001c, Hypericum Depression Trial Study Group 2002, Wang et al. 2003). Furthermore, only 32.7% of treated patients with disorders were classified as receiving at least minimally adequate treatment in the prior year (see Table 25–9). The probability was lowest in the General Medical sector (12.7% vs. 44.5% in the Psychiatrist sector and 46.5% in the Nonpsychiatrist Specialty sector). This finding is of concern in light of a shift that appears to be occurring between sectors, with expanded use of the general medical sector for mental health services (by 17.9% of NCS-R respondents vs.13.3% a decade earlier in the original NCS) (Kessler et al. 1999).

## Future Directions

As outlined in this chapter, progress in enumerating the rates of mental disorders in adults in the general population, and documenting the extent of unmet need, has been extensive. However, considerable additional work remains for psychiatric epidemiologists in the future (Kessler 2000).

Perhaps the most fundamental work that is needed is ongoing refinement of our current conceptualization of mental disorders. Important questions have been raised by the high rates of mental disorders observed in recent population-based surveys, including whether there may have been overdiagnosis among individuals with clinically insignificant symptoms (Regier et al. 1998, Narrow et al. 2002). In part, because of such concerns, new requirements that symptoms be clinically significant were added to many disorder criteria in DSM-IV-TR. However, far from settling the issue, these new requirements have themselves sparked a healthy debate (Spitzer 1998).

A closely related topic of considerable importance is whether mental disorders would be better conceptualized dimensionally as occurring on a continuum, rather than categorically as "cases" and "noncases." Researchers and clinicians may ultimately find that the two conceptualizations are far from mutually exclusive and, in fact, highly complementary. For example, adding the dimensional view to the currently prevailing categorical view of mental disorders, allows identification of subsyndromal psychopathology in individuals who may later develop full-blown disorders. Another advantage of adding a dimensional conceptualization is that it could provide compelling arguments against the stigmatization that comes from rigid distinctions between the normal and pathological.

**Table 25–8 Twelve-Month Prevalence and Severity of DSM-IV-TR/WMH-CIDI Disorders ($n$ = 9282)**

| | Total | | Severity* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Serious | | Moderate | | Mild | |
| | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) |
| I. Anxiety Disorders | | | | | | | | |
| Panic disorder | 2.7 | (0.2) | 44.8 | (3.2) | 29.5 | (2.7) | 25.7 | (2.5) |
| Agoraphobia without panic | 0.8 | (0.1) | 40.6 | (7.2) | 30.7 | (6.4) | 28.7 | (8.4) |
| Specific phobia | 8.7 | (0.4) | 21.9 | (2.0) | 30.0 | (2.0) | 48.1 | (2.1) |
| Social phobia | 6.8 | (0.3) | 29.9 | (2.0) | 38.8 | (2.5) | 31.3 | (2.4) |
| Generalized anxiety disorder | 3.1 | (0.2) | 32.3 | (2.9) | 44.6 | (4.0) | 23.1 | (2.9) |
| Posttraumatic stress disorder† | 3.5 | (0.3) | 36.6 | (3.5) | 33.1 | (2.2) | 30.2 | (3.4) |
| Obsessive--compulsive disorder‡ | 1.0 | (0.3) | 50.6 | (12.4) | 34.8 | (14.1) | 14.6 | (5.7) |
| Separation anxiety disorder§ | 0.9 | (0.2) | 43.3 | (9.2) | 24.8 | (7.5) | 31.9 | (12.2) |
| Any anxiety disorder‖ | 18.1 | (0.7) | 22.8 | (1.5) | 33.7 | (1.4) | 43.5 | (2.1) |
| II. Mood disorders | | | | | | | | |
| Major depressive disorder | 6.7 | (0.3) | 30.4 | (1.7) | 50.1 | (2.1) | 19.5 | (2.1) |
| Dysthymia | 1.5 | (0.1) | 49.7 | (3.9) | 32.1 | (4.0) | 18.2 | (3.4) |
| Bipolar I–II disorders | 2.6 | (0.2) | 82.9 | (3.2) | 17.1 | (3.2) | 0.0 | (0.0) |
| Any mood disorder | 9.5 | (0.4) | 45.0 | (1.9) | 40.0 | (1.7) | 15.0 | (1.6) |
| III. Impulse-control disorders | | | | | | | | |
| Oppositional-defiant disorder§ | 1.0 | (0.2) | 49.6 | (8.0) | 40.3 | (8.7) | 10.1 | (4.8) |
| Conduct disorder§ | 1.0 | (0.2) | 40.5 | (11.1) | 31.6 | (7.5) | 28.0 | (9.1) |
| Attention-deficit/hyperactivity disorder§ | 4.1 | (0.3) | 41.3 | (4.3) | 35.2 | (3.5) | 23.5 | (4.5) |
| Intermittent explosive disorder | 2.6 | (0.2) | 23.8 | (3.3) | 74.4 | (3.5) | 1.7 | (0.9) |
| Any impulse-control disorder§,¶ | 8.9 | (0.5) | 32.9 | (2.9) | 52.4 | (3.0) | 14.7 | (2.3) |
| IV. Substance disorders | | | | | | | | |
| Alcohol abuse† | 3.1 | (0.3) | 28.9 | (2.6) | 39.7 | (3.7) | 31.5 | (3.3) |
| Alcohol dependence† | 1.3 | (0.2) | 34.3 | (4.5) | 65.7 | (4.5) | 0.0 | (0.0) |
| Drug abuse† | 1.4 | (0.1) | 36.6 | (5.0) | 30.4 | (5.8) | 33.0 | (6.8) |
| Drug dependence† | 0.4 | (0.1) | 56.5 | (8.2) | 43.5 | (8.2) | 0.0 | (0.0) |
| Any substance disorder† | 3.8 | (0.3) | 29.6 | (2.8) | 37.1 | (3.5) | 33.4 | (3.2) |
| V. Any disorder | | | | | | | | |
| Any‖ | 26.2 | (0.8) | 22.3 | (1.3) | 37.3 | (1.3) | 40.4 | (1.6) |
| One disorder‖ | 14.4 | (0.6) | 9.6 | (1.3) | 31.2 | (1.9) | 59.2 | (2.3) |
| Two disorders‖ | 5.8 | (0.3) | 25.5 | (2.1) | 46.4 | (2.6) | 28.2 | (2.0) |
| Three or more disorders‖ | 6.0 | (0.3) | 49.9 | (2.3) | 43.1 | (2.1) | 7.0 | (1.3) |

*Percentages in the three severity columns are repeated as proportions of all cases and sum to 100% across each row.

†Assessed in the Part II sample (n = 5692)

‡Assessed in a random one-third of the Part II sample (n = 1808)

§Assessed in the Part II sample among respondents aged 18–44 years (n = 3199)

‖Estimated in the Part II sample. No adjustment is made for the fact that one or more disorders in the category were not assessed for all Part II respondents.

¶The estimated prevalence of any impulse-control disorder is larger than the sum of the individual disorders because the prevalence of intermittent explosive disorder, the only impulse-control disorder that was assessed in the total sample, is reported here for the total sample rather than for the subsample of respondents among whom the other impulse-control disorders were assessed (Part II respondents in the age range 18–44). The estimated prevalence of any impulse-control disorder, in comparison, is estimated in the latter subsample. Intermittent explosive disorder has a considerably higher estimated prevalence in this subsample than in the total sample.

Results of future psychiatric epidemiologic studies will only be as good as the instruments that are used for the assessment, the memories of the respondents who are asked to recall their internal states throughout their lifetimes, and the willingness of subjects to divulge sensitive and potentially stigmatizing symptoms. Until we have a means of verifying self-reports against a gold standard, improvements in measurement will be needed (Fennig and Bromet 1992). In addition to developing new instruments and establishing their psychometric properties, the advantages and limitations of several new low-cost modes of administering surveys (e.g., via interactive voice-response telephone technology, computerized self-assessments, and the Internet) should be explored as well.

Data from future longitudinal studies will be especially important. Only longitudinal studies can shed light on both the natural history of disorders as well as the extent to which early treatment can mitigate the course

**Table 25–9** **Percent of Patients Who Received at Least Minimally Adequate Treatment in Those Sectors by 12-Month DSM-IV-TR/WMH-CIDI Disorder[†]**

| | Healthcare | | | | | | | | | | Nonhealthcare | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mental health specialty | | | | | | | | | | | | | | | |
| | Psychiatrist | | Nonpsychiatrist‡ | | Any | | General Medical[§] | | Any | | Human Services[‖] | | Self-Help¶ | | Any Service Use | |
| | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) | % | (*SE*) |
| I. Anxiety disorders | | | | | | | | | | | | | | | | |
| Panic disorder | 58.6 | (9.0) | 48.2 | (9.0) | 55.3 | (7.7) | 20.6 | (4.7) | 41.2 | (5.3) | 19.0 | (7.8) | –** | –** | 39.8 | (5.1) |
| Agoraphobia without panic disorder | -- | -- | -- | – | – | – | – | – | 42.1 | (8.1) | – | – | –** | –** | 41.1 | (7.2) |
| Specific phobia | 46.2 | (6.6) | 50.6 | (5.5) | 49.9 | (5.5) | 15.7 | (3.6) | 34.4 | (4.1) | 16.3 | (4.6) | –** | –** | 33.6 | (4.0) |
| Social phobia | 51.6 | (7.5) | 53.0 | (4.2) | 55.9 | (5.4) | 14.8 | (3.8) | 38.7 | (3.9) | 20.7 | (5.4) | –** | –** | 38.2 | (3.8) |
| Generalized anxiety disorder | 51.5 | (11.5) | 69.1 | (8.9) | 60.7 | (7.7) | 20.2 | (4.2) | 43.7 | (5.6) | 24.0 | (9.0) | –** | –** | 42.5 | (5.5) |
| Posttraumatic stress disorder | 45.8 | (8.3) | 56.6 | (6.7) | 56.6 | (5.5) | 12.8 | (4.0) | 42.0 | (4.3) | 20.1 | (6.6) | –** | –** | 40.4 | (3.6) |
| Obsessive--compulsive disorder | – | – | – | – | – | – | – | – | – | – | – | – | –** | –** | – | – |
| Separation anxiety disorder | – | – | – | – | – | – | – | – | – | – | – | – | –** | –** | – | – |
| Any anxiety disorder | 46.1 | (6.5) | 50.5 | (4.0) | 51.5 | (4.8) | 13.4 | (1.9) | 34.3 | (3.0) | 18.9 | (2.9) | –** | –** | 33.8 | (2.8) |
| II. Mood disorders | | | | | | | | | | | | | | | | |
| Major depressive disorder | 43.2 | (7.4) | 53.2 | (3.8) | 52.0 | (5.1) | 14.9 | (2.7) | 38.0 | (3.7) | 22.0 | (5.8) | –** | –** | 37.5 | (3.1) |
| Dysthymia | 45.7 | (10.8) | 60.1 | (10.9) | 53.1 | (9.2) | 29.2 | (6.4) | 43.1 | (5.6) | – | – | –** | –** | 40.7 | (5.3) |
| Bipolar I--II disorders | 47.7 | (7.2) | 49.8 | (5.8) | 53.9 | (5.9) | 9.0 | (3.5) | 38.8 | (3.9) | 20.9 | (8.9) | –** | –** | 39.2 | (4.2) |
| Any mood disorder | 44.4 | (5.8) | 52.1 | (3.1) | 52.3 | (3.8) | 14.3 | (1.9) | 38.5 | (2.4) | 21.2 | (4.7) | –** | –** | 38.3 | (2.2) |
| III. Impulse-control disorders | | | | | | | | | | | | | | | | |
| Intermittent explosive disorder | – | – | – | – | 36.4 | (9.5) | 7.8 | (5.1) | 26.1 | (6.5) | – | – | –** | –** | 21.8 | (5.4) |

**Table 25–9 Percent of Patients Who Received at Least Minimally Adequate Treatment in Those Sectors by 12-Month DSM-IV-TR/WMH-CIDI Disorder† *Continued***

| | Healthcare | | | | | | | | | | Nonhealthcare | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mental health specialty | | | | | | | | | | | | | | | |
| | Psychiatrist | | Nonpsychiatrist‡ | | Any | | General Medical§ | | Any | | Human Services⊠ | | Self-Help¶ | | Any Service Use | |
| | % | (SE) | % | (SE) | % | (SE) | % | (SE) | % | (SE) | % | (SE) | % | (SE) | % | (SE) |
| IV. Substance disorders | | | | | | | | | | | | | | | | |
| Alcohol abuse | – | – | 41.2 | (10.3) | 36.5 | (6.4) | 5.5 | (3.3) | 27.4 | (5.5) | – | – | – | – | 29.1 | (5.2) |
| Alcohol dependence | – | – | – | – | 39.1 | (7.8) | – | – | 31.9 | (6.9) | – | – | – | – | 37.4 | (6.4) |
| Drug abuse | – | – | – | – | 28.9 | (7.7) | – | – | 22.6 | (5.8) | – | – | – | – | 28.2 | (5.3) |
| Drug dependence | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Any substance disorder | – | – | 37.3 | (6.5) | 34.9 | (4.5) | 5.3 | (2.9) | 26.1 | (3.7) | – | – | – | – | 28.6 | (3.8) |
| V. Composite | | | | | | | | | | | | | | | | |
| Any mental disorder | 44.5 | (5.3) | 46.5 | (3.3) | 48.3 | (3.4) | 12.7 | (1.6) | 33.4 | (2.2) | 16.9 | (2.5) | 16.7 | (5.1) | 32.7 | (1.9) |
| (*n*) †† | 177 | | 208 | | 294 | | 329 | | 504 | | 117 | | 53 | | 565 | |

†Missing cell entries indicate that the number of patients with the disorder who were treated in the sector was less than 30, in which case no estimate was made.

‡Nonpsychiatrist defined as psychologists or other nonpsychiatrist mental health professional, social worker, or counselor in any setting other than a mental health specialty setting. Use of a mental health hotline removed from the definition since it is not considered to be adequate treatment.

§General medical defined as primary care doctor, other general medical doctor, nurse, any other health professional not previously mentioned.

⊠Human services professional defined as religious or spiritual advisor, social worker, or counselor in any setting other than a specialty mental health setting.

¶Standard definition of complementary and alternative medicine reduced to self-help only because only self-help is considered adequate treatment.

**By definition, self-help is considered inadequate treatment for all disorders other than substance.

††Weighted number of respondents with a 12-month DSM-IV-TR/WMH-CIDI disorder seeking treatment in each service sector.

and avert long-term disabilities. Longitudinal studies can also help answer questions concerning the temporal relationships between disorders, such as which disorders are primary in patients with comorbidity (e.g., both mood and substance disorders) or how transitions can occur between disorders. Such studies are also critically needed to identify early signs and symptoms that predict the subsequent onset of disorders, which can, then, be used in future primary prevention efforts. Longitudinal studies are also critical to improve the adequacy of treatment. In the industrial quality sciences, repeated application of data collection using consistent methods is an integral part of continuous cycles of improvement (Berwick 1989). While analogous cycles of continuous quality improvement have been called for in health care, they have failed to take hold especially in the general population, in part, because of the lack of the requisite longitudinal data collection on which the process depends (Blumenthal 1995, Blumenthal and Kilo 1998). Examination of temporal trends between the original NCS and NCS-R have already shown lack of change in disorder prevalence (Kessler et al. 2005) and suicidality in the United States (Kessler et al. 2005), suggesting efforts and changes in the past decade have not been sufficient. Such comparisons between the original NCS and NCS-R provide evidence that longitudinal application of population-based psychiatric epidemiologic surveys hold great promise for identifying and reducing burdens as well as understanding and improving poor-quality care. Repeating population-based surveys using consistent methodology can serve as the nation's quality improvement and assurance system.

Additional research shedding light on the epidemiology of mental disorders in special populations needs to be undertaken. For example, greater enumeration of mental disorders in children and the identification of modifiable, early-life risk factors for the development of subsequent mental disorders in adulthood, are especially important areas. However, such research will require advances in the nosology of psychopathology in childhood and adolescence, the development of means to accurately combine information provided by children with responses from other informants, and the development of new methods to overcome the potentially long periods of observation needed before many disorders onset in prospective studies (Kessler 2000). Further psychiatric epidemiologic study of the elderly is also needed and would benefit from advances in obtaining accurate retrospective recall of aspects of mental disorders from earlier decades, especially under circumstances of potentially diminished cognition.

In addition to these needs in descriptive epidemiology, there is a need to expand our knowledge from a clinical epidemiology perspective. Whereas community studies now use sophisticated sampling techniques and state-of-the-art assessment tools, many clinical studies of onset and course suffer from poor sampling schemes and psychometrically unproven measurement tools. For example, the majority of clinical studies rely on consecutive admissions rather than first-episode or even first-admission samples, introducing the potential for bias by chronically ill users of service (Cohen and Cohen 1984). Thus, conditions such as nonaffective acute remitting psychosis, found in patients in the first-contact study of the World Health Organization, have gone unnoticed in clinical research conducted in the United States (Susser and Wanderling 1994). Identifying samples at the time of their first episode of disorder is crucial for understanding such basic issues as the course of alcohol abuse or the course of major depression, and the risk factors associated with better or worse prognosis.

Such future clinical epidemiologic research will require new methodologic advances on several fronts. For example, Fennig et al. (Fennig et al. 1994) have shown that the initial diagnosis in a first-admission psychotic sample is difficult to determine (primarily because of substance abuse comorbidity) and can change over time. Such diagnostic instability causes first-admission samples selected on the basis of a cross-sectional diagnosis to contain false-positives and exclude potential false-negatives. The false-positives are not a major problem because individuals later discovered to have a different disorder can be dropped from a study. The false-negatives are a greater impediment because they will have been excluded from the sample even though their symptom pattern might evolve into the disorder. Longitudinal approaches to diagnosis will need to be implemented, as was done in the study by Tohen et al. (Tohen et al. 1990, 1992) of outcome in mania.

Understanding the treatment needs of individuals in the general population who are found to have diagnosable mental disorders and characterizing the treatment experiences of the chronically mentally ill should also remain a high priority. While earlier surveys have revealed enormous unmet needs for treatment, information on the pathways into and through formal and nontraditional sources of care, and the extent to which individuals with mental disorders take steps on these pathways is very limited. Mental health services research will need to identify actionable barriers that prevent access to care. Because effective treatment also requires adequate treatment intensity and duration, investigators will need to understand and improve adherence to treatments that are initiated. With growing constraints on health care resources and the rising popularity of certain psychotropic medications, research on inappropriate use, overuse, and the cost-effectiveness of treatments is certain to increase in importance in the future as well.

Most psychiatric epidemiological studies of risk factors have investigated psychosocial and demographic risk factors and failed to consider potential familial and biological variables. Progress has been made to integrate familial variables, although the sources of information on familial mental disorders have often been meager and inadequate. Meanwhile, biological research has often relied on small, clinically diagnosed samples. It seems timely to consider the complex interplay between psychosocial and biological variables and better integrate the two types of risk factors' research under a single umbrella.

Psychiatric epidemiologists strive to identify the causes of mental disorders with the ultimate goal of designing and targeting the application of interventions for primary and secondary disease prevention. Interventions suggested by the results covered in this chapter include those to increase access and initiation of treatments, such as renewed community awareness and screening programs, new means for financing mental health services, and expansion of treatment resources for underserved areas (Jacobs 1995, Hirschfeld et al. 1997, Mechanic and McAlpine 1999, Kessler et al.

2001a, Bender 2002, Rost et al. 2002). Future interventions also clearly need to focus on improving the intensity and effectiveness of care that is given to patients with mental disorders. A related challenge is understanding why non–health care treatments such as CAM have such great appeal and whether legitimate aspects of this appeal (e.g., greater patient-centeredness) can be adopted in evidence-based treatments. Proven disease management programs that enhance treatment adequacy and adherence (Katon et al. 1995, Wells et al. 2000, Schoenbaum et al. 2001, Simon et al. 2001, Katon et al. 2002) as well as establishing performance standards hold promise for enhancing treatments and monitoring the impacts of interventions in the future (Substance Abuse and Mental Health Services Administration 1996, National Committee for Quality Assurance 1997). However, increasing uptake of such successful programs and treatment models will almost certainly require addressing existing barriers, such as competing clinical demands and distorted incentives for effectively treating mental disorders, as well as providing purchasers with metrics to help them understand what their return-on-investment (ROI) will be for improving mental health service use in America (Klinkman 1997, Williams 1998, Williams et al. 1999, Frank et al. 2003, Pincus et al. 2003, Wang et al. 2003).

A final way in which psychiatric epidemiology can become a uniquely powerful tool is when data from the United States are pooled, supplemented, and compared with comparable data from other countries. Policy makers need specific designs they can implement to achieve their goals. Some techniques employed in managed care systems (e.g., gatekeeping, increased cost-sharing, utilization review, prior approval, etc.) could presumably be brought to bear on unnecessary use but not underuse—in fact, they may worsen unmet needs for treatment. The impacts of other policies, delivery system features, and means of financing that policy makers could implement, are essentially unknown (Burgess et al. 2004). For these reasons, collection of detailed data on the mental health policies, delivery system features, and means of financing mental health care in different countries is a promising area for future research (Saxena et al. 2003). When merged with psychiatric epidemiologic data on mental disorders and treatments, such combined data could shed light on the impacts of policies, delivery system, and financing features, and help policy makers choose ones that achieve their desired goals (Mezzich 2003). These are but a few of the many contributions from psychiatric epidemiology that will be needed to achieve the laudable goals set forth in the recent President's New Freedom Commission for alleviating the tremendous burden from mental disorders (President's New Freedom Commission on Mental Health).

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CHAPTER

# 26 Cognitive Psychology

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## Introduction

Cognitive psychology and more recently cognitive neuroscience are among the dominant models people use to view themselves, in both health and illness. News media constantly publicize evidence of neural bases for the processes that make us human, such as memory, emotion, and self-regulation. Similarly, the public increasingly considers psychiatric illness through the lens of cognitive and neural dysregulation, and patients themselves use the language of neuroscience and cognitive psychology to describe their symptoms as rooted in brain disruption and problematic ways of thinking (Luhrmann 2001). Finally, treatment options employed by psychologists and psychiatrists have changed drastically with the application of cognitive models. Cognitive behavioral therapy has proven to be as efficacious in the treatment of depressive symptoms and more efficacious in preventing relapse than pharmacological treatments (Beck 1976, David 2004, Hollon et al. 2006). Currently, there is an increasing emphasis on assessing the effect of pharmacological interventions on the cognitive processes believed to underlie daily functioning in people with debilitating psychiatric disorders such as schizophrenia (Green 2007).

This chapter will provide an outline of basic cognitive processes and the brain structures responsible for them. For each core process described here, we will provide examples of psychiatric conditions that involve disruption of that process as well as a brief consideration of treatment implications. Given the constraints of a single chapter, our description of core processes and their relevance to disorders and their treatment is necessarily selective. We begin with a brief history of the origins of modern cognitive psychology and then discuss the rationale for viewing cognition as a set of modular, yet connected, functional information-processing steps rooted in the brain.

## Historical Review of the Cognitive Framework

Although the empirical and theoretical study of cognition dates back over a century (Ebbinghaus 1885/1964, James 1904), our modern view of cognition is far more recent. For almost the first half of the twentieth century, *cognition*—the internal processes that occur between an organism's exposure to a stimulus and its response—was largely ignored in favor of observable behavior. In fact, cognition was often viewed as epiphenomenal, a side effect of the relationship between stimuli and responses, which in itself had little impact or consequence. Two major trends sparked the rebirth of cognition as a topic of central interest in psychology. The first was the inability of behaviorism to describe language production, which demonstrated complexities greater than would be expected by stimulus–response relationships (Chomsky 1959). The second was the appearance of a compelling model to replace behaviorism: the analogy of the human mind to a computer.

### The Mind–Computer Analogy

Computer technology developed at an incredible rate beginning in the late 1940s and captured the attention of the general public and psychologists alike. As championed by Newell and Simon (1972), among others, comparisons between human cognitive functioning and computers advanced the understanding of cognition in at least two significant ways. The first is that both the human minds and the computers operate through *information processing*: the storage, manipulation, and transformation of information. These steps were ignored in behaviorism, but application of the computer analogy suggested that they could be studied empirically. The analogy was especially apt for conceptualizing such processes as the storage and retrieval of information from memory, the allocation of attention, and problem solving.

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The second advancement in the understanding of cognition brought about by the mind–computer analogy was the conceptualization of cognition at multiple *levels of analysis*, from the concrete and materialistic to the more abstract. For example, a computer can be understood in terms of its hardware—the physical *structures* through which information passes, which constrain the processing steps available to it—or in terms of its software—the *functions* it is programmed to use to manipulate information. These two levels of analysis interact with and depend on each other for a complete understanding of a computer's processes. Similarly, cognitive processes can be described as the communication between populations of neurons, or as the transformation of information. Both of these levels of analysis are *modular* or comprised of multiple, separable components (Fodor 1983). A cognitive psychologist describing long-term memory will appeal to multiple steps necessary for encoding, some of which are independent of each other. A functional neuroanatomist would similarly describe multiple brain regions involved in memory, also in some cases working independently. Cognitive and neural levels of analysis levels can be fruitfully applied to the same cognitive phenomenon and can often provide a more complete view of it when considered simultaneously (Marr 1982).

### Contributions of Cognitive Neuroscience

While early cognitive psychology was often divorced from consideration of the structure or function of the brain (Neisser 1967), this is no longer the case. Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow researchers to observe the functioning of the living human brain. PET allows examination of neuronal activity in terms of localized changes in blood flow, and fMRI does so in terms of changes in blood oxygenation. Electrical signals measured outside the skull by electroencephalograms (EEG) and related techniques allow for much more specific analysis of the time course of activation the brain, at the expense of precise spatial localization. More than simply allowing another level of analysis, imaging technology has often provided clarifications about the borders between modular processes. These advances enable psychologists to determine whether particular cognitive processes are unified or distinct, when behavioral studies alone could not draw such distinctions. For example, neuroimaging studies provided critical data, suggesting that visual imagery is functionally similar to actual vision (Kosslyn and Thompson 2003) and that implicit and explicit memories are distinct (Schacter 1992, Schacter et al. 1996). Since consideration of both the functional and structural levels of analysis provides a more complete understanding of cognition, we will describe core cognitive processes in terms of their information-processing roles and the brain regions involved.

### Influences of Cognitive Psychology on Treatment for Psychiatric Illness

It is worth noting at the outset that treatment and therapies for various illnesses described below have often been informed by knowledge from cognitive psychology. The cognitive revolution in psychology co-occurred with an analogous shift in clinical and psychiatric practice: a dominant use of behavioral therapy gave way to cognitive behavioral therapy (for a review of this shift, see David 2004), which emphasizes correcting biases in attention, executive function, and memory. Various forms of cognitive-behavioral therapy (CBT) have become extremely popular and proven to be effective for the treatment of depression, anxiety, eating disorders, and personality disorders such as borderline personality disorder. CBT is also currently being applied with considerable success to the treatment of schizophrenia (Beck and Rector 2005). Cognitive therapies involve putting insights about cognitive processes to use, by providing patients with knowledge about their own cognitive functioning and methods through which they can learn to change maladaptive cognition with practice. Examples of CBT approaches aiming to modify different types of maladaptive cognitive processes (e.g., attentional or interpretive biases) in the treatment of various psychiatric disorders will be discussed throughout this chapter.

While CBT is theoretically motivated by cognitive psychology, the potential for methods and findings from this field to inform diagnostic decisions and evaluation of treatment outcomes remains largely untapped. The profiles of illnesses in the DSM (DSM-IV-TR, American Psychiatric Association 2000) have a focus on symptomatic behaviors rather than on the cognitive symptoms that may underlie them. Just as our understanding of psychiatric illnesses can be improved by considering them at multiple levels of analysis, considering symptoms as patterns of distortion in one or several core cognitive processes may also further understanding of psychiatric disorders. Contemporary measures of cognitive function—examples of which will be briefly described in the chapter—could be used to create profiles of illnesses to aid in diagnosis and to point to potential avenues of remediation. Similar measures could also be used to specify the cognitive changes engendered by CBT, pharmaceutical, and other therapies (see Green 2007, for description of such an effort in the case of schizophrenia).

Finally, we have yet to apply much of the currently and potentially available information from neuroimaging to improve our understanding of cognitive dysfunction in illness. For example, preliminary neuroimaging studies (i.e., Goldapple et al. 2004) have found that CBT and pharmacological treatments cause similar improvement in depressive symptomatology but affect brain function in unique ways. The medications appeared to have their beneficial effect by remediating abnormalities in the function of subcortical brain regions. CBT affected cortical regions likely to be more susceptible to voluntary control, perhaps reflecting the conscious effort involved in enacting the learning strategies of CBT as well as its role in promoting the development of compensatory routes for effective information processing to replace those creating vulnerability to dysfunction. A major challenge to psychiatry in upcoming years will be to incorporate information about both cognitive and neural functions into diagnosis and treatment assessment (Kandel 1998).

## Overview of Core Cognitive Processes

The contents and processes of the mind were thought of as a "black box" by behaviorism: ineffable at best and uninteresting at worst. Now that many psychologists have spent their careers examining the contents and workings of behaviorism's "black box"—the mind—we can discuss each of

them in turn. We focus mainly on what are known as *higher-level cognitive processes* (attention, executive functioning, memory and mental representation, and social cognition), because much of the research on the cognitive bases of psychiatric difficulties has focused on these processes. However, we note that difficulties in *lower-level cognitive processes* such as the early stages of transforming sensory input into perceptions and the general speed of sensory information processing have been implicated in disorders involving pervasive cognitive difficulties. For example, schizophrenia appears to involve a core inability to gate or inhibit new information until current sensory information has been sufficiently processed, as well as a generally slower speed of information processing (Walker et al. 2004).

Throughout the chapter, we emphasize the integration of cognitive with emotional processes. Although once viewed as distinct phenomena having little to do with each other, a growing literature has made clear the fact that emotion interacts with and influences every facet of cognition in ways that are relevant for psychopathology. Emotional stimuli capture attention (Moray 1959, Nummenmaa et al. 2006), enhance memory (LaBar and Cabeza 2006), and affect decision making (Greene et al. 2001, McClure et al. 2004). Cognitive control efforts can be hijacked by emotion, and, through executive processes, emotion can be enhanced or diminished (Ochsner and Gross 2005, Ochsner et al. 2004b). As such, emotion may most efficiently be described as an overarching part of many cognitive processes, rather than its own modular component process.

## Attention

### Attentional Filters and Attentional Capture

The brain is constructed to carry out many functions in parallel. Yet, there is a limit to the amount of sensory information it can meaningfully process, and so conscious processing must often work in serial (Sternberg 1966). Given that our resources are inadequate for processing everything in the environment, we use *attentional filters* to select which stimuli to focus on (Broadbent 1958, Treisman 1969). Research on attention has emphasized three facets of selective attention: an *alerting system* that can be harnessed to achieve and maintain sensitivity to certain incoming stimuli, an *orienting system* involved in the selection of information from sensory input, and an *executive system* that monitors and resolves conflict among thoughts, feelings, and responses to help ensure attention to selected stimuli. Evidence supporting attentional filters comes primarily from studies in which participants are presented with competing stimuli and asked to attend to only one of multiple channels (e.g., auditory or visual; Neisser and Becklen 1975). During such tasks, participants fail to encode information coming from the unattended channel. Under certain conditions, most participants will ignore even striking visual information, such as a gorilla walking through a hallway (Simons and Chabris 1999).

Yet unattended information is not lost to awareness and can still have an impact on behavior. For example, when people are asked to make lexical decisions about whether an attended homonym belongs to a category (e.g., deciding if "bear" is an animal), their performance is facilitated by unattended category-relevant cues (e.g., "hibernate") and inhibited by irrelevant cues (e.g., "naked," which suggests an alternate meaning of the homonym; see Johnston and Wilson 1980). Furthermore, salient or distinctive unattended stimuli have a particularly strong effect on perceptual tasks and are easy to find regardless of the number of distractors present (Shiffrin and Gardner 1972), suggesting that they "*capture*" attention even when being willfully ignored (Remington et al. 1992, Yantis and Hillstrom 1994).

How can nonattended, willfully ignored cues affect behavior? One theory is that during many tasks investigating attentional capture, salient distractors are presented repeatedly, causing participants to expect them. This expectancy may create a bias toward perceiving unattended stimuli and cause subjects to regularly switch their attention from attended to unattended-but-expected stimuli (Simons 2000). The fact that expected stimuli are particularly likely to capture attention is relevant to the attentional biases shown by people with anxiety disorders and depression (discussed below).

### Neural Basis of Attention

Neuroimaging studies of attention in healthy humans have focused primarily on demonstrating that engagement of the sensory cortex in processing stimuli is attention dependent (see Figure 26–1 and Table 26–1): that is, even the most basic perceptual experience (e.g., visual processing) can be amplified or diminished by the presence or absence of attention. These studies show that attention modulates neural activity in the sensory cortices related to vision (McMains and Somers 2004, Somers et al. 1999), audition (Jancke et al. 1999), touch (Johansen-Berg et al. 2000), and pain (Bantick et al. 2002). Furthermore, both attention and enhancement of basic sensory activity increase later explicit and implicit memory for stimuli (Vuilleumier et al. 2005). However, a true understanding of the effects of attention requires a theory about the cognitive and neural mechanisms that cause attention to be directed toward goal-relevant stimuli. For example, emotional or self-relevant information tends to capture attention (Moray 1959), and neuroimaging studies have demonstrated that fear-related stimuli can trigger affect-related activity in the brain even when presented preattentively and masked by nonemotional stimuli (Whalen et al. 1998, 2004).

### Attentional Difficulties in Psychiatric Disorders

Attentional difficulties have been examined in two ways. First, *basic problems in the alerting, orienting, or executive control systems* have been identified in a variety of disorders (see Posner and Rothbart 2007). For example, difficulties in the alerting system have been found in normal aging and in attention-deficit disorder. People with autism show a dampening in the orienting system relative to normal control subjects for both social and nonsocial stimuli. People with schizophrenia and Alzheimer's disorder show difficulties in maintaining attention on particular stimuli in the presence of distractor stimuli, potentially helping explain their difficulties in staying on track in conversations and the tasks of daily life.

Second, specific types of *biases in attention* have been identified (see Mathews and MacLeod 2005, for a recent review). Such biases are to be expected, given basic evidence that the allocation of attention to particular types of stimuli is influenced by their importance to the individual (i.e., expectancies for particular stimuli to be of consequence

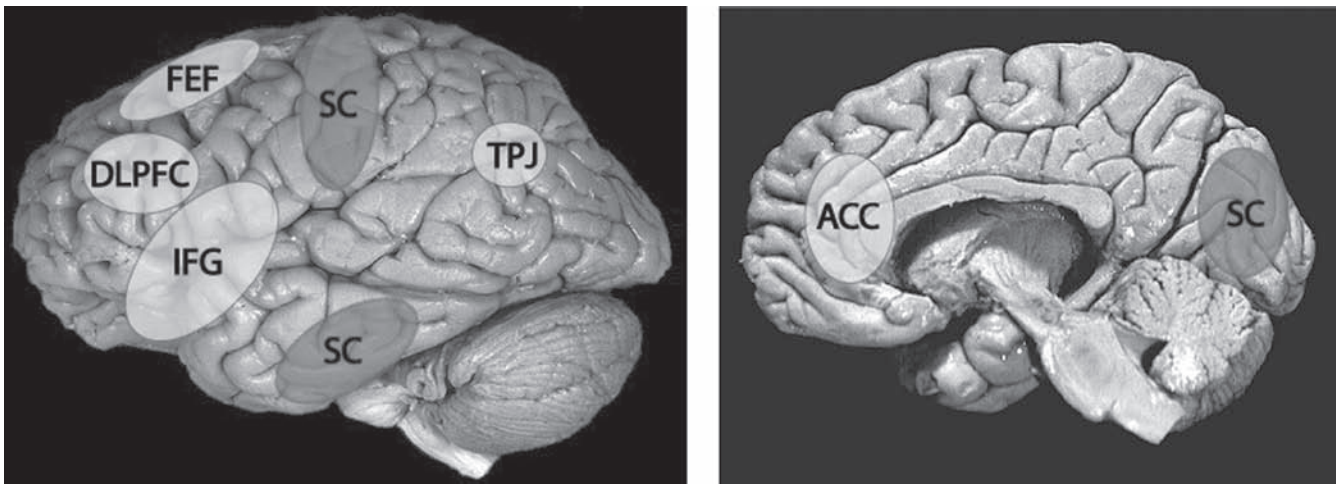



**Figure 26–1** *Some of the brain regions and cognitive processes involved in attentional deployment and executive function. Darkly labeled regions are targeted by lightly labeled ones, according to the theory of Miller and Cohen (2001), as well as others. Note that regions that are not shown would not be visible from the surface because they are located subcortically. FEF, frontal eye fields; TPJ, temporal parietal junction; IFG, inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; SC, sensory cortices. (See Color Plate VIII)*

for the self, developed through the individual's cognitive-social learning history) and by current mood states. For example, when dispositional and contextual factors increase the extent to which an individual expects negative outcomes (e.g., harm, social rejection, and failure), he/she becomes more susceptible to attentional capture by cues consistent with those negative expectations, with implications for mood, thought patterns (e.g., rumination), and memory. Furthermore, the fact that attentional capture can occur outside of conscious awareness implies that vulnerability to this phenomenon is not entirely under the individual's control. For example, recovering addicts exposed to people, places, or things associated with the object of their addiction may have their attention captured by cues that trigger relapse behavior, despite their best intentions.

The association between anxiety and attentional disruption by threat stimuli is well established by evidence from several experimental paradigms. In tasks that make conflicting demands on attention (e.g., the *Stroop task*, which is described in more detail below), research has demonstrated attentional draw by threat-related stimuli in social anxiety (Grant and Beck 2006, Spector et al. 2003) and generalized anxiety (Taghavi et al. 2003). To further determine the nature and time course of attentional disruption by various kinds of stimuli (e.g., words or pictures with threatening, neutral, or pleasant content), researchers have employed variations of *dot-probe* and *exogenous cueing* tasks that assess attention by measuring how quickly the individual responds to a visual cue that appears in the location of the stimulus versus another location. Studies have demonstrated that stimuli relevant to threats of potential rejection have a disruptive effect on attention for people high in rejection sensitivity and insecure attachment (Berenson et al. 2007, Dewitte et al. 2007), social anxiety and clinical social phobia (Garner et al. 2006, Mogg et al. 2004b, Musa et al. 2003), posttraumatic stress disorder in abused children (Pine et al. 2005), and generalized anxiety disorder (Bradley et al. 1999). The fact that the attentional bias associated with anxiety occurs even during masked exposures to threat stimuli suggests that it is immediate and relatively automatic

**Table 26–1 Brain Regions Involved in Attentional Deployment and Executive Function**

| Region | Function | Conditions in Which Disrupted |
|---|---|---|
| | **Alerting** | |
| Locus coeruleus (not shown) | Maintaining arousal necessary for alerting | Normal aging |
| Right lateral frontal cortex | "Tuning" alerting toward relevant stimuli | Attention deficit disorder |
| | **Orienting** | |
| Frontal eye fields (FEF) | Guiding and maintaining visual attention | Autism |
| Temporal parietal junction (TPJ) | Orienting toward unexpected or novel stimuli | Schizophrenia |
| | **Executive control** | |
| Inferior frontal gyrus (IFG) | Maintaining information in working memory | Alzheimer's dementia |
| Dorsolateral prefrontal cortex (DLPFC) | Manipulating information in working memory, modulating sensory processing | Schizophrenia<br>Addictions |
| Anterior cingulate cortex (ACC) | Error monitoring, recruiting DLPFC to manipulate information | Borderline personality disorder<br>Antisocial personality disorder |
| Sensory cortices (SC) | Sensory processing modulated by DLPFC as a function of salience | |

(Mathews and MacLeod 2005). Studies have further begun to show that attentional disruption by threat stimuli may involve the tendency to immediately orient attention toward threat, as well as maintaining either (1) a vigilant pattern of delayed disengagement of attention from the threat stimulus or (2) a vigilant-avoidant pattern of quick disengagement from it (Garner et al. 2006, see also Koster et al. 2006).

Depression has also been associated with distinct attentional biases. Relative to the immediate bias associated with anxiety, the attentional bias associated with depression appears to occur at a later stage, suggesting the involvement of more strategic processes (Mathews and MacLeod 2005). Compared to nondysphoric individuals, those with major depression show delayed disengagement of attention from negative stimuli (Koster et al. 2005, Leyman et al. 2007). Individuals with current and/or remitted depression also attend to depressogenic stimuli such as negative words and sad faces more than to happy stimuli (e.g., Gotlib et al. 2004, Joormann and Gotlib 2007, Ladouceur et al. 2006). Some evidence suggests that the pattern of focusing attention on negative versus positive stimuli may predate the development of depression in individuals at high familial risk (Joormann et al. 2007) and may also persist after remission (Paelecke-Habermann et al. 2005). In another study, the persistence of attentional bias for sad faces after current depressive symptoms were controlled was predicted by chronic "ruminative brooding" (Joormann et al. 2006).

### *Implications for Therapeutic Intervention*

An intervention targeting attention is usually basic to all cognitive therapy exercises and techniques: that is, individuals are taught to monitor specific thoughts, feelings, and behaviors relevant to the symptoms targeted for change and to keep structured records of these processes. By learning to do this, individuals not only attend to and become more aware of the cognitive and situational antecedents of problematic behaviors, but are also forced to take notice of the positive (or less negative) aspects of their lives, such as when negative expectations and beliefs are disconfirmed, a feared situation is tolerated without catastrophe, a pleasant activity succeeds in temporarily improving mood, or an urge to engage in self-defeating behavior is successfully resisted. Attentional biases often lead individuals to overlook these positive developments, so they miss out on these reasons for hope and opportunities to learn from success. An important feature of the detailed monitoring and record-keeping characteristic of cognitive therapy is to help increase access to overlooked information so as to counteract attentional biases and, in the case of psychotic disorders, provide evidence for use in reality testing. Cognitively trained psychologists have also begun to develop computerized exercises that aim to reduce negative attentional biases, through repetitive practice attending to positive stimuli (Dandeneau and Baldwin 2004). Future interventions for attentional biases are likely to increasingly involve computerized cognitive remediation tasks like these.

## Top-Down Control of Attention and Executive Functions

Theories of attention tell us about the processes involved in extracting discrete meaning from a wild abundance of sensory information. However, the ability to filter out competing stimuli by their perceptual differences from targets by itself is not enough by itself to facilitate goal-related behavior. As Desimone and Duncan (1995) put it: "an attentional system … would be of little use if it were entirely dominated by bottom-up biases" (p. 199). Of particular interest to psychopathology and therapeutic intervention is an understanding of how "top-down", controlled processes work to guide attention toward goal-relevant stimuli. The study of *working memory* and *executive function* has explored how the brain transforms goals into adaptive deployment of attention, memory encoding, and inhibition of nonrelevant stimuli. These processes are highly relevant to many psychiatric disorders, which often include failures to inhibit irrelevant thoughts and percepts, or difficulties staying "on task."

The term "*top-down*" or "*controlled*" processing refers to cognition that meets the following four criteria: it is relatively *slow* compared to automatic processing; it is *effortful* and susceptible to interference from competing tasks; it occurs in a *serial*, as opposed to parallel, fashion; and it is *flexible*, being easily adjusted to meet current goals. Perhaps predictably, "bottom-up" or "automatic" processing is considered to be any type of cognition that meets the opposite criteria. Many dual process models have explored the distinction between these types of processing (Chaiken and Trope 1999, Wegner and Bargh 1998), but in order to understand how these models apply to directing attention, we can use an example dating back to the first half of the twentieth century.

Perhaps the single most famous example of the need for top-down control over attention comes from the Stroop task, invented over 70 years ago and named after its originator (Stroop 1935). The task requires participants to read a list of color names aloud as quickly as possible. In one condition, each word is printed in the color congruent with its name (i.e., "red" is printed in red). In another, words are printed in incongruous colors (i.e., "red" is printed in blue). Participants must sometimes read the word in print, and other times must indicate the color the ink use to print the word. This task requires participants to use multiple top-down control processes, many of which are also needed when trying to solve problems, to study for examinations, or even to control emotional responses (see below). These processes can be broadly split into two categories: (1) maintenance and manipulation of relevant information. (2) controlling attention and responses based on this information. In the following sections, we will discuss each of these processes, drawing on the classic example of the Stroop task to illustrate them.

### Executive Control of Attention and Working Memory

(1) *Maintenance and manipulation of relevant information in working memory*. Before a participant in the Stroop task begins reading words or colors, he/she must actively have in mind—in *working memory*—the correct type of information to focus on (i.e., "words" or "colors"). The distinction between active, short-term retention of information and long-term storage has been recognized for over a century. Current models describe short-term or working memory as a set of processes for storing and manipulating a limited amount of information needed to accomplish a goal (Baddeley 1992, 2003, Baddeley and Hitch 1974). Working memory includes three modules mediated by activity of the prefrontal and parietal cortices: two modules that store and

maintain spatial and verbal information, and a third module, the central executive. Current theory and evidence indicate that the central executive interacts with other executive functions to select, maintain, and manipulate goal-relevant information in the other two modules and that these processes occur in the prefrontal cortex (Braver and Bongiolatti 2002, Braver and Ruge 2006, Smith and Jonides 1999). Specific executive processes include allocating to, updating, and manipulating information stored in the buffers, as well as protecting their contents from interference and maintaining temporal coding. Studies of single neurons in monkeys and neuroimaging in humans both show that the inferior frontal cortex remains active in the interval between a subject learning information and the subject using that information in a response (Cohen et al. 1997, Funahashi et al. 1989). An individual's ability to hold in mind the correct set of information to respond to during the Stroop task thus depends on these processes of working memory.

(2) *Executive function in controlling attention and selecting responses*. Once relevant information is selected and maintained by working memory, how does a Stroop task participant ensure that this information assists in quick and accurate responses? A major theory proposed by Miller and Cohen (2001) suggests that the prefrontal cortex is again centrally involved and that it works to strengthen connections between relevant stimulus features and responses. For example, during incongruent trials on the Stroop task, a participant may see the word "red," printed in green, and have to read the name of the color. In this situation, the color in which the word is printed and the word itself compete for the participant's attention and response. The conflict between possible responses is detected and monitored in the anterior cingulate cortex surrounding the corpus callosum (Botvinick et al. 2001, Bush et al. 2000, Carter et al. 1998), which then can recruit more executive control from the prefrontal cortex. The prefrontal cortex, in turn, biases perception of incoming information toward relevant cues (i.e., the shape and order of letters; see Miller and Cohen 2001). Recent evidence suggests that during visual search, this process is fundamentally sensory. That is, the prefrontal cortex actually intensifies brain activity in regions related to perceiving relevant visual cues, causing them to "pop out" more easily in attention (Egner and Hirsch 2005).

## Role of Inhibition in "Top-Down" Processing

### *Control of Prepotent Responses*

If top-down processing during the Stroop task biases attention toward the goal-relevant aspect of a stimulus (the letters and words themselves), what is the cognitive and neural fate of goal-irrelevant or distracting stimuli (in this case, the color that the words are printed in)? According to Miller and Cohen (2001), irrelevant stimuli are inhibited at multiple levels, allowing their effect on behavior to be minimized. This inhibition can be incidental: since irrelevant stimuli are unattended, they may be processed less strongly by the sensory cortex (see the "Attention" section above) and also produce less of an effect on memory (see the "Memory" section below). However, inhibition can also be active and effortful, as when people attempt to stop themselves from performing a "prepotent" or preferred response, such as naming the color a word is printed in, hitting the gas pedal when a light turns green, or (for some people) smoking a cigarette after dinner. Several lines of research have studied inhibition, finding that it is often quite successful and that it relies on the same top-down processing mechanisms—instantiated in the lateral prefrontal cortex—that underlie other aspects of executive function. Such studies have most often used "*Go–No-Go*" paradigms in which participants have to respond to most letters as quickly as possible and—if a certain letter appears—to stop themselves from responding. Such studies (and those using the related *stop signal task*) have found that the lateral frontal cortex is necessary for such inhibition (Aron et al. 2004, Aron and Poldrack 2006). Research on drug abuse has found impaired inhibitory performance in individuals who abuse cocaine, as well as abnormalities in activation of the anterior cingulate (also necessary for executive function) during inhibitory control tasks (Hester and Garavan 2004). Inhibitory control may also be affected in other psychiatric disorders such as schizophrenia (Barch 2005a).

### *Control of Memory and Emotion*

Other applications of executive control have particular clinical relevance. For example, frontally mediated executive control processes are recruited for the regulation of emotional responses. If instead of using words, a Stroop task is designed such that participants must ignore the negative or positive valence of a word in order to respond quickly, similar behavioral and neural effects predict their success at screening out such information (Compton et al. 2003, Etkin et al. 2006). Furthermore, the ability to "tune out" emotional information in such tasks (and the associated anterior cingulate and prefrontal activation) is impeded in posttraumatic stress disorder (Shin et al. 2001) and other anxiety disorders (Bishop et al. 2004).

Moving beyond reaction time differences in affective Stroop tasks, prefrontal executive processes are also involved in consciously regulating emotional responses to affectively laden stimuli. The motivation to study such processes comes from a long-standing literature on emotional appraisal. Appraisal theory posits that bottom-up emotional responses to stimuli (such as autonomic arousal) are relatively undifferentiated and by themselves cannot create an entire emotional experience. Instead, some interpretation (or *appraisal*) is a necessary step in the experience of emotion. In support of this idea, empirical work has demonstrated that top-down appraisals of emotional stimuli are necessary to the experience of emotions (Lazarus 1991, Scherer et al. 2001) and can affect physiological responses to emotional stimuli (Pecchinenda 2001). Emotional appraisals can also affect interpretations of external or internal emotional cues, such as whether physiological arousal is experienced as elation or anger (Schachter and Singer 1962). Following general appraisal theory, a related literature has explored the effects and neurocognitive bases of "reappraisal," or top-down regulation of emotional responses. In a common paradigm, participants are asked to reappraise an emotional stimulus so that it will affect them less. Behavioral and psychophysiological studies have shown that, indeed, top-down reappraisal can affect emotional responses (Gross 1998, 2002, Lazarus and Alfert 1964, Richards and Gross 2000). More recent neuroimaging studies have shown that such reappraisal depends on brain systems quite similar to those involved in executive control (Beauregard et al. 2001,

Etkin et al. 2006, Ochsner et al. 2002, Ochsner and Gross 2005). While few studies have examined neural effects of reappraisal in clinical populations, at least one has shown dysregulated activity in response to "emotional labeling" in participants who had high-risk childhoods (Taylor et al. 2006). Failure to regulate emotional responses is central to many psychiatric disorders, and further studies are needed to explore whether these deficits are part of a more generalized dysregulation of executive or inhibitory function.

## Problems of Executive Functioning in Psychiatric Disorders

Effective executive functioning (alternatively termed self-regulation) can be viewed as involving the ability to activate and deploy psychological mechanisms that enable the inhibition of stimulus-driven, emotion-laden responses under stress in a flexible manner, taking into account the current situation's demands and one's long-term goals. Thus, to be considered effective, the executive or self-regulatory system involves self-regulation that is *flexible*, *strategic*, and *discriminative*. Importantly, deficiencies in the system can involve over- as well as undercontrol. A regulatory system involving overcontrol may contribute to the relatively inflexible strategy of avoiding exposure to social threat that characterizes social phobia or the reclusive behavior of some people with schizophrenia, for example. In contrast, undercontrol characterizes the impulsive behavior of people with borderline personality disorder, antisocial personality disorder, and other disorders involving approach/appetitive behavior (such as the manic phase of bipolar disorder and addictive disorders).

A number of different forms of difficulties have been studied in relation to various disorders. These include: (1) Difficulties *maintaining attentional control when processing conflicting stimuli*, often assessed in a basic visual discrimination task in which participants identify the direction of a target arrow that is surrounded by flanker arrows in the conflicting versus congruent direction (e.g., Posner et al. 2003). (2) Difficulties in *behavioral inhibition*, that is, in the ability to stop oneself from impulsively behaving in ways that have negative consequences. This ability is often assessed using the passive avoidance learning task, involving a Go/No-Go task in which study participants learn by trial and error to press a button when some stimuli appear and refrain from pressing it when other stimuli appear (Newman and Schmitt 1998). (3) Difficulties *flexibly adapting behavior to changes* in reward and punishment contingencies over time, an ability that requires both properly calibrated monitoring of these contingencies and the ability to use them to respond strategically. Difficulties in this area characterize many forms of maladaptive behavior, such as when someone persists with a behavior pattern long after its cost/benefit ratio has plummeted, or when someone fails to strategically pursue long-term goals because they too readily alter their course when minor setbacks or tempting distractions arise. The probabilistic reversal task (Hornak et al. 2004) taps the ability to adapt to new contingencies and extinguish prior response patterns as necessary.

These types of difficulties may reflect a basic failure of executive functioning or a vulnerability of otherwise adequate functioning to being overwhelmed under conditions of emotional arousal. In the case of most disorders, research to address this question has either not been undertaken or yielded inconclusive results.

### *Protective Role of Effective Executive Functioning*

Beyond its direct effects on specific psychiatric symptoms and disorders, executive functioning may have important effects on psychopathology as a moderator of the impact of other vulnerabilities. For example, the heightened vulnerability for certain forms of psychopathology associated with such risk factors as temperamentally high emotionality, exposure to adversity in early attachment relationships, chronic or traumatic stress, or conduct-disordered peer influences may be reduced or neutralized in individuals with sufficient executive capacity to optimally regulate emotion, resist impulsive decisions that would expose the self to further risks, and plan for the future.

Evidence for such a moderation effect of executive functioning has been found in people at risk of emotional and interpersonal difficulties because of heightened sensitivity to interpersonal rejection. This defensively motivated disposition encompasses a tendency to anxiously expect, readily perceive, and react intensely to cues of rejection and has been shown to increase vulnerability to interpersonal aggression, depression, substance use, social avoidance, and borderline personality symptomatology (Pietrzak et al. 2005). Effective executive functioning has been shown to either reduce or neutralize the vulnerabilities associated with rejection sensitivity in several studies. In one study, executive functioning was indexed by the amount of time a 4-year-old child spent waiting for a larger, preferred reward rather than opting for an immediately available smaller one (Ayduk et al. 2002). This delay ability reflects the competency to disengage attention from emotional information that typically induces a here-and-now mindset and to inhibit a dominant, prepotent response in favor of a less accessible, subdominant response that is more adaptive (see Mischel and Ayduk 2004 for review). When study participants were subsequently reassessed at the age of 28 years, rejection sensitivity was related to negative self-image, drug use, ineffective coping, and educational underachievement only among participants who had difficulty delaying gratification at the age of 4 years (Ayduk et al. 2000, Study 1). Recently, Ayduk et al. (in press) extended these findings to symptoms of borderline personality disorder.

In line with these findings, Judd (2005) has argued that neurocognitive impairment (either genetic or acquired) may represent a central factor determining whether children in abusive family environments develop borderline personality disorder, because such impairment would exacerbate the negative impact of insecure attachment on metacognitive processes involved in self-regulation. In a related vein, evidence suggests that high baseline IQ (which reflects a general cognitive ability including executive functioning) can help protect trauma-exposed individuals from developing posttraumatic stress disorder (Macklin et al. 1998, Silva et al. 2000). Executive functioning is likely to be a key moderator of the links between risk factors and other forms of psychopathology as well.

### *Implications for Therapeutic Intervention*

Several cognitive therapy interventions target problems in self-regulation. Monitoring of thoughts and feelings around

problematic impulsive behaviors such as occur in conduct disorder, substance abuse, or binge eating helps to identify modifiable triggers and increase the period of controlled cognitive processing preceding behaviors that might otherwise occur immediately upon impulse without thought of the consequences. In addition, mindfulness-based cognitive treatments have been developed to help individuals with such conditions as borderline personality disorder (Linehan 1993) and major depressive disorder (Segal et al. 2001) gain distance from their immediate feelings, thoughts, and urges. *Mindfulness* involves the ability to simply notice thoughts and feelings without feeling involved in them or compelled to act on them. Meditation exercises in which the individual practices maintaining control of their attention and shifting it away from self-defeating thoughts and urges constitute an important part of this approach, and there is evidence that meditation increases control over attention (Slagter et al. 2007).

Computerized attention training exercises have also been shown to increase executive control, as well as IQ and brain development in children (Rueda et al. 2005), and may have utility in cognitive treatment for impulsive behavior disorders. Attentional control training has also been employed in the treatment of schizophrenia, with the aim of reducing cognitive deficits and increasing resistance to distraction by both external and internal stimuli, although evidence for the effectiveness of this approach is still inconclusive (for example, see Hogarty et al. 2004, Pilling et al. 2002). Difficulties maintaining goal-relevant information in working memory have been posited to contribute to the pervasive lack of motivation that characterizes schizophrenia, but at the same time, such motivational deficits can impede both accurate assessment of cognitive functioning and effective engagement in cognitive remediation tasks for many individuals with this disorder (Barch 2005b).

## Memory and Representation

One of the most important cognitive abilities is the retention of information over time and the ability to retrieve information when it is necessary or appropriate. Memory is important both because it allows experiences from the past to be reinstated and relived and because it allows people to use concepts gained over time to categorize and understand events and solve problems (Jonides 1995). Disorders involving loss of memory, such as Alzheimer's and other forms of dementia, are both increasingly common and devastating in their costs to individuals, families, and society. Specific difficulties involving the organization and retrieval of memories are also being investigated in a variety of other disorders.

Memory can be broadly divided into "*explicit*" (or "declarative") memory—which can be described, such as recalling a recent birthday party or knowing the year the French revolution occurred—and "*implicit*" (or "nondeclarative") memory—which cannot be described but nonetheless affects future behavior and perception, for example a well-learned skill or a classically conditioned response. The formation, retrieval, and effects of each type of memory will be discussed in turn. In discussing memory generally, two points that will appear frequently are worth mentioning.

First, memory depends on representations, or the specific neural and cognitive states that correspond to an object or event in the world. These representations are not abstract but rather depend on and cause reinstantiation of sensory and motor states specific to that object or event. In other words, both behavioral and neuroimaging work increasingly suggest that thinking about or remembering a recent birthday party with friends involves literally "re-living" that experience, with much of its perceptual, cognitive, and emotional details intact (Barsalou et al. 2003, Pecher et al. 2004).

Second, the formation of long-term memories is at least partially dissociable from processes of attention and working memory (Cave and Squire 1992). Indeed, often implicit memory is gained in the absence of attention, as often occurs during the priming of behavior with apparently incidental cues (Gabrieli et al. 1993, Postle et al. 1996, Schacter and Buckner 1998). Yet the aspects of a representation that are attended to are more likely to be encoded in long-term memory. This suggests that long-term memory is partially independent of executive processes, attention, and working memory (again suggesting modularity of these processes) but, nonetheless, interacts with all of these functions in encoding specific details of events. Hence, attentional biases in psychiatric disorders could contribute to distortions of memory seen in patient populations.

### Explicit Memory

How do people remember their last birthday party, where they put their keys, or when they first rode a bicycle? While many people experience memory as working passively, like a camera recording and then replaying events, behavioral and neuroscientific research suggest that both *encoding* (the formation of memories) and *retrieval* are active processes. While a more active reconstruction is more adaptive than passive replaying of events in many ways, it also explains the retrieval of false memories, as caused by source misattribution and misinformation effects (Loftus and Hoffman 1989, Roediger and McDermott 1995).

#### *Encoding*

Several factors are known to affect the ways memories are encoded, and most of these have been studied by examining aspects of encoding that predict later success at retrieval. Three major findings in this area are especially worth mentioning: (1) attention. (2) level of processing. (3) the match between encoding and retrieval on variables such as processing level, context, and mood. We will discuss these processes in turn, along with the brain regions underlying them (see also Figure 26–2 and Table 26–2).

First, as mentioned above, *attention* is important to successful encoding, and information that is ignored is less likely to be well remembered. This effect is most often seen during divided attention tasks: when participants are asked to remember a list of words while concurrently performing a demanding task encoding success suffers (Craik et al. 1996). Furthermore, a key brain area commonly found to be active during encoding, the inferior frontal gyrus, is also central to working memory maintenance and is inhibited when participants encode information while performing a secondary task (Uncapher and Rugg 2005). The role of attention in encoding is intuitive to anyone who has ever forgotten where he/she placed their keys while thinking intently about something else. However, while attention is an important aspect of encoding, it is neither necessary nor sufficient for successful memory formation.

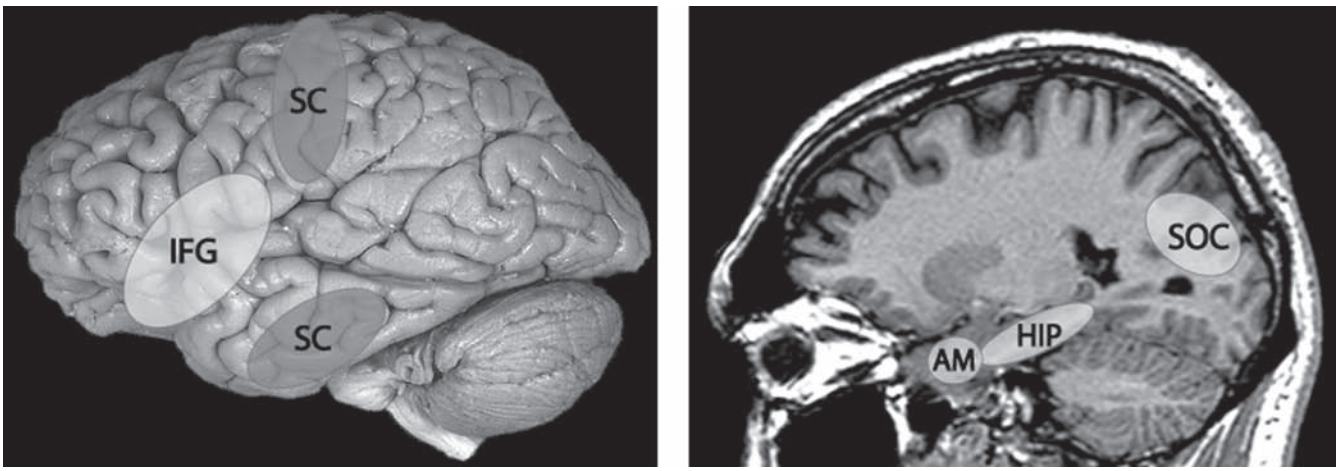



**Figure 26–2** *Some of the brain regions and cognitive processes involved in the encoding, binding, and retrieval of explicit and implicit memory. IFG, inferior frontal gyrus; HIP, hippocampus; AM, amygdala; SOC, superior occipital cortex. (See Color Plate VIII)*

It is not only attention but also the specific object of one's attention that predicts strong memory formation. That is, attending to meaningful information will serve memory more than attending to superficial information—a phenomenon known as *level of processing* (Craik and Lockhart 1972). In a classic demonstration of this effect, Craik and Tulving (1975) asked participants to make three types of decisions about a list of words: whether they were printed in upper or lower case letters (shallow encoding), whether they rhymed with another target word (intermediate encoding), or whether they belonged to a particular semantic category. Memory increased linearly as a function of the depth with which words were encoded. More recent work has shown that deep encoding of word lists activates the inferior frontal gyrus (Kapur et al. 1994), which predicts more successful encoding of both verbal and visuospatial information (Brewer et al. 1998, Wagner et al. 1998).

Finally, level of processing probably does not entirely explain successful retrieval because it does not take into account the level of processing at which an event must later be retrieved. For example, children studying for a national spelling bee may benefit more from intently studying the stems and silent letters in each word than by understanding their meanings. Memory in such cases is best served not by deep encoding, but by *encoding that matches* the level of retrieval needed for the task (Morris et al. 1977). Other related theories suggest that beyond the way that material is encoded, matching the internal and external contexts of encoding and retrieval also improves memory. For example, material learned underwater is better remembered when under water (Godden and Baddeley 1975), and material learned under the influence of marijuana is better remembered when also under the influence (but being under the influence worsens retrieval overall; Eich et al. 1975).

Matching of mood states at encoding and retrieval also improves recall. That is, events or stimuli encoded when in a positive or negative mood state are better retrieved under similar moods (Blaney 1986, Bower 1981). Speculation that this effect reflects the greater accessibility of mood-congruent memories when in a similar state is supported by neuroimaging data (Lewis and Critchley 2003, Lewis et al. 2005). Such accessibility effects are prevalent in psychiatric disorder, as for example in depressed individuals, who have a bias toward recalling negatively valenced experiences (Lloyd and Lishman 1975) and also show abnormal neural activity while recalling sad experiences (Elliott et al. 2002). Relating these biases to general memory and attention processes, we can speculate that they involve both a bias toward attending to negative cues during encoding and a heightened accessibility of negative memories due to negative mood at retrieval.

### *Binding and Retrieval*

Similar to encoding, explicit retrieval is an active process, involving reconstruction of the details and experiences accompanying a memory. (Because it is most relevant to clinical disorders, we will concentrate on the retrieval of *episodic memories*, explicit memories of specific past events.)

**Table 26–2 Brain Regions Involved in the Encoding, Binding, and Retrieval of Explicit and Implicit Memory**

| Region | Function | Conditions in Which Disrupted |
|---|---|---|
| Inferior frontal gyrus (IFG) | Encoding of explicit memory | Major depressive disorder |
| Hippocampus (HIP) | Encoding and binding explicit memories, reinstantiating original experience at retrieval | Posttraumatic stress disorder<br>Alzheimer's dementia |
| Amygdala (AM) | Enhanced encoding of arousing stimuli, implicit fear conditioning | |
| Superior occiptial cortex (SOC) | Deactivated in perceptual priming | |
| Sensory cortices | Re-activated during retrieval of explicit memory | |

Before a memory can be retrieved, however, it must be stored as a coherent representation by the brain. In other words, dissociated memories of candles, friends, kazoos, and fears of getting old are not enough to comprise a full memory of a past experience. These memories must instead be bound together, a process that occurs in the medial temporal lobe, in a structure called the hippocampus (Eldridge et al. 2000). During *binding*, the sensory, cognitive, and affective components and context of an experience (together known as the signature of a memory, or an "engram"; see Schacter 1997) are associated with each other. Importantly, these components are not stored as abstract concepts, but rather as *traces of the actual state experienced at encoding*. Thus, encoding a sound recruits brain regions involved in audition, and retrieval of that sound's memory reactivates part of that same sensory cortex; the same is true for visual memory (Wheeler et al. 2000). Similarly, brain areas related to taste become active when participants look at pictures of food (Simmonset al. 2005), and brain areas controlling motor function become engaged by looking at pictures of manipulable objects (Chao and Martin 2000).

These findings underscore the concept that retrieval of explicit memories depends on modality-specific representations (Martin and Chao 2001) and involves "reliving" sensory and motor aspects of past events. Later, recalling or being confronted with a single sensory component of an episode (a cue) can lead to *pattern completion*, in which related traces from the episode are retrieved and activated together, as a function of the hippocampus (McClelland et al. 1995). As such, a single cue can often bring back the rest of a memory automatically. This is especially relevant to individuals suffering from posttraumatic stress disorder, who experience *flashbulb memories* (or *flashbacks*) during which they are unable to stop a flood of sensory information related to their traumatic experiences.

### *Neural Mechanisms of Emotional Influences on Explicit Memory*

The hippocampus, the brain region most directly responsible for binding and (with the inferior frontal gyrus) episodic encoding, is part of the medial temporal lobe. Adjacent to it is the amygdala, a brain region classically associated with negative emotions and more recently with high arousal and the maintenance of vigilance under threat (Davis and Whalen 2001, LeDoux 2000). The close spatial proximity between these regions is reflected in the strong and prevalent effects that emotion and arousal can have on memory. For example, participants shown emotional pictures later remember only emotional details of those pictures, forgetting nonemotional details, and this effect is mediated by their level of physiological arousal upon encountering the emotional stimuli (Cahill et al. 1994). Arousal leads to improved memory under attentional load (Kensinger and Corkin 2004), and even in amnesia (Hamann et al. 1997), suggesting that emotional memories may take a "different route" to being encoded than nonemotional ones, one fundamentally dependent on the amygdala (Anderson and Phelps 2001, Sharot et al. 2004). Enhancement of memory for valenced but nonarousing events may be supported by connections between the amygdala and the hippocampus (LaBar and Cabeza 2006). Again, individuals with posttraumatic stress disorder demonstrate abnormal activation of affect-related brain circuitry during symptom provocation (Rauch et al. 1996, Shin et al. 1997), suggesting neural mechanisms through which memories of trauma can come to dominate their mental lives.

## Implicit Memory

Implicit memory includes any processing of stimuli that cannot be recalled consciously but, nonetheless, affects behavior. Implicit memory is both behaviorally and neurally distinct from explicit memory, providing another example of the modularity of cognition. For example, individuals with a complete inability to encode explicit memories as a result of hippocampal damage can nonetheless learn skills (Corkin 2002), express preferences and cognitive dissonance reduction (Lieberman et al. 2001), and learn classically conditioned associations (Bechara et al. 1995).

### *Priming*

One of the most common examples of implicit memory is priming: the increased accessibility of a percept or concept after it is encountered, even without conscious awareness. For example, participants subliminally presented with words on a screen (e.g., "cat") will not be able to explicitly recall any of these words. However, when asked to complete a word stem including letters from a briefly presented word (e.g., "ca_"), they will most often complete it with the primed word instead of with other possibilities. This phenomenon is known as *perceptual priming*, because the perceptual features of a stimulus are made accessible through priming without awareness that the stimulus has been presented. *Conceptual priming*, a closely related effect, occurs when the semantic content and associates of a primed stimulus are made accessible. For example, after seeing the word "cat" subliminally, participants will be faster at making decisions about whether a cat is an animal than after being primed with unrelated words or with nonwords (for review, see Roediger 1990).

### *Social and Affective Priming*

Interestingly, priming can also affect social and emotional behavior and concept accessibility. For example, participants shown negative words subliminally will be faster at making judgments about other negative words (Murphy and Zajonc 1993). Similarly, participants completing word stems describing personality traits will be more likely to unwittingly ascribe those traits to someone who is described to them (Higgins et al. 1977) and to act in ways congruent with that trait (Bargh et al. 1996) A similar process can be seen as accounting for the phenomenon known as *transference* (e.g., Freud 1912/1963). That is, subtle cues from a therapist or another person in an individual's current environment can remind the individual of someone significant in his/her past and lead the mental representation of this previous other to become activated. When this happens, and it may do so without the individual even realizing it, information stored in the representation of the past other comes to influence the inferences, memories, emotions, motivations, and self-perceptions the person experiences in the present moment. Numerous studies of the transference process as defined in these cognitive terms have demonstrated profound effects of past others on our responses to new people in our lives (see Andersen and Chen 2002 for a review).

### Abnormalities of Memory in Psychiatric Disorders

Empirical studies over the last two decades have demonstrated significant deficits in recognition and recall among clinically and subclinically depressed individuals. Generally, memory performance is most consistently impaired for explicit (consciously directed) memory (e.g., Brand et al. 1992, Colby and Gotlib 1988, Danion et al. 1991, Elliott and Greene 1992, Sweeny et al. 1989, Watts and Sharrock 1987). With respect to implicit memory, the evidence of memory deficits in depression are inconsistent and may depend on the particular task used to assess it (Jenkins and McDowall 2001). However, the research does clearly demonstrate that a *mood-congruent memory bias* (see Matt et al. 1992 for a review) leads to more negativistic recall among individuals with depression, as is consistent with Beck's cognitive theory of the disorder (Beck 1976). Overall, relative to control subjects, individuals with depression or dysphoric mood display enhanced memory for negative autobiographical memories and experimentally presented stimuli, but they show poorer memory for positively toned memories and stimuli. In addition, both currently and formerly depressed individuals have difficulty retrieving specific memories of events from their own lives (Mackinger et al. 2000, Wessel et al. 2001). Such *overgeneral autobiographical memory* has also been associated with *depressive rumination* (e.g., Watkins and Teasdale 2001) and may well result from the depressed person's repeated analysis of current or past difficulties in an attempt to make sense of them.

Memory deficits and overgeneral autobiographical memories are also characteristic of individuals with posttraumatic stress disorder (McNally et al. 1995). On standard memory tests these individuals show *proactive interference*, an impairment in the ability to encode and retrieve new information (e.g., Bremner et al. 1993, Sutker et al. 1993). Moreover, similar to what occurs in individuals with depression, the severity of current posttraumatic stress symptoms biases the content of stimuli and personal memories that are recalled. In several studies, individuals with posttraumatic stress disorder, who were currently highly symptomatic, recalled having experienced a greater number of traumatic events that they had not mentioned during a prior interview (Southwick et al. 1997). This finding highlights that memories are not singular or permanent but reconstructed anew from encoded elements throughout the brain whenever they are recalled. Hence, memories are subject to change over time and influenced by current factors including current clinical state.

*Source misattribution* is another clinically relevant memory difficulty in which people are able to recall an event but identify its source incorrectly; they cannot always reliably distinguish events that happened to them from events they have imagined, dreamed about, or heard about as having happened to someone else. This phenomenon may potentially contribute to false memory, and highly suggestible people as well as those with vivid imaginations appear to be more susceptible to it. Source misattribution is beginning to be considered in relation to dissociative disorders and some personality disorders, including borderline, narcissistic, and histrionic. In addition, there has been speculation that hallucinations and delusions in schizophrenia may involve source misattribution: internally generated thoughts may be misattributed to external sources, moreover, physiological responses to expected threats may be misinterpreted as responses to threats present in external reality (Beck and Rector 2005).

Evidence is also emerging that people vulnerable to social threat may *organize* information differently in memory from more secure individuals. Specifically, when people judge the attributes of a person they know in a timed judgment task, low self-esteem leads negative or positive cues to heighten accessibility of similarly valenced attributes of the person, but this effect does not occur when people judge the attributes of inanimate objects (Graham and Clark 2006). The tendency to organize interpersonal knowledge in memory by valence may develop to facilitate processing of threat in individuals who have been sensitized to it, but as a result, any negativity on the part of a close other tends to trigger a cascade of negative, threat-consistent associations that erode relationship stability (Murray and Holmes 1994, 1999, Graham and Clark 2006). At its extreme, this pattern resembles the idealization/devaluation criterion of borderline personality disorder, sometimes referred to as splitting (Fairbairn 1954, Kernberg 1976). Berenson and Downey (2007) found preliminary evidence for this pattern in the timed interpersonal judgments made by a small sample of people with borderline personality disorder relative to healthy controls.

#### *Implications for Therapeutic Intervention*

The fact that memories are continually reconstructed speaks directly to the need for caution regarding the accuracy of events reported during treatment, including the controversy over recovered memories of early traumatic events. Although traumatic events do really happen, the nature of memory makes the veracity of any particular memory of such an event impossible to discern. Likewise, there is the real possibility that false memories could arise in the course of treatment, as recall continues to be shaped by current influences (McNally 2003). But beyond these cautions, the nature of memory suggests that it may be usefully targeted for intervention. Specifically, reprocessing of troubling experiences in a new context appears to be beneficial in a wide range of treatment modalities, including narrative therapies, and various CBTs for trauma involving exposure to memories, thoughts, and feelings about the traumatic event in a context of relative safety (Foa et al. 2000).

## Uniquely Social Cognition

Social cognition emerged as a field over the last 50 years, drawing upon theories and methods from both cognitive and social psychology (see also Chapter 27) to understand the ways that people form, maintain, and change their impressions of themselves and other people (for review, see Fiske and Taylor 1991). While many textbooks and reviews of cognitive psychology do not include discussions of social cognition, we feel it is worth doing so for two reasons. First, many psychiatric illnesses (such as autism, borderline personality disorder, antisocial personality disorder, and schizophrenia) are especially crippling in the social domain, affecting people's abilities to accurately judge and adaptively interact with others (Baron-Cohen 1994, Bateman and Fonagy 2004, Blair 2005). Second, recent research in cognitive neuroscience confirms that

social cognition recruits brain areas not engaged during nonsocial cognition, suggesting that it is a modular process incorporating unique information-processing steps (Mitchell 2006).

## The Uniqueness of Social Stimuli

Analyses of speech collected in natural settings demonstrate that over half of human conversation revolves around social topics (Dunbar 2004). Given the centrality of social stimuli, it makes sense that attention, memory, and other cognitive processes should have evolved to ably handle such information; however, this would not imply a necessity for unique mechanisms. After all, it is straightforward to assume that people attend to and remember others using the same processing steps and brain systems they would use to attend to and remember flashing checkerboards, or ferns, or player pianos. To be unique, social cognition must entail processes that differ qualitatively—in their cognitive and neural substrates—from those used for nonsocial stimuli, rather than being simply the application of generic cognitive processes to the social world.

One of the forces driving the recognition of social cognition as modular and dissociable from nonsocial cognition was the characterization of autism, a developmental illness that causes severe impairments in social cognition, often while sparing nonsocial cognitive abilities (especially in more mild forms of autism spectrum disorder; Baron-Cohen 1994). Autism also provides a picture of just how critical social cognition is to daily functioning: individuals with this disorder have severe problems understanding and behaving appropriately in social situations. Autism and related illnesses specifically affect the ability to see other people as *intentional agents*, with internal states such as thoughts, feelings, and goals, and it is in that one sense that people differ from all other stimuli. Indeed, most of us not only have the ability to perceive internal states, but also have a tendency to do so, even anthropomorphizing nonanimate objects when their movement could be construed as intentional (Heider and Simmel 1944). The tendency to perceive internal states is adaptive, because they are often the best predictor of behavior (Dennett 1987). Social cognition, which could be described as *how people make sense of others and themselves*, largely involves tuning into those internal states.

Recent neuroimaging studies provide the most convincing evidence that unique, modular processes underlie social cognition. In such studies, participants are asked to make judgments about the states or traits of either intentional agents such as people or nonintentional agents such as clothing, computers, or vegetables. Studies like these have revealed a set of brain regions, including the medial prefrontal cortex, posterior cingulate cortex, and superior temporal sulci, that are uniquely engaged in making inferences about intentional agents (Mitchell et al. 2002, 2005; see Figure 26–3 and Table 26–3). Furthermore, these brain areas are not engaged while thinking about people per se but rather respond selectively to imagining the internal mental or emotional states of intentional agents (Fletcher et al. 1995, Goel et al. 1995, Hynes et al. 2006, Ochsner et al. 2004a, Saxe and Kanwisher 2003), and even to the apparent intentional states of inanimate objects (Castelli et al. 2000). Finally, these brain regions are underactive in individuals with autism, both chronically and when attending to intentions (Castelli et al. 2002, Kennedy et al. 2006). Together, these data support a view of social cognition as modular and unique.

## Cognitive Processes in Social Interaction

Effective interaction with others in the real world requires a combination of social and nonsocial cognition. Perceivers must integrate many types of information to correctly identify the internal states of others and the correct ways to respond to these states. In order to accomplish this processing, many systems, including working memory, long-term memory, attention, emotion, and social cognition, are simultaneously necessary. Downey et al. (in press) described three factors that allow for successful social interactions: (1) empathy. (2) cognitive perspective taking. (3) motivation. We will briefly discuss each of these factors, because they may be uniquely affected in different psychiatric illnesses.

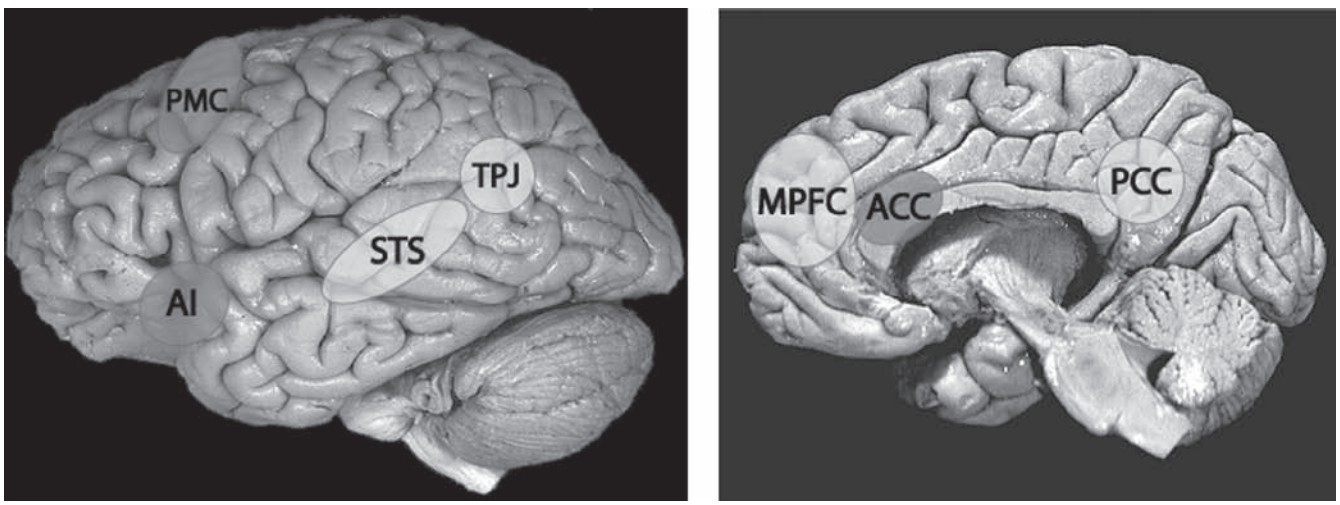



**Figure 26–3** *Some of the brain regions and cognitive processes involved in uniquely social cognition. Darkly labeled regions are predominantly involved in shared representations, lightly labeled ones are predominantly involved in cognitive attribution and perspective taking, though this is by no means a definitive division of labor. Note that the anterior insula, while presented on the surface of the cortex, is underneath the cortex. MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; TPJ, temporoparietal junction; STS, superior temporal sulcus; ACC, anterior cingulate cortex; AI, anterior insula; PMC, premotor cortex. (See Color Plate VIII)*

**Table 26–3 Brain Regions Involved in Uniquely Social Cognition**

| Region | Function | Conditions in Which Disrupted |
|---|---|---|
| Medial prefrontal cortex (MPFC) | Attributing states and traits to people (both self and other) | Antisocial personality disorder<br>Autism<br>Schizophrenia<br>Borderline personality disorder |
| Posterior cingulate cortex (PCC) | Attributing states and traits to people (both self and other) | |
| Temporoparietal junction (TPJ) | Judging mental states of others | |
| Superior temporal sulcus (STS) | Perceiving biological motion (i.e., eye gaze), and processing social significance of movement | |
| Anterior cingulate cortex (ACC) | Processing pain-related emotion for pain in both self and others | |
| Anterior insula (AI) | Processing pain and disgust in both self and others | |
| Premotor cortex (PMC) | Using motor representations to understand movements and intentions of others (mirror neurons) | |

(1) *Empathy*: It is difficult to watch someone get kicked in the shins without wincing, and this automatic reactivity to others has often been thought of as a precursor to empathy (Preston and de Waal 2002) and prosocial behavior (Batson et al. 2003). An often-cited factor in empathy that has been termed *shared representations* refers to a perceiver's tendency to "put themselves in the place" of someone else and as such simulate for themselves what that other person could be feeling (Gallese 2003, Smith 1790/2002). More recently, a neural mechanism for shared representations has been found in the domain of *motor cognition* (Blakemore and Decety 2001). That is, thinking of executing an action engages the motor regions of the brain involved in actually performing it (Decety et al. 1994, Jeannerod and Decety 1995), and observing or simulating the actions of other people engages similar motor regions (Ruby and Decety 2001). Such work dovetails with the discovery, in nonhuman primates, of *mirror neurons* that fire both when monkeys perform an action and when they see another monkey performing it and are often invoked as the source of shared representations (Rizzolatti and Craighero 2004, Rizzolatti et al. 1999, 2001).

There is evidence that shared representations accompany the perception not only of actions but also of other people's sensations, such as pain (Botvinick et al. 2005, Singer et al. 2004), disgust (Wicker et al. 2003), and touch (Keysers et al. 2004). Such studies have also demonstrated that brain regions responding to emotional experience (such as the anterior cingulate, anterior insula, and amygdala, see Figure 26–3) can be engaged by witnessing physical states and emotions in others (Carr et al. 2003, Decety and Jackson 2004, 2006). More evidence for such vicarious emotion underlying empathy has come from psychophysiological studies of observational fear learning, demonstrating that watching someone else receive shocks can create arousal and conditioned fear responses in an observer (Olsson and Phelps 2004). Such results have led to theories that social cognition and empathy consist mainly in these shared representations, which allow an observer to "translate" the bodily states of a social target into an experience they can share. However, there is little evidence that complex internal states could be understood by simple imitation; furthermore, the brain regions involved in simulating sensation and action are separate from those involved in perceiving intentional states. It is more likely that shared representations are one of a few important facets of cognition necessary for understanding others. The integration of empathy with more "top-down" social cognitive components described below may take place in association cortex, such as the medial and orbitofrontal cortex, which have been shown to be engaged during emotion recognition tasks (Vollm et al. 2006), and become functionally connected to the anterior cingulate and anterior insula when subjects watch others in pain (Zaki et al. 2007).

(2) *Cognitive perspective taking*: Perspective taking (also known as "*theory of mind*") is the ability to understand the point of view of another person, even when that point of view diverges from one's own. For example, the *false belief task* is a classic assessment of perspective taking in which participants are presented with the story of a character with a mistaken mental state and then asked to infer what the character's mistaken mental state is (e.g., "Sally places a ball inside toy box A, but while she turns her back Anne moves it to toy box B. Where will Sally look for the ball?"). Unlike shared representations, perspective taking does not occur automatically and requires effort and attention on the part of the perceiver. Indeed, when under attentional load, people often fail to make the correct inferences about other people's mental states (Gilbert et al. 1989). Working memory may also be critical to perspective taking in false belief tasks, because participants are required to maintain multiple perspectives in mind at once and inhibit their own knowledge while making inferences about others' false beliefs. Support for this idea comes from developmental work showing that theory of mind improves in parallel with the development of executive functions (Carlson and Moses 2001).

(3) *Motivation*: While motivation is not uniquely social, it is an important ingredient of successful social cognition and may be affected in disorders that include altered social information processing. For example, information that can be threatening to a close relationship is often actively ignored (Simpson et al. 1995), yet people high in the need to belong, or those who have just experienced rejection, instead prioritize the detection of potential threat in social cues (Pickett et al. 2004). Motivations may be important in explaining social-cognitive biases in various emotional disorders, such as heightened responsiveness to potential threat in anxious individuals, and dejected withdrawal among those who readily interpret social cues as confirmation of their negative self-image. Finally, because it is in the context of social bonds that essential social-cognitive skills are honed with corrective feedback and practice, a lack of social motivation that isolates people from emotionally trusting relationships (in autism, schizophrenia, or schizoid personality disorder, for example) may contribute to pervasive difficulties understanding and effectively interacting with others.

## Social Cognitive Difficulties in Psychiatric Disorders

### *Emotional Empathy in Psychopathy*

In a recent review of empathy, Blair (2005) argued that while autism is associated with deficits in cognitive perspective taking (see below), it is less consistently associated with abnormalities in empathic emotional responding. The opposite is true of psychopathy: while psychopathic individuals do not consistently demonstrate difficulty in *recognizing* the emotions of others (Kosson et al. 2002, Richell et al. 2003), they show an attenuation or absence in their *response* to others' emotions or pain. Abnormalities of emotional empathy in psychopathy have been demonstrated through multiple experimental paradigms, for example psychopathic individuals show a lack of vicarious conditioning toward pain in others (Aniskiewicz 1979). Furthermore, neuroimaging investigations of psychopathy indicate structural and functional deficits in both basic and social emotion processing that may underlie a lack of remorse for antisocial acts. For example, psychopathic individuals show a volumetric decrease in the orbitofrontal cortex, which is associated with the extent of their violent criminal behavior (Raine et al. 2000). In recent functional imaging investigations, psychopathic criminals showed less activation in the amygdala during an emotional memory task (Kiehl et al. 2001) and less activation in the extrastriate visual cortex when observing emotional facial expressions (Deeley et al. 2006). All of these findings suggest that psychopathy may involve a generalized lack of reactivity to affective stimuli, which manifests itself in part as a failure in emotional empathy (Kiehl 2006).

### *Perspective Taking and Motivation in Autism and Schizophrenia*

Human interactions require a continuously updated understanding of mental states, and indeed descriptions of mental states are central to a majority of conversation (Dunbar 2004). Profound difficulties understanding the mental states of others thus make individuals with autism cut off from and bewildered by a substantial part of the world around them (for a personal account of autism's impact on social functioning, see Grandin 1996). The last 20 years has seen an increase in the study of autism and its related social-cognitive impairments, using both cognitive and neuroimaging methodologies. The resulting work suggests that autism spectrum disorder may have multiple effects on the social-cognitive axes described above. For example, impairments of cognitive perspective taking in autism, which are well documented by routine failures on the false belief task described previously (Leslie 1994), map onto failures to activate related brain regions such as the medial prefrontal cortex (Baron-Cohen et al. 1999, Castelli et al. 2002, Happe et al. 1996). Individuals with autism have also been shown to have deficits in the mirror-neuron system associated with shared motor representations (Dapretto et al. 2006, Hadjikhani et al. 2005). Although it has been posited to be at the root of social-cognitive deficits in autism (Oberman and Ramachandran 2007), mirror system dysfunction has not been conclusively tied to difficulties in motor empathy or understanding intentions in others. However, there is evidence that individuals with autism have difficulties identifying emotional facial expressions and that this may be tied to the way in which they process facial information. For example, they do not attend to other people's eyes, a crucial social signal for nonautistic individuals (Pelphrey et al. 2002, Ristic et al. 2005). This abnormality in autism is shared by people with amygdala damage (Spezio et al. 2007a, 2007b), and there is emerging evidence that amygdala dysfunction may directly contribute to impaired deployment of attention to social cues in autism (Dalton et al. 2005). Thus, autism appears to involve both neural and cognitive abnormalities affecting multiple aspects of social cognition.

Difficulties of a social-cognitive nature have also been well documented in schizophrenia and are central predictors of social and vocational outcome among individuals with the disorder (e.g., Kee et al. 2003, Mueser et al. 1996). Some of the problems that arise for people with schizophrenia in social situations are related to their deficient regulation of attention, such that distracting thoughts intrude upon and disorganize their speech or leave few cognitive resources to spare for participating in conversation much at all (Melinder and Barch 2003). Nonspecific factors such as cognitive slowing and a pervasive lack of motivation may also contribute to social interaction difficulties (Barch 2005a). Yet other primary symptoms of schizophrenia can be conceptualized in explicitly social-cognitive terms. Delusions involve biased information processing in which percepts are overinterpreted as personally relevant and externally caused. In turn, hypervigilant attention to cues consistent with the delusion and poor self-correction of erroneous interpretations lead delusional ideas to be maintained and intensified over time (Beck and Rector 2005). However, with the exception of particular delusion-consistent cues, individuals with schizophrenia demonstrate poor utilization of cues from the social environment, including failure to concentrate visual attention on relevant features of faces or social contexts, and deficits in recognition of others' facial affects and mental states in perspective-taking tasks (for a review, see Green et al. 2005). They have trouble understanding their own internal states as well and tend to interpret these states in terms of concrete factors external to their own mind (as when a self-critical thought is understood as a persecutory auditory hallucination; Beck and Rector 2005). Impaired cognitive understanding of social situations in schizophrenia hence appears to involve many factors, including perceptual difficulties, cognitive biases, a shortage of cognitive resources for examining and correcting delusional and hallucinatory explanations for experiences, and a lack of motivation to interact with others who might offer alternative explanations. Information-processing and neural mechanisms of schizophrenia symptomatology represent important areas for future investigation on the interface between social and nonsocial cognition.

### *Motivation and Interpretive Biases in Anxiety Disorders and Depression*

Individuals with anxiety disorders and depression also show social-cognitive difficulties in that they interpret the world around them in characteristically distorted ways. Like people with schizophrenia, people with these disorders show a personalization bias, in that they accord environmental cues more significant for the self and the future than is really the case. For example, individuals with anxiety disorders often interpret ambiguous or benign stimuli as threats with which

he/she will be unable to cope, and depressed persons interpret them as evidence of being worthless and without hope for the future. As such, interpretational biases in these illnesses may relate to subsequently biased memory. However, unlike the externalizing attributions that occur in schizophrenia, attributions in anxiety disorders and depression typically involve assumptions of exaggerated personal vulnerability or deficiency, consistent with the affective states associated with these disorders.

Negative interpretive biases have been demonstrated in several types of experimental tasks assessing responses to ambiguous stimuli. The emotion identification task, for example, presents participants with images depicting emotional states in graded, computer-generated blends (e.g., of a neutral face with a sad face) and assesses the strength with which an emotional expression must be present for the participant to identify it. Another task asks participants to identify the meaning of words that are ambiguous in that they can be interpreted as having either negative or neutral content (e.g., "sink"). Research shows that individuals with social phobia are able to correctly identify angry facial expressions at lower intensity than control or depressed participants (Joormann and Gotlib 2006). A similar pattern involving a heightened detection, specifically of threatening expressions, has been shown among abused children (Pollak and Kistler 2002) and adults who are high in sensitivity to rejection (Olsson and Downey 2007). Individuals with generalized anxiety disorder interpret ambiguous words with more threat-related meanings than do controls (Mogg et al. 2004a). Depressed individuals, compared to socially phobic individuals and controls, require a higher intensity of happiness to be present in a facial expression before they will correctly identify it as happy. Moreover, unlike the socially phobic, depressed individuals correctly identify sad faces at lower thresholds than angry faces (Joorman and Gotlib 2006). In another study, clinically depressed individuals interpreted ambiguous words as having more negative meanings and also recalled more negative words later, relative to controls (Mogg et al. 2006). Further evidence suggests that a negative bias in interpreting ambiguous stimuli can prospectively predict dysphoric reactions to stress (Pury 2002) and later depression diagnosis (Rude et al. 2003).

In spite of their contribution to mood states that are aversive and that impair ordinary functioning, the biased patterns of interpretation associated with anxiety disorders and depression make sense from a motivational standpoint. After all, it is more adaptive to perceive a safe situation as dangerous than to overlook a real danger by assuming that it is safe. Likewise, recognition of when pursuit of a goal will inevitably fail is functional, in that disengagement from the goal prevents wasting valuable resources (Oatley and Johnson-Laird 1987). In these disorders, however, inaccurate assumptions about the base rate of negative outcomes lead such self-protective motivations to be invoked more frequently than is warranted, with both current mood states and mood-congruent biases of attention and memory (previously discussed) perpetuating negatively biased interpretations. Viewing the self and others through such a negatively biased perspective can, in turn, lead to maladaptive behavior and negative social outcomes. Hence, the negative social-cognitive biases that occur in emotional disorders may be understood in terms of basic self-protective motivations gone awry.

### *Implications for Therapeutic Intervention*

Cognitive therapy interventions address biases in expectations and interpretations by identifying, challenging, and modifying the distorted automatic thoughts and underlying beliefs (maladaptive assumptions and negative schemas) from which they arise (for examples of interventions, see Leahy and Holland 2000). To do this requires detailed information about the contexts in which symptoms occur, including perceptions of antecedent events, and the specific thoughts the individual had about them. For example, a depressed individual who felt particularly despondent after taking an examination may report preoccupation with examination questions he/she was unable to answer and thoughts in which assumptions are being made about what the missed questions mean about the self and the future ("I'm doing badly in this class," "I'm stupid," and "I'll always be a failure"). Modifying depressogenic thoughts involves identifying the errors implicit in them and deliberately rehearsing less distorted counterstatements ("I also got a lot of questions right," "I've gotten plenty of good grades so I can't be stupid," and "even if this grade isn't my best it is just one class not my whole life"). After engaging in these exercises over time, the individual may also be able to identify basic maladaptive assumptions that repeatedly underlie his/her problematic thought patterns ("If I'm not perfect then I'm worthless"). The notion that a set of basic maladaptive assumptions about the self and others can underlie even quite pervasive psychiatric difficulties is the foundation for cognitive therapy for personality disorders (Young 1990). Thoughts that promote anxiety and panic (e.g., "this elevator will crash," "everyone is noticing how anxious I am," and "my heart is pounding so fast that I'll die") are also effectively modified with cognitive therapy. However, because avoidance and cognitively overwhelming anxious arousal are endemic to anxiety disorders, graded exposure exercises and training in relaxation techniques are typically used to ensure that the person is sufficiently exposed to and able to cope with the situations that elicit anxiogenic thoughts. Cognitive therapy has also been applied to modify the interpretive biases that make people with schizophrenia so convinced of their delusions and hallucinations. Framing these experiences in terms of thought patterns with particular contexts and antecedents, the therapist guides the person through examining the evidence for and against particular explanations for their experiences (Beck and Rector 2005).

The quality of the therapeutic relationship is universally important in all forms of treatment but is a particularly critical and challenging aspect of treatment of disorders where social-cognitive difficulties lead to low ability to trust others. For individuals with schizophrenia, establishing trust is no small therapeutic goal, given their motivational deficits and pervasive misinterpretation of others' intentions. Yet without trust it would be impossible to engage the patient in revealing and challenging his/her assumptions about the world; hence, the first stage of cognitive therapy for schizophrenia is solely focused on the establishment of trust in the treatment relationship (Beck and Rector 2005). By contrast, for individuals with borderline personality disorder, mistrustful tendencies to misinterpret and overreact in social interactions are typi-

cally accompanied by strong motivation for the rewards of social connection. Hence, so long as it does not succumb to volatile interpersonal patterns, the therapeutic relationship can readily become a crucial leverage point for engaging the patient in the direction of change.

Various forms of social skills training also directly target social-cognitive difficulties that lead to volatile relationships and isolation, often through a combination of didactic instruction and practice. The skills-training sessions that are an integral part of dialectical behavior therapy for borderline personality disorder include material to address specific problem areas of social interaction. For example, sessions focusing on how to make or refuse a request specifically highlight the importance of cognitive perspective taking so that the level of firmness and persistence of interpersonal behavior be appropriate to the situation and the other person's response (Linehan 1993).

## Conclusions: Modularity and Integration

This chapter has focused on unpacking the workings of a few core cognitive processes and then examining possibilities of how these processes may be disrupted in psychiatric illness. We have presented topics such as attention, memory, and executive function as modular, discussing them independently of each other. Modularity is an important concept in cognitive neuroscience and psychology, in that it allows us to "carve nature at its joints" and understand the uniqueness of different processes in our mental toolkit. However, at another level, this modularity is simply descriptive. It is difficult to imagine executive function, for example, proceeding normally in the complete absence of long-term memory or representation. And nowhere is this clearer than in the study of psychiatric disorders, which often include deficits cutting across cognitive, social, and emotional domains. Indeed, to forge integrative cognitive models of mental illness, it is critical to understand the interactions between disparate cognitive functions. Luckily, this is precisely the direction that cognitive neuroscience has recently taken. When functional neuroimaging emerged about 20 years ago, the major aim of most researchers was to discover the loci of various cognitive processes. Now, however, just as much work goes into understanding the circuitry of brain areas responsible for interactions between cognitive and emotional systems using new theoretical models and analysis techniques. Neuroscientific models of mental illness should follow suit, moving away from explaining single structural or functional abnormalities in cognitive and neural function and toward integrative views of both function and dysregulation.

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CHAPTER

# 27 Social Psychology

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## Introduction

By training, interest, and definition as a medical specialty, the field of psychiatry emphasizes the medical treatment of psychopathology (illnesses or disorders) of individual patients (children and adults). Social psychology scientifically studies, often by experimentation, the way in which behaviors and cognitions of persons usually without preexisting psychopathology are shaped by the social environment and influenced by the real or imagined presence of other people (Allport 1954). The social psychologist is not so much focused on individual differences, but rather in determining scientifically the general principles that determine how social influences affect the behaviors of all people. This chapter is not meant to cover exhaustively the implications of the social psychology literature for clinical psychiatry, and due to space limitations it is beyond the scope of this chapter to survey the vast field of social psychology.

In this chapter, we focus mainly on persons without major mental disorders, in order to illustrate to the reader some of the fundamental principles involved in interpersonal behavior, the formation of the "self" via feedback from other people, and some of the fundamental principles involved in interpersonal behavior. In the chapter 26, the authors describe the principles of normal cognitive processes, and illustrates how disordered cognitive processing can distort an individual's ability to follow the "rules" of interpersonal functioning that are illustrated in this chapter, including the loss of ability to detect, interpret, and calculate the relative benefits and costs of chosen behaviors.

The loss of the ability to engage in the interpersonal dynamics that are described in this chapter is well known to all psychiatrists because it occurs in individuals with the major mental disorder of schizophrenia as well as other major disorders including the dementias. In schizophrenia, the person often loses or does not develop the cognitive skills (social cognition) that are required to understand the "rules" of social relationships (Burns 2006). Social cognition includes face perception, emotional processing, self-reference and working memory and a "theory of mind," by which one assumes that another individual possesses a mind just like one's own, so therefore one can attribute mental states to others and engage cognitively in the social arena (Grady and Keightley 2002).

Social cognition at a cellular level is thought to involve "mirror neurons" in Broca's area, the premotor cortex, the superior temporal sulcus, and the posterior parietal cortex in humans (Rizzolatti et al. 1996, Decety and Grezes 1999, Buccino et al. 2004). Mirror neurons normally simulate actions that one sees another person do, and internally "represent" this action for us. As such, this system may provide the basis for shared human experience. If this cortical system is damaged as occurs in schizophrenia, interpersonal relatedness or "social cognition" is gravely impaired. This phenomenon will be described in more detail in the chapter 26. It has been argued that the sense of alienation often experienced by persons with schizophrenia, and the depression and "disembodiment" that they sometimes experience, are related to impairments in social cognition.

We will now describe some of the challenges that social systems present for all of us.

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## Attributional Style and Vulnerability to Depression

Social psychology's *attribution theory* plays a central role in one of several cognitive vulnerability models of depression (Alloy et al. 1999). Attribution theory elucidates how people explain events and experiences in their lives, and the adaptational consequences of those explanations. The theory, developed by Heider (1958) and later elaborated by Jones and Davis (1965), Kelly (1967), and Weiner (1974), dominated social psychology during the 1970s. Attribution theory concerns itself with how individuals "attribute" or explain the behavior of other people, events, or their own behavior. Attribution theory proposes that people attribute a given behavior either to causes outside of the person or to some factor within the person who is performing the action ("dispositional" or "internal" factors). Responsibility for the behavior is assigned or not assigned depending on the attribution of the cause of the behavior. Factors that determine attribution include effect on self-esteem (i.e., one's bad behavior is more likely to be attributed to outside causes than is one's good behavior), universality of the behavior (everyone behaves in that manner, so it is just a habit or manifestation of conformity), and unusual nature of the particular behavior at a given time. Embedded in the concept of attribution is the assumption that individuals try to determine why others act as they do (Weiner 1974), and that these explanations for behavior occur *after* the fact.

The concept of *locus of control* (Rotter 1966) is grounded in expectancy-value theory, and is related to attribution theory but concerns expectation for *future* events, and what influences them. "Internal control" refers to the idea that the individual believes s/he can control a future outcome while "external control" refers to the belief that the outcome is outside of one's control. Later revisions of the locus of control model, including that of Levenson (1973), proposed three dimensions: internality, chance, and powerful others. According to this model, a person can assess a proportion of control of an event to a combination of one or more of these factors simultaneously.

Around the same time as attribution theory was developed, coincidentally Seligman's (1975) animal model of *learned helplessness* was proposed as a way to understand the development of depression. But by the late 1970s investigators and clinicians became increasingly disenchanted with the learned helplessness model. In response to numerous critiques, Abramson et al. (1978) offered a "reformulated learned helplessness model of depression." Drawing on the success of attribution theory in explaining behavior, they argued that unlike an infrahuman, when a person experiences helplessness, she asks herself why she is helpless. According to the reformulated model, the answer to that question—a causal attribution or causal explanation—determines the breadth, depth, and duration of the individual's depressive symptoms. If she explains her helplessness as due to a temporally *stable* factor, her symptoms will endure. Similarly, if she attributes her helplessness to a factor that will affect many life domains, that is, a *global* causal factor, her subsequent depression will manifest itself broadly in everyday life.

A later modification of the model, known as the *hopelessness model of depression* (Abramson et al. 1989), refers to people's characteristic *styles* of explaining negative life events. Rather than focusing on explanations for specific encounters, the model postulates that people maintain an explanatory style. Individuals who characteristically believe that negative events are produced by stable and global causes are more likely to experience a depressive episode, especially after a stressful life event (Table 27–1).

**Table 27–1 Hopelessness Model of Depression in Social Context**

*Question*: "Why am I lonely and unpopular?" *Depressive Explanatory Answer*:

1. There are permanent causes for my unpopularity and rejection by my peers (Attribution Theory) and that I cannot change (Locus of Control), and this will affect many areas of my life forever.
2. I could have done little to influence the way people have reacted to me in the past (Attribution).
3. I can do nothing to improve my personal relationships in the future (Locus of Control).

As a cognitive vulnerability model, the hopelessness model of depression shares with Beck's (1987) theory of depression the notion that certain ways of thinking about oneself and the world leave some people vulnerable to depression. In Beck's theory, the cognitive vulnerability involves believing that one's worth is contingent on being perfect or on others' approval, whereas in the hopelessness model the vulnerability is the inclination to make stable and global causal attributions for negative life encounters. Although the hopelessness model hypothesizes that individuals vulnerable to depression also "catastrophize" about negative events and tend to infer from these events that they are personally flawed, we focus here on the model's attributional component.

Until recently, most studies providing support for the hypothesis that a "depressive attributional style" is a cognitive vulnerability for depression had examined attributional style as a predictor of subsequent depressive symptoms rather than the onset on a major depressive episode. But findings from the Temple-Wisconsin Cognitive Vulnerability to Depression Project (CVD; Alloy et al. 2000) demonstrate that people's inferential styles, which include their interpretation of the causes, consequences, and self-relevant implications of negative life encounters, predict the onset of major depressive episodes among individuals who have never before been depressed, and recurrence among those who have previously experienced a depressive episode. These findings are most relevant to clinical psychiatry.

Haeffel et al. (2005) distinguish two strategies that have been used to test cognitive vulnerability models, including the attributional component of the hopelessness model. The more widely used approach is the remitted depression paradigm (Just et al. 2001), in which the cognitive tendencies of individuals with a lifetime history of depression in full remission are compared to the tendencies of a never depressed comparison group. The second strategy, found in more recent tests of cognitive vulnerability models, involves a behavioral high-risk design, in which nondepressed individuals considered to be at high or low risk for depression based on their cognitive tendencies are followed over years to determine whether the high-risk group, for example participants with a depressive attributional style, is more likely to experience a subsequent episode of major depression.

The CVD study began by recruiting from two universities a large sample of nondepressed college freshmen with no other mental disorders. These students were identified as being at high or low risk for depression based in part on their attributional styles. They completed a structured diagnostic interview, and were followed every 6 weeks for 2.5 years and then every 4 months for another 3 years. Among these young adults who were not currently depressed but had a lifetime history of depression, those deemed as high risk for depression based on their attributional style were more likely than their low-risk counterparts to develop a depression recurrence during the course of the study (27% vs. 6%). Similarly, among study participants with no prior depression history, those at high risk were more likely than their low-risk counterparts to develop a first onset major depression (17% vs. 1%; see Alloy et al. 1999). Thus, attributional style predicted prospectively both first onset depression and recurrence. Using a different large sample of college students and a remitted depression design, Haeffel et al. (2005) found that young adults who had experienced their last major depressive episode on average more than a year prior to study participation showed a stronger tendency than their never depressed peers to endorse stable and global causal explanations for negative life events, even after controlling for current levels of depressive symptoms. Most recently, Alloy et al. (2006) found that the prospective link between depressive attributional style and subsequent depression was specific to depressive disorders; although cognitively high-risk young adults in the CVD sample were indeed at risk for subsequent first onset depression or recurrence, they were not more likely to experience the onset of an anxiety or other Axis I disorder.

Overall, there is now converging evidence that the social psychological construct of attributional style distinguishes never depressed from previously depressed individuals, predicts first onset depressions as well as recurrences, and appears to be specific to depression. Evidence suggesting that cognitive therapy for depression reduces relapse rates at least in part by decreasing patients' tendencies to make stable and global explanations for negative events (DeRubeis and Hollon 1995), and that preventive interventions designed to interfere with a depressive explanatory style appear to protect against subsequent depressive symptoms (Gillham et al. 1995), underscore the clinical and public health implications of attributional style and the potential clinical utility of attribution theory for psychiatric practice.

Although proponents of cognitive vulnerability models have been careful to distinguish (presumably modifiable) cognitive vulnerabilities from (immutable) genetic or biological traits (Just et al. 2001), we encourage psychiatric investigators and clinicians to pay greater attention to possible links between genetic and cognitive vulnerabilities to depression and other mental disorders. We can imagine, for example, that a polymorphism in the serotonin transporter gene may leave affected individuals vulnerable to biased information processing, including biased attributional tendencies. But even if genetic and cognitive vulnerabilities do not ultimately unfold in a mediated fashion, they may have additive or synergistic effects that would have important etiologic, preventive, diagnostic, and treatment implications.

## Finding Benefits and Experiencing Growth through Adversity

The positive illusions framework and the concept of benefit-finding were derived in part from the social psychology theories concerning attribution and locus of control.

It has become almost axiomatic in the psychiatric literature to consider contact with reality a key feature of emotional health (e.g., Jahoda 1958). Yet more than two decades of social psychological investigation indicates that mild positive illusions, that is, positively skewed reality distortions especially among physically ill persons, may underlie positive mental health and recovery from physical illness (Taylor and Brown 1988, Taylor et al. 2000). Although there has been some debate in the literature regarding the emotional and physical health advantages of positive illusions (e.g., Colvin and Block 1994), and the findings are not yet conclusive, a growing body of social psychological literature points to the potential benefits of *positive illusions* (Table 27–2).

**Table 27–2 Positive Illusions**

Normal human perception is marked by three *positive illusions*, which are mild positive distortions of reality (Taylor and Brown, 1988):

1. Self-enhancement
2. Unrealistic optimism
3. An exaggerated perception of personal control

We focus here on one aspect of this area of investigation: Finding benefits and experiencing growth in the face of adversity. The traditional psychiatric literature has understandably focused on the negative emotional consequences of trauma, adversity, and serious illness. And indeed, this traditional perspective has advanced our understanding of phenomena such as posttraumatic stress disorder (PTSD). Yet this focus on the negative sequelae of adversity has led clinicians to interpret patient reports of benefits or personal growth following serious illness or loss as an indicator of denial, avoidance, or maladaptive wishful thinking.

The empirical literature paints a far more nuanced and provocatively hopeful picture. More than 300 empirical investigations and theoretical formulations have now been published in the area of *benefit-finding and growth following adversity* (Lechner et al., in press). People regularly report growth or benefits in the form of enhanced relations with others, positive personal change such as gained wisdom and strength, and changes in life philosophy. To be sure, the association between benefit-finding and positive adjustment has yielded some inconsistent results (see Linley and Joseph 2004, Stanton et al. 2006, Zoellner and Maercker 2006 for reviews). Nonetheless, several of the better designed studies with longitudinal predictions suggest that benefit-finding, rather than being an indicator of maladaptive wishful thinking, can be an adaptive resource. We now review these studies briefly, which were originally reviewed by Tennen and Affleck (2002).

As part of a study of *adjustment to bereavement*, Davis et al. (1998) interviewed people who had 6 months earlier lost a parent, spouse, partner, child, or sibling, and who had been followed since their loved one had been in hospice care. These bereaved individuals were asked if they had found

anything positive in the loss. Seventy-three percent endorsed some benefit. Davis et al. (1998) found that benefit-finding 6 months after the loss predicted distress levels 7 months later, even after controlling for both distress during the loved one's hospice care and the extent to which the loss "made sense" to the participant.

In a study of *mothers whose infants were in neonatal intensive care*, Affleck and Tennen (1991) asked these mothers whether they had found any benefits from their child's hazardous delivery and hospitalization. Three-fourths of the study participants endorsed at least one benefit. Benefit-finding predicted not only mothers' own well being, but also her child's developmental test scores 18 months later, even after controlling for the severity of the infant's perinatal medical problems. These findings should interest infant and child psychiatrists and consultation liaison psychiatrists.

In another study that should interest consultation liaison psychiatrists, Affleck et al. (1987) asked a large sample of men, who had seven weeks earlier survived their *first heart attack*, whether they experienced any benefits or gains from the heart attack. Eight years later, those men who had reported at least one benefit were in better cardiac health and were less likely to have suffered another attack over the subsequent 8 years. These findings controlled for the severity of the first attack.

Psychiatrists have become increasingly familiar with the negative consequences of traumatic encounters, particularly PTSD. In a study of people who experienced one of three disasters involving extensive property damage and loss of life—a severe tornado, a plane crashing into a hotel lobby, or a mass shooting—McMillen et al. (1997) interviewed survivors 4 to 6 weeks after the incident and again 3 years later. Through a structured diagnostic interview, they assessed lifetime mental disorders. Individuals who reported benefits soon after experiencing the disaster were less likely to meet criteria for PTSD 3 years later. This prospective relationship is remarkable because it controlled for injury during the disaster, gender, and the number of preincident psychiatric diagnoses, each of which made a unique contribution to the longitudinal prediction of PTSD.

As the prognosis for HIV+ individuals has improved, psychiatrists have had the opportunity to become more involved in their long-term care. Bower et al. (1998) interviewed *bereaved HIV-seropositive men* on average 8 months after they had lost a close friend or partner to AIDS. Every 6 months they were examined for AIDS' signs and symptoms, and were interviewed regarding their health behaviors. Benefit-finding predicted subsequent CD4 T lymphocyte decline and a lower rate of AIDS-related mortality over the next 4 to 9 years, and neither of these associations was mediated by health behaviors. On the other hand, the prospective relationship between benefit-finding and mortality was fully mediated by a less rapid decline in CD4 lymphocytes.

Finally, psychiatrists are called upon frequently to assist *chronic pain patients* cope more effectively with their pain. Tennen et al. (1992) assessed benefit-finding among rheumatoid arthritis (RA) patients before the patients completed and submitted in the next day's mail a diary of their daily pain, mood, and pain-related activity limitations each evening for 75 days. Perceived benefits at the start of the study moderated the relationship between pain severity and activity limitations. In other words, with increased levels of daily pain, RA patients who had endorsed more benefits reported fewer days during which their activities were limited by that day's pain (Table 27–3).

Social psychology's *positive illusions framework* has fueled keen interest in benefit-finding and perceived growth in the face of adversity and trauma. The theoretical and empirical literature in this area is beginning to change the way some mental health clinicians conceptualize people's responses to traumatic encounters. Indeed, this line of inquiry holds the potential to influence more generally our understanding of stress reactions and may offer clues to new therapeutic approaches. Yet the study of benefit-finding and posttraumatic growth is based almost completely on people's retrospective reports of personal change over time. Within social psychology there is a convincing body of evidence demonstrating the *limits of personal autobiographical memory*, including evidence that people are unreliable in reporting personal change (see Tennen and Affleck, in press, for a review). Although new methodologies offer the promise of detecting personal change more reliably, a widely used tool in clinical psychiatry—the depression rating scale—continues to rely on patients' recalled experience and changes in experience. We now turn to depression rating scales and to what social psychological research might contribute to how psychiatrists assess depression based on patient self-reports.

**Table 27–3 How Benefit-Finding Can Enhance Interpersonal Growth Following Adversity**

- Enhanced relations with others
- Positive personal change (wisdom, strength)
- Change in life philosophy

## Self-Report Depression Rating Scales: A Social Psychological Perspective

Depression may be the most frequently studied phenomenon in psychiatry, and it is surely the most common disorder seen in general psychiatric practice. Depression severity scales completed by the patient, as well of those completed by the psychiatrist but based largely on the patient's report, have become a mainstay of psychiatric practice and research. These scales require patients to recall their symptoms, typically over several days to a few weeks. The ease with which patients complete these scales has been interpreted as a reflection of the accuracy of their recollections. However, an impressive literature at the interface of social and cognitive psychology, reviewed recently by Tennen (2006), suggests that such symptom reports are almost surely fraught with recall decay and systematic bias.

All depression rating scales ask patients to recall their sadness, guilt, sleep quality, and other depressive symptoms over the previous few days to 2 weeks. Yet evidence from the social psychology literature indicates that when asked to recall recent emotional experiences, people actually *reconstruct* that experience based on an *implicit theory of change* and a variety of cognitive heuristics (Kahneman 1999, Ross and Wilson 2003). When patients attempt to recall their mood during the past week or 2, they most likely retrieve particular moments, that is, episodic memory, from that time frame. Because episodic memory fades rapidly, patients completing a depression rating scale may also draw upon their beliefs about their moods.

People provide different answers depending upon whether mood is reported in real time or retrospectively (Robinson and Clore 2002). Depressive symptoms recalled over just a few days can also be influenced by the most intense experience during that time, by the most recent experience, or by the individual's emotional state when completing the depression measure (Stone et al. 1999). The social psychological literature indicates that these reporting inaccuracies are not simply random error, but rather *systematic* bias in recalled emotional symptoms. Retrospections over time periods longer than a week, commonly required in depression measures and structured clinical interviews, show increasing levels of bias as people begin to draw on their beliefs about their mood rather than reporting on their accurately recalled mood (Tugade et al. 2007).

Depression rating scales also require patients to average their experience over time. Such averaging has been shown to lead patients to rely on cognitive "shortcuts," which are typically different from the average of recent emotional experiences as they were actually experienced (Robinson and Clore 2002), and different from the experiences clinical investigators and psychiatric clinicians assume they are capturing in depression rating scales. This empirically documented distinction between emotional experience as it unfolds in real time and recalled emotional experience also suggests that for a pharmacological or psychotherapeutic treatment to be found effective, the treatment would need to change not only experience itself, but the *recollection* of that experience as measured by depression scales (Moskowitz and Young 2006).

Some items on depression rating scales require patients to estimate recent symptom *change*s, such as worrying more than usual, or being more irritated than usual. The social psychological literature, however, tells us that people are even less accurate when reporting symptom changes than when reporting recollected symptoms because such judgments require recalling oneself at two different times and then making a comparison (Ross and Wilson 2003). Stone (2005) has demonstrated how reports of symptom change may not reflect actual change.

Most depression rating scales also ask patients to recall how their own responses covaried with changes in everyday life situations. For example, these scales ask patients whether they felt more cheerful if something good happened, or whether they blamed themselves when they experienced a negative outcome. Again, the empirical literature at the interface of social and cognitive psychology reveals that a patient who expects a relationship between a particular change in her social environment and her behavior will overestimate the magnitude of any relation that might exist, or even infer a relation when none exists.

Paper diaries, electronic pagers, and palmtop computers can measure symptoms closer to their real-time occurrence. This approach has been called a *daily process method* (Tennen et al. 2000), *ecological momentary assessment* (Stone et al. 1999), and *experience sampling* (Csikszentmihalyi and Larson 1987). Lenderking et al. (2004) showed that daily depression symptom assessments were more sensitive than traditional weekly assessments in detecting early response to antidepressant treatment. Kranzler et al. (2004) used daily symptom reports to examine the mechanisms of therapeutic action in a pharmacotherapy trial. And Gunthert et al. (2005) used daily reports to show that depressed patients who began cognitive therapy with a relatively less pronounced negative emotional response to everyday negative encounters showed greater reduction in depressive symptoms over the course of treatment (Table 27–4).

**Table 27–4 Techniques for Measuring Real-Time Occurrence of Symptoms**

- Daily process method
- Ecological momentary assessment
- Experience sampling

## The Self

Psychiatry, social psychology, and cognitive psychology have one of their most intimate interfaces around the concept of the self. The literature on the self within the fields of psychiatry and cognitive psychology is covered elsewhere in this section (see chapter 28 and chapter 26). We touch on a few important points here to establish a foundation for integrating some of the contributions of social psychology with those of psychiatry.

Psychiatry has generally focused on the psychopathology of the individual and the pathology of the individual self, especially with respect to normal and abnormal development of the self in the context growth within the nuclear family. Freud (1957) believed that for infants and even for normal adults, psychological investment in the self remained more important than investment in other people. Later, psychoanalysts (Winnicott, Bowlby, and others) argued that the bond between mother and infant was primary or very important and existed from early infancy.

Melanie Klein and Otto Kernberg (Klein 1930, Kernberg 1975) observed that the interpersonal relationships within the family during a child's development sometimes generated a complex world of internalized mental representations of these other persons ("objects"). Some patients who experience dysfunctional family relationships develop intense feelings of aggression and envy, and such patients, suffering from the self-disorder of narcissism, develop pathological mental processes, structures, and behaviors in an effort to compensate for these intense feelings. Kohut (1977) proposed that the self could develop only within the context of intrapsychic representations of other people ("self-objects"), and that self-object relationships established and maintained a cohesive sense of self, which was associated with an ongoing sense of positive self-regard and self-esteem. He believed that damage to the formation of the self resulted in the development of defensive and compensatory mental structures and behaviors to try to maintain self-esteem, and argued that an individual with a self-disorder was preoccupied with the experience of the damaged self. In general, maintaining self-esteem has been a prominent feature of most theories of the self that currently are described in the psychiatric literature.

## The "Self" within Social Psychology

Social psychology studies the normal self within its ongoing broader interpersonal and social context, and often begins with a focus on cognitive elements and changes in cognition rather than a focus on emotion or affect. However, in the area of the "self" within social psychology, the more

affectively laden concept of self-esteem maintenance has become prominent. The concept of self-esteem includes the belief that there is a human need to see the self as good, competent, and decent, and that this need has both an evaluative and a cognitive component. The importance of the evaluative component is illustrated by the observation that all people at times distort their cognitions, and the interpretations of these cognitions, in order to raise their self-esteem (Aronson et al. 2007).

### Self-Evaluation Maintenance Theory

*Self-evaluation maintenance theory* (Tesser and Campbell 1982) focuses on emotional arousal and predicts that emotional arousal affects self-evaluation maintenance processes, and that people will downgrade their ratings of others in order to maintain their own sense of self-worth. This theory may have relevance for understanding the private versus public behavior of individuals with narcissistic traits, particularly when that person feels envious of another.

In one study of self-evaluation maintenance theory, participants rated another person's performance less favorably when the task was important to the rater's own abilities (Tesser and Campbell 1982). In a related experiment (Morf 1993), students with varying degrees of "narcissism," as measured by the Narcissistic Personality Inventory, were either slightly or substantially outperformed on a task that was important to their own self-esteem. The more narcissistic individuals *anonymously* (but not necessarily publicly) rated the other person more negatively than did the less narcissistic individuals, and the more ego-relevant the task, the more the private ratings of the other person were downgraded (Table 27–5).

**Table 27–5 Self–Evaluation Maintenance Theory**

People will downgrade their ratings of other people in order to maintain their own sense of self-worth. *Self-evaluation maintenance theory* has implications for understanding the concepts of *envy* and *narcissism*.

## The Cognitive Approach to the Self: The Multidimensional Social Self

Deaux (1992) has developed a social psychological model of relationships between self and mental health that revolves around *self-definition* and the impact of challenges to self-definition on mental health functioning. In this model, self-maintenance is at the center of maintaining overall mental health, and she proposes a framework for conceptualizing the multidimensionality of the social self that includes self-categorization, evaluation of the self, importance of the self, attachment, sense of interdependence, and social embeddedness and behavior (Ashmore et al. 2004). Deaux's theory has relevance for our understanding of the self within its cultural context, particularly since observations from social psychology inform us of how culture and gender may partly determine how people view the self with respect to interdependence and social embeddedness. In Western cultures, for example, people typically view the self as independent of the thoughts, feelings, and actions of other people, and define the self on the basis of the individual's own thoughts, feelings, and actions. By contrast, in non-Western cultures, the self is usually defined in a more interdependent manner, in terms of relationships to other people. People from these cultures assume that their thoughts, feelings, and behaviors are often determined by the behaviors of others (Bochner 1994, Triandis 1989) (Table 27–6).

## Cognitive Continuity: Self-Verification Theory

*Self-verification theory* (Swann 1983, 1990, 1997, Giesler et al. 1996) predicts that people want others to provide verification and continuity in their experience of the self (the self-schema). According to self-verification theory, if the individual's beliefs about the self are correct, interpersonal relationships will proceed more predictably. Self-verifying information is judged to be more valid than non-verifying information (Swann 1997) and is remembered better (Swann and Read 1981). Individuals with negative self-views tend to solicit unfavorable information about themselves from others, and self-verification theory proposes that they do so because this promotes perceptions of prediction and control by fostering intrapsychic and interpersonal coherence and stability. By contrast, individuals with high levels of self-esteem solicit favorable feedback.

**Table 27–6 Multidimensional Social Self-Theory**

Self-maintenance is at the center of maintaining overall mental health. The social self is multidimensional and includes the characteristics we attribute to ourselves (self-categorization), how we evaluate ourselves, how important we believe we are, to whom we feel attachment and its intensity, how interdependent with others we believe we are, and how much we believe our behavior is governed or determined by the expectations and the behaviors of others. *Multidimensional social self-theory* has implications for understanding the roles of *culture and gender* in self-definition, and also draws upon the literature from *attribution theory* and *locus of control theory*.

In research studies conducted by Swann and his colleagues, when mildly depressed and nondepressed college students were given bogus ratings of apparent artistic or athletic ability after an interview, and then told they could follow up with a clinician to hear more about their ratings, nondepressed students did not want to hear any more about their supposed limitations. Depressed students did. Both groups were willing to hear more praise about what they perceived to be their strong points. In another study series, it was determined that married people with negative self-views were more inclined to remain in relationships with spouses who thought poorly of them. Finally, people with low self-esteem were more inclined to quit their jobs when told they were receiving pay increases as compared to pay decreases.

Depressed people who hold negative views of the self may seek self-verification of their negative self-views, even when this contributes to lowered self-esteem and increasing depression (Giesler et al. 1996). In a comparison of clinically depressed persons, nondepressed persons with low self-esteem and nondepressed persons with high self-esteem, 82% of the depressed participants chose to receive unfavorable feedback, as compared with 64% of the low self-esteem participants and 25% of the high self-esteem

participants. The depressed persons also tended to ignore opportunities to experience favorable feedback, although they wanted feedback of some kind and were not passive. Clinically depressed children and adolescents expressed more interest in negative feedback than did their non-depressed counterparts, and this association was more related to cognitive rather than to emotional aspects of their self view (Joiner and Wagner 1995).

Unlike persons with chronically low self-esteem, however, the low self-esteem experienced by the depressed individual may be state dependent, and subject to remission when depression lifts. Clinically, this fluctuation in self-assessment by a patient who is seen on an ongoing basis may perplex both the patient and the treating psychiatrist. Nevertheless, during the depressed state, the patient likely will hold tenaciously to her/his negative self-evaluation, and attempt during those times to confirm that self-view and act on it, sometimes with tragic results.

There is evidence that people with low self-esteem pursue social relationships and social situations that confirm their core self-conceptions, and display cues that communicate how they perceive themselves and want to be perceived by others (identity cues). People also interact in ways that elicit feedback from others that confirm their predominant self-conceptions, and selectively attend to and process interpersonal feedback including negative self-concept. From the standpoint of psychiatry, transference and projective identification could be viewed as a way of interacting to get the psychiatrist to confirm the negative view of the self. Swann and Read (1981) have demonstrated empirically that if people with negative self-views think that their interaction partner views them favorably, they will intensify their efforts to appear unworthy of this positive regard (Table 27–7).

**Table 27–7 Self-Verification Theory**

*Self-verification theory* predicts that people want others to provide continuity in their experience of the self (the *self-schema*). It has implications for understanding *depression and understanding of transference and projective identification* because individuals with negative self-views tend to (unwittingly or unconsciously) solicit unfavorable information about themselves from others, possibly to promote the perception of prediction and control by fostering intrapsychic and interpersonal coherence and stability.

## Schemas and Their Relationship to Construction of the Self

The situational activation of cognitive schemas is "automatic" and as such is outside the individual's control and awareness. Cognitive "schemas" are used to look at ambiguous external and internal situations (see the chapter 26, this section). *Schemas* are based on previously acquired information, and are mental structures that automatically, quickly, and often stereotypically (without one's awareness) organize knowledge about perceptual experiences. This influences the information we notice and think about (Payne, 2001, Correll, et al. 2002, Janicik and Larrick, 2005). Individuals within different cultures also learn differing *cultural causal theories* (often attribution models) about what explains our own and others' behavior and feelings (Nisbett and Wilson 1977, Gavanski and Hoffman 1987, Wilson 2002). *Implicit personality theories* are types of popular schemas that people use to group various kinds of personality traits together to draw conclusions about the nature of other individuals. These implicit personality theories also differ among cultures, and cultural assumptions are embedded in them.

One popular implicit cultural theory that has been experimentally demonstrated is the American assumption that "what is beautiful is also good" (Dion et al. 1972). As a result of this popular "theory," beautiful children and adults get more parental attention, more teacher attention in school, and faster promotions at work. This finding has implications for psychiatrists who treat individuals who do not meet cultural standards of beauty, and can provide insight when advising members of the criminal justice system and other social institutions.

People also use "self-schemas" to organize information about themselves (Markus 1977). This information, and the way in which it is organized, contributes to the development and maintenance of the self. Like other schemas, self-schemas are "short-cuts" and exert their effects especially in ambiguous circumstances where some of the information is consistent with the schema and the rest is ambiguous. Self-schemas tend to be self-perpetuating, and so the view of the self is not easily changed (Shadel et al. 2004). The intractability of personality disorders may be related to this phenomenon.

## When Facts and Self-Schemas Collide: Cognitive Dissonance as a Theory of the Self

Leon Festinger (1957) was inspired to develop the theory of cognitive dissonance after he observed that members of a UFO doomsday cult *increased* their proselytization after the leader's prophecy *failed*. Cognitive dissonance originally was proposed as a theory of attitude change but now is viewed as a self-theory (Aronson et al. 2007). *Cognitive dissonance* is a feeling of discomfort caused by performing an action that is discrepant from one's customary self-conception (conscious view of the self). The theory proposes that dissonance is strongest when a discrepancy has been noticed between a core area of one's self-concept and one's overt behavior, because this creates a feeling of "shame." This leads to either change in attitude, change in behavior, some kind of self-affirmation, (Shakespeare's "The lady doth protest too much, methinks."), or some rationalization of the behavior (Table 27–8).

**Table 27–8 Cognitive Dissonance**

*Cognitive dissonance* is a feeling of discomfort caused by performing an action that is discrepant from one's self-conception, leading to a feeling of shame and lowered self-esteem. The theory has implications for understanding *self-affirmations* and *rationalizations*, and may have importance in understanding when patients "flee awareness" through substance abuse, *interpersonal confrontations, suicide attempts, or dissociation*.

Not included in Festinger's theory, but sometimes observed clinically, is that when one realizes that current social behavior and the self's internal standards and values are not in harmony, one may "flee awareness"

(Carver 2003, Duvan and Silva 2001, Phillips and Silva 2005). Self-destructive behaviors such as substance abuse, histrionic interpersonal confrontations, and perhaps even some suicide attempts may represent a person's attempt to distract his or her conscious awareness from the discrepancy between shame about current social behavior and discrepancies with internal standards of the self (Baumeister 1991). Dissociation can be thought of as a form of flight as well (e.g., "fugue states").

### Obedience to Authority and Diffusion of Responsibility

It has been argued that the traumatic experiences of the Holocaust gave birth to the field of social psychology. Psychiatrists looked for an explanation in individual pathology, developing the construct of the "authoritarian personality" (Adorno et al. 1950) to describe a set of character traits related to acceptance of authoritarian doctrines.

More chilling to students of the evolving field of social psychology were the observations of Holocaust survivor and political philosopher Hannah Arendt, who argued that many of the principal perpetrators of the Holocaust, such as Adolf Eichman, were not authoritarian or particularly aggressive "monsters" but rather ordinary bureaucrats who did what they were told without questioning orders. Although the acts that were carried out proved to be stressful to some perpetrators, this stress merely prompted them to search for less personal methods of accomplishing their mission, such as delegating part of the duties to subordinates and remaining in one's office or leaving the environment for a time (Browning 1998). Arendt argued that the Holocaust, for the most part, was carried out by ordinary people caught up in social forces that affected their behavior. Social psychologists set out to understand the nature of these forces.

In an effort to determine experimentally whether ordinarily nonviolent people would ignore obvious injustice and inflict pain on another person in response to social pressure, Stanley Milgram (1975) conducted a now famous series of experiments. He demonstrated that 61–66% of the people who were studied, despite sometimes feeling extreme emotional stress about doing so, were willing to subject "others" to very painful electric shocks (or so they believed) when told to do so by an authority figure. Further, none of the minority of participants who did refuse to administer these shocks insisted that the experiments be terminated, nor checked on the welfare of the "victims." Milgram developed two main theories to explain his results: "*conformism*" due to a lack of a reference point about how to behave in an unfamiliar situation, and "*agenic state theory*" which argued that the person who is obedient comes to view himself as an instrument for carrying out another's wishes, and feels no responsibility for his actions (a variant of attribution theory). A contemporary example of this latter phenomenon, called "*moral disengagement*," can be found in studies of prison guards who are assigned to be members of execution teams (Osofsky et al. 2005).

A corollary to the phenomenon of disengagement occurs in group situations and is referred to as the "*bystander effect*" (Latane and Darley 1970). No individual may help another in need if others are also available to do so because, despite the observers being aware that the victim needs help, the responsibility to act is distributed among all of the persons who are present and as a result no one feels responsible to take action first ("*diffusion of responsibility*") (Table 27–9).

In addition to the power of these social forces in determining obedience to authority and the social forces that drive helping behavior, an individual is also influenced by *attributional style* (described earlier) and other personality factors of that individual. People who attribute other peoples' misfortunes to "uncontrollable forces" are more likely to help someone "in need" than are people who believe that others have control over their own lives and problems (Schmidt and Weiner 1988). Psychiatrists working in community settings have encountered the complex situation where a very depressed, potentially suicidal person needs help and is surrounded by potential helpers. The psychiatrist advises that the patient requires assistance (invoking obedience to authority). The "helpers" do not act because "someone else should help the patient, such as the agency staff" (diffusion of responsibility) and/or the patient "is creating his own problems and can solve them himself" (attributional style).

**Table 27–9 Obedience to Authority and Diffusion of Responsibility**

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|---|
| *Moral disengagement*. It occurs when the obedient person comes to view him or herself as an instrument for carrying out another's wishes, and feels no responsibility for the action (related to *attribution theory*). |
| *Bystander effect*. Observers of a victim see other bystanders present, and each bystander feels less responsibility to help because each one believes (1) someone else will help or should help and (2) each bystander feels less personal responsibility because the others are there also ("*diffusion of responsibility*") |

## Summary

In this chapter, we have discussed the ways in which the constructs and findings of social psychology can enrich the field of psychiatry. We introduced the concept of "social cognition." We demonstrated how attribution theory plays a role in several cognitive vulnerability models of depression, as well as in helping behavior and popular cultural causal assumptions about behavior and personality. We also described how positively skewed reality distortions (positive illusions) contribute to resilience in the face of adversity, and how adversity can contribute to personal growth.

We explained the social psychological perspective on self-report depression scales, and how patient "recall" of past emotional states and symptom changes may actually represent reconstructions based on implicit personal theories of change and other cognitive distortions. The situational activation of cognitive schemas, and their relationship to the experience of the self, are fruitful areas for future investigation at the interface of psychiatry and social psychology.

We compared some of the social psychological theories of the experience of the self with those commonly alluded to in the psychiatric literature: specifically, how the theories of Freud, Klein, Kernberg, and Kohut contrast with self-theories within social psychology such as self-evaluation maintenance theory, the multidimensional social self, and

self-verification theory. We also used social psychological models of self-maintenance to explain the apparently paradoxical behavior of individuals with low self-esteem, and depressed patients, as they seek *negative* feedback. Finally, we explained the relevance to psychiatric practice of cognitive dissonance theory and the concepts of obedience to authority, diffusion of responsibility, and the bystander effect.

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CHAPTER

# 28 Psychoanalytic Theories

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Psychoanalysis is a clinical therapy originally developed by Sigmund Freud (1856–1939) for the treatment of the neuroses. The term also refers to a theory of psychopathology underlying the therapeutic practice; a general theory of the mind, based on the understanding arising from the clinical procedure and other sources; and a mode of research into mental life that is inherent in and inextricably intertwined with the therapeutic process. Although the contemporary practice of psychoanalysis derives historically from Freud's original contributions, it has evolved like any other discipline. Freud's written work can no longer be regarded as constituting a definitive contemporary account of psychoanalysis. Indeed, it would be difficult for current psychoanalysts to agree definitively on what constitutes psychoanalysis. What these chapters hope to impart is how psychoanalytic theory has evolved, often in disparate directions, and how modern psychoanalytic theories inform our understanding of our often complex mental processes, motivations, and behaviors. For both ease of reference and the sake of historical continuity, this section is in part organized around the contributions of those individual thinkers who have had a major impact on the development of psychoanalysis. Beginning with Freud and the inception of psychoanalysis, the section traces the important trends in the maturation of analytic theory and its current state of development.

## Development and Major Concepts

### Freud's Contributions

#### Dreams

Freud's study (1900, 1901) of dreams during his self-analysis and in his work with patients resulted in an elaborate understanding of the workings of the mind. The analysis of dreams continues to hold a prominent position in psychoanalytic practice. Dreams provide a wealth of information about the influence of unconscious wishes, fantasies, and defensive processes in the shaping of conscious mental content. Without the benefit of contemporary electrophysiological data, Freud believed that dreams functioned to preserve sleep and to prevent awakening, in the presence of nocturnal stimuli, both exogenous (e.g., noise, tactile stimulation) and endogenous (ongoing mental conflict) that must be managed to preserve sleep. Dreams give expression to unconscious wishes in disguised form and generally represent their fulfillment or gratification. Analysis of dreams can provide

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conscious access to unconscious drives, wishes, fantasies, and associated repressed infantile memories, providing what Freud called the "royal road to the unconscious."

The dream that is remembered on awakening is referred to as the *manifest dream.* It is the product of mental activity that has woven together a number of conscious and unconscious elements into a hallucinated experience that is recalled like a story or a play. Its component elements include sensory stimuli occurring during sleep, the day residue, and the latent dream content. The *day residue* consists of experiences of events of the preceding day or days, often associated in the mind with unconscious wishes. The *latent dream content* is the set of unconscious infantile urges, wishes, and fantasies that seek gratification during the dreaming state of blocked motor discharge and regression.

Freud hypothesized a *dream censor* whose function is to keep the unconscious latent content from conscious awareness, thereby preventing the emergence of anxiety and awakening from sleep. The surreal and fantastic quality of the remembered manifest dream is a reflection of the influence of *primary process* unconscious mentation (Table 28–1) (depiction of immediate gratifications, absence of the rules of logic of conscious thought, merging of past and present, absence of negatives, loss of distinction between opposites, and representation of a whole by a part) and of the activity of the *dream work*, a set of mental mechanisms designed to disguise and distort the latent content in keeping with the function of the dream censor.

**Table 28–1 Primary Process Thinking**

| |
|---|
| Does not follow rules of logic |
| Spatial and temporal relationships are not preserved |
| Thoughts and actions are equivalent |
| "Dream language" |

The specific mechanisms of the dream work include condensation, displacement, symbolization, and projection. *Condensation* is a process by which several unconscious elements are represented by a single image or event in the dream. In *displacement*, the psychic intensity or emotional charge belonging to a latent element is attached to a more neutral or innocuous dream image, creating a shift of emotional emphasis and directing attention away from an unconsciously charged element. *Symbolization* is a mechanism by which an unconscious idea is represented in the dream by something else, usually associatively connected (e.g., a gun symbolizing a penis). Freud emphasized that there are few symbols common to everyone; symbols that are chosen by an individual are most often unique to that individual. The mechanism of *projection* results in the depiction of unconscious wishes or motives originating in other figures in the dream, placing them outside oneself. Finally, the various images and themes of the dream are organized by the process of *secondary elaboration* into the relatively coherent story line of the manifest dream (Figure 28–1).

In psychoanalytic treatment, the analysis of dreams attempts to take this process backward, starting with the patient's narration of the dream and then observing the patient's associations to the manifest elements, with the goal of obtaining insight into the dreamer's unconscious wishes, memories and infantile fantasies, and processes of defense. Even with our understanding of the origin of neurophysiological dream activity, the process of dream analysis continues to provide a rich source of data about the associative connections between mental representations, memories, unconscious wishes and fantasies, and the construction of thought (Winson 1985, Reiser 1990).

## Childhood Sexuality

In his analyses of adult patients and observations of children, Freud (1905a) became convinced of the influence of early sexual fantasies on the formation of neurotic symptoms and of the universality of sexual wishes throughout life, including early childhood. The term *sexuality* is used in this context to refer not exclusively to adult genital sexuality but to a variety of body stimulations that are pleasurable and sensually gratifying. He postulated a developmental sequence of body zones that become primary foci of erotic sensations and mental organization (Table 28–2): oral, anal (including perianal and urethral), and genital (phallic). During development, there is a more or less orderly progression from one zone to the next, with pleasure being derived from sucking, biting, tasting, touching, looking, smelling, filling, emptying, penetrating, and being penetrated. The urge to do each of these, in relation to each specific erotogenic zone, is referred to as a *component instinct.* In adult sexuality, the component instincts come together in forepleasure and sexual intercourse. If one of the component instincts predominates exclusively in adult sexual behavior, a *perversion* results. In the neuroses, the repressed component instincts become an unconscious source of symptom formation.

Each phase of psychosexual development brings with it specific types of mental organization related to where pleasurable sensations are localized, means of accomplishing

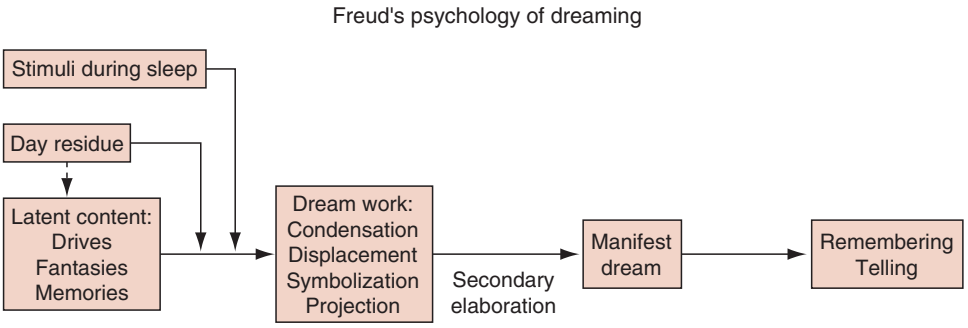



**Figure 28–1** *Dream formation.*

**Table 28–2 Freud's Stages of Psychosexual Development**

| |
|---|
| Oral: birth to 18 mo |
| Anal: 18 mo to 3 yr |
| Genital: 3 to 6 yr |
| Latency: 6 yr to puberty |
| Adolescence: puberty |

gratification, persons or objects of most significance to the fulfillment of erotic strivings, and characteristic fantasies and conflicts. *Fixation* (Table 28–3) at a particular phase of development may occur if there is insufficient mastery of issues pertinent to that phase. Fixations result in continued manifestations of phase-specific issues in a person's behavior, influencing later personality adjustment (e.g., the anal organization of the obsessional character). *Regression* (Table 28–3), a return to a less mature level of mental organization, may occur in the context of stressors or conflict that overtax the adaptive capacities of an individual. Regression, which often serves defensive or self-protective purposes, will be determined both in kind and in degree, by fixations in psychosexual development.

**Table 28–3 Responses to Developmental Stress**

| Regression |
|---|
| Use of behavioral and emotional solutions from a developmental phase earlier than the present conflict |
| **Fixation** |
| Overreliance on behavioral and emotional solutions from the phase in which the conflict occurs |

**Table 28–4 Characteristics of Developmental Phases**

| Oral |
|---|
| Urgency of needs |
| Extreme dependency |
| No consideration of others |
| Low frustation tolerance |
| Separation anxiety |
| **Anal** |
| Need for control and autonomy |
| Orderliness, obstinacy, punctuality |
| Beginning dyadic relationships |
| Conflict over autonomy and compliance |
| Guilt |
| **Genital** |
| Oedipus complex |
| Emergence of genital sexuality |
| Concerns about self-image |
| Shift from dyadic to triadic relationships |
| **Latency** |
| Waning of Oedipus complex |
| Decreased emphasis on sexual gratification |
| Focus on same-sex relationships |
| Emphasis on development of autonomous ego functions |
| **Adolescence** |
| Recapitulates early phases |
| Separation from family |
| Important bonds with peers |
| Revival of sexual interest |
| Identity formation |

The first of the phases described by Freud is the *oral phase* (Table 28–4), which encompasses approximately the first 18 months of life. During this phase, the mouth, lips, and tongue are the primary sources of sensual gratification. The activities of sucking, swallowing, mouthing, and biting as well as the experience of being held during feeding form a cognitive template for the organization of fantasy and relatedness to others. The infant at this stage is dependent on mother for nurturance, protection, and sustenance. A favorable outcome of this stage is the establishment of a capacity to feel trust and safety in a dependent relationship, a sureness that needs will be recognized and gratified, and a minimum of conflict about aggressive wishes occurring during moments of frustration. Excessive neglect or deprivation during this period may result in adult feelings of interpersonal insecurity, mistrust, envy, depression, excessive dependency, anticipation of rejection by others, and proneness to moments of diffuse rage (Abraham 1916, Meissner 1985).

The *anal phase* (see Table 28–4) emerges with the development of increasing neuromuscular control of the anal and urethral sphincters and takes place from about 18 months to 3 years. Sensual pleasure becomes most highly localized in the anal and rectal mucosa. Fantasy organizes around anal pleasure and anal functions, such as withholding, expelling, and controlling. Because of the child's increased motor skills, language development, and emerging autonomy, she or he is expected to take more of an active part in self-care activities, including using the toilet. Related to toileting, power struggles may ensue around the child's soiling or withholding. Anger is felt toward those in control of this educative process, but the child also wishes to please them. The child in the anal phase experiences considerable ambivalence around expelling versus retaining (giving versus keeping), obedience and submission versus defiance and protest, and cleanliness and orderliness versus messiness. The working through of these areas of intense ambivalence can be complicated if the parents are overly controlling, critical, punitive, or rigidly intolerant of the child's expressions of aggression and willfulness. Fixation at this stage results in a personality organized around anal erotism and its associated conflicts, characterized by wishes to dominate and control people or life situations, rigidity, defiance and anger toward authority, neatness, orderliness, messiness, parsimony, frugality, and obstinacy (Freud 1908, Abraham 1921, Salzman 1980, Shengold 1988).

The *phallic* or *phallic-oedipal* or *genital phase* (see Table 28–4) occurs from the ages of 3 to about 5 or 6 years. At the onset of this period, sensual pleasure has become most highly focused around the genitals, and masturbatory sensations more closely resemble the usual sense of the word *sexual*. The child at this time has become even

more autonomous and has more sophisticated motor and language skills, conceptual capabilities, and elaborate fantasies. The child is better able to recognize feelings of love, hate, jealousy, and fear; has a more distinct recognition of the anatomical difference between the sexes; and appreciates that the parents have an intimate sexual relationship from which the child is excluded. Thinking about relatedness to others shifts from the largely dyadic (mother–child) quality of the prephallic phases to an appreciation of relational triangles.

Freud recognized in his patients' associations that there were regularly occurring incestuous fantasies and wishes toward the parent of the opposite sex that were involved in the formation of neurotic difficulties. He termed this phenomenon the *Oedipus complex*, in reference to the story of Oedipus, who unknowingly killed his father and married his mother. In the midst of the Oedipus complex, the child wishes to possess exclusively the parent of the opposite sex and to eliminate the parent of the same sex. The jealousy and murderous rage felt toward the same-sex parent are accompanied by fears of retaliation and physical harm. Because these fantasies are associatively linked to pleasurable genital sensations, the child has specific unconscious fears of being castrated, which Freud referred to as the *castration complex*.

The oedipal phase proceeds differently in boys and girls. The little boy has maintained his primary attachment to his mother, but he now wants to sleep with her, see her naked, touch her, and marry her. He feels jealousy and hostility toward his father, seen as his rival. His fears of retaliatory castration, while wanting to maintain his loving relationship with father, lead him to renounce his wishes and to strengthen his identification with his father. He seeks to become more like father and to find someone else like mother.

Freud's ideas about the girl's Oedipus complex have stirred much criticism and controversy. Freud (1924b, 1925) believed that the little girl comes to recognize her lack of a penis with feelings of loss, narcissistic injury, anger at mother, and envy of men. She turns toward father to provide her with a penis substitute in the form of a baby. She fantasizes a rivalry with mother and fears punishment, loss of love, and genital damage. Eventually she returns to her identification with mother. Whereas the castration complex leads to the resolution of the Oedipus complex in boys, the castration complex precedes and creates the Oedipus complex in girls. A number of contemporary theorists have disputed Freud's views of feminine development, citing observational evidence of girls' primary feminine identification, positive experience of their female genitals, and wishes to have a baby before the oedipal situation (Blum 1976, Kleeman 1976, Stoller 1976, Gilligan 1982, Chehrazi 1986). Envy of men may be seen, in a sociohistorical context, as a by-product of cultural devaluation of women (in an egalitarian society, a predominating sense of penis envy may indicate neurotic or narcissistic difficulties). Boys too are susceptible to fantasies of genital inferiority on comparing their small penises to larger adult genitals (Horney 1932).

Successful passage through the phallic phase includes resolution of the Oedipus complex and repression of oedipal fantasies. The child internalizes the parental prohibitions and moral values and demonstrates a greater capacity to channel instinctual energies into constructive activities. Excessive conflict or traumatization during this phase may lead to a personally organized around oedipal fantasies and conflicts or a proneness to defensively regress to anal or oral organization.

During the *latency phase* (see Table 28–4), from age 6 years to puberty, play and learning take a prominent position in the child's behavioral repertory as cognitive process mature further. Although Freud believed that the sexual urges become relatively quiescent during this phase, observation indicates that they are expressed in derivative form in the child's play (Sarnoff 1976). At puberty, and through adolescence, genital urges once again predominate, but there is now a consolidation of sexual identity and a movement toward adult sexuality (Figure 28–2).

## Libido Theory

Freud's continued consideration of the sources and nature of the sexual drives led to his dynamic model of the mind referred to as *libido theory* (Table 28–5). This theory attempted to explain the observation that behavior and mental activity are not only triggered by external stimuli (as in the reflex arc) but also generated by primary internal processes. As a biologist, Freud hoped to understand the somatic origins of mental activity and used the concept of *instinct* (*Treib*, "drive") to do so. The psychoanalytic use of the term instinct differs from that of biology, which refers to innate, inherited, unlearned, stereotypical, species-specific behaviors. Freud (1915) defined instinct as "a concept on the frontier between the mental and the somatic, as the psychical representative of the stimuli originating within the organism and reaching the mind, as a measure of the demand made upon the mind for work in consequences of its connection with the body." Regardless of the specifics of their physiological origins, derivatives of the instincts are experienced mentally as compelling urges and a source of motivation.

Although Freud had given up the idea that sexual traumatization was always the cause of psychoneurotic symptoms, he maintained the view that the sexual instinct played an etiological role in the neuroses and that sexual stimulation exerted a predominant force on mental activity throughout life. Freud termed this force *libido*. The discharge of libido is experienced as pleasure; the welling up of libido without discharge is felt as tension or unpleasure. According to the *pleasure principle*, the individual seeks pleasure (through the discharge of libidinal tension) and avoids unpleasure. The primary process quality of unconscious mentation follows the pleasure principle as it maintains its focus on the gratification of wishes. As the mind develops, conscious mentation becomes more governed by the *reality principle* (Freud 1911a), involving a shift from fantasy to perception of and action on reality. The secondary process form of conscious thought follows the reality principle. Under the influence of the reality principle, gratification of wishes may be delayed with the aim of eventually achieving greater and/or safer pleasure.

The sexual instinct has four defining components: source, pressure (or impetus), aim, and object (Freud 1905a, 1915). *Source* refers to the biological substrate of the instinct. *Pressure* is the amount of force or "demand for work" of the instinct. The *aim* is the action designed to accomplish release of tension and satisfaction. An *object* is the target

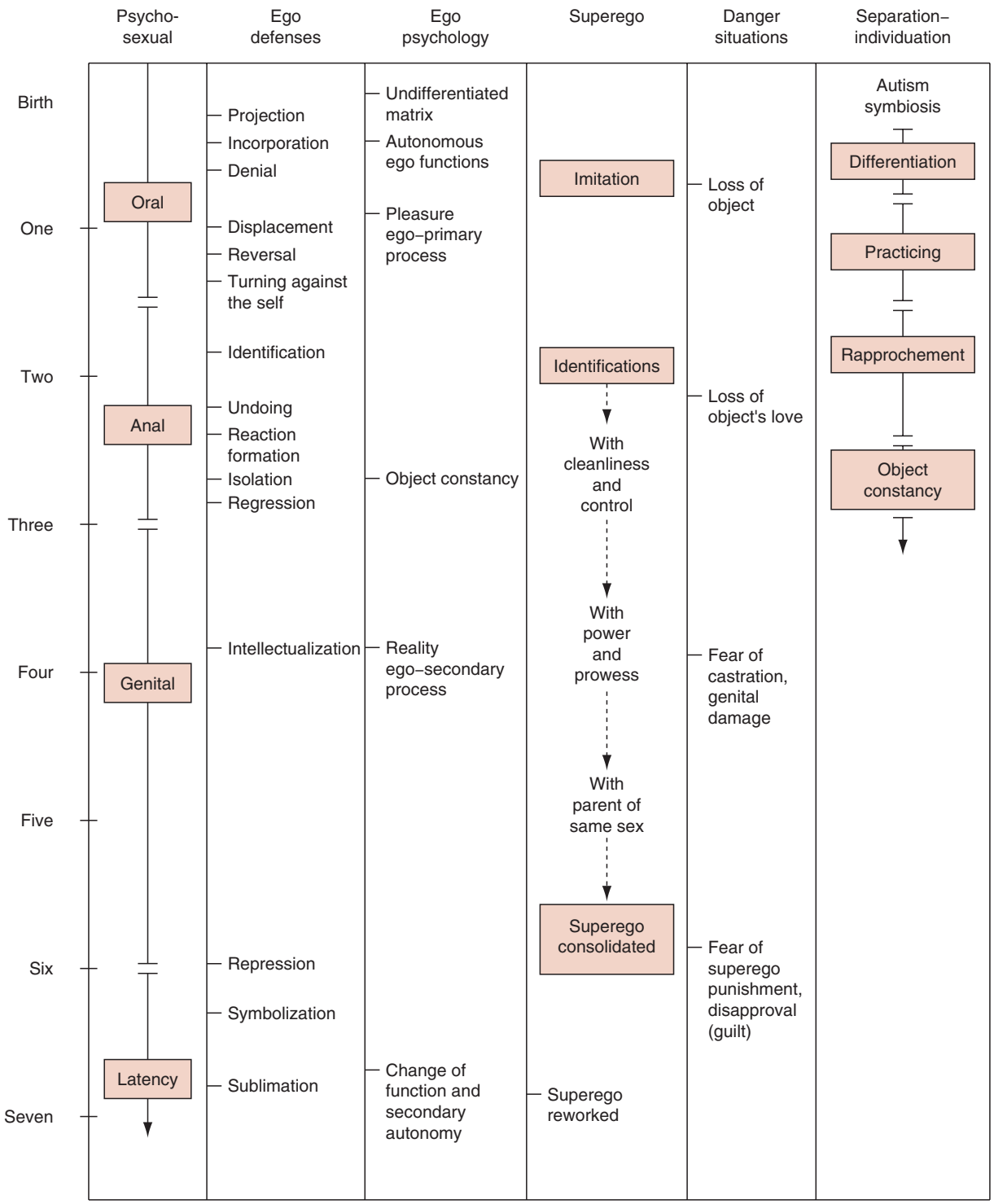



**Figure 28–2** *Parallel lines of development. (Source: Inderbitzin LB and James ME [1994] Psychoanalytic psychology. In Human Behavior: An Introduction for Medical Students, 2nd ed., Stoudemire A [ed]). JB Lippincott, Philadelphia, p 131.)*

of desire, the person or thing through which gratification is accomplished. Freud (1914a, 1915) went on to theorize that libido can be invested in or attached to representations of others in the mind or to the mental structures themselves, a phenomenon referred to as *cathexis.* Libido invested in mental representations of others is termed *object libido*; cathexis of the libido to the ego or self-representation is referred to as *ego-libido*. Although the libido theory has been criticized because it was based on 19th century German scientism, it has served as a useful metaphor to understand pleasure, attachments, and the dynamic processes of mental activity.

## From the Topographical to the Structural Model

As psychoanalytic theory developed during the 20 years after Freud's writing (1900) of *The Interpretation of Dreams*, it was built on the foundation of the *topographical theory*

**Table 28–5 Libido (Drive) Theory**

| |
|---|
| Assumes that biological "needs" (drives) fuel behavior |
| The aim of behavior is to gratify the drive |
| Drives are either sexual or aggressive in nature |

(Table 28–6). This theory was able to explain the observations that patients under hypnosis, or using free association, were able to become consciously aware of memories or motives for which they had no prior conscious awareness, the causal role of these elements in symptom formation and other psychological events, and the apparent opposition the mind exerted against the awareness or recall of these unconscious elements.

**Table 28–6 Topographical Theory**

| |
|---|
| **Unconscious** |
| Contents |
| Drives |
| Repressed ideas and affects |
| Uses primary process thinking |
| **Conscious** |
| Contents |
| Sensory input from environment |
| Nonrepressed feelings and ideas |
| Uses secondary process thinking |
| **Preconscious** |
| Has access to both the conscious and the unconscious |
| Mental effort brings some preconscious material to the conscious |
| Uses secondary process thinking |

According to the topographical theory, three regions or systems of the mind exist as defined by their relationship to conscious thought: the conscious, preconscious, and unconscious. The *conscious* mind registers sensations from the outside world and from internal processes and is the agency of ordinary wakeful thought. Conscious mentation follows the reality principle and uses secondary process logic. The *preconscious* includes mental contents that can gain access into consciousness by the focusing of attention. The *unconscious* is defined from three basic angles: descriptively, it consists of all mental processes and contents operating outside conscious awareness; dynamically, these processes and contents are kept actively repressed or censored by the expenditure of mental energy to prevent the anxiety or repugnance that would accompany their conscious recognition; and as a mental system, it is a part of the mind that operates in accordance with the pleasure principle using primary process logic.

Over time, Freud encountered clinical phenomena that were not adequately accounted for by the topographical model. Resistance to free association did not appear to be governed by conscious processes, but rather was operating unconsciously. In addition, the topographical model did not help explain self-defeating behavior and the unconscious need for punishment. In time, Freud revised his theory of mental systems to include the structural model, but the useful conception of the dynamic unconscious and the particular qualities of conscious, preconscious, and unconscious mentation have been retained.

## Theory of Narcissism

Freud (1914a) was led to his theory of narcissism by his consideration of a number of psychological phenomena including psychosis, hypochondria, different types of loving or erotic attachments, and the relationship of self-love or self-regard to the judgmental processes of the conscience. The term narcissism was derived from the myth of Narcissus, who fell in love with his own reflection, and hence, refers broadly to self-love. Freud noted that although a narcissistic attitude had been described as a component of certain psychiatric disorders, narcissism was seen more extensively and could be considered a part of normal development. Using the terminology of libido theory, Freud observed that psychotic individuals, with their turning inward and away from the external world and with their megalomaniacal preoccupations, appeared to have withdrawn libido from objects and attached it to the ego (self); however, phenomena similar to megalomania, such as magical thinking and overestimation of wishes and thoughts, could be seen early in normal development. During earliest infancy, libido is originally attached to ego, a state called *primary narcissism.* Libido then becomes attached progressively to love objects in the form of object libido. This can be withdrawn back to the ego, referred to as *secondary narcissism*.

In all mental functioning, it is possible to observe the balance between libido deployed toward objects and libido withdrawn into the ego. For example, when a person is in love, much libido is attached to the loved object, even to the extent that the person feels himself or herself diminished (from decreased ego libido). During physical illness or hypochondriacal states, libido is pulled toward the ego so the person appears preoccupied with the body and uninterested in the world. According to the pleasure principle, the mind seeks to discharge libido, and if it is dammed up, symptoms will result. In neurotic persons, excess object libido has accumulated and, undischarged, produces anxiety. In psychotic persons, ego libido has been prevented from being discharged outward, so it is discharged inward, resulting in hypochondriacal anxiety and megalomania.

Narcissistic phenomena are involved in certain love and erotic relationships. In infancy, the primary attachment to mother has a self-preservative quality involving ego libido and is referred to as an *anaclitic* attachment. Some adults continue to seek out anaclitic love attachments, wishing to be fed and protected. Other individuals may form narcissistic attachments, looking for someone who resembles oneself, the way one was, or the way one would like to be. Often the love of parents for their children may involve a revival of their own narcissism, reflected in the overvaluation or overindulgence of a child.

Internal judgmental processes and self-regard are also addressed by the theory of narcissism. In normal adults, most evidence of the operation of ego libido has been repressed. A new target of self-love has been constructed, the *ego ideal*, a forerunner of the superego concept, consisting of ideas and wishes for how one would like to be.

Similarly, love objects may become the subject of idealization. Freud theorized a separate psychic agency that attends to ensuring narcissistic satisfaction and measuring the self-reflection, censoring, and repression. Living up to the ideal, loving oneself, and being loved reflect attempts to restore a state comparable to the primary narcissism of infancy.

## Melancholia

In *Mourning and Melancholia*, Freud (1917) developed a theory to explain processes of guilt, internal self-punishment, and depression. To do this, he contrasted states of grief or mourning with the condition of melancholia. Both have in common the experience of pain and sadness, and both are brought on by the experience of loss, but the person in mourning maintains her or his positive self-regard, whereas the person with melancholia feels dejected, loses interest in the world, shows a diminished capacity to love, inhibits all activities, and exhibits low self-regard in the form of self-reproaches. In mourning, libido is gradually withdrawn from the object attachment; in melancholia, the ego feels depleted or comes under attack as though "one part of the ego sets itself over against the other, judges it critically, and as it were, takes it as its object." This critical agency (again a theoretical forerunner of the superego) comes to operate independently of the ego.

The self-accusations of the person with melancholia seem to fit best with criticism that might be leveled against the lost object. In the case of suicidal impulses, the melancholic person seems to be directing at himself or herself the sadism and murderous wishes felt toward the disappointing or lost other. Freud theorized that in the context of the loss of an ambivalently held object, the ego incorporates, or forms a narcissistic identification with, the object. Hostility originally felt toward the object is now directed at the self, giving rise to feelings of torment, suffering, and self-debasement. A predisposition to melancholia may thus result from forming narcissistic object attachments and identifications.

## Dual-Instinct Theory

Over time, Freud's theory of aggression evolved. He had originally considered two types of instincts, the sexual and the ego (self-preservative) instincts, and considered sadism to represent a fusion of the two, with hostility occurring in the context of frustrated libidinal strivings. However, this theory did not adequately address psychological situations in which destructive tendencies seem to be operating independently of libidinal or self-preservative drives. In addition, certain types of pathological conditions seemed to defy the pleasure principle in that experiences of unpleasure were continuously repeated, a phenomenon referred to as the *repetition compulsion* (Freud 1920, 1923, 1924a). Patients with traumatic neuroses were observed to think and dream repeatedly of the painful experiences that brought on their disorder. Other patients with masochistic qualities unconsciously set up life situations in which they suffer. Some individuals in psychoanalytic treatment manifest *negative therapeutic reactions*, in which insights that ought to lead to symptomatic improvement produce worsening instead.

Freud concluded that there must be a separate instinct of aggression, whose aim is destructiveness. The aggressive drive is at work in impulses to harm, in the desire for control and power, in sadistic or masochistic behaviors, in guilt and depression, and in the persecutory fears of paranoid individuals. Freud theorized two general forces at work in the human psyche: the *life instinct* (Eros or libido), operative in positive, synthetic constructive activities; and the *death instinct* (Thanatos), which propels the human organism toward destruction, disarray, and eventually entropy. Although the concept of a death instinct has been rejected by most psychoanalysts, the concept of an aggressive drive and its related conflicts has been of considerable clinical utility.

## Structural Model

On the basis of the preceding considerations, Freud (1926, 1933) revised his theory of the mind into what is now known as the structural or tripartite model (Table 28–7). He conceived of three mental agencies operating in the psyche: the id, the ego, and the superego. The *id* is the biological source of instinctual drives, operating unconsciously and following the pleasure principle. The activity of the id generates the motivational push for gratification of sexual and aggressive wishes.

**Table 28–7 Structural Theory**

| Id |
|---|
| First to develop |
| Completely unconscious |
| Contains all drives |
| Ruled by pleasure principle |
| No awareness of reality |
| **Ego** |
| Second structure to develop |
| Operates on reality principle |
| Mediates conflict among id, ego, and superego |
| Provides reality testing |
| Monitors quality of interpersonal relations |
| Provides synthesis and coordination |
| Carries out primary autonomous functions |
| Defends against anxiety |
| **Superego** |
| Third structure to develop |
| Self-criticism based on moral values |
| Self-punishment |
| Self-praise based on ego ideal |
| Most functions are unconscious |

The *ego* grows out of the id early in human development; it was initially defined by Freud as the "organized portion of the id." Its functions include perception, interpretation of perceptions, voluntary movement, modulation of affects and impulses, cognition, memory, judgment, and adaptation to reality. Subject to conflicting forces from the id, the superego, and reality, the ego synthesizes mental compromises that provide gratification of instinctual wishes in accord with reality considerations and the moral demands of the superego.

The *superego*, which develops as a growth of both the ego and id, consists of the moral standards, values, and

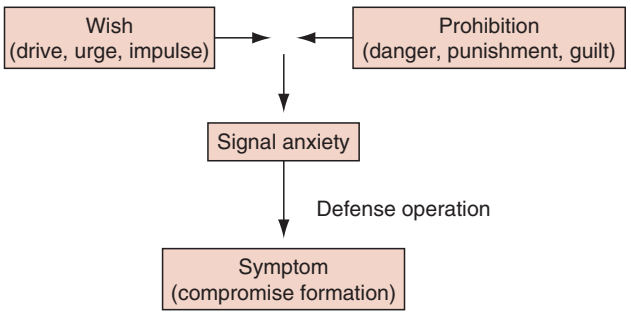



**Figure 28–3** *Freud's theory of symptom formation.*

prohibitions that have been internalized throughout childhood and adolescence. It is the source of internal punishment, which is felt as guilt, and of internal reward. Early in development, the superego has a harsh and archaic quality. During maturation under optimal conditions, it becomes less harsh and comes to include loving components as well. In the structural model, the ego ideal (discussed earlier) is considered a component of the superego, accounting for feelings of shame and pride.

### Anxiety and Symptom Formation

With the elaboration of the structural theory, Freud progressively viewed the nature of anxiety and the origin of symptoms (Figure 28–3) differently. According to his original theory, anxiety resulted from the accumulation of undischarged sexual tensions, caused by inadequate sexual activity in the actual neuroses or by inhibitions due to repression in the psychoneuroses. Later, it became clear that anxiety was more closely related to fear, occurring in response to perceived dangers, either external or internal. This led to a focus on the ego, one of whose functions is to anticipate and negotiate danger situations (Freud 1926). A dangerous or traumatic situation is one in which excessive stimulation threatens to overwhelm the ego's capacity for delay and compromise.

The original traumatic situation is birth, at which time the immature psychic apparatus of the newborn cannot manage the upsurge of instinctual tensions accompanying extrauterine life. During subsequent development, other characteristic danger situations arise (Table 28–8). Because of the helplessness and vulnerability of the infant, the major danger during the oral phase is *loss of the primary object*, typically mother. Later, as the child has greater autonomy and a sense of the separateness of parental objects, *loss of the object's love comes* to be the leading danger. During the phallic phase, the principal danger is the threat of *castration or body injury.* As the superego develops, the primary danger becomes *guilt*, the internalized punishment or loss of love of the superego.

**Table 28–8 Typical Situations of Danger**

| |
|---|
| Fear of instincts (traumatic overstimulation) |
| Fear of object loss |
| Fear of loss of love |
| Fear of castration (body injury) |
| Fear of guilt (moral anxiety) |

In this model, then, the ego is able to anticipate the potentially traumatic danger situations associated with unconscious wishes or impulses that are pushing toward conscious awareness. It mobilizes a small amount of alerting anxiety, referred to as *signal anxiety*, which in turn activates repression and many other defensive operations to prevent the wish or impulse from emerging into conscious awareness.

The ego has as one of its tasks the continual formation of *compromises* among id wishes, the prohibitions, and moral standards of the superego, and the dictates of reality. If these compromises are successful, anxiety will operate predominantly on a signal level and behavior will be both sufficiently gratifying and acceptable in reality. A *symptom neurosis* occurs if these compromises are felt as uncomfortable, painful, or maladaptive. For example, in the development of a phobia, a conflictual unconscious wish and its associated fantasies have been successfully displaced outward, or externalized, and attached to something in the environment that can be avoided. Although the compromise works, in that it prevents conscious recognition of the wish and its associated unconscious fears, the resulting phobic avoidances may lead to a restriction of adaptive functioning. In the neuroses, there is recognition of the difficulties created by symptoms and acknowledgment of a desire to change. In the *character neuroses*, on the other hand, problem behaviors and modes of experiencing, which result from rigid and repetitive use of particular defense constellations, are felt as relatively comfortable and *ego-syntonic*. Because character-disordered individuals often resist the notion that their life difficulties are the result of their own internal processes, a first order of business in their psychoanalytic treatment is to transform their defenses and compromises into *ego-dystonic* experiences in order to create the motivation to change.

## Post-Freudian Ego Psychology

### Ego, Defense, and Adaptation

With the publication of *The Ego and the Mechanisms of Defense*, Anna Freud (1936) categorized and developed the first comprehensive theory of mechanisms of defense (Table 28–9). In discussing the preliminary stages of defense that are first used by the ego to avoid pain from the external world, she succeeded in integrating two main themes in the development of the ego concept: defense and relations with external reality. Anna Freud advocated a shift of the analyst's attention to the ego as "the proper field" for observation, in order to get a picture of its functioning in relation to the other two psychic structures, id and superego. In contrast to impulses of the id that push toward consciousness, the unconscious aspects of the ego do not push toward conscious awareness and therefore offer a greater challenge to the analyst. "All the defensive measures of the ego against the id are carried out silently and invisibly" (Hartmann 1939, p. 8) and must be inferred from their influence on the patient's associations. This requires a shift in the analyst's method of observation. This more detailed methodical attention to the mind's surface, which includes manifestations of unconscious ego activities, provides a much clearer view of the actual workings of the mental apparatus.

In describing three types of transference (transference of the libidinal impulses, transference of defense, and acting

**Table 28–9 Ten Mechanisms of Defense (Anna Freud)**

| | |
|---|---|
| Repression | This process consists of the expelling and withholding from conscious awareness an idea or feeling. It may operate by excluding from awareness what was once experienced on a conscious level, or it may curb ideas and feelings before they have reached consciousness. |
| Regression | This means a return to a previous stage of development or functioning to avoid the anxieties or hostilities involved in later stages; a return to earlier points of fixation embodying modes of behavior previously given up. |
| Reaction formation | This is a method for the management of unacceptable impulses by permitting expression of the impulse in antithetical acceptable form. |
| Isolation | This process is characterized by the intrapsychic splitting or separation of affect from content, resulting in repression of either idea or affect or the displacement of affect to a different or substitute content. |
| Undoing | A forbidden offensive act is ritualistically and magically nullified by atonement, often by religious or self-punitive expiation. |
| Introjection (identification) | Introjection nullifies or negates the loss by taking on characteristics of the object, thus in a sense internally preserving the object. |
| Projection | Unacceptable impulses or ideas are attributed to someone or something else. |
| Turning against the self | Aggressive impulses originally directed toward someone else (the object) are directed back to the self. |
| Reversal | This is turning into the opposite and often applies to affects. |
| Sublimation (displacement) | The gratification of an impulse whose goal is retained, but whose aim or object is changed from a socially objectionable one to a socially valued one. |

out), Anna Freud emphasized the importance of interpreting defense first to effect the dynamic struggle at the exact point where it is occurring. The conflict between emergent wishes and the defenses against them is a repetition in the here-and-now of earlier infantile struggles, and learning how and why the patient's defenses take the particular form they do also valuable information about the development of the ego. Her recommendation that the analyst listen from a point equidistant from id, ego, and superego emphasized the importance of observing neutrally the influence of all three psychic agencies. However, the analyst's activity (intervention) always begins with and is directed toward the ego, and in this sense, the analyst is actually "nearer" to the ego than to the id or superego. The ego wards off not only derivatives of instinctual drives but also *affects* that are intimately connected with the drives. She advocated that priority be given to the interpretation of the defenses against affects as well as defenses against instinctual drives.

Anna Freud's emphasis on the adaptive nature and purpose of defense was further elucidated by Hartmann (1939), who sought to establish a separate biological substrate for the ego in the concept of adaptation. The ego was to maintain a dynamic equilibrium among the instinctual pressures, internal ideals and prohibitions, and the external environment. Its aims were safety and optimal adaptation to inner and outer demands. The ego's coordinating function was further elaborated by Nunberg (1931), who referred to the ego's synthetic function. Waelder (1930) described, in similar terms, the importance of viewing all ego functions from the perspective of an ego-coordinated interaction of trends within the mind representing all the psychic agencies in their instinctual and inhibitory modes. He referred to this as the principle of multiple function. Hartmann further emphasized that it is a mistake to assume that a current function or meaning can be equated with or reduced to its historical precursors and referred to this common type of error as the genetic fallacy.

## Modern Structural Theory

Modern structural theory embraces the presupposition underlying Freud's structural hypothesis that psychoanalysis is primarily a psychology of conflict. That is to say, psychoanalysis approaches mental life from the standpoint of intrapsychic forces in conflict and the compromises that are the outcomes of such intrapsychic conflict. The progressive loosening of modern structural theory from Freud's reified formulations of id, ego, and superego has resulted in a more clinically based focus on the components of psychic conflict (drive derivatives, anxiety, depressive affect, defenses, reality, and moral considerations) accompanied by an enlargement of the experiential and dynamic realm of conflict. Modern structural theory can be seen as a kind of systems theory because it stresses the interrelatedness of all psychic structures and associated behaviors.

These several trends—the jettisoning of Freud's energy concepts, the expansion of the components of conflict, and adoption of an experience-near clinical language to describe conflict—come together in the work of Charles Brenner, whose contributions of the past four decades chronicle the successive steps in the emergence of modern structural theory as a wide-ranging psychology of conflict and compromise formation. Brenner (1982) proposed a substantive revision of Freud's structural theory (Brenner 1971a, 1971b, 1979), not only arguing against the extraanalytical (i.e., biological) presuppositions that Freud imported to the structural model, but also calling into question the theoretical soundness of Freud's definitions of the three psychic structures.

These revisions, taken together, constitute a new language for structural theory. As early as 1971, Brenner argued against the broad, biological meaning Freud imputed to the drives. He defended Freud's theory of the aggressive drive, which derived from "the accumulation of psychoanalytic evidence," but not his theory of a biological death instinct. He went on to redefine the drives as "generalizations" about two classes of "wishes" corresponding to two types of motivation. The language of drives was, thus, replaced by a language of wishes—wishes as uniquely individual drive derivatives. Brenner did not see the id, Freud's repository for the drives, as being as constitutionally determined from the beginning of life and as relatively independent of experience as Freud did. He stressed that from birth, drive-related activities, whether libidinal or aggressive, are influenced by experiential factors that gain expression in ego development.

Because clinical analysis could not support the idea that ego development is separate from drive expression and drive gratification, it followed for Brenner that a sharp distinction between ego and id, even a sharp "heuristic" distinction, could not be maintained. Furthermore, what psychoanalytic theory included under the notion of ego functions is distinguishable from drive, and drive derivatives, only in situations of conflict. Ego functions are the executants of drives and therefore come into opposition to drives only when drive derivatives evoke unpleasure and defense. Conflict is the sine qua non of structural theory.

In stressing the role of the ego in drive gratification from the beginning of life, Brenner was implicitly parting company with Freud, who was content to locate repressed wishes first in the unconscious in the topographical model, and ultimately in the "id of the structural model." Brenner (1982) also radically redefined the concept of the superego, construing it to be a compromise formation functionally analogous to other compromise formations revealed by psychoanalytic investigation: neurotic symptoms, dreams, delusions, character traits, and so forth. He continued to stress that the superego, as a compromise formation, entered into psychic conflict along with id and ego.

## Other Psychoanalytic Perspectives

### Object Relations Theory

There is no unitary theory of object relations; rather, it is a variety of theories that differ from each other in important ways and are often contradictory. For some theorists, the concept of "object relations" refers primarily to interpersonal relations; others emphasize that the concept refers not to external interpersonal relationships but to specific intrapsychic structures. In this latter sense, object relations theory can be defined as "a system of psychological explanation based on the premise that the mind comprises elements taken in from outside, primarily aspects of the functioning of other persons. This occurs by means of the processes of internalization. This model of the mind explains mental functions in terms of relations between the various elements internalized" (Moore and Fine 1990). The concept of an inner world inhabited by mental representations of the self and of objects is central to all object relations theories. This inner world is constructed by the individual through the more or less successful integration of the internalized representations of real significant external figures with whom the subject has interacted. In Schafer's terms (1968, p. 9), "Internalization refers to all those processes by which the subject transforms real or imagined regulatory interactions with his environment, and real or imagined characteristics of his environment, into inner regulations and characteristics." It is the internalized mental representations of self and objects that influence external interpersonal relations.

Most object relations theorists have worked with patients who suffered from severe, frequently psychotic, psychopathological conditions. Finding previous theories insufficient to conceptualize or treat these disorders, they have searched for new ways to understand their patients. Although all acknowledge their debt to Freud as the originator of the psychoanalytic theory of the mind, object relations theorists were dissatisfied with Freud's psychoanalytic libido theory, which stressed that the motivation in human beings to relate to others results from internal drives for need gratification.

The term *object* occurred in Freud's writings as early as 1905, and he defined the object of an instinct in 1915 as "the thing in regard to which or through which the instinct is able to achieve its aim." According to libido theory, the object is the creation of the drives. Where there is no inner tension, the *pleasure principle* reigns, and there is simply a state of quiescence (as with the satiated infant falling asleep at the breast). The prototype for the earliest object relationship is the sucking infant, in whom hunger causes buildup of tension, which is discharged during nursing. The breast is the original object. It gradually becomes associated with need satisfaction in the first few weeks of life. Freud's choice of the term object, which he used to describe the significant other in human relationships, demonstrates the influence of the mechanistic approach that was guiding his conceptualization. (Freud's libido theory is more fully discussed in an earlier section of this chapter.)

Libido theory was criticized for its disregard of the person as a social animal, in conjunction with a growing recognition that the existence and quality of our relationships with others determine our adaptations from infancy onward. Freud's struggle to incorporate object relations can be traced in a series of papers (Freud 1914a, 1915, 1917) culminating in *Beyond the Pleasure Principle* (Freud 1920).

#### Melanie Klein

Klein's theoretical formulations grew out of her observations of the psychotic children she treated. Although some of her controversial ideas have never gained acceptance in mainstream American psychoanalytic thought, her formulations about the importance of aggression and envy, particularly in more primitively organized patients, as well as her understanding of primitive defensive operations, have been central in the thinking of later object relations theorists.

Klein believed that fantasy exists from the beginning of life and is by definition the mental expression of the instincts. She conceptualized the neonate as having an active inner world of fantasy based on its innate libidinal and aggressive drives and their aims. The death instinct is central to Klein's theories. It finds its expression in earliest infancy in aggression against the object and the self.

Klein modified Freud's theories of psychological development drastically. As mentioned, she focused predominantly on infancy, describing two psychological "positions" during the first year of life (which was for Freud the oral stage of development). These are the paranoid–schizoid position (Table 28–10) during the first 6 months of life and the depressive position during the second 6 months. The

**Table 28–10 Characteristic Defense of Paranoid–Schizoid Position**

| |
|---|
| Projection |
| Introjection |
| Projective identification |
| Splitting |
| Idealization |
| Omnipotence |
| Denial |

paranoid–schizoid position is characterized by the defenses of projection, introjection, projective identification, splitting, idealization, omnipotence, and denial (Klein 1946).

These defenses are termed primitive defenses because they have their origin in early development, in contrast to the higher level defenses that evolve later. *Projection* is the defensive externalization of a threatening internal impulse, ideal, or feeling. Because this is the predominant defense of earliest infancy, the young infant believes that the dangerous impulse, idea, or feeling, which actually originated from within as a manifestation of its own intense drives, is coming from an external source. Therefore, the feared threat is perceived as external rather than internal. This results in anxiety about being attacked from without, termed paranoid anxiety. *Introjection* takes place when an external object is taken inside (in fantasy) and becomes part of the internal rather than the external world. The paranoid position is characterized by projection and introjection taking place in cycles. *Projective identification*, as conceptualized by Klein, is a complicated primitive defense that involves the projection of an internal object (usually a bad one) into an external object, followed by identification with the external object that is now experienced by the infant as having been contaminated by the bad object. *Splitting* is the intrapsychic separation of the object into different partial objects. Typically, an unrealistically all-good (idealized) object and an equally unrealistically all-bad object are constructed. For Klein, the innate aggressive drive of the infant is central and the paranoid–schizoid position is viewed as a "normal" early psychosis from which the infant gradually emerges. In the course of normal development, in the presence of adequate parenting that provides the consistent availability of predominantly benign external objects, the cycle of projection and introjection gradually results in the introjection of more benign aspects of the external object (parent or other caretaker), and the bad internal object is gradually detoxified.

In the depressive position, infants, who have now developed the capacity to accept the existence of an external good object (for example, the nurturing breast of mother), are for the first time "grateful" to caretakers. However, this too presents a problem, for the infants now fear that their attacks on the giving object (which in the paranoid position they had felt justified in making) will damage the good object. This leads to infants' making efforts to repair the damage as well as to the emergence of self-directed aggression (guilt). Just as paranoid anxiety was central during the paranoid–schizoid position, depressive anxiety takes center stage during the depressive position. Infants now fear in the loss of caretakers. The depressive anxiety is defended against by denial and by a fantasy of being omnipotently able to restore the (idealized) good object. This is the "manic defense," for Klein a normal part of the depressive position in the second 6 months of life (Klein 1940).

## Donald W. Winnicott

Donald W. Winnicott was both a practicing pediatrician and a psychoanalyst for most of his professional life. He worked with many categories of patients—including regressed adults, disturbed and delinquent adolescents, and problem children—and treated mother–infant–toddler pairs. Working with such a diverse population of patients, he experienced the deficiencies of both the libido and the structural theories. The libido theory focuses on drives and anergic concepts; the structural theory concentrates on oedipal development and in Freud's formulation, places the "narcissistic neuroses" (i.e., the psychoses) in a separate group without a framework for treatment. Although he found the existing theories to be problematic, Winnicott attempted to fit his ideas within them. He handled his disagreements with Freud's ideas by reinterpreting them to meet his need to deal with highly disturbed early relationships. For example, he reworked the Oedipus complex to emphasize Klein's conflict between love and hate, rather than Freud's conflict between instinctual desires and fear of castration. (Winnicott acknowledged his debt to Klein, particularly with reference to the depressive position.) Another way in which Winnicott reinterpreted Freudian theory was to focus on the central function of an early maternal "holding environment." This primacy of early bonding contradicted Freud's concept of "primary narcissism," which held that the infant is at first not oriented toward others and that relationships become important only later, secondary to drive frustration. Winnicott simply changed Freud's meaning and said that what he *really* meant by primary narcissism was the state of early dependence on the mother.

Every individual, according to Winnicott, develops *true* and *false selves*. Insofar as the mother is empathically attuned in to her child, without intruding on the child, there is a core of feeling of wholeness and goodness from which the true self develops. With appropriate "mirroring," the child learns to play, to be creative, and to be alone with comfort. Those developmental achievements *create* the *fundamental organizer*, the true self (at times also called the *ego* by Winnicott). However, insofar as there is a mismatch in the relationship, the child's development is stunted, and the child develops a false self. In healthy people, the false self is relatively minimal. It is represented by politeness and social manners; however, in extreme states of illness, it may be the main self-representation. The genesis of such a severe pathological process is based on the seduction of the infant into complying with the imposed demands of the unempathic mother. The infant then develops false relationships; the child learns to live by imitating, becomes less spontaneous and creative, and is unable to play. A lifelong feeling of unreality and futility results. One positive function of the false self is that it protects the nascent true self from a damaging environment (Winnicott 1965, pp 140–152). Therapy of individuals with a dominant false self begins with accepting that self, and it proceeds through periods of negative transference and profound dependence toward a more full development and expression of the (previously hidden) true self.

Winnicott regarded psychoneuroses as grouped around defenses (especially repression), in contrast to psychoses, which result from annihilation anxiety and the breakdown of defenses. He believed that the breakdown has its roots in the original breakdown of "good enough" mothering and a consequent inadequate development of the true self. Winnicott (1965, pp 124–139) maintained that the psychoses are analyzable and that there is a gradation from normality through psychoneuroses and psychopathy to psychosis. However, psychotic patients *do* bring particular transference and countertransference problems to the analysis. Because

psychotic patients evoke annihilation anxiety in the analyst, countertransference hate is inevitable and is difficult to cope with, despite such compensations as being paid and being able to end the hour. These patients answer love by evoking hate; this is really a test to see whether the analyst can hate them "objectively." The task of the analyst is to keep the hate latent, as the mother must when the infant frustrates her, until the patient has become healthier through the analytical process. The analyst must then tell the patient about the way the hatred had been evoked and how the analyst held it in abeyance until the patient was stronger (Winnicott 1947, pp 194–203).

Winnicott's *transitional object* is a concrete, real external object (unlike the intrapsychic objects that we have being discussing). It is the infant's first "not me" possession and is imbued with attributes of both mother and infant. The transitional object evolves out of activities occurring in the "space" between infant and mother. These activities generally have close links to the mouth or the mother's body. For example, the child may at first put a fist or thumb in the mouth or stroke the corner of a blanket. The blanket gradually becomes special and essential to the child (the familiar security blanket). A stuffed toy such as teddy bear or even a hard toy may become a transitional object. This process is based on the facilitating, appropriate response of the mother. The blanket may become smelly, yet it must not be washed; and the teddy bear may become tattered, yet it must accompany the toddler everywhere. The evolution of the transitional object is the precursor of the child's ability to play. As an intermediary object, the transitional object also serves as a precursor of the ability to be alone. There is wide variation as to when the transitional object develops, but it usually evolves from about 4 to 12 months (Winnicott 1971).

## John Bowlby

Bowlby began his study of the attachment of children to their caregivers in the late 1940s. His work was contemporaneous with that of Spitz, who observed the profound depression produced in infants who were deprived of human contact (Spitz 1946). He came to differ with Spitz in his interpretation of the meaning of the observations, but their actual observations are highly consistent with each other. Bowlby collaborated initially with James Robertson in his naturalistic observations of young children who are separated from their mothers (much more briefly than the anaclitically depressed infants observed by Spitz) because of the mother's hospitalization (Robertson and Bowlby 1952). The observations clearly confirmed that separation produced extreme distress in children and that there were significant long-term adverse effects on the children as a result of even relatively brief separations. These initial observations, combined with the fact that there was at the time no adequate theoretical framework for understanding the profound effects of separation, led Bowlby to research and formulate theories about attachment, separation reactions, related anxiety, depression, and psychopathological processes originating in disturbances in attachment.

Bowlby's major thesis was that the child's tie (attachment) to the object, for which he preferred the term attachment figure, is primary and instinctive (in the sense of instincts shared by humans and animals rather than in Freud's sense of instinctual drives). This attachment is *not* secondary to the gratification of any drive. It is independent of the need for food and warmth and of any other striving. He strongly opposed the theoretical position that there is *ever* an early objectless state. Bowlby buttressed his argument with observations of nonhuman primates. He made the point that human infants are born in such a helpless state that the majority of the observable early attachment behavior must be on the part of the mother, whereas in some other primates, the baby is able to cling from the time it is born. In all primates, great distress is observed when mother and baby are separated, and the effects of separation are long-lasting, producing visible anxiety and a marked increase in clinging at ages when the clinging is decreasing in unseparated animals. He referred to the work of Harlow and Harlow (1962), whose experimental work on maternal deprivation in monkeys is now considered classic. Harlow's observations supported Bowlby's thesis that there is a primary need for clinging and contact. His motherless monkeys strongly preferred to cling to a soft cloth dummy mother that provided no nourishment than to a hard wire dummy mother that was equipped with a bottle of milk. In addition, monkeys raised without their mothers were highly abnormal in interaction with other monkeys later in life, despite the fact that their needs for nourishment, shelter, and warmth had been met.

Bowlby went on to extend his observations of attachment behaviors and responses to separation across various cultures, citing anthropological observations. "No form of behavior is accompanied by stronger feeling than is attachment behavior. The figures towards whom it is directed are loved and their advent is greeted with joy. So long as a child is in the unchallenged presence of a principal attachment-figure, or within easy reach, he feels secure. A threat of loss creates anxiety, and actual loss sorrow: both, moreover, are likely to arouse anger" (Bowlby 1969, p. 209). For Bowlby, the unpleasurable affects of anxiety, grief, and anger were *secondary* to the thwarting of attachment. His theoretical position was in many ways in keeping with the views of Winnicott, Fairbairn, and Guntrip.

## Margaret Mahler

Mahler primarily used the libido theory's drive model in describing the first few weeks of life, which are centered on achieving homeostasis and which she called the "normal autistic phase" (Mahler et al. 1975). According to Mahler, the newborn does not differentiate internal from external stimuli; there is only tension and satiation. By the second month, the infant begins the "normal symbiotic phase," in which there is a relationship characterized by an "omnipotent fusion," a "delusion of a common boundary" with "the need-satisfying object." From the infant's perspective, mother and child are a "dual unity." If the symbiotic period progresses normally, the infant begins to develop "memory islands" and a "core sense of self," which are preparatory for the "hatching' that will occur at about 5 months. In her description of this period, Mahler used the concepts of libido theory but also referred to both Rene Spitz's observations of the first months of life* and to Winnicott's concept of the holding environment.

What follows these earliest months, the period from about 5 months to beyond 3 years, is termed "the psychological birth of the human infant" by Mahler. During this time,

the stages of the separation—individuation process occur. Mahler formulated a series of subphases of this process. In summary, the subphases are the following:

1. *Differentiation*: 4 to 8 or 9 months. During these months, there is the "first tentative" pushing away from "completely passive lap-babyhood." The 5- to 6-month-old infant gradually begins to creep. During this time, transitional objects develop (a term coined by Winnicott and discussed earlier in this section). The infant soon begins differentiating, with more or less anxiety, the faces of strangers from primary caretakers.
2. Practicing
   a. *Early*: 7 months to about 1 year. This subphase overlaps with differentiation. Infants begin to crawl and stand. They become upset if they end up too far away, frequently paddling back to mother for "emotional refueling."
   b. *Practicing subphase proper*: about 12–18 months. This subphase begins with walking and ushers in a "love affair with the world." The children are frequently elated, curious, and adventurous. They are delightful to observe but must be carefully watched because they are likely to dash blithely into precarious situations. They tend to be impervious to minor falls and other mishaps.
3. *Rapprochement*: gradually, from about 15 to 22 months or more, the carefree behavior gives way to anxiety about separation and fear of "object loss." The toddler is learning that "the world is not his oyster" (Mahler et al. 1975, p. 78). The child alternates between demanding, negativistic, challenging behavior, and seeking love and approval by "wooing" behavior.
4. "The child on the way to object constancy": 24 months to 3 years and beyond.

Mahler was careful to blur the boundaries of each of the subphases. She stated that for all of our lives, we are "both fully 'in' and at the same time basically separate from the world 'out there'" (Mahler et al. 1975, p 3). The optimal unfolding of phases depends on the emotional availability of the mothering person. If it is disrupted in the earliest months, the result can be the development of an infantile psychosis *either* because of lack of maternal availability or empathy or because, for constitutional reasons, the infant is unable to respond to the mothering. Regardless of whether the cause is environmental or constitutional, if the symbiotic mother—infant relationship fails to provide safe "anchoring" or discourages hatching, the separation—individualization process cannot proceed normally. Later phases may also be disrupted, for example, by overprotective mothering, which inhibits independence, or because of precocious motor development, which may lead the infant to separate physically from the mother before psychological readiness for that degree of separation. In addition, Mahler (1972, p. 494) stated that the success or failure of the rapprochement subphase lays "the foundation for subsequent relatively stable mental health or borderline pathology."

## Otto Kernberg

Otto Kernberg believed that it is possible to integrate an ego psychological approach to the understanding of mental functioning with an objects relations perspective. His major contributions have stemmed from his work on the psychoanalysis and psychotherapeutic treatment of patients with severe character disorders, particularly those with borderline personality organization, as well as patients with narcissistic character (Kernberg 1984). This section summarizes his contributions to object relations theory.

The primitive defenses of splitting and projective identification, first described by Klein, are central to the diagnosis of borderline personality disorder as conceived by Kernberg. Kernberg's depiction of the inner world of borderline and psychotic patients is, however, uniquely his own. Splitting breaks up the internal representation of objects and of the self into part object representations, each with an associated affect. Thus, objects are perceived as either all good or all bad in relationship to the self. Projective identification, first conceptualized by Klein (1937) as a primitive defense of the paranoid–schizoid position (see section on Klein), was further elaborated by Kernberg. The central feature of projective identification, according to Kernberg, is that projective identification which always involves the projection of an internal object relation with its associated affect. When projection is effective, the subject eliminates the unacceptable impulse or idea from any connection with the self. In contrast, in projective identification, the connection to the unacceptable contents is preserved along with the tie between the part self and the part object. The connection cannot be totally eliminated.

Kernberg envisioned the inner world of the borderline or psychotic patient as being populated by numerous unintegrated part self-part object dyads that are each linked by a predominant affect. These internal nuclei are kept separate by the defense of splitting. The borderline individual projects these pathological inner contents onto any significant other with whom he or she interacts. Which of these self-object-affect structures is active can shift from moment to moment; this results in the chaotic and shifting pattern of relationships that is the essence of what is observed clinically in patients with borderline psychopathological disorders (who can be described as being stably unstable). Depending on what happens in the course of an interaction, the relationship between the patient and other can shift rapidly, for example, from that of the good nurturing mother interacting with the blissfully nursing infant with a sense of mutual pleasure, to that of the rageful depriving mother interacting with the rageful deprived infant. Such a shift can occur instantaneously in the course of an interview if the interviewer does something that is perceived by the patient as being depriving or attacking.

## Erik H. Erikson

Erikson, a psychoanalyst and integrative theoretician, contributed to psychoanalytic theory and to the practice of American psychiatry. He divided the entire life cycle into eight stages, thus extending into adulthood Freud's notion of infantile psychosexual stages while at the same time broadening Anna Freud's concept of the developmental lines of childhood. Erikson (1959) considered each stage of psychological development to have its own critical developmental task. Furthermore, he believed that the achievements and failures of earlier stages influence later stages, whereas later stages modify and transform earlier ones. As shown

**Table 28–11 Erikson's Stages of Development**

| Psychosexual Stage | Psychosocial Crisis | Basic Strength |
|---|---|---|
| Oral–sensory (infancy) | Basic trust vs. basic mistrust | Hope |
| Anal–muscular (early childhood) | Autonomy vs. shame and doubt | Will |
| Genital–locomotor (play age) | Initiative vs. shame and guilt | Purpose |
| Latency (school age) | Industry vs. inferiority | Competence |
| Puberty (adolescence) | Identity vs. identity confusion | Fidelity |
| Genitality (young adulthood) | Idtimacy vs. isolation | Love |
| Procreativity (adulthood) | Generativity vs. stagnation | Care |
| Generalization of sensual modes (old age) | Integrity vs. despair | Wisdom |

*Source*: Modified from Erikson EH (1982) The Life Cycle Completed. WW Norton, New York, pp 32–33). Copyright 1985 WW Norton.

in Table 28–11, Erikson (1982) linked each *psychosexual* stage to a particular body zone or zones. In each stage, the individual negotiates a phase-specific *psychosocial* developmental task toward the achievement of specific *strengths.* In this model, each individual evolves a mode of interpersonal and intrapsychic functioning with emergent social capacities uniquely adapted to a particular social milieu. The "crises" of each stage are normative, not pathological ones, and the developmental tasks are never fully resolved in each stage but continue to be worked out throughout the life span.

To simplify, life begins with the oral-sensory stage of infancy, marked by the potential development of what Erikson called basic trust aiming toward the achievement of a sense of hope. In early childhood, the second or anal-muscular stage, the toddler struggles with the task of developing a sense of autonomy aiming toward the capacity for strength of will. Relative degrees of failure at this stage may predispose the child to shame and doubt. Next, Erikson's play age, coinciding with the nursery school-age or preschool-age child, is marked by the genital-locomotor stage or third stage of development. Here the child's task is to develop a sense of initiative as opposed to further shame or guilt. The lasting achievement of this stage is a sense of purpose. In the fourth stage, the school-age child, in what is traditionally called the stage of latency, tries to master the crisis of industry versus inferiority aiming toward the development of a sense of competence. At puberty, the fifth stage, the task of adolescence is to navigate the familiar "identity crisis" (see later) as each individual struggles with a degree of "identity confusion." The lasting outcome of this stage can be a capacity for fidelity. Young adulthood, at the stage of genitality or sixth stage, is marked by the crisis of intimacy versus isolation, out of which may come the achievement of a capacity for love. In the procreative period of adulthood, the seventh stage, the individual may develop a capacity for generativity at the risk of stagnation. Out of this struggle comes the ability to care. Finally, Erikson viewed the wisdom of old age, the eighth stage, as a summation of all the achievements of the previous seven stages. Similarly, he considered that all of the modes of functioning in the previous psychosexual stages come into play at this stage. Hence, the task of old age is to develop a sense of integrity at the risk of despair.

## Self-Psychology

Within psychoanalysis, Freud (1911b) posited that psychological investment in the self (narcissism) antedated and always remained more important than interest in others or the external world. Heinz Kohut (1971) held that the meaning of self could be empathically comprehended. He viewed empathic comprehension as the fundamental mode of psychoanalytic investigation (Kohut 1959). It is the knowledge of the other's experience, what it is like to be in that person's shoes. Empathy is the understanding of another's complex psychological experience as whole. He used the term self to refer to a center of initiative, experience, or the core of personal being. Kohut largely ignored the long history of the idea of self in religion, philosophy, and psychology. He did not address the conceptual complexities that result from attempts to be more precise about the ideal (Meissner 1986) or the evidence that the self-experience varies dramatically across cultures. Like Freud (1905a, 1905b), who claimed that the sexual quality of experience was immediately apparent, Kohut claimed the self-experience was directly knowable to us all. Many other authors have addressed the question of the meaning of the self. They have put forward such ideas as the continuing experience of one's affective responses (Emde 1983) or the sense of that which absolutely belongs to one (Goldberg 1983).

Kohut's singular contribution was the idea of the *self-object.* Clinical observations led him to believe that the self could survive and prosper only in the context of experience with others. These clinical experiences find support by observations of infants and young children that consistently show that appropriate psychological interactions with others are essential for early psychological development (Stern 1985). These experiences Kohut called self-objects, that is, objects (in the psychoanalytic sense of intrapsychic representation of other people) that are necessary for the well-being of the self. Kohut was speaking of intrapsychic experiences, not interpersonal relations. Intrapsychic experience may be contingent on interpersonal events. Self-objects remain essential throughout life. Contrary to psychoanalytic theories like Mahler's that characterize maturity in terms of autonomy (Mahler 1975) self-psychology views mature people as ordinarily dependent on others for appreciation, comradeship, meaning, and solace.

The study of self-psychology began with the realization that many symptoms of psychological distress could be understood as arising from disorders of the self. These include symptoms involving direct experiences of an endangered, enfeebled, or fragmented self; and symptoms arising from unsatisfactory attempts to protect an endangered self. Sometimes the symptoms of self-pathology are acute, but more often they are chronic states whose intensity varies as the self is felt to be more or less in danger. Examples of these symptoms include certain depressive states, traumatic states, hypochondriasis, some forms of rage, and direct experiences of profound disorganization. Many symptoms are understandable as attempts to repair an impaired or endangered self. These include relations with

others designed to achieve urgently needed self-object experiences and activities designed to soothe or stimulate the self.

When development goes well, self-objects ensure that the painful experiences of living are not overwhelming. The child may experience painful and distressing events but not to such an extent that the capacity to maintain a cohesive and vigorous sense of self is threatened. Responsive self-objects maintain a milieu in which the child reels safe, appreciated, and able to comfortably idealize others in a developmentally appropriate way. The environment empathically comprehends and supports the child (Stern 1985). In such an environment, the child thrives. She or he can increasingly maintain self-object functions that were performed by others in their physical absence.

Several types of self-object failures seem to lead to later disorders of the self. Early deprivation of human responsiveness is psychologically and physically devastating to infants (Spitz 1945). Less severe deprivations may result in serious lack of adequate experiences with caretaking self-objects. For example, children of depressed mothers do not receive ordinary enthusiastic responsiveness, engagement, and mirroring (Cohler 1984, Radke-Yarrow et al. 1985). Many difficulties in life may deprive a child of needed self-object experiences. These include loss of a parent, parents who are psychologically unavailable because of personal pathological processes or life circumstances, caretakers who are made anxious by and therefore avoid developmentally appropriate demands (e.g., for the opportunity to idealize), and caretakers deficient in empathy who do not comprehend the child's developmental needs.

## Relational Perspective, Interpersonal Psychoanalysis, Social Constructivism, and Intersubjectivity

### Relational Perspective

There is a momentum in contemporary psychoanalytic writing toward the full appreciation that the analyst's personal involvement in the analytic process is both inevitable and useful (Mitchell 1988b, Hoffman 1992b, Renik 1993a, Gill 1994, Hoffman 1994, Roughton 1994). This relational perspective does not constitute a new psychoanalytic theory but, in fact, links together loosely a wide range of theoretical models, including interpersonal psychoanalysis, British object relations theory, self-psychology, intersubjectivity, and social constructivism. The relational perspective addresses a different understanding of the role of the analyst as well as different ways of thinking about the basic motivational forces in human development.

This cluster of otherwise diverse and often competing theories has in common a greater emphasis on the actual here-and-now interaction between analyst and analysand, whether this is viewed in interpersonal or intrapsychic terms. It encompasses the participant observation of the interpersonalists, the projective identification and transference-countertransference focus of the British object relationists, the empathic immersion and self-object phenomena of the self psychologists, the analyst's stance *within* the observational field of the intersubjectivists, and the social constructivists' emphasis on the effect of the analyst's personal emotional presence on the analysand's experience.

These theoretical perspectives also have in common a deemphasis of Freud's drive theory as the basic motivational force and a greater emphasis on some version of the idea that the human organism seeks attachment and relations with others, not just drive discharge, as a basic motivational system. In this relational perspective, the individual as a separate entity is not the basic unit of study. Rather, the focus is on the interactional field, whether as mother-infant or analyst-analysand (Mitchell 1988b).

The dividing line between this relational perspective and the work of some contemporary classical analysts is less than sharp and clear, particularly in the clinical interchange. As in most psychoanalytic controversies, theoretical explanations tend to sharpen conceptual differences, even when clinical practice reveals much similarity and overlap in what is actually said and done. Some writers, Winnicott and Loewald, for example, continued to use the terms *drive* and *instinct* but expanded their meanings to include a relational perspective. Loewald (1978) redefined instinct not as an innate given but as developing out of interactions between the infant and the infant's human environment. Although they may differ in degree and in balance, drive theorists and relational theories agree—as Freud himself repeatedly stressed—that both innate and experiential factors are influential, and it seems more useful to view the two stances as dialectical rather than as dichotomous.

Nevertheless, there are significant differences of emphasis, and certain points are more easily clarified by highlighting the contrasting points of view. The more rigorously analysts adhere to classical theory, the more they will work from the perspective of a one-person psychology, in which the locus of the psychoanalytic process is within the analysand's mind and in which everything is understood through the prism of intrapsychic compromise formation, unconscious fantasy, and psychic reality. Resistance and transference are the unfolding of the analysand's inner world in this new analytical setting, in which repetition of old experiences and response patterns is fostered, and the interpretive focus is on intrapsychic defensive operations that interfere with free association. The actual persona and the person and the behavior of the analyst are considered less important in determining the nature of transference and resistance. The analyst's position outside the observational field is thought to allow a more objective perspective from which to make confident interpretations of the analysand's intrapsychic experience and to monitor the analyst's own countertransference reactions that might have a negative impact on the interpretive work.

However, there has been an evolution of thinking among many analysts on these issues, so that differences between classical and relational perspectives are less striking than when each is presented in its most defining form. Many analysts may still accept the basic tenets of classical theory yet incorporate a degree of relational perspective in their clinical writing and may, for example, work comfortably within a clinical perspective that focuses on the here-and-now in the transference (Gill 1982), that recognizes countertransference as an ongoing source of data (Jacobs 1986), and that considers enactments to be inevitable and to provide useful insight (Chused 1991, McLaughlin 1991, Renik 1993a, Roughton 1994).

Nevertheless, the relational perspective is defined by its much greater emphasis on a two-person psychology, both

in the developing individual and in the clinical experience (Bachant and Richards 1993). The infant and the analysand both seek contact and interaction. Development and therapeutic effect both are seen as mediated through relationships. The locus of the psychoanalytic process is the interactive field of the two persons, event though the primary purpose is the understanding of the inner world of the analysand. As such, there is a tilt toward viewing the analytical relationship more in interpersonal terms rather than solely through the prism of the analysand's intrapsychic experience. Analysts are more likely to use their acknowledged subjectivity as a tool than to distance themselves behind a presumed objectivity. Transference is more often interpreted in its immediate manifest response to the actual person and behavior of the analyst than as a distorted perception of a neutral, objective analyst. Although interpretation and insight are still considered essential aspects of the analysand process, the therapeutic effects of the relationship are accorded a more prominent place.

Object relations, self psychology, and intersubjectivity are discussed elsewhere; the remainder of this section concentrates on interpersonal psychoanalysis and social constructivism as important embodiments of the relational perspective.

## Interpersonal Psychoanalysis

In the late 1970s, a divergent approach to psychoanalytic theory and practice began to coalesce in the work of Harry Stack Sullivan, Erich Fromm, Freida Fromm-Reichmann, and Karen Horney around some commonly held assumptions. They shared the belief that classical drive theory was fundamentally flawed and that Freudian theory underemphasized social and cultural influences in explaining normal and pathological developments of personality. In discarding drive theory and emphasizing cultural influences, these analysts have often been misunderstood as having a "sociological" view of the individual as molded passively by the environment; their clinical work has been criticized as being superficial and ignoring passions and deeper conflicts. As Greenberg and Mitchell (1983) pointed out, however, this is a serious misreading of their work. Deep, intense passions and conflicts are not ignored, but these analysts rejected the idea that they arise as derivatives of instinctual drives. Rather, they see passion and conflict arising in the relationships with others, whether real or imagined.

At about the same time that this interpersonal tradition was developing in the United States, another major contribution to the shift from a drive model to a relational model came from W. R. D. Fairbairn in Edinburgh, working in relative isolation from his Kleinian colleagues in England. Unlike Sullivan, Fairbairn did not emphasize cultural factors so much as challenge the basic understanding of libido theory and assumptions about psychosexual development. Still working within the Freudian framework, he sought to redefine the basic motivational principle of libido not as pleasure seeking but as object seeking. Fairbairn, like others who are now identified under the umbrella of the relational perspective, saw the human experience as a search for contact and attachment, not as a set of instinctual tensions seeking release (Greenberg and Mitchell 1983).

Fairbairn had an important influence on British object relations theory and deserves recognition, along with Sullivan, as one of the seminal thinkers in what has lately been characterized as the relational perspective. It would not be correct, however, to identify him with interpersonal psychoanalysis, which is the movement that diverged sharply from classical psychoanalysis under the influence of Sullivan and those who followed him in the United States.

Sullivan introduced the term *interpersonal* in 1927, and it is his name that has been most closely identified with that perspective. He saw the human mind as inherently dyadic and from earliest infancy in constant responsive interaction with its caretakers. Research on infants supports such a view (Stern 1985). Although the terms interpersonal and intrapsychic have come to represent a dichotomy in much of psychoanalytic discourse, Sullivan did not reject the concepts associated with the intrapsychic perspective so much as object to the exclusion of the interpersonal from the classical perspective. What he did uncompromisingly oppose was drive theory because, as understood at that time, the drives as the primary motive force arose independently in the id and were sheltered from the interpersonal field. As Mitchell (1988a) has pointed out, the concept of drive has been increasingly "interpersonalized" in later theoretical developments, so that contemporary interpersonalists find the concept less objectionable.

Sullivan was not an integrative theorizer or a compelling writer in the ways that Freud was. In addition, he was not a rebel from orthodox psychoanalysis, as were other innovators. He came from the world of general psychiatry with a talent for working with patients suffering from schizophrenia in an operationalist methodology, and he tended not to use the language of psychoanalysis but to develop his own nomenclature. These factors, apart from the perceived merit of his ideas, have made him less known to more traditional psychoanalysts. Even some contemporary interpersonalists believe that Sullivan's theories lacked a sufficient conception of the inner world (Mitchell 1988a). For example, he explained mental disorder as the result of inadequate interpersonal communication due to the interfering effect of anxiety (Levenson 1983). Those who have studied his work stress that what sounds naïve in his explanations is nevertheless grounded in a depth understanding of the human condition and a respect for the uniqueness of the individual, and this allowed him to be uncommonly effective with patients. These therapeutic principles have endured and are now finding new credibility in the current interest in the relational perspective. More in-depth study of Sullivan's ideas and of interpersonal psychoanalysis than can be presented here is recommended for those interested (Sullivan 1953 and 1956, Guntrip 1961, Mullahy 1970, Greenberg and Mitchell 1983, Levenson 1983, Antonovsky 1987, Mitchell 1988a).

## Social Constructivism

Hoffman (1983, 1991, 1992a, 1992b, 1994,) has introduced a new paradigm for understanding the psychoanalytic situation, which he calls social constructivism. The "social" part of the term refers to the analyst's personal presence and involvement in the analytical situation, and thus it is linked to the interpersonal and the relational perspectives. However, Hoffman emphasized that beyond the shift from drive to relational issues of those perspectives, his new paradigm proclaims a shift from a positivist to a

constructivist model as well. That is, not only is the analyst personally involved in the analytical situation, but personal involvement is wedded to the construction of meaning for the patient, because the analyst's understanding is always a function of her or his perspective at any given moment. In Hoffman's view, the analyst is continually implicated in "constructing" the patient's experience, and not to attend to that aspect of the analytical relationship is to miss the vital issue.

Constructivism generally refers to the concept that meanings are generated, as texts are interpreted, rather than there being one true meaning awaiting discovery. Hoffman's social constructivism goes further. It is not simply an interpreting of reality but a shaping of it through the mutual and reciprocal influences in the interpersonal analytical relationship. He also contrasted his view with the constructivism of Schafer (1983), which he described as concerned primarily with the effect that the analyst's theoretical bias or occasional countertransference has on the way the analysand's story emerges. Hoffman objected to Schafer's view of countertransference as occasional and undesirable and to be overcome. He wanted to free analysts to be themselves and to speak their minds, constrained only by the purposes of the analysis (Hoffman 1992a, 1992b, 1994).

Lest this sound like casting off all knowledge and previous experience in favor of uncharted spontaneity, Hoffman (1992b) was quick to assure his readers that he was advocating a subtle diminishing of the authority of theory in favor of a subtle increase in respect for the analyst's awareness of and use of personal subjective experience in guiding what he or she does and says. Subjective experience, for both analyst and analysand, is a continuous stream, only a small fraction of what can be attended to at any given moment. What is selected from that stream of experience is influenced by the unconscious determinants what include the patient's transference and the analyst's countertransference. Hoffman's point is that it is impossible to avoid the analyst's influence in this subtle selection. Therefore, rather than attempting to control subjectivity and remain outside the action, analysts should feel free in their subjectivity and embrace the uncertainty of this freedom (1992a).

Hoffman made the point that patients are extremely sensitive to certain facets of their analysts' ambiguous responses to them. What is often called distortion in the transference is instead a highly selective attention to something present in the analyst, sometime that one patient notices but another will ignore (Hoffman 1983). As Racker (1968) has said, interpreting the transference fully means being receptive to the patient's interpretation of the countertransference.

Hoffman (1992b, p 302) was careful to place these innovations within a firm psychoanalytic frame, and he detailed its features, which include "a circumscribed time and place; the asymmetry of personal expression in the process; a primary interest in exploring the patient's experience, a commitment by the analyst to critical reflection on his or her own participation; and a sense of the relationship as a whole as a means of promoting the patient's development. Every interaction in this context is experienced by the analyst as a psychoanalytic interaction. There are no exceptions. . . . the stamp of the analytic situation should never be lost on the participants."

Social constructivism is Hoffman's term, and it is his papers that most fully explore these concepts. Nevertheless, Gill's contribution to this concept must also be acknowledged, as Hoffman carefully does. Through a series of works in the past 15 years, Gill's thinking about transference and mutual influence and constructivism has evolved in this direction, although he may not have gone as far as Hoffman. Gills (1994, p 156) view of transference is "the analysand's plausible experience of the relationship. It is based on the contributions of both participants to the here-and-now interaction as well as on their respective past experiences." Countertransference is defined similarly as based on contributions of both participants in present interaction and from past experiences. Although Gill kept his roots in classical theory, he adopted a constructivist perspective, and he insisted that psychoanalysis is both a one-person and a two-person psychology, that the innate and experiential are always working together, and that the analytical situation is a continuing interaction between two participants that must be the subject of a mutual exploration (Gill 1994).

### Intersubjectivity

Intersubjectivity in psychoanalysis refers to the dynamic interplay between the analyst's and the patient's subjective experiences in the clinical situation. To some extent, all schools of psychoanalysis agree on the significance of intersubjectivity in psychoanalytic work. However, in the current psychoanalytic literature, the concept of intersubjectivity constitutes a major epistemological and clinical challenge to the "classical" paradigm, which is grounded in the positivist scientific orientation. Intersubjectivity embodies the notion that the very formation of the therapeutic process is derived from an inextricably intertwined mixture of the clinical participants' subjective reactions to one another. Knowledge of the patient's psychology is considered contextual and idiosyncratic to the particular clinical interaction. This interaction nexus is considered the primary force of the psychoanalytic treatment process.

The intersubjective position is that mental phenomena cannot be sufficiently understood if approached as an entity that exists "within" the patient's mind, conceptually isolated from the social matrix from which it emerges. Intersubjectivists see the analyst and the patient together constructing the clinical data from the interaction of both members' particular psychic qualities and subjective realities. The analyst's perceptions of the patient's psychology are always shaped by the analyst's subjectivity. Conversely, the patient's psychology is not conceptualized as something discoverable by the external, unbiased observer (Hoffman 1991, Ogden 1992a, 1992b, Spezzano 1993, Ogden 1994).

## Conclusion and the Future

Over a hundred years ago, Freud began his investigation into the human psyche, and there have been many additions and revisions to his theories of mental life, as was laid out in this chapter. Increasingly, the discipline of psychoanalysis is confronted with new knowledge from neuroscience and with the need for empirical research to ground psychoanalysis in the sciences. This may lead to revisions of long-held theories within psychoanalysis, but may also give a biological basis for psychoanalysis as well (Olds 2006). For example, the discovery of mirror neurons in monkeys

(Rizzolatti and Arbib 1998) gives a biological basis for identification and projective identification, two major theories in psychoanalysis. When a monkey picks up a morsal of food and puts it in its mouth, there is a particular pattern on EEG, in the premotor cortex, which coordinates this activity. They discovered that a motionless monkey watching this activity has the same pattern in its premotor cortex. This is the basic concept of mirror neurons. This same phenomenon has been shown for human affect. The person observing the affect of another will have the same brain activity. As this example demonstrates, this exciting dialogue between psychoanalysis and other sciences can bring new understanding of mental life and inform psychoanalytic theory, just as psychoanalysis can contribute to knowledge in other sciences.

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## Glossary of Psychoanalytic Terms*

| | |
|---|---|
| **Abreaction** | The discharge of affect associated with a traumatic memory. Abreaction may be brought about by hypnosis or free association. |
| **Adaptive point of view** | A metapsychological framework that considers how the developing mind is influenced by environmental realities. In this model, the ego is thought of as the "organ" of adaptation. |
| **Aggressive drive** | One of the primary instinctual drives, aggression includes the urge to harm or destroy, the urge to dominate or prevail over others, and strivings toward mastery. The aggressive drive is a major source of intrapsychic conflict. |
| **Anal** | Stage of psychosocial development from about 18 months to 3 years during which pleasures and conflicts center on defecation and urination and their symbolic derivatives. In addition, which increased cognitive and motor development, issues of mastery, autonomy, obedience, and defiance are observed. |
| **Cathexis** | The attachment of mental energy to a thought or memory, resulting in an increased emotional or motivational intensity associated with the thought or memory. |
| **Character (personality) disorder** | Habitually and generally inflexible patterns or behaviors that are ego-syntonic, that is, cause little subjective discomfort and are experienced as appropriate, reasonable, and justified. Such behavior may actually cause problems in adaptive functioning and interpersonal relationships. |

*Source: Abstracted from Moore and Fine (1990)

**Compromise formation** An activity of the ego that attempts to solve conflicts between opposing forces operating in the mind, in particular the gratification of instinctual wishes that are prohibited by the superego or by reality. Compromises may take many forms, including character traits, neurotic symptoms, dreams, and fantasies, adaptive behavior, and transference.

**Conscious** The portion of mental activity and content that is directly available to immediate perception (as opposed to unconscious or preconscious). Conscious mention obeys rational, secondary process logic.

**Countertransference** Attitudes and feelings of the psychiatrist toward the patient. As narrowly defined, countertransference comes about as a result of activation of wishes, fantasies, or conflicts from the psychiatrist's life. More broadly defined, countertransference also includes reactions to the patient's projections or role enactments. Countertransference responses have the potential to have a negative impact on the therapeutic approach to the patient and also to provide data about unconscious processes occurring in patient and psychiatrist.

**Defense mechanism** Specific unconscious operations used by the ego to protect against the fantasied danger associated with conscious awareness or unconscious wishes. Examples include repression, displacement, reaction formation, projection, isolation, and undoing.

**Depressive position** In Kleinian theory, a constellation of internal object relations, defenses, and anxieties in which others are viewed ambivalently (as containing both goodness and badness, as opposed to the split objects of the paranoid–schizoid position) and in which fear and guilt are felt around the fantasy that one's aggressive impulses may destroy the needed and love object.

**Developmental point of view** Metapsychological perspective that emphasizes the progressive unfolding of stages of development and focuses on the contribution of childhood experience to the psychology of the adult.

**Dynamic motivational point of view** Metapsychological perspectives that considers the actions of mental forces (wishes or needs inherent in the nature of humans), which may be in opposition to one another, resulting in conflict and compromise.

**Dynamic unconscious** The content and processes of the system, which unconscious are kept outside conscious awareness by repression.

**Ego** In structural model, the mental agency that is positioned between the physiologically based instinctual urges and the outer world. Its functions include mediating between the pressures of the id, superego, and reality and the variety of processes or perception, cognition, memory, motor behavior, and learning.

**Ego ideal** The portion of superego functions that includes goals, ideals, and standard of thought and behavior. It is involved in the experience of self-esteem, pride, and shame.

**Empathy** A mode of knowing or perceiving the emotional or psychological state of another, in which the quality of experience of one person in momentarily shared by another.

**Envy** A primitive emotion of desire, of wanting what the other has, combined with a hostile wish to destroy or spoil the source of that which is desired.

**Fixation** The persistence of modes of gratifying impulses, reacting defensively to perceived danger, and relating to objects that belong to earlier stages of psychosexual development. Points of fixation can be returned to in the process of regression.

**Free association** The basic activity in psychoanalytic treatment in which the patient reports everything that comes to mind without the usual selectiveness used in conventional discourse.

**Id** In the structural model, the collection of unconscious drives and drive derivatives that continually push for gratification.

**Insight** The conscious recognition and comprehension of previously unconscious mental content and conflicts, as occurs during psychoanalytic treatment. Insight is typically accompanied by adaptive behavioral changes.

**Instinctual drives** Innate motivational forces originating within the organism that seek discharge or gratification. In Freud's theory, drives are characterized by their source, aim, and object. The two basis instincts are the sexual and the aggressive.

**Internalization** A process by which aspects and functions of need-gratifying relationships are taken into the self and represented its psychic structure. Types of internalization include incorporation, introjection, and identification.

**Interpretation** The principle type of therapeutic intervention in psychoanalytic treatment that brings to the patient's attention observations about his or her mental processes and their underlying motives, conflicts, compromises, wishes, needs, and patterns of object relations. The expected outcome of interpretation is insight, psychic structural change, and symptomatic improvement.

**Latency** Stage of psychosexual development between the approximate ages of 5 and 12 years in which the sexual drives and conflicts are less apparent and the major activities of the child are learning and other social approved channels of gratification.

**Libido** Term originally used to refer to sexual desire but later used by Freud to describe the metapsychological concept of mental "energy" that could be deployed toward and attached to various mental representations or psychic structures.

**Metapsychology** An abstract conceptual framework used to organize, systematize, and orient clinical observations.

**Narcissism** In its original use, narcissism refers to self-love, but the term was elaborated theoretically by Freud to refer to the libidinal cathexis of the self (or ego). In modern theory, aspects of character organization, self-experience, affect regulation, and object relations are discussed along the dimension of normal versus pathological narcissism.

**Neurosis** A set of psychiatric syndromes characterized by abnormalities of emotions, attitudes, behavior, and thought and that have in common (in psychoanalytic theory) their origins in unconscious psychic conflict. Classic neuroses include hysteria, obsessions, phobias, and certain types of neurosis are ego-dystonic, that is, are recognized by the patient as abnormal and alien to the self.

**Object** As defined by Freud, a person or thing through which instinctual needs can be gratified. The inner mental schemas or constructions that conceptualize other persons are referred to as object representations. The theory of object relations examines the relationship of the self to internal objects and the interpersonal enactments of those mental phenomena.

**Object constancy** A developmental achievement in which mental representations of love objects are experienced as constant and stable, despite their availability or unavailability.

**Oral** The stage of psychosexual development occurring in the first 18 months of life, during which the oral and perioral areas provide the major source of sensual pleasure. Because the infant is extremely dependent during this stage, optimal development requires considerable parental attunement to the needs of the infant; if this is provided satisfactorily, the infant should acquire a sense of trust and a sense that the world is safe and that the infant's needs will be met.

**Paranoid–schizoid position** In Kleinian theory, the earliest and most primitive mental organization, in which there is a predominance of the defenses of projective identification, splitting, primitive denial, and idealization. During moments of frustration in this stage, there is the experience of diffuse rage and persecutory anxiety.

**Phallic-oedipal** Stage of psychosexual development for approximately 3–6 years of age, during which the genitals become the major source of sensual pleasure. During this stage, the child develops an intense desire to possess exclusively the parent of the opposite sex and to eliminate the other parent who is perceived as a rival. The jealous conflict of this triangular relationship, with accompanying fantasies of retaliation by castration, leads eventually to identification with the parents and the development of the superego.

**Pleasure–unpleasure principle** The tendency of the mental apparatus to seek pleasure and avoid principle unpleasure. According to Freud's libido theory, pleasure is attained through drive discharge, and unpleasure represents the buildup of undischarged mental energy.

**Preconscious** In the topographical theory, mental content and processes that are not conscious but can be readily accessed by the direction of attention.

**Primary process** Type of mentation associated with the unconscious, characterized by irrationality and a predominant emphasis on wish fulfillment and drive discharge. Primary process logic involves many of the mechanisms and qualities seen in dreams, including symbolization, displacement, condensation, absence of negatives, and timelessness.

**Psychic determinism** A central idea of psychoanalysis, which asserts that all psychological events are influenced and shaped by past experiences that nothing in mental life occurs solely by chance.

**Psychosexual development** The sequence of development of the instinctual drives as theorized by Freud, in which the expression of drives centers on and is organized around specific erotogenic zones (oral, anal, genital) that shifts in emphasis as the infant grows and develops.

**Regression** A shift in the organization of mental functioning to a more developmentally immature level, often occurring defensively in the context of anxiety associated with higher level functioning but also seen in sleep and dreaming, love and sex, esthetic and religious experiences, and psychoanalytic treatment.

**Repetition compulsion** A controversial concept that descriptively refers to the tendency to repeat certain distressing or painful experiences during the course of life; also referred to as the neurosis of destiny.

**Resistance** The opposition to free association and other aspects of participation in psychoanalytic treatment, activated to prevent the emergence of unconscious wishes and their associated anxieties.

**Secondary process** Rational, logical, linear, controlled thought that characterizes conscious mentation and follows the rules of Aristotelian logic.

**Self** The total person including the body and the psychic organization; the center of subjectivity; the nuclear core of the personality.

**Self-object** In self-psychology as developed by Kohut, objects who provide an interpersonal function that optimally contributes to the maintenance of cohesive self-experience (e.g., mirroring or idealizability).

**Separation–individuation** Developmental process elaborated by Mahler in which the infant progressively emerges from the symbiotic unity with mother and forms a sense of individual selfhood and a sense of differentiation from love objects. The subphases of this process include "hatching" (differentiation), practicing, rapprochement, and "on the way to object constancy."

**Structural model** Also known as the tripartite mode, Freud's later model of the mind that divides the mind into three structures: id, ego, and superego.

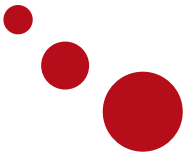
**Superego** Mental structure that includes the functions of moral standards, ideals, prohibitions, and conscience, and generates the affect of guilt and shame.

**Therapeutic alliance** The rational, conscious relationship between patient and psychiatrist based on the mutual agreement to work together cooperatively for the patient's benefit.

**Topographical model** Freud's first systematic model of the mind classifying three regions of mental functioning: conscious, preconscious, and unconscious.

**Transference** The unconscious displacement of feelings, attitudes, and expectation from important persons of childhood onto the person of the analyst or the analytic relationship.

**Unconscious** Set of mental processes and content that operates outside conscious awareness. Unconscious mentation tends to be irrational; obeys primary process logic; and may be revealed through dreams, parapraxes, and free associations.



SECTION V

Andrew E. Skodol, Section Editor

# *Manifestations and Assessments of Psychiatric Illness*

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CHAPTER

# 29 Psychopathology Across the Life Span

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Psychopathology is the study of the nature and causes of mental disorders. Because definitive etiologies for most mental disorders have not been identified, psychopathology for the most part is focused on the myriad manifestations of psychiatric illness. An elusive concept itself, mental disorder has been defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000, p. xxxi) as "a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom."

The manifestations of psychiatric illness can be grouped into five broad domains of human functioning: (1) consciousness, orientation, memory, and intellect; (2) speech, thinking, perception, and self-experience; (3) emotions; (4) physical functioning; and (5) behavior and adaptive functioning. These five areas encompass the processes by which humans know about themselves and the world around them; how they think, reason, learn, and express themselves; how they feel and express these feelings; how they perceive their bodies, experience their sensations, and perform essential functions; and how they act and react to both internal and external stimuli.

Each of these major domains of psychopathology is the subject of one of the chapters in this section. In addition, Chapter 30 discusses techniques and tests to elicit the manifestations of psychiatric illness during a psychiatric evaluation of an adult patient and Chapter 31 discusses the assessment of children and adolescents. Chapter 32 addresses the specialized areas of neuropsychological and neurophysiological testing and Chapter 33 presents guidelines for the use of brain imaging techniques to aid in the differential diagnosis of neuropsychiatric conditions. Finally, Chapter 39 describes the variation in the manifestations of psychiatric illness, depending on the particular ways in which mental distress or disorder is conceived, experienced, and expressed according to a person's cultural context.

In this chapter, we discuss the ways in which psychiatric illness presents across the life span and in which the manifestations of disorder may vary according to the patient's developmental life stage (e.g., infancy, childhood, adolescence, adulthood, and late life). We also discuss variation by gender, because psychiatric disturbance often takes different forms in men and in women. Fundamental to our discussion is the notion that different life stages (and genders) are associated with differential incidence and prevalence rates of particular mental disorders as a result of the developmental tasks of the epoch and corresponding stressors (Rutter 1989a). Thus, developmental considerations may help to explain both the origins of individual disorders and their course (Rutter and Taylor 2002). In addition, age appears to have a pathoplastic effect on the manifestations of psychiatric illness such that the same disorder may have different manifestations at different ages.

## Continuity, Persistence, and Progression Across the Life Cycle

Epidemiological research suggests that considerable stability or continuity of mental disorders can be observed from childhood into adolescence, at least for broad diagnostic groupings. In particular, behavior disorders in childhood are associated with increased risk of behavior disorders in adolescence, especially for boys, and childhood emotional disorders are associated with increased risk of adolescent emotional disorders, especially for girls (Costello and Angold 1995). The more severe the disorder, the more likely it is to persist (Cohen et al. 1993a). In addition, epidemiological surveys of adults indicate that the age at onset of disorders for many patients was during adolescence (Burke et al. 1990) and that most adults with mental disorders had received a diagnosis before 15 years of age (Kim-Cohen et al. 2003), further reinforcing the notion of persistence or progression of disorders from childhood across the life span. Continuity

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can be either homotypic, that is, when the same disorder is observed over time, or heterotypic, when there is continuity of disorder but a different diagnosis (Costello et al. 2003). Homotypic continuity indicates chronicity of disorder over time, while heterotypic continuity suggests a shared vulnerability to mental disorder of genetic or environmental origin (Krueger et al. 2002). Juvenile-onset forms of disorders tend to be associated with more severe childhood risks and have a worse prognosis in adulthood. Thus, early identification becomes imperative for prevention efforts.

## Stress-Diathesis Model of Psychopathology

Theories of the causes of mental disorders are many and are the subjects of other chapters. For simplicity, we take the position that etiology in psychopathology is multifactorial. Most mental disorders are likely to be caused by both a predisposition or a vulnerability at the level of brain biochemistry and experience with acute life events or chronic stressful life circumstances. Such a model helps to explain why a person with a strong family history of depression, for example, may be asymptomatic for long periods but may experience depression after a loss. In a population-based survey of female twin pairs, severely stressful events such as the death of a close relative, assault, serious marital problems, and divorce or breakup significantly predicted the onset of major depression in the month of occurrence. For individuals at highest genetic risk for depression, the probability of onset of major depression was significantly higher after stressful events than for individuals at lowest genetic risk, suggesting "genetic control of sensitivity to the depression-inducing effects of stressful life events" (Kendler et al. 1995). Overall sensitivity to stressful life events may be moderated by a functional variant in the serotonin transporter gene (Caspi et al. 2003), which may make individuals more sensitive to mild stressors (Kendler et al. 2005). High levels of lifetime exposure to adversity have also been causally implicated in the onset of depressive and anxiety disorders (Turner and Lloyd 2004). Some disorders, however, may be the result solely of psychosocial stressors.

## Resilience

In addition to understanding the development and progression of psychopathology in terms of vulnerabilities and risks, recent interest has turned to consideration of protective factors and resilience as mediators of the course of mental disorders (Rutter 1985). Psychobiological, personality, and social behavioral factors have been identified that together may serve to protect a person from stress (Charney 2004). Resiliency refers to individual differences or life experiences that help people to cope with adversity, make them better able to deal with stress in the future, and confer protection from the development of mental disorders. A number of neurotransmitters, neuropeptides, and hormones have been linked to the psychobiological response to stress and to long-term psychiatric outcome, including cortisol, coticotropin-releasing hormone, neuropeptide Y, galanin, dopamine, serotonin, testosterone, and estrogen. Adaptive individual traits include intelligence, optimism, self-confidence or efficacy, sociability, internal locus of control, and active style of coping. Protective life experiences are often the product of strong "social support," both within the family and in the outside community. Perceived social support from a caregiver has been shown to be protective against the development of depression in maltreated children, even if they were genetically vulnerable (Kaufman et al. 2004). Integration of biological, psychological, and social processes hold promise for a fuller understanding of both normal and abnormal development and especially of the critical role of resilience in development (Masten 2001, Rutter 2002a).

## Pathoplastic Effects of Age

Age appears to influence psychopathology in three ways (Table 29–1). A few mental disorders appear almost to be age specific and not to occur outside a certain age range. Feeding disorder of infancy or early childhood (failure to thrive) is a disturbance restricted to the first several years of life because of a child's total dependence on caregivers for food during this time. Dementia of the Alzheimer's type is much more common after the age of 65 years; few cases develop before the age of 50 years.

**Table 29–1 Pathoplastic Effects of Age**

| |
|---|
| Age specificity of disorders |
| Usual age at onset |
| Age effects on symptom expression |

More commonly, disorders that may occur at virtually any age have a usual onset at certain stages in life. Mental retardation, learning disorders, disruptive behavior disorders, and elimination disorders, among others, usually have their onset and are first diagnosed during childhood. The median age at onset for the first psychotic episode of schizophrenia is in the early-to-mid 20s for men and in the late 20s for women (American Psychiatric Association 2000).

Most mental disorders can occur at various times in life's stages. Some of these are expressed differently depending on age. For example, although the core symptoms of major depression are the same regardless of a person's age, in children somatic symptoms, irritable mood, and social withdrawal may be especially common. In depressed elderly persons, cognitive symptoms such as memory loss, disorientation, and distractibility may predominate.

## Problems of Childhood

### Individual Differences

Children differ from each other in ways that affect their psychological functioning from birth. They differ in intelligence, in temperament, and in genetic endowment for both risk for and resilience against mental disorder.

Intelligence is the ability to reason, plan, think abstractly, solve problems, understand, and learn. Average intelligence is associated with a score of 100 (IQ) on a standardized intelligence test. About 67% of children have IQs between 85 and 115 and about 95% between 70 and 130. Estimates of the heritability of IQ range from 0.4 to 0.8 (Plomin 1990) and indicate that heredity plays a larger role than environment. Higher intelligence is correlated with successful adaptation in life, and substantially reduced

intelligence is associated with developmental and behavioral problems and functional impairment (see the discussion of mental retardation).

Children also differ at birth in certain fundamental behavioral predispositions, such as emotionality, activity, and sociability, called temperament (Buss and Plomin 1975). Thus, some children are born with a calm and placid nature; others are inclined to be active and energetic. Thomas et al. (1968) found that some children showed particular clusters of temperamental characteristics. "Difficult" children had irregular sleeping and eating patterns, tended to withdraw from new situations, were not adaptable, and had intense and negative reactions to stimulation. "Easy" children were biologically regular, adaptive, and in good moods; they had positive reactions to new situations and reactions to stimuli that were mild in intensity. "Slow-to-warm-up" children had initial withdrawal responses, slow adaptation, and mild reactions. Some aspects of temperament have been shown to be remarkably stable throughout childhood and adolescence and into adult life (Kagan et al. 1988, Chess and Thomas 1977). A shy, inhibited temperament may predispose to the development of childhood anxiety disorders and to inhibited, avoidant personalities in adult life (Biederman et al. 1990). A difficult temperament has been thought to be a predisposition for behavior disorders (Thomas and Chess 1984).

More recent work suggests that temperament may be a unifying basis for understanding personality/psychopathology relationships (Clark 2005). Three broad temperament dimensions—negative affectivity (emotionality, neuroticism, and harm avoidance), positive affectivity (approach and extraversion), and disinhibition (novelty seeking vs. constraint, effortful control)—differentiate through developmental processes into personality traits and, at their extremes, are risk factors (diatheses) for psychopathology, especially under adverse life experiences. For childhood disorders, one proposal suggests that conduct disorder arises from low fear response and high incentive approach, attention deficit hyperactivity disorder from low effortful control and strong approach, and anxiety disorders from high negative emotionality and low effortful control (Nigg 2006). The concept of goodness of fit between an individual's capacities and behavioral style and the expectations and demands of others in the environment may be important in determining outcome. In one of the few studies to test the goodness of fit hypothesis, high childhood novelty seeking in combination with high maternal novelty seeking was associated with child attention problems, whereas the combination of high child harm avoidance and high paternal harm avoidance was associated with child internalizing problems (Rettew et al. 2006).

Inheritance has been shown to play a role in the development of certain developmental disabilities, enuresis, schizophrenia, and mood and anxiety disorders. As mentioned earlier, heredity does not indicate with certainty that an individual will develop a mental disorder. Instead, a susceptibility is inherited, and some life experiences or other environmental factors are often required for a disorder to become manifest. Factors that lead to greater resilience in the face of adversity (Rutter 1985) and consequently lessen the risk of mental disorder, such as intelligence, adaptability, and sociability, also have genetic components.

## Types of Problems

Psychopathology in childhood falls into five major groups of problems (Table 29–2). Many of the disorders of childhood appear to be severe forms of problems that are more or less continuously distributed, common, and "normal" occurrences. Thus, clinical depression may appear to be a severe form of sadness and disappointment, conduct disorder a severe form of aggressiveness, and anorexia nervosa a severe form of adolescent dieting and dissatisfaction with body shape (Rutter and Sandberg 1985). However, although dieting and concerns about body shape may be relatively common among young women, anorexia nervosa is actually quite rare, suggesting a discontinuity between normal problems and psychopathology. Therefore, identification of a clinically significant disorder involves consideration of both the quantitative severity of a disturbance and its persistence and qualitative distinctions, such as the impact of the problems on the child's functioning, continued development, and adaptation to life (Rutter 1989b). Differences between cases and noncases may depend on fundamental differences in biology, personality, or social environment.

**Table 29–2 Psychopathology in Childhood**

| |
|---|
| Developmental problems |
| Emotional problems |
| Behavioral problems |
| Problems in physical functioning |
| Psychosexual problems |

A recent review of epidemiological studies of childhood and adolescent psychiatric disorders yielded a median prevalence of 12% for problems considered functionally impairing, although prevalence rates among studies varied widely (Costello et al. 2005). For example, one study showed that while the 3-month prevalence rate of any disorder was 13.3% in a group of children aged 9–13 years, the risk of having at least one psychiatric disorder by the age of 16 years was much higher (Costello et al. 2003). Another international epidemiological review estimated a prevalence of psychopathology ranging from 10% to 20% in young people (Fombonne 2002). Overall rates of mental disorders and rates of individual disorders are lower when impairment criteria are more stringent and higher when they are relaxed. Rates are lowest when the need for treatment is included in the criteria for disorder. Rates vary by the age range of the population studied, whether the children are evaluated in clinical settings or in the community, and the period of time over which the disorder can be present (Cohen et al. 1996). Rates are also influenced by who provides information and how many sources of information are used. In general, children are usually more aware of their emotional problems than are their parents, but parents report more behavioral problems (understandably) than do their children. The more people who provide information on symptoms, the more diagnoses are made. More boys than girls are affected until the age of 11 years; more girls than boys are affected from the age of 12 years and older. The cooccurrence of several disorders (i.e., comorbidity) is common in childhood, which raises questions both about the diagnostic systems being employed and also the relationships of various disorders with one another (Caron and Rutter 1991, Taylor

and Rutter 2002). As can be seen in Table 29–3, comorbidity both within and between disorder types can be observed.

**Table 29–3 Common Patterns of Comorbidity in Childhood**

| Disorder Type or Specific Disorder | Comorbid Disorders |
|---|---|
| Intellectual (mental retardation) | Attention-deficit/hyperactivity disorder |
| | Pervasive developmental disorders |
| | Stereotyped movement disorder |
| | Mood disorders |
| | Disorders due to general medical condition |
| Learning disorders | Other learning disorders |
| | Conduct disorder |
| | Oppositional defiant disorder |
| | Attention-deficit/hyperactivity disorder |
| | Major depressive disorder |
| | Dysthymic disorder |
| | Communication disorders |
| | Medical conditions (e.g., lead poisoning, fetal alcohol syndrome) |
| Motor skills disorders (developmental coordination disorder) | Communication disorders |
| Communication disorders | Other communication disorders |
| | Learning disorders |
| | Motor skills disorders |
| | Enuresis |
| | Attention-deficit/hyperactivity disorder |
| Pervasive developmental disorders | Mental retardation |
| | Pica |
| | Communication disorders |
| | General medical conditions |
| Anxiety disorders | Other anxiety disorders |
| | Major depressive disorder |
| | Behavioral disorders |
| Depressive disorders | Anxiety disorders |
| Behavioral disorders | Other behavioral disorders |
| | Learning disorders |
| | Communication disorders |
| | Mood disorders |
| | Anxiety disorders |
| | Substance use disorders |
| | Somatoform disorders |
| | Tourette's disorder |
| | Mental retardation |
| Feeding disorders | Mental retardation |
| Elimination disorders | Other elimination disorders |
| | Parasomnias |
| | Oppositional defiant disorder |
| | Conduct disorder |
| Tourette's disorder | Obsessive–compulsive disorder |
| | Attention-deficit/hyperactivity disorder |
| | Learning disorders |

*Source*: Data from American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Rev. APA, Washington, DC.

Thus, children with learning disorders are likely to have more than one disorder and are likely to have communication and behavior disorders as well. Children with behavior disorders may also have more than one and are likely to have learning and communication disorders. Mood and anxiety disorders co-occur and are found additionally in children with learning and behavior disorders.

Recently, interest has increased in identifying emotional and behavioral disorders in preschool children. Despite the relative lack of research on preschool psychopathology, using developmentally appropriate diagnostic criteria indicates that rates of common disorders and patterns of comorbidity are similar to those seen in later childhood (Egger and Angold 2006). At risk children from high SES families may be identified as early as infancy (family histories of psychopathology and greater family stress during infancy), whereas those from low SES families may be identified as preschoolers (Essex et al. 2006). In a birth cohort followed for 3 years, the number of behavioral and emotional problems observed in the young children increased with the number of mental health problems (depressive episode, substance abuse, and domestic violence) experienced by the mother in the first year after birth (Whitaker et al. 2006).

## Developmental Problems

Childhood is a time of growth, physical and social maturation, and the acquisition of skills necessary to deal independently and successfully with the environment. Children who are greatly delayed in their development or who never acquire the requisite skills or maturity associated with their developmental stage have developmental problems. Developmental disorders fall into five main types: intellectual, learning, motor skills, communication, and pervasive developmental disorders.

Significantly subaverage intelligence recognized before the age of 18 years and accompanied by impairment in adaptive functioning is called mental retardation. Approximately 1% of the population is estimated to be mentally retarded. Boys are slightly more likely to be diagnosed with mental retardation than are girls (American Psychiatric Association 2000).

Intelligence is defined by the IQ, which is measured by a standardized, individually administered test, such as the Wechsler Intelligence Scale for Children (Revised) or the Stanford-Binet Intelligence Scale. Subaverage intelligence is indicated by a score of approximately 70 or below on one of these tests, corresponding to approximately two standard deviations below mean intelligence scores. Mental retardation is commonly specified by degree of severity as mild, moderate, severe, or profound (Table 29–4). Impairment in mental retardation is the inability to meet functional standards for the person's age and sociocultural group and is exhibited by deficits in communication skills, self-care, home living, interpersonal relations, self-direction, academic skills, work, leisure, health, or safety.

The causes of mental retardation can be grouped from most to least common as follows (American Psychiatric Association 2000):

1. Alterations in embryonic development, such as those caused by chromosomal abnormalities or fetal exposure to drugs or toxins.

**Table 29–4 Severity of Mental Retardation**

| Level | IQ Range | % Of Population with Mental Retardation* |
|---|---|---|
| Mild | 50–55 to 70 | 80 |
| Moderate | 35–40 to 50–55 | 12 |
| Severe | 20–25 to 35–40 | 7 |
| Profound | Below 20–25 | 1 |

*Data from Scott S (1994) Mental retardation. In Child and Adolescent Psychiatry: Modern Approaches, 3rd edition, Rutter M, Taylor E, and Hersov L (eds). Blackwell Scientific, Oxford, UK, pp 616–646.

2. Environmental deprivation and other mental disorders, such as autism.
3. Problems of pregnancy and the perinatal period, such as fetal malnutrition, hypoxia, infection, trauma, or prematurity.
4. Hereditary abnormalities, such as inborn errors of metabolism or chromosomal aberrations.
5. Medical conditions of infancy or childhood, such as central nervous system (CNS) infection or trauma, or lead poisoning.

Previously a "two-group" approach was followed concerning the causes of mental retardation—one group was considered to have a clear biological etiology, while the other group had no evident organic basis for the disability. With advances in genetic technologies, the field has shifted toward a behavioral genetic approach. That is, researchers are investigating the interplay between genetic predispositions and environmental and psychosocial influences (Volkmar and Dykens 2002).

Mental retardation may be recognized at birth if it is due to a condition like Down's syndrome with physical manifestations. Likewise, it can be noted readily after a severe medical illness affecting the CNS. Severe retardation is commonly associated with lifelong functional impairment and shortened life expectancy. Milder forms of mental retardation may be responsive to appropriate training and support so that impairment in adaptive functioning is no longer apparent.

Children with mental retardation often have other problems besides their intellectual deficits and may be diagnosed with behavioral, emotional, or other developmental disorders as well.

When a child's performance on standardized achievement tests falls substantially below what would be expected given her or his IQ, age, and schooling, the child is said to have a learning disorder. Learning disorders may involve primarily subaverage reading, mathematical, or writing ability. Rates of significant underachievement in reading range from 3 to 9% of school children, depending on measurement methods employed, with boys outnumbering girls by 3 or 4 to 1 (Snowling 2002). Learning deficits adversely affect the child's academic functioning or other activities of daily living that require proficiency with these skills. Vision or hearing impairment may also interfere with academic achievement. Learning disorders are diagnosed in children with limited sight or hearing only when the deficits are even greater than would be expected given the sensory problem. Children with learning disorders also often have other behavioral and emotional problems (Jorm et al. 1986, Rourke and Fuerst 1991).

Specific learning disorders are usually diagnosed when formal training in reading, mathematics, or writing begins in school. If the child is significantly above average in intelligence, the learning deficits may not be recognized until after several years of school. Most untreated learning disorders persist into adult life, with consequent emotional and behavioral problems and varying degrees of functional impairment, depending on environmental opportunities and demands (Snowling 2002).

Motor skills disorder involves marked impairment in motor coordination. Incoordination is of such a degree of severity that it limits the child's ability to locomote or to perform tasks in school (such as handwriting) or otherwise interferes with activities of daily living, such as getting dressed. Developmental coordination disorder has been estimated to affect as many as 6% of children between the ages of 5 and 11 years (American Psychiatric Association 2000). Traditionally, boys have been observed to have the disorder more frequently than girls, but recent studies have shown similar rates across genders. The discrepancy has been explained either as a result of a tendency for boys to be referred for testing or services more readily than girls or greater social pressures for boys to excel in sports than girls (Spagna et al. 2000). The problems of coordination indicative of a motor skills disorder are to be distinguished from those associated with neurological disorders such as cerebral palsy. Motor skills problems also tend to persist, at least into the teens, with self-esteem and school problems typical of other learning disorders (Loose et al. 1991).

Communication disorders subsume problems in self-expression using language, in understanding language, in articulating appropriate speech sounds, and in speech fluency and timing. Communication problems may be acquired as a result of CNS infection, toxin exposure, or trauma or may be developmental, that is, not associated with neurological insults of known origin. Children may not develop an age-appropriate amount of speech, range of vocabulary, complexity of speech, or appropriate grammatical construction. If these problems significantly interfere with academic achievement or social development, an expressive language disorder is diagnosed. If a child is also unable to understand words and sentences, a receptive-expressive language disorder is present. If a child has a significant problem in pronouncing or articulating sounds required for speech, the impairment is referred to as phonological disorder. If a child has a problem in the fluency or patterning of speech, such that there are sound, syllable, or word repetitions plus frequent pauses, broken words, and sound prolongations, the problem is called stuttering.

The developmental types of expressive or mixed language disorders affect approximately 3–5% of children; the acquired types are more rare (American Psychiatric Association 2000). Phonological disorder occurs in 2–3% of children and stuttering in about 1%. The sex ratio for language disorders and stuttering has been estimated to be as high as three boys to one girl. Differences in rates are attributed to differences in study sampling practices, testing procedures, and diagnostic criteria (Johnson and Beitchman 2000).

Communication disorders become evident as language becomes more complex. Severe problems with expressive or receptive language of a developmental type (i.e., not acquired through CNS disease) are evident in the first 2 or 3 years of life. More subtle disturbances may not become apparent until the demands of formal schooling occur. Articulation and stuttering problems are also usually apparent before the child begins school. In many instances, communication disorders are time limited or reversible. The prognosis for acquired types of language disturbance may be poorer than for the developmental type and depends on the nature and severity of CNS damage.

Sometimes children have many different problems in development, involving communication, social skills, and behavior. When these problems are extremely deviant for the child's developmental stage, they are diagnosed as pervasive developmental disorders (Rutter and Schopler 1992). The subtypes of the pervasive developmental disorders are discussed in Chapter 45. The prototype disturbance is called autistic disorder. Children with autistic disorder fail to develop the abilities to interact socially and to communicate effectively, and frequently have restricted and stereotyped behavior patterns and interests. They are socially isolated, uninterested in peer activity or sharing, and apparently unable to have reciprocal interactions either nonverbally or emotionally with others (Lord and Rutter 1994). They also either do not speak or speak in limited or idiosyncratic ways. A typical repetitive, stereotyped behavior is hand or finger flapping. Boys are four to five times more likely than girls to have autism. Moderate mental retardation is a common additional problem. Autistic disorder has traditionally been considered to be rare: DSM-IV-TR states that it affects only about five children in 10,000 (American Psychiatric Association 2000). Recently, however, the rate of reported pervasive developmental disorders has increased, with greater awareness of these problems and attention to diagnosis and the identification of a "spectrum" of autistic disorders. A recent epidemiological survey found a prevalence of almost 60 per 10,000 for all pervasive developmental disorders and 22 per 10,000 for autistic disorder itself (Chakrabarti and Fombonne 2005). The disorders continue to be found much more commonly (85.9%) in boys. The social deficits characteristic of autism spectrum disorders can be found fairly commonly in the general population, are continuously distributed, and moderately to highly heritable (Constantino and Todd 2003).

A variety of perinatal factors have been associated with autism, including advanced parental, especially paternal age, being the firstborn child, mother having threatened abortion and induced labor, fetal distress, delivery by Caesarian section, and Apgar score less than 6 at 1 minute (Glassen et al. 2004, Reichenberg et al. 2006). More of these factors have been found for cases of autism than for PDD NOS (pervasive developmental disorder not otherwise specified) or Asperger's syndrome. They reflect underlying genetic problems or the interactions of such factors with the environment.

The most severe developmental problems are evident in infancy. The infant with autism may manifest limited eye contact, facial responsiveness, and smiling and may be difficult to hug or may appear to dislike physical contact. Restricted social relationships emerge, however, after the third or fourth year of life. For children with other pervasive developmental disorders, infancy may be normal, with the onset of the abnormal behavior occurring months or even years after birth. In milder forms, such as Asperger's syndrome (Tantum 1988), in which communication skills are spared, a pervasive developmental disorder may not be recognized until preschool or the actual beginning of school. The course after diagnosis is variable, depending on the subtype. In some cases, there is limited improvement; in other cases, there is progressive deterioration. Autism diagnosed at the of age 2 years had high diagnostic stability at the age of 9 years in a recent follow-up study (Lord et al. 2006). Pervasive developmental disorders cause lifelong impairment: persons with intellectual impairment need supervised living and working situations; those with normal intelligence and higher levels of language acquisition may achieve a degree of independence by their 30s (Lord and Bailey 2002). Outcome studies indicate that approximately two-thirds of children with autism are unable to lead an independent existence, and one-third make some social and educational gains. Patients with a history of autism may be diagnosed with personality disorders as adults (Anckarsater et al. 2006). About one-tenth of all individuals with autism may have a good outcome with some social life and adequate functioning at work or at school (Volkmar and Klin 2000).

## Emotional Problems

The emotional problems of children involve anxiety, depression, and mania. Although these problems have counterparts in adults, children frequently experience and express their disturbances of feelings or emotions differently from adults. Because of their more limited vocabulary and understanding of emotional life, children may not express their emotional distress verbally as well as some adults do. Thus, even in the emotional disorders of childhood, disturbances in behavior and in physical functioning are apt to be prominent in the clinical presentation. Children are not unlike so-called alexithymic adults, whose expression of emotions is indirect and nonverbal.

Because some childhood anxieties are common and have an adaptive function, and the severity of anxiety at various stages of childhood and adolescence appears to be on a continuum, it is often unclear where normal fears shade into pathological states (Klein and Pine 2002). Thus, animal phobias appear in early childhood, when normal children may also have milder fears of animals; pathological and normal performance anxieties occur in late childhood; and social anxiety, both mild and severe, has its usual onset in adolescence (Öst 1987). An exception is pathological separation anxiety, which has a peak age at onset in community and clinical samples in late childhood (Bird et al. 1988, Last et al. 1992), although normal, developmentally appropriate separation anxiety occurs during the first year of life. Rates of anxiety disorders tend to decline with increasing age in childhood and adolescence (Cohen et al. 1996).

A child with separation anxiety fears separation from home or from attachment figures such as parents. A common first expression occurs when the child is faced with going to school (or preschool) for the first time. The young child may refuse to go to school, may exhibit clinging behavior, or may complain of physical symptoms such as headache or stomachache. Other, early, nonschool-related manifestations of separation anxiety include insistence on

sleeping with parents, nightmares, and fears of the dark. Separation anxiety may be precipitated by a stressful event, such as a family death or illness or a move or change of schools. Older children express the fear that calamity will happen either to themselves or to the person(s) to whom they are attached. The course of separation anxiety may wax and wane, but whenever a developmentally appropriate separation is imminent, such as going away to college, a susceptible person is anxious in anticipation of it and may actually avoid the separation or come home prematurely. Separation anxiety disorder is more common among girls. About 4% of children may have the disorder (American Psychiatric Association 2000). Children with separation anxiety disorder may also have mood disorders. Adult separation anxiety disorder may be more common than previously suspected (over 6% prevalence) (Shear et al. 2006). About one-third have an onset in childhood that persists, but the rest have an adult onset.

Selective mutism is an emotional condition in which a child has ceased speaking in certain situations (e.g., at school), although the child has normal or near-normal speech and does, in fact, speak in other situations (e.g., with friends or parents) (Tancer 1992). It has been suggested that this syndrome is more properly regarded as an anxiety disorder, rather than a speech and language disorder, although some children with selective mutism do have language problems that may make them self-concious about speaking. Girls are two to three times more likely to manifest selective mutism than boys, and evidence has shown that it is more likely to be related to temperament rather than abuse or trauma (Bishop 2002). Reluctance to speak when first entering school occurs in about 1% of children (Brown and Lloyd 1975) and usually remits spontaneously.

Fear of social or performance situations in which a child is exposed to the scrutiny of others and is afraid of being humiliated or embarrassed is called social phobia. Shy or fearful temperament is a predisposing factor. Social phobia may be manifest by the young child by crying, tantrums, clinging to familiar figures (parents), or mutism. The slightly older child may not wish to play with peers or may refuse to go to school. Social phobia may be more limited (i.e., restricted to a performance situation such as speaking in class) or more generalized (i.e., involving a fear of most social situations). The prevalence of social phobia in children is about 1% (Anderson et al. 1987, Costello et al. 1988). The course of social phobia is often characterized by exacerbations caused by life stressors and social demands followed by remissions when situations pass or stabilize.

Some children may be excessive worriers in general. They may worry about school performance, athletic prowess, appearance and popularity, parental expectations, potential catastrophic events, and so on. Children who worry excessively are said to have generalized anxiety disorder. About 3-4% of preadolescent children may be affected (Anderson et al. 1987, Costello et al. 1988). They may also be excessively conforming and perfectionistic and insecure to the point of extreme self-consciousness and needs for reassurance. Generalized anxiety is also likely to have a fluctuating course, with more symptoms during times of stress.

Children may develop compulsive behavioral rituals involving counting, checking, washing, or ordering. Boys are more likely to be affected than girls, especially before the age of 7 years (Swedo et al. 1989a). Preoccupation with rituals and obsessional thoughts may lead to impaired school performance. Parents are likely to bring compulsive behaviors to clinical attention as they do in the case of the behavior disorders. Children are less likely than are adults to recognize their behaviors as excessive and unreasonable.

Traumatic events in childhood are common. Two-thirds of children may experience at least one traumatic event by the age of 16 years (Copeland et al. 2007). Children may develop post-traumatic stress symptoms or disorder (PTSD) or other anxiety or depressive disorders after a severely traumatic event (Hoven et al. 2005, Meiser-Stedman et al. 2005, Roussos et al. 2005). Girls may be more vulnerable than boys. In children, distressing dreams are usually nightmares; reliving experiences are often reenactments of the traumatic event in play. Separation difficulties may occur. Memory problems, avoidance of situations reminiscent of the trauma, and hyperarousal symptoms are also reported (Yule 2002). Diminished interest and responsiveness may be evident only to others, as children tend not to report such complaints on their own. Children with PTSD sometimes feel they will never live to be adults or become preoccupied with "telling" the future. Somatic complaints such as headaches and stomachaches are common. Childhood risk factors for developing PTSD include experiencing multiple traumas, externalizing behavior problems (increasing exposure to traumatic events), mood and anxiety problems (increasing reactivity), and family and environmental adversity (Koenen et al. 2007, Storr et al. 2007). Higher intelligence among young children has been found to decrease both risk of exposure to trauma and of PTSD development throughout childhood and adolescence (Breslau et al. 2006).

Moody periods are common in children, but children may also exhibit prolonged and persistent disturbances of mood, usually depression. Although study estimates vary by assessment method, one estimate of the prevalence of major depression among young children is between 0.5% and 2.5% (Harrington 1994). Again, feelings of depression may not be experienced by children in the same way as by adults or may not be readily articulated (Rutter 1986). Children who are depressed may be more likely to complain of boredom or of being unable to have fun. They may become socially withdrawn and tend to want to stay at home rather than attend school (Harrington 1994). Depressed children cry and express self-criticism and thoughts about death. Energy level is significantly diminished, and depressed children tend to sleep significantly more than usual. Eating habits may change. Irritability and somatic complaints may be prominent symptoms. In prepubertal children, depressive episodes tend to occur in association with behavior or anxiety disorders (Angold and Costello 1993). Although prepubertal depression has been shown to be strongly familial (Harrington et al. 1993), depressive episodes are frequently triggered by some type of loss, such as the death of a parent, a divorce, a serious illness, or a move to a new town or neighborhood, often in the context of chronic adversity (Goodyer et al. 1988). Although some studies report the childhood sex ratio for depressive disorders at about 1:1 (Fleming et al. 1989, Velez et al. 1989), there is also evidence of greater prevalence in boys (Angold et al. 1998). By adolescence, more girls than boys are affected (Angold et al. 1998, McGee et al. 1990).

**Table 29–5 Continuity of Antisocial Behavior Across the Life Span**

| Temperamental Predispositions | | Childhood or Adolescent Psychopathology | | Early or Middle Adult Life Personality |
|---|---|---|---|---|
| Irregular biological patterns, social withdrawal, intense and negative reactivity, inflexibility | → | Oppositional defiant disorder<br>Attention-deficit/hyperactivity disorder<br>Conduct disorder | → | Antisocial personality disorder* |

*Comorbidity with substance-related disorders is likely.

Although the vast majority of preadolescent children with depressive episodes recover within 2 years (Kovacs et al. 1984a), up to 70% are likely to have another episode within 5 years (Kovacs et al. 1984b). Children who also have chronic mild depression have a poorer short-term outcome (Asarnow et al. 1988). Patients whose symptom picture most resembles that of severe adult-like presentations and who do not have comorbid conduct disorder are more likely to have continuity of depressive illness into adult life. Older depressed children may have a worse prognosis than younger ones (Kovacs et al. 1989, Harrington et al. 1990). Childhood major depressive disorder also appears to increase the risk for the development of personality disorders in young adulthood (Kasen et al. 2001).

Mood and anxiety disorders commonly occur together in childhood. In roughly one-third of cases anxiety begins first, in one-third depression begins first, and in one-third the onset is simultaneous (Moffitt et al. 2007). Mood disorders in adolescence and young adulthood may be best predicted by internalizing problems in childhood and anxiety disorders by social problems and externalizing behaviors (Roza et al. 2003).

The manifestations of mania in younger children may involve irritability, emotional lability, hyperarousal, or admixtures of dysphoria and hypomania, as well more typical symptoms of hyperactivity, grandiosity, pressure of speech, and distractibility (Carlson 1990, Strober et al. 1989, Leibenluft et al. 2003). Children themselves are more likely to report classic symptoms than their parents, who focus more on problematic behavior (Tillman et al. 2004). Episodes of mania in children may last only a couple of days, but long episodes and chronic, unremitting patterns of mania and mixed mood disturbances have also been observed (Axelson et al. 2006, Geller et al. 2004, Birmaher et al. 2006), suggesting a spectrum of bipolar illness in children. One-third to one-half of children with major depressive episodes may show bipolar disorder by adolescence (Geller et al. 1994, Chengappa et al. 2003). Early-onset bipolar disorders may have a poorer prognosis than later onset disorders (Geller et al. 2004). Children with severe mood dysregulation also are diagnosed with attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and oppositional-defiant disorder (Brotman et al. 2006).

## Behavior Problems

Behavior problems in children fall into the general groupings of oppositional behavior, hyperactivity, excessive aggressiveness, and conduct disturbance. An appropriate degree of control over behavior is a necessary development for a child to function in a family, in school, and with peers.

A certain amount of oppositional behavior toward parents is a normal phenomenon in the preschool years (e.g., the "terrible twos"). When oppositional behavior is excessive, given a child's developmental stage, and adversely affects social or academic functioning, it is pathological (Keenan and Wakschlag 2004). Oppositional children are negative, hostile, and defiant. They frequently lose their temper; are argumentative with adults; defy rules and expectations set by adults; are easily annoyed and deliberately annoy others; and are angry, resentful, spiteful, and vindictive. In the preschool years, oppositional children are often those who have difficult temperaments (e.g., high reactivity, difficulty being soothed) and who are hyperactive. When the problem is not associated with hyperactivity, it is often the result of a family in which parents have not been able to set appropriate standards for behavioral compliance in their children or to set limits with appropriate punishments when expectations for behavior are deliberately opposed. Oppositional behavior is sometimes a forerunner of conduct disorder (Schachar and Wachsmuth 1990, Loeber et al. 1991) (Table 29–5). Oppositional behavior causing significant social or academic impairment is diagnosed as oppositional defiant disorder. The disorder is common among children in the community with a psychiatric condition and may affect nearly 6% of children overall (Rey 1993). Oppositional defiant disorder is twice as common in boys as in girls 12 years of age or younger. Oppositional defiant disorder has been shown to be a strong disk factor for the later development of conduct disorder in boys but not girls (Rowe et al. 2002). In adolescence, more girls may have the disorder, along with depression and anxiety.

Hyperactivity is also common in young children. Hyperactivity is not a problem unless it is severe enough to preclude a child's focusing attention on learning or play activities. The hyperactive child is constantly fidgeting and squirming, moves about constantly as if driven by a motor, and shows signs of impulsivity. Much of the motor activity is not goal directed and has a disorganized, chaotic quality. Thus, qualitative differences in activity as well as quantitative differences are significant (Schachar and Tannock 2002). Hyperactive children do not play well and demand constant attention and supervision. The inattentive child is easily distracted and forgetful, seems unable to organize activities, cannot follow instructions, and does not appear to listen.

Sometimes hyperactivity is evident from the age of 3 years, but more often it is diagnosed after the child begins school, when the behaviors may become disruptive and interfere with forming peer relations and with learning. Hyperactivity with attention deficits occurs two to nine times more commonly in boys than girls (predominantly inattentive types have a less pronounced gender ratio) and affects about 3–5% of children (American Psychiatric Association 2000). Gender differences in ADHD clinical correlates are not evident in children who have not been referred for clinical attention (Biederman et al. 2005). Most children diagnosed with ADHD around the age of school entry

continue to demonstrate symptoms and impairment well into elementary school (Lahey et al. 2004), although the types of symptoms expressed over time may change (Lahey et al. 2005). Both boys and girls with a diagnosis of ADHD are at increased risk for developing other comorbid behavioral, addictive, mood, and anxiety disorders by young adulthood (Biederman et al. 2006a, 2006b).

Mannuzza and Klein (2000) have estimated that two-thirds to three-quarters of children with ADHD will experience symptoms into adolescence, with relative social and academic deficits, and at times, conduct disorder behaviors. One-quarter to one-third will meet criteria for antisocial disorder in later adolescence and a significant minority will become involved with drug abuse; ongoing ADHD symptoms seem to be implicated. However, while some difficulties may persist into adulthood, a majority go on to function adequately in social and occupational areas and two-thirds who originally received a diagnosis of ADHD show no mental disorder as adults (Mannuzza and Klein 2000). A small percentage (about 10%) of patients (Mannuzza et al. 1993) have continuing subtle problems into adult life, which lead them to be emotionally labile with problems controlling moods and temper, and to be disorganized and distractible with problems in sustaining effort and completing tasks (Wender et al. 1985). By the age of 25 years, only 4% of boys continue to have ADHD (Mannuzza et al. 1998). Inattention symptoms decline at a slower rate than hyperactivity or impulsivity symptoms (Biederman et al. 2000).

Assertiveness, aggressiveness, and expression of anger are also on a continuum of severity and adaptiveness in children. Children can be excessively passive, or they can have a problem with too much aggression if they repeatedly and consistently hit, bite, or kick others; destroy property (including toys); or injure animals. When excessive aggression toward other people or animals, destruction of property, deceitfulness or theft, or other serious violations of parental or school rules are repetitive and persistent, a conduct disturbance exists. Conduct disturbance beginning in childhood tends to be much more common in boys than girls (Offord et al. 1987). Boys and girls also differ in their antisocial behaviors. Boys tend to have fighting, stealing, and school discipline problems; girls exhibit lying, truancy, running away, substance abuse, and prostitution.

The causes of conduct disturbance are multiple and can include interrelated genetic, biological, and environmental factors. For example, child abuse has been identified as a causal risk factor, and in turn, child abuse affects cognitive, emotional, and neuroendocrinological processes. As well, there seems to be causal relationship between familial presence of conduct and antisocial behavior, but it has been very difficult, even in twin studies to tease out the genetic and environmental aspects of etiology (Earls and Mezzacappa 2002). Excessive aggressiveness and conduct problems have been shown to be hereditable (Scourfield et al. 2004), while environmental factors such as parental neglect, poor quality of parenting, parent-child conflict, and malnutrition also exert strong influences on a variety of childhood externalizing problems (Kolvin et al. 1988, Burt et al. 2003, Liu et al. 2004). Growing up in a family in which violence and abuse are modeled by parents may also promote aggressive patterns of dealing with problems by children. Physical abuse of children themselves tends to provoke a panoply of negative, impulsive, angry, and aggressive behaviors. Television and the movies provide reinforcement for the aggression-prone child's behavior. Lack of consequences for inappropriate aggressiveness, excessive physical punishment, and inconsistency of parental response to hurtful or destructive acts of children all tend to exacerbate conduct problems.

Conduct disorder is sometimes seen as early as 4 to 5 years of age (Kim-Cohen et al. 2005). It is most frequently diagnosed in later childhood or early adolescence, however, and is rare in onset after the age of 16 years. Early onset, hyperactivity or inattention, poor peer relationships, and family discord and disorganization predict a worse prognosis, with a significant number of children developing antisocial personality as adults (Robins 1991, Zoccolillo et al. 1992). Conduct disorder with an onset in childhood and a persistent course has been shown to be associated with greater physical and mental health burden at the age of 32 years than adolescent-onset conduct or conduct disorder limited to childhood (Odgers et al. 2007). Children with conduct disorder also often have problems with mood and anxiety disturbances and substance abuse. A developmental progression from ADHD to conduct disorder to alcohol or tobacco use to abuse of marijuana and other street drugs has been observed (Kuperman et al. 2001). Childhood disruptive behavior disorders as a group have also been shown to predict the development of personality disorders in young adulthood, with an increased effect when multiple, comorbid childhood disorders are present (Kasen et al. 1999). One notable study that followed over 1000 children from the age of 3 to 26 years, showed that a significant number of those who met criteria at the age of 26 years for a wide variety of mental disorders (i.e., affective and anxiety disorders, not only antisocial personality disorder), had been diagnosed with conduct and/or oppositional defiant disorder in childhood (Kim-Cohen et al. 2003).

## Disturbances in Physical Functioning

A number of developmental tasks of childhood involve primarily physical functions. These include developing proper eating and sleeping habits (Stein and Barnes 2002), and bowel and bladder (Clayden et al. 2002) control. Disturbances may occur in these functions during childhood.

The eating disturbances of early childhood are rumination, failure to thrive (feeding disorder), and pica (Minde and Minde 1986). Rumination involves regurgitation and rechewing of food, without any structural anomaly or physiological disturbance to account for it. The problem is rare and is diagnosed most often in the first year of life. This early-onset syndrome occurs in developmentally normal children in association with a disturbed caretaker-child relationship (Mayes et al. 1988). Rumination may also be associated with mental retardation and may occur somewhat later in these children. It usually remits spontaneously.

Failure to thrive is a syndrome that also most commonly begins during the first year of life and consists of a child not eating enough to grow or in fact losing weight. Again, the feeding disturbance occurs in the absence of a medical condition, such as a disorder of intestinal absorption, which could cause weight loss. The behavior may remit after hospitalization, but long-term problems including mental retardation, developmental delays, and behavior problems are common (Oates et al. 1985).

Pica is a syndrome of eating non-nutritional substances, such as paint, plastic, string, or hair (Bicknell 1975). Older children eat animal droppings, sand, insects, leaves, or pebbles. Pica usually begins in infancy or the first years of life. It may be associated with mental retardation, or it may develop as a result of child neglect. It usually remits spontaneously, although it may occasionally persist into adolescence and rarely into adulthood. Pica in early childhood has been shown to be associated with bulimic symptoms in adolescence (Marchi and Cohen 1990).

Developing a regular sleep pattern is also a task of early childhood. Abnormal behavioral or physiological events occurring in association with sleep are called parasomnias (Mahowald and Ettinger 1990). The common parasomnias are nightmares, sleep terrors, and sleepwalking (Anders 1982). Nightmares are extremely frightening dreams that rapidly awaken children and leave them frightened and unable to go back to sleep. Sleep terrors involve awakening in a panic without recall of a dream and being confused, disoriented, and somewhat unresponsive to others (Thorpy 1990). Sleepwalking involves rising from bed and walking about, unresponsive to others. Disturbed sleep may also be the result of an emotional disorder (such as the nightmares of PTSD) or a general medical condition, such as epilepsy. Nightmares are common in children before the age of 5 years; more girls than boys may have them. Sleep terrors are much rarer and occur most often in school-age boys. Sleepwalking is more common (1–5%) (American Psychiatric Association 2000) in school-age and prepubescent children. Most often parasomnias resolve on their own during adolescence.

When toilet training becomes significantly delayed, a child may have an elimination problem. A 4-year-old child (or a child with a mental age of at least 4 years) who repeatedly passes feces into clothing or onto the floor has encopresis. Encopresis may occur in children who have never had bowel control or whose previously established bowel control is interrupted by psychosocial stress (Clayden et al. 2002). Constipation caused by physical disease or anxiety with resulting overflow incontinence is the most common mechanism. Encopresis is familial, is strongly related to the sphincter abnormality of enuresis, and may be preceded by an early history of sluggish bowel movements. Therefore, constitutional determinants of bowel motility are likely to be important in many cases. Usually, the incontinence is involuntary; occasionally, it may be deliberate and suggest an oppositional pattern of behavior. The latter children are often generally aggressive and from socially disadvantaged families. Encopresis is more common in boys than in girls. Encopresis can be a persistent problem with exacerbations and remissions, but it usually resolves by late childhood.

A child who repeatedly voids urine into clothing or bedding after the age (or mental age) of 5 years has enuresis. Enuresis can also be primary (i.e., the child has never been continent) or secondary. Data from the US National Interview Survey showed that at the age of 5 years, 36% of boys and 30% of girls had wet the bed at least once in the prior year; 16% of both genders wet infrequently; and 5% of boys and 1% of girls wet the bed nightly (Byrd et al. 1996). Bedwetting declined with age, with all but about 1% of cases having remitted by the age of 17 years. Enuresis has been shown to occur in families and to be associated with biological dysfunctions in circadian rhythms and bladder function, as well as other developmental delays (Clayden et al. 2002). Inadequate or inconsistent toilet training and psychosocial stressors, such as entering school or the birth of a sibling, may also predispose to elimination problems. Elimination disorders frequently co-occur with disruptive behavior disorders.

Disorders of movement may also afflict children. Tics are sudden, rapid, recurrent, nonrhythmic stereotyped motor movements or vocalizations that are not caused by medications or other drugs or by general medical conditions. Motor tics can be simple, abrupt movements such as eye blinking, head jerks, or shoulder shrugs, or more complex behaviors such as facial expressions or arm gestures. Vocal tics can vary from simple throat-clearing sounds to more complex speech, including obscenities (Leckman and Cohen 2002). Tics ordinarily appear during childhood or early adolescence. They may be transient or chronic. Although twin and family studies indicate that genetic factors are involved in the etiology of tic disorders (Pauls and Leckman 1986), these disorders are also exacerbated by stress. In the rare (5–30 cases per 10,000 children, 1–2 cases per 10,000 adults) (American Psychiatric Association 2000) prototype disorder, Tourette's disorder, there are both motor and vocal tics, but either may also occur alone. Tics are up to three times more common in boys than in girls. Tourette's disorder is often seen in association with obsessive-compulsive disorder.

Another motor abnormality of children that is unrelated to a general medical disorder is characterized by repetitive, seemingly driven, and nonfunctional motor behavior, such as hand shaking or waving or body rocking. The movements may also cause bodily injury, such as in head banging, self-biting, picking at the skin, or hitting one's own body. The so-called stereotyped movement disorders may be associated with mental retardation. Stereotyped movements may also be precipitated by stressful events and may be persistent or may subside after adolescence. The motor movements are similar to those seen in pervasive developmental disorders, but in stereotyped movement disorders, severe social skills and communication deficits are absent. Boys tend to have head banging as a symptom, whereas in girls self-biting may be more prevalent.

## Psychosexual Problems

Interest in sexuality and sexual play are common in childhood. Sexual activities between children may be heterosexual or homosexual. The concept of a sexual identity as a boy or as a girl has usually developed by the age of 3 years (Ehrhardt and Meyer-Bahlburg 1981). Occasional cross-gender behavior in dressing or play also occurs in many normal children. When a child, usually a boy, actually develops a strong and persistent preference to be the other sex, the child has a gender identity problem. Such children may insist that they are the opposite sex, dress and play as if they are, and prefer friends of the other sex. They may also repudiate aspects of their own sex, such as having a penis. Most children with a gender identity disorder no longer report cross-gender identification or discomfort with or sense of inappropriateness in gender role by adolescence (American Psychiatric Association 2000).

Table 29–6 summarizes the estimated prevalence and sex distribution of DSM-IV-TR mental disorders seen in children.

**Table 29–6 Prevalence and Sex Distribution of Mental Disorders of Childhood**

| Type of Problem | Specific Disorder | Estimated Prevalence* | Predominant Sex |
|---|---|---|---|
| Developmental | | | |
| Intellectual | Mental retardation | Rare | Male |
| Learning | Reading disorder | Less common | Male |
| Motor skills | Developmental coordination disorder | Common | Male |
| Communication | Expressive language disorder | Less common | Male |
| | Mixed receptive–expressive language disorder | Less common | Male |
| | Phonological disorder | Less common | Male |
| | Stuttering | Rare | Male |
| Pervasive | Autistic disorder | Very rare | Male |
| | Rett's disorder | Very rare | Female (only) |
| | Childhood disintegrative disorder | Very rare | Male |
| | Asperger's disorder | Very rare | Male |
| Emotional | | | |
| Anxiety | Separation anxiety disorder | Less common | Female |
| | Specific phobia | Less common | Female |
| | Social phobia | Rare | Female |
| | Generalized anxiety disorder | Less common | Female |
| | Obsessive-compulsive disorder | Rare | Equal |
| | Posttraumatic stress disorder | NK | Female |
| | Selective mutism | Very rare | Female |
| Mood | Major depressive disorder | Rare | Equal |
| Behavioral | Oppositional defiant disorder | Common | Male |
| | Attention-deficit/hyperactivity disorder | Less common | Male |
| | Conduct disorder, childhood onset | Common | Male |
| Physical functioning | Rumination disorder | NK | Male |
| Eating | Feeding disorder | NK | Equal |
| | Pica | NK | NK |
| Sleep | Nightmare disorder | NK | Female |
| | Sleep terror disorder | NK | Male |
| | Sleepwalking disorder | Less common | Equal |
| Elimination | Encopresis | Rare | Male |
| | Enuresis | Common | Male |
| Sexual | Gender identity disorder | Less common | Male |
| Tic | Tourette's disorder | Very rare | Male |

*Prevalence estimates are as follows: common, >5%; less common, 2–5%; rare, 1–2%; very rare, <1%.
NK, not known.

## Problems of Adolescence

Adolescence is the period of life between puberty and 19 years. For the great majority of children, the physiological events of puberty signify the end of childhood. Achievement of financial independence from the family of origin through work and formation of love relationships outside the family usually signify the end of adolescence and the beginning of adulthood. In the modern world, these goals may not be attained until the early or middle 20s or later. There are many important developmental phases in adolescence. Although moody, confused, and rebellious "adolescent turmoil" is no longer considered the norm for young people, some emotional troubles are fairly common. These may turn out to be symptomatic of nothing more than the stresses and strains of normal development, or they may be the early signs of significant psychological disturbance.

### Adolescent Development

Early in adolescence, children become more independent of parents and mature sexually. Passage through puberty can be stressful. In middle adolescence, children attempt to further their development of an independent identity, experiment with sexual behavior, develop intellectual capacities such as reason and abstraction, and acquire values and morals. In late adolescence, the task is separation, with the concurrent development of a plan for work and discovery of loving relationships outside the nuclear family.

### Types of Problems

Common problems of adolescence are listed in Table 29–7. Rarely, schizophrenia may have a late adolescent onset. As might be expected, comorbidity is common among disorders of adolescence. Table 29–8 summarizes these patterns.

**Table 29–7 Psychopathology in Adolescence**

| |
|---|
| Identity problems |
| Emotional problems |
| Behavioral problems |
| Problems in self-image and physical functioning |

### Identity Problems

Identity issues are at the crux of adolescent development. Therefore, distress about issues concerning long-term goals, values, peer loyalties, sexual orientation and behavior, and lifestyle is common in this age group. Although most identity problems are worked through during adolescence without serious sequelae, unresolved problems may indicate the presence of mood or anxiety disorders or form the nucleus for the development of behavioral or characterological problems in adulthood.

**Table 29–8 Common Patterns of Comorbidity in Adolescence**

| Disorder Type or Specific Disorder | Comorbid Disorders |
|---|---|
| Mood disorders | Anxiety disorders<br>Substance use disorders<br>Eating disorders |
| Anxiety disorders | Other anxiety disorders<br>Mood disorders |
| Substance use disorders | Substance-induced disorders<br>Other substance use disorders |
| Conduct disorder | Conduct disorder<br>Substance use disorders<br>Mood disorders |
| Pathological gambling | Mood disorders<br>Substance use disorders<br>Anxiety disorders |
| Trichotillomania | Substance use disorders<br>Mood disorders<br>Anxiety disorders |
| Eating disorders | |
| Anorexia nervosa | Major depressive disorder<br>Obsessive–compulsive disorder<br>Substance use disorders<br>Avoidant personality disorder<br>General medical conditions |
| Bulimia nervosa | Major depressive disorder<br>Dysthymic disorder<br>Anxiety disorders<br>Substance use disorders<br>Borderline personality disorder |
| Narcolepsy | Mood disorders<br>Substance-related disorders<br>Generalized anxiety disorder<br>Sleepwalking disorder<br>Enuresis |
| Body dysmorphic disorder | Mood disorders<br>Anxiety disorders<br>Personality disorders |

*Source*: Data from American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Rev. APA, Washington, DC.

## Emotional Problems

Depressive episodes are much more common in adolescents than in younger children, with girls more frequently affected than boys (Harrington 2002). From 2% to 10% of teenagers, develop a full-blown major depressive episode (Cicchetti and Toth 1995). Teenagers of ages 14–17 years have a suicide attempt rate of 8–9%, and major depression, especially among girls, is a commonly associated disorder (Shaffer and Gutstein 2002). About one-third of adolescents with clinical depression have a parent with a mood disorder. Episodes of major depression, like less serious adjustment problems, may be precipitated by a breakup of a romantic relationship, an academic disappointment, a family argument, or the suicide of a friend or family member.

Episodes of mood disorder during adolescence may be a continuation of childhood-onset disorder. The risk of recurrence of major depression of childhood is up to 40% (Kovacs et al. 1984b) within a 2-year period. Ninety percent of adolescents with a major depressive episode may recover within 2 years (Strober et al. 1993), although each episode may last nearly 6 months. Children and adolescents with major depressive disorder have an elevated risk of recurrence of mood disorders into young adulthood (Harrington 2002) and adolescents with subthreshold depressive symptoms may progress to full depressive disorders by young adulthood (Fergusson et al. 2005). Adolescents with persistent or recurrent internalizing disorders are at risk for mental disorders up to 40 years later (Colman et al. 2007). In about 10–15% of adolescents with recurrent depressive episodes, mania, with excitement and extreme energy, can develop and alternate with episodes of depression, indicating a bipolar mood disorder (Strober et al. 1993). Most bipolar disorders in adolescents improve significantly following hospitalization, but many continue to have residual symptoms and impairments (DelBello et al. 2007).

Major depression in adolescents is frequently accompanied by anxiety, substance use, behavior (young men), and eating (young women) disorders (Rohde et al. 1991). Comorbidity is associated with more suicidal behavior (Foley et al. 2006) and treatment seeking.

A common age at onset for panic disorder is late adolescence (Horwath and Weissman 2000). About 1 in 200 adolescents may develop panic disorder (Lewinsohn et al. 1993). Panic disorder is characterized by sudden, unexpected panic attacks, which consist of a feeling of intense fear and a constellation of characteristic symptoms, such as palpitations, sweating, trembling, shortness of breath, choking, chest pain, nausea, dizziness, paresthesias, hot flashes, and feelings of going crazy or of dying. Panic disorder is more common among young women than young men. The course tends to be chronic, with waxing and waning of symptoms. Follow-up studies suggest that about one-third to one-half of affected people can be healthy and living normal lives, despite fluctuating or recurring symptoms (Pine 2000). Panic attacks among adolescents may be risk factors for developing other anxiety disorders or substance use disorders in young adulthood (Goodwin et al. 2004).

Social phobia also has a common onset in the teens (Schneier et al. 1995). Between 1% and 2% of teenagers may be affected (McGee et al. 1990 Cohen et al. 1993a). Fears of being humiliated or embarrassed in front of others may develop abruptly after a humiliating experience or may develop more gradually, in the context of a childhood history of social inhibition or shyness. In adolescents, social phobia may lead to poor school performance, avoidance of dating, and general social isolation. The duration is frequently lifelong (Table 29–9), although the severity of symptoms may fluctuate depending on life's demands. By early-to-middle adult life, a limited social phobia, such as in speaking in front of a group, may become a more generalized and pervasive pattern of social inhibition, feelings of inadequacy,

**Table 29–9 Continuity of Social Anxiety Across the Life Cycle**

| Temperamental Predispositions | | Childhood or Adolescent Psychopathology | | Early or Middle Adult Life Personality |
|---|---|---|---|---|
| Shy, inhibited, fearful of strangers and novel situations, high reactivity | → | Social phobia* | → | Avoidant personality disorder† |

*Other anxiety disorders such as separation anxiety disorder or generalized anxiety disorder may also occur.

†Comorbidity with other personality disorders, such as dependent personality disorder, and with mood and anxiety disorders is likely.

and hypersensitivity to negative evaluation characteristic of avoidant personality disorder (Skodol et al. 1995). In the community, social phobia is more common among women, although more men may seek treatment for it.

Obsessive-compulsive disorder has a modal age at onset between 6 and 15 years for boys and may affect as many as 2% of adolescents (Whitaker et al. 1990, Flament et al. 1988). Obsessive-compulsive disorder is characterized by persistent and intrusive anxiety-provoking thoughts. The obsessions of children and adolescents most often involve contamination, danger to self or others, symmetry, or moral issues (Rapoport and Swedo 2002). A person may perform repetitive behaviors, such as hand washing, ordering, or checking, or mental acts, such as praying, counting, or repeating words. Compulsive behaviors are performed rigidly, according to rules that are aimed at reducing anxiety or preventing something from happening. Among children and adolescents, rituals are more common than obsessions; washing rituals are the most common. Predominant symptoms often change over time. Symmetry and counting are common during grade school, excessive washing occurs frequently in early adolescence, and thoughts and behaviors with sexual themes arise in later adolescence. The course of obsessive-compulsive disorder is chronic, with waxing and waning of symptoms. In a 2-year follow-up of adolescents, symptoms and impairment persisted (Berg et al. 1989). As many as 30-50% of adult patients with obsessive-compulsive disorder report a childhood or adolescent onset (Karno and Golding 1991, Carter et al. 1995).

Posttraumatic stress disorder may become a persistent, chronic problem for adolescents in the absence of treatment (Goenjian et al. 2005). The occurrence of new traumatic events is a negative prognostic indicator (Perkonigg et al. 2005). Israeli adolescents (especially boys) exposed to recurrent terrorism have been found to engage in high levels of risk-taking behaviors, raising the possibility of a cycle of traumatic stress and post-traumatic stress symptomatology (Pat-Horenczyk et al. 2007).

Adolescent anxiety and depressive disorders result in a two- to three-fold risk anxiety and depressive disorders in young adulthood (Pine et al. 1998). The continuity effects are relatively nonspecific, except for simple and social phobias that persist. Even though most adolescent emotional disorders disappear by young adulthood, most adult disorders are preceded by adolescent disorders.

## Behavior Problems

Experimentation with psychoactive substances is common in adolescence. More than 50% of 14-year-old boys and girls have had experience in drinking alcohol (Johnston et al. 1993). Although use of most substances of abuse is apparent for adolescents, alcohol, tobacco, and marijuana are the drugs of choice, and overall drug use by adolescents increased in the 1990s, with one-half to three-quarters of older adolescents having taken an illicit drug at some time (Weinberg et al. 2002). Initially, pathological drug use in the teens is in the form of episodes of intoxication, that is, clinically significant, maladaptive behavioral and physiological changes secondary to recent substance ingestion. Eight percent of eighth-graders, 18% of tenth-graders, and 30% of twelfth-graders reported that they had been intoxicated with alcohol in the past month (Johnston et al. 1993). The maladaptive changes of intoxication may include inappropriate sexual or aggressive behavior; mood lability; impaired judgment or increased risk taking; or impaired social, academic, or occupational functioning. Substance withdrawal is rare in adolescence, but it may occur if the drug has been taken in sufficiently high quantities for a sufficiently long time. Substance abuse or dependence (i.e., maladaptive patterns of substance use leading to social, occupational, legal, or physical problems) may also develop in adolescence, although an early onset of these types of problems usually suggests additional conduct problems. Most substance-related problems are more common in boys than in girls. In addition, there is ample evidence for a gateway effect—that is, use of a drug such as marijuana can frequently lead to use of more harmful drugs, and heavy use of marijuana significantly increases the likelihood of progressing to "harder" drugs (Rutter 2002b).

Recurrent substance intoxication often leads to substance abuse. Although the adverse social consequences of substance abuse often remain relatively stable over time (Helzer 1994), abuse evolves into dependence most commonly with drugs that have a high potential for the development of tolerance, withdrawal, and patterns of compulsive use. These substances include alcohol, cocaine, opioids, and sedative, hypnotic, and anxiolytic drugs. The course of substance dependence is extremely variable, ranging from complete remission after successful treatment or the development of a life-threatening physical ailment secondary to drug use to chronicity. Early use of drugs or alcohol by adolescents predicts persisting problems (Robins and Przybeck 1985). Use of drugs by adolescents has been shown to be associated with elevated rates of delinquency, unemployment, divorce, and abortions in young adulthood (Kandel et al. 1986). Co-occurring mental disorders, such as mood disorders and personality disorders, increase the risk of poor outcomes.

Conduct problems of adolescence may be a continuation of childhood problems or may arise de novo during the teenage years. Estimates of the prevalence of conduct disorder from general population studies range from less than 1% to more than 10% (American Psychiatric Association 2000). Conduct problems of adolescence are more serious than conduct problems of childhood. The greater freedom, independence, and physical strength of adolescents increase the risk that aggressive or destructive behavior will harm others. Conduct problems that commonly emerge during adolescence include burglary, mugging, armed robbery, rape, and use of knives and guns in arguments and fights.

Persistence of childhood conduct problems into adolescence and evolution of more severe aggressive and destructive behaviors portend a continuation of antisocial behavior and substance abuse in adult life (Cohen et al. 2007, Myers et al. 1998). Persistent deviant peer group involvement in boys can be predicted by a behavioral profile of hyperactivity, fearlessness, and low prosocial behaviors as early as kindergarten (Lacourse et al. 2006). Premature menarche leading to affiliation with older, more deviant peers has been associated with higher rates of conduct disorder in adolescent girls (Burt et al. 2006). Onset of conduct disorder in adolescence, however, suggests a better prognosis (Robins 1966). Conduct disorder has also been shown to be associated with premature death

from violent causes (Rydelius 1988, Yeager and Lewis 1990) or substance abuse (Laub and Vaillant 2000).

Externalizing disorders (conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence) share a common underlying heritable vulnerability (Hicks et al. 2004). Neurobehavioral disinhibition in affect, behavior, and cognition in childhood has been shown to predict substance use disorder in adolescence (Tarter et al. 2003). Genetic vulnerability to heavy drinking is greater in men than in women (King et al. 2005). Shared environmental influences have also been implicated that are stronger for initiation and use of substances than for problem use (Kendler et al. 2003, Rhee et al. 2003). Unique environmental experiences may determine which type of substance a person will use or misuse.

Teenage boys are particularly vulnerable to developing pathological gambling. Adolescent gamblers are more likely than nongamblers to have substance use disorders and depression (Lynch et al. 2004). Gambling behavior can become an addiction with greater and greater amounts of time and money spent on gambling, with deleterious financial, social, and sometimes legal consequences. Personality characteristics of high negative emotionality, low constraint, risk taking, and impulsivity are shared by individuals with pathological gambling and those with substance use disorders (Slutske et al. 2005). Gambling may be regular or episodic, but the course is chronic. Gambling behavior increases during times of stress. Pathological gambling frequently becomes associated with mood, anxiety, and substance use disorders (Roy et al. 1988) by middle age, with resultant reduced quality of life (Scherrer et al. 2005). The relationship between pathological gambling and major depression in men is largely influenced by overlapping genetic factors (Potenza et al. 2005).

Trichotillomania is the behavior of recurrent pulling out of one's own hair (Swedo 1993). Common areas of the body for hair pulling are the scalp, eyebrows, eyelashes, and beard. There is an increasing sense of tension that is relieved after hair pulling. The behavior shares features of both impulsive and compulsive behavior problems (Skodol and Oldham 1996). Trichotillomania appears to be more common among girls than boys. The peak ages at onset are between 5 and 8 years and again at about the age of 13 years. The symptoms may be continual with significant hair loss resulting or may be episodic. Trichotillomania is commonly associated with mood, anxiety, and substance use disorders (Swedo et al. 1989b, Christenson et al. 1991).

## Problems in Self-image and Physical Functioning

Disturbances in body image and eating behavior have peak ages at onset during adolescence and early adulthood. Anxiety disorders in general and obsessive-compulsive disorder in particular are common in the childhood histories of individuals with eating disorders (Kaye et al. 2004). Genetic, personality, perinatal, and socioenvironmental factors have ben implicated in the development of eating disorders (Bulik et al. 2006, Favaro et al. 2006, The McKnight Investigators 2003, Wade et al. 2004). Eating disorders are more common in white than in black women (Striegel-Moore et al. 2003).

A girl with anorexia nervosa (90% of those with eating disorders are female) refuses to maintain her body weight above minimally normal and has an intense fear of becoming fat. In addition, she has a disturbance in the way her weight and body shape are experienced, such that she denies the seriousness of her low weight and places excessive importance on her weight and shape for self-esteem. Girls with anorexia nervosa become amenorrheic. They may also engage in binge eating and purging behavior (Halmi 1985). The prevalence of anorexia nervosa among females is approximately 0.5% (American Psychiatric Association 2000). Anorexia nervosa occurs most commonly in industrialized countries (Pate et al. 1992), where the ideal of physical attractiveness is to be thin, and may be increasing over time (Lucas et al. 1991). The onset is often after a stressful life event. Patients with anorexia nervosa may experience episodes of major depression (Herzog et al. 1992) or have obsessions and compulsions about issues in addition to food, weight, and body shape. The course of anorexia nervosa is variable, ranging from a single adolescent episode to a chronic, lifelong, and deteriorating course. Although persistence of the diagnosis of anorexia nervosa was recently found to be only 10% over a 12-year follow-up period, low body weight and perfectionism were common and rates of comorbid mood, anxiety, and substance use disorders were high (Sullivan et al. 1998). Factors associated with a good prognosis include an early age at onset, hysterical personality, good parent-child relationship, early treatment, and high socioeconomic status. Factors associated with a poor prognosis include bulimia, vomiting, and compulsivity (Steinhausen et al. 1991). Mortality in serious cases may be 10% (American Psychiatric Association 2000). Mortality may be predicted by low body weight (Hebebrand et al. 1997), severity of alcohol use (Keel et al. 2003), and delay in receiving treatment (Millar et al. 2005).

In bulimia nervosa, there are recurrent episodes of binge eating in which large amounts of food are consumed in an out-of-control mode, accompanied by compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or enemas; fasting; or excessive exercise. Bulimia nervosa is more common than anorexia nervosa; it is estimated to occur in 1–3% of women (American Psychiatric Association 2000). Childhood adversities, particularly maladaptive behavior on the part of fathers, contribute to the development of eating disorders in adolescence or early adulthood (Johnson et al. 2002). Patients with bulimia nervosa may also have mood disorders, problems with substance abuse or dependence, or other problems of impulse control, which predict future outcome (Keel et al. 2000). The mean age at onset is slightly later for bulimia nervosa than that for anorexia nervosa. The behavior usually persists for several years, at least, and may be chronic or intermittent. In a recent community-based study, between one-half and two-thirds of girls with bulimia nervosa had some symptoms of an eating disorder over a 5-year follow-up period. Each year a third remitted and a third relapsed (Fairburn et al. 2000). In clinical samples, 50% may recover after 5–10 years (Keel and Mitchell 1997). After 10 years, about 10% of patients may still have bulimia nervosa, although an additional 20% will have some continuing symptoms. Duration of the disturbance before seeking treatment, substance abuse (Keel et al. 1999), greater body image disturbance, and worse psychosocial functioning (Keel et al. 2005) predict a worse prognosis. Persistence of disturbed eating behaviors into

**Table 29–10 Prevalence and Sex Distribution of Mental Disorders of Adolescence**

| Type of Problem | Specific Disorder | Estimated Prevalence* | Predominant Sex |
|---|---|---|---|
| Emotional | | | |
| Mood | Major depressive disorder | Common | Female |
| | Bipolar disorder | NK | Equal |
| Anxiety | Panic disorder | Very rare | Female |
| | Social phobia | Rare | Female |
| | Obsessive–compulsive disorder | Rare | Male |
| Behavioral | | | |
| Substance related | Alcohol intoxication | Very common | Male |
| | Substance abuse | Common | Male |
| Disruptive | Conduct disorder | Very common | Male |
| Impulse control | Pathological gambling | Very rare | Male |
| | Trichotillomania | Rare | Female |
| Self-image and physical functioning | | | |
| Eating | Anorexia nervosa | Very rare | Female |
| | Bulimia nervosa | Less common | Female |
| Sleep | Narcolepsy | Very rare | Equal |
| Somatoform | Body dysmorphic disorder | NK | Equal |

*Prevalence estimates are as follows: common, > 5%; less common, 2–5%; rare, 1–2%; very rare, < 1%. NK, not known.

early adulthood is accompanied by the development of personality disorders in many cases. Bulimia nervosa has been shown to be associated with borderline personality disorder in contrast with anorexia nervosa, which was found to be associated with avoidant personality disorder (Skodol et al. 1993). Binge-eating disorder (without purging) has also been documented to be a chronic disorder (Pope et al. 2006).

Although adolescents tend to sleep late, excessive daytime sleepiness may become a problem during adolescence. Excessive sleepiness may indicate the onset of narcolepsy, a rare disorder characterized by sleep attacks, accompanied by cataplexy (sudden, bilateral loss of muscle tone), and/or hypnopompic or hypnogogic hallucinations or sleep paralysis (Regestein 1994a). The excessive sleepiness of narcolepsy is persistent over time. Poor nocturnal sleep may develop later in middle age. Persons developing narcolepsy may have had a childhood history of a parasomnia, such as sleepwalking disorder, or an elimination disorder, such as enuresis. Comorbidity with major depressive disorder, dysthymic disorder, generalized anxiety disorder, and substance-related disorders on a concurrent or lifetime basis is also common (American Psychiatric Association 2000). There are equal numbers of males and females with narcolepsy.

A preoccupation with an imagined or exaggerated defect in appearance may develop in adolescence. Unlike the normal concerns of adolescents with their physical appearances, excessively time-consuming concerns that cause great distress or interfere with functioning suggest body dysmorphic disorder. Common complaints involve imagined or slight defects of the face or head or preoccupation with the shape or size of some body part (Phillips 1991). The obsessive preoccupation with the perceived defect and frequently accompanying mirror checking and excessive grooming behaviors suggests a continuity with obsessive-compulsive disorder or with the weight and shape preoccupations and accompanying behaviors of anorexia nervosa. The course of body dysmorphic disorder is chronic, at least over the short term (Phillips et al. 2006). Persons with the disorder may seek repeated and unnecessary surgical corrections of their perceived disfigurements, which rarely result in improvements in their conditions (Hollander and Phillips 1993). Suicidal ideation and attempts are common (Phillips and Menard 2006). Men and women are equally likely to be diagnosed with the disorder.

Table 29–10 summarizes the estimated prevalence and sex distribution of DSM-IV mental disorders commonly seen in adolescents.

## Problems of Early Adulthood

The period between the ages of 20 and 30 years is commonly referred to as early adulthood.

### Early Adult Development

Developmental tasks of early adulthood include achieving emotional and financial independence from parents and forming intimate relationships with people outside the family of origin. Stage-specific stressors include leaving home, education and career choice, in some cases service in the armed forces, finding and maintaining employment, courtship and marriage, and sexual relations, among others.

### Types of Problems

Problems of young adulthood fall mostly into the categories listed in Table 29–11. By the end of early adulthood, people have passed through the ages of greatest risk for first onset of the majority of recognized mental disorders. Comorbidity between disorders becomes the rule rather than the exception. In a population survey in the US covering a 12-month period, of those who met criteria in the prior year for a mental disorder (26% of the sample), 22% carried two diagnoses and 23% had three or more diagnoses (Kessler et al. 2005b).

**Table 29–11 Psychopathology in Early Adulthood**

| |
|---|
| Emotional problems |
| Problems of behavior and adaptive functioning |
| Problems in physical functioning |
| Problems in reality testing |

The relationships between comorbid "disorders" are complex. Whether they indeed represent independent entities with distinctive etiologies, pathogenetic mechanisms, and outcomes, or merely reflect different ways in which fundamental psychopathological disturbances are manifest over time, between sexes, or across aspects of psychological functioning remains to be determined. In some cases, one disorder is clearly antecedent to another. Examples include disorders of childhood, such as separation anxiety disorder or conduct disorder, that evolve into adult versions—in these cases, panic disorder with agoraphobia or antisocial personality disorder, respectively. Sometimes, as in the case of ADHD, residual symptoms persist and form the basis for developing problems such as substance abuse or personality dysfunction. At other times, a second disorder may develop as a consequence of a primary disorder—in reaction to it or as a complication. Examples include major depressive disorder developing after a person has been incapacitated by panic disorder with agoraphobia, or sedative, anxiolytic, or alcohol abuse developing because the person attempted to self-medicate for the condition. Alternatively, disorders appear more or less contemporaneously and reflect an underlying diathesis or vulnerability. Thus, patients present with several disorders, all suggestive of a problem of generalized impulsivity, such as bulimia nervosa, a substance use disorder, and an impulse control disorder (e.g., kleptomania). Personality disorders often develop in the context of underlying traits affecting specific capacities such as impulse control or interpersonal relatedness, as dysfunction becomes widespread.

Table 29–12 summarizes patterns of comorbid mental disorders in early adulthood.

**Table 29–12 Common Patterns of Comorbidity in Early Adulthood**

| Disorder Type | Comorbid Disorders |
|---|---|
| Mood disorders | Other mood disorders |
| | Anxiety disorders |
| | Eating disorders |
| | Substance-related disorders |
| | Personality disorders |
| Anxiety disorders | Other anxiety disorders |
| | Mood disorders |
| | Substance-related disorders |
| | Eating disorders |
| | Somatization disorder |
| | Personality disorders |
| Dissociative disorders | Mood disorders |
| | Post-traumatic stress disorder |
| | Substance-related disorders |
| | Somatoform disorders |
| | Personality disorders |
| Substance use disorders | Other substance-related disorders |
| | Mood disorders |
| | Anxiety disorders |
| | Personality disorders |
| | Schizophrenia and other psychotic disorders |
| | Eating and sleep disorders |
| | Impulse control disorders |
| Impulse-control disorders | Mood disorders |
| | Anxiety disorders |
| | Substance-related disorders |
| | Eating disorders |
| | Personality disorders |
| Personality disorders | Other personality disorders |
| | Psychotic disorders |
| | Mood disorders |
| | Anxiety disorders |
| | Eating disorders |
| | Substance-related disorders |
| | Impulse control disorders |
| | Somatoform disorders |
| Sexual disorders | |
| Sexual dysfunctions | Other sexual dysfunctions |
| | Mood disorders |
| | Anxiety disorders |
| | Substance-related disorders |
| Paraphilias | Sexual dysfunctions |
| | Personality disorders |
| Somatoform disorders | Mood disorders |
| | Anxiety disorders |
| | Substance-related disorders |
| | Dissociative disorders |
| | Personality disorders |
| Factitious disorders | Substance-related disorders |
| | Personality disorders |

*Source*: Data from American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Rev. APA, Washington, DC.

## Emotional Problems

Although disturbances in mood can occur at any age, the peak ages of onset of mood disorders are probably in the 20s. Mood disturbances may be acute and episodic or insidious and chronic. They may be relatively mild or severe and may be accompanied by psychotic features or suicidal behavior. The most common mood disorders are major depressive disorder, dysthymic disorder, bipolar disorder, and cyclothymic disorder.

Major depressive disorder is characterized by episodes of severe depression that impair functioning. The lifetime risk for major depressive disorder is estimated to be between 10% and 25% and the point prevalence in adult women from 5% to 9% (American Psychiatric Association 2000). About twice as many women are affected as men. Heritability of major depression is higher in women than in men (Kendler et al. 2006). Initial episodes of major depressive disorder are often precipitated by a psychosocial stressor. Men and women both experience stressful life events—men more legal and work-related events and women more interpersonal events—prior to the development of a major depressive episode and appear equally sensitive to them (Kendler et al. 2001). More than 50% of people who have a major depressive episode have a second episode, and as the number of episodes increases, the likelihood of having subsequent episodes (Solomon et al. 2000) and the severity of the episodes also increase (Maj et al. 1992). The time period between episodes generally decreases with recurrences. In all, about 85% of recovered patients will experience a relapse over 15 years (Mueller et al. 1999). About two-thirds of episodes of major depressive disorder resolve completely, about 40% within 3 months and 60% within 6 months (Keller et al. 1992b, Coryell et al. 1994). Full remission would be characterized by absence of symptoms, return to usual self and usual level of functioning, and the presence of features of positive mental health, such as optimism and self-confidence (Zimmerman et al. 2006). The average duration for an episode is about 20 weeks (Solomon et al. 1997). Chronicity or partial remission characterizes the others.

Over 12 years of follow-up, most patients will have been symptomatic at some level, although subsyndromal symptoms are much more common and lasting than full-blown

episodes (Judd et al. 1998). Incomplete recovery from an episode appears to predict a more severe, relapsing, and chronic course (Judd et al. 2000b), as do psychotic symptoms during the initial episode (Coryell et al. 1996). Comorbid depression and anxiety also predicts a more chronic course (Merikangas et al. 2003). Despite this tendency toward chronicity, people continue to recover from depressive episodes, even those characterized by a lengthy period of illness (Mueller et al. 1996). The course of major depressive disorder is similar for men and women (Simpson et al. 1997). Persistent depressive symptoms are associated with persistent impairment in functioning, proportional to the severity of the symptoms (Judd et al. 2000a). Traits of personality that make a person vulnerable to major depression (neuroticism, low self-esteem, and poor coping skills) persist after remission and psychosocial disability after remission often reflects poor premorbid functioning (Ormel et al. 2004a, 2004b). Major depression has been associated with increased mortality from suicide and from natural causes (Osby et al. 2001, Pennix et al. 2001). Suicide in major depression is associated with pessism, impulsive/aggressive personality traits, prior suicide attempt, and comorbid substance use disorders, particularly involving alcohol and nicotine (Dumais et al. 2005, Oquendo et al. 2004).

Nearly 5–10% of persons with major depressive episodes develop bipolar disorder. Dysthymic disorder sometimes precedes the development of major depressive disorder. Panic disorder, obsessive-compulsive disorder, both anorexia nervosa and bulimia nervosa, substance-related disorders, and several different personality disorders are often found in association with major depressive disorder.

Dysthymic disorder is characterized by milder depressive symptoms that are chronic. They are more often cognitive (e.g., low self-esteem, pessimism, feelings of inadequacy) than vegetative (e.g., insomnia, loss of appetite) (Keller et al. 1995). It has an insidious onset, usually persists for years (although symptoms may fluctuate), and often is complicated by episodes of superimposed major depressive disorder (the so-called double depression) (Keller and Shapiro 1982, Klein et al. 2000). Dysthymic disorder is about half as common as major depressive disorder. The sex ratio for dysthymic disorder is 1:1. Persons with dysthymic disorder with or without concomitant major depressive episodes had a poorer outcome than persons with major depression alone during a 2-year follow-up period (Wells et al. 1992). Dysthymic disorder is often found in persons with personality disorders and substance use disorders.

Manic episodes characterize bipolar I disorder. Manic episodes are periods of persistently elevated, expansive, or irritable mood. Bipolar I disorder is relatively rare compared with major depressive disorder, affecting 0.4-1.6% of persons on a lifetime basis (American Psychiatric Association 2000). Bipolar I disorder is equally common in men and women. The first episode of what eventually becomes bipolar I disorder is more likely to be a depressive episode in women than in men, whose initial episode is more likely to be manic, and age at onset of manic episodes is earlier in men (Kennedy et al. 2005). About 90% of persons with bipolar I disorder have recurrent episodes (Keller 1985, Keller et al. 1993). Patients with bipolar I disorder have more lifetime episodes, in general, than patients with recurrent major depressive disorder (Winokur et al. 1993). Subsyndromal symptoms between episodes may occur in 50% or more of patients and substantially increase the risk of relapse into full mood episodes (Keller et al. 1992a, Keck et al. 1998, Tohen et al. 2003). From 15% to 25% of patients with bipolar I disorder have persistent mood disturbance and functional impairment (Winokur et al. 1993, Carlson et al. 1974). The course of both Bipolar I and II is dominated by more depressive episodes than manic or hypomanic phases, and the depression is equally or more impairing than the mania (Judd et al. 2005). Rapid cycling between manic and depressive episodes is associated with increased depressive morbidity and serious suicide attempts (Coryell et al. 2003) and a generally more severe course of illness (Schneck et al. 2004). A small number of people may have unipolar mania over the course of many years, without depressive episodes (Solomon et al. 2003).

If a person has hypomanic episodes characterized by shorter duration of mood elevation and less impact on functioning than in a manic episode, the person is said to have bipolar II disorder (Dunner 1983). Mixed hypomanic (euphoric and depressive symptoms occurring together are common in women with bipolar disorder (Suppes et al. 2005). Bipolar II and other subthreshold bipolar disorder are more common than bipolar I in the general population (Merikangas et al. 2007). Bipolar disorders are often accompanied by anxiety, eating, and substance-related disorders and ADHD, which are generally related to a poorer prognosis (Nolan et al. 2004, Simon et al. 2004). Substance dependence is associated with recurrence of mood episodes (Tohen et al. 1990). Bipolar II disorder may be comorbid with borderline personality disorder.

Cyclothymic disorder is characterized by a chronic mood disturbance with numerous periods of hypomanic and depressive symptoms that are not as severe as in bipolar I disorder or major depressive disorder. Persons with cyclothymic disorder are at increased risk for a bipolar disorder.

Although several anxiety disorders have their onset most often in childhood or adolescence, as previously described, others have increased risk for onset in early adult life. In particular, many cases of acrophobia (fear of heights) and situational phobias, such as of elevators, flying, or closed places, develop in early adulthood (American Psychiatric Association 2000). Women, previously married people, and the unemployed and disabled are more likely to have some form of panic disorder (Kessler et al. 2006). Obsessive-compulsive disorder has a later age at onset in women than in men, during the 20s rather than the teens. Acute stress disorder and PTSD can occur at any age but are prevalent in young adults.

Disorders such as panic disorder, other specific phobias, social phobia, and generalized anxiety disorder, which are more likely to begin in childhood or adolescence, may persist or recur during early adult life. The median onset age of anxiety disorders is 11 years; anxiety disorders are more common in women (Kessler et al. 2005a). The lifetime prevalence of panic disorder in the adult population is estimated to be 4.7% (Kessler et al. 2005a); the 1-year prevalence rate is 2.7% (Kessler et al. 2005b). Phobias are common in the community. The lifetime rate is estimated to be 12.5% (Kessler et al. 2005a) and the 1-year rate 8.7% (Kessler et al. 2005b). The lifetime prevalence rate of social phobia is

12.1% (1 year: 6.8%), generalized anxiety disorder is 5.7% (1 year: 3.1%), and obsessive-compulsive disorder has an estimated lifetime prevalence of 1.6% (1 year: 1.0%) (Kessler et al. 2005a, 2005b). Episodes of panic disorder may be precipitated by disruptions in important interpersonal relationships; social phobia may occur after new demands in school or the workplace for speaking to a group. Childhood phobias that persist into adulthood remit infrequently (American Psychiatric Association 2000). Rates of remission of panic disorder over 5 years are about 40% in both men and women, although recurrence rates are higher among women (Yonkers et al. 1998). Women with early adult-onset panic disorder tend to have attacks that persist into older age (Regier et al. 1988). Comorbidity with other anxiety disorders is common for all types of anxiety disorders. The course of most anxiety disorders is chronic, with social phobia having the smallest probability of recovery (Bruce et al. 2005). High percentages of people with anxiety disorders also suffer from mood disorders and may develop substance-related disorders as a result of efforts to treat their anxiety with alcohol or medications. Cormorbity worsens the clinical course of anxiety disorders. Anxiety disorders are independent risk factors for subsequent suicide attempts (Sareen et al. 2005).

Although psychological reactions to extremely stressful events can occur, like the events themselves, at any age, much of what is known about these reactions has been learned from populations of young adults. These populations include soldiers in combat (Kulka et al. 1990, Solomon and Mikulincer 2006), refugees (Kinzie et al. 1990, Weine et al. 1998), and community subjects who have experienced crime victimization (Breslau et al. 1991, 1998), child abuse (Widom 1999), natural or human-made disasters (Havenaar et al. 1997, Goenjian et al. 2000), terrorism (Shalev and Freedman 2005) or life-threatening injury, such as traffic accidents (Ursano et al. 1999), or illness (Helzer et al. 1987, Davidson et al. 1991).

Immediately after an event in which a person experiences or witnesses actual or threatened death or serious injury or threat to physical integrity, which arouse feelings of helplessness, fear, or horror, an acute stress reaction may occur. These reactions are characterized by (1) dissociative symptoms, such as feeling numb or detached, derealization, or depersonalization; (2) reexperiencing symptoms, such as recurrent images, thoughts, dreams, or flashbacks of the traumatic event; (3) avoidance of stimuli that arouse recollections of the trauma; and (4) symptoms of hyperarousal, such as hypervigilance, exaggerated startle response, and difficulty in sleeping. Acute stress reactions resolve within a month of a stressor and may serve an adaptive function, limiting painful thoughts and feelings associated with the stressor (Koopman et al. 1995). When the symptoms persist, the disorder is known as PTSD. Dissociative symptoms are less prominent in PTSD than in acute stress disorder. PTSD may also have a delayed onset—months or even years after the traumatic event. The lifetime prevalence of PTSD in the US community population has been found to be 6.8% (Kessler et al. 2005a).

The severity, duration, and proximity of a person's exposure to a traumatic event influence the risk of developing either an acute stress disorder or PTSD (March 1993). Acute stress reactions which do not resolve (Classen et al. 1998), peritraumatic dissociation (Shalev et al. 1996) or emotional numbing in response to the stressor (Epstein et al. 1998) predict later PTSD. Social support, family history, childhood experiences, personality variables such as hostility and low self-efficacy (Heinrichs et al. 2005), neurocognitive deficits (Kremen et al. 2007, Parslow and Jorm 2007), and preexisting mental disorders also affect risk. Men and women appear equally vulnerable.

Re-experiencing, avoidance, and hyperarousal symptoms may fluctuate over the course of PTSD. Intrusion symptoms may be more common early in the course and avoidant symptoms may become more common later (Blank 1993). About one-half of cases resolve in a few months; others may persist for years. PTSD is frequently accompanied by mood, psychoactive substance use, personality, and other anxiety disorders (Davidson and Foa 1991). PTSD has been shown to increase risk for later coronary heart disease (Kubzansky et al. 2007).

Dissociative disturbances may occur in the absence of re-experiencing or avoidance symptoms, often in response to severe stress (Spiegel and Cardena 1991). Dissociative states all involve isolation of memory and emotions from normal states of consciousness, disturbance in sense of identity or sense of self, and experiences of intense absorption or focused concentration (Putnam 1995). The exact prevalences of dissociative amnesia, fugue (inability to recall one's past, unexpected travel), depersonalization, and identity (multiple personality) disorders are not known, but all are probably relatively rare. The course of dissociative problems is usually chronic but fluctuating, with exacerbations occurring in association with episodes of stress or trauma. Dissociative disturbances may be more common among women.

Dissociative amnesia is seen in association with conversion disorder, mood disorders, or a personality disorder. Fugue states may be seen, in addition, in PTSD and in association with substance-related disorders. Depersonalization can be seen in substance-related disorders and hypochondriasis. Persons with dissociative identity disorder may also have mood disorders, eating disorders, sexual disorders, substance-related disorders, sleep disorders, or borderline personality disorder (American Psychiatric Association 2000).

Milder, time-limited reactions to stressors of any severity may also occur. These are common occurrences that might follow the breakup of a romantic relationship or the loss of a job. The symptoms may be of depression, anxiety, or disturbance of conduct. They cause temporarily decreased performance at school or work or impairment in social relationships. Provided that the consequences of the stressor are resolved (i.e., the person resumes dating or obtains a new job), the course of the symptoms and impairment should be less than 6 months.

## Behavior and Adaptive Functioning

Problems with various types of impulsive behaviors and problems with adaptive functioning in general seem particularly prone to become manifest in early adulthood. These problems may develop, in part, secondary to the increased stresses of movement away from the protective environments of school and family that characterize the period.

Although experimentation with substances ordinarily begins in adolescence and some personal, social, or legal problems secondary to maladaptive patterns of use (abuse)

may have already occurred, the full syndrome of dependence on alcohol or other substances may not emerge until the 20s. Dependence on substances is characterized not only by symptoms of physiological dependence, such as tolerance or withdrawal, but also by a pattern of loss of control over substance use (Rounsaville and Kranzler 1989). The prevalence of substance abuse or dependence varies widely depending on the substance. Alcohol dependence and nicotine dependence are common, with lifetime prevalence estimates ranging between 15% and 20%. Amphetamine and cannabis dependences affect 1.5–5% of the population and opioid dependence less than 1% (American Psychiatric Association 2000). The course of substance dependence is variable, and depends somewhat on the class of substance and its route of administration. In general, frequent substance intoxication may lead to repeated episodes of substance abuse, which can develop into substance dependence, although the frequency of progression is variable. For example, in three 4- to 5-year follow-up studies, the range of alcohol-abusing men who progressed to alcohol dependence was from 3.5% (Schuckit et al. 2000, 2001) to 30% (Hasin et al. 1990). Episodes and recurrences are commonly precipitated by stressors or accompany episodes of other mental disorders, such as major depressive disorder. For drugs of abuse, men are more likely to have substance-related problems than are women.

A childhood history of conduct disorder or ADHD frequently precedes the development of substance abuse or dependence. A history of mood or anxiety disorders is common in persons with nicotine dependence. Concurrent antisocial personality disorder is common in people with substance use disorders that involve illegal and expensive drugs such as cocaine, heroin, or amphetamines. Substance use disorders can develop in the context of PTSD and often complicate the course of mood, anxiety, and psychotic disorders. Co-occurring mental disorders often lead to further complications secondary to substance use and a poorer overall prognosis.

Other problems of impulse control involving assaultive acts or destruction of property (intermittent explosive disorder), fire setting (pyromania), or stealing (kleptomania) may begin in early adult life (McElroy et al. 1995). Social gambling may progress to become pathological gambling.

Of major significance in the 20s is the stabilization of patterns of perceiving, relating to, and thinking about the environment and oneself that we call personality. Also, however, in the 20s, the potential for the development of inflexible and maladaptive traits that cause distress or interfere with effective social and occupational functioning may arise. Thus, personality disorders may become evident.

The standard guidelines for the diagnosis of personality disorders refer to a pattern of inner experience and behavior that has an onset in adolescence or early adulthood and is stable and of long duration. Some traits or behaviors that are forerunners of adult personality disorders, such as mood lability and impulsivity for borderline personality disorder or conduct disorder for antisocial personality disorder, are often evident in childhood or adolescence (Rey et al. 1995, Bernstein et al. 1996). Personality disorder-related traits appear to decline from adolescence into early adulthood (Johnson et al. 2000a, Lenzenweger 1999, Lenzenweger et al. 2004), but those who develop personality disorders have elevated traits as adolescents. A variety of childhood and adolescent mental disorders are associated with the development of personality disorders in young adults, including major depressive disorder, childhood disruptive behavior disorders, and childhood anxiety disorders (Kasen et al. 1999, 2001). Because adolescent development is often a period of rapid growth and change, it is difficult to conceptualize a stable personality pattern during the teenage years. However, adolescents with personality disorders are at risk for violence and criminal behavior, as well as major mental disorders and suicidality in adulthood (Johnson et al. 1999, 2000b). Evidence of personality pathology in adolescence is also significantly associated with later development of substance use disorders (Cohen et al. 2007).

Personality disorders presumably arise from interactions between a person's temperamental traits and predispositions and his or her experiences with parents, siblings, peers, and others (Millon and Davis 1995). Innately high versus low levels of arousal, activity, and sociability may either become reinforced by life's experiences to harden into exaggerated and inflexible personalities or be balanced by a fortuitous combination of chance and parental planning over the years leading to adulthood. Personality disorders show improvement over time despite the assumptions of stability in the definition of personality disorder (Grilo et al. 2004, Zanarini et al. 2006). Some criteria are more stable and trait like, while others appear to reflect behaviors that are situationally dependent and intermittently expressed (McGlashan et al. 2005, Zanarini et al. 2007). The prevalence of individual personality disorders ranges from about 2% to 3% for the more common varieties, such as schizotypal, antisocial, borderline, and histrionic, to 0.5–1% for the least common, such as narcissistic and avoidant (American Psychiatric Association 2000).

Personality disorders fall into three clusters (Table 29–13) that have some descriptive validity: the odd-eccentric cluster (paranoid, schizoid, and schizotypal), the dramatic-emotional cluster (antisocial, borderline, histrionic, and narcissistic), and the anxious-fearful cluster (avoidant, dependent, and obsessive-compulsive) (Kass et al. 1985). The disorders in each of the three clusters may share some underlying common vulnerability factors involving cognition, affect and impulse control, and behavioral maintenance or inhibition, respectively, and may have a spectrum relationship to certain syndromal mental disorders (Siever and Davis 1991). Thus, paranoid or schizotypal personality disorders may be observed to be premorbid antecedents of delusional disorders or schizophrenia; borderline personality disorder is seen in association with mood and anxiety disorders and with disorders of impulse control, such as bulimia nervosa, ADHD, or a substance use disorder; and avoidant personality disorder is seen with generalized social phobia. Comorbidity between personality disorders (Oldham et al. 1992) and related other mental disorders is substantial (Oldham et al. 1995). The presence of any personality disorder in the early 20s is associated with compromised quality of life a decade later (Chen et al. 2006), and severe personality disorders, such as schizotypal or borderline, are associated with high degrees of functional impairment and extensive utilization of mental health treatment resources (Skodol et al. 2002, Bender et al. 2001). Functional impairment in personality disorders may be more stable than personality psychopathology itself (Skodol et al. 2005). Patients

**Table 29–13 Descriptive Features of Personality Disorders in Three Clusters**

| Cluster | Specific Disorder | Descriptive Features |
|---|---|---|
| Odd-eccentric | Paranoid | Distrust and suspiciousness; others' motives interpreted as malevolent |
| | Schizoid | Detachment from social relationships; restricted range of emotional expression |
| | Schizotypal | Discomfort in close relationships; cognitive or perceptual distortions; eccentricities of behavior |
| Dramatic-emotional | Antisocial | Disregard for and violation of the rights of others |
| | Borderline | Instability in interpersonal relationships, self-image, and affects; marked impulsivity |
| | Histrionic | Excessive emotionality and attention seeking |
| | Narcissistic | Grandiosity, need for admiration, lack of empathy |
| Anxious-fearful | Avoidant | Social inhibition, feelings of inadequacy, hypersensitivity to negative evaluation |
| | Dependent | Submissive and clinging behavior; need to be taken care of |
| | Obsessive–compulsive | Preoccupation with orderliness, perfectionism, and control |

*Source*: Adapted from American Psychiatric Association (2000) Diagnostic and statistical Manual of Mental Disorders, 4th edition, Text Rev. APA, Washington, DC.

whose personality disorders persist are more impaired as young adults than those whose personality disorders remit (Skodol et al. 2007). Cluster A personality disorders and antisocial and narcissistic personality disorders are diagnosed more frequently in men than in women. Borderline, histrionic, and dependent personality disorders are diagnosed more frequently in women than in men.

## Disturbances in Physical Functioning

Certain disturbances in physical functioning are likely to become manifest in early adult life. These include disturbances in sexual functioning, sleep disturbances, and some physical complaints that cannot be fully explained on the basis of a known general medical condition.

Disturbances of sleep, including both insomnia (Reynolds et al. 1994) and hypersomnia (Regestein 1994b), commonly develop in young adults. Insomnia and hypersomnia may occur in association with another mental disorder, a general medical condition, or use of a substance, or may be independent of other pathological conditions (primary). Insomnia is much more common than hypersomnia in association with other mental disorders, such as major depressive disorder, bipolar disorder, or a psychotic disorder. Sleep disorders related to another mental disorder are more common in women because of the parallel increased prevalence of mood and anxiety disorders among women (American Psychiatric Association 2000).

Primary insomnia often begins acutely after a period of psychosocial or medical stress. The common complaint of young adults is difficulty falling asleep. Women are more often affected than men. Because of conditioning and hyperarousal, a sleeping problem can become persistent. Some cases remit after resolution of the stressor; others are chronic or episodic for many years. Insomnia secondary to another mental disorder (e.g., schizophrenia, mood, and anxiety disorders) (Nofzinger 1994) or a medical condition (e.g., chronic obstructive pulmonary disease, asthma) (Sateia 1994) usually follows the course of the underlying disorder. The course of insomnia related to substances depends on the particular substance involved. Primary hypersomnia rarely resolves without treatment.

Certain disturbances characterized by physical complaints without known medical etiology have a high incidence rate in early adulthood. Specifically, conversion reactions, hypochondriasis, and somatization disorder can be first diagnosed in this age group.

Conversion disorder is a rare disturbance characterized by unexplained symptoms or deficits affecting voluntary motor or sensory functions. Conversion disorders are more common in women than in men (American Psychiatric Association 2000). Psychological stressors or conflicts invariably precede the initiation or exacerbation of the symptoms. The onset is usually abrupt and symptoms remit within 2 weeks. Recurrences are common, and a single recurrence predicts future problems. Paralysis and blindness have a better prognosis than tremor or seizures (Toone 1990).

Hypochondriasis is a preoccupation with fears of having or the belief that one has a serious disease. It is equally common in men and in women and has a general population prevalence of 1–5% (American Psychiatric Association 2000). The course is usually chronic, with waxing and waning of symptoms. Over a 4- to 5-year period, patients with hypochondriasis will show a decline in symptoms and an improvement in psychosocial functioning, but two-thirds will continue to have the disorder (Barsky et al. 1998). Hypochondriasis is often seen in association with anxiety disorders (Barsky et al. 1994) or depression. Comorbid personality disorder suggests a poorer prognosis.

People with somatization disorder have multiple physical complaints involving pain, gastrointestinal symptoms, sexual symptoms, and pseudoneurological symptoms that cause them to seek repeated medical evaluations and treatments. The disorder is more common among women, with a prevalence estimated as 0.2–2.0% among women and less than 0.2% in men (American Psychiatric Association 2000). Initial symptoms, often menstrual complaints, are commonly present during adolescence, and the full syndrome is typically present by the age of 25 years (symptoms begin before the age of 30 years by definition). The course is chronic but fluctuating (Guze et al. 1986). Conversion disorder may progress to somatization disorder (Kent et al. 1995). Major depressive disorder, panic disorder, substance-related disorders, and cluster B personality disorders are frequently comorbid (American Psychiatric Association 2000).

Rarely, a person may intentionally produce or feign physical symptoms to become a patient, but not for obvious reasons. The so-called factitious disorders are more

common in men than in women. The course may be episodic or chronic. The onset usually follows a hospitalization for a bona fide general medical condition or another mental disorder. Severe personality psychopathology is usually present.

## Psychosexual Problems

Sexual experimentation begins in adolescence and, although some adolescents may have ongoing sexual relations, sexual behavior becomes an expected part of life in the 20s. Thus, the 20s seem to be a common period for the onset of sexual dysfunctions. Premature ejaculation is a common problem in young men and is often present from their first experiences with intercourse. With further sexual experience and aging, most men learn to control and delay orgasm. Premature ejaculation may recur after a period of sexual abstinence or secondary to performance anxiety with a new partner. Vaginismus (involuntary spasm of the muscles of the vagina) is a problem that can affect young women having their first experiences with intercourse. Inhibited orgasm is also a problem of younger women; orgasmic capacity in women increases with age. Disorders of sexual arousal (e.g., deficient desire or excitement) usually develop during adulthood, after a period of normal sexual interest, in association with psychological distress, stressful life events, or interpersonal difficulties. The exact prevalence of the psychosexual dysfunctions is unknown, although problems with desire and orgasm are more common among women (Nathan 1986, Spector and Carey 1990). Psychosexual dysfunctions are likely to have significant adverse affects on marital and other interpersonal relationships.

Paraphilias are disorders of sexual aim. Persons with paraphilias are sexually aroused by fantasies, urges, and behaviors that involve non-human objects, suffering or humiliation, children, or other nonconsenting persons. Paraphilias include exhibitionism (exposure of genitals), fetishism (use of inanimate objects), frotteurism (touching or rubbing), pedophilia (sexual activity with children), sexual masochism (self-suffering), sexual sadism (sexual excitement derived from the suffering of others), transvestic fetishism (cross-dressing), and voyeurism (watching). Paraphilias have a usual age at onset from late adolescence into early adult life. Except for sexual masochism (male-to-female ratio of 20:1), paraphilias are almost never found in women. The actual prevalence of paraphilias is also unknown, but pedophilia, voyeurism, and exhibitionism are most commonly found in clinics specializing in their treatment (American Psychiatric Association 2000). Multiple paraphilias may coexist; when one subsides, another may emerge or become more prominent (Abel et al. 1988). Sexual dysfunctions and personality disorders may be comorbid.

## Problems in Reality Testing

Problems in reality testing are reflected in abnormalities of speech, thinking, perception, and self-experience. They are suggestive of psychotic disorders such as schizophrenia. Although schizophrenia and its counterpart disorder of briefer duration, schizophreniform disorder, may have an onset in late adolescence (or in later adulthood), the most common age at onset is in early adult life. There is a distinct sex difference in median age at onset for the first psychotic episode of schizophrenia: for men the onset is in the early-to-middle 20s; for women the onset is in the late 20s. The lifetime prevalence of schizophrenia is estimated to be 0.5–1.5% (American Psychiatric Association 2000).

The onset of schizophrenia may be acute, but more often an insidious prodrome develops before the first psychotic episode (Keith and Matthews 1994, Klosterkotter et al. 2001). The usual prodrome consists of the gradual onset of social withdrawal, loss of interest in school or work, poor personal hygiene, and unusual behavior. Occasionally, there are psychotic symptoms present from childhood (Poulton et al. 2000) or other psychiatric disorders during adolescence (Weiser et al. 2001). As mentioned earlier, cluster A personality disorders may be evident before the onset of schizophrenia. Obstetrical and other perinatal complications have been implicated in the development of schizophrenia (Dalman et al. 1999, Jones et al. 1998).

The symptoms of the acute phase of schizophrenia consist of delusions; hallucinations; disorganized speech; grossly disorganized or catatonic behavior; and/or negative symptoms such as affective flattening, alogia, or avolition. Schizophrenia inevitably has a significant negative impact on functioning in work, social relations, and self-care. In the first 6 months of a schizophrenia-like illness, the disorder is called schizophreniform disorder. About one-third of patients receiving this diagnosis recover fully; the other two-thirds eventually progress to schizophrenia or schizoaffective illnesses (Beiser et al. 1988). Good prognostic signs in schizophreniform disorder are an acute onset (i.e., without prodromal deterioration), good premorbid social and occupational functioning, confusion and perplexity as part of the acute psychotic episode, and absence of blunted or flat affect.

The long-term course of schizophrenia is variable, but few persons recover fully. Some may experience good control of positive symptoms with medications and have reasonably stable clinical courses. Others show progressive deterioration with increasing functional disability. Negative symptoms are more persistent than positive symptoms (Arndt et al. 1995). Factors associated with a better prognosis in schizophrenia include good premorbid adjustment, acute onset, later age at onset, insight, being female, precipitating events, associated mood disturbance, brief duration of active phase symptoms, consistent compliance with medications, good interepisode functioning, minimal residual symptoms, absence of structural brain abnormalities, normal neurological examination, a family history of mood disorder, and no family history of schizophrenia (Table 29–14). There is some controversy over whether or not early treatment with antipsychotic medications confers a better prognosis (Ho et al. 2000, Craig et al. 2000). The paranoid subtype of schizophrenia appears to be the least severe; the disorganized subtype is the most severe (Kendler et al. 1984, Fenton and McGlashan 1991). Relapse following recovery from an episode is common (Robinson et al. 1999). Comorbid substance-related disorders may complicate the course of schizophrenia.

Patients who have illness episodes that are characterized by major episodes of mood disturbance, either depressed or manic, accompanied by schizophrenia-like psychotic symptoms and whose delusions and hallucinations are also present when mood symptoms are not, are said to have schizoaffective disorder. The prognosis for schizoaffective disorder, in general, and especially the bipolar type, is better

**Table 29–14 Good Versus Poor Prognostic Factors in Schizophrenia**

| Characteristic | Prognosis | |
|---|---|---|
| | Good | Poor |
| Premorbid adjustment | Good | Poor |
| Mode of onset | Acute | Insidious |
| Age at onset | Late | Early |
| Insight | Good | Poor |
| Sex | Female | Male |
| Precipitating events | Present | Absent |
| Mood disturbance | Present | Absent |
| Treatment with antipsychotics | Early | Late |
| Medication compliance | Consistent | Inconsistent |
| Duration of psychotic symptoms | Brief | Prolonged |
| Interepisode functioning | Good | Poor |
| Residual symptoms | Few | Many |
| Structural brain abnormalities | Absent | Present |
| Neurological examination | Normal | Abnormal |
| Family history | Mood disorder | Schizophrenia |

*Source*: American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Rev. APA, Washigton, DC, p. 309.

than that for schizophrenia, as might be expected given the factors described as good prognostic signs in schizophrenia (Kendler 1987, 1994). Compared with schizophrenia, schizoaffective disorder occurs more frequently in women (American Psychiatric Association 2000).

The vast majority of disorders with typical onset in early adult life persist or recur in middle adult life. Some of these disorders may also have their initial onset after the age of 30 years. Table 29–15 summarizes the estimated prevalence and sex distribution of mental disorders of early adulthood.

## Problems of Middle Adult Life

### Middle Adult Development

Middle adult life may be applied to ages 30-65 years, which are characterized developmentally by consolidation and generativity in career and family life. Although potentially the most productive years of life, they are also fraught with obstacles and frustrations in the achievement of personal goals. Common stressors include marriage and divorce, parenting, career setbacks, recognition of unattainable goals, and death of parents. Any of these may serve as the focus of a midlife crisis.

### Types of Problems

Psychosocial stressors may precipitate episodes of already existing disorders of virtually any type or initiate disorders de novo. Relatively few disorders have a typical onset between 30 and 65 years (Table 29–16). They include particular anxiety, psychotic, sleep, and substance-related disorders, and disorders associated with general medical conditions.

### Anxiety Disorders

Although panic disorder most frequently presents in late adolescence, there is a second peak in age at onset distribution in the middle 30s (Fyer et al. 1995). Onset after the age of 45 years is unusual. The lifetime and 1-year prevalences of panic disorder thus peak between the ages of 30 and 44 years (Eaton et al. 1991). Panic attacks with intense fear and discomfort and accompanying symptoms are more likely to be spontaneous and unexpected early in the course of panic disorder. With long standing, chronic panic disorder, the recurrence of attacks tends to become associated with various situations that predispose to or precipitate them. Thus, in an effort to avoid situations from which escape might be difficult or help unavailable, a patient with recurrent panic attacks may develop agoraphobia.

### Psychotic Disorders

A psychotic disorder with onset from middle-to-late adult life is delusional disorder (Kendler 1982). Delusional disorder differs symptomatically from the schizophrenia-related conditions discussed previously in having delusions involving situations that can occur in real life (nonbizarre), such as being followed, poisoned, infected, loved at a distance, or deceived by a spouse or lover, or having a disease. Behavior is not obviously odd or bizarre. Patients with delusional disorder are likely to have premorbid personalities that are extroverted, dominant, and hypersensitive, in contrast to patients with schizophrenia, whose premorbid personalities are typically introverted, submissive, and schizoid (Kendler 1980). In addition, delusional disorder usually has a much less severe impact on overall psychosocial functioning. Delusional disorder, in general, is equally common among men and women, although the jealous subtype may be more common among men. It is a rare disorder, affecting only about three persons in 10,000 (American Psychiatric Association 2000). The course of delusional disorder is quite variable. It may remit without relapse, have full periods of remission with subsequent relapses, or become chronic. Delusional disorders may develop in the context of obsessive-compulsive or body dysmorphic disorders, if the affected person becomes unable to recognize that her or his belief (obsession) or preoccupation is excessive or unreasonable; that is, she or he loses the ability to test reality.

### Sleep Disorders

Breathing-related sleep disorders most frequently lead to clinical evaluation in persons between 40 and 60 years of age. Excessive sleepiness or insomnia is caused by obstructive or central sleep apnea syndrome or central alveolar hypoventilation syndrome. Obstructive sleep apnea is more common in men than in women; women may develop the syndrome after menopause, however. The prevalence of obstructive sleep apnea is estimated as 1–10% and is even higher in the elderly (American Psychiatric Association 2000). Technically, these disorders are neurological or respiratory in nature but are encountered by psychiatrists evaluating patients with problems related to sleeping (Thorpy 1994). Central sleep apnea is common among elderly persons with CNS or cardiac disease. The course of breath-related sleep disorders is chronic.

### Substance-Related Disorders

Because the peak onset of alcohol dependence is in the 20s to middle 30s, some alcohol-related disorders, which tend to develop in the context of dependency, may not become

**Table 29–15 Prevalence and Sex Distribution of Mental Disorders in Early Adulthood and Middle Adult Life**

| Type of Problem | Specific Disorder | Estimated Prevalence* | Predominant Sex |
|---|---|---|---|
| Emotional | | | |
| Mood | Major depressive disorder | Very common | Female |
| | Dysthymic disorder | Very common | Female |
| | Bipolar I disorder | Rare | Equal |
| | Bipolar II disorder | Very rare | Female |
| | Cyclothymic disorder | Very rare | Equal |
| Anxiety | Specific phobia | Very common | Female |
| | Social phobia | Very common | Female |
| | Panic disorder† | Less common | Female |
| | Obsessive–compulsive disorder | Less common | Equal |
| | Acute stress disorder | NK | NK |
| | Post-traumatic stress disorder | Less common or common | NK |
| | Generalized anxiety disorder | Less common | Female |
| Dissociative | Dissociative amnesia | NK | NK |
| | Dissociative fugue | Very rare | NK |
| | Depersonalization disorder | NK | NK |
| | Dissociative identity disorder | NK | Female |
| Adjustment | Adjustment disorder | Very common | Equal |
| Behavior, adaptive functioning | | | |
| Substance use | Alcohol dependence | Very common | Male |
| | Amphetamine dependence | Less common | Male |
| | Cannabis dependence | Less common | Male |
| | Cocaine abuse | Very rare | Equal |
| | Hallucinogen abuse | Very rare | Male |
| | Inhalant abuse | NK | Male |
| | Nicotine dependence | Very common | Male |
| | Opioid dependence | Very rare | Male |
| | Sedative dependence | Rare | Female |
| Substance-induced | Alcohol-induced persisting amnestic disorder† | NK | Male |
| Impulse control | Intermittent explosive disorder | Rare | Male |
| | Kleptomania | Rare | Female |
| | Pyromania | Rare | Male |
| | Pathological gambling | Less common | Male |
| Personality | Paranoid personality disorder | Rare | Male |
| | Schizoid personality disorder | NK | Male |
| | Schizotypal personality disorder | Less common | Male |
| | Antisocial personality disorder | Less common | Male |
| | Borderline personality disorder | Less common | Female |
| | Histrionic personality disorder | Less common | Female |
| | Narcissistic personality disorder | Very rare | Male |
| | Avoidant personality disorder | Very rare | Equal |
| | Dependent personality disorder | NK | Female |
| | Obsessive–compulsive personality disorder | Rare | Male |
| Physical functioning | Premature ejaculation | NK | Male (only) |
| Sexual dysfunction | Vaginismus | NK | Female (only) |
| Paraphilias | All | NK | Male |
| Sleep | Primary insomnia | NK | Female |
| | Primary hypersomnia | NK | NK |
| | Breathing-related sleep disorder§ | Common | Male |
| Somatoform | Conversion disorder | Very rare | Female |
| | Hypochondriasis | NK | Equal |
| | Somatization disorder | Rare | Female |
| | Pain disorder‡ | Very common | Female |
| Factitious | Factitious disorder | NK | Male |
| Reality testing | Schizophrenia | Very rare | Equal |
| | Schizophreniform disorder | Very rare | Female |
| | Schizoaffective disorder | Very rare | Female |
| | Delusional disorder§ | Very rare | Equal |

*Prevalence estimates are as follows: very common, >10%; common, 5–10%; less common, 2–5%; rare, 1–2%; very rare, <1%.
†Second peak in incidence in middle adult life.
‡Peak in age at onset in middle adult life.
NK, not known.

**Table 29–16 Disorders with Onset in Middle Adult Life**

| |
|---|
| Panic disorder |
| Delusional disorder |
| Breathing-related sleep disorder |
| Substance-induced disorders |
| Disorders due to general medical conditions |
| Pain disorder |

problems until middle adult life. These include episodes of alcohol withdrawal, amnestic syndrome, and dementia (Table 29–17). Alcohol-induced persisting amnestic disorder (Korsakoff's syndrome) is a severe impairment in memory secondary to thiamine deficiency and is associated with prolonged heavy alcohol ingestion. Korsakoff's syndrome usually develops after the age of 40 years and usually persists indefinitely, leading a person to require lifelong custodial care. Amnestic syndrome can also develop after prolonged and heavy use of sedatives, hypnotics, or anxiolytic drugs. Unlike the course of alcohol-induced disorder, the course of amnestic disorder associated with other sedative drugs is more variable and full recovery is possible. An amnestic syndrome can also develop after treatment with anticonvulsants or with exposure to environmental toxins, such as lead, mercury, insecticides, or industrial solvents. Full syndromes of dementia may also develop and persist after chronic alcohol ingestion or from other drugs or toxins.

### General Medical Conditions

Because medical conditions have increased incidence during adult life, psychopathological conditions resulting from the direct physiological effects of general medical conditions are on the rise. General medical conditions (and their treatments) can cause delirium, dementia, amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, catatonic disorder, sexual dysfunction, sleep disorder, and personality disorder. A general medical condition is likely to be the cause of a psychiatric syndrome under the following circumstances (American Psychiatric Association 2000):

1. A temporal relationship can be observed between the onset, exacerbation, or remission of the general medical condition and that of the mental disorder.
2. There are features of the psychiatric disturbance that are atypical of the primary mental disorder. Included would be an atypical age at onset, unusual symptoms, or symptoms that are disproportionately severe given the overall clinical picture.
3. There is an association established in the medical literature between the general medical condition and the psychiatric syndrome.
4. Previous episodes or a family history of the primary mental disorder is absent.

The actual age at highest risk, the sex distribution, and the clinical course of these disturbances are determined by the underlying medical condition. Neurological, endocrine, neoplastic, cardiovascular, infectious, and miscellaneous other medical illnesses have been implicated in the etiology of secondary mental disorders (Popkin and Tucker 1994). Medical conditions can also act as psychosocial stressors (Popkin et al. 1987), in which case the prognosis also depends on the management of the stress and the treatment of the mental disorder.

Pain is a common problem among adults. Estimates are that from 10% to 15% of adults in the US have some work impairment in any given year caused by back pain alone (American Psychiatric Association 2000). Pain may be associated with a general medical condition only, in which case it is not considered a mental disorder. When psychological factors are judged to play an important role in the onset, severity, exacerbation, or maintenance of pain, then a mental disorder is present, whether or not a medical condition also plays a role. Most pain syndromes that present to mental health professionals are chronic. Women appear to have a greater risk for at least certain chronic pain conditions, such as headaches and musculoskeletal pain. Pain disorder is often associated with mood and anxiety disorders.

The estimated prevalence and sex distribution of the few mental disorders with a peak in age at onset in middle adult life are included in Table 29–15.

## Problems of Late Life

### Late Life Development

The developmental demands of late life are many. Coping with physical illness, disability, or a diminished capacity for physical activity; adapting to retirement or reduced productivity at work; and dealing with grief after the loss of friends or a spouse are all frequent and challenging tasks. Maintaining emotional equilibrium by finding a new balance between desirable and undesirable events and circumstances (Baltes 1987) is a major undertaking.

### Types of Problems

Risk for mood disturbances in late life remains high. Other emotional problems, substance abuse, and problems in physical functioning and in reality testing may occur. However peak age of risk is mainly for memory impairment associated with the dementias (Gurland 1996) (Table 29–18).

**Table 29–17 Continuity of Substance-Related Problems Across the Life Cycle**

| Early Adolescent Psychopathology | | Late Adolescent Psychopathology | | Psychopathology of Early Adulthood | | Psychopathology of Middle Adult Life |
|---|---|---|---|---|---|---|
| Substance intoxication | → | Substance abuse | → | Substance dependence | → | Substance withdrawal<br>Substance induced persisting amnestic disorder<br>Substance induced persisting dementia |

| Table 29–18 Psychopathology in Late Life |
|---|
| Memory impairment |
| Emotional problems |
| Substance abuse |
| Problems in physical functioning |
| Problems in reality testing |

## Memory Impairment

Dementia is characterized by multiple cognitive deficits, invariably including memory impairment but also such deficits as aphasia, apraxia, agnosia, and disturbance in executive functioning (e.g., planning, organization, abstraction). Dementia represents a decline in cognitive abilities that interferes with successful adaptive functioning. The decline in memory and intellectual functioning of dementia must be distinguished from analogous declines that occur with normal aging processes (Crook et al. 1986, Blackford and LaRue 1989). In addition to significant memory loss (Palmer et al. 2002), executive, decision-making dysfunction may herald the eventual development of Alzheimer's disease (AD) (Chen et al. 2001). The cause of dementia (Table 29–19) may be degenerative CNS conditions such as Alzheimer's or Parkinson's disease; nondegenerative CNS conditions such as cerebrovascular disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, viral and prion encephalitides, or brain tumor; or systemic illnesses such as anemia, renal or hepatic failure, hypothyroidism, vitamin $B_{12}$ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, or human immunodeficiency virus infection (Miller and Gustavson 2000, Reichman 2000). Chronic use of or exposure to substances, including alcohol and environmental toxins, may also cause dementia. States of delirium related to the side effects of medications, acute infections, and other conditions may be mistaken for dementias.

Not all of the potential causes of dementia are increased in prevalence in late life. The most common types, however, such as the Alzheimer's type and vascular type, usually present after the age of 65 years and progressively increase in frequency with increasing age. From 2% to 4% of the population older than 65 years are estimated to have Alzheimer's dementia. In most ethnic groups, the majority of dementias are due to AD; vascular dementia is less common (Livingston et al. 1990b, Folstein et al. 1991). After the age of 85 years, 20% or more of the population is estimated to have a dementia. Women may be slightly more likely to develop AD than men. Men are more likely to develop vascular dementia (Folstein et al. 1991). Other causes of dementia in the elderly are much less common (Fratiglioni et al. 1991).

| Table 29–19 Causes of Memory Impairment Disorders in Late Life | |
|---|---|
| Disease or Illness Class | Specific Type |
| Central nervous system diseases | Alzheimer's disease<br>Parkinson's disease<br>Cerebrovascular disease<br>Pick's disease<br>Creutzfeldt–Jakob disease<br>Subdural hematoma<br>Brain tumor<br>Epilepsy<br>Infections |
| Systemic illnesses | Anemia<br>Renal failure<br>Hepatic failure<br>Hypertension<br>Heart disease<br>Diabetes<br>Fluid and electrolyte imbalances<br>Vitamin deficiencies<br>Infections |
| Toxins | Medications<br>Substances<br>Environmental toxins |

The course of dementia may be progressive, static, or remitting, depending on the underlying cause and the availability of effective treatment. The course of AD is slowly progressive, with an insidious onset, gradual loss of cognitive functions, and eventual neurological impairment (Cummings and Benson 1992). Behavioral disturbance, particularly agitation, is persistent in patients with AD (Devanand et al. 1997, Levy et al. 1996). The average duration from symptom onset to death is 8–10 years. Vascular or multi-infarct dementia has a more abrupt onset and a stepwise and fluctuating course corresponding to the events of cerebrovascular disease (Loeb and Gandolfo 1983, Small 1985).

Major and minor depression may be comorbid with Alzheimer's dementia in over 50% of cases (Starkstein et al. 2005). Both major and minor depressions are associated with more severe psychopathology, functional impairment, and social dysfunction. Depressive symptoms in the elderly may be associated with subsequent cognitive decline (Yaffe et al. 1999, Bassuk et al. 1998, Chodosh et al. 2007) and may increase the risk for developing AD (Devanand et al. 1996, Ownby et al. 2006) or be an early manifestation of the disease (Chen et al. 1999, Ganguli et al. 2006). Psychosis occurs in over 40% of patients with AD and may be associated with more rapid cognitive decline (Ropacki and Jeste 2005).

Mild cognitive impairment (MCI) in the elderly may predict subsequent conversion to AD in individuals with multiple cognitive impairments, not only memory deficits (Talbert et al. 2006). The presence of the risk factor gene apolipoprotein E epsilon4 allele appears to accelerate the onset of AD (Khachaturian et al. 2004) and the rate of brain atrophy (Chen et al. 2007). Heritability of AD is high for both men and women, nongenetic risk factors also play a role and may be a focus for interventions to decrease risk or delay onset (Gatz et al. 2006). AD brain pathology is more likely to be clinically expressed as dementia in women than in men (Barnes et al. 2005).

The elderly are also at highest risk for developing deliria. Delirium is a disturbance of consciousness, with reduced ability to focus, sustain, or shift attention. There are changes in cognitive functioning, such as memory impairment or disorientation; the development of perceptual disturbances, such as illusions and hallucinations; and agitation. The symptoms develop rapidly and tend to fluctuate during the course of the day.

There are many causes for delirium. General medical conditions include systemic infections, metabolic disorders, fluid and electrolyte imbalances, hepatic or renal disease, thiamine deficiency, postoperative states, hypertensive encephalopathy, postictal states, and head trauma. Many

substances, including prescribed medications, may also produce delirium. The elderly are particularly susceptible to developing delirium because many of the medical conditions mentioned have an increased prevalence in this age group and the CNS vulnerability of the population is increased. In the age group older than 65 years, 10–15% of those hospitalized have a delirium on admission and another 10–40% develop a delirium while hospitalized (American Psychiatric Association 2000). The in-hospital fatality rate for elderly delirious patients is 10–65% (Tune 2000). Because more women survive to an advanced age, more cases of delirium are encountered among women; however, male gender may be a risk factor for delirium in the elderly (American Psychiatric Association 2000).

## Emotional Problems

Problems with depressed mood are common among the elderly. Although the prevalence of major depressive disorder is only about 1–2% (Blazer et al. 1987, Weissman et al. 1991), other depressive disorders including dysthymic disorder and atypical depression raise the rates to between 2% and 4%, and when subthreshold but clinically significant depressive symptoms are included, the rates rise to between 10% and 15% or higher (Livingston et al. 1990a Blazer and Williams 1980, Gurland et al. 1983). Women continue to be at greater risk for depression during late life (Dewey et al. 1993). One form of the so-called minor depression, that is, depression that is not stress related and whose symptoms are below the threshold for major depression, has been found to be unique among persons older than the age of 60 years (Blazer et al. 1989): depressive complaints coupled with cognitive impairment. In addition, wide swings in mood (emotional lability) and sudden expressions of strong emotions (emotional incontinence) can occur in elderly patients with brain lesions.

Depressive symptoms and depressive disorders are common in people with physical illnesses and physical disability (Gurland et al. 1988, Turner and Noh 1988, Wells et al. 1993) but tend to improve as physical status improves (von Korff et al. 1990). Depression may increase the severity, awareness, and reporting of the symptoms of physical illness (Barsky et al. 1988). A majority of people older than the age of 65 years have at least one chronic physical disorder (Verbrugge 1990), so it is not surprising that comorbidity between depressive disorders and physical illnesses is substantial among the elderly or that risk for depression in the elderly would be elevated (Roberts et al. 1997). A meta-analysis of 20 studies of risk factors for depression among elderly community members found bereavement, sleep disturbance, disability, prior depression, and female gender to be significant (Cole and Dendukuri 2003). Overall, depression worsens the morbidity and mortality associated with medical illnesses in the elderly (Krishnan et al. 2002).

Both depressive and manic mood disturbances resulting from the direct physiological effects of general medical conditions are seen in the elderly. The causes may be AD, Parkinson's disease, stroke, vascular dementia, and other CNS, cardiovascular, traumatic, metabolic, neoplastic, and endocrine diseases. Because the elderly are more likely to be taking prescribed medications for medical conditions, substance-induced mood disturbances are also encountered.

The elderly are at risk for suicide (Pierce 1987, Hawton and Fagg 1990), particularly after the first onset of a major depressive disorder late in life (Pierce 1987, Conwell et al. 1991), after a psychosocial stressor such as divorce or bereavement (Livingston et al. 1990a), or in the context of alcoholism (Hawton and Fagg 1990) or a serious physical illness (Conwell et al. 1990). With advancing age, the frequency of attempted suicide decreases but the frequency of completed suicide increases.

Depression-induced cognitive impairment, also known as depressive dementia or pseudodementia, is a particular problem among the elderly (Stoudemire et al. 1989, Rabins and Pearlson 1994). Patients with pseudodementia cannot recall material presented to them to remember but can recognize familiar material, whereas patients with irreversible dementias are impaired in both free recall and recognition memory. MCI, detectable by neuropsychological testing, and complaints of difficulty with memory occur in many cases of "pure" depressive disorder in elders. In approximately 10% of depressive disorders in elders (15% of cases referred to clinics for memory disorders), a more prominent dementia-like syndrome presents. Depressive symptoms usually respond to treatment with concomitant improvement in cognitive impairment. However, most patients with more severe depressive pseudodementia eventually develop a true dementia in subsequent years (Kral 1983, Kral and Emery 1989).

The course of major depression in the elderly may be characterized by a more insidious onset than younger age groups (Berger et al. 1998) and higher relapse rates than in middle age (Mitchell and Subramaniam 2005), but overall outcome may not be worse (Alexopoulos et al. 1996). Concomitant physical illness, disability, cognitive impairment, and more severe depression (Cole et al. 1999), as well as onset late in life (Alexopoulos et al. 1996) and psychosis (Flint and Rifat 1998) have been shown to be associated with worse outcomes.

Problems with anxiety are common among the elderly, affecting up to 20% of the population older than the age of 65 years at any given time (Blazer et al. 1991). Specific phobias are the most common disturbance, with an estimated 1-month prevalence rate of 4.8% (Eaton et al. 1991). Although most anxiety disorders in the elderly have an onset at an earlier stage in life, a few persons may experience the first onset in late life. Agoraphobia may develop in late life, precipitated by physical illness or a traumatic incident (Lindesay 1991). Anxiety disorders, as well as mood disorders, may be secondary to general medical conditions, such as cardiovascular, pulmonary, and neurological diseases. Use of prescription medications and withdrawal from alcohol or sedative, hypnotic, or anxiolytic drugs may also cause anxiety symptoms.

## Substance Abuse

Contrary to common clinical opinion, substance abuse late in life may affect a significant minority of elderly persons. Increasing biological sensitivity to most psychoactive drugs, aggravation of common comorbid medical conditions by substances, and the occurrence of drug interactions between psychoactive substances and prescribed medications all make excessive substance use a likely clinical problem for the elderly (Atkinson 2000). Elderly patients with substance

use disorders may present with uncontrolled medical illnesses; with secondary substance-related disorders such as amnestic syndrome, delirium, or dementia; or with general and nonspecific signs and symptoms of deterioration, such as poor personal hygiene, malnutrition, muscle weakness, gait disturbances, frequent falls or other injuries, or mood or behavior changes.

Alcohol problems are the most common substance use problems among the elderly, with a prevalence of 4–20% depending on the clinical setting in which the patients are seen (Atkinson 2000, Liberto et al. 1992). Estimates are about 1% in the general population (Grant 1997). Although alcohol abuse tends to decline with advancing age, in part because of premature deaths among early-onset alcohol abusers, up to one-half or more of elders with problem drinking have onset in middle or late life (Atkinson 1990). These disorders may be precipitated by age-specific stressors such as retirement or loss of significant others through death. The course and outcome of late-onset alcoholism may be better than for early-onset alcoholism, with milder symptoms and more frequent spontaneous remission (Atkinson 1994, Moos et al. 1991). Rates of alcoholism after 85 years are negligible.

Another common substance-related problem among the elderly is dependence on sedative, hypnotic, or anxiolytic drugs. These drugs are most often prescribed to elderly patients for insomnia or anxiety and are taken sometimes for many years, with physical dependence resulting. Benzodiazepines are associated with excessive daytime sedation, ataxia, and cognitive impairment, and cessation of treatment may result in recurrence, rebound, or frank withdrawal symptoms.

## Disturbances in Physical Functioning

Sleep disorders and problems with pain are among the most common disturbances in physical functioning in the elderly. Sleep disturbances have been found to affect 12–15% of the population older than 65 years (Ford and Kamerow 1989). Sleep disturbances in the elderly may be a consequence of depression or a risk factor for developing depression. Psychosocial stressors, medical illness, and increasing physical limitations in general all contribute to the disturbances of sleep and mood in the elderly. The course of sleep disturbance in the elderly often depends on the identification of an underlying condition and its successful treatment.

Medical and psychiatric illnesses make pain a special problem among the elderly. Psychosocial stressors may interfere with a patient's ability to cope with the pain of a medical condition. Twenty five to 50% of community-dwelling elderly suffer from pain. Acute pain in the elderly most commonly results from surgery or injury or from musculoskeletal conditions, such as arthritis (Clark 2000). Mental disorders in the elderly that can present with pain as a major complaint include major depressive disorder, dysthymic disorder, panic disorder, and any of the somatoform disorders.

## Reality Testing

Late-onset schizophrenia or paraphrenia is a psychotic illness with a first onset after the age of 65 years. Seven percent of hospitalized patients with schizophrenia appear to have had an onset after the age of 60 years and 3% after the age of 70 years (Harris and Jeste 1988). In paraphrenia, distinctive psychopathological features include more frequent persecutory delusions and auditory hallucinations and less frequent formal thought disorder and negative symptoms. A common way in which the circumstances of the elderly may shape the expression of a delusion is the so-called partition delusion that some strangers, substance, or force enters the patient's home through the walls. This phenomenon is thought to be related to the social isolation and homebound existence common in the elderly (Pearlson and Petty 1994). The premorbid personalities of persons developing schizophrenia late in life are schizoid or paranoid. Occupational adjustment, however, has usually been adequate until middle adult life (McGlashan 1994). Once the condition develops, the course is chronic with a poor prognosis. Paraphrenia is significantly more common in women than in men.

Other conditions that may cause psychotic syndromes in the elderly are early-onset schizophrenia, delusional disorder, mood disorders with psychotic features, Alzheimer's and vascular dementias, and other medical conditions, substances, and prescribed medications.

Table 29–20 summarizes the estimated prevalence and sex ratio of selected mental disorders of late life.

**Table 29–20 Prevalence and Sex Distribution of Mental Disorders in Late Life**

| Type of Problem | Specific Disorder | Estimated Prevalence* | Predominant Sex |
|---|---|---|---|
| Memory impairment | Dementia of Alzheimer's type | Less common | Female |
| Emotional | Vascular dementia | Rare | Male |
| Mood | Major depressive disorder | Rare | Female |
| | Other depressive disorders | Less common | Female |
| | Minor depression | Very common | Female |
| Anxiety | Specific phobia | Common | Female |
| | Panic disorder | Very rare | Female |
| | Generalized anxiety disorder | Rare | Female |
| | Obsessive-compulsive disorder | Very rare | Equal |
| Substance use | Alcohol abuse or dependence | Rare | Male |
| Physical functioning Sleep | All sleep disorders | Very common | NK |
| Somatoform | Pain disorder | Very common | NK |
| Reality testing | All nonaffective psychotic disorders | Very rare | Equal |

*Prevalence estimates are as follows: very common, >10%; common, 5−10%; less common, 2−5%; rare, 1−2%; very rare, <1%.
NK, not known.

## Conclusion

Psychopathology occurs throughout the life span, from infancy to death. Certain forms of psychopathology are limited to specific stages in life, but most have an onset in childhood or adolescence and can be observed at any stage. Particular disorders have a peak age at onset during specific intervals of the life span. Some seem related to the developmental themes of the stage in which they tend to develop. The manifestations of psychopathology may change in expression in relationship to age. Men and women differ in their susceptibilities to certain disorders, the age at which they are at greatest risk, certain symptom patterns, and, in some cases, in their prognoses.

Given the wide range of psychopathology encountered across the life span, clinicians must cast a wide net in collecting diagnostically relevant information. They must exert good clinical judgment in interpreting the information collected, including a judicious weighing of the evidence supporting diagnostic criteria. They must view patients through the filter of their cultural context. And they must apply accepted diagnostic algorithms to reach the most accurate diagnosis for each patient's problem. The remaining chapters in this section are meant to assist in these endeavors.

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CHAPTER

# 30 Clinical Evaluation and Treatment Planning: A Multimodal Approach

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Every psychiatric evaluation must be specific to the context in which it occurs. The evaluation of a patient in the psychiatric emergency room is different from the evaluation of a graduate student applying for psychoanalysis, a member of a couple who seeks consultation for marital distress, or an indicted prisoner who is being evaluated for competence to stand trial. In each case, the evaluation and treatment plan are tailored to the situation.

In this chapter, we present an outline of the most thorough approach to psychiatric evaluation—that is, the one most typically followed when someone is admitted to a psychiatric inpatient unit. The complete psychiatric evaluation consists of the psychiatric interview; physical examination, including neurological assessment; laboratory testing; and, as appropriate, neuropsychological testing, structured interviews, and brain imaging. The results of the evaluation are then used to assess risk, reach tentative, and, if possible, definitive diagnoses, and complete initial and comprehensive treatment plans. Clearly, the length, detail, and order of the evaluation need to be modified when it is conducted in different settings. The clinician needs to assess the goals of the interview, the patient's tolerance for questioning, and the time available. Table 30–1 shows the variation of the psychiatric evaluation with the type of setting.

## Psychiatric Interview

Despite the advent of brain imaging tests, standardized diagnostic criteria, and structured rating scales, the psychiatric interview (Table 30–2) remains the cornerstone of clinical evaluation in psychiatry. Whether it is conducted in a busy psychiatric emergency room, an inpatient ward, or an outpatient office, the psychiatric interview is essential for establishing rapport with the patient, initiating the therapeutic alliance, eliciting the psychiatric history, and performing the Mental Status Examination (MSE). When conducted skillfully, the interview may appear to be a relaxed and casual conversation, but it is actually an extremely precise diagnostic tool composed of specific elements: the identifying information, the chief complaint, the history of present illness, the past psychiatric history, the personal history, the family history, the medical history, the substance use history, and the MSE. The essential features of the psychiatric interview are highlighted here. For a more complete discussion of the psychiatric interview, see Chapter 3 (The Psychiatric Interview).

Before beginning the interview, the psychiatrist should introduce himself or herself, explain the purpose of the interview, and try to make the patient as comfortable as possible. The interview gives the most accurate information when the psychiatrist and the patient speak in a language in which they are both fluent. When this is not possible, a translator should be used, preferably one with mental health training or experience. Even then, some of the subtleties of the patient's communication are lost.

### Identifying Information

Most interviewers find it helpful to begin with a few questions designed to identify the patient in a general way. Asking the patient's name, age, address, marital status, and occupation provides a quick general picture and begins the interview with emotionally neutral material. If the interviewer chooses to begin in this way, it is important to complete this section rapidly and then give the patient a chance to respond to open-ended questions. This allows the interviewer to get a more accurate sense of the patient's spontaneous speech patterns, thought processes, and thought content. If the patient becomes too disorganized in response to this change, the

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**Table 30–1** Psychiatric Evaluation and Treatment Planning

| Setting | Psychiatric Interview and MSE | Physical or Neurological Examination, Laboratory Assessments, Brain Imaging | Treatment Planning |
|---|---|---|---|
| Emergency room | Most often lengthy and extensive, except as limited by patient's ability or willingness to communicate. Parallel history is often important. | Physical examination is often performed; other tests and examinations are ordered as indicated. | Primary focus is on disposition. |
| Psychiatric inpatient unit | Extensive, but complete information may be obtained in a series of interviews over time. Parallel history is often important. | Physical and neurological examinations and laboratory tests are always performed. Other tests and examinations are ordered as indicated. | Comprehensive and formal plans are developed focusing on treatment and eventual disposition. |
| Consultation liaison service | Depth of interview is highly variable depending on reasons for referral and patient's medical condition. An attempt is made to obtain a complete MSE. | Most medical information is obtained from the chart and by speaking to the referring physician. Psychiatric consultant may request further assessment. | Recommendations focus on reasons for referral and are made to the primary treatment team. |
| Outpatient office or clinic | Urgency of situation is assessed. In nonurgent situations, the initial interview usually focuses on the chief complaint and MSE. | Medical information is obtained as needed, usually by referral to a general practitioner or specialist. | Planning may be formal or informal, depending on applicable regulatory and reimbursement requirements as well as clinical considerations. |
| Third-party interviews (e.g., for court, disability determinations) | Interview addresses the reason for referral and may be narrowly focused but contains a complete MSE. | Assessments are ordered according to the purpose of the interview. | Not usually relevant except for recommendations pertaining to the purpose of the interview. |

**Table 30–2** Psychiatric Interview

| |
|---|
| Greeting |
| Identifying information |
| Chief complaint |
| History of present illness |
| Past psychiatric history |
| Personal history |
| Family history |
| Medical history |
| Substance use history |
| Mental status examination |

psychiatrist can revert to more focused questions to structure and organize the interview. If it is possible, within the context of the interview, other pieces of identifying information, such as the patient's ethnic group and religious affiliation, should be obtained.

## Chief Complaint

At the start, the interviewer wants to ascertain exactly why the patient is seeking psychiatric help at this time, or, if the patient is not requesting help, the patient's understanding of the purpose of the evaluation. The interviewer may begin with a fairly general question, such as "What brings you to the hospital at this time?" The patient may have a long history of psychiatric illness, but the chief complaint refers only to the acute problem that necessitates the current intervention. The interviewer should try to help the patient distinguish the chief complaint from any chronic problems, as in the following example:

***Interviewer:*** *Can you tell me what brings you to see a psychiatrist at this time?*
***Patient:*** *Well, I have had schizophrenia for 25 years.*
***Interviewer:*** *I see. But my guess is that something happened recently that has prompted you to come in today, rather than several months ago.*
***Patient:*** *Oh, yes. Yesterday my wife kicked me out of the house. I'm homeless.*

Here, the patient's chief complaint is homelessness; the schizophrenia is part of his psychiatric history. Although a psychotic patient may offer a chief complaint that seems incoherent or unrealistic, it is important to collect the chief complaint in the patient's words and later look to other sources of information for additional history. Similarly, in response to the question, "What brings you to seek psychotherapy at this time?" a patient may begin to answer by detailing his or her childhood, but the interviewer should help the patient to focus on current issues that precipitated the consultation. Some patients may not be able to cite a chief complaint: "My wife sent me" or "There's no problem. I don't know why the police picked me up." Even these answers give the interviewer information about the patient's current situation, which can be elaborated on by asking the patient for more details.

It is important to remember that while a clinician may form his or her own ideas about the patient's problems, understanding what the patient feels he or she needs help with is critical, both for forming an alliance with the patient and because most patients ultimately engage and follow up in treatment to address what they feel is troubling them (as opposed to what the clinician or others believe they need).

When the interview is being conducted for a third party—for example, to determine whether a patient is eligible

for disability—the chief complaint is replaced by the purpose of the interview. The psychiatrist should review such purpose with the patient and discuss the limits of confidentiality.

## History of Present Illness

Having obtained the chief complaint, the interviewer should clarify the nature of the present illness. By definition, the present illness begins with the onset of signs and symptoms that characterize the current episode of illness. For example, the present illness of a manic patient with chronic bipolar disorder, who was asymptomatic for the past 3 years, would begin with the onset of the current episode of mania. The interviewer should determine the duration of the present illness, as well as precipitating factors such as psychosocial stressors, substance use, discontinuing medication, and medical illnesses. The patient should be allowed to tell the story, and the clinician should follow up with specific diagnostic questions. For example, a patient who tells a story of 6 months of sadness after the death of a relative should then be asked about vegetative symptoms of depression, suicidal ideation, and guilty rumination. Particular attention should be paid to behaviors or statements that would indicate that the patient may be at an increased risk of hurting himself or causing harm to another person.

## Past Psychiatric History

The interviewer should ask for information regarding any previous episodes of psychiatric illness or treatment, including hospitalization, medication, outpatient therapy, substance use treatment, use of complimentary treatments (e.g., herbal, acupuncture), self-help groups, and consultation with culture-specific healers such as shamans. The duration and effectiveness of treatment should be ascertained, as well as the patient's general experience of her or his psychiatric treatment to date. Again, significant suicidal or violent ideation or behavior are relevant parts of a patient's past psychiatric history.

## Personal History

No interview is complete without some understanding of the patient's background and life circumstances (Table 30–3). Within the constraints of the interviewer's time and the patient's tolerance for further questioning, the clinician should inquire about the patient's upbringing, educational and vocational history, interpersonal relations, and current social situation. It is important to inquire about the patient's sexual history and to ask about the risk factors for human immunodeficiency virus (HIV) infection, such as a history of multiple partners, unprotected vaginal and anal intercourse, and intravenous drug use. This information is important not only for the assessment and diagnosis of the present illness but also for treatment planning. The relevance of the information outlined in Table 30–3 depends on the purpose of the evaluation and the age of the patient, and some of the information may only be available from third party informants (e.g., parents of a patient).

**Table 30–3 Personal History**

| |
|---|
| **Prenatal History** |
| Wanted vs. unwanted pregnancy |
| History of maternal malnutrition or maternal drug use (including prescription drugs) |
| Circumstances of birth (vaginal delivery vs. cesarean section) |
| History of birth trauma |
| Birth order |
| **Early Childhood (0–3 years)** |
| Temperament |
| Major milestones, including speech and motor development |
| History of toilet training |
| Early feeding history, including breast-feeding |
| Early behavioral problems (e.g., nightmares and night terrors, enuresis and encopresis, aggressive behavior) |
| Early relationships with parents and siblings |
| History of significant early illnesses or hospitalizations |
| History of early separations from caregivers |
| **Middle Childhood–Latency (3–11 years)** |
| Early school history, including any evidence of cognitive impairment |
| Relationships with siblings and peers |
| Early personality development |
| History of behavioral problems (e.g., separation anxiety, school phobia, aggressive behavior) |
| **Adolescence (12–18 years)** |
| Psychosexual development, including experience of puberty and menarche, masturbatory history, and early sexual behavior |
| Later school history |
| Later personality development |
| History of behavioral or emotional problems (e.g., substance abuse, eating disorders) |
| **Adulthood** |
| Marital history or history of relationships with significant others |
| History of child-rearing |
| Sexual history |
| Occupational and educational history |
| Religious history |
| Current living situation |

## Family History

The interviewer should ask the patient specifically about any relatives with a history of psychiatric illness or treatment, suicide, or substance use. This information may be of diagnostic importance. For example, a patient who presents with a first episode of acute psychosis may have any one of a number of disorders, but a family history of affective disorders may lead the interviewer to suspect a diagnosis of bipolar disorder or major depression with psychotic features rather than schizophrenia. This information is also important for treatment planning, particularly if the patient's primary caregivers are also psychiatrically ill or also abuse substances. Similarly, family history is relevant for certain behaviors, such as suicide, where a positive family history may place the patient at an increased risk for the same behavior.

## Medical History

A careful review of a patient's medical history is an important part of the psychiatric interview because medical conditions can dramatically affect psychiatric status. Many medical disorders such as endocrinological conditions (thyroid disease, pheochromocytomas, pituitary adenomas), neurological disorders (Parkinson's disease, central nervous system neoplasms, Wilson's disease, stroke

syndromes, head trauma), and infectious diseases (HIV infection, meningitis, sepsis) can have manifestations that include psychiatric symptoms (see Chapter 52). When such a disorder is suspected, a rigorous inquiry is essential. A review of all of the patient's medications, including over-the-counter preparations and alternative remedies, is important because many of these substances can produce or exacerbate psychiatric symptoms. For example, propranolol taken for hypertension may produce symptoms of depression, and scopolamine taken for motion sickness may induce delirium. Moreover, the toll of chronic, debilitating medical conditions or the acute onset of a catastrophic, physical illness may be accompanied by secondary psychiatric symptoms that can be fully understood only in the context of the patient's medical condition.

In addition, the medical history is a prerequisite for beginning psychotropic medication or other somatic treatments as it allows the psychiatrist to weigh potential toxicities, side effects, and drug interactions based on the patient's physical vulnerabilities and concurrent medications.

## Substance Use History

The interviewer should inquire about which substances are used, under what circumstances, and the quantity, variety, and duration of use (Table 30–4). A question such as "Do you drink alcohol?" is likely to be answered with a quick "No." A better question, such as "How much alcohol do you drink?" communicates to the patient that the clinician is not making a value judgment and is more likely to elicit an accurate answer. Similarly, asking about each substance separately as opposed to a blanket question such as "Have you ever used illegal drugs?" is more likely to result in a positive response. The interviewer must be sure to ask about past and current drug injection, including the sharing of injection equipment, to assess for HIV risk factors (Table 30–5).

**Table 30–4 Substance Use History**

| |
|---|
| Survey of drugs that have been used include: |
| Alcohol |
| Opioids (heroin, methadone, analgesics) |
| Stimulants (cocaine, crack, amphetamines, ecstasy) |
| Depressants (benzodiazepines, barbiturates) |
| Hallucinogens (cannabis, lysergic acid diethylamide [LSD], mescaline) |
| Phencyclidine |
| Nicotine |
| Caffeine |
| Over-the-counter preparations |
| Pattern of usage |
| Age of first use |
| Period of heaviest use |
| Pattern or frequency of current use |
| Route of administration (injected, intranasal, inhaled, oral) |
| Periods of sobriety/abstinence |
| Symptoms of tolerance or dependence |
| Medical history, including HIV status and history of hepatitis, and/or cirrhosis—note ongoing substance use despite knowledge that it could worsen medical conditions |
| History of treatment for substance use |
| Legal history—note relationship to drug use. |

**Table 30–5 Human Immunodeficiency Virus Risk Factors**

| |
|---|
| **Parenteral** |
| Use of shared needles or drug works in the course of drug injection or amateur tattooing |
| Receipt of blood, blood products, or organ transplant in the US between 1978 and 1985 (risk periods may vary for patients who have resided in other countries) |
| Maternal–fetal transmission (pediatric cases) |
| Occupational exposure among health care workers and laboratory technicians through needle-stick injuries and other significant exposures (uncommon) |
| **Unsafe Sexual Activity** |
| Most common for men: unprotected anal intercourse with other men; unprotected vaginal or anal intercourse with women who are known to be HIV-positive, are sex workers, or are injection drug users or sexual partners of injection drug users; multiple heterosexual partners |
| Most common for women: unprotected anal or vaginal intercourse with men who are known to be HIV-positive, are injection drug users, are the sexual partners of injection drug users, are bisexual, or were treated for hemophilia or coagulation disorder when blood products were contaminated; multiple heterosexual partners |
| **Cofactors** |
| Compromise of the skin or mucous membranes, especially through the presence of sexually transmitted infections, which increases the likelihood of transmission on exposure to HIV-infected body fluids |
| Use of noninjection drugs, especially alcohol, crack cocaine, and methamphetamine, through association with high-risk sexual activity |
| **Environmental Context** |
| Risk behavior while living or traveling in geographic areas with high rates of HIV infection, through increased likelihood of exposure to HIV-infected body fluids |

## Mental Status Examination

The MSE is a structured way to assess a patient's mental state at a given time. Unlike the parts of the interview that focus on the history, the MSE provides a descriptive snapshot of the patient at the interview. Much of the information needed for the evaluation of appearance, behavior, and speech is gathered without specific questioning during the course of the interview. However, the interviewer generally wants to ask specific questions to assess the patient's mood, thought process and content, and cognitive functioning. Bearing in mind the outline of the MSE (Table 30–6) ensures that the interview is comprehensive. The components of the MSE are described in the following paragraphs.

- **Appearance.** The interviewer should note the patient's general appearance, including grooming, level of hygiene, and attire.
- **Behavior.** This includes the patient's level of cooperativeness with the interview, motor excitement or retardation, abnormal movements (e.g., tardive dyskinesia, tremors), and maintenance of eye contact with the interviewer.
- **Speech.** The psychiatrist should carefully assess the patient's speech for rate, fluency, clarity, and volume. The interviewer may want to question the patient directly about his or her speech. For example, the psychiatrist can gain valuable diagnostic information by asking

**Table 30–6 Mental Status Examination**

I. Appearance
II. Behavior (includes attitude toward the interviewer)
III. Speech
IV. Mood and affect
V. Thought
  A. Thought process
  B. Thought content
VI. Perception
  A. Hallucinations
    1. Auditory
    2. Visual
    3. Other (somatic, gustatory, tactile)
  B. Illusions
VII. Cognition
  A. Level of awareness
  B. Level of alertness
  C. Orientation
    1. Person
    2. Place
    3. Time
  D. Memory
    1. Immediate
    2. Short term
    3. Long term
  E. Attention (digit span)
  F. Calculations
  G. Fund of knowledge
  H. Abstractions
    1. Similarities
    2. Proverbs
  I. Insight
  J. Judgment

a patient with pressured speech if she or he is able to modulate the rate of the speech or by asking whether a dysarthric patient is aware of not speaking clearly. A bipolar patient who is in the midst of a manic episode is not able to slow down her or his speech; a fast-talking anxious person is able to do so. Similarly, a patient whose dysarthria is secondary to ill-fitting dentures is aware of this problem whereas an intoxicated person is not. It is helpful to clarify whether patients with a speech abnormality feel that this is their normal speech pattern or a new problem.

- **Mood and Affect.** The interviewer should be aware of the patient's mood and affect. This may be evident from the way in which the patient answers other questions and tells the history, but specific questions are often indicated. The patient's mood is a pervasive affective state, and it is often helpful to simply ask, "What has your mood been like lately?" or "How would you describe your mood?" In contrast, affect is the way in which one modulates and conveys the state of one's feeling from moment to moment. The clinician judges the congruity between the material the patient is presenting and the accompanying affect; for example, an appropriate affect would be reflected by sadness when discussing the death of a loved one or happiness when describing a child's accomplishments. The clinician is also interested in whether the patient is capable of displaying a broad range of affect or whether affect is more limited (e.g., a constricted affect in a depressed patient), as well as whether the affect is labile (shifts too rapidly).
- **Thought.** The clinician should assess the patient's thought process and content. Thought process is the form of the patient's thoughts—are they organized and goal directed or are they tangential, circumstantial, or loosely associated? (See Chapter 35 for definitions and examples.) If the patient's thought processes are difficult to understand, the clinician can indicate his or her difficulty in following what is being said and then assess the patient's response to this intervention. Some patients—such as patients with stroke who have nonfluent aphasias—may appear to have disorganized speech but are aware that they are not making sense, whereas those with fluent aphasias, psychosis, and delirium are not necessarily aware of their impairments. The psychiatrist should ask specifically about the patient's thought content, including delusions (grandiose, persecutory, somatic), obsessions, phobias, and suicidal and violent (or even homicidal) ideation. The presence of delusional material is often obvious from unsolicited statements made by the patient, and in very delusional patients, the interviewer may have difficulty in getting the patient to focus on anything else because of the perceived importance of the delusional content to the patient. Although the above questions should be asked with tact and empathy, they should always be asked. For example, patients are generally relieved that the interviewer has broached the subject of suicide, and simply asking the question does not give patients ideas that they have not had before.
- **Perception.** Clinicians must inquire about hallucinations of all types, i.e, auditory, visual, tactile, olfactory, and gustatory. Auditory hallucinations are the most common type of hallucination, and it is important to assess whether the patient is actually experiencing voices as coming from the outside, as opposed to, for example, an individual "hearing" one's own thoughts. It is less common for a psychotic patient to experience visual hallucinations as a result of a psychotic illness alone, and such cases should prompt a work up for other medical or neurological conditions. Hallucinations must also be distinguished from illusions, which are misperceptions of actual external stimuli. While patients may deny hallucinations, an interviewer should note in his MSE whether a patient nevertheless appears to be responding to internal stimuli.
- **Cognition.** Every psychiatric interview should include some assessment of the patient's cognitive functioning (see also Chapter 32 [Neuropsychological Testing]). This includes the patient's level of awareness, alertness, and orientation (to person, place, and time). If there is a question about the patient's memory, formal memory testing may be done to assess short-term, intermediate, and long-term memory. A patient who can answer questions for 30 min is clearly attentive, but any doubts about the patient's attentiveness should prompt a formal assessment—for example, asking the patient to recite a series of digits forward and backward. Before assessing the patient's calculations and fund of knowledge, it is

important to ascertain the patient's level of education. Formal assessment of the patient's ability to abstract may be unnecessary for a patient who has used abstract constructions throughout the interview, but the interviewer may want to ask formally for interpretations of similes and proverbs. It is often helpful to begin with simple constructions—for example, asking the patient the meaning of such phrases as "He has a warm heart" or "Save your money for a rainy day." Patients whose native language is not English may have difficulty in this area that does not reflect a lack of ability to abstract.

The interviewer should gain a full understanding of the patient's insight into the illness by asking why, in the patient's opinion, he/she is currently in need of psychiatric care and what has caused the problems the patient is experiencing. Finally, the interviewer should learn about the patient's judgment. This is best assessed in terms of the circumstances of the patient's life—for example, asking a mother how she would deal with a situation in which she had to leave her children to go to the store, or asking a chronically ill person what he does when he sees that he is running out of medicine.

The interviewer may want to use the Mini-MSE to quantify the degree of cognitive impairment of a patient with obvious cognitive abnormalities. This can be useful as an initial diagnostic tool, as well as a means of assessing changes in cognitive function over time. The Mini-MSE is outlined in Figure 30–1. To the extent that a patient displays cognitive deficits that appear out of proportion to a tentative diagnosis, and depending on the parallel history obtained, more formal neuropsychiatric testing may be warranted.

## Physical Examination

The physical examination is an important part of the comprehensive psychiatric evaluation for several reasons. First, many patients who present with psychiatric symptoms may have underlying medical problems that are causing or exacerbating the presenting symptoms. For example, an agitated, delirious patient may be septic, or a patient being treated for an autoimmune disorder who develops new onset paranoia may have a steroid-induced psychosis. Second, the patient's physical capacity to tolerate certain psychiatric medications, such as clozapine or lithium, must be assessed. Finally, many patients who present to a psychiatrist have had inadequate medical care and should be routinely examined to assess their general level of physical health. This is especially true for patients with chronic mental illness or substance abuse. In some settings, such as emergency rooms and inpatient wards, the psychiatrist may want to perform the physical examination; in others, it may be more appropriate to refer the patient to a general practitioner for this purpose. Genital, rectal, and breast examinations can usually be included even for anxious and paranoid patients, but when they must be postponed, care should be taken to complete them at a later time. A same-sex chaperone is necessary for the security of both the patient and the examiner.

Certain aspects of the information obtained in the psychiatric interview should alert the psychiatrist to the need for a physical examination. Any indication (Table 30–7) from the history that the psychiatric symptoms followed physical trauma, infection, medical illness, or drug ingestion should prompt a full physical examination. Similarly, the acute

| *Maximum* Score | Score | |
|---|---|---|
| | | ORIENTATION |
| 5 | ( ) | What is the (year) (season) (date) (day) (month)? |
| 5 | ( ) | Where are we: (state) (county) (town) (hospital) (floor)? |
| | | REGISTRATION |
| 3 | ( ) | Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them untill he learns all 3. Count trials and record. Trials |
| | | ATTENTION AND CALCULATION |
| 5 | ( ) | Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world backwards. |
| | | RECALL |
| 3 | ( ) | Ask for the 3 objects repeated above. Give 1 point for each correct. |
| | | LANGUAGE |
| 9 | ( ) | Name a pencil, and a watch (2 points)<br>Repeat the following "No ifs, ands or buts." (1 point)<br>Follow a 3-stage command:<br>"Take a paper in your right hand, fold it in half, and put it on the floor" (3 points)<br>Ready and obey the following:<br>CLOSE YOUR EYES (1 point)<br>Write a sentence (1 point)<br>Copy design (1 point) |
| _____ | | Total score |
| | | ASSESS level of consciousness along a continuum _____<br>Alert Drowsy Stupor Coma |

**Figure 30–1** *Mini-Mental State Examination. (Source: Folstein MF, Folstein SE, and McHugh PR [1975] "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12, 189–198. Reprinted with permission from Elsevier Science, Pergamon Imprint, Oxford, England.)*

**Table 30–7 Indications for Physical Examination**

**History of medical illness**
Current symptoms of medical illness, particularly fever, neurological symptoms, or cardiovascular abnormalities
Evidence while taking history of altered mental status or cognitive impairment
History or physical evidence of trauma, particularly head trauma
Rapid onset of symptoms
New onset of psychosis, depression, mania, panic attacks
New onset of visual, tactile, or olfactory hallucinations
New-onset psychiatric symptoms after age 40
Family history of physical illness that could cause psychiatric illness

onset of psychiatric symptoms in a previously psychiatrically healthy individual, as well as symptoms arising at an unusual age, should raise questions about potential medical causes (Table 30–8).

New-onset psychosis or mania in a previously healthy 65-year-old person is representative of a case requiring pursuit of a medical condition as the cause because these disorders do not commonly present at this age. Any gross physical abnormalities, such as gait disturbances, skin lesions, eye movement abnormalities, lacerations, flushed skin, or drooling, should raise the interviewer's suspicion that there might be an underlying medical condition. Urinary or fecal incontinence is also highly suggestive of a medical etiology. Stigmata of drug or alcohol use or abuse, such as dilated or pinpoint pupils, track marks, evidence of skin popping, or frank evidence of intoxication (e.g., alcohol on the breath), should also signal the need for a more thorough physical examination. Abnormalities of speech, such as impaired fluency or dysarthria, may indicate the presence of an underlying medical disturbance. Many mood problems may be caused by physical disorders, and even apparently healthy patients with dysthymia may have hypothyroidism that can be treated medically. Finally, any cognitive disturbances, such as disorientation, fluctuating level of alertness, inattentiveness, or memory problems, are, until proved otherwise, evidence of a physical problem that is causing psychiatric symptoms. In such situations, careful attention should be paid to the patient's vital signs, neurological examination

**Table 30–8 Physical Illnesses That May Present with Psychiatric Symptoms**

| Neurological | Metabolic |
|---|---|
| Amyotrophic lateral sclerosis | Acute intermittent porphyria |
| Epilepsy—particularly partial complex seizures (e.g., temporal lobe epilepsy) | Electrolyte imbalance |
| Huntington's disease | Hepatic encephalopathy |
| Multi-infarct dementia | Hepatolenticular degeneration (Wilson's disease) |
| Normal-pressure hydrocephalus | Hypoxemia |
| Parkinson's disease | Uremic encephalopathy |
| Pick's disease | **Nutritional** |
| Stroke syndromes (cerebrovascular disease) | Vitamin $B_{12}$ deficiency |
| **Rheumatological (Autoimmune)** | Central pontine myelinolysis |
| Systemic lupus erythematosus | Folate deficiency (megaloblastic anemia |
| Temporal arteritis | General malnutrition |
| **Infectious** | Nicotinic acid deficiency (pellagra) |
| Acquired immunodeficiency syndrome | Thiamine deficiency (Wernicke–Korsakoff syndrome) |
| Brain abscess | **Traumatic, Particularly Head Trauma** |
| Encephalitis | **Toxic** |
| General infection (e.g., urinary tract) | Environmental toxins |
| Meningitis | Intoxication with alcohol or other drugs |
| Syphilis, particularly neurosyphilis | **Neoplastic** |
| Tuberculosis | Carcinoma (general) |
| Viral hepatitis | Central nervous system tumors (primary or metastatic) |
| **Endocrine** | Endocrine tumors |
| Adrenal hyperplasia (Cushing's syndrome) | Pancreatic carcinoma |
| Diabetes mellitus | |
| Hypo- or hyperparathyroidism | |
| Hypo- or hyperthyroidism | |
| Hypothalamic dysfunction | |
| Panhypopituitarism | |
| Pheochromocytoma | |

(see the Section titled Neurological Examination), and any indications of infection.

In a hospital setting, a physical examination, including a careful assessment of the patient's vital signs (including orthostatic measurements), cardiovascular status, and pulmonary status, precedes the prescription of the most psychiatric medications. For example, newer antipsychotic medications should not be prescribed without taking into account a patient's weight, and the presence of or risk for developing diabetes mellitus and dyslipidemias, given the side-effect profile of many of these medications. Psychiatrists should pay particular attention to a patient's cardiovascular status (e.g., electrocardiographic abnormalities, orthostatic hypotension, decreased cardiac ejection fraction) before beginning tricyclic antidepressants, which may induce cardiac conduction disturbances and thus must be used with caution for patients with such cardiac abnormalities as arrhythmias or other conduction abnormalities. If beta-blockers such as propranolol are being considered, patients should be evaluated for the presence of asthma, which may be exacerbated by these drugs.

Physical examination may also be warranted during treatment with medication if physical symptoms arise. For example, fever and a change of mental status during a course of neuroleptics require a full physical and neurological examination to rule out neuroleptic malignant syndrome. Urinary retention induced by medications with anticholinergic side effects requires an abdominal examination to assess bladder fullness. Anticholinergic-induced constipation may warrant abdominal or rectal examination to assess for impaction. Increased blood glucose levels or significant weight gain may necessitate a reevaluation of the risks and benefits associated with one of the atypical antipsychotics. When patients are seen in office-based practices, the psychiatrist most often obtains a careful medical history and may complete simple procedures such as blood pressure and weight checks but will usually refer the patient to another physician for a complete physical examination.

## Neurological Examination

In the hospital setting, every patient should have a thorough neurological examination. Patients who have a history of neurological disturbances, such as strokes, seizure disorders, central nervous system neoplasms, dementias, and movement disorders, should be carefully evaluated, perhaps by a neurologist. The neurological examination should rule out any lateralizing neurological signs which would point toward the presence of a focal lesion. Unilateral weakness or abnormalities in pupil size or eye movements might suggest a focal neoplasm, infection (such as toxoplasmosis), intracranial bleeding, or a stroke, which may explain such psychiatric symptoms as confusion, sudden onset of speech difficulties, psychosis, or even depression. Stiffness and cogwheel rigidity are classical signs of Parkinson's disease, a disorder which may be associated with such psychiatric symptoms as depression, psychosis, and dementia.

Patients with acquired immunodeficiency syndrome should also be carefully evaluated neurologically because many neurological manifestations of advanced HIV-related illness (including HIV-associated dementia and central nervous system opportunistic infections) and the medicines administered to treat these illnesses may produce psychiatric symptoms, including depression, delirium, mania, and psychosis. Gait should be carefully examined in psychiatric patients because certain neurological conditions in which gait disturbances are prominent, such as normal-pressure hydrocephalus, tertiary syphilis (tabes dorsalis), and combined system disease (caused by vitamin $B_{12}$ deficiency) may produce a variety of psychiatric symptoms.

## Psychological and Neuropsychological Testing

Psychological and neuropsychological tests are standard instruments used to measure specific aspects of mental functioning. They are usually administered by psychologists or other professionals who have been trained in their use and interpretation. In most cases, several tests, often referred to as a *battery*, are performed together. These test results must then be interpreted in the context of the broad clinical picture of the patient. The neuropsychological evaluation is discussed in detail in Chapter 32 (Neuropsychological Testing).

Because of the time and expense involved, testing is usually reserved for situations in which there is some uncertainty about a patient's diagnosis, cognitive capacity, or psychological functioning. There are, however, times when psychological testing is essential—for example, IQ testing to establish the severity of mental retardation. In addition, giving simple tests of cognitive functioning, such as asking the patient to copy Bender Gestalt diagrams (Figure 30–2),

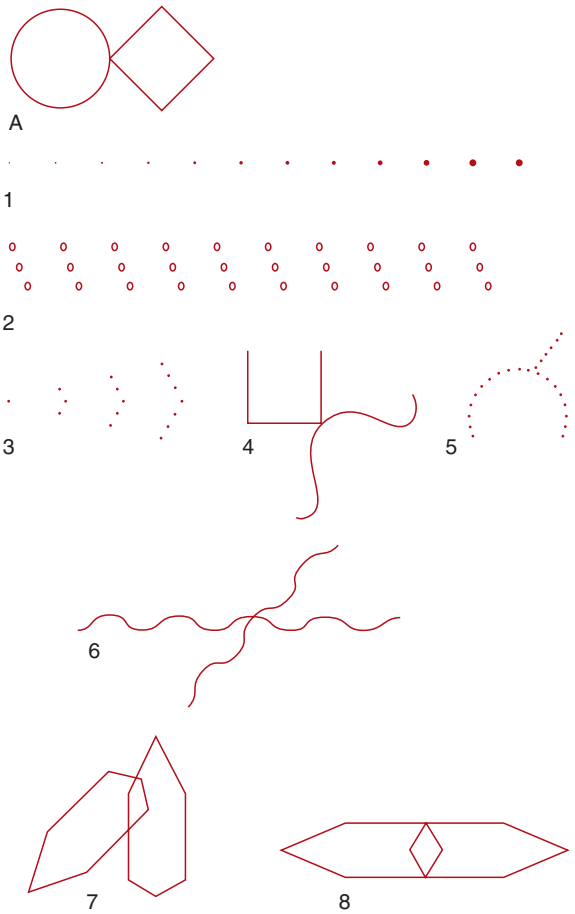



**Figure 30–2** *Bender Visual-Motor Gestalt Test.*

**Table 30–9 Common Psychological and Neuropsychological Tests**

| Name of Test | General Purpose |
|---|---|
| Bender Gestalt Test | Subject's reproduction of geometric designs used to screen for neuropsychiatric impairment |
| Grooved Pegboard | A test of speed and dexterity that can be used to assess subcortical neuropsychiatric impairment |
| Minnesota Multiphasic Personality Inventory* | Multiple true–false questions designed to assess psychopathology and personality |
| Rorschach Test | Ten inkblot designs; subject's associations used to assess thinking disturbances and psychological conflicts and defenses |
| Thematic Apperception Test | Emotionally suggestive pictures portraying one or more people; used to elicit stories that reveal psychological development and motivation |
| Wechsler Adult Intelligence Scale—Revised | Eleven subscales; used to assess verbal and performance IQ in adults |
| Wechsler Memory Scale | Memory test battery for adults that yields a "memory quotient" |
| Wisconsin Card-Sorting Test | Assesses various frontal lobe functions, such as executive functions, concept formation, and problem solving |

can be helpful as one aspect of assessing central nervous system impairment caused by a medical condition. Evaluating both children and adults for significant learning disabilities is an essential component of a psychiatric evaluation, given the level of functional impairment that such disabilities may cause, and the importance of distinguishing among impairments caused by learning disabilities, psychiatric disorders, and low IQ. Table 30–9 lists some of the most commonly used tests in adult populations.

### Structured Clinical Instruments and Rating Scales

Structured instruments and rating scales have been developed primarily for research purposes. They allow investigators to compare the findings in different studies by ensuring that similar data and criteria have been used to establish diagnoses and to measure the presence and severity of psychiatric symptoms and their response to treatment. Many types of mental health professionals and, in some cases, nonclinicians can be trained to administer these rating scales.

Although many practicing clinicians do not commonly use structured instruments to assess or follow patients, a small number of rating scales have come to be used routinely in clinical practice. For example, the Abnormal Involuntary Movement Scale (Figure 30–3) is often used to monitor patients receiving antipsychotic medication for the presence of tardive dyskinesia, and the Global Assessment of Functioning Scale (Figure 30–4), which is a slight modification of the Global Assessment Scale, is now used in Axis V in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV-TR). In other areas, such as suicide and violence risk assessment, clinical judgment supplemented by structured or semistructured instruments, is becoming more common place. Moreover, the use of standardized instruments in clinical practice may help ensure, among other things, a more comprehensive evaluation and improved tracking of symptomatology over time.

Table 30–10 shows some of the most commonly cited structured instruments and rating scales for adults. Hundreds of other specialized scales are also in use to assess such diverse areas as specific symptoms clusters, personality disorder, aggressive behavior, sexual practices, stressful life events, and quality of life.

Table 30–11 gives an example of how these different rating scales approach the assessment of two symptoms: guilt, a purely subjective state of mind; and suicide risk, an inclination that is assessed using both subjective and behavioral components. It is important to keep in mind that these instruments are not a substitute for a more thorough assessment for risk of danger to self or others (see the Section titled Assessment of Risk).

## Laboratory Assessments

A variety of laboratory tests can aid in the clinical evaluation of the psychiatric patient (Table 30–12).

### Serological Evaluations

Blood tests are particularly helpful in ruling out medical causes of psychiatric symptoms.

#### Toxicology

When the clinician suspects that the ingestion of a substance has caused the presenting symptoms, a urine toxicology screen (Table 30–13) and blood alcohol level determination are indicated. (It is important to remember that alcohol is detectable in the blood for only a matter of hours and that a level of zero may indicate that the symptoms are due to a withdrawal syndrome, and thus does not rule out alcohol as an inciting factor.) Depending on the purpose and setting of the evaluation, testing for certain drugs may also be performed on blood, sweat, saliva, and hair. Although the technology is relatively new, hair in particular offers a means of detecting drug use over a longer retrospective time period than testing by other methods (i.e., up to several months). If the patient is known to be taking certain psychiatric medications, such as lithium, tricyclic antidepressants, and anticonvulsants, levels of these medications should be tested as toxic levels may cause a variety of psychiatric symptoms. A variety of other medications, substance of abuse, and toxins can alter mental status (see Table 30–21 for those that can present as medical emergencies) and testing for their presence may be necessary depending on the patient's history and symptoms.

#### Complete Blood Count

The complete blood count is part of the general laboratory evaluation of a new patient. It is used to screen for multiple

INSTRUCTIONS: Complete Examination Procedure before making ratings.
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.

Code: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

| | | (Circle One) | | | | |
|---|---|---|---|---|---|---|
| FACIAL AND ORAL MOVEMENTS: | 1. Muscles of facial expression<br>e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing | 0 | 1 | 2 | 3 | 4 |
| | 2. Lips and perioral area<br>e.g., puckering, pouting, smacking | 0 | 1 | 2 | 3 | 4 |
| | 3. Jaw<br>e.g., biting, clenching, chewing, mouth opening, lateral movement | 0 | 1 | 2 | 3 | 4 |
| | 4. Tongue<br>Rate only increase in movement both in and out of mouth, NOT inability to sustain movement | 0 | 1 | 2 | 3 | 4 |
| EXTREMITY MOVEMENTS: | 5. Upper *(arms, wrists, hands, fingers)*<br>include choreic movements, (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic) | 0 | 1 | 2 | 3 | 4 |
| | 6. Lower *(legs, knees, ankles, toes)*<br>e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot | 0 | 1 | 2 | 3 | 4 |
| TRUNK MOVEMENTS: | 7. Neck, shoulders, hips<br>e.g., rocking, twisting, squirming, pelvic gyrations | 0 | 1 | 2 | 3 | 4 |
| GLOBAL JUDGMENTS: | 8. Severity of abnormal movements | None, normal 0<br>Minimal 1<br>Mild 2<br>Moderate 3<br>Severe 4 | | | | |
| | 9. Incapacitation due to abnormal movements | None, normal 0<br>Minimal 1<br>Mild 2<br>Moderate 3<br>Severe 4 | | | | |
| | 10. Patient's awarness of abnormal movements<br>Rate only patient's report | No awarness 0<br>Aware, no distress 1<br>Aware, mild distress 2<br>Aware, moderate distress 3<br>Aware, severe distress 4 | | | | |

**Figure 30–3** *Abnormal Involuntary Movement Scale. (Source: Guy W [1976] ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Rockville, MD, USA, p 534.)*

problems, most commonly infections and anemia. In cases in which alcoholism is suspected or the mean corpuscular volume indicates a macrocytic anemia, vitamin $B_{12}$ and folate levels should be tested. Vitamin $B_{12}$ deficiency may lead to combined system disease, which can present with psychiatric symptoms such as irritability and forgetfulness in the early stages and dementia or frank psychosis in the later stages. The complete blood count is routinely used to monitor white blood cell counts in patients taking clozapine due to the risk of agranulocytosis. Additional emergency complete blood counts may be necessary if such a patient develops fever, malaise, or other symptoms of infection while on clozapine. Certain mood stabilizers, such as carbamazepine and divalproex sodium, can induce a variety of blood dyscrasias.

## Blood Glucose

The blood glucose test is an inexpensive, essential test in the evaluation of patients with a new onset of central nervous system dysfunction, psychosis, affective disorders, and anxiety disorders. Hypoglycemia may produce lethargy and vegetative symptoms that may mimic those of depression, and hyperglycemia may produce anxiety and delirium. This test is clearly indicated for known diabetics who present with the first onset of psychiatric symptoms. Atypical antipsychotic medications, such as clozapine and olanzapine, can

| Code | (**Note:** Use intermediate codes when appropriate, e.g., 45, 68, 72.) |
|---|---|
| 100 \| 91 | **Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.** |
| 90 \| 81 | **Absent or minimal symptoms** (e.g., mild anxiety before an exam), **good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g., an occasional argument with family members). |
| 80 \| 71 | **If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g, difficulty concentrating after family argument); **no more than slight impairment in social, occupational, or school functioning** (e.g., temporarily falling behind in schoolwork). |
| 70 \| 61 | **Some mild symptoms** (e.g., depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.** |
| 60 \| 51 | **Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflicts with peers or coworkers). |
| 50 \| 41 | **Serious symptoms** (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job). |
| 40 \| 31 | Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school). |
| 30 \| 21 | **Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends). |
| 20 \| 11 | **Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication** (e.g., largely incoherent or mute). |
| 10 \| 1 | **Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.** |
| 0 | Inadequate information. |

**Figure 30–4** *Global Assessment of Functioning Scale. Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Copyright 2000. APA.*

elevate blood sugar, increasing the risk of a patient developing diabetes.

## Kidney Function Tests

The blood urea nitrogen and creatinine levels are important measures of kidney function. Kidney function tests are used to screen for kidney failure and hypovolemic states (in which blood urea nitrogen and creatinine levels increase). Both of these states can cause mental status changes. It is also essential to perform these tests before beginning therapy with lithium, which is cleared by the kidneys.

## Liver Function Tests

These tests, which check for levels of various enzymes in the liver and certain products made by the liver, are indicated when there is some suspicion that liver disease is present. They help the clinician to screen for hepatic encephalopathy, hepatitis, alcoholism, and biliary tract disease. They include creatine kinase, which is often elevated in neuroleptic malignant syndrome as well as in other conditions in which muscle rigidity is prominent. Monitoring of liver function tests is essential with some psychotropic medications such as divalproex sodium and nefazodone. Moreover, since many medications are metabolized by liver enzymes, potentially toxic levels can accumulate when liver disease is present. Medication doses may need to be adjusted and/or certain medications may even need to be discontinued when liver function is impaired.

## Thyroid Function Tests

Both hypothyroidism and hyperthyroidism can mimic the symptoms of psychiatric disorders. Hyperthyroidism may mimic anxiety disorders, psychosis, or mania, and hypothyroidism may mimic dysthymia and depression. Thyroid function tests are therefore indicated in cases of new onset of a mental illness. In addition, thyroid function should always be tested when initiating lithium therapy and periodically thereafter because lithium may cause hypothyroidism.

## Syphilis Screening

These tests should be done for any patient with new-onset psychosis. They have become particularly important with the increasing incidence of syphilitic infection associated with the HIV epidemic. Positive serologic results in the presence of unexplained psychiatric symptoms necessitate a lumbar puncture to test for neurosyphilis.

## Blood Cultures

Blood cultures are indicated in the evaluation of medically ill patients who develop fever and psychiatric symptoms such as confusion, disorientation, and agitation because this delirium may be secondary to sepsis.

## HIV Antibody Testing

The Center for Disease Control and Prevention (2006) now recommends routinely offering HIV antibody testing to all patients. In addition, psychiatric patients have elevated rates of HIV infection when compared to the general population due to the frequent presence of HIV-related risk behaviors. (see Table 30–5). HIV infection should always be suspected in cases of unexplained central nervous system dysfunction, and when psychiatric illness is accompanied by suggestive medical findings such as thrush or swollen

**Table 30–10 Common Structured Instruments and Psychiatric Rating Scales**

| Name of Scale | General Purpose |
|---|---|
| Abnormal Involuntary Movement Scale (AIMS) | Brief structured assessment of abnormal movements; used to rate presence and severity of tardive dyskinesia |
| Beck Depression Inventory (BDI)* | A 20-item rating scale for depression; focuses on mood and cognition |
| Brief Psychiatric Rating Scale (BPRS) | An 18-item scale that rates current severity of psychopathology |
| Composite International Diagnostic Interview (CIDI) | Diagnostic instrument developed for use by nonclinicians to conduct community surveys |
| Global Assessment of Functioning Scale (GAFS) | Overall psychosocial functioning rated on a scale from 0 to 100; used as Axis V of DSM-IV-TR |
| Hamilton Depression Rating Scale | A 17–21-item scale that rates the severity of depressive symptoms; strong focus on somatic problems |
| Inventory of Depressive Symptomatology | Severity of signs and symptoms of depression; both self-report and clinician administered versions |
| Nurses' Observation Scale for Inpatient Evaluation | 80 items used to rate the behavior of hospitalized patients by staff |
| Overt Aggression Scale | Rates aggression in four categories: verbal, physical against self, physical against objects, physical against other people |
| Personality Disorder Examination | Items that rate six areas of personality functioning, which are analyzed by computer with a series of algorithms to generate personality disorder diagnoses |
| Present State Examination | Continually updated semistructured diagnostic interview used in international research and tied to the manual on the International Classification of Diseases (most recently ICD-10) |
| Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) | Scale to assess degree of enjoyment and satisfaction in past week |
| Schedule for Affective Disorders and Schizophrenia (SADS) | Semistructured questions, similar to the Structured Clinical Interview for DSM-IV-TR but more detailed, for establishing diagnoses of affective disorders and schizophrenia |
| Social Adjustment Scale (SAS) | Assesses level of social functioning and roles; both self-report and clinician administered versions |
| Structured Clinical Interview for DSM-IV-TR (SCID) | Semistructured questions used to establish DSM-IV-TR Axis I and Axis II diagnoses |
| Symptom Checklist* (SCL-90) | Ninety-item self-report instrument used to assess psychopathology |

* These instruments are self-administeresd.

lymph nodes. Clinicians should be aware of state and local requirements regarding consent and counseling when HIV testing is performed. Regardless of these requirements, some patients may need additional education and/or support.

### Pregnancy Testing

It is advisable to perform pregnancy testing (e.g., serologic test for the presence of human chorionic gonadotropin b-subunit) for all women of childbearing age before conducting imaging studies or initiating therapy with any psychotropic medication or other somatic treatment. Clinicians should be especially careful in this regard with respect to medications associated with fetal malformations such as anticonvulsants and benzodiazepines.

## Urine Testing

Urine tests for pregnancy are often indicated in the emergency room setting in which an immediate result is required before the initiation of various imaging studies and/or drug therapy. Urinalysis also assists in diagnosing certain medical conditions that can alter mental status such as diabetic ketoacidosis and urinary tract infection with sepsis.

## Cerebrospinal Fluid Evaluation

Lumbar puncture may be indicated to test for infections, including meningitis, neurosyphilis, toxoplasmosis, and tuberculosis of the central nervous system. It is indicated in the evaluation of patients with an acute change of mental status, who present with symptoms such as confusion, disorientation, or decreased or fluctuating alertness when accompanied by fever (Table 30–14). It is also an important part of the evaluation of patients who have new-onset seizures or who are suspected of having neuroleptic malignant syndrome because these symptoms may be caused by central nervous system infections. In cases in which increased cerebrospinal fluid pressure is suspected, lumbar puncture should be preceded by computed tomographic (CT) scanning to evaluate for mass lesions.

## Electrocardiogram

Because it is important to screen for conduction disturbances and cardiac arrhythmias before beginning therapy with tricyclic antidepressants, an electrocardiogram should precede the initiation of therapy. An electrocardiogram is also indicated before beginning certain other psychotropic medications that may produce electrocardiographic changes (Tables 30–15 and 30–16). An electrocardiographic

**Table 30–11 Comparison of Rating Scales for Assessing Guilt and Suicide Risk**

| Rating Scale | Guilt | Suicide Risk |
|---|---|---|
| Beck Depression Inventory. Patient picks best answer. | 3 = I feel as though I am very bad or worthless.<br>2 = I feel quite guilty.<br>1 = I feel bad or unworthy a good part of the time.<br>0 = I don't feel particularly guilty. | 3 = I would kill myself if I had the chance.<br>2 = I have definite plans about committing suicide.<br>1 = I feel I would be better off dead.<br>0 = I don't have any thoughts of harming myself. |
| Symptom Checklist. Patient rates on a 5-point scale from not at all to extremely. | How much were you bothered by blaming yourself for things?<br>The idea that you should be punished for your sins?<br>Feelings of guilt? | How much were you bothered by thoughts of ending your life?<br>Thoughts of death or dying? |
| Structured Clinical Interview for DSM-IV-TR. Semistructured interview. Rater selects:<br>1 = Absent or false<br>2 = Subthreshold<br>3 = Threshold or true | *Interviewer asks:* "How did you feel about yourself? (worthless?)" If no, "What about feeling guilty about things you had done or not done? (nearly every day?)"<br>*Interviewer rates:* Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). | *Interviewer asks:* Were things so bad that you were thinking a lot about death or that you would be better off dead? What about thinking of hurting yourself?<br>*Interviewer rates:* Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide. |
| Schedule for Affective Disorders and Schizophrenia. Semistructured interview. Rater selects answers on a 6-point scale from not at all to extreme. | *Interviewer asks:* Do you blame yourself for anything you have done or not done? What about feeling guilty? Do you feel you have done anything wrong? (Do you deserve punishment?) Do you feel you have brought this on yourself?<br>*Interviewer rates:* Feelings of self-reproach or excessive or inappropriate guilt for things done or not done, including delusions of guilt.<br>*Further questions:* Assess delusions of guilt or sin. | *Interviewer asks:* When people get upset or depressed or feel hopeless, they may think about dying or even killing themselves. Have you? (Have you thought how you would do it? Have you told anybody about suicidal thoughts? Have you actually done anything?)<br>*Interviewer rates:* Suicidal tendencies, including preoccupation with thoughts of death or suicide.<br>*Further questions:* Assess gestures, attempts, risk-rescue factors, medical lethality.<br>0 = Thoughts of suicide absent. |
| Hamilton Depression Rating Scale. Rater selects best answer. | 0 = Feelings of guilt are absent.<br>1 = Self-reproach, feelings of having let people down.<br>2=Ideas of guilt or rumination over past errors or sinful deeds.<br>3 = Present illness is a punishment; delusions of guilt.<br>4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations. | 1 = Feels life is not worth living.<br>2 = Wishes he or she were dead or any thoughts of possible death to self.<br>3 = Suicide ideas or gesture.<br>4 = Attempts at suicide (any serious attempt rates 4). |
| Brief Psychiatric Rating Scale. Rater selects answer on a 7-point scale where<br>1 = Not present<br>7 = Extremely severe | Overconcern or remorse for past behavior. Rate on the basis of patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety, or neurotic defenses. | |

tracing of a patient who took an overdose of tricyclic antidepressants is shown in Figure 30–5.

## Electroencephalography

A history of brain injury or head trauma is often an indication for an electroencephalogram (EEG) in the work-up of mental status changes or psychiatric symptoms. Depending on the patient's presentation, the patient with new-onset psychosis should also have an EEG because partial complex seizures may produce psychosis. Symptoms suggesting temporal lobe epilepsy (TLE) (Figure 30–6), such as hyperreligiosity, hyposexuality, and hypergraphia, also indicate that an EEG should be obtained, including nasopharyngeal leads, to best evaluate electrical activity in the temporal lobes. One must keep in mind that the yield on a single EEG may be low and that consultation with an epileptologist may be indicated in cases in which suspicion for TLE is high. EEGs may be useful in the assessment of insomnia and other sleep disturbances.

Abrupt onset of psychiatric symptoms such as psychosis, mania, or personality change, or the presence of visual, olfactory, or tactile hallucinations suggest central nervous system dysfunction, which may warrant evaluation by electroencephalography.

## Brain Imaging

Several methods of brain imaging are available to assist in diagnostic assessment. Table 30–17 lists the indications for brain imaging.

**Table 30–12 Common Laboratory Tests for Evaluation of Psychiatric Patients**

| Sero logic |
|---|
| Toxicology screen (blood) |
| Complete blood count |
| Blood glucose |
| Kidney function tests |
| Liver function tests |
| Thyroid function tests |
| Syphilis serology |
| HIV antibody test |
| Pregnancy test |
| Blood cultures |
| Vitamin $B_{12}$ and folate levels |
| **Urine** |
| Toxicology screen (urine) |
| Dipstick for protein and glucose |
| Pregnancy test |
| **Lumbar Puncture** |
| **Electrocardiogram** |
| **Chest Radiograph** |

CT scans and magnetic resonance imaging (MRI) can be used to assess brain structure, and are useful in detecting such abnormalities as mass lesions (central nervous system neoplasms, certain infections, and hemorrhage), calcifications, atrophy, or areas of infarction. Mass lesions should be suspected when the patient has papilledema, or has focal or lateralizing abnormalities such as focal weakness, unilateral disturbances in reflexes, and increased pupillary size. Other situations that call for brain imaging include the work-up of a patient with dementia to look for brain atrophy or lacunar infarctions; the evaluation of new-onset psychosis, acute onset of aphasia or memory loss, and neglect syndromes; the evaluation of normal-pressure hydrocephalus (a syndrome characterized by a wide-based gait, dementia, and urinary incontinence); and demyelinating conditions.

Whereas CT and MRI provide visualization of brain structure, functional MRI, positron emission tomography (PET), single photon emission computed tomography (SPECT), and regional cerebral blood flow allow investigators to study brain functioning by assessing which areas of the brain are stimulated during various types of mental activity. At present, these tests have greater relevance to research than they do to clinical assessment. [For a complete discussion of brain imaging, see Chapter (33).]

**Table 30–13 Urine Toxicology Screen**

| Drug | Approximate Duration of Detectability* |
|---|---|
| Amphetamines | 2–4 days |
| Barbiturates | 2–4 days for short acting, up to 30 days for long acting |
| Benzodiazepines | Up to 30 days |
| Cocaine | 1–3 days |
| Opiates | 1–3 days |
| Phencyclidine | 2–7 days for casual use, up to 30 days for chronic use |
| Tetrahydrocannabinol (Marijuana) | 1–3 days for casual use, up to 30 days for chronic use |

*May vary widely depending on the amount ingested, compound, physical state of subject, and other factors.

*Source:* Cone EJ (1997) New developments in biological measures of drug prevalence. NIDA Research Monograph 167, 108-129.

**Table 30–14 Indications for Lumbar Puncture (Cerebrospinal Fluid Evaluation) in Psychiatric Patients**

| |
|---|
| Rapid onset of new psychiatric symptoms, including delirium, psychosis |
| New-onset psychiatric symptoms with fever |
| New-onset neurological symptoms (e.g., seizures, paralysis) |
| Suspected neuroleptic malignant syndrome (e.g., while taking antipsychotics, patient develops fever, tremor, dystonia, autonomic instability, mental status changes) |
| New-onset psychiatric symptoms with a known history of HIV infection or neoplasm (if space-occupying lesion is suspected, brain imaging should precede lumbar puncture) |

## Special Assessment Techniques

In certain situations, special assessment techniques may be indicated in the psychiatric evaluation of patients who are unable or unwilling to cooperate. These situations include the assessment of patients who are mute, have amnesia, or intentionally provide false information. In general, special techniques are employed only after all conventional ways to obtain the necessary information have been exhausted, including the use of other informants where available and appropriate.

**Table 30–15 Indications for Electrocardiography**

| |
|---|
| Assessment of cardiac functioning before beginning |
| Tricyclic antidepressants |
| Lithium |
| Thioridazine |
| Ziprasidone |
| β-blockers |
| Electroconvulsive therapy |
| Drug overdoses (need varies with substance or substances ingested) |

**Table 30–16 Common Electrocardiographic Abnormalities Seen with Psychotropic Medication**

| Medication | Abnormality |
|---|---|
| Tricyclic antidepressants | Increased PR, QRS, or QT intervals |
| Lithium | T wave flattening or inversion |
| | Sinoatrial block |
| | Sick sinus syndrome |
| Antipsychotics | |
| Clozapine | Sinus Tachycardia |
| Mesoridazine | Increased QTc interval |
| Pimozide | Increased QTc interval |
| Thioridazine | Increased QTc interval |
| Ziprasidone | Increased QTc interval |

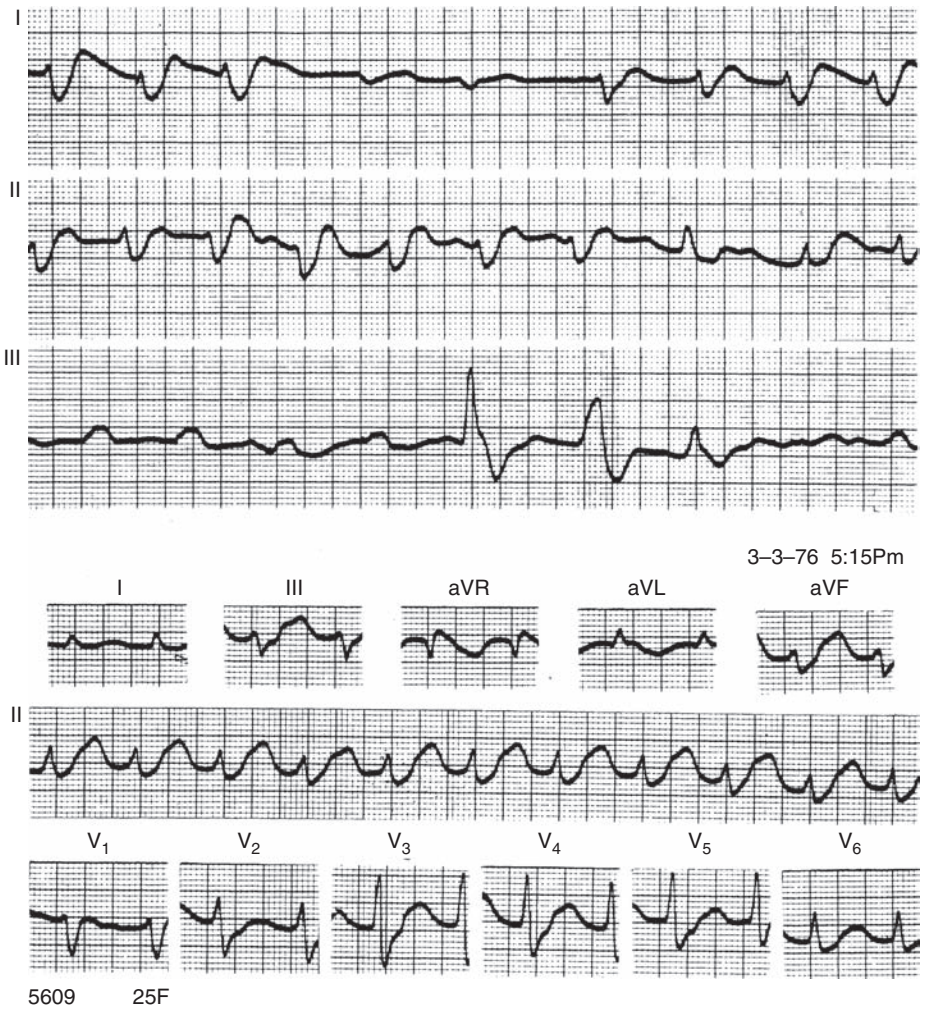



**Figure 30–5** *DTricyclic antidepressant overdose. The patient was a 25-year-old woman who took 500 mg of imipramine (Tofranil) 4 h before the 5 pm tracing was recorded. The three standard limb leads show wide QRS complexes of varying morphology. The exact rhythm cannot be determined. She had severe hypotension at this time. Fifteen minutes later, the tracing shows probable supraventricular rhythm with intraventricular conduction defect. [Source: Chou TC (1991) Electrocardiography in Clinical Practice, 3rd edition. WB Saunders, Philadelphia, PA, USA, p. 481.]*

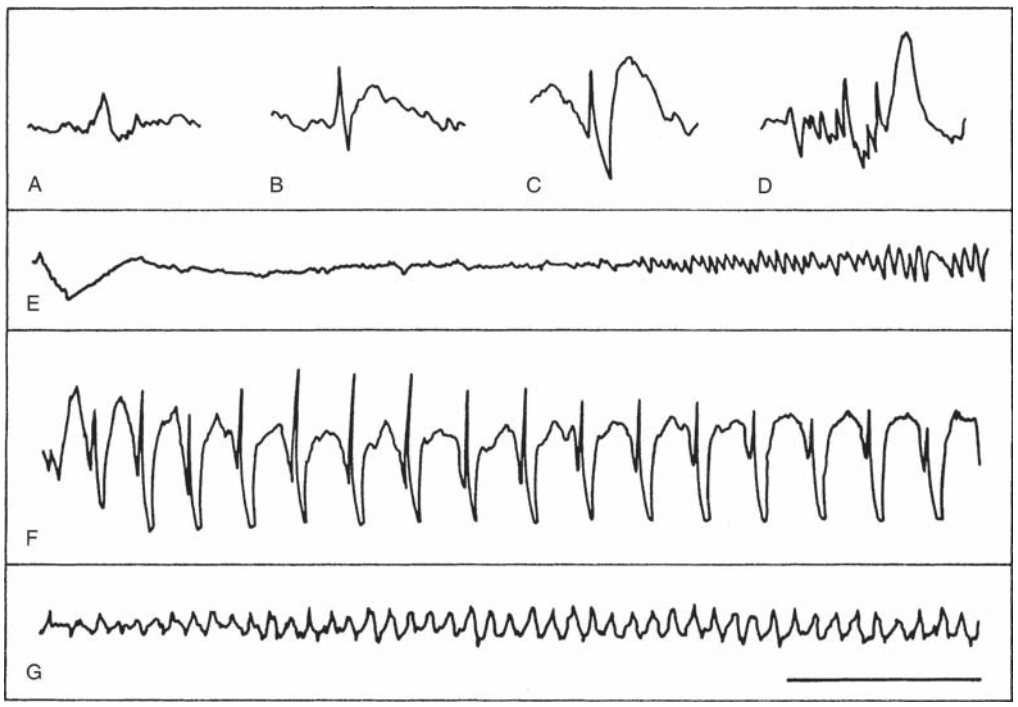



**Figure 30–6** *Examples illustrate waveforms of typical interictal EEG transients and ictal EEG discharges. (A) Interictal sharp wave. (B) and (C) Interictal spike-and-wave complexes. (D) Interictal polyspike-and-wave complex. (E) Recruiting rhythm typical of generalized convulsion onsets. (F) Repetitive spike-and-wave discharges typical of absence seizures. (G) Rhythmic pattern seen with temporal lobe seizures. Line at the bottom right of the figure represents 1 s. [Source: Wyngaarden JB, Smith LH, and Bennett JC (1992) Cecil Textbook of Medicine, 19th edition. WB Saunders, Philadelphia, PA, USA, p 2208.]*

| Table 30–17 | Indications for Brain Imaging |
|---|---|
| History of head trauma | |
| Papilledema or focal neurological findings on physical examination | |
| New-onset psychosis | |
| New-onset psychiatric symptoms after age 40 (including affective disorder and personality change) | |
| Rapid onset of psychiatric symptoms | |
| History of neurological symptoms (including seizures) | |
| Evidence of cognitive impairment | |
| Abnormal electroencephalogram | |
| Abnormal lumbar puncture | |

Hypnosis can aid in the recovery of repressed memories. For example, a patient who presents with a conversion symptom may be able to recall the forgotten traumatic events that precipitated it. The usefulness of hypnosis is limited by the patient's susceptibility to the procedure and by concern that the interviewer's suggestions can produce false memories [see also Chapter 94].

Another approach available for similar purposes is to use a sedative during the interview to produce disinhibition and allow the patient to speak more freely or to access otherwise unavailable memories. Intravenous amobarbital sodium is the best known of the medications used for this purpose. Caution must be exercised to avoid oversedation, to monitor for side effects of the medication, and to ensure that the interviewer does not inappropriately influence the patient's answers.

The assessment of a patient who is suspected of intentionally providing false information or malingering can become uncomfortable and problematic because it may require techniques that seem at odds with the establishment of the therapeutic alliance. A careful assessment of the patient's motives and the potential for secondary gain, confronting the patient with inconsistencies, physical assessment of implausible somatic complaints, and the use of other informants, prior medical records, and other documents can all help establish the validity of what the patient is saying. When the case involves the commission of a crime, an assessment of the patient's capacity to understand his or her actions may be important for the disposition plan.

However, because psychiatric evaluation depends on what the patient tells the interviewer and there are few objective means of clarification, outside of forensic settings it is best for the interviewer not to be overly concerned about the possibility of being intentionally misled. Establishing the truthfulness of the patient's story usually takes place over an extended period.

## Treatment Planning

The psychiatric evaluation is the basis for developing the case formulation, initial treatment plan, initial disposition, and comprehensive treatment plan.

## Case Formulation

The case formulation is the summary statement of the immediate problem, the context in which the problem has arisen, the assessment of risk, and the tentative diagnosis. The latter two areas are described next in more detail.

### Assessment of Risk

The assessment of risk is the most crucial component of the formulation because the safety of the patient, the clinician, and others is the foremost concern in any psychiatric evaluation. Four areas are important: suicide risk, assault risk, life-threatening medical conditions, and external threat. While comprehensive and accurate documentation is always a goal for mental health professionals, it is of particular relevance in the area of risk assessment. Furthermore, risk should be viewed as existing on a continuum from very low risk to very high risk, as opposed to merely being present or absent.

While no one source can be said to define the standard of care for assessing the risk of violence or suicide in psychiatric patients, it is clear that psychiatrists need to be able to conduct an adequate risk assessment. Authorities in this area argue that an individual clinician's clinical experience may not be enough, and particularly in the area of violence risk assessment, the risk assessment tools grounded in evidence-based risk factors are increasingly being employed to supplement the clinician's experience and judgment (e.g., HCR-20, see Webster et al. 1997; VRAG, see Quinsey et al. 2006). The use of such instruments, among other things, increases the likelihood of a comprehensive assessment and decreases the chance that a clinician will engage in an idiosyncratic assessment that does not take into account the robust risk factors identified in the psychiatric literature.

#### *Suicide Risk*

The risk of suicide is the most common life-threatening situation that mental health professionals encounter. Its assessment is based on both an understanding of its epidemiology, which alerts the clinician to potential danger, and the individualized assessment of the patient. Suicide is the 11th leading cause of death in the US. In the past century, the rate of suicide has averaged 12.5 per 100,000 people. Studies of adults and adolescents who commit suicide reveal that more than 90% of them suffered from at least one psychiatric disorder, and as many as 80% of them consulted a physician in the months preceding the event. An astute risk assessment therefore provides an opportunity for prevention.

For those who complete suicide, the most common diagnoses are affective disorder (45–70%) and alcoholism (25%). In certain psychiatric disorders, there is a significant lifetime risk for suicide, as listed in Table 30–18. Panic disorder is associated with an elevated rate of suicidal ideation and suicide attempts but estimates of rates of completed suicide are not well established. Additionally, while rates of suicide for individuals with anorexia nervosa appear high, there is a great deal of comorbidity with other psychiatric disorders that puts these individuals at risk for suicide, making the increase in risk associated with anorexia difficult to estimate.

Suicide rates increase with age. Women attempt suicide more often than men, but men are three to four times more

| Table 30–18 | Estimated Lifetime Rates of Completed Suicide by Diagnosis |
|---|---|
| Major affective disorders: 10–15% | |
| Alcoholism: 10–15% (comorbid depression usually present) | |
| Schizophrenia: 10% (often during a postpsychotic depressive state) | |
| Borderline and antisocial personality disorders: 5–10% | |

likely than women to complete suicide. Whites have higher rates of suicide than other groups.

A patient may fit the diagnostic and demographic profile for suicide risk, but even more essential is the individualized assessment developed by integrating information from all parts of the psychiatric evaluation. This includes material from the present illness (e.g., symptoms of depression, paranoid ideation about being harmed), past psychiatric history (e.g., prior attempts at suicide or other violent behavior), personal history (e.g., recent loss), family history (e.g., suicide or violence in close relatives), medical history (e.g., presence of a terminal illness), and the MSE (e.g., helplessness, suicidal ideation).

The most consistent predictor of future suicidal behavior is a prior history of such behavior, which is especially worrisome when previous suicide attempts have involved serious intent or lethal means. Among the factors cited as having an association with risk of suicide are current use of drugs and alcohol; recent loss, such as of a spouse or job; social isolation; conduct disorders and antisocial behavior, especially in young men; the presence of depression, especially when it is accompanied by hopelessness, helplessness, delusions, or agitation; severe anxiety and/or panic attacks; certain psychotic symptoms, such as command hallucinations and frightening paranoid delusions; fantasies of reunion by death; and severe medical illness, especially when it is associated with loss of functioning, intractable pain, or central nervous system dysfunction. Table 30–19 lists the risk factors for suicide. It should be noted that assisted suicide is now more openly discussed among people with terminal illnesses and has gained some measure of acceptability. Nonetheless, the vast majority of people who are bereaved or suffer from a serious medical illness do not end their lives by suicide. Adequate end-of-life care should forestall requests for assisted suicide. Although suicidal intent may be lacking, patients who are delirious and confused as a result of a medical illness are also at risk of self-injury.

It is essential to be clear about whether the patient has passive thoughts about suicide or actual intent. Is there a plan? If so, how detailed is it, how lethal, and what are the chances of rescue? The possession of firearms is particularly worrisome, because nearly two-thirds of documented suicides among men and more than a third among women have involved this method.

Factors that may protect against suicide include convictions in opposition to suicide; strong attachments to others, including spouse and children; and evidence of good impulse control. The usefulness of so-called "suicide contracts" as a prevention strategy is questionable, and may create a false sense of security, particularly at the beginning stages of treatment before a strong therapeutic alliance has been established.

In addition to the assessment of risk factors, it is important to decide whether the possibility of suicide is of immediate concern or represents a long-term ongoing risk.

**Table 30–19 Risk Factors for Suicide**

| Category | Risk Factors for Suicide |
|---|---|
| Demographic | White |
| | Male |
| | Older age |
| | Divorced, never married, or widowed |
| | Unemployed |
| Historical | Previous suicide attempts, especially with serious intent, lethal means, or disappointment about survival |
| | Family history of suicide |
| | Victim of physical or sexual abuse |
| Psychiatric | Diagnosis: affective disorder, alcoholism, panic disorder, psychotic disorders, conduct disorder, severe personality disorder (especially antisocial and borderline) |
| | Symptoms: suicidal or homicidal ideation; depression, especially with hopelessness, helplessness, anhedonia, delusions, agitation; severe anxiety or panic attacks; global insomnia; mixed mania and depression; psychotic symptoms, including command hallucinations and persecutory delusions |
| | Current use of alcohol or illicit drugs |
| | Recent psychiatric hospitalization |
| Environmental | Recent loss such as that of a spouse or job |
| | Social isolation |
| | Access to guns or other lethal weapons |
| | Social acceptance of suicide |
| Medical | Severe medical illness, especially with loss of functioning or intractable pain |
| | Delirium or confusion caused by central nervous system dysfunction |
| Behavioral | Antisocial acts |
| | Poor impulse control, risk taking, and aggressiveness |
| | Preparing for death (e.g., making a will, giving away possessions, stockpiling lethal medication) |
| | Well-developed, detailed suicide plan |
| | Statements of intent to inflict harm on self or others |

### *Risk of Violence*

Unlike those who commit suicide, most people who commit violent acts have not been diagnosed with a mental illness, and data clarifying the relationship between mental illness and violence are limited. The most common psychiatric diagnoses associated with violence are substance-related disorders. Conduct disorder, antisocial personality disorder, and psychopathy [a construct referring to a severe form of antisocial personality (Hart 1998)], by definition, involve aggressive, violent, and/or unlawful behavior. Sex offenders may meet criteria for a paraphilia, such as pedophilia or sexual sadism.

In the absence of comorbid substance-related disorders, most people with such major mental illnesses as affective disorders and schizophrenia are not violent. But data from the National Institute of Mental Health Epidemiological Catchment Area Study suggest that these diagnoses are associated with a higher rate of violence than that found among individuals who have no diagnosable mental illness. The MacArthur Violence Risk Assessment Study found that this was only true for psychiatric patients with substance abuse (Steadman et al. 1998).

Table 30–20 lists the risk factors for violence. As with suicide, the best predictor of future violence is a history of past violence. Information from the psychiatric evaluation that helps in this assessment includes the present illness (e.g., preoccupation with vengeance, especially when

**Table 30–20 Risk Factors for Violence**

| Category | Risk Factors |
|---|---|
| Demographic | Young |
| | Male |
| | Limited education |
| | Unemployed |
| Historical | Previous history of violence to self or others, especially with high degree of lethality |
| | History of animal torture |
| | Past antisocial or criminal behavior |
| | Violence within family of origin |
| | Victim of physical or sexual abuse |
| Psychiatric | Diagnosis: substance-related disorders, antisocial personality disorder; conduct disorder; intermittent explosive disorder; pathological alcohol intoxication; psychoses (e.g., paranoid, toxic) |
| | Symptoms: physical agitation; intent to kill or take revenge; identification of specific victim(s); psychotic symptoms, especially command hallucinations to commit violence and persecutory delusions |
| | Current use of alcohol or other drugs |
| Environmental | Access to guns or other lethal weapons |
| | Living under circumstances of violence |
| | Membership in violent group |
| Medical | Delirium or confusion caused by central nervous system dysfunction |
| | Disinhibition caused by traumatic brain injuries and other central nervous system dysfunctions |
| | Toxic states related to metabolic disorders (e.g., hyperthyroidism) |
| Behavioral | Antisocial acts |
| | Agitation, anger |
| | Poor impulse control; risk taking or reckless behavior |
| | Statements of intent to inflict harm |

accompanied by a plan of action), psychiatric history (e.g., childhood conduct disorder), family history (e.g., exposure as a child to violent parental behavior), personal history (e.g., arrest record), and the MSE (e.g., homicidal ideation, severe agitation). Other predictors of violence include possession of weapons and current illegal activities. There is considerable overlap between risk factors for suicide and those for violence, and similar to suicide, the use of specialized instruments and tools to assess the risk of violence, particularly in forensic settings, is becoming more widespread.

### *Life-Threatening Medical Conditions*

It is essential to consider life-threatening medical illness as a potential cause of psychiatric disturbance. Clues to this etiology can be found in the present illness (e.g., physical complaints), family history (e.g., causes of death in close family members), medical history (e.g., previous medical conditions and treatments), physical examination (e.g., abnormalities identified), and MSE (e.g., confusion, fluctuation in levels of consciousness). Laboratory assessment, brain imaging, and structured tests for neuropsychiatric impairment may also be essential.

Probably, the most common life-threatening medical situations that the psychiatrist evaluates are acute central nervous system changes caused by medical conditions and accompanied by mental status alterations. These include increased intracranial pressure or other cerebral abnormalities, severe metabolic alterations, sepsis, toxic states, and alcohol withdrawal (see Table 30–21). Patients may be at risk of death if these states are not quickly identified.

### *External Threat*

Some patients who present for psychiatric evaluation are at risk as a result of life-threatening external situations. Such patients can include battered women, abused children, and victims of catastrophes who lack proper food or shelter. Information about these conditions is usually obtained from the present illness, the personal history, the medical history, and physical examination.

## Differential Diagnosis

The differential diagnosis is best approached by organizing the information obtained in the psychiatric evaluation into five domains of mental functioning according to the disturbances revealed by the evaluation (see Table 30–22 and the subsequent chapters in this section for more detail). After organizing the information into these five domains, the psychiatrist looks for the psychopathological syn-

**Table 30–21 Life Threatening Medical Emergencies That May Present with Altered Mental Status**

| Central Nervous System Disorders |
|---|
| Elevated intracranial pressure due to cerebral edema, intracranial bleeding, or mass lesions |
| CNS infections including bacterial meningitis, cerebral malaria, and viral encephalitis |
| Transient ischemic attack, impending stroke, or stroke |
| **Systemic Illness** |
| Accidental or intentional overdose/toxicity/withdrawal/interaction of medications, substances of abuse, or toxins, including but not limited to: acetaminophen, alcohol, antidepressants (including serotonin syndrome), aspirin, beta-blockers, calcium channel blockers, carbon monoxide, cyanide, digoxin, heavy metals, hydrocarbons, insecticides, insulin, iron, isoniazid, isopropyl alcohol, methanol, muscle relaxants, neuroleptics (including neuroleptic malignant syndrome), opiods, sedative-hypnotics, solvents, stimulants (including amphetamines and cocaine), and certain venomous bites |
| Acute Wernicke's encephalopathy |
| Hepatic encephalopathy |
| Hyperpyrexia/heat stroke |
| Hypoglycemia |
| Hypoxia |
| Malignant hypertension |
| Sepsis |
| Severe electrolyte imbalance of which hyponatremia is most common |
| Severe acid-base imbalance, including diabetic ketoacidosis |
| Shock-including hypovolemic (e.g., blood loss, dehydration), septic, and cardiogenic |
| Thyroid storm |
| Uremia |

Note: The categories listed above often overlap, e.g., acetaminophen overdose causing hepatic encephalopathy.

**Table 30–22 Categorizing Features of Mental Disturbance**

| Area of Mental Functioning | Examples of Relevant Evidence of Disturbance |
|---|---|
| Consciousness, orientation, and memory | Abnormalities on interview or MSE, especially impairments in awareness; alertness; orientation to person, place, time; immediate, short-term or long-term memory; attention; calculations; fund of knowledge; abstractions |
| | Past history of foregoing |
| | Positive substance use history |
| | Risk factors for HIV; positive HIV antibody result |
| | Focal neurological findings on physical examination |
| | Laboratory and brain imaging abnormalities |
| | Impairments on neuropsychological testing |
| Speech, thinking, perception, and self-experience | Abnormalities on interview or MSE, especially disturbances of speech, thinking, reality testing, and presence of hallucinations, delusions |
| | Past history of foregoing |
| Emotions | Abnormalities on interview or MSE, especially labile, depressed, expansive, elevated, irritable mood, and inappropriate affect, anger, or anxiety |
| | Past history of foregoing |
| | Positive scores for mood disturbance on structured interviews |
| Physical signs and symptoms; physiological disturbances | Physical or neurological findings indicative of medical or mental disorder |
| | Laboratory abnormalities |
| | Past medical illnesses |
| | Positive substance use history |
| Behavior and adaptive functioning | Personality dysfunction |
| | Impaired social or occupational functioning |
| | Impaired activities of daily living |
| | Impulsive, compulsive, or avoidant behaviors |
| | History of behavioral or functional disturbances |
| | Personal history (highest levels of achievement) |

dromes and potential diagnoses that best account for the disturbances described. A complete diagnostic evaluation includes assessments on each of the five axes of DSM-IV-TR (Table 30–23).

Disturbances of consciousness, orientation, and memory are most typically associated with delirium related to a general medical condition or a substance use disorder. Memory impairment and other cognitive disturbances are the hallmarks of dementia. Results of the history, physical examination, laboratory testing, and brain imaging often help in defining the specific etiology. Neuropsychological testing is particularly useful in the diagnosis of subcortical dementia, such as that caused by Huntington's disease and HIV infection. Dissociative disorders and severe psychotic states may also present with disturbances in this domain without evidence of any medical etiology. Cognitive impairment caused by mental retardation is established by intelligence testing.

**Table 30–23 DSM-IV-TR Multiaxial System**

| | |
|---|---|
| Axis I | Clinical disorders |
| | Other conditions that may be a focus of clinical attention |
| Axis II | Personality disorders |
| | Mental retardation |
| Axis III | General medical conditions |
| Axis IV | Psychosocial and environmental problems |
| Axis V | Global assessment of functioning |

*Source:* American Psychiatric Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC, USA.

Disturbances of speech, thinking, perception, and self-experience are common in psychotic states that can be seen in patients with such diagnoses as schizophrenia and mania, as well as in central nervous system dysfunction caused by substance use or a medical condition. Disturbances in self-experience are also common in dissociative disorders and certain anxiety, somatoform, and eating disorders. Cluster A personality disorders may be associated with milder forms of disturbances in this domain.

Disturbances of emotion are most typical of affective and anxiety disorders. These disturbances may also be caused by substance use disorders and general medical conditions. Mood and affect disturbances accompany many personality disorders and may be especially pronounced in borderline personality disorder.

Physical signs and symptoms and any associated abnormalities revealed by diagnostic medical tests and past medical history are used to establish the presence of general medical conditions, which are coded on Axis III. When a medical disorder is causally related to a psychiatric disorder, a statement of this relationship should appear on Axis I. Physical signs and symptoms may also suggest diagnoses of mood or anxiety disorders or states of substance intoxication or withdrawal. Physical symptoms for which no medical etiology can be demonstrated after thorough assessment suggest somatoform or factitious disorders or malingering, although the possibility of an as-yet-undiagnosed medical condition should still be kept in mind.

Information about behavior and adaptive functioning is useful for diagnosing personality disorders, documenting psychosocial and environmental problems on Axis IV, and assessing global functioning on Axis V. This information is also useful for diagnosing most psychiatric disorders, which typically include criteria related to abnormal behaviors and functional impairment.

When all information has been gathered and organized, it may be possible to reach definitive diagnoses, but sometimes this must await further evaluation and the development of a comprehensive treatment plan.

## Initial Treatment Plan

The initial treatment plan follows the case formulation, which has already established the nature of the current problem and a tentative diagnosis. The plan distinguishes between what must be accomplished now and what may reasonably be postponed for the future. Treatment planning works best when it follows the biopsychosocial model and takes into account the treatment time frame, e.g., brief hospitalization, long-term outpatient care, etc.).

### *Biological Intervention*

This includes an immediate response to any life-threatening medical conditions and a plan for the treatment of other less acute physical disorders, including those that may contribute to an altered mental status. Prescription of psychotropic medications based on a patient's presenting symptoms, psychiatric history, and tentative diagnosis is the most common biological intervention.

### *Psychosocial Intervention*

This includes immediate plans to prevent violent or suicidal behavior and address adverse external circumstances. An overall strategy must be developed that is both realistic and responsive to the patient's situation. Developing this strategy requires an awareness of the social support systems available to the patient; the financial resources of the patient; the availability of services in the area; the need to contact other agencies, such as child welfare or the police; and the need to ensure child care for dependent children.

## Initial Disposition

The primary task of the initial disposition is to select the most appropriate level of care after completion of the psychiatric evaluation. Disposition is primarily focused on immediate goals. After referral, the patient and the treatment team develop longer term goals.

### *Hospitalization*

The first decision in any disposition plan is whether hospitalization is required to ensure safety. There are times when a patient presents with such severe risk of harm to self or others that hospitalization seems essential. In other cases, the patient could be managed outside the hospital, depending on the availability of other supports. This might include a family who can stay with the patient or a crisis team in the community able to treat the patient at home. The more comprehensive the system of services, the easier it is to avoid hospitalization, and many mental health systems offer intensive outpatient services to avoid expensive inpatient care. Because hospitalization is associated with extreme disruption of usual life activities and by itself can have many adverse consequences, plans to avoid hospitalization are usually appropriate as long as they do not compromise safety.

### *Day Programs, Crisis Residences, Supervised Housing, and Assertive Community Treatment*

Housing interventions provide ongoing supervision but at a lower level than that available within the hospital. They are most often used to treat patients with alcohol and substance use disorders and/or severe mental illness. Crisis housing can be useful when a patient cannot safely return home, when caregivers need respite, and when the patient is homeless. Other forms of supervised housing usually have a waiting period and may not be immediately available.

There are many different types of and names for day-long programming, including partial hospitalization, day treatment, psychiatric rehabilitation, and psychosocial clubs. Depending on the nature of the program, it may provide stabilization, daily medication, training in social and vocational skills, and treatment of alcohol and substance use problems. Long-term day programs should generally be avoided if a patient is functioning successfully in a daytime role, such as in a job or as a homemaker. In these instances, referral to a day program may promote a lower level of functioning than the patient is capable of.

Assertive community treatment (ACT) is a intensive program that operates 24 hours a day and combines outreach techniques with a broad array of services to keep patients in the community. ACT teams can often be utilized to prevent, substitute for, or reduce the time spent in inpatient psychiatric treatment.

### *Outpatient Medication and Psychotherapy*

The most common referral after psychiatric evaluation is to psychotherapy and/or medication management. In office-based settings, the psychiatrist decides whether she or he has the time and expertise to comprehensively treat the patient, and makes referrals to other practitioners as appropriate. Hospital staff usually have a broad overview of community resources and refer accordingly. There are high rates of dropout when patients are sent from one setting to another. These can be reduced by providing introductions to the treatment setting and/or conducting follow-up to ensure that the referral has been successful.

## Comprehensive Treatment Planning

The psychiatric evaluation usually continues beyond the initial disposition. The providers assuming responsibility for the patient, who may be inpatient staff, outpatient staff, or private practitioners, complete the evaluation and take responsibility for developing the comprehensive treatment plan. This plan covers the entire array of concerns that affect the course of the patient's psychiatric problems. In hospital settings, the initial treatment plan is usually completed within 24–72 h after admission, depending on applicable standards, followed by a comprehensive treatment plan after more extensive evaluation.

The comprehensive treatment plan usually includes more definitive diagnoses and a well-formulated management plan with central goals and objectives. For severely ill or hospitalized patients, every area is usually covered (Table 30–24). It is best for the patient and, as appropriate, the family, to have input into the plan. The comprehensive treatment plan guides and coordinates the direction of all treatment for an extended time, usually months, and is periodically reviewed and updated. For more focal psychiatric problems (e.g., phobias, sexual dysfunctions) and more limited interventions (e.g., brief interpersonal, cognitive, and behavioral therapies in office-based practices), the comprehensive treatment plan may focus on only several of the possible areas.

**Table 30–24 Areas Covered by Comprehensive Treatment Plan**

| |
|---|
| Mental health |
| Diagnoses on five axes |
| Psychiatric management, including medications |
| Physical health |
| Medical diagnoses |
| Medical management, including medications |
| Personal strengths and assets |
| Rehabilitation needs |
| Educational |
| Occupational |
| Social |
| Activities of daily living skills |
| Use of leisure time |
| Living arrangements |
| Social supports and family involvement |
| Finances |
| Personal finances |
| Insurance coverage |
| Eligibility for social service benefits |
| Legal or forensic issues |
| Central goals and objectives |
| Listing of treatment team members |
| Evidence of participation by patient and, as appropriate, family members and others |
| Criteria for discharge from treatment |

## Conclusion

The psychiatric evaluation is a method of collecting present and past psychological, biological, social, and environmental data for the purpose of establishing a comprehensive picture of the patient's strengths and problems, including the psychiatric diagnoses, and developing treatment plans. It is the essential beginning of every course of psychiatric treatment and, when carried out successfully, integrates a multimodal approach to understanding mental illness and providing clinical care.

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CHAPTER

# 31 The Initial Psychiatric Evaluation of Children and Adolescents

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There are currently only about 6000 child psychiatrists in some sort of clinical practice in the United States, whereas there are between 7 and 12 million children with psychiatric illnesses, as identified by DSM-IV-TR criteria (Costello and Pantino 1987, US Public Health Service 1999). Most of these children will not see a child and adolescent psychiatrist, and their care must be undertaken by general psychiatrists, other physicians, and mental health care providers. The assessment of children and adolescents should utilize the caution and competence required by a physician treating an individual patient with a broad concern for that patient's development in the context of family, school, and society.

Medical care must begin with diagnosis. A comprehensive diagnostic assessment should address the medical and psychiatric condition of the child; the child's emotional, cognitive, social, and linguistic development, and the nature of the child's relationship with his or her family, school, and social milieu. Evaluations must address not only a narrow consideration of clinical diagnosis but also a larger set of issues that are truly biopsychosocial. Children are today served by a variety of individuals and agencies, each possessing their own particular agendas and separately approaching physicians and other consultants. These agendas must be recognized and served, given today's consumer-oriented society. At the same time, we have a responsibility to those individuals seeking our professional services to educate them with the wider range of concerns that may be affecting a given child's life or families' outcome.

Referrals may come from a variety of various social and legal agencies such as courts and departments of human services, from teachers or schools, or from other physicians. Many referrals come directly from parents, who are often generally very concerned about their child's impaired functioning and suffering. They may bring to the process a mixed heritage of concern, guilt, and shame, frequently fearing that they will be judged as they seek assistance help. Concurrent with this are often ambivalent feelings of love and frustration toward a difficult child. The duty of all psychiatrists is to recognize all these needs and address them in a manner that is not only authoritative but also tactful and empathetic.

## Elements of the Psychiatric Evaluation

### Collateral and Preliminary Information

Today, most children who are seen by child and adolescent psychiatrists have already received a great deal of attention from other professionals. To fail to gather information from them prior to a formal evaluation is a serious mistake, leading to wasted time and frustrated relationships. If at all possible, it is usually most efficient to speak directly with a referring professional. This is especially true in the case of primary care physicians, who may have a long-standing relationship with the child and family. Other mental health professionals referring a child usually have conducted their own evaluation. Children's school records can be a rich source of information about a child's cognitive and emotional development. Examination of this data can enrich an evaluation; similarly, failure to do so can lead to embarrassing lapses.

Often a child and adolescent psychiatrist's first personal encounter in evaluating/assessing a patient is with another professional—a clinician, or an educator, or a case worker who has sought the examination. The enormous value of their information has already been discussed. The clinician must also recognize the sensitivities of these people: they may be grateful for the opportunity to talk with the psychiatrist and eager in their expectation of the evaluation,

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perhaps even to an unrealistic degree. At the same time, the act of seeking a consultation may, at least unconsciously, signify to them a failure on their part. They may be concerned that their relationship with the child or family will in someway be disrupted or supplanted, or that they will be criticized by the psychiatrist.

## Parents

Parents bringing their child to a child psychiatrist come with a rich and often contradictory mix of feelings. Frequently they reach the psychiatrist at the end of a long, complicated process of evaluations and treatment attempts. They are almost invariably concerned over their child's condition and prospects. In a way that may be difficult for those who are not parents to understand fully, they may have many fears about the consequences of a psychiatric referral, as do referring professionals. They may feel that they will be judged or, in extreme cases, that their children will be removed from their care. In a more subtle way, they may also worry that their relationship with their child will be supplanted or superseded. They may be concerned about the moral and philosophic basis of the psychiatrist's approach, fearing that parental ethical standards and religious beliefs may in some way be contradicted. Sometimes, they may have unrealistically optimistic or hopeful fantasies of "absolution" of unconscious guilt, or of quick cures. Usually, more often than not, parents have no idea of the specifics of psychiatric assessment or treatment. Their opinions have been formed by mass media and public prejudice. The psychiatrist needs to understand how the parents feel about the referral and what they expect to gain from it.

A great deal of information should be obtained collected from parents, since they know the child best. The details of this data collection, including various outlines for its organization, are described elsewhere in this book. Most child and adolescent psychiatrists today use a traditional medical format to organize their data, with headings such as Chief Complaint, History of Present Illness, Past Medical History, Family History, and Review of Systems. More often than not, the specifically medical aspects of these data are already available. Not infrequently, however, families have not received regular primary medical pediatric care. In these cases, it is incumbent on the psychiatrist as physician to take a comprehensive medical history in addition to acquiring other information. In all these areas of questioning, psychiatrists collect data as do all other physicians, usually attempting to organize the information in a chronologic fashion. What is unique about a psychiatric evaluation is that physicians find not only the specific data but also their affective implications. In other words, they inquire to find out not only as to what specifically happened but also how it made the child or family members feel and what consequences/impact it had on their lives.

Another area of inquiry of particular relevance to physicians treating children is the developmental history. The developmental history elicited by a psychiatrist should in many ways be similar in depth and breadth to that obtained by a developmental pediatrician, with a special emphasis on the social and affective consequences of developmental phenomena. Some developmental processes or stages may inherently be more or less comfortable for some parents, and that there is a wide range of variation in the degree of comfort and discomfort that development engenders. Developmental assessment begins with asking about a child's conception, prenatal history and delivery. Questions about fine and gross motor milestones, speech development, toilet training, sleep patterns are essential. In older children stages of puberty and physical growth and the feelings around it should be asked. Finally, we must be aware of the great variations in developmental patterns and expectations found among different cultures.

The family has an immense and profound influence on the development of each of its members and may be viewed as a unique entity. It is therefore invaluable, as part of a comprehensive psychiatric observation, to ideally spend some time in the company of the entire family. The opportunity to observe firsthand how the members of a family act with each other/interact can be enriching for a clinician attempting to understand the consequences of each family member's behavior on the others. In addition, if this observation is done early, it may serve as a more comfortable entrance to the evaluation process for a shy or otherwise recalcitrant child or otherwise uncooperative family member.

## Meeting the Child

In practice, most clinicians develop a somewhat personal style of interaction usually formed by psychodynamic and interactional approaches and also more structured empirical techniques. Clinicians in any setting realize that, outside of the specific requirements of a structured interview instrument, they need to be flexible in their approach. The schemes that we use for reporting an interview are generally best conceived as devices for retrospective organization rather than templates for an interview. This is of particular importance with children. Any pediatrician knows that in the course of a physical examination one does what one can when one can. Similarly, in the psychiatric interview with the child, one must be flexible and mobile both verbally and physically. The order of the interview will depend on the age of the child. Generally, younger children will be seen after meeting with the parents alone. Adolescents often are given the choice to be seen first without parents. This allows for the development of rapport and trust with the teenager. Information from the parents is usually obtained with the teenager in the room, as they can be suspicious about what the parents will say about them.

One of the most vital elements of an initial psychiatric interview with the child is the establishment of a productive relationship—in other words, "making friends." The clinician must keep in mind how children feel in the context of an interview. Children may share or reflect the same complicated and ambivalent mixture of fear, shame, hope, and misapprehension that their parents bring to the process, and they often have not been fully prepared by the parents or others for the interview. Such preparation, if it can be done by parents prior to bringing the child in, can be helpful. Many children, in our experience, have been told nothing at all, other than "Come along, we are going to see someone." Or they may have been told that they are going to see a doctor, which can convey fears of injections and manipulations. Some children may have been led to assume that the evaluation is part of a punitive process. Others may feel that by virtue of referral they have been singled out in some way as "weird" or "crazy." Concurrently, the child may expect to

see the physician as some sort of remote, distant, punitive, or bizarre figure. All these issues must be promptly investigated and addressed in a developmentally appropriate fashion for a productive interview to ensue.

How one handles the above issues is affected by one's own personality and training, and by the circumstances of the child and family. Preschool children are seldom able to sustain any type of formal interview, although they may answer some questions during play activities or while "on the run." Their preoperational style of cognition makes the standard interview format, with its attention toward consequence and chronology, irrelevant. One assesses these children through observation and interaction. By contrast, the school-age child often will have some comprehension of the psychiatrist's role. It may help to introduce one's self as a "talking doctor" or "problem doctor" who deals with the problems that many children have (generalization may make the child feel less singled out) through conversation as well as traditional somatic treatments, and who does not give injections in the office setting. Older children and adolescents can often be asked directly about why they were brought to evaluation, as well as their opinions about its necessity and desirability. With school-age children, an initial request about what sort of problems they may have encountered in their life may be met with diffidence or avoidance. In this instance, simply playing together at some mutually acceptable activity may be an important first step. Older children and adolescents may at this time be able to tolerate tactful questions or the mention of other material or information. They will still benefit from the opportunity to talk or interact about areas that they like, perhaps later in the interview. A frequent icebreaker employed by child and adolescent psychiatrists is drawing. Children who are seated in the waiting room while their parents are being interviewed can be given the opportunity to draw a picture of their family or some other subject of interest to them, their family, or another picture. Such a drawing can serve as both a projective device and a conversation starter later in the process. Of course, children can also be encouraged to draw at other times during the interview.

In many instances, children do not respond to a standard, direct, complaint-centered line of questioning, even after several attempts by the clinician. The clinician is then best advised to relent and ask the child to talk about more general aspects of his or her life. The patient can be encouraged to tell the physician about his or her family, including each individual member and their relationship. School can easily be discussed touching on academic issues, behavior aspects and a child's social life. In doing so, the clinician can often assemble a broad picture of the child's life as well as specific medical information about phenomenology. Some areas will need to be more directly pursued, usually later in the interview when a presumably more trusting relationship has been established. These include items that are considered part of the mental status examination such as the presence of affective symptomatology (including suicidal ideation or plans) and psychotic phenomena (including hallucinations, delusions, or ideas of reference). Not every child needs to be asked about these things, since for some merely inquiring in an initial interview can be disruptive or fearful. Nevertheless, these issues must be pursued if there is any indication of a disorder in the given area. Suicidal ideation in particular must be pursued in the context of any affective disorder. Other important behavioral areas such as sexual behavior, drug abuse, and health-risk behaviors may also need to be pursued.

The issue of confidentiality warrants special consideration. Psychiatrists must use their clinical skill to moderate two conflicting demands: the child's right as a patient to confidentiality as versus the right of parents and, in some instances, other agencies or institutions to be aware of the child's needs and requirements. In our experience, most parents want to know what their child is thinking; concurrently, most children want their parents to understand them, although they may prefer to conceal some specific details. Younger children may be told that they have a right to hold secrets, but that their parents also have a right to know what in general is going on in their lives. Adolescents and their parents may be told that they have a right to confidentiality, but that some information involving a serious risk to themselves or others could be shared. Conflicts over confidentiality often overlie larger family issues that, when addressed, make the confidentiality issues moot or irrelevant.

Child and adolescent psychiatrists have traditionally been encouraged to pursue children's fantasies in the course of an evaluation. The different approaches to this tend to be highly personalized by each clinician and may include asking a child for three wishes, positive or negative animal identifications (what animal would you like or not like to be), story completion, response to fables, or other techniques. Few if any of these approaches, as used idiosyncratically in an unstructured interview, have ever been validated. They should not be treated as sources of empirical data in and of themselves. They can, however, be useful probes to seek other information that can be validated and, more important, that relates to specific emotional concerns of an individual child or adolescent.

Often nonmedical professionals refer to the psychiatric evaluation as the "mental status exam," but in fact this examination is not always used in evaluating children and adolescents. However, a formal mental status examination must be pursued when there is evidence of a thought disorder. In these instances, the type of examination used with adults generally suffices for adolescents as well. In younger children, the mental status examination is often a list of observations that is retrospectively organized from the content of the interview thus far described (the outline of this examination is summarized in Table 31–1). In most child and adolescent psychiatric assessments, these parameters are not all specifically cited but are mentioned as part of the narrative or may be drawn from inference by the reader. If the patient in question possibly has a major thought or affective disorder, however, specific adherence to this outline may be useful.

## Standardized Assessment Instruments

Structured interviews, rating scales, and questionnaires and structured interviews have become more widely used in child and adolescent psychiatry in recent years, although their primary venue remains in research settings. In many cases, a comprehensive evaluation can be conducted and reported without requiring the use of these instruments; and some instruments may require a degree of time and expense unavailable outside a research setting. However, as diagnostic

**Table 31–1 Mental Status Examination Outline**

1. Physical appearance
2. Separation from parent
3. Manner of relating
4. Orientation to time, place, and person
5. Central nervous system functioning
6. Reading and writing
7. Speech and language
8. Intelligence
9. Memory
10. Thought content
11. Quality of thinking and perception
12. Fantasies and inferred conflicts
13. Affects
14. Object relations
15. Drive behavior
16. Defense organization
17. Judgment and insight
18. Self-esteem
19. Adaptive qualities
20. Positive attributes
21. Future orientation

Adapted from Lewis ME and King RA (2002) Psychiatric assessment of infants, children. and adolescents. In *Child and Adolescent Psychiatry: A Comprehensive Textbook*, 3rd edition, Lewis ME (ed). Williams & WIlkins, Baltimore, MD, USA, p. 531.

categorization under the DSM system has become more standardized and reproducible, clinicians are more frequently using validated instruments to clarify, quantify, or affirm impressions that come from their personal evaluations. Specific instruments are considered below. Some instruments are part of a formal psychological evaluation performed by clinical psychologists-others are readily available for use without additional specialized training.

## Psychological Evaluation

Today, many patients who come to a child and adolescent psychiatrist have already been assessed through psychological testing. Although most psychiatrists do not administer the majority of these tests, it is necessary for them to understand the tests available and how to interpret their results. The most frequently used instruments include the Wechsler, Rorschach, and Bender Gestalt tests, the Thematic Apperception Test (TAT), achievement tests, and drawings. There are limitations to the strictly intrapersonal perspective, however, since children should be understood within the context of their lives (Mooney and Harrison 1987) Assessment techniques should be broad and should include measures that assess the child "in action." Psychological techniques suggested for this type of assessment include parent/teacher questionnaires, intelligence and achievement testing, drawings, projective testing, child questionnaires, behavioral assessment, play observations, and family interaction.

### Parent and Teacher Questionnaires

Questionnaires are often quick effective ways to get important information from people not directly available such as teachers, for the assessment. They also provide a way to ascertain information directly from the parents. The Eyberg Child Behavior Inventory (Eyberg and Ross 1978) is a straightforward 36-item questionnaire that can be completed by parents of children who are 2−7 years of age (Eyberg and Ross 1987). The Eyberg is relatively simple to fill out and yields information on a wide variety of disruptive behavioral problems.

The Parenting Stress Index (PSI) by Abidin (1995) is filled out by parents of children ranging in age from 1 month to 12 years (a short form is available). The PSI provides Child and Parent Domain. The total stress score combines both domains and allows for an analysis of the source of stress. This, can be used to assess the degree to which the child's behavior is stressful versus the difficulty the parents have in adjusting to their parenting roles. PSI results are also helpful in communicating with parents; the clinician can report, for example, that the parents provided the information that they feel depressed or that they are experiencing communication barriers with their spouse. With this technique, parents are less likely to be defensive, and the clinician can be more reflective and understanding rather than intrusive.

The Child Behavior Checklist is completed by parents or teachers of children ages 4−16 years (Achenbach 1991a, 1991b, Achenbach and Rescorla 2000).The accompanying additional Youth Self-Report Scale is completed by youngsters from 11−18 years of age. These questionnaires have the advantage of providing a behavior profile which gives information on the following dimensions: withdrawn; somatic complaints; anxious/depressed; social problems; attention problems; delinquent problems; and aggressive behavior. While not strictly diagnostic, they can provide an additional source of information or suggest areas to be explored further in the clinical interview. Separate forms are used for boys and girls ages 4−5, 6−11, and 12−16 years.

There is a wide variety of attention deficit hyperactivity disorder (ADHD) rating scales available for ascertaining the presence of symptoms at school, home and other settings. Detailed description of the merits of various tests is discussed by Collett et al. (2003). The most widely used is the Conners' Rating Scales-Revised. It provides teacher- and parent-rating ADHD index and can be used to assess children at risk for this disorder. The McCarney Attention-Deficit Disorders Evaluation Scale Conners (1997) is an empirically based attention-deficit hyperactivity disorder (ADHD) index that can also be used to assess children at risk for ADHD (McCarney 1995). It condenses the three subscales of inattentiveness, impulsivity, and hyperactivity to two scales: inattentiveness and impulsivity/hyperactivity. These scales can also be used to assess improvements from the use of psychoactive medication.

### Cognitive Assessment

Intelligence testing is both overrated and underrated. There is often too much emphasis on intelligence quotient (IQ) scores per se. Psychological tests provide a wide range of information regarding strengths, weaknesses, learning style, and needs. There are many important personal qualities that intelligence tests do not measure, however, such as creativity, determination, and persistence over a period of time.

There are many factors other than difficulties with intellectual functioning that can lead to low IQ scores. These include cultural or linguistic differences: distractibility or anxiety, refusal to cooperate, and disabling conditions.

Intelligence tests give a wide range of information about children's abilities in several areas of functioning. The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) provides subtest and composite scores in specific verbal and performance areas as well an overall cognitive score which reflects representing general intellectual ability (Wechsler 2003). This revised edition has updated norms, new subtests, and greater emphasis on discrete domains of cognitive functioning.

The Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III), available since 2002, offers an assessment of the intelligence of children ages 2 years, 6 months through 7 years, 3 months (Wechsler 2002). Like the other Wechsler tests, it provides an overall cognitive score as well as scores for verbal and performance abilities (Tables 31–2 and 31–3).

Ability testing provides us with information on the pattern of strengths and weaknesses that can affect the student's ability to function in the classroom, including the special needs and learning style of the student. These in turn, can influence the presentation of any psychiatric symptoms.

**Table 31–2 The WISC-III Subtests Grouped According to Scale**

| Verbal | Performance |
|---|---|
| 2. Information | 1. Picture Completion |
| 4. Similarities | 3. Coding |
| 6. Arithmetic | 5. Picture Arrangement |
| 8. Vocabulary | 7. Block Design |
| 10. Comprehension | 9. Object Assembly |
| 12. Digit Span† | 11. Symbol Search* |
| | 13. Mazes† |

*Supplementary subtest that can substitute only for Coding.

†Supplementary subtest.

From Wechsler D (1991) *Wechsler Intelligence Scale for Children-Third Edition: Manual*. Harcourt Brace Jovanovich, New York, NY, USA, p. 5

Children who have marked discrepancies between verbal and performance IQ scores can experience difficulty functioning in the classroom. Any child who has a severe deficit may be significantly affected even if many other subtest scores are average or above average. Children with high verbal scores but low performance scores struggle with the production of work in the classroom. Children with high performance scores and low verbal scores are often impulsive, action-oriented individuals who have difficulty reflecting or using language to process their experience. Some children such as the learning disabled (LD)/gifted child, have complex combinations of cognitive abilities. Children with ADHD often score low on one or more subtests of the WISC-IV. There is tremendous variability in the relative abilities of children with ADHD, which can negatively affect performance on structured tests in varied ways.

The Stanford-Binet Intelligence Scale-Fourth Edition yields scores for Verbal Reasoning, Abstract/Visual Reasoning, Quantitative Reasoning, and Short-Term Memory (Thorndike et al. 1986). The current edition includes many performance items and so has addressed earlier criticism of the Binet that it was too verbally oriented. Using either the WISC-IV or the Binet to ascertain strengths can provide useful information for guiding an individual in school and in making later career choices as well as treatment decisions.

The Leiter International Performance Scale-Revised has the strong advantage of being a nonverbal test of intelligence (Leiter 1997). It can be used to evaluate children with sensory, or motor, deficits or language problems, or those who speak a different language from the examiner. This test is certainly less culturally loaded than other IQ tests, but there is no evidence on whether it is "free" of cultural bias.

A quick assessment of intelligence is provided by the Kauffman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman 1990). This can be used for children, adolescents, and adults from the ages of 4−90 years. It requires 15−30 minutes to administer and has only two subtests. It can be useful for establishing a baseline of intelligence but does not provide in-depth information on strengths and weaknesses.

The Woodcock-Johnson-III Tests of Achievement (WJ-III) (Woodcock et al. 1989 and the Wechsler Individual Achievement Test-Second Edition (Smith et al. 2002) provide information on basic academic skills such as reading, writing, and math ability.

The diagnosis of developmental disabilities or mental retardation should never be made on the basis of IQ alone. Rather, one should consider the pattern of strengths and weaknesses on IQ tests, assess adaptive and other behaviors, and use common sense.

When assessing a child, it is important to seek multiple sources of data, including information on the child's personal and social sufficiency at home, at school, and in the community. The Vineland Adaptive Behavior Scales can be used to measure communication, daily living skills, socialization, and motor skills in children from birth to 18 years and 11 months of age or in low-functioning adults (Sparrow et al. 1984).

## Drawings

The seminal work of DiLeo (1983) describes the relationship between characteristics shown in the patient's drawings and the patient's behavior and overall development. Drawing can be used both as a means of assessment and as a means of initiating and maintaining a relationship with a child.

Clinicians use subjectivity as well as their clinical experience in interpreting children's drawings. The age and developmental level of the child must be considered in the interpretation of drawings, and the clinician should be familiar with what is normative for specific developmental

**Table 31–3 Scales Derived from Factor Analyses of the WISC-III Subtests**

| Factor I Verbal Comprehension | Factor II Perceptual Organization | Factor III Freedom From Distractibility | Factor IV Processing Speed |
|---|---|---|---|
| Information | Picture Completion | Arithmetic | Coding |
| Similarities | Picture Arrangement | Digit Span | Symbol |
| Vocabulary | Block Design | | Search |
| Comprehension | Object Assemble | | |

From Wechsler D (1991) *Wechsler Intelligence Scale for Children – Fourth Edition: Manual*. Harcourt Brace Jovanovich, New York, NY, USA, p. 7.

levels. Drawing characteristics that have interpretive significance include the use of space, the quality of line, orientation of objects, shading (as an indicator of anxiety), integration of the human figure drawings, symmetry and balance, and overall style. Drawings are also reflective of cognitive development. The drawing of a person "yields an overview of intellectual maturity." The Draw-a-Person test (DPT), the Kinetic Family Drawing (KFD) by Burns and Kaufman (1972), and the House-Tree-person test (HTP) by Buck (1970) are systematic approaches to the assessment of children's drawings.

## Child Questionnaires

The Children's Depression Inventory (CDI) is the most widely used popular child questionnaire for assessing depression in children. It was developed by Kovacs (1992) based on the Beck Depression Inventory for adults. The long form has 27 items, and a short form (CDI-S) has 10 items. It is suitable for children ages 7−17 years of age and requires only a third-grade reading level, the lowest of any childhood depression measure.

The Child Anxiety Scale (CAS) can be useful in some instances for children 5 through 12 years of age. (Gillis 1980) It involves 20 straightforward questions in which a child marks on either a red circle or a blue circle. It can be administered by the clinician or with an audiotape.

The Sentence Completion Test for Children is a simple, two-page sentence completion form with 25 items, useful for children ages 5 through 12 years. It may be read out loud or filled out in writing by the patient. Incomplete Sentences Blank forms are useful for young people in high school or college (Rotter 1977). They provide insight into emotional state and inner feelings that might not be verbally expressed in a direct interview.

To aid in assessing teens for substance abuse issues, the adolescent form of the Substance Abuse Subtle Screening Inventory (SASSI) is available for ages 12 through 18 (Miller 1990). Many teenagers will give significant information regarding substance abuse habits on a questionnaire when they may volunteer no information in an interview.

## Play Observations

Children use play as their natural medium for self-expression and as an avenue for cognitive development. It can, therefore, be useful to incorporate some opportunity to observe unstructured play in child assessment procedures. Typically, a dollhouse, large blocks, puppets, and vehicles can be used. Children's personalities are revealed in the way that they approach these toys. Straightforward observation of their behavior can indicate how they typically behave in similar situations.

Singer (1973) has described how fantasy allows children to delay gratification and to deal more effectively with frustration, which in turn has implications for their success in the classroom. By studying preschool children, Parten (1932) identified five ways that children play: (1) in solitary play, children are unaware of others and play alone; (2) in onlooker play, children watch others play; (3) in parallel play, children play side by side with little interaction with others; (4) in associative play, children interact and share; and (5) in cooperative play, they relate to each other, helping and taking turns. Piaget described three types of play—practice games, symbolic games, and games with rules—through which children learn the rules of social exchange and enhance their sense of competence and self-esteem (Pulaski 1976).

## Family Interaction

Family interaction should be an important consideration in any assessment of children. Family sessions can be utilized for diagnostic purposes and are also particularly useful when working with children and their parents to teach child management techniques for externalizing disorders such as ADHD and oppositional defiant disorder (ODD). In each family, however, the child's role strongly affects his or her feelings, attitudes, and behaviors, and clinicians should assess these characteristics when planning for treatment. Baumrind (1991) demonstrated that a child's personality characteristics are closely related to the structure of that child's family, and Hetherington and Parke (1986) compared parenting styles with children's behavior and self-esteem.

It is important for clinicians to assess parental warmth and emotional availability. These two factors are important to the child in terms of seeking approval. Parents showing these traits may be more likely to teach alternative social responses to the child. Clinicians should also evaluate parental control. Parental restrictiveness or permissiveness can lead to difficulties in child functioning. A permissive family can cause problems of neglect and may also harm a child's adaptive ability. Authoritarian family approaches may have the advantage of preparing children to deal with rules and limits but the disadvantage of limiting overall individual competence. Finally, one must recognize the profound effect of extended family interaction, both for children who have an intact nuclear family and for those who are being raised by other family members including grandparents. Often, extended family members play a large role in the upbringing of a child.

## Educational Assessment

Unfortunately few children receive an educational evaluation which may be an extremely useful part of the child's assessment and rehabilitation, especially as psychiatric treatment progresses. An educational assessment takes into account a child's psychiatric diagnosis and how they contribute to learning difficulties and are the basis for development of an educational plan to ensure a child's academic success.

Children are asked to learn basic academic and social skills upon which their performance is judged and compared to that of other children. If children succeed, they learn that success provides opportunities and social status. If, on the other hand, they fail for whatever reasons their self-esteem can be diminished and they learn about failure and restricted opportunities. Professionals involved with children who are experiencing difficulty in school must understand the devastating impact that school failure has on a child's life and act quickly to resolve the situation.

The educational assessment of children is a specialized process that directly addresses overall academic achievement. The assessment process must be a collaborative approach, which includes not only the teachers, parents, diagnosticians but also the child. The child must be not only the subject but a part of the process. The outcome of any

assessment should provide information that allows teachers, parents, and others to create positive learning environments: environments that allow students to assume control of their own academic destiny. The performance of the child is not viewed in isolation but as part of a large ecosystem with many interdependent variables.

Individuals who conduct educational evaluations are often called diagnostic educators. They must be able to collect the data needed to identify a learner problem and then use those data to devise educational intervention strategies. The diagnostic educator identifies and analyzes the child's learning patterns and helps the classroom teacher to implement instructional methods specific to the child. The teacher must understand the cause and nature of learning disabilities as well as methods of accommodating them in the classroom. The diagnostic educator uses a school-based problem-solving team to help facilitate change in attitudes, approaches, and assessment of outcomes. The educational diagnostician's role involves interpreting performance in the classroom, and teaching experience often validates these individuals' credentials.

## Indications for an Educational Evaluation

The psychiatrist often can request an educational evaluation when there is a question about school performance or the need to adjust a child's educational program. The problem may be a new issue or a chronic or crisis situation. The cause of problematic behavior must be identified and an intervention plan developed. Whatever the difficulty, it is important to remember that children cannot usually develop coping mechanisms on their own or adjust their school environment to help them better meet expectations. If professionals are reluctant to obtain an assessment there can be misdirected, inefficient, and often disappointing results.

## Legislation and Rights

Children with disabilities have a legal right to a free and appropriate education, and schools are legally obligated to fulfill these needs although they may resist fulfilling this obligation due to limited resources. Parents often require the assistance of mentors and professionals to ensure that their children's needs are in fact met. Historically, classroom teachers have assessed children by trying to discover what they do or do not know and why they have learned some things and not others. If a teacher is skilled and the school system supportive, this method can be effective. The individual capabilities of the teacher and the random sensitivity of the system, however, do not ensure that all children experiencing problems in school will be appropriately identified and provided with the necessary adaptations.

The enactment of US Public Law (PL) 94-142, the Education of Handicapped Children Act of 1975, improved this process, mandating that all children ages 5−21 years with an identified handicap will have a free and appropriate education. It outlined procedures to determine eligibility for special education services and appropriate programming. The law was revised in 1990, in 1997, and reauthorized in 2004 and has been renamed Individual with Disabilities Education Act (IDEA) (Ohio Department of Education 2004). This legislation emphasizes educating children in the least restrictive learning environment possible, one that can provide inclusion in the general curriculum. The legislation also provides a specific set of procedures for identifying a child's disability and determining an appropriate educational plan. Refer to Table 31–4 for more detail. Any child suspected of a disability must have a multifactored evaluation (MFE), which assesses all areas related to the suspected disability, and an individualized education program (IEP) conference to review the MFE data, determine eligibility for special services, and define the least restrictive learning environment possible.

**Table 31–4 Identifying a Child's Disability: Procedural Safeguards**

| Stage | Components |
|---|---|
| Pre-referral | Parents discuss program with teacher and request intervention, or school requests referral for evaluation in writing. |
| Referral | School explains referral process to parent. Parents receive copy of parent's rights. Parents give permission for testing |
| Evaluation | Parents participate in and contribute to team evaluation activities. School completes evaluation and team determines eligibility for special education services. |
| IEP meeting | Parents participate in IEP activities. Evaluation team jointly develops IEP. Parent gives consent for placement to receive special education services which will enable child to participate in general education curriculum. |
| Annual review | School and Parents review child's progress and current IEP. |
| Reevaluation | School initiates reevaluation every 3 years. Parents initiate sooner needs of child change |
| Independent educational evaluation | Parent has a right to an independent evaluation if there is a disagreement over the evaluation. School may initiate due process if evaluation team believes the evaluation is fair and accurate. |

IEP = individual education program

Adapted from Ohio Department of Education Office for Exceptional Children (2004) *Whose Idea Is This? A Resource Guide for Parents*. Columbus, OH, USA.

Schools must provide by law an MFE for any child suspected of having a disability. The referral can be made by the parents, school personnel, or community agency personnel. If parents are making the referral, they should do so in writing, indicating that they suspect that their child has a disability and requires an MFE. If the school district refers the child, the parents must be contacted by the school and asked to give their consent to evaluate.

The school is obligated to hold an IEP conference to review the results of the MFE, determine eligibility for services, and, plan an appropriate education program. This meeting must include parents as joint decision makers. Once a child is enrolled in special education, the school district is obliged to conduct an annual review of the child's progress and notify parents of current IEP goals. A reevaluation by

the school district is mandated every 3 years. Parents should be notified about and informed about this process. It should be noted that all too often the initiation of a thorough educational assessment requires initiative on the part of the parents.

### The Educational Evaluation

The purpose of the education evaluation is to gather the data necessary for determining eligibility for special education services and to identify specific learning needs and intervention strategies. Eligibility is ultimately a procedural and legal decision that depends on current levels of performance and standardized data; the identification of specific learning needs requires additional data emphasizing an analysis of the student's learning patterns, the school environment, and other social and cultural influences (Table 31–5).

**Table 31–5 The Function of School Personnel in Resolving School Issues**

| School Personnel | Issue(s) |
|---|---|
| Principal | School entry |
| Principal and teacher | Classroom issues |
| | Curriculum |
| | Instruction |
| | Environmental variables |
| Support services | School adjustment |
| School psychologists | Referral and assessment |
| Speech/language therapist | Behavior Management |
| Reading specialist | Individualized intervention |
| OT/PT | |
| Administration personnel | Procedural issues |
| Principal | Eligibility for special services |
| Pupil Personnel director | Due process procedures |
| Superintendent | School safety |
| | Quality control |
| | Curriculum guidelines |

The components of an educational assessment are background information, descriptive data, test data, and the educational plan. Background information includes school history, pertinent medical history, the presenting problem, the duration of the problem, and the effect the problem has had on the child's development at home and in school. Test data usually include both norm- and criterion-referenced testing of academic achievement, general knowledge, and specific skill mastery. These instruments may include those that are part of a typical psychological evaluation as described earlier, as well as more specialized measures. Descriptive data, especially classroom observation, can yield information about a child's behavior, attention, and general ability to adapt to school expectations.

### Educational Plan

The final component of an educational evaluation is the educational plan, which provides a framework for creating solutions. In general, the educational diagnostician and the teacher must find two solutions: (1) a way to evaluate the child's knowledge of content that does not employ a weak skill as the method of testing and (2) a plan to improve knowledge and, when possible, deficient skills. In the past, solutions have focused on requiring the child to improve performance through remediation and, of course, "try harder" without meaningful environmental adjustments. Creating a more accessible learning environment that emphasizes strengths and decreases negative outcomes is vital for children with learning problems to succeed. The psychiatrist participates as evaluator, consultant, support, and strong advocate who can be invaluable to the success of an educational plan.

## Laboratory Assessment

Laboratory assessment has become a more frequent part of psychiatric evaluation in recent years. Often, patients will have already undergone a comprehensive laboratory assessment, even including neuroimaging, by their referring physicians; the burden of further assessment of these patients is thus not borne by the psychiatrist.

Conversely, some patients will have had little if any laboratory workup, and such assessments may be necessary in an orderly, stepwise fashion. For example, patients might receive standard hematologic and chemical screenings prior to exotic endocrinologic and nutritional assessments. Similarly, it is seldom appropriate to seek an expensive and complicated neuroimaging procedure in a patient who has not yet received a neurologic examination.

Given both the immense advances in neuroimaging and the intense media coverage devoted to this progress in recent years, some patients and families will assume that procedures such as computed tomography (CT) or magnetic resonance imaging (MRI) scanning are an essential part of the psychiatric examination. This, of course, is frequently not the case as these interventions are not without risk and cost to family and society. Clinicians are best advised to deal with these demands by recognizing the underlying motivations of concern, anxiety, or entitlement that evoke these requests. At the same time, as physicians, child and adolescent psychiatrists must be aware of the rare but poignant circumstances in which gross central nervous system pathology, such as vascular malformations and space-occupying lesions, may manifest themselves.

The electroencephalogram (EEG) continues to be useful in the neurobiological assessment of children and adolescents. Among the illnesses relevant for EEG assessment is autism. Differentiation of Landau−Kleffner syndrome, which has a specific treatment from autism, is very important. Since autism has a seizure incidence of about 20−30% with a peak risk for onset in early adolescence; the clinician should consider ordering an EEG as part of a workup for any unusual change in the adolescents clinical condition. EEG differences from normal have been seen in Attention Deficit Hyperactivity Disorder, conduct disorder, and learning disorders but the findings are nonspecific and EEG is generally not helpful for guiding treatment.

## Outcome of the Evaluation

### Presentation of Findings and Recommendations to Parents and Referring Sources

In the past, some psychiatrists, perhaps out of a unique conception of confidentiality, have been reluctant or even

reclusive in sharing their findings with others. In some instances, this practice has even been used with parents who may have been told merely to continue bringing their child for treatment. Such positions were, thankfully, relatively unusual, and current demands for consumer orientation and accountability now make them utterly untenable. Parents and referring professionals or agencies are entitled to a concise and comprehensible statement of findings and recommendations. The delivery of this information depends on the needs of the child and the relationship of the child to these individuals or agencies.

As noted previously, parents approach psychiatric evaluation with a rich mixture of concerns, hopes, and fears, which often occur at the time of the interview. We have met parents who could give a verbatim account of their contact years earlier with a professional regarding their child; the affective intensity of this moment seared it into memory. The fashion in which this powerful circumstance is addressed can profoundly affect the subsequent conduct of the patient's treatment. It is a truism that at such moments, parents may hear only the first thing told to them. Indeed, it often may be enough in one interview to discuss a single major piece of information and attempt thereafter to address its affective consequences. If diagnostic impressions or therapeutic recommendations are complicated, parents may need a frequent restatement of this content, perhaps accompanied by written or audiovisual supplements and aids. Many parents require a series of contacts to fully understand and process this information. Given the limitations in contact imposed by some care-management agencies, it may be helpful to incorporate into these process case managers or other professionals, who have a relationship with the family. In our experience, however, the ultimate responsibility as well as the ultimate effectiveness in dealing with these issues resides with the diagnosing physician. Psychiatrists must first and foremost address the affective consequences of whatever information is being presented. To fail to do so is not only inhumane but is likely to seriously undermine the subsequent physician-family relationship and the family's compliance with treatment recommendations.

## Sharing Information with Other Physicians, Schools, and Agencies

Since many patients seek child and adolescent psychiatrists as a result of a referral from physicians, schools, or other agencies, information must frequently be shared regarding the patient's condition, prognosis, and treatment. It is axiomatic that information on any patient cannot be released without the expressed (and usually written) permission of the patient or, in the case of a minor, his or her legal guardian. The content of shared information and the manner in which it is communicated should be discussed in advance with patients, families, or guardians. Information should be released only as requested, and psychiatrists should avoid automatic release of entire reports or clinical notes.

In general, referring sources shouldn't be given detailed information about members of the family other than the patient. This is especially important in educational settings, since many school records are virtually public documents. The type of information shared with a referring physician may be very different from that shared with the school.

## Consultation, Collaboration, and Advocacy

Children's needs are addressed in our culture by a variety of people including but not limited to parents, professionals, and educators. Even when a child has a major mental illness whose psychiatric needs may be paramount, it is usually impossible for a child and adolescent psychiatrist to function alone. The psychiatrist will be asked to consult with other professionals and educators. Such consultation may be an intermittent advisory relationship, or it may involve ongoing collaboration in which child and adolescent psychiatrists and other professionals interact in discipline-specific roles.

In today's environment of competition for social and educational resources and need for active intervention in the lives of children and families who are in danger, the psychiatrist has a special role of advocacy. This role may evolve as a result of a request by a patient and family or the psychiatrist's perception that some special intervention or communication is required. Despite the changing and challenged role of physicians in our society, the psychiatrist can still be an important and invaluable agent in the workings of educational, social, and legal systems.

## Conclusion

Child and adolescent psychiatry has a unique role within medicine. It provides diagnostic assessment, therapeutic services, consultation, and advocacy for children and their families. In a broad biopsychosocial context, psychiatrists attempt to best meet the needs of children and families by serving in a fashion informed by scientific rigor, personal sensitivity, and social responsibility.

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CHAPTER

# 32 Neuropsychological Assessment and Neurophysiological Evaluation

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## Overview

Neuropsychology is the study of brain–behavior relationships. While psychology is the scientific study of behavior and mental processes, neuropsychology firmly places that study in the context of its underlying neural structures and mechanisms. Neuropsychology makes use of standardized and normed tests, behavior rating scales, and experimental procedures to elucidate brain–behavior relations, and its methods have both clinical and research applications in psychiatry (Keefe 1995, Lezak et al. 2004, Flashman 2004, Seidman 1994). The unique benefit of a neuropsychological approach in patient care is that it facilitates an integrated, biopsychosocial explanation of behavior, combining hypotheses about brain dysfunction with psychometrics and an understanding of the individual's cognitive strengths and weaknesses, personality, current stressors, and everyday socioenvironmental context to inform patient management. From a research perspective, neuropsychology's contributions to psychiatry include understanding the cognitive correlates of psychiatric disorders, their relationship to the neuropathology of a disorder, the extent to which they are specific and/or progressive, and their role in treatment (e.g., medication effects, rehabilitation, and therapy) and functional outcome. For example, over the past two decades, schizophrenia has been reconceptualized as a disorder with core cognitive deficits which are not merely complicating comorbidities but intrinsic components of its phenomenology and related neurodevelopmental pathology that are themselves a viable and important focus of treatment (Green 2007, Seidman 1990).

A different approach to understanding brain function involves neurophysiological evaluation. While neuropsychology is particularly useful in identifying intact and disordered components of information processing (e.g., attention, working memory, executive functions) from which brain function is inferred, neurophysiological methods provide more direct measurement of neural processing and events in real time. Its primary method, the noninvasive electroencephalogram (EEG), records the millisecond-by-millisecond electrical activity of the brain that results from neuronal firing (Niedermeyer et al. 2004). Event-related potentials (ERPs) and event-related oscillations (EROs) extracted from the ongoing EEG in the context of an internal or external event or stimulus permit examination of the rapidly changing patterns of brain activities that underlie cognitive function and dysfunction (Gevins 1998). As psychiatry has increasingly integrated cognitive and affective neuroscience into its conceptual framework and practice, the value of experimental and applied neuropsychology and neurophysiology has grown accordingly. This chapter will review the contributions of neuropsychology and neurophysiology to the practice of psychiatry.

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## Assessment of Brain Dysfunction by Neuropsychological Testing

Until the 1970s, psychological evaluation of psychiatric patients usually consisted of a psychodiagnostic test battery (Holt 1968). Such assessments were primarily oriented to personality dynamics or diagnostic judgments about "functional" versus "organic" etiologies, depending upon the degree to which a psychiatric patient's disorder was thought to be associated with obvious brain pathology. Common referral questions included "Is there an organic component?" to a patient's clinical presentation, and a clinical psychologist would attempt to determine the presence or absence of "organicity" (brain damage) on the basis of pathognomonic signs. Inferences about "organicity" were most often derived from individually administered tests including the Wechsler Adult Intelligence Scale, Bender–Gestalt, Draw-A-Person, Minnesota Multiphasic Personality Inventory, Rorschach, and supplemental memory tests. Although this clinical process had some success in identifying brain dysfunction, its conceptual and empirical limitations were well established by the 1980s (Lezak et al. 2004, Reitan and Wolfson 1993, Seidman and Toomey 1999). Many organic test impairments were associated with confounding factors (e.g., poor motivation, psychosis, low IQ) and thus produced false-positive diagnoses, and many manifestations of brain damage (e.g., language deficits, memory problems) were not reflected in the single visual–motor test (e.g., Bender Gestalt) typically used to assess "organicity," leading to false-negative diagnoses.

The basic assumption underlying the outmoded concept of organicity—that brain damage is unitary and could be identified by performance on single tests—was faulty (Flashman 2004). Rather, the cognitive and behavioral manifestations of brain dysfunction vary dramatically depending on the kind, size, and location of the neurodevelopmental or acquired pathology, as well as the period of brain development during which it occurs. Other person variables such as age at testing and age at disorder onset, sex, education, and handedness mediate the expression of brain dysfunction on neuropsychological tests (Heaton et al. 1996). The organicity construct and its measurement have been replaced by a more differentiated understanding of brain–behavior relationships and comprehensive neuropsychological approach. In this model, the clinical neuropsychologist attempts to determine whether the clinical picture and test performance data are consistent with a neurobehavioral or neuropsychiatric syndrome (Feinberg and Farah 1997, Flashman 2004).

While the traditional psychodiagnostic battery remains useful in contributing to a meaningful, integrated understanding of an individual that goes beyond psychiatric diagnosis (e.g., personality style/dynamics, assets, liabilities, conflicts, stress tolerance), contemporary neuropsychological assessment is organized around measurement of a broader range of functions and referral questions. Table 32–1 summarizes the broad range of domains of neuropsychological function most commonly assessed. Importantly, neuropsychological assessment requires consideration of neurological (brain) and psychological (behavioral, cognitive, personality) variables, and their interaction with the environment. The two approaches may be appropriately used conjointly when both personality and neuropsychological factors are to be assessed, such as in articulating various aspects of complex neuropsychiatric disorders such as temporal lobe epilepsy (Greenberg and Seidman 1992, Table 32–2) or attention-deficit/hyperactivity disorder (ADHD; Weinstein et al. 1991, Table 32–3). For such cases, a careful evaluation of personality and neuropsychological functions may enhance goal setting and choice of type of psychotherapy or other treatment and rehabilitation interventions (Seidman 1994).

**Table 32–1 Domains of Neuropsychological Function**

| |
|---|
| Premorbid and Current Intellectual Ability |
| Sensory–Motor Functions |
| Perceptual Functions |
| Attention/Concentration |
| Language Functions |
| Visuospatial Functions |
| Working Memory |
| Executive Functions |
| Declarative and Procedural Learning and Memory |
| Academic Achievement Skills: Reading, Math, Spelling, Writing |
| Mood, Personality, Adaptive Functions, and Effort/Motivation |

**Table 32–2 Selected Tests Useful in the Neuropsychological Assessment of Adults with Temporal Lobe Epilepsy**

| Neuropsychological Tests |
|---|
| Wechsler Adult Intelligence Scale-III (Wechsler 1997a) |
| Wechsler Memory Scale-III (particularly Logical Memory Stories, Visual Reproductions, and Paired Associate Learning Tests; Wechsler 1997b) |
| Auditory and Visual Consonant Trigrams (Peterson and Peterson 1959) |
| California Verbal Learning Test-II (Delis et al. 2000) |
| Rey–Osterrieth Complex Figure (Osterrieth 1944, Rey 1941) |
| Boston Naming Test-2 (Kaplan et al. 2001) |
| Controlled Oral Word Association Tests of Verbal Fluency (Borkowski et al. 1967) |
| Wisconsin Card Sorting Test (Heaton et al. 1993) |
| **Personality Tests** |
| Minnesota Multiphasic Personality Inventory-2 (Hathaway and Mckinley 1989) |
| Thematic Apperception Test (Morgan and Murray 1935) |
| Bear–Fedio Temporal Lobe Inventory (Bear and Fedio 1977) |
| Rorschach Inkblot Test (Rorschach 1942) |

*Source*: Adapted from Greenberg and Seidman (1992).

## Neuropsychological Examination Compared with Other Examinations

Neuropsychological testing provides information regarding diagnosis; cognitive, perceptual, and motor capacities or deficits; and treatment recommendations (Table 32–4). Experienced clinicians use test data to determine the presence or absence of brain dysfunction, to localize the damage, and to establish the etiology (Milberg et al. 1996). Moreover, a comprehensive functional assessment can lead to neurologically meaningful subgroups of disorders (as in different types of developmental disorders, verbal and nonverbal) that may have relevance to treatment, such as in the application of different strategies of cognitive rehabilitation or school placement (Weinstein and Seidman 1994).

**Table 32–3 Selected Tests Useful in the Neuropsychological Assessment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder**

| Neuropsychological Tests |
|---|
| Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler 2003) |
| Wide Range Achievement Test-4 (WRAT4; Wilkinson and Robertson 2006) |
| Stroop Color and Word Test (Golden et al. 2003) |
| Auditory Continuous Performance Test (Weintraub 2000) |
| Conners (Visual) Continuous Performance Test (Conners 1995) |
| Wisconsin Card Sorting Test (Heaton et al. 1993) |
| Delis–Kaplan Executive Function System (DKEFS; Delis et al. 2001) |
| California Verbal Learning Test-Children's Version (CVLT-C; Delis et al. 1994) |
| Children's Memory Scales (CMS; Cohen 1997) |
| Rey–Osterrieth Complex Figure: Developmental Scoring System (Bernstein and Waber 1996) |
| Cancellation Tests (Weintraub 2000) |
| Motor Response Inhibition Tests (Benson and Stuss 1982) |
| **Behavior Rating Inventories and Personality Tests** |
| ADHD Rating Scale-IV (DuPaul et al. 1998) |
| Child Behavior Checklist (CBCL; Achenbach and Rescorla 2001) |
| Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al. 2000) |
| Thematic Apperception Test (Morgan and Murray 1935) |
| Sentence Completion Tests (Rotter 1977) |

*Source*: Adapted from Seidman et al. (2001).

**Table 32–4 Common Uses of Neuropsychological Testing**

| |
|---|
| Reliably, validly, and as completely as possible measure the behavioral and cognitive correlates of brain functions. |
| Determine the basis of "adaptive" failures in academic, vocational, social or self-care functioning. |
| Document the nature and severity of neurocognitive deficits. |
| Differential diagnosis—identify the characteristic profile associated with a neurobehavioral or neuropsychiatric syndrome. |
| Clarify the relationship of behavioral or cognitive change to specific psychiatric or neuromedical disorders or treatments. |
| Monitor neuropsychological status in the context of development/aging, recovery, and/or treatment. |
| Describe neuropsychological strengths, weaknesses, and strategy of problem solving. |
| Assess the patient's feelings about and compensations to a deficit or disorder. |
| Provide recommendations for management, rehabilitation, or treatment. |
| Contribute to legal decision making: competency, criminal responsibility, or civil damages. |

Most neuropsychologists, regardless of theoretical orientation, agree on a number of basic characteristics that define clinical neuropsychological evaluations. The goal in a neuropsychological examination is to reflect reliably, validly, and as completely as possible the behavioral correlates of brain functions (Weintraub 2000). The greatest relevance of testing lies in capacity to inform recommendations for everyday living and treatment planning (Lezak et al. 2004). Developmental neuropsychological assessment as applied in work with children is particularly sensitive to issues related to how observed behavior is related to neuromaturational status, developmental history and expectations, immediate environmental demands (including at home and school), and sociocultural context (Baron 2003, Bernstein 2000). In particular, the clinician is oriented to the impact of neuropsychological strengths and weaknesses in school, family, and other settings.

All neuropsychological approaches assess some aspects of intelligence, reasoning and abstraction, attention (sustained and selective), "executive" and self-control functions (set shifting, planning, and organizational capacity), learning and memory (e.g., working memory, declarative), language, perceptual (i.e., auditory and visual) and constructional tasks, and sensory and motor functions. Comprehensive test batteries can be quite lengthy, because the human brain–behavior relationship is quite complex. Test data are interpreted in the context of many factors including the age, sex, education, and handedness of the patient.

Although the data-gathering approach of the neuropsychologist can be well integrated with a psychodynamic orientation (Seidman 1994, Seidman and Toomey 1999), a few distinctions between the approaches are noteworthy. In the psychodynamic approach, the examiner reduces test structure to assess "projective" components and to discern underlying

**Clinical Vignette 1**

In this vignette, a neuropsychological examination led to the unexpected identification of a focal brain lesion that accounted for the patient's current clinical picture. A 69-year-old woman had been seen regularly for at least 5 years by her psychiatrist. She had a long history of bipolar disorder and was treated with lithium carbonate. At the time she was evaluated by the neuropsychology service, she had been admitted to an inpatient psychiatric service because of increasingly agitated behavior. During the course of her stay, she repeatedly complained about a "lithium tremor in my right hand." This was initially interpreted as irrational because (1) the patient often spoke in a thought-disordered way familiar to her doctor, and her current complaint was not considered unusual for her, and (2) it was considered unlikely that lithium would cause a unilateral tremor self-reported by the patient but not diagnosed by the physician. Neuropsychological testing was requested and revealed a number of putative abnormalities pointing to left frontal cerebral dysfunction. Despite the fact that the patient was right-hand dominant, she was consistently and significantly slower with her right than left hand on the Finger-Tapping Test (Reitan and Wolfson 1993). On the Boston Naming Test (Kaplan et al. 2001), she made a significant number of paraphasic naming errors and had long latencies of response. On Trail Making B (Army Individual Test Battery 1944), she made many perseverative errors and missed a target stimulus on the right side of the test page. Subsequently, a CT scan revealed a large cyst affecting primarily her left frontal lobe. The patient was transferred to the neurosurgery service, where the cyst was successfully drained before her discharge. Because we could not follow up this patient, we never learned whether her mood symptoms were alleviated by the surgical treatment.

*Source:* Adapted from Seidman (1994).

motives, wishes, and thought processes (Holt 1968) whereas the neuropsychologist is usually structuring and encouraging, attempting to find out what the patient can best achieve and by what process (Kaplan 1990). Moreover, neuropsychologists conducting a clinical assessment typically make use of the history, symptom data, and medical records, as well as test data per se, rather than relying on test data alone.

The neuropsychological evaluation covers the same functions as the Mental Status Examination used by psychiatrists and neurologists but in a more elaborated, deep, and quantified manner (Strub and Black 1985, Weintraub 2000). When contrasted with the typical Mental Status Examination, neuropsychological testing is the following: broader, in that more differentiated functions are assessed; deeper, in that far more items compose a task or function, usually arranged from simple to difficult; and more quantified, in that there is more sophisticated scoring of data, as well as the provision of normative data on different samples. In addition, the administration of neuropsychological testing is more standardized. The neurologist's assessment of cranial nerves, sensory–motor function, and coordination (more "elementary" functions) and the neuropsychologist's assessment of "higher" cognitive functions complement each other well.

## Types of Referral Questions in Psychiatry

The neuropsychological examination has three general aims: (1) identification of neuropsychological dysfunction leading to inferences regarding the presence, type, and etiology of brain dysfunction; (2) comprehensive assessment of cognitive, perceptual, and motor strengths and weaknesses as a guide for treatment; (3) assessment of the level of performance over a broad range of neurocognitive functions, for both initial evaluation and measurement of change over time.

Clinical Vignette 2

In this vignette, the neuropsychological examination identified a nonverbal learning disability, attentional problems, and depression and was used to help frame the patient's psychotherapy. A 21-year-old man was referred with the goal of assessing the reasons for his lifelong school difficulties. It was clear to the referring psychiatrist that the patient had significant conflicts regarding achievement, variable motivation, and problems with assertiveness; however, the psychiatrist suspected that primary cognitive difficulties might be contributing to the picture. On the Wechsler Adult Intelligence Scale—Revised (Wechsler 1981), the patient had a Verbal IQ of 121, a Performance IQ of 100, and a Full-Scale IQ of 113, certainly indicative of college-level intellectual ability. However, he showed significant discrepancies between rather high verbal reasoning abilities and rather poor arithmetical calculation and visual–spatial skills. Moreover, he worked rather slowly on all visual–motor tasks, and his piecemeal strategy (Kaplan 1990) for constructing the Rey–Osterrieth Complex Figure (Osterrieth 1944, Rey 1941) was developmentally immature. He approached the figure by drawing small details, without recognizing the gestalt, and this inefficient strategy appeared to be responsible for his poor reconstruction of the figure on recall conditions. He also demonstrated attentional difficulties on a continuous performance test (CPT) (Rosvold et al. 1956) indicating difficulties in sustaining attention or vigilance. These difficulties were entirely consistent with the results of a pediatric neuropsychological examination done when he was 7 years old, on the basis of which a "developmental perceptual organization disorder" was reported.

Personality testing with the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Hathaway and Mckinley 1989) and the Thematic Apperception Test (Morgan and Murray 1935) indicated mild depression, poor self-esteem, anxiety about achievement, and a defensive style emphasizing minimization and denial. These traits were reformulated as, in part, secondary reactions to a primary, lifelong learning disability. The patient was effectively treated once or twice weekly with supportive, psychoeducational psychotherapy by a psychotherapist who was sophisticated in combining neuropsychology and psychotherapy. Moreover, he was adjunctively treated with fluoxetine at 20 mg/day, which contributed to considerable improvement. He felt more energetic and decisive and more able to focus and sustain his attention. Over time, this progress led to an improved social life; a more balanced focus on school, work, and play; and better school performance.

*Source*: Adapted from Seidman (1994).

## Differential Diagnosis

Although experienced neuropsychologists may achieve a greater than 90% accuracy in diagnosing brain dysfunction (Milberg et al. 1996, Reitan and Wolfson 1996), the referring clinician needs to discuss with the neuropsychologist the merits of using neuropsychological examination (comprehensive or brief) compared with other methods such as the neurological evaluation or specialized neurodiagnostic techniques. For example, neuropsychological evaluation is labor intensive (a full battery can take as much as 3–8 hours to administer, not to mention scoring, interpretation, and report writing) and is thus expensive. However, the neuropsychological examination is unique in providing a comprehensive, empirically grounded picture of mental function. Neuropsychological evaluation may be especially helpful when the clinician wants both differential diagnostic information and a profile of adaptive strengths and weaknesses or when neuropsychological testing is perceived as a less threatening diagnostic procedure by a patient who is resistant to other testing.

For many disorders, such as Alzheimer's disease, there are no reliable and valid in vivo laboratory tests, and these can be best diagnosed with the aid of neuropsychological profiles (Moss and Albert 1992). Other disorders, such as schizophrenia or schizophreniform psychoses associated with temporal lobe epilepsy, may present broadly overlapping and confusing pictures on clinical psychiatric and electroencephalographic evaluation that may be clarified by neuropsychological testing. For example, a distinctly focal and lateralized neuropsychological deficit (e.g., verbal memory deficit and mild word-finding difficulty in the absence of other neuropsychological deficits) is more characteristic of temporal lobe epilepsy than of schizophrenia, where the typical deficits are more widespread (Greenberg and Seidman 1992, Seidman et al. 1992).

The neuropsychologist frequently encounters many typical neuropsychiatric differential diagnostic questions, but the conceptual framework of the diagnostic process differs substantially from the organic versus functional dichotomy of earlier approaches. She or he may frame the question,

"Is there neuropsychological deficit consistent with focal or diffuse brain dysfunction?" (i.e., restricted executive deficits associated with frontal lobe dysfunction versus widespread impairment consistent with a dementing process). The neuropsychologist may ask, "Can this clinical symptom picture be correlated with test scores to identify a cluster of deficits characterizing a specific subtype of neurobehavioral syndrome?" (e.g., the high rate of forgetting found in Alzheimer's disease). Alternatively, the neuropsychologist may conclude that cognitive dysfunction is indeed present but may be static or not essential to the syndrome being evaluated (i.e., developmentally based language problem in a case of adult-onset traumatic brain injury).

## Characterization of Adaptive Strengths and Weaknesses and Treatment Planning

Perhaps the most clinically useful contribution of the neuropsychological examination compared with that of neurological or other neurodiagnostic evaluation is in providing a broad description of the patient's capacities and deficits and the impact of these resources and limitations on the patient's adaptation. This profile is essential for treatment planning, which may include rehabilitation efforts generally and psychotherapy specifically (Weinstein et al. 1991). In the context of a feedback session, a neuropsychological assessment can be a therapeutic process and intervention.

For example, although it may be clear that a patient has schizophrenia, the disorder is heterogeneous with respect to manifestations of brain dysfunction (Seidman 1983, 1990), and it is often helpful to identify the cognitive and behavioral approaches to support success in educational, vocational, and daily living settings (Liberman et al. 1982, Medalia et al. 2003, Velligan et al. 2000). Subtle learning disabilities may be identified in a student who is anxious and depressed about failures in school but is unable to pinpoint the cause. Referrals of this type are wide ranging; they include high school students who have a specific spelling disability, college students who are quite bright but are unable to learn required foreign languages, and graduate students in mathematics, science, or medicine who are failing subjects requiring visual–spatial analysis. All of these people may benefit from counseling about career choice, recommendations for compensatory learning strategies, and psychotherapy to deal with the impact on self-esteem, mastery, and identity (Seidman 1994).

Identification of a neurologically based cognitive deficit may also help a patient come to terms more realistically with narcissistic injuries associated with failure experiences. Some patients are greatly relieved when they learn that the basic origin of their problem is in their brain and not in their mind or "self." Others, of course, become depressed because they perceive damage to the brain as irremediable. Neuropsychological data can aid the family of a handicapped or vulnerable child (e.g., with schizophrenia or learning disability) by helping them develop realistic expectations for their child so that secondary emotional problems can be minimized and a maximally supportive environment can be constructed (Seidman 1994).

## Assessment of Change Over Time

A common concern in clinical psychiatry is the assessment of change over time. Changes in cognitive and behavioral functioning associated with aging and development (e.g., mild cognitive impairment, manifestations of dyslexia), progression of or deterioration associated with a disorder (e.g., Alzheimer's disease, epilepsy, schizophrenia, renal disease, diabetes), recovery (e.g., mild head injury/concussion, neurosurgery, abstinence from substance abuse), or treatments (e.g., medications, electroconvulsive therapy) have important clinical and functional implications. While

### Clinical Vignette 3

In this vignette, the issue of stability of neuropsychological functioning early in the course of schizophrenia and the problem of distinguishing capacity from performance are addressed. As is apparent in Table 32–5, there were dramatic fluctuations over a year when testing was done three times at approximately 6-month intervals. Moreover, changes were not equivalent across tasks; performance on certain tasks was fairly stable and performance on others changed markedly along with the exacerbations and remissions of the patient's psychosis.

The patient was an 18-year-old single man, right-handed, high school student when his behavior began to deteriorate at the beginning of his senior year. Six months later, he had a florid psychotic episode including acute catatonic symptoms resulting in a 7-month inpatient psychiatric hospitalization. The patient had a good premorbid history, was a better than average student without evidence of learning disabilities, and had no documented neurological problems. However, he was drinking alcohol and using some drugs at least once or twice weekly during the period before hospitalization. He had a normal EEG and a mildly abnormal CT scan including slightly enlarged lateral ventricles, unilateral visibility of the right temporal horn, and prominence of the anterior interhemispheric tissue.

The patient was initially given the neuropsychological battery 4 months (time 1) into his first hospitalization. This was after his acute catatonic symptoms had abated, and he was cooperative with the evaluation. Although he was not fully stable at that time, he was quite testable and had been receiving a stable dose of medication for about 6 weeks (haloperidol, 20 mg/day). His second evaluation (time 2) took place 7 months later, when as an outpatient he was in significant remission and had not been taking any medication for more than a month. The third evaluation (time 3) took place 6 months later, when he had been readmitted after decompensation and was once again taking haloperidol (20 mg/day). He remained quite engageable and cooperative throughout all three examinations, during which he was tested by the same examiner.

In reviewing Table 32–5 it is clear that the overall neuropsychological performance parallels the patient's change in clinical status, from initial acute psychosis (time 1) to outpatient remission (time 2) to exacerbation of the psychosis (time 3). Whereas he was quite impaired in some areas at time 1 (e.g., verbal fluency at the seventh percentile), his overall picture suggested average intellectual abilities and only mild to moderate attention and conceptual dysfunction.

At time 2, during the patient's best clinical state, he was dramatically improved in all areas previously assessed but showed significant impairment on the WCST, which had not been previously administered. At time 3, when most of the tests were re-administered, he declined most significantly on the Wechsler Adult Intelligence Scale, less so on other tasks, and remained impaired on the WCST.

This vignette illustrates that in patients early in the course of an illness in which significant clinical fluctuation may occur, a cross-sectional assessment may accurately measure current performance but not accurately measure capacity. A related issue demonstrated here is that repeated evaluations may help identify a person's underlying capacities or deficits. We assume that trait contributions (i.e., reliable enduring capacities or deficits) can best be determined by tasks that remain relatively constant, whereas state effects can best be seen on tests that vary most in association with exacerbation or remission of the illness. By both criteria, time 2 is the time most likely to yield trait and capacity data. At this point, the overall performance is relatively high and psychosis relatively minimal. At time 2, most of the patient's test scores are at their highest and thus the "signal to noise" ratio is probably the clearest. It is of interest that at this point in time the patient performed rather badly on the WCST (as he did 6 months later), had a lower Verbal IQ than Performance IQ, had some difficulties on visual confrontation naming and spelling, and had only a small right-handed dominance for motor speed. These deficits were apparent in the context of good overall performance, good motor tapping speed, excellent sustained attention, and only mild or marginally impaired conceptual dysfunction. The data suggest that the difficulties in time 2 (WCST, verbal skills) are due to trait deficits probably reflecting the subtle cerebral dysfunction of schizophrenia. It is not unusual for executive deficits, in particular, to be associated with brain abnormalities in schizophrenia (Goldberg et al. 1987, Seidman et al. 1994).

*Source:* Adapted from Seidman (1990).

there are important psychometric challenges to measuring clinically significant change (Barr 2002, Chelune 2003), monitoring cognitive status by repeated testing contributes to diagnostic and treatment decision making. Baseline testing early in the course of an illness such as schizophrenia or dementia can be compared with later evaluations to clarify the course of the disorder or to assess the impact of various interventions. At present, the considerable value of assessing change in cognition (particularly in clinical trials) is best exemplified by the recent National Institute of Mental Health initiative to encourage development of new pharmacological and psychosocial interventions for cognitive deficits in schizophrenia known as MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia; Green et al. 2004, Marder and Fenton 2004, Nuechterlein et al. 2004). Given that cognitive deficits are increasingly viewed as robust and reliable influences on functional outcome among individuals with schizophrenia, the need for a standard battery to index baseline cognitive deficits and treatment-related changes was recognized and spurred this novel initiative. The MATRICS battery comprises seven relatively independent cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition.

## The Flexible, Hypothesis-Testing Approach to Assessment

The assessment of the multiple functions that have been described can be performed with various degrees of depth and flexibility. For example, we have noted that a comprehensive examination may last from 3 to 8 hours, whereas a shortened screening examination may take only an hour or two, covering the same functions more superficially. Moreover, even briefer "bedside" evaluation may be most appropriate for patients who cannot be tested by conventional methods. The increasing prevalence of patients presenting with cognitive disorders (especially elderly patients), combined

**Table 32–5 Repeated Neuropsychological Assessment—Clinical Vignette 3**

| Function | Test Variable | Time | | |
|---|---|---|---|---|
| | | 1 | 2 | 3 |
| Intelligence | Wechsler Adult Intelligence Scale | 101 | 105 | 97 |
| | Verbal IQ | | | |
| | Performance IQ | 88 | 113 | 102 |
| | Full-scale IQ | 95 | 108 | 99 |
| | Verbal-performance difference | *V*>*P*+13 | *V*<P−*8* | *V*<*P*−*5* |
| Abstraction | Visual–verbal test | 24 | 12 | 10 |
| Attention (sustained visual) | Continuous Performance Test, omission% | 3.7 | 0 | |
| | Late errors (raw) | 7 | 2 | |
| | Omissions (raw) | 8 | 2 | |
| | Reaction time (s) | 0.47 | 0.44 | |
| Executive | Wisconsin Card categories | | 2 | 2 |
| | Perseverative response | | 36 | 26 |
| Language | Boston Naming (selected items) | 9/15 | 11/15 | 10/15 |
| | Spelling | 7/14 | 11/14 | 10/14 |
| | Verbal fluency (FAS), percentile | 7 | 84 | 80 |
| Motor | Finger-tapping speed | | | |
| | Right | 43.6 | 50.4 | 44.8 |
| | Left | 40.6 | 48.2 | 41.4 |
| | Asymmetry, R–L% difference | 6.9 | 4.1 | 7.6 |

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with resource limitations, may redefine the way in which neuropsychologists practice. Milberg (1996) noted that evaluations must be "efficient, designed to reflect current knowledge of brain function and the developmental characteristics of older patients." He suggested that specialized "microbatteries" should be developed to serve as brief, cognitively specific assessment instruments.

This approach has developed over the past decade, as managed care approaches have led practitioners to devise more efficient procedures. The neuropsychologist often begins with a series of short, focused tests and adds others' as questions need to be addressed in more detail. An example of this is in the assessment of ADHD. In this syndrome, the diagnosis is made by DSM symptoms and history. Yet the clinician may want to address the degree of formal attention or executive dysfunction that is present. This typically leads the examiner to evaluate vigilance (using a CPT), response inhibition (such as by use of the Stroop Test), and organizational skills (such as by use of the Rey–Osterrieth Complex Figure). Because learning disabilities such as reading or arithmetic disability overlap commonly with ADHD (Semrud-Clikeman et al. 1992) and contribute to executive dysfunctions (Seidman et al. 2001) and long-term school outcome (Faraone et al. 2001), it may also be important to add a number of tests to address the presence of co-occurring learning disability. Thus, the examiner may bring in measures of phonological processing (for assessment of dyslexia) (Willcutt et al. 2001) and/or measures of mathematical and spatial ability, to assess nonverbal learning disability (Weintraub and Mesulam 1983).

Neuropsychological evaluations differ not only in length but also in conceptual focus and in selection of the particular instruments that compose a battery of tests. In general, three batteries are used commonly throughout the US: the Halstead–Reitan Battery (Reitan and Wolfson 1993), the Luria–Nebraska Battery (Golden et al. 1980), and a flexible, hypothesis-testing approach typified by the Boston process neuropsychological approach (Goodglass and Kaplan 1979, Holmes-Bernstein and Waber 1990, Kaplan 1990, Milberg et al. 1996). The decision to use one or the other of these approaches depends to some extent on the training of the practitioner, the nature of the referral questions, and a number of other factors discussed in more detail elsewhere (Seidman and Toomey 1999).

Neuropsychological examination requires attention to the outcome of problem solving and, perhaps more important, to the process of performing tasks (Table 32–6).

**Table 32–6 Analyses Used by Clinicians to Evaluate Neuropsychological Data**

| |
|---|
| Level of performance relative to normative expectation |
| Level of performance compared with patient's own premorbid ability (e.g., variation across test scores) |
| Process of problem solving (e.g., constructing a figure in a piecemeal, disorganized strategy) |
| Pathognomonic signs or clusters of deficits (e.g., high rate of forgetting in Alzheimer's disease) |
| Comparison of the two sides of the body on sensory, motor, and perceptual performance |
| Identification of differential patterns of test scores associated with specific disease |

Reitan and Wolfson (1996) have articulated four types of analyses that clinicians use to evaluate neuropsychological data: (1) *level of performance* refers to the absolute deviation and dispersion of individual test scores compared with normative expectancies and within-patient (across different tests for the same subject) scatter of scores; (2) *left–right comparisons* are made on sensory, perceptual, and motor performances, presented to, or executed by, the two sides of the body; (3) *pathognomonic signs* are special features of extremely poor performance or specific clusters of test scores pointing clearly to the existence of discrete disorders; and (4) *differential patterns* are large arrays of test profiles that are predictive of disease or damage.

The Boston process neuropsychological approach is not a battery of identical items or tests routinely administered, such as the Halstead–Reitan and Luria–Nebraska batteries, but rather reflects a flexible, hypothesis-testing, qualitative approach to neurobehavioral syndrome analysis (Goldberg and Costa 1986). The Boston process approach involves a combination of qualitative and psychometric features that reflects the integration of the behavioral neurological orientation exemplified by Geschwind (1979) and Luria (1980) with the rigorous quantification of the American research tradition in psychology. Many neuropsychologists around the world use variations of the clinical, qualitative process approach in that they have a flexible approach to battery construction in the context of relatively shared neurobehavioral knowledge.

The process approach starts with a small set of core measures and then focuses in more specifically and intensively as hypotheses are developed. On the assumption that neurological dysfunction is reflected in psychological tests, the examiner looks for nonspecific indicators of impairment at the same time that she or he scans for highly selective deficits, or a configuration of deficits that allow the inference that a lateralized or localized brain dysfunction is present.

Some of the nonspecific (nonlocalizing) deficits found commonly are the following: impairment in conceptual thinking, slowing of ideational processes, perseveration, reduced scope of attention, stimulus boundedness (concretely being drawn to details at the expense of the big picture), and impairment of memory (Goodglass and Kaplan 1979). The set of lateralizing and localizing signs and deficits is too extensive to list completely here but broadly speaking includes disorders of functions previously addressed, such as many aspects of language, attention, visual–spatial performance, and motor ability.

The Boston approach, when oriented toward a relatively comprehensive examination, usually includes but is not limited to tests such as these: the Wechsler Adult Intelligence Scale-III (Wechsler 1997a), the Wechsler Memory Scale-III (Wechsler 1997b), the Rey–Osterrieth Complex Figure (Rey 1941, Osterrieth 1944), a test of visual-constructional and organizational ability, the Wisconsin Card Sorting Test (WCST; Grant and Berg 1948), which assesses various components of executive function such as the capacity to shift set (Goldberg 2001), the Boston Naming Test, a measure of visual confrontation naming ability, and the Category Test, a measure of abstraction ability. Certain tasks or brief batteries may be utilized for specific populations of patients, such as the Dementia Rating Scale

(Mattis 1988) or the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan 1983). Descriptions of many of these tests can be found in more comprehensive texts (Lezak et al. 2004).

The process approach utilizes the four basic principles of interpretive analysis described earlier, but emphasizes the way in which the patient attains a score and the preserved functions that the scores reflect rather than the achievement per se. For example, a dynamic serial picture of the process of problem solving is recorded while a patient is putting the block designs together (Figure 32–1). In this way, such behaviors as featural priority (emphasis on details), contextual priority (emphasis on the gestalt), and hemispatial priority (the tendency to work on one side of visual space) can be assessed. Right-hemisphere-damaged patients tend to work on the right side of space and use a detail-oriented strategy, whereas left-hemisphere-damaged patients tend to work in the reverse field and with the reverse strategy (Kaplan 1990, Milberg et al. 1996).

Kaplan (1990) suggested that qualitative data may better reflect an underlying brain lesion, because impairment may be demonstrated even if the final score is correct. This perspective is partially supported by a study by Heaton and collaborators (Adams and Brown 1986, Heaton et al. 1981).

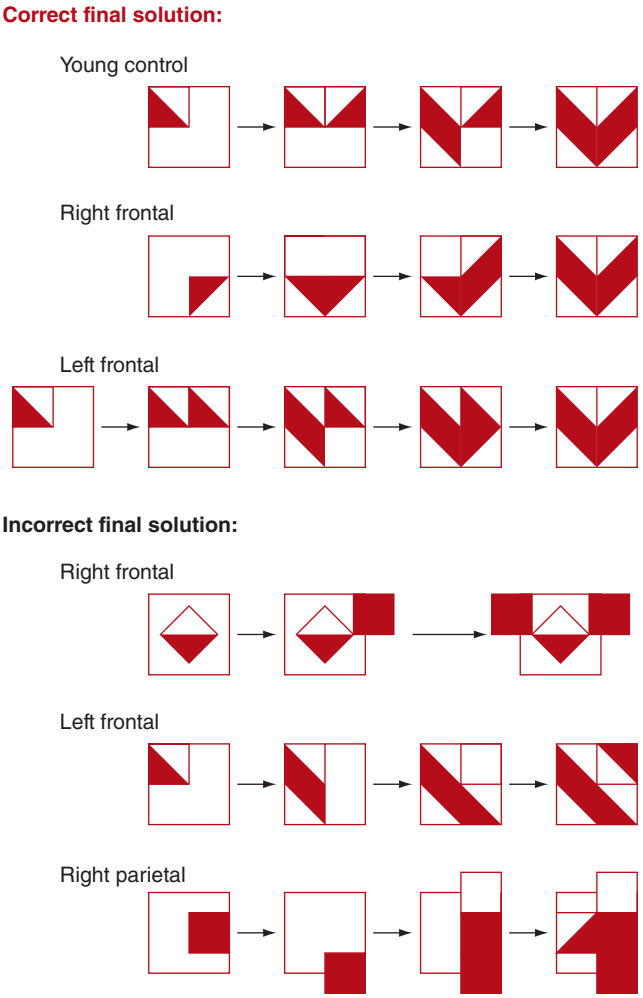



**Figure 32–1** *Block Design: feature versus context.*

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They demonstrated that clinicians who rated Halstead–Reitan battery results had better success in classifying brain damage than did a psychometric formula approach relying heavily on level of performance. The authors believed that the superiority of the clinicians was related to their ability to supplement test scores with consideration of the qualitative and configural features of their data. The process approach is consistent with this interpretation in that it is performed by highly trained clinicians rather than by technicians.

The process or flexible approach seems well suited to psychiatry because problem-solving approaches are less likely to be affected by motivational deficits than are level of performance and pathognomonic signs. Process variables are probably less susceptible to conscious faking, as a patient would be unlikely to know the neurological rules governing the process, and may also be less susceptible to practice and repetition effects, which can confound the interpretation of scores. Moreover, it is important to know "how," not just "if," a person solves a problem.

## Limitations of Reliability and Validity

Despite the obvious role of quantification in neuropsychological testing, interpretation of test data ultimately depends on the knowledge base, training, and skill of the clinician. Neuropsychological test scores are an indirect measure of the status of the brain, as contrasted with direct measures of structure by magnetic resonance imaging (MRI) or function by positron emission tomography (PET), functional MRI, or EEG. In a psychiatric setting, where problems of motivation, effort, cooperation, and stage of the illness are ubiquitous, analysis of neuropsychological data must go beyond the level of performance deficits because many studies have shown performance to be especially affected by functional (emotional) factors. Process analyses oriented to focal syndromes and focused on the relative efficiency of the two sides of the body and hemispace may enhance predictive validity.

The patient's clinical state may change, and repeated testing when the patient's clinical status is optimal often clarifies the nature of the diagnosis. Selective deficits found in the context of otherwise good performance when patients are tested in their best state can be considered most valid. Neuropsychologists must also take into account the effect of medication on neuropsychological function and distinguish medication effects from the patient's adaptive ability. Different medications are likely to produce different effects. For example, Trimble and Thompson (1986) have demonstrated that, for epileptic patients and normal subjects, anticonvulsants have negative effects on most measures of neuropsychological testing. On the other hand, Cassens and colleagues (1990) have demonstrated that (traditional) antipsychotic medications have negligible or mildly positive effects on most measures of neuropsychological testing in chronic schizophrenia, with the exception of a negative effect on motor performance. Spohn and Strauss (1989) have indicated that typical antipsychotic medications tend to improve attentional performance, such as on versions of the CPT. The newer atypical antipsychotics, generated a substantial amount of initial enthusiasm as "cognitive enhancers" (Harvey and Keefe 2001), but their putative-increased efficacy compared to first generation "typical" antipsychotics is now considered to be more modest (Mishara and Goldberg 2004).

## Neurophysiological Assessment

A variety of techniques are now available that can provide more direct assessments of brain function in psychiatric patients. These include not only neuroimaging techniques (PET scans and functional MRI), but also electrophysiologic measures, such as the EEG and evoked potentials or ERPs. Electrophysiologic measures have the advantage of being economical and noninvasive, and allow continuous monitoring of brain electrical activity with a temporal resolution that surpasses that of neuroimaging measures. The EEG has traditionally been used in psychiatry to screen for brain disorders. In a conventional clinical EEG, a highly trained reader uses visual inspection of brain waves recorded from scalp electrodes. The presence of epileptiform discharges, spikes, or generalized slowing of brain electrical activity is associated with known central nervous system pathology. In patients who have a history of head trauma or where epilepsy is suspected, a clinical EEG should be done to rule out specific neurological disorders (see Table 32–7). When evaluating for epilepsy, several EEGs may be necessary for accurate results because epileptiform activity is not consistently present (Boutros 1992). The EEG can also play an important role in the diagnosis of dementia, delirium, and other cognitive disorders. Generalized EEG slowing in Alzheimer's dementia is correlated with the degree of cognitive impairment and with decreased regional cerebral blood flow (Hughes and John 1999). In elderly psychiatric patients, a clinical EEG is of value for distinguishing dementia and pseudodementia associated with depression. This is of importance for treatment selection because EEG abnormality in elderly patients is negatively associated with clinical response to antidepressants (Boutros 1992).

Clinical Vignette 4

In this vignette, the patient is a 30-year-old man with a 13-year history of schizophrenia. This case illustrates the beneficial clinical effects of one of the "atypical" antipsychotic medications, clozaril, on neuropsychological function, suggesting that certain components of schizophrenic "dementia" are reversible in some patients (Buchanan et al. 1994).

This patient's first episode of psychosis occurred in high school shortly before the end of the junior year. At age 17 years, he was admitted to the hospital in an acutely agitated state, hallucinating and suicidal. After some remission was achieved with 40 mg/day of haloperidol, the patient was given a psychodiagnostic test battery that included a Wechsler Adult Intelligence Scale. At that time, he had a Verbal IQ of 121, a Performance IQ of 111, and a Full-Scale IQ of 121.

During the next 5 years, the patient was hospitalized 10 times for a total of 27 months of hospitalization. On one of those occasions (4 years after initial testing), he was re-administered the Wechsler Adult Intelligence Scale—Revised, receiving a Verbal IQ of 109 (a 17-point drop from previous testing), a Performance IQ of 112, and a Full-Scale IQ of 111. Although the patient was not subsequently hospitalized, he remained in a chronically disorganized phase of illness until his medication was changed from typical neuroleptics to clozapine in the 12th year of the illness. Within months of the start of this treatment, the patient's illness diminished significantly, leaving residual paranoid delusions and only episodic, mild disorganization. The patient demonstrated a remarkable increase in insight and sociability.

Shortly before clozaril treatment began, the patient had another neuropsychological evaluation. At that point, his IQ estimate was only 83, and he was grossly impaired on an auditory CPT (15 of 30 correct), on the WCST (0 categories sorted, 125 perseverative responses), and on the Wechsler Memory Scale—Revised, Logical Memories Immediate Recall (5 of 50 bits recalled). He had mild olfactory deficits (31 of 40) on the University of Pennsylvania Smell Identification Test (UPSIT) (Doty 1984). Two-and-a-half years later, after 12 months of clozaril treatment, the patient showed dramatic improvement in neuropsychological functions. His IQ estimate was now 113, relatively close to his premorbid range. At this point, he performed within normal limits on the auditory CPT (29 of 30), logical memories (31 of 50), and the UPSIT (37 of 40). Although his performance on the WCST was significantly improved from the previous evaluation, he remained severely compromised on this task (3 categories sorted, 68 perseverative responses). Thus, in this case, neuropsychological and symptomatic improvements were strongly associated with the introduction of a new medication. Illustrations relevant to this vignette are presented in Figures 32–2 through 32–4.



**Figure 32–2** *Clock drawing by a man with schizophrenia. Note the excessive detail and elaboration of clock features; this is unusual among healthy or brain-injured individuals. Nonetheless, the patient set the clock to read "10 after 11" correctly (Clinical Vignette 4).*

**Table 32–7 Indications for Clinical EEG Assessment of Psychiatric Patients**

1. Rule out specific neurological disorders
2. History of head trauma or suspicion of epilepsy
3. Differentiating pseudodementia secondary to depression and true dementia
4. First presentation of psychosis
5. Pre- and post electroconvulsive therapy
6. Evaluating sleep disorders

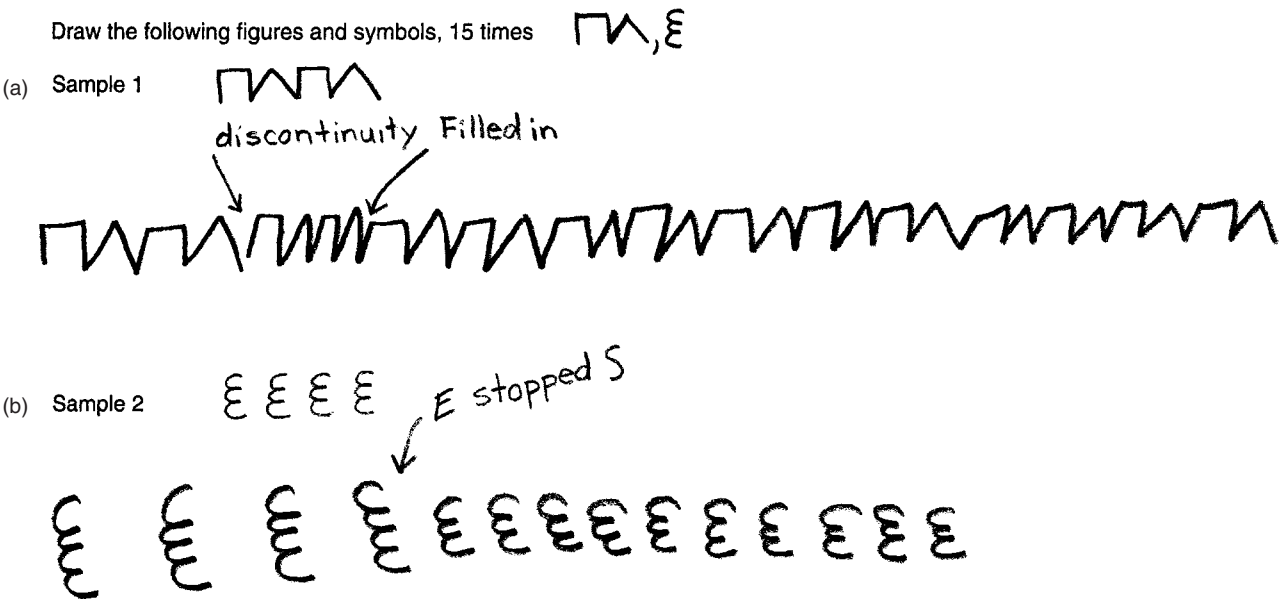



**Figure 32–3** *Graphic sequences. (a) The subject has trouble with smooth continuity in drawing an open square and triangle because of concretely assuming that only two pairs of figures should be drawn attached. The subject later fills in the missing figures. (b) The subject draws an extra loop on the first four reproductions of multiple loops. Perseveration often reflects dysfunction in attention and inhibitory systems, which are relatively common impairments in schizophrenia (Clinical Vignette 4).*

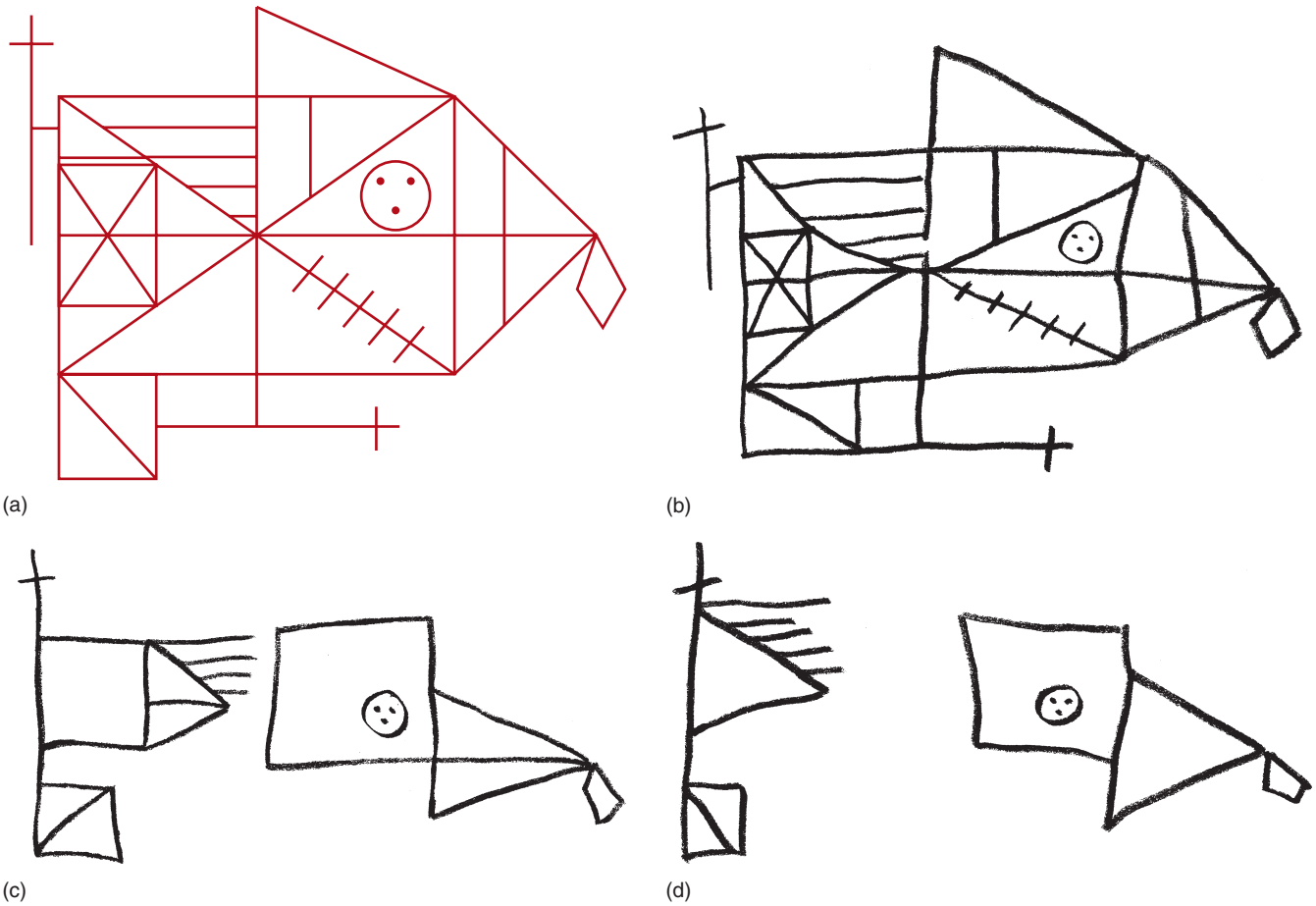



**Figure 32–4** *(a) The Rey–Osterrieth Complex Figure. (b) Patient copy of the Rey–Osterrieth Complex Figure. Although an accurate final reproduction, the patient's approach was segmented and marked by a piecemeal focus on small details to "build up" the whole figure. (c) Immediate "incidental" recall reproduction—the subject was not told to memorize the figure for later retrieval. This is a remarkably fragmented reconstruction in which the patient remembers many of the details in rough proximity to their appropriate place but is unable to create a whole (gestalt). (d) On 20-min delayed recall, the patient lost more information, retaining only individual fragments of the original design. These data were produced by a man with schizophrenia (Clinical Vignette 4), despite substantial clinical and neuropsychological improvement after treatment with clozapine.*

Patients who experience their first psychotic episode are also candidates for a clinical EEG because brain lesions and seizure disorders, such as temporal lobe epilepsy, can cause psychotic symptoms that are clinically indistinguishable from functional psychoses. For instance, in a case report (Miyaoka et al. 2001), a 51-year-old woman with no history of psychosis or epilepsy had an abrupt onset of psychosis with auditory and somatic hallucinations, delusions, and loosening of associations. A clinical EEG revealed epileptiform discharges with diffuse sharp and slow waves, but CT and MRI scans were normal. The patient's epileptiform discharges disappeared following treatment with sodium valproate and she showed complete clinical remission after EEG improvement. This case illustrates how clinical EEG can have an impact on both diagnosis and treatment selection in patients having a psychotic disorder. EEG recordings before, during, and after electroconvulsive therapy (ECT) for depression also have clinical relevance (Hughes 1996, Small 1999). Patients with pretreatment EEG abnormalities may respond less well to ECT (Drake and Shy 1989), and changes in EEG after ECT generally accompany clinical improvement (Sackeim et al. 1996). Reviews of clinical EEG findings in childhood and adult psychiatric disorders show that 30 to 60% of referrals have abnormal EEGs (Hughes 1996, Small 1999), which underscores the importance of clinical EEG evaluations in psychiatry.

One of the limitations of routine clinical EEG is that it is dependent on the trained eye of the reader and is therefore subject to human error and may miss subtle abnormalities in the EEG tracing. Digital recording and processing of EEG led to the development of more quantitative approaches to EEG assessment. In quantitative EEG (qEEG), a fast Fourier transform is used to quantify the amount of activity (power) at each frequency in the EEG waveform and this power spectrum is typically divided into four frequency bands—delta, theta, alpha, and beta. Quantitative EEG provides objective, quantitative measures not available by routine visual assessments. A joint report by the American Academy of Neurology and the American Clinical Neurophysiology Society concluded that qEEG techniques should be used "…only as an adjunct to and in conjunction with traditional EEG interpretation." (Nuwer 1997, p. 284). Although qEEG has received considerable application in psychiatric research, its use in clinical evaluations has been limited. There is general agreement that qEEG can be useful for differential diagnosis of dementia and depression, and in the diagnosis of Alzheimer's disease (Hughes and John 1999, Rodin 1999). Quantitative EEG can also be of value in screening for possible spikes and seizures in long-term monitoring, for example during sleep or ambulatory EEG recording (Nuwer 1997), and in monitoring the effects of drug treatment on brain activity (Itil 1982). There have also been attempts to develop qEEG measures that could be used as adjuncts for psychiatric diagnosis (John et al. 1988), but additional clinical research is needed to demonstrate its clinical utility in this context (Nuwer 1997, Rodin 1999). In an extensive review of the qEEG findings for psychiatric disorders, Hughes and John (1999) point to the problem of heterogeneity of psychiatric disorders such as schizophrenia, which may account for some conflicting qEEG findings. One of the potential uses of qEEG could be identifying more homogeneous subtypes that share a common pathophysiology. For instance, Sponheim and colleagues (2000) found that a subtype of schizophrenia with a specific qEEG abnormality frequently reported for this disorder, that is, augmented low-frequency and diminished alpha-band activity, showed structural brain deficits and ocular motor dysfunctions not seen in patients without this qEEG abnormality. Techniques for topographic mapping of qEEG measures, using current source density (Tenke and Kayser 2005) or Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al. 1994) analyses, are now being applied in psychiatric research and may lead to clinical applications for improving diagnosis and treatment selection.

Brain potentials evoked by auditory stimuli (e.g., clicks or tones) have been used in both clinical and research contexts in psychiatry. Brain stem evoked potentials (BSEPs) refer to seven positive potentials evoked during the first 12 ms after hearing a click. BSEPs have proven useful for assessment of hearing in infants and uncooperative patients, and in the assessment of brainstem lesions and multiple sclerosis (Celesia and Brigell 1999). A later event-related P3 or P300 potential, typically recorded during an "oddball" target detection task, refers to a positive potential that peaks 300 to 500 ms after onset of an infrequent target tone. The strongest case for the clinical utility of the P3 potential is in aging and dementia (Polich 1999). Longer P3 latency distinguishes patients with dementia from those with pseudodementia secondary to depression, and patients with Alzheimer's disease from healthy subjects (Ford et al. 1997, Frodl et al. 2002, Polich and Herbst 2000). Although P3 provides a useful index of cognitive efficiency, it has less value for the differential diagnosis of psychiatric disorders such as schizophrenia because it lacks specificity. Earlier negative potentials, in particular N1 or N2, are reduced in schizophrenia, but not in depressed patients or in epilepsy patients and may therefore have greater specificity (Bruder et al. 1998, Ford et al. 2001, Kayser et al. 2001). One of the main obstacles to clinical application of ERPs as well as qEEG in psychiatric diagnosis has been the lack of standardized methods and normative data (Polich 1999), but some progress is now being made in this regard (Thatcher et al. 2003).

A new direction for potential clinical application of neurophysiological measures and neuropsychological tests in psychiatry is the identification of patients within a given diagnostic category who have a specific physiologic or cognitive abnormality and who may respond best to a specific form of treatment (Bruder et al. 1999). There are reports of differences between depressed patients who respond to an antidepressant and those who do not in neurocognitive function (Dunkin et al. 2000, Taylor et al. 2006), qEEG measures (Bruder et al. 2001, Pizzagalli et al. 2001), P3 latency (Alexopoulos et al. 1997), and loudness dependency of auditory evoked potentials (Mulert et al. 2007). This suggests that further research be directed to evaluating the potential utility of these measures as clinical aids for selecting treatments for individual patients. As normative data are acquired and standardized methods implemented, the use of quantitative EEG and ERP measures is likely to increasingly complement the clinical neuropsychological exam.

## Summary

This chapter contains a relatively broad overview of the role of neuropsychological testing and neurophysiological

assessment in psychiatric practice. The increased recognition that many psychiatric syndromes (e.g., schizophrenia, ADHD) can be understood as neuropsychological disorders requires greater attention to the functional capacities and deficits of the affected individuals. Moreover, the increasing prevalence of disorders of cognitive functioning, especially in the elderly, is leading to an increased need for assessment. Neuropsychological testing can be helpful in diagnosis, treatment planning, and assessing change over time, such as in response to interventions (e.g., medications). Neuropsychological assessment can include both cognitive and personality measures, so that the patient's cognitive problems can be understood psychodynamically in terms of meaning, experience, conflict, and adaptive capacity (Seidman 1994). The flexible use of assessment, at the bedside or in extended evaluation, may be of great benefit to both patient and clinician. Neurophysiological assessment can complement neuropsychological testing by allowing a more direct measure of brain functioning, by providing real-time measures of information processing, and by measuring cognition at a more elemental level.

One final note regarding the use of neuropsychological tests in research: neuropsychological tests have many applications in neuropsychiatric research, although caution must be exercised in drawing inferences about brain localization from individual cognitive deficits (Keefe 1995). Our ability to infer the neuroanatomy of any neuropsychiatric disorder from cross-sectional neurocognitive studies is limited by many factors, such as variations in clinical stage or state, the effects of medications, and the interpretive difficulties posed by developmental alterations in brain organization found in many psychiatric illnesses (Goldberg and Seidman 1991). Of course, neuropsychological tests need not be evaluated in isolation, but may benefit from converging evidence in the neurophysiologic domain.

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CHAPTER

# 33 Brain Imaging in Psychiatry

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## Introduction

The development of noninvasive techniques for assessing brain structure, function, and chemistry has progressed rapidly, since the innovation of computed tomography in the early 1970s through the current generation of imaging methods. We now use a number of neuroimaging modalities in the conduct of psychiatric research, and can state with little fear of contradiction that no other method of neuroscientific investigation has done more to advance our knowledge of the pathophysiology of mental disorders than has *in vivo* neuroimaging. Moreover, it is now clear that without a practical understanding of commonly employed imaging methods, the psychiatrist cannot stay abreast of our professional literature. This chapter will review common methods of neuroimaging, equipping the clinician with the practical knowledge of imaging techniques needed to digest related scientific articles. We will not review specific imaging-based research findings, leaving that to those chapters addressing the pathophysiology of specific psychiatric disorders.

Beyond the use of imaging in research, we have recently seen the expansion of neuroimaging into clinical psychiatry beyond the traditional role of aiding in the differential diagnosis of neuropsychiatric conditions to rule out a general medical cause (e.g., brain tumor) for altered mental status ("rule out organic"). We will discuss these emerging clinical applications, along with speculations about the future of imaging in clinical psychiatry.

Contemporary neuroimaging modalities can be roughly divided into either structural modalities or functional modalities. Structural modalities are designed to produce anatomic images of the body, and include computed tomography (CT) and magnetic resonance imaging (MRI). Functional modalities produce images that reflect some aspect of physiologic function, and include positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS). We may subdivide function imaging into methods that measure regional metabolism or blood flow, versus those that probe specific neurochemical pathways, that is, *molecular imaging*.

## Structural Imaging Modalities

### CT

Standard X-ray imaging has been used as a medical diagnostic tool for over a century. X-rays are differentially attenuated, depending on the material through which they pass (higher attenuation in dense material such as bone and lower attenuation in less dense material such as air and fluid). Radiological procedures use different detection systems to quantitate attenuation. Standard X-ray procedures involve X-ray generators producing X-rays that pass in a unidirectional manner through tissue and then impact on X-ray sensitive film. CT, developed in the 1970s, is simply the use of standard X-rays with newer technology for acquisition and image reconstruction (Gibby and Zimmerman 1992). CT scanners utilize multiple X-ray generators and detectors (scintillation crystals) arranged in a ring-like fashion; these detectors send information regarding attenuation to a computer. The body part of interest is placed inside this ring and X-rays pass through the tissue in a multidirectional manner. The area of interest is imaged in a slab-wise or slice-wise manner (thus the term "tomography") as it progresses through the CT scanner, the data from which is integrated and processed to produce a completed CT image (see Figure 33–1).

As is the case for many standard X-ray procedures, the use of contrast agents with CT can increase the likelihood of identifying a lesion that may otherwise be missed or provide additional information about the lesion (Osborn 1994). Radiopaque contrast material introduced intravenously allows visualization of lesions that compromise the integrity of the blood-brain barrier (e.g., cerebrovascular accident (CVA), tumor, inflammation) because the contrast leaks from the intravascular space. Contrast media which enhance

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the visibility of pathology by CT are typically iodine-based and may be either ionic or nonionic. Ionic contrast is less expensive than nonionic contrast, but is associated with a greater risk of side effects (Gibby and Zimmerman 1992). In addition to allergic and idiosyncratic reactions (Shehadi 1982), chemotoxicity may present as impaired renal function or even renal failure, with important main risk factors being preexisting renal insufficiency, diabetes mellitus, volume depletion, nephrotoxic drug use, and preprocedural hemodynamic instability (McCullough et al. 2006). In the brain, chemotoxic reactions manifest as seizures. Such reactions occur in approximately 1 in every 10,000 cases but may develop in 1–10% of cases in which gross disruption of the blood-brain barrier is present (Witten et al. 1973). Nonionic contrast is less likely to cause idiosyncratic or chemotoxic reactions (Lasser et al. 1997), but the cost remains higher than that of ionic contrast (White and Halden 1986). The clinician might bear in mind that U.S. plaintiff's attorneys have taken a recent interest in alleged reactions to radiologic or MRI contrast materials.

### Advantages and Limitations of CT

1. CT offers excellent spatial resolution (<1 mm) and is effective at distinguishing tissues with markedly different X-ray attenuation properties (e.g., bone vs. soft tissue vs. fluid vs. gas).
2. CT is useful for the detection of acute bleeding (less than 24–72 h old) but less helpful in subacute bleeding (more than 72 h old) and in severely anemic patients (hemoglobin below 10 g/dl), as in both cases the hemorrhage may tend toward becoming isodense with surrounding gray matter (Osborn 1994). In addition, CT is an excellent modality for imaging bone. CT is the imaging modality of choice for acute trauma or when an acute bleed or ischemia is suspected.
3. CT is not helpful in visualizing subtle white matter lesions due to CT's poor ability to distinguish between the X-ray attenuation properties of different soft tissue densities.
4. CT uses ionizing radiation and thus is strongly contraindicated in pregnancy. Women of childbearing potential should undergo a pregnancy screen prior to having a CT scan.
5. Patient anxiety is usually less during a CT scan than during an MRI scan because the scanning environment is traditionally more open, quieter, and scanning time is brief.
6. CT is best for patients with ferro-metallic implants (e.g., foreign bodies, some aneurysm clips, pacemakers, etc.) as MRI is contraindicated in this patient population.

## MRI

MRI does not use X-rays but instead exploits the magnetic properties of hydrogen atoms in water molecules to construct a representation of tissue (Horowitz 1992). An MRI scanner is comprised of coil (or antenna) detectors arranged in a ring-like fashion. Initially during an MRI scanning session, radiofrequency irradiation is produced by the scanner and directed at the body. This results in excitation of hydrogen atom nuclei in body tissue. Next the radiofrequency irradiation source is turned off, resulting in relaxation of the hydrogen atom nuclei. As the hydrogen

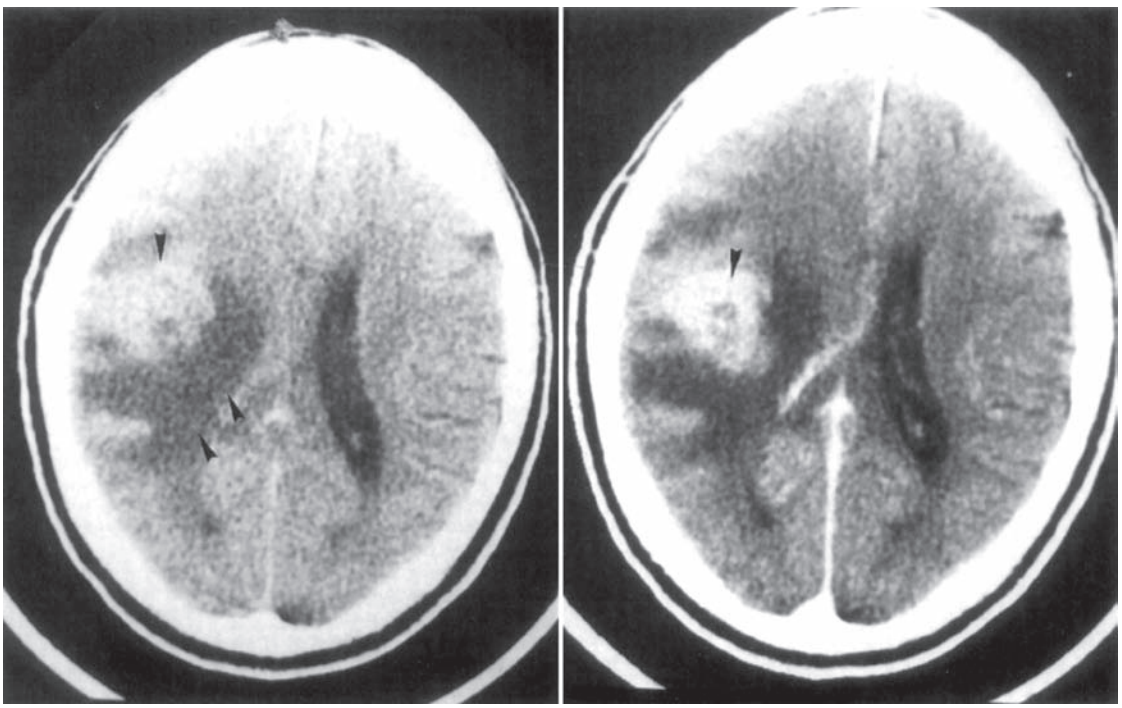


**Figure 33–1** *Left panel: Axial CT in a patient with a high-grade glioma demonstrating abnormal increased density with hemorrhage and/or calcification (arrow) with adjacent edema (arrows) resulting in mass effect on the cortex and lateral ventricle. Right panel: Following the administration of intravenous contrast there is abnormal contrast enhancement (arrow).* *© Mosby*

atom nuclei relax, they give off energy that is detected by MRI scanner. Different components of the relaxation process exist and occur at different rates (called T1 and T2) in different tissues. Specific imaging parameters (T1-weighted versus T2-weighted) are selected according to the clinical circumstances (see Figure 33–2). T1-weighted images are typically used for optimal visualization of normal anatomy, and depict gray matter as dark and white matter as light. T2-weighted images (also referred to as proton density images) are typically used to detect areas of pathology. In T2-weighted images blood appears dark (useful for detecting hemorrhaging) because of the paramagnetic properties of iron in hemoglobin while water appears light (useful for detecting regions with increased water content such as tumors or edema).

Gadolinium is used as the contrast medium for MRI studies because of its paramagnetic properties (Bradley et al. 1993). Like CT contrast, it is introduced intravascularly. Once injected, gadolinium alters the local magnetic environment (i.e., tissue relaxation times). The use of MRI contrast highlights vascular structures and aids in the detection of pathology in areas where blood vessel walls or the blood-brain barrier is compromised. Contrast is also used in *magnetic resonance* angiography (MRA) which creates detailed vascular images without the need for arterial catheterization. Gadolinium causes fewer adverse reactions than does CT contrast, though the role of gadolinium exposure in the evolution of certain severe disorders (e.g., nephrogenic systemic fibrosis) remains under investigation, particularly (as with radiologic contrast media) in individuals with pre-existing renal dysfunction.

Variations in pulse sequence and other parameters form the basis for the variety of available MRI sequences and applications, only a few of which will be discussed herein. MRI can detect the movement of water molecules within tissues, and forms the basis for *diffusion weighted imaging* (DWI) and *diffusion tensor imaging* (DTI). DWI is well suited to detecting recent infarction in the brain, and may be used to rule out such strokes in patients with new mental status changes (Albers 1998). DTI is of great interest to psychiatric research because it allows remarkably detailed assessments of white matter tracts, extending researchers' ability to test hypotheses concerning circuit abnormalities (Mori and Zhang 2006). DTI is based upon the observation that, while water diffuses equally in all directions in a Brownian fashion in gray matter, in axon-rich tissues, that is, major white matter tracts, the predominant direction(s) of water diffusion is defined by the direction in which axons course. DTI therefore indicates the vector and degree of restriction (anisotropy) of water diffusion within white matter-rich tissues, hence is a measure of structural integrity and directionality. Further refinements have allowed imaging scientists to create visually brilliant reconstructions of white matter tracts known as *tractography* (Figure 33–3).

Virtually all structural brain imaging research utilizes MRI rather than CT due to the superior spatial resolution of MRI. The most straightforward use of MRI in structural brain imaging research is the use of specific structural MRI acquisition parameters to produce morphometric quality structural images that may be used to precisely calculate the volumes of brain structures in individuals.

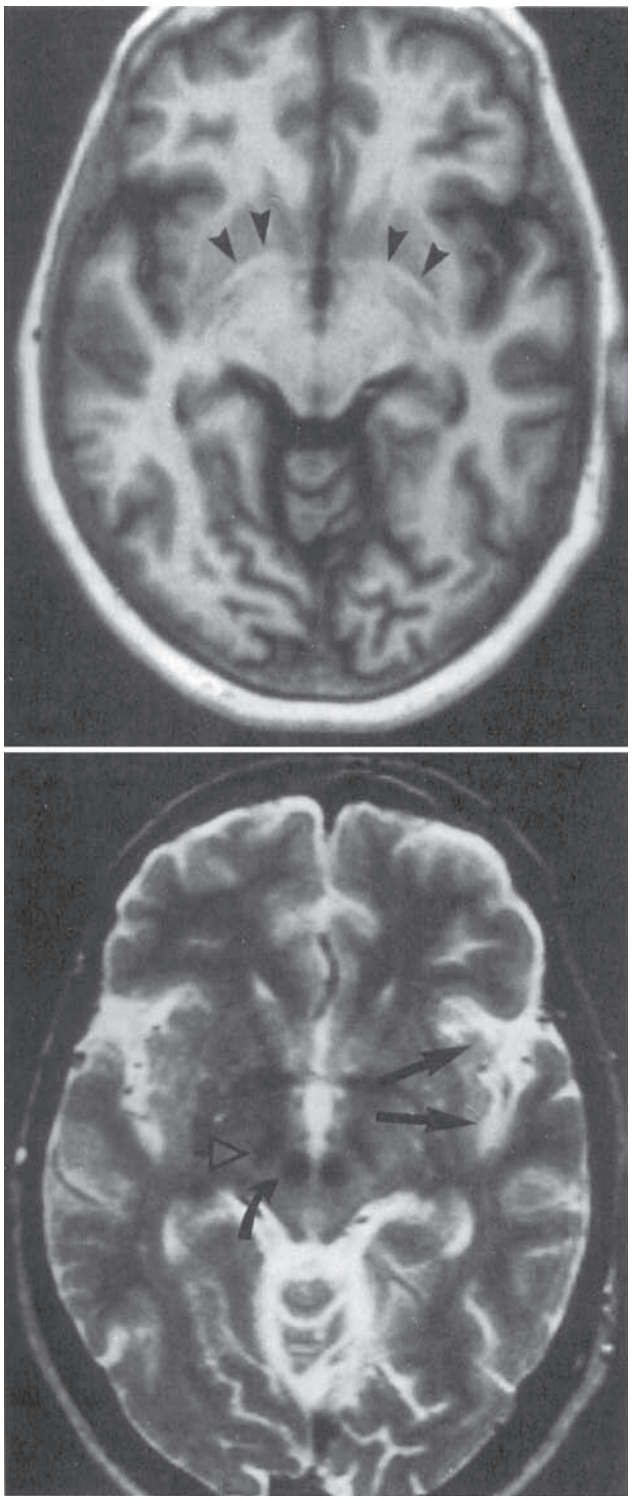


**Figure 33–2** *Axial scans through the bicommissural plane. Upper panel: T1-weighted MR image. Anterior commissure (arrowheads). Lower panel: T2-weighted MR image. The paramagnetic material in the red nucleus (curved arrow) makes it appear larger and better defined. The substantia nigra (open arrow) is now visible. The cerebrospinal fluid in the sylvian tissue (arrows) has become bright (high signal).* *© Williams & Wilkins*

There is a recent trend toward MRI machines that generate field strengths higher than the 1.5 Tesla fields typically seen in clinical MRI labs. These scanners result in improved signal-to-noise ratios, thus improving the sensitivity and

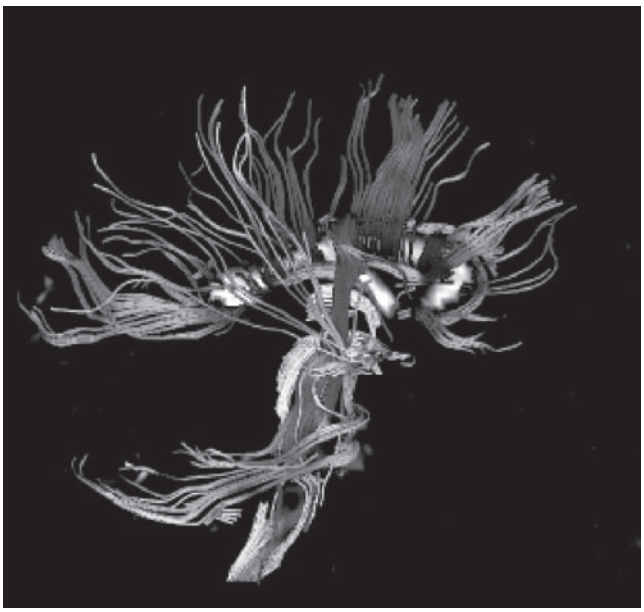


**Figure 33–3** *Diffusion tensor tractography image demonstrating major white matter tracts in the human brain. © Wallace-Kettering Neuroscience Institute (See Color Plate IX)*

detail of which MRI is capable. This is generally true for all MRI sequences and applications.

### Advantages and Limitations of MRI

1. MRI provides excellent spatial resolution and superior soft-tissue contrast in comparison to CT (i.e., more useful for the visualization of gray-white matter edges and white matter lesions).
2. MRI is superior for surveying the posterior fossa and brainstem.
3. Fresh blood from an acute bleed (less than 48–72 hr) is not easily distinguished from gray matter, although this has certainly improved with new MR methods. Subacute bleeding (greater than 48–72 hr) or chronic hematomas are easily identified with MRI.
4. MRI does not use ionizing radiation, and so if an imaging study is unavoidable in pregnancy, it is preferable to CT.
5. For the same reason as #4 above, MRI is preferred when a patient requires several serial imaging studies in a short period of time.
6. MRI is contraindicated in patients with ferro-metallic implants because such objects can cause artifacts, shift position or absorb heat within the magnetic field causing burn injuries, and, in the case of mechanical devices such as pacemakers, malfunction within the magnetic field.
7. As many as 10% of patients undergoing MRI scanning experience significant anxiety during the imaging session, although only about 1% of patients are unable to complete an MRI study as a result of clasustrophobia (Eshed et al. 2007). This is likely due to a number of factors, including the deep, tunnel-like architecture and noisiness of MRI scanners. Pretreatment of potentially anxious patients with benzodiazepines or other sedatives/hypnotics before undergoing MRI may be helpful in these situations.

### CT versus MRI

1. CT is still the modality of choice for patients with suspected acute bleeds or acute trauma.
2. MRI is superior to CT for the differentiation of white from gray matter and the identification of white matter lesions.
3. MRI is superior to CT for the detection of posterior fossa and brainstem pathology.
4. CT is recommended if MRI is contraindicated (i.e., paramagnetic protheses; inability to tolerate scanner time, noise, or confinement).
5. MRI is recommended if radiation exposure is contraindicated (i.e., young children or women of childbearing potential).

## Functional Imaging Modalities

### PET

PET uses positron-emitting isotopes to quantitate various measures of brain function (e.g., cerebral blood flow, cerebral glucose metabolism, neuroreceptor characterization, etc.) (Cherry and Phelps 1996). As the name indicates, these unstable isotopes emit positrons which then soon collide with the electrons of surrounding atoms. The annihilation event that occurs after a positron collides with an electron produces gamma radiation. These gamma rays are what PET scanners detect. A PET scanner (see Figure 33–4 consists of a ring of scintillation detectors designed to detect gamma rays. Opposing detectors in the ring are coupled to form a coincidence circuit. Following a positron–electron annihilation event, the resulting gamma rays project from one another at 180°. When events are detected by opposing detectors, an annihilation event is presumed to have occurred at some point along the imaginary line connecting the opposing detectors. Lines of response, which localize the annihilation event in tissue, are produced from these coincidence events. Computers sum all of the coincidence events, localize them in tissue, and then create cross-sectional images (tomographs).

One cannot speak generically of a "PET scan"; the particular radioactive tracer used in concert with scanning defines the applications of the test. Different positron-emitting nuclides ($^{18}F$, $^{15}O$, $^{11}C$, etc.) can be coupled with a number of molecules to produce tracers that are used to quantitate various measures of brain function, and each radioisotope has a characteristic half-life ($^{18}F \approx 110$ min; $^{15}O \approx 2$ min, $^{11}C \approx 20$ min). For example, $^{18}F$-fluoro-deoxy-glucose (FDG) is used to measure cerebral glucose metabolism (Reivich et al. 1997). FDG and glucose are taken up by cells in the same way and this uptake is proportional to the metabolic demands of the cell. Once inside the cell, both FDG and glucose begin the same metabolic pathway. At a certain point in this pathway, however, FDG is unable to continue and becomes trapped in the cell whereas glucose is able to continue. This trapped FDG, labeled with $^{18}F$ so that it can be detected by the PET scanner, serves as a marker of metabolic activity (see Figure 33–5). This is relevant because cerebral glucose metabolism is tightly coupled with neuronal activity.

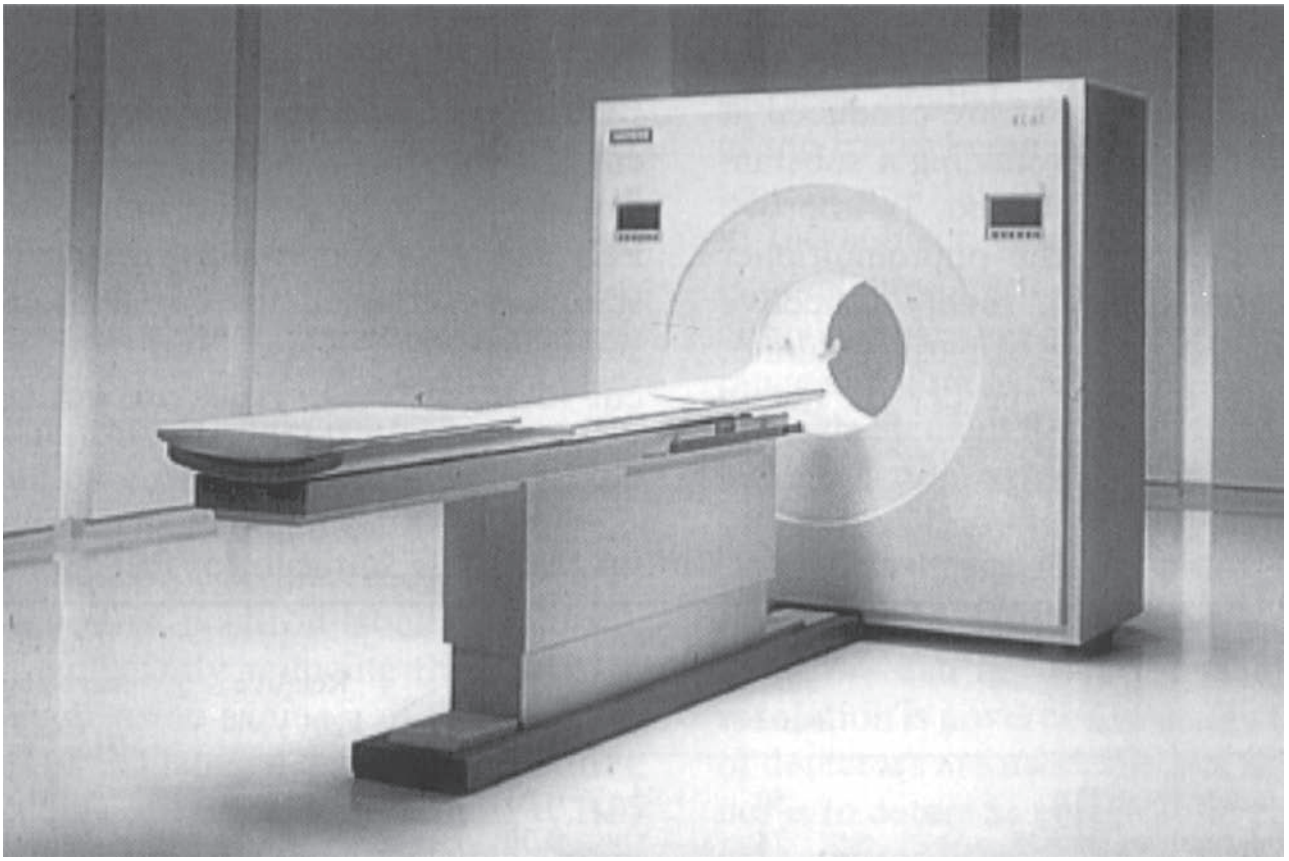


**Figure 33–4** *An ECAT EXTRACT HR PET scanner. © Academic Press*

In terms of the actual protocol, this means that a clinical or research subject must engage in the desired mental activity (such as a specific cognitive task, rest, etc.) for about 35 min during which the above uptake process occurs. Only after this point has been reached will the subject move to the scanner for his scan. Thus, FDG PET is ideal for examining regional glucose metabolism during a mental process that can be done fairly continuously over such a magnitude of time. This suits some experiments much better than others.

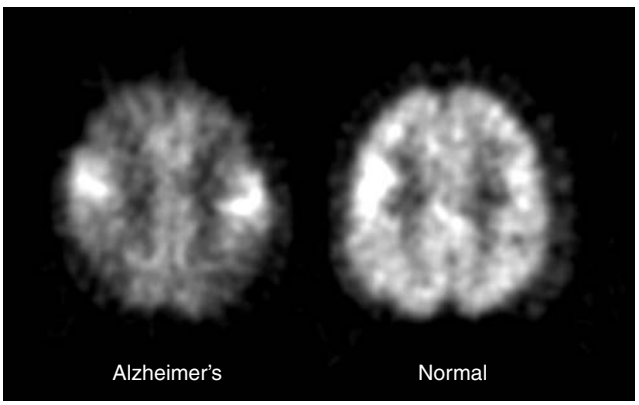



**Figure 33–5** *FDG-PET images in the axial plane. FDG-PET measures cerebral glucose metabolism which is tightly coupled to neuronal activity. The FDG-PET image of a normal volunteer (right) shows uniform metabolism throughout the cortex. The image of the patient with Alzheimer's disease (left) shows the characteristic pattern of decreased metabolism throughout the cortex except in the somatosensory cortex, which is preserved (sometimes referred to as the "ear-muff sign").*

The isotope $^{15}O$, either inhaled as $^{15}O$-carbon dioxide or injected as $^{15}O$-water or $^{15}O$-butanol in PET studies to measure cerebral blood flow, has a half-life of approximately 2 min. This means that it is washed out of the body in only 10 min (half-life times 5). Thus, in a 2-hr period as many as 12 separate scanning sessions of 1–2 min each can be completed in a single individual. Researchers take advantage of this ability to perform multiple scans within minutes of one another by having subjects perform different tasks (usually including a control condition) during separate scans. Afterwards differences in cerebral blood flow between the scans can be determined; these differences indicate which brain regions were activated or deactivated during each task when compared to the control condition (see Figure 33–6).

Interpretation of clinical PET scans is usually done in the manner traditionally applied to radiologic and MRI images, in which a trained and experienced nuclear medicine physician determines the relative normalcy of the image based on visual inspection. Research scans, on the other hand, are analyzed and interpreted using statistical methods. This may first require the superimposition of the PET image onto a more anatomically precise MRI structural image ("co-registration"). Statistical methods may involve a pixel-by-pixel comparison of an averaged PET brain for the experimental subjects vs. those in the control group (*statistical parametric mapping*, or SPM). In other cases, analysis may require that researchers may do laborious

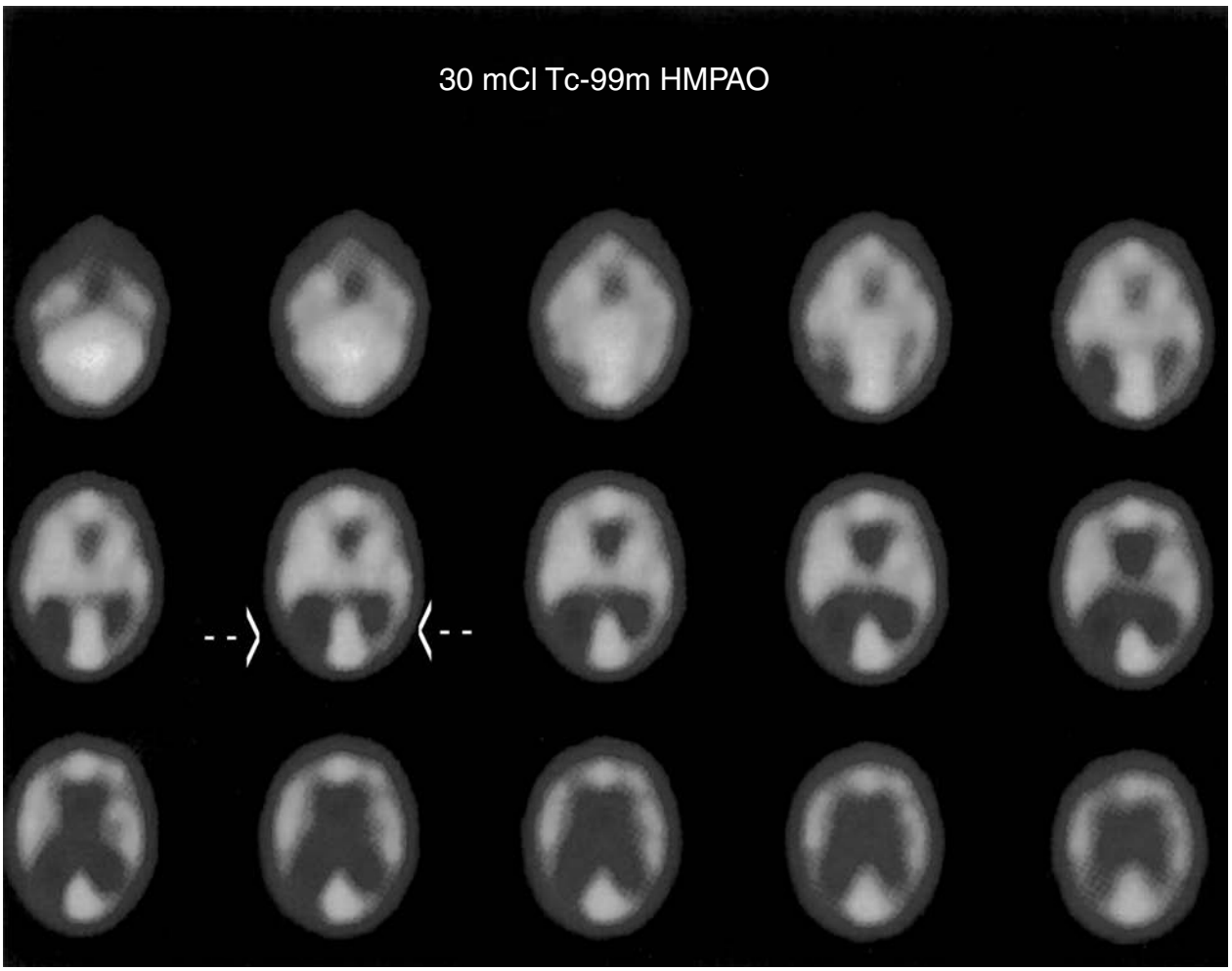



**Figure 33–6** *Illustration of the methodology for PET activation studies using blood flow tracers such as $^{15}$O-carbon dioxide or $^{15}$O-water. A series of scans are acquired in activated and control states and are subtracted to produce a different image. A statistical test is applied to the data to determine which changes in the difference image are statistically significant. This example shows the robust response to a hemifield stimulation of the visual system with a reversing checkerboard pattern using $^{15}$O-water as the tracer. The activated area in the visual cortex can clearly be seen, even prior to substraction. © Academic Press (See Color Plate X)*

manual tracings of the region of interest on each subject's MRI, creating a mask that is overlaid upon each subject's PET image from which quantitative values are drawn.

There are now a number of commercial radiopharmaceutical firms that are able to affordably produce and rapidly deliver $^{18}$F-based tracers to hospital or research PET labs ($^{18}$F is the only commonly used isotope with a long enough half-life for such commercial distribution). This trend has dramatically changed the number of PET labs, since the short half-lives of positron-emitting isotopes previously required an on-site cyclotron, radiophysicist, radiochemist, radiopharmacist, etc, the cost of which severely limited the number of labs. Today we find PET scanners—formerly found almost exclusively in university health science centers— in many general hospitals. Labs without a cyclotron are limited almost exclusively to FDG, so clinical and research applications that require tracers other than FDG are still limited to labs with an on-site cyclotron.

There now also exist commercially available PET/CT machines that combine both imaging modalities within the same frame, allowing for essentially simultaneous structural and functional images with automated co-registration. Combined PET/MRI machines are under development as well.

### Advantages and Limitations of PET

1. PET is the traditional gold standard of functional neuroimaging modalities.
2. Only PET can measure cerebral glucose metabolism.
3. A larger number of radioligands, especially those used for neuroreceptor characterization, are available for PET.
4. PET offers excellent spatial resolution (~4 mm).
5. Even with the advent of commercial radiopharmaceutical firms, PET is still expensive.

## SPECT

SPECT is most commonly used to construct images of regional cerebral blood flow (see Figure 33–7), although it may be used for neuroreceptor characterization as well. As is the case with PET, SPECT detects gamma rays produced by unstable isotope component of radioligands. However, the gamma rays that SPECT is designed to detect result from

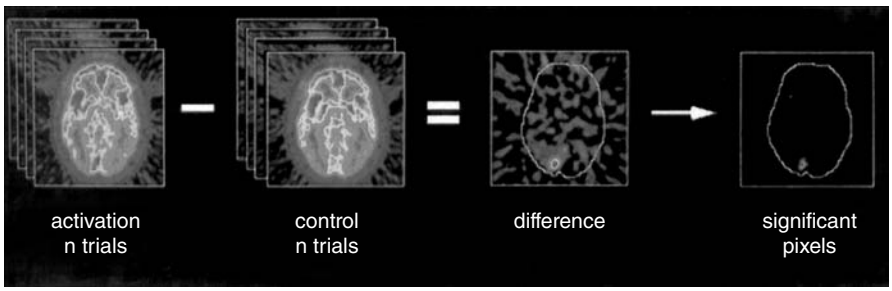



**Figure 33–7** *Serial axial HMPAO SPECT images from an individual with Binswanger's disease. HMPAO SPECT measures cerebral blood flow which is tightly coupled to neuronal activity. Note that there is generalized decrease in cortical activity compared with cerebellum. Additionally, small marked focal defects are seen in the cortex (arrowheads). © Mosby (See Color Plate X)*

photon emission rather than the positron/electron annihilation events that PET is designed to detect. Gamma rays that result from photon emission behave differently from the gamma rays produced by positron/electron annihilation in that they do not project 180° from one another. Rather, gamma rays resulting from photon emission project through the imaging field in a more random fashion. Thus, SPECT is unable to use coincidence circuits like those used in PET to localize the sources of the annihilation event. This is the primary reason that SPECT cameras have slightly poorer spatial resolution than PET cameras.

SPECT cameras are comprised of an array of collimators and radiation detectors that are designed to detect gamma rays. SPECT collimators are typically lead blocks containing thousands of very small holes. The collimators are placed between the subject and the radiation detectors. The holes in the collimator are long and narrow so that only photons of an essentially parallel trajectory are able to pass through and reach the detector.

A number of tracers used to measure cerebral blood flow are available for use with SPECT, although by far the most commonly used tracer is 99m-Technetium-HMPAO, which is directly injected into the intravascular space (Leonard et al. 1986). Other SPECT tracers available for measuring cerebral blood flow include $^{123}$I-iodo-amphetamine and Tc-Ethyl cysteinate dimer. As opposed to PET, there are no SPECT tracers available for measuring glucose metabolism. Because SPECT tracers have a significantly longer half-life than those used for PET, SPECT studies can generally only be conducted once a day. Depending upon the half-life of the tracer, PET studies can often be conducted multiple times in a day. This may facilitate certain experimental designs.

### Advantages and Limitations of SPECT

1. SPECT is more affordable than PET and does not require a cyclotron for production of nuclides.
2. Currently SPECT provides inferior spatial resolution (~6–8 mm) compared with PET.
3. Typically SPECT spatial resolution worsens as one attempts to image deeper brain structures although this has become less of an issue with the introduction of newer generation SPECT cameras.

## PET versus SPECT

1. PET provides superior spatial resolution, especially for deeper brain structures.
2. PET offers a broader array of radioligands for use in receptor studies and is the only modality that allows for the measurement of metabolism.
3. SPECT is less expensive than PET and is still more widely available.
4. Multiple PET scans may sometimes be done within a day whereas SPECT is limited to one study per day.

## fMRI

Expanding upon the basic principles underlying standard structural MRI, fMRI allows investigators to assess brain function. Using either a standard or, preferably, a high speed MR scanner with specific image acquisition parameters, indices of cerebral blood flow can be measured (see Figure 33–8). While structural MRI studies rely on excitation and relaxation of hydrogen atoms in water, fMRI takes advantage of the paramagnetic properties of hemoglobin to measure blood flow and volume. fMRI is sometimes also known as *blood oxygenation level dependent (BOLD) MRI*, and the hemodynamic response to neuronal activity is sometimes referred to as the BOLD effect. fMRI has distinct advantages when compared to PET and SPECT and these include:

- fMRI does not expose subjects to radiation and its relative safety has been documented
- The spatial resolution of fMRI is at least equal to if not superior to that of PET
- The temporal resolution of fMRI is vastly superior to that of PET or SPECT. While the temporal resolution of $^{15}$O PET is 1–2 min, that of fMRI is limited only by the hemodynamic response to changes in neuronal activation, on the order of 4–6 s.

The major disadvantage of fMRI when compared to PET or SPECT is that no satisfactory techniques for receptor neuroimaging have yet been developed for fMRI, and metabolism cannot be measured directly. As with SPECT, the investigator infers a relationship between neuronal activity and blood flow.

While fMRI currently has little to no clinical utility, it may be useful in clinical situations in the future. One area of research that shows particular promise is the use of arterial spin labeling (ASL) with fMRI. This method produces maps of resting cerebral blood flow (Wintermark et al. 2005). Because ASL data can be obtained without exposure to radiation, this technique may be used instead of PET or SPECT for evaluation of dementia or seizures in the future.

## MRS

MRS uses specific acquisition parameters and a standard MR scanner just as fMRI does, although MRS measures the levels of various chemicals in the brain (Henry et al. 2001). The technique is very similar to that of nuclear magnetic

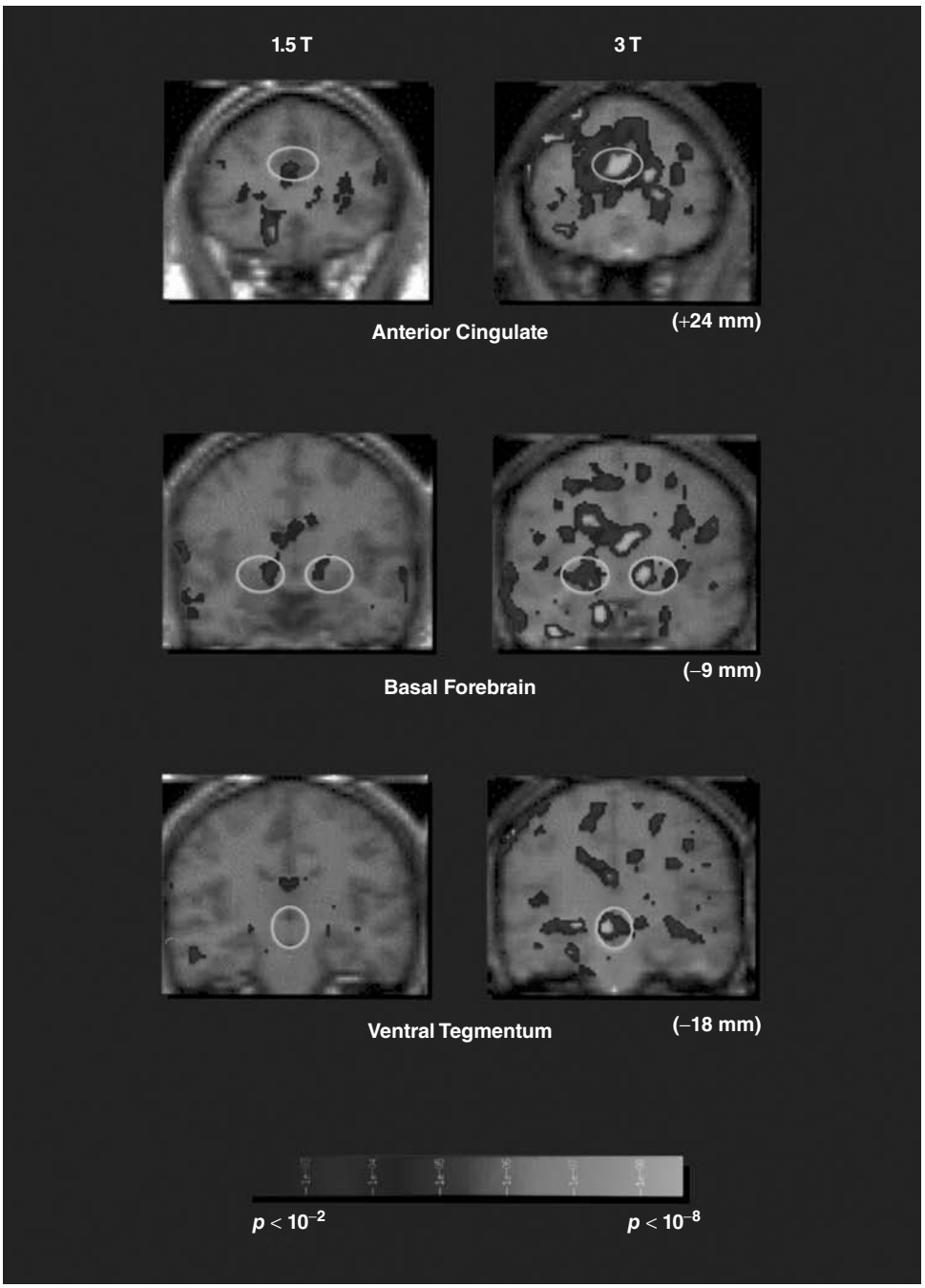



**Figure 33–8** *fMRI activation study where subjects were given either intravenous cocaine or saline at different times. When the saline condition is subtracted from the cocaine condition (see Figure 33–6 for activation study overview), statistically significant activation associated with administration of cocaine was demonstrated in regions associated with the reward circuitry of the brain. Also note that when this study is conducted using a 3 Tesla (unit used to quantitate the strength of a magnetic field) MR scanner, the findings are much more robust than when using a less powerful 1.5 Tesla MR scanner. (See Color Plate XI)*

resonance used in analytic chemistry. A number of MRS-visible nuclei can be assessed in vivo including phosphorous (31P) and hydrogen (1H). Phosphorous MR spectra provide quantitative data regarding phospholipid metabolites and markers of high-energy phosphate metabolism. Proton (1H) MR spectra provide measures of N-acetyl aspartate (NAA, a cell marker specific for neurons) as well as some compounds that may be involved in cell membrane formation and second messenger systems. In addition, MRS is able to measure concentrations of some drugs in the brain including lithium (Renshaw and Wicklund 1988) and some fluorinated compounds such as fluoxetine (Renshaw et al. 1992). Compared to other functional neuroimaging modalities, MRS has less spatial resolution (from 1 to 150 cubic centimeters depending upon the spectra being generated) due to its low sensitivity, although this is improving with the use of higher field MRI scanners. Currently, there is no clinical utility for MRS, though monitoring levels of drugs in the brain may be a future application.

## In Vivo Neurochemical Research: Molecular Imaging

A large number of radioligands used for neuroreceptor characterization are available for both PET and SPECT studies. These radioligands generally bind to a specific neurotransmitter binding sites (including post-synaptic receptors, pre-synaptic reuptake sites, enzymatic binding sites, etc), allowing PET or SPECT to quantify the spatial distribution

of the binding site of interest. Radioligands are available for characterizing dopamine receptors (including $D_1$, $D_2$, and reuptake sites, see Figure 33–9), serotonin receptors (including 5-$HT_{1A}$, 5-$HT_2$, and reuptake sites), benzodiazepine receptors, opioid receptors, and many other receptor systems. These receptor neuroimaging techniques can be used in a number of research paradigms including comparing populations with and without psychiatric illness to elucidate the pathophysiology of the psychiatric illness and perhaps aid in diagnosis as well as for determining pharmacodynamics and pharmacokinetics of available therapeutics and investigational compounds. Lastly, recent work has focused on using PET to study neuronal function at a level deeper than the surface receptors. Preliminary studies show promise for using PET to image second messenger systems and even gene expression (MacLaren et al. 2000).

An emerging form of molecular imaging involves the use of MRI, employing nanoparticulate complexes that include neuroreceptor binding moieties and MR contrast material such as gadolinium or iron. Similar technology is more advanced in other fields of medical research; nanoparticle-based neuropsychiatric MR molecular imaging is still in early stages of development as researchers address technical and safety issues related to the use of nanoparticles, crossing of the blood-brain barrier, etc. As with each new advance in neuroimaging, the possibility of being able to perform serial molecular imaging studies without rate-limiting ionizing radiation creates new possibilities for assessing previously untestable hypotheses.

## Other Imaging Technologies

Other neuroimaging techniques that do not rely upon radiation or the magnetic resonance effect are presently used in psychiatric research. Magnetoencephalography (MEG) is such a technique. MEG is based upon the observation (in accordance with Faraday's Law of Induction and Maxwell's

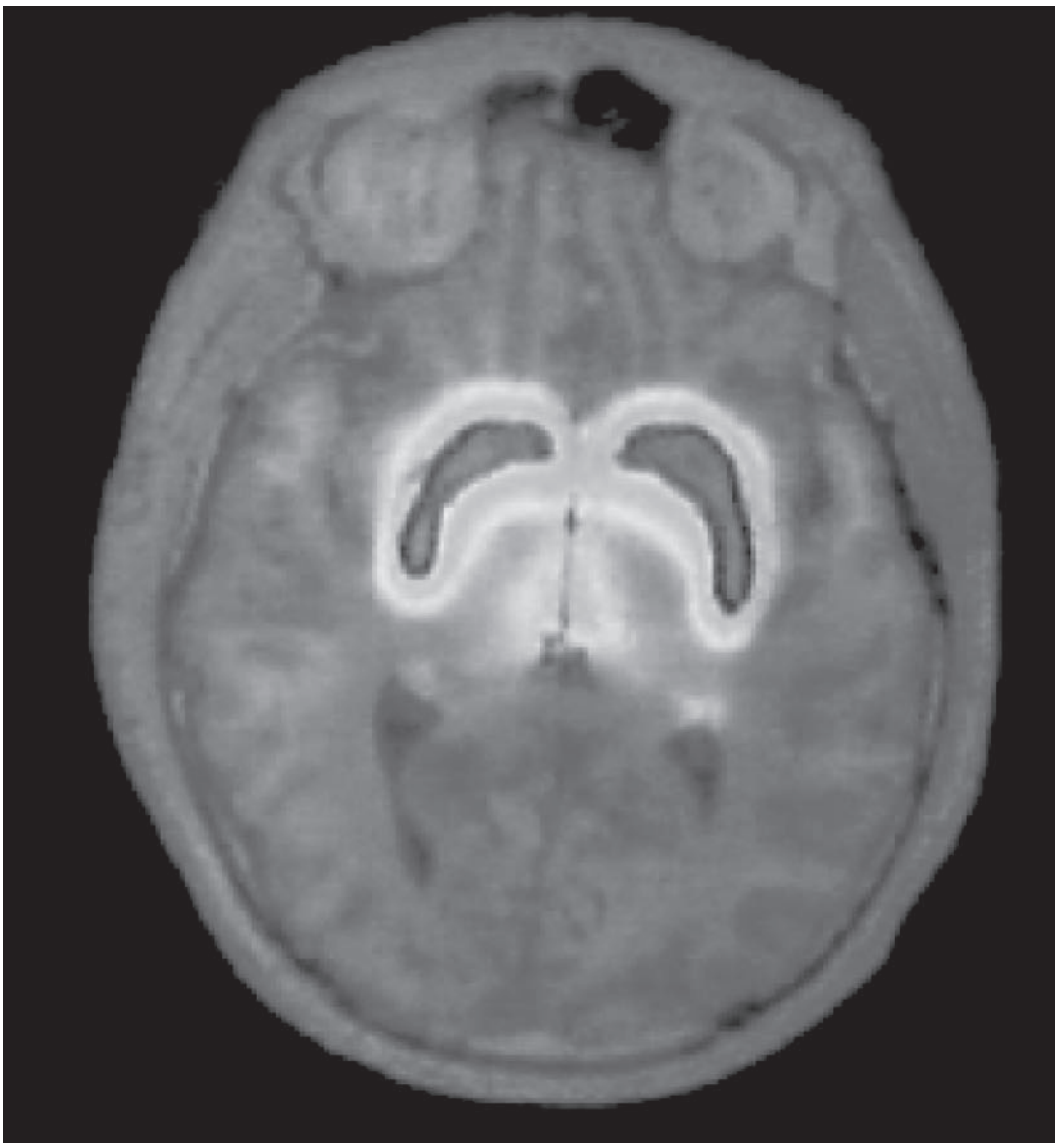


**Figure 33–9** *Molecular imaging. $^{18}$F-Fallypride is a dopamine receptor radioligand with high affinity for $D_2$ and $D_3$ dopamine receptors. The highest concentration of binding is seen in the dorsal striatum (caudate and putamen), followed by the thalamus and temporal and prefrontal cortices. (See Color Plate XII)*

equations) that passing a current through a conductor—in this case a depolarizing neuronal projection—produces a corresponding magnetic field around the conductor. This technique which was first introduced about 40 years ago, now utilizes an array of super-cooled superconducting quantum interference devices (SQUIDs) contained within an assembly that fits over the subject's head, to detect these minute magnetic changes associated with cortical activity. While one can argue that this method is more akin to electroencephalography (EEG) than neuroimaging, there has been significant growth in the number of MEG labs performing neuropsychiatric research, and is thus worthy of mention. MEG's temporal resolution is measured in milliseconds, and may be uniquely suited to examining some disease-related abnormalities in neural circuits.

Diffuse Optical Imaging (DOI) employs near-infrared light, and exploits the infrared absorptive properties of hemoglobin and deoxy-hemoglobin. DOI can thus measure hemodynamic responses in the brain. DOI is inexpensive, portable, and has temporal and spatial resolving abilities that compare favorably to fMRI.

## Clinical Use of Imaging in Psychiatric Populations

As stated earlier, the use of clinical neuroimaging by psychiatrists has traditionally been limited to structural studies (CT, MRI) to detect neurological lesions or diseases that may produce psychiatric symptoms. We are now seeing clinical imaging applications that may provide solid affirmative diagnostic evidence for psychiatric conditions, most notably the dementias. When a clinician is contemplating using the various currently available neuroimaging modalities a number of factors must be considered including the indications, risks, costs, advantages, and limitations. This chapter reviews these factors and provides general guidelines for the use of neuroimaging in psychiatric practice.

### Structural Imaging to Detect a Neurological Etiology for Psychiatric Symptoms

There have been numerous studies, dating back to 1978, assessing the utility of CT imaging in psychiatric populations. Across these studies, which represent a diverse population totaling 1346 patients, 29.5% of patients exhibited diffuse cortical atrophy while 12% of patients exhibited focal abnormalities (Renshaw and Rauch 1999). The likelihood of detecting an abnormal finding increased with age, with an abnormal neurological examination, with an altered mental status, and with a history of head trauma or alcohol abuse. When MRI became available in the 1980s, changes in the neuroimaging literature reflected a shift away from CT and toward the use of MRI in psychiatric populations. To our knowledge, the largest study of the use of MRI in psychiatric populations was conducted at McLean Hospital over a 5-year period and included all 6200 patients who received an MRI during that time (Rauch and Renshaw 1995). Because finding an abnormality following structural neuroimaging is of questionable value if it does not alter the treatment or outcome, this study focused on treatable findings. The study found that 99 patients (1.6%) had unexpected and potentially treatable findings including hemorrhage, temporal lobe cysts, tumors, vascular malformations, and hydrocephalus. Most importantly, multiple sclerosis was newly diagnosed in 0.8% of the subjects, a rate that is approximately 13 times higher than the prevalence of multiple sclerosis in the general population (Lyoo et al. 1996). For those psychiatric patients with newly diagnosed multiple sclerosis in this study, the largest subgroup had been diagnosed with refractory affective illness.

A number of studies have found an increased incidence of white matter lesions, more easily detected with MRI than CT, in psychiatric populations. When subsequent studies also revealed that as many as 30% of healthy control subjects over age 60 have white matter abnormalities of no apparent clinical significance, researchers began to question the relevance of white matter lesions in psychiatric illness. Subsequent evidence was presented which suggested that subcortical and white matter lesions are more prevalent in patients with late life onset depression and psychosis (Becker et al. 1995).

### General Guidelines for Structural Neuroimaging

On the basis of existing data, we have suggested criteria for appropriate structural brain imaging (Dougherty and Rauch 2001):

1. Patients with acute changes in mental status (including changes in affect, behavior, or personality) plus at least one of three additional criteria:
   - Age greater than 50 years
   - Abnormal neurological exam (especially focal abnormalities)
   - History of significant head trauma (i.e., with extended loss of consciousness, neurological sequelae, or temporally related to mental status change in question).
2. New onset psychosis.
3. New onset delirium or dementia of unknown cause.
4. Possibly for treatment refractory patients.
5. Possibly prior to an initial course of electroconvulsive therapy (may be helpful in identifying lesions that may lead to an adverse outcome such as aneurysms, tumors, arteriovenous malformations, hydrocephalus, and basal ganglia infarction).

We estimate that adherence to the criteria listed above should yield positive findings in 10–45% of cases. However, only 1–5% will produce findings that lead to specific medical intervention. Lastly, if structural neuroimaging is indicated, one should use MRI unless the problem is an acute trauma or an acute bleed is suspected.

### Indications for Use of Functional Imaging in Psychiatric Populations

Functional neuroimaging modalities include PET, SPECT, and functional MRI, and are now used in clinical situations as aids for the diagnosis of psychiatric conditions, though psychiatric use of functional imaging lags well behind that seen in fields such as cardiology and oncology (including brain tumors). Also, the use of ligands for neuroreceptor characterization is being increasingly used for the diagnosis and assessment of basal ganglia diseases such as Parkinson's disease. Still, most applications of functional neuroimaging in psychiatry occur in the field of research. However, a clinical role for functional neuroimaging in dementia, traumatic brain injury (TBI), seizures, and possibly other conditions are evolving and showing promise.

### Dementia

As characteristic functional neuroimaging profiles emerge for various forms of dementia, the role of PET, SPECT, and MRI in the evaluation of dementia is expanding. For example, Alzheimer's disease is associated with characteristic hypoperfusion and reduced glucose metabolism in bilateral temporo-parietal regions (see Figure 33–5). Some studies have indicated that SPECT and PET neuroimaging can offer better than 90% sensitivity and specificity in distinguishing Alzheimer's disease from other kinds of dementia (Silverman et al. 2001, Bonte et al. 2001), though the diagnostic accuracy for fMRI is not as yet well established, somewhat unfortunately because of the convenience of obtaining an additional functional sequence during the structural MRI session that many of these patients will undergo as part of their diagnostic workup. Other dementias such as frontotemporal dementias (e.g., Pick's disease) and multi-infarct dementia may also be diagnosed by combining clinical evidence with functional imaging findings. With the introduction of cholinesterase inhibitors for treatment of dementia, early diagnosis of Alzheimer's disease may have greater import than in the past. Some PET studies of healthy older subjects with normal cognitive function who are homozygous for the apolipoprotein E epsilon 4 allele (a gene associated with the development of Alzheimer's disease) reveal that these subjects have temporo-parietal hypoperfusion before the onset of disease (Small et al. 1995, Reiman et al. 1996). Initiation of treatment with cholinesterase inhibitors or other drugs being developed, in these individuals prior to the onset of symptoms of dementia may prove to be of great value.

### Seizures

Some seizures, especially complex partial seizures, are not always detected by EEG. EEG measures cortical surface electrical activity but is less efficacious if the seizure focus is deeper in the brain. PET and SPECT images typically demonstrate ictal hypermetabolism and interictal hypometabolism (Krausz et al. 1996, Theodore and Gaillard 2000). This allows for the detection of seizure foci during the predominant interictal period. To evaluate a possible seizure disorder, functional neuroimaging is usually performed in conjunction with EEG. PET and MEG are also useful for more precise localization of seizure foci in a patient with a known seizure disorder if neurosurgical intervention is indicated. In such patients, fMRI or MEG can be used to preoperatively map functionally critical cortical areas (e.g., language, primary motor cortex) in order to guide surgical excision of epileptogenic tissues while sparing vital functions.

### TBI

Psychiatrists often examine and treat patients with psychiatric symptoms who have suffered a potentially etiologic head injury. In some cases, such as those involving severe TBI that was immediately followed by the emergence of psychiatric symptoms, the diagnostic nexus is fairly obvious. But in the 80% of cases that are classified as mild TBI based upon loss of consciousness < 30 min, Glascow Coma Scores of 13–15, and posttraumatic amnesia < 24 hr, the causal relationship between the head trauma and subsequent psychiatric problems may be less obvious. In such cases, functional imaging may offer more useful information than that provided by a structural imaging study alone. Injured brain tissue, after the acute stage, may show metabolic depression and reduced perfusion on FDG PET and SPECT, respectively, although research findings have been thus far inconsistent (Belanger et al. 2007). fMRI shows promise as well though with a smaller evidence base. In terms of structural imaging, DTI and another MRI variant, magnetization transfer imaging (MTI), both seem to show greater diagnostic sensitivity than the more typically ordered T1- or T2-weighted sequences.

Expert testimony concerning neuroimaging evidence and TBI has now become a fairly common phenomenon in forensic psychiatric practice. Such evidence is often presented to mitigate guilt in criminal defendants, or to support claims of psychic injury in civil litigants.

### Clinical Use: Final Comments

There are psychiatrists, some of whom have SPECT imaging suites within their offices, who obtain functional imaging studies across diagnostic groups in their clinical practices. Interpretation is most typically done by visual inspection by an experienced clinician rather than by using statistical methods, and clinical decisions such as medication selection are sometimes based upon these results (poster by Pavel et al. 2005). While such clinical decision-making may lack the statistical foundation found in neuroimaging research, it remains to be seen whether these practitioners are pioneers or simply represent false starts.

## Summary

Neuroimaging technology has evolved considerably during the last few decades, and has done more to advance our understanding of the neurobiology of mental disorders than any other neurobiological method. Currently available neuroimaging modalities have increasing clinical utility in psychiatric populations. Although there are still substantial limitations on the amount of information that neuroimaging provides in the clinical setting, the continued evolution of neuroimaging technology offers great promise for the future.

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CHAPTER

# 34 Consciousness, Orientation, and Memory

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Consciousness, orientation, and memory are three closely linked and interdependent biological processes: a person cannot be oriented without intact memory; memory is related critically to one's level of consciousness. Correspondingly, these three functions are mediated or affected by many of the same neurotransmitters and neuroanatomical structures (Mesulam 1990). However, recent developments have established important distinctions between even consciousness and attention (Koch and Tsuchiya 2006), undermining the notion that consciousness is entirely identical to those cognitive processes upon which it depends.

The usual definition of cognition (from the Latin *cognitio*) is an intellectual process by which knowledge is gained by perceptions or ideas. In essence, cognition is the means by which an individual knows or relates to the world. Cognitive changes due to cerebral dysfunction have been well described historically. Hippocrates, in the 5th century BCE, ascribed all mental and emotional activity (including mental illness) to the brain. Soranus, in 100 AD, described *phrenitis*, a disease associated with acute fever, involving foolish gesticulations, disturbed perceptions, and occasional unresponsiveness. Soranus attributed this condition, which most would now call delirium (see the following text), to a disturbance of the brain (Ackernecht 1959).

## Nature of Consciousness

A confusing array of terms has been used to describe consciousness, including awareness, attention, arousal, and vigilance (Benson 1994). Semantics aside, consciousness poses difficulties for precise understanding. Consciousness is readily evident in oneself but not necessarily in others, it is difficult to define, and it has no clear utility. Prominent among current models of consciousness is that of a relatively passive perceiver of ongoing mental activity (Kinsbourne 2006, Tannenbaum 2006, Seth et al. 2006). Consciousness is not universally regarded as a "sensibly continuous" stream ala William James (1890), but, may, on the contrary, consist of distinct fragments of experience. Consciousness corresponds to a gamma synchrony of around 40 Hz, roughly corresponding to the frames of mental activity that are experienced by the highly trained meditator (Hameroff 2006).

## Levels of Consciousness

Most pathological conditions of forebrain or midbrain structure or function can affect the individual's level of consciousness. A change in consciousness manifests itself functionally in the way the person responds to the surrounding environment. In their classic monograph on stupor and coma, Plum and Posner (1982) classified the spectrum of changes in consciousness as alterations of "stimulus-response" (Table 34–1).

This model provides a practical method for the physician to classify levels of consciousness. Accordingly, alert wakefulness (or the normal state) is a condition in which a subject is able to respond immediately and appropriately in all sensory modalities to stimuli. As consciousness becomes increasingly impaired with a dulling of alertness and cognitive functioning, responses become delayed or incomplete and require increasing external stimulation until no response, or only primitive responses, can be elicited. Even at the coma stage of depressed consciousness, there may be many levels of consciousness according to the patient's ability to respond to stimuli. The Glasgow Coma Scale (GCS) (Table 34–2) is very widely used to rate coma severity and to monitor the process of recovery (Taesdale and Jennet 1974, Gabbe et al. 2003).

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**Table 34–1 Alterations of Consciousness**

| State* | Definition |
|---|---|
| Hypervigilance | Increased scanning of environment, arousal<br>Difficulty in focusing or shifting attention |
| Alert wakefulness | Subject responds immediately in all sensory modalities |
| Lethargy | State of drowsiness, inaction, indifference<br>Responses delayed or incomplete<br>May need increased stimulation to respond |
| Obtundation | More indifferent<br>May maintain wakefulness but little more stupor<br>Subject can be aroused by vigorous and continuous external stimulation |
| Coma | Psychological and motor responses to stimulation either completely lost or reduced to rudimentary responsiveness, (e.g., withdrawal, sucking, chewing, swallowing) |
| Catatonia | Dramatic reduction of psychomotor activity presenting as rigidity, waxy flexibility, mutism, and negativism |
| **Partial Alterations of Consciousness** | |
| Dissociation | Unintegrated perceptions |
| Depersonalization | Feels detached from world |
| Derealization | Environment seems unreal |
| Déjà vu | Feeling of familiarity |
| Jamais vu | Feeling of unfamiliarity |
| Unilateral neglect | Unawareness of a body part |

*The causes are the same for all states: anxiety, stress, paranoia, drugs, and central nervous system damage.

**Table 34–2 Glasgow Coma Scale (Age 4 to Adult)**

| Eyes | Score |
|---|---|
| **Open** | |
| Spontaneously | 4 |
| To verbal command | 3 |
| To pain | 2 |
| No response | 1 |
| Best Motor Response | |
| **To Verbal Command** | |
| Obeys | 6 |
| **To Painful Stimulus** | |
| Localizes pain | 5 |
| Flexion-withdrawal | 4 |
| Flexion—abnormal muscle bending | 3 |
| Extension—involuntary straightening | 2 |
| No response | 1 |
| Best Verbal Response | |
| Oriented and converses | 5 |
| Disoriented—confused conversation | 4 |
| Inappropriate words | 3 |
| Incomprehensible sounds | 2 |
| No response | 1 |
| Glasgow Coma Scale (GCS) Total | 3–15 |

The GCS is a simple measure that assesses a patient's motor responses, eye-opening, and verbal responses. The minimum score of 3 reflects a fully impaired level of consciousness while a score of 14 (maximum 15) indicates the patient is conscious, conversant, and oriented, although recent memory may still be impaired. One does not awaken from coma suddenly as from sleep, but through a much more gradual and step-wise process. Once a patient has achieved verbal response when recovering from concussion, the Galveston Orientation and Amnesia Test (GOAT) and other instruments provide more detailed assessment of orientation and memory for events before and after brain injury, and is a useful measure with more detailed scaling to evaluate a patient's cognitive status (Levin et al. 1979, Tate et al. 2006). The duration of coma and severity of memory loss after brain insult [posttraumatic amnesia (PTA)] predict the extent of recovery and degree of residual neurological impairment (de Guise et al. 2006).

A classification of levels of consciousness that is limited to deficits, however, omits some disturbances seen in psychiatric illness. A broader perspective of alterations in consciousness also encompasses increased stimulus-responsiveness, as in hypervigilance (Silverman 1968). Many psychiatric conditions associated with increased anxiety or arousal are also associated with hypervigilance (Tucker et al. 1969, Harrow et al. 1972). A hypervigilant individual may respond indiscriminately to stimuli and can become distracted or unable to focus attention (Table 34–3). Thus, vigilance, like arousal, more generally follows the well-known inverted U association of arousal and performance: some amount increases performance, but excessive amounts detract from performance (e.g., Sjoberg 1977). Hypervigilance can be induced by stimulant drugs (e.g., amphetamines and cocaine), is seen in paranoid psychosis, and is characteristic of posttraumatic stress disorder.

Catatonia is a state of marked underreactivity to the environment, accompanied by disturbed motor activity. The syndrome complicates mood disorders, less often schizophrenia, and still less often a variety of neurologic and medical conditions. Consistent with a disturbance in

**Table 34–3 Types of Experience From People in Hypervigilant States**

| |
|---|
| When I try to read something, each bit I read starts me thinking in 10 different directions at once. |
| When I try to concentrate on the major issues, I find myself paying attention to all sorts of tiny things instead of the important things. |
| Often, I find myself paying attention to the silliest little things going on around me, and I waste a lot of energy that way. |
| I am attending to everything at once and, as a result, I do not really attend to anything. |
| If I am distracted by too much noise, I can't move. If I am walking across the room, for example, and someone turns on the radio, I may freeze in my tracks for a moment or two. |
| When people are talking, I have to think what the words mean. I can pay attention to one person, but if there are three or four people speaking at once, I get confused. |
| Noises all seem to be louder—as if someone had turned up the volume. |
| If I am talking to someone and they cross their legs or scratch their heads, for example, I get distracted and forget what I am saying |

consciousness, patients usually do not clearly remember the episode (Fink and Taylor 2003).

Delirium has as its hallmark waxing and waning of consciousness or acuity of attention. It is caused by any of several adverse influences on cognition (quite often multiple adversities) on the vulnerable person, common among these pharmaceuticals, metabolic derangements, and infections. Those most vulnerable include the demented and the elderly (Inouye 2006). Delirium can superficially mimic many neurological and psychiatric conditions, including stupor.

## Qualitative Changes in Consciousness

Qualitative changes in consciousness without clear changes in the overall level of alertness occur commonly, and can represent normal or psychopathological functioning (Silverman 1968). These changes are primarily mediated by responses to sensory stimuli and the ability to sustain a focus of attention that causes a partial change in the level of consciousness. For example, a person going to the dentist, if anxious about the experience, is likely to focus considerable attention on the drill, and the experience of pain will probably be intensified. However, if the person attempts to focus attention on music or other distracting stimuli, then pain and discomfort should be diminished. Deliberately shifting the focus of attention underlies many relaxation techniques as well as hypnosis. Consequently, cortical activity can modify sensory input and thereby modify attention, arousal, and anxiety, while anxiety can, in return, modify consciousness.

In psychopathological states, the functions of cognitive input, or sensory and motor functions, are more clearly related to qualitative alterations of consciousness (see Table 34–1). Dissociation has been defined by Spiegel (1994) as, "a separation of mental events that would ordinarily be processed together—a discontinuity of memory, identity, perception, motor function, or consciousness." Conditions such as dissociative identity disorder, dissociative fugue, hypnotic trance, or conversion disorder would all be classified as partial alterations of consciousness in that one's consciousness of the body (e.g., people who cannot move their legs) is separated from awareness, but, in general, the rest of the ability to relate to the world is intact. Similar types of splitting of consciousness can be seen with central nervous system damage. Neurologic conditions are very readily confused with dissociative identity disorder (paroxysmal conditions such as epilepsy) and conversion disorder (epilepsy, movement disorders, and loss of neurologic function). Postconcussive amnesia resembles dissociative fugue. Lesions of the nondominant parietal lobe and associated thalamus can produce a "neglect syndrome" or anosognosia, which is somewhat reminiscent of dissociation. This condition has been called "a denial of illness," although it represents an implicit unawareness of bodily functions or neurologic deficits resulting from the lesion, which may be associated with left hemiparesis. For example, a patient with a paralyzed arm denies that the arm is paralyzed; even when shown the paralyzed arm, the person might deny ownership of the arm (Weinstein and Kahn 1955, Vuilleumier 2004).

Derealization (a sense of detachment from the environment) and depersonalization (a sense of detachment from oneself) are other qualitative changes in consciousness associated with dissociative disorders; indeed, depersonalization disorder is recognized as a distinct disorder in DSM-IV-TR. A sense of numbing or detachment is one diagnostic feature of posttraumatic stress disorder, and is similar to derealization. Arousal and anxiety are related to all of these phenomena, both in terms of related mental disorders and of pathophysiology (Frewen and Lanius 2006, Giesbrecht et al. 2007).

Still other qualitative changes in consciousness include déjà vu (in which the patient experiences a feeling of familiarity in an unfamiliar place) and its converse, jamais vu (in which the patient experiences feelings of unfamiliarity in a familiar place—another phenomenon overlapping with derealization), which may also be associated with increased anxiety levels (Brauer et al. 1970).

Like the level of consciousness, the quality of consciousness can impact on cognitive function. Obviously, that which is experienced (learned) in a state inaccessible to another dissociated state, will not be fully accessible to the person in that other state. This would apply to such uncommon conditions as dissociative fugue and dissociative identity disorder. More generally, the concept of state-dependent learning applies to the less extreme variations in consciousness described earlier, and might detract from cognitive efficiency across these states as well.

### Physiology of Alterations in Consciousness

Consciousness is traditionally attributed to the brain stem and the reticular structures, but also depends on the coordinated activities of the thalamus, hypothalamus, and basal forebrain, which integrate and relay information to the cortex. Norepinephrine (originating in the locus coeruleus), dopamine (from the ventral tegmentum) and serotonin (from the raphe nuclei) have long been considered important in promoting wakefulness, although the role of serotonin is mixed. Glutamate (widespread), acetylcholine (from the pedunculopontine tegmental nucleus), histamine (from the tuberomammillary nucleus), orexin (from the lateral hypothalamus and perifornical area), and adenosine also promote wakefulness. GABA (from the hypothalamic ventrolateral preoptic nucleus) promotes sleep (Miller and O'Callaghan 2006, Szabadi 2006).

Sleep is an important example of an alteration of consciousness because sleep is really a suspension of consciousness. Sleep shows a clear pattern of cycles and stages when it is studied with electroencephalography. However, sleep differs from coma in that the comatose patient cannot be aroused, and the electroencephalogram in coma fails to show the usual cycles and stages of sleep; the impact of cortical, sensory, and motor inputs is not apparent. General anesthesia via the inhalational gases seems to be mediated by GABA-A receptors and excitatory amino acids (Hameroff 2006).

## Memory

> The man who thinks over his experiences most and weaves them into systematic relations with each other will be the one with the best memory.
>
> William James

Memory is perhaps the most recognized and valued aspect of cognition, nearly ubiquitous in mental status assessments and present in some of the earliest intelligence tests (Kramer and Delis 1998). As one could readily imagine, the quality

of our conscious experience would be greatly altered in the absence of memory. Awareness would be fragmented, presumably lacking in the richness of our common conscious experience. Memory is fundamental to all learning and development, including personality and interpersonal relationships (Singer 1995). Memories also provide reference points for our perception of time. Memories are dynamic, providing fitting frameworks for highly individualized views of reality (Tranel and Damasio 1995). Just as memory functions largely outside of conscious awareness (Rugg 1995), we are often less than fully conscious of the extent to which even mild memory deficits can interfere with one's social and occupational functioning (Squire 1982), and the extent to which nearly all psychotherapies rely on intact learning and memory.

For many patients with brain injury, memory deficits (amnesia) may develop in the absence of other significant cognitive problems (Cohen and Squire 1980, Squire 1987). This has been termed amnestic disorder since the publication of *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III). Retrograde amnesia refers to the inability to recall experiences prior to an event (usually a cortical insult) and is attributed to disruption of the consolidation of memory as a result of this event (Gold 2006). Retrograde amnesia typically evidences a temporal gradient where events closest to the time of trauma are more difficult to recall. Anterograde amnesia refers to the inability to learn new information from the time of brain insult forward. The most common form of amnesia, anterograde amnesia may be partial or complete and has been observed to frequently be a consequence of damage to the medial-temporal and diencephalic brain structures (Milner 2005). Posttraumatic amnesia (PTA) refers to the time period after head injury where consciousness has yet to return to normal and learning new information remains impaired. PTA often includes a time period encompassing both retrograde and dense anterograde amnesia. The duration of PTA in patients recovering from brain injury is often an even stronger predictor of residual neurological dysfunction than duration of coma (Rees 2003). It should also be appreciated that amnesia does not uniformly reflect damage to cortical regions in which memory is processed or stored, as it may emerge as a consequence of damage to the neural system that normally participates in memory formation and storage without itself being a site of storage (Squire 1987). Disruption at any stage of memory can result in amnesia, due to the multiple neural systems involved in memory formation, storage, and retrieval (Reeves and Wedding 1994). Indeed, the boundaries between the cognitive effects of direct brain trauma and those of psychological trauma can be uncertain (Rees 2003, Elzinga and Bremner 2002).

Prior to the 20th century, neuropathological studies of patients presenting with Korsakoff's syndrome helped to first identify the significance of the midline diencephalic regions to amnesia. The famous surgical case of H.M. initially linked the medial-temporal lobes to normal memory functioning. H.M. developed intractable epilepsy, which was surgically addressed by a bilateral anterior temporal pole resection that left him with dense anterograde amnesia without retrograde amnesia (Squire 1987, Milner 2005). This illustrative case focused research attention on anterior temporal lobe structures, the hippocampus and the amygdala, as primary memory sites. We have learned since that unilateral lesions typically result in much milder memory impairment. Many subsequent cases of patients with amnesia due to medial-temporal and other damage, associated with a variety of conditions including trauma, anoxia, arterial occlusions, viral encephalopathies, tumors, and neurodegenerative disorders, significantly advanced our understanding of memory functioning (Reeves and Wedding 1994, Strub and Black 1988).

The most influential and misleading subtyping of memory, derived from William James' 19th century formulation (James 1890), is into short- and long-term. Originally, and technically, short-term memory refers to recall immediately after presentation or during rehearsal; long-term memory refers to recall after any delay, however brief. Recall of information learned years ago is distinguished as remote memory. Confusion arises when "short-term memory" is used to refer to recall after relatively brief delays (Kramer and Delis 1998). For clinical descriptive purposes, memory is often subdivided into three basic types—immediate, recent, and remote—distinguished by the time interval between presentation of the stimuli and retrieval. Immediate memory may refer to the registration of information as a memory trace for several seconds or more, corresponding to both sensory and sometimes short-term memory described earlier. Recent memory assumes some period of memory storage, and might include a person's recall of day-to-day events, and may refer to information learned hours, days, or even weeks ago. Remote memories typically include memories of events or knowledge learned years ago, usually premorbidly or before a brain injury (Strub and Black 2000).

Natural divisions between various forms of memory may be observed in brain-injured patients. Foremost is the distinction between declarative and nondeclarative memory that is frequently noted in patients with amnesia. Declarative memory is that which can be consciously recollected, such as facts and figures acquired through learning that can be "declared" as knowledge (Reeves and Wedding 1994). Declarative memory permits storage of information in association with particular times and places and affords a sense of familiarity about previous events, allowing knowledge bases to be accessed for applications other than those to which learning initially occurred (Cohen and Squire 1980). Declarative memory and new learning are greatly diminished by medial-temporal (hippocampal) damage, whereas nondeclarative and remote memory tend to be spared (Squire 1982).

Declarative memory may be subdivided into semantic and episodic memory, as also reflected in brain injury research. Episodic memory refers to the memory for events that can be placed within a temporal framework or that have happened at a particular time in a person's life. As such, episodic memory stores the cumulative events in an individual's life and, in essence, functions as an autobiographical memory. Head-injured patients evidencing medial-temporal lobe dysfunction have often lost recollections of time- and place-specific experiences (Reeves and Wedding 1994). In contrast to episodic memory, semantic memory refers to general knowledge or organized information, such as facts, formulas, and vocabulary. Since semantic memory does not refer to particular events in a person's past, it may remain quite intact, even when episodic memory is impaired.

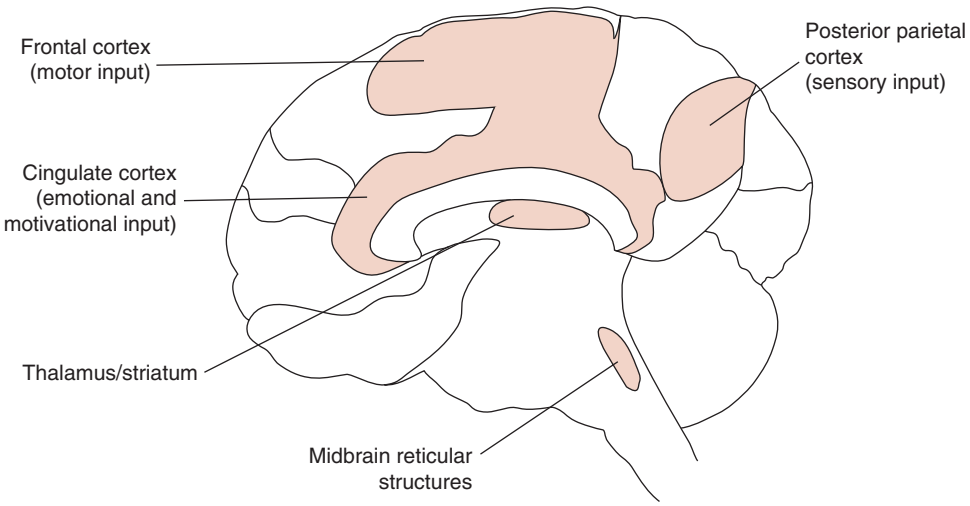



**Figure 34–1** *Interacting brain regions that relate to consciousness.*

Nondeclarative memory includes several types of memory, sharing only their lack of usual conscious accessibility. Nondeclarative memory includes sensory–perceptual and motor skills learning (procedural memory) as well as conditioning and priming. These forms of learning are not directly accessible to conscious recollection, retrievable as specific facts, or stored with respect to specific time or place (Reeves and Wedding 1994). Therefore, nondeclarative memory is implicit and tends to be available only by engaging in specific behaviors or cognitive operations and is thus essentially a memory without record. With enough repetition, some declarative memory transforms into procedural memory (a synonym for procedural memory is reflexive memory). Psychodynamic psychotherapy deals in nondeclarative more than declarative memory, for example by working through transference behaviors more than by rendering explicit advice. Numerous case studies of amnestic patients with medial-temporal lobe damage have shown that while they are unable to learn new declarative information, they retain roughly normal procedural learning abilities (Squire 1987). The repeated observation that procedural memory functioning does not demand the same integrity of the medial-temporal regions that is required for declarative memory, demonstrates that procedural memory and declarative memory rely on separate anatomical systems of neural networks. Knowledge is less complete, but these are thought to include the basal ganglia, cerebellum, and motor and sensory cortical areas.

Prospective memory is an additional category of memory functioning that has developed from the cognitive rehabilitation field, and refers to remembering to perform some particular action at a specific future time or place (Figure 34–1). Remembering to turn off the oven after cooking dinner or remembering to bring the necessary change to take the bus are examples of prospective memory tasks. Since prospective remembering is dependent on internal prompting, it may rely on an attentional or supervisory system, and does appear to involve the frontal lobes (Burgess et al. 2003). Prospective memory may be as much an executive function (others of which include self-monitoring, planning, organizing, and integrating information) as a form of memory (Fish et al. 2007).

Whereas the hippocampus has traditionally been regarded as the most crucial site for declarative memory and for memory formation, this memory system also includes several other brain structures. The amygdala integrates different sensory modalities and input from associated structures that receive input from sensory-specific cortical areas and multimodal association areas (Phelps 2004). Extensive afferent and efferent pathways to and from the neocortex converge on the parahippocampal gyrus, providing both hippocampus and amygdala with interconnections to ongoing cortical activity at memory storage sites (Moscovitch et al. 2005). The memory system also includes the mamillary nuclei, which project to the anterior nucleus and receive input from the hippocampal formation through the fornix, and the ventromedial frontal cortex, which receives projections from the anterior nucleus (Moscovitch et al. 2005). Numerous therapeutically relevant or potentially relevant neurotransmitter systems, including acetylcholine, gamma-amino-butyrate (GABA), insulin, angiotensin, and glutamate/AMPA/NMDA mediate and influence memory processes (Amadio et al. 2004).

Memory is uniformly understood as a staged process, but the specific breakdown of stages varies in a confusing manner. The formation of memory may be viewed most basically as involving three stages: (1) acquisition, (2) consolidation, and (3) storage (Squire 1987). Acquisition refers to the input of information from the sensory organs and cortices representing a sensory memory level of storage of brief duration. Consolidation refers to the progressive strengthening of memory traces in order for information to become permanent. Rehearsal and mental elaboration of material may consolidate that information in the short-term memory area of storage and develop a more robust representation of the information. Consolidation of information in short-term memory promotes transfer of the material to long-term memory storage. After transfer to long-term memory storage, information may be further consolidated for the creation of a more enduring memory trace or record (Tranel and Damasio 1995) (Figure 34–2). A somewhat more elaborated model (Kramer and Delis 1998) proceeds from attending, to processing (mental manipulation of the information), to encoding (transforming physical information into a mental representation), to storage. Processing and encoding may be distinct and important processes, as shall be seen in the following text.

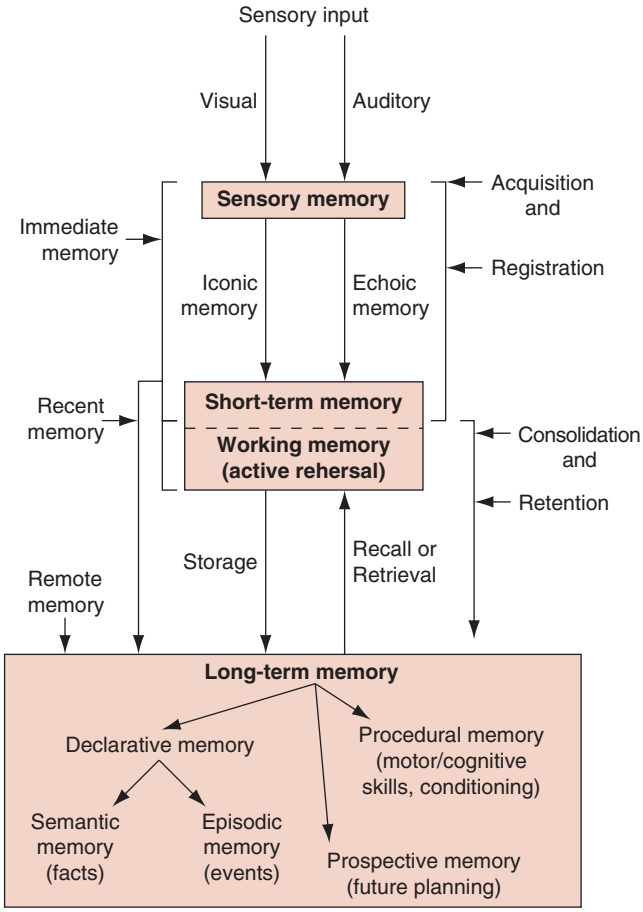



**Figure 34–2** *Merged models of human memory.*

In the initial sensory memory stage, where information is first "registered," the sensory information that is perceived and processed in the primary and secondary sensory areas of the cerebral cortex may remain briefly available immediately after presentation in a sort of neural memory buffer. Sensory memory for visual stimuli or iconic memory may last no more than half a second as a persistence of the visual trace on the retina (Squire 1987). Sensory memory for auditory information, or echoic memory, may persist for up to several seconds in a phonological sensory loop replaying whatever was heard most recently (e.g., phone numbers), if not displaced by new auditory stimuli.

Once sensory memory is registered, the active mental process of focusing on or attending to the information usually involves repetition of the information for retention in short-term memory storage. Sometimes referred to as brief or immediate memory, short-term memory has traditionally been considered to be limited to 7 ± 2 bits of information. Processing (manipulating and analyzing) new information represents a more complex level of short-term memory processing that is commonly referred to as working memory. Information in short-term memory is more likely to be successfully transferred to and retained in the long-term memory stage the more often it is repeated or maintained in short-term memory by elaborative working memory processes such as rehearsal and association (Kramer and Delis 1998). The biological basis of short-term memory has been attributed to sensory-specific neurochemical activation of short synaptic circuits, but this brief pattern of synaptic circuit activation is thought to be easily disrupted by further neurochemical activation resulting from the introduction of new information (Squire 1987).

Recall of information from long-term memory inherently requires the successful progression of information from registration after the sensory memory stage to more persisting elaboration of information in short-term memory storage for consolidation and transfer to long-term memory storage. That information must be transferred back to short-term working memory for recall. Retrieved long-term memory traces may be maintained by association with new short-term memory information and further integrated and synthesized in working memory for further consolidation in long-term memory storage. Long-term memories are not necessarily static memory traces, but rather reflect more of a dynamic record that may be updated and modified to reflect ongoing experience (Kramer and Delis 1998). Memory recall (or recognition) is thought to represent a reactivation and retrieval of knowledge from long-term memory storage to a form accessible to consciousness, as in the recall of specific information or a perceptual motor skill. Functional imaging studies are finding that retrieval of long-term memories also involve the hippocampus and other medial temporal lobe structures (Eldridge et al. 2005, Rekkas and Constable 2005).

Clinical Vignette 1

Ms. A, a married, right-handed, 37-year-old social worker, was evaluated approximately 6 months after an episode of adenovirus encephalitis. The neurological examination was nonfocal and unremarkable. She was oriented to person and place, but not time. She was able to follow two-step commands but not three-step commands. With apparently intact short-term memory, she could complete six digits forward and repeat a four-word list immediately, but she had no recall after 1 min, reflecting severe deficit in delayed memory. She showed pronounced emotional lability, with exaggerated emotional responses, and obsessive thought patterns.

Like many other amnestic patients, she evidenced pronounced anterograde amnesia with impairment on formal tests of new learning ability. She displayed a significant retrograde amnesia of 1 week for events prior to the onset of encephalitis. Although her fund of information, visual–spatial functions, and praxis were intact, she displayed subtle aphasia, reduced verbal comprehension, and severe word-finding difficulties. She was able to sustain her attention for long periods when engaged in familiar activities, but her attentional capacity deteriorated rapidly for complex or unfamiliar demands, particularly, when a new learning component was required, such as following a recipe. Her procedural memory appeared to be well preserved as she was observed to be able to carry out a number of prior learned activities quite competently, such as household chores of laundry, cleaning, and driving in places familiar to her before encephalitis. She exhibited moderate impairment in attempting to learn semantic information and could not recall her previous day's activities, reflecting episodic memory impairment. Because of her difficulty generalizing or transferring new learning to unfamiliar situations, rehabilitation efforts were conducted

*(continues)*

within her home environment to capitalize on her relatively spared procedural memory. Owing to her semantic and episodic memory deficits, Ms. A was unable to meaningfully participate in psychotherapy. Her family members engaged in family education counseling efforts to better understand her deficits, to learn practical approaches to compensate for her memory problems, and to maintain a predictable schedule and structured environment to minimize Ms. A's emotional and behavioral dyscontrol.

The biological basis of long-term memory is thought to be a consequence of the synthesis of proteins and RNA in neurons which develops a sequence of molecules encoded with information that are synaptically connected during the time "permanent" learning has occurred (Tranel and Damasio 1995). Molecular changes in a distributed array of neurons correspond to the long-term memory of a life event. In this fashion, the molecular consolidation of long-term memory is thought to create a relatively stable record of information. Functional imaging reveals that encoding into long-term memory involves the hippocampus and association cortex (Otten et al. 2002, Eldridge et al. 2005, Kong et al. 2006). Once long-term memory storage has been completed, the successful recall of that information involves entirely different processes. While the capacity of long-term memory storage is vast, memories in long-term storage are vulnerable to decay and susceptible to distortion, as in the cases of delusional memories and false memories (Loftus and Loftus 1980).

In working memory, one or more multiple sources of information are temporarily maintained and manipulated in an on-line fashion for periods of several seconds. Since the integration of information in working memory involves a synthesis of many subtasks such as organizing, monitoring, planning, and selecting information, working memory is highly dependent on the integrity of the prefrontal cortex. Since memory dysfunction due to frontal lobe pathology tends to be more associated with deficits in regulating attention and organizing or sequencing information, such working memory disturbance has been referred to as executive memory dysfunction (Shimamura et al. 1991). On detailed psychometric assessment of memory functioning, frontal lobe or executive memory dysfunction is usually distinguishable from memory disorders resulting from damage to the diencephalic midline or the medial-temporal regions, although this distinction may require detailed testing to clarify. Consistent evidence now indicates that the dorsolateral prefrontal cortex participates in retrieval of long-term memory (Gilboa 2004, Sakai 2003), and may serve an executive role in organizing memory resources (Rypma 2006).

## Intelligence

> We should take care not to make the intellect our god; it has, of course, powerful muscles, but no personality.
>
> Albert Einstein

One of the most important factors determining how a person negotiates or knows the world is the capacity for learning, reasoning, and understanding summarized by the term intelligence. While many different forms of intelligence may be theorized and measured in some fashion such as social, musical, and emotional intelligence, our focus of interest is measurement of the intellect's higher mental capacities for acquiring, understanding, and manipulating knowledge. Early intelligence quotient (IQ) expert David Wechsler believed that intelligence could be determined by the sum of many different specific abilities, and defined intelligence as "an aggregate or global capacity of an individual to act purposefully, to think rationally, and to deal effectively with his/her environment" (Wechsler 1944). Exactly which cognitive skills and abilities provide reliable and valid measures of intelligence has been an issue of considerable controversy over the past century, with numerous theoretical models of intelligence proposed. Over 30 years ago, Thorndike et al. (1973) offered a multimodal model of intelligence that still conceptually parallels the modern-day assessment of intellectual functioning. They defined three key areas of intelligence: (1) abstract or verbal intelligence concerns the ability to use symbols; (2) practical intelligence, the facility to manipulate objects; and (3) social intelligence, the facility to deal with human beings.

The origins of modern-day intelligence tests date to efforts in France (Binet and Simon 1905) and, subsequently, in the United States to develop standardized intelligence tests for identification of children in public school systems with learning and intellectual disabilities. The goal in those days was not much different than it is today; to provide improved curricula and remedial teaching for developmentally delayed and other special needs students. With World War I, a need for the US military to evaluate new recruits and select officers for training prompted the development of group-administered intelligence tests assessing verbal and nonverbal (visual) abilities, called the Army Alpha and Army Beta Tests, respectively (Anastasi and Urbina 1997). After working as an Army intelligence examiner, David Wechsler developed the first in a series of individually administered IQ tests called the Wechsler–Bellevue Intelligence Scale, that gave equal weight to both verbal and visual abilities in determining overall intelligence (Wechsler 1944). Separately measuring various verbal and visual abilities, the subtests were combined to determine an individual's Verbal IQ separate from the visual or Performance IQ, before both were merged for an overall Full-Scale IQ. This distinction between verbal and performance cognitive abilities has proved over the years to be the most pragmatic approach to evaluating intelligence for most purposes. In addition, the Wechsler Scale's approach of generating deviation IQs based on standard scores—rather than on the MA/CA (mental age divided by chronological age) formula that had been used previously to compute IQs—has helped to establish the various Wechsler Intelligence Scales that have been standardized for preschoolers, children, adolescents, and adults as the gold standard measures of intelligence (Kaufman and Lichtenberger 1999). Global measures of intelligence like the Wechsler Full-Scale IQ (FSIQ) serve as the foundation for numerous state laws determining service eligibility for both children and adults. Individual IQ assessment is a basic requirement to determine qualification for social security disability. In many areas of life, a global IQ score such as the FSIQ is often regarded as representing the most general estimate of a person's ability, against which other measures

of ability, specialized skills, or traits are compared (Tulsky et al. 2001).

The reasons for intelligence testing today are many, but, in clinical practice, usually have to do with evaluating cognitive impairment or decline in neuropsychiatric disorder. For the physician, information derived from the clinical psychologist's interpretation of Wechsler Adult Intelligence Scale III (WAIS-III) test results may be invaluable in helping to identify disorders usually first diagnosed in childhood or adolescence and to help determine diagnoses of dementia, amnestic, and other cognitive disorders. Intelligence assessment alone for patients with such known or suspected disorders is inadequate to evaluate the full range of cognitive strengths and limitations a patient may exhibit. It is generally necessary to evaluate multiple areas of cognitive ability with a neuropsychological evaluation. Integration of IQ results with findings from these other tests—which might cover attention, language, academic functioning, immediate and delayed verbal and memory, visual–spatial problem solving, motor and sensory–perceptual functioning, executive functions, and emotional functioning—is crucial to place these other findings in a context of overall intellectual ability, which is essential for treatment planning (Anastasi and Urbina 1997).

The design of the Wechsler Intelligence Scales involves the use of multiple subtests summing up to two equally weighted intelligence summary scores representing verbal and visual–spatial functions. Thus, there are three IQ scores or indexes: Verbal Intellectual Functioning (VIQ), Performance Intellectual Functioning (PIQ), and overall Intellectual Functioning or Full-Scale IQ (FSIQ). The three IQ scores are standardized to have a mean of 100 and a standard deviation of 15 (Wechsler 1997). Accordingly, two-thirds of the population in the United States would be expected to have a FSIQ between 85 and 115. Nearly 95% of the population score within 2 standard deviations of 100 or have IQs between 70 and 130. Demonstration of overall intellectual functioning below 70 roughly corresponds to a diagnosis of mental retardation.

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV-TR) (American Psychiatric Association 2000), requires concurrent deficits or impairment in adaptive functioning in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety, and an IQ below around 70 for a diagnosis of mental retardation. Mild mental retardation generally corresponds to a FSIQ range from 50–55 to approximately 69. Moderate mental retardation reflects IQ levels from 35–40 to 50–55; severe mental retardation corresponds to IQ levels from 20–25 to 35–40; and profound mental retardation is designated for IQ levels below 20–25. IQs between 70 and 79 are classified as borderline mental retardation, IQs between 80 and 89 are low average and IQs between 90 and 109 are considered to be in the average range. High average IQs are between 110 and 119 while superior range IQs correspond to scores between 120 and 129. A very superior level of intelligence (FSIQ 130 and above) in conjunction with demonstration of exceptional abilities in other areas is the standard for "giftedness." The WAIS-III ceiling for reliable FSIQ measurement of 155, which some would classify as genius range, is over 3.5 standard deviations above the mean. The WAIS-III is, thus, capable of identifying individuals with exceptional intellectual abilities.

Numerous intelligence tests have been developed in recent decades, but the WAIS IQ tests remain the standard and most widely used instruments for the clinical assessment of intelligence between the ages of 16 and 89 (Wechsler 1997). Wechsler's distinction in the late 1930s between verbal and visual abilities also proved enduring, and compatible with subsequent studies of brain functioning. Many investigations supported associations between left-hemisphere functions and VIQ subtest performances, and between right hemisphere visual–spatial functions and PIQ subtest performances. The multiple subtest profile design of the Wechsler scales, which allows assessment of significant discrepancies between verbal and visual–spatial cognitive ability, has been most important to our still-emerging understanding of verbal and nonverbal learning disabilities.

The WAIS-III national standardization sample (N = 2450) was stratified according to age, sex, race/ethnicity, geographic region, and level of education on the basis of distributions from the 1995 US census data (Wechsler 1997). This normative sample consisted of persons distributed across 13 age groups with 100–200 subjects per group between the youngest group (ages 16–17) and oldest group (ages 85–89). The WAIS-III consists of 14 subtests with seven measuring verbal and seven assessing visual–spatial abilities (Table 34–4). The Verbal IQ scale is composed of the subtests: information, digit span, vocabulary, arithmetic, comprehension, similarities, and letter-number sequencing. The visual–spatial or Performance IQ index consists of subtests: picture completion, picture arrangement, block design, matrix reasoning, symbol search, object assembly, and digit symbol. Each of these 14 subtests yield a separate subtest scale score with a mean of 10 and a standard deviation of 3. To some extent, each subtest measures a relatively

**Table 34–4 Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) Subtests**

| Subtests | Cognitive Abilities |
|---|---|
| **Verbal** | |
| Information | Long-term general knowledge |
| Digit Span | Brief auditory memory |
| Vocabulary | Word knowledge |
| Arithmetic | Quantitative reasoning |
| Comprehension | Verbal comprehension |
| Letter–Number Sequencing | Flexible sequential processing |
| Similarities | Abstract verbal reasoning |
| **Performance** | |
| Picture completion | Perceptual organization |
| Picture arrangement | Sequential reasoning |
| Block design | Visual–motor reproduction |
| Matrix reasoning | Visual–spatial reasoning |
| Digit symbol | Psychomotor speed |
| Symbol search | Visual perceptual speed |
| Object assembly | Visual–motor construction |

*Source:* Wechsler D 1997 The WAIS-III administration and scoring manual, 3rd edition. The Psychological Corporation, San Antonio, TX, USA. Copyright 1997 The Psychological Corporation. Reproduced by permission. All rights reserved.

distinct cognitive ability or skill with a proportion of variance unique to itself. Each subtest also shares interrelated abilities and a common variance with other verbal and visual subtests requiring knowledge of subtest error-variances and specificity for IQ profile interpretation (Kaufman and Lichtenberger 1999).

The WAIS-III's major enhancement or structural change from the previous Wechsler adult test of intelligence, the Wechsler Adult Intelligence Scale (Revised) (WAIS-R), was the addition of four new factor analytically derived index scores, in addition to the traditional VIQ, PIQ, and FSIQ index scores. Based on scores from 11 of the 14 IQ subtests, the two new verbal ability indexes are called the Verbal Comprehension Index, incorporating word and factual knowledge with verbal reasoning, comprehension, and expression, and the Working Memory Index, reflecting the ability to hold information in mind while manipulating that information. The two new visually oriented indices are the Perceptual Organization Index, measuring visual–spatial integration, reasoning and problem solving, and visual–motor construction ability, and the Processing Speed Index, including speed of visual processing, problem solving, and perceptual motor speed. Applying these alternate indexes to IQ interpretation can increase the understanding of a patient's cognitive ability structure and reliably identify when significant discrepancies exist between indices. In situations where extreme variability exists between the IQ indexes or factors making up the FSIQ, the FSIQs may no longer reflect a unitary construct and, therefore, may not be interpreted reliably (Kaufman and Lichtenberger 1999). In order to calculate the new index scores and a patient's VIQ, PIQ, and FSIQ index scores, though, a full WAIS-III test administration requires nearly 2 hours.

Some verbal subtests evaluate what are traditionally regarded as "fluid" cognitive abilities involving attention, concentration, and working memory, which tend to be highly sensitive to brain injury, as well as the attention–memory and other cognitive disturbances associated with acute psychiatric disorders. Examples of this are the similarities and arithmetic subtests. Other subtests, such as information and vocabulary, evaluate more stable cognitive abilities. These subtests are thought to evaluate information in long-term memory storage such as language and academic skills and abilities (Larrabee et al. 1985). These overlearned abilities are often referred to as "crystallized" cognitive abilities. Consistent with expectations from the diffuse cortical distribution of long-term memory storage, crystallized cognitive abilities are less sensitive to brain injury than the "fluid" abilities. Although these "hold" subtests are often reported as estimates of premorbid intellectual ability, they may also evidence decline in advanced or severe neuropsychiatric disorders such as global dementia.

Where reliable premorbid IQ results are not available, intellectual assessments are relatively insensitive to frontal lobe-associated cognitive dysfunction. Subtests that measure "fluid" cognitive abilities, such as the Digit Span subtest tend to be more adversely affected by frontal lobe pathology, but the declines may be too subtle to reliably detect by IQ assessment alone. Verbal intellectual functioning, in general, is strongly associated with level of education, so that more years of education tends to increases one's measured Verbal IQ. The performance subtests, in general, evaluate the ability to solve novel visual–spatial problems and are less dependent on formal schooling than verbal subtests. These visually mediated subtests are usually more susceptible to decline in cases of acute psychiatric disorders, head injury, or other cases of generalized and diffuse cognitive dysfunction, such as most of the degenerative dementias (Anastasi and Urbina 1997).

Due to the standard error of measurement, IQ scores and indexes are not regarded as precise quantitative measures. They are more accurately considered to reflect a level or range of intelligence within which the patient is functioning. Whether the clinical goal of IQ assessment is to aid differential diagnosis or to determine whether a patient's intellectual abilities have declined, the standard error of measurement is always an important interpretative consideration. Controlled standardized test administration procedures are also required for reliable assessment of a patient's intellectual functioning to allow valid interpretation of the results. As with any assessment of a patient's cognitive functioning, numerous factors may affect measured levels of IQ functioning, including poor rapport with the examiner, lack of effort and motivation, medical and psychiatric conditions that compromise attention and memory capacity, sensorimotor limitations, and especially language and cultural discrepancies from the standardization sample. Computerized printouts of intellectual test results do not take such factors into account. Usually, the expertise of a psychologist with training in psychological assessment is necessary for reliable interpretation of IQ and neuropsychological test results. Accurate clinical diagnosis frequently requires the convergence of findings from many specialties, and reliable interpretation of intellectual or neuropsychological test results is important for integration with neurological, radiological, and psychiatric findings. Competent interpretation of IQ findings should incorporate (1) the patient's current level of verbal, visual, and overall intellectual functioning and the validity and reliability of the IQ test results, (2) comparison of a patient's current IQ functioning to normative or appropriate clinical samples and measures of premorbid functioning, (3) significant differentials between IQ indexes and subtest scores to illustrate cognitive deficits and strengths or preserved areas of cognitive functioning, (4) multiaxial diagnoses, and (5) any limitations of the database.

## Clinical Evaluation

The cognitive evaluation is highly important in identifying reversible medical and neurological causes for psychiatric disturbances. The central nervous system has only a limited number of responses to any type of disturbance, so identical symptoms evident on mental status exam may be due to a variety of causes (Table 34–5). For example, a dementia syndrome could well be due to depression, a toxic exposure, head trauma, tumor, seizure disorder, encephalitis, or, even, a severe stressor.

Thus, the longitudinal history of the syndrome is often key to differentiating its cause. Most dementias do not manifest themselves as abrupt changes in personality and behavior, rather developing over months to years. With the current emphasis on specific diagnostic criteria, one is sometimes inclined to think the diagnostic task is done when the patient's current symptoms fit DSM-IV-TR criteria. However, this reflects the patient's symptoms only at one point in time.

**Table 34–5 Major Cognitive and Behavioral Systems Areas**

| | |
|---|---|
| Cognitive | |
| | Orientation |
| | Affect modulation |
| | Memory |
| | Intelligence |
| | Judgment |
| Behavioral | |
| | Affect |
| | Arousal |
| | Mood |
| | Anxiety |
| | Perception |
| | Personality |
| | Motor |

Although it has its limitations, the cross-sectional profile of behaviors and abilities does have diagnostic value. It can suggest a medical etiology, especially if the presentation is atypical for dementia or amnestic disorder, and particularly, if the cognitive examination is dominated by inattention and disorientation (signs of delirium). The cross-sectional picture can also point to a psychological origin (pseudodementia in the context of depression and/or anxiety) when the patient complains of cognitive difficulties, highlights failures, and shows inconsistent performance across different modalities. The opposite is often the case in early stages of dementia: patients tend if anything to deny and conceal their deficits.

## Evaluation of Orientation

The changes in orientation most often seen in central nervous system dysfunction relate to knowing time, place, and person. The sequence of the loss of these functions often correlates with the severity of insult to the brain (Table 34–6). For example, orientation to time is generally the first function lost and usually indicates early or mild damage. In light of the diagnostic significance of orientation to time, the Mini-Mental State Examination explores time orientation by requesting the patient to provide day of the week, month, date, year, and season (Folstein et al. 1975). Orientation to place is often lost next; one often sees large signs with such patients' names identifying their rooms. Disorientation to self is uncommon in a fully conscious and coherent person. Orientation testing can be unreliable, as chronically disoriented patients may learn compensation techniques.

**Table 34–6 Major Causes of Disorientation**

| |
|---|
| Sensory deprivation |
| Fluctuating levels of consciousness |
| Damage to central nervous system, particularly causing memory impairment |
| Drugs and toxins |
| Fever |
| Hyperarousal or hypervigilance |

## Evaluation of Intelligence

When evaluating intelligence, an experienced clinician often estimates the actual IQ with relative accuracy taking into account the patient's level of education, occupation, and clinical presentation. However, specific testing is needed to obtain the most reliable estimate as well as to delineate specific cognitive deficits and assets. In most cases of generalized or diffuse brain damage, verbal functions are, often, better preserved than visual–spatial functions. Thus, with brain damage, one will often see marked disparity between the verbal and performance scores on the WAIS-IQ scales with reductions in PIQs. Consequently, although one may have a good verbal interaction with a patient, there may be severe deficits in the visual–spatial performance areas that may not be readily apparent and should be psychometrically evaluated. Useful screening measures for visual–spatial dysfunction are the figure drawings and sentence writings in the Mini-Mental State Examination (Folstein et al. 1975), the Bender Gestalt Test, the Clock Test (Lezak 2004), and the Block Design and other WAIS-III performance subtests (Wechsler 1997).

## Evaluation of Memory

Like all assessments of a patient's cognitive functioning, valid memory test results are contingent on adequate attention, motivation, and patient effort. Memory dysfunction associated with neuropsychiatric disorder is, therefore, easily misdiagnosed, resulting in inappropriate and costly interventions. Depression or anxiety can result in reduced effort and motivation confounding memory evaluation, and severe depression may induce deficits in attention and memory for some patients. Subclinical depressive disorders may present with complaints of memory or other cognitive difficulty, but, typically, do not show objective evidence of memory impairment on formal testing. The detection of cognitive deficits secondary to depression in patients with clinically significant depression will usually require more detailed psychometric memory testing than is typically afforded by the memory assessment of a brief mental status exam. Complaints of memory dysfunction tend to be more prominent in patients with acute as opposed to recurrent or chronic depression and the extent of "actual" memory impairment secondary to depression can vary widely (Strub and Black 2000). For some patients with major depression, their complaints about difficulty with memory, attention, and other cognitive functioning may offer an avenue for expression of emotional distress, serving as an alternative to somatic complaints. Complaints of memory difficulty in depressed patients have been demonstrated to be highly correlated with the severity of depression but unrelated to actual impairment in objective measurement of memory functioning. Antidepressant treatment that significantly improved depressive symptoms in patients with major depression was conversely associated with a significant decrease in patient complaints of memory problems (Claypoole et al. 1998).

When evaluating a patient for memory deficits associated with dementia, identification of the etiology is always crucial to determine whether the cognitive impairments may be reversible. If appropriate treatments improve dementia symptoms and memory impairments, it is important to determine the persistence of cognitive impairment following treatment. The differential diagnosis between depression

and dementia may be clinically challenging, particularly, for those patients who are in the early stages of decline (Nussbaum 1994). The onset of depression, especially for patients without premorbid psychiatric history, may be primary to both the neuropathological process and/or secondary to the patient's perceived loss of functioning. Treating depression in these patients may temporarily improve memory along with other cognitive functions, yet it is difficult to cancel out the adverse memory effects of depression from those of dementia. Effortful and demanding memory tasks have been shown to be differentially impaired in patients with depression, while dementia patients typically exhibit impairments in both effortful and automatic memory processing tasks (Nussbaum 1994). Longitudinal evaluation of a patient's memory functioning is usually required to address the complex interactions between the effects of depression and dementia on memory functioning, particularly, as late-life depression without cognitive impairment can be a harbinger of dementia (Baldwin et al. 2006, Brodaty et al. 2003).

Basic memory functions are relatively easy to evaluate clinically. Assessment should involve short-term auditory memory and brief attention span provided by digit span repetition tasks (registration), verbal learning capacity, and efficiency of recall of recently learned verbal and visual information after a brief delay. Long-term memory may be evaluated by recall for remote personal history (episodic memory) and historical facts (semantic memory). A good deal of information can be learned about a patient's memory from tests of learning capacity that offer a learning curve, and from the linear and sequential or disorganized way in which the patient relates his or her life history. This may require confirmation by others. The ability to recall numbers forward and backward, like the Digit Span subtest of the WAIS-III, is usually the standard test of short-term (immediate) auditory memory, and also demonstrates adequate registration. Most adults should be able to repeat at least six numbers forward and five backward. This ability may decrease slightly with age, and most patients should be given at least two trials. It is also important to start out slowly by asking patients to remember and repeat only two or three numbers before progressing to larger strings of numbers. Amnestic patients may exhibit normal performance on forward digit span due to intact sensory memory, but will tend to exhibit impairments with the more challenging backward digit span trials that challenge working memory. Remote memory is reflected by the temporal sequence and order in which the patient conveys past information, but information is best confirmed by others. There are some patients who tend to confabulate (fill in memory deficits with material that they create to hide these deficits). A simple test to check for confabulation is to ask the patient, "Have you seen me before?" Frequently, patients who confabulate will assure you that they have met you and will talk about where and when this took place.

Dissociated states and amnestic conditions also present a difficult problem in differential diagnosis. Most often, amnesia due to brain damage is patchy, with little pattern to gaps beyond a possible temporal gradient, or it can be total for brief historical periods in the patient's life, as in transient global amnesia (Quinette et al. 2006). Fugue states or psychogenic amnesia usually relate to traumatic or psychosocial precipitants and have a sudden onset in the absence of organic disorder; often, there is some gain to the individual for not remembering (e.g., to manage guilt, it is to her or his advantage not to remember). Frequently testing the patient's knowledge in a number of different areas can clarify the dissociative or "functional" nature of an amnestic complaint; for example, when a patient claims to have complete amnesia from birth on, but can, often, still perform various mathematical functions, and name the months of the year. Neuropsychological testing may be necessary to clarify memory and other cognitive difficulties that screen positive on the screening cognitive examination.

### Evaluation of Judgment and Insight

Mental status examinations also involve estimates of judgment and insight. Direct questions about judgment attempt to determine whether the patient is aware of what normal, social interaction or responses are. For example, a frequently asked question is, "What should you do if you are in a theater and notice a fire?" Alternatives might be, "Why are laws necessary?" or "Why should people stay away from bad company?" Such questions serve the stated purpose, but superficially, and with uncertain relevance to the real world. Judgment must be examined in the context of recent behavior, the patient's intelligence, memory, and the integrity of other cognitive functions; diagnosis and treatment adherence. A patient may have the sense to quietly exit the hypothetical burning theater, but relate a personal history replete with examples of very poor choices.

Insight may be measured in terms of the patient's understanding of his or her condition and need for treatment. There are many facets of insight, including the presence or absence of a problem, the presence or absence of a personal (as opposed to environmental) problem, of a mental or psychological (as opposed to purely physical) problem, regarding the particular type of psychological problem (e.g., a psychotic patient may argue that the problem is only stress), regarding the need for treatment or the specific type of treatment (inpatient or outpatient, antipsychotic medication or antibiotic), etc. The term lack of insight is occasionally overused; the clinician should avoid concluding that the patient lacks insight, when it might be reasonable for the patient (or even another clinician) to disagree. In either event, the patient's view of the problem, whether insight or not, is critical, as it largely dictates the physician's approach to treatment.

## Conclusion

The biologically and psychologically interdependent functions of consciousness, orientation, and memory are the primary aspects of how we appreciate and negotiate life. They are so basic and central to our lives that we often take them for granted because in most cases they function automatically. However, their separate evaluation is critical for each patient because they are sensitive indicators of how the central nervous system is functioning and of the current and future capacities of the patient to function independently.

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CHAPTER

# 35 Alterations of Speech, Thought, Perception, and Self-Experience

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No laboratory test has yet been developed that defines or determines the severity of any psychiatric disorder. Neither is there a laboratory probe that characterizes the content of an individual's thoughts. Instead, these determinations are based to a large extent on the verbal productions of patients. The routine psychiatric "laboratory" thus exists as interactions between psychiatrist and patient primarily, although not exclusively conversational in nature, designed to elicit characteristic signs and symptoms. Some principles of psychiatric phenomenology may be worth making explicit to put this unique interview process in perspective.

First, psychiatric disorders do not intrude on all realms of brain or cognitive function equally. To quote Hughlings Jackson (1932): "In every insanity there is morbid affection of more or less of the highest cerebral centres or, synonymously, of the highest level of evolution of the cerebral sub-system. …" In other words, it is precisely our advanced and most developed faculties, those faculties that define us as human and as individuals, which are altered by psychiatric conditions. These include a person's willfulness, the rich tapestry of emotions directing that willfulness, the ability to know and judge one's own behavior and that of others, and the ability to express in words complex ideas, including ideas about how one experiences oneself and one's own mental processes. These domains, by virtue of their complexity, are often difficult to objectify.

Second, these higher level processes are integrative; consciousness examined, therefore, via a psychiatric interview does not cleave readily along the traditional subdivisions of mental capacity, that is, perception, belief, emotion, thought, and language. Each of these domains informs, guides, and constrains the others. Given that psychiatric disorders involve higher level mental processes, it is the rule rather than the exception that a psychiatric disorder in a particular person will also cut across different higher level capacities, producing alterations that interweave language, belief, thought, perception, and emotion. Recognizing how these different capacities are realigned with respect to each other—rather than identifying an impairment within a single domain—offers the most informative phenomenological approach to the patient.

Third, contextual factors that shape personal beliefs, expectations, and behaviors must always be attended to. These factors include personal and family history, cultural background, and current circumstances. All too often we are left having to make difficult distinctions between the boundary of normalcy and pathological conditions when such information becomes critical. When does healthy vigilance in a dangerous environment cross over to paranoia? When does mourning the loss of a loved one become a morbid preoccupation? Under what settings might a loose association, in fact, really be a poetic turn of phrase? When is experiencing an angelic presence a predictable outcome of religious worship rather than a delusion? Along these lines, it should be kept in mind that psychiatric manifestations fall along a continuum, ranging from normal variants to the most extreme cases (Strauss 1969). The presence of intermediate phenomena, which, in isolation, are not readily classified as either pathological or normal, has been clearly documented (Strauss 1969).

With these caveats in mind, we shall attempt to characterize major aspects of psychiatric phenomenology.

## Disorders of Speech

Patients produce a range of speech behaviors that have clinical significance. Central to this discussion is the concept of *formal thought disorder*. This term unfortunately ignores the linguistic nature of deviant discourse but has heuristic value insofar as it implies that such deviance reflects how ideas

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flow from one to another during the course of speaking rather than the specific content of ideas themselves.

The *sine qua non* of formal thought disorder is "looseness of association" or "derailment." These terms refer to speech that the psychiatrist cannot "follow," that is, where the overall intention or point of the utterance becomes lost as the speaker shifts idiosyncratically from one frame of reference to another (Andreasen 1979). Consider the following example taken from Hoffman et al. (1982):

> ***Interviewer:*** *Tell me about where you live.*
> ***Patient:*** *I live in one place and then another place. They're black and white you know. That's why I love Christmas and stuff because, you know*, it's *different colors. I used to live in Brooklyn.*

Here the patient seems to be responding to the interviewer's prompt but switches to a Christmas motif that fails to elaborate on the "where I live" theme and does not, in itself, make a point. Of note is that each of the sentences, when considered separately, is quite ordinary and grammatical. Deviance reflects the juxtaposition of phrases and sentences.

A more complex form of derailment is illustrated by the following (Hoffman 1986):

> ***Interviewer:*** *Did you ever try to hurt yourself?*
> ***Patient:*** *I cut myself once when I was in the* kitchen trying to please *David. I was scared for life because if David didn't want me then no man would.*

Here the patient seems to be talking about two frames of reference, the first pertaining to cutting herself, presumably while preparing food, and the second pertaining to reasons for being suicidal. The shift is without warning, that is, the patient did not help the listener by saying, "I never intentionally hurt myself but I was so upset about David that. . . ."

Another related type of discourse production deviance is "flight of ideas." Some authors have not distinguished flight of ideas from derailment (Andreasen 1979), but there is some empirical evidence that the two terms can refer to similar but distinct phenomena (Hoffman et al. 1986). Flight of ideas also refers to speech with shifts in frame of reference, but when the shifts in frame of reference are less idiosyncratic. At times, such shifts can be instigated by similarity of sound of particular words rather than topical relationships (clang association). Most important, the speaker seems to retain the ability to flesh out particular themes or topics when he or she is able to remain within a particular frame of reference. In contrast, looseness of association suggests a sustained inability to fully and coherently elaborate on or remain attentive to *any* theme or topic. Flight of ideas is associated with mania and various medical conditions or substance-induced psychotic states (e.g., thyrotoxicosis, amphetamine-induced psychosis). This form of thought disorder is typically accompanied by pressured speech, that is, speech produced at an abnormally rapid rate that is difficult to interrupt (Andreasen 1979).

A less severe type of formal thought disorder is referred to as "tangentiality." Here, the shifts in frame of reference are less abrupt and, at any particular time, the speaker seems to offer a coherent message. Over time, however, the speaker clearly strays from the original frame of reference. For example:

> ***Interviewer:*** *Can you tell me where you live?*
> ***Patient:*** *I live in Connecticut. We live in a 50-year-old Tudor house that is very much a home. The house shows my personality. It is comfortable and modest. My husband's personality is very different. He is a very closed-off person who makes people feel ill at ease.*

An even milder form of formal thought disorder is "circumstantiality," sometimes referred to as "digressive speech." Here, the shifts in frame of reference occur, but the speaker is able to return to the original conversational point:

> ***Interviewer:*** *What are your thoughts about politics?*
> ***Patient:*** *Well, I'm most interested in national politics, you know, what the President is doing. I think that a lot of our problems are up to him to solve. But I don't know then again if any human being can pull off what he's gotta do. People always promise more than they deliver. That's been my experience all along, teachers, bosses, parents. My life is just one disappointment followed by the next. It gettin' so that I just expect the worst. And that's probably gonna be the case with our new President.*

Formal thought disorder, if prominent, is generally associated with the more severe psychiatric illnesses (e.g., schizophrenia, bipolar disorder, psychotic or mood disorders that are due to general medical conditions or that are substance induced) but does not occur inevitably in these conditions. Milder examples of formal thought disorder are frequently seen in patients with a range of diagnoses, including major depressive disorder, schizotypal personality disorder, and cyclothymic disorder.

Of note is that each of the segments just discussed does not demonstrate any intrinsic alterations in inferential reasoning. Instead, difficulties reflect the flow of sentences and the degree that each coheres to a common theme or topic. Actual breakdowns in reasoning are referred to as illogical thinking. A now classic example was cited by Arieti (1974):

> *I am a virgin.*
> *The Virgin Mary is a virgin.*
> *Therefore I am the Virgin Mary.*

Perseveration reflects the repeated use of particular words or phrases. It is commonly seen in patients with memory impairments resulting from dementia or lesions involving the hippocampal system, and less often in patients with schizophrenia.

Another speech impairment is defined by reduced conversational output and is referred to as poverty of speech. Spontaneous speech is markedly diminished or absent, and responses to questions are met with replies consisting of only a few words. Poverty of speech, or alogia, can be seen in schizophrenia and depression. Patients with anterior aphasia also demonstrate poverty of speech because of impairment in the motor areas of the brain dedicated to speech production. Patients with so-called fluent aphasia (associated with posterior lesions) can also demonstrate poverty of speech during their recovery process; it is likely that these patients curtail their speech production as they become increasingly aware of its intrinsic disorganization. Extreme poverty of speech is

known as *mutism* and can be seen in schizophrenia, dissociative disturbances, catatonic syndromes, and a wide range of brain lesions. Catatonic syndromes are also associated with echolalia, in which the speaker automatically reproduces words or phrases uttered by the interviewer. Thought blocking is extreme poverty of speech that occurs episodically. Patients with this symptom report either that their minds "just go blank" or they are flooded with racing thoughts and cannot sort out a particular message to articulate. Thought blocking is often accompanied by considerable anxiety, which often worsens this symptom. When the patient perseverates on the same word, phrase, or theme, especially if the patient is vague or elliptical, poverty of content of speech can occur even if a normal amount of speech is produced. Poverty of content of speech is most closely associated with schizophrenia and various aphasic syndromes.

Concrete speech involves the use of literal meaning. Verbalizing in conceptually abstract contextual frames is absent, as is the ability to use metaphor:

> ***Question:*** *What happened recently that brought you into the hospital?*
> ***Answer:*** *A taxi came*.

At times, patients produce "lower level" impairments in word construction and selection and in sentence syntax, which provide important clinical information. Consider, for instance, the following utterances:

> he is a *grassical* person
> (Hoffman and Sledge 1984)
> he still had *fooch* with *teykrimez*,
> I'll be willing to betcha
> (Chaika 1974)

These nonwords are characteristic of patients with aphasia caused by impairment of dominant cerebral hemisphere speech centers but can also be produced sporadically by patients with severe schizophrenia.

Another type of lexical deviance occurring in schizophrenic and aphasic speech reflects words inappropriately combined with grammatical endings or other words:

> attain *vigoration* and *strength*
> (Hoffman and Sledge 1984)
> stated not necessarily *factuated*
> (Vetter 1968)
> that's a lie-truth
> (Bleuler 1950)

Slips of the tongue are nonwords that reflect the exchange of phonemes within a phrase:

> *soul hecond* path (intended: whole second path)
> (Chaika 1974)
> or the fusion of words within a phrase:
> a *prettiotic* idea (intended: a pretty idiotic idea)
> (Fromkin 1975)

In general, spontaneously produced nonwords that are not slips of the tongue are referred to as neologisms in the psychiatric literature and paraphasias in the neurology literature.

Patients can also demonstrate word-finding problems that result in inappropriate insertion of lexical elements into sentences. A "mild" example is

> He owns a store on Fifth Avenue, and that's never mentioned because that is his *side-kick (intended: side-line)*.
> (Hoffman and Sledge 1988)

An example of a more severe error in word selection corresponds to a noun inappropriately inserted into a verb-slot of sentence structure:

> fish *school* in their own communities
> (Hoffman and Sledge 1988)

Psychotic and aphasic patients, moreover, may also produce paragrammatisms, that is, utterances in which word order or word combinations deviate from acceptable syntactic forms. An example (which also includes a paraphasia) that still expresses the remnants of grammatical structure follows:

> *That's why, you know, the fact there was no stigmatism (sic) attached to that clearly explained in the record why you were put back*.
> (Hoffman and Sledge 1984)

More deviant utterances of this type are referred to as word salad or incoherence:

> *The honest bring-back-to-life doctors agents must take John Black out through making up design meaning straight neutral underworld shadow tunnel.*
> (Chaika 1974)

Severely psychotic patients may produce sporadic neologistic or paragrammatical constructions. Prolonged social isolation or sustained alienation from other human beings, coupled with bizarre ideation, may, over time, lead the schizophrenic patient to disregard the constraints of ordinary language. If persistently expressed during most utterances, such deviance is much more likely to be produced by patients with aphasia caused by a lesion of the dominant hemisphere (Lecours and Vanier-Clement 1976). Patients with temporal lobe epilepsy may, at times, produce mild, episodic word generation difficulties and paragrammatisms, but these generally occur in the absence of formal thought disorder, as defined earlier.

With stuttering, there is a clear interruption of the flow, rhythm, and completeness of syllables, words, and phrases, but meaning and context are unaffected. Speech is spasmatic and uncoordinated, and, like other dysarthrias, appears related to problems in the muscular coordination.

Finally, it should be noted that most of us are far from perfect speakers. Slips of the tongue, errors in word selection, garbled words, tangentiality, and even frank looseness of associations can be produced sporadically by normal individuals, especially under conditions of heightened arousal or fatigue. Therefore, an important aspect of speech behavior is self-monitoring and subsequent correction of momentary speech irregularities. A failure to recognize and correct

one's own speech irregularities may be an important clue that a significant pathological condition is being expressed. Table 35–1 summarizes disorders of speech.

**Table 35–1 Disorders of Speech**

| Disorder | Definition |
|---|---|
| Looseness of association | Idiosyncratic shifts in frame of reference, failure in elaborating topic |
| Flight of ideas | Shifts in frame of reference, but greater coherence and meaning within the frame |
| Clang association | Shift in frame of reference driven by phonetic similarity of words rather than topical relationships |
| Pressured speech | Speech produced at an abnormally high rate |
| Tangentiality | Less abrupt shifts in frame of reference; at any given time, message is coherent, with deviation from initial topic |
| Circumstantiality | Similar to tangentiality, but with return to the original topic |
| Illogical thinking | Breakdowns in reasoning |
| Perseveration | Inappropriate repetition of words or phrases |
| Poverty of speech | Reduced conversational output |
| Neologism | Nonword phonetic combinations used as words |
| Paragrammatism | Ungrammatical word sequences |
| Word salad or incoherence | Combination of words or phrases that renders utterance devoid of decodable meaning |
| Mutism | Persistent total absence of speech |
| Thought blocking | Episodic interruption of speech |

## Disorders of Thought

First, a simple observation. Many psychiatric disorders present with repetitive mental content, and almost all psychiatric disorders impose some curtailment on content variance. Consider, for instance, the psychotic person who harbors the belief that the Central Intelligence Agency is spying on him. He might find evidence for this belief in unaccounted-for clicks on the telephone (thus, the telephone is being bugged); cars whose license plates contain the letters C, I, or A; or myriad other pieces of data that he relentlessly "discovers" in his daily life. Almost independently of the range of input information received, the patient ends up drawing the same conclusion and is unwilling to consider alternative explanations for these experiences. Depressed patients often have certain negative ideas that they constantly return to. Their minds can become remarkably adept at discovering evidence in daily experience that they are worthless or that they do not deserve to live. Heroin addicts cannot help but think about the next fix, their "works" (the tools used to inject the drug), and the person who supplies the drug. Patients with posttraumatic stress disorder are condemned to relive certain memories of the trauma.

How does psychiatric nomenclature distinguish among these experiences? First, consider delusions. These are false beliefs that are not widely endorsed by other members of the societal group. However, this cannot be all that there is to the definition because we are all liable to have false beliefs whether they are societally endorsed or not. Delusions are false beliefs that are invulnerable to invalidation even if the patient is presented with overwhelming evidence to the contrary. For instance, a delusional patient will believe that her room is bugged even after the room has been completely torn apart looking for the bug.

In contrast, obsessions are preoccupations that the patient is able to acknowledge as being irrationally based. Compulsions are repetitive actions due to obsessions. There are a number of fairly typical obsessions, including a preoccupation with dirt, contamination, or disease, which may be accompanied by ritualized behavior such as repeated hand washing. Repetitive checking is another typical obsessive syndrome, in which the individual is preoccupied with and repeatedly attempts to correct certain potentially dangerous situations (e.g., stoves or irons left on, leaving doors unlocked). Repeated verification of the fact that no such risk exists only temporarily alleviates the anxiety associated with the preoccupation. It is as if the patient cannot retain the memory that the front door was checked minutes earlier. Checking is often conducted in a ritualized fashion, for instance, by repeating the check a predetermined number of times while repeating the Lord's Prayer. A third common syndrome is obsessional orderliness. Here, certain objects need to be arranged in precise order, at times to an absurd degree. Obsessions are generally associated with anxiety and the expectation that terrible consequences will occur (e.g., the house will burn down, the family will be killed) if ritualized behaviors are not completed. Even though the patient will acknowledge that these preoccupations are not rationally based, they can come to dominate his or her entire life. These preoccupations are future-oriented. Patients are condemned to ask themselves repeatedly, "What can I do to avert future disaster?"

Ruminations generally have a basis in a true past experience of the patient. A typical example is a preoccupation with the loss or betrayal of a loved one. Ruminations, in general, are concerned with the irreversibility of certain past events and are associated with affects such as remorse and sadness.

When severe, obsessions and ruminations can assume psychotic proportions. In other words, the patient's awareness of the irrationality of the preoccupation is lost. Persistent compulsions can evolve into belief, as illustrated in the following vignette.

Clinical Vignette 1

A 19-year-old man had a long-standing compulsion to pick up trash on the street and endlessly sort through this collection at home. The elusive nature of "insight" was particularly striking in this patient. Although he found these habits disturbing and attempted to resist them, over time he began to express the conviction that these activities were his "special mission" in life and, later, that the objects were commanding him to perform the rituals.

*Source: Adapted from Fenton and McGlashan (1986). Copyright 1986 American Psychiatric Association. Reprinted with permission.*

Delusions commonly invoke "unseen" forces or processes (aliens, secret agents, microelectronics, the devil)

because they de facto are difficult or impossible to verify by direct experience. This contributes to the irrefutability of the delusion. A more subtle example of this same phenomenon (in this case accompanied by a clinical depression) is as follows:

Clinical Vignette 2

A 38-year-old woman read in the newspaper that an automobile accident resulting in the death of a boy occurred on a country road near her home. She determined that she had driven down that road the same night, although she could not recall seeing the boy. Nonetheless, she became convinced that she killed him. Police reports and the absence of any telltale damage to her car did not diminish her belief. What haunted her was that she could not go back in time to view the accident. This "opportunity" to absolutely ascertain the truth was forever lost. She consequently attempted to give money to the family of the deceased and attempted to arrange for her own arrest.

The "invisibility" of delusional material also applies to many somatic delusions, such as the belief that the insides of one's body are rotting (typically associated with psychotic depression or schizophrenia). A common delusion among patients with schizophrenia in rural Africa is that a snake has occupied one's intestines. In these cases, the fact that one cannot directly look inside one's own body sustains the delusional conviction.

Certain common themes cut across a spectrum ranging from normal to psychotic. Many otherwise normal individuals can be said to have overvalued ideas. These are pet peeves (e.g., the government collects too many taxes) or fixed beliefs (e.g., all men cannot be trusted) that are viewed as meritorious and, therefore, are often shared with or imposed on other people. In contrast, an obsession is a preoccupation that is associated with anxiety, is often viewed as being unhelpful or irrational because day-to-day activities are disrupted, and may thereby be kept entirely private by the patient. In cases of characterological narcissism, all the ideas arising from an individual are more or less overvalued: "What I do, think, or say should be paid attention to by others." Grandiosity takes this theme one step further: "What I do, think, or say is better than what others do, think, or say." Grandiose delusions reflect the extreme case, namely, fixed beliefs that go beyond attributions of individual value or worth by distorting reality, for example, "I am really a rock star, the Pope, Jesus Christ, the next President, the illegitimate son of Queen Elizabeth." The mirror opposite of this spectrum is also evident. A failure to positively endorse one's own ideas or self-worth can evolve into hopelessness, suicidality, and a sense of worthlessness.

Another theme that is expressed across the spectrum of normality to psychosis involves attributing negative intentions to other persons or groups of people. The normal variant is suspiciousness, that is, a cautious attitude derived from the possibility that certain individuals may be harboring malevolent wishes. In contrast, a phobia reflects fearfulness, not related to the intentions of others but instead to the nonhuman environment (fear of heights, elevators, dogs, and so forth). Paranoia reflects a level of suspiciousness that alters routine activities in nonadaptive ways and is accompanied by a tendency to misinterpret ambiguous events or actions in a fashion that reinforces the attribution of malevolent intentions of others. Intrinsic to the nature of paranoia is the belief in some more or less organized "plot." For instance, if a person has become paranoid at work it is often accompanied by the belief that one or more individuals share a common goal (e.g., coworkers are trying to get the patient fired), rather than a general, free-floating fearfulness. This leads inexorably to certain types of inferences that are consistent with the paranoid orientation: for instance, that a filing error committed while the patient was working was actually "planted" by a coworker. This belief orientation can reach the level of a paranoid or persecutory delusion, in which reality testing is consistently and obviously distorted to maintain the belief orientation that others are intending harm. The mechanistic basis of paranoia is uncertain. Current experimental evidence suggests that anomalous internal experiences and exaggerated anticipation of threat are important contributing factors (Freeman 2007).

Frequently associated with a paranoid orientation is self-referential thinking, also known as ideas of reference. Individuals with this symptom erroneously attribute high personal relevance or salience to incidental environmental events. They may, for instance, believe that people are paying special attention to them on the street or that strangers seem to be talking about them behind their backs. Numbers on license plates may appear to contain coded messages, and the movement of people or vehicles within the patient's vicinity may signal special meaning (generally sinister). Other patients report receiving messages from the television or radio, giving them the uncanny sense that the radio or television announcer, song, or commercial somehow has broadcast a message directly to them. Even the specific words or syntax used by others in conversation may seem deliberate and significant, hiding an underlying message. While self-referential thoughts most commonly warn of possible danger, patients with grandiosity may also become self-referential, leading to an expanded sense of self-importance. In any case, self-referential thinking, in turn, can lead to frank paranoid ideation. The individual, in an attempt to make sense of a series of self-referential percepts (and, perhaps, other abnormal experiences such as hallucinations), develops a cognitive scheme that accommodates and explains the "evidence" at hand. Each subsequent instance further confirms the impression that a nefarious plot has been directed toward the patient. This is compounded by the tendency of delusional people toward a hasty reasoning and decisional style in which conclusions are drawn from smaller data sets than are required by nondelusional people (Freeman et al. 2004). Aberrant attribution of salience and subsequent delusion development is at the center of recent hypotheses regarding excess dopamine in psychotic disorders and the role of antipsychotic drugs (Kapur 2003).

Some patients, particularly those who have paranoid tendencies, report abnormal beliefs referred to as delusions of thought control or possession. This involves the belief that other individuals or powers can actually direct the content of one's own thoughts. These include thought broadcasting (that others can read their minds), thought insertion or deletion (that an external agent has placed alien thoughts or removed the patient's own thoughts from his or her mind), or that they themselves are capable of mind reading.

Related delusions of other types of external control, such as that one's actions, emotions, or bodily functions are under the control of an external agent, may be seen as well.

A related, usually milder, self-referential focus is seen with magical thinking. In magical thinking, one's own thoughts, feelings, or behaviors are believed unrealistically to influence external events and history, for example, wishing harm on another can actually make it happen. Magical thinking is frequently seen in earlier developmental stages, as in the child's chant, "step on a crack, break your mother's back."

Often, many disordered elements of thought present simultaneously. The following clinical vignette is an illustration.

Clinical Vignette 3

When Mr. S entered the hospital, he was 26 years old, single, and had been continuously ill for 9 years, during which time he had been hospitalized 12 times. Despite adequate medication, he could slip into a confused state replete with paralyzing ambivalence and a fragmented delusional paranoid experience in which he felt assaulted by painful tactile hallucinations. During some agitated periods, Mr. S seemed to be experiencing an elemental dread about possessing some powerful, aggressive, evil force capable of destroying his most cherished objects and himself. Once, while pacing, he said to his therapist, "Get out of here! I'm insane! You're breathing my air!" Later, he told his therapist that mental illness could be passed through the air like germs. While agitated, he often hid his face and later told his therapist it was so he could not see the flesh peeling off his evil skull, the sight of which could destroy the therapist by driving him insane.

*Source: Adapted from McGlashan (1986).*

Mr. S's world was filled with delusions (he was assaulted by the therapist), magical thinking (psychosis is contagious by proximity), grandiosity (he had the power to destroy others), and projected paranoid ruminations (the therapist should fear him and avoid his destructiveness).

Other kinds of thought content disturbances reflect how patients perceive their own mental or perceptual processes. A common example of this sort of disturbance is racing thoughts. Here, thoughts and mental images occur so rapidly that patients themselves cannot keep track of what they are thinking. Often, but not inevitably, racing thoughts are accompanied by speech irregularities such as looseness of association or tangentiality. Some patients can compensate for such thought content disturbances by reducing the rate or amount of speech produced.

A variety of repetitive thoughts, obsessions, ruminations, or delusions may be depressive and self-destructive in content, especially among the mood disorders, schizophrenic disorders, and borderline personality disorders. Hopelessness, feelings of personal worthlessness, and guilt are frequent cognitive schemas that accompany downturns in mood. In their most severe forms, such ideas become delusional reality as convictions that one is dead, dying, doomed, or dangerous. Unrealistic worries about one's health, or hypochondriasis, can become nihilistic somatic delusions that one's brain is dust or one's insides have turned to excrement.

Suicidal thoughts are also common and often of major concern. Passive suicidal ideation consists of wishes to be dead, but with no clear intent or plan. Active thoughts about killing or hurting oneself, especially if elaborated into a plan, represent incremental leaps in dangerousness and, often, require hospitalization and careful monitoring. Unfortunately, such ideation can be unpredictable and not always congruent with a depressed mood, as in psychotic states.

Tables 35–2 and 35–3 summarize disorders of thought content.

**Table 35–2 Disorders of Thought Content**

| Disorder | Definition |
|---|---|
| Delusion | False belief not endorsed by social group, relatively impervious to invalidation |
| Obsession | Preoccupation acknowledged by patient to be irrational and associated with anxiety |
| Compulsion | Repetitive actions based on obsession |
| Rumination | Preoccupation generally associated with the irreversibility of past events |
| Overvalued idea | Frequently endorsed idea, often imposed on others |
| Grandiosity | Belief that one's ideas, capacities, or actions are generally superior to those of others |
| Suspiciousness | A cautious attitude based on possible malevolent intentions of others |
| Phobia | Persistent and irrational fear of delineated aspects of nonhuman environment (e.g., "germs," heights) |
| Paranoia | Level of suspiciousness altering thinking and behavior in nonadaptive ways |

**Table 35–3 Alterations in the Experience of One's Own Thought and Perception**

| Disorder | Definition |
|---|---|
| Racing thoughts | Thoughts or images experienced as occurring at excessive rate |
| Thought broadcasting | One's own thoughts experienced as being transmitted to another person or agency |
| Thought control | Other people or forces controlling or directing one's thoughts |
| Magical thinking | An irrational belief that thoughts can change external events without intervening actions |
| Referential thinking (Ideas of reference) | Perceptions of other people's actions or speech accompanied by belief that they are directed to, or are in reference to, the self |

Clinical Vignette 4

A 22-year-old man with two prior episodes of disorganized schizophrenia stopped his neuroleptic medication. Two months later, he lost a bet when his favorite soccer team was beaten in World Cup competition. After the game, while watching a late night television talk show, he became disgusted with what he considered to be a poor performance of the talk show host and decided to kill himself. He took a massive and potentially lethal overdose of a relative's benzodiazepines and was later taken to the emergency department when he could not be aroused by his family.

## Perceptual Disturbances

Sensory impressions of the external world obviously form the basis of much conscious experience. However, much of our conscious experience is generated internally. How do I know that I am thinking of a particular person? I "see" an image of that person in my mind, or inwardly "say" the name. Indeed, we can experience internally generated images involving one or more of all five sensory realms. We can "hear" a piece of music as well as imagine the smell of coffee, a feeling of cotton on the forearm, or hitting a good tennis backhand. All are different kinds of internally generated images that reaccess representational capabilities emerging from the senses. We ordinarily do not label such internally generated images as indicative of psychopathology.

As indicated in our introductory remarks, there is a continuum between ordinary self-generated imagery and pathological hallucination (Hoffman 1986, Strauss 1969). Consider first illusions, namely, external sensory impressions that have been temporarily imbued with a novel interpretation. An example is seeing a cloud pattern that resembles the profile or face of, for instance, a famous figure or one's father. This experience in itself would not be considered pathological. This same experience becomes a delusional perception if the person maintains the conviction that the face was not an accidental pattern but was in some sense an actual visual recreation of Abraham Lincoln's face (or the father) that was somehow intended by some force or agency. Here, pathology is intrinsic to inferences that are generated about the percept (delusional attributions) rather than the percept itself.

At the other end of the axis are hallucinations, which in their purest form are percepts that occur spontaneously (i.e., in the absence of particular sensory triggers).

Illusions and hallucinations are underappreciated aspects of normal experience. Preoccupation with another person (e.g., a lost loved one, a feared authority figure) can result in a fleeting visual illusion among normal individuals, for instance, momentarily seeing the longed-for person in a crowd or at a distance. A person in mourning may see the silhouette of the lost person in a shadow or hear that person's voice speaking. A common and normal experience is to misperceive indistinct sounds as a spoken word corresponding to one's own name. Complex visual scenes and sounds can be experienced during daydreams, or at the onset of sleep or waking (Foulkes and Fleisher 1975, Foulkes and Vogel 1965). When especially vivid, such imagery is referred to as hypnagogic hallucination when occurring at sleep onset and hypnopompic hallucination when occurring during drowsiness on waking from sleep. Dreams themselves are clearly hallucinations. Imagery can be quite vivid and ordinarily the dreamer has the sustained conviction of the reality of the dream. It is reasonable to assume that illusion and hallucination are not intrinsically pathological; pathology reflects the duration, prominence, circumstances of occurrence, as well as the relative intractability of beliefs that emerge in response to the experience. For instance, the normal individual quickly realizes that the identity of a misapprehended person was mistaken; the momentary hallucination of a daydream is not retained as an accurate reflection of reality. The psychotic person, on the other hand, may not be able to mentally correct the original misapprehension.

Psychotic states can result in hallucinations related to any one of the five senses. Visions of objects or persons, smells, and tactile sensations can be reported by patients with schizophrenia, mood disorders, similar states caused by medical conditions or induced by drugs, and various forms of epilepsy.

Among schizophrenic patients, however, the most common sensory modality of hallucinations is auditory. Auditory hallucinations can consist of various meaningless sounds (e.g., buzzes, hums, or rumbles), but most commonly spoken words, phrases, or sentences are heard (Hoffman 1986). Hallucinated speech consists of one or many "voices" that ordinarily have distinct acoustic characteristics (such as male versus female, high versus low pitched). For schizophrenic patients, hallucinated voices tend to use words and phrases that are constrained in terms of meaning. For instance, one voice will tend to be highly critical (repetitively using the same words, such as "you are ugly"), whereas another "voice" will repeat reassuring words such as, "I love you." Hallucinations can express verbal content that is not grammatical, for instance, strings of numbers or jumbled phrases. These hallucinations tend to be repeated and, in time, special meanings are attributed to them by the patient. For instance, one schizophrenic patient repeatedly heard the spoken numbers "three-nine" and came to believe that this was a message from her brother, who was 39 years old. Later, she concluded her brother was actually speaking to her.

Hallucinated "voices" sometimes "sound" similar to the actual voice of someone in the person's past but more often are experienced as completely foreign. Occasionally, the acoustic qualities of the hallucinated voice are the same as the patient's own speaking voice. A common denominator is that all are experienced as alien, out of control of the patient, and generated by some outside or nonself agency (often another person, e.g., the CIA, Satan, or God, or increasingly commonly, microelectronic devices). The attribution of alien willfulness is a primary determinant of the level of distress and pathology associated with the hallucination (Hoffman 1986). Vividness of voices (loudness and clarity of the hallucinations) and the degree that the spoken message deviates from the patient's ordinary thoughts also contribute to overall distress and disruptiveness. Voices that criticize and command the patient to undertake destructive actions such as suicide or assault are especially disruptive and ominous. Some cases of auditory hallucinations consist of multiple speakers carrying on conversations with one another.

Auditory hallucinations are also commonly reported by patients with certain types of dissociative disorders. These hallucinations generally have distinct acoustic characteristics associated with particular internalized "personalities," with running commentaries or conversational speech that lack the recurrent or idiosyncratic semantic content of "voices" characteristic of schizophrenia. Most often, the hallucinated voices reported by patients with dissociative identity disorder are "heard from within."

So-called functional hallucinations are intermediate phenomena; they are percept-like and are attributed to an external reality but are merely triggered by an external stimulus. These experiences are not classified as illusions because percepts clearly depart from information derived from an

external stimulus. Functional hallucinations of speech are often reported by psychotic patients, prompted by, for instance, the background noise of running water, fans, or the hum of a refrigerator. For a given patient, the content and vocal characteristics of "voices" triggered by external sound are generally similar or identical to their spontaneous hallucinated "voices."

Table 35–4 summarizes disorders of perception.

**Table 35–4 Disorders of Perception**

| Disorder | Definition |
|---|---|
| Illusions | Sensory impressions temporarily imbued with a novel interpretation |
| Delusional perception | Delusional misinterpretation of a perception or illusion |
| Hallucination | Percept occurring in the absence of any particular sensory triggers |
| Functional hallucination | Percept-like, triggered by an external stimulus but clearly departing from information intrinsic to stimulus |

## Disorders of Identity and Will

Some of the most fascinating expressions of psychopathology emerge as disorders of self-experience, variably manifested as problems of will, identity, self-integration, or self-awareness.

Disorders of will (also known as conative functions) are seen most commonly in psychotic states. Loss of willfulness is seen at its most extreme in catatonic waxy flexibility, echolalia, and echopraxia, but in milder forms it can frequently be detected in schizophrenia, depression, obsessive–compulsive disorder, and posttraumatic states. Mania, in contrast, might be characterized as an overabundance of willful intentions.

Patients who experience thought control believe that certain of their thoughts are willed by some agency or person outside their mind or body. Often, different instances of thoughts that are experienced as being controlled have similar content. For instance, a patient might involuntarily and repetitively experience the thought of wanting to kill a spouse. If experienced as his or her own thought, this experience would be classified as an obsession. If the patient believes that the thoughts are placed in his or her head by the devil, these experiences would be identified as thought control of delusional proportion.

Another example of a disorder of will is the delusion of passivity. In this delusion, patients believe that their actions are controlled by some other being or agency.

Among the most striking forms of identity disturbance are distortions of body image, which contain sensory and cognitive elements to varying degrees. With the phantom limb phenomenon after an amputation, for example, the lost arm or leg retains its perceptual reality. In some forms of transsexualism, body distortion is more ideational, that is, the person harbors the conviction that he is really a female trapped in a male body. In this case, reality testing of the actual anatomy is retained, unlike some cases of severe anorexia nervosa in which the patient insists that she is obese despite clear and objective evidence to the contrary. A variety of body image distortions are displayed in body dysmorphic disorder. These are usually cosmetic in nature; imagined defects in appearance become overwhelming obsessions and compel afflicted patients to seek out plastic surgery or other body-altering treatments on repeated occasions. If these ruminations reach delusional intensity and conviction, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV-TR) (American Psychiatry Association 2000) identifies the syndrome as delusional disorder, somatic type. In this disorder, distortions may become more bizarre (such as a belief of having two heads) and may be accompanied by hallucinations of foul body odor or of insects crawling under the skin (formication).

Dissociation and its related disorders form sets of phenomena that are rich in complexity, often perplexing diagnostically, and occasionally sensational and dramatic in presentation. Dissociation refers to the splitting off of thoughts, feelings, or behaviors from everyday integrated awareness. The dissociative process may involve specific ideas, moods, or deeds, or it may involve complex patterns of behavior, that is, personality states.

It is important to note that dissociation is a normal adaptive mental function. Our everyday tasks of focusing attention and compartmentalizing experience involve dissociation. Normal dissociation is also displayed more explicitly in the phenomenon of hypnosis. The ability to enter different levels of hypnotic trance may be normally distributed in the population. Some people cannot experience hypnosis; other people enter deep trances easily (somnambulists); most people range somewhere in between. The trance state is a mixture of intense absorption with one idea or activity, dissociation from other experiences and sensations, and heightened suggestibility to instruction and demand characteristics of the social situation (Orne 1959, Spiegel and Spiegel 1987). In dissociated hypnotic trance states, anesthesia can occur by suggestion (McGlashan et al. 1969), and other alterations in consciousness can be induced that mimic many of the DSM-IV-TR dissociative disorders, for example, positive and negative (pseudo)hallucinations, voluntary muscle (conversion) paralysis, posthypnotic amnesias, and posthypnotic suggestion.

The phenomenology of posttraumatic disorders may represent another form of normal dissociation insofar as dissociation represents a normal response to major stress ("I am not here" or "This is not happening to me") that fosters adaptation under extreme conditions. The subsequent interaction between reexperiencing memories (often with hallucinatory vividness) and symptoms of distancing or numbing may also represent dissociation at work in modulating the psychological processing and integration of trauma. When the dissociative process is prolonged and perseverative, however, it becomes pathological, and disorder supersedes adaptation.

A relatively common dissociative disorder of self-experience is depersonalization. Patients with this syndrome report that they feel detached or estranged from themselves. Other associated symptoms include feeling like an automaton, a sense that one is actually outside one's own body, or feeling that parts of one's body are detached from each other (Jaspers 1911). A related symptom is derealization, which consists of the experience that one's self is somehow removed from the world, or that the immediate sensations of the environment are unreal or somehow inaccessible. This

constellation of experience can be seen normally at times of exhaustion or bereavement and is associated with many psychiatric disorders, including schizophrenia, panic disorder, substance-induced states, and dissociative disorders, or it may occur as a separate disorder. The most intense and concrete form of derealization may be hysterical conversion, in which sensory anesthesia or motor paralysis ensues based on a dissociated idea.

Other dissociative disorders less frequently encountered involve amnesias, that is, whole time periods lost to memory, usually associated with some negative experience. Rarely, patients may develop a fugue state, that is, amnesia of their entire past in which they adopt a new identity in life. Most publicized but perhaps rarest of all is dissociative identity disorder, or the appearance of more than one distinct identity or personality states in the same person. Several personality states are the rule, usually manifested one at a time and usually dissociated from each other with varying levels of awareness. These identities or personality states have their own characterological profiles. When a person with dissociative identity disorder is in a particular personality, he or she may talk and dress differently and even assume a different name.

Some psychotic syndromes appear related to dissociation and depersonalization, at least on a phenomenological level. The midiidentification syndromes represent such entities. Examples include Capgras' syndrome, in which patients report that other people are no longer real or are doubles, and Fregoli's syndrome, in which patients believe that a seeming multiplicity of persons are actually one individual reappearing in various disguises. These beliefs can extend to family members and friends, that is, individuals who are known intimately by the patient. This experience is captured in the well-known movie *Invasion of the Body Snatchers*.

Another rare disorder of identity is called pseudologia phantasica. In this disorder, patients are compelled to enact certain belief orientations or assume certain roles even though they know that it is "all an act." An example of this disorder is given in the following vignette.

**Clinical Vignette 5**

A 28-year-old woman, during a period of 2 years, was compelled to portray herself as the daughter of a famous actress. This included changing her name, writing factitious letters from the actress to herself, and arranging for herself to receive fake telephone calls and telegrams. All the while she was very afraid that she would be discovered as a fraud.

Probably related to pseudologia phantasica is Munchausen's syndrome. The syndrome is named after Baron von Munchausen, a German soldier and traveler of the eighteenth century who was legendary for his exaggerated tales of accomplishment. The medical use of the term is restricted to patients who feign medical disorders. These individuals, for instance, may swallow blood and induce vomiting to mimic a bleeding ulcer or present in an emergency department with all the signs and symptoms of a perforated appendix. These individuals are often successful in obtaining extensive medical treatment, including multiple major surgical interventions. Patients who feign the symptoms of mental disorders to become patients (but not for external incentives, such as obtaining financial benefits) are diagnosed as having a factitious disorder.

Finally, dissociation is common among psychotic disorders as an obvious curtailment or incongruity of feeling with respect to expressed ideas. The former is referred to as blunted affect, the latter as inappropriate affect. Both are common in schizophrenia.

**Clinical Vignette 6**

Mr. B's onset of schizophrenia came at age 14. By age 21, he had experienced three hospitalizations covering a total of 2 years. He seldom experienced differentiated feelings and reported bafflement with people who did. In one therapy session, he said, "I have an assumption that I'm alive," and he noted that he couldn't "hold on to" feelings about people from the past like his mother and father. He said "You see, I would die if I was feeling . . . I don't have natural reality like others because I'm not living. I'm always in a place of ever death … you have a language that I don't understand though I know you want me to learn it. You want me to want."

*Source: Adapted from McGlashan (1986).*

Agnosias are massive deficits in self-experience usually related to brain damage. They consist of failures to recognize major changes in one's self and functioning. For example, in autotopagnosia, there is denial of hemiparesis and/or blindness (usually left sided) secondary to right parietal lesions, most frequently resulting from stroke. Sometimes, the raw sensory data are intact but the patient is unable to interpret their significance and meaning. In visual agnosia, objects and people are seen but not recognized. In astereognosis, objects cannot be recognized by touch. In prosopagnosia, faces cannot be identified.

The most common and striking agnostic deficit is anosognosia, in which the patient steadfastly refuses to acknowledge that she or he has any illness despite overwhelming evidence to the contrary. Sometimes disability is acknowledged cognitively but not affectively or conatively. The patient persistently ignores the problem and behaves as though it is not there even when the presence of the disorder is acknowledged on direct questioning. This anosodiaphoria or indifference to disability is seen in a milder, functional form as *la belle indifférence*, or calmness in the face of disability associated with conversion hysteria.

Unawareness of illness can take many other forms and is commonly part of psychiatric disorders, especially the psychoses (Prigatano and Schacter 1991). Some form and degree of illness denial or lack of awareness can be seen in most cases of schizophrenia, although the effect of this deficit on judgment and treatment compliance is hard to predict.

Insight is a complex construct with many levels, and loss of insight can become manifest at each level. Complete insight into schizophrenic illness, for example, involves understanding the nature of schizophrenia as a psychotic mental disorder and the lifelong treatment implications of having that diagnosis. At a less than complete level, patients acknowledge that something is wrong and that they need help. Insight is further truncated in patients who deny illness but recognize that others think differently and want the

patients to accept treatment for everyone's peace of mind. Many patients deny vehemently that illness is present when asked, but nonetheless behave in total compliance with the treatment expectations presented to them. Finally, there are those, unfortunately all too common, who are unaware of their illness and noncompliant with treatment. Here, lack of insight has a profound and, often, destructive effect on judgment.

Table 35–5 summarizes disorders of self-experience.

**Table 35–5 Disorders of Integrated (Self) Experience**

| Disorder | Definition |
|---|---|
| Distortions of will | Misattribution of personal responsibility for mental and/or behavioral events, the self experienced as passively controlled or actively manipulating others' thoughts, feelings, or behaviors |
| Distortions of body image | Misapprehension of body sensation, anatomy, or function |
| Dissociation | Splitting off of thoughts, feelings, or behaviors from everyday integrated conscious awareness |
| Depersonalization | Estrangement or detachment from a sense of personal, existential presence |
| Derealization | Perception of the world without a simultaneous feeling or conviction of its reality |
| Blunted affect | Diminution or absence of associated feeling |
| Inappropriate affect | Incongruous association of idea and feeling |
| Agnosia | Deficits in recognition and understanding |
| Anosognosia | Deficit in recognizing and/or understanding obvious neurologically determined disability |
| Unawareness of illness | Truncated insight into psychiatrically determined disability ranging from inattention to complete denial |

## Conclusion

Our psychiatric nomenclature reflects the fact that disorders of speech, thought, perception, and self-experience fall along a continuum ranging between normal and extremely disturbed. We have tended to discuss each manifestation singly. However, it should again be stressed that symptoms in one realm commonly cross over and influence or induce symptoms in other realms. For instance, a patient with a delusion or severe obsession might be pulled conversationally off track during a clinical interview, producing tangentiality or circumstantiality. A pattern of illusory misperceptions, for instance, momentarily seeing the face of a deceased relative on multiple occasions, could induce the delusion that the relative has come back to life. Moreover, this process could work in reverse; delusional preoccupations often induce misperceptions that support the delusion.

No particular sign or symptom is pathognomonic of a specific psychiatric disorder. Clinical assessment is, instead, designed to generate a gestalt consisting of multiple signs and symptoms that tend to cluster together, which identifies particular psychiatric disorders. These disorders are discussed individually in later chapters.

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CHAPTER

# 36 Emotions

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## Behavioral, Neurological, and Cognitive Components of Emotion

Emotion is a subjectively experienced feeling that is related to affect and mood. The experience of emotion occurs through a set of expressive behaviors, the function of the nervous system, and cognitive perception or appraisal. Emotion has behavioral, somatic, and psychic components.

Emotions are not a single response but a collection of responses and are always varied and complex. Emotions are induced by objects or situations that come from interactions with the environment, or from within as representations of internal milieu states. Both internal and external perceptual recall can occur outside of consciousness and induce an emotional response. Emotions are linked to certain inducers and result in consistent responses suggesting their early specification in the nervous system (Damasio 2000).

Charles Darwin's (1872) work on facial expression pioneered the role of expressive behaviors in emotion. Darwin stated that the complex behavioral actions associated with emotions occur to relieve or gratify sensations or desires and that the same movements are repeatedly performed through force of habit. Furthermore, when the opposite state of mind is induced, there is an involuntary tendency to perform movements of the opposite nature. He believed that the behavioral expression of emotion is driven by the nervous system independent of will and, to a large part, independent of habit.

The basic patterns of emotional expression are present at birth and vary little with age and across cultures. By 3 months of age, infant and adult facial expressions of certain emotions are similar (Emde et al. 1978, Emde 1980). The facial expressions and emotions of infants differ little cross-culturally (Bowlby 1973), although more recently this has been brought into question (Camras et al. 2003). It is this nonverbal expression of emotion that the infant uses to communicate with the parent and that the parent uses to determine the needs of the infant. Although emotional expression is considered innate, it can be modified through learning and maturation (Barlow 1988).

Ten basic, fundamentally different expressions of emotion have been proposed by Izard (1977) (Table 36–1).

**Table 36–1 Izard's Ten Basic Emotions**

| |
|---|
| Anger |
| Contempt |
| Disgust |
| Fear |
| Guilt |
| Interest |
| Joy |
| Sadness or distress |
| Shame |
| Surprise |

These different emotions can be combined with one another to produce distinct behavioral reactions within and between individuals (Barlow 1988). The basic emotions are differentiated not only by behavioral expression but also at the psychophysiological and neurobiological levels. The expressive behavioral tradition for the study of emotion assumes that it is the expressive behavior that results in the experience of affect through autonomic or central nervous system activation and that facial expression is the primary component of emotion (Barlow 1988).

A related theory, known as the James–Lange theory (James 1890), proposes that body changes that differ between the basic emotions are a response to a predisposing event, but the sensation of these body changes, and not the event, leads to the expression of the emotion. The view that emotional expression is hardwired is incomplete because the behavioral, experiential, and somatic or physiological components of emotion are often not correlated (Barlow 1988).

The role of the nervous system in the study of emotion was initiated by Walter Cannon (1929) in experiments in which he surgically removed areas of animal brains. These studies of emotion as primarily a function of the brain suggested that the areas of the brain associated with emotion are phylogenetically more ancient and primitive. Pathological emotions involve the deep brain structures more than the cerebral cortex. Emotional activation may occur without the activation of higher cognitive processes and perhaps through connections with the retina (Moore 1973, Zajonc 1984). The

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deep brain structures that may mediate emotions include the limbic system (including the hypothalamus, septum, hippocampus, amygdala, and cingulum) as well as other bodies (such as the thalamus, locus coeruleus, median raphe nuclei, and dentate nuclei of the cerebellum) and the connections between them. This general neuroanatomical pathway for emotion was originally posited by Papez (1995). Research attempting to locate brain structures associated with specific emotions has been conducted in humans through insertion of electrodes that stimulated or coagulated different parts of the cortex and the deep brain (Delgado 1972, Smirnov 1966). The subjective emotions elicited in these studies were accompanied by motor and autonomic changes only in the deep brain structures. Site-specific emotional expression has not been demonstrated; the emotion expressed varies under somewhat different conditions, and different structures may produce similar emotional responses (Izard 1977, Panksepp 1982, Plutchik 1980).

The neocortex and the cortex have also been demonstrated to play a role in emotion. Orbitomedial frontal leukotomy, for example, reduces anxiety (Marks et al. 1966, Tan et al. 1977). Laterality of cortical involvement has been demonstrated by some investigators, although the evidence is conflicting (Leventhal and Tomarken 1986). The right side of the cortex is more involved in unpleasant emotions and the left in pleasurable emotions (Fox and Davidson 1986, Mayes 1979). Perception and expression of emotion may be a right hemisphere function. Right hemisphere damage impairs the ability to express emotions through inflection of the tone of voice (Ross and Mesulam 1979). The roles of right and left hemispheres can be grouped into four categories of theories (Kolb and Taylor 2000): The right hemisphere is dominant over the left with respect to various aspects of emotions (Gainotti 1988, Ley and Bryden 1982); the two hemispheres have complementary specialization for control of mood (Sackeim et al. 1982), such as the left hemisphere being dominant for positive emotions and the right for negative emotions; right hemisphere is dominant for emotional expression parallel to the left's dominance for language (Ross 1984); and the right hemisphere is dominant for the perception of emotion-related cues including facial expression, body posture, and prosody (Adolphs et al. 1996, Rapcsak et al. 1989).

The frontal lobe is involved in the process of interpreting the emotions of others, in particular those from facial expressions. The temporal lobe, and in particular the amygdala, has a role in the perception of emotion, such as fear (Kolb and Taylor 2000). The recall of past experiences requires an intact temporal lobe memory system (Squire et al. 1993). When the hippocampus and related cortical areas are damaged, conscious memories cannot be formed; however, learning not involving conscious memories remains intact, such as unconscious emotional memories formed in the amygdala. Intense stress may alter the function of the hippocampus even in adults with a normal hippocampus (Diamond and Rose 1994), resulting in failure to form conscious memories of a trauma, while at the same time forming unconscious emotional memories (LeDoux and Muller 1997). The anterior cingulate is associated with monitoring of errors and detecting completeness or responses, as well as reappraisal of negative emotional stimuli (Carter et al. 1998, Gerhring and Knight 2000).

The prefrontal cortex is involved with regulation of emotions, as demonstrated by the famous case of Phineas Gage (Harlow 1868), who became impulsive, restless, and disrespectful after damage to the anterior part of his frontal lobe by a railroad iron bar exiting through his forehead from an explosion. Activation in the orbitofrontal and inferior frontal cortex is associated with suppressing and reappraising negative emotional stimuli. Increased prefrontal cortex activity is believed to decrease amygdala activity, a key brain region related to extinction—the weakening of a response to a stimulus, during regulation of emotions (Quirk and Beer 2006). The medial prefrontal cortex integrates cognitive affective information and regulates the hypothalamic pituitary adrenal axis in response to emotional stress (Radley et al. 2006). The regulation of fear after extinction has been found to involve the hippocampal–prefrontal cortex (Kalisch et al. 2006). The role of the prefrontal cortex in extinction has broad clinical implications, as some emotional disorder are characterized by a resistance to extinction of learned emotional anxiogenic stimuli and an avoidance of situations with the potential to induce extinction (Sotres-Bayon et al. 2006) (see Figure 36–1). Table 36–2 provides a summary of damage to specific areas of the brain associated with emotional regulatory deficits.

Neurotransmitters and their presynaptic and postsynaptic receptors seem to mediate emotion within the central nervous system. The possible role of norepinephrine in depression has been suggested by the catecholamine deficiency hypothesis. Many antidepressant drugs increase synaptic concentrations of norepinephrine, whereas reserpine, a catecholamine-depleting drug, causes depressive symptoms (Bunney and Davis 1965, Schildkraut 1965). The indolamine hypothesis postulates that depression results from deficits in serotonin. The gamma-aminobutyric acid, noradrenergic, glumatergic, and serotoninergic systems have all been shown to mediate forms of anxiety.

A third approach to the study of emotion has been based on the cognitive characterization of emotion. Two competing cognitive explanations have been posited: the appraisal theory and Lang's bioinformational approach. The appraisal theory (Schacter and Singer 1962) suggests that emotion is a result of the individual's appraising the context of a situation, attributing a causal relationship after the perception of a generalized, undifferentiated arousal state. There is little evidence to support this theory in its entirety, because emotion can occur in the absence of arousal (Barlow 1988). Emotion has also been viewed by alternative appraisal theories as an adaptive behavior, which follows changes in the environment that are evaluated in terms of their potential impact on the individual (Lazarus 1968, Lazarus et al. 1970). The appraisal model suggests that an evaluation or appraisal of the environment is connected to the initial stimulus preceding and modifying the emotion. For subsequent stimuli, a reappraisal of the earlier situation may ensue. The emotional response is case-based on associative reasoning and provides a preparedness function (Ortony et al. 1988). Appraisal theory has difficulty explaining irrational emotions (Barlow 1988) unless information is appraised and processed by use of an unconscious process (MacLeod et al. 1986). A modification of this theory is the modal model of emotion that has three elements: one, emotions arise when an individual

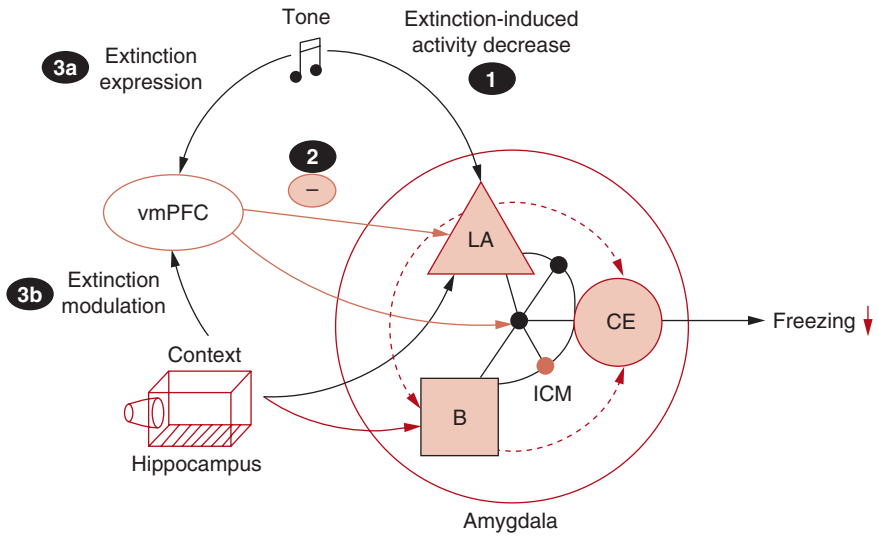



**Figure 36–1** *Fear extinction: neural model. vmPFC = ventral medial prefrontal cortex; LA = lateral amygdala; B = basal amygdala; CE = central nucleus; ICM = intercalated cell masses. [Reproduced from Sotres-Bayon et al. (2005) with permission of Elsevier.]*

attends to a situation and sees it relevant to their goals; two, emotions result in changes in subjective experience, behavior, and central and peripheral physiology; and third, a response that may be modulated. Emotions are regulated by five families of processes: situation selection, situation modification, attentional deployment, cognitive change, and response modification (Gross and Thompson 2007) (see Figure 36–2).

An alternative cognitive explanation of emotion is the bioinformational approach (Lang 1985). Emotion involves processing and accessing information stored in memory. Information on both the stimulus and the response is stored in memory. This information is then interpreted on the basis of the significance of the event, allowing expression of the appropriate emotion in intensity consistent with the stimulus.

Research into emotional states based on factor-analytical approaches has resulted in various models to characterize the range of emotional expression. Factor analysis of dimensions of affect and personality has given rise to dimensional models, which are considered theoretical models to describe not only emotion but also personality. Dimensional models usually attempt to describe emotions in only two or three bidirectional dimensions, such as Eysenck (1967) two-factor model. One axis is called introversion–extroversion, and the other neuroticism–stability. In

**Table 36–2 Areas of Damage Associated with Deficits in Regulation of Emotion**

| | |
|---|---|
| Lack of knowledge of social rewards | Temporal lobe, OFC, and DIPFC |
| Impaired filtering of emotional information | OFC |
| Failure to maximize positive emotion | OFC |
| Impaired reversal learning | OFC |
| Failure to accomplish goals | DIPFC and OFC |
| Impaired response to anticipated startle | OFC |
| Aberrant sexual behaviors | Temporal lobe, amygdala, and OFC |
| Increased rage, violence, explosive temper, aggression, hostility, anger, irritability, irreverence, and lability | Temporal lobe, amygdala, caudate, ACC, and OFC |
| Increased anxiety | OFC and PFC |
| Increased pride | OFC |
| Impulsiveness | VMPFC |
| Change in subjective emotional experience | OFC and ACC |
| Placidity, passivity, and apathy | Temporal lobe, amygdala, caudate, ACC, OFC, and lateral PFC |
| Depression and less happiness | OFC and DIPFC |
| Blunted affect | Temporal lobe, OFC, and DIPFC |
| Loss//reduction of anger or fear | Temporal lobe, amygdala, thalamus, ACC, and OFC |
| Lack of embarrassment | OFC |
| Impaired reflexive smiling | Corticomotor strip and corticobulbar connections |
| Inappropriate crying or laughing | OFC, lateral PFC, caudate, and temporal lobe |
| Impaired posed facial expressions | Extrapyramidal system (basal ganglia) |

ACC = anterior cingulate cortex; DIPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex; VMPFC = ventromedial prefrontal cortex.

*Source*: Reproduced from Beer (2007, pp. 71–72) with permission of Guilford Press.

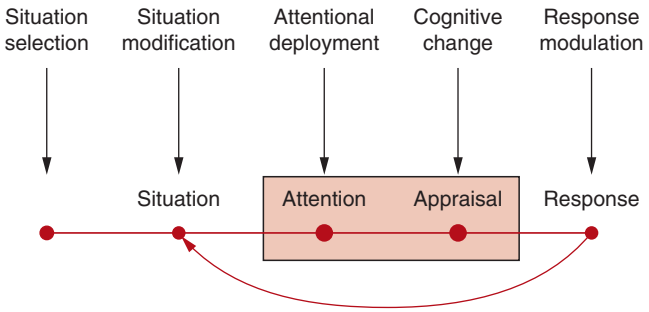



**Figure 36–2** *Modal model using a feedback loop highlighting five families of emotional regulation strategies. [Reproduced from Gross and Thompson (2007, p. 10).]*

Eysenck's biological theory, emotions are associated with an individual's level of arousal that is set either too high or too low by the reticular-activating system. Extroverts seek out greater stimulation because of low levels of arousal, whereas introverts, who have high levels of arousal, need less stimulation. Neuroticism is theorized to involve the autonomic nervous system; neurotic individuals have increased reactivity in the autonomic nervous system. Emotion results from the interaction of these two axes and the limbic system.

An alternative approach is the circumplex model, in which emotions are placed in a circular order reflecting their relationship to other emotions. The opposite emotion is on the other side of the circle. Tellegen (1985) created a circumplex model that is divided into eight sections: strong engagement, high negative affect, unpleasantness, low positive affect, disengagement, low negative affect, pleasantness, and high positive affect. This model can be used to capture the distinction between an anxious, depressed, or manic mood and affect, as well as to demonstrate that these moods are a continuum. An anxious mood is considered to be a high negative affect, with descriptors such as distressed, fearful, hostile, jittery, nervous, and scornful. A depressed mood in the circumplex model would be a low positive affect, including descriptors such as being drowsy, dull, sleepy, and sluggish. A manic affect would be captured by terms in the high positive affect dimension: active, elated, enthusiastic, excited, peppy, and strong.

The strength of an emotion may be amplified, attenuated, or maintained, which is referred to as emotional regulation (Thompson 1994) or affective style (Davidson 1998). Through this process the individual can be distracted from aversive stimuli and generate imagery to replace unwanted emotions (Derryberry and Reed 1996), making it difficult to interpret where emotions end and regulation begins.

## Assessment of Mood and Affect in the Clinical Interview

Two terms are often used to refer to an individual's emotion: affect and mood (Table 36–3). In the absence of a psychopathological process, affect fluctuates with time and context and ranges from sadness to anger to elation, depending on the emotional state. Affect can be expressed through autonomic responses, body movements, and alterations in speech to concrete or abstract stimuli. Observing a violent act exemplifies a concrete stimulus that could lead to the expression of fear; hearing the abstract term love could result in the expression of an elated affect. Speech changes that reflect affect include tone of voice, vocalization, and word selection. Visible autonomic changes that may reflect changes in affect include sweating, trembling, blushing, and becoming flush. Changes in posture, alterations in facial expression, reactive responses, and grooming movements are body changes seen in expression of affect. Reactive movements include movements of the body and face made in response to a novel stimulus, such as in a startle response, when an individual jumps or turns and looks at the stimulus. Changes in facial movements of the mouth, nose, and eyes are found with different affective states. Manipulation of one's appearance is common in states of discomfort; individuals may fix their hair, clean their nails, scratch, or straighten their clothes.

**Table 36–3 Affect and Mood**

| | |
|---|---|
| Affect | The observable behavior seen in the expression of emotion. Affect responds to changes in emotional states. |
| Mood | A sustained and pervasive emotion. Mood is frequently the reported emotional state. |

Affect has three functions: self-perception, communication, and motivation (Othmer and Othmer 1994). Self-perception is the emotional value judgment or the affective response associated with affect. This function of affect tells one whether an experience is good or bad. A smile or an accelerated heart rate is an example of self-perception. The expression of affect communicates to others our emotional response to events, interactions, behavior, and situations. Affect precedes a behavioral response or motivates it. For example, anger is a precursor to aggression.

Social and cultural norms determine whether an affect is appropriate or disturbed for a given situation. Disturbances in affect (Table 36–4) may be quantitative or qualitative and include blunted, flat, inappropriate, labile, and restricted or constricted affect (American Psychiatric Association 2000, p. 819). An appropriate affect, the normal condition, is exemplified by people who are able to express the full range of emotions in a manner consistent with their thoughts and speech.

Evaluation of affect consists of monitoring gestures, body movements, and facial expressions. Because adults are frequently capable of controlling facial expression in attempts to intentionally or unintentionally suppress their affect, other behavioral gestures may give clues to the underlying affect. The quality, duration or mobility,

**Table 36–4 Disturbances in Affect**

| | |
|---|---|
| Blunted | Severe reduction in the intensity of emotional expression |
| Fixed | Display of only one particular emotion, and absence of range and mobility of affect |
| Flat | Near absence of affective expression |
| Inappropriate | Emotional expression and thought content do not coincide |
| Labile | Repeated, rapid, and abrupt variability in affective expression occurs |
| Restricted or constricted | Mild-to-moderate reduction in emotional expression |

appropriateness, intensity, range, and reactivity or control over the affect should be considered.

The range of the affect is characterized by the variety of emotional expressions noted in a session. Normal individuals express different feelings at different times. Patients who appropriately express many different emotions have a full or broad range of affect. A restricted range of affect is seen in individuals who have a limited emotional expression, whereas a fixed or immobile affect is found in those who display only one type of emotion. The intensity of affect (the strength of the emotional expression) normally varies according to the situation. Those with limited emotional expression may have a blunted or a flattened affect. The mobility of affect is the ease and speed with which one moves from one type of emotion to another. Changes in the type and intensity of emotional expression normally occur gradually. Reduced mobility in affect is also referred to as constricted affect. When the affect is extremely constricted to one emotion, it is called a fixed or immobile affect. When no affect is displayed, it is reported to be flat. Pathologically increased mobility of affect is referred to as labile. The reactivity is the extent to which the affect changes in response to an environmental stimulus. When the patient does not respond to the examiner's provocation, such as joking, the affect is nonreactive (Manschreck and Keller 1989, Trzepacz and Baker 1993) (Table 36–5).

**Table 36–5 Description of Affect**

| Parameter of Affect | Normal | Abnormal |
|---|---|---|
| Appropriateness | Appropriate | Inappropriate |
| | Congruent | Incongruent |
| Intensity | Normal | Blunted |
| | | Exaggerated |
| | | Flat |
| | | Heightened |
| | | Overly dramatic |
| Mobility | Mobile | Constricted |
| | | Fixed |
| | | Immobile |
| | | Labile |
| Range | Full range | Restricted range |
| Reactivity | Reactive | Nonreactive |
| | Responsive | Nonresponsive |

*Source*: Reproduced from Trzepacz and Baker (1993) with permission of Oxford University Press.

Mood and affect are related but differ in their pattern of stability over time. Affect fluctuates, whereas mood is a more pervasive and sustained emotional state (American Psychiatric Association 2000, p. 825). Unlike affect, which is observed, mood is not always readily discernible or observed but may need to be reported. An alexithymic person is unable to verbalize or has difficulty describing or being aware of emotions or moods. Mood colors an individual's perception of the environment. Mood can be characterized as dysphoric, elevated, expansive, irritable, or euthymic (Table 36–6). Mood is described by its quality, stability, reactivity, intensity, duration, and congruence with thought content

**Table 36–6 Mood States**

| | |
|---|---|
| Dysphoric | Includes sustained emotional states such as sadness, anxiety, or irritability |
| Elevated | Exaggerated feeling of well-being, euphoria, or elation |
| Expansive | Lack of restraint in expressing feelings |
| Irritable | Easily annoyed or angered |
| Euthymic | Mood in the normal range |

(Table 36–7). A particular mood is not necessarily abnormal or pathological but must be evaluated in the context of the patient's entire history and psychiatric mental status examination.

Emotions are not defining characteristics of just Axis I disorders but also of Axis II personality disorders. Almost

**Table 36–7 Clinical Assessment of Mood**

| | |
|---|---|
| Evaluate its quality | How do you feel? |
| | What is your mood like? |
| Evaluate its stability | Do you always feel like this? |
| Evaluate its reactivity | Does your mood ever change? |
| | When does your mood change? |
| Evaluate its intensity | What is it like to feel this way? |
| | On a scale of 1–10, how would you rate your mood? |
| Evaluate its duration | How long have you felt this way? |
| Evaluate whether the mood is congruent with the thought content | |

all of the Axis II disorders contain at least one specific emotion that is affect related. Table 36–8 lists the specific criteria that are affect related for each of the personality disorders (Clark 2000). In borderline personality disorder emotional dysregulation, the inability to change or regulate emotional cues, experiences, actions, verbal responses, and nonverbal expression has been proposed to explain their greater emotional sensitivity, greater emotional reactivity, and slower return to baseline arousal (Figure 36–3) (Linehan 1993).

## Emotional Expression of Anxiety

### Spectrum of Anxiety

Anxiety is an emotion characterized by apprehension and anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension (American Psychiatric Association 2000, p. 820). The perceived danger may be either an internal or an external fear. The physiological manifestations of anxiety (Table 36–9) may present as symptoms of activation of the autonomic nervous system. Anxiety is a normal reaction to a situation where immediate danger exists and may result in physical harm. Anxiety is also a normal response to situations that pose a threat to self-esteem or psychological well-being. Pathological anxiety occurs in situations where there is no real physical or psychological danger or when the emotional

**Table 36–8 Affect-Related Personality Disorder Criteria**

| Disorder | Criteria |
|---|---|
| Anger/irritability | |
| Paranoid | Quick to react angrily to perceived character attacks |
| Antisocial | Irritability and aggressiveness |
| Borderline | Inappropriate, intense anger |
| Anxiety | |
| Schizotypal | Excessive social anxiety associated with paranoid fears |
| Avoidant | Avoids interpersonal contact because of fears of criticism, disapproval, or rejection |
| | Fears of being shamed or ridiculed |
| Dependent | Excessive need to be taken care of indicated by:<br>• Fears of separation<br>• Fears of loss of support or approval<br>• Fears of being left to take care of self |
| Restricted emotionality | |
| Schizoid | Restricted emotional range in interpersonal settings |
| | Appears indifferent to praise or criticism |
| | Coldness, detachment, or flattened affectivity |
| Schizotypal | Inappropriate or constricted affect |
| Emotional deficits | |
| Antisocial | Lack of remorse |
| Narcissistic | Lack of empathy |
| Emotion related | |
| Borderline | Frantic efforts to avoid abandonment |
| | Chronic feelings of emptiness |
| Narcissistic | Often envious of others or believes that others are envious of self |
| Dependent | Uncomfortable and helpless when alone because of fears of being unable to care for self |
| | Clinging and submissive behavior |
| Obsessive–compulsive | Shows rigidity and stubbornness |

*Source*: Reproduced from Clark (2000, p. 186) with permission of Oxford University Press. Updated by authors using DSM-IV-TR criteria.

reaction is disproportionate in intensity to the actual danger (Spielberger and Rickman 1990).

## Etiology of Anxiety

Traditionally, the emotion of anxiety has been dichotomized into fear and neurotic anxiety. Fear, or objective anxiety, as conceptualized by Freud (1936, 1959), consisted of three components: a real external danger, an accurate perception of the danger as potentially harmful, and an emotional response of anxiety, which varied in intensity proportional to the magnitude of the objective danger. Neurotic anxiety, as Freud described it, was also a psychobiological process; however, the danger was from within, in the form of forbidden instinctual drives that were punished in childhood, repressed, and subsequently about to escape from the individual's control (Spielberger 1966). Fear and anxiety may be present in varying proportions in a given situation. Elucidating the cause of the affect is more important clinically than determining whether the emotion is fear or anxiety (Uhde and Nemiah 1989).

More recent theories of the emotion of anxiety can be divided into stimulus- and response-oriented theories. The former construct suggests that stimulus events serve to initiate the emotional response. It is the nature of the event (the thoughts, feelings, and situation associated with the event) that precipitates the response. An example of a stimulus-oriented theory is Goldstein (1940) catastrophic reaction. A situation that represents a threat to the individual's existence, physical or psychological, is necessary for impairment of objective behavior resulting in the subjective experience of anxiety.

Fear may result in anxiety disorder when it becomes greater than warranted or occurs in inappropriate situations. LeDoux (2000) has proposed that anxiety may develop as a conditioned response to fear following exposure to the unconditioned stimuli, not dissimilar to conditioned response proposed by Pavlov (1927). Subsequently, exposure to a conditioned stimulus meditated by the amygdala leads to activation of a defensive behavior, autonomic arousal, hypoalgesia, somatic reflex potentiation, and pituitary–adrenal axis activation.

The response-oriented approach focuses on the resultant affect. The response-oriented theorists hold that the anxiety response is the same regardless of the stimulus. Anxiety is an innate emotion resulting from a neurophysiological response that can be modified through learning. Pathological anxiety differs from normal anxiety by the increased intensity, frequency, and duration of the neurophysiological response.

The trait–state dichotomy (Cattell and Scheier 1961) of anxiety is an outgrowth of the response-oriented theorists. Trait is viewed as a personality feature, whereby the individual consistently behaves anxiously despite the situation. State refers to momentary feelings of anxiety. Despite some detractors to this theoretical distinction (Allen and Potkay 1981), the validity of this dichotomy has been shown in research demonstrating trait anxiety to remain stable over time and to be impervious to stress, despite circumstances (Spielberger and Rickman 1990). The stimuli that elicit anxiety, according to trait–state anxiety theory (Figure 36–4), may be either intrapsychic or from environmental sources. Anxiety from situations that threaten personal adequacy is found more often in individuals with high trait anxiety.

Other cognitive theories of anxiety are outgrowths of the response-oriented view. Beck and colleagues (1974) believed that anxiety results from a misperception of danger or an unrealistic heightened expectation of harm. The degree of the anxiety is directly proportional to the anticipated severity of the adversity and the degree to which the individual cognitively distorts these fears (Table 36–10). The phenomenology and maintenance of anxiety has been proposed to be a result of counterproductive efforts to regulate emotions. That core features of anxiety, such as worry and behavioral avoidance, are maladaptive attempts to regulate uncomfortable or unwanted emotions (Campbell-Sills and Barlow 2007).

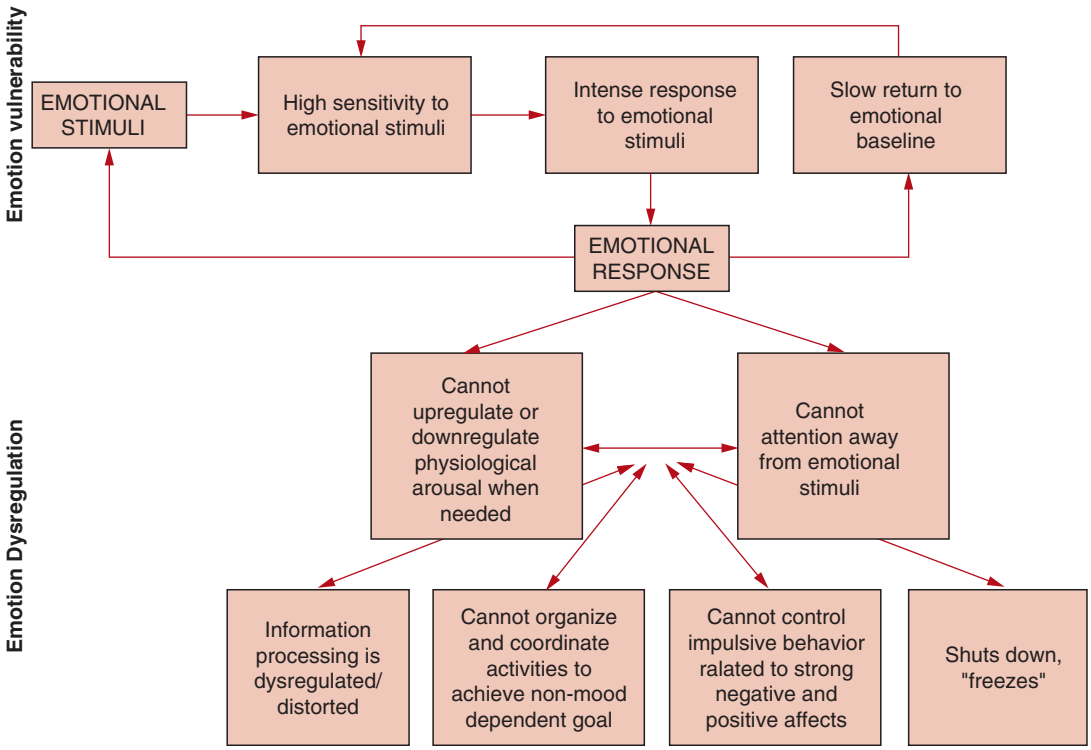



**Figure 36–4** *Pervasive emotion dysregulation. [Reproduced from Linehan et al. (2007, p. 584).]*

Kagan and colleagues have suggested that behavioral inhibition in childhood may be an antecedent of anxiety disorders in adulthood. Children with an inhibited temperament tend to be timid with people, objects, and situations that are novel or unfamiliar. They have found that children of parents with panic disorder with agoraphobia, including those with comorbid major depressive disorder, are at increased risk of behavioral inhibition; children identified as having behavioral inhibition have high rates of childhood-onset anxiety disorders; behavioral inhibition is associated with familial risk for anxiety disorders; children with behavioral inhibition and anxiety disorders have greater familial anxiety disorders; and children who remain inhibited over time are at highest risk of anxiety disorders (Rosenbaum et al. 1993).

**Table 36–9 Physiological Manifestations of Anxiety**

| |
|---|
| Elevated blood pressure |
| Cardiac discomfort |
| Palpitations |
| Tachycardia |
| Diaphoresis |
| Dizziness |
| Dry mouth |
| Irregularities in breathing |
| Hyperventilation |
| Musculoskeletal disturbances |
| Restlessness |
| Tremors |
| Weakness |

## Clinical Presentation of Anxiety

Anxiety is an emotion that may be present in many psychiatric disorders as well as other medical conditions (Table 36–11). Anxiety may be a prominent feature in numerous neurological disorders, hypoxic states, and endocrine disorders. Uremia, posthepatitis syndrome, infectious mononucleosis, porphyria, febrile illnesses and chronic infections, systemic malignancies, carcinoid syndrome, and hypoglycemia have been implicated in producing states of anxiety. Inflammatory diseases and some vitamin deficiencies have also been implicated. A number of toxic agents have been shown to result in anxiety (Cummings 1985).

Anxiety is a common symptom in psychosis, mood disorders, organic disorders, delirium and dementia, and somatoform disorders. Anxiety is the prevailing mood state in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revised (DSM-IV-TR) anxiety disorders: panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive–compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified (NOS). Anxiety is also the prominent feature in adjustment disorders with anxiety.

The clinical presentation of anxiety symptoms varies with the specific disorder. Panic attacks may be present in nearly all the specific anxiety disorders. A panic attack is described as a sudden, discrete period of intense apprehension, fearfulness, or terror associated with physical symptoms including shortness of breath, palpitations, and chest discomfort. During a panic attack, the individual frequently

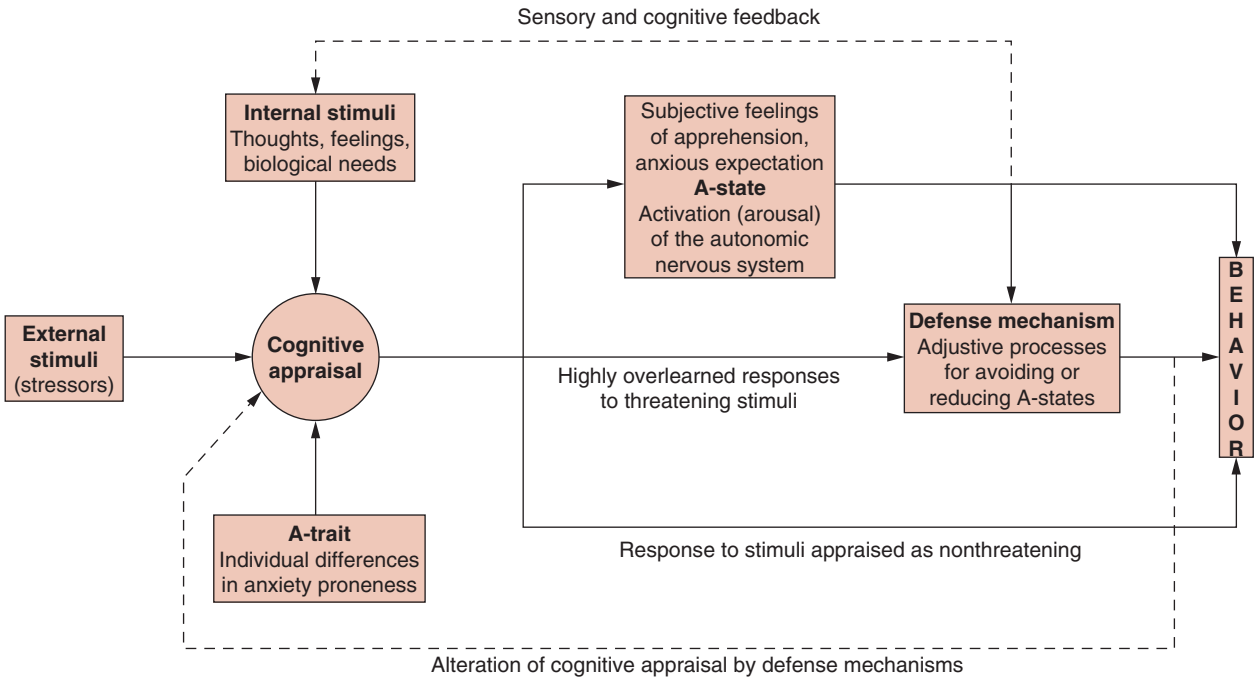



**Figure 36–3** *A trait–state conception of anxiety. [Reproduced from Spielberger (1966, p. 17).]*

**Table 36–10 Theories of Anxiety**

| |
|---|
| Objective–neurotic |
| Stimulus oriented |
| Response oriented |
| Trait–state |
| Cognitive |

has feelings of impending doom, a fear of losing control, a sense of imminent danger, and an urge to escape. Panic attacks are divided into three characteristic types by the onset of the attack in relation to the presence or absence of a situational stimulus (Table 36–12). Unexpected panic attacks occur spontaneously, unassociated with a situational trigger. Situationally bound panic attacks occur immediately on exposure to or in anticipation of a situational cue. Situationally predisposed panic attacks are more likely to occur on exposure to a specific stimulus but do not necessarily occur immediately. Unexpected panic attacks are necessary for a diagnosis of one of the panic disorders. Situationally bound panic attacks are characteristic of social and specific phobias. The situationally predisposed panic attack occurs in panic disorder, specific phobias, or social phobias.

The characteristic presentation of anxiety in phobic disorders is a persistent, irrational fear of a specific object, activity, or situation that results in a desire to avoid it. When exposed to the stimulus, the phobic individual experiences intense, autonomic symptoms associated with fear. The response is frequently difficult to distinguish from the anxiety of panic disorder, which is characteristically spontaneous and not situationally provoked. Anxiety symptoms associated with increased arousal, reexperience of a traumatic event, and avoidance of stimuli reminiscent of the trauma are characteristic of both acute and posttraumatic stress disorders. Obsessions, persistent ideas, thoughts, impulses, or images that are intrusive and inappropriate result in the distress and anxiety characteristic of obsessive–compulsive

**Table 36–11 Anxiety Presenting in Medical Conditions**

| | |
|---|---|
| Neurological disorders | Cerebral neoplasms, cerebral syphilis, cerebral trauma, cerebrovascular disease, encephalitis, epilepsy, Huntington's disease, migraine, multiple sclerosis, postconcussional syndrome, subarachnoid hemorrhage, and Wilson's disease |
| Hypoxia | Anemia, cardiac arrhythmias, cardiovascular disease, and pulmonary insufficiency |
| Endocrine disorders | Adrenal dysfunction, disorders of female virilization, parathyroid dysfunction, pheochromocytoma, pituitary dysfunction, and thyroid dysfunction |
| Inflammatory diseases | Polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, and temporal arteritis |
| Vitamin deficiencies | Pellagra and vitamin $B_{12}$ deficiency |
| Other systemic disorders | Carcinoid syndrome, chronic infections, febrile illnesses, hypoglycemia, infectious mononucleosis, porphyria, posthepatitis syndrome, uremia, and systemic malignancies |
| Toxic agents | Alcohol, amphetamines, arsenic, benzene, cannabis, caffeine, carbon disulfide, mercury, organophosphates, penicillin, phosphorus, sulfonamides, sympathomimetic agents, and vasopressors |

*Source*: Reproduced from Cummings (1985, p. 214) with permission of Allyn & Bacon.

**Table 36–12 Types of Panic Attacks and DSM-IV-TR Anxiety Disorder**

| Type | Onset | Situational Trigger | DSM-IV-TR Diagnoses |
|---|---|---|---|
| Unexpected | Spontaneous | Unassociated | Panic disorder |
| Situationally bound | Immediate | On exposure | Social phobia<br>Specific phobia |
| Situationally predisposed | Not always immediate | On exposure | Panic disorder<br>Social phobia<br>Specific phobia |

disorder. The associated compulsion is a repetitive behavior or mental act, the goal of which is to prevent or reduce anxiety resulting from the obsession. Generalized anxiety disorder is characterized by excessive worrying, often about routine life circumstances. The object of worry may shift from one concern to another. Associated with generalized anxiety disorder are physiological symptoms, including muscle tension presenting as trembling, twitching, feeling shaky, or muscle aches or soreness. Autonomic aspects to the anxiety may be present, including cold, clammy hands, dry mouth, sweating, nausea or diarrhea, urinary frequency, and trouble swallowing. Individuals with generalized anxiety disorder frequently have an exaggerated startle response.

Clinical Vignette 1

A 45-year-old man was seen in the emergency department. He was dressed in a hospital gown and was observed to be hyperventilating, clutching his chest. He kept yelling out, "I'm dying, I'm having a heart attack, I can't breathe." His electrocardiogram, laboratory, and physical examination findings were all normal except for an elevated blood pressure. The patient was diaphoretic and restless and also complained of thirst. This was his third presentation this week to the emergency department. The patient was admitted to the coronary care unit on the other two occasions, with no evidence of a myocardial infarction. He appeared to be irritable and anxious. His speech was loud. When interviewed, he acknowledged feeling "wound up, nervous, and anxious." His affect during the interview was labile, full range, reactive, and mainly appropriate but exaggerated. He stated that he did not know what caused these attacks and that they came "out of the blue." Between episodes, he felt somewhat "nervous" but mainly "all right."

## Emotional Expression of Depression

### Spectrum of Depression

Depression refers not only to an emotional state that is characterized by brief or mild periods of sadness or being "down" but also to a clinical condition characterized by depressed mood. A sense of helplessness or loss of self-esteem is often present in a depressed mood. Sadness, dejection, self-reproach, helplessness, despair, feelings of rejection, pessimism, and boredom may be terms used to describe the dysphoric, painful, or unpleasant feelings associated with depression (Hamilton 1982). Depressed mood states are present in simple unhappiness, grief or bereavement, demoralization, and mood disorders.

Demoralization is a condition of low self-esteem, helplessness, hopelessness, sadness, and anxiety (Dohrenwend et al. 1980). Demoralization is experienced in a variety of situations including severe physical illness, chronic illness, and conditions of marginalization as well as psychiatric disorders. The degree to which an individual is demoralized can be considered her or his psychological temperature and may provide a conceptual continuity of depressive symptoms from normalcy to clinical disorder.

Sadness appropriate to a real loss is part of mourning or grief. The depressed affect accompanying grief differs from other depressed states by a sense of relief felt with the expression of grief (Jacobson 1974). A depressed mood accompanied by poor appetite, weight loss, and insomnia commonly occurs during bereavement. If bereavement is also associated with morbid preoccupation with worthlessness, guilt about things other than actions taken or not taken by the survivor at the time of death, thoughts of death other than the survivor feeling that he or she would be better off dead or should have died with the deceased person, prolonged and marked functional impairment, marked psychomotor retardation, or hallucinatory experiences other than thinking that he or she hears the voice of or transiently sees the image of the deceased person, this suggests that the bereavement is beyond the expected norm and that a major depressive episode is present. The duration and expression of normal bereavement vary considerably among different cultural groups.

### Etiology of Depression

Theories of the origins of pathological depressed mood states can be found in the Hippocratic writings of the fourth and fifth centuries. These early writings defined melancholia to be a prolonged state of depression, with associated aversion to food, despondency, sleeplessness, irritability, and restlessness. Of the four humors, blood, yellow bile, black bile, and phlegm, an excess of black bile was thought by the ancient Greeks to play a distinct role in the development of melancholia. The introduction of the term depression as a substitute for melancholia in the mid-1800s began to signify a psychological and not merely physiological understanding of depressive mood states. Modern conceptualizations of the etiological origins of the emotion of depression encompass a broad theoretical spectrum, including early environmental, personality, psychodynamic, cognitive, life events and social stress, and neurobiological theories.

Early environmental theories considered parental loss, parental separation, and parental style to be risk factors for depression. There is little evidence in experimental controlled studies to support a relationship between parental loss by

death in childhood and depression in adulthood (Crook and Eliot 1980, Tennant et al. 1980, Canetti et al. 2000). The role of parental separation appears to be more complex; separations involving family discord, such as divorce, may have a long-term impact (Canetti et al. 2000); and studies that have suggested a role for parental death in major depression in adulthood have found a more robust role for parental separation (Agid et al. 1999). However, methodological issues in this area of research continue to create speculation as to the validity of such findings (Tennant 1988), in particular, the lack of adequate accounting of the effects of genetic and environmental factors preceding the loss. Parental styles from rejecting and indifferent to overprotective and controlling have been posited to predispose to adult depression; however, evidence of a causal relationship is yet to be demonstrated. Adult attachment, insecure attachment, has been shown to lead to depressive symptoms in adulthood through its impact on self-worth contingencies and self-esteem (Roberts et al. 1996).

There are four major models for the role of personality in depression: vulnerability model, complication model, spectrum model, and pathoplasty model. The vulnerability or predispositional model considers that certain antecedent personality characteristics render an individual vulnerable to the development of depression. An example of this model is Cloninger (1987) theory that neurobiological processes interact with heritable personality traits. He stated that there are three underlying dimensions of personality defined by their stimulus–response characteristics that are genetically and neuroanatomically based: novelty seeking, harm avoidance, and reward dependence (Figure 36–5). Susceptibility to reactive dysphoria is primarily determined by high reward dependence and reduced by high harm avoidance and high novelty seeking (Cloninger 1986).

The complication model is the reverse of the predispositional model. According to this model, clinical depression leads an individual to change the way she or he interacts with others or perceives herself or himself. The spectrum model proposes a continuum between temperament and mood disorders. Pessimism, moodiness, passivity, negativity, and low energy may be personality characteristics that represent the same genetic endowment in normal or milder depressive states as in pathological syndromes. Akiskal and Akiskal (1992) have suggested that cyclothymic, depressive, and hyperthymic temperaments represent the subclinical foundations from which affective episodes arise (Table 36–13). The mechanism postulated by the fourth model, the pathoplasty model, that symptomatic expression and course of depression are influenced by personality characteristics has not been demonstrated in studies measuring personality attributes before the development of a depressive episode (Angst and Clayton 1986, Hirschfeld et al. 1989, Lewinsohn et al. 1988, Nystrom and Lindegard 1975).

The psychodynamic understanding of depression has evolved with the development of psychoanalytic theory. It holds that depression is the result of disturbance of self-esteem in the context of failed interpersonal relationships. These childhood relationships are internalized and reactivated with the onset of depression. These object relationships are also externalized into current relationships. There is a close relationship between the individual's intimate interpersonal interactions and the maintenance of self-esteem in depression (Gabbard 1994).

The best-known cognitive theory of depression is put forward by Beck (1967). Beck claimed that the principal etiological agent in the development of depression is inaccurate cognitions. It is these distorted thoughts that result in the self-defeating and pathological emotional responses experienced by individuals with depression. The study of dogs

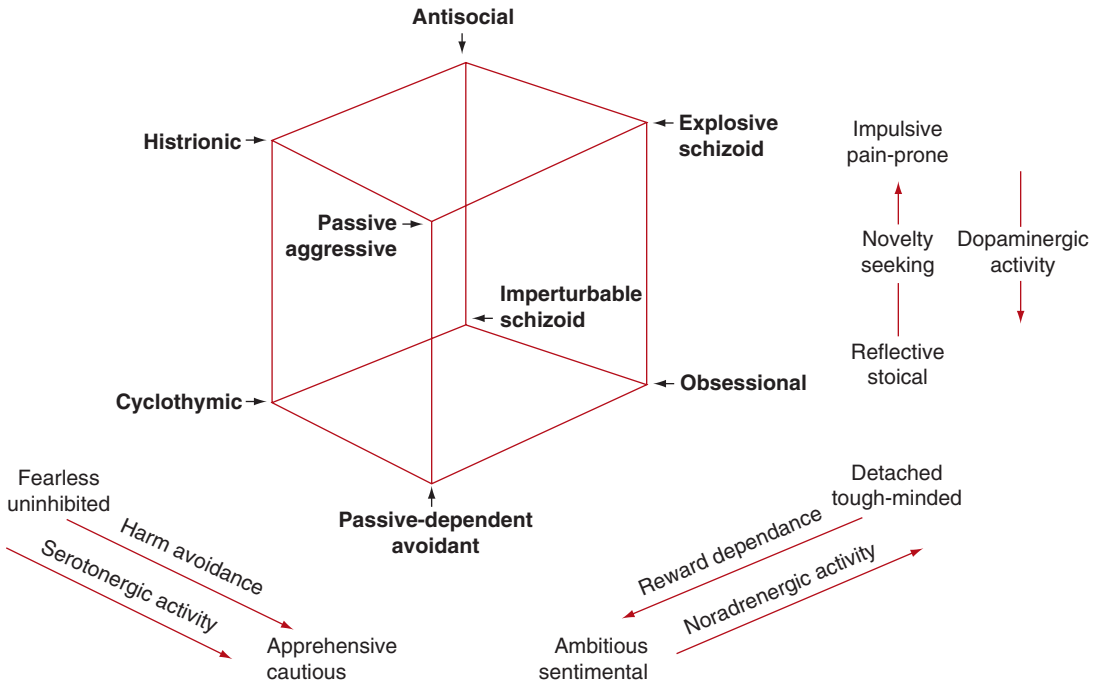



**Figure 36–5** *Three-way interaction of personality and monoaminergic transmission. [Reproduced from Cloninger (1986) with permission of Oxford University Press.]*

**Table 36–13 Spectrum of Temperament and Mood**

| Temperament | Clinical Features |
|---|---|
| Cyclothymic temperament | Hypersomnia vs. decreased sleep |
| | Introverted vs. uninhibited |
| | Taciturn vs. talkative |
| | Unexplained tearfulness vs. jocularity |
| | Psychomotor inertia vs. restlessness |
| | Lethargy vs. eutonia |
| | Dulling of senses vs. keen perceptions |
| | Slow witted vs. sharp thinking |
| | Shaky self-esteem |
| | Pessimistic brooding vs. optimism |
| Depressive temperament | Gloomy, humorless, or incapable of fun |
| | Given to worry, brooding, or pessimistic |
| | Introverted, passive, or lethargic |
| | Long sleeper or insomnia |
| | Preoccupied with inadequacy and failure |
| | Skeptical, overcritical, or complaining |
| | Self-critical, self-reproachful, and guilty |
| | Reliable, dependable, and devoted |
| Hyperthymic temperament | Cheerful, overoptimistic, or exuberant |
| | Warm, people seeking, and extroverted |
| | Overtalkative and jocular |
| | Overconfident, self-assured, or grandiose |
| | Short sleeper |
| | High energy level and full of plans |
| | Overinvolved and meddlesome |
| | Uninhibited and stimulus seeking |

exposed to inescapable shock has led to the learned helplessness model of depression. Seligman (1974) found that animals developed a passive acceptance of the condition in subsequent situations when escape was possible. In the learned helplessness condition, the animal was unable to initiate adaptive responses. This model was thought to apply to depression, when individuals perceive themselves as helpless and behave passively.

Individuals with depression have been shown to exhibit an attentional bias toward negative emotional cues, an attentional bias away from positive emotional cues, and an enhanced memory for negative emotional material (Leppänen 2006). Some of these abnormalities in the processing of emotional information have been noted in healthy controls who are at risk of developing mood disorders. Responsiveness to positive emotional cues is blunted in depression, although this is not supported by all studies and there is a question as to whether this reflects comorbid anxiety.

Theories of social stress have examined stressful life events (Brown and Harris 1978) and social support (Aneshensel and Stone 1982, Williams et al. 1981) as etiological factors in the development of depression. Such studies have demonstrated a cause-and-effect role for these social risk factors; however, these models can explain only a small proportion of the variance for the occurrence of depression.

Based on epidemiological studies of twin pairs, men and women have been shown to have more similarities than differences. Three pathways to depression in men and women were suggested, characterized by internalizing symptoms (genetic risk factors, neuroticism, low self-esteem, early-onset anxiety, and past history of major depression), externalizing symptoms (males: genetic risk factors, conduct disorder, and substance misuse; females: conduct disorder, substance misuse, and past history of major depression), and adversity and interpersonal difficulty (low parental warmth, childhood sexual abuse and parental loss, low education, lifetime trauma, low social support, history of divorce, past history of major depression, marital problems, and stressful life events) (Kendler et al. 2002, Kendler et al. 2006). In both sexes, genetic factors were important in the pathways to neuroticism, substance misuse, lifetime traumas, past history of major depression, and risk of major depression in the past year. The genetic factors for both genders are mediated partially by personality, increased exposure to traumatic events, and substance misuse. Childhood parental loss and low self-esteem had a more potent effect on men than on women.

Physiological explanatory models have become the primary focus in understanding the origins of depression. Subcortical and limbic brain structures and their ascending projections are believed to mediate depression. Biochemical theories have implicated disturbances in norepinephrine, serotonin, and dopamine in the pathogenesis of depression. Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has been consistently observed in patients with major depression, presenting as elevation of basal cortisol dexamethasone-mediated negative feedback resistance, increased cerebrospinal fluid levels of corticotropin-releasing factor (CRF), and a blunted adrenocorticotropic hormone (ACTH) response to challenge with exogenous CRF (Plotsky et al. 1998). None of these etiological mechanisms, biological or psychological, is sufficient to explain the development of the pathological expression of the emotion of depression.

## Clinical Presentation of Depression

A dominating depressed mood state may be seen in numerous general medical disorders (Table 36–14) as well as in psychiatric disorders. A number of neurological conditions may result in a depressed mood including Parkinson's disease. In cerebrovascular disease, depression is more common with frontal lobe lesions than with posterior hemisphere lesions, and it is more common with left- rather than right-sided infarcts (Robinson et al. 1984). Cardiopulmonary disease, renal disease and uremia, systemic neoplasms, porphyria, Klinefelter's syndrome, postoperative states, and acquired immunodeficiency syndrome may all present with disorders of emotion, often depression. Less common but documented are deficiencies of vitamin $B_{12}$, folate, and vitamin C resulting in depression. Endocrine disorders, inflammatory diseases, bacterial and viral infections, and a broad spectrum of pharmaceutical agents may result in development of depressed mood states. Of the hypertensive drugs,

**Table 36–14 Depression Presenting in Medical Conditions**

| | |
|---|---|
| Neurological disorders | Central nervous system infections, cerebral neoplasms, cerebral trauma, cerebrovascular disease, epilepsy, Huntington's disease, hydrocephalus, multiple sclerosis, narcolepsy, Parkinson's disease, and progressive supranuclear palsy |
| Endocrine disorders | Addison's disease, Cushing's syndrome, hyperaldosteronemia, hyperparathyroidism, hyperthyroidism, hypoparathyroidism, and hypothyroidism |
| Inflammatory diseases | Polyarteritis nodosa, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, and temporal arteritis |
| Vitamin deficiencies | Folate, vitamin $B_{12}$, and vitamin C |
| Other systemic disorders | Acquired immunodeficiency syndrome, cardiopulmonary disease, Klinefelter's syndrome, porphyria, postoperative states, renal disease, uremia, and systemic neoplasms |
| Toxic agents | Analgesics, antibacterial and antifungal agents, anti-inflammatory agents, antineoplastic drugs, cardiac and hypertensive drugs, neurological agents, psychotropic drugs, sedatives and hypnotics, steroids and other hormonal agents, and stimulants and appetite suppressants |

*Source*: Reproduced from Cummings (1985, p. 184) with permission of Allyn & Bacon.

reserpine, methyldopa, and propranolol have been the most widely implicated in the literature, although the evidence for the latter is weak (Kohn 2001).

Depression is a mood state that is at some point present in almost all of the DSM-IV-TR mood disorders: major depressive disorder, dysthymic disorder, depressive disorder NOS, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder NOS, mood disorder due to a general medical condition, substance-induced mood disorder, and mood disorder NOS. A depressed mood also predominates in adjustment disorders with depressed mood. Depressed mood may also color other psychiatric disorders including the anxiety disorders, dementia, schizophrenia, and schizoaffective disorder, depressive type.

The mood disturbance characterized by a major depressive episode involves both cognitive and vegetative symptoms. These vegetative symptoms, referred to as such because they are unconscious and involuntary, include changes in appetite or weight, sleep, energy, and psychomotor activity. The cognitive changes include feelings of worthlessness or guilt; difficulty in thinking, concentrating, or making decisions; and recurrent thoughts of death or suicidal ideation, plans, or attempts. Loss of interest or anhedonia, the inability to experience pleasure, is another cardinal feature. Although not necessary for a diagnosis of a major depressive episode, a depressed mood is usually present. The mood in a major depressive episode is often described as depressed, sad, hopeless, empty, discouraged, or down. The depressed mood is not always acknowledged or recognized by the patient and may need to be inferred from the patient's demeanor or facial expression. The affect is revealed by the slowed and hypophonic speech produced (Greden et al. 1981). "Facial masking" with little or no facial muscle response to emotional stimuli is often seen (Schwartz et al. 1976). The posture is frequently bowed, steps are shortened, and there is a general lack of spontaneous activity (Kupfer et al. 1974). In children and adolescents, an irritable mood rather than a sad mood may be present. Individuals with major depressive episodes may also demonstrate other emotional states including irritability, anxiety, phobias, obsessive ruminations, and excessive worry, in particular about physical complaints.

The depressed mood seen in individuals with dysthymic disorder differs little from that found in major depressive disorder, except in the number and duration of the associated cognitive and vegetative features. The DSM-IV mood disorders field trials (Keller et al. 1995) suggested that cognitive symptoms are more characteristic of dysthymia than vegetative symptoms are. The depressed mood found in dysthymic disorder is typically described as sad or "down in the dumps" and is chronic (at least 2 years in duration).

The depression in an adjustment disorder with depressed mood is a response to an identifiable psychosocial stressor but is not severe enough to meet criteria for another Axis I disorder. The dominant features include a depressed mood, tearfulness, and feelings of hopelessness.

Clinical Vignette 2

A 35-year-old woman presented to the outpatient clinic. She appeared disheveled with stains on her clothes, sullen, and tearful. She sat in the chair with a slumped posture, at times looking down at the floor. Her speech was of a normal rate and tone. She appeared to be sad. Her affect during the interview was flat and constricted but reactive and appropriate. She displayed a full range of affect. These clinical observations of her affect and the following interview provided a subjective report of her emotional state.

*Interviewer:* What brought you to the clinic?
*Patient:* I feel weak, my stomach hurts.
*Interviewer:* What is your mood like?
*Patient:* I'm nervous.
*Interviewer:* Do you mean you are anxious or sad?
*Patient:* Sad, very sad.
*Interviewer:* How long have you been this way?
*Patient:* A long time.
*Interviewer:* Days, weeks, months?
*Patient:* Two months.
*Interviewer:* So, you didn't always feel this way.
*Patient:* Oh, no! Thank goodness no [with a chuckle].
*Interviewer:* How about now, in the last 2 months?
*Patient:* Most of the time I'm down, but there are times I feel better, particularly when I have company.
*Interviewer:* How sad do you feel? Is this the worst that you have ever felt?
*Patient:* I'm not sure what you mean.
*Interviewer:* Well, let's say 1 is your worst and 10 is when you are feeling the best.
*Patient:* I guess I'm a 2. I'm not yet to the point of killing myself.

## Emotional Expression of Euphoria

Euphoria is defined as intense elation often associated with feelings of grandeur. Euphoria, elation, exultation, and ecstasy are synonyms that describe an exceedingly pleasurable mood. These emotions can be a part of normal experience. Euphoric states are achieved during sexual pleasure, when one is in love, after achieving a long-sought goal, or just when life is going well. Religious experiences can also result in feelings of euphoria. When euphoria goes beyond the range of normal experience and becomes a psychiatric problem, mania or hypomania is present.

Euphoric mood states may be induced by numerous drugs, neurological conditions, systemic medical disorders (Table 36–15), and psychiatric illnesses. The psychiatric conditions in which euphoric mood predominates are among the DSM-IV-TR mood disorders: bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder NOS, mood disorder due to a general medical condition, substance-induced mood disorder, and mood disorder NOS. Euphoria is also characteristic of schizoaffective disorder, bipolar type. Euphoric mood states are characterized as being either a manic episode or a hypomanic episode.

**Table 36–15 Euphoria Presenting in Medical Conditions**

| | |
|---|---|
| Neurological disorders | Huntington's disease, postencephalitic Parkinson's disease, Wilson's disease, general paresis of syphilis, viral encephalitis, cerebral neoplasms, cerebral trauma, thalamotomy, cerebrovascular accidents, multiple sclerosis, temporal lobe epilepsy, Pick's disease, Kleine–Levin syndrome, and Klinefelter's syndrome |
| Other systemic disorders | Uremia, dialysis dementia, hyperthyroidism, pellagra, carcinoid syndrome, and vitamin $B_{12}$ deficiency |
| Toxic agents | Amphetamines, baclofen, bromide, bromocriptine, cimetidine, cocaine, hydralazine, isoniazid, levodopa, metrizamide, procarbazine, procyclidine, phencyclidine, sympathomimetics, and yohimbine |

*Source*: Reproduced from Cummings (1985, p. 191) with permission of Allyn & Bacon.

The elevated mood of a manic episode is described as euphoric, unusually good, cheerful, or high. It is viewed as excessive and may seem to have an infectious quality. The quality of the mood is expansive with indiscriminate enthusiasm for interpersonal, sexual, and occupational interactions. Speech during a manic episode is pressured, loud, rapid, and difficult to interrupt. Lability and irritability of mood are often seen in manic episodes. The expression of the euphoric mood seen in a hypomanic episode is similar to that of a manic episode; however, it is not as severe and consequently does not result in psychotic features, hospitalization, or marked impairment in social or occupational functioning as seen in manic episodes.

## Emotional Expression of Apathy

Apathy is characterized by a dulled emotional tone associated with detachment or indifference. The apathetic individual is often described as a "bump on a log." Abulia refers to conditions of severe apathy, the loss of will to act, and inability to make decisions or to set goals. This differs from avolition, one of the negative symptoms of schizophrenia, in that the wish to do something is present, but the desire is without energy (Edgerton and Campbell 1994). The abulic patient may be immobile, be virtually unresponsive, or appear even comatose. Harry Stack Sullivan introduced a psychodynamic explanation for the existence of apathy as an emotion expressed in personality development (Mullahy 1952). He considered apathy an early security operation, a means of reducing awareness and susceptibility to interpersonal tension and of dealing with anxiety.

Bleuler (1924) pointed out that apathy to the extent that there is no affect probably does not even occur in psychoses or in the most severe organic brain injury. Lack of interest in almost everything that occurs is seen among some individuals with schizophrenia and dementia. DSM-IV-TR includes negative symptoms as a characteristic of schizophrenia. Affective flattening, alogia, and avolition may all characterize the emotional expression of apathy (Table 36–16). Individuals with severe major depressive episode may also present as apathetic, because they may not be able to discern their own feelings. Frontal lobe syndromes involving the orbital regions typically result in unresponsiveness to environmental stimuli. Individuals with frontal lobe syndromes often lack initiative and are unmotivated and disinterested in their daily activities. Apathy is also characteristically seen in Alzheimer's disease and other dementias, delirium, Huntington's disease, Korsakoff's syndrome, and Parkinson's disease. Individuals with right hemisphere strokes compared with left-sided lesions have a greater risk of presenting with apathy (Marin et al. 1995).

**Table 36–16 Characteristics of Apathy**

| | |
|---|---|
| Affective flattening | The face appears immobile, unresponsive with poor eye contact and reduced body language. |
| | Range of emotional expression is diminished most of the time. |
| Alogia | Poverty of speech is manifested by brief, laconic, and empty replies. |
| | Fluency and productivity of speech are decreased. |
| Avolition | There is inability to initiate and persist in goal-directed activities. |

## Emotional Expression of Hostility, Anger, and Rage

Hostility, anger, and rage are aggressive emotions. These emotions are characterized by heightened vigilance in response to a sense of threat. Often there is a tendency to act and engage the threatening stimulus. There is heightened physiological tone in preparation for a behavioral response. This behavioral response varies with societal and cultural norms and ranges from the adaptive–constructive response of assertiveness to the destructive response of violence (Yager 1989).

Individual differences in expressing and experiencing aggressive emotions may be cultural, developmental, and temperamental. An infant's temperament at birth may

predispose to increased expression of aggressive emotions in adulthood (Chess and Thomas 1986). Organic brain injuries may result in violent acts. Psychological and social contributions may increase the likelihood that an individual will express anger, hostility, or rage. For example, children from violent families or who are abused often become violent and abusive themselves (Kempe and Helfer 1980). Males with schizophrenia may misinterpret neutral faces as angry, whereas women with schizophrenia misinterpreted them as sad (Weiss et al. 2007). This finding suggests that gender differences in aggressive behavior in schizophrenia may be related to cognitive styles. Stimulant use, alcohol use, and other drugs of abuse can increase the experience of aggressive emotions; additionally, disinhibition increases the risk of violent behavior.

Aggressive emotions are present in aspects of everyday life and as part of the range of emotional expression in many psychiatric disorders. There are a number of psychiatric disorders in which the behavioral outcome of aggressive emotions is violence either directed toward others as in antisocial personality disorder, intermittent explosive disorder, and sexual sadism or directed toward oneself as in borderline personality disorder.

## Disturbances of Affect Incongruent with Mood

In certain neuropsychiatric disorders, the emotion expressed by the patient—the mood—is dissociated from the affect—what is observed. There are primarily three conditions in which this is seen: pseudobulbar palsy, ictal affective alterations, and dysprosody.

Patients with pseudobulbar palsy have exaggerated emotional expression with unintended laughing or unmotivated crying, and sometimes a mixture of both. The emotion expressed may be unrelated to the mood or in disproportionate intensity to the emotion experienced. The emotions expressed are difficult for the patient to discontinue. Dysarthria and dysphagia are associated features in many individuals with pseudobulbar palsy. Most cases are a result of bilateral vascular accidents involving the cerebral cortex or the internal capsule. Bilateral interruption of descending cortical fibers disinhibits responses integrated at the lower central nervous system. Exaggerated emotional expression results from release of intrinsic motor programs of the limbic system and related subcortical structures (Cummings et al. 1983).

Mood changes may be induced by focal seizure activity. Laughter is more common than crying as an ictal manifestation, but both may occur in the same patient. The laughter is stereotyped, inappropriate, and not stimulus induced. The patient views the expressed affect not as pleasurable, but rather as disagreeable (Sethi and Rao 1976).

Prosody is the affective and inflectional coloring of speech. Prosody involves speech melody, pauses, intonation, stresses, and accents during articulation. Neurological insults to the basal ganglia, cerebellum, and brain stem may result in dysprosody as well as dysarthria. Dysprosody reduces the patient's ability to communicate emotion.

## Conclusion

Emotions are a feeling state that is described in the psychiatric mental status examination by affect and mood. Affect and mood are not separate entities, although they are often considered as such. Any observable event or body feeling from which the psychiatrist makes an inference about affect could also be incorporated into determining the mood (Owens and Maxmen 1979). The important point in the description of emotions in the mental status examination is to obtain both a subjective report and an objective evaluation. It is the patient's described and observed emotion that allows the psychiatrist to properly distinguish and subsequently make a diagnosis of disorders that are related to anxiety, depression, euphoria, apathy, hostility, and anger.

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CHAPTER

# 37 Physical Signs and Symptoms

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Mental disorders are syndromes consisting of sets of symptoms. The terminology that psychiatrists use to refer to these syndromes is one of convention. The research that helps define our terminology has limitations and, therefore, describes only a portion of any sample of patients (Becker and Kleinman 1991). The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) and the *International Classification of Diseases*, 10th revision (ICD-10) present categories for a large number of mental disorders. However, how individuals experience their symptoms and what is described to the physician may not fit easily into phenomenological, nosological systems such as DSM-IV-TR and ICD-10. The brain, in response to mental activity in the person's mind, may express the disorder only psychologically, that is, with thoughts and emotions. The brain also has control over the body via both humoral and neuronal systems and may express the disorder physiologically. Therefore, the consequences of mental distress can be expressed psychologically, along with somatic manifestations, or mental distress can be expressed somatically, with minimal psychological experience.

The environment, culture, childhood experiences, previous experiences with physicians, and the person's family influence the patient's experience of distress. How the patient expresses distress will have a crucial impact on the physician's ability to arrive at an accurate diagnosis. Culture has the most powerful influence on the expression of symptoms (Kleinman 1988). The influence of culture may determine which of the symptoms in a disorder are expressed and how they are expressed. Culture influences the meaning that one attributes to symptoms. The cultural explanations of illness also help define the person's behavior and "sick" role (Ton and Lim 2006). Patients' beliefs regarding the origin of their symptoms, both medical and psychological, have implications in terms of what patients conceal/reveal during the diagnostic evaluation. The outcome of the evaluation diagnostically, i.e., whether the symptoms are diagnosed as medical or as mental, has meaning for the individual, may have legal implications, and may have an impact on the role the person plays in society (Becker and Kleinman 1991). The diagnosis of a "medical" illness carries with it certain rights and privileges, including the reduction of certain responsibilities; however, people with "mental" problems potentially suffer from stigma and prejudice attached to psychiatric disorders. These beliefs influence the patient, his or her family, the patient's physician, and potentially impact directly upon the patient–physician relationship. The ability of a patient to work with his or her physician plays an important role in determining the success of medical interventions. How patients relate to their physicians derives from childhood experiences that result in secure or insecure attachments. Those patients who have difficulty in establishing a working alliance are less likely to adhere to the physician's recommendations (Ciechanowski et al. 2001).

Industrially developed nations, particularly those with Western cultures, are more likely to focus on psychological symptoms as the core manifestations of psychiatric illness; in contrast, somatization is much more the norm in non-Western cultures and underdeveloped countries. The reported prevalence of disorders such as depression and anxiety may vary widely across cultures, depending on the criteria used for the diagnosis. An individual's acceptance of receiving a psychiatric diagnosis, rather than a medical diagnosis for the same set of symptoms, is influenced by the stigma attached to psychiatric disorders in that person's culture. Personal characteristics and cultural beliefs also influence the expression of symptoms in forms that are not somatic and thus are determinants of what information the physician is able to obtain from the patient. The information the physician obtains, and more importantly, the information that remains unknown, influence the accuracy of the diagnostic process.

The powerful role that culture plays is not only a major point of interest of cross-cultural psychiatry but also the one with considerable practical significance. The "culture" of the United States is heterogeneous, reflecting many different points of view regarding physical and mental illness. Immigrants from other countries bring with them their

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cultural views retaining these cultural beliefs, though apparently assimilated. The psychological framework that defines psychiatric disorders for physicians may not be the one to which any portion of a particular population of patients subscribes. Physicians inevitably encounter patients from cultures whose metaphors of distress vary widely. Many patients are likely to present with a variety of physical complaints, particularly to their primary care physicians, and a significant portion of these patients have psychiatric problems (Ormel et al. 1990). In spite of advances in our understanding of the neurobiology of psychiatric disorders, mental illness remains associated with stigma in the US. Despite the importance of mental disorders in detracting from the overall well-being of patients, the accurate diagnosis of these disorders in primary care settings is quite low (Ormel et al. 1990, Sherbourne et al. 1994). General practitioners are less likely to recognize generalized anxiety disorder when patients present with a physical complaint (Munk-Jørgensen et al. 2006).

Physical signs and symptoms may be magnified or minimized depending on the patient's personality traits or personality disorder. Personality traits may be exacerbated by a medical illness limiting the person's ability to handle the stress of being in the sick role. These patients may be clingy/dependent when first encountered, only to become angry/hostile when their physicians withdraw from the unremitting neediness. They may communicate their needs through vague physical complaints, while being uncooperative with the medical evaluation. This may compromise the delivery of medical care in a variety of ways (Muskin and Haase 2001). Physicians experience them as "difficult patients" and avoid contact as much as possible, compounding the problem with the patient. At times, the physician may feel compelled to order many procedures or obtain many consultations (not psychiatric) to placate a patient (Mozian and Muskin, in press). In the evaluation of a patient, one must be mindful of the interplay of culture, personality, family influence, and previous experience to better understand if this set of signs and symptoms is a consequence of mental distress expressed psychologically with somatic manifestations or mental distress expressed somatically with minimal psychological experience.

## Evaluation of Physical Signs and Symptoms

All patients presenting with "psychiatric" symptoms require a careful and complete physical examination. Routine blood tests should include a complete blood count; determination of serum glucose and electrolyte levels; testing for hepatic, renal, and thyroid function; and testing for sexually transmitted infections. Urinalysis, an electrocardiogram, and a chest radiograph should also be obtained. Neuroimaging is an important diagnostic tool to exclude neurological disorders that may initially present with psychological symptoms. A thorough medical history and a family history of medical illness are crucial components of an adequate psychiatric evaluation. In many cases, the psychiatrist is the only physician who obtains a history from the patient leading to counseling and testing to determine the patient's HIV status.

Psychiatric disorders can alter the way in which patients manage their health and health care. Patients with depression are at risk for metabolic disturbances secondary to anorexia. Of particular importance is dehydration, which may alter serum electrolytes and magnify some of the side effects of antidepressant treatment, such as orthostatic hypotension. Patients who are admitted with dehydration or who have been found at home in a dehydrated and malnourished state should be screened for depression. Agitated states, such as mania and schizophrenia, place patients at risk for a variety of medical problems. Increased motor activity for days or even weeks can affect joints and can lead to malnutrition and exhaustion. Inattention to intercurrent medical problems because of impaired judgment and agitation may lead to severe infections that would otherwise be easily treated.

Patients with mood disorders, both depressed and bipolar, as well as patients with a broad range of psychoses, may become noncompliant with medication regimens to which they were previously adherent during exacerbations of the psychiatric disorders. Failure to take necessary medications or follow a restricted diet worsens the underlying medical disorder. Primary care physicians may not be aware of the patient's psychiatric disorder and thus cannot understand why the patient has become nonadherent.

## Physical Manifestations of Anxiety

Anxiety is an internal feeling state of fear in which the person does not know the cause of the fear. It is not a pleasant experience. Research has shown that anxiety at low levels of intensity can be motivating and increase performance (Yerkes and Dodson 1908). Increased levels of anxiety result in greater degrees of discomfort and dysfunction. At all levels of intensity, anxiety is commonly associated with physical symptoms. Some anxiety disorders such as panic disorder are always associated with physical symptoms. There is no organ system that is immune from physical symptoms associated with anxiety. The differential diagnosis for patients who have symptoms thought to be related to anxiety must always include a medical condition (Table 37–1).

As a rule, symptoms that fall into the following four categories should be considered as potentially resulting from anxiety:

1. symptoms that have persisted over long periods of time;
2. symptoms that change character over time but do not worsen in intensity;
3. repeated negative evaluations searching for a medical illness that would explain the symptoms;
4. symptoms that do not match the description of known medical conditions.

Difficult-to-diagnose medical conditions pose a challenge for the physician, as many of these patients may be misdiagnosed as having psychiatric rather than medical conditions (Hall 1980). This should not result in patients being misdiagnosed with psychiatric disorders rather than medical disorders. Patients with panic disorder typically present to primary care physicians for medical evaluation. They may complain of chest pain, shortness of breath, a variety of abdominal symptoms, headaches, visual disturbances, and so on, and are convinced that their symptoms are indicative of a serious medical disorder (Sheehan and Sheehan 1982). A common presentation, particularly in the emergency department, is a young person with complaints of chest pain and shortness of breath. The symptoms suggest to the person that she/he is having a heart attack. The intensity of

**Table 37–1** Physical Manifestations of Anxiety by Organ System

| |
|---|
| **Cardiovascular System** |
| Palpitations |
| Tachycardia |
| Substernal pressure, precordial pain not related to exertion |
| Facial flushing |
| Feelings of having a heart attack |
| **Pulmonary System** |
| Shortness of breath |
| Sense of inability to get enough air (sense of suffocation) |
| Repeated yawning or sighing |
| Feeling of a tight band around the chest or throat |
| Excessive dryness of the mouth |
| **Gastrointestinal System** |
| Epigastric discomfort, pain, distress, fullness |
| Belching, heartburn |
| Feeling of being unable to swallow |
| Nausea |
| Diarrhea or constipation |
| Anorexia or overeating to calm anxieties |
| **Nervous System** |
| Difficulty in concentrating, poor memory |
| Dizziness, lightheadedness, syncope (typically no loss of consciousness) |
| Insomnia, including difficulty in falling and staying asleep |
| Nightmares |
| Headaches |
| Blurred vision |
| Numbness or tingling of the extremities and/or periorally |
| Tremors, muscle pain, or stiffness |
| Weakness of extremities |
| Inability to sit still or to relax, feeling of being tense |
| **Genitourinary System** |
| Increased frequency of urination |
| Alterations in menses |
| Decreased libido |
| Impotence, anorgasmia, dyspareunia |

the symptoms, and the patient's conviction that something must be wrong medically to generate such discomfort, often convince the patient's physician that there must be a medical cause for these symptoms (Muskin 1985). This leads to an exhaustive, but negative, medical evaluation. The negative workup often results in the patient being told, "Nothing is wrong." Telling the patient that "nothing is wrong" is not reassuring. There clearly is something wrong as the patient experiences frightening physical symptoms. Teaching physicians to explain that the negative evaluation indicates there is no obvious medical cause for the symptoms is really a *positive* outcome; however, that information is insufficient for the patient. The physician needs to add that the symptoms may result from, or have been exacerbated by, a psychiatric etiology. Exploring that etiology is as important for the patient's well-being as any "medical" evaluation. Indicating a willingness to continue to treat the patient along with a psychiatrist prevents the patient from feeling either abandoned by the primary care physician or stigmatized by having a "mental disorder."

Patients with anxiety often complain of feeling weak, having fatigue even with normal duration of sleep, and becoming exhausted with minimal exertion. Patients may offer no complaint of feeling anxious and may not appear anxious, or they may complain of feeling anxious regarding their physical symptoms. We separate *signs* (the observable phenomena or laboratory results) from *symptoms* (subjective experiences that patients offer as their chief complaint). The signs of anxiety are irritability, pacing, or restlessness during the history or physical examination. There can be a cold, clammy feeling to the skin and a fine tremor. In cases of severe hyperventilation, a patient may demonstrate Chvostek's sign, which is tetany (tonic muscular contractions, tremors, and parasthesias) caused by a low serum calcium level resulting from the hyperventilation-induced respiratory alkalosis. At electrocardiography, a sinus tachycardia may be observed and patients may have elevated systolic blood pressure. A systolic ejection murmur of mitral valve prolapse may be heard in some patients with panic disorder (Gorman et al. 1981), but mitral valve prolapse does not appear to cause panic disorder (Crowe et al. 1982).

Symptoms of anxiety are the subjective experiences that patients offer as their chief complaint. These symptoms commonly affect the cardiovascular, pulmonary, gastrointestinal, nervous, or genitourinary systems. It is not known why one organ system is affected in one patient but not in another; however, patients have varying tolerance for symptoms. People may ignore symptoms in one organ system but focus their as well as the physician's attention on symptoms in another system that they find more distressing (Muskin 1985).

Patients may have one, some, or all of the symptoms listed in Table 37–1. This is not an exhaustive list, and patients may complain of many other physical problems. It must always be kept in mind that patients may have both a psychiatric disorder and a medical disorder. A thorough medical evaluation of the patient's complaint must precede the final decision that the symptoms originate exclusively from an anxiety disorder. It is never appropriate to tell the patient that his or her symptoms are "all in your head." Every patient deserves to understand that a psychiatric diagnosis

**Clinical Vignette 1**

Mr. T was a 20-year-old college senior who had been evaluated medically by several physicians prior to the psychiatric consultation. He complained of nausea and experienced one or two episodes of vomiting. Repeated medical workups were not revealing. His family physician told his parents that Mr. T had a severe psychiatric disorder. He was a straight "A" student and an athlete. Although handsome, he rarely dated. The psychiatrist was able to elicit all the symptoms of panic disorder and a history of repeated panic attacks. The only symptoms that Mr. T cared about were nausea and vomiting. He feared he would vomit on a date or in a public situation and would be embarrassed. Mr. T was successfully treated with desipramine at a dose of 300 mg. Symptom-free, he graduated from college, and easily obtained employment. The fears of a serious psychiatric disorder were not substantiated as he had a successful marriage and a career as an executive who traveled around the world for his company.

refers to a real illness. It is worth keeping in mind that patients with anxiety disorders are significantly more likely to have comorbid cardiac disorders, hypertension, gastrointestinal/genitourinary problems, and migraine compared to patients without anxiety disorders (Härter et al. 2003).

## Physical Manifestations of Mood Disorders

Mood disturbance, like anxiety, commonly presents with physical symptoms. An unhappy emotion can be a normal reaction to a variety of life events, and most people would refer to this as depression. A sense of bereavement is also a normal response to life events, including the loss of a relationship, the death of an important individual, the loss of a body function, or the loss of a body part. The sadness in these situations may be accompanied by some somatic symptoms, typically a decrease in appetite or some disturbance in sleep. It is not surprising that people experience some alteration of their mood during such circumstances. Sadness, depression, and feeling blue may be experienced in reaction to some physical malady or may be a component of the medical disorder. Some patients have such severe agitation that they do not experience themselves as primarily depressed. Their anxiety is so dramatic that the physician misses the diagnosis of depression. Mixed anxiety and depression is common and should be a diagnostic consideration in anxious patients with any degree of mood alteration.

Many women experience some degree of mood alteration after the birth of a child. A woman may fail to distinguish the progression from postpartum blues into mood disorder because she is sleep deprived, fatigued, and normally occupied by the activities of caring for a newborn. Postpartum depression can be a serious illness, endangering the life of both mother and child. It is not a rare disorder, occurring in approximately 15% of women (O'Hara et al. 1990, Wisner and Wheeler 1994, Gaynes et al. 2005). Women with a history of major depression have a risk of 10–25% of experiencing an episode of postpartum depression (O'Hara 1995, Garvey et al. 1983). Obtaining a history of a prior postpartum depression is crucial as there is a 50% risk of another episode with subsequent births.

As is the case with anxiety, patients with depression often go to their primary care physicians with somatic, not psychological, complaints. Almost five times as many patients with depression spend days in bed with physical symptoms as people in the general population (Wells et al. 1988). Studies using structured psychiatric interviews have shown that the point prevalence of major depressive disorder ranges from 4.8 to 8.6% in primary care outpatient settings. Of adult medical inpatients, 14.6% meet criteria for major depressive disorder (Feldman et al. 1986).

People with depression typically present with complaints of fatigue, insomnia, lack of energy, and poor appetite. Many people continue to go to work and maintain their routine in spite of how miserable they feel. Typically, patients have a medical rationale to explain their physical complaints, such as anemia, vitamin deficiency, or the possibility that they have cancer. In a study performed in primary care clinics around the world, 69% of patients meeting DSM-IV-TR criteria for major depression have a somatic presentation (Simon et al. 1999). Study countries included Brazil, China, France, Germany, Greece, India, Italy, Japan, Nigeria, Turkey, The Netherlands, the UK, and the US. Half of these patients have unexplained medical symptoms (Simon et al. 1999). Physicians in primary care settings see the majority of patients with depression and should always consider a mood disorder in patients for whom the medical evaluation proves unrewarding.

Patients with insomnia are often convinced that their insomnia is the *cause* of the other physical symptoms that might otherwise be considered as part of a depression (fatigue, aches and pains, anorexia, anhedonia). Sleep disturbance, fatigue, nonspecific musculoskeletal complaints, or multiple complaints in patients seen in primary care settings correlate highly with depression (Gerber et al. 1992). The simple inquiry, "How are you sleeping?" may open the door to complaints otherwise unspoken, and lead to a diagnosis of a mood disorder. In addition, many patients have a variety of vague physical discomforts when they are depressed, such as headaches, backaches, and muscle aches. They may also have gastrointestinal symptoms such as indigestion, change in food preferences, or decreased appetite. In the primary care setting, such complaints may lead to numerous tests that are not diagnostic and are expensive.

In the absence of targeted questioning, patients may not talk about decreased interests in usual activities, decreased sexual interest, feelings of low self-esteem, or suicidal thoughts. The alterations in concentration and memory that occur in depression may be concealed because patients fear that the symptoms are indicative of senility. Similar to the patients with anxiety disorders, depressed patients may experience "sadness" about their lack of energy and other physical symptoms, but neglect to mention any other changes in their emotions. Patients may be delusional, but mood-congruent delusions, such as a patient's intense fear that the physical symptoms are a result of an occult malignancy, may have a surface validity and not seem obviously delusional. Thus, the physical symptoms, and/or the patient's beliefs about the cause of the symptoms, may delay or prevent the accurate diagnosis of depression.

Severely depressed patients may present with a picture resembling that of a dementia. Slowed thinking, long response time to questions, inability to pay attention, and failure on cognitive testing (typically "I don't know" rather than an incorrect answer) may convince family and physician that the person has an "organic" problem.

Reliance upon the vegetative symptoms of depression may cause diagnostic confusion in patients with medical illness. Many disease states and/or medical treatments can cause the vegetative symptoms associated with depression such as insomnia, fatigue, anorexia, and weight loss. Although it is understandable that someone might be sad as a reaction to a medical illness, the reasonable nature of the reaction does not rule out the possibility of a mood disorder. Severe indecisiveness, hopelessness, failure to respond appropriately and emotionally to improvement in the medical condition, or dissatisfaction with medical care out of proportion to the norm, may indicate a mood disorder (Cavanaugh 1994). Why some people develop a mood disorder during or after unfortunate life events, such as a serious physical illness or the loss of a significant person, is not yet known. Nevertheless, symptoms of depression such as anhedonia, hopelessness, worthlessness, indecisiveness, and insomnia should be sought out as they have been shown to be predictors of death in hospitalized medical patients (Furlanetto et al. 2000).

Clinical Vignette 2

Mr. C was referred for a psychiatric evaluation while an inpatient on a medical ward because his primary care physician was convinced that the patient had a depression. Mr. C complained of fatigue, sadness, and inability to cooperate with physical rehabilitation following a recent hip replacement. He had been treated with a serotonin reuptake inhibitor before admission without success. Although unhappy about his inability to regain full use of his leg, and afraid he would not be able to dance at his daughter's wedding, he had no other symptoms of depression. The psychiatric consultant discontinued the antidepressant. Mr. C had "heavy" eyes and blurred vision that resulted in an ophthalmology consultation. He had a positive edrophonium (Tensilon) test and was diagnosed with myasthenia gravis. This eventually led to surgery for a thymoma. The subsequent hospital course was extremely difficult. After several weeks, Mr. C became tearful, anxious, and severely indecisive about his care. He was unable to sleep. In spite of continued improvement medically, he was consistently fearful that he would die. After 2 weeks of treatment with a serotonin reuptake inhibitor for his depression, and a benzodiazepine to treat his insomnia, Mr. C felt less depressed. He was no longer tearful and was able to engage actively in decisions regarding discharge planning. Mr. C left the hospital walking, smiling, and ready to enjoy his daughter's wedding.

## Physical Disorders Causing Secondary Mental Symptoms

Numerous medical disorders have behavioral components, such as the mood disruption that occurs with many different endocrine disorders or the psychiatric symptoms that may occur with a disorder such as systemic lupus erythematosus. Many different aspects of the experience of being physically ill can exert either a psychological and/or a physiological effect on patients. A patient's mental status or a patient's ability to experience and express emotion may change as a result of the direct effects of a medical condition on the patient's brain. For example, cerebrovascular accidents have a direct effect on brain tissue and thus on mental function. Conditions that alter blood flow to the brain, such as arrhythmias, hypotension, or vascular disease, also alter cognition. Systemic disorders including sepsis, disturbances in electrolyte and glucose metabolism, and a variety of intoxications all have effects on the brain and thus influence thinking and emotion. Neurological problems, as well as substance overdose or withdrawal, can present with behavioral dyscontrol and perceptual disturbances that may look like a psychotic episode.

Medical illness also has global effects on the body. There may be changes in the person's appetite, sleep, or libido. From a psychodynamic perspective, medical illness has a regressive effect on the psychological functioning of the patient such that she/he may be less able to cope with the demands of the current situation (Strain and Grossman 1975). Regression can be understood as an alteration in the coping skills employed by the individual reflective of an earlier stage of psychological development. Patients may also have psychological reactions, such as anxiety or depression, in response to their alterations in cognitive function. How a patient copes with illness may be as challenging for the physician as the illness itself (Gazzola and Muskin 2003, Groves and Muskin 2005).

Psychiatric patients (i.e., patients who have a psychiatric diagnosis known to their physicians) may have medical disorders that are not diagnosed because the presenting symptom appears to be mental (so-called functional) rather than physical (so-called organic). This is the reverse of the situation described in the sections on the physical manifestations of anxiety and of mood disorders, in which patients present with symptoms that are taken to be the result of a general medical condition, rather than the somatic manifestations of a psychiatric disorder. Hall (1980) notes nine mythological characteristics of patients who are diagnosed as having functional medical complaints (Table 37–2). If the physician holds these myths to be axiomatic truths, this belief will impede the appropriate evaluation of the patient's underlying or concomitant medical disorder. The nine characteristics in Table 37–2 are a reminder that every clinical situation must be fully evaluated, no matter how obvious it seems that the complaints are functional.

**Table 37–2** Mythological Characteristics of Patients with Functional Medical Complaints

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| A history of anxiety or unusual behavior since childhood or adolescence |
| The patient evidences a multiplicity of symptoms that involve several organ systems |
| The patient evidences unusual symptoms that are difficult for the physicians to deal with |
| A history of atypical response or failure to respond to treatment |
| A history of doctor shopping |
| A failure to carry out the physician's recommendations |
| The absence of concern in the face of serious complaints |
| Symptom onset concomitant with, or exacerbated by, particular people or stressful life events |
| Apparent secondary gain resulting from physical symptoms |

*Source:* Hall RCW (ed) (1980) Psychiatric Presentation of Medical Illness: Somatopsychic Disorders. SP Medical & Scientific Books, New York, NY, USA, p 4.

In a review of 658 consecutive psychiatric outpatients, careful medical evaluation revealed that 9.1% of the psychiatric cases had a medical illness that produced the psychiatric symptoms (Hall et al. 1978). Depression, confusion, and anxiety were the most common presentations. Cardiovascular and endocrine disorders were most commonly the cause

Clinical Vignette 3

Ms. P, a 38-year-old successful businesswoman and mother of two teenagers was seen in psychiatric consultation 2 days after the removal of a pheochromocytoma. She described feeling sad and gave a history of several years of intermittent episodes of palpitations, headaches, tremulousness, and flushing. Her physician had told her she was overwhelmed by being a "supermom" and anxious because of chronic marital problems. Ms. P was told to see a psychotherapist, a recommendation she did not follow. She would not have consulted an endocrinologist, and would not have had successful surgery for her pheochromocytoma, had a friend not heard a radio program about medical disorders that cause anxiety-like symptoms.

of the psychiatric symptoms. Infections, pulmonary disease, gastrointestinal problems, hematological disorders, a variety of central nervous system disorders, and cancers were also found as the actual etiology of the "psychiatric" symptoms.

No convenient system exists to connect any one medical disorder with a particular set of psychiatric symptoms. Disorders such as systemic lupus erythematosus, acquired immunodeficiency syndrome, and pancreatic carcinoma regularly have a psychiatric presentation, particularly symptoms of mood disorders. This is of special importance in patients with acquired immunodeficiency syndrome (Perry and Tross 1984, Dilley et al. 1985, Navia et al. 1986a, 1986b, Johannet and Muskin 1990). Patients with hallucinations, especially visual hallucinations, should receive a full workup to exclude a medical etiology for their symptoms. Another worthy consideration in patients with symptoms of anxiety or depression is a subclinical thyroid disorder (Cooper 2001, Singer et al. 1995).

Clinical Vignette 4

A 44-year-old executive was hospitalized for the treatment of ophthalmic herpes. When seen for a pain consultation, she was found to be agitated and "psychotic." The psychiatric consultant noted that she had a fluent aphasia. The agitation was actually her distress regarding her sudden inability to communicate, and not from a psychosis. The psychiatrist recommended a neurological consultation. A CAT scan of her head revealed several lesions scattered on the left side of her brain. As a glioblastoma with satellite lesions was a strong diagnostic consideration, a brain biopsy was performed. This procedure led to a diagnosis of toxoplasmosis. The patient gave no risk factors for human immunodeficiency virus infection except for unprotected sex several years before the admission. She tested positive for human immunodeficiency virus. Her "psychosis" cleared with treatment of the opportunistic infection and the resolution of the aphasia.

Clinical Vignette 5

Mrs. O complained of feeling sad, with anorexia, weight loss, fatigue, and periods of tearfulness. These symptoms began following the physical and cognitive decompensation of a family member who required placement in a nursing home. She had retired from a successful career and noted she had never been physically ill in the prior seven decades of her life. She was reluctant to take any form of medication, but as her symptoms increased, she agreed to take a serotonin reuptake inhibitor. She also agreed to have a medical evaluation that revealed a low TSH with a high normal $T_4$. Her response to antidepressant treatment was incomplete until she was treated for the subclinical hyperthyroidism by radioactive iodine. Following that treatment, she remained euthymic without antidepressant therapy.

## Intoxication and Withdrawal

When the clinical presentation is one of anxiety, agitation, confusion, paranoid ideation, or psychosis, it is important to consider that the patient is *intoxicated* by any one of a variety of substances. Conversely, the same presentation can occur in patients *in withdrawal* from a substance. Patients who are intoxicated have positive serum or urine toxicologic test results, whereas patients who are withdrawing typically have none of the substances in their blood or urine. However, in cases of chronic substance abuse, particularly with alcohol, patients may have serum levels of alcohol that, for them, are too low to prevent withdrawal. When this fact is not recognized, the patient's behavior can be a source of confusion in the diagnostic evaluation. The physician may not realize that the anxious patient is actually delirious. Patterns of substance abuse vary considerably, and many patients use more than one substance simultaneously. In complex cases, it is worth considering the possibility that the patient is withdrawing from a substance that was not included in the history (Muskin et al. 1998b).

Clinical Vignette 6

An 87-year-old woman was admitted to the neurology department with confusion and agitation. She was not able to give a coherent history, but her family reported that she had been a department store executive and that she was devoutly religious. Her medical evaluation was completely negative except for the change in her mental status. During the next day her agitation worsened. Her daughter reported that her mother had several large shopping bags of prescription medications in her bedroom, undoubtedly accumulated over many years. In her delirious state, the patient denied taking any of these medications except for "my Centrum at bedtime." The psychiatric consultant suggested that *Centrum* (a multivitamin) might actually be *Centrax* (prazepam, a benzodiazepine with a long half-life). The psychiatrist suggested that the patient was in a benzodiazepine withdrawal delirium. An intramuscular administration of lorazepam brought the delirium under control, with rapid improvement in the patient's agitation. The patient was detoxified using oral lorazepam during the next week. She remained fully oriented and without confusion. Her family removed her collection of medications before she returned home.

## Agitation

Many medical disorders may have psychiatric presentations with either depression or anxiety symptoms. There are also patients who present with symptoms that are mixtures of agitation and depression or mixtures of lethargy and anxiety. In some clinical situations, a patient's agitation may be difficult to differentiate from anxiety. Anxiety is typically a feeling that remains throughout the day, with increases or decreases in the intensity of the feeling in the setting of a clear sensorium. Confusion, disorientation, and a fluctuating level of consciousness often accompany agitation. Some patients demonstrate a pattern of agitation alternating with sedation. Of particular diagnostic importance are symptoms in an elderly patient that are thought to represent anxiety, but the patient is actually suffering from a delirium. Delirium may be the presenting picture in elderly patients and may be the consequence of a variety of metabolic, hemodynamic, infectious, and pharmacological factors. The possibility of an anticholinergic delirium should always be entertained for a geriatric patient who seems anxious. Numerous medications that are commonly prescribed for geriatric patients have anticholinergic side effects. Although the potency of the anticholinergic effect

for any one drug may be small, the additive effects of several drugs can produce an anticholinergic delirium (Tune et al. 1992). Over-the-counter (OTC) analgesic agents that are "PM" contain diphenydramine, which has anticholinergic properties. Patients taking several pills daily may present with agitation that is actually an anticholinergic delirium. A variety of medications including benzodiazepines, dopaminergic agents, narcotics, and OTC/prescription hypnotics have the potential to cause delirium, particularly in the elderly (Medical Letter 2000, Inouye 2006). Patients with delirium may be misdiagnosed with anxiety if they are agitated, or may be misdiagnosed with depression if they have a hypoactive delirium.

A complete evaluation always includes an investigation of the patient's medications. This includes currently prescribed medications, ones the patient still possesses from prior prescriptions, and OTC medications. Many patients use alternative therapies but do not inform their physician of the treatment (Eisenberg et al. 1998, Kenny et al. 2001). In addition, many people use an alternative therapy without consulting a practitioner of complementary and alternative medicine (Eisenberg et al. 1998, Kenny et al. 2001). Thus, the investigation of a delirium should also include an inquiry regarding the use of herbs, neutraceuticals, and other alternative medicines (see Chapter 108). Psychiatric symptoms can be caused by such a large number of medications that it is always worthwhile to consult a reference when a patient is taking a medication new to the physician (Medical Letter 1993, 1998). Steroids, antihypertensive medications, $H_2$ blockers, isotretinoin, and interferon should always be considered as a causative factor if the patient develops depression during treatment with one of these agents (Wholley and Simon 2000, Wysowski et al. 2000, Mussleman et al. 2001). See Tables 37–3 and 37–4 for guides regarding medical disorders that may present with symptoms suggestive of a depression or of an anxiety disorder.

**Table 37–3 Medical Disorders with Depression-Like Symptoms**

| |
|---|
| Acquired immunodeficiency syndrome |
| Cancer: intracranial tumors, pancreatic carcinoma, and others |
| Central nervous system: Parkinson's disease, multiple sclerosis |
| Diabetes |
| Heavy metal toxicity: lead, mercury (agitation, apathy, psychosis) |
| Hyperthyroidism or hypothyroidism (lethargy and anxiety) |
| Hyperadrenalism (Cushing's disease) |
| Adrenocortical insufficiency (Addison's disease) |
| Hyperthyroidism or hypoparathyroidism |
| Pernicious anemia |
| Systemic lupus erythematosus |
| Viral infections: hepatitis, pneumonia |

**Table 37–4 Medical Disorders with Anxiety-Like Symptoms**

| |
|---|
| Acquired immunodeficiency syndrome |
| Cardiac disease: arrhythmias, anginal variants |
| Central nervous system disorders: multiple sclerosis, head injury, encephalitis, Wilson's disease, Huntington's disease, vitamin $B_{12}$ deficiency |
| Hyperthyroidism or hypothyroidism |
| Hyperparathyroidism or hypoparathyroidism |
| Hypoglycemia (islet cell adenoma or medication induced) |
| Intracranial tumors |
| Pheochromocytoma |
| Porphyria |
| Virilizing syndromes in women: adrenal, ovarian, pituitary (tumors and disorders) |
| Withdrawal: particularly early phases of alcohol, barbiturate, and benzodiazepine withdrawal |

## Physical Symptoms without Known Etiology

Although physical presentations of psychiatric disorders are a common occurrence, some psychiatric disorders involve complaints of physical problems, without an underlying anxiety disorder or affective illness. These patients are people for whom psychological matters are expressed via their bodies. It is estimated that as many as 10% of all medical patients have no medical illness but still receive a diagnostic evaluation and medical treatment (Ford 1986).

Patients who have either somatoform or factitious disorders assume the rights that accompany the role of the physically sick without the organic pathology on which the role is based. The individual is presumed to be weakened by the underlying disease. In being sick a person is thus excused from everyday responsibilities, without being blamed and penalized. A sick person is not expected to recover by force of will alone and can expect to be cared for by others. The "sick" role does carry with it certain obligations. The person who claims to be ill is expected to seek medical attention in order to discover the cause of the symptoms. She/he is expected to accept appropriate treatment for the malady. There is an expectation from family and physicians that the "sick" person desires to return to being well.

When people become ill for physiological reasons, the sick role is imposed upon them involuntarily. What is unique about patients with a somatoform or factitious disorder, and is often extremely frustrating for their physicians, is that these patients *take on* the sick role for psychological reasons. The underlying "motivation" that results in the person's complaint of a somatic problem may be unconscious, or it may be part of a conscious plan to create or fake a medical problem.

Patients with somatizing disorders do have an illness; they experience themselves as not being well. This experience impairs their lives. They may or may not have a disease, that is, there may or may not be an objective evidence of organic impairment. Although people may use somatic symptoms for either conscious or unconscious gain, it is possible that both a psychiatric illness and a medical disease are present. Some patients have clear evidence of disease but claim not to have an illness (i.e., they do not have an experience of being ill) and they are noncompliant with the treatment. Some patients of this group have psychosis, delirium, or dementia as the source of their denial of illness. There may be a small group who has maladaptive denial of physical illness (Strauss et al. 1990, Muskin et al. 1998a).

Somatic expression of psychological problems occurs commonly and typically is not severe enough to lead to medical attention. The queasy stomach before an examination and the headache in anticipation of or during an undesirable activity are well known. For some people, psychic

experiences are readily translated into bodily experiences and such individuals seek treatment for their physical ailments, unaware of this psychological mechanism.

Physicians may play a role in the continuation of the psychiatric disorder by accepting the patient's complaints without a thorough evaluation of the patient's history, and without obtaining a detailed history of prior treatment. Physicians are often unaware that the patient's somatic complaints are both a metaphor for psychic suffering and the patient's intense need to be taken care of by someone. If the patient's psychology is not understood, no attempt can be made to understand the kind of help the person requires. In this setting, the patient is compelled to continue to complain of physical problems. A physician may find it impossible to believe that the patient is unaware of what appear to be obvious psychodynamic issues. The physician's anger or neglect may motivate the patient to seek "better" care, which often translates into consulting a different medical doctor, not pursuing psychiatric treatment.

There is limited time available during any clinical encounter and thus it is impossible to review every symptom about which a patient complains. Any physical complaint could be a "real" medical disorder or a symptom of a somatoform disorder. There are certain "qualities" about how a patient with somatoform disorder presents that are worth reviewing. A patient with a somatoform disorder frequently will consult several physicians simultaneously or in rapid sequence. In contrast to the average medically ill patient who tries to give an adequate history but often leaves out many details, a patient with somatoform disorders describes symptoms in exquisite detail, including dates of onset of the complaints, the character of the symptoms, and the precipitants of the symptoms. Such patients often bring the physician the results of previous laboratory and physical examinations. Although the diagnostic evaluation of the complaints typically does not yield positive findings, there are some patients who have a medical disorder that is exacerbated by a somatoform disorder. In these situations, positive physical findings emerge during the workup. One clue to the physician in such cases is that the patient's complaints exceed what would be expected from the physical or laboratory findings. In other cases, physical or laboratory abnormalities initially lend support to the patient's complaints but are eventually found not to be etiologically related to the presumed illness.

The manner and extent to which a patient manifests physical symptoms reflect childhood experiences and personality characteristics. An estimated 30–60% of patients in primary care settings complain of symptoms that have no medical basis (Kirmayer and Robbins 1991). The term *somatization* describes the development, persistence, and preoccupation with unexplained medical symptoms. The establishment of a link from childhood trauma to adult somatic preoccupations has been an attempt to explain the phenomenon. Attachment styles develop early in life, dependent upon interactions between children and their caregivers. Such styles of attachment impact on how individuals expect others to behave, especially during times of dependency, and particularly with people upon whom the person depends for support and advice, i.e., the physician (Stuart and Noyes 1999). The attachment style has a positive or negative influence on how a patient will interact with the physician. People with secure attachment styles experienced reliable caregiving as children, have positive views of the self and others, and can depend upon others comfortably. Insecure attachment styles result from rejecting or traumatic experiences from caregivers. These people have negative views of the self and others. They wish to be close but fear rejection, oscillating between behaviors of approach and avoidance. It is obvious how differently people with these two styles of attachment will behave with physicians. Childhood trauma fosters insecure attachment styles that influences adult levels of somatization in women (Waldinger et al. 2006). Trauma in childhood does not predict an insecure attachment style in men, for whom childhood trauma and attachment style are important independent predictors of adult somatization (Waldinger et al. 2006).

In conversion disorders, patients present with dysfunction of systems typically under voluntary control, such as the motor system, or have symptoms involving the special senses. Patients may have seizure-like symptoms without any evidence of a seizure disorder or may have confirmed electroencephalographic findings that do not correlate with the symptoms. DSM-IV-TR does not require that there be an unconscious conflict that is expressed via the physical dysfunction, but there must be an evidence of a precipitant for the symptoms. The symptoms are often notable for lacking anatomical validity; for example, glove anesthesia of the hand is not in keeping with the innervation of the hand. The symptoms do have causality that is logical from a psychological and symbolic perspective. The patient who is "blind" may have a need not to "see." Coming to an understanding of the precipitant for the disorder through careful questioning, sometimes aided by hypnosis, may be of value in the resolution of the symptoms. An interview using amobarbital (Amytal) should be considered as a second choice given the higher degree of risk. Some physicians may find it impossible to believe that patients who have a conversion disorder are not aware that their psychology is the "cause" of the symptoms.

Patients with conversion disorders are not necessarily hysterical in demeanor. Whereas some patients may seem unnaturally calm about their malady, a phenomenon known as *la belle indifférence*, patients may also present with extreme distress caused by the sudden alteration in their physical functioning. The spectrum of intentionality in patients with medically unexplained motor or sensory symptoms or deficits runs from conversion to malingering. Conversion is unconscious and yields psychological gains that are outside the person's awareness. This must be differentiated from malingering, which is entirely conscious and for the purpose of more readily apparent external incentives.

In somatization disorder, formerly known as Briquet's syndrome, patients have multiple complaints that have persisted for many years and have resulted in medical treatment(s). Patients may have a history of numerous surgical procedures and of taking many different medications. To fulfill the diagnostic criteria, patients must have complaints involving multiple organ systems and a history that begins relatively early in life, that is, before the age of 30. People with somatization disorder suffer greatly from their constant attempts to obtain treatment. They are at risk of becoming physically dependent on prescribed medications such as narcotics. They may also suffer serious adverse effects

Clinical Vignette 7

A psychiatric consultation was requested for Ms. H, a 33-year-old woman who was admitted with paresis of the right hand. Her symptoms had developed slowly during the previous day, and she had a history of a stroke 5 years prior to this admission. The patient had a history of taking oral contraceptives, and was overweight, both considered by her doctors to be risk factors for a stroke. Ms. H was tearful about the sudden change in her physical condition and expressed concern about how her mother would manage the care of her 6-year-old son. Further questioning revealed Ms. H's guilty feeling that an angry encounter with her ex-husband might have precipitated this stroke. Her belief was that she should never lose her temper. She also revealed that she went to church daily, prayed often, and occasionally "spoke in tongues." She was hypnotized during the consultation and was highly hypnotizable (Grade 4) using the Hypnotic Induction Profile (Spiegel 1973, Spiegel and Spiegel 2004). While in the trance, state she talked about having the wish to punch her ex-husband during the argument. Prior to the cessation of the trance, Ms. H was given the suggestion that she would have greater use of her hand and that her strength would progressively increase over the next day. Ms. H had a complete recovery the next day and was able to use her hand without difficulty. She was referred for outpatient psychotherapy to resolve the difficulties with her ex-husband, with whom she had continued contact because of their child.

from unnecessary medications that are prescribed, or from taking combinations of medications. They have morbidity resulting from surgical and medical procedures and may put themselves at risk by undergoing simultaneous treatments, without informing their physician(s).

Pain is a frequent complaint of many patients. Pain is a subjective experience and all pain, no matter what the origin, can be modulated by the individual's emotional state. No test exists to prove or disprove a patient's experience of pain. Therefore, the physician must always consider both the possibility that the discomfort is caused by some general medical condition not yet diagnosed, *and* that the pain is a psychological symptom. The patient's subjective experience does not guide the diagnosis in differentiating pain derived from an undiscovered physical source from pain that is a symptom of a somatoform disorder.

Patients who present with chronic pain syndromes should also be evaluated for depression. Even when there is evidence that such a patient is clinically depressed, the chronic pain may still result from a medical illness. Treatment for the pain is often not successful unless the mood disorder is treated. As tolerance for pain varies considerably, it can be difficult to assess a patient's complaint. Patients' pain is real, as is their suffering, even if the treatment does not involve analgesics. Tricyclic antidepressants have shown to be effective in the treatment of certain pain syndromes, without accompanying depression (Max et al. 1992). In the absence of depression, selective serotonin reuptake inhibitors have not shown to be particularly effective as analgesics in all conditions (Max et al. 1992). Medications that work in one pain syndrome may not work in others, and efficacy of one medication in a particular condition does not indicate that all of the drugs will work (Sindrup and Jensen 1999, Ansari 2000).

Whether the patient's pain is best treated with analgesics, antidepressants, psychotherapy, or a combination of therapies must be determined clinically. Physicians who are not well trained in the use of oral and parenteral narcotic analgesics often encounter a problem that results in patient–physician discord. Many physicians harbor an unsubstantiated fear of causing narcotic addiction, in spite of the evidence indicating a low incidence of iatrogenic addiction (Perry 1984). It is no surprise that the inadequate treatment of pain with narcotic analgesics is a well-documented phenomenon (Marks and Sachar 1973, Sriwatanakul et al. 1983, Kanner and Foley 1981). Inadequate treatment of pain can result in exactly what the physician fears, that is, drug-seeking behavior. As the patient realizes that the pain will not be alleviated because the medication will not be given in adequate doses or frequently enough, she/he begins to utilize manipulative techniques to obtain narcotic analgesics (Weissman and Haddox 1989). The failure to recognize that a patient is not being adequately treated for pain can result in anger at the physician to the point that the patient may want to leave the hospital in spite of the medical consequences (Albert and Kornfeld 1973).

The fear of being ill can reach such proportions that it causes great suffering in the absence of any medical disorder. In hypochondriasis, patients persist in the belief that they are or will become ill, and complain of symptoms for which no medical cause can be found. Their fears of illness endure despite medical evidence to the contrary. The fear is not delusional, that is, the person can consider the possibility that he or she is not ill. The patient's fear of having an illness should not occur only while experiencing a panic attack, and the fear must last for a period of at least 6 months. Transient fears of having an illness may occur in stressful settings, but this is not hypochondriasis, that is, medical students often fear having the illness that they are studying at

Clinical Vignette 8

Ms. A consulted a psychiatrist because of feelings of depression, anxiety, and a history of difficulties in relationships with men. She had an overwhelming fear that she had acquired immunodeficiency syndrome but had no physical symptoms with the exception of fatigue. Although she could consider the possibility that she was not infected, she believed her sexual history had exposed her to the virus. At the age of 28 years, she had sexual experiences with nine men. The idea of being tested to rule out acquired immunodeficiency syndrome was too frightening because she was convinced that she would test seropositive, and she thus refused to have an HIV test. Treatment of her depression with fluoxetine, and psychotherapy focused on her overstimulating relationship with her father as a little girl resulted in complete disappearance of her fears. She started a relationship with a man and, when appropriate, recommended that they *both* be tested for human immunodeficiency virus before becoming sexually involved. They both tested negative and began a sexual relationship. There was no return of her ruminations about HIV infection. The couple married and there was no return of the hypochondriacal symptoms during a postpartum depression (requiring antidepressant treatment) after the birth of her first child.

the moment. This fear dissipates when the person reads the next chapter in the medical text. Patients with hypochondriasis have a high degree of psychiatric comorbidity, particularly mood and anxiety disorders (Barsky et al. 1992). Hypochondriacal patients without other Axis I disorders appear to have a lifestyle of worrying about their body, misinterpreting normal bodily experiences as signifying illness, and increasing their discomfort by focusing on their physical experience. These patients are different from the individuals who develop hypochondriasis in response to a life stress or develop it secondary to another physical disorder. Following treatment for a malignancy, some patients may have symptoms of hypochondriasis, checking for lumps, worrying about a cough or bleeding hemorrhoids. These worries may persist until the patient has reached one of the significant milestones of survival (e.g., 5 years).

Body dysmorphic disorder is a preoccupation with a defect of physical appearance in an individual who has a consensually normal appearance. This bodily defect may be imagined or it may be an exaggeration of an actual but insignificant physical attribute (Phillips 1991). Patients who have anorexia nervosa, for example, someone who regards his or her body as excessively fat in spite of a thin appearance and restricted caloric intake, are not included in the body dysmorphic diagnostic category. The disorder was previously termed dysmorphophobia, and patients with such beliefs were described by Morselli more than 100 years ago (Phillips 1991). Patients' preoccupation with their "deformity" can result in withdrawal from social engagement, repeated consultations with physicians, and attempts to correct the imagined defect with plastic surgery or cosmetic maneuvers. Individuals with delusional beliefs about a physical defect are diagnosed as having delusional disorder; somatic type. However, it may be difficult to make this distinction (Thomas 1985). Treatment of patients diagnosed with body dysmorphic disorder using antipsychotics has not been particularly successful. It has also been argued that the distinction between body dysmorphic disorder and obsessive–compulsive disorder may be blurred in some patients (Tynes et al. 1990).

Clinical Vignette 9

A 50-year-old woman was brought to the hospital by her partner with complaints of confusion, memory impairment, and amnesia. The patient left her home following an argument with her partner had not returned home the night before the admission. Her partner reported that the patient had gone to move her car. There were no signs of physical trauma but the patient was missing all of the jewelry she had worn the night before. An empty bottle of oxycodone was found in her car, but she tested negative for all substance on a toxicology screen. A consultation was requested to evaluate the patient for transient global amnesia thought to be secondary to a presumed sexual assault. The psychiatrist asked that the patient have an MRI that was read as consistent with carbon monoxide poisoning, primarily impacting on the hippocampus.

## Factitious Symptoms

Perhaps no group of patients produces more negative reactions in physicians than those who create medical conditions or overtly lie about being ill. When the truth is discovered, such patients are likely to engender anger rather than empathy from their physicians. Physicians commonly fail to distinguish people who have psychological needs that are met by assuming the role of being sick (factitious disorder) from people who feign illness for reasons of personal gain (malingering). There is no physical presentation that cannot be factitiously replicated. Common medical conditions seen in these patients include infection, wounds that do not heal, hypoglycemia, anemia, bleeding, rashes, neurologic symptoms (seizures, dizziness), vomiting, diarrhea, pain, fever of undetermined origin, and symptoms of autoimmune or connective tissue disease. Patients may feign physical illness, psychological illness, or a combination of both (Phillips et al. 1983). When patients feign physical or sexual abuse, there is typically no corroboration for their story. Patients with factitious disorder are more likely to be women than are patients with Munchausen's syndrome, the most severe form of factitious disorder (Phillips 2001).

There is a risk of patients developing serious medical conditions secondary to what they do in order to induce symptoms, particularly in Munchausen's syndrome. Patients with factitious symptoms may leave the hospital precipitously when confronted with the discovery of their behavior. Some of these patients may become acutely suicidal when they are confronted. This risk, and how the risk will be handled, should be considered prior to the decision to confront the patient. Overall, confrontation has not been very successful in altering patients' behavior (Phillips 2001). It is difficult for some nonpsychiatric physicians to comprehend why people would make themselves ill in order to assume the sick role. As psychiatrists, one of our responsibilities is to help our colleagues understand how the sick role confers

Clinical Vignette 10

A 28-year-old nurse presented with a long history of aseptic blisters covering her entire body. These were painful and resulted in scarring of her skin. She gave a history of numerous workups, none of which yielded a cause for her condition. She also gave a history of the violent death of her husband and young child in a motor vehicle accident. The pastor of her church confirmed that she had come to him during her grief. During her hospital stay, she was a model patient who was well liked by all of the staff. When the workup for the continued blistering was negative, the staff suspected that she might be inducing her symptoms. Simultaneously the psychiatrist happened upon an article indicating that patients with factitious mourning often describe a violent death of the loved one, but there is no corroborating information (Phillips 2001). A search of her room revealed a syringe and a container of insecticide. Confrontation of the patient with this information resulted in an overt suicide attempt. A discussion with the patient revealed that she held the fixed conviction that no one would care for her if she were not medically ill. She was aware of her need to obtain concern and caring by being ill and could conceive of no other alternative for herself. It was necessary to hospitalize her in the psychiatric service, because she remained dangerously suicidal once her behavior was known and her creation of the "illness" was prevented.

special rights including freedom from responsibilities the patient fears she/he cannot fulfill. Such considerations are of paramount importance to the patient and must be a part of the therapy to allow the person to find adaptive methods of dealing with their psychological needs. This may allow them to give up feigning physical symptoms.

There are also patients who assume the sick role for different kinds of personal gain. These include obtaining relief from financial responsibilities by pretending to be ill, obtaining money from disability insurance, eluding legal proceedings, or avoiding other unpleasant life events. Malingering is not considered a psychiatric disorder but is a conscious behavior in which the sick role is created to receive external incentives.

## Conclusion

Nothing is more rewarding for a physician than solving the diagnostic puzzle of a complex presentation of physical and psychological signs and symptoms, resulting in the patient's return to health. This challenge exists for psychiatrists and nonpsychiatrists, both of whom see many such patients. Patients report their symptoms and their subjective experience, but it is the physician who puts that information into a differential diagnostic formulation. The physician's understanding of the role of culture and cultural biases toward mental illness and of the physical components of mood and anxiety disorders results in a consideration of a psychiatric diagnosis. This process occurs even in the absence of the patient's complaint of psychological symptoms. Instances in which patients' physical complaints are parts of mood and anxiety disorders may cause diagnostic confusion for physicians who consider only medical diagnoses.

There are patients who insist that they have a medical problem and whose claim is not confirmed by physical examination or laboratory testing. The psychological need to have a physical complaint is the psychiatric disorder for this group of patients. At the other end of this physical–psychiatric continuum are patients, without obvious physical discomfort to suggest a medical condition, who may be misdiagnosed as having a psychiatric disorder because their presentation is atypical, or their complaints are primarily in the domain of how they feel or how they think. Our unique role as physicians enables us to pay attention to all symptoms without the bias of a mind–body dualism. When it comes to the diagnostic consideration of a psychiatric versus a medical condition, we know that it is not *either/or* but it often is *both*. Holistic medicine, a term first coined in the 1920s by a South African statesman, has come to be used by practitioners outside of the medical tradition (Muskin 2000). It is clear that the modern practice of medicine, in which we seek to understand and care for the *entire* patient, is truly what is meant by holistic medicine.

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CHAPTER

# 38 Behavior and Adaptive Functioning

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To function adaptively means to behave in such a way that one's attitudes and actions are well matched to the demands and constraints of the external environment and that one's sense of internal discomfort or distress is minimized. Therefore, by definition, the ability to adapt depends both on the individual's behavioral repertoire and on the external environment. A person's capacity for adaptive functioning is so crucial that it has been studied in situations ranging from adaptation to long-term missions in outer space (Eksuzian 1999) to the self-management of life-threatening illnesses such as chronic heart failure (Buetow et al. 2001). This chapter focuses on the ingredients that shape personality and the ways in which personality in turn affects the behavior. Several systems for thinking about personality are described. In addition, the domains in which individuals are typically expected to function are reviewed, with particular attention to the ways in which various personality styles affect functioning in each domain. Patterns of behavior that are frequently pathological in nature, such as impulsive, compulsive, and avoidant behaviors, are examined. Finally, approaches to the assessment of behavior and adaptive functioning in the psychiatric interview are reviewed.

## Personality Style

An individual's personality style has a great influence on his or her behavior and adaptive functioning. Personality is shaped from a blend of inborn temperament, genetic strengths and vulnerabilities, and the impact of positive and negative life experiences. Psychiatry is moving toward an improved understanding of human behavior that focuses on the ways that these factors interact with one another.

There is evidence of striking variation among neonates in their capacity to tolerate frustration, which reflects their inborn temperaments (Thomas et al. 1963). Such individual differences in temperament form the biological substrate that interacts with early development. Temperament affects the degree to which different infants are susceptible to distress as well as their variations in attachment style (Rothbart and Ahadi 1994). Mr. A's high tolerance for frustration was an advantage as an infant; his mother considered him an easy baby who was not too demanding. In contrast, only when Mr. B's repeated bouts of colic in his first year of life ended could he assume the role of family prankster.

Clinical Vignette 1

Mr. A, a successful 48-year-old attorney, is married and has three children. He has enjoyed the position of partner in his large corporate law firm for many years, yet he continues to work long hours. He often wishes he had enough time and energy to really enjoy his children, but he does manage to spend weekends with his family at their country home. He feels satisfied with his work and particularly enjoys his days in court, where he is known as a polished orator and a tough opponent who is likely to make clever legal arguments. His wife sometimes complains that he is too dedicated to work and too worried about money to enjoy the rewards of his labor. She wishes he would let loose and have fun more often, but she is generally satisfied with their marriage.

As a baby, Mr. A was considered easy, seldom ruffled by the inevitable delays of gratification in being fed and changed. He was a bright and cheerful child until age 10 years, when his father was killed in a car accident while driving home from work. After his father's death, his mother noticed that he became serious and sad, responding to the loss by becoming the "little man" of the family and by always watching out for his little brother, 3 years younger. His mother was particularly worried about this because her sister had a history of severe depression. In high school, he was class president and an excellent track-and-field athlete. No one was surprised when he studied in government college and entered law school.

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Genetic factors of various types also play a role in development, particularly when they interact with environmental factors. Mr. A's mother was correct to be concerned that both his father's death when Mr. A was young and her sister's history of depression placed him at higher risk. Brown and Harris (1989) have demonstrated a clear link between early loss of a parent and vulnerability to depression in the face of later stressful life events. Extending these findings, Kendler et al. (2002) demonstrated increased risk for major depression in subjects with parental death and parental separation and in alcohol dependence after parental separation but not parental death. Interestingly, the impact of parental death on rates of depression was less long-lasting than was the impact of parental separation.

Clinical Vignette 2

Mr. B is a 35-year-old divorced advertising executive. He enjoys his powerful role within his company and is well known for his impressively slick presentations. However, one problem for Mr. B in his career has been his difficulty in keeping personal and work lives separate; during his fling with a junior colleague, his coworkers noted that he was more concerned with flirting than with finishing an important project. He seems to delight in the macho image he projects, basking in the attention of women at work and annoying other men with his tales of previous romantic conquests. These behaviors have kept Mr. B from being promoted to an even more prominent position. Mr. B's family suspects that he will never have a successful marriage until he stops being a "ladies' man."

As a baby, Mr. B was fussy and difficult owing to repeated bouts of colic in the first year of life. Once he recovered, however, he rapidly became the family entertainer. The youngest of five children, he was known for his antics and pranks. When he entered adolescence, Mr. B became engrossed in bodybuilding and football, quickly learning that his athletic prowess made him the heartthrob of his high school class. Mr. B's father had also been a star athlete and responded to his athletic interests by coaching and encouraging him.

Although Mr. B was intelligent and graduated near the top of his high school class, he was far more interested in organizing parties. College was initially rough for Mr. B, who by then had become accustomed to being on top at high school. In college, he changed his major several times, trying to figure out what image he was trying to build for himself. His fantasies of becoming a National Football League defensive back were dashed by a knee injury during his junior year, which was largely the result of his overtraining and insistence on pushing himself to his limits. After this, Mr. B devoted himself to learning all about the business world instead. Networking and social chatter came naturally to Mr. B, allowing him to rise rapidly within the advertising world. In fact, he proposed to his wife soon after they met at a business cocktail party; she was his boss' date for the evening. The marriage ended less than 2 years later when she discovered the affair with his coworker.

Inherited characteristics can also be protective; because Mr. A is intelligent, he was able to become a talented lawyer. In contrast, Mr. B has no family history of mental illness. His hypermasculine style is reminiscent of his father's and is influenced both by genetics and by his relationship with his father. While genetic factors are thought to account for between 30 and 60% of the variance in adult personality traits (Carey and DiLalla 1994), more recent studies increasingly suggest that shared and nonshared environmental factors rather than genetics may play a substantial role in accounting for the observed quality of infant–caregiver interactions (Roisman and Fraley 2006).

Life experiences also have an impact on an individual and affect her or his behavior for better or worse. After his father's death, Mr. A developed responsibility and conscientiousness atypical of a 10-year old in addition to incurring a greater risk of depression. In contrast to the death of Mr. A's father, which was beyond his control, Mr. B's knee injury was probably the result of his own actions. His injury ended his dream of playing professional football but helped point him in the direction of a successful business career. Considering whether particular experiences are the result of fate in contrast to whether they are partially brought about by the person's own actions can be important in thinking about their impact and meaning.

While psychiatrists have long suspected links between early life experiences, especially traumatic ones, and adult psychopathology, these connections are just now being clearly, empirically demonstrated. For example, in one recent study, childhood verbal abuse conferred an increased likelihood of borderline, narcissistic, paranoid, schizoid, and schizotypal personality disorder during adolescence that was independent of other facts like temperament, physical and sexual abuse, use of corporal punishment, parental psychopathology, and co-occurring psychiatric disorders (Johnson et al. 2001). Further, as the relationships between genetic propensities expressed as temperament or personality factors and environmental influences have been explicated, some fascinating interactions have emerged. For example, one recent study suggested that high levels of the personality trait of sensation seeking, which appears to be genetically mediated, might result in a high incidence of adverse life events that would in turn help to precipitate depression (Farmer et al. 2001). More recently, research suggests that genetic factors may moderate the risk of depression in response to stressful life events. For example, the depressogenic effects of stressful life events was significantly greater in groups of women with two short alleles on their serotonin transporter gene than for those with one or no short allele. This functional polymorphism in the serotonin transporter gene was demonstrated to moderate the association between stressful life events and depression by affecting the processing of negative emotion in those with two short alleles (Jacobs et al. 2006). In practice, the reciprocal interactions of the intrapsychic experiences of a person, his or her genetics, and current and past environmental influences make the evaluation of how these factors interact difficult. Oldham (2005) note that a fair amount of the reason we behave as we do relates to "hardwiring," such as temperament, which is clearly heritable. But beginning in earliest life, the influence of the family caretakers and environmental experiences begin to create a bidirectional process. For example, a placid temperament in an infant elicits reactions in parents and caretakers, which in turn affects the development of personality style. This process continues throughout childhood and adult life. For example, Mr. A's affective state after the loss of his father probably colored his behavior in the world as

well as his experience of relationships and events in daily life. Separating aspects of functioning related to his affective state from external reality would be a problem and probably impossible.

Thinking about personality, style and behavior go hand in hand; as Oldham (2005) have pointed out, "in many important ways we are what we do. The 'what' of personality is easier to come by than the 'why' and each of us has a personality style that is unique, almost like a fingerprint. At a school reunion, recognition of classmates not seen for decades derives as much from familiar behavior as from physical appearance."

Personality styles have been described in a variety of ways with use of different models of normal personality variation. These models are either categorical or dimensional in nature. In a categorical model, a person is described as meeting or not meeting the criteria for various diagnostic categories. In a dimensional model of personality, a person is evaluated in terms of the blend of various traits or factors he or she possesses, measured on a continuum. In general, as a person moves toward the extreme end of a given continuum in the dimensional model, she or he becomes more likely to meet the criteria for a categorical diagnosis. Some dimensional models set a threshold beyond which a given characteristic is likely to be a problem or pathological.

The categorical model is a more common approach to diagnosis within clinical psychiatry and within medicine in general. However, if Mr. A does not have obsessive–compulsive personality disorder, the unique characteristics of his personality style will not be captured within a categorical model. In addition, the categorical model suggests that the categories in which diagnoses are given are not overlapping. In contrast, a dimensional model allows the retention of important information about a person's blend of traits but says less about how pathological these patterns are, and is more difficult to use clinically than a straightforward categorical diagnosis. It now seems clear that useful information is gained from both categorical and dimensional approaches to examining personality. At present, the conceptualization of personality disorders within the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) "represents the categorical perspective that personality disorders are qualitatively distinct syndromes" but it is acknowledged that "an alternative to the categorical approach is the dimensional perspective that personality disorders represent maladaptive variants of personality traits that merge imperceptibly into normality and into one another" (American Psychiatric Association 2000). Oldham and Skodol (2000), among others, urged that elements of both categorical and dimensional systems be included when revisions are made in DSM-V, and a joint committee of the American Psychiatric Association and the National Institute of Mental Health concluded that there was a clear need for dimensional models to be developed and for their usefulness to be compared with existing typologies (Widiger and Mullins-Sweatt 2005).

It is likely that certain ways of looking at personality are more useful for a particular purpose than others. For example, an examination of three-dimensional representations of DSM-IV-TR personality disorders and standard categories. In an empirical study of 668 patients comparing personality disorder categories, dimensional representations of those categories based on criteria counts and three- and five-factor personality dimensions with respect to their associations with psychosocial functioning, DSM-IV-TR dimensions best predicted functional impairment (Skodol et al. 2005). However, it may be that the three- or five-factor model would better predict treatment response or development of a therapeutic alliance in treatment, for example.

Taking an even longer view, Depue and Lensenweger (2006) have suggested that the ultimate goal would be the development of a neurobehavioral dimensional model of personality in which personality disturbance is seen "as the product of a matrix of highly interactive systems of neurobehavioral processes" that "interacts with the environment through time and across context, including developmental transitions, to allow for the emergence of personality pathology." Others have proposed a prototype-matching approach to diagnosing personality disorders in which models of various personality styles are constructed and psychiatrists make diagnosis by matching their patient to the best available prototype (Westen and Shedler 2000). A large new collaborative longitudinal study of personality disorders is currently underway and will provide empirical evidence as to the utility of various approaches to studying personality over time, as well as yielding important information about the course of personality disorders measured in a variety of ways (Gunderson et al. 2000).

In current DSM-IV-TR terms, Mr. A does not meet the full criteria for any of the 10 personality disorders even though he shows some features of obsessive–compulsive personality disorder. He is excessively devoted to work to the exclusion of leisure and has a tendency to be overly cautious with money. In contrast, Mr. B would receive a diagnosis of histrionic personality disorder because he is often sexually seductive, is uncomfortable when he is not the center of attention, and consistently uses his physical appearance to draw attention to himself. He is emotionally shallow and tends to portray himself as a "hip" advertising executive. Although others may not see their relationships with him as intimate, Mr. B tends to assume that his relationships are more intimate than they actually are. However, a diagnosis of histrionic personality disorder would still mean overlooking those aspects of Mr. B's personality that are narcissistic in nature but do not meet full criteria for narcissistic personality disorder (Farmer et al. 2001).

Oldham and Morris (1995) translated each of the personality disorders of the DSM-IV-TR system into a less pathological collection of categories that describe normal personality styles. In their system, a cross between a categorical and a dimensional model, conscientiousness is the positive personality trait that in excess becomes obsessive–compulsive personality disorder. In Mr. A's case, both the positive aspects of his conscientiousness in helping him to achieve his goals at work and the negative impact of this trait on his wife and children when he works too hard are evident. In this model, being dramatic is a character style that when overdone becomes histrionic; self-confidence in excess becomes narcissism. A literature review by Widiger and Costa (1994) supports the hypothesis that DSM-IV-TR personality disorders represent extreme variants of normal personality traits. Table 38–1 summarizes the personality style–personality disorder continuum described by Oldham and Morris.

A continuum model such as this one acknowledges that whereas too much of a good thing may constitute

**Table 38–1** Oldham and Morris' Personality Style-Personality Disorder Continuum

| Style | DSM-IV-TR Disorder |
|---|---|
| Vigilant | Paranoid |
| Solitary | Schizoid |
| Idiosyncratic | Schizotypal |
| Adventurous | Antisocial |
| Mercurial | Borderline |
| Dramatic | Histrionic |
| Self-confident | Narcissistic |
| Sensitive | Avoidant |
| Devoted | Dependent |
| Conscientious | Obsessive–compulsive |

a disorder, everyone's personality consists of traits that can be adaptive or maladaptive. The quantity rather than the quality of a given trait is often what makes it a problem or adaptive. Similarly, flexibility and variability are important determinants of a person's adaptive capacity.

Examples of dimensional models of personality include the five-factor model (Widiger et al. 1994, Widiger 2000, Stone 2002), Cloninger's seven-factor model (Cloninger 1987, Cloninger et al. 1993, Gillespie and Cloninger 2003), and the biogenic spectrum model of Siever and Davis (1991). The five-factor model of personality was first suggested by McDougall (1932), and was elaborated and updated by Digman (1990) and McCrae and Costa (1987) among others. In the five-factor model, personality traits are described in terms of a taxonomy of five dimensions. These include neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Someone with an obsessive–compulsive personality style, such as Mr. A, is likely to score high on the factor of conscientiousness in the five-factor model. Conscientiousness encompasses the degree to which competence, order, dutifulness, achievement, self-discipline, and deliberation are likely to be important to an individual. In addition, those with obsessive–compulsive disorder are likely to score high in terms of neuroticism, meaning that they have excess amounts of traits such as anxiety, hostility, depression, and self-consciousness. Those with obsessive styles or personality disorders typically score low on factors such as extraversion, openness, and agreeableness. In contrast, Mr. B scores high on traits such as gregariousness and excitement seeking (extraversion) as well as fantasy and artistic sensibility (openness). However, he has particular difficulty in being appropriately conscientious. As Stone (2002) has noted, examining Mr. A and Mr. B in this dimensional way allows greater diagnostic subtlety because it allows clinicians to set down all of the relevant strong and weak points of an individual's character as well as to evaluate that these facets may facilitate (such as conscientiousness) or impede (such as low openness) treatment. Table 38–2 summarizes the factors of the five-factor model and their relationship to DSM-IV-TR categories.

A second dimensional model of personality is Cloninger's seven-factor model of temperament and character (Cloninger 1987, Cloninger et al. 1993) (Table 38–3). In this model, a patient's behavior is evaluated on seven separate dimensions. Four of the seven dimensions are related to temperament and have been shown to be independently heritable, manifested early in life, and involved in early perceptual memory and habit formation. These four dimensions include novelty seeking, harm avoidance, reward dependence, and persistence. Mr. A is particularly attuned to avoiding harm, and his behavior is typically characterized by a high degree of persistence; he is cautious and thoughtful in approaching new situations and doggedly pursues his goals. Mr. B ranks high on Cloninger's dimensions of novelty seeking and reward dependence; he is quickly bored by things that are not new and exciting and actively seeks the approval and attention of others. Figure 38–1 is a schematic representation of Cloninger's model.

**Table 38–2** The Five-Factor Model

| Factor | Traits | DSM-IV-TR Example |
|---|---|---|
| Neuroticism | Anxiety | High in borderline |
| | Hostility | Low in schizoid |
| | Depression | |
| | Self-consciousness | |
| | Impulsiveness | |
| | Vulnerability | |
| Extraversion | Warmth | High in histrionic |
| | Gregariousness | Low in avoidant |
| | Assertiveness | |
| | Activity | |
| | Excitement seeking | |
| | Positive emotions | |
| Openness | Fantasy | High in schizotypal |
| | Esthetics | Low in paranoid |
| | Feelings | |
| | Actions | |
| | Ideas | |
| | Values | |
| Agreeableness | Trust | High in dependent |
| | Straightforwardness | Low in narcissistic |
| | Altruism | |
| | Compliance | |
| | Modesty | |
| | Tender-mindedness | |
| Conscientiousness | Competence order | High in obsessive–compulsive |
| | Dutifulness | Low in antisocial |
| | Achievement striving | |
| | Self-discipline | |
| | Deliberation | |

Cloninger also describes three dimensions of character, namely, self-directedness, cooperativeness, and self-transcendence. The blend of these three characteristics that an individual possesses helps to determine self-concept, such

**Table 38–3** Cloninger's Seven-Factor Model of Temperament and Character

| Temperament Factor | Behavioral Effect |
|---|---|
| Harm avoidance | Behavioral inhibition |
| Reward dependence | Motivation for behavior |
| Novelty seeking | Initiation of exploration |
| Persistence | Maintenance of behavior |
| **Character Factor** | **Self-Concept Effect** |
| Self-directedness | Sense of self as autonomous |
| Cooperativeness | Sense of self as part of community |
| Self-transcendence | Sense of self in the universe |

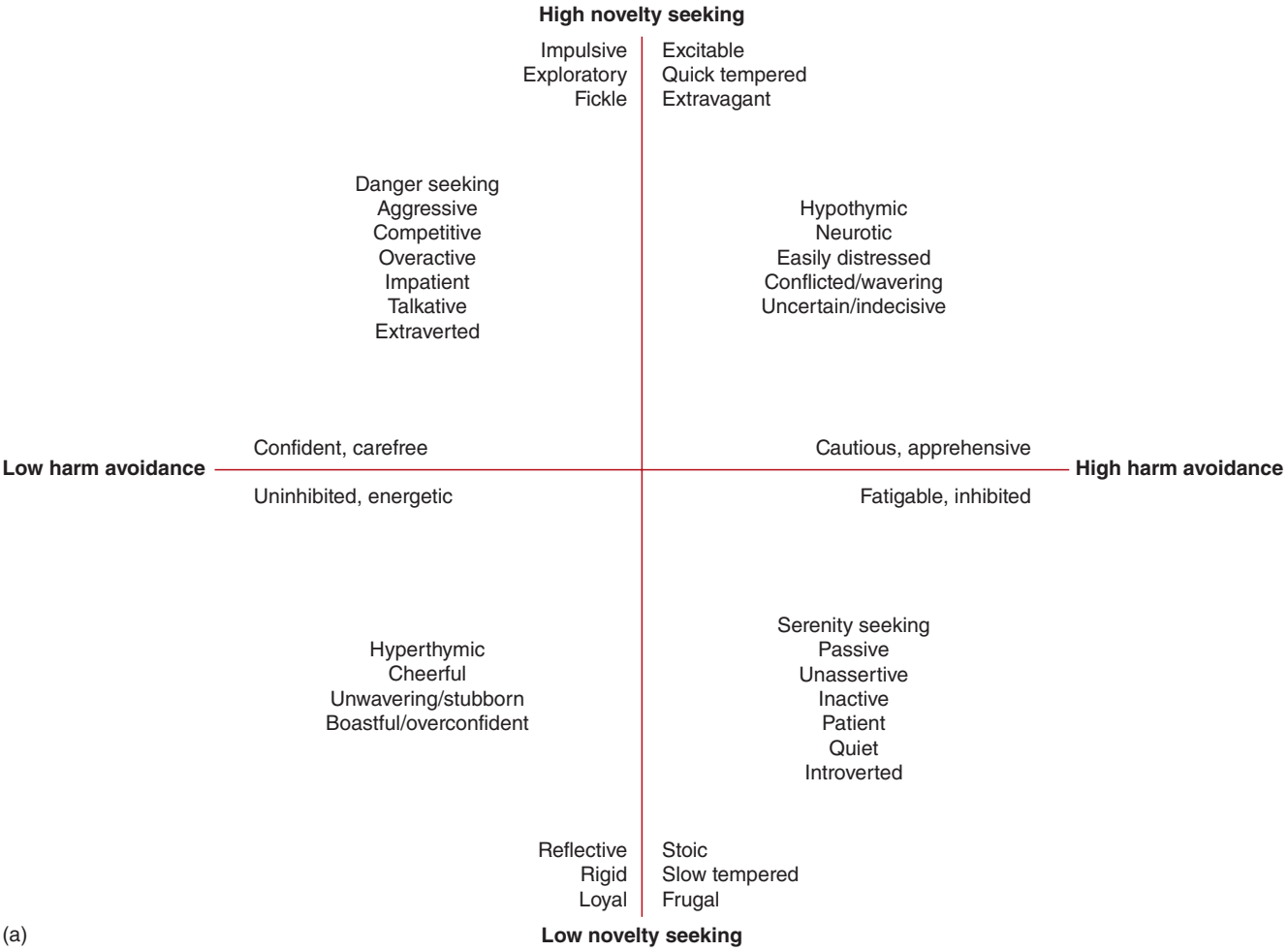
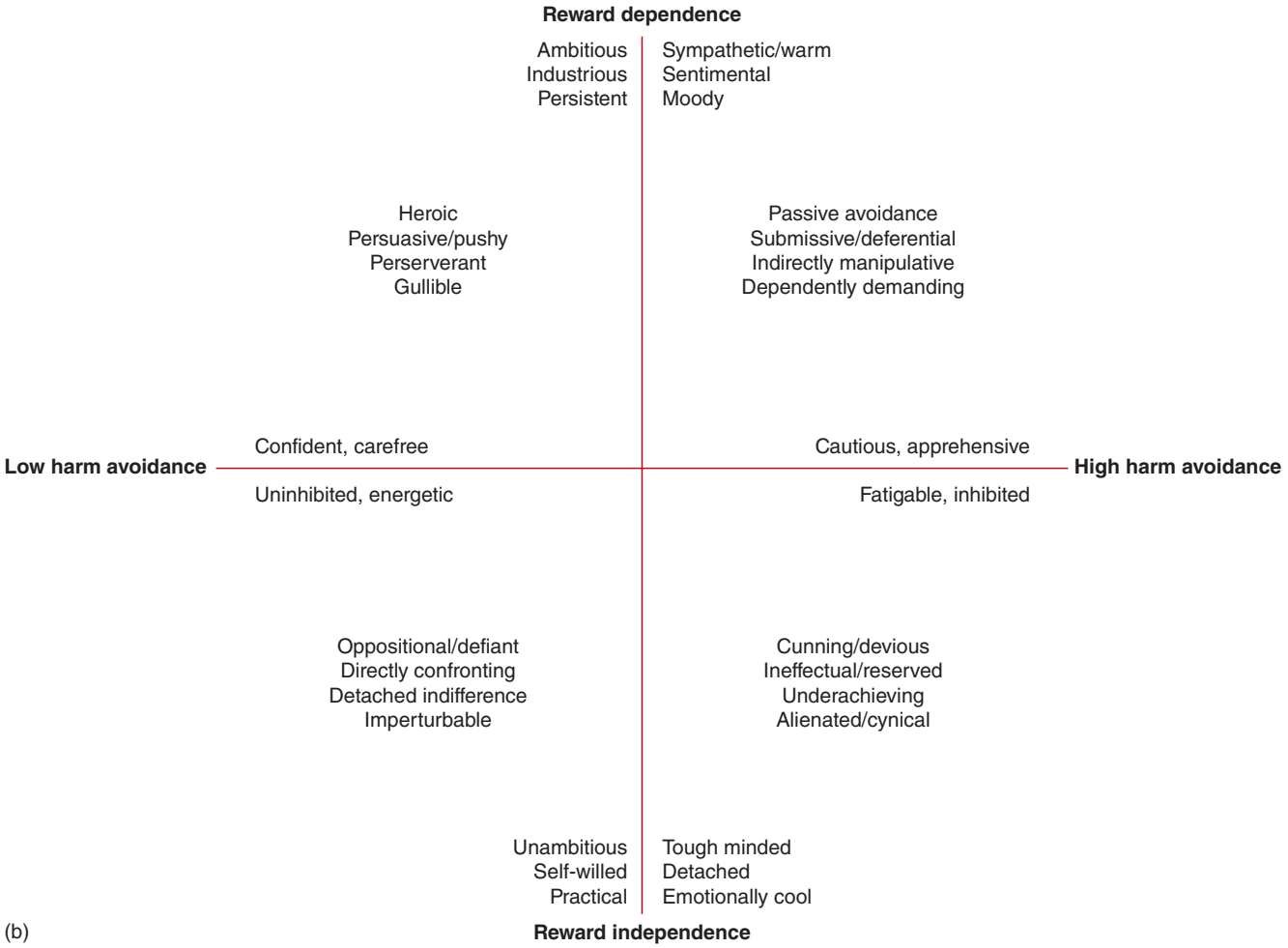



**Figure 38–1** *Cloninger's model: harm avoidance, reward dependence, and novelty seeking. [Reproduced from Cloninger (1987) with permission of American Medical Association.]*




(b)

**Figure 38–1** *Continued*

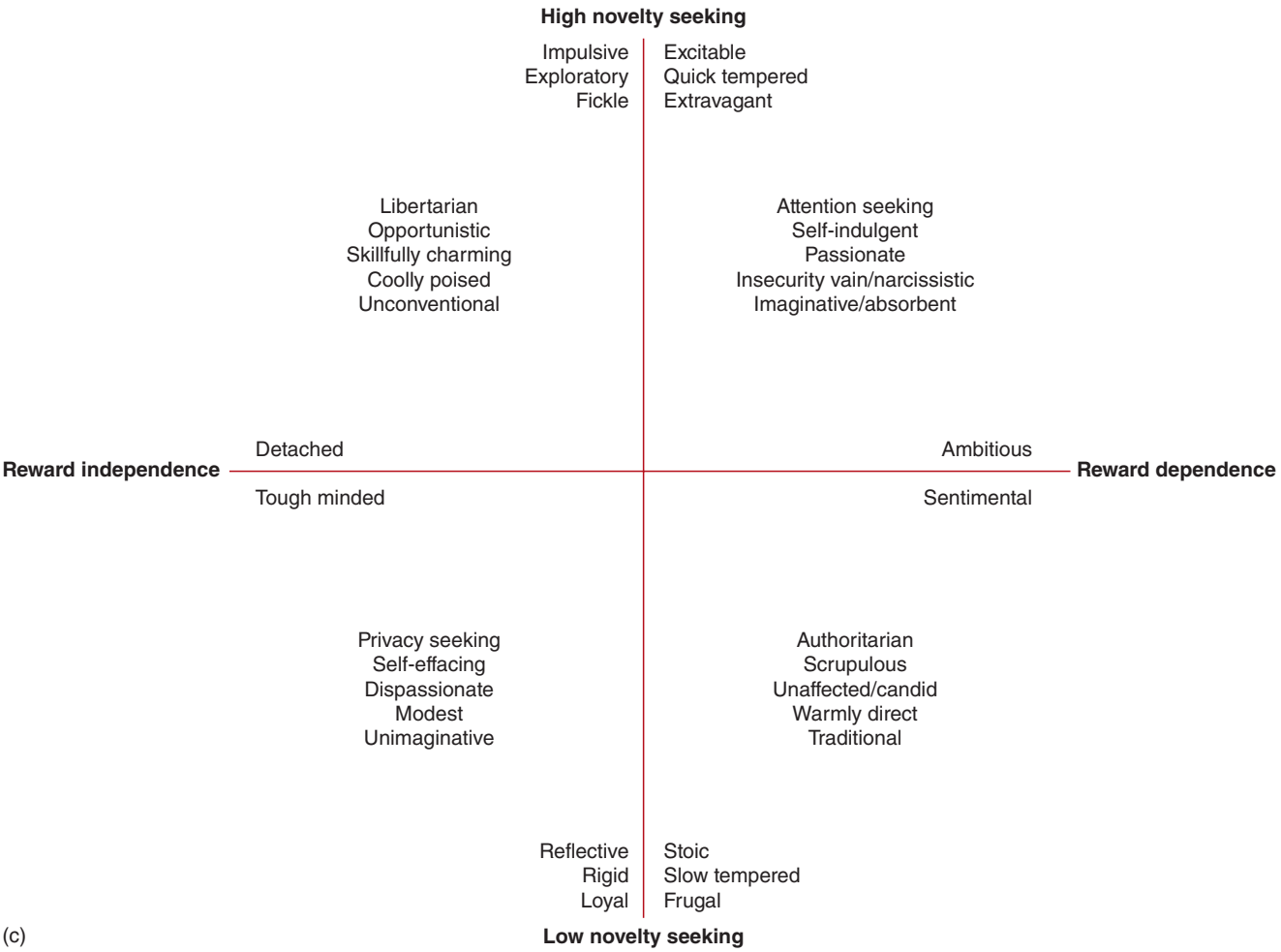



**Figure 38–1** *Continued*

as whether the individual identifies himself or herself as an autonomous individual, as an integral part of humanity, and as a part of the universe as a whole. Those with low degrees of self-directedness and low degrees of cooperativeness are more likely to have personality disorders (Svrakic et al. 1993). Someone as relatively well adapted as Mr. A is likely to rate high on the traits of self-directedness, cooperativeness, and self-transcendence. In contrast, Mr. B may be less self-directed and less cooperative than Mr. A.

A third dimensional model of personality is the biogenic spectrum model of Siever and Davis (Siever and Davus 1991, Coccaro and Siever 2005). This model proposes that certain personality styles and disorders are associated with and are characterological variants of various Axis I disorders. Thus, personality disorders are not extreme variants of normal but are characterological variants of Axis I disorders. For example, Mr. A's obsessive–compulsive style may be a variant of anxiety disorder; Mr. B's histrionic personality disorder may be a variant of an impulse control disorder. The biogenic spectrum model may be useful in guiding treatment, such as using anxiolytics to treat avoidant personality disorder because it is considered to be on a spectrum with Axis I anxiety disorders. There is growing evidence that the biogenic spectrum model is useful for at least some Axis I/Axis II disorders. One example is the link between schizophrenia and schizotypal personality disorder in which those with the Axis II disorder demonstrate a better capacity for buffering in certain frontal brain regions as shown by functional imaging as compared with those with the full-blown Axis I disorder (Kirrane and Siever 2000). Table 38–4 presents details of the biogenic model.

**Table 38–4** The Biogenic Model and DSM-IV-TR

| Axis I Disorder | Example of Axis II Variant |
|---|---|
| Mood | Borderline |
| Anxiety | Avoidant |
| Impulse control | Antisocial |
| Psychotic | Schizoid |

## Domains of Functioning

Each person's unique personality style is reflected in the various domains in which the person functions. Domains of functioning in which people are evaluated include social and interpersonal functioning, occupational functioning, and leisure. Within DSM-IV-TR, Axis V, the Global Assessment of Functioning, provides a 100-point scale with which to rate a person's overall level of adaptation. It provides a useful global rating of adaptive function that assesses the degree of symptoms and the capacity to function in social

and occupational spheres (American Psychiatric Association 1994).

## Social and Interpersonal Functioning

Interpersonal styles greatly affect social functioning, which in turn has a large impact on both work- and leisure-time functioning. Distinctive individual personality styles affect a person's perception of the importance of relationships with others as well as the quality and depth of the bonds they can form. Those with solitary traits are unlikely to crave and seek close relationships, whereas those with a devoted style become uneasy and feel incomplete if they are not with others. Vigilant people are cautious of the attentions of others, whereas dramatic types thrive on the admiration of their peers. Those who are mercurial often run "hot" and "cold" in their relationships with others, sometimes expressing their feelings in ways that offend others; sensitive types are easily affected by the perspectives and behavior of others but tend to keep their feelings to themselves.

The Social Adjustment Scale (Weissman et al. 1974, 2001) provides a quantitative way to investigate several types of interpersonal functioning (Table 38–5) including a person's relationships with family of origin, spouse or partner, children, work colleagues, and friends and acquaintances. Some questions assess the degree of overt fighting and friction that is present in these relationships and whether it causes the person to minimize or avoid contact with others.

**Table 38–5** The Social Adjustment Scale

| Domain* | Assessment Questions |
|---|---|
| Work | Time lost? |
| Outside home | Impaired performance? |
| At home | Feelings of inadequacy? |
| At school | Friction with coworkers? |
| | Distress about work? |
| | Disinterest in work? |
| Social | Impaired leisure activities? |
| | Diminished contacts with others? |
| | Diminished social interactions? |
| | Reticence to have social contacts? |
| | Friction within social contacts? |
| | Hypersensitivity? |
| | Social discomfort? |
| | Loneliness? |
| | Boredom? |
| | Diminished dating? |
| | Disinterest in dating? |
| Interpersonal | Friction? |
| Extended family | Reticence? |
| Spouse or partner | Withdrawn? |
| Parental functioning | Dependency? |
| Family unit | Rebellion? |
| | Worry? |
| | Guilt? |
| | Resentment? |
| | Submissiveness? |
| | Domineering behavior? |
| | Lack of affection? |
| | Sexual interest, frequency, problems with partner? |
| | Lack of involvement? |
| | Impaired communication? |

*Each domain is scored on a 5-point scale ranging from 1 (not a problem) to 5 (an extreme problem). In addition, a global score in each domain is assigned by the use of the same scale.

The degree to which a person feels reticent about being reasonably open within each relationship and the degree to which others are depended on to provide various forms of help, such as advice and financial support, are also important indicators of the quality of interpersonal connections. In addition, the scale provides a way to assess whether someone initiates contact with others, whether the individual feels an urge to be defiant or rebellious, and whether the individual feels overly concerned, guilty, or resentful within each relationship. Inherent in these assessments of functioning is an assumption that to be successful, relationships should be interpersonally relatively free of friction and arguments, reciprocal, and supportive. In addition, each person's experience of the relationship should be comfortable and relatively conflict free.

Benjamin's Structural Analysis of Social Behavior (Figure 38–2) provides another means of assessing recurrent patterns in a person's interactions with others (Benjamin 1986b). It has three dimensions: (1) the focus of the interaction, (2) affiliation–hostility, the tone of the interaction (loving versus hating), and (3) interdependence–independence, which can address the dimensions of enmeshment vs. differentiation. The focus in the Structural Analysis

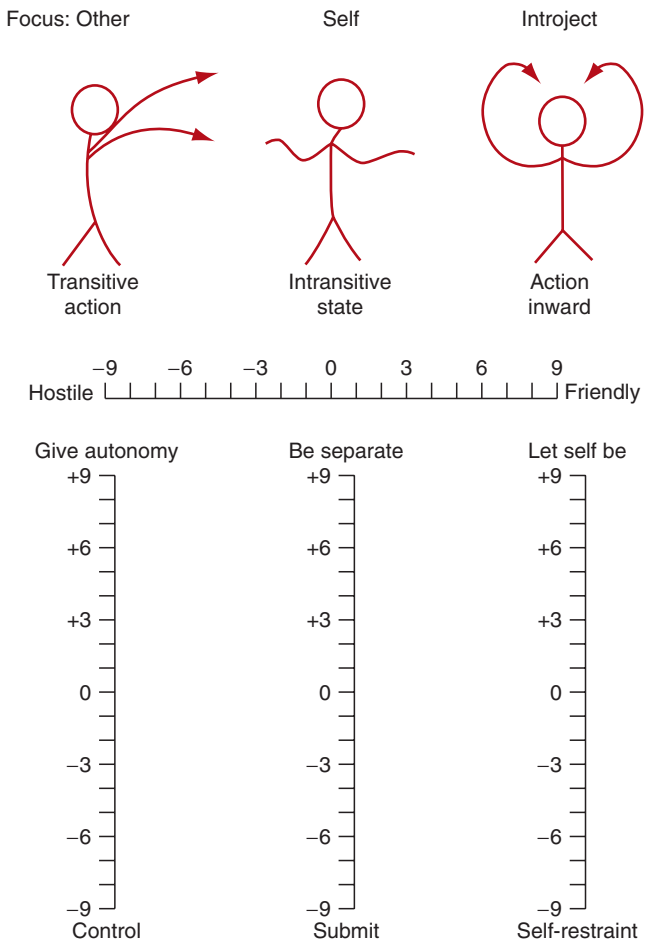



**Figure 38–2** *The three dimensions of the Structural Analysis of Social Behavior model. Therapy content and process expressed in interactional terms can be coded in terms of the three dimensions: focus, love versus hate, and interdependence. Viewing all relationships in terms of these dimensions makes parallels among early and current relationships more apparent. [Reproduced from Benjamin (1986a).]*

of Social Behavior can be on another person, on oneself in relation to another person, or on inward, internal aspects of the self. As an example, a woman cleans house and runs errands with her family in mind; the focus is on others, and the tone of the action is friendly. The act of running the household suggests that the woman influences others in the family, so the score on the third dimension is in the controlling-interdependent direction. The Structural Analysis of Social Behavior is widely used in research settings as an assessment tool to describe and quantify a person's mode of interpersonal functioning in various relationships (Benjamin et al. 2006).

### Occupational Functioning

Assessing adaptive occupational functioning requires examining the ways in which an individual completes tasks, takes and gives orders, delegates responsibilities, and cooperates with others. Job situations also require an ability to balance demands, obey regulations, and make decisions. Clearly, success in these tasks in part depends on one's capacity for interpersonal functioning. A patient who is mercurial in personal relationships is also likely to have difficulty with coworkers. Work is often the central domain of concern for those with conscientious styles and for those with aggressive styles. For people with these styles of functioning, work is synonymous with fun. In contrast, for those with other personality styles, occupational functioning can be a problem because it is given too little importance. Leisurely people get by with the bare minimum of work, whereas those who are adventurous like challenges but tend to have difficulty with authority at work. Those with a devoted style tend to remain loyal even to jobs they dislike; thus, the problem with work for them is an intrapersonal problem rather than an interpersonal one.

Weissman's Social Adjustment Scale also provides a means of evaluating a person's occupational functioning. The scale focuses on both externally observable behaviors, such as number of days lost in a month and the degree of impairment of performance at work, as well as internal states, such as feeling inadequate, angry, and distressed at work. In addition, whether a person is distressed, disinterested, and bored by work is also assessed. These questions begin to suggest what adaptive occupational functioning comprises, namely, that it consists of being engaged and feeling satisfied about and competent at work. In addition, the Social Adjustment Scale assesses whether these positive internal states are reflected in work performance and relationships with superiors and subordinates.

### Leisure

The capacity to enjoy leisure depends in part on other external demands and responsibilities as well as financial and other resources. A single mother with four young children must work harder than many mothers and is less likely to have time, money, and energy available for leisurely pursuits. Yet, leisure is more than time left over from work and family. The gusto with which leisure activities are pursued and the types of activities that are chosen are affected by a person's characteristic style. In contrast to the work domain, those with a leisurely style are likely to enjoy their free time and to have myriad hobbies and interests; those with conscientious styles may approach leisure as another job, by working hard at trying to have fun. Those with aggressive styles may choose competitive leisure pursuits, such as sports, in which they can pit their prowess against others; solitary types may prefer solo leisure pursuits that do not involve others.

The Social Adjustment Scale may be used to evaluate how well developed and specific a patient's interests are as well as the frequency with which such activities are pursued. It can be helpful in assessing whether a person's leisure-time contacts with others are diminished. The Social Adjustment Scale quantifies aspects of leisure, such as how many social events one has attended in the last month. The experience of loneliness or boredom during free time as well as the person's ability to compensate for these painful states yields a measure of leisure-time adaptation.

## Assessing Behavior and Adaptive Functioning in the Clinical Interview

Finding out about a patient's personality style, level of adaptive functioning, and usual patterns of behavior is one of the major tasks of the psychiatric interview. A psychiatrist gains important information from what a patient and those people close to the patient say about her or his behavior. However, a psychiatrist also gains invaluable information by closely observing the person during the interview itself. Whether the psychiatrist is quickly sizing up an agitated patient during a psychiatric emergency or carefully noticing how a patient shifts in the chair during a psychotherapy session, the ability to observe a patient's behavior is one of a psychiatrist's most important tools. A patient's appearance, attitude, and motor behaviors during an interaction with the psychiatrist provide important clues to personality, capacity for interpersonal interactions, and potentially problematic behavior patterns.

### Appearance

Observing a patient's appearance includes making a judgment about the overall physical impression of the person reflected by grooming, clothing, poise, and posture. The ability to appear well kept is impaired in many psychiatric disorders, ranging from the psychotic patient who appears disheveled after being up for several nights to the depressed

Clinical Vignette 3

Mr. C, a young schizophrenic man, attempted to avoid hospitalization by beginning to shave more regularly and cutting his fingernails. However, he remained unwilling and unable to have his hair cut, attempting to disguise its length by wearing it up under a baseball cap when going outside.

Clinical Vignette 4

Ms. D, a middle-aged woman, came to the emergency department claiming that she had run out of Valium and that her prescribing physician was out of town. Her story was convincing and the resident physician was about to give her a prescription when he noted on close examination that she had a dirty hem on both her pants and her jacket sleeves, which seemed inconsistent with her presentation of herself as an executive secretary. After pressing her for more details of her story and consulting with another emergency department, he determined that the patient was actually a homeless woman who got prescriptions from hospitals and then sold them on the street.

patient dressed in dark, somber tones, and slumped in the chair. Clothing often reveals aspects of personality; patients with extroverted, histrionic, or dramatic personalities often wear brightly colored, unusual clothes and are often garishly made up. Problems with appearance can suggest the possibility of other functional impairments as well.

The motivation and degree of volitional control over appearance must usually be inferred; the character of Klinger in the television series *M*A*S*H* appeared dressed in female clothing in an attempt to earn a discharge from the Army. On the other hand, a patient may try to disguise a psychiatric disorder by focusing on making her or his appearance as normal as possible.

At times, appearance may provide an important clue of an inconsistency in a patient's verbal presentation and suggest a serious behavior problem.

### Attitude and Cooperation

The interviewer can also detect a patient's attitude and willingness to cooperate during an examination. Attitude and cooperation are related but not identical concepts; a paranoid patient may have a suspicious attitude but may cooperate by answering the interviewer's questions nonetheless. Often, however, a person's attitude and ability to cooperate are both affected by psychiatric illness. Patients may be friendly or hostile, seductive, defensive, or apathetic. During the psychiatric interview, they may seem attentive or disinterested and be frank or evasive and guarded. Again, each of these attitudes and the degree of cooperation a patient exhibits can depend on the underlying psychiatric state or can reflect a conscious manipulation on the part of the patient for the sake of achieving a desired goal. Attitude and degree of cooperativeness with an interviewer yield data about a patient's capacity to establish rapport and relate to others, thereby suggesting the person's general level of interpersonal functioning.

### Motor Behavior

The astute examiner can also observe motor behaviors that provide clues to a patient's internal state. First, the overall level of activity should be noted. Behavioral activity is often quantitatively increased in patients with mania or anxiety disorders, whereas it may be decreased in those with depression or intoxication. In addition, impulsivity can sometimes be revealed by motor behaviors, as when a person pounds on a wall or hurls an object. Motor behavior can also provide clues to personality; the dramatic patient often gesticulates freely during conversation, whereas the obsessive patient often conveys a sense of constricted facial movements and gestures. The types of behaviors associated with overactivity may include restlessness, pacing, hand-wringing, or other forms of agitation. In contrast, psychomotor retardation is a slowing of the usual body movements. A depressed patient with psychomotor slowing may be observed sitting perfectly still, staring into space. Similarly, patients with underlying neurological disorders such as Parkinson's disease or those who are taking medicines that produce parkinsonism may exhibit motor slowing in the form of lack of facial expressiveness and loss of the body movements and gestures that often accompany speech.

Other types of motor behaviors may be unusual or qualitatively different from those observed in normal people. Tics are sudden, rapid, involuntary stereotyped movements, or vocalizations. Examples of simple tics include facial grimaces, blinking, and neck jerking or shrugging as well as throat clearing, coughing, barking, or snorting vocal sounds. More complex motor tics include jumping, touching, or grooming behaviors as well as vocalizations consisting of complex phrases, socially unacceptable obscene words (coprolalia), or repeating of one's own words or the words of others (palilalia and echolalia, respectively). These tics are exacerbated by stress and anxiety and can be voluntarily suppressed for a time, although they are ultimately experienced as irresistible. They are generally believed to disappear during sleep.

Another clinically relevant way of approaching the task of assessing a patient's behavior was suggested by Halleck (1994). He suggested that in addition to focusing on appearance, attitude, and cooperation in the clinical evaluation, the interviewer can assess (1) the patient's physical and emotional attractiveness; (2) his or her means of seeking control and whether control is a central issue; and (3) the degree to which the patient is dependent, passive, aggressive, attention seeking, private, or exploitative in his or her behaviors. Although patients with different styles have different motives for and various ways of expressing these types of behaviors, examining their behavior in each of these categories is likely to provide a productive additional approach to evaluating behavior and adaptive functioning.

## Problematic Patterns of Behavior

Problematic patterns of behavior, such as impulsivity, compulsivity, and avoidance, cut across diagnostic groups; looking for these patterns can be a fruitful way of characterizing the aspects of maladaptive functioning. Each of these three patterns can arise from a wide array of psychiatric problems. For example, intoxicated people are often disinhibited and impulsive, acting in ways that they would not act if they were sober. However, a manic patient may also be impulsive, often spending money freely or engaging in sexual activity without considering the consequences of these actions. Labeling each of these patterns of behavior impulsive is an important first step in reaching a diagnosis. In addition, finding one type of impulsive behavior should prompt the psychiatrist to look for others and to predict that the patient may act impulsively in the future.

### Impulsive Behaviors

Impulsive behaviors are actions that arise without much delay between the formation of an idea or desire and its gratification in action. Not all impulsive behavior is pathological; in a muted and well-modulated form, impulsivity is closer to spontaneity, as Mr. E's necklace purchase suggests. Certain personality styles, such as dramatic characters, are

Clinical Vignette 5

Mr. E, 34 years old, has a flair for choosing the right gifts for others. While shopping, he sees an expensive necklace that is perfect for his girlfriend and buys it. The time elapsed between seeing the necklace and finding himself at the register, credit card in hand, is less than 3 minutes. Although a little nervous about making such a big purchase, he decides he will pay off the necklace in several installments and give it to his girlfriend for Christmas.

Clinical Vignette 6

Ms. F, 23 years old, is undergoing evaluation in the emergency department after a suicide attempt by acetaminophen overdose. She reports that the attempt followed a fight with her boyfriend, after which she locked herself in the bathroom and swallowed several handfuls of pills before he broke the lock on the door and called for help. In the emergency department, Ms. F is tearful and angry that her boyfriend wants to break up with her. He has been restricted from visiting her in the emergency department because she attempted to strike his head and chest with her fists when he was initially allowed to see her. Her psychiatric history is notable for two past suicide attempts by pill ingestion, frequent episodes of binging on food and then purging, repeated episodes of burning herself with a cigarette and scratching her wrists with a steak knife, and problem weekend bouts of drinking accompanied by blackouts.

more likely to be spontaneous or impulsive than others. Mr. E's capacity to decide rapidly results in the perfect gift for his girlfriend. In contrast, a person with a conscientious style might decide to think about the purchase for a few days, then return to buy the necklace only to find it gone.

However, in its more extreme forms, impulsivity is often pathological, as the case of Ms. F shows. A number of behaviors that seem dissimilar may have impulsivity as the common and uniting thread. In DSM-IV-TR terms, Ms. F's history suggests a panoply of disorders including major depressive disorder, bulimia nervosa, impulse control disorder not otherwise specified (cigarette burns), alcohol dependence, and a borderline personality disorder (stormy interpersonal relationships and self-injurious behaviors, such as substance abuse, suicide attempts, and self-mutilation). However, all of her problem behaviors may be more parsimoniously described as impulse-ridden than by reference to each DSM-IV-TR diagnosis.

Another advantage of thinking about impulsivity as a distinct pattern of problem behavior is that impulsivity in one sphere is often accompanied by impulsive behaviors in other arenas. Thus, on learning that Ms. F has overdosed on pills, the emergency department psychiatrist should already be wondering about self-mutilation, eating disorders, and substance abuse. Thinking about impulsivity more generally across an array of impulsive behavioral types has already proved useful in eating disorder research. In a study of the relationship between impulsivity and eating disorders, Fahy and Eisler (1993) reported that 51% of 67 bulimic subjects interviewed had at least one other form of impulsive behavior. These subjects also reported more severe eating disturbances and were less quick to respond to treatment with medication than were bulimic subjects without other comorbid forms of impulsivity. Fernández-Arandaa et al. (2006) demonstrated lifetime prevalence rates of 23.8% for other impulse control disorders among women with bulimia nervosa including compulsive buying in 17% and intermittent explosive disorder in 13%. Corstorphine et al. (2007) suggested that any reported childhood trauma, and especially sexual abuse, was associated with a higher number of impulsive behaviors and with the presence of multi-impulsivity in eating disordered patients and was associated with self-cutting and substance abuse. Whiteside and Lynam (2003) suggested that four personality dimensions were differentially related to impulsive behavior including urgency, sensation seeking, (lack of) premeditation, and (lack of) perseverance. Using this model, Claes et al. (2005) demonstrated that patients with bulimia showed consistently more urgency and sensation seeking and less premeditation and perseverance than restrictive anorexia nervosa patients, with the binging–purging anorectic subtype being situationed between these two groups.

Behaviors that are frequently impulsive in nature include self-mutilation and suicide, substance abuse, pathological gambling, binging and purging eating behaviors, and hair pulling. In addition, urges to steal (kleptomania), to set fires (pyromania), or to engage in sexually perverse or unusual behaviors (paraphilias) also result in impulsive behaviors (Table 38–6).

**Table 38–6** Impulsive, Compulsive, and Avoidant Patterns of Behavior

| Pattern | Examples |
|---|---|
| Impulsive | Self-mutilation<br>Suicide<br>Substance abuse<br>Pathological gambling<br>Binging and purging<br>Hair pulling<br>Kleptomania<br>Pyromania<br>Paraphilias |
| Compulsive | Hand washing, checking<br>Sexual compulsions<br>Food restriction |
| Avoidant | Agoraphobia<br>Simple phobias (e.g., acrophobia)<br>Social phobia |

Different types of impulsive behaviors are often experienced in similar ways by patients. One hallmark of impulsive acts is that they are often preceded by a growing internal sense of tension and discomfort that is reduced by the impulsive act itself. Whether the act is hair pulling (trichotillomania) that results in baldness or pathological gambling that has severe financial consequences, the person is likely to feel that she or he can no longer tolerate the internal tension and that giving in to the impulse will provide relief to an uncomfortable internal state.

Clinical Vignette 7

Ms. G, a 21-year-old woman with borderline personality disorder, carved the word "monster" on her arm. Of this act she said, "I was feeling so tense and angry, like there was a tornado inside of me. As I focused on the small red lines I made with the razor, I began to feel better. The physical pain let me center my attention on my body, and my angry feelings seemed to fade away."

A second characteristic of impulsive acts is that they are often frankly pleasurable at the moment of action even if the person is extremely remorseful afterward.

Clinical Vignett 8

Mr. H, a 23-year-old college senior, sought help for his paraphilia, namely, exhibitionism. He would resist the urge to exhibit his genitals to a woman for weeks but would eventually feel that the desire was irresistible. As he noted the look of shock or surprise on the woman's face when he exhibited his penis, he would often ejaculate. However, after this, he would feel ashamed, remorseful, afraid that the woman would recognize him on the street, and convinced that she would notify the police and he would be arrested.

A third hallmark of impulsive behaviors is that patients are often relatively impervious to the consequences of their actions at the time and tend to underestimate their chances of being caught.

Clinical Vignette 9

Ms. I, a 50-year-old financially comfortable housewife, came for treatment after being arrested for shoplifting (kleptomania). She was puzzled by her urges, stating, "I feel compelled to steal things even though I don't need them and could easily buy them. Half the time I throw them away afterward." Although she felt that she could resist these urges if a security guard was in plain view, she recognized that the threat of being arrested did not deter her at the moment of the theft.

Patients with impulsive patterns of behavior also tend to underestimate the chances of being caught by a spouse or friend.

Clinical Vignette 10

Mr. J, a 43-year-old married executive, engaged in cross-dressing (transvestic fetishism). He frequently masturbated to orgasm while wearing his wife's lingerie, paying little attention to whether his wife would suspect him when she discovered the soiled undergarments.

In addition, the impulsive nature of the action itself may increase the odds of apprehension and punishment.

Clinical Vignette 11

Mr. K, a 35-year-old construction worker, experienced irresistible urges to set fires (pyromania). He often did so in a hasty and unpremeditated fashion at construction sites where he worked. Because his actions were poorly planned and executed, he was at risk of being seen setting the fires. Firefighters rapidly concluded that the fires were the result of arson. In addition, Mr. K tended to feel compelled to stay and watch the consequences of his actions, enjoying the sight of the fire itself as well as the various equipment used to extinguish it. This meant he was remaining at the scene of his crime for an extended time.

Another feature common to impulsive behaviors is that they often involve a binge, an episode of engaging in a behavior that seems out of control and cannot be terminated by the patient. Often, the binge ends only when an external constraint forces the patient to abandon the action. An eating binge and the relapse of an alcoholic person are often similarly described: "Once I started eating (drinking) I couldn't stop. I just kept on stuffing myself (ordering drinks) until I was too exhausted and sick (drunk and broke) to continue."

It is noteworthy that impulsively binging on a substance such as alcohol sets the stage for further impulsive behaviors secondary to intoxication.

Apart from the clinical utility of thinking of various impulsive behaviors in similar terms, there is also evidence of an underlying biological defect that commonly gives rise to a variety of impulsive behaviors. Linnoila et al. (1993) reviewed a number of studies in support of the idea that low cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid, the main by-product of serotonin metabolism, was related to impaired impulse control as well as increased aggressiveness. They cited several types of studies that supported this relationship, including studies demonstrating that (1) patients with unipolar depression who made violent suicide attempts often had low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, (2) there is a strong negative correlation between lifetime aggressive behaviors and cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, and (3) young abstinent alcoholic men had lower cerebrospinal fluid levels of 5-hydroxyindoleacetic acid than control subjects did. More recently, links between the personality trait of impulsiveness, the behavior of deliberate self-harm, and specific serotonin receptor genotypes have been established (Evans et al. 2000). In addition, evidence that a deletion/insertion polymorphism within the 5-HT transporter promoter gene has been implicated in several psychopathological phenotypes related to disturbed impulse control. Retz et al. (2004) found a significant excess of the short (s) allele and the s/s genotype in patients characterized by recurrent and overt violent behavior in a group of 153 males referred for forensic psychiatric examination.

## Compulsive Behaviors

In its muted form, compulsivity can be seen as carefulness or attention to detail. It is easy to see how such attention to detail is helpful in a variety of settings in daily life. Many jobs, such as Ms. L's, depend on thoroughness and a willingness to keep working until the books are balanced to the last penny. However, compulsive behaviors become a problem when they begin to consume much more time than necessary and when they are a response to nonsensical thoughts (obsessions), as in Mr. M's case.

At first glance, compulsive patterns seem to be the opposite of impulsive patterns of behavior. In compulsive

Clinical Vignette 12

Ms. L is a 45-year-old accountant who audits the records of banks for the Federal Reserve. A married mother of two, she is frequently upset when she is unable to leave work on time to be with her family. However, her job demands attention to detail both in reviewing the records and in presenting her reports to her boss. She is frequently able to pick up banking record errors that others have not noticed. Of course, such careful attention to detail is time-consuming and often causes her to work overtime.

Clinical Vignette 13

Mr. M is a 48-year-old executive who suffers from obsessive–compulsive disorder. Despite treatment with a variety of medications including fluoxetine and clomipramine, he has been unable to rid himself of the idea that he has accidentally hit someone while driving to work. Any bump in the road that he notices sets off this obsessive worry, and he feels compelled to circle back to the scene to double-check that he is not guilty of a hit-and-run accident. Sometimes he is not reassured by this initial check and continues to circle the area until "something clicks" and he feels certain that he has not hit anyone. This behavior makes Mr. M as much as 2 hours late for work.

behaviors, a person repetitively behaves in a stereotyped way. Yet repeated impulsive behaviors can become difficult to distinguish from compulsive ones. Is a young female patient who repeatedly gives in to the urge to pull her hair out impulsive or compulsive or both?

In fact, there is evidence that impulsive and compulsive behaviors tend to co-occur in the same individual. In one study, impulsive aggression was found to be common in patients with obsessive–compulsive disorder (Stein and Hollander 1993). The authors theorized that obsessive–compulsive disorder and impulsivity may both arise from a similar problem in the self-regulation of behavior due to a neuroanatomical lesion in the serotoninergic system. They found that treating the obsessive–compulsive disorder with serotonin reuptake inhibitors also decreased these patients' impulsive aggression, which led Hollander and Rosen (2000)to conceptualize impulse control disorders as a subset of the obsessive–compulsive spectrum with underlying commonalities in serotonergic dysfunction giving rise to both impulsive and compulsive behaviors. In this model, disorders of impulsivity and compulsivity have in common the inability to delay or inhibit repetitive behaviors (Hollander et al. 2005). Empirical evidence supporting the concept of an obsessive–compulsive spectrum in which impulsivity is a subset exists, such as Skitch and Hodgkins' (2004) study of 262 pathological gamblers who demonstrated significantly elevated scores on measures of both impulsivity and compulsivity.

The compulsions of obsessive–compulsive disorder, food-restricting behaviors such as those found in anorexia nervosa, and compulsive sexual behavior are common types of compulsivity (see Table 38–6). Like impulsive behaviors, compulsions share common features and are experienced in similar ways by patients. However, the driving force behind compulsive behaviors is not the gratification of impulses, but rather the prevention or reduction of anxiety and distress.

Clinical Vignette 14

Ms. N is a 34-year-old woman with obsessive–compulsive disorder who has recurrent, intrusive thoughts about having been contaminated with germs by objects she has touched. These thoughts are pervasive and extremely anxiety producing. She attempts to neutralize them by compulsively cleaning her house and washing her hands. When treated by use of a technique called flooding in which she was not permitted to wash her hands despite her obsessional thought, she became overwhelmingly anxious and panicky.

The concept that compulsive behavior is an attempt to reduce anxiety is easy to understand when the behavior is a response to an obsessive thought. However, even when the compulsive behavior is sexual in nature, it is driven by the need for anxiety reduction rather than by sexual desire (Coleman 1992).

Clinical Vignette 15

Mr. O is a 38-year-old man who is distressed by the compulsion to masturbate that he feels nearly every morning on awakening with an erection. He describes the activity in detached terms, stating, "I think it's a waste of time. I don't enjoy it. I'm often making a mental list of things I have to do at work or even watching morning television programs while I'm masturbating. But I feel nervous for the rest of the day if I don't do it."

## Avoidant Behaviors

As with impulsivity and compulsivity, avoidance in its modulated form can be positive; learning from past negative experiences and avoiding prior mistakes are important capacities. Mr. P's avoidance of automated teller machines at night seems a sensible and self-protective decision. In contrast, Ms. Q's fears about social interactions with others at work are a problem; avoiding social situations also means avoiding a chance for promotion.

Clinical Vignette 16

Mr. P is a 55-year-old man who was robbed at gunpoint 1 year ago after visiting an automated teller machine to withdraw money. Since the robbery, he has felt somewhat afraid when using the automated teller machine in the daytime, although this fear has diminished over time. He has avoided needing to use the automated teller machine at night by carefully planning his finances since the robbery.

Clinical Vignette 17

Ms. Q is a 40-year-old woman who works in a university library. She has gradually become more accustomed to dealing with patrons at the reference desk but continues to prefer the solitary task of looking for books that are misshelved. Despite her boss's encouragement, she has decided not to apply for a higher level job that would involve teaching groups of new employees about the library computer system. She realizes that she is passing up a good career opportunity, but she also recognizes that the public speaking and writing on the board that this new position would entail are terrifying to her. She worries that she will stammer and blush and make a fool of herself in front of the group. Even now, she feels uncomfortable on her lunch break because she is reluctant to join other employees in the cafeteria.

One prevalent condition that gives rise to avoidant behavior is agoraphobia (see Table 38–6). The agora was a crowded open-air market in ancient Athens. The word agoraphobia

literally means "fear of the agora" (Stedman's Medical Dictionary 1982). Modern situations equivalent to the agora include those in which a person is outside of the home alone, in a crowd, standing in line, on a bridge or in a tunnel, or in a bus, train, or car. In each of these situations, help may not be readily available in case of an emergency. Thus, agoraphobia is a condition in which a person has anxiety about being in places or situations from which escape is likely to be embarrassing or difficult. For many people with agoraphobia, the situation they dread is having a panic attack in public. Often what began as a spontaneous attack becomes linked to the situation in which the attack occurred so that the person becomes afraid of that particular place or activity.

Clinical Vignette 18

Mr. R is a 26-year-old man who had his first panic attack while attending church. Because he was sitting in the middle of a pew, he was forced to climb over several people to flee during the attack. He felt this was both scary and embarrassing. Since this initial attack, he has avoided sitting anywhere other than in the back row at the end of the pew while attending services. He feels relatively comfortable sitting in this location because he can escape quickly if another attack occurs. He is not bothered by sitting in the middle of a row at the movies or in a theater.

Avoidant behaviors usually arise from a patient's history of being fearful or concerned that he or she will become fearful in a given situation. Because of the past history or the perceived threat, the anxiety-provoking situation is avoided. Avoiding the situation means avoiding the fear and anxiety the situation threatens to produce. For example, Marshall et al. (1992) studied 50 adults in a variety of settings that had the potential to induce phobic avoidance of heights. They found that catastrophic thinking (i.e., imagining various ways of falling) was especially common among those who were afraid of heights and that it was closely correlated with avoidance of height situations. Children with school phobias often avoid school by feigning illness. They are likely to become terrified when school attendance is enforced by their parents, clinging to the parent and crying to avoid being left at school alone.

In a prospective study of over 2000 adolescents, sensitivity to anxiety as assessed by the Anxiety Sensitivity Index among other measures predicted behavioral avoidance, supporting the idea that anxiety sensitivity is a precursor to avoidance behavior. In this study, anxiety sensitivity predicted avoidant behavior regardless of whether or not acute panic had been experienced, suggesting that those who fear autonomic arousal even in the absence of the experience of actual autonomic arousal are more likely to avoid situations that threaten to generate that sensation (Wilson and Hayward 2006).

Another feature common to avoidant behaviors is that they become self-reinforcing and tend to worsen in severity over time if left untreated. This is due to the fact that what Gorman et al. have termed "the fear network" is an evolutionarily conserved brain circuit comprising amygdala, hippocampus, and prefrontal cortex whose job is self-preservation. Given this central role in survival, the fear network tends to react robustly in those with a predisposition to anxiety disorders and to be difficult to quell once stimulated.

A further common feature of avoidant behaviors is their tendency to heighten anticipatory anxiety and precipitate the very reactions that a person is afraid of.

Clinical Vignette 19

Mr. S is a 38-year-old man who began having panic attacks in his early twenties. After one unexpected attack while he was on the subway, he began to ride the bus instead. Before long, he had another panic attack on the bus, and began walking to work. Walking took about 1 hour, but he persisted until he had a panic attack in the street. After this attack, Mr. S avoided leaving his house unless accompanied by another person, often his brother who lives nearby. His agoraphobia forced him to quit work and apply for disability compensation.

Clinical Vignette 20

Ms. T, a 24-year-old student, recognized that she was mildly afraid of heights. However, she wished to climb the Mayan temple at Chichén Itzáa during her vacation in Mexico. As she started the steep climb to the top, she began to feel anxious and to anticipate arriving at the top and being unable to descend from the monument. Pausing to try to calm down, she turned to look at the ground and began to feel overwhelmingly anxious and afraid of falling. She decided to descend at once but found that her legs felt shaky and weak, making the climb especially frightening. On making it down from the stairs, she vowed never to climb such a monument again.

## Conclusion

In evaluating the adaptiveness of a person's behavior, an understanding of the strengths and weaknesses of various character styles and the constraints and demands of the external environment is essential. Behavior is the final common pathway for the expression of genetics, temperament, personality traits, and psychiatric symptoms. Behavior is an observable entity in a field where many important aspects of a patient's internal life must be inferred by the psychiatrist. Although some behaviors are clearly more adaptive than others, emphasizing the strengths of a person's capacities is important. Even pathological behaviors often represent a person's best attempt at adaptation; a paranoid patient who installs extra locks on the door may be doing the best she or he can in the face of illness to survive, to cope, and to adapt to the environment the patient perceives around her or him.

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CHAPTER

# 39 Culture and Psychiatric Diagnosis

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## Introduction

In the 1990s, many authors began proposing a multilevel analysis for understanding psychopathological phenomena. This fact might indicate a paradigm change for the explanation of human behavior, both normal and pathological. Examining the integration and interaction of biopsychosocial variables in order to explain psychopathological behavior requires simultaneous attention to biological processes, psychological experiences, and the sociocultural context of those persons who suffer from them. However, many authors claim that the tendency to look for biological and psychological explanations for psychiatric disorders has led researchers to underemphasize the importance of sociocultural factors in psychopathological manifestations (Agbayani-Siewert et al. 1999, Aneshensel and Phelan 1999, Fabrega 1993).

From the outset, psychopathological research has usually assumed that mental disorders exist as "objective" states and can be evaluated with universal and standardized criteria, forgetting, in part, the impact of social, economic, cultural, and political factors in the explanation of psychopathological disorders. This oversight is all the more critical when comparing culturally distinct groups. However, in the last 30 years, this oversight has been mitigated by significant contributions in cross-cultural research whose objective has been to understand the cultural component of psychopathology.

This research, which has increased dramatically since the 1970s and 1980s, was consolidated via the creation of a group working on cross-cultural studies for the preparation of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 1994, Mezzich et al. 1993). The Manual contains three kinds of information relating to cultural factors: (a) in the clinical presentation of disorders, a discussion of cultural variants of each disorder, called symptoms dependent on culture and gender; (b) guidelines for a "cultural formulation" of the clinical presentation to help clinicians perform a culturally sensitive diagnosis; and (c) a description of "culture-bound" syndromes, including the name of the disorder, the cultures in which it has been diagnosed, and a brief description of the psychopathology associated with each clinical presentation (the last two sections are included in Appendix I of the DSM-IV-TR). The *International Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) has also been revised and updated to account for cultural factors, as evidenced by the emergence of new diagnostic systems such as the *Chinese Classification of Mental Disorders* and the *Latin American Guide for Psychiatric Diagnosis* (Berganza et al. 2001, Mezzich et al. 2001, Mezzich and Salloum 2007). While both of these culturally sensitive diagnostic manuals recognize the value of local cultural requirements to enhance the validity of psychiatric diagnosis, they also illustrate the complementary need to integrate such systems of diagnosis into a global and reliable diagnostic language (Lee 1993, Berganza et al. 2001).

In spite of the advantages suggested by the publication of DSM-IV-TR and other diagnostic systems for the consideration of cultural factors, critical voices continue to call into question how the DSM-IV-TR treats the subject of culture. For example, Brown et al. (1999) claim that researchers have not paid sufficient attention to the ways race, ethnicity, and culture relate to one another and to psychopathology. Despite the apparent conflict between recognizing national and cultural traditions in psychiatric diagnosis and practice on the one hand and, on the other, the drive to find a common diagnostic language that can be applied universally across cultural boundaries, the importance of integrating these two perspectives continues to be discussed (Fabrega 2001).

The existence of a rich modern tradition of cross-cultural research and debate led directly to the increased

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attention to cultural factors in DSM-IV and DSM-IV-TR. In turn, the publication of the manual stimulated continued research on the influence of cultural factors on the etiology, symptomatology, course, and treatment outcome of psychopathological disorders. In this chapter, we will focus on cultural considerations pertinent to the use of diagnostic criteria in ethnically and culturally diverse populations. We will also comment briefly on related culture-bound syndromes.

## Specific Cultural Considerations

### Cognitive Disorders

Less attention has been paid to cultural variants of the cognitive disorders than to other psychopathological forms, probably because of the widespread assumption that this group of disorders is influenced exclusively by biological factors. Nevertheless, these disorders show several kinds of social, cultural, and ethnic influences. Given the etiologically based subtyping of the cognitive disorders, these influences are exerted, first, by effects on the nature and rates of the diseases that are the causative agents of these disorders (Lin and Fabrega 1997).

Socioeconomic factors influence the prevalence rates of diseases affecting the brain. Low industrialization of a country or the poverty of a particular social group tends to increase the rates of infectious diseases, nutritional disorders, toxic exposures (e.g., lead), head injuries, endocrinological abnormalities, and seizure disorders among others (Cruickshank and Beevers 1989). This, in turn, may result in differences in the rates of the subtypes of dementia, of delirium, and of other specific cognitive syndromes (Spector 1979, Westermeyer and Canino 1997).

Cultural factors, such as prohibitions against substance use and variations in sexual mores, also affect the rates of alcohol- and drug-related syndromes as well as of acquired immunodeficiency syndrome (AIDS)-related organic mental disorders (Agarwal and Goedde 1990, Kaslow and Francis 1989). Ethnic determinants are also important. Hypertension and strokes have been suggested to be more prevalent among the African-Americans and some Asian groups; this may result in different rates of multi-infarct dementia (de la Monte et al. 1989). In addition, research on Alzheimer's dementia is currently evaluating reports of lower rates among the Chinese and the Chinese-Americans as well as the African-Americans (de la Monte et al. 1989, Zhang et al. 1990). The detection and assessment of the cognitive disorders are also influenced by social and cultural factors. Social groups that tolerate and even expect substantial decreases in decision-making and self-care among older persons may not be regarded as pathological milder degrees of disorientation among the elderly (Ikels 1991). Educational-level and cultural differences appear to exert separate but intermingled effects on the inappropriately high identification of cognitive impairment with the Mini-Mental State Examination (MMSE) among several ethnic groups, including the Hispanic, Taiwanese, Chinese, Southeast Asian (Williams 1987), and Afro-Caribbean populations (Richards et al. 2000). Based on a review of the literature and consultations with members of the aboriginal community, Cattarinich et al. (2001) note that differing degrees of acculturation within and between aboriginal groups create problems for cognitive evaluations. On the basis of these and other findings, some researchers have begun to question the adequacy of the MMSE and other cognitive assessment instruments, and as a consequence some practitioners have begun modifying their methods.

### Substance Use Disorders

Sociocultural factors exert considerable influence over some aspects of substance use disorders and not others. The prevalence rates of alcohol and drug abuse and dependence vary significantly across different cultures. Lifetime rates for alcoholism, for example, range from 23% among the American Indians to 0.45% among the population of Shanghai (Helzer and Canino 1992). Specific local factors that affect degree of risk for substance-related disorders include patterns of use, attitudes toward substance consumption, accessibility of the drug, physiological reactions to the same drug, and family norms and patterns (Westermeyer and Canino 1997) (Table 39–1). Recent studies of teenagers find that different ethnic groups in the US experience different rates of substance abuse (Turner and Gill 2002). Of even greater concern is the epidemiological finding that rates of alcohol and other substance abuse are higher among the US-born Mexican-Americans than among Mexico-born migrants, and increase with length of stay in the US, indicating either a pathogenic impact of the US residence, a loss of protective social factors with migration, or both. These findings suggest that interventions should be tailored to the needs of different minority and immigrant populations, particularly as substance abuse has been related to other psychological disorders (Vega et al. 1998, Lee 2001, Griffin et al. 2000). In part, these differences may be influenced by the way the local culture influences the definition of pathological substance use through differences in the perception of the impairment caused by high consumption and frequent intoxication (Osterberg 1986). Particular cultural views toward drinking in children, the value of moderation, the tolerance for intoxication, and the association of drinking with family activities and special social occasions appear to influence the degree of risk for alcoholism (Valliant 1986). The availability of a substance also increases its rates of abuse and dependence (Helzer and Canino 1992). Sociocultural factors such as religious proscriptions may exert their influence in this fashion. Heath (2001) has remarked on the long tradition of drug inhalation, from tobacco to hallucinogens, in tropical South America, which contradicts the perception in North America of drug inhalation as a novel, and therefore aberrant, trend (Kirmayer and Groleau 2001).

**Table 39–1 Sociocultural Factors Related to Substance Use Disorders**

| |
|---|
| Attitudes toward substance consumption |
| Accessibility of drugs |
| Local patterns of drug use |
| Ethnic-specific physiological reactions to various drugs |
| Immigrant status (protective in some cases) |
| Religious proscriptions |
| Male gender |
| Urban life |
| Lower education |

Several aspects of substance use disorders appear to be less affected by cultural factors. Such aspects include the comorbidity patterns, the nature of dependence syndromes, the age at onset, and the results of laboratory tests and physical examinations (Westermeyer 1989). For example, alcoholism is associated in many societies with abuse of other substances, mania, and antisocial personality as well as with depression and anxiety (Anthony and Helzer 1991). Alcoholism and drug abuse are reliably more common among men, although the sex ratio can vary from 2:1 to 4:1 (Helzer and Canino 1992, Robins et al. 1981). Drug abuse is also more prevalent among urban populations, the less educated, and the young (Anthony and Helzer 1991). The physical symptoms as well as the temporal relationship between onset of use and dependence are substance-specific and also fairly similar across cultures (Berger and Westermeyer 1977).

## Schizophrenia and Related Psychotic Disorders

The cross-cultural presentation and course of schizophrenia are among the best-studied aspects of cultural psychiatry. Research has revealed both cross-cultural similarities and differences, both of which are important for elucidating the biological and environmental bases of the disease. A "spectrum" of schizophrenic syndromes—consisting of a combination of certain positive and negative psychotic symptoms—has been found nearly everywhere, although the specific content of hallucinations and delusions as well as the prevalence of visual and other nonauditory hallucinations varies (Krassoievitch et al. 1982, Ndetei and Vadher 1984). Significant cross-cultural variation has been found, however, in several features of the syndrome. Its distribution is not uniform, ranging from 1 in a 1,000 in the non-Western societies to more than 1% in the West; its highest prevalence is displayed in economically and technologically advanced, urbanized, and bureaucratized societies (Kleinman 1988, Warner 1985). Its phenomenology varies with cultural setting, with much higher rates of catatonia in India and of hebephrenia in Japan than in the West. Most important, the course and outcome of schizophrenia are markedly better in nonindustrialized countries, even when cultural differences in outcome assessment and in acuteness of presentation are taken into account (Sartorius et al. 1986, Lin and Kleinman 1988, Kulhara and Chakrabarti 2001). Variations in outcome are thought to be related in part to different attitudes toward persons with the disorder, a set of culturally patterned interactions studied under the rubric of expressed emotion (Jenkins and Karno 1992) (Table 39–2). Other cross-cultural variations with regard to schizophrenia include higher misdiagnosis among patients from devalued and ethnic minority groups (Good 1992/1993), differences in cultural and gender-related conceptions regarding the expression of emotion that complicate the assessment of flat affect (Karno and Jenkins 1997), and culturally syntonic experiences that may be mistaken for schizophrenic symptoms. The latter include the accepted appearance of hallucinations among the bereaved Native Americans (Hultkrantz 1979) or reports of perceptual alterations among the distressed Puerto Ricans (Guarnaccia et al. 1992).

Cross-cultural differences have also been detected in emotional processing among the German, American, and Indian subjects with schizophrenia. Face discrimination performance was most impaired in the Indian subgroup (Habel et al. 2000). Another study comparing the German natives and the Turkish immigrants with schizophrenia also found cross-cultural differences, this time in higher indices of hostile excitement and depression among the immigrant group (Haasen et al. 2001).

**Table 39–2 Sociocultural Factors Associated with Better Outcome in Persons Experiencing Schizophrenia**

| |
|---|
| Residence in nonindustrialized society |
| Social attitudes toward persons experiencing the disorder |
| Culturally patterned interactions |
| Well-knit support systems |

Clinical Vignette 1

A 28-year-old mainland Chinese man living in the US for several years was hospitalized in a psychiatric ward with delusions and hallucinations of 2 weeks duration. These began after he took up the practice of *qi-gong*, a form of meditation, as treatment for his severe intermittent backaches and chronic exhaustion. According to the patient, feelings of qi ("vital energy") were circulating in the "wrong directions" in his body, and he heard the voices of supernatural beings commenting on how he should practice *qi-gong*. He denied depressed mood, appetite or weight changes, substance abuse, or a history of psychosis. The results of extensive medical evaluation, including electroencephalography and magnetic resonance imaging, were normal. Haloperidol follow-up information was unavailable because he did not keep his appointments after discharge.

Transient psychotic symptoms in connection with qi-gong practices are not uncommon, but duration for more than a few days is unusual. The patient's picture meets criteria in the Chinese classification system for qi-gong-induced psychosis (a DSM-IV-TR culture-bound syndrome) and probably neurasthenia, because of his prodromal somatic symptoms. Brief duration of psychosis in the absence of confusion and emotional turmoil qualified the patient for a DSM-IV-TR diagnosis of psychotic disorder not otherwise specified (NOS), but if psychosis were to persist, a diagnosis of schizophreniform disorder could also be considered.

*Source:* Adapted from Mezzich et al. (1993).

## Mood Disorders

Contemporary cross-cultural research on mood disorders has focused on unipolar depression syndromes, revealing extensive cultural patterning as well as significant similarities. For example, the World Health Organization Collaborative Study on Depression found a core depressive syndrome in the five countries studied, but it also revealed substantial cross-cultural differences in symptom presentation, affect conceptualization, level of severity, and influence of acculturation, despite a methodology that tended to accentuate similarities at the expense of local differences (Marsella et al. 1985).

Culture and other social factors, such as class and gender, influence the interpretation of and exposure to stressors that predispose to depression (Brown and Harris 1978). The specific characteristics of the dysphoria of depressive illness also vary cross-culturally. For example, among the Hopi in North America, feelings of guilt, shame, and sinfulness are separate experiences displaying distinct relationships to subtypes of depression (Manson et al. 1985). Whereas reports of irritability, rage, and "nervousness" are prominent descriptors of depressive affect among the Puerto Ricans and other Latinos (Lewis-Fernández 2002). The frequent combination of depression and anxiety noted around the world, particularly in primary care settings, has fueled the DSM-IV-TR proposal for a mixed anxiety-depression disorder (Katon and Roy-Byrne 1991).

In addition, most cross-cultural studies have found a significantly higher rate of somatic complaints associated with depression (and anxiety) among the non-Western groups than in the Western settings, including the presence of unique symptoms (e.g., "heat or water in the head" and "crawling sensation of worms and ants" in the Nigerian cultures) (Marsella et al. 1985, Ebigbo 1982). Emotional complaints are often present as well but may not be considered the source of distress or impairment. The mix of emotional and somatic symptoms has also been found to vary by sex in some studies (Clark et al. 1981, Guarnaccia et al. 1989). For example, a study comparing the Puerto Ricans, Mexican-Americans, and Cuban-Americans on the Center for Epidemiologic Studies Depression Scale of depressive symptoms found that the women in all three groups tended to endorse depressive and somatic scale items together as a single factor. This happened significantly more often than was done by the men (Guarnaccia et al. 1989).

Finally, the threshold at which dysphoria becomes disorder is affected by cultural factors. The 2-week duration criterion for major depression, an important proxy for pathological intensity, may vary among some non-Western groups. Manson et al. (1985) found that the Hopi identify five distinct indigenous syndromes related to depression, only one of which shares significant parameters with Western depressive disorder. This folk syndrome, however, differed from major depression in its average duration of 1 week, not 2, although still causing comparable morbidity. On the basis of this, duration criterion for major depressive disorder when it is used with the Hopi patients should be shortened (Manson et al. 1985). Conversely, in a study of the Bambui community in Brazil, researchers were surprised to find depressive episodes averaging 1 month, higher than that observed in similar studies in many other societies (Vorcaro et al. 2001).

The substantial overlap of depression with anxiety, somatoform, and dissociative disorders implies a higher probability of under-recognition or misidentification of affective disorders in many ethnocultural groups (Kirmayer and Groleau 2001). These findings raise serious issues about the universality of the prototypical representation of depression in the North American psychiatry and the operational criteria of the depressive disorders, and tend to support the phenomenological expansion of the depression categories (Manson 1997, Kirmayer and Groleau 2001).

Clinical Vignette 2

A 69-year-old traditional Hopi man was brought by his granddaughter to a general medical clinic. She reported finding her grandfather in his current deteriorated state on arriving to visit her family during a college break 2 days before. The patient described a 6-day history of weight loss; disrupted sleep; fatigue; agitation; difficulty in being effective; loss of libido; trouble thinking clearly; and a sense of sinfulness, shame, and not being likable. The examining physician also noted psychomotor retardation but no evidence of psychosis or guilty ruminations.

The patient explained that he was suffering from *uu nung mo kiw ta*, an indigenous Hopi syndrome. This syndrome had afflicted him several times in the past and he assured the physician that it would pass shortly, never lasting more than about 6–9 days. He attributed his presentation at the clinic to his granddaughter's insistence. He did not deny his marked deterioration from normal functioning, but attributed it instead to his "heart being broken" over a shocking family revelation. He was planning to seek the help of a traditional healer when his granddaughter arrived. He received a diagnosis of depressive disorder NOS.

*Source:* Case elaborated from illness description in Manson et al. (1985).

## Anxiety Disorders

The effect of culture on anxiety is similar to that on depression, especially since cross-cultural studies have shown a marked tendency for anxiety and depression to overlap (American Psychiatric Association 1994). Cultural factors affect the precipitants, symptom presentations, pathological thresholds, and specific syndrome criteria of the anxiety disorders (Good and Kleinman 1985). For example, the cross-cultural validity of criterion A for the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) generalized anxiety disorder (GAD) has been challenged because it restricts the diagnosis of chronic pathological anxiety to a disturbance stemming from undue worry in the absence of actual stressors or excessive worry after minor stress. This leaves out the much larger group of patients in developing societies and devalued minorities in the West who experience chronic pathological anxiety as a result of recurrent stress (Lewis-Fernández and Kleinman 1995).

Cultural and ethnic elements have been invoked to explain local differences in anxiety disorder prevalence that persist after controlling for other social factors. For example, the higher rate of simple phobia, social phobia, and agoraphobia among the African-Americans, as compared to whites (Neal and Turner 1991), has been attributed to the stress resulting from racial discrimination (Brown et al. 1990). In fact, the cross-cultural epidemiological literature reveals a complex pattern of similarities and differences with regard to the anxiety disorders, and opinions differ as to the role of culture in this process (Guarnaccia and Kirmayer 1997). For example, it is presently unclear why the Mexicans born in Mexico, when compared with those born in the US, show a markedly lower rate of anxiety and other disorders. Suggested explanations include selective migrations, different thresholds for perceiving and reporting a

disorder stemming from distinct cultural interpretations of what constitutes a "hard life" and acceptable suffering, and a combination of both explanations (Shrout et al. 1992).

Multiple cross-cultural studies point to the coappearance of anxiety, depression, somatoform complaints, and dissociative symptoms among the non-Western groups. A markedly somatic idiom predominates, often in the form of culturally specific symptoms (Ebigbo 1982). These often coalesce distinctively as culture-bound syndromes characterized also by specific etiological factors, demographics, patterns of impairment, and help-seeking choices (Hughes et al. 1997). It is far from clear that this represents the comorbidity of the Western disorders rather than a different organization of pathological experience (Maser and Dinges 1992). Examples include *ataque de nervios* among the Latinos, koro in the Asian communities, and *taijin kyofusho* among the Japanese (Guarnaccia and Kirmayer in press). Each of these disorders exhibits significant differences that prevent simple one-to-one correlations with the established Western categories (Weiss 1996).

Clinical Vignette 3

A 42-year-old Puerto Rican man is referred to a regional mental health center by his own physician for treatment of chronic *nervios* (nerves). The patient describes a 4-year history of recurrent but intermittent symptoms of anxiety and depression since he hurt his back and was unable to return to agricultural work. He "awakens" with his symptoms several days a month but denies continuous symptoms for more than a few days. He feels partially handicapped by his symptoms, despite their intermittency, because he has been unable to sustain gainful work even after his back condition improved.

He describes exquisite reactivity to even minor stresses (e.g., watching crime news on television), resulting in acute nervousness, trembling, and crying. In addition, during his "bad days," he reports anxiety, sadness, difficulty falling asleep, irritability, a wish to isolate himself, chest pressure, easy fatigue, dizziness (*mareos*), "thinking too much," generalized worry that feels "out of control," low selfesteem, occasional tearfulness, and hearing his name called out when alone and sensing the presence of someone behind him. On one of these symptomatic days, he "saw" a man dressed in black who approached him and then disappeared, causing him intense fear. His irritability can lead to aggressive outbursts in which he breaks objects and insults his family, which he calls *ataques de nervios* (nervous attacks). Later he regrets his actions during one of these episodes. He denies changes in his appetite, history of substance abuse, symptoms of formal thought disorder, panic attacks, and past exposure to trauma.

Because of the intermittent nature of the symptoms, which persisted despite improvement of the acute precipitating stressor, the patient received DSM-IV-TR diagnoses of anxiety disorder NOS and depressive disorder NOS.

*Source:* Case composed by Lewis-Fernández from unpublished clinical material.

## Somatoform Disorders

In a survey of international use of DSM-III and DSM-III-R, somatoform disorders were among the more problematic diagnoses (Maser et al. 1991), probably because of their cross-cultural limitations (Kirmayer and Weiss 1997). First, many nosologies around the world do not distinguish between mood, anxiety, somatoform disorders, and dissociative disorders, because sufferers report single syndromes that run across boundaries of the diagnostic categories (Lewis-Fernández 1992). This is similar to the situation with depression, where a single description of the disorder has led to under-recognition and misidentification of depressive syndromes in many ethnocultural groups (Kirmayer and Groleau 2001). Demarcating somatoform conditions in these settings may create artificial distinctions that confound accurate diagnosis. Examples include neurasthenia in China and other Asian settings, and *nervios* in Latin America (Lin 1989, Angel and Guarnaccia 1989).

Second, the idioms of distress of many societies rely on somatic complaints for the expression of nonpathological, personal, and social predicaments. Interpretations of these communication mechanisms as a somatoform disorder may result in overpathologization (Kirmayer and Robbins 1991). In addition, the use of somatic idioms varies according to intracultural factors, such as gender and class, which in turn may determine who receives a somatoform diagnosis. For example, conversion symptoms appear to be more common in rural and less educated sector of the non-Western societies, and particularly in family or social structures that allow few opportunities for protest (Kirmayer and Weiss 1997, Nichter 1981).

Third, the symptom lists of DSM-III-R and DSM-IV-TR do not canvas the rich variety of somatic symptoms reported in other parts of the world, such as the complaints of worms and ants in the head described earlier (Ebigbo 1982). Examples of other common somatic symptoms include chronic fatigue; heat in the feet, chest, or head; painful "gas" that moves from the abdomen around the flank to the back; "brainache"; and feeling presences when alone or among others.

Fourth, in most of the world, the degree to which symptoms are medically unexplained is difficult to ascertain owing to the marked limitation of diagnostic tests and medical personnel. Moreover, the high prevalence of endemic disease in the underdeveloped countries, often with protean and inchoate manifestations, may also confound the assessment of the somatoform disorders. This may result in overdiagnosis if organic causes are not identified, or underdiagnosis if organic explanations are uncritically accepted for systemic illness (Kirmayer and Weiss 1997).

Clinical Vignette 4

A 45-year-old Igbo woman in Nigeria presents to a local general medical clinic complaining of multiple somatic symptoms occurring every day, almost all day, for 7 months. Among other symptoms, she is particularly distressed by sensations of heat in her head and "inside" her body, heaviness in her head and hammer-like headaches, dizziness, palpitations, the sense that her head is "breathing" and the feeling that there is water or worms in it, "painful" vision and decreased visual acuity, generalized weakness, pain in the "marrow of the bones" in her hands and legs, sweating, easy fatigue, itching all over her body, and minor cramping.

She complains that her body is "out of order" but that nobody seems to believe her. She denies depressed mood, significant sleep, or appetite disturbances, and prior history of somatization, and her somatic descriptions are not of delusional proportions. She rejects the physicians' attributions of her symptoms to her concurrent menopause, explaining that in her experience with other women, her symptoms go beyond average for this condition. However, she did note that she has been upset by the loss of her childbearing capacity. She explains that if the physicians do not find a physical cause, she will seek the help of a traditional healer.

The patient received a DSM-IV-TR diagnosis of undifferentiated somatofom disorder.

*Source:* Case elaborated from illness description in Ebigbo (1982).

## Dissociative Disorders

Syndromes characterized by pathological dissociation are common worldwide, but the current concepts of dissociative disorders do not appear to account for their phenomenological variety (Lewis-Fernández 1992, Gonzalez et al. 1997). For example, a study performed in an outpatient psychiatric clinic in India found that more than 90% of dissociative disorder cases did not fulfill criteria for the specified categories, ironically receiving instead a DSM-III diagnosis of atypical dissociative disorder. Distressing trance states and possession trance episodes constituted most of these cases (Saxena and Prasad 1989). These instances of misdiagnosis again call to question the usefulness of some of the standard diagnostic categories of the North American psychiatry (Kirmayer and Groleau 2001). Many indigenous illness syndromes around the world display salient features of pathological dissociation. Some of these syndromes are characterized by involuntary possession trance—dissociative alterations in identity attributed to the invasion by external spirits or agents—distinguished from dissociative identity disorder by their episodic and remitting course, the nature and number of their alternative identities, and their gradual response to treatment. These syndromes have been identified in India, western Africa, China, Malaysia, Brazil, and the Caribbean, among many other settings (Lewis-Fernández 1994, Ward 1989, Spiegel and Cardena 1991).

Other dissociative syndromes are characterized by alterations of consciousness and memory, during which the person runs around in an agitated state (Arctic *pibloktoq*); attacks others indiscriminately (Malayo-Indonesian *amok*); undergoes convulsive movements, screaming fits, and aggressive acts toward self or others (Caribbean *ataque de nervios*); or lies as if dead, suffering from specific perceptual alterations; hears and understands what is happening but cannot see or move ("falling out" among the African-Americans in southern US, Bahamian "blacking out," and Haitian *indisposition*) (Gonzalez et al. 1997, Cardena et al, 2002, Weidman 1979). In a recent study, Lewis-Fernández et al. (1997) confirmed the association between *ataque de nervios* and dissociation. Among the female Puerto Rican psychiatric outpatients, *ataque* frequency was directly related to self- and clinician-ratings of dissociative symptoms and disorders. Of note, patients with and without *ataque* did not differ on measures of childhood trauma, which was uniformly high among subjects (Lewis-Fernández et al. 1997). The proposed dissociative trance disorder category in DSM-IV-TR would provide a Western nosological niche for these disorders, although not without the risk of overpathologizing some culturally accepted instances of these behaviors (Lewis-Fernández 1992).

In fact, extensive cross-cultural research reveals that most dissociative experiences around the world are completely normal, usually forming part of religious and ritual events (Lewis-Fernández 1994). The Western emphasis on pathological experiences of dissociation that result from overwhelming trauma probably stems from the relative absence of normal dissociation among the dominant Western groups and from the acknowledgment by mental health professionals of the sequelae of physical and sexual abuse (Ross 1991, Martinez-Taboas 1991). Depersonalization, considered one of the most common psychiatric symptoms in the West (Steinberg 1991), is a greatly desired goal for Hindu yogis, revealing the substantial cultural patterning of dissociative experience (Castillo 1991).

Clinical Vignette 5

A 17-year-old recently married a Hindu woman starts to undergo episodes of pathological possession trance 2 weeks after moving to her mother-in-law's house in a different village in India. Her first episode is proceeded by a generalized convulsion, rolling on the ground, loud screaming, and a period of unconsciousness. On regaining semiconsciousness with a start, the woman speaks and behaves as the ghost of a dead cousin. Shouting loudly, she berates her in-laws and her new husband, who try to force the spirit out by pinching and other noxious stimuli. Minutes later, the woman again enters near-unconsciousness, moaning softly, signaling the temporary departure of the spirit. During a period of hours, she lapses between near-unconsciousness and full possession several times.

These recent attacks recur for 3 weeks, with mounting aggressiveness, despite the ministrations of traditional healers, who diagnose "possession syndrome." The patient improves slightly only after her father travels to see her and takes her back on an extended visit to her family of origin following up a referral to a regional healing temple.

*Source:* Adapted from Lewis-Fernández (1994).

## Sexual Disorders

Research on cross-cultural influences on sexual disorders is limited, owing to the lack of uniform descriptive methodology and to the fact that the major ethnic minorities in the US do not seek medical treatment for this class of complaints (Davis and Herdt 1997). Some cross-cultural studies have concluded that the paraphilias as currently characterized in the DSM-IV-TR are determined by specific features of the Western society, such as demographical size and complexity (whereby individuals may escape social sanction through anonymity), the nonavailability of partners, and the primacy of masturbatory activities as sexual outlets (Rooth 1973, Gebhard 1971). Despite a few small clinical studies that found similar rates of sexual dysfunctions among the

African-American populations (Fisher 1980, Finkle and Finkle 1978), most cross-cultural research suggests that sexual response is influenced by cultural and ethnic considerations. Racist stereotypes, machismo, anxiety about infertility, and the tendency toward somatization of mood disorders as impotence have been cited as etiological factors of sexual dysfunction in the African-American and Latino populations (Wyatt 1982, Espin 1984). In addition, the ethnographical literature shows that the standards for sexual competence differ across the cultural spectrum and that many societies display a more flexible approach to issues of sexual orientation than is assumed by the diagnostic categories (Davis and Whitten 1987, Herdt 1990).

This cross-cultural diversity complicates the assessment of the sexual disorders. At present, it is unclear whether certain culture-bound syndromes involving sexual organs, such as *koro* among the Asians (characterized by the fear of genital retraction) or *dhat* in India (involving obsession or anxiety about semen loss), should be categorized among the sexual or the somatoform disorders (Davis and Herdt 1997).

## Eating Disorders

Research has disclosed a significant cultural effect on the patterning and distribution of the eating disorders. An important determinant appears to be the Western premium on thinness as an esthetic and moral value (Ritenbaugh 1982, Nichter and Nichter 1991, Banks 1992). Cases of eating disorder have been found in many non-Western societies and several ethnic minorities in the US, but their presenting features often differ somewhat from the DSM-IV-TR criteria for anorexia nervosa and bulimia nervosa (Shisslak et al. 1989).

Groups at high risk include those experiencing rapid acculturation to the Western society, such as immigrants or those living in areas undergoing accelerated industrialization (Ritenbaugh et al. 1997). For example, one study found a 12% prevalence of DSM-III eating disorders among the Egyptian female college students in London and no evidence of these conditions among a similar sample in Cairo (Nasser 1986). Although it is as yet unclear exactly how acculturation predisposes the non-Caucasians to eating disorders, as a rule these conditions are more prevalent among the Caucasians than persons of other ethnic backgrounds (Wildes et al. 2001). Bulimia nervosa appears more common than anorexia nervosa among the US minorities and is often associated with higher than average weight, female sex, and sometimes, older age, for example, among the American Indian groups (Rosen et al. 1988). Anorexia nervosa has been found among lower socioeconomic class samples in several cultures but often characterized by atypical features, such as the absence of distorted body image or of the fear of gaining weight (Suematsu et al. 1985, Lee et al. 1989). Cross-cultural studies have proposed more flexible diagnostic criteria for anorexia nervosa so that abdominal fullness, epigastric pain, or distaste for food may be accepted instead of intense fear of weight gain to account for the severe restriction of food intake or other weight-losing behavior (Lee 1991).

## Adjustment Disorders

The effect of culture on the adjustment disorders is pervasive. Culturally based interpretations are essential to the appraisal of the repertoire of behavioral and emotional responses that pattern both normal and disordered reactions to stress (Jenkins and Kinzie 1997). Whereas some experiences are uniformly stressful (e.g., natural disaster), others may make sense only within particular cultural contexts (e.g., facing deadlines, witchcraft accusations) (Fabrega and Mezzich 1987). In addition, the judgment of what constitutes a maladaptive response to a stressor must be made in relation to what exceeds cultural norms (Kleinman 1988). Diagnosis of an adjustment disorder may be a particular problem among refugee populations. These groups have undergone distressing experiences, but their intensively challenged coping styles may be unknown to caregivers in the host country (Beiser 1996).

## Personality Disorders

The current configuration of the personality disorders has received substantial cross-cultural challenge. Even the basic concept of personality as a set of individual internal traits is considered inseparable from the Western cultural assumptions on individuality by many authors (Lewis-Fernández and Kleinman 1993). Difficulties in the reliable assessment of these disorders within the Western cultures may be due to the degree to which these conditions are determined by social and contextual factors. These factors include adaptational strategies toward adverse communal environments (including the relative value of aggression or avoidance), family-based customs and traditions, occupational and educational options, and cultural methods of child-rearing (Alarcon and Foulks 1997). It is striking, for example, that the antisocial personality disorder is nearly absent among the Hutterites, an ethnoreligious enclave living for more than a century in the US and Canada (Favazza 1985). Intracultural diversity may be more important in this respect than cross-cultural difference. For example, in his studies of affective and personality disturbances among the Inuit and the Yoruba, Leighton (1981) was unable to disentangle cultural influences from "the much more powerful effects" of gender, age, and class.

Epidemiological assessment of DSM-III antisocial personality disorder has been performed as part of the Epidemiological Catchment Area study using a clearly operationalized survey instrument, the Diagnostic Interview Schedule (Robins et al. 1984). This yielded similar prevalence rates in the US and Puerto Rico (Canino et al. 1987). However, low reliability rates for the diagnosis of personality disorders across standardized instruments raise serious doubts about the validity of this aspect of the Epidemiological Catchment Area study data (Perry 1992). One World Health Organization study was able to identify cases of most of the *International Classification of Diseases* personality disorders in 15 urban clinic samples in Africa, Asia, North America, and Europe (Paris 1991), but the cross-cultural validity of the definitions of these categories had been criticized earlier by Shepherd and Sartorius (1974).

## The Case of Culture-Bound Syndromes and Idioms of Distress

Investigation of so-called culture-bound syndromes was geared for decades toward incorporation of these "exotic" categories into the Western nosologies (Simons and Hughes 1985). The term "culture-bound" (Table 39–3) was used to

**Table 39–3 Culture-Bound Syndromes and Idioms of Distress Listed in DSM-IV-TR**

| |
|---|
| *amok* |
| *ataques de nervios* |
| bilis and colera |
| *boufe delirante* |
| brain fag |
| *dhat* |
| falling out or blacking out |
| ghost sickness |
| *hwa-byung* |
| koro |
| *latah* |
| *locura* |
| *mal de ojo* |
| *nervios* |
| *pibloktoq* |
| *qi-gong psychotic reaction* |
| *rootwork* |
| *sangue dormido* |
| *shenjing shuairuo* |
| *shenjing shenkui* |
| *shin-byung* |
| *spell* |
| *susto* |
| *taijin kyofusho* |
| *zar* |

describe a certain number of psychiatric disorders whose phenomenologies made them distinct from the Western categories and that theoretically could be singled out as unique to a particular cultural setting (Hughes et al. 1997). The clear implication was that the Western categories were not culture-bound but rather universal, and that proper characterization would disclose a translation key for specific non-Western syndromes. However, these conditions have been studied more critically to understand instead the culture-bound nature of the Western classification schemes themselves and to enable the appropriate treatment of patients whose understandings and presentation of illness conform to these indigenous categories (Good 1994, Good and Delvecchio Good 1982).

Contemporary cultural psychiatry recognizes that all classification schemes are inherently cultural and subjects Western nosologies to the same kind of social analysis that it continues to apply to the indigenous nosologies (Lewis-Fernández and Kleinman 1995). In this modern sense, "cultural-bound syndrome" is an inherited and controversial term that is used in practice to describe psychiatric categories, whether they are part of the Western or non-Western nosologies, on whose emergence, manifestation, or course culture is thought to exert a particularly strong influence (Hahn 1985, Guarnaccia 1993). The term continues to refer to relatively consistent illness categories with characteristic courses ("syndromes") and specific labels, some of which are discussed in this chapter (e.g., *amok, taijin kyofusho*, anorexia nervosa). The organizing principle that unifies a syndrome conceptually can be (1) a collection of symptoms, which can follow diverse classificatory schemes (descriptive); (2) a cause, including an immediate precipitating context (etiological); or (3) a response to treatment (Good and Delvecchio Good 1982).

"Idiom of distress" is a newer term, which was coined to refer to a more general level of analysis (Nichter 1981). Rather than denoting specific syndromes, the term refers to the more general illness "languages" of social groups, the culturally preferred ways of expressing distress, such as by somatic complaints, psychologizing explanations, possession or witchcraft terminology, oppositional or violent behavior illnesses due to "nerves," or attributions of inexplicable misfortune. In this sense, a given idiom of distress, such as somatization, can be expressed as multiple culture-bound syndromes such as *ataques de nervios*, neurasthenia, "brain fag," and so on. DSM-IV-TR presented a substantial list of culture-bound syndromes and idioms of distress in one of its appendices.

Contemporary use of this terminology allows us to understand certain difficulties in the integration of the Western and non-Western categories of psychiatric illness (Lewis-Fernández 1992, Wig 1983). First, the Western nosologies are based at present nearly exclusive on descriptive parameters. Wary of "theoretical" causes, our current diagnostic system privileges a formal definition of psycho-pathological processes. Most indigenous nosologies, on the other hand, distinguish illness from normality at least as much on the basis of contextual characteristics as on descriptive ones. These include assessments regarding appropriateness of the symptom in the particular setting at the specific time in question, the relative sufficiency of precipitating stressors, and the nature and quality of the human relationships of the sufferer. These discrepancies between the organizing principles of the Western and non-Western nosologies prevent an easy consolidation of psychopathological criteria across cultures.

Second, nosologies also differ in the configurations of their phenomenologies (Kleinman 1988, Weiss 1996, Good and Delvecchio Good 1982). The symptoms of many culture-bound syndromes, such as *amok* in Malaysia, or *ataque de nervios* in Puerto Rico, are composed of a variety of behavioral and experiential elements that are considered by the Western nosologists to belong to separate diagnostic categories. The characteristic presentations of these conditions exhibit diverse combinations of dissociative, psychotic, anxiety, depressive, characterological, and somatic symptoms (Lewis-Fernández 1992). Significant phenomenological variation occurs among individual cases, which are nevertheless unifying under a single nosological label.

These differences in definitions of illness and phenomenological organization between the Western and non-Western categories ensure that the two nosologies are overlapping as global systems. From the psychiatric perspective, a cohort of individuals identified by a cohort indigenous label will prove to be diagnostically heterogeneous or even nonpathological. The obverse is that almost homogeneous psychiatric cohorts will appear locally verse. A nomographical, one-to-one relationship between the Western and non-Western nosologies appears, thus unattainable (Weiss 1996). What is achievable is the systematic characterization of individual cases of persons suffering from culture-bound syndromes in terms of the Western categories of psychiatric illness, retaining at the same time an account of their distinct definitions

of illness, idioms of distress, unique symptoms, and other associated factors in the form of a cultural formulation (Mezzich and Good 1997) (Table 39–4). This iterative process of translation will result eventually in a comprehensive cultural psychiatry that integrates diverse local and professional classifications of psychiatric illness with the goal of more effective communication and care of patients.

**Table 39–4 Components of the DSM-IV-TR Outline for a Cultural Formulation**

| |
|---|
| Cultural identity of the individual |
| Cultural explanations of the individual's illness |
| Cultural factors related to psychosocial environment and levels of functioning |
| Cultural elements of the relationship between the individual and the clinician |
| Overall cultural assessment for diagnosis and care |

In spite of the importance of including culture-bound syndromes in the DSM-IV-TR, Guarnaccia and Rogler (1999) warn that important methodological issues remain unaddressed, since DSM-IV-TR does not include a system of norms to delimit the range of psychiatric disorders that relate to particular culture-bound syndromes, nor include these cultural conditions within the established disorder categories.

## Conclusion

The importance of culture in the understanding of psychopathology is revealed by the literature summarized in this chapter. However, future studies must evolve to include psychological and psychiatric measures that are relevant and appropriate for distinct cultural groups, since many cross-cultural studies utilize the Western concepts to explain the modes of expression of psychopathological manifestations (Kirmayer and Groleau 2001), ways of seeking aid, use of mental health services, or treatment outcome, without taking into account their close relationship with cultural factors (Aneshensel and Phelan 1999). At the same time, new possibilities are emerging for the application of cultural information to diagnostic systems and the diagnostic process. This chapter has focused on some of the most conspicuous contributions aimed at enhancing the cultural suitability of DSM-IV-TR, and thus on the use of diagnostic categories and criteria in multicultural settings. Other contributions, such as the glossary of culture-bound syndromes and idioms of distress and the guidelines for a cultural formulation, have been referred to succinctly. Cultural developments are also being worked into the family of classifications of the ICD-10 (Mezzich 1995). All these efforts promise to increase the applicability and usefulness of the new diagnostic systems for our multicultural world. Further, they may encourage psychiatrists and the field as a whole to stay focused on the person of the patient and his or her context to augment the validity of diagnosis and the effectiveness of clinical care.

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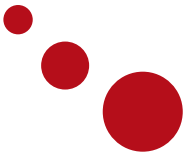
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SECTION VI

Michael B. First, Section Editor

# *Disorders*

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CHAPTER

# 40 Psychiatric Classification

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## Introduction

There is a natural human predilection to categorize and classify for simplifying and organizing the wide range of observable phenomena and experiences that one is confronted with, thus facilitating both their understanding and their predictability. Many (if not most) of the mental disorders that afflict contemporary individuals have occurred in antiquity. For example, the first recorded depiction of mental illness dates to 3000 BC Egypt with a description of the syndrome senile dementia attributed to Prince Ptah-hotep (Mack et al. 1994) The current system for the diagnosis of mental disorders, the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) (American Psychiatric Association 1994) is just the latest example from the long and colorful history of psychiatric classification. Although there was a more recent Text Revision, DSM-IV-TR (American Psychiatric Association 2000), we will refer to DSM-IV as the "current" version since it primarily differs from DSM-IV-TR with respect to the textual descriptions of the disorders. The classification, diagnostic terms, and virtually all of the diagnostic criteria are identical (First and Pincus 2002).

## Goals of a Classification System

Perhaps the most important goal of a psychiatric classification is to allow mental health practitioners and researchers to communicate more effectively with each other by establishing a convenient shorthand for describing the mental disorders that they see (First 1992). For example, saying to a colleague that a patient has major depressive disorder can convey a great deal of information in only a few words. First of all, it indicates that depressed mood or loss of interest is a central aspect of the presenting problem and that the depression is not the kind of "normal" mood fluctuation that lasts for only a few f days but rather that it persists every day for an extended period of time, at least 2 weeks. Furthermore, one can expect to find a number of additional symptoms occurring at the same time, like suicidal ideation and changes in appetite, sleep, energy, and psychomotor activity. Finally, information is also communicated about what is not to be found in this patient—specifically, that the depression is not caused by the direct physiological effects of alcohol, other drugs, medications, or a general medical condition, that the depression does not represent simple bereavement, and that there is no history of schizophrenia or manic or hypomanic episodes.

DSM-IV also facilitates the identification and management of mental disorders in both clinical and research settings. Most of the DSM-IV diagnostic labels provide considerable and important predictive power. For example, making a diagnosis of bipolar disorder suggests the choice of treatment options (e.g., mood stabilizers), that a certain course may be likely (e.g., recurrent and episodic), and that there is an increased prevalence of this disorder in family members. By defining more or less homogeneous groups of individuals for study, DSM-IV can also further efforts to understand the etiology of mental disorders. The operationalized definitions in the manual have been a reflection of, and a major contribution to, the development of an empirical science of psychiatry. DSM-IV also plays an important role in education. In its organization of disorders into major classes, the system offers a structure for teaching phenomenology and differential diagnosis. DSM-IV is also useful the psychoeducation of patients and their families by showing patients that their pattern of symptoms is not mysterious and unique but rather something that has been identified and studied in others.

## Approaches to Classification

### Etiological vs. Descriptive

Historically, there have been two fundamental approaches to formulating systems of psychiatric classification: etiological and descriptive (First 1994). Etiology-based classification systems organize categories around pathogenetic processes so that disorders corresponding to a particular category share the same underlying cause. Although such systems tend to have relatively few categories and therefore

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are easy to use, their ultimate value is constrained by the limited extent to which underlying etiological factors have been elucidated. For example, the 16th century Swiss physician Paracelsus developed a classification system in which he divided psychotic presentations into three types of disorders on the basis of the presumed etiology. The first category, vesania, for disorders caused by poisons, is analogous to current-day substance-induced disorders. Insanity, for diseases caused by heredity, is analogous to modern disorders such as schizophrenia and bipolar disorder, which appear to have a strong familial component. His category of lunacy, which described a periodical condition influenced by the phases of the moon, has no analogous condition today because we know that the phases of the moon are not a direct cause of psychopathological conditions.

Because the etiological basis for most psychiatric conditions remains unknown, etiological classification systems tend to be based instead on a particular conceptualization of or theory about the process of mental disorders. Although such classifications may be heuristically useful to proponents of the particular conceptualization that forms the basis of the system, they are often considerably less useful for proponents of different etiological principles, which greatly limits their utility. For this reason, a descriptive approach to classification has proved to be of greater utility given our current level of understanding. The descriptive approach aims to eschew particular etiological theories and instead relies on clinical descriptions of presenting symptoms. This approach, advanced by the work of the 19th century psychiatrist Emil Kraepelin (Kraepelin 1992) formed the basis for the system of classification of the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition (DSM-III) introduced in 1980. As a result, DSM-III and its successors, the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSM-III-R) and DSM-IV, have proved to be useful in a variety of different settings and by psychiatrists of widely different backgrounds and conceptual orientations.

## Syndrome vs. Symptom

Given that the manual lacks a specific etiological conceptualization, what is its organizing principle? The fundamental element is the syndrome, that is, a group or pattern of symptoms that appear together temporally in many individuals (First et al. 1992). It is assumed that these symptoms cluster together because they are associated in some clinically meaningful way, which perhaps may reflect a common etiological process, course, or treatment response. Alternatively, individual symptoms could have been emphasized as the fundamental conceptual entities so that a person's disorder would be classified by enumerating all of his or her relevant symptoms. In fact, historically, there have been classifications that have been symptom based. For example, Boisser de Sauvages proposed a medical classification that arranged presenting symptoms into numerous classes, orders, and genera, comparable to the classification of plants and animals. This approach generated 2,400 disorders, each of which was essentially a symptom.

Although it was hoped that the syndromes identified in the DSM represented relatively homogeneous subpopulations of patients, over the past two plus decades since the publication of these definitions in DSM-III in 1980, the goal of discovering common etiologies for each of the DSM-defined syndromes has remained elusive. Epidemiologic and clinical studies have shown extremely high rates of comorbidities among the disorders, undermining the hypothesis that the syndromes represent distinct etiologies. Furthermore, epidemiologic studies have shown a high degree of short-term diagnostic instability for many disorders. With regard to treatment, lack of specificity in treatment response is the rule rather than the exception. The efficacy of many psychotropic medications cuts across the DSM-defined categories. For example, the selective serotonin reuptake inhibitors have been demonstrated to be efficacious in a wide variety of disorders from many different sections of the DSM, including Major Depressive Disorder, Panic Disorder, Obsessive–Compulsive Disorder, Dysthymic Disorder, Bulimia Nervosa, Social Anxiety Disorder, Posttraumatic Stress Disorder, Generalized Anxiety Disorder, Hypochondriasis, Body Dysmorphic Disorder, and Borderline Personality Disorder. Results of twin studies have also contradicted the DSM assumption that separate syndromes have a different underlying genetic basis. For example, twin studies have shown that Generalized Anxiety Disorder and Major Depressive Disorder may share the same genetic risk factors (Kendler 1996, Kendler et al. 2007) and evidence from molecular genetics research (Berrettini 2000, Berrettini 2003) indicates that three of the putative susceptibility loci associated with DSM-defined bipolar disorder also contribute to the risk of DSM-defined schizophrenia.

Given these clear limitations in the syndromal approach, it is important that users of the DSM resist the temptation to reify the DSM diagnostic categories as if they were actual diseases. They are best viewed as clinically useful constructs that are helpful in facilitating communication and record keeping and in selecting treatment. As more information about the causes of mental disorders become evident over the next decades, it is more than likely that the syndromal approach will be replaced by a classification system that is more reflective of the underlying etiology and pathophysiology. A hypothetical example (Table 40–1) of what such a classification system might look like is described in the white paper on Basic Neuroscience and Genetics, (Charney et al. 2002) included as part of the DSM-V Research Agenda. (Kupfer et al. 2002b).

## Categorical vs. Dimensional

The diagnoses included in DSM-IV are defined categorically, that is, diagnostic criteria are provided that indicate whether an individual's clinical presentation either meets or does not meet the diagnostic criteria for a particular disorder. This method of classification is similar to what is used in the rest of medicine, that is, a patient either has or does not have pneumonia, etc. This tendency to define illness in terms of categories is undoubtedly due to the fact that it is reflective of basic human thought processes, embodied by the use of nouns in everyday speech to indicate categories of "things" (e.g., chairs, tables, dogs, cats, etc.).

In principle, however, variation in symptomatology can be represented by a set of dimensions rather than by multiple categories. An example of this in medicine is blood pressure, which is measured along a continuum from low to high. (It only becomes categorical when we apply the label "hypertension" to indicate that a patient has a significant

**Table 40–1 Outline for a Possible Future Classification System**

- Axis I: Genotype
  - Identification of disease/symptom related genes
  - Identification of resiliency/protective genes
  - Identification of genes related to therapeutic responses and side effects to specific psythotropic drugs
- Axis II: Neurobiological Phenotype
  - Identification of intermediate phenotypes (neuroimaging, cognitive function, emotional regulation) related to genotype
  - Relates to targeted pharmacotherapy
- Axis III: Behavioral Phenotype
  - The range and frequency of expressed behaviors associated with genotype, neurobiological phenotype, and environment
  - Relates to targeted therapies
- Axis IV: Environmental Modifiers or Precipitants
  - Environmental factors which alter the behavioral and neurobiological phenotype
- Axis V: Therapeutic Targets and Response

*Source*: Kupfer DJ, First MB, and Regier DA (2002) A Research Agenda for DSM-V. American Psychiatric Publishing, Washington, DC, p 72.

elevation in blood pressure that puts him or her at risk for developing serious illness). Dimensional approaches to describing psychiatric symptomatology have been proposed as well. For example, Wittenborn, Holzberg and Simon (Wittenborn et al. 1953) developed a multidimensional representation of the phenomena of psychotic illness nearly 50 years ago and since then others have developed dimensional models to portray the symptomatology of depressive and anxiety disorders, schizophrenia, personality disorders, and even the entire range of psychopathology (Mineka et al. 1998, Peralta and Cuesta 2000, Peralta et al. 2002, Clark 2005, Krueger et al. 2005, Watson 2005).

While a categorical approach to classification has important heuristic appeal, it may not represent the true state of things. Implicit in the categorical approach is an assumption that mental disorders are discrete entities, separated from one another, and from normality, either by recognizably distinct combinations of symptoms or by demonstrably distinct etiologies. While this has been shown to be the case for a small number of conditions (Down's syndrome, fragile X syndrome, phenylketonuria, Alzheimer's and Huntington's diseases and Jacob-Creutzfeldt disease, for example), there is little evidence supporting the applicability of this model for most other psychiatric disorder. Indeed, in the last twenty five years, the categorical approach has been increasingly questioned as evidence has accumulated that so-called categorical disorders like major depressive disorder and anxiety disorders, and schizophrenia and bipolar disorder seem to merge imperceptibly both into one another and into normality with no demonstrable natural boundaries. (Goldberg 1996, Widiger and Samuel 2005).

Dimensional approaches do have some clear advantages. First of all, the commonly observed phenomena of excessive comorbidity (i.e., an individual receiving multiple simultaneous DSM diagnoses) is arguably a direct result of having a categorical system with more than 250 categories. (First 2005b) A dimensional approach, which would characterize an individual's psychopathology by indicating the extent of his or her psychiatric symptomatology across a number of dimensions, virtually eliminates apparent comorbidity. For example, consider an individual who presents with depression, anxiety, and social avoidance. Using the DSM-IV categorical system, criteria might be met for three diagnoses (i.e., major depressive disorder, social phobia, and generalized anxiety disorder) thus warranting a diagnosis of all three disorders on Axis I. A dimensional approach may simply indicate that the person has "high scores" on the depression, anxiety, and social avoidance dimensions. Another advantage of the dimensional approach is that it avoids setting particular thresholds for distinguishing between pathology and normality. Rather than categorically saying that an individual has major depressive disorder, a dimensional approach might say that the person is high on the depression dimension.

Dimensional approaches have other advantages as well. Research studies using dimensional scales as end points have much greater power to detect differences in groups than do studies focusing on changes in dichotomous categories (Cohen 1983, Kraemer et al. 2004). Furthermore, continuous dimensions more closely model the lack of sharp boundaries between disorders and between disorder and normality and can be developed using empirical methods that would facilitate research into the underlying etiology and pathophysiology of mental disorders (Goldberg 1996, Smoller and Tsuang 1998). Finally, dimensions can be helpful in indicating the severity of the disorder, which is clinically-relevant in making treatment decisions. For many disorders in the DSM-IV the range of appropriate treatments is related to the severity of the disorder. (Andrews et al. 2007), For example, while either cognitive therapy alone or antidepressant medication alone are both reasonable options for the treatment of mild to moderate major depressive disorder, cognitive therapy by itself would not be an appropriate option for the treatment of severe forms of major depressive disorder . In such cases, treatment options would include one or more antidepressant medications or electroconvulsive therapy.

There are some practical problems that may potentially limit the utility of adopting a dimensional approach (First 2005a). First of all, clinicians are accustomed to thinking in terms of diagnostic categories, and the existing knowledge base about the presentation, etiology, epidemiology, course, prognosis, and treatment is based on these categories. Furthermore, decisions about the management of individual patients (e.g., whether to treat and with what type of treatment) are also much easier to make if the patient is thought of as having a particular disorder (with its associated prognostic and treatment implications) rather than as a profile of scores across a series of dimensions. One of the challenges for the future is to craft dimensional approaches that have sufficient clinical utility to warrant the increased complexity. (First and Westen 2007).

## History of the DSM Classification System

### DSM I and DSM-II

The predecessors of DSM-IV arose from the need to develop a classification system of mental disorders for statistical,

epidemiological, and reporting purposes. The first official international classification of mental disorders, the sixth revision of the *International Classification of Diseases* (ICD-6), was considered unacceptable by most countries because of its heavy reliance on unproven etiological concepts. The *Diagnostic and Statistical Manual of Mental Disorders,* First Edition (DSM-I) was published in 1952 as an alternative to ICD-6 and included glossary definitions of the various disorders (American Psychiatric Association 1952). The *Diagnostic and Statistical Manual of Mental Disorders,* Second Edition (DSM-II) (American Psychiatric Association 1968) was published in 1968. Like DSM-I, DSM-II retained many etiological concepts (e.g., neuroses).

## DSM-III

After reviewing early drafts of ICD-9 in the early 1970s, the American Psychiatric Association opted to develop DSM-III (American Psychiatric Association 1980) because of concerns that the international nature of the ICD-9 resulted in inconsistent terminology and definitions and that the subtyping was inadequate for clinical and research use. DSM-III represented a major paradigm shift from the etiologically based frameworks of DSM-I and DSM-II. It adopted a descriptive approach that was meant to facilitate communication between mental health professionals operating under various theoretical orientations that continue to flourish in the psychiatry and psychology.

Two innovations were introduced into DSM-III. Each DSM-III disorder was defined by use of explicit diagnostic criteria, which greatly improved the reliability of the system and provided researchers with well-defined categories for scientific study. DSM-III also included a multiaxial system for evaluation that facilitated the use of a biopsychosocial model of evaluation by separating (and thereby calling attention to) developmental and personality disorders (Axis II), physical conditions (Axis III), stressors (Axis IV), and level of adaptive functioning (Axis V) from the presenting diagnoses (Axis I).

## DSM-III-R

In 1987, DSM-III-R was published (American Psychiatric Association 1987) Although originally intended only as a fine-tuning to correct inconsistencies and problems identified after the publication of DSM-III (Boyd et al. 1984, Spitzer and Williams 1987), more substantive changes were made, many reflecting new evidence not available to the developers of DSM-III. Although the publication of DSM-III-R demonstrated that the system is self-correcting, DSM-III-R has been criticized as being too much of a change occurring too soon after the adoption of DSM-III.

## DSM-IV

DSM-IV was envisioned as a modification and refinement of previous editions of the manual rather than a radical reconceptualization (Frances et al. 1989, Frances et al. 1990). The most significant change in DSM-IV is in the process by which DSM-III-R was revised to produce DSM-IV (Widiger et al. 1991). Prior revision efforts were guided almost exclusively by expert consensus. Although these experts were certainly familiar with the then-current state of knowledge about the psychiatric disorders, their decisions were subject to potential biases. In contrast, whenever possible, DSM-IV decisions were based on a systematic review of the then-current empirical database.

The method used to establish an empirical basis for changes in DSM-IV was divided into three stages. As a first step, the approximately 150 questions most deserving consideration for DSM-IV were identified (Widiger et al. 1990). Each of these then received an extensive and systematic review of the literature to determine what evidence was available and what additional evidence would need to be collected to support possible changes. One obvious shortcoming of relying on the literature reviews was that many important questions arose that were not addressed by the published literature. The second stage of the process was to conduct a series of approximately 40 data reanalyses of previously compiled data sets to supplement the evidence available from published studies. Although useful in generating new criteria sets for DSM-IV, the data reanalyses were limited by the fact that the data were collected before the DSM-IV process. Therefore, a series of 12 focused field trials were conducted (Table 40–2). Each field trial drew subjects from at least five different sites (with a minimum of 50 patients per site) (Kline et al. 1993). The field trials served to test the performance characteristics of the proposed criteria sets and to compare them with the DSM-III, DSM-III-R, and ICD-10 criteria sets. A summary of the results of the empirical review process as well as the rationale for the changes in DSM-IV is published in the four volume *DSM-IV Sourcebook* (Widiger et al. 1994, Widiger et al. 1996, Widiger et al. 1997, Widiger et al. 1998).

**Table 40–2 DSM-IV Focused Field Trials**

| |
|---|
| Schizophrenia |
| Mood disorders |
| Panic disorder |
| Mixed anxiety-depressive disorder |
| Obsessive–compulsive disorder |
| Posttraumatic stress disorder |
| Somatization disorder |
| Sleep disorders |
| Pervasive developmental disorders |
| Disruptive behavior disorders |
| Substance dependence |
| Antisocial personality disorder |

The following example serves to illustrate this three-stage process. One of the main goals of the DSM-IV revision process was to improve the clinical utility of the criteria sets. In this regard, several of the DSM-III-R criteria sets had been identified as being particularly difficult to apply in clinical settings. One of the most cumbersome criteria sets was that for somatization disorder, which provided a list of 35 different unexplained physical symptoms, of which at least 13 were required for a diagnosis. A literature review was first conducted to investigate the performance characteristics of the DSM-III-R criteria set. It demonstrated, as expected, that the DSM-III-R definition was among the most reliable and valid in the manual. Any attempt to modify the criteria set would therefore have to result in a criteria set that defined the same group of patients as did DSM-III-R and be comparably reliable. A more user-friendly criteria set

was generated through the data reanalysis process. Data sets of patients with somatization disorder were pooled, and different diagnostic algorithms were investigated. The resulting proposed criteria set required symptoms for a period of several years that occur in the following pattern: at least four pain symptoms, two gastrointestinal symptoms, one sexual symptom, and one conversion symptom. To ensure the generalizability of this proposed criteria set, a focused field trial was conducted that compared this simplified definition with the original DSM-III-R definition, along with DSM-III, ICD-10, and the historical definition of Briquet's syndrome. The field trial found that all of the definitions identified essentially the same group of patients with comparable reliability, providing empirical support for the DSM-IV decision to replace the DSM-III-R criteria set for somatization disorder. (Yutzy et al. 1995).

## DSM-IV-TR

During the DSM-IV revision process, some criticisms were voiced about the rapid pace of DSM revisions, arguing that undertaking an extensive revision of the classification every 7 years was disruptive to researchers and was not necessarily justified by the pace of psychiatric research. (Zimmerman 1988). DSM-IV was timed for publication 1994 in order to coincide with the publication of ICD-10 in 1992. In the absence of any externally imposed time frame (given that there was no anticipated date for starting work on ICD-11) it was decided that the interval between DSM-IV and the next revision would be greatly extended to least 16 years (i.e., DSM-V will not come out until 2012). One consequence of this is the effect on the currency of the DSM-IV text, which was based on a literature review that extended only to mid 1992. Thus, in order to maintain continued clinical utility and educational value, a revision of the DSM-IV text was begin in 1996 (First and Pincus 2002) Following the DSM-IV precedent of only making changes if supported by data, changes to the text were made based on a comprehensive review of the literature relevant to the text categories that was published since 1992. The text revision (American Psychiatric Association 2000), called "DSM-IV-TR" to distinguish it from DSM-IV, was published in June 2000.

## DSM-V

In advance of starting work on DSM-V, a DSM-V research planning process was initiated in order to (1) stimulate research that will enrich the empirical data base prior to the start of the DSM-V revision process and (2) devise a research and analytic agenda that would facilitate the integration of findings from animal studies, genetics, neuroscience, epidemiology, clinical research, cross-cultural, and clinical services research, which will lead to the eventual development of an etiologically based scientifically sound classification system (Kupfer et al. 2002a, Regier et al. 2002).

The first phase of the research planning process involved the development of a series of white papers. Rather than organizing the white paper workgroups around the traditional diagnostic categories, the workgroups which were set up to develop the white papers focused instead on cross-cutting issues, which included (1) a basic nomenclature workgroup, focusing on a variety of issues that had to do with the way disorders are classified in the DSM, (2) a neuroscience and genetics workgroup whose focus was to develop a basic and clinical neuroscience and genetics research agenda to guide the development of a future pathophysiologically based classification, (3) a developmental science workgroup which outlined a research agenda to inform developmental aspects of the diagnostic classification, (4) a workgroup focusing on two major gaps in the DSM-IV, namely inadequacies in the classification of personality disorders and of relational disorders, (5) a mental disorders and disability workgroup which focused on disentangling the concepts of symptom severity and disability, and a (6) culture and psychiatric diagnosis workgroup which considered cross-cultural issues in diagnosis and classification. The first six white papers were published as a monograph in 2002 (Kupfer et al. 2002b). Three additional white papers, one focusing on gender issues, one focusing on diagnostic issues in the geriatric population, and one focusing on mental disorders in infants and young children were commissioned subsequently and appear in a recently published second volume of the research agenda. (Narrow et al. 2007).

The second phase of the DSM-V Research Planning Process consisted of eleven research planning conferences (plus a methods conference) from 2004–2007 under the title "The Future of Psychiatric Diagnosis: Refining the Research Agenda." Unlike the white papers in the first phase which focused on general cross-cutting issues, these conferences for the most part focussed on specific diagnostic topics. The primary goals of these conferences were to stimulate the empirical research necessary to allow informed decision making regarding crucial diagnostic deficiencies identified in DSM-IV and ICD-10 and to promote international collaboration in order to increase the likelihood of developing a future unified DSM/ICD (i.e., each conference have two co-chairs, one from the US and the other outside the US, each included an equal number of the US and international participants, and half the conferences took place outside of the US). The eleven diagnostic-topic focused conferences covered Dimensional Approaches Personality Disorders (December 2004, Arlington, VA, USA); Substance-Related Disorders (February 2005, Rockville, MD); Stress-Induced and Fear Circuitry Disorders (June 2005, Arlington, VA, USA); Dementia (September 2005, Geneva, Switzerland), Deconstructing Psychosis (February 2006, Arlington, VA, USA); Obsessive–Compulsive Spectrum Disorders (June 2006, Arlington, VA, USA); Dimensional Approaches to Diagnosis (July 2006, Bethesda, MD, USA); Somatic Presentations (September 2006, Bejing, China); Externalizing Disorders of Childhood (February 2007, Mexico City, Mexico); Comorbidity of Anxiety and Depression (June 2007, London, UK); and Public Health Implications (September 2007, Geneva, Switzerland).

Based on the material presented at these research conferences, it is unlikely genetics, neuroimaging findings, or biological markers will be incorporated into the diagnostic criteria for disorders in DSM-V. Evidence from the conferences does strongly support the incorporation of dimensional approaches along with categorical approaches in DSM-V; the challenge will be to formulate dimensions that will be useful to both researchers and clinicians. Finally, developmental approaches to diagnoses will be more prominent, with definitions being modified to reflect differing presentations across the life span.

## DSM-IV Overview

The remainder of this chapter provides an overview of the DSM-IV multiaxial system as well as a presentation of some of the organizational principles of the various diagnostic groupings included in the DSM-IV classification. The other chapters in the Disorders section of this textbook are organized according to their presentation in the DSM-IV Classification and provide detailed information regarding the diagnosis, etiology and pathophysiology, epidemiology, course, and treatment of these DSM-IV disorders.

## DSM-IV Multiaxial System

The multiaxial system was first introduced by DSM-III (Williams 1987) in order to encourage the clinician to focus his or her attention during the evaluation process on issues above and beyond the psychiatric diagnosis. Use of the multiaxial system requires that information be noted on each of five different axes, each axis devoted to a different aspect of the evaluation process. Axes I, II, and III are the diagnostic axes and divide up the diagnostic pie into three separate domains. Axis I is for "clinical syndromes and disorders," an admittedly confusing name since Axis II and Axis III are also diagnostic axes. The most accurate name for Axis I is "diagnoses not coded on Axis II and Axis III" since Axis II and Axis III were carved out of Axis I specifically to draw attention to certain disorders that clinicians were more likely to overlook.

That said, Axis II is designated for coding Personality Disorders and Mental Retardation. There have been many recent criticisms of the coding of Personality Disorders on Axis II. Critics correctly point out that there is no firm conceptual basis for this division. Although disorders on Axis II tend to be lifelong and pervasive, a number of disorders on Axis I (e.g., Schizophrenia, Autistic Disorder, Dysthymic Disorder) fit this description as well. Others have made the incorrect assumption that categories on Axis II are unresponsive to medication treatment, which is at odds with more recent evidence that medications are often helpful in the treatment of personality disorders. The fact is that the Axis I/Axis II division was made on strictly pragmatic grounds. It was introduced in DSM-III as a way of drawing attention to a set of disorders that were thought not to be given adequate attention by mental health professionals. First introduced in DSM-III, Axis II was designed to draw attention to certain disorders that were thought to be overshadowed in the face of the more florid Axis I presentations. In DSM-III, Axis II was reserved for personality disorders in adults and specific developmental disorders in children. In DSM-III-R, the developmental disorders (i.e., mental retardation, pervasive developmental disorders, specific developmental disorders) were coded on Axis II along with the personality disorders. In DSM-IV, Axis II was modified once again so that only personality disorders and mental retardation remain on Axis II. Certainly the placement of personality disorders on a separate axis has increased both their clinical visibility and their importance as a subject for research studies. Whether the Axis I/Axis II division has finally outlived its usefulness remains a topic of heated debate, and will be revisited during the DSM-V deliberations.

Axis III, like Axis II, is intended to encourage clinicians to pay special attention to conditions that they tend to overlook; in this case, clinically relevant general medical conditions. The concept of "clinically relevant" is intended to be broad. For example, it would be appropriate to list hypertension on Axis III even if its only relationship to an Axis I disorder is its impact on the options for the choice of antidepressant medication.

Psychosocial stressors are well-known to play an important role in the etiology, maintenance, and management of a number of mental disorders. Axis IV provides the psychiatrist with the opportunity to list clinically relevant psychosocial and environmental problems (e.g., homelessness, poverty, divorce). To facilitate a comprehensive evaluation of such problems, DSM-IV includes a psychosocial and environmental checklist that allows the psychiatrist to indicate which types of problems are present and relevant (Figure 40–1).

Mental disorders differentially impact on individual's level of functioning. For example, one patient with Schizophrenia may function quite well, being able to live in the community, marry and have a family, and maintain a steady job whereas another patient with Schizophrenia may function quite poorly, requiring chronic institutionalization. Since both of these patients have symptoms that meet the diagnostic criteria for Schizophrenia, their important differences in functioning is not captured by the clinical diagnosis alone. Some of the differences in functioning may be due to different symptom profiles or symptom severities. Other differences may be related to resilience factors or different levels of psychosocial support. Whatever the reason, the DSM-IV multiaxial system provides the clinician with the ability to indicate the patient's overall level of functioning on Axis V, using the Global Assessment of Functioning (GAF) Scale (Figure 40–2). This GAF scale has been criticized because it is not actually a "pure" measure of an individual's ability to function, since it incorporates symptom severity into the scale (e.g., level 41–50 is for "serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) or any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job)". For this reason, the DSM-IV includes a scale (the Social and Occupational Functioning Scale (SOFAS)) that relies exclusively

Check:

__ Problems with primary support group (childhood, adult, parent–child). Specify: _____

__ Problems related to the social environment. Specify: _____

__ Educational problems. Specify: _____

__ Occupational problems. Specify: _____

__ Housing problems. Specify: _____

__ Economic problems. Specify: _____

__ Problems with access to health care services. Specify: _____

__ Problems related to interaction with the legal system/crime. Specify: _____

__ Other psychosocial problems. Specify: _____

**Figure 40–1** *DSM-IV Axis IV. (Modified from: American Psychiatric Association [2000], Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Rev. APA, Washington, DC, p 36.)*

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

| Code | (Note: Use intermediate codes when appropriate, e.g., 45,68,72.) |
|---|---|
| 100<br>\|<br>91 | Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of many positive qualities. No symptoms. |
| 90<br>\|<br>81 | Absent or minimal symptoms (e.g., mild anxiety before an examination), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members). |
| 80<br>\|<br>71 | If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in school work). |
| 70<br>\|<br>61 | Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships. |
| 60<br>\|<br>51 | Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or coworkers). |
| 50<br>\|<br>41 | Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job). |
| 40<br>\|<br>31 | Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger chlidren, is defiant at home, and is failing at school). |
| 30<br>\|<br>21 | Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home or friends). |
| 20<br>\|<br>11 | Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute). |
| 10<br>\|<br>1 | Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death. |
| 0 | Inadequate information |

**Figure 40–2** *GAF Scale. (Source: American Psychiatric Association [2000], Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Rev. APA, Washington, DC, p 34.)*

on functioning in its appendix of Criteria Sets and Axes Provided for Further Study (DSM-IV-TR, p. 817–818). An example of a DSM-IV multiaxial evaluation for a hypothetical patient is shown in Table 40–3.

**Table 40–3 Example of DSM-IV Multiaxial Evaluation***

| | |
|---|---|
| Axis I | 296.23 Major depressive disorder, single episode, severe but without psychotic features, with postpartum onset 307.51 Bulimia nervosa |
| Axis II | 301.6 Dependent personality disorder<br>Frequent use of denial |
| Axis III | Rheumatoid arthritis |
| Axis IV | Partner relational problem |
| Axis V | GAF = 35 (current) |

*GAF, Global Assessment of Functioning Scale score.

## DSM-IV Classification and Diagnostic Codes

The "DSM-IV Classification of Mental Disorders" refers to the comprehensive listing of the official diagnostic codes, categories, subtypes, and specifiers (see Figure 40–3). It is divided into various "diagnostic classes" which group disorders together based on common presenting symptoms (e.g., Mood Disorders, Anxiety Disorders), typical age-at-onset (e.g., Disorders Usually First Diagnosed in Infancy, Childhood, and Adolescence), and etiology (e.g., Substance-Related Disorders, Mental Disorders Due to a General Medical Condition).

The diagnostic codes listed in the DSM-IV are derived from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), the official coding system for reporting morbidity and mortality in the US. That is the reason why the codes go from 290.00

## DSM-IV-TR CLASSIFICATION

NOS = Not Otherwise Specified.

An x appearing in a diagnostic code indicates that a specific code number is required.

An ellipsis (...) is used in the names of certain disorders to indicate that the name of a specific mental disorder or general medical condition should be inserted when recording the name (e.g., 293.0 Delirium Due to Hypothyroidism).

If criteria are currently met, one of the following severity specifiers may be noted after the diagnosis:

Mild
Moderate
Severe

If criteria are no longer met, one of the following specifiers may be noted:

In Partial Remission
In Full Remission
Prior History

### Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence

#### MENTAL RETARDATION

Note: *These are coded on Axis II.*

317 Mild Mental Retardation
318.0 Moderate Mental Retardation
318.1 Severe Mental Retardation
318.2 Profound Mental Retardation
319 Mental Retardation, Severity Unspecified

#### LEARNING DISORDERS

315.0 Reading Disorder
315.1 Mathematics Disorder
315.2 Disorder of Written Expression
315.9 Learning Disorder NOS

#### MOTOR SKILLS DISORDER

315.4 Developmental Coordination Disorder

#### COMMUNICATION DISORDERS

315.31 Expressive Language Disorder
315.32 Mixed Receptive-Expressive Language Disorder
315.39 Phonological Disorder
307.0 Stuttering
307.9 Communication Disorder NOS

#### PERVASIVE DEVELOPMENTAL DISORDERS

299.00 Autistic Disorder
299.80 Rett's Disorder
299.10 Childhood Disintegrative Disorder
299.80 Asperger's Disorder
299.80 Pervasive Developmental Disorder NOS

#### ATTENTION-DEFICIT AND DISRUPTIVE BEHAVIOR DISORDERS

314.xx Attention-Deficit/Hyperactivity Disorder
.01 Combined Type
.00 Predominantly Inattentive Type
.01 Predominantly Hyperactive-Impulsive Type
314.9 Attention-Deficit/Hyperactivity Disorder NOS
312.xx Conduct Disorder
.81 Childhood-Onset Type
.82 Adolescent-Onset Type
.89 Unspecified Onset
313.81 Oppositional Defiant Disorder
312.9 Disruptive Behavior Disorder NOS

#### FEEDING AND EATING DISORDERS OF INFANCY OR EARLY CHILDHOOD

307.52 Pica
307.53 Rumination Disorder
307.59 Feeding Disorder of Infancy or Early Childhood

#### TIC DISORDERS

307.23 Tourette's Disorder
307.22 Chronic Motor or Vocal Tic Disorder
307.21 Transient Tic Disorder
*Specify if*: Single Episode/Recurrent
307.20 Tic Disorder NOS

#### ELIMINATION DISORDERS

—.— Encopresis
787.6 With Constipation and Overflow Incontinence
307.7 Without Constipation and Overflow Incontinence
307.6 Enuresis (Not Due to a General Medical Condition)
*Specify type:* Nocturnal Only/Diurnal Only/Nocturnal and Diurnal

#### OTHER DISORDERS OF INFANCY, CHILDHOOD, OR ADOLESCENCE

309.21 Separation Anxiety Disorder
*Specify if*: Early Onset
313.23 Selective Mutism
313.89 Reactive Attachment Disorder of Infancy or Early Childhood
*Specify type:* Inhibited Type/Disinhibited Type
307.3 Stereotypic Movement Disorder
*Specify if:* With Self-Injurious Behavior
313.9 Disorder of Infancy, Childhood, or Adolescence NOS

### Delirium, Dementia, and Amnestic and Other Cognitive Disorders

#### DELIRIUM

293.0 Delirium Due to ... [*Indicate the General Medical Condition*]
—.— Substance Intoxication Delirium (*refer to Substance-Related Disorders for substance-specific codes*)
—.— Substance Withdrawal Delirium (*refer to Substance-Related Disorders for substance-specific codes*)
—.— Delirium Due to Multiple Etiologies (*code each of the specific etiologies*)
780.09 Delirium NOS

#### DEMENTIA

294.xx Dementia of the Alzheimer's Type, With Early Onset (*also code 331.0 Alzheimer's disease on Axis III*)
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
294.xx Dementia of the Alzheimer's Type, With Late Onset (*also code 331.0 Alzheimer's disease on Axis III*)
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
290.xx Vascular Dementia
.40 Uncomplicated
.41 With Delirium
.42 With Delusions
.43 With Depressed Mood
*Specify if:* With Behavioral Disturbance

*Code presence or absence of a behavioral disturbance in the fifth digit for Dementia Due to a General Medical Condition:*

294.10 = Without Behavioral Disturbance

294.11 = With Behavioral Disturbance

294.1x Dementia Due to HIV Disease (*also code 042 HIV on Axis III*)
294.1x Dementia Due to Head Trauma (*also code 854.00 head injury on Axis III*)
294.1x Dementia Due to Parkinson's Disease (*also code 331.82 Dementia with Lewy Bodies on Axis III*)
294.1x Dementia Due to Huntington's Disease (*also code 333.4 Huntington's disease on Axis III*)
294. 1x Dementia Due to Pick's Disease (*also code 331.11 Pick's disease on Axis III*)
294. 1x Dementia Due to Creutzfeldt-Jakob Disease (*also code 046.1 Creutzfeldt-Jakob disease on Axis III*)
294. 1x Dementia Due to ... [*Indicate the General Medical Condition not listed above*] (also code the general medical condition on Axis III)
—.— Substance-Induced Persisting Dementia (*refer to Substance-Related Disorders for substance-specific codes*)
—.— Dementia Due to Multiple Etiologies (*code each of the specific etiologies*)
294.8 Dementia NOS

#### AMNESTIC DISORDERS

294.0 Amnestic Disorder Due to ... [*Indicate the General Medical Condition*}
*Specify if*: Transient/Chronic
—.— Substance-Induced Persisting Amnestic Disorder (*refer to Substance-Related Disorders for substance-specific codes*)
294.8 Amnestic Disorder NOS

**OTHER COGNITIVE DISORDERS**

294.9 Cognitive Disorder NOS

**Mental Disorders Due to a General Medical Condition Not Elsewhere Classified**

293.89 Catatonic Disorder Due to ... [*Indicate the General Medical Condition*]

310.1 Personality Change Due to ... [*Indicate the General Medical Condition*]

*Specify type*: Labile Type/ Disinhibited Type/Aggressive Type/Apathetic Type/Paranoid Type/Other Type/ Combined Type/ Unspecified Type

293.9 Mental Disorder NOS Due to... [*Indicate the General Medical Condition*]

**Substance-Related Disorders**

*The following specifiers apply to Substance Dependence as noted:*

[a]With Physiological Dependence/Without Physiological Dependence

[b]Early Full Remission/Early Partial Remission Sustained Full Remission/ Sustained Partial Remission

[c]In a Controlled Environment

[d]On Agonist Therapy

*The following specifiers apply to Substance-Induced Disorders as noted:*

[1]With Onset During Intoxication/[w]With Onset During Withdrawal

**ALCOHOL-RELATED DISORDERS**

**Alcohol Use Disorders**

303.90 Alcohol Dependence[a,b,C]

305.00 Alcohol Abuse

**Alcohol-Induced Disorders**

303.00 Alcohol Intoxication

291.81 Alcohol Withdrawal

*Specify if*: With Perceptual Disturbances

291.0 Alcohol Intoxication Delirium

291.0 Alcohol Withdrawal Delirium

291.2 Alcohol-Induced Persisting Dementia

291.1 Alcohol-Induced Persisting Amnestic Disorder

291.x Alcohol-Induced Psychotic Disorder

.5 With Delusions[1,W]

.3 With Hallucinations[1,W]

291.89 Alcohol-Induced Mood Disorder[1,W]

291.89 Alcohol-Induced Anxiety Disorder[1,W]

291.89 Alcohol-Induced Sexual Dysfunction[1]

291.82 Alcohol-Induced Sleep Disorder[1,W]

291.9 Alcohol-Related Disorder NOS

**AMPHETAMINE (OR AMPHETAMINE-LIKE)-RELATED DISORDERS**

**Amphetamine Use Disorders**

304.40 Amphetamine Dependence[a,b,c]

305.70 Amphetamine Abuse

**Amphetamine-Induced Disorders**

292.89 Amphetamine Intoxication

*Specify if:* With Perceptual Disturbances

292.0 Amphetamine Withdrawal

292.81 Amphetamine Intoxication Delirium

292.xx Amphetamine-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Amphetamine-Induced Mood Disorder[1,w]

292.89 Amphetamine-Induced Anxiety Disorder[1]

292.89 Amphetamine-Induced Sexual Dysfunction[1]

292.85 Amphetamine-Induced Sleep Disorder[1,W]

292.9 Amphetamine-Related Disorder NOS

**CAFFEINE-RELATED DISORDERS**

**Caffeine-Induced Disorders**

305.90 Caffeine Intoxication

292.89 Caffeine-Induced Anxiety Disorder[1]

292.85 Caffeine-Induced Sleep Disorder[1]

292.9 Caffeine-Related Disorder NOS

**CANNABIS-RELATED DISORDERS**

**Cannabis Use Disorders**

304.30 Cannabis Dependence[a,b,c]

305.20 Cannabis Abuse

**Cannabis-Induced Disorders**

292.89 Cannabis Intoxication

*Specify if:* With Perceptual Disturbances

292.81 Cannabis Intoxication Delirium

292.xx Cannabis-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.89 Cannabis-Induced Anxiety Disorder[1]

292.9 Cannabis-Related Disorder NOS

**COCAINE-RELATED DISORDERS**

**Cocaine Use Disorders**

304.20 Cocaine Dependence[a,b,c]

305.60 Cocaine Abuse

**Cocaine-Induced Disorders**

292.89 Cocaine Intoxication

*Specify if:* With Perceptual Disturbances

292.0 Cocaine Withdrawal

292.81 Cocaine Intoxication Delirium

292.xx Cocaine-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Cocaine-Induced Mood Disorder[1,W]

292.89 Cocaine-Induced Anxiety Disorder[1,W]

292.89 Cocaine-Induced Sexual Dysfunction[1]

292.85 Cocaine-Induced Sleep Disorder[1,W]

292.9 Cocaine-Related Disorder NOS

**HALLUCINOGEN-RELATED DISORDERS**

**Hallucinogen Use Disorders**

304.50 Hallucinogen Dependence[b,c]

305.30 Hallucinogen Abuse

**Hallucinogen-Induced Disorders**

292.89 Hallucinogen Intoxication

292.89 Hallucinogen Persisting Perception Disorder (Flashbacks)

292.81 Hallucinogen Intoxication Delirium

292.xx Hallucinogen-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Hallucinogen-Induced Mood Disorder[1]

292.89 Hallucinogen-Induced Anxiety Disorder[1]

292.9 Hallucinogen-Related Disorder NOS

**INHALANT-RELATED DISORDERS**

**Inhalant Use Disorders**

304.60 Inhalant Dependence[b,c]

305.90 Inhalant Abuse

**Inhalant-Induced Disorders**

292.89 Inhalant Intoxication

292.81 Inhalant Intoxication Delirium

292.82 Inhalant-Induced Persisting Dementia

292.xx Inhalant-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Inhalant-Induced Mood Disorder[1]

292.89 Inhalant-Induced Anxiety Disorder[1]

292.9 Inhalant-Related Disorder NOS

*(Continues)*

**NICOTINE-RELATED DISORDERS**

**Nicotine Use Disorder**

305.1 Nicotine Dependence[a,b]

**Nicotine-Induced Disorder**

292.0 Nicotine Withdrawal

292.9 Nicotine-Related Disorder NOS

**OPIOID-RELATED DISORDERS**

**Opioid Use Disorders**

304.00 Opioid Dependence[a,b,c,d]

305.50 Opioid Abuse

**Opioid-Induced Disorders**

292.89 Opioid Intoxication

*Specify if:* With Perceptual Disturbances

292.0 Opioid Withdrawal

292.81 Opioid Intoxication Delirium

292.xx Opioid-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Opioid-Induced Mood Disorder[1]

292.89 Opioid-Induced Sexual Dysfunction[1]

292.85 Opioid-Induced Sleep Disorder[1,W]

292.9 Opioid-Related Disorder NOS

**PHENCYCLIDINE (OR PHENCYCLIDINE-LIKE)-RELATED DISORDERS**

**Phencyclidine Use Disorders**

304.60 Phencyclidine Dependence[b,c]

305.90 Phencyclidine Abuse

**Phencyclidine-Induced Disorders**

292.89 Phencyclidine Intoxication

*Specify if:* With Perceptual Disturbances

292.81 Phencyclidine Intoxication Delirium

292.xx Phencyclidine-Induced Psychotic Disorder

.11 With Delusions[1]

.12 With Hallucinations[1]

292.84 Phencyclidine-Induced Mood Disorder[1]

292.89 Phencyclidine-Induced Anxiety Disorder[1]

292.9 Phencyclidine-Related Disorder NOS

**SEDATIVE-, HYPNOTIC-, OR ANXIOLYTIC-RELATED DISORDERS**

**Sedative, Hypnotic, or Anxiolytic Use Disorders**

304.10 Sedative, Hypnotic, or Anxiolytic Dependence[a,b,c]

305.40 Sedative, Hypnotic, or Anxiolytic Abuse

**Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders**

292.89 Sedative, Hypnotic, or Anxiolytic Intoxication

292.0 Sedative, Hypnotic, or Anxiolytic Withdrawal

*Specify if:* With Perceptual Disturbances

292.81 Sedative, Hypnotic, or Anxiolytic Intoxication Delirium

292.81 Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium

292.82 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Dementia

292.83 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Amnestic Disorder

292.xx Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder

.11 With Delusions[1,W]

.12 With Hallucinations[1,W]

292.84 Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder[1,W]

292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorderw[W]

292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction[1]

292.85 Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder[1,W]

292.9 Sedative-, Hypnotic-, or Anxiolytic-Related Disorder NOS

**POLYSUBSTANCE-RELATED DISORDER**

304.80 Polysubstance Dependence[a,b,c,d]

**OTHER (OR UNKNOWN) SUBSTANCE-RELATED DISORDERS**

**Other (or Unknown) Substance Use Disorders**

304.90 Other (or Unknown) Substance Dependence[a,b,c,d]

305.90 Other (or Unknown) Substance Abuse

**Other (or Unknown) Substance-Induced Disorders**

292.89 Other (or Unknown) Substance Intoxication

*Specify if:* With Perceptual Disturbances

292.0 Other (or Unknown) Substance Withdrawal

*Specify if:* With Perceptual Disturbances

292.81 Other (or Unknown) Substance-Induced Delirium

292.82 Other (or Unknown) Substance-Induced Persisting Dementia

292.83 Other (or Unknown) Substance-Induced Persisting Amnestic Disorder

292.xx Other (or Unknown) Substance-Induced Psychotic Disorder

.11 With Delusions[1,W]

.12 With Hallucinations[1,W]

292.84 Other (or Unknown) Substance-Induced Mood Disorder[1,W]

292.89 Other (or Unknown) Substance-Induced Anxiety Disorder[1,W]

292.89 Other (or Unknown) Substance-Induced Sexual Dysfunction[1]

292.85 Other (or Unknown) Substance-Induced Sleep Disorder[1,W]

292.9 Other (or Unknown) Substance-Related Disorder NOS

**Schizophrenia and Other Psychotic Disorders**

295.xx Schizophrenia

*The following Classification of Longitudinal Course applies to all subtypes of Schizophrenia.*

Episodic With Interepisode Residual Symptoms (*specify if:* With Prominent Negative Symptoms)/Episodic With No Interepisode Residual Symptoms/ Continuous (*specify if:* With Prominent Negative Symptoms)

Single Episode In Partial Remission (*specify if:* With Prominent Negative Symptoms)/Single Episode In Full Remission

Other or Unspecified Pattern

.30 Paranoid Type

.10 Disorganized Type

.20 Catatonic Type

.90 Undifferentiated Type

.60 Residual Type

295.40 Schizophreniform Disorder

*Specify if:* Without Good Prognostic Features/With Good Prognostic Features

295.70 Schizoaffective Disorder

*Specify type:* Bipolar Type/ Depressive Type

297.1 Delusional Disorder

*Specify type:* Erotomanic Type/Grandiose Type/Jealous Type/Persecutory Type/ Somatic Type/Mixed Type/Unspecified Type

298.8 Brief Psychotic Disorder

*Specify if:* With Marked Stressor(s)/Without Marked Stressor(s)/With Postpartum Onset

297.3 Shared Psychotic Disorder

293.xx Psychotic Disorder Due to... [*Indicate the General Medical Condition*]

.81 With Delusions

.82 With Hallucinations

—.— Substance-Induced Psychotic Disorder (*refer to Substance-Related Disorders for substance-specific codes*)

*Specify if:* With Onset During Intoxication/With Onset During Withdrawal

298.9 Psychotic Disorder NOS

**Mood Disorders**

*Code current state of Major Depressive Disorder or Bipolar I Disorder in fifth digit.*

1 = Mild

2 = Moderate

3 = Severe Without Psychotic Features

4 = Severe With Psychotic Features

*Specify:* Mood-Congruent Psychotic Features/Mood-Incongruent Psychotic Features

5 = In Partial Remission

6 = In Full Remission

0 = Unspecified

*The following specifiers apply (for current or most recent episode) to Mood Disorders as noted:*

[a]Severity/Psychotic/Remission Specifiers [b]Chronic/[c]With Catatonic Features/[d]With Melancholic Features/[e]With Atypical Features/[f]With Postpartum Onset

*The following specifiers apply to Mood Disorders as noted:*

[g]With or Without Full Interepisode Recovery/ [h]With Seasonal Pattern/[i]With Rapid Cycling

**DEPRESSIVE DISORDERS**

296.xx Major Depressive Disorder,

.2x Single Episode[a,b,c,d,e,f]

.3x Recurrent[a,b,c,d,e,f,g,h]

300.4 Dysthymic Disorder

*Specify if:* Early Onset/Late Onset
*Specify if:* With Atypical Features

311 Depressive Disorder NOS

**BIPOLAR DISORDERS**

296.xx Bipolar I Disorder,

.0x Single Manic Episode[a,c,f]

*Specify if:* Mixed

.40 Most Recent Episode Hypomanic[g,h,i]

.4x Most Recent Episode[a,c,f,g,h,i]

.6x Most Recent Episode[a,c,f,g,h,i]

.5x Most Recent Episode Depressed[a,b,c,d,e,f,s,h,i]

.7 Most Recent Episode Unspecified[g,h,i]

296.89 Bipolar II Disorder[a,b,c,d,e,f,s,h,i]

*Specify* (*current or most recent episode*). Hypomanic/ Depressed

301.13 Cyclothymic Disorder

296.80 Bipolar Disorder NOS

293.83 Mood Disorder Due to... [*Indicate the General Medical Condition*]

*Specify type:* With Depressive Features/With Major Depressive-Like Episode/With Manic Features/With Mixed Features

—.— Substance-Induced Mood Disorder (refer to Substance–*Related Disorders for substance–specific codes*)

*Specify type:* With Depressive Features/With Manic Features/ With Mixed Features

*Specify if:* With Onset During Intoxication/ With Onset During Withdrawal

296.90 Mood Disorder NOS

**Anxiety Disorders**

300.01 Panic Disorder Without Agoraphobia

300.21 Panic Disorder With Agoraphobia

300.22 Agoraphobia Without History of Panic Disorder

300.29 Specific Phobia

*Specify type:* Animal Type/ Natural Environment Type/ Blood–Injection–Injury Type/ Situational Type/ Other Type

300.23 Social Phobia

*Specify if:* Generalized

300.3 Obsessive–Compulsive Disorder

*Specify if:* With Poor Insight

309.81 Posttraumatic Stress Disorder

*Specify if:* Acute/Chronic

*Specify if:* With Delayed Onset

308.3 Acute Stress Disorder

300.02 Generalized Anxiety Disorder

293.89 Anxiety Disorder Due to ... [*Indicate the General Medical Condition*]

*Specify if:* With Generalized Anxiety/With Panic Attacks/With Obsessive–Compulsive Symptoms

—.— Substance-Induced Anxiety Disorder (*refer to Substance–Related Disorders for substance-specific codes*)

*Specify if:* With Generalized Anxiety/With Panic Attacks/ With Obsessive–Compulsive Symptoms/With Phobic Symptoms

*Specify if:* With Onset During Intoxication/With Onset During Withdrawal

300.00 Anxiety Disorder NOS

**Somatoform Disorders**

300.81 Somatization Disorder

300.82 Undifferentiated Somatoform Disorder

300.11 Conversion Disorder

*Specify type:* With Motor Symptom or Deficit/With Sensory Symptom or Deficit/With Seizures or Convulsions/With Mixed Presentation

307.xx Pain Disorder

.80 Associated With Psychological Factors

.89 Associated With Both Psychological Factors and a General Medical Condition

*Specify if:* Acute/Chronic

300.7 Hypochondriasis

*Specify if:* With Poor Insight

300.7 Body Dysmorphic Disorder

300.82 Somatoform Disorder NOS

**Factitious Disorders**

300.xx Factitious Disorder

. 16 With Predominantly Psychological Signs and Symptoms

.19 With Predominantly Physical Signs and Symptoms

.19 With Combined Psychological and Physical Signs and Symptoms

300.19 Factitious Disorder NOS

**Dissociative Disorders**

300.12 Dissociative Amnesia

300.13 Dissociative Fugue

300.14 Dissociative Identity Disorder

300.6 Depersonalization Disorder

300.15 Dissociative Disorder NOS

**Sexual and Gender Identity Disorders**

**SEXUAL DYSFUNCTIONS**

*The following specifiers apply to all primary Sexual Dysfunctions:*

Lifelong Type/Acquired Type Generalized Type/Situational Type Due to Psychological Factors/Due to Combined Factors

**SEXUAL DESIRE DISORDERS**

302.71 Hypoactive Sexual Desire Disorder

302.79 Sexual Aversion Disorder

**SEXUAL AROUSAL DISORDERS**

302.72 Female Sexual Arousal Disorder

302.72 Male Erectile Disorder

**ORGASMIC DISORDERS**

302.73 Female Orgasmic Disorder

302.74 Male Orgasmic Disorder

302.75 Premature Ejaculation

**SEXUAL PAIN DISORDERS**

302.76 Dyspareunia (Not Due to a General Medical Condition)

306.51 Vaginismus (Not Due to a General Medical Condition)

**SEXUAL DYSFUNCTION DUE TO A GENERAL MEDICAL CONDITION**

625.8 Female Hypoactive Sexual Desire Disorder Due to ... [*Indicate the General Medical Condition*]

608.89 Male Hypoactive Sexual Desire Disorder Due to ... [*Indicate the General Medical Condition*]

*(Continues)*

607.84 Male Erectile Disorder Due to... [*Indicate the General Medical Condition*]

625.0 Female Dyspareunia Due to ... [*Indicate the General Medical Condition*]

608.89 Male Dyspareunia Due to... [*Indicate the General Medical Condition*]

625.8 Other Female Sexual Dysfunction Due to... [*Indicate the General Medical Condition*]

608.89 Other Male Sexual Dysfunction Due to... [*Indicate the General Medical Condition*]

—.— Substance-Induced Sexual Dysfunction (*refer to Substance-Related Disorders for substance-specific codes*)

*Specify if:* With Impaired Desire/ With Impaired Arousal/With Impaired Orgasm/With Sexual Pain

*Specify if:* With Onset During Intoxication

302.70 Sexual Dysfunction NOS

**PARAPHILIAS**

302.4 Exhibitionism

302.81 Fetishism

302.89 Frotteurism

302.2 Pedophilia

*Specify if.* Sexually Attracted to Males/Sexually Attracted to Females/Sexually Attracted to Both

*Specify if:* Limited to Incest

*Specify if:* Exclusive Type/ Nonexclusive Type

302.83 Sexual Masochism

302.84 Sexual Sadism

302.3 Transvestic Fetishism

*Specify if:* With Gender Dysphoria

302.82 Voyeurism

302.9 Paraphilia NOS

**GENDER IDENTITY DISORDERS**

302.xx Gender Identity Disorder

.6 in Children

.85 in Adolescents or Adults

*Specify if:* Sexually Attracted to Males/Sexually Attracted to Females/ Sexually Attracted to Both/Sexually Attracted to Neither

302.6 Gender Identity Disorder NOS

302.9 Sexual Disorder NOS

**EATING DISORDERS**

307.1 Anorexia Nervosa

*Specify if:* Restricting Type; Binge-Eating/Purging Type

307.51 Bulimia Nervosa

*Specify if:* Purging Type/ Nonpurging Type

307.50 Eating Disorder NOS

**Sleep Disorders**

**PRIMARY SLEEP DISORDERS**

**Dyssomnias**

307.42 Primary Insomnia

307.44 Primary Hypersomnia
*Specify if:* Recurrent

347.00 Narcolepsy

780.57 Breathing-Related Sleep Disorder

327.3x Circadian Rhythm Sleep Disorder

.31 Delayed Sleep Phase Type

.35 Jet Lag Type

.36 Shift Work Type

.30 Unspecified Type

307.47 Dyssomnia NOS

**Pamsomnias**

307.47 Nightmare Disorder

307.46 Sleep Terror Disorder

307.46 Sleepwalking Disorder

307.47 Parasomnia NOS

**SLEEP DISORDERS RELATED TO ANOTHER MENTAL DISORDER**

327.02 Insomnia Related to... [*Indicate the Axis I or Axis II Disorder*]

327.15 Hypersomnia Related to... [*Indicate the Axis I or Axis II Disorder*]

**OTHER SLEEP DISORDERS**

327.xx Sleep Disorder Due to... [*Indicate the General Medical Condition*]

.01 Insomnia Type

.14 Hypersomnia Type

.44 Parasomnia Type

.8 Mixed Type

—.— Substance-Induced Sleep Disorder (*refer to Substance-Related Disorders for substance-specific codes*)

*Specify type:* Insomnia Type/ Hypersomnia

Type/Parasomnia Type/ Mixed Type

*Specify if:* With Onset During Intoxication/With Onset During Withdrawal

**Impulse Control Disorders Not Elsewhere Classified**

312.34 Intermittent Explosive Disorder

312.32 Kleptomania

312.33 Pyromania

312.31 Pathological Gambling

312.39 Trichotillomania

312.30 Impulse Control Disorder NOS

**Adjustment Disorders**

309.xx Adjustment Disorder

.0 With Depressed Mood

.24 With Anxiety

.28 With Mixed Anxiety and Depressed Mood

.3 With Disturbance of Conduct

.4 With Mixed Disturbance of Emotions and Conduct

.9 Unspecified

*Specify if:* Acute/Chronic

**Personality Disorders**

Note: *These are coded on Axis II*

301.0 Paranoid Personality Disorder

301.20 Schizoid Personality Disorder

301.22 Schizotypal Personality Disorder

301.7 Antisocial Personality Disorder

301.83 Borderline Personality Disorder

301.50 Histrionic Personality Disorder

301.81 Narcissistic Personality Disorder

301.82 Avoidant Personality Disorder

301.6 Dependent Personality Disorder

301.4 Obsessive–Compulsive Personality Disorder

301.9 Personality Disorder NOS

**Other Conditions That May Be a Focus of Clinical Attention**

**PSYCHOLOGICAL FACTORS AFFECTING MEDICAL CONDITION**

316 ... [*Specified Psychological Factor*] Affecting... [*Indicate the General Medical Condition*]

*Choose name based on nature of factors:*

Mental Disorder Affecting Medical Condition

Psychological Symptoms Affecting Medical Condition

Personality Traits or Coping Style Affecting Medical Condition

Maladaptive Health Behaviors Affecting Medical Condition

Stress-Related Physiological Response Affecting Medical Condition

Other or Unspecified Psychological Factors Affecting Medical Condition

**MEDICATION-INDUCED MOVEMENT DISORDERS**

332.1 Neuroleptic-Induced Parkinsonism

333.92 Neuroleptic Malignant Syndrome

333.7 Neuroleptic-Induced Acute Dystonia

333.99 Neuroleptic-Induced Acute Akathisia

333.82 Neuroleptic-Induced Tardive Dyskinesia

333.1 Medication-Induced Postural Tremor

333.90 Medication-Induced Movement Disorder NOS

**OTHER MEDICATION-INDUCED DISORDER**

995.2 Adverse Effects of Medication NOS

**RELATIONAL PROBLEMS**

V61.9 Relational Problem Related to a Mental Disorder or General Medical Condition

V61.20 Parent-Child Relational Problem

V61.10 Partner Relational Problem

V61.8 Sibling Relational Problem

V62.81 Relational Problem NOS

**PROBLEMS RELATED TO ABUSE OR NEGLECT**

V61.21 Physical Abuse of Child *(code 995.54 if focus of attention is on victim)*

V61.21 Sexual Abuse of Child (*code 995.53 if focus of attention is on victim*)

V61.21 Neglect of Child (*code 995.52 if focus of attention is on victim*)

—.— Physical Abuse of Adult

V61.12 (if by partner)

V62.83 (if by person other than partner) (*code 995.83 if focus of attention is on victim*)

—.— Sexual Abuse of Adult

V61.12 (if by partner)

V62.83 (if by person other than partner) (*code 995.83 if focus of attention is on victim*)

**ADDITIONAL CONDITIONS THAT MAY BE A FOCUS OF CLINICAL ATTENTION**

VI5.81 Noncompliance With Treatment
V65.2 Malingering

V71.01 Adult Antisocial Behavior

V71.02 Child or Adolescent Antisocial Behavior

V62.89 Borderline Intellectual Functioning

Note: *This is coded on Axis II*

780.93 Age-Related Cognitive Decline

V62.82 Bereavement

V62.3 Academic Problem

V62.2 Occupational Problem

313.82 Identity Problem

V62.89 Religious or Spiritual Problem

V62.4 Acculturation Problem

V62.89 Phase of Life Problem

**ADDITIONAL CODES**

300.9 Unspecified Mental Disorder (nonpsychotic)

V71.09 No Diagnosis or Condition on Axis I

799.9 Diagnosis or Condition Deferred on Axis I

V71.09 No Diagnosis on Axis II

799.9 Diagnosis Deferred on Axis II

**MULTIAXIAL SYSTEM**

Axis I Clinical Disorders
Other Conditions That May Be a Focus of Clinical Attention

Axis II Personality Disorders Mental Retardation

Axis III General Medical Conditions

Axis IV Psychosocial and Environmental Problems

Axis V Global Assessment of Functioning

**Figure 40–3** *DSM-IV-TR Classification. Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Copyright 2000. American Psychiatric Association*

to 319.00; they are actually derived from the mental disorders section of a much larger coding system for all medical disorders that extends from 001 to 999. Clinicians working in the US are required to use ICD-9-CM in order to get reimbursement from both government agencies (e.g., Medicare and Medicaid) and private insurers. To insure that users of the DSM-IV are able to meet this requirement without doing any cumbersome code conversions, the DSM-IV contains the current ICD-9-CM codes. Because the ICD-9-CM codes are updated on a yearly basis (i.e., every October 1), the DSM-IV codes have to be similarly updated as changes to the codes in the ICD-9-CM mental disorder section occur. Although these changes have been relatively infrequent, they have necessitated some changes to the DSM-IV codes. When new printings of DSM-IV-TR are needed, the codes in these new printings are updated to reflect those codes that are in effect at the time of the printing. All coding updates are summarized on the DSM-IV-TR web site (www.dsm4tr.org).

## Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence

The classification begins with Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence. The provision of a separate section for so-called childhood disorders is for convenience only. Although most individuals with these disorders present for clinical attention during childhood or adolescence, it is not uncommon for some of these conditions to be diagnosed for the first time in adulthood (e.g., Attention-deficit/Hyperactivity Disorder). Moreover, many disorders included in other sections of the DSM-IV have an onset during childhood (e.g., Major Depressive Disorder). Thus, a clinician evaluating a child or adolescent should not only focus on those disorders listed in this section but also consider disorders from throughout the DSM-IV. Similarly, when evaluating an adult, the clinician should also consider the disorders in this section since many of them persist into adulthood (e.g., stuttering, learning disorders, tic disorders).

The first set of disorders included in this diagnostic class (Mental Retardation, Learning Disorders and Motor Skills Disorders, and Communication Disorders) are covered in detail in Chapters 48, Chapter 49, and Chapter 50, respectively in this book. While these are not strictly speaking regarded as mental disorders, they are included in the DSM-IV to facilitate differential diagnosis and to increase recognition of these conditions among mental health professionals. Autism and Other Pervasive Developmental Disorders are discussed in Chapter 51 of this book and are characterized by gross qualitative impairment in social relatedness, in language, and in repertoire of interests and activities. Disorders covered include Autistic Disorder, Asperger's Disorder, Rett's Disorder, and Childhood Disintegrative Disorder. Attention-deficit/Hyperactivity Disorder and Other Disruptive Behavior Disorders (Chapter 52) are grouped together because they are all characterized (at least in their childhood presentations) by disruptive behavior. Chapter 53 on Feeding Disorders includes the DSM-IV categories of Pica, Rumination Disorder, and Feeding Disorder of Infancy and Early Childhood (also known as "failure to thrive"). Tic Disorders (Chapter 54), Elimination and Childhood Anxiety Disorders (Chapter 55) and Stereotyped

Movement Disorder and Reactive Attachment Disorder (Chapter 56) conclude the childhood section.

## Delirium, Dementia, Amnestic Disorder, and Other Cognitive Disorders

In DSM-III-R, delirium, dementia, amnestic disorder, and other cognitive disorders were included in a section called "organic mental disorders," which contained disorders that were due to either a general medical condition or substance use. In DSM-IV, the term *organic* was eliminated because of the implication that disorders not included in that section (e.g., schizophrenia, bipolar disorder) do not have an organic component (Spitzer et al. 1992). In fact, virtually all mental disorders have both psychological and biological components, and to designate some disorders as organic and the remaining disorders as nonorganic reflected a reductionistic mind-body dualism that is at odds with our understanding of the multifactorial nature of the etiological underpinnings of disorders.

DSM-IV replaced each unitary organic mental disorder (e.g., organic mood disorder) with its two component parts (e.g., mood disorder due to a general medical condition and substance-induced mood disorder). Because of their central roles in the differential diagnosis of cognitive impairment, delirium, dementia, and amnestic disorder are contained within the same diagnostic class in DSM-IV and are discussed in Chapter 57 of this book.

Whereas both delirium and dementia are characterized by multiple cognitive impairments, delirium is distinguished by the presence of clouding of consciousness, which is manifested by an inability to appropriately maintain or shift attention. DSM-IV includes three types of delirium: delirium due to a general medical condition, substance-induced delirium, and delirium due to multiple etiologies.

Dementia is characterized by clinically significant cognitive impairment in memory that is accompanied by impairment in one or more other areas of cognitive functioning (e.g., language, executive functioning). DSM-IV includes several types of dementia based on etiology, including dementia of the Alzheimer's type, vascular dementia, a variety of dementias due to general medical and neurological conditions (e.g., human immunodeficiency virus infection, Parkinson's disease), substance-induced persisting dementia, and dementia due to multiple etiologies.

In contrast to dementia, amnestic disorder is characterized by clinically significant memory impairment occurring in the absence of other significant impairments in cognitive functioning. DSM-IV includes amnestic disorder due to a general medical condition and substance-induced persisting amnestic disease.

## Mental Disorders due to a General Medical Condition Not Elsewhere Classified

This diagnostic class includes all of the specific mental disorders due to a general medical condition, and is discussed in Chapter 58 of this book. In DSM-IV, most of the mental disorders due to a general medical condition have been distributed throughout the various diagnostic classes alongside their "nonorganic" counterparts in the classification. For example, mood disorder due to a general medical condition and substance-induced mood disorder are included in the mood disorders section of DSM-IV. Two specific types of mental disorder due to a general medical condition (i.e., Catatonic Disorder due to a General Medical Condition and Personality Change due to a General Medical Condition) are physically included in this diagnostic class.

## Substance-Related Disorders

The term *substance* in DSM-IV has a broader meaning than merely a drug of abuse. It also includes medication side effects and the consequences of toxin exposure. Two types of substance-related disorders are included in DSM-IV: substance use disorders (dependence and abuse), which describe the maladaptive nature of the pattern of substance use; and substance-induced disorders, which cover psychopathological processes caused by the direct effects of substances on the central nervous system. Criteria sets for Substance Dependence, Substance Abuse, Substance Intoxication, and Substance Withdrawal that apply across all drug classes are included before the substance-specific sections of DSM-IV A discussion of these so-called "generic" criteria is covered in Chapter 59 of this book. Detailed discussions of each of the DSM-IV drug classes is covered in the subsequent chapters of this book as follows: Alcohol-Related Disorders in Chapter 60, Caffeine-Related Disorders in Chapter 61, Cannabis-Related Disorders in Chapter 62, Cocaine-Related Disorders in Chapter 63, Phencycline-Related Disorders in Chapter 64, Hallucinogen-Related Disorders (including MDMA) in Chapter 65, Inhalant-Related Disorders in Chapter 66, Nicotine-Related Disorders in Chapter 67, Opioid-Related Disorders in Chapter 68, and Sedative, Hypnotic, or Anxiolytic-Related Disorders in Chapter 69.

## Schizophrenia and Other Psychotic Disorders

The title of this diagnostic class is potentially misleading for two reasons: (1) there are other disorders that have psychotic features there are not included in this diagnostic class (e.g., Mood Disorders with Psychotic Features, delirium) and (2) it may incorrectly imply that the other psychotic disorders included in this section are related in some way to Schizophrenia (which is only true for Schizophreniform Disorder and possibly Schizoaffective Disorder). Instead, what ties together all of the disorders in this diagnostic class is the presence of prominent psychotic symptoms. Included here Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Shared Psychotic Disorder, and Brief Psychotic Disorder, each of which is discussed in this book in varying detail in Chapter 70.

It should be noted that the definition of the term "psychosis" has been used in different ways historically and is not even used consistently across the various categories in the DSM-IV. The most restrictive definition of psychosis (used in Substance-Induced Psychotic Disorder) requires a break in reality testing such that the person has delusions or hallucinations with no insight in the fact that the delusions or hallucinations are caused by taking drugs. A somewhat less restrictive definition of psychosis (not used in DSM-IV but advocated by some members of the DSM-IV Psychotic Disorders Workgroup as more appropriate for Substance-induced psychosis) includes hallucinations or delusions even if the person has insight into their origin

(e.g., it would include an individual who was hallucinating after taking PCP even if he were aware that the hallucinations were due to the PCP). A much broader definition of psychosis (utilized in the definition of Schizophrenia, Schizophreniform, and Brief Psychotic Disorder) goes beyond delusions and hallucinations to include grossly disorganized speech and catatonic or grossly disorganized behavior as evidence for psychosis. Finally, the term psychosis was in the past used the most broadly to refer to any condition that caused serious functional impairment (e.g., "affective psychosis" is used in ICD-9 to refer to major mood disorders). This definition is not used at all in DSM-IV.

## Mood Disorders

This diagnostic class includes disorders in which the predominant disturbance is in the individual's mood. Although the term "mood" is broadly defined to include depression, euphoria, anger, and anxiety, the DSM-IV generally restricts mood disturbs to depressed, elevated, or irritable mood.

The mood disorders section begins with the criteria for mood episodes (major depressive episode, manic episode, hypomanic episode, mixed episode), which are the building blocks for the episodic mood disorders. The codable mood disorders come next and are divided in the depressive disorders (i.e., major depressive disorder and dysthymic disorder, described in this book in Chapter 71) and the bipolar disorders (i.e., bipolar I disorder, bipolar II disorder, and cyclothymic disorder, described in Chapter 72). Finally, the many specifiers that provide important treatment-relevant information close this section. Several so-called "subthreshold mood disorders" (i.e., they are characterized by depression but fall short of meeting the diagnostic criteria for either major depressive disorder or dysthymic disorder) are included in DSM-IV appendix B, for Criteria Sets and Axes Provided for Further Study. These include minor depressive disorder, brief recurrent depressive disorder, mixed anxiety depressive disorder, post-psychotic depressive disorder of schizophrenia (all briefly described in Chapter 71), and premenstrual dysphoric disorder (described in detail in Chapter 73).

## Anxiety Disorders

The common element joining these disparate categories together is the fact the anxiety is a prominent part of their clinical presentation. This grouping has been criticized because of evidence suggesting that at least some of the disorders are likely to be etiologically distinct from the others. Most particularly, obsessive–compulsive disorder and posttraumatic stress disorder seem to share little in common with the other anxiety disorders. In fact, a separate diagnostic classes for Stress-Related Disorders (that would also include Adjustment Disorders and perhaps Dissociative Disorders) and for Obsessive–Compulsive Spectrum Disorders (which might also include trichotillomania, tic disorders, hypochondriais, body dysmorphic disorder and other disorders characterized by compulsive behavior) have been proposed.

Detailed discussions of the various anxiety disorders are covered in several chapters in this section of this book: Panic Disorder With and Without Agoraphobia in Chapter 74, Social and Specific Phobias in Chapter 75, Obsessive–Compulsive Disorder in Chapter 76, Posttraumatic Stress Disorder and Acute Stress Disorder in Chapter 77, and Generalized Anxiety Disorder in Chapter 78.

## Somatoform Disorders

This diagnostic class includes disorders in which the defining feature is a physical complaint or bodily concern that is not better accounted for by a general medical condition or another mental disorder. These disorders (which are discussed in this book in detail in Chapter 79) can be divided into three groups based on the focus of the individual's concerns: (1) focus on the physical symptoms themselves (Somatization Disorder, Undifferentiated Somatoform Disorder, Pain Disorder, and Conversion Disorder, (2) focus on the belief that one has a serious physical illness (Hypochondriasis), and (3) focus on the belief that one has a defect in physical appearance (Body Dysmorphic Disorder).

## Factitious Disorders

This diagnostic class contains only one disorder: Factitious Disorder, which describes presentations in which the individual intentionally produces or feigns physical or psychological symptom in order to fulfill a psychological need to assume the sick role. It is discussed in detail in Chapter 80 of this book. Factitious Disorder should always be distinguished from malingering, in which the individual is also pretending to have physical or psychological symptoms. The difference is that in malingering, the person's motivation is to achieve some external gain (e.g., disability benefits, lessening of criminal responsibility, shelter for the night). For this reason, unlike Factitious Disorder, malingering is not considered a mental disorder.

## Dissociative Disorders

The common element to this group of disorders is the symptom of dissociation, which is defined as a disruption in the usually integrated functions of consciousness, memory, identity, and perception. Four specific disorders are included (Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder, and Depersonalization Disorder) and are discussed in this book in detail in Chapter 81.

## Sexual and Gender Identity Disorders

This diagnostic class contains three relatively disparate types of disorders, linked together only by virtual of their involvement in human sexuality. Sexual Dysfunctions refer to disturbances in sexual desire or functioning, Paraphilias refer to unusual sexual preferences that interfere with functioning (or in the case of preferences that involve harm to others like Pedophilia, merely acting on those preferences), and Gender Identity Diosrder refers to a serious conflict between one's internal identity of maleness or femaleness (gender identity) and one's anatomical sexual characteristics. These categories are discussed in this book in detail in Chapter 82.

## Eating Disorders

Although the name of this diagnostic class focuses on the fact that this disorders in this section are characterized by abnormal eating behavior (refusal to maintain adequate body weight in the case of Anorexia Nervosa and discrete episodes of uncontrolled eating of excessively large amounts of food in the case of Bulimia Nervosa), of near

equal importance is the individual's pathological overemphasis on body image. A third category, which is being actively researched but has not been officially added to the DSM-IV is binge eating disorder (i.e., it is included in the appendix of criteria sets and axes provided for further study). Like Bulimia Nervosa, individuals with binge eating disorder have frequent episodes of binge eating. However, unlike Bulimia Nervosa, these individuals do not do anything significant to counteract the effects of their binge eating (i.e., they do not purge, use laxatives or diet pills or excessively exercise). All three disorders are described in this book in Chapter 83.

## Sleep Disorders

Sleep disorders are grouped into four sections on the basis of presumed etiology (primary, related to another mental disorder, due to a general medical condition, and substance induced). Two types of primary sleep disorders are included in DSM-IV: dyssomnias (problems in regulation of amount and quality of sleep) and parasomnias (events that occur during sleep). The dyssomnias include Primary insomnia, Primary hypersomnia, Circadian rhythm sleep disorder, Narcolepsy, and Breathing-related sleep disorder, whereas the parasomnias include Nightmare disorder, Sleep terror disorder, and Sleepwalking disorder. Sleep Disorders are described in detail in this book in Chapter 84.

## Impulse-Control Disorders Not Elsewhere Classified

As is suggested by the title of this diagnostic grouping, no one diagnostic class in DSM-IV comprehensively includes all of the impulse control disorders. A number of disorders characterized by impulse control problems are classified elsewhere (e.g., Conduct Disorder, Attention-deficit/Hyperactivity Disorder, Oppositional-defiant Disorder, Delirium, Dementia, Substance-Related Disorders, Schizophrenia and Other Psychotic Disorders, Mood Disorders, Antisocial and Borderline Personality Disorders). What ties together the disorders in this class is that they present with clinically significant impulsive behavior and that they are not better accounted for by one of the mental disorders included in other parts of DSM-IV. Five such disorders are included here: Intermittent Explosive Disorder, Pathological gambling, Pyromania, Kleptomania, and Trichotillomania. These are discussed in this book in Chapter 85.

## Adjustment Disorders

All DSM-IV categories (except Not Otherwise Specified (NOS) categories) take priority over adjustment disorder. This category is intended to apply to maladaptive reactions to psychosocial stressors that do not meet the criteria for any specific DSM-IV disorder. These are discussed in Chapter 86 of this book.

## Personality Disorders

This diagnostic class is for personality patterns that significantly deviate from the expectations of the person's culture, are pervasive, and lead to significant impairment or distress. Ten specific personality disorders are included in DSM-IV: Paranoid personality disorder (pervasive distrust and suspiciousness of others), Schizoid personality disorder (detachment from social relationships and a restricted expression of emotions), Schizotypal personality disorder (acute discomfort with close relationships, perceptual distortions, and eccentricities of behavior), Antisocial personality disorder (disregard for the rights of others), Borderline personality disorder (instability of personal relationships, instability of self-image, and marked impulsivity), Histrionic personality disorder (extensive emotionality and attention seeking), Narcissistic personality disorder (grandiosity, need for admiration, and lack of empathy), Avoidant personality disorder (social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation), Dependent personality disorder (excessive need to be taken care of), and Obsessive–compulsive personality disorder (preoccupation with orderliness, perfectionism, and mental and personal control at the expense of flexibility, openness, and efficiency). These are discussed in detail in this book in Chapter 87.

## Other Conditions That May Be a Focus of Clinical Attention

This section of DSM-IV is for problems that are not mental disorders but that may be a focus of attention or treatment by a mental health professional. *Psychological factors affecting medical condition* is intended to allow the psychiatrist to note the presence of psychological factors (e.g., Axis I or II disorder) that are adversely affecting the course of a general medical condition, including factors that interfere with treatment and factors that constitute health risks to the individual. (This condition is described in Chapter 88 of this book). Six specific *medication-induced movement disorders* (discussed in this book in Chapter 89) are also included because of their importance in treatment and differential diagnosis; five are related to neuroleptic administration, and one (medication-induced postural tremor) is most often associated with the use of lithium carbonate. Although these are best considered medical conditions, by DSM-IV convention they are coded on Axis I.

**Table 40–4 Criteria Sets and Axes Provided for Further Study**

| |
|---|
| Postconcussional disorder |
| Mild cognitive disorder |
| Caffeine withdrawal |
| Postpsychotic depression of schizophrenia |
| Simple deteriorative disorder |
| Minor depressive disorder |
| Recurrent brief depressive disorder |
| Premenstrual dysphoric disorder |
| Mixed anxiety-depressive disorder |
| Factitious disorder by proxy |
| Dissociative trance disorder |
| Binge-eating disorder |
| Depressive personality disorder |
| Passive-aggressive personality disorder (negativistic personality disorder) |
| Defensive Functioning Scale |
| Global Assessment of Relational Functioning Scale |
| Social and Occupational Functioning Assessment Scale |

*Source*: American Psychiatric Association (2000).

Relational problems (discussed in this book in Chapter 90) include parent-child, partner, and sibling relational problems. Relational problem related to a mental disorder or general medical condition applies to situations in which one member of the relational unit has a mental disorder or a general medical condition. In such situations, the relational dynamics can negatively affect the individual's condition or vice versa (or both). *Problems related to abuse or neglect* (physical abuse, sexual abuse, and child neglect) have been introduced into DSM-IV because of the clinical and public health significance of these conditions.

## Appendix Categories

DSM-IV aims to be on the trailing edge rather than the cutting edge of research (Pincus et al. 1992). New categories were considered for inclusion only if there was a substantial research literature behind them. Although there were proposals for more than 100 new categories to be introduced into DSM-IV, only a handful of new categories were added. Text and criteria for another 17 proposed categories have been included in a DSM-IV appendix, Criteria Sets and Axes Provided for Further Study (Table 40–4). These criteria sets have been included to provide a common language for researchers and psychiatrists who are interested in further investigating their potential utility and validity.

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CHAPTER

# 41 Diagnostic Classification in Infancy and Early Childhood

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Infancy and early childhood is characterized by dynamic relationships between the different dimensions of human development, including emotional, social, language, cognitive, regulatory–sensory processing, and motor capacities. No classification system currently exists that describes challenges in each of these areas of functioning and the relationships between them. A dynamic, developmental, and multiaxial approach that includes all the relevant dimensions of human development is especially vital during these formative years when not only are the brain and mind growing more rapidly, than they ever will again, but they are literally forming the relationships between its different components. Attending to these interconnected components is essential in classifying disorders as the basis for meaningful intervention planning and research.

The new Interdisciplinary Council on Developmental and Learning Disorders Diagnostic Manual for Infants and young Children (ICDL-DMIC) utilizes a comprehensive approach which includes interactive, neurodevelopmental, regulatory-sensory processing, language, and learning disorders (Interdisciplinary Council on Developmental and Learning Disorders 2005). It emphasizes the multiple relationships between different areas of development and can identify those infants and young children who present with a specific type of problem but often have challenges in other areas of functioning. For example, a preschooler with an impulse control problem will often have challenges in terms of caregiver/child-interaction patterns and different aspects of sensory processing, language, and cognition. Similarly, children with language problems may also often evidence contributions from challenges in motor planning and sequencing and other aspects of sensory processing. Challenges in any area can derail healthy emotional development and relationships.

The ICDL-DMIC introduces the concept of the developmental pathways which guides understanding of why particular symptoms develop related to the way the child reacts to and comprehends different sensations and plans actions (an expression of his or her biological patterns), the ways in which the caregiving environment interacts with these individual differences (within the normative range of individual differences, but not at the level of a disorder), and the levels or stages of emotional and intellectual organization that are negotiated through these interactions. These interrelated elements constitute the Developmental, Individual Difference, Relationship-based (DIR) model (Greenspan and Wieder 1997). ICDL-DMIC was conceptualized over a thirty year period, beginning with the research conducted at the Clinical Infant Development program (by The National Institute of Mental Health (NIMH) which is a part of the National Institutes of Health (NIH); a component of the U.S. Department of Health and Human Services) when leading infant researchers (Reginald Lourie, Selma Fraiberg, T. Berry Brazelton, Julius Richmond, Ed Ziegler, Katherine Barnard, and many others) met to formulate the critical factors essential for infant metal health. This led to the Task Force at Zero to Three (National Center for Clinical Infant Programs 1994), The National Center for Infants, Toddlers, and Families, which developed the first Diagnostic Classification (DC 0–3), chaired by Greenspan and Wieder, and then to the Interdisciplinary Council on Developmental and Learning Disorders

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(ICDL) Task Force, which formulated the ICDL-DMIC in 2005.

The ICDL Task Force expanded the classification system to include language and learning disorders, and a new developmentally based framework for regulatory–sensory processing disorders (RSPD) and neurodevelopmental disorders of relating and communicating (NDRC) (autism spectrum disorders, multisystem developmental disorders, etc.) to provide a comprehensive and systematic method for presenting a rich, detailed clinical picture of each infant or young child and his or her family along with a framework for systematically organizing these rich descriptions into clinically meaningful categories. Thus, the goal of the ICDL-DMIC is to formulate a truly clinically useful approach that will facilitate research into etiological factors and inform effective intervention approaches that are tailored to the unique developmental profiles of each child and family.

## An Interdisciplinary Approach to Classification

This classification system integrates all components of development and functioning which have been traditionally addressed by different disciplines. It is designed for professionals credentialed to do diagnoses. It can also be used by all disciplines as a roadmap to understanding the interactions between the different components of the child's development, their family, and environment in order to guide assessments and interventions. It augments other existing diagnostic systems such as ICD-10, DSM IV-TR, and DC: 0-3R. For the reason that the ICDL-DMIC is an interdisciplinary tool that supports the integration of knowledge from different disciplines, it will, for example, guide the mental health professional to integrate what has been learned about development, regulatory–sensory processing, language, visuospatial, and learning capacities into their mental health expertise. Similarly, the ICDL-DMIC will help pediatricians, occupational, physical, and speech and language therapists, educators, and professionals from other disciplines in their ability to integrate their understanding of the impact of emotional development, interactive disorders, and family and environmental factors on adequate, constricted or disordered functioning.

## The Need for a Comprehensive Multidimensional Developmental Approach

The need for a developmentally-based classification system in infant and early childhood mental health that includes neurodevelopmental, regulatory–sensory processing, language, and learning disorders is based on a number of challenges that now face clinicians and researchers working with infants, young children, and their families.

Symptom-based diagnostic approaches which rely on lists of categorical symptoms that are readily observable are used in the belief that they facilitate reliable judgments. The symptom-based approach, however, has not demonstrated the clinical validity, including predicting clinical course or informing clinical practice, to the degree hoped for. For many diagnoses, the reliability among practicing clinicians making the diagnosis has also been disappointing (Buruma 2005).

The most significant weakness in the symptom-based approach has been the confusion it has brought regarding the boundaries between disorders and the usefulness of the diagnostic categories for planning optimal treatment approaches. The degree to which many conditions evidence comorbidity with other conditions illustrates the problem with a symptom-based approach that is not sufficiently grounded in an understanding of etiological factors or the developmental pathways leading to disordered functioning. For example, often the symptom-based approaches have designated diagnostic categories, including boundaries between conditions, based simply on the consensus of experts, including decisions about how many of the symptoms are necessary for the diagnosis (e.g., three out of five, rather than two out of five). Yet there are insufficient studies documenting what it means if the patient meets only two out of five (i.e., there is no data supporting a clear line between having two items versus having three items of the criteria set). Therefore, most evidence points to a dimensional approach where symptoms or disorders may be expressed in varying degrees (i.e., shades of gray) rather than clear "you have it or you don't." Many difficulties exist in terms of degrees of challenge, rather than with clear boundaries.

The length of time symptoms need to be manifested for a disorder to be diagnosed is another example of overspecificity, that is symptoms must be present for at least X number of weeks. Again, there is insufficient data on the implications of a patient evidencing it two days less than the indicated two weeks. Most importantly, studies of prognosis and predictive validity are hampered by not controlling for the appropriateness of the treatment program the patient is receiving. For example, most children with autism are believed to continue to evidence the symptoms of the disorder five to eight years in the future. But how many of these children were in inappropriate or inadequate treatment programs? Prognosis with an optimal treatment program is not yet definitively known, due to the lack of comparative clinical trials of the most promising approaches and lack of a sufficient number of long-term naturalistic studies (Committee on Educational Interventions for Children with Autism for National Research Council 2001).

Reliability studies are also fraught with problems. Criteria that are easy to agree on are not necessarily the criteria that are meaningful for clinical planning or research on etiological factors and developmental pathways. In general, there is a healthy tension between the goal of capturing the true complexity of multifaceted clinical phenomena and developing criteria that can be reliably judged and employed in research. It is vital to embrace this healthy tension and pursue a stepwise approach where complexity and clinical usefulness is a cornerstone for efforts at increasingly systematic operational definitions and research on reliability and clinical validity. A scientifically based system is one that recognizes a stepwise progression that begins with accurate recognition and description of complex clinical phenomena and builds gradually through a series of steps toward empirical validation. Recognizing this will enable us to climb the steps of science without skipping over any important ones. If we sacrifice meaningful categorization for quick reliability, we will wind up with a system fraught with problems. Diagnostic agreement does not imply clinical validity. Therefore, the next goal is to improve our conceptual framework by deepening and broadening it. At present, it is important to acknowledge that we do not yet have an

empirically validated diagnostic system for mental health, developmental, and learning disorders of infancy and early childhood. We do have emerging data and a great deal of clinical experience. Therefore, an accurate statement of the field is that it is currently operating on expert consensus with supportive, but incomplete data.

## Multidimensional Classification Based on the DIR Model

As indicated, dimensional approaches tend to be based on an implicit understanding that most mental health and developmental disorders are based on complex dynamic, developmental processes. We have formulated a developmental, biopsychosocial model to describe the processes that contribute to mental health, development, regulatory-sensory processing, language, and learning disorders in infancy and early childhood—DIR approach. The DIR approach focuses on Developmental capacities (D)—the level of emotional, social, and intellectual functioning (technically called functional emotional developmental capacities). It also focuses on biologically based Individual processing differences (I) in the way an infant or young child reacts to and comprehends different sensations, such as auditory, visuospatial, or tactile, as well as the way in which the child plans, sequences, and executes actions. It also focuses on the Relationships (R), including child/caregiver/family and other relationship patterns.

## Unique Features of the ICDL-DMIC Multiaxial System

Comprehensiveness and systematization guided the ICDL work groups in creating this manual. Only a diagnostic system that describes the full complexity of disordered functioning and characterizes different subtypes can provide a basis for basic research on underlying etiologies and developmental pathways. A number of unique features operationalize this perspective. For example, each of the primary disorders classified under the heading "Interactive Disorders" is described in terms of its clinical phenomena, presenting symptoms, developmental pathways, and therapeutic implications. In addition, each disorder is described along a number of axes, which attempts to capture and emphasize an important component of, and/or contributor to, the disorder. These include the infant's or young child's level of emotional and social functioning, child-caregiver and family interaction patterns, motor planning and processing differences (regulatory sensory processing profile), language functioning, visuospatial capacities, and unique stressors that may be affecting the child and his or her family. Each Axis is briefly described below and summarized in Figure 41–1.

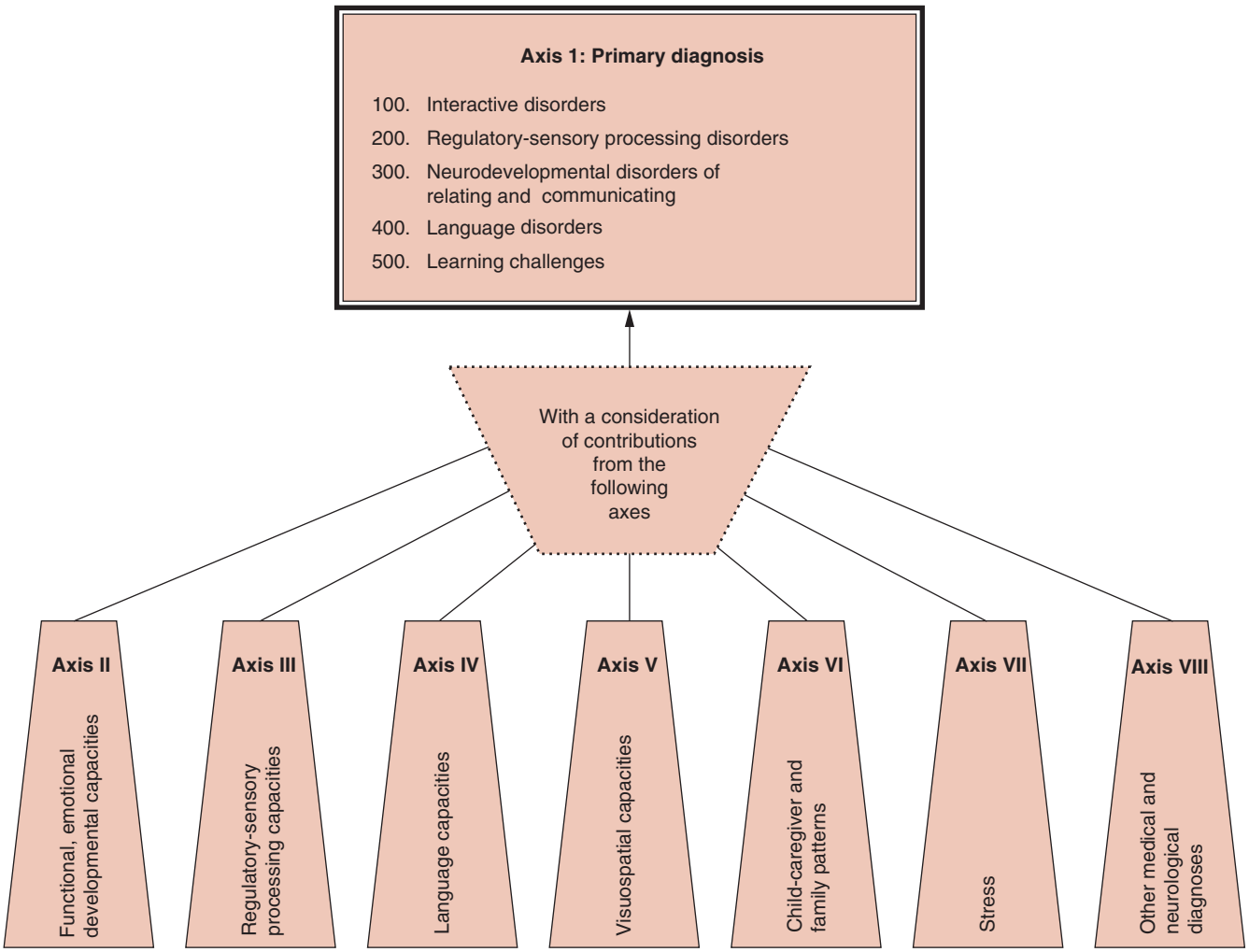



**Figure 41–1** *Diagram of multiaxial approach.*

### Axis I: Primary Diagnosis
The broad diagnostic category—Interactive Disorder, RSPD, Neurodevelopmental Disorder of Relating and Communicating, Language Disorder, and/or Learning Challenges—and the specific type of disorder within the category.

### Axis II: Functional Emotional Developmental Capacities
The relative mastery of each of the functional emotional developmental capacities, including shared attention and regulation, engagement and relating, two-way intentional, affective signaling and communication, long chains of coregulated emotional signaling and shared social problem solving, creating symbols or ideas, building bridges between ideas-logical thinking.

### Axis III: Regulatory-Sensory Processing Capacities
The regulatory–sensory processing capacities, in terms of self-regulation, sensory modulation, sensory discrimination, and sensory-based motor abilities, including postural control and motor planning

### Axis IV: Language Capacities
Includes gestural and verbal communication (comprehension and production) at each developmental level

### Axis V: Visuospatial Capacities
The progressive development of visuospatial aspects of body awareness and sense thinking, location of the body in space, relation of objects to the self and other objects and people, conservation of space, visual logical thinking, and representational thought

### Axis VI: Child-Caregiver and Family Patterns
Characteristics of infant or child-caregiver interaction patter ns and family or environmental patterns

### Axis VII: Stress
Stressors related to situations, conditions or events in the family's or child's life which can impact the child's emotional functioning and development when appropriate protective factors or adequate resiliency is not evident

### Axis VIII: Other Medical and Neurological Diagnoses

## Selecting a Primary Diagnosis
Most infant and early childhood disorders are characterized by multiple elements or dimensions, for example, interactive and family patterns, and regulatory–sensory processing patterns. These disorders include anxiety and mood disorders, disruptive behavior, elective mutism, as well as sleep, eating, and elimination disorders. A multiaxial approach will allow a systematic description of each of the contributing elements. Before concluding on a primary diagnosis, all the axes must be fully evaluated in order to determine the various dimensions contributing to the presenting problems. Once all this information is considered, clinical reasoning will guide the experienced clinician in selecting the predominant pattern and identifying how the developmental pathway contributes to the symptom choice.

The decision process would first consider *the most comprehensive* disorder where multiple elements of development are derailed. For example, NDRC includes RSPD, Language Disorder, and emotional constrictions. When relating and communicating are not significantly derailed then the RSPD are considered next to see if the presenting behavioral patterns are coupled with motor and/or regulatory–sensory processing challenges. When a regulatory–sensory processing contribution is significant, it will take precedence over the interactive elements in the designation of the primary diagnosis. If interactive challenges dominate, it becomes the primary disorder.

With Interactive Disorders there is so much overlap in symptoms, the clinician must consider when the symptom is part of a broader disorder such as anxiety, mood or disruptive behavior, and when it is itself the primary disorder. For example, if a child with Anxiety Disorder also has sleep problems, but the sleep problem is intermittent or a temporary disruption of a developmental capacity already mastered, along with possible other disruptions in eating or toileting, then an additional diagnosis would not be necessary. However, if the sleep problem is very intense or of longer duration, and also meets the description of the primary disorder, then it could be considered a second primary diagnosis. Similarly, if a child manifests disruptive or oppositional behavior, Anxiety Disorder or Disruptive Behavior Problem could be considered and the differentiating consideration would be whether the child has a pattern of impulse control problems in various situations or emotional states. If not, then Anxiety Disorder may be the only primary diagnosis selected. More than one diagnosis is permitted under this system. In addition, as indicated earlier, we emphasize a Language Disorder or Learning Challenge can be used as a second primary diagnosis when a child evidences a significant difficulty in either of these areas of functioning. In other words, clinical reasoning must determine if the multiple symptoms are significant enough to constitute an additional diagnosis or are part of the primary problem.

## Clinical Thresholds for Diagnosis
Deciding when a behavioral or emotional pattern constitutes a disorder rather than a disruption or variation within the normal range presents the clinician with a challenge. This can be especially difficult during the first five years when development is proceeding rapidly and has so much variation influenced by individual differences. It is also a challenge when so many of the same symptoms can relate to different disorders given the limited number of symptoms in the infant's and young child's repertoire.

Since we are currently operating on expert consensus with supportive, but incomplete, data, this classification system utilizes *functional or operational considerations* to make the clinical judgment of whether the presenting problems cross the clinical threshold to be considered a disorder. The following hierarchy should be considered:

- Is the child functioning within his or her age-expected functional developmental capacities? What is the range of the child's comprehension and expression of emotions with gestures and/or words or play, in comparison to age expectations? See Axis II (Functional Emotional

Developmental Capacities) as well as the other clinical assessments.

- How well is the child functioning within the family structure on a daily basis including routines of sleep, meals, play, relating to family, caregivers and sibling interactions? Is the environment stable? Is the child stable?
- Is the child adapting to daycare or preschool adequately and able to enjoy these environments and learning experiences?
- Is the child participating in expected social interactions, developing friendships, and able to play with peers?
- What are the child's emerging attitudes and feelings toward him or herself and others (e.g., angry, depressed, suspicious, etc.) in comparison to what is expected for his or her age (e.g., some degree of negativism is expected during the preschool years)?

The child may present significant challenges in any one of these areas which may be sufficient to warrant a diagnosis such as difficulties in relating and communicating. In some cases, more than one area may be involved but the problem may not be spilling over significantly to preschool or peer play, such as a disorder of emotional range and stability where constrictions are significant and family interactions cannot support healthier emotional development. Sometimes, the threshold is not crossed until the preschool brings the problem to the attention of the family—the problem may not be perceived or evidenced at home, yet is significantly impeding the child's adaptation at school. The greater the number of areas of functioning that are involved, the more likely a diagnosis is indicated.

Furthermore, in addition to the detailed descriptions of the primary diagnosis (Axis I) to guide clinical judgment, Axes II through VII require a clinical formulation indicating the degree to which impairment is evident. The more severe the impairment or delay of the expected developmental capacities, the greater the evidence for the disorder(s). Clinical judgment relies on evaluating the functional or operating areas and each of the dimensions in this multiaxial system to determine if the clinical threshold for a diagnosis has been crossed.

Even when the clinical threshold is not crossed, the diagnostic process and evaluation provides the parent with a better understanding of their child's profile of strengths and vulnerabilities and allow anticipatory guidance to better support the development of the child and family in the future.

## Axis I: Primary Diagnosis

Interactive disorders are characterized by the way a child perceives and experiences his emotional world and/or by a particular maladaptive child-caregiver interaction pattern (Greenspan 1992). The caregiver's personality, fantasies and intentions; the child's emerging organization of experience; and the way these come together through child-caregiver interactions are important components of the basis for understanding the nature of the difficulty and for devising an effective intervention plan. As with all infant and early childhood disorders, it is also important to consider the child's constitutional-maturational variations, and family and environmental factors (Axes VI and VII). Although each child has a unique regulatory–sensory processing profile, constitutional-maturational variations are not a major contributing factor in interactive disorders, as they are in the category of RSPD.

**100. Interactive Disorders**[1]
*101. Anxiety Disorders*
*102. Developmental Anxiety Disorder*
*103. Disorder of Emotional Range and Stability*
*104. Disruptive Behavior and Oppositional Disorder*
*105. Depression*
*106. Mood Dysregulation-Bipolar Patterns*
*107. Attentional Disorder*
*108. Prolonged Grief Reaction*
*109. Reactive Attachment Disorder*
*110. Traumatic Stress Disorder*
*111. Adjustment Disorders*
*112. Gender Identity Disorder*
*113. Elective Mutism*
*114. Sleep Disorder*
*115. Eating Disorder*
*116. Elimination Disorder*

The evaluating clinician must also consider the interaction patterns characteristic of each of the six developmental levels and determine which patterns have been negotiated successfully and which are absent or constricted. These are captured in Axis II. Regardless of the symptom, the goal of treatment is not only to alleviate it, but also to facilitate the child's progress toward an age-appropriate developmental level and toward an age-appropriate degree of stability and range of thematic experience.

Symptoms that can reflect an interactive disorder include anxiety, fears, behavior control problems, and sleeping and eating problems. The same symptoms can be reflective of any number of diagnoses. This is understandable in light of the limited number of behaviors or limited expression of feelings infants and young children are capable of. This category also includes transient situational adjustment reactions, such as a child's response to his mother's return to work. It also includes certain reactions to trauma in which the response does not involve multiple aspects of development.

The abbreviated version of the primary disorder "101. Anxiety Disorder" illustrates the ICDL-DMIC approach to Axis I. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail regarding the other primary disorders in Axis I.

### 101. Anxiety Disorder

Infants and young children may evidence persistent levels of anxiety and fear which impede age-expected ranges

[1]The Work Group on Interactive Disorders includes: Serena Wieder, Ph.D., Lois Black, Ph.D., Griffin Doyle, Ph.D., Barbara Dunbar, Ph.D., Barbara Kalmanson, Ph.D., Lori Jeanne Peloquin, Ph.D., Ricki Robinson, M.D., MPH., Ruby Salazar, LCSW, Rick Solomon, M.D., Rosemary White, OTR, Molly Romer Witten, Ph.D.

of emotions and functioning. In infants and very young preverbal children anxiety is of a more generalized nature, in which symptoms such as excessive fearfulness, tantrums, agitation, avoidance, panic reactions, and worries are in evidence on a persistent basis even when the child is not threatened by separation from a primary caregiver. In the older child anxiety can take the form of specific fears or verbalized worries, obsessions or preoccupations, excessive tantrums, distress and agitation, and avoidance or counterphobic behaviors. The child may talk about his or her fears but not respond to reassurances, or may have a freeze, fight or flight reaction and is clearly distressed and fearful and cannot carry on usual routines and activities without significant disruptions during the day or night. At all ages, hypervigilant behavior can be an indicator of an anxiety disorder, and has been observed even in very young infants (3 to 4 months of age). The child may appear frightened, overly reactive, and overly focused, as though there were imminent danger. Infants who are abused may show this reaction quite early in their development, although it can manifest itself at any time.

For any form of anxiety, consider the following potential sources. First, is the anxiety primarily related to a RSPD (see 200. RSPD) Second, is the anxiety primarily related to expected developmental transitions or tasks the child is having difficulty mastering? Third, is the anxiety primary related to infant-caregiver interactions? The primary source of the anxiety may not always be clear.

Interactive elements are evident in situations where the primary caregiver *is not providing ongoing personal security* and may be unable to alleviate the anxiety through such strategies as helping the child anticipate what might be causing the anxiety, problem solving conversations, practice in pretend play, preparing the child for what will occur; and soothing, and reassuring the child sufficiently if the anxiety increases. The caregiver may also be anxious and distressed and anticipate the child's anxiety and feel ill equipped to help, or feel annoyed, or overly worried. He or she may also be bringing his or her own anxieties to the situation at hand, such as social inhibition, or a specific phobia such as fear of dogs, or over- identifying with the child who reminds him or her of similar childhood experiences. In either case, the interaction between the child and caregiver increases the anxiety and distress and makes it difficult to support the child.

**The Developmental Pathway:** A particular type of infant-caregiver interaction combined with a particular regulatory–sensory processing profile often results in the child evidencing excessive anxiety. Individuals prone to anxiety tend to be over-reactive to sensations like sound and touch and to experience and express affect intensely. The caregiver then overreacts to the child's emotional communications. As a consequence, the child feels overwhelmed and dysregulated. The anxious child constantly feels overwhelmed and experiences dysphoric or unpleasant affects associated with being overwhelmed (as opposed to loss or rupture in the relationship as the depressed child might experience).

**Therapeutic Implications:** The child prone to anxiety require long chains of especially soothing, reciprocal emotional interactions; therapy needs to focus on use of affects as a *symbolic signal* to cope and not escalate or panic, on expectations that relationships will intrude or overwhelm. Along with verbal awareness of his affective and interactional patterns as well as symbolic elaboration in play and conversation, the anxiety-prone individual needs to experience new ways of engaging in interactive, affective exchanges and signaling.

RSPD, involving symptom patterns such as inattention, over-reactivity, and sensory seeking, and refer to those challenges where differences in the child's constitutional and maturational variations, in terms of sensory over- or under-reactivity, visuospatial, auditory and language processing, or motor planning and sequencing difficulties are a primary contributor to the child's challenges.

**200. Regulatory-Sensory Processing Disorder (RSPD)[2]**

***Sensory Modulation Challenges (Type I)***

*201. Over-Responsive, Fearful, Anxious Pattern*
*202. Over-Responsive, Negative, an Stubborn Pattern*
*203. Under-Responsive, Self-Absorbed Pattern*
- *203.1 Self-Absorbed and Difficult to Engage Type*
- *203.2 Self-Absorbed and Creative Type*

*204. Active, Sensory Seeking Pattern*

***Sensory Discrimination Challenges (Type II) and Sensory-Based Motor Challenges (Type III)***

*205. Inattentive, Disorganized Pattern*
- *205.1 With Sensory Discrimination Challenges*
- *205.2 With Postural Control Challenges*
- *205.3 With Dyspraxia*
- *205.4 With Combinations of 205.1-205.3*

*206. Compromised School and/or Academic Performance Pattern*
- *206.1 With Sensory Discrimination Challenges*
- *206.2 With Postural Control Challenges*
- *206.3 With Dyspraxia*
- *206.4 With Combinations of 206.2-206.3*

***Contributing Sensory Discrimination and Sensory-Based Motor Challenges***

*207. Mixed Regulatory-Sensory Processing Patterns*
- *207.1 Attentional Problems*
- *207.2 Disruptive Behavioral Problems*
- *207.3 Sleep Problems*
- *207.4 Eating Problems*
- *207.5 Elimination Problems*
- *207.6 Elective Mutism*
- *207.7 Mood Dysregulation, including Bipolar Patterns*
- *207.8 Other Emotional and Behavioral Problems Related to Mixed Regulatory-Sensory Processing Difficulties*
- *207.9 Mixed Regulatory-Sensory Processing Difficulties where Behavioral or Emotional Problems Are Not Yet in Evidence*

[2]Work Group members include: Lucy J. Miller, Ph.D., OTR, Marie Anzalone, Sc.D., OTR, Sharon A. Cermak, Ed.D., OTR/L, Shelly J. Lane, Ph.D., OTR, Beth Osten, M.S., OTR/L, Serena Wieder, Ph.D., Stanley I. Greenspan, M.D.

All children evidence their own unique regulatory–sensory processing patterns. These variations are important to consider when constructing a developmental profile for a specific infant or child and his or her family. RSPD, however, should be considered when the child's motor and sensory differences are contributing to challenges that interfere with age-expected emotional, social, language, cognitive (including attention), motor, or sensory functioning, RSPD gives rise to some of the same symptoms and behaviors as interactive disorders, including nightmares, withdrawal, aggressiveness, fearfulness and anxiety, sleeping and eating disturbances, and difficulty in peer relationships. However, RSPD involves clearly identifiable constitutional–maturational factors in the child.

The diagnosis of RSPD involves a distinct behavioral pattern *and* a sensory modulation, sensory–motor, sensory discrimination or attentional processing difficulty. When both a behavioral and a sensory pattern are not present, other diagnoses may be more appropriate. For example, an infant who is irritable and withdrawn after being abandoned may be evidencing an expectable type of relationship or attachment difficulty. An infant who is irritable and overly responsive to routine interpersonal experiences, in the absence of a clearly identified sensory, sensory–motor or processing difficulty, may have an anxiety or mood disorder. Sleep and eating difficulties, in the absence of identifiable sensory responsivity or sensory processing differences, are classified as disorders in their own right. Further evaluation is then needed to determine whether the cause is an interactive disorder or some other underlying problem that does not fall within our three broad categories. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

## Type I: Sensory Modulation Challenges

Sensory Modulation Challenges (such as over-responsivity, under-responsivity, and sensory-seeking) are characterized by an inability to grade the degree, intensity, and nature of responses to sensory input. Often the child's responses do not fit the demands of the situation. The child therefore demonstrates difficulty achieving and maintaining an optimal range of performance and adapting to challenges in daily life.

## Type II: Sensory Discrimination Challenges

Sensory Discrimination Challenges are problems discerning the characteristics of sensory stimuli. The result is a lessened capability to interpret or give meaning to the specific qualities of stimuli, to detect similarities and differences among stimuli, and to differentiate the temporal and/or spatial qualities of stimuli. Children can perceive that stimuli are present and can modulate their responses to the stimuli, but cannot tell precisely what or where the stimulus is. Children with this challenge have difficulty interpreting the spatial and temporal qualities of sensory input and, as such, cannot use time and space information or other specific characteristics of the sensory experience to guide performance.

## Type III: Sensory-Based Motor Challenges (Postural Regulation Difficulties and Dyspraxia)

Postural challenges refer to difficulty stabilizing the body during movement or at rest in order to meet the demands of the environment or of a given motor task. Postural problems are characterized by inappropriate muscle tension, hypo- or hypertonic muscle tone, inadequate control of movement, and/or inadequate muscle contraction to achieve movement against resistance. Postural difficulties frequently occur in the presence of vestibular, proprioceptive, and visual–motor problems, and include poor stability in the trunk, poor righting and equilibrium reactions, poor trunk rotation and/or poor ocular control.

Postural challenges can occur with or without a motor planning disorder, although it is often observed with dyspraxia, particularly in difficulty with bilateral integration activities (e.g., doing activities that require use of both sides of the body together such as riding a bike, pumping a swing, etc.) and with rhythmical activities (e.g., bouncing a ball, clapping on the beat). Dyspraxia is an impairment in the ability to plan, sequence and execute novel or unfamiliar actions. It is characterized by Zawkward and poorly coordinated motor performance, which can be observed in gross motor, fine motor and/or oral motor abilities. To be diagnosed with sensory-based dyspraxia, deficits must manifest in processing of sensory information in one or more of the following sensory domains: tactile, kinesthetic, proprioceptive, or vestibular. Visual–motor and visual spatial deficits usually accompany this difficulty also.

These children learn by trial and error, with decreased ability to generalize skills to other similar motor tasks. Execution of discrete motor skills (e.g., standing, walking, pincer grasp) may be adequate. However, the performance of complex tasks may be compromised, including tasks that require one or more of the following: significant sequencing, important timing aspects, rhythm of motor action, or subtle adaptation in the "moment of action." All three patterns involve inattentive, disorganized behavioral patterns and school performance and academic problems.

NDRC involve symptom patterns, such as self-absorption, perseveration, and dysfunctional communication and refers to developmental disorders, including autism spectrum disorders, where there are significant difficulties with the fundamental capacities to relate, communicate, and think.

**300. Neurodevelopmental Disorders of Relating and Communicating (NDRC)[3]**

*301. Type I - Early Symbolic, with Constrictions*
*302. Type II - Purposeful Problem Solving, with Constrictions*
*303. Type III - Intermittently Engaged and Purposeful*
*304. Type IV - Aimless and Unpurposeful*
*Other Neurodevelopmental Disorders (Including Genetic and Metabolic Syndromes)*
*Children Who Are Difficult to Classify*

[3]Since the description of multisystem developmental disorders in DC:0-3, a work group of the ICDL has developed the current classification of NDRC. The Work Group members include: Serena Wieder, Ph.D., Lois Black, Ph.D., Griffin Doyle, Ph.D., Barbara Dunbar, Ph.D., Barbara Kalmanson, Ph.D., Lori-Jean Peloquin, Ph.D., Ricki Robinson, M.D., M.P.H., Ruby Salazar, LCSW, Rick Solomon, M.D., Rosemary White, OTR, Molly Romer Witten, Ph.D., and Stanley I. Greenspan, M.D.

These categories include the kinds of problems that are currently conceptualized in DSM-IV-TR, but not in a sufficiently developmental or comprehensive manner.

NDRC often include regulatory–sensory processing difficulties. If, however, basic relating, communicating, and thinking are disrupted, the problems would be classified under this category. RSPD may also involve interactive difficulties. However, if constitutional-maturational variations are a significant contribution, the problems are classified in this category. Interactive Disorders may involve constitutional and maturational variations as well as infant-caregiver interactions. However, in Interactive Disorders, the constitutional-maturational variations are not in the "clinical" (i.e., disordered) range and the major contributor to the problems stems from the caregiver–child interaction and related family and environmental patterns.

The only exception to the principles stated above relates to disorders involving trauma. These are classified under Interactive Disorders. Reactions to trauma may involve regulatory–sensory processing changes, such as sensory over-responsiveness; responses to trauma may also often involve anxiety or depression. When a clear trauma can be identified and is clinically thought to be responsible for the symptoms, priority is given to the diagnosis of traumatic stress disorder.

Table 41–1 is a very brief overview of the types of NDRC and is provided as a summary to facilitate the use of this framework in a variety of clinical and research settings. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

Language Disorders include challenges in communication in the context of a developmental framework that considers all components of language (e.g., gestures, motor, sensory, social, etc.). These can constitute a primary disorder when not part of another major disorder such as NDRC. Language capacities also have their own profile (see Axis IV) because of the significance of language in development, as well as its impact on overall development. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

Learning challenges are included in this classification in order to identify the early pathways associated with later learning differences and challenges at school age. The goal is to optimize early interventions which may head off or ameliorate these challenges later. These include learning difficulties in reading and reading comprehension, math, and written expression, as well as organizational capacities (i.e., executive functioning). See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

## Axes II-VIII

In addition to the detailed descriptions of the primary diagnosis, evaluation of the functional or operating areas and Axes II-VIII determines if the clinical threshold for a diagnosis has been crossed. The more severe the impairment or delay of the expected developmental capacities, the greater the evidence for the disorder(s).

Below is a brief description outlining Axes II-VIII. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

### Axis II: Functional Emotional Developmental Capacities

Axis II identifies six basic functional emotional developmental capacities, which depend on critical affective interactions (Table 41–2). These capacities initially emerge in a developmental progression at the ages indicated. In optimal development, as a child grows, he or she continues to develop each capacity to a higher level. Yet, each child may first evidence these processes at ages that are later than expected and/or to different degrees. See ICDL-DMIC (Interdisciplinary

**Table 41–1 Overview of Clinical Subtypes of NDRC and Related Motor and Sensory-Processing Profile**

***301. Type I***
Early Symbolic, with Constrictions: Intermittent capacities for attending and relating; reciprocal interaction; and, with support, shared social problem-solving and the beginning use of meaningful ideas (i.e., with help, the child can relate and interact and even use a few words, but not in a continuous and stable age-expected manner).
Children with this pattern tend to show rapid progress in a comprehensive program that tailors meaningful emotional interactions to their unique motor and sensory processing profile.

***302. Type II***
Purposeful Problem Solving, with Constrictions: Intermittent capacities for attention, relating, and a few back-and-forth reciprocal interactions, with only fleeting capacities for shared social problem-solving and repeating some words.
Children with this pattern tend to make steady, methodical progress.

***303. Type III***
Intermittently Engaged and Purposeful: Only fleeting capacities for attention and engagement. With lots of support, occasionally a few back-and-forth reciprocal interactions. Often no capacity for repeating words or using ideas, although may be able to repeat a few words in a memory-based (rather than meaningful) manner.
Children with this pattern often make slow but steady progress, especially in the basics of relating with warmth and learning to engage in longer sequences of reciprocal interaction. Over long periods of time, often gradually master some words and phrases.

***304. Type IV***
Aimless and Unpurposeful. Similar to Type III above, but with a pattern of multiple regressions (loss of capacities). May also evidence a greater number of associated neurological challenges, such as seizures, marked hypotonia, etc.
Children with this pattern often make very, very slow progress. The progress can be enhanced if the sources of the regressive tendencies can be identified.

Other Neurodevelopmental Disorders (including Genetic and Metabolic Syndromes)

Children Who Are Difficult to Classify.

**Table 41–2 Basic Functional Emotional Developmental Capacities Which Depend on Critical Affective Interactions**

| Level/Expected Emotional Function | Developmental Level |
|---|---|
| **Level 1:** Shared Attention and Regulation | Between birth to 3 months |
| **Level 2:** Engagement and Relating | Between 2 and 6 months |
| **Level 3:** Two-Way Purposeful Interaction | Between 4 and 9 months |
| **Level 4:** Shared Social Problem Solving | Between 9 and 18 months |
| **Level 5:** Creating Symbols and Ideas | Between 18 and 30 months |
| **Level 6:** Building Logical Bridges Between Ideas: Logical Thinking | Between 30 and 48 months |

Council on Developmental and Learning Disorders 2005) for more detail.

## Axis III: Regulatory-Sensory Processing Capacities

This axis reviews the same regulatory sensory processing capacities described in Axis I and is used when the individual differences do not interfere with age-expected emotional, social, cognitive, or learning capacities. The purpose is to capture which pattern or developmental pathway may be contributing to the child's challenges, but is not a primary diagnosis.

**400. Language Disorders[4] with compromises in**
*401. Self-Regulation and Interest in the World*
*401.1 In Comprehension*
*401.2 In Production*
*401.3 In Both Comprehension and Production*
*402. Forming Relationships: Attachment and Engagement*
*402.1 In Comprehension*
*402.2 In Production*
*402.3 In Both Comprehension and Production*
*403. Intentional Two-Way Communication*
*403.1 In Comprehension*
*403.2 In Production*
*403.3 In Both Comprehension and Production*
*404. First Words: Sharing Meanings in Gestures and Words*
*404.1 In Comprehension*
*404.2 In Production*
*404.3 In Both Comprehension and Production*
*405. Word Combinations: Sharing Experiences Symbolically*
*405.1 In Comprehension*
*405.2 In Production*
*405.3 In Both Comprehension and Production*
*406. Early Discourse: Reciprocal Symbolic Interactions with Others*
*406.1 In Comprehension*
*406.2 In Production*
*406.3 In Both Comprehension and Production*

**500. Learning Challenges[5]**
***Emerging Learning Challenges with compromises in***
*501. Functional Emotional Developmental Levels*
*502. Auditory Processing and Language*
*503. Visuospatial Capacities*
*504. Regulatory-Sensory Processing Patterns*
*505. A Combination of the Above Areas*

***Early Challenges in Reading and Language Arts with compromises in***
*506. Functional Emotional Developmental Levels*
*507. Auditory Processing and Language*
*508. Visuospatial Capacities*
*509. Regulatory-Sensory Processing Patterns*
*510. A Combination of the Above Areas*

***Early Challenges in Math with compromises in***
*511. Functional Emotional Developmental Levels*
*512. Auditory Processing and Language*
*513. Visuospatial Capacities*
*514. Regulatory–Sensory Processing Patterns*
*515. A Combination of the Above Areas*

***Early Challenges in Reading Comprehension with compromises in***
*516. Functional Emotional Developmental Levels*
*517. Auditory Processing and Language*
*518. Visuospatial Capacities*
*519. Regulatory–Sensory Processing Patterns*
*520. A Combination of the Above Areas*
***Early Challenges in Written Communication with compromises in***
*521. Functional Emotional Developmental Levels*
*522. Auditory Processing and Language*
*523. Visuospatial Capacities*
*524. Regulatory–Sensory Processing Patterns*
*525. A Combination of the Above Areas*

***Early Challenges in All Learning Areas with compromises in***
*526. Functional Emotional Developmental Levels*
*527. Auditory Processing and Language*
*528. Visuospatial Capacities*
*529. Regulatory-Sensory Processing Patterns*
*530. A Combination of the Above Areas*

*Note*: A child may evidence early challenges in a number of areas (e.g., reading, math, and organizing capacities).

[4]Work Group members included: Sherri Cawn, M.A., CCC-SLP; Sima Gerber, Ph.D., CCC; Cindy Harrision, M.Sc., SLP; Diane Lewis, M.A., CCC-SLP; Jane R. Madell, Ph.D., CCC A/SLP; Stuart G. Shanker, D.Phil.; Amy M. Wetherby, Ph.D., CCC-SLP; Stanley I. Greenspan, M.D.

[5]The ICDL Work Group on Learning Challenges included: Pat Lindamood, M.S., CCC-SLP, Robert L. Hendren, D.O., Joan Mele-McCarthy, D.A., Kytja Voeller, M.D., Harry Wachs, O.D., Serena Wieder, Ph.D., and Stanley I. Greenspan, M.D.

### Axis IV: Language Capacities

Differences in language functioning, just as differences in regulatory–sensory function and family patterns, contribute to the primary symptom patterns of the child. It is also parallel to the functional emotional developmental stages because both are describing the presymbolic as well as the symbolic levels of the child's overall functioning and communication. The language capacities, including gestural and verbal communication, however, focus on communication, particularly from the toddler through the preschool years.

### Axis V: Visuospatial Capacities

This Axis addresses six visuospatial capacities, which develop during infancy and early childhood (preschool) years, which interact simultaneously with the other sensory processing capacities and support or impede emotional and cognitive development. It is important to remember that all the capacities overlap and that the clinician should keep the developmental continuum in mind, as opposed to just focusing on a chronology of milestones. These six capacities are shown in Table 41–3 below. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

**Table 41–3 Visuospatial Capacities Which Interact Simultaneously with Other Sensory Processing Capacities and Support or Impede Emotional and Cognitive Development**

| Visuospatial Capacities |
|---|
| 1. Body Awareness |
| 2. Location of the Body in Space (involves location of own body parts in relation to each other, location of the body as a whole in its immediate surroundings; and location of the body in terms of the broader environment) |
| 3. Relation of Objects to Self and Other Objects and People |
| 4. Conservation of Space |
| 5. Visual Logical Reasoning |
| 6. Representational Thought (drawing, thinking, visualizing) |

### Axis VI: Child-Caregiver and Family Patterns

Axis VI describes the overall functioning of the caregiver and the degree to which the caregiver is able to support the child's negotiation of each developmental level. Since caregiver and family patterns affect children in every group of disorders, and not just the interactive disorders, it is included as a separate axis. Table 41–4 outlines the guidelines to observe each caregiver's interaction with the child.

**Table 41–4 Guidelines for Observing Caregiver Interaction with Child**

| |
|---|
| 1. Caregiver tends to comfort the infant or child |
| 2. Caregiver tends to find appropriate levels of stimulation to interest the infant or child |
| 3. Caregiver tends to pleasurably engage the infant or child |
| 4. Caregiver tends to read and respond to the infant's or child's emotional signals and needs in most emotional areas |
| 5. Caregiver tends to encourage the infant or child to move forward in development |

See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

### Axis VII: Stress

The purpose of this axis is to identify and consider the possible contribution stress may be having on the presenting symptom patterns. Stressors related to situations, conditions, or events in the family's (or child's) life can impact the child's emotional functioning and development depending on the resources of the child and the family's ability to mobilize adequate protective factors and support at the time of the stress. The following sequence can be used to assess the impact of the stress.

1. Identify and list the possible sources of stress
2. Determine the onset, severity and duration of the stressors identified
3. Assess the changes in the child's functioning and mental health possibly influenced by the stressors.

See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

### Axis VIII: Other Medical and Neurological Diagnoses

Careful listing of medical disorders facilitates the clinician's thorough investigation and the exploration of possible relationships with the child's mental health, developmental, and learning challenges. See ICDL-DMIC (Interdisciplinary Council on Developmental and Learning Disorders 2005) for more detail.

## Conclusion

The ICDL-DMIC presents an innovative approach to the assessment and diagnosis of infants and young children and their families. It features a multidimensional classification system which uniquely considers the emerging functional emotional developmental capacities of the infant and young child and the developmental pathway to symptom patterns. By also assessing the regulatory, language, and visuospatial capacities of the infant, in addition to stress and medical conditions, the ICDL-DMIC integrates all the interactive aspects of developmental capacities, individual differences, and the impact of relationships.

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CHAPTER

# 42 Childhood Disorders: Intellectual Disability

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## Mental Retardation

> All that inhabit this great earth,
> Whatever be their rank or worth,
> Are kindred and allied by birth,
> And made of the same clay.
>
> *Henry Wadsworth Longfellow, 1878*

### Introduction

This chapter does not describe a single disease but a heterogeneous set of conditions affecting persons who are characterized by having a pattern of persistently below normal intellectual and adaptive functioning. The study of intellectual disabilities is highly important in psychiatry, as persons with these conditions face increased risks for comorbid mental disorders of all types, the diagnosis and treatment of which often require knowledge of special approaches and skills.

In this chapter, the term "intellectual disability" and "mental retardation" will be used synonymously. Intellectual disability is also considered under the umbrella term "developmental disability" that broadly includes individuals facing disabilities attributable to mental and/or physical impairments with origins before age 22. The term "learning disability" has also been used in the United Kingdom replacing reference to mental retardation. As in the United States, Europe, Canada, and Australia, the use of the term "intellectual disability" is increasingly taking hold, as this is believed to carry less stigmatizing connotation than the term mental retardation. The American Association on Mental Retardation (AAMR) in 2006 has changed its name to the American Association of Developmental and Intellectual Disabilities (AADID). The President's Committee on Mental Retardation has followed suit as the Committee for People with Intellectual Disabilities. The term intellectual disability is therefore currently universally accepted in both the professional and scientific literature.

The chapter is organized under two major parts. The first part focuses on basic concepts of intellectual disability proper, and the second on issues related to diagnosis, treatment, and prevention of mental disorders in persons with intellectual disability.

## INTELLECTUAL DISABILITY

### Concept of Intellectual Disability

The following are the basic concepts of intellectual disability and the psychiatric approaches to it, on which this chapter is based:

1. Intellectual disability is not a single or a specific disorder or disease. The term refers to a heterogeneous set of disabilities or conditions that describe the level of a person's functioning in defined domains. Intellectual disability therefore does not have a single cause, mechanism, course, or prognosis and does not necessarily last a lifetime.
2. Persons diagnosed as having intellectual disability represent a wide spectrum of abilities as well as disabilities, clinical presentations, and behavioral patterns.
3. Persons with intellectual disability do not have unique personalities or behavioral patterns that are specific to intellectual disability, although characteristic behavioral phenotypic patterns may be frequently seen in certain intellectual disability-associated syndromes.
4. Maladaptive behaviors should not automatically be seen as part of the intellectual disability or implying underlying brain disorder. As in all individuals, these behaviors may also be related to life experiences; they

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can also be a symptom of mental illness comorbid with the intellectual disability.
5. The range of mental disorders experienced by persons with intellectual disability is similar to that among typical persons in the general population.

Although intellectual disability ("mental retardation") is listed as a mental disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), it is not a unique nosological entity. Intellectual disability is different from other conceptualizations in the DSM by virtue of implying specific underlying assumptions about an affected person's functioning in a normal environment. The diagnosis of intellectual disability refers to the level of a person's current intellectual and adaptive functioning that is below an objective cut-off point. In this sense, by definition, intellectual disability cannot just be a set of behavioral criteria with specific inclusion and exclusion rules, but it entails specific assumptions about a person's cognitive skills and adaptive environment. The diagnosis, although primarily administrative, therefore carries inherent ethical and societal responsibilities in defining a group of persons who are in need of supports and educational services. Thus, intellectual disability or mental retardation, as an Axis II diagnosis in the DSM-IV-TR, cannot have a single cause, mechanism, course, or prognosis. It has to be differentiated from other tangible diagnosis, if known, of underlying medical condition(s) that also need to be listed on Axis III.

## Definitions of Intellectual Disability and Its Scientific Evolution

In antiquity, most probably only severe forms of intellectual disability were recognized, or rather physical deformations and disabilities with which it could be associated. Avicenna in the 1st century A.D. recognized that there were various levels of intelligence (Scheerenberger 1983). The Talmud, as early as the 2nd century A.D. recognized that certain persons had significant impairments in cognitive capacity. The "shoteh," one of three types of persons with limited capacity (besides deaf and minor) was defined as someone who goes out at night alone, sleeps in the cemetery, and tears own clothes. This was variably interpreted as a person with mental illness or intellectual disability.

Fitz-Herbert, in 1534, suggested what could have been the earliest intelligence test for the diagnosis of intellectual disability: "And he who shall be said to be a sot and idiot from his birth, is such a person who cannot account or number 20 pence, nor can tell who was his father or mother, nor how old he is, etc. so as it may appear that he hath no understanding or reason what shall be for his profit, nor what for his loss" (Scheerenberger 1983). Willis, in the 17th century, recognized that intellectual disability could be of varying degrees: "Some are unable to learn their letters but can handle mechanical arts; others who fail at this can easily comprehend agriculture; others are unfit except to eat and sleep" (Szymanski and Crocker 1989). John Locke, English physician and philosopher, in 1690, differentiated mental illness from mental retardation (which were then commonly seen as one entity) as: "Herein seems to lie the difference between idiots and madmen, that madmen put wrong ideas together and reason from them, but idiots make very few or no propositions and reason scarce at all" (Scheerenberger 1983).

In 1800 when the young French physician, Jean Marc-Gaspard Itard, arrived in Paris, one of his teachers was Philippe Pinel, a founder of modern psychiatry, who had just written an influential book on psychiatric diagnosis promoting the nonviolent management of mental patients, thus originating the concept of "moral" or psychological treatment of mental patients and enriching our understanding of the theory of mental disorders "with all the insights that the empirical approach affords." Itard tried this optimistic empirical approach in the treatment of his much-celebrated patient "Victor of Aveyron." It was subsequently Itard's student Edouard Seguin who later set out to prove that persons with mental and intellectual disabilities were in fact educable. In 1839, Seguin created the first ever-special needs school in Paris dedicated to the education of children with mental disabilities. In 1846, Seguin published his treatise on the "*Moral Treatment, Hygiene, and Education of Idiots and Other Backward Children*" and subsequently moved to the United States continuing his work with the establishment of his "Physiological School" in New York City. He subsequently served as the first president of the "Association of Medical Officers of American Institutions for Idiotic and Feebleminded Persons" later known as the AAMR (recently renamed AADID). Seguin's work was a major inspiration on Maria Montessori in Rome whose methods subsequently became very influential worldwide on unleashing the social and academic "potentialities" for the early education of children.

In 1905, Alfred Binet and Theodore Simon in France published the first version of what became later the first modern intelligence test. However, it was not designed to assess "intelligence," but rather to predict which children would require and benefit from receiving education through special instruction. They classified children with intellectual disability into four grades of severity, according to the number of test tasks they completed; the later versions gave the child's mental age (Scheerenberger 1983). These tests were soon translated into English and introduced in the United States by Henry Goddard. Many revisions and new tests followed. Lewis Terman's revision of 1916, known as the Stanford-Binet Intelligence Scale, introduced the concept of intelligence quotient (IQ) and classified intellectual disability according to its scores. A number of Terman's initial tests were administered to non-English speaking or nonschooled populations and led to biased "scientific" conclusions that justified discriminatory educational practices at a time of educational segregation and eugenics. Unlike Simon and Binet who emphasized rehabilitation of children, Terman's approach proposed to use IQ scores to classify children according to job expectations.

The first international conference fostering interdisciplinary cooperation in intellectual disability was held in London on the "Scientific Study of Mental Deficiency." The British psychiatrist and medical geneticist, Lionel Penrose, was first to acknowledge the unique importance of the scientific study of intellectual disability in his address by emphasizing that "these unfortunate mentally handicapped individuals can reveal, unwittingly, information of the utmost

value to the rest of the human community, and we may well be grateful to them for their service." Penrose's Colchester study, in 1938, was the first scientific study of the genetics of intellectual disability (then termed mental deficiency). His book on *Biology of Mental Defect* (1949) pioneered the study of various chromosomal causes of intellectual disability including Down syndrome. In a similar light, Arnold Gesell in the United States, both as psychologist, and later as pediatrician, pioneered the importance of empirical and humanitarian study of children's cognitive development. As a student of Henry Goddard at the Vineland School for persons with mental disabilities he had become interested in studying children with disabilities. He became interested on aspects of nature and nurture and was one of the earliest scientists to caution against prematurely attributing mental disabilities to specific causes. Gesell was also an early proponent for establishment of a nationwide system of early preschool education in the United States that saw the seeds for the subsequent inception of Head Start programs. In 1949, Gesell argued that the "developmental philosophy of child care should have far-reaching implications for a better understanding of ourselves" and of our "democratic way of life." The roots of a societal commitment in the United States to the care and education of persons with special needs was thus emerging.

## Definition of Intellectual Disability (AAMR or AADID)

Since its inception, the AAMR has published 10 definitions of intellectual disability. The initial 1910 definition required the presence of a "mental defect" and an inability to manage ordinary affairs (corresponding to today's impairment in cognitive capacity and adaptive behavior), this included the classifications of "idiots" (mental age of 2 years or younger), "imbeciles" (mental age of 2–7 years), and "morons" (mental age of 7–12 years). The definition published by AAMR, in 1959, proposed three diagnostic criteria: subaverage intellectual functioning, impairment in adaptive behavior, and onset in the developmental period (Heber 1959). The subaverage intellectual functioning was meant to be one standard deviation or more below the population mean (IQ of approximately 85), and the developmental period referred to age 16 years or less. Five degrees of severity of mental retardation based on the IQ scores were introduced: borderline, mild, moderate, severe, and profound. In 1973, the definition was again changed in that the IQ cut-off point was 2 standard deviations (approximate IQ of 70), thus eliminating the category of "borderline mental retardation." The developmental period was increased to 18 years or younger. As the result of these changes, the number of persons who could be labeled as having intellectual disability (mental retardation) thus decreased considerably.

The current definition, published in 2002 is as follows:

## The AAMR Definition of Mental Retardation (American Association on Mental Retardation 2002)

Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before age 18.

## Five Assumptions Essential to the Application of the Definition:

1. Limitations in present functioning must be considered within the context of community environments typical of the individual's age peers and culture.
2. Valid assessment considers cultural and linguistic diversity as well as differences in communication, sensory, motor, and behavioral factors.
3. Within an individual, limitations often coexist with strengths.
4. An important purpose of describing limitations is to develop a profile of needed supports.
5. With appropriate personalized supports over a sustained period, the life functioning of the person with mental retardation generally will improve.

Significant limitation in intellectual functioning is defined as at least 2 standard deviations below the mean as measured by the assessment instrument. The standard error of measurement for the instrument (usually between 3 and 5 points) should be taken into consideration. Persons with intellectual disability can be classified in various ways such as by IQ levels, or intensity of supports they require, depending on the purpose for which the diagnosis is used. Significant limitation in adaptive behavior is defined as performance of at least 2 standard deviations below the mean on an instrument based on general population norms. This manual emphasizes the requirement for detailed assessment of individuals and their needs in all relevant domains, including psychological and emotional, and is by far the most modern and comprehensive available.

## DSM-IV-TR Definition

DSM-IV-TR (American Psychiatric Association 2000) defines mental retardation (intellectual disability) in a manner generally compatible with the AAMR definition, however, subclassification into degrees of severity is retained. Intellectual disability is coded on Axis II, as conceptually it is thought to fit more congruently with personality disorder conceptualization listed here, than with mental illnesses listed on Axis I. It was also expected that placement on Axis II will encourage clinicians to diagnose both intellectual disability and mental disorders when faced with a person who has such comorbidity, rather than these latter conditions being conveniently subsumed under the diagnosis of intellectual disability.

**DSM-IV-TR Criteria**

**Mental Retardation**

A. Significantly subaverage intellectual functioning: an IQ of approximately 70 or below on an individually administered IQ test (for infants, a clinical judgment of significantly subaverage intellectual functioning).

B. Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected

*(continues)*

DSM-IV-TR Criteria *continued*

for his or her cultural group) in at least two of the following areas: communication, self-care, home- living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.

C. The onset is before age 18 years.

| *Severity* | *Approximate IQ Range* | *Code* |
|---|---|---|
| Mild | 50–55 to approx. 70 | 317 |
| Moderate | 35–40 to approx. 50–55 | 318 |
| Severe | 20–25 to approx. 35–40 | 318.1 |
| Profound | Below 20–25 | 318.2 |
| Undiagnosed | | 319 |

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### International Classification of Diseases Definition (ICD-10)

The ICD-10 definition uses a rather outdated language based only on IQ estimated by intelligence tests; adaptive behaviors are mentioned only in supplementary roles. The definition is as follows: "A condition of arrested or incomplete development of the mind, which is especially characterized by impairment of skills manifested during the developmental period, skills which contribute to the overall level of intelligence, that is, cognitive, language, motor, and social abilities. Retardation can occur with or without any other mental or physical condition" (World Health Organization 2006). There are five subcategories, based on IQ levels:

### Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The method of defining the level of severity differs slightly between the two systems. The ICD-10 Diagnostic Criteria for Research define the levels using exact cut-off scores: Mild is defined as 50–69, Moderate is defined as 35–49, Severe is defined as 20–34, and Profound is defined as below 20. In contrast, DSM-IV-TR provides somewhat greater flexibility in relating severity to a given IQ score by defining severity levels using overlapping scores (i.e., mild is 50–55, moderate is 35–40 to 50–55, severe is 20–25 to 35–40, and profound is below 20–25). Within the overlapping range, the severity is determined by the level of adaptive functioning.

### Contrasting Definition of Developmental Disability

The term "developmental disability" is in fact an administrative one; it is nevertheless often used interchangeably with intellectual disability or mental retardation. The term was defined in the Developmental Disabilities Assistance and Bill of Rights Act (2000) as: severe, chronic disability due to a mental or physical impairment; manifested before age 22; likely to continue indefinitely; resulting in substantial functional limitations in three or more of the major life activities (as in self-care, receptive and expressive language, learning, mobility, self-direction, capacity for independent living, and economic self-sufficiency). In contrast to the narrower term intellectual disability, the notion of developmental disability is therefore not dependent on standardized measures of intelligence or adaptive function. Thus not every case of intellectual disability is a developmental disability, unless severe functional limitations are also present.

### Prevalence of Intellectual Disability

There have been various models for estimating the prevalence of intellectual disability. A model based on IQ score alone used the expected statistical distribution of intelligence levels. The past definition based only on an IQ that was 1 standard deviation or greater below the mean implied that almost 15% of the population could be classified as having intellectual disability. With the introduction of the diagnostic criterion of impairment in adaptive behavior and an IQ cutoff at 2 standard deviations below the mean (approximately 70), the prevalence of intellectual disability was commonly thought to be about 2.3% of the population (Larson et al. 2001). More recent population-based studies, using multiple methods of ascertainment and a current definition of intellectual disability, suggest that the prevalence might be closer to 1%. In the study of McLaren and Bryson (1987), the prevalence of mild intellectual disability was 0.37–0.59%, whereas the prevalence of moderate, severe, and profound intellectual disability was 0.3–0.4%. Based on results of the 1994/1995 National Health Interview Survey Disability Supplements (NHIS-D), Larson et al. (2001) estimated the prevalence of intellectual disability in noninstitutionalized population of the US to be 0.78%. When age is considered, the highest prevalence is in the school-age group, when the child cannot meet the expectations of academic learning. United States Department of Education indicated the prevalence of intellectual disability among school-age children (6–17 years of age) to be 1.14%, with variations reported by different states (Massey and McDermott 1995). Conversely, some persons who are diagnosed with mild intellectual disability when of school age lose that diagnosis in adulthood when their good adaptive skills are more relevant than their academic achievement. However, prevalence based on administrative data (e.g., attendance in special education classes), may not be accurate. For example, children with intellectual disability and comorbid conditions such as autism may in fact carry solely a diagnosis of autism, as this may be considered less stigmatizing.

## Patterns of Comorbidity

Other mental and physical disorders frequently cooccur or are truly comorbid with intellectual disability. Intellectual disability may be part of the clinical manifestation of a given disorder or syndrome. Alternatively, an insult to the Central Nervous System (CNS) might cause both intellectual disability and another disorder; examples may include seizures.

### CNS Problems

Intellectual disability reflects in part the function of the CNS. Sometimes there are discrete lesions that are identifiable, and at other times brain morphology appears normal on routine imaging tests. It is common for individuals with intellectual disability to also have other medical, developmental, and behavioral issues. These conditions may be part of the same etiologic presentation or associated with it. A person with intellectual disability, with cognitive and adaptive skill

**Table 42–1 Disorders Often Associated with Intellectual Disability**

| Study | Subjects (Degree of Retardation; *n*; Age) | % with Seizures | CP (%) | Visual Impairment (%) | Hearing Disorder (%) | Speech Disorder (%) | Mental Disorder (%) |
|---|---|---|---|---|---|---|---|
| Gustavson et al. (1977a) | Severe; 121; school age | 30 | 18 | 12 | 4 | | |
| Gustavson et al. (1977b) | Severe; 161; school age | 36 | 19 | 10 | 6 | | |
| Hagberg et al. (1981) | Mild; 91; school age | 12 | 9 | | 7 | | 31 |
| McQueen et al. (1987) | IQ <55; 221; school age | 23 | 15.4 | 13 | 11 | 65.6 | 9 |

functioning significantly below age expectation, may also have delays in other developmental domains such as language, gross motor, fine motor, and social skills. There often is overlap in at least some of the domains. For example, an individual with autism may have intellectual disability in addition to disturbances in the domains of communication, social skills, and behavior. A person with cerebral palsy (CP) may also have intellectual disability, along with speech and language impairment. Table 42–1 summarizes the early studies demonstrating the association of various disorders with mild and severe intellectual disability. It is to be noted that the additional disabilities are more often associated with severe than with mild intellectual disability because of the more severe pathological brain condition. Petersen et al. (2007) have also found an increased risk for congenital anomalies in all children with intellectual disability compared to the general population, although more notable in those with more significant cognitive impairment.

### *Motor*

CP, the commonest motor manifestation, is defined as a "disorder of movement and posture secondary to a static encephalopathy, with the insult to the brain occurring prenatally, perinatally, or in early childhood (Taft and Matthews 1992). While CP represents a nonprogressive CNS insult, there may be aspects of motor and other system function that do change over time. CP has been associated with hypoxic–ischemic events during labor and delivery, however, there are often other causes (Nelson 2002). Advances in brain imaging techniques (computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)) have greatly improved the possibilities to ascertain the etiology and pathology of CP. Perinatal risk factors include the premature infant with positive findings on cranial ultrasound or evidence of periventricular leukomalacia, perinatal hypoxic-ischemic encephalopathy in the full-term infant, neonatal seizures, and cortical arterial infarct (Wood 2006). Some children do not have these risk factors, although etiologic factors may include infections, genetics, metabolic disorders, toxic exposures, and trauma.

Individuals with CP may have cognitive skills within or above normal range, or may have intellectual disability ranging from mild to profound. The reported proportion of children with CP who also have intellectual disability varies widely due to differences in study populations and diagnostic criteria. Overall, approximately 20% of persons with intellectual disability also have CP. When the motor difficulties are severe, other medical problems may arise. Individuals may have disorders of the feeding and digestion, consisting of problems with chewing, swallowing, gastroesophageal reflux, gastric mobility, and aspiration. There may be chronic respiratory issues, due to difficulties clearing secretion. The presence of spasticity contributes to difficulties with ambulation and increases the likelihood for development of scoliosis, hip displacement, and joint contractures. Motor speech disorders may exist, affecting communications skills and speech intelligibility.

### *Language*

While communication has a motor component, there is also a more symbolic aspect of language that affects the ability to understand language and express oneself both verbally and nonverbally (Costello 2006). Individuals with profound intellectual disability may be nonverbal, although nonverbal communication such as gestures or facial expressions may be used. Other individuals are able to use augmentative communication devices, operating switches or using keyboards to express their wishes. Language disorders may occur in the context of cognitive and hearing impairments, as well as genetic disorders, brain injury, and other conditions that may affect neurological functioning.

### *Behavior*

Individuals with intellectual disability have been found to have a higher rate of behavioral and psychiatric disorders compared to the general population. Thirty to forty percent of individuals with intellectual disability have been reported to present with behavioral abnormalities (Dykens and Hodapp 2001). Specific behavioral profiles have also been identified in individuals with syndromes associated with intellectual disability. Self-injurious behaviors (SIB) as a rule are not commonly seen in the general population. Individuals with intellectual disability, particularly those with more severe intellectual disability, and individuals with autism and certain psychiatric disorders may present with SIB (Schroeder et al. 2001). Repetitive behaviors such as rocking or stereotypic hand movements may be seen in individuals either with significant intellectual disability or autism. While reduced attention may be seen in individuals with intellectual disability, attention may also be commensurate with level of cognitive function and significant language processing difficulties. There also is an increased incidence of intellectual disability in children with autism and autism spectrum disorders, including pervasive developmental disorder not otherwise specified (PDD-NOS) with estimates ranging from 50–75% (Johnson and Walker 2006).

### *Seizures*

Seizure disorders are seen in 0.5% of the general population and in approximately 20% of persons with intellectual

disability. There is a direct relationship between the level of cognitive functioning and incidence of seizure disorders. Seizures represent an abnormal conduction of neurophysiologic signals associated with significant brain anomalies, as well as more subtle disruptions in neuronal connection. As intellectual disability reflects CNS functioning, it is not surprising that there is an increased incidence of seizure disorders in those with intellectual disability.

The type of seizure may also provide both prognostic and etiologic information. "Infantile spasms" are often seen in children with significant disabilities and generally carry a poor prognosis, with later development of Lennox-Gastaut syndrome, or infantile seizures, associated with such conditions as Tuberous Sclerosis (or Tuberous Sclerosis Complex) (TSC). Myoclonic seizures, in turn, may be associated with metabolic disorders. Complex-partial seizures are associated with behavioral and sensory manifestations, including illusions, hallucinations, and alterations in consciousness and awareness. Interictal changes may include mood changes, anxiety, as well as fear, elation, or depression. Problems with attention, focus, behavioral outbursts, and regression of developmental skills may be associated with undiagnosed and treated seizure disorders. These may be difficult to distinguish at initial examination in an individual with intellectual disability with pre-existing cognitive and behavioral difficulties and may be overlooked. Long-term encephalographic recording by telemetry with simultaneous videotaping of behavior may be performed to clarify the possible relationship between the seizures and the behavior in question. At times, seizure control may require more than one anticonvulsant trial or a combination of anticonvulsants. There always needs to be a balance between control of seizures and medication-related side effects, which may include tiredness, somnolence, irritability, behavioral, and cognitive problems, as well as abnormalities in blood chemistries and hematological indices.

### *Sensory Impairments*

Sensory problems are common in persons with intellectual disability, although the prevalence data vary greatly. Hearing loss may be present with different genetic, metabolic, infectious, and acquired etiologies, and may be associated with intellectual disability (Neault 2006). Hearing loss may be sensorineural or conductive, and, in turn, may be congenital or acquired. Reliable hearing assessment needs to be done on any child with language delay even in the context of a normal neonatal hearing screen. Visual impairment due to retinopathy of prematurity (ROP) may occur in infants born prematurely due to oxygen use. Optic atrophy, with associated visual impairment, is also often identified in individuals with significant intellectual disability associated with brain abnormalities. Visual impairments have been found to be as high as 50% in individuals with intellectual disability when strabismus and refractive errors are included.

## Etiology and Pathophysiology of Intellectual Disability

### General Considerations

A variety of biomedical insults can disrupt the integrity of the CNS and affect cognitive function. It should be kept in mind, however, that the diagnosis of intellectual disability takes into account a persons' overall level of functioning, encompassing current intellectual and adaptive skills, as well as the intensity of needed levels of support (American Association on Mental Retardation 2002). A person's general state of health, associated disabilities, environmental supports, and psychological factors may all affect a person's ability to function independently. While congenital or acquired etiologic factors may be the primary cause for cognitive delays, these other factors may impact a person's functional outcome.

It is important to understand the primary etiology for a person's intellectual disability for a number of reasons:

- Treatment possibilities such as early implementation of a phenylalanine-free diet in phenylketonuria (PKU) or thyroid hormone replacement in congenital hypothyroidism, both of which may result in intellectual disability if untreated.
- Prevention such as primary prevention of the recurrence of a condition such as developmental delays secondary to fetal alcohol syndrome (FAS).
- Genetic counseling for the family regarding recurrence risk of particular disorders such as maternal transmission of Fragile X syndrome (fraX).
- Early recognition and treatment of complications known to be associated with the particular presentation or syndrome such as hypothyroidism in Down syndrome.
- Research on causation and prevention.
- Impact on public policy for development of community supports.
- Prognostic information provided to families regarding the natural or anticipated trajectory of a particular disorder
- Support for the family and other caregivers dispelling misconceptions and anxieties related to the uncertainty about the cause.

For these reasons, it is important for physicians, including psychiatrists, to ascertain whether a person with intellectual disability to whom they provide care has had appropriate medical evaluation to determine a potential unifying medical diagnosis for his or her presentation.

### Approaches to Classification of the Causation of Intellectual Disability

Many of the classification systems for intellectual disabilities have been based on the timing of the insult to the CNS. This approach was used by Yannet (1945) who divided the causes into prenatal, perinatal, and postnatal, plus genetic. In Heber's classification (Heber 1959), more emphasis was put on the presumed nature of the intellectual disability. The eight main categories were: (1) infection, (2) intoxication, (3) trauma or physical agent, (4) disorder of metabolism, growth, or nutrition; (5) new growths, (6) unknown prenatal influences, (7) unknown or uncertain cause, with the structural reactions manifested, and (8) an uncertain or presumed psychological cause, with the functional reaction alone manifested. The successive classification systems developed by AAMR also follow the timing approach (American Association on Mental Retardation 2002).

Some reports indicate that the prevalence of diagnosable biomedical causes of intellectual disability varies

**Table 42–2 Early Studies Underscoring Causes of Intellectual Disability by Timing of CNS Exposure and Unknown Factors**

| Study | Cohort (*n*; age) | % of Study Population* | | | |
|---|---|---|---|---|---|
| | | **Prenatal** | **Perinatal** | **Postnatal** | **Unknown** |
| | | *Studies of persons with severe mental retardation* | | | |
| Gustavson et al. (1977a) | 121; 5–16 yr | 73 | 10 | 5 | 12 |
| Gustavson et al. (1977b) | 161; 5–16 yr | 68 | 8 | 2 | 22 |
| McQueen et al. (1986) | 221; 7–10 yr | 59 | 10 | 4 | 27 |
| | | *Studies of persons with mild mental retardation* | | | |
| Blomquist et al. (1981) | 171; school age | 43 | 7 | 7 | 43 |
| Hagberg et al. (1981) | 91; school age | 23 | 18 | 2 | 55 |

*The percentages are of subjects in each study in whom the retardation was thought to be due to causation at the pre-, peri-, or postnatal period, respectively, or the cause could not be found.

with the degree of the disability. Identifiable etiologies for individuals have varied greatly, based on differences in samples, methods of assessment, and diagnostic criteria. Severe intellectual disability has long been associated with prenatal etiologies in 59–73% of patients, although such a cause has been reported in 23–43% of individuals with mild intellectual disability (Table 42–2). The classification used here by Welska and Kaski (1999, 2001) reflects both the timing and the type of the causative process, which will affect the development and function of the CNS (Table 42–3). However, with newer diagnostic and genetic tests, etiology has been reported to be identifiable in 50% of individuals presenting at a tertiary care center, regardless of level of cognitive skills (van Karnebeek et al. 2005). The goals of the etiologic evaluation are to elucidate the earliest developmental cause as well as other coexisting factors because their effects are usually interactive and cumulative (McLaren and Bryson 1987).

## Prenatal Causes

There may be prenatal causes of intellectual disability that may be genetically determined, may represent a de novo genetic mutation, may be multifactorial, or may result from an intrauterine insult that affects fetal development such as

**Table 42–3 Etiological Classification of Mental Retardation Based on the Timing and Type of the Central Nervous System Insult*, †**

| Division and Group | Percent | Examples |
|---|---|---|
| **Prenatal: genetic disorders** | 32 | |
| Chromosomal aberrations | | Trisomy 21, trisomy 13m cri du chat syndromes |
| Malformations due to microdeletions | | Angelman's and Prader-Willi syndromes, William's syndrome, Rubinstein-Taybi syndrome |
| Monogenic mutations | | Tuberous sclerosis, metabolic disorders, fragile X syndrome |
| Multifactorial mental retardation | | "Familial" mental retardation |
| **Malformations, cause unknown** | 8 | |
| Malformations of the CNS | | Holoprosencephaly, lissencephaly, neural tube defects |
| Multiple malformation syndromes | | de Lange's syndrome, Sotos' syndrome |
| **Prenatal: disorders due to external causes** | 12 | |
| Maternal infections | | Rubella and HIV, cytomegalovirus, and *Toxoplasma* infections |
| Toxins | | Fetal alcohol syndrome, fetal hydantoin syndrome |
| Toxemia, placental insufficiency | | IUGR, prematurity |
| Other | | Radiation, trauma |
| **Perinatal causes** | 11 | |
| Infections | | Meningitis, herpes |
| Delivery problems | | Asphyxia, trauma |
| Other | | Hypoglycemia, hyperbilirubinemia |
| **Postnatal causes** | 8 | |
| Infections | | Meningitis, encephalitis |
| Toxins | | Lead poisoning |
| Other CNS disorders | | Cerebrovascular accidents, tumors, traumas |
| Psychosocial problems | | |
| **Unknown causes** | 25 | |

*These data are based on the Finnish National Board of Social Welfare registry of persons, with mental retardation, who were receiving special services in the 1980s. There were about 19,000 persons in that registry. In about 4%, no etiological information was recorded (unpublished data).
†CNS: central nervous system, HIV: human immunodeficiency virus, IUGR: intrauterine growth retardation.

exposures to toxins or teratogens, infections, abnormalities in perfusion, or poorly controlled metabolic disorders.

### *Chromosomal Disorders*

Chromosomal evaluations are performed cytogenetically; the normal karyotype being 46 XX or 46 XY. Abnormalities in the number of chromosomes may result in disorders that affect cognition or learning, and may result in syndromes that cause intellectual disability. There may be additional chromosomes (polyploidy) or missing chromosomes (monosomy). Monsomy of autosomal chromosomes are incompatible with life, although monosomy of a sex chromosome (XO) may result in a syndrome that is not generally associated with intellectual disability (Winnepenninckx et al. 2003).

**Down Syndrome.** Down syndrome is the most common polyploidy and chromosomal disorder that causes intellectual disability (Johnson and Walker 2006). The vast majority of individuals with Down syndrome are found to have an extra chromosome 21 on cytogenetic testing. In trisomy 21 the extra chromosome in the egg or the sperm results from nondisjunction in the meiotic stage. When such a gamete becomes fertilized the fetus will have an extra chromosome 21 in all cells for a total of 47 chromosomes. In mosaicism, some cells have 47 chromosomes, and others have 46 because of an error in one of the first cell divisions of the fertilized egg. The percentage of cells with trisomy 21 may vary, which may then have an effect on the phenotypic presentation and the degree to which a person is affected by the syndrome; children with normal intelligence have been described.

The common physical characteristics of a person with Down syndrome are upward-slanted palpebral fissures, flat and low nasal bridge with epicanthal folds, small mouth and ears, transverse palmar creases, short and wide palms, and a characteristic dermatoglyphic pattern (Figure 42–1). Children with Down syndrome present with significant hypotonia that affects acquisition of motor milestones, as well as notable delays in expressive language skills. The degree of intellectual disability varies from severe to mild with a mean IQ of approximately 50; most children have mild to moderate intellectual disability. Down syndrome occurs in 1 in 800 live births, although increases significantly with maternal age 35 years and older. The incidence in women older than 40 years of age is approximately 1 in 40 live births. As the majority of children born with Down syndrome are from mothers who are less than 35 years of age, the



**Figure 42–1** *A young man with Down syndrome and a trisomy 21 karyotype.*

American College of Obstetrics and Gynecology recently recommended that all pregnant women be offered screening tests that would identify a fetus with Down syndrome (American College of Obstetrics and Gynecology 2007).

Children with Down syndrome present as adorable, affectionate, and generally quite social. Individuals with Down syndrome, however, may also present with various behavioral and psychiatric problems. Younger and less verbal children have been diagnosed with problems with attention deficit hyperactivity disorder and oppositional behavior. Older and more verbal adolescents and adults are vulnerable to pathological grief responses in the face of traumatic loss, as well as generalized anxiety and major affective disorders, often also leading to a regression in adaptive functioning. Approximately, 7% of children with Down syndrome also meet diagnostic criteria for autism spectrum disorders (Johnson and Walker 2006). The prevalence of autism-like behaviors increases with increasing severity of intellectual disability. Early diagnosis and intervention, including speech and language, occupational, physical, and behavioral therapies and developmental stimulation, are essential to enable these children to reach their developmental potential.

Individuals with Down syndrome are at risk for a number of associated health problems. It is important to be aware of this to enable early diagnosis and treatment as well as prevention. The Committee on Genetics of the American Academy of Pediatrics (AAP) has recently published guidelines concerning health supervision for children with Down syndrome, in order to identify these potential medical problems throughout a person's lifetime (American Academy of Pediatrics 2001). There is an increased risk for congenital heart defects (in 40–50% of persons), gastrointestinal atresias (in 12%), Hirschprung disease (<1%), and leukemia (<1%). Hearing loss, mostly conductive, secondary to otitis media (75%) requires identification and treatment in order to avoid additional factors that negatively impact speech and language development. Respiratory and ear infections are common, partially attributable to anatomical features and to deficiencies in cellular immunity. Obstructive sleep apnea is seen frequently among persons with Down syndrome. Infants with Down syndrome have an increased risk of congenital cataracts compared to the general population (Kallen et al. 1996), which become more frequent and may significantly affect vision with increasing age into adulthood (Fulton et al. 2006). Approximately 50% of individuals have ocular findings. The subject's age, specific intellectual disability (ID) syndrome, and severity of cognitive impairment have all been noted to be related to higher prevalence of ocular disorders. The most frequently reported ocular findings include optic atrophy, cataract, keratoconus, and strabismus; in addition, the most prevalent refractive error was hypermetropia (Pires da Cunha et al. 1996). Gluten intolerance is diagnosed in 4–20% of individuals with Down syndrome and should be kept in mind in cases of gastrointestinal problems. Atlanto-axial instability (AAI) is seen in 10% of individuals with Down syndrome, and potentially could result in sensory or motor neurological problems. While there is some difference of opinion regarding screening for AAI, most providers follow AAP guidelines based on requirements for participants in Special Olympics. Cervical spine X-rays are recommended between the ages of 3 and 5 years, before participation in sports activities. They are also recommended with onset of related neurological symptoms and prior to general anesthesia (Martin 1997). Hypothyroidism may be congenital or may develop later, the incidence increasing with age. It may negatively affect cognitive function, and is treatable with thyroid replacement therapy. Regular thyroid function screening is therefore recommended.

Overall, the quality of life and the life expectancy for individuals with Down syndrome has improved markedly in recent decades due to improved living conditions, developmental and educational interventions, availability of antibiotics, and possibilities for surgical correction of anomalies, especially those affecting the heart. Adults with Down syndrome may have cognitive decline associated with neuropathological changes of Alzheimer's type dementia at a relatively early age. However, the neuropathological changes may not necessarily be accompanied by clinical symptoms of dementia until the 5th or 6th decade of life (Alvarez 2006).

**Partial Chromosomal Anomalies.** A person may have a normal number of chromosomes with structural changes of the chromosome itself. There may be deletions, in which the part of the chromosome that is missing can be visualized with a microscope. There may be inversions, in which a portion of the chromosome has broken off and the inverted section become part of the chromosome. There are also ring chromosomes in which there may be deletions at both ends that subsequently unite. A translocation reflects the part of a chromosome transferred to another one.

In cases of Down syndrome caused by unbalanced translocation there are 46 chromosomes. However, chromosomal material from 47 chromosomes is present because an extra chromosome 21 is attached (translocated) to another chromosome, usually chromosome 14 (designated as t(14;21)). In about half of translocation cases a parent (usually the mother) has a balanced translocation: 45 chromosomes with t(14;21). If a child has Down syndrome due to a translocation, the parents should be examined for the presence of a balanced translocation. This is important in genetic counseling because when the mother or father has a t(14;21) translocation, there is a 1 in 10 or a 1 in 20 chance, respectively, of having a child with Down syndrome. The characteristic phenotype of Down syndrome is basically the same in trisomy 21 and in translocation.

In situations in which there is a deletion, the presentation of the person may vary based on the size and location of the deletion on the chromosome, although it is usually associated with intellectual disability (Winnepenninckx et al. 2003). The best-known example of a chromosome deletion syndrome is *cri du chat* syndrome, which is characterized by a high-pitched voice and is caused by a deletion in chromosome region 5p15.2–p15.3.

Ring chromosomes occur when the ends of the chromosome fuse together. In addition to complete monosomy seen in Turner syndrome, 45, XO, there are also instances in which ring X chromosome results in partial monosomy. While Turner syndrome is usually associated with learning disabilities, particularly on performance tasks, girls with ring chromosome have presented with intellectual disability, as well as other cognitive and behavioral disorders (Moldavsky

et al. 2001). It should be noted that most fetuses with chromosomal aberrations are not viable. About 40–50% of spontaneously aborted fetuses have a chromosomal anomaly.

### *Malformation Syndromes due to Microdeletions*

These syndromes had previously been classified as malformation syndromes of unknown origin (see later in the chapter), but because of the described findings of microdeletions, they are now placed in a separate category between chromosomal aberrations and monogenic mutations (Table 42–4).

Microdeletions refer to loss of a few genes, and are not visible cytogenetically. The use of DNA probes and fluorescence in situ hybridization (FISH), in which the chromosomes are treated with specific fluorescent dyes to reveal deviant genes, has brought new light to many of the malformation syndromes previously classified as being of unknown origin. FISH studies are often used when a particular disorder or syndrome is suspected based on the phenotypic or clinical presentation. The same submicroscopic deletions (microdeletions) of DNA have been reported in chromosome 15q11–13 in the *Prader–Willi syndrome* and *Angelman syndrome*. In Prader–Willi syndrome, the paternally derived information at that site is usually absent, although it may also be associated with maternal unisomy or, less frequently, when each of the two chromosome 15 are from the mother. With Angelman syndrome, there is missing maternal information, from maternal deletion, or less frequently, from paternal uniparental disomy (Dykens and Hodapp 2001). Mutations may also be seen in the UBE3A gene (Moldavsky et al. 2001). Individuals with Angelman syndrome may present with moderate to profound intellectual disability, are nonverbal, ataxic, frequently laugh, and hold their arms flexed in such a manner to sometime be referred to as Happy Puppet syndrome. Infants with Prader–Willi syndrome are generally hypotonic, feed poorly, and present with small hands and feet. They later exhibit excessive appetite and hyperphagia that lead to severe obesity. Prader–Willi syndrome is usually associated with mild to moderate intellectual disability. Approximately 70% of the individuals with these syndromes have *de novo* deletions without recurrence risk in the family. The rest have several complicated genetic patterns that need advanced techniques for diagnostic assessment. Because this syndrome has no clear pathognomonic features it may remain undiagnosed and such individuals might even be referred for psychiatric treatment because of an eating disorder. Obviously, psychological factors are not the primary cause here but supportive psychotherapy might be helpful. The treatment is based on behavioral modification and imposing strict environmental limits on food intake, as well as necessary educational programming.

Initially it was found that one of four persons with the *Rubinstein–Taybi syndrome* had a microdeletion in chromosome 16p13.3 (Breuning et al. 1993). However, it has been discovered that only a small percentage of these patients have deletions that are identifiable with usual chromosome or FISH studies, with others having abnormalities at the molecular level. This microdeletion syndrome has been found to be due to inactivation of a single gene (Ligon et al. 1997).

**Table 42–4 Examples of Various Malformation Syndromes Associated with Intellectual Disability**

| Syndrome | Features |
|---|---|
| **Chromosomal aberrations** | |
| Trisomy 21: Down syndrome | See text |
| Trisomy 13 syndrome | IQ < 50, growth retardation; polydactyly; holoprosencephaly; ear, eye, and scalp defects; CHD |
| Deletion 5p: cri du chat syndrome | IQ 20–50, growth retardation, microcephaly, cat-like cry, hypertelorism, epicanthus |
| **Malformation syndromes due to microdeletions** | |
| Prader-Willi syndrome | IQ 20–80, almond-shaped eyes, small hands and feet, cryptorchidism, hypotonia, obesity |
| Angelman's (happy puppet) syndrome | IQ < 50, ataxia, seizures, microbrachycephaly, large mouth, prognathism, jerky gait |
| Williams' syndrome | IQ 40–80, long philtrum, prominent lips, supravalvular aortic stenosis, loquatious, "cocktail party manners," hypercalcemia in infancy |
| Rubinstein-Taybi syndrome | IQ 20–85, growth retardation; beaked, long nose; broad thumbs; narrow palate |
| **Malformation syndromes of unknown cause** | |
| de Lange's syndrome | IQ < 50, growth retardation, microcephaly, hirsutism, synophrys, anteverted nostrils |
| Sotos' syndrome | Sometimes mental retardation, large size, macrocephaly, prognathism, downward-slanting palpebral fissures |
| **Prenatal infections** | |
| Congenital rubella | ± Mental retardation, microcephaly, hearing loss, cataracts, CHD, microphthalmia, retinal pigmentation |
| Toxoplasmosis | ± Mental retardation hydrocephalus microcephaly, chorioretinitis, cataracts, intracranial calcifications, hepatosplenomegaly |
| **Toxic agents** | |
| Fetal hydantoin syndrome | ± Mental retardation, growth retardation, short nose, hypertelorism, cleft lip, CHD |

*CHD, Congenital heart disease.

*Source:* Data from Jones KL (1988) Smith's Recognizable Patterns of Human Malformation, 4th ed. WB Saunders, Philadelphia.

Microdeletion of 7q11.23 is present in 90–99% of individuals with *Williams syndrome*. The visuospatial abnormalities that are specifically associated with this syndrome may be due to loss of the LIM-kinase I gene (Moldavsky et al. 2001). The phenotype of the Williams syndrome includes short stature, aortic stenosis or other congenital heart defects, and hypercalcemia in childhood. The facial appearance is characteristic and may include periorbital fullness, a long philtrum (groove on upper lip), full lips with open mouth, a stellate iris pattern, and early graying of hair. The behavioral phenotype may also be characteristic and includes an outgoing personality and overwhelming talkativeness that might even tax the caregivers' patience. The symptoms vary, however, and even autistic disorder and aggressiveness have been found in these individuals.

*Velocardiofacial syndrome* (VCFS), also called Shprinzen or CATCH 22 syndrome is usually associated with microdeletion at chromosome 22q11.2 (Ligon et al. 1997). It has been associated with cleft palate, velopharyngeal incompetence, congenital heart or major vascular anomaly, hypocalcemia, and immunodeficiency. Persons with this syndrome often have normal cognitive skills, although may present with language and motor delays as a young child, learning disabilities when older, and less frequently with intellectual disability (Wang et al. 2000). This syndrome is associated with a significant risk for psychiatric disorders including bipolar disorder, major depression, and other psychoses. The prevalence of VCFS is estimated to be 1 in 2,000 live births, thus it should be considered in the differential diagnosis of psychiatric patients.

### *Submicroscopic Rearrangements*

The telomeres of chromosomes are rich in genes and possess characteristics that lend themselves to misbalances. Tests evaluating the subtelomeric area, or functional end of the chromosome, have been used to identify submicroscopic abnormalities that are not visible with standard techniques. The application of FISH to the subtelomeric area of all chromosomes has been used to identify abnormalities such as deletions, duplications, and translocations in these areas. It has been reported that 7.4% of children with moderate to severe intellectual disability and normal karyotype testing will have an identifiable subtelomeric abnormality. It has been suggested that between 4% and 35% of apparently idiopathic intellectual disability is a result of rearrangements in the subtelomeric area (Sogaard et al. 2005, Moeschler and Shevel 2006, Velagaleti et al. 2005, Shoumans et al. 2005). Many clinicians will obtain subtelomeric FISH studies in children with intellectual disability without an identifiable etiology when chromosome analysis is normal (Moeschler and Shevell 2006); others performed this test with additional criteria, particularly in the context of dymorphology of severe ID and a family history of developmental delay (Sogaard et al. 2005, Velagaleti et al. 2005).

Genomic microarrays, or comparative genomic hybridization (CGH), is a newer technique that evaluates structural abnormalities on the entire chromosome (Moeschler and Shevell 2006). Identification of submicroscopic chromosomal abnormalities has been reported to occur in 15–24% of patients with idiopathic intellectual disability (Shoumans et al. 2005). CGH has been used to characterize known genetic syndromes such as identifying the CHD7 gene responsible for Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness (CHARGE) syndrome. It has been used to characterize subtelomeric imbalances such as Williams syndrome (Moeschler and Shevell 2006). This technique has been also used in lieu of subtelomeric FISH testing. Array-CGH has been utilized to identify chromosomal changes idiopathic ID in whom prior testing has been negative.

Comparative genomic hybridization testing is used as an adjunct, not a replacement, for other genetic tests. (Mao and Pevsner 2005). High resolution karyotype and other FISH studies continue to play important roles in the evaluation of ID. While CGH may identify abnormalities not visible with other methods, there are also single nucleotide polymorphism (SNP) oligonucleotide arrays that have been used for rapid molecular karyotyping of a small amount of DNA to detect subtle deletions and duplications (Rauch et al. 2004).

Syndromes due to microdeletions had previously been classified as malformation syndromes of unknown origin, but because of the described findings of microdeletions, they are now placed in a separate category between chromosomal aberrations and single gene defects (Table 42–4).

### *Single Gene Defects*

A mutation in a single gene results in defective enzymes or proteins. These defects may cause an accumulation of substrate, inability to stop the formation of a damaging end product or block the production of a needed substrate. There may be defects in receptor or transport systems, as well as alterations of proteins. Inheritance of these monogenic mutations may be autosomal dominant, autosomal recessive, X-linked, or mitochondrial.

## Disorders with Autosomal Dominant Inheritance

### *Tuberous Sclerosis Complex*

TSCis an example of the disorders in this group associated with intellectual disability. It is caused by a mutation in a gene affecting the formation of the ectodermal layer of the embryo. Because the skin and the CNS develop from this layer, abnormalities are seen in both. The skin lesions include angiofibromas in the form of macules on the cheeks (adenoma sebaceum), with a butterfly-like distribution, especially after puberty. Café au lait macules or nonpigmented ash leaf–shaped areas are also found. Intellectual disability, epilepsy, and calcifications in the brain are seen, as are tumors. Epileptic seizures often begin as infantile spasms, which alert the physician to look for other symptoms of this disorder. If TSC is diagnosed, both parents should be examined carefully because the mutation is inherited in about 28% of cases. Because of the dominant inheritance, the risk of recurrence is 50% for each pregnancy among affected families. The expression of this gene mutation varies from small skin discolorations (which may indicate a carrier state) to multiple disabling conditions. It is a relatively rare disorder (with a prevalence of 1 in 30,000 to 1 in 50,000 live births), but it may be found in about 0.5% of persons with severe intellectual disability. The early onset infantile seizures, anatomical location of tubers in the temporal lobe, or associated disruption in the temporal lobe function, are all

predictive of a greater degree of onset of autism spectrum disorders or autism-like symptoms. The seizures therefore need to be treated proactively.

### *Other Disorders with Autosomal Recessive Inheritance*

Most metabolic disorders belong to this category. They are caused by single mutated genes that disturb the metabolism by deficient enzyme activity. The risk of healthy carrier parents having an affected child is 25% for each pregnancy. The diagnosis is made by detection of abnormal metabolic products in the urine, blood, or tissues and/or by low or absent enzyme activity. When there is high clinical suspicion and the possibility of gene detection, direct DNA techniques might be used. The metabolism of amino acids, carbohydrates, lipids, and mucopolysaccharides are affected in different disorders. A few examples of inborn errors of metabolism are given in Table 42–5.

PKU is the best known and most common of the metabolic disorders. The incidence of PKU varies among populations. The incidence in the US is 1 in 8,000 live births among Whites and about 1 in 50,000 live births among African–Americans. The enzymatic defect is diminished activity of phenylalanine hydroxylase, which leads to a high serum phenylalanine level affecting, among other things, myelination of the CNS. The phenylalanine hydroxylase gene has been mapped to 12q22–24.1. Prenatal diagnosis and carrier detection are possible, and all newborns are screened for PKU in most developed countries. It was described in 1934 by Folling in ten children with ID, hypertonia, and hyperreflexia, with a musty odor in urine and sweat. Seizures and tremors are common, as are eczema and psychotic manifestations. The clinical symptoms can be prevented by use of a low-phenylalanine diet soon after birth. Increasingly, a lifelong low-phenylalanine diet is recommended to prevent later deterioration in cognitive functions. Women with PKU who are successfully treated do not have clinical manifestations themselves but still have phenylalanine blood levels high enough to cause brain damage to a fetus if they become pregnant. To avoid this, strict adherence to the diet is important before they become and during pregnancy. The diet requires restriction

**Table 42–5 Examples of Inborn Errors of Metabolism Causing Intellectual Disability**

| Disorder | Enzyme Defect | Onset/Life Expectancy | Clinical Features | Laboratory Diagnosis/Treatment |
|---|---|---|---|---|
| **Aminoacidurias** | | | | |
| PKU | Phenylalanine hydroxylase | I/A | If not on diet: vomiting, musty odor, eczema, seizures, tremors, psychosis | U: ferric chloride test; gene locus 12q22–24; diet: low in phenylalanine |
| Homocystinuria | Cystathionine β-synthetase | I/A | Seizures, venous thromboses → cerebrovascular accidents, Marfan's habitus, malar flush, lens subluxation, often MR | U: cyanide-nitroprusside test |
| **Lysosomal disorders glycoproteinoses** | | | | |
| Mannosidosis | Mannosidase | 6–36 mo/A | Coarse facial features, short stature, skeletal changes, hepatosplenomegaly, loose joints, hearing loss, ataxia | U: oligosaccharides |
| I-cell disease | Multiple lysosomal hydrolases | I/2–8 yr | Early facial feature coarsening, short stature, stiffness of joints, gum hyperplasia | U: sialyl oligosaccharides |
| **Mucopolysaccharidoses** | | | | |
| MPS I (Hurler's) | L-Iduronidase | I/10 yr | Early facial feature coarsening, hepatosplenomegaly, growth failure, corneal clouding, skeletal changes | U: heparan sulfate, dermatan sulfate |
| MPS II (Hunter's) | Iduronidate sulfatase | I/15 yr | Symptoms milder and progression slower than in MPS I | U: heparan sulfate, dermatan sulfate |
| **Sphingolipidoses** | | | | |
| Tay-Sachs ($GM_2$) | $GM_2$ ganglioside–*N*–acetylhexosaminidase | 3–6 mo/2–3 yr | Hypotonia → rigidity, macular cherry red spot → blindness, seizures, hyperacusis | Serum hexosaminidase assay |
| Metachromatic leukodystrophy | Arylsulfatase A deficiency | 1–4 yr/10–15 yr | Gait disturbance, ataxia, motor incoordination | U: metachromatic cells, sulfatase A assay; sural nerve biopsy |

*All disorders cause mental retardation except that in homocystinuria it does not occur in every case. Dietary treatment benefits patients with PKU and galactosemia. Prenatal diagnosis is available for all disorders. Inheritance is autosomal recessive, except for MPS II and Lesch-Nyhan, which are X linked. I, Infancy; A, adulthood; U, urinary; MR, mental retardation.

*Source:* Adapted from Nelhaus G, Stumpf DA, and Moe PG (1984) Neurologic and muscular disorders. In Current Pediatric Diagnosis and Treatment, 8th ed., Kempe CH, Silver HK, and O'Brien D (eds). Large Medical Publications, Los Altos, CA, pp. 628–711; Robinson A, Goodman SI, and O'Brian D (1984) Neurologic and muscular disorders. In Current Pediatric Diagnosis and Treatment, 8th ed., Kempe CH, Silver HK, and O'Brien D (eds). Lange Medical Publications, Los Altos, CA, pp. 992–1030. Copyright 1984 Appleton & Lange.

of proteins, including meats, fish, milk, bread, cake, nuts, and even vegetables. A phenyalanine-free dietary supplement is required to ensure adequate nutritional support, which may be unpleasant for some and may also produce side effects (Levy 1999). There are new treatments that are being developed that would allow for a less restrictive diet such as an oral agent phenoptin (6R-BH4) that would potentially reduce blood levels phenylalanine levels (Shuett 2004).

### X-Linked Intellectual Disability

X-linked intellectual disability may occur as often as 1 in 600 males; it is felt to account for 10–20% of intellectual disabilities that are inherited (Winnepenninckx et al. 2003). While Down syndrome is the most common congenital form of intellectual disability, fraX is the most common inherited form of ID. The estimated prevalence is 1 in 4000 males and 1 in 6000 females (Walker and Johnson 2006), although other studies have estimated the female prevalence to be half that seen in males (American College of Medical Genetics 2006).

FraX was first reported by Lubs (1969) and was connected to the clinical syndrome by Harvey in 1977 (Harvey et al. 1977). Because of a constriction at the location Xq27.3, the FRAXA site, it appears as if the chromosome is fragile and a part of it is breaking off. Demonstrating this phenomenon requires a folate-poor cell culture/medium. It has been studied more consistently since the early 1980s when the connection with folate-poor medium was identified. Methylation of fully mutated gene causes inactivation of FMR1-protein (FMR1P), which is the basic defect in the fraX (Tassone et al. 1999). The FMRIP has been noted to be involved in both pre- and postnatal development of the brain (Dykens and Hodapp 2001).

The genetic defect involved in the fragile X-linked mental retardation has been traced to the *FMR1* gene, an unstable region in which there is a mutation consisting of repeats of the triplet nucleotide cytosine-guanine-guanine (CGG). The normal X chromosome contains 5–50 copies of this triplet; asymptomatic female or male carriers have 50–200 copies (premutation), and affected individuals have over 200 copies (full mutation). The range of the triplet repeats can be demonstrated by the Southern Blot Technique, which is used for the diagnosis of fraX and the carrier state (Figure 42–2). Half the children born to carrier women receive the X chromosome with the mutated *FMR1* gene. It remains as a premutation approximately 20% of the time or increases to a full mutation (triplet repeat expansion), which causes ID. The premutation that expands to the full mutation is only transmitted by females. Females with premutations have an increased risk of ovarian failure (American College of Medical Genetics 2006). Approximately, half of females with a full mutation present with cognitive deficits such as learning disabilities, borderline intellectual functioning, and intellectual disability. Approximately 20% of the sons of carrier females with a premutation have normal intelligence and phenotype but are carriers; these sons transmit the premutation to all their daughters who, through expansion of the unstable repeats of the triplet nucleotide CGG, might produce affected children.

The physical features that are associated with fraX are more notable in boys and become more prominent

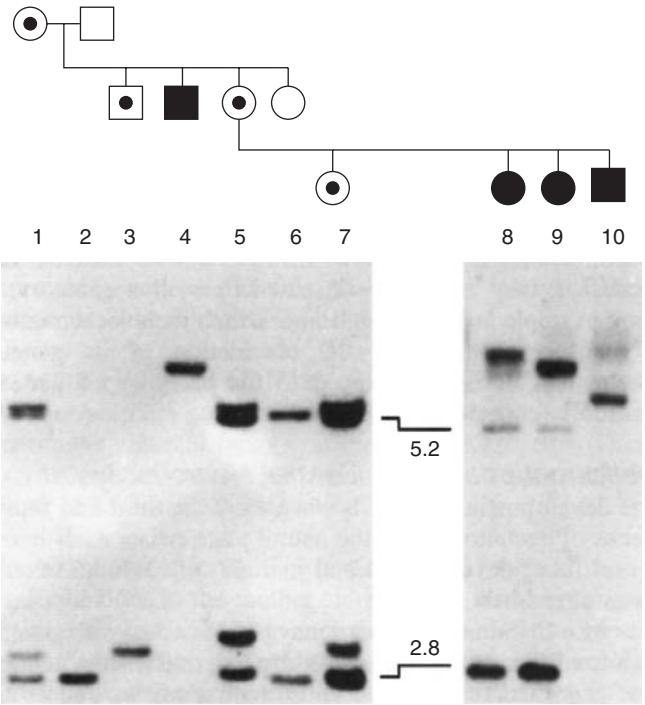



**Figure 42–2** *fraX: molecular analysis by Southern blot and pedigree. Inheritance of the fragile X mutation and unstable element in a three-generation family. Genomic DNA was digested with EcoRI and methylation-sensitive EagI and probed with StB12.3 (Courtesy: Mandel JL, Department of Human Genetics, University Hospital Nijmegen, the Netherlands). Double digestion allows the detection of methylation in addition to $CGG_n$ amplification. Normal fragment sizes are 2.8 kilobase (kb) and 5.2 kb for active and inactive X chromosomes, respectively, as seen in the normal male and female (lanes 2 and 6). The normal fragment is lacking and is replaced in carrier males by a fragment larger than 2.8 kb (lane 3) and in affected males by a fragment larger than 5.2 kb (lanes 4 and 10), indicating methylation (inactivation) of the FMR1 gene. In carrier and affected females, in addition to enlarged premutation alleles (lanes 1, 5, and 7) or methylated full mutation (lanes 8 and 9) alleles or fragments, normal-sized fragments of 2.8 and 5.2 kb derived from a normal X chromosome are present. □, Normal male; ▣, carrier male; ■, affected male; ○, normal female; ⊙, carrier female; ●, affected female. (Courtesy: Va¨isa¨nen ML, Department of Clinical Genetics, Oulu University Central Hospital, Oulu, Finland.)*

with the onset of puberty. Characteristic phenotypical features include an oblong face, prominent ears and jaw, and macroorchidism. They are often restless and hyperactive and have a short attention span. Their developmental milestones, especially speech development, are delayed. Most have moderate intellectual disability, but it may be severe in others. Male carriers do not have intellectual disability. Females with fraX who have the full mutation and are symptomatic usually have learning disabilities or mild intellectual disability. Behavioral symptoms have been described in these individuals—hyperactivity and social withdrawal in about 50% and depression in about 25% (Mandel et al. 1992).

Males with fraX may present with anxiety, hyperactivity, reduced attention span, and delayed developmental milestones, particularly, in the area of speech and language skills. They also may exhibit social withdrawal with reduced eye contact, echolalia, abnormal staccato speech, stereotypic motor behavior, and unusual responses to sensory stimuli. Approximately 25–35% of children with Fragile X syndrome, however, have been noted to meet diagnostic criteria for an autism spectrum disorder (Walker and Johnson 2006).

*Rett Disorder* is associated with mutations in the MECP2 encoding methyl-CPG-binding protein 2 and is an X linked dominant disorders (Moldavsky et al. 2001, Amir et al. 1999). This protein is necessary in differentiation of tissues during organogenesis. Identification of this abnormality is performed by molecular genetic testing (Moeschler and Shevell 2006). Males have very rarely been identified with this disorder, as the hemizygous MECP2 gene is not compatible with life (Winnepenninckx et al. 2003). The DSM-IV-TR currently includes Rett Disorders as one of the Pervasive Developmental Disorders (PDD). Girls with this disorder generally exhibit normal early development and head circumference. Between, approximately, 5 and 48 months of age, there is deceleration of head growth. Communication and social interaction may be affected and there also stereotypical hand movements that are symmetrical, midline, and prevent the purposeful use of the hands. Other symptoms include ataxia, tremor, poorly coordinated gait, bruxism, hyperventilation, spasticity, and seizure disorder. The deterioration is initially rapid although later plateaus. Thirty families with more than one affected female have been studied. In only five of such multiplex families the MECP2 mutation was seen and other mutations that were found were "nonsense" or "missense" suggesting a different mechanism (Webb and Latif 2001). In this group also a few boys were seen with atypical milder symptoms.

### *Mitochondrial*

Much has been learned in recent years about mitochondrial genetics and the mutations to mitochondria DNA (mtDNA) that are responsible for a number of inherited diseases. The inheritance of these disorders is different from that seen in Mendelian genetics, as inheritance is primarily maternal (Taylor and Turnbull 2005). An example of such a disorder is Leigh syndrome, which is a progressive neurodegenerative disorder that affects the brainstem, basal ganglia, thalamus, cerebellum, and spinal cord. Leigh syndrome is genetically heterogeneous and involves abnormalities in energy metabolism. The most common defect is in oxidative phorphorylation (Online Mendelian Inheritance of Man (OMIM)). Children may present with psychomotor delay, hypotonia, seizures, and lactic acidosis (Dimauro and Schon 2003). Stresses such as acute illnesses or anesthesia, may be associated with regression of developmental skills.

### *Multifactorial Intellectual Disability and Complex Disorders*

The etiology of intellectual disabilities may also be complex or multifactorial, with the interaction of a number of genetic and environmental factors. Approximately, 50–75% of individuals with autism present with intellectual disability (Johnson 2006). It is considered to be a disorder that is highly heritable, although the genetics and the phenotypic presentation are felt to be very complex and heterogeneous. There is a high monozygotic twin concordance, as well as a broader developmental phenotype that is seen in families with a child with an autism spectrum disorder. Different techniques have been used to study the genetics of autism, including positional cloning, study of candidate genes, and evaluation of chromosomal abnormalities (Wassink et al. 2004).

More than half the individuals with mild intellectual disability have no other disability. Their speech development in childhood is delayed, and at school age they might be described as immature. Some of their first-degree relatives have a history of educational problems. A history of mental illness is also common in these families. The environmental factors and the family's socioeconomic situation are often suboptimal. However, with improvement in medical technologies, there has been an increase in identification of biologic factors.

In a large epidemiologic study in California of individuals with intellectual disability of unknown etiology, social and biologic factors were identified as important contributing factors to the etiologies for both mild and severe intellectual disability. Low birth weight was the strongest risk factor for both mild and severe intellectual disability. An increased risk of mild and severe intellectual disability was identified for children whose mothers were of advanced age and low maternal education (Croen et al. 2001).

The Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) monitored intellectual disability (mental retardation), cerebral palsy, hearing loss, vision impairment, and autism in 8-year-old children in the Atlanta metropolitan area. In this study, the prevalence of mild intellectual disability in Black males was four and three times greater in 1996 and 2000, respectively, compared to White males. The prevalence of moderate to profound intellectual disability was also higher in Black males compared to White in both years, although the differences were not as marked as in the mild intellectual disability groups (Bhasin et al. 2006). Various explanations have been put forth for the differences in mild intellectual disability, including prenatal factors such as diabetes, sickle cell anemia, and others. Socioeconomic factors that impact results of cognitive testing have also been noted.

Historically, the probability of identifying etiologic factors for individuals with severe intellectual disability has been noted to be greater than for those with mild intellectual disability. However, in a tertiary care setting, approximately half of the patients were identified as having a unifying medical diagnosis for their intellectual disability with use of an extensive algorithm for medical assessment, regardless of the level of intellectual disability. Newer tests, including FISH studies for suspected disorders, subtelomeric FISH for a high index of suspicion of nonspecific genetic disorders, karyotype microarray analyses, and other studies were used (van Karnebeek et al. 2005).

## Prenatal Causes: Malformations and Malformation Syndromes of Unknown Cause

Congenital anomalies are structural malformations that are present at birth. They may be associated with multifactorial inheritance and also may be of unknown etiology. There may be a single primary anomaly affecting one structure, or a multiple malformation syndrome in which there are several observed anomalies with the same etiology. These multiple malformation syndromes may be the result of chromosomal abnormalities, single gene defects, de novo mutations, maternal conditions, intrauterine infections, toxicity of drugs or teratogens. They usually occur during organogenesis of the embryo and are seen in approximately 3% of newborns. Up to 40% of persons with intellectual disability of unknown cause have three or more major or minor anomalies.

Major malformations result from an intrinsic error in organogenesis such as cleft lip and palate. Minor malformations or dysmorphic features such as epicanthal folds and transverse palmar creases do not cause functional problems. Minor dysmorphology may serve as indicators of disturbance in organogenesis and a prenatal etiology for a child's developmental presentation. Deformation is defined as an abnormality of a body part caused by mechanical compression such as club-foot. Disruption is destruction of a previously normal structure. These should not be considered malformations because their origin is extrinsic and they usually occur later than malformations (Graham 1992).

The causation and pathogenesis of many syndromes have been identified with medical diagnostic advances, sometimes leading to changes in the classification of disorders. Although Down syndrome is associated with a number of malformations, it is now categorized as a genetic disorder (chromosomal aberrations) because of the understanding of its genetic mechanism. Angelman and Williams syndromes, formerly classified as malformation syndromes of unknown origin, are now considered microdeletions, a subgroup of genetic causation.

### *Malformations of the CNS*

The development of the CNS begins at the third and fourth weeks of gestation when the neural plate twists itself into a neural tube; development and maturation continue several years after birth. The CNS malformations may be connected with genetic abnormalities or may be caused by external insults and are then classified accordingly.

*Neural tube defects* are examples of severe CNS malformations known to be multifactorial, with both extrinsic and genetic contributing factors. *Anencephaly* originates when the neural tube fails to close at the beginning of CNS development. This condition is associated with absence of a significant portion of brain and skull, resulting in stillborn birth or death soon thereafter. With adequate folate supplementation before conception and during the first trimester of pregnancy, 50–70% of these anomalies can be prevented. Since mandatory folate fortification of cereal grains in January 1998, there have been approximately 1340 live births with spina bifida and 840 births with anencephaly, representing a 26% decline in estimated average cumulative incidence of neural tube defects (Center for Disease Control, 2004). Before fortification in 1995–1996, the average annual spina bifida and anencephaly cases per 10,000 live births were 6.4 and 4.2, respectively, following fortification in 1999–2000, the rates were 4.1 and 3.5, respectively. Neural tube defects range from anencephaly, incompatible with life, to an asymptomatic, usually undiagnosed, occult *spina bifida*. *Meningomyelocele* is a neural tube defect characterized by various neurological deficits, depending on the level of involvement of the spinal cord. It is often associated with other CNS malformations, especially hydrocephalus, which may be associated with mental retardation. However, individuals with severe disabilities associated with meningomyelocele may have intact intelligence.

*Holoprosencephaly* occurs when the forebrain fails to closure during CNS development, resulting in a single-lobed brain rather than double-lobed cerebral hemispheres. Severity of symptoms is associated with the degree of brain impairment. Holoprosencephaly is associated with mid-facial anomalies and may occur as part of other syndromes such as trisomy 13. *Microcephaly* may also be associated with chromosomal anomalies, and may have autosomal dominant, recessive, or X-linked inheritance. Microcephaly may also result from arrested brain growth caused by extrinsic factors such as prenatal and neonatal viral infections as well as intracranial hemorrhage.

Disturbances during the cell migration that occurs from 7 to 24 weeks of gestation may result in cortical gyrus anomalies—*lissencephaly* (nongyral cortex) and *pachygyria* (broad gyri). These may also be associated with chromosomal deletions. An example is the *Miller–Dieker syndrome* with multiple major and minor anomalies. Smaller areas of heterotopias are also caused by disorders in migration. Periventricular and subcortical heterotopias have been associated with seizures, and intracortical heterotopias have been noted to occur in individuals with reading disorders and schizophrenia (Chevassus-Au-Louis et al. 1998). Agenesis of the *corpus callosum* also may also occur from a disturbance of cell migration and may be present in a number of syndromes. Occasionally, it is also seen on neuroimaging studies of nonsymptomatic individuals. Hydrocephalus (enlargement of ventricles with increased cerebrospinal fluid volume) may be the result of an unknown malformation, but it can also have X-linked inheritance, develop in connection with meningomyelocele, or result from pre-, neo-, or postnatal infection, tumors, and other causes.

### *Malformation Syndromes of Unknown Origin*

An estimated 50% or more of the malformation syndromes have no known cause. Many of these syndromes are known by the name of their discoverer (see Table 42–5). In clinical practice, however, one often encounters malformation syndromes that have not been formally described and named, with improved genetic techniques, the cause of many of these malformations will certainly be delineated.

## External Prenatal Causes

External prenatal causes include the deleterious effects of identifiable external factors on the developing fetus. These external prenatal causes are estimated to be responsible for 6–18% of mental retardation cases (McQueen et al. 1986, Gillberg 1997).

### *Maternal Infections*

Viral infections in the mother can interfere with organogenesis, and the earlier in pregnancy they occur the more severe their effect will be, as exemplified by *congenital rubella*. Rubella infection during the first month of pregnancy affects the organogenesis of 50% of embryos. Infection in the third month of pregnancy disturbs the development of 15% of fetuses. Various systems are affected that may result in intellectual disability, microcephaly, hearing and vision impairment, congenital heart disease, and behavior problems. Fortunately, the incidence of congenital rubella has greatly decreased because of the availability of immunization to prevent this infection.

*Congenital cytomegalovirus* (CMV) infection may result in microcephaly, sensorineural hearing loss, and psychomotor retardation. Antibodies against cytomegalovirus are found in approximately 80% of adults. Depending on

the population, primary infections occur during 2–5% of pregnancies. CMV inclusion bodies are seen in urine specimens of newborns who were infected prenatally.

*Congenital toxoplasmosis* may result in significant problems in about 20% of infected infants (hydrocephalus, microcephaly, psychomotor retardation, visual and hearing impairment) and result in milder developmental problems later in life. Congenital toxoplasmosis may be prevented by avoiding ingestion or exposure to raw or undercooked meat, or exposure to contaminated soil or cat litter.

*Congenital human immunodeficiency* virus (HIV) infection has been recognized as being associated with abnormal neurodevelopmental outcome. HIV-positive children were found to be more apt to present with abnormal motor and cognitive outcome during the first 2½ years of life, compared to congenital HIV exposure that did not cause infection. The children were considered to have abnormal motor and cognitive development if they if they had 2 SD or more delays on testing using the Bayley Scale of Infant Development. Early identification of these delays is felt to be important in order to initiate aggressive antiviral treatments (Chase et al. 2000).

In a German study of 41 children born to HIV–positive mothers, neurological symptoms were described at 1–7 years of age (Schmitt et al. 1991). HIV encephalopathy was characterized by microcephaly, progressive neurological deterioration, mental retardation, cerebellar symptoms, and behavioral changes. Prophylactic intravenous immunoglobulin therapy with and without zidovudine was often able to prevent regression. Improvement was seen with zidovudine treatment.

## Toxic Substances

The most important of the teratogenic substances is ethanol, which is the cause of FAS. The prevalence of this syndrome varies around the world. Its occurrence in industrialized countries is estimated to be about one in 1,000 newborns. The diagnosis of FAS requires that a child's weight or height be less than the 10th percentile. The child presents with notable dysmorphology including the presence of a smooth philtrum, thin vermilion, and short palpebral fissures. In addition, when alcohol is used heavily during pregnancy, there is evidence of CNS dysfunction, including microcephy, developmental delays or functional deficits. In a milder condition, called fetal alcohol spectrum disorder only two of the three dysmorphic facial features may be present, and one other characteristic such as growth retardation or developmental problems, are seen (Riley and McGee 2005). Social environmental factors during the early years have an important role in the outcome. (Figure 42–3).

Some "prescription drugs" may have various teratogenic effects. *Fetal hydantoin syndrome* (FHS) is the result of intra-uterine exposure to hydantoin (dilantin) which has long been known as being contraindicated during pregnancy, and alternative drugs are recommended for seizure control in pregnant women.

## Toxemia of Pregnancy and Placental Insufficiency

Intrauterine growth retardation has many causes, the most important being maternal toxemia with its consequences,



**Figure 42–3** *A woman with facial features associated with fetal alcohol syndrome: (1) smooth philtrum, (2) thinned upper vermilion, (3) hypoplastic midface, (4) low and flat nasal bridge, (5) epicanthal fold, (6) short palpebral fissure, (7) low-set ears, and (8) microcephaly.*

ending in insult to the CNS (Figure 42–4). Prematurity may be of maternal or fetal origin. When it is connected with fetal developmental deviations, the prognosis depends on the infant's general condition. Prematurity and especially intrauterine growth retardation predispose to many perinatal complications, which may result in insult to the CNS and developmental problems.

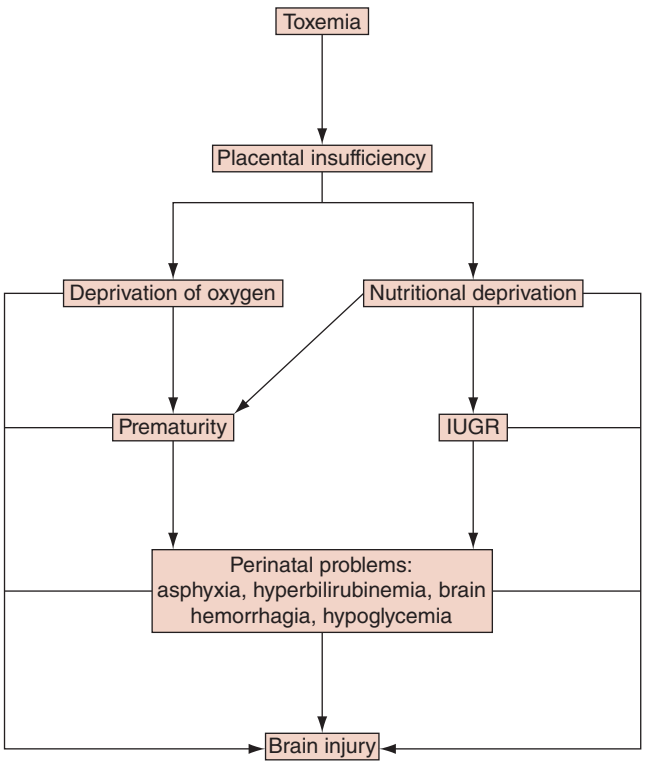



**Figure 42–4** *Toxemia of pregnancy and its consequences.*

## Perinatal Causes

This period refers to 1 week before birth to 4 weeks after birth.

### *Infections*

During the neonatal period, the most important infection from the point of view of its developmental sequelae is herpes simplex type 2. The neonate infected during a vaginal delivery may develop encephalitis within 2 weeks. Early treatment with acyclovir may alleviate the otherwise poor outcome—microcephaly, profound mental retardation, and neurological deficits. Neonatal bacterial infections such as sepsis and meningitis, also may have long-term consequences on developmental outcome.

### *Hypoxia and Ischemia*

Hypoxemia and reduced cerebral blood flow may result in hypoxic-ischemic encephalopathy (HIE). The degree of impairment depends on the severity of the insult and the amount of resultant damage from reperfusion. Cerebrovascular events occur in term infants approximately 1 in 4000 term births, yet occur with greater frequency in the preterm infant (Alix 2006). Overall, severe HIE affects 2–4 per 1000 live births, with a 50–75% mortality rate (Raju 2006). Ischemic injury to the developing white matter, particularly in premature infants, has been associated with damage to the periventricular white matter. Periventricular leukomalacia (PVL) occurs in 4–26% of premature infants in neonatal intensive care units, and frequently is associated with cerebral palsy, cognitive and visual impairment. PVL may occur because of ischemia/reperfusion injury or due to cytokine-induced damage after fetal or maternal infection (Zach 2006).

Neurological symptoms during the neonatal period have a strong association with prenatal developmental deviation, later neurological integrity, and intellectual level. For these reasons, infants with perinatal problems need a thorough examination for dysmorphic features and close follow-up because multiple disabilities might become evident later in life.

### *Other Perinatal Problems*

ROP (formerly referred to as retrolental fibroplasia) is a potentially blinding eye disorder that primarily affects premature infants weighing about 2¾ pounds or less, born before 31 weeks of gestation. There are 14,000–16,000 annual births in the US affected by ROP. More than 90% of them are in the mild category and improve without medical treatment. About 1,100–1,500 infants require treatment and about 400–600 infants in the US become legally blind from ROP. The incidence of ROP was much more common when premature infants were routinely given 100% oxygen. However, since 1954, reduction of the level of oxygen and better methods of control of oxygen level administered to premature infants has reduced the incidence of ROP. Today, with smaller and more premature infants being saved, ROP remains as a major cause of blindness in childhood. ROP is often associated with other CNS damage, intellectual and other developmental problems. Besides the fragility of retinal vessels that can cause blindness, extremely low birth weight infants are also at risk for intracranial hemorrhage, as well as hypoglycemia resulting from a lack of hepatic glycogen storage. These neonatal problems may have results similar to those of asphyxia. Hyperbilirubinemia may result from increased destruction of red cells (e.g., hemolysis due to maternal–child blood group incompatibility) or decreased excretion of bilirubin (e.g., due to an immaturity of liver function). High level of bilirubin may result in kernicterus and may be associated with cerebral palsy, sensorineural hearing loss, and intellectual disability.

## Postnatal Causes

### *Infections*

Bacterial and viral infections of the brain during childhood may cause meningitis and encephalitis and result in significant neurological sequelae. The number of these complications has decreased because of improved treatment and the availability of immunizations such has been seen in the case of the Haemopholis influenza (Hib) vaccine.

### *Toxic Substances*

*Lead poisoning* is still an important cause of intellectual disability in the US. The most frequent source of lead is pica—ingestion of flaking old lead-based paint. Other sources of lead have been certain fruit tree sprays, some glazed pottery, and fumes from burning automobile batteries. In 1995, leaded fuel accounted for only 0.6% of total gasoline sales in the United States. On January 1, Clean Air Act banned all sale of leaded gasoline for use in on-road vehicles. Therefore leaded gasoline is no longer considered to be a major source of lead poisoning in the Unites States, although it remains a significant contributor in developing countries. Gastrointestinal symptoms dominate in acute poisoning. Headache may be associated with increased intracranial pressure, which may even lead to coma. Late manifestations include developmental delays and intellectual disability, ataxia, seizures, and personality changes.

Among childhood malignancies, brain tumors are second in frequency after leukemia. Of these, 70–80 are gliomas, symptoms of which depend primarily on the location of the tumor. Some tumors are benign and treatable, although most have deleterious effects resulting in various neuropsychiatric symptoms depending on their location and extent. In addition, treatment such as surgery and radiation might affect the integrity and function of the brain. Other chronic illnesses in childhood such as congenital heart disease, diabetes and asthma, and/or the effects of the treatment protocols, have been noted to potentially have both short- and long-term effects on the CNS either directly or indirectly through other systems such as immunologic, hematologic, vascular, and pulmonary. As a result, developmental outcome may be affected based on the intensity, duration, and timing of these insults (Armstrong 2006). Traffic accidents, drowning, and other traumas are the most common causes of death during childhood, and are responsible for intellectual and developmental disabilities in survivors. Near-drowning is often devastating, although improvement of functional capacity may be achieved in some situations by rehabilitation because of the ability of the developing brain to recover.

### *Psychosocial Problems*

The developmental level of a growing individual depends on the integrity of the CNS and on environmental and

psychological factors. The importance of environmental stimulation for child development has been appreciated since research on children in institutions showed that development was severely affected in an environment with emotional deprivation, even if there was adequate physical care. Poverty predisposes the child to many developmental risks such as teenage pregnancies, malnutrition, abuse, poor medical care, and deprivation. Severe maternal mental illness is another risk factor for developmental and behavioral problems. Mothers with severe and chronic illness might have difficulty in providing adequate care and stimulation. Children of mothers who have serious mental illness (SMI) including schizophrenia are at risk for the development of cognitive deficits, which may not be secondary to maternal illness but may represent a genetically determined predisposition to schizophrenia. Psychotic illness in a child has also been shown to be associated with a decline in cognitive abilities.

## Unknown Causes

There is much variation in the report of unknown etiology for intellectual disability, due to epidemiologic challenges related to reliable classification systems, populations studied, and methods of assessment (Leonard and Wen 2002). When a unifying medical diagnosis or etiology cannot be found, it is usually assumed that the developmental presentation was prenatally determined. Severe intellectual disability has been noted to have identifiable causes in 45–80% of the time, with biological causes identified in less than half of those with mild intellectual disability (Roberts et al. 2004). No etiologies were identified for severe intellectual disability in 22% by Strømme and Hagberg (2000), 49% individuals by Cans et al. (1999), and 65% by Croen et al. (2001). In some studies, no differences were found between the severe and mild intellectual disability groups in the ability to identify an etiology. van Karnebeek et al. (2005) was able to identify etiologies in half of the children evaluated in a tertiary care center, regardless of level of cognitive functioning.

## Biomedical Etiological Assessment of Intellectual Disability

Biomedical causes of intellectual disability have their origin in genetic or external factors or injury causing structural or functional disturbances of the CNS. The structural changes may or may not be recognizable by available clinical neuroimaging techniques such as CT, MRI, PET, and single-photon emission computed tomography. Newer advances using laser scanning methods have provided a way to better understand events that occur during brain development on a cellular level during neurogenesis, cell migration, and synaptic connections (Haydar 2005). As medical technology becomes more sophisticated, it is hoped that it will be possible to recognize the biological causes in an increasing number of individuals with intellectual disability.

Intellectual disability associated with syndromes and disorders with obvious phenotypical features is usually recognized earliest such as in the case of Down syndrome. The diagnosis is then confirmed by chromosomal or other appropriate laboratory studies. If there was a suspicion of a family's risk for a genetic disorder before the birth (such as through prior genetic counseling), appropriate studies are performed in the neonatal period. Some cases of congenital intellectual disability (e.g., PKU) are discovered in the course of routine neonatal screening. Newborns with perinatal risk factors like prematurity and asphyxia should be followed up closely for later manifestations of developmental delay. Other children might come to medical attention because of a delay in achieving developmental milestones or regression in a previously normal developmental pattern. Finally, many children with milder intellectual disability will be referred for diagnostic assessment when they reach school age because of failure in academic learning.

### *Elements of Biomedical Assessment*

**First Stage Work-Up.** The medical evaluation of a child with intellectual disability is performed in order to determine potential etiologic factors and a unifying medical diagnosis. This assessment needs to be performed in a systematic fashion, beginning with a thorough history and physical examination to guide the medical workup. Identifying a cause provides diagnostic clarification to medical providers and families, prognostic information, and recurrence risk information.

The scheme for assessing the etiology of intellectual disability is summarized in Figure 42–5. At any point in which a genetic diagnosis is made, consideration should be given to referral to a geneticist to guide subsequent medical assessments and provide genetic counseling to the family.

**History.** A detailed history includes prenatal factors such as difficulties with conception, maternal illness, premature labor, medication, bleeding and other medical problems during the pregnancy. Birth history needs to review problems with labor and delivery that may impact developmental outcome such as fetal distress, abruptio placenta, and hypoxia. Weight, length, and head circumference at birth must be assessed, particularly with relationship to the gestational age, and provide information regarding potential issues such as intrauterine growth retardation. Neonatal problems such as respiratory distress, infection, and seizures, should be noted. Medical history should include review of illnesses, injuries, and surgeries. The rate of recovery from illnesses and identification of associated episodes of regression of developmental skills need to be explored as a screen for metabolic disorders. Information also needs to be obtained regarding nutrition and feeding issues, elimination and sleep problems, medications, immunizations, as well as a complete review of systems. Developmental history should include inquiry about the various developmental domains, including receptive and expressive language, gross and fine motor skills, play and social abilities, self-help abilities. In addition to milestones, it is important to determine the rate of acquisition of skills and the developmental trajectory such as steady slow progress, an apparent reduced rate of developmental gains or plateau, or loss of skills. This type of information may indicate etiologic factors for the intellectual disability. The family history should include a three-generation pedigree, especially occurrence in the family of similar cases, developmental and learning disorders, congenital anomalies, mental disorders, multiple miscarriages, and consanguinity. A social history is also obtained to evaluate environmental and psychosocial factors that may contribute to developmental outcome.

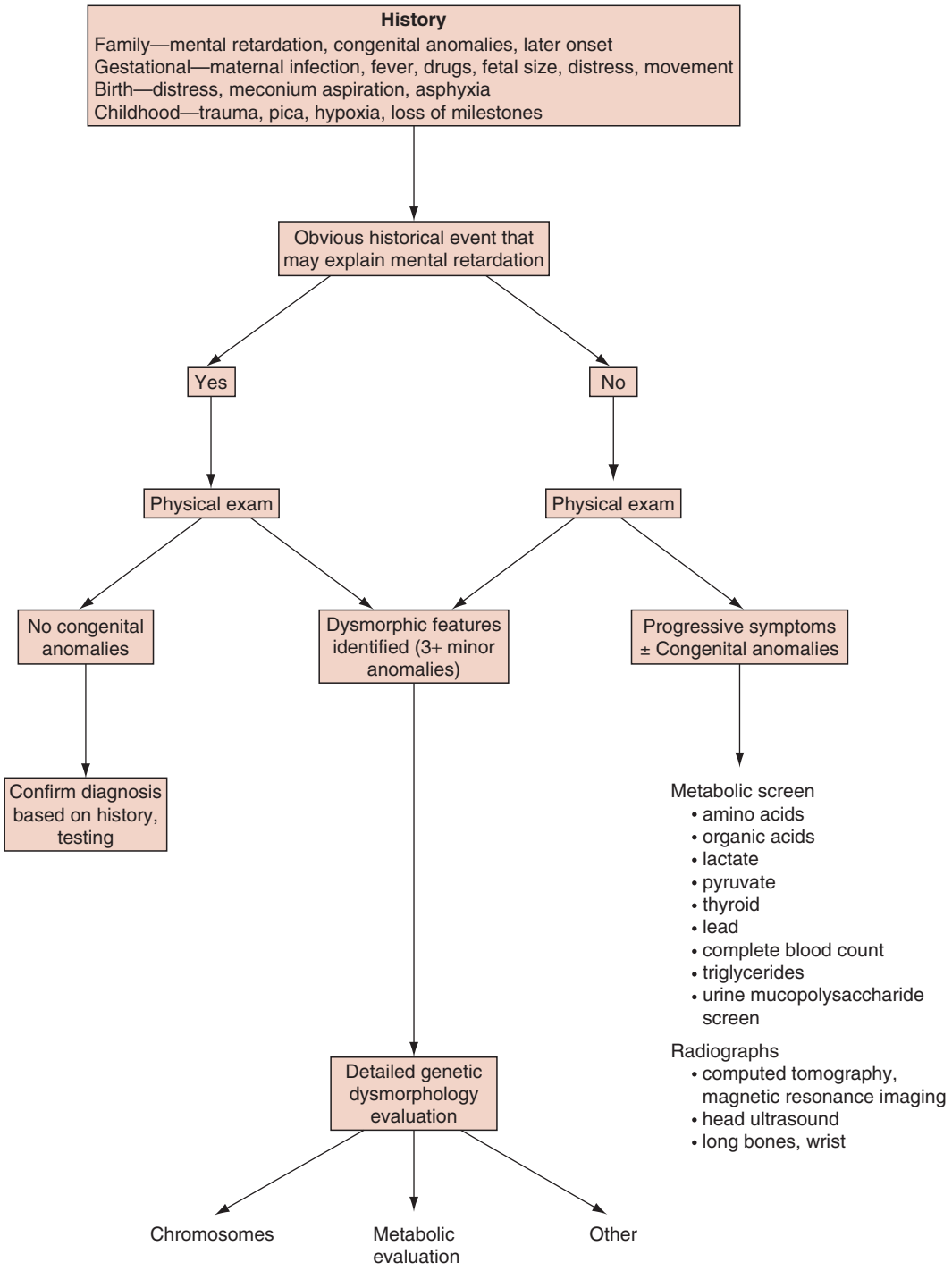



**Figure 42–5** *Diagnostic approach to intellectual disabilities.*

**Physical Examination.** The physical examination should focus on searching for phenotypical manifestations of syndromes associated with ID, or other physical features suggestive of etiologic factors. It should include evaluation of growth parameters, including height, weight, and head circumference. Height and head circumference should be proportional; situations may occur in which head circumference is significantly large or small relative to height. Body mass index should be reviewed to identify failure to thrive or obesity. Phenotypical and dysmorphic features should be identified as indicators for prenatal influences. The general physical examination should closely evaluate skin for evidence of neurocutaneous lesions. Middle ear effusions, corneal opacities, and low oromotor tone should be noted. Evaluation of the neck should rule out the presence of thyroid abnormalities and findings suggestive of a syndrome such as a webbed neck. Cardiopulmonary abnormalities need to be identified. Hepatosplenomegaly is sometimes seen in storage and other metabolic diseases. Lumbosacral dimples or tufts may be present in subtle neural tube defects. Neurological examination should evaluate a child's responsiveness to his or her environment, social

interaction, and language skills. Cranial nerve abnormalities should be identified, as should abnormalities in muscle mass, tone, strength, movement patterns, and reflexes. Emphasis should be placed on motor and reflex asymmetries. The presence of an abnormal neurological exam should guide the decision to obtain imaging studies of the brain and spinal cord.

**Diagnostic Studies.** Upon completion of the history and physical examination, a working hypothesis for the etiology for the intellectual disability is often obtained and will guide the medical workup. Hearing testing should be done on every child with a language delay, and vision should be evaluated to rule out refractive, metabolic, certain neurological and other disorders. In addition to previously mentioned history taking and physical examination, the following: banded karyotype and fragile X studies by DNA method for both males and females with unexplained ID. Banding should occur at least at the 500 G level, with some centers providing high resolution karyotype (≥ 650 bands) (Walker and Johnson 2006, Roberts et al. 2004, Moeschler and Shevell 2006). These studies are essential if the family history is positive or if the physical and behavioral phenotype are without major findings. Metabolic studies and blood chemistries may need to be considered in the context of a history of regression of developmental skills, organomegaly, distinct feature suggestive of a particular genetic syndrome (e.g., mucopolysaccharidosis), in certain instances of sensorineural hearing loss and/or migraine. Magnetic resonance spectroscopy may also be used to further delineate certain metabolic disorders. Failure to thrive and poor growth may be associated with some metabolic, chromosomal, endocrine, CNS, and gastrointestinal disorder, as well as nutritional and psychosocial factors, requiring an evaluation consistent with the presenting features. Lead screening should be done on every child, particularly in the child with developmental delays, hyperactivity, and atypical features. Neuroimaging, preferably MRI, is to be performed if the patient has neurological symptoms, cranial abnormalities, microcephaly, or macrocephaly (Curry et al. 1997). CT scans are often used when evaluating osseous structures of lesions. Neurophysiologic testing such as routine or long-term monitoring electroencephalogram (EEG), should be considered for behaviors suggestive of seizures, staring episodes, paroxysmal outbursts without known precipitants, developmental regression, or a high index of suspicion for a seizure disorder despite a prior normal EEG.

After this basic workup, the probable cause or at least timing of the injury should become apparent, thus allowing discussion with the family concerning possible inheritance. If there are significant congenital anomalies, more than three dysmorphic features, a high index of suspicion of a genetic etiology despite normal initial genetic testing, or positive results from genetic studies, consultation with a geneticist should be sought. If there is a suspicion of a progressive neurological disorder, consultations with a neurologist are needed, as well as a geneticist and a neurological ophthalmologist. In certain situations, biopsies of muscle, skin, or other tissues are helpful.

**Prenatal Diagnosis.** Prenatal diagnostic methods are increasingly available. Amniocentesis is useful in diagnosing chromosomal and metabolic disorders; chorionic villus sampling (CVS) is used for chromosomal and molecular genetic studies. Amniocentesis or CVS with chromosomal studies are usually recommended for women 35 years or older. Prenatal diagnostic studies should be made available to everyone requesting them and should be used if there is a known risk for a genetic or congenital problem. Even if the parents do not plan a therapeutic abortion, if the results are positive for a certain disorder, they will be able to prepare for the birth of a child with special needs and to marshal supports. The American College of Obstetrics and Gynecology has provided new recommendations for screening of all pregnant women for Down syndrome, regardless of age. The screening recommendations include an ultrasound that evaluates the thickness of the back of the neck of the fetus, nuchal translucency, blood test to measure pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) in the first trimester. Those with positive findings are then offered genetic counseling and CVS or mid-trimester amniocentesis. Neural tube defect screening done by evaluating the level of alpha-fetoprotein (AFP) should be offered in the mid-trimester to those women who elect only first-trimester screening for Down syndrome (American College of Obstetrics and Gynecology 2007). AFP, hCG, unconjugated estriol (uE3), and Inhibin-A may also be performed in the mid-trimester to assist in the screening for Down syndrome.

Ultrasound of the fetus to evaluate for major malformations is often performed at approximately the 20th week of gestation. Carrier screening, which is increasingly available for certain recessive disorders, should be offered to all persons in high-risk populations such as Ashkenazi Jews for Tay–Sachs disease. Careful counseling is necessary to help the prospective parents decide on all available options if they are found to be positive for the particular trait.

## Differential Diagnosis of Intellectual Disability

The diagnosis of intellectual disability itself should be relatively straightforward as it reflects the current level of intellectual and adaptive functioning. Some persons with learning disorders or communication disorders might appear to have low level of functioning, but appropriate psychological and communication testing will demonstrate that their impairment is in the development of specific skills and is not generalized. Dementia can be diagnosed at any age, whereas intellectual disability is diagnosed only if the onset is before age 18 years. However, both disorders might be diagnosed in persons younger than age 18 (see discussion of mental disorders due to a general medical condition further on). It is often asked how one differentiates between intellectual disability and autistic disorder. Actually, such a question is erroneous because these disorders are not mutually exclusive; in fact, most persons with autism also have intellectual disability. An uncomplicated intellectual disability is not associated with qualitative impairment in social interaction and communication, which is diagnostic of autistic disorder.

## Course and Natural History of Intellectual Disability

The development of an individual with intellectual disability depends on the type and extent of the underlying

disorder, associated disabilities and disorders, environmental factors (such as general health, education, treatment, and other services), and psychological factors (cognitive abilities, comorbid psychopathological conditions). Some general principles concerning the developmental trajectories of various intellectual disability–associated disorders and syndromes are seen in Figure 42–6.

Life expectancy depends on a number of factors already discussed. Persons with profound intellectual disability with associated multiple disabilities and an inability to ambulate or self-feed have a much shorter life expectancy according to an extensive study conducted in California (Eyman et al. 1990).

When the patient is a person with intellectual disability, even ordinary ailments may be difficult to diagnose (and may become life-threatening) as the person may be unable to describe the complaints because of communication difficulties. Physical pain and other discomforts are often communicated by these individuals through their behavior such as aggression or SIB, leading to a psychiatric referral while the physical disorder remains undiagnosed. Many syndromes predispose the person to certain health problems that have to be anticipated. Illnesses typical of Down syndrome have been discussed earlier. Nonambulatory persons are at risk for both respiratory and urinary tract infections. Gastroesophageal reflux is common and often leads to aspiration and anemia.

## Habilitation and Treatment Approaches to Intellectual Disability

### Evolution of Attitudes to Persons with Intellectual Disability

The information that has survived from ancient times on the treatment of persons with intellectual disability refers primarily to those with external physical abnormalities which

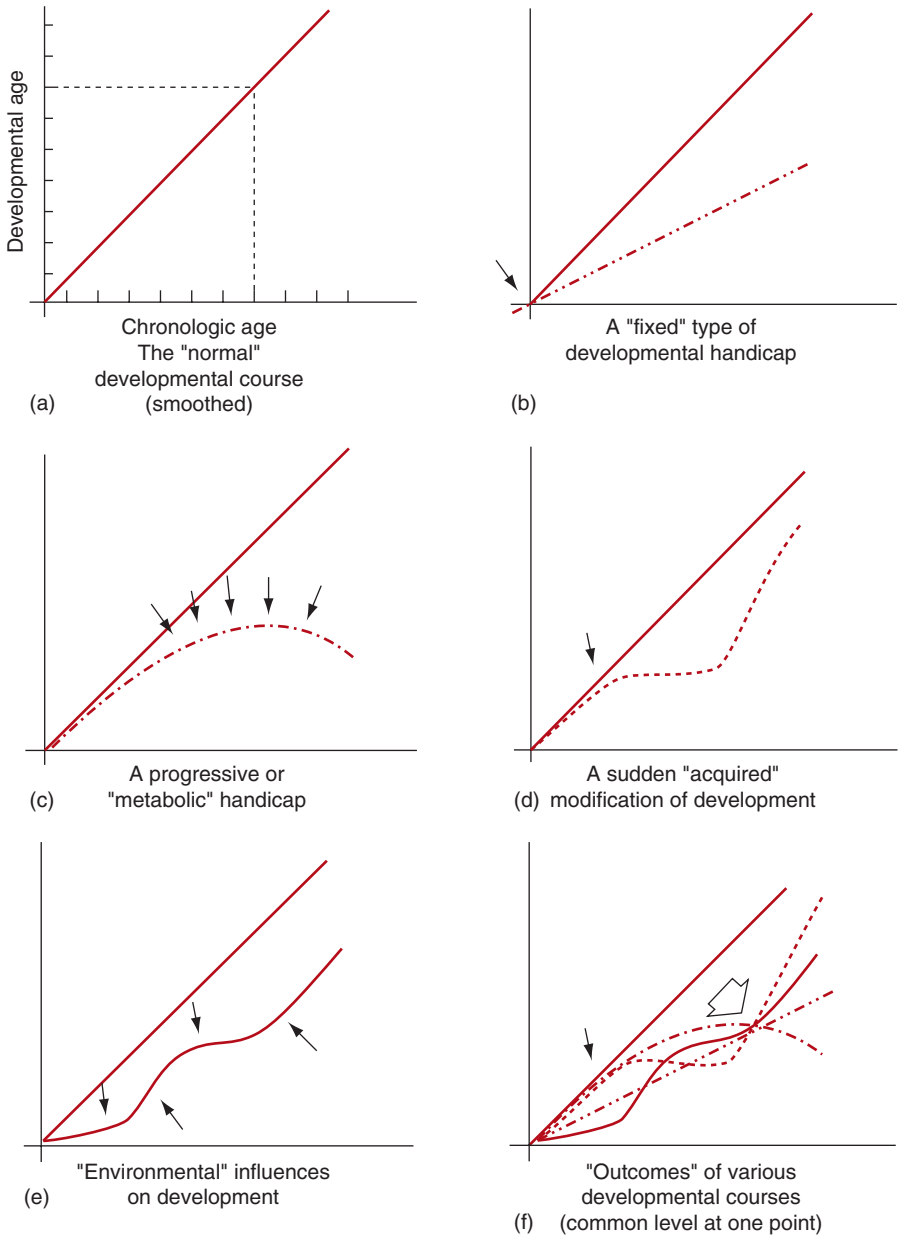



**Figure 42–6** *Schematic representation of patterns of developmental disorders (arrows refer to the point of insult): (a) normal developmental course; (b) fixed, nonprogressive type of developmental disorder; (c) metabolic type of disorder of development in which the manifestations of the underlying process (e.g., Tay–Sachs disease) occur after birth and evolve into a progressively deteriorating course; (d) acquired developmental disorder: the curve represents normal development up to a point of insult (arrow) to the CNS; (e) environmental disorder of development: a fluctuating course, with periods of stress (downward arrows) and periods of nurturance or positive intervention, or both (upward arrows); (f) outcomes: the convergence (arrow) of the various developmental courses represents the point at which the physician becomes aware of the developmental disorder (Source: Szymanski et al. 1989, Mental retardation. In American Psychiatric Press Review of Psychiatry, Vol. 8, Tasman A, Hales RE, and Frances AJ (eds). American Psychiatric Press, Washington, DC, USA, p. 227).*

might have been associated with intellectual disability. In antiquity the attitudes to people with disabilities included rejection, as well as protection (review, Berkson 2004). Persons with mild intellectual disability and without external deformities were probably accommodated in productive tasks in primitive agriculture and industry. In some cultures such as in Sparta and Rome, infants with deformities were not permitted to live. Aristotle, in *Politics*, stated that there should be a law that deformed children should not be permitted to live (Scheerenberger 1983). In those early periods intellectual disability was probably not differentiated from mental illness. The Jewish, Moslem, and early Christian traditions included people with disabilities among those who should be given care and protection (Scheerenberger 1983). Leviticus 19:14 forbids cursing the deaf or placing obstacles before the blind (Berkson 2004). The Talmud listed three types of persons with limited capacity: deaf persons, minors and "*shoteh*" (person with intellectual disability or with mental illness). Interestingly, it described how the "shoteh" could function according to society's expectations. For example, he could perform ritual slaughter if was supervised by a non-shoteh. Thus, the focus was on how such individuals could be integrated within the community (Lifshitz and Merrick 2001). In John 9, Jesus states that one's blindness was not a punishment for sinning. The Quran (Surah IV, v. 5) calls for helping the "weak of understanding" (Berkson 2004). Still, it was unclear to what degree there was differentiation between mental illness and intellectual disability. In Roman writings terms "amens" and "demens" were used which were interpreted as referring to intellectual disability and mental illness, respectively (discussion in Berkson 2006). In the middle age, however, individuals with disabilities were gradually assumed to be a product of sin—often of the sexual union of a woman with the devil—and possessed by demons. In his writings, Martin Luther described a child with intellectual disability whom he saw as a changeling who should have been drowned (Scheerenberger 1983). Some towns cared for persons with intellectual disability or mental illness in orphanages, poorhouses, or in a humane manner in the equivalent of foster homes such as in Geel, Belgium. Many abandoned children with intellectual disability were placed in hospitals where they had little chance of surviving.

The modern care of persons with mental disorders, initiated at the end of the 18th century by Philipe Pinel in Paris, also affected the care of persons with intellectual disability. His focus was on "moral" management (gentle and humane care, education, recreation), rather than on inducing obedience (Scheerenberger 1983). Paradoxically, in our times, there are still some who focus primarily on "behavioral control" of persons with intellectual disability, even by means of aversive behavioral modification. Itard, a student of Pinel, in his work with Victor, the "Wild Boy of Aveyron" (an abandoned, possibly autistic child), laid the foundation for the development of special education. Another of Pinel's students, Edouard Seguin, devoted his professional life to the study and treatment of intellectual disability. His work formed the basis of the enlightened and educational approach to the care of persons with intellectual disability and to the change of institutions from custodial asylums to education-oriented schools.

In the colonial era, the American approach to intellectual disability followed that of England. Persons with intellectual disability together with persons with mental illness were kept in poorhouses or "farmed out" at public expense to the lowest bidder. Toward the middle of the century, developments in Europe started to influence the approach to intellectual disability in the US. The ideas of Sequin were the basis for the earliest school for children with intellectual disability in the US, which was established in 1847 by HP Wilbur in Barre, Massachusetts. In 1848, Seguin emigrated to the US and was instrumental in the development of a number of special schools, as well as in founding (with six other physicians) the Association of the Officers of the American Institutions for Feeble Minded (the predecessor of the American Association of Mental Retardation and currently the American Association on Intellectual and Developmental Disabilities) in 1876. Seguin viewed the mission of the residential facility as educating children with intellectual disability (who could not be accommodated in schools in the community) and then returning them to their families. He advocated small institutions located in the students' communities as well as provision of services to children living with their families (Scheerenberger 1983).

The first state-funded residential school was founded in Massachusetts by Samuel Gridley Howe, at first as a division of a school for the blind in 1848 and as a separate institution in 1855. Almost from the beginning, Howe was against inhumane treatment of persons with intellectual disability, stating in an 1869 report to the Governor of Massachusetts: "it would be demonstrated that no idiot need be confined or restrained by force…." Within the next 25 years, there were 15 public institutions (Scheerenberger 1983). At first they followed the precepts of Sequin's "moral treatment," but later they changed, reflecting developments in medicine and in society's perception of intellectual disability. Several factors contributed to this (Donaldson and Menolascino 1977). Developments in neurology led to a more pessimistic view of intellectual disability as being due to an incurable brain defect. Genealogical studies led to a mistaken belief that intellectual disability was hereditary and associated with criminality and other social maladjustment. This was later reinforced with the introduction of intelligence testing, which "discovered" a high prevalence of persons with mild intellectual disability (termed morons) among socially maladjusted persons (probably resulting from poverty and lack of education rather than intellectual disability). Finally, with the introduction of psychoanalytic theories, psychiatrists became less interested in persons with intellectual disability who were seen as unable to benefit from dynamically oriented psychotherapy. As a result, institutions shifted from educating persons with intellectual disability and protecting them from abuse to protecting the society from them. The period that followed up to the first half of the 20th century, the "tragic interlude," witnessed the building of large institutions (although no more than 10% of persons with intellectual disability were institutionalized at one time), the introduction of laws on involuntary sterilization, and segregated special education (Donaldson and Menolascino 1977).

A number of developments led to the next period, culminating in the current recognition of the rights of persons with intellectual disability to services and inclusion in society. Research on the effects of attachment and deprivation resulting from institutionalization documented the environmental factors in the genesis of intellectual disability, as

well as the salutary effect of a stimulating environment and education (Skeels and Dye 1942). In fact, it was a sort of a *de´jà vu* of the work of Itard and Sequin. The work of a parents' organization (National Association for Retarded Citizens, currently known as The ARC) contributed to a gradual improvement in institutions, to deinstitutionalization, and to community-based care. The US Supreme Court 1954 decision in *Brown v. Board of Education* ending racial segregation in schools, and the civil rights movement in general, sent the message that all kinds of segregation—educational and otherwise—were wrong. Many important lawsuits on behalf of persons with mental disabilities followed and the most relevant are summarized in Table 42–6, and important statutory developments in Table 42–7.

## Education of Children with Intellectual Disability

Laws providing for educational opportunities for children with disabilities have evolved in the United States over the years, since 1896, when the first successful special class for children with intellectual disability was established in Providence, RI (Sarason and Doris 1975). Such classes were commonly self-contained and separate, frequently housed in separate buildings. Starting with early nineteen-seventies, the concept of educational placement in a least restrictive alternative was introduced and codified in legislation. In 1972, Massachusetts adopted a special education law; the current Chapter 71B—Chapter 766 of the Acts of 1972—guaranteeing public education and all necessary services to all children of 3–22 years of age; placement is according to service needs rather than diagnostic labeling, interdisciplinary core assessment with parents' participation, and an educational plan specifying goals to be achieved. The parents have the right to reject the plan and appeal it. The federal PL 94-142 of 1975 was modeled on Chapter 766.

Originally the term "mainstreaming" was used, later supplanted by "inclusion." The norm now is that the overwhelming majority of intellectually disabled children can be educated jointly with nondisabled ones, in "integrated" classrooms, if provided with appropriate educational and other supports and therapies (such as special education teachers and aides, modified curriculum, language therapy), However, even with intensive supports some children are still educated in separate classes, usually because they require very structured settings and/or have major behavior management needs. If a child's needs cannot be provided for in the public schools, the local school systems have an option (with parent's consent) to place the child on public expense in a special private school (day or residential).

The outcomes of separate–special vs. inclusive education are still studied. In their review of relevant studies, Lipsky and Gartner 1997 found that the special needs students included in regular classes did better academically and even if the difference was not marked, the inclusive placement was more liked by the parents and educators and was cost-effective. The social and behavioral outcomes were also favorable, ascribed to factors such as using nondisabled peers as role models, availability of friendship networks, and of social contacts. On the other hand, students in inclusive placements may still experience significant stigma (Cooney et al. 2006).

Right to free and appropriate public education (FAPE) is currently guaranteed to all children and youth in the United States by federal law. It was first introduced as the Education for All Handicapped Children Act, Public Law

**Table 42–6 Summary of Lawsuits Applying to the Rights of Persons with Intellectual Disability**

| Year | Lawsuit | Court's Findings |
|---|---|---|
| 1969 | Wolf v. Legislature of the State of Utah | All children have the right to public education regardless of the level of retardation |
| 1972 | Pennsylvania Association for Retarded Citizens v. Commonwealth of Pennsylvania | Every child with disabilities can be educated; the state must provide such education; due process in appropriate medical and psychological evaluations is required |
| 1972 | Mills v. Board of Education | Exclusion of a child (with behavior problems) from school was unconstitutional; specialized education to be provided; term "equal educational opportunity" used* |
| 1970–2003 | Wyatt v. Stickney (and Partlow State School) | Persons in institutions have a constitutional right to treatment: Set minimal standards of care, including qualified staffing, medical care, and privacy; prohibited the indiscriminate use of psychotropic agents; required the least restrictive setting |
| 1974 | .Donaldson v. O'Connor | Nondangerous individuals cannot be involuntarily committed to custodial institutions. Civilly committed persons have a constitutional right to treatment |
| 1974–1987 and follow-up through 1998 | Halderman v. Pennhurst State Hospital and School | Persons in institutions have a right to minimal habilitation and the least restrictive environment. Eventually court ordered closing of institutions and placement of their residents in the community. The follow-up case focuses on provision of appropriate care in the community, including psychiatric care and avoidance of unnecessary use of psychotropic agents |
| 1981–82 | Youngberg v. Romeo | Person with ID, involuntarily committed, has constitutional right to habilitation; reasonable safety; freedom from unreasonable restraints |
| 1995–99 (Implementation still ongoing) | Olmstead v. L.C. | Unnecessary segregation of individuals with mental disabilities in institutions may constitute discrimination. Placement and services in the community (most appropriate integrated setting) are required if recommended by state's own professionals and unopposed by the individual |

*Fiedler and Prasse (1996).

**Table 42–7 Laws Relevant to Rights of Persons with Disabilities**

| Year | Law | Summary |
|---|---|---|
| 1975 | PL 94-142: EHA | Free appropriate public education and related services for all children with specified disabilities age 3–21; written individualized educational program (IEP) to be developed for each child, which includes child's needs, educational goals and services to be provided, based on appropriate evaluation and due process, with parents' participation and consent; procedures for independent evaluation; procedures for parental appeal. Education to be provided in least restricted environment (LRE), in regular classes, unless it cannot be done satisfactorily |
| 1983 | PL 98-199 (amendment to EHA) | Encouraged services for preschoolers. |
| 1986 | PL 99-457 (amendment to EHA) | Added: Part B; preschool services (lowering eligibility age for services to age 3), and Part H; states must provide children with developmental disabilities 0–3 years of age with early intervention services; develop multidisciplinary programs |
| 1990 | PL 100-476 (amendment to EHA) | Name of the law changed to IDEA; required additional programs: transition and assistive technology services, rehabilitation counseling, social work; included children with autism and traumatic brain injury as eligible for services |
| 1992 | Americans with Disabilities Act (ADA) | Comprehensive act on rights of persons with disabilities and protection against discrimination |
| 1997 | PL 105-17 (amendment to IDEA) | Improvement and strengthening of the law; additional focus on diversity, safety, parental roles and parents–teachers partnership |
| 2004 | PL 108-446 (amendment to IDEA) | Requires states to enforce the law; funding sanctions if goals not met; funding for preventive services for nondisabled students with behavioral/academic problems; mandated post-secondary transition planning starting at age 16; established standards for highly qualified teachers |

(PL) 94–142, in 1975, with later amendments known as Individuals with Disabilities Education Act (IDEA). Briefly, it covers all children with disabilities from birth to age 21 years; provides the right to diagnostic, treatment, and support services for the child and the family; requires maximally feasible mainstreaming, periodic reassessments, and provision of an individualized education program. The evolution of IDEA is summarized in Table 42–7. In addition, the states have their own laws and regulations which are continuously evolving. Clinicians and educators dealing with persons with disabilities should be familiar with such laws in their jurisdictions. Information about them can be usually found on Web sites, some of which are listed at the end of this chapter.

Another important development in the habilitation of persons with intellectual disability has been the Americans with Disabilities Act (ADA), first adopted in 1990 and periodically revised since. The ADA prohibits discrimination on the basis of disability in employment, government, public accommodations, transportation, and telecommunications. A disability is defined as a physical or mental impairment that substantially limits one or more major life activities. Title I of ADA requires employers with 15 or more employees to provide individuals with disabilities with equal opportunities and to make reasonable accommodation for them if they are otherwise qualified. Title II requires that State and local governments give people with disabilities an equal opportunity to benefit from all of their programs, services, and activities (and provide architectural and other accommodations necessary to that end such as access). Title III covers businesses and nonprofit service providers. They must comply with basic nondiscrimination requirements that prohibit exclusion, segregation, and unequal treatment. Title IV addresses telephone and television access for people with hearing and speech disabilities.

Another important piece of legislation has been the Civil Rights of Institutionalized Persons Act (CRIPA) of 1990, which authorizes the US Attorney General to investigate conditions of confinement at State and local government institutions including correctional facilities, and institutions for people with psychiatric or developmental disabilities. Over the years numerous institutions for persons with intellectual disability were investigated and conditions in them were markedly improved through court orders or court approved settlements. One of the most common findings has been poor mental health care in these facilities, including inappropriate use of psychotropic drugs (*Source*: U.S. Department of Justice; http://www.ada.gov/cguide.pdf).

## Overall Goals of Treatment of Persons with Intellectual Disability

Intellectual disability is a functional disability: thus, the goal of treatment is reduction or elimination of the disability. There are three aspects to the treatment:

1. Treatment of the underlying disorder that is causative of intellectual disability, for example, PKU
2. Treatment of the comorbid disorders that add to the functional disability physically or mentally
3. Interventions targeted at the functional disability of the intellectual disability itself: educational, habilitative and supportive approaches depending on the person's individualized needs

## Overall Principles of Treatment of Persons with Intellectual Disability

The current approach to the services for persons with intellectual disability is based on the following principles:

- Normalization principle (Nirje 1969). This refers to "making available to the mentally retarded patterns and conditions of everyday life that are as close as possible to the norms and patterns of the mainstream of society." This has largely evolved into the *principle of inclusion*, which is usually interpreted as an active effort to include persons with intellectual disability in all normal aspects and opportunities of society's life, through providing them with supports necessary for success. An excellent description of inclusion is as follows: "Inclusion means that all people, regardless of their abilities, disabilities, or health care needs, have the right to: be respected and appreciated as valuable members of their communities; participate in recreational activities in neighborhood settings; work at jobs in the community that pay a competitive wage and have careers that use their capacities to the fullest; and attend general education classes with peers from preschool through college and continuing education." (*Source*: Institute for Community Inclusion, Children's Hospital, Boston: http://www.communityinclusion.org/doc.php?doc_id=18&type=project&id=40)
- The ultimate goal is to eventually end segregated services and education and provide persons with intellectual disability with the necessary specialized support services in regular educational, living, and work settings.
- Right to community living. This confers the right to live with a family, preferably one's own or a substitute one if necessary (foster or adoptive). This includes moving individuals living in large residential facilities to as normal a setting as possible, for example, community residences, supervised apartments, and foster homes. Furthermore, children as well as adult are not to be institutionalized regardless of the level of disability. However, some children are still placed in special residential schools (usually private) for specific reasons, typically medical or behavioral needs that require specialized treatment. Historically, the majority of persons with intellectual disability lived at home and no more than 10% were in institutions at any point. However, institutions played a disproportionate role in attitudes to their care. At their peak in 1967, there were 194,650 persons living in them: this number dropped to 41,653 in 2004 (Prouty et al. 2005). Data from the National Health Interview Survey on Disability and the Residential Information Systems Project indicate that an estimated 92% of all Americans with ID/DD live with family members, spouses or alone; 6% live in community-supported living arrangements; 1% live in large institutions; 1% live in nursing homes. Between 1960 and 2004, 176 of large state institutions or units for people with intellectual disability were closed. By 2004, ten states closed all their institutions. In contrast, the number of persons living in small (less than six persons) residences in the community between 1977 and 2002 increased 12-fold, from 20,184 to 263,415 (1205%). The number of children and youth in large state institutions decreased from over 91,000 in 1964 (47.6% of all residents) to 1600 (4%) in 2004. One-third of the states have eliminated admission of children and youth altogether (Schoultz et al. 2005).
- Employment of adults in the community according to their abilities. This is an important aspect of inclusion. The current trend is to employ them in competitive job markets with supports such as vocational training and supports by job coaches. However, many individuals, especially with severe degrees of disability, are still placed in sheltered workshops or occupational–recreational day programs.
- Use of normal community services and facilities. This includes activities such as shopping, banking, transportation, recreation) through training and ongoing supports.
- Advocacy and appropriate protective measures. This ensures protections against inappropriate use of pharmacological and behavioral measures as substitutes for active education and treatment, inclusion in research programs without proper, truly informed consent, and general exploitation and abuse.

## Prevention of Intellectual Disability

### Primary Prevention

The goal of primary prevention is to prevent intellectual disability from arising in the first place. To be effective, it should encompass medical, public health, educational, and other measures. Examples include, immunizations to prevent congenital rubella, measles (encephalitis), and Rh mother–child incompatibility; measures to prevent lead poisoning and teenage pregnancies; provision of prenatal vitamin supplementation (to prevent neural tube defects); better neonatal care; measures to prevent substance abuse in pregnancy and childhood trauma (e.g., the use of infant car seats), and early intervention and enrichment programs for children at psychosocial risk. It is a question of personal values whether prenatal diagnosis and elective termination of pregnancy (e.g., if Down syndrome is found) would be called primary prevention, as childbirth rather than the disorder is prevented.

### Secondary Prevention

Secondary prevention includes measures to recognize conditions that can lead to intellectual disability as early as possible and to treat them to prevent the disability. Examples include the early diagnosis and treatment of PKU, and other metabolic conditions and congenital hypothyroidism.

### Tertiary Prevention

Tertiary prevention could be called habilitation as well (Rowitz 1986) because it aims to attain a functional level that is as good as possible in the presence of intellectual disability. It includes both biomedical and sociocultural measures such as early intervention for disabled infants, proper education, multifaceted family support, and prevention or early treatment of comorbid disorders that could reduce functioning, both medical and mental.

### Prevention of Psychosocial Dysfunction

An essential part of tertiary prevention consists of preventing psychosocial dysfunction because mental disorders are an important cause of maladaptation in persons with intellectual disability (Szymanski 1987). This category can also be subdivided. *Primary prevention* includes proper education and employment and opportunities to achieve in life so that the person can develop a sense of self-worth and self-esteem;

training in social skills and sexuality; and provision of appropriate social supports and recreation. *Secondary prevention* includes early diagnosis and treatment of emerging mental disorders rather than a focus on behavioral crisis intervention only. *Tertiary prevention* includes good psychiatric care and habilitation as well as a proper milieu when a person has a chronic mental illness (including substance abuse) that requires continuous care. In all situations prevention has to include measures directed both at the person and at the environment (caregivers, services, public policies).

## MENTAL DISORDERS IN PERSONS WITH INTELLECTUAL DISABILITY

Although at the advent of psychiatry, intellectual disability had been considered as an important and integral province of psychiatry, starting in the early part of the 20th century, there was a loss of interest in persons with intellectual disability largely in part due to emergence of psychoanalysis with its predominant focus on communication involving prerequisite development of good language skills and cognitive abilities. In the late 1970s interest revived in this branch of psychiatry, termed "neurodevelopmental neuropsychiatry" (Harris 1995 2006). Nevertheless, unlike in the United Kingdom and Australia there has not been a systematic emphasis on training of psychiatrists in neurodevelopmental psychiatry in the US, especially in terms of mental health care of adults with intellectual disability.

The same mental disorders occur in persons with intellectual disability as in those without intellectual disability: thus, the discussion of definition, etiology, pathophysiology, natural history of specific mental disorders, described elsewhere in other chapters of this textbook, applies here as well. This section focuses only on those aspects of mental disorders that might be modified by the presence of intellectual disability.

### Prevalence of Psychopathology in Persons with Intellectual Disability

Accurate assessment of prevalence of mental disorders in persons with intellectual disability is difficult, for a number of reasons (Dykens 2000, Kerker et al. 2004). First, one common problem is the selection of representative samples of persons with intellectual disability in studies involving the general population. Many earlier studies focused on persons living in large residential institutions which resulted in an overestimation of the prevalence of emotional and behavioral disorders since these disorders were a common reason for institutionalization. Conversely, other studies involving select community samples excluded institutionalized individuals. Studies of referred individuals in mental health clinics have also tended to be biased as a common reason for referral involves emotional and behavioral concerns. In turn, studies involving unselected populations such as those of persons receiving services through community-based programs have tended to miss individuals not able to attend such programs (or have not been accepted by them), often because of behavior problems. Second, the assessment of persons with intellectual disability has also varied from detailed evaluation by means of psychological and developmental tests, inappropriate use of such tests, or lack of development of structured or semi-structured measures to assess them. Inconsistent use of diagnostic criteria of mental disorders, particularly before the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) (American Psychiatric Association 1980), was commonplace. Many studies then did not use standard diagnoses in persons with intellectual disability and referring to these disorders in general terms such as "psychiatric illness," "mental health condition," "behavior disorder" (Kerker et al. 2004). Methods of diagnosis have also differed. In summary therefore, diagnosis of mental disorders in this population has remained difficult, particularly for clinicians untrained and inexperienced with persons with intellectual disability (American Psychiatric Association 1991). Third, an important obstacle to accurate diagnosis of comorbid mental disorders in persons with intellectual disability has been "diagnostic overshadowing"—a tendency of clinicians to overlook the true co-occurrence of mental disorders in the presence of intellectual disability (Reiss et al. 1982). This obstacle still leads to undue exclusion of persons with intellectual disability from services that may be available for other more specific diagnoses such as children with attention-deficit/hyperactivity disorder who have been recognized to have comorbidity with anxiety and affective disorders as early mid-1980s with the advent of DSM-III (Biederman et al. 1986, Munir et al. 1987). A fourth problem has been the issue of persons with intellectual disability serving as informants. Studies of persons with intellectual disability have therefore exclusively relied on clinical interviews with caregivers or on retrospective clinical records review. Some studies have used a variety of structured and semi-structured diagnostic instruments, which were designed to measure behaviors or personality features, but not necessarily to arrive at a direct categorical diagnosis of a mental disorder (see review by Dykens 2000 and Kerker et al. 2004). Finally, some large-scale studies used diagnoses included administrative and surveillance but not necessarily direct epidemiological datasets reported to state offices by various agencies, without consideration of the manner in which such diagnoses were systematically made. There have been few controlled studies of persons with intellectual disability.

It is therefore not surprising that with these methodological problems there have been wide variations in the prevalence of psychopathology in persons with intellectual disability, ranging from under 30% to over 71% (Table 42–8), although most agree that it is significantly higher than in persons without intellectual disability. The representative studies are summarized in Table 42–8. Virtually all types of mental disorders have been described in persons with intellectual disability, although their reported prevalence also varies from study to study (Dykens 2000).

Despite its influential beginnings in developmental epidemiology, difficulties in measurement of mental disorders in intellectual disability, including autism spectrum disorders, had led children with intellectual disability and autism to be excluded from the proposed but subsequently abandoned national studies on Use, Need, Outcomes, and Cost of Child and Adolescent Populations (UNOC-CAP) project by NIMH. Yet, an NIMH-sponsored consensus report subsequently considered autism as one of the most reliable diagnosis in psychiatry and their exclusion was not

**Table 42–8 Selected Studies of Demonstrating Variation in the Prevalence of Psychopathology in Persons with Intellectual Disability**[*,†]

| Study | Age | Study Cohort | Assessment Method | Psychopathology | |
|---|---|---|---|---|---|
| | | | | Subjects | Controls |
| Rutter et al. (1970a,b) | 9–11 | Entire cohort, Isle of Wight | Parent and teacher interviews, behavioral scales, multiaxial criteria | 30–42% | 6–7% |
| Lund (1985) | ≥ 20 | Cluster sample of total Danish ID population, National Registry | Adaptive and maladaptive behavior schedules; clinical interviews; DSM-III criteria | 27% | No controls |
| Gostason (1985) | 20–60 | Random stratified sample of 122 Ss residing in a Swedish county, located through a national registry | Psychopathology rating scale; Eysenck Personality Inventory; psychiatric interviews; DSM-III criteria | MI/ID: 33%<br>SE/ID: 71% | 23% |
| Gillberg et al. (1986) | 3–17 | Representative 4-year birth cohort (144 Ss) from a city in Sweden | Structured parent and subject psychiatric interviews, behavioral observations: DSM-III criteria | MI/ID: 57%<br>SE/ID: 64% | No controls |
| Iverson and Fox (1989) | ≥ 21 | Random stratified sample of 165 Ss drawn from those receiving MR services in a midwestern county | Psychopathology Instrument for MR Adults (PIMRA), client or informant response; DSM-III criteria | MI/ID: 55%<br>MO/ID: 32%<br>SE-PR/ID: 26% | No controls |
| Linna et al. (1999) | 8 | Children attending special schools for "educationally subnormal" or training schools in Finland. | Parent and teacher questionnaires, Children's Depression Inventory | Psychiatric disturbance: 50%<br>Depressive disturbance: 11% | 24%<br>6.6% |
| Strømme and Diseth (2000) | 8–13 | 5-year birth cohort, Akershus County, Norway, diagnosed with ID | IQ or developmental tests; parent and child interview and record review; diagnosis per ICD-10 criteria | Psychiatric diagnosis in 33% of Ss with IQ50–70 and in 42% with IQ <50 | No controls |
| Emerson (2003) | 5–15 | Random sample of 264 of 10438 UK children; diagnosis of ID made per parental report or attendance in special classes or teacher's report | Carer & some subject interview, teacher survey by mail; diagnosis by ICD–10 criteria (computer-assisted ratings) | Any disorder: 39% Emotional disorder: 9.5%<br>Anxiety disorder: 8.7%<br>Depression: 1.5%<br>Conduct disorder: 25% Hyperkinesis: 8.7% PDD: 7.6%<br>Psychosis: 0.0% | 8.1% 4.1%<br>3.6% 0.9%<br>4.2% 0.9%<br>0.1% 0.0% |

*Source*: Bregman JD (1991) Current developments in the understanding of mental retardation. Part II: Psychopathology. Journal of the American Academy of Child and Adolescent Psychiatry 30, 861–872.

[*]These studies included subjects with mild to severe mental retardation.

[†]MR: mental retardation, DS: down syndrome, S-PMR: severe to profound mental retardation, ICD-9: International Cassification of Diseases, 9th revision, Ss: Subjects, IQ: Intelligence quotient, MI/ID: Mild intellectual disability, MO/ID: Moderate intellectual disability, SE/ID: Severe intellectual disability, SE-PR/ID: Severe/profound intellectual disability.

justified (Bristol et al. 1996) **[**. In terms of standardized "respondent-based" interviews, administered by lay interviewers, the field of developmental disabilities has continued to provide leadership. Recent advances in diagnosis of autism using the Autism Diagnostic Observational Schedule (ADOS-G) by means of activity-based observational ratings is an important more recent example (Lord et al. 1997). The developmental limitations of the subjects in terms of social communication and speech are no longer a hindrance to diagnosis in this activity-based observational schedule. Before the advent of ADOS-G, however, the developmental approach to measurement has had a distinguished beginning in the history of psychiatry as in the work of Binet (1908) described earlier in the chapter, emphasizing the "fluidity" rather than the content of a person's thoughts—also influencing Piaget's genetic epistemology (Piaget 1953); therefore, the construction and choice of questions as well as aspects of a respondent's functioning are all relevant to the diagnostic process in persons with intellectual disability. Furthermore, this applies not only to persons with intellectual disability, but can be generalized to individuals with SMI, often presenting with impairments in multiple domains of functioning that includes cognition (Mueser et al. 1997). As diagnostic criteria for many mental disorders are behaviorally defined structured interviews remain limited by their textually defined restrictions and difficulties in semantic understanding.

## Intellectual Disability and Behavioral Patterns

### Risk Factors for Psychopathology

A number of factors have been proposed as relevant to the increased risk of persons with intellectual disability to develop psychopathology. These have been reviewed by

Dykens (2000) and are summarized below. Although her paper focused on children, it is equally relevant to adults as well.

### Cognitive and Adaptive Impairments

By definition persons with intellectual disability have reduced ability to deal with requirements and stresses of life. Even individuals who received good education and were able to develop reasonably good adaptive skills, often depend on structure and familiarity of behavioral "scripts" they were taught. They may have difficulties in adapting to changes in routine or making decisions in the face of unexpected events, and therefore may respond with anxiety. Furthermore, poor communication skills interfere with understanding explanations or instructions and with communicating own thoughts and feelings; persons with intellectual disability therefore may resort to behavioral means as a form of communication. In fact it is often observed that such behavioral responses including anxiety and aggression may abate, when an individual acquires better communication skills, or is given a more developmentally appropriate channel of expression.

### Psychological Factors

In the past, it has been widely held that persons with intellectual disability have a limited "personality" in common. These presumed traits, often contradictory, included: passivity, aggressiveness, attention getting, shyness, talkativeness, lack of sexual drive, and hyper or hypo sexuality (Reiss 1994). However, it is now more widely held that a full spectrum of personalities can be encountered among persons with intellectual disability, as in the general population (Szymanski and Kaplan 2006). Nevertheless, persons with intellectual disability are more likely to show certain characteristics such as low self image (Szymanski and Crocker 1989) often related to their experiences of failure, perception that adults important to them (especially parents) are disappointed with them, and negative comparison between themselves and their age peers (Reiss 1994, Dykens 2000). This might be associated with an "outerdirectedeness" (relying on others for self-assessment) and "learned helplessness" which is seen as associated with psychopathology such as depression.

### Environmental–Social Factors

Despite marked progress in development of care systems and services, persons with intellectual disability continue to encounter social rejection and stigma. Much of this is related to our cultural values; in some cultural contexts the stigma being more pronounced than in others. One aspect of stigma is related to public or professional ignorance of intellectual disability, including fears that it is associated with violent behavior. Persons with intellectual disability are well aware of such negative experiences, since they now live in the community. Such psychosocial factors have been found to correlate with development of depression (Reiss and Benson 1985). Peer attitudes are of great importance in adjustment of children with intellectual disability. Much progress has been done in schools where a peer-buddy system provides social and other support to disabled children and may protect them against bullying and teasing, which is common, especially if a child has unusual phenotypical features (Dykens 2000). Persons with intellectual disability are at risk for being abused, for reasons such as being seen as easy victims and unable to defend themselves. Such inherent abuse, unknown to the caregivers, might lead to behavioral disturbance and psychopathology. Family-related factors in stigma are important as well since family support and acceptance are essential to the preservation of the affected child's progress. This requires not only love and acceptance but also promotion of the child's strengths (i.e., an appreciation of the child's abilities as well as disabilities) without putting on him or her unrealistic demands and expectations. Parental advocacy is often essential in procuring services to which the child is entitled and much depends on such parental understanding of the child's needs.

Behavioral patterns and psychopathology may also be influenced by biomedical factors. As has been shown in the early epidemiological studies by Rutter and Tizard in the Isle of Wight, persons with intellectual disability have long been known to have seizure disorder, especially if their cognitive impairment is severe. In turn, seizures may be comorbid with mental disorders (review, Dykens 2000). Blindness may be associated with CNS damage and mental retardation and congenitally blind children may exhibit behavioral patterns of consistent with co-diagnosis of autism spectrum disorders. Persons with intellectual disability also commonly have manifest comorbid medical disorders and may be in treatment with medications, which might have a range of behavioral side effects. The influence of these various factors on the functioning and behavior is depicted in Figure 42–7.

## Behavioral Phenotypes

Association of behavioral/personality traits with certain conditions underlying intellectual disability has long been noted. For example, persons with Down syndrome are often deemed to be overtly friendly, social, "prince charming" types, but these features have also been explained as a result of others' accepting and perhaps infantilizing attitudes towards them. With progress in genetics, the concept of "behavioral phenotypes," first introduced by Nyhan in 1972, has now gained popularity. Dykens has defined behavioral phenotypes as "the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioral and developmental sequelae relative to those without the syndrome" (Dykens 1995, Dykens et al. 2000). This view holds that certain behavioral and cognitive patterns are more frequently seen in certain genetic syndromes than in persons without these syndromes, irrespective of coexistence of intellectual disability. Dykens has also noted that in few genetic syndromes certain behaviors might be unique: for example, extreme overeating in Prader–Willi or extreme self-mutilation by biting in Lesch–Nyhan syndromes as referred to in Nyhan's original description of a behavioral phenotype. The concept of behavioral phenotypes is not espousing a genetic determinism: it does not mean that all behaviors (Table 42–9) are predetermined genetically, or that people with a certain syndrome must behave in a certain way. For example, there are individuals with Down syndrome who present with autism spectrum characteristics, more prevalent in those with severity of language and cognitive delays. Even if there is a genetic predisposition to a behavior, other factors—psychosocial, environmental, and biological

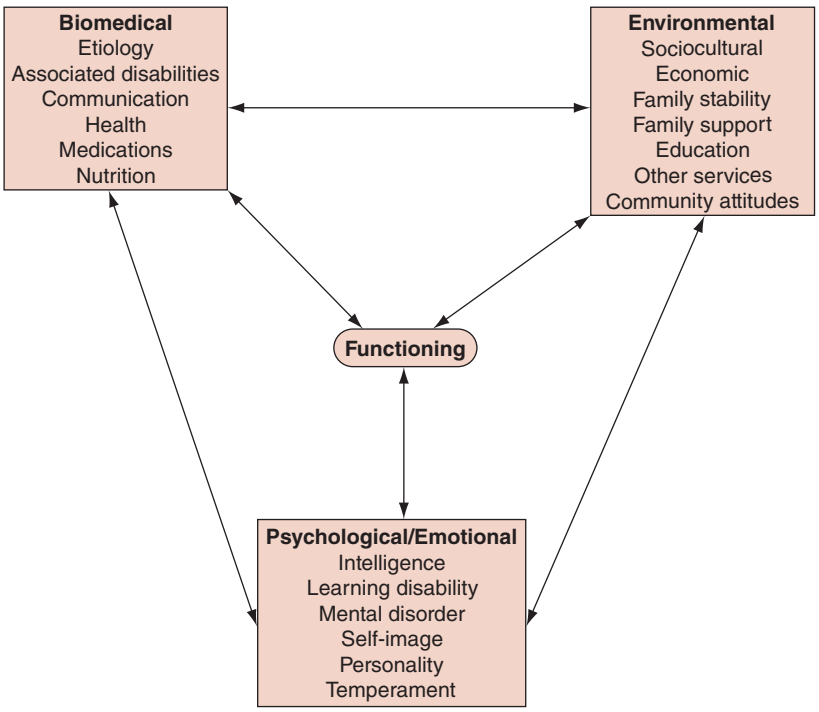



**Figure 42–7** *Schematic representation of transactional relationship of various factors influencing the development of adaptive and maladaptive behaviors in persons with mental retardation.*

(including comorbid medical disorders)—contribute to the final behavioral manifestations. The knowledge of genetic (or other) etiology of intellectual disability therefore is not to be used again to reclassify individuals, but to understand them, their strengths, as well as their weaknesses and needs. Yet, the concept of behavioral phenotype is most important both for research on genetics of behavior and for planning of services for the individual. For example, knowledge of the nature and course of cognitive and language deficits associated with Down, Prader–Willi, or Williams syndrome, will permit us in planning for appropriate educational curricula and services.

## Diagnosis of Mental Disorders in Persons with Intellectual Disability

### Phenomenology and Variations in Presentation

There is no evidence that mental disorders in persons whose intellectual disability are basically different from mental disorders seen in the general population. However, the clinical manifestations may be modified by many factors that include: cognitive impairment; communication skills; associated sensory, motor, and other disabilities; the environmental niche; and life experiences. The most important of these attributes is the presence or absence (or degrees of development) of verbal language. This is to be expected since many if not most of the current diagnostic criteria of mental disorders are based on a patient's verbal productions. For instance, it might be impossible to recognize the presence of thought disorder in a nonverbal person; similar variations are also encountered in typically developing young children. The successive editions of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association have tried to address this problem in different ways. Psychiatrists have been advised to assess whether the symptoms are present to a degree inconsistent with the developmental level (criteria for attention-deficit/hyperactivity disorder, DSM-IV-TR) (American Psychiatric Association 2000, p. 92). However, assessing what is the developmental level appropriate for the given individual is presumably left to the clinician's judgment. If a person cannot describe his or her own mood, observations made by others can be substituted (criteria for major depressive episode, DSM-IV-TR) (American Psychiatric Association 2000, p. 356).

### Use of Psychiatric Diagnostic Categories with Persons with Intellectual Disability

The standard criteria for the diagnosis of mental disorders can be used with almost all persons who have intellectual disability: however, they may to be modified in the context of person's level of communication skills and developmental level (American Academy of Child and Adolescent Psychiatry 1999). With individuals who have mild degree of intellectual disability and presumably a relatively good communicative language, the usual diagnostic criteria of DSM-IV-TR can be used. These individuals, while verbal, might use simpler and concrete language. In some disorders many criteria reflect observable behaviors and vegetative signs and thus the diagnosis can be made also in persons who do not have communicative language. Obtaining detailed history from several informants who are familiar with the individual is crucial, as they can often describe changes in mood and affect, which the patient may find difficult or impossible to verbalize. The DSM-IV-TR also has "mono-symptomatic" disorders based on a domain of clinical manifestations which does not necessarily seem to be part of another mental disorder (e.g., stereotypic movement disorder) distinct from the stereotyped repetitive behaviors in autism spectrum disorders. As a last resort, a Not Otherwise Specified (NOS) category can be used. In a majority of cases, with a careful consideration and

**Table 42–9 Features of Some of the Behavioral Phenotypes**

| Syndrome | Pathology | Physical Phenotype | Behavioral Features |
|---|---|---|---|
| Down | Trisomy 21, translocation, mosaicism | Dysmorphic face, hands associated disorders: CHD, thyroid, leukemia, diabetes, deafness, cataracts | MR: PR to MI, expressive language problems: grammar, articulation. Most are social, have sense of humor, imitation, but may be stubborn. Psychopathology occurs but less than in other syndromes. More prone to depression, Alzheimer dementia |
| Prader-Willi | 15q11–13 microdeletion, paternal origin or maternal uniparental disomy 15 | Obesity, short stature, small hands/feet, hypotonia | MR: in two thirds IQ in MI range or above, unusual skills with jigsaw puzzles. Early feeding problems, from 3–4 years marked hyperphagia, even of nonfoods, stubbornness, impulsivity, tempers, compulsivity, aggression, SIB (skin picking), possibly at risk for psychotic and affective symptoms |
| Angelman | 15q11–l3 microdeletion, maternal origin | Dysmorphic face (wide mouth, large tongue, thin upper lip, seizures, ataxia) | MR: PR-SE, no expressive speech, appear happy, inappropriate laughter, smiling, overactive, sleep problems |
| Fragile X | In *FMR1* gene excessive COG repeats: 200 + in full mutation, 50–200 in premutation carriers (amplifies when passed maternally) | Dysmorphic (males): face, large ears, postpubertal macroorchidism | Full mutation males: MR mostly in MO-MI range, weak in sequential processing, sustained attention. Anxiety, perseverative language, ADHD-like, gaze aversion, aggression, stereotypies, PDD-like behaviors.<br>Full mutation females: IQ level related to FMR1 protein production. Behavior similar to males, but less pronounced |
| Williams | Microdeletion on 7q11–23 (elastin gene) | Dysmorphic face (full cheeks, wide mouth, flat nasal bridge), supravalvular aortic stenosis, hypercalcemia, multiple motor deficiencies | IQ: most in MI/MO MR range, few higher. Strengths in verbal language, especially vocabulary, face recognition, musical. Poor visual–spatial skills, overly social, often indiscriminately, but poor in keeping friends, marked tendency to anxiety, overactivity and impulsivity |
| Lesch-Nyhan | HPRT deficiency (gene on X chromosome) | CP, choreoathetosis, hyperuricemia (almost always males) | MR: MI/MO, nonvolitional self-biting (upper extremities and mouth) and dysarthric speech anxiety |
| Velocardiofacial | Microdeletion 22q11.2 | CHD, aplasia of thymus, cleft palate, dysmorphic face, hypocalcemia | IQ: about half in MI/MO MR range. NVLD, high rate of mental disorders (ADHD, psychosis) |

MR, mental retardation; PR, profound; MI, mild; MO, moderate; SE, severe; CHD, congenital heart defect; SIB, self-injurious behavior; CP, cerebral palsy; NVLD, nonverbal learning disability.

*Source:* Harris J (1995) Developmental Neuropsychiatry. Oxford University Press, New York, pp. 463–186; Dykens EM, Hodapp RM, and Finucane BM (2000) Genetics and Mental Retardation Syndromes. Brookes Publishing, Baltimore.

assessment one can find an appropriate DSM-IV-TR category that best approximates a patient's clinical presentation. However, it is a general consensus of the developmental disabilities clinicians that the DSM-IV-TR is not well adapted to the diagnosis of mental disorders comorbid with significant intellectual disability, especially if the person is nonverbal. There have been efforts to develop diagnostic criteria for persons with intellectual disability. A diagnostic manual for mental disorders in persons with intellectual disability, the "DM-ID," has recently been published by the National Association on Dual Diagnosis (NADD) (Fletcher et al. 2007). This clinical guide focuses on limitations in applying DSM-IV-TR criteria to people with intellectual disability. This is a welcome addition to the many chapters on intellectual disability in psychiatric textbooks discussing how diagnostic criteria can be adapted to this population (Szymanski et al. 1998, American Academy of Child and Adolescent Psychiatry 1999). The "DC–LD" (Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation) (Royal College of Psychiatrists 2001), although based

primarily on professional consensus rather than on empirical data, has also been found useful in practice, especially with persons who have a moderate to profound degree of intellectual disability (Felstrom et al. 2005). In clinical field trials of 709 cases the DC–LD diagnosis and clinical assessment agreed in 96.3% (Cooper et al. 2003). Suggested modifications of diagnostic criteria are discussed below in section on specific mental disorders.

## Behavior Disorders

A common reason for referral for psychiatric consultation is to determine whether a person with intellectual disability has a "behavior disorder" or a mental disorder. The DSM-IV-TR does not have the diagnostic category of "behavior disorder," although it is included in the ICD-10 (World Health Organization 2006). Another commonly used term is "challenging behaviors", which is very broad and nonspecific. It is commonly applied to aggressive and SIB. It can only indicate that the caregivers find the behavior in question challenging to them (or to their authority).

While there is no clear definition of "behavior disorder," it is usually meant to refer to a behavioral problem that is severe enough to warrant intervention, but which is not a part of diagnosable mental disorder. It is often applied to a deliberate misbehavior, learned response, and "attention-getting" behavior. However, in the clinical presentation of every defined mental disorder, there might be elements of learned behavior—for example, caused by the responses of persons in the patient's environment. The danger of such ill-defined, nonspecific category is that clinicians faced with a difficult case might be tempted to use it, rather than attempt to make a more specific diagnosis that might lead to a more focused treatment. Thus, it is preferable to avoid dichotomizing abnormal behaviors into "behavior" and "mental" disorders, but rather to try to decide which mental disorder the behavioral manifestations are part of (Szymanski 1994). Possibly "behavior disorder" could be employed to denote a maladaptive behavior that is clearly a function of situation and environment, and not primarily of the individual. A commonly seen example might be an individual living in a large residential institution, who in a well-staffed workshop setting is otherwise very cooperative, happy, and hardworking, but becomes irritable, negativistic, even aggressive in the afternoon, when he returns to an understaffed group where he lives. A maladaptive behavior may also serve as a form of communication if the person has poor language skills or when the caregivers do not respond to other attempts to communicate. In any case, it is essential that a comprehensive psychiatric diagnostic assessment be made to ensure that the behavior in question is not a part of a diagnosable mental disorder.

Hopefully, the future edition of the Diagnostic and Statistical Manual will be better adapted to the needs of persons with intellectual disability, especially in delineating the co-occurrence of common mental disorders. An introduction of another axis listing behavioral phenotypical manifestations, in addition to axes listing the formal diagnoses, has been recommended (Royal College of Psychiatrists 2001).

## Dual Diagnosis

This term is used frequently when mental illness and intellectual disability coexist. However, the term remains confusing, since for most mental health professionals, it also refers to comorbidity of mental illness and substance abuse. Furthermore, often the term is used to categorize persons with comorbidity, rather than to define their heterogeneous group of disorders. Finally, the terms may lead to stigmatization of a person so labeled from an otherwise appropriate program (Szymanski and Grossman 1984).

## Assessment

### Special Issues in the Psychiatric Assessment of Persons with Intellectual Disability

The basic principles of the psychiatric diagnostic assessment of persons who have intellectual disability are the same as those for persons who do not have intellectual disability. However, the clinical approaches may have to be modified. The scope of the assessment might have to take into account multiple needs and problems, and in addition, these individuals depend on multiple providers for multiple services (Table 42–10). The clinical techniques have to be modified according to the patient's discrete developmental levels in various domains, and in particular, communication skills. Not all needs and problems listed in Table 42–10 apply at all times to all individuals, but their relevance to the particular situation has to be carefully considered. In accordance with the principle of biopsychosocial integration, all these factors and their mutual interaction and contribution to the patient's problems and general functioning must be considered. Thus, the presenting problems must be assessed in the comprehensive context of a patient's abilities and disabilities and not as an isolated issue (Szymanski and Crocker 1989).

**Table 42–10 The Multi Principle (Persons with Mental Retardation Have Multiple Needs, Providers, and Services**

| | |
|---|---|
| Caregivers and providers | Parents, family, teachers, attendants, counselors, supervisors, physicians, therapists |
| Disabilities | Cognitive, specific learning, sensory, motor, language, associated medical |
| Need to learn | Self-care, communication, use of community services, recreation, self-direction, social skills |
| Need therapies | Various medical, language, physical, occupational, vocational |
| Need opportunities | Work, education, recreation, social, coordinated health care |

Such assessment may require longer time than usual, but in the long run time is saved since good diagnostic understanding of the patients and their circumstances leads to appropriate treatment rather than random trials of many therapies. A cursory ascription of comorbid mental disorders with sequential trial of medication remedies in an ad hoc manner often leads to further complications, as seen in the discussion below on psychopharmacological management of persons with intellectual disability who present with emotional and behavioral problems.

#### *Outline for Obtaining a History*

**Informants.** All involved caregivers should be interviewed if possible (parents, teachers, direct care workers, supervisors in

workshops). Direct care staff members (e.g., from the group home and workshop supervisors) are particularly important because they can provide a firsthand description of a person's behavior. Exploring the following areas is important.

**Reason for Referral.** Most adults with intellectual disability come to the attention of a psychiatrist because they are brought by caregivers, usually because their behaviors are deemed disruptive to others. It is important to consider that not in all instances such behaviors are "maladaptive" but represent an appropriate adaptation to inappropriate environmental conditions, lack of psychosocial supports or intolerance of the caregivers. A typical example is when a person who has intellectual disability and lives in an understaffed setting discovers that the overworked staff will give attention first to those who are disruptive rather than to those who are quiet. On the other hand, a depressed individual with more internalizing problems might be neglected if quiet and not creating problems. Exploring the length of time that symptoms have been present might disclose that they have existed for a long time but that the referral has happened only now because of caregiver burnout, reduction in staffing in the facility, or other environmental changes. The caregivers' expectation is frequently for a quick prescription of a medication remedy that has not yet been tried, to control the behavior in question. Familiarity of the prescribing physician with the program and activity schedule (and any changes thereof) of the person with intellectual disability is important.

**Presenting Symptoms.** Concrete, longitudinal data and a factual description of the behavior should be obtained and correlated with concurrent environmental events and treatment interventions. For example, was the aggression physical or verbal? Did it involve use of objects as weapons? Did it result in injury? Did it occur spontaneously, without obvious reason or, for example, after a staff person tried to physically force the client to comply with an order? Often, concrete behavioral data already exist, having been collected by trained behaviorists or behavioral psychologists at the school, workshop, or group home. Converting them into a graphical timeline is most helpful, as it might disclose a pattern such as correlation with other events or a cyclical nature of the presenting symptoms. It is important to find out in what situations the presenting symptoms occur as well as in what situations they do not occur. For instance, it is not uncommon to find that an individual acts aggressively at an understaffed group home but not at the workshop where structure and interesting tasks are offered, or vice versa. Obviously, psychotropic medications may not be an answer in this case. Detailed description of any changes in mood and affect is essential, especially with nonverbal patients in new or transitional situations. Astute caregivers who know them well usually will notice depressed mood, sad appearance, anhedonia, confusion, irritability, etc.

**Medication History.** The history of intake of psychotropic as well as nonpsychotropic drugs is essential. Unfortunately, caregivers often provide only a list of drugs, dosages, and starting and discontinuation dates, without information about the reasons they were prescribed and their effects. Close to half of persons with intellectual disability referred for mental health evaluation have been found to be on nonpsychotropics that could produce psychiatric symptoms as their side effects (Royal College of Psychiatrists 2001). Common examples in this population used to be barbiturates leading to overactivity and beta-blockers leading to depression, although these practice patterns are lessening with the advent of novel psychotropic agents.

**History of Complementary and Alternative Medicines (CAM).** CAM treatments have been increasingly used for persons with developmental disabilities, as in the general population. Hyman and Levy (2005) in a lead article in a journal issue devoted to CAM cite studies showed that 45% of children visiting an emergency department and up to 36% of adults in the National Health Interview Survey used CAM. The parents may resort to CAM for several reasons: anecdotal reports of great effectiveness, seeking cure (about which physicians rarely talk), sense of control in managing the child's treatment and the (erroneous) belief that these treatments are completely safe. Full review of CAM interventions is beyond the scope of this chapter and may be impossible as new ones are reported almost daily. Defining CAM is difficult and probably the best description is as a treatment, which has not been proven effective and safe in a scientific manner, which would be expected of any treatment in this era of evidence-based medicine.

Some examples include:

- Nutritional supplements (high doses of selected vitamins or multivitamin complexes, trace metals, minerals, amino acids).
- Drugs and biologicals (variably used such as piracetam, donepezil, growth hormone, secretin, cell therapy). It should be kept in mind that over-the-counter supplements are not manufactured to standards of approved drugs and it may be difficult to know the bioavailable dose of the presumably active ingredient and possibly toxic other ingredients. Some physicians have been noted to even prepare and sell proprietary mixtures of vitamins and supplements, but the parents do not know their ingredients. There have also been case reports of persons using CAM substances brought from their countries of origin which contained lead, leading to lead poisoning.
- Diets: yeasts-free, gluten and casein-free.
- Procedures: facilitated communication, auditory integration, massage, aromatherapy, facial plastic surgery for children with Down syndrome (to remove the appearance characteristic for that syndrome), and numerous others.

Clinical Vignette 1

A four-year-old child with autism was seen for a follow-up assessment. He appeared to be grossly malnourished and had lost weight compared to an initial developmental assessment few months earlier. The child's mother had denied any history of intercurrent illness. On close questioning about the child's nutritional status she noted that he was recently started on yeast-free, casein-free and additive-free diet. It turned out that it eliminated most nutritional components. Intensive counseling and follow-up by a pediatrician and nutritionist was instituted and the child's nutritional and developmental status improved.

Clinician's attitude to the family using CAM is critical. A priori negative response, criticizing the parents or ridiculing the treatment must obviously be avoided. Optimally, the clinician should be knowledgeable with these treatments and should ask specific questions. Many families, when asked a general question about the treatments and medications the patient had been prescribed, may not mention CAM, considering them as nonmedical interventions, but will respond if the clinician asks specific questions such as enumerating all the interventions by name. If the clinician is not familiar with a given treatment, the parents might be asked to provide further information and a background literature search may indeed be done later. Firstly, all possible adverse effects of any treatment or intervention should be ruled out. Later, any available studies on the positive and adverse effects of the treatment should be reviewed and shared with the family (Clinical Vignette 1).

**General History.** ***Nature of the Disability*****:** Past assessments should be critically reviewed and new ones requested if needed. Many older individuals did not have adequate assessment of the etiology of their disability and even if they did, it might not reflect genetic and other advances that have occurred since the assessment was made. For instance, chromosomal analysis before the early 1980s could not have disclosed fraX. Past assessments of general adaptive behavior and cognitive and communication skills, should be reviewed, considering strengths and deficits in all critical areas and possible regression (Shevell 2006).

***Medical and Psychiatric History*****:** This is essential for several reasons. The incidence of medical conditions in persons with intellectual disability is high and they are often undiagnosed (Royal College of Psychiatrists 2001). Ryan and Sunada (1997) found, that 75% of 1135 adults referred for psychiatric assessment had a medical problem, almost always previously undiagnosed, or undertreated. Almost half of that sample was receiving psychotropic medication that could potentially have psychiatric side effects. A nonverbal person may communicate physical pain and discomfort through behavior. Assessing pain in them may be difficult, but caregivers who know them well might recognize it better than clinicians. It is important to communicate with the patients' primary care providers to understand what has already been ruled out, for example, pain related to ear infection, dental caries, gastrointestinal discomfort/chronic constipation, or menstrual cycle. A functional decline may also be due to a CNS pathology related to an onset of physical or neurological illness. A medical condition might have psychiatric manifestations. Thyroid disorders, systemic lupus erythematosus, Helicobacter Pylori infections (reportedly more common in persons with intellectual disability in group settings) can each be associated with behavioral problems (Wallace et al. 2002), as can any painful medical condition, especially in persons with limited communication skills. Thus, a detailed and critical review of recent medical evaluation, if any, is necessary without any underlying assumption that these conditions have been ruled out. A "generic" physical examination may not be sufficient if it did not take into consideration disorders that persons with the intellectual disability syndrome in question are prone to (for example, diabetes, thyroid disorders, hearing impairment, in persons with Down syndrome). In this respect, the education of psychiatrists in such associated medical conditions in persons with intellectual disability, in addition to the adaptations of the diagnostic criteria for mental disorders in the future diagnostic manuals, ought to be considered. If there is doubt, a focused medical evaluation should be requested. The usual history of psychiatric treatment, hospitalizations, and diagnoses should be reviewed.

*Past and Current Services*: Detailed description of past and present services that the patient has received should be obtained. These include educational and vocational services and behavioral management programs. They should be evaluated in terms of appropriateness, consistency, and effectiveness. Often, a referral is made to the psychiatrist with the request that he or she prescribe a "chemical restraint" to "control aggression," because the "behavioral program" did not work. A detailed history might disclose, for instance, that the aggression happens only when the person is forced to engage in a workshop in table tasks which are too difficult considering the person's poor fine motor skills and developmentally short attention span, or that a child is overactive and irritable only at school, where he or she is placed in a classroom inappropriate to his or her developmental level. A recent vignette involved a request for the psychiatrist to prescribe elbow restraints for a young boy with Down syndrome engaging in SIB in a classroom setting without an adequate assessment of the child's behaviors or development of a behavioral intervention program. The request was also relayed through an aide in the classroom setting without full consultation of the parents. Although such incidents occur relatively rarely and reflect urgent needs they too often also reflect an inadequate plan of care for persons with intellectual disability. The role of the psychiatrist in such circumstances is to help develop a comprehensive approach following a detailed assessment of the situation, too often not possible over a short time span.

***Milieu Events*****:** Systematic exploration might be required to find out about important events such as losses (e.g., siblings moving out of the house), relocations (e.g., to a group home), or sexual abuse (as suggested by behavioral changes similar to those seen in sexually abused children).

***The Family*****:** The knowledge, understanding, and reaction of family members (including siblings) to the patient's disabilities should be explored tactfully. The psychiatrist should be careful not to convey personal feelings through the questions such as expressing condolences for their having a child with intellectual disability, whereas the parents might see the care of the child as a positive challenge. Many dedicated parents may view their child's condition as a positive life-changing experience for them and their family. In particular, the parents should not be viewed as patients, and their normal "chronic sorrow" should not be confused with pathological depression (Olshansky 1962). The family members' patterns of management of the patient should be explored in terms of limit setting, consistency, appropriateness of expectations to the patient's abilities, capability to advocate for services, and participation in support activities such as parents' organizations. Another important topic is the parents' ability to balance the needs of the child with intellectual disability with the needs of other children.

## Approaches to the Patient's Interview

The way in which the patient's interview is approached will depend on the patient's communication skills and cooperation; this may range from an age-appropriate verbal

interview to observation only. The communication skills have to be explored first through brief, noncommittal conversation and questioning of the caregivers. If necessary, the caregivers might be used as interpreters of the patient's poorly intelligible speech or sign language. Directive measures and structure are often necessary to help the patient focus, but leading questions and suppression of spontaneous expression must be avoided. While firm and clear behavioral limits may have to be established at the interview's onset if necessary, a great deal of support is needed. Noncondescending verbal and social reinforcement, as appropriate for developmental age, will let the patient know that the interviewer is appreciative of her or his abilities. The adult patients should also be approached respectfully—if possible, in a manner appropriate to the chronological age—and not as children. However, communication with them should be on the level they can understand, and their understanding should be ascertained. When asked if they understood a question, many patients tend to say "yes," but the content of their answers may disclose the degree of understanding that needs to be attended. Persons with intellectual disability are afraid to be perceived as inadequate and instead of saying that they did not understand the question, they tend to agree with the interviewer's last statement. Thus, asking open-ended questions is preferable to giving a choice of answers. For the same reason structured mental-status type of questions might be counter-productive. Leading questions should also be avoided. These issues need to be taken into consideration in research involving studies in persons with intellectual disability. If the level of verbal skills permits, one should always explore the patient's self-image, including understanding of his or hers own disability as well as strengths.

Nonverbal interviewing techniques include behavioral observations, spontaneous and directed (structured) play (as developmentally and age appropriate), and other structured tasks. Optimally, the patient should be observed in normal situations such as home, school or work. While it may not be possible due to time constraints, observation of the patient in the office/clinic waiting room may provide valuable insight into general behavior, and social interaction.

### *Behavioral Measurement Instruments*

There are many instruments developed for assessment of psychopathology and behavior of persons with intellectual disability (see review, O'Brien et al. 2001). They are particularly useful for nonmental health professionals as screening instruments, as well as for measuring change over time to assess treatment results. They are not meant to replace clinical diagnostic evaluation by a psychiatrist (American Academy of Child and Adolescent Psychiatry 1999). Some of them are: *The Diagnostic Assessment for the Severely Handicapped (DASH-II),* designed to measure emotional problems in adults with severe to profound intellectual disability, utilizing history from a primary caregiver and resulting in a clinical diagnosis based on DSM-III-R; *Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD)*, a semi-structured protocol for interview with the patient and a caregiver that may result in a diagnosis based on ICD-10, particularly of major depressive disorder, agoraphobia, generalized anxiety and panic disorder; *Psychopathology Instrument for Mentally Retarded Adults (PIMRA)*, for persons with mild to moderate mental retardation, in patient and caregiver versions, that gives a diagnosis based on DSM-III (only schizophrenia and depression subscales have been validated), and *Reiss Screen for Maladaptive Behavior*, designed to screen for psychopathology and maladaptive behavior in adults, particularly to identify individuals needing further assessment. *The ABC-Aberrant Behavior Checklist* (Aman et al. 1995) has been described as more useful for adults with intellectual disability than the GAF scale (Global Assessment of Functioning) of the DSM-IV-TR (American Psychiatric Association 2000), (Shedlack et al. 2005). Finally, the Developmental Behavior Checklist (DBC), a 96-item checklist that is completed by parents or teachers is currently used to assess behavioral and emotional symptoms in children and adolescents with intellectual disability over a six-month reference period (Einfeld and Tonge 1995). Each behavioral description is scored on a 3-point likert scale where (0 = *not true as far as you know*, 1 = *somewhat or sometimes true*, and 2 = *very true or often true*). The DBC can be completed in 10–15 minutes and is analogous to the Child Behavior Checklist (CBCL) or Teacher Report Form (TRF) developed by Achenbach for more typically developing children and adolescents.

### Functional Analysis of Behavior

The functional analysis of behavior usually refers to systematic collection and interpretation of data on the antecedents and consequences of the behaviors of the person in question. It is important that the focus be broad and not be restricted to immediate events but also on settings and underlying events. For instance, a person might engage in SIB when demands are made to perform in a workshop and the result might be that he or she is permitted to abandon the task. More extended analysis might show, however, that there was no such behavior in the past and that it has been occurring since the person was given new tasks that are too difficult.

## Evaluation of Clinical Data

The clinical observations should be interpreted in light of a patient's life experiences, learning, understanding, and communication level. The global IQ or overall mental age of a patient alone is therefore not a good guide here. In particular, the psychiatrist should:

1. Assess clinical presentation in light of the patient's communication ability, cognitive level, associated disabilities (e.g., sensory), life experiences, environmental factors and cultural background. One should differentiate between behaviors appropriate for an earlier age and those that are pathological in any age (e.g., true hallucinations). Not all disruptive behaviors are an expression of a mental disorder: for example, an overworked staff might promote aggressive acting out by attending to the patients only when they become aggressive. However, one should not simply explain all such behaviors as attention-getting. Conversely, persons who do not manifest disruptive behaviors might have a mental disorder, for example, a depressed individual who is considered behaving well because he is very quiet. Evaluations and consultations with other disciplines should be sought as needed; these include, for example, clinical psychologists, neuropsychologists, speech and language pathologists, occupational therapists, and neurologists.

2. Assess and understand the dynamic, ongoing transactional relationships among the various factors contributing to the person's development (see Figure 42–7).
3. Try to make a formal Axis I and/or Axis II DSM-IV-TR diagnosis (besides intellectual disability) whenever clinically justified. The diagnostic criteria can usually be adapted to the patient's developmental level, as delineated previously. However, diagnosis does not mean listing the disorder's code and name only. To be constructive, the diagnostic statement should include description of strengths, impairments, and need for supports and services in each discrete domain of the individual's functioning, as well as in the environment (school/workshop, community and family). It should not merely repeat the diagnostic criteria but describe how they are satisfied in the particular case by history and clinical observation, as well as why other diagnoses in the differential are ruled out. The five dimensions of intellectual disability of the AAMR (American Association on Mental Retardation 2002) listed above are a useful guide to diagnostic assessment.

## Diagnosis of Specific Mental Disorders

Detailed chapters in this textbook are devoted to all aspects of specific mental disorders. Therefore, in this section only aspects relevant to the diagnosis of most common mental disorders in persons who also have intellectual disability will be discussed.

### Mental Disorders Due to a General Medical Condition

In the DSM-IV-TR, the term "*Mental Disorders Due to a General Medical Condition*" replaces the time-honored "*Organic Mental Disorders*" of earlier editions. This term is intended to be used only when "there is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition" (American Psychiatric Association 2000, p. 182). However, this category had often been used inappropriately as a catchall diagnosis on the presumption that if the person had intellectual disability which is the result of CNS dysfunction, all coexisting behavioral problems were also the product of the same neuropathological condition and a part of intellectual disability, often assumed also to be different from "normal" mental disorders. Such reasoning might be used, for instance, if a car accident at the age of 10 years caused brain injury that resulted in intellectual disability and an emergence of personality features consistent with the particular type of neuropathological condition. It would not be appropriate, for example, if a person with intellectual disability manifested symptoms consistent with psychotic disorder at the age of 15 years. The "general medical condition" should therefore be diagnosed as specifically as possible, rather than as something like "chronic encephalopathy of unknown origin" (a common diagnosis in a not-so-remote past). For mental disorder due to a general medical condition, the specific general medical condition is coded on Axis III. Of course, not diagnosing "organicity" does not necessarily mean that the symptoms are independent of CNS dysfunction.

In the DSM-IV-TR, the section Mental Disorders Due to a General Medical Condition includes Catatonic Disorders Due to a General Medical Condition, Personality Change Due to a General Medical Condition and Mental Disorders Due to a General Medical Condition Not Otherwise Specified. Other mental disorders meeting the criteria for Due to a General Medical Condition (such as mood disorders, anxiety disorders, psychotic disorders and others) are in sections on these disorders. Delirium, Dementia, and Amnestic and Other Cognitive Disorders constitute a separate section.

Persons with certain intellectual disability–associated syndromes are at increased risk for developing medical conditions that produce psychiatric symptoms. For example, persons with Down syndrome are at risk for Alzheimer-type dementia. However, clinical manifestations are rarely found before age 45 to 50 years, though 75% might show them by age 60 years (Hodapp 1996).

#### Diagnosis of Dementia in Persons with Intellectual Disability

Intellectual disability can be diagnosed only if the onset is before age 18 years, whereas dementia can be technically diagnosed at any age. However, according to DSM-IV-TR, the diagnosis of dementia does not depend simply on the presence of low IQ and poor adaptive skills: both memory impairment and at least one other specified cognitive disturbance representing a decline from a previous level of functioning must be deemed present. Such decline and cognitive impairment might be difficult if not impossible to determine in infants and very young children. Therefore, DSM-IV-TR advises that making a diagnosis of dementia concurrent with intellectual disability might not be appropriate before 4–6 years of age, and in general it is not made if the condition is sufficiently characterized by the diagnosis of intellectual disability alone (American Psychiatric Association 2000, pp. 47–48). This approach avoids an automatic double diagnosis in all cases of intellectual disability from an acquired postnatal cause. However, such double diagnosis is appropriate in persons with intellectual disability who also meet criteria for dementia (such as an individual with Down syndrome, who develops Alzheimer-type dementia).

#### *Side Effects of Medications*

The side effects of medications are of importance in this population as the use of various drugs is frequent because of high prevalence of associated medical, neurological, and mental disorders. Common examples include: adverse behavioral symptoms associated with commonly used psychotropic medications (i.e., SSRI antidepressants and atypical antipsychotic agents), and less commonly depressive symptoms associated with beta-blockers prescribed "for aggression," The DSM-IV-TR has a category of "Medication-Induced Adverse Effects of Medication Not Otherwise Specified" that could be used here.

### PDD and Autism Spectrum Disorders

In the DSM-IV-TR the umbrella category of PDD is subdivided into: Autistic Disorder; Asperger's disorder; PDD-Not otherwise Specified (PDD-NOS); Rett's disorder; and Childhood Disintegrative Disorder. In the last two disorders (introduced in the DSM-IV-TR), deceleration in development or major skill losses are diagnostic features. PDD is increasingly referred by clinicians and researchers as a spectrum condition or autism spectrum disorder (ASD). On the one end of the

spectrum are persons with more severe impairments in social communication, language development and stereotyped behavioral disturbances with intellectual disability; on the other end of the spectrum, are individuals with normal or above average intelligence with autism or Asperger's disorder. PDD in general, and autistic disorder in particular, have often been confused with intellectual disability, especially when the person has a delay in speech development, is nonverbal, and manifests stereotypic and repetitive behaviors, which may also be present to a significant degree in intellectual disability. In the recent years there has been considerable concern about the rising prevalence of new diagnoses of autism (see review: Shattuck 2006). The observed increases in prevalence have, in part, been attributed to the broader DSM–IV TR (American Psychiatric Association 2000) definition of the disorder, increased public awareness, earlier diagnosis, change in diagnostic practices, better ascertainment of individuals with varying degrees of severity, and "diagnostic substitution" of autism for what in the past were attributed only to intellectual disability (Volkmar et al. 2004). Given the consistent rise in the number of new cases of autism, a true increase in the prevalence of ASD cannot be ruled out. The explanation of these trends is beyond the intended scope of this chapter. Needless to say, both the educational and health care services have witnessed a surge in the numbers of young children with ASD that may also present with varying degrees of intellectual disability, although many parents view the diagnosis of ASD as being more directive in guiding early educational services for their children. Shattuck (2006) analyzing special education data found that between 1994 and 2003 administrative prevalence of autism increased from 0.6 to 3.1/1000. About three quarters of children with core autism are believed to have some degree of intellectual disability (Fombonne 1999), although this proportion is lower in broader ASD.

In PDD, there are major impairments in interpersonal reciprocal interaction and in social communication. Conversely, persons with uncomplicated intellectual disability have an ability to relate to others (according to their developmental level). Person with very significant intellectual disability who are nonverbal may have impairments in social interactive skills. However, on closer and prolonged observation many if not most of them will demonstrate at least some nonverbal social communication skills and interpersonal attachments, to familiar caregivers who are responsive to them. Thus, intellectual disability and a PDD are not mutually exclusive, and the correct differential diagnostic question is whether the person has a PDD and whether it is associated with intellectual disability. The diagnosis can be made even in persons with significant intellectual disability and no verbal language on the basis of clinical observations and detailed developmental and current history. A diagnostic/screening instrument has also been developed to aid identification of ASD comorbid with intellectual disability (Kraijer and de Bild 2005). The diagnosis might be a problem with adults who have both autism and intellectual disability, but on whom the latter diagnosis cannot be confirmed because the early developmental history is unavailable.

In some intellectual disability–associated known syndromes clinical manifestations consistent with at least some of the presentation of autism (Clinical Vignette 2) might be found such as in fraX, and particularly TSC and 22q11.2 deletion syndrome.

Clinical Vignette 2

John, a 28-year-old man, was referred from his workplace where he was accused of sexual harassment of a female coworker. During the interview, he was anxious and fidgety, had limited eye contact, spoke in a pedantic manner, dwelling on minute details. He was well oriented and there was no evidence of psychotic thought disorder. He stated that he never had friends but wanted to have a girlfriend. He recently met a new coworker in an elevator and when she told him "see you later" he understood that she wanted to have a date. He started to bring her flowers daily and asked her out until she filed the complaint. Past history from John and his father indicated that he was always a quiet and strange child, with little eye contact, was unemotional, had no friends, was obsessive about order, and was interested only in mathematical calculations in which he was quite good. His early development was normal except that he spoke in sentences only at 4 years of age. When he was 7 years of age he was taken to a psychiatrist who thought that he had "early childhood schizophrenia" and mild intellectual disability. The parents disagreed, and he had no other contacts with mental health professionals. He attended special classes for learning disabled children and later his father arranged a job for him in the mail room of a law firm where he was a partner. Family history was negative for mental and developmental disorders. John refused to have any tests besides a psychiatric interview.

The history strongly suggested previously undiagnosed autistic disorder with some cognitive delay. Individual psychotherapy with cognitive–behavioral orientation was recommended with the focus of educating John about his condition as well as his abilities, and teaching him appropriate social behaviors and skills. He also entered a support group for young people with high functioning autism. With his permission, several sessions were held with his coworkers who subsequently became very supportive of him.

## Attention-Deficit Hyperactivity and Disruptive Behavior Disorders

Persons of any age who have intellectual disability are frequently referred to a psychiatrist with a complaint of "short attention span" (Reiss 1990, review: Antshel et al. 2006) or a disruptive behavior. Not attending, however, to school or work tasks, or not being compliant, does not necessarily warrant an automatic diagnosis of an attention-deficit/hyperactivity disorder. In the DSM-IV-TR, the majority of the diagnostic criteria for attention-deficit/hyperactivity disorder is based on observable behaviors and therefore can readily be applied to nonverbal persons, including those with intellectual disability. However, the criteria also state that the symptoms must be inconsistent with the developmental level. Thus, a high level of activity and short attention span in a 6-year-old child with severe intellectual disability, who has learned to walk recently and busily explores the environment, is not necessarily pathological. Antshel et al. (2006) after review of relevant studies concluded that attention-deficit/hyperactivity disorder may be a valid diagnosis in children with intellectual disability. They also noted that the current assessment measures of attention-deficit/hyperactivity have not been validated for persons with intellectual disability, with the exception of Aberrant Behavior

Checklist (ABC) (Aman and Singh 1986), and that further research is needed on prevalence of attention-deficit/hyperactivity symptoms in persons with intellectual disability. In clinical practice it may not be easy to decide whether the behaviors in question are developmentally appropriate for the individual, considering developmental level, chronological age, education received, environmental factors, and presence of associated disabilities such as sensory impairments. It is important to ascertain that at least some impairment is present in two or more settings, as required by DSM-IV-TR criteria. This would help to avoid diagnosing attention-deficit/hyperactivity disorder in situations such as when the child in an inappropriate academic placement for his abilities is disruptive and inattentive at school, but not in other settings (Clinical Vignette 3). In fact, the prevalence of attention-deficit/hyperactivity in persons with intellectual disability is thought to be more threefold more common in persons without intellectual disability than in the general population (15 v. 5%).

Although less specific than attention-deficit/hyperactivity, other categories of disruptive disorder (oppositional, conduct and disruptive disorder NOS) also represent common reasons for psychiatric referral for persons with intellectual disability. This diagnosis is made in the same manner as in persons without intellectual disability, given the behaviorally specified criteria. It is essential to consider the behaviors in question in the context of the nature and severity of the intellectual disability, profile of cognitive and communication skills, appropriateness of environmental supports and services, and whether the behaviors are generalized or specific to certain settings and caregivers.

As in persons without intellectual disability, attention-deficit/hyperactivity may be associated with other disorders such as mood disorder and anxiety disorder, which should each be diagnosed even if the disruptive behavior is the reason for referral (Pearson et al. 2000).

Clinical Vignette 3

Billy, an 11-year-old student in a special class for children with learning disorders, was referred because he was easily frustrated, impulsive, did not finish his school assignments, refused to do his homework, did not stay in his seat, was loud in class and interrupted other children's play. Billy had no friends and was teased by other children. His attention span was short but was better on tasks which he liked and was proficient in. He had anger outbursts and made statements such as "I am not a retard." He had problems in falling asleep. His parents, both successful professionals, had little patience with him as did his older sister, an honor student. His full-scale IQ was 65 with marked scatter. His past neurological examination, sleep deprived EEG, and genetic assessment (including chromosomes/fragile X) were negative. During the interview he greeted the psychiatrist warmly and said that he did not want "tests" since he was not "stupid." He talked about wanting to be a pilot or a doctor. He was markedly distractible and fidgety. When he was asked about his school he became abruptly uncooperative and angry.

Billy was seen as a child with mild intellectual disability and with symptoms suggesting attention-deficit/hyperactivity probably of the combined type, complicated by inappropriate school placement with learning disabled but bright children. He was aware of his shortcomings and rejection by peers and that his parents were disappointed with him, and his self-esteem was low. The treatment recommendations included placement in an inclusive classroom with support of a trained aide; appropriate educational supports, individual psychotherapy with the goal of improving his self-image and social skills; family therapy to facilitate his acceptance by his family; a behavioral program utilizing positive reinforcement to deal with his disruptive behavior; and a low dose stimulant medication to address his inattention and poor impulse control problems.

## Stereotypic Movement Disorder

This diagnosis is most frequently used in persons who have intellectual disability if a stereotypic behavior is leading to significant functional impairment, if it is the focus of treatment, and if it is not better accounted for by another diagnosis. Thus, not all self-stimulatory behaviors often seen in persons with intellectual disability (and for that matter, also in persons without intellectual disability) qualify for this diagnosis. Self stimulatory-like behaviors occur in young typical children as well as in persons with blindness, especially congenital type, characteristically in the form of head turning from side to side. In fact, almost every "normal" person will engage from time to time in some stereotypic behavior such as fiddling with an object, in situations of stress or when attention is focused on a particular task such as intense studying or prayer.

The DSM-IV-TR permits adding the specification "with SIB" to the diagnosis of stereotypic movement disorder. SIB is one of the major reasons for psychiatric referral of persons with intellectual disability (rather than the stereotypy alone), especially with increasing severity and frequency and is unquestionably one of the most difficult clinical behaviors to treat effectively. SIB is defined as repetitive behavior resulting in tissue damage that requires medical treatment and that is not better accounted for by other diagnoses. Examples include head banging, self-biting, hitting, eye bashing, poking and gouging (to the point of blinding oneself), and picking at skin and body orifices. The prevalence is thought to be up to 3% of the persons with intellectual disability, but it varies—the highest prevalence being reported in persons with severe or profound disability who live in institutions and may range as high as 70%. In a study of an unselected population of persons with moderate to profound intellectual disability, 14% displayed some degree of SIB (Hillery and Mulcahy 1997). Topography of SIB may be quite varied and may include such diverse behaviors as rumination and extreme aerophagia that may be even life threatening. Risk factors (besides severity of intellectual disability) include blindness, PDD, and certain syndromes such as Cornelia de Lange syndrome, fraX, Prader–Willi syndrome (skin picking in particular), Rubinstein–Taybi syndrome and Lesch–Nyhan disorder. In the latter, some of the most dramatic and crippling self-mutilations are seen, usually inflicted by self-biting of limbs, and if restrained, of mouth and tongue. Environmental conditions are also an important factor in SIB,

either causing or maintaining the behavior that originated for different reason (see Clinical Vignette 4, below). Inappropriate, understaffed programming, overcrowding, lack of developmentally appropriate activities, and lack of staff attention unless the client displays "challenging" behavior may all contribute to development of SIB. The prevalence and severity of SIB usually peaks in adolescence and early adulthood and is reduced in later age. Unfortunately, SIB also occurs quite spontaneously and unpredictably in children with a range of developmental disorders, including autism usually associated with severe to profound intellectual disability and the sensory issues in autism may drive the SIB behaviors. A child with autism and intellectual disability with comorbid SIB is often also exhibits a range of sensory reactivity issues (e.g., clothing, food, noise) that exacerbate stereotypes repetitive behaviors; SIB being a manifestation of stereotyped repetitive behaviors that takes a life of its own once activated.

Clinical Vignette 4

David, a 20-year-old with Cornelia de Lange syndrome, with severe intellectual disability, was nonverbal and lived in a residential school. He has always engaged in some degree of self-stimulatory hand movements and head-scratching, but over the past 2 months he developed head banging that was severe enough to lead to multiple scalp cuts. A behavioral program based on time-out when he banged his head helped only when he stayed in the time-out room. A psychiatrist followed him one day at school and observed that the head banging occurred primarily just before, during, and after visits to the bathroom. On physical examination an anal fissure was found. It was successfully treated and head banging subsided for a while but then recurred to a lesser degree. David was thought to have stereotypic movement disorder not uncommon in people with Cornelia de Lange syndrome, which was later complicated by self-injurious head banging, linked initially to the painful anal fissure, but later maintained by "secondary gain," that is avoiding tasks when he was in the time-out room. His behavioral program was modified: time-out was stopped and the head banging ceased when he started receiving rewards when he did not do it. His self-stimulatory behaviors decreased when he was started on an SSRI antidepressant.

Differentiating Stereotypic Movement Disorder from Obsessive-Compulsive Disorder (OCD) may be difficult. Compulsive behaviors in the latter are often more complex, ritualistic and involve a response to an obsession thought. However, ascertaining an obsession may not be possible with nonverbal persons with intellectual disability (American Psychiatric Association 2000, pp. 133). It is possible that a self-restraint (such as holding hands in one's pockets to avoid self-hitting) seen sometimes in persons with intellectual disability and SIB, may be an indirect indication that this behavior is ego-dystonic, and more similar to an OCD behavior, although the ego-syntonic v. ego-dystonic distinction may be less useful in children and adolescents with OCD than perhaps in adults. Stereotypic Movement Disorder should be differentiated from motor tics, including those that occur as a side effect of a stimulant medication, and from trichotillomania that is limited to hair pulling.

In diagnostic evaluation of SIB, various underlying conditions should be ruled out. A painful and undiagnosed medical condition is not infrequently a precipitating factor: for example, an ear infection or migraine might lead to head banging. The SIB may be related to an underlying, previously undiagnosed, another mental disorder (such as depressive disorders, impulse-control disorder, and anxiety disorder) treatment of which may also ameliorate the self-injury (Tsiouris et al. 2003). However, the cause of the final clinical presentation is usually multifactorial and, besides biological factors, may include learned responses to an environmental situation and coexistence of other psychopathological conditions such as depression and psychosis, treatment of which might also ameliorate the SIB. Thus, a comprehensive assessment of all possible factors is needed (Gualtieri 1989). In a fair number of patients, no underlying condition or causation can be found akin to an "essential hypertension" suggesting perhaps a multi-factorial etiology. Current studies are investigating mechanism of SIB; the possible role of endogenous opioids (Sandman 1990), dopamine receptors and serotonin systems in association with compulsive behaviors (King 1993) have been explored. A comprehensive review of the subject has been done by Harris (1995, 2006).

## Pica and Eating Disorders

Pica is defined by the DSM-IV-TR as eating nonnutritive substances for at least one month, which is developmentally inappropriate and culturally not sanctioned. Pica is encountered primarily in persons with severe intellectual disability in whom it might create major health problems such as nicotine toxicity from ingesting cigarettes butts, lead toxicity due to eating lead-based paint chips or ingestion of objects that requires surgery for their removal. More than half of these individuals have been found to have zinc deficiency (Lofts et al. 1990).

Other eating disorders are also common. Up to 19% of adults with intellectual disability living in the community, and up to 42% of those in institutions may have eating disorder and obesity is frequent (review: Gravestock 2000). Persons with Down syndrome tend to be overweight, but anorexia has been also described and sometimes may occur in association with stress or loss related regression associated with depression. Overeating and obesity is a characteristic feature in Prader–Willi syndrome. Rumination is also a major health problem as it may lead to aspiration and pneumonia.

## Schizophrenia and Other Psychotic Disorders

In the early years of psychiatry the differentiation between intellectual disability (especially severe) and psychosis was not clear; in particular, the self-stimulatory motor behaviors of persons with significant disability were confused with catatonia. Kraepelin's concept of "propfschizophrenie" suggested a syndrome of schizophrenia "grafted" on intellectual disability (Catinari et al. 2005). At the present true schizophrenia in persons with intellectual disability is thought to be the same disorder as in persons without; however, similar to other mental disorders in this population, the manifestations may be modified depending on developmental level and, in particular, language skills. The prevalence of schizophrenia in persons with intellectual

disability is estimated at about 2–3% (Fraser and Nolan 1994). Recent studies suggest that low intellectual ability might be a risk factor for schizophrenia and other psychotic disorders (David et al. 1997). Certain genetic syndromes also carry a heightened risk for psychotic disorders including schizophrenia. Vorstman et al. (2006) have found psychotic symptoms in 16 of 60 children with the 22q11.2 deletion (Velo-Cardio-Facial Syndrome) and in 7 of them the impairment was severe enough to warrant a formal diagnosis of psychotic disorder.

As described elsewhere in this textbook, the DSM-IV-TR diagnostic criteria for schizophrenia include delusions, hallucinations, and disorganized speech, the manifestation of which requires a certain degree of verbal language. However, the presence of grossly disorganized behavior coexisting with negative symptoms is sufficient to meet the diagnostic criteria for schizophrenia. Sometimes the person's behavior and affect might give a clue as to whether he or she is responding to visual or auditory hallucinations. In persons with some verbal language, evidence of hallucinations or delusions might be detected with careful interviewing and observation that avoid leading questions. For instance, one person with mild intellectual disability when asked if he "heard voices," answered in the affirmative, later clarifying that he "was not deaf." Talking to oneself, which is seen in some persons with intellectual disability as well as in ASDs, might be similar to behavior in young children who rehash the day's events or talk to an imaginary friend, if there is no evidence that they are responding to actual auditory hallucinations. However, the nature of the hallucinations or delusions cannot be assessed unless the person has good language abilities; thus, diagnosis of a subtype of schizophrenia is not possible, and a more general category including psychotic disorder NOS may have to be used.

The lower the patient's language abilities, the more the diagnosis has to rely on behavioral and affective manifestations. In fact, it had been suggested that an accurate diagnosis of schizophrenia may not be possible in persons with an IQ less than 50 (Reid 1993). Conversely, in persons with mild intellectual disability and good language capacities, the clinical presentation and diagnosis of schizophrenia are similar to those in persons without intellectual disability, although the content of delusional thinking might be less sophisticated. However, one should not confuse the concreteness of thinking due to reduced cognition with thought disorder of schizophrenia. Isolated, unusual beliefs have to be assessed in the context of the patient's learning, explanations received previously, and the patient's culture and cognitive ability to understand that these beliefs are unusual. Thus, the whole clinical picture, rather than single symptoms, has to be considered (Reiss 1992). For instance, a child with mild to moderate intellectual disability might truly believe that he hears a voice of a deceased parent admonishing him if he had been told that such an experience is possible. A good longitudinal history from caregivers who are familiar with the patient should help decide whether these features have been always present or emerged at a certain point in life and have been associated with a functional decline.

The following clinical vignettes (Clinical Vignettes 5–8) illustrate problems in diagnosis of psychotic disorders in persons with significant intellectual disability:

**Clinical Vignette 5**

Elisabeth was referred with suspicion of paranoid psychosis. She was 25 years old. At age 5 years, she was diagnosed as having mild intellectual disability of unknown etiology. After finishing high school in special classes, she was employed cleaning tables in an office cafeteria. Four months prior to referral her parents arranged for her to live in a community residence. Around that time she was noticed to become irritable, was fearful of men, and she refused to take showers, which was ascribed to being a reaction to leaving her parents. Behavior modification program did not help. A month prior to referral she became uncooperative at work, complained that the cafeteria customers were saying that she was bad, that no one liked her, and that she was followed by people who wanted to hurt her. During the interview she was distressed, well oriented, and confirmed the above history. She denied having hallucinations. She was wearing a hearing aid. When she was asked what she meant by "bad," she started to cry and said that she did bad things with a boy. She said that she dreamt every night about it. Her parents were interviewed and reluctantly disclosed that 5 months earlier they found that Elisabeth was sexually accosted in a shower by a 20-year-old neighbor. He was charged with rape but the defending lawyer claimed that Elisabeth agreed to have sex. She was then found to be pregnant and the parents arranged for an abortion. Elisabeth was not told what had happened to her and in fact she never had sexuality education. The parents told her that she was bad since she did not resist the man physically. Also, it transpired that the batteries of her hearing aid ran out a month prior to referral and were not changed until a day prior to her seeing the psychiatrist. Elisabeth was judged to have symptoms of Post-traumatic Stress Disorder (PTSD) related to the experiences of rape and abortion. People close to her had told her that she was a bad person. She believed it and assumed that cafeteria customers talked about it, since she could not hear them. There was no evidence of psychotic thought disorder. The recommendations included supportive psychotherapy with a female therapist experienced with persons with intellectual disability and with adjunctive course of an SSRI antidepressant. She was taught skills necessary to be a competent witness, testified in court, and the perpetrator was found guilty of raping a disabled person.

**Clinical Vignette 6**

Heidi, a 23-year-old woman, was referred from her sheltered workshop because of "noncompliance." She had Down syndrome, functioned within the severe range of intellectual disability, was nonverbal, but could understand a few verbal commands and knew some signs. Previously she had been a good worker doing simple assembly work until about 2 months earlier when she started gradually to withdraw, appeared preoccupied, and refused to do her work. The counselor, who knew her for several years, felt that her personality had changed, going from an expressive and affectionate person to becoming a "bland" one, often laughing for no reason. She still ate and slept well and liked to go on trips to shopping malls. She did not display unusual fears. There was no history of traumatic or unusual environmental events. She recently had a detailed

*(continues)*

Clinical Vignette 6 *continued*

medical assessment which was normal, including thyroid screen and an EEG. Behavioral modification program based on "time-out" when she was noncompliant did not help. During a visit to her workshop she was observed to become intermittently preoccupied, to look around with a startled expression, and to vocalize jargon-like sounds. She backed into a corner and made gestures as though trying to push someone away. She appeared to be a little consoled when her favorite counselor approached her. Family history was positive for schizophrenia in her brother and maternal aunt.

Heidi's behavior observed during the visit suggested auditory and perhaps visual hallucinations. Due to the lack of expressive language the presence of thought disorder could not be ascertained, and only a tentative diagnosis of Psychotic Disorder NOS was made. Her symptoms did not warrant diagnosis of a mood disorder nor was there evidence of PTSD. She responded well to a low dose of an atypical neuroleptic.

## Mood Disorders

Mood disorders, depression in particular, had been rarely diagnosed in the past in persons with intellectual disability, and are probably still underdiagnosed, for several reasons (Szymanski 1980b). First, it had been thought that these individuals cannot become depressed because of insufficient cognitive abilities (Gardner 1967) or, as viewed by some, that their behavior problems were learned as a result of environmental deprivation (both these views denied in effect that these persons could have normal human emotions). Second, poor language capacities made the diagnosis difficult. Third, depressed persons who do not disturb others are often unnoticed in understaffed facilities. However, case reports on depression in persons with intellectual disability had been appearing, and the literature indicates that there is sufficient evidence that depression can occur often in this population (Sovner and Hurley 1983). The prevalence of mood disorders in persons with intellectual disability and in the general population is thought to be similar (Reiss 1994). In the field trials of DC–LD affective disorder was diagnosed in 101 of 709 cases (Cooper et al. 2003).

The majority of the DSM-IV-TR diagnostic criteria for major depressive episodes and for manic episodes can be well used even if language is poorly developed. The diagnosis in verbal persons with mild intellectual disability follows the same principles as in persons without intellectual disability. Furthermore, self-report instruments may be reliably used with them (Esbensen et al. 2005). In individuals with more significant disability who have poor communication skills the history of behavioral change observed by caregivers who know them well will help to make the diagnosis. The expression of the symptoms may be modified by the person's developmental level and environmental factors (Szymanski et al. 1998, American Academy of Child and Adolescent Psychiatry 1999). For example: there may be no subjective report of depressed mood, but the carers could have observed change from happy to sad appearance, tearfulness, irritability. The individual may not be able to complain of anhedonia but there may be a history of refusal to engage in previously pleasurable activities. The agitation, inability to concentrate, decreased productivity at work, pacing, can be reported as well. Feelings of worthlessness may be expressed by statements such as "nobody likes me." Teachers and counselors could have observed decrease in productivity, lack of concentration on tasks or even regression of skills. Vegetative signs can be prominent. While recurrent thoughts of death and suicidal ideation may not be verbalized, suicide does occur in women with and without mild intellectual disability at the same rate, whereas men with mild intellectual disability have suicide rate lower than men without it (Patja et al. 2001). Some individuals are referred primarily because of aggressive and other disruptive behaviors (Reiss 1994). Under pressure to perform, a person with undiagnosed depression who lacks the means to explain how she or he feels might strike out toward others in self-defense. There is an unequivocal correlation between depressed mood and poor social skills and supports (Reiss and Benson 1985). The "relocation syndrome" in persons abruptly moved to a new placement might actually lead to depression, following a loss of familiar environment and familiar social supports.

The differential diagnosis of depression may include dementia since these individuals may appear as losing skills. In persons with Down syndrome the differential diagnosis will include hypothyroidism and Alzheimer-type dementia for which these individuals are at risk. In uncomplicated depression there is usually no evidence of loss of memory. The individual might be noncompliant and may not perform even familiar tasks but this occurs because of lack of motivation. On the other hand, in dementia, a person may attempt to do a task but may have lost the necessary skills. Presence of vegetative symptoms, depressed mood, and anhedonia will support the diagnosis of depression. The diagnosis is more difficult when depression accompanies dementia. As alluded to earlier, anorexia with significant weight loss has often been clinically observed in depressed persons with Down syndrome.

The DSM-IV-TR diagnostic criteria for manic episode can be also used with persons with intellectual disability, as documented in a study of Cain and colleagues (2003). The nature of the behavior in manic episodes will be similarly affected by a person's adaptive skills and opportunities. A persistently elevated, irritable mood may be expressed in noisy and agitated behavior, aggression and noncompliance. Unrealistic behavior unusual for the individual (e.g., attempts to drive a car) sometimes may reflect grandiosity or elated expectations. Unlike in typical subjects with hypomanic/manic behaviors, persons with intellectual disability and elated mood with no money or credit cards will not go on shopping sprees, but may engage in confused, disruptive, overactive behavior, screaming, aggression and destructiveness. Sudden inappropriate sexual behavior may be seen as well (American Academy of Child and Adolescent Psychiatry 1999). Rapid cycling bipolar disorder has been also described in this population, with mood, behavioral and vegetative changes occurring as frequently as every several days.

The issue of cyclical behavior changes has to be approached carefully as it may not necessarily be an evidence of the cyclic affective disorder, but may reflect behavior changes in response to environmental events such as staff changes in residential facilities. It may even be a sign of mood disorder with seasonal features (seasonal affective

Clinical Vignette 7

Daniel, a 28-year-old man with Down syndrome and mild-to-moderate intellectual disability, was the older child of two surgeons and had a 3-year younger brother, a brilliant college graduate. Daniel had a history of excellent adjustment, pleasant personality, had been friendly and active in community activities, and held a job at the local Pizza Hut. Two years prior to referral his brother married and moved out of the house. Daniel was the best man at his brother's wedding. Soon after that he appeared preoccupied and started asking why he could not marry. His parents were at loss as what to answer. He became sad, had trouble sleeping, lost weight, did not enjoy his work or recreation, and gradually stopped talking almost entirely. Neurological and medical assessments, including thyroid screen, were negative. His counselor at his day program felt that Daniel was just trying to get attention and initiated a behavior modification program that included punishment (spraying ammonia into his face) if he was noncompliant, with no improvement. He was put by his family physician on a SSRI antidepressant which helped only initially and was stopped because of agitation. His father's psychiatric colleague (with no experience in intellectual disability) suggested a course of ECT, as according to him, no other treatment worked with people with Down syndrome. Daniel received a total of 70 ECTs in the course of a year, which resulted in moderate memory loss but otherwise no improvement. During the interview Daniel had a sad expression with evidence of psychomotor retardation. He did not talk but appeared listening and became fidgety when the psychiatrist suggested that he probably missed his brother and felt lonely.

By history, Daniel had developed major depressive disorder following his brother's wedding and he was probably eager to talk about it, but apparently no one responded. The punitive behavioral treatment and later ECT, if anything, deepened his depression. A recommendation of supportive psychotherapy, another trial of an antidepressant, and a behavioral program based on positive reinforcement was made.

Clinical Vignette 8

Barbara was diagnosed at 3 years of age with severe intellectual disability due to marked delay in her global development. Exhaustive genetic evaluation failed to clarify its etiology. She never developed expressive speech, but understood simple commands and knew about 30 signs. She lived with her very supportive parents, attended special classes and was a friendly, well-related and pleasant person. At 17 years of age she became gradually withdrawn, cried often, did not enjoy car rides with her parents (previously her favorite activity), lost appetite and weight, and slept poorly. When she was pressed to complete school tasks she became aggressive, prompting psychiatric referral. She was diagnosed with a major depressive episode and was put on an SSRI antidepressant. Over the next 2 months she gradually improved. Her appetite returned, she became cooperative, and slept better. However, in the third month she again developed insomnia, roamed the house at night singing or screaming, was hyperactive, laughed for no obvious reason, and became aggressive if told to go to sleep. Detailed medical evaluation failed to disclose any general medical condition. There was no history of traumatic environmental events. She was diagnosed as having a psychotic episode and treated with an atypical neuroleptic. She improved dramatically at first, but in a month she was where she started; presenting with the same symptoms that led initially to the diagnosis of depression. This time a diagnosis of Bipolar Disorder NOS was made and she was treated with carbamazepine. She improved rapidly. Her mood stabilized, she slept and ate well, again became cooperative at school and home and returned to her "old self."

disorder) that has been described in this population and that may respond to light treatment.

## Anxiety Disorders

Various types of anxiety disorders have been described in this population (review Bailey and Andrews 2003). It is important to distinguish between anxiety as a transient symptom and as a manifestation of an anxiety disorder in which the required diagnostic criteria are fully endorsed and the severity is such that distress or functional impairment are present. Situational anxiety is common in persons with intellectual disability who are exposed to stresses that they find difficult to cope with; in some ways the anxiety serves a protective role helping to avoid uncertain situations. Conversely, lack of anxiety in persons who do not understand that a certain situation is unsafe, may expose them to danger; for example, running across the street disregarding the traffic. As with other mental disorders, anxiety disorders in persons with mild intellectual disability and good language skills are manifested and diagnosed in essentially the same manner as in the general population. In individuals with lower functioning and lesser language skills, behavioral expression of anxiety may predominate (review: Bailey and Andrews 2003). This may include irritability, crying, hiding, agitation, SIB and aggression. In these individuals the diagnosis is more difficult, but many DSM-IV-TR criteria are based on observable behaviors that can be ascertained in them. Generalized anxiety disorder may be manifested by restlessness, reduced concentration, irritability, muscular tension, and diaphoresis, as well as sleep disturbance. The worries, if not verbalized, will have to be inferred from the individual's general behaviors. The underlying concerns might go undiagnosed if the person resorts to disruptive behaviors on which the caregivers focus instead. While panic disorders have been reported in this population, there is a possibility that an episode of otherwise unexplained aggression may in fact be a panic attack; phobias have been described in this population as well (review: Bailey and Andrews 2003). These include agoraphobia, social phobia and various specific phobias. The predominant symptoms might be behavioral, as the individual might not be able to recognize (and describe) the fears as excessive or unreasonable. If he or she tries to avoid the phobic situation, the caregivers may not understand it, may think that he just has a behavior problem, and may force him to be exposed to the phobic stimuli. The individual might then resort to aggressive behavior, which might then become the focus of treatment. As in diagnosis of all mental disorders in this population, the symptoms

have to be interpreted in light of individual's developmental level/cognitive skills. For example, he/she may not be able to recognize that the fear is excessive or unreasonable. DSM IV-TR acknowledges that in children this feature may be absent: the same may apply to adults with significant intellectual disability. In fears related to certain places or individuals, the possibility of posttraumatic stress disorder (e.g., caused by abuse that the person cannot describe) has to be considered, as well as realistic fear of harm. For example, an individual who fears to stay in his room in a residence, may be afraid of a new, aggressive roommate, rather than have claustrophobia. Avoidance of others by persons with intellectual disability and undiagnosed autistic disorder might be misdiagnosed as social phobia. Increased prevalence of anxiety disorders has been described in Williams syndrome, Fragile-X syndrome, as well as Down syndrome.

### Posttraumatic Stress Disorder (PTSD)

This disorder occurs in this population but is probably underdiagnosed, since persons with reduced communication skills may not be able to report what had happened to him or her. Ryan (1994) reported on a series of 51 individuals with intellectual disability who met the DSM-III-R criteria for PTSD. Turk et al. (2005) who reviewed the relevant literature and report on two persons with Fragile-X syndrome and PTSD stress the need to view the presenting symptoms in light of premorbid functioning as a baseline. The DSM-IV-TR diagnostic criteria include history of an exposure to an event "that involved actual or threatened death or a serious injury" (American Psychiatric Association 2000, p. 467). However, a person with significant intellectual disability may not recognize it or, conversely, may perceive as threatening events that are not traumatic to an average age-peer. Thus, the individual's understanding of the event in question has to be carefully explored. The criteria also include modifications applicable to children which can be applicable to persons with developmental level below their chronological age. It should be kept in mind that a person with intellectual disability who was nonviolently sexually abused may not (at least immediately) realize that it was an abuse and may not react with fear, helplessness, or horror as apparently required by the criteria. In fact, sometimes, sexual abuse/exploitation is perceived as an expression of "friendship" by persons who are routinely rejected by their "normal" peers. Thus PTSD should be always considered as a differential diagnosis in this population.

### Obsessive Compulsive Disorder (OCD)

In persons with mild intellectual disability and good verbal skills the diagnosis may be made using the standard diagnostic criteria. The differential diagnosis from ritualistic behaviors, and perseverations, and stereotypies such as those seen in stereotypic movement disorder may be difficult if the person does not have sufficient language to describe the persistent and intrusive thoughts that cause the anxiety, which the compulsions are designed to prevent, nor that it is ego-dystonic. The latter can sometimes be inferred from observable behavior such as self-restraint to prevent self-injury. The DSM-IV-TR provides a qualifier "with poor insight" if the persons cannot recognize that the obsessions and compulsions are unreasonable and excessive. Compulsive behaviors in persons with intellectual disability might be misdiagnosed as stereotypic movement disorder. Conversely, stereotypic behaviors in persons with significant intellectual disability (especially comorbid with pervasive developmental disorder) might be misdiagnosed as OCD. Adherence to routines might also be adaptive and even encouraged by the caregivers.

The possibility of relationship of OCD and SIB/stereotypic movement disorder has been raised. Both include repetitive behaviors. However, SIB, in contrast to OCD, tends to be more frequent in people with lower IQ.

## Personality Disorders

Over the years, many myths have accumulated concerning the personality patterns of persons with intellectual disability—that they have uniform personality features resulting from organic brain damage and that they all are aggressive, passive, and dependent. Actually, these persons display a spectrum of personality traits that is as wide as that in the general population. Three factors that are generally common to persons with intellectual disability and that might influence their behavioral traits have been suggested: cognitive deficits (underlying, for instance, concrete thinking), neurological dysfunction (sometimes leading to a short attention span), and adverse environmental experiences that lead to changes in behavior (Szymanski and Crocker 1989). The DSM-IV-TR differentiates between personality traits and personality disorders. The former are "enduring patterns of perceiving, relating to, and thinking about the environment and oneself (American Psychiatric Association 2000)." Thus, they are part of a person's uniqueness and are not necessarily maladaptive. In contrast, personality disorders are diagnosed when the traits are maladaptive, inflexible, and lead to significant distress or impairment in functioning. Usually they are diagnosed in adolescence or early adulthood, but if they are diagnosed before age 18 years, the symptoms must have been present for at least 1 year. They are assessed in the context of a person's culture, age, social background, habits, customs, and values. This is particularly relevant in the case of persons who have intellectual disability and those in whom learning and living opportunities are unusual—for example, living in institutions or being sheltered by their families. The caregivers not infrequently reward passivity, dependence, and overcompliance. The depriving institutional environments teach the individual that attention-seeking and disruptive behaviors bring attention from the staff, even if the attention is negative. The reactions of the important persons and realization of the differences between oneself and one's peers often lead to a low self-image. The last is probably the closest to a universal personality feature of persons with intellectual disability.

Various studies have described maladaptive personality features in up to 56% of persons with intellectual disability, which have been seen as underlying the high prevalence of psychopathological conditions in this population (Reiss 1994). All types of personality disorders might be seen. The diagnosis of dependent personality disorder might be difficult because dependency on others might be based on reality resulting from a lack of various skills. Avoidance traits may be seen in persons with fraX who avert their gaze and are prone to anxiety. Borderline personality disorder might be seen in persons with a mild degree of ID.

### Aggression

Aggressive behavior directed against people or property (destructiveness) is one of the most frequent reasons (if not the most frequent) for referring persons with intellectual disability to a psychiatrist and an important factor preventing successful inclusion in the community. The actual behaviors may range from occasional swearing (verbal aggression) to serious violence (Harris 1995). In a recent Canadian survey of service providers for adults with intellectual disability living in the community, over half were reported as exhibiting aggression in the past year; about one-quarter being physical aggression (Crocker et al. 2006). As expected, persons with more severe disability (and poor communication skills) tended to physical aggression while those with milder disability towards verbal aggression. Whether a particular behavior is called aggression (except for clear physical aggression) depends on the caregiver's perception. Thus, in obtaining the history it is necessary to obtain a concrete description of the behavior in question, preferably from several informants. Prolonged direct observation of the patient may be necessary to resolve unclear cases. Aggression is a behavioral symptom and not a single diagnostic entity or disorder, nor does it have a singular underlying explanation. Thus one cannot talk about a unique treatment for aggression (except for symptomatic emergency measures). Psychiatrists are often asked how they treat aggression in persons with intellectual disability. The answer is, of course, that it is done in the same manner as in persons without intellectual disability: an accurate diagnostic assessment comes first. Different factors must be considered in assessing the cause of aggressive behavior (Harris 1995, 2006). It might be associated with a defined mental disorder, for example, psychosis (e.g., aggression following a command hallucination, a delusion), anxiety, borderline or antisocial personality, or depression. It may occur as a part of akathisia after rapid withdrawal of a medication. The factor of learning will reinforce aggressive behavior if it brings a reinforcing response by the caregivers. A pathological brain condition such as rage attacks after brain injury or associated with complex-partial seizures, may also lead to aggression. Often, several causative factors are involved, all of which require evaluation and intervention.

The DSM-IV-TR has a category of Intermittent Explosive Disorder that can be used, provided that another mental disorder has been ruled out as the cause of the aggressive behavior.

### Adjustment Disorders

Emotional or behavioral symptoms that are a response to a stressor, that cause distress or functional impairment, and that are not related to another Axis I disorder, are categorized as adjustment disorders. One example of such a stressor, common in the lives of persons with intellectual disability, is a precipitous move to an unfamiliar living or school setting, as the result of which the individual becomes confused and anxious, and exhibits maladaptive behavior. Another example might be when an adolescent with mild intellectual disability is teased, called a "retard," and told that he or she will never have a girlfriend or boyfriend or live independently. In such situations, a variety of behaviors emerge ranging from depressed mood to imitating the acting out of his adolescent nondisabled peers. The condition might become chronic because the stressor never really disappears.

## Forensic and Legal Issues in Intellectual Disability

### Criminal Behavior

Following introduction of IQ testing in the early 20th century, it was soon discovered that many criminal offenders tested within the intellectual disability range (including "borderline mental retardation" range). This led to the concept of "moral morons" or "moral imbecility," and the belief that intellectual disability predisposed to crime. Pseudo-scientific studies such as "The Kallikaks" by Goddard in 1912 (published by the Breeder's Association), purported to show the inheritance of intellectual disability and antisocial behavior through several generations. No consideration was given to factors such as poverty and lack of education.

There are no accurate epidemiological data on prevalence of criminality among persons with intellectual disability, for several, chiefly methodological, reasons. Not all jurisdictions routinely do diagnostic cognitive assessment of offenders and those that do, usually limit it to IQ tests (often group ones) and use various instruments. There is an agreement that persons with intellectual disability are overrepresented in the prison population, at rates from 4% to a high (in Western Australia) of 20% (reviews: Riches et al. 2006, Petersilia 1997). There may be several factors involved here. Persons with intellectual disability are more likely to be arrested as they may lack cunning to avoid it. They may be exploited by nondisabled criminals who encourage them to commit an offense. They may admit to an offense which they did not commit, in order to please the police or even to present themselves as savvy criminals. Police and court personnel may not recognize their disability, or conversely, may release them even if clearly guilty. Prisoners with intellectual disability are at serious risk of abuse or exploitation by other inmates and have less chance for parole as they may not have enough skills to conform to prison rules. Some states have special diversion programs in the community to rehabilitate offenders with intellectual disability.

*Competency to stand trial* question is usually brought up if the disability is obvious. In most jurisdictions the law does not differentiate between intellectual disability and mental illness. The diagnosis of either is not a priori an evidence of incompetency. Competency to stand trial includes ability to understand the charges, the consequences if convicted, and an ability to aid the attorney in the defense. Depending on their jurisdiction, person deemed not competent to stand trial, may be committed (and recommitted) to a mental hospital for evaluation. Following a landmark U.S. Supreme Court decision in Jackson v. Indiana in 1972, there is a maximum time an incompetent person can be held without having a trial, or being committed under civil statutes.

Insanity *defense* is used rarely for persons with intellectual disability, although technically it can. A person with significant disability may commit an offense without knowing that it is an offense but usually he/she is not charged criminally, but released to caregivers, or hospitalized.

*Competency to testify* (or rather its lack) is often brought up in defense of an offender against a person with disability. For example a person accused of a rape of an

intellectually disabled woman routinely claims that she is not competent to testify against him. (Conversely, the claim may be that she was competent to give a valid consent for consensual sex). The diagnosis of intellectual disability does not automatically disqualify the witness. To be competent, the witness has to understand the concept of truth and perjury, and has to be able to recollect and to describe relevant events. A person with intellectual disability may feel intimidated in the courtroom and therefore in some jurisdictions may be permitted to testify separately via video, similarly to a child witness.

*Death penalty* for persons with intellectual disability has been a hot topic in the recent years. State laws varied in this repect. In a landmark case of Atkins v. Virginia in 2002, the U.S. Supreme Court ruled that "execution of criminals who were mentally retarded is held to constitute cruel and unusual punishment in violation of Federal Constitution's Eighth Amendment."

**Roles of psychiatrists**. Psychiatrists are usually called to perform competency assessment. They should be well versed in the legal definition of competency in question in their jurisdiction. The usual principles of obtaining history and interviewing should be followed, as described earlier in this chapter. Considerable time may be required to gain the individual's cooperation. The focus should be not primarily on the diagnosis of intellectual disability but on assessing discreet skills required for the particular competency. For example, to be a competent witness the person should understand the concept of truth; the need to tell the truth; the penalty for perjury; have ability to recall and describe events; and differentiate between own fantasy and observed facts. The past history in this respect is important as well.

## Noncriminal forensic issues

**Guardianship.** Up to the age of majority (18 in most jurisdictions) a person is not considered fully legally competent and the parents (or legal guardians) are responsible for him/her. Upon achieving that age every person is presumed to be a legally competent adult, unless a court rules that he/she is not competent and appoints a legal guardian. The diagnosis of intellectual disability does not automatically mean incompetence. Most states now recognize partial competency, in that a person may make certain decisions and a guardian makes other decisions, typically concerning major medical treatments, program changes or money matters. The guardian's powers are also limited. Typically the guardian cannot consent to sterilization or to institutionalization: court order is necessary for that. Any clinician caring for an individual approaching age of majority should advise the family to apply to the court for competency determination. This determination in most jurisdictions involves examination by a licensed social worker and psychiatrist or other physician, who are trained and/or experienced in the field of intellectual disability.

**Parental competency in child protection cases.** Psychiatric assessment is often requested in these cases. Parents who have intellectual disability are overrepresented here, primarily on charges of neglect rather than abuse. The presence of the disability does not disqualify a parent: rather lack of parental competency has to be proven, as with any other parent in such case (except when a woman with severe/profound disability, usually with a history of being raped, delivers a child). Many advocates for rights of persons with intellectual disability argue for their right to be parents, and for their right to receive all services and supports to enable them to be successful in this respect. There is little reliable literature on persons with intellectual disability as parents. Mørch et al. (1997) surveyed all public health nurses in Norway (where health care, prenatal care and social support services are some of the best and universal) concerning children born to parents with intellectual disability. They identified 126 children who had at least one parent with intellectual disability and estimated the prevalence to be 430 children under 16 (in a population of 4 million). In this study sample 43% of the children appeared to have learning difficulties and 40% "suffered of failures of care." The problems that often compound parent's difficulties include poor parenting and independence skills, financial and housing problems, lack of support (many are single mothers), inability to find and access services. Many of these parents can function relatively well with supports as long as they have one young child, but fail when they have to deal with additional children, with different needs and personalities, and especially when the child achieves adolescence and strives for own independence.

## Overall Goals of Psychiatric Treatment of Persons with Intellectual Disability

The overall goal of all medical therapies, including psychiatric care of persons with intellectual disability, is to promote the optimal growth and development and ensure optimal physical, emotional, and social well-being of individuals concerned. Treatment of persons with intellectual disability therefore involves multimodal approaches. In addition to psychiatric interventions that will be described in this section, parental support and counseling, special education, speech and language, occupational, and physical therapies, sensory integration therapy, and social skill training may also help to assure optimal outcome. The goals of psychiatric treatment are to minimize symptoms associated with a specific mental disorder, prevent harmful behaviors (e.g., aggression, SIB), facilitate access to educational, social and community inclusion programs, maximize beneficial effects of nonmedical interventions, and improve the quality of life for the individual and the family.

Treatment is aimed at helping to facilitate improved functionality in educational, social and community settings. Psychiatrists should understand the indications for, side effects of, and limitations of any therapeutic intervention. The individual with intellectual disability and their families should be involved in the treatment planning process as much as possible, despite any developmental limitations. Every effort should be made to help the individual understand the reasons for the treatment, expected results, and possible side effects. This approach will prevent the development of negative attitudes or misperceptions toward the use of the psychotropic medication in these individuals. When this is done, the individual becomes an effective partner in the intervention (Tsai 2001).

The most common mistake made by mental health clinicians treating persons with intellectual disability is to consider suppression (usually with medications) of single problems (as a rule disruptive behavior) as the only goal of

treatment. This approach has been the rule in the past when people with intellectual disability were not expected to achieve any measure of independence; keeping them docile was deemed to be a more important goal. Such approaches are reemerging, partly related to pressures to achieve a fast and inexpensive symptomatic improvement. Fortunately, in the past three decades the concept of the quality of life (QOL) has been assuming a central role as the goal of treatment of persons with intellectual disability. Numerous scales to measure the QOL have been designed, usually focused on concrete indicators related to factors such as services or health and typically reflecting the view of the caregivers. More recently the importance of the subjective aspects of QOL has been stressed: the individual's subjective feeling of contentment, well-being, and satisfaction with own life as opposed to the caregiver's satisfaction. In other words, personal happiness of the person with mental retardation is now stressed as a goal of habilitation as well as specific treatment (Szymanski 2000). The measurement of the latter is not easy with nonverbal persons, and even with verbal ones, considering their tendency to answer in a way to please the questioner. Thus, both self-report from the individual and observations by a trained team of professionals are needed. A sense of positive self-image is an essential component of happiness for persons with mental retardation, as for everyone else. This is often difficult for the former to acquire, due to the awareness of being "different" from others, at least in terms of many abilities, and due to frequent rejection and teasing.

The goal of any form of psychiatric treatment of persons with intellectual disability is to contribute to this sense of satisfaction with one's own life, in the context of a comprehensive treatment program. Suppression of behaviors inconvenient to caregivers is not enough, especially if they are a response to an inadequate habilitation program and the treatment (usually medications) is used in lieu of such program. Furthermore, medications may suppress a person's functioning through side effects such as drowsiness. The mental health clinician should not assume that "nonpsychiatric" problems are taken care of by someone else, but should take an active part in the team's assessment of various factors contributing to the clinical presentation, as well as the person's need for various supports (see Figure 42–7). This is not to say that the psychiatrist should be in charge of behavioral modification or vocational rehabilitation, but that these approaches should be closely coordinated with specific psychiatric treatments and should be targeted toward the common therapeutic goal.

### Prerequisites for a Successful Treatment Program

1. *Comprehensive diagnostic understanding*. Based on the psychosocial model of the interaction of the various factors (see Figure 42–6), this should follow the guidelines described earlier. The purpose is not to elucidate and treat a single diagnosis (e.g., treating depression with an antidepressant) but to understand all factors causing and perpetuating the problem, and the patient's strengths, which should be developed. The diagnostic evaluation should consider past and developmental history and include detailed patient interview or observation.
2. *Developing goals of treatment*. Both the ultimate goal and the intermediate objectives should be established. For instance, the goal might be elimination of depression and preparation for a move to semi-independent living. The intermediate objectives might include amelioration of insomnia, anhedonia, and aggressive outbursts.
3. *Developing treatment priorities*. If possible, less intrusive and simpler approaches might be tried first, for example, manipulation of the milieu. If these efforts are unsuccessful, other approaches might be tried, for example, medications. Often the treatments have a synergistic effect and should be used together. For instance, stimulants might improve a person's attention and reduce impulsivity, making the patient more responsive to behavioral therapy that teaches methods of appropriately expressing refusal, rather than through aggression.
4. *Monitoring treatment results*. Because multiple caregivers may be involved, it may be difficult to obtain consistent, reliable, and concrete data. Using a behavioral rating scale, or even developing a simple one for a particular patient, helps measure the behaviors or symptoms and monitor progress. Such objective data are essential as global caregivers' impressions, although important, may be misleading. For instance, caregivers might feel safer knowing that a patient is on medication and might report behavior as improved, while data might not support that.
5. *Avoidance of indefinite treatment*. The treatment should be result driven, that is, it should be continued only and as long as it can be proven, by measurable results, to be effective.
6. *Team collaboration*. All involved caregivers, including family and professionals, should be in agreement about the nature, goals, side effects, and results of the treatment. This can be achieved by open discussion and education and is especially important when psychotropic drugs are used. If some difference of opinion remains concerning which treatment should be used, the team can agree on the order in which the various approaches should be tried (usually the least intrusive ones are used first).

## Pharmacotherapy

### Legacy of Inappropriate Use of Psychotropic Drugs

Psychotropic agents and traditional antipsychotic medications in particular have had a long legacy of indiscriminate use in persons with intellectual disability, especially among those residing in large residential institutions. These agents were used nonspecifically, primarily highlighting their (side) effects to induce docility and suppress disruptive behaviors, even though such behaviors may have been appropriate reactions to abnormal, understaffed, institutional, depriving environments (Tu and Smith 1983). The early epidemiological research on the use of psychotropic agents focused on their pattern of use in residential facilities. In the 1970s, up to 86% of residents were receiving these drugs, and more than half of these drugs were antipsychotic agents (Rinck 1998).

The abuse of psychotropic agents inevitably led to a backlash, mostly among nonmedical professionals, resulting in hostility to the use of any medications, even if they were clearly indicated for the treatment of a diagnosed mental disorder. The early standards of institutional care were set by Health Care Financing Administration (HCFA), currently known as Centers for Medicare and Medicaid Services (CMMS). It perpetuated the image of psychotropic agents as harmful and to be used only as a last resort. Such attitudes, which are still encountered, in effect deny persons with intellectual disability appropriate medication treatment for mental disorders. Some institutional administrators engaged in a sort of "numbers game," seeing the lower percentage of individuals in a program who are receiving psychotropic agents as an indicator that their program was better. The percentages however were deceptive; with well-adjusted persons being transferred to the community, institutions became de facto mental hospitals predominantly for persons with mental disorders and intellectual disability. Thus, it was no surprise that many residents were maintained on these agents. More important however is that a large proportion of individuals receiving psychotropics did not need these agents, and many persons with intellectual disability did not receive any drugs that would otherwise have benefited from them.

The widespread inappropriate use of psychotropic drugs among persons with intellectual disability also made them an early target of class action suits on behalf of residents of large, public institutions. The 1971 Supreme Court Wyatt v. Stickney decision which ruled unconstitutional the way mental health patients were warehoused in state institutions for long periods of time without treatment also stated that, "residents shall have a right to be free from unnecessary or excessive medication . . . Medication shall not be used as punishment, for the convenience of staff, as a substitute for a habilitative program, or in quantities that interfere with the resident's habilitation program" (Rinck 1998).

It is of interest that early research on individuals residing in the community indicated low rates of psychotropic use, in the 20–30% range, depending on the study (Rinck 1998). It appears that these rates might now be higher, possibly reflecting pressures for quick symptomatic treatment. It is not unusual to encounter individuals who were successfully weaned off medications in institutions but were quickly put back on them when placed in the community, at the first sign of behavioral problems, even if they were a normal and transient reaction to the stress of relocation.

Research on the effectiveness of psychotropic drugs in persons with intellectual disability has also been affected by methodological shortcomings, including small sample size, lack of control groups, treatment of nonspecific symptoms, and inherent tendency not to report negative findings (Bregman 1991). The reliability of diagnoses was also unclear, especially since diagnoses could sometimes be made *post hoc*, to justify the use of medication. There is also no uniform agreement on the definition of psychotropic drug use. For instance, certain drugs may have both medical and psychiatric uses such as anticonvulsants, that are used both for the treatment of seizures and for affective disorders. There is no convincing evidence that there is a different response to psychotropic drugs in persons with and those without intellectual disability, all other factors being equal (Bregman 1991). Yet, most of the existing studies have been on the effectiveness of a drug on a nonspecific group of persons with intellectual disability, without consideration of the etiology of the intellectual disability. More appropriate would be studies of drug action in persons with intellectual disability of a specific etiology compared with their action on persons with the same mental disorder but without intellectual disability. What still remains different in the pharmacotherapy of persons with intellectual disability is the difficulty of making an accurate diagnosis of comorbid mental disorders and the special need for concurrent interventions in this population.

## General Considerations

The modern approach to rational use of psychotropics among persons with individual disability is reflected in the new 1997 HCFA (CMMS) guidelines. The main points of the HCFA guidelines include:

1. Prior to use of any psychotropic medications: rule-out medical, psychosocial, and other causes for presenting problems; document diagnosis and differential diagnosis; first try less intrusive interventions, including psychotherapy, as appropriate; and collect baseline behavioral data.
2. After psychotropic medication has been started: it must be a part of comprehensive treatment program; it should not interfere with the patient's functioning; adverse reactions should be monitored; drug effectiveness should be monitored, including effect on quality of life; dose reduction should be considered if not clinically contraindicated (American Academy of Child and Adolescent Psychiatry 1999).

In principle, the use of psychotropic drugs for persons with intellectual disability does not inherently differ from their use with persons without intellectual disability. Therefore, as psychopharmacology is dealt with extensively elsewhere in this book, only some issues relevant to persons with intellectual disability are mentioned in this section. Some misperceptions remain. Although persons without any intellectual disability are usually treated with drugs for major depressive disorder, schizophrenia, and so on, unfortunately, it is still a common practice to prescribe psychotropic agents for persons with intellectual disability for nonspecific "behavioral difficulties." In one study, only 25% of persons receiving psychotropic agents had a formal psychiatric diagnosis (it is not clear how many had an adequate, comprehensive assessment rather than just a label) (Jacobson 1988). It is therefore important to emphasize at the outset that such nonspecific treatment does not make sense. For example, aggressive behavior might be part of the presentation of major depressive disorder, anxiety, psychosis, or even a justified anger in an otherwise mentally healthy person. Each of these situations requires different treatment strategies; it is illogical to refer to a single treatment "for aggression" but nevertheless this practice survives disproportionately more in the practice of pharmacotherapy among persons with intellectual disability. The practice is often encountered in institutional settings, especially those lacking in habilitative programs.

Another practice is a "Christmas Tree Approach": this approach reflects adding subsequent drugs, without

discontinuing the previous ones which failed to reduce the undesirable behaviors, in the absence of any evidence that the combination has a synergistic effect. Some individuals, especially those in institutions, have therefore ended up taking a combination of psychotropic agents without evidence that any one of them has been effective. A more effective approach is to introduce a systematic follow-up with regular assessments as noted earlier. However, the practice of pharmacotherapy should neither focus on nonspecific set of behaviors, nor should it focus on a single target behavior, but on a person's global functioning. Some follow-up approaches follow the premise (without basis) that there is a linear relationship between the drug dose and the frequency of certain behavior and attempt to titrate the drug accordingly. Periodic tapering of the drug (unless clinically contraindicated) should also be considered in a rational manner when necessary to ascertain its effectiveness.

## Principles of Pharmacological Interventions in Persons with Intellectual Disability

Where necessary and possible, a functional behavioral analysis should be carried out before the initiation of pharmaceutical intervention. Other factors to be considered, aside from the appropriateness of an individual's educational or vocational program, include deciding whether the targeted symptoms might more likely respond to educational or behavioral interventions (Melmed et al. 2006). When considering pharmacological intervention within the context of an associated mental disorder, target outcomes are identified and assigned a rating of frequency, duration or severity. These target behaviors may change with a person's chronological age or as the person progresses developmentally. If target outcomes are not met, a reevaluation of the treatment plan is in order to reconsider the scope of treatments and any challenges with compliance or adherence to the plan by all those involved in the individual care. The presence of other disorders that might be compounding or aggravating the underlying problems ought also to be considered. Specifying appropriate target outcomes, especially when long-term treatment is envisioned, can help parents who are often overwhelmed and need encouragement. Symptom severity monitoring should in and of itself help to provide positive reinforcement to caregivers, especially when improvements in functioning, however small, can be ascertained.

Pharmacological intervention in persons with intellectual disability ought to be carefully considered in association with a clear sense of what is being treated and what the expected outcomes are (Melmed et al. 2006). Intervention can be grouped under the following main objectives:

1. Improvement of interfering *primary symptoms* associated with co-occurring mental disorder in persons with intellectual disability; there is no medication (psychotropic or otherwise) that is specifically effective in treating intellectual disability per se.
2. Improvement of *secondary symptoms* associated with a co-occurring mental disorder (e.g., as in inattention, disruptive behaviors, tantrums, self-injurious, or aggressive behaviors seen in autism and intellectual disability). These symptoms can also occur as a maladaptive response to transitions, sensory stimulation, poor communication ability, and regulatory skills; thus, it is important to address these concerns with a combined behavioral modification and pharmacological approach.

There is a paucity of well-designed randomized clinical trials involving mental disorder in persons with intellectual disability. Therefore, as a first general principle, it is important to start with the lowest recommended dose and titrate the dose upward slowly, as persons with intellectual disability may be particularly sensitive to side effects such as disinhibition, irritability, and reduced sleep. Their interpretation and ability to report the physical sensation of the side effects might also vary significantly. As a second general principle in prescribing medication in individuals with intellectual disability it is important to simplify the medication schedule in terms of the number of concurrently administered medications; use of low dose of medication and titrating doses up/down with care for any emerging side effects, especially with respect to behavioral activation, oversedation, and cognitive interference. Vital signs and growth parameters ought to be measured as recommended for each class of psychotropic medication as described elsewhere in this textbook for typical populations.

Periodic discontinuation of medication is also recommended. Treatment may not be needed when behavioral and environmental variables are in flux. Psychiatrists working with persons with intellectual disability should familiarize themselves with the need for combined psychosocial and educational strategies and should not prescribe psychotropic medications with inadequate information, aiming, for example, for symptom suppression seemingly without consideration of the potential negative impact of the medication on the demeanor, adaptive functioning, or quality of life of the individual.

A school age child with an intellectual disability who is acting up secondary to a great deal of sensory stimulation in an inappropriate educational setting is unlikely to respond to short-term pharmacological strategies, especially if this strategy is urgently requested as a means of behavioral control. Pharmacological interventions, therefore, should be especially integrated as part of a child's IEP. Obstacles to the success of such an integrated approach to pharmacotherapy are summarized in Table 42–11 below.

In particular, it is important to emphasize the importance of comorbidity among various classes of mental

**Table 42–11** Obstacles to the Success of an Integrated Approach to Pharmacotherapy

| |
|---|
| Poorly justified choice of psychotropic medications |
| Lack of defined comorbid mental disorder |
| Misclassification of symptoms of a mental disorder |
| Lack of defined behavioral interventions |
| Absence of systematic behavioral data collection |
| Poor communication between the psychiatrist and behavior therapist despite presence of a behavioral plan |
| Prescription of medications for extended periods with limited regard to dynamic changes in the immediate environment |
| Use of polypharmacy regimens with poor attempt over time to optimize medication mix and dose |

disorder in persons with intellectual disability. In doing so, it is also important to call attention to the problem of misclassification of various symptoms that may be common within presumed comorbid disorder categories. For example, it is important to distinguish symptoms of attention-deficit/hyperactivity, from symptoms of primary mania or secondary hypomania related to medication-related adverse effects as in behavioral activation. Another example includes differentiation of "ego-syntonic" symptoms involving repetitive stereotyped behaviors in autism spectrum disorder and characteristic "ego-dystonic" symptoms associated with obsessive-compulsive disorder. There is a need for evidence-based studies looking at comorbidity of mental disorders in persons with intellectual disability syndromes.

The outline below is useful largely from a review by Kalachnik et al. (1998) and Rinck (1998), as well as on the American Academy of Child and Adolescent Psychiatry (1999), and the Health Care Financing Administration (1997).

***Purpose of Pharmacotherapy***. Psychotropic drugs in persons with intellectual disability ought to be utilized to treat a diagnosed mental disorder toward the goal of maximizing the person's quality of life. They should not be used merely to suppress a single, objectionable target behavior without regard to the effect on a person's global adjustment, functioning, and quality of life. They cannot be used akin to inherent punishment, for staff convenience (as in understaffed settings), in lieu of appropriate habilitative program (e.g., if such a program is unavailable or its quality is poor), or in dosages that interfere with a person's quality of life (Rinck 1998, p. 52).

***Context of Pharmacotherapy***. The psychotropic drugs are to be used as part of a comprehensive treatment plan and habilitation programming designed and supervised by an interdisciplinary team of which the psychiatric clinician is an integral part. They should not be prescribed merely in brief "psychopharmacology consultation" or "medication review" session in isolation from other aspects of the treatment. Adequate number of psychiatrists ought to be trained for the care of persons with intellectual disability and the shortfall of qualified personnel should not justify use of proxy physicians to hand out prescriptions without requisite expertise or supervision even though it may meet minimum administrative guidelines for prescribing and may seem "cost effective" for institutional purposes.

***Prerequisite Steps for Pharmacotherapy.*** Comprehensive psychiatric diagnostic assessment, following the guidelines described earlier (see also Figure 42–6), and resulting in a diagnosis of mental disorder is an essential initial step. Other steps include: the presence of a comprehensive treatment plan and evidence that less intrusive measures have not been effective (such as behavior modification, psychotherapies, and milieu supports); comprehensive evaluation to rule out medical conditions that could have caused the presenting symptoms; existence of a reliable system to collect behavioral data individualized to the particular patient that measures occurrence of symptoms considered to be an index of the person's mental disorder. This should also provide reliable baseline data and a functional analysis of behavior that would assess the influence of immediate and more remote antecedents and consequences of patient's behaviors and other symptoms.. Finally, satisfaction of all relevant regulatory and legal requirements, especially obtaining informed consent of the patient and/or legal guardian.

***Follow-up on Drug Effectiveness.*** A psychiatrist experienced in treatment of persons with intellectual disability and members of the interdisciplinary treatment team should ideally follow the patient's progress regularly (at least quarterly), based on changes in individualized index behaviors, symptoms, general adjustment, functioning, and well-being. Presence of side effects and their findings should be communicated among the members of the team. Behavioral changes should be documented by reliable data. The follow-up should include a direct psychiatric interview and/or observation of the patient. The implementation of all aspects of the treatment program and not just the medications should be monitored and adjusted as needed to insure that medications are not used in lieu of, but concurrently with, a habilitation program.The medication should be tried at an effective dose for an adequate period of time. If there is no clear evidence of effectiveness it should be discontinued appropriately. It should be kept in mind that "ups and downs" are to be expected such as in reaction to environmental and physical stressors common in the lives of these patients. Medication effectiveness should therefore be judged by a pattern evident over a reasonable period of time and not by one-point observations. For the same reason, preset dosage schedules linking dosage changes to specific frequencies of index behaviors are impractical. Multiple medications should be tried only if there is evidence that a combination is known to be more effective than a single medication.

***Dose Reduction Discontinuation.*** A trial dose reduction and possibly discontinuation should be regularly considered but should be implemented only if not contraindicated clinically. Discontinuation, if attempted, should be gradual, and it may need a prolonged period depending on the type of medication and expected withdrawal effects. It is essential that all involved caregivers be aware of the possibility of such effects and be ready to deal with them, rather than demand immediate cessation of the discontinuation trial; this is particularly important with atypical neuroleptics. As-needed (PRN) use of medications is best avoided to prevent unnecessary use, or limited to clear situations.

***Monitoring Side Effects.*** Side effects should be monitored regularly through direct examination (especially important in the care of nonverbal persons), including laboratory tests, EKGs, tardive dyskinesia exams, as appropriate for the particular drug. Possible drug interactions should be monitored as these patients are often on multiple medications.

## Review of Classes of Psychotropic Medications

Only issues specific to persons with intellectual disability are discussed here. For a full discussion, relevant other chapters in this book should be consulted.

The topography of available psychotropic medications for persons with mental disorders and intellectual disability is changing rapidly, as for all other populations. The traditional antidepressants (e.g., tricyclics) and antipychotics (e.g., chlorpromazine, thioridazine) and neuroleptics

(e.g., haloperidol ) that were once popular are recommended as a last resort. In the following discussion, only the salient usages of major groups of pharmacological agents are discussed.

## Stimulants and Nonstimulant Medications

Generic short acting stimulants drugs such as methylphenidate and dextroamphetamine have long been proven effective in the treatment of attention-deficit hyperactivity disorder (Arnold et al. 1998). In persons with intellectual disability these agents have been studied primarily in children and adolescents with mild intellectual disability as well as pervasive development disorders. Their effectiveness in persons with significant intellectual disability is less certain. If a patient with intellectual disability is engaging in self-stimulatory behaviors, close observation or use of sample videotapes of behaviors at home or work setting behaviors can provide a useful backdrop to distinguish stereotypies and mannerisms from emerging tics or other abnormal movements (e.g., choreoathetoid movements). As described earlier, establishing a diagnosis of comorbid attention-deficit/hyperactivity disorder in persons with intellectual disability is not straightforward, especially in those with severe intellectual disability, as the symptoms of inattention and poor impulse control, have to be assessed in the context of the patient's developmental level. Persons with intellectual disability with comorbid attention-deficit/hyperactivity disorder, regardless of their level of functioning (Ehlers and Gilberg 1993), may be eligible for treatment with stimulants. There is more evidence that persons with intellectual disability with a higher level of verbal and adaptive skills may respond better to stimulants. A number of long-acting stimulant agents (e.g., Adderall XR, Concerta, Metadate, Ritalin-LA, Focalin XR) and new atypical agents (e.g., Strattera (atomoxetine)) have been successful in targeting some individuals with attention-deficit/hyperactivity disorder. A concern with the use of stimulants in persons with intellectual disability in general has been the observation that they can lead to activation, with mood irritability, agitation, as well as sleep difficulties. Increased stereotypies, obsessive–compulsive symptoms and anxiety are also seen (Aman and Langworthy 2000).

Pharmacological studies of the treatment of attention-deficit/hyperactivity disorder symptoms in persons with intellectual disability with specific syndromic diagnoses such as Fragile X, Cornelia de Lange, Down and Williams have led to mixed findings. When using stimulants in young children, particular caution is advised in those with comorbid autism spectrum disorders. Nonetheless, as the relative index of safety of these medications is quite high, many clinicians have continued to initiate an empirical trial of a stimulant or nonstimulant agent under circumstances when clinically warranted.

## Antidepressants

The principal uses of antidepressant medications, as in the general population, include treatment of depression as well as anxiety, panic, and OCD (Sovner et al. 1998). Selective serotonin reuptake inhibitors (SSRIs) are now first-line drugs because of their low side effect profile. Tricyclic antidepressants, principally the secondary amines such as desipramine, were once extensively used in the treatment of attention-deficit/hyperactivity disorder, especially if stimulants and clonidine were not effective, but these agents are no longer recommended in view of their potential cardiac effects related to unforeseen yet relatively rare conduction difficulties. The tricyclic antidepressants ought not to be excluded in special situations where the person with intellectual disability has not responded to SSRIs or venflaxine and remains significantly depressed. Precipitation of activation, hypomania, and seizures by tricyclic antidepressants also present problems in the intellectual disability population, and careful baseline assessment is necessary. The SSRIs appear to be moderately effective in decreasing interfering symptoms of anxiety associated with transitions and sensory stimulation, as well as in diminishing repetitive thoughts, rituals, and preoccupations in ASD with or without intellectual disability.

The SSRIs are also effective, in part, for the treatment of symptoms of restlessness and hyperactive-impulsive behaviors if they are secondary to anxiety-related behaviors especially in nonverbal persons with intellectual disability. No single SSRI has been shown to be superior for this purpose. Early controlled trials with fluoxetine and fluvoxamine in adults with ASD with or without intellectual disability showed significant benefits over placebo, although a subsequent controlled trial of fluvoxamine in children and adolescents revealed a lower response (McDougle et al. 2000). An open label study using low-dose fluvoxamine reported a response in only 17% of individuals (Martin et al. 2003). SSRIs are used in practice to treat depression, anxiety, and obsessive, compulsive and ritualistic behaviors Steingard et al. 1997). There are a few studies, mostly case reports, that have suggested that selective serotonin reuptake inhibitors might be helpful in reducing self-stimulatory and SIB, although the improvement might be short-lived and pharmacotherapy of SIB remains a major challenge (King 2000).

## Antipsychotics

The use of both the traditional and atypical antipsychotic drugs in persons with intellectual disability is the same as that for the general population—primarily for the treatment of associated psychotic symptoms or as an emergency treatment of dangerous and disruptive-aggressive behavior. The main target symptoms potentially responsive to atypical antipsychotics include severe tantrums and disruptive behaviors, agitation, aggressive behaviors, comorbid major affective disorders, and, more rarely, psychosis. Unfortunately, despite the recent success of using low dose atypical antipsychotics, there is an important legacy of abuse of traditional antipsychotics in persons with intellectual disability especially in institutional settings. It is important not to assume that a person by virtue of having intellectual disability also suffers from schizophrenia or schizoaffective disorder, leading to persistent use of antipsychotic agents. Both the traditional and atypical antipsychotics have long been used for "off-label" indications as mentioned above including aggression, destructiveness and disruptive behaviors. If an antipsychotic medication is effective in alleviating such behaviors, it does not necessarily mean that the person with intellectual disability suffers from a comorbid psychotic disorder. Nevertheless, there has been a tendency to justify such "off-label" use by perhaps ascribing a non-specific

diagnosis such as psychotic disorder not otherwise specified. The traditional antipsychotic agents (such as haloperidol, perphenazine, among others) ought to be considered as medications of last resort given their important extrapyramidal side effects. Many older adults with intellectual disability may have been on the traditional older antipsychotics for years, often for no clear reasons and many suffer from tardivie dyskinesia or have developed Parkinsonian symptoms.

The use of atypical antipsychotics in persons with intellectual disability (including risperidone, olanzapine, quetiapine, aripiprazole, among others) also pose particular difficulties. If a trial is indeed justified, extended observation by trained staff and close monitoring of liver function tests, EKG, and fasting blood sugar and lipids are necessary. Individuals with intellectual disability are more vulnerable to most of the side effects of these agents. They are generally unable to communicate subjective feelings of sedation or restlessness (akathisia) due to their cognitive limitations and difficulties in communication. Furthermore, drowsiness associated with treatment with these agents have a proportionately greater negative effect on learning and on general level of activity in persons with intellectual disability than among typical individuals A common mistake is to confuse withdrawal symptoms or increased extrapyramidal symptoms upon discontinuation, leading to resumption of the medication Weight gain remains as the most common side effect of atypical antipsychotic agents in persons with intellectual disability, as these individuals are especially prone to excessive eating, poor dietary regulation of food content, lack of exercise, and other lifestyle issues related to their disability. The secondary effects of weight gain in terms of cardiovascular function, elevation of blood sugar and lipids are also of considerable concern. Nutritional intervention is recommended for individuals who demonstrate significant weight gain during treatment or who are overweight at the outset. A full lipid panel with fractionation of cholesterol are recommended annually, with quarterly fasting total triglycerides and cholesterol during the first year of treatment. Fasting blood sugar levels, liver function tests, prolactin, and electrocardiograms should also be monitored.

The discontinuation of antipsychotic medications should be gradual and slow to minimize side effects from withdrawal, including behavior problems such as irritability, insomnia, SIB, and aggression (Gualtieri et al. 1986).

There are case reports of successful use of clozapine in persons with intellectual disability and comorbid schizophrenia or bipolar disorder who otherwise have not responded to other mood-stabilizing agents. The need for weekly blood tests may be a problem in less than cooperative persons.

Risperidone is the most studied among the major atypical antipsychotic medications among children and adolescents with ASD (McDougle et al. 1998). There have been two double-blind placebo controlled studies. The Research Units in Pediatric Psychopharmacology (RUPP) Autism Network (McCracken et al. 2002), funded as part of a National Institutes of Health multisite trial, looked at the safety and efficacy of risperidone in 101 children and adolescents with autism. Risperidone was effective and well-tolerated for the treatment of tantrums, aggression, or SIB. Risperidone therapy was associated with an average weight gain of 2.7 ± 2.9 kg, as compared with 0.8 ± 2.2 kg with placebo ($P < 0.001$). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group ($P < 0.05$ for each comparison). In two thirds of the children with a positive response to risperidone at eight weeks, the benefit was maintained at six months. Similarly, a Canadian study by Shea et al. (2004) involving 79 subjects reported efficacy of risperidone in autism as well as the broader pervasive developmental disorder phenotype. By alleviating the interfering behavioral problems, the atypical antipsychotics can allow persons with ASD in the presence of or absence of intellectual disability to be more amenable in terms of improved social interactions. In low-dosage ranges, the atypical antipsychotics are rarely associated with extrapyramidal symptoms or l tardive dyskinesia. Nevertheless, there are higher rates of irritability, serious aggressive behaviors, and SIB in children with autism in the presence of increasing degree of intellectual disability, making it highly likely that medication will be more likely to be used in the group with autism in the presence of intellectual disability.. This is an important ethical concern, that is, behavior control in a more vulnerable group. Criteria for discontinuation and long-term risk of use of risperidone ought also to be considered in this group. On the other hand, vulnerable children ought not to be deprived of the benefit of psychotropic medications, (see review: Yan and Munir 2004) . However, irrespective of these concerns, psychotropic medication cannot be a sole means of management of undesirable behavior, especially for the more severely compromised children.

SIB seen in ASD and intellectual disability are poorly responsive to pharmacological interventions, including atypical neuroleptics.

## Anticonvulsants

Persons with intellectual disability experience both clinical or subclinical seizures at a much higher risk than in the general population and, therefore, should have a full baseline neurological assessment. *Significant* clinical and subclinical seizures, if left untreated, can lead to deleterious effects. As seizures can emerge at any time, they should be ruled out as possible contributory factors for any change in behavior (tantrums, irritability, and agitation), sleep, and regulatory functions. There is also an increased incidence of newly onset seizures in seizure-free individuals with ASD as they progress through puberty and adolescence. Pharmacological treatment with sodium valproate has been used in particular children with ASD who present with a developmental regression in milestones or seizures, sometimes in the context of Landau–Kleffner syndrome. Sodium valproate has also been used with modest success in the treatment of secondary symptoms of hypomania in association with irritability, silly or elated moods, temper outbursts, and agitation. Clinicians have been apt to translate their experience from sodium valproate to other anticonvulsants; lamotrigine has not been as effective, and the most commonly used anticonvulsants after valproate for targeting behaviors have been carbamazepine and oxycarbamazepine.

## Alpha agonists

The use of clonidine hydrochloride and guanfacine hydrochloride can effect a modest reduction in impulsivity,

hyperactivity and irritability (McDougle et al. 2003, Jaselskis et al. 1992). Drowsiness has been reported as a main side effect and often can target sleep difficulties commonly reported in young children with autism and related disorders. Clonidine is a presynaptic alpha-2-adrenergic agonist more commonly used in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. There also have been case reports of clonidine being effective in the treatment of persons with fragile-X associated with disruptive behaviors (Hagerman et al. 1998). Again, drowsiness, hypotension, bradycardia, and less commonly skin reaction (from topical patch) need to be monitored. Many of these side effects can be mitigated by use of a moderate dose to begin with, especially since persons with intellectual disability are less likely to report feelings of drowsiness. Clonidine has also been reported to be effective to some extent in the treatment of akathisia related to neuroleptic drug withdrawal (Sovner 1995).

### Antianxiety Drugs

Benzodiazepines have been used for alleviation of anxiety, but their side effects such as paradoxical rage reactions, adverse effects on cognition, and serious withdrawal symptoms argue against their chronic use, and a trial of a SSRI might be preferable. Occasional use might be helpful in emergency situations in which extreme anxiety is present as well as in preparation for anxiety-inducing procedures as well as other special situations that may require sedation such as air travel. Nevertheless, if benzodiazepines are to be recommended in such circumstances they ought to be tried before under controlled circumstances to predict undue effects such as disinhibition that may make the situation worse.

Benzodiazepines are still used for the treatment of general anxiety and panic disorders, but usually only when there is no response to antidepressants. There is still a fair amount of combined use of neuroleptics and anxiolytics, especially in institutionalized persons with history of aggression. However, this may lead to significant CNS depression and the benzodiazepine use might actually lead to disinhibition (Werry 1998). Therefore, prolonged use of anxiolytics to control undesirable behaviors is generally not recommended (Werry 1998). As with other medications, comprehensive diagnostic assessment is a prerequisite to the use of anxiolytics. In particular, environmental anxiety-provoking factors have to be ruled out and, if present, have to be dealt with in addition to pharmacological means if these are used. Buspirone, a nonsedating and nontolerance forming anxiolytic agent with a short half-life, has also been used in treatment of persons with intellectual disability experiencing symptoms of anxiety and restlessness but its usefulness has not been substantiated.

### Lithium

The use of these agents in persons with and without intellectual disability is again similar. Lithium carbonate, the original mood stabilizer, was shown effective for bipolar disorders, mixed affective states with mood lability, as well as affective disorders with underlying CNS dysfunction in persons with intellectual disability dating back to the 1970s. However, Lithium was noted to have considerable side effects, especially in circumstances lacking close oversight of lithium blood levels, thyroid function tests and renal function. In addition, managing regular blood drawings is difficult in individuals who might otherwise be less than cooperative. Lithium carbonate has therefore been gradually, but not altogether, supplanted by increasing acceptance of anticonvulsants, including valproic acid, carbamazepine, more recently oxycarbamazapine, as well as other agents such as topiramate and lamotrigine, although the latter also requires close oversight with respect to hematological complications and risk of Steven Johnson syndrome. Currently, the primary use of lithium is for the treatment of comorbid bipolar disorder and for augmentation of antidepressants. There are also studies indicating to the effectiveness in some individuals with impulsive aggressive behavior but again caution is needed not to engage in treatment of individual target behaviors but to develop a systematic behavioral management approach (Craft et al. 1987). As seizures are frequently associated with intellectual disability, these drugs offer a parsimonious way of managing both the potential for seizures as well as behavioral problems associated with comorbid mental disorders.

### Other Psychotropic Agents

Propranolol and other beta-adrenergic blockers have been used following the earlier reports on the beneficial effects in rage attacks associated with a definite pathological brain condition (Williams et al. 1982). They have been tried extensively in all kinds of aggressive behavior, often with mixed or poor results. Depression might be a side effect of these agents, leading to reduction in the person's functioning, even if the aggressive behaviors might appear to improve, because of apathy induced by the drug. They may be also effective in the treatment of anxiety, especially its somatic symptoms, and for akathisia related to neuroleptic drugs.

Naltrexone, an oral antagonist of endogenous opioid receptors, has been tried in a number of studies in cases of severe SIB, following some case reports of earlier successes with a similar agent, naloxone, which had to be administered parenterally. It appears that it is effective in 35–70% of cases, at least for a short time (Sandman et al. 1998).

### Other Treatments

For many years there have been reports of beneficial effects of a variety of treatments, especially in children with PDD, Down syndrome, and fraX syndrome. These treatments include various nutritional supplements, vitamin supplements (such as megavitamins, various combinations of vitamins, minerals and enzymes, $B_6$, $B_6$ with magnesium, folic acid, etc.), and dietary interventions (as in restriction of food additives, gluten, casein, or yeast). Often these approaches generate considerable excitement among families Nevertheless, there is a need for replicated well designed studies for assessing CAM (American Academy of Child and Adolescent Psychiatry 1999, Singh et al. 1998). The situation may be difficult to oversee as the use of CAM can be implemented by many families without consultation of their physician. However, one should bear in mind that persons with developmental disabilities in general, and especially those with autism and PDD, may have unusual eating habits resulting in highly idiosyncratic and restricted diets. Therefore, in such cases a nutritional consultation may be advisable. If a deficiency is found, an appropriate

supplementation and correction of dietary habits is of course, needed. One example is zinc deficiency associated with pica, which was shown to disappear or decrease after treatment with 100 mg of chelated zinc for 2 weeks (Lofts et al. 1990). Although not an absolute contraindication, electroconvulsive therapy (ECT) has fallen into disuse in persons with intellectual disability as a direct consequence of past inappropriate uses, need for informed proxy consent and strict certification requirements. Occasional case reports of its successful use can still be found in the literature.

## Psychosocial Interventions

### Programmatic and Educational Approaches

The goal of these interventions is to provide a proper living and programmatic environment. For instance, certain persons easily become over stimulated, anxious, and disruptive in large and noisy workshop settings; for those individuals arranging for a smaller and quieter workroom is preferable, but certainly may prove more involved than the temptation to prescribe a psychotropic agent. The vocational and educational program for a person with intellectual disability should be individualized and the focus ought to be on developing the person's strengths and providing an opportunity for his or her ultimate success in adapting to situations and feeling valued and productive. In turn, this is likely to lead to results such as an improvement in self-image. Many persons with severe intellectual disability are placed in prevocational training indefinitely, for example, screwing or unscrewing nuts and bolts, although no one expects them to ever be employed on an assembly line. They often engage in a struggle with caregivers because of their noncompliance and may resort to aggression, which leads to removal for a "time out" and thus avoidance of a boring task. Creating more suitable tasks is now becoming the norm—these now involve making rounds to collect or deliver materials in schools, hospitals, nursing homes, or hotels—might be more interesting and appropriate. This may involve stacking shelves in a supermarket, assisting in meals-on-wheels; often the social interactions the persons with intellectual disability experience in such settings also prove more meaningful. Functional analysis of behavior is an invaluable guide to these interventions. As discussed previously, such approaches should be explored prior to resorting to use of medications for disruptive behaviors.

### Psychotherapies

Both individual and group psychotherapies have been effectively used in persons with intellectual disability dating back to the 1930s (Stacey and DeMartino 1957), and there continue to be many case reports on their success. Psychotherapy in this population is more akin to work with children, inasmuch as in both situations the therapist has to adapt the techniques to the developmental needs of the patient. It is also important to emphasize at the outset that the treatment ought to be guided by the patient's needs and responses and not by the therapist's theoretical orientation. Detailed techniques that can be used have been described (Szymanski 1980a, Szymanski and Rosefsky 1980). The indications are: the presence of concerns and conflicts, especially about one's situation and self-esteem; impairments in interpersonal skills or stressors related to relationships or losses; and other emotional problems known to improve through supportive psychotherapy such as need to prepare for important changes and transitions. The prerequisites include communication skills permitting a meaningful interchange with the therapist, an ability to develop even a minimal relationship, and the availability of a trained, experienced, and unprejudiced therapist who is comfortable working in a team setting. From applicable literature, Reiss and Benson (1985) summarized the guidelines for psychotherapy in this population, which include the following:

1. Appropriate goals should be set and should be reconciled with the expectations of the caregivers, the therapist, and the patient. Common goals include improvement in self-image and impulse control, learning to express feelings in a socially appropriate manner, and understanding in a constructive manner one's own disabilities and strengths.
2. The verbal techniques should be adapted to the patient's language and cognitive level, and the nonverbal ones should be age appropriate.
3. Limits and directive nature should be used as needed: nondirective therapy might lead to a patient's confusion. The therapist has to be active (supportive but not paternalistic), has to use herself or himself liberally as a treatment tool, and has to be able to focus on the immediate reality rather than just intellectualize.
4. A mix of techniques, for example, cognitive psychotherapy and behavior modification, may be required.
5. As in all treatment modalities, the therapist should be involved in all aspects of the patient's program and collaborate with other providers and with the family.

Group psychotherapy might be particularly effective in helping patients handle issues related to the understanding of their own disability and learn social skills because of the peer support the group offers (Szymanski and Rosefsky 1980). In general, therapy should be seen as a cognitive learning process, using the therapist's support and leading patients to the acquisition of understanding and necessary skills, both of concrete behaviors and of handling one's own emotions. Group psychotherapy should be differentiated from group counseling which usually is educational in nature, focused on a specific subject (e.g., sexuality education), and does not have to be conducted by a mental health professional with a therapeutic goal and plan.

### Behavioral Therapy

Behavioral techniques are described elsewhere in this chapter and their application in persons with intellectual disability has been long-standing (Jansen 1980). Detailed functional analysis is a prerequisite. This treatment should optimally use rewards which should be age appropriate, preferably social, and the frequency of rewarding should be adapted to a person's cognitive level, so that he or she can understand why they are given. Consistency and generalization among different settings are essential. Thus, if such techniques are successfully used at the school, the family or other caregivers should be trained to use them at home as well. The focus should not only be on elimination of objectionable behaviors but on teaching appropriate replacement behaviors.

Aversive techniques involving active punishment (electric shocks, spraying of noxious substances into a person's face) are not to be used except in a few controversial settings. There is a professional consensus that these techniques should not be used at all, or only when all other techniques have failed and the patient's behavior poses severe danger to herself or himself or to others (such as intractable SIB). Even then, these techniques should be used only if proved effective and for a limited time.

## Psychiatrist–Patient Relationship: Models of Delivery of Psychiatric Services

The psychiatric care of persons with intellectual disability has often followed a path different from the care provided to the general population. A common service model has been the medication clinic, in which the psychiatrist is given little, if any, time to examine the patient and to interview the caregivers. Instead, behavioral information, which is often brief and sketchy, is presented by caregivers and focuses primarily on disruptive behaviors. The psychiatrist is expected to prescribe medications and has no voice in, or knowledge of, other interventions that might be used. In some cases, the psychiatrist does the actual prescribing; in others, the psychiatrist serves as a consultant to primary physicians who may or may not follow the recommendations given. This model is obviously inadequate, even if there is another professional providing psychotherapy or behavioral therapy. It also exposes the psychiatrist to legal responsibility (Woodward et al. 1993). This model has been used in institutions, especially to save on the expense of having a staff psychiatrist to provide adequate services.

The proper psychiatric care of persons with intellectual disability is actually more time-consuming than the care of persons without intellectual disability because of the multi-modal nature of the treatments described previously. To understand a patient's clinical presentation and provide the input necessary for all relevant aspects of treatment, the psychiatrist has to have adequate time to interview all involved caregivers, observe and interview the patient, make a home or program visit if necessary, and discuss the recommendation with all involved. Thus, an interdisciplinary team approach is essential. It might not be realistic for all patients seen in the community, but it should be followed in all treatment-resistant cases and in residential facilities where, as a rule, there are more difficult patients (Szymanski et al. 1980, Szymanski and Leaverton 1980). In most cases in the community, if a team forges a good working relationship and regular communication, exchange of information and coordination via e-mail or telephone might be sufficiently productive. Some states have developed successful models of such coordinated care (that provide for health, housing, vocational and social services) for persons who have both intellectual disability and mental illness (Polgar et al. 2000). In all situations, psychiatrists will best use their knowledge and training in biological and behavioral aspects of medicine to help other professionals synthesize the biopsychosocial aspects of a patient's clinical presentation and treatment program.

## Conclusion

The World Health Organization (2001) report on caring for persons with mental disorders has emphasized the disproportionately high global burden of intellectual disabilities. The treatment gap in diagnosis and interventions among persons with intellectual disability remain unmet worldwide (Erol et al. 2005). The National Research Council (2001) on educational interventions in developmental disabilities had identified seven key areas for improvement that include: (1) early diagnostic assessments, (2) understanding of the effect on families and role of families in care, (3) development of appropriate goals for educational and rehabilitation services, (4) salient characteristics of effective interventions and educational services, (5) development of public policy initiatives to ensure access to educational and rehabilitative programs, (6) improvement in the training of professionals, and (7) enhancement of future research. Development of requisite expertise in the training and education of both adult and as well as child and adolescent psychiatrists in caring for the mental health needs of persons with intellectual disability is also an important critical concern. Finally, parent-guided and both publicly and privately supported organizations are particularly useful in developing "actionable" steps to improve outcomes in this population. This has proven to be very important in raising public awareness and garnering research-funding support in this area.

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CHAPTER

# 43 Childhood Disorders: Learning and Motor Skills Disorders

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Reading Disorder
Mathematics Disorder
Disorder of Written Expression
Learning Disorder Not Otherwise Specified
Developmental Coordination Disorder

For children and adolescents, school is their "workplace." Successful school performance is essential for psychological growth and development. Social competency and social skills are developed and then shaped within the family and in the school but practiced and mastered in the school. The development of a positive self-image and self-esteem is based on successes in school. Feedback from the school concerning academic performance and social interactions influences the parents' image of their child or adolescent. Thus, if something interferes with success in school, the impact will affect the emotional, social, and family functioning of the child and adolescent.

Academic performance requires the integrated interactions of the cognitive, motor, and language functions of the brain. As detailed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), if brain dysfunction results in cognitive difficulties, it is called a learning disorder; in motor difficulties, a motor skills disorder; and in language difficulties, a language disorder. This chapter focuses on the learning disorders and the motor skills disorder. Chapter 44 reviews the communication disorders, including language disorders.

Key for the mental health professional is the understanding that the underlying neurological dysfunctions that result in learning disorders and motor skills disorder have an impact on more than academic performance. These disabilities affect every aspect of the individual's life during each stage of psychosocial development (Silver 1989, 2006). Of further importance is our knowledge of a continuum of neurologically based disorders that are often found together. Part of this continuum includes learning disorders, motor skills disorders, and language disorders. If a child has one of these disorders, there is a high likelihood, possibly up to 50%, that he or she will also have one or more of other disorders to be discussed later in this chapter.

## Definitions

Public education laws use the term learning disabilities. DSM-IV-TR uses the terms learning disorders and motor skills disorder. It is helpful to understand that these terms reflect the diagnostic system used but refer to the same set of difficulties.

Public school systems use the Federal definition, based on the initial public law, PL 94–142, The Education for all Handicapped Children, and its revisions. The most recent revision is PL 108–446, the Individuals with Disabilities Education and Improvement Act (IDEA 2004). In this law, a learning disability is defined by inclusionary and exclusionary criteria:

> Specific learning disabilities means a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which may manifest itself in an imperfect ability to listen, think, speak, read, write,

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spell, or to do mathematical calculations. The term includes such conditions as perceptual handicaps, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia. The term does not include children who have learning problems which are primarily the result of visual, hearing, or motor handicaps, or mental retardation, of emotional disturbance, or of environmental, cultural, or economic disadvantage.

The *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) was the first medical diagnostic system to refer to these problems. In DSM-III, the concept of learning disabilities was not used. The focus was on the areas of academic difficulty, and the term used was academic skills disorders. The specific types of disorders reflected general areas of difficulty: developmental arithmetic disorder, developmental expressive writing disorder, and developmental reading disorder. There was no reference to motor disorders. These disorders were listed, along with language disorders, under the broad category of specific developmental disorders. This focus on developmental disorders reflected the facts that they were found in children and adolescents and that they greatly affected all aspects of development. This term did not reflect the reality that, for most persons, these disabilities will last throughout their lives. The *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) maintained the focus on specific developmental disorders and on the same three general areas of difficulty. However, motor skills disorder was added.

In DSM-IV and DSM-IV-TR, the term academic skills disorders was changed to learning disorders. Three subtypes of learning disorders are identified: reading disorder, mathematics disorder, and disorder of written expression. Only developmental coordination disorder is listed under the category motor skills disorder.

## Diagnosis

It is important to understand that the criteria used in DSM-IV-TR as well as the criteria used by school systems is based on education law. In clinical practice, the psychiatrist must focus on helping families, work with their school system to identify and to address the needs of their child or adolescent. Thus, the psychiatrist must know and understand the educational criteria used by public school systems.

The research on neurologically based learning disorders stresses not the specific skill disorders but the underlying processing problems. Psychological and educational diagnostic tests clarified the areas of learning abilities and learning disabilities covering the four steps involved in processing information (Table 43–1). Thus, although one assesses for problems with reading, mathematics, or writing, it is important in the diagnostic process to explore what the underlying processing problems are that result in these skill disorders. It is equally critical to know an individual's learning strengths as it is to know his or her disabilities. Interventions must build on these strengths to compensate for the disabilities.

**DSM-IV-TR Criteria**

**Reading Disorder**

A. Reading achievement as measured by individually administered standardized tests of reading accuracy or comprehension, is substantially below that expected, given the person's chronological age, measured intelligence, and age-appropriate education.

B. The disturbance in criterion A significantly interferes with academic achievement or activities of daily living that require reading skills.

C. If a sensory deficit is present, the reading difficulties are in excess of those usually associated with it.

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**DSM-IV-TR Criteria**

**Mathematics Disorder**

A. Mathematical ability, as measured by individually administered standardized tests, is substantially below that expected given the person's chronological age, measured intelligence, and age-appropriate education.

B. The disturbance in criterion A significantly interferes with academic achievement or activities of daily living that require mathematical ability.

C. If a sensory deficit is present, the difficulties in mathematical ability are in excess of those usually associated with it.

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**Table 43–1 Areas of Psychological Processing That Affect Learning**

| Area of Processing | Examples |
|---|---|
| Input | Visual perception, auditory perception |
| Integration | Sequencing, abstracting, organizing, executive function |
| Memory | Working memory, short-term memory, long-term memory |
| Output | Language output, motor output |

## DSM-IV-TR Criteria

The criteria in DSM-IV-TR for establishing the diagnosis of a learning disorder are as given on this page and page 3. For each of these diagnostic categories, the criteria in DSM-IV-TR is that if a general medical (e.g., neurological) condition or sensory deficit is present, the disorder should be coded on Axis III.

Within the motor skills disorder section of DSM-IV-TR, there is only one specific disorder, developmental coordination disorder. The criteria given on this page and on page 3

**DSM-IV-TR Criteria**

**Disorder of Written Expression**

A. Writing skills, as measured by individually administered standardized tests (or functional assessments of writing skills), are substantially below those expected given the person's chronological age, measured intelligence, and age-appropriate education.

B. The disturbance in criterion A significantly interferes with academic achievement or activities of daily living that require the composition of written texts (e.g., writing grammatically correct sentences and organized paragraphs).

C. If a sensory deficit is present, the difficulties in writing skills are in excess of those usually associated with it.

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establish this diagnosis. If the developmental coordination disorder is due to a general medical (e.g., neurological) condition, the diagnosis is not made and instead the causative general medical condition is coded on Axis III.

Often, the child or adolescent will have difficulties in learning separate from the basic skills of reading, writing, and mathematics. Examples are: organizational problems, executive function problems, and processing speed problems. These areas of difficulty may be coded under Learning Disorders Not Otherwise Specified.

**DSM-IV-TR Criteria**

**Learning Disorder Not Otherwise Specified**

A. This category is for disorders in learning that do not meet criteria for any specific learning disorder, for example, a disorder in which spelling skills are substantially below those expected given the person's chronological age, measured intelligence, and age-appropriate education.

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## Educational Criteria

The federal guidelines for determining whether a student in a public school is eligible for special programs for learning disabilities list four criteria that must be addressed (Silver and Hagin 1993):

1. Documented evidence indicating that general education has been attempted and found to be ineffective in meeting the student's educational needs.
2. Evidence of a disorder in one or more of the basic psychological processes required for learning. A psychological process is a set of mental operations that transform, access, or manipulate information. The disorder is relatively enduring and limits ability to perform specific academic or developmental learning tasks. It may be manifested differently at different developmental levels.
3. Evidence of academic achievement significantly below the student's level of intellectual function (a difference of 1.5–1.75 standard deviations between achievement and intellectual functioning is considered significant) on basic reading skills, reading comprehension, mathematical calculation, mathematical reasoning, or written expression.
4. Evidence that the learning problems are not due primarily to other handicapping conditions (i.e., impairment of visual acuity or auditory acuity, physical impairment, emotional handicap, mental retardation, cultural differences, or environmental deprivation).

In the 2004 revision of the Individuals with Disabilities Education Act, an alternative to the above-described discrepancy model for assessment is proposed. It is referred to as the "Response to Intervention" model. This assessment uses a three-tier approach to helping students having difficulty learning. Formal testing may be done after Tier 2 interventions; however, the U.S. Department of Education Rules and Regulations for the revised law suggest but do not require that formal testing be done.

If a student shows difficulty learning, he or she enters Tier 1. Here, high-quality instructions and behavioral supports are provided by the teacher in the general education

**DSM-IV-TR Criteria**

**Developmental Coordination Disorder**

A. Performance in daily activities that require motor coordination is substantially below that expected given the person's chronological age and measured intelligence. This may be manifested by marked delays in achieving motor milestones (e.g., walking, crawling, sitting), dropping things, "clumsiness," poor performance in sports, or poor handwriting.

B. The disturbance in criterion A significantly interferes with academic achievement or activities of daily living.

C. The disturbance is not due to a general medical condition (e.g., cerebral palsy, hemiplegia, or muscular dystrophy) and does not meet criteria for a pervasive developmental disorder.

D. If mental retardation is present, the motor difficulties are in excess of those usually associated with it.

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classroom. If the student does not make progress, he or she moves to the Tier 2 level of intervention. More specialized instruction is provided by the teacher or a special education teacher provided in a smaller group. If progress is still not found, the student moves to Tier 3. In Tier 3, more individualized intervention is provided, now exclusively by special education personnel. If little or no progress is noted, the student can be identified as having a disability and is eligible for an Individualized Education Program (discussed later).

It is critical to understand why a student is not learning. Thus, most professionals believe that formal psychological and educational testing (discussed in Chapter 44) should be done before an Individualized Education Program is written. Unfortunately, the 2004 revisions of IDEA leave open the option for some school systems to move from Tier 3 to an Individualized Education Program without such an assessment.

It is important to remember that the presence of a central nervous system processing deficit is essential for the diagnosis of a learning disability in a public school setting. A child might meet the discrepancy criteria in DSM-IV-TR, but without central processing deficits in functions required for learning, this student may not be considered by his public school system as having a learning disability. Further adding to the difficulty in working with the public school system is the reality that different school systems might use different criteria to determine what constitutes a significant discrepancy between potential and actual achievement. Thus, a child might meet the criteria to be identified as having a learning disability in one school system and not qualify in another.

## Diagnosis of a Learning Disorder or Motor Skills Disorder

If a child or adolescent is experiencing academic difficulty, she or he would normally be referred to the special education professionals within their public school system. If a student is in a private school, such a referral would be made to the public school nearest to the student's home. However, a student with academic difficulties often presents with emotional, behavioral, or attentional problems and is more likely to be referred to a mental health professional. It is critical to understand this potential referral bias. This mental health professional must clarify whether the presenting emotional, behavioral, and/or attentional problems are causing the academic difficulties or whether these problems are a consequence of the academic difficulties with the resulting frustrations and failures experienced by the individual, the teacher, and the parents (Bender 1987, Hunt and Cohen 1984, Silver 1989, 1993, 2006, Valletutti 1983).

It is all too common for teachers and parents to "blame the victim." The student who is doing poorly in school is described as lazy or unmotivated and not trying hard enough. If a student is not doing well academically, it is much more productive to step back and question why the student is not doing well. The presenting behaviors are a diagnostic clue, not a diagnosis.

The evaluation of a child or adolescent with academic difficulties must explore whether these school problems are primarily the result of an emotional, social, or family problem or whether the unrecognized learning disorder and/or motor coordination disorder so frustrates the student that secondary emotional, social, or family problems develop.

The evaluation of a child or adolescent with academic difficulties and emotional or behavior problems includes a comprehensive assessment of the presenting emotional, behavior, social, or family problems as well as a mental status examination. The psychiatrist should obtain information from the child or adolescent, parents, teachers, and other educational professionals to help clarify whether there might be a learning disorder or motor skills disorder and whether further psychological or educational studies are needed. Descriptions by teachers, parents, and the child or adolescent being evaluated will give the psychiatrist clues that there might be one of the learning disorders or a motor skills disorder.

The DSM-IV-TR criteria cover major skill areas: reading, mathematics, and writing. When assessing a student who is struggling in school, it is helpful to understand the many forms each of these skill difficulties might take. Later, a developmental model for understanding school skill expectations will be discussed, allowing the clinician to assess if the level of reading is at expected grade level or not.

Children who experience problems in reading might have difficulty with the first task in learning to read, that is, putting sounds and letters together and decoding the word. They might read each word in a disjointed manner, knowing a few words on sight and struggling with unfamiliar words or they might have difficulty with visual tracking, skipping words or lines. Others might have difficulty with the next skill needed in reading. They can decode the words but they have difficulty comprehending what they have read. Others might have difficulty with yet the next skill needed in reading. They can decode and comprehend but have difficulty retaining what they have read (referred to as reading fluency). They get to the end of the chapter and do not retain what they read. Children with mathematical difficulties may have a problem recognizing numbers and not confusing subtle differences in shape (e.g., 6 and 9). The earliest skills involve learning what is called the "base 10" concept (all number systems are in units of 10) and what is referred to as the "conservation of numbers" (i.e., numbers are fixed entitites; one cannot create a number from nothing or make a number disappear). Later, one must learn multiplication and division, then fractions and decimals. These skills are built on to learn higher math concepts. For each of these steps in learning, some students might have difficulty remembering facts (e.g., the times tables) and some might have difficulty retaining and applying these facts. Some have the ability to do calculations in their head but have difficulty when they must write out and show the steps involved in solving the problem. They might make careless errors or have problems with visual–spatial tasks or with sequencing the information. Some might have difficulty shifting from one operational concept to another.

Children who have difficulties with writing may have a problem with the fine motor skill of handwriting, referred to as a graphomotor problem. They grasp the pencil or pen differently and might hold tightly. They might write slowly and their hand gets tired. Printing might be preferred over cursive. Separate from this motor problem, students might have difficulty with written language—spelling, grammar, punctuation, capitalization. Still others might have difficulty organizing their thoughts and getting them onto the paper.

In addition to reading, writing, and math difficulties, students might struggle with problems of organization and

executive function. Organization problems might impact on keeping track of their materials. They lose, forget, or misplace their papers, notebook, books, and other materials. They might leave items at home when they go to school or items in school when they come home. Often, these students have equal difficulty keeping tract of their personal belongings (jackets, pencils) and organizing their bedroom. Organizational problems can also involve the ability to organize information in meaningful way in order to learn it or to know what information is important to know.

Some may have difficulty organizing the information in their head when they must answer a verbal or written question. Executive function refers to the ability to think through a task, establish the steps needed to solve the task, start the process, make modifications in these steps later if needed, and complete the task in a timely way. Students with these problems struggle to start complex tasks and often have difficult with time planning.

Children and adolescents with a developmental coordination disorder may show evidence of fine motor or gross motor difficulties. The fine motor problems might result in difficult with coloring and cutting, learning to button, zip, or tie, holding a pencil or pen when writing, or controlling eating utensils, resulting in a preference to eat with fingers or scoop with a spoon. Thus, it is important for the clinician to realize that the child with a handwriting problem might have other fine motor problems that impact on his or her life. Gross motor problems might result in difficulty with coordination when walking, running, jumping, or climbing. These motor problems might include visual motor difficulties (using visual input to tell muscles what to do) or visual spatial problems (knowing where one is in space, bumping into things).

Within the educational system individuals with developmental coordination disorder in which the motor problem has a sensory component (e.g., tactile, vestibular, proprioceptive) are considered to have a Sensory Processing Disorder. This disorder is based on concepts about the relationship between the neurological processes, behavior challenges, daily life skills, and sensory–motor abilities (Ayres 1972, Bundy and Murray 2002, Koomar and Bundy 2002). If one or more sensory systems are not processing properly, the result is sensation that is not properly modulated or discriminated or the responses are not properly graded to the sensory input. Three processing systems relevant to developmental coordination disorder are the tactile system, the vestibular system, and the proprioceptive system. Visual perception is an essential component of sensory integration as well.

Occupational therapists are trained to diagnose and to treat this disorder. The tactile system involves the sense of touch and the stimulation of skin surfaces. Some children will have problems with tactile defensiveness characterized by over-responsiveness to tactile stimuli that is perceived as neutral by others. These children experience discomfort when touched by another person especially if the touch is unexpected. For example, infants with tactile defensiveness often resist being held or fed. Older children may complain about tags on the back of their shirts, seam in socks, or other rough surfaces. It is not unusual for children to respond aggressively or by withdrawal (e.g., "fight or flight" responses), when they are accidentally jostled while in line.

The vestibular system enables individuals to detect motion. The vestibular system allows children to know where their body is in space and where their head is in relation to gravity. Children with vestibular disorders fall frequently and may be terrified of activities in which their feet are required to leave the ground. They often have difficulty mastering riding a two-wheel bike or going down stairs with one foot on each step. Some children with vestibular impairments will have weak upper trunk muscles, poor core stability, and low endurance.

The proprioceptive system processes incoming messages from the muscles or joints. If the fine motor proprioceptive system is impaired, the result might include difficulty with such fine motor skills such as coloring, cutting, writing, buttoning, zipping, tying, and controlling eating utensils. If the gross motor proprioceptive system is impaired, the child might have difficulty with running, jumping, skipping, and climbing.

## The Educational Curriculum and Diagnosis

Professionals working with children and adolescents understand the importance of knowing developmental stages. Whether one is assessing for psychological or social levels of behavior or cognitive, motor, or language abilities, it is difficult to determine if someone is at age/grade level, delayed, or advanced in any psychological expectation without knowing the age-expected norms.

This need is equally essential when assessing a child or adolescent with academic difficulties to determine of he or she has a learning or motor skills disorder. What should the student be able to do in first grade, third grade, fifth grade, middle school, high school? The answer is based on a knowledge of cognitive, motor, and language development and the curriculum demands of the school system. Educational curriculum is based on knowledge of brain development and, thus, cognitive, language, and motor development.

***Reading.*** In preschool, students are expected to learn two basic requirements for learning to read. First is rapid letter recognition and second is the ability to know what sound goes with each letter. These letters are called graphemes and the sounds are called phonemes. In first grade, the student learns to put the correct phoneme to the correct grapheme and "sound out" words. After a word has been sounded out frequently, most students recognize the word as a whole and can read it without the need to decode (sight reading). In second grade, these skills are developed further, leading to increased speed. Students who struggle to learn these skills often end up in the lower reading groups. Third grade brings a new set of demands. The assumption is that the student can now read. The focus shifts to knowing what has been read, reading comprehension. Books are assigned and the student reads them. Gradually, through third and fourth grade, the length and complexity of the books increase. By the end of fourth grade it is assumed that the student can read, comprehend, and retain what they have read. These skills are critical because by fifth grade and beyond the assumption is that one can read, comprehend, and retain. The focus shifts now to using these skills to learn subject content. The subject taught (history, literature, science) becomes the focus.

***Writing.*** In preschool, students start to learn the letters of the alphabet and numbers. They learn to recognize each and to form each. During first and second grade, the focus

is on forming each of these symbols correctly and on the line. Capitalization and punctuation facts are introduced. Initially, spelling might be "creative;" however, soon, correct spelling is expected. Concepts of grammar are introduced. By third grade, it is assumed that the student can write with basic spelling, capitalization, and punctuation. Grammar skills are improved as well as the student's ability to get his or her thoughts organized and onto the page. Then, in third grade the focus shifts from "can you write" to "what have you written;" for example, book reports, journals. These skills are improved in fourth. By fifth, the assumption is that writing skills are in place. The focus shifts from using writing skills to learning subject content. Thus, the focus is on the subject taught with the assumption that the writing skills are there.

***Mathematics.*** In preschool, kindergarten, even in first grades students are taught the two basic concepts described earlier in this chapter, base ten and conservation of numbers. In third grade, multiplication and division skills are added. By fourth, multiplying and dividing three and four digit numbers, fractions, and decimals are added. By fifth grade, these skills are assumed to be present. They are used to introduce higher-level math such as algebra and beyond.

***Organization and Executive Function.*** These skills are introduced and taught in first through fifth grades. Such skills include organizing one's notebook, backpack, and papers as well as keeping track of assignments and when assignments are due. In middle school, there is an increased expectation that the student will be able to organize increasing amounts and complexities of information and produce fuller answers to questions as well as to write more elaborate papers and do projects. Teachers help students learn how to do these skills and provide a structure for learning these skills. By high school, the teacher's assistance and support may be removed. The student is expected to function independently. Thus, some students with organizational problems manage through middle school then have significant difficulties in high school.

Given the above academic and developmental information, it is possible to ask parents, children, and adolescents a series of questions, designed like a systems review, to screen for possible learning or motor disorders. These questions can be asked in a brief period of time and provide clinical clues suggesting a possible problem with skills or with underlying processing problems. Like any other "systems review," the answers must be assessed based on the student's age and grade level (see Table 43–2).

## Differential Diagnosis

The presenting problem is academic difficulty. The differential diagnostic process must clarify the reasons for the academic difficulty. A "decision tree" for academic difficulties developed by Ostrander and Silver is useful for exploring all of the possible reasons for such difficulties (Figure 43–1).

When the presenting problem is academic difficulties, there are three principal areas of inquiry concerning the factors contributing to the student's difficulties. The first involves considerations that are related to the child's or adolescent's psychiatric, medical, or psychoeducational status. The second area of inquiry is family functioning. The third area to explore involves the environmental and cultural context in which the student functions.

### Evaluation of the Child or Adolescent

Difficulties in academic performance of children or adolescents can be related to a range of psychiatric, medical, or cognitive factors. To best determine the primary source of academic difficulties, the evaluation should involve a comprehensive examination of these areas. The psychiatric evaluation should clarify whether there is a psychopathological process. If one is present, it is useful first to determine whether the problems relate to a disruptive behavior disorder, including attention-deficit/hyperactivity disorder (ADHD), or to another psychiatric disorder. In particular, the disruptive behavior disorders have high comorbidity with academic difficulties. A full assessment should clarify whether a disruptive behavior disorder is causing the difficulty with academic performance or is secondary to this difficulty. Disruptive behavior disorders can result in the student being unavailable for learning or being so disruptive as to require removal from a general education setting. However, equally possible is that the frustration and failures caused by a learning disorder or motor skills disorder can be manifested by a disruptive behavior disorder. In some cases, the disruptive behavior disorder coexists with learning or motor skills disorder and the relationship is less clear. Children with ADHD have particular difficulty maintaining attention, and possibly with processing information. As a result, the same variables that have an impact on their attention might also have an impact on their ability to learn. In such instances, they may have a learning disorder and ADHD.

Internalizing disorders such as depression or anxiety may result in an uncharacteristic disinterest in or avoidance of school expectations. If one of the internalizing disorders is present, it is important to clarify whether it is a comorbid condition or secondary to the frustrations and failures resulting an academic difficulty.

Other psychiatric disorders will impact on availability for learning or on academic performance. The clinician must clarify if the primary problems relate to a pervasive developmental disorder or a psychotic disorder. Substance use, misuse, and abuse may be the primary cause for the academic difficulties or might reflect the individual's efforts to cope with the stresses resulting from the academic difficulties.

The medical evaluation is necessary to explore the influence of health factors on the individual's availability and ability to learn. Problems in acquiring academic content can be significantly affected by most visual and hearing deficits. Generally poor health can influence the stamina, motivation, and concentration needed to focus adequately on academic demands. Medications used for any purpose might cause sedation or other side effects that may affect the child's ability to learn. Early developmental insults can result in global or focal deficits in neurological development. Undiagnosed seizures, especially petit mal and partial complex seizures, can result in difficulties in general cognitive functioning, specific deficits in memory, and problems with attention.

The evaluation of cognitive, academic, and neuropsychological functioning is critical to any assessment of learning problems. Results of this psychoeducational assessment will indicate the parameters of the individual's academic and cognitive liabilities while identifying his or her assets. In some instances, borderline cognitive development or mental retardation may be the primary explanation for learning difficulties. Developmental delays are particularly evident with

**Table 43–2 Screening Questions**

| Reading | Organization |
|---|---|
| Is reading something you like to do or have to do? | What does your notebook look like? Your binder? Is it a mess with papers falling out or in the wrong place? |
| When you read, do you have any problems sounding out the words? | What about your desk? Your locker? Your bedroom? |
| Do you ever skip words or lines? | Do you have difficulty organizing your thoughts or the facts you are learning into concepts so that you can understand and learn? |
| Do you find sometimes that you can read the words but don't understand what you have read? | Do you find that you can read a chapter and think you understand it; yet, you have trouble organizing the information when you have to write about it? |
| Do you find that you can read and understand, but that you don't retain what you have read? | |
| Do you get papers back and realize that you misread the questions or instructions or the word problems in math? | |
| **Mathematics** | **Memory** |
| Do you feel you know your basic facts in addition, multiplication, and division? | Do you find that you understand what you read as you are reading, yet, not retain the information by the end of the chapter or book? |
| Do you lose points because you misread the question or word problem? | Do you study and know information then find the next day that you forgot it? |
| Do you make careless errors when doing calculations, such as adding when you meant to subtract or skipping steps? | When talking, do you sometimes know what you want to say but as you are talking you forget your train of thoughts? |
| Do you have trouble remembering the formula or equation to use? | |
| **Writing** | **Motor** |
| How would you describe your handwriting? Is it described as messy? | Do you have difficulty writing neatly or writing fast enough? |
| Can you write fast enough to finish your work, copy from the board, or take notes? | Do you hold your pencil or pen differently than others? |
| When you look at what you wrote, do you have any problems with spelling, with grammar, punctuation, or capitalization? | Can you run, jump, and climb as well as your friends? |
| Do you have any problems getting the thoughts in your head onto the page? | Do you sometimes knock things over or bump into things? |
| | Do you have difficulty with buttoning, zipping, tying? How about cutting food and eating? |
| | In sports, do you have difficulty with throwing, hitting, and catching? |
| **Sequencing** | **Language** |
| When you write or speak, do you sometimes have difficulty getting everything in the right order? Do you sometimes start in the middle, go to the beginning, jump to the end? | When the teacher is speaking in class, do you have trouble understanding or keeping up? |
| Can you name the months of the year? (let child do) Fine, now what comes after August? (Ask how the child got the answer. Was it necessary to return to January and count up?) | Do you sometimes misunderstand people and, therefore, give the wrong answer? |
| When using the dictionary, do you have trouble using the alphabet? Do you sometimes have to return to "a" and go up to know where the next letter will be? | When people are talking, do you find that you have to concentrate so hard on what they say that you sometimes fall behind and miss what is being said? |
| | Does this problem sometimes cause you to get lost when the teacher is talking in class? |
| **Abstraction** | Do you sometimes have trouble getting your thoughts organized when you speak? |
| Do you understand jokes when your friends tell them? | Do you sometimes have a problem finding the word you want to use? |
| Do you sometimes get confused when people seem to say something, yet they tell you they meant something else? | |

*Source:* Silver (2004) Attention Deficit Hyperactivity Disorder. A Clinical Guide to Diagnosis and Treatment for Health and Mental Health Professionals, 3rd edition. American Psychiatric Press, Washington, DC, pp 71–74.

a preschool child; rapid and uneven developmental changes can lead to considerable variability in findings derived by measures of intellectual functioning. If any of the clinical evaluations yield results suggestive of a learning disorder, a more involved psychoeducational assessment is needed. An appropriate psychoeducational evaluation will reveal the magnitude of the child's learning difficulties as well as the nature of the child's cognitive assets and deficits. From this understanding, appropriate interventions can be designed and special accommodations can be initiated.

## Family Evaluation

A family evaluation must include an assessment of the parents and of the entire family. A judgment is made on the order in which these assessments are best done. The first clinical question is whether the family is functional or dysfunctional. If the family is largely functional, there may be "normal" parenting issues that may be contributing to the child's difficulties. If there is no evidence of a psychopathological process within the family, alternative explanations should be considered for the learning disorder.

Normal parenting issues may include the time or energy that parents have in relating to the child's academic difficulties. For example, a single parent may be overwhelmed with responsibilities associated with child-rearing and, as a result, be unavailable to facilitate the child's educational progress. In families in which both parents work, the demands associated with work may leave little energy for helping the child with academic challenges. There could be family values that affect the child's educational functioning. The psychiatrist may also learn that education is not a family priority and that this may be in conflict with the demands and the expectations of the school.

If the family is found to be dysfunctional, the psychiatrist must assess whether the dysfunction is caused by issues involving both parents, problems with one parent,

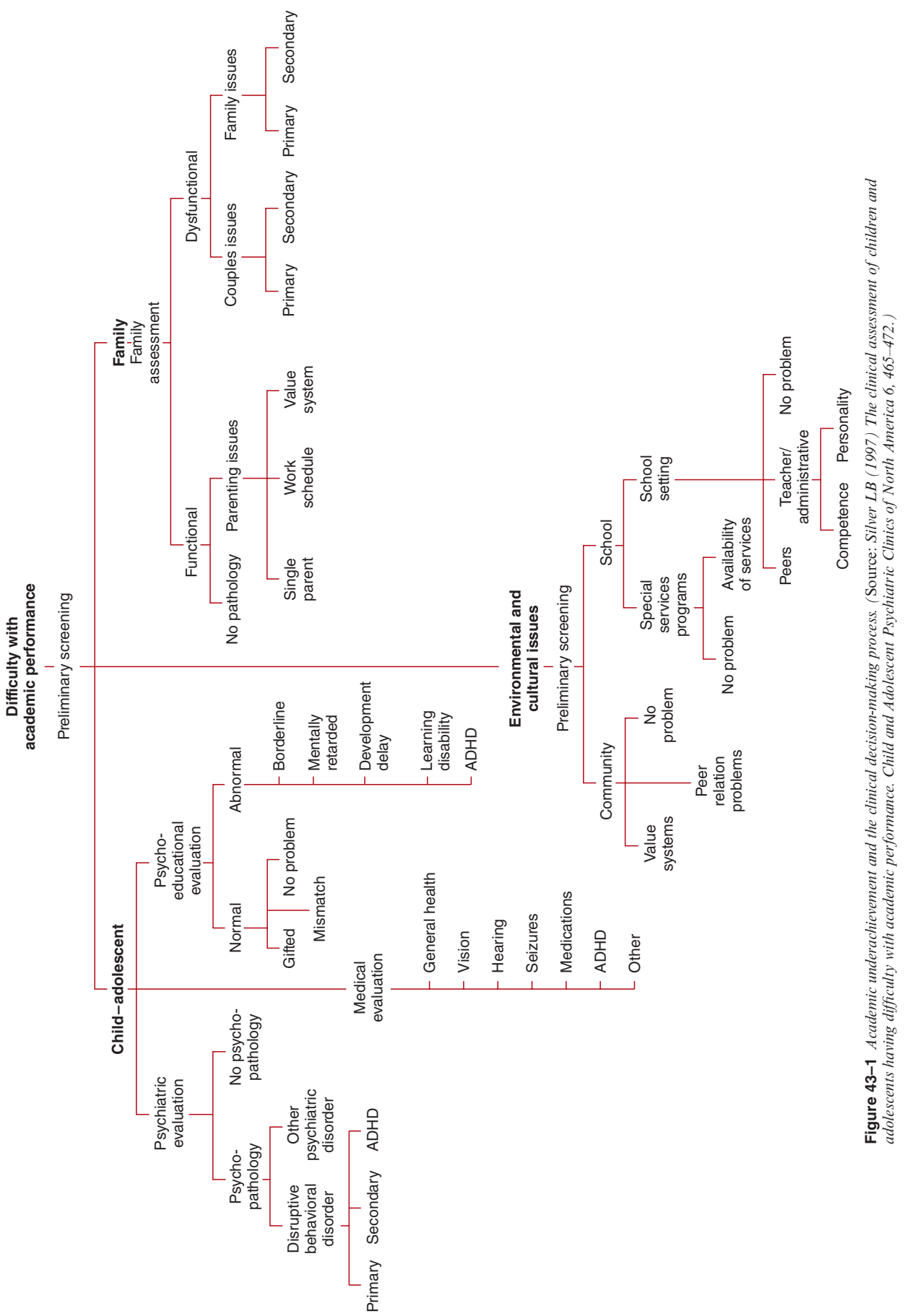



**Figure 43–1** *Academic underachievement and the clinical decision-making process.* (Source: *Silver LB (1997) The clinical assessment of children and adolescents having difficulty with academic performance. Child and Adolescent Psychiatric Clinics of North America 6, 465–472.*)

or broader family difficulties. If there is stress between the parents that results in marital difficulties, the psychiatrist should clarify whether these problems are primary or secondary to the presenting academic problems. That is, the marital stress may be contributing to the child's academic difficulties or may be influenced by the stress of having a child who has a learning disorder. The assessment may clarify that one parent is having psychological problems that are contributing to the couple's or family's stress. If there is family dysfunction, the psychiatrist must clarify, when possible, the difficulties that are having an impact on the family. It should be clarified whether the family dysfunction is primary or secondary to the child's academic difficulties.

## Environmental and Cultural Assessment

Learning problems are attributed to cognitive deficits or behavior problems in the child or adolescent. Environmental factors involving the school or community, however, can also contribute to academic difficulties. Thus, the psychiatrist should be aware of how social, cultural, and institutional structures can influence learning. In many instances, such an awareness is developed over time and in the process of conducting a clinical practice. Data collection within this context is accomplished through formal and informal observations of the system and the cultural milieu. Through ongoing interactions with the community and the school system, a psychiatrist may develop an appreciation of the community values and the general programmatic resources provided by the school. With this understanding as a backdrop, one can conduct a more direct assessment of how specific environmental or school considerations can affect a given individual.

A child or adolescent with specific needs may be further impaired because of a limited range of services offered by the school system. For example, a child's learning disorder may require special accommodations and services within a specific classroom; however, the school may not have allocated sufficient resources to make these accommodation or services available. In addition, the effectiveness of school programs can be influenced by interpersonal considerations, such as the competence and personality of the teacher or school administrator. School personnel may be misinformed or uninformed about a particular psychiatric condition or have insufficient training to effectively address a particular learning difficulty. Although uncommon, more troubling influences on a child's learning can emerge when the school personnel exhibit biases or personality difficulties that affect the teacher's ability to teach. In addition to problems associated with school personnel, the degree to which the child's peers value academic success can either motivate or discourage a student from reaching his or her academic potential. An assessment of school-based interpersonal conflicts and alliances can provide valuable insights into their influence on learning. Whereas the school exerts a more direct influence on learning, the community influence is less direct, although no less profound. For example, the value system of some communities includes high expectations for academic accomplishments, whereas other communities view academic success as largely unobtainable. Similarly, inappropriate peer pressure can either minimize or degrade the importance of academics. In most affluent communities, unusually high academic standards can place pressure on a student who has average intellectual capabilities.

## Epidemiology

The true prevalence of these disorders is not known. The difficulty is that many case definitions are used in different studies. Even if the discrepancy model is used, the amount of discrepancy required may vary. The Centers for Disease Control and Prevention (1987) attempted to establish the prevalence of learning disabilities. These researchers concluded that because the definition and the diagnostic criteria have not been fully standardized, consistency in the design of prevalence studies has not been maintained. Thus, accurate analyses of data over time are not possible. In the absence of good prevalence data, these researchers concluded that between 5 and 10% was a reasonable estimate of the percentage of persons affected by learning disabilities.

In DSM-IV-TR, prevalence figures are noted for each of the learning disorders and motor skills disorders. The prevalence of reading disorder in the United States is estimated at 4% of school-age children. It is estimated that 1% of school-age children have a mathematics disorder. No data are noted for disorder of written expression. The prevalence of developmental coordination disorder is estimated to be as high as 6% for children in the age range of 5–11 years.

## Comorbidity Patterns

Comorbidity studies suggest that there is a continuum of neurologically based disorders often found together. The common theme appears to be that something impacted on the developing brain very early in pregnancy, causing areas of the brain to develop differently. For some of these individuals, there is a familial pattern, suggesting a genetic theme. For others, the reasons are not clear. There is increasing concern with the impact of environmental toxins found in the air, water, and food that act as developmental and neurologic toxins and impact on brain development.

This continuum may include cortical-based disorders (learning, language, or motor disabilities or organization/executive function disabilities). Individuals with these cortical-based disorders may also have ADHD or a pattern of emotional regulatory problems, including anxiety disorders, depression, anger control difficulties, or obsessive–compulsive disorder.

Many also have tic disorders. Recently, bipolar disorder has been added to this list (see Table 43–3)

**Table 43–3 Continuum of Neurologically Based Disorders**

| | |
|---|---|
| 1. Cortical-based Disorders | Learning Disabilities |
| | Language Disabilities |
| | Motor Disabilities |
| | Organization/Executive Function Disabilities |
| 2. Attention-Deficit/ Hyperactivity Disorder | |
| 3. "Regulatory Disorders" | Anxiety Disorders |
| | Depression |
| | Intermittent Explosive Disorder |
| | Obsessive–Compulsive Disorder |
| 4. Tic Disorders | Chronic Motor Tic Disorder |
| | Chronic Vocal Tic Disorder |
| | Tourette's Disorder |
| 5. Bipolar Disorder | |

Statistical studies supporting the concept of a continuum of neurologically disorders include the following. For individuals with learning disabilities, 20–25% have ADHD (Halperin et al. 1984, Silver 1981). Between 70 and 80% of individuals with ADHD have a learning disability (Silver 1981). About 60% of patients with Tourette's disorder have a learning disability (Hagin et al. 1982, Hagin and Kugler 1988). Further, 50% of individuals with Tourette's disorder have ADHD (Comings 1990, Comings and Comings 1988). Fifty percent of patients with Tourette's disorder have obsessive–compulsive disorder (Frankel et al. 1986, Pauls et al. 1990).

## The Cortical Disorders

The learning and motor cortical-based disorders are discussed in this chapter. The language disorders are discussed in Chapter 44.

### Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is discussed in Chapter 44.

### Regulatory Disorders

Several areas of the brain are needed to regulate emotions and thoughts. If these systems are not working efficiently, the individual might experience difficulty regulating anxiety, mood, anger, or thoughts and actions. The clinical outcome might be an anxiety disorder, depression, intermittent explosive disorder, or obsessive–compulsive disorder. Characteristic of these disorders is that the behaviors have been chronic and pervasive in history and that there is often a familial history of similar problems.

It is true that individuals who struggle in school or who are hyperactive, inattentive, and impulsive might be anxious, depressed, or have difficulty with anger. However, if these behaviors are secondary to the frustration and failure associated with the learning disorders, the clinical history shows that the behaviors started at a certain time (perhaps starting school after a summer break) and only occur during certain times (in class, homework time).

Comorbidity studies suggest that this pattern of disorders is frequently found together. Thus, if the individual has any one of the disorders noted, there is a higher than would be expected possibility that he or she will also have one or more of the other disorders. Thus, it is likely that a child or adolescent with a learning disability will also have ADHD; he or she may also have an anxiety disorder and/or clinical depression and/or an anger-control problem, and/or obsessive–compulsive disorder. Equally true, he or she might have a tic disorder or bipolar disorder. An excellent review of these patterns of comorbidity can be found in Brown (2000).

### What About the Disruptive Behavioral Disorders?

It is not uncommon for children and adolescents with learning disorders or a motor skills disorder to have psychiatric disorders other than those discussed above. These are the Disruptive Behavioral Disorders, Oppositional Defiant Disorder (discussed in Chapter 44) and Conduct Disorder (discussed in Chapter 44).

Both of these disorders are reflective of the coping mechanisms children and adolescents might use to handle stress. All too often, the unrecognized and unaddressed stresses relate to lack of school and social success resulting from learning disabilities and/or motor disabilities.

Studies of youths diagnosed as having a conduct disorder or young adults diagnosed as having a personality disorder, especially the borderline type, show that about one-third have unrecognized or recognized and poorly treated learning disabilities (Forness 1981, Hunt and Cohen 1984). Similar findings have been observed with adolescent boys in detention centers (Berman and Siegal 1976, Keilitz et al. 1979, Lewis et al. 1979, Mauser 1974, Robbins et al. 1983).

Treatment approaches must be designed to address both the emotional and behavioral problems and the underlying causes for the life stresses, the learning disabilities, or motor skills disorder. Efforts to treat the presenting emotional or psychological difficulties without efforts to treat the underlying academic problems do not usually succeed.

## Social Problems

The learning disabilities that result in learning disorders or motor skills disorder may directly contribute to peer problems by interfering with success in doing activities required to interact with certain age groups. Examples are visual perception and visual–motor problems that interfere with the ability to quickly do such eye–hand skills as catching, hitting, or throwing a ball and fine motor problems that interfere with the ability to tie shoes or properly control eating utensils.

Successful peer interactions are essential to social success. If the learning disabilities or motor skills disorder prevents the individual from being successful in a sport or to do the required tasks for a club or activity, he or she will have social problems. Individuals with a language disability may have a problem with small talk or with quickly processing and responding to conversations (Silver 2006).

Recent research has clarified what are now called pragmatic social skill difficulties. These children have what is believed to be a neurological basis that involves a dysfunction in the brain's right hemisphere. These children have difficulty understanding the subtle visual or auditory cues that are essential in nonverbal communication (Hazel and Schumaker 1988, Rourke 1987, 1988, Rourke and Fuerst 1991). They lack the ability to read social cues that most know intuitively.

These nonverbal communications that are so essential for social interactions might include visual or auditory inputs.

### Visual Perceptions

- Facial expressions: Facial movements and poses communicate emotion. Effective eye contact and the appropriate interpretation of facial expressions (happy, anger, frustration …) are essential.
- Postures and gestures: Postures refers to the positions of the entire body that convey messages that might conflict with spoken words, confusing communication efforts. Gestures involve parts of the body, such as hand and arm movements that communicate meaning.
- Interpersonal space and touch: People have a personal comfort space around them. If a child stands too close to others while talking, that child is violating the rules of personal space. A child who touches others

inappropriately, either in terms of the location or the intensity of the contact (e.g., hugging), breaks one of the unwritten laws of touch and might cause anger or rejection. There are cultural differences that determine how comfortable each person is with space and touch.

### Auditory Perception

- Paralanguage: Those aspects of sound that communicate emotion and are used either independently or with words; for example, whistling or humming or the tone, intensity, and loudness of voice.
- Rhythm and time: Rhythm includes speech patterns, attitudes, and speed of movement or speech. Time refers to the speed of speech. Problems arise when the child is out of sync with others.

Children and adolescents with pragmatic social skill problems have difficulty correctly reading the other individual. They often have equal difficulty understanding how others might read their nonverbal cues. The facial expression and body stance suggest that the child is angry. The other person asks, "Why are you angry?" The child responds, "I'm not angry."

Children and adolescents with these pragmatic social skill problems have difficulty with relationships. Without knowing why, they seem to annoy peers and adults. Without understanding, they do not understand what they are doing and have little idea how to change. For most, pointing out what they do is not successful. They need to be taught these pragmatic skills and then shown how to use them.

## Differences in Developmental, Gender, and Cultural Presentations

Earlier studies often noted an increased prevalence of learning disabilities in boys. The ratio ranged from 3:1 to 5:1 and higher (Ackerman et al. 1983, Rutter et al. 1970, 1976). Some studies suggested that this increased prevalence in boys may, in part, be explained by referral bias. Because they are more likely to exhibit more physical aggression and loss of control, boys are more likely to be referred for study (Berry et al. 1985). Girls tend to be more verbal and display less physical aggression. Girls with learning disabilities tend to have more cognitive, language, and social problems and to have significant academic difficulties (Lyon 1997, Shaywitz et al. 1995, Vogel 1990). In the Shaywitz studies (Shaywitz et al. 1990), all children in a specific grade were evaluated for a possible learning disability. These data were compared to the students who had been identified by their school system as having a learning disability. The school-identified population showed a 3:1 ratio of boys to girls. The Shaywitz data, based on assessing all children, showed a ration of 1:1. Johnson and Blalock (1987) also found no specific cognitive differences or patterns of problems between the sexes.

## Etiology

### Cognitive and Language Studies

The specific constructs for understanding the probable cognitive and language bases for the specific learning disorders and motor skills disorder are discussed under each subtype in the section on treatment. The premise is that there are neurologically based processing problems that result in the disabilities.

### Neurological Studies

Earlier research focused on the concept of brain damage (Knobloch and Pasamanick 1959, Towbin 1971). Subtle central nervous system damage may result from circulatory, toxic, metabolic, or other forms of insult to the fetal nervous system during a critical period of prenatal development, perinatal stress to the brain, or stress to the nervous system during a critical period of prenatal development, prenatal stresses to the brain, or stress to the nervous system during the critical early ears of life (e.g., trauma, fever, inflammation). There may be a spectrum of disorders caused by prenatal, perinatal, and postnatal brain damage. Depending on location, extent of damage, time of life, and developmental stage at the time of damage, the stress might cause fetal or neonatal death, cerebral palsy, epilepsy, or mental retardation. The less severe forms might produce a variety of learning disorders.

More of the later research focused on physiological changes rather than on structural changes, that is, on the types of impacts that might affect the developing nervous system, causing areas of the brain to "wire itself" differently than expected. Galaburda et al. (1985), doing microscopic studies of brains of individuals known to have learning disabilities, showed a consistent pattern of cortical cells that maintained an earlier developmental stage of migration and development, suggesting that something had an impact on the brain during development, halting or slowing down the normal developmental stages. Some of the factors studied as possibly contributing to the stress that results in neurological dysfunction are maternal cigarette smoking during pregnancy, use of alcohol or drugs during pregnancy, convulsions during pregnancy, low fetal heart rate during the second stage of labor, lower placental weight, breech presentations, and chorionitis.

Research has also focused on the genetic basis for these disorders. Several studies have shown a familial pattern in approximately 40–50% of children with learning disabilities (Cantwell 1975, Morrison and Stewart 1971, Silver 1971). In longitudinal studies of twins, identical pairs are more likely than fraternal pairs to be concordant for academic difficulties (McCarty and McCarty 1969). Recent findings suggest a possible connection between environmental toxins and the increased incidence of developmental, learning, and behavioral problems (PSR 2000). The National Academy of Science released two studies (NAS 2000a, 2000b) on general developmental and specific neurologic toxins. U.S. companies reported to the Environmental Protection Agency that in 1998 they released a total of 1.2 billion pounds of chemicals into the nation's air and water that have the potential to affect the way a child's body and brain develop. More than half (53%) of these are known or suspected to be developmental or neurologic toxins. There is great concern about the impact of these environmental toxins on the increased incidence of developmental, learning, and behavioral problems.

Research in reading disorders shows an inability to segment the written word into the underlying phonologic components (Shaywitz 1996, Talial 1985). This deficit in

phonological awareness impairs decoding, preventing word identification. This basic deficit in what is essentially a lower-order linguistic function blocks access to higher order linguistic processes and impairs the child's ability to gain meaning from text. Thus, the child has difficulty with reading fluency and with text comprehension. It is not uncommon to find a spelling disability associated with a reading disorder because spelling requires the same phonologic skills as reading.

Studies of the brain using functional magnetic resonance imaging clearly shows a difference in brain function between individuals who have no reading problems and those with a reading disorder (Shaywitz et al. 1998). Brain activation patterns differ significantly between groups of individuals with a reading disability and those without, showing relative underactivation in posterior regions (Wernicke's area, the angular gyrus, and striate cortex) and related overactivation in an anterior region (inferior frontal gyrus). These results are seen as confirming that the impairment in reading disorders is phonologic in nature and these brain activation patterns may provide neural proof for this impairment.

Research in disorders of written expression focus on the need for immediate and automatic carrying out of most of the lower level mental activities required for skilled writing. These lower level mental activities guide handwriting, spelling, word choice, and the construction of sentences that conform to the conventions of written language. Lower-level mental activities also guide the construction of textural connections, specifically, spacing and punctuation. The writer's attention can then focus on the content, organization, and clarity of the task. One can shift attention between levels of mental processing without losing control of the flow of the text. Difficulties with lower-level mental activities appear to be the source of the problem in expressive writing disorders (Torgeson 1982).

Research on mathematics achievement suggests that there may be four primary factors involved: language, conceptual, visual–spatial, and memory (Bryan and Pearl 1979). In addition, knowing how to use the correct strategy is important (NAS 2000a). Proficiency in mathematics requires more than computational skills. The difficulty might be in an inability to develop a systematic plan for problems solving. Memory is also essential to the ability to do mathematics. One must retain basic number facts. In addition, it is necessary to remember specific equations or other steps necessary to solve a problem. Once a problem is started, students must remember where they are in the process as they proceed from step to step.

## Treatment

Treatment is directed at the underlying disabilities by use of educational interventions. Psychological interventions are also directed at any existing emotional, social, or family difficulties.

### Educational Interventions

The goal of general and special education interventions is to help children and adolescents overcome or compensate for their learning disorders or motor skills disorder so that they can succeed in school.

These efforts involve remedial and compensatory interventions and use a multisensory approach that facilitates building on all areas of strength while compensating for any areas of weakness. These efforts are to be provided in as close to a general education classroom setting as possible. It is essential that the classroom teacher knows how to adapt the classroom, curriculum, and teaching style to best accommodate each student's areas of difficulty.

#### Educational Interventions for Reading Disorders

Longitudinal research indicates that children with reading disabilities who struggle with the early stages of reading, particularly the development of phonological awareness and decoding, are faced each year with increasing obstacles to literacy development (Adams and Bruck 1995, Torgeson and Burgess 1994). Because they cannot pronounce words and read fluently, they struggle to comprehend and gain conceptual knowledge (Beck and Juel 1995, Shaywitz et al. 1995). Reading problems become a threat to children's entire education and future (Hall and Moats 1999, Juel 1988). Approximately 40% of students with learning disabilities drop out of school (Lichtenstein and Blackorby 1995, Malian and Love 1998).

The process of reading involves two tasks, decoding or word recognition and reading comprehension. Only after these two steps can someone store and retain the information (reading fluency). Decoding refers to the act of transcribing a printed word into speech. Comprehension refers to the process of interpreting the message or meaning of the text. Decoding is unique to reading and is different from the recognition of words in speech; however, the linguistic skills that subserve reading comprehension are the same for both reading and listening (Gough and Tunmer 1986).

Most students with a reading disorder have difficulty acquiring the knowledge and skills essential for rapid automatic decoding. Reading comprehension, thus, is limited by weak decoding skills. Because spelling uses the same knowledge as word recognition, it is also frequently impaired.

Direct instruction in reading is considered the essential treatment for a student with a reading disorder. These efforts are provided by a person trained to use appropriate remedial methods. These methods emphasize explicit instruction in letter–sound associations. This instruction is described as a multisensory approach. For example, children see a letter and hear its name and sound; they trace the letter, saying its name and sound; and then they write the letter, repeating its name and sound.

Sounds and letters are blended to form words. Reading, spelling, and writing are often taught simultaneously. Instruction involves extended practice and is supplemented by speech segmentation training and study skills instructions. Parents are asked to read to the children to enhance appreciation of reading and to give the children access to knowledge normally obtained by reading.

Once reading decoding becomes automatic, the focus shifts to reading comprehension and to retaining the information obtained from the reading. Each step must be addressed and techniques provided to help the student master each step.

Reading disorders are not "cured." With appropriate interventions, children and adolescents with reading disorders learn to read and spell at a slower rate than normally developing individuals do. It is essential for these students to learn compensatory skills and for the classroom teacher to provide essential accommodations.

## Educational Interventions for Mathematics Disorders

Children and adolescents with a mathematics disorder may have a wide range of symptoms, including delays in the acquisition of basic spatial and number concepts, problems learning and using number words and number facts or writing numbers correctly and in correct alignment when doing computations and difficulty in applying arithmetic skills when solving everyday problems (Fleischner and Garnett 1993, Kose 1992). Because mathematics achievement is highly dependent on the quality of instruction offered students, it may be that a significant number of those students who are found to have a mathematics disorder in fact do not have an intrinsic mathematics disorder, but rather have not had appropriate instruction (Carnine 1991).

The understanding of the reasons for difficulty mastering mathematics is less advanced than the understanding for reading disorders. Studies clarify predictable stages through which children progress when they are learning to do arithmetic calculations (Ginsburg 1992). Initially, the child learns informal knowledge about numbers, based on experience and strategies that develop without instruction. Relying on this informal knowledge, children devise counting procedures for solving quantitative problems. Problems often arise when children are introduced to the formal knowledge about mathematics that is presented in school. This formal knowledge depends on understanding and the correct application of complex algorithms that are not intuitively clear to the child. Problems may arise when children are asked early in their school years to memorize number facts. Children with delays in the development of information-processing strategies that are fundamental to memory may soon fall behind.

Treatment for a mathematics disorder involves general concerns and specific interventions. Initially, the problem of anxiety, withdrawal, defeatism, or other responses to repeated failure must be addressed (Torgeson 1982). Much of the teaching of mathematics is based on criticism of failure. The emphasis is on getting the right answer rather than on problems solving. Because of this overfocus on getting the right answer, children may have performance anxiety or feel that they are stupid in mathematics. For some, the premature pressure for speeded answers can short-circuit reasoning and foster impulsivity, resulting in the belief that mathematics has little to do with thinking. Students who have difficulty with mathematics memory may be deprived of compensatory techniques, which only adds to the problem. They are told that it is shameful to use their fingers or to mark down intermediate calculations or to use a calculator. These techniques are considered equivalent to cheating.

Sometimes, the difficulties in middle school or high school mathematics reflect poor teaching in the earlier grades. Further, mathematics learning is instruction-bound. Absenteeism, missed lessons, and inconsistency of instruction can leave gaps that result in persistent confusion. Students with learning disabilities in the areas that result in deficits in short-term memory, language, attention, or spatial perception and students with ADHD are especially susceptible to weak instruction. Appropriately focused and systematic instruction in improving mathematics abilities may be all that is needed for this student.

Specific interventions focus on the underlying difficulties. Some students have problems related to acquiring the conceptual underpinnings of the subject; some have problems related to procedural learning, recall of discrete information, and self-monitoring. Remedial efforts must take into account the student's areas of learning abilities and learning disabilities.

## Educational Interventions for Disorders of Written Expression

Traditionally, little emphasis has been placed on writing in the early school grades. Much more time is spent on reading instruction. This approach is justified by the observation that receptive language skills in infants emerge before spoken words. Because infants can understand before they can speak, it has been assumed that school-age children should read before they write. Until reading skills are well established, writing is usually assigned a minor role with regard to instruction. Both reading and writing require the ability to attach the correct sounds (phonemes) to the correct symbols (graphemes). Reading requires the ability to decode letters into sounds and to blend these sounds into words. Writing requires outflow of the language or sounds in the brain back into graphic symbols. Thus, reading and writing problems are frequently seen together.

It is helpful to distinguish between a fine motor problem that results in difficulty with the mechanics of writing, a graphomotor problem, and a language-based learning disability that results in problems with the language of writing. Individuals with a disorder of written expression might have a fine motor problem but always have a language-based disorder, resulting in difficulty with spelling, grammar, punctuation, capitalization, or composition.

Poor spelling might be the first indicator of a writing disorder. By third or fourth grade, additional writing problems are apparent. Children with a writing disorder exhibit grammatical and punctuation errors at the sentence level. Paragraphs are poorly organized. In later grades, the ability to get thoughts onto the page in an organized way may be seen. In later grades, the speed of processing information may result in difficulty taking notes.

Treatment for a writing disorder might involve a skills approach or a holistic approach. Skills programs are often used with younger children and focus on letter–sound associations, with emphasis on reading and spelling (Cox 1984, Slingerland 1971). Children may be asked to listen carefully for the sounds in words and then to represent these sounds with written letters, saying each letter aloud as it is written.

The holistic approach to writing begins with the student's ideas. It involves a series of highly structured steps for narrowing ideas to one topic, writing a first draft, reading it aloud to an audience of peers, and then refining organization and language. The final step involves working on mechanics in preparing for "publishing" a draft for peers to read.

Most efforts combine these two approaches. Children with a writing disorder need direct, sequential instructions in letter–sound associations and in spelling rules as well as in sentence structure and the connections between sentences and paragraphs that make text cohesive. Even with good remedial interventions, writing requires enormous effort because this disorder is not curable and must be compensated for, and this compensation must continue into adulthood. Appropriate accommodations, such as using a computer, may be needed throughout the individual's education and career.

### Educational Interventions for Developmental Coordination Disorders

The approaches for helping children and adolescents with this disorder focus on academic skills, life skills, and athletic skills. That is, the focus of intervention might be on specific skills needed for school (e.g., handwriting), on dressing and other life skills (e.g., buttoning, zipping, tying, eating), or on skills needed to do better in sports (e.g., catching, hitting, throwing, running).

Occupational therapists work in all of these areas using sensory integrative approaches involving visual, visual–motor, gross motor, fine motor, proprioceptive, and vestibular stimulation and, when possible, strengthening to improve functioning. Within school systems, the special education professional may work on handwriting and the adaptive physical education teacher may work on sports-related activities.

## Psychotherapeutic Interventions

Learning disorders affect all aspects of the child's or adolescent's life. The same processing problems that interfere with reading, writing, mathematics, language, and motor skills may interfere with communicating with peers and family, with success in sports and activities, and with such daily life skills as dressing oneself or cutting food (Silver 2006).

Lack of success in school can lead to a poor self-image and low self-esteem (Black 1974, Bryan and Pearl 1979, Rogers and Saklofske 1985, Shaw and Levine 1982). These individuals might feel that they have minimal control over their life and compensate by trying to be in more control. Some individuals may become anxious or depressed, or may develop a disruptive behavior disorder.

Genetic and family studies show that in about 40% of children and adolescents with learning disorders, there is a familial pattern (discussed earlier). Thus, from an early identification perspective, each sibling must be considered as possibly having a learning disorder. Also, there is a 40% likelihood that one of the parents may also have a learning disorder. This parent may not have known of this problem. If this is true, for the first time the parent may be able to understand a lifetime of difficulties or underachievement. Further, when the psychiatrist offers suggestions for the parent, the parent's areas of difficulty must be considered. The psychiatrist should not ask a mother to be more organized when she has been just as disorganized as her child all of her life.

Some children or adolescents may need specific individual, behavioral, group, or family therapy. If so, it is critical that the therapist understand the impact that the learning disorder has had on the individual and how these disabilities might affect the process of therapy. Students with social skills difficulty, especially those with pragmatic social skill disorders will benefit from group social skills training.

### Education of the Individual and Family

Once the diagnosis is established, it is critical for the psychiatrist to explain to the individual and to the parents what the problems are, focusing not only on the areas of difficulty but also on the areas of strengths. The data from formal testing is important in knowing what to review with parents. If the report is too technical, the psychiatrist should discuss the findings with the person who did the test so that it is possible to explain the results to others.

Parents must understand this information so that they can develop a better understanding of their child or adolescent (Silver 2006). Mental health professionals working with these individuals must understand the concept of learning disabilities (learning disorders) and motor skills disorders well enough to teach the individual and family members what the areas of disabilities and abilities are, as well as the effects these disabilities have had on peer, family, and school activities.

The child or adolescent needs to begin to understand and to rethink concepts of self. Parents will have to modify their images of their son or daughter and modify their responses and behaviors. Siblings may gain a new understanding of the family problems.

If the presenting behavior problems are not serious, it may be best first to provide family education and to give some time to see how this knowledge affects the family. Concurrently, the parents are taught how to advocate for the necessary services within the school system. It may be that once the academic issues are addressed and the family begins to change, the behavior problems will diminish and no further help will be needed.

If needed, the next step is family counseling. Parents are taught how to use their knowledge of their son's or daughter's strengths and weaknesses to modify family patterns; select appropriate chores, choose appropriate activities, sports, and camps; and address stresses within the family (Silver 2006). Once they are taught the necessary knowledge about their child or adolescent and the concepts of intervention, families can often move ahead, creatively working out their own problems.

### Individual Therapy

For some children and adolescents, individual behavioral therapy or psychotherapy may be indicated to help them develop new strategies for interacting with peers, teachers, and parents. The models for this therapy are the same as for any other therapeutic approach. However, knowledge of these disorders and school history help both the therapist and the individual with the learning disorder better understand how certain problems or patterns of behaviors evolved. Because this form of therapy requires listening and talking, it is important for the therapist to know whether the individual has a language disability that might impact on their ability to communicate. If so, the therapist has to develop ways of accommodating these problems if therapy is to progress. If a speech and language therapist is working with the individual, she or he might offer suggestions.

### Family Therapy

The initial phases of family therapy might focus on helping the identified patient regain control over his or her behavior and helping the parents retake control of the family. A behavioral management approach is often the first intervention.

The model of family therapy used will depend on the needs of the family and the orientation of the therapist. It is important for the therapist to keep in mind the impact the disabilities has on the individual and the family. It is also important to keep in mind the impact these disabilities might have on this individual's ability to participate in the

family therapy. As with individual therapy, if the individual has difficulties with oral communication, he or she might have difficulty participating in the sessions. Accommodations will be needed.

### Social Skills Training

Children and adolescents with learning and/or motor disorders often have problems with peer relationships (Hazel and Schumaker 1998, Rourke 1988). There appears to be an association between poor peer relationships and a high risk for later psychological problems as well as dissatisfaction and loneliness (Asher and Wheeler 1985). Poor childhood social skills and peer acceptance have been related to adjustment problems in adulthood (Gresham and Elliott 1989, Wiener et al. 1990). Thus, it is important to address these problems early.

As noted earlier in this chapter, the social skills difficulties might be secondary to the learning and/or motor problems. Alternatively, they might be another reflection of a dysfunctional nervous system, pragmatic social skills problems. In both situations, social skills training is helpful.

Such interventions attempt to enhance social–cognitive skills and are directed at altering specific behavior patterns (Dodge 1989, McIntosh et al. 1991). Social–cognitive approaches are based on those cognitive processes that are related to competent, prosocial behavior. Targets of intervention are directed toward the underlying cognitive variables that are linked to positive peer acceptance.

In general, the enhancement of social–cognitive skills typically involves three kinds of skill development: (1) accurate interpretation of social situations; (2) effective use of social behaviors in interactions with others; and (3) the evaluation of one's own performance and the ability to make adjustments, depending on the environmental context. The first step typically requires the clinician to provide direct instructions concerning the relevant skills (e.g., reading body language, conversational skills). The skills taught are then modeled by the clinician, stressing the positive outcomes associated with these skills. In the process, the clinician will confront and restructure thoughts that may inhibit the desired behaviors. The child is then required to rehearse the skills within the group with the clinician providing reinforcement and corrective feedback. Generalization is stressed through homework assignments whereby skills are attempted in the natural environment and classroom (Dodge 1989, McIntosh et al. 1991).

### Use of Medications

No medication has been found to be effective for treating learning disorders or motor skills disorders. If the individual also has ADHD, it is important that medication be used to minimize the hyperactivity, inattention, and/or impulsivity so that the student can be available for learning.

## Summary

Research on the etiology as well as on the brain dysfunction involved with learning disorders and motor skills disorders have resulted in a better understanding of these neurologically based disorders. Scientifically based interventions now lead to better results within the educational setting.

It is critical for the clinician working with these children and adolescents to understand the impact these disabilities have on school, peer, and family life. To label the resulting behaviors and design a treatment plan based on these behaviors will not be successful. The disabilities and the impact of the disabilities must be addressed if any success is to be achieved.

Educational and academic success is critical to psychosocial growth and development as well as to the individual's role within the family, with peers, and when participating in activities or sports. It is critical for the clinician to recognize clinical evidence of these disorders and to make the proper referral to clarify the disorders. It is equally essential to collaborate with the educational and other professionals working with the child or adolescent.

Clinical Vignette 1

Billy started first grade and did not do well. He did not master the early skills of reading and writing. The school decided to have him repeat first grade. He struggled through this year but fell further and further behind. When he entered third grade, he was overwhelmed. He knew that he was a year older than the other students. He was unable to do the work in class or at home and he felt frustrated and stupid. Soon, he began to clown around in class and to get into fights with the other students.

Two other things happened during this third-grade year. First, his teacher became frustrated. She was trying to help him learn and he was not making progress. He was disrupting the class and preventing her from teaching the other children. The teacher handled her frustration by blaming the parents. She called them, "Billy is not completing his schoolwork." "His homework is incorrect." "He is teasing and fighting with the other children." She seemed to be saying to the parents, "Do something. Fix your kid." She did not realize that the parents were just as confused and frustrated as the teacher. Second, the parents began to disagree on parenting decisions. One felt that the best way to help Billy was to be firm and strict and the other felt that the best way was to be understanding and permissive. They began to argue with each other and became less available to support each other.

Finally, the principal asked the parents to come to school. They were informed that Billy was not making academic progress. They were also told that the reason for his failure was that he was emotionally disturbed because of the apparent marital conflicts. The parents were encouraged to see a mental health professional.

The psychiatrist found clinical evidence suggesting that Billy had difficulty with reading, reading comprehension, handwriting, and written language. He found Billy to be frustrated with a poor self-image and low self-esteem. The parents seemed to be competent people who were also frustrated with Billy's difficulties. A full psychoeducational evaluation was requested. The results showed Billy to be of above-average ability but to have significant learning disabilities.

The psychiatrist concluded that the primary diagnosis was the learning disability. The emotional, behavioral, social, and family problems were secondary to the frustrations and failures experienced by Billy, his parents, and his teacher. By working with the family, he helped to get Billy identified as having a disability and to obtain the necessary services to help him succeed. His behavioral problems diminished and then ceased.

Clinical Vignette 2

Danny was referred at age 7 years because his teacher and his parents thought he was depressed. The following is part of the process notes of the first session. The child's comments are noted; the psychiatrist's comments are in parenthesis.

(Tell me about school.) I don't like to make mistakes. (Oh.) I get angry and frustrated. (What do you do?) Sometimes I feel like crying but I tough it out. (You can't cry?) The kids would think I was a baby. (What else do you feel?) I get angry with myself. I say I'm dumb or stupid or can't learn. (How do you feel when you say these things?) Bad. I'm just a jerk. (What do you do with these feelings?) I distract myself until they go away.

(Danny, why do you think you feel this way?) I don't know. (Could it have something to do with school?) I don't read or do math good. (And the other kids…?) They do it easier. (When you say that, you look upset.) Yea.

(What else happens in school?) I get scared sometimes that the teacher will be angry with me. (I see.) If she doesn't like my work she sends me back to do it again. I get mad because I did my best. (What do you do?) I distract myself and push it out of my mind. Then I do the work. (How do you push away such angry feelings?) I get busy with the work. (Don't you feel like yelling or throwing something, or …?) No, that would be bad.

(You know, Danny, I get the feeling that you don't like yourself too much.) There's nothing to like. (You mean you cannot think of anything about yourself that is good?) I guess I'm alive. (As I listen to you I begin to feel very sad. I wonder if you feel the same way.) Yea.

(How do your Mommy and Daddy feel?) They love me. (Oh?) I'm their child. (And that's the reason.) I guess. (You guess?) Well, sometimes I think that Mommy wanted a girl because they don't cause as much trouble as boys. But, they may want a boy to carry on the family name. (So, you may not like yourself and now I hear you say that maybe your parents don't like you either.) Sometimes I think that.

You know, Danny, I think the real problem is that you don't like yourself.) Yea. (And, you look so sad right now. How long have you had such feelings and thoughts?) I think they started in first grade. I couldn't do some of the work. The teacher used to make me do it again. The other kids got smiles from the teacher. I just got disappointed looks.

(What do you think was the problem in first grade?) I don't know. (You seemed to have trouble doing the school work.) Yea. (You know, I've worked with other boys and girls with problems like yours. Sometimes they worry that their problems are because they are bad and being punished or because there's something wrong with their head or maybe because they're stupid or retarded. I wonder what kind of thoughts you have.) I do think about these things. Maybe. Sometimes I think that maybe I'm retarded. (Retarded?) Yes. (That would be pretty upsetting to think that you were retarded.) Yea. (Maybe we had better find out what the problems are so that you won't have to worry about things that may not be true.) I'm just too dumb to learn anything. (I can see why you might think that way. Only, I bet you can learn. Only, maybe something is getting in the way. I'd like to find out what it is so that we can do something about it.) I can't do anything right.

Last year at the pool I hit my head a couple of times. (And, maybe that caused the problems?) Maybe that's why I'm so dumb. (I don't think that is the reason you are having trouble in school. But then, I guess it's hard for you to believe me.) There's no hope for me.

After this session, sessions with the parents, and conversations with Danny's teacher, a full psychoeducational evaluation was done. He was found to be bright but to have significant learning disabilities. He was depressed with a poor self-image and low self-esteem. However, these clinical problems were secondary to the unrecognized and untreated learning disabilities.

## Special Considerations in the Doctor–Patient Relationship

School is the life work of the child and adolescent. Thus, it is essential that psychiatrists be aware of learning and motor skills disorders. It is critical to differentiate between the child whose emotional, social, or family problems result in secondary academic and school problems and the child whose learning, language, or motor problems result in secondary emotional, social, or family problems. The interventions are very different for each.

Once a learning or motor skills disorder is identified, the psychiatrist must understand education law and policy in order to assist parents in getting the best placement and the fullest services for the child. If medication is needed in school, the psychiatrist must know the proper school procedures for directing how this is done.

If a child or adolescent with learning, language, or motor disabilities is seen in psychotherapy, group therapy, family therapy, or any other form of psychological intervention, it will be essential that the psychiatrist understand how these disabilities might present themselves in the session and how to accommodate to them.

## Comparison of DSM IV/ICD-10 Diagnostic Criteria

In ICD-10, the DSM-IV-TR reading disorder is referred to as "Specific Reading Disorder" and the DSM-IV-TR Mathematics Disorder as "Specific Disorder of Arithmetic Skills." For both of these learning skills disorders, the ICD-10 Diagnostic Criteria for Research suggest that the cutoff be two standard deviations below the expected level of reading achievement and mathematics achievement respectively. In contrast, DSM-IV-TR does not specify a score cutoff, instead recommending that the score be "substantially below that expected given the person's chronological age, measured intelligence, and age-appropriate education." Furthermore, in contrast to DSM-IV-TR which permits both to be diagnosed if present, ICD-10 Specific Reading Disorder takes precedence over Specific Disorder of Arithmetic Skills so that if criteria are met for both, only the reading disorder is diagnosed.

ICD-10 does not include a Disorder of Written Expression (as in DSM-IV-TR). Also, ICD-10 includes a Specific Spelling Disorder. DSM-IV-TR includes spelling problems as part of the definition of Disorder of Written Expression but requires writing problems in addition to spelling in order to warrant this diagnosis.

Finally, DSM-IV-TR Coordination Disorder is referred to in ICD-10 as "Specific Developmental Disorder of motor function." Furthermore, the ICD-10 Diagnostic Criteria for Research suggest that the cutoff be two standard deviations below the expected level on a standardized test of fine or gross motor coordination.

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CHAPTER

# 44 Childhood Disorders: Communication Disorders

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Expressive Language Disorder
Mixed Receptive–Expressive Language Disorder
Phonological Disorder
Stuttering
Communication Disorder Not Otherwise Specified

## Introduction

The disorders of communication have traditionally been insufficiently familiar to psychiatrists, despite the fact that psychiatric practice is founded upon communication. A knowledge of these disorders is of especially crucial importance in the care of children, since they are deeply interwoven in all aspects of normal development, psychopathology, and the functions of daily life.

The relationship among language, cognition, and their disturbances continue to stimulate a mass of research and speculation beyond the scope of this chapter (Friel-Patti 1992, Paul 2002). Thus, the classification of these disorders has always been controversial. Prior to the elaboration of DSM-III (American Psychiatric Association 1980) in the late 1970s, they were frequently regarded by psychiatrists as psychopathology manifested by a single symptom, as were elimination disorders, tics, and learning disorders. DSM-III represented an attempt to consolidate the approach of psychiatrists with that of other disciplines. It presented these disorders as specific developmental disorders grouped with academic skill disorders, resulting from the inadequate development of some specific language or speech skill. Deficits due to other demonstrable physical or neurological disorder were regarded as separate conditions. The linkage of language and academic skills or learning disorders, while plausible, has remained controversial, and in DSM-IV-TR (American Psychiatric Association 2000), they are regarded as separate although often associated conditions. This section includes both disorders of speech, the oral representation of language, and disorders of language itself. The disorders included in this section are expressive language disorder (ELD), mixed receptive–expressive language disorders (MRELD), phonological disorder (PD), stuttering, and communication disorder not otherwise specified (CDNOS). These disorders share many common features, as noted in Table 44–1 (common features). Selective mutism is not regarded as a disorder of communication per se, and is included among other disorders of childhood.

## Expressive and Mixed Expressive-Receptive Language Disorders

### Diagnosis

#### Definition and Diagnostic Features

ELD denotes an impairment in the development of expressive language. Its diagnosis requires the use of one or more standardized assessment measures that are individually administered. When appropriate instruments are unavailable, as for example, in the case of a member of a population for whom no instrument has been standardized, this diagnosis may be made through a thorough functional investigation of an individual's language ability. Individuals with this disorder have expressive language scores well below those obtained from measures of nonverbal intelligence and receptive language. DSM-IV-TR does not require any particular degree of discrepancy in scores.

The presence of a test score by itself does not define the condition: the affected individual must have clinical symptoms that might include disturbances of vocabulary, grammar (e.g., tenses), or syntax (e.g., sentence length or complexity). The diagnosis of this condition also requires that the individual having it experiences social, academic, or occupational difficulties directly related to the condition. The presence of an MRELD or a pervasive developmental disorder (PDD) supersedes this diagnosis, and it is not made in their presence. Similarly, it may not be made in the presence of mental retardation, motor or sensory deficits, or

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**Table 44–1 Features Common to All Communication Disorders**

| |
|---|
| Inadequate development of some aspect of communication |
| Absence (in developmental types) of any demonstrable causes of physical disorder, neurological disorder, global mental retardation, or severe environmental deprivation |
| Onset in childhood |
| Long duration |
| Clinical features resembling the functional levels of younger normal children |
| Impairments in adaptive functioning, especially in school |
| Tendency to occur in families |
| Predisposition toward boys |
| Multiple presumed etiological factors |
| Increased prevalence in younger age range |
| Diagnosis requiring a range of standardized techniques |
| Tendency toward certain specific associated problems, such as attention-deficit/hyperactivity disorder |
| Wide range of subtypes and severity |

*Source*: Reproduced from Baker (1990)

environmental observation, unless the expressive language difficulties experienced are beyond what would be expected for individuals with these conditions. This condition may be acquired, as from a medical condition affecting the central nervous system (CNS), or it may be developmental, in the sense of arising early in life without known origin.

The manifestations of this condition vary with age and severity. Vocabulary, word finding, sentence length, variety of expression, and grammatical complexity may all be reduced. Most children with this disorder demonstrate a slower than expected rate of language development, associated with the developmental subtype. Often auxiliary words or prepositions are omitted, resulting in a telegraphic sort of speech: "He was going to school" becomes "He going school." Word order of essential importance in English may be garbled: "Him like too me" for "I like him too." Words or phrases may be repeated to the degree that speech may be echolalic, perseverative, or both. Conversation may be tangential with sudden inappropriate changes of topic, or conversely, perseveration. Pragmatic difficulties, such as in initiating or terminating conversations, and much avoidance of conversation are also frequently seen. Because of these problems, these patients frequently are regarded as socially inappropriate or inept and at times may be suspected of having a formal thought disorder. These children frequently have associated learning problems because of their difficulty in responding verbally to exercises. They may have motor coordination problems and various other neurodevelopmental abnormalities documented upon neurological examination, EEG, or neuroimaging, although no consistent patterns are seen.

The adoption of the category MRELD in DSM-IV-TR represented the most significant change from previous classification systems, which posited the existence of receptive language disorders in a solitary form. The existence of this category reflects the clinical observation that receptive language disorders in children seldom, if ever, can occur without concurrent (and perhaps resultant) problems with expression. DSM-IV-TR notes that this is in direct contrast with such entities as Wernicke's aphasia in adults, which affects reception alone. Children with these conditions have significant

**DSM-IV-TR Criteria 315.31**

**Expressive Language Disorder**

A. The scores obtained from standardized individually administered measures of expressive language development are substantially below those obtained from standardized measures of both nonverbal intellectual capacity and receptive language development. The disturbance may be manifest clinically by symptoms that include having a markedly limited vocabulary, making errors in tense, or having difficulty recalling words or producing sentences with developmentally appropriate length or complexity.

B. The difficulties with expressive language interfere with academic or occupational achievement or with social communication.

C. Criteria are not met for mixed receptive–expressive language disorder or a pervasive developmental disorder.

D. If mental retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the language difficulties are in excess of those usually associated with these problems.

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**DSM-IV-TR Criteria 315.31**

**Mixed Receptive–Expressive Language Disorder**

A. The scores obtained from a battery of standardized individually administered measures of both receptive and expressive language development are substantially below those obtained from standardized measures of both nonverbal intellectual capacity. Symptoms include those for expressive language disorder as well as difficulty understanding words, sentences, or specific types of words, such as spatial terms.

B. The difficulties with receptive and expressive language significantly interfere with academic or occupational achievement or with social communication.

C. Criteria are not met for a pervasive developmental disorder.

D. If mental retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the language difficulties are in excess of those usually associated with these problems.

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measurable deficits in standardized individual assessments, of both receptive and expressive language, compared to their similarly assessed nonverbal intelligence. These deficiencies may occur in both verbal and sign languages; may interfere with social, academic, and occupational function; and, by definition in DSM-IV-TR, do not occur in the presence of a PDD. This condition may be acquired from some CNS injury or may be purely developmental. In the latter case, affected individuals exhibit a persistent pattern of delayed language development, in which speech develops late and advances slowly. Children with this disorder may manifest any and all of the symptoms of ELD. They also have difficulty with various aspects of receptive language, including misunderstanding of individual words or whole statements and deficits in auditory processing skills (sound discrimination and association, recall, storage, and sequencing).

Children with MRELD may have all the problems of ELD. In addition, they do not understand all that they hear. The deficits may be mild or severe, and at times deceptively subtle, since patients may conceal them or avoid interaction. All areas and levels of language comprehension may be disturbed. Thus, the child may not understand speech that is rapid, certain words or categories of words such as abstract quantities, or types of statements such as conditional clauses. This may cause these children to seem not to hear or attend, or to misbehave by not following commands correctly. At times, when conversation is redirected to them in a slower or more concise fashion, they may understand and respond belatedly and thereby be accused of willful avoidance. More severely impaired children may not understand the rules of syntax or word order and thus may be unable to distinguish between subjects and objects or questions and declarations. Often, in more severe cases, disabilities may be multiple and pervasive, affecting processing, recall, and association. Children with these disorders may fail to understand pragmatic or social conventions of language. For example, they may fail to comprehend the verbal and nonverbal signals that accompany a change of topic or the end of a conversation. Such deficits have immense social consequences. They may even cause the child to be misidentified as having a PDD. A very severe acquired language disorder is seen in Landau–Kleffner syndrome (acquired epileptic aphasia), accompanied by seizures and other CNS dysfunctions, and usually occurring between the ages of 3 and 9 years.

## Assessment

### *In the Psychiatric Interview*

It is essential that the psychiatrist seeing children is familiar with the expected milestones of speech and language development (see in section B of diagnostic decision tree [Figure 44–1]). This knowledge forms the basis for effective observation in a clinical setting. The clinician should ask the parents or guardians about the child's speech and language, both in terms of development and in terms of current function. Paul (1982, 2002) and Gulley (2005) provide detailed outlines for this, but much can be learned from even a few questions: Does the child seem to hear and understand what is being said? Does the child require visual prompts? Does the child in fact use spoken language to communicate? How long and complicated are his sentences? Does the child "make sense" to outsiders? Can he/she be clearly understood even by strangers? Which sounds does the child find difficult? Does the child use unusual volume, pitch, or nasality? Does he/she observe the rules of conversation? Parent–child communication should also be observed.

Children must be assessed in an environment that fosters verbal communication and observed in a variety of interactions because their speech and language vary so much over time in quantity and quality. For younger children, this may best be done in the context of a play situation. Rutter (1987) recommends that the clinician assesses *inner language*, comprehension, production, phonation, and pragmatics. "Inner language" means symbolization, which may be observed in a younger child by the child's representational use of play materials. For example, a block could be a house or a vehicle. "Comprehension" is assessed through conversation and the use of developmentally appropriate questions and commands, especially with nonverbal augments or prompts. The clinician should note how well a child can follow and draw inferences from a conversation. "Production" refers to speech, its fluency, and intelligibility. "Phonation" refers to the utterance of vocal sounds produced by the larynx. "Pragmatics" are those aspects of language that render it useful for social communication beyond the most concrete level. Does the child appreciate the nuances of his/her partner's conversation, as for example when they signal beginnings and endings of conversations, topic changes, or the patient's turn to talk?

Pragmatic language involves nonverbal elements. Deficiencies in this area impair abstraction and may render the individual almost "robot like." In all cases, observations should be made in as relaxed a fashion as possible, avoiding interrogation or rote exercises. If a child fails to communicate a given item, necessary help including nonverbal prompts should be offered, so that the child has the experience of success. A sense of failure will stifle communication.

### *In the Classroom*

In school settings, all of the phenomena seen in a clinical interview may also be pursued. Children with communication disorders often feel challenged by the demands of the classroom and may limit or withdraw from conversation entirely. Thus, the task-oriented group setting of the classroom may not elicit a child's best communication. It may, however, demonstrate the practical effectiveness of the child's everyday efforts. At the same time, teachers sometimes have more individual conversations with children than even their parents do, and their experiences may make them the first adults to detect communication problems. In many areas, young children receive some type of formal communication screening in school. Therefore, teacher input is essential in the evaluation of these children.

## By the Speech and Language Pathologist

A number of instruments are available for the assessment of communication. Some of these are listed in Table 44–2. Most are beyond the training of physicians whose most important contributions are interview skills and medical assessment, but a familiarity with them can help the physician develop a repertoire and knowledge of screening measures. Because of the complex comorbidity of these disorders, they are often best assessed by an interdisciplinary team (McKirdy 1985, Bagnato and Neisworth 1991, Klykylo

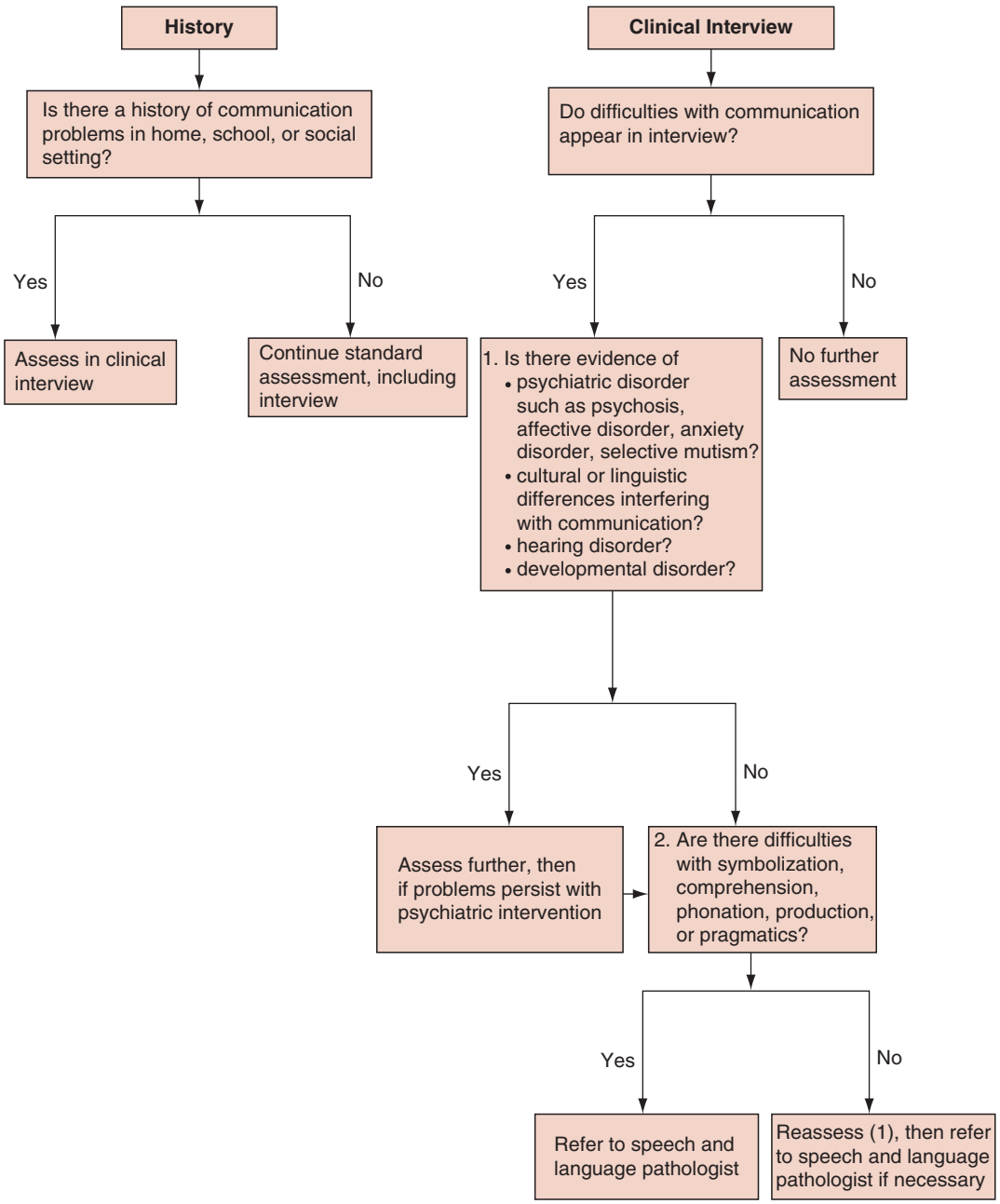



**Figure 44–1** *Diagnostic decision tree.*

2005). The team's activities are usually coordinated by a case manager, who often is a pediatrician or a child and adolescent psychiatrist, and who usually has primary clinical responsibility in the case. The audiologist is an essential contributor to this process, since, in the first place, one must rule out a hearing disorder in any communication disorder. Children of any age, even infants, can be assessed audiologically. Psychological assessment is necessary to delineate the child's cognitive abilities and may also cast light on the child's emotional state through projective testing. Medical specialists including pediatric neurologists and otorhinolaryngologists, as well as child and adolescent psychiatrists, should be appropriately involved. The educational specialist or liaison special educator has particular competence in developing an education prescription for the child, in assisting the family in the procedural (and at times legal) efforts required to arrange appropriate educational services, and in helping classroom teachers to develop effective pedagogic approaches.

## Epidemiology

Past reports of prevalence and incidence of communication disorders have been complicated by variations in setting, case finding, and diagnostic criteria. Numbers from 1% to 13% have been posited for the prevalence of language disorders and numbers as high as 32% for speech disorders (Baker 1990, Weindrich et al. 2000). Acquired language disorders are reported to be less common than the developmental types. Overall, between 3% and 7% of all children were suspected of having a developmental ELD. MRELD is less common but may still be seen in as many as 3% of school-age children.

**Table 44–2 Language Tests**

| Tests | Ages | Functions Assessed |
|---|---|---|
| **Language tests** | | |
| Sequenced inventory of communication development (SICD) | 0–4–4–0 | Sound discrimination, auditory memory, and receptive and expressive language |
| Test of early language development (TELD) | 3–0–7–11 | Receptive and expressive language; oral and pointing responses |
| Test of language development (TOLD) | 4–0–9–0 | Auditory discrimination and memory, receptive and expressive language, and oral and pointing responses |
| Test of adolescent language (TOAL) | 11–0–17–5 | Receptive and expressive language; oral and written responses |
| Clinical evaluation of language function (CELF) | 5–0–17–0 | Screening test for auditory memory, receptive and expressive language, and oral responses |
| Fluharty preschool speech and language screening test | 2–0–6–0 | Screening test for articulation and language disorder |
| **Tests of specific functions** | | |
| Peabody picture vocabulary test (PPVT) | 1–9–18–0 | Receptive auditory vocabulary; pointing to pictures |
| Token test | 3–0–12–0 | Receptive auditory syntax; following verbal instructions |
| Goldman–Fristoe–Woodcock auditory selective attention test | 3–0–12–0 | Auditory memory; pointing to pictures |
| Goldman–Fristoe–Woodcock test of auditory discrimination | 3–0–adult | Auditory discrimination of words; pointing to pictures |
| Expressive one-word vocabulary test (EOWVT) | 3–0–12–0 | Expressive vocabulary; picture naming |
| Arizona Articulation Proficiency Scale | 3–0–11–0 | Speech articulation; picture naming |

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## Comorbidity

PD is especially common among children with these disorders. In addition, many of these children may present at least some manifestations of learning disorders. Other conditions that are broadly considered as neurodevelopmental are also noted in these children, such as motor delays, coordination disorders, and enuresis. The extent of these associations, while apparently considerable, is difficult to quantify because of methodologic variations in the literature. The combination of these disorders and the stresses they create frequently lead to adjustment disorders and social withdrawal.

Among children with a psychiatric diagnosis made first, there is a remarkably increased likelihood of speech and language disorders, which often go undetected (Cohen et al. 1993). Typical are the studies of Beitchman (1985) who found more than four times the prevalence of psychiatric illness in kindergartners with communication disorders compared to nondisordered children. Some studies also suggest that psychiatric illness is associated with greater severity of communication problems. For example, in Cantwell and Baker (1991), in a population of 302 children with a psychiatric diagnosis as well as a speech and language disorder, the subjects were more likely to have multiple or more severe language disorders than speech- and language-disordered children who were psychiatrically well. Unfortunately, language disorders too often are unsuspected by parents and professionals alike.

Cantwell and Baker (1991), in their seminal work, found that the most common psychiatric disorder among children with communication disorders overall was attention-deficit/hyperactivity disorder (ADHD), representing 19% of their sample of 600 children referred for a communication evaluation. The combination of language and disruptive behavior disorders appears to be associated with greater severity of impairment in both disorders. Some authors have speculated that ADHD may be concordant with a putative entity known as central auditory processing disorder (CAPD), which refers to deficits in the processing of audible signals and which can be subsumed under the DSM-IV-TR language disorders. A total concordance is unlikely, but Riccio and associates (1994) suggest that 50% of children with CAPD also have ADHD. Ongoing work in neuroimaging and brain activity measurement may be expected to delineate this area more fully.

## Course

Contrary to some popular beliefs, language disorders do not always spontaneously resolve, nor do children always "grow out of it." In general, the course of these disorders is lengthy, and the more severe disorders are usually more persistent. Language disorders of the developmental type are generally recognized gradually as children grow up; the less severe cases are identified later in childhood or adolescence. Language disorders acquired secondary to other medical illnesses tend to occur more precipitously and can appear at any age. In the case of ELD, DSM-IV-TR reports that most children with this condition acquire more or less normal language abilities by late adolescence but that subtle deficits may persist. The prognosis is worse in the case of MRELD, and only a minority of these children are free from some communication problems in adulthood. Even when their communication skills seem grossly normal, subtle deficits may persist, and they may go on to manifest learning disorders. The prognosis for individuals with

acquired language disorders must be assessed according to the severity of injury or medical illness, as well as the premorbid state of the child, in each case.

### Differential Diagnosis

ELD and MRELD are distinguished from each other by the presence or absence of receptive problems. Children with autism may have any or all of the characteristics of the language disorders. However, they have many additional problems including the use of language in a restricted and often stereotypic fashion rather than for communicative purposes. They also have difficulties with a wider range of interactions with persons and objects in their environment and exhibit a restricted range of behaviors. The language impairments of mental retardation, oral-motor deficits, or environmental deprivation are not diagnosed in this category, unless they are well in excess of what is expected. Language impairment due to environmental deprivation tends to improve dramatically with environmental improvement. Sensory deficits, especially hearing impairment, may restrict language development. Any indication of potential hearing impairment, no matter how tenuous, should prompt a referral for an audiologic evaluation. Obviously, hearing and language disorders can and do coexist. Some children develop an acquired aphasia as a complication of general medical illness. This condition is usually temporary; only if it persists beyond the acute course of the medical illness is a language disorder diagnosed.

### Differences in Developmental, Gender, and Cultural Presentation

All communication disorders have a male-to-female predominance. In all, the prevalence of these disturbances is comparable in magnitude to many other common psychiatric disorders of childhood.

It is imperative that clinicians recognize the range of cultural and linguistic backgrounds that inform children today. The predictable variations of accent, grammar, syntax, and vocabulary that children will exhibit must not be misidentified as signs of a language disorder. In addition, children may live in multilingual environments, and their fluency in different languages must be considered.

## Etiology and Pathophysiology

### Genetic Factors

Many clinicians believe that communication disorders tend to "run in families," but the extent to which this is true is unclear. No clear mechanisms of transmission have been elucidated, but a number of instances of family aggregation have been reported. At least one of these (Gopnik and Crago 1991) suggested the presence of a single dominant-autosomal gene. Tomblin (1989) reported increased concordance of language disorders among siblings. An increasing number of family studies now suggest that these disorders are familial. Prominent among these is the twin's early development study (TEDS) in the UK (Plomin and Dale 2000). These reports cannot absolutely prove any genetic hypothesis; however, they are provocative and suggestive of a polygenetic basis. Marcus and Rabagliati (2006) have provided a thoughtful perspective on the possible contribution of "generalist" versus "modular," that is, language-specific genes to these disorders. Plomin (2001) in an authoritative review suggests that the application of a quantitative trait loci (QTL) model may elucidate the variable pattern of transmission and presentation of these disorders. This area of inquiry is complicated not only by methodologic issues, but also by larger controversies over the degree to which specific features of language, such as grammar, arise from a "preprogrammed" genetic base. The recent work of Baker (2001) influenced by the model of Chomsky (1988) suggests that grammar in all language may be a product of an innate and limited series of "hard-wired" options.

### Neurobiological Factors

Baker (1990) and others propose that communication disorders arise from at least three interrelated sets of factors: neurophysiologic (including structural), cognitive–perceptual, and environmental. The great majority of children with communication disorders give no evidence of specific CNS damage. Thus, in these children, minimal or subclinical damage has been postulated. The relative frequency of "soft" neurological signs and lateral dominance problems in this population provokes this speculation. However, at this time no clear neurophysiologic mechanisms or pathology can be correlated with these disorders, despite the appeal of this model to many physicians. Some interesting findings are emerging, however. For example, recent reports of magnetic resonance imaging (MRI) studies in stuttering (Foundas et al. 2001) have suggested anatomical differences in Broca's and Wernicke's areas of the left cerebral cortex in affected subjects. In a minority of children with communication disorders, a neuropathologic cause is painfully apparent. Localizable brain damage may arise from trauma, infection, vascular disease, or neoplasm. Perinatal factors such as prematurity, low birth weight, and asphyxia have also been implicated. A number of toxic agents have been associated with communication disorders, particularly lead. Recently, concerns have been raised about prenatal alcohol exposure (Abkarian 1992) and also about the physical sequelae of abuse and neglect (Law and Conway 1992).

### Psychological Factors

These hypotheses relate communication disorders to various deficits in the reception, acquisition, processing, storage, or recall of different elements of communication. Work in this area has largely been pursued through a multidisciplinary model addressing children with "developmental" communication disorders. Perceptual hypotheses posit that speech or language develops improperly because of a failure of input, that is a failure of the child to perceive or process communicated information. Without proper input, proper communication cannot come about. At times, a related model of perceptual immaturity has also been proposed. This model has undeniable intuitive appeal but does not, by itself, explain why language development may not "catch up" despite age and maturation (Table 44–3). More purely cognitive hypotheses have also been proposed. Their details are beyond the scope of this chapter, but they implicate deficits in symbolization, categorizing, hierarchical processing, and related areas. The concordance between communication and learning disorders supports these hypotheses. However, not all children with communication disorders have cognitive deficits. Some authors (Friel-Patti 1992, Helmuth 2001)

**Table 44–3 Hypotheses about Influencing Factors in Communication Disorders**

| Types of Hypotheses | Specific Hypotheses |
|---|---|
| Neurological impairments | Specific localizable brain damage |
| | Subclinical (minimal) brain damage |
| Perceptual deficits | Deficits in auditory discrimination |
| | Deficits in auditory attention |
| | Deficits in auditory figure-ground |
| | Deficits in auditory memory |
| | Deficits in auditory–visual association |
| | Deficits in the processing of specific linguistic units |
| Cognitive deficits | Deficits in symbolic or concept development |
| | Deficits in anticipatory imagery |
| | Deficits in sorting or categorizing |
| | Deficits in hierarchical processing |
| Environmental factors | Inadequate parent–child interaction |
| | Socioeconomic factors (large family size, lower social class, late birth order, and environmental deprivation) |
| | Medical factors (e.g., prematurity and history of recurrent otitis media) |
| Multifactorial etiology | Combinations of all of the above |

*Source*: Reproduced from Baker (1990).

propose that there are certain language-specific abilities; this notion is invigorated by the phenomenology of Williams syndrome, in which affected individuals may have good language skills in the presence of mental retardation.

### Social/Environmental Factors

This category is generally taken to refer to the psychosocial environment of the child, although general medical factors such as perinatal complications or recurrent otitis media may also be included. In this way, the category may at times be overlapped with perceptual deficits; both interfere with input. Inadequate or pathologic parent–child interaction has been associated with the rate of language acquisition, although not so clearly with eventual outcome. Other socioeconomic variables such as class, family size, income, and birth order all clearly affect the amount of verbal interaction children receive and have also been implicated. Some authors (Law and Conway 1992) have attempted to elucidate specific effects on language of child abuse, mainly in regard to syntactic form, but this is speculative at best. No definitive relationship between any psychosocial factor and the type or severity of communication disorder has been established.

## Treatment

### Treatment Goals

Speech and language therapy typically has three major goals: the development and improvement of communication skills with concurrent remediation of deficits, the development of alternative or augmentative communication strategies where required, and the social habilitation of the individual in regard to communication. Thus, a very great range of approaches and components must be employed in treating children with communication disorders. The speech and language pathologist (SLP) plays the most direct role in treatment of these conditions: this role is illustrated by the diagnostic treatment tree (Figure 44–2). SLPs may employ an exceedingly wide range of techniques with children. Their work, not unlike medical psychotherapy, requires both science and art. As in child psychotherapy, the participation of parents is necessary. Parent–infant work involves demonstration and modeling of language-stimulation techniques. Individual therapy can usually be begun by 3 years of age, and early initiation of therapy is frequently recommended. Individual sessions can include traditional exercises along with seemingly less structured but nonetheless carefully directed verbal and play interactions. A lay observer of a session might recognize exercises of the "Peter-piper-picked-a-peck" type as therapeutic. However, the same session might also include periods of seemingly free play or undirected conversation that, in fact, subtly model and direct the patient in the skills of speech and language. Group therapy can also be used especially in the development of language skills applied to a social context, but it should not be regarded as a low-budget substitute for individual treatment. In any treatment regimen, constant monitoring and regular reassessment are necessary,

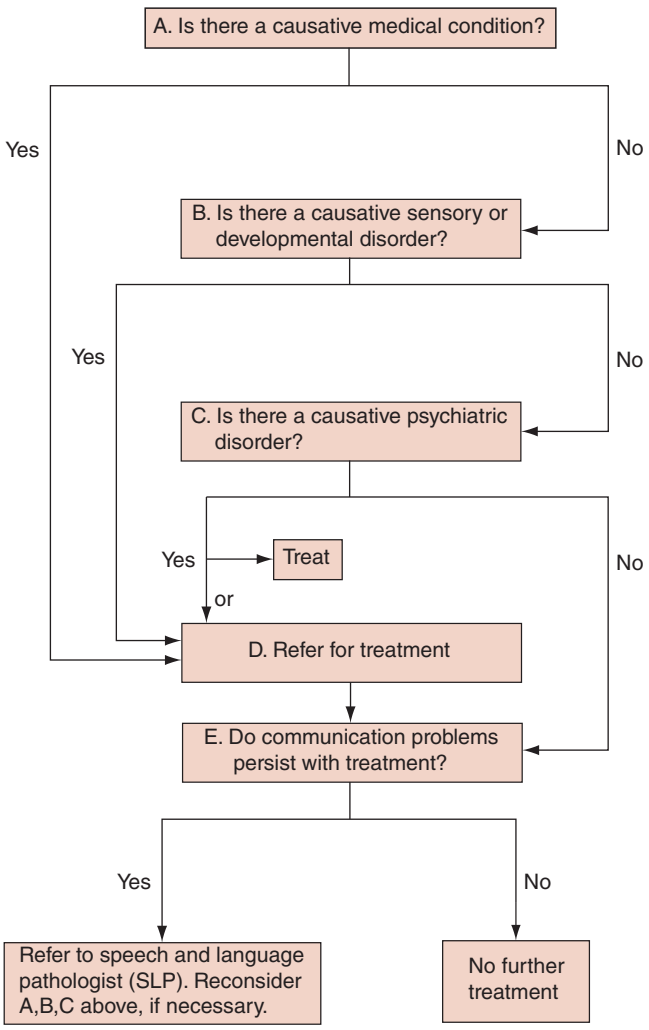



**Figure 44–2** *Diagnostic treatment tree.*

**Table 44–4 Indications for Referral for Communication Evaluation**

| |
|---|
| *Language* |
| • The child does not use any single words by 16–18 months. |
| • At 18 months, the child cannot follow simple instructions such as "Give me your shoe" or cannot point to body parts or common objects following a verbal request. |
| • The child does not combine words for short utterances by the age of 2 years. |
| • The child does not communicate with complete sentences by the age of 3 years. |
| • At 3 years, the child echoes parts of questions or commands rather than responding appropriately. For example, when asked "What's your name?" The child responds, "Your name." |
| • Sentence structures are still short and noticeably defective at the age of 4 years. |
| • At 4 years, the child uses words incorrectly or frequently substitutes an associative word for the intended word. For example, the child may say "cut" for "scissors" or "dog" for "cow." |
| *Articulation* |
| • The child does not babble using consonant sounds (particularly b, m, d, and n) by 8 or 9 months of age. |
| • The child uses mostly vowel sounds and gestures for communication after 18 months. |
| • The speech is usually unintelligible at the age of 3 years. |
| • The child frequently omits consonants in words at the age of 3 years. |
| • The speech is difficult to understand at the age of 4 years. |
| • At the age of 6 years, the child is still unable to produce many sounds. |
| • The child is omitting, substituting, or distorting any sounds after the age of 7 years. |
| • The child is embarrassed or disturbed by his/her speech at any age. |
| *Voice* |
| • The voice is hoarse, harsh, breathy, or of poor quality. |
| • The voice is always too loud or too soft. |
| • The pitch is inappropriate for the child's age or sex. |
| • Pitch breaks occur frequently. |
| • The voice is hyponasal or hypernasal. |
| • There is nasal air emission, a nasal "rustle," snorting, or a nasal grimace during speech. |
| *Stuttering* |
| • The parents have expressed a concern about stuttering. |
| • The child has an abnormal number of repetitions, hesitations, prolongations, blocks, or disruptions in the natural flow of speech. |
| • The child exhibits tension during speech. |
| • The child avoids speaking situations due to a fear of stuttering. |
| • The child considers him/herself to be a stutterer. |

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as is ongoing support to parents who must reinforce the treatment at home. Similarly, regular reconsultation with other professionals from the multidisciplinary team may be required (Table 44–4).

## Somatic Treatments

Drug therapy for these disorders remains at best controversial. The psychiatrist will be required to treat associated conditions, and communication performance may improve with such treatment.

## Psychosocial Factors

Individual and family psychotherapy may be a useful augment in reducing the stress these children encounter.

## Issues in the Clinician–Patient Relationship

The psychiatrist may have a major role in the treatment of communication disorders. These children and their families may present for psychotherapy or other treatment for disorders based on or related to communication problems. Thus, the psychiatrist may, in the first place, be a case finder or a case manager, facilitating the evaluation and treatment of these disorders by a multidisciplinary team. The demonstrated psychiatric comorbidity of these disorders will necessitate the psychiatrist's involvement on many levels, both as a clinician primarily treating a child and as a therapist, counselor, and agent of advice and support for the entire family. Psychotherapy does not directly address language disorders, although older literature has cited improvement in stuttering following family and individual treatment. The psychotherapist must, in any event, be sensitive to the manner in which communication disorders can affect or interfere with the therapeutic process. Nonverbal augments or prompts should be sensitively provided to children who need them.

## Treatment-Refractory Patients

Outcome studies of communication therapy, especially for the language disorders, have often been complicated by multiple theories of language development, diagnostic and methodologic variations, lack of standardization of therapeutic techniques, and comorbidity. Thus, the literature in this area is relatively sparse and not always conclusive. Like the outcome of psychotherapy this is a difficult area to study. The quality of work in this area has been enhanced by the development of empiric measures such as the therapy outcome measure (Roulstone et al. 2004).

Nonresponse to initial treatment may be common, requiring patience and persistence. It is important to note in assessing these issues that, even when communication therapy does not lead to apparent improvements in language beyond developmental improvements, it may still facilitate the child's use of extant language for environmental and self-control (Goldstein and Hockenberger 1991). ELD and MRELD patients with comorbid phonation disorder have a poorer prognosis (Lewis and Fairbairn 1992).

## Special Factors Influencing Treatment

### *Academic Comorbidity*

It should come as no surprise that children with communication disorders, and especially with language disorders, are academically vulnerable. Education, as we know it, especially for younger children, is largely based on language. Bashir and Scavuzzo (1992) suggest that these children's vulnerability arises from the persistence of these disorders in the face of the continuing need for language in school. Moreover, even if a language disorder has been remediated, children may have failed in the meantime, and it is immensely hard for many children in many schools to succeed again, once they have failed for any reason. A further complication is the comorbidity of LD in these children. In all, some 50–75% of children with language disorders will

have persistent academic problems (Aram and Hall 1989). They tend to learn less at any given time and learn more slowly than their peers (Shaywitz 1989). These children need ongoing comprehensive special educational services and regular reevaluation of their educational needs.

## Demographic and Cultural Issues in Treatment

The relationship of socioeconomic status (SES) with the occurrence of communication disorders is not altogether certain. Many studies indicate a positive correlation between communication disorders and low SES, but other work suggests that this correlation is weak at best. The need for clinicians to avoid regarding variations in accent and dialect as pathological has been cited. Very little empirical literature on cultural variations in communication therapy is extant. McCrary (1992) and others have pointed out the need for cultural sensitivity in treatment, citing the efforts of ASLHA in this area.

## Phonological Disorder

### Diagnosis

#### Definition and Diagnostic Features

This condition was formerly known as articulation or developmental articulation disorder. It is characterized by an individual's failure to use speech sounds appropriate for one's developmental level and dialect. The affected individual may substitute one sound for another (e.g., /l/ for /r/), omit certain sounds entirely, or exhibit other errors in organization, use, or production of sounds. By definition, in DSM-IV-TR these difficulties interfere with social, academic, or occupational functions. The symptoms may occur during development without discernible cause or they may be related to CNS, motor, or sensory dysfunction or to environmental deprivation. In the latter cases, speech difficulties must be in excess of those usually associated with the particular problem for the diagnosis to be made. This condition ranges in severity from very mild problems to severe disorders, which render speech totally unintelligible.

This condition is characterized by persistent errors in the production of speech. These include omission, substitution, or distortion of sounds. Omissions include single or multiple sounds: "I go o coo o the but" (I go to school on the bus) or "I re a boo" (I read a book). Substitutions include w/l, t/s, w/r, and d/g: "I taw a wittle wed wadio. It pwayed dood music." A common distortion is lisping. A frontal lisp leads to an /s/ sound resembling /th/. A lateral lisp, with sound coming from the sides of the mouth, leads to a "slushy" /s/ sound: "Shuffering shnakes!" Defects in the order of sounds or insertions of extraneous sounds may also be heard: "catht" for "cats." The occurrence of these errors is persistent but not constant. Baker (1990) points out that "conditioning factors" such as the location within a word or the rate or length of a statement may determine whether a phonologic error is produced. Only some sounds are usually affected, as for example, in lisping the misarticulation of sibilants. Some articulation errors are expected in early childhood, especially involving sounds that are usually mastered at a later age (in English /l/, /r/, /s/, /z/, /th/, and /ch/); these errors are not regarded as pathological unless they persist and result in adverse consequences to the individual. It is estimated that 90% or more of children have mastered the more difficult sounds by the age of 6–8 years.

**DSM-IV-TR Criteria**

**Phonological Disorder**

A. Failure to use developmentally expected speech sounds that are appropriate for age and dialect (e.g., errors in sound production, use, representation, or organization such as, but not limited to, substitutions of one sound for another [use of /t/ for target /k/ sound] or omissions of sounds such as final consonants).

B. The difficulties in speech sound production interfere with academic or occupational achievement or with social communication.

C. If mental retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the speech difficulties are in excess of those usually associated with these problems.

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#### Epidemiology

PD occurs in approximately 2% of 6- and 7-year-olds, but this prevalence falls to 0.5% by the age of 17 years.

#### Comorbidity

Children with this problem may present with clearly associated causal factors such as anatomic malformations, neurological diseases, or cognitive disorders, although most do not. They do have a higher prevalence of language disorders, with all their associated problems, than do normal controls. Even if they are free of language disorders they are still more likely to have ADHD, although probably not as commonly as do children with language disorders. Children with PD, especially when associated with stuttering or hyperactivity, are prone to social discrimination and isolation with subsequent consequences.

#### Course

The course of PD is much more encouraging than those of other communication disorders. Milder cases may not be discovered until the child starts school. These cases often recover spontaneously, especially if the child does not encounter adverse psychosocial consequences because of his/her speech. Severe cases associated with anatomic malformations may at times require surgical intervention, and its course and outcome depend on its success. Between these two extremes are children who gradually improve, often to the point of total remission, and whose improvement may be accelerated by speech therapy.

#### Differential Diagnosis

Some articulation errors are expected in early childhood, especially involving sounds that are usually mastered at

a later age (in English /l/, /r/, /s/, /z/, /th/, and /ch/); these errors are not regarded as pathological unless they persist and result in adverse consequences to the individual. It is estimated that 90% or more of children have mastered the more difficult sounds by the age of 6–8 years. Problems limited to voice alone are included under CDNOS.

### Differences in Developmental, Gender, and Cultural Presentation

The male-to-female predominance in communication disorders and the need for clinicians to avoid regarding variations in accent and dialect as pathological have been cited. Very little empirical literature on cultural variations in communication therapy is extant. McCrary (1992) and others have pointed out the need for cultural sensitivity in treatment, citing the efforts of ASLHA in this area. These conditions should be distinguished from the normal dysfluencies that occur among young children. For example, misarticulation of some sounds, such as /l/, /r/, /s/, /z/, /th/, and /ch/, is common among preschoolers and resolves with age. As with the language disorders, these diagnoses are given in the case of motor or sensory deficit, mental retardation, or environmental deprivation, only if the disorder is much more severe than expected in these conditions.

## Etiology and Pathophysiology

The general range of genetic, neurobiological, and psychological factors that influence ELD and MRELD are felt to be influential in PD as well. Review of social and environmental factors reveals a considerable amount of overlap, with potentially complex interrelationships of causality and concurrence. Clinical observation seldom, if ever, suggests a unitary causality of communication disorders in real patients. Thus, these conditions in most patients are ultimately described as multifactorial. The clinician should be aware that many or all of the factors cited may be present in any communication-disordered patient and may have complex effects on communication as well as other aspects of the patient's life.

## Treatment

Treatment goals for PD are comparable to those for other communication disorders, heartened by the generally good prognosis of this condition. Somatic treatments are not appropriate for this condition, although they may be employed for comorbid psychiatric disorders. These patients may encounter the same psychosocial factors and present similar issues in clinical relationships as do those with other communication disorders.

### Special Factors Influencing Treatment

Children with PD may have persistent academic problems. These are generally less severe than those with language-disordered children, unless both types of disorders are present. Lewis and Fairbairn (1992) reported mild but persistent problems with reading and spelling in individuals with PD, even into young adulthood. Subjects tended to steadily improve over time, however. Although most of the subjects and all the adolescents and adults were considered normal speakers, they tended to show subtle phonological problems on specialized tests. Children with an associated language disorder fared less well.

# Stuttering

## Diagnosis

### Definition and Diagnostic Features

Stuttering is one of the most commonly recognized disorders of speech. Some occurrence of the symptoms of stuttering is normal in the earlier stages of development, and the condition is properly diagnosed only when the symptoms are perceived to be in excess of what is developmentally expected. Similarly, since occasional symptoms appear in the speech of nearly all persons, the diagnosis is not made unless the disturbances interfere with social, academic, or occupational functioning. The condition may be associated with motoric or sensory deficits; when this is the case, the diagnosis is made only when symptoms exceed those expected with these problems. The characteristic symptoms of stuttering, as shown in the DSM-IV-TR criteria for stuttering, are disturbances in fluency (such as repetitions of sounds, syllables or words, interjections, and circumlocutions) and in time patterning (sound prolongations, broken words, and blocking). "Cluttering," the disturbance in rate and length of speech noted in DSM-III-R, is subsumed in DSM-IV-TR under CDNOS, or ELD.

The familiar symptoms of this disorder are noted in section A of its DSM-IV-TR criteria. Stuttering is the communication disorder most easily recognized by both the lay public and the physicians. It varies in severity among individuals. It may be more or less evident in different

**DSM-IV-TR Criteria**

**Stuttering**

A. Disturbance in the normal fluency and time patterning of speech (inappropriate for the individual's age), characterized by frequent occurrences of one or more of the following:

   (1) sound and syllable repetitions
   (2) sound prolongations
   (3) interjections
   (4) broken words (e.g., pauses within a word)
   (5) audible or silent blocking (filled or unfilled pauses in speech)
   (6) circumlocutions (word substitutions to avoid problematic words)
   (7) words produced with an excess of physical tension
   (8) monosyllabic whole-word repetitions (e.g., "I-I-I-I see him")

B. The disturbance in fluency interferes with academic or occupational achievement or with social communication.

C. If a speech-motor or sensory deficit is present, the speech difficulties are in excess of those usually associated with these problems.

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situations and may vary over time. It is typically most severe when the affected child is stressed or anxious, and especially when communication is expected. Children who stutter can sing or talk to themselves without difficulty. Because of its often gradual onset, children are at first frequently not aware of its presence. Over time they may become more anxious and withdraw from conversation, as the degree of social discrimination they experience increases. Stuttering may be accompanied by various movements that may seem either to express or to discharge anxiety, such as blinking, grimacing, or hyperventilation. Sometimes children who stutter may attempt to stop momentarily by slowing down or pausing in their speech, but this is frequently unsuccessful and leads to an exacerbation. Thus, a pattern of habitual fear and avoidance emerges.

### Assessment
Assessment of this disorder is conducted through a comprehensive speech and language evaluation, as described earlier.

### Epidemiology
Stuttering occurs in approximately 1% of children aged 10 years and younger, declining modestly to 0.8% in later adolescence. All communication disorders have a male-to-female predominance; that of stuttering is as high as 3:1.

### Comorbidity
There is much less literature extant addressing the comorbidity of stuttering compared to other communication disorders. Other communication disorders are more frequently reported in those with stuttering rather than in normal controls. Stuttering is frequently accompanied by many linguistic mechanisms and social maneuvers to avoid its manifestation. Conversely, it appears more frequently and intensely in affected individuals when they experience anxieties or stress. The literature is replete with anecdotal and biographical accounts of the social and occupational discrimination, disappointment, and low self-esteem faced by persons with this condition. The negative stereotype of stutterers in society is well documented. They have been mocked in drama and cinema (including cartoons) for centuries and all too often are regarded as intellectually impaired.

### Course
Stuttering usually appears in early childhood, as early as 2 years of age, and frequently has its onset around the age of 5 years. The onset of stuttering is typically regarded as gradual, with repetition of initial consonants or first words or phrases heard in the beginning. However, a study by Yairi and colleagues (1993) suggested that often early stuttering takes on a moderate-to-severe form and that identification of problems in this period has been affected by parents' tendency to postpone professional consultation. Children are generally not aware of this condition in themselves until it is pointed out to them by others. The disorder can wax and wane during childhood. By early adolescence it abates spontaneously in some cases, and from 60% to 80% of individuals eventually recover totally or to a major extent. DSM-IV-TR asserts that spontaneous recovery typically occurs before the age of 16 years. Stuttering may persist into adulthood, often leading to adverse social and occupational consequences.

### Differential Diagnosis
These conditions should be distinguished from the normal dysfluencies that occur among young children. For example, misarticulation of some sounds, such as /l/, /r/, /s/, /z/, /th/, and /ch/, is common among preschoolers and resolves with age. As with the language disorders, these diagnoses are given in the case of motor or sensory deficit, mental retardation, or environmental deprivation, only if the disorder is much more severe than expected in these conditions. Problems limited to voice alone are included under CDNOS.

### Differences in Developmental, Gender, and Cultural Presentation
The male-to-female predominance of communication disorder and the need for clinicians to avoid regarding variations in accent and dialect as pathological have been cited.

## Etiology and Pathophysiology

### Genetic Factors
A genetic basis for stuttering has been proposed for many years. The Yale Family Study of Stuttering (YFSS) suggested that 15% of first-degree relatives of stutterers are affected at some time in their lives (Kidd 1983). A concordance of 77% in identical twins and 32% in fraternal twins has also been reported (Howie 1981). These reports were subsequently confirmed by other studies (Yairi et al. 1996, Andrews et al. 1991). Recent linkage studies implicate several susceptibility loci and support a hypothesis that the genetic component to stuttering has significant sex effects (Suresh et al. 2006).

### Neurobiological Factors
The special phenomenology of stuttering suggests the possibility of dyssynchrony between phonation and articulation, as reported by Perkins (2001). The neurobiologic aspects of the other communication disorders are also considered relevant to this condition. Techniques including qEEG, PET, and fMRI are being employed to elucidate the role of hemispheric asymmetry (Özge et al. 2004), dysfunctions of basal ganglia circuitry (Alm 2004), and many other factors.

### Psychological Factors
In the past, various psychodynamic etiologies have been proposed for stuttering; these have been more stigmatizing than illuminating. The association between the exacerbation of stuttering and stress is well known, however. Work in this area has frequently confounded predisposing, triggering, and maintaining factors (Schulze and Johannsen 1991).

### Social/Environmental Factors
Review of these influences reveals a considerable amount of overlap, with potentially complex interrelationships of causality and concurrence. Clinical observation seldom, if ever, suggests a unitary causality of communication disorders in real patients. Thus, these conditions in most patients are ultimately described as multifactorial. The clinician should be aware that many or all of the factors cited may be present in any communication-disordered patient and may have

complex effects on communication as well as other aspects of the patient's life.

## Treatment

### Treatment Goals

The treatment of stuttering has provoked special interest in recent years, particularly as its adverse consequences in adulthood have been recognized. Approaches to this problem address both the mechanics of speech and the associated attitudinal and affective patterns. Guitar (1985) notes that therapists attempt to modify speech rhythm and speed, leading subjects to regularize rhythm, and as a temporary measure prolong their speech. Thus, patients might be heard speaking in a slow, drawnout, sing-song fashion. Much attention is also directed to respiration, airflow, and "gentle" onset of phonation. This necessitates a multimodal approach (Healey et al. 2004) and family involvement.

### Somatic Treatments

In the 1960s and 1970s, some reports of haloperidol treatment for stuttering emerged. However, enthusiasm was tempered by recognition of this agent's side effects (Andrews and Dozsa 1977), and it is very seldom used for this condition today. There have been occasional reports of treatment of stuttering in the past with tricyclic antidepressants and, more recently, selective serotonin reuptake inhibitors (SSRIs) (Stager et al. 1995, Schreiber and Pick 1997). The rationale for these treatments appears to be a hypothetical connection between stuttering and other compulsive behaviors. These accounts are provocative but do not suggest any real indication for these medications for stuttering alone. A recent case report (Van Wattum 2006) and earlier studies (Maguire et al. 2000) have suggested the possibility that risperidone, a novel antipsychotic, might be useful, but its potential utility must be weighed carefully against its known adverse effects. Moreover, stuttering related to olanzepine and clozapine has been reported (Bär et al. 2004).

### Outcome

The literature on the outcome of treatment for stuttering is somewhat more complete than for the other communication disorders, since symptoms of this disorder can be readily quantified by electronic and other means. Success rates for various treatments of up to 70% have been reported, although with varying follow-up periods and relapse rates (Guitar 1985). Some SLPs specialize in the treatment of this disorder (Rafuse 1994).

As in all communication disorders, the psychiatrist may have a major role in the treatment of children and their families.

## Communication Disorder Not Otherwise Specified

This category includes disorders that do not meet criteria for other specific communication disorders or do so incompletely. DSM-IV-TR cites voice disorders of pitch, loudness, quality, tone, or resonance, as an example. The presence of this heterogeneous category reflects the multifactorial and mixed nature of communication disorders in

**DSM-IV-TR Criteria**

**Communication Disorder Not Otherwise Specified**

This category is for disorders in communication that do not meet criteria for any specific communication disorder; for example, a voice disorder (i.e., an abnormality of vocal pitch, loudness, quality, tone, or resonance).

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Clinical Vignette 1 • Phonation Disorder

RD presented as a 5-year-old girl, the only child of professional parents who had attempted for many years prior to her birth to conceive a child. Her birth was received with joy and relief, and her parents admitted to having indulged her, even by their privileged standards. Her developmental history was unremarkable, except for some slight delay in toilet training compared to her age-mates. She received appropriate well-child care and had no major illnesses or injuries. Her adjustment to preschool was considered appropriate when she entered at the age of 3 years, and she got along well with the other children for 2 years. She enjoyed the preschool, where individuality was accepted and encouraged. Her parents sought psychiatric evaluation for her after she reported being fearful about returning to school. When her parents questioned her, she stated that new children had come to her school for kindergarten and they were teasing her. The teacher informed the parents that new students were in fact present, but that no teasing had been observed. Upon evaluation, a picture emerged of concerned parents who were sensitive to their child's emotional state and had sought to remedy their inexperience with children through a great deal of study and inquiry. RD appeared initially as a somewhat anxious child, who separated from her mother with mild trepidation but soon relaxed with the psychiatrist. She was able to relate openly, gave no evidence of a major thought or affective disorder, and seemed to be of average intelligence. She exhibited a number of articulation errors, substituting /w/ for /l/ and /r/ and /th/ for /s/ and omitting or dropping a number of closing sounds. She stated that she was shocked at the comments of her new classmates that her speech was infantile. These children were as of yet unaccustomed to the uncritical atmosphere of the school. She had never thought that her speech was unusual, nor had her parents who believed it was normal for a child of her age. The teacher explained that she had noticed some errors in RD's speech but did not wish to offend her or her parents by pointing them out. The psychiatrist intervened by helping the child to understand that some children adopted "grown-up" speech later than others and that her progress could be assisted by a helping adult. The psychiatrist referred the family to a SLP, whose session the parents described to the child as a "conversation party." The psychiatrist worked with the parents in joint brief focal psychotherapy, addressing issues related to the parents' sense of failure because of their child's problem and their delay in recognizing it. After 6 months, RD's speech had improved and was accepted as normal by her

classmates. By the age of 9 years her speech was regarded as entirely normal by her parents and teachers, and she was functioning well in all spheres. However, she continued to have subtle phonological findings as an adolescent.

Clinical Vignette 2 • Receptive–Expressive Language Disorder

GB, a 6-year-old boy, who lived with his parents and several siblings in an isolated area, was referred by a family physician at a rural health center who felt that he might have autism. He was a child of normal appearance and good general health who exhibited no speech whatsoever. The family physician had tested his hearing and believed that it was adequate; his parents agreed, since they found that he had always been able to respond to a wide range of sounds, from bird calls to thunder. They had deferred medical attention until GB was identified by the regional school as a student entitled to special educational services. The parents were medically unsophisticated but attentive and devoted. They felt that GB was "slow," but that little could be done for him, and that the family would always take care of him. They felt that they could communicate with him with gestures and reported that his older siblings were especially adept at this. The family traveled to a university diagnostic center. Psychiatric evaluation disclosed a cheerful, interactive child, who could engage in some mimetic play and was sensitive to the moods of others. On psychological evaluation, GB exhibited low average cognitive ability on some nonverbal instruments and some receptive ability when given nonverbal prompts. Speech and language evaluation, along with family observation by all members of the diagnostic team, disclosed a severe MRELD for spoken language. However, GB and his siblings had developed a sign language that enabled them to communicate needs and wants, as well as to describe affects and comment, etc., on many activities in their home. They were referred as a group to a SLP at their county seat. The pathologist was able to teach GB Ameslan (standard sign language), and eventually he also developed a limited oral vocabulary. Other team members were able to document nearly average nonverbal intelligence and rule out other major psychopathology. Nonetheless, GB's school district proposed placing him in a classroom for severely mentally handicapped children. The psychiatrist was able to offer supportive psychotherapy to the parents, who had been devastated by the proposal, while the liaison special educator set about locating a class for language-disabled children in an adjacent county. GB was able to enter this class after the local school district was convinced of its educational and legal advisability. He did well there and subsequently completed a vocational program in automobile mechanics. As a late adolescent, he still has a limited vocabulary and reads at a sixth-grade level but can follow mechanical and schematic diagrams well and relates appropriately with his classmates.

many children who may have multiple mixed symptoms of more than one disorder. Its treatment requires addressing of all the components of the various disorders represented.

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CHAPTER

# 45 Childhood Disorders: The Pervasive Developmental Disorders

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Autistic Disorder
Asperger's Disorder
Childhood Disintegrative Disorder
Rett's Disorder

## Introduction

The pervasive developmental disorders (PDDs) represent a class of developmental disorders characterized by impairments spanning multiple domains of functioning. Five disorders fall within the class of PDDs and will be discussed in this chapter: autistic disorder, Asperger's disorder (AD), pervasive developmental disorder—not otherwise specified (PDD-NOS), childhood disintegrative disorder (CDD), and Rett's disorder (RD). The term "autism spectrum disorder" (ASD) is usually reserved for the first three disorders (autistic disorder, AD, and PDD-NOS), as evidence suggests these disorders share common phenotypic and etiologic features distinguishing them from RD and CDD. The ASDs are characterized by impairments in social and communicative abilities, along with rigid and repetitive patterns of behavior (e.g., motor mannerisms, resistance to change, and idiosyncratic interests and preoccupations). Social disability is considered the hallmark and, diagnostically speaking, most germane feature of the disorders. The disorders vary in terms of severity, age of onset, presence of communicative impairments, and repetitive and restricted interests, but all ASDs require evidence of impairment within the domain of social behavior for diagnosis. ASDs have become a focus of international, professional, and popular attention in recent years. A study by the Center for Disease Control and the Autism and Developmental Disabilities Monitoring Network estimates the prevalence of ASDs in the United States to be 1 in 150 people (2007); once considered a rare disorder, ASDs are now certain to be encountered by practicing psychiatrists. Significant strides have been made in terms of psychosocial interventions; these therapies ameliorate symptoms primarily through compensatory strategies addressing areas of vulnerability. Psychopharmacology offers a promising treatment approach, but the effects of currently available medications are limited to associated features, such as aggression or irritability, without directly altering the core social impairments of the disorders. These advancements in psychosocial and somatic approaches have improved outcome for individuals with PDDs. Research in the genetic and neurobiological underpinnings of the PDDs has already been fruitful, and it is hoped that continued research can move the field closer toward biomarkers for early detection and biologically based interventions.

## Autistic Disorder

### Diagnosis

#### Definition and Diagnostic Feature

Autistic disorder is the most extensively studied and best understood of the ASDs. "Autistic disorder" is the descriptor used in the DSM, but, in practice, the terms, "autism,"

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"childhood autism," "infantile autism," and "early infantile autism" are used synonymously. The condition is characterized by marked and sustained impairment in social interaction, communication, and restricted or stereotyped patterns of behaviors and interest evident by 3 years of age. See DSM-IV-TR criteria for Autistic Disorder (American Psychiatric Association 2000).

Diagnosis of autism requires a minimum of six behavioral criteria, at least two from the domain of social impairment and one from each of the other two areas of impairment (communication and restricted/repetitive behaviors). Contrasting the disorder from more general intellectual impairment, these social and communicative deficits are considered with respect to overall developmental level. In children with global cognitive impairment, social and communicative skills are typically commensurate with broad intellectual functioning; in autism, these areas of function represent selective weakness. Thus, it is always vital to evaluate symptoms of autism in the context of broad developmental level.

Social disability represents the earliest appearing and most focal impairment in autism and the other ASDs. One of the early appearing manifestations of the disorder is reduced interest in interpersonal interactions. In typical development, children are drawn toward other human beings from birth; infants show strong preferences to look at human faces and display a characteristic bias toward gazing to the eyes. This pattern persists throughout development, and, even in adulthood, the eyes remain the most important focus of the human face, as they provide the richest information about affect and attention. Parents of children with autism often note that, even in infancy, these children fail to demonstrate this gravitation toward other people, instead preferring to explore objects in their environment (often in atypical, repetitive ways). This disinterest in other people manifests as reduced social overtures, less looking to the face of others and using eye contact communicatively, and decreased *joint attention behaviors*. Joint attention refers to actions intended to direct or draw the attention of another person. For example, a child might look to his mother, look to an interesting object in the environment, and then look back to his mother to gauge her reaction to it (when a child uses joint attention to ascertain the affective valence of another, this joint attention behavior is called *social referencing*). Children with autism are much less likely to attempt to use gestures or language for social purposes, or to show things or comment on things to parents, than for practical purposes, such as requesting a

**DSM-IV-TR Criteria for Autistic Disorder**

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

   (1) Qualitative impairment in social interaction, as manifested by at least two of the following:

      (a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction,

      (b) failure to develop peer relationships appropriate to developmental level,

      (c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing or pointing out objects of interest to other people)

      (d) lack of social or emotional reciprocity,

   (2) Qualitative impairments in communication as manifested by at least one of the following:

      (a) delay in or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

      (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

      (c) stereotyped and repetitive use of language or idiosyncratic language

      (d) lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level

   (3) Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

      (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

      (b) apparently compulsive adherence to specific, nonfunctional routines or rituals

      (c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

      (d) persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

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desired item. They show reduced range and atypical quality of facial expressions and often fail to use these expressions to communicate to others in their environment. These atypical reactions to other people and to the human face have been demonstrated in laboratory studies; in experimental paradigms that monitor patterns of gaze while children are viewing social scenes, people with autism (by the second year of life) demonstrate atypical looking patterns, gazing less at the eyes and more at mouths and objects in the environment (Klin et al. 2002a). Figure 45–1 illustrates characteristic gaze patterns in an adult with autism as compared to a typical adult. Other research studies have documented that children with autism respond appropriately to inanimate objects in their environment, showing selective impairments when responding to sounds or overtures produced by other people (Dawson et al. 1998). This trend is observed in naturalistic environs as well; because children with autism commonly fail to orient when their name is called, parents often express initial concern that the child is hearing impaired. Though these dysfunctions are evident at the most basic levels of social interaction, individuals with autism also display impairments in higher order aspects of social interaction. These difficulties have been interpreted as reflective of impairment in social cognition. They are poor at empathizing and taking on the perspective of others (Klin 2000) and possess an underdeveloped *theory of mind,* that is, the ability to appreciate another's mental states as distinct from one's own (Baron-Cohen 1983).

Despite the fact that impaired social interaction, the hallmark of ASDs, is found in all children with autism, degree of impairment and style of interaction vary widely from child to child. Wing and Gould (1979a) developed a system for classifying these interpersonal styles. Many children are aloof, or isolated from interpersonal interaction and unlikely to initiate or respond to social overtures. Children in this class, however, may enjoy interactions of a physical or rough-and-tumble nature. A second class of children is described as passive. Although these children may respond to social interaction, they tend not to seek it out. A third descriptive category of social interaction, often observed among high-functioning and more verbal children with autism, is an "active but odd" presentation. In this case, the child may seek social interaction but do so in an awkward, atypical fashion.




**Figure 45–1** *Fixations of an adult with autism (black line) and a typical viewer (white line) while viewing a conversation on film. (Source: Reprinted, with permission from the American Journal of Psychiatry 159, 909–916. © APA.)*

Language is usually significantly impaired in individuals with autism. It has historically been estimated that as many as half of individuals with autism never develop functional speech; but this proportion is decreasing due to improved detection and intervention procedures, along with recognition of high-functioning forms of the disorder (Tager-Flusberg et al. 2005). Nevertheless, language impairments represent a core phenotypic feature, with delays in the acquisition of language representing the most frequent presenting complaint. Usual patterns of language acquisition (e.g., playing with sounds and babbling) may be reduced in frequency or altogether absent. Children with autism commonly manipulate a parent's hand (as if the hand were a disembodied tool) instead of making more conventional requests. In contrast to children with language impairment alone, children with autism display an apparent reduced drive to communicate and tend not to compensate through nonverbal means, such as gesture or eye contact.

When individuals with autism do develop speech, their language is atypical in several respects (Paul and Sutherland 2005). They frequently display immediate or delayed echolalia, or repetition of previously heard speech. Immediate echolalia often takes the form of repeating statements or questions uttered to the child and has been considered the child's attempt to "respond" despite lacking comprehension of the verbiage or the ability to formulate an appropriate response. Immediate echolalia is often observed in typical language development as a tool for acquiring speech; it follows that it is considered a positive predictor for functional language development in children with autism. Delayed echolalia is also common and may manifest as repeating snippets of previous conversations or movie dialog. These utterances may be nonreciprocal and noncommunicative in nature or may be incorporated into functional language. For example, a child might repeat a parent's admonishment aloud every time they become anxious that they have done something wrong or use lines from movie dialog appropriately in real-life situations analogous to the movie scene. The term "stereotyped speech" refers to the application of these rote, scripted speech patterns in this fashion. Because of the rote and inflexible manner in which speech is learned and utilized, children with autism often produced idiosyncratic patterns of speech that are functional but odd. For similar reasons, children with autism often reverse pronouns, commonly referring to themselves in the second person.

The syntax and morphology of language are typically intact in individuals with autism who develop speech. However, they have particular difficulty with social uses of language (pragmatics). Thus, humor and sarcasm are often misconstrued as a person with autism may fail to appreciate the speaker's communicative intent and interpret the jest literally (Dennis et al. 2001). Indeed speech in individuals with autism tends to be excessively concrete, both in terms of production and comprehension. The prosody of individuals with autism is usually inappropriate, with flat intonation and halting pacing, sometimes described as "robotic." Deficits in pragmatic communication, particularly the ability to have a back-and-forth conversation, are prevalent. The language and communicative deficits in autism differ from those characterizing pure language impairments in their

focal social difficulties, as well as the severity of language delays (Paul and Sutherland 2005). Research has not yet clarified whether pragmatic impairments reflect difficulty with the abstraction of these linguistic constructions or disregard of their purely social utility.

Impairments in play are included with the symptom class of impaired communication. Children with autism show reduced interest in imaginative or pretend play. This co-occurs with unusual ways of using toys, in particular exploring the physical properties of objects rather than using them for intended functional and symbolic purposes. For example, rather than using a toy car as such, a child with autism might hold the car upside down and repeatedly spin its wheels. Often children with autism will peer closely at such an object, sometimes moving it across their field of vision or looking at it from the corner of their eye.

These behaviors appear geared toward basic forms of sensory self-stimulation, and, more generally speaking, children with autism are commonly reported to display both hyper- and hyposensitivity to sensory stimuli. Children with autism may be oversensitive to sounds, for example, reacting strongly to the sound of a vacuum cleaner. There may be heightened sensitivity to touch (tactile defensiveness), though many children display increased pain threshold. Many children enjoy vestibular sensations such as spinning or swinging. Children with autism often smell or taste objects in unusual ways. Indeed, *pica*, or the placement of inedible objects in one's mouth, is common in individuals with autism.

Individuals with autism often exhibit pronounced motor stereotypies. These behaviors can include hand flapping or rapid finger movements (often in front of the eyes), body rocking, or tensing their extremities while jumping up and down. Stereotypies, though not unique to autism and seen in other disorders, including severe mental retardation and sensory impairments, represent a common and distinctive feature of the disorder, often emerging around age 3. They appear to represent a form of self-regulation and often are most evident during periods of heightened arousal, such as excitement or apprehension. These behaviors often abate in adolescence and adulthood, particularly among high-functioning individuals. Some children with autism have been reported to display *echopraxia*, or the imitation of other's motor movements without comprehension of intent or function. Otherwise, the fine and gross motor function of children with autism tend to be appropriate to their developmental level. Increased level of baseline motor activity is common in autism, particularly in preschool years, though passivity and reduced interest in exploring the environment can also manifest as decreased levels of physical activity. Self-injurious behavior, such as biting or striking, can occur in autism, especially among low-functioning children. Head banging is also common, particularly among the most intellectually impaired. Aggression against other people can also be observed. This usually stems from frustration with an inability to communicate effectively coupled with poor understanding of the impact of aggression on other people, rather than from malicious intent. As such, the appropriate intervention is to understand the elicitors of these behaviors and the function they serve for their child and then modify the environment and teach replacement behaviors so as to obviate the need for aggression as a communicative tool.

Children with autism often have difficulty in tolerating change and variation in routine, or, as termed by Kanner, an "insistence on sameness." For example, a minor change in routine, such as driving an alternate car or using an alternate entrance to a building, might be responded to with significant distress. Parents often report that their child performs activities in methodological, specific ways. Furthermore, the child may display interest in a repetitive activity, such as ripping up pieces of paper or repeatedly dropping objects into a heat vent.

A majority of children with autism display cognitive impairment. It has been estimated that approximately 75–80% of individuals with autism are classified as intellectually disabled, with about 30% falling in the mild to moderate range and 45% in the severe to profound range. Comparable to typical children, IQ scores are relatively stable and predictive of outcome (Klin et al. 2005c). Current trends toward earlier detection and intervention, along with increased recognition of higher functioning forms of the disorder, are likely to decrease the proportion of individuals with autism with intellectual disability. On measures of cognitive ability, children with autism tend to display deficits in abstract reasoning, verbal concept formation, and integration skills, as well as tasks involving social insight. In contrast, relative strengths are usually observed in the areas of rote learning and memory skills and visual-spatial problem solving. Individuals with autism display a bias toward perceiving and processing information at the level of local details rather than the global level, or the "big picture"; they have difficulty "seeing the forest for the trees." This processing bias is reflected in greater success on parts-to-whole tasks, rather than tasks requiring them to process a *gestalt*. Consistent with the prevalent impairment in language, children with autism also tend to display stronger performance on measures of nonverbal ability relative to verbal ability. A small percentage of individuals with autism, approximately10%, display savant skills, or specific abilities that dramatically exceed their own broader intellectual ability or the abilities of their typically developing counterparts. These skills may take the form of musical or drawing ability or exceptional feats of memory, such as the ability to name days of the week corresponding to dates several years in advance ("calendar calculators"; Hermelin 2001). A common isolated strength in children with autism is facility in decoding letters and numbers, or *hyperlexia* (Newman et al. 2006).

Children with autism often display disturbances in patterns of sleeping and eating. They may sleep in idiosyncratic patterns with recurrent awakening at night for long periods; among lower functioning individuals, this can present a safety risk as these children are then unsupervised as others in the house remain asleep. Eating disturbances may involve seeking or avoiding particular foods based on texture, color, or smell. Many children with autism resist all but a limited repertoire of foods and refuse to try new foods.

Poor affect modulation and displays of emotions inconsistent with contextual events are also seen in autism, including abrupt mood changes and laughing for no apparent reason. Temper tantrums are common, particularly in reaction to demands and unexpected changes in routine. Higher functioning individuals may display intense anxiety in social situations; they may also develop depression in adolescence, resulting from negative social experiences over the years and augmenting insight into their own social limitations.

Clinical Vignette 1: Autism

Bobby was the only child born to affluent parents after a medically unremarkable pregnancy. There were no complications during labor or delivery, and he immediately took to bottled formula without notable colic or gas problems. Bobby's parents report that he was an independent infant and that he often preferred to be placed in his crib or play mat; when held, he frequently cried or arched his back until he was put down. His parents first reported concerns at 12 months, when Bobby had not developed any spoken language and showed little interest in developmentally appropriate social games or play. When his parents contacted his pediatrician about these concerns, they were comforted by the notion that his development was still within normal limits. Additional concerns mounted as his parents noticed a failure to orient when adults called his name, despite rapid attending to the sound of the family computer rebooting. A hearing test at 18 months was administered with negative results, and Bobby was referred to a specialist in ASDs. An evaluation at 24 months revealed intact gross and fine motor skills, with delayed visual-spatial reasoning and expressive–receptive language. Evaluators noted that Bobby's social and play skills were delayed with respect to his overall developmental level. Bobby showed little interest in toys as such, preferring to roll a car back and forth in front of him while peering at it from the corner of his eye. Evaluators noted that he demonstrated little interest in adults as social partners, and engaged others only to meet his needs. His typical manner of issuing requests was to put another person's hand on a desired object without accompanying words or nonverbal communication. Family history revealed no difficulties in his immediate family, though his parents reported that the paternal grandfather had been a loner who had difficulty holding down a job. Medical assessment included normal EEG and genetic screening. Bobby was referred to early intervention services, and an intervention program based on discrete trials was implemented in a developmental preschool and at home. Bobby began using several single words to make requests at 34 months, and, with the use of an exchange-based augmentative communication system, he was able to request his preferred foods and activities. In social situations with peers, Bobby engaged in some aggression; this was addressed through functional behavior analysis and responded quickly to a positive behavior modification program. As his language skills increased, Bobby became increasingly interested in interactions with his family and other children, and he enjoyed opportunities to interact with typical peers with adult facilitation. Bobby's cognitive skills crystallized in the borderline range, and he worked in a doctor's office, performing janitorial tasks under close supervision. Though Bobby did not develop sufficient adaptive functioning to allow for independent living, he lived with his parents until their passing, at which point he moved in with his older sister.

## History of the Diagnostic Concept

The diagnostic category, "autism," dates to 1943, when Leo Kanner described 11 cases of "autistic disturbances of affective contact." These children failed to relate to other people from very early in life and showed unusual patterns of communication (e.g., echolalia and pronominal reversal). Moreover, they responded in atypical ways to their environment, engaging in repetitive and ostensibly unproductive actions with objects and exhibiting a strong preference for sameness in routine and physical environment. Kanner provided a developmental context for his observations and emphasized the centrality of deficits in social relatedness. Though many of Kanner's original descriptors have been incorporated into current diagnostic conceptualizations of the disorder, several of his statements contradict current understanding of autism. Kanner's description suggested that children with autism possess intact intellectual ability, but subsequent evidence has shown that cognitive impairment tends to co-occur with autism. Kanner also erroneously speculated that autism might develop secondary to anomalous parental care and might be biased toward more educated or affluent families. Subsequent research demonstrated both of these points to be false; autism is distributed equivalently across socioeconomic strata and is not attributable to pathological parenting.

Kanner's use of the term "autism" referenced Bleuler's use of the term to refer to self-centered thinking in schizophrenia. Though now understood to have distinct psychopathological origins, the negative symptoms of schizophrenia (social withdrawal, blunted affect) resembled some of the social symptoms of autism. Although Kanner's articulation of the phenomenology of autism distinguished it from childhood schizophrenia, perhaps due to the overlapping terminology or perhaps due to the severity of dysfunction, a relationship between the disorders was mistakenly assumed for years. The first (American Psychiatric Association 1952) and second editions (American Psychiatric Association 1968) of the *Diagnostic and Statistical Manual of Mental Disorders* did not recognize autism as a distinct disorder, viewing it instead as a form of childhood schizophrenia. Progress toward distinguishing the two disorders resulted from studies of large groups of "psychotic" children, who were observed to fall into early and late onset groups. The early onset group (prior to approximately 6 years of age) tended to exhibit the characteristics that had been described by Kanner. Conversely, children with later onset "psychosis" (after age 5 or 6) presented with more prototypically positive symptoms of schizophrenia (e.g., delusions, hallucinations). These early versus late onset psychoses mapped onto current conceptualizations of autism and childhood schizophrenia, respectively. Observation of familial co-occurrence also suggested that the disorders were distinct.

In 1978, Rutter provided a more viable operational definition of autism. He described social delay and deviance independent of mental retardation, communication problems without respect to intellectual function, and atypical behaviors (stereotyped movements and mannerisms) with onset prior to 30 months. This definition, along with an increasing body of research on autism, provided groundwork for inclusion of the disorder in the DSM-III (American Psychiatric Association 1980) in the newly created taxon of PDDs. The disorder was termed, "infantile autism" to emphasize its early onset. Criteria for the condition were monothetic and most germane to younger children with autism; "residual infantile autism" was included to describe individuals who had been diagnosed with infantile autism but no longer met diagnostic criteria. This diagnostic conceptualization was criticized for its lack of consideration of developmental factors, and a developmental emphasis was addressed in DSM-III-R (American Psychiatric Association 1987). In

this revision, the condition was described by detailed criteria grouped into three categories: social impairment, communicative disturbance, and restricted and repetitive behaviors. Under the newly introduced system of multiaxial assessment, the condition was placed on Axis II. Only two diagnoses, autistic disorder and PDD-NOS, were included in the PDDs in DSM-III-R.

The current diagnostic criteria (see DSM-IV-TR criteria for Autistic Disorder) were first published in DSM-IV (American Psychiatric Association 1994). These criteria were based on the results of a large field trial, spanning multiple international sites that examined appropriateness of diagnostic conceptualization. The diagnostic criteria preserved the conceptual triad of impairments, while making an age of onset requisite for the diagnosis. DSM-IV-TR diagnostic criteria also introduced consistency with internationally utilized criteria for the PDDs, as reflected in the 10th edition of the International Classification of Diseases (World Health Organization 1992). In publishing of the DSM-IV-TR, the PDDs were returned to Axis I.

## Assessment

Diagnostic assessment of autism and related conditions has traditionally been made according to clinical judgment of the presence of DSM-IV-TR criteria. Diagnostic evaluation entails a thorough developmental history, emphasizing early social development (e.g., interest in others, eye contact and joint attention behavior, atypical or repetitive behaviors, and onset and nature of communication). In conceptualizing a diagnosis of an ASD, the practitioner should attempt to verify that symptoms have been stable and evident since early childhood. In addition to an exhaustive developmental history, direct observation of the child is requisite to assess social and communicative characteristics, as well as the presence of preoccupations or atypical behaviors. Ideally, observation should occur across settings, including the clinic's reception area (e.g., contacts with other children or with family members), the hallways (e.g., how the child interacts initially with the examiners), and during a face-to-face examination. Often, the social disability in ASD is most pronounced during periods when social expectations are unclear. It is therefore important to interview the child without providing the support characteristically provided by adults interacting with children with special needs. This can include volunteering information about oneself (to see if a child asks for clarification), waiting out awkward pauses, and asking open-ended questions. Topics of inquiry should include social relationships, interests, use of leisure time, self-awareness, insight into other people's intentions and beliefs, and understanding of figurative language. Considering the likelihood of relative proficiency interacting with adults among high-functioning individuals, collateral information from educators and parents about behavior in social settings with peers offers extremely useful additional information. Other areas of inquiry should focus on obsessive, compulsive, and ritualized behaviors, as well as the presence of symptoms of anxiety and depression. The patient's thought processes and reality testing should also be probed.

Numerous screening and diagnostic measures have been developed for ASDs in recent years. These instruments include self-report, parent/teacher report, and direct observation measures. Extant diagnostic instruments have not been reliably demonstrated to be effective in making a differential diagnosis among ASDs (Campbell 2005). The current "gold standard" diagnostic protocol for ASDs consists of a parent interview, the Autism Diagnostic Interview—Revised (Lord et al. 1994), and a semistructured conversation/play-based interview, the Autism Diagnostic Observation Schedule (Lord et al. 2000). Both of these instruments are publicly available, but they require specific training to administer and score reliably. Though this combination of diagnostic measures represents best practice for diagnosing children with an ASD, it does not provide criteria for differential diagnosis among ASDs. Though great progress has been made in standardizing diagnostic approaches, this task continues to rely on the judgment of experienced clinicians.

Because ASDs are associated with difficulties in multiple domains of functioning, children thought to be at risk for ASD should be referred for a multidisciplinary assessment by an experienced team (Klin et al. 2005c). A comprehensive interdisciplinary assessment will involve a thorough developmental and health history, psychological assessment (cognitive ability, psychomotor control, adaptive function), communication assessment (receptive/expressive language, nonverbal communication, nonliteral language, pragmatics, prosody, and content, and, in young children, gaze and joint attention behaviors; Paul 2005), and a formal diagnostic evaluation, ideally using the standardized diagnostic assessments described above. An assessment of adaptive skills is also critical given the prevalence of discrepancies between intellectual level and adaptive functioning in this population (Klin et al. 2007). Consultation regarding behavioral management, motor disabilities, neurological concerns, psychopharmacology, college-readiness, or vocational training may also be indicated. As in the assessment of any childhood disorder, an accurate profile of the individual's strengths and weaknesses will be of greater utility than simply obtaining a diagnostic label. The level of cognitive function establishes a frame of reference upon which other developmental areas (including social, communication, imagination, and adaptive skills) can be evaluated; this is critical in considering differential diagnoses, as individuals with autism display social impairments in excess of those predicted based on intellectual impairment alone.

From the perspective of the physician on a multidisciplinary team, it is important to conduct a careful medical and family history (Volkmar et al. 1999). Genetic screening for various inherited metabolic disturbances is indicated, because some inherited disorders are associated with autism (e.g., phenylketonuria). Chromosome analysis and, possibly, genetic consultation are indicated in the presence of mental retardation or signs of inherited disorders, such as fragile X syndrome. Hearing tests have often been conducted by the time a child is referred for specialized evaluation; when usual audiologic assessment procedures cannot be employed, brainstem auditory evoked response testing is indicated. Neurologic consultation should be obtained if the child has signs suggestive of overt seizure disorder or other evidence of gross neurological dysfunction or if unusual features are present (e.g., late onset). Electroencephalogram (EEG) and neuroimaging scans may be appropriate at these times (Minshew et al. 2005), but they are not recommended as standard assessment procedures. In general, a reasonable search for possible contributing factors is advisable as

indicated by history and examination, with an eye toward balancing likely yield and resource consumption.

## Epidemiology

Initial epidemiological research on autism (Lotter 1966) suggested a prevalence rate of 4.5 in 10,000 individuals. Higher prevalence rates of broadly defined ASDs have been reported in subsequent studies with a trend toward increasing prevalence. Fombonne (2005) reviewed epidemiological studies of ASDs and found prevalence rates for autistic disorder ranging from 0.7 to 72.6 per 10,000, with the smallest sample sizes resulting in the highest estimates. Fombonne's *conservative* prevalence estimate for ASDs was 36.4 per 10,000; his *best* estimate of the prevalence rate for ASDs was 60 per 10,000. A recent meta-analysis of prevalence studies calculated a lower rate of 20 per 10,000 for ASDs (Williams et al. 2006). A 2007 report from the Center for Disease Control reported an average of 1 in 150 children carrying a diagnosis of an ASD in the United States (Autism and Developmental Disabilities Monitoring Network Principal Investigators 2007). Though prevalence estimates have drastically increased in recent years, little evidence supports an actual change in the incidence of autism. Instead, rising prevalence rates likely reflect changes in diagnostic criteria, increased awareness of autism and ASDs, and greater service availability (Fombonne 2005). Comparability among epidemiological studies is complicated by inconsistency in diagnostic criteria used over time and across studies (Ehlers and Gillberg 1993).

In general, ASDs are more common in males than females. A ratio of approximately 4:1 has traditionally been reported (Fombonne 2005), although the recent CDC report indicated ratios ranging between 1.8 and 5.5 to 1. This ratio varies, however, as a function of intellectual functioning, with an increased ratio of boys to girls (greater than or equal to 6.0:1) in individuals with autism without cognitive impairment and a decreased ratio (as low as 1.5:1) among individuals with moderate to severe cognitive impairment. The prevalence of autism is fixed across racial and socioeconomic groups (Yeargin-Allsopp et al. 2003).

## Comorbidity Patterns

A variety of psychiatric conditions have been associated with autistic disorder. From a clinical standpoint, the strength of these associations and their underlying relationship is secondary to the variable presentation of the disorder, which, on the whole, renders making other psychiatric diagnoses unfruitful. Symptoms of depression and anxiety may become prominent in higher functioning adolescents, when they often venture into the social (and romantic) realm and, in so doing, become painfully aware of their limitations. Though diagnostic criteria for attention-deficit hyperactivity disorder (ADHD) specify that the symptoms do not occur in the context of a PDD, ADHD is frequently diagnosed in children with autism. A recent study (Leyfer 2006) found that 55% of a sample of 109 children with autism had a significantly impairing ADHD syndrome and that 31% of the sample had symptoms that met DSM-IV-TR criteria for the disorder, with the majority falling into the category of "inattentive type."

Research suggests correlations among autism and a number of medical conditions. Approximately 15–20% of children with autism experience comorbid epilepsy. Seizure onset appears to have two peaks of incidence, first in infancy, and then in adolescence (Volkmar and Nelson 1990, see Figure 45–2). Tuberous sclerosis, an autosomal dominant disorder characterized by benign tumors (hamartomas) in various organ systems, is associated with a range of phenotypes including mental retardation and seizure disorder. Between 20 and 50% of children with tuberous sclerosis meet diagnostic criteria for autism; the frequency of tuberous sclerosis among individuals with autism is much greater than in the typical population (Rutter 2005). These children are also more likely to suffer from epilepsy. It is not yet known whether the association between autism and tuberous sclerosis is mediated by epilepsy, the presence of localized brain lesions, or direct genetic effects. Between 15 and 25% of children with fragile X syndrome, a condition with a clear genetic basis, meet diagnostic criteria for autism. Fragile X is characterized by behavioral difficulties including attention problems, impulsivity, and anxiety. The defect has been identified as a triplet repeat of cytosine–guanine–guanine on the X-chromosome, which may amplify in successive generations. The condition is associated with a characteristic facial dysmorphology, enlarged testicles, and mental retardation. The vast majority of children with fragile X exhibit some behaviors typically attributed to autism, including social withdrawal and stereotypies; however, the pathophysiological relationship between the genetic abnormality of fragile X and autistic behaviors has yet to be clarified. Associations between autism and several other disorders, including phenylketonuria, neurofibromatosis, and congenital rubella have also been reported, but such relationships have not been conclusively demonstrated (Fombonne 2005). As an example, the "autistic-like" features of congenital rubella diminish with time, but the diagnostic process is confounded by persisting sensory deficits and mental retardation.

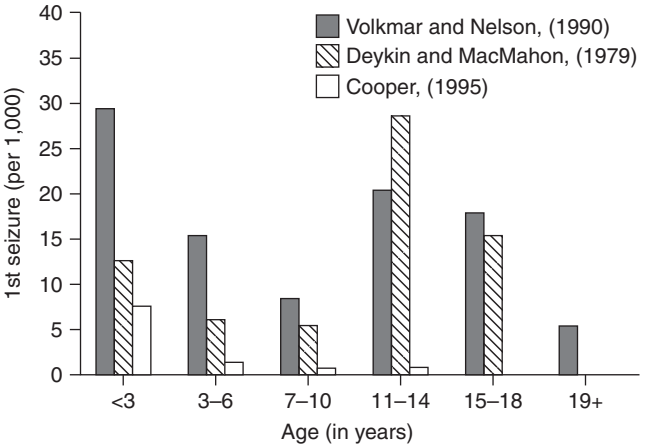



**Figure 45–2** *Rates of epilepsy (recurrent seizures) in two samples of individuals with autism/PDD (Volkmar and Nelson 1990, Deykin and MacMahon 1979) and a normative British sample (Cooper 1965). (Source: Data from Volkmar and Nelson [1990].)*

Much attention has recently been focused on the incidence of gastrointestinal irregularities in autism. Research is preliminary and further investigation is required to explore potential relationships among gastrointestinal pathology and autism. Such research must explore both causal and contributory factors, as well as consideration of gastrointestinal

symptoms as a generic stressor that can exacerbate existing symptomatology in individuals who cannot otherwise communicate their distress.

In summary, although early reports suggested that nearly half of the cases of autism were associated with a specific medical conditions (Gillberg 1992), recent, more stringent data suggest that this rate may actually be closer to 5% (Fombonne 2005).

## Course

The heterogeneity of autism is particularly evident in the diversity of clinical courses it can follow. No factor has yet been identified to distinguish these children from typically developing children in the first months of life. In a retrospective study of video footage, children younger than 6 months who developed autism were less likely than their peers to focus on social stimuli (Maestro et al. 2002). This phenomenon, revealed by careful scrutiny of home video, is rarely perceived by parents or professionals at the time. By 24 months, however, 90% of parents of children with autism express concern, for reasons including delayed speech, irritability, and passivity (de Giacomo and Fombonne 1998). Given that most of the behaviors used to diagnose autism (e.g., language, intentional prosocial behaviors) have not emerged in infancy, it is quite possible that true age of onset differs from the age at which the symptoms become recognizable. Figure 45–3 illustrates reported age of onset from the DSM-IV field trial. By definition, the onset of autism is prior to age 3, but greater awareness and better screening and diagnostic instruments have facilitated early identification of the condition (Coonrod and Stone 2005, Lord and Corsello 2005). The most common first sign is a failure to develop language. Some parents may be concerned that the child is deaf, while others note that their child responds too dramatically to ambient noise. Occasionally, parents report that their child was passive, essentially "too good." This passivity is usually accompanied by a lack of interest in social interaction or failure to display characteristic enthusiasm for looking at faces. By school age, many children with autism become more responsive socially, develop some response to joint attention (e.g., become able to follow a point), and, in some cases, become more socially drawn to familiar people (Loveland and Tunali-Kotoski 2005). Basic language skills and simple gestures may improve considerably, although other skills may remain deviant. Self-stimulatory and other problematic behaviors, such as self-abuse, can become more common and more difficult to manage as children with autism age.

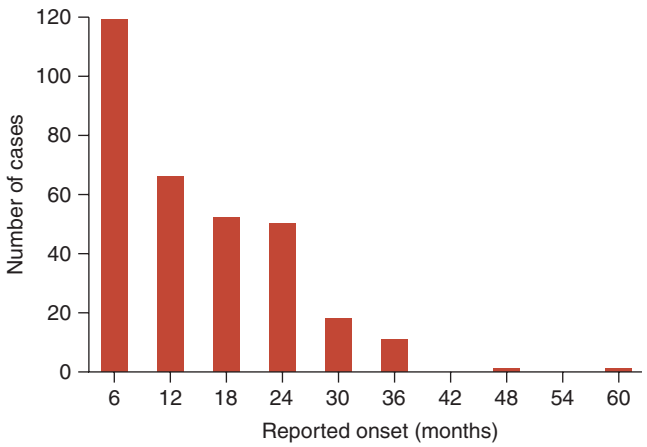



**Figure 45–3** *Age of onset in autism (DSM-IV field trial). (Source: Reprinted, with permission, from Volkmar and Klin [2005].)*

A proportion of children who are ultimately diagnosed with autism are reported to have experienced normal development followed by a pronounced regression during which acquired developmental abilities were lost. Typically, language skills are reported to be lost. For example, a vocabulary of several words may suddenly disappear, sometimes permanently. The majority of regressions are reported in children aged between 18 and 24 months. Estimates of the prevalence of regression in this population have a broad range, from 15 to over 50%, but larger studies have tended toward lower estimates. Children who are reported to have experienced a regression tend to have worse outcomes than their nonregressive counterparts in the domains of receptive and expressive language, play activities, and cognitive ability (Bernabei et al. 2007). Assessment of regression in autism is complicated by limitations of retrospective parent report. Several studies using home videos or methods of inquiry designed to improve recollection by providing temporal cues and comparing recollections with an objective developmental metric suggest that many, if not most, children experiencing regressive autism actually displayed indicators of aberrant development prior to the reported regression.

A wide range of outcomes are observed in children with autism. Some children, for example, never develop speech, whereas a small minority are able to live independently. The majority of children with autism show improved social relatedness, communication, and adaptive skills as they age. Several prognostic predictors have been identified, including the presence of communicative speech, nonverbal intellectual level, and response to educational interventions. The majority of children remain socially isolated, even as they enter the school environment. For example, their interactions may be restricted to circumscribed activities, such as "tickling" games, and when left alone they will fail to initiate social interaction, focusing instead on self-directed, solitary activities. However, significant gains are often made in the social domain and in communication during the early school years; particularly when a structured and intensive program is being followed. Adolescence often is associated with a relative social decline, as the complexity of normal interactions increases exponentially. Although outcome appears to be improving, many adults with autism remain significantly impaired (Shea and Mesibov 2005). Those who are able to achieve personal and occupational self-sufficiency still exhibit residual difficulties in interpersonal interaction. In a recent study in the United Kingdom, the majority of individuals with autism continued to require extensive support in adulthood and were unable to live independently (Howlin et al. 2004). On the basis of standardized cognitive, language and attainment tests and information on social, communication and behavioral problems, many individuals experience what can be considered suboptimal outcomes. Despite historically poor prognosis, the recent development of early screening techniques coupled with refined interventions focused on realistic life skills is significantly improving the prognosis for individuals with autism. Social and adaptive abilities, along with level of language skills

and nonverbal intelligence, are important predictors of independence and long-term diagnosis (Howlin 2005). Early detection and intervention are increasing the proportion of adults who can attain self-sufficiency and independent function. Indeed, studies conducted in the past 20 years demonstrate increased proportion of individuals with better outcomes and decreased proportion of those experiencing the poorest outcomes (e.g., institutional placement; Howlin 2005).

## Differential Diagnosis

Autism must be differentiated from other PDDs, from other developmental disorders (e.g., mental retardation and language disorders), and from sensory impairments, particularly deafness. Both history and current examination are helpful in distinguishing autism from other disorders in the PDD class. In autism, the onset is most often progressive and beginning well before the third birthday, compared to the regressive patterns of onset noted in RD (normal development for 6 months followed by physical changes and degeneration of function) and CDD (normal development followed by deterioration of function after a child's second birthday). As described in greater detail in the section on AD, confusion still surrounds discriminant validity of AD and high-functioning autism. According to current DSM-IV-TR criteria, a diagnosis of autism takes precedence over a diagnosis of AD. The early preservation of language skills in AD and the later age at which parents become concerned may be helpful diagnostic features. In higher functioning individuals with autism there is sometimes trouble distinguishing autism from the personality disorders that involve social isolation, for example, schizoid personality disorder. Table 45–1 lists differential features of autism and the other PDDs.

Severe autism can be difficult to differentiate from mental retardation. Mental retardation often coexists with autism, and the frequency of autistic-like symptoms increases with more severe retardation (Wing and Gould 1979b). Differential diagnosis focuses on specifying a social deficit greater than that predicted by cognitive impairment or developmental delay. In mental retardation, social skills can be usually expected to be commensurate with abilities in the areas of cognition and communication. The diagnostic discrimination is more complicated in persons with severe and profound retardation. In these individuals, the presence of motor stereotypies is common; these "autistic-like behaviors" often confuse diagnosticians, who mistakenly assume them to be defining characteristics of autism.

In suspected regressive autism, other disorders, including selective mutism, RD, CDD, language disorder, schizophrenia, and degenerative CNS disorders are important diagnostic considerations. Typically, children who have experienced severe neglect exhibit delayed or deviant social skills. In these cases, other features of autism are not present and the social deficits are likely to remit with appropriate care. In childhood onset schizophrenia there usually has been a long period (many years) of normal development prior to the onset of the psychotic symptoms that characterize the disorder. In some instances, the diagnosis can only be clarified with certainty over time.

**Table 45–1 Differential Diagnostic Features of Autism and Nonautistic Pervasive Developmental Disorders**

| Feature | Autistic Disorder | Asperger's Disorder | Rett's Disorder | Childhood Disintegrative Disorder | Pervasive Developmental Disorder—Not Otherwise Specified |
|---|---|---|---|---|---|
| Age at recognition (months) | 0–36 | Usually >36 | 5–30 | >24 | Variable |
| Sex ratio | M>F | M>F | F (?M) | M>F | M>F |
| Loss of skills | Variable | Usually not | Marked | Marked | Usually not |
| Social skills | Very poor | Poor | Varies with age | Very poor | Variable |
| Communication skills | Usually poor | Fair | Very poor | Very poor | Variable |
| Circumscribed interests | Variable (mechanical) | Marked (facts) | Not applicable | Not applicable | Variable |
| Family history | Sometimes | Frequently | Not usually | No | Sometimes |
| Seizure disorder | Common | Uncommon | Frequent | Common | Uncommon |
| Head growth deceleration | No | No | Yes | No | No |
| IQ range | Severely impaired to average or above | Average or above | Severely impaired | Severely impaired | Severely impaired to average or above |
| Outcome | Poor to good | Fair to good | Very poor | Very poor | Fair to good |

*Source:* Adapted from Volkmar and Cohen (1991), with permission from Lippincott-Raven.

### Differences in Developmental, Gender, and Cultural Presentations

The majority of studies do not support Kanner's initial impression that autism is overrepresented in children from upper socioeconomic groups. Educated parents with financial resources may be more likely to seek and obtain referrals for evaluation, and thus may be overrepresented in clinical samples. Current efforts made by governmental organizations and private interest groups to increase awareness of autism are intended to increase access to diagnostic and intervention services for children from diverse socioeconomic backgrounds.

## Etiology and Pathophysiology

### Genetic Factors

Autism is currently considered one of the most heritable of childhood disorders. Twin studies show increased concordance rates among monozygotic twin (60–92%) compared to dizygotic twins (0–10% (Bailey et al. 1995). Family studies have demonstrated a rate of recurrence in siblings of approximately 5–10% (Jones and Szatmari 1988, Ritvo et al. 1989), a dramatic increase relative to the general population. Even unaffected siblings are at increased risk for various developmental difficulties; the co-occurrence of isolated symptoms in the absence of the complete syndrome is called the broader phenotype of autism. Research suggests that heritability is complex, involving multiple interacting genes (Risch et al. 1999). Numerous genetic studies have revealed several possible chromosomal regions involved in autism, including 2q, 7q, and 17q (Freitag 2007). A recent collaborative study implicated regions on chromosome 11 (Szatmari et al. 2007).

### Neurobiological Factors

Although neurobiological factors are recognized as important in the pathogenesis of autism, neither specific biological markers nor pathogenic mechanisms have been identified. A variety of EEG abnormalities may be seen in autism, with incidence of EEG abnormalities in autism (in the absence of a clinical seizure disorder) ranging from 10 to 83% (Minshew et al. 2005). The incidence of abnormal EEGs is significantly higher in mentally retarded autistic individuals. Studies on auditory brainstem evoked potentials in autism indicate normal functioning of auditory brainstem pathways. The most robust neuroanatomical findings in autism, and in ASDs more generally, are of increased brain volume, especially with respect to temporal lobe white matter; current evidence suggests normal brain size at birth followed by overgrowth during the second year of life (Hazlett et al. 2005, Courchesne et al. 2001). Neuroanatomical differences have also focused on reduced size of the corpus callosum (Minshew et al. 2005). FMRI and event-related potential studies of hemodynamic and electrophysiological brain responses have detected abnormalities in brain activity associated with face processing mechanisms in the inferotemporal cortex (Dawson et al. 2005, Schultz 2005). An emerging body of research suggests problems with functional connectivity among separate brain regions in ASDs (Just et al. 2004) and atypical function of the motor mirror neuron system. Autopsy studies of a small number of autistic individuals have failed to reveal gross brain abnormalities. However, microscopic analysis has revealed reduced neuronal size and increased cell packing density in the hippocampus, amygdala, mammillary body, anterior cingulate cortex, and septum. Furthermore, decreased numbers of Purkinje cells and granule cells in the neocerebellarcortex have been described (Minshew et al. 2005). Neurochemical studies of ASDs have also produced inconsistent results. The most robust finding is elevated blood serotonin levels, but other studies have reported atypicalities in peptide excretion, neuroendocrine/HPA function, amino acid levels, uric acid excretion, and central cholinergic and gabaergic receptors (Anderson and Hoshino 2005).

### Psychological Factors

Several influential cognitive theories of the social dysfunction in autism have been proposed. One hypothesis posits that there is a lack of a central drive for coherence, with the consequent focus on dissociated fragments rather than integrated "wholes," leading to a fragmentary and overly concrete experience of the world. Another hypothesis posits deficits in "executive functioning," that is, in the capacity to abstract rules, inhibit irrelevant responses, shift attention, and, generally speaking, to "multitask." This hypothesis lacks specificity to autism since a range of developmental psychiatric conditions share such deficits. Another hypothesis posits that autism is caused by an inability to attribute mental states to others. Without such a "theory of mind," individuals with autism are presumed to be unable to infer the thoughts and motivations of others. This impairs their ability to predict the behavior of others and to formulate an appropriate response. The theory argues that this results in the observed lack of reciprocity in communication and social contact. Although the topic of much research, this hypothesis neither accounts for the very early social abnormalities in autism nor is specific to autism.

### Social/Environmental Factors

For some time during the 1950s and 1960s, autism was assumed to occur secondary to poor parenting. Subsequent evidence has demonstrated that this is not the case. Several studies have shown increased rates of early medical complications in children with autism, reflecting the operation of genetic, as well as perinatal, factors. The genetic predisposition to autism may interact with perinatal factors in producing the syndrome. Some researchers have examined the role of immunological factors in autism. There has been a suggestion that maternal antibodies directed against the fetus may be produced in utero. There also have been reports of autism associated with viral infections. Though numerous environmental factors have been postulated to interact with genes to play an etiologic role in ASDs, research has not borne out consistent correlations (Wing and Potter 2002). Falling in this category are various hypotheses regarding factors contained in vaccines, such as mercury-derived preservatives and the weakened viruses themselves; though these continue to receive extensive attention in both research publications and the popular press, large studies to date have not supported a causal, or even correlative, relationship between vaccines and autism.

## Treatment

### Treatment Goals

No curative treatment for autistic disorder is known, and a definitive intervention does not exist for any of the core features of the disorder. Several elements have been identified by the National Research Council (2001) as common among the most effective nonpharmacological interventions: implementation in early childhood (the earlier, the better), structure, frequency, and intensity. For individuals with autism, as any child with special needs, treatment should focus on making academic content and real-life skills accessible. Given the social and communicative vulnerabilities that characterize autism, treatment should also focus on the development of age-appropriate social and communicative abilities, aiming to teach through explicit instruction the skills that are not naturally acquired during development. Recommended interventions focus on (a) devising strategies to utilize strengths (e.g., cognitive or memory skills) to compensate for areas of difficulty, (b) modifying environments to provide optimal support for learning and socialization, and (c) minimizing disruptive behaviors. Intervention programs should be tailored to the individual needs of the child, based on a thorough multidisciplinary assessment as described above. Nearly all intervention programs will include acquisition of basic social and communication skills (especially pragmatic communication), adaptive functioning, and, depending on what is developmentally appropriate, academic or vocational skills (Attwood 2000, Howlin 1999, Myles and Simpson 1997, Ozonoff et al. 2002). Intervention must also incorporate techniques to encourage generalization of acquired skills beyond the context of instruction. Appropriate intensive education should also provide support and training for parents.

### Somatic Treatments

#### *Psychopharmacology*

The decision to medicate a child with autism is a difficult one as no proscribed treatment regimen comprehensively addresses the symptoms of autism. In general, drugs can be used to treat associated features of autism, but none exist to address the primary social dysfunction (though it is hoped that amelioration of behaviors that interfere with learning and social interaction can yield social benefits). Furthermore, all effective drugs carry notable side effects. Various classes of pharmacological agents have been used to target the symptoms associated with autism with mixed results. Prior to initiating drug treatment, a thorough physical examination should be conducted, including baseline laboratory studies (tests of liver and renal function, ECG, urinalysis, and blood count). Goals for treatment should be clearly defined, and data to monitor progress aggressively sought. Valuable information can come from the staff of the child's educational and behavioral programs, and it may be appropriate to recruit these staff to collect behavioral data. When doing so, data should be collected over a period of time during a subportion of which the drug is introduced, effectively "blinding" the data collectors to reduce reporting bias.

Atypical antipsychotics, a class of medicines used traditionally for the treatment of psychotic disorders, have been used to treat disruptive behaviors in autism. A large multisite, placebo controlled study examined the efficacy of the antipsychotic risperidone for the treatment of aggression, tantrums, and self-injury in children with ASDs with compelling improvements in these target symptoms (McCracken et al. 2002). Furthermore, modest improvements in hyperactivity, repetitive behavior, socialization, communication, and daily living skills were also noted during this trial. In 2006, the Food and Drug Administration approved risperidone to treat aggression, tantrums and self-injury in children with autism between the ages of 5 and 16; this was the first approved on-label application for a drug to treat autism. Although risperidone is now considered the standard for this use, other equally potent members of the atypical antipsychotic class might also be effective, varying more in side effect profile than in efficacy. The side effects of the atypical antipsychotics, however, can be significant, thus they must be used carefully and toward an explicit and specific goal.

The selective serotonin reuptake inhibitors (SSRIs), developed for the treatment of depression, may ameliorate several groups of symptoms in the population with autism, in particular repetitive behaviors and anxiety. Although these drugs are usually well tolerated, concerns about potential for akathisia, behavioral activation, and agitation suggest that they must be prescribed judiciously. A recent meta-analysis highlighted these concerns and called for larger randomized control trials (Kolevzon et al. 2006).

Several other drug classes have been used in this population, with mixed results. The antiepileptics, a class of drugs also used for their ability to stabilize mood, have been used extensively in individuals with autism for the treatment of seizures. Research examining their effectiveness in treating mood lability, aggression, and repetitive behaviors in this group has shown inconsistent effectiveness. Stimulants are effective for the treatment of ADHD in typically developing children, and some studies have shown them to be effective for the treatment of similar symptoms in the autism population. However, reports of exacerbation of stereotypies and worsened social withdrawal have also been described. Glutamatergic agents, such as d-cycloserine, show some promise of effectiveness, pending additional research (King 2006). Others, such as secretin, although originally met with great enthusiasm after anecdotal reports of dramatic recoveries, have failed to show results under systematic study. Various chelating agents, used pursuant to controversial theories of mercury playing a causal role in development of the disorder, have failed to show effectiveness, but have been implicated in adverse outcomes (Brown et al. 2006). Advances in the understanding of the brain mechanisms underlying the symptoms of autism are constantly being made in multiple disciplines, including genetics, neurobiology, and neuroimaging. This information, it is hoped, will lead to pharmacological interventions that more specifically target the mechanisms underlying autistic symptomatology.

#### *Complementary and Alternative Therapies*

A variety of theories of both the etiology and pathophysiology of autism have generated an array of unproven treatments. Although many of these therapies are benign, others, such as behavior modification by electric shock, are potentially harmful and raise important questions about the limits of intervention. Still others have been examined

with no demonstrated efficacy, such as modifications in diet. Information about these treatments is often communicated both by word of mouth and the Internet; published studies consist primarily of case reports. Many times, enthusiasm for alternative therapies precedes adequate investigation of the approach.

A particular concern is that complementary and alternative medicine (CAM) may have a divisive effect on the relationship between mainstream practitioners and parents. Wong and Smith (2006) described several reasons cited by parents for not disclosing the use of CAM to their child's physician. Chief among these was "physicians' lack of knowledge about CAM." Another significant factor was anticipated disapproval. Thus, the mainstream is charged with maintaining a clearing-house on these topics, and individual practitioners working with autism must keep abreast of the information and maintain nonjudgmental, working relationships with parents. In advising parents of children with autism, the first concern for alternative therapies should be the child's safety. Then a consideration of the cost and the time involved in the therapy is appropriate to ensure that there is no interference with more established forms of therapy underway.

## Psychosocial Treatments

### *Education*

Children with autism require intensive, highly structured special education from educators specifically trained to work with individuals on the autism spectrum. Early, continuous intervention is highly desirable and has measurable effects on later intellectual and communicative functioning. Educational interventions are best provided over a full day of school on a year-round basis, as breaks are poorly tolerated and can result in loss of skills. Classroom settings with a low student to teacher ratio (ideally individualized instruction) are ideal. For the most impaired children, goals should include teaching the child (1) to tolerate individual adult guidance in performing tasks, or acquiring "learning to learn skills," (2) to follow a daily routine, (3) to develop functional communication, and (4) to move from concrete associations to understanding concepts. Learning environments should minimize distractions; individual workstations and physical prompting may be necessary. The use of highly predictable and consistent routines supports the child's own internal sense of order, scheduling, and organization of experiences to promote learning. Children with autism often learn skills in response to very concrete instruction and limited to specific settings. Therefore, it is important to ensure that the child uses acquired skills spontaneously and can generalize these skills to other settings. Children with autism may acquire a considerable vocabulary and yet fail to use these words for effective communication. Therefore, any efforts toward enhancing language acquisition should focus on the communicative function of language. For example, vocabulary expansion should focus on words that are relevant to meeting a child's basic needs. Children who do not vocalize should be engaged in programs focused on alternative forms of communication, such as written signs, communication boards, and other forms of augmentative communication. The utilization of these alternative forms of communication should not derail development of vocal communication in children for whom this represents a realistic goal.

For older or intellectually able children, educational program should focus on social and communication skills training. The skills to navigate challenging situations should be rehearsed and scripted; concrete social and communication skills (e.g., eye gaze, voice modulation, gesture, posture, proximity, greeting behaviors, conversation, and social mores) should be taught in a very explicit fashion. This education should move from static concrete representations of social interaction to increasingly dynamic, realistic contexts. Correspondingly, the teaching environment for social skills therapy may alternate between small group instruction (allowing for teaching and practice with adult facilitation and feedback) to naturalistic settings (starting with adult facilitation and fading support over time). Successful techniques used for this purpose include modeling of behaviors by an instructor, self-observation, role-playing, and the use of individualized social stories.

### *Behavior Therapy*

Even among the lowest functioning children on the autism spectrum, behavior modification techniques have been successfully employed to establish desired behaviors and reduce problem behaviors. Behavior modification may reinforce appropriate behaviors and lessen inappropriate ones, facilitating involvement in educational programming (Lovaas 1987). Most educational programs for children with autism utilize behavioral management techniques, although they vary in the degree to which these are integrated into the comprehensive educational program. Behavior therapy is particularly useful in the management of disruptive behaviors, including difficulties in attention and compliance, tantrums and self-injurious behavior. The first step entails functional behavior analysis to identify environmental antecedents and the purposes these behaviors serve for a child. Next, behavioral techniques, such as shaping or extinction, are used to decrease effectiveness of maladaptive behaviors and promote a desired alternative behavior. Behavioral principles are also utilized for learning, including the promotion of early cognitive skills such as categorization and elicitation of vocalization and speech. An appropriate behavior curriculum should place special emphasis on generalization and self-initiated skills. It is also important to ensure that the child would not benefit from more typical teaching modalities, as behavior therapy can be resource intensive.

### *Psychotherapy*

As a biological etiology for autism has been recognized, psychodynamic and unstructured play therapies have been rendered less focal in the treatment of children with autism. Individual psychotherapy may be appropriate for higher functioning individuals presenting with anxiety and depressive symptoms. In these cases, psychotherapy should focus on explicit problem-solving skills rather than undirected, insight-oriented approaches. Cognitive–behavioral therapy tailored specifically to individual profiles of strengths and weaknesses may be helpful with adolescents and adults. Organized social interactions (social groups) may be extremely effective, providing opportunities to learn and practice social skills with peers.

## Asperger's Disorder

### Diagnosis

#### Definition and Diagnostic Features

AD is currently differentiated from other ASDs by the preservation of linguistic and cognitive abilities despite profound social disability and circumscribed interests (American Psychiatric Association 2000). AD is named after an Austrian pediatrician, Hans Asperger. In 1944, at approximately the same time when Leo Kanner described children with "autism" in the United States, Asperger described a group of school-aged boys with intact cognitive and language skills but difficulties with social interaction (Asperger 1944). He called the disorder "autistic personality disorder." Asperger noted poor social integration, reduced nonverbal communication, idiosyncratic verbiage, strong (and often unusual) areas of interest, limited empathy, clumsiness, and behavior problems. Asperger suggested that these difficulties did not emerge before 3 years of age, and he commented on the apparent heritability of the disorder.

In 1981, Lorna Wing translated Asperger's manuscript into English, introducing the diagnostic concept into American psychiatry and elaborating upon it (Wing 1981). Wing modified Asperger's original characterization by describing symptoms of the disorder evident during the first 24 months of life including disinterest in others, decreased prelinguistic verbalizations, reduced sharing of interests, stereotypic speech, and limitations in imaginative play. Subsequent to Wing's publication, diagnostic criteria for AD were incorporated into the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1994).

Clinicians and researchers continue to struggle with the most appropriate diagnostic conceptualization of AD, especially in terms of distinguishing it from other high-functioning ASDs. Current diagnostic criteria in the DSM-IV-TR; see DSM-IV-TR criteria for Asperger's Disorder) distinguish AD from autism based on the absence of language delays and the preservation of cognitive ability and daily living skills (American Psychiatric Association 2000). Specific diagnostic criteria require that an individual demonstrate two symptoms within the social domain and at least one symptom from the domain of restricted, repetitive, and stereotyped behaviors. The diagnosis of AD also requires that the social disturbance be significant enough to detrimentally impact functioning in terms of self-sufficiency, employment, or other important areas of functioning.

One of the most striking clinical features of AD is the focused pursuit of specific areas of interest. This is typically evident by grade school, when many children with AD have accumulated volumes of information about a narrow area of expertise. The particular topic of interest is not always consistent across development. The content of circumscribed interests may be unusual or developmentally inappropriate (e.g., interest in public transit or electronic circuitry), but some interests are atypical only in degree (e.g., interest in sea animals). The circumscribed interests characteristic of AD possess an obsessive and intrusive quality, often in the absence of a practical, contextual understanding of the topic. For example, a child might be interested in memorizing the model numbers of vacuum cleaners without any interest in learning to use them.

These circumscribed interests complicate the social interactions of people with AD. Although some children with

**DSM-IV-TR Criteria for Asperger's Disorder**

A. Qualitative impairment in social interaction, as manifested by at least two of the following:
   (1) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction,
   (2) failure to develop peer relationships appropriate to developmental level,
   (3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing or pointing out objects of interest to other people)
   (4) lack of social or emotional reciprocity

B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following
   (1) delay in or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
   (2) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
   (3) stereotyped and repetitive use of language or idiosyncratic language
   (4) lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level

C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning

D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

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AD display disinterest in social interaction or engagement with peers, many actively pursue social contact. However, long-winded, fact-based monologs, characteristic of these children, often alienate them from peers. Unfortunately, for many children with AD, a desire for social companionship evident in early childhood may diminish over time after repeated failed social encounters. Deficits in empathizing have been reported to be more subtle than in individuals with autism (Kaland et al. 2002). Intact cognitive skills often allow children with AD to approximate typical social skills in clinical contexts or those in which expectations are clear; these skills look worse in the context of rapid, fluid social interactions (Klin et al. 2002a). Children with AD may distill social interactions to determine rules of behavior and guidelines for social interaction. Subsequent application of these rules may lead to awkward social behaviors, such as inappropriate, sustained eye contact or theatrical use of gestures, conveying, at best, social naiveté to their peers (Klin et al. 2005a).

Preserved linguistic facility in AD only requires that children with AD acquire language "on time." Language acquisition and use tends to be atypical in several respects. Children with AD may possess a precocious vocabulary while still quite young. Speech quality is often pedantic, and children with AD may speak intrusively and at great length about their interests. The comments of a conversational partner may be ignored, talked over, or nominally regarded. The volume of speech is often loud or inappropriately modulated. Tone is frequently observed to be nasal with poor prosody and limited use of affective inflection (Ghaziuddin and Gerstein 1996). A failure to appreciate the listener's perspective and a consequent omission of background information and transitional phrases may result in speech patterns that appear loose or tangential.

Clumsiness has been noted as a feature of the disorder since Asperger's initial account. Children with AD often appear to move awkwardly, and they often have difficulty accomplishing childhood tasks that require motor dexterity. Research has documented unusual gait patterns, odd posture, poor handwriting, problems with visual motor integration, and proprioception (Tantam 1988, Gillberg 1990, Weimer et al. 2001). Poor motor coordination skills have not been demonstrated to be a unique feature of AD versus other high-functioning ASDs (Smith 2000, Green et al. 2002).

Individuals with AD often exhibit a distinctive neuropsychological profile. Klin et al. (1995) compared individuals with AD to those with high-functioning autism (HFA) on a variety of neuropsychological measures. Individuals with AD exhibited deficits in fine and gross motor skills, visual motor integration, visual-spatial perception, nonverbal concept formation, and visual memory despite normal articulation, verbal output, auditory perception, vocabulary, and verbal memory. Other studies have reported that AD is associated with stronger verbal abilities relative to performance abilities, with particular weakness in visual-spatial organization and graphomotor skills (Ghaziuddin and Mountain-Kimchi 2004, *Ehlers* 1997). This neuropsychological profile is often referred to as nonverbal learning disability (NLD; Rourke 1989). In contrast, individuals with other high-functioning ASDs typically demonstrate the reverse pattern, that is, lower scores on measures of verbal functioning (Reitzel and Szatmari 2003). Some researchers have argued that individuals with AD possess greater broad cognitive ability than individuals with HFA, irrespective of verbal ability or verbal–nonverbal discrepancy (Miller and Ozonoff 2000). Understanding of the utility of neuropsychological profile as a distinguishing feature of AD is complicated by use of heterogeneous diagnostic schemes in research studies (Klin et al. 2005b).

### Clinical Vignette 2: Asperger's Disorder

Adam was the third of three children born to a social worker and an office manager. No medical problems were reported during pregnancy or birth, and his medical and family history was unremarkable. His pediatrician expressed mild concern during the first 24 months of his life because his motor milestones (e.g., sitting up, walking) consistently fell at the late end of normal limits. His language development was precocious; he had amassed a formidable vocabulary by 12 months and, by 24 months, was using four to five word sentences. He displayed great interest in trains and dinosaurs, and he spent large amounts of time as a young child examining books about these topics. His parents viewed his facility with language and extensive knowledge favorably and perceived him to be intellectually gifted. They noted that Adam had great difficulty putting aside these activities; he also became extremely flustered with unexpected changes in his schedule. They worked around this rigidity by providing Adam with extensive notice before any activity or change in schedule was initiated. First concerns emerged at age 4, when Adam was expelled from nursery school for physical aggression. His preschool teachers reported that he was extremely possessive of his favorite toys and would strike children who attempted to play with them. This behavior pattern continued into grade school, and Adam was considered a "behavior problem" by many of his teachers. Adam displayed minimal interest in developing friendships, preferring to focus upon a newfound interest, American history. In third grade, Adam was referred for a psycho-educational evaluation because of difficulties with math. Results of testing indicated a significant discrepancy between his strong verbal skills and his weak visual-spatial abilities and poor fine motor control. The evaluator noted his strong preoccupation with a particular topic and its intrusive effects on adaptive functioning in the social and academic realms. Despite his strong language skills, the evaluator described poor conversation skills, a tendency to speak in a pedantic tone, and poor modulation of the volume and inflection of his voice. The evaluator diagnosed Adam with Asperger's Disorder. He began participation in social skills groups at school and enrolled in individual therapy to work on his understanding of social mores and for explicit instruction in social behavior. He developed several social relationships based around his area of interest (with a local historical society). As Adam approached adolescence, he became increasingly interested in social interaction and romantic relationships. At this time, Adam became acutely aware of his social difficulties and experienced depression, which was successfully addressed through pharmacotherapy. Adam graduated high school, enrolled in a junior college transition program for individuals with developmental disabilities, and eventually obtained a bachelor's and obtained employment as a library employee.

## Assessment

Assessment for AD is as described above for autism. Though diagnostic screeners have been developed to identify individuals with AD, none have yet been shown to reliably and accurately differentiate individuals with AD from those with other ASDs, especially HFA (Lord and Corsello 2005).

## Epidemiology

Fombonne and Tidmarsh (2003) reviewed epidemiological studies of AD and found prevalence rates ranging from 0.3 to 48.4 per 10,000; the authors suggested a working prevalence rate of 2.6 per 10,000 for AD. The condition is more prevalent in males than females, with a reported ratio of 9 to 1.

## Comorbidity Patterns

The most common disorders co-occurring with AD are depression and anxiety. Research estimates of comorbid anxiety and/or depression in individuals with AD are as high as 65%, and some researchers have suggested that these elevated rates distinguish AD from HFA (Ghaziuddin et al. 1998, 2002, Green et al. 2000). Other data suggest, however, that individuals with AD and HFA are equally at risk for problems with anxiety and depression (Kim et al. 2000). Anxiety in AD may stem from violations of their rigid routines and rituals or social anxiety, that is, a preoccupation with failing during social encounters. Serious depressive symptoms may also be experienced, often in the context of social failure and loneliness. Hyperactivity and inattention are common among children with AD (Eisenmajer et al. 1996, Schatz et al. 2002), and many children with the disorder are often initially misdiagnosed with attention-deficit/hyperactivity disorder. Some studies have associated AD with Tourette's syndrome (Kerbeshian and Burd 1986, Littlejohns et al. 1990, Marriage et al. 1993), obsessive–compulsive disorder (Thomsen 1994), and psychotic conditions (Gillberg 1985). Researchers have investigated and rejected the notion that preserved intellectual function coupled with limited empathy may predispose individuals with AD to violent or criminal behavior (Everall and LeCouteur 1990, Ghaziuddin et al. 1991). As described above, the unique neuropsychological profile of nonverbal learning disability has also been associated with AD (Stein et al. 2004).

## Course

Because, by definition, children with AD develop language and self-help skills in a timely manner, these red flags are not evident in early childhood. Therefore, these children are not typically identified until later in development. Furthermore, the more subtle impairments associated with AD, such as impairments in social reciprocity and special interests, may not be evident until a child attains the developmental level of a typical grade school student. Research indicates that diagnosis of AD is most commonly made after 4 years of age (Szatmari et al. 2003) and often as late as 11 years (Howlin and Asgharian 1999, Gillberg and Cederlund 2005). Though research in the early detection and diagnostic stability of AD is complicated by inconsistencies in diagnostic systems, a recent study suggests that diagnosis of AD cannot be rendered with reliability prior to age 4 (McConachie et al. 2005).

Despite later diagnosis, parents of children with AD retrospectively report concerns about their child's behavior, social motivation, language, play, or insistence upon sameness before age 3 (Gilchrist et al. 2001) and as early as 20 months of age (Chakrabarti and Fombonne 2005). In contrast to other ASDs, the disabilities associated with AD may not be readily evident in the context of social interactions with adults, who are often charmed by what they perceive as precocity. Subtle indicators in early childhood may be approaching adults for instrumental rather than social reasons. For example, children with AD might use language or gesture to engage adults for making requests (e.g., "That toy is out of reach") instead of sharing interests (e.g., "That toy is interesting to me"). By preschool age, strong interests in a particular subject matter are commonly evident. The social disability associated with AD is often first noticed when children encounter public settings with peers, such as daycare or preschool. These children may actively avoid interactions with other children or make social overtures in atypical ways (e.g., by abruptly introducing a fact about a special interest). Another early indicator of AD may be behavioral rigidity. This trait can manifest as ritualizing daily activities, such as dressing in a particular sequence, or stringently adhering to a schedule. Rigidity can interfere with social interactions, and children with AD may become upset when other children fail to do things "right."

Asperger's (1944) initial description of these children predicted positive outcomes based on the presence of intact cognitive ability and the potential for the application of special skills in gainful employment. Compared to lower functioning individuals with ASD, more positive outcome can indeed be expected, especially in the domains of academics and self-help skills (Gillberg 1991). Differential outcome compared to other high-functioning ASDs is still under investigation, and some have suggested that comparable outcomes may be expected of individuals with AD and HFA (Szatmari et al. 1989). Adolescents with AD continue to have difficulty with independent self-care and organization, and they exhibit ongoing disturbances in social and romantic relationships. Studies of young adults with AD report that most remain at home despite high cognitive potential, but a minority marry and work independently (Tantam 1991).

## Differential Diagnosis

The great majority of children with ASDs experience early delays and deviance in language acquisition and cognitive impairment and are thus readily distinguished from children with AD. Differential diagnosis between AD and HFA is more difficult, and research has yet to conclusively demonstrate that the two disorders are reliably distinctive. By strict diagnostic criteria, AD differs from HFA in terms of appropriate developmental attainment of language milestones. Social and communication deficits may be less severe in AD, and motor mannerisms may not be evident. In contrast, circumscribed interests are more salient and motor awkwardness is more common in AD. In DSM-IV-TR, if the child meets criteria for autism, this should take precedence over a diagnosis of AD. Given the nonspecific diagnostic criteria for PDD-NOS (described in detail in the PDD-NOS section below), the distinction between AD and PDD-NOS is less consistent. Individuals with AD tend to display more significant social impairment with less pronounced communication deficits. Children with AD also

exhibit intense, circumscribed interests that are a focus of verbiage. Cognitively able, verbal children will often be diagnosed with PDD-NOS in lieu of AD if they fail to present with such preoccupations. Clinical reports stress circumscribed interests, verbosity, and motor clumsiness in AD versus PDD-NOS. Schizoid personality disorder shares some of the social features, but individuals with this disorder do not show the level of severity of social impairment nor the early developmental patterns characteristic of AD. For these reasons, a detailed developmental history documenting early onset and continuity of symptoms may be important in the differential diagnosis.

## Etiology and Pathophysiology

### Genetic Factors

Many case reports have reported AD, ASD, or autistic-like traits in family members of those with AD, particularly among fathers (Gillberg and Cederlund 2005, Ghaziuddin 2005). Klin et al. (2005b) reported rates of ASDs or subclinical autistic features (the broader autism phenotype) in parents and grandparents of probands with AD that were triple the rate found for the same relatives of probands with HFA (17% vs. 5%). Though this finding suggests that AD may have an even stronger genetic component than autism (Volkmar and Klin 2000), the preponderance of research suggests shared genetic mechanisms common to all ASDs (Frith 2004). Though no clear genetic etiology has been established for AD, some studies have reported specific genetic abnormalities in case studies of patients with AD: translocations (balanced and de novo) (chromosomes 1, 5, 11, 13, 14, 15, 17) (Anneren et al. 1995, Tentler et al. 2001, Cederlund and Gillberg 2004, Tentler et al. 2003), autosomal fragile site (Saliba and Griffiths 1990), fragile X syndrome (Bartolucci and Szatmari 1987), Fragile Y, and 21p+ (Cederlund and Gillberg 2004).

### Neurobiological Factors

Several reports of medical abnormalities associated with AD have appeared, but no factors have been reliably associated with AD across studies. Wing (1981) reported a high frequency of perinatal problems (nearly half of her original sample) among individuals with AD. Other reports have associated AD with medical conditions, including aminoaciduria (Miles and Capelle 1987) and ligamentous laxity (Tantam et al. 1990). A case series by Gillberg (1989) reported high frequencies of medical anomalies common to both AD and autism, but these results have not been consistently replicated (Rutter et al. 1994). Increased rates of epilepsy have been observed among individuals with AD (Cederlund and Gillberg 2004). Anomalies have also been detected in eye movements and visual scanning in individuals with ASDs (Sweeney et al. 2004), particularly when viewing social scenes (Klin et al. 2002b), but these findings have not yet been shown to distinguish AD from other ASDs. Neurochemical research has not revealed anomalies specific to AD (Anderson and Hoshino 2005). Neuroimaging research has not revealed any common pathologies among individuals with AD, both with respect to typical individuals and in terms of differentiation among other ASDs. Berthier et al. (1990) reported MRI results indicating left frontal macrogyria and bilateral opercular polymicrogyria in patients with AD. Other studies have reported gray tissue anomalies (McAlonan et al. 2002, Kwon et al. 2004), left temporal lobe damage (Jones and Kerwin 1990), left occipital hypoperfusion (Ozbayrak et al. 1991), and dysmorphology superior to the ascending ramus of the Sylvian fissure proximal to the intersection of the middle frontal gyrus and the precentral sulcus (Volkmar et al. 1996). Functional imaging has also failed to detect reliable differences among AD and other ASDs. SPECT imaging has suggested abnormal right hemisphere functioning in AD (McKelvey et al. 1995). Other research has found dysfunction in brain regions subserving social cognition (anterior cingulate cortex, prefrontal cortex, temporoparietal junction, amygdala, and periamygdaloid cortex (Schultz and Robins 2005). Abnormal functional connectivity among brain regions has also been implicated in AD (Welchew et al. 2005).

### Psychological Factors, Social/Environmental Factors

Hypothesized psychological and social factors are as described for autism.

## Treatment

### Treatment Goals

As with autistic disorder, no cure exists for AD. Aside from considerations relevant to linguistic capability, verbal strengths, or nonverbal vulnerabilities, comparable treatment guidelines apply to AD and other high-functioning ASDs (Mesibov 1992).

### Somatic Treatments

#### *Psychopharmacology*

Medications are frequently prescribed for individuals with AD despite limited data on efficacy. As with autism, there are no medications that address the core social and communicative features of AD; thus treatment should be targeted at ameliorating symptoms and maximizing adaptive gains. In combination with behavioral interventions, they may be effective in treating the constellation of symptoms associated with AD, including anxiety, depression, inattention, and aggression. The specific classes of agents discussed in the section on autism are utilized for the same reasons in AD. It has been argued that individuals with AD may have atypical responses to medications, even when compared to other individuals with ASD (McDougle et al. 1998), but data remain inconclusive. Very few studies of pharmacological interventions for AD exist. The atypical antipsychotics risperidone and olanzapine have shown efficacy to diminish externalizing behavior (e.g., aggression and agitation) associated with AD, to improve global functional levels, and to lowering AD symptomatology (McCracken et al. 2002, Milin et al. 2006). A thorough appreciation of the wide range of symptoms manifest in AD is essential for the prescriber. Polypharmacy should be avoided when possible, and a clear notion of what is being targeted should be maintained. Information about progress should be obtained from all members of the care team, and medications that are not meeting the explicit predetermined goals should be reevaluated.

### *Complementary and Alternative Therapies*

As with autism, a host of complementary and alternative treatments exist for AD. Limited research exists to support most of these treatments.

### *Psychosocial Treatments*

As in autism, treatment of AD is essentially supportive and symptomatic, and, to a great extent, treatment guidelines overlap with those for individuals with HFA. No systematic research has demonstrated unique efficacy of any one intervention modality (Klin and Volkmar 2003). As children with AD are often quite verbal and perform well academically, parents often encounter resistance in seeking services. However, targeting their profound social impairments and deficient adaptive skills should indeed be incorporated into any educational intervention. Learning strategies and social mores are best taught in an explicit and rote fashion using a parts-to-whole verbal instruction approach, providing the child with explicit steps to perform effectively. Specific treatment guidelines should be developed according to the individual's unique neuropsychological profile. The acquisition of self-sufficiency skills should be a priority, and a tendency to rely on rigid rules and routines can be exploited toward this end.

A verbal algorithm approach may be applied to social problem solving and for handling the requirements of troublesome situations that can be anticipated (e.g., encountering novelty or frustration). Specific teaching should address recognition of troublesome situations and selection of the appropriate strategy to employ. Social and communication skills are best taught by a communication specialist in the context of both individual and small group therapy. Communication therapy should include use and decoding of nonverbal behaviors, social awareness, perspective-taking skills, and interpretation of nonliteral language. Adults with AD should be trained for and placed in jobs appropriate to their social and neuropsychological characteristics (including job application and interview skills). It is preferable that employment does not entail intensive social demands, time pressure, or the need to quickly improvise or generate solutions to novel situations. Anecdotal evidence suggests that individuals with AD may benefit from participation in support groups. Opportunities for social interaction may be built around special interests (e.g., hobby groups). Supportive psychotherapy may be helpful in dealing with feelings of despondency, frustration, and anxiety; a cognitive–behavioral, problem-solving focus is likely to yield greater benefit than insight-oriented approaches.

## Childhood Disintegrative Disorder

### Diagnosis

#### Definition and Diagnostic Features

CDD is a relatively rare condition in which clinical features resembling autism develop after a period of normal development. The disorder was first described by Theodore Heller (Heller 1908), who termed the condition *dementia infantilis*; subsequently, it has also been referred to as disintegrative psychosis or Heller's syndrome. Nearly 200 cases have now been reported in the literature (Volkmar et al. 2005). The DSM-IV-TR definition (see DSM-IV-TR criteria for Childhood Disintegrative Disorder) of the disorder specifies ostensibly normal development for at least the first 2 years of life followed by clinically significant loss of previously acquired skills in at least two areas (expressive or receptive language, social skills, bowel or bladder control, play, or motor skills). The individual must also exhibit qualitative impairment in social interaction, communication, and restricted, repetitive, and stereotyped patterns of interest as defined for autism. The regression in skills must occur before age 10 years. By definition the condition is not better accounted for by another PDD.

**DSM-IV-TR Criteria for Childhood Disintegrative Disorder**

A. Apparently normal development for at least the first 2 years after birth as manifested by the presence of age-appropriate verbal and non-verbal communication, social relationships, play, and adaptive behavior.

B. Clinically significant loss of previously acquired skills (before age 10 years) in at least two of the following areas:
   (1) expressive or receptive language
   (2) social skills or receptive language
   (3) bowel or bladder control
   (4) play
   (5) motor skills

C. Abnormalities of functioning in at least two of the following areas:
   (1) qualitative impairment in social interaction (e.g., impairment in nonverbal behaviors, failure to develop peer relationships, lack of social or emotional reciprocity)
   (2) litative impairments in communication (e.g., delay or lack of spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, lack of varied make-believe play)
   (3) restricted, repetitive, and stereotyped patterns of behavior, interests and activities, including motor stereotypies and mannerisms.

D. The disturbance is not better accounted for by another specific Pervasive Developmental Disorder or by Schizophrenia.

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Clinical Vignette 3: Childhood Disintegrative Disorder

Ralph developed typically throughout infancy, and his developmental milestones were all on time. Shortly after his third birthday, his phrase speech diminished, and he began showing less social initiative. During the span of a few months, his speech disappeared completely. He also lost bowel control and began displaying motor stereotypies and engaging in repetitive behavior with objects. He no longer responded when his parents or siblings called his name, and he displayed enjoyment in interactions with other people only when interactions involved tickling or being spun in the air. A battery of medical tests, including MRI and clinical EEF, were administered with negative results. Ralph was enrolled in a small private school for children with autism. He developed minimal functional communication and transitioned to institutional care in adulthood.

### Assessment
Assessment procedures are essentially the same as for autism except that more extensive medical evaluations are indicated to rule out other medical conditions associated with developmental deterioration, such as neurolipidosis and Addison–Schilder's disease. These include the search for inherited disorders (e.g., of metabolism) or other conditions characterized by developmental deterioration. A neurological assessment, including EEG and an MRI scan, should be obtained.

### Epidemiology
Epidemiological data are limited but the disorder appears to be extremely rare, with prevalence estimates in the range of 1 in 100,000 children (Volkmar et al. 2005).

### Comorbidity Patterns
In general, children with this condition have limited communication skills and severe intellectual disability. A variety of medical conditions, for example, the neurolipidoses, metachromatic leukodystrophy, Addison–Schilder's disease, and subacute sclerosing panencephalitis, can be associated with loss of developmental skills, and these would be diagnosed as comorbid if their presence is documented. Usually, however, intensive medical investigation does not reveal the presence of such conditions.

### Course
Usually, the onset of CDD is between the ages of 3 and 4 years. There may be nonspecific agitation or anxiety prior to developmental deterioration; the onset may be gradual or abrupt. The loss of skills is of great concern to parents who typically seek extensive medical evaluations to determine the cause of the deterioration in the child's development. In most instances (probably about 75% of cases), after the developmental deterioration, the child's behavior stabilizes, with no further deterioration but minimal subsequent gains. In some cases, a partial recovery occurs (e.g., recovery of single word or phrase speech), and, rarely, children make a more substantive recovery. If the condition is associated with a progressive neuropathological process, deterioration can be progressive; otherwise life expectancy is normal. It appears that the outcome of the condition is worse than that for autism (Volkmar and Cohen 1989).

### Differential Diagnosis
CDD may be differentiated from regressive autism based on the timing and severity of loss of skills. For a diagnosis of autism, the difficulties must be evident prior to age 3; if loss of skills occurs subsequent to the third birthday, CDD is the more appropriate diagnosis. Furthermore, in most cases of regressive autism, the child will typically not have progressed to speaking in sentences (as may be the case for children who develop CDD), and other signs of disturbance (e.g., social difficulties) are likely to be present prior to any perceived regression. Differential diagnosis from RD can be based on Rett's characteristic head growth deceleration and specific clinical features. The syndrome of acquired aphasia with epilepsy (Landau–Kleffner Syndrome) is characterized by development of an aphasia, but, unlike CDD, social interest and nonverbal communicative skills are often preserved.

### Differences in Developmental, Gender, and Cultural Presentations
The condition is about five times more common in males than females. It is likely that some early reports of females actually represented misdiagnosed cases of RD.

## Etiology and Pathophysiology
Various lines of evidence support the importance of neurobiological factors in the pathogenesis of CDD, though no unique etiologic or pathologic features have been revealed. Seizures are sometimes observed, and the EEG is reported to be abnormal in about half of cases.

## Treatment
Treatment is as for autism with an emphasis on use of special educational and behavioral interventions to help the child reacquire lost skills and gain new abilities. Pharmacological interventions may be helpful in dealing with agitation and stereotyped mannerisms if these interfere with the child's functioning.

# Rett's Disorder

## Diagnosis

### Definition and Diagnostic Features
Rett's disorder (RD), also called Rett's syndrome, is a rare genetic neurodevelopmental disorder that almost invariably affects females. The disorder is characterized by a period of normal development, usually the first 6 months of life, followed by deceleration of head growth, social withdrawal, and a generalized slowing of development. A regressive phase follows, during which previously acquired receptive and expressive language skills are lost. During this period, motor skills, specifically purposeful hand skills, also regress and are replaced by characteristic hand stereotypies of hand-wringing and washing motions (Van Acker et al. 2005). This regression may take place insidiously over a prolonged course or more abruptly in the span of several days. Generally around the age of 3, this regression slows, leaving severe mental retardation and neurological deficits, including spasticity, seizures, and trouble coordinating breathing and eating (Moser et al. 2007). Improvements in social engagement are often seen during this plateau. During early puberty, there is generally further deterioration in

motor function, with progressive scoliosis and muscle wasting. Children with RD often become wheelchair bound.

## Assessment

The unique natural history must be considered when evaluating suspected cases of RD and is particularly important in generating differential diagnoses. For children who meet clinical diagnostic criteria for RD (see DSM-IV-TR criteria for Rett's Disorder), a work-up described as for autism is indicated. It is particularly important to do both a comprehensive neurological evaluation, including EEG monitoring for seizure activity, as well as molecular genetic analysis to confirm mutation in the gene associated with RD. Once a diagnosis of RD is confirmed, or when it is strongly suspected, the patient should be examined to rule out seizures, reflux disease, cardiac anomalies, and respiratory anomalies.

### DSM-IV-TR Criteria for Rett's Disorder

A. All of the following:

(1) apparently normal prenatal and perinatal development

(2) apparently normal psychomotor development through the first 5 months after birth

(3) normal head circumference at birth

B. Onset of all of the following after the period of normal development:

(1) deceleration of head growth between ages 5 and 48 months

(2) loss of previously acquired purposeful hand skills between ages 5 and 30 months with the subsequent development of stereotyped hand movements (e.g., hand-wringing or hand washing)

(3) loss of social engagement early in the course (although often social interaction develops later)

(4) appearance of poorly coordinated gait or trunk movements

(5) severely impaired expressive and receptive language development with severe psychomotor retardation

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### Clinical Vignette 4: Rett's Syndrome

There was nothing abnormal about Rebekah's prenatal course, and she was born at full term without complications to a mother in her 20s with no medical problems. She met her developmental milestones and gave no cause for alarm, until, at 8 months she seemed to lose interest in playing, and withdrew socially. At her next visit to the pediatrician, it was noticed that her head circumference, which like her height and weight had been in the 50th percentile, was in the 25$^{th}$ percentile for her age. Otherwise, Rebekah seemed well, so the pediatrician and parents decided to keep a close eye on her but otherwise do nothing. Over the next 4 months, Rebekah became hypertonic and began to have trouble picking up objects she had played with in the past. She also began to chew her fingers, as well as to wring her hands, as if she was washing them. At her next visit to the pediatrician, at 1 year old, her head circumference was even smaller relative to the norm, and she was now only in the 25th percentile for weight. This surprised her parents who thought she had been eating well, if having some trouble swallowing. The pediatrician was alarmed by what they described, ordered genetic testing, and ultimately diagnosed Rett's. Although intensive supports were put in place, Rebekah continued to deteriorate, never learning to walk, and having frequent seizures, as well as trouble breathing. She did, however, regain her interest in social exchanges and through her childhood enjoyed being around people very much. As she entered her teens, she experienced further muscle wasting and spasticity, but her seizures began to abate, and she continued to take joy in social exchanges.

## Epidemiology

RD occurs in less than 0.01% of live births (Van Acker et al. 2005). Varied reports of the incidence of the disorder from across the world may be attributed to diagnostic differences but highlight the fact that a diversity of racial and ethnic groups are affected. Contrasting to the male bias in affected individuals for the other PDDs, RD almost invariably affects females, reflecting the X-linked genetic basis of the disorder.

## Comorbidity Patterns

The severe neurological impact of RD leads to diverse sequelae. Thus it is difficult to untangle comorbid conditions from those that may be attributable to the primary process. The majority (60–70%) of children with the disorder experience epileptiform activity of some sort that can be difficult to distinguish clinically from stereotypies. Aside from motor difficulties with feeding, the majority of children with the syndrome also have abnormal digestive system functioning, including reflux disease and disrupted motility. As a result, these children often suffer from malnutrition and a secondary failure to thrive (Lotan and Zysman 2006).

## Course

RD is characterized by a period of normal development, followed by a progressive deterioration. The functional level of patients with the disorder is variable, with a significant number of children retaining some functional skills and approximately half retaining their ability to walk. Table 45–2 lists the clinical features of each of the stages of RD.

## Differential Diagnosis

The clinical manifestations of RD are distinct at each stage of the disorder; thus differential diagnosis will vary according to stage at presentation. Primary among these considerations at the earlier stages are other PDDs, including autism and CDD. Later in development, disorders with neurological manifestations, including, but not limited to,

**Table 45–2 Rett's Disorder: Clinical Characteristics and Differential Diagnosis by Stage**

| Stage | Clinical Characteristics | Differential Diagnosis |
|---|---|---|
| Early onset stagnation stage<br>Onset: 6–18 months<br>Duration: months | Developmental stagnation<br>Deceleration of head/brain growth<br>Disinterest in play activity<br>Hypotonia | Benign congenital hypotonia<br>Prader–Willi syndrome<br>Cerebral palsy |
| Rapid destructive phase<br>Onset: 1–4 years<br>Duration: weeks to months | Rapid developmental regression with irritability<br>Loss of hand use<br>Seizures<br>Hand stereotypies: wringing, clapping, tapping, mouthing<br>Autistic manifestations<br>Loss of expressive language<br>Insomnia<br>Self-abusive behavior (e.g., chewing fingers, slapping face) | Autism<br>Psychosis<br>Hearing or visual disturbance<br>Encephalitis<br>Infantile spasms (West syndrome)<br>Tuberous sclerosis<br>Ornithine carbamoyl transferase deficiency<br>Phenylketonuria<br>Infantile neuronal ceroid lipofuscinosis (INCL) |
| Plateau stage<br>Onset: 2–10 years<br>Duration: months to years | Severe mental retardation/apparent dementia<br>Amelioration of autistic features<br>Seizures<br>Typical hand stereotypies: wringing, tapping, mouthing<br>Prominent ataxia and apraxia<br>Spasticity<br>Hyperventilation, breath-holding, aerophagia<br>Apnea during wakefulness<br>Weight loss with excellent appetite<br>Early scoliosis<br>Bruxism | Spastic ataxic cerebral palsy<br>Spinocerebral degeneration<br>Leukodystrophies or other storage disorders<br>Neuroaxonal dystrophy<br>Lennox–Gastaut syndrome<br>Angelman syndrome |
| Later motor deterioration<br>Onset: 10+ years<br>Duration: years | Combined upper and lower motor neuron signs<br>Progressive scoliosis, muscle wasting, rigidity<br>Decreasing mobility: wheelchair bound<br>Growth retardation<br>Improved eye contact<br>Staring, unfathomable gaze<br>Virtual absence of expressive and receptive language<br>Trophic disturbance of feet<br>Reduced seizure frequency | Unknown degenerative disorder |

*Source:* Adapted from RSDW (1988), with permission from John Wiley & Sons.

encephalitis, chromosomal disorders, tuberous sclerosis, and Landau–Kleffner syndrome, must be considered.

## Etiology and Pathophysiology

### Genetic Factors

RD is associated with de novo mutations in the *MeCP2* gene found on the X-chromosome and associated with DNA methylation and the regulation of multiple genes responsible for brain development and regulation (Amir et al. 2000). Associated downstream alterations in neuroanatomy and neurochemistry have been identified. The *MeCP2* gene appears to be expressed only after neurons have reached a certain level of development corresponding to the natural history of the disorder (Shahbazian et al. 2002).

### Neurobiological Factors

RD is accompanied by diminished brain volume and a host of neurochemical changes in the central nervous system. Changes in the immunological system, such as autoantibodies to nerve growth factor, also occur and appear to be associated with the changes to the nervous system (Gratchev et al. 2001).

### Psychological Factors

The social changes in RD have similarities to the core social deficits observed in autism; whether a psychological model of the social disruption in Rett's can be derived from a model for autism remains to be explored.

### Social/Environmental Factors

The majority of cases of Rett's result from a known genetic mutation. As such, neither social nor environmental factors contribute significantly to the onset and course of the disorder. Several case reports have described the Rett's phenotype subsequent to an environmental factor, but insufficient information exists to support specific associations.

## Treatment

### Treatment Goals

Rett's has no cure, nor has a definitive therapy been identified to alter its course. Thus, the current targets of treatment are symptoms and sequelae. Addressable factors can be loosely categorized into motor/neurological deficits, social communication deficits, and medical sequelae. To address the neurological changes, experts in occupational and physical therapy, orthopedics, and neurology should be utilized. The social and communication deficits require experts in speech and language, as well as child psychologists or psychiatrists experienced in the treatment of developmental disorders. A pediatrician with experience in Rett's is recommended to coordinate both general treatment and treatment of medical complications. Given the characteristic gastrointestinal complications, a nutritionist is also recommended (Lotan and Zysman 2006).

### Somatic Treatments

A variety of pharmacological therapies (dopamine agonists and antagonists, L-carnitine, tyrosine, and melatonin, among others) have been employed to target the underlying pathophysiology of RD, but no compelling effects have been recorded. The seizures associated with the syndrome should be addressed in the same way that they are in any child with a seizure disorder. A variety of antiepileptic agents are effective. Gastrointestinal symptoms should be addressed on a case-by-case basis, and both antireflux and motility enhancing agents may be indicated. Because children with RD are generally small in stature and vulnerable to malnutrition, great care must be taken to plan diets appropriately. A high calorie diet rich in calcium is essential. No current treatment exists to address the basic neurological insults in RD; however, given the defined genetic basis of the disorder, current research is investigating whether the abnormal gene could be swapped or repaired in vivo. Recent results from a mouse model of the disorder raise the possibility that the neurological defects that accompany the disorder may be reversible with the development of successful gene therapy (Guy et al. 2007).

### Psychosocial Treatments

Raising a child with Rett's places considerable strain on a family, and psychosocial support for the family is an important aspect of treatment. This includes helping to ensure an appropriate educational setting and plan, as well as assistance accessing resources and services. The challenge that these children present to the clinician is also considerable, demanding vigilance, patience, and above all compassion.

## Pervasive Developmental Disorder—Not Otherwise Specified

## Diagnosis

PDD-NOS, or atypical autism, refers to a residual category. As such, rather than being characterized by a set of distinct features, the definition of this category reflects the *absence* of defining features required for other PDDs. The diagnosis denotes a subthreshold form of autism, or a manifestation of autism that is atypical in terms of onset patterns or symptomatology. Diagnosis requires that the child exhibit autistic-like social difficulty along with impairment in either communication or restricted/repetitive interests or behaviors. Thus, PDD-NOS describes a diverse group of children who do not meet strict criteria for autism or another PDD despite social and communicative and/or behavioral deficits. The limited available evidence suggests that children with PDD-NOS may be diagnosed later than children with autism and intellectual deficits may be less prevalent (Dahl et al. 1986). Persons with PDD-NOS may experience better outcomes because of milder symptomatology, stronger social motivation, or preserved communicative or cognitive abilities (Towbin 2005). Though patterns of regularly co-occurring phenotypes are likely to yield subgroups in this diagnostic category in the future, current research has not refined this undifferentiated diagnostic class.

Clinical Vignette 5: PDD-NOS

Jonathan was an only child born to an engineer and an office manager, at 29 and 25 years of age, respectively. He experienced difficulties with breastfeeding in early infancy, failing to latch appropriately until approximately 6 weeks. He eventually became proficient at breastfeeding, but, when transitioned to solid foods, displayed extreme pickiness in terms of the textures he would consume. Parent reports indicate that he was a pleasant baby who was easily soothed, but he failed to develop a regular sleep schedule until his second year of life. Jonathan met all motor and language milestones, though pediatric records indicate low tone throughout infancy. Parents report reduced social interest throughout infancy, specifically less looking at people than expected and infrequent smiling at other people. During the second year of life, Jonathan's pediatrician referred his family for an evaluation, and Jonathan began receiving early intervention to address social development. At an evaluation at age 48 months, Jonathan presented with intellectual abilities comparable to same age peers and slightly delayed language skills on standardized speech and language assessment instruments. He displayed an interest in particular movies, and, when left to his own devices, often recited lines of dialog from the film to himself. Though his speech production was fluent and used for a variety for purposes, including social bids, he showed odd tone and volume modulation and could not maintain reciprocity in conversation. During discussion, he often failed to respond to the statements of his conversational partner or commented about his own train of thought. Jonathan's use of nonverbal communicative behaviors was inconsistent; when highly motivated or engaged in a preferred activity, he directed gaze, expressions, and gestures, to others, but failed to use these behaviors a majority of the time. For example, his gaze was observed to wander about the room when being introduced to others or saying hello. His interest in movies dominated his play interactions in a repetitive fashion. His parents report that, as a younger child, his play consisted of straightforward reenactment of favorite scenes, but he developed the ability to deviate from these scripts and introduce novel twists to the characters' actions. In play with evaluators, he rigidly directed play, failed to incorporate ideas or requests of his partner, and resisted playing with human figurines. At school, he showed an interest in peers, but, partially due to his restricted interests and inflexible style of play, had great difficulty successfully engaging with peers and spent most free time alone. Evaluators ruled out a diagnosis of Asperger's disorder because Jonathan failed to display verbosity and the strong desire to engage others regarding his area of interest.

## Summary

Considerable progress in understanding the biological basis of autism has been made during the last half century. The validity of the disorder is now well established, but knowledge regarding the validity and definition of other ASDs remains quite limited. Continued research is needed to establish diagnostic validity, and the development of highly reliable operational definitions for these disorders and autism remains an important research priority. Brain imaging techniques and genetic studies are likely to continue to elucidate underlying pathophysiological mechanisms. The study of conditions such as CDD may be particularly appropriate to attempt to clarify underlying pathologic mechanisms. At present, it is likely that the diagnostic category reflects multiple etiologic pathways corresponding to the heterogeneous outcomes observed in the disorder.

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CHAPTER

# 46 Childhood Disorders: Attention-Deficit and Disruptive Behavior Disorders

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Attention-Deficit/Hyperactivity Disorder
Oppositional Defiant Disorder
Conduct Disorder

## Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) are the most frequently occurring and researched disorders of childhood, and there is an increasing recognition that they continue into adulthood in a subset of individuals (Kessler et al. 2006). ADHD and CD are highly impairing conditions, associated with considerable burden to patients, their families and society. Approximately, 4.4 million children and adolescents, 4–17 years of age, have been diagnosed with ADHD with the estimated annual cost to society of childhood ADHD being $36–52 billion annually (Pelham et al. 2007).

ADHD, ODD, and CD share many core symptoms, associated features, and impairments. Each condition can present with disruptive behavior, academic underachievement, and poor social skills; impulsivity is often present. Consequently, there is a high degree of mutual comorbidity; almost all children with CD also have ODD, and 60–70% of children with ADHD have ODD. Because of their many commonalities, as well as the predominance of disruptive behavior, the three disorders were grouped together in DSM-III-R (American Psychiatric Association 1987), and collectively referred to as the Disruptive Behavior Disorders (DBDs). However, as there is now agreement that ADHD and CD are separable diagnoses with relatively distinct correlates and outcome, and the predominantly inattentive subtype of ADHD is less often associated with disruptive behavior, the class name was changed to Attention-deficit and Disruptive Behavior Disorders (AD-DBDs).

Because of the many similarities in clinical presentation, the high rates of comorbidity, and commonalities related to risk, longitudinal course, and outcome, ADHD, ODD, and CD will be discussed together in this chapter.

## Diagnosis

### Definition and Diagnostic/Clinical Features

#### Diagnosis and Core Features

##### *ADHD*

ADHD is defined by a persistent pattern of inattention and/or hyperactivity–impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development. There are nine inattention items, six of which are required to meet the symptom threshold. Likewise, there are nine hyperactivity–impulsivity items with the threshold again set at six. Because all the individuals have some of these behaviors at least some

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of the time, more in some settings or situations than the others, and because the expected frequency varies as a function of age and gender, it is explicitly stated that behaviors must occur more frequently than the expected in individuals of the same age and gender, in a comparable situation. To highlight the developmental nature of the disorder, at least some symptoms must be present before the age seven. Severity is demonstrated by impairment in social, academic, or occupational functioning, and the occurrence of at least some symptoms in more than one setting.

**DSM-IV-TR Criteria**

**Attention-Deficit/Hyperactivity Disorder**

A. Either (1) or (2)

(1) Six (or more) of the following symptoms of "inattention" have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Inattention*

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.

(b) often has difficulty sustaining attention in tasks or play activities.

(c) often does not seem to listen when spoken to directly.

(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.

(e) often has difficulty organizing tasks and activities.

(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.

(g) often loses things necessary for tasks or activities.

(h) is often easily distracted by extraneous stimuli.

(i) is often forgetful in daily activities.

(2) Six (or more) of the following symptoms of "hyperactivity–impulsivity" have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Hyperactivity*

(a) often fidgets with hands or feet or squirms in seat.

(b) often leaves seat in classroom or in other situations in which remaining seated is expected.

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness).

(d) often has difficulty playing or engaging in leisure activities quietly.

(e) is often "on the go" or often acts as if "driven by a motor."

(f) often talks excessively.

*Impulsivity*

(g) often blurts out answers before questions have been completed.

(h) often has difficulty awaiting turn.

(i) often interrupts or intrudes on others.

B. Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school[work] and at home).

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## Attention-Deficit/Hyperactivity Disorder

ADHD can be diagnosed in individuals of all ages, although it is sometimes difficult to establish the childhood onset of symptoms in older individuals, and to reconcile the manner in which symptoms present in adults with the behavioral descriptions in the predominantly child-oriented item list. There are three subtypes of ADHD, which reflect the nature and relative frequency of current symptoms: Combined (what was previously meant by the term ADHD), Predominantly Inattentive, and Predominantly Hyperactive–impulsive. The latter two subtypes were introduced because the DSM-IV-TR Field Trials found that the children with threshold symptomatology in one domain only had impairment that was not accounted for by other disorders. However, symptoms from both domains are present in the majority of cases, regardless of the subtype.

### *ODD*

The essential feature of ODD is a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that persists for at least six months. As in ADHD, behaviors must occur more frequently than is typically observed in individuals of comparable age and developmental level, and accompanied by clinically significant impairment in social, academic, or occupational functioning. The forerunner of ODD, Oppositional Disorder (OD), was first introduced in DSM-III (American Psychiatric Association 1980), and described children who were oppositional but not necessarily disruptive. The list of behavioral descriptors was broadened to include minor conduct problems in DSM-III-R (American Psychiatric Association 1987), and the disorder was renamed ODD. The DSM-IV-TR (American Psychiatric Association 1994) criteria eliminated one symptom and added an impairment criterion. The latter change was intended to distinguish behavior termed pathological from the normal spectrum of oppositional behavior and the minor disruptive acts all children exhibit at one time or other.

**DSM-IV-TR Criteria**

**Oppositional Defiant Disorder**

A. A pattern of negativistic, hostile, and defiant behavior lasting at least 6 months, during which four (or more) of the following are present:
   (1) often loses temper.
   (2) often argues with adults.
   (3) often actively defies or refuses to comply with adults' requests or rules.
   (4) often deliberately annoys people.
   (5) often blames others for his or her mistakes or misbehavior.
   (6) is often touchy or easily annoyed by others.
   (7) is often angry and resentful.
   (8) is often spiteful or vindictive.

*Note*: Consider a criterion met only if the behavior occurs more frequently than is typically observed in individuals of comparable age and developmental level.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

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## CD

CD describes a repetitive and persistent pattern of behavior in which the basic rights of others or major age appropriate societal norms or rules are violated. At least three items from a list of 15 heterogeneous but serious behavioral offenses must be present during the past year, with at least one present in the last six months. The one year time duration reflects the infrequent nature of many of these behaviors. Again, symptoms must be present in more than one setting and cause significant impairment in functioning. Adults with conduct problems may be diagnosed CD, provided they do not meet criteria for Antisocial Personality Disorder (ASPD). Subtypes of CD are determined by age of onset of symptoms. Childhood onset subtype describes individuals who had at least one of the behaviors before the age 10, while Adolescent Onset subtype describes individuals whose CD behaviors all began after the age 10.

### Associated Features and Impairment

In addition to the core (i.e., defining) features of the ADDBDs there are also many associated features—that is, characteristics which are frequently but not always present, and which extend beyond the boundaries of diagnosis. It is important to appreciate associated features of the ADDBDs, as these are often highly predictive of impairment. Key associated features include: (i) problems related to learning, academic under-achievement or occupational attainment, (ii) problems in affect regulation, which may include having a "short fuse" or problems in anger management, (iii) being unable to understand or appreciate social cues

**DSM-IV-TR Criteria**

**Conduct Disorder**

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of three (or more) of the following criteria in the past 12 months, with at least one criterion present in the past 6 months.

Aggression to people and animals
   (1) often bullies, threatens, or intimidates others.
   (2) often initiates physical fights.
   (3) has used a weapon that can cause serious physical harm to others.
   (4) has been physically cruel to people.
   (5) has been physically cruel to animals.
   (6) has stolen while confronting a victim.
   (7) has forced someone into sexual activity.

Destruction of property
   (1) has deliberately engaged in fire setting with the intention of causing serious damage.
   (2) has deliberately destroyed others' property.

Deceitfulness or theft
   (1) has broken into someone else's house, building or car.
   (2) often lies to obtain goods or favors or to avoid obligations.
   (3) has stolen items of nontrival value without confronting a victim.

Serious violations of rules
   (1) often stays out at night despite parental prohibitions, beginning before age 13 years.
   (2) has run away from home overnight at least twice while living in parental or parental surrogate home.
   (3) is often truant from school, beginning before age 13 years.

B. The disturbance in behavior causes clinically significant impairmant in social, academic or occupational functioning.

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and other issues related to social context, (iv) problematic family and/or peer relationships, (v) aggression, (vi) low self-esteem, and (vii) substance abuse. The degree to which these features are present likely relates in important ways to the nature and severity of the core features and/or comorbidity, but cannot always be anticipated from these alone. For example, an academic and vocational underachievement may be related to the presence of comorbid learning disorders (LD), but may be seen independent of LD. Persistent

academic underachievement can lead to school failure, dropping out before graduating or prematurely terminating educational pursuits. Social impairments are frequently present, but need not reflect specific cognitive/skill deficits (e.g., inability to read social cues).Hyperactive–impulsive and aggressive behaviors are often annoying or offensive to others, and resultant peer rejection is seen in all age groups, including preschool children and adults. Cognitive, behavioral, and social impairments associated with the AD-DBDs often have profound effects on psychological development and functional status, with resultant difficulty negotiating age-appropriate developmental tasks. In adolescents and adults, this can include the capacity for forming and maintaining intimate relationships, parenting, educational, and occupational attainment and financial status (Biederman et al. 2006a). Impairments in self-esteem are often but not always present, presumably because self-esteem reflects the interactive effects of several constitutional, psychological, cognitive, social, and family-related variables.

## Assessment

### Clinical Assessment

Clinical assessment of the AD-DBDs requires a multisource; multimethod approach. Generally, adults are considered to be the best informants of cognitive and disruptive behavior in children, although older children and adolescents may provide important data regarding inattention, internalizing symptoms and infrequent or covert behaviors such as antisocial acts. Assessment procedures are similar for ADHD, ODD, and CD, with diagnosis determined from DSM-IV-TR criteria based on information obtained from parents/caretakers and teachers/school professionals regarding the presence and severity of the core symptoms in school, home, and social settings; age of onset; duration of symptoms; and degree of impairment. There are several available structured and semi-structured diagnostic interviews, although these are more often used in research settings. However, regardless of the approach taken in assessment, it is essential to inquire directly regarding the presence and duration of the core symptoms and associated features of the primary disorder, symptoms of frequently occurring comorbid conditions, and the degree to which symptoms cause impairment of age-appropriate developmental functions.

### Rating Scales

Several professional organizations such as American Academy of Pediatrics (2001) and American Academy of Child and Adolescent Psychiatry (Pliszk 2007) recommend the use of rating scales in assessment, as they offer an efficient and systematic method of collecting and evaluating clinical information across different settings, in context of age and gender-based norms. Using rating scales during baseline assessment ensures that all symptoms are assessed in a developmentally appropriate manner. Obtaining periodic ratings over the course of treatment is desirable for measuring change in the number and severity of symptoms over time. Concordance of teacher and parent ratings has consistently been found to be in the low- moderate-range. Parents are knowledgeable regarding their child's day to day behavior at home, including relationships with parents, siblings and peers. Many parents are also knowledgeable regarding their children's behavior in school, and can be trained to improve the accuracy of their reports. However, regardless of how well informed parents are, teacher ratings provide specific information regarding cognitive and behavioral function in a structured classroom setting, compared with children of the same age and gender in the same situation.

There are many different rating scales which measure behavioral and attentional function in children and adolescents. Broad-based scales survey a wide range of behaviors, and are therefore excellent for comprehensive assessment and screening. Commonly used broad-based scales with solid age and gender-based norms are the Conners (1998a, 1998b) Parent and Teacher Rating Scales, the Achenbach (1991a, 1991b) Child Behavior Checklist and Teacher Report Form, and the Behavioral Assessment Scales for Children (BASC-2) (Reynolds and Kamphaus 2004). In addition to assessing symptoms of ADHD and conduct problems (mainly oppositional behaviors), they have factors describing internalizing symptoms (i.e., depression, anxiety) and several other domains of function (Table 46–1). In addition to rating clinical symptoms, the BASC-2 has a section for adaptive skills (e.g., adaptability, social skills), and a supplemental scale for frontal lobe/executive function. A newer scale that aims to more specifically rate executive function in children of age 5–18 years is the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al. 2000). Parents rate children on eight functional domains: inhibitory control, cognitive flexibility, emotional control, initiating tasks or activities, working memory/vigilance, planning/organization, organizing materials, and self-monitoring capacity.

Other rating scales for ADHD more specifically evaluate DSM symptoms—including the Swanson, Nolan, and Pelham (SNAP) Parent and Teacher Rating Scales (Swanson 1992), the ADHD Rating Scale (ADHD-RS-IV), parent and teacher versions (DuPaul and Stoner 1994) and the Vanderbilt ADHD Parent and Teacher Ratings Scales (Wolraich et al. 2003, Wolraich et al. 1998). These scales provide dimensional ratings of DSM symptoms which closely coincide with interview-based diagnoses of ADHD. In addition, the SNAP-IV and Vanderbilt include the DSM ODD items, and the Vanderbilt covers a variety of other mood, anxiety and conduct problem behaviors. Similar to these DSM-based instruments, the revised Conners has subscales for DSM-total, DSM-inattention and DSM-hyperactivity/impulsivity symptoms to maximize compatibility with DSM-IV-TR diagnosis.

Several rating scales have been developed to measure the spectrum of oppositional/aggressive behavior. The Inattention, Overactivity With Aggression (IOWA) Conners (Loney and Milich 1982, Pelham et al. 1989) is comprised of 5 items from the Conners which are (relatively) divergently valid for inattention/cognitive impairment, and 5 items which are divergently valid for aggression. The New York Teacher Rating Scale (Miller et al. 1995) includes the DSM items for both ODD and CD, as well as a number of other disruptive and/or aggressive behaviors (Table 46–2). The Overt Aggression Scale (OAS) (Yudofsky et al. 1986) is an observer-rated instrument originally designed to measure aggressive behavior in inpatient settings. The Over Aggression Scale-Modified (OAS-M) (Coccaro et al. 1991) obtains this information via self/other report format suitable for outpatient settings, but with little validating data in children.

**Table 46–1 Frequently Used Rating Scales for Assessment of ADHD and ODD Symptoms**

| Scale | Description/Features/Comments | Scale Available From |
|---|---|---|
| | **Child/Adolescent** | |
| Revised Conners Parent and Teacher Rating Scales | Broad-based scale; most frequently used for ADHD and oppositional behavior; also rates internalizing symptoms; some aggression items load with internalizing behaviors (e.g., emotional lability); gender-based norms for children of age 3–17 | Multi Health Systems, Inc., www.mhs.com |
| IOWA Conners | 10 item scale derived from the Conners; 5 items divergently valid for inattention/overactivity and 5 for aggression/oppositional behavior | Loney J and Milich R (1982). Hyperactivity, inattention, and aggression in clinical practice. Advances in Developmental and Behavioral Pediatrics 3, 113–121. |
| Achenbach Child Behavior Checklist (CBCL) and Teacher Rating Form (TRF) | Broad-based scale with separate factors for ADHD, aggression, delinquency; excellent for screening; gender-based norms for children of age 4–18 years; separate scale for 2 and 3 year olds | Achenbach System of Empirically Based Assessment (ASEBA), Inc., www.ASEBA.org |
| BASC-2 | Broad-based scale; has sections for clinical symptoms, adaptive skills (e.g., adaptability, social skills), and frontal lobe/executive function (supplemental scale). | AGS Publishing, Inc., www.agsnet.com |
| SNAP-IV | Rates frequency and severity of ADHD on a single 0–3 scale; 18 items correspond to the actual DSM-IV-TR criteria; DSM-IV-TR iteration includes ODD items; used in MTA study | www.adhd.net/snap-iv-form.pdf |
| ADHD-Rating Scale (Parent; Teacher versions) | Like SNAP; rates frequency and severity of DSM ADHD symptoms; has been used in adults but items are not developmentally sensitive, and norms for children and adolescents only; used as an investigator-administered interview in several clinical trials of ADHD medications | Guilford Press, www.guilford.com |
| Vanderbilt ADHD Rating Scale (Parent and Teacher versions) | Similar to SNAP-IV and ADHD-RS for ADHD, but also has the DSM items for ODD, 12 criteria for CD, 7 screening criteria for anxiety/depression, and 8 additional items for academic performance and social function | www.peds.mc.vanderbilt.edu/VCHWEB_1/rating~1.html |
| BRIEF | Parent report of executive function in children of age 5–18 years; measures eight domains: inhibitory control, cognitive flexibility, emotional control, initiating tasks or activities, working memory/vigilance, planning/organization, organizing materials, and self-monitoring capacity. | Psychological Assessment Resources, Inc., www.parinc.com |
| | **Adolescent Self-Report** | |
| Conners-Wells | Self-report scale based on the Conners. | Multi Health Systems, Inc., www.mhs.com |
| YSR (Achenbach) | Self-report scale based on the Achenbach. | Achenbach System of Empirically Based Assessment (ASEBA), Inc., www.ASEBA.org |
| | **Adult** | |
| Brown ADD Scale | Rates inattention/executive dysfunction; items extend beyond DSM definition; 5 domains: organizing work, sustaining attention and concentration, sustaining alertness and effort, managing frustration and other emotions, and using working memory; good for high functioning adults with inattentive subtype | The Psychological Corporation, http://harcourtassessment.com |
| Conners Adult ADHD Rating Scale | Large item set of developmentally relevant items; extends beyond DSM definition, but DSM subscale maps onto diagnosis; self-report and "other-report" versions | Multi Health Systems, Inc., www.mhs.com |
| Wender–Reimherr Adult Attention Deficit Disorder Scale | Retrospective symptom scales provide age of onset data; less clearly tied to DSM-IV-TR ADHD. | Fred W. Reimherr, MD, Mood Disorders Clinic, Department of Psychiatry University of Utah Health Science Center Salt Lake City, UT, USA |
| Barkley's Current Symptoms Scale | Dimensional scale linked to semi-structured interview; uses actual DSM items but not re-worked for adults; rates behavior in the past 6 months; self and other informant reports. | Barkley and Murphy (1998) |
| Adult Self-Report Scale v1.1 (18-item symptom assessment and 6-item screener) | 18 ADHD item self-report scale and 6 item screener; developmentally relevant for adult manifestations of ADHD symptoms; rates frequency, not severity, on a 0–4 scale | www.med.nyu.edu/Psych/training/adhd.html and website of the World Health Organization, Geneva, Switzerland |
| Adult Investigator Symptom Report Scale (AISRS) | Interviewer administered dimensional scale; rates 18 DSM-IV-TR ADHD criteria; developmentally sensitive for adult manifestations; 6 ASRS screen items are stem questions, followed by the other 12 | Lenard Adler, MD, Adult ADHD Program NYU School of Medicine New York, NY, USA adultADHD@med.nyu.edu |

**Table 46–2 Frequently Used Rating Scales for CD/Aggression**

| Scale | Description/Features/Comments | Scale Available From |
|---|---|---|
| | **Child/Adolescent** | |
| New York Teacher Rating Scale | Items from the Revised Behavior Problem Checklist, Conners Teacher Rating Scale-Revised, IOWA Conners Teacher Rating Scale, DSM-IV-TR item lists for ODD and CD, and other items for CD and global impairment; four domains: defiance, physical aggression, delinquent aggression, and peer relations | Laurie S. Miller, Ph.D. Institute for Children at Risk New York University Child Study Center 550 First Avenue New York, NY 10016 Laurie.miller.2@med.nyu.edu |
| OAS | Observation-based measure of physical aggression for use in residential settings; rates four domains: verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against others | Yudofsky et al. (1986) |
| OAS-Modified | Modification of the OAS; provides self-report of behaviors rather than observation-based reports, which is better suited to outpatient settings | Emile Coccaro, M.D. Department of Psychiatry University of Chicago Chicago, IL, USA |
| Children's Aggression Scale (Parent; Teacher) | Measures frequency and severity of aggressive acts in different settings (e.g., home vs. school); five domains: verbal aggression, aggression against objects and animals, provoked physical aggression, unprovoked physical aggression, and use of weapons. | Psychological Assessment Resources, Inc., www.parinc.com |
| | **Adolescent/Adult** | |
| Buss–Perry Aggression Scale | Self-report measure used in adolescents and adults; rates four domains: physical aggression, verbal aggression, anger, and hostility. | Buss and Perry (1992) |

The Buss–Perry Aggression scale (Buss and Perry 1992) is a self-report measure which has been used in adolescents as well as adults, and provides information on four domains of aggressive behavior: physical aggression, verbal aggression, anger, and hostility. The Children's Aggression Scale (CAS), parent (Halperin et al. 2002) and teacher (Halperin et al. 2003) versions, likewise measures the full range of physically aggressive behavior, but was specifically developed for use in children and adolescents. There are five factors: verbal aggression, aggression against objects and animals, provoked physical aggression, unprovoked physical aggression, and use of weapons.

Despite their many benefits, rating scales have several limitations. Contextual and categorical features of diagnostic categories are often not included, and low frequency or episodic behaviors can be missed. In addition, raters often differ in their threshold for considering different behaviors to be problematic, and behavior differs across situations. The resultant low level of agreement is often considered to be a limitation. However, it illustrates the importance of obtaining information from multiple informants, across multiple settings. Most importantly, rating scale data should be used to augment information obtained from direct clinical assessment, and should not be used alone for purposes of diagnosis.

## Diagnostic Interviews

Several structured and semi-structured clinical interviews have been designed for assessment of children and adolescents, including the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS), (Kaufman et al. 2000), Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al. 2000), Diagnostic Interview for Children and Adolescents (DICA) (Reich 2000), Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello 2000), and Child Assessment Schedule (CAS) (Hodges et al. 1982). In general, reliability coefficients of interview-generated diagnoses are higher when data are collected from adult rather than child informants, and higher for disruptive/externalizing than internalizing disorders. Reliability and validity coefficients for CD are somewhat higher than for ADHD, presumably because the behaviors are more clearly evident. Interviewing children is less essential for developing a full profile of symptomatology, but is particularly useful for evaluating symptoms or associated impairments less frequently observable by parents and teachers, understanding how the child views his/her own symptoms and associated impairments (essential for developing a therapeutic alliance), and eliciting adverse effects (AEs) of medication treatments.

## Structured Assessment Methods for Adult ADHD

There are now several structured rating scales and diagnostic interviews to aid in the assessment of ADHD in adults, which evaluate symptoms in a developmentally appropriate manner. This is important because symptoms often present differently in adults than children, and the threshold for determining when symptoms cause impairment is often different in adults (Table 46–1).

The Conners Adult ADHD Rating Scale (Conners et al. 1999) and Wender–Reimherr Adult Attention Deficit Disorder Scale (Wender 1995) are self-report scales which assess a wide range of developmentally relevant symptoms for ADHD and associated behaviors. The Conners has a DSM subscale that maps onto the ADHD diagnosis fairly well. Also, the Conners is available in self-report and "other-report" formats, the latter for completion by a spouse or significant other—analogous to parent and teacher reporting in children. The Wender–Reimherr includes items that retrospectively assess childhood onset of symptoms. Other adult ADHD rating scales utilize actual DSM items, or adaptations of these items, in a dimensional format,

including: 1) the Barkley Current Symptoms Scale (Barkley 1998) and the ADHD-RS (DuPaul et al. 2001), each of which uses the actual 18 DSM-IV-TR items, 2) the Adult ADHD Self Report Scale (ASRS) v1.1 Symptom Checklist (Kessler et al. 2005), which is derived from the same DSM items but adapts them for use by adults in an 18 item self-report format and a 6-item screener, and 3) the Adult ADHD Investigator Symptom Rating Scale (Adler and Cohen 2004); a symptom-based interview that utilizes adult specific stem questions for different ADHD domains and adult specific prompts. The ASRS was developed in collaboration with the World Health Organization, reflecting the high level of attention that ADHD has received world-wide. Finally, the Brown Attention-Deficit Disorder (ADD) scales (Brown 1996) assess the presence, severity and consequences of cognitive and executive dysfunctions in a self-report format. Corresponding scales for use in children and adolescents have also been developed (Brown 2001).

Currently available structured or semi-structured interviews for ADHD in adults include the Conners Adult ADHD Diagnostic Interview (CAADID) (Epstein and Kollins 2006), the Barkley Current Symptoms Scale (Barkley 1998), the Brown ADD Scale Diagnostic Form (Brown 1996) and the Adult Clinician Diagnostic Scale (ACDS) v1.2 (Adler and Cohen 2004). The ACDS is an adaptation of the Kiddie-SADS ADHD module (which had previously been used to assess adults as well as children, since the main structured interviews for adults did not include ADHD) utilizing developmentally appropriate prompts specific for adult ADHD. Consequently, the ACDS v1.2 has been used in more recent ADHD trials.

## Neuropsychological Assessment

Neuropsychological testing is not required to diagnose ADHD, ODD or CD. However, neuropsychological and/or educational tests of cognitive, linguistic, perceptual, motor and academic functioning can be used to augment the clinical assessment of attentional function, to provide normed data required for the diagnosis of mental retardation and specific learning disabilities, and to assess the adequacy of school placement. Furthermore, testing is often required to justify the need for supplemental services or to request accommodations during exams or standardized tests (i.e., extended time, other special circumstances). Intellectual capacity or intellectual quotient (IQ) and academic achievement are both routinely assessed, using tests such as the Wechsler Intelligence Scale for Children (i.e., WISC-IV, or the Wechsler Adult Intelligence Scale (i.e., WAIS) and the Wechsler Individual Achievement Test (i.e., WIAT), respectively. Additional assessment of executive functions such as vigilance, working memory and cognitive conflict resolution is often undertaken, using tests such as the Continuous Performance Test, Wisconsin Card Sorting Test, Stroop Word-Color Association Test, and Test of Working Memory. Because tests of executive function lack specificity, and because only a subgroup of individuals with ADHD have executive function deficits, these tests should not be used for purposes of diagnosis. However, it is important to identify individuals with neurocognitive disabilities and provide appropriate remediation, as the presence of comorbid executive function deficits and ADHD is associated with a high degree of impairment (Biederman et al. 2006b).

## Laboratory Measures

There are no physical findings or laboratory measures which reliably distinguish the AD-DBDs from each other, other disorders or normal controls. However, since several medical conditions can mimic ADHD, obtaining targeted laboratory assessments may be useful. Routine screening for thyroid disorders had been advocated; based on the findings indicating a high association of generalized resistance to thyroid hormone and ADHD in several families. However, the vast majority of individuals with ADHD do not have abnormal thyroid function, and whether to obtain thyroid indices should be guided by clinical presentation. Similarly, while research studies have used neuroimaging methods to identify characteristic patterns of brain structure or function in individuals with ADHD and CD, findings to date have neither been consistent nor specific enough to recommend that these methods be used for diagnosis.

A variety of objective devices, such as wrist actometers and acceleration-sensitive actographs, have been used to quantify activity level in individuals with ADHD, ODD and CD. These devices provide judgment-free assessments of activity level and can be used to evaluate the accuracy of information obtained from clinical interviews and rating scales. Actigraphs also have intuitive appeal for use in clinical settings; they are relatively small, and interface with computer software which download and analyze data. Actigraph measures in children, obtained during a one hour neuropsychological test session in an outpatient setting, were found to have high specificity but relatively lower sensitivity relative to clinical diagnosis (i.e., many false negatives). Actigraphs therefore cannot be used alone to diagnose ADHD. However, they could have a role in augmenting interpretation of data obtained from measures which have high sensitivity and low specificity (i.e., good for screening, but many false positives), such as continuous performance tests of vigilance.

A measure which has recently been used in research settings to quantify on-task behavior and task completion is the Permanent Product Measure of Performance (PERM-P) (Wigal and Wigal 2006). Children are instructed to complete mathematics worksheets containing a large number of problems within a specified time period. Measures of interest include both the number of problems attempted and the number completed correctly. Since the PERM-P is not intended to measure mathematics ability or intelligence, but rather task completion, it is essential that the problems be simple enough to be considered rote and boring. Therefore, several different sets of problems are available, based on the child's grade level. Children with ADHD treated with medication have been shown to complete more math problems, without sacrificing accuracy, in several studies.

Structured observation approaches have been used in both playroom and school settings to provide a quantitative assessment of behavior. Structured playroom assessments quantify activity level by recording the number of times the child crosses grids marked on the floor, touches toys that he/she is told not to use, and the amount of time spent on a particular task. In school settings, trained raters are used to quantify the amount of time children with ADHD spend on-task, in their seats, etc, often in comparison with non-ADHD children. These quantitative approaches are quite time consuming and do not translate easily to the clinical setting. However, less structured observation of children's

classroom behavior is not infrequently undertaken as part of a comprehensive clinical evaluation, particularly in challenging cases.

## Epidemiology

ADHD, ODD, and CD are all highly prevalent disorders, although there is considerable variability across studies, reflecting not only differences in populations but also variability in assessment methods and the definition of caseness. In preschool children, the prevalence of ADHD is estimated to be 2%–8%. The rate increases to 4%–12% in elementary school-age children and declines in adolescence to about 6%. The first large epidemiologic study of ADHD in adults in the U.S. found the prevalence to be 4–5%, or approximately 60% what it is in school-age children (Kessler et al. 2006). Impairment from residual symptoms is common in adulthood; approximately two-thirds of the children with ADHD continue to have some symptoms causing impairment as adults, even if they do not meet criteria for the full diagnosis. The prevalence of ADHD is quite stable world-wide, with rates that are comparable to those in the US, in both industrialized and developing countries, when similar instruments are used (Faraone et al. 2003).

The lifetime prevalence of ODD is estimated to be 10.2%, and is somewhat higher for males (11.2%) than females (9.2%). The presence of either active or remitted ODD significantly predicts subsequent onset of other disorders. Virtually all children with ODD (92.4%) also meet criteria for at least one other lifetime DSM-IV-TR disorder, including: mood (45.8%), anxiety (62.3%), impulse-control (68.2%), and substance use (47.2%) disorders. Both early onset ODD (before age 8) and ODD plus comorbidity predict a more chronic course, with less robust and less immediate improvement following treatment (Nock et al. 2007). The prevalence of CD is considerably lower than ODD in childhood, with rates estimated to be as low as 1% in school age children but increasing several fold in adolescence. The percentage of boys with conduct problems in an epidemiologically derived birth sample who had childhood onset of CD symptoms and maintenance of CD symptoms through adolescence was 10.5% (Odgers et al. 2007). Several other subgroups were identified: 19.6% developed conduct problems for the first time during adolescence; 24.3% had conduct problems in childhood but subsequently desisted; and 45.6% had persistent but low levels of conduct problems (45.6%) and did not meet criteria for CD. Findings from this and numerous other studies have shown that early onset conduct problems constitute a risk for later in life antisocial behaviors, accidents, disease, health problems and mortality, while some have hypothesized that such risk is related to CD regardless of age of onset.

## Comorbidity Patterns

Conduct problems, including oppositional behavior, defiance, aggression and delinquency, account for the majority of comorbidity in children with ADHD. Data from several epidemiological studies (Maughan et al. 2004) indicate that ODD and CD are present in 40–70% of the children with ADHD. These comorbidity figures are not unidirectional. Among children with ODD and/or CD in these same studies, 40–60% also had ADHD. In addition, the percentage of children with ADHD and comorbid disruptive behavior (i.e., some clinically significant problems are present, but the full diagnosis is not met) is greater still. The prevalence of comorbid ADHD/ODD/CD/aggression is thought to be higher in clinical than epidemiologic samples, since the co-occurrence of these conditions is highly impairing and often leads to referral. Rates of comorbidity appear to vary across clinical settings, with an over-representation in psychiatric compared to pediatric settings.

Lifetime rates of comorbid depression and anxiety are also quite high among children with ADHD, with published prevalence rates of 15–35% for depression and 25–50% for anxiety disorders (Spencer et al. 2007b). Consistent with the longitudinal course of depression and anxiety disorders, the prevalence of these conditions increases in individuals with ADHD during adolescence and adulthood. Both comorbid depression and anxiety must be distinguished from the consequences of chronic underachievement, such as demoralization and fearful anticipation secondary to chronic poor performance. Other neuropsychiatric conditions which frequently co-occur with the AD-DBDs include Tourette's disorder (TS) and developmental LD. Approximately 50–60% of individuals with TS also have ADHD, and many of these have ODD or CD as well. A much smaller percentage of individuals with TS also have ADHD, owing to differences in prevalence of the two conditions. The rates of specific LD among youth with ADHD range from 20–90%, with the lower figure reflecting actual LD and the higher rates indicative of more broadly defined academic underachievement. Academic underachievement is also highly prevalent among youth with CD, although rates of actual LD are lower. Rates of school drop-out are also elevated, often in association with a confluence of psychosocial as well as cognitive risk factors.

The extent to which ADHD and bipolar disorder occur comorbidly has been controversial, with prevalence rates in some samples estimated to be 15% or higher (Spencer et al. 2007b). However, prevalence estimates in other samples are much lower. These discrepancies may in part reflect potential symptomatic overlap, as well as the manner in which symptoms of bipolar disorder are operationalized. Youth with ADHD + bipolar disorder generally present with mood lability, agitation, conduct problems, and various other impairments. They do not typically cycle like later onset bipolar patients, but rather have severe behavioral dysregulation. These children almost always meet criteria for CD as well. It is not clear whether children diagnosed with ADHD + comorbid bipolar disorder are neurobiologically similar to those with more classic symptoms of bipolar disorder, and whether these children develop more classical bipolar disorder later in life. Comorbidity with ADHD is extremely common among children with bipolar disorder, occurring up to 90% of the time. In adolescent onset bipolar disorder, comorbidity with ADHD remains high, but is substantially lower than in the child-onset group.

It is well known that depression in children is frequently comorbid with the acute onset of behavior problems, with 60% of youth with major depression meeting criteria for CD. In addition, it is well known that anxiety and depression frequently co-occur. The co-occurrence of ADHD with these other disorders is also not uncommon, meaning that three or more disorders are often present. For example,

approximately two-thirds of the children with ADHD and comorbid anxiety disorders in the Multimodal Treatment Study of Children with ADHD (MTA) also had CD (March et al. 2000) In both this sample and others, the symptomatic and functional status of children with ADHD plus anxiety disorder is altered when CD is also present (Newcorn et al. 2004). Consistent with this observation, individuals with ADHD and comorbid internalizing and externalizing disorders had the highest degree of impairment in the MTA study (Jensen et al. 2001).

In addition to psychiatric comorbidity, a variety of medical conditions can co-occur with ADHD, including epilepsy, sleep disorders, thyroid disease, post-infectious and/or post-traumatic encephalopathy and sensory impairments. More often, it is important to rule out these conditions. Finally, many medications which are prescribed to children can mimic the symptoms of ADHD and/or ODD. Examples include anticonvulsants (e.g., phenobarbital), antihistamines, decongestants, bronchodilators (e.g., theophylline) and systemic steroids. Before diagnosing ADHD in the presence of these and other medical conditions, it is essential to determine that the ADHD symptoms are not better accounted for by the other condition and/or its treatment, and that the trajectory of ADHD symptoms follows an independent longitudinal course.

## Course

### ADHD

Many symptoms of ADHD are observable during the preschool years, with hyperactivity–impulsivity and aggression predominating. Attentional symptoms are usually reported after hyperactivity–impulsivity symptoms. However, it is likely that these behaviors are present from early on but are not reported until the child enters school, when there are increased environmental and cognitive demands. Hyperactivity–impulsivity symptoms are frequently associated with oppositional behaviors, giving the appearance of a simultaneous, rather than a sequential onset. Approximately two-thirds of the children with ADHD continue to have attentional, behavioral, and emotional problems well into adolescence and adulthood. Inattention symptoms remain high, and can be associated with difficulty working independently, poor academic performance and educational attainment, unemployment and/or lower occupational status, and lower earning potential. Inattention and related impairments drive treatment in the large majority of adults with ADHD. Hyperactivity–impulsivity symptoms generally decline in adolescence but can be highly impairing when they persist—even if they are "subthreshold." Functional consequences of persistent hyperactivity–impulsivity may include impairments in driving, early sexual activity, sexually transmitted diseases, early pregnancy, substance abuse and delinquent behavior, all of which are elevated in samples of ADHD children followed longitudinally (Barkley et al. 2006). These represent some of the most challenging long-term sequellae of ADHD, although these outcomes most often occur in individuals with ADHD and comorbid CD. Families of these children tend to be less stable, have higher divorce rates, and move more frequently. First-degree relatives have been found to have higher rates of antisocial behaviors, substance abuse, and depression.

### ODD/CD

The developmental course of oppositional behavior is highly variable. During the preschool years, transient oppositional behavior is very common. However, if oppositionality persists, there is heightened risk for escalation to more clinically significant disruptive behavior. There are two possible developmental trajectories. In most oppositional children, who are usually not physically aggressive, oppositional behaviors peak in mid-childhood, around the age 8 and decline after that. In others, oppositional behavior escalates to delinquent behaviors (Burke et al. 2002). The early presentation of physical aggression is a key predictor of this latter trajectory, as physically aggressive children are more likely to progress from early oppositional behaviors to more severe and disabling conduct problems. Coexistent ADHD speeds the escalation to more severe conduct problems, resulting in elevated rates of ASPD and substance use disorders in adulthood.

The developmental course of CD is highly gender dependent. In boys, symptoms of CD often begin in preschool years, with age of onset peaking in mid-childhood. There are substantial individual differences in the adolescent outcomes of CD, ranging from worsening to sustained recovery, (Lahey et al. 2002). The development of conduct problems typically follows a progressive course, beginning with rule violations, such as poor school attendance, and escalating to aggression towards animals and people. In girls, CD symptoms are less often aggressive in nature and have their onset at a later age. Longitudinal studies have found that the childhood-onset ($<12$ years) CD in girls may be predicted by paternal ASPD, while adolescent-onset CD ($\geq 12$ years) tends to be associated with family conflict. In addition, lifetime CD significantly predicts academic, psychiatric and sexual behavior problems in girls with ADHD at follow-up. (Monuteaux et al. 2007). When CD begins in adolescence, the problems are likely to diminish by adulthood. However, CD which begins in preschool or childhood years is more likely to persist and escalate to antisocial, delinquent and criminal behavior. (Satterfield et al. 2007). Recent findings suggest that family-genetic risk factors play a stronger role in the occurrence of childhood onset CD, while family-environmental risk factors are more salient in the incidence of adolescent-onset CD (Spencer et al. 2007b).

## Differential Diagnosis

There is very little overlap in the defining characteristics of ADHD, ODD and CD. However, the frequent co-occurrence of inattention, hyperactivity, impulsivity, oppositionality and aggression suggests that these symptoms are closely related, and therefore difficult to disentangle both heuristically and in clinical practice. Nevertheless, the distinctiveness of ADHD and CD has been demonstrated in several epidemiologic studies (Maughan et al. 2004) which have examined correlates of the two conditions. Children with ADHD have a persistent pattern of developmental problems and cognitive impairments, while those with CD more often come from lower SES backgrounds and experience high levels of psychosocial adversity. These findings are consistent with the hypothesis that CD may be a more environmentally driven condition than ADHD, although they do not preclude genetic/neurobiologic contributions to the pathogenesis of CD, as well as psychosocial mechanisms for ADHD.

Data from both epidemiologic and clinical studies indicate that children who are comorbid for ADHD and CD present with risk factors and associated features characteristic of both disorders, consistent with data (Maughan et al. 2004) which indicate that comorbid CD accounts for the poorest outcome among children with ADHD, and conversely, that comorbid ADHD confers increased risk for poor outcome in children with CD.

The core symptoms of ADHD and ODD are also not identical, despite the very high rate of comorbidity. For example, ODD symptoms, such as "loses temper," "actively defies," and "swears" are not characteristic of children with ADHD only, and can therefore be used to distinguish the two disorders. Children with ADHD who have high levels of hyperactive/impulsive symptoms are at greatest risk for also having ODD. Nonetheless, approximately 30% of the children with ADHD and comorbid ODD have predominantly inattentive subtype (Newcorn et al. 2005).

Because 90% of the children with CD also meet criteria for ODD, the two conditions are not diagnosed together. The fact that virtually all youth with CD also have ODD led to the hypothesis that ODD represents a developmental precursor of CD. However, the majority of children with ODD do not develop CD, supporting the existence of independent diagnoses. In cases where ODD precedes CD, the onset of CD is typically before the age 10 (childhood onset CD). In children with onset of CD after the age 10, symptoms of ODD and ADHD are usually not present during early childhood. It has been shown that children with ODD demonstrate less impairment and are more socially competent than children with CD. Children with CD generally come from less advantaged families and have greater conflict with school and judicial systems than those with ODD only. Family adversity scores in children with ODD are usually intermediate between those of children with CD and normal children.

Symptoms of ADHD overlap with several other psychiatric diagnoses. Generalized anxiety disorder is often characterized by agitation and restlessness, as well as inattention to salient stimuli. However, these symptoms generally occur in response to some perceived fear stimulus, and do not reflect the individual's overall capacity for self-regulation and information processing, as in ADHD. Likewise, decreased concentration and poor academic achievement are frequently present in major depression and other mood disorders. Depressive disorders are often episodic, and while academic decline is often present in both disorders, it is more often acute and precipitous in depressive disorders. Nevertheless, youth with major depression often also have dysthymia, and academic achievement in individuals with ADHD may vary from one school year to the next. Consequently, chronicity of course may not distinguish the two conditions. Age of onset of academic impairment is generally earlier in ADHD. However, when ADHD is present in individuals with high IQ, particularly those with predominantly inattentive subtype, onset or recognition of symptoms may be later.

Finally, although it would not seem difficult to distinguish ADHD and schizophrenia, it is not uncommon for child-onset schizophrenia to present with a variety of negative symptoms including inattention, underachievement and lack of motivation, which are also present in a subset of youth with predominantly inattentive ADHD. Similarly, youth with Asperger's disorder often present with inattention symptoms, and their aloofness can be misinterpreted as a reflection of inattentiveness. The nature of social impairment and the developmental course of symptoms can often distinguish the disorders. However, it is also possible that symptoms of both conditions are present.

### Differences in Developmental, Gender, and Cultural Presentations

In school age children, boys have higher rates than girls for all three disorders. The combined subtype accounts for the majority of cases of ADHD in both genders, although the relative proportion of cases with inattentive subtype is higher in girls than boys. In clinic settings, the ratio of boys to girls is about 9:1, but in community samples, this decreases to approximately 3:1. Teachers tend to identify fewer girls than boys as having ADHD symptoms, presumably because girls are less often disruptive. In ADHD children with predominantly hyperactive–impulsive subtype, the male to female ratio is approximately 4:1 (Gershon 2002). The gender ratio falls to 2:1 in the predominantly inattentive subtype. For both genders, the prevalence of the full syndrome declines with age, with predictors of persistence including severity of ADHD in childhood, family history of ADHD and comorbidity (Barkley et al. 2006). Cross-sectional prevalence estimates in referred samples of adults indicate that males and females are equally affected, which suggests that different types of patients may present for treatment in childhood and adulthood.

There are also important gender differences in the clinical presentation and longitudinal course of ODD and CD. Most studies have found that early onset CD is much more characteristic of boys than girls, primarily due to the fact that boys are more physically aggressive than girls. Consistent with this observation, CD in girls is much less directly confrontational than in boys, with "relational" aggression more often present (Ohan and Johnston 2005). Recent longitudinal findings indicate that the prevalence of new onset CD in adolescence is higher in girls than boys, and the overall rates of CD are not different in girls and boys by mid-late adolescence. However, the higher rates of childhood onset CD among girls in some studies suggest that there are multiple pathways to CD in girls.

An accumulation of data support the contention that ADHD is a worldwide disorder, with findings of similar prevalence (approximately 5%) in the developed and the developing countries, from both Western and Eastern hemispheres (Faraone et al. 2003). However, in US studies, there appear to be cultural differences in the degree of acceptance of both the diagnosis and its treatment, as well as differences in access to care (National Institutes of Health 2000). For example, the use of stimulants in school age boys is approximately twice as high in Caucasians as compared with African-Americans. Further, data from several regional studies examining patterns of stimulant medication use highlight the extent to which treatment in different communities is divergent.

## Etiology and Pathophysiology

### Genetic Factors

Several parallel lines of research document the prominent role of genetics in the etiology of the AD-DBDs, and further

suggest that these disorders may share common familial vulnerabilities. The heritability of ADHD was determined to be 0.76 in a meta-analysis of data from 20 twin studies (Faraone et al. 2005), which is almost as high as the heritability for schizophrenia, and substantially higher than for many psychiatric disorders. While some reports have estimated the heritability for childhood antisocial behaviors to also be equally high, results of most other studies suggest that it is more moderate, that is, 0.3–0.7 (Slutske et al. 1997).

Findings from pharmacological, neuroimaging and animal studies implicating dopaminergic and noradrenergic neural circuits in the pathophysiology of ADHD have inspired a large number of gene association studies. Candidate genes related to DA neurotransmission found to be positively associated with ADHD include the dopamine receptor D2 (DRD2), D4 (DRD4), and D5 (DRD5) receptor genes as well as the dopamine transporter. In addition, candidate genes related to release (SNAP-25) and metabolism of DA (e.g., Catechol-O-methyl transferase (COMT), Monoamine oxidase-A (MAO-A)) are associated with increased risk for ADHD. The association of the DRD4 gene with ADHD has been the best replicated and most robust thus far. The high risk polymorphism, 7-repeat allele, was found to have an odds ratio of 1.4 in a meta-analysis of 8 case-control and 14 family studies (Faraone et al. 2005). There has also been relatively high agreement regarding the association of SNAP-25 (i.e., synaptosomal-associated protein 25 gene, which is a neuron-specific protein implicated in exocytotic catecholamine release) and ADHD. The possible involvement of COMT in ADHD is of particular interest, given the role of COMT in aggression and substance abuse risk, the frequent comorbid occurrence of ADHD and CD, and the relationship of this comorbidity to risk for adolescent addiction. At the same time, some of the initial enthusiasm that followed from positive findings in relatively low *n* studies with other candidate genes has waned, as preliminary positive reports have either not replicated or have been found to have little predictive value. For example, the odds ratio in a recent meta-analysis of DAT1 across numerous studies was only 1.04 (Li et al. 2006).

Some of the above candidate genes have also been examined in pharmacogenomic studies. The first such report found the homozygous 10-repeat allele of DAT1 to be associated with lower response to methylphenidate (MPH). However, results of subsequent studies have been equivocal. Although there have been several replications, two recent studies did not support any association of DAT1 and MPH response, and one other suggested an association of the 9,9 polymorphism with nonresponse (Stein et al. 2005). There have been fewer studies examining response to MPH as a function of DRD4 genotype. In one study, the likelihood of response was not different as a function of DRD4 genotype, but the presence of one or two copies of the 7-repeat allele was associated with higher MPH dose (Hamarman et al. 2004), supporting the hypothesized role of DRD4 in mediating a blunted intracellular response to DA.

A number of studies have also examined the role of noradrenaline (NE)-related genes in ADHD, given the strong evidence from basic science investigations regarding the role of NE in cognitive/attentional processes and ADHD (Arnsten 2006). Initial investigations did not find an association between ADHD and the norepinephrine transporter gene (NET), adrenergic 2A (ADR2A), or the adrenergic alpha 1C and 2C receptor genes. However, emerging evidence supports positive associations of ADHD with the NET1, the Taq 1 polymorphism within the gene for DBH (the enzyme which converts DA to NE), and several studies have found an association with the ADR2A gene—particularly as regards cognitive deficits and/or learning. In addition, the ADR2A gene has been found to predict response to MPH (Polanczyk et al. 2007), consistent with findings from animal studies indicating that that MPH enhances NE as well as DA. Finally, the association of ADHD with DRD4 genotype could possibly reflect the role of the DRD4 receptor in regulating noradrenergic neurotransmission, as NE is a potent agonist of the DRD4 receptor.

There have also been positive associations of ADHD and various serotonin system genes, including the serotonin transporter (5-HTT or SLC6A4) and the serotonin receptor 1B, 1D, and 2A genes (Faraone and Khan 2006), although not consistently so. It is interesting to consider whether variability in findings related to 5-HT genotype could reflect sample differences related to the presence of comorbid CD. This would be consistent with findings pointing to the familial basis of childhood conduct problems. Likewise, differences attributable to gender could contribute to variability across studies. Results from an Australian cohort of 889 twin families found an environmentally mediated role of parental conduct problems in the etiology of behavior problems in males, while common genetic risk accounted for the entire intergenerational transmission in females (D'Onofrio et al. 2007). A similar gender specific dissociation was reported in 87 adopted children, (Cadoret et al. 2003) linking the serotonin-transporter promoter region (5HTTLPR) with other genetic risk factors and behavioral disturbances. A possible gender-related interaction with 5HTTLPR was suggested by differential association between the 5HTTLPR short variants (SS or SL) and symptom counts for CD, aggression and ADHD as a function of gender; the association between ADHD and the short 5HTTLPR genotype was higher in males and lower in females. In addition, there was an increased risk for the externalizing behavior in individuals with the long (LL) variant of 5HTTLPR and antisocial biologic parentage, and also increased risk for externalizing behavior in individuals with one or more 5HTTLPR short variants (SS or SL) in conjunction with a genetic diathesis for alcoholism.

The hypothesized association between CD and 5-HT candidate genes is based on the well-accepted role of 5-HT neurotransmission in modulating impulsive/aggressive behavior. Positive findings for several 5-HT system genes (e.g., 5-HT transporter and 5-HT receptor 1B and 2A genes) have been reported in relation to impulsive/aggressive behaviors, but not all studies have categorically linked genotype to CD. These findings suggest the importance of genetic factors in the development of CD, and point to a possible role for 5-HT, but additional research is required.

## Neurobiological Factors

Recent advances in neuroimaging implicate neural circuits centered in the prefrontal cortex and striatum, as well as the brainstem catecholamine systems that innervate these

circuits, in the pathophysiology of ADHD. The prefrontal cortex and the striatum are part of a complex neural system that mediates inhibitory control processes. The prefrontal cortex receives higher-order sensory input and inhibits the processing of irrelevant sensory stimuli through reciprocal connections with temporal and parietal association cortices. In turn, the prefrontal cortex exerts inhibitory control over motor functions through well-organized connections with the caudate nucleus, and indirectly with the globus pallidus, which feeds back to the prefrontal cortex via thalamic nuclei.

Morphological studies using magnetic resonance imaging (MRI) in children and adolescents have generally found that cortical size is reduced in ADHD, as is the volume of several key structures, including the four major cortical lobes (frontal, parietal, occipital, and temporal) and the subcortical nuclei (e.g., putamen, caudate). These findings provide evidence that anomalies in the prefrontal cortex and basal ganglia (i.e., fewer prefrontal-corticostriatal fibers and less striatal feedback to prefrontal regions). may be uniquely associated with ADHD (Castellanos et al. 2002). The finding of reduced volume in the anterior genu region of the corpus callosum in children with ADHD is consistent with this hypothesis. Volumetric differences between ADHD and non-ADHD children in other brain areas, such as cerebellum, hippocampus and amygdala, further suggest that brain anomalies in ADHD extend beyond the prefrontal cortex and striatum to the posterior and subcortical regions that communicate with these frontal circuits. The regions most consistently found to be smaller in children with ADHD have been the dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, and cerebellum (Seidman et al. 2005).

An emerging literature has examined the developmental trajectory of regional brain volume in ADHD. Findings thus far indicate that volumetric differences in most regions remain parallel for ADHD patients and controls during childhood and adolescence. However, there are notable exceptions. The relative decrease in volume of caudate and putamen which is seen in children with ADHD does not seem to persist into adolescence—perhaps reflecting the relative decrease in observed hyperactive/impulsive symptoms developmentally (Castellanos et al. 2002). Similarly, decreased cortical thinning of the right parietal region over normal development was associated with more favorable outcome in 222 youth with ADHD who were positive for the DRD4 7-repeat allele (Shaw, Gornick et al. 2007). Combining genetic and neuroimaging methods offers an opportunity to better understand the neurodevelopmental effects of genetic polymorphisms, and by extension, neurobiological mechanisms related to variability in ADHD pathophysiology.

Several recent studies have examined whether relative differences in brain morphology are influenced by prior stimulant treatment—since many of the subjects in initial studies were previously medicated. The majority of findings support the view that genetic and/or early environmental influences on brain development in ADHD are relatively nonprogressive and unrelated to prior stimulant treatment (Castellanos et al. 2002). However, one study did find that the volume of brain structures implicated in ADHD (e.g., caudate, anterior cingulate cortex) differed as a function of preexisting treatment history (Semrud-Clikeman et al. 2006).

Neuroimaging studies investigating receptor density and binding properties using single photon emission computerized tomography (SPECT), positron emission tomography (PET), or regional brain activation associated with information processing (i.e., functional MRI (fMRI)) have yielded important information regarding the pathophysiology of ADHD and mechanisms of action of medication treatments. Results of one series of studies documented the increase in extracellular DA following administration of clinical doses of MPH (Volkow et al. 2005), presumably providing a link to the mechanism of stimulant action. More controversial has been whether there is increased density of DA transporters (DAT) in ADHD, which could account for the hypothesized hypo-dopaminergic state in this disorder. Several studies have reported increased density of striatal DAT in adults with ADHD (Spencer et al. 2007a), but others have not found this to be the case (Volkow et al. 2007). Nevertheless, the inverse linear relationship between density of DAT and self-reports of inattention in both ADHD subjects and controls in the latter study suggests that, whether or not DAT density accounts for the hypo-dopaminergic state in ADHD, functionally decreasing DAT via treatment with stimulants (which bind to DAT) should improve attention.

More recent studies employing fMRI have examined the level of activation of prefrontal–striatal–thalamic regions (i.e., increased blood flow, generally taken to reflect use of the region) in subjects with ADHD in association with performance on inhibitory control tasks. Results of most studies have documented reduced striatal and increased prefrontal activation during response inhibition tasks, but there have also been contradictory findings. In addition, differences in activation extend to a variety of other regions. For example, in comparison with non-ADHD controls, adolescents with ADHD were found to have significantly greater activation of the left anterior cingulate cortex, right ventrolateral prefrontal cortex, and left basal ganglia during the dual task of interference control and response competition (Schulz et al. 2005). The notion that ADHD and non-ADHD youth process information differently is attractive, and potentially lines up well with the proposed neurobiological basis of ADHD. However, differences in group activation across studies could also reflect variability in task demands and corresponding differences in performance.

There have been fewer morphological and functional imaging studies of CD. Neuroanatomical investigation of children with ADHD alone and ADHD with comorbid CD found that morphological findings in cerebellum which have previously been reported in ADHD samples (i.e., smaller volumes of the left and total posterior superior and inferior lobes of the vermis) are present whether or not CD is also present. Morphological findings more specifically linked to CD include significantly reduced right temporal lobe and right temporal gray matter volumes, and possible reduced prefrontal volume (Kruesi et al. 2004). Findings from fMRI studies suggest differences in both cortical/executive and limbic function in adolescents with CD, as indicated by reduced activation in both anterior cingulate cortex and amygdala (Stadler et al. 2007). These findings could reflect impairment in both the recognition and cognitive control of emotional stimuli in patients with CD, which presumably might be associated with an increased propensity for aggressive behavior.

A more extensive literature has examined the neurochemical basis of CD, with particular emphasis on the role of NE and serotonin (5-HT). Reduced noradrenergic function in children with CD is suggested by findings of low cerebrospinal fluid (CSF) concentration of methoxyhydroxyphenylglycol (MHPG) (metabolite of NE) and reduced activity of the enzyme dopamine-$\beta$-hydroxylase (which converts DA to NA), perhaps reflecting the role of NE in mediating behavioral arousal. Other research has examined the role of central serotonergic (5-HT) function in aggression and antisocial behavior, since antisocial adults have consistently been characterized as having a hypo-serotonergic state—as indicated by reduced CSF levels of 5-HT metabolites and reduced prolactin response to the 5-HT releaser/reuptake blocker fenfluramine. In contrast, the hypothesized inverse relationship between 5-HT and aggression has been less clearly demonstrated in studies in children. While the reasons for this are unclear, it is well known that aggression is more common in children than adults, and only about half of aggressive children continue to be aggressive over time. It would therefore seem unlikely that a single biological mechanism could explain the entire phenomenon. Consequently, one series of studies examined cross-sectional and longitudinal characteristics of aggressive children divided according to the level of central 5-HT responsivity in childhood. Those with reduced central 5-HT function were found to have numerous risk factors for persistence of aggression. Further, lower 5-HT responsivity in childhood predicted aggression in adolescence, adding variance above and beyond that accounted for by childhood aggression (Halperin et al. 2006). Finally, children with decreased 5-HT were more likely to develop ASPD in young adulthood (Flory et al. 2007). Interestingly, children with low 5-HT responsivity were quite sensitive to environmental events normally associated with CD, while those with high 5-HT responsivity were relatively protected. This suggests that 5-HT functioning may be a necessary but not sufficient condition for the persistence and escalation of aggression in youth, as high levels of psychosocial risk are also required. These findings highlight the importance of considering interactions among environmental and biological risk factors in the etiology of CD.

## Psychological Factors

Neuropsychological models of ADHD have often focused on the primacy of executive dysfunction, as suggested by deficiencies in higher order cognitive functions such as inhibitory control, planning, working memory, and shifting sets. This model has been supported by a convergence of evidence from numerous studies examining neuropsychological test performance in both children and adults with ADHD compared to controls, results of neuroimaging studies indicating differences in structure and/or function in key fronto-striatal brain regions implicated in attention and self-regulatory function, and findings linking mechanisms of action of stimulant medications to many of these same regions. However, the results of several recent studies pose significant challenges for this model, including: (1) inconsistent findings in studies examining performance on specific neuropsychological tests of executive function in ADHD probands and controls; (2) results of large meta-analytic studies indicating that although groups of children with ADHD perform more poorly than controls on a wide array of executive function measures, the effect sizes for the various measures are low, particularly after controlling for potentially confounding variables such as intelligence, academic achievement and comorbidity; and (3) findings from studies in individuals with ADHD and controls which indicate that although executive function deficits are higher in individuals with ADHD than controls, only about half of the subjects with ADHD have executive function deficits. Further, it has been observed that the time course for neurodevelopment of the frontal lobe, which is ongoing throughout childhood and adolescence and is not complete until early adulthood, does not match the developmental course of ADHD, which begins in early childhood in the majority of cases, and is characterized by a decline in hyperactivity but less consistent decreases in inattention and cognitive impairment over time. This led to the speculation that neurodevelopment of the frontal lobe and associated functions might be associated with improvement in ADHD symptoms rather than the etiology of the disorder (Halperin and Schulz, 2006).

Taken together, the relatively high rates of executive dysfunction in ADHD and the above documented heterogeneity in this domain suggest that multiple pathways may be implicated. In addition to executive dysfunction, proposed the core deficits include cognitive-energetic factors, faulty time perception and delay aversion. The latter model is consistent with the observations that individuals with ADHD are attracted to stimulation and are very sensitive to reward, and suggest an alternative model of ADHD implicating ventral striatal reward circuitry (Sonuga-Barke 2005). Reward sensitivity is also prominent in youth with CD and substance abuse, conditions which frequently co-occur with ADHD. Models of ADHD that incorporate the construct of reward sensitivity are also consistent with findings supporting the efficacy of contingency management treatment approaches (Pfiffner et al. 2000).

The cognitive-energetic model (Sergeant 2005) of ADHD is based on the observation that some individuals with the disorder have a slow and variable response style—perhaps reflecting impairment in cognitive mechanisms related to arousal and alertness, resulting in an apparent lack of preparedness to receive information and respond. This model is attractive for understanding individuals with predominantly inattentive subtype, who have often been described as having a sluggish demeanor and cognitive tempo. In addition, it is consistent with findings from neuropsychological research which indicate that individuals with ADHD have difficulty maintaining readiness to respond, and perform better on tasks where there is a shorter interval between stimuli.

## Social/Environmental Factors

A variety of social/environmental factors are known to increase risk for ADHD and CD. Results of several studies have found that maternal use of alcohol, nicotine, cocaine and other drugs of abuse during pregnancy substantially increase risk for ADHD and conduct problems in offspring, possibly related to toxic effects on neurodevelopment of catecholamine systems and/or alterations in gene expression. The clinical presentation of children with fetal alcohol syndrome, including hyperactivity, complex learning problems (e.g., attentional problems, mixed expressive/receptive language and mathematics disorders), and/or disruptive

behavior is consistent with this hypothesis. However, interpretation of findings is complicated by the fact that rates of ADHD, substance abuse and conduct/antisocial disorders are likely increased in mothers who use alcohol, nicotine or other drugs during pregnancy, especially given the high degree of publicity regarding the potential deleterious effects of these behaviors. Thus, gene-environment interactions are likely involved.

A variety of other environmental risk factors have also been implicated in the etiology of the AD-DBDs. Exposure to high levels of lead increases risk for ADHD and other cognitive and behavioral problems, with recent findings indicating that even moderately elevated plasma levels may be associated with elevated risk. Other studies have focused on the possibility that exposure to environmental toxins, such as PCBs and mercury, can increase risk for ADHD (for review: Williams and Ross 2007).

Numerous social–familial factors have been shown to increase risk for the AD-DBDs. For example, shared family, peer and neighborhood risk factors have been implicated in the etiology of ODD and CD, and to a lesser degree ADHD. These so-called adversity factors include large sibships, parental separation, single parent households, child neglect, parental conflict, and poverty. Compromised child-rearing practices such as harsh physical discipline and poor supervision are also associated with elevated risk for ODD and CD. The most salient familial risk factor for CD is parental criminality, which likely has both environmental and genetic components. Delinquent peer membership and repeated victimization by peers also contribute to the development of CD and aggression, as does residing in a neighborhood with high rates of crime, poverty, and/or unemployment is associated with an earlier onset of CD. Recent data indicate that the experience of abuse, family violence or other traumatic events in early childhood may also be associated with increased risk for attentional and conduct problems. The above factors seem to operate in an additive fashion, with the probability of CD increasing linearly when there is aggregation of risk. Of note, these same psychosocial adversity factors increase risk for ADHD and ODD. Finally, a multitude of less serious but problematic parent-child interactions may influence the development and course of oppositional and disruptive behavior. Consistent with this observation, reductions in negative and ineffective parenting practices at home were shown to mediate improvement in children's social skills at school in children with ADHD, combined subtype. However, improvement in the child's behavior was only achieved when changes in parenting practices were fairly robust.

## Treatment

### Treatment Goals

Treatment of the AD-DBDs requires consideration of not only the core symptomatology, but also the full extent of cognitive, social, and psychological impairments that are often present. Given the wide-ranging nature of disruptive behavior, the high rates of comorbidity, and the presence of associated features such as academic underachievement, poor peer relations, and low self-esteem, multimodal treatments (i.e., psychopharmacolgic and psychosocial) are often warranted. It is very important to undertake psychoeducational efforts to instruct the patient and family regarding the nature of symptoms, and the many ways they can affect individuals at home, work, school, and other areas of life. It is also important to assist families in finding and accessing available support services and related resources, and assist them in implementing accommodations as required across settings.

In initiating psychosocial and/or medication therapy, it is important to identify specific target behaviors associated with impairment in one or more settings, and to systematically assess change in the number and severity of these behaviors. In addition, it is important to assess comorbidity at baseline and over the course of treatment. In some instances, good response can be achieved with unimodal treatment (e.g., medication treatment for uncomplicated ADHD or ADHD + ODD; psychosocial treatment for ADHD + anxiety disorders, or behavioral intervention in ODD without other comorbidity). However, the presence of more severe conduct problems often requires combination treatment. As there are no specific medication treatments for ODD and CD, it is important to evaluate and identify comorbid disorders responsive to medication.

### Somatic Treatments

Psychopharmacological treatment of the AD-DBDs can be traced to 1937, when benzedrine was first noted to produce behavioral improvement in a heterogeneous group of post-encephalitic children. Over the ensuing 70 years, there have been literally thousands of publications and several hundred controlled clinical trials on the effects of psychostimulant treatment, making it the best studied and validated medication treatment in child and adolescent psychiatry. Stimulants are the most frequently prescribed psychotropic medications in children, with prescription rates of 10–12% or higher in school age boys. There is also an US Food and Drug Administration (FDA)-approved nonstimulant, atomoxetine, and several other nonstimulant medications have been used "off-label" (e.g., bupropion, alpha-2 adrenergic agonists, modafinil and venlafaxine) because of known noradrenergic effects. Pharmacotherapy of ODD and CD is less solidly evidence-based, although findings from recent studies suggest that ODD symptoms in youth with comorbid ADHD + ODD are reasonably well treated using approved medications for ADHD. Treatment of CD is more complex, with many available medications used off-label, none of which can be recommended as fully evidence-based.

### Psychostimulants

#### Psychostimulant Efficacy

Stimulants remain the most effective first-line treatment in uncomplicated ADHD, and have demonstrated effects in reducing disruptive behavior above and beyond their effects in ADHD. The majority of studies with stimulants have been conducted in school age children, and mostly boys. However, there are now ample data indicating that stimulants are effective in both males and females with ADHD across the lifespan, with efficacy of both MPH and amphetamine demonstrated in controlled trials in girls, and in mixed populations of adolescents and adults.

Literature reviews linked to the establishment of professional guidelines rate the evidence-base for acute stimulant treatment to be quite strong, for example, American

Academy of Pediatrics (2001); effect sizes for the core ADHD symptoms (i.e., inattention, hyperactivity and impaired self-regulatory capacity) in children and adolescents generally range from 0.8–1.0.

There are also treatment-related improvements in a variety of associated features and functional domains—including oppositionality, behavioral noncompliance, impulsive aggression, peer interactions, family dynamics, and ratings of self-esteem. Ensuring that the positive effects of treatment extend to these domains is essential to optimizing response. Improvement in academic productivity and accuracy has also been demonstrated, however, the hypothesized change in long-term academic achievement with treatment has been more difficult to substantiate.

## Psychostimulant Classes and Formulations

There are several different stimulant formulations, divided among the two major classes, MPH and amphetamine (AMP), including immediate and extended release formulations and branded and generic products. Because stimulants have a short pharmacodynamic half-life and never functionally reach steady state, the medication has to be delivered relatively continuously over the course of the day. This is accomplished via administration of immediate-release formulations multiple times daily, or via extended duration formulations designed to replicate the pharmacokinetics of multiple daily dosing. Extended duration stimulant formulations are easy to use, decrease the potential for stigma associated with administration of medication during the school day, and presumably increase adherence to treatment. Consequently, treatment with long-acting stimulants has become the first-line approach.

MPH and AMP are both three dimensional molecules with d and l stereoisomers. Most MPH formulations contain the racemic form, but there are also immediate-release and extended-release forms of d-MPH, which is the active stereoisomer. There are now many long-acting formulations of d,l-MPH, with activity generally ranging from 8–12 hr. The original formulation, MPH-SR, embedded the active medication in a wax matrix, which produced extended duration but generally less robust response than immediate release formulations. The various second generation extended-release MPH formulations have different mechanisms of action. Several of these (e.g., d,l-MPH-CD, d,l-MPH-LA, d-MPH-XR) are double pulse formulations, which mimic twice daily administration of immediate-release MPH. In contrast, OROS-MPH uses an osmotically-controlled delivery system to produce constant and gradually increasing plasma levels over the course of the day. There is also a transdermal d,l-MPH formulation, with duration of action extending until approximately 3 hr after the patch is removed, potentially up to 15 hours. Together, the different MPH formulations represent the most often prescribed medications for ADHD.

The AMP class of stimulants includes both dextroamphetamine (DEX) and mixed amphetamine salts (MAS). The latter is a mixture of several amphetamine compounds, 75% of which is DEX. MAS-XR, a double pulse version of MAS, is the most frequently prescribed single medication for ADHD. A pro-drug formulation of DEX, lisdexamfetamine (LDX), covalently binds DEX to the amino acid l-lysine—rendering it inactive until it is metabolized in the gastrointestinal system. Release of DEX is more gradual when controlled through this metabolic pathway, and associated with decreased reports of euphoria in substance abusers. Intravenous or other nonoral routes of administration do not alter the kinetics of drug administration, also decreasing risk for abuse. Also, the duration of action of LDX is much longer than for other formulations of DEX.

Determining which stimulant class and formulation is best for the individual patient will often depend on judgments regarding the nature of impairment, duration of required coverage, and variability in individual response. Despite slight differences in mechanism of action, profiles of response and AEs, the different stimulant classes and formulations are relatively comparable in clinical efficacy and tolerability at the group level (James et al. 2001). However, there are frequently individual differences in response and/or tolerability. While most patients will respond to both MPH and AMP, certain individuals have selectively better response or tolerability with one or the other. Preferential response can be reflected in sensitivity to dose as well as adequacy of response. It is therefore important to begin treatment using a low dose, regardless of whether the patient has previously been treated with a different stimulant class. Relative differences in response and tolerability within a class are smaller, but there may be individual preferences for one or another formulation based on perceived efficacy and/or tolerability, duration of action or mode of delivery. These data underscore the importance of trying different medications if symptom management or tolerability is suboptimal.

In addition to selecting the best medication for the individual patient, it is important to consider individual differences related to both need for coverage (i.e., tasks that are best undertaken while medication is active) and duration of medication response. Since unregulated ADHD symptoms produce impairments in psychological, social and academic/vocational, and other functional domains, it is often important to maintain symptom control throughout the day. The inconvenience associated with multiple dosing with immediate release stimulants has been considerably improved through the development of effective extended-duration formulations. However, because symptom management is often required for longer than any of these medications remain effective, particularly in adults, and because the nature and severity of symptoms often differs over the course of the day, extended-release and immediate-release formulations are often used together. Formulations with longer activity than those currently available are currently being investigated in clinical trials.

## Stimulant Adverse Effects

The most common AEs of stimulants are headache, abdominal pain, decreased appetite (with or without weight loss), and initial insomnia. There are slight increases in pulse and BP, which are not very meaningful at the group level but may be important in some individuals, particularly adults. Affective changes, including blunted affect, irritability, and mood lability can also be seen, either at peak dose or when the dose wears off. Use of longer acting stimulants tends to minimize mood lability and other AEs that are often considered to reflect the "on-off effects" which may occur with IR preparations. Despite initial concerns that motor or vocal tics can develop or be exacerbated, a convergence of evidence indicates that stimulant treatment does not necessarily

exacerbate tics and can be used safely in many cases. However, it is important to obtain a history of tic behaviors and examine the patient for tics, both prior to initiating medication and periodically over the course of treatment.

It is also important to monitor height and weight, and obtain a family history of growth in children treated with stimulants, as decreases in weight and growth attainment have long been recognized. Findings from initial studies indicated that slowing of growth occurs early in treatment, but then stabilizes and catches up over time. However, the MTA found that acute use of immediate-release stimulants, administered 3 times daily, 7 days per week, produced a slowing of growth by approximately 1 cm per year over the first 24 months of treatment in medication treated versus un-medicated subjects. Although the decrease in growth trajectory flattened after the initial treatment period, it did not "catch up" to the curve for the unmedicated group by 36 months (Swanson et al. 2007). Interpretation of these data are complicated by the fact that the ADHD children in this and most other clinical trials were larger than age and gender-based norms, so it is not clear whether this degree of slowing of growth is actually a concern. In addition, the overwhelming majority of subjects in this study received immediate release stimulants. Results from industry-funded trials with newer extended release formulations have generally found less flattening of the growth curve. While there is some lingering question as to whether flattening of growth trajectory is more problematic with AMP than MPH it is not a problem for the majority of stimulant-treated youth, regardless of medication class.

The relationship of stimulant treatment to cardiovascular risk was carefully reviewed after post-marketing surveillance identified 12 cases of sudden cardiac death in children taking MAS. However, approximately half of the reports were in patients with underlying structural heart defects; several others had other complicating circumstances, including use of additional medications, and others still had a positive family history of sudden death or other acute cardiac events. Given these findings, and considering that the risk for sudden death in patients taking stimulants does not exceed the base rate in the general population (0.6–6/100,000 per year) (Wilens et al. 2006), the FDA issued a warning for cardiovascular risk, but not a black box (www.fda.gov/cder/drug/infopage/ADHD). Prior to initiating stimulant treatment, it is essential to screen for a history of obstructive cardiac problems or a family history of early cardiac disease or death. However, it is not essential to obtain routine electrocardiograms (ECGs), since even a normal ECG does not guarantee the absence of a structural cardiac defect. Obtaining an echocardiogram and expert medical consultation should be considered in patients with arrhythmias, hypertension, structural cardiac defects, or a family history of untoward cardiac events.

A final safety consideration relates to the potential for stimulant misuse, abuse and diversion. Longitudinal data indicate that up to 11% of youth with ADHD report selling their medications, and 22% of those with comorbid CD or SUD reported misusing their medications (Wilens et al. 2006). College students are a population at particular risk, based on findings from several self-report surveys. It is therefore important to directly discuss issues related to abuse and diversion with adolescents and young adults, as well as parents of younger children, and to screen for signs and symptoms of substance abuse in monitoring treatment. Stimulant abuse and dependence generally occur in the context of other addiction disorders, and it is unlikely that patients will abuse their stimulant medication if other substance abuse is not also present. There are apparently not differences in the extent to which MPH and AMP are abusable, based on studies of mechanisms of action in humans and primates; both medications are associated with self-administration behavior in animals and produce subjective effects in humans associated with drug reinforcement or reward (i.e., wanting to use it again).

## Atomoxetine (ATX)

ATX is the only FDA-approved nonstimulant medication for ADHD, and it is labeled for use in both children and adults. It is a highly selective norepinephrine reuptake inhibitor that is structurally distinct from both the stimulants and the tricyclic antidepressants. ATX increases synaptic norepinephrine (NE) in multiple brain regions, and dopamine (DA) levels in prefrontal cortex (Bymaster et al. 2002). ATX has low potential for abuse because it does not bind to receptors (i.e., dopamine, gamma-aminobutyric acid, opioid) associated with abuse potential, and does not increase DA in the striatum or nucleus accumbens.

Numerous controlled trials have demonstrated that ATX is effective in managing the core ADHD symptoms, with apparently equivalent response in inattentive and hyperactive–impulsive domains. Effect sizes for the core ADHD symptoms are in the medium to large range, somewhat lower than for stimulants at the group level. Treatment is associated with a reduction in impairment across several domains of function, including positive parental reports of child self-esteem, as well as social and family function in acute trials. Longer-term treatment was associated with improvement in learning and academic function in one study.

ATX is dosed on a weight-based schedule—with the target dose being 1.2 mg/kg. The precise duration of action is not known, however, the medication is effective whether administered once or twice daily, despite the fact that the half life in the large majority of people is 4–5 hr. ATX is metabolized via the cytochrome P (CYP) 2D6 system; 7% of individuals have a genetic polymorphism which makes them poor metabolizers. In these individuals, the half life of ATX is approximately 19 hr, and blood medication levels are much higher for any given dose. However, it is not necessary to determine CYP2D6 genotype prior to treatment, as studies using blind titration in slow and extensive metabolizers found that end of titration doses were nearly equivalent. Nonetheless, there is some suggestion that poor metabolizers have slightly better efficacy and slightly higher rates of AEs. ATX administration does not affect the pharmacokinetic properties of concomitant medications metabolized via CYP2D6 substrates. However, medications that alter CYP2D6 function, such as the fluoxetine and paroxetine, affect the metabolism of ATX—essentially converting many individuals from being extensive to poor metabolizers.

ATX has generally been well tolerated in clinical trials, with measured safety and tolerability data now extending to 5 years. The most commonly occurring AEs include sedation, nausea and vomiting, decreased appetite, weight loss, and increase in pulse and blood pressure (comparable

to stimulants). Irritability and increased aggression can also be seen, particularly in individuals with comorbid mood or behavioral syndromes. Longitudinal data indicate that effects on growth trajectory are relatively small in comparison to national norms, particularly after accounting for the initial effects of decreased appetite (Spencer et al. 2005). There is no specific risk for cardiovascular AEs or changes in ECG. However use of ATX is cautioned in patients with hypertension, tachycardia, or a history of cardiovascular or cerebrovascular disease, because it can increase blood pressure and heart rate.

There are two FDA warnings in effect for ATX—for liver toxicity and suicidal ideation. In 2004, post-marketing surveillance identified 2 cases (out of approximately 2 million exposures) of acute hepatotoxicity, although no cases have subsequently been reported. In both instances, patients had abdominal pain, jaundice, and substantially elevated liver function tests, which resolved with medication discontinuation. Obtaining routine liver function tests before initiating ATX treatment is not recommended, due to the very low frequency of liver toxicity, the fact that it cannot be predicted from baseline laboratory indices, and the clear presence of symptoms when it occurred. However, in patients at risk, or in those who develop abdominal pain or jaundice in association with treatment, a thorough work-up is indicated.

The FDA review of suicidal behavior in children treated with ATX was part of a larger investigation of suicidal behavior in youth treated with anti-depressant medications, since ATX shares a common mechanism of action (i.e., NE reuptake inhibition) with known anti-depressants (e.g., desipramine). Premarketing data were reviewed in 2200 children and adolescents from 12 short-term clinical trials (1357 treated with atomoxetine and 852 with placebo). There was a small but statistically significant increased rate of suicidal ideation—approximately 4 per 1,000 patients. Six cases were identified, and all were prepubertal children. Five of the six had ideation only, with uncertain intent. There was a nonlethal medication overdose in the 6th case. Consequently, there is a "black box" warning for suicidal ideation in the first few months of treatment (see FDA Web site: www.fda.gov/cder/drug/advisory/atomoxetine.htm). In evaluating and following patients treated with ATX, it is important to obtain a careful history of mood problems and/or suicidal behavior prior to starting medication, to educate patients and families regarding the importance of reporting changes in mental status, and to re-examine patients frequently at the beginning of treatment. Particular attention should be given to the acute emotional changes, including increased sadness, tearfulness, irritability, anger, or euphoria. As with other treatments, it is also wise to review the manner in which medications are stored and administered, and the importance of keeping medications away from young children.

### Buproprion

Buproprion is chemically unrelated to other known antidepressants. Multi-center studies in both children and adults (Wilens et al. 2005) with ADHD found that buproprion was effective, although less so than stimulants. Buproprion may be particularly useful in the treatment of comorbid ADHD + depression, since it is an approved anti-depressant in adults. In addition, because it is not a stimulant, it may be effective in treating comorbid ADHD + substance abuse. Bupropion has been found to reduce ADHD symptoms in trials of adolescents and adults with ADHD and comorbid substance abuse (with several different substances studied), often in the context of other comorbid disorders (i.e., CD, depression). In addition, it has been shown to decrease craving and/or abuse in some of these studies.

### Other

The noradrenergic tricyclic antidepressants, principally imipramine and desipramine, have been the most extensively studied and, until the mid-1990s, were the most often prescribed nonstimulant medications for ADHD. However, these medications are now infrequently used in children due to cardiac AEs. Tachycardia and postural hypotension are commonly seen, but are not often problematic. Prolongation of the PR and QT intervals may be a greater source of concern, so the premedication work-up should include an ECG. Prior to using tricyclics to treat children with ADHD, families should be informed that there have been several sudden deaths in children taking desipramine, although it has been argued that data from pharmacoepidemiologic studies and rates of sudden death in the general population do not support the conclusion that tricyclics have a high degree of cardiovascular toxicity in children.

There are preliminary data indicating that venlafaxine, a mixed serotonergic–noradrenergic reuptake inhibitor, might be useful for ADHD, based on reports of improved attention, concentration, and other cognitive functions in adults and children. The most commonly reported side effects are nausea and sedation, but light-headedness and changes in cardiovascular indices can occur. Open study findings have suggested that venlafaxine monotherapy may be an effective treatment for adults with comorbid ADD and major depression. However, double-blind, placebo-controlled trials have not been conducted. Although no precise recommendations for dosing in ADHD can be offered, it should be noted that the noradrenergic effects of venlafaxine are not substantive unless relatively higher doses are used.

Monoamine oxidase inhibitors (i.e., MAOIs) are nonspecific enhancers of monoamine neurotransmission, and the MAOI tranycyopromine was used successfully to treat a small group of children with ADHD, with effects found to be comparable to DEX. However, using MAOIs in children and adolescents is impractical, given the likelihood of dietary indiscretions and the availability of several approved and better studied off-label treatments.

### Alpha2-Adrenergic Agonists

Since the mid-1980s, there has been considerable interest in the use of alpha2- adrenergic agonists in the treatment of ADHD and aggression. Behavioral over-arousal and aggression are common targets of treatment, with more uncertainty regarding their role for inattention. Initial research and clinical use was with clonidine, a mixed alpha-2 agent. However, clonidine is quite short-acting, and treatment may be limited by sedation. There have also been concerns regarding cardiovascular toxicity—particularly following the occurrence of three sudden deaths in youth treated with the combination of clonidine + MPH. Results of subsequent studies (e.g., Tourette's Syndrome Study Group 2002) found that the treatments are each effective, and can be used

together safely, with no appreciable ECG changes and incremental improvement in symptoms.

More recent efforts have examined the potential role for guanfacine, initially in the treatment of youth with ADHD + tic diorders, and subsequently in youth with ADHD alone. Guanfacine is relatively selective for alpha-2A receptors, which play a major role in the regulation of attention (Arnsten 2006), and it has a longer half-life and duration of action than clonidine. The immediate release formulation of guanfacine generally requires 2–3 times daily dosing. Pilot studies have suggested reduction of inattention as well as hyperactive–impulsive behaviors.

An extended release formulation of guanfacine was studied in youth with ADHD, and received an approvable letter from the FDA in June, 2007. Findings from a double-blind, fixed-dose, multicenter trial in children and adolescents receiving 1 to 4 mg per day of guanfacine extended release or placebo, found significant reduction in ratings of ADHD symptoms in all dose groups. Adverse effects included dizziness, fatigue, headache, irritability, nausea, sedation, somnolence, and upper abdominal pain. A subsequent open-label, extension trial evaluated the long-term safety and efficacy up to 24 months, with good maintenance of therapeutic effect, good safety and reasonable tolerability.

### Modafinil

Modafinil is a novel cognitive enhancer and wake-promoting agent, which is structurally and pharmacologically different from other agents used for the treatment of children with ADHD. It selectively activates cortex and modulates several different neurotransmitters, including hypocretin, histamine, norepinephrine, gamma-aminobutyric acid, and glutamate. Modafinil is FDA approved for the treatment of narcolepsy and shift work sleep disorder, as well as for adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. It is a schedule 4 stimulant, with evidence suggesting only limited potential for large-scale abuse.

Several clinical trials evaluated the efficacy and tolerability of a new formulation of modafinil, as well as the effects of acute discontinuation (Swanson et al. 2006), with significant improvement in ratings of ADHD symptoms both at home and school. However, despite receiving an approvable letter from the FDA in 2005, the new formulation was ultimately not approved by the FDA, due to concerns that the occurrence of a skin rash in one subject could potentially indicate elevated risk for Stevens-Johnson syndrome. The relative absence of cardiovascular AEs suggests that modafinil could be useful for treating selected adults with ADHD, and possibly older children, provided they are nonresponders or nontolerators of approved medication treatments.

### Serotonin Reuptake Inhibitors

There are several open studies and case reports using fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in the treatment of children with AD-DBDs—both with and without comorbid mood disorder. The rationale for this approach is linked to results of studies in adults implicating serotonergic mechanisms in aggression, and the successful use of fluoxetine in treating a subgroup of adults with impulsive aggression. The frequent co-occurrence of mood and anxiety disorders in youth with ADHD and CD suggests a possible role for the SSRIs. However, there have not been controlled studies of SSRI treatment of either ADHD or CD, and the potential role of SSRIs in treating comorbid ADHD/CD/Depression is inferential only.

### Atypical Antipsychotics

Neuroleptic medications have been used for decades to treat children with severe behavioral problems characterized by aggression and combativeness. First generation antipsychotics such as Chlorpromazine, Thioridazine, and Halperidol were FDA-approved for this indication, however, they are rarely used as primary treatments. More recent study has focused on the potential utility of the atypical neuroleptics. The best controlled data are for risperidone, with several controlled trials documenting utility in treating aggressive symptoms and even hyperactivity (Schur et al. 2003). Several of the above studies were conducted in individuals with developmental disabilities and/or subaverage IQ (for example, see Aman et al. 2005); others examined behavioral disturbance in the context of mood dysregulation. Open studies and case reports are available for several of the other atypical anticpsychotic medications—most notably quetiapine. Additionally, there have been open reports with aripiprazol. The latter is of considerable interest because of the occurrence of metabolic syndromes following use of other atypical antipsychotics.

### Mood and Behavior Stabilizing Medications

A variety of other pharmacotherapeutic agents have been utilized off label in the treatment of aggression and episodic dyscontrol, although efficacy in the treatment of CD has not been established. Studies with lithium have yielded mixed results. Positve results were reported in the well-controlled studies of aggressive children, impulsive–aggressive adolescents and young adult delinquents. However, the effect size in several more recent studies in children and adolescents was only modest. Further, concerns regarding potential AEs and the need to follow blood levels represent potential drawbacks for widespread use of lithium in children.

Several anti-epileptic medications have been investigated, again with mixed results, although there continues to be substantial off-label use in the treatment of aggression. The best data are for sodium valproate, which was shown to be effective in a controlled trial of adolescents with aggression, chronic temper outbursts, and mood lability (Donovan et al. 2000). Initial placebo-controlled data for carbamezapine in youth with aggressive CD were promising, but subsequent studies did not replicate the finding. Several of the newer antiepileptic medications used to treat mood and bipolar disorders may also be relevant for youth with CD—including topiramate and lamotrigine. The former is attractive because it does not result in the weight gain—unlike most other neuroleptic or anticonvulsant mood and behavior stabilizing medications. However, it can result in cognitive dulling, particularly at higher doses. Lamotrigine has been used to treat behavioral disturbance in the context of depressive/bipolar syndromes, however, it has been associated with risk for Stevens-Johnson syndrome, particularly in young children. There is an older literature with beta-adrenergic blockers such as propranolol in the treatment of aggression, primarily in children with mental retardation. However, controlled trial data are lacking.

## Psychosocial Treatments

A variety of psychosocial therapies are useful for treating children with AD-DBDs. Systematically studied psychosocial interventions include home based interventions/parent training, classroom-based behavior modification, social skills training and intensive summer treatment programs (Wells et al. 2000). Since family, peer and school interactions are important in the morbidity and maintenance of these disorders, it is important to utilize psychosocial treatments to target each of these areas. Psychoeducational interventions are almost always indicated. In contrast to these more structured and symptom oriented approaches, individual play therapy with children is generally ineffective in decreasing symptoms of the AD-DBDs. However, there may be a role for this and other less structured therapies in treating problems related to adjustment, self-esteem, and comorbidity.

Psychoeducational intervention should begin at the time of diagnosis, as it helps patients/families understand the nature of the disorder and learn to restructure the environment to improve management of the condition. Helping families appreciate that the AD-DBDs have a substantive neurobiological basis can have positive effects in reducing negative global attributions and maintaining a positive sense of self-efficacy and self-esteem. Highlighting common impairments and teaching patients/families to anticipate them is also helpful. Also, it is important to counsel families regarding the range of aids and/or structural accommodations that are available and can be accessed.

Behavior therapy (BT) has been successfully utilized in the AD-DBDs, either alone or in combination with other interventions. Most behavioral approaches in involve working with parents and/or teachers as the agents of change. The focus is on decreasing the frequency of problematic behaviors and/or increasing the rate of desirable behaviors through the environmental manipulation and/or the contingency management techniques. Parent management training is one of the most common approaches, consisting of group and/or individual sessions which offer a combination of psycho-education, instruction in behavioral treatment approaches, and interventions which facilitate their implementation. Contingency management, in which rewards or privileges are earned for meeting stipulated desired or prosocial behaviors, and rewards are withheld or punishments applied for rule violations (Pfiffner et al. 2000), is often used. Time-out may be utilized to remove the child from a negative situation or to interrupt certain undesired behaviors.

Use of contingency management in the children with AD-DBDs is linked to the observation that individuals with ADHD and disruptive behavior are highly sensitive to reward. Requirements for successful implementation are the clear elaboration of target behaviors, including the gains to be achieved in meeting behavioral expectations and the consequences of falling short. It is desirable that the child participate in some aspects of the treatment in order to understand how the behavioral plan will work, and to provide input into the selection of rewards. This is extremely important to engage the child and maintain motivation over time. It is essential that rewards reflect the individual values of the child and his/her milieu, and not be onerous for the parent in terms of cost or personal values. It is also important to appreciate the need to change rewards over the course of treatment, as the child's perception of the reward changes or the child grows too familiar with it. While the frequent shifting of behavioral targets and/or rewards can be seen as an impediment to implementing BT, it is actually one of its major assets. The flexible nature of BT makes it possible to develop interventions that are tailored to the problems and needs of the child and family, to target specific tasks or settings, and to adapt the treatment to changing needs and/or impairments as they arise.

BT can be structured to incorporate tasks related to cognitive function, homework completion, social interactions, and a variety of other tasks or behaviors. Programs often target school behavior and performance via contingency management strategies implemented at home which support selected target outcomes at school. Consultation with teachers is often used to augment home-based interventions. School-based BT programs can be implemented by a variety of personnel, including classroom teachers, guidance counselors, teacher assistants and paraprofessional aids. When specific interventions or supplemental personnel are introduced to meet the needs of an individual child, it is important to do so in a manner that minimizes stigma. An alternative approach is to incorporate aspects of BT into overall classroom management strategies, or to utilize paraprofessionals to accomplish a broader range of behavioral objectives for the class, and not only those of the individual child.

A variety of psychosocial approaches can be used target problems with attention and other cognitive skills, self-perceptions, and social function—many of which are impaired in individuals with AD-DBDs. Cognitive–behavioral therapy (CBT) approaches are best reserved for older children, adolescents and adults, and can only be implemented when there is sufficient behavioral control. Cognitive–behavioral approaches are based on the premise that certain undesirable, thoughts, perceptions and behaviors are over-learned, and that a structured, symptom-focused intervention can help patients reframe how they think about or manage behavior, and to implement self-regulatory or other compensatory strategies. Examples of CBT include training in self-monitoring, anger control and self-reinforcement. CBT is theoretically well suited to helping patients manage problems with task engagement, completion and organization, and also to minimize secondary problems related to self-esteem, demoralization or anxiety. Specific interventions designed to improve attention and organizational skills in adolescents and adults with ADHD are currently being investigated, but are not yet widely available.

Social skills training is based on the recognition that symptoms of ADHD, ODD and CD often affect social function, and that many individuals with AD-DBDs have specific impairments in self-observation and/or reading social cues. Social skills training is best offered in a group setting which replicates the outside milieu as much as possible—since generalization of gains to other settings is difficult to achieve. To address this potential limitation, an intensive Summer Treatment Program (STP) has been developed (Pelham et al. 2000)—which offers social skills programming in combination with cognitive/educational remediation, using a variety of contingency management principles, and augmented by parent behavior management training—in the context of what is essentially a summer day camp. This approach is well suited to provide the requisite variety and intensity of

behavioral interventions, in a setting that closely replicates normal school and summer programming, and in a manner that is engaging and enjoyable to children, supportive of family needs, and not stigmatizing.

## Comparing Response to Medication, Psychosocial and Combination Treatments

The MTA compared 14 months of randomized treatment with medication, psychosocial treatment or the combination with each other and community standard treatment in 579, 7–10-year old, children with combined subtype ADHD. The medication arm consisted of algorithmically driven treatment with immediate release MPH given three times daily, followed by trials with DEX or other medications if these were not effective. The psychosocial arm consisted of a variety of interventions, including: an intense parent behavior management training program, ongoing consultation to the classroom teacher, a summer treatment program and a paraprofessional aid program (Wells et al. 2000). The 14 month intent-to-treat analyses indicated that, for ADHD symptoms, treatments that included medication performed better than other treatments (MTA Cooperative Group 1999a). This finding was replicated in a different two-site comparative medication–psychosocial trial using a similar but slightly different design (Abikoff et al. 2004). For non-ADHD symptoms in the MTA study, only combined treatment was statistically superior to community standard care. Combined treatment was not significantly different from medication only, but there was a small difference in effect size favoring the combined treatment in several different analyses. When the different variables from these analyses were incorporated into a single composite measure (i.e., defining a broader definition of response, and increasing statistical power) combined treatment was demonstrated to be superior to both unimodal treatments (Conners et al. 2001). Age, gender and comorbid CD/ODD did not moderate the primary intent to treat findings, however, behavioral treatment alone was more effective in children with comorbid ADHD and anxiety disorders than in those without anxiety disorders (MTA Cooperative Group 1999b).

Longitudinal follow-up of the MTA sample has yielded a complex pattern of results. The effect size favoring randomization to medication treatment was reduced by approximately 50% at 24 months posttreatment, 10 months after the active study treatment ended. By the 36 month assessment, there was no longer a significant advantage for the group originally randomized to medication (Jensen et al. 2007). Analyses using latent class modeling of response and grouping of subjects according to naturalistic treatment selection (i.e., the treatment chosen after the study ended) indicated that membership in the various response classes was mainly not determined by whether or not subjects were treated with medication. However, within several of the classes, there was modest benefit associated with medication treatment (Swanson et al. 2007). These findings suggest that the longitudinal course of ADHD may be predominantly accounted for by a multiplicity of constitutional and environmental factors, and not treatment per se. Seen in this context, the role of long-term treatment would be to modify the course within the limitations imposed by these various constitutional and environmental factors.

## Special Factors Influencing Treatment

### Comorbidity

Results of numerous studies indicate that the children with and without aggression respond equally well to stimulant treatment in reduction of ADHD symptoms. In addition, stimulant treatment can ameliorate conduct problems independent of its effect on ADHD. In the MTA study, comorbid ODD/CD did not moderate the beneficial effects of treatment on ADHD symptoms, however, response was superior when medication was used (MTA Cooperative Group 1999b). The best outcome in this comorbid group was seen with combined treatment (Jensen et al. 2001). The absence of moderator effects of comorbid ODD has been replicated with the new longer acting stimulant formulations, and has also been extended to atomoxetine.

Other research has examined whether comorbid LD moderates stimulant response, with the overall observation that cognitive measures associated with ADHD improve irrespective of LD. When LD is present remediation is often also required. Improvement in cognitive function is thought to follow a linear dose-response curve, however, there have been questions about whether this is equally true for the different ADHD subtypes (Stein et al. 2003), and whether there are deleterious effects on cognition if higher doses are used. One early study found that optimal cognitive performance was achieved with low dose DEX (i.e., 0.3 mg/kg). Optimal behavioral function was achieved with high dose (i.e., 1.0 mg/kg), but there was an associated decline in cognitive function. Findings from animal studies support the hypothesis that high doses of stimulants may be associated with decreased cognitive performance, however, most clinical trials have not found this to be so—either because the relative dosing of stimulants is lower in humans, and/or because it is difficult to distinguish cognitive inflexibility and perseveration from vigilance. A related issue is whether optimal dose varies as a function of comorbidity. Findings from studies with both stimulants (e.g., Spencer et al. 2006) and atomoxetine (Newcorn et al. 2005) do indicate that higher dosing is required in ADHD + ODD. An earlier study found that low dose MPH was sufficient for ADHD and either comorbid internalizing or externalizing disorders, but the combination required higher dose treatment.

Studies of stimulant response in children with ADHD children and comorbid anxiety have yielded inconsistent findings. Earlier investigations found stimulants to be effective in reducing ADHD symptoms in the comorbid group, though response was less robust and there was heightened sensitivity to AEs. However, more recent studies have found that stimulant medication is equally effective in ADHD youth with and without anxiety disorders (e.g., MTA Cooperative Group 1999a). Furthermore, stimulants do appear to not increase anxiety at the group level, and may reduce anxiety in some children (Abikoff et al. 2005), possibly due to a reduction in secondary anxiety following the expected improvements in performance associated with treatment of ADHD. Stimulant treatment did not significantly improve anxiety symptoms, but the study was not powered adequately to show this. Subsequent addition of fluoxetine treated anxiety successfully, and was generally tolerated well.

ATX may be particularly useful in the treatment of ADHD and several comorbid disorders, with the best data

thus far in comorbid anxiety and tic disorders. Children and adolescents with ADHD and anxiety disorders treated with ATX showed significant improvement in *both* ADHD (ES = 1.0) and anxiety symptoms (ES = 0.5) (Geller et al. 2007). Also, ATX did not worsen preexisting tics in subjects with ADHD + chronic motor tic disorders, and improvement in tic severity was seen in the subgroup of subjects with TS (Allen et al. 2005). Improvement in ODD symptoms in youth with ADHD + comorbid ODD has been more inconsistent, with findings varying across studies. However, as with stimulants, co-occurrence of ODD symptoms does not alter response of ADHD symptoms to ATX. Finally, there has been interest in whether ATX can be used to treat children with PDD spectrum disorders and ADHD symptoms. Findings from a small, randomized, crossover pilot study found that ATX significantly reduced hyperactive symptoms in this population with relatively good tolerability (Arnold et al. 2006).

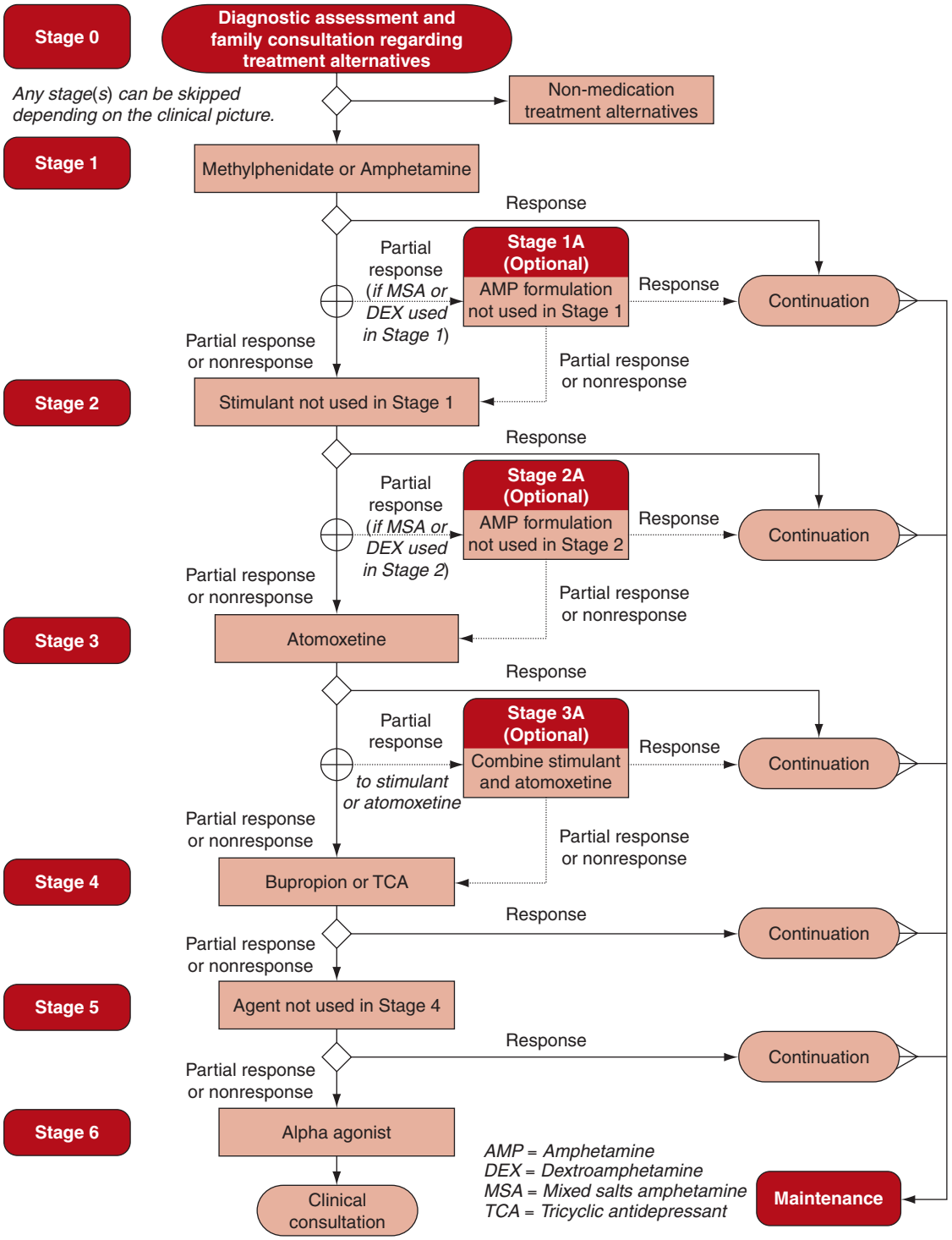



**Figure 46–1** *Texas algorithm for the pharmacologic treatment of ADHD.* (Source: *Pliszka et al. (2006) Journal of the American Academy of Child and Adolescent Psychiatry 45(6), 642–657.*)

### Developmental Effects

Although ADHD had previously been primarily considered a disorder of school age children, an emerging literature has evaluated treatment response across the lifespan. There now are large studies in preschool children, adolescents and adults with ADHD, all demonstrating positive effects. However, age-specific differences in response are also observed. For example, effect sizes of medication treatment were lower in a multi-site, multimodal treatment study in preschool children than in previous studies with school age children and adolescents (Greenhill et al. 2007). This may be due to the lower doses used in treatment, the requirement that intensive psychosocial treatment be given before medication and/or the greater severity of early onset cases. Effect sizes of approved treatments for ADHD (i.e., d–MPH-XR, d,l-AMP-XR, atomoxetine) are also lower in adults than they are in children—particularly at FDA-approved doses, which are lower for the two approved stimulant formulation in adults than in children. Also contributing to the lower effect size in adults is the fact that placebo effects increase along with the age of the sample—with somewhat larger placebo effects observed in adolescents compared to children, and even larger placebo effects in adults. Finally, the objectives and targets of both medication and psychosocial treatments vary considerably as a function of age, so differences in the nature and magnitude of response should not be surprising. For example, since adults have a higher proportion of inattention symptoms, and these are often difficult to observe directly (there is no analogue for teacher ratings in adults), information is most often obtained via self-report—potentially introducing greater susceptibility to expectancy bias.

## Treatment Algorithms and Practice Guidelines

The fact that there are multiple available medications for the AD-DBDs, and no way to accurately predict who will respond optimally to one or the other, means that treatment is conducted empirically in sequential fashion. The goal of treatment is to normalize symptoms as best possible, without sacrificing tolerability and patient/family satisfaction. Incomplete responders or poor tolerators of any one medication class should have trials of additional treatments until

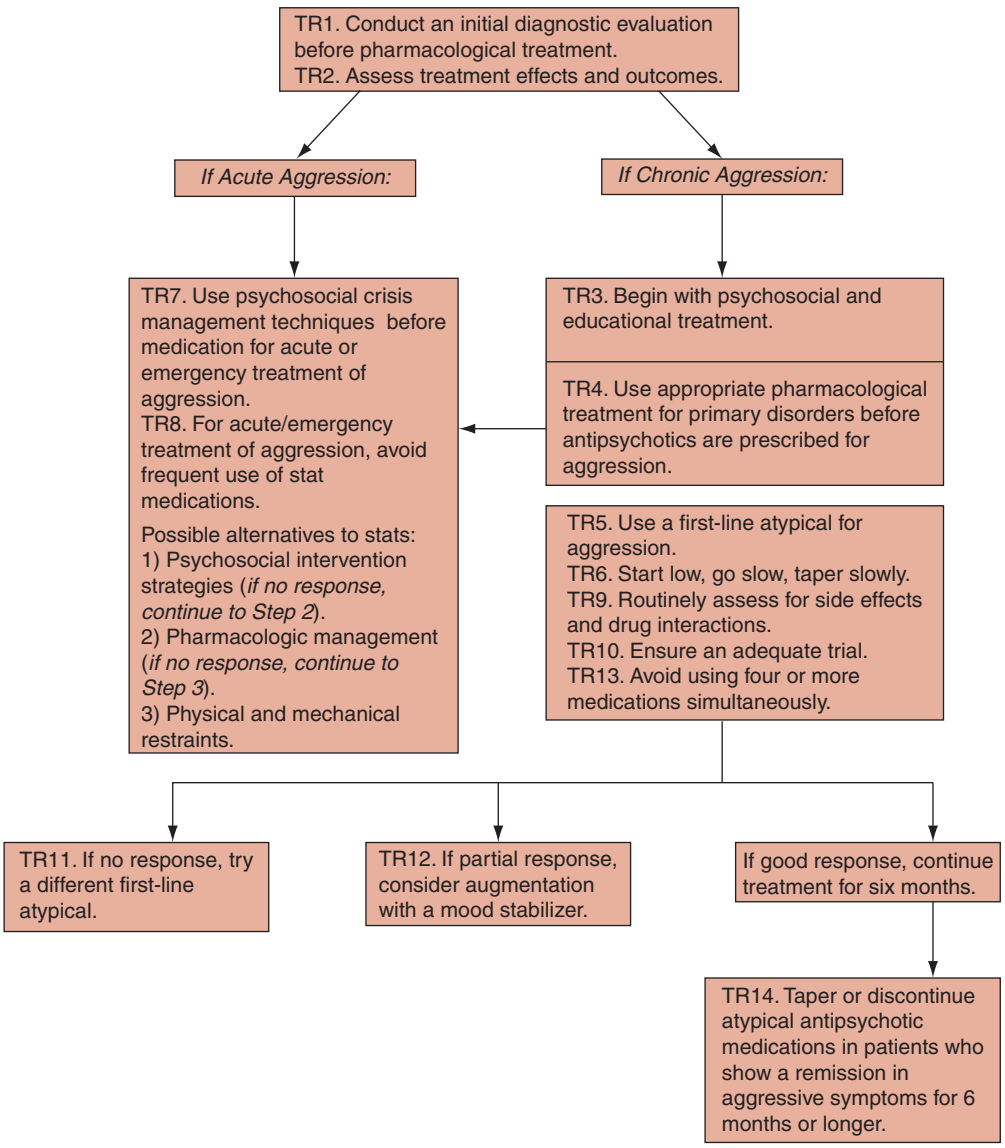



**Figure 46–2** *TRAAY recommendations for treatment of aggression in youth. (*Source: *Pappadopulos (2003) Journal of the American Academy of Child and Adolescent Psychiatry 42(2), 145–161.)*

the optimal medication and dose have been determined. Various treatment guidelines or practice parameters have been developed to reinforce the use of evidence-based treatments, and to help guide treatment selection in various contexts. This is important because it is often difficult to translate findings from results in pristine clinical trials, conducted in carefully selected patients, to the complex and diagnostically heterogeneous patients more often encountered in real-world settings. These guidelines are generally derived from a composite of published research and expert opinion, and offer a clinical standard of care that practitioners can use to inform treatment selection and sequencing of treatments – often in the absence of a suitable evidence-base for several of the specific treatments. Guidelines for the treatment of ADHD include those from the American Academy of Pediatrics (2001) and the American Academy of Child and Adolescent Psychiatry (Piszka et al. 2007). Recommendations based on expert opinion have also been developed for ADHD (i.e., the Texas Medication Algorithm project (Piszka et al. 2006) (see Figure 46–1)) and aggression in youth (i.e., treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY) (Schur et al. 2003, Pappadopulos et al. 2003)). Treatment algorithms for ADHD reflect the multitude of approved and nonapproved treatments, and the many different clinical presentations which may affect how these treatments are used—including the frequent occurrence of comorbidity. The most recent Texas Medication Algorithm project revisions included elimination of pemoline as a treatment option, based on severe liver toxicity, addition of atomoxetine to the algorithm, and refining guidelines for treating ADHD with comorbid depression, aggressive behaviors, and tic disorders (see Figure 46–1). The TRAAY recommendations (see Figure 46–2) primarily focus on the use of atypical antipsychotics, but also describe the various psychosocial and medication treatments and propose how they can be used sequentially.

In summary, treatment algorithms provide sensible common starting points for treatment selection, and offer decision-trees that are flexible enough to be modified for the individual patient. However, they should be viewed as general guidelines for care rather than absolute rules. Further, frequent updates are required to reflect the rapidly changing evidence-base in the field.

## Conclusions

The AD-DBDs are a group of disorders that represent a significant public health problem in terms of morbidity and cost to society, and carry substantial risk for poor outcome. Together they account for the majority of referrals to child and adolescent psychiatry services. In recent years, there has been an increasing recognition that symptoms of AD-DBDs often begin early in life and persist into adulthood. There has been considerable progress in elucidating the genetic and neurobiological bases of these disorders. A plethora of new medication treatments for ADHD have become available over the past decade, revolutionizing the way care is delivered. These and other medications have also been used effectively in treating ODD and CD. However, clinical treatment and research is complicated by the high prevalence of comorbidity, which has an important role in moderating clinical presentation, response to treatment and longitudinal course. A variety of pharmacological and psychosocial interventions have been found to be effective when administered alone or in combination over the short term. However, demonstrating long-term benefits of treatment continues to be a challenge.

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CHAPTER 47

# Childhood Disorders: Feeding and Related Disorders of Infancy or Early Childhood

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Feeding Disorder of Infancy or Early Childhood
Rumination Disorder
Pica

## Introduction

Feeding is an essential yet highly complex behavior. It requires the successful integration of a number of different aspects of development and function, which in turn are related to different bodily systems. In addition, infant feeding is dependent on a nurturing relationship with a caregiver. When one or more of the prerequisites for successful feeding (e.g., gut motility, swallow reflex, and appetite) are delayed, dysfunctional, disturbed or absent, significant problems may ensue. Gastrointestinal disorder, attachment problems in the relationship between mother and child, and structural abnormalities of the mouth or tongue can lead separately or together to the final common pathway of problems in feeding. Feeding disorders therefore straddle different professional boundaries and benefit from an integrated multidisciplinary approach to assessment and treatment (Rommel et al. 2003).

In view of the complexity of feeding behavior, and need for co-coordinated, integrated multiple system functioning, it is perhaps unsurprising that feeding problems are relatively common in infants and young children. Feeding problems can occur in children having normal development, those having developmental disability or disorder, and those suffering from a whole range of medical conditions. Such children can present to the clinician with one or more of different types of difficulty, the most common of which are summarized in Table 47–1. Some feeding problems may be relatively short lived and can be regarded as part of a

**Table 47–1** Common Presenting Features of Feeding Disorders in Infants and Young Children Seen by Behavioral Specialists

- **Delayed or absent development of feeding skills** (related to history of mechanical or structural difficulties in being able to feed—problems in latching, sucking, chewing, and swallowing—and/or early enteral feeding in context of medical conditions)
- **Difficulty managing or tolerating ingested fluids or foodstuffs** (e.g., problems with gagging, retching, choking, and vomiting)
- **Reluctance or refusal to eat certain tastes and textures** (e.g., fear of lumpy foods and avoidance of introducing novel foods)
- **Lack of appetite or interest in food** (e.g, in the context of neglect and psychosocial failure to thrive)
- **Utilizing feeding behaviors to comfort, self-soothe, or self-stimulate** (e.g., regurgitating, chewing, and ingesting nonfoodstuffs)

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normal developmental trajectory, appropriately managed by information, advice, and reassurance. Others may be a direct result of oral motor dysfunction, gastrointestinal, or other medical conditions, and require investigation and first-line management by speech and language specialists or by pediatric physicians or surgeons. The remainder may be best understood as—or in the context of—behavioral, emotional, and relationship disturbances that are manifest as an inability, or unwillingness, to feed or eat normally, and it is this latter group that forms the focus of this chapter. A significant number of young children presenting with feeding disorders will have had early histories of problematic feeding, requiring medical intervention, but the condition is considered to have resolved sufficiently to allow normal feeding to place. While feeding disorders may come to the attention of a wide range of professionals, and may be appropriately treated and managed by representatives of other disciplines, the material included in this chapter has been selected with the specific intention of informing and guiding mental health professionals.

It may be helpful at this stage to refer briefly to the use of some key terms, in particular to the common distinction made between "feeding" and "eating." Feeding generally denotes something that happens in the context of a relationship, whereas eating generally denotes an action of an individual. Feeding refers to what happens in the two-way relationship between the child and the carer, and in this sense it may be considered a relational process. Problem feeding can then be understood and managed in this context, which means that attention and input need to be provided to both the child and the caregiver. The term "eating" tends to be used in older children and individuals who self-feed and are more likely to make their own choices about dietary intake.

Davies et al. have called for a reconceptualization of feeding and feeding disorders within such an interpersonal context, pointing out that current diagnostic criteria (see below) are focused on the child as an individual (Davies et al. 2006). They suggest that this is illogical given the dyadic nature of the feeding relationship and have suggested revised criteria for a diagnosis of "feeding disorder between parent and child." It could be argued that such a move might enhance the clinical utility of the diagnosis (Kendall and Jablensky 2003), in at least two important ways: through assisting clinicians in choosing effective interventions and in predicting future clinical management needs (see further First et al., 2004, for discussion of choosing clinical utility as a criterion for diagnostic revision).

This chapter is concerned with feeding and related problems in infants and young children that meet a number of conditions:

1. They are not fully accounted for at the time of presentation by an underlying medical problem, although such a problem may have contributed to the development of the feeding disorder.
2. They are clinically significant in terms of having an adverse effect on one or more areas of development (typically growth, but other areas such as social development may also be affected).

The three formally diagnosable disorders described in this chapter in detail are feeding disorder of infancy or early childhood, rumination disorder, and pica (American Psychiatric Association 2000).

**DSM-IV-TR Criteria**

**Feeding Disorder of Infancy or Early Childhood**

A. Feeding disturbance as manifested by persistent failure to eat adequately with significant failure to gain weight or significant loss of weight over at least 1 month.
B. The disturbance is not due to an associated gastrointestinal or other general medical condition (e.g., esophageal reflux).
C. The disturbance is not better accounted for by another mental disorder (e.g. rumination disorder) or by lack of available food.
D. The onset is before age 6 years.

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## Feeding Disorder of Infancy or Early Childhood

### Diagnosis

#### Definition and Diagnostic Features

The main presenting feature of Feeding Disorder of Infancy or Early Childhood (307.59) is weight loss or failure to gain weight due to feeding disturbance. The current diagnostic criteria are not specific about the extent or severity of the weight loss or failure to gain weight, or about the origin or nature of the feeding disturbance. However, they are explicit that at the time of diagnosis it must not be directly due to a medical condition or more clearly accounted for by another mental disorder. Also, the criteria are explicit that the feeding problem must not be due to lack of food and that the weight loss or failure to gain weight must be at least of 1-month duration.

It should be noted that many children presenting to clinics because of problem feeding will not fulfill diagnostic criteria for feeding disorder despite significant, persistent feeding disturbance. For example, children who have become "stuck" on enteral feeding, despite there being no longer any medical reason for this, or children who eat only pureed foods, despite having no oropharyngeal difficulties, will tend not to meet the weight criterion. Such children have clear emotional and behavioral aspects to their presentation, and yet do not clearly fit any available diagnostic category. Keen diagnosticians can sometimes tuck them away in "not otherwise specified," "other," or "unspecified" categories of other disorders, for example, anxiety disorders, but this seems far from satisfactory. In addition, the term, "feeding disorder" when correctly applied includes children with a wide range of different features associated with the required failure to eat adequately and failure to gain weight or significant weight loss. Because of the many associated characteristics, there have been several attempts to find ways to subclassify feeding disorders to satisfactorily take account of the many different ways in which these children

present. Different researchers and authors have adopted different conceptual frameworks and approached subgrouping from different perspectives. This has resulted in inconsistent and idiosyncratic use of terminology with, as a consequence, limited scope for co-ordinated clinical and research endeavor. This remains a major challenge for the field. Some examples of attempts at subgrouping feeding disorders are set out below:

## Organic versus Nonorganic Origin

Dividing feeding disorders into those with organic and nonorganic origin has been popular in the past, with many authors distinguishing between types of presentation on this basis (e.g., Weir 1979). Chatoor et al. have proposed criteria for subgroups of types of feeding disorders amongst children presenting with nonorganic failure to thrive, including "infantile anorexia" and "feeding disorder of mother–infant reciprocity" (previously called feeding disorder of attachment) (Chatoor et al. 1997). Making a distinction between organic and nonorganic presentations assumes that feeding disorders are *either* related to structural or functional abnormalities related to the mouth and gastrointestinal system *or* are triggered by social and environmental factors. This has been criticized because it is relatively rare to find a single cause to explain feeding disorders in children; it is most often the case that the feeding disorder appears to result from the combination and interaction of physical and psychosocial factors. In addition, the term "nonorganic" often seems to be made without rigorous assessment that might exclude any organic component. For example, Reilly et al. 1999 found that of 47 children with nonorganic failure to thrive, 36% had oral motor dysfunction; these authors concluded that the use of the term "nonorganic" in such children is questionable, and along with others have called for a redefinition (Ramsay et al. 1993).

## Biopsychosocial Approaches

Because of difficulty with a dichotomous system, a number of authors have distinguished feeding disorders based on three or more groups of contributing factors.

The three areas most commonly documented as having an etiological contribution in children with feeding problems are structural or oral problems (e.g., oropharyngeal functional abnormality), medical problems (e.g., gastroesphogeal reflux), and psychosocial or behavioral problems (e.g., aversion of lumps and relationship problems). For example, in one study of 700 children under the age of 10 with feeding disorders, 86% had an underlying medical disorder, 61% had some oropharyngeal dysfunction, and 18% had a behavioral problem (Rommel et al. 2003). These conditions occurred alone or in combination, which highlights the difficulty in assigning feeding difficulties to specific categories.

In response to the fact that categories appear not to be mutually exclusive and fail to adequately capture children with feeding disorders of mixed etiology, Burklow et al. (1998) identified five categories of feeding disorders, reflecting the types of referrals received by their multidisciplinary feeding team. They report satisfactory interrater reliability for this categorization (88%):

1. *structural abnormalities*—anatomic abnormalities associated with the physical structures required for eating;
2. *neurological conditions*—brain injury, learning disabilities, musculoskeletal disorders, and autistic spectrum disorders (ASD);
3. *behavioral and psychosocial*—poor environmental stimulation, dysfunctional child—caregiver interaction, negative feeding behaviors shaped by reinforcement and/or emotionally based difficulties;
4. *cardiorespiratory problems*—compromised cardiovascular and respiratory systems, complication coordination of sucking, swallowing, and breathing; and
5. *metabolic dysfunction*—metabolic diseases and syndromes that interfere with normal feeding patterns.

These authors categorized a series of 103 children referred because of concerns about poor oral intake and difficulties sustaining growth. Using the above categorization they reported the following as most frequently coded combinations: structural–neurological–behavioral (30%), neurological–behavioral (27%), behavioral (12%), structural–behavioral (9%), and structural–neurological (8%). Of interest is the reported 85% in whom behavioral issues were coded, compared to neurological conditions in 73% and structural abnormalities in 57%. A source of puzzlement is the lack of a category to cover gastroenterological conditions. Nevertheless, this study very clearly demonstrates that the majority of children with feeding disorders have a behavioral component to their presentation and that in the majority of patients, biological and behavioral components interact. The authors conclude that feeding problems are best conceptualized as biobehavioral conditions (Burklow et al. 1998).

## Subgrouping Based on Presenting Characteristics of the Feeding Problem

Crist and Napier-Phillips (2001) provide an example of an attempt to subdivide on the basis of presenting behavioral features. They used a measure of feeding behavior devised by their group (the Behavioral Pediatrics Feeding Assessment Scale — see later section on assessment) in a clinical series of 249 children with feeding problems with and without related medical issues, and in 96 control children. They subsequently conducted a factor analysis of data obtained and identified five common patterns of problematic feeding behavior: picky eating, general toddler refusal, toddler refusal of textured foods, general refusal in older children and stalling. Interestingly, they found that the difference between the clinical and the control groups appeared to lie in parental report of the frequency with which the child engages in the problematic behavior, rather than differences in the nature of the behaviors exhibited.

## Subgrouping Based on Presence or Absence of Mental or Developmental Disability

Some authors make a distinction between children with feeding disorder who are on the autistic spectrum or have significant learning disability and those who do not. Often the presenting features of the feeding problem can be the same (e.g., unwillingness to take solids, or a very narrow range of accepted foods) but the treatment approach may differ considerably. However, as with feeding disorders in children with no developmental disability or disorder, there can be a significant medical component to the presentation. Schwartz et al. 2001 report the results of diagnostic

Clinical Vignette 1

**Food Selectivity in a 6-Year-Old Boy with Childhood Autism**

Chris is a 6-year-old boy who was diagnosed with childhood autism at the age of 4. His local pediatrician referred him to a feeding clinic because of his very restricted diet. Chris was breast-fed for 6 weeks and moved onto bottle feeding with no problems. He was introduced to purees at 5 months and this went well. When parents attempted to introduce more lumpy foods Chris would vomit. His progress with feeding was delayed and he progressed to mashed food at age 3. At age 4, rusks (in the UK, rusks are biscuits given to infants, sometimes soaked in milk and mashed up) were introduced, but by age 5 his range of foods narrowed and he would only accept pureed fruits, oatmeal cereal, and cow's milk. Chris's parents then reintroduced an infant formula feed, as they were concerned about the nutritional inadequacy of his diet. He would only accept milk from a bottle with a nipple.

At presentation, Chris was accepting only toast, yogurts, crispbread, a particular type of savory snack, and infant formula from a bottle. His diet was more than sufficient in terms of calories, and he presented as slightly overweight; however, it was lacking in a number of essential vitamins and minerals. His presentation was typical of a selective eater on the autistic spectrum in that he chose to eat foods from a limited range of food groups (mainly, carbohydrate and dairy). His chosen foods were also similar in color and were from a narrow range or textures (crunchy or soft). He was also selective in terms of utensils, in that he would not take his formula feed from a cup or glass, although he would take water in this way.

Chris was also observed to exhibit ritualistic behavior around food, where he would require his caregiver at home or at school to touch each item of food before he would eat it. It seemed likely that Chris's autism was contributing to a rigidity and fear of novelty, making it difficult to introduce new foods into his diet.

There were many components to Chris's treatment. Initially, his nutritional needs were addressed by slowly fading out the infant formula feed and introducing a fortified milk shake. As he was overweight, Chris's appetite was manipulated by restricting his access to his preferred food very gradually while carefully monitoring his weight. Chris was then slowly introduced to new food of a similar texture over a number of sessions, beginning with having food on the plate, progressing through to touching, licking, and tasting. Work was done with Chris's family to ensure continuity at home and to manage parental anxiety.

evaluation in 79 children with moderate-to-severe developmental disability and report that 56% demonstrated gastroesphogeal reflux, and 27% had oropharyngeal dysphagia.

Feeding difficulties in children with autistic spectrum disorder (ASD) most commonly focus on selectivity by texture, taste, brand, presentation, or appearance, which may or may not result in failure to gain weight or weight loss. Technically without this, as mentioned earlier, such children do not fulfill existing diagnostic criteria for feeding disorder, despite presenting with significant feeding problems (see Vignette 1). Although a number of children with ASD will not fulfill formal diagnostic criteria for feeding disorder, they do commonly present to behavioral feeding clinics. Other problematic aspects at presentation in children with ASD include food refusal, failure to eat the usual family diet, inappropriate rate of eating, obsessive eating patterns, failure to accept novel foods, and inappropriate mealtime routines. These features at presentation may be a result of the attention to detail, perseveration, fear of novelty, sensory impairments, and biological food intolerances, which are all common in children with ASD. However, Schreck and Williams (2006) have challenged this view with the results of an informant-based questionnaire study, which surveyed parents of 138 children with ASD. Their findings revealed that the children were selective in the foods they accepted, but that this seemed to be more related to the family's reported eating preferences than features of ASD per se. They conclude that their study found no evidence to support the commonly held view that typical features of autism, such as difficulty changing routines or sensory processing problems (e.g., difficulties with textures), are related to selectivity in feeding in this group.

The selective eating typically found in children with ASD can also be identified in children without diagnosed developmental disorder. Such children refuse to eat outside of a narrow range of preferred foods, and their feeding disturbance appears to be a highly circumscribed problem in a child who is otherwise developing and functioning within a normal range. These children often prefer carbohydrate-based food of bland flavors and colors and have a tendency to be more risk averse than may of their peers (see further Bryant-Waugh and Lask 2007, Nicholls et al. 2001). For a clinical example of food selectivity in the context of ASD, see Vignette 1.

## Assessment

In the remainder of this section, discussion is not limited to feeding disorder, but includes the range of presentations of feeding problems seen in behavioral feeding clinic settings.

It is evident that comprehensive assessment is required in order to determine which of a range of potential factors may be relevant to the development and maintenance of a feeding problem in any one child. Effective feeding depends on the presence of required physical, social, and environmental factors. Assessment therefore needs to cover all these areas, to identify where difficulties might have existed or still exist that contribute to the feeding disorder. Table 47–2 gives the main areas usefully included in a comprehensive assessment. The specific nature and extent of the underlying features ascertained through assessment will help to guide treatment.

There does not appear to have been much focus on the development of standardized, validated assessment measures of feeding problems. Typically, centers seem to have developed their own assessment questionnaires (e.g., Douglas and Harris 2001, Harris and Booth 2006). One exception to this is Crist et al.'s Behavioral Pediatrics Feeding Assessment Scale (Crist et al. 1994, Crist and Napier-Phillips 2001). This is a 35-item questionnaire, which measures parent and child behaviors in the context of feeding problems in children aged 9 months to 7 years. Use of the scale generates four scores: child's behavior—frequency, child's behavior—problems, parents' feelings/strategies—frequency, and parents' feelings/strategies—problems. Psychometric properties for this scale are acceptable, with alphas for internal consistency for the behavioral items and the overall measure reported as 0.74–0.88 and test–retest coefficients between 0.82 and 0.85 (Crist et al. 1994). This measure has been used

| Table 47–2 | Main Components of Comprehensive Assessment of Feeding Disorder |
|---|---|
| **Physical** | Growth and development—observation and caregiver report |
| | Nutritional status—dietary analysis of current intake |
| | Oral motor/swallow problems |
| | Gastroenterological problems |
| | Food allergies |
| | Other chronic illness |
| | Medical history |
| | Feeding history—breast- or bottle-fed, weaning attempts |
| | Parent's feeding pattern and stature in childhood |
| **Psychological** | Child's general behavior |
| | Child's attitude to messy play/eating |
| | Signs of oral aversion (e.g., refusal to brush teeth) |
| | History of forced feeding |
| **Social** | Interaction between child and caregiver—observe mealtime |
| | Caregiver support network |
| | Family relationship with health care system |
| | Structure of family mealtime |
| | Family's attitude to mealtimes |
| **Environmental** | Caregiver mental health, Caregiver relationship with food |
| | Family life events |
| | School's input around feeding |
| | Previously tried strategies |
| | Feeding problems in siblings |
| | Caregiver conception of problem (e.g., medical/psychological) |
| | Caregiver aims |

by other authors (e.g., Burklow et al. 2002) and represents a useful tool for clinicians and researchers in this field.

Most clinicians regard direct observation of feeding behavior and interaction as an essential component of assessment (e.g., Babbitt et al. 1994, Chatoor et al. 2001). Observation of the feeding behavior allows visual assessment to be made of oral motor function, including chewing and swallowing ability, as well as assessment of sensory function and sensitivities. Direct observation typically involves the feeding dyad, that is, the caregiver and the child. However, Fosson and Wilson (1987) suggest that whole-family assessment is preferable. They report on the observational assessment of 34 families, with an infant diagnosed as having nonorganic failure to thrive. This study revealed that interactional factors often assumed to be contributing to the feeding problem, such as failure of the mother to respond appropriately to the infant's cues, and apparent poor emotional attachment were observed in only 26% of the cases. They identified many other family interactional problems that appeared to be relevant to the feeding process, including sibling rivalry, displaced maternal anger, the mother being undermined, and chaotic family interactions. They conclude that observational assessment of early childhood feeding problems should include family assessment of functioning at mealtimes (Fosson and Wilson 1987).

The process of comprehensive assessment as outlined in Table 47–2 might highlight the need for further investigation before treatment can safely be commenced. For example, in a child with a history of chest infections, presenting with gagging and a refusal to swallow, a videofluoroscopy may be indicated. Such an investigation assesses oropharyngeal function and motility and can provide essential information for the treating team about whether it is safe to proceed with the promotion and encouragement of oral feeding.

In view of the diagnostic requirement for feeding disorder that there should be failure to gain weight or there should be an actual weight loss, a number of children may not get adequate access to assessment of clinically significant feeding problems. For example, children who are very selective about the range of foods they will eat may not exhibit weight or growth problems, as their overall energy intake may be satisfactory. Such children might then not be considered a priority for assessment and treatment despite often extremely poor nutritional status and behavior that represents a significant challenge to caregivers.

## Epidemiology

The overall estimates for prevalence of feeding disorder and feeding difficulties in children are very difficult to ascertain with any reliability. Researchers have tended to use different definitions, to have focused on specific subcategories of feeding disorders, or to have focused on children with particular disorders or syndromes. The prevalence rate of feeding disorders in the general pediatric population is reported as being about 25% (Babbitt et al. 1994), and although this general figure of one in four children in pediatric populations seems to be widely quoted, it is difficult to be entirely confident that this is accurate given the variability in use of the term feeding disorder. Rates are reported to be higher in children with developmental disability, with rates ranging up to 80% (Manikam and Perman 2000). Feeding difficulties, though not necessarily formal feeding disorder, are particularly common in children with pervasive developmental disorders. On reviewing the literature specifically in relation to children with ASD, Ledford and Gast (2006) report that up to 89% of children with ASD have problem feeding behaviors. Feeding problems are also common in children with neurological impairment (such as cerebral palsy, sensorineural deafness, and severe vision loss), with one study of 271 such children reporting 89% needing help with feeding, 56% experiencing choking episodes, 28% having feeding times of over 3 hours, and 20% having parents finding mealtimes to be stressful and not enjoyable (Sullivan et al. 2000). Other groups identified as particularly at risk include infants of premature birth, children with craniofacial anomalies, and those with certain genetic syndromes (such as Russell–Silver syndrome) (Lifschitz 2001). These studies combined suggest that problematic feeding behavior, which reaches clinical significance, is relatively common in a number of groups of children. This needs to be distinguished from any statements about rates of feeding disorder, as children with this diagnosis represent only a subset of children seen in feeding clinics.

## Comorbidity

Levels of comorbidity differ across the varying presentations of feeding problems. Timimi et al. report that in a cohort of 20 children presenting between 4 and 7 years of age with

extremely selective eating behaviors (95% of whom had onset of feeding difficulties before the age of 18 months), 30% had obsessions and compulsions and 40% had social and school attendance difficulties (Timimi et al. 1997). As previously mentioned, Axis II developmental disorders and Axis III physical conditions are common concomitants of an Axis I Feeding Disorder.

## Course

Surprisingly little is known about the course and prognosis of feeding disorders in infancy and early childhood, and much useful work remains to be done in this area.

In a follow-up study of 24 children with early (aged between 3 and 12 months) refusal to eat with no apparent medical cause, compared to controls, children with early refusal to eat seemed to have an equally good general prognosis with respect to health, growth, and development at 4 years (Dahl and Sundelin 1992). However, although weight and height were within the normal range, less variability in weight and height was noted compared to controls. In addition, children with early refusal to eat were at increased risk of problems with their eating patterns and behavior, with 71% reported by their parents as still having minor feeding problems and 42% reported as being hyperactive (Dahl and Sundelin 1992).

An important and much quoted longitudinal study by Marchi and Cohen (1990) demonstrated an association between specific aspects of problematic infant feeding behavior (inadequate intake, choosiness, slow feeding, and lack of interest in food—all based on maternal report) and later development of symptoms of anorexia nervosa in adolescence. This research suggests that selectivity in early and middle childhood is predictive of elevated levels of symptoms of anorexia nervosa, but not bulimia nervosa in adolescence (Marchi and Cohen 1990).

In terms of the long-term implications of early feeding problems, the occurrence of disease in adults (including cardiovascular and respiratory disease) has been observed to be associated with low birth weight and with weight at 1 year (Barker 1994). One explanation is that nutritional deficiencies at critical points of development can lead to irreversible changes in physiological functioning (Barker et al. 1993), which highlights the long-term importance of maintaining adequate nutrition in childhood.

## Differential Diagnosis

A diagnosis of feeding disorder of infancy or early childhood should be made only where there is significant weight loss or failure to gain weight. Where other medical conditions are directly and fully responsible for feeding impairment or weight loss, feeding disorder should not be diagnosed. Such conditions might include gastrointestinal, endocrine, or neurological conditions. However, as stated above, there is often an overlap between presenting features, with feeding disorder becoming appropriate as a diagnosis in situations where the level of disturbance is significantly greater than might be seen in other children with similar medical conditions or greater than predicted on the basis of the medical condition alone.

Because feeding disorders may be conceptualized as interactional disorders, a consideration of differential diagnoses must also include maternal or primary caregiver issues. For example, O'Brien et al. (2004) found relatively high rates of depression in mothers of infants presenting with poor weight gain. In some cases, treatment of the mother's condition can result in improvement in the infant's weight.

## Etiology and Pathophysiology

Feeding disorders are generally regarded in most cases as multidetermined disorders. Conditions and factors implicated in etiology usually fall under three main headings: structural or oral, medical, behavioral, or psychosocial. Sometimes the treatment for an underlying medical condition can in itself contribute to the development or maintenance of a feeding problem. For example, a frequent complication of early tube feeding is that children go on to exhibit a resistance to oral feeding. This may stem from aversive experiences around the mouth, nose, and esophagus, such as intubation, which means that the child associates stimulation of this area with the previous traumatic experiences they have had (Benoit and Coolbear 1998) and hence will avoid it where possible. Children with early histories of inability to adequately feed orally, and who required tube feeding as neonates, represent a significant proportion of those presenting with feeding disorders and difficulties to specialist services.

Rommel et al. (2003) found a significant correlation between prematurity and feeding problems, which has been used to support the hypothesis that the origin of feeding disorders is more likely to be neurophysiologic than experiential or environmental (Ramsay et al. 1993). However, it is important to note that these premature babies are also likely to experience adverse experiences, such as ventilation and intubation, and can also spend time in incubators, which may lead to disrupted early attachments, which may in turn contribute to feeding problems (see Vignette 2 for an example of oral food aversion in a 5-year-old born prematurely).

There is a body of existing research examining whether and to what extent feeding disorders in children are related to parental characteristics and interactional processes between caregiver and child. Stein et al. (1995) compared 30 mothers of children with a feeding disorder with mothers of children with a behavioral disorder and with a community sample of mothers. Significantly higher rates of disturbed eating habits and attitudes were found in the mothers of children with feeding disorders, compared to the other groups. Such research is of interest in highlighting intergenerational aspects of feeding and eating problems, but it is not clear from this type of study whether the link between childhood feeding problems and maternal eating disturbance is primarily due to genetics or social learning.

Whelan and Cooper (2000) sought to confirm this link between childhood feeding problems and maternal eating disorder in a community study, which included filming family meals to achieve objective ratings of feeding problems. They found that mothers of children with feeding problems had markedly raised rates of past and current DSM-IV-TR eating disorder diagnoses, thus leading them to conclude that there is a strong and specific link between the two. This work was later extended to attempt to investigate mechanisms responsible for the relationship between reported feeding problems in childhood and eating disturbance in mothers in a further observational study (Cooper et al. 2004). They discovered two environmental variables—"mealtime disorganization" and "maternal strong control and disharmony"—as mediating the association between child and maternal disturbance.

Clinical Vignette 2

**Case of Oral Food Aversion in a 5-Year-Old Boy Who Was Born Prematurely with Considerable Medical Problems**

Andrew was born at 25 weeks weighing 650 grams at birth with a tracheoesophageal fistula. He was ventilated at birth. After his fistula repair Andrew was still unable to eat due to collapsed lungs. He remained in hospital for 6 months.

Andrew was bottle fed for about 1 week and was then fed by gastrostomy tube. His parents attempted forced feeding at 1 year and he began to show such strong oral aversion that he could not be kissed without gagging and retching.

Andrew had 19 dilatations of the esophagus before he was 3, where his very restricted esophagus would be manually stretched. Due to constant vomiting Andrew had a Nissens fundoplication at 1 year and remained on oxygen until he was 18 months. Andrew's parents separated when he was 3.

Over the years Andrew has agreed to try small amounts of various foods; however, he will not swallow food and continues to require gastrostomy feeding, despite the fact that there is no longer any medical reason why Andrew cannot eat.

It is likely that the reasons for Andrew's feeding difficulties are multifactorial. He had a number of very aversive invasive procedures around the mouth and esophagus, including ventilation and dilatations of the esophagus. He could not be fed orally at birth because of his fistula, which did not allow him to develop feeding skills in the normal way. Andrew's parents' separation may have introduced secondary gains for not eating, as they would unite to attend hospital appointments regarding his feeding.

Andrew's long-term gastrostomy feeding means he did not get the opportunity to develop skills required for eating and he may have immature oral motor skills and a lack of pleasure in eating. He may also have no understanding of hunger, as all his nutritional requirements are met by the tube feeding. A period of forced feeding is likely to have compounded his oral food aversion.

Andrew's treatment consisted of 12 fortnightly sessions lasting half a day and had many components, utilizing a multidisciplinary team. Because Andrew was very ill as a baby, his parents found it difficult to set firm boundaries. His parents were seen individually by a family therapist to work through these feelings and to educate them about strategies to improve Andrew's feeding, such as graded exposure and basic behavioral principles. They were also supported by the therapist and the dietician to slowly reduce the volume of tube feeding to increase Andrew's appetite. Some targeted work was done with Andrew around messy play and cooking by the team play specialist, to desensitize him to the touch and smell of food. He was rewarded using stickers and he learned to get pleasure out of food. Andrew and his family took part in group lunch sessions with his therapist, who modeled positive interactions around feeding. As Andrew had never been weaned, he was initially introduced to stage 1 purees, as his feeding skills were not consistent with his chronological age. Occasionally, his speech and language therapist attended to monitor his oromotor skills and his swallow. There were firm expectations for Andrew to take gradual steps toward oral feeding. He was rewarded for his progress with praise and stickers.

Such studies have important implications for assessment and treatment of feeding disorders, underlining the importance of attending to contextual and environmental factors.

In another observational study of mother–child feeding interactions, Ammaniti et al. demonstrated an association between specific maternal characteristics (dysfunctional eating attitudes, anxiety, depression, and hostility), specific characteristics of the child (anxiety/depression, somatic complains, and aggressive behavior), and dysfunctional interaction during feeding (Ammaniti et al. 2004). These authors conclude that their research supports the importance of assessing features specific to the child, features specific to the primary caregiver(s), and features of interaction around feeding to enable effective, targeted interventions.

Chatoor et al. have conducted many studies over a number of years aimed at better understanding the association between reciprocal relationship issues and feeding disorders (e.g., Chatoor et al. 1988). While it is acknowledged that feeding problems can and do arise in infants and young children with secure attachment relationships with caregivers, Chatoor et al. have proposed that insecure attachment relationships may intensify feeding problems and report an association between severity of attachment insecurity and severity of feeding disorder (Chatoor et al. 1998). An interesting study investigating touch patterns found that children aged 9–34 months with feeding disorders received less maternal affectionate and unintentional touch than the study controls (Feldman et al. 2004). The children with feeding disorders also displayed less affectionate touch, more negative touch, and were more rejecting of the mother's touch. These authors conclude that proximity and touch between the caregiver and the child are disturbed in feeding disorders, suggesting fundamental problems in the relationship. Lucarelli et al. (2003) compared mother–child interaction in children whose feeding disorder had an underlying organic cause, to those in whom there was no underlying medical condition, and found higher rates of dysfunctional interactions in both groups compared to controls. Such research raises the important question of whether it is the feeding disorder that contributes to the dysfunctional interaction or the interaction problems that maintain the feeding disorder.

There are relatively few studies investigating the role of fathers in young children's problematic feeding and eating behaviors. One Finnish study aimed to investigate whether problem feeding behaviors at the age of 13 months and 5 years were associated with parental eating habits and attitudes, in a sample that included 375 fathers (Saarilehto et al. 2001). The authors found that the fathers' difficulty in maintaining an ideal weight significantly predicted the persistence of problems at 5 years. They interpret their findings as suggesting that eating attitudes and behaviors of both parents are reflected in the feeding and eating behavior of young children. However, a recent review has concluded that there is as yet no consensus regarding the nature of the relationships between parent and child disturbance in relation to feeding and eating and that the mechanisms for intergenerational mechanisms remain to be firmly established (Coulthard et al. 2004).

## Treatment

In practice most infants and young children with feeding disorders will be treated in a multidisciplinary team context,

which because of the complexity and multifaceted nature of these disorders is generally considered to contribute to better patient care. Multidisciplinary involvement in treatment is also considered essential, given the fact that the majority of feeding problems stem from an underlying medical and/or oral problem (Rommel et al. 2003). The mental health practitioner must therefore be aware of the role of other disciplines in treatment in this area, and in practice, many young children with feeding problems will receive collaborative input from a number of specialties.

## Treatment Goals

The main aim of interventions designed for children with feeding disorders is to facilitate the establishment of nutritionally adequate oral feeding that is experienced positively. The detailed background to any one child's feeding difficulties is likely to vary from that of another, as are the specific features at presentation. Treatment therefore ideally needs to be individualized to the child's cognitive, psychological, and physical needs and context. A multicomponent approach to treatment including interventions targeted to the child, to the caregiver, to the interaction between the child and the caregiver(s), and to the broader environment is usually recommended (e.g., Davies et al. 2006). Table 47–3 summarizes the main treatment interventions offered to children with feeding disorders.

**Table 47–3 Treatment Approaches in Feeding Disorders**

**Improve Nutritional Status**

*Promote weight gain*
*Address nutritional deficits*
*Consider appropriateness of feed*

**Behavioral Approaches**

***Escape extinction:*** *removing reinforcer to a response in order to decrease occurrence of response, for example, withdrawal of food after refusal reinforces refusal of food*

***Differential reinforcement:*** *positive reinforcement of desired behavior coupled with removal of reinforcement for undesired behavior, for example, ignoring food refusal and praising food acceptance*

***Premack principle:*** *requiring a nonpreferred activity to be completed before allowing a preferred activity to take place, for example, taking a nonpreferred food before being given a preferred food*

***Behavioral momentum:*** *the principle that a low probability command will be more readily followed when proceeded by a high probability command, for example, giving a preferred food before a nonpreferred food*

**Liaise with Wider Service Systems and Schools**

*Ensure that there is a consistent approach*

**Facilitate Oral Intake**

*Desensitization*
*Anxiety reduction*
*Skill acquisition exercises*
*Open window of appetite*
*Texture manipulation*

**Educate and Support Caregiver**

*Address caregiver–child interaction*
*Increase understanding of behavioral principals*
*Promote routine around feeding*
*Manage anxiety*
*Address unresolved psychological issues affecting feeding*

At present, treatment research in this area remains lacking, resulting in the evidence base for treatment of feeding disorders deriving mostly from clinical case series and expert consensus. There is a significant case report literature on therapeutic interventions on infants and children with feeding disorders, which have focused on stimulating the hunger–satiety cycle, reinstating hunger cues and feeding reflexes, improving oral motor skills, and improving caregiver's attitudes, emotional state, and family functioning with varied outcomes. For a comprehensive account of treatment interventions for infants with feeding problems, see Wolke et al. (2006). For a useful, detailed description of the process of weaning children off gastrostomy tubes onto oral intake within a behavioral feeding program, see Byars et al. 2003.

The development of empirically validated treatment protocols specific to identified patterns of presentations could enhance the effectiveness of treatment of feeding disorders and is much needed. However, it could be argued that because the development and maintenance of feeding problems is so specific to any one individual, effective standardized treatment protocols will be difficult to achieve expect for highly circumscribed subgroups of children. Some authors have suggested that a way forward might be to conduct detailed functional analyses of feeding behavior, using a number of different procedures to clearly identify effective components of treatment (Najdowski et al. 2003).

## Somatic Treatments

### *Nutritional Interventions*

Attention to the detail of the child's nutritional intake is an important aspect of assessment, which may require attention as part of treatment. Aside from the negative impact on growth and physical functioning, inadequate nutrition may be associated with increased irritability and decreased interest in and energy for nonessential activities, such as play (Stallings et al. 1993), which can hinder development. Significant developmental progress has been shown to accompany improved nutritional status (Sanders et al. 1990).

The most common nutritional interventions focus on addressing the micronutrient content of the diet, plus the provision of structured routines and schedules to promote the development of hunger and satiety. For example, in cases where children are progressing from enteral to oral feeding, stability or increase in weight and height can allow for the volume of tube feed to be reduced, which can create a window of appetite and increase the tube-fed child's interest in oral feeding. However, research suggests this strategy alone is significantly less effective in moving children on to full oral feeding, than when combined with behavioral interventions—see below (Benoit et al. 2000).

Children who have had feeding problems since infancy are unlikely to have the necessary oral motor skills to eat food that would be regarded as suitable for their chronological age. Normally developing children tend to progress through a series of increasingly complex textures during the development of their feeding skills. It is likely that children need to have experience of processing food of one consistency in order to develop the skills required to move onto the next (Morris and Klein 2000). Skill acquisition is an important component of treating feeding disorders (Babbitt et al. 1994). Food should be introduced according to the

child's ability, experience, and developmental level, rather than their age in order not to compound a preexisting feeding disorder (see Vignette 3). When inappropriate textures have been introduced too early, the whole process of weaning through stages needs to be reestablished.

A number of children present with "pouching" or "packing," which is the holding of food in the mouth for lengthy periods. In some children this is related to poor skill acquisition and an inability to manage certain textures. Patel et al. (2005) have shown that offering less textured foods can help to reduce this behavior and promote weight gain. In other children, packing or pouching may result from avoidance behavior often arising in the context of a history of reflux or vomiting. In such instances progress may be made through desensitization, graded exposure, and positive reinforcement (see below).

Clinical Vignette 3

**Solid Food Aversion in a 3-Year-Old Boy with Downs Syndrome**

Damon is a 3-year-old boy with Downs syndrome. He was referred to a feeding clinic by his local pediatrician, who was concerned that Damon was drinking only fortified milk shakes and would refuse any solid food or purees. Damon was a healthy baby born at full term, with no heart problems. He spent 9 days in neonatal intensive care due to difficulties in establishing oral feeding. At this stage he was nasogastrically tube fed with his mother's expressed breast milk with a combination of bottle and breast-feeding being introduced after a few days. At 9 months, Damon was introduced to first-stage purees, such as baby rice. His parents then slowly introduced other purees, such as vegetables and fruits. Damon was not selective and would eat any food, provided it was finely pureed.

At 18 months, Damon's parents were advised by a local speech and language therapist to move him on to more textured food. Initially this went well, but as they began to offer him more lumpy food he began to start to refuse solid food. His parents were reassured by professionals that children do not starve themselves and that he would eventually accept the lumpier food. Initially, he refused the more complex textures, accepting only pureed sweet foods, but then he began to refuse all solids and purees and would drink only milky liquids. In desperation, forced feeding was attempted by members of the extended family.

Damon has delayed developmental milestones and delayed cognitive development. It is also likely in children such as this that their feeding and oral motor skills are also delayed. It may be that Damon was introduced too early and too quickly to more solid food, which he was unable to cope with and which undermined his confidence for eating solid foods. His confidence was likely to be shaky, given his early difficulty in establishing oral feeding, and would be further affected by well-meaning attempts at forced feeding. Damon's texture selectivity is likely to be a protective mechanism in response to his inability to cope with lumpy foods.

Damon and his family attended fortnightly sessions in a feeding clinic. His parent's were supported by their therapist to develop realistic expectations for Damon with regard to his feeding and development. Through cohesive multidisciplinary team working the family learned to have trust in professionals after receiving conflicting advice in the past. His weight was monitored and with the support of the dietician and therapist, Damon's access to milk was limited to after mealtimes. He was introduced to soft, high-calorie weaning foods, initially of a milky texture, such as yogurts. He was encouraged to self-feed, which was appropriate for his developmental level and this enabled him to self-regulate his intake and develop trust in caregivers after incidences of forced feeding in the past. He was given lots of praise for eating. Damon also had messy play sessions with the play specialist to allow him to gradually feel comfortable with the texture of foods and to have fun with food.

## Psychosocial Treatments

Psychosocial interventions can be targeted at the child, the caregiver(s), the interaction between child and caregiver, and/or the interaction with the child's family and wider social and educational system (Davies et al. 2006).

### *Individual*

Behavioral interventions, often based on reinforcement contingencies, have been used with reported success by a number of authors. Cooper et al. (1995) describe the successful treatment of four young children with severe feeding difficulties, using individually tailored multicomponent behavioral treatment packages. Techniques used include escape extinction (where the reinforcer to a response is removed in order to decrease the occurrence of this response), contingent attention (praise), contingent reward, noncontingent access to toys and social interaction as distracters during mealtimes, presentation of choice, and warm-up procedures. These authors report that escape extinction was shown to be a necessary treatment component in each case. Benoit et al. (2000) give an example of this technique: the removal of a spoon after gagging or refusal reinforces gagging or refusal as a response to food. Nonremoval of or reoffering the spoon is an extinction procedure designed to alter the gagging and refusal response. However, the 1995 Cooper paper included only four children and extinction as a technique is one that many caregivers and clinicians find difficult to deliver. Other behavioral treatments used in feeding disorders include the Premack principle, time-out plus reinforcement, and negative reinforcement. (The basis of the Premack principle is that a reliably occurring behavior in the child—such as watching a favorite children's program—can be used as a reinforcer for a less reliably occurring behavior, for example, self-feeding a yogurt; in other words, the child is rewarded for eating the yogurt through watching the TV program; O'Brien et al. 1991.) In children who are progressing from tube feeding to oral feeding, behavioral therapy can focus on reducing fear of swallowing (Benoit et al. 2000).

### *Interaction between Caregiver and Child*

Research suggests that parents of feeding-disordered children are more negative and coercive in their feeding practices and engage in higher levels of aversive instruction giving, aversive prompting, and negative eating-related comments (Sanders et al. 1993). For this reason intervention is needed to improve the interaction between parent and child to facilitate a more positive feeding environment.

A significant part of successfully treating many children with feeding disorders is the provision of guidance, support, and reassurance to parents and caregivers. Parent training is considered by many to be a key aspect of treatment (e.g., Babbitt et al. 1994). Advice can be provided on the use of structured mealtime and snack routines, the mealtime

Clinical Vignette 4

**Example of Individual and Parent Work Done with 3-Year-Old Boy with Feeding Disorder**

Alan was born at 28 weeks' gestation by emergency caesarean and spent 9 weeks in neonatal intensive care. He was bottle fed and vomited after each feed. He was diagnosed with reflux and given appropriate medication. A milk-free diet was recommended by the pediatrician as a precautionary measure. Alan had a gastrostomy inserted at 9 months of age, due to very poor oral intake, and was given a formula feed via the tube overnight. Alan would take sips of water orally but would not take solids.

At 3 years of age, Alan was seen for treatment at a behavioral feeding clinic. Graded exposure was used to treat Alan's food aversion, using a puppet called "Bert." Initially, Alan was asked, along with the puppet, to sniff different food and nonfood items. With the help of the puppet Alan talked about what smells he liked and smells he did not like. He then played a game where all the smells were placed in black jars and, while blindfolded, he and Bert had to guess which smell was which, receiving a sticker for each correct answer. This task was designed to be attainable and Alan experienced success in this task and became used to doing what was asked of him.

Alan then moved onto touching foods. Along with "Bert" he did painting with food, progressing to finger painting and hand painting and finally moving onto nose prints. There was no expectation to taste any food at this stage and Alan learned to have fun with food and to comply with requests. Each task was very attainable and built slightly on the previous task. Alan did not experience failure in his tasks, which were framed as "work" but also had an emphasis on fun.

Alan then moved on to tiny tastes of food. He was exposed to several different flavors and he picked his favorite, along with "Bert" who also tasted the food and picked his favorite. Both "Bert" and Alan received stickers for each taste.

From there Alan progressed to having a whole spoon of his favorite taste. He was given a sticker for each spoon he swallowed, a medium-sized "gift" for half a yogurt and a large-sized "gift" for a whole yogurt. Over a period of six sessions Alan progressed from sniffing foods to eating full yogurts and the rewards were reduced as success and expectations increased.

Meanwhile, work was also done with Alan's mother, who due to his prematurity and his poor early health felt very guilty and found it very difficult to set firm boundaries. Work was done with Alan's mother to work through these feelings at each session and to ensure that she would continue to maintain Alan's progress between sessions with firm boundaries, expectations, and goals.

environment (e.g., comfortable appropriate seating, quiet, and distraction free). Often parents may be understandably anxious about allowing their child to self-feed, particularly when there has been a history of choking, aspiration, or extreme allergic reaction. Management of parental anxiety is based on a good understanding of the child's history, previous parental response to distress and medical intervention, and support networks available to the parents. In children who have had a difficult period with medical conditions, parents may feel guilty about the distress the child has experienced. Treatment intervention will need to include a focus on this aspect of the presentation in order to facilitate appropriate development of skills (see Vignette 4). A number of publications are available that provide information, ideas, and accounts of experiences of other parents, which many find extremely reassuring and helpful (e.g., Ernsperger and Stegen-Hanson 2004, Legge 2001).

### *Interventions Targeted at the Wider Context*

Liaison with other adults involved with the child is also a commonly recommended treatment component. Nursery, day care staff, and teachers will often be required to implement consistent feeding regimes. For example, Ogata et al. report on a single-case design intervention study of four young children with pervasive developmental disorder. They describe individually designed interventions that were carried out in the classroom and highlight the importance of balancing opportunities for social interaction, with encouraging sufficient nutrient intake in such children (Ogata et al. 2000).

## Rumination Disorder

## Diagnosis

### Definition and Diagnostic Features

Rumination Disorder is the DSM diagnostic term used in the case of a feeding disorder characterized by the repeated regurgitation or bringing backup of swallowed or partially digested food. Such food is then rechewed before being swallowed again, or in some cases spat out. Food tends to be regurgitated and rechewed a number of times. This can happen during feeding, or shortly after feeding, and can have significant adverse consequences in terms of nutritional status and other medical complications. Rumination disorder typically develops in infants below the age of 1 year, but a condition of diagnosis is that there should have been a period of normal feeding prior to the regurgitation. Rumination disorder can also be diagnosed in older individuals, including children, adolescents, and adults. It may be associated with pervasive developmental delay, developmental disability, or other psychiatric disorder. Irrespective of age, the behavior must be present for a minimum of 1 month before diagnosis is appropriate, with rumination occurring frequently, usually daily. The regurgitation must be distinguished from

**DSM-IV-TR Criteria**

**Rumination Disorder**

A. Repeated regurgitation and rechewing of food for a period of at least 1 month following a period of normal functioning.

B. The behavior is not due to an associated gastrointestinal or other general medical condition (e.g., esophageal reflux).

C. The behavior does not occur exclusively during the course of anorexia nervosa or bulimia nervosa. If the symptoms occur exclusively during the course of mental retardation or a pervasive developmental disorder, they are sufficiently severe to warrant independent clinical attention.

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gastroesophageal reflux, or vomiting due to other medical causes, and in older individuals must not be better explained by an eating disorder (anorexia nervosa or bulimia nervosa).

Of interest to note is that in the ICD-10 classification of mental and behavioral disorders, unlike in DSM-IV-TR, rumination disorder is not identified as a separate diagnostic category (World Health Organization 1993). Instead, rumination and regurgitation are included as symptoms under the diagnosis of Feeding Disorder of Infancy and Childhood (F98.2). It is also important to note that infant regurgitation and infant rumination syndrome have also been proposed as being two separate disorders within the classification system for childhood functional gastrointestinal disorders proposed by Rasquin-Weber et al. 1999, also known as Rome II. In this classification scheme, the subgroup of vomiting disorders consists of infant regurgitation, infant rumination syndrome, and cyclical vomiting syndrome. Diagnostic criteria for infant rumination differ from those for DSM-IV-TR Rumination Disorder in a number of respects: there is a requirement for the behavior to have been present for 3 months rather than 1; it is not specified that there should have been a preceding period of normal functioning; there is a relatively narrow age at onset specified (3–8 months) unless all other diagnostic requirements are met (i.e., it can, in some circumstances, be diagnosed in infants with onset over 8 months as long as all other criteria are met) and attention is drawn to a lack of distress in the infant, poor interactions with others, and the behavior not occurring during sleep. This classification system was subsequently updated and revised (Rasquin et al. 2006) to provide Rome III criteria for childhood functional gastrointestinal disorders. Infant rumination syndrome remained unchanged but criteria were added for adolescent rumination syndrome to take account of the observation that rumination occurs across the age range. A number of authors use the term "rumination syndrome" in relation to older children, adolescents, and adults (e.g., Chial et al. 2003, Malcolm et al. 1997). As with the term "feeding disorder," there is variation in the use of the terms "rumination," "rumination disorder," and "rumination syndrome."

## Assessment

A major consequence in infants and young children with rumination disorder is the tendency to weight loss, with the related risk of malnutrition and susceptibility to infection, disease, and even death (Franco et al. 1993). Growth and physical development may be impaired if basic nutritional requirements are not met. Other complications of rumination include halitosis, dental damage, electrolyte abnormalities, and abdominal pain. Some authors have described a typical posture adopted by infants with rumination disorder, which is characterized by an arched back, backward tilt to the head, and contraction of abdominal muscles, representing attempts to regurgitate part digested food, while others describe the regurgitation as "effortless" (Nicholls 2004).

Assessment will typically include a medical and developmental history and present state evaluation including the following:

- feeding history (must have been normal prior to rumination);
- onset and development of rumination behavior, with identification of any triggers for behavior;
- medical history of gastrointestinal problems and other medical conditions;
- present weight, height, and calculation of body mass index centile or Z-score;
- presence of concurrent medical complications related to vomiting and regurgitation, for example, dehydration, aspiration pneumonia, and stomach ulcer;
- blood tests to check electrolytes and nutritional disturbances and deficiencies; and
- presence of concurrent or associated psychosocial disturbances.

Assessment also usefully includes direct observation both during and after feeding. This enables observation of the swallow, plus identification of the typical posture mentioned above.

## Epidemiology

As mentioned above, there is considerable variability in the use of terms in relation to rumination disorder; thus, it is very difficult to make clear statements about incidence and prevalence. A number of authors use terms such as "uncommon" or "relatively rare" (e.g., Franco et al., 1993, in relation to rumination in infancy). Rumination disorder typically develops within the first year of life, and many children grow out of it spontaneously. Where it occurs in older individuals it may be misdiagnosed, or in the case of adolescents and adults, not result in a clinical referral, sometimes due to embarrassment on the part of the sufferer. The symptom of rumination is nonspecific and may result in an individual being referred to one of a number of different types of clinic (e.g., gastroenterology, behavioral feeding, etc.), and thus again, consistent figures are hard to come by. Consequently, it is very difficult to know how many people of different ages are affected. Olden 2001 reports that "rumination" occurs in 6–10% of developmentally disabled children living in institutions.

Primary prevention of rumination disorder is not possible. Secondary prevention in the form of early behavioral intervention at initial observation of regurgitating and rechewing behavior may well help to minimize its establishment, thereby reducing the risk of adverse medical complications.

## Course

Rumination disorder tends to run a different course depending on the type of patient it occurs in. In most infants, it does tend to resolve over time, and the child eventually returns to normal feeding. However, in a few it can be associated with choking, serious medical complications, and can result in death. In older children, particularly those with pervasive developmental delay and developmental disability, it can be a more refractory problem, often developing into a long-standing habitual behavior that may prove very hard to address. In older patients who develop rumination disorder in the context of anxiety, or other psychiatric symptoms, its course will often be associated with the course of the comorbid psychiatric presentation.

## Differential Diagnosis

Alternative causes of regurgitation or vomiting will need to be ruled out. The most obvious are gastrointestinal conditions

and disorders, such as gastroesophageal reflux, pyloric stenosis, or gastrointestinal infections. Further investigation and examination by a physician, involving laboratory tests as appropriate, may be required to rule out primary medical causes. Many infants experience periods of vomiting or posseting, which can be distinguished from rumination disorder by the absence of the characteristic preparatory movements and apparent pleasure derived from the behavior. Regurgitating and spitting out food has also been well described as a symptom of an eating disorder in older individuals (Birmingham and Firoz 2006, Eckern et al. 1999). Anorexia nervosa and bulimia nervosa will therefore need to be ruled out.

### Differences in Developmental, Gender, and Cultural Presentations

Within the current DSM system, we have seen that rumination disorder can occur across the age range. In infants it has been reported as occurring at a higher rate in boys than in girls (Mayes et al. 1988). In older individuals it has been found to be more prominent in females than males (Chial et al. 2003). It occurs in individuals of normal intelligence and in those with mental retardation, with apparent differences in function (see next section).

## Etiology and Pathophysiology

A range of etiological mechanisms have been proposed in understanding the development of rumination disorder. The main etiological factors include the following:

- stress and anxiety combined with inadequate communication strategies or coping mechanisms may trigger the disorder, and
- need for stimulation.

In infants, anxiety and stress have been postulated as deriving from problematic aspects of the mother–infant relationship, as well as from physical illness. Rumination has been associated with neglect or failure to establish a close emotional bond with a primary caregiver. The behavior can be understood as a means of self-stimulation, self-soothing, and/or as an expression of distress. The repeated regurgitation and chewing may be a soothing behavior that the child uses to reduce anxiety or gain comfort. In children with pervasive developmental disorder, it may be understood as similar to other repetitive behaviors that the child engages in.

It seems likely that rumination disorder as defined by DSM-IV-TR is a learned behavior, which may or may not have had an underlying medical trigger. In some cases there may have been an early history of reflux or an episode of vomiting or other illness. For the diagnosis to be made, these must no longer be the main cause of the regurgitation. They may however have resulted in increased caregiving, so that an infant might learn to associate vomiting with eliciting positive attention.

Rumination disorder is not in itself currently understood as a disorder with high heritability, although research in this area is lacking. However, it can be associated with ASD and other pervasive developmental disorders, which do have a strong genetic component. It seems most likely that in most cases of rumination disorder in infants and young children, nonshared environmental influences combined with cognitive capacity and temperament might best account for its development.

## Treatment

### Treatment Goals

Rumination Disorder is characterized by problematic behavior; the usual goal of treatment is to alter that behavior and address any adverse sequelae (e.g., low weight and malnutrition). As with most childhood disorders, treatment planning will require a consideration of features specific to the child and to the child's environment.

### Psychosocial Treatments

Attention is usually paid to both the feeding situation and the interaction during feeding. For example, the infant's posture during and after feeding is important, and advice may be given to change this. The classic arching of the back can often be remedied by encouraging attention and physical contact after feeding. Greater interaction between mother and child can be helpful both during and after feeding. This can serve to distract the child from the need to self-sooth or self-stimulate, thereby reducing the problem behavior. Particularly in children with rumination disorder in the context of pervasive developmental disorder, reducing distraction and other external forms of stimulation while feeding is taking place can significantly reduce regurgitating behavior. A general emphasis on establishing feeding and mealtimes as calm, nonthreatening, and enjoyable is advised.

Behavioral approaches, in particular, operant conditioning, have been documented as having positive outcomes in infants and young children with rumination disorder. The practice of ignoring undesirable behavior and rewarding desirable behavior with praise and attention is widely used and recommended by many clinicians. However, this is often not effective in situations where the behavior in itself serves a positive function, such as self-soothing or comfort; ignoring it is unlikely to result in diminution of the behavior (see Vignette 5).

Another behavior modification technique, aversive conditioning, used to be a recommended treatment approach for rumination disorder. Such an intervention consisted of an unpleasant stimulus being delivered contingent on regurgitation, usually in the form of a sour or hot substance being placed on the child's tongue. This technique raises ethical concerns and its effectiveness proved to be inconsistent (Olden 2001). It is now no longer widely used, with a current clear preference for distraction, environmental changes, and emphasis on promoting interaction and reinforcement of desirable behavior (e.g., Franco et al. 1993).

In the case of significant problems in the relationship between the main caregiver(s) and the infant, treatment may be primarily focused on improving the bond between the two. Typically, this will involve encouraging the caregiver to respond appropriately to the infant's cues, not just around feeding but also in other areas of activity and interaction, thereby helping the infant to learn to communicate. This may in practice involve working with one or both parents. In some instances, caregivers present to the clinician with strong negative feelings toward the child. They may have been told that there is no obvious medical cause for the child's behavior, which in some cases seems to contribute to a sense of frustration and induces a sense of powerlessness. Such negative feelings will need to be addressed, as otherwise they may serve to perpetuate the behavior.

Clinical Vignette 5

**Rumination Disorder in an 11-Month-Old Girl**

Cara was seen in the Feeding Clinic at the age of 11 months. She had been bottle fed from birth and had started weaning at 4 months onto purees. Initially, she had fed with no problems and her growth and weight had been satisfactory. At 6 months she had moved onto jars of baby food and then to finger foods, but still had not made the transition to taking fluids from a beaker or cup. Regurgitation was reported to have started at around the age of 6–7 months and by the time of presentation, Cara was regurgitating and rechewing throughout the day. She was also reported to have vomit in her bed some mornings. Cara's weight and behavior were a cause for significant concern.

Cara was the fourth child of Louise, 25. Louise had her first child at the age of 17, and had her four children by two different partners, both of whom no longer lived with the family. Cara's father had left a few months previously after a period of frequent arguing and disagreements. Louise now received some support from her parents and worked part-time. The team's understanding of the context for the problem was that Cara's family situation was very unsettled. Louise had multiple demands on her time and while she had bottle fed and then weaned Cara initially, she had passed over the task of feeding Cara to others whenever possible, including her two older children (age 7 and 5). Louise had struggled with depression and stress and had found it difficult to establish a close bond with Cara. She was house proud and wanted her children to look clean and well cared for. She spent many hours cleaning, washing, and tidying, and little time with Cara. Whereas she had spent more time with her until around the age of 6 months, this had gradually reduced. Cara's regurgitation was understood in the context of an increasingly distant relationship with her mother, a chaotic feeding regime, and relatively long periods of time being left without direct stimulation. In Cara's case, regurgitation and rechewing appeared to be self-soothing, comforting behaviors, which she engaged in when she was alone or in her cot. Louise's exasperation at soiled sheets and clothes was understood as a further tension in their relationship. Cara's deteriorating physical state contributed to Louise's depression and feelings of being unable to cope with her. Treatment consisted of encouraging positive interaction around feeding and at other times, seeking out practical sources of support for Louise, and establishing a regular mealtime routine for the whole family. Recommendations to ignore the regurgitation were not made, as this was deemed to be likely to be ineffective given the specific context for Cara's problem.

### Somatic Treatments

Medication is not generally recommended as treatment for DSM-IV-TR Rumination Disorder in infants and young children.

## Pica

## Diagnosis

### Definition and Diagnostic Features

Pica is the diagnostic term used to denote individuals with a specific form of eating disturbance characterized by the ingestion of nonfoodstuffs, which must have persisted for at least 1 month prior to diagnosis. The term "pica" is usually held to come from the Latin word for magpie (*picus*), referring to the indiscriminate feeding habits of these birds. Substances ingested by individuals with pica may include chalk, soil, plaster, clay, paint, paper, cloth, sand, hair, plastic, coal, insects, wood, pebbles, and animal feces—in effect anything that can be put into the mouth. Some clinicians also use the term to include the eating of foodstuffs in a raw or unprepared form, such as flour or raw potatoes, although technically such substances are not "nonnutritive," as specified in the diagnostic criteria (see below).

In their historical review, Parry-Jones and Parry-Jones 1992 conclude that there is no evidence to suggest that at any time before the 20th century was pica regarded as a separate disorder. Drawing from documents from the 16th century when the term "pica" was first used, they conclude that it was for centuries regarded as a symptom of other disorders. However, in both of the current main classification systems, DSM-IV-TR (APA 2000) and ICD-10 (WHO 1993), pica does appear as a separately diagnosable disorder.

Using the DSM-IV-TR classification scheme, pica can be diagnosed in individuals of all ages. However, ICD-10 refers only to "pica of infancy and childhood." A further difference between the two classification systems is that in DSM-IV-TR, pica may be diagnosed in the context of another mental disorder (e.g., mental retardation, pervasive developmental disorder, and schizophrenia), whereas in ICD-10 it is specified that the child should have no other mental disorder with the exception of mental retardation (World Health Organization 1993). Pica is also well known to occur in pregnancy and in individuals with nutritional deficiencies. In this chapter pica will be discussed specifically in relation to young children as an emotional/behavioral disorder. Within this age group, children with pervasive developmental disorder and mental retardation are most likely to display this behavior. When occurring in association with these disorders, the pica must be considered sufficiently severe to warrant clinical attention in its own right in order to justify a diagnosis. Pica can also occur in children with no other mental disorder.

It is well recognized that children go through a "mouthing" stage as part of normal development and that most normally developing children ingest some nonnutritive materials during this period. For this reason, ICD-10

**DSM-IV-TR Criteria**

**Pica**

A. Persistent eating of nonnutritive substances for a period of at least 1 month.
B. The eating of nonnutritive substances is inappropriate to the developmental level.
C. The eating behavior is not part of a culturally sanctioned practice.
D. If the eating behavior occurs exclusively during the course of another mental disorder (e.g., mental retardation, pervasive developmental disorder, schizophrenia), it is sufficiently severe to warrant independent clinical attention.

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requires a minimum chronological or mental age for diagnosis of 2 years, while DSM-IV-TR states that the ingestion of nonfoodstuffs is inappropriate to the developmental level of the individual.

## Assessment

A comprehensive review of the child's nutritional intake is recommended in all cases of childhood pica. This will include attending to the specifics of the problematic eating behavior, including possible underlying physical causes for it, the presence of any complications arising from the ingestion of nonnutritive substances, the child's psychosocial environment, and the presence of conditions such as mental retardation or pervasive developmental disorder.

Eating nonnutritive substances can be the result of nutritional deficiencies, in particular, iron deficiency. In order to rule this out as primary cause, a nutritional assessment of daily diet should be considered. However, it is possible for lead poisoning, which may result from pica, to result in iron deficiency, in which case it can be hard to disentangle whether the deficiency is cause or effect. In the same way, the ingestion of poisonous substances may contribute to brain damage and learning disability in the child, as well as developmental disabilities increasing the risk of ingesting nonnutritive substances. A further reason for carrying out a dietetic review is because pica may affect appetite, which in turn may result in reduced consumption of normal food, leading to nutritional deficiency.

The effects of eating nonfoodstuffs can range from being relatively harmless to potentially fatal. An important aspect of assessment is therefore to determine exactly what is being eaten and to assess quantities eaten. The most common harmful outcomes of pica in children include lead poisoning, other accidental poisoning, parasitic infestation, infections, gastrointestinal obstruction, the formation of bezoars, and/or laceration. The clinician will ideally need to match the substance ingested with the presence of any symptoms in the child to determine appropriate medical treatment. However, in young children, information about ingested substances will often depend on parental or caregiver report, and the child's behavior may not have been directly observed. In some cases parents are not aware of the nature and extent of the child's behavior. Clearly, the severity of the consequences will vary considerably, depending on the substance in question. Where this is not known, delay in diagnosis and appropriate management may occur.

The presence of abdominal pain and other gastrointestinal symptoms, such as constipation, diarrhea, vomiting, loss of appetite, abdominal distension, and nausea, should always be assessed, due to the possibility of blockage, damage, infection, or infestation. In relation to specific medical investigations, blood lead screening, imaging studies, and endoscopy may be indicated.

The third component of assessment for pica (besides the nature of the behavior and any possible complications) is to obtain a good understanding of the child's psychosocial environment. Some children presenting with pica may be unsupervised or understimulated for long periods, and in some children, the development of secure attachment relationships may have been disrupted. A narrow focus on symptoms and complications alone would miss these aspects of presentation.

Finally, assessment for the presence of mental retardation or pervasive developmental disorder is an important part of attempting to understand the function and context for the behavior and will influence approaches to treatment.

## Epidemiology

As mentioned previously, in children, pica most commonly occurs in those with pervasive developmental disorder and mental retardation. There are some prevalence figures for pica in institutionalized adults (e.g., 9.2% of 607 such adults—McAlpine and Singh 1986), but rates overall for infants and young children are difficult to ascertain. Much of the literature is based on case report studies.

## Comorbidity

The main comorbid presentations of pica are mental retardation and pervasive developmental disorder.

## Course

As with rumination disorder, pica may be a transient disorder, which remits spontaneously, or may be a more established behavioral problem depending on the type of patient. In children with severe forms of mental retardation or pervasive developmental disorder, the behavior may be left untreated, or if interventions are attempted, difficult to alter and thus persist. The prognosis is additionally varied in relation to those particular substances that are ingested. It can range from being harmless to resulting in death. In general, though, most authors describe pica as most commonly remitting in young children, usually after a period of a few months.

As with rumination disorder, primary prevention of pica is not possible. Observation of the child's eating habits, supervision of feeding, and appropriate guidance and training regarding what is and what is not suitable to eat may prevent the establishment of significant problems.

## Differential Diagnosis

Mouthing is a normal developmental stage, usually occurring around the age of 18–24 months, and the accidental ingestion of nonnutritive substances is not uncommon. Pica should be diagnosed only when eating inedible substances persists for 1 month and is inappropriate for the individual's developmental level.

In cases when consumption of nonnutritive substances occurs during the course of another mental disorder, such as pervasive developmental disorder or Kleine–Levin syndrome, a diagnosis of pica should only occur in instances where the eating of nonnutritive substances is severe enough to require additional and independent treatment.

Korman 1990 describes three cases of children presenting with pica resulting from iron-deficiency anemia. In all of these children the anemia was secondary to malabsorption related to celiac disease. Treatment in these cases consisted of observing a gluten-free diet. In all these children this resulted in a growth spurt plus complete resolution of pica. This author recommends that where pica is persistent and combined with growth delay, celiac disease should be considered even in the absence of gastrointestinal symptoms.

## Differences in Developmental, Gender, and Cultural Presentations

Pica occurs across cultures, and in some societies the practice of eating nonfoodstuffs is culturally sanctioned and not considered disordered. For example, in some African countries and in India, the practice of eating soil is not uncommon; indeed, soil may be made available for sale for this purpose. For this reason both DSM-IV-TR and ICD-10 definitions state that the behavior must not be part of a culturally sanctioned practice. Although pica often occurs in people living in poverty (possibly due to nutritional deficiencies), it can be present in individuals from all social groups. In childhood, it occurs in both boys and girls, and in older individuals with mental retardation it is also reported roughly equally across both males and females. In adults without mental retardation and not living in poverty, pica occurs most often in the context of pregnancy. It is relatively rare in adolescent and adult males of normal intelligence, where there is no cultural practice of eating nonfoodstuffs.

Pica is not usually diagnosed below the age of 18 months (24 months if using ICD-10 criteria). It becomes less common with age in individuals of normal intelligence with no developmental disorder.

## Eiology and Pathophysiology

Parry-Jones and Parry-Jones 1992 report that over the centuries a variety of causes have been identified for pica, including those remaining closely associated with our current understanding of factors contributing to its development, such as developmental disability, nutritional deficiencies, pregnancy, and emotional deprivation.

As mentioned in the section on assessment, it is often difficult to distinguish the precise cause of pica in any one individual. Mineral deficiencies (e.g., iron, zinc, and calcium) are often cited, but not all children with pica are mineral deficient, and not all substances eaten contain the missing substance. In children with developmental disability, pica may result from a persistent habit of mouthing objects and/or lack of discriminatory ability. Its persistence is usually understood in terms of behavioral learning theory; the behavior is associated with a positive reward (e.g., comfort) and therefore persists. Lack of stimulation, lack of supervision, self-soothing, comfort seeking, and hunger have all been suggested as underlying the development and persistence of the unusual feeding behavior.

## Treatment

### Treatment Goals

As with other types of feeding problem, the main aims of treatment for pica are twofold: to address the behavior and to manage and treat any adverse consequences. Again, this will in many cases require multidisciplinary input.

### Psychosocial Treatments

In terms of addressing the behavior itself a range of behavioral strategies are reported in the literature. As with rumination disorder, the more aversive techniques, such as contingent aversive taste, smell, or sensory stimuli, which were widely used a few decades ago, have become much less common. The more positive behavioral strategies based on positive reinforcement and discrimination training tend to be more widely used. As in so many areas of managing children's problem behavior, there has been a clear shift away from associating directly aversive consequences (e.g., unpleasant stimuli, punishment, and deprivation), with engaging in the problem behavior, to the encouragement of normal behavior through positive consequences for altering behaviors in that direction.

Addressing the behavior will in most cases also include psychosocial and environmental interventions, such as altering the physical environment to reduce availability of nonnutritive substances, improving supervision, and working on promoting interaction and stimulation. In some children, pica seems to be related to a lack of sensory stimulation, and thus a focus on providing alternative sensory experiences can help to reduce or eliminate the inappropriate feeding behavior.

Finally, educational input may be required for parents and caregivers to alert them to the risks of eating certain substances.

### Somatic Treatments

There are no medications specific to the management of eating nonnutritive substances. However, depending on what has been ingested, a range of medications may need to be administered to manage the consequences. As mentioned previously, pica may result in significant levels of malnutrition, including vitamin and mineral deficiencies, which may indicate a need for nutritional supplementation. It is unlikely though that where a nutritional deficit is identified at assessment, nutritional treatment of that deficit alone will be sufficient. Nevertheless, there are some small case studies in the literature that suggest otherwise; for example, Arbiter and Black 1991 describe two children with a diagnosis of pica referred to a child psychiatry clinic. Both these children had undiagnosed iron-deficiency anemia, which when treated led to resolution of pica.

### Special Factors Influencing Treatment

Similar to rumination disorder, where pica occurs in the context of mental retardation or pervasive developmental disorder, it can prove more difficult to alter the behavior. The effectiveness of discrimination training may be limited in such children and reward-based reinforcement approaches less potent. However, environmental manipulation, distraction, stimulation, and interaction are all useful techniques, and with consistent application, pica can be successfully managed.

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CHAPTER

# 48 Childhood Disorders: Tic Disorders

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Tourette's Disorder
Chronic Motor or Vocal Tic Disorder
Transient Tic Disorder

It has been more than 100 years since Gilles de la Tourette first described the often complex and puzzling disorder that now bears his name, Gilles de la Tourette syndrome (Tourette's disorder (TD)). In the past 30 years, efforts to increase awareness of TD (and other tic disorders), improve diagnostic accuracy, decrease stigma, and stimulate research have largely been successful. Research has demonstrated that tic disorders are more common than previously thought, have a genetic etiology, and are often complicated by co-occurring behavioral and emotional problems. Improved understanding of tic disorders and common co-occurring disorders as well as increased availability of efficacious treatments has resulted in the promise of better outcomes and less stigma for individuals with TD.

Despite the opportunity for enhanced outcomes, inadequate dissemination of assessment and treatment advances has left many with TD without access to knowledgeable medical professionals. Modern psychiatrists are ideally suited to integrate research findings into improved diagnostic and treatment approaches. As such, this chapter is intended to close the dissemination gap by reviewing and updating the knowledge base and discussing evidence-based approaches to addressing the complex treatment needs of patients with TD and other tic disorders.

## Diagnosis

### Phenomenology

#### Tics

The cardinal features of TD and tic disorders are the presence of motor and/or vocal tics. Tics are defined as sudden, repetitive movements, gestures, sounds, or utterances that typically mimic some fragment of normal behavior. Tics are characterized as simple or complex.

Simple motor tics are usually brief, rapid movements of individual muscle groups (e.g., eye blinking, head shaking, shoulder shrugging, etc.). Complex motor tics are typically slower, rhythmic, and involve multiple muscle groups (e.g., simultaneous eye deviation, dystonic postures, even sequences of simple motor tics). Some complex motor tics appear more purposeful, such as stereotyped crouching and hopping, repetitive touching or rubbing, and, less commonly, obscene gestures (copropraxia).

Simple vocal tics are usually brief staccato-like sounds caused by quick diaphragmatic contractions and resulting forceful movement of air through the nose and mouth. They include sniffing, throat-clearing, grunting, whistling, and animal noises. Complex vocal tics include utterances such as words, phrases, and repeating one's own words (palilalia) or the words of others (echolalia). Uttering obscene words/phrases (coprolalia) or other socially inappropriate word/phrases is not essential for diagnosis and is uncommon with approximately 10% of TD cases so affected (Robertson 2003).

Tics typically begin in early childhood (5–7 years of age), wax and wane in severity, and change in kind and character over time. Tics are exacerbated by excitement, stressful events and internal tension. Conversely, there is often an attenuation of symptoms during periods of focused, productive activity, deep relaxation and sleep. Tics are involuntary, but they may appear to be volitional as they can be suppressed for brief periods and may appear in reaction to environmental events (e.g., mimicking another's mannerisms

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or speech). In some individuals, tics are preceded by a thought or physical sensation referred to as a "premonitory urge" (Leckman et al. 1993a). Patients noting premonitory urges often describe a period of persistent "inner tension" prior to the tic and a quiescent period of varying length following the tic. Although reported by a majority of adults with TD, premonitory urges are described by fewer than half of youths with the disorder and may be a function of increasing introceptive awareness during adolescence (Banaschewski et al. 2003).

### Diagnostic Criteria for the Tic Disorders

There are four diagnostic categories included in the tic disorders section of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000): (1) TD, (2) chronic motor or vocal tic disorder (CTD), (3) transient tic disorder (TTD), and (4) tic disorder not otherwise specified (TD, NOS), which is a residual category for tic disorders not meeting the duration or age criteria of the other categories (see DSM-IV-TR Criteria boxes). Diagnostic decisions are typically based on the presence of motor and/or vocal tics, duration of tic symptoms, age of onset, and absence of contributory medical conditions or medications. Other diagnostic schemas have been developed for research purposes (i.e., genetic and epidemiological studies) and include special diagnostic modifiers. For instance, tic disorders not witnessed by a knowledgeable observer are termed tic disorders *by history*; the modifiers *possible*, *probable*, and *definite* are also added as estimates of diagnostic confidence of a tic disorder diagnosis in such cases (The Tourette Syndrome Classification Study Group 1993).

**DSM-IV-TR Criteria**

**Tourette's Disorder**

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)

B. The tics occur many times a day, (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

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**DSM-IV-TR Criteria**

**Chronic Motor or Vocal Tic Disorder**

A. Single or multiple motor or vocal tics (i.e., sudden, rapid, recurrent, non-rhythmic, stereotyped motor movements or vocalizations), but not both, have been present at some time during the illness.

B. The tics occur many times a day nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

E. Criteria have never been met for Tourette's disorder.

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**DSM-IV-TR Criteria**

**Transient Tic Disorder**

A. Single or multiple motor and/or vocal tics (i.e., sudden, rapid, recurrent, non-rhythmic, stereotyped motor movements or vocalizations).

B. The tics occur many times a day, nearly every day for at least 4 weeks, but for no longer than 12 consecutive months.

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

E. Criteria have never been met for Tourette's disorder or chronic motor or vocal tic disorder.

*Specify* if:

**Single Episode or Recurrent**

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## Diagnostic Assessment

### Clinical Presentation

Prior to the 1980s, only patients with severe and clinically obvious tics were diagnosed with TD. The majority of these patients were adults who were correctly diagnosed only when their tic symptoms became disabling and when classic symptoms such as coprolalia appeared. Despite experiencing

distress or stigmatization, adults with mild tics may not have pursued evaluation and treatment due to a lack of awareness in the lay and professional communities. Children during this era may not have been identified by their parents or were seen as having other behavioral or psychiatric difficulties by clinicians (i.e., hyperactivity or anxiety). In turn, tic symptoms may have been relabeled as fidgeting or anxious habits and subsumed under other diagnoses.

As medical and public knowledge regarding tic disorders increased, younger children with milder symptoms presented for treatment. Today, the challenge is often not identification of the tic disorder, but rather proper identification of co-occurring psychiatric difficulties, which often are more disabling than tics.

The family's initial concern usually determines the medical specialty first consulted regarding tic symptoms. Children with an affected parent usually present directly to a neurologist or psychiatrist for evaluation. Symptom-wise parents typically seek evaluation early in the course of their disorder, often before a clear diagnosis can be made or tic-suppressing treatment is necessary. Parents with limited exposure to tic disorders may initially consult their pediatrician, incorrectly consult an eye doctor for blinking, or an allergist for sniffing and throat clearing. More than half of families who ultimately pursue expert consultation learn about tic disorders through the media. Although the media has increased public awareness, many parents who first learn about TD from dramatic cases in the media can be fearful that early tic symptoms lead invariably to a debilitating, lifelong disorder. Tic disorders are also frequently identified during evaluation for other disorders such as attention-deficit/hyperactivity disorder (ADHD). When the TD diagnosis is made as part of an evaluation for other problems, it can be particularly difficult for the family and the patient to cope with the additional and unexpected diagnosis.

Although most cases of TD are identified in childhood, some individuals first seek an assessment as adults. Adults who present for evaluation will likely have a lifelong history of tics, but may not have been severely affected earlier in their lives. They often seek evaluation after their child was diagnosed or following a media story about TD. They may have experienced associated psychosocial stigma, been misdiagnosed, or even subjected to inappropriate treatments. For these adults, the relief provided by formal diagnosis may be attenuated by resentment for incorrect misdiagnoses and related treatment failures or simply the challenge of understanding themselves anew.

## Tic Severity Ratings

The rating of tic severity begins with identifying specific movements and/or sounds as well as associated distress and impairment. A typical starting point is asking patients and their families about the life-time presence of common motor tics proceeding from head to toe through common muscle groups. Questions related to the presence of simple sounds and more complex vocalizations are best completed after assessment of motor tics as vocal tics usually develop later than motor tics. After identifying the types of tics, elucidating information about the number, frequency, forcefulness, intrusiveness, and social impact of tics, as well as the patient's ability to suppress tics provides information about impairment. Premonitory sensations or urges, while not critical to diagnosis, may also impair academic, psychosocial, or occupational functioning. Identifying the characteristic course of tic disorders is also important for diagnostic confidence (i.e., childhood onset with simple motor tics in the face).

Tics associated with greater impairment include exaggerated, disruptive, and/or painful movements, vocalizations that call attention to the patient, tics that are socially unacceptable (i.e., coprolalia, copropraxia, etc.), and those with intrusive premonitory urges. Symptom severity is frequently correlated with impairment, but not always. The lack of congruity between tic severity and impairment may be accounted for by the patient's ability to cope with severe symptoms and the availability of social support. When patients appear to be more impaired than his or her tic severity warrant, an extended evaluation focusing to identify co-occurring conditions or problems with social support may be necessary.

In addition to direct clinical observation, a number of structured and semi-structured instruments are available for the evaluation of tic symptom severity (Scahill et al. 2006). Assessment instruments, including the commonly used Yale Global Tic Severity Scale (Leckman et al. 1989), follow the clinical approach described above.

## Assessment of Co-occurring Conditions

Whereas tic severity and impairment are often correlated, many patients with mild tics are most impaired by the co-occurring conditions ADHD, OCD, and Learning Disorders (LD). An adequate assessment of these conditions is part of any comprehensive evaluation. The methods of assessment of these conditions are similar to those used in patients without TD. The exception is the assessment of tic-related obsessive–compulsive symptoms, for example, touching, tapping, rubbing, "evening up," repeating actions, stereotypical self-mutilation, staring, echolalia, and palilalia. Although these symptoms are often omitted from the traditional psychiatric and neurological review of symptoms, tic-related obsessions and compulsions should always be part of the routine evaluation of patients with tics. Similarly, before the diagnosis of ADHD is made in a child with tics a review of the impact of tics, premonitory sensations, anxiety and obsessive–compulsive symptoms assures that impairment in attention and problems with motor restlessness are not secondary to other problems.

## Assessment of Other Psychiatric Disorders

It is standard for any psychiatric evaluation to rule out all other psychiatric disorders. In complex cases of TD, the multitude of behavioral and emotional symptoms can be formulated in a number of different ways. Behavioral and emotional problems can be seen as components of the TD diathesis, as a reaction to having a chronic disorder, or as part of an independent psychiatric disorder that is complicating the clinical picture. Clinical formulations that oversimplify and do not consider the presence of multiple independent disorders may lead to incorrectly attributing unrelated symptoms to TD and may result in diagnostic imprecision and treatment failures. It is important to identify all possible psychiatric disorders in patients with TD so that the hierarchy of disabling conditions can be identified and treatment initiated accordingly. For example, an older teenage boy with a long history of TD, ADHD, impulse

control and behavior problems, and a difficult relationship with his parents presents with increasing impulse control problems, intrusive sexual comments and behavior, insomnia, and substance abuse. Although it would be parsimonious to consider this clinical presentation an exacerbation of TD, it would be clinically prudent to rule out the presence of other treatable conditions, such as a substance use disorder, major depressive disorder, or bipolar disorder. A positive family history of one of these disorders would provide additional support for the diagnosis. Table 48–1 highlights some of the complex presentations often found in TD psychiatry and specialty clinics.

**Table 48–1 Complex Clinical Presentations in TD**

| |
|---|
| Tics + ADHD + OCD + LD + major depressive disorder |
| Tics + ADHD + OCD + LD + separation anxiety disorder |
| Tics + ADHD + OCD + LD + panic disorder |
| Tics + ADHD + OCD + LD + bipolar disorder |
| Tics + ADHD + OCD + LD + autism–pervasive developmental disorder |
| Tics + ADHD + OCD + LD + substance abuse |
| Tics + ADHD + OCD + LD + conduct disorder |
| Tics + ADHD + OCD + LD + personality disorders |

### Psychosocial Issues

Psychosocial issues can play a role in tic severity and in overall adaptation and impairment. Identification of a child's strengths as well as areas of needed support provides the basis for a balanced understanding of the child. Assessment of family, peer, and school support along with assessment for the presence of opportunities to be intellectually, physically, and socially challenged is also important. The appropriate balance between support and challenge in children is critical for long-term development. An environment that is too protective limits opportunities for building skills. An environment that is too challenging can lead to frustration, anger, and maladaptive coping.

### Physical Examination

Tic assessment requires a careful evaluation of observable tic symptoms, however, the absence of tic symptoms during an evaluation is not uncommon and should not necessarily lead to clinical doubt. Tic expression is known to vary based on environmental factors and some patients are able to suppress symptoms for short periods of time (Piacentini et al. 2006). Beyond the observation of tic symptoms in the interview, there are no pathognomonic physical examination findings. Patients with TD have been noted to have nonfocal and nonspecific subtle neurological findings ("soft" signs). If tic suppression with antipsychotic agents is considered, a structured method for documenting complex movements at the pretreatment evaluation is useful in establishing a baseline. This approach aids in monitoring disease progression, treatment gains, or developing antipsychotic-induced movements.

### Laboratory Evaluation

No specific laboratory or imaging tests are helpful in making the diagnosis or assessing a patient with TD. Laboratory assessment maybe done as part of a routine health screen or in anticipation of medication interventions. Currently, laboratory testing for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS) and group A beta-hemolytic streptococcal (GABHS) infections include throat culture, if strep pharyngitis symptoms are present. Antistrep antibody titers and other screens for antineuronal antibodies are considered experimental at this time (Rizzo et al. 2006, Singer et al. 2005).

## Epidemiology

TD is recognized as a global phenomenon, suggesting that the prevalence, presentation, and course of TD are similar across countries, cultures, and ethnicities (Robertson 2003). However, great variability in assessment strategies, definition of impairment, treatment approaches, access to appropriate medical care, help seeking behavior and, importantly, acceptance of people with TD (i.e., stigmatization) likely exists and may explain differences in prevalence estimates in different countries, ethnic groups and over time.

The availability of more clearly defined diagnostic criteria and more rigorous epidemiological studies has improved prevalence estimates in recent years. Currently, tic disorders are considered relatively common with 4–18% of school-aged children affected (Robertson 2003). Tic disorders are more common in children than adults and people with mild symptoms are much more common than those with severe, complex symptoms. TD is currently considered to affect approximately 1% of school-aged children with males four times more commonly affected than females (Robertson 2003). The number of adults with severe tic disorders requiring tic suppression treatment is estimated to be approximately 0.1% (Scahill et al. 2001).

## Course of the Tic Disorders

Tic symptoms usually begin in childhood with an average age of diagnosis of 7 years. Even though current diagnostic criteria allow for an age of onset up to 18 years, it is unusual for symptom onset to occur during the teenage years and adulthood. Facial and ocular tics (i.e., blinking, squinting, eye darting, or eye rolling) typically appear first. In many patients, motor tics remain isolated to the face. Motor tics appearing in other anatomical regions often present sequentially from the head and face to the neck, shoulders, trunk, and extremities. Motor tics typically precede vocal tics. Initial tic symptoms (motor or vocal) are often simple in character, with complex symptoms developing later.

Longitudinal studies suggest that tic severity peaks during the latency age and early teen years. Most patients experience a subsequent decline in tic severity during the middle to late teenage years (Leckman 2003, Lin et al. 2007). Approximately, one-third of individuals with tic disorders will experience a complete remission of tics as they reach adulthood. Research has demonstrated that few patients experience a severe or deteriorating course (Leckman et al. 1998). Some research studies have indicated that marked or severe tics in childhood tend to persist into adulthood (Bloch et al. 2006), while others have found childhood tic severity to be a poor predictor of later severity (Leckman et al. 1998).

## Co-occurring Symptoms or Disorders

### Comorbidity

Tourette disorder can be complicated by a broad range of co-occurring emotional and behavioral problems (Gaze et al. 2006). Common co-occurring symptoms include attention and learning problems, obsessive–compulsive behaviors, difficulty with impulse control, depressed mood, anxiety, behavior problems, and substance use. In some patients, these problems reach diagnostic significance, but in others they are less severe. The most common co-occurring disorders are ADHD (50–60%) and obsessive–compulsive disorder (OCD; 30–70%). These co-occurring problems, when present, are typically more disabling than the tic disorder and are often the reason patients seek clinical services. The exact relationship of these co-occurring conditions to TD is a matter of some controversy. Some conceptualize the TD phenotype narrowly (i.e., motor and vocal tics only), seeing co-occurring conditions as independent. Others subsume various co-occurring problems within a broad TD phenotype.

Careful attention to the TD phenotype is critical for scientific exploration of etiology and pathophysiology, but is also important for assessment and treatment. For patients whose symptoms meet TD diagnostic criteria, but who also have multiple co-occurring conditions (e.g., OCD, ADHD, and LD) a simple moniker—Tourette's disorder—can have great power for advocacy, but is an obvious oversimplification and can lead to poorly conceptualized treatment. Conceptualizing the same child as having TD plus OCD, ADHD, and LD may lack parsimony, but facilitates clear treatment hierarchies and hopefully more effective treatment strategies.

Despite the power that the TD diagnosis can have for advocacy, some caution is warranted. To illustrate, Billy, a bright and academically successful 11-year-old boy, had motor and vocal tics, but no co-occurring conditions. The diagnosis of TD was helpful at school with teachers becoming more understanding of his movements and sounds. However, as he approached middle school, he was not accepted into the gifted and talented program based only on the school's presumption that his TD might also relate to problems with attention and learning, anxiety and perhaps depression. In this example, the TD patient was inappropriately encumbered by the perception of an overly broad TD conceptualization. The opposite problem can also occur. Jesse was a 7-year-old boy who had moderately severe tics. The initial evaluation focused on tics and did not include a full assessment of common co-occurring problems. As such, moderate to severe OCD symptoms were overlooked. Jesse's clinician was comfortable with the diagnosis and treatment of TD and started him on an antipsychotic medication. Jessie experienced little to no reduction in tics, his OCD worsened, and he experienced increased impairment at home, school, and with his peers. Jesse was seen in consultation and his treatment was subsequently reoriented toward his OCD with symptom improvement following.

### ADHD

Upward of 50% of clinically ascertained children and adolescents with TD may experience problems with attention, concentration, over-activity, or impulse control (Gaze et al. 2006). Relative to youth suffering from TD alone, those with TD + ADHD experience greater behavioral and social problems (Robertson 2006). The course of ADHD symptoms in persons with Tourette's syndrome (TS) is similar to that in children with ADHD only (Erenberg 2005). In both groups (i.e., TD + ADHD and ADHD only) symptoms of hyperactivity typically attenuate before puberty, whereas problems with attention and concentration may continue into adulthood. Additionally, ADHD symptoms usually precede the onset of tic symptoms in patients with TD + ADHD. The estimated frequency of ADHD in community samples is lower (8%) than in clinic populations (41%) (Apter et al. 1993, Caine et al. 1988, Erenberg 2005). The lowest prevalence estimate of ADHD in TD (8%), occurred in a sample of older teens assessed for current ADHD status, not lifetime diagnosis (Apter et al. 1993). Though the point prevalence of ADHD in this sample was more than twice than that in the general population, factors such as sample age and examination for current status probably led to an underestimate of lifetime ADHD in this population. The higher prevalence rates of ADHD in clinical compared to epidemiological samples raises the concern that clinical sample rates overestimate the true prevalence (Pauls et al. 1988).

With increasing awareness of the frequent co-occurrence of ADHD and TD more adults with these conditions are seeking treatment. Despite a growing literature on assessment methods and treatment of adults with ADHD, there is a lack of information on the prevalence, course, and impact of ADHD in adults with TD.

### Obsessive–Compulsive Symptoms

Obsessions are stereotyped, persistent, and intrusive thoughts, impulses, or images that are experienced as unwanted and senseless by the affected individual. Obsessions commonly experienced by patients with OCD include fears of contamination, harm coming to oneself or others, losing control of one's impulses and being unable to remember important facts. Compulsions are repetitive behaviors or mental acts that an individual feels driven to perform in response to the obsession (American Psychiatric Association 2000). Compulsions commonly seen in OCD include repeated or stereotyped washing, grooming, checking (e.g., locks, switches, or doors), and other senseless rituals including counting, ordering, and hoarding. Because these thoughts and related behaviors are common in the general population, persons are considered "disordered" only when the obsessions or compulsions become time-consuming and impairing.

Differences in OCD symptoms in individuals with OCD alone and individuals with TD + OCD have been noted in several studies. Patients with TD + OCD tend to have greater concern with physical symmetry, ordering, exactness, and impulse control (Labad et al. 2007, Leckman et al. 1994). These concerns lead to what are termed tic-related compulsive behaviors and include "evening up" (e.g., ensuring that socks are pulled up evenly) and "just right" behaviors (i.e., arranging toys until it feels right) (Leckman et al. 1994, Leckman 2003). The absolute number of concerns appears to be greater in patients with TD + OCD compared to patients with OCD (George et al. 1993) (Table 48–2). Patients with TD + OCD typically report multiple concerns

**Table 48–2 Differential Diagnosis of Tics**

Simple, rapid movements
- Myoclonus
- Chorea
- Seizures

Simple, sustained movements
- Dystonia
- Athetosis

Complex or sustained movements
- Mannerisms
- Stereotypies
- Restless legs

*Source*: Jankovic J (1992) Diagnosis and classification of tics and Tourette syndrome. Advances in Neurology 58, 7–14.

such as symmetry, violent or sexual images or urges, and worries about losing control. Patients with isolated OCD typically have a single concern, which their symptoms coalesce around (i.e., contamination, cleanliness, or hygiene). Some investigators have argued that the obsessions and compulsions in TD + OCD are more sensory–motor in character, whereas those in OCD are more cognitive and affective (Miguel et al. 2001, Miguel et al. 2000).

Recent factor analytic studies have identified common subtypes of OCD including: pure obsessions, contamination, symmetry/ordering, and hoarding groups (Baer 1994, Cullen et al. 2007, Hasler et al. 2007, Leckman et al. 2003). Subtype information serves to identify and define unique clinical presentations. For example, the contamination group is least comorbid with other psychiatric disorders and is more responsive to both behavioral and pharmacological treatments, whereas the hoarding group appears less responsive to treatment.

Although there are no longitudinal studies regarding the course of co-occurring obsessive–compulsive symptoms in persons with TD, the natural course of OCD symptoms includes worsening in adolescence and adulthood whereas TS symptoms tend to decrease as patients transition into adolescence and adulthood.

### Relationship between TD and Commonly Co-occurring Symptoms

Research aimed at clarifying the relationship between TD and co-occurring conditions has yielded conflicting results. Some support a broad TD phenotype that includes numerous co-occurring conditions and symptoms (Comings 1995). Others support a circumscribed phenotype consistent with DSM-IV diagnostic criteria (Pauls et al. 1993). Despite the existence of divergent conceptualizations, there is general agreement that CTD (motor or vocal) is a milder form of TD and that some forms of OCD and ADHD are an alternative expression of the common genetic diathesis (LaBuda and Pauls 1993, Stewart et al. 2006). The relationship between TD and other psychiatric disorders (i.e., ODD, LD, MDD) is less clear. Some have argued that an ascertainment bias accounts for increased rates of other co-occurring conditions in TD (Pauls et al. 1993). Others argue that a common genetically based neurochemical abnormality underlies TD and various co-occurring conditions (Comings 2001).

### Differential Diagnosis

Tics disorders have many characteristics that differentiate them from other movement disorders (Jankovic 1992). Perhaps the most unique aspect of tics, in terms of differential diagnosis, is the presence of a childhood history of simple motor tics in the face. This presentation is not consistent with other movement disorders. Movement disorders such as chorea and dystonia are associated with continuous movements where as tics are intermittent. Other episodic, paroxysmal dyskinesias are more often characterized by choreiform and dystonic movements. Myoclonic movements and exaggerated startle responses are, like tics, brief and intermittent, but are usually large-muscle movements that occur in response to a patient-specific stimulus.

Complex tics can be more difficult to differentiate from other complex movements. In individuals with no clear-cut or simple motor tics, it may be difficult to differentiate complex motor tics or "camouflaged" tics (i.e., tics made to appear purposeful) from a mannerism, gesture, or stereotypy. Mannerisms or gestures typically lack the involuntary, repetitive, and stereotyped nature of tics. Stereotypies tend to occur more commonly (but not exclusively) in children and adults with developmental disabilities and mental retardation (Jankovic 1992). However, it is not uncommon in tertiary referral centers to treat developmentally disabled children and adults who present with both tics and stereotypies. It is also possible to have a tic disorder and another movement disorder. For example, tic movements can co-occur with dystonia. When tic symptoms have an atypical presentation, onset, course a consultation with a movement disorders expert is suggested.

## Etiology and Pathophysiology

### Genetic Factors

A greater concordance rate for monozygotic than dizygotic twins in studies of TD provides powerful evidence for the genetic etiology of TD. Segregation analysis of family study data has been used to identify the exact pattern of genetic transmission and the range of phenotypic expression of TD. Early studies identified TD as an autosomal dominant condition, however, recent studies have identified a complex pattern of inheritance that includes multiple genes and environmental factors. Linkage studies of TD, based on the autosomal dominant assumption, have not been successful. Candidate gene studies based on neurotransmitter and cortico-striato-thalamo-cortical (CSTC) circuit hypotheses have also been unsuccessful in identifying the TD gene(s). Recently, results from a large study which used a complex, new computer program to combine multiple data sets and thereby assess linkage has resulted in promising results.

#### Twin Studies

Evidence from twin studies suggests an important role for both genetic and nongenetic factors in the development of TD. Two large twin studies (Price et al. 1985, Hyde et al. 1992) and a follow-up study (Walkup et al. 1987) showed high concordance rates in monozygotic twins for TD and for tic disorders. In both of the studies, the concordance rate for TD in monozygotic twins was more than 50%. When calculated for the presence of TD in one twin and any tic disorder in the other, concordance rates approached 100%. The

concordance rate for monozygotic twins is also significantly higher than the concordance rate in dizygotic twins (Price et al. 1985), suggesting a powerful role for genetics in TD. However, twin studies have consistently identified significant differences in tic severity between twins in monozygotic pairs suggesting a role for nongenetic factors in the development of tic severity.

### Segregation Analyses and Models of Inheritance

There have been a number of TD family studies which have been subjected to segregation analysis. (Comings and Comings 1987, Eappen et al. 1993, LaBuda and Pauls 1993, Pauls et al. 1991, Pauls and Leckman 1986). In contrast to early studies, which suggested TD was an autosomal dominant, single major gene condition, more recent studies suggest a more complex pattern of inheritance such as a mixed model (i.e., one major gene with contributions from minor genes and the environment) (Walkup et al. 1996) and an unrestricted, nonMendelian model (Seuchter et al. 2000).

### Linkage Studies

Despite a large number of linkage studies, no TD gene has been identified to date. A number of hypotheses have been offered to explain the inability of the linkage studies to reliably identify the TD gene(s) (Pauls 1992, Wilke et al. 1992). Linkage data analytic methods require definition of model parameters including mode of inheritance, gene frequency, penetrance, and rates of phenocopies all of which are either unknown or debated (Cerullo et al. 2007). As a result, linkage analyses which assume an autosomal dominant model of inheritance and low gene frequency may not be accurate if the pattern of inheritance is more complex or the gene is more common (Seuchter et al. 2000, Walkup et al. 1996). Other problems include errors in phenotypic identification of affected individuals leading to both false-positive and false-negative diagnoses. Diagnosing moderate to severe TD can be relatively straightforward, but milder cases, or cases in which there is no direct, observable evidence of tics during the interview are difficult to reliably evaluate.

### Candidate Genes

Pursuing linkage at a specific site on the genome through the use of a candidate gene is another method for identifying the genetic locus of a given disorder. Choosing a candidate gene is often related to hypotheses regarding both the gene and the etiology of a given disorder. In TD, genes involved in the underlying neurobiology including CSTC circuit abnormalities, neurotransmitter systems (e.g., dopamine, serotonin, and the noradrenergic system) and synaptic proteins have been perceived as ideal candidate genes. Many candidate gene studies have utilized genes identified by the Human Genome Project. The vast majority of candidate gene studies have not found consistent associations (Cerullo et al. 2007, van de Wetering 1993). In the few positive studies, the candidate gene accounts for only a small portion of the risk (Grice et al. 1996) and none of these studies have been replicated.

### Chromosomal Abnormalities

Nonfamilial cases of a disorder where there is also an identified chromosomal abnormality suggest a causative association regarding the development of a disorder. Pedigree data suggest that chromosomal abnormalities occur more frequently in family members of TD probands and may be a fruitful area of study. The SLITRK1 gene, a promising candidate gene, was found near an inversion at chromosome 13q (Abelson et al. 2005). The SLTRK1 has shown an overlapping expression pattern in brain regions previously implicated in TD and has been associated with abnormal dendritic growth in neuronal cells (Abelson et al. 2005, Grados and Walkup 2006, Züchner et al. 2006). Although the SLTRK1 finding is helpful in advancing our understanding of gene-based neural correlates of TD, it is not a major casual gene and its specificity to TD has recently been called into question (Wendland et al. 2006).

#### *Tourette Syndrome Association International Genetics Consortium Sibpair Study*

Sibpair genetic studies offer a number of advantages over large family linkage studies or candidate gene studies. Sibpair studies do not require a specific hypothesis regarding mode of inheritance and gene frequency or a hypothesis regarding a specific genetic site's involvement. The sibpairs method assumes that the genetic material shared by two or more affected siblings should include the genetic material associated with the development of the disorder. Collecting sibpair data allows researchers to identify the genomic sites of increased sharing among all the affected sibpairs and in turn leads to a decrease in the number of sites likely to be associated with the condition under study. The sibpair method is less sensitive to misdiagnoses and modeling assumptions and has been successfully used to identify the multiple genes involved in juvenile-onset diabetes (Davies et al. 1994).

The first sibpairs study of TD identified two sites with maximum likelihood scores (MLS) of >2 (>99/100 chance of being true). The identified sites were on chromosome 4q and 8p (The Tourette Syndrome Association International Consortium for Genetics 1999). Although these results suggest that TD genetic material may be in these regions, MLS of >3 (>99/1000 chance of being true) are typically the threshold for meaningful significance in genetic studies due to the considerable potential for chance findings.

Subsequent to these findings, the Consortium conducted the largest genetic linkage study yet undertaken. In this study, independent sibpairs and separate multigenerational families were collectively examined ($N$ total = 2,040). Results demonstrated strong linkage to a region on chromosome 2p23.2 ($-\log p = 4.42$, $p = 3.8 \times 10^{-5}$) at marker D2S144 for both sibpairs and multigenerational relatives with Tourette's or chronic tic disorders (The Tourette Syndrome Association International Consortium for Genetics 2007). Further exploration of this genetic region is currently underway.

## Neurobiology of TD

Most speculation regarding sites of neurological dysfunction in tic disorders have focused on the basal ganglia (BG) and bidirectional connections between the frontal cortex and limbic system. Abnormalities in these structures, interconnections, or neurotransmitter substrates could readily cause the wide variety of motor, sensory–motor, cognitive, and affective symptoms seen in patients with TD (Cerullo et al. 2007, Singer and Walkup 1991). Elucidating the nature and location of neuroanatomical dysfunction in TD

is facilitated by sophisticated imaging methods, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emitted tomography (SPECT) as well as increasing access to high-quality postmortem brains. These techniques have revealed subtle abnormalities in the BG, cortical, and limbic regions of the brain in subjects with TD relative to controls. Despite the excitement of these initial findings, there is, to date, no characteristic anatomical abnormality that can be used for diagnosis.

## Neuroanatomical Abnormalities

Existing functional neuroimaging studies suggest that TD is broadly characterized by dorsal premotor and motor area cortical hyperactivity, BG hypometabolism and hypoperfusion, and paralimbic abnormalities (Butler et al. 2006). More specifically, TD is associated with decreased caudate and thalamic activity, coupled with increased activity in the lateral and medial premotor cortex, supplementary motor areas, anterior cingulate gyrus, dorsolateral-rostral prefrontal cortex, inferior parietal cortex, putamen, caudate, primary motor cortex, Broca's area, superior temporal gyrus, insula, and claustrum (Shavitt et al. 2006). Motor tics have been linked to excess thalamic excitation and/or impaired sensorimotor cortical inhibition (Cerullo et al. 2007, Stern et al. 2000). Vocal tics appear to be associated with activity in the post-rolandic language regions, insula, caudate, thalamus, and cerebellum (Stern et al. 2000).

Imaging studies have identified left–right asymmetry in the BG (i.e., larger left-sided BG structures) (Singer et al. 1993, Peterson et al. 1993, Peterson et al. 2003). Although MRI studies have demonstrated larger dorsolateral prefrontal regions in children with TD, these regions were smaller for adults with Tourette's. Interestingly, Bloch (2005) in a retrospective longitudinal magnetic resonance imaging (MRI) study (average follow-up interval = 7.5 years) demonstrated that caudate nucleus volumes were significantly and inversely correlated with the persistence of tic (and OCD) symptom severity in early adulthood, but not with severity at the time of initial evaluation. This finding may link tic and OCD symptom persistence in adulthood with morphological disturbances within the BG, but may also represent an adaptive rather than pathogenic process (Gerard and Peterson 2003).

Brain scans during voluntary tic suppression and the natural state may be another approach to identify regions of interest. Brain regions with large changes in signal intensity included the BG, thalamus, and cortical regions associated with attention-demanding tasks (Peterson et al. 1998). Functional neuroimaging studies have demonstrated that the deactivation of the areas in the ventral BG (i.e., putamen and globus pallidus) in addition to partial activation of the prefrontal cortex and dorsal BG (i.e., caudate nucleus) are involved in voluntary tic suppression (Shavit et al. 2006).

Imaging studies focused on identifying differences between males and females with TD document a lack of normal asymmetry in the globus pallidus in males, but not in females (Singer et al. 1998). Differences between males and females in corpus callosum morphology were not replicated in a comparison of subjects with TD only, TD + ADHD and matched controls (Zimmerman et al. 2000).

Anatomical studies of postmortem brain specimens have been limited by the few brains available. In a study of a single brain specimen, a pattern of immature cell development was noted in portions of the BG (Haber et al. 1986).

## Neural Circuitry Abnormalities

There is a growing body of evidence that supports the hypothesis that TD is caused by dysregulation of CSTC circuits. Impaired cortical inhibition of motor movements could be caused by decreased cortical activity resulting from brainstem input (Cerullo et al. 2007). Excess thalamic activity has also received considerable attention in the literature. Either hyperactivity of the direct pathway (i.e., striatum to globus pallidus interni (GPi)/substantia nigra pars reticula (SNpr) to the thalamus and cortex) or hypoactivity of the indirect pathway (i.e., striaturm to globus pallidus externa (GPe) to subthalamic nucleus to GPi/SNpr), could result in excess movement via disinhibition of thalamo-cortical motor pathways (Butler et al. 2006) (see Table 48–3 and Figure 48–1).

Several studies have demonstrated BG hypometabolism and hypoperfusion, which suggests indirect pathway dysfunction in TD. Despite this intriguing possibility, it has been argued that such a model cannot adequately account for the waxing and waning course of TD.

It has been proposed that by examining *matrisomes* (i.e., specific areas of functional homogeneity) researchers

**Table 48–3 Direct and Indirect Pathways of the BG**

| Pathway | Path | # inhibitory pathways (–) | Description | Dopamine receptors |
|---|---|---|---|---|
| Direct | striatum$^-$ →GPi/SNr$^-$ →thalamus$^+$ →cortex | 2 (even) | Cortical activity that excites cells in the striatum that participate in the direct pathway leads to inhibition of areas of the GPi and SNr, which in turn removes their tonic inhibition from the thalamus. (This removal of inhibition by inhibition is called "disinhibition".) | D1 (stimulatory) |
| Indirect | striatum$^-$ →GPe $^-$ →STN $^+$ →GPi/SNr$^-$ →thalamus$^+$ →cortex | 3 (odd) | In contrast, cortical activity that excites the striatal cells in the indirect pathway is thought to inhibit the thalamus (by inhibiting the disinhibition). | D2 (inhibitory) |

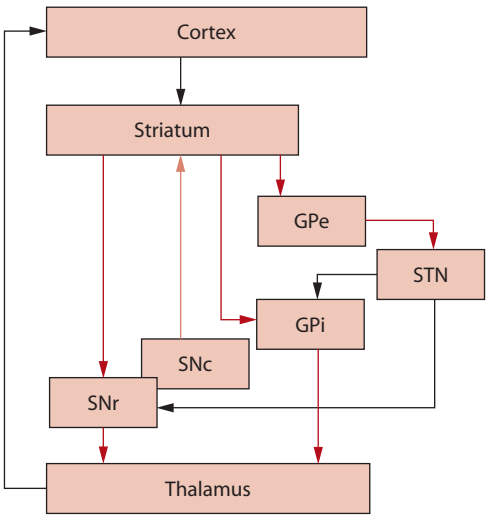



**Figure 48–1** *Neurotransmitters of the Direct and Indirect Pathways. Glutaminergic pathways are in black, dopmamine pathways are in light red, and GABA pathways are in dark red.*

may be able to further refine the CSTC model to account for the repetitious and stereotyped nature of tics as well as the waxing and waning course. One proposed hypothesis is that matrisomes become abnormally active resulting in the inhibition of the normal suppression of unwanted movment by the ventral BG. Stated differently the ventral BG inhibition results in disinhibition of the thalamo-cortical circuits leading to the production of tics (Mink 2006).

Electroencephalogram (EEG) studies are useful to understand the timing and sequence of cortical events. It is also is helpful in understanding the relationship of cortical and subcortical structures (i.e., cortical coherence). It has been shown that there is increased cortical coherence between sensorimotor areas and the prefrontal and mesial frontal cortex during voluntary tic suppression (Serrien et al. 2005). Enhanced frontomesial networks in TD may reflect a change in brain function associated with tic suppression.

## Neurochemical Abnormalities

A number of neurochemical abnormalities underlying TD have been proposed based on observations that some pharmacological agents reduce tics. Tic suppression with dopamine blockers such as haloperidol and alpha-adrenergic agonists such as clonidine have implicated the dopamine–acetylcholine and adrenergic systems, respectively. Similarly, the serotonin system has been implicated due to the positive therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) in patients with OCD. The specific role of various neurochemicals and related receptors in TD remains unclear. It is possible that they have a primary role or are secondary to abnormalities in circuitry or specific brain regions. In addition, a better understanding of the neurotransmitters involved in BG interconnection are leading to some improvement in conceptualizing how medication might impact brain functioning.

### *Dopamine*

Much of the support for the role of dopaminergic overactivity in TD stems from observations that pharmacological agents that diminish dopaminergic activity also decrease tic severity in patients with TD. The majority of speculation regarding the mechanism of dopaminergic overactivity in TD has focused on either dopamine excess or dopamine receptor hypersensitivity.

In the first proposed mechanism, excess dopamine activity (DA) causes hyperexcitation of thalamic neurons and hyperstimulation of the cortex. In contrast, the second proposed mechanism suggests that excess DA activity in the ventral tegemental area (VTA) causes increased activation in the frontal cortex via mesocortical pathways leading to diminished inhibition (Cerullo et al. 2007). However, enhanced DA activity could also result from striatal supersensitive postsynaptic receptors, dopamine hyperinervation, increased presynaptic DA production and release, elevated release without increased presynaptic production, or cortical DA abnormalities (Cerullo et al. 2007). PET and single-photon emission computed tomography (SPECT) studies of TD patients have found an increase in presynaptic dopamine, DA transporters, postsynaptic DA D2 receptors, and greater DA release in the BG relative to health controls (Singer et al. 2005).

A study by Minzer et al. (2004), identified increase densities of D2 and dopamine transporter (DAT) in the prefrontal cortex of patients with TD. Increased DA stimulation in the striatum and subsequently the thalamus and cortex may lead to tic symptoms. Additionally, D2 receptor activation on inhibitory neurons would in turn disinhibit pyramidal cells leading to striatal overstimulation and tic formation (Minzer et al. 2004).

### *Serotonin*

There are few definitive studies on the role of other neurochemical systems in TD. However, because pharmacological agents that impact serotonin activity are associated with benefits in OCD symptom severity the serotoninergic system has been implicated in TD. Further evidence comes from postmortem brain studies demonstrating trends toward decreases in levels of serotonin, its precursor tryptophan, and its primary metabolite 5-hydroxyindoleacetic acid, in subcortical regions (Anderson et al. 1992) in spite of normal levels in the cerebral cortex (Singer et al. 1990). These findings, in conjunction with presumably normal and significant serotoninergic innervation of the striatum, suggest possible abnormalities of the metabolism of serotonin and its precursor tryptophan (Albin 2006, Anderson et al. 1992).

### *Norepinephrine*

Following the success of alpha-2 agonists (i.e., clonidine) in reducing tic severity, there has been a surge in interest regarding norepinephrine in tic generation. To date, little is known about the precise role of norepinephrine in TD, however, noradrenergic fibers project widely to the prefrontal cortex from the locus ceruleus (Singer and Minzer 2003).

### *Glutamate*

It has been suggested that a primary role of dopamine in the striatum is to modulate glutamatergic corticostriatal neurotransmission. Moreover, it has been postulated that the close proximity of dopamanergic and glutamanergic terminals may create cross modulation of neurotransmission both pre and postsynaptically (Albin 2006). Additionally, animal studies have lead to hypotheses regarding the role of

excessive forebrain glutamate production and TD (McGrath et al. 2000).

### *Opiates*

The opioid system has a role in movement control and is localized within the BG. A preliminary postmortem brain study identified a decrease in levels of the opioid dynorphin A in striatal fibers projecting to the globus pallidus (Haber et al. 1986). The finding of decreased dynorphin in brain tissue has not been replicated and is difficult to accept in light of a report of elevated cerebrospinal fluid dynorphin A concentrations in patients with TD compared with control subjects (Leckman et al. 1988). The effectiveness of opiate antagonists in the treatment of patients with TD is mixed; some investigators report improvement (Sandyk 1985), and others report few responders (Erenberg and Lederman 1989).

## Social/Environmental Factors in the Etiology of TD

Evidence supporting a genetic etiology for TD is compelling; however, there is also evidence that environmental factors may interact with genes in tic symptom development, expression, and severity. Environmental factors associated with increases in symptom severity can occur throughout development and include prenatal development. Studies of Tourette's subjects show protracted vomiting by a subject's mother during pregnancy (Leckman et al. 1990) or prenatal maternal smoking (Mathews et al. 2006) are risk factors for increased tic severity. Due to the preponderance of males with TD, it has been postulated that intrauterine exposure to androgenic hormones may be a factor in the development of tics and in tic severity (Peterson et al. 1992). An open-label study of flutamide, an antiandrogenic hormone, identified significant, but transient, tic reduction in adult men, which suggests at least a partial role for sex hormones in tic severity (Peterson et al. 1994). Family-genetic and twin studies have also been useful for identifying factors associated with tic severity. For instance, twin studies of TD have identified an association between birth weight and tic severity (Hyde et al. 1992, Leckman et al. 1987). As such, differences in intrauterine environment may be associated with tic severity.

Environmental influences on tic symptoms can extend well beyond the pre- and perinatal time periods. For instance, it is not uncommon for persons with TD to identify specific environmental stimuli which elicit particular tic symptoms (e.g., a particular class in school), precede a bout of symptoms (e.g., increases in room temperature) or precede the development of a new tic symptom (e.g., post-nasal drip). Clinical wisdom also suggests that stressful or exciting life experiences may increase tic symptoms whereas soothing activities requiring or those requiring sustained attention tend to decrease tic symptoms.

In addition there is emerging behavioral theory which suggests that environmental factors can shape tic symptoms severity and complexity over time. This theoretical approach to tic symptom severity has been stimulated both by the apparent efficacy of behavioral treatment for tic severity and emerging findings in neuroscience suggesting that the neurocircuitry involved in TD has the capacity for adaptation/learning (Graybiel 2005).

## Autoimmunity and TD

In several reports (Kiessling et al. 1993, Swedo et al. 1994), the development of tics as well as obsessive–compulsive symptoms in children and adolescents have been associated with group A GABHS infection. The underlying mechanism is proposed to be similar to that involved in the development of Sydenham's chorea, in which antibodies developed in the course of infection cross-react with BG tissues, resulting in the characteristic choreiform movement disorder of Sydenham's. In Sydenham's chorea there was often a time lag of 1–9 months between acute infection and the development of the characteristic movement disorder. Patients with TD and OCD were described as having increases in tics and obsessive–compulsive symptoms in association with a recent history of a streptococcal infection or elevated antistrep antibodies. Case reports have also described subjects with the abrupt onset or exacerbation in symptoms occurring in parallel with antibody increases and with MRI changes in caudate size (Giedd et al. 1996). These cases have been given the acronym PANDAS (Swedo et al. 1998). However, two recent prospective longitudinal studies did not demonstrate a clear linkage between GABHS infection and the development of tic symptoms (Luo et al. 2004, Perrin et al. 2004). Moreover, a pilot study regarding the use of prophylactic penicillin to prevent neuropsychiatric exacerbations in children who had PANDAS was unsuccessful (Garvey et al. 1999). Finally, while penicillin and azithromycin prophylaxis was found to be effective in decreasing streptococcal infections and subsequent neuropsychiatric symptom exacerbations in children in a *PANDAS* subgroup (Snider et al. 2005), others have raised methodological concerns regarding relatively small sample size and the lack of a pill placebo control (Budman 2005).

As a result of recent findings, the PANDAS–TD link remains controversial. Skeptics suggest that the possibility of chance association is high given that tics, obsessive–compulsive symptoms, and streptococcal infections are common events in childhood. Despite some negative findings, more research is necessary to further explore the relationship between PANDAS and TD.

# Treatment

## Standard Approaches to Treatment

### Educate the Patient and Family about Tic Disorders

Given the difficulties patients and their families often experience before finding appropriate care, the initiation of treatment can be a delicate process. Many families are frightened by the implications of childhood "neuropsychiatric" disorders and often envision a grim prognosis. After the initial evaluation is complete it is essential to provide general education regarding the course, treatment, and prognosis for tic disorders to allay fears (Table 48–4). Most patients and families find comfort in knowing that the majority of persons with tics have consistent improvement in tic severity as they progress through adolescence and into adulthood. They are also pleased to hear that tic symptoms are often not physically or psychologically impairing and that only a small portion of patients are significantly disabled directly as a result of tic symptoms. In this regard, it is often helpful to

cite examples of sports personalities or other public figures that have identified themselves as having TD and are doing well both personally and professionally.

**Table 48–4 Goals of Treatment**

- Educate the patient and family about tics and co-occurring disorders.
- Create a hierarchy of the clinically impairing conditions.
- Treat the impairing conditions using somatic, psychological, and rehabilitative approaches.
- Aid in creating a supportive, yet challenging psychosocial milieu.

## Educate the Family about Co-occurring Disorders

Once issues and concerns regarding the tics are discussed and clarified, the focus shifts to the to co-occurring conditions. Treating co-occurring ADHD, LD, and OCD is especially important because they are often the most impairing conditions. The transition from discussing tic suppression to treating co-occurring problems is often complicated. Patients, families, and psychiatrists understandably are focused on tic symptoms. Tics are easily observable and a clear target for medication management. Co-occurring conditions, especially internalizing disorders, have less obvious symptoms and are more challenging to treat when identified. However, failure to correctly identify co-occurring conditions is perhaps the most common pitfall in TD treatment. Pursuing tic suppression without treating co-occurring conditions may not lead to optimum outcome.

## Create a Hierarchy of the Clinically Impairing Conditions

Creating the hierarchy of the most impairing conditions is the next major step in treatment. Psychiatrists typically create some clinical hierarchy for treatment as part of their initial formulation. In TD, it is essential that a conscious effort be made to formulate, organize, and create treatment hierarchies which appreciate the potential multitude of complex clinical presentations. For example, children with moderate tics, separation anxiety with associated school refusal should initially be considered for a SSRI for separation anxiety and behavioral treatment for school refusal rather than antipsychotics for tic suppression (The Research Units on Pediatric Psychopharmacology Anxiety Study Group 2001). This example is prioritized in this way because it is possible that successful treatment of anxiety may reduce substantial impairment and may have secondary effects on tic symptom severity.

## Treat the Impairing Conditions

This section focuses on the basic strategies for tic suppression followed by treatment of common co-occurring disorders. As most psychiatrists are familiar with the treatment for specific disorders particular emphasis is placed on the complexities of clinical management in this section.

### *Tic Suppression: Pharmacological*

Reduction in tic symptom severity rather than the elimination of tics is the goal of pharmacological intervention (see review: Scahill et al. 2006). Haloperidol, a typical antipsychotic has been used for more than 30 years to effectively suppress motor and phonic tics. Since haloperidol, several additional first and second generation antipsychotics have been shown to be effective in the treatment of tic symptoms including fluphenazine, pimozide and risperidone. In Europe, the substituted benzamides, sulpiride and tiapride, have also been shown to be useful.

As new antipsychotic medications become available, clinical trials for tic suppression invariably occur. Of the second generation antipsychotics, risperidone appears to be most effective. Evidence for the efficacy of olanzapine and quetiapine has been mixed. Open trials and case series with clozapine are few, but uniformly negative. Antipsychotics with unique mechanisms of action such as aripiprazole and tetrabenazine may also be effective for tic suppression. The major drawback of antipsychotic medications is the frequent and significant side effects. Given the limitations of antipsychotic medications, efforts to identify other tic-suppressing agents are ongoing. Other medications that demonstrate efficacy are described below.

**Haloperidol.** Haloperidol is a high-potency antipsychotic that preferentially blocks dopamine D2 receptors. Historically, haloperidol has been considered the treatment of choice for tic suppression. It is effective in a clear majority of patients, but relatively few patients appear to tolerate the side effects to obtain tic-suppressing benefits. Doses of haloperidol in the range of 1–4 mg/day are usually adequate for tic suppression. Starting dosages are low (0.25–0.5 mg/day), with small increases in dose (0.25–0.5 mg/day) every 5–7 days until tic symptoms are manageable. Haloperidol is usually given at bedtime, but with low doses, some patients may require twice-a-day dosing for optimal tic control.

Side effects include those commonly seen with antipsychotics, such as sedation, extrapyramidal symptoms including acute dystonic reactions and akathisia, weight gain, cognitive dulling, and anticholinergic side effects. There have also been reports of subtle, difficult to recognize, side effects with antipsychotics including clinical depression, separation anxiety, panic attacks, and school avoidance (Bruun 1988). Dose reduction is the most prudent response to side effects, although the addition of anticholinergic medications for the extrapyramidal symptoms can be useful.

Dose reduction in individuals who have been administered antipsychotics long-term may be complicated by withdrawal dyskinesias and significant tic worsening or rebound. Withdrawal dyskinesias are choreoathetoid movements of the orofacial region, trunk, and extremities that appear after antipsychotic discontinuation or dosage reduction and tend to resolve in 1–3 months. Tic worsening beyond pretreatment baseline level (i.e., rebound) can last up to 1–3 months after discontinuation or dose reduction. Withdrawal symptoms can be mitigated by slow downward adjustment of antipsychotic medications. Tardive dyskinesia, which is similar in character to withdrawal dyskinesia, most often develops during the course of treatment or is "unmasked" with dosage reductions. Due to relatively low dosages, rarely have cases of tardive dyskinesia been reported in patients with TD.

**Fluphenazine.** Fluphenazine has D2 and D1 receptor-blocking properties that may make it a more ideal

compound for tic suppression. In clinical trials fluphenazine has demonstrated similar efficacy for tic suppression, but milder side effects compared to other antipsychotics including haloperidol (Borison et al. 1982), even with long term treatment (Silay et al. 2004). Fluphenazine is slightly less potent than haloperidol so starting doses are somewhat higher (0.5–1 mg/day), as are the range of treatment doses (1.5–10 mg/day).

**Pimozide.** Pimozide is a potent and specific blocker of dopamine D2 receptors. Its side effect profile is generally similar to that of the other antipsychotics, although it appears to have fewer sedative and extrapyramidal side effects than haloperidol. In contrast to either haloperidol or fluphenazine, pimozide has calcium channel blocking properties that can affect cardiac conduction times. The co-administration of other medications that affect cardiac conduction, such as the tricyclic antidepressants (TCAs), is generally contraindicated. Baseline and follow-up electrocardiograms are important for adequate management of patients. Beginning treatment with a dose of 0.5–1 mg/day is prudent, although with pimozide's long half-life, every-other-day dosing can be used to decrease the effective daily dose. Increases of up to 1 mg/day can occur every 5–7 days until symptoms are controlled. Most patients experience clinical benefit with few side effects with doses of 2–6 mg/day. Higher doses can be associated with more side effects. Studies comparing pimozide and haloperidol in patients with TD document benefit for both but no clear superiority of one over the other (Sallee et al. 1997, Shapiro et al. 1989). Pimozide at 1–4 mg/day was also useful in decreasing tics and improving some aspects of cognition that are commonly impaired in ADHD (Sallee and Rock 1994). The potential to have impact on both TD and ADHD symptoms with a single drug is an advantage that pimozide may have over other antipsychotics.

**Sulpiride and Tiapride.** Both of these agents are substituted benzamides available only in Europe. Like pimozide, they are unique in their combination of relatively specific dopamine D2 receptor-blocking activity and the potential for reduced risk of extrapyramidal symptoms and tardive dyskinesia. Typical starting dosages of tiapride are 50–100 mg/day with typical daily dosages ranging 150–500 mg/day. Sulpiride is typically started at 100–200 mg/day with daily dosages ranging 200–1000 mg/day. While both agents have demonstrated efficacy in tic suppression (Eggers et al. 1988, Robertson et al. 1990), it is unlikely that these agents will become available in the US.

The second-generation antipsychotics appear to have replaced the first-generation antipsychotics as the mainstay of treatment for the psychotic disorders. Given the potentially lower risk for tardive dyskinesia, atypical antipsychotics have also been assessed for tic suppression in patients with TD. Recent concerns about weight gain and metabolic side effects have dampened the enthusiasm for these agents. To date there are only small controlled or open trials to guide the clinician in the use of these agents.

**Risperidone.** Risperidone has been effective in reducing tic symptom severity in two controlled trials (Dion et al. 2002, Scahill et al. 2003) and may have the added benefit of augmenting SSRIs in treating tic-related OCD (McDougle et al. 2000). Dose adjustment of risperidone is similar to other antipsychotics – start with low dose risperidone at 0.25–0.5 mg/day with upward adjustments every 5–7 days to 1–4 mg/day in single or divided doses until adequate tic suppression is achieved.

**Ziprasidone.** The side effects, especially weight gain, have dampened the enthusiasm for the second generation antipsychotics risperidone, olanzapine, and quetiapine. In a small double-blind placebo controlled pilot-study ($N = 8$) with children and adolescents, ziprasidone was found to be effective in reducing tic symptoms with dosages ranging 5–40 mg/day (Sallee et al. 2000). The mean daily dose at the end of treatment was 28 ± 10 mg/day. There were few side effects including a low incidence of weight gain, however, some subjects experienced somnolence and akathisia at higher dosages (i.e., 40 mg/day), which were resolved by lowering the dosage. Concern regarding the impact of ziprasidone on cardiac conduction times especially QTc was not supported in this trial (Sallee et al. 2000).

**Olanzapine.** Olanzapine in low doses does not appear to have the same tic-suppressing power as the first generation antipsychotics which may be related to olanzapine's relatively weak dopamine D2 blocking activity. An open-label study suggests that olanzapine can effectively control tic symptoms at final average dosages of 10.9 mg/day (Budman et al. 2001). Starting olanzapine dosages are typically 2.5–5.0 mg/day, with eventual daily dose ranging 2.5–12.5 mg/day.

**Quetiapine and Aripiprazole.** To date, only open case series of quetiapine and aripiprazole are available. When used, typical starting dosages for quetiapine are 25–50 mg/day, with typical daily dosages ranging 75–150 mg/day. As dosing strategies have changed since quietiapine was launched, higher doses may be more effective but have not been studied. As for aripirazole, starting dosages have ranged from are 2.5–5.0 mg/day, with typical daily dosages ranging 10–20 mg/day.

**Clonidine and Guanfacine.** There is a long history of the use of the alpha-adrenergic agonist clonidine for suppression of tics and ADHD symptoms. Whereas controlled trials have shown that some patients benefit with symptom reduction, the overall effect of clonidine for tic suppression and ADHD is more modest than that achieved with the "gold standards" (haloperidol and the stimulants, respectively) for these conditions (Goetz 1993). Given clonidine's mild side effect profile, it is often the first drug used for tic suppression, especially in those children with TD and ADHD.

Treatment is initiated at 0.025–0.05 mg/day and increased in increments of 0.025–0.05 mg/day every 3–5 days or as side effects (sedation) allow (Scahill et al. 2006). Usual effective treatment doses are in the range of 0.1–0.3 mg/day and are given in divided doses (4–6 hours apart). Higher doses are associated with side effects, primarily sedation, and are not necessarily more effective. The onset of action is slower for tic suppression (3–6 weeks) than for ADHD symptoms. Side effects, in addition to sedation, include irritability, headaches, decreased salivation, and hypotension and dizziness at higher doses. Interestingly, owing to clonidine's short half-life, some patients experience mild

withdrawal symptoms between doses. More severe rebound in autonomic activity and tics can occur if the medication is discontinued abruptly (Leckman et al. 1986). Some patients find that clonidine and guanfacine in the transdermal patch form provides a more stable clinical effect and avoids multiple doses each day. Children are usually stabilized on oral doses before they are switched to the patch. A rash at the site of the patch is a common complication of treatment.

Guanfacine is an alpha-2-adrenergic agonist that potentially offers greater benefit than clonidine for tic suppression because of differences in site of action, side effects, and duration of action. On the basis of animal models, it is hypothesized that guanfacine is likely to have a greater impact on attention without the significant sedation associated with the nonselective alpha-2-adrenergic agonist clonidine (Arnsten et al. 1988). Guanfacine's long half-life offers the advantage of twice-a-day dosing, which is more convenient than the multiple dosing required with clonidine (Scahill et al. 2001). Starting doses are 0.5 mg/day with increases of 0.5 mg every 5–7 days up to 3–4 mg/day.

**Benzodiazepines.** Benzodiazepines can be useful in decreasing co-occurring anxiety in patients with TD and as an adjunct to SSRIs for OCD in TD. In addition, clonazepam appears also to be somewhat useful in tic reduction for Tourette's and ADHD patients. In a small study examining the benefit of clonazepam as an adjunct to clonidine, dosages of 0.5–4 mg/day (in 2–3 divided doses) was associated with additional tic reduction in children and adolescents without deleterious effects on ADHD symptoms (Steingard et al. 1994). Because sedation is a significant side effect at these dosages, an extended titration phase of 3 to 6 months may be necessary. Similarly, a slow taper is required to avoid withdrawal symptoms (Goetz 1992). As clonazepine has a long half-life, once a day dosing is possible chronically.

**Pergolide.** Agonist activity on presynaptic dopamine receptors results in decreased dopamine release and may result in decreased tic severity in people with TD. A variety of dopamine agonists have been used in single case studies with mixed results. Pergolide, a mixed dopamine agonist used for treating Parkinson's disease and restless leg syndrome has recently been removed from the market due to concerns regarding the development of cardiac fibrosis. Small clinical trials demonstrated modest efficacy of pergolide for tic suppression (Gilbert et al. 2000, Gilbert et al. 2003).

**Other Somatic Treatments.** Case reports of successful electroconvulsive therapy (ECT) treatment in patients with TD have described significant co-occurring conditions including OCD and psychotic symptoms (Karadenizli et al. 2005, Trivedi et al. 2003) and exacerbations of TD concurrent with the onset of severe depression in adulthood (Rapoport et al. 1998). The effective use of ECT for appropriate indications (i.e., psychosis and severe depression) in people with TD should not be surprising and suggests ECT may be used successfully when TD is complicated by co-occurring conditions that are potentially responsive to ECT.

Repetitive transcranial magnetic stimulation (rTMS) has been used experimentally in OCD, depression and TD. Case reports in TD document that rTMS appears to be a safe procedure, but of variable efficacy (Chae et al. 2004, Orth et al. 2005, Mantovani et al. 2006). Trials that described minimal benefit used a short course (i.e., 1–2 treatments/2400 pulses) of 1HZ stimulation in the motor and premotor areas and led investigators to conclude that while rTMS may be a promising treatment, different approaches may be required to be effective (Orth et al. 2005). In a departure from previous trials, Mantovani et al. (2006) demonstrated good benefit using a longer course of treatment (i.e., 10 days/12,000 pulses) of 1HZ stimulation at a different site—the supplemental motor area.

**Infection and Autoimmune-Based Treatments.** Several treatment studies have been undertaken based on the hypothesis that some forms of TD or OCD may be an autoimmune reaction to Group A $\beta$-hemolytic streptococcal infection. Based on the beneficial effects of penicillin prophylaxis in preventing recurrences of rheumatic fever, a similar strategy was employed in a crossover design in subjects meeting criteria for PANDAS (Garvey et al. 1999). Garvey et al. (1999) found no differences in neuropsychiatric symptom improvement between the penicillin and placebo groups. However, these findings should be viewed with caution as there were several methodological flaws in this study including inadequate baseline assessment, incomplete prophylaxis in the PCN arm and carry over effects due to the crossover design. In regard to the later, penicillin given during the first "active" phase may have provided continued protection against streptococcal-triggered exacerbations in the second "placebo" phase. A second study of antibiotic prophylaxis used a longer but retrospective baseline and a parallel group design of two active agents but did not include a placebo arm so no conclusion about the antibiotic prophylaxis can be drawn from this study (Snider et al. 2005).

After small open trials with immunomodulatory treatments such as plasma exchange or intravenous immunoglobulin (IVIG), a larger trial comparing these methods to sham IVIG was undertaken (Perlmutter et al. 1999). At 1 month, the IVIG and plasma exchange groups demonstrated improvements in obsessive–compulsive symptoms. The plasma exchange group also demonstrated reductions in tic symptoms at one month. At one-year follow-up, symptoms remained improved from baseline on all measures for both the IVIG and plasma exchange groups, with the most meaningfully significant improvements in obsessive–compulsive and tic symptoms. Although this study is encouraging, there are a number of methodological problems that caution against the use of these treatments in clinical practice (Singer 1999). The most significant being a broken blind in the IVIG and placebo groups due to obvious active treatment side effects including nausea, vomiting, and headaches.

### *Tic Suppression: Nonpharmacological*

**Habit Reversal Training (HRT).** Although pharmacological interventions remain the first-line treatment for tic disorders, evidence suggests that HRT is effective for tic suppression (Himle et al. 2006). Behavioral interventions for tics combine anecdotal reports from adults with TD regarding the use of particular strategies to decrease tic severity and principles of learning theory. One of the great benefits of behavioral treatment is their compatibility with medication and other psychosocial treatments such as exposure and

response prevention for OCD. Behavioral treatments for tic management can be used as a first-line treatment, an alternative to medication or as an adjunct to medication in those who have had a partial response or cannot tolerate higher or more effective doses of tic suppressing medication.

From the perspective of HRT, tics can be triggered, exacerbated and potentially maintained by environmental stimuli such as specific settings, interpersonal interactions, emotions, cognitions, and other internal experiences, consistent with the stimulus-response pattern of classical conditioning. Furthermore, as tics are known to momentarily relieve the discomfort associated with premonitory sensation, the tic behavior can thus be shaped and elaborated via negative reinforcement.

HRT was initially described by Azrin and Nunn in 1973. The two principle components of HRT are awareness training and competing response training. Awareness training involves learning to become aware of and eventually monitor premonitory urges (e.g, building tension, tickle, itch, etc.) and subsequent tic behavior (e.g., head shaking). Competing response training involves learning to perform an alternative behavior utilizing the same muscle groups used to carry out the tic. An appropriate competing response is one that is socially acceptable, relatively inconspicuous, does not cause pain, and can be held for at least a minute or until the urge dissipates. The purpose of HRT is to disrupt reinforcement cycles by performing an alterative and less conspicuous behavior (i.e., competing response) when facing triggering stimuli. Once the reinforcement cycles are interrupted and tics decrease in frequency and severity, the voluntary competing response can be stopped. To illustrate, a patient with a premonitory sensation in the shoulder would voluntarily tense the opposing shoulder muscle (competing response) for a minute or until the urge dissipates. HRT often involves additional steps, such as creating a hierarchy of tics to be targeted as well as providing relaxation training and cognitive restructuring. A functional analysis typically accompanies HRT to identify antecedents and consequences that reinforce or maintain tic symptoms.

Published clinical trials of HRT (approximately 200 patients in total) evidence marked reductions in tic frequency with treatment gains maintained at follow-up. Interestingly, patients also report decreases in premonitory urges with successful treatment. As a result of these studies HRT has been classified as "probably efficacious" according to the American Psychological Association's 1995 Task Force on Promotion and Dissemination of Psychological Procedures (see Carr and Chong 2005). Although evidence is accumulating to support the efficacy of HRT, the variability in subject recruitment, interventions and assessment of outcome suggest larger and more definitive studies are needed.

There are no published, systematic studies of other psychosocial interventions for tic reduction in patients with TD. Case reports of *massed practice*—repeating the tic voluntarily over and over until severity decreases—have not demonstrated efficacy. Most current treatment efforts are based on a combination of traditional psychosocial interventions, clinical judgment, and psychoeducation. Behavioral training in the form of neurofeedback is an emerging treatment that has yet to establish clinical utility.

**Individual and Family Psychotherapy.** Individual psychotherapy can be useful for support, development of awareness, or addressing personal and interpersonal problems more effectively. Appropriate areas for psychosocial intervention are best identified by a functional assessment and targeting domains of impairment.

Family therapy can be useful when families have problems adapting, interacting and communicating. Although psychoeducation is beneficial for most families, some have problems fully appreciating the involuntary nature of tics and may inadvertently create a harsh or critical environment. Parents may also inadvertently lower general expectations due to confusion regarding what constitutes tic symptoms. Variability among professionals regarding what constitutes tic related behaviors leads some parents to conceptualize all maladaptive behaviors as involuntary and therefore fail to hold their children responsible for non-tic behaviors. Parents also decrease expectations in an effort to minimize stress on their child with tic disorders. For children with TD to do well, they need support from their family to develop effective self-control in areas not affected by TD so that optimal adaptation can occur.

In newly diagnosed adults, psychotherapy oriented toward adequate adjustment to the diagnosis is important but not always easy. Adult patients frequently experience a mixture of relief and anger or resentment related to their past experiences with inadequate assessment, incorrect diagnosis and discrimination. Severely affected adults may also need psychotherapy to address the psychological and psychosocial difficulties related to having a chronic illness.

**Other Psychosocial Interventions.** For children, active intervention at school is essential to create a supportive, yet challenging, academic and social environment. Efforts to educate teachers, principals, and other students can result in increased awareness of TD and tolerance of the child's symptoms.

Many young adults find TD support and social groups important for interpersonal contact and continued development. Efforts to keep people with TD working are important, as are rehabilitation efforts for those who are not working. Finding housing and obtaining disability or public assistance may be necessary for the most disabled patients with TD.

Perhaps the most useful educational intervention is to make the patient aware of the Tourette Syndrome Association, both national and local chapters. This and other self-help groups can be useful as a source of support and education for patients, families, and psychiatrists.

**Genetic Counseling.** One question commonly asked by young adults with TD is their risk for having a child with TD. Given the fact that many who present for clinical attention with TD have co-occurring conditions, genetic counseling of people with TS should include not only the risk for TD but also the risk for other neuropsychiatric problems such as ADHD or OCD. As the base rate of neuropsychiatric disorders is high, it is not uncommon for spouses of people with TD to also have a neuropsychiatric disorder. In providing counseling to these couples it is important that genetic counseling be conducted in regard to TD as well as other conditions that may be present in the young couple's history.

## Treatment of Co-occurring Psychiatric Disorders in TD

This section focuses on the special complexities of treating psychiatric disorders such as ADHD and OCD that commonly co-occur with TD. In general, the treatment approaches for ADHD and OCD are similar in patients with and without TD, with some notable differences. The details of the specific treatment approaches for ADHD and OCD in patients without co-occurring TD are addressed in separate chapters.

## Treatment of ADHD

### Nonpharmacological Approaches

The nonpharmacological approaches to ADHD in TD are similar to approaches in children without TD. The presence of a structured environment with consistent and positive behavioral management both at home and at school can produce significant improvement in ADHD symptoms. There are programs available for children with ADHD that include intensive and specific behavioral approaches. In spite of advances in nonpharmacological treatments, some families and psychiatrists, for a variety of reasons, find developing and implementing behavioral programs for children with ADHD difficult and do not take full advantage of the benefits of behavioral approaches.

### Pharmacological Approaches

The major challenge in the treatment of ADHD in TD is the perceived risk of substantial tic exacerbations from the stimulant medication.

In the early 1970s, a number of reports of induction or exacerbation of tics by stimulant medications raised concerns that stimulants could be causing tics *de novo* or that increases in tic severity would endure even if stimulant medications were discontinued. Others noted, however, that tic induction or exacerbation was relatively infrequent and that the beneficial effects in some patients with TD outweighed any negative impact on tic severity (Law and Schachar 1999, Sanchez-Ramos and Weiner 1993).

Results of short and long-term controlled trials with stimulants in TD are positive and support a role for stimulants in patients with TD plus ADHD (Gadow et al. 1995, Gadow and Sverd 1990, The Tourette Syndrome Study Group 2002). In the most recent study, children with ADHD and a chronic tic disorder ($N$ = 137) were randomly assigned to clonidine alone, methylphenidate alone, clonidine plus methylphenidate or placebo for the treatment of their ADHD. The results suggest that all the active treatments were superior to placebo with the combination treatment being the most effective. Moreover, the percentage of children with worsening of tics was similar across treatment conditions (20% for methylphenidate alone, 26% for clonidine alone, 22% for placebo), and tic severity lessened across all active treatment groups. Other side effects were predictable with sedation commonly associated with clonidine treatment (The Tourette Syndrome Study Group 2002). Given the controversy regarding the coadministration of clonidine and methylphenidate (Wilens et al. 1999) it is important to note the absence of cardiac side effects in children on combined medication.

Stimulant medication is currently the treatment of choice for children with tics and ADHD. For those who experience tic worsening the combination of stimulants plus alpha agonists are recommended (Pliszka et al. 2006). In light of the above, informed consent prior to initiating stimulant medication should include information regarding the risks for new onset of tics or tic exacerbations. In Table 48–5 is a partial listing of topics that might be useful to address when consenting patient and parents about stimulant treatment. Alternatives to stimulant medication for ADHD are described below.

**Table 48–5 Consent for Stimulants**

- Tics go up and down, usually increase with excitement and stress, and decrease with calm focused activity. Such changes will likely continue to occur while on stimulant medications. Such tic worsening should not be attributed to medication.
- Predictable exacerbation each year–starting and ending school, winter holidays, vacations, parties, etc. Tic increases after starting stimulants at these times may be better attributed to life events rather than medication.
- Over the lifetime tics tend to decrease in mid to late teens.
- It is possible that there is greater risk for tic exacerbations on stimulants in younger children than teens.
- Controlled trials demonstrate that tics go up, go down, or stay the same with stimulant treatment. In approximately 20% of children, tics will increase regardless of treatment with medication or placebo. There is no clear association as previously thought.
- Long-term studies suggest that when tics do appear to increase on stimulants there is a reasonable chance they are reversible with discontinuation of stimulant medication.
- Parents must understand the following: "If you are willing to start your child on stimulants, you need to understand that your child's tics may go up on stimulants and not come down with medication discontinuation. Or if there are no tics now, they may start and continue. This is very unfortunate. It could be related to medication but it might have been the natural course of your child's disorder."
- Doctors should understand the following: Do not start if parents are not really prepared to deal with an increase in tic severity. It is better for parents to not start stimulant medication until gaining knowledge, experience, and perspective while under your care and can make a conscious risk-benefits decision.

#### *Clonidine and Guanfacine*

Clonidine and guanfacine are alpha-2 adrenergic agonists used for tic suppression and for ADHD alone and in combination with stimulants (The Tourette Syndrome Study Group 2002). Both clonidine and guanfacine have demonstrated efficacy for ADHD in TD (The Tourette Syndrome Study Group 2002, Scahill et al. 2001, respectively). Dosing of the alpha agonists for ADHD is similar to that for tic suppression and is described above.

#### *Atomoxetine*

Atomoxetine is a serotonin–norepinephrine reuptake inhibitor (SNRI) that has been demonstrated effective (Kratochvil et al. 2006) and is approved for the treatment of ADHD in children. Despite a handful of case studies showing an increase in tics on atomoxetine, a double-blind placebo controlled study of children and adolescents with ADHD and TD or CTD demonstrated that atomoxetine resulted

in reduction of both ADHD symptoms and tic severity (Allen et al. 2005). Atomoxetine is considered a safe and effective alternative to stimulants, and is more often prescribed over clonidine for youth with ADHD + tics (Johnston et al. 2006). Atomoxetine is dosed on a mg/kg/day basis or on a total daily dose basis for older teens and adults. Good ADHD control may take up to 4–6 weeks of treatment. Some clinicians combine atomoxetine and stimulants to improve overall ADHD control.

#### *Desipramine*

Desipramine is a tricyclic antidepressant with prominent noradrenergic activity that has been noted to improve attention and concentration in children and adolescents with TD plus ADHD (Spencer et al. 2002). Desipramine was superior to placebo in reducing inattention and hyperactivity/impulsivity (71% versus 0%) and motor and phonic tics (58% versus 5%). Symptom improvement is often significant with lower doses than needed for depression. Side effects are generally limited. The cardiac side effects of increased heart rate and elevation in blood pressure are usually not clinically significant (Wilens et al. 1993); however, reports of sudden death in children and adolescents (Riddle et al. 1993) have resulted in marked reductions nationally in the use of desipramine in this population.

#### *Nortriptyline*

Nortriptyline is another trycyclic antidepressant with some noradrenergic activity that has been used for the treatment of ADHD. A chart review of youth with ADHD + tics treated with nortriptyline documented moderate to marked improvement in both ADHD and tics (Wilens et al. 1993). Although the concern regarding sudden death is less with nortriptyline than with desipramine, it is prudent to obtain baseline and follow-up electrocardiograms.

#### *Bupropion*

Bupropion is often used for the treatment of ADHD in children given its long half-life and dopaminergic activity. There is little clinical data supporting its efficacy in ADHD or in ADHD with tics. Children may experience an exacerbation of tics on bupropion (Spencer et al. 1993), but caution is warranted regarding over-interpreting this finding given the lack of a controlled comparison with placebo in this report.

## Treatment of OCD

### Nonpharmacological Approaches

The positive role of cognitive–behavioral treatments of OCD is well established in children and adults. Three randomized controlled trials have emerged providing empirical support for the efficacy of cognitive–behavioral therapy (CBT) in youth (Barrett et al. 2004, de Haan et al. 1998, Pediatric OCD Treatment Study Team 2004), and CBT with exposure and response prevention is considered the standard of care for pediatric OCD (Franklin et al. 2002). Existing reports of children comorbid with OCD and tics show a poor response to SSRI monotherapy and suggest that CBT or CBT plus medication should be recommended for these youngsters (March et al. 2007). The only specific report of CBT or other nonpharmacological treatments of OCD in children with TD is a case study reporting success of exposure and response prevention in reducing tics and OCD symptoms (Woods et al. 2000). CBT for OCD and HRT for tics share the same conceptual framework and many of the same treatment elements. The use of these treatments in tandem for patients with TD and OCD may be useful.

### Pharmacological Treatments

The number of agents available for the treatment of OCD in patients with and without TD is increasing. SSRIs (e.g., fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram) are recommended as the first line. Clomipramine, a tricyclic antidepressant, is often used and may be particularly useful when patients do not tolerate the SSRIs. The choice of sertonergic agent depends on the side effect profile, the potential drug interactions, and the psychiatrist's familiarity with the drug. See Chapter 71 for a detailed description of pharmacological treatments for OCD. As the response to antiobsessional medications for patients with tics and OCD is less optimal compared to individuals with OCD alone (Geller et al. 2003, March et al. 2007), augmentation strategies with antipsychotics are recommended when patients have suboptimal response to initial treatment (McDougle et al. 1994, 2000).

The SSRIs have generally mild and somewhat similar side effect profiles. Despite the similarities among these medications, they are chemically different, especially in their metabolic pathway and patterns of drug interaction. The patterns of drug interaction are especially important because in children with complex presentations, multiple drugs are often used simultaneously. The potential for drug interactions with the SSRIs requires medication choices to be based on specific characteristics of the patient and the metabolic and drug interaction profile of the medication. Reports of a small increase in the potential for suicidal ideation and behavior while taking antidepressants has resulted in a warning in the product labeling for all antidepressants. For OCD the magnitude of the benefit outweighs this small risk (Bridge et al. 2007).

## Treatment-Refractory Cases

Strategies for approaching two types of treatment-refractory symptoms are discussed here: (1) patients who are truly treatment-refractory, despite conventional and heroic treatments, and present with severe and impairing symptoms of TD and OCD and (2) patients, often children, who are clinically complex, enigmatic, and whose impairment is disproportionally greater than tic, obsessive–compulsive, or ADHD symptoms would suggest.

### Treatment-Refractory Tics

Perhaps the most important "treatment" in patients with severe, incapacitating tics is a full clinical re-evaluation to assess the adequacy of previous evaluations and treatment efforts. Inadequate prior evaluations and treatment are not uncommon in treatment-refractory patients.

Three alternative treatment strategies are available for truly treatment-refractory tics. When a single tic or a few tics are refractory and impairing, the injection of botulinum toxin into the specific muscle group can be helpful. It is essential to collaborate with a neurologist experienced in using botulinum toxin (Jankovic 1994). This strategy is

most useful for painful, dystonic tics as well as those that are socially conspicuous and disabling. Botulinum toxin has a long duration of action, but the effect typically decreases 2–4 months post-injection; thus repeated injections may be necessary. Side effects are few, but may include excessive weakness in the affected muscle. Some patients reported a subsequent loss of premonitory urges following treatment.

There is a small and developing literature regarding the use of neurosurgical approaches to reduce tic severity. In the past 40 years, over 60 case reports have described ablative surgical approaches for reducing tic severity most often with limited success (Temel et al. 2004). As the exact pathophysiology of TS is unknown the surgical targets chosen have been based on conjecture and vary considerably. The patients described in these case series have invariably been severe, often suffering from significant co-occurring conditions and refractory to conventional treatments. At this time, there is little to no evidence, supporting the use of ablative surgical treatments for reducing tic severity.

More recently, there have been a small number of case reports describing the use of deep brain stimulation (DBS) for reducing tic severity (Neimat et al. 2006). DBS has been used successfully and is indicated for essential tremor, Parkinson's disease, some forms of epilepsy and more recently in dystonia, including childhood onset dystonia. Experimental uses have been reported in treatment refractory OCD (Greenberg et al. 2006) and depression (Mayberg et al. 2005). Although the actual number of reported TD cases has been few, media reports of "miraculous" outcomes have intensified the interest in this treatment modality. Much remains unknown about DBS for reducing tic severity including the mechanism by which brain stimulation reduces tic severity, the best target for stimulation, the optimum stimulation settings, the impact on co-occurring conditions, the minimum age for this approach and the potential for unusual behavioral side effects (Flaherty et al. 2005). As TD is often most severe in latency and early adolescence with improvement for the majority of patients in late teens and early 20s, it has been proposed that DBS be restricted to those in their mid-20s who have severe, persistent or worsening symptoms (Mink et al. 2006). Others have advocated that DBS should not be restricted from younger patients with severe TD who are significantly disabled, have been refractory to all forms of conventional treatment and are actively accumulating academic, occupational and social impairment. This is particularly true if the risks for neurosurgical side effects are known and can be included in the risk benefit ratio (Poysky and Jimenez-Shahed 2007). At this time it is recommended that patients considering DBS for severe TD undergo this procedure at academic centers of excellence that include experts in the assessment and treatment of TD (neurology and psychiatry) as well as experienced neurosurgical teams (Mink et al. 2006).

## Treatment-Refractory OCD

A similarly thorough and exhaustive re-evaluation is critical for patients with OCD and TD who present as treatment-refractory. Diagnostic re-evaluation focuses on considering all possible disabling psychiatric disorders and their hierarchical organization based on impairment.

Pharmacological re-evaluation is especially critical because there are an increasing number of new medications and potential medication combinations. Rather than repeatedly changing from one antiobsessional agent to another, consideration should be given to augmentation strategies. Augmentation often takes less time and may offer synergistic benefits. As noted above low-dose antipsychotic augmentation is the best first choice. Lithium and thyroid hormone are proven augmenters of antidepressants for depression, yet neither is proven as effective in OCD. Due to the frequent overlap of OCD and major depression, lithium or thyroid augmentation may be the next best choice especially if depression is prominent in the presentation. Lithium or thyroid hormone can be added to the SSRI or to the SSRI plus antipsychotic combination. Other augmenting agents are supported only by anecdotal evidence.

Treatment-refractory or malignant OCD has been the psychiatric disorder most frequently successfully treated with neurosurgical interventions in the modern era. Whereas it is a major treatment intervention, the surgical approaches are somewhat better defined, and the outcome in severe cases can be positive. Also, medical centers are available that specialize in the pre-surgical workup and the neurosurgical procedure (Mindus and Jenike 1992).

## Clinically Complex Patients

Patients can become clinically complex when additional diagnoses are present or when otherwise straightforward treatments are challenging to implement. Patients may be significantly impaired and present diagnostic dilemmas even without severe tics or OCD symptoms.

### Diagnosis

In clinically complex patients, the diagnostic challenge is not an accurate assessment of tics, ADHD, OCD symptoms, or LD, although this is important. For complex patients, the diagnostic goal is to identify the presence of other conditions or factors that may not be addressed by the current treatment or may actually be interferring with the current treatment approach. It is often undiagnosed psychiatric conditions (beyond TD, OCD, ADHD, and LD) that ultimately culminate in treatment failures (see Table 48–1).

### Treatment Implementation

Psychiatrists with complex patients may consider altering their treatment approach to ensure comprehensive care. Developing a relationship with the patient and other major figures in the patient's life is necessary in order to appreciate the entire clinical picture and to effectively orchestrate treatment. Because it is increasingly difficult for the psychiatrist to be as involved as necessary, problems with poorly coordinated team efforts and the psychiatrist's lack of awareness of important clinical issues can have a negative impact on the treatment of a patient.

Experience in tertiary care centers suggests that expanded time with the parents is a critically important approach to care. Psychiatrists who form a treatment partnership with families, respecting and addressing their concerns, educating them about TD, training them to evaluate and manage complex behaviors, and empowering them to be an effective advocate for their child, are providing optimal care. In working directly with families, the collection of important information regarding the family's and patient's functioning is direct and regular, and often small, but

targeted interventions can produce changes in family functioning that have a positive ripple effect throughout the life of the child. Although focusing on the family will not make all complex patients with TD easier to treat, less than adequate contact will certainly create barriers to clinical care.

### Pharmacological Treatment Dilemmas

It is often difficult to get accurate information from young patients regarding treatment response and side effects. Children, parents, and psychiatrists, despite adequate collaboration, may differentially conceptualize target symptoms, side effect profiles, and what constitutes a positive clinical response. Reporting bias as a result of ambiguity makes all but the most robust clinical responses difficult to observe. A lack of a clinical response in complex patients may be related to inadequately monitoring medication effects and/or inadequate treatment trials (Walkup 1995).

Clinically complex patients may not respond robustly to a particular medication and may require multiple medication trials to identify medications or combinations that offer maximal benefit. Sequential treatment trials are difficult for children and families looking for a single powerful intervention. However, optimal benefit in clinically complex patients usually requires sequential trials, medication combinations, and combined medication and psychosocial interventions. Increased treatment complexity can result in an added risk of confusion, which is minimized by an excellent communication among patient–family–psychiatrist.

For psychiatrists, the continued proliferation of psychotropic medications can result in less expertise regarding the range of medication-specific clinical effects and side effects. In clinically complex patients, the prescription of unfamiliar medications may be necessary but may add to the risk that a trial will be discontinued prematurely because of doubt about a side effect. In addition, unusual side effects such as apathy or disinhibition syndromes (Hoehn-Saric et al. 1990, 1991) seen in some patients receiving specific SSRIs, may go unnoticed and add to clinical morbidity.

Pharmacological interventions offer great promise for treating TD. However, clinical experience suggests that building excellent diagnostic skills, creating relationships with the patient and family, and developing a keen eye for effects and side effects are necessary for benefits to be maximized. Less intensive efforts may make patients appear more complex than necessary.

## Conclusion

TD and the other tic disorders are model neuropsychiatric disorders with childhood onset. Many of the research efforts in the clinical and basic science of TD, outlined in this chapter, have set a standard for research efforts in other childhood neuropsychiatric disorders. Future research efforts will continue to focus on identifying the basic genetic and neurobiological mechanisms in TD as well as the complex prevention and rehabilitation efforts necessary to minimize morbidity and maximize long-term functioning.

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CHAPTER

# 49 Childhood Disorders: Elimination Disorders and Childhood Anxiety Disorders

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Enuresis (Not Due to a Medical Condition)
Encopresis
Separation Anxiety Disorder
Selective Mutism

## Enuresis

### Definition

Functional enuresis is usually defined as the intentional or involuntary passage of urine into bed or clothes in the absence of any identified physical abnormality in children older than 4 years of age (see the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), criteria for enuresis). Although there is no good evidence that the condition is primarily psychogenic, it is often associated with a psychiatric disorder, and enuretic children are frequently referred to mental health services for treatment.

### Course and Natural History

The acquisition of urinary continence at night is the end stage of a fairly consistent developmental sequence. Bowel control during sleep marks the beginning of this process and is followed by bowel control during waking hours. Bladder control during the day occurs soon after and finally, after a variable interval, nighttime bladder control is achieved. Most children achieve this final stage by the age of 36 months. With increasing age, the likelihood of spontaneous recovery from enuresis becomes less (Oppel et al. 1968), so that, for instance, 40% of 2-year-olds with enuresis become dry in the next year and 20% of enuretic 3-year-olds become dry before age 4 years, but only 6% of enuretic 4-year-olds become dry in the following year. The chronic nature of the condition is further shown in the study by Rutter et al. (1973), in which only 1.5% of 5-year-old bed wetters became dry during the next 2 years. In a recent epidemiologic study, at 7.5 years, 15.5% of children were found to still wet the bed, but most wet once a week or less. Only 2.6% met DSM-IV-TR criteria of Nocturnal Enuresis (wetting at least twice a week). Both daytime wetting and bed-wetting was found in 3.3% of children, with 2.3% having both daytime soiling and bed-wetting (Butler et al. 2005).

Nocturnal enuresis is as common in boys as girls until the age of 5 years, but by age 11 years, boys outnumber girls 2:1 (Oppel et al. 1968, Rutter et al. 1973, Essen and Peckham 1976). Not until the age of 8 years do boys achieve the same levels of nighttime continence that are seen in girls by the age of 5 years (Verhulst et al. 1985). This appears to be due to the slower physiological maturation in boys. In addition, the increased incidence of secondary enuresis (occurring after an initial 1-year period of acquired continence) in boys further affects the sex ratio seen in later childhood. Daytime enuresis occurs more commonly in girls (Blomfield and Douglas 1956, Hallgren 1956, Jarvelin et al. 1988) and is associated with higher rates of psychiatric disturbance (Rutter et al. 1973). Recent approaches to classification (Butler et al. 2006) have strayed from the primary/secondary distinction in favor of

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**DSM-IV-TR Criteria**

**Enuresis (Not Due to a Medical Condition)**

A. Repeated voiding of urine into bed or clothes (whether involuntary or intentional).

B. The behavior is clinically significant as manifested by either a frequency of twice a week for at least 3 consecutive months or the presence of clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning.

C. Chronological age is at least 5 years (or equivalent developmental level).

D. The behavior is not due exclusively to the direct physiological effect of a substance (e.g., a diuretic) or a general medical condition (e.g., diabetes, spina bifida, a seizure disorder).

*Specify* type:

**Nocturnal only:** passage of urine only during nighttime sleep

**Diurnal only:** passage of urine during waking hours

**Nocturnal and diurnal:** a combination of the two subtypes above

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seeing nocturnal enuresis as mono- or polysymptomatic (i.e., associated with daytime indicators of bladder dysfunction, such as urgency or increased frequency).

## Etiology and Pathophysiology

Identifying a cause for enuresis is not a simple task despite numerous descriptions of correlations or associations between enuresis and a wide variety of biological and psychosocial factors. It has been suggested (Butler and Holland 2000) that there are 3 processes that alone or in combination can engender various forms of enuresis: (1) lack of arginine vasopressin release during sleep (which would normally decrease urine production), (2) overactivity of the bladder (uninhibited bladder contractions) or low functional bladder capacity (e.g., volume of urine voided after the child has postponed urination for as long as possible), and (3) inability of the child to wake up in response to sensations of a full bladder.

Biological factors described include a structural pathological condition or infection of the urinary tract (or both), low functional bladder capacity, abnormal antidiuretic hormone (ADH) secretion, abnormal depth of sleep, genetic predisposition, and developmental delay. Evidence has also been found for sympathetic hyperactivity (Dundaroz et al. 2001a) and delayed organ maturation as seen by delay in ossification (Dundaroz et al. 2001b). Touchette et al. (2005) have demonstrated an association between enuresis and developmental delay with impaired acquisition of gross motor (sitting/crawling) and language milestones in future bed-wetters.

Obstructive lesions of the urinary outflow tract, which can cause urinary tract infection (UTI) as well as enuresis, have been thought to be important, with a high prevalence of such abnormalities seen in enuretic children referred to urologic clinics (Cohen 1975). This degree of association is not seen at less specialized pediatric centers, however, and most studies linking urinary outflow obstruction to enuresis are methodologically flawed (Shaffer et al. 1979). Structural causes for enuresis should be considered the exception rather than the rule (Sorotzkin 1984).

The association between UTI and enuresis has been demonstrated in two main ways. UTI has been found to occur frequently in children, especially girls, and a large proportion (85%) of them have been shown to have nocturnal enuresis (Savage et al. 1969). Also, in 10% of bed-wetting girls, urinalysis results show evidence of bacterial infection (Dodge et al. 1970). The consensus is that as treating the infection rarely stops the bed-wetting; UTI is probably a result rather than a cause of enuresis (Forsythe and Redmond 1974).

The concept that children with enuresis have low functional bladder capacities has been widely promoted (Starfield 1967). Shaffer et al. (1984) found a functional bladder capacity one standard deviation lower than expected in 55% of a sample of enuretic children in school clinics. Although low functional capacity may predispose the child to enuresis, successful behavioral treatment does not appear to increase that capacity. It seems rather that in treated individuals, the sensation of a full (small) bladder promotes waking to pass urine so that enuresis does not occur (Fielding 1980). Reduction of nocturnal secretion of ADH has been described in a small number of children with enuresis (Norgaard et al. 1985, Rittig et al. 1989). This deficiency may produce excessive amounts of dilute urine during the night and overwhelming bladder capacity causing enuresis. Several mechanisms are associated with enuresis including increased nocturnal urine volume, small nocturnal functional bladder capacity, increased spontaneous bladder contractions, and the inability to arouse to the stimulus of a large and/or contracting bladder. This may identify two main groups of children with enuresis—those who demonstrate nocturnal spontaneous bladder contractions (detrusor dependent enuresis) and those with nocturnal polyuria (volume dependent enuresis).

It is widely believed by parents that children who have enuresis at night sleep more deeply and are especially difficult to wake. This subjective opinion was not supported by Boyd's study (1960), comparing the time it took to awaken normal children and children with enuresis. Furthermore, enuresis had been shown to occur randomly with regard to stage of sleep, and any relationship is due to the amount of time spent in that stage (Mikkelsen and Rapoport 1980). A recent study (Wolfish 2001), however, has shown that children with enuresis were difficult to arouse in the first two-thirds of the night, which was also seen to be associated with the period of greatest wetting frequency. In addition, a study (Hunsballe 2000) looking at EEG power analysis showed that enuretics had a significant increase in the EEG delta power component during baseline sleep compared with controls, whereas no difference was detected with conventional polysomnographic techniques.

The evidence for some genetic predisposition is strong. Approximately 70% of children with nocturnal enuresis

have a first-degree relative who also has or has had nocturnal enuresis (Bakwin 1961). Twin studies have shown greater monozygotic (68%) than dizygotic (36%) concordance (Bakwin 1971). An association between enuresis and early delays in motor, language, and social development has been noted in both prospective community samples (Essen and Peckham 1976, Fergusson et al. 1986) and a large retrospective study of clinical subjects (Steinhausen and Gobel 1989). Genetic factors are probably the most important in the etiology of nocturnal enuresis but somatic and psychosocial environmental factors have a major modulatory effect. Most commonly, nocturnal enuresis is inherited via an autosomal dominant mode of transmission with high penetrance (90%). However, a third of all cases are sporadic, and the difference between sporadic and familial forms is not known. Four gene loci associated with nocturnal enuresis have been identified but the existence of others is presumed (locus heterogeneity) (von Gontard et al. 2001). Many psychosocial correlates have also been described, including delayed toilet training, low socioeconomic class, stress events, and other child psychiatric disorders. Prospective studies from New Zealand (Fergusson et al. 1986) and from kibbutz-raised children in Israel (Kauffman 1962) suggest that higher rates of enuresis are seen in children in whom toilet training is delayed until after the age of 18 months. The data on social class and enuresis are unclear. Early reports (Oppel et al. 1968, Rutter et al. 1973) linked various indices of social disadvantage to increased prevalence of enuresis, however, multivariate studies (Fergusson et al. 1986) failed to demonstrate a relationship between primary enuresis and psychosocial disadvantage or social class, or both. Stress events seem to be more clearly associated with secondary enuresis. Reported events include the birth of a younger sibling (Werry and Cohrssen 1965), early hospitalizations, (Douglas 1973), and head injury (Chadwick 1985).

Psychiatric disorder occurs more frequently in enuretic children than in other children. The relative frequency of disorder ranges from two to six times that in the general population and is more frequent in girls, in children who also have diurnal enuresis, and in children with secondary enuresis (Rutter et al. 1973, Essen and Peckham 1976). There have been no specific types of psychiatric disorder identified in children with enuresis (Mikkelsen and Rapoport 1980).

There is little evidence that enuresis is a symptom of underlying disorder because psychotherapy is ineffective in reducing enuresis (Werry and Cohrssen 1965), anxiolytic drugs have no antienuretic effect, tricyclic antidepressants exert their therapeutic effect independent of the child's mood (Blackwell and Currah 1973), and purely symptomatic therapies, such as the bell and pad, are equally effective in disturbed and nondisturbed children (Young and Morgan 1973).

A further explanation for the association is that enuresis, a distressing and stigmatizing affliction, may cause the psychiatric disorder. However, although some studies have shown that enuretic children who undergo treatment become happier and have greater self-esteem (Behrle et al. 1956, Baker 1969), other studies show that psychiatric symptoms do not appear to lessen in children who are successful with a night alarm (Shaffer et al. 1984, Moffat et al. 1987).

A final possibility is that enuresis and psychiatric disorder are both the result of joint etiological factors such as low socioeconomic status, institutional care, large sibships, parental delinquency, and early and repeated disruptions of maternal care (Rutter et al. 1973, Essen and Peckham 1976, Miller et al. 1960). Shared biological factors may also be important in that delayed motor, speech, and pubertal development, already shown to be associated with enuresis, have proven to be more frequent in disturbed enuretic children than in those without psychiatric disorder.

## Diagnosis and Differential Diagnosis

The presence or absence of conditions often seen in association with enuresis, such as developmental delay, UTI, constipation, and comorbid psychiatric disorder, should be assessed and ruled out as appropriate (Figure 49–1). Other causes of nocturnal incontinence should be excluded, for example, those leading to polyuria (diabetes mellitus, renal disease, diabetes insipidus) and, rarely, nocturnal epilepsy.

## Assessment

### History

Information on the frequency, periodicity, and duration of symptoms is needed to make the diagnosis and distinguish functional enuresis from sporadic seizure-associated enuresis. If there is diurnal enuresis, an additional treatment plan is required. A family history of enuresis increases the likelihood of a diagnosis of functional enuresis and may explain a later age at which children are presented for treatment. Projective identification by the affected parent—whereby the parent does not separate feelings about himself having the diagnosis and the current experience of the affected child—may further hinder treatment. For subjects with secondary enuresis, precipitating factors should be elicited, although such efforts often represent an attempt to assign meaning after the event.

Questions that are useful in obtaining information for treatment planning include "Why is this a problem?" and "Why does this need treatment now?" because these factors may influence the choice of treatment (is a rapid effect needed?) or point to other pressures or restrictions on therapy. It is important to inquire about previous management strategies—for example, fluid restriction, nightlifting (getting the child out of bed to take them to the toilet in an often semi-asleep state), rewards, and punishments—used at home. Parents often come with the assertion that they have tried everything and that nothing has helped. Examining the reasons for failure of simple strategies is useful for ensuring that more sophisticated treatments do not befall the same fate. There is little evidence that fluid restriction is useful, although nightlifting may be beneficial for the large number of children who never reach professional attention. Rewards are usually material and are given only for unreasonably high performance levels, with the delay between action and reward being too long. Physical punishment and verbal chastisements, ineffective at best, may well maintain the enuresis. Punishment is often too harsh and tends to be applied inconsistently depending on parental mood. If specific treatments have been prescribed, either behavioral or pharmacological, it is

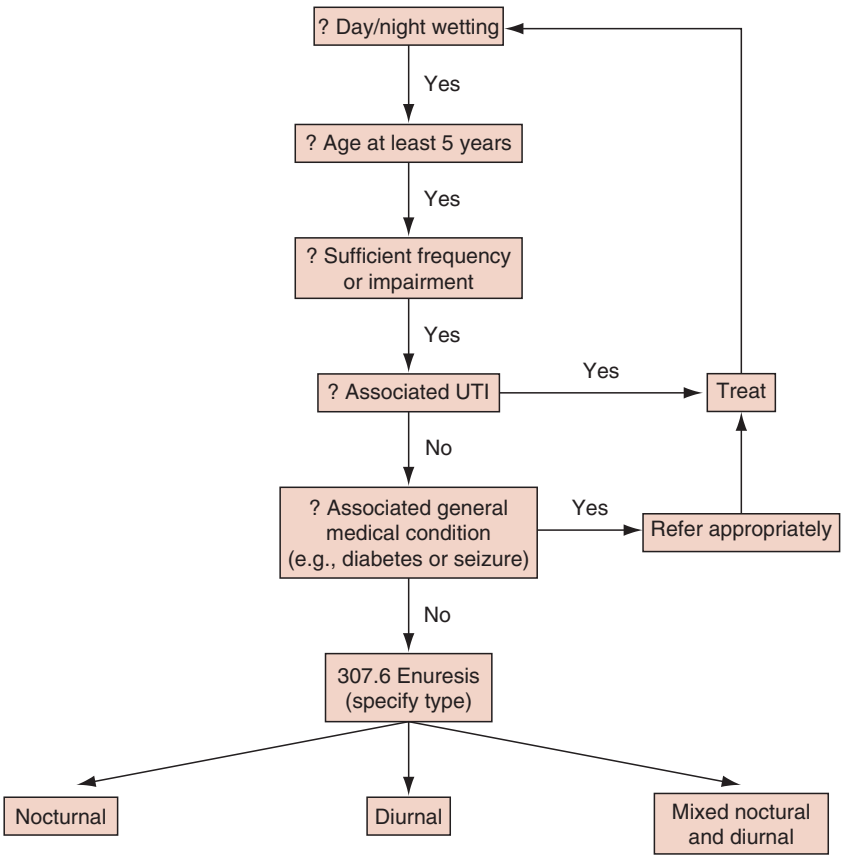



**Figure 49–1** *Diagnostic decision tree for enuresis.*

important to discover the reasons they may have failed, for example, parental discord, noncompliance, or relapse after an initial response.

### Mental Status Examination

The child's views and any misconceptions that he or she may have about the enuresis, its causes, and its treatment should be fully explored. Asking the child for three wishes may help determine whether the enuresis is a concern to the child. This may unmask marked embarrassment or guilt from behind a facade of denial about the problem and can be educational for parents who believe their children could stop wetting "if only they wanted to or tried harder." Pictures drawn by the child that describe how the child views himself or herself when enuresis is a problem and when it is not is appropriate for younger children and can graphically illustrate the misery experienced by children with enuresis.

### Physical Examination

All children should have a routine physical examination, with particular emphasis placed on detection of congenital malformations, which are possibly indicative of urogenital abnormalities. A midstream specimen of urine should be examined for the presence of infection. Radiological or further medical investigation is indicated only in the presence of infected urine, enuresis with symptoms suggestive of recurrent UTI (frequency, urgency, and dysuria), or polyuria.

## Treatment

Practical management for nocturnal enuresis is presented in Table 49–1. Studies suggest that only a minority of children with enuresis are ever assessed and treated (Miller et al. 1960, Foxman et al. 1986) and that many of those who are referred do not receive adequate treatment. Many families, and clinicians, seem to accept bed-wetting as part of normal childhood.

The overall goals of treatment can depend on the reason for referral. Commonly, the child is brought to the physician before some planned activity, for example, a family vacation or a trip to camp, and the need is for a rapid (e.g., pharmacological) short-term therapy. A gradual behavioral approach would not likely meet with much approval even though it may offer a chance for a permanent cessation of wetting.

### Standard Treatment

About 10% of children have a reduction in the number of wet nights after a single visit to a clinician in which the only intervention was the recording of baseline wetting frequency and simple reassurance (Shaffer et al. 1968). Such reassurance should make clear that enuresis is a biological condition that is made worse by stress and that may be associated in a noncausal way with other psychiatric disorders. Younger children can be told that their problem is shared by many others of the same age. The excellent prognosis for patients who comply with therapy should be stressed. Recording the frequency of enuresis can be achieved by using a simple star chart. This is most effective if performed by the child, who records each dry night with a star. The completed chart is then shown to the parents on a daily basis, and they can provide appropriate praise and reinforcement.

| Table 49–1 | Practical Management of Nocturnal Enuresis |
|---|---|
| Stage 1 | Assessment |
| | Obtain history: frequency, periodicity, and duration of wetting.<br>Why is this a problem? Why now?<br>Mental status: views and misconceptions (parent and child).<br>Discover reasons for previous failure or failures.<br>Perform routine physical examination (any minor congenital abnormalities?).<br>Midstream specimen of urine must be obtained.<br>Radiology and further physical investigation is needed only if symptoms or evidence of UTI (dysuria and frequency or positive culture results) or polyuria. |
| Stage 2 | Advice |
| | Education that enuresis is common and not deliberate.<br>Aim to reduce punitive behavior.<br>Transmit optimism: however, anticipate disappointment at no instant cure.<br>Preview the stepwise recovery and warn of the possibility of relapse. |
| Stage 3 | Baseline |
| | Use star chart.<br>Focus on positive achievements (be creative).<br>Examine the effect of simple interventions (e.g., lifting) |
| Stage 4 | Night Alarm |
| | First-line management unless important to obtain rapid short-term effect.<br>Demonstrate night alarm equipment in the office.<br>Telephone follow-up within a few days of commencing therapy.<br>*Or*<br>Drug Therapy |
| | If rapid suppression of wetting is needed (e.g., before vacation or camp, to defuse aggressive or hostile situation between child and parents and siblings).<br>When family has *proved* incapable of using the equipment.<br>After failure or multiple relapses.<br>Medication of choice: DDAVP, (Desmopressin)20–40 μg at night |

### *Waking and Fluid Restriction*

Although systematic studies have failed to show any effect of these interventions with enuretic inpatients, it may be that waking and fluid restriction work for the majority of enuretic children who are not referred for treatment. If waking does appear to reduce the number of wet nights from baseline, a more systematic application may be indicated.

### *Surgery*

Based on the premise that enuresis is causally associated with outflow tract obstruction, various surgical procedures have been advocated, for example, urethral dilatation, meatotomy, cystoplasty, and bladder neck repair (Mahoney 1971). This cannot be supported because, in addition to the dubious concept of outflow tract obstruction per se, the surgery does not alter the urodynamics of the bladder. Reported positive treatment effects are slight (no controlled studies exist), and there remains a significant potential for adverse effects (urinary incontinence, epididymitis, and aspermia).

### *Pharmacotherapy*

Although it has been repeatedly demonstrated that temporary suppression rather than cure of enuresis is the usual outcome of drug therapy, it remains the most widely prescribed treatment in the US (Foxman et al. 1986). Four classes of drugs have principally been employed: synthetic AHDs, tricyclic antidepressants, stimulants, and anticholinergic agents.

**Synthetic ADH.** A number of randomized double-blind placebo-controlled trials have shown that the synthetic vasopeptide DDAVP (desmopressin) is effective in the treatment of enuresis (Dimson 1986, Miller and Klauber 1990). The drug is usually administered intranasally, although oral preparations of equal efficacy have been developed (equivalent oral dose is 10 times the intranasal dose). It has been shown (Miller et al. 1989) that almost 50% of children are able to stop wetting completely with a single nightly dose of 20−40 μg of DDAVP given intranasally. A further 40% are afforded a significant reduction in the frequency of enuresis with this treatment. As with tricyclic antidepressants, however, when treatment is stopped, the vast majority of individuals relapse (Leebeek-Groenewegen et al. 2001). A meta-analysis (Glazener and Evans, 2002) showed that desmopressin (20 μg) was more effective than placebo with 1.34 fewer wet nights per week but that only 20% of treated subjects achieved dryness (2% placebo). Side effects of this medication include nasal pain and congestion, headache, nausea, and abdominal pain. Serious problems of hyponatremic hypovolemia leading to seizures are rare, but should be considered if young children show the prodromal symptoms (nausea, vomiting and headache) during initiation of DDAVP therapy (Thumfart et al. 2005). Prevention of excessive water intake (not greater than 240 mL (8oz) after nighttime administration of desmopressin is advisable. It is also important to be aware that intranasal absorption is reduced when the patient has a cold or allergic rhinitis. The mode of action of desmopressin is unknown. It may reduce the production of nighttime urine to an amount less than the (low) functional volume of the enuretic bladder, thereby eliminating the urge to micturate. It is uncertain whether desmopressin administration is correcting a natural deficiency of vasopressin or is exerting a true pharmacological effect. With regard to identifying those most likely to respond to DDAVP treatment, it has been found (Kruse et al. 2001) that those most likely to be permanently dry are older children who respond to lower dose (20 μg) desmopressin and who do not wet frequently.

**Tricyclic Antidepressants.** The short-term effectiveness of imipramine and other related antidepressants has also been demonstrated via many randomized double-blind, placebo-controlled trials (Shaffer et al. 1968, Rapoport et al. 1980, Simeon et al. 1981). Imipramine reduces the frequency of enuresis in about 85% of bed wetters and eliminates enuresis in about 30% of these individuals. Nighttime doses of 1−2.5 mg/kg are usually effective (Jorgensen et al. 1980), and a therapeutic effect is usually evident in the first week of treatment. Relapse after withdrawal of medication is almost inevitable, so that 3 months after the cessation of tricyclic antidepressants, nearly all patients will again have

enuresis at pretreatment levels (Shaffer et al. 1968). Side effects are common and include dry mouth, dizziness, postural hypotension, headache, and constipation. Toxicity after accidental ingestion or overdose is a serious consideration, causing cardiac effects, including arrhythmias and conduction defects, convulsions, hallucinations, and ataxia. Concern has been expressed about the possibility of sudden death (presumably caused by arrhythmia) in children taking tricyclic drugs. The mode of action for tricyclic antidepressants is unclear. It does not appear to depend on their antidepressant properties because response is unrelated to the presence or absence of mood symptoms. One observation is that tricyclic agents seem to increase functional bladder volumes (Shaffer et al. 1979), possibly resulting from noradrenergic reuptake inhibition (Rapoport et al. 1980).

**Stimulant Medication.** Sympathomimetic stimulants such as dexamphetamine have been used to reduce the depth of sleep in children with enuresis; because, as discussed previously, there is no evidence that enuresis is related to abnormally deep sleep, their lack of effectiveness in stopping bed-wetting is no surprise (McConaghy 1969). Used in combination with behavioral therapy, there is some evidence that stimulants can accentuate the learning of nocturnal continence (Young and Turner 1965).

**Anticholinergic Drugs.** Drugs such as propantheline, oxybutynin, and terodiline can reduce the frequency of voiding in individuals with neurogenic bladders, reduce urgency, and increase functional bladder capacity. There is no evidence, however, that these anticholinergic drugs are effective in bed-wetting, although they may have a role in diurnal enuresis (Wallace and Forsythe 1969, Elmer et al. 1988). Side effects are frequent and include dry mouth, blurred vision, headache, nausea, and constipation (Baigrie et al. 1988).

### *Psychosocial Treatments*

The night alarm, originally developed by Pfaundler (1904), was first used in children with enuresis by Mowrer and Mowrer (1938). This system used two electrodes separated by a device (e.g., bedding) connected to an alarm. When the child wet the bed, the urine completed the electrical circuit, sounded the alarm, and the child awoke. All current night alarm systems are merely refinements on this original design. A vibrating pad beneath the pillow can be used instead of a bell or buzzer, or the electrodes can be incorporated into a single unit or can be miniaturized so that they can be attached to night (or day) clothing. With treatment, full cessation of enuresis can be expected in 80% of cases. Reported cure rates (defined as a minimum of 14 consecutive dry nights) have ranged from 50−100% (Forsythe and Butler 1989, Butler 1991).

The main problem with this form of enuretic treatment, however, is that cure is usually achieved only within the second month of treatment (Kolvin et al. 1972). This factor may influence clinicians to prescribe pharmacological treatments that, although more immediately gratifying, do not offer any real prospect of cure. It has been suggested that adjuvant therapy with methamphetamine (Young and Turner 1965) or desmopressin (Bollard and Nettlebeck 1981) will reduce the amount of time before continence is achieved. Using a louder auditory stimulus (Finley and Wansley 1977) or using the body-worn alarm (Butler et al. 1990) may also improve the speed of treatment response. Factors associated with delayed acquisition of continence include failure of the child to wake with the alarm, maternal anxiety, and a disturbed home environment, although no influence has been seen regarding the age of the child or the initial wetting frequency (Young and Morgan 1973, Dische et al. 1983).

A further consequence of the delayed response to a night alarm is that families fail to persist with treatment and may abandon the treatment too soon. Premature termination can occur in as many as 48% of cases (Turner et al. 1970) and is more common in families that have made little previous effort to treat the problem, in families that are negative or intolerant of bed-wetting, and in children who have other behavioral problems (Wagner and Johnson 1988). Aspects of treatment that may also reduce compliance with the alarm include failure to understand or follow the instructions, failure of the child to awaken, and frequent false alarms (Turner et al. 1970). The only reported side effect of treatment with the night alarm is "buzzer ulcers" caused by the child lying in a pool of ionized urine. This problem has been eliminated with modern transistorized alarms that do not employ a continuous, relatively high voltage across the electrodes to detect enuresis (Malem et al. 1982).

Relapse after successful treatment, if it occurs, will usually take place within the first 6 months after cessation of treatment. It is reported that approximately one-third of children relapse (Doleys et al. 1977), however, no clear predictors of relapse have been identified (Fielding 1985). Strategies aimed at reducing relapse rates, such as overlearning (Houts et al. 1984) or intermittent reinforcement paradigms (Finley et al. 1973), have not been demonstrated to be of clinical value (Forsythe and Butler 1989). A recent review (Butler and Gasson 2005) of alarm treatment that combined 20 studies meeting quality criteria, reported that an overall 65% success (>14 successive dry nights) rate was seen, with 42% relapsing following cessation of treatment. Improved success was seen in studies that emphasized behavioral reinforcement of rapid waking to the alarm and was thought more appropriate for those with mono-symptomatic nocturnal enuresis (e.g., absence of daytime frequency and urgency).

The mode of action of the night alarm can be explained using theories of classical or operant conditioning. In classical conditioning, bladder distention or a sense of the need to pass urine becomes associated with the auditory signal, leading to the conditioned response of waking. Operant conditioning theories would view the alarm as a punishment to be avoided and may explain why individuals still become dry when the alarm is placed in the bed but is not switched on (Deleon and Mandell 1966). Social learning is also important because the night alarm and associated systematic recording may help the family focus on dry nights and provide contingent rewards (praise) for rapid response to the auditory signal. Successful treatment with the nighttime alarm results in reduced nocturnal urine volume, possibly mediated by increased production of arginine vasopressin (Oredsson and Jorgensen 1998). Table 49–2 presents various remedies for night alarm problems.

**Dry Bed Technique.** An elaborate collection of interventions has been designed by Azrin et al. (1974) and includes high fluid intake (an attempt at "over-learning"), retention

| Table 49–2 | Problem Solving for the Night Alarm *If …* |
|---|---|
| Bell "does not work" | Check position, connections, and batteries.<br>If using separating sheet, check that it is porous.<br>Check that child is not turning off equipment.<br>Place alarm out of easy reach. |
| Child does not wake | Make alarm louder.<br>Parent should wake child. |
| Child does not become dry | Ensure compliance. Ensure that child responds promptly.<br>Use adjuvant DDAVP or dextroamphetamine.<br>Ensure that child has role (e.g., change own bed-sheets) after alarm. |
| False alarms | Ensure that separating sheet is big enough, not soiled, and will insulate.<br>Use thicker nightclothes. |
| Relapse | Repeat treatment.<br>Consider overlearning after response to re-treatment. |

control training, training the child to awaken rapidly (using a nighttime alarm), and rapid reinforcement for correct daytime micturition. Without the use of a night alarm, the program produces no better effects than no treatment at all (Nettlebeck and Langeluddecke 1979). In view of the intensive effort needed by the family and adverse effects on pre-school children, such as increased temper tantrums or social withdrawal (Mattsson and Ollendick 1977), the value of the dry bed technique remains questionable.

### *Ultrasonic Bladder Volume Alarm*

Although the traditional enuresis alarm has good potential for a permanent cure, the child is mostly wet during treatment. Furthermore, the moisture alarm requires that the child make the somewhat remote association between the alarm event and a full bladder after the bladder has emptied. In an exploratory study (Pretlow 1999), a new approach to treating nocturnal enuresis was investigated using a miniature bladder volume measurement instrument during sleep. An alarm sounded when bladder volume reached 80% of the typical enuretic volume. Two groups were studied. Group 1 used the nighttime device alone; Group 2, in addition, had supplementary daytime bladder retention training (aiming to increase functional capacity). In Groups 1 and 2, the mean dryness rate before study initiation versus during the study was 32.9 and 9.3% versus 88.7 and 82.1%, respectively. Nighttime bladder capacity increased 69% in Group 1 and 78% in Group 2, while the cure rate was 55% (mean treatment period 10.5 months) and 60% (mean treatment period 7.2 months), respectively. On this data, bladder volume tracking seems to be a promising treatment for nocturnal enuresis in that it prevents the enuretic event, appears to facilitate a permanent cure, and is noninvasive.

**Acupuncture.** The efficacy of traditional Chinese acupuncture has been studied (Serel et al. 2001) in a small ($n$ = 50) clinical sample. It was reported that within 6 months, 86% of patients were completely dry and a further 10% of patients were dry on at least 80% of nights. Relapse rates appeared better than with psychopharmacologic agents.

### Summary

In the last 30 years, there have been approximately 50 randomized trials conducted, involving over 3,500 children treated pharmacologically or behaviorally for primary nocturnal enuresis. The quality of many of these trials is poor with very few trials comparing drugs with each other, or drugs versus, or combined with alarms or other behavioral interventions, and few having adequate follow-up periods. Desmopressin and tricyclics appeared equally effective while on treatment, but this effect was not sustained after treatment stopped. It is clear that further comparisons between drug and behavioral treatments are needed, and should include relapse rates after treatment is finished.

## Assessment and Management of Diurnal Enuresis

Daytime enuresis, although it can occur together with nighttime enuresis, has a different pattern of associations and responds to different methods of treatment. It is much more likely to be associated with urinary tract abnormalities, including UTI, and to be comorbid with other psychiatric disorders. As a result, a more detailed and focused medical and psychiatric evaluation is indicated. Urine should be checked repeatedly for infection, and the threshold for ordering ultrasonographical visualization of the urological system should be low. The history may make it apparent that the daytime wetting is situation specific. For example, school-based enuresis in a child who is too timid to ask to use the bathroom could be alleviated by the teacher's tactfully reminding the child to go to the bathroom at regular intervals.

Observation of children with diurnal enuresis (Fielding et al. 1978) has established that they do experience an urge to pass urine before micturition but that either this urge is ignored or the warning comes too late to be of any use because of an "irritable bladder." Therefore, treatment strategies are based on establishing a pattern of toileting before the times that diurnal enuresis is likely to occur (usually between 12 noon and 5 pm) and using positive reinforcement to promote regular use of the bathroom (Berg et al. 1982).

Portable systems that can be worn on the body and use a sensor in the underwear as well as an alarm that can be worn on the wrist have been developed. Halliday et al. (1987) studied two versions of this apparatus—one in which the alarm sounding was contingent on the sensor's detecting wetness in the underwear, and another in which the alarm merely went off at predetermined intervals. Interestingly, success rates (two-thirds of children were cured and mostly maintained continence for a full 2-year follow-up period) showed no significant differences between the wetness alarm and the simple timed alarm. A simple therapeutic alternative, therefore, is to buy the child a digital watch with a countdown alarm timer.

Unlike nocturnal enuresis, drug treatment with tricyclic antidepressants such as imipramine is ineffective (Meadow and Berg 1982), whereas the use of anticholinergic agents such as oxybutynin and terodiline shows a therapeutic impact on the frequency of daytime enuresis (Baigrie et al. 1988, Pfaundler 1904).

Clinical Vignette 1

John, an 8-year-old boy, was the sixth child in a sibship. He was brought by his mother for treatment of nocturnal enuresis which was occurring on average five times a week, with no particular pattern. Two of his elder brothers had also wet the bed until the age of 10 and 13 years, respectively, as had his biological father who was no longer living with the family. The mother had become exasperated with John's wetting and had begun punishing him by forcing him to wash his bedclothes by hand every morning before school. His brothers made fun of him, and peers at school avoided him because he frequently came to school still smelling of stale urine. He was not allowed to have anything to drink after 6 pm, and a star chart was currently being used without much success. No praise was given for the 2 dry nights per week because his mother was convinced that this meant the enuresis was deliberate. John drew a picture describing the terror and anxiety of having a wet night. His three wishes were to stop wetting, to get a Nintendo machine of his own, and to find a real dinosaur fossil.

The initial management included an explanation of the condition, microbiological analysis of a midstream specimen of urine, and instructions on baseline recording using the star chart. Overt punishments were eliminated, although John was expected to help change his sheets, and effort was expended in trying to help his mother praise him for the dry nights he was able to achieve. After a 2-week baseline period, urinalysis results came back negative and the frequency of enuresis remained at 4 to 5 nights per week. John and his mother were instructed in the use of a night alarm and were telephoned 2 days later to check on any problems. It appeared that John was not waking with the buzzer, and they were instructed to place the alarm unit on an old cookie tin to amplify the sound. Dry nights were recorded on John's chart, with verbal praise after each one.

An initial target of 3 dry nights per week was set, with the promise of a trip to the movies for John and the two brothers who shared a bedroom with him. This was achieved the first week, although it took a further 6 weeks before he went a full week without a wet bed. After 2 weeks of continence, the restriction on nighttime fluids was relaxed without incident. Six months later, he remained dry, and school and home relationships were markedly improved.

# Encopresis

## Definition

Encopresis is usually defined as the intentional or involuntary passage of stool into inappropriate places in the absence of any identified physical abnormality in children older than 4 years (see DSM-IV-TR criteria for encopresis).

The distinction is drawn between encopresis with constipation (retention with overflow) and encopresis without constipation. Other classification schemes include making a primary–secondary distinction (based on having a 1-year period of continence) or soiling with fluid or normal feces.

## Course and Natural History

Less than one-third of children in the US have completed toilet training by the age of 2 years (Steubens and Silber 1974), with a mean age of 27.7 months (Brazelton 1962). Bowel control is usually achieved before bladder control.

The age cutoff for "normality" is set at 4 years, the age at which 95% of children have acquired fecal continence (Stein and Susser 1967). As with urinary continence, girls achieve bowel control earlier than boys.

DSM-IV-TR Criteria

**Encopresis**

A. Repeated passage of feces into inappropriate places (e.g., clothing or floor) whether involuntary or intentional.

B. At least one such event a month for at least 3 months.

C. Chronological age is at least 4 years (or equivalent developmental level).

D. The behavior is not due exclusively to the direct physiological effect of a substance (e.g., laxatives) or a general medical condition except through a mechanism involving constipation.

*Code* as follows:

**787.6 Encopresis, with constipation and overflow incontinence:** there is evidence of constipation on physical examination or by history.

**307.7 Encopresis, without constipation and overflow incontinence:** there is no evidence of constipation on physical examination or by history.

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## Epidemiology

The overall prevalence of encopresis in 7- and 8-year-old children has been shown to be 1.5%, with boys (2.3%) affected more commonly than girls (0.7%). There was a steadily rising likelihood of continence with increasing age, until by age 16 years the reported prevalence was almost zero (Bellman 1966). Rutter and coworkers (1970) reported a rate of 1% in 10- to 12-year-old children, with a strong (5:1) male/female ratio. Retrospective study of clinic-referred encopretic children has shown that 40% of cases are primary (true failure to gain control), with a mean age of 6.7 years, and 60% of cases are secondary, with a mean age of 8 years (Levine 1975). Eighty percent of patients were constipated, with no difference in this feature seen between primary and secondary subtypes.

## Etiology and Pathophysiology

No clear single causative pathway has been established. The constipated–nonconstipated distinction does, however, generate some specificity in terms of associations that may be important etiologically. Within the first year of life, children can show a tendency toward constipation (Levine 1982), with concordance for constipation being six times more frequent in monozygotic than in dizygotic twins (Bakwin 1971). Fecal retention and reduced stool frequency between

12 and 24 months of age can predict later encopresis (Levine 1975). Encopretic children with constipation and overflow are found to have rectal and colonic distention, massive impaction with hard feces, and a number of specific abnormalities of anorectal physiology. These abnormalities, which may be primary or secondary to constipation, include elevated anal resting tone, decreased anorectal motility and weakness of the internal anal sphincter (Loening-Baucke and Younoszai 1982), and dysfunction of the external anal sphincter, for example, contraction during defecation (Wald et al. 1986, Loening-Baucke et al. 1987).

Encopresis may occur after an acute episode of constipation following illness or a change in diet (Pettei and Davidson 1988). In addition to the pain and discomfort caused by attempts to pass an extremely hard stool, a number of specific painful perianal conditions such as anal fissure can lead to stool withholding and later fecal soiling. Stressful events such as the birth of a sibling or attending a new school have been associated with up to 25% of cases of secondary encopresis (Levine 1975). In nonretentive encopresis, the main theories center on faulty toilet training. Stress during the training period, coercive toileting leading to anxiety and "pot phobia," and failure to learn or to have been taught the appropriate behavior (Anthony 1957, Berg and Jones 1964) have all been implicated. True fecal urgency, which may have a physiological or pathological basis, may also be important in a small proportion of cases (Woodmansey 1967).

It has been asserted that primary encopresis is more common in children from lower socioeconomic class families who received neglectful toilet training (Anthony 1957). No link was found, however, between social class and encopresis in general (Stein and Susser 1967, Rutter et al. 1970), or in primary encopresis specifically (Olatawura 1973).

## Diagnosis and Differential Diagnosis

Although the diagnosis can rarely be confused with other less odoriferous conditions, the main efforts during the diagnostic process are to establish the presence or absence of constipation and, to a lesser extent, distinguish continuous (primary) from discontinuous (secondary) soiling (Figure 49–2). Hersov (Taylor and Hersov 1994) listed three types of identifiable encopresis in children: (1) it is known that the child can control defecation, but she or he chooses to defecate in inappropriate places; (2) there is true failure to gain bowel control, and the child is unaware of or unable to control soiling; and (3) soiling is due to excessively fluid feces, whether from constipation and overflow, physical disease, or anxiety. In practice, there is frequently overlap among types or progression from one to another. Unlike enuresis, fecal soiling rarely occurs at night or during sleep, and if present, is indicative of a poor prognosis (Levine 1982). Soiling due to anal masturbation has been reported, although this causes staining of the sheets rather than full stools in the bedclothes (Clark et al. 1990).

## Phenomenology

In the first group, in which bowel control has been established, the stool may be soft or normal (but different from fluid-type feces seen in overflow). Soiling due to acute stress events (e.g., the birth of a sibling, a change of school, or parental separation) is usually brief once the stress has abated, given a stable home environment and sensible management. In more severe pathological family situations, including punitive management or frank physical or sexual abuse (Boon 1991), the feces may be deposited in places deliberately to cause anger or irritation, or there may be associated smearing of feces on furniture and walls. Other covert aggressive antisocial acts may be evident, with

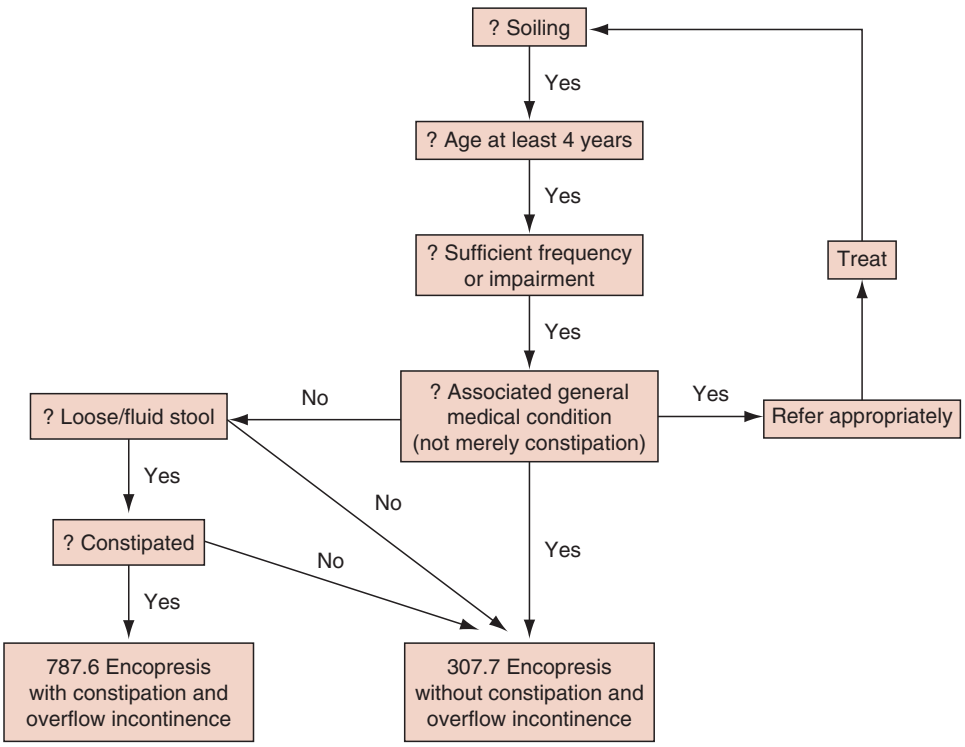



**Figure 49–2** *Diagnostic decision for encopresis.*

considerable denial by the child of the magnitude or seriousness of the problem.

In the second group, in which there is failure to learn bowel control, a nonfluid stool is deposited fairly randomly in clothes, at home, and at school. There may be conditions such as mental retardation or specific developmental delay, spina bifida, or cerebral palsy that impair the ability to recognize the need to defecate and the appropriate skills needed to defer this function until a socially appropriate time and location. In the absence of low IQ or pathological physical condition, patients have been reported as having associated enuresis, academic skills problems, and antisocial behavior. They present to pediatricians primarily and are usually younger (age 4–6 years) than other encopretic individuals. It is thought that this type of soiling is considerably more common in socially disadvantaged, disorganized multiproblem families (Anthony 1957, Berg and Jones 1964, Easson 1960) because of faulty or inconsistent training or stresses during the sensitive period of training.

In the third group, excessively fluid feces are passed, which may result from conditions that cause true diarrhea (e.g., ulcerative colitis) or, much more frequently, from constipation with overflow causing spurious diarrhea. A history of retention, either willful or in response to pain, is prominent in the early days of this form of encopresis, although later it may be less apparent because of fecal overflow. Behavior such as squatting on the heels to prevent defecation or marked anxiety about the prospect of using the toilet (although rarely amounting to true phobic avoidance) may be described.

The issue of whether a comorbid psychopathological condition is common appears to depend on where encopretic cases are sampled. Gabel et al. (1986) found some elevation in behavioral disturbance in a pediatric sample, although it was less severe than that seen in new cases in a child psychiatric outpatient clinic. Less than 13% of encopretic children had ever been referred to a mental health specialist. Similarly, Loening-Baucke et al. (1987) showed only modest elevations in Child Behavior Checklist scores and primarily in the Behavior Problem Scale. In contrast, child psychiatric studies have shown higher levels of psychopathological features, both anxiety-withdrawal and aggression (Bellman 1966, Warson et al. 1954). A large cohort study of over 8,000 children from the UK (Joinson et al., 2006) has recently examined the rates and types of psychopathology seen in children who soil frequently, occasionally, or not at all. Rates of attention-deficit hyperactivity disorder (ADHD) (9.2%, 4.0%, 1.9%) and oppositional defiant disorder (11.9%, 3.1%, 1.9%), as well as separation anxiety, social phobia, and generalized anxiety disorders (GADs), were elevated in the frequent soilers, compared to both occasional and nonsoiling controls. Controlling for developmental delay reduced the strength of the observed asocial but the increases remained statistically significant. A variety of antisocial behaviors (including bullying) as well as obsessive/compulsive symptoms were also seen to be associated with severity of encopresis.

Interestingly, a recent study (Stevenson and Goodman 2001) looked at the association between preschool behavior problems (measured at age 3 years) and later adult criminal convictions. It was found that the risk of having any adult conviction was related to soiling, daytime enuresis, activity level, and management difficulties, and that having an adult violent offense was related to recent-onset daytime enuresis, management difficulties, and temper tantrums. The only other predictors of later convictions were the child's gender and social competence at age 3 years. Family and social circumstances at age 3 years did not predict later convictions.

## Issues and Further Assessment

Having identified the presence of encopretic behavior and formed some idea of the type of encopresis (primary, secondary, or retentive, or a combination), the remaining task is to discover the presence and extent of any associated conditions, both medical and psychological. The comprehensive assessment process should include a medical evaluation, psychiatric and family interviews, and a systematic behavioral recording.

The medical evaluation comprises a history, review of systems, physical examination, and appropriate hematological and radiological tests. Although the vast majority of patients with encopresis are medically normal, a small proportion have pathological features of etiological significance. Physical causes of encopresis without retention include inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), central nervous system disorders, and sensory disorders of the anorectal region or pelvic floor muscles (e.g., spina bifida, cerebral palsy). Organic causes of encopresis with retention include Hirschsprung's disease (aganglionosis in intermuscular and submucous plexuses of the large bowel extending proximally from the anus), neurogenic megacolon, hypothyroidism, hypercalcemia, chronic codeine or laxative usage, anorectal stenosis, and fissure (Fleisher 1976). It should also be remembered that these conditions rarely have their first presentation with encopresis alone.

The physical assessment should include an abdominal and rectal examination, although a plain abdominal radiograph is the most reliable way to determine the presence of fecal impaction. Anorectal manometry should be considered in the investigation of children with severe constipation and chronic soiling, especially those in whom Hirschsprung's disease is suspected (Clayden and Agnarsson 1991).

Psychiatric and family interviews should include a developmental history and a behavioral history of encopresis (antecedents, behavior, and consequences). Specific areas of stress, acute or chronic, affecting the child or family, or both, should be discovered. Associated psychopathological conditions are more commonly found in the older child, in secondary encopresis, and when soiling occurs not only in clothes. Anxiety surrounding toileting may indicate pot phobia, coercive toileting, or a history of painful defecation. A history should be obtained of the parents' previous attempts at treatment together with previously prescribed therapy so that reasons for previous failure can be identified and anticipated in future treatment planning.

## Treatment

Practical management for encopresis is presented in Table 49–3.

### Standard Treatment

The principal approach to treatment is predicated on the results of the evaluation and the clinical category assigned.

| Table 49–3 | Practical Management of Encopresis |
|---|---|
| Stage 1 | Assessment |
| | Whether primary or secondary.<br>Is there physical cause?<br>Presence or absence of constipation.<br>Presence or absence of acute stress.<br>Presence or absence of psychiatric disorder including phobic symptoms or smearing.<br>ABC (antecedents, behavior, consequences) of encopresis including secondary gain.<br>Discover reasons for previous failure or failures. |
| Stage 2 | Advice |
| | Education regarding diet, constipation, and toileting.<br>Aim to reduce punitive or coercive behavior.<br>Transmit optimism; however, anticipate disappointment at no instant cure.<br>Preview the stepwise recovery and warn of the possibility of relapse. |
| Stage 3 | Toileting |
| | Baseline observation using star chart.<br>Focus on positive achievements, e.g., toileting, rather than soiling.<br>High-fiber diet (try bran in soup, milk shakes).<br>Toilet after meals, 15 min maximum.<br>Check that adequately rising intra-abdominal pressure is present.<br>Graded exposure scheme if "pot phobic." |
| | *with* |
| | Laxatives |
| | Indicated if physical examination or abdominal radiograph shows fecal loading.<br>Medication of choice: Senokot syrup (senna) up to 10 mL b.i.d., lactulose syrup up to 30 mL (20 mg) b.i.d.<br>Dosage will be reduced over time; titrate with bowel frequency. |
| | Enemas |
| | Microenema (e.g., bisacodyl, 30 mL) if the bowel is excessively loaded with rock-like feces. |
| Stage 4 | Biofeedback |
| | Consider after relapse or failure to respond to toileting or laxatives. |

This differentiates between the need to establish a regular toileting procedure in patients in whom there has been a failure to learn this social behavior and the need to address a psychiatric disorder, parent–child relationship difficulties, or other stresses in the child who exhibits loss of this previously acquired skill in association with these factors. In both cases, analysis of the soiling behavior may identify reinforcing factors important in maintaining dysfunction. Detection of significant constipation will, in addition, provide an indication for adjuvant laxative therapy.

## Behavioral Treatments

Behavioral therapy is the mainstay of treatment for encopresis. In the younger child who has been toilet trained, this focuses on practical elimination skills, for example, visiting the toilet after each meal, staying there for a maximum of 15 min, using muscles to increase intra-abdominal pressure, and cleaning oneself adequately afterward. Parents or caretakers, or both, need to be educated in making the toilet a pleasant place to visit and should stay with the younger child, giving encouragement and praise for appropriate effort. Small children whose legs may dangle above the floor should be provided with a step against which to brace when straining. Initially, a warm bath before using the toilet may relax the anxious child and make it easier to pass stool. Systematic recording of positive toileting behavior, not necessarily being clean (depending on the level of baseline behavior), should be performed with a personal star chart. For the child with severe anxiety about sitting on the toilet, a graded exposure scheme may be indicated.

## Role of the Family in Treatment

Removing the child's and family's attention from the encopresis alone and focusing onto noticing, recording, and rewarding positive behavior often defuses tension and hostility and provides the opportunity for therapeutic improvement. Identifying and eliminating sources of secondary gain, whereby soiling is reinforced by parental (or other individuals') actions and attention, even if negative or punitive, make positive efforts more fruitful. Some investigators advocate mild punishment techniques, such as requiring the child to clean his or her own clothes after soiling (Doleys et al. 1977), although care must be taken to prevent this from becoming too punitive. In certain settings, particularly school, attempts are made to prevent soiling by extremely frequent toileting that, although keeping the child clean, does not promote and may even hinder the acquisition of a regular bowel habit. Formal therapy, either individual or family based, is indicated in only a minority of patients with an associated psychiatric disorder, marked behavioral disturbance (e.g., smearing, other aggressive soiling), or clear remediable family or social stresses.

## Physical Treatments

In patients with retention leading to constipation and overflow, medical management is nearly always required, although it is usually with oral laxatives or microenemas alone. The use of more intrusive and invasive colonic and rectal washout or surgical disimpaction procedures is nearly always the result of the clinician's impatience rather than true clinical need.

Uncontrolled studies of combined treatment with behavioral therapy and laxatives reported marked improvement in symptoms (not cure) in approximately 70−80% of patients (Levine and Bakow 1976, Loening-Baucke 1992). Berg et al. (1982) reported the first double-blind randomly controlled trial of the laxative Senokot (senna concentrate) and behavioral therapy, which showed no significant advantage for the laxative by 3 months. A more recent controlled randomized trial (Nolan et al. 1991) comparing behavioral therapy in retentive primary encopresis with and without laxatives showed that at 12-month follow-up, 51% of the combined treatment (laxative plus behavioral therapy) group had achieved remission (at least one 4-week period with no soiling episodes), compared with 36% of the behavioral therapy only group ($p = 0.08$). Partial remission (soiling no more than once a week) was achieved in 63% of patients with combined therapy versus 43% with behavioral therapy alone ($p = 0.02$). Patients receiving laxatives achieved remission significantly sooner, and the difference in the Kaplan–Meier

remission curves was most striking in the first 30 weeks of follow-up ($p$ = 0.012). When patients who were not compliant with the toileting program were removed from the analysis, however, the advantage of combined therapy was not significant. These results must also be viewed in light of Bellman's (1966) findings in a follow-up study of 186 clinic patients with encopresis, which reported a 50% spontaneous remission rate at 2 years. It should also be noted that approximately 15–20% of patients fail to respond to or comply adequately with initial combined treatment (Levine 1982, Nolan et al. 1991).

### Biofeedback Therapy

The finding that some children with treatment-resistant retentive encopresis involuntarily contract the muscles of the pelvic floor and the external anal sphincter, effectively impeding passage of stool (Loening-Baucke and Cruickshank 1986), has led to efforts to use biofeedback in this instance. Olness et al. (1980) used visual feedback of internal and external sphincter pressures measured by an anal balloon in 40 children, who were chronic soilers, in whom conventional treatment had failed in association with emphasizing regular toileting. Normal bowel habits were acquired by 24 children (Doleys et al. 1977). It has similarly been reported that as few as six sessions of biofeedback therapy can lead to a significant reduction in symptom frequency for as many as 86% of previously treatment-resistant patients (Loening-Baucke 1995). This has been challenged by van Ginkel et al. (2001) who showed that anorectal manometry offered no additional advantage over conventional therapy (dietary advice, diary, toilet training, oral laxatives, and enemas) in chronic constipation/encopresis. It is possible, however, that biofeedback is principally of benefit to nonretentive chronic soilers (van Ginkel et al. 2000).

Clinical Vignette 2

John was a 6-year-old boy, the only child of a farmer and his wife both of whom had strong obsessional traits and were excessively fastidious and house-proud. As a 6-month-old baby, John had been prescribed senna for about 3 months around the time he began a fully solid diet. He was investigated for Hirschsprung's disease but rectal biopsy results were negative. Toilet training was started at age 15 months because his mother was anxious to have John out of diapers by the age of 2 years. Accordingly, John was placed on the "pot" whenever he appeared to need it. This averaged 15 times a day. He would eat sitting on the pot and watch television there, and the family would not travel anywhere without this receptacle just in case John showed any sign of needing to evacuate his bowels. When, by age 2 years, John had not established a regular toileting habit, the parents gave up and placed him back in diapers. A further brief yet frenzied effort at training occurred at age 3 years because he would be unable to attend a local pre-school program if he was not bowel trained. Not surprisingly, John was not permitted to attend nursery school. Soon after starting kindergarten, his school became exasperated with John who was soiling his clothes with almost fluid feces on a regular basis. After consulting with his mother, they assigned John a nonteaching aide who would, in a fashion similar to John's mother, be responsible for taking him to the bathroom on an increasingly frequent basis. When John continued to soil his pants despite hourly toileting, the school urged John's parents to seek a specialist referral.

On presentation, John seemed to be a bright, if somewhat indolent, child who on the surface was not bothered by his soiling, but on further examination was upset by the fact that he had few friends and was not allowed to go swimming with his class. Physical examination showed a distended abdomen, with marked fecal impaction around the hepatic flexure of the colon. He was prescribed lactulose and senna twice daily, and a toileting program was designed. Because he was a fan of the television characters the Power Rangers, an elaborate chart embodying the important elements of this show was designed in consultation with John. Initial targets consisted of going to the bathroom for 15 min after each meal, with initial stars given for trying to pass anything. His mother was taught to place a hand on his abdomen to check for adequate muscular effort. Later behavioral targets became progressively more difficult. Soiling was deemphasized, and considerable effort was expended in assuaging parental anxiety that John would ever be able to pass the accumulated fecal masses. After 5 days, an enormous amount of feces was passed in the evening after a warm bath. Both John and his mother were overjoyed. This pattern was repeated over the next week, with an abdominal radiograph confirming that the colon and rectum were no longer impacted. By 6 weeks, John had established a regular thrice-daily toileting pattern, with only once-weekly accidents. Despite a high-fiber diet, efforts to reduce the laxatives completely were thwarted by recurrent retention, and the decision was made to continue with long-term fecal softeners. By 6 months, John was completely clean.

## Other Disorders Specific to Children and Adolescents

Compared to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (Oppel et al. 1968), DSM-IV (Rutter et al. 1973) eliminated overanxious and avoidant disorders with the thought that the criteria sets for GAD and social phobia (SP) could be successfully applied to the majority of anxious children with those diagnoses. With these changes, the only unique anxiety disorder of children and adolescents remaining is separation anxiety disorder (SAD). It remains unclear how successful this nosological change will prove to be, since, although the GAD criteria set has shown some validity in distinguishing GAD children from those with other anxiety disorders (Tracey et al. 1997), it is likely that a large number of subjects previously diagnosed with overanxious disorder do not meet GAD criteria.

Selective mutism (SM), the failure to speak in certain social situations, although not currently classified as an anxiety disorder, has shown a strong association with social phobia and appears to respond, sometimes dramatically, to anxiolytic medication (Dummit et al. 1997).

## SAD

### Definition

SAD is typified by developmentally inappropriate and excessive anxiety concerning separation from home or attachment figures (see DSM-IV-TR for SAD).

**DSM-IV-TR Criteria**

**Separation Anxiety Disorder**

A. Developmentally inappropriate and excessive anxiety concerning separation from home or from those to whom the individual is attached, as evidenced by three (or more) of the following:

(1) recurrent excessive distress when separation from home or major attachment figures occurs or is anticipated

(2) persistent and excessive worry about losing, or about possible harm befalling major attachment figures

(3) persistent and excessive worry that an untoward event will lead to separation from a major attachment figure (e.g., getting lost or being kidnapped)

(4) persistent reluctance or refusal to go to school or elsewhere because of fear of separation

(5) persistently and excessively fearful or reluctant to be alone, or without major attachment figures at home, or without significant adults in other settings

(6) persistent reluctance or refusal to go to sleep without being near a major attachment figure or to sleep away from home

(7) repeated nightmares involving the theme of separation

(8) repeated complaints of physical symptoms (such as headaches, stomachaches, nausea, or vomiting) when separation from major attachment figures occurs or is anticipated

B. The duration of the disturbance is at least 4 weeks.

C. The onset is before age 18 years.

D. The disturbance causes clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning.

E. The disturbance does not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and, in adolescents and adults, is not better accounted for by panic disorder with agoraphobia.

*Specify* if:

Early Onset: if onset occurs before age 6 years.

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## Natural History and Course

The community prevalence of SAD is generally estimated to be around 4% in children and young adolescents; it decreases in prevalence from childhood through adolescence (Moreau and Weissman 1993). A recent large twin study reported that at age 6, the prevalence was 7.4% for DSM-IV-defined SAD (using symptom criteria only) but only 2.8% when requiring clinically significant impairment (Bolton et al. 2006). As with community subjects, in clinically referred children and adolescents (aged 5–18 years) with anxiety disorders, SAD is found (Last et al. 1992) to be the most frequently occurring disorder, with a lifetime prevalence of 44.7%. The age of onset has been reported to be 4−7 years, with earlier onset being associated with clinical status and comorbidity (Biederman et al. 1997, Keller et al. 1992). However, in a recent study (Egger and Angold 2006) of preschool children (aged 2−5 years), SAD was found in 2.4%. Separation anxiety, particularly in younger samples, is found more frequently in girls than boys—with a ratio as high as 2.5:1 (Anderson et al. 1987). In a 3−4-year prospective study (Last et al. 1996) of subjects with anxiety disorders, 29% of children had SAD (21% had SAD as their primary diagnosis) at baseline. On follow-up, 92% of children previously diagnosed with SAD no longer had symptoms that met full criteria for SAD, although 25% had developed a new disorder, most frequently a depressive disorder. Finding that 50% of adult panic patients had experienced separation anxiety during childhood, it has been hypothesized (Gittleman and Klein 1984) that separation anxiety may be a childhood precursor to adult panic disorder and agoraphobia. In a study (Zitrin and Ross 1988) using a phobic control group, 48% of female agoraphobia patients had previous separation anxiety, as opposed to 20% of controls. Rates among males were not significantly different, however. The influence of comorbidity is also important in understanding the link between parental and offspring anxiety disorders. Although rates of separation anxiety are increased in the offspring of mothers with panic disorder, this has been found to be largely the result of parental separation anxiety (Biederman et al. 2006). A specific link between maternal phobic anxiety and child separation anxiety has also been demonstrated (Bernstein et al. 2005). In all, the evidence is uneven and it is difficult to be definitive since most studies are retrospective, focus on separation anxiety symptoms rather than the full disorder, and/or fail to include an appropriate control group.

## Etiology and Pathophysiology

Sensitivity to suffocation cues, important in the carbon dioxide ($CO_2$) challenge paradigm in panic disorder and respiratory response, may differentiate children with anxiety disorder, and separation anxiety in particular, from children without an anxiety disorder (Pine et al. 1998). Inhalation of air containing raised $CO_2$ concentration results in increased catecholamine release throughout the body and perceived anxiety. This response appears mediated via the locus coeruleus, a group of norepinephrine-containing neurons originating in the pons and projecting to all major brain areas. The locus coeruleus forms part of the reticular activating system (RAS) and functions to regulate noradrenergic tone and activity. Hypothalamic and thalamic nuclei also play a role in the perception of and response to external threats. They act by transmitting arousal information from the RAS to limbic and cortical areas involved in sensory integration and perception. The thalamus is thought to have a role in the perception of anxiety, whereas the hypothalamic nuclei mediate the response by the neuroendocrine system.

Experiments in rhesus monkeys inducing separation anxiety suggest roles for both the locus coeruleus/noradrenergic system as well as the hypothalamic–pituitary axis (HPA) (Chrousos and Gold 1992). Urinary cortisol has been shown to be raised (indicative of HPA overactivity) in infants aged 1 year who demonstrated extreme distress when separated from their primary attachment figure (Tennes et al. 1977).

Separation anxiety, when developmentally appropriate, is seen via attachment theory as an adaptive response that infants use to enhance proximity to their caregivers (Bowlby 1973). In this, when the infant has adequate proximity to the caregiver in a given context, attachment behaviors (separation anxiety symptoms) subside and are replaced by alternate behaviors. On the basis of their response to various experimental paradigms, infants can be categorized into having a different type of attachment. Although the nosology of attachment has varied, the most frequently described type of pathological attachment is known as "insecure attachment." Excessive distress on separation evinced by insecurely attached infants appears to be the earliest manifestation of SAD, but this pattern is not specific, in that it can be the precursor of other types of anxiety (e.g., social phobia/avoidant disorder, panic disorder) in childhood (Manassis et al. 1995) and adolescence.

Parenting behaviors are also hypothesized as being involved in the etiology of separation anxiety. Anxious parenting, possibly in response to observed distress in the child, seeks to prevent the child from experiencing further distress, thereby limiting exposure and the development of adaptive coping. Parental intrusiveness, a tendency to take over tasks that children are (or could be) performing independently, leads to failure by the child to experience mastery, and to develop inappropriate dependence on the parent. Such intrusiveness has been found (Wood 2006) to be linked to child separation anxiety, but not to other anxiety disorders.

## Diagnosis and Differential Diagnosis

The assessment strategy will depend upon the child's age, symptom profile, the sources of available information, and the purpose of the assessment. As discussed above, separation anxiety is normal at some ages and is maximal around 14 months of age (Crowell and Waters 1990). A study by Last et al. (1992) of outpatients with SAD revealed age differences but no gender differences in symptom profile and numbers of symptoms. The most prevalent symptoms in young children (aged 5–8 years) are worry about losing or about possible harm to an attachment figure, and reluctance or refusal to go to school. Children aged 9−12 years most frequently reported recurrent excessive distress when separated from home or attachment figures, whereas adolescents (aged 13–16 years) had physical symptoms on school days. More symptoms were reported with decreasing age.

The usual unstructured clinical interview can, in view of its poor reliability and variable symptom coverage, be supplemented by standardized diagnostic interviews such as the Diagnostic Interview Schedule for Children (DISC) or the Anxiety Disorder Interview Schedule (ADIS) which have shown acceptable test–retest reliability and validity (Shaffer et al. 1999, Silverman and Rabian 1995). In addition, there are a large number of self-report questionnaires that can assess children's fears and anxieties, either to detect anxiety disorders in community samples or to distinguish between the different anxiety disorders in clinically referred children. The most useful of these are the Multidimensional Anxiety Scale for Children (MASC) (March et al. 1997) and the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al. 1997). These have been shown to have good test–retest reliability, internal consistency, and can differentiate not only anxious children from nonanxious children but also distinguish specific anxiety disorders from each other. Particularly with younger children, there is value to direct observation of the child either in determining the diagnosis or in behavioral analysis (Glennon and Weisz 1978).

Other issues in assessment of separation anxiety include: the relative value of information from differing methodologies (i.e., unstructured interview, structured interview, self-report questionnaires, and direct observation), how to integrate information from separate informants, and also the cultural validity of most measures of anxiety.

Differential diagnoses to consider include GAD, where the anxiety is more free-floating, less situation-specific and occurs independent of separation from the primary attachment figure, and social phobia. Children with social phobia will display a fear of social situations where they may be the object of public scrutiny. This anxiety may be ameliorated by the presence of a familiar person but will not occur exclusively when the attachment figure is absent, as with separation anxiety.

School refusal has long been associated with SAD, though this relationship holds mainly for younger children when school nonattendance is most closely linked to fear of separation, whereas in adolescents fear of school and other social situations in which they feel they are being evaluated is more typical. It is important in the assessment of school nonattendance, a frequent impairment associated with SAD, to distinguish anxiety-related school refusal from conduct disorder–related truancy. Typically the school-refusing child will stay at home or with parents, whereas the truanting child will go off with peers. In the presence of school refusal, a useful approach (Kearney and Silverman 1999) is to attempt to categorize the behavior as fulfilling one of the four following functions:

1. Avoidance of stimuli provoking specific fearfulness or anxiety (e.g., separation).
2. Escape from aversive social or evaluative situations (e.g., social phobia).
3. Attention-getting behavior (e.g., physical complaints/tantrums).
4. Positive tangible reinforcement (e.g., parental collusion).

## Treatment

Following a good behavioral and functional analysis, the most frequently employed clinical approach to the treatment of separation anxiety and school refusal is behavioral. The principles of systematic desensitization to feared objects or situations will be employed, gradually increasing the amount of separation that can be tolerated in a graduated fashion. Systematic desensitization usually has three components. Firstly, a response incompatible with anxiety (often progressive muscular relaxation, but can be imagery or breathing exercises) is taught. The second component

is the collaborative construction of a hierarchy of feared situations. These will range from the very mild (producing mild disquiet) to the most anxiety provoking (avoided at all costs!). It is important to include a great deal of specificity in describing these situations, including the duration spent in the feared situation, the degree to which others are involved, and the distance from home/attachment figure. After ranking these feared situations, the final component of treatment is the regular progression of exposure to feared situations whilst employing anxiety management techniques. It is important that the child is allowed to exercise some control over the speed with which new settings are experienced. The avoidance of reinforcement of unwanted behaviors and the promotion of fear-coping strategies is similarly important.

In the particular example of school refusal associated with separation anxiety, it is important to encourage an early return to school so that secondary impairments (academic failure and social isolation) are minimized. Generally, if the period of absence has been less than 2 months, then return is very often successful; longer than 2 months is frequently associated with much greater difficulty negotiating adequate attendance. Many clinicians consider failure to attend school due to anxiety a relative psychiatric emergency in view of the data on poor outcome when prompt return is not achieved.

In older subjects, cognitive approaches may be more successful than the primary behavior strategies usually employed with younger children. Cognitive approaches postulate that the child's maladaptive thoughts, beliefs, and attitudes (schema) cause or maintain the experience of anxiety. Treatment consists of identifying negative self-statements ("I can't ever do this") or external beliefs ("If I'm not there my Mom won't be able to cope"), and replacing them with more adaptive beliefs.

There have been very few controlled studies of the psychosocial treatment of SAD per se (the majority being either small case-studies/series or are focused principally on school refusal, with little diagnostic homogeneity). A review (Thyer and Sowers-Hoag 1988) of the behavioral treatment of SAD showed positive responses in all studies to hierarchical exposure treatment (*in vivo* or in imagination), often combined with operant techniques. In view of the extensive comorbidity between the various anxiety disorders, most treatment studies of childhood anxiety include a large proportion of cases of separations anxiety. Data are rarely presented on outcomes for SAD separately, although there is no evidence that these symptoms are unusually responsive or resistant to CBT delivered individually or in a group format.

A recent review (Cartwright-Hatton et al. 2004) of the treatment of child and adolescent anxiety suggests that CBT is an effective intervention for childhood and adolescent anxiety. The observed remission rate in CBT treated subjects (56.5%) was higher than that in the control groups (34.8%), with a pooled odds ratio of 3.3 (95% CI = 1.9–5.6), suggesting that CBT has a significant effect. While many children with SAD benefit from receiving CBT, over a third maintained the diagnosis at the end of treatment. Despite the comparative strength of the evidence for CBT, it is not known whether CBT is effective in the long term, and whether it is as effective as other treatments. For some groups, particularly very young children, it is likely that traditional CBT will never be appropriate.

Pharmacological treatment studies of separation anxiety have tended to focus on samples with school refusal behavior and various diagnostic status or on subjects with a variety of comorbid anxiety disorders including SAD. Early studies (Klein et al. 1992, Berney et al. 1981) used imipramine or clomipramine with varying success (the presence of separation anxiety was not specifically associated with treatment response). More recently, the Research Unit on Pediatric Psychopharmacology Anxiety Study Group (2002) investigated 128 children with anxiety disorders (social phobia, SAD, and/or GAD aged 6−17 years). Subjects who failed to respond to an initial 3 weeks of psychological treatment were randomly assigned to a double-blind, placebo-controlled trial of fluvoxamine up to a maximum of 300 mg/day for 8 weeks. Children randomized to fluvoxamine showed significantly greater drops in anxiety disorder symptoms compared to placebo ($p < 0.001$). Pure cases of separation anxiety were very hard to find in this clinical sample, but therapeutic effect was seen in all symptom areas. A study (Birmaher et al. 2003) of 74 children and adolescents aged 7−17, again with mixed anxiety disorders (SAD, Social Phobia and GAD), showed 61% of subjects on fluoxetine to have significant improvement in global functioning compared to only 35% of controls.

Considering safety and efficacy, the SSRIs appear to be the first-line treatment for SAD, but more studies are needed to confirm preliminary results. SSRI treatment in responders should be continued for a 1-year period, but there are little data to support this. Tricyclic antidepressants and benzodiazepines may be considered when the child has not responded to SSRIs or when adverse effects have exceeded benefits. There is very little evidence on the treatment of children younger than 6 years of age—and specifically there are no controlled trials that attempt to evaluate a treatment specifically for young anxious children. This lack of evaluated treatment options is concerning in light of mounting evidence that many anxiety disorders have a very early onset, and that separation anxiety is not uncommon in this age group.

In practice, however, clinicians often combine drug and psychosocial treatments, capitalizing on differences in dose-response and time-response parameters. There is some evidence that treatments can be additive (each treatment having unique benefits) or synergistic (the benefit of the combination is greater that the additive combination). Alternatively, when combining drug and psychosocial treatments, a lower dose of one or both may be possible, with a resultant decrease in expense, inconvenience, or adverse events. Drug effects are often seen sooner than those due to exposure-based therapy, though it is hoped that the slower to emerge benefits of therapy may be more long lasting.

**Clinical Vignette 3**

Alex was an 8-year-old boy who lived with both parents and was referred by his pediatrician with a history of school refusal and recurrent abdominal pain, for which no organic cause could be found. Since commencing middle school (which begins at grade 3) Alex had been reluctant to separate from his mother, with frequent physical

complaints on school mornings. He expressed little anxiety verbally, though he was clingy and acted younger than his stated years. At the time of presentation, Alex had been off school for 5 weeks. Despite negative physical and radiological examinations, Alex continued to complain of severe stomach pains and nausea that prevented him from attending school.

Alex's symptoms first occurred at age 4 when he was unable to tolerate separation at pre-kindergarten. If left there he would frequently become so distressed that he would end a crying spell with vomiting, at which point his mother would be summoned and Alex would return home with her. Starting Kindergarten there were similar separation anxiety problems. These persisted for 3 months, though his school attendance was ensured by being dropped off by father on his way to work. In 1st and 2nd grades, anxiety symptoms were transitory at the start of each new school year and following return from extended vacation periods, but were not associated with significant school absence.

The current symptoms occurred during the summer vacation, prior to changing schools for 3rd grade. They were precipitated by Alex suffering a bout of food-poisoning. Mother, who had Crohn's disease, nursed him most assiduously and when Alex started having recurrent abdominal pain, worried that he had the juvenile form of this disorder. He developed increasing separation anxiety, following the mother from room to room. He became concerned about a rash of recent burglaries and that his mother would be home alone in the mornings once he returned to school. Alex was reluctant to sleep alone in his own room and began to require his mother to lie alongside him until he dropped asleep.

Upon interview Alex was a small pale child who clung excessively to his mother and frequently looked at her prior to answering questions. Father, appearing somewhat impatient sat at some distance from his wife and Alex. It was apparent early on that the relationship between parents was strained with obvious dissonance between mother and father about the nature, cause, and required management of Alex's symptoms. After a lengthy session, mother seemed a little more willing to accept that Alex's abdominal symptoms were anxiety related and that continued absence from school was counterproductive. It was agreed that, after discussion with his school, Alex would return promptly to school on the following Monday and that the family would return for a further session after school on Wednesday.

On their return it was reported that Alex had become unwell on Sunday night, and, although the family were fairly clear that he wasn't severely ill, mother took him to the pediatrician in the morning and on to school for the afternoon session. Although he remained at school, after marked initial distress, he came home very angry with his mother, and she was reluctant to take him the following day. Alex was willing to speak on his own to the psychiatrist, and he disclosed numerous fears about the welfare of his mother and his belief that she needed him at home. He also was ambivalent about missing school, realizing that he was missing his friends.

It was then negotiated that his father would take Alex to school each morning for the first 2 weeks, and that a series of family meetings would be supplemented by individual cognitive–behavioral work with Alex. A reward scheme would be established for Alex going to school despite abdominal pain, and for remaining at school. This approach proved successful and Alex was able to attend school. Abdominal pain was much reduced and over the next few weeks Alex was able to verbalize more his fears and concerns about whether his parents would get divorced (it was later disclosed that the parents had a brief separation during the early part of the year). Ongoing cognitive–behavioral sessions focused on Alex's fears and on strategies to encourage greater independence (couched in terms of "growing up"). Following the winter break, Alex once more expressed reluctance to return to school, but with encouragement (and firm expectations by both parents) he did not miss attendance, despite a great deal of anticipatory anxiety.

## Selective Mutism

### Definition

The essential feature of selective mutism is the persistent failure to speak in specific social situations (e.g., school, or with peers) where speaking is expected, despite speaking in other situations (e.g., home) (see DSM-IV-TR for Selective Mutism).

### Epidemiology

Previously referred to as *elective mutism*, in DSM-IV-TR the condition was renamed *selective mutism*, so as to be less judgmental (doesn't speak rather than chooses not to speak). The prevalence is usually reported as 0.6−7 per 1,000 (Brown and Lloyd 1975, Fundudis et al. 1979), with higher incidence in females rather than males (Hayden 1980).

When subjects failing to speak in the first few weeks of school (a DSM-IV-TR requirement) are excluded, rates

**DSM-IV-TR Criteria**

**Selective Mutism**

A. Consistent failure to speak in specific social situations (in which there is an expectation for speaking, e.g., at school) despite speaking in other situations.

B. The disturbance interferes with educational or occupational achievement or with social communication.

C. The duration of the disturbance is at least 1 month (not limited to the first month of school).

D. The failure to speak is not due to a lack of knowledge of, or comfort with, the spoken language required in the social situation.

E. The disturbance is not better accounted for by a communication disorder (e.g., stuttering) and does not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder.

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do not exceed 2 per 1,000. Onset is usually in the pre-school years, but the peak age of presentation and diagnosis is between 6 and 8 years (Dow et al. 1995). A study of the long-term outcome of selective mutism has recently been reported (Steinhausen et al, 2006). This showed that the symptoms had improved considerably by young adulthood. However, the selectively mute children did have significantly higher rates of phobic disorder (42% vs. 0%) and any psychiatric disorder (57% vs. 23%) than controls at follow-up (mean age 21.5 years).

A high incidence of insidious onset of refusal to speak with anyone except family members is reported. The other typical picture is one of acute onset of mutism on starting school (Hayden 1980, Kolvin and Fundudis 1981).

## Etiology

Three basic theories have been proposed to explain the etiology of selective mutism and describe distinct groups of children: children who are negative, oppositional, and controlling; traumatized children; and children who have severe anxiety, chiefly social phobia. Although early psychodynamic theorists (Hayden 1980) described an enmeshed relationship between mother and child, the father being distant and ineffectual, and a conflicted relationship between the parents, controlled studies of selective mutism do not find family functioning worse compared to the families of other emotionally disturbed children (Kolvin and Fundudis 1981, Wilkins 1985) or children with social phobia (Yeganeh et al 2006). Associated features include a history of delayed speech and articulation problems, and possibly, increased incidence of enuresis and/or encopresis (Dow et al. 1995, Kolvin and Fundudis 1981, Wilkins 1985). There may be a family history of general shyness, or of elevated levels of anxiety in the parents (Hayden 1980, Kolvin and Fundudis 1981). A recent review (Cohan et al. 2006) suggests that selective mutism develops due to a series of complex interactions (e.g., a strong genetic loading for anxiety interacts with an existing communication disorder, resulting in heightened sensitivity to verbal interactions and mutism in some settings). In children with selective mutism as well as meeting DSM-IV criteria for Social Phobia, more than half also meet criteria for another comorbid disorder, including generalized anxiety (26%) and oppositional defiant (29%) disorder (Yeganeh et al 2006). These rates are higher than those seem in social phobia not complicated by failure to speak in certain situations.

## Assessment

Prior to making a diagnosis of selective mutism, a comprehensive evaluation should be conducted to rule out other explanations for mutism and to assess important comorbid factors. For obvious reasons, the parental interview will form the mainstay of evaluation but, as discussed below, direct observation (and interview if possible) of the child can afford important diagnostic information.

It is important to obtain information of the nature of the onset (insidious or sudden), any uncharacteristic features (i.e., not talking to family members, abrupt cessation of speech in one setting, absence of communication in all settings) suggestive of other neurological or psychiatric disorders (e.g., pervasive developmental disorders, acquired aphasias), and any history of neurological insult/injury, developmental delays, or atypical language and/or speech. The assessment should also include the degree to which nonverbal communication or non-face-to-face communication is possible, the presence of anxiety symptoms in areas other than speaking, social and behavioral inhibition, and medical history including ear infections, and hearing deficiencies. Parents will be able to give information on where and to whom the child will speak, the child's speech and language complexity at home, articulation problems, use of nonverbal communication (e.g., gestures), any history of speech and language delays, and the possible importance of bilingualism (where primary language is not English). It can be useful to have the parents provide an audiotape of the child speaking at home.

The child evaluation can assess the presence of anxiety and social inhibition (willingness to communication through gesture or drawing). Physical examination of oral sensory and motor ability may provide evidence of neurological problems (i.e., drooling, asymmetry, orofacial weakness, abnormal gag reflex, impaired sucking or swallowing). Specialist audiometry (pure tone and speech stimuli as well as tympanometry and acoustic reflex testing) may provide evidence of hearing and/or middle ear problems that can have a significant effect on speech and language development. Cognitive abilities may be difficult to assess, but the performance section of the WISC-R (Wechsler 1974) or Raven's Progressive Matrices (Raven 1976) as well as the Peabody Picture Vocabulary Test (Dunn and Dunn 1981) may be useful in the nonverbal child.

## Treatment

Treatment has long been regarded as difficult and prognosis poor. Approaches have included behavioral therapy, family therapy, speech therapy, and more recently, pharmacological agents (Cline and Baldwin 1994). Unfortunately most published studies are single case reports, with very few controlled studies.

Behavioral treatment focuses on mutism as a means of getting attention and/or escaping from anxiety. A controlled study (Calhoun and Koenig 1973) of eight subjects with random assignment to treatment (teacher and peer reinforcement of verbal behavior) or control showed significant increases in mean number of vocalizations after 5 weeks of treatment. These gains were not, however, maintained at 12-month follow-up. Other techniques have included graded exposure, shaping, and modeling. The goal of a treatment program should be to decrease the anxiety associated with speaking whilst encouraging the child to interact verbally.

Regarding pharmacotherapy, early success with phenelzine in a 7-year-old girl with mutism and shyness (Golwyn and Weinstock 1990) led to the use of SSRI medication in cases of selective mutism with associated anxiety (principally social phobia). Successful case reports were followed by open and controlled studies using fluoxetine. An open trial of 21 children using a mean dose of 28.1 mg/day showed improvement in 76% of cases (Dummit et al. 1996). A placebo-controlled double-blind study showed mixed results, though both groups remained highly symptomatic. More chronic (>14 weeks) treatment was recommended (Black and Uhde 1994).

Clinical Vignette 4

Alice was a 7-year-old Caucasian girl who presented to a psychiatric outpatient clinic for evaluation following failure to speak in any social situations outside home. She attended 2nd grade where she was doing well academically with great accommodations having been made by teachers and peers in order to cope with her inability to speak. At home she was reported to be talkative and somewhat oppositional. She would talk using a bizarre baby language with her 6-year-old brother, but at other times would apparently speak normally with her parents. Father was a computer programmer with a schizoid personality and who himself spoke only in a whisper, allowing his wife to speak for him at most points in the evaluation. There was no evidence of any developmental delays, though toilet training was reportedly very difficult because of oppositional defiance. Alice presented as a shy child who did not like to separate much from father and who did not interact with the clinician. She was, however, very well able to communicate her wishes with gestures and facial expressions. Physical examination revealed no neurological or hearing abnormalities.

Initial treatment was principally behavioral with school aiming to encourage more verbal behavior, reducing the amount of help given to her by teachers and peers, so that she needed to express herself verbally. Speech therapy was provided to encourage the production of sounds and linguistic skills. Response to this in the first few weeks was disappointing with an increase in oppositional behavior and little change in verbal utterances. Attendance at weekly therapy appointments was sporadic, and parents seemed unhappy with the slow progress. After 6 months with Alice still not talking at school, it was decided on consultation with parents to have a trial of treatment with fluoxetine. Following a physical examination by her pediatrician and an electrocardiogram, treatment was commenced at 2.5 mg/day increasing to 10 mg after 2 weeks. After 5 days of treatment Alice began to talk more freely in familiar settings. By the sixth week of treatment she was talking in all settings. Medication was continued for 6 months, at which time it was tapered slowly and stopped. At follow-up she was reported talking without problems—in fact maybe talking too much now! Parents continued to seek psychiatric help for Alice, who was displaying more persistent oppositional behavior at home and at school, and also for her younger brother who had markedly reduced speech at school.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

In contrast to DSM-IV-TR, which establishes a minimum duration of 3 months for encopresis, the ICD-10 Diagnostic Criteria for Research has set a minimum duration of 6 months. In ICD-10, this disorder is referred to as "Nonorganic Encopresis."

For enuresis, the ICD-10 Diagnostic Criteria for Research have a different frequency threshold: at least twice a month in children aged under 7 years and at least once a month in children aged 7 years or more. In contrast, DSM-IV-TR requires either a frequency of twice a week for at least 3 consecutive months (regardless of age) or else the presence of clinically significant distress or impairment. Furthermore, ICD-10 includes a very strict exclusion criterion, preventing a diagnosis of enuresis to be made if there is any evidence of another mental disorder. In ICD-10, this disorder is referred to as "nonorganic enuresis."

For SAD, the DSM-IV-TR and ICD-10 symptom items are almost identical. The ICD-10 Diagnostic Criteria for Research are narrower in that the age of onset must be before age 6 and the diagnosis cannot be made if the presentation is "part of a broader disturbance of emotions, conduct, or personality." The DSM-IV-TR criteria and ICD-10 Diagnostic Criteria for Research for selective mutism are almost identical. In ICD-10, the disorder is referred to as "elective mutism."

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CHAPTER

# 50 Stereotyped Movement Disorder and Reactive Attachment Disorder

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This chapter describes two disorders that tend to occur in association with socially deprived environments, most often occurring in individuals who have developmental delays or mental retardation. Stereotyped Movement Disorder involves abnormal motor behaviors and Reactive Attachment Disorder (RAD) involves abnormal social behaviors.

## Stereotyped Movement Disorder

Stereotypic Movement Disorder is characterized by repetitive, seemingly driven, nonfunctional movements including hand waving, head banging, body-rocking, fiddling with fingers, self-biting, or hitting various parts of one's own body. These behaviors can be problematic for a number of reasons because they may result in self-injury, affect general health, result in significant social stigmatization, interfere with acquisition of new skills, and interfere with performance of existing skills.

### Diagnosis

Stereotypic movements are found throughout the population. They are more common, of greater intensity, and potentially more self-injurious, however, in individuals living in restrictive environments or having disorder-induced sensory deprivation. Restrictive environments usually mean institutional settings with inadequate social or environmental stimulation. Disorder-induced sensory deprivation occurs in blindness, autism, and mental retardation. Stereotypic movements seem to provide a soothing, arousal reducing, and possibly pleasurable function to individuals with histories of stimulation deprivation. As with most other DSM-IV-TR diagnoses, stereotypic movements must be sufficiently severe to become a focus of treatment (American Psychiatric Association 1999).

### Definition and Diagnostic Features

Stereotypies are repetitive, driven, and nonfunctional motor behavior. Stereotypic Movement Disorder is defined in the DSM IV-TR (American Psychiatric Association 1999) as stereotypic movements that interfere with regular functioning or cause self-injury that requires medical intervention or would if the stereotypic movement was not restricted. Several similar conditions are excluded, including stereotypic movements in the setting of pervasive developmental disorder, trichotillomania, compulsions, and substance use. While these are exclusions from the diagnosis of Stereotypic Movement Disorder, some of these exclusions will be touched on in this section, as they contribute some information about pathophysiology of stereotypic movements and self-injurious behaviors.

Berkson (1983) described stereotypies as voluntary, lacking variability, persisting over time, being immutable even when the environment changes and being inconsistent with the person's expected development.

The self-injurious behavior discussed in this chapter occurs in conjunction with stereotypic movements, which may or may not be different from other self-injurious behaviors, particularly those associated with affective, psychotic, and personality disorders. Those self-injurious behaviors tend to be more episodic and associated with cognitions, depersonalization, and negative feelings about oneself. The self-injurious behaviors associated with stereotypic behaviors have a more repetitive and driven quality to them.

### Assessment

Stereotypic movements are problematic when they interfere with a person's overall functioning, become socially stigmatizing, or result in self-injury. They can be observed by

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clinicians, reported by caregivers, or reported by the patient. Since a visit to a clinic or from a provider may be a stimulating experience, the stereotypic movement may not be readily observable by a clinician. Stereotypic movement ratings are part of several assessment scales designed for individuals with intellectual disabilities and Pervasive Developmental Disorders. For example, the Diagnostic Assessment for the Severely Handicapped-II (DASH-II) (Sturmey et al. 2004), has a scale for stereotypic movements and another for self-injurious behavior. The Stereotyped Behavior Scale (SBS) (Rojahn et al. 1997) was developed as a behavior rating scale for adolescents and adults with mental retardation. The common feature of scales used to assess stereotyped behavior is that they ask a clinician, caregiver, or patient to report on direct observations of behavior.

### Epidemiology

Stereotypic movements are relatively common. For example, as many as 90% of typically developing children engage in body rocking as a normal part of motor development, and 10% of normally developing 2-year-olds engage in head-banging while having tantrums (Berkson et al. 2001). Stereotypic movements are present but rare in populations of adults with average intelligence (Mendez and Mirea 1998) These behaviors are predictably longer-lived and more impairing in developmentally delayed populations. In fact, the more severe the level of retardation, the more likely the person is to exhibit stereotypic movements, and the more likely these stereotypic movements will be self-injurious. Another study found that individuals with profound mental retardation were more likely to have stereotypic behaviors and self-injury than those with severe mental retardation (Matson et al. 1997) New York and California state agency data sets of more than 130,000 people with mental retardation also showed increasing amounts of self-injurious behavior with increasing deficits in functioning (Schroeder et al. 2001).

More severe forms of stereotyped behavior with self-injury occurred in 4.6% of a sample of 3- to 40-month-old children with developmental disabilities. Less severe forms of stereotyped behavior were much more common, however; 100% of the children in this sample engaged in body rocking (Berkson et al. 2001). Other studies have shown as many as 17% of individuals with developmental disabilities engaging in repetitive self-injurious behavior, some very frequently (Schroeder et al. 2001). Although up to two-thirds of adults with mental retardation living in institutions exhibited stereotypic behavior, the number of adults with mental retardation residing in the community and exhibiting stereotypies appears to be much lower. A national survey of more than 25,000 mentally retarded, community-residing individuals in Germany found a prevalence of self-injurious behavior of 1.7% (Rojahn 1986).

### Comorbidity

Stereotypic Movement Disorder occurs most frequently in people with mental retardation, or pervasive developmental disorders. Because they both are related to conditions of neglect, Stereotypic Movement Disorder may co-occur with RAD. Several other conditions are also associated with stereotypic movements. Some genetic syndromes associated with Stereotypic Movement Disorder are Lesh-Nyhan Syndrome, associated with stereotypic self-biting of the forearms, Prader-Willi Syndrome associated with skin picking of the back of the hands, and Fragile X Syndrome.

### Differential Diagnosis

The stereotypic behaviors of Stereotypic Movement Disorder must be distinguished from a variety of other movements. Like most other DSM-IV TR diagnoses, the behaviors must be severe enough to cause impairment in functioning. Stereotypic Movement Disorder is often diagnosed in people with Mental Retardation. However, stereotypic movements are considered a feature of Pervasive Developmental Disorders and therefore would not be given a separate diagnosis when they occur in such individuals. Tics are generally simpler motor movements with a less-driven quality, however, some complex tics can be more difficult to differentiate from stereotypic movements. Neurological conditions with involuntary movements also tend to follow recognizable patterns that are typical for the neurological condition, and generally have a less driven quality. Tardive dyskinesia also follows generally recognizable patterns, including following antipsychotic use and having typical facial or truncal movements.

Stereotypic Movement Disorder must also be distinguished from a variety of different behaviors. Compulsions associated with Obsessive-Compulsive Disorder can look like stereotypic movements. Compulsions, though, are generally more complex than stereotypic behaviors. Compulsions are performed in order to reduce anxiety associated with an obsessive thought and compulsions are usually associated with rigid rules (e.g., washing left hand first twenty times, followed by the right hand twenty times).

Developmentally appropriate self-stimulatory behaviors such as thumb sucking can be differentiated from Stereotypic Movement Disorder by the appropriateness of the behavior to the patient's developmental level, changes in the behavior in response to the environment, and extinction of the behavior as the patient progresses in development.

Trichotillomania is another condition that must be distinguished from stereotypic movement disorder. By definition, trichotillomania refers only to hair pulling, and while it may be similar in repetitiveness, have a similar driven quality, and result in similar self-harm, it should not also be diagnosed as Stereotypic Movement Disorder. Factitious Disorder with Predominantly Physical Signs and Symptoms can be differentiated from Stereotypic Movement Disorder because the purpose of the movements is for medical attention.

Self-mutilation associated with Personality Disorders, Mood Disorders, and Psychotic Disorders can also be differentiated from Stereotypic Movement Disorder. The self-mutilation of Stereotypic Movement Disorder is associated with the repetitive, driven movement. Self-mutilation in other disorders is not associated with a movement, but rather with depersonalization, cognitions, and feelings about one's self.

## Etiology and Pathophysiology

Stereotypic Movement Disorder has a multifactorial pathophysiology involving a complex interaction between several neurological pathways, psychological factors, and social factors.

### Neurobiological Factors

Considerable research had addressed the neurobiology of stereotypies. Dopaminergic, serotinergic, and endogenous opioid systems have been associated with stereotypic movements and self-injurious behavior.

The dopaminergic system, specifically hypodomaninergic function in the striatum, has been tied to the development of stereotypic movements. Animal studies show a link between early deprivation, disruption of the dopamine system, and the development of stereotypic movements. Some human studies have supported this model. In one study, individuals with stereotypic movements had lower plasma homovanillic acid levels, a metabolite of dopamine and thus a marker of lower dopamine levels (Lewis et al. 1996). In addition, adults with stereotypic movements have decreased blink rates and greater motor slowness than matched controls, both of which have been associated with decreased dopamine system functioning (Bodfish et al. 1995, Lewis et al. 1996).

Serotonin has been studied in mental retardation and autism since the 1950s. Increased platelet uptake of serotonin in people with autism has been associated with decreased 5-HT2 receptor binding and an increase in stereotyped and self-injurious behaviors. Treatment with serotonin reuptake inhibitors has been associated with decreased stereotypic behavior in people with autism. Acute tryptophan depletion causes an increase in stereotypic behaviors in individuals with autism (Cook and Leventhal 1996, Schroeder et al. 2001).

The opioid system has also been studied in conjunction with stereotypic movements and self-injurious behavior. Several studies show that between 30% and 70% of patients with self-injurious behavior have dysregulated endogenous opioid systems (Schroeder et al. 2001). Patients with both stereotypic behaviors and self-injurious behaviors were found to have elevated β-endorphin plasma levels (Sandman et al. 1990). This finding led to the hypotheses that stereotypic and self-injurious behavior has the function of either indicating increased pain tolerance or addiction to endogenous opioids (Schroeder et al. 2001).

A group of animal studies have proposed a coping function for stereotypic movements, examining corticosterone levels as a marker of arousal. Mittleman et al. (1991) induced stereotypic movements with amphetamines, and then measured corticosterone levels. Corticosterone was significantly lower in the animals that had more stereotypic movements, supporting the hypothesis that stereotypies serve a function of reducing stress. Nevertheless, other studies have seemed to give opposite results, including a study by Wurbel and Stauffacher (1996) which looked at corticosterone levels in mice with a stereotypy of gnawing wire. Results here showed no increase in corticosterone when the mice did not have access to gnawing. The evidence remains inconclusive on the biological aspects of the coping function of stereotypic movements.

### Genetic Factors

Though little is known about the genetic factors affecting stereotypic movements, several genetic syndromes do predispose people to stereotypic movements and self-injurious behavior. These syndromes have unique mechanisms likely resulting in changes in the dopaminergic neurons and other changes leading to stereotypic movements.

Lesh-Nyhan Syndrome, for example, is associated with stereotyped self-biting that usually results in self-injury. The genetic mechanism here is indirect and not fully explicated. The genetic abnormality in Lesh-Nyhan is a dysfunctional enzyme, hypoxanthine-guanine-phosphoribosyl-transferase (HPRT). This leads to a buildup of purine, which results in an accumulation of uric acid in body fluids including cerebrospinal fluid. Positron emission tomography studies of patients with Lesh-Nyhan Syndrome show decreased numbers of dopamine transporters and decreased DOPA-decarboxylase. These findings indicate a reduction in dopaminergic neurons, possibly due to a loss of arborization. The stereotypic movements are then caused by abnormalities in the dopamine system, although other abnormalities probably also contribute to the self-injurious behavior (Schroeder et al. 2001).

### Psychological Factors

Stereotypic movements may be understood as a form of operant behavior that is maintained and reinforced by consequences of the behavior. In addition, other factors may contribute to the timing and intensity of the behavior. For example, the behavior will be decreased in the presence of social stimulation. Stereotyped behavior is also decreased following strenuous exercise, although not following mild exercise (Rapp and Vollmer 2005b).

Stereotypic and self-injurious behaviors may develop and persist in the absence of stimulation. Functional analysis of stereotypic behavior shows it can be maintained by positive reinforcement (e.g., sensory stimulation), negative reinforcement (e.g., removal of an unpleasant physical stimulus), or some combination of social and nonsocial reinforcement (e.g., social positive and automatic reinforcement) (Rapp and Vollmer 2005b).

### Social/Environmental Factors

Deprivation is the environmental factor most associated with stereotypic behavior. The self-stimulating effect of stereotypies has long been proposed as its function, thus explaining the increased prevalence of stereotypies in individuals living in institutions.

## Treatment

There are many different treatments for Stereotypic Movement Disorder, including several classes of medications, as well as behavior plans and social interventions. In approaching treatment, the first step should be addressing the patient's deprivation with social interventions, if possible. Behavioral treatments and medications can be used secondarily as needed for management of the patient's symptoms.

### Somatic Treatments

No medications have been approved by the Food and Drug Administration for the treatment of Stereotypic Movement Disorder. However, several classes of medication have shown some efficacy in treatment of this disorder.

Serotonin reuptake inhibitors have shown some efficacy in treating stereotypic movement disorders. A placebo-controlled trial of Clomipramine in 11 patients showed efficacy in 10 of them. These patients maintained a decrease in stereotypies even when the Clomipramine was discontinued (Rapp and Vollmer 2005a). The effect is

postulated to be due to a serotonin mechanism, as a study comparing clomipramine with desipramine and placebo showed clomipramine to be more effective in decreasing repetitive and compulsive behavior (Gordon 1992). Other evidence of serotonergic medications being effective is limited to case reports. Fluoxetine, Paroxetine, Citalopram, and Mirtazapine have been reported helpful in some case studies, but not consistently. One study, for example, showed fluoxetine and paroxetine were of no benefit in 40% of 37 adults with developmental disabilities. In this study, 25% of subjects had some deterioration, while 35% showed some reduction in perseverative and maladaptive behaviors (Branford et al. 1998). Other studies of selective serotonin reuptake inhibitors (SSRIs) have been equivocal at best, showing no clear benefit for antidepressants.

Antipsychotics are some of the most commonly prescribed drugs for people with mental retardation and behavioral problems. Antipsychotic medication was prescribed to 17−56% of the residents of group homes for mentally retarded people (King 2002). Studies and even case reports for stereotypic movements and self-injurious behaviors are sparse over the past decade, and previous studies were often seriously methodologically flawed. Despite widespread use of antipsychotics to treat stereotypies, they have limited evidence of efficacy and significant side effects, and some have suggested their use may not be appropriate (Rapp and Vollmer 2005b).

A few recent studies have provided modest support for use of antipsychotics. A pilot study of seven adults with severe mental retardation and stereotypic self-injurious behavior were given a 15-week trial of olanzapine. Three of the seven showed "clear improvement," while one additional person showed marginal improvement (McDonough et al. 2000). In the Autism literature, there are some studies that show improvement in stereotypic and self-injurious behavior with risperidone (McDougle et. al. 2005, Hellings et al. 2001).

One study of Valproic Acid in treatment of stereotypic behavior in autistic children showed a significant reduction in the stereotypic behavior in 13 patients as measured by the Children's Yale-Brown Obsessive Compulsive Scale (C-YBOCS) (Hollander 2006).

Opioid receptor blockers have been used for the treatment of self-injurious behavior with some efficacy. About 80% of patients in controlled studies had some decrease in self-injurious behavior with Naltrexone, and 47% of patients had a 50% or greater decrease in their behaviors (Symons et al. 2004). Specific studies, however, have varied greatly, and all studies include a significant number of opiod-blocker nonresponders; even the responders have not had as dramatic a decrease in self-injurious behavior as the endogenous opioid model would predict (Symons et al. 2004).

### Psychosocial Treatments

Behavioral therapies have been used to treat stereotypic and self-injurious behaviors (Clinical Vignette 1). Because most stereotypic movements are automatically reinforced, interventions involving environmental enrichment, differential reinforcement, and punishment were behavioral techniques that at least temporarily decreased stereotypic movements. Much work has been done in this area and the results are often quite successful (Rapp and Vollmer 2005b).

Clinical Vignette 1

Gina, a 42-month-old female, was brought in by her foster mother at the suggestion of the day-care center staff. During unstructured times in day care, Gina gots on her hands and knees and rocked back and forth vigorously. She did this for minutes at a time, and continued until her teacher physically stopped her. While engaging in this rocking behavior, Gina did not play and had to be physically redirected repeatedly. Neither staff at the center nor the foster mother understood why she did this, and they were worried that the intensity of this body rocking was so high that she might hurt herself. In fact, she had bruise and abrasians on her knees.

Gina had been with this foster family for the past 7 months. She lived with her biological mother prior to that. Gina's biological mother was not around much and left Gina and her 5-year-old brother with other family members and friends for days and even weeks at a time. Usually, Gina was put in the family room with the television on and left for hours at a time. Eventually, she was removed from her home because she was missing meals and her pediatrician diagnosed failure to thrive. Gina had been doing well with her foster family. They were providing consistent care and plenty of structure and stimulation. Initially, they had observed Gina rocking back and forth in a sitting position, but immediately attended to this behavior, providing her social stimulation and extra structure at times they noticed she engaged in these behaviors. Within a couple of months, these behaviors had stopped at home. The day care center provided structure and stimulation during the morning, but the afternoon staff was less skilled. It was during unstructured times in the afternoons that Gina's behaviors became problematic. Gina was switched to another class in the afternoons, and her body rocking extinguished over the next several months.

## REACTIVE ATTACHMENT DISORDER

Although social abnormalities in young children raised in abnormal environments have been described for many years, it was not until the publication of DSM-III (American Psychiatric Association 1980) that RAD appeared in psychiatric nosologies. The disorder described aberrant social behaviors in young children that were believed to derive from being reared in caregiving environments lacking in species typical nurturance and stimulation, such as in instances of maltreatment or institutional rearing. Subsequent to the original description of the disorder, the criteria have been revised to include two major types of abnormalities. These include an emotional withdrawn/inhibited type and an indiscriminately social/disinhibited pattern.

Despite descriptive studies of social abnormalities in deprived and maltreated children dating back more than half a century, systematic research on RAD has appeared only since the late 1990s. Nevertheless, findings to date are reasonably consistent about most features of the disorder (Zeanah and Smyke, in press).

### Diagnosis

#### Definition and Diagnostic Features

According to DSM-IV-TR (American Psychiatric Association 1999), RAD is a disturbance in social

relatedness that is apparent across most developmental contexts. It appears in the first 5 years of life, and it must be distinguished from pervasive developmental disorders. That is, presence of a pervasive developmental disorder precludes the diagnosis. Two clinical patterns are apparent, an emotionally withdrawn/inhibited type and an indiscriminately social/disinhibited type. These abnormal behaviors must be due to pathogenic care that the child has received.

## Assessment

As with most other disorders of early childhood, RAD is best assessed through a combination of interviewing and direct-behavioral observation. A detailed history of the child's caregiving experiences is important in order to establish that deficiencies were sufficient to account for the child's social abnormalities. Therefore, details of the child's caregiving history, with attention to neglect, changes in primary caregiving relationships, or significant losses of primary caregivers should be determined.

Structured interviews may be used to inquire about specific signs of the disorder (Smyke et al. 2002, Zeanah et al. 2004, Zeanah et al. 2005), and often are used to make the diagnosis. Standardized observational procedures that elicit the child's responses to familiar and unfamiliar caregivers in order to distinguish between the child's responses to putative attachment figures and to unfamiliar adults have been used in research and also may be useful in clinical settings (Boris et al. 2004, Zeanah et al. 2005).

Interviews and observations should include questioning about the child having one or more adults from whom he or she seeks comfort, reassurance, nurturing, and protection, particularly, in times of distress. In addition, failing to use the attachment figure for comfort, as occurs in the emotionally withdrawn/inhibited pattern, and exhibiting overly familiar behaviors with unfamiliar adults, as occurs in the indiscriminate/disinhibited pattern should be identified.

The clinical examination provides an opportunity to observe and stimulate attachment behaviors. The child's reaction on first meeting the interviewer (a stranger) can provide information about how a child references and/or seeks comfort from a caregiver in the context of a new person and setting. In addition, asking a parent to leave the room for a brief separation from the child can activate the child's attachment system and provide valuable information about how a child uses a parent upon reunion. Multiple observations and agreement between historical information and directly observed behaviors increase confidence in the diagnostic findings.

For a number of years, standardized observations of attachment behaviors were studied for assessment of attachment classifications rather than used diagnostically to assess RAD. However, a clinical assessment of attachment involving a stranger, separations and reunions, and the introduction of a robot as a mildly distressing stimulus also has been used reliably to diagnosis attachment disorders in a clinical context (Boris et al. 2004). The use of standardized procedures provides the clinician the opportunity to observe children's patterns of attachment behaviors in a consistent manner, reducing the influence of other variables.

## Epidemiology

Though epidemiologic data are limited, RAD is a rare disorder. In a study of 300 2−5-year-old children recruited from pediatric clinics in Durham, North Carolina, Egger et al. (2006) found no cases of RAD. Because pathogenic care is required to make the diagnosis, only children with histories of severe deprivation, such as maltreated children and those raised in institutions are eligible. Even in high-risk groups, the diagnosis is uncommon. For example, in a study of currently and formerly institutionalized children in Bucharest, Romania, at 54 months of age, fewer than a third of the children met criteria for RAD (Zeanah and Smyke, in press).

## Comorbidity

There are no studies to date of comorbidity in RAD. Nevertheless, reasonable speculation is possible given what is known about the etiology of the disorder. Because of the conditions known to give rise to RAD, namely maltreatment and institutional deprivation, other disorders known to arise in similar conditions of risk may co-occur. Chief among these is developmental delays, particularly, mental retardation and language disorders. In addition, because physical abuse may co-occur with neglect, Posttraumatic Stress Disorder (PTSD) has been reported to co-occur with the emotionally withdrawn/inhibited type of RAD (Hinshaw-Fuselier et al. 1999).

Attention Deficit Hyperactivity Disorder (ADHD) also is known to be overrepresented among children raised in institutions, and it is possible that the social impulsivity that occurs in the emotionally withdrawn inhibited type of RAD co-occurs with the more cognitive and behavioral impulsivity that occurs in ADHD. This has not been examined systematically, but it remains one of the important questions about the disorder.

## Course

Though relevant data remain scarce, findings to date suggest that the emotionally withdrawn/inhibited and the indiscriminately social types of RAD have different courses over time.

Only one longitudinal study has examined the course of the emotionally withdrawn type of RAD (Zeanah and Smyke, in press). In the Bucharest Early Intervention Project (BEIP) (Zeanah et al. 2003), young children living in institutions were randomly assigned to either continued institutional care or to removal from institutions and placement in foster care. The children in these two groups were followed from 2−4 years at regular intervals. In the institutionalized group, signs of the emotionally withdrawn/inhibited type of RAD persisted, but in young children placed with foster families, signs of the disorder disappeared within a few weeks to a few months (Zeanah and Smyke, in press). Although data are limited, to date no one has shown that formation of attachment is precluded, suggesting that the emotionally withdrawn/inhibited pattern of RAD remains responsive to intervention.

In contrast, several studies have demonstrated that the indiscriminate social/disinhibited type of RAD is one of the most persistent social abnormalities in young children raised in institutions. Even following adoption or placement in foster care, signs of indiscriminate/disinhibited RAD may persist

for years (Chisholm 1998, Hodges and Tizard 1989, Rutter et al., in press, Zeanah and Smyke, in press). In the BEIP, young children in foster care had some reduction in signs of indiscriminate behavior, but this was primarily in those who had received the intervention when they were younger. These data suggest that for some children, there may be a critical period after which amelioration of the indiscriminately social/disinhibited pattern becomes far more difficult.

### Differential Diagnosis

When considering a diagnosis of the emotionally withdrawn inhibited type of RAD, one must consider mental retardation and autistic spectrum disorders in the differential diagnosis. Most children with RAD will demonstrate significant concurrent developmental delays, but this may be distinguished from children who have solely delayed development.

Focused attachment occurs in typically developing children at 7–9 months of age. Therefore, as long as the child has a cognitive age of at least 10 months, one may distinguish the emotionally withdrawn/inhibited type of RAD from mental retardation because in the former attachment behaviors are either absent, quite limited or aberrant. In mental retardation, the child has attachment behaviors readily discernible. RAD should not be diagnosed in children younger than 10 months of age because infants are not expected to manifest focused attachment behaviors much prior to that. The emotionally withdrawn/inhibited type may not be diagnosed if the child meets criteria for autism or pervasive developmental disorder not otherwise specified. RAD may be distinguished from autism in that in the latter there is a selective impairment in pretend play and a selective impairment in the initiation and response to joint attention, that is, the shared focus on an object of interest; neither of these impairments is present in RAD. In addition, although children with RAD often have stereotypies, they do not exhibit the kind of interest in restricted, repetitive interests and behaviors seen in children with pervasive developmental disorders.

The indiscriminately social/disinhibited type of RAD must be distinguished from nondisordered children with high levels of sociability, as well as from children with ADHD. The former distinction is guided by detailed questioning, by assessing impairment, and by experience of the evaluator, as there are no clearly identified cut off scores on standardized measures. Highly sociable children may be inclined to engage readily with unfamiliar adults, but they are probably not as willing to leave readily with a stranger, as has been reported for children with the indiscriminate/disinhibited type of RAD. Indiscriminate/disinhibited RAD may be distinguished from ADHD because the impulsivity in RAD is limited to social situations and because there is no reason for the child to demonstrate hyperactivity or distractibility.

### Differences in Presentation

There are no known effects of gender or culture related to the presentation or prevalence of RAD. Age of onset is specified as within the first 5 years of life, but most likely the disorder is present from the latter part of the first year of life. Only one study has examined indiscriminate behavior in children placed in institutions after the first 3 years of life. No indiscriminate behavior was detected in young children who entered institutional care later following initial home rearing (Wolkind 1974).

## Etiology

Unlike most DSM-IV-TR disorders, the etiology of RAD is specified in the criteria. The social abnormalities must be due to pathogenic care that the child received. Although pathogenic care is not described, examples are children who have limited opportunities to form selective attachments, such as those who experience frequent foster placement or institutional rearing. A consensus is that the key ingredient of pathogenic care related to the development of RAD is social neglect. What remains unclear is why two distinctive subtypes of RAD arise in similar conditions of risk but are phenomenologically different and have different courses and correlates.

### Genetic and Neurobiological Factors

There are no known genetic risk factors for RAD. Nevertheless, because most children in socially-deprived environments do not develop RAD, an unresolved question is whether biological differences, including genetic polymorphisms, may confer vulnerability or risk to children experiencing severe deprivation. This has yet to be explored.

An intriguing finding possibly related to the indiscriminate/disinhibited type of RAD derives from work on Williams Syndrome, a microdeletion syndrome of the 7th chromosome. In addition to cognitive delays and physical abnormalities such as facial dysmorphology and supravalvular aortic stenosis, children with Williams Syndrome also demonstrate high levels of indiscriminate behavior, despite having no histories of deprivation (Jones et al. 2000). The phenotypic similarities raise questions about a specific genetic vulnerability to RAD.

There have been no direct studies of possible neurobiological contributors to RAD. Nevertheless, children raised in institutions, an environment known to increase risk for RAD, also have been shown to have long-term disturbances in cortisol metabolism (Gunnar and Vazquez 2006) and in brain functioning (Chugani et al. 2001). Nevertheless, the direct association of signs of RAD and these neurobiological abnormalities remains to be explored.

### Social/Environmental Factors

RAD is one of the few disorders in DSM-IV-TR (American Psychiatric Association 1999) that includes the etiology as a criterion for diagnosis. Specifically, pathogenic care is supposed to account for the signs and symptoms of abnormal attachment and social behaviors seen in the disorder. Extreme caregiving environments, such as being raised in institutions or in conditions of social neglect are necessary for the disorder to occur. In fact, signs of the disorder are readily apparent in young children being raised in institutions (Smyke et al. 2002, Zeanah et al. 2005) and in maltreated children (Boris et al. 2004, Zeanah et al. 2004).

Within institutional settings, the emotionally withdrawn/inhibited pattern of RAD has been associated with quality of the caregiving that the child received (Zeanah et al. 2005). With regard to the indiscriminately social/disinhibited pattern, however, children adopted out of institutions show indiscriminate behavior proportionate to the degree

of deprivation they experienced, as defined by length of time they were institutionalized (O'Connor et al. 2003). On the other hand, this type of RAD has not been associated with the quality of care the child received in an institutional setting.

Other than the indiscriminate behavior described in Williams Syndrome (Jones et al. 2000) and in fetal alcohol syndrome (FAS) (Jacobson and Jacoboen 2003, no cases of children exhibiting signs of RAD have been described in the absence of a history of severe neglect. There have been no systematic studies of signs of indiscriminate behavior in FAS, though this is an important area to examine because of the likely overlap of social neglect in children who experienced significant prenatal alcohol exposure. Similarities in the presentation of children with Williams Syndrome and RAD underscores the importance of the pathogenic care criterion as a distinguishing feature of RAD.

## Treatment

Despite limited data, the guiding principle of treatment of RAD is that enhancing the caregiving environment of the child leads to elimination of signs of disordered attachment behavior (American Academy of Child and Adolescent Psychiatry 2005). To date, there are a number of case reports demonstrating just that (Hinshaw-Fuselier et al. 1999, Zeanah and Boris 2000, Zeanah et al. 1993).

The primary goal of treatment for the emotionally withdrawn/inhibited type of RAD is creating the possibility for the child to develop a focused attachment relationship to a primary caregiver. Ordinarily, this happens quickly once a child is in a reasonably typical caregiving environment. Attachment behaviors in young children placed into foster care, for example, begin to develop within days of initial placement (Stovall and Dozier 2000).

The goal for treatment of the indiscriminate disinhibited type of RAD is to increase the child's reliance on attachment figures and decrease their engagement with unfamiliar adults. Clinicians often advise that adoptive families limit the contacts of children adopted out of institutions for a period of several months, in order to give the child an opportunity to form selective attachments to them and to reduce the confusion of transitioning from an institutional setting to a family. There are, however, no studies that have addressed this advice. Indeed, from studies of children adopted out of institutions, long-term stability of indiscriminate/disinhibited behavior is clear (Chisholm 1998, Rutter et al., in press).

No medications are indicated for RAD. Somatic treatments are used only to treat co-morbid disorders. The disorder results from atypical caregiving environments and may be ameliorated by enhanced caregiving relationships.

Caregiver characteristics and behaviors known to foster secure attachments include knowing and valuing the child as an individual, being sensitive and responsive to the child's needs, and placing the child's needs ahead of their own needs (Clinical Vignette 2). These are the characteristics and behaviors that clinicians want to create. Two approaches known to enhance attachment promoting behaviors in caregivers include showing mothers videotapes of sensitive caregiving and coaching them about how to be more sensitive with their infants (van den Boom 1994) and Circle of Security (Hoffman et al. 2007), a group-based intervention designed to teach caregivers about their own emotional responses to their children and to help them recognize when young children miscue them about their needs. Neither of these has yet been applied to children diagnosed with RAD, however. Studies of treatment of RAD are urgently needed to reduce morbidity and enhance social adaptation in the child.

Clinical Vignette 2

Lindsey was a 41-month-old girl who was removed from her mother at age 32 months and placed in foster care. Before that, she had a history of neglect and witnessing extensive partner violence between her mother and mother's boyfriend. She was dismissed from her childcare center for spitting, hitting, biting, and having a "demonic look" earlier in the year. At the time she came into care, Lindsey did not check back with her foster mother in unfamiliar settings, showed affection towards total strangers, and her foster mother reported having to hold her hand in public settings (such as the mall) to prevent her from "wandering off" with strangers. This caused her foster mother considerable worry and restricted the number of times she was willing take Lindsey out in public.

When seen for evaluation, Lindsey was active, running, climbing, and doing summersaults, repeatedly calling attention to herself. Despite her foster mother's admonitions, she ran into the offices of other clinicians several times, and she approached and tried to kiss several adults in the waiting area. She walked into the receptionist's area and linked her arm around the receptionist's arm. In the office, she made a show of falling down and stating she was hurt, expressing the desire to be rescued.

A behavioral plan was implemented to assist her foster mother in managing Lindsey's behavior. Her foster mother was advised to restrict Lindsey's contact with unfamiliar adults and to talk with her about appropriate behavior with strangers. In a follow-up three months later, the foster mother reported that in a new daycare setting that was warmer but more structured than the initial setting, Lindsey's behavior settled down considerably. Her eagerness to hug and kiss strangers was reported to be declining, but she continued to approach unfamiliar adults.

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CHAPTER

# 51 Dementia, Delirium, and Other Cognitive Disorders

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Dementia
- Dementia of the Alzheimer Type
- Vascular Dementia
- Substance-Induced Persisting Dementia
- Dementia due to Other General Medical Conditions
- Dementia due to Multiple Etiologies

Delirium
- Delirium due to a General Medical Condition
- Substance Intoxication Delirium
- Substance Withdrawal Delirium

Amnestic Disorders
- Amnestic Disorder due to a General Medical Condition
- Substance-Induced Persisting Amnestic Disorder

This chapter reviews dementia, delirium, amnestic, and other cognitive disorders. Traditionally, these conditions have been classified as organic brain disorders to distinguish them from such diseases as schizophrenia, mania, and major depressive disorder, the so-called functional disorders. With the publication of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), the distinction between functional and organic disorders was eliminated. Significant research into the neurobiological aspects of psychiatric disorders and the utilization of sophisticated neurodiagnostic tests such as positron emission tomographic scanning in schizophrenics led to the inescapable conclusion that every psychiatric condition has a biological component. Thus the term functional became obsolete and even misleading.

The conditions formerly called organic are classified in DSM-IV-TR into three groupings: (1) delirium, dementia, and amnestic and other cognitive disorders; (2) mental disorders due to a general medical condition; and (3) substance-related disorders (First 1994). Delirium, dementia, and amnestic disorders are classified as cognitive because they feature impairment in such parameters as memory, language, or attention as a cardinal symptom. Each of these three major cognitive disorders is subdivided into categories that ascribe the etiology of the disorder to a general medical condition, the persisting effects of a substance, or multiple etiologies. A "not otherwise specified" category is included for each disorder (First 1994).

In the case of delirium, the primary disturbance is in the level of consciousness with associated impairments in orientation, memory, judgment, and attention. Dementia features cognitive deficits in memory, language, and intellect. The amnestic disorder is characterized by impairment in memory in the absence of clouded consciousness or other noteworthy cognitive dysfunction. In general, the cognitive disorders should represent a decline from a previous higher level of function, of either acute (delirium) or insidious (dementia) onset, and should interfere with the patient's social or occupational functioning (First 1994).

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## Dementia

Dementia is defined in DSM-IV-TR as a series of disorders characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, the persisting effects of a substance, or multiple etiologies (e.g., the combined effects of a metabolic and a degenerative disorder) (First 1994). The disorders constituting the dementias share a common symptom presentation and are identified and classified on the basis of etiology. The cognitive deficits exhibited in these disorders must be of sufficient severity to interfere with either occupational functioning or the individual's usual social activities or relationships. In addition, the observed deficits must represent a decline from a higher level of function and not be the consequence of a delirium. A delirium can be superimposed on a dementia, however, and both can be diagnosed if the dementia is observed when the delirium is not in evidence. Dementia typically is chronic and occurs in the presence of a clear sensorium. If clouding of consciousness occurs, the diagnosis of delirium should be considered. The DSM-IV-TR classification of dementia is reviewed in Table 51–1.

**Table 51–1 DSM-IV-TR Classification of Dementia**

| |
|---|
| Dementia of the Alzheimer type |
| Early onset vs. late onset |
| Uncomplicated |
| With delirium |
| With delusions |
| With depressed mood |
| Vascular dementia |
| Uncomplicated |
| With delirium |
| With delusions |
| With depressed mood |
| Dementia due to head trauma |
| Dementia due to Parkinson's disease |
| Dementia due to HIV disease |
| Dementia due to Huntington's disease |
| Dementia due to Pick's disease |
| Dementia due to Creutzfeldt-Jakob disease |
| Dementia due to other general medical conditions (e.g., neurosyphilis, normal-pressure hydrocephalus) |
| Substance-induced persisting dementia |
| Dementia due to multiple etiologies |
| Dementia not otherwise specified |

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### Clinical Features

Essential to the diagnosis of dementia is the presence of cognitive deficits that include memory impairment and at least one of the following abnormalities of cognition: aphasia, agnosia, apraxia, or a disturbance in executive function (First 1994).

Memory function is divided into three compartments that can easily be evaluated during a Mental Status Examination. These are immediate recall (primary memory), recent (secondary) memory, and remote (tertiary memory). Primary memory is characterized by a limited capacity, rapid accessibility, and a duration of seconds to minutes (Karp 1984). The anatomic site of destruction of primary memory is the reticular activating system, and the principal activity of the primary memory is the registration of new information. Primary memory is generally tested by asking the individual to repeat immediately a series of numbers in the order given. Because primary memory testing measures such parameters as attention, concentration, and ability to follow instructions, the results are often abnormal for the demented patient. This loss of ability to register new information accounts in part for the confusion and frustration the demented patient feels when confronted with unexpected changes in daily routine.

Secondary memory has a much larger capacity than primary memory, a duration of minutes to years, and relatively slow accessibility. The anatomic site of dysfunction for secondary memory is the limbic system, and individuals with a lesion in this area may have little difficulty repeating digits immediately, but show rapid decay of these new memories. In minutes, the patient with limbic involvement may be totally unable to recall the digits or even remember that a test has been administered (Karp 1984). Thus, secondary memory represents the retention and recall of information that has been previously registered by primary memory. Clinically, secondary memory is tested by having the individual repeat three objects after having been distracted (usually by the examiner's continuation of the Mental Status Examination) for 3–5 min. Like primary memory, secondary recall is often impaired in dementia. Patients with an early or mild dementia may be able to retrieve memories if given some sort of clue, such as "…one of the objects you missed was a color." Giving clues to the demented patient with a primary memory loss is pointless, because the memories were never registered. Wernicke-Korsakoff syndrome is an example of a condition in which primary memory may be intact while secondary recall is impaired.

Tertiary (remote) memory has a capacity that is probably unlimited, and such memories are often permanently retained. Access to tertiary memories is rapid, and the anatomical dysfunction in tertiary memory loss is in the association cortex (Karp 1984). In the early stages of dementia, tertiary memory is generally intact. It is tested by instructing the individual to remember personal information or past material. The personal significance of the information often influences the patient's ability to remember it. For example, a woman who worked for many years as a seamstress might remember many details related to that occupation, but could not recall the names of past presidents or three large cities in the United States. Thus, a patient's inability to remember highly significant past material is an ominous finding. Collateral data from informants is essential in the proper assessment of memory function. In summary, primary and secondary memories are most likely to be impaired in dementia, with tertiary memory often spared until late in the course of the disease.

In addition to defects in memory, patients with dementia often exhibit impairments in language, recognition, object naming, and motor skills. Aphasia is an abnormality of language that often occurs in vascular dementias involving the dominant hemisphere. Because this hemisphere controls verbal, written, and sign language, these patients may have significant problems interacting with people in

their environment. Patients with dementia and aphasia may exhibit paucity of speech, poor articulation, and a telegraphic pattern of speech (nonfluent, Broca's aphasia). This form of aphasia generally involves the middle cerebral artery with resultant paresis of the right arm and lower face (Henderson 1990). Despite faulty communication skills, patients with dementia with nonfluent aphasia have normal comprehension and awareness of their language impairment. As a result, such patients often present with significant depression, anxiety, and frustration.

By contrast, patients with dementia with fluent (Wernicke's) aphasia may be quite verbose and articulate, but much of the language is nonsensical and rife with such paraphasias as neologisms and clang (rhyming) associations. Whereas nonfluent aphasias are usually associated with discrete lesions, fluent aphasia can result from such diffuse conditions as dementia of the Alzheimer type. More commonly, fluent aphasias occur in conjunction with vascular dementia secondary to temporal or parietal lobe CVA. Because the demented patients with fluent aphasia have impaired comprehension, they may seem apathetic and unconcerned with their language deficits, if they are in fact aware of them at all. They do not generally display the emotional distress of patients with dementia and nonfluent aphasia (Table 51–2).

**Table 51–2 Classification of Aphasias**

| Type | Language | Comprehension | Motor |
|---|---|---|---|
| Wernicke's (receptive) | Impaired Fluent Articulate Paraphasias | Impaired | Normal |
| Broca's (expressive) | Nonfluent Sparse Telegraphic Inarticulate | Intact | Right hemiparesis |
| Global | Nonfluent Mute | Impaired | Variable right hemiplegia |

Patients with dementia may also lose their ability to recognize. Agnosia is a feature of a dominant hemisphere lesion and involves altered perception in which, despite normal sensations, intellect, and language, the patient cannot recognize objects. This is in contrast to aphasia in which the patient with dementia may not be able to name objects, but can recognize them (Berg et al. 1994). The type of agnosia depends on the area of the sensory cortex that is involved. Some demented patients with severe visual agnosia cannot name objects presented, match them to samples, or point to objects named by the examiner. Other patients may present with auditory agnosia and be unable to localize or distinguish such sounds as the ringing of a telephone. A minority of demented patients may exhibit astereognosis, inability to identify an object by palpation.

Demented patients may also lose their ability to carry out selected motor activities despite intact motor abilities, sensory function, and comprehension of the assigned task (apraxia). Affected patients cannot perform such activities as brushing their teeth, chewing food, or waving good-bye when asked to do so (Kaufman 1990a).

The two most common forms of apraxia in demented patients are ideational and gait apraxia. Ideational apraxia is the inability to perform motor activities that require sequential steps and results from a lesion involving both frontal lobes or the complete cerebrum. Gait apraxia, often seen in such conditions as normal-pressure hydrocephalus, is the inability to perform various motions of ambulation. It also results from conditions that diffusely affect the cerebrum.

Impairment of executive function is the inability to think abstractly, plan, initiate, and end complex behavior. On Mental Status Examination, patients with dementia display problems coping with new tasks. Such activities as subtracting serial sevens may be impaired.

Obviously, aphasia, agnosia, apraxia, and impairment of executive function can seriously impede the demented patients' ability to interact with their environment. An appropriate Mental Status Examination of the patient with suspected dementia should include screening for the presence of these abnormalities.

## Mental Status Examination

The findings on the Mental Status Examination vary depending on the etiology of the dementia. Some common abnormalities have been discussed previously (see earlier section on clinical features). In general, symptoms seen on the Mental Status Examination, whatever the etiology, are related to the location and extent of brain injury, individual adaptation to the dysfunction, premorbid coping skills and psychopathology, and concurrent medical illness (Slaby and Erle 1993).

Disturbance of memory, especially primary and secondary memory, is the most significant abnormality. Confabulation may be present as the patient attempts to minimize the memory impairment. Disorientation and altered levels of consciousness may occur, but are generally not seen in the early stages of dementia uncomplicated by delirium. Affect may be affected as in the masked facies of Parkinson's disease and the expansive affect and labile mood of pseudobulbar palsy after cerebral injury. The affect of patients with hepatic encephalopathy is often described as blunted and apathetic. Lack of inhibition leading to such behavior as exposing oneself is common, and some conditions such as tertiary syphilis and untoward effects of some medication can precipitate mania. The Mental Status Examination, in conjunction with a complete medical history from the patient and informants and an adequate physical examination, is essential in the evaluation and differential diagnosis of dementia (Table 51–3).

## Physical and Neurological Examinations in Dementia

The physical examination may offer clues to the etiology of the dementia; however, in the elderly, one must be aware of the normal changes associated with aging and differentiate them from signs of dementia. Often the specific physical examination findings indicate the area of the central nervous system affected by the etiological process. Parietal lobe dysfunction is suggested by such symptoms as astereognosis, constructional apraxia, anosognosia, and problems with two-point discrimination (Kaufman 1990a). The dominant hemisphere parietal lobe is also involved in Gerstmann's syndrome, which includes agraphia, acalculia, finger agnosia, and right–left confusion.

**Table 51–3 Evaluation of Dementia**

- Medical history and physical examination
- Family interview
- Routine laboratory
  - Chemistry (SMA 20)
  - Urinalysis
  - Hematology (complete blood count)
- Other routine tests
  - Chest radiography
  - Electrocardiography
- Specialized laboratory
  - Thyroid functions
  - VDRL (fluorescent treponemal antibody screen if indicated)
  - Drug screen
  - Vitamin $B_{12}$ and folate levels
  - Cerebrospinal fluid analysis (if indicated)
  - HIV testing (if indicated)
- Other studies
  - Computed tomography or magnetic resonance imaging
  - Electroencephalography

Reflex changes such as hyperactive deep tendon reflexes, Babinski's reflex, and hyperactive jaw jerk are indicative of cerebral injury. However, primitive reflexes such as the palmomental reflex, which occurs in 60% of normal elderly people, and the snout reflex seen in a third of elderly patients are not diagnostically reliable for dementia (Wolfson and Katzman 1983).

Ocular findings such as nystagmus (as in brain stem lesions), ophthalmoplegia (Wernicke-Korsakoff syndrome), anisocoria, papilledema (hypertensive encephalopathy), cortical blindness (Anton's syndrome), visual field losses (CVA hemianopia), Kayser–Fleischer rings (Wilson's disease), and Argyll Robertson pupils (syphilis, diabetic retinopathy) can offer valuable clues to the etiology of the cognitive deficit (Victor and Adams 1974).

Movement disorders including tremors (Parkinson's disease, drug intoxication, cerebellar dysfunction, Wilson's disease), chorea (Huntington's disease, other basal ganglia lesions), myoclonus (subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, Alzheimer disease, anoxia), and asterixis (hepatic disease, uremia, hypoxia, carbon dioxide retention) should be noted.

Gait disturbances, principally apraxia (normal-pressure hydrocephalus, inhalant abuse, cerebellar dysfunction) and peripheral neuropathy (Korsakoff's syndrome, neurosyphilis, heavy metal intoxication, solvent abuse, isoniazid or phenytoin toxicity, vitamin deficiencies, and HIV spectrum illnesses), are also common in dementia. Extrapyramidal symptoms in the absence of antipsychotics may indicate substance abuse, especially phencyclidine abuse, or basal ganglia disease. Although the many and varied physical findings of dementia are too numerous to mention here, it should be obvious that the physical examination is an invaluable tool in the assessment of dementia (Table 51–4).

**Table 51–4 Physical Signs Associated with Dementia or Delirium**

| Physical Sign | Condition |
|---|---|
| Myoclonus | Creutzfeldt-Jakob disease<br>Subacute sclerosing panencephalitis<br>Postanoxia<br>Alzheimer's disease (10%)<br>AIDS dementia<br>Uremia<br>Penicillin intoxication<br>Meperidine toxicity |
| Asterixis | Hepatic encephalopathy<br>Uremia<br>Hypoxia<br>Carbon dioxide retention |
| Chorea | Huntington's disease<br>Wilson's disease<br>Hypocalcemia<br>Hypothyroidism<br>Hepatic encephalopathy<br>Oral contraceptives<br>Systemic lupus erythematosus<br>Carbon monoxide poisoning<br>Toxoplasmosis<br>Pertussis, diphtheria |
| Peripheral neuropathy | Wernicke-Korsakoff syndrome<br>Neurosyphilis<br>Heavy metal intoxication<br>Organic solvent exposure<br>Vitamin $B_{12}$ deficiency<br>Medications: isoniazid, phenytoin |

## Associated Features and Behavior

In addition to the diagnostic features already mentioned, patients with dementia display other identifying features that often prove problematic. Poor insight and poor judgment are common in dementia and often cause patients to engage in potentially dangerous activities or make unrealistic and grandiose plans for the future. Visual–spatial functioning may be impaired, and if patients have the ability to construct a plan and carry it out, suicide attempts can occur. More common is unintentional self-harm resulting from carelessness, undue familiarity with strangers, and disregard for the accepted rules of conduct.

Emotional lability, as seen in pseudobulbar palsy after cerebral injury, can be particularly frustrating for caregivers, as are occasional psychotic features such as delusions and hallucinations. Changes in their environment and daily routine can be particularly distressing for demented patients, and their frustration can be manifested by violent behavior.

## Epidemiology

The prevalence of dementias is not precisely known. Estimates vary depending on the age range of the population studied and whether the individuals sampled were in the general community, acute care facilities, or long-term nursing institutions. A review of 47 surveys of dementia conducted between 1934 and 1985 indicated that dementia increased exponentially, doubling every 5 years up to age 95 years, and that this condition was equally distributed among men and women, with Alzheimer's dementia (AD) much more common in women (Slaby and Erle 1993). Other dementias such as those related to cerebrovascular diseases are more common in males, so while overall the distribution of dementia is equal between men and women, some types are more common in men and others more commonly diagnosed in women. A National Institute of

Mental Health Multisite Epidemiological Catchment Area study revealed a 6-month prevalence rate for mild dementia of 11.5% to 18.4% for persons older than 65 years living in the community (Kallmann 1989). The rate for severe dementia was higher for the institutionalized elderly. Fifteen percent of the elderly in retirement communities, 30% of nursing home residents, and 54% of the elderly in state hospitals were severely demented (Cummings and Benson 1983).

Studies suggest that the fastest growing segment of the US population consists of persons older than the age of 85 years, 15% of whom are demented (Henderson 1990). Half of the US population currently lives to the age of 75 years and one quarter live to the age of 85 (Berg et al. 1994). A study of 2000 consecutive admissions to a general medical hospital revealed that 9% were demented and, of those, 41% were also delirious on admission (Erkinjuntii et al. 1986). The cost of providing care for demented patients exceeds $100 billion annually (about 10% of all health care expenditures) and the average cost to families in 1990 was $18,000 a year (Berg et al. 1994).

## Course

The course of a particular dementia is influenced by its etiology. Although historically the dementias have been considered progressive and irreversible, there is, in fact, significant variation in the course of individual dementias. The disorder can be progressive, static, or remitting (First 1994). In addition to the etiology, factors that influence the course of the dementia include (1) the time span between the onset and the initiation of prescribed treatment, (2) the degree of reversibility of the particular dementia, (3) the presence of comorbid psychiatric disorders, and (4) the level of psychosocial support.

The previous distinction between treatable and untreatable dementias has been replaced by the concepts of reversible, irreversible, and arrestable dementias. Most reversible cases of dementia are associated with shorter duration of symptoms, mild cognitive impairment, and superimposed delirium. Specifically, the dementias caused by drugs, depression, and metabolic disorders are most likely to be reversible. Other conditions such as normal pressure hydrocephalous, subdural hematomas, and tertiary syphilis are more commonly arrestable.

Although potentially reversible dementias should be aggressively investigated, in reality, only 8% of dementias are partially reversible and about 3% fully reversible (Kaufman 1990b). There is some evidence to suggest that early treatment of demented patients, particularly those with Alzheimer's type with such agents as donepezil (Aricept) which acts as an inhibitor of acetylcholinesterase, and galanthamine (Reminyl) may slow the rate of progression of the dementia although some investigators doubt the ability of these agents to slow the rate of progression.

## Differential Diagnosis

Memory impairment occurs in a variety of conditions including delirium, amnestic disorders, and depression (First 1994). In delirium, the onset of altered memory is acute and the pattern typically fluctuates (waxing and waning) with increased proclivity for confusion during the night. Delirium is more likely to feature autonomic hyperactivity and alterations in level of consciousness. In some cases a dementia can have a superimposed delirium (Figure 51–1).

Patients with major depression often complain of lapses in memory and judgment, poor concentration, and seemingly diminished intellectual capacity. Often these symptoms are mistakenly diagnosed as dementia, especially in elderly populations. A thorough medical history and Mental Status Examination focusing on such symptoms as hopelessness, crying episodes, and unrealistic guilt in conjunction with a family history can be diagnostically beneficial. The term *pseudodementia* has been used to denote cognitive impairment secondary to a functional psychiatric disorder, most commonly depression (Korvath et al. 1989). In comparison with demented patients, those with depressive pseudodementia exhibit better insight regarding their cognitive dysfunction, are more likely to give "I don't know" answers and may exhibit neurovegetative signs of depression. Pharmacological treatment of the depression should improve the cognitive dysfunction as well. Because of the rapid onset of their antidepressant action, the use of psychostimulants (methylphenidate, dextroamphetamine) to differentiate between dementia and pseudodementia has been advocated by some authors (Frierson et al. 1991). Some authors have proposed abandonment of the term pseudodementia, suggesting that most patients so diagnosed have both genuine dementia and a superimposed affective disorder (Figure 51–2).

An amnestic disorder also presents with a significant memory deficit, but without the other associated features such as aphasia, agnosia, and apraxia. If cognitive

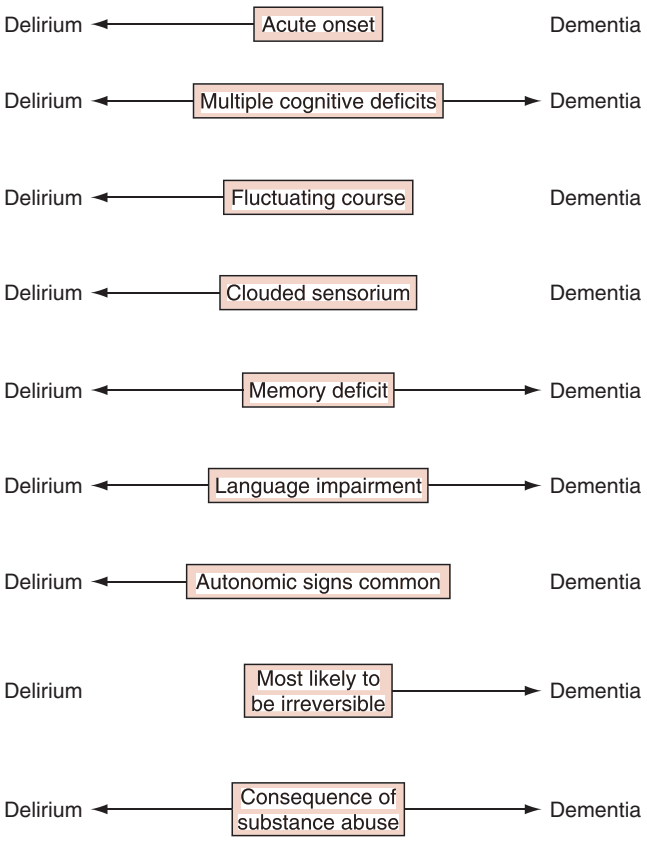



**Figure 51–1** *Differentiation of delirium and dementia.*

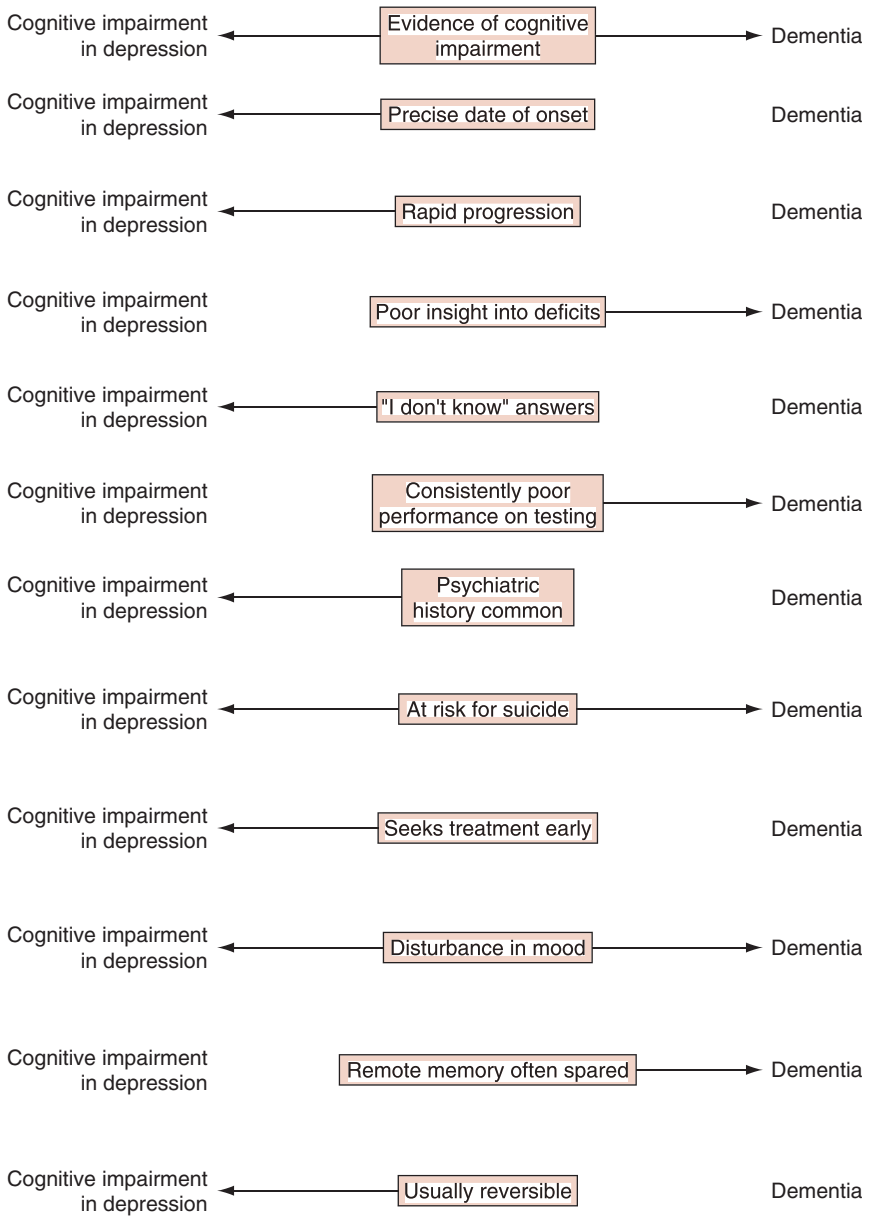



**Figure 51–2** *Differential diagnosis of dementia and cognitive impairment in depression.*

impairment occurs only in the context of drug use, substance intoxication or substance withdrawal is the appropriate diagnosis. Although mental retardation implies below average intellect and subsequent impairment in other areas of function, the onset is before 18 years of age and abnormalities of memory do not always occur. Mental retardation must be considered in the differential diagnosis of dementias of childhood and adolescence along with such disorders as Wilson's disease (hepatolenticular degeneration), lead intoxication, subacute sclerosing panencephalitis, HIV spectrum disorders, and substance abuse, particularly abuse of inhalants.

Patients with schizophrenia may also exhibit a variety of cognitive abnormalities, but this condition also has an early onset, a distinctive constellation of symptoms, and does not result from a medical condition or the persisting effects of a substance. Factitious disorder must be distinguished from dementia. Unlike dementia, this condition presents with inconsistent symptoms that, although similar in some respects, are not totally consistent with those of a dementia. For example, a patient with Factitious Disorder with psychological symptoms (in this case dementia) might have equal impairment in all phases of memory, while patients with dementia usually have better remote than recent memory. Dementia must also be distinguished from benign senescence (normal aging). Only when such changes exceed the level of altered function to be expected for the patient's age is the diagnosis of dementia warranted (First 1994).

## Degenerative Causes of Dementia

### Dementia of the Alzheimer Type

#### Historical Perspective

In 1906 Alois Alzheimer reported a case of presenile dementia in a 51-year-old woman who displayed progressive memory loss and disorientation. His presentation was published in *Allgemeine Zeitschrift für Psychiatrie and Psychisch-Gerichtliche Medizin* in 1907. His

DSM-IV-TR Criteria

**Dementia of the Alzheimer Type**

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in criteria Al and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin $B_{12}$ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

*Code* based on type of onset and predominant features:

**With early onset:** if onset is at age 65 years or below
**294.11 With delirium:** if delirium is superimposed on the dementia
**294.12 With delusions:** if delusions are the predominant feature
**294.13 With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**294.10 Uncomplicated:** if none of the above predominates in the current clinical presentation

**With late onset:** if onset is after age 65 years
**294.3 With delirium:** if delirium is superimposed on the dementia
**294.20 With delusions:** if delusions are the predominant feature
**294.21 With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**294.0 Uncomplicated:** if none of the above predominates in the current clinical presentation

*Specify* if:

**With behavioral disturbance**

**Coding note:** Also code 331.0 Alzheimer's disease on Axis III.

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closing paragraph described the condition that was later to bear his name and serves as an eloquent call for continued research (Karp 1984).

> In summary, we are apparently confronted with a distinctive disease process. An increasing number of unusual diseases have been discovered during the past few years. These observations show that we should not be satisfied to take a clinically unclear case and, by making great efforts, fit it into one of the known disease categories. Undoubtedly, there are many more psychiatric diseases that are included in our textbooks. Often a subsequent histological examination would show the peculiarity of the case. Then gradually we would be able to separate individual diseases clinically from the large classes of diseases in our textbooks and define their clinical characteristics more precisely (Wilkins and Brody 1969).

Two years earlier, Alzheimer had written of miliary plaque formations that often appeared in the brains of patients with senile dementia (Bick 1994). He and his coworkers subsequently described neurofibrillary changes and granulovacuolar degeneration in senile and presenile dementia (Bick 1994). Almost 90 years later, Alzheimer's disease is the most common form of dementia and remains a major focus of scientific investigation.

## Epidemiology

Alzheimer's disease is the most common cause of dementia, accounting for 55–65% of all cases (Korvath et al. 1989). There were fewer than 3 million causes in 1980, but the

Census Bureau predicted that there will be more than 10 million American citizens with Alzheimer's disease by the year 2050 (Evans 1990). Prevalence of the disease doubles with every 5 years between the ages of 65 and 85 years (Katzman and Kawas 1994). Some authors separate Alzheimer's disease into senile and presenile forms, but the two disorders represent the same pathological process (Berg et al. 1994). Significantly, however, early-onset Alzheimer's disease is associated with a more rapid course than later onset disease (Lezak 1983). The disease has a prevalence of 6–8% in individuals 65 years or older (Muralee et al. 2004).

Alzheimer's disease affects women three times as often as men, for unknown reasons. Furthermore, at least one study suggests that dementia, including Alzheimer's, is more common in black than in white American women. (Heyman et al. 1991) Comparison of population studies in diverse countries shows strikingly similar prevalence rates (Katzman and Kawas 1994).

Longitudinal studies have revealed the importance of family history as a risk factor; however, no consistent genetic pattern has been established. Nonetheless, the incidence of progressive dementias including Alzheimer's in first-degree relatives older than 90 years approaches 50% (Korvath et al. 1989). For Alzheimer's alone, the probability of developing dementia if a first-degree relative (parent or sibling) is afflicted is four times than of the general population, and if two or more first-degree relatives have the disease the risk is increased eightfold compared with a normal sample of US citizens (Katzman and Kawas 1994). Forty-three percent of monozygotic twins are concordant for the disorder, compared with only 8% of dizygotic twins (Berg et al. 1994).

In addition to age, gender, and family history, the presence of Down's syndrome, a history of head trauma, and a low level of education have been proposed as risk factors. Most studies concur that individuals with trisomy (Lezak 1983) develop the features of AD by age 35 years; however, studies looking at the possibility that families with a member who has AD are more likely to produce offspring with Down's syndrome have had inconclusive results (Burger and Vogel 1973). Significant head injury, as either a single incident or a chronic occurrence as in sports injuries, increases the risk of developing Alzheimer's by a factor of 2 (Katzman and Kawas 1994). An uneducated person older than 75 years is about twice as likely to develop dementia as one who has 8 years or more schooling (Katzman and Kawas 1994). Risk factors found in some, but not all studies include myocardial ischemia in the elderly, birth to a mother older than age 40 years, and exposure to aluminum (Katzman and Kawas 1994). For a more detailed examination of risk factors in AD, please see *Alzheimer's Disease*, edited by Terry and Colleagues (Terry et al. 1994).

## Pathology

The etiology and pathogenesis of Alzheimer's disease are unknown. Multiple agents and pathways are likely involved in this disorder (Markesbery and Ehmann 1994). Many hypotheses have been proposed regarding the cause and progression of Alzheimer's disease including genetic factors, slow or unconventional viruses, defective membrane metabolism, endogenous toxins, autoimmune disorders, and neurotoxicity of such trace elements as aluminum and mercury (Markesbery and Ehmann 1994).

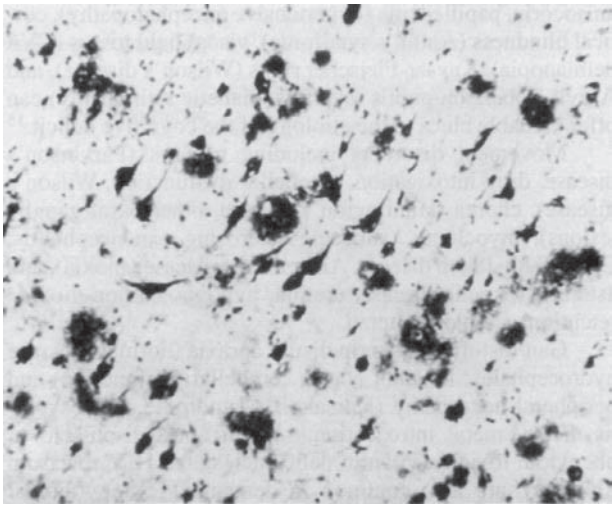


**Figure 51–3** *Numerous neuritic plaques and neurofibrillary tangles in a patient with Alzheimer's disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

The brains of patients with Alzheimer's disease contain many senile plaques, neurofibrillary tangles, and Hirano's bodies (Berg et al. 1994) (Figures 51–3 and 51–4). There is degeneration of nerve cells, but the significant atrophy seen on neurodiagnostic examination may be more the result of shrinkage of neurons and loss of dendritic spines than of actual neuronal loss (Wolf 1980). The atrophy is most apparent in the associational cortex areas, and early on the primary motor and sensory areas are relatively spared (Figures 51–5 and 51–6). Significant degenerative changes in neurons are seen in the hippocampus, locus ceruleus, and nucleus basalis of Mynert (Berg et al. 1994). With advancing disease, these changes, in effect, separate the hippocampus from the remainder of the brain. Initially, the parietal and temporal regions are most affected by plaques and tangles, accounting for the memory impairment and parietal lobe-associated syndromes (some apraxias, hemi-attention, anosognosia, Gerstmann's syndrome) occasionally associated with

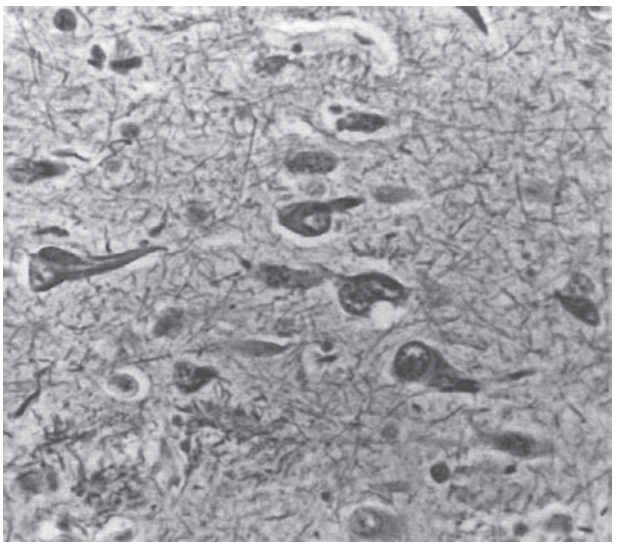


**Figure 51–4** *Intraneuronal neurofibrillary tangles with neuritic plaques in a patient with Alzheimer's disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

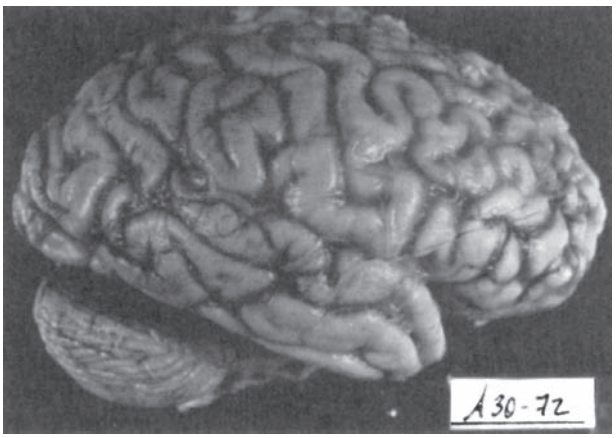



**Figure 51–5** *Gross specimen showing prominent frontal lobe atrophy in a patient with Alzheimer's disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

Alzheimer's disease. Neurofibrillary tangles do not correlate with the severity of the dementia; however, the concentration of neuritic plaques is directly associated with the severity of the disease (Kaufman 1990a).

Neurochemically, the brains of patients with Alzheimer's disease exhibit significant cholinergic abnormalities (Kaufman 1990b). There is a profound decrease in acetylcholine (Ach) in almost all patients, as well as decreased immunological activity of somatostatin- and corticotropin-releasing factors (Kaufman 1990b). The enzyme required for Ach synthesis, choline acetyltransferase, is also greatly reduced. Other studies suggest involvement of noradrenergic and serotoninergic systems in later onset disease and diminished y-aminobutyric acid (GABA) (Kaufman 1990b). Specifically, the noradrenergic deficiencies seen in younger patients may be connected to changes in the locus ceruleus, and abnormalities of serotonin to effects on the raphe nuclei (Korvath et al. 1989). The serotoninergic neurons of the raphe nuclei in patients with Alzheimer's disease contain 6–39 times as many neurofibrillary tangles as those of age-appropriate control subjects, and noradrenergic neurons from the locus ceruleus of patients with Alzheimer's disease show neuronal loss of 40–80% (Korvath et al. 1989). Unfortunately, despite these observed neurochemical abnormalities, neurotransmitter-related treatment with cholinergic and GABergic agents has proved largely unsuccessful.

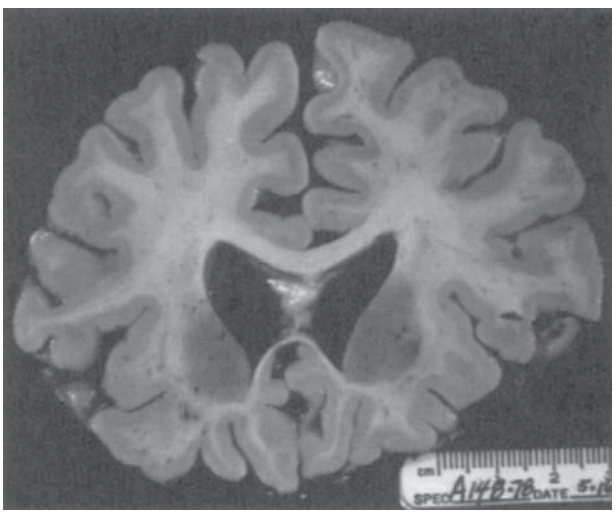


**Figure 51–6** *Cortical and white matter atrophy. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

Although the involvement of cholinergic transmission along the hippocampus and nucleus basalis is essential to the ability to learn new information, it seems that many of the symptoms of Alzheimer's disease are not explainable solely on the basis of cholinergic abnormalities. Thus, investigators have examined a number of other potential etiological or contributory agents.

Some researchers have investigated the role of B-amyloid protein in Alzheimer's disease, and some assert that this material, a significant component of all plaques, is a major contributor to the neurodegenerative changes in the disease as both an initiator and a promotor of the disease (Cotman and Pike 1994). Supporting this assertion are genetic studies of families with inheritable forms of presenile dementia, which show that disease occurrence is linked to mutations involving B-amyloid-related systems (Kidd 1963). This hypothesis targets the protein found in senile plaques; other investigators have focused on the neurofibrillary tangles and the identification of a major component of its helical filament, the tau protein (Kidd 1963, Wisniewski et al. 1976). Specifically, these researchers analyzed the possibility that modification of tau protein, predominantly by phosphorylation, is an important feature of AD (Delacourte and Defossez 1986, Grundke-Igbal et al. 1986, Nukina and Ihara 1986).

Aluminum, the third most common element in the universe, is absorbed from the gastrointestinal tract, lungs, nasal passage, and skin (Ganrot 1986, Perl and Good 1987, Terry et al. 1994). Dollken (1897) first demonstrated that aluminum injected in rabbits produced degeneration of neurons. Scherp and Church (1937) reported various neurological abnormalities including nystagmus, ataxia, and death in rabbits 10–18 days after a single injection of aluminum. Klatzo et al. (1965) discovered neurofibrillary tangles in rabbits receiving intracerebral injections of aluminum. Crapper and Dalton (1972) reported increased aluminum in the brain of patients with Alzheimer's disease, with about a quarter of such samples showing concentrations three standard deviations above the control values. Other studies of bulk brain aluminum in patients with Alzheimer's disease have shown no such elevation (Markesbery and Ehmann 1994). The current consensus appears to be that although aluminum and other elements such as iron and mercury might accelerate neuronal degeneration in AD, these elements are not primary etiological agents.

The role of genetic factors in the development of AD has received increased attention as the role of the apolipoprotein E4 allele as a major genetic susceptibility risk factor has been confirmed by numerous studies (Katzman 1994). Corder et al. (1993) studied 234 members of 42 families with late-onset AD. Of 95 affected members, 80% had the E4 allele, compared with 26% in the general population (Corder et al. 1993). Furthermore, in these families, 91% of those homozygous for Er had developed Alzheimer's disease by 80 years of age, evidence that the APOE e4 allele is causing these familial cases (Corder et al. 1993). In a study of 176 autopsy specimens of confirmed AD, Schmechel and coworkers in 1993 found that 65% of patients carried at least

one apolipoprotein E e4 gene (Katzman 1994). Examination of all such studies indicates that between 25% and 40% of AD cases can be attributable to this marker, making its presence one of the most common risk factors yet discovered for AD (Corder et al. 1993, Katzman 1994).

Finally, several studies suggest that changes in membrane function, metabolism, and morphology are involved in the pathology of AD. Nonetheless, the basic molecular defect responsible for AD dementia has not been defined (Pettegrew et al. 1994).

The neuropathology of Alzheimer's disease should be compared with the normal neuropathic effects of aging. These include the following:

1. The leptomeninges become more fibrotic and are more adherent to the brain surface with increased opacity.
2. The ventricles show slight to moderate enlargement that increases with the passage of time.
3. The distance between the dura and the brain is increased.
4. Sulci widen and gyri become narrower.
5. The number of neurons decreases slightly.
6. The weight of the brain decreases in the fourth and fifth decades, with significant decrease by the age of 80 years.
7. Neurofibrillary tangles and senile plaques occur in virtually every elderly individual by the 10th decade of life (Berg et al. 1994).

## Laboratory and Radiological Findings

The role of laboratory determinations in the evaluation for AD is to exclude other causes of dementia, especially those that may prove reversible or arrestable. Before death, AD is largely a diagnosis of exclusion. Throughout the course of this disorder, laboratory values are essentially normal. Some nonspecific changes may occur, but electroencephalography and lumbar puncture are not diagnostic. As the disease progresses, computed tomography (CT) and magnetic resonance imaging (MRI) may show atrophy in the cerebral cortex and hydrocephalus ex vacuo (Figure 51–7). MRI may show nonspecific alteration of white matter (leukoariosis), and eventually the electroencephalogram (EEG) shows diffuse background slowing.

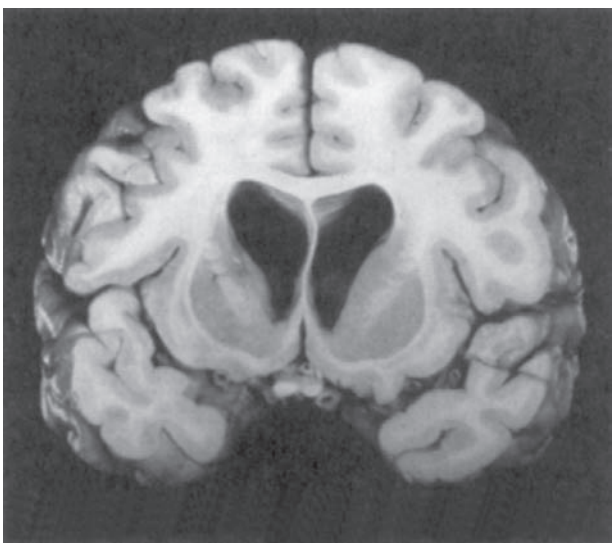


**Figure 51–7** *Hydrocephalos ex vacuo in a patient with Alzheimer's disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

Pneumoencephalography has demonstrated enlarged ventricles and widening of cortical sulci in Alzheimer's disease, and positron emission tomography in the later stages shows decreased cerebral oxygen and glucose metabolism in the frontal lobes. At present, in the workup of a patient with a slowly progressive dementia, a good family history and physical examination and laboratory and radiographic tests to rule out other causes of dementia are the most effective tools in the diagnosis of Alzheimer's disease.

## Clinical Features

The course and clinical features of AD parallel those discussed for dementia in general. Typically, the early course of AD is difficult to ascertain because the patient is usually an unreliable informant, and the early signs may be so subtle as to go unnoticed even by the patient's closest associates (Karp 1984). These early features include impaired memory, difficulty with problem solving, preoccupation with long past events, decreased spontaneity, and an inability to respond to the environment with the patient's usual speed and accuracy (Karp 1984). Patients may forget names, misplace household items, or forget what they were about to do. Often the individuals have insight into these memory deficits and occasionally convey their concerns to family members. Such responses as "You're just getting older," and "I do that sometimes myself" are common from those so informed, and as a result the patient becomes depressed, which can further affect cognitive functioning. Anomia, or difficulty with word finding, is common in this middle stage of Alzheimer's disease. Eventually the patient develops schemes, word associations, and excuses ("I never was very good in math") to assist in retention and cover up deficits. The patient may also employ family members as a surrogate memory (Karp 1984).

Because memory loss is usually most obvious for newly acquired material, the patient tries to avoid unfamiliar activities. Typically, the patient is seen by the physician when confusion, aggression, wandering, or some other socially undesirable behavior ensues. At that time, disorders of perception and language may appear. The patient often turns to a spouse to answer questions posed during the history taking. By this time the affected individual has lost insight into his or her dementia and abandons attempts to compensate for memory loss (Karp 1984). Finally, in the late stage of Alzheimer's disease, physical and cognitive effects are marked. Disorders of gait, extremity paresis and paralysis, seizures, peripheral neuropathy, extrapyramidal signs, and urinary incontinence are seen, and the patient is often no longer ambulatory. The aimless wandering of the middle stage has been replaced by a mute, bedridden state and decorticate posture. Myoclonus occasionally occurs. Significantly, affective disturbances remain a distinct possibility throughout the course of the illness. AD progresses at a slow pace for 8–10 years to a state of complete helplessness.

## Treatment

The two principles of management in AD are to treat what is treatable without aggravating existing symptoms and to support caregivers, who are also victims of this disease.

Despite the significant decrease in ACh and choline acetyltransferase in Alzheimer's disease, treatments based on the cholinergic hypothesis have been unsuccessful (Kaufman 1990a). With the goal of increasing the central nervous system concentrations of ACh, precursors of ACh including choline and lecithin have been tried, as well as centrally acting anticholinesterases such as physostigmine and tetrahydroacridine, with the hope of decreasing ACh metabolism (Kaufman 1990b). ACh agonists such as areocholine, oxotremorine, and bethanechol have been investigated and release of ACh has been stimulated from cerebral neurons by using piracetam (a cyclic relative of GABA) and nafronyl oxalate (Praxilene) (Kaufman 1990b). These pharmacological interventions have yielded inconsistent results and been largely ineffective.

Because vasopressin levels are slightly decreased in the hippocampus of patients with Alzheimer's disease and somatostatin is adversely affected as well, attempts were made to replace these agents with little effect. In the belief that improving blood flow might be of benefit, such agents as the metabolic enhancer and vasodilator ergoloid mesylates (Hydergine—an ergot alkaloid) were tried. Hydergine did seem to have some benefit; however, these effects may have been related to its mild antidepressant action (Jenike et al. 1986, Kaufman 1990b). Onset of action of any beneficial effects of Hydergine was quite long.

Corticotropin release is promoted by corticotropin-releasing factor, which is decreased in patients with AD, but clinical trials with corticotropin were disappointing (Ferris et al. 1976, Sominen et al. 1985). Animal studies suggested that the opioid antagonist naloxone (Narcan) increases memory performance; however, trials with this agent and the oral, long-acting antagonist naltrexone (Trexan) were unproductive (Henderson et al. 1989, Hyman et al. 1985, Thal 1994). Other unsuccessful drug trials included the use of the monoamine oxidase B inhibitor l-deprenyl, thiamine, and nicotine (Blass et al. 1988, Nolan et al. 1991, Tariot et al. 1987).

Despite lackluster effects of physostigmine, a second cholinesterase inhibitor had shown promise (Mohs et al. 1985). Tetrahydroaminoacridine (tacrine) produced significant cognitive improvement in 16 of 17 patients with AD in an early study (Summers et al. 1986). Subsequent studies have been less impressive, but significant improvement in a number of scales measuring cognitive performance illustrated the benefit of this agent for some patients. Side effects, particularly hepatic and cholinergic, were noted; however, in 1993 the US Food and Drug Administration approved tacrine for the treatment of AD (Thal 1994). Donepezil (Aricept) and Exelon (rivastigmine) inhibitors of acetylcholinesterase have also been utilized in an attempt to enhance cholinergic function by inhibiting its breakdown. This agent must be given early in the course of the dementia. Namenda (memantine) can be used in patients with more advanced dementia and is often used in combination with Donepezil.

Donepezil has been approved for mild to moderate Dementia. It comes in 5 and 10 mg tablets and the recommended dose is 5 mg at bedtime for the first 4–6 weeks and then 10 mg at bedtime. Side effects include nausea, diarrhea, muscle cramps, fatigue, anorexia, gastrointestinal bleeding, vertigo and urinary incontinence. Memantine is approved for moderate to severe dementia, and is prescribed according to the following schedule: week one: 5 mg every morning; week two: 5 mg every morning and 5 mg every evening; week three: 10 mg every morning and 5 mg every evening; week four: 10 mg twice a day. Side effects of Memantine include dizziness and syncope, confusion, headache, constipation, anemia, and frequent micturition. The efficacy of Donepezil and memantine was demonstrated in clinical trials that documented improvement in the Alzheimer's Disease Assessment Scale (Donezepil) and the Alzheimer's Disease Activity of Daily Living Scale (Memantine), which measure cognitive function and ability to perform activities of daily living. Both agents showed a 2–3 point difference in these scales after 6 months to a year of treatment. In those instances where improvement is not demonstrated after an adequate trial of Donezepil, the addition of Memantine has been beneficial for some patients. Many clinicians, when treating patients with severe Dementia will start Donezepil and Memantine simultaneously.

Whereas much attention has been focused on research aimed at understanding and altering the pathogenesis of AD, less work has been done regarding appropriate pharmacotherapy of the varied psychological manifestations of the disease. Depression is often associated with AD. If antidepressant medication is to be used, low doses (about one-third to one-half of the usual initial dose) are advised, and only agents with minimal anticholinergic activity should be employed. Appropriate choices would be the selective serotonin reuptake inhibitors such as paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft). Even these agents have the potential to increase confusion in Alzheimer's patients. Agents such as Trazodone (Desyrel) and Mirtazapine (Remeron) have occasionally been employed because of their sedating properties. If tricyclic antidepressants are used, the secondary amines (desipramine, nortriptyline) are recommended over the tertiary ones (amitriptyline, doxepin). Careful attention to the possible side effects of these agents, particularly orthostatic hypotension, lowering of the seizure threshold, excessive fatigue, urinary retention, constipation, confusion, and accelerated memory impairment, is suggested. Most clinicians now feel that tricyclic antidepressants are inappropriate for this patient population.

Anxiety and psychosis, particularly paranoid delusions, are common in AD. Benzodiazepines can be disinhibiting in such patients and may exacerbate confusion. They should be avoided if possible. If minor tranquilizers are required, agents with a shorter duration of action (e.g., lorazepam, oxazepam) are preferred. Antipsychotic medications with high anticholinergic potential (thioridazine, chlorpromazine) may also affect memory adversely. While these agents have been favored in the past because of their tendency to produce sedation, newer agents such as olanzepine (zyprexa), risperdone (risperdal), and Quetiapine (Seroquel) have been reported to have lower incidences of neuroleptic-related side effects (Lerner et al. 2000, Teste et al. 2000, Torres et al. 2001). Haloperidol has less anticholinergic activity but has a greater tendency toward extrapyramidal effects. Some studies have associated the use of atypical antipsychotics to treat agitation and aggressiveness in Alzheimer's patients with a higher incidence of sudden deaths in rare cases (Schneider et al. 2005).

Therefore, these agents should be reserved in most cases for those demented patients with both agitation and psychosis. If they are used, cardiac parameters such as QTc interval length should be monitored, and the lowest possible effective dose should be employed (Friedman 2006). In such patients, where agitation (and not psychosis) is a major factor, the use of low dose Valproic acid has been helpful (Hanson and Galvez-Jimenez 2004). These agents will be discussed in more detail in the consideration of management of delirious states. In summary, the psychopharmacological management of AD is designed to ameliorate cognitive deficits if possible; control agitated, psychotic, and dangerous behavior, and treat any underlying psychiatric disorder (e.g., major depression) that might be comorbid with dementia.

The appropriate management of AD entails more than psychopharmacological intervention. Other elements of the treatment plan should be environmental manipulation and support for the family.

In the attempt to maintain patients with Alzheimer's disease in their homes for as long as possible, some adjustments of their environment are important. Written daily reminders can be helpful in the performance of daily activities. Prominent clocks, calendars, and windows are important, and an effort should be made to minimize changes in the patient's daily activities. Repeated demonstrations of how to lock doors and windows and operate appliances are helpful, and arranging for rapid dialing of essential telephone numbers can be important. Maintaining adequate hydration, nutrition, exercise, and cleanliness is essential.

The family of the patient with Alzheimer's disease is also a victim of the disease. Family members must watch the gradual deterioration of the patient and accept that a significant part of their own lives must be devoted to the care of the individual. Difficult decisions about institutionalization and termination of life support are distinct possibilities, and the patients often turn their anger and paranoia toward the caregiver. Education is a valuable treatment tool for families. Information about the disease and peer support is available through Alzheimer's associations, and many such agencies provide family members with a companion for the patient to allow the family some time away. Many studies suggest that the primary reason for institutionalization of these patients is the tremendous burden of care they pose for their families. Aimless wandering seems to be a particularly disturbing behavior. Unfortunately, the unfamiliar surroundings of a nursing home often increase the patient's level of confusion and anxiety.

For these reasons, family members are at risk for depression, anxiety syndromes, insomnia, and a variety of other psychological manifestations. Should these occur, they should be promptly treated. The National Alzheimer's Education and Referral Service can be accessed by calling 1-800-621-0379.

## Dementia due to Pick's Disease

Pick's disease is a rare form of progressive dementia clinically indistinguishable from Alzheimer's disease. It is about one-fifth as common as AD (Nolan et al. 1991). Pick's disease occurs in middle adult life and has a duration that varies from 2 to 15 years. It has a strong familial tendency, but definite genetic pattern has not been established (Kaufman 1990b). ACh levels are reduced.

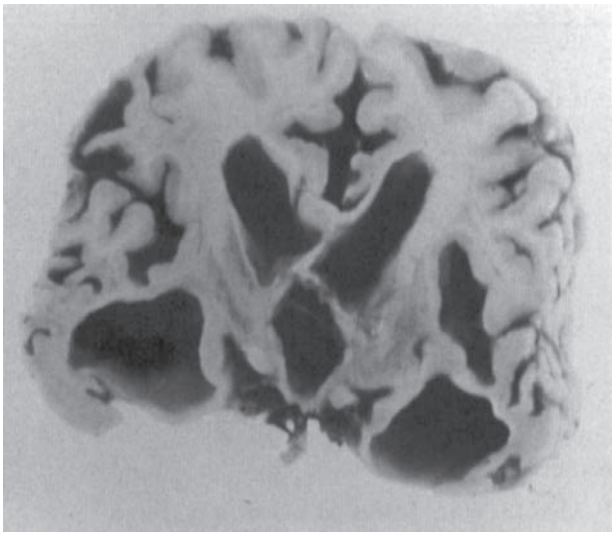


**Figure 51–8** *Severe lobar sclerosis and atrophy in a patient with Pick's disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

The pathology of Pick's disease involves prominent changes (e.g., sclerosis, atrophy) in the frontal and temporal lobes (Figure 51–8). The parietal and occipital lobes are spared. Alzheimer himself noted the argentophilic (staining silver) intraneuronal inclusion of Pick's bodies.

The clinical features of Pick's disease are quite similar to those of Alzheimer's disease, and since neither condition is curable, an elaborate differential diagnosis is unnecessary. Because of parietal sparing, such features as apraxia and agnosia are less common in Pick's disease, and visual–spatial ability, often impaired in Alzheimer's disease, is preserved (Kaufman 1990b). Given the prominent changes in the frontal lobe, disinhibited behavior, loss of social constraints, and lack of concern about appearance and matters of personal hygiene occur relatively early in Pick's disease. Such speech disorders as echolalia and logorrhea are common, and patients with Pick's disease are more likely to develop Klüver–Bucy syndrome (orality, hyperphagia, hypersexuality, placidity) indicative of damage to the temporal lobes (Torres et al. 2001). Significant memory impairment may occur relatively late in the course, and eventually the patient becomes listless, mute, and ultimately decerebrate and comatose. The treatment of Pick's disease is symptomatic.

## Dementia due to Parkinson's Disease

James Parkinson did not consider cognitive deficits to be a feature of the disease that now bears his name (Berg et al. 1994). In fact, although dementia rarely occurs as an initial symptom of Parkinson's disease, it is found in nearly 40% of such patients older than 70 years of age (Kaplan et al. 1994). Approximately one million people in the United States have the disease with 50,000 new cases being diagnosed each year. The prevalence for persons over 60 is 1%. The disease results from loss of dopamine production in the basal ganglia, and can be idiopathic or postencephalitic. Usually the patient is 50 years of age or older, and unlike Alzheimer's and Pick's dementias, this disease occurs slightly more often in men (Berg et al. 1994). Dementia most commonly occurs in cases of Parkinson's disease in which the decline has been rapid and response to anticholinergics has been poor.

The pathology of Parkinson's disease involves depigmentation of the so-called pigmented nuclei of the brain (locus caeruleus, substantia nigra). These nuclei then contain eosinophilic Lewy bodies. As in Alzheimer's disease the cerebral cortex of many of these patients contains many senile plaques and neurofibrillary tangles, loss of neurons, and decreased concentrations of choline acetyltransferase (Kaufman 1990c). Patients with parkinsonian dementia also have reduced choline acetyl transferase (CAT) in the cerebral cortex and substantia nigra (Kaufman 1990c).

The clinical features of Parkinson's disease are well described, with the cardinal triad being tremor, rigidity, and bradykinesia. Associated features include postural instability, a festinating gait, micrographia, seborrhea, urinary changes, constipation, hypophonia, and an expressionless facial countenance. The tremor in Parkinson's disease has a regular rate and is most prominent when the patient is sitting with arms supported; it has therefore been described as "intention tremors." Paranoid delusions and visual hallucinations may occur, but auditory hallucinations are rare. Antipsychotics with low incidence of entrapyramidal symptoms such as quetiapine are recommended.

The pharmacological treatment of Parkinson's disease involves the use of a number of categories of medication. These include Selegiline (Eldepryl, Somerset) a selective monoamine oxidase inhibitor, Levodopa, other dopamine agonists (Pramipexole {Mirapex}, Bromocriptine, Pergolide mesylate {Permax, Elan}, Amantidine), and various anticholinergic agents (benztropine). Selegiline should not be given to patients on antidepressant medication, and there is a risk that dopaminergic agents may produce/activate psychosis or mania and anticholinergic drugs may increase confusion. When discontinuing levodopa after a long course of treatment, the drug should be tapered so as to prevent a discontinuation syndrome similar in nature to the neuroleptic malignant syndrome. Some medications (Metoclopramide, Droperidol, several antipsychotics) may produce Parkinsonian features such as masked facies, sparsity of speech, and tremor) and in those cases the appropriate course of treatment is to discontinue the offending medication (Mamo et al. 2002). Several researchers are looking into the possibility of using embryonic stem cells implants as treatment for Parkinson's disease and several other conditions.

Deep brain stimulation (DBS) is a surgical procedure used to treat Parkinson's disease in those patients whose symptoms cannot be adequately controlled with medication. DBS uses a surgically implanted, battery operated medical device called a neurostimulator to deliver electrical stimulation to targeted areas of the brain that control movement, blocking the abnormal nerve signals that cause tremor and other Parkinson's disease symptoms. The usual targets of stimulation are the thalamus, subthalamic nucleus, and the globus pallidus. The tip of the electrode is positioned within the targeted brain area and an extension wire is passed under the skin. The third component, the neurostimulator, is implanted lower in the chest or under the skin over the abdomen. Ideally, electrical impulses are sent from the neurostimulator up along the extension wire and into the brain where they interfere with and block the electrical signals that cause Parkinson's disease symptoms.

## Dementia due to Huntington's Disease

Dementia is also a characteristic of Huntington's disease, an autosomal dominant inheritable condition localized to chromosome 4. Unfortunately, this condition does not become apparent until age 35–45 years, usually after childbearing has occurred. Fifty percent of offspring are affected. There is also a juvenile form of the disease. Huntington's disease affects about 4 in 100,000 people, making it a significant cause of dementia in middle-aged adults (Teste et al. 2000).

The pathology of Huntington's disease involves selective destruction in the caudate and putamen (Teste et al. 2000). In the caudate nuclei, GABA concentrations are reduced to 50% of normal (Teste et al. 2000). The frontal lobes of the cerebral cortex are also involved, but GABA and choline acetyltransferase concentrations are normal.

The most noticeable clinical feature of Huntington's disease is the movement disorder, which involves both choreiform movements (frequent movements that cause a jerking motion of the body) and athetosis (slow writhing movements). In the juvenile form of Huntington's disease, which represents about 3% of all cases, the chorea is replaced by dystonia, akinesia, and rigidity, and the course of the disease is more rapid than in the adult form (Teste et al. 2000). In the early stages of the disease, the chorea is not as noticeable and may be disguised by the patient by making the movements seem purposeful.

The dementia typically begins between 1 year before or 1 year after the chorea and, unlike patients with other dementias, patients with Huntington's disease are often well aware of their deteriorating mentation. This may be a factor in the high rates of suicide and alcoholism associated with this condition. Although attempts have been made to increase ACh and GABA concentrations in these patients, such pharmacological interventions have been unsuccessful, and the dementia is untreatable. Genetic counseling is indicated.

## Vascular Dementia

Vascular dementia usually results from multiple CVAs or one significant CVA. It is generally considered the second most common cause of dementia after Alzheimer's disease, accounting for about 10% of all cases (Kaufman 1990b, Korvath et al. 1989). Men are twice as likely as women to be diagnosed with this vascular dementia (Torres et al. 2001). Vascular dementia is characterized by a stepwise progression of cognitive deterioration with accompanying lateralizing signs. It is always associated with evidence of systemic hypertension and usually involves renal and cardiac abnormalities. Risk factors for the development of a vascular dementia include those generally associated with obstructive coronary artery disease, including obesity, hypercholesterolemia, smoking, hypertension, stress, and lack of exercise. The actual incidence of vascular dementia has decreased somewhat with better standards of care, improved diagnostic techniques, and lifestyle changes.

Vascular dementia and Alzheimer's are sometimes difficult to distinguish because of overlaps in symptoms, pathology, and comorbidity patterns. In addition, many patients have concomitant Alzheimer's and Vascular dementia ("mixed dementia"). In one study, concomitant Alzheimer's disease was present in 77% of Vascular

**DSM-IV-TR Criteria**

**Vascular Dementia**

A. The development of multiple cognitive deficits manifested by both

   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:

      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensorplantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.
D. The deficits do not occur exclusively during the course of a delirium.

*Code* based on predominant features:

**290.41 With delirium:** if delirium is superimposed on the dementia
**290.42 With delusions:** if delusions are the predominant feature
**390.41 With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**209.40 Uncomplicated:** if none of the above predominates in the current clinical presentation

*Specify* if:

**With behavioral disturbance**

**Coding note:** Also code cerebrovascular condition on Axis III.

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dementia patients. In addition, vascular factors contribute to the development of dementia in patients with Alzheimer's and Alzheimer's and Vascular dementia share several risk factors and have shared pathology (e.g., lacunae, white matter lesions). The presence of mixed Vascular dementia and Alzheimer's disease in combination has been underestimated in the older population.

## Clinical Features

Vascular dementia is characterized by the early appearance of lateralizing signs. Spasticity, hemiparesis, ataxia, and pseudobulbar palsy are common. Pseudobulbar palsy is associated with injury to the frontal lobes and results in impairment of the corticobulbar tracts. It is characterized by extreme emotional lability, abnormal speech cadence, dysphagia, hyperactive jaw jerk, deep tendon reflexes, and Babinski's reflex.

CT, MRI, and gross specimens show cerebral atrophy and infarctions, with the radiological procedures showing multiple lucencies and the gross specimens revealing distinct white matter lesions (Hershey et al. 1987, Kaufman 1990b) (Figures 51–9 to 51–11). The EEG is abnormal but nonspecific, and positron emission tomography reveals hypometabolic areas (Kaufman 1990b). Vascular dementia is differentiated from AD on the basis of its mode of progression, early appearance of neurological signs, and radiographical evidence of cerebral ischemia.

## Treatment

Primary prevention and secondary prevention are important in the treatment of cerebrovascular disorders. Lifestyle changes are effective in arresting the progress of the disease; however, no known pharmacological treatment can reverse the effects of a completed stroke (Korvath et al. 1989).

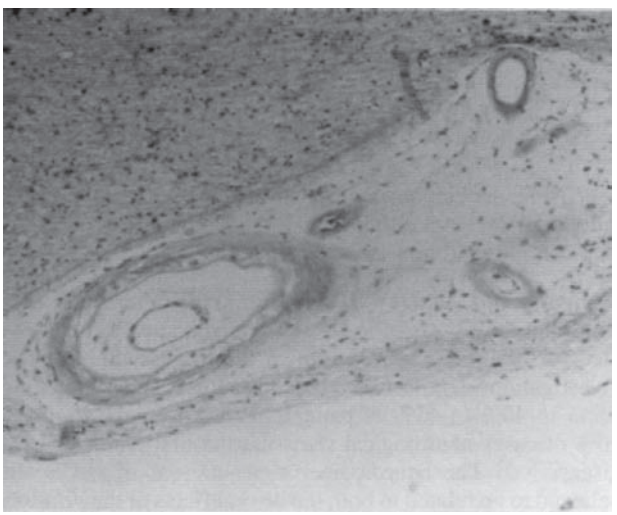


**Figure 51–9** *Arteriosclerotic vessels in cerebral ischemia. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

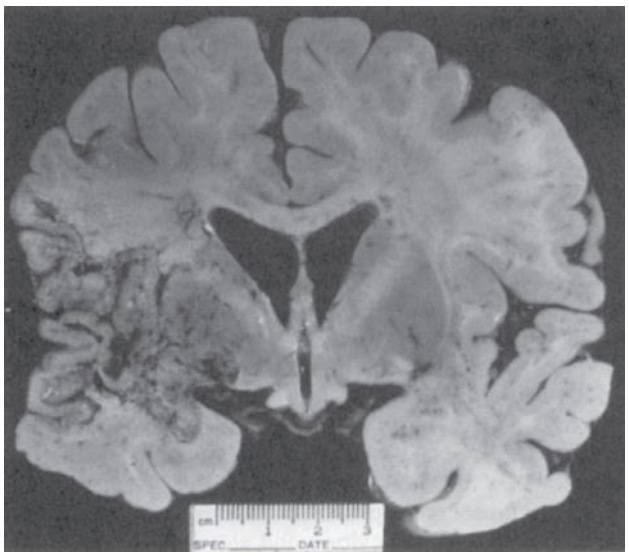


**Figure 51–10** *Subacute left frontotemporal infarction. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

Such interventions as anticoagulants for frequent transient ischemic attacks after a cerebrovascular event is excluded, aspirin for decreasing platelet aggregation, and surgical removal of obstructing plaques probably do not reverse the mental state (Korvath et al. 1989).

Depression occurs in 50–60% of patients with CVAs and responds to traditional antidepressants. Amitriptyline, in less than antidepressant doses, improves both CVA depression and pseudobulbar palsy. Selective serotonin reuptake inhibitors (SSRI's) should be avoided after an acute hemorrhagic stroke because of their tendency to increase bleeding time. In ischemic stroke patients who are prescribed warfarin, such agents as paroxetine and fluoxetine, which affect warfarin metabolism, should be avoided. Physical rehabilitation is essential and often results in an improvement in mood and outlook.

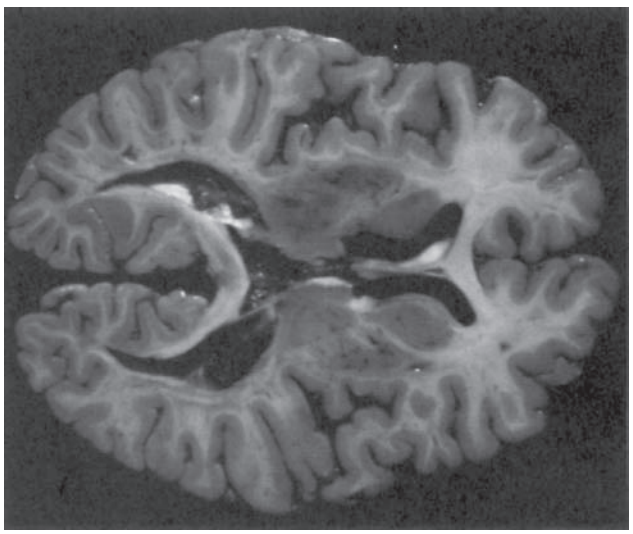


**Figure 51–11** *Multiple lucencies in basal nuclei with reduced white matter in vascular dementia. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

## Infectious Causes of Dementia

### Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis is an infectious cause of dementia that usually appears in childhood. The average age at onset is 10 years, and most patients are male and live in rural areas (Kaufman 1990b, Ziber et al. 1983). It is diagnosed on the basis of periodic complexes on the EEG and an elevated measles titer in the cerebrospinal fluid (CSF). The CT scan shows cerebral atrophy and dilated ventricles. Myoclonus and dementia are prominent features.

It has been postulated that a mutant measles virus is the infectious agent, based on the high CSF measles antibody titer and the fact that the disease is virtually nonexistent in children who have been vaccinated for measles (Kaplan et al. 1994). Affected patients show an insidious onset of impairment of cognition usually preceded by behavioral problems.

### Creutzfeldt-Jakob Disease

Dating from original descriptions by Creutzfeldt in 1920 and Jakob in 1921, this disease has received intense scientific scrutiny (Karp 1984). The primary features of Creutzfeldt-Jakob disease are dementia, basal ganglia and cerebellar dysfunction, myoclonus, upper motor neuron lesions, and rapid progression to stupor, coma, and death in a matter of months. The disease generally affects people 65 years of age or older, with a life expectancy of 1 month to 6 years after onset and an average life span of 15 months. The clinical and pathological features of Creutzfeldt-Jakob have been produced experimentally by injecting animals with brain tissue from affected adults. It has unknowingly been transferred to humans by organ transplantation, cerebral electrodes, and pituitary growth hormone (Marzewski et al. 1988, Rappaport and Graham 1987). These incidents, although tragic, illustrated the infectious nature of this condition, and the agent of transmission is believed to be a prion-containing protein (not DNA or RNA). These prions have been detected in the cerebral cortex of autopsy specimens of both patients with Creutzfeldt-Jakob disease and victims of kuru, a fatal disease transmitted by cannibalism (Kaplan et al. 1994, Prusiner 1987). Slow viruses have also been implicated as infectious agents in kuru. Creutzfeldt-Jakob has been transmitted to humans who consumed animals contaminated with the disease (so-called Mad Cow Disease).

The memory loss in Creutzfeldt-Jakob disease involves all phases of memory, with recent (secondary) memory the most impaired. Personality changes, immature behavior, and paranoia are early signs, and virtually every aspect of brain functioning can be involved. Motor disorders including rigidity, incoordination, paresis, and ataxia usually follow.

As with subacute sclerosing panencephalitis, the EEG in Creutzfeldt-Jakob disease shows periodic complexes and biopsy specimens reveal a characteristic spongiform encephalopathy and occasional amyloid plaques (Kaufman 1990b) (Figure 51–12).

### Acquired Immunodeficiency Syndrome

AIDS was first described in the United States in 1979. Two years later, the Center for Disease Control and Prevention announced the unexplained occurrence of Pneumocystis carnii pneumonia and Kaposi's sarcoma in previously

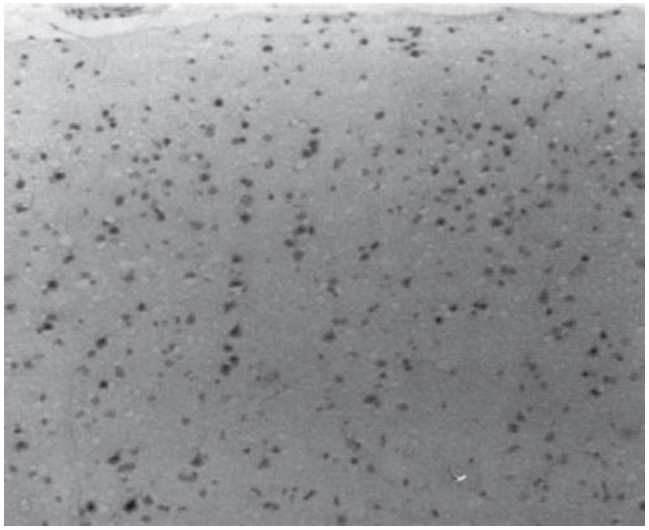


**Figure 51–12** *Spongiform encephalopathy in a patient with Creutzfeldt–Jakob disease. (Courtesy of Joseph Parker, MD, Duke University Medical Center, Durham, NC.)*

healthy homosexual men (Wilson et al. 1991). Since then the number of AIDS cases has risen exponentially. The CDC reports that as of December 31, 2005, 988,376 individuals had been diagnosed with AIDS in the United States. Nine thousand children under age 13 have been diagnosed. Deaths from AIDS-related illnesses have reached 550,394 in the United States alone. Worldwide, about 40 million people, including 3 million children have AIDS. Forty-eight percent of the worldwide cases are women, and 95% of AIDS cases are in undeveloped countries. The number of people infected is postulated to be as much as 50–100 times the number of people diagnosed with AIDS and 80–90% of people infected have not been tested.

In the developed countries, the death rate from AIDS has been on the decline since the advent of new medication regimens utilizing traditional anto-retrovirals and the newer protease inhibitors. These medication cocktails have also decreased the incidence of AIDS Dementia Complex, so that physicians are now more likely to see AIDS-related Delirium secondary to infection, metabolic disarray, and medication rather than traditional AIDS dementia.

In the truest sense, AIDS is not a disease but an increased susceptibility to a variety of diseases caused by loss of immunocompetence. It may result from infection with HIV, a retrovirus that attaches to the CD4 molecule on the surface of the T4 (thymus-derived) lymphocyte. Then, using reverse transcriptase, the virus reverses the usual sequence of genetic information and becomes integrated into the host cell's DNA (Kaufman 1990b). The ultimate result is destruction of the T4 cell, replication of the virus, a defect in cell-mediated immunity, and the development of various opportunistic infections and neoplasms.

The epidemiology of HIV spectrum disease has changed significantly in the 16 years since its identification. Initially, homosexual and bisexual men with multiple partners were, according to the Center for Disease Control and Prevention, the highest risk group. Intravenous drug abusers and recipients of tainted blood products were soon added to high-risk groups. In the 1990s the number of new infections among homosexual men decreased significantly and rates for women, intravenous drug abusers who shared contaminated needles, and infants born to infected mothers increased significantly. Intravenous drug abusers, regardless of sexual orientation, represent the fastest growing population of the newly infected people. Conversely, instances of transmission by blood products have decreased since the development of laboratory testing for HIV antibodies. The Center for Disease Control and Prevention has now established a reactive HIV antibody screen, presence of an opportunistic condition, and a CD4+ cell count of 200 or less (normal being 1000–1500) as criteria for the diagnosis of AIDS.

AIDS is now best considered as part of the spectrum of HIV infection (Wilson et al. 1991). There are four stages of infection.

*Stage 1: Acute Infection:* Most infected persons remember no signs or symptoms at the time of the initial infection. The acute syndrome follows infection by 4–6 weeks and is characterized by fevers, rigors, muscle aches, maculopapular rash, diarrhea, and abdominal cramps. These symptoms, often mistaken for those of influenza, resolve spontaneously after 2–3 weeks.

*Stage 2: Asymptomatic carrier:* This stage follows the acute infection. The patient is without symptoms for a variable amount of time. The mean symptom-free period has increased significantly since the disease was first identified and is now about 10 years. Most of the estimated 2 million infected Americans are at this stage. Even though these individuals are asymptomatic, they are carriers of the disease and can infect others.

*Stage 3: Generalized adenopathy:* In older terminology, this stage was referred to as the AIDS-related complex. It is characterized by palpable lymph nodes that persist for longer than 3 months. These nodes must be outside the inguinal area and due to no other condition except HIV.

*Stage 4: Other diseases:*

1. Constitutional symptoms such as lingering fever, wasting syndromes, and intractable diarrhea.
2. Secondary infections including *P. carinii* pneumonia, cytomegalovirus retinitis, parasitic colitis, and oral esophageal thrush.
3. Secondary neoplasms such as Kaposi's sarcoma and B-cell lymphomas.
4. Neurological diseases (AIDS dementia complex).

Thus, the diagnosis of AIDS is made when an infected individual develops either a CD4+ cell count of less than 200 or a certain condition listed in stage 4 (Wilson et al. 1991).

## Dementia due to HIV Diseases

Initially, the behavioral abnormalities observed in HIV-positive patients were attributed to the emotional reaction to the disease. Subsequent investigations demonstrated that neurological complications occur in 40–45% of patients with AIDS, and in about 10% of cases neurological signs are the first feature of the disease (Berg et al. 1994, Pajeau and Roman 1992). The neurological signs present in AIDS are believed to be related to both the direct effects of the virus on cells (such as macrophages) that enter the central nervous system and the neurological conditions that opportunistically affect these patients. Ho et al. 1987 reported

that 90% of the brains of AIDS patients examined showed neuropathological abnormalities. AIDS dementia must be considered in the differential diagnosis of dementia in older patients, because about 10% of AIDS patients are older than 50 years of age (Berg et al. 1994, Scharnhorst 1992).

Patients with AIDS dementia present with impairments of cognitive, behavioral, and motor systems. The cognitive disorders include memory impairment, confusion, and poor concentration. Behavioral features include apathy, reclusivity, anhedonia, depression, delusions, and hallucinations. Motor symptoms include incoordination, lower extremity paresis, unsteadiness, and difficulty with fine motor movements like handwriting and buttoning clothes (Berg et al. 1994, Kaufman 1990b, Scharko et al. 2006). As the disease progresses, parkinsonism and myoclonus develop.

Localizing signs such as tremors, focal seizures, abnormal reflexes, and hemiparesis can result. The protozoan *Toxoplasma gondii* commonly infects the central nervous system and can be diagnosed by CT or by increased toxoplasmosis antibody titers (Kaufman 1990b). Discrete cerebral lesions are also produced by fungi such as *Candida* and *Aspergillus*, *Mycobacterium tuberculosis*, and viruses such as cytomegalovirus and papovavirus. Papovavirus causes progressive multifocal leukoencephalopahty (Kaufman 1990b). Tertiary syphilis has increased significantly since the advent of AIDS, and neoplasms such as lymphomas, metastatic Kaposi's sarcoma, and gliomas are also causes of AIDS dementia.

Many confounding factors can increase cognitive dysfunction in AIDS, including a high incidence of drug and alcohol abuse; medications such as histamine $H_2$ receptor antagonists (cimetidine), corticosteroids, narcotics, and antiviral drugs (e.g., zidovudine {formerly azidothymidine, AZT}) that increase confusion; and coexistent depression (Table 51–5).

The CT scan shows cerebral atrophy and MRI reveals nonspecific white matter abnormalities (Kaufman 1990b). Neoplasms and lesion such as toxoplasmosis are also visible. Lumbar puncture reveals a pleocytosis and elevated protein levels, and autopsy demonstrates an atrophic brain with demyelination, multinuclear giant cells, and gliosis of the cerebral cortex (Kaufman 1990b).

**Table 51–5 Neuropsychiatric Effects of AIDS-Related Drugs**

| Drug | Use | Effects |
|---|---|---|
| Ketoconazole (Nizoral) | Antifungal | Severe depression<br>Suicidality (rare) |
| Foscarnet | Cytomegalovirus retinitis<br>Herpes | Depression<br>Confusion |
| Ganciclovir | Cytomegalovirus retinitis | Anxiety<br>Psychosis |
| Trimethoprim | *Pneumocystis* pneumonia | Hallucinations<br>Depression<br>Apathy |
| Pentamidine | *Pneumocystis* pneumonia | Delirium<br>Hallucinations |
| Interferon alpha | Cancer | Depression |
| Rifampin | Tuberculosis | Delirium<br>Behavioral changes |
| Isoniazid | Tuberculosis | Memory disturbance<br>Psychosis |
| Dronabinol (Marinol) | Appetite stimulant<br>Wasting syndrome<br>Nausea | Depression<br>Anxiety<br>Psychosis<br>Euphoria |
| Zalcitabine (DDC) | Antiviral | Psychosis<br>Amnesia<br>Confusion<br>Depersonalization<br>Depression<br>Mania<br>Suicidality<br>Mood swings |
| Didanosine | Antiviral | Anxiety |
| Zidovudine (AZT) | Antiviral | Confusion, mania<br>Depression, anxiety |

## Treatment

The increase in life span of patients affected by HIV is directly related to improvements in treating the opportunistic conditions that occur. Aerosol pentamidine as prophylaxis for *P. carinii* pneumonia and ganciclovir for cytomegalovirus retinitis are examples of effective intervention. The use of antiviral agents has generated some controversy. Zidovudine, the first antiviral treatment for AIDS approved by the US Food and Drug Administration, increased or stabilized $CD4^+$ cell concentrations in early studies. Later investigations revealed that zidovudine has a narrow window of effectiveness and may not be appropriate immediately after such exposure as a needle stick. Side effects of zidovudine include blood dyscrasias, peripheral neuropathy, seizures, lymphomas, confusion, anxiety, mania, and a Vernicke-Korsakoff type of picture (Kaufman 1990b).

Studies suggest that administration of zidovudine to HIV-positive patients during pregnancy, intravenously during delivery, and to the neonate for 6 weeks after birth can decrease the percentage of infants who seroconvert from 30% to as low as 10%. However, results of studies of the effectiveness of zidovudine in children already HIV-positive have been disappointing.

Subsequent antiviral agents such as dideoxyinosine and dideoxycytidine (DDC) have been associated with painful neuropathy and pancreatic disorders. DDC in particular can produce serious neuropsychiatric complications. Combined therapy with two antiviral agents may be more effective than single-drug therapy. May pharmaceutical companies are combining two antivirals into a single pill, and the development of protease inhibitor agents such as indinavir (Crixivan) and nelfinavir (Viracept) have been especially effective in retarding the progression of the disease.

The treatment of neuropsychiatric disorders in AIDS involves utilizing agents that are least likely to interfere with other medications prescribed, or to exacerbate the symptoms of the disease. AIDS-related depression has responded well to the selective serotonin reuptake inhibitors (SSRIs) and to psychostimulants. Some HIV drugs can have interactions with SSRIs, particularly ritonavir (Norvir) and the

SSRIs themselves, especially paroxetine and fluoxetine can interact with other agents the HIV patient may have been prescribed, such as antiarrhythmics, benzodiazepines, and anticonvulsants by inhibiting the cytochrome P-450 enzyme system. Careful attention to drug–drug interactions, using lower starting doses of certain psychiatric drugs, and monitoring of blood levels of affected medications are recommended. Among the psychostimulants, methylphenidate is preferred to dextroamphetamine, because of the latter's tendency to produce dyskinesias. Use of stimulants for treating in patients with a history of substance abuse is not recommended. Anticholingeric agents have a number of side effects such as mydriasis, decreased gastrointestinal motility, postural hypotension; however, low dose tricyclic antidepressants are often used for their sedative, analgesic, and appetite stimulant properties. Most antidepressants and some mood stabilizers and antipsychotics can cause bone marrow suppression so they should be used with care, and hematologic parameters routinely monitored. Lithium carbonate, which produces a leukocytosis, may be of benefit in recurrent unipolar and treatment-resistant depression, but may potentiate AIDS-related diarrhea. Many of the drugs used to treat AIDS-related conditions may produce untoward psychiatric effects. Depression has been well documented as a side effect of indinavir (Crixivan), and nelfinavir (Viracept) has been associated with anxiety, depression, mood lability, and even suicidality. St. Johns Wort may decrease the concentration of many of the protease inhibitors and is therefore contraindicated in patients taking these agents.

In summary, AIDS dementia is best treated by identifying the associated medical condition, instituting appropriate therapy, and managing behavior in the interim.

## Neurosyphilis

During the late 19th century, neurosyphilis was responsible for a significant number of admissions to psychiatric hospitals (Kaufman 1990b). The condition had decreased in incidence after the causative agent (*Treponema pallidum*) was identified and penicillin treatment became readily available. The rise of AIDS in the 1980s and 1990s has led to an increase in the number of diagnosed cases of neurosyphilis (Kaufman 1990b). Infection with *T. pallidum* is generally divided into four stages (Summergrad et al. 1993).

Primary syphilis occurs 3–6 weeks after contact with the organism. The symptoms include a chancre at the site and regional lymphadenopathy. Affected persons are infectious.

Secondary syphilis begins 6–8 weeks after the primary stage. It is manifested by a maculopapular rash over the trunk, and especially over the soles of the feet and palms. The person is constitutionally ill with fever and adenopathy. Occasionally, secondary syphilis is asymptomatic in the last few weeks.

Latent syphilis presents with a normal examination and seropositivity. If patients with latent syphilis continue to have a normal CSF profile 2 years after diagnosis, they are at low risk for neurosyphilis.

Late syphilis consists of ongoing inflammatory disease most likely in the aorta or nervous system (neurosyphilis), the latter occurring in about 10% of patients. The neurosyphilis of the late stage can consist of (1) asymptomatic neurosyphilis, (2) meningovascular syphilis, and (3) parenchymal neurosyphilis. The parenchymal neurosyphilis consists of general paresis, which occurs about 20 years after infection and includes cognitive impairment, myoclonus, dysarthria, personality changes, irritability, psychosis, grandiosity, and mania (Summergrad et al. 1993, Ross et al. 1990). Untreated general paresis leaves the patient a helpless invalid. The second form of parenchymal neurosyphilis is tabes dorsalis with onset 25–30 years after initial infection. Tabes features loss of position and vibratory sense, areflexia in lower extremities, chronic pain, ataxia, and incontinence (Summergrad et al. 1993).

The original screening test for syphilis is the Venereal Disease Research Laboratory (VDRL) test or the Rapid Plasma Reagin (RPR) test. These tests have a significant false-positive rate, especially in the elderly and in patients with addictions and autoimmune disorders (Kaufman 1990b). The VDRL test may revert to negative after a number of years, and 20–30% of patients in the stage of late syphilis have a negative (nonreactive) VDRL result. A more specific test is the fluorescent treponemal antibody screen, which is positive 95% of the time in neurosyphilis. The false-positive rate for the fluorescent treponemal antibody screen is extremely low, and reversion to a nonreactive estate is unlikely. In addition to a positive VDRL result, the CSF in patients with neurosyphilis generally shows pleocytosis.

Dementia secondary to neurosyphilis produces various physical findings in advanced cases. These may include dysarthria, Babinski's reflex, tremor, Argyll Robertson pupils, myelitis, and optic atrophy. Although notorious, delusions of grandeur in neurosyphilis are rare. A reactive CSF VDRL result or a positive serum fluorescent treponemal antibody result in a patient with neurological symptoms who cannot document treatment should be treated with appropriate therapy. Penicillin often improves cognitive deficits and corrects CSF abnormalities, but complete recovery is rare.

## Dementia due to Head Trauma

Head trauma is the leading cause of brain injury for children and young adults (Berg et al. 1994). It is estimated that more than 7 million head injuries and 500,000 related hospital admissions occur in the United States annually (Berg et al. 1994, Bond 1986). Traumatic head injuries result in concussions, contusions, or open head injuries, and the physical examination often reveals such features as blood behind the tympanic membranes (Battle's sign), infraorbital ecchymosis, and pupillary abnormalities (Berg et al. 1994). The psychiatric manifestations of an acute brain injury are generally classified as a delirium or amnestic disorder; however, head trauma-induced delirious states often merge into a chronic dementia. Episodes of repeated head trauma, as in dementia pugilistica (punchdrunk syndrome), can lead to permanent changes in cognition and thus are appropriately classified as demented states. The punchdrunk syndrome is seen in aging boxers and includes dysarthric speech, emotional lability, slowed thought, and impulsivity (Berg et al. 1994, Jordan 1987, Kaufman 1990b, Mawdsley and Fergusen 1953).

A single head injury may result in a postconcussional syndrome with resultant memory impairment, alterations in mood and personality, hyperacusis, headaches, easy fatigability, anxiety, belligerent behavior, and dizziness. Alcohol abuse, postural hypotension, and gait disturbances are often associated with head injuries that result in dementia.

## Substance-Induced Persisting Dementia

In instances in which the features of dementia result from central nervous system effects of a medication, toxin, or drug of abuse (including alcohol), the diagnosis of dementia due to the persisting effects of a substance should be made (First 1994). The most common dementias in this category are those associated with alcohol abuse, accounting for about 10% of all dementias (Korvath et al. 1989). The diagnosis of alcohol abuse dementia requires that the cognitive changes persist after the cessation of alcohol use and are not the result of changes in mentation associated with early abstinence, amnestic episodes (blackouts), or Wernicke-Korsakoff syndrome. In addition to various nutritional deficiencies and the toxic effects of alcohol itself, alcohol abusers are more prone to develop dementia as a result of head trauma and chronic hepatic encephalopathy.

**DSM-IV-TR Criteria**

**Substance-Induced Persisting Dementia**

A. The development of multiple cognitive deficits manifested by both

(1) memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)

(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

(c) agnosia (failure to recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C The deficits do not occur exclusively during the course of a delirium and persist beyond the usual duration of substance intoxication or withdrawal.

D. There is evidence from the history, physical examination, or laboratory findings that the deficits are etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).

**Code:** [specific substance]-induced persisting dementia:

(291.2 alcohol; 292.82 inhalant; 292.82 sedative, hypnotic, or anxiolytic; 292.82 other [or unknown] substance)

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### Epidemiology of Alcohol-Induced Dementia

Chronic alcohol abuse is the third leading cause of dementia. It affects a higher proportion of women than men, and alcohol-induced dementia is a relatively late occurrence, generally following 15–20 years of heavy drinking (Korvath et al. 1989). Dementia is more common in individuals with alcoholism who are malnourished. The CT scan shows cortical atrophy and ventricular dilatation after about 10 years with neuronal loss, pigmentary degeneration, and glial proliferation (Korvath et al. 1989). The frontal lobes are the most affected, followed by parietal and temporal areas (Korvath et al. 1989). The amount of deterioration is related to age, number of episodes of heavy drinking, and total amount of alcohol consumed over time.

### Clinical Features

Alcohol-induced dementia secondary to the toxic effects of alcohol develops insidiously and often presents initially with changes in personality. Increasing memory loss, worsening cognitive processing, and concrete thinking follow. The dementia may be affected by periodic superimposed delirious states including those caused by recurrent use of alcohol and cross-sensitive drugs, respiratory disease related to smoking, central nervous system hemorrhage secondary to trauma, chronic hypoxia related to recurrent seizure activity, folic acid deficiency, and higher rates of some neoplasms among those with alcoholism (Table 51–6).

**Table 51–6 Central Nervous System Sequelae of Alcohol Abuse**

| |
|---|
| Blackouts |
| Dementia |
| Marchiafava-Bignami disease |
| Wernicke-Korsakoff syndrome |
| Hepatic encephalopathy |
| Delirium tremens |
| Withdrawal seizures |
| Episodic dyscontrol (pathological intoxication) |
| Alcoholic hallucinosis |
| Head injury |

### Treatment

The presence of dementia makes the treatment of alcoholism more difficult. Most treatment programs depend on education about substance abuse, working the 12 steps, some degree of sociability, and such relatively abstract concepts as secondary gratification and a higher power. Such treatment programs are often reluctant to engage in the painstaking repetition that patients with alcohol-induced dementia often require. These patients may become frustrated in peer support groups such as Alcoholics Anonymous. Despite these obstacles, patients with alcoholism who complete a treatment program and remain sober do have some improvement in their mental state. There is an initial improvement that peaks at 3–4 weeks, followed by a slow but steady improvement detected at 6–8 months. In general, the presence of a cognitive

deficit (dementia) dictates an alcohol treatment program that is behavior based, concrete, structured, supportive, and repetitive. Some medications such as Acamprosate (Campral) and V: Vitrol (extended release Naltrexone) have been shown to decrease craving in alcoholics and may be of some benefit as part of an overall rehabilitation program.

### Other Substances

Many other agents can produce dementia as a result of their persisting effects. Exposure to such heavy metals as mercury and bromide, chronic contact with various insecticides and use of various classes of drugs of abuse may produce dementia. In particular, the abuse of organic solvents (inhalants) has been associated with neurological changes (Byrne and Kirby 1990, Errebo-Knudson and Olsen 1986, Grabski 1961, Knox and Nelson 1966). The inhalants are generally classified as anesthetics (halothane, chloroform, ether, nitrous oxide), solvents (gasoline, paint thinner, antifreeze, kerosene, carbon tetrachloride), aerosols (insecticides, deodorants, hair sprays), and nitrites (amyl nitrite). The solvent category is particularly toxic to the brain. In addition, acute anoxia may result from the common practice of inhaling a substance with a plastic bag around the head. Such neurological findings as peripheral neuropathy, paresis, paresthesias, areflexia, seizures, signs of cerebellar damage, and Babinski's sign are common. Although the cerebellum is often involved, any area of the cerebral cortex may be affected (Grabski 1961) (Table 51–7).

**Table 51–7 Neurological Effects of Selected Inhalants**

| Agent | Use | Effect |
|---|---|---|
| *n*-Hexane | Organic solvent | Peripheral neuropathy |
| Methyl butyl ketone | Paint thinner | Polyneuropathy |
| Toluene | Paint thinner | Cognitive dysfunction |
| | | Cerebellar ataxia |
| | | Optic neuropathy |
| | | Sensorineural hearing loss |
| | | Dementia |
| Trichloroethylene | Metal degreasing | Trigeminal neuropathy |
| | Extracting oils | |
| Methylene chloride | Paint stripping | Carbon monoxide poisoning |
| | Aerosol propellant | Hypoxic encephalopathy |
| 1,1,1 -trichloroethane | Solvent | Cerebral hypoxia |
| | Industrial degreasing | |

## Dementia due to Other General Medical Conditions

### Normal-Pressure Hydrocephalus

Normal-pressure hydrocephalus is generally considered the fifth leading cause of dementia after Alzheimer's, vascular, alcohol-related, and AIDS dementias. Long considered irreversible but often merely arrestable, normal-pressure hydrocephalus is a syndrome consisting of dementia, urinary incontinence, and gait apraxia (Benson et al. 1970, Fisher 1982, Kaufman 1990b). It results from subarachnoid hemorrhage, meningitis, or trauma that impedes CSF absorption (Kaufman 1990b).

Unlike other dementias, the dementia caused by normal-pressure hydrocephalus has physical effects that often overshadow the mental effects (Karp 1984). Psychomotor retardation, marked gait disturbances, and in severe cases, complete incontinence of urine occur (Karp 1984). A cisternogram is often helpful in the diagnosis, and CT and MRI show ventricular dilatation without cerebral atrophy. CSF analysis reveals a normal opening pressure, and glucose and protein determinations are within the normal range.

The hydrocephalus can be relieved by insertion of a shunt into the lateral ventricle to drain CSF into the chest or abdominal cavity, where it is absorbed. Clinical improvement with shunting approaches 50% with a neurosurgical complication rate of 13–25% (Black 1980, Kaufman 1990b). Infection remains the most common complication.

### Wilson's Disease

Hepatolenticular degeneration (Wilson's disease) is an inherited autosomal recessive condition associated with dementia, hepatic dysfunction, and a movement disorder. Localized to chromosome 13, this disorder features copper deposits in the liver, brain, and cornea (Cartwright 1978, Chung et al. 1986, Kaufman 1990b). Symptoms begin in adolescence to the early 20s and cases are often seen in younger children (Berg et al. 1994, Saito 1987). Wilson's disease should be considered along with Huntington's disease, AIDS dementia, substance abuse dementia, head trauma, and subacute sclerosing panencephalitis in the differential diagnosis of dementia that presents in adolescence and early adulthood. Personality, mood, and thought disorders are common, and physical findings include a wing-beating tremor, rigidity, na, dystonia, and the pathognomonic Kayser-Fleischer ring around the cornea (Kaufman 1990b, Starosta-Rubinstein et al. 1987). Wilson's disease can mimic other conditions including Huntington's disease, Parkinson's disease, atypical psychosis, and neuroleptic-induced dystonia (Berg et al. 1994). Slit-lamp ocular examination, abnormal liver function tests, and markedly decreased serum ceruloplasmin levels are diagnostic. Chelating agents such as penicillamine, if administered early, can reverse central nervous system and non-neurological findings in about 50% of cases (Berg et al. 1994, Kaufman 1990b).

### Other Medical Conditions

In addition to the conditions mentioned previously, other medical illnesses can be associated with dementia. These include endocrine disorders (hypothyroidism, hypoparathyroidism), chronic metabolic conditions (hypocalcemia, hypoglycemia), nutritional deficiencies (thiamine, niacin, vitamin $B_{12}$), structural lesions (brain tumors, subdural hematomas), and multiple sclerosis (Mortell 1946, Peterson 1968, Plum et al. 1962).

### Dementia due to Multiple Etiologies

Dementia may have more than one cause in a particular patient. Certain types of dementia tend to occur together, including alcohol-induced persisting dementia and dementia caused by head trauma, vascular dementia, and dementia of the Alzheimer type, and alcohol abuse dementia and a nutritional dementia. For the purpose of DSM-IV-TR diagnosis,

DSM-IV-TR Criteria

**Dementia due to Other General Medical Conditions**

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of one of the general medical conditions listed below.

D. The deficits do not occur exclusively during the course of a delirium.

**294.9 Dementia due to HIV Disease**

**Coding note**: Also code 043.1 HIV infection affecting central nervous system on Axis III.

**294.1 Dementia due to Head Trauma**

**Coding note**: Also code 854.00 head injury on Axis III.

**294.1 Dementia due to Parkinson's Disease**

**Coding note**: Also code 332.0 Parkinson's disease on Axis III.

**294.1 Dementia due to Huntington's Disease**

**Coding note**: Also code 333.4 Huntington's disease on Axis III.

**290.10 Dementia due to Pick's Disease**

**Coding note**: Also code 331.1 Pick's disease on Axis III.

**290.10 Dementia due to Creutzfeldt-Jakob Disease**

**Coding note**: Also code 046.1 Creutzfeldt-Jakob disease on Axis III.

**294.1 Dementia due to… [Indicate the General Medical Condition Not Listed Above]**

For example, normal-pressure hydrocephalus, hypothyroidism, brain tumor, vitamin $B_{12}$ deficiency, intracranial radiation

**Coding note:** Also code the general medical condition on Axis III.

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all conditions contributing to the dementia should be diagnosed.

## Treatment of Dementia

Most of the treatment strategies for dementia have been discussed previously (see treatment of dementia of the Alzheimer type). In summary, the management of dementia involves (1) identification and, if possible, correction of the underlying cause; (2) environmental manipulation to reorient the patient; (3) intervention with the family by means of education, peer support, providing access to community organizations, discussing powers of attorney, living wills, and institutionalization if appropriate, and arranging therapy if indicated; and (4) pharmacological management of psychiatric symptoms and behavior. For psychotic patients, low dose antipsychotics with minimal anticholinergic potential and occasionally short-acting benzodiazepines (e.g., lorazepam) are the drugs of choice. Because depression occasionally accompanies dementia, pharmacotherapy with antidepressants of low anticholinergic and hypotensive potential is often indicated. For patients with dementia secondary to drug or alcohol abuse, appropriate referral for rehabilitation is essential. Some elderly patients may be further disinhibited by benzodiazepines. Tables 51–8 to 51–10 summarize the causes of dementia.

# Delirium

Delirium (acute confusional state, toxic metabolic encephalopathy) is the behavioral response to widespread disturbances in cerebral metabolism (Engel and Roman 1959, Lipowski 1983, 1987, 1989, 1990). The term *delirium* is derived from the Latin for "off the track," and some have labeled the condition reversible madness (Lipowski 1983, 1989, Tobias et al. 1988). Like dementia, delirium is not a disease but a syndrome with many possible causes that result in a similar constellation of symptoms. DSM-IV-TR describes five categories of delirium based on etiology (Table 51–11).

## Historical Perspective

Delirium was reported as early as Hippocrates' time by Celsus in the first century AD (Korvath et al. 1989). In 1813, Sutton described the syndrome of delirium tremens and its relationship to alcoholism and Wernicke described the condition that bears his name (Korvath et al. 1989). Lipowski (1983, 1987, 1990) proposed a concept of delirium that would include a variety of behavioral syndromes,

**Table 51–8 Causes of Dementia**

Vascular
- Multiinfarct
- CVA
- Binswanger's disease

Degenerative
- Alzheimer's disease
- Pick's disease
- Huntington's disease
- Parkinson's disease

Toxic
- Medications
- Alcohol
- Poisons
- Inhalants
- Heavy metals

Infectious
- HIV spectrum illness
- Neurosyphilis
- Creutzfeldt-Jakob disease
- Kuru
- Subacute sclerosing panencephalitis

Metabolic
- Chronic hypoglycemia
- Electrolyte imbalances
- Vitamin deficiencies

Endocrine
- Thyroid abnormalities
- Parathyroid abnormalities

Trauma
- Single head injury
- Dementia pugilistica

Neoplastic
- Primary brain tumor
- Metastatic brain tumor

some global, others focal, and others that would mimic the common functional disorders (Korvath et al. 1989).

## Epidemiology

The overall prevalence of delirium in the community is low, but delirium is common in hospitalized patients. Lipowski (1987) reported studies of elderly patients and suggested that about 40% of them admitted to general medical wards showed signs of delirium at some point during the hospitalization. Because of the increasing numbers of elderly in this country and the influence of life-extending technology, the population of hospitalized elderly is rising; so is the prevalence of delirium. The intensive care unit, geriatric psychiatry ward, emergency department, alcohol

**Table 51–9 Causes of Dementia in Adolescence**

- Huntington's disease (juvenile type)
- Hepatolenticular degeneration (Wilson's disease)
- Subacute sclerosing panencephalitis
- AIDS
- Substance abuse (especially inhalants)
- Head trauma

**Table 51–10 Causes of Dementia in Children**

- Head injury (including child abuse)
- Subacute sclerosing panencephalitis
- AIDS

**Table 51–11 DSM-IV-TR Classification of Delirium**

- Delirium due to a general medical condition (indicate the condition)
- Substance intoxication delirium
- Substance withdrawal delirium
- Delirium due to multiple etiologies (indicate the etiologies)
- Delirium not otherwise specified

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**DSM-IV-TR Criteria**

**Dementia due to Multiple Etiologies**

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance has more than one etiology (e.g., head trauma plus chronic alcohol use, dementia of the Alzheimer's type with the subsequent development of vascular dementia).

D. The deficits do not occur exclusively during the course of a delirium.

**Coding note:** Use multiple codes based on specific dementias and specific etiologies, e.g., 290.0 dementia of the Alzheimer's type, with late onset, uncomplicated; 290.40 vascular dementia, uncomplicated.

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treatment units, and oncology wards have particularly high rates of delirium (Korvath et al. 1989, McNicoll et al. 2003). Massie et al. (1983) reported that 85% of terminally ill patients studied met criteria for delirium, as did 100% of postcardiotomy patients in a study by Theobald (1977). Overall, it is estimated that 10% of hospitalized patients are delirious at any particular point in time (Korvath et al. 1989).

Predisposing factors in the development of delirium include old age, young age (children), previous brain damage, prior episodes of delirium, malnutrition, sensory impairment (especially vision), sleep deprivation, and alcohol dependence. Other risk factors include use of physical restraints, sensory deprivation, use of a Foley catheter, and frequent room changes. In general, the mortality and morbidity of any serious disease are doubled if delirium ensues (Cole 2004, Korvath et al. 1989). The risk of dying is greatest in the first 2 years after the illness, with a higher risk of death from heart disease and cancer in women and from pneumonia in men (Francis et al. 1990). Overall, the 3-month mortality rate for persons who have an episode of delirium is about 28%, and the 1-year mortality rate for such patients may be as high as 50% (Kaplan et al. 1994).

## Pathophysiology

ACh is the primary neurotransmitter believed to be involved in delirium, and the primary neuroanatomical site involved is the reticular formation (Korvath et al. 1989). Thus, one of the frequent causes of delirium is the use of drugs with high anticholingeric potential. Patients with impaired cholinergic transmission, such as those with Alzheimer's disease, are especially susceptible. As the principal site of regulation of arousal and attention, the reticular formation and its neuroanatomical connections play a major role in the symptoms of delirium. The major pathway involved in delirium is the dorsal tegmental pathway projecting from the mesencephalic reticular formation to the tectum and the thalamus (Kaplan et al. 1994).

## Clinical Features

According to DSM-IV-TR, the primary feature of delirium is a diminished clarity of awareness of the environment (First 1994). Symptoms of delirium are characteristically global, of acute onset, fluctuating, and of relatively brief duration. In most cases of delirium, an often overlooked prodrome of altered sleep patterns, unexplained fatigue, fluctuating mood, sleep phobia, restlessness, anxiety, and nightmares occurs. A review of nursing notes for the days before the recognized onset of delirium often illustrates early warning signs of the condition.

Several investigators have divided the clinical features of delirium into abnormalities of (1) arousal, (2) language and cognition, (3) perception, (4) orientation, (5) mood, (6) sleep and wakefulness, and (7) neurological functioning (Kaplan et al. 1994).

The state of arousal in delirious patients may be increased or decreased (Foreman and Milisen 2004). Some patients exhibit marked restlessness, heightened startle, hypervigilance, and increased alertness. This pattern is often seen in states of creased alertness. This pattern is often seen in states of withdrawal from depressive substances (e.g., alcohol) or intoxication by stimulants (phencyclidine, amphetamine, lysergic acid diethylamide). Patients with increased arousal often have such concomitant autonomic signs as pallor, sweating, tachycardia, mydriasis, hyperthermia, piloerection, and gastrointestinal distress. These patients often require sedation with neuroleptics or benzodiazepines. Hypoactive arousal states such as those occasionally seen in hepatic encephalopathy and hypercapnia are often initially perceived as depressed or demented states. The clinical course of delirium in any particular patient may include both increased and decreased arousal states. Many such individuals display daytime sedation with nocturnal agitation and behavioral problems (sundowning).

Perceptual abnormalities in delirium represent an inability to discriminate sensory stimuli and to integrate current perceptions with past experiences (Engel and Roman 1959, Lipowski 1983, 1987, 1989, 1990, Massie et al. 1983, Theobald 1977, Tobias et al. 1988). Consequently, patients tend to personalize events, conversations, and so forth that do not directly pertain to them, become obsessed with irrelevant stimuli, and misinterpret objects in their environment (Engel and Roman 1959, Lipowski 1983, 1987, 1989, 1990, Tobias et al. 1988). The misinterpretations generally take the

**DSM-IV-TR Criteria**

**Delirium due to… [Indicate the General Medical Condition]**

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

**Coding note:** If delirium is superimposed on a preexisting dementia of the Alzheimer's type or vascular dementia, indicate the delirium by coding the appropriate subtype of the dementia, e.g., 290.3 dementia of the Alzheimer's type, with late onset, with delirium.

**Coding note:** Include the name of the general medical condition on Axis I, e.g., 293.0 delirium due to hepatic encephalopathy; also code the general medical condition on Axis III.

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form of auditory and visual illusions. Patients with auditory illusions, for example, might hear the sound of leaves rustling and perceive it as someone whispering about them. Paranoia and sleep phobia may result. Typical visual illusions are that intravenous tubing is a snake or worm crawling into the skin or that a respirator is a truck or farm vehicle about to collide with the patient. The former auditory illusion may lead to tactile hallucinations, but the most common hallucinations in delirium are visual and auditory.

Orientation is often abnormal in delirium. Disorientation in particular seems to follow a fluctuating course, with patients unable to answer questions about orientation in the morning, yet fully oriented by the afternoon. Orientation to time, place, person, and situation should be evaluated in the delirious patient. Generally, orientation to time is the sphere most likely impaired, with orientation to person usually preserved. Orientation to significant people (parents, children) should also be tested. Disorientation to self is rare and indicates significant impairment. The examiner should always reorient patients who do not perform well on this parameter of the Mental Status Examination, and serial testing of orientation on subsequent days is important.

### Language and Cognition

Patients with delirium frequently have abnormal production and comprehension of speech. Nonsensical rambling and incoherent speech, may occur. Other patients may be completely mute. Memory may be impaired, especially primary and secondary memory. Remote memory may be preserved, although the patient may have difficulty distinguishing the present from the distant past (Kaplan et al. 1994).

### Mood

Patients with delirium are susceptible to rapid fluctuations in mood. Unprovoked anger and rage reactions occasionally occur and may lead to attacks on hospital staff. Fear is a common emotion and may lead to increased vigilance and an unwillingness to sleep because of increased vulnerability during somnolence. Apathy, such as that seen in hepatic encephalopathy, depression, use of certain medications (e.g., sulfamethoxazole [Bactrim]), and frontal lobe syndromes, is common, as is euphoria secondary to medications (e.g., corticosteroids, DDC, zidovudine) and drugs of abuse (phencyclidine, inhalants).

## Neurological Symptoms

Neurological symptoms often occur in delirium. These include dysphagia as seen after a CVA, tremor, asterixis (hepatic encephalopathy, hypoxia, uremia), poor coordination, gait apraxia, frontal release signs (grasp, suck), choreiform movements, seizures, Babinski's sign, and dysarthria. Focal neurological signs occur less frequently.

### Sleep-Wakefulness Disturbances

Sleeping patterns of delirious patients are usually abnormal. During the day they can be hypersomnolent, often falling asleep in mid sentence, whereas at night they are combative and restless. Sleep is generally fragmented, and vivid nightmares are common. Some patients may become hypervigilant and develop a sleep phobia because of concern that something untoward may occur while they sleep.

## Causes of Delirium

The cause of delirium may lie in intracranial processes, extracranial ones, or a combination of the two. The most common etiological factors are as follows (Francis et al. 1990).

### Infection Induced

Infection is a common cause of delirium in hospitalized patients. The usual abnormalities in hematology, serology, and vital signs are abnormal except in persons (elderly, chronic alcohol abusers, chemotherapy patients, those with HIV spectrum disease) who may not be able to mount the typical response. Bacteremia septicemia (especially that caused by gram-negative bacteria), pneumonia, encephalitis, and meningitis are common offenders. The elderly are particularly susceptible to delirium secondary to urinary tract infections.

### Metabolic and Endocrine Disturbances

Metabolic causes of delirium include hypoglycemia, electrolyte disturbances, and vitamin deficiency states. The most common endocrine causes are hyperfunction and hypofunction of the thyroid, adrenal, pancreas, pituitary, and parathyroid.

Metabolic causes may involve consequences of diseases of particular organs, such as hepatic encephalopathy resulting from liver disease, uremic encephalopathy, and post-dialysis delirium resulting from kidney dysfunction, and carbon dioxide narcosis and hypoxia resulting from lung disease. The metabolic disturbance or endocrinopathy must be known to induce changes in mental status and must be confirmed by laboratory determinations or physical examination, and the temporal course of the confusion should coincide with the disturbance (Francis et al. 1990). In some individuals, particularly the elderly, brain injured, and demented, there may be a significant lag time between correction of metabolic parameters and improvement in mental state.

### Low-Perfusion States

Any condition that decreases effective cerebral perfusion can cause delirium. Common offenders are hypovolemia, congestive heart failure, and other causes of decreased stroke volume such as arrhythmias, and anemia, which decreases oxygen binding. Maintenance of fluid balance and strict measuring of intake and output are essential in the overall management of delirious states.

### Intracranial Causes

Intracranial causes of delirium include head trauma, especially involving loss of consciousness, postconcussive states, and hemorrhage; brain infections; neoplasms; and such vascular abnormalities as CVAs, subarachnoid hemorrhage, transient ischemic attacks, and hypertensive encephalopathy.

### Postoperative States

Postoperative causes of delirium may include infection, atelectasis, lingering effects of anesthesia, thrombotic and embolic phenomena, and adverse reactions to postoperative analgesia. Patients who have undergone open heart surgery are particularly at risk for microemboli and subsequent

confusion. General surgery in an elderly patient has been reported to be followed by delirium in 10–14% of cases and may reach 50% after surgery for hip fracture (Lipowski 1989, Schneider et al. 2002, Hanson and Galvez-Jimenez 2004).

## Sensory and Environmental Changes

Many clinicians underestimate the disorienting potential of an unfamiliar environment. The elderly are especially prone to develop environment-related confusion in the hospital. Individuals with preexisting dementia, who may have learned to compensate for cognitive deficits at home, often become delirious once hospitalized. In addition, the nature of the intensive care unit often lends itself to periods of high sensory stimulation (as during a "code") or low sensory input, as occurs at night (Kaufman 1990a). Often, patients use such external events as dispensing medication, mealtimes, presence of housekeeping staff, and physicians' rounds to mark the passage of time. These parameters are often absent at night, leading to increased rates of confusion during nighttime hours (Cameron 1941). Often, manipulating the patient's environment (see section on treatment) or removing the patient from the intensive care unit can be therapeutic.

**DSM-IV-TR Criteria**

**Substance Intoxication Delirium**

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

(1) the symptoms in criteria A and B developed during substance intoxication

(2) medication use is etiologically related to the disturbance

**Note:** This diagnosis should be made instead of a diagnosis of substance intoxication only when the cognitive symptoms are in excess of those usually associated with the intoxication syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

**Note:** The diagnosis should be recorded as substance-induced delirium if related to medication use.

**Code:** [specific substance] intoxication delirium:

(291.0 alcohol; 292.81 amphetamine [or amphetamine-like substance]; 292.81 cannabis; 292.81 cocaine; 292.81 hallucinogen; 292.81 inhalant; 292.81 opioid; 292.81 phencyclidine [or phencyclidine-like substance]; 292.81 sedative, hypnotic, or anxiolytic; 292.81 other [or unknown] substance [e.g., cimetidine, digitalis, benztropine])

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## Substance Intoxication Delirium

The list of medications that can produce the delirious state is extensive (Table 51–12). The more common ones include such antihypertensives as methyldopa and reserpine, histamine ($H_2$) receptor antagonists (cimetidine), corticosteroids, antidepressants, narcotics (especially opioid) and nonsteroidal analgesics, lithium carbonate, digitalis, baclofen (Lioresal), anticonvulsants, antiarrhythmics, colchicine, bronchodilators, benzodiazepines, sedative-hypnotics, and anticholinergics. Of the narcotic analgesics, meperidine can produce an agitated delirium with tremors, seizures, and myoclonus (Slaby and Erle 1993, Cameron 1941). These features are attributed to its active metabolite normeperidine, which has potent stimulant and anticholingeric properties and accumulates with repeated intravenous dosing (Eisendrath et al. 1987, Slaby and Erle 1993). In general, adverse effects of narcotics are more common in those who have never received such agents before (the narcotically naive) or who have a history of a similar response to narcotics.

**Table 51–12 Selected Drugs Associated with Delirium**

| | |
|---|---|
| Antihypertensives | Indomethacin |
| Amphotericin B | Ketamine |
| Antispasmodics | Levodopa |
| Antituberculous agents | Lidocaine |
| Baclofen | Lithium |
| Barbiturates | Meperidine |
| Cimetidine | Morphine |
| Corticosteroids | Procainamide |
| Colchicine | Pentamidine |
| Contrast media | Tricyclic antidepressants |
| Digitalis | Zalcitabine (DDC) |
| Ephedrine | Zidovudine (AZT) |

Lithium-induced delirium occurs at blood levels greater than 1.5 mEq/L and is associated with early features of lethargy, stuttering, and muscle fasciculations (Blass et al. 1988). The delirium may take as long as 2 weeks to resolve even after lithium has been discontinued, and other neurological signs such as stupor and seizures commonly occur. Maintenance of fluid and electrolyte balance is essential in lithium-induced delirium. Facilitation of excretion with such agents as aminophylline and acetazolamide helps, but hemodialysis is often required (Kaplan et al. 1994).

Principles to remember in cases of drug-induced delirium include the facts that (1) blood levels of possibly offending agents are helpful and should be obtained, but many persons can become delirious at therapeutic levels of the drug, (2) drug-induced delirium may be the

result of drug interactions and polypharmacy and not the result of a single agent, (3) over-the-counter medications and preparations (e.g., agents containing caffeine or phenylpropanolamine) should also be considered, and (4) delirium can be caused by the combination of drugs of abuse and prescribed medications (e.g., cocaine and dopaminergic antidepressants).

The list of drugs of abuse that can produce delirium is extensive. Some such agents have enjoyed a resurgence after years of declining usage. These include lysergic acid diethylamide, psilocybin (hallucinogenic mushrooms), heroin, and amphetamines. Other agents include barbiturates, cannabis (especially dependent on setting, experience of the user, and whether it is laced with phencyclidine ["superweed"] or heroin), jimsonweed (highly anticholingeric), and mescaline. In cases in which intravenous use of drugs is suspected, HIV spectrum illness must be ruled out as an etiological agent for delirium.

The physical examination of a patient with suspected illicit drug-induced delirium may reveal sclerosed veins, "pop" scars caused by subcutaneous injection of agents, pale and atrophic nasal mucosa resulting from intranasal use of cocaine, injected conjunctiva, and pupillary changes. Toxicological screens are helpful but may not be available on an emergency basis. Some agents such as cannabis have long half lives so both qualitative and quantitative assays are recommended.

## Substance Withdrawal Delirium

Alcohol and certain sedating drugs can produce a withdrawal delirium when their use is abruptly discontinued or significantly reduced. Withdrawal delirium requires a history of use of a potentially addicting agent for a sufficient amount of time to produce dependence. It is associated with such typical physical findings as abnormal vital signs, pupillary changes, tremor, diaphoresis, nausea and vomiting, and diarrhea. Patients generally complain of abdominal and leg cramps, insomnia, nightmares, chills, hallucinations (especially visual), and a general feeling of "wanting to jump out of my skin."

Some varieties of drug withdrawal, although uncomfortable, are not life threatening (e.g., opioid withdrawal). Others such as alcohol withdrawal delirium are potentially fatal. Withdrawal delirium is much more common in hospitalized patients than in patients living in the community. The incidence of delirium tremens, for example, is 1% of all those with alcoholism, but 5% of hospitalized alcohol abusers. Improvement of the delirium occurs when the offending agent is reintroduced or a cross-sensitive drug (e.g., a benzodiazepine for alcohol withdrawal) is employed. When treating patients in withdrawal with high doses of benzodiazepines, oxygen saturation levels should be monitored closely, and shorter acting agents (e.g., Lorazepam, Alprazolam, Oxazepam) should be used in those individuals with significant pulmonary or hepatic diseases. The causes of delirium are summarized in Table 51–13.

**DSM-IV-TR Criteria**

**Substance Withdrawal Delirium**

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

**Note:** This diagnosis should be made instead of a diagnosis of substance withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

**Code:** [specific substance] withdrawal delirium:

(291.0 alcohol; 292.81 sedative, hypnotic, or anxiolytic; 292.81 other [or unknown] substance)

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**Table 51–13 Causes of Delirium**

| |
|---|
| Medication effect or interaction |
| Substance intoxication or withdrawal |
| Infection |
| Head injury |
| Metabolic disarray |
| Acid-base imbalance |
| Dehydration |
| Malnutrition |
| Electrolyte imbalance |
| Blood glucose abnormality |
| Carbon dioxide narcosis |
| Uremic encephalopathy |
| Hepatic encephalopathy |
| Cerebrovascular insufficiency |
| Congestive heart failure |
| Hypovolemia |
| Arrhythmias |
| Severe anemia |
| Transient ischemia |
| Acute CVA |
| Endocrine dysfunction |
| Postoperative states |
| Postcardiotomy delirium |
| Environmental factors |
| Intensive care unit psychosis |
| Sleep deprivation |

## Assessment

Appropriate workup of delirious patients includes a complete physical, mental status, and neurological examination (Table 51–14).

History taking from the patient, any available family, previous physicians, the old chart, and the patient's current nurse is essential. Previous delirious states, etiologies identified in the past, and interventions that proved effective should be elucidated. The appropriate evaluation of the delirious patient is reviewed in Figure 51–13.

**Table 51–14 Managing the Delirious Patient**

| |
|---|
| Identify and correct the underlying cause. |
| Protect the patient from unintentional self-harm. |
| Stabilize the level of sensory input. |
| Reorient patient as often as possible. |
| Employ objects from the patient's home environment. |
| Provide supportive therapy (fever control, hydration). |
| Streamline medications. |
| Correct sleep deprivation. |
| Manage behavior with appropriate pharmacotherapy. |
| Address postdelirium guilt and shame for behavior that occurred during confusion. |

## Differential Diagnosis

Delirium must be differentiated from dementia, because the two conditions may have different prognoses (Lipowski 1982, 1983). In contrast to the changes in dementia, those in delirium have an acute onset (Lipowski 1987). The symptoms in dementia tend to be relatively stable over time, whereas clinical features of delirium display wide fluctuation with periods of relative lucidity. Clouding of consciousness is common in delirium, but demented patients are usually alert. Attention and orientation are more commonly disturbed in delirium, although the latter can become impaired in advanced dementia. Perception abnormalities, alterations in the sleep–wakefulness cycle, and abnormalities of speech are more common in delirium. Most important, a delirium is more likely to be reversible than is a dementia.

Delirium and dementia can occur simultaneously; in fact, the presence of dementia is a risk factor for delirium (Fick et al. 2005). Some studies suggest that about 30% of hospitalized patients with dementia have a superimposed delirium.

Delirium must often be differentiated from psychotic states related to such conditions as schizophrenia or mania and factitious disorders with psychological symptoms. Generally, the psychotic features of schizophrenia are more constant and better organized than are those in delirium, and patients with schizophrenia seldom have the clouding of

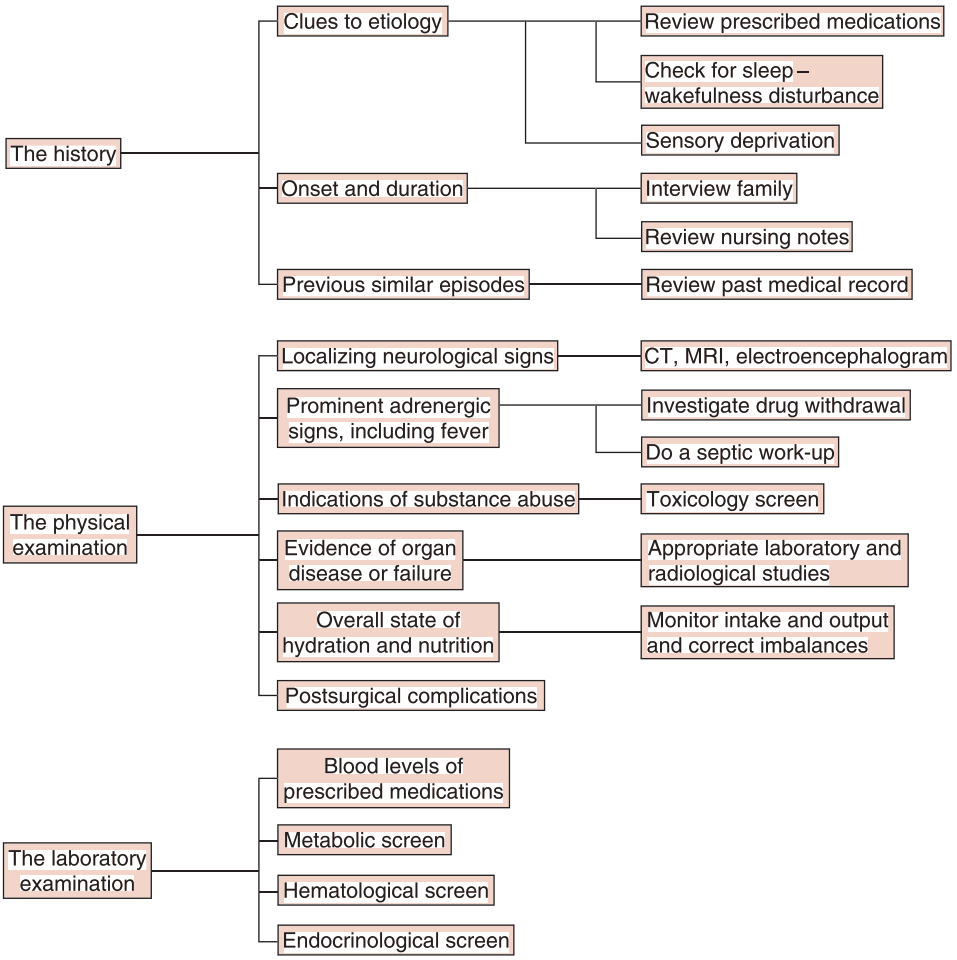



**Figure 51–13** *Evaluation of delirium.*

consciousness seen in delirium. The "psychosis" of patients with factitious disorder is inconsistent, and these persons do not exhibit many of the associated features of delirium. Apathetic and lethargic patients with delirium may occasionally resemble depressed individuals, but tests such as EEG distinguish between the two. The EEG demonstrates diffuse slowing in most delirious states, except for the low-amplitude, fast activity EEG pattern seen in alcohol withdrawal (Pro and Wells 1977, Obrecht et al. 1979, Brenner 1985, Lipowski 1987). The EEG in a functional depression or psychosis is normal.

### Treatment

Once delirium has been diagnosed, the etiological agent must be identified and treated. For the elderly, the first step generally involves discontinuing or reducing the dosage of potentially offending medications. Some delirious states can be reversed with medication, as in the case of physostigmine administration for anticholinergic delirium. However, most responses are not as immediate, and attention must be directed toward protecting the patient from unintentional self-harm, managing agitated and psychotic behavior, and manipulating the environment to minimize additional impairment. Supportive therapy should include fluid and electrolyte maintenance and provision of adequate nutrition. Reorienting the patient is essential and is best accomplished in a well-lit room with a window, clock, and visible wall calendar. Familiar objects from home such as a stuffed animal, favorite blanket, or photographs are helpful. Patients who respond incorrectly to questions of orientation should be provided with the correct answers, and because these individuals often see many consultants, physicians should introduce themselves and state their purpose for coming at every visit. Physicians must take into account that impairments of vision and hearing can produce confusional states, and the provision of appropriate prosthetic devices may be beneficial. Around-the-clock accompaniment by hospital-provided "sitters" or family members may be required.

Despite these conservative interventions, the delirious patient often requires pharmacological intervention. The liaison psychiatrist is the most appropriate person to recommend such treatment. The drug of choice for the agitated, delirious patients has traditionally been haloperidol (Haldol) (Gelfand et al. 1992). It is particularly beneficial when given by the intravenous route and some authors have reported using dosages as high as 260 mg a day without adverse effect (Gelfand et al. 1992, Steinhart 1983, Tesar et al. 1985, Fernandez et al. 1988, Carter 1986). Extrapyramidal symptoms may be less common with haloperidol administered intravenously as opposed to orally and intramuscularly (Menza et al. 1987). In general, doses in the range of 0.5–5.0 mg intravenously are used, with the frequency of administration depending on a variety of factors including the patient's age. An electrocardiogram should be obtained before administering haloperidol. If the QT interval is greater than 450, use of intravenous haloperidol can precipitate an abnormal cardiac rhythm known as Torsades de pointes (Kriwisky et al. 1990, Moss 1993, Glassman and Bigger 2001). Lorazepam has also been proven effective in doses of 0.5–2.0 mg intravenously. Some authors have suggested that haloperidol and lorazepam acts synergistically when given to the agitated delirious patient (Menza et al. 1987). If the delirium is secondary to drug or alcohol abuse, benzodiazepines or clonidine should be used. For patients who are mildly agitated or amenable to taking medications by mouth, oral haloperidol or lorazepam is appropriate. Recent studies have advocated the use of newer atypical antipsychotics for management of behavior and psychotic features in delirium (Torres et al. 2001, Kriwisky et al. 1990, Moss 1993, Glassman and Bigger 2001, Tran et al. 1997, Sipahimalani and Massand 1997, 1998, Graver 2000). Such agents as Quetiapine, Olanzapine, and Risperdone have been used successfully to treat delirium. Newer agents may have lower incidences of dystonias and dyskinesias, but still carry the risk of QT interval prolongation, particularly in patients with electrolyte abnormalities (Glassman and Bigger 2001). Quetiapine and Olanzapine are quite sedating and occasionally a combination of bedtime Olanzepine and "as needed" haloperidol is utilized. Olanzepine may raise blood glucose levels and precipitate weight gain, but is available as a Zydis preparation which is absorbed through the oral mucosa and can therefore be given to patients who are unable to take medications by mouth (Osser et al. 1999, Bettinger et al. 2000). There has been some cases of sudden death in patients simultaneously taking parenteral Lorazepam and parenteral olanzepine so this combination should be avoided. Parenteral forms of ziprasidone and aripriprazole are also available. Whatever antipsychotic is chosen, the patient should be carefully monitored for muscle rigidity, unexplained fever, tremor, and other warning signs of neuroleptic side effects, especially neuroleptic malignant syndrome.

### Outcome of Delirium

After elimination of the cause of the delirium, the symptoms gradually recede during 3–7 days. Some symptoms in certain populations may take weeks to resolve. The age of the patient and the period of time the patient was delirious affect the symptom resolution time (Kaplan et al. 1994). In general, the patient has a spotty memory for events that occurred during delirium. Comments from the staff ("You're not as confused today") or the presence of a sitter or use of wrist restraints, may cause patients to wonder why they required these interventions. Patients who wake up in restraints are often quite distraught wondering what behavior they have engaged in that required them to be tied down. Patient should be reassured that they were not responsible for their behavior while delirious and that no one hates or resents them for the behavior they may have exhibited. As mentioned earlier, delirious patients have an increased risk of mortality in the next year (Weddington 1982). Patients with underlying dementia show residual cognitive impairment after resolution of delirium, and it has been suggested that a delirium may merge into a dementia (Kaplan et al. 1994).

## Amnestic Disorders

The amnestic disorders are characterized by a disturbance in memory related to the direct effects of a general medical condition or the persisting effects of a substance (First 1994). The memory impairment should interfere with social and occupational functioning and represent a significant decline from the previous level of functioning. The amnestic disorders are differentiated on the basis of the etiology of the memory loss. These disorders should not be diagnosed if the memory deficit is a feature of a dissociative disorder, is

**DSM-IV-TR Criteria**

**Amnestic Disorder due to… [Indicate the General Medical Condition]**

A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.

B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.

C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition (including physical trauma).

*Specify* if:

**Transient:** if memory impairment lasts for 1 month or less

**Chronic:** if memory impairment lasts for more than 1 month

**Coding note:** Include the name of the general medical condition on Axis I, e.g., 294.0 amnestic disorder due to head trauma; also code the general medical condition on Axis III.

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associated with dementia, or occurs only in the presence of clouded sensorium, as in delirium (Table 51–15).

## Epidemiology

The exact prevalence and incidence of the amnestic disorders are unknown (Kaplan et al. 1994). Memory disturbances related to specific conditions such as alcohol abuse and head trauma have been studied and these appear to be the two most common causes of amnestic disorders. Kaplan et al. (1984) reported that in the hospital setting the incidence of alcohol-induced amnestic disorders is decreasing while that of amnestic disorders secondary to head trauma is on the rise (Korvath et al. 1989). This may be related to rigorous efforts by hospital personnel to decrease the incidence of iatrogenic amnestic disorder by giving thiamine before glucose is administered.

**Table 51–15 DSM-IV-TR Classification of Amnestic Disorders**

| |
|---|
| Amnestic disorder due to a general medical condition (indicate the condition) |
| Substance-induced persisting amnestic disorder |
| Amnestic disorder not otherwise specified |

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## Etiology

Amnesia results from generally bilateral damage to the areas of the brain involved in memory. The areas and structures so involved include the dorsomedial and midline thalamic nuclei, such temporal lobe-associated structures as the hippocampus, amygdala, and mamillary bodies (Kaplan et al. 1994, Korvath et al. 1989). The left hemisphere may be more important than the right in the occurrence of memory disorders. Frontal lobe involvement may be responsible for such commonly seen symptoms as apathy and confabulation (Kaplan et al. 1994, Korvath et al. 1989).

The specific causes of amnestic disorders include (1) systemic medical conditions such as thiamine deficiency; (2) brain conditions, including seizures, cerebral neoplasms, head injury, hypoxia, carbon monoxide poisoning, surgical ablation of temporal lobes, electroconvulsive therapy, and multiple sclerosis; (3) altered blood flow in the vertebral vascular system, as in transient global amnesia; and (4) effects of a substance (drug or alcohol use and exposure to toxins) (Torres et al. 2001, Hodges and Warlow 1990, Melo et al. 1992, Fisher and Adams 1964).

**DSM-IV-TR Criteria**

**Substance-Induced Persisting Amnestic Disorder**

A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.

B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.

C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia and persists beyond the usual duration of substance intoxication or withdrawal.

D. There is evidence from the history, physical examination, or laboratory findings that the memory disturbance is etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).

**Code:** [specific substance]-induced persisting amnestic disorder:

(291.1 alcohol; 292.83 sedative, hypnotic, or anxiolytic; 292.83 other [or unknown] substance)

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Conditions that affect the temporal lobes such as herpes infection and Klüver-Bucy syndrome can produce amnesia. Among drugs that can cause amnestic disorders, triazolam (Halcion) has received the most attention, but all

benzodiazepines can produce memory impairment, with the dose utilized being the determining factor (Kirk et al. 1990) (Table 51–16).

**Table 51–16 Causes of Amnestic Disorders**

- Types simplex encephalopathy
- Substance-induced (alcohol) blackouts
- Wernicke–Korsakoff syndrome
- Multiple sclerosis
- Kltiver–Bucy syndrome
- Electroconvulsive therapy
- Seizures
- Head trauma
- Carbon monoxide poisoning
- Metabolic
  - Hypoxia
  - Hypoglycemia
- Medications
  - Triazolam
  - Barbiturates (thiopental sodium)
  - Diltiazem (Cardizem)
  - Zalcitabine (DDC)
- Cerebrovascular disorders

## Clinical Features

Patients with amnestic disorder have impaired ability to learn new information (anterograde amnesia) or cannot remember material previously learned (retrograde amnesia). Memory for the event that produced the deficit (e.g., a head injury in a motor vehicle accident) may also be impaired (Torres et al. 2001, Garquonine 1991).

Remote recall (tertiary memory) is generally good, so patients may be able to relate accurately incidents that occurred during childhood but not remember what they had for breakfast. As illustrated by such conditions as thiamine amnestic syndrome, immediate memory is often preserved. In some instances, disorientation to time and place may occur, but disorientation to person is unusual.

The onset of the amnesia is determined by the precipitant and may be acute as in head injury or insidious as in poor nutritional states (Nolan et al. 1991). DSM-IV-TR characterizes short-duration amnestic disorder as lasting less than 1 month and long-duration disorder lasting 1 month or longer. Often individual slack insight into the memory deficit and vehemently insist that their inaccurate responses on a Mental Status Examination are correct.

## Selected Amnestic Disorders

### Blackouts

Blackouts are periods of amnesia for events that occur during heavy drinking (Tarter and Schneider 1976). Typically, a person awakens the morning after consumption and does not remember what happened the night before. Unlike delirium tremens, which is related to chronicity of alcohol abuse, blackouts are more a measure of the amount of alcohol consumed at any one time. Thus, blackouts are common in binge pattern drinkers and may occur the first time a person ingests a large amount of alcohol. Blackouts are generally transient phenomena, but may persist for weeks or months after cessation of drinking. The memory of a particular event is lost forever, however the blackouts will end if the individual stops drinking and avoids those agents such a benzodiazepines that have a cross-sensitivity with alcohol.

They may be produced by agents with cross-sensitivity to alcohol, such as benzodiazepines. Blackouts should not be confused with alcohol-induced dementia, which presents with cortical atrophy on CT scans, associated features of dementia, and a usually irreversible course.

### Korsakoff's Syndrome

Korsakoff's syndrome is an amnestic disorder caused by thiamine deficiency. Although generally associated with alcohol abuse, it can occur in other malnourished states such as marasmus, gastric carcinoma, and HIV spectrum disease (Reulen et al. 1985, Victor 1987). This syndrome is usually associated with Wernicke's encephalopathy, which involves ophthalmoplegia, ataxia, and confusion, with all three features of this triad recognized in about one-third of cases. The ocular signs include nystagmus, bilateral lateral rectus palsies, and conjugate nerve palsies. The gait ataxia is likely to be a combination of polyneuropathy and cerebellar damage.

Unlike patients with delirium tremens, those with Wernicke's are likely to be much less agitated and do not have the autonomic signs common in delirium tremens.

Of patients who survive Wernicke's encephalopathy, a percentage have Korsakoff syndrome, which is characterized by the inability to recall information (retrograde amnesia), the inability to assimilate new information (anterograde amnesia), decreased spontaneity and initiative and confabulation. Only about 20% of patients who develop Korsakoff's will fully recover. The prevention of Wernicke's involves the administration of thiamine before giving glucose in any form. These patients are likely to be hypomagnesemic as well and magnesium should be given unless the patient has severe renal disease or significant cardiac conduction prolongation. Autopsy findings have placed the incidence of Wernicke's encephalopathy between 0.8% and 2% of the general population. The incidence can be as high as 12% in a population of alcoholics. Pathologically, Wernicke-Korsakoff syndrome has been associated with hemorrhage into the mamillary bodies.

### Head Injury

Head injuries can produce a wide variety of neurological and psychiatric disorders, even in the absence of radiological evidence of structural damage. Delirium, dementia, mood disturbances, behavioral disinhibition, alterations of personality, and amnestic disorders may result (Torres et al. 2001). Amnesia in head injury is for events preceding the incident and the incident itself, leading some physicians to consider these patients as having factitious disorders or being malingerers. The eventual duration of the amnesia is related to the degree of memory recovery that occurs in the first few days after the injury (Torres et al. 2001, Garquonine 1991, Saneda and Corrigan 1992). Amnesia after head injury has become a popular plot device in novels and motion pictures, many of which depictions have erroneously suggested that a second blow to the head is curative.

## Differential Diagnosis

Amnestic disorders must be differentiated from the less disruptive changes in memory that occur in normal aging,

the memory impairment that is accompanied by other cognitive deficits in dementia, the amnesia that might occur with clouded consciousness in delirium, the stress-induced impairment in recall seen in dissociative disorders, and the inconsistent amnestic deficits caused by factitious disorder. Patients with dementia, for example, will have impairment in other cognitive areas as well as memory. Patients who are delirious will have altered sensorium, adrenergic signs, and abnormalities in other domains including orientation and attention. Patients with dissociative disorders who may have amnesia (as in a fugue state or dissociative amnesia) will have the other DSM- IV-TR criteria associated with that diagnosis. Patients who are feigning a memory loss or have Factitious Disorder with Psychological Features will have "near miss" answers and inconsistent memory loss, along with the other features associated with that diagnosis.

## Treatment

As in delirium and dementia, the primary goal in the amnestic disorders is to discover and treat the underlying cause. Because some of these conditions are associated with serious psychological states (e.g., suicide attempts by hanging, carbon monoxide poisoning, deliberate motor vehicle accidents, self-inflicted gunshot wounds to the head, and chronic alcohol abuse), some form of psychiatric involvement is often necessary. In the hospital, continuous reorientation by means of verbal redirection, clocks, and calendars can allay the patient's fears. Supportive individual psychotherapy and family counseling are beneficial.

### Clinical Vignette 1

A 75-year-old woman presented to the emergency room with complaints of memory loss and inability to "think straight." For the past month, she and her family had noted a marked change in her mental state that "seemed to happen overnight." She would forget the names of her grandchildren and showed little interest in activities she had previously enjoyed. Apparently, she had been hospitalized twice in the past for depression, but had never exhibited cognitive impairments. On the Mental Status Examination, she exhibited marked psychomotor retardation and a blunted affect. She was oriented only to person and all three spheres of memory were significantly impaired. In fact, she responded to most questions with a shrug of her shoulders and the comment "I don't know." As the interview continued she became more frustrated with her inability to perform, and asked the physician to "stop asking all these questions." She was hospitalized and a complete work-up was initiated.

The evaluation for dementia revealed negative results of drug and heavy metal screening, the absence of any potentially offending medications, normal CT and MRI scans, and a normal EEG. Chemistry assays, hematology, thyroid functions, vitamin studies, serological tests for syphilis, chest radiography, and urinalysis were normal. Psychological testing revealed inconsistent cognitive deficits.

A psychiatric consultation was obtained, and it was recommended that a trial of psychostimulants be undertaken to rule out the possibility of depression as the cause of her cognitive impairment. The following day she received methylphenidate 2.5 mg at 7:00 am and 2.5 mg at noon before lunch. She tolerated the medication well, and her dose was increased to 7.5 mg on the second day. By the third day, she demonstrated improvement in her affect, concentration, and attention span, and in subsequent days her cognition improved significantly. Eventually, she had a complete recovery and the methylphenidate was discontinued after 2 months without relapse.

This case illustrates the difficulty in distinguishing dementia from cognitive impairment in depression. Features suggestive of depression included the relatively rapid onset, the patient's insight into the cognitive deficits, presence of some vegetative signs of depression, absence of an identified medical condition judged to be responsible, pervasive yet inconsistent cognitive deficits, a past history of treatment for depression, and a positive response to a psychostimulant trial. The psychostimulant was chosen because the onset of action is faster than that of the other antidepressant agents. The principle problems encountered in treating a patient such as this are the tendency of physicians to underdiagnose depression in the elderly and the hesitancy of many caregivers to use psychostimulants for the treatment of depression.

### Clinical Vignette 2

A 33-year-old man was referred to the emergency department because of a change in his mental status. According to the family, he had become markedly agitated, paranoid, and, at times, belligerent. In addition, they reported nausea and vomiting for the past 36 hours. Because he appeared by clinical examination and laboratory testing (urinalysis, complete blood count) to be dehydrated, the patient was admitted to the medicine service. A psychiatric consultation was requested on the third hospital day.

On psychiatric evaluation, the patient gave a history of being HIV-positive for 3 years as a result of intravenous drug use. He denied using drugs or alcohol for the past year. Since being diagnosed HIV-positive, he had taken zidovudine and Bactrim daily. This patient also had a history of bipolar disorder that had been stabilized with lithium carbonate. During the interview, the patient was disoriented in all spheres except person. He thought he was at home in his kitchen. He had poor primary and secondary memory and tended to talk about distant events as it they were occurring at the present time. He felt that someone was torturing his daughter and had even wandered down to the basement of the hospital looking for her. There were visual and auditory hallucinations, and physical examination revealed a tremor accentuated with intention, reflex abnormalities, ataxia, and mild aphasia. His therapist and family reported that they had "never seen him like this," even during past exacerbations of his bipolar disorder.

Laboratory studies showed no signs of acute infection, a $CD4^+$ cell count of 10, a low therapeutic lithium level, and a negative drug screen. Complete blood count and urinalysis values had reverted to normal after hydration. Chest radiography was unremarkable, and CT and MRI scans showed only mild atrophy. Zidovudine, Bactrim, and lithium had been discontinued at the time of admission.

The patient was started on haloperidol with some improvement in his psychotic features, but his overall cognitive state continued to deteriorate. The patient

*(continues)*

Clinical Vignette 2 *continued*

eventually required nursing home placement. This complicated case illustrates the difficulty in determining the specific diagnostic category for an observed cognitive impairment. Dementia related to HIV disease, acute mania, persisting effects of a substance, delirium, and cognitive impairment (delirium, dementia, mood disturbance) secondary to medication (see Table 51–12) were all considered. Based on his past history, laboratory examination, HIV-positive status, markedly reduced $CD4^+$ cell count, and associated physical findings, the patient was diagnosed as having an acute delirium. Since his cognitive status continued to deteriorate once his metabolic parameters normalized, he was diagnosed with dementia as well, the latter being related to his HIV-spectrum illness.

Clinical Vignette 3

A 68-year-old white male was admitted to the hospital for mental status changes. His wife reported that he had been getting increasingly forgetful and argumentative over the past 2 years. At first the changes had been subtle, but in the past few months his cognition and behavior had declined significantly. She felt unable to care for him at home. The patient's primary care physician had started him on Donepezil about six months ago without much improvement. Once the patient was hospitalized, he became even more agitated and combative and felt that the nurses were trying to kill him. He was started on Valproic acid for behavior control, with as needed doses of lorazepam and risperidone. The lorazepam seemed to make him more agitated and his QTc increased to 500 ms on Risperdal, so both were discontinued. His behavior improved somewhat with the addition of low dose aripriprazole. The dementia workup (looking for other medical causes) was essentially negative, and he only scored a "10" on the Mini Mental Status evaluation. The diagnosis was Alzheimer's Dementia and since his symptomatology was severe, his physician decided to add memantine at 5 mg a day with plans to gradually increase it to 10 mg twice a day. The combination of Valproic Acid, Aripriprazole as needed, memantine, and donepezil produced some improvement in his behavior and he was discharged to a nursing facility.

The management of agitation and other behavioral problems is difficult in Alzheimer's patients. Benzodiazepines are often disinhibiting in this population and atypical antipsychotics may cause cardiac difficulties and may increase confusion by virtue of their anticholinergic effects. Valproic acid has been helpful in managing such patients, and aripriprazole is not as likely to produce abnormities of cardiac conduction as do other atypicals. Nonetheless, all atypical antipsychotics should be used with caution in this population. In more severely demented patients, the combination of donepezil and memantine has shown some benefit.

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CHAPTER

# 52 Mental Disorders Due to a General Medical Condition

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Psychotic Disorder
Mood Disorder
Anxiety Disorder
Catatonic Disorder
Personality Change

## Introduction

This chapter deals with disorders characterized by mental symptoms that occur due to the direct physiological effect of a general medical condition. In evaluating patients with mental symptoms of any sort, one of the first questions to ask is whether those symptoms are occurring as part of a primary psychiatric disorder or are caused by a general medical condition, and Figure 52–1 presents a decision tree designed to help in making this decision. The first step is to review the history, physical examination, and laboratory tests to see if there is evidence for the presence of a general medical disorder that could plausibly cause the mental symptoms in question. In making this determination, one looks not only for a temporal correlation (e.g., the onset of a psychosis shortly after starting or increasing the dose of a medication), but also keeps in mind well-documented associations between certain mental symptoms (e.g., depression) and certain general medical conditions (e.g., Cushing's syndrome). If it appears, at this point, that the mental symptoms could indeed be occurring secondary to a general medical condition, the next step involves determining whether or not these symptoms could be better accounted for by a primary psychiatric disorder. For example, consider the case of a 45-year-old man with a history of recurrent major depression, currently euthymic, who begins a course of steroids for asthma and then, within a week, becomes depressed. The steroids are stopped but the depression continues. In this case, if the depression had cleared shortly after stopping the steroids, one might make the case that the depression occurred secondary to the steroid treatment; the persistence of the symptoms, however, argues strongly that this depression represents rather a recurrence of the major depression.

Once it appears that the mental symptoms in question could well directly result from a general medical condition and could not be better accounted for by a primary psychiatric disorder, then it remains to classify these symptoms into one of the specific types noted in Figure 52–1, and to proceed to the appropriate section below. There is also, at the end of the decision tree, a residual category for "unspecified" mental symptoms, and in this chapter two such syndromes, not uncommonly found in consult-liaison work, are included, namely pseudobulbar palsy and the Klüver–Bucy syndrome.

In caring for patients with mental disorders due to a general medical condition, the question arises as to whether or not symptomatic treatment for these mental symptoms should be offered. Figure 52–2 provides a general treatment algorithm designed to help answer this question. First, one must determine whether the mental symptoms demand emergent treatment. Consider, for example, a postictal psychosis characterized by delusions of persecution, which prompt the patient to become assaultive: here, even though the condition itself will eventually resolve spontaneously, symptomatic treatment of the psychosis is required to protect the patient or others. In cases where the mental symptoms do not present an emergency, one looks to whether the underlying general medical condition is treatable or not. For example, in the case of psychosis due to Huntington's disease, as

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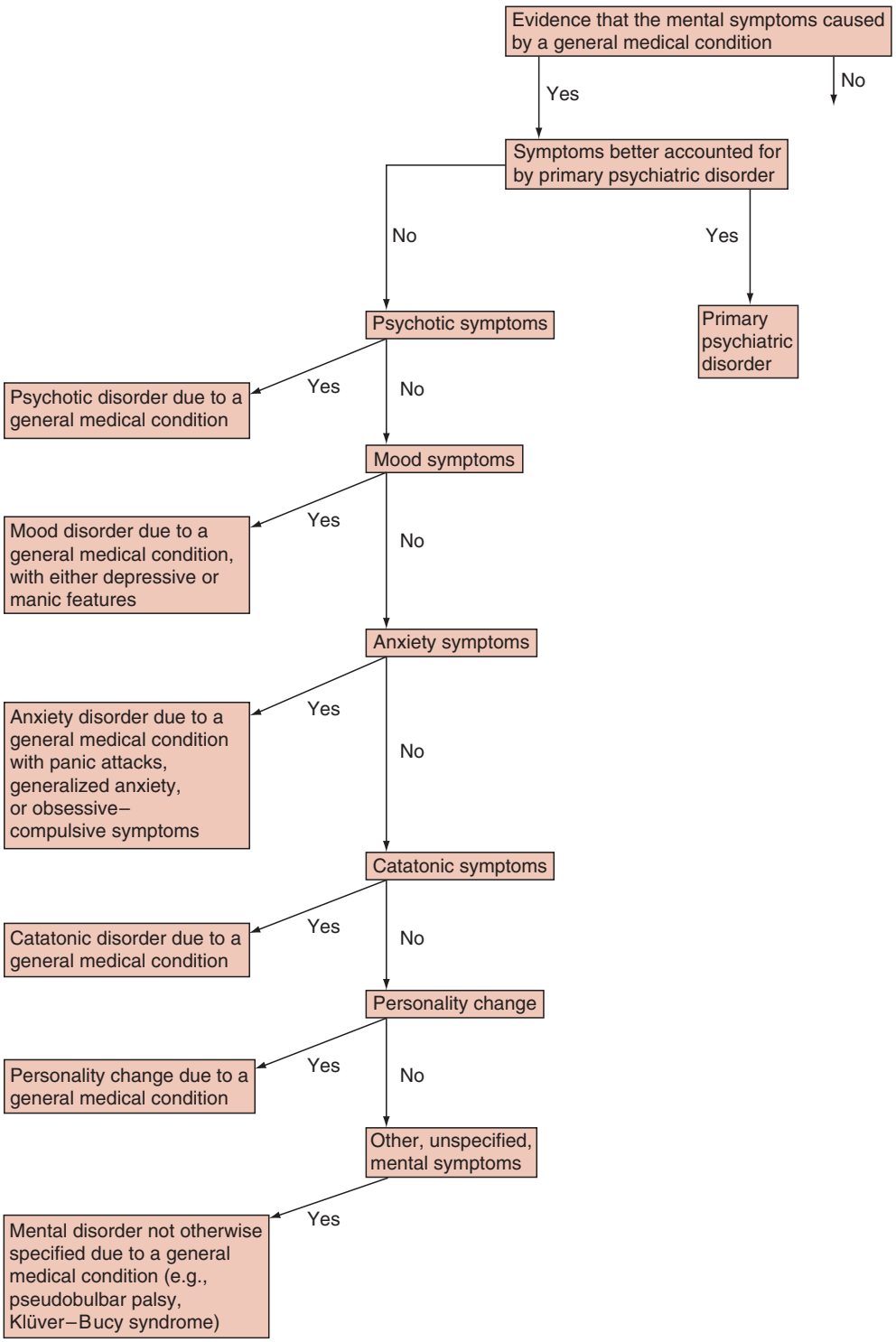



**Figure 52–1** *Diagnostic decision tree.*

the underlying condition is not treatable, one generally proceeds directly to symptomatic treatment. In cases where the underlying condition is treatable, one must make a judgment as to whether, with treatment of the underlying general medical condition, the mental symptoms will resolve at a clinically acceptable rate. Consider, for example, a patient with anxiety due to hyperthyroidism who has just begun treatment with an antithyroid drug. In such a case, the decision as to whether to offer a benzodiazepine as symptomatic treatment for the anxiety depends not only on the severity and tolerability of the anxiety, but also on the expected time required for the antithyroid drug to resolve the hyperthyroidism; here, clearly, considerable clinical judgment is required.

## Psychotic Disorder Due to a General Medical Condition

### Definition

A psychotic disorder due to a general medical condition is characterized clinically by hallucinations or delusions

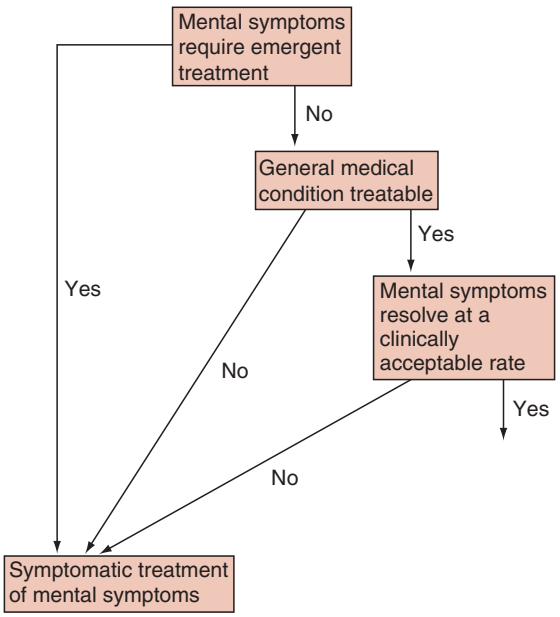



**Figure 52–2** *General treatment algorithm.*

occurring in a clear sensorium, without any associated decrement in intellectual abilities. Furthermore, one must be able to demonstrate, by history, physical examination, or laboratory findings, that the psychosis is occurring on the basis of a general medical disorder.

## Etiology and Pathophysiology

Of all the causes of psychosis, the most commonly encountered are three primary psychiatric disorders, namely, schizophrenia, schizoaffective disorder, and delusional disorder, each of these being covered elsewhere in this text. Table 52–1 lists the various secondary causes of psychosis, dividing them into those occurring *secondary to precipitants* (e.g., medications), those occurring *secondary to diseases with distinctive features* (e.g., the chorea of Huntington's disease), and finally a group occurring *secondary to miscellaneous causes* (e.g., cerebral tumors).

Psychosis occurring *secondary to precipitants* is perhaps the most common form of secondary psychosis. Among the various possible precipitants, substances, that is to say, drugs of abuse, are perhaps the most common, but these are treated in the chapters on stimulants, hallucinogens, phencyclidine, cannabis, and alcohol. After drugs of abuse, various medications are the next most common precipitants, and of the medications listed in Table 52–1, the most problematic are the neuroleptics themselves. It appears that in a very small minority of patients treated chronically with neuroleptics, a "supersensitivity psychosis" (or, as it has also been called, on analogy with tardive dyskinesia, "tardive psychosis") may occur. Making such a diagnosis in the case of patients with schizophrenia may be difficult, as one may well say that any increase in psychotic symptoms, rather than evidence for a supersensitivity psychosis, may merely represent an exacerbation of the schizophrenia; in the case of patients treated with antipsychotics for other conditions (e.g., Tourette's syndrome), however, the appearance of a psychosis is far more suggestive, as it could not be accounted for on the basis of the disease for which the neuroleptic was prescribed. Of the dopaminergic drugs capable of causing a psychosis, levodopa is the most common (Celesia and Barr 1970, Fenelon et al. 2000, Moskovitz et al. 1978); although direct-acting dopamine agonists as bromocriptine and lergotrile (Serby et al. 1978) and pramipexole (Almeida and Ranjith 2006) may also be at fault, they are much less likely causes than is levodopa itself. The other medications noted in Table 52–1 only very rarely cause a psychosis.

Of the various encephalitides, which may have a psychosis as a sequela, the most classic is encephalitis lethargica (von Economo's disease) (Fairweather 1947), a disease that, though no longer occurring in epidemic form, may still be seen sporadically. Other encephalitides, such as Herpes simplex encephalitis (1973 Rennick *et al.* 1973) may also, albeit rarely, have a psychosis as one of their sequelae.

Of the psychoses *secondary to diseases with distinctive features*, the psychoses of epilepsy are by far the most important, and these may be ictal, postictal, or interictal. Ictal psychoses represent complex partial seizures and are immediately suggested by their exquisitely paroxysmal onset. Postictal psychoses are typically preceded by a "flurry" of grand mal or complex partial seizures and, importantly, are separated from the last of this "flurry" of seizures by a "lucid" interval lasting from hours to days. Interictal psychoses appear in one of two forms, namely, the psychosis of forced normalization and the chronic interictal psychosis. The psychosis of forced normalization appears when

**DSM-IV-TR Criteria**

**Psychotic Disorder Due to … [Indicate the General Medical Condition]**

A. Prominent hallucinations or delusions.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder.

D. The disturbance does not occur exclusively during the course of a delirium.

Code based on predominant symptom:

**.81 With Delusions:** if delusions are the predominant symptom

**.82 With Hallucinations:** if hallucinations are the predominant symptom

**Coding note:** Include the name of the general medical condition on Axis I. e.g., 293.81 Psychotic Disorder Due to Malignant Lung Neoplasm. With Delusions: also code the general medical condition on Axis III (see Appendix G for codes).

**Coding note:** If delusions are part of a preexisting dementia, indicate the delusions by coding the appropriate subtype of the dementia if one is available e.g., 290.20 Dementia of the Alzheimer's Type. With Late Onset. With Delusions.

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**Table 52–1 Causes of Psychosis Due to a General Medical Condition**

Secondary to Precipitants

Medications
- Neuroleptics (supersensitivity psychosis) (Chouinard and Jones 1980, Steiner et al. 1990)
- Dopaminergic drugs
- Disulfiram (Bicknell and Moore 1960)
- Sympathomimetics (Lambert 1987)
- Bupropion (Golden et al. 1985)
- Fluoxetine (Mandalos and Szarek 1990)
- Baclofen (upon discontinuation) (Swigar and Bowers 1986)
- Levetiracetam (Mula et al. 2003)
- Topiramate (Kober and Gabbard 2005)

Other precipitants
- Postencephalitic psychosis
- Posttraumatic brain injury (Buckley et al. 1993, Hillbom 1951, Nasrallah et al. 1981)

Secondary to Diseases with Distinctive Features

- Associated with epilepsy
- Ictal psychosis (Ellis and Lee 1978, Wells 1975)
- Postictal psychosis (Kanner et al. 1996, Lancman et al. 1994, Logsdail and Toone 1988, Savard et al. 1991, DeGreef et al. 1995)
- Psychosis of forced normalization (Pakainis et al. 1987)
- Chronic interictal psychosis (Kristensen and Sindrup 1979, Perez and Trimble 1980, 1963a, 1963b)

Encephalitic onset
- Herpes simplex encephalitis (Drachman and Adams 1962, Johnson et al. 1972, Williams and Lerner 1978, Wilson 1976)
- Encephalitis lethargica (Kirby and Davis 1921, Meninger 1926, Sands 1928)
- Infectious mononucleosis (Raymond and Williams 1948)

With other specific features
- Huntington's disease (chorea) (Bolt 1970, Heathfield 1967)
- Sydenham's chorea (Hammes 1992)
- Chorea gravidarum (Beresford and Graham 1950, Wilson and Preece 1932)
- Manganism (parkinsonism) (Abd El Naby and Hassanein 1965)
- Creutzfeldt–Jakob disease (myoclonus) (Brown et al. 1984)
- Hashimoto's encephalopathy (myoclonus) (Cohen et al. 1996)
- Wilson's disease (various abnormal involuntary movements) (Beard 1959, Jackson and Zimmerman 1919)
- AIDS (thrush, *Pneumocystis* pneumonia) (Bulrich et al. 1988, Harris et al. 1991)
- Systemic lupus erythematosus (arthralgia, rash, pericarditis, pleurisy) (Devinsky et al. 1989, Johnson and Richardson 1968, Lim et al. 1988, Miguel et al. 1994)
- Hyperthyroidism (tremor, tachycardia) (Hodgson et al. 1992, Ingham and Nielsen 1931)
- Hypothyroidism (cold intolerance, voice change, constipation, hair loss, myxedema) (Asher 1949, Reed and Bland 1977, Karnosh and Stout 1935)
- Cushing's syndrome ("Cushingoid" habitus, e.g., "moon" facies) (Trethowan and Cobb 1952, Hertz et al. 1955)
- Adrenocortical insufficiency (abdominal complaints and dizziness) (Cleghorn 1951, McFarland 1963)
- Hepatic porphyria (abdominal pain) (Hirsch and Dunsworth 1955, Mandoki and Sumner 1994)
- Spinocerebellar ataxia (ataxia) (Chandler and Bebin 1956)
- Dentatorubro-pallidoluysian atrophy (ataxia) (Adachi et al. 2001)
- Prader–Willi syndrome (massive obesity) (Clarke 1993)

Secondary to Miscellaneous Causes

- Cerebral tumors
- Cerebral infarction
- Multiple sclerosis (Fontaine et al. 1994, Geocaris 1957, Langworthy et al. 1941, Mathews 1979, Parker 1956)
- Neurosyphilis (Rothschild 1940, Schube 1934)
- Vitamin B12 deficiency (Smith 1929, Evans et al. 1983)
- Metachromatic leukodystrophy (Hyde et al. 1992, Muller et al. 1969)
- Subacute sclerosing panencephalitis (Cape et al. 1973, Salib 1988)
- Fahr's syndrome (Chabot et al. 2001, Francis and Freeman 1984)
- Thalamic degeneration (Deymeer et al. 1989)
- Velo–cardio–facial syndrome (Bassett and Chow 1999, Murphy et al. 1999)

anticonvulsants have not only stopped seizures but have essentially "normalized" the EEG: a disappearance of the psychosis with the resumption of seizure activity secures the diagnosis. The chronic interictal psychosis, often characterized by delusions of persecution and reference and auditory hallucinations, appears subacutely, over weeks or months, in patients with longstanding, uncontrolled grand mal or complex partial seizures.

Encephalitic psychoses are suggested by such typical "encephalitic" features such as headache, lethargy, and fever. Prompt diagnosis is critical, especially in the case of herpes simplex encephalitis, given its treatability.

The other specific features listed in Table 52–1 are fairly straightforward. In the past, the differential between Huntington's disease and schizophrenia complicated by tardive dyskinesia was difficult; today, the availability of genetic testing has greatly simplified this diagnostic task.

Of the *miscellaneous causes* capable of causing psychosis, cerebral tumors are perhaps the most important, with psychosis being noted with tumors of the frontal lobe (Strauss and Keschner 1935), corpus callosum (Murthy et al. 1997), and temporal lobe (Gal 1958, Keschner et al. 1936, Malamud 1967, Strobos 1953, Tucker et al. 1986). Suggestive clinical evidence for such a cause includes prominent headache, seizures, or certain focal signs, such as aphasia. Cerebral infarction is likewise an important cause, and is suggested not only by accompanying focal signs, but also by its acute onset: infarction of the frontal lobe (Hall and Young 1992), temporoparietal area (Peroutka et al. 1982, Thompson and Nielsen 1949), and thalamus (Feinberg and Rapcsak 1989) have all been implicated. Neurosyphilis should never be forgotten as a differential possibility in cases of psychosis of obscure origin, and an FTA (fluorescent treponemal antibody) is appropriate in such cases. Vitamin $B_{12}$ deficiency, likewise, should be borne in mind, especially as this may present with psychosis without any evidence of spinal cord or hematologic involvement. The remaining disorders listed in Table 52–1 are extremely rare causes of psychosis, and represent the "zebras" (for those who are unfamiliar with this usage, a "zebra" is a rare but notable syndrome) of this differential listing. Among these "zebras," however, one is of particular interest, namely velo–cardio–facial syndrome. This genetic disorder, characterized by cleft

palate, cardiovascular malformations and dysmorphic facies (micrognathia and prominent nose), and, often, mental retardation, also appears, in a substantial minority of cases, to cause a psychosis phenotypically very similar to that caused by schizophrenia.

## Assessment and Differential Diagnosis

As noted earlier, psychotic disorder due to a general medical condition is a disorder that by definition occurs in a clear sensorium, without any associated decrement in intellectual abilities: both delirium and dementia are commonly accompanied by hallucinations and delusions, but these conditions are clearly distinguished from psychotic disorder due to a general medical condition by the presence of confusion or significant intellectual deficits. When these features are present, one should proceed to the differential for delirium and dementia described in another chapter of this book (see DSM-IV-TR criteria).

In most cases, a thorough history and physical examination will disclose evidence of the underlying cause of the psychosis in question. In those cases, however, where the patient's symptomatology is atypical for one of the primary causes of psychosis (e.g., schizophrenia), yet the history and physical examination fail to disclose clear evidence for another cause, a "laboratory screen," as listed in Table 52–2, may be appropriate. Clearly, one does not order all these tests at once, but begins with those most likely, given the overall clinical picture, to be most informative.

**Table 52–2 A "Laboratory Screen" for Secondary Psychosis**

| |
|---|
| Serum or urine drug screen |
| Testosterone level (reduced in anabolic steroid abusers) |
| Red blood cell mean corpuscular volume (elevated in alcoholism and many cases of $B_{12}$ deficiency) |
| Liver transaminases (elevated in alcoholism) |
| HIV testing |
| FTA |
| $B_{12}$ levels (or, for increased sensitivity, a methylmalonic acid level) |
| ANA |
| Antithyroid antibodies (antithyroid peroxidase and antithyroglobulin) (present in Hashimoto's encephalopathy) |
| Free T4, TSH |
| Cortisol and ACTH levels and 24-hour urine for free cortisol |
| Copper and ceruloplasmin levels |
| MRI |
| EEG |
| Lumbar puncture |

## Epidemiology and Comorbidity

The overwhelming majority of patients with a chronic psychosis have one of the primary disorders, that is, schizophrenia, schizoaffective disorder, or delusional disorder; secondary causes of psychosis are relatively uncommon.

## Course

This is determined by the underlying cause. For example, whereas a psychosis occurring secondary to a medication, such as a dopaminergic drug, generally clears within days of discontinuation of the drug, the psychosis due to a chronic condition, such as Huntington's disease, is likewise chronic.

## Treatment

Treatment, if possible, is directed at the underlying cause. In those cases where such treatment is unavailable or ineffective, or where control of the psychosis is emergently required, neuroleptics are indicated. Although conventional neuroleptics, such as haloperidol, have long been used successfully, newer atypical agents, such as olanzapine or risperidone, may be better tolerated. In general, it is best to start with a low dose (e.g., 2.5 mg of haloperidol, 5 mg olanzapine, or 1 mg of risperidone) with incremental increases, if necessary, performed slowly.

Clinical Vignette 1

Ziegler (1930) reported a case of "myxedema madness" in a 48-year-old woman who, at the age of 45 years, had undergone radiation treatment for Grave's disease. She was treated with thyroid hormone, but eventually became noncompliant. Soon thereafter "she began to feel that her husband was paying attention to another woman and that he was trying to do away with her by means of gas or the electric chair. During a game at a party in her own home during the holidays in 1928, she refused to sit in a chair designated for her, thinking it might be a plot to kill her. She also felt that her husband was trying to poison her and refused to take desiccated thyroid gland at home on account of such a belief. On several occasions subsequently, when desiccated thyroid hormone was administered in sufficient quantity, at the repeated and urgent request of her physician, the delusions entirely disappeared and she felt so much better that she concluded that it would be foolish to be taking medicine and discontinued taking it. On such occasions, the psychosis would slowly return in the same form as before."

# Mood Disorder Due to a General Medical Condition

Mood disorders due to general medical conditions may occur either with depressive features or manic features, and each is covered in turn.

## With Depressive Features

### Definition

A mood disorder secondary to a general medical condition with depressive features is characterized by a prominent and persistent depressed mood or loss of interest, and by the presence of evidence, from the history, physical examination, or laboratory tests, of a general medical condition capable of causing such a disturbance. Although other depressive symptoms (e.g., lack of energy, sleep disturbance, appetite change, or psychomotor change) may be present, they are not necessary for the diagnosis.

### Etiology and Pathophysiology

The overwhelming majority of cases of depression occur as part of one of the primary mood disorders, including major depressive disorder, dysthymic disorder, bipolar disorder, cyclothymic disorder, or premenstrual dysphoric disorder, all of which are covered elsewhere in this text. The various secondary causes of depression are listed in Table 52–3.

In utilizing Table 52–3, the first question to ask is whether the depression could be *secondary to precipitants*.

**Table 52–3** Causes of Depression Due to a General Medical Condition

Secondary to Precipitants

Medications
- Propranolol (Petrie et al. 1982, Pollack et al. 1985)
- Interferon, both interferon-beta 1b (Neilley et al. 1996) and interferon-alpha (Torriani et al. 2004)
- ACTH (Falk et al. 1979)
- Prednisone (Wolkowitz et al. 1990)
- Reserpine (Jensen 1959, Quetsch et al. 1959)
- Alpha-methyldopa (DeMuth 1983)
- Levetiracetam (Mula et al. 2003)
- Nifedipine (Hullett et al. 1988)
- Ranitidine (Billings and Stein 1986)
- Metoclopramide (Friend and Young 1997)
- Bismuth subsalicylate (Supino-Viterbo et al. 1977)
- Pimozide (Bloch et al. 1997)
- Subdermal estrogen/progestin (Wagner 1998, Wagner and Berenson 1994)

Anticholinergic withdrawal ("cholinergic rebound") (Dilsaver et al. 1983)

Poststroke depression (Robinson et al. 1984, Vataja et al. 2001)

Traumatic brain injury (Federoff et al. 1992)

Whiplash (Ettlin et al. 1992)

Secondary to Diseases with Distinctive Features

Hypothyroidism (hair loss, dry skin, voice change) (Tonks 1964, Whybrow et al. 1969, Nickel and Frame 1958)

Hyperthyroidism (weight loss with *increased* appetite, tachycardia, and, in the elderly, atrial fibrillation or congestive heart failure) (Trzepacz et al. 1988)

Cushing's syndrome (moon facies, hirsutism, acne, "buffalo hump," abdominal striae) (Haskett 1985)

Chronic adrenocortical insufficiency (nausea, vomiting, abdominal pain, postural dizziness) (Varadaraj and Cooper 1986)

Obstructive sleep apnea (severe snoring) (Millman et al. 1989)

Multiple sclerosis (various focal findings) (Rabins et al. 1986)

Down's syndrome (Collacott et al. 1992)

Epilepsy
- Ictal depression (Weill 1955, 1956, 1959, Williams 1956)
- Chronic interictal depression (Mendez et al. 1986)

Occurring as Part of Certain Neurodegenerative or Dementing Disorders

Alzheimer's disease (Burns et al. 1990, Starkstein et al. 1997)

Multi-infarct dementia (Cummings et al. 1987)

Diffuse Lewy body disease (Klatka et al. 1996)

Parkinson's disease (Mayeux et al. 1986, Starkstein et al. 1990)

Fahr's syndrome (Slyter 1979, Trautner et al. 1988)

Tertiary neurosyphilis (Storm-Mathisen 1969)

Limbic encephalitis (Corsellis et al. 1968)

Miscellaneous or Rare Causes

Cerebral tumors (Ironside and Guttmacher 1929)

Hydrocephalus (Jones 1993, Pujol et al. 1989)

Pancreatic cancer (Pujol et al. 1989, Fras and Pearson 1967)

New variant Creutzfeldt–Jakob disease (1997a, 1997b)

Hyperparathyroidism (Karpati and Frame 1964)

Systemic lupus erythematosus (Ainiala et al. 2001, Dennis et al. 1992)

Pernicious anemia (Fraser 1960)

Pellagra (Hardwick 1943)

Lead encephalopathy (Schottenfeld and Cullen 1984)

Hyperaldosteronism (Malinow and Lion 1979)

Of the various possible precipitants, substances of abuse (e.g., as seen in alcoholism or during stimulant withdrawal) are very common causes, and these are treated in their respective chapters. Medications are particularly important; however, it must be borne in mind that most patients are able to take the medications listed in Table 52–3 without untoward effect: consequently, before ascribing a depression to any medication it is critical to demonstrate that the depression did not begin before the medication was begun, and ideally, to demonstrate that the depression resolved after the medication was discontinued. Anticholinergic withdrawal may occur within days after abrupt discontinuation of highly anticholinergic medications, such as benztropine or certain tricyclic antidepressants, and is characterized by depressed mood, malaise, insomnia, and gastrointestinal symptoms such as nausea, vomiting, abdominal cramping, and diarrhea. Poststroke depression is not uncommon, and may be more likely when the anterior portion of the left frontal lobe is involved; although spontaneous remission within a year is the rule (Astrom et al. 1993, Robinson et al. 1987), depressive symptoms, in the meantime, may be quite severe (Lipsey et al. 1986). Both head trauma and whiplash injuries may be followed by depressive symptoms in close to half of all cases.

Depression may occur *secondary to diseases with distinctive features*, and keeping such features in mind whenever evaluating depressed patients will lead to a gratifying number of diagnostic "pick-ups." These features are noted in Table 52–3, and are for the most part self-explanatory; depression associated with epilepsy, however, may merit some further discussion. Ictal depressions are, in fact, simple partial seizures whose symptomatology is for the most part restricted to affective changes. The diagnosis of ictal depression is suggested by the paroxysmal onset of depression (literally over seconds); although such simple partial seizures may last only minutes, longer durations, up to months, have also been reported. Interictal depressions, rather than occurring secondary to paroxysmal electrical activity within the brain, occur as a result of long-lasting changes in neuronal activity, perhaps related to "kindling" within the limbic system, in patients with chronically recurrent seizures, either grand mal or, more especially, complex partial (Indaco et al. 1992, Perini et al. 1996). Such interictal depressions are of gradual onset and are chronic.

Depression *occurring as part of certain neurodegenerative or dementing disorders* is immediately suggested by the presence of other symptoms of these disorders, such as dementia or distinctive physical findings, for example, parkinsonism.

The *miscellaneous or rare causes* represent, for the most part, the "zebras" in the differential for depression, and should be considered when, despite a thorough investigation, the diagnosis of a particular case of depression remains unclear.

**DSM-IV-TR Criteria**

**Mood Disorder Due to . . . [Indicate the General Medical Condition]**

A. A prominent and persistent disturbance in mood predominates in the clinical picture, and is characterized by either (or both) of the following:

(1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.

(2) elevated, expansive, or irritable mood.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., Adjustment Disorder With Depressed Mood in response to the stress of having a general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* type:

**With Depressive Features:** if the predominant mood is depressed but the full criteria are not met for a Major Depressive Episode

**With Major Depressive-Like Episode:** if the full criteria are met (except Criterion D) for a Major Depressive Episode (see p. 327)

**With Manic Features:** if the predominant mood is elevated, euphoric, or irritable

**With Mixed Features:** if the symptoms of both mania and depression are present but neither predominates

**Coding note:** Include the name of the general medical condition on Axis I. e.g., 293.83 Mood Disorder Due to Hypothyroidism. With Depressive Features: also code the general medical condition on Axis III (see Appendix G for codes).

**Coding note:** If depressive symptoms occur as part of a preexisting dementia, indicate the depressive symptoms by coding the appropriate subtype of the dementia if one is available, e.g., 290.21 Dementia of the Alzheimer's Type. With Late Onset. With Depressed Mood.

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## Assessment and Differential Diagnosis

Although the foregoing list of possible causes of depression due to a general medical condition is long, utilizing it in the clinical evaluation of depressed patients need not be burdensome. Evidence for most of the *precipitants*, *diseases with distinctive features*, and *neurodegenerative or dementing disorders* will be uncovered in the course of a standard interview and examination and, after using the list a few times, the physician will immediately recognize their diagnostic relevance. The *miscellaneous or rare* "zebras," as with zebras in any other branch of medicine, are only considered when one is at the end of one's diagnostic rope, a situation often reached when patients fail to respond to treatment that, if the diagnosis were correct, should have led to relief, but did not.

## Epidemiology and Comorbidity

Depression is the most common of psychiatric symptoms and although, as noted earlier, the vast majority of cases of depression occur as part of one of the primary depressive disorders (most commonly major depressive disorder), depressions due to a general medical condition, in certain settings, should nevertheless, by virtue of their frequency, receive prime diagnostic consideration. Examples include treatment with corticosteroids as in multiple sclerosis or collagen–vascular diseases and cases of cerebral infarction involving the left frontal area.

## Course

Most medication-induced depressions begin to clear within days of discontinuation of the offending medication; depression as part of withdrawal from stimulants or anabolic steroids clears within days or weeks, and from anticholinergics, within days. Poststroke depression, as noted above, typically remits within a year. The course of depression secondary to head trauma or whiplash is generally prolonged, though quite variable. Most of the other conditions or disorders in the list are chronic, and depression occurring secondary to them likewise tends to be chronic: exceptions include depression in multiple sclerosis, which may have a relapsing and remitting course (Dalos et al. 1983), corresponding to the appearance and disappearance of appropriately situated plaques.

## Treatment

Treatment efforts should be directed at relieving, if possible, the underlying cause. When this is not possible, antidepressants should be considered. Controlled studies have demonstrated the effectiveness of both nortriptyline (Robinson et al. 2000) and citalopram (Anderson et al. 1994) for poststroke depression, and nortriptyline for depression seen in Parkinson's disease (Anderson et al. 1980). For other secondary depressions, citalopram is probably a good choice, given its benign side-effect profile and notable lack of drug–drug interactions; nortriptyline should be used with caution in patients with cardiac conduction defects (as it may prolong conduction time) and in those at risk for seizures as in head trauma (Wroblewski et al. 1990) as this agent may also lower the seizure threshold.

Clinical Vignette 2

Kraepelin (1913) reported the case of a 40-year-old man who "had been irritable for 2 years, … and he slept badly …. At home, he expressed ideas of sin—that he had made false entries in his books and would be locked up, and was bringing ruin on his friends as well as himself." The patient was admitted, and, during a hospital interview, Kraepelin described him as follows:

> You will see at once that the man, aged 40 years, whom I am bringing before you today is suffering

*(continues)*

Clinical Vignette 2 *continued*

from depression. This haggard-looking patient, very pale and ill-nourished, sits in a languid attitude, staring straight before him with a gloomy, listle\ss air, and pays us no particular attention. He hardly even turns his head when spoken to, but he answers in a low voice and very laconically…. He says … there is nothing left of himself but "this miserable skeleton."

Kraepelin felt the diagnosis would have been difficult "if the *physical examination* of the patient had not brought complete enlightenment. We see that not only is the right pupil more dilated than the left, but both are completely *inactive to light*, although the reaction to distance is maintained."

Kraepelin's diagnosis was neurosyphilis, a diagnosis made on the basis of finding Argyll Robertson pupils on the routine physical examination. Further history confirmed the diagnosis, revealing, as it did, the occurrence of secondary syphilitic rash some 12 years prior to admission.

## With Manic Features

### Definition

Mood disorder due to a general medical condition with manic features is characterized by a prominent and persistently elevated, expansive, or irritable mood, which, on the basis of the history, physical or laboratory examinations, can be attributed to an underlying general medical condition. Other manic symptoms, such as increased energy, decreased need for sleep, hyperactivity, distractibility, pressured speech and flight of ideas, may or may not be present.

### Etiology and Pathophysiology

The vast majority of cases of sustained, elevated, or irritable mood occur as part of four primary disorders, namely bipolar I disorder, bipolar II disorder, cyclothymic disorder, and schizoaffective disorder (bipolar type). Cases of elevated or irritable mood secondary to other causes (e.g., secondary to treatment with corticosteroids) are much less common. Table 52–4 lists secondary causes of elevated or irritable mood, with these causes divided into categories designed to facilitate the task of differential diagnosis.

In utilizing Table 52–4, the first step is to determine whether the mania could be *secondary to precipitants*. Substance-induced mood disorder related to drugs of abuse is covered in the relevant substance-related disorders chapters in this textbook. Of the precipitating factors listed in Table 52–4, medications are the most common offenders. Before, however, attributing the mania to one of these medications, it is critical to demonstrate that the mania occurred only after initiation of that medication; ideally, one would

**Table 52–4** Causes of Mania Due to a General Medical Condition

Secondary to Precipitants

Medications
- Corticosteroids or adrenocorticotrophic hormone (Minden et al. 1988)
- Anabolic steroids (Pope and Katz 1994)
- Levodopa (Celesia and Barr 1970)
- Pramipexole (Singh et al. 2005)
- Ropinirole (Singh et al. 2005)
- Zidovudine (Wright et al. 1989)
- Interferon alpha (Constant et al. 2005)
- Oral contraceptives (Sale and Kalucy 1981)
- Isoniazid (Chaturvedi and Upadhyaya 1988)
- Clarithromycin (Abouesh and Hobbs 1998)
- Buspirone (Price and Bielfeld 1989)
- Procyclidine (Coid and Strang 1982)
- Procarbazine (Mann and Hutchinson 1967)
- Propafenone (Jack 1985)
- Baclofen, upon discontinuation after long-term use (Kirubakaren et al. 1984)
- Reserpine upon discontinuation after long-term use (Kent and Wilber 1982)
- Methyldopa upon discontinuation after long-term use (Labbatte and Holzgang 1989)

Closed head injury (1993a)
Hemodialysis (Cooper 1967)
Encephalitis (Hohman 1921, Moskovich et al. 1995)
Aspartame (Walton 1986)
Metrizamide (Kwentus et al. 1984)

Secondary to Diseases with Distinctive Features

Hyperthyroidism (proptosis, tremor, tachycardia) (Trzepacz et al. 1988)
Cushing's syndrome (moon facies, hirsutism, acne, "buffalo hump," abdominal striae) (Haskett 1985)
Multiple sclerosis (various focal findings) (Rabins et al. 1986)
Cerebral infarction (sudden onset with associated localizing signs)
Sydenham's chorea (Reaser 1940)
Chorea gravidarum (Wilson and Preece 1932)
Hepatic encephalopathy (asterixis, delirium) (Murphy et al. 1948)
Uremia (asterixis, delirium) (El-Mallakh et al. 1987)
Epilepsy
- Ictal mania (Mulder and Daly 1952)
- Postictal mania (Kanemoto et al. 1996)

Occurring As Part of Certain Neurodegenerative or Dementing Diseases

Alzheimer's disease (Burns et al. 1990)
Neurosyphilis (Storm-Mathisen 1969)
Huntington's disease (Bolt 1970)
Creutzfeldt–Jakob disease (Lendvai et al. 1999)

Miscellaneous or Rare Causes

Cerebral tumors
Systemic lupus erythematosus (Johnson and Richardson 1968)
Vitamin B12 deficiency (Coggaus 1984)
Metachromatic leukodystrophy (Besson 1980)
Adrenoleukodystrophy (Weller et al. 1992)
Tuberous sclerosis (Khanna and Borde 1989)

also want to show that the mania spontaneously resolved subsequent to the medication's discontinuation. Of the medications listed, corticosteroids, such as prednisone, are likely to cause mania, with the likelihood increasing in direct proportion to dose: in one study (Wolkowitz et al. 1990), 80 mg of prednisone produced mania within five days in 75% of subjects. Levodopa is the next most likely cause, and in the case of levodopa the induced mania may be so pleasurable that some patients have ended up abusing the drug (Giovannoni et al. 2000). Anabolic steroid abuse may cause an irritable mania, and such a syndrome occurring in a "bulked up" patients should prompt a search for other clinical evidence of abuse, such as gynecomastia and testicular atrophy (Pope and Katz 1994). Closed head injury may be followed by mania either directly upon emergence from postcoma delirium (Bakchine et al. 1989, Bracken 1987), or after an interval of months (Clark and Davison 1987, Nizamie et al. 1988). Hemodialysis may cause mania, and in one case (Jack et al. 1983) mania occurred as the presenting sign of an eventual dialysis dementia. Encephalitis may cause mania, as, for example, in postinfectious encephalomyelitis (Moskovich et al. 1995, Paskavitz et al. 1995), with the correct diagnosis eventually being suggested by more typical signs such as delirium or seizures. Encephalitis lethargica (Von Economo's disease; European Sleeping Sickness) may also be at fault, with the diagnosis suggested by classic signs such as sleep reversal or oculomotor paralyses (Hohman 1921). Aspartame taken in very high dose caused mania and a seizure in one patient (Walton 1986), and metrizamide myelography prompted mania in another (Kwentus et al. 1984).

Mania occurring *secondary to disease with distinctive features* is immediately suggested by these features, as listed in Table 52–4. Some elaboration may be in order regarding mania secondary to cerebral infarction. This cause, of course, is suggested by the sudden onset of the clinical disturbance, with the mania being accompanied by various other more or less localizing signs; what is most remarkable here is the variety of structures that, if infarcted, may be followed by mania. Thus, mania has been noted with infarction of the midbrain (Blackwell 1991, Kulisevsky et al. 1995), thalamus (either on the right side [Cummings and Mendez 1984, Bogousslavsky et al. 1988, Kulisevsky et al. 1993] or bilaterally [McGilchrist et al. 1993, Gentilini et al. 1987]), anterior limb of the internal capsule and adjacent caudate on the right (Starkstein et al. 1990), and subcortical white matter or cortical infarction on the right in the frontoparietal (Jampala and Abrams 1983, Starkstein et al. 1988) or temporal (Starkstein et al. 1988) areas. Mania associated with epilepsy may also deserve additional comment. Ictal mania is characterized by its paroxysmal onset, over seconds, and the diagnosis of postictal mania is suggested when mania occurs shortly after a "flurry" of grand mal or complex partial seizures.

Mania *occurring as part of certain neurodegenerative or dementing diseases* is suggested, in general, by a concurrent dementia, and in most cases the mania plays only a minor role in the overall clinical pictures. Neurosyphilis, however, is an exception to this rule, for in patients with general paresis of the insane (dementia paralytica) mania may dominate the picture.

Of the *miscellaneous or rare causes* of mania, cerebral tumors are the most important to keep in mind, with mania being noted with tumors of the midbrain (Greenberg and Brown 1985), tumors compressing the hypothalamus (e.g., a craniopharyngioma [Malamud 1967]) or a pituitary adenoma (Alpers 1940), and tumors of the right thalamus (Stern and Dancey 1942), right cingulate gyrus (Angelini et al. 1980), or one or both frontal lobes (Gross and Herridge 1988).

## Assessment and Differential Diagnosis

In most cases of mania *secondary to precipitants*, the cause (e.g., treatment with high dose prednisone) is fairly straightforward; in cases *secondary to diseases with distinctive features or occurring as part of certain neurodegenerative or dementing diseases*, the cause is generally readily discernible if the clinician is alert to the telltale distinctive features (e.g., a Cushingoid habitus) and to the presence of dementia indicating one of the dementing disorders listed in Table 52–4. *The miscellaneous or rare causes* represent the "zebras" in the differential of secondary mania, and are generally only resorted to when other investigations prove unrewarding.

As a rule, it is very rare for mania to constitute the initial presentation of any of the disease or disorders listed in Table 52–4; thus, other evidence of their presence will become evident during the routine history and physical examination. Exceptions to the rule include neurosyphilis (Binder and Dickman 1980), vitamin $B_{12}$ deficiency (Goggans 1984), and Creutzfeldt–Jakob disease (Lendvai et al. 1999); however, in all these cases continued observation will eventually disclose the appearance of other evidence suggestive of the correct diagnosis.

It must always be kept in mind that certain medications (e.g., antidepressants) may precipitate mania in patients with bipolar disorder; in such cases, history will reveal earlier episodes of either depression, or mania, or both and such cases of mania should not be considered secondary.

## Epidemiology and Comorbidity

Compared to cases of primary mania (e.g., bipolar disorder), secondary mania is relatively rare. In certain settings, however, secondary mania may be so common as to merit a "top" position on the differential diagnosis; a prime example would be when prednisone is used in high doses, as in the treatment of multiple sclerosis or rheumatoid arthritis.

## Course

Most cases of medication-induced mania begin to clear in a matter of days; for other causes, the course of the mania generally reflects the course of the underlying disease.

## Treatment

Treatment, if possible, is directed at the underlying cause. In cases where such etiologic treatment is not possible, or not rapidly effective enough, pharmacologic measures are in order. Mood stabilizers, such as lithium or divalproex used in a fashion similar to that for the treatment of mania occurring in bipolar disorder, are commonly used: both lithium (Siegal 1978) and divalproex (Abbas and Styra 1994) are effective in the prophylaxis of mania occurring secondary to prednisone; case reports also support the use of lithium for mania secondary to zidovudine (O'Dowd and McKegney 1988) and divalproex for mania secondary to closed head injury. As between lithium and divalproex, in cases where there is a risk for seizures (e.g., head injury, encephalitis, stroke, or tumors), divalproex clearly is preferable.

In cases where emergent treatment is required, before lithium or divalproex could have a chance to become effective, oral or intramuscular haloperidol or olanzapine, or oral risperidone, may be utilized, again much as in the treatment of mania in bipolar disorder.

Clinical Vignette 3

Liebson (2000) reported the case of a 53-year-old man with a right thalamic hemorrhage, who presented with headache and left-sided hemiparesis and hemianesthesia. Four days later he displayed significant anosognosia for his hemiparesis; more remarkable, however, was the change in his mood. One week after the stroke his "mood was remarkably cheerful and optimistic … he was noted to praise extravagantly the hospital food, and the nurses found him "talkative." When he arrived on our ward 11 days after the stroke he was flirtatious with female staff and boasted of having fathered 64 children. His girlfriend was surprised when he kissed her in front of the staff because he had never publicly displayed affection before. He reported excellent energy and expansively invited all the staff to his home for Thanksgiving…The mania resolved gradually over a 10-week period after (the) stroke."

## Anxiety Disorder Due to a General Medical Condition with Panic Attacks or with Generalized Anxiety

### Definition

Pathologic anxiety secondary to a general medical condition may occur in the form of well-circumscribed and transient panic attacks or in a generalized, more chronic form. As the differential diagnoses for these two forms of anxiety are quite different, it is critical to clearly distinguish them.

Panic attacks have an acute or paroxysmal onset, and are characterized by typically intense anxiety or fear, which is accompanied by various "autonomic" signs and symptoms, such as tremor, diaphoresis, and palpitations. Symptoms rapidly crescendo over seconds or minutes and in most cases the attack will clear within anywhere from minutes up to a half-hour. Although attacks tend to be similar to one another in the same patient, there is substantial interpatient variability in the symptoms seen.

Generalized anxiety tends to be of subacute or gradual onset, and may last for long periods of time, anywhere from days to months, depending on the underlying cause. Here, some patients, rather than complaining of feeling anxious per se, may complain of being worried, tense, or ill at ease. Autonomic symptoms tend not to be as severe or prominent as those seen in panic attacks: shakiness, palpitations (or tachycardia), and diaphoresis are perhaps most common.

### Etiology and Pathophysiology

Panic attacks are most commonly seen in one of the primary anxiety disorders, namely, panic disorder, agoraphobia, specific phobia, social phobia, obsessive–compulsive disorder, or posttraumatic stress disorder, all of which are covered elsewhere in this book. The causes of secondary panic attacks are listed in Table 52–5. Substance-induced anxiety disorder related to drugs of abuse (e.g., cocaine, cannabis, LSD) is covered in the relevant substance-related disorders chapters in this textbook; clozapine has also been associated with panic attacks (Bressan et al. 2000). Partial seizures and paroxysmal atrial tachycardia are both characterized by their exquisitely paroxysmal onset, over a second or two; in addition, paroxysmal atrial tachycardia is distinguished by the prominence of the tachycardia and by an ability, in many cases, to terminate the attack with a Valsalva maneuver. Hypoglycemia is often suspected as a cause of anxiety, but before the diagnosis is accepted, one must demonstrate

**Table 52–5** Causes of Panic Attacks Due to a General Medical Condition

| |
|---|
| Partial seizures (Biraben et al. 2001) |
| Paroxysmal atrial tachycardia |
| Hypoglycemia |
| Angina or acute myocardial infarction |
| Pulmonary embolus |
| Acute asthmatic attack |
| Pheochromocytoma (Starkman et al. 1985) |
| Parkinson's disease (Vazquez et al. 1993) |

DSM-IV-TR Criteria

**Anxiety Disorder Due to … [Indicate the General Medical Condition]**

A. Prominent anxiety, Panic Attacks, or obsessions or compulsions predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., Adjustment Disorder With Anxiety in which the stressor is a serious general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* if:

**With Generalized Anxiety:** if excessive anxiety or worry about a number of events or activities predominates in the clinical presentation

**With Panic Attacks:** if Panic Attacks (see p. 395) predominate in the clinical presentation

**With Obsessive–Compulsive Symptoms:** if obsessions or compulsions predominate in the clinical presentation

**Coding note:** Include the name of the general medical condition on Axis I, e.g., 293.89 Anxiety Disorder Due to Pheochromocytoma. With Generalized Anxiety; also code the general medical condition on Axis III (see Appendix G for codes).

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the presence of "Whipple's triad": hypoglycemia (blood glucose ≤45 mg/dL), typical symptoms, and the relief of those symptoms with glucose. Angina or acute myocardial infarction can present with a panic attack, with the diagnosis being suggested by the clinical setting, for example, multiple cardiac risk factors. A pulmonary embolus, at the moment of its lodgment in a pulmonary artery, may also present with a panic attack, and again here the correct diagnosis is suggested by the clinical setting, for example, situations, such as prolonged immobilization, which favor deep venous thrombosis. Acute asthmatic attacks are suggested by wheezing, and pheochromocytoma by associated hypertension. Parkinson's disease patients treated with levodopa may experience panic attacks during "off" periods.

Generalized anxiety is most commonly seen in the primary psychiatric disorder, generalized anxiety disorder, and is discussed elsewhere in this book; it may also be an integral part of withdrawal from alcohol and sedative/hypnotics, also discussed elsewhere in this text. The secondary causes of generalized anxiety are listed in Table 52–6. Sympathomimetics and theophylline, as used in asthma and COPD, are frequent causes, as is caffeine and many of the antidepressants. Hyperthyroidism is suggested by heat intolerance and proptosis, and Cushing's syndrome by the typical Cushingoid habitus (i.e., moon facies, hirsutism, acne, "buffalo hump," and abdominal striae). Hypocalcemia may be suggested by a history of seizures or tetany. Both chronic obstructive pulmonary disease and congestive heart failure are suggested by marked dyspnea. Stroke and traumatic brain injury may be followed by chronic anxiety, but this is seen in only a minority of these patients.

**Table 52–6** Causes of Generalized Anxiety Due to a General Medical Condition

| |
|---|
| Sympathomimetics |
| Theophylline |
| Caffeine |
| Various antidepressants (tricyclics, SSRIs, etc.) |
| Hyperthyroidism (MacCrimmon et al. 1979) |
| Cushing's syndrome (Kelly 1996) |
| Hypocalcemia (Lawlor 1988) |
| Chronic obstructive pulmonary disease |
| Congestive heart failure |
| Poststroke (Castillo et al. 1993, 1995, Starkstein et al. 1990) |
| Posthead traumatic brain injury (Fann et al. 1995, 1993b) |

## Assessment and Differential Diagnosis

Should one be fortunate enough to observe a patient during the panic attack, it is critical, in addition to carefully noting the specific symptoms of the attack, to obtain vital signs, auscultate the heart and lungs, perform an EKG, and obtain blood for glucose and toxicology.

In evaluating a patient who complains of chronic anxiety, it is important, before deciding that this is, indeed, a case of pathologic generalized anxiety, to first determine whether or not the patient has a depression, whether it be primary or secondary: depression is often accompanied by anxiety, and such anxiety clears upon adequate treatment of the depression. Assuming that the patient, however, is not depressed, a workup should include the following: auscultation of the heart and lungs; CBC and liver enzymes (looking for the telltale "alcoholic" combination of an elevated mean corpuscular volume and elevated transaminases); thyroid profile; cortisol level and calcium level.

## Epidemiology and Comorbidity

Although epidemiologic studies are lacking, the clinical impression is that anxiety secondary to a general medical condition is common.

## Course

This is determined by the underlying cause.

## Treatment

Treatment is directed at the underlying cause, and this is sufficient for all cases of secondary panic attacks and most cases of secondary generalized anxiety; exceptions include poststroke and posttraumatic brain injury anxiety, and in these cases benzodiazepines have been used with success.

Clinical Vignette 4

Rush et al. (1977) describe a patient with simple partial seizures that manifested as panic attacks. The patient, at the age of 44 years, began to have "attacks of palpitation accompanied by dizziness, faintness and anxiety . . . (which) occurred during wakefulness and sleep, and, if asleep, the patient was awakened by them." At the age of 49 years, he was evaluated and an electroencephalogram, obtained in between attacks, "revealed mild slowing with intermittent, low-voltage, sharp waves over the right temporal region. Because of the paroxysmal nature of the attacks and the electroencephalographic abnormality, the patient was reevaluated utilizing telemetry." During telemetry, the patient had an attack: "he was pale and mildly diaphoretic and was tightly gripping his chair . . . no abnormal movements were detected . . . (he) remained fully alert and was not incontinent." Concurrent with the attack, ictal electroencephalographic activity was observed on the right. At craniotomy a glioma was removed from the right frontal lobe and the attacks subsequently did not recur.

## With Obsessive–Compulsive Symptoms

### Definition

Obsessions consist of unwanted, and generally anxiety-provoking, thoughts, images, or ideas that repeatedly come to mind despite patients' attempts to stop them. Allied to this are compulsions, which consist of anxious urges to do or undo things, urges that, if resisted, are followed by rapidly increasing anxiety, which can often only be relieved by giving into the compulsion to act. The acts themselves, which the patients feel compelled to perform, are often linked to an apprehension on the patients' part that they have done something that they ought not to have done or have left undone something that they ought to have done. Thus, one may feel compelled to repeatedly subject the hands to washing to be sure that all germs have been removed, or to repeatedly go back and check on the gas to be sure that it had been turned off.

**Table 52–7** Causes of Obsessions And Compulsions Due to a General Medical Condition

| |
|---|
| Postencephalitic (Mulder et al. 1951, Jelliffe 1929) |
| Postanoxic (Escalona et al. 1997, LaPlane et al. 1984, 1989) |
| Posttraumatic brain injury (Hillbom 1960, McKeon et al. 1984) |
| Clozapine (Baker et al. 1992) |
| Olanzapine (Mottard and de la Sablonniere 1999) |
| Risperidone (Alevizos et al. 2002) |
| Sydenham's chorea (Swedo et al. 1989, Swedo et al. 1993) |
| Huntington's disease (Anderson et al. 2001) |
| Simple partial seizures (Kroll and Drummond 1993, Mendez et al. 1996) |
| Infarction of the basal ganglia or right parietal lobe (Giroud et al. 1997, Simpson and Baldwin 1995) |
| Fahr's syndrome (Lopez-Villegas et al. 1996) |

### Etiology and Pathophysiology

In the vast majority of cases, obsessions and compulsions occur as part of certain primary psychiatric disorders, including obsessive–compulsive disorder, depression, schizophrenia, and Tourette's syndrome. Those rare instances where obsessions and compulsions are secondary to a general medical condition or medication are listed in Table 52–7.

In most cases, these causes of secondary obsessions or compulsions are readily discerned, as for example, a history of encephalitis, anoxia, traumatic brain injury, or treatment with certain second generation antipsychotics, such as clozapine, olanzapine, or risperidone. Sydenham's chorea is immediately suggested by the appearance of chorea; however, it must be borne in mind that obsessions and compulsions may constitute the presentation of Sydenham's chorea, with the appearance of chorea being delayed for days (Swedo et al. 1989). Ictal obsessions or compulsions, constituting the sole clinical manifestation of a simple partial seizure, may, in themselves, be indistinguishable from the obsessions and compulsions seen in obsessive–compulsive disorder, but are suggested by a history of other seizure types, for example, complex partial or grand mal seizures. Infarction of the basal ganglia or parietal lobe is suggested by the subacute onset of obsessions or compulsions accompanied by "neighborhood" symptoms such as abnormal movements or unilateral sensory changes. Fahr's syndrome, unlike the foregoing, may be an elusive diagnosis, only suggested perhaps when CT imaging incidentally reveals calcification of the basal ganglia.

### Assessment and Differential Diagnosis

Most causes of secondary obsessions and compulsions are picked up on the routine history and physical examination, with the possible exception of ictal cases, and here it is critical to make a close inquiry as to a history of other seizure types: ictal EEGs are not reliable here, as they are often normal in the case of simple partial seizures. In doubtful cases a "diagnosis by treatment response" to a trial of an anticonvulsant may be appropriate.

### Epidemiology and Comorbidity

As noted earlier, secondary obsessions and compulsions are relatively rare.

### Course

Although the course of obsessions and compulsions due to fixed lesions, such as those seen with head trauma or cerebral infarction, tends to be chronic, some spontaneous recovery may be anticipated over the following months to a year.

### Treatment

When treatment of the underlying cause is not possible, a trial of an SSRI, as used for obsessive–compulsive disorder, might be appropriate.

Clinical Vignette 5

Laplane et al. (1984) described the case of a "41-year-old healthy man (who) was stung on the left arm by a wasp. He immediately sustained a convulsive coma for 24 hours, then adopted intensive choreic movements … and impairment of gait. These extrapyramidal symptoms diminished over several months . . . .

"Two years after the encephalopathy, he began to show stereotyped activities. The most frequent consisted in mental counting, for example, up to twelve or a multiple of twelve, but sometimes it was a more complex calculation. Such mental activities sometimes were accompanied by gestures, such as a finger pacing of the counts. To switch on and off a light for 1 hour or more was another of his most common compulsions. When asked about this behavior he answered that he had to count . . . that he could not stop it . . . that it was stronger than him . . . .

"Neurological examination showed abnormal movements . . . .He had a permanent facial rictus with some facial or mandibular movements somewhat resembling tics. With his finger movements it was difficult to distinguish between involuntary or 'voluntary' activity associated with mental counting. Walking was a mixture of parkinsonism and choreic disturbances.

"Standard and sleep EEG were normal. CT scans were performed in the orbito-meatal plane . . . .The main lesions consisted of low density areas bilaterally in the internal part of the lenticular nucleus."

## Mental Conditions Due to a General Medical Disorder Not Elsewhere Classified

## Catatonic Disorder Due to a General Medical Condition

### Definition

Catatonia exists in two subtypes, namely, stuporous catatonia (also known as the akinetic or "retarded" subtype) and excited catatonia, and each will be described in turn.

Stuporous catatonia is characterized by varying combinations of mutism, immobility, and waxy flexibility; associated features include posturing, negativism, automatic obedience, and "echo" phenomena. Mutism ranges from complete to partial: some patients may mumble or perhaps utter brief, often incomprehensible, phrases. Immobility, likewise, ranges in severity: some patients may lie in bed for long periods, neither moving, blinking, or even swallowing; others may make brief movements, perhaps to pull at a piece of clothing or to assume a different posture. Waxy flexibility,

also known by its Latin name, *cerea flexibilitas*, is characterized by a more or less severe "lead pipe" rigidity combined with a remarkable tendency for the limbs to stay in whatever position they are placed, regardless of whether the patient is asked to maintain that position or not. Posturing is said to occur when patients spontaneously assume more or less bizarre postures, which are then maintained: one patient crouched low with his arm wrapped over his head, another stood with one arm raised high, and the other stuffed inside his belt. Negativism entails a mulish, intractable, and automatic resistance to whatever is expected, and may be either "passive" or "active." Passively negativistic patients simply fail to do what is asked or expected: if clothes are laid out they will not dress; if asked to eat or take pills, their lips remain frozen shut. Active negativism manifests in doing the opposite of what is expected: if asked to come into the office, the patient may back into the hallway or if asked to open the eyes wide to allow for easier examination, they may cramp the eyes closed. Automatic obedience, as may be suspected, represents the opposite of negativism, with affected patients doing exactly what they are told, even should it place them in danger. Echo phenomena represent a kind of automatic obedience: in echolalia patients simply repeat what they hear and in echopraxia they mimic the gestures and activity of the examiner. It should be noted that in negativism, automatic obedience, and echo phenomena there is nothing natural or fluid about the patient's behavior. To the contrary, movements are often awkward, wooden, and tinged with the bizarre.

**DSM-IV-TR Criteria**

**Catatonic Disorder Due to…[Indicate the General Medical Condition]**

A. The presence of catatonia as manifested by motoric immobility, excessive motor activity (that is apparently purposeless and not influenced by external stimuli), extreme negativism or mutism, peculiarities of voluntary movement, or echolalia or echopraxia.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder (e.g., a Manic Episode).
D. The disturbance does not occur exclusively during the course of a delirium.

**Coding note:** Include the name of the general medical condition on Axis I. e.g., 293.89 Catatonic Disorder Due to Hepatic Encephalopathy: also code the general medical condition on Axis III (see Appendix G for codes).

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Excited catatonia manifests with varying degrees of bizarre, frenzied, and purposeless behavior. Such patients typically keep to themselves: one marched in place, all the while chanting and gesticulating; another tore at his hair and clothing, broke plates in a corner then crawled under the bed where he muttered and thrashed his arms.

## Etiology and Pathophysiology

Stuporous catatonia, in the majority of cases, occurs as part of such primary psychiatric disorders as schizophrenia, a depressive episode of either major depression or bipolar disorder, or a manic episode of bipolar disorder, and these are discussed elsewhere in this text. The causes of catatonia due to a general medical condition or medications are listed in Table 52–8.

Stuporous catatonia occurring in association with epilepsy is often suggested by a history of grand mal or complex partial seizures. Ictal catatonia is further suggested by its exquisitely paroxysmal onset, and postictal catatonia by an immediately preceding "flurry" of grand mal or complex partial seizures. Psychosis of forced normalization is an interictal condition distinguished by the appearance of symptoms subsequent to effective control of seizures. The chronic interictal psychosis is also, as suggested by the name, an interictal condition, which, however, appears not after seizures are controlled but rather in the setting of ongoing, chronic uncontrolled epilepsy. Of medications capable of causing catatonia, antipsychotics are by far the most common. Viral encephalitis is suggested by concurrent fever and headache: herpes simplex

**Table 52–8 Causes of Catatonia Due to a General Medical Condition**

| Stuporous Catatonia |
|---|
| Associated with epilepsy |
| Ictal catatonia (Engel et al. 1978, Gomez et al. 1982, Lim et al. 1986, Shah and Kaplan 1980) |
| Postictal catatonia (Logsdail 1988) |
| Psychosis of forced normalization (Pakainis et al. 1987) |
| Chronic interictal psychosis (Kristensen and Sindrup 1979, 1963a, 1963b) |
| Medication |
| Antipsychotics (Gelenberg and Mandel 1977) |
| Disulfiram (Reisberg 1978, Weddington et al. 1980) |
| Benzodiazepine withdrawal (Rosebush and Mazurek 1996) |
| Viral encephalitis (Abrams and Taylor 1976, Kim and Perlstein 1970, Misra and Hay 1971) |
| Herpes simplex encephalitis (Raskin and Frank 1974) |
| Encephalitis lethargica (Kirby and Davis 1921) |
| Focal lesions, especially of the frontal lobes (Belfer and d'Autremont 1971, Thompson 1970) |
| Miscellaneous conditions |
| Hepatic encephalopathy (Jaffe 1967) |
| Limbic encephalitis (Tandon et al. 1988) |
| Systemic lupus erythematosus (Lanham et al. 1985, Mac and Pardo 1983) |
| Lyme disease, in stage III (Pfister et al. 1993) |
| Subacute sclerosing panencephalitis, in stage I (Koehler and Jakumeit 1976) |
| Tay–Sachs disease (Rosebush et al. 1995) |
| Thrombotic thrombocytopenic purpura (Read 1983) Excited Catatonia |
| **Excited Catatonia** |
| Viral encephalitis (Penn et al. 1972) |

encephalitis should always be considered in such cases, given its treatability; further it must be kept in mind that although encephalitis lethargica no longer occurs in epidemics, sporadic cases still do occur. Focal lesions capable of causing catatonia are typically found in the medial or inferior portions of the frontal lobes. The miscellaneous conditions listed are all quite rare causes of catatonia.

Excited catatonia, in the vast majority of cases, is caused by either schizophrenia or bipolar disorder (during a manic episode): only rarely is it seen due to a general medical condition, as for example, a viral encephalitis.

### Assessment and Differential Diagnosis

Stuporous catatonia must be distinguished from akinetic mutism and from stupor of other causes. Akinetic mutes (Cairns et al. 1941) appear quite similar to immobile and mute catatonics; akinetic mutes, however, lack such signs as waxy flexibility, posturing, and negativism, all of which are typically seen in catatonia. Stupor of other causes is readily distinguished from catatonic stupor by the salient fact that catatonics remain alert, in stark contrast with the somnolence or decreased level of consciousness seen in all other forms of stupor.

Excited catatonia must be distinguished from mania. Mania is typified by hyperactivity, which at times may be quite frenzied: the difference with catatonia is that patients with mania want to be involved, whereas those with catatonia keep to themselves; as Kraepelin (Bear et al. 1982) noted, in catatonia "the excitement, even when extremely violent, frequently takes place within the *smallest space*. The patients have not as a rule any tendency to influence their surroundings, but their restlessness exhausts itself in wholly aimless activity."

### Epidemiology and Comorbidity

Stuporous catatonia due to a general medical condition overall is, in general, a rare condition.

### Course

This is determined by the course of the underlying cause.

### Treatment

In addition to treating, if possible, the underlying cause, catatonia may be symptomatically relieved by lorazepam given parenterally in a dose of 2 mg; in severe cases wherein lorazepam is not sufficiently effective and the patient is at immediate risk, consideration should be given to emergency ECT, which is typically dramatically effective, generally bringing relief after but a few treatments.

Clinical Vignette 6

Lim et al. (1986) described a case of ictal catatonia occurring in the midst of a complex partial seizure. The patient was a 67-year-old man who was brought to the hospital after being confused for two weeks. When examined, he "sat quietly in a chair, with no spontaneous speech or movement. He responded to questions with few words and manifested frequent echolalia and perseveration …. On the third hospital day the patient suddenly became catatonic. His mouth and eyes were opened widely with dilated reactive pupils. He held his arms and legs rigidly in the air and would maintain his extremities in any bizarre posture indefinitely." An EEG demonstrated spiking in the left fronto-central area; the patient was given intravenous phenytoin and recovered completely.

## Personality Change Due to a General Medical Condition

DSM-IV-TR Criteria

**Personality Change Due to … [Indicate the General Medical Condition]**

A. A persistent personality disturbance that represents a change from the individual's previous characteristic personality pattern. (In children, the disturbance involves a marked deviation from normal development or a significant change in the child's usual behavior patterns lasting at least 1 year).

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (including other Mental Disorders Due to a General Medical Condition).

D. The disturbance does not occur exclusively during the course of a delirium and does not meet criteria for a dementia.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* type:

**Labile Type:** if the predominant feature is affective lability

**Disinhibited Type:** if the predominant feature is poor impulse control as evidenced by sexual indiscretions, etc.

**Aggressive Type:** if the predominant feature is aggressive behavior

**Apathetic Type:** if the predominant feature is marked apathy and indifference

**Paranoid Type:** if the predominant feature is suspiciousness or paranoid ideation

**Other Type:** if the predominant feature is not one of the above, e.g., personality change associated with a seizure disorder

**Combined Type:** if more than one feature predominates in the clinical picture

**Unspecified Type**

**Coding note:** Include the name of the general medical condition on Axis I, e.g., 310.1 Personality Change Due to Temporal Lobe Epilepsy: also code the general medical condition on Axis III (see Appendix G for codes).

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## Definition

The personality of an adult represents a coalescence of various personality traits present in childhood and adolescence, and is generally quite enduring and resistant to change. Thus, the appearance of a significant change in an adult's personality is an ominous clinical sign and indicates the presence of intracranial pathology. Patients themselves may not be aware of the change; however to others, who have known the patient over time, the change is often quite obvious: such observers often note that the patient is "not himself" anymore.

In most cases, the change is nonspecific in nature: there may be either a gross exaggeration of hitherto minor aspects of the patient's personality or the appearance of a personality trait quite uncharacteristic for the patient. Traits commonly seen in a personality change, as noted in DSM-IV-TR, include lability, disinhibition, aggressiveness, apathy, or suspiciousness.

In addition to these nonspecific changes, there are two specific syndromes, which, though not listed in DSM-IV-TR, are well described in the literature, namely, the *frontal lobe syndrome* and the *interictal personality syndrome* (also known as the "Geschwind syndrome").

The *frontal lobe syndrome* is characterized by a variable mixture of disinhibition, affective changes, perseveration, and apathy. Disinhibition manifests with an overall coarsening of behavior. Attention to manners and social nuances is lost: patients may eat with gluttony, make coarse and crude jokes, and may engage in unwelcome and inappropriate sexual behavior, perhaps by propositioning much younger individuals or masturbating in public. Affective changes tend toward a silly, noninfectious euphoria; depression, however, may also be seen. Perseveration presents with a tendency to persist in whatever task is currently at hand, and patients may repeatedly button and unbutton clothing, open and close a drawer, or ask the same question again and again. Apathy is characterized by a lack of motivation. Though patients may experience some urges or consider some actions, their plans, if they occur at all, often come, as it were, stillborn, and, lacking in motivation, apathetic patients may either never come to the point of action, or, if they do get started, soon find themselves indifferent, after which they give up.

The *interictal personality syndrome*, a controversial entity (Bear et al. 1982, Rodin and Schmaltz 1984) is said to occur as a complication of longstanding uncontrolled epilepsy, with repeated grand mal or complex partial seizures. The cardinal characteristic of this syndrome is what is known as "viscosity," (Waxman and Geschwind 1975) or, somewhat more colloquially, "stickiness." Here, patients seem unable to let go or diverge from the current emotion or train of thought: existing affects persist long after the situation that occasioned them, and a given train of thought tends to extend itself indefinitely into a long-winded and verbose circumstantiality or tangentiality. This viscosity of thought may also appear in written expression as patients display "hypergraphia" producing long and rambling letters or diaries (Hermann et al. 1988). The inability to "let go" may even extend to such simple acts as shaking hands, such that others may literally have to extract their hand to end the handshake. The content of the patient's viscous speech and writing generally also changes, and tends toward mystical or abstruse philosophical speculations. Finally, there is also a tendency to hyposexuality, with an overall decrease in libido (Blumer 1970, Blumer and Walker 1967).

## Etiology and Pathophysiology

A personality change is not uncommonly seen as the prodrome to schizophrenia; however, in such cases the eventual appearance of the typical psychosis will indicate the correct diagnosis.

Personality change of the nonspecific or of the frontal lobe type, as noted in Table 52–9, may occur *secondary to precipitants* (e.g., traumatic brain injury), *secondary to cerebral tumors* (especially those of the frontal or temporal lobes), or *as part of certain neurodegenerative or dementing*

**Table 52–9 Causes of Personality Change of the Nonspecific or Frontal Lobe Type**

| |
|---|
| **Secondary to Precipitants** |
| Traumatic brain injury (Brooks et al. 1986, Max et al. 2001, Oder et al. 1992, Roberts 1976, Thomsen 1984) |
| Head trauma with subdural hematoma (Cameron 1978) |
| Postviral encephalitis (Friedman and Allen 1969, McGrath et al. 1997) |
| Gunshot wounds (Lebensohn 1947, Lishman 1973) |
| Cerebral infarction |
| **Secondary to Cerebral Tumors** |
| Frontal lobe* (Avery 1971, Frazier 1936, Hunter et al. 1968, Williamson 1896) |
| Corpus callosum* (in its anterior part) (Alpers and Grant 1931, Beling and Martland 1919, Moersch 1925) |
| Temporal lobe (Keschner et al. 1936, Strobos 1953) |
| **Occurring As Part of Certain Neurodegenerative or Dementing Disorders** |
| Pick's disease* (Litvan et al. 1997, Mendez et al. 1993) |
| Fronto-temporal dementia* (Brun et al. 1994, Heutink et al. 1997, Neary et al. 1993) |
| Alzheimer's disease* (Mega et al. 1996, Petry et al. 1988) |
| Amyotrophic lateral sclerosis* (Cavalleri and De Renzi 1994, Massman et al. 1996, Neary et al. 1990, Peavy et al. 1992) |
| Progressive supranuclear palsy* (Venry et al. 1996) |
| Cortico-basal ganglionic degeneration* (Bergeron et al. 1996) |
| Multiple system atrophy* (Critchley and Greenfield 1948, Robbins et al. 1992) |
| Huntington's disease (Pflanz et al. 1991) |
| Wilson's disease (Bridgman and Smyth 1994, Dening and Berrios 1989, Starosta-Rubinstein et al. 1987, Walshe and Yealland 1992) |
| Lacunar syndrome* (Ishii et al. 1986) |
| Normal pressure hydrocephalus (Rice and Gendelman 1973) |
| AIDS (Navia et al. 1986) |
| Neurosyphilis (Storm-Mathisen 1969) |
| Creutzfeldt–Jakob disease (Brown et al. 1994, Roos et al. 1973) |
| **Miscellaneous Causes** |
| Granulomatous angiitis (Koo and Massey 1988) |
| Vitamin B12 deficiency (Lindenbaum et al. 1988) |
| Limbic encephalitis (Alamowitch et al. 1997) |
| Metachromatic leukodystrophy (Hageman et al. 1995) |
| Adrenoleukodystrophy (Schaumburg et al. 1975) |
| Mercury intoxication (O'Carroll et al. 1995) |
| Manganism (Abd El Naby and Hassanein 1965) |

*Particularly likely to cause a frontal lobe syndrome.

*disorders*. Finally, there is a group of *miscellaneous causes*. In Table 52–9, those disorders or diseases that are particularly prone to cause a personality change of the frontal lobe type are indicated by an asterisk. The interictal personality syndrome occurs only in the setting of chronic repeated grand mal or complex partial seizures, and may represent microanatomic changes in the limbic system, which have been "kindled" by the repeated seizures (Adamec and Stark-Adamec 1983, Bear 1979).

In the case of personality change occurring *secondary to precipitants*, the etiology is fairly obvious; an exception might be cerebral infarction, but here the acute onset and the presence of "neighborhood" symptoms are suggestive. In addition to infarction of the frontal lobe, personality change has also been noted with infarction of the caudate nucleus (Mendez et al. 1989, Petty et al. 1996) and of the thalamus (Sandson et al. 1991).

Personality change occurring s*econdary to cerebral tumors* may not be accompanied by any distinctive features, and indeed a personality change may be the only clinical evidence of a tumor for a prolonged period of time.

Personality change *occurring as part of certain neurodegenerative or dementing disorders* deserves special mention, for in many instances the underlying disorder may present with a personality change; this is particularly the case with Pick's disease, fronto-temporal dementia, and Alzheimer's disease. The inclusion of amyotrophic lateral sclerosis here may be surprising to some, but it is very clear that, albeit in a small minority, cerebral symptoms may not only dominate the early course of ALS, but may even constitute the presentation of the disease. In the case of the other neurodegenerative disorders (i.e., progressive supranuclear palsy, cortico-basal ganglionic degeneration, multiple system atrophy, Huntington's disease, and Wilson's disease) a personality change, if present, is typically accompanied by abnormal involuntary movements of one sort or other, such as parkinsonism, ataxia, or chorea. The lacunar syndrome, occurring secondary to multiple lacunar infarctions affecting the thalamus, internal capsule, or basal ganglia, deserves special mention as it very commonly causes a personality change of the frontal lobe type by interrupting the connections between the thalamus or basal ganglia and the frontal lobe. Normal pressure hydrocephalus is an important diagnosis to keep in mind, as the condition is treatable; other suggestive symptoms include a broad-based shuffling gait and urinary urgency or incontinence. AIDS should be suspected whenever a personality change is accompanied by clinical phenomena suggestive of immunodeficiency, such as thrush. Neurosyphilis may present with a personality change characterized by slovenliness and disinhibition. Creutzfeldt–Jakob disease may also present with a personality change, and this appears particularly likely with the "new variant" type: the eventual appearance of myoclonus suggests the correct diagnosis.

The *miscellaneous causes* represent the diagnostic "zebras" in the differential for personality change. Of them two deserve comment, given their treatability: granulomatous angiitis is suggested by prominent headache, and vitamin $B_{12}$ deficiency by the presence of macrocytosis or a sensory polyneuropathy.

## Assessment and Differential Diagnosis

Personality change must be clearly distinguished from a personality disorder. The personality disorders (e.g., antisocial personality disorder, borderline personality disorder), all discussed elsewhere in this book, do not represent a change in the patient's personality but rather have been present in a lifelong fashion. In gathering a history on a patient with a personality change, one finds a more or less distinct time when the "change" occurred; by contrast, in evaluating a patient with a personality disorder, one can trace the personality traits in question in a more or less seamless fashion back into adolescence, or earlier.

The frontal lobe syndrome, at times, may present further diagnostic questions, raising the possibility of either mania, when euphoria is prominent, or depression, when apathy is at the forefront. Mania is distinguished by the quality of the euphoria, which tends to be full and infectious in contrast with the silly, shallow, and noninfectious euphoria of the frontal lobe syndrome. Depression may be distinguished by the quality of the patients' experience: depressed patients definitely feel something, whether it be a depressed mood or simply a weighty sense of oppression. By contrast, the patient with apathy generally feels nothing: the "mental horizon" is clear and undisturbed by any dysphoria or unpleasantness.

MRI scanning is diagnostic in most cases: where this is uninformative, further testing is dictated by one's clinical suspicions (e.g., HIV testing).

The interictal personality syndrome must be distinguished from a personality change occurring secondary to a slowly growing tumor of the temporal lobe. In some cases, very small tumors, which may escape detection by routine MRI scanning, may cause epilepsy, and then, with continued growth, also cause a personality change. Thus, in the case of a patient with epilepsy who develops a personality change, the diagnosis of the interictal personality syndrome should not be made until a tumor has been ruled out by repeat MRI scanning.

## Epidemiology and Comorbidity

Personality change is common, and is seen with especial frequency after traumatic brain injury and as a prodrome to the dementia occurring with such neurodegenerative disorders as Pick's disease, fronto-temporal dementia, and Alzheimer's disease.

## Course

This is determined by the underlying cause; in the case of the interictal personality syndrome it appears that symptoms persist even if seizure control is obtained.

## Treatment

Treatment, if possible, is directed at the underlying cause. Mood stabilizers (e.g., carbamazepine) may be helpful for lability and disinhibition. Antipsychotics (e.g., a second generation agent such as quetiapine) may be helpful with suspiciousness and may also attenuate disinhibition. Antidepressants (e.g., an SSRI) may relieve depressive symptoms. Regardless of which agent is chosen, it is prudent, given the general medical condition of many of these patients, to "start low and go slow." In many cases, some degree of supervision will be required.

Clinical Vignette 7

Moersch (1925) described a 54-year-old man in whom, three months earlier, "a gradual mental change had been observed. The patient lost his ambition and interest in work . . . he became careless . . . and seemed little concerned about his shortcomings. For two weeks before his examination he had been content to sit aimlessly at home, or to play with his children. He voided at any time and even defecated in his clothes . . . .During general examination, the patient was indifferent and aimless, would sit and look at a newspaper, which might be upside down. He was oriented in all spheres, and his attention might be held for a few moments when aroused. He would follow his son about in a fairly good-natured manner, but always object to being examined, saying that he was not sick. He showed considerable perseveration, repeating movements at times for long periods. For example, one evening he sat before a wash bowl for over a half-hour, turning the faucets on and off."

This patient's frontal lobe syndrome, manifest with apathy, disinhibition, and perseveration, constituted the presentation of a tumor of the anterior portion of the corpus callosum, to which the patient eventually succumbed.

## Mental Disorder Not Otherwise Specified Due to a General Medical Condition

This is a residual category in DSM-IV-TR for those clinical situations in which the mental disorder occurring secondary to a general medical condition does not fall into one of the specific categories described earlier. Of these various disorders, two are worthy of detailed description, namely, pseudobulbar palsy and the Klüver–Bucy syndrome. Both disorders are commonly seen in dementia clinics, and their occurrence often prompts a request for psychiatric consultation.

## Pseudobulbar Palsy

### Definition

When fully developed, this syndrome is characterized by emotional incontinence (also known as "pathological laughing and crying"), dysarthria, dysphagia, a brisk jaw-jerk and gag reflex, and difficulty in protruding the tongue (Langsworthy and Hesser 1940).

The most remarkable aspect of the syndrome is the emotional incontinence. Here, patients experience uncontrollable paroxysms of laughter or crying, often in response to minor stimuli, such as the approach of the physician to the bedside (Lieberman and Benson 1977). Importantly, despite the strength of these outbursts, patients do not experience any corresponding sense of mirth or sadness; some may attempt to stop the emotional display, only to become acutely distressed at their inability to do so: one patient, who experienced "gales of laughter" whenever he attempted to speak, "felt foolish and ashamed, and had tears in his eyes because he could not 'control the laughter'" (Davison and Kelman 1939). Some may go out of their way to avoid having these paroxysms: in one case, described by Wilson (1924), the patient "used to walk about the hospital with his eyes glued to the ground (because) if he so much as raised them to meet anyone else's gaze he was immediately overcome by compulsory laughter, which sometimes lasted for 4 or 5 minutes."

### Etiology and Pathophysiology

Pseudobulbar palsy results from bilateral interruption of corticobulbar fibers (Besson et al. 1991), with this interruption occurring anywhere from the cortex (Davison and Kelman 1939, Wilson 1924) through the centrum semiovale (Ishii et al. 1986) to the internal capsule (Colman 1894) and down to the midbrain and pons (Asfora et al. 1989). Thus "released" from upper motor neuron control, the bulbar nuclei act reflexively, creating, in a sense, a kind of "spasticity" of emotional display. The various disorders capable of causing such a bilateral interruption are listed in Table 52–10.

*Vascular disorders* are by far the most common cause of bilateral interruption of the corticobulbar tracts, as may be seen with infarctions of the cortex or with lacunar infarctions in the corona radiata or internal capsule. Although in some cases it appears that the syndrome occurs after only one stroke, further investigation typically reveals evidence of a preexisting lesion on the contralateral side, a lesion that had been clinically "silent" (Besson et al. 1991). Other vascular causes include Binswanger's disease, characterized by diffuse white matter damage in the centrum semiovale, and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), characterized by both subcortical infarctions and a widespread leukoencephalopathy.

Of the *neurodegenerative disorders* associated with pseudobulbar palsy, the most prominent is amyotrophic lateral sclerosis, wherein approximately one half of patients are eventually so affected (Gallagher 1989).

Of the *miscellaneous causes*, cerebral tumors, which bilaterally compress or invade the brainstem (Achari and Colover 1976, Cantu and Drew 1966, Shafqat et al. 1998), are particularly important.

### Assessment and Differential Diagnosis

The diagnosis should be suspected whenever patients present with exaggerated and uncontrollable emotional displays. Lability of affect, as may be seen in mania, is ruled out by the fact that the labile patient, while displaying the affect, also experiences a congruent emotional feeling: by contrast in emotional incontinence the patient often feels nothing, except perhaps consternation at the unmotivated and uncontrollable

**Table 52–10 Causes of Pseudobulbar Palsy**

| |
|---|
| Vascular Disorders |
| Large vessel cortical infarctions (Wilson 1924) |
| Subcortical lacunar infarctions (Ishii et al. 1986) |
| Binswanger's disease (Caplan and Schoene 1978) |
| CADASIL (Bergmann et al. 1996) |
| Certain Neurodegenerative Disorders |
| Amyotrophic lateral sclerosis (Ironside 1956, Ziegler 1930) |
| Progressive supranuclear palsy (Menza et al. 1995) |
| Alzheimer's disease (Starkstein et al. 1995) |
| Miscellaneous Causes |
| Cerebral tumors |
| Traumatic brain injury |
| Multiple sclerosis (Feinstein et al. 1997) |
| Behcet's syndrome (Motomura et al. 1980) |

emotional display. Inappropriate affect, as may be seen in schizophrenia, is similar to emotional incontinence in that patients with schizophrenia may not experience any corresponding feeling: in schizophrenia, however, one sees other accompanying symptoms, such as mannerisms, hallucinations, and delusions, symptoms that are absent in pseudobulbar palsy. "Emotionalism," as may be seen after strokes, may suggest the diagnosis, especially given the clinical setting; however here, as with lability, patients also experience a concurrent feeling that is congruent with the emotional display.

Findings on the neurologic examination are also helpful. Bilateral interruption of corticobulbar tracts, as noted above, typically leads to cranial nerve dysfunction with dysarthria, dysphagia, and brisk jaw-jerk and gag reflexes. Given the proximity of the corticospinal tracts, one often also finds evidence of long-tract damage, such as hemiplegia or Babinski signs.

MRI scanning is generally diagnostic in cases secondary to vascular lesions, tumors, and multiple sclerosis. Amyotrophic lateral sclerosis is suggested by the gradual progression of upper and lower motor neuron signs and symptoms; progressive supranuclear palsy by the presence of parkinsonism and supranuclear gaze palsy, and Alzheimer's disease by the long history of a gradually progressive dementia.

### Epidemiology and Comorbidity

Pseudobulbar palsy is not uncommon: as noted above, it is found in almost half of patients with amyotrophic lateral sclerosis (Gallagher 1989). It may also be seen in a much smaller, but still clinically significant, proportion of patients with vascular lesions (Besson et al. 1991), Alzheimer's disease (Starkstein et al. 1995), and multiple sclerosis (Feinstein et al. 1997).

### Course

The overall course of the syndrome reflects the course of the etiologic disorder. The appearance of dysphagia, however, is an ominous sign, carrying, as it does, the risk of aspiration.

### Treatment

In addition to treating, if possible, the underlying cause, various medications may be used to reduce the severity of the emotional incontinence. In cases due to stroke, both tricyclic and SSRI antidepressants are effective: of the tricyclics, one may use amitriptyline (in doses of 50–75 mg) (Schiffer et al. 1985) or nortriptyline (in doses of 50–100 mg) (Robinson et al. 1993), and of the SSRIs, citalopram (in a dose of 20 mg) (Andersen et al. 1993). In cases due to amyotrophic lateral sclerosis (Brooks et al. 2004) or multiple sclerosis (Panitch et al. 2006), a combination of dextromethorphan (30 mg) and quinidine (30 mg), given twice daily, is also effective: in this preparation quinidine, of itself, is inactive and merely serves to inhibit the metabolism of dextromethorphan. Of all these agents, citalopram is the easiest to use; remarkably, full relief is often obtained in a matter of days.

Clinical Vignette 8

SA Kinnier Wilson (1924) provided a classic example of emotional incontinence following bilateral cerebral infarctions:

"A woman of age 57 years had suffered from left hemiplegia for one year, when a second stroke occurred involving the right side. Ever since the latter, the daughter remarked that her mother had become, as she put it, 'hysterical," laughing and crying at nothing.

"On examination the patient was seen to have a distinctly vacant, apathetic facial expression at rest. She was able to move the facial muscles voluntarily on both sides, though there was slight weakness of the left corner of the mouth. On the slightest stimulus, even when the observer simply came to her bedside, she at once assumed a lugubrious expression, her mouth opened widely, and a long, almost noiseless bout of weeping ensued, lasting for many seconds, even minutes, at a time.... During the spasmodic crying, both sides of the face moved equally, and the eyes suffused with tears. Laughing attacks were extremely rare in comparison."

## Klüver–Bucy Syndrome

### Definition

In 1939, Klüver and Bucy (1939) noted some striking behavioral changes in monkeys that had been subjected to bilateral temporal lobectomy, and in so doing described the syndrome that now bears their names. Specifically, they described five characteristics, which they named "hypermetamorphosis," "psychic blindness," "oral tendencies," "emotional changes," and "changes in sexual behavior." Given that this nomenclature is somewhat idiosyncratic to these authors, some concrete examples, taken from their article, may enable the reader to gain a sense of the syndrome as it appeared in the monkeys.

The hypermetamorphosis of these animals was manifested by "an excessive tendency to take notice of and to attend and react to every visual stimulus...(and) to contact every object as soon as possible." Furthermore, this interest in things was indiscriminate: being psychically "blind," the animals would approach objects "no matter whether they are very large or very small, dead or alive, edible or inedible, moving or stationary...(they) seem to be just as eager to examine the tongue of a hissing snake, the mouth of a cat, faeces, a wire cage or a wagon as a piece of bread." Once in contact with an object, the "oral tendencies" often became apparent in that the monkeys typically put "the object into the mouth, biting gently, chewing, licking, touching with the lips and smelling (it)." Should another, perhaps dangerous, animal have been approached, the "emotional changes" immediately became apparent, in that the monkeys failed to show any "emotional reactions...generally associated with anger and fear"; indeed, "after being attacked and bitten by another animal (they) may approach this animal again and again in an attempt to examine it." Finally, and in addition to all the foregoing changes, there were "changes in sexual behavior" manifested by an overall "increase in sexual activity" that was "blind," and could manifest with increased masturbation or an indiscriminant approach to others, regardless of their sex.

Over time, changes in the original nomenclature used to describe the syndrome have been made so as to facilitate clinical practice. Thus, although the term hypermetamorphosis has survived, "psychic blindness" has fallen into disfavor and most authors speak of a kind of "agnosia." The

"oral tendencies" are now referred to as hyperorality, and the "emotional changes" as "emotional placidity." Finally, the varied "changes in sexual behavior" are now simply referred to as hypersexuality. Thus, the full syndrome is characterized by hypermetamorphosis, agnosia (albeit of a peculiar kind), hyperorality, emotional placidity, and hypersexuality. Some examples of the syndrome in humans follow.

The first example demonstrates hypersexuality, hyperorality, agnosia, and emotional placidity. The patient was a 31-year-old woman, who, after recovering from a herpes simplex encephalitis, "made inappropriate sexual advances to female attendants, both manually and orally. At home, she was constantly chewing and swallowing, and all objects within reach were placed in her mouth . . . including toilet paper and faeces . . . Her affect was characterized by passivity and a pet-like compliance with those attending her" (Lilly et al. 1983).

The second example provides examples of hypermetamorphosis, hyperorality, agnosia, and hypersexuality. The patient, a 58-year-old man who had suffered from Alzheimer's disease for 6 years, "spent much of his time examining ordinary objects such as the doorstep, ashtrays, or spots on the floor. He placed many objects in his mouth and occasionally ate soil from plant containers . . . he rubbed his genitals so frequently that he developed an excoriation on the shaft of his penis" (Lilly et al. 1983).

Finally, there is the case of a 46-year-old man, who, during a complex partial seizure, "was observed grabbing for objects on his bedside table, and he masturbated in front of the nursing staff. He also placed objects in his mouth, chewed on tissue paper, and attempted to drink from his urine container" (Nakada et al. 1984). Here, there are hypermetamorphosis, hypersexuality, hyperorality, and agnosia.

## Etiology and Pathophysiology

The various causes of the Klüver–Bucy syndrome are listed in Table 52–11: in each case, bilateral damage or dysfunction of the temporal lobes has occurred. The mechanism of such bilateral damage in the case of precipitants is fairly straightforward. The neurodegenerative disorders listed have a predilection for the temporal lobes, and this is particularly the case in Pick's disease and fronto-temporal dementia. Indeed, the appearance of the Klüver–Bucy syndrome early in the course of a dementia is a significant diagnostic clue to one of these two disorders; in the case of Alzheimer's disease, the syndrome, if it does occur, is generally seen only late in the course. Of the miscellaneous causes, an ictal Klüver–Bucy syndrome is suggested by its exquisitely paroxysmal onset and by the occurrence of other symptoms typical for a complex partial seizure, such as confusion, and a postictal Klüver–Bucy syndrome by the history of an immediately preceding generalized seizure. Adrenoleukodystrophy, the last in the list, is an extremely rare cause of the Klüver–Bucy syndrome.

**Table 52–11** Causes of The Klüver–Bucy Syndrome

| Secondary to Precipitants |
|---|
| Bilateral temporal lobectomy (Terzian and Dalle Ore 1955) |
| Traumatic brain injury with bilateral damage to temporal lobes (Lilly et al. 1983) |
| Herpes simplex encephalitis (Greenwood et al. 1983, Marlowe et al. 1975, Shoji et al. 1979) |
| Complex partial status epilepticus (Mendez and Foti 1997) |
| Heat stroke (Pitt et al. 1995) |
| **Occurring as Part of Certain Neurodegenerative Disorders** |
| Pick's disease (Cummings and Duchen 1981) |
| Fronto-temporal dementia (Heutink et al. 1997) |
| Alzheimer's disease (Mendez et al. 1993, Teri et al. 1988) |
| **Miscellaneous Causes** |
| Ictal (Nakada et al. 1984) |
| Postictal (Anson and Kuhlman 1993) |
| Adrenoleukodystrophy (Powers et al. 1980) |

## Assessment and Differential Diagnosis

The combination of hyperorality and hypersexuality often brings the patient to medical attention: although the full syndrome presents little diagnostic difficulty, as it is not mimicked by any other condition, partial syndromes, consisting primarily of hypermetamorphosis and hypersexuality, may suggest mania. The differential rests on the presence or absence of pressured speech and activity, findings typical of mania but absent in the Klüver–Bucy syndrome.

## Epidemiology and Comorbidity

The full Klüver–Bucy syndrome is, overall, rare; in dementia clinics, however, full or partial Klüver–Bucy syndromes are commonly seen.

## Course

The course depends on the underlying cause; in some cases, the syndrome itself may have a fatal outcome, as in Clinical Vignette 9.

## Treatment

The underlying cause, if possible, is treated. There are no controlled studies regarding symptomatic treatment; anecdotally, overall improvement has been reported with

**Clinical Vignette 9**

Mendez and Foti (1997) describe a 40-year-old with epilepsy secondary to old infarction of the left temporo-parietal area. Grand mal status epilepticus occurred, lasting several hours, during which the patient sustained anoxic damage to both temporal lobes. Upon recovery from the status, the patient "had a voracious appetite and indiscriminate eating habits, which included paper towels, plants, styrofoam cups, and even feces. At one point, he drank urine from a catheter bag. The patient was no longer his assertive self and had become quite docile. He tended to wander about the ward touching objects or people and made inappropriate comments of a sexual nature . . . On the day of his death . . . he had wandered about the ward picking up whatever he could find and putting it into his mouth . . . (and) had a respiratory arrest after stuffing his mouth with surgical gauze . . . . Neuropathological examination disclosed an old infarction in the left posterior cerebral artery territory, virtual absence of the left anterior temporal lobe, and atrophy of the right parahippocampal gyrus, hippocampus and amygdala."

carbamazepine, sertraline, and various antipsychotics: should an antipsychotic be used, consideration may be given to a second generation agent such as risperidone or quetiapine.

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CHAPTER

# 53 General Approaches to Substance and Polydrug Use Disorders

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Substance Abuse
Substance Intoxication
Substance Withdrawal
Substance Dependence

## Definition

### Substance Dependence and Abuse

Substance use problems occur on a spectrum from use to dependence (see Figure 53–1). It is important to understand this entire spectrum in order to properly diagnose, prevent progression of, and treat an individual patient's problem. Substance use that does not meet criteria for a disorder may influence management and prognosis of co-occurring disorders, and recent evidence has demonstrated the effectiveness of very brief counseling sessions in reducing use and problems in patients not yet dependent on substances (Saitz 2005).

The definitions of substance abuse and dependence are based on the dependence syndrome of Griffith Edwards (Edwards and Gross 1976). Although this syndrome originally had 10 criteria, the DSM-IV-TR criteria for dependence have been reduced to 7, including tolerance and withdrawal (the first 2 criteria) and a pattern of compulsive use (criteria 3–7). Polysubstance dependence is used when an individual uses at least three substances and only meets three or more dependence criteria when all three substances are considered as a group but not for any single substance. For example, when a young adult has been arrested related to the use of cannabis, cannot stop using cocaine, and drinks alcohol despite making his depression worse. However, he or she does not meet dependence criteria for any of these single substances, when considered alone. The severity of dependence can be indicated by the number of criteria met (from a minimum of three to a maximum of seven) and by whether or not physiological dependence occurs (i.e., whether there is tolerance or withdrawal) because physiological dependence is associated with a higher risk for immediate general medical problems and a higher relapse rate. The five criteria indicating compulsive use alone may define substance dependence if at least three occur at any time in the same 12-month period. Physiological dependence is much more likely with some drugs, such as opioids and alcohol, and is infrequent with other classes of drugs, such as hallucinogens.

This section reviews the application of the dependence syndrome to a variety of abused drugs and uses the number of dependence syndrome criteria met as a measure of severity. Treatment-seeking opioid users are likely to meet most of the dependence syndrome criteria, and therefore their use is at the high end of severity. Cannabis users, in contrast, are likely to meet relatively few dependence syndrome criteria, and therefore their use is of a lesser degree of severity. Individuals with alcohol or cocaine dependence tend to demonstrate a much wider variability in the number of dependence criteria met, with the proportion of patients having relatively low levels of dependence approximately equal to those having extremely high levels of dependence. Thus, the severity of substance dependence is variable depending on the type of drug abused. Some substances such as steroid are of research interest but have not been clearly identified as producing the acute reinforcement or dependence and withdrawal symptoms that characterize the abuse of other substances. The heavy use

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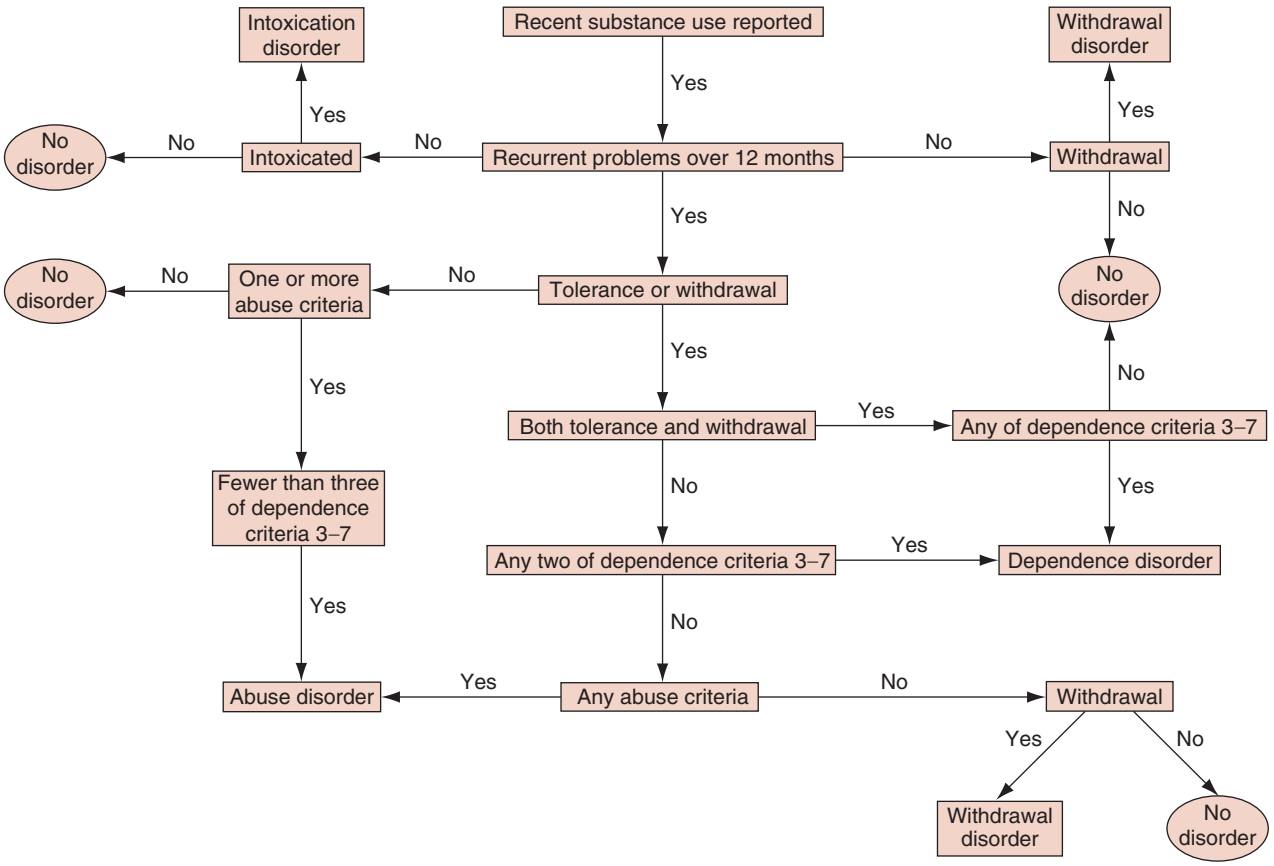



**Figure 53–1** *Spectrum of substance use.*

**DSM-IV-TR Criteria 305.x**

**Substance Abuse**

A. Amaladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.

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of anabolic steroids by body builders, with the associated possible medical complications, has raised important public health issues, however.

Substance abuse is a maladaptive pattern of substance use leading to significant adverse consequences manifested by psychosocial, medical, or legal problems or use in situations in which it is physically hazardous that must recur during a 12-month period. Since a diagnosis of substance dependence preempts a diagnosis of abuse, tolerance, withdrawal, and compulsive use are generally not present in individuals with a diagnosis of substance abuse. Since caffeine and nicotine generally do not cause psychosocial or legal problems and since it is not physically hazardous to use caffeine and nicotine, a diagnosis of abuse does not apply to these substances. The two abuse criteria focusing on legal and interpersonal problems are not among the dependence criteria.

## Substance Intoxication

Substance intoxication is a reversible substance-specific syndrome with maladaptive behavioral or psychological

changes developing during or shortly after using the substance. It does not apply to nicotine. Recent use can be documented by a history or toxicological screening of body fluids (urine or blood). Different substances may produce similar or identical syndromes and, in polydrug users, intoxication may involve a complex mixture of disturbed perceptions, judgment, and behavior that can vary in severity and duration according to the abuser's setting when the substances are having their effect. For example, an abuser can take a mixture of stimulants (cocaine) and hallucinogens (phencyclidine) at a RAVE party and feel euphoric, happy, full of energy, and dancing with great energy, but when the police visit the party, the abuser will become paranoid, irritable, sometimes violent and behave in almost a completely opposite way while under the influence of the same drugs, but now in a different setting. Concomitant use of some substances, for example cocaine and alcohol are often used to enhance pleasurable characteristics while ameliorating dysphoric effects. It should be noted that physiological intoxication is not in and of itself necessarily maladaptive and would not justify a diagnosis of the DSM-IV-TR category substance intoxication. For example, caffeine-induced tachycardia with no maladaptive behavior does not meet the criteria for substance intoxication.

**DSM-IV-TR Criteria 303.0**

**Substance Intoxication**

A. The development of a reversible substance specific syndrome due to recent ingestion of (or exposure to) a substance. Note: Different substances may produce similar or identical syndromes.
B. Clinically significant maladaptive behavioral or psychological changes that are due to the effect of the substance on the central nervous system (e.g., belligerence, mood lability, cognitive impairment, impaired judgment, impaired social or occupational functioning), and develop during or shortly after use of the substance.
C. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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### Substance Withdrawal

Substance withdrawal is a syndrome due to cessation of, or reduction in, heavy and prolonged substance use. It causes clinically significant impairment or distress and is usually associated with substance dependence. Withdrawal can also be associated with the use of opioids for the management of chronic pain with abrupt cessation of opiate use. The symptoms of withdrawal are often the opposite of intoxication with that substance. The more severe syndromes may be broken down broadly into activating and sedating (see Table 53–1). The withdrawal syndrome usually lasts several days to 2 weeks.

**Table 53–1** Intoxication and Withdrawal Syndromes

| |
|---|
| Activating During Intoxication<br>Sedating During Withdrawal |
| Amphetamines<br>Cocaine<br>MDMA (Ecstasy)<br>Phencyclidine<br>Ketamine |
| Sedating During Intoxication<br>Activating During Withdrawal |
| Alcohol<br>Opioids<br>Benzodiazepines<br>Barbiturates<br>Other Sedatives<br>Cannabis |

**DSM-IV-TR Criteria 291.8**

**Substance Withdrawal**

A. The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy and prolonged.
B. The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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## Diagnosis and Assessment

### Phenomenology and Variations in Presentation

The diagnosis of substance abuse and dependence is made by eliciting an appropriate history, performing laboratory tests to confirm drug use, and observing the physiological manifestations of tolerance and withdrawal. A diagnostic decision tree is presented in Figure 53–2.

The phenomenology and variations in presentation among abused substances are related to the wide range of substance-induced states as well as the conditions under which the patient is brought to treatment. The emergency department patient who is acutely intoxicated or suffering from a polydrug overdose can present a wide-ranging and confusing diagnostic picture. Depending on the amount of each drug ingested and the time since ingestion, the likelihood of a life-threatening overdose can be difficult to predict. Similarly, distinguishing substance intoxication or withdrawal from an underlying mood or psychotic disorder, or from chronic anxiety disorders, requires careful observation for a period of several hours to several days, in conjunction with urine toxicological screens, to institute proper

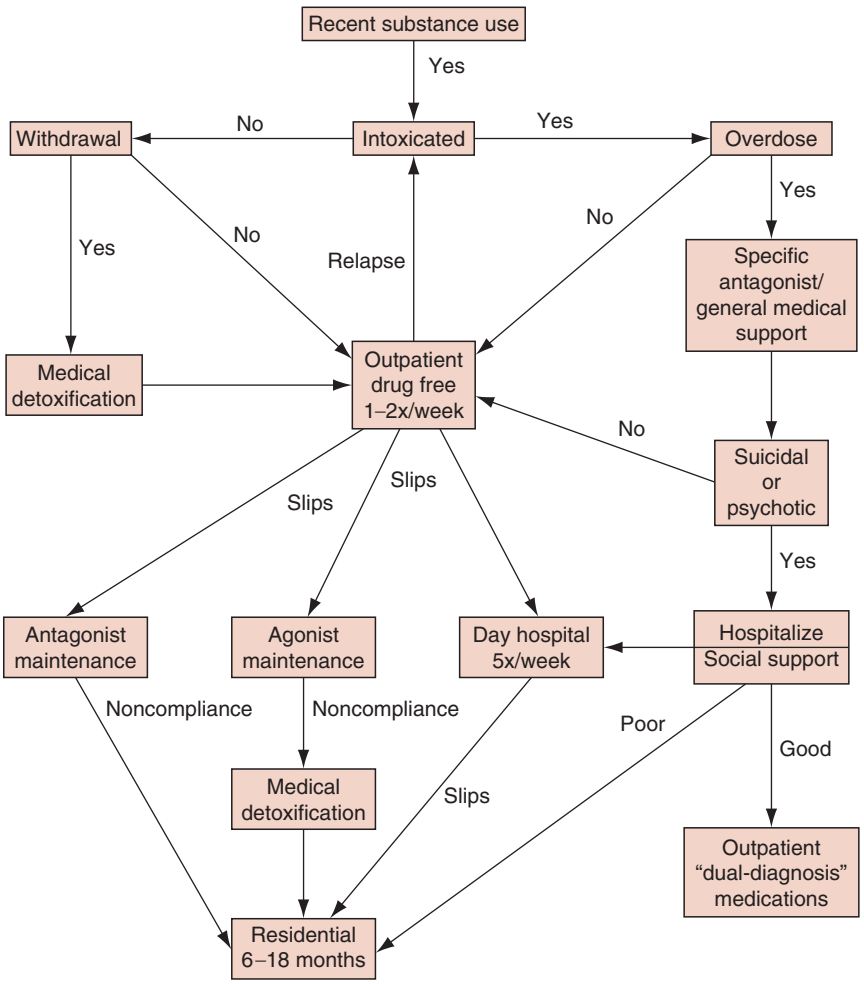



**Figure 53–2** *Diagnostic decision tree for substance use disorders.*

treatment. Many patients who use illicit "street" drugs may not know precisely what drugs they have ingested and certainly will not have a good idea of the precise amount. In addition, patients who are dependent on substances producing significant withdrawal syndromes, such as opioids and alcohol, may have a mixed picture of early intoxication and overdose followed by an evolving withdrawal syndrome; alcohol and sedative withdrawal may produce psychiatric complications (e.g., hallucinations) as well as medical complications (e.g., seizures).

The severity of withdrawal symptoms may, in part, be determined by the setting. For example, studies of opioid-dependent patients have shown that the expression of withdrawal symptoms may be substantially less when no medication treatment is available for symptom relief. As a further example of this phenomenon, individuals with opioid addiction who have been in prison without access to opioids for several years may experience opiate withdrawal when they return to the neighborhoods where they previously used heroin. Thus, they develop withdrawal symptoms without having taken any opiates at all! This conditioned withdrawal phenomenon further supports the importance of setting in the presentation of withdrawal symptoms.

Finally, the issues of motivation for seeking treatment and a tendency to deny substance use can have important influences on the patient's presentation. The patient who presents for treatment because of dysphoric feelings in the context of drug dependence is likely to articulate the severity of his or her problem adequately and even exaggerate some aspects of present discomfort. In contrast, the automobile driver forced to come to a treatment program because of a driving-while-intoxicated offense is likely to minimize her or his alcohol use or any associated complications.

## Special Issues in the Psychiatric Examination

Two special issues in the psychiatric examination of substance dependence include (1) the source of information when obtaining the history of substance use and related problems and (2) the management of aberrant behaviors. Information about a patient's substance use history can be provided not only by the patient but also by employers, family members, and school officials. When patients self-report the amount of substance used, there is a tendency to underreport the severity and duration of use; particularly, if the patient is being referred to treatment by an outside source, such as the family, the employer, or the legal system. Objective verification of the exact amount of substance use is sometimes difficult, but the critical issues in arriving at a diagnosis of substance dependence do not depend on the precise amount of substance used. Tolerance and withdrawal can be assessed independently by using tests such as the naloxone challenge and the barbiturate tolerance test. In

DSM-IV-TR Criteria 303.9

**Substance Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  (b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:
  (a) the characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances)
  (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Specify if:

**With physiological dependence:** evidence of tolerance or withdrawal (i.e., either item 1 or 2 is present)

**Without physiological dependence:** no evidence of tolerance or withdrawal (i.e., neither item 1 nor 2 is present)

Course specifiers (see text for definitions):

**Early full remission**

Early partial remission

Sustained full remission

Sustained partial remission

On agonist therapy

In a controlled environment

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general, significant others' estimates of the amount of drug use by the patient can be a good source of data. Standardized assessment tools such as the Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al. 1995), Drug Abuse Screening Test (DAST) (Skinner 1982), and the Addiction Severity Index (ASI) (McLellan et al. 1980) may assist in both the diagnosis and treatment planning. Thus, the initial evaluation of substance abuse and dependence may involve a wider range of interviews than would occur with many other types of psychiatric patients.

Aberrant behaviors potentially requiring management include intoxication, violence, suicide, impaired cognitive functioning, and uncontrolled affective displays. The evaluation of an intoxicated patient can address only a limited number of issues. These issues are primarily related to the safety of the patient and other individuals who may be affected by his or her actions. Thus, a medical evaluation for signs of overdose or major cognitive impairment is critical, with consideration of detaining the patient for several hours or even days if severe complications are evident. Intoxication with sedating drugs such as alcohol can lead to significant motor and cognitive impairment, which would have an impact on a patient's capacity to drive a motor vehicle. When a patient drives a car to an evaluation and is obviously intoxicated, the psychiatrist has an obligation to prevent the patient from getting back into the driver's seat of that vehicle until the effects of that drug intoxication have worn off. This may involve contacting the police to restrain the patient from driving at least temporarily. Similar issues of police restraint can arise when an intoxicated patient becomes violent and has threatened to harm his or her employers or family members. Judgment and impulse control may be substantially affected by drugs, but these effects may be temporary, and a short-term preventive intervention may be sufficient to avert substantial harm to the patient or others.

Temporary suicidal behavior may be encountered in a variety of substance addictions, particularly those with alcohol and stimulants. Suicidal ideation may be intense but may clear within hours. During the evaluation session, it is important to elicit the precipitants that led the patient to seek treatment at this time and to keep the evaluation

focused on specific data needed for the evaluation of substance dependence, its medical complications, and any comorbid psychiatric disorders. Many patients spend a great deal of time detailing their drug-abusing careers, but in general these stories do not provide useful material for the evaluation or for future psychotherapeutic interventions. Similarly, the evaluation should not become focused on the affective aspects of a patient's recent life because affect is frequently used as a defense to avoid discussing issues of more immediate relevance such as precipitants or to act as a pretext for obtaining benzodiazepines or other antianxiety agents from the physician. Substances of abuse have generally been a way of managing affect and these patients need to develop alternative coping strategies.

## Physical Examination and Laboratory Findings

The physical examination is critical for the assessment of substance addiction, particularly before pharmacotherapy is initiated. Many signs of drug withdrawal require a physical examination and cannot rely entirely on history. Because the general medical complications of substance addiction are also substantial, the most clearly ill patients must have a formal general medical evaluation. Vital signs (blood pressure, pulse, and so on) are an essential beginning, but a full examination of heart, lungs, and nervous system is minimally necessary. Transmissible infectious diseases, such as AIDS, tuberculosis, Hepatitis C, and sexually transmitted infections, are common among illicit drug users and require screening for adequate detection. With alcohol dependence, a wide range of gastrointestinal complications have been described, particularly liver dysfunction. Elevated mean corpuscular volume, thrombocytopenia, and elevations of liver transaminases, amylase, lipase, and triglycerides are common.

Urine toxicological screens can be sensitive for detecting drug use within the previous 3 days for opiates and cocaine. Urine screens for other abused drugs such as cannabis can remain positive for as long as a month in heavy users. A breathalyzer can be used for detecting alcohol use within an 8- to 12-hour period after use. These tests may aid in the diagnosis and management of intoxication and withdrawal, but a nondetectable level of alcohol and drugs does not preclude a diagnosis of substance abuse or dependence. Specific biological tests can also aid in the diagnosis of dependence; for example, a naloxone challenge test assesses opioid dependence by precipitating withdrawal symptoms. Associated medical findings on physical examination include "track marks" in intravenous drug users, nasal damage in intranasal drug users, pulmonary damage in drug smokers, hepatosplenomegaly in alcoholics, and dental caries in opiate users. Opiate users develop dental caries due to the blockade of the pain of toothaches, so that they do not notice dental problems until they are well advanced.

## Differences in Developmental, Gender, and Cultural Presentations

From a developmental perspective, the most important impact of substance abuse and dependence is in adolescence when substance misuse can disrupt schooling and have important medical consequences because of its direct hormonal effects. For example, opioids can increase prolactin levels and at the same time decrease corticosteroid and testosterone levels. These hormonal effects can have a direct impact on the expression of secondary sex characteristics as well as sexual behaviors during adolescence. Another critical developmental effect is during the gestational period of unborn children to substance using mothers. These children may be born with a significant neonatal withdrawal syndrome from drugs such as opioids or may have behavioral and congenital abnormalities secondary to the substance misuse by their mothers; for example, fetal alcohol syndrome in the infants of mothers who are alcohol dependent during pregnancy and the hyperactivity that has been noted in infants born to cocaine-dependent mothers.

At the other extreme of life, in the geriatric population, substance addiction might have an important iatrogenic contribution. Many chronic debilitating diseases are associated with significant pain and may be treated with opioids. Similarly, sleep disorders in the elderly are often treated with sedatives (such as benzodiazepine and barbiturates) that produce tolerance and dependence. Although most of these patients will not experience patterns of substance abuse, some patients may begin to seek out these medications from multiple physicians (so-called doctor shopping), and experience significant psychosocial impairment. Patterns of drinking may change with changing family and work roles. This change of pattern coupled with enhanced physiologic effects of alcohol may lead to falls, cognitive deficits, or late onset alcohol dependence.

Sex differences in the presentation of substance addiction problems can be related to the setting in which these problems are detected. For example, young women may come to the attention of the substance abuse treatment provider during or soon after pregnancy. When a child is born with the fetal alcohol syndrome, the mother should be identified as having a substantial problem with alcohol requiring treatment referral. In contrast, the criminal justice system is more likely to identify substance addiction in males and to insist that they get ongoing treatment as a condition of parole or probation.

Some drug abuse patterns are also more common in women than in men. For example, the phenomenon of sex for crack frequently occurs in female cocaine addiction, but men infrequently obtain cocaine using this approach. Finally, although men are more likely than women to misuse drugs generally, some drugs, such as androgenic steroids, are significantly overrepresented in male drug abusers.

Cultural differences in the presentation of drug addiction can be striking. For example, the use of hallucinogens by Native Americans in religious ceremonies shows none of the abusive characteristics of adolescent hallucinogen addiction in middle-class America. Alcohol use can vary based on the amount of alcohol that is considered culturally acceptable in various geographical settings. Thus, Muslims tend to use no alcohol, but may smoke opium in Middle Eastern countries. Among the French, however, the ingestion of larger amounts of alcohol is more normative and may not reflect alcohol dependence, while opium use would be uncommon. The cultural difference between doctor shopping for sedatives and opioids is considerably different from that associated with buying these same drugs on the illicit street market. Gender and family structure are significant sociodemographic correlates of drug use, with use being,

on average, higher among males than females, and higher among students who do not live with either of their parents than among those who live with at least one of their parents.

Because of the relative lack of information about cultural differences in drug use among adolescents, large empirical studies have begun to address these issues. The Monitoring the Future Project has been used to examine empirically the prevalence, trends and sociodemographic correlates of drug use among nationally representative samples of 8th, 10th and 12th graders from 1975 through 2005. Alcohol is the drug most widely used by youth, followed by tobacco and marijuana. By 12th grade, African American youth have the lowest use of substances, Whites the highest. Heavy drinking was reported by 12% of African American, 33% of White, and 25% of Hispanic students in 2005. Whites have higher use of most illicit substances, but Hispanic youth report more inhalants, stimulants, and heroin (Johnston et al. 2006).

### Differential Diagnosis

The differential diagnosis of substance-induced intoxication and withdrawal can involve a wide range of psychiatric disorders. Distinguishing substance intoxication and withdrawal from these other disorders is usually facilitated by a structured interview to elicit whether the range of psychiatric symptoms are appropriately timed after the most recent substance use. During acute intoxication in polydrug users, the differential diagnosis might include an acute psychotic disorder, mania, delirium, dementia, or several specific anxiety disorders. Among these anxiety disorders are generalized anxiety disorder, panic disorder, and obsessive–compulsive disorder. Distinguishing these disorders from acute intoxication or withdrawal with a mixture of drugs most frequently requires that the psychiatrist wait 24–72 hours to determine whether the symptoms persist and, therefore, whether they are independent of the drug use. While the DSM-IV-TR criteria for substance-induced disorders suggest waiting for a "substantial period of time" (e.g., about a month) to distinguish various substance-induced disorders from those not related to substance abuse, the introduction of pharmacological treatments such as antidepressants does not require such a lengthy delay. Thus, diagnostic and therapeutic distinctions may be different when evaluating the patient.

A previous history of schizophrenia, bipolar disorder, or other major psychiatric disorder that is consistent with the presenting symptoms may also be helpful in arriving at an accurate diagnosis. When patients present with psychotic or manic behavior during drug intoxication, it may be necessary to use symptomatic treatment such as a benzodiazepine or neuroleptic agent to conduct an examination. Because neuroleptic agents lower the seizure threshold, they are most often used in conjunction with a benzodiazepine or other anticonvulsant. A symptomatic response to these medications should not be considered confirmation of an underlying diagnosis of psychotic disorder, however. Furthermore, some drugs, such as phencyclidine, may produce a sustained psychotic state that lasts longer than the usual 72 hours after acute intoxication.

Antisocial and borderline personality disorders are commonly considered in the differential diagnosis of substance-dependent patients. Many of the behaviors that characterize these personality disorders are also common to the use of illegal and illicit drugs. In establishing these personality disorders, particularly antisocial personality, it is important to ascertain whether the behaviors are independent of the activities needed to obtain drugs. If many of the antisocial or borderline characteristics are specifically tied to the patient's use of drugs, these characteristics should resolve with drug abstinence and should not be considered diagnostic of a personality disorder.

The symptoms of drug withdrawal frequently overlap with those of depressive disorders, and this differential diagnosis can be particularly difficult. Furthermore, the syndrome of protracted withdrawal can include sleep and appetite disturbance as well as dysphoria that mimics dysthymic disorder and other affective disorders. Some drugs, such as opioids, appear to be minimally psychotoxic and are unlikely to produce affective syndromes. Thus, in heroin dependence, a differential diagnosis can be made several days after completing acute detoxification or while the patient is receiving agonist maintenance. With other drugs, such as stimulants, sedatives and alcohol, depressive symptoms may be more persistent after acute detoxification, which leads to a more difficult differential diagnosis. Thus, conservatively, the psychiatrist should wait 4–6 weeks after acute detoxification to determine a diagnosis of affective disorder in these substance-dependent patients. However, waiting this long is often impractical in the clinical setting where the maintenance of sustained abstinence may depend on relief of depressive symptoms using either medications or psychotherapy. In this regard, clinical compromises are addressed in subsequent chapters.

## Epidemiology

### Prevalence

Wide cultural variations in attitudes toward substance consumption have led to widely varying patterns of substance misuse and prevalence of substance-related disorders. Relatively high prevalence rates for the use of virtually every substance occur between the ages of 18 and 24 years, with intoxication being the initial substance-related disorder, usually beginning in the teens. In the United States, it is estimated that 8.1% of the population used at least one illicit drug in 2005, and that 22.7% of the population has engaged in binge drinking according to the 2005 National Survey on Drug Use and Health (SAMHSA 2006). Recent use of marijuana has declined, nonmedical use of prescription medications has increased, while use of cocaine and heroin has remained stable over the last several years. Tolerance and withdrawal require a sustained period of use, and these manifestations of physical dependence for most drugs of abuse typically begin in the 20s and early 30s. Twelve-month prevalence estimates for any substance use disorder range from 8 to 10% (SAMHSA 2006, Kessler et al. 2005). Of the estimated 22.2 million Americans with a substance use disorder, 15.4 million had an alcohol use disorder, 3.6 million a drug use disorder, and 3.3 million had both an alcohol and a drug use disorder (SAMHSA 2006). Although most substance-related disorders are more common in men than in women, sex ratios can vary considerably with different drugs of abuse.

### Comorbidity Patterns

Serious psychological distress is considerably more prominent in those who use substances. In 2005, 22% of illicit drug users reported serious psychological distress in comparison to 9.6% of adults who did not use illicit drugs (SAMHSA 2006). In both the Epidemiological Catchment Area study and the National Comorbidity Survey, substance abuse and dependence were the most common comorbid disorders, usually appearing in combination with affective and anxiety disorders. In the National Comorbidity Survey (Kessler et al. 2005) the lifetime rate of substance abuse was 27% and the rate of comorbid depression among these substance abusers was 19%. Furthermore, 80% of these depressed substance-abusing subjects had more than one psychiatric disorder; only 20% had only one psychiatric disorder. In the Epidemiological Catchment Area study (Regier et al. 1984) 75% of daily substance users had a comorbid psychiatric disorder. In studies of treatment-seeking substance abusers, the rates of other psychiatric disorders are almost uniformly higher than those in community samples, but the rates of excess comorbidity in these abusers vary with the specific abused drug. For example, in the Epidemiological Catchment Area study the lifetime rate of major depression in the community was 7%, whereas the major depression rates for substance users seeking treatment were 54% for opioids, 38% for alcohol, and 24% for cocaine. More recent studies such as the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study have focused on adolescents (Kandel et al. 1999). In the MECA study the rates of mood and disruptive behavior disorders are much higher among adolescents with current substance use disorders (SUD) than among adolescents without SUD. Comparison with adult samples suggests that the rates of current comorbidity of SUD with psychiatric disorders are the same among adolescents as adults, but the comorbidity of lifetime disruptive disorders or antisocial personality disorder with SUD is lower among adolescents than among adults.

## Course and Natural History

The natural history of substance dependence characteristically follows the course of a chronic relapsing disorder, although a large number of individuals who experiment with potentially abusable drugs in adolescence do not go on to acquire dependence. The initial phase of the natural history of experimenting with drugs has been well described in studies by Kandel (1975) who has used the concept of gateway drug use and its evolution into more serious drug dependence during adolescence and the early 20s. The later phases of dependence are characterized in the 20- to 30-year follow-up studies of individuals with alcoholism and those with opioid addiction by Vaillant (Vaillant 1988, Vaillant 1983, Laub and Vaillant 2000). He has documented the natural history after age 20 years in delinquent boys, which is most closely synonymous with having lifetime conduct disorder using DSM-IV-TR criteria, and found high mortality rates by age 40 years in those delinquent boys who later become substance users. In his most recent studies following 475 delinquent boys and 456 matched nondelinquent comparison boys from age 14 years until age 65 years, he found that 13% of the delinquent and only 6% ($N = 28$) of the nondelinquent subjects died unnatural deaths. These deaths were significantly associated with abuse of alcohol during adulthood and childhood delinquency, and these two factors completely accounted for the other associations of adult crime, dysfunctional home environment, and poor education with the increased mortality. Thus, using substances may have a critical impact on later health, but having a conduct disorder as a child increases this risk, perhaps due to related behaviors such as unwillingness to seek out appropriate health care. Clearly, these studies open more questions about the interaction of substance abuse and childhood behaviors that may not include substance abuse.

The course of substance dependence is variable and may involve full or partial remission with six course specifiers available in the DSM-IV-TR. In order for a patient with dependence to be considered "in remission," none of the dependence or abuse criteria can be met for at least 1 month. Remission can then be further characterized as either early (less than 12 months) or sustained (lasting 12 months or longer) and partial (one or more criteria for abuse or dependence have been met) or full (no criteria for dependence or abuse). Because the first year of remission carries a particularly high risk for relapse, it has been chosen as the minimum required time for sustained remission. Two additional specifiers apply for special circumstances, such as when the patient is receiving agonist therapy or is in a controlled environment where access to substances is potentially limited (such as jail or a therapeutic community).

Outcome studies across substance type and treatment setting consistently show decreases in substance use, associated problems, and societal costs. Forty to 60% of treated patients will enter full remission with an additional 15–30% achieving partial remission. The most substantial cost benefits come from reduced crime, increased productivity, and decreased health care costs (McLellan et al. 2000).

## Etiology and Pathophysiology

The cause of substance addiction depends on a variety of genetic, neurobiological, psychological, and social and environmental factors. Neurobiological factors can overlap with genetic predisposition as well as with the psychological substrates for positive and negative reinforcement by abused substances (Nestler 2000). Finally, environment is critical not only for simply exposure to the abused substances themselves (cocaine is not available in many parts of the rural world), but also because the social supports and community setting often protect against substance abuse and dependence, as well as experimentation itself.

### Genetic Factors

Family genetic studies have found rates of substance dependence three to four times higher in identical twins than in dizygotic twins (Cloninger 1999). Although no single genetic marker or specific genetic defect has been confirmed, work has suggested that some alleles associated with variations in the dopamine receptor may be more common in substance-dependent individuals than in those who are not dependent. Similarly, risk factor studies have found that the sons of individuals suffering from alcoholism have a general hyporesponsiveness to alcohol and sedative drugs when compared with the sons of individuals without alcoholism.

## Neurobiological Factors

The neurobiological substrates for positive and negative reinforcement by abused substances have been examined in a wide range of animal studies. The neuronal pathways underlying positive reinforcement appear to converge on the dopaminergic pathways leading from the ventral tegmental area in the brain stem to the nucleus accumbens, which is part of the basal ganglia (Spanagel and Weiss 1999). Most drugs of abuse appear to act through this pathway to produce positive reinforcement and reward. Some abused drugs, such as stimulants, affect this pathway directly by increasing the amount of dopamine available to stimulate the cells in the nucleus accumbens. Other drugs, such as opioids, appear to have effects on the dopaminergic cells in the ventral tegmental area through specific opioid receptors and thereby indirectly affect the nucleus accumbens. Human research suggests that the nucleus accumbens itself has few opioid receptors. The reinforcing effects of alcohol and benzodiazepines may be through gamma-aminobutyric acid receptors. These gamma-aminobutyric acid receptors also appear on the dopaminergic cells located in the ventral tegmental area. The positive reinforcing effects of hallucinogenic drugs are less clear. For example, marijuana interacts with a specific cannabinoid receptor that is widely distributed in the brain, and it does not appear to have a direct interaction with the dopaminergic systems in the ventral tegmental area. Other hallucinogenic drugs, such as lysergic acid diethylamide, have critical effects on serotoninergic systems, which may act on the nucleus accumbens to facilitate dopamine neurotransmission indirectly. Animal studies delineating these reinforcement pathways in the brain have shown that these systems are important for general hedonic tone and the reinforcing properties not only of abused drugs but also of pleasures derived from activities that are considered healthy alternatives to abusing substances. Thus, interventions targeted at these fundamental neuropathways might also interfere with the pleasures of normal daily living.

The negative reinforcers involved in substance dependence include the relief of withdrawal symptoms (Koob and Le Moa 2001). The neurobiological systems responsible for symptoms of withdrawal are multiply determined. Two brain systems that appear to be particularly important during withdrawal are the noradrenergic system in the locus ceruleus of the brain stem and the dopaminergic system that terminates in the nucleus accumbens. The nucleus accumbens is more broadly a part of the limbic circuit, which generally is associated with mood and emotion.

The role of the locus ceruleus in drug withdrawal has been clearly delineated during opiate withdrawal (Kosten and Hollister 2001). The locus ceruleus contains opioid receptors that inhibit locus activity when exposed to morphine. During opiate withdrawal, the locus has high levels of nerve activity, and this nerve activity appears to result from the release of chronic inhibition of the locus by morphine administration. After chronic morphine inhibition, the second-messenger system (cyclic adenosine monophosphate) hypertrophies. This hypertrophy is expressed as locus hyperactivity when morphine is removed.

After chronic administration of cocaine, opioids, or alcohol, there is an increased stimulation threshold in the nucleus accumbens so that the same level of stimulation in the nucleus produces less positive reinforcement. This might be interpreted as a type of negative reinforcement after chronic drug usage. In summary, at least two and probably more neural circuits are recruited into the negative reinforcement associated with substance dependence and thereby are important pathophysiological factors.

Positive and negative reinforcement may not entirely explain the development and maintenance of addiction and the risk of relapse that continues years after cessation of use. Dopamine projections from the midbrain to the prefrontal cortex appear to be responsible for reward-related learning (Hyman 2005). Dopamine release from drugs such as amphetamine, cocaine, and opioids is significantly larger than that from natural rewards such as food and sex, leading to overlearning and persistence of the memory of the pleasure of drug use and the people, places, and things associated with the experience.

## Psychological Factors

Psychological factors related to etiology include high rates of depressive disorders and sensation seeking, which are found in individuals prone to substance addiction. The association of sensation seeking with substance addiction suggests that drugs enhance pleasant sensations, such as a high. However, abused drugs may provide potential control of aggressive impulses, which can be a component of sensation seeking that adolescent abusers often would like to control chemically rather than develop the cognitive abilities needed to control aggression. Whether abused drugs serve as self-medication for individuals with these psychological disturbances (e.g., depression, impulsivity, and poor control of aggression) has not been resolved clearly because the age at onset for major psychiatric disorders, such as depression, is older than the age at onset for substance abuse and dependence (Khantzian 1985). Childhood precursors of substance abuse and dependence, including shy and aggressive behaviors, can also be precursors of later depressive disorders as well as of antisocial personality disorder, the adult expression of aggressive impulsivity.

## Social and Environmental Factors

Finally, social factors, including peer and family influences, which are not dependent on genetic inheritance, are important in leading to initial drug exposure. Kandel (1975) has conducted longitudinal studies of "gateway drug" usage by adolescents, and these original concepts have been expanded over the last 25 years to recognize their treatment implications. These gateway drugs are tobacco, alcohol, and marijuana. Adolescents who begin using gateway drugs in their early teens are more likely to have substance dependence in their 20s than are adolescents who begin use in their late teens. Delaying the initiation of these gateway drugs and their associated intoxication by 1–2 years substantially decreases the later risk of the development of substance dependence. This association between early gateway drug use and later dependence may be related to the relatively higher rates of conduct disorder and failure to complete school in those who acquire a substance-related disorder in early adolescence. Life stressors related to peers and family are also possible causative factors in substance dependence and their associated comorbid psychiatric disorders (see Clinical Vignette 1). The treatment implications of this

model have been examined with long-term follow-up data from randomized prevention trials to determine the extent to which participation in a cognitive-behavioral skills-training prevention program has led to less illicit drug use than for untreated controls. In one large-scale study, data were collected by mail from 447 individuals who were contacted after the end of the 12th grade, 6.5 years after the initial pretest. Results indicated that students who received the prevention program (Life Skills Training) during junior high school reported less use of illicit drugs than controls. These results also support the hypothesis that illicit drug use can be prevented by targeting the use of gateway drugs such as tobacco and alcohol when children are entering adolescence (Botvin et al. 2000).

Clinical Vignette 1

Vulnerability to AIDS was associated with significant posttraumatic stress disorder (PTSD) in a spouse of a patient in our methadone maintenance program. Mr. and Ms. T had both been patients in our methadone maintenance program for more than 2 years. They had stopped using illicit drugs since starting methadone treatment and had restabilized their lives with their two children. He had been working since starting treatment after being unemployed for several months before treatment, and they had been living in a comfortable apartment for almost 2 years. Although he had been intermittently ill during the previous year with seemingly minor infections, these illnesses did not prepare them for his hospitalization with *Pneumocystis* pneumonia followed by a diagnosis of AIDS. His health deteriorated rapidly, and he died less than 6 months after the diagnosis of AIDS. They had both refused to be tested for human immunodeficiency virus when they entered treatment, and she continued to refuse, even after his diagnosis. They had shared needles when using drugs; thus, the probability that she was also infected was high.

During the 6 weeks just before he died, she experienced some symptoms of anticipatory grief, including difficulty sleeping and loss of appetite. Psychotherapeutic treatments were instituted, and she seemed to respond well. The funeral was upsetting, but she appeared to work through the loss of her husband with a typical, several-week course of grief. Six months later, however, she began using cocaine at the urging of a friend. She was using cocaine about twice a week for 3 weeks when nightmares about her dead husband's illness recurred, and she lost interest in most activities, including caring for her children. She had classic alarm symptoms of PTSD, including being easily startled, an inability to concentrate, sleeplessness, and avoiding activities that reminded her of his illness. This last symptom was particularly problematic because it meant that she would not get any medical care and continued to refuse testing for AIDS. Because of these disturbing events and the urging of her drug treatment counselor, she stopped using cocaine, but the PTSD symptoms continued.

Treatment for her PTSD involved both psychotherapy and pharmacotherapy. The psychotherapy was focused on the trauma of the loss of her husband as well as her own vulnerability. She was concerned about the impact on her children if she were to get AIDS, but this fear had led to denying the possibility of her own infection and to pulling away emotionally from her children. The psychotherapy was enhanced by pharmacological treatment with the tricyclic antidepressant imipramine. Treatment was at first attempted without this medication, but the patient could not discuss any traumatic material with the therapist. Within 2 weeks after starting the imipramine, she began sleeping and concentrating better and engaging in productive psychotherapy.

This case illustrates several points about the association of stress with substance abuse. First, patients with substance use disorders, particularly heroin addicts, can have substantial stressors in their lives, such as early deaths of spouses and vulnerability to fatal illnesses. Second, they may have problems in adjusting to these stressors, and these problems may be somewhat delayed in presentation (e.g., the PTSD was delayed for 6 months after the actual loss). Third, substance use (e.g., the cocaine use) may be an initial response to a psychological stress, even though this may worsen the stress-related symptoms. Fourth, pharmacological treatments may enhance the psychotherapy needed for these stress-induced disorders. This last point suggests that PTSD may have a neurobiological substrate; this provides a rationale and target for pharmacological interventions with this stress-related disorder.

## Goals

The most important goal of any treatment is abstinence from the abused drug. Issues of "controlled use" are debated by some psychiatrists, but controlled use is usually not a realistic goal for dependent patients. A critical, first treatment goal with substance addiction is often acute treatment of overdose. A psychiatrist must be aware of specific therapies, such as naloxone for opioid overdose and flumazenil for benzodiazepine or other sedative overdose. The polydrug user often has combined toxicity from drug interactions, such as alcohol with cocaine or prescription medications. For dependence on a drug with a significant withdrawal syndrome such as opioids or alcohol the initial treatment involves either agonist stabilization, such as methadone maintenance, or medical detoxification with benzodiazepines when necessary. After detoxification or stabilization, prevention of relapse may occur through a variety of behavioral or other psychotherapeutic approaches. Reduction in drug use without total abstinence using agonist maintenance (e.g., methadone) may be an early priority, together with the provision of essential social services for legal problems, housing, and food. After stabilization, vocational rehabilitation and various psychotherapeutic issues may be addressed, including the management of affect, such as depression. For patients with psychosis, inpatient treatment or interventions with medication may be required before detoxification can occur.

Other treatment goals include total abstinence and family involvement. Patients often advocate for controlled use of some substances such as alcohol use by the patient receiving methadone maintenance or the continued smoking of marijuana or even tobacco by individuals formerly suffering from alcoholism. This can lead to a serious conflict in treatment goals, and increases the risk of relapse to the primary substance or the development of an additional dependence disorder. Another goal is to change the role of family members from "enablers" or codependents with the substance user to treatment allies. These family members

need to be engaged in treatment to work as active collaborators in the therapeutic plan for the patient. Although family treatment is commonly applied to many psychiatric disorders, it can have a particularly powerful impact with adolescent substance users to eliminate family behaviors that reinforce the drug taking.

## Standard Treatments

### Psychiatrist–Patient Relationship

The first issue in the psychiatrist–patient relationship is approaching the substance user who denies a problem. This patient must be approached in such a way that the substance use problem will become accessible for treatment. This may involve an "intervention," in which a variety of the significant others and social supports of the user are brought together to confront the potential patient about his or her SUD. Family and employers are important contributors to such an intervention.

Once the substance use problem is clearly identified, a series of other issues arise, including confidentiality versus necessary disclosures, comorbid psychiatric disorders, medical evaluations, and potential for relapse. Patients need to be assured of confidentiality in order to get them to be open with the therapist, since the use of illicit drugs can be associated with a variety of illegal activities. Confidentiality must be balanced against the need to disclose to their family about behaviors that can lead to a relapse of substance use. Psychiatric assessment is critical because of the high rates of depression and the risk of suicide in this population. A full medical assessment generally is essential because of the high rates of infectious and gastrointestinal diseases directly related to substance abuse and dependence. Medical assessment is also essential to determine whether active medical detoxification is necessary. Finally, a psychotherapeutic issue early in treatment may be distinguishing between "slips" and a full relapse. Slips are common in substance users, and patients must be prepared for them and not consider them failures that will inevitably lead to full relapse and dependence. Slips are more fully covered in the section on psychosocial treatments.

### Pharmacotherapy

Pharmacotherapy can have several roles in substance dependence treatment, including treatment of overdose and acute intoxication (naloxone, flumazenil), detoxification or withdrawal symptom relief (benzodiazepines, clonidine), blockage of drug reinforcement (naltrexone), development of responses to the abused substance (disulfiram), anticraving medications (acamprosate), treatment of psychiatric comorbidity (antidepressants), and substitution agents to produce cross-tolerance and reduce drug craving (methadone and buprenorphine). A key element in the treatment of many dependence-producing drugs is the need for detoxification, which may last from 3 days to as long as 2 weeks. Detoxification is essential if antagonist pharmacotherapies, such as naltrexone for opioid dependence, or aversive agents, such as disulfiram for alcoholism, are to be employed. Conversely, agonist maintenance treatment, such as methadone or buprenorphine for heroin dependence, does not require detoxification before beginning treatment. Using these agonists usually requires regular clinic attendance by the patient and relatively prolonged treatment of 1–2 years, with some patients continuing agonist therapy for up to 20 years.

A treatment decision tree is presented in Figure 53–3 and outlines potential roles for pharmacotherapy and psychotherapy.

### Psychosocial Treatments

A wide range of psychosocial treatments are available in SUD, ranging from long-term residential treatments (6–8 months) to relatively low-intervention outpatient medication-free treatments with once-weekly hour-long therapy. Most patients with substance dependence will require a more intensive counseling approach than can be delivered in the outpatient setting. Other treatment approaches include

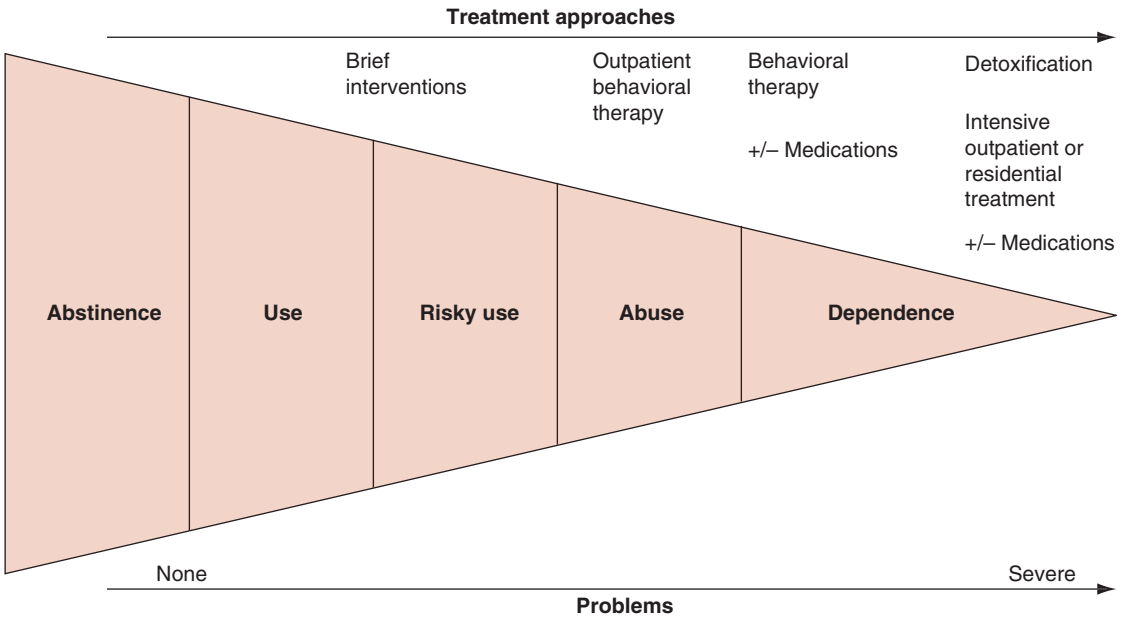



**Figure 53–3** *Treatment decision tree for substance use disorders.*

inpatient treatment specifically designed for detoxification and day hospital and evening programs focusing on the prevention of relapse. Clinicians should be familiar with the type of programs available, and the need for continued follow-up and a program of relapse prevention.

Evidence-based psychotherapeutic approaches include twelve-step facilitation (TSF), motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), and contingency contracting. TSF therapy is based on the principles of Alcoholics Anonymous (AA), and key components include peer support, admission of loss of control, and commitment to abstinence. MET bolsters commitment to change by exploring the pros and cons of substance use, and developing discrepancy between the behavior of drinking alcohol and the patient's goals. CBTs including relapse prevention therapy (Somers and Marlatt 1992) assist patients in identifying risk factors for drinking and developing tools to prevent relapse. Contingency contracting, in which various aversive or rewarding contingencies are put in place for periods of up to 6 months to prevent relapse, has been particularly effective in stimulant and opiate dependence.

In Project MATCH, TSF, MET, and CBT were compared in a large cohort of alcohol-dependent subjects, and results demonstrated significant improvement with all three therapies, but no significant differences among treatments (Project MATCH 1997). Referral should be based upon available resources and patient preference. Rehabilitation can be done on an inpatient or an outpatient basis. Matching patients to the most appropriate program is based on severity of addiction, medical and psychiatric comorbidity, and resource availability. A distinction should be made between treatment and participation in a self-help group. Self-help groups are complementary to both intensive psychotherapeutic and pharmacological interventions. AA is readily available and has been of unquestionable value to many people suffering from an addictive disorder. Becoming familiar with the 12 steps of AA by attending an open meeting can assist clinicians in understanding more about substance dependence and in referring patients to 12-step programs.

## Special Treatment Features

### Psychiatric Comorbidity

Comorbid psychiatric disorders, particularly depressive and anxiety disorders, are extremely common in substance abuse and dependence, with lifetime rates approaching 50% in individuals addicted to opioids. Although the rate of major psychotic disorders among SUD is relatively low, the rate of substance use in patients with schizophrenia or bipolar disorder may be as high as 50%.

Splitting treatment between a mental health clinic and substance abuse clinic can be a significant problem for the coordinated management of the patient with co-occurring disorders. A prominent problem in the management of SUD with comorbid psychiatric disorders is medication management within a substance abuse treatment setting because of limited psychiatric resources. In mental health settings, the need for monitoring, using urine toxicological screens for illicit drugs and breath testing for alcohol, can pose difficult logistic and boundary problems. Integrated treatments have been developed using social skills training combined with relapse prevention behavioral therapies as well as pharmacological adjuncts to either typical or atypical neuroleptics for patients with schizophrenia.

Another special factor in treatment is the relationship between many patients and the legal system—for example, parole, probation, work release programs, or other alternatives to incarceration—because this requires the psychiatrist to report to these agencies. Contingencies must be developed with these patients to clarify the content of this reporting as well as to obtain a specific release of confidentiality so that these reporting requirements can be fulfilled.

### General Medical Comorbidity

Treatment of a comorbid medical condition is essential in SUD because many do not seek medical care and may be seen only by the psychiatrist. The most important current comorbid disorder in SUD is AIDS, which is spread primarily by intravenous drug use but increasingly is also spread through sexual activity between drug users. Other areas of medical comorbidity include vitamin deficiencies, infectious diseases, and gastrointestinal disorders, such as cirrhosis, gastrointestinal bleeding, and peptic and duodenal ulcers. Stimulant users may experience cerebrovascular accidents. Also, dementing disorders need particular consideration in conjunction with alcoholism, inhalant abuse, and sedative dependence. With polysubstance use medical complications can be intensified. For example, use of alcohol and cocaine together produces the metabolite cocaethylene and enhances cardiotoxicity whereas combinations of alcohol and other sedatives can lead to respiratory depression, coma, and death.

### Demographical and Psychosocial Considerations

Substance abusers are often young but seek treatment only after a delay of 5–10 years; the average age of patients presenting for treatment is 32 years. Because most substance use problems develop earlier in life, parenting issues are critical, specifically issues of drug use during pregnancy, which can lead to fetal alcohol syndrome, low birth weight, premature delivery, and opiate withdrawal in infants. Neonatal withdrawal requires specific attention and treatments that differ from adult treatment. Geriatric substance misuse, particularly of prescribed medications, is not well recognized and frequently underdiagnosed. Treatment of these geriatric patients with multiple medical problems and complex medical interactions requires careful monitoring by the psychiatrist.

### Treatment-Refractory Patients

A variety of escalating treatment interventions can be applied to patients who are refractory to treatment. If initial detoxification with outpatient follow-up care is ineffective, several levels of intensified interventions can be applied, such as agonist maintenance with methadone for patients addicted to opioids, disulfiram treatment for patients with alcoholism, and perhaps antidepressants for stimulant use disorders. Further interventions can include residential placement for up to 2 years to enable full psychosocial rehabilitation of refractory patients. (See Clinical Vignette 2 for an illustration of such an escalating intervention, when the outpatient tapering of an abusable medication failed and

Clinical Vignette 2

A 22-year-old man with a 3-year history of cocaine dependence presented with major depressive disorder. Because he had been refractory to selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, and augmentation using lithium or thyroid hormone, methylphenidate was added to maintenance treatment with a tricyclic antidepressant. The psychiatrist warned the patient about the risk in prescribing methylphenidate given his past problems with cocaine and warned that a medication change might be necessary if he experienced a cocaine-like high from the methylphenidate. Within 3 weeks, the patient called the psychiatrist telling him that he had been taking twice the daily prescribed number of pills. The psychiatrist recognized a developing addiction to methylphenidate and began to taper the schedule of methylphenidate administration. Within 3 days, the patient had exhausted a week's supply. The psychiatrist then informed the patient that outpatient detoxification had failed and recommended hospitalization.

This case illustrates how a psychiatrist is often confronted with the issue of whether to use an addictive medication to treat a primary psychiatric disorder in a patient who also has a known substance use disorder. Other examples of this dilemma are common—a psychiatrist determines that an alcoholic patient suffers from an underlying generalized anxiety disorder and that the patient's drinking may be fueled, in part, by efforts to subdue the anxiety. The patient, currently abstinent but craving alcohol, is given a trial of buspirone for anxiety, but the medication is ineffective. Should a benzodiazepine trial be initiated? Similarly, should a patient with cocaine dependence in remission with a certain diagnosis of residual attention deficit disorder be given a trial of methylphenidate?

Two clinical questions often arise: Is use of addictive medication flatly contraindicated in patients with substance dependence in remission, or is such medication prohibited only in instances of use of drugs of the same class (e.g., alcohol and benzodiazepines and methylphenidate and cocaine)? In general, a psychiatrist should never rule out the use of any addictive drug if there are good symptom-based reasons for prescribing it. Nor should the psychiatrist assume that an addicting drug of one class (e.g., opiates) will be safe for an individual who abused another class, such as stimulants. However, in any situation in which a potentially addicting drug is considered for use in a remitted substance user, considerable caution and limit setting is warranted. Finally, inpatient management may become necessary for the evaluation and use of these risky treatment interventions.

inpatient treatment was then instituted.) Figure  also provides a treatment decision tree detailing a series of escalating treatment levels.

## Other Substance Use Disorders: Anabolic Steroids and Nitrites

This group of substance-related conditions most notably includes anabolic steroids and nitrite inhalants. These both have psychoactive effects and can have consequences for the individual and broad public health, which suggest that future research may lead to their inclusion in future psychiatric classifications as separate disorders.

In 1988, a survey of male high school seniors showed that anabolic steroids had a lifetime use rate of 6.6% (Buckley et al. 1988). Thus, by the late 1980s widespread abuse of anabolic steroids was occurring among males as well as females. Multiple types of steroid derivatives were being used in order to make the lipid soluble steroids more water soluble and easier to administer than the intramuscular injections that were typically required. Because of this abuse, anabolic steroids were added to Schedule III of the Controlled Substances Act in 1990.

The clinical effects of anabolic steroids are related to a typical "cycle" 4–18 weeks on steroids and 1 month to 1 year off. While taking the steroids the primary effects sought by users are increasing muscle mass and strength, not euphoria. In the context of an adequate diet and significant physical activity, these individuals appear quite healthy, and they are unlikely to appear for treatment of their anabolic steroid use. However, some of the adverse cardiovascular, hepatic, and musculoskeletal effects of steroids as well as virilization in women may bring these users to medical attention. Severe cases of acne can also bring some adolescents to medical attention. Abuse of other psychoactive drugs may occur in up to a third of these steroid users, but generally is relatively low compared to other substance abusers.

Heavy use can increase aggression, change libido and sexual functions, and induce mood changes with occasional psychotic features (Brower et al. 1991, Su et al. 1993) In studies comparing doses of 40–240 mg/day of methyltestosterone in a double blind inpatient trial, irritability, mood swings, violent feelings, and hostility were greater during the high dose period than at baseline. Androgenic steroids' tendency to provoke aggression and irritability has raised concerns about violence toward family members by abusers. Prospective trials have reported mood disturbances in over 50% of body builders using anabolic steroids, as well as cognitive impairment including distractibility, forgetfulness, and confusion.

Dependence symptoms have included a withdrawal syndrome with common symptoms being fatigue, depressed mood, and desire to take more steroids. Other common dependence symptoms are using the substance more than intended, continuing to use steroids despite problems worsened by its use and the excessive spending of time relating to obtaining steroids. Because few clinical laboratories are equipped to conduct steroid tests and these tests are quite expensive, these signs of dependence and some common laboratory abnormalities are usually used to access the diagnosis.

Anabolic steroid abuse leads to hypertrophied muscles, acne, oily skin, needle punctures over large muscles, hirsutism in females, and gynecomastia in males. Heavy users can also develop edema and jaundice. Common laboratory abnormalities include elevated hemoglobin and hematocrit, elevated low-density lipoprotein cholesterol, elevated liver function tests, and reduced luteinizing hormone levels.

Mental health professionals may have these patients come to their attention due to the excessive aggression, loss of sexual ability, or mood disturbances. Treatment approaches are generally symptomatically oriented toward controlling the depressed mood and the psychotic features, but longer term interventions such as peer counseling by former body builders and group support may be of value.

Nitrite inhalants are sometimes considered within the category of inhalant abuse and produce intoxication with mild euphoria, muscle relaxation, and a change in time perception. Concern has been raised about their impairing immune functioning, a decrease in oxygen-carrying capacity of the blood and toxicity with severe headache, vomiting, and hypotension. No physical dependence or withdrawal syndrome has been described with these drugs, and a fuller discussion of them can be found in the section on inhalants.

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CHAPTER

# 54 Substance Abuse: Alcohol Use Disorders

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Alcohol Dependence
Alcohol Abuse

## Definition

Alcohol consumption occurs along a continuum, with considerable variability in drinking patterns among individuals. There is no sharp demarcation between "social" or "moderate" drinking and "problem" or "harmful" drinking. It is clear, however, that as the average daily amount of alcohol consumed and frequency of intoxication increase, so does the incidence of medical and psychosocial problems. The focus of this chapter is the alcohol use disorders which, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 1994), include alcohol abuse and alcohol dependence.

## Etiology and Pathophysiology

Alcohol dependence is a complex, multifaceted disorder which has long been recognized to run in families. There is substantial evidence from twin research and adoption studies that a major genetic component is operative in the development of dependence. Nonetheless, the disorder is etiologically complex, with a variety of other vulnerability factors (Gelernter 1995). It has been estimated that there is a sevenfold risk of alcohol dependence in first-degree relatives of alcohol-dependent individuals, with male relatives of male alcohol-dependent individuals having the greatest risk for the disorder. However, the majority of alcohol-dependent individuals do not have a first-degree relative who is alcohol dependent. This underscores the fact that the risk for alcohol dependence is also determined by environmental factors, which may interact in complex ways with genetics.

### Genetic/Environmental Contributions and Clinical Manifestations

In a review of population-based twin studies of alcohol dependence published since 1992, heritability estimates (i.e., the proportion of risk attributable to genetic factors) ranged between 0.52 and 0.64, with no substantial sex difference (Kendler 2001). One study conducted in Sweden using data from temperance board registration showed that the estimate of the genetic contribution to risk of the disorder was stable across four birth cohorts over a 50-year period, despite a rapidly changing social environment (Kendler et al.1997).

The majority of adoption studies have shown an excess of alcohol dependence in adopted-away offspring of biological parents (McGue 1994). Among studies conducted in the past 30 years, the risk ratio has varied between 1.6 and 3.6 in males and between 0.5 (an effect statistically indistinguishable from 1 or no effect) and 6.3 in females (McGue 1994).

Despite evidence that a genetic factor is influential in the transmission of alcohol dependence, exactly how risk of the disorder is transmitted remains unknown. Alcohol dependence appears to be a polygenic disorder with multiple genes acting either in additive or interactive ways. Two molecular genetic approaches that have been used to identify the genes that influence risk of alcohol dependence are candidate gene studies and linkage studies. Candidate gene studies are population-level investigations in which genetic loci that code for proteins thought to be important in the etiology of the disorder are examined in samples of unrelated individuals. In this approach, a statistical comparison of allele frequencies at

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the candidate locus is made between affected individuals and control subjects. In contrast, linkage studies are conducted at the family level. Individuals from families that manifest the disorder (or in the case of a putative protective effect, families that do not manifest the disorder) are examined genetically. Statistical methods are applied in an effort to identify regions of chromosomes that may contain disease genes.

## Candidate Gene Studies

The best-known example of genetic variation affecting risk for alcohol dependence involves candidate genes that are not directly relevant to alcohol's neuropharmacologic effects, including variant forms of the alcohol-metabolizing enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) (Gelernter 1995). The mechanism of this effect depends upon the metabolism of alcohol, first to acetaldehyde by ADH and then to acetate by acetaldehyde dehydrogenase. Acetaldehyde is toxic and produces a flushing reaction characterized by a set of uncomfortable symptoms including facial flushing, lightheadedness, palpitations, and nausea. Thus, increased metabolism of ethanol or decreased metabolism of acetaldehyde, either of which can result in increased acetaldehyde concentrations, produces an aversive effect which could decrease the risk of alcohol dependence. There is, in fact, evidence that a variant that greatly reduces or eliminates ALDH function (occurring mostly in Asian populations) is protective against alcohol dependence, and ADH variants that increase function may also be protective (Thomasson et al. 1991).

Genes encoding proteins in the serotonergic and opioidergic neurotransmitter systems have also been targeted as candidate genes for alcohol dependence. A polymorphism consisting of a repetitive sequence of base pairs in the promoter region of the serotonin transporter protein (genetic locus SLC6A4) is of particular interest. The allele with the smallest number of repeats, commonly called the "short" (S) allele, has lower transcriptional activity, leading to marked reductions in messenger ribonucleic acid (MRNA) levels, serotonin binding, and serotonin uptake in both platelets and lymphoblasts, compared with the "long" (L) allele (Greenberg et al. 1999). Findings from studies examining whether 5′-HTTLPR alleles are associated with alcohol dependence in humans are not consistent. Similarly studies focusing on the gene encoding the μ-opioid receptor (genetic locus OPRM1) have failed to provide convincing evidence of association to alcohol dependence.

## Linkage Studies

Two large linkage studies have been conducted in an effort to identify chromosomal regions that contain genes that modify risk for alcohol dependence. The larger of these two projects, the Collaborative Study on the Genetics of Alcoholism (COGA), includes more than 9,000 adults and nearly 1,500 children and adolescents (Hesselbrock et al. 2001). A genomic scan of the COGA samples showed that chromosomes 1 and 7 each have a region containing one or more genes that increase risk of alcohol dependence (Hesselbrock et al. 2001). In addition, COGA found evidence for a "protective factor" on chromosome 4 (Reich et al. 1998).

A linkage study has also been reported from a sample of 152 subjects belonging to extended pedigrees in a southwestern American-Indian tribe (Long et al. 1998). A genome-wide scan was performed on 172 sibling pairs from this sample. Evidence for linkage to alcohol dependence was obtained for regions on chromosomes 4 and 11. Three closely linked loci on chromosome 4 map onto the Type I ADH gene cluster in proximity to the region on this chromosome that was identified as linked to a "protective factor" by COGA.

These linkage studies, in parallel with candidate gene studies, may help to explain the specific mechanisms involved in the increased risk some individuals have for developing alcohol dependence and the interaction of genetic and environmental factors in its etiology.

## Etiological Subtypes of Alcoholics

Another approach to understanding the etiology of alcoholism is to identify distinct subtypes of persons with alcohol dependence. A variety of typologic approaches have been proposed to simplify the diverse phenomena associated with alcoholism (Hesselbrock and Hesselbrock 2006). These include unidimensional approaches based on drinking history, drinking pattern, severity of alcohol dependence, family history of alcoholism, gender, personality style, comorbid psychopathology, cognitive impairment, and sociopathy, as well as multidimensional approaches that combine these characteristics into meaningful clusters. One of the best known of these typologies is the Type 1/Type 2 distinction developed by Cloninger et al. (1981) from studies of adopted sons of Swedish alcoholics (see Table 54–1).

Type 1 alcoholics are characterized by the late onset of problem drinking, rapid development of behavioral tolerance to alcohol, prominent guilt and anxiety related to drinking, and infrequent fighting and arrests when drinking. Cloninger also termed this subtype "milieu-limited," which emphasizes the etiologic role of environmental factors. In contrast, Type 2 alcoholics are characterized by early onset of an inability to abstain from alcohol, frequent fighting and arrests when drinking, and the absence of guilt and fear concerning drinking. Cloninger postulated that transmission of alcoholism in Type 2 alcoholics was from fathers to sons, hence the term *male-limited* alcoholism. Differences in the two subtypes are thought to result from differences in three basic personality

**Table 54–1 Cloninger's Alcoholism Typology**

| | Type 1 | Type 2 |
|---|---|---|
| Onset of problem drinking | Late onset | Early onset |
| Tolerance | Rapid development of behavioral tolerance | Not specified |
| Mood issues | Prominent guilt and anxiety about drinking | Absence of guilt and anxiety about drinking |
| Personality traits | High reward dependence | Low reward dependence |
| | High harm avoidance | Low harm avoidance |
| | Low novelty seeking | High novelty seeking |

*Source*: Adapted from Cloninger CR, Bohman M, and Sigvardsson S (1981) Inheritance of alcohol abuse: Cross-fostering analysis of adopted men. Archives of General Psychiatry 38, 861–868. Copyright 1981 American Medical Association.

(i.e., temperament) traits, each of which has a unique neurochemical and genetic substrate (Cloninger 1987). Type 1 alcoholics are characterized by high reward dependence, high harm avoidance, and low novelty seeking. In contrast, Type 2 alcoholics are characterized by high novelty seeking, low harm avoidance, and low reward dependence.

Babor et al. (1992) used statistical clustering techniques to derive a dichotomous typology (Type A vs. Type B) similar to that proposed earlier by Cloninger. The analysis identified two homogeneous subtypes that may have important implications for understanding the etiology of different forms of alcoholism. Cloninger's Type 1 alcoholic shares with the Type A alcoholic a later onset of alcohol-related problems and the absence of antisocial characteristics. Cloninger's Type 2 alcoholic shares with the Type B alcoholic an early onset of alcohol-related problems and the presence of antisocial characteristics, particularly when intoxicated. The Type A/Type B classification has been successful in predicting outcome following alcoholism treatment (Litt et al. 1992). Its relevance to the matching of alcoholics to different psychotherapies has been supported by some studies (Litt et al. 1992) but not by others (Project MATCH Research Group 1997a, b).

Implicit in the subtyping theories that have been developed to explain different clinical varieties of alcoholism is the notion that there are a variety of plausible etiological factors in addition to or mediated by genetic predisposition. Three such factors are pharmacological vulnerability, affective dysregulation, and personality disorder. The evidence for pharmacological vulnerability as an etiological factor is based on studies showing reduced sensitivity to the effects of alcohol in adult children of alcoholics (Schuckit and Smith 1996, Pollock 1992). Other evidence comes from research on the effects of $ALDH_2$, $ADH_2$, and $ADH_3$ polymorphisms in individuals of Asian ancestry in which aversive reactions to the effects of alcohol are associated with reduced risk of alcohol dependence (Thomasson et al. 1993). A second etiological factor is affect dysregulation, which proposes that alcoholism is caused by repeated use of alcohol to 'self-medicate' negative affective states such as anxiety and depression. This theory is supported by research indicating strong associations between alcohol problems, mood disorders, and life stress (Kessler et al. 1997, Helzer and Pryzbeck 1988). The third etiological factor that has received considerable research support is deviance proneness or behavioral undercontrol, as indicated by hyperactivity, distractibility, sensation seeking, impulsivity, difficult temperament, and conduct disorder. These conditions are hypothesized to contribute to school failure and association with deviant peers, which then provide a context for heavy drinking and drug use (Sher and Trull 1994, Sher 1991).

In summary, despite considerable progress in the identification of risk factors for alcohol dependence, the interactions among genetic, familial, psychological, interpersonal, and environmental influences remain so complex that there is little consensus about etiology at this time.

## Pathophysiology

### Neuropharmacology

Taken in large doses, alcohol is considered to have anesthetic or depressive properties. It also has the ability to elicit euphoria when administered in small doses to susceptible persons (Begleiter and Porjesz 1999). This phenomenon may be mediated by direct activation by alcohol of the mesolimbic dopaminergic circuit, particularly the ventral tegmental area (VTA) and the nucleus accumbens (NAc) (Brodie et al. 1999). Anxiolysis and relaxation also appear to be part of the spectrum of the rewarding effects of alcohol, though these effects appear to be mediated by activation of GABAergic neurotransmitter system.

In contrast to other addictive substances (e.g., nicotine, cocaine, and opioids) and despite its significant effect on dopaminergic neurotransmission, the existence of specific alcohol binding sites on neuronal membranes has not been conclusively established. The lack of an alcohol receptor has led to the hypothesis that some alcohol effects, particularly those observed when it is administered at large doses, may be explained by disturbances in fluidity of the bi-layer lipid neuronal membrane. Changes in fluidity of neuronal membranes may affect the structure and function of neurotransmitter receptors and ion channels. However, this hypothesis has failed to explain alcohol-rewarding effects that occur at lower doses.

On the other hand, alcohol administration appears to have effects across the major neurotransmitter systems (i.e., opioidergic, serotonergic, GABAergic, and glutamatergic). These systems are affected by both acute and chronic alcohol administration. They appear to play a major role in mediating the rewarding effects of alcohol by modulating the firing of dopaminergic neurons in the VTA and the release of dopamine in the NAc.

### Opioidergic Neurotransmission

Findings derived from animal models of alcoholism support a relationship between alcohol administration and opioidergic neurotransmission. Hypothalamic synthesis, release, and binding of endogenous opioids such as beta-endorphin and enkephalin to μ-opiate receptors have been shown to be stimulated by alcohol administration (Eskelson et al. 1980). Disturbances in opioidergic neurotransmission have been reported among alcoholic patients and their unaffected adult children (i.e., paternal history–positive or PHP, Topel 1988). Both groups show lower plasma and cerebrospinal fluid (CSF) concentrations of beta-endorphin than adult children of nonalcoholic subjects (i.e., paternal history–negative or PHN; Gianoulakis et al. 1989), and after alcohol administration, PHP individuals show a greater increase or normalization of their beta-endorphin levels (Gianoulakis et al. 1989, 1996). These findings suggest that an inherited or acquired deficiency in endogenous opioid activity may be present among the offspring of alcoholics. This deficiency might lead them to drink to remediate this deficiency (opioid deficiency hypothesis; Gianoulakis et al. 1996). Further support for the opioidergic hypothesis of alcoholism derives from the study of opioid antagonism on alcohol consumption. Opioid antagonists reliably decrease alcohol preference across a range of experimental conditions and across different animal species. Several placebo-controlled clinical trials in humans show efficacy of the opioid antagonists naltrexone (Volpicelli et al. 1992, O'Malley et al. 1992, Anton et al. 2006) and nalmefene (Mason et al. 1999) as adjuncts to the psychosocial treatment of alcoholism (discussed later).

### Serotonergic Neurotransmission

Serotonin (5-HT) also appears to play a role in modulating alcohol consumption (LeMarquand et al. 1994a). In rodents acute administration of alcohol is associated with an increment in the brain concentration of 5-HT, and central infusion of 5-HT enhances dopaminergic tone in the VTA (Brodie and Bunney 1996). In contrast, chronic administration of alcohol is associated with low central nervous system (CNS) concentrations of 5-HT. This reduction in serotonergic tone after chronic ethanol administration appears to be associated with behavioral disinhibition and impulsive aggression (Higley et al. 1996). Administration of serotonin reuptake inhibitors decreases alcohol consumption in rodents that show preference for alcohol (Gill and Amit 1989). Whether this phenomenon is due to a dampening of the reinforcing effects of alcohol or to a generalized reduction of consummatory behaviors is unclear (Gill and Amit 1989).

Data derived from humans also has suggested that disturbances in central serotonergic functioning may be involved in alcohol and drug dependence, particularly among substance-dependent patients diagnosed with a comorbid antisocial personality disorder. For example, in comparison to controls, antisocial alcoholics have lower basal CSF levels of 5-HIAA (Virkkunen et al. 1994).

### GABAergic Neurotransmission

Behavioral responses to alcohol resemble the effects of pharmacological agents that predominantly affect GABAergic neurotransmission (i.e., benzodiazepines, barbiturates, and neurosteroids), suggesting a significant involvement of this system in the pharmacological effects of alcohol. Cross-tolerance with alcohol and the effectiveness of benzodiazepines and barbiturates in treating alcohol withdrawal symptoms also support this notion. Neurons that express $GABA_A$ receptors containing the alpha-1 subunit, such as cerebellar Purkinje neurons, appear to be sensitive to the effects of alcohol (Criswell et al. 1993). However, electrophysiologic responses to alcohol in neurons expressing $GABA_A$ receptors appear to be inconsistent (Harris 1999). It has been suggested that such inconsistencies may be due to the existence of alcohol-sensitive receptors and alcohol resistant receptors, determined by subunit composition and posttranslational processes (Mihic and Harris 1995). Strains of mice that differ in sleep sensitivity to alcohol (i.e., short sleep/long sleep [SS/LS] mice) show differential alcohol sensitivity of $GABA_A$ receptors. $GABA_A$ receptors in SS mice are resistant to alcohol, whereas $GABA_A$ receptors in LS mice are alcohol-sensitive (Allan and Harris 1986). Interestingly, individuals who are children of alcoholic fathers show increased resistance to induction of body sway and incoordination by alcohol administration. This finding suggests that people at risk for alcohol dependence experience decreased sensitivity to the effects of alcohol on the GABAergic system, and that this abnormality may be under genetic control (Schuckit 1994).

### Glutamatergic Neurotransmission

Alcohol also affects the glutamatergic neurotransmitter system. Acute administration of alcohol antagonizes *N*-methyl-d-aspartate (NMDA) receptors (where glutamate acts as an agonist), whereas chronic administration increases these receptor sites (Chu et al. 1995). This latter finding reflects the fact that alcohol withdrawal symptoms and other neurotoxic effects of alcohol are mediated by glutamate. Furthermore, alcohol withdrawal appears to be associated with increased glutamate concentrations and decreased dopamine levels in the NAc (Dahchour et al. 1998). Findings concerning the efficacy of acamprosate (which exerts effects on the NMDA receptor) in the treatment of alcohol dependence suggest that this neurotransmitter system may have a major role in the disorder (Kranzler et al. 2000).

### Cholinergic Neurotransmission

Studies in rodents have shown that the alcohol-induced dopamine release in the NAc can be antagonized by the central nicotinic receptor antagonist mecamylamine (Söderpalm et al. 2000). These findings suggest that the mesolimbic dopamine-activating and reinforcing effects of alcohol are both mediated in part by central nicotinic acetylcholine receptor activation. In healthy humans (Blomqvist et al. 2002), pharmacological manipulation of the nicotinic cholinergic receptor with mecamylamine reduces the stimulant effects of acute alcohol administration during the ascending limb of the blood alcohol curve. This finding suggests that blockade of nicotinic receptors may be a useful strategy in reducing alcohol consumption in alcoholics.

In summary, alcohol's rewarding effects appear to be mediated by activation of the mesolimbic dopaminergic circuit particularly the VTA and the NAc. Alcohol reinforcement can also be explained by its effects on major neurotransmitter systems (i.e., opioidergic, serotonergic, GABAergic, glutamatergic and cholinergic) modulating the firing of dopaminergic neurons in the VTA and the release of dopamine in the NAc.

## Assessment and Differential Diagnosis

### Phenomenology and Variations in Presentation

Diagnostic criteria for alcohol use disorders in DSM-IV-TR (American Psychiatric Association 1994) are very similar to those employed in the *International Classification of Diseases*, Tenth Edition (ICD-10) (World Health Organization 1992), which in turn were based upon the alcohol dependence syndrome (ADS) concept of Edwards and Gross (1976). ADS is a conception of alcoholism that includes biological, cognitive, and behavioral elements.

The DSM-IV-TR diagnosis of *alcohol dependence* is given when three or more of the seven criteria are present (see DSM-IV-TR for alcohol dependence). Because physiological dependence is associated with greater potential for acute medical problems (particularly acute alcohol withdrawal), the first criteria to be considered are tolerance and withdrawal. The remaining criteria reflect the behavioral and cognitive dimensions of ADS: (a) impaired control (i.e., alcohol is consumed in larger amounts or over a longer period of time than was intended; there is a persistent desire or unsuccessful efforts to cut down or control drinking; the individual continues to drink despite knowledge of a persistent or recurrent physical or psychological problem), and (b) increased salience of alcohol (i.e., a great deal of time spent drinking or recovering from its effects; important social, occupational, or recreational activities are given up or reduced due to drinking).

### Alcohol Dependence

### Alcohol Abuse

Once a diagnosis of alcohol dependence is given, a specification is made concerning course. *Early remission* is used if no criteria (*full remission*) or fewer than three symptoms (*partial remission*) of alcohol dependence are present for at least 1 month, but less than 12 months. *Sustained remission* is used if no symptoms (*full remission*) or fewer than three symptoms (*partial remission*) of alcohol dependence are present for at least 12 months. Finally, if the individual is in a setting in which he or she has no access to alcohol, the course specifier *in a controlled environment* is added.

*Alcohol abuse* is considered to be present only if the individual's drinking pattern has never met criteria for alcohol dependence and he or she demonstrates a pattern of drinking that leads to clinically significant impairment or distress, as evidenced by one or more of the four criteria in DSM-IV-TR for alcohol abuse.

Clinical Vignettes 1 and 2 provide case histories that illustrate the clinical presentation of various alcohol use

**DSM-IV-TR Criteria**

**Alcohol Dependence**

A maladaptive pattern of drinking as manifested by three or more of the following during a 12-month period:

(1) Tolerance, that is, either:
  (a) a need for markedly more alcohol to achieve intoxication
  (b) markedly diminished effect despite continued consumption of the same amount of alcohol

(2) Withdrawal, that is, either:
  (a) two or more signs or symptoms (autonomic hyperactivity, tremor, insomnia, nausea or vomiting, transient illusions or hallucinations, psychomotor agitation, anxiety, grand mal seizures) within several hours of stopping or reducing heavy, prolonged drinking
  (b) consuming alcohol or a related substance (e.g., benzodiazepines) to relieve or avoid withdrawal symptoms

(3) Alcohol is often consumed in larger amounts or over a longer period than was intended

(4) There is a persistent desire to cut down or control drinking

(5) A great deal of time is spent in drinking or recovering from drinking

(6) Important social, occupational, or recreational activities are given up or reduced because of drinking

(7) Drinking is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.

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**DSM-IV-TR Criteria**

**Alcohol Abuse**

A maladaptive pattern of drinking as manifested by one or more of the following during a 12-month period:

(1) Recurrent drinking resulting in a failure to fulfill major role obligations at work, school, or home

(2) Recurrent drinking in situations in which it is physically hazardous

(3) Recurrent alcohol-related legal problems

(4) Continued drinking despite having persistent or recurrent social or interpersonal problems caused or exacerbated by drinking

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**Clinical Vignette 1**

Mr. B is a 40-year-old, married, African-American grocery store owner who presents in a hospital's emergency department at 5 am complaining of nausea, followed by vomiting of bright red blood. He is accompanied by his 19-year-old daughter, who succeeded in convincing her father to go to the hospital, rather than to work. Mr. B had no history of hospitalizations. He denied recent medical or psychiatric problems, saying he had not been to a doctor's office for more than 15 years. Mr. B denied use of illicit or prescription drugs. Although he admitted drinking on a daily basis, he said he wasn't an alcoholic. Upon specific questioning he revealed that he drank only beer, consuming in excess of 12 cans each day. Over the preceding 2 years he had been drinking only beer, but prior to that time he drank vodka on a daily basis, often in excess of a pint per day. He became increasingly alarmed, agitated, and tremulous as the interview progressed.

Family history provided by the patient's daughter revealed that both of the patient's parents were deceased. His father, who was alcoholic, had died from a myocardial infarction at age 42 years. His mother developed alcohol dependence after her husband's death; she died of stomach cancer at age 55 years. Mr. B married at age 20 years and was divorced due to problems related to his drinking. There had been repeated marital conflicts over the 6 years prior to divorce, twice resulting in separations. The couple's only child lived with her mother, but came to stay with her father when she learned that he was feeling ill.

In the emergency department, Mr. B was kept nothing by month (*nil per os* (npo)) and intravenous fluids were begun for hydration. Suction through a nasogastric tube produced 5 cc of dark, clotted blood. Emergency endoscopy showed inflamed, hemorrhagic gastric mucosa, with no active bleeding. There were no indications of esophageal varices, Mallory–Weiss tears, or other lesions. Prior to endoscopy the patient received lorazepam 2 mg IV, which dramatically reduced his agitation. He was then admitted to the medical service. The next day he agreed to be seen in consultation by a psychiatrist.

*(continues)*

Clinical Vignette 1 *continued*

During the interview with the psychiatrist, Mr. B admitted that he had previously come to the hospital with many of the same symptoms, although he had not previously vomited blood. Each time he had been treated with drugs that helped him calm down. He acknowledged that he had been told his symptoms resulted from heavy drinking, but he denied drinking "any more than most people." Two years earlier he had switched from vodka to beer and had limited his intake to 6 beers per day in an effort to avoid the gastrointestinal problems. Although he had felt some nervousness and malaise at that time, his abdominal pain and nausea gradually improved. Subsequently, his beer consumption gradually increased and during the preceding 3 months the gastrointestinal symptoms reappeared.

The patient first consumed alcohol at age 14. He began regular drinking at age 18 years, drinking about a 6-pack of beer, 2–3 times per week after work or on weekends. At age 26 years he started his own business. The pressures of owning a business, combined with the freedom it permitted, led him to drink daily. As his consumption increased he found that drinking beer at work was too conspicuous, so he began drinking vodka, which he could do surreptitiously. As his business gradually floundered, he became increasingly irritable both at work and at home. Mr. B began arguing regularly with his wife, who complained about his drinking. Eventually, his wife and daughter moved to a house in a neighboring town.

The patient denied ever having experienced a seizure, but acknowledged multiple blackouts following particularly heavy drinking. Over the preceding year he had begun drinking beer early in the day to steady his hands. Toward the end of the interview, Mr. B stated that recently he had begun to think that what people had been telling him about his drinking was true. He exclaimed loudly, "I've had enough. What can I do about this? I'm willing to try anything now." Upon resolution of his gastric hemorrhage and alcohol withdrawal symptoms, Mr. B was referred to a partial hospitalization program for rehabilitation.

Final DSM-IV-TR Diagnoses:

I. Alcohol Dependence, with physiological dependence; Alcohol Withdrawal, with perceptual disturbances
II. None
III. Upper Gastrointestinal Bleeding (Hemorrhagic Gastritis) Macrocytic AnemiaAlcoholic Hepatitis

Clinical Vignette 2

Ms. C is a 28-year-old, white female, who separated from her husband 3 years ago. She is the mother of a 2-year-old boy and 6- and 12-year-old girls. The patient has been unemployed for 6 months, her most recent job having been as a barmaid. She was referred for substance abuse treatment from court, following arraignment on a charge of possession of narcotics. After 4 days in an inpatient rehabilitation program, she had stopped going to group meetings, spending most of her time alone in her room crying. She aroused particular concern in the treatment staff when she reported feeling that her life was no longer worth living. During the preceding year the patient had twice attempted suicide by taking an overdose of pills that she bought illicitly. On both occasions she was hospitalized briefly for observation.

When interviewed by the program psychiatrist, Ms. C complained that she missed her children too much to remain in treatment. With the help of her mother, she had been caring for her children, though the situation was being monitored by the child welfare agency after a charge of neglect had been filed by the children's paternal grandmother. Ms. C acknowledged that completion of the rehabilitation program would probably help her to retain custody of her children, but she reported that she felt sad and discouraged, especially during the evening. She described recurrent periods of depressed mood since age 14 years, associated with initial and middle insomnia, low energy level and poor self-esteem. She had been suffering from these symptoms for approximately 2 months prior to admission. She also complained of decreased appetite and concentration, but denied recent weight loss, anhedonia, psychomotor retardation, or current suicidal ideation. When pressed concerning the onset of depressive symptoms, Ms. C indicated that they were generally worse when she used alcohol and cocaine heavily.

A substance use history revealed that Ms. C had begun smoking cigarettes when she was 11 years old, becoming a regular smoker at age 12. At the time of admission she was smoking about 1 pack of cigarettes daily. She also reported consuming alcohol and cannabis regularly for 13 years. She first drank alcohol at age 12, beginning regular drinking while a freshman in high school. Shortly thereafter she was introduced to marijuana, which she gradually increased to daily use, a practice that she continued until the time of admission. She began heavy drinking (up to 10 beers per day, 3–4 times per week) when she was 17 years old and a junior in high school. Since that time her drinking gradually increased, such that during the month prior to admission the patient reported drinking about a pint of spirits daily. She also reported a 5-year history of regular cocaine use, initially intranasally. Two years prior to admission she began smoking the drug and during the month prior to admission she reported smoking about $100 worth of cocaine 2−3 times per week. Although she had experimented with LSD, diazepam, and intranasal heroin, she denied regular or recent use of these drugs. She also denied intravenous drug use. One month earlier she was found to be HIV seronegative. The patient had never before been treated for substance abuse.

The patient acknowledged having a number of alcohol- and drug-related problems, especially the legal and child custody issues. Although her husband is also a substance abuser, she felt that her substance use had contributed to their breakup. While intoxicated they both became verbally and at times physically abusive toward one another. After not drinking for a day she often became tremulous and felt nauseated and weak. She denied any history of delirium tremens. While smoking cocaine she had on occasion become alarmed by a painful tightness in her chest, accompanied by palpitations and by transient paranoid ideation.

Family history revealed that both of the patient's parents were alcoholic, her father having died of cirrhosis of the liver when Ms. C was 16 years old. The patient's mother was in recovery, with nearly ten years of sobriety. The patient's paternal grandfather, who had also been alcoholic, died before she was born. Ms. C is an only child. She reported that alcohol was readily available in her house and that sharing it with high school friends enhanced her popularity. She did well in school until 7th grade, when she began to find school boring. Ms. C was first arrested for shoplifting when she was 14 years old. She also began to have behavior problems

at school around that time and was suspended for stealing money. At age 16 years, Ms. C left school due to her first pregnancy. She was subsequently arrested for shoplifting, disturbing the peace, and immediately prior to admission, for possession of cocaine.

Based upon the history and symptomatology at the time of evaluation, the psychiatrist decided to postpone pharmacotherapy pending longitudinal evaluation of her depressive symptoms. Daily monitoring of symptoms was implemented using the Beck Depression Inventory (BDI) (Beck et al. 1961). In addition, cognitive-behavioral therapy of depression was initiated by the addiction counselor who had been working with Ms. C. Over the subsequent week the patient's depressive symptoms declined (with the BDI score decreasing from 25−19), but she continued to have difficulty participating in the treatment program. Fluoxetine 20 mg every morning was initiated and was well tolerated during the subsequent week. After completing the 21-day inpatient program, the patient was discharged to outpatient aftercare, where medication management was continued.

Final DSM-IV-TR Diagnoses

I. Alcohol Dependence, with physiological dependence; Cocaine Dependence, Cannabis Dependence; Major Depressive Disorder
II. Antisocial Personality Disorder
III. None

disorders and the application of DSM-IV-TR diagnostic criteria in evaluating alcoholic patients. In addition to alcohol abuse and dependence, there is another important group of alcohol-related disorders described in DSM-IV-TR as alcohol-induced disorders. These will be described briefly before returning to a discussion of assessment issues.

## Alcohol Intoxication

A DSM-IV-TR diagnosis of alcohol intoxication is given when, shortly after alcohol consumption, there are maladaptive behaviors such as aggression or inappropriate sexual behavior, or there are psychological changes such as labile mood and impaired judgment. Clinical signs indicative of alcohol intoxication include slurred speech, lack of coordination, unsteady gait, nystagmus, impairment of attention and memory, and in the most severe cases, stupor and coma. Alcohol intoxication may also present with severe disturbances in consciousness and cognition (alcohol intoxication delirium), especially when large amounts of alcohol have been ingested or after alcoholic intoxication has been sustained for extended periods. Usually, this condition subsides shortly after alcohol intoxication ends. Physical and mental status examinations accompanied by analysis of blood and urine allow the clinician to rule out general medical conditions or psychiatric disorders mimicking this condition. In this regard, urine toxicology is a valuable tool in ruling out intoxication with benzodiazepines, barbiturates, or other sedatives that can present with a similar clinical picture. Collateral information from relatives or friends confirming the ingestion of alcohol is also useful

The blood alcohol level (BAL) is frequently used as a measure of alcohol intoxication, although this measure is less reliable in persons with a high degree of tolerance to alcohol. Alcohol is metabolized in the average adult at a rate of 1 oz or 7−10 g/hr. When this clearance rate is surpassed, signs of alcohol intoxication begin to appear. During the ascending limb of the BAL curve, euphoria, anxiolysis and mild deficits in coordination, attention, and cognition can be observed at levels between 0.01 and 0.10%. Marked deficits in coordination and psychomotor skills, decreased attention, ataxia, impaired judgment, slurred speech, and mood lability can be observed at a greater BAL. Severe intoxication, characterized by lack of coordination, incoherent thoughts, confusion, nausea, and vomiting can be observed at BALs between 0.20 and 0.30. However, at these levels some heavy drinking individuals who have developed tolerance to the effects of alcohol may not appear intoxicated and may perform well on psychomotor or cognitive tasks. Stupor and loss of consciousness often occur when the BAL is between 0.30 and 0.40. Beyond this level, coma, respiratory depression, and death are possible. It should also be noted that alcohol intoxication is often associated with toxicity and overdose with other drugs, particularly those with depressant effects on the CNS.

## Alcohol Withdrawal

Alcohol withdrawal is a condition that follows a reduction in alcohol consumption or an abrupt cessation of drinking in alcohol-dependent individuals. In addition to significant distress, alcohol withdrawal is also associated with impairment of social, occupational, and other areas of functioning. Uncomplicated cases of alcohol withdrawal are characterized by signs and symptoms of autonomic hyperactivity, and may include increased heart rate, increased blood pressure, hyperthermia, diaphoresis, tremor, nausea, vomiting, insomnia, and anxiety. Onset of symptoms of uncomplicated alcohol withdrawal usually occurs between 4 and 12 hr following the last drink. Symptom severity tends to peak around the second day, usually subsiding by the fourth or fifth day of abstinence. After this period, less severe anxiety, insomnia, and autonomic symptoms may persist for a few weeks, with some individuals experiencing a protracted alcohol-withdrawal syndrome up to 5 or 6 months after cessation of drinking. A small but significant number of alcohol dependent individuals (10%) can experience complicated alcohol-withdrawal episodes. Alcohol withdrawal delirium (also known as delirium tremens) can occur in 5% of the cases, usually between 36 and 72 hr following alcohol cessation. In addition to signs of autonomic hyperactivity, this condition is characterized by illusions, auditory, visual, or tactile hallucinations, psychomotor agitation, fluctuating cloudiness of consciousness, and disorientation. Grand-mal seizures associated with alcohol-withdrawal occur in 3−5% of the cases, typically within the first 48 hr following reduction or cessation of drinking. In both instances of complicated alcohol withdrawal, lack or delay in instituting proper treatment is associated with an increased mortality rate. Prior history of delirium tremens and/or alcohol-withdrawal seizures, older age, poor nutritional status, comorbid medical conditions, and history of high tolerance to alcohol are predictors of increased severity of alcohol withdrawal.

## Alcohol-Induced Persisting Amnestic Disorder (AIPAD)

Continuous heavy alcohol consumption can lead to several neurological deficits caused by thiamin deficiency. Among

them, AIPAD, also known as a Korsakoff's psychosis, due to the fantastic confabulatory stories described by patients suffering this condition) is prominent. Profound deficits in anterograde memory and some deficits in retrograde memory characterize this condition. Patients cannot retain or learn new information and experience profound disorientation to time and place. The severity of anterograde memory deficits typically leads Korsakoff's patients, who are unaware of their deficit, to reconstruct forgotten events by confabulating. Korsakoff's amnestic disorder is usually preceded by several episode of Wernicke's encephalopathy, characterized by confusion, ataxia, nystagmus, and gaze palsies. When this condition subsides, the characteristic memory deficits of Korsakoff's psychosis become prominent.

Cessation of drinking can lead to an improvement in memory with approximately 20% of the cases demonstrating complete recovery. However, in most cases memory deficits remain unchanged, and in some instances long-term care is needed despite sobriety.

### Alcohol-Induced Persisting Dementia

Continuous heavy drinking is also associated with progressive and gradual development of multiple cognitive deficits characterized by memory impairment, apraxia, agnosia, or disturbances in executive functioning. These deficits cause serious impairment in social and occupational functioning and persist beyond the duration of alcohol intoxication and alcohol withdrawal. History, physical exam, and laboratory tests should be utilized to determine whether these deficits are etiologically related to the toxic effects of alcohol use. Other factors associated with this condition are poor nutritional status and vitamin deficiencies, as well as history of head trauma. It is believed that this condition is associated with the repeated occurrence of Wernicke's encephalopathy. Atrophy of frontal lobes and increased ventricular size have been described in this condition. Continuous alcohol consumption exacerbates the dementia, whereas drinking cessation is associated with improvement and even recovery of cognitive deficits.

### Alcohol-Induced Mood Disorder (AIMD)

AIMD, characterized by depressed mood and anhedonia, as well as elevated, expansive, or irritable mood, frequently develops as a consequence of heavy drinking. Onset of symptoms can occur during episodes of alcohol intoxication or withdrawal, and may resemble a primary major depressive, manic, hypomanic, or a mixed episode. In contrast to the dysphoria and lack of energy observed during episodes of alcohol withdrawal, severity, and duration of alcohol-induced mood symptoms are greater than what is usually expected, warranting independent attention by the clinician. Although mood disturbances are common among alcoholic patients entering treatment (80%), alcohol-induced mood symptoms tend to subside within 2–4 weeks following alcohol cessation. Evidence that the mood disturbances are not better explained by a primary mood disorder should be sought by the clinician. Evidence suggesting a primary mood disorder includes onset of mood symptoms preceding onset of alcohol abuse and persistence of mood symptoms after alcohol cessation or during extended periods of abstinence. Regardless of the primary or secondary nature of mood symptoms, given the high prevalence of suicide among alcoholics, clinicians should closely monitor the patient for emerging suicidal thoughts, implementing more intensive treatment (discussed later) if necessary.

### Alcohol-Induced Anxiety Disorder (AIAD)

Although alcohol has anxyolitic properties at low doses, heavy alcohol consumption can induce prominent anxiety symptoms. Alcohol-induced anxiety (AIA) symptoms more commonly include generalized anxiety symptoms, panic attacks, and phobias. In order to establish this diagnosis, clinicians must rule out other general medical conditions or psychiatric disorders that can mimic this problem. AIA may develop during alcohol intoxication or withdrawal, but its severity and duration are typically worse than the anxiety normally observed during the course of these conditions. An onset of drinking preceding the anxiety syndrome, and improvement or remission of anxiety during periods of abstinence, suggest AIAD. Monitoring the course of these symptoms for several weeks after alcohol cessation can be useful in determining their nature. Usually, a substantial improvement of anxiety will be observed during this period, suggesting a direct relationship of anxiety to alcohol. In some cases, a full remission of symptoms is not observed until after 3–4 weeks of abstinence.

### Alcohol-Induced Psychotic Disorder

This disorder is characterized by prominent hallucinations or delusions that are judged by the clinician to be due to the effects of alcohol. The psychotic symptoms usually occur within a month of an alcohol intoxication or withdrawal episode, and the patient is characteristically fully alert and oriented, lacking insight that these symptoms are alcohol-induced. Although onset of psychotic symptoms can occur during or shortly after alcohol intoxication, delirium or alcohol withdrawal delirium, alcohol-induced hallucinations, and/or delusions do not occur exclusively during the course of these conditions. Evidence that hallucinations and delusions are not part of a primary psychotic disorder include: atypical or late age of onset of psychotic symptoms, onset of alcohol drinking preceding the onset of psychiatric symptoms, and remission of psychotic episodes during extended periods of abstinence. Usually, alcohol-induced psychotic symptoms tend to subside within a few weeks of abstinence, although in a subset of patients psychotic symptoms can become chronic, requiring long-term treatment with antipsychotic medication. In these cases clinicians are obligated to consider a schizophrenic or a delusional disorder as part of the differential diagnosis.

### Alcohol-Induced Sleep Disorder (AISD)

Heavy alcohol consumption can be associated with a prominent disturbance of sleep. At intoxicating BALs, especially when blood alcohol levels are declining, sedation and sleepiness can be observed. Alcohol intoxication induces an increase in nonrapid eye movement (NREM) sleep, whereas rapid eye movement (REM) sleep density decreases. Subsequently, there is an increase in wakefulness, restless sleep, and vivid dreams or nightmares related to a reduction in NREM sleep and a rebound in REM sleep density. During alcohol withdrawal, sleep is fragmented and discontinuous with an increase in REM sleep. After withdrawal, patients

frequently complain of sleep difficulties and may experience superficial and fragmented sleep for months or years.

In contrast to the primary sleep disorders (PSD), AISD is characterized by an onset of drinking preceding the sleep disturbance and by remission of symptoms during the course of sustained abstinence. AISD can occur during the course of a typical alcohol intoxication or alcohol withdrawal episode. However, duration and severity of the sleep disturbances exceed those typically observed during these conditions. Given that protracted alcohol-withdrawal symptoms are frequent among abstinent alcoholics, onset of AISD can occur up to 4 weeks after initiation of alcohol abstinence. History of a previous PSD and/or persistence of sleep disturbances for more than 4 weeks following intoxication or acute withdrawal are highly suggestive of a PSD. Differential diagnosis is complicated by the fact that heavy alcohol consumption can co-occur and exacerbate other psychiatric disorders that present with sleep disturbances (e.g., mood disorders, anxiety). Alcohol consumption can also intensify other sleep problems such as narcolepsy or breathing-related sleep disorders.

### Alcohol-Induced Sexual Dysfunction

Although small doses of alcohol in healthy individuals appear to enhance sexual receptivity in women and facilitate arousal to erotic stimuli in men, continuous and/or heavy drinking may cause significant sexual impairment. Alcohol-induced sexual dysfunction is characterized by impaired desire, impaired arousal, and impaired orgasm, or sexual pain. It is also associated with marked distress or interpersonal conflicts. Onset of these impairments usually occurs during alcohol intoxication but duration of symptoms exceeds the uncomplicated course of alcohol intoxication. Symptoms usually subside after 3−4 weeks of alcohol abstinence. Persistence of symptoms beyond this time may suggest a primary sexual dysfunction or a sexual dysfunction due to the medical complications of alcoholism (e.g., neuropathy, alcoholic-liver disease). Onset of a recurrent sexual dysfunction preceding the onset of alcohol abuse also suggests a primary disorder. Use of other substances, particularly those prescribed for the treatment of alcohol withdrawal such as benzodiazepines or barbiturates, should be ruled out as a cause of the sexual dysfunction.

## Assessment of Alcohol Use Disorders

Comprehensive assessment provides the basis for an individualized plan of treatment. Depending upon the severity of alcohol dependence, the nature of comorbid medical and psychiatric pathology, the presence of social supports, and evidence of previous response to treatment, decisions can be made concerning the most appropriate intensity, setting, and modality of treatment.

Although denial of alcohol-related problems is legendary among alcoholics, there is substantial evidence that a valid alcohol history can be obtained, given adequate assessment procedures and the right conditions (Babor et al. 1990). A complete alcohol history should include specific questions concerning average alcohol consumption, maximal consumption per drinking occasion, frequency of heavy drinking occasions, and drinking-related social problems (e.g., objections raised by family members, friends, or people at work), legal problems (including arrests or near-arrests for driving while intoxicated (DWI)), psychiatric symptoms (e.g., precipitation or exacerbation of mood or anxiety symptoms), and alcohol-related medical problems (e.g., alcoholic gastritis or pancreatitis).

It is crucial that questions concerning alcohol consumption and related problems be asked nonjudgmentally in order to enhance the likelihood of accurate reporting. The optimal approach to history-taking begins with reassuring the patient that information provided will be kept confidential. The interviewer should first ask questions that are least likely to make the patient defensive (e.g., a review of systems or psychiatric symptoms, without relating these to alcohol use), and begin questions with *how*, rather than with *why*, to reduce the appearance of being judgmental (Schottenfeld 1994).

### Screening

Systematic clinical assessment often begins with routine screening to identify active cases, as well as persons at risk. During the past 25 years, a number of self-report screening tests have been developed to identify alcoholics as well as persons at risk of alcohol problems. Perhaps the most widely used alcohol screening test is the CAGE Test (Ewing 1984), which contains only four questions: (1) Have you ever felt you ought to *cut* (the "C" in CAGE) down on your drinking? (2) Have people *Annoyed* (A) you by criticizing your drinking? (3) Have you ever felt bad or *Guilty* (G) about your drinking? (4) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover that is, an *Eye* opener (E)? Reliability and validity studies of this test have been conducted in diverse samples (e.g., psychiatric inpatients, ambulatory medical patients, prenatal clinics), with generally acceptable levels of sensitivity (Babor and Kadden 1985). There are several variants on the CAGE. For example, the TWEAK (Russell et al. 1991) contains slight modifications of the items (Tolerance, Worried, Eye-opener, Amnesia, Cutdown) that are geared toward pregnant women.

The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al. 1993, Babor and Higgins-Biddle 2001a), a 10-item screening instrument, may be used as the first step in a comprehensive and sequential alcohol use history. The AUDIT (Table 54–2) covers the domains of alcohol consumption, alcohol dependence, and alcohol-related consequences. It has been shown to be sensitive and specific in discriminating alcoholics from nonalcoholics, and is superior to other tests in identifying hazardous drinkers, that is, those heavy drinkers who have not yet experienced serious harm from their drinking. The AUDIT total score increases with the severity of alcohol dependence and related problems, and can be used as part of a comprehensive approach to early identification and patient placement (Babor and Higgins-Biddle 2001a, 2001b). Because the misuse of both prescribed and illicit drugs is common among alcoholics, screening should also include other psychoactive substances, including tobacco products.

### Psychiatric History and Examination

Diagnostic assessment in specialized treatment facilities, such as detoxification centers, residential programs, partial hospital programs, and outpatient clinics, should be

**Table 54–2 Alcohol Use Disorders Identification Test**

| | | | | |
|---|---|---|---|---|
| 1. How often do you have a drink containing alcohol? | | | | |
| (0) Never | (1) Monthly or less | (2) Two to four times a month | (3) Two or three times a week | (4) Four or more times a week |
| 2. *How many drinks containing alcohol do you have on a typical day when you are drinking? (Code number of standard drinks) | | | | |
| (0) 1 or 2 | (1) 3 or 4 | (2) 5 or 6 | (3) 7 or 8 | (4) 10 or more |
| 3. How often do you have 6 or more drinks on one occasion? | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 4. How often during the last year have you found that you were not able to stop drinking once you had started? | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 5. How often during the last year have you failed to do what was normally expected from you because of drinking? | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 7. How often during the last year have you had a feeling of guilt or remorse after drinking? | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 8. How often during the last year have you been unable to remember what happened the night before because you had been drinking | | | | |
| (0) Never | (1) Less than monthly | (2) Monthly | (3) Weekly | (4) Daily or almost daily |
| 9. Have you or someone else been injured as a result of your drinking? | | | | |
| (0) No | | (2) Yes, but not in the last year | | (4) Yes, during the last year |
| 10. Has a relative or friend or a physician or other health care worker been concerned about your drinking or suggested you cut down? | | | | |
| (0) No | | (2) Yes, but not in the last year | | (4) Yes, during the last year |
| Record sum of individual item scores here _____. | | | | |

*The AUDIT is scored by adding the numerical values associated with each response category. Scores between 8 and 15 suggest the initiation of brief advice focused on the reduction of hazardous drinking. Scores between 16 and 19 suggest brief counseling and continued monitoring. Scores of 20 or above clearly warrant further diagnostic evaluation for possible alcohol dependence.

conducted with a standard interview schedule. If it is not possible to use a complete psychiatric interview, such as the Composite International Diagnostic Interview (CIDI) (Robins et al. 1989) or the Structured Clinical Interview for DSM (SCID) (First et al. 1996), then the alcohol sections of these interviews should be used. Given the lack of reliability in unstructured clinical diagnosis, it is imperative that programs specializing in the treatment of alcohol dependence use a structured interview to conduct and report their diagnostic evaluations.

An important purpose of clinical assessment is to obtain an estimate of illness severity. The number of DSM symptoms obtained using a structured interview or the total score on the AUDIT screening test can serve this purpose. The Composite Score from the Drug and Alcohol section of the Addiction Severity Index (ASI) (McLellan et al. 1992) is another useful measure of severity.

Assessment of psychological function should focus on measures of depression, anxiety, and more global psychological distress. Instruments that are generally reliable, valid, and acceptable in a variety of health care settings include the Beck Depression Inventory (Beck et al. 1961) and the Symptom Checklist 90-Revised (Derogatis 1977). One subscale of the ASI assesses overall psychiatric severity, including number of inpatient and outpatient treatment episodes, medication status, and lifetime and current symptomatology (McLellan et al. 1992).

There has been considerable attention devoted to the role of motivation and patient readiness to change, as critical ingredients in treatment planning for alcoholics. The University of Rhode Island Change Assessment Scale (URICA) is a 32-item questionnaire designed to measure the stages of change across diverse problem behaviors (Prochaska and DiClemente 1992). The URICA score profiles have been used to predict treatment response in research on addictive behaviors such as smoking and alcoholism. The readiness to change questionnaire (RCQ) (Rollnick et al. 1992) is a shorter instrument developed for the same purpose.

## Relevant Physical Examination and Laboratory Findings

Medical illness is a common consequence of heavy drinking even in the absence of physical dependence. Early in the course of alcohol use disorders individuals may show no physical or laboratory abnormalities. But as drinking progresses, it is widely manifested throughout most organ systems. A thorough physical examination is indicated if, in the history, there is evidence of medical problems. The physical examination provides essential information about the presence and extent of end-organ damage, and should be focused on the systems most vulnerable to developing alcohol-related pathology: the cardiovascular system, the gastrointestinal system, and the central and peripheral nervous systems. The physician should also be alert to other acute alcohol-related signs, including alcohol withdrawal or delirium, intoxication or withdrawal from other drugs, and the acute presentation of psychiatric symptomatology. Other systemic or nonspecific health problems associated with alcohol dependence include malnutrition, muscle wasting, neuritis, specific vitamin deficiencies, infectious diseases (such as tuberculosis, dermatitis, pediculosis, and hepatitis), and trauma secondary to fights and accidents (Arif and Westermeyer 1988) (Table 54–3).

A variety of laboratory tests can be helpful in assessing the effects of alcohol consumption. Patients experiencing alcohol use disorders are typically reluctant to seek help

**Table 54–3 Health Problems Commonly Associated with Chronic Drinking, Acute Intoxication and Alcohol Dependence**

| |
|---|
| Malnutrition, muscle wasting, neuritis, vitamin deficiencies |
| Infectious diseases (e.g., tuberculosis) |
| Trauma secondary to fights, accidents |
| Self-inflicted injuries, suicide |
| Cancers (head and neck cancers, lever cancer, female breast cancer) |
| Maternal and perinatal conditions (low birth weight, intrauterine growth retardation) |
| Cardiovascular disease (e.g., ischaemic heart disease, cerebrovascular disease) |

or tend to underreport the frequency and intensity of their drinking. Diagnostic laboratory markers can help to detect individuals who deny or minimize their alcohol consumption. Laboratory testing can also help to resolve diagnostic dilemmas among patients whose self-report information and physical findings are inconclusive (Allen and Litten 2001).

Laboratory testing can also assist the clinician in providing objective, nonjudgmental feedback to alcoholic patients on the negative physical consequences of excessive drinking. Laboratory determinations should be repeated biweekly at the initial phase of treatment, and monthly during the aftercare. Results should be graphically presented to the patient in an easy-to-comprehend format with reference to normal values. This allows the patient to appreciate the decline and eventual stabilization of laboratory indexes, thereby enhancing motivation to maintain sobriety. Laboratory tests can also help to detect relapse to the extent they are sensitive to heavy drinking. Early identification of relapse can prevent the reinstatement of alcohol dependence. It can diminish adverse consequences of heavy drinking by promoting modifications to the original treatment plan and by prompting more aggressive therapeutic interventions.

Several laboratory tests, particularly those related to hepatic function (e.g., serum transaminases, bilirubin, prothrombin time, and partial thromboplastin time) have been commonly used by clinicians. Other laboratory tests (e.g., gamma-glutamyl transpeptidase (GGTP), carbohydrate-deficient transferrin (CDT), mean corpuscular volume (MCV) of erythrocytes) can be used as objective indicators of heavy drinking (Peterson 2004). Elevation in GGTP occurs in approximately three-fourths of alcoholics before there is clinical evidence of liver disease. It is considered to be one of the earliest indications of heavy alcohol consumption and is widely available clinically (Holt et al. 1981). GGTP levels usually return to normal limits after 4−5 weeks of abstinence (Salaspuro 1986). As with GGTP, elevations of the transaminases serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are common in other liver diseases. However, elevations in the transaminases are less sensitive indicators of heavy drinking, with SGOT being elevated in 32−77% of alcoholics, while elevations in SGPT have been observed in 50% of alcoholics (Holt et al. 1981). In contrast to the use of absolute values of SGPT and SGOT, the ratio of SGPT to SGOT may provide a more accurate indicator of heavy drinking. A ratio greater than 2 is more likely to be related to heavy alcohol consumption whereas a ratio below 1 would suggest a different etiology (Sharpe et al. 1996). Elevation of MCV, which has also been associated with folate deficiency, is more prominent in alcoholics, especially among those who are smokers. Though MCV can assist clinicians in identifying patients who are drinking excessively, particularly when this marker is used in combination with GGTP (or CDT), this is not an efficient indicator of relapse because of the 2−4-month period of abstinence that is needed for its normalization (Irwin et al. 1988).

CDT is more specific than most routine laboratory tests for the identification of heavy alcohol consumption (Peterson 2004). In contrast to GGTP, CDT elevations are associated with few conditions other than heavy drinking (Litten et al. 1995, Murawaki et al. 1997). Whenever possible, CDT and GGTP should be used together, with a positive case defined by elevated scores in either test. This approach increases the likelihood of identifying individuals experiencing alcohol use disorders (Allen and Litten 2001). CDT appears to detect relapse to heavy drinking among patients in alcohol treatment more accurately than other laboratory tests (Litten et al. 1995, Allen and Litten 2001).

In a clinical setting where laboratory results are generally not immediately available, the alcohol breath test, which measures the amount of alcohol in expired air (providing an estimate of venous ethanol concentration), is valuable. Although its accuracy depends on the patient's cooperation (which in an intoxicated patient is often problematic), the alcohol breath test can be a reliable and inexpensive method for assessing recent alcohol consumption. Venous blood levels should be obtained if dangerously high levels of intoxication are suspected, when a patient is comatose, or for medical–legal purposes. A BAL greater than 150 mg/dl in a patient showing no signs of intoxication (i.e., no dysarthria, motor incoordination, gait ataxia, nystagmus, or impaired attention) can be interpreted to reflect physiological tolerance (DSM-IV-TR) (American Psychiatric Association 1994, Holt et al. 1981). In nontolerant individuals, a BAL in excess of 400 mg/dl can result in death, and 300 mg/dl indicates a need for emergency care.

Another laboratory evaluation that is indicated in alcoholics is a urine toxicology screen. To identify drug use that the patient may not admit or recognize, including presption drug medications, the screen should include opiates, cocaine, cannabis, and benzodiazepines. Routine urinalysis, blood chemistries, hepatitis profile, complete blood count, and serologic test for syphilis and (for the female patient) serum testing for pregnancy should also be obtained.

## Gender and Developmental Presentations

There are substantial differences in the prevalence of alcoholism among different gender, age, and racial/cultural groups. Unfortunately, the high prevalence among young adult and middle-aged males often leads to inadequate consideration of the possibility that women and the elderly may drink excessively.

### *Women*

Women are more likely to abstain from alcohol, and if they do drink, they are more likely to consume less alcohol than men. Nevertheless, in comparison to men, problem drinking among women is more likely to be associated with negative mood states, particularly depression, anxiety, and somatic symptoms (Lesieur and Blume 1993). Alcoholic women

identify negative emotions and interpersonal conflicts as antecedents of a relapse to drinking more frequently than men (Annis and Graham 1995) and substance-dependent women more frequently report depressive and anxiety symptoms as motivators for treatment. These reports are consistent with epidemiological and clinical studies which show that women who are diagnosed with alcohol or drug dependence experience higher rates of mood and anxiety disorders than their male counterparts (Helzer et al. 1987). Furthermore, it is more common among women that mood and anxiety disorders precede the onset of substance use and dependence (Kessler et al. 1996). Alcoholic women have a *negative profile* of situations surrounding their alcohol use, characterized by solitary drinking and greater severity of alcohol dependence, whereas alcoholic men tend to have a *positive profile*, characterized by social drinking and drinking in the context of positive emotions (Annis and Graham 1995). Studies comparing male and female alcoholics (Parrella and Filstead 1988) have found that women are significantly older than men when a variety of alcohol-related milestones occur, including regular drunkenness, loss of control over drinking, first drinking problems, drinking to relieve withdrawal symptoms, first attempt to stop drinking, and realization that alcohol use is a problem. These studies have also found that women exhibit more rapid progression than men between the time of first regular intoxication and first treatment (Randall et al. 1999).

Despite drinking for fewer years at lower levels, women have an increased sensitivity to toxic effects of alcohol on body organs (Nixon 1993). Alcoholic women are more likely to develop liver damage and, in general, alcoholic liver diseases tend to progress faster among women than men (Becker et al. 1996). The five-year mortality rate among alcoholic women is almost twice the mortality rate of alcoholic men. Alcoholic women appear to be more susceptible to alcohol-induced brain damage, evidenced by greater widening of the cerebral sulci and fissures in CT scans of the brain (Jacobson 1986), as well as poorer performance in cognitive testing (Nixon 1993). The concept of "telescoping" has been used to describe the course of symptom progression observed among women who, despite beginning heavy drinking later than men, experience alcohol-related problems and seek treatment sooner than men (Piazza et al. 1989).

Since alcohol is distributed in the aqueous phase, greater body fat composition among women reduces the volume of distribution. This, combined with smaller average body mass, translates into higher BALs for women in response to a specified level of alcohol consumption (Goldstein 1992). In addition, less first-pass metabolism due to less gastric oxidation of ethanol may also contribute to the higher blood levels obtained by women following an equivalent dose of ethanol (Frezza et al. 1990). Compared with men, women with alcohol problems are also at greater risk of comorbid drug abuse/dependence (Lex 1992). Perhaps, as a consequence of these differences, women alcoholics who seek treatment do so earlier in the course of the disorder than do men (Nixon 1993).

Because heavy drinking among women is most prevalent during the childbearing years, it has important public health implications for prenatal alcohol exposure and possible fetal alcohol spectrum disorders (FASDs, Wattendorf and Muenke 2005). A variety of adverse outcomes have been related to heavy drinking in pregnant women, although the minimum amount of alcohol and the pattern of consumption necessary to produce such effects are not known. Heavy drinking in pregnant women may produce malnutrition in both the mother and the fetus, as well as spontaneous abortion, preterm delivery, and intrauterine growth retardation (Hannigan et al. 1992). FASDs are estimated to occur in as many as 1 in 100 live births (Finnegan and Kandall 1992). The most severe manifestation of FASD is fetal alcohol syndrome (FAS), a constellation of morphological and developmental defects resulting from high-dose prenatal alcohol exposure. FAS is estimated to occur in 1 in 1000 to 1 in 300 live births (Finnegan and Kandall 1992). Prenatal or postnatal growth retardation, CNS involvement, and characteristic facial dysmorphology are necessary for a diagnosis of FAS (Sokol and Clarren 1989).

Since FASDs can be avoided, the evaluation of pregnant patients should routinely include questions about alcohol and other substance use. Routine screening with an instrument such as the AUDIT, or the Tolerance-Annoyance, -Cut down, and -Eye opener (T-ACE test), supplemented by questions concerning drug use, may also be useful with pregnant women. The T-ACE, as described in Table 54–4, is the first screening test developed for pregnant women (Sokol et al. 1989). The T-ACE is used to screen for pregnancy risk drinking, defined here as the consumption of 1 ounce or more of alcohol per day while pregnant. Those pregnant women who are identified as high risk drinkers or drug users should be provided with a brief intervention, appropriate clinicial evaluation and referral, if necessary (Finnegan and Kandall 1992).

**Table 54–4 The T-ACE Screening Test***

| | |
|---|---|
| **T** | **Tolerance**: How many drinks does it take to make you feel high? |
| **A** | Have people **Annoyed** you by criticizing your drinking? |
| **C** | Have you ever felt you ought to **Cut down** on your drinking? |
| **E** | **Eye opener**: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? |

*According to Sokol et al. (1989), scores are calculated as follows: An answer of "more than two drinks" to question T is considered a positive response and counts for 2 points. Affirmative answers to questions A, C, and E are counted as 1 point for each. A total score of 2 or more points on the T-ACE indicates a positive screen for pregnancy risk drinking.

### *Adolescents*

There are a number of features that distinguish adolescents with alcohol abuse/dependence from adult alcoholics. As might be expected, adolescents have comparatively short histories of heavy drinking. A corollary to this is the rarity of physiological dependence on alcohol and alcohol-related medical complications among adolescents. Diagnosis of alcohol dependence is further complicated by the possible confusion of hangover symptoms with withdrawal phenomena, and the rapid development of alcohol tolerance (Winters 2001). Nonetheless, the use of alcohol and other psychoactive drugs contributes in important ways to morbidity and mortality in adolescents, the leading causes of which are motor vehicle accidents, homicide, and suicide. The values and behavior of the peer group are important

elements in the evaluation of alcohol use and abuse in the adolescent. The evaluation of adolescents with an alcohol disorder must also take into account other prominent developmental issues, including internal and externalizing disorders, as well as the conflict inherent in asserting one's independence from the family.

A number of instruments have been developed for the assessment of substance use symptoms and disorders in adolescents (Winters 2001). As is generally true in dealing with adolescents, given their economic and emotional dependence, whenever possible a thorough family evaluation is important for understanding the adolescent's substance use and related problems.

### *The Elderly*

Although heavy drinking is less prevalent in the elderly, it is nonetheless an important source of morbidity in this group. Elderly alcoholics suffer from more chronic medical problems and poorer psychosocial functioning than elderly nonalcoholics (Finlayson et al. 1988). The increased use of prescription medications in the elderly increases the potential for adverse pharmacokinetic interactions with alcohol. In addition, decreased cognitive functioning associated with heavy alcohol use can increase medication errors and noncompliance in this group (Ofman 1992).

The manifestations of alcohol dependence in the elderly are often more subtle and nonspecific than those observed in younger individuals (Ofman 1992, Graham 1986). Because self-reported alcohol consumption may be particularly unreliable in the elderly, other sources of information such as family and neighbors should be used to identify heavy drinkers (Graham 1986). The following areas should be systematically evaluated in the elderly when heavy drinking has been identified: untreated medical illness, prescription drug abuse, psychiatric comorbidity, cognitive impairment, functional assessment, and need for social services (Ofman 1992).

Similar to the approach used with younger adults, alcohol dependence in the elderly has been classified by age of onset. It has been estimated that about two-thirds of elderly alcoholics began heavy drinking prior to age 60, while the remaining one-third began heavy drinking after the age of 60 (Atkinson and Kofoed 1982). Late-onset alcoholism appears to be more common among women and people of higher socioeconomic status and is less frequently associated with a family history of alcoholism (Ofman 1992). As might be expected, older alcoholics with early-onset alcoholism also have more alcohol-related medical and psychosocial problems and are more likely to require alcoholism treatment (Ofman 1992),

## Epidemiology and Comorbidity

### International Patterns of Drinking and Types of Alcohol Problems

Alcohol in beverage form is among the most widely used psychoactive drugs in the world. Because of its widespread distribution and the readiness with which it is consumed in a variety of settings, people do not generally think of beverage alcohol as a drug. Nonetheless, its complex pharmacologic actions, including a panoply of psychoactive effects, have led societies throughout the world to surround alcoholic beverages with a variety of rules and regulations governing their use (Babor et al. 2003). Despite these efforts at control, excessive drinking, with its adverse effects is widespread.

Patterns of drinking and the types of problems associated with alcohol misuse differ markedly throughout the world (Room et al. 2002). While the highest alcohol consumption rates are generally found among the industrialized countries of Europe and the North American continent, the lowest consumption rates are found in developing countries that are dominated by Islam, which proscribes the use of alcohol. The percentage of drinkers in adult populations ranges from a high of 86% in the North and Central European countries to less than 10% of adults in Islamic countries such as Pakistan and Iraq (Room et al. 2002). According to recent estimates from the World Health Organization's (2007) Expert Committee, the evidence of alcohol's impact on health through its intoxicating, dependence-producing, and toxic qualities is extensive. Alcohol is estimated to cause a net harm of 3.7% of all deaths, and 4.4% of the global burden of disease, as measured in Disability Adjusted Life Years lost (DALYs). Neuropsychiatric disorders, mainly made up of alcohol use disorders, account for the highest proportion of alcohol-attributable DALYs.

In the wine-producing Mediterranean countries (i.e., Spain, Portugal, Italy, France, and Greece), the pattern of drinking and the type of alcoholism have historically been associated with the consumption of wine as a dietary supplement, as well as for its effects as a social lubricant, medicine, and stimulant for manual workers. Wine is typically consumed in moderation by a large segment of the population, and it is used more for its social and presumed nutritional value than for its psychological effects. Drunkenness is uncommon, considering the high level of daily consumption, and there are few legal restrictions on the availability of alcoholic beverages. However, given their high levels of alcohol consumption, it is not surprising that the wine-producing countries of Europe lead the world in many indicators of alcohol-related chronic health problems (Babor et al. 2003).

In contrast to the preponderance of wine drinking in the Mediterranean region, the use of distilled spirits predominates in the northern periphery of Europe. In countries such as Norway, Sweden, Finland, Poland and Russia, there is a separation of drinking from dietary functions and the deliberate use of alcohol to produce intoxication. Heavy drinking is concentrated in a relatively small portion of the male population. As might be expected from this pattern of drinking, problems in spirits-drinking countries consist largely of alcohol-related accidents, public intoxication, and social disruption. In the predominantly beer-drinking countries of Germany, Austria, Belgium, the US, and the UK, per capita consumption tends to be intermediate between the wine-drinking and spirits-drinking countries. These countries are characterized by more diversified drinking customs.

World trends in alcohol consumption indicate that levels of alcohol use have been stable or slightly decreasing in Western Europe and the US since 1960. Alcohol consumption in the US, for instance, dropped from 2.8 gallons of ethanol per person in 1982 to 2.2 gallons per person in 2004 (Lakins et al. 2006). After a period of increased

consumption that peaked in the late 1970s and early 1980s, alcohol consumption in African countries has also been in decline. Conversely Asian countries such as China, South Korea, and Thailand have experienced steady increases in alcohol consumption since the late 1970s (Babor et al. 2003, Room et al. 2002).

Advances in the assessment of drinking behavior and its consequences have made it possible to estimate the prevalence of alcoholism in different cultural contexts (Helzer and Canino 1992). Cross-national studies employing structured diagnostic interviews have found lifetime prevalence rates of alcohol abuse/dependence that vary from as low as 0.45% (among Chinese in Shanghai) to a high of 23% (among US-born Mexican-Americans) (Helzer and Canino 1992). In addition to the overall differences in lifetime prevalence rates in different countries, the prevalence of alcohol dependence varies considerably within countries as a function of demographic characteristics, such as sex, age, geographic region and population density (Helzer and Canino 1992, Substance Abuse and Mental Health Services Administration 2001).

## Patterns of Drinking and Types of Alcohol Problems in the US

Table 54–5 shows the prevalence rates of lifetime, past year, and past month drinking, including binge and heavy drinking, for different gender, age and racial/ethnic groups, as determined by the 2005 National Household Survey of Drug Use and Health (Substance Abuse and Mental Health Services Administration 2006). As shown in the table, the majority (87.8%) of the US population 18 and older has used alcohol in their lifetime, and more than half (55.9%) report current drinking. The highest rates of current use are among young adults aged 18−25 years, with males predominating. Non-Hispanic whites have the highest prevalence of drinking (91.4% lifetime use and 60.3% past month use), while Asians are least likely to drink (67.2% lifetime and 41.8% current). The prevalence of drinking is positively associated with education level; persons with less than a high school education are almost half as likely to report past month drinking as college graduates (36.7% compared to 69.4%).

Approximately one in four persons aged 18 years and older (24.1%) reported binge drinking (defined as five or more drinks per occasion) in the past month, and 7.1% reported heavy alcohol use (Table 54–5). Both binge and heavy drinking are more likely among men than women. Young adults aged 18−25 are twice as likely to binge drink and three times as likely to report heavy alcohol use compared to those 26 or older. Asians have the lowest levels of binge drinking and heavy alcohol use (13.9 and 2.2%, respectively), whereas Native Americans have the highest rates (36.2 and 12.8%, respectively).

Regarding the prevalence of alcohol disorders in the US, the most authoratitative estimates derive from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Grant et al. 2006). Based on face-to-face interviews with a national probability household sample of 43,093 adults 18 and older, the survey found that the past-year prevalence of DSM-IV-TR alcohol disorder was 8.5%, including 4.7% with alcohol abuse and 3.8% with alcohol dependence (Grant et al. 2006). In addition, the Substance Abuse and Mental Health Services Administration's (SAMHSA) collects data annually from approximately 70,000 persons aged 12 or older through the National Survey of Drug Use and Health (NSDUH). The 2005 NSDUH found the 1-year prevalence

**Table 54–5 Percentages of Adults Aged 18 or Older Reporting Lifetime Alcohol Use, Past Month Alcohol Use, Past Month Binge Drinking, and Past Month Heavy Alcohol Use, US, 2005**

| Demographic Characteristic | Lifetime | Past Month | Binge Use | Heavy Drinking |
|---|---|---|---|---|
| Total sample | 87.8 | 55.9 | 24.1 | 7.1 |
| Gender | | | | |
| Male | 91.2 | 63.3 | 33.0 | 11.2 |
| Female | 84.0 | 49.1 | 15.4 | 3.2 |
| Age | | | | |
| 18–25 | 85.7 | 60.9 | 41.9 | 15.3 |
| 26+ | 88.2 | 55.1 | 21.0 | 5.6 |
| Origin and race | | | | |
| Non-Hispanic White | 91.4 | 60.3 | 24.6 | 7.9 |
| Non-Hispanic Black | 81.4 | 45.3 | 22.7 | 4.8 |
| American Indian/Alaska native only | 86.5 | 46.9 | 36.2 | 12.8 |
| Native Hawaiian/Pacific Islander | * | * | 28.2 | 5.9 |
| Asian only | 67.2 | 41.8 | 13.9 | 2.2 |
| More than one race | 87.9 | 53.4 | 23.0 | 6.0 |
| Hispanic | 80.8 | 46.7 | 25.8 | 6.2 |
| Education | | | | |
| <High school | 75.3 | 36.7 | 23.2 | 6.0 |
| High school graduate | 86.7 | 50.3 | 25.1 | 7.5 |
| Some college | 92.0 | 61.0 | 26.9 | 8.7 |
| College graduate | 92.8 | 69.4 | 20.9 | 5.7 |

*Low precision; no estimate reported.

*Note*: "Binge" Alcohol Use is defined as drinking five or more drinks on the same occasion on at least 1 day in the past 30 days. By "occasion" is meant at the same time or within a couple hours of each other. Heavy Alcohol Use is defined as drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days; all Heavy Alcohol Users are also "Binge" Alcohol Users.

*Source*: Substance Abuse and Mental Health Services Administration (SAMHSA) (2006) National Household Survey on Drug Abuse (Office of Applied Studies). Rockville, MD, USA.

of DSM-IV-TR alcohol abuse and dependence among the total population of persons 12 and older to be 7.7%, a prevalence rate that has remained statistically unchanged since 2002 (Substance Abuse and Mental Health Services Administration 2006). Differences in the rates of disorder across various studies have been attributed to differences in measurement procedures and sampling approaches (Regier et al. 1998).

The rates of alcohol use disorder vary by gender, age, race, ethnicity, socioeconomic status, and geographic location. The prevalence of alcohol disorder is consistently found to be higher among men than women, often at a ratio of two to one or greater (Grant et al. 2006, Kessler et al. 1997, Substance Abuse and Mental Health Services Administration 2006). Evidence suggests, however, that the gender differential has narrowed among more recent cohorts of young adults, in part due to an increased likelihood of early onset drinking among women and the subsequent emergence of drinking problems (Nelson et al. 1998). As shown in Table 54–6, the highest rates of alcohol abuse and dependence occur among young adults, with a gradual decline associated with increasing age. In the 2001–2002 NESARC, the prevalence rate for alcohol disorder was 16.2% among 18−29-year-old adults, dropping to 9.7% among those 30−44-year-old, 5.4% in the 45−64-year-old group, and 1.5% among those aged 65 years and older (Grant et al. 2006). Analyses of the NESARC data according to racial and ethnic background indicate that the highest prevalence rates of alcohol abuse and dependence occur among Native Americans (5.6 and 6.4%, respectively), while the lowest rates were found for Asians (2.1% for abuse and 2.4% for dependence). There is a negative association between education level and alcohol dependence (Kandel et al. 1997), and 1-year alcohol dependence risk is highest among the unemployed (Substance Abuse and Mental Health Services Administration 2006). Urban residence is associated with higher rates of alcohol dependence (Substance Abuse and Mental Health Services Administration 2000). Analyses of the 1999 NHSDA also show regional differences in the rates of alcohol dependence among the population aged 18 years and older, ranging from 3.4% in the Northeast and South, to 4% in the Midwest and 4.2% in the Western states (Substance Abuse and Mental Health Services Administration 2000).

**Table 54–6 Past Year Prevalence of DSM-IV-TR Alcohol Abuse and Alcohol Dependence among Adults Aged 18 or Older, US, 2001–2002**

| Demographic Characteristic | Alcohol Disorder | |
|---|---|---|
| | Abuse | Dependence |
| Total | 4.7 | 3.8 |
| Gender | | |
| Male | 6.9 | 5.4 |
| Female | 2.6 | 2.3 |
| Age | | |
| 18–29 | 7.0 | 9.2 |
| 30–44 | 6.0 | 3.8 |
| 45–64 | 3.5 | 1.9 |
| 65 or older | 1.2 | 0.2 |
| Race/Ethnicity | | |
| Non-Hispanic White | 5.1 | 3.8 |
| Non-Hispanic Black | 3.3 | 3.6 |
| American Indian/Alaska native only | 5.6 | 6.4 |
| Asian, Native Hawaiian/ Pacific Islander | 2.1 | 2.4 |
| Hispanic/Latino | 4.0 | 4.0 |

*Note*: Alcohol abuse and dependence are based on the definition found in the Diagnostic and Statistical Manual of Mental Disorders, FourthEdition, Text Revision. (DSM-IV-TR).
*Source:* Grant et al. (2006) The 12-month prevalence and trends in DSM-IV-TR alcohol abuse and dependence: United States 1991–1992 and 2001–2002, with permission from Elsevier.

Adverse consequences of drinking include a variety of social, legal, and medical problems (Babor et al. 1987). Overall, alcohol-related mortality in 1988 totaled 107,800 deaths, or about 5% of all deaths in the US, putting it among the top four causes of death (Stinson and DeBakey 1992). Of alcohol-related deaths, approximately 17% were directly attributable to alcohol, 38% resulted from diseases indirectly attributable to alcohol and 45% were attributable to alcohol-related traumatic injury (US Department of Health and Human Services 1994). Alcohol-related mortality declined during the last few decades of the 20th century. The age-adjusted mortality rate from liver cirrhosis in 1993 (7.9 deaths/100,000 persons) was almost half the 1970 rate (14.6 deaths/100,000) (Saadatmand et al. 1997), and alcohol-related automobile fatalities fell to a 2-decade low of 33.6% (Lane et al. 1997). Nonetheless, age-adjusted rates of liver cirrhosis in 1988 remained higher for males (43.4 deaths/100,000 population) than females (19.4 deaths/100,000 population) and for nonwhites (57.2 deaths/ 100,000 population) than whites (32 deaths/100,000 population) (Stinson and DeBakey 1992).

As noted previously in this chapter, alcohol-related morbidity is manifested in virtually all organ systems. The primary chronic health hazard associated with heavy drinking is cirrhosis of the liver, which in 1988 was the ninth leading cause of death in the US (U.S. Department of Health and Human Services 1994). Although the percentage of drivers in fatal crashes with BALs in excess of the legal limit has declined in recent years, alcohol intoxication remains a major contributor to this and other types of accidental injury, as well as to suicide and homicide (U.S. Department of Health and Human Services 2000). In addition, heavy drinking has been implicated in such health conditions as FASDs, esophageal cancer, chronic pancreatitis, nutritional deficiencies, cardiomyopathy, hypertension, and neurological problems (U.S. Department of Health and Human Services 2000). The social consequences of alcohol abuse and dependence are equally serious, with heavy drinking contributing to a variety of family, work, and legal problems. The economic impact of alcoholism is substantial. Alcohol abuse and dependence contribute to unemployment, reduced productivity in the workplace, and crime, as well as increased costs for health care (U.S. Department of Health and Human Services 2000). It has been estimated that the nonhealth related costs associated with alcohol abuse reached approximately $13 billion in 1992, owing in part to costs associated with crime committed while under the influence of alcohol (Martin 2001). In summary, the annual cost of heavy drinking and alcohol-related disorders in the US (both in dollars and in suffering) is enormous. Successful efforts to reduce the burden of illness attributable to alcohol could produce substantial

reductions in the social, economic, and personal costs of alcohol-related problems.

## Psychiatric Comorbidity in Individuals with an Alcohol Use Disorder

High rates of psychiatric disorders have been found in both clinical and community samples of alcohol-dependent individuals (Regier et al. 1990, Kessler et al. 1994, 1997, Ross 1995, Helzer and Pryzbeck 1988). These studies show a consistent association between alcohol abuse/dependence and a variety of other psychiatric symptoms and disorders. The Epidemiological Catchment Area (ECA) study, for example, revealed that 36.6% of those with a lifetime alcohol use disorder received at least one other psychiatric diagnosis, which is nearly double the rate for community respondents with no lifetime alcohol disorder (Regier et al. 1990). The evidence from the National Comorbidity Survey (NCS) study showed that co-occurring disorder is more likely with alcohol dependence than alcohol abuse (Kessler et al. 1997). Among individuals with one or more psychiatric disorders, 22.3% also had a lifetime alcohol disorder, substantially greater than the overall lifetime prevalence of alcohol abuse/dependence (13.5%). Women diagnosed with an alcohol disorder appear to be at greater risk for a comorbid psychiatric disorder. The NCS found that 72% of females with a lifetime alcohol abuse diagnosis had experienced one or more co-occurring psychiatric disorders, compared to 57% of men who had a lifetime history of alcohol abuse. While the prevalence of comorbid disorders was greater with alcohol dependence, the gender differential was smaller: 86% of women and 78% of men with lifetime alcohol dependence had had other lifetime DSM-III-R disorders (Kessler et al. 1997).

The most frequent co-occurring diagnoses are for other drug use disorders, conduct disorder, antisocial personality disorder, anxiety disorders, and affective disorders. The relative risks for different types of disorder vary somewhat by gender (Helzer and Pryzbeck 1988, Kessler et al. 1997). Among women, anxiety and affective disorders are the most common co-occurring disorders. Among men with a history of alcohol abuse or dependence, drug disorders and conduct disorder account for the largest proportion of comorbid cases.

Drug abuse/dependence is common among both men and women with an alcohol use disorder. In the NCS, slightly less than half of alcohol dependent respondents (41% of men and 47% of women) and approximately one-third of alcohol abusers had a history of a drug use disorder (Kessler et al. 1997). In the ECA study, 21.5% of individuals with a history of alcohol disorder also met criteria for a lifetime drug use disorder (odds ratio (OR) = 7.1) (Regier et al. 1990). Among individuals with a drug use disorder in the ECA study, 47.3% also had an alcohol disorder. The association was strongest for individuals with cocaine abuse/dependence, among whom 84.8% also had an alcohol use disorder (OR = 36.3). Other drug abuse/dependence diagnoses with an OR in excess of 10 included barbiturates, opiates, amphetamines, and hallucinogens (Regier et al. 1990).

Problem drinkers have a significantly increased risk of the antisocial personality disorder (ASPD), compared to those in the population with no alcohol use disorder. Although ASPD was present in only 14.3% of individuals with an alcohol use disorder in the ECA study, this translated into an OR of 21 (Regier et al. 1990). Given that 73.6% of ECA respondents with ASPD also had a drinking pattern that met criteria for alcohol abuse/dependence, there is substantial overlap between the disorders, which is in part attributable to the overlap in diagnostic criteria (e.g., antisocial behavior that is manifest as a consequence of intoxication).

Evidence from multiple studies indicates that individuals with an alcohol use disorder experience a two to threefold increased risk of depressive disorders (Swendsen et al. 1998). The ECA study showed mood disorders to be present in 13.4% of those with an alcohol use disorder (OR = 1.9) (Regier et al. 1990). Conversely, 21.8% of individuals with a mood disorder also had an alcohol use disorder. Of the mood disorders, bipolar disorder is particularly common among individuals with an alcohol use disorder, with 5.1% having a form of bipolar disorder. Conversely, among individuals with bipolar disorder, 43.6% have a comorbid alcohol use disorder (OR = 5.1). Other mood disorders, although generally more common, show substantially lower odds ratios with alcohol use disorders. Specifically, major depressive disorder, which is present in 16.5% of individuals with an alcohol use disorder, has an odds ratio of only 1.3. Similarly, dysthymic disorder, although present in 20.9% of individuals with an alcohol use disorder, has an odds ratio of only 1.7. Among individuals with an alcohol use disorder, women were about four times as likely as men to receive a diagnosis of either bipolar disorder or major depressive disorder (Helzer and Pryzbeck 1988). There is also a sex differential with respect to the order of onset of diagnoses. In men, alcoholism is the antecedent diagnosis in 78% of cases of comorbid mood disorder, while for women major depressive disorder is the antecedent diagnosis in 66% of cases of comorbidity (Helzer and Pryzbeck 1988). The NCS study found a similar gender difference in the sequencing of comorbid affective disorders and alcohol use disorders (Kessler et al. 1997).

Anxiety disorders have also been found to be highly prevalent among individuals with an alcohol use disorder (Regier et al. 1990, Kessler et al. 1997, Swendsen et al. 1998). The ECA study found that 19.4% of those with alcohol abuse/dependence had a comorbid anxiety disorder (Regier et al. 1990). However, because these disorders are also highly prevalent in the general population, they have an odds ratio of only 1.5. Among individuals with an anxiety disorder, 17.9% have a comorbid alcohol use disorder. Of the anxiety disorders, panic disorder appears to have the strongest association with alcohol use disorder: 28.7% of individuals with that disorder also have an alcohol use disorder (OR = 2.6). Obsessive–compulsive disorder (OR = 2.1) is intermediate between panic disorder and phobias (OR = 1.4) (Regier et al. 1990). Among individuals with an alcohol use disorder, women were more than three times as likely as men to have panic disorder, and more than twice as likely to have phobia (Helzer and Pryzbeck 1988). Evidence suggests that the onset of social phobia occurs prior to the onset of alcohol use disorder, and that self-medication may play a role in the co-occurrence of the two disorders (Merikangas et al. 1998). A history of posttraumatic stress disorder (PTSD) has been found among 10.3% of men and 26.2% of women

with alcohol dependence (Kessler et al. 1997). In the NCS study, the onset of an anxiety disorder appeared to precede the onset of an alcohol use disorder for women more than men (Kessler et al. 1997).

Among individuals with an alcohol use disorder, the prevalence of schizophrenia is 3.8%, which is almost three times the rate of that disorder in the general population (Regier et al. 1990). Conversely, among patients with schizophrenia, the prevalence of a comorbid alcohol use disorder is 33.7% (OR = 3.3). Considerable attention has been focused on the substantial problems encountered in treating patients with schizophrenia and comorbid alcohol and drug abuse/dependence (National Institute of Mental Health 1990).

Comorbidity influences treatment-seeking behavior. Although the majority of individuals with an alcohol use disorder do not seek treatment, comorbidity increases the likelihood of using both mental health and substance abuse treatment services (Wu et al. 1999). This was demonstrated by an analysis of the ECA data, which found that 55.0% of individuals with an alcohol use disorder seeking treatment in a mental health or substance abuse setting had a comorbid nonsubstance use disorder, compared with only 24.4% of individuals with an alcohol use disorder who had not sought treatment (Regier et al. 1990). Data from the ECA study also revealed that, even after controlling for the severity of alcohol use disorder, the number of comorbid nonsubstance diagnoses in individuals with an alcohol disorder is significantly correlated with the frequency with which they seek treatment for psychiatric and medical problems (Helzer and Pryzbeck 1988).

Given these findings from general population surveys, it is not surprising that in clinical settings individuals with an alcohol use disorder also have a high prevalence of comorbid psychiatric disorders. Consistent with the patterns observed in the general population, the most common comorbid disorders are major depressive disorder, ASPD, drug dependence, and anxiety disorders (Hesselbrock et al. 1985, Ross et al. 1988). However, the prevalence of comorbid disorders observed in clinical samples appears to vary as a consequence of a number of factors, including the method of assessment, the sample studied, and the recency of heavy drinking (Grande et al. 1984, Kranzler and Liebowitz 1988). Given the overlap in the diagnostic criteria for alcohol dependence and ASPD, and the effects of chronic heavy drinking on mood and anxiety symptoms, care must be taken to differentiate transient, alcohol-related signs and symptoms from persistent features.

Powell et al. (1982) used a structured diagnostic interview to examine the lifetime prevalence of comorbid DSM-III-R disorders among 565 male inpatient veterans being treated for alcohol dependence. They found that 63% of patients had psychiatric symptoms that met criteria for a psychiatric diagnosis in addition to alcohol dependence. The most common comorbid diagnosis was depression (42% of all patients), followed by mania (20%) and ASPD (20%). Comorbid drug abuse was present in 12% of patients, with panic attacks, phobic disorder, and obsessive–compulsive disorder each diagnosed in approximately 10% of patients. A comorbid diagnosis of schizophrenia was present in 4% of patients. The onset of comorbid disorders, with the exception of depression and obsessive–compulsive disorder occurred prior to the onset of alcoholism.

Hesselbrock et al. (1985) evaluated a group of 321 individuals with an alcohol use disorder recruited from three different inpatient settings. These investigators found that 75% of men and 80% of women received one or more lifetime diagnoses in addition to alcohol abuse/dependence. For the entire group, drug abuse was the most prevalent lifetime diagnosis (45%), followed by ASPD (41%), major depressive disorder (38%), phobia (27%), obsessive–compulsive disorder (12%), panic disorder (10%), mania (4%), and schizophrenia (2%). Gender differences were also evident, with the most common comorbid diagnosis being ASPD among men (49%) and depression among women (52%). With respect to disorders other than ASPD, the onset of most comorbid disorders in women preceded the onset of alcohol abuse, while among men most comorbid disorders followed the onset of alcohol abuse.

Ross et al. (1988) evaluated the prevalence of comorbid psychiatric disorders in a sample of 501 patients seeking treatment. Among patients with a current alcohol use disorder ($n$ = 370), 25% had comorbid drug abuse/dependence. Patients who received both alcohol and drug abuse/dependence diagnoses had a higher prevalence of other lifetime psychiatric diagnoses (95%) than those with only an alcohol diagnosis (78%). The most common disorder among patients with combined alcohol and drug abuse/dependence was ASPD (79%), followed by psychosexual dysfunctions (48%), major depressive disorder (36%), phobias (36%), dysthymic disorder (23%), obsessive–compulsive disorder (18%), panic disorder (17%), pathological gambling (14%), schizophrenia (11%), and mania (3%). A similar distribution was evident among patients with no comorbid drug diagnosis, although in each case the prevalence was lower. With respect to the order of onset, alcohol abuse/dependence most commonly occurred after the onset of ASPD, schizophrenia, phobias, and panic disorder. Onset of the other comorbid disorders relative to alcohol abuse was more variable.

In summary, both community and clinical studies underscore the importance of ASPD and drug abuse/dependence as comorbid diagnoses in individuals with an alcohol disorder. The odds ratios obtained for these disorders in community studies indicate that these associations are elevated not only as a function of greater treatment-seeking behavior in affected individuals, but also because of potential commonalities in the etiology and development of alcohol abuse/dependence. That is, genetic and/or psychosocial risk factors for the development of ASPD are likely to overlap with factors that increase risk for alcohol and drug use disorders. Similarly, the risk factors for alcohol and drug use disorders may overlap with those for schizophrenia and bipolar disorder. In contrast, although anxiety disorders and depression are highly prevalent in clinical samples of alcohol-dependent individuals, their association with alcohol dependence appears largely due to chance, since these disorders are also highly prevalent in the general population.

Given a high rate of psychiatric comorbidity, it is axiomatic that a careful psychiatric assessment should be conducted in patients being seen for alcohol treatment, and that alcohol use and associated problems be evaluated in patients seen primarily for other psychiatric conditions. Because the presence of comorbid disorders may have important implications for the development of alcoholism

and its prognosis, the assessment of comorbid psychopathology is an essential element in the clinical evaluation. When comorbid diagnoses are present, an effort should be made to ascertain the order of onset of each disorder since treatment and prognosis may follow from such information (Schuckit 1985).

## Course and Natural History

Schuckit et al. (1993) found that the symptoms of alcohol dependence appear in the following sequence in a sample of male veteran alcoholics: (1) heavy drinking during the late twenties; (2) interference with functioning in multiple life areas during their early thirties; (3) loss of control, followed by an intensification of social and work-related problems, and onset of medical consequences in the mid- to late thirties; and (4) severe long-term consequences by the late thirties and early forties. This relatively predictable order of progression is consistent with previous studies. However, as mentioned above, women appear to experience many of these milestones at a later age than men (Parrella and Filstead 1988, Piazza et al. 1989).

The study by Schuckit et al. (1993) showed no effect of onset age, family history of alcoholism, or comorbid psychiatric diagnoses on the order of symptom appearance. However, other features defining the course of alcoholism, particularly the response to treatment, vary as a function of patient-related variables, including age of onset, severity of alcohol dependence, and comorbid psychiatric disorders. There is consistent evidence that early age of onset is a predictor of greater severity of alcoholism and a poorer response to treatment (Bohn and Meyer 1994, Babor et al. 1992). Greater severity of alcohol dependence has also been shown to predict poorer treatment outcome (Lindstrom 1992).

While considered to be important in the development of alcoholism, comorbid psychiatric disorders also have prognostic significance (Meyer 1986). Rounsaville et al. (1987) found that psychiatric diagnosis at the time of treatment intake predicted a variety of 1-year posttreatment outcomes. Among males, the presence of a comorbid lifetime diagnosis of ASPD, major depressive disorder, or drug abuse/dependence was associated with poorer drinking outcomes. Among females, the presence of major depressive disorder predicted a better outcome on drinking-related measures, while those patients with ASPD or drug abuse/dependence had a poorer prognosis. Three-year posttreatment outcomes in this group of alcoholics also showed comorbid ASPD, major depressive disorder, and drug abuse/ dependence to be associated with poorer outcomes, irrespective of gender. It is notable, however, that at 3-year follow-up major depressive disorder was not associated with a protective effect for women alcoholics (Kranzler et al. 1996b).

Other investigators have found no difference in drinking outcomes when comparing primary alcoholics (i.e., those for whom alcohol dependence is the first and predominant disorder) and alcoholics with a comorbid mood disorder (Schuckit 1985, O'Sullivan et al. 1988, Powell et al. 1992). However, as might be expected, alcoholics with comorbid depression have greater psychiatric severity at follow-up than primary alcoholics (O'Sullivan et al. 1988, Powell et al. 1992). Variable findings have also been reported concerning the prognostic significance of ASPD and drug abuse among alcoholics. Both Powell et al. (1992) and Schuckit (1985) found that, compared with primary alcoholics, alcoholics with either primary ASPD or a primary drug abuse diagnosis (i.e., individuals in whom these disorders preceded the onset of alcohol dependence) did not differ on alcohol-related outcomes. However, in one study (Schuckit 1985), alcoholics with these primary diagnoses reported more illicit drug use and poorer social functioning during the posttreatment period. Furthermore, Liskow et al. (1990) found that alcoholics with a lifetime drug diagnosis in combination with ASPD had poorer alcohol-related outcomes.

Although a number of studies have shown that patients experience substantial improvement during the year following alcoholism treatment (Lindstrom 1992), Vaillant (1983) found that treatment had minimal effects on long-term outcome. More long-term treatment outcome studies are needed to examine the impact of different kinds of alcoholism treatment on the course of the disorder. Additional studies are also needed to clarify both the prognostic significance of patient-related variables, including comorbid psychiatric disorders, and their interaction with different kinds of treatment.

## Treatment

### Goals, Setting, and Costs of Treatment

When a determination has been made that an individual is drinking excessively, the nature, setting and intensity of the intervention must be determined in order to address the specific treatment needs of the patient. Among heavy drinkers without evidence of alcohol dependence, a brief intervention aimed at the reduction of drinking may suffice. In contrast, patients with alcohol dependence typically have a more complex set of needs to address, as indicated in Table 54–7.

**Table 54–7 Goals of Alcoholism Treatment**

| |
|---|
| Promote complete abstinence from alcohol. |
| Stabilize acute medical (including alcohol withdrawal) and psychiatric conditions, as needed. |
| Increase motivation for recovery. |
| Initiate treatment for chronic medical and psychiatric conditions, as needed. |
| Assist the patient in locating suitable housing (e.g., moving from a setting in which drinking is widespread), as needed. |
| Enlist social support for recovery (e.g., introduce to 12-step programs and, when possible, help the patient to repair damaged marital and other family relationships). |
| Enhance coping and relapse prevention skills (including social skills, identification and avoidance of high-risk situations). |
| Improve occupational functioning. |
| Promote recovery through participation in structured aftercare treatment or self-help groups. |

* Adapted from Schuckit (1994). Reprinted with permission from American Psychiatric Press Inc.

### Treatment Goals for Patients with Alcohol Dependence

Figure 54–1 describes a process for the management of patients with alcohol abuse and dependence. The algorithm is written from the perspective of a community-based or consultation/liaison psychiatrist who does not necessarily

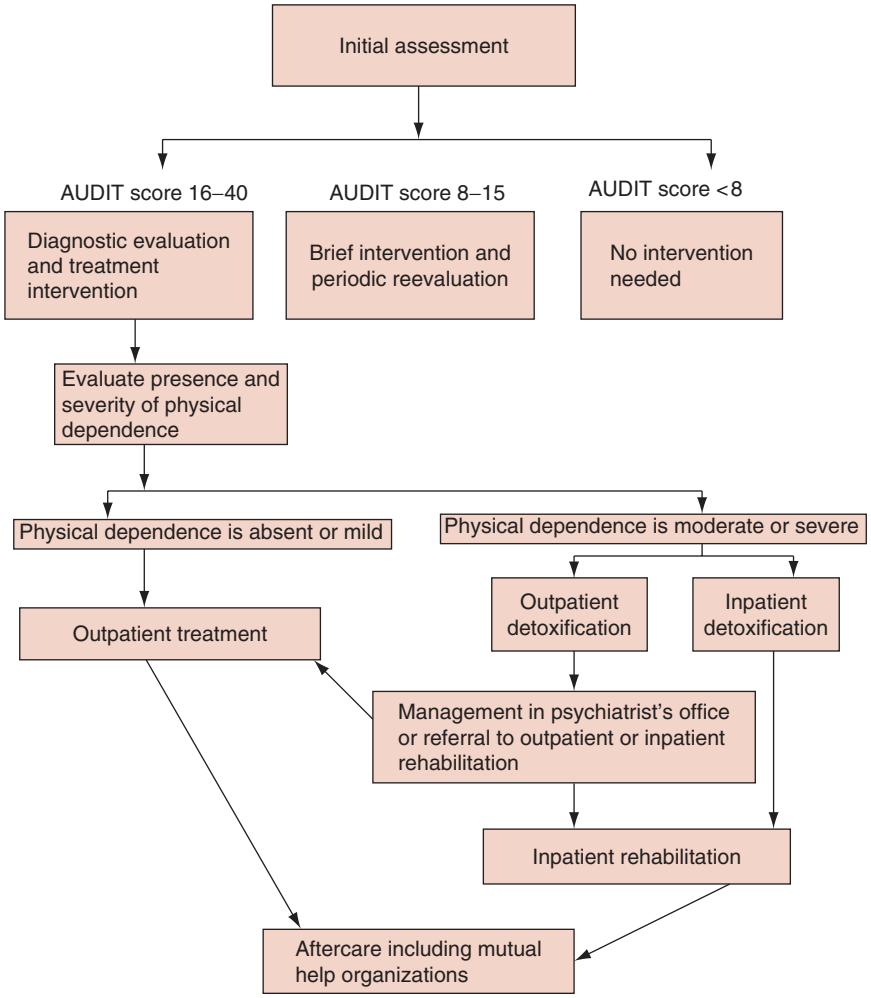



**Figure 54–1** *Algorithm for the identification and management of patients with alcohol abuse and dependence.*

have specialized training in addiction medicine. Following the initial assessment, using a screening test like the CAGE or AUDIT, the patient is referred to either a diagnostic evaluation or a brief intervention with further monitoring. Brief interventions are characterized by their low intensity and short duration. They typically consist of one to three sessions of counseling and education. They are intended to provide early intervention, before or soon after the onset of alcohol-related problems. Brief interventions seek to motivate high-risk drinkers to moderate their alcohol consumption, rather than promote total abstinence with specialized treatment techniques. They are simple enough to be delivered by primary care practitioners and are especially appropriate for psychiatric patients whose at-risk drinking meets criteria for alcohol abuse rather than dependence.

During the past 2 decades, numerous randomized controlled trials have been conducted to evaluate the efficacy of brief interventions. The results of these trials have been summarized in several integrative literature reviews and meta-analyses (Kahan et al. 1995, Wilk et al. 1997, Poikolainen 1999, Whitlock et al. 2004). The cumulative evidence shows that clinically significant effects on drinking behavior and related problems can follow from brief interventions. Nevertheless, the results have not always been consistent across studies (Poikolainen 1999). Furthermore, there is little evidence that these interventions are beneficial for alcohol dependent individuals (Mattick and Jarvis 1994).

If the patient's screening results and diagnostic evaluation provide evidence of alcohol dependence, the next step is to differentiate between mild and more severe levels of physical dependence to determine the need for detoxification. If withdrawal risk is low, the patient may be referred directly to outpatient therapy. If the withdrawal risk is moderate or high, outpatient or inpatient detoxification is indicated.

There are a number of potentially life threatening conditions for which alcoholics are at increased risk. The presence of any of the following requires immediate attention: acute alcohol withdrawal (with the potential for seizures and delirium tremens), serious medical or surgical disease (e.g., acute pancreatitis, bleeding esophageal varices), and serious psychiatric illness (e.g., psychosis, suicidal intent). In the presence of any of these emergent conditions, acute stabilization should be the first priority of treatment.

The presence of complicating medical or psychiatric conditions is an important determinant of whether detoxification and rehabilitation are initiated in an inpatient or an outpatient setting. Other considerations are the alcoholic's current living circumstances and social support network. Women with children are sometimes unwilling to enter residential treatment unless their family needs are taken care

of. In the patient without these complicating features, the major focus should be on the establishment of a therapeutic alliance, which provides the context within which rehabilitation can occur. In addition to participation in structured rehabilitation treatment, the patient should be made aware of the widespread availability of Alcoholics Anonymous (AA) and the wide diversity of its membership.

Residential settings include hospital-based rehabilitation programs, freestanding units, and psychiatric units. With the growth of managed care in the 1990s, there was a dramatic reduction in the average length of stay for residential treatment and a shift in emphasis to less costly outpatient treatment settings. In many populations, outpatient programs produce results comparable to those of inpatient programs. Conclusions regarding equal effectiveness of inpatient and outpatient treatment must, however, be limited to clients who are appropriate for each type of program (Finney et al. 1996). Some studies comparing outpatient with inpatient treatment have not controlled for the possibility that patients who choose outpatient settings are less severely alcohol dependent, less physically ill, or less psychiatrically impaired. Inpatient treatment may be indicated when motivation is weak to continue treatment, when patients are psychotic, depressed, or suicidal, and when there are medical complications. Other factors that affect the choice of treatment setting include patients' social stability and the number and severity of their symptoms, as well as the ability of programs to respond to individual needs An obstacle to ambulatory treatment is the high rate of attrition usually encountered among more severely impaired alcoholics (Seixas 1983).

An obvious question is whether some treatment modalities are more cost-effective than others. In one analysis of treatment modalities used in the US, the range of treatment costs across settings was enormous, with a high of $585 per day for hospital-based care and a low of $6 per visit at social model, nonresidential programs. Nevertheless, the research evidence on the cost-effectiveness of different treatment modalities has consistently found that the more expensive modalities do not necessarily produce better treatment outcomes (Holder et al. 1991, Goodman et al. 1997).

In response to concerns about the inappropriate use of expensive residential treatment, patient placement criteria have been developed for adults and adolescents to standardize the way in which patients are assigned to different types and intensities of care. The *Patient Placement Criteria for the Treatment of Substance-Related Disorders*, second edition, revised, of the American Society of Addiction Medicine (2001) (ASAM) provides detailed guidelines for both adult and adolescent patient placement at five levels of care corresponding to DSM diagnostic criteria and specific admission and discharge patient characteristics. The decision to refer the patient to a particular level of care is based on the following considerations: acute intoxication and withdrawal, biomedical conditions, emotional/behavioral conditions, acceptance of treatment, relapse potential, and recovery environment.

Another approach to patient placement and treatment matching is based on the notion that patients should initially be matched to the least intensive level of care that is appropriate, and then stepped up to more intensive treatment settings if they do not respond (Institute of Medicine 1990). This approach is consistent with the ASAM criteria, which specify that inpatient treatment should not be recommended unless the patient has failed at outpatient treatment. Matching can also be guided by theoretically derived hypotheses. This strategy relies on the cumulative evidence of research to suggest the kinds of treatments most likely to produce favorable outcomes with different types of patients. An example is the assignment of patients with ASPD to cognitive behavioral treatment, based on evidence (Kadden et al. 1989) that these patients have better outcomes with structured therapy.

The possibility of rational treatment/patient matching continues to attract interest, and there is some evidence to suggest that patients with certain characteristics (e.g., severe dependence, high levels of anger, social networks that support drinking) respond marginally better to certain types of therapy (e.g., Twelve-Step Facilitation, motivational enhancement, cognitive behavioral) (Babor and Del Boca 2003, Ouimette et al. 1999). In one study, McLellan et al. (1993) compared the range and intensity of service delivery and associated outcomes in two inpatient and two outpatient substance abuse treatment programs for alcohol- or cocaine-dependent patients. In areas of patient functioning other than substance use (i.e., health, employment, family, and psychiatric), patients who were treated in programs with services that met their particular areas of need showed the greatest improvement in those areas after discharge. These findings suggest the importance of incorporating a range of services within specialized treatment facilities to meet the diverse psychosocial needs of alcoholic patients.

Despite treatment, some alcoholics relapse repeatedly. For many emergency department personnel, the multiple recidivist alcoholic has come to personify the disorder. For clinicians involved in the delivery of alcoholism rehabilitation services, these individuals' apparent unresponsiveness to treatment may contribute to frustration and a sense of futility. Presently, long-term residential treatment appears to be the only option for alcoholics who do not respond to more limited efforts at rehabilitation. Unfortunately, the availability of such care in many states is limited as a consequence of the effort to deinstitutionalize psychiatric patients.

Finally, the importance of continuing care by means of aftercare groups, and other mutual help organizations cannot be overestimated. The value of these resources as well as the newer pharmacological and nonpharmacological interventions developed in the past 2 decades are discussed in subsequent sections of this chapter.

## The Management of Alcohol Withdrawal

An important initial intervention for a substantial number of alcohol-dependent patients is the management of alcohol withdrawal through detoxification. Many patients who have experienced an alcohol-related problem may not have developed a dependence syndrome and therefore may experience no significant physiological disturbance on cessation of drinking. Other patients who have low to moderate levels of dependence are unlikely to experience serious withdrawal symptoms. However, many patients with a history of chronic drinking (especially those with prior experience of an abstinence syndrome) are likely to experience withdrawal symptoms, and for some patients, alcohol withdrawal can be

life threatening. Such diversity in symptomatology requires a diversified approach to patient management. The objectives in treating alcohol withdrawal are the relief of discomfort, prevention or treatment of complications, and preparation for rehabilitation. Successful management of the alcohol withdrawal syndrome provides a basis for subsequent efforts at rehabilitation.

Careful screening for concurrent medical problems is an important element in detoxification. Administration of thiamine (50–100 mg by mouth or IM) and multivitamins is a low-cost, low-risk intervention for the prophylaxis and treatment of alcohol-related neurological disturbances. Good supportive care and treatment of concurrent illness, including fluid and electrolyte repletion, are essential (Naranjo and Sellers 1986).

Social detoxification, which involves the nonpharmacological treatment of alcohol withdrawal has been shown to be effective. It consists of frequent reassurance, reality orientation, monitoring of vital signs, personal attention, and general nursing care (Naranjo and Sellers 1986). Social detoxification is most appropriate for patients in mild-to-moderate withdrawal. The medical problems commonly associated with alcoholism may substantially complicate therapy, so that care must be taken to refer those patients whose condition requires medical management.

Increasingly, detoxification is being done on an ambulatory basis, which is much less costly than inpatient detoxification (Hayashida et al. 1989). Inpatient detoxification is indicated for serious medical or surgical illness, and for those individuals with a past history of adverse withdrawal reactions or with current evidence of more serious withdrawal (e.g., delirium tremens).

A variety of medications have been used for the treatment of alcohol withdrawal. However, due to their favorable side effect profile, the benzodiazepines have largely supplanted all other medications (Naranjo and Sellers 1986). Although any benzodiazepine will suppress alcohol withdrawal symptoms, diazepam and chlordiazepoxide are often used, since they are metabolized to long-acting compounds, which in effect are self-tapering. Because metabolism of these drugs is hepatic, impaired liver function may complicate their use. Oxazepam and lorazepam are not oxidized to long-acting metabolites and thus carry less risk of accumulation.

Although carbamazepine appears useful as a primary treatment of withdrawal (Malcolm et al. 1989), the liver dysfunction that is common in alcoholics may affect its metabolism, which makes careful blood level monitoring necessary. Antipsychotics are not indicated for the treatment of withdrawal except in those instances where hallucinations or severe agitation are present (Naranjo and Sellers 1986), in which case they should be added to a benzodiazepine. In addition to their potential to produce extrapyramidal side effects, antipsychotics lower seizure threshold, which may be particularly problematic during alcohol withdrawal.

## Therapeutic Modalities: Nonpharmacological

A variety of treatment components are delivered within the context of rehabilitation services. In many programs a combination of therapeutic interventions is provided to all clients, based on the assumption that multiple components have a greater chance of meeting at least some of each client's needs. Therapeutic approaches most often employed in both residential and outpatient programs include behavior therapy, group therapy, family treatment, and pharmacotherapy. Regarding specific treatment modalities, the weight of evidence suggests that behavioral treatments are likely to be more effective than insight-oriented or family therapies (Miller and Hester 1986). Nevertheless, recent research (Babor et al. 2003, Ouimette et al. 1999) also indicates that Twelve-Step Facilitation, which is based on the principles of AA, is as effective as more theory-based therapies. Controlled studies provide little support for the effectiveness of psychodynamic psychotherapy, although such treatment has been shown to be helpful in the treatment of drug abuse (Institute of Medicine 1989).

Cognitive and behavior therapies are among the most investigated theory-based treatments. Behavioral elements most frequently employed in treatment programs are relapse prevention, social skills training, contingency management and cognitive restructuring. Aversion therapy, based on Pavlovian conditioning theory has been virtually abandoned in the USA. Although it has been shown that the sight, smell, and taste of alcohol will acquire aversive properties if repeatedly paired with noxious stimuli (e.g., chemically-induced nausea and vomiting), the procedure is expensive and has not been shown to be superior to less heroic methods.

Behavior therapists stress the importance of teaching new, adaptive skills designed to alter the conditions that precipitate and reinforce drinking, as well as developing alternative ways of coping with persons, events, and feelings that serve to maintain drinking. A number of studies have demonstrated the benefits of teaching social and other coping skills (Institute of Medicine 1990). One example of this approach in "relapse prevention" which focuses on identifying and coping with situations that represent high risk for heavy drinking. Research on cognitive–behavioral treatments (Institute of Medicine 1989) have provided the empirical basis for elaboration of a generalized relapse prevention strategy (Marlatt 1985).

The deleterious effects of alcoholism on marriages and families have been a source of concern to both clinicians and researchers. Alcoholism creates major stress on the family system by threatening health, interpersonal relations, and the economic functioning of family members. Although research has shown a strong association between healthy family functioning and positive outcome following alcoholism treatment (Moos and Moos 1984), little systematic evaluation has been undertaken to assess the efficacy of family approaches, either to reduce alcohol problems or to improve family functioning.

Most studies have involved marital rather than family treatment. A trial of behavioral marital therapy was conducted by O'Farrell et al. (1985). Alcoholics and their spouses were treated in aftercare for 10 weeks. At follow-up, behavioral marital therapy was found to have enhanced marital well-being more than did interactional couples therapy, while a no-marital-therapy control group showed no significant change. There was no differential improvement in drinking behavior among the three groups. Subsequently, McCrady et al. (1986) showed behavioral marital therapy to be superior to control treatments in both the reduction of drinking and maintenance of sobriety.

In addition to specific treatment for alcoholic couples or families, self-help groups for family members of alcoholics have grown substantially. Al-Anon, although not formally affiliated with AA, shares the structure and many of the tenets of the 12 Steps of AA. Al-Anon and AA meetings are often held jointly. Alateen groups, sponsored by Al-Anon for children of alcoholics, are available as well.

## Therapeutic Modalities: Pharmacological

Although the benzodiazepines have played a key role in the treatment of alcohol withdrawal, pharmacotherapy has not yet had a demonstrable effect on other aspects of alcoholism treatment. Disulfiram, an alcohol-sensitizing drug, has been approved for clinical use in the US since the 1940s, but it has not been widely prescribed. During the past decade, however, medications have begun to play a more important role both in the treatment of comorbid psychiatric disorders in alcoholics and in the rehabilitation of alcohol dependence. In dually diagnosed patients, medications that reduce psychiatric symptomatology may also reduce the risk of drinking. Independent of their effects on comorbid psychopathology, medications that reduce drinking may enhance the alcoholic's participation in psychosocial treatment. This rationale is similar to that underlying the combination of medications with psychotherapy in the treatment of depressive or anxiety disorders.

In the following sections, we discuss three types of pharmacotherapy for alcoholics: alcohol-sensitizing drugs, medications to treat comorbid psychopathology, and medications to directly reduce drinking. The reader is referred to detailed reviews of these topics for additional information (Swift 1999, Garbutt et al. 1999, Kranzler 2000).

### Alcohol-Sensitizing Drugs

Medications such as disulfiram or calcium carbimide cause an unpleasant reaction when combined with alcohol. The efficacy of such drugs in the prevention or limitation of relapse in alcoholics has not been demonstrated. However, these drugs may be of utility in selected samples of alcoholics with whom special efforts are made to ensure compliance.

Disulfiram (Antabuse) is the most commonly used alcohol-sensitizing medication and the only one approved for use in the US. When given in a single daily dose of 125−500 mg, disulfiram binds irreversibly to ALDH, permanently inactivating this enzyme. When alcohol is consumed, it is metabolized to acetaldehyde which accumulates due to inhibition of the enzyme that metabolizes it. Elevated levels of acetaldehyde are responsible for the aversive effects associated with the disulfiram−ethanol reaction (DER).

In addition to its effects on ALDH, disulfiram inhibits a variety of other enzymes. Disulfiram also reduces clearance rates of a number of medications. Common side effects of disulfiram include drowsiness, lethargy and fatigue (Chick 1999). More serious adverse effects, such as optic neuritis, peripheral neuropathy, and hepatotoxicity are rare. The exacerbation of psychotic symptoms in patients with schizophrenia, and occasionally their appearance in other individuals as well as the development of depression may be linked to inhibition of the enzyme dopamine-beta-hydroxylase. As with its neuropathic effects, the psychiatric effects of disulfiram are uncommon and may only occur at higher dosages of the medication.

Although disulfiram has been used in the treatment of alcoholism for more than 50 years, the few placebo-controlled studies that have been conducted have not shown the drug to have substantial efficacy. In a multicenter trial conducted by the U.S. Department of Veterans Affairs (VA) more than 600 male alcoholics were assigned randomly to groups receiving either 1 mg of disulfiram/day or 250 mg/day, or to a control group that was told they were not receiving disulfiram (Fuller et al. 1986). Results revealed a direct relationship between compliance with any of the three treatment regimens and complete abstinence. Among patients who resumed drinking, those taking the 250-mg dosage of disulfiram had significantly fewer drinking days than did patients in the other two groups. However, there was no significant difference among the three groups with respect to a variety of outcome measures, including length of time to first drink, unemployment, social stability, or number of men totally abstinent.

Disulfiram is usually given orally. Although the daily dosage prescribed in the US has been limited to 250–500 mg/day, some patients require in excess of 1 g/day of disulfiram to reach blood levels sufficient to produce the DER (Brewer 1984). The requirement that disulfiram undergo bioactivation before it can inhibit ALDH (Yourick and Faiman 1991) may explain the need for a higher dosage in some patients. At the dosage that is used clinically, faulty bioactivation in some individuals may yield too low a concentration of the active metabolite to inhibit ALDH.

Many practitioners believe that by enhancing compliance with disulfiram it is possible to increase the individual's commitment to abstinence from alcohol. Depot formulations would remove the need for voluntary compliance but they have not been shown to be reliable and are not approved by the Food and Drug Administration (FDA). However, a variety of approaches to enhancing voluntary compliance with disulfiram therapy have been employed (Allen and Litten 1992). These include the use of incentives, contracting with the patient and a significant other to promote the patient's taking disulfiram, providing additional information to the patient, behavioral training, and social support.

Azrin et al. (1982) found that disulfiram was superior to placebo when combined with a program of stimulus control training, role playing, communication skills training, and recreational and vocational counseling. Chick et al. (1992) compared supervised disulfiram treatment with placebo as an adjunct to the outpatient treatment of alcoholism. Under these circumstances, disulfiram significantly increased abstinent days and decreased total drinks consumed. Supervised adherence may be an essential element in the successful use of disulfiram (Brewer et al. 2000). Because substantial efforts are required to promote adherence to a disulfiram regimen (Azrin et al. 1982), use of the drug outside of a well-organized treatment program is probably unwarranted.

Given the limited efficacy of disulfiram for the prevention of relapse, it should not be used as a first line treatment for alcohol dependence. However, if a patient has not responded to other pharmacological treatments and is motivated to take disulfiram, it may be beneficial. Whenever disulfiram is prescribed, patients should be warned about its hazards, including the need to avoid over-the-counter (OTC) preparations with alcohol and drugs that interact adversely

with disulfiram, as well as the potential for a DER to result from alcohol used in food preparations.

## The Treatment of Psychiatric Comorbidity in Alcoholics

Comorbid psychiatric disorders may contribute to the development or maintenance of heavy drinking (Meyer 1986). Efforts to treat the comorbidity may have beneficial effects on drinking outcomes. Following detoxification, many alcoholics complain of persistent anxiety, insomnia, and general distress. These symptoms may last for weeks or months and may be difficult to differentiate from the emergence of diagnosable psychiatric disorders. Irrespective of their etiology, negative emotional states, including frustration, anger, anxiety, depression, and boredom, have been shown to contribute to relapse in a substantial proportion of alcoholics (Marlatt 1985).

A variety of medications have been employed to treat comorbid psychiatric symptoms and disorders in alcoholics. Indications for the use of these medications in alcoholics are similar to those for nonalcoholic populations, but there is added potential for adverse effects due to comorbid medical disorders and the pharmacokinetic effects of acute and chronic alcohol consumption. The use of these medications in alcoholics therefore entails additional considerations that can only be arrived at through careful psychiatric diagnosis.

### *Treatment of Depressive Symptoms Disorders*

Depressive symptoms are common early in alcohol withdrawal, but they often remit spontaneously with time (Dorus et al. 1987). For depression that persists beyond the period of acute withdrawal, an antidepressant is probably warranted. In general, placebo-controlled trials of tricyclic antidepressants (TCAs) in depressed alcoholics have not provided evidence of efficacy. Research in this area, however, was characterized by substantial methodological limitations (Ciraulo et al. 1982). Most studies of TCAs in depressed alcoholics used a therapeutically inadequate dosage of the medication, with no effort made to compensate for the fact that both cigarette smoking and heavy drinking can stimulate liver enzymes that metabolize drugs. Placebo-controlled trials of imipramine (Nunes et al. 1993, McGrath et al. 1996) and desipramine (Mason et al. 1996), which take these considerations into account, suggest that TCAs reduce depressive symptoms in depressed alcoholics.

In a study of alcoholics with secondary depression (i.e., depression that was present prior to the onset of alcohol dependence), in which desipramine or placebo treatment was initiated after eight days of abstinence (Mason et al. 1996), the active drug was found to be superior in reducing both depressive symptoms and heavy drinking. The time course of the response suggests that the common practice of requiring a period of 2−4 weeks before initiating antidepressant therapy may be excessive.

There are a limited number of studies using selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depressive disorder in alcoholics. In a placebo-controlled trial of fluoxetine for relapse prevention in alcoholics (Kranzler et al. 1995), individuals with current major depressive disorder who received the active medication showed a greater reduction in depressive symptoms than those receiving placebo. In a 12-week study (Cornelius et al. 1997), fluoxetine was superior to placebo in reducing both depressive symptoms and total alcohol consumption in patients diagnosed with major depressive disorder and alcohol dependence. Sertraline has also been shown to reduce depressive symptoms among inpatient alcoholics, although the medication's effects on preventing relapse to drinking have not been evaluated (Roy 1998). The serotonergic antidepressant nefazodone has also been shown in one study (Roy-Byrne et al. 2000) to reduce depressive symptoms in depressed alcoholics, but no direct effect on drinking behavior was observed.

Early studies of lithium (Kline et al. 1974, Merry et al. 1976) showed that patients treated with the drug experienced fewer days of pathological drinking than those receiving placebo. However, a multicenter double blind placebo-controlled trial (Dorus et al. 1989) in 457 male alcoholics, of whom approximately one-third were depressed, found no significant differences between lithium-treated and placebo-treated patients on any outcome measures, including number of drinking days, alcohol-related hospitalizations, and severity of depression. The lack of efficacy was observed for both the depressed and the nondepressed groups. This large, carefully conducted trial suggests that if lithium has a role in alcoholism treatment, it is probably limited to the treatment of those alcoholics with comorbid bipolar disorder. A study by Fawcett et al. (2000), in which there was no advantage to lithium over placebo in alcoholics who were not selected for a comorbid psychiatric disorder, is consistent with this conclusion. In summary, although it has been argued that most instances of postwithdrawal depression will spontaneously remit within a few days to several weeks (Schuckit 1983, Brown and Schuckit 1988), there is still a substantial number of patients whose severe and persistent depression requires treatment. Given the superior safety profile of SSRIs, particularly in relation to risk of suicide by medication overdose, use of these drugs is preferable to the use of TCAs.

### *Treatment of Anxiety Symptoms/Disorders*

A number of studies have shown chlordiazepoxide to be effective in the maintenance of alcoholics in long-term outpatient treatment (Kissin 1975, Rosenberg 1974). However, the potential for additive CNS depression produced by the concurrent use of alcohol and benzodiazepines is well recognized. Furthermore, the use of benzodiazepines may itself result in tolerance and dependence and may increase depressive symptoms (Schuckit 1983). Although this concern may be exaggerated (Ciraulo et al. 1988) and all benzodiazepines may not be equal in their capacity to produce dependence in alcoholics (Jaffe et al. 1983), generally speaking, the use of benzodiazepines in alcoholics is probably best limited to detoxification.

Buspirone (Taylor et al. 1985) is a nonbenzodiazepine anxiolytic that is less sedating than diazepam or clorazepate, does not interact with alcohol to impair psychomotor skills, and has a low potential for abuse. A double blind, placebo-controlled trial of buspirone in alcoholics (Bruno 1989) found significantly greater retention in treatment and greater decreases in alcohol craving, anxiety, and depression in buspirone-treated patients. Both groups showed significant declines in drinking. Similarly, Tollefson et al. (1992) found that buspirone-treated subjects were less likely to discontinue

treatment prematurely and had greater reductions in anxiety than placebo-treated subjects. Greater "improvement in drinking" was also observed for the active drug group, although quantitative measures of alcohol consumption were not reported in this study, confirming previous studies. Kranzler et al. (1994) found that, in anxious alcoholics, buspirone was superior to placebo in terms of retention in treatment. Regardless of whether a specific anxiety disorder was present, buspirone treatment reduced anxiety among subjects with the highest anxiety symptom scores. The active drug also delayed relapse to heavy drinking. In contrast, a placebo-controlled study (Malcolm et al. 1992) of alcoholic veterans in aftercare showed no differences between patients treated with buspirone or placebo on measures of anxiety or alcohol consumption. In comparison with the other three studies, the patients in this study were more severely alcohol dependent and the medication was not administered in the context of a psychosocial treatment program. In summary, when combined with appropriate psychosocial treatment, buspirone appears useful in the treatment of alcoholics with persistent anxiety.

Currently, antipsychotics are indicated only in alcoholics with a coexistent psychotic disorder or for the treatment of alcoholic hallucinosis (Naranjo and Sellers 1986). Several placebo-controlled studies have found no advantage in the use of phenothiazines for treatment of anxiety, tension, and depression following detoxification (Jaffe et al. 1992). Because of their capacity to lower seizure threshold, antipsychotics should be used with caution in this population.

## Drugs That May Directly Reduce Alcohol Consumption

A number of specific neurotransmitter systems have been implicated in the control of alcohol consumption, including endogenous opioids, catecholamines, especially dopamine, and serotonin. Although these systems appear to function interactively in their effects on drinking behavior, efforts to use medications to treat excessive drinking have increasingly focused on agents that have selective effects on specific neurotransmitter systems.

### *Opioid Antagonists*

An extensive literature supports the role of opioidergic neurotransmission in the pathophysiology of alcohol consumption and related phenomena. For example, small doses of morphine increase alcohol intake in experimental animals (Hubbell et al. 1986). In contrast, opioid antagonists, such as naltrexone, decrease ethanol consumption and self-administration (Siviy et al. 1982). Effects similar to those in animals have been reported in some, but not all, studies of naltrexone for the treatment of alcohol dependence (Kranzler and Van Kirk 2001). The considerable variability in findings concerning the efficacy of naltrexone underscores the need to identify the circumstances under which the medication exerts its therapeutic effects.

In the first double blind, placebo-controlled trial, Volpicelli et al. (1992) found that naltrexone was superior to placebo in delaying the time to relapse and reducing the rate of relapse to heavy drinking among patients in a VA treatment program. Naltrexone did not affect subjects' "sampling" of alcohol, but reduced the return to heavy drinking following consumption of a small amount of alcohol. In this study, naltrexone also reduced patients' reported desire for alcohol. The results suggested that naltrexone may be particularly useful for subjects who present with high levels of craving and somatic symptoms (Volpicelli et al. 1995).

These findings were replicated and extended in a study that examined the utility of naltrexone in combination with two different psychotherapies (O'Malley et al. 1992). In that study, naltrexone was more efficacious in preventing the initiation of drinking when paired with supportive therapy than when used in combination with coping skills training. On the other hand, once the subject sampled alcohol, naltrexone plus coping skills/relapse prevention training was better at preventing a full-blown relapse, indicating that the efficacy of naltrexone was enhanced by teaching subjects specific strategies for avoiding alcohol (O'Malley et al. 1992). Individuals with higher levels of craving and poorer cognitive functioning derived the greatest benefit from naltrexone compared with placebo (Jaffe et al. 1996). During a 6-month posttreatment follow-up period, the beneficial effects of naltrexone diminished gradually over time (O'Malley et al. 1996).

Kranzler et al. (1998) found that alcoholics treated with a sustained-release (i.e., depot) formulation of naltrexone had detectable plasma concentrations of the drug for more than 30 days following injection. Furthermore, the active formulation was superior to placebo in reducing the frequency of heavy drinking in these subjects. However, in a subsequent study, these investigators (Kranzler et al. 2000) found no advantage for oral naltrexone over placebo on measures of alcohol consumption. In this study, naltrexone treatment was associated with a high rate of adverse events. Though there were no serious adverse events, the ones that were observed decreased the rates of both medication compliance and study completion (Oncken et al. 2001).

In contrast, Anton et al. (1999) found that naltrexone in combination with cognitive–behavioral therapy was superior to placebo in reducing the percentage of days abstinent, number of drinks per drinking day, and time to relapse to heavy drinking during a 12-week treatment trial. During a 14-week, posttreatment follow-up period, these subjects showed a gradual increase in relapse rates, drinking days, and heavy drinking days (Anton et al. 2000), and the difference between naltrexone and placebo treatments was not statistically significant. Consistent with the results reported by O'Malley et al. (1996), these findings suggest that treatment with naltrexone is warranted for longer than 12 weeks. Results from a multicenter, 12-week trial of naltrexone treatment for alcohol abuse and dependence showed no effects on drinking outcomes (Chick et al. 2000a). However, among compliant subjects, naltrexone was superior to placebo on a number of alcohol-related outcomes.

Two additional studies showed positive effects of naltrexone, particularly on heavy drinking. Monterosso et al. (2001) compared naltrexone 100 mg/day with placebo in the first 12-week phase of a multiphase double blind trial. Naltrexone was superior to placebo on the number of heavy drinking days. In addition, individuals with a high pre-treatment level of craving and those with high familial loading for alcoholism were more likely to benefit from naltrexone treatment. Heinala et al. (2001) compared naltrexone 50 mg/day with placebo, study medication being paired with either coping skills or supportive therapy. During

the initial 12 weeks of treatment, they found an advantage for naltrexone in preventing relapse to heavy drinking only when combined with coping skills therapy. During a subsequent 20-week period, when subjects were given the same medication, they were told to use it only when they craved alcohol (i.e., "targeted treatment"; Kranzler et al. 1997). Beneficial effects of the medication that were observed during the initial period of daily treatment were generally sustained with targeted treatment. These results suggest that concomitant coping skills therapy is needed if naltrexone is to reduce heavy drinking (Heinala et al. 2001). The investigators also observed that an initial period of abstinence is not required for the medication to be efficacious and that naltrexone targeted to alcohol craving is effective in maintaining the reduction in heavy drinking following a period of daily medication (Heinala et al. 2001).

Morris et al. (2001) conducted a trial of naltrexone in male alcoholics in Australia. Treatment with the active medication or placebo was combined with a weekly skills group. In the total sample, fewer naltrexone-treated patients relapsed to heavy drinking. Among patients completing the 12-week trial, naltrexone treatment reduced total alcohol consumption. Monti et al. (2001) examined the effects of naltrexone in combination with two different psychotherapeutic interventions in a 12-week trial in which patients were recruited from a partial hospital treatment program. Although they found no effects of the active medication, among patients who were medication compliant on at least 70% of days, naltrexone treatment resulted in fewer heavy drinking days and fewer drinks/drinking day than placebo. In a multicenter trial conducted in the VA (Krystal et al. 2001), more than 600 veterans with severe alcohol dependence were randomly assigned to receive 12 months of naltrexone, 3 months of naltrexone followed by 9 months of placebo, or 12 months of placebo. There were no significant group differences at either the 3-month or the 12-month evaluation points. In contrast to most of the other studies of naltrexone, the VA study used 12-Step facilitation therapy, rather than coping skills psychotherapy. In addition, the severity of the subjects' alcohol dependence was greater than in most previous studies. Consequently, these findings have limited relevance to the outpatient treatment of nonveterans, particularly when coping skills psychotherapy is employed.

Another opioid antagonist, nalmefene, has also been evaluated in alcohol-dependent subjects. In an initial pilot study (Mason et al. 1994) and a subsequent larger trial (Mason et al. 1999), the medication was shown to be well tolerated and to be superior to placebo in reducing relapse.

The most comprehensive clinical trial to date of naltrexone therapy is the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study conducted at 11 sites with nearly 1,400 patients (Anton et al. 2006). The study explored a variety of treatment methods—alone and in combination—within the context of medical management. Naltrexone in combination with a brief behavioral therapy delivered by licensed health care professionals was more effective than more intensive behavioral therapy. Naltrexone was associated with more abstinent days and reduced the risk of a heavy drinking day after a relapse. The effects, however, tended to be short-lived, with no advantage evident 1-year later after medication had been suspended. The findings from this study underscore the notion that naltrexone with medical management potentially may be delivered by primary care clinicians who frequently deal with alcoholic patients not having acces to traditional alcohol treatment programs.

In summary, naltrexone appears to produce a modest effect on drinking behavior among alcoholics (Kranzler and Van Kirk 2001). However, given the comparatively small overall effect of the medication, a variety of other factors, including medication compliance, the severity and chronicity of alcohol dependence, and the choice of concomitant psychotherapy, may determine whether an effect of the medication is observed.

### *Serotonergic Medications*

Another major focus of research on medications to treat alcoholism has been the role of the indoleamine neurotransmitter, serotonin (5-HT). 5-HT has been shown consistently to exert an influence over alcohol consumption in preclinical models of drinking behavior (LeMarquand et al. 1994a) but, data on human drinking are less consistent (Kranzler 2000).

Naranjo et al. (1990) found that fluoxetine 60 mg/day reduced average daily alcohol consumption by approximately 17% from baseline levels, while treatment with fluoxetine 40 mg/day or placebo had no effect. But a placebo-controlled trial of fluoxetine 60 mg/day in combination with coping skills psychotherapy in outpatient alcoholics showed no overall advantage to the active drug on drinking outcomes (Kranzler et al. 1995). Kabel and Petty (1996) showed no effect of fluoxetine 60 mg/day, compared with placebo, among veterans with severe alcoholic problems.

Another SSRI whose effects on alcohol consumption have been extensively examined is citalopram. At a dosage of 40 mg/day, citalopram was initially reported to reduce the number of drinks consumed per day and increase the number of abstinent days in a sample of nondepressed, early-stage problem drinkers (Naranjo et al. 1987). Using a similar design, these findings were replicated (Naranjo et al. 1992). However, Balldin et al. (1994) found no effect of citalopram 40 mg/day on alcohol intake among heavy drinkers.

One explanation for the variable findings in studies of whether SSRIs reduce drinking is the diversity of study samples. The initial studies were conducted in nontreatment-seeking heavy drinkers. Subsequent studies, which have shown differential effects based on severity, suggest that SSRIs are efficacious only in subgroups of alcoholics. For example, Gerra et al. (1992) found an effect of fluoxetine only in alcoholics with a positive family history of alcoholism. In contrast, Kranzler et al. (1996a) found that high-risk/severity alcoholics (i.e., Type B, who have an earlier age of alcoholism onset, more sociopathic features, greater concomitant drug use) had poorer drinking outcomes when treated with fluoxetine, compared with placebo, and that low risk/severity alcoholics (Type A) had somewhat better outcomes on the active medication. Balldin et al. (1994) found an effect of citalopram only among drinkers in the lower range of alcohol consumption in their patient sample. Pettinati et al. (2000) found that later-onset alcoholics drank on fewer days and were more likely to be abstinent in a 12-week treatment trial if they received sertraline than if they were treated with placebo.

In a similar vein, although not an SSRI, ondansetron (a 5-$HT_3$ antagonist) was shown to produce a selective beneficial effect in alcoholics with onset of problem drinking before age 25 (Johnson et al. 2000). At a dosage substantially lower than that used to exert the anti-emetic effects for which the medication is FDA approved, ondansetron was superior to placebo in terms of days abstinent and the intensity of alcohol intake on days when patients did drink. Among alcoholics with onset of problem drinking at age 25 years or later, the effects of ondansetron on drinking behavior were, in nearly all respects, comparable to those of placebo. These findings suggest that prospective studies that aim to match alcoholic subtypes with serotonergic medications may reveal a useful role for such medications in the treatment of alcohol dependence, but the evidence to date does not support their use of SSRIs in routine clinical practice.

### *Acamprosate*

Acamprosate, an amino acid derivative, affects both gamma-aminobutyric acid (GABA) and excitatory amino acid (i.e., glutamate) neurotransmission (the latter effect most likely being the one that is important for its therapeutic effects in alcoholism). The medication is approved for use throughout Europe, and in the US since 2005.

Multicenter studies have been conducted in Belgium, the Netherlands and Luxembourg (Geerlings et al. 1997), Austria (Whitworth et al. 1996), Germany (Sass et al. 1996), and Italy (Poldrugo 1997, Tempesta et al. 2000). All of these studies showed significant advantages for acamprosate over placebo. However, in a study conducted in the UK (Chick et al. 2000b), no beneficial effects of the active drug on drinking behavior were observed. Moreover, the COMBINE study (Anton et al. 2006) found no significant effect of acamprosate on drinking vs. placebo, either by itself or with any combination of naltrexone and cognitive behavioral therapy.

Acamprosate does not interact with alcohol or diazepam. It has no addictive potential and can be used safely with antidepressants. It should not be prescribed to patients with renal insufficiency or severe hepatic failure, nor to women who are pregnant or breast-feeding. Given the rather consistent evidence of the efficacy of acamprosate in alcoholism rehabilitation (Kranzler and Van Kirk 2001), and the benign side effect profile of the medication, it appears to hold considerable value for the treatment of alcohol dependence.

### *Summary*

Additional research is required before medications are likely to play a meaningful role in the postwithdrawal treatment of alcohol dependence. One currently useful strategy is the identification of comorbid psychopathology in alcoholics, with pharmacotherapy directed toward reducing both psychiatric symptoms and alcohol consumption. In addition, the opioid antagonist naltrexone, which is capable of yielding a modest effect overall in reducing drinking behavior, appears to be of considerable value in some individuals. Further research is required with naltrexone to determine the optimal dosage, duration of treatment, and psychosocial treatment strategies with which to use the medication. The question of whether the medication is most efficacious for alcoholics with high levels of craving for alcohol remains an important one. The SSRIs fluoxetine, citalopram, and sertraline may be of value in subgroups of heavy drinkers, particularly those with a later onset of problem drinking. In contrast, ondansetron may be useful in alcoholics with an early onset of problem drinking. Prospective replication of this serotonergic matching strategy is required, however, before it can be recommended for general clinical use. Finally, acamprosate may be useful in the pharmacological management of alcohol dependence but further research is required to explain why the COMBINE study failed to replicate previous findings.

## AA and Mutual Help Organizations

Although mutual help societies composed of recovering alcoholics are not considered a formal treatment, they are often used as a substitute, an alternative, and an adjunct to treatment (McCrady and Miller 1993). Mutual help groups based on the 12 Steps of AA have proliferated throughout the world. To the extent that AA and other mutual help groups are more numerous than outpatient treatment, they may constitute a significant resource for problem drinkers who are attempting to reduce or stop drinking.

With an estimated 100,000 groups and more than 2.2 million members in 150 countries, AA is by far the most widely utilized source of help for drinking problems in the US (Humphreys 2004). In addition, a number of self-help organizations have modeled themselves after AA, basing recovery from drug abuse, overeating, and other behavioral disorders on the 12 Steps of AA (see Table 54–8). Unfortunately, clinicians often refer patients to self-help groups such as AA without consideration of the patient's needs and without adequate monitoring of the patient's response (Emrick 1994). Not all people are willing to endorse the AA emphasis on spirituality and its disease concept of alcoholism, which requires lifelong abstinence as the only means to recovery. Greater familiarity with AA may help clinicians to identify those patients who might benefit from this approach.

Although it is regarded as one of the most useful resources for recovering alcoholics, the research literature supporting the efficacy of AA is limited (Miller and McCrady 1993). Attendance at AA tends to be correlated with long-term abstinence (Vaillant 1983, Humphreys 2004) but this may reflect motivation for recovery. The type of motivated alcoholic that persists with AA might do just as well with other forms of supportive therapy. In fact, the few random assignment studies that have been conducted (Walsh et al. 1991, Brandsma et al. 1980) do not indicate that AA (or similar programs) is more effective than other types of treatment.

Personality variables do not appear to differentiate between alcoholics who affiliate with AA and those who do not (Ogborne and Glaser 1981), although there is some evidence that AA is less successful among persons with major psychiatric disorders and those of low socioeconomic status (Ogborne and Glaser 1981).

Infrequent attempts have been made to assess the efficacy of AA using controlled research designs because of methodological challenges, such as self-selection and ethical concerns about random assignment to treatment

**Table 54–8 The 12 Steps of Alcoholics Anonymous**

1. We admitted we were powerless over alcohol—that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God *as we understood Him*.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed, and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong, promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God *as we understood Him*, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.

The 12 Steps are reprinted with permission of Alcoholics Anonymous World Services, Inc. Permission to reprint this material does not mean that AA has reviewed or approved the contents of this publication, nor that AA agrees with the views expressed herein. AA is a program of recovery from alcoholism. Use of the 12 Steps in connection with programs and activities that are patterned after AA but address other problems does not imply otherwise.

conditions. Nevertheless, several large-scale, well designed studies (Project MATCH Research Group 1997a, 1998, Ouimette et al. 1999, Walsh et al. 1991) suggest that AA can have an incremental effect when combined with formal treatment, and AA attendance alone may be better than no intervention. When AA is combined with a 12-week individual therapy called Twelve-Step Facilitation (TSF), one study (Babor and Del Boca 2003) found that TSF not only increased affiliation with AA, it also had a demonstrable effect on clients whose social networks contained many drinking companions. This study suggested that AA is effective because it helps to change the drinker's social environment, rather than through some form of spiritual conversion.

Walsh et al. (1991) showed that workers who were randomly assigned to a three-week inpatient alcoholism rehabilitation program had significantly better alcohol-related outcomes than workers who were assigned to mandatory AA attendance only. Workers assigned to a third group were allowed to choose their treatment. This group had outcomes that were intermediate between the other two groups. Outcomes were worse among individuals abusing both alcohol and cocaine. A study of long-term outcomes of treated and untreated alcoholics (Timko et al. 2000) indicated that individuals who obtain help for a drinking problem, especially in a timely manner, have better outcomes over 8 years than those who do not receive help, but the type of help they receive (e.g., self-help or formal treatment) makes little difference in long-term outcomes.

## Special Features Influencing Treatment

### Psychiatric Comorbidity

There is considerable evidence that links the outcome of alcoholism treatment to comorbid psychopathology. General measures of psychopathology (McLellan et al. 1983), as well as the specific diagnoses of drug abuse, drug dependence, ASPD and major depressive disorder have been shown to predict poorer outcomes in alcoholics (Rounsaville et al. 1987, Kranzler et al. 1996b). The extent to which treatment of concomitant psychopathology enhances alcoholism treatment outcome is unclear.

Some discussion has already been provided concerning the pharmacotherapeutic approach to treating comorbid psychiatric disorders in alcoholics. Such pharmacotherapy should be considered within the context of a more generalized approach, given the interactional nature of psychiatric and addictive disorders. Ries (1993) has distinguished among serial, parallel and integrated models for treating these disorders. The serial model involves the treatment of one disorder, followed by the treatment of the second disorder. For example, a psychotic alcoholic might first be treated on a general psychiatric unit and once his acute psychosis is controlled, transferred to an alcoholism rehabilitation program. The parallel treatment approach involves concurrent, but separate, treatment of both the psychiatric and the alcohol use disorder. An example of this approach would be the case of a depressed alcoholic who is seen in an addictions program biweekly for his alcohol dependence, but who receives medication and weekly cognitive therapy for depression in a psychiatric clinic. The integrated model involves the treatment of both disorders in a single treatment setting at the same time. This approach requires that personnel with expertise in both the addictions and psychiatric treatment be available in a single location. Each of these approaches has advantages and disadvantages. For example, the integrated model, while it provides the most comprehensive approach, is the most difficult and costly to configure and may, therefore, not be feasible for many treatment providers.

Osher and Kofoed (1989), in advocating an integrated approach to patients with comorbid psychiatric and addictive disorders, have described four phases of treatment with this patient population: (1) engagement of dually diagnosed patients in the treatment programs, (2) persuading these patients to accept long-term abstinence as an appropriate goal of treatment, (3) active treatment, during which efforts are focused on the development of attitudes and the acquisition of skills necessary for sobriety, and (4) relapse prevention, which involves the long-term maintenance of sobriety and extends beyond the acute treatment period.

### Demographic Features

#### *Adolescents*

Despite a paucity of controlled, age-specific treatment outcome studies of adolescents with alcohol use disorders, the need for prevention and specialized treatment for this group is clear. The literature indicates that in substance-abusing adolescents some treatment is better than no treatment, relapse rates are high, and there is no consistent support for the superiority of any single treatment

modality (Brown et al. 1989). However, several factors have been associated with better treatment outcome: later onset of problem drinking, pretreatment attendance at school, voluntary entrance into treatment, active parental input, and availability of ancillary adolescent-specific services, including those pertaining to school, recreation, vocational needs, and contraception (Kaminer 1994, Catalano et al. 1990–1991).

Brown et al. (1989) found that the adolescents who relapsed following inpatient treatment did so most frequently (60%) in response to social pressures to drink or use drugs, with 33% indicating that their relapse was an attempt to cope with negative affect and 27% identifying interpersonal conflict as a precursor to relapse. Accordingly, relapse prevention techniques, including social skills training (e.g., assertiveness techniques, communication skills, strategies for controlling anger) and techniques for managing high-risk situations may be particularly useful for adolescents (Kaminer 1994).

Because many adolescents have not yet fully developed formal operational thinking, treatment efforts should be concrete and goal oriented. Furthermore, the clinician should consider the potential impact on treatment of other cognitive problems: learning disabilities, attention-deficit/hyperactivity disorder, and other psychopathology which may previously have gone undiagnosed. Treatment of the adolescent with an alcohol use disorder also requires an appreciation of the importance of modeling, imitation and peer pressure, which are intrinsic to identity development. The use of age-appropriate support groups (e.g., Alateen) may be particularly useful in this regard.

### *Geriatric Patients*

In addition to the high prevalence of medical problems, pharmacokinetic and pharmacodynamic variables can affect treatment outcome in elderly alcoholics. For example, Liskow et al. (1989) found that elderly alcoholics, despite having drunk less than younger patients during the month prior to admission, had more severe alcohol withdrawal symptomatology and required a higher dosage of chlordiazepoxide. These investigators speculated that the observed differences might delay the entry of elderly alcoholics into rehabilitation.

A wide variety of treatment approaches (Ofman 1992) have been adapted to suit the needs of the elderly alcoholic, ranging along a continuum of intensity that includes multidisciplinary inpatient treatment programs, outpatient individual therapy, group therapy or day treatment, and outpatient recovery support groups. Despite evidence that among the elderly early-onset alcoholics show greater severity than late-onset alcoholics, outcomes following treatment are not substantially different for these groups (Ofman 1992). Treatment programs with experience in treating the elderly alcoholic are better able to coordinate rehabilitation with medical and social service providers, including case management and home visits (Ofman 1992). These programs may also be best able to provide specialized peer treatment for elderly alcoholics.

An important question in treating elderly alcoholics is the extent to which specialized treatment services improve outcome. Kofoed et al. (1987) found that patients treated in special elderly peer groups remained in treatment longer and were more likely to complete treatment than those treated in mixed-age groups. These investigators concluded that elder-specific treatment has differential therapeutic value.

Changes in the demographic features of AA participants (Blazer 1989) suggest that the current cohort of elderly alcoholics has less experience with self-help groups at a time when AA is attracting younger members who are more likely to have comorbid drug abuse/dependence. As a consequence, the elderly can be expected to experience increased difficulty affiliating with AA. This, along with evidence indicating an advantage for age-specific treatment in the elderly, suggests that special efforts should be made to help the elderly alcoholic locate AA meetings that include a substantial proportion of older participants. Age-appropriate AA groups may be especially beneficial to the older alcoholic who is isolated and lonely and for whom the prospect of helping others may help to combat feelings of uselessness (Blazer 1989).

### *Gender (Including Pregnancy)*

As described above, epidemiological and clinical studies have shown that alcohol abuse and dependence have become quite common among women, as historical gender differences in drinking problems have diminished during the past 25 years. This trend has promoted greater awareness of the impact of alcohol use on women's health and the importance of gender as a potential determinant of treatment outcome. Nonetheless, the vast majority of studies related to alcohol use and its effects, including the diagnosis and treatment of alcohol dependence, have involved men (Nixon 1993, Lex 1992). The recent requirement by the National Institutes of Health and the FDA that women and minorities be actively recruited to participate in health-related research should help to increase knowledge about alcoholism treatment outcome in these groups.

To guide the treatment of alcoholism in women, Blume (1992) suggests that evaluation should include special attention to the identification of physical abuse, sexual abuse, medical problems, psychiatric comorbidity, the presence of alcoholism and drug abuse in spouses, and alcohol-related birth defects in children. To enable women with children to participate in treatment, the availability of childcare services is critical, although it must generally be arranged independent of treatment. Blume (1992) also lists the following special treatment needs of women: information about the effects of substance use on the fetus, parenting skills, couples and family therapy, sober female role models, assertiveness training, and an awareness of sexism and its consequences. Special care must also be taken to avoid creating iatrogenic drug dependence in women (e.g., through the use of benzodiazepines to treat comorbid anxiety and depressive symptoms). While these are useful guidelines for treating alcoholic women, empirical research is needed to evaluate these and other issues more systematically.

### *Ethnic and Cultural Issues and Treatment*

In 1991 approximately two-thirds of patients in alcoholism treatment were white, 17% were black and 12% were Hispanic (U.S. Department of Health and Human Services 1994). Although socioeconomic and cultural issues should be addressed in alcoholism treatment (Franklin 1989),

guidelines for such treatment are based largely on common sense, rather than systematic outcome evaluation. Obviously, where language barriers exist, special efforts must be made to ensure adequate communication. Treatment providers should also be aware of their patients' traditional patterns of drinking, how drinking may be influenced by acculturation, differences among ethnic groups in their perception of alcohol-related problems, the impact of sociocultural differences between patients and providers, and how prevailing social (e.g., family) relationships can affect treatment outcome.

## Conclusion

During the past 30 years significant progress has been made in the scientific study of alcohol dependence and its treatment. On the basis of evidence reviewed in this chapter, a number of conclusions appear warranted at this time:

1. People with alcohol-related problems are heterogeneous with respect to demographic features (e.g., age, gender, race/ethnicity), age of onset of heavy drinking, severity of alcohol dependence, comorbid psychopathology, genetic vulnerability, and other prognostic factors.
2. The available evidence suggests that any treatment for alcohol dependence is better than no treatment. The majority of those treated demonstrate improvement, but many of these alcoholics may improve with minimal treatment.
3. The intensity of treatment has not been shown to produce pronounced differences in outcome (Moos and Moos 2003). Similarly, medical inpatient treatment, while more costly, is not demonstrably more effective than nonmedical residential or outpatient treatment. For patients with serious comorbid medical and psychiatric disorders, medical inpatient treatment may, nonetheless, be necessary. Some evidence indicates that continuing aftercare helps to maintain abstinence following short-term intensive rehabilitation in inpatient settings.
4. There is little evidence that any one treatment approach is superior. There is some support for certain kinds of behavior therapy and AA, but the effectiveness of disulfiram seems to depend on patient characteristics and compliance. Several kinds of carefully specified and theoretically derived therapeutic approaches show promise as a basis for a new generation of ambulatory treatments. These include the relapse prevention strategies that teach the alcoholic how to avoid high-risk relapse situations, and new pharmacologic agents (e.g., naltrexone) that appear to reduce the alcoholic's risk of relapse by dampening the reinforcement potential of alcohol. Continued improvements in treatment outcome will depend upon successfully matching treatment settings and modalities to the specific needs of the individual patient.

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CHAPTER

# 55 Substance Abuse: Amphetamine Use Disorders

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Amphetamine Intoxication
Amphetamine Withdrawal

Most mental health and medical professionals in the United States consider the psychostimulant cocaine as representative of the entire class of psychostimulant drugs. While far less literature exists regarding other psychostimulants, illicit abuse of substances such as methamphetamine and illicit use of prescribed substances such as methylphenidate (Ritalin) represent a growing health concern (Anglin et al. 2002). While the major abused psychostimulant in the United States is cocaine, this is not the case in several Western US cities, nor in the state of Hawaii (Rawson et al. 2002a). Worldwide abuse or regular use of amphetamines is more than double that of cocaine.

Consistent with the schema put forward by the DSM-IV-TR, this chapter defines the amphetamine-like substances to include the phenylisopropylamines amphetamine (AMPH), methamphetamine (METH), and phenylpropanolamine (PPA), the natural substances ephedrine and pseudoephedrine, and phenylethylamines including methylphenidate and pemoline. While METH and AMPH cause the vast majority of abuse and dependence, use of any of these substances has been associated with abuse and dependence, so as a class these will be referred to as amphetamine-type stimulants, or ATS, in this chapter.

By far, the most widely abused ATS is METH, which is commonly known as meth, speed, crank, CR, wire, and jib, and in its recrystallized smoked form, ice, crystal, or glass. Legitimate forms of METH prescribed for attention-deficit/hyperactivity disorder (ADHD) and weight control (Methedrine, Desoxyn, and Adipex) undoubtedly represent a miniscule source of the total amount abused each year. AMPH, most prevalent in Western Europe, is commonly known as amp, bennies, dex, or black beauties, and is prescribed as Adderall, Dexedrine, and Dextrostat in the treatment of ADHD, narcolepsy, weight control, and depression. Other agents that have been designated as Schedule II controlled substances by the Drug Enforcement Administration are methylphenidate (Ritalin, Concerta) and phenmetrazine (Preludin). Given the widespread prescription of Ritalin in the United States for ADHD and narcolepsy, its diversion to abuse appears rare (Kollins et al. 2002). On the street, Ritalin is known as Rits or Vitamin R. Pemoline (Cylert) is a Schedule IV agent, also used to treat ADHD and narcolepsy. A large number of Schedule III and IV phenylethylamines (benzphetamine, diethylproprion, mazindol, phendimetrazine, phenmetrazine, and phentermine) are used for weight control. There is no specific evidence that these substances represent a significant source of illicit diversion, and they are not further discussed in this chapter. ATS agents are also widely available in over-the-counter (OTC) preparations. As discussed below, PPA has been removed from the market, but ephedrine and pseudoephedrine are still very widely used as decongestants, and less so, phenylephrine and propylhexidrine (Gorelick and Cornish 2003). An excellent tabulation of currently available formulations of prescribed ATS agents is found in Greenhill et al. 2003.

Diversion of prescription medications for illicit use is not a major source of illicit precursor synthesis of METH or AMPH. Unfortunately, a large amount of stimulant abuse that is not easily quantified occurs at rave parties and other venues for experimentation (Poulin 2001). Drug use among such individuals probably represents substance misuse and is less likely to meet formal criteria for abuse. However, it is uncommon that those that go on to amphetamine dependence continue to supply their habit through licit sources. Further, medically appropriate use of synthetic stimulants does not appear to pose a significant risk for the induction of substance-use disorders. This has been most closely examined for the widely prescribed methylphenidate (Ritalin) for

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ADHD; in this case, treatment may actually reduce the risk of developing substance abuse by controlling ADHD, itself a risk factor for substance abuse (Biederman et al. 1999). Further, methylphenidate poses a low risk for medical complications (Rappley 1997). With increasing distribution in the adult population, there may be concern that this picture may change (Levin et al. 1999). It has been postulated that the persistence of peripheral autonomic effects, as well as much longer half-life in the striatum, accounts for its low abuse potential relative to cocaine (Volkow et al. 1995, Volkow et al. 1999).

The socially acceptable and very desirable effects of prescribed ATS, weight loss and productivity enhancement, make widespread use, and thus abuse, unavoidable. Students and athletes appear particularly at risk for development of stimulant abuse, given that both exposure to licit and illicit sources and the pressures to use are high (Murray 1998, Teter et al. 2003). Of course, those whose jobs require sleep cycle reversal, long hours and so on, such as truck drivers, also appear at high risk (Akerstedt and Ficca 1997).

AMPH-like substances, especially METH, are most commonly injected or smoked by heavy users (Murray 1998). Its low melting point, similar to crack cocaine, makes it well suited as a smokable agent (Cho 1990). These routes provide the most rapid onset of action, though peak blood levels and half-lives are approximately the same as for the oral route (Cook et al. 1993, Lebish et al. 1970). Most likely, abuse by those experimenting with the agent is oral. Through the mid 1990s, the oral and intravenous routes were still the most popular (Hall and Hando 1993). Methylphenidate displays a significantly shorter half-life (2-4 hours) than AMPH and METH, reaching peak levels in 1–3 hours (Volkow et al. 1995). Methylphenidate abuse, however, is mainly through the intravenous route with crushed tablets (Parran and Jasinski 1991) though it may also be snorted (Garland 1998).

## Diagnosis

Consistent with the DSM-IV-TR perspective functionally equating amphetamines with cocaine, those diagnostic categories that are included are identical to those for Cocaine-Related Disorders, with the sole exception of omitting the specifier "With Onset During Withdrawal" from the diagnostic category Amphetamine-Induced Anxiety Disorder. For the substance use disorders, amphetamine (ATS) abuse and dependence will be discussed below. Of the substance-induced disorders, the critical diagnoses of ATS intoxication and withdrawal are described. The specific complications of delirium, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunctions, and sleep disorders all are described under intoxication. Amphetamine-induced mood and sleep disorders also allow for specifiers of onset during withdrawal.

### Amphetamine Dependence

ATS dependence is diagnosed when a maladaptive pattern of use leads to clinically significant impairment or distress, as defined by three or more of the following that occur during the same 12-month period: (1) evidence of tolerance, (2) occurrence of withdrawal, or the reuse of the substance to alleviate withdrawal, and (3) compulsive use of amphetamines as defined by three or more of the following: using more than intended, (4) desire or efforts to reduce use, (5) occupying significant time in drug-related activities, (6) loss of social, occupational, or recreational pursuits, or (7) continued use despite known adverse, physical, or psychological consequences.

### Amphetamine Abuse

The diagnosis of ATS abuse requires a maladaptive pattern of use that does not meet the criteria for dependence, and that results in clinically significant impairment or distress. In the preceding 12 months, recurrent substance use must result in one or more of the following: failure to meet major role obligations, placement of the user in physical danger, legal entanglements, or social/interpersonal problems.

### Amphetamine Intoxication

Specific diagnostic criteria are provided for ATS intoxication (see DSM-IV-TR diagnostic criteria below). These include recent use of an ATS (criterion A), clinically significant maladaptive behavioral or psychological changes

**DSM-IV-TR Criteria 292.89**

**Amphetamine Intoxication**

A. Recent use of amphetamine or a related substance (e.g., methylphenidate).

B. Clinically significant maladaptive behavioral or psychological changes (e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension, or anger; stereotyped behaviors; impaired judgment; or impaired social or occupational functioning) that developed during, or shortly after, use of amphetamine or a related substance.

C. Two (or more) of the following, developing during, or shortly after, use of amphetamine or a related substance:

1. tachycardia or bradycardia
2. pupillary dilation
3. elevated or lowered blood pressure
4. perspiration or chills
5. nausea or vomiting
6. evidence of weight loss
7. psychomotor agitation or retardation
8. muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
9. confusion, seizures, dyskinesias, dystonias, or coma

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

*Specify* if:

**With Perceptual Disturbances.**

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**Table 55–1 Maladaptive Behaviors Listed in Criterion B of Amphetamine Intoxication, with Comments and Explications in Parentheses**

| |
|---|
| Euphoria or affective blunting (felt to occur in longer-term users) |
| Changes in sociability (e.g., being hypertalkative, more interactive or more withdrawn, increased libido) |
| Hypervigilance (with ideas of reference that can proceed to frank paranoia) |
| Interpersonal sensitivity |
| Anxiety, tension, or anger (agitated behavior and altercations are common) |
| Stereotyped behavior (picking at skin, grooming, pacing, disassembly/reassembly of objects) |
| Impaired judgment (often seen as sexual promiscuity) |
| Impaired social or occupational functioning |

**Table 55–2 Physiological Disturbances Listed in Criterion C of Amphetamine Intoxication, with Comments and Explications in Parentheses**

| |
|---|
| Tachycardia or reflex bradycardia |
| Papillary dilatation |
| Elevated or lowered blood pressure |
| Perspiration or chills |
| Nausea or vomiting |
| Evidence of weight loss |
| Psychomotor agitation or retardation (an excited delirium is described as for cocaine, along with tremor) |
| Muscle weakness, respiratory depression, chest pain, or cardiac arrhythmia |
| Confusion, seizures, dyskinesias, dystonias or coma (Headaches and tinnitus are additional neurological symptoms that have also been described as occurring) |

occurring after the use of the ATS (criterion B), two or more specified physiological changes after the use of the ATS (criterion C), and the requirement that the condition is not accounted for by another mental or medical condition (criterion D). A specifier "with perceptual disturbances" is included.

The specifics of criteria B and C provide a useful clinical consensus of the syndrome of ATS intoxication (see Table 55–1 for a list of the maladaptive behaviors of Criterion B, with comments by the author in parentheses). Importantly, psychosis and paranoia are experienced by approximately one-third of ATS-dependent subjects (Williamson et al. 1997, Harris and Batki 2000) and occur at a significantly greater rate than for cocaine or Ecstasy. With chronic use, the incidence of psychosis increases (Hall et al. 1996). Furthermore, the occurrence of psychotic symptoms correlates with heavier use, co-use of benzodiazepines, and preexisting mental illness (Vincent 1998). Cognitive disturbances include visual, tactile, and auditory hallucinations. Visual hallucinations often suggest an underlying "organic" cause to psychosis, and formication, the feeling of "bugs crawling under the skin" is highly suggestive of ATS or cocaine intoxication. Psychosis in the presence of an intact sensorium, where the subject is aware that the hallucinations are not real, may differentiate ATS-induced psychosis from psychotic states such as schizophrenia. Nonetheless, ATS-induced psychosis shares many features with other acute psychotic states (Griffith et al. 1969, Snyder 1973, Flaum and Schulz 1996). A wide range of ATS dosages can induce psychosis, likely because individuals vary in tolerance (Bell 1973). Of concern, ATS-induced psychosis can sometimes persist for months following cessation of drug use (Buffenstein et al. 1999). Recently, an intriguing finding is that such prolonged METH-induced psychosis is associated with the presence of nine or fewer repeat alleles in the VNTR polymorphism of the human DAT1 gene (Ujike et al. 2003). This 3' untranslated (i.e., the region of RNA not coding for proteins) region polymorphism could affect mRNA half-life, and relate to the prolonged depression of DAT levels following chronic METH exposure. Interestingly, while psychosis would appear to be a fairly drastic symptom during intoxication, it appears to be a relatively common drug reaction among nonabusing methylphenidate users. Cherland and Fitzpatrick (1999) found 6 of 98 children with signs of psychosis. Appropriate use of PPA also is associated with psychosis (Goodhue et al. 2000, Norvenius et al. 1979). Women appear to be at greater risk, as do those with preexisting mood or psychotic disorders (Marshall and Douglas 1994).

The physiological disturbances in criterion C are listed in Table 55–2, again with author's comments in parentheses.

## Amphetamine Withdrawal

While the intoxicated state is characterized as euphoric, expansive, and activated, and often presents with agitation, violence, and/or psychosis, ATS withdrawal is characterized by decreased energy and mood. The clinician often evaluates such individuals who become suicidal during

**DSM-IV-TR Criteria 292.0**

**Amphetamine Withdrawal**

A. Cessation of (or reduction in) amphetamine (or a related substance) use that has been heavy and prolonged.

B. Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:
   1. fatigue
   2. vivid, unpleasant dreams
   3. insomnia or hypersomnia
   4. increased appetite
   5. psychomotor retardation or agitation

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

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the "crash." The period of most intense withdrawal may last days, though a protracted state of depression and low energy often persists for weeks (Kramer et al. 1967, Murray 1998). Resurgence of craving when exposed to drug-associated environmental cues probably persists for years, as is the case with other substance-dependence disorders. The occurrence of ATS withdrawal usually occurs in those that have progressed from the diagnosis of abuse to dependence.

The ATS withdrawal diagnosis requires cessation or reduction of ATS use that has been heavy or prolonged (criterion A), dysphoric mood and at least two physiologic changes that occur from a few hours to days after cessation of use (i.e., fatigue; vivid, unpleasant dreams; insomnia and hypersomnia; increased appetite; psychomotor retardation or agitation) which cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (criteria B and C); and the requirement that the condition is not accounted for by another mental or medical condition (criterion D) (see DSM-IV-TR diagnostic criteria above).

Both the longer half-lives of ATS relative to other psychostimulants, as well as the broader-spectrum effects on nerve terminal catecholamine levels, result in prolonged withdrawal and abstinence states. ATS withdrawal states occur in some 87% of users (Cantwell and McBride 1998, Schuckit et al. 1999). The acute phase appears to last up to 5 days, with some symptoms persisting for weeks, possibly months, following the acute phase (Srisurapanont 2001a, Watson et al. 1972).

Since neurocognitive impairment occurs early in withdrawal, clinicians should be cognizant that instructions to individuals in withdrawal be kept simple and written out (Kalechstein et al. 2003). Decision making, as has been known anecdotally for years, appears affected (Paulus et al. 2003). If individuals with amphetamine dependence fail to appear in follow-up, outreach attempts are necessary to keep the individuals engaged. EEG data support alterations during early withdrawal (Newton et al. 2003). Over months, these cognitive deficits may partially remit to a greater extent than in opiate abusers (Rogers et al. 1999, Ornstein et al. 2000). Severe craving marks the early withdrawal phase, leading to high recidivism. Sleep disturbance is accompanied by increase in REM sleep (Watson et al. 1972).

## Epidemiology

After cannabis, worldwide ATS (principally METH and AMPH) are regularly used or abused by some 35 million individuals (United Nations Drug Control Program 2003). In contrast, cocaine is used by 15 million worldwide, and heroin by 10 million. The United Nations Office of Drug Control Report (2003) showed that, except for cannabis, more new countries reported use of ATS than any other illicit substance. Interestingly, while cocaine is the most widely used psychostimulant in the Americas, outside of these areas, especially in the Far East and Southeast Asia, Oceana, and Western Europe, ATS abuse is far more prevalent (United Nations Drug Control Program 2003). It is estimated that two-thirds of the world's ATS abusers live in Asia, with Thailand experiencing perhaps the most severe epidemic (Ahmad 2003). The long half-life and relatively inexpensive nature (approximately 25% the cost of use of cocaine) make it possible to continue use for years without adverse sequelae necessitating treatment or incarceration. (Simon et al. 2002b). However, it seems likely that users in the workplace may suffer increased use of other health care services, loss of workplace attendance and so on.

It is estimated that 5–10% of adults have a lifetime prevalence of nonprescription ATS use, 0.5% in the last year, and 0.2% in the prior month (SAMHSA 2003). Roughly, 5% of adults in the United States have had a history of nonprescribed use of ATS drugs, 1% in the prior year, and 0.4% in the prior month. ATS dependence and abuse combined have approximately a 1.5% lifetime prevalence according to DSM-IV-TR. The performance-enhancing effects of ATS place students faced with competitive stress such as high-achievers and athletes at high risk (Bailey 1987, Conrad et al. 1988). Since performance enhancement is much more pronounced under conditions of sleep deprivation, abuse by those in repetitive, sleep-shifted occupations, such as truck drivers, is also high (Heishman 1998).

The prevalence of ATS use appears particularly related to supply routes, perhaps because its sole source of production is synthetic, and not grown. While originally diverted from pharmaceutical supplies (such as via the US armed forces into Japan in the 1950s), and synthesized by biker gangs, it is now produced by a more wide variety of small producers, as well as "superlabs" producing 10–100 lb batches in Mexico where precursor supplies are not legislatively limited (Karch 2002). Small production sites are likely to remain because its synthesis is relatively easy, and provides for personal use as well as excellent profit margins. Further, precursor supply interdiction appears to affect large producers to a far greater extent than the small backyard labs (Cunningham and Liu 2003).

METH is the predominant form of ATS used in the world today. This is especially true in the United States west of the Mississippi, in Hawaii, Taiwan, Japan, and Southeast Asia (Rawson et al. 2002a). METH-related emergency room admissions represent a small but rapidly growing problem in these regions (Karch 2002). The demographics of METH use are also unusual for the United States. METH use, as well as deaths related to METH use, is predominantly male (86%) and Caucasian (75%), as well as surprisingly old (mean 36.8 years of age). (Karch 2002). Use in the last several years appears to be spreading beyond the typical unemployed, single Caucasian males that originally characterized users during past epidemics (Baberg et al. 1996).

The clandestine nature of production in small "mom and pop" labs, and the release of easily detected noxious fumes, makes rural production, and thus rural use, a particular problem. These demographics present problems for smaller health-treatment resources ill equipped to handle mental health issues integrally linked to antisocial and violent behavior.

## Patterns and Routes of Use

ATS is regarded as highly addictive, with some 50% who initially experiment illicitly with ATSs progressing to dependence (Woody et al. 1993). Heavy users, especially of METH, most commonly inject or smoke. These routes appear to have the highest potential to result in dependence (Gorelick and Cornish 2003). Its low melting point, similar to crack cocaine, makes it well suited as a smokable substance. Most likely, abuse by those experimenting with the agent is

oral. Indeed, even OTC preparations containing ephedrine and pseudoephedrine are commonly abused (Tinsley and Watkins 1998). Through the mid 1990s the oral route, and intravenous, were still the most popular (Hall and Hando 1993). Methylphenidate abuse, however, is mainly through IV route with crushed tablets (Parran and Jasinski 1991), though it may also be snorted (Garland 1998).

It is believed that ATS smoking and IV abuse lead to more rapid dependence than oral and snorted abuse. By the smoking route METH reach the brain in seconds, and the initial "rush" occurs soon thereafter, with peak effects at 2–4 minutes. Intravenously, ATS probably peak slightly later, though this conclusion is based on the extension of studies with cocaine (Telang et al. 1999).

There are two main patterns of heavy use—binge use and chronic use. In binge use ("speed runs"), increasing amounts are used over a few days, usually ended by exhaustion of resources, the user, or the onset of adverse events, such as intense agitation or psychosis. The second pattern of use in dependent individuals is chronic, repeated use over long periods. This pattern is sustained both by IV and smoking routes, as well as oral use.

Methylphenidate is believed to be less addictive than other ATS for several reasons. It appears to be cleared from human brain sites far more slowly than cocaine (Volkow et al. 1995) and so should show a reduced addictive potential. Further, it appears to cause less euphoria than AMPH (Klein and Wender 1995). In the main, ATS taken by the oral route reach maximum plasma level in 1–3 hours, but half-life of effect is more varied. Methylphenidate, PPA, and phenylephrine have half-lives of 2 to 2.5 hours, significantly shorter than those for AMPH (7–34 hours) and METH (6–15 hours) (Baselt 1999).

As with other stimulants, adverse subjective effects experienced by users may be tempered by co-use of depressants, including alcohol and benzodiazepines, but there are no large studies of such comorbidity.

METH is cleared from the body by several routes. Approximately 45% is excreted unchanged in the urine, though this can be increased by acidification of the urine (Cook et al. 1993, Wan et al. 1978); conversely, ingestion of sodium bicarbonate can reduce elimination and concentrations in the urine (to hinder detection) (Braithwaite et al. 1995). Approximately 20% is N-demethylated to form AMPH (Caldwell et al. 1972). This fact is used to advantage in distinguishing METH positive urines that result artifactually from current analytic processes with ephedrine testing (where no AMPH is found) to positives where both METH and AMPH are present (supporting actual METH use). These compounds undergo further metabolism via oxidation (forming norephedrine and other active metabolites), parahydroxylation (also to active compounds), and deamination (to inactive products). All phenylisopropylamines competitively inhibit CYP2D6 (Wu et al. 1997).

## Medical Complications

For heavy users, a number of general consequences of ATS dependence will be obvious; malnutrition and cachexia from sleep deprivation, exposure to the elements and so on. Skin disorders, including infections and lesions from "picking" are common. More serious are ATS-related deaths due to cardiac arrhythmias, stroke, and rhabdomyolysis that have been documented since the 1950s. These problems were similar to those reported for the more widely abused cocaine. Concern over unique toxicity further increased when "ice," the smokable form of METH, began to be seen in Japan in the late 1970s (Cho and Wright 1978). Still there is only approximately 1 METH-related death for every 10 related to cocaine, and the reasons that may be are described below. Also as described below, a number of factors place ATS users at high risk for contraction of HIV, and likely Hepatitis B and C, infection.

Some of the medical complications result from exposure to contaminants during ATS use. The production methods for ATS determine what contaminants are present in illicit manufacture. Contaminants are both toxic, as well as stimulants in their own right (Soine 1986). In the United States, the "red phosphorous" route of conversion of (−) ephedrine (to METH) and (+) pseudoephedrine (to DEX) is nearly exclusive today. Contaminants such as 2-phenylmethyl-phenylethylamine are common to both processes. Now that it is recognized that ephedrine is being illicitly diverted in the United States, its importation is also being regulated. METH cooks occasionally resort to other cold remedies and stimulants, but these appear to represent minor supply sources, for example, substitution of phenylpropylamine (PPA) leads to production of DEX.

For methylphenidate, the principal complications occur only when the drug is diverted to illicit intravenous use. Its formulation makes talcosis resulting from IV use prominent, where the lungs (Schmidt et al. 1991) and eyes (Lederer and Sabates 1982) are most affected. There are case reports of catecholamine toxicity with intentional overdose, and the complication pattern is not unique compared to METH.

Many of the cardiovascular complications for ATS described below result from peripheral catecholamine toxicity. This explains why the principal drug interactions of concern involve the psychotropics that are meant to augment catecholamine function. Of most concern are the monoamine oxidase inhibitors, whose action can potentiate ATS toxicity for 2–3 weeks following cessation of use. Similarly, tricyclic antidepressants can potentiate effects of ATS, as well as increase absorption and slow hepatic metabolism (Gorelick and Cornish 2003). However, off-label use of ATS to augment tricyclics is not uncommon, and at least one study has found that desipramine and stimulants (i.e., methylphenidate and dexadrine) have no clinically significant interaction in children (Cohen et al. 1999).

### *HIV and Immunomodulatory Effects*

It is now appreciated that intravenous drug use is the fastest growing route for transmission of HIV infection (NIDA Research Report, 2002). In addition, ATS use is associated with unsafe sexual behaviors, including participation in unprotected sex and involvement with multiple sexual partners (Molitor et al. 1998, Chesney et al. 1998, Zule and Desmond 1999). This results from the drug's acute effect of enhancing libido and impairing judgment, and from the association of ATS use with sexual behavior among gays (Shoptaw et al. 2002). In the Shoptaw study, two-thirds of treatment-seeking ATS users were HIV positive. Once HIV has been contracted, ATS abuse leads to accelerated CNS and cardiovascular toxicity (Nath et al. 2001, Yu et al. 2003). METH and AMPH are immunomodulators, and in fact,

may be immunotoxic to peripheral T cells, mitogen-stimulated lymphocytes, and spleen cells (Yu et al. 2003). METH use and HIV infection may synergistically interact to accelerate the course of the HIV infection (Phillips et al. 2000).

### *Pulmonary*

In the Karch autopsy series (1999) of individuals who died from ATS use, pulmonary edema was present in 70% of cases, as well as pneumonia (8.2%), and emphysema (5.1%). Birefringent crystals at bifurcation of pulmonary vessels is associated with intravenous abuse of crushed pills that contain insoluble fillers such as talc, microcrystalline cellulose, corn starch, or cotton fibers. With sufficient deposition, small vessel thrombosis and granuloma formation ensues (Tomashefski and Hirsch 1980). The changes ultimately reduce pulmonary perfusion, and increase pulmonary vascular resistance (Kringsholm and Christoffersen 1987). Possibly because of an increased ratio of intravenous drug abuse to other routes, heroin abusers are more prone to progress to pulmonary thromboembolic complications than are stimulant abusers. Less commonly, oral tablet consumption by the IV route results in pulmonary amyloid formation (Shah et al. 1998).

### *Gastrointestinal*

In METH-related deaths, the sum of liver-related complications was second highest among organ systems. Fatty liver (16.2%), cirrhosis (9.0%), portal triaditis (6.1%), and hepatitis (4.1%) were detected (Karch et al. 1999b). This may relate to the high comorbidity with alcohol dependence, though the exact contribution is unknown. One patho-physiological connection may be hepatotoxicity secondary to excessive alpha2-adrenergic stimulation (Roberts et al. 1997). ATS, including pemoline (Cylert) and methylphenidate (Ritalin) have been specifically implicated as hepatotoxins, though this appears to be rare, idiosyncratic hepatocellular damage (Nehra et al. 1990, Mehta et al. 1984).

### *Cardiovascular*

Both cocaine and ATS cause similar vascular toxicity, largely related to catecholamine excess (Todd et al. 1985a, b). Hearts of stimulant abusers develop areas of fibrosis and contraction band necrosis, and usually are increased in weight. Typically, interstitial fibrosis with myocyte hypertrophy is found at autopsy (Karch 2002). As well, coronary artery disease is accelerated. At autopsy, 16.4% of METH-related deaths showed moderate to severe coronary artery disease (Karch et al. 1999b). Aortic dissection is a less well known but catastrophic complication of METH use (Swalwell and Davis 1999). Yu et al. (2003) also argue that immunosuppressive effects of ATS lead to enhanced cardiotoxicity. Cardiotoxic effects are partly reversible (Islam et al. 1995).

Case reports of myocardial infarction that occurs following ATS are known for use by any route (Furst et al. 1990 Packe et al. 1990, Derreza et al. 1997). Limited data indicate that infarctions result from coronary spasm rather than the results of fixed lesions. Why are myocardial infarction rates with METH so much less than those with cocaine? Karch hypothesizes that the prolonged nature of insult required to damage the fairly hardy cardiovascular system is more the exception than the rule in human users; many more people experiment with ATS than become regular users. Further, hyperthermia, more common with METH than cocaine results in the production of heat shock proteins that may be protective of ischemic damage (Maulik et al. 1995). Cardiomyopathy also appears more rarely in METH use than for cocaine (Smith et al. 1976, Call et al. 1982, Jacobs 1989). The phenomenon clearly occurs at increased rates relative to controls with METH (Matoba et al. 1986, Hong et al. 1991). While most ATS seem similar, methylphenidate may produce a unique pattern of lamellated ultrastructural lesions in the heart (Henderson and Fischer 1995). Of note, heart failure in children treated with Ritalin is so rare as to be at the case report level.

### *Central Nervous System*

As opposed to the medical complications described above, which often are discerned at autopsy, CNS effects including psychosis and stroke are common presenting symptoms in emergency departments.

Seizures are one of the most common presentations of ATS intoxication to emergency rooms (Alldredge et al. 1989). In association with an uncontrollable delirium, they can quickly lead to death if not controlled. Following decreases in ATS blood levels, individuals who abuse ATS are not left at increased risk for reoccurrence of seizures unless CNS lesions from prior stroke have developed.

Strokes associated with ATS can be ischemic or hemorrhagic in nature. These are seen with METH that is taken IV (Imanse and Vanneste 1990, Yen et al. 1994, O'Brien 1998, Pettiti et al. 1998), smoked (Rothrock et al. 1988, Yen et al. 1994), or taken orally (Delaney and Estes 1980). Intracerebral hemorrhage, or a combination of intracerebral and subarachnoid hemorrhage, appear to be the most common stroke type (Harrington et al. 1983). Similar to cocaine, the frontal lobes are most commonly involved, followed by the basal ganglia. These are the same areas where dopamine depletion appears to be the most prominent, and differs from the areas of highest involvement with hyptertensive hemorrhagic stroke, where the basal ganglia and hypothalamus are most commonly involved.

The alleged connection between hemorrhagic stroke and phenylpropylamine (PPA; ±norephedrine) prompted its withdrawal from the market in 2000 (Kernan et al. 2000). Widely used in cold and cough remedies, it was also popular as an appetite suppressant. Compared to METH and AMPH, it has much higher affinity for alpha-adrenergic receptors than beta. Thus, the agent has greater affects on peripheral blood pressure. However, its overall pattern of toxicity is again consistent with catecholamine excess, though cerebral vasculature seems more affected than coronary or pulmonary vessels (Karch 2002).

Ischemic stroke most commonly follows embolism (Pettiti et al. 1998). In some cases, this appears related to an intimal fibrinoid necrosis and mixed cellular infiltrates that results in luminal compromise (Citron et al. 1970, Stafford et al. 1975, Bostwick 1981). A number of oral agents, including methylphenidate and ephedrine, have been implicated in vasculitis (Trugman 1988, Schteinschnaider et al. 2000).

Hyperthermia is related to a number of causes in those presenting with METH intoxication. Increased motor activity, with reduced heat dissipation from peripheral vasoconstriction is the proximate cause. It is also likely that direct affects on hypothalamic thermal regulation exist.

In humans, METH use is correlated over time with declines in N-acetylaspartate levels in basal ganglia and frontal white matter (Ernst et al. 2000, Nordahl et al. 2001). These changes, however, are not correlated with gross histopathologic changes in METH-related deaths. A clue that dopamine declines might be related to functional incapacities, however, is the fact that hyperthermic crises during METH use appear to be related to basal ganglia depletion of dopamine (DA) (Bowyer et al. 1994).

### *Renal*

Rhabdomyolysis is clearly the major concern for renal impairment; there does not appear to be independent toxicity to the kidney (Karch 2002). However, METH is an increasingly common cause of rhabdomyolysis (Richards et al. 1999), and is often associated with hyperthermia. Myoglobin and myoglobin breakdown products cause tubular obstruction. Renal damage results from hypotension and renal ischemia secondary to metabolic derangements secondary to rhabdomyolysis, including phosphorus and potassium imbalance, and tubular obstruction due to catabolic product accumulation.

### *Effects on the Fetus*

Fetal loss, developmental delay, and subsequent learning disabilities are potential complications of ATS use during pregnancy. While widely quoted, it appears that perinatal complications may be more rare than expected (Catanzarite and Stein 1995, also see Plessinger and Woods 1998). This is despite the fact that fetal exposure is widespread (Oro and Dixon 1987). Karch puts forward the argument that the about-to-be-born fetus is protected from AMPH-related toxicity because it has already been prepared for the catecholamine surge that occurs during childbirth by down-regulation of catecholinergic receptors. Preclinical studies indicate METH also concentrates in the fetus (Stek et al. 1993), supported by a limited number of human autopsy cases (Stewart and Meeker 1997). In reported cases, fetal death was not attributable to drug presence; conversely pregnancy may increase the risk of METH use (more common than cocaine) (Vega et al. 1993). METH also concentrates in breast milk (Steiner et al. 1984), but ill effects on children remain controversial (Briggs et al. 1975, Eriksson et al. 1978, Little et al. 1988a, b, Joffe and Kasnic 1994). Most recent studies support a small effect of newborn birthweight, and a low incidence (4%) of overt ATS withdrawal in newborns of METH-dependent mothers (Smith et al. 2003).

## Etiology

ATS operate as indirect sympathomimetics to enhance catecholamine release, and at higher doses, serotonin release. Practically speaking, these agents increase peripheral norepinephrine (NE) levels in the sympathetic nervous system, and centrally, dopamine, norepinephrine, and serotonin levels. Release of central dopamine appears to be the primary action mediating the addictive potential of ATS, but release of NE mediates many of the toxic and peripheral effects (Wilens and Spencer 1998, Sevarino et al. 2000). Postsynaptically, the principal peripheral effects are to stimulate alpha and beta adrenergic receptors. In virtually all actions, the D-stereoenantiomer of the compounds at their alpha-carbon center is 3–5 times more active than the L-enantiomer (Gorelick and Cornish 2003). The precise mechanisms by which these agents affect synaptic levels of neurotransmitters is best understood for AMPH, METH, and methylphenidate.

Acutely there are four identified molecular targets of AMPH. In the dopamine system, AMPH acts as a false substrate for the dopamine transporter (DAT) (Amara and Sonders 1998). This transporter is the principal exchange mechanism by which released dopamine (DA) is cleared from the synapse and recycled into the synaptic nerve terminals. Elegant studies have now determined that AMPH results in elevation of intracellular sodium, causing the kinetics of DA exchange through the DAT to favor outward movement of DA (Khoshbouei et al. 2003, Jones et al. 1999). AMPH is internalized where it enhances release of vesicular stores of DA (and NE) into the cytoplasm where exchange via the DAT occurs. This appears to be through inhibition of vesicular monoamine transporter (VMAT) (Boja and Meil 1998), an action shared by cocaine (Brown et al. 2001). VMAT partial knockout mice show enhanced locomotor stimulation by AMPH, reduced reward, and absent sensitization (Uhl et al. 2000). AMPH is selective for releasing newly synthesized cytoplasmic catecholamine stores before enhancing vesicular release; methylphenidate acts more on vesicular pools (Greenhill et al. 2003). A key difference appears to be METH's selectivity for action at the DAT, and not on vesicular transport or cytoplasmic DA release (Seiden et al. 1993, Volkow et al. 1995). Third, AMPH inhibits the DA degradative enzyme catechol-o-methyltransferase (COMT), which would sustain extracellular levels of dopamine. Finally, intracellular monoamine oxidase A is inhibited, an action not found for cocaine. This last action would raise levels of both DA and NE, but it is unclear if levels reached in vivo would achieve this effect (Rothman et al. 2001). A prominent difference between cocaine and ATS agents is the lack of sodium transporter inhibition by the latter (Hoffman and Lefkowitz 1990).

ATS has similar effects on the NE system. In fact, ATS may be more potent at releasing NE centrally than DA (Rothman et al. 2001). Both AMPH and METH appear to affect both the DAT and NET, while methylphenidate is more selective for the DAT (Giros et al. 1996). Whether this relates to the abuse-liability hierarchy, where both METH and AMPH appear more addictive than methylphenidate, is unknown (Langer et al. 1986). Norepinephrine transporter (NET) knockout mice are hypersensitive to the locomotor stimulating effects of AMPH (Xu et al. 2000). Serotonin system effects of ATS are even less well understood, though the serotonin transporter (5HTT) is also antagonized by ATS.

The neuroanatomical substrates of ATS agents are also being characterized. By virtue of their lipophilicity, these agents easily cross the blood-brain barrier and show selective accumulation in various brain loci. In particular, the striatum is an area of accumulation for methylphenidate (Volkow et al. 1995). The neostriatum (caudatoputamen and nucleus accumbens) is particularly activated by ATS agents, as well as projections to the orbitofrontal regions and other limbic areas. The neocortex appears inhibited. In more primitive areas of the brain, the ascending reticular activating system and medullary respiratory centers are activated.

A rich literature exists in animal studies supporting the development of neurobiological adaptations to chronic ATS exposure. In humans, the development of tolerance to acute effects such as euphoria and anorexia, the persistent potential for relapse once one has become addicted, and the ability to reexperience psychotic symptoms with low doses of ATS exposure long after chronic use, support long-term changes in humans as well (Sato et al. 1983, 1992, Wilens and Spencer 1998). Sensitization to amphetamines can be demonstrated with eye blink in humans (Strakowski et al. 2001) but only if subjects have not had prior exposure to amphetamines (Comer et al. 2001). This would argue that at least to this marker, sensitization is achieved quickly. Tolerance to ATS also can develop after only several exposures (Gorelick and Cornish 2003).

The DA depletion hypothesis has long been used to explain the long-term effects of psychostimulant abuse (Dackis and Gold 1985). In animals, METH and AMPH dose-dependently reduce the activity of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, and DA levels in the nerve terminals decline (Koda and Gibb 1973). AMPH seems to be less neurotoxic than METH in these models (Ellison and Switzer 1993). Nonetheless, DA recovery in rat striatum is remarkably slow, taking months, more consistent with neuroadaptations such as neuronal sprouting rather than resynthesis of depleted stores (Cass and Manning 1999).

The issue of whether DA is depleted in chronic users is critical to understanding imaging findings in chronic METH-dependent individuals that support long-term changes in the DAT. Reductions in DAT can be demonstrated in the caudate and putamen (Wilson et al. 1996, McCann et al. 1998, Volkow et al. 2001a). These reductions correlated with motor and cognitive impairments, and were present in users abstinent for over 11 months. While animal studies support nerve terminal degeneration with high-dose METH administration, in humans it appears other neuronal markers, for example VAMT, are still present, and recovery may be possible over a period of years (Wilson et al. 1996, Volkow et al. 2001b). Sekine and colleagues have demonstrated that DAT reductions are also prominent after chronic METH use in the orbitofrontal and dorsolateral prefrontal cortices, the amygdala, and the nucleus accumbens (Sekine et al. 2001, 2003). Except for the amygdala, these reductions correlated with length of use, and the positive subscale of the Brief Psychiatric Rating Scale. The fact that dopamine D2 receptor function is reduced in the striatum may explain orbitofrontal dysfunction (Volkow et al. 2001c). These findings clearly support long-term alterations caused by METH, but it is unclear why DAT levels would be reduced in the presence of depleted DA levels. There are limited data that oxidative products of DA might specifically inactivate the DAT (Cho and Melega 2002, Hastings et al. 1996, Bindoli et al. 1992).

METH also is neurotoxic to striatal serotonin nerve terminals, again inducing long-term changes in animals (Cass 2000). At high doses, METH appears to permanently destroy serotonin nerve terminals (Woolverton et al. 1989). Surprisingly, little is known about the effects of acute or chronic ATS exposure on the NET.

Preclinical studies also support the importance of glutamatergic transmission in modulating dopaminergic areas, and in turn affecting the development of sensitization to psychostimulants (Vanderschuren and Kalivas 2000). Animal studies (Zhang et al. 2001) show METH and cocaine do not acutely elevate the glutamate in the striatum or nucleus accumbens. After chronic exposure, rechallenge with METH increased caudate glutamate and decreased nucleus accumbens glutamate, while cocaine increased glutamate in both regions. Acute METH decreased glutamate in substantia nigra and ventral tegmentum, while cocaine increased glutamate in the same regions. Thus, glutamate effects remain to be discerned, but support important differences between cocaine and ATS. Kalivas and colleagues (Pierce and Kalivas 1997) hypothesize that chronic AMPH exposure will recruit glutamatergic cortical inputs to the nucleus accumbens, mirroring environment cue association with drug reward. Further, glutamate antagonists block the development of locomotor sensitization to stimulants (Vanderschuren and Kalivas 2000).

While the long-term adaptations to ATS and cocaine are usually held to be similar, the bulk of studies have been with cocaine only (White and Kalivas 1998, Robinson and Berridge 2000). Cross sensitization between cocaine and AMPH can be demonstrated (Bonate et al. 1997). However, given the differing pharmacology of cocaine and ATS, it is not surprising that evidence does exist that long-term processes such as sensitization can vary between cocaine, AMPH, and methylphenidate (Vanderschuren and Kalivas 2000).

## Treatment

There are few studies that specifically address the treatment of ATS use disorders. This reflects the traditional focus on cocaine use disorders. Even for cocaine, effective pharma-cotherapies are lacking compared to treatment of alcohol- and opiate-dependent individuals. Behavioral treatment approaches remain the mainstay of treatment of psychostimulant use disorders, and those whose efficacy is supported in the cocaine use disorders are assumed will be effective for ATS use disorders. Outcomes in psychosocial treatment cohorts do appear to be similar (Huber et al. 1997, Rawson et al. 2000).

Several unique aspects of ATS addiction must be addressed for treatment to be effective. Because ATS users begin to experience adverse consequences of their use later than comparable cocaine addicts, they appear to be more ambivalent to enter treatment, probably because they reason that since they have gotten along fairly well up to that point, why should they begin the difficult process of treatment? Thus, treatment entry and retention rates are lower than those for individuals with cocaine dependence, and necessitates outreach programs to enhance treatment engagement (Huber et al. 1997). A number of co-occurring problems, such as high HIV and hepatitis infection rates, homelessness, and child-rearing difficulties must be integrated into the treatment approach. Further, the continued neurocognitive deficits in METH-dependent individuals increase the need to apply outreach attempts to noncompliant individuals (Simon et al. 2000a).

Association with difficult-to-alter behaviors (sexual/social and weight loss) means those "rewards" must be coopted by substitution of other options, such as referral to self-help groups for weight loss. As for any addiction, the

need to separate reinforcing social contacts from the addict's lifestyle is a difficult process. Abuse by those seeking performance enhancement may be targeted through education programs and drug screening programs, such as those that have been so successful in the military (Rawson et al. 2002a).

## Treatment of ATS Intoxication

Management of acute intoxication is guided by the presenting medical and psychiatric symptoms. In ATS intoxication, there are no direct receptor targets to achieve blockade; though dopamine receptor blockade theoretically should be useful in blocking acute and or chronic affects of ATS, this has not proven to be the case (Sevarino et al. 2000). Anxiety and agitation are first treated by an environment that reduces stimulation and provides orientation, with staff providing reassurance and talk downs (Khantzian and McKenna 1979). Physical restraints should be avoided, as these may worsen rhabdomyolysis or hyperthermia. When nonpharmacological means are insufficient, benzodiazepines, typically lorazepam or diazepam, are first-line treatments since they protect against imminent seizures. Antipsychotics for agitation should be avoided because of the risk of worsening hyperthermia or rhabdomyolysis if neuroleptic malignant syndrome were to occur, and their ability to lower seizure threshold. However, since benzodiazepines run the risk of disinhibiting some individuals, typical antipsychotics are often the preferred choice. Indeed, in one controlled trial, intravenous droperidol was significantly faster than intravenous lorazepam in sedating ATS-intoxicated psychotic individuals (Richards 1997, 1998).

For psychosis and paranoia, high potency antipsychotics, typically haloperidol, are used. This avoids the anticholinergic effects that may worsen delirium and hyperthermia. There is no reason to assume that atypical antipsychotics, such as intramuscular ziprasidone, might not be effective in this population, though there are no trials examining this. While there are no controlled trials on the treatment of ATS-induced psychosis (Srisurapanant et al. 2001c), it appears the psychotic symptoms do not differ from those in schizophrenia in their response to acute intramuscular injection of typical neuroleptics (Angrist 1974). While preclinical literature would argue that DA or serotonin blockade should block the acute subjective effects of ATS use, clinical evidence has not supported this (Wachtel et al. 2002).

The management of medical sequelae of ATS intoxication, most commonly nontraumatic chest pain, is well described in Wilkins et al. (2003). If oral use of the ATS is suspected or confirmed, charcoal gastric lavage is indicated. Acidification of the urine with ammonium chloride solution or cranberry juice may be used to enhance ATS excretion, though should be avoided if rhabdomyolysis is a concern, since this would worsen dissociation and precipitation of myoglobin (Karch 2002), or where renal or hepatic dysfunction are an issue (Hurlbut 1991). Basic life support and initial management are needed for critical conditions such as myocardial ischemia or arrythmia, stroke or seizures, hyperthermia and rhabdomyolysis. Hypertension and tachycardia, if not responsive to benzodiazepine sedation, may require treatment with an alpha-adrenergic blocker, typically phentolamine. Agents with beta blockade activity, such as propanolol and labetolol, must be avoided as alpha-adrenergic tone can increase, leading to a worsening of the clinical condition (Ramoska and Sacchetti 1985).

## Treatment of ATS Withdrawal

Emergency considerations in the withdrawal phase of ATS intoxication are principally psychiatric. The week following cocaine withdrawal is associated with increased risk of silent myocardial ischemia (Nademanee et al. 1989). Because this is hypothesized to result from coronary vasospasm, this may not generalize to ATS withdrawal. Otherwise, medical complications of ATS withdrawal, such as myalgias, involuntary motor movements and so on can be treated symptomatically and should spontaneously remit.

The use of antidepressants for 3–4 weeks following cessation of ATS use is suggested, because depression is a hallmark of ATS withdrawal (Watson et al. 1972, Ellinwood 1975). Often, allowing the individual increased time to sleep and reestablishment of normal nutrition is quite helpful. Where needed, the use of trazodone for sleep or short-term benzodiazepines for anxiety is needed along with antidepressant therapy.

## Psychosocial Treatments for ATS Dependence

Cognitive behavioral therapy forms the basis of many treatments for psychostimulant dependence (NIDA Research Report 2002). NIDA-sponsored treatment efforts mainly have focused on those with cocaine dependence, but there is no reason to assume that these approaches cannot form the basis of treatment for ATS use disorders. Contingency incentives, skills training, and family member participation are helpful for maintaining cocaine abstinence (Higgins et al. 1993). An extension of such a combined approach, termed the community-reinforcement-plus-vouchers approach, is described in the Treatment Improvement Protocol Series (TIPS) 33: Treatment for Stimulant Use Disorders (CSAT 1999). This approach combines couples counseling, vocational training and skills training (community reinforcement, see Meyers and Smith 1995), and contingency management through rewards for negative urine testing. This combined approach for treatment of cocaine dependence is shown to improve treatment retention and decrease drug use (Higgins et al. 1993, 1994). Further, the approach has been manualized to improve consistency among clinicians (Budney and Higgins 1998).

Contingency management by itself is likely to improve outcomes in ATS use disorders (Stitzer and Higgins 1995, Petry and Martin 2002). Besides rewards for negative urines, more general targets such as improved compliance with treatment, improved employment efforts, and decreased legal involvement can be utilized to more broadly impact the consequences of ATS use. In fact, the drug court approach (i.e., an alternative corrections system that routes addicts to the "drug court" rather than the traditional court system) may be particularly applicable to stimulant dependence because it is so concretely consequence based (Rawson et al. 2002a). Coordination between mental health services, social services resources, and the criminal justice system will be critical in reducing overall ATS use (Rawson et al. 2002a).

The manualized Matrix Model is a second integrated treatment approach utilized in southern California

for ATS-dependent individuals (Rawson et al. 1990). This combined approach of group and individual counseling, along with encouragement to participate in 12-step programs, incorporates elements of drug counseling, psychoeducation, motivational enhancement, relapse prevention (see below), family involvement, and case management. The Matrix approach is associated with large reductions in METH use, a decrease in high-risk sexual behavior, improved employment status, and reduced paranoia, though problems with depression persist (Shoptaw et al. 1994, Huber et al. 1997, Rawson et al. 2002b). More focused application of motivational interviewing and motivational enhancement therapy to stimulant use disorders, developed to improve treatment engagement and achievement of abstinence, is in its infancy (Carroll et al. 2002).

Several other psychosocial treatments might be applied to individuals with ATS use disorders (Marlatt and Gordon 1985). Relapse prevention is also recommended in the TIPS protocol. This approach, easily combined with widely used drug counseling, systematically teaches individuals the skills needed to avoid drug use through training in assertiveness and refusal skills, how to cope with craving, how to deal with relapses, and how to recognize patterns of behavior or thinking that lead to relapse. Again, controlled trials support the efficacy of this approach for individuals with cocaine dependence (Carroll 1994).

Network therapy, meant to engage family and community in supporting drug-free functioning, appears well suited to ATS abuse and dependence, where acquisition appears more linked to community networks than stressful street "buys."

There is some controversy as to whether these various treatment modalities, applied under real-world conditions, are superior to the widely applied "drug counseling," whether or not through certified addiction counselors, which loosely applies group counseling, supportive expression session, and case management (Wells et al. 1994, Woody 2003). The NIDA Cocaine Psychotherapy Study examined the effects of psychotherapy (cognitive behavioral therapy or supportive-expressive psychotherapy), individual drug counseling, or no additional treatment, on cocaine-dependent subjects participating in group-drug counseling. Though all groups displayed reductions in cocaine use and risky sexual behaviors, the combined group-individual drug counseling cohort had superior outcomes to the other three groups, which did not differ significantly from each other (Crits-Christoph et al. 1999).

Residential treatment for pregnant women and the homeless is likely to be of benefit for stabilization of ATS-dependent subjects, though there is no specific indication for stimulants (Hughes et al. 1995). The prolonged nature of ATS-induced withdrawal, and the association with aggressivity and violence, will often make inpatient psychiatric stabilization necessary. It is unknown whether transition to therapeutic communities or half-way houses will be of greater benefit to ATS-dependent subjects that those with other substance use disorders, or be superior in outcome to outpatient-based programs (Mueller and Wyman 1997).

## Pharmacotherapy for ATS Dependence

As is the case with cocaine use disorders, effective pharmacotherapies for amphetamine use disorders are not available (Sevarino et al. 2000). Pharmacotherapy trials for ATS agents have not focused on dopaminergic mechanisms, but on serotonergic/noradrenergic mechanisms (Srisurapanont et al. 2001b). Galloway et al. (1996) reported that the tricyclic antide-pressant imipramine, improved treatment retention (33.0 median days vs. 10.5 days) in 32 METH-dependent subjects. However, craving, use, and depression scores were not significantly affected. While open-label trials indicated that fluoxetine might be effective in reducing AMPH use in dependent outpatients, Batki et al. (2000), in a randomized, double-blind study failed to confirm this using fluoxetine at 40mg/day in METH-dependent subjects.

It had long been known that depletion of DA and NE with alpha-methyltyrosine would antagonize the acute euphoric affects of AMPH in humans, though tolerance to the effect developed within a week (Jonsson et al. 1971). In a very small study involving four subjects, desipramine, a tricyclic antidepressant with prominent norepinephrine effects, reduced amphetamine use and craving, but did not improve treatment retention (Tennant et al. 1986).

In parallel to the successful use of opiate agonist maintenance therapy for heroin dependence, there are open trials of dexamphetamine elixir, at 10–90/mg per day being used for controlled maintenance of ATS-dependent subjects (Charnaud and Griffiths 1998, White 2000). While randomized, prospective studies are not yet reported, a reduction of intravenous use of one-half to two-thirds was seen in these prior studies.

In conclusion, the main role of pharmacotherapy is acute symptomatic relief, and treatment of comorbid conditions. Behavioral treatments and self-help groups remain the mainstay of treatment for the many individuals suffering from ATS dependence.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 criteria sets for other stimulant intoxication and withdrawal are almost the same as the DSM-IV-IR criteria sets for amphetamine intoxication and withdrawal except that the ICD-10 diagnostic criteria for research include drug craving as an additional item. ICD-10 combines amphetamines and caffeine into a single substance class, referred to as "other stimulants, including caffeine."

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CHAPTER

# 56 Substance Abuse: Caffeine Use Disorders

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Caffeine Intoxication
Caffeine Withdrawal
Caffeine Dependence
Caffeine-Induced Anxiety Disorder
Caffeine-Induced Sleep Disorder

## Introduction

Caffeine is the most widely used mood-altering drug (Gilbert 1984). Across the world caffeine use occurs in a variety of different but culturally well-integrated social contexts, such as the coffee break in the United States, teatime in the United Kingdom, and kola nut chewing in Nigeria. In the United States, dietary surveys indicate that 87% of the population consumes food and beverages containing caffeine. Among caffeine consumers, average daily intake is 193 mg, with men aged 35–54 years having the highest intakes (336 mg/day) (Frary et al. 2005). Figure 56–1 shows trends in annual per capita consumption of the three major dietary sources (soft drinks, coffee, and tea).

Table 56–1 shows typical caffeine content in common foods and medications. It is noteworthy that the range of caffeine contents within a class of food or medication can vary widely. Because habitual consumption of coffee or caffeinated soft drinks with meals is so prevalent, it may not be recognized as caffeine consumption. The widespread use of caffeine can make the recognition of psychiatric disorders associated with caffeine use particularly difficult. However, it is important for the psychiatrist to recognize the role of caffeine as a psychoactive substance capable of producing a variety of psychiatric syndromes. In this chapter five disorders associated with caffeine use are reviewed: caffeine intoxication, caffeine withdrawal, caffeine dependence, caffeine-induced anxiety disorder, and caffeine-induced sleep disorder.

## Caffeine Intoxication

### Diagnosis

#### Definition and Diagnostic Features

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) defines caffeine intoxication as a set of symptoms that develop during or shortly after caffeine use (American Psychiatric Association 2000). There may be two kinds of presentation associated with caffeine intoxication. The first presentation is associated with the *acute* ingestion of a large amount of caffeine and represents an acute drug overdose condition. The second presentation is associated with the *chronic* consumption of large amounts of caffeine and results in a more complicated presentation.

Caffeine intoxication has long been recognized as a syndrome produced by the ingestion of an excessive amount of caffeine. For example, Rugh (1896) reported the case of a traveling salesman who had nervousness, involuntary contractions in the arms and legs, a sense of impending danger, and sleep disturbance in the context of excessive coffee consumption used to maintain a highly active pace of work. Similar reports of caffeine intoxication can be found throughout the medical literature of the 1800s and early 1900s with observations of motor unrest, insomnia, tachycardia, irritability, headache, emotional lability, anxiety, and gastrointestinal disturbances associated with excessive use of

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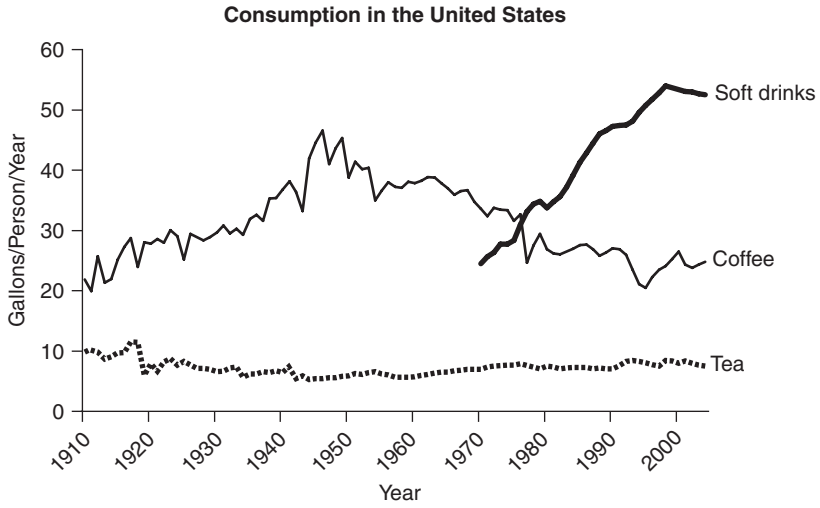



**Figure 56–1** *Annual per person consumption of caffeine in the United States from 1910 to 2004. Shown are major dietary sources of caffeine: coffee, tea, and soft drinks (i.e., flavored carbonated beverages); soft drink consumption data are not available before 1970. (Source: US Department of Agriculture.)*

caffeine. Thus, caffeine intoxication represents a psychiatric disorder that has been well described for at least 100 years.

## Assessment

The primary features of caffeine intoxication can be found in the diagnostic criteria from DSM-IV-TR. The diagnostic decision tree for caffeine intoxication disorder, caffeine-induced anxiety disorder, and caffeine-induced sleep disorder is shown in Figure 56–2. One study that utilized a random-digit-dial telephone survey of 162 users of caffeine, examined the types of symptoms reported by persons who had experienced some features of caffeine intoxication (Hughes et al. 1998). Results from that study showed that two-thirds of participants had experienced at least one of the DSM-IV-TR symptoms related to caffeine intoxication in the previous year. The most common symptoms reported, in decreasing order of frequency, were frequent urination, restlessness, insomnia, nervousness, and excitement (all were at rates greater than 20%). In addition, 24% reported heart pounding in response to high caffeine use (although this is not one of the DSM-IV-TR criteria).

In a study of 124 general hospital patients, the most common somatic symptoms patients reported as associated with caffeine intake (i.e., symptoms not specified as associated with either caffeine intoxication or caffeine withdrawal) were in descending order of frequency: diuresis, insomnia,

**Table 56–1 Caffeine Content of Foods and Medications**

| Substance | Typical Content | Range |
|---|---|---|
| Brewed coffee | 200 mg/12 oz | 107–420 mg |
| Instant coffee | 140 mg/12 oz | 40–260 mg |
| Espresso | 70 mg/shot | 60–95 mg |
| Decaffeinated coffee | 8 mg/12 oz | 0–12 mg |
| Brewed tea | 80 mg/12 oz | 60–180 mg |
| Instant tea | 60 mg/12 oz | 20–70 mg |
| Canned or bottled tea | 20 mg/12 oz | 8–32 mg |
| Caffeinated soft drink | 40 mg/12 oz | 22–72 |
| Caffeinated water | 100 mg/16.6 oz | 60–200 mg |
| Energy drinks | 75 mg/8 oz | 33–280 mg |
| Cocoa beverage | 7 mg/6 oz | 2–10 mg |
| Chocolate milk | 4 mg/6 oz | 2–7 mg |
| Dark chocolate | 30 mg/1.5 oz | 5–35 mg |
| Milk chocolate | 10 mg/1.5 oz | 2–10 mg |
| Coffee ice cream or yogurt | 50 mg/8 oz | 8–85 mg |
| Caffeinated gum | 33 mg/stick | – |
| Caffeine-containing analgesics | 32 or 65 mg/tablet | 32–130 mg (2 tablets) |
| Stimulants | 100 or 200 mg/tablet | 75–350 mg |
| Weight-loss/sports nutrition | 80–250 mg/tablet | 40–250 mg/tablet |

*Sources:* Juliano and Griffiths (2005); McCusker et al. (2003, 2006a, 2006b); Redux Beverages LLC.

**DSM-IV-TR Criteria**

**Caffeine Intoxication**

A. Recent consumption of caffeine, usually in excess of 250 mg (e.g., more than 2–3 cups of brewed coffee).

B. Five (or more) of the following signs, developing during, or shortly after, caffeine use:

(1) restlessness
(2) nervousness
(3) excitement
(4) insomnia
(5) flushed face
(6) diuresis
(7) gastrointestinal disturbance
(8) muscle twitching
(9) rambling flow of thought and speech
(10) tachycardia or cardiac arrhythmia
(11) periods of inexhaustibility
(12) psychomotor agitation

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (e.g., an anxiety disorder)

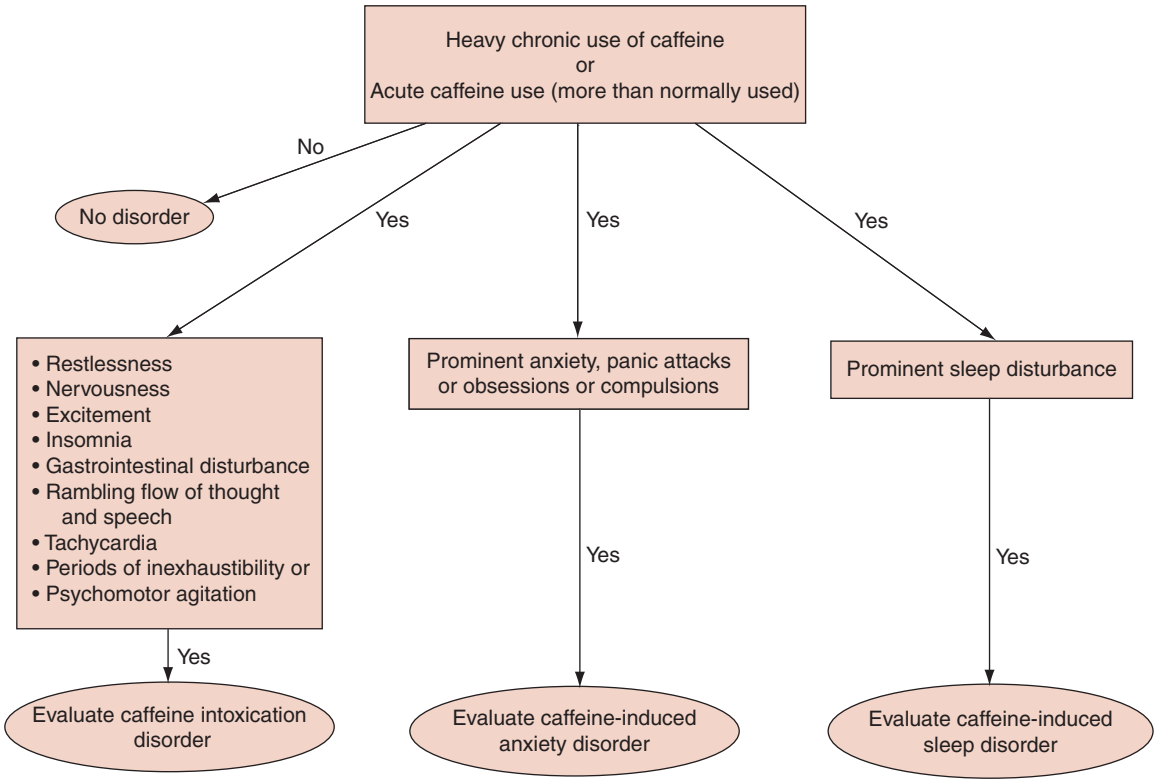



**Figure 56–2** *Diagnostic decision tree for caffeine intoxication disorder, caffeine-induced anxiety disorder, and caffeine-induced sleep disorder.*

withdrawal headaches, diarrhea, anxiety, tachycardia, and tremulousness (Victor et al. 1981).

In addition to the characteristics of caffeine intoxication noted in DSM-IV-TR there have been reports of fever (Reimann 1967), irritability, tremors, sensory disturbances, tachypnea (Greden 1974), headaches (Shirlow and Mathers 1985, Stoffer 1979), vomiting and seizures (Kerrigan and Lindsey, 2005) associated with cases of caffeine intoxication. Although a wide variety of symptoms of caffeine intoxication have been reported, the most common signs and symptoms appear to be anxiety and nervousness, diuresis, insomnia, gastrointestinal disturbances, tremors, tachycardia, and psychomotor agitation.

## Epidemiology

Despite the long history of recognition of caffeine intoxication, there is little information available about the prevalence or incidence of caffeine intoxication either in the general community or in selected populations. There is one study that examined caffeine intoxication in the community, and five studies that examined rates of caffeine intoxication in special populations.

The study that addresses the prevalence of caffeine intoxication in the community was briefly mentioned above (Hughes et al. 1998). In that telephone survey of 162 caffeine users in Vermont, two-thirds of the participants reported at least one DSM-IV-TR caffeine intoxication symptom and 7% fulfilled DSM-IV-TR criteria for caffeine intoxication. These results suggest that caffeine intoxication and symptoms related to excessive caffeine use may be quite common in the general community.

Four studies examined the rate of caffeine intoxication in special populations. A recent population-based study of 3,603 adult twins found that 29% reported occasions of feeling ill or shaky or jittery after drinking caffeinated beverages (Kendler et al. 2006). In a 1975 survey of 220 psychiatric patients and control subjects, none of the participants had symptoms of caffeine intoxication (Furlong 1975). A 1976 survey of 135 inpatients on a psychiatric unit found two cases (1.5%) of caffeine intoxication (Winstead 1976). A 1981 survey of college students found 1.3% with high caffeine consumption, and these high caffeine consumers had high levels of symptoms associated with caffeine intoxication (Gilliland and Andress 1981). Finally, a 1990 survey of college students found that 19% reported a history of caffeine intoxication (Bradley and Petree 1990).

Thus, it would appear that the incidence of caffeine intoxication in the general community is about 7% per year, and it may be higher in selected populations at greater risk for caffeine intoxication (e.g., students). However, there clearly is a need for better characterization of both the prevalence and the incidence of caffeine intoxication, using rigorous criteria for the diagnosis and representative sampling techniques.

## Comorbidity Patterns

Reports on comorbidity have often failed to distinguish chronic high caffeine consumption from a formal diagnosis of caffeine intoxication. In addition, reports on caffeine intoxication have generally failed to distinguish between a single acute episode of caffeine intoxication and a state of chronic caffeine intoxication.

The previously mentioned study of adult twins found that caffeine toxicity (occasions of feeling ill or shaky or jittery after drinking caffeinated beverages) was significantly and positively associated with each of seven diagnoses: major depression, generalized anxiety disorder, panic disorder,

adult antisocial disorder, alcohol dependence, and cannabis and cocaine abuse/dependence. The odds ratios were similar across all disorders, although it was highest with generalized anxiety disorder (Kendler et al. 2006). There have been case reports of caffeine intoxication occurring in athletes and bodybuilders (Stillner et al. 1978; FitzSimmons and Kidner, 1998) and in patients with eating disorders (Sours 1983, Christo et al. 2003, Pallanti et al. 2006). The symptoms of caffeine intoxication can mimic those of anxiety and mood disorders (Greden 1974).

There are also comorbid conditions associated with excessive caffeine consumption (i.e., habitual use of large amounts of caffeine without evidence of acute caffeine intoxication). Surveys of psychiatric patients have found high rates of excessive caffeine consumption, particularly among patients with schizophrenia (Greden et al. 1978, Rihs et al. 1996, Strassnig et al. 2006, Gurpegui et al. 2006). Furlong (1975) reported that higher coffee consumption was associated with the diagnosis of a personality disorder, and Winstead (1976) reported that higher caffeine consumption was more likely in patients with psychotic disorders, but not in patients with depressive neurotic disorders. Case reports have described patients with chronic schizophrenia eating large amounts of instant coffee powder for the pleasurable effect produced by the coffee (Benson and David 1986). Such excessive caffeine consumption may exacerbate chronic psychiatric conditions (Winstead 1976, Zaslove et al. 1991, Tondo and Rudas 1991, De Freitas and Schwartz 1979, Mikkelsen 1978).

The relationship between caffeine consumption and anxiety disorders is considered in more detail later (in the section on caffeine-induced anxiety disorder), but it is worth noting here that patients with panic disorder appear to have lower caffeine consumption (Lee et al. 1988), and that patients with panic disorder and patients with generalized anxiety disorder may be more sensitive to the effects of caffeine (Bruce et al. 1992, Boulenger et al. 1984).

Excessive caffeine consumption has repeatedly been observed to be associated with smoking tobacco and alcohol and other substance use disorders (Russ et al. 1988, Christo et al. 2003, cf. section on caffeine dependence).

Another psychiatric condition associated with the excessive consumption of caffeine is delirium, which may be present in cases of extreme caffeine intoxication. For example, caffeine-induced delirium has been reported in a man who acutely consumed coffee, cola, and 800 mg of caffeine (tablets) while competing in the Iditarod dogsled race held between Anchorage and Nome, Alaska (Stillner et al. 1978). He experienced tremor, an alteration in his level of consciousness, anxiety, visual illusions and hallucinations, vertigo, and impaired memory consistent with an episode of delirium. Other cases of probable caffeine-induced delirium have also been reported (McManamy and Schube 1936, Shen and D'Souza 1979).

Although it is extremely rare, another psychiatric condition that can be associated with excessive caffeine consumption is suicide (Tanskanen et al. 2000a, 2000b). After adjusting for potential covariates, one study reported that the risk of suicide was 58% higher among heavy coffee drinkers than moderate coffee drinkers (Tanskanen et al. 2000b).

Finally, heavy caffeine consumption has been shown to be a risk factor for chronic daily headache in adults and in children (Scher et al. 2004, Hering-Hanit and Gadoth 2003).

## Course

In the patient who is not tolerant to caffeine, acute caffeine ingestion producing caffeine intoxication is a time-limited condition that will rapidly resolve with cessation of caffeine use, consistent with the relatively short half-life of caffeine (3–6 hours) (Balogh et al. 1992). In a patient who has caffeine intoxication superimposed on chronic caffeine use, abrupt termination of all caffeine use may lead to caffeine withdrawal symptoms (described in detail in the section on caffeine withdrawal). Because symptoms of caffeine withdrawal can partially overlap with symptoms of caffeine intoxication (e.g., nervousness and anxiety), the time course of symptom resolution can be expected to be protracted, lasting several days to a week or more.

Although caffeine intoxication usually resolves without significant complications, adverse events can occur. In 2005, 4,656 caffeine exposures were reported to poison centers in the United States, with half requiring treatment in a health care facility (Lai et al. 2006). Overdose with caffeine may be fatal (Mrvos et al. 1989, Garriott et al. 1985, Kerrigan and Lindsey 2005), and there are reports of suicide death by caffeine overdose (Bryant 1981, Holmgren et al. 2004). If there is evidence that a patient has significantly overdosed on caffeine, then it should be treated as a medical emergency requiring intensive monitoring, symptomatic treatment (e.g., for tachycardia, arrhythmias, and seizures), aspiration of the stomach, and assessment of the serum caffeine level (>100 micrograms/mL is generally considered lethal). Caffeine overdose has also been treated successfully with hemoperfusion or hemodialysis (Nagesh and Murphy 1988, Holstege et al. 2003).

## Differential Diagnosis

The diagnosis of caffeine intoxication is based on the history and clinical presentation of the patient. Ideally, the extent of caffeine exposure can also be assessed by a serum or saliva assay of the caffeine level. In the past, caffeine use has often been overlooked in patients presenting with symptoms consistent with a caffeine use disorder (Doucette and Willoughby 1980). However, it may be that there is presently a greater awareness of the deleterious effects of caffeine, making psychiatrists more sensitive to the inclusion of caffeine in a differential diagnosis, and patients more aware of the possible role of excessive caffeine in somatic and psychological symptoms.

Several conditions should be included in the differential diagnosis of caffeine intoxication (Table 56–2). These include other substance abuse-related disorders (amphetamine or cocaine intoxication; withdrawal from sedatives, hypnotics, anxiolytics, or nicotine), other psychiatric disorders (panic disorder, generalized anxiety disorder, mania, sleep disorders), medication-induced side effects (e.g., akathisia), and somatic disorders (e.g., pheochromocytoma, hyperthyroidism, gastroesophageal reflux, arrhythmia). Caffeine intoxication may present with a wide variety of clinical features, and the possibility of caffeine intoxication should be included in the differential diagnosis for patients with nonspecific complaints, or presentations that do not readily fit into a known diagnostic pattern.

**Table 56–2 Differential Diagnosis of Caffeine Intoxication**

| | |
|---|---|
| Manic episode | Panic disorder |
| Amphetamine/cocaine intoxication | Generalized anxiety disorder |
| Sedative, hypnotic or anxiolytic withdrawal | Medication-induced side effect (e.g., akathisia) |
| Nicotine withdrawal | Sleep disorders |

## Etiology and Pathophysiology

### Individual Differences and Genetic Factors

Although caffeine intoxication is clearly related to caffeine ingestion, it is not simply the result of a person's consuming a high dose of caffeine. Rather, caffeine intoxication represents the relationship between the dose of caffeine consumed, the degree of acquired tolerance to caffeine in that person, and the individual's sensitivity to caffeine. In addition to individual differences due to acquired tolerance, substantial differences in sensitivity to caffeine effects have been documented. For instance, drug discrimination studies have shown that the threshold for caffeine discrimination can vary over a tenfold range of doses (Griffiths et al. 1990 a, Mumford et al. 1994). Although heavy caffeine consumption is more common in men than women, rates of caffeine toxicity are similar (Kendler et al. 2006).

There is a genetic basis to individual differences to caffeine intoxication. An association has been demonstrated between caffeine-induced anxiety and adenosine $A_{2A}$ receptor gene polymorphisms associated with panic disorder (Alsene et al. 2003, Hamilton et al. 2004). A study of adult twins showed that monozygotic twins had significantly higher concordance rates of caffeine toxicity than dizygotic twins, resulting in an estimated heritability of 45% (Kendler and Prescott 1999). Another twin study demonstrated moderate comorbidity between caffeine toxicity and a wide range of psychiatric and substance use disorders (Kendler et al. 2006). Analysis of these relationships within monozygotic pairs suggest that this relationship is largely correlated rather than causal.

### *Acquired Tolerance*

Tolerance represents a decrease in responsiveness to a drug due to drug exposure. As described in more detail in the section on caffeine dependence, complete tolerance to the subjective effects of caffeine occurs when very high caffeine doses are administered daily (750–1200 mg/day). Thus a sensitive person with no tolerance to caffeine might have signs and symptoms of caffeine intoxication in response to a relatively low dose of caffeine (such as 200 mg, the amount found in a typical serving of brewed coffee) (Table 56–1), whereas another person with a high daily consumption of caffeine would show no evidence of intoxication with a similar dose.

## Pharmacological Mechanism of Action

The principal cellular site of action of caffeine is the adenosine receptor, where caffeine functions as an antagonist at both $A_{2A}$ and $A_1$ receptors (Fredholm et al. 1999). Adenosine produces a wide variety of physiological effects, including decreasing spontaneous electrical activity in brain, inhibiting neurotransmitter release in brain, decreasing spontaneous and operant motor activity, dilating central vasculature, producing antidiuresis, inhibiting renin release, and inhibiting gastric secretion and lipolysis (Daly 1993). As an antagonist of adenosine many of caffeine's actions are opposite to those produced by adenosine (e.g., central nervous system stimulation, decreased cerebral blood flow, increased renin release and diuresis, increased gastric secretions, and stimulation of respiration).

Neuropharmacology and behavioral studies show that caffeine effects are mediated by blockade at both $A_{2A}$ and $A_1$ receptors (Karcz-Kubicha et al. 2003, Halldner et al. 2004, Kuzmin et al. 2006) and there is evidence that both receptors can form functional receptor heteromers, including $A_1$–$A_{2A}$, $A_1$–$D_1$, $A_{2A}$–$D_2$, and $A_{2A}$–$D_3$ heteromers (Ferre et al. 2005, Fuxe et al. 2005). The relationship between adenosine and dopamine functioning has become an area of particular interest and study. Caffeine enhances dopaminergic activity by competitive antagonism of receptors that are colocalized and functionally interact with dopamine receptors (Ferre et al. 1997, Cauli and Morelli 2005, Fredholm et al. 2005). Basal adenosine functioning exerts a negative modulation of dopaminergic functioning, with activity at $A_{2A}$ and $A_1$ receptors, respectively, affecting $D_2$ and $D_1$ binding characteristics and signaling pathways. Consistent with this mechanism of increased dopaminergic activity, preclinical behavioral studies show that caffeine produces behavioral effects similar to classic dopaminergically mediated stimulants such as cocaine and amphetamine, including increased locomotor activity and stimulant-like discriminative stimulus effects. Also, a number of these effects are blocked by dopamine antagonists (Fredholm et al. 1999, Garrett and Griffiths 1997), or abolished in adenosine receptor knockout mice (El Yacoubi et al. 2000, Halldner et al. 2004). Furthermore, as discussed in the section on caffeine dependence, caffeine produces dopamine release in the shell of the nucleus accumbens similar to classic drugs of abuse including the stimulants. Although dopaminergically mediated effects may be important to understanding the amphetamine-like stimulant effects of low and moderate doses of caffeine, dopaminergic mechanisms may be only partially relevant to understanding the clinical manifestations of caffeine intoxication that emerge at high toxic doses of caffeine.

Caffeine's direct effects on adenosine and indirect effects on dopamine occur at concentrations similar to those attained after typical dietary doses of caffeine. Caffeine can also exert effects on phosphodiesterase and intracellular calcium, although with typical dietary doses of caffeine, blood levels of caffeine are believed to be too low to appreciably affect these nonadenosine mechanisms of action. Thus, adenosine antagonism appears to be the primary mechanism for caffeine's effects. It is not known whether these other mechanisms may mediate some of the clinical effects produced when caffeine concentrations are elevated (e.g., as may occur with caffeine intoxication).

## Treatment

The first step in evaluating a patient with a possible diagnosis of caffeine intoxication is to obtain a history about all recent caffeine consumption. The possible use of beverages and medications—both prescription and over-the-counter (OTC) diet aids and energy pills—should be reviewed. Some beverages (e.g., caffeine-containing soft drinks) and

medications (e.g., energy pills, aids to combat sleep, or diet pills) may not be recognized by the patient as containing caffeine. The amount of caffeine acutely consumed should help clarify the diagnosis of caffeine intoxication, although it is important to determine whether the patient has been chronically consuming high doses of caffeine. If this is the case, the patient may be tolerant and, therefore, less likely to be experiencing caffeine intoxication. However, some clinicians have reported that caffeine intoxication can occur even in the context of chronic caffeine use. If the patient is unable to provide an accurate history of recent caffeine consumption (e.g., because of delirium after a caffeine overdose), the patient should be emergently evaluated and medically monitored.

The primary approach to the treatment of caffeine intoxication is to teach the patient about the effects of excessive caffeine consumption. In patients who are resistant to accepting the role of caffeine in their presenting symptoms, it may be useful to suggest a trial off of caffeine as both a diagnostic and a potentially therapeutic probe.

## Caffeine Withdrawal

### Diagnosis

#### Definition and Diagnostic Features

Symptoms of caffeine withdrawal have been described in the medical literature for more than 170 years (Griffiths and Woodson 1988a). For example, Bridge (1893) reported on a series of patients who had various conditions he thought were associated with the use of coffee or tea. He concluded that the cessation of coffee could be beneficial, although patients were at risk for developing a severe headache acutely with abrupt termination, and he recommended "reducing the rations of coffee gradually through a week or more of time."

Arguably, the caffeine withdrawal syndrome has been more rigorously and completely characterized than withdrawal from any other drug. A recent review summarized results of 66 reports on caffeine withdrawal, most of which were published within the last 10 years (Juliano and Griffiths 2004). In addition to headache, the best validated caffeine withdrawal symptoms are tiredness/fatigue, sleepiness/drowsiness, dysphoric mood (e.g., miserable, decreased well-being/contentedness), difficulty concentrating, depression, irritability, nausea/vomiting, and muscle aches/stiffness) (Table 56–3). Sign and symptom categories that have also been implicated in caffeine cessation include yawning, heavy feelings in arms and legs, work difficulty/unmotivated, craving/strong desire to use caffeine, impaired behavioral and cognitive performance (objectively measured), increased cerebral blood flow, and EEG changes (Juliano and Griffiths 2004).

**DSM-IV-TR Research Criteria**

**Caffeine Withdrawal**

A. Prolonged daily use of caffeine.

B. Abrupt cessation of caffeine use, or reduction in the amount of caffeine used, closely followed by headache and one (or more) of the following symptoms:

(1) marked fatigue or drowsiness
(2) marked anxiety or depression
(3) nausea or vomiting

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiologic effects of a general medical condition (e.g., migraine, viral illness) and are not better accounted for by another mental disorder.

**Table 56–3 Signs and Symptoms of Caffeine Withdrawal**

| |
|---|
| Headache |
| Tiredness, fatigue |
| Sleepiness, drowsiness |
| Dysphoric mood |
| Difficulty concentrating |
| Depression |
| Irritability |
| Nausea or vomiting |
| Muscle aches or stiffness |

*Source:* Juliano and Griffiths (2004).

#### *DSM-IV-TR Diagnosis of Caffeine Withdrawal*

Although caffeine can produce a withdrawal syndrome, the Substance Use Disorders Work Group for DSM-IV-TR recommended including caffeine withdrawal as a proposed diagnosis rather than an official diagnosis to encourage further research on the range and specificity of caffeine withdrawal symptoms (Hughes 1994). The DSM-IV-TR research criteria for a diagnosis of caffeine withdrawal are shown on this page. In 1994, the Work Group for DSM-IV-TR had several concerns about the inclusion of a diagnosis of caffeine withdrawal in DSM-IV-TR: only headache, fatigue, and drowsiness were well-validated symptoms, the symptoms of fatigue and drowsiness appeared to overlap, and the three caffeine abstinence symptoms had a high prevalence in the general population and also had several other etiologies (Hughes 1994). The great majority of the research literature on caffeine withdrawal has been published since 1994 when the DSM-IV-TR Work Group formulated their criteria for the research diagnosis. This new research literature provides better validation of a wider range of symptoms (Table 56–3). The proposed criteria for a DSM-IV-TR research diagnosis of caffeine withdrawal require the presence of headache and one or more of the following: marked fatigue or drowsiness, marked anxiety or depression, nausea or vomiting. Problems with this approach are that it does not reflect the independence of headache and nonheadache withdrawal symptoms (discussed below), it excludes several well validated withdrawal symptoms (dysphoric mood, difficulty concentrating, and irritability), and it includes a symptom (anxiety) that was not shown to be valid in double-blind experimental studies. On the basis of the expanded research literature, it has been proposed (Juliano and Griffiths 2004) that part B

of the DSM research criteria be changed to indicate that the caffeine withdrawal diagnosis requires: abrupt cessation of caffeine use or reduction in the amount of caffeine used closely followed by three or more of the following: (1) headache, (2) fatigue or drowsiness, (3) dysphoric mood, depressed mood, or irritability, (4) difficulty concentrating, and (5) nausea, vomiting, or muscle pain/stiffness. The new criteria address the 1994 DSM-IV-TR Work Group concerns that there were too few validated symptoms and there may be overlap between fatigue and drowsiness. Although it remains true that some of the proposed symptoms have high prevalence and may have other etiologies, this is also true of other withdrawal diagnoses recognized by DSM (e.g., cocaine withdrawal, nicotine withdrawal and opioid withdrawal).

### *Headache*

The most common feature of caffeine withdrawal is headache (Table 56–4) (Lader et al. 1996, Juliano and Griffiths 2004). About 50% of individuals in double-blind studies report headache, which is often moderate to severe in intensity. Caffeine withdrawal headache is typically described as gradual in development, diffuse, throbbing, and sometimes accompanied by nausea and vomiting. It is relieved with caffeine consumption and it may be worsened with physical exercise and Valsalva maneuver. Double-blind studies of caffeine withdrawal have shown that headache generally occurs 12–24 hours after the last dose of caffeine (mean 19 hours), although headache onset as late as about 40 hours has been documented. Caffeine withdrawal headache usually resolves within 2–4 days, although some subjects continue to report sporadic headaches for as long as 11 days after cessation of caffeine use (Juliano and Griffiths 2004).

**Table 56–4 Features of Caffeine Withdrawal—Headache**

| |
|---|
| Gradual onset between 12 and 40 h |
| Worse with exercise, Valsalva maneuver |
| Can be accompanied by flu-like symptoms (including nausea, vomiting) |
| Diffuse, throbbing, severe |

Clinical reports, correlation analyses, and cluster analysis of withdrawal symptoms indicate that nonheadache signs and symptoms of caffeine withdrawal do not always covary with the presence of headache, and can occur in the absence of headache (Juliano and Griffiths 2004). This indicates that nonheadache symptoms represent distinct features of the caffeine withdrawal syndrome that can occur independently of headache.

## Clinically Significant Distress or Impairment in Daily Functioning in Caffeine Withdrawal

When symptoms of caffeine withdrawal occur, the severity can vary from mild to extreme. At its worst, caffeine withdrawal has been repeatedly documented to produce clinically significant distress or impairment in daily functioning and, on rare occasions, to be totally incapacitating (Bridge 1893, 1990b, Lader et al. 1996, Strain et al. 1994, Dreisbach and Pfeiffer 1943, Kingdon 1833, Silverman et al. 1992, Greden et al. 1980, Goldstein et al. 1969, Rainey 1985, Cacciatore et al. 1996, Hampl et al. 1994, Richards et al. 2004, Svikis et al. 2005). For example, in a double-blind caffeine withdrawal evaluation, 73% of individuals whose pattern of caffeine use met criteria for DSM-IV-TR substance dependence on caffeine reported functional impairment in normal activities during an experimental withdrawal phase (Strain et al. 1994).

Several rigorous blind studies indicate that the incidence of moderate to severe headache is about 50% in healthy normal subjects abstaining from caffeine (Lader et al. 1996, Dreisbach and Pfeiffer 1943, Silverman et al. 1992). One of these studies reported that 28% of those reporting headache also reported nausea and sickness (Lader et al. 1996). Dews et al. (1999) reported that 22% of 18 subjects who previously reported experiencing withdrawal symptoms showed substantial decreases in their ratings of daily functioning (e.g., work and leisure activities) during caffeine abstinence. The relatively lower rate of severe withdrawal symptoms in this study may be due to methodological shortcomings (Griffiths et al. 2003). On the basis of a comprehensive review of the literature, the overall median incidence of clinically significant distress or functional impairment was estimated to be 13% in prospective experimental studies and 9% in retrospective surveys in normal subjects (Juliano and Griffiths 2004).

## Assessment

The key steps in establishing a diagnosis of caffeine withdrawal are to determine the history of the person's caffeine consumption from all dietary sources, and then establish whether there has been a significant decrease in caffeine intake. The diagnostic decision tree for caffeine dependence disorder and caffeine withdrawal disorder is shown in Figure 56–3. Caffeine withdrawal is probably more common than is generally recognized, and it seems there is a tendency for people to attribute the symptoms of caffeine withdrawal to other etiologies besides caffeine (e.g., having the flu, or a bad day). Caffeine withdrawal may be particularly common in medical settings where patients are required to abstain from food and fluids, such as before surgical procedures and certain diagnostic tests. In addition, caffeine withdrawal may occur in settings where the use of caffeine-containing products is restricted or banned, such as inpatient psychiatric wards.

### *Caffeine Withdrawal in Children and Newborn Infants*

Although most research on caffeine withdrawal has been conducted in adults, several studies document that children also experience withdrawal effects during caffeine abstinence (Goldstein and Wallace 1997, Bernstein et al. 1998, 2002, Hale et al. 1995). There is also one report of eight infants with suspected caffeine withdrawal born to mothers who had heavy caffeine consumption during their pregnancies (range: 200–1800 mg/day) (McGowan et al. 1988). Symptoms begun an average of 19 hours after birth, were primarily irritability, jitteriness and vomiting, and resolved spontaneously.

## Epidemiology

There are two types of studies that have examined the prevalence/incidence of caffeine withdrawal. In the first, caffeine withdrawal is experimentally induced, and in the second, there is an epidemiologic assessment of the prevalence/incidence of caffeine withdrawal, usually through the use of some form of a retrospective questionnaire. The

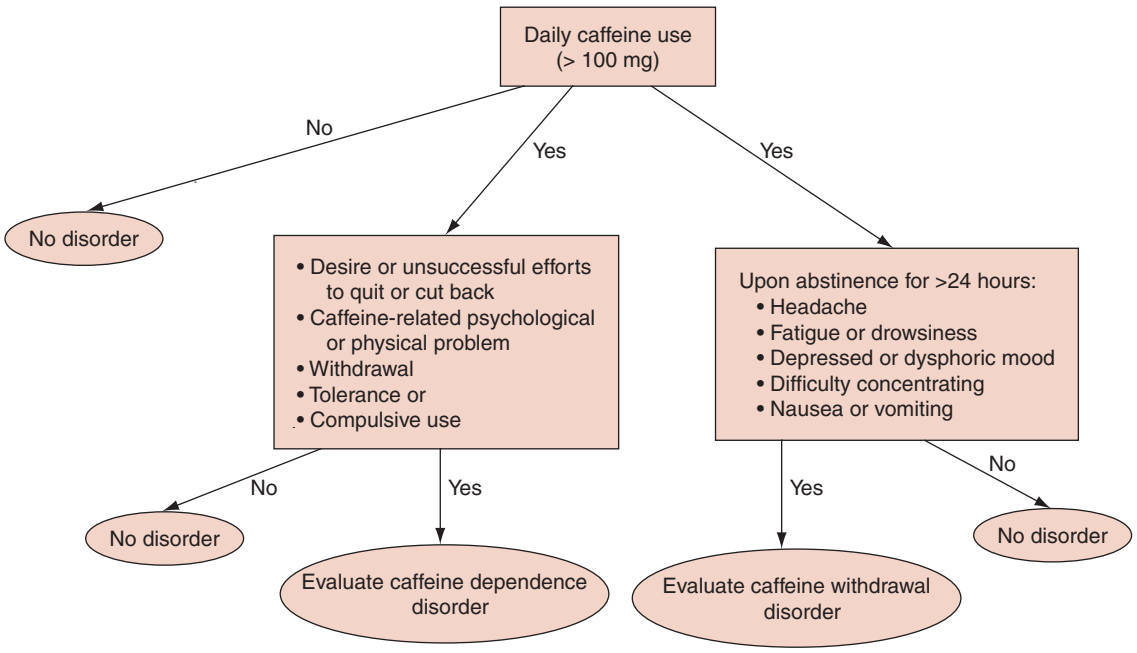



**Figure 56–3** *Diagnostic decision tree for caffeine dependence disorder and caffeine-withdrawal disorder.*

median percentage of individuals reporting headache in 19 experimental studies was 47%, ranging from 9% to 100% across studies. In 7 studies that assessed headache severity, the median percentage of individuals reporting moderate, severe or maximum headache was 50% (Juliano and Griffiths 2004). On the basis of a comprehensive review of the literature, the median incidence of clinically significant distress or functional impairment from caffeine withdrawal in prospective experimental studies with normal subjects was 13%, ranging from 10 to 55%. This rate is similar to the 14% rate of functional impairment reported in a recent caffeine withdrawal trial in pregnant women (Svikis et al. 2005), but lower than the 73% rate of functional impairment observed in individuals who met criteria for DSM-IV-TR substance dependence on caffeine (Strain et al. 1994).

Survey studies have also been conducted to determine the prevalence/incidence of caffeine withdrawal. Two population-based survey studies showed a 24% incidence of caffeine withdrawal using the DSM-IV-TR research criteria (Hughes et al. 1998, Kendler and Prescott 1999). In the study by Hughes and colleagues 44% of caffeine users reported having stopped or reduced caffeine use for at least 24 hours in the past year. Of those, 41% reported that they experienced one or more DSM-IV-TR-defined caffeine withdrawal symptom. Among individuals who stopped caffeine use in an attempt to abstain permanently, 71% reported experiencing one or more DSM-IV-TR-defined symptoms, and 24% reported having headache plus other symptoms that interfered with performance. In a review of 7 survey studies, the median percentage of caffeine users reporting caffeine withdrawal headache was also 24%, ranging between 8 and 56% (Juliano and Griffiths 2004). Finally, in a more recent survey study of women who abstained from caffeine for a day or more, 49%, 39%, and 2% reported headache, fatigue, and nausea or vomiting, respectively (Svikis et al. 2005). On the basis of a comprehensive review of the literature, the incidence of clinically significant distress or functional impairment from caffeine withdrawal varied between 2.6 and 11% (median 9%) in general survey studies, and was 21% in caffeine-dependent adolescents (Juliano and Griffiths 2004, Oberstar et al. 2002).

It is possible that survey studies underestimate the rate of caffeine withdrawal. Many caffeine consumers may be unaware of their vulnerability to caffeine withdrawal symptoms, because their routine habitual consumption never involves a period of sustained abstinence, and they may misattribute withdrawal symptoms such as headache, nausea, and muscle aches to other ailments such as viral infection. Furthermore, since as little as 25 mg/day of caffeine is sufficient to suppress withdrawal (Evans and Griffiths 1999), even small amounts of caffeine that are unknowingly consumed during presumed caffeine abstinence may result in underestimates of the frequency of withdrawal.

## Comorbidity Patterns

Patients with high daily caffeine consumption (Evans and Griffiths 1999, Weber et al. 1997), or patients with a history of frequent headaches (Weber et al. 1997) may be at increased risk for developing caffeine withdrawal or caffeine withdrawal headaches. A study of adult twins found that a measure reflecting caffeine withdrawal (comprised of summing several caffeine withdrawal symptoms plus tolerance) was significantly and positively associated with each of seven diagnoses: major depression, generalized anxiety disorder, panic disorder, adult antisocial disorder, alcohol dependence, and cannabis and cocaine abuse/dependence (Kendler et al. 2006).

### *Postanesthesia Headache and Caffeine Withdrawal*

Headache is one of the most frequent postoperative side effects after general anesthesia, with the incidence varying from 13 to 80% (Fennelly et al. 1991) and caffeine abstinence being a contributor. Studies in patients required to abstain from caffeine in preparation for an operative procedure have shown that a history of preoperative caffeine is associated with an increased risk for postoperative headache

(Nikolajsen et al. 1994) and that this risk may be dose-related (Fennelly et al. 1991, Galletly et al. 1989). In patients with a history of caffeine consumption who received caffeine on the day of a surgical procedure, the rate of postoperative headaches was lower than in those who received placebo (Weber et al. 1997, Hampl et al. 1995).

### Course

Caffeine withdrawal generally begins 12–24 hours after discontinuing caffeine use. The peak of caffeine withdrawal generally occurs within 20–50 hours, and the duration of caffeine withdrawal is generally 2 days to about 1 week (Juliano and Griffiths 2004). The possibility of withdrawal headaches occurring up to 21 days has been suggested (Richardson et al. 1995). An example of the time course of caffeine withdrawal symptoms is shown in Figure 56–4. In this study four volunteers, who initially received 100 mg/day of caffeine in capsules, were switched under double-blind conditions to placebo for a period of 12 days (Griffiths et al. 1990b). Symptoms of headache, lethargy/fatigue/tired/sluggish, and impaired concentration peaked on days 1 or 2 after placebo substitution and progressively returned toward prewithdrawal levels over about a week (Figure 56–4).

## Differential Diagnosis

Caffeine withdrawal should be considered when evaluating individuals presenting with headaches, fatigue, sleepiness, mood disturbances or impaired concentration. The differential diagnosis of caffeine withdrawal includes: viral illnesses; sinus conditions; other types of headaches such as migraine, tension, postanesthetic; other drug withdrawal states such as amphetamine or cocaine withdrawal; and idiopathic drug reactions.

## Etiology and Pathophysiology

### Individual Differences and Genetic Factors

There is considerable variability, both between people and within the same person across episodes, in the manifestations, time course, and severity of caffeine withdrawal (Griffiths et al. 1990b, Hughes et al. 1993). Other than the role of chronic maintenance dose (discussed below), very little is known about the determinants of individual differences in caffeine withdrawal. The results of one study suggested that individuals who eliminated caffeine slowly were less likely to experience sedation during withdrawal (Lader et al. 1996). Two studies suggest that females may be more likely than males to report functional impairment produced by caffeine withdrawal (Strain et al. 1994, Dews et al. 1999).

There is evidence that genetic factors may play a role in some differences between individuals. One study of female twins found that there was a significantly greater concordance of DSM-IV-TR-defined caffeine withdrawal among monozygotic than dizygotic twins, resulting in an estimated heritability of 35% (Kendler and Prescott 1999).

### Pharmacological Factors

#### *Maintenance Dose of Caffeine*

Several studies have found either the presence of caffeine withdrawal, or its severity are more likely as the daily maintenance dose of caffeine is increased (Evans and Griffiths 1999, Nikolajsen et al. 1994, Fennelly et al. 1991, Galletly et al. 1989), although this relationship is relatively weak because it has not been observed in some studies (Hughes

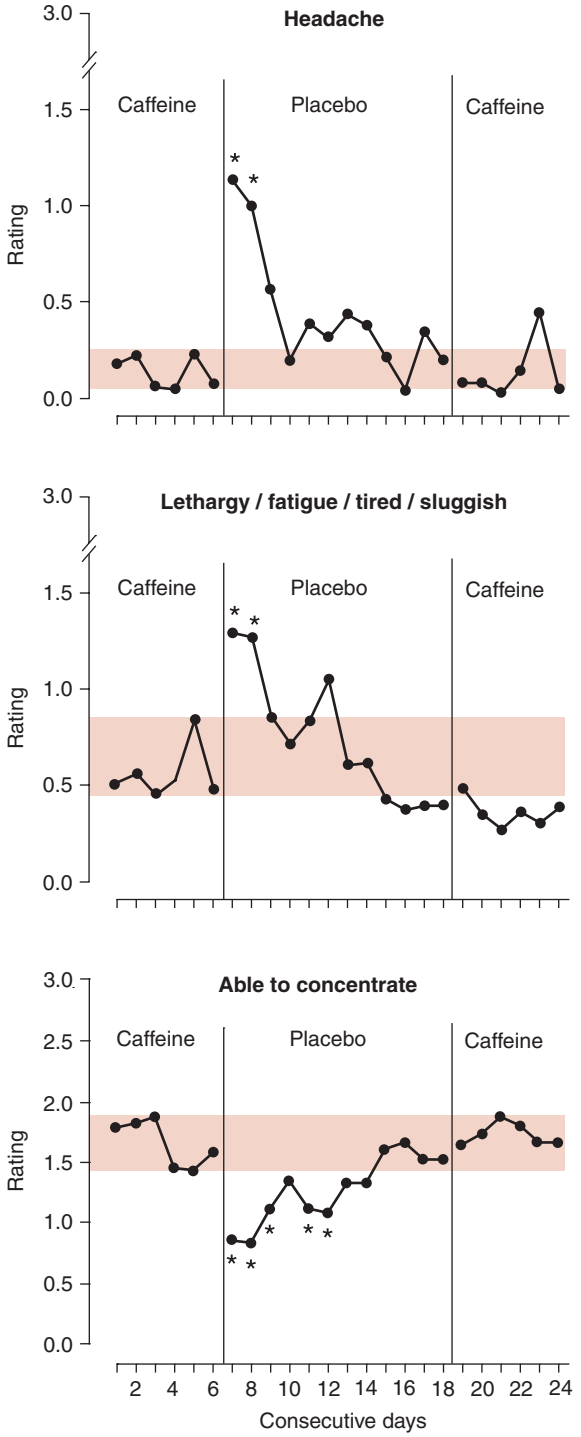



**Figure 56–4** *Time course of caffeine withdrawal symptoms in four volunteers. Under double-blind conditions subjects received capsules containing either 100 mg/day of caffeine or placebo. Assessments included subject ratings of headache, feelings of lethargy/fatigue/tired/sluggish, and ability to concentrate. Ratings ranged from 0 (not at all) to 3 (very much). Shaded areas indicate the range of means from the initial 6-day caffeine period. Asterisks indicate placebo days that are significantly different from the initial caffeine period ($P \leq 0.05$). (Source: Reproduced from Griffiths et al., [1990b], with permission of American Society for Pharmacology and Experimental Therapeutics.)*

et al. 1993, Lader et al. 1996), and some studies have shown no or only very mild symptoms after stopping high doses of caffeine in some individuals (Griffiths et al. 1986, Strain et al. 1994). It has been shown that caffeine withdrawal can occur with surprisingly low doses of caffeine—as low as 100 mg/day (Griffiths et al. 1990b, Evans and Griffiths 1999), which is the equivalent of about one cup of brewed coffee or two to three caffeinated soft drinks per day (Table 56–1).

### *Duration of Caffeine Exposure*

Caffeine withdrawal has been shown to occur after relatively short-term exposure to daily caffeine (Evans and Griffiths 1999, Dreisbach and Pfeiffer 1943). One study showed that significant withdrawal occurred after only 3 consecutive days of 300 mg/day caffeine, with somewhat greater severity shown after 7 and 14 consecutive days of exposure (Evans and Griffiths 1999). Another study showed that caffeine withdrawal headache occurred in three individuals who normally abstained from caffeinated beverages but were given 600–750 mg/day caffeine for 6 or 7 days (Dreisbach and Pfeiffer 1943).

### *Caffeine Suppression of Caffeine Withdrawal*

Low doses of caffeine are capable of suppressing caffeine withdrawal (Watson et al. 2000). One study showed that a small dose of only 25 mg/day was sufficient to suppress caffeine withdrawal headache in people maintained on 300 mg/day (Evans and Griffiths 1999). This finding suggests that a substantial percentage reduction in caffeine consumption is necessary to manifest the full caffeine withdrawal syndrome.

## Pharmacological Mechanism of Action

Antagonism of adenosine at adenosine receptors is the primary molecular mechanism underlying most of the central and peripheral physiological effects of caffeine after acute administration (see section on "caffeine intoxication"). Chronic caffeine consumption has been shown to produce compensatory upregulation of the adenosine system, resulting in an increase in functional sensitivity to adenosine during caffeine withdrawal (Paul et al. 1993, Kaplan et al. 1993, Varani et al. 1999). Because adenosine produces sedation and cerebral vasodilation (Daly 1993) and has been implicated in headache (Guieu et al. 1998), increased sensitivity to endogenous adenosine, particularly in vascular and neural tissue in brain, may be a mechanism underlying the common caffeine withdrawal symptoms of fatigue and headache. Studies have shown that caffeine abstinence produces increases in cerebral blood flow and cerebral blood flow velocities (Field et al. 2003, Jones et al. 2000, Couturier et al. 1997, Mathew and Wilson 1985). These findings are consistent with a vascular explanation of caffeine withdrawal symptoms since blood flow has been implicated in headache (Moskowitz et al. 1989, Olesen 1991). Another physiological effect documented during caffeine abstinence is a change in quantitative EEG. Two studies (Jones et al. 2000, Reeves et al. 1995) showed increases in theta activity, an effect generally correlated with drowsiness, which is a common caffeine withdrawal symptom.

## Treatment

There have been few studies attempting to address the treatment of caffeine withdrawal, although it has frequently been observed that the symptoms of caffeine withdrawal can be alleviated with the consumption of caffeine (Evans and Griffiths 1999, Dreisbach and Pfeiffer 1943), and this approach is probably best. One report indicated that experimentally induced caffeine withdrawal headaches responded to aspirin (Dreisbach and Pfeiffer 1943). If the medical recommendation is made to eliminate or substantially reduce caffeine consumption, then it may be useful to recommend a tapering dose schedule rather than abrupt discontinuation. Caffeine tapering (or "fading") is described in more detail in the section on "caffeine dependence."

**Clinical Vignette 1: Caffeine Withdrawal**

Ms. E, a 37-year-old married woman, presented with a chief complaint of episodic headaches, especially noted on weekends. Her family history was notable for alcoholism in her mother, but there was no other psychiatric illness in the family. She was a college graduate employed full time as a clerk, had been married for 16 years, and had two healthy children. She met her husband in college and described her marriage as stable and her husband as supportive. She did not smoke tobacco, drank alcohol rarely (once every 2 to 3 months, typically one to two drinks), and did not use illicit drugs. Ms. E was not taking prescription medications, had no chronic medical illnesses, and had no past psychiatric history.

She reported that she began consuming caffeine by drinking soft drinks as a child and regularly drank soft drinks as she was growing up. She began drinking coffee in college and used coffee regularly when she needed to study late at night. Her current beverage of choice was coffee, which she drank without cream or sweetener, and she drank a total of five to six large mugs each day. There was a coffee maker in her office, and her first consumption of coffee every morning was at work. She spaced her subsequent coffee use during the course of the day, with her last mug late in the afternoon at work. At one point when she was scheduled for outpatient surgery, staff had considered canceling the procedure because of her developing a severe headache after morning abstinence from caffeine. When pregnant, she had tried but had been unable to reduce her use of coffee.

She reported that she typically developed headaches in the late mornings or early afternoons and described them as diffuse, throbbing headaches that were bilateral. She had no aura, no photophobia, and no nausea or vomiting. The headaches were not clearly related to stress, and she thought they occurred primarily on weekends. Other symptoms associated with her headaches included feeling "dragged out," tired, and sleepy. She had tried taking aspirin and acetaminophen for the headaches and reported only partial relief with these medications. A work-up by her primary care physician revealed no disease that would account for her headaches.

Ms. E's history of caffeine use and the nature of her headaches suggested that she might be experiencing caffeine withdrawal. On weekends, she would not drink coffee. She was counseled to try drinking a mug of coffee the next time she felt her characteristic headache, and she found this intervention produced full relief from her headache and also alleviated her feeling of lethargy. She then underwent a program of caffeine fading to decrease the overall amount of caffeine she was consuming. Once she achieved a steady level of one mug of coffee per day, she found she was able to skip a day of consuming coffee without experiencing a headache.

## Caffeine Dependence

### Diagnosis

#### Definition and Diagnostic Features

Before discussing the definition of caffeine dependence using DSM-IV-TR criteria, it is useful to distinguish physical dependence from a clinical diagnosis of substance dependence. Physical dependence is indicated by the presence of a withdrawal syndrome after cessation of use of the substance. A clinical diagnosis of dependence encompasses several features of pathologic use of a psychoactive substance, which can include (but is not limited to) evidence of physical dependence. These distinctions between physical dependence and a clinical syndrome of dependence often have clouded discussions of caffeine dependence. As described in the previous section, numerous reports now document the existence of a caffeine withdrawal syndrome indicating that caffeine can produce physical dependence. Although considerably fewer studies have been published, there is growing evidence that caffeine can also produce a syndrome of clinical dependence. Currently, DSM-IV-TR utilizes a set of generic criteria to define a clinical syndrome of substance dependence. Notably, DSM-IV-TR states, "A diagnosis of Substance Dependence can be applied to every class of substances except caffeine." It is noteworthy, however, that a diagnosis of substance dependence due to caffeine is recognized by ICD-10 (WHO 1992a, 1992b), the international diagnostic system developed by the World Health Organization that uses very similar diagnostic criteria to DSM-IV-TR.

The clinical features of individuals with caffeine dependence were described in a series of 16 cases described by Strain et al. (1994). Most of these individuals reported physical or psychological problems from caffeine use which had prompted multiple unsuccessful attempts to cut down or quit caffeine use, often in response to physicians' recommendations. Most reported tolerance to caffeine and withdrawal when attempting to completely abstain. A double-blind withdrawal trial showed functional impairment in most cases. For the group, median daily caffeine intake was 357 mg with a wide range of 129–2,548 mg. The preferred vehicle was almost equally divided between soft drinks and coffee.

#### Clinically Significant Distress or Impairment Associated with Caffeine Dependence

Much in the same way that cigarette smoking was not considered a "real" form of drug dependence several decades ago, personal experience with normative caffeine use may render some clinicians relatively insensitive to the extent of distress or impairment associated with caffeine dependence in some individuals. A brief description of the three diagnostic criteria most relevant to understanding the clinical significance of the syndrome is presented below.

##### *Substance Use is Continued Despite Knowledge of having a Persistent or Recurrent Physical or Psychological Problem That is Likely to have been Caused or Exacerbated by the Substance*

Fourteen percent of caffeine users in a general population survey met this criterion, with most (13%) reporting that a physician or counselor had advised them to stop or reduce caffeine use within the last year (Hughes et al. 1998). Medical and psychological problems attributed to caffeine included heart, stomach and urinary problems, and complaints of anxiety, depression, insomnia, irritability, and difficulty thinking. A higher rate of endorsement of this criteria (43%) occurred in a study of pregnant women who had been advised to quit caffeine use during pregnancy (Svikis et al. 2005). When asked about caffeine use prior to pregnancy, 21% indicated that they had previously been told by a health care professional that they should cut back or quit caffeine because of a medical condition including, fibrocystic breast disease, headaches, pregnancy, insomnia, and stomach problems. Not surprisingly, the highest rates of endorsement of this criterion of

**DSM-IV-TR Criteria**

**Substance Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  (b) markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:
  (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances)
  (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

continued use despite harm has come from studies that interviewed caffeine dependent individuals. In four such studies, the prevalence varied from 57 to 94% (Strain et al. 1994, Oberstar et al. 2002, Richards et al. 2004, Jones and Lejuez 2005). In the case series described by Strain et al. 44% of the subjects reported physical conditions such as acne rosacea, pregnancy, palpitations, and gastrointestinal problems that had led physicians to recommend reduction or elimination of caffeine; all had failed to comply with the recommendation.

### *Persistent desire or unsuccessful efforts to cut down or control substance use*

The desire to control caffeine use is usually closely related to the recognition of an associated physical or psychological problem, often identified by a physician as described above. In two survey studies, the rate of endorsement of this criterion was 56% (Hughes et al. 1998) and 45% (Svikis et al. 2005). In four studies of caffeine dependent individuals, the prevalence varied from 60 to 89% (Strain et al. 1994, Oberstar et al. 2002, Richards et al. 2004, Jones and Lejuez 2005). In the study by Richards et al. 82% of a group of 38 individuals were sufficiently distressed by their caffeine use to enroll in a caffeine treatment study.

### *Withdrawal*

Many caffeine dependent individuals continue to use caffeine to avoid experiencing withdrawal symptoms. In four studies in caffeine dependent persons, the rate of endorsement of withdrawal or use to avoid withdrawal ranged from 73 to 100% (Strain et al. 1994, Oberstar et al. 2002, Richards et al. 2004, Jones and Lejuez 2005). As described in more detail in the prior section on the caffeine withdrawal diagnosis, symptoms of caffeine withdrawal can vary from none to extreme. On the basis of a comprehensive review of the literature, the overall median incidence of clinically significant distress or functional impairment was estimated to be 13% in prospective experimental studies in normal subjects and 9% in retrospective surveys in normal subjects (Juliano and Griffiths 2004).

## Assessment

Caffeine dependence may be an unrecognized condition with a higher prevalence than is generally appreciated. Clinicians do not typically think to inquire about caffeine use and about problematic use consistent with a diagnosis of caffeine dependence (see Figure 56–3 for diagnostic decision tree). However, probing for evidence of caffeine dependence may be useful, and it would be reasonable to focus upon the DSM-IV-TR criteria for dependence that are more appropriate for a substance that is widely available and generally culturally accepted. Thus, the clinician should probe for evidence of tolerance, withdrawal, continued use despite a doctor's recommendation that the person cut down or stop using caffeine, use despite other problems associated with caffeine, often using larger amounts or over a longer period than intended, or persistent desires and/or difficulties in decreasing or discontinuing use. For research purposes, a section for the diagnosis of caffeine dependence according to DSM-IV-TR or *International Classification of Diseases*, 10th Revision (ICD-10) criteria is now available on the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), which is a reliable and valid structured interview focused on substance use disorders (Cottler et al. 1989, Compton et al. 1996).

## Epidemiology

Two survey studies provide information on the prevalence of caffeine dependence in the general population based upon standardized diagnostic criteria. In a random telephone survey of residents of Vermont (Hughes et al. 1998), 162 out of the 202 surveyed participants reported current caffeine use. Assessing the seven generic DSM-IV-TR criteria for dependence, 30% of the 162 current caffeine users fulfilled criteria for a diagnosis of caffeine dependence by endorsing three or more dependence criteria. When just the four criteria that seemed most applicable to caffeine were assessed: (use despite harm; desire to quit; withdrawal; and tolerance), only 9% fulfilled three or more criteria. Using all seven criteria, Svikis et al. 2005 reported a 57% lifetime prevalence of caffeine dependence among 44 women who reported some caffeine use in the three months before becoming pregnant.

Further information about rates of endorsement of the individual criteria for caffeine dependence is provided by five published reports of individuals who fulfilled criteria for dependence (Strain et al. 1994, Oberstar et al. 2002, Richards et al. 2004, Jones and Lejuez 2005). Rates of endorsement, respectively, of the four most relevant criteria were (1) use despite harm (94%, 58%, 84%, 57%); (2) desire to quit (81%, 83%, 89%, 60%); (3) withdrawal (94%, 100%, 97%, 73%); and (4) tolerance (75%, 92%, 76%, 70%).

## Comorbidity Patterns

Comorbid conditions associated with excessive caffeine consumption are discussed in the previous section on caffeine intoxication. Four studies provide information about comorbidity in individuals with caffeine dependence. In a previously described study of 44 pregnant caffeine-using women (Svikis et al. 2005), those who had a caffeine dependence diagnosis were almost nine times more likely to report a history of daily cigarette smoking, compared to women without the diagnosis (44% vs. 5%). Furthermore, women with both caffeine dependence and a family history of alcoholism were six times more likely to have a lifetime diagnosis of alcohol abuse or dependence. In the study described above by Strain et al. (1994), which characterized DSM-IV-TR-diagnosed caffeine dependence in 16 adults, it was found that two subjects (13%) had an additional current psychiatric diagnosis (both being anxiety disorders), and 69% had other psychiatric disorders in remission. Most commonly, these other disorders were other psychoactive substance use disorders (63%) followed by mood disorders (44%), anxiety disorders (25%), or eating disorders (19%). Among the psychoactive substance use disorders, the most commonly abused substance was alcohol; 57% of the participants in the study had a past diagnosis of alcohol abuse or dependence. Five of the subjects in the study (32%) were nicotine cigarette smokers and, notably, four of these five had a history of an alcohol disorder (suggesting a clustering of caffeine dependence, smoking and alcohol abuse/dependence, as discussed below). A third study showed that the severity of caffeine dependence was significantly correlated with the severity of the alcohol dependence, however, dependence on caffeine and nicotine were not correlated (Hughes et al. 2000). A final study, which compared 5 caffeine dependent adolescents with 16 noncaffeine dependent

adolescents, found no significant differences between the groups in rates of various psychiatric disorders including nicotine and alcohol dependence (Oberstar et al. 2002).

### Course

While there are no studies that have specifically examined the course and natural history of caffeine dependence, like other drug dependence syndromes caffeine dependence appears to be a chronic relapsing disorder. In the study described above by Strain et al. (1994), caffeine dependent participants reported recurrent efforts to discontinue caffeine use, with failures to discontinue use or frequent relapses.

### Differential Diagnosis

The diagnosis of caffeine dependence includes symptoms that can also contribute to a diagnosis of caffeine intoxication and caffeine withdrawal, and both of these conditions should be included in the differential diagnosis of a patient with possible caffeine dependence. Since intoxication and withdrawal symptoms can contribute to the diagnosis of dependence, conditions that overlap with these caffeine-related disorders should also be considered (and are reviewed above in their respective sections). When considering a patient for a possible diagnosis of caffeine dependence, the clinician should also consider other substance dependence syndromes—especially those related to stimulants—in the differential diagnosis. Finally, the possible presence of other psychiatric conditions, such as depressive and anxiety disorders, should be assessed. These disorders may be more commonly found among patients with caffeine dependence, and some of their presenting features (e.g., low mood, anxiety, disturbed sleep) can overlap with the symptoms of caffeine intoxication and withdrawal which commonly occur in caffeine dependence.

## Etiology and Pathophysiology

### Genetic Factors

Genetic studies suggest that caffeine use problems have an underlying biological basis, part of which may be shared with other commonly abused substances. One study examined women who were instructed to stop caffeine use during their pregnancy (Svikis et al. 2005). Women with a lifetime diagnosis of caffeine dependence and a family history of alcoholism had higher levels of caffeine use and lower rates of abstinence throughout pregnancy, and also reported higher rates of past cigarette smoking and problematic use of alcohol and other drugs. Twin studies comparing monozygotic and dizygotic twins showed heritabilities of heavy caffeine use, caffeine tolerance, and caffeine withdrawal that ranged between 35 and 77% (Kendler and Prescott 1999, Swan et al. 1997, Pedersen 1981, Partanen et al. 1966). Other twin studies examining caffeine use, alcohol use, and cigarette smoking concluded that a common genetic factor (polysubstance use) underlies the use of these three substances, with 28–41% of the heritable effects of caffeine use (or heavy use) shared with alcohol and smoking (Swan et al. 1997, Hettema et al. 1999).

### Behavioral/Psychological Factors

#### *Caffeine Subjective Effects*

Many studies have shown that caffeine in low to moderate doses (20–200 mg) produces mild positive subjective effects of increased feelings of well-being, alertness, energy, concentration, self-confidence, motivation for work, and desire to talk to people (Griffiths et al. 2003). The profile of positive effects with caffeine is qualitatively similar to that produced by *d*-amphetamine and cocaine, which may reflect a common dopaminergic mechanism of action. High doses of caffeine (e.g., 800 mg) produce negative subjective effects such as anxiety and nervousness, especially in people who are not tolerant to caffeine (Chait 1992, Evans and Griffiths 1991).

#### *Caffeine Reinforcement*

Consistent with its ability to produce mild positive subjective effects, low to moderate doses of caffeine have also been shown to function as a reinforcer in humans—that is, when given the choice under experimental conditions, some people will consistently choose to consume caffeine rather than placebo (Griffiths et al. 2003). The profile of positive subjective and reinforcing effects may help explain the wide and regular consumption of caffeine containing substances. However, not everyone uses caffeine, and it appears that some people tend to prefer caffeine and others do not. Caffeine choosers tend to report positive subjective effects from caffeine, while nonchoosers report negative subjective effects (Goldstein et al. 1969, Evans and Griffiths 1992), and people who have symptoms of caffeine withdrawal when they abstain from caffeine are more likely to choose to consume caffeine when given the choice (Hughes et al. 1993).

#### *Caffeine Conditioned Flavor Preferences*

Studies have shown that repeated pairing of a novel flavored drink with caffeine results in increased ratings of flavor preference, while pairing of a novel flavored drink with placebo results in decreased ratings of pleasantness (Rogers et al. 1995, Yeomans et al. 1998, Tinley et al. 2003). In caffeine dependence, it seems likely that the development of such conditioned flavor preferences over many days of self-administration plays a role in development of strong preferences for specific types or even brands of caffeine-containing beverages.

#### *Caffeine Tolerance*

Tolerance refers to a decrease in responsiveness to a drug due to drug exposure. Complete tolerance to caffeine's subjective, pressor, and neuroendocrine effects has been demonstrated when very high doses of caffeine (750–1200 mg/day spread throughout the day) are administered daily (Evans and Griffiths 1992, Robertson et al. 1981). Partial tolerance to the sleep disruptive effects of caffeine has also been demonstrated (Bonnet and Arand 1992). At lower doses similar to those usually consumed, complete caffeine tolerance does not occur. Two survey studies indicate 8% (Hughes et al. 1998) and 50% (Svikis et al. 2005) of current caffeine users reported tolerance (Hughes et al. 1998), whereas the prevalence of tolerance ranged from 70 to 92% in four studies of caffeine dependent individuals (Strain et al. 1994, Oberstar et al. 2002, Richards et al. 2004, Jones and Lejuez 2005). Although tolerance is one of the criteria for making a diagnosis of caffeine dependence (see DSM-IV-TR criteria for substance dependence), it is not clear what role the development of tolerance may have in the development of clinical dependence upon caffeine.

### *Role of Caffeine Withdrawal in Maintaining Caffeine Consumption*

Caffeine withdrawal, described in detail in a separate section above, is a distinct clinical syndrome characterized by symptoms including headache, fatigue, sleepiness, dysphoric mood, difficulty concentrating, depression, irritability, nausea/vomiting, and muscle aches/stiffness (Table 56–3). Caffeine consumption alleviates caffeine withdrawal symptoms and avoidance of withdrawal symptoms associated with caffeine abstinence has been shown to be an important mechanism of the reinforcing effects of caffeine (Juliano and Griffiths 2004). Withdrawal also plays an important role in the development of preferences for flavors paired with caffeine (Rogers et al. 1995, Yeomans et al. 1998, Tinley et al. 2003).

### *Caffeine Use and Alcohol or Drug Abuse*

The conclusion suggested by the genetic studies described above is that a common genetic factor underlies joint use of caffeine, cigarettes, alcohol, and other drugs. This is consistent with findings of studies on the co-occurrence of use of caffeine, nicotine and alcohol (Kozlowski et al. 1993, Talcott et al. 1998). Kozlowski et al. (1993) found that severity of alcoholism was directly related to use of caffeine and cigarettes, and they conclude that dependence on caffeine, nicotine and alcohol may be governed by the same factors. Other studies indicate that heavy use of caffeine is related to heavy use of alcohol (Istvan and Matarazzo 1984) and that the severity of caffeine dependence increases as the severity of alcohol dependence increases (Hughes et al. 2000). Significantly higher levels of caffeine consumption have also been noted in abstinent alcoholic individuals versus nonalcoholic individuals (Doucette and Willoughby 1980). Other groups at risk may include substance abusers (Russ et al. 1988, Hays et al. 1998, Christo et al. 2003). A study of individuals whose pattern of caffeine use fulfilled DSM-IV-TR diagnostic criteria for substance dependence on caffeine found that almost 60% had a past diagnosis of alcohol abuse or dependence (Strain et al. 1994).

### *Caffeine Use and Nicotine/Cigarette Smoking*

Epidemiological studies have shown that cigarette smokers consume more caffeine than nonsmokers (Istvan and Matarazzo 1984, Swanson et al. 1994), and experimental studies have shown that cigarette smoking and coffee drinking tend to covary temporally within individuals (Emurian et al. 1982, Lane 1996). Higher consumption of caffeine in smokers may be partly due to the increased metabolism of caffeine in smokers (Brown et al. 1988, Parsons and Neims 1978). As described above, twin studies and a study by Kozlowski et al. (1993) also indicate the co-occurrence of caffeine use and cigarette smoking, and Svikis et al. (2005) reported that women fulfilling caffeine dependence diagnostic criteria were more likely to report a history of daily cigarette smoking than women without the diagnosis. However, one study showed no correlation between severity of caffeine and nicotine dependence when the number of diagnostic criteria endorsed were used as the measure of severity (Hughes et al. 2000). Preclinical research indicates that chronic caffeine administration can enhance the reinforcing effects of nicotine (Tanda and Goldberg 2000).

### *Energy Drinks and Caffeine as a "Gateway" Drug*

A notable marketing trend in the United States has been the recent emergence of a new class of high caffeine energy drinks with suggestive names such as "Full Throttle," "AMP Energy"and "Cocaine." Advertising, which is targeted primarily to young males, directly promote stimulant and performance enhancing effects of these products and appear to glorify drug use. As discussed above, an association between heavy caffeine use, smoking, and alcohol/drug abuse has been shown. Whether caffeine serves as a "gateway" to other forms of drug dependence as suggested by some studies (Collins et al. 1997, Pallanti et al. 2006) bears further investigation.

## Pharmacological Mechanism of Action

As has been discussed in the sections on caffeine intoxication and caffeine withdrawal, antagonism of the endogenous neuromodulator adenosine at adenosine receptors is the primary cellular mechanism underlying most of the effects of caffeine, including the mood and performance stimulant effects as well as the physiological effects and symptoms accompanying caffeine abstinence. Considerable data also suggest that the central stimulant effects of caffeine may be dopaminergically mediated (Ferre et al. 1997, Garrett and Griffiths 1997, Fredholm et al. 1999, 2005). More specifically, it is established that caffeine enhances dopaminergic activity by competitive antagonism of central adenosine receptors that are colocalized and functionally interact with dopamine receptors (Ferre et al. 1997, Fredholm et al. 1999, Ciruela et al. 2006). As a competitive antagonist at adenosine receptors, caffeine is believed to produce most of its low- to moderate-dose stimulant behavioral effects by removing the negative modulatory effects of adenosine from dopamine receptors, thus, stimulating dopaminergic activity (Ferre et al. 1997, Fredholm et al. 1999, Garrett and Griffiths 1997). Furthermore, dopamine release in the nucleus accumbens shell has been proposed as a specific neuropharmacological mechanism underlying the addictive potential of many drugs including the abused stimulants (Di Chiara and Bassareo, 2007), and in vivo microdialysis studies have shown an increase in dopamine release in the nucleus accumbens shell after local or systemic administration of caffeine (Solinas et al. 2002, Quarta et al. 2004a, Quarta et al. 2004b). The failure of some studies to reproduce these findings (Acquas et al. 2002) was shown to be related to a more restricted caffeine-responsive area in the nucleus accumbens shell (Borycz et al. 2007). Thus, although caffeine is a less efficacious behavioral stimulant than cocaine and amphetamine, it appears to share the common mechanism of increased dopaminergic activity with these classic stimulant drugs of abuse.

## Treatment

In a survey of physicians' practices, it was found that over 75% of medical specialists recommend that patients reduce or eliminate caffeine for certain conditions including anxiety, insomnia, arrhythmias, palpitations and tachycardia, esophagitis/hiatal hernia, and fibrocystic disease (Hughes et al. 1988). However, stopping caffeine use can be difficult for some people. For example, in a diagnostic study of caffeine dependence (Strain et al. 1994), subjects reported

physical conditions such as acne rosacea, pregnancy, palpitations, and gastrointestinal problems that led physicians to recommend that they reduce or eliminate caffeine; all reported that they were unable to follow their doctor's recommendations.

While there have been no systematic studies which have examined the treatment of people with a clearly established diagnosis of caffeine dependence, several studies with heavy caffeine consumers demonstrated efficacy of a structured caffeine reduction treatment program (i.e., caffeine fading) in achieving substantial reductions in caffeine consumption (James et al. 1985, 1988, Bernard et al. 1981, Foxx and Rubinoff 1979). These reports have generally noted success with a combination of gradual tapering of caffeine, self-monitoring of daily caffeine use, and reinforcement for decreased use. When attempting to reduce or eliminate caffeine use, several steps may be useful (Table 56–5). Since many individuals are not knowledgeable about sources of caffeine in their diets, education and history taking are likely to be important components of treatment. During caffeine tapering it may be useful for the patient to consume extra noncaffeinated fluids, to avoid herbal preparations which contain caffeine or other psychoactive drugs, to avoid the use of anxiolytics, and to maintain a diary throughout the time they are progressively decreasing their caffeine use in order to monitor their progress. Abrupt cessation of caffeine should be avoided in order to minimize withdrawal symptoms and increase the likelihood of long-term compliance with the dietary change. No data about the probability of relapse is currently available, although relapse after caffeine reduction has been reported (James et al. 1988).

**Table 56–5 Method for Eliminating or Reducing Caffeine Use**

Step 1: Educate patient about sources of caffeine. For example, some individuals might not be aware that caffeine is present in noncola soft drinks or analgesics.

Step 2: Use a daily diary to have the person identify all sources of caffeine in their diet. Calculate the total milligrams of caffeine consumed on a daily basis. Self-monitoring should be continued during the reduction phase.

Step 3: Determine a modification goal in collaboration with the patient. Some individuals may want to completely eliminate caffeine, while others may want to reduce their consumption. Individuals who want to reduce consumption but avoid withdrawal symptoms if they omit caffeine for a day should limit their intake to no more than 50 mg/day.

Step 4: Generate a graded dose reduction (i.e., fading schedule) of caffeine use. Reasonable decreases would be 10–25% of the initial dose every few days. Allow for individualization of the caffeine fading. Rather than attempting to progressively eliminate consumption of the preferred caffeine beverage, it may be useful to suggest that the patient substitute decaffeinated for caffeinated beverages. In the case of coffee or tea, caffeine fading can be accomplished by mixing caffeinated and decaffeinated beverages together and progressively increasing the proportion of decaffeinated beverage.

Step 5: Discuss the possibility of relapse with the patient. Discuss triggers (i.e., antecedent conditions) for caffeine use and offer coping strategies for high-risk relapse situations. Suggest that the patient continue to self-monitor caffeine consumption.

Clinical Vignette 2: Caffeine Dependence

Mr. S, a 32-year-old single man, presented with a chief complaint of problems controlling his caffeine use. His family history was notable for a major depressive episode in a sister, and posttraumatic stress disorder in a brother who had served in Vietnam. He was a college graduate employed full-time as a nurse. He smoked a pack of cigarettes a day, drank alcohol in moderation, and occasionally used nonsteroidal antiinflammatory medication for low back pain resulting from a motor vehicle accident when he was in his early twenties. He was not taking regular-prescription medications. He had taken opioids for several months after the motor vehicle accident and felt he may have been "on the verge of abusing them". However, he discontinued their use when he realized his reliance on them, and had not used opioids since that time.

He tried a caffeinated beverage (coffee) at age 12 years but did not like it and did not currently drink coffee. However, he started drinking caffeinated soft drinks regularly in nursing school when he would need to work evening or night shifts. His current consumption included seven to eight 16- oz bottles of caffeinated cola per day. He typically had his first soft drink within 10 to 15 minutes after arising in the morning and then spaced his consumption during the course of the day (with his last use in the evening). Physicians had recommended that he cut down or stop his caffeine use because of complaints of gastrointestinal problems and palpitations, but he had been unable to do so. His roommate had frequently objected to his caffeine use, and Mr. S had responded by decreasing the amount he drank at home and increasing the amount he drank at other locations, such as work. He had attempted to quit by abruptly terminating his soft drink use on several occasions but always relapsed because of headache and fatigue. He drank soft drinks in his car and had a minor car accident once while drinking a soft drink when driving. Mr. S also frequently drank and spilled soft drinks in bed.

Because of Mr. S's problems with his caffeine use, a plan was generated to attempt to decrease his caffeine use over a period of several weeks. Mr. S began by maintaining a daily diary documenting all of his caffeine consumption and then attempted to gradually taper his caffeine use by switching to decaffeinated soft drinks. Whereas this was initially successful, he eventually relapsed to his previous level of caffeine use.

## Caffeine-Induced Anxiety Disorder

### Diagnosis

#### Definition and Diagnostic Features

In addition to the symptom of anxiety that can be a component of caffeine intoxication, caffeine can also produce anxiety disorder, caffeine-induced anxiety disorder (American Psychiatric Association 2000) (see DSM-IV-TR criteria). Although there has been no work using this specific set of diagnostic criteria, the clinical features of the disorder have been described (Greden 1974, Uhde 1990) and there have been several studies examining the relationship between caffeine and anxiety in general, and this work is reviewed here.

Substance-induced anxiety disorders in general are distinguished by prominent anxiety symptoms that are

directly related to a psychoactive substance (American Psychiatric Association 2000). Whereas the form of the disorder can resemble panic disorder, generalized anxiety disorder, social phobia, or obsessive–compulsive disorder, a patient with a substance-induced anxiety disorder does not need to manifest all the diagnostic criteria of one of these conditions to justify making the diagnosis of a substance-induced anxiety disorder.

**DSM-IV-TR Criteria**

**Substance-Induced Anxiety Disorder**

A. Prominent anxiety, panic attacks, or obsessions or compulsions predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

   (1) the symptoms in Criterion A developed during, or within 1 month of, substance intoxication or withdrawal

   (2) medication use is etiologically related to the disturbance

C. The disturbance is not better accounted for by an anxiety disorder that is not substance induced. Evidence that the symptoms are better accounted for by an anxiety disorder that is not substance-induced might include the following: The symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence suggesting the existence of an independent nonsubstance-induced anxiety disorder (e.g., a history of recurrent nonsubstance-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the anxiety symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the anxiety symptoms are sufficiently severe to warrant independent clinical attention.

### Assessment and Differential Diagnosis

The diagnosis of caffeine-induced anxiety disorder is based on evidence of an anxiety disorder etiologically related to caffeine (see Figure 56–2 for the diagnostic decision tree). Other diagnoses to consider include caffeine intoxication, a primary anxiety disorder, and an anxiety disorder due to a general medical condition. Caffeine-induced anxiety disorder can occur in the context of caffeine intoxication, but the anxiety symptoms associated with the caffeine-induced anxiety disorder should be excessive relative to the anxiety seen in caffeine intoxication (American Psychiatric Association 2000). In addition to these conditions, substance-induced anxiety disorder can be produced by a variety of other psychoactive substances (e.g., cocaine).

### Epidemiology, Comorbidity and Course

There are no specific data on the prevalence or incidence of caffeine-induced anxiety disorder, comorbid conditions or the natural history of caffeine-induced anxiety disorder.

## Etiology and Pathophysiology

### Individual Differences and Genetic Factors

Individual differences and genetic factors that contribute to caffeine-induced anxiety were discussed in the section on caffeine intoxication. As described below, individuals with anxiety disorders are particularly sensitive to the anxiogenic effects of caffeine.

### Neurobiological and Psychological Factors

Caffeine's ability to produce anxiety has been studied in two populations: persons without an anxiety disorder, and those with an anxiety disorder. While these studies do not directly assess for a caffeine-induced anxiety disorder, they provide information about the relationship between anxiety and caffeine.

#### *Caffeine-Induced Anxiety in Normals*

Studies with volunteers that do not have an anxiety disorder show that acute doses of caffeine produce increased ratings of anxiety (Nickell and Uhde 1994, Griffiths et al. 2003). These effects are dose related, and high acute doses of oral and intravenous caffeine have been shown to produce panic attacks in persons without an anxiety disorder (Lin et al. 1997, Telch et al. 1996, Nickell and Uhde 1994). Thus, excessive acute caffeine consumption can mimic panic attacks, while chronic caffeine consumption can mimic generalized anxiety (Uhde 1990).

#### *Caffeine's Anxiety-Inducing Effects in Persons With Anxiety Disorders*

Individuals with panic disorder report greater caffeine-induced anxiety than matched controls (Boulenger et al. 1984, Lee et al. 1985). Experimental studies show that caffeine exacerbates anxiety symptoms in individuals with generalized anxiety disorder (Bruce et al. 1992) and panic disorder (Beck and Berisford 1992, Charney et al. 1985) more than in control subjects. Interestingly, patients with anxiety disorders generally have lower levels of caffeine consumption than healthy controls (Rihs et al. 1996, Lee et al. 1985, 1988, Uhde 1990). This suggests that some people (such as patients with an anxiety disorder) may avoid caffeine use because of anxiety effects produced by caffeine.

Finally, it has also been shown that patients with high caffeine consumption have higher rates of anxiolytic use

than patients with moderate or low caffeine use (Greden et al. 1981). This relationship does not appear to be reciprocal, as benzodiazepine users have levels of caffeine intake which are similar to nonusers (Cooper et al. 2004). It is not known whether some patients consume higher levels of caffeine to antagonize the sedative effects of minor tranquilizers, whether minor tranquilizers are prescribed in response to the anxiogenic effects produced by higher doses of caffeine (Roache and Griffiths 1987), or whether some underlying factors (e.g., personality) may account for the increased use of caffeine and anxiolytics together.

### Pharmacological Mechanism of Action

As discussed in the prior sections on caffeine intoxication, caffeine withdrawal, and caffeine dependence, antagonism of the endogenous neuromodulator adenosine at adenosine receptors is the primary cellular mechanism underlying most of the effects of caffeine, including those related to the anxiety-inducing effects.

### Treatment

Guidelines for treatment should generally follow those recommended for the treatment of caffeine dependence (see earlier). Thus, an initial, careful assessment of caffeine consumption should be conducted, and a program of gradual decreasing caffeine use should be instituted (see Table 56–5). Abrupt cessation of caffeine use should be avoided to minimize withdrawal symptoms and to increase the likelihood of long-term compliance with the dietary change. Given the etiological role of caffeine in caffeine-induced anxiety disorder, the prudent course of treatment would avoid the use of pharmacological agents such as benzodiazepines for the treatment of the anxiety disorder until caffeine use has been eliminated. A temporary caffeine-free trial may be useful in persuading skeptical patients about the role of caffeine in their anxiety symptoms. Bruce and Lader (1989) reported that instructions to stop all caffeine use for 1 week led to a significant improvement in more than half of individuals who presented for treatment at an anxiety clinic, with some requiring no further treatment.

## Caffeine-Induced Sleep Disorder

### Diagnosis

#### Definition and Diagnostic Features

Psychoactive substances can produce sleep disorders distinct from the sleep disturbances associated with intoxication or withdrawal produced by that substance (American Psychiatric Association 2000). It has long been recognized that caffeine-containing products can produce sleep disturbances, primarily in the form of insomnia. For example, Chavanne (1911) wrote that "black coffee will make some people lie awake and try to stare through the ceiling. . . ." Although caffeine primarily produces insomnia, there are case reports of hypersomnia associated with acute use of caffeine (Regestein 1989).

The primary feature of a substance-induced sleep disorder is a sleep disturbance directly related to a psychoactive substance (see DSM-IV-TR Criteria) (American Psychiatric Association 2000). The form of the disorder can be insomnia, hypersomnia, parasomnia, or mixed, although caffeine typically produces insomnia. In general, sleep disturbance can often be a feature of substance intoxication or withdrawal (although sleep disturbance does not typically occur with caffeine withdrawal), and caffeine-induced sleep disorder should be diagnosed in patients who are having caffeine intoxication only if the symptoms of the sleep disturbance are excessive relative to what would typically be expected.

In addition to caffeine-induced sleep disorder, it is worth noting that complaints of poor sleep that are not severe enough to qualify as a "disorder" may also be related to caffeine use. It is not uncommon for patients to complain of sleep difficulties while failing to recognize the possible

**DSM-IV-TR Criteria**

**Substance-Induced Sleep Disorder**

A. A prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

   (1) the symptoms in Criterion A developed during, or within a month of, substance intoxication or withdrawal

   (2) medication use is etiologically related to the sleep disturbance

C. The disturbance is not better accounted for by a sleep disorder that is not substance induced. Evidence that the symptoms are better accounted for by a sleep disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent nonsubstance-induced sleep disorder (e.g., a history of recurrent nonsubstance-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Note:** This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the sleep symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

role of caffeine ingestion in their complaints (Brown et al. 1995). A careful assessment of caffeine use, including time of use and quantity, should be included in the evaluation of a patient with sleep difficulties, even if these sleep problems do not constitute a sleep disorder.

### Assessment and Differential Diagnosis

The diagnosis of a caffeine-induced sleep disorder is based on evidence of a sleep disorder etiologically related to caffeine (see Figure 56–2 for diagnostic decision tree). Other diagnoses to consider include caffeine intoxication and caffeine withdrawal, a primary sleep disorder, insomnia or hypersomnia related to another mental disorder, and a sleep disorder due to a general medical condition (American Psychiatric Association 2000). A caffeine-induced sleep disorder can occur in the context of caffeine intoxication or caffeine withdrawal, but the sleep symptoms associated with the caffeine-induced sleep disorder should be excessive relative to the sleep disturbance seen in caffeine intoxication or caffeine withdrawal (American Psychiatric Association 2000).

Although caffeine consumption may decrease with age, the elderly commonly report increased sleeping problems that may be exacerbated by caffeine (Curless et al. 1993). Occult caffeine consumption in the form of analgesic medication may produce sleep problems in the elderly (Brown et al. 1995). An association between disturbed sleep and caffeine consumption has been reported in adolescents (Pollak and Bright 2003, Orbeta et al 2006).

As with caffeine-induced anxiety disorder, a trial of caffeine abstinence may be useful in confirming the diagnosis and helping to convince a skeptical patient about the etiological significance of caffeine in their sleep disorder.

### Epidemiology and Comorbidity

There are no specific data on the prevalence, incidence, or comorbidity patterns of caffeine-induced sleep disorder.

### Course

There is little information available on the course or natural history of caffeine-induced sleep disorder. Sleep disturbances due to caffeine are more likely to occur in people who are not regular caffeine consumers (Colton et al. 1968). In a study of caffeine use as a model of acute and chronic insomnia, subjects maintained on a high dose of caffeine (1200 mg/day) for 1 week demonstrated some adaptation to the sleep-altering effects of caffeine (Bonnet and Arand 1992). Thus, caffeine-induced sleep disorder may be a time-limited condition that reflects relatively acute responses to the effects of caffeine.

### Beneficial Effects of Caffeine on Performance Degraded by Sleep Loss

Although caffeine can produce a sleep disorder, it should be noted that caffeine's effects on sleep may also serve beneficial effects under certain circumstances. Numerous studies have demonstrated that caffeine can improve alertness and performance that have been degraded by sleep loss (Bonnet et al. 2005). In general, it appears that caffeine dose-dependently reverses the effects of 1–2 days of sleep deprivation. Compared to lower acute doses, 600 mg of caffeine shows greater efficacy in attenuating the effects of sleep deprivation over a several hour period of time, although lower doses of caffeine are not necessarily ineffective and may exert beneficial effects that are primarily shorter in duration (Reyner and Horne 2000). However, naps can also improve performance in sleep-deprived individuals, and combining caffeine with naps may be particularly effective in counteracting the effects of sleep deprivation (Reyner and Horne 1998, Bonnet et al. 1995).

## Etiology and Pathophysiology

Caffeine-induced sleep disorder by definition is etiologically related to caffeine. Caffeine's effects on sleep can depend on a variety of factors, such as the dose of caffeine ingested, the individual's tolerance to caffeine, the time between caffeine ingestion and attempted sleep onset, and the ingestion of other psychoactive substances. The effects of caffeine on various measures of sleep quality are an increasing function of dose (Karacan et al. 1976, Hindmarch et al. 2000). Caffeine administered immediately prior to bedtime or throughout the day has been shown to delay onset of sleep and rapid eye-movement sleep, reduce total sleep time, alter the normal stages of sleep, and decrease the reported quality of sleep (Hindmarch et al. 2000, Goldstein 1964, Snel 1993). For example, in a study of subjects who consumed a capsule containing either placebo or 200 mg of caffeine before their usual bedtime, average time to sleep onset was 44 minutes after placebo and 77 minutes after caffeine (Goldstein 1964). Notably, for some subjects in this study, sleep onset after caffeine ingestion was delayed as long as 240 minutes. Although there is less evidence that caffeine consumption early in the day disrupts sleep, one study found that a single dose of 200 mg caffeine taken in the morning produced small but significant effects on the following night's total sleep time, sleep efficiency and EEG power spectra (Landolt et al. 1995).

### Individual Differences and Genetic Factors

Caffeine–induced sleep disturbance is greatest among individuals who are not regular caffeine users (Snel 1993, Colton et al. 1968). It is not known if this difference is due to acquired caffeine tolerance or to preexisting population differences in sensitivity to caffeine. Although some acquired tolerance to the sleep disrupting effects of caffeine has been demonstrated (Bonnet and Arand 1992), complete tolerance may not occur. Therefore, regular consumers of caffeine may still experience caffeine-induced sleep problems (Drapeau et al. 2006, Goldstein 1964, Goldstein et al. 1965). In addition to sleep disruption, studies have shown that caffeine withdrawal after acute abstinence from chronic caffeine can increase sleep duration and quality (Juliano and Griffiths 2004).

Genetic factors that contribute to individual differences in sensitivity to caffeine were discussed in the section on caffeine intoxication. Genetic variations of adenosine deaminase and an $A_{2A}$ receptor gene polymorphism have been shown to affect intensity and sleep architecture (Retey et al. 2005).

## Pharmacological Mechanism of Action

As discussed in the prior sections on caffeine intoxication, caffeine withdrawal, and caffeine dependence, antagonism of the endogenous neuromodulator adenosine at adenosine

receptors is the primary cellular mechanism underlying most of the effects of caffeine, including those related to the sleep disrupting effects.

### Treatment

There are no studies on the treatment of caffeine-induced sleep disorder. As for other conditions associated with caffeine use, such as caffeine dependence, caffeine intoxication, and caffeine-induced anxiety disorder, general guidelines for caffeine reduction can be recommended. These include an initial assessment of total caffeine consumption followed by a program of gradually decreasing caffeine use (see Table 56–5). Abrupt cessation of caffeine use should be avoided to minimize withdrawal symptoms and to increase the likelihood of long-term compliance with the dietary change. Given the etiological role of caffeine in caffeine-induced sleep disorder, the use of pharmacological agents or other interventions to improve sleep should be avoided until an adequate trial off caffeine establishes the presence of a noncaffeine-related sleep disorder.

## Conclusion

Caffeine is the most widely consumed mood-altering drug in the world. In the United States, almost 90% of adults and children consume caffeine regularly. Habitual consumption of caffeinated soft drinks, coffee, or tea with meals is extremely common and may not be readily recognized as caffeine consumption. The cultural integration of caffeine use can make the identification of psychiatric disorders associated with caffeine use difficult. This chapter reviews five disorders associated with caffeine use (caffeine intoxication, caffeine withdrawal, caffeine dependence, caffeine-induced anxiety disorder, and caffeine-induced sleep disorder) and documents that the prevalence of caffeine-induced psychiatric syndromes is higher than may be commonly appreciated.

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CHAPTER

# 57 Substance Abuse: Cannabis-Related Disorders

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Cannabis Intoxication
Cannabis Abuse
Cannabis Dependence
Cannabis Intoxication Delirium
Cannabis-Induced Psychotic Disorder
Cannabis-Induced Anxiety Disorder

## Introduction

Cannabis refers collectively to the psychoactive products of the hemp plants *Cannabis sativa* and *Cannabis indica*. Although it had previously been thought that only the female plant produces psychoactive agents, it is now known that the male plant also produces comparable amounts of the psychoactive substance, delta-9-tetrahydrocannabinol (THC). Cannabis products include: marijuana, which is the leaves, stems, and flowers of the plant; sinsemilla, which is just the flowering tops of the plant; and hashish, which is the sticky resin exuded by the plant. Although there are important differences between these products, convention holds that the term "marijuana" is used in place of the less specific "cannabis" in both common parlance and in the literature.

## Epidemiology of Cannabis Abuse and Dependence

Cannabis is the most widely used illicit drug in the world, and in the United States. The World Health Organization estimated that during the 1990s, there were 141 million cannabis abusers worldwide, accounting for 2.5% of the world population (World Health Organization 1997). In the United States it is estimated that 25 million people (10.6%) aged 12 or older reported using marijuana in the past year. The Substance Abuse and Mental Health Service Administration (SAMHSA) further estimates that 3.1 million people (1.3% of the population) use marijuana daily (Substance Abuse and Mental Health Services Administration 2004). A conservative estimate is that 8% of people who try marijuana will develop cannabis dependence (Wagner and Anthony 2002). A recent study noted that rates of marijuana use among college students has trended upward, from 27.9% in 1993 to 33.3% in 2005 (The National Center on Addiction and Substance Abuse at Columbia University (CASA) 2007). While recent studies have shown that overall rates of marijuana use have been stable for the past decade, the rates of people suffering from marijuana abuse and dependence have increased slightly between the early 1990s and 2002, with the increase being statistically significant (Compton et al. 2004).

## A Brief History of Cannabis

### Eastern World

It is likely that cannabis originated in Central Asia and was cultivated extensively first in China, as far back as 10,000 BCE. It was later cultivated in India. The hemp plant was grown for its tough fiber, which was used in making cloth and ropes. In addition, seeds of the hemp plant were an important source of food and cooking oil (Iverson 2000). Cannabis was spread via trade from China and India to Persia. From Persia cannabis reached the Arab world, and the Arabs spread cultivation down the east coast of Africa (Courtwright 2001).

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In addition to being a standard agricultural product, cannabis was also grown for its psychoactive properties. Cannabis was used in many traditional Chinese medicines as well as in traditional Indian ayurvedic remedies (Iverson 2000). It was also used as an intoxicant. In the mystical Islamic tradition, Sufism, rituals made use of the psychoactive properties of cannabis. Another famous group who used cannabis was the Hashishins (from which we get our word *assassin*), a group rumored to carry out killings while intoxicated with cannabis. While stories of this group have been used to the advantage of cannabis opponents, little is actually known about them or the role cannabis played in the activities of their group, for example, whether they used the drug to embolden them to commit murders, whether the drug was given to them by their superiors to keep them docile, or whether they used it in a manner similar to that of their contemporaries.

### Western World

Cannabis was grown for fiber by the ancient Greeks, and was used to make the sails used by their navies. Cannabis continued to be cultivated through the time of the Romans. The Roman physicians Galen, Oribasius and Dioscorides wrote of the psychoactive properties of the cannabis plant (Iverson 2000). Cannabis was cultivated as a fiber crop throughout Europe, used in the production of ropes, sails and cloth. These products were widely used; in fact, our word *canvas* comes from the Dutch pronunciation of "cannabis" (Iverson 2000). Cannabis cultivation occurred in the Spanish, British, and French colonies in the Americas. While the slaves and lower classes that worked these plantations smoked cannabis for recreation, the ruling classes preferred tobacco (Courtwright 2001). Interestingly, despite the widespread cultivation of cannabis in Europe, it was not until Napoleon's army encountered cannabis-smoking Arabic people in Egypt that Europeans became familiar with the psychoactive and intoxicating properties of these plants (Iverson 2000). Although European literati began smoking cannabis in the late 1800s, cannabis was principally used in patent medicines in the United States, rather than as an intoxicant per se. Cannabis, not being perceived as a problem of the magnitude of cocaine or opiates, was not included in the Harrison Act of 1914 (Musto 1999). Cannabis smoking was introduced in the United States by Mexican laborers who entered the country in the first decades of the 1900s (Courtwright 2001). Fueled in part by a concern about a novel intoxicant unfamiliar to mainstream American society, and propelled by racist caricatures of an intoxicated and dangerous ethnic "other," cannabis was effectively outlawed in 1937. Cannabis smoking, popularized by jazz musicians, gained counter-culture cache in the 1930s and 1940s (Jonnes 1996). The use of cannabis was brought to middle and upper class America through the experience of the Beat writers, and later the "counter-culture" youth movement of the 1960s (Courtwright 1999).

## Methods of Use

The most common method for using cannabis is smoking. One popular method for doing this is by using a pipe. These pipes can be made of metal, stone, glass, or other heat resistant materials. A bong is a specific kind of pipe that works by drawing the smoke through a layer of water, which both cools and removes tar from the smoke. Pipes and bongs come in an incredible array of colors, shapes and sizes. People who used these devices to smoke typically quantify their use in terms of the number of pipe "bowls" they smoke.

Another popular way in which cannabis is smoked is by rolling it into cigarettes, or "joints." More recently, the "joint" has increasingly given way to the "blunt." A blunt is a cannabis cigar, named for a specific kind of widely available mass-produced cigar called a Phillies Blunt™. A blunt is made by slitting open a cigar wrapper, removing some or all of the tobacco within and replacing it with cannabis. The cigar is then resealed and smoked. To quantify use, we typically ask how many joints are smoked each day or each week. Our conversion, given the larger size of a cigar wrapper compared to a cigarette paper, is that one blunt is roughly equivalent to three joints. However, our experience has shown that the amount of cannabis placed in a joint or a blunt can vary considerably from person to person.

A third way cannabis is "smoked" is by using a vaporizer. A vaporizer works on the principle that THC volatilizes at a lower temperature than that at which cannabis combusts. Cannabis is electrically heated in a sealed glass container. When the THC volatilizes into a "vapor" and fills the chamber, this vapor is inhaled, theoretically obviating ingesting the carcinogens that arise from pyrolysis. Although the manufacturers of vaporizers have supported research that purportedly shows that these devices achieve this goal, there are no peer-reviewed data that support these claims.

Another way in which cannabis is used is by ingesting it. Given that THC is highly lipophilic, it readily leaves the plant and enters a substance like butter or oil when heated. This THC-laden butter or oil can then be used in the preparation of other foods, such as brownies (yielding the so-called "space cakes"). Cannabis can also be steeped as a tea.

Another common way cannabis is used is in hashish. Hashish is the purified resin produced by the cannabis plant, minus the actual plant material. Hashish is primarily made in one of two ways. The first way is from rolling cannabis plants between the palms of one's hands. The sticky resin deposits itself on the skin, and this resin can then be scraped off and formed into larger lumps. The second method for making hashish comes from sifting cannabis through progressively finer sieves. The plant fibers are removed, and the resin remains, in a light powder form. This can then be heated and compressed into cakes. Hashish is typically smoked, but it can be eaten.

A final common way cannabis is used is in the production of cannabis oil, also known as hashish oil. This is usually formed by soaking cannabis plants in alcohol, which allows the lipophilic THC to enter the alcohol solution. The resulting supernatant can be heated or simply left to sit to allow the alcohol to evaporate. The sticky amber colored substance that remains is hashish oil. This product can be smoked, typically by placing a drop of oil onto heated metal and then using a straw to inhale the smoke that is produced.

Cannabis use can be quantified by a function of the frequency of use and the amount used. The amount used can be expressed as a functional unit of use (e.g., the number of "bowls," joints, or blunts used in a given day or week) or in weight (e.g., a quarter ounce is used over a month). Another method for quantifying use is to ascertain how much money

**Table 57–1 THC Contents of Cannabis Products (Iverson 2000)**

| Cannabis Product Name | Part of Cannabis plant | THC Content (%) |
|---|---|---|
| Marijuana | Leaves and small stems | 1.0–3.0 |
| Sinsemilla | Compressed sterile, female flowering heads | 3.0–8.0 |
| Hashish | Cannabis resin | 10.0–15.0 |
| Cannabis or hashish oil | Alcohol extract of cannabis resin | 20.0–60.0 |

is spent on use. Marijuana and sensimilla are typically sold in increments of $5 ("nickel bags") or $10 ("dime bags"). The difficulty with this is that price varies with geography and quality of the product in ways that can be highly variable and difficult to predict.

The average potency of different cannabis products can be found in Table 57–1.

There are data supporting the contention that cannabis potencies are increasing (ElSohly et al. 2000). Some authors have noted that the issue of rising potency of cannabis is one that periodically recurs in the national dialogue, and that the issue is rendered moot as cannabis smokers will "autotitrate" or smoke to a desired level of intoxication irrespective of drug potency (Mikuriya and Aldrich 1998). However, it has been observed that rates of alcoholism increased after the widespread manufacture and sale of more potent distilled spirits (Courtwright 1999). It has been hypothesized that the small but detectable increase in the prevalence of cannabis dependence is due to the increased potency of the drug (Compton et al. 2004).

## Neuropsychological Effects of Cannabis Use

There are a number of acute neuropsychological effects that result from smoking cannabis. These include problems with short-term memory, sustained and divided attention, and complex decision making (Ehrenreich et al. 1999, Pope et al. 1995, 1997, 2001, Pope 1996, Schwartz et al. 1989, Solowij et al. 1991, Solowij et al. 1995). In addition, acute use of cannabis increased measures of impulsivity on a computerized task (Lane et al. 2005). Neuropsychological deficits are more apparent when high-potency cannabis products are used (Ramaekers et al. 2006). However, users who are tolerant to the effects of cannabis do not show neuropsychological deficits after acute use (Hart et al. 2001).

A number of authors have described an "amotivational syndrome" associated with cannabis use, characterized by a lack of motivation, ambition and direction in life (Kupfer et al. 1973, Campbell 1976, Hendin and Haas 1985). This syndrome appears to be the result of continuous intoxication and resolves with the cessation of cannabis use (Johns 2001). A study of chronic users showed that after a 28 day period of abstinence the user's neuropsychological deficits resolved and they reported increased productivity and satisfaction in their work and social lives (Pope et al. 2001, Gruber et al. 2003). In summary, the intoxicating effects of cannabis can cause a number of neuropsychological deficits, these are less pronounced in tolerant individuals, they can lead to subjective complaints, and they resolve with abstinence.

## Psychosocial Aspects of Cannabis Use and Related Disorders

Early exposure to cannabis has been demonstrated to be an independent risk factor for continued cannabis use, other drug use, juvenile offending and unemployment (Fergusson and Horwood 1997). Also, a significant relationship has been demonstrated between the degree of cannabis use and the likelihood to commit certain violent crimes (Friedman et al. 2003). Further, an association between cannabis use and risky sexual behavior has been found (Kingree et al. 2000, Kingree and Betz 2003). For those individuals that develop cannabis dependence, the consequences of their addiction are as serious as those of addictions to other illicit drugs. The medical, legal, and psychiatric impairment associated with cannabis dependence appears roughly comparable to that of cocaine dependence (Budney et al. 1998).

A common notion is that cannabis is a "gateway drug" whose use leads in some causal fashion to the use of other, "harder" drugs. In support of this it has been noted that among adolescents cannabis use comes temporally before the use of harder drugs (Yamaguchi and Kandel 1984, Yamaguchi and Kandel 1984). However, temporal precedence does not imply causality. It is likely that adolescents who choose to use cannabis in the first place are more socially marginalized and exhibit behavioral problems compared to those who do not, and that those who use cannabis early tend to affiliate with more delinquent peers (Fergusson and Horwood 1997).

## Endocannabinoid System

Two subtypes of cannabinoid receptors have been identified so far. The first, the CB1 receptor, is expressed on the axons, terminals, and somata of neurons. The second, the CB2 receptor, is expressed primarily on immune cells. CB1 receptor is abundant in the brain, more so than opioid or dopamine receptors, and are dense in the striatum, globus pallidus, substantia nigra, hippocampus and cerebellum (Rodriguez de Fonseca et al. 2005). Both CB1 and CB2 receptors are coupled to inhibitory G proteins and inhibit adenylyl cyclase and active MAP kinase. In addition, CB1 receptors inhibit presynaptic calcium channels of the N and P/Q type and activate inwardly rectifying potassium channels. This receptor subtype also affects a number of other signaling mechanisms. There are likely to be other cannabinoid receptors that have yet to be identified (Mackie 2006). THC seems to function as a partial agonist at the CB1 and CB2 receptors (Mackie 2006).

There are a number of endogenous substances that bind to these receptors. These endocannabinoids are derivatives of arachadonic acid. The first of these to be identified is anandamide, whose name comes from Sanskrit for "internal bliss." In addition there is 2-arachidonoylglycerol (2-AG), virodhamine, and nolandin (Rodriguez de Fonseca et al. 2005). The endocannabinoid system seems to modulate neuronal plasticity, and function to preserve the structure and function of major brain circuits. This is important for homeostatic behavior such as eating, sleeping, reproducing and relaxing and other motivated behaviors. In addition, endocannabinoids modulate the immune system, vascular

beds, gastrointestinal motility, and nociception (Rodriguez de Fonseca et al. 2005). The endocannabinoid system also appears to play a role in maintaining emotional homeostasis, for example by facilitating the extinction of aversive memories (Marsicano et al. 2002).

Activation of the mesocorticolimbic dopamine system has been implicated in reinforcing drug-taking behavior (Koob 1992). The cell bodies of this system originate in the ventral tegmental area and project to forebrain areas, including the nucleus accumbens (Koob 1992). THC has been shown to increase dopamine release in the nucleus accumbens (Tanda et al. 1997). Although cannabinoids have been shown to interact with a number of neurotransmitter systems including the GABAergic, glutamtergic, and cholinergic systems, its interactions with this dopaminergic system and with the opioid system is thought of be of primary importance in facilitating dependence (Tanda and Goldberg 2003).

## Cannabis Related DSM-IV-TR Diagnoses

### Cannabis Intoxication

The most elemental cannabis related diagnosis is that of intoxication. In order to make this diagnosis (see DSM-IV-TR Criteria 292.89) the patient must have used cannabis recently and be having some psychological or behavioral change as a result. In addition a person must be experiencing two of the following four signs and symptoms: conjunctival injection, increased appetite, dry mouth, and tachycardia. The symptoms also cannot be better accounted for by another medical or mental condition. There is also a specifier, "with perceptual disturbances" if the intoxicated individual is experiencing illusions or hallucinations without losing reality testing or being delirious.

In addition, there are a number of other physiological and psychological effects of cannabis described in the literature that do not appear in the DSM. These are listed in Table 57–2. (Hall and Solowij 1998, Ameri 1999, Perez-Reyes 1999).

### Cannabis Abuse

Criteria for cannabis abuse (see DSM-IV-TR Criteria 305.20) are met when an individual's cannabis use persists despite adversely affecting his or her life. To be diagnosed with Cannabis Abuse, over a 12-month period as a function of cannabis use an individual must have any one of the following: recurrent episodes of failing to fulfill obligations at work, school, or home; recurrent episodes of cannabis use when using results in physical danger; recurrent legal difficulties; or recurrent arguments or disputes with others. A simple mnemonic device to remember these criteria is "FOLD" (see DSM-IV-TR Criteria 305.20): for Fights

**DSM-IV-TR Criteria**

**Cannabis Intoxication**

**A.** Recent use of cannabis

**B.** Clinically significant maladaptive behavioral or psychological changes (e.g., impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that developed during or shortly after cannabis use.

**C.** Two (or more) of the following signs, developing within 2 hr of cannabis use:

1. conjunctival injection
2. increased appetite
3. dry mouth
4. tachycardia

**D.** The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

**Specify if:** With Perceptual Disturbances: This specifier may be noted when hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of a delirium. Intact reality testing means that the person knows that the hallucinations are induced by the substance and do not represent external reality. When hallucinations occur in the absence of intact reality testing, a diagnosis of Substance-Induced Psychotic Disorder, With Hallucinations should be considered.

**Table 57–2 Physiological Effects of Cannabis**

| |
|---|
| Common |
| Tachycardia |
| Increased apptite |
| Dry mouth/ thirst |
| Conjunctival injection |
| Constipation |
| Decreased intraocular pressure |
| Mydriasis |
| Mild bronchoconstriction followed by bronchodilation |
| Mild analgesia |
| Mild anti-emetic effects |
| Decreased libido |
| Uncommon |
| Ataxia |
| Ptosis |
| Miosis |
| Drowsiness |
| Bradycardia |
| Hypotension |
| Peripheral vasoconstriction |
| Hypothermia |
| Psychological Effects of Cannabis Intoxication |
| Common |
| Euphoria |
| Distortions in perception (e.g., time) |
| Enhancement of sensations |
| Uncommon |
| Anxiety |
| Restlessness |
| Depersonalization/Derealization |
| Paranoid ideation |

**DSM-IV-TR Criteria**

**Cannabis Abuse**

**A.** A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period.

1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school or home (e.g., repeated absences or poor work performance related to substance use; substance related absences, suspensions or expulsions from school; neglect of children or household)
2. recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

**B.** The symptoms have never met the criteria for Substance Dependence for this class of substance.

**Mnemonic:**

**F** ights (social and interpersonal problems)—*from criterion 4*

**O** bligations — *from criterion 1*

**L** egal problems — *from criterion 3*

**D** anger — *from criterion 2*

and arguments about cannabis use, Obligations are not met because of cannabis use, Legal problems due to cannabis use, and Danger resulting from cannabis use. In addition, to be diagnosed with Cannabis Abuse an individual cannot ever have met criteria for Cannabis Dependence.

## Cannabis Dependence

According to the current conventions in the DSM-IV-TR, the diagnosis of Cannabis Dependence is hierarchically supra-ordinate to the diagnosis of Cannabis Abuse (i.e., if a person meets, or has met in the past, criteria for Cannabis Dependence the diagnosis of Cannabis Abuse is obviated as Dependence "trumps" Abuse). In general, Cannabis Dependence is conceived of being of greater severity than Cannabis Abuse. The hallmarks of the dependence syndrome are that one has lost control of one's use of cannabis and as a result the drug has become incorporated into the individual's physiology, psychology, and social world. Criteria for Cannabis Dependence (see DSM-IV-TR Criteria 304.30) are met if three of the following are met over a

**DSM-IV-TR Criteria**

**Cannabis Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. tolerance, as defined by either of the following:
   a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance
2. withdrawal, as manifested by either of the following:
   c. the characteristic withdrawal syndrome for the substance
   d. the same (or a closely related) substance is taken to relieve or avoid the withdrawal syndrome
3. the substance is taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
6. important social, occupational, or recreational activities are given up or reduced because of substance use
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

**Mnemonic:**

**W** ithdrawal — *from criterion 2*

**H** ealth problems — *from criterion 7*

**A** mount has increased — *from criterion 3*

**T** olerance — *from criterion 1*

**C** ut down — *from criterion 4*

**A** ctivities given up — *from criterion 6*

**T** ime pursuing drug has increased — *from criterion 5*

12-month period: tolerance; withdrawal; using more cannabis or over a longer period of time than intended; there is a persistent desire to cut down or control one's use; an increasing amount of one's time is spent in the pursuit, use, and recovery from using cannabis; important activities are

given up or reduced because of cannabis; or cannabis use is continued despite ongoing mental or physical health problems which are caused or exacerbated by cannabis use.

Although the DSM-IV-TR and earlier editions do not recognize the diagnosis of cannabis withdrawal there is a well-characterized withdrawal state demonstrated in cannabis dependent individuals when the drug is removed. Cannabis withdrawal is characterized by anxiety, irritability, decreased mood and food intake, and physical discomfort (Haney et al. 1999a, 1999b, Kouri and Pope 2000). Most treatment-seeking cannabis-dependent patients report cannabis withdrawal symptoms, and these symptoms tend to be more severe in heavier users (Budney et al. 1999). It is important to note that physiological dependence (comprised of tolerance and/or withdrawal) is neither necessary nor sufficient to diagnose the dependence syndrome. A useful mnemonic for remembering these criteria is WHAT CAT (see DSM-IV-TR Criteria 304.30): Withdrawal, Health Problems, Amount has increased, Tolerance, desire to Cut down, Activities given up, Time spent use has increased. The validity of the concept of cannabis dependence has been shown to be equivalent to that of alcohol, opiate, stimulant and sedative dependences (Morgenstern et al. 1994).

## Cannabis Intoxication Delirium

We have been unable to locate any reports of this diagnostic entity despite its inclusion in the DSM (see DSM-IV-TR Criteria 292.81). There are a number of repots of acute onset of a "toxic psychosis" of confusion, memory problems and hallucinations after using cannabis (Talbott and Teague 1969, Tennant and Groesbeck 1972, Chopra and Smith 1974, Chaudry 1991, Andre et al. 2006). However, these reports either predate the clinical entity of Cannabis Intoxication Delirium or insufficient clinical material is presented to ascertain if this is the best diagnostic label for the condition described. Interestingly, two of the most recent descriptions of toxic confusion in the literature both involve cases where cannabis was ingested rather than smoked (Chopra and Smith 1974, Chaudry et al. 1991). It seems possible that, given the slower onset of action of THC when ingested rather than smoked, it is more difficult to "autotitrate" (Mikuriya and Aldrich 1998) to the desired level of intoxication when ingesting rather than smoking cannabis, leading users to "overshoot the mark." Regardless, given the widespread use of cannabis and the relative paucity of reports of cannabis intoxication delirium, we conclude that this must be a rare clinical entity. If this diagnosis is suspected, other causes of delirium should be aggressively excluded, especially if the delirium doesn't resolve in a week (Johns 2001).

**DSM-IV-TR Criteria**

**Cannabis Intoxication Delirium**

**A.** Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

**B.** A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

**C.** The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

**D.** There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

(1) the symptoms in Criteria A and B developed during Cannabis Intoxication

(2) medication use is etiologically related to the disturbance

**Note:** This diagnosis should be made instead of a diagnosis of Cannabis Intoxication only when the cognitive symptoms are in excess of those usually associated with the intoxication syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

## Cannabis Induced Psychotic Disorder

There has long been an observed link between cannabis use and psychotic illness. Fifteen percent of cannabis users report having had some psychotic symptoms after having used cannabis (Thomas 1996). This tends to remit with the resolution of intoxication (Hall and Solowij 1998). The diagnostic criteria for Cannabis Induced Psychotic Disorder is listed below (see DSM-IV-TR Criteria (With Delusions 292.11, With Hallucinations 292.12)) Some investigators believe that cannabis use has been shown to be an independent risk factor for the development of psychotic illnesses (Arseneault et al. 2004, Henquet et al. 2005). However, there is no evidence that heavy cannabis use leads to a psychotic illness that persists after abstinence (Johns 2001). There is little evidence to support the contention that cannabis-induced psychotic disorders arise in previously asymptomatic individuals (Thomas 1993). If psychotic symptoms persist for more than 24–48 hr after intoxication they are likely referable to a previously undiagnosed psychiatric disorder (Johns 2001, Gruber and Pope 1994).

**DSM-IV-TR Criteria**

**Cannabis-Induced Psychotic Disorder**

**A.** Prominent hallucinations or delusions. Note: Do not include hallucinations if the person has insight that they are substance induced.

**B.** There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

1. the symptom in Criterion Adeveloped during, or within a month of, Substance Intoxication
2. medication use is etiologically related to the disturbance

**C.** The disturbance is not better accounted for by a Psychotic Disorder that is not substance induced. Evidence that the symptoms are better accounted for by a Psychotic Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is evidence that suggests the existence of an independent non-substance-induced Psychotic Disorder (e.g., a history of recurrent non-substance-related episodes).

**D.** The disturbance does not occur exclusively during the course of a delirium.

**Note:** This diagnosis should be made instead of a diagnosis of Substance Intoxication or Substance Withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Specify if: With Delusions or With Hallucinations
Specify if: With Onset During Intoxication

### Cannabis Induced Anxiety Disorder

The most commonly reported adverse reaction to cannabis is acute anxiety or panic attacks (Hall and Solowij 1998, Johns 2001, Thomas 1996). This is particularly common among women and infrequent or naive users of cannabis (Hall and Solowij 1998, Thomas 1996). The mind-set of the user and the setting in which the use takes place therefore likely contribute to the effect of the drug to produce these anxiety reactions. The DSM-IV-TR provides criteria for the diagnosis of Cannabis-Induced Anxiety Disorder (see DSM-IV-TR Criteria 292.89). We have been unable to find reports of de novo onset of a true Cannabis Induced Anxiety Disorder in an individual without a preexisting Axis I mental illness. In a given individual, anxiety or panic that lasts longer than several days is likely due to an underlying psychiatric disorder (Johns 2001).

**DSM-IV-TR Criteria**

**Cannabis-Induced Anxiety Disorder**

**A.** Prominent anxiety, Panic Attacks, or obsessions or compulsions predominate in the clinical picture.

**B.** There is evidence from the history, physical examination, or laboratory findings of either (1) or (2): There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

1. the symptom in Criterion A developed during, or within a month of, Substance Intoxication
2. medication use is etiologically related to the disturbance

**C.** The disturbance is not better accounted for by an Anxiety Disorder that is not substance induced. Evidence that the symptoms are better accounted for by an Anxiety Disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is evidence that suggests the existence of an independent non-substance-induced Psychotic Disorder (e.g., a history of recurrent non-substance-related episodes).

**D.** The disturbance does not occur exclusively during the course of a delirium.

**E.** The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Note:** This diagnosis should be made instead of a diagnosis of Substance Intoxication or Substance Withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

**Specify if:**

With Generalized Anxiety
With Panic Attacks
With Obsessive-Compulsive Symptoms
With Phobic Symptoms

**Specify if:** With Onset During Intoxication

## Treatment of Cannabis Related Disorders

### Psychotherapy Trials

A variety of psychosocial interventions have been studied in cannabis dependence (see Table 57–3). Early work in treating cannabis dependence was based on anecdotal experience and advocated exercise, eating well, pulmonary care, treating insomnia, conducting a behavioral assessment, and 12-step programs (Zweben and O'Connell 1988, Miller et al. 1989). Other early work included open studies described treatments for cannabis dependence using aversion therapy with emetic agents (Morakinyo 1983) and electric shock (Smith et al. 1988).

A later uncontrolled study described an "integrated brief intervention" for marijuana dependence (Lang et al.

**Table 57–3 Psychotherapy Trials in Cannabis Dependence**

| Study | *N* | Admission Criteria | Design | Intervention | Control Group | Outcome Measure | Follow-up interval | Monitoring | Results |
|---|---|---|---|---|---|---|---|---|---|
| Morakinyo 1983 | 9 | Brought to the hospital for psychosis related to "heavy (cannabis) use" | Case series | Aversion therapy using emetic agent and hypertonic saline | None | Relapse to cannabis use | To relapse | Self-report and collateral report. | Average length of abstinence was 9 months (range = 6–14 months). |
| Smith et al. 1988. | 22 | Self-report (responded to an advertisement-details unclear) | Case series | Aversion therapy using THC-free marijuana and faradic stimulation followed by 3 weekly sessions of group therapy | None. | Abstinence rates, number of marijuana cigarettes smoked | After aversion therapy, conclusion of treatment, then 6 and 12 months posttreatment | Self-report. | Abstinence rate was 73% at 12 months. Mean number of marijuana cigarettes smoked dropped dramatically. No p values calculated |
| Stephens et al. 1994 | 212 | Responded to an advertisement for people who wanted help quitting marijuana use | Randomized. | Relapse prevention (RP) vs. Social support group (SSP) | Each other | Number of times marijuana used QD, number of days of use in the past 90 days using 4 point scale, other drug use, Drug Abuse Screening Test (DAST) | 1, 3, 6, 9, and 12-month posttreatment | Self-report, collateral report and urine toxicology screens at 3 and 6 month | Significant reductions in amount and frequency of marijuana use and associated problems, but not difference between treatment modalities |
| Lang et al. 2000 | 33 | Self-reported "problem users" recruited from health care and drug abuse treatment centers, as well as a radio advertisement | Case series | Integrated brief assessment (a 2.5 hr session plus a self-help booklet) | None. | Frequency of cannabis use (% days/ week, % days/ month | 1 and 3 months | Self report | Mean number of days of use per week and month appeared to decrease, and mean number of "bongs" used decreased, and fewer "problems" reported, but no p values were calculated |
| Stephens et al. 2000 | 291 | Used marijuana at least 50 of the past 90 days | Randomized | 14 session relapse prevention social support (RPSG) vs. 2 session individualized assessment and intervention (IAI) | Delayed treatment control group (DTC) and each other | Number of times marijuana used QD, number of days of use in the past 90 days using 4 point scale, other drug use, dependence scale based on DSM criteria | 4, 7, 14 and 16 months posttreatment (only at 4 months for DTC group) | Self-report and collateral report | No differences were found between RPSG and IAI groups. However, significant reductions noted (both in number of days used and times used per day), depressive symptoms, and problems associated with marijuana use for both groups compared to DTC |

**Table 57–3 Psychotherapy Trials in Cannabis Dependence** *continued*

| Study | *N* | Admission Criteria | Design | Intervention | Control Group | Outcome Measure | Follow-up interval | Monitoring | Results |
|---|---|---|---|---|---|---|---|---|---|
| Budney et al. 2000 | 60 | DSM-III-R criteria for dependence and have used in the last 30 days. | Randomized | Motivational enhancement (M) vs. M plus behavioral coping skills therapy (MBT) versus MBT plus a voucher program (MBTV) | Each other | DSM-III-R checklist, Drug Abuse Screening Test (DAST), Addiction Severity Index (ASI), University of Rhode Island Change Assessment (URICA), Situational Confidence Questionnaire (SCQ), Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI) | Weekly for the 14 weeks of treatment in each study condition | Twice-weekly urine toxicology screens and self-report | MBTV group had longer duration of abstinence and more abstinent subjects compared with MBT or M (which did not differ from each other in this regard). MBT and M did show significant decreases in ASI, self-reported days of marijuana use and marijuana-related problems, and the BSI |
| Copeland et al. 2001 | 229 | Outpatients stating a desire to reduce cannabis use | Randomized | 6 sessions of cognitive behavioral therapy (6CBT) compared to a single session of CBT (1CBT) | Delayed treatment group (DTC) and each other | Use in the last three days, Composite International Diagnostic Interview (CIDI), Severity of Dependence Scale (SDS), Cannabis Problem Questionnaire (CPQ), Symptom Checklist 90 (SCL-90), Beck Depression Inventory (BDI) | 24 weeks after the initial assessment (average time to follow-up was 237 days after the last treatmentsession for treatment groups or after the initial assessment for DTC group) | Urine toxicology screens and self-report | Neither group had significantly more abstinence compared to each other or the DTC group. Both treatment groups had less severe cannabis dependence and fewer cannabis-related problems compared to the DTC group. The 6CBT group differed from the 1CBT group in that they reported less cannabis consumption and had lower scores on the SDS |
| Marijuana Treatment Project 2004 (Stephens et al. 2002) | 450 | DSM-IV-TR diagnosis of cannabis dependence and had used cannabis 40 of the past 90 days | Randomized | 2 sessions of motivational enhancement therapy (MET) vs. 9 sessions of MET plus cognitive behavioral therapy and case management | Delayed treatment control (DTC) group and each other | SCID, ASI, time line follow back (TLFB) to measure the frequency of marijuana consumption, BDI and the state portion of the State-Trait Anxiety Inventory (STATI), marijuana problem scale (MPS) | Follow up at 4, 9, and 15 months after randomization (DTC group only followed to 4 months after randomization) | Urine toxicology screens, self and collateral interviews at 4 and 9 months; self report only at 15 months | At the 4 and 15-month follow-up (but not the 9 month) , the 9 session CBT group was more likely to be abstinent than the 2 session group, which was in turn more likely to be abstinent than the DTC group |

*(continues)*

**Table 57–3 Psychotherapy Trials in Cannabis Dependence** *continued*

| Study | *N* | Admission Criteria | Design | Intervention | Control Group | Outcome Measure | Follow-up interval | Monitoring | Results |
|---|---|---|---|---|---|---|---|---|---|
| Cannabis Youth Treatment (CYT) 2004 (Dennis et al. 2002) | 600 | Self-report of one or more DSM-IV-TR criteria for cannabis abuse or dependence and cannabis use in the past 90 days | Randomized | Trial 1 (incremental arm): 5 session Motivational Enhancement Treatment/ Cognitive Behavioral Therapy (MET/CBT5) vs. 12 session Motivational Enhancement Treatment/ Cognitive Behavioral Therapy (MET/CBT12) vs Family Support Network (FSN) + MET/CBT 12<br><br>Trial 2 (alternative arm): MET/CBT5 vs. Adolescent Community Reinforcement Approach (ACRA) vs. Multidimensional Family Therapy (MFT) | In both trials each group was compared with the other groups in that trial (no placebo or wait-list controls) | (1) Days of abstinence between randomization and 12-month follow-up. (2) "Being in recovery" defined as living in the community and reporting no past-month substance use or dependence problems at the 12-month interview | Follow-up at 3, 6, 9 and 12 months | Self-report | In both trials, each treatment condition increased days of abstinence and percentage of subjects in recovery. However, no significant differences were found between any treatment condition in either trial |
| Martin et al. (2005) | 73 | People between ages 14–19 who used cannabis at least once in the past month who responded to recruitment aimed at young people and concerned parents | Open, no control group (pretest/ posttest design) | The Adolescent Cannabis Check Up: one session of parental education, two sessions of assessment and feedback, 1 optional CBT session | None | Number of days of cannabis use, mean amount used per week, DSM-IV dependence symptoms, Severity of Dependence Scale (SDS) | 3 and 6 months after the final session | Self-report and urine toxicology screens | Significant decreases from baseline in amount and frequency of use at 3 months, and in days of use and number of dependence symptoms at 6 months |

**Table 57–3 Psychotherapy Trials in Cannabis Dependence** *continued*

| Study | *N* | Admission Criteria | Design | Intervention | Control Group | Outcome Measure | Follow-up interval | Monitoring | Results |
|---|---|---|---|---|---|---|---|---|---|
| Budney et al. (2006) | 90 | Self-report of one or more DSM-IV criteria for cannabis abuse or dependence and cannabis use in the past 90 days | Randomized | Voucher only group (V), Cognitive Behavioral Therapy only group (CBT), combination of Cognitive Behavioral Therapy plus voucher group (CBT + V) | Each group controlled for the others | Weeks of continuous abstinence, Addiction Severity Index (ASI), the Time Line Follow-Back (TLFB), the Marijuana Problem Scale (MPS), the Brief Symptom Inventory (BSI) and Beck Depression Inventory (BDI) | Weekly during the 14 weeks of the intervention, then monthly for the next 12 months | Twice-weekly urine toxicology and self-report during the intervention. | At the end of treatment, the V group had significantly more abstinence from marijuana than the participants in the CBT group<br>Over the 12 months of follow-up, the CBT+V group had significantly greater abstinence rates than the CBT only group, but not the V group. Over the follow-up period, significantly higher remission of DSM-IV symptoms with<br>CBT+V group compared to the V only group, but not CBT. All groups also showed improved ASI, BDI, and BSI scores over the follow-up period, but no group demonstrated superiority over the others. |

2000). This intervention consisted of a 2.5-hr assessment and intervention that provided education and use-reduction strategies along with a self-help booklet. At 1- and 3-month follow-up the investigators found that the mean number of days during which marijuana was used decreased, the amount of marijuana used decreased and that subjects reported fewer "problems," but it was not reported whether these differences were statistically significant.

The feasibility of a brief intervention for adolescent cannabis users was studied by Martin et al. (Martin et al. 2005) This open trial enrolled 73 adolescent cannabis users in a brief intervention based on the Marijuana Check-up (Stephens et al. 2004). The Adolescent Cannabis Check-up consists of one session of education for the teen's parent, two sessions for assessment and feedback for the teen, and then an optional session of cognitive behavioral therapy. Follow-up obtained 3 months after the intervention showed significant reductions from baseline in both quantity and frequency of cannabis use as well as in the proportion of subjects qualifying for dependence diagnoses. Repeat follow-up at 6 months revealed significant reductions from baseline in both number of days of use and in the number of dependence symptoms subjects endorsed.

A number of randomized controlled trials of various psychotherapies have also been performed. Stephens, Roffman and Simpson adapted the relapse prevention model of Marlatt and Gordon to treat marijuana dependence (Stephens et al. 1994). They randomized 212 treatment-seeking marijuana users to 10 two-hr group therapy sessions of either relapse prevention or social support therapy. The subjects were reassessed at 1, 3, 6, 9, and 12-month follow-up and had booster group therapy sessions at three and 6 months. The investigators found that both groups significantly reduced the amount and frequency of marijuana use and had fewer marijuana-associated problems, but neither treatment showed an advantage over the other.

Stephens, Roffman, and Curtin performed a second trial with relapse prevention to compare extended treatments to brief treatments (Stephens et al. 2000). Two hundred ninety one treatment-seeking individuals who frequently used marijuana were randomized to 14 sessions of a relapse prevention and social support group, two sessions of an individualized assessment and intervention that included motivation enhancement and cognitive-behavioral techniques focused on stopping marijuana use, or a delayed treatment control group. The investigators reported that up to 16 months after the intervention, compared to the control group both of the therapy groups had significantly reduced their marijuana use in terms of the number of days and the amount of marijuana used per day and experienced fewer depressive symptoms. Interestingly, neither the extended nor the brief treatment was more successful than the other for any outcome measure.

A second study investigating the effect of treatment duration recruited 229 outpatients who had stated a desire to reduce cannabis use and randomized them to a single session of cognitive behavioral therapy, six sessions of cognitive behavioral therapy, or a delayed control group (Copeland et al. 2001). The subjects were reassessed at 24 weeks after treatment conclusion. Neither treatment group had significantly more days of abstinence or percentage of subjects who maintained continuous abstinence compared to each other or the control group. However, subjects in both CBT groups were equally likely to report complete abstinence during the month prior to the follow-up and have fewer cannabis-related problems compared to the control group. The six session CBT group did show a small advantage compared to the one session CBT group in that, on average, they reported less cannabis consumption and had lower scores on the Severity of Dependence Scale.

Budney et al. performed a randomized study investigating the effect of the addition of vouchers to therapies for marijuana dependence (Budney et al. 2000). The investigators enrolled 60 subjects, all of whom met criteria for marijuana dependence, and randomized them to: (1) four 90-min sessions of motivational enhancement therapy (M), (2) Fourteen 60-min sessions of motivation enhancement plus behavioral coping skills training (MBT), or (3) MBT plus a voucher program (MBTV) using vouchers with a cash value for negative urine toxicology screens. They reported that the MBT and M groups showed reductions in a number of marijuana-related symptom scores, but did not differ from each other with respect to levels of actual marijuana use. However, the MBTV group had significantly more and longer periods of continuous abstinence compared with the other two treatment conditions. The subjects in the voucher group were also significantly more likely to be abstinent at the end of the study compared to the other two groups.

This same group recently published the results of a follow-up study of the use of vouchers in therapy for cannabis dependence (Budney et al. 2006). In this 14-week study, 90 treatment-seeking adults who met criteria for cannabis dependence were randomly assigned to one of three conditions: (1) Abstinence-based vouchers only (V), where participants received vouchers with a monetary value for each marijuana-free urine toxicology screen but didn't receive therapy apart from a self-help pamphlet, (2) Cognitive-behavioral therapy (CBT), which consisted of 14 weekly therapy sessions. Vouchers were given for urine toxicology screens were also collected in this condition, but the value was the same irrespective of the presence or absence of evidence of marijuana use, and (3) CBT plus abstinence-based vouchers (CBT+V), which added the voucher program of the V group to the course of psychotherapy received by the CBT group.

At the end of treatment, participants in the voucher group had significantly more abstinence from marijuana than the participants in the CBT-only group. There were no significant differences in the abstinence rates between CBT+V and V, suggesting that CBT did not enhance the effect of the voucher program during treatment. Over the 12 months of follow-up, the CBT+V group had significantly greater abstinence rates than the CBT only group, but not the V group. However, significantly higher remission levels, defined as meeting no DSM-IV-TR dependence criteria, were observed in the CBT+V group compared to the V only group. These results imply that a voucher-only program was effective in producing continuous abstinence during the time the vouchers were offered (i.e. during treatment). However, after treatment ended cognitive behavioral therapy helped maintain the early gains facilitated by a voucher system.

To date, the largest therapy trial targeting cannabis dependence is the Cannabis Youth Treatment (CYT) study. This study randomized 600 adolescent users to one of five

different types of psychosocial interventions (Dennis et al. 2002, Diamond et al. 2002, Dennis et al. 2004, French et al. 2002). As described in our recent review paper (Nordstrom and Levin 2007) the five treatments tested were: (1) five sessions that included two motivational enhancement therapy and three cognitive behavioral therapy sessions (MET/CBT5), (2) twelve sessions that included two motivational enhancement therapy and ten cognitive behavioral therapy sessions (MET/CBT12), (3) family support network (FSN), a multi-component treatment designed to be added to MET/CBT12, (4) the adolescent community reinforcement approach (ACRA) that is comprised of 10 individual sessions and four sessions with the caregivers to educate them how to support the adolescent's abstinence, and (5) twelve sessions of a multidimensional family therapy (MDFT) which is a family-focused therapy designed to work individually with adolescents and their families.

The CYT study was performed as two separate clinical trials. The "incremental" trial compared the three treatments that increase in intensity in a stepwise fashion: MET/CBT5, MET/CBTI2, and FSN (which is added to MET/CBT12). The "alternative" trial compared treatments which varied in both type and length: MET/CBT5, ACRA, and MDFT. Follow-up data were obtained at three, six, nine, and 12 months. The two clinical outcomes were: (1) days of abstinence between the randomization date and the 12-month follow-up interview and (2) whether the adolescent was in recovery (defined as reporting no substance use, abuse, or dependence problems while living in the community) at the end of the study. The team reported that in both the incremental and alternative trials each treatment condition increased the number of subjects in recovery and days of abstinence, but that in neither trial did any one treatment show greater effectiveness than any other.

Another recent, large, multisite trial is the Marijuana Treatment Project (MTP) (Stephens et al. 2002, Steinberg et al. 2002, Marijuana Treatment Project Research G 2004). The MTP evaluated 450 cannabis dependent subjects were randomized to one of three treatment arms: (1) a two-session motivational enhancement intervention, (2) a nine-session treatment that added cognitive behavioral therapy and case management to the motivational enhancement sessions, and (3) a delayed treatment control group. The investigators gathered self and collateral report data at four and 9-month follow up periods, and performed a brief self-report phone check-in at 15 months. The investigators found that both treatment groups had comparable rates of improvement that were larger than those seen in the control group. Also, at the four and 15-month follow-up (but not the 9-month follow-up) the group that had the longer course of therapy was more likely to report being abstinent than the group that had a shorter course of therapy, which, in turn, was more likely to report being abstinent than the control group. Although it is unclear why the differences in abstinence between groups dissipated at 9 months and then reappeared at 15 months, this finding might be due to the lower standard used to ascertain abstinence at the 15-month follow-up (i.e. no urine was collected at that time point).

Three main findings arise from considering the studies of psychotherapy for cannabis dependence: (1) a number of psychotherapies have been shown to be helpful in the treatment of this disorder (2) with the exception of using vouchers alone or adding them to another therapy (Budney et al. 2000, Budney et al. 2006) no form of psychotherapy performs robustly better than any other (3) longer psychotherapies do not appear to be more advantageous than shorter therapies.

### Pharmacologic Trials

A number of pharmacologic agents have been studied for their potential as treatments of cannabis dependence (Table 57–4). The majority of these studies have been performed in the laboratory setting with nontreatment seeking research participants. Comparably fewer trials have been performed in clinical settings for patients with cannabis dependence with or without psychiatric co-morbidity.

## Pharmacotherapy in Cannabis Self Administration or Intoxication

One laboratory study investigated the effects of naltrexone when given with oral THC in heavy marijuana smokers (Haney et al. 2003). Compared to placebo, pretreatment with naltrexone was shown to significantly increase high-dose oral THC's effects on a number of ratings of feeling "high," and this effect was attained without raising serum THC levels.

The CB-1 selective antagonist SR141716 (now known as Rimonabant) has been shown to decrease ratings of marijuana drug effect in a dose-dependent fashion (Huestis et al. 2001). The investigators found that a 90 mg dose of Rimonabant taken before cannabis was smoked reduced both subjective drug effects and objective drug effects. Of note, the dose of Rimonabant used in clinical trials for the treatment of obesity was 20 mg a day (Van Gaal et al. 2005). The impact of Rimonabant on cannabis self-administration has not been published, and it is unclear if the effects described would lead to clinically meaningful reductions in cannabis use. Specifically, it is uncertain whether treatment-seeking THC-dependent individuals would adhere to a regimen of a CB-1 antagonist given that compliance is such a notable problem with naltrexone for the treatment of opiate dependence (Kosten and Kleber 1984, Kleber 1985). The use of cannabinoid receptor antagonists may require the implementation of additional psychosocial treatment approaches to enhance compliance.

In addition to cannabinoid antagonists, agonists have also been studies in cannabis use. Hart et al. investigated the effect of oral THC on marijuana self-administration (Hart et al. 2002). The investigators found that by the third day of maintenance with oral THC, subjects reported that the positive subjective effects of marijuana were reduced, although this did not affect their choice to self-administer marijuana.

### Pharmacotherapy in Cannabis Withdrawal

A number of laboratory studies have been conducted investigating the effects of pharmacotherapeutic agents on cannabis withdrawal. Haney et al. also reported on the use of oral THC replacement therapy in attenuating marijuana withdrawal under experimental conditions (Haney et al. 2004). Compared to placebo, oral THC decreased ratings of anxiety, sleep difficulty, feeling "miserable," "chills" and marijuana craving and reversed decreases in food intake. Oral THC did not affect ratings of irritability or social

**Table 57–4 Pharmacologic Trials in Cannabis Dependence**

| Study | Medication | *N* | Dose | Marijuana use Condition | Design | Outcome Measures | Follow-up Intervals | Monitoring | Results |
|---|---|---|---|---|---|---|---|---|---|
| Laboratory studies (subjects not seeking treatment) | | | | | | | | | |
| Haney et al. (2001) | Bupropion SR | 10 | 300 mg | Marijuana withdrawal | Randomized, double-blind, placebo controlled cross-over | Various measures of marijuana withtdrawal | N/A | N/A | Bupropion worsened measures of irritability, restlessness, depression and trouble sleeping |
| Huestis et al. (2001) | SR141716 | 63 | 1–90 mg | Effects of smoked marijuana | Randomized, double-blind, placebo controlled | Various measures of marijuana intoxication | N/A | N/A | SR141716 partially blocked the acute effects of smoked marijuana |
| Hart et al. (2002) | Oral THC | 12 | 10–20 mg | Marijuana self-administration | Single-blind placebo controlled | Self-administered marijuana use | N/A | N/A | Neither dose of oral THC affected self-administration of marijuana |
| Haney et al. (2003) | Naltrexone | 9 | 50 mg | Effects of oral THC | Randomized, placebo controlled | Various measures of marijuana intoxication | N/A | N/A | Naltrexone significantly increased high-dose THC's pleasurable effects without raising blood levels of THC |
| Haney et al. 2003 | Nefazodone | 7 | 450 mg | Marijuana withdrawal | Randomized, double-blind, placebo controlled cross-over | Various measures of marijuana withdrawal | N/A | N/A | Nefazodone decreased ratings of anxiety and muscle pain |
| | Divalproex sodium | 7 | 1500 mg | Marijuana withdrawal | Randomized, double blind, placebo controlled cross-over | Various measures of marijuana withdrawal | N/A | N/A | Divalproex decreased ratings of marijuana craving but increased ratings of anxiety, irritability and tiredness |
| Haney et al. (2004) | Oral THC | 7 | 10 mg 5 × a day | Marijuana withdrawal | Randomized, double-blind, placebo controlled cross-over | Various measures of marijuana withdrawal | N/A | N/A | Oral THC decreased ratings of marijuana withdrawal and craving, and reversed decreases in food intake. |
| Clinical trials | | | | | | | | | |
| Cornelius et al. (1999) | Fluoxetine | 22 | 20–40 mg | Marijuana abusing depressed alcoholics | Randomized, double-blind placebo controlled | Days of marijuana use and number of marijuana cigarettes used | Weekly for 12 weeks | Self-report | The placebo group used 20x more marijuana cigarettes and had 5x more days of use |
| Levin et al. (2004) | Divalproex sodium | 25 | 1500–2000 mg | Marijuana dependence | Randomized, double-blind placebo controlled cross over | (1) Mean weekly quantitative THC-COOH urine levels (2) Mean weeks of "strict abstinence" (3) Mean weeks of "assumed abstinence" (4) Percentage of participants with 2 or more weeks of "assumed abstinence" | Twice weekly for 12 weeks | Self-report and urine toxicology screens | No difference between drug and placebo in any measure of marijuana use |
| McDowell et al. (2006) | Nefazodone or bupropion | 130 | 300 mg BID (nefazodone)<br>150 mg BID (bupropion) | Marijuana dependence | Randomized, double-blind, placebo controlled | (1) Marijuana use, based on urine and self-report data<br>(2) Marijuana withdrawal, based on the Withdrawal checklist | Twice weekly for 13 weeks | Self-report and urine toxicology screens | No differences were found between either drug or placebo in terms of abstinence or withdrawal symptoms |

withdrawal. Of note, no intoxication was produced with oral THC, with doses up to 10 mg, five times a day, in this heavy cannabis-using group.

Haney et al. studied the use of bupropion in marijuana withdrawal (Haney et al. 2001). The investigators found that compared to placebo, maintenance on bupropion worsened measures of mood and self-reported sleep quality during experimentally induced marijuana withdrawal. Another antidepressant that has been studied in marijuana withdrawal is nefazodone (Haney et al. 2003). Nefazodone was shown to decrease ratings of anxiety and muscle pain, but not irritability, malaise or poor sleep quality, during cannabis withdrawal.

Divalproex sodium was also investigated for utility in cannabis withdrawal (Haney et al. 2004). During experimentally induced abstinence, compared to placebo, divalproex sodium decreased marijuana craving but increased ratings of anxiety, irritability and tiredness.

### Pharmacotherapy in Cannabis Dependence

There has been one published pharmacologic treatment trial that has specifically targeted cannabis dependence (Levin et al. 2004). Levin et al. performed a randomized controlled double-blind study in which 25 subjects who met DSM-IV-TR criteria for cannabis dependence were randomized to either divalproex sodium (dosed to blood levels between 50 ng/ml and 120 ng/ml) or placebo. At the end of the six-week trial there were no differences between the divalproex sodium and placebo groups, with few individuals achieving abstinence.

Another randomized, controlled double blind study examined the use of bupropion and nefazodone in cannabis dependence (McDowell et al. 2006). In this study of 130 treatment-seeking cannabis dependent individuals were randomized to either placebo, bupropion 300 mg/day or nefazodone 600 mg/day. At study end, neither medication was significantly more effective than placebo in either initiating abstinence from cannabis or alleviating the symptoms of cannabis withdrawal.

### Pharmacotherapy in Dual Diagnosis

A number of trials have indirectly investigated the input of pharmacologic interventions in cannabis abusing individuals with comorbid psychiatric illness. Geller studied the use of lithium in bipolar adolescents with substance use disorders (Geller et al. 1992, 1998). Of the 25 subjects enrolled in the randomized placebo-controlled trials, 64% were dependent on either marijuana and alcohol or marijuana alone. Over the study there were significantly fewer positive urine toxicology screens for the lithium group compared to the placebo group. The utility of lithium to specifically decrease marijuana use was not presented. Interestingly, there are preclinical data demonstrating that lithium can attenuate cannabis withdrawal in rats, perhaps by modulating oxytocinergic activity (Cui et al. 2001), raising the possibility that lithium might be worthy of further study in THC-dependent individuals.

Riggs et al. carried out a randomized placebo-controlled trial of pemoline in a group of adolescents with attention-deficit/hyperactivity disorder (ADHD) and comorbid substance use disorders (Riggs et al. 2004). In this sample, 74% of the subjects were dependent on cannabis. Compared to placebo, the investigators found that pemoline attenuated the symptoms of ADHD but did not change substance use as measured by the number of positive urine toxicology screens or in the number of days drugs were used in the past month. In this study as well, the specific effects on cannabis relative to other drugs of abuse were not described.

In another study, Cornelius et al. conducted a secondary analysis of a randomized placebo-controlled trial of fluoxetine in a group of 22 depressed alcoholic inpatients that also met DSM-III-R criteria for marijuana dependence (Cornelius et al. 1999). Among the cannabis dependent patients, the fluoxetine and placebo groups did not differ in the amount or frequency of marijuana use prior to admission. During the 12 weeks of the study there was a significant group-time effect on marijuana use, and the cumulative number of marijuana cigarettes smoked over the study was 20 times higher in the placebo group compared to the fluoxetine group.

A number of factors limit the conclusions that can be drawn regarding the use of pharmacologic agents in the treatment of cannabis dependence. The first is that existing studies all had small sample sizes. Second, to date only two clinical trials have specifically targeted cannabis dependence (Levin et al. 2004, McDowell et al. 2006). Third, while some medications have shown promise in laboratory studies it is unclear if they would be useful in clinical settings. Medications that attenuate the intoxicating effects of cannabis or that lessen the symptoms of withdrawal could potentially be of use in initiating abstinence from cannabis. Medications that block the psychoactive effects of cannabis, decrease drug craving, or improve psychiatric symptoms might be of use in the prevention of relapse once initial abstinence has been attained.

## Conclusion

Cannabis has a long history of use for its psychoactive properties but is a relative newcomer to the Western world as an intoxicant. Nowadays cannabis is widely used and it causes serious problems in a minority of those who use it. However, given the large numbers of people who use cannabis, that relative minority translates into a substantial population of problem users. Given this reality, clinicians need tools in their armamentaria with which to treat cannabis-use disorders. There are a number of psychotherapies that have proven to be effective for the treatment of cannabis-related disorders. So far, no medications have been found to be effective for the treatment of these maladies. However, as clinical trials continue and as we further our understanding of the endocannabinoid system useful medications will likely be developed.

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CHAPTER

# 58 Substance Abuse: Cocaine Use Disorders

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Substance (Cocaine) Abuse
Substance (Cocaine) Dependence
Cocaine Intoxication
Cocaine Withdrawal

## Introduction

Cocaine is a central nervous system stimulant produced from the coca plant. Coca has been grown in the Andean Region of South America since 3000 BC. In 1860, cocaine was first synthesized from the dried Peruvian coca leaf in a German laboratory. In the 1960s cocaine became an extensively used illicit drug, with heaviest consumption in the United States, Canada, and Latin America. Cocaine is consumed in several preparations. Cocaine hydrochloride powder is usually snorted through the nostrils, or it may be mixed in water and injected intravenously. Cocaine hydrochloride powder is also commonly heated (cooked up) with ammonia or baking soda and water to remove the hydrochloride, thus forming a gel-like substance that can be smoked (freebasing). "Crack" cocaine is a precooked form of cocaine alkaloid that became popular in the 1980s. It is sold on the street as small "rocks." Abundant supplies and relatively low prices for cocaine (the equivalent of 1 g of cocaine can be purchased for as little as $25–$50 and a vial of crack (two or three small rocks) can be had for about $10) have contributed to the prevalence of cocaine abuse and dependence as well as other related cocaine use disorders.

## Epidemiology

The National Household Survey on Drug Abuse (NHSDA) reported that in 2005, 2.4 million Americans were current cocaine users with 1.5 million classified as cocaine abusers (SAMHSA 2005). Since 1975, the Monitoring the Future (MTF) study has annually examined the extent of drug abuse among 8th–12th graders. Use of cocaine decreased significantly among 12th graders, from 6.2% in 1999 to 5.0% in 2000; crack cocaine use in 2000 decreased from 2.7% to 2.2% for 12th graders. This was the first decrease in cocaine and crack cocaine use among 12th graders since the early 1990s. Crack use by 8th graders also decreased from a 10-year high of 2.1% in 1998 to 1.8% in 1999, which remained constant in 2000 (Johnson et al. 2001). While cocaine use has shown a downward trend, several statistics indicate that cocaine abuse is still a serious threat to the public. For example, cocaine-related emergency department visits constituted 29% of all drug-related visits in 2000, more than for any other illicit substance (SAMHSA 2001b). The National Drug Threat Assessment 2001 (National Drug Threat Assessment 2001—The Domestic Perspective, by the National Drug Intelligence Center, NDIC) reported that availability and demand for cocaine continues to be high.

### Gender Differences in Cocaine Use Disorders

While men continue to have a higher rate of current cocaine use than women, the gap is narrowing (SAMHSA 2005). Cocaine use in women has been steadily rising for the past three decades. For example, for those born during 1946–1950 versus those born during 1966–1977, the male-to-female ratio for cocaine use at age 35 declined from 2.8 to 1.4. For those born in the years 1971–1975, cocaine use in early teenage years was actually more common in females than in males (SAMHSA 1996).

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Some studies have reported that women cocaine abusers differ from men in several respects, including responses to the direct administration of cocaine (Kosten et al. 1993, Kosten et al. 1996, Lukas et al. 1996, McCance-Katz et al. 2001). One study that examined responses to intranasal cocaine use in casual cocaine users reported that men have more rapid onset of effects and more intense drug effects than did women (Lukas et al. 1996). Another study using higher doses of cocaine administered nasally reported more anxiety in women (Kosten et al. 1996). One study reporting on the effects of administration of repeated doses of intranasal cocaine showed that women reported greater ratings of perception of overall mental and physical well-being than did men (McCance-Katz et al. 2001, McCance-Katz et al. 2005). However, several studies that have found no significant differences in responses for men and women when given intravenous (Mendelson et al. 1999) or intranasal (Collins et al. 2006) cocaine. Yet, neuroimaging studies utilizing single photon emission computed tomography (SPECT) have shown that cocaine-dependent women had fewer perfusion abnormalities (Chang et al. 1999, Gottschalk et al. 2001, Levin et al. 1994) and less frontal cortex neuronal loss than men with comparable cocaine use history (Chang et al. 1999, Kaufman et al. 2001). Another neuroimaging study found that regional cerebral blood flow between abstinent cocaine-dependent men and women differed in the medial and orbitofrontal cortex which may lead to a better understanding of different relapse characteristics between men and women (Adinoff et al. 2006). Another study performed in abstinent cocaine-dependent individuals found fewer EEG abnormalities in women when compared to men (King et al. 2000).

Much of the research on substance abuse treatment efficacy is based predominantly on male samples. However, nearly 4% of pregnant women and 10% of women who were not pregnant reported use of an illicit drug in the past month (SAMHSA 2005) and women represented about 38% of substance abuse treatment admissions during 2004–2005 (SAMHSA 2005). Cocaine dependence in women is as severe as that in men, however women often receive less treatment for their substance abuse (McCance-Katz et al. 1999). Studies have also suggested that cocaine dependence can develop more rapidly in women than in men with women being 3–4 times more likely to become cocaine dependent within 24 months of cocaine onset (McCance-Katz et al. 1999, O'Brien and Anthony 2005). In a study of treatment seeking cocaine abusers, women used cocaine by more addictive routes (smoked, intravenous) than did men in this sample (McCance-Katz et al. 1999). Cocaine-dependent women in treatment have been shown to have a lower overall level of social adjustment than men who are more likely to be employed, support themselves financially, and finance their own drug habits (McCance-Katz et al. 1999, Weiss et al. 1997). More women may have a mood disturbance that meets diagnostic criteria for major depressive disorder than men, although men have been shown to more often have a diagnosis of antisocial personality disorder (Magura et al. 1998, Weiss et al. 1997). It has also been reported that women experience increased craving for cocaine in response to cocaine-specific cues (Robbins et al. 1999). These findings suggest that newly abstinent women may experience greater levels of psychological distress and intense craving that may persist for some time following abstinence. The more rapid course of addiction and the slower recovery from depressive symptoms could indicate that the course following cocaine abstinence could be more severe in women. In terms of response to treatment interventions, outcomes in women are improved if their specific needs, for example prenatal and childcare, are addressed (Kissin et al. 2001, Kosten et al. 1993, Weiss et al. 1997). Further, a recent analysis found that men treated with disulfiram for cocaine dependence had better outcomes than women (Nich et al. 2004), emphasizing the likelihood of significant differences in responses to psychosocial and pharmacological treatments for cocaine use disorders by gender differences and the need to adequately include women in substantial numbers in treatment clinical trials.

Cocaine is one of the most frequently abused illicit drugs during pregnancy (SAMHSA 2005). It has been estimated that 0.3% of pregnant women are cocaine users (SAMHSA 2005) The risks of cocaine and other substance abuse during pregnancy are significant not only for women but also for their unborn children who may be at increased risk of vascular injury to the central nervous system (Frank et al. 1999). Abuse of cocaine has been linked to placental abruption, preterm labor, and low birth weight (Buehler 1995, Buehler et al. 1996). Abuse and neglect of children are also common consequences of parental addiction (Luthar et al. 1998, Suchman and Luthar 2000). Some studies have suggested that children exposed to cocaine *in utero* do not appear to have permanent sequelae attributable to maternal cocaine abuse (Frank et al. 2001, Hurt et al. 1997, Richardson 1998, Richardson et al. 1996, Richardson et al. 1999, Smeriglio and Wilcox 1999). However, Griffith et al. found that cocaine-exposed children had lower verbal reasoning scores than nonexposed children (Griffith et al. 1994) while another study demonstrated that cocaine-exposed boys have lower IQ scores at age 4 when compared with nonexposed counterparts (Bennett et al. 2002). Further, some researchers have shown that cocaine exposure effects head circumference which in turn effects development (Azuma and Chasnoff 1993, Behnke et al. 2002, 2006).

## Relationship of Psychiatric Disorders to Cocaine Abuse and Dependence

Earlier epidemiological surveys had failed to identify demographic characteristics, personality traits, or features of early cocaine use that differentiate noncompulsive and heavy use (Schnoll et al. 1985). However, recent studies suggest that a particular personality trait known as novelty or sensation seeking may play an important role in the initiation of cocaine use (Laviola et al. 1999). Additionally, comorbid conditions related to cocaine abuse are abuse of other substances (Birnbach et al. 2001, Usdan et al. 2001, Withers et al. 1995) and comorbid psychiatric illness (Volkow 2001). Several studies have documented the high rate of comorbid psychiatric disorders in cocaine abusers entering treatment. These disorders include mood disorders (major depressive disorder, bipolar disorders), schizophrenia, posttraumatic stress disorder, attention-deficit/ hyperactivity disorder, anxiety disorders, and antisocial personality disorder (Brady et al. 1998, Brown et al. 1998, Cassidy et al. 2001, Clure et al. 1999, Dixon 1999, Eames et al. 1998, Marlowe et al. 1997, Najavits et al. 1997, Schmitz et al. 2000, Sherwood Brown et al. 2001, Skinstad and Swain 2001, Thomas et al. 1999, Westermeyer et al. 1997). Mood disorders often temporally follow

the onset of cocaine abuse in patients presenting for treatment, while attention-deficit/hyperactivity disorder and antisocial personality disorder precede the onset of cocaine abuse (Clure et al. 1999, McMahon et al. 1999). However, while high levels of depressive symptoms during treatment were associated with greater craving for cocaine, alcohol, and other substances, only limited evidence exists regarding the influence of depression on treatment course and outcome (Carroll et al. 1995a, Brown et al. 1998, Simpson et al. 1999).

It is important to note that comorbid psychiatric illnesses are common among cocaine users. Furthermore, the diagnosis of a comorbid primary psychiatric disorder can be challenging to make in cocaine abusers because psychiatric symptoms may be the result of cocaine abuse or acute abstinence. When psychiatric disorders co-occur with cocaine use disorders, it is important to provide treatment for both disorders. Cocaine use disorders will not generally resolve with treatment of the psychiatric disorder alone, nor will substance abuse treatment resolve a comorbid psychiatric disorder.

## Course and Natural History

Cocaine produces a sense of intensified pleasure in most activities and a heightened sense of alertness and well being. Anxiety and social inhibition are decreased. Energy, self-esteem, and self-perception of ability are increased. There is enhancement of emotion and sexual feeling (Bolla et al. 1998, Leshner and Koob 1999). Pleasurable experiences, although heightened, are not distorted and hallucinations are usually absent. The person engaging in low-dose cocaine use often receives positive feedback from others responding to the user's increased energy and enthusiasm. This, in combination with the euphoria experienced by the user, can be reinforcing, and cocaine use is perceived as free of any adverse consequences. The duration of cocaine's euphoric effects depends on the route of administration. The faster the drug is absorbed and occupies receptors of the "brain rewarding region," the more intense the euphoric effects (Koob 1999, Leshner and Koob 1999, Ward et al. 1997a).

Cocaine and alcohol are often consumed together. In addition to the synergistic effects of cocaine and alcohol in humans, an active metabolite, cocaethylene, with cocaine-like pharmacological properties is formed and users of both drugs simultaneously report enhanced euphoria (Andrews 1997, Hart et al. 2000, McCance-Katz et al. 1993, McCance-Katz et al. 1998a).

Cocaine users quickly learn that higher doses are associated with intensified and prolonged euphoria, resulting in increasing use of the drug and progression to cocaine dependence. The abuser is focused on the cocaine-induced euphoria and begins to compulsively pursue this effect. These behaviors become pivotal in the lives of cocaine abusers who continue drug abuse despite the presence of increasing personal and social consequences (Bolla et al. 1998, Ward et al. 1997a).

The psychoactive effects of cocaine are similar to those of amphetamine; the main difference in terms of abuse liability is in cocaine's much shorter duration of action. Whereas the plasma elimination half-life for cocaine is approximately 90 min, this drug produces pharmacodynamic tachyphylaxis resulting in rapidly diminishing psychoactive effects in the presence of continued cocaine in the plasma. This phenomenon explains the "half-life" of cocaine-induced euphoria, (which is approximately 45 min after intranasal use and 5 min after intravenous and smoking administration) as well as characteristic binge use in which cocaine is repetitively administered over short intervals (Jufer et al. 2000, Mendelson et al. 1999, Moolchan et al. 2000). During binge use, the drug may be administered as frequently as every 10 min, resulting in rapid mood changes. Cocaine binges reportedly can last as long as 7 days, although the average length is 12 hours (Evans et al. 1999, Foltin and Fischman 1997, Foltin and Fischman 1998, Pottieger et al. 1995, Ward et al. 1997b).

Uncontrolled use of cocaine often begins with either increased access and resultant escalating dosages and frequency of administration or a change from intranasal use to a route of administration with more rapid onset of effects (i.e., intravenous or smoked) (Foltin and Fischman 1998, Ward et al. 1997a). These characteristics are integral to the development of high-dose binging with cocaine. Such binges produce extreme euphoria and vivid memories. These memories are later contrasted with current dysphoria to produce intense craving, which perpetuates the binge use pattern (Margolin et al. 1996, Uslaner et al. 1999). Addicts report that during binge use, thoughts are focused exclusively on the cocaine-induced effects. Normal daily needs, including sleep and nourishment, are neglected. Responsibilities to family and employer and social obligations are given up. This continues until the supply of cocaine is exhausted.

Binges are often separated by several days of abstinence; cocaine-dependent individuals average 1 to 3 binges per week. This is in contrast to use patterns for opiate and alcohol dependence which often produce physiological dependence necessitating daily consumption to prevent withdrawal symptoms. This differentiation is crucial to an understanding of the syndrome of cocaine dependence (Evans et al. 1999, Pottieger et al. 1995). Although the prediction of development of cocaine use disorders is not possible on an individual basis, it is clear that those who progress to binge use of the drug will be significantly affected and constitute the treatment-seeking population. The cocaine abuser is likely to be ambivalent about the need for treatment, and the treatment dropout rate is high (ranging from 38 to 73%). Dropout usually occurs early in treatment (during the initial evaluation process) (Chou et al. 1998, Fiocchi and Kingree 2001, Siqueland et al. 1998, Simpson et al. 1997).

Newly abstinent cocaine abusers may experience a triphasic abstinence pattern, although this varies by individual, that includes a period of acute abstinence, sometimes referred to as the "crash," lasting several hours to several days consisting of dysphoria, fatigue, insomnia or hypersomnia, increased appetite, and either psychomotor agitation or retardation, subsequent to the more intensive "crash" phase. A more chronic withdrawal period sometimes occurs characterized by minor depressive symptoms and cocaine craving lasting 2–10 weeks. This may then be followed by an extinction phase characterized by intermittent drug craving that becomes increasingly manageable with continued abstinence.

Like other drug and alcohol use disorders, cocaine use disorders are chronic relapsing illnesses that present substantial challenges in the treatment process. Cocaine abusers are at high risk for relapse, particularly in the first few months of treatment related to acute craving often in the context

of ongoing psychosocial stressors that result from or have been exacerbated by cocaine abuse. Newly abstinent cocaine abusers often lack adequate coping skills necessary to avoid cocaine use, which take time to acquire in the treatment process. Although the ability to cope with cocaine craving improves with continued abstinence, relapse to cocaine abuse or other drug and alcohol abuse will continue to be a risk for those with a history of a cocaine use disorder who relapse to cocaine abuse. Repeated treatments may be required for those with cocaine use disorders. Treatment modalities include inpatient hospitalization for medical or psychiatric complications of cocaine abuse, partial hospital programs, self-help groups, psychotherapy (usually group or family therapy for patients with primary cocaine use disorders), or some combination of these treatments according to the clinical presentation of the patient (see later in the chapter).

## Etiology and Pathophysiology

### Genetic Vulnerability to Cocaine Abuse and Dependence

Heritability or genetic vulnerability may play an important role in the development of cocaine addiction. Epidemiological studies of twins suggest that while both genetic and environmental factors play a role in twin concordance of cocaine use, concordance of abuse and dependence are more influenced by genetic factors (Kendler and Prescott 1998, Kendler et al. 2000). While no single gene has been definitively linked to cocaine use disorders, certain alleles may play a role in the development of cocaine use disorders and/or clinical manifestations of these disorders. Population-based genetic association studies have yielded some interesting preliminary results. For example, an association between cocaine-induced paranoia and an allelic polymorphism in the dopamine transporter protein (DAT) (allele 9) has been described (Gelernter et al. 1994). Another study reported on a haplotype at the dopamine beta-hydroxylase (DBH) locus associated with low plasma DBH activity that appears to be associated with cocaine-associated paranoia, (Cubells et al. 2000). The tryptophan hydroxylase gene, responsible for the majority of serotonin production in neurons has been shown to have no association with cocaine dependence (Dahl et al. 2006). A genome-wide linkage scan conducted in families with at least one subject affected with cocaine dependence suggested a linkage signal for cocaine dependence on chromosome 10 and two suggestive linkages for cocaine dependence for European Americans on chromosome 3. Further, this study showed a suggested linkage on chromosome 9 for cocaine-associated paranoia in the African American sample, while heavy or moderate cocaine use in the European American sample was associated with chromosomes 12 and 18, respectively (Gelernter et al. 2005). Such findings together with ongoing candidate gene studies using genetic engineering techniques and genome mapping may contribute to important advances in our understanding of genetic vulnerability to cocaine abuse and dependence (Kuhar et al. 2001).

### Neurobiological Changes Related to Acute Cocaine Use

Cocaine has effects on multiple neurotransmitters, including release and reuptake blockade of dopamine, serotonin (5-hydroxytryptamine [5-HT]), and norepinephrine (Hemby 1999, Koob 1999). The most widely accepted explanation of cocaine-induced euphoria is that dopamine reuptake inhibition results in increased extracellular dopamine concentration in the mesolimbic and mesocortical reward pathways in the brain. Numerous studies have provided evidence for the importance of dopamine in the reinforcing properties of cocaine. For example, 6-hydroxydopamine lesions of dopaminergic terminals in the nucleus accumbens produce extinction-like responding and a reduction in cocaine self-administration. Similar lesions in other areas of the brain (frontal cortex and caudate nucleus) do not alter cocaine self-administration (Schenk et al. 1991, Brown and Fibiger 1993, Reavill et al. 1998).

*In vivo* brain microdialysis and neuroimaging studies using functional magnetic resonance imaging (fMRI), PET, and SPECT, have provided additional direct evidence that the limbic region and other dopamine rich structures in the brain are associated with cocaine reward (Gatley and Volkow 1998, London et al. 1999, Hommer 1999). Cocaine-induced euphoria has been associated with activity in many areas of the brain but primarily in the prefrontal cortex as evidenced by reduced cerebral glucose metabolism (London et al. 1996, Bolla et al. 1998, London et al. 1999) and reduced cerebral blood flow (rCBF) (Pearlson et al. 1993, Breiter et al. 1997, Gollub et al. 1998). Moreover, SPECT neuroimaging has shown that the euphoric effects of cocaine are associated with blockade of the dopamine transporter (Malison et al. 1995, 1998a, Volkow et al. 1999). Cue-induced craving increases activation in the limbic regions including dorsolateral prefrontal cortex, cerebellum, anterior cingulate, and amygdala (London et al. 1990, Childress et al. 1999, Garavan et al. 2000). These structures have been linked to memory and learning. The amygdala, in particular, is linked to the emotional aspect of memory (Rolls 2000, Cahill 2000, LeDoux 2000). Studies using fMRI technology showed that cocaine-specific cues activated the same limbic regions activated by other pleasurable stimuli (such as sex in cocaine users) but had almost no effect on nonusers (Childress et al. 1999, Garavan et al. 2000, Stein 2001).

Another important phenomenon related to acute cocaine administration is that of "acute tolerance." A single dose of cocaine has been shown experimentally to reduce the response to a second identical dose given 100 min later as measured by extracellular dopamine levels and motor activity (Bradberry 2000). The finding of "acute tolerance" is consistent with the binge pattern of cocaine use in which abusers consume escalating doses of cocaine in an attempt to recapture the intense euphoria of the initial cocaine dose (Bradberry 2000).

There may also be other neurochemical processes important to both the positive and the negative reinforcing properties of cocaine. Although dopamine reuptake inhibition is important to the reinforcing effects of cocaine, it cannot fully account for these effects. Numerous agents that are dopamine reuptake inhibitors are not abused by humans and are not self-administered by animals. These include benztropine, nomifensine, and mazindol. Similarly, other agents that are not abused by humans mimic neurochemical actions of cocaine on noradrenergic or serotoninergic systems. Studies have shown that "knockout" mice lacking the genes for either the dopamine or serotonin transporters continue to find cocaine rewarding (Miner et al. 1995, Sora et al. 1998, Uhl et al. 1996). However, when both transporter

genes were deleted, cocaine-induced reward/reinforcement behavior was completely blocked (Sora et al. 2001). Therefore, it is likely that the pleasurable effects of cocaine involve multiple neurotransmitters and none of the known singular neurochemical actions of cocaine provides a full explanation for cocaine addiction.

### Neurobiological Changes Related to Long-Term Cocaine Use

A growing body of evidence indicates that chronic cocaine administration can result in sustained neurophysiological changes in brain systems that regulate psychological processes, specifically pleasure and hedonic responsivity (Bolla et al. 1998). This has been postulated to underlie a physiological addiction to cocaine with associated withdrawal phenomena that are manifested clinically as a psychological syndrome (Koob and Nestler 1997). Long-term cocaine administration in animals is associated with an increase in dopamine transporter binding sites, a decrease in intracranial electrical self-stimulation in dopaminergic brain reward areas, such as the nucleus accumbens, and an increase in the voltage required to elicit intracranial electrical self-stimulation (Richter et al. 1995, Weiss et al. 2001b). These findings imply that an alteration in brain reward regions affected by cocaine occurs with chronic use and is also associated with blunted responses to usual reward stimuli such as sex and food. The impairment of brain rewarding systems resulting from cocaine self-administration in rodents has been shown to be reversed with administration of bromocriptine, a dopaminergic agonist (Markou and Koob 1992). Interestingly, withdrawal from chronic self-administration of cocaine was reported to be associated with depletion of extracellular serotonin in the nucleus accumbens (Parsons et al. 1995) and an increase in serotonin transporter binding sites in the brainstem (Mash et al. 2000), resulting in a decrease of serotonin availability in synapses (Jacobsen et al. 2000). Given the role of serotonin in depression and anxiety, the findings are supportive of clinical observations of periods of anhedonia in cocaine abusers following initiation of abstinence (Weiss et al. 2001a). Neurophysiological changes that could help to explain these experimental and clinical observations include findings in animal studies of dopaminergic, alpha-adrenergic, and beta-adrenergic receptor supersensitivity with chronic cocaine administration (Hemby 1999). Dopaminergic autoreceptor supersensitivity results in a net decrease of dopaminergic neurotransmission. Animal studies in which cocaine is continuously administered have confirmed that such changes occur (Clay et al. 1998, Kuhar and Pilotte 1996, Pilotte et al. 1996). Chronic administration of cocaine has also been shown to alter the activity or expression of diverse types of cellular proteins in specific target neurons within the central nervous system. Prominent examples include signaling proteins, G proteins, second-messenger synthetic enzymes, and protein kinases (Carlezon et al. 1998, Hwang et al. 2001, Kelz et al. 1999, Nestler 2001). In addition, recent work has focused on a role for transcription factors and associated alterations in gene expression in mediating part of this long-lasting, drug-induced, molecular and behavioral plasticity (Nestler 1997, 2001).

## Diagnosis of Cocaine Use Disorders

The initial evaluation period should include the collection of a complete history of all substance abuse (including alcohol and drug abuse), which is essential to accurate diagnosis and appropriate treatment. The history includes the circumstances under which each drug was used, the psychoactive effects sought and obtained, the route of administration, age of onset of each drug used, and the frequency and amount of each drug used. Cocaine abusers frequently abuse other drugs and alcohol to enhance euphoria or to alleviate dysphoric effects associated with cocaine abuse (e.g. agitation, paranoia). A thorough history with diagnosis of other substance use disorders is important to treatment planning. Patients may need detoxification from other substances prior to initiation of cocaine abuse treatment. It is also important to monitor clinically for relapses to any substance abuse during treatment for cocaine use disorders because the use of other drugs and alcohol often leads to resumption of cocaine abuse. In addition, a thorough history of current and previous substance abuse is important so that treatment can be individualized and patients can be helped to develop coping skills that will assist them in specific situations that they identify as placing them at high risk for relapse.

A careful psychiatric history with particular attention to onset of psychiatric symptoms in relation to drug use is essential. The determination of a premorbid psychiatric illness is critical to providing appropriate treatment. For persons in whom substance abuse is an attempt to self-medicate an underlying mental illness, the introduction of psychotropic medication in conjunction with ongoing treatment for the substance abuse will improve both the psychiatric disorder as well as the substance use disorder(s). Conversely, the evaluation of temporal onset of psychiatric symptoms may preclude erroneous use of psychotropic medication in cases in which the psychiatric symptoms are in fact cocaine-induced and spare the patient exposure to the potential side effects of these medications.

A complete physical examination is necessary to determine whether medical complications of substance abuse are present. Common medical problems seen in those with cocaine use disorders include poor nutrition, vitamin deficiencies, anemia, human immunodeficiency virus (HIV) infection, and sexually transmitted diseases. In those who self-administer the drug by injection or who abuse other drugs in addition to cocaine by the intravenous route, endocarditis, abscesses, cellulitis, and Hepatitis B and C occur with regularity. The clinical evaluation should include blood studies to determine the presence of abnormalities and urine toxicology screen to determine recent drug use.

**DSM-IV-TR Criteria**

**Substance (Cocaine) Abuse**

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions,

*(continues)*

**DSM-IV-TR Criteria** *continued*

or expulsions from school; neglect of children or household)

(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.

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## Cocaine Use Disorders

### Cocaine Abuse

Substance abuse is described by DSM-IV-TR as a maladaptive pattern of substance use demonstrated by recurrent and significant adverse consequences related to repeated use. For example, there may be neglect of obligations to family or employer, repeated use in hazardous situations, legal problems, and recurrent social or interpersonal problems. These problems must recur within the same 12-month period. The intensity and frequency of use are less in cocaine abuse than in cocaine dependence. Episodes of abuse may occur around paydays, days off from work or weekends, holidays or special occasions and may be characterized by brief periods (hours to days) of high-dose binge use followed by longer periods of abstinence or nonproblem use.

### Cocaine Dependence

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) defines the essential features of substance dependence as a cluster of cognitive, behavioral, and physiological symptoms indicating continued use of the substance despite significant consequences of use. There is a pattern of administration that usually results in tolerance to and compulsive self-administration of the drug and

**DSM-IV-TR Criteria**

**Substance (Cocaine) Dependence**

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:

(a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect

(b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:

(a) the characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances)

(b) the same (or a closely related) substance taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), using the substance (e.g., chain-smoking), or recovering from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

*Specify* if:

With physiological dependence: evidence of tolerance or withdrawal (i.e., either item 1 or 2 is present)

Without physiological dependence: no evidence of tolerance or withdrawal (i.e., neither item 1 nor 2 is present)

*Course specifiers*

Early full remission

Early partial remission

Sustained full remission

Sustained partial remission

On agonist therapy

In a controlled environment

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may produce a withdrawal syndrome on cessation of drug use. Cocaine dependence can develop quickly after initiation of use because of the potent euphoria produced by the drug. The route of administration is related to the development of cocaine dependence; smoked and intravenous routes are more highly correlated with dependence than the intranasal route of administration.

Cocaine has a short half-life requiring frequent dosing to maintain the "high" (binge use). Persons with cocaine dependence often spend large amounts of money for the drug and may be involved in illegal activities to obtain cocaine. Binges may be separated by several days while the individual recovers or attempts to obtain more money for drug purchase. Illegal activities such as theft and prostitution are often engaged in to obtain cash for cocaine. Obligations such as employment and childcare are often neglected. Tolerance to cocaine effects develops quickly, resulting in larger amounts of drug use with time. This is often associated with mental or physical complications of use including paranoia, aggressive behavior, anxiety and agitation, depression, and weight loss. Withdrawal symptoms, most prominently dysphoric mood, may be seen but are usually short-lived and clear within several days of abstinence.

## Cocaine Intoxication

The clinical effects of cocaine intoxication are characterized initially by euphoria (referred to as high) and also include agitation, anxiety, irritability or affective lability, grandiosity, impaired judgment, increased psychomotor activity, hypervigilance or paranoia, and sometimes hallucinations (visual, auditory, or tactile) may occur. Physical symptoms that can accompany cocaine intoxication include hypertension, tachycardia, hyperthermia, mydriasis, nausea, vomiting, tremor, diaphoresis, chest pain, arrhythmia, confusion, seizures, dyskinetic movements, dystonia, and, in severe cases, coma. These effects are more frequently seen in high-dose binge users of cocaine. Cardiovascular effects are probably a result of sympathomimetic properties of cocaine (i.e., release of norepinephrine and blockade of norepinephrine reuptake).

**DSM-IV-TR Criteria**

**Cocaine Intoxication**

(A) Recent use of cocaine.

(B) Clinically significant maladaptive behavioral or psychological changes (e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension, or anger; stereotyped behaviors; impaired judgment; or impaired social or occupational functioning) that developed during, or shortly after, use of cocaine.

(C) Two (or more) of the following developing during or shortly after cocaine use:
- (1) tachycardia or bradycardia
- (2) pupillary dilation
- (3) elevated or lowered blood pressure
- (4) perspiration or chills
- (5) nausea or vomiting
- (6) evidence of weight loss
- (7) psychomotor agitation or retardation
- (8) muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
- (9) confusion, seizures, dyskinesias, dystonias, or coma

(D) The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

*Specify if*:

With perceptual disturbances

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## Cocaine Withdrawal

The principal feature of substance withdrawal is development of a substance-specific maladaptive behavioral change, which may have associated physiological and cognitive components, resulting from the cessation of or reduction in heavy and prolonged substance use. The syndrome is characterized by significant distress or impairment in function. Symptoms must not be better explained by a mental or physical disorder. Cocaine withdrawal develops within a few hours to a few days after stopping or reducing cocaine use that has been heavy and prolonged. The syndrome is characterized by dysphoria and two or more physiological changes including fatigue, vivid and unpleasant dreams, insomnia or

**DSM-IV-TR Criteria**

**Cocaine Withdrawal**

(A) Cessation of (or reduction in) cocaine use that has been heavy and prolonged.

(B) Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after criterion A:
- (1) fatigue
- (2) vivid, unpleasant dreams
- (3) insomnia or hypersomnia
- (4) increased appetite
- (5) psychomotor retardation or agitation

(C) The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

(D) The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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hypersomnia, hyperphagia, and psychomotor agitation or retardation. Anhedonia and craving for cocaine can be part of the withdrawal syndrome. Depression and suicidal ideation are the most serious complications and require individualized assessment and treatment. The syndrome may last up to several days but generally resolves without treatment.

## Other Cocaine-Induced Disorders

DSM-IV-TR also specifies additional cocaine-induced disorders described in other diagnostic groupings with which they share phenomenology (Table 58–1). These include cocaine intoxication delirium, cocaine-induced psychotic disorder, cocaine-induced mood disorder, cocaine-induced anxiety disorder, cocaine-induced sleep disorder, and cocaine-induced sexual dysfunction. These disorders are diagnosed instead of intoxication or withdrawal only if symptoms are in excess of those usually associated with cocaine intoxication or cocaine withdrawal and warrant independent clinical attention. In addition, the psychiatrist should pay careful attention to the temporal relationship of the psychiatric symptoms and cocaine abuse. Symptoms that are severe enough to warrant consideration of one of these diagnoses should also dissipate with continued abstinence from cocaine. Symptoms that worsen after cessation of cocaine use in a period of 1–4 weeks should be reevaluated and other Axis I or Axis III disorders considered with modification of the treatment plan as clinically indicated.

**Table 58–1 Other DSM-IV Cocaine-Induced Disorders**

| | |
|---|---|
| 292.89 | Cocaine intoxication<br>*Specify if:* with perceptual disturbances |
| 292.0 | Cocaine withdrawal |
| 292.81 | Cocaine intoxication delirium |
| 292.11 | Cocaine-induced psychotic disorder, with delusions<br>*Specify if:* with onset during intoxication |
| 292.12 | Cocaine-induced psychotic disorder, with hallucinations<br>*Specify if:* with onset during intoxication |
| 292.84 | Cocaine-induced mood disorder<br>*Specify if:* with onset during intoxication/with onset during withdrawal |
| 292.89 | Cocaine-induced anxiety disorder<br>*Specify if:* with onset during intoxication/with onset during withdrawal |
| 292.89 | Cocaine-induced sexual dysfunction<br>*Specify if:* with onset during intoxication |
| 292.89 | Cocaine-induced sleep disorder<br>*Specify if:* with onset during intoxication/with onset during withdrawal |
| 292.9 | Cocaine-related disorder not otherwise specified |

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## Medical Complications of Cocaine Abuse

Cardiac toxicity is one of the leading causes of morbidity and mortality associated with cocaine use. The risk of myocardial infarct is well established in cocaine use (Pitts et al. 1997, 1998) and is not related to dose, route, or frequency of administration (Lange and Hillis 2001). The risk of acute myocardial infarction is increased 24-fold in the first hour immediately following cocaine use in those who are otherwise at relatively low risk for such events (Mittleman et al. 1999). Another potential source of medical comorbidity is the concomitant use of cocaine and alcohol which leads to the formation of cocaethylene, a compound with properties similar to those of cocaine (Hart et al. 2000, McCance et al. 1995). Cocaethylene has been associated with a 40-fold increase in risk for acute cardiac events and 25-fold increase in sudden death (Keegan 1991) and places users at heightened risk for toxicity than with either drug alone (McCance-Katz et al. 1998). Detection of recent cocaine use by urine toxicology screen has been observed in 25% of those reporting to urban emergency departments and 7% of those evaluated at suburban hospitals and found to have evidence of myocardial infarct (Hollander et al. 1995). About half of the patients with cocaine-related myocardial infarction have no evidence of atherosclerotic coronary artery disease (Hollander et al. 1997a, b). Identifying and diagnosing cocaine-related myocardial infarction can be difficult. The hallmarks of myocardial infarct are a constellation of physical symptoms including chest pain, electrocardiogram (ECG) abnormalities, and elevated creatine kinase. Cocaine abusers with chest pain may have ECG abnormalities that are not specific for myocardial infarct (Hamad and Khan 2000, Hollander et al. 1994, 1998a, Weber et al. 2000). Cocaine abusers also are often found to have nonspecific elevations in creatine kinase without myocardial infarction (Hollander et al. 1998b). Therefore, the diagnosis of cocaine-related myocardial infarction is often based on the physician's clinical judgment. Evaluation of serum troponin I, a cardiac marker that is not affected by recent cocaine use, can be helpful in determination of whether a myocardial infarct has occurred (Hollander et al. 1998b, Lange and Hillis 2001).

The pathophysiology of cocaine-related myocardial infarction is probably multifactorial. The sympathomimetic effects of cocaine increase myocardial oxygen demand by increasing heart rate, systemic blood pressure, and left ventricular contractility while reducing oxygen supply through its coronary artery vasoconstriction effects (Baumann et al. 2000). Cocaine-induced coronary artery vasoconstriction is thought to be mediated by an alpha-adrenergic mechanism since it can be reversed with phentolamine, an alpha-adrenergic antagonist, and is exacerbated by propranolol, a beta-adrenergic antagonist (Hollander 2001, Lange and Hillis 2001). The vasoconstrictive effects of cocaine are more prominent in segments of the coronary artery with preexisting atherosclerotic lesions. Consequently, cocaine users with atherosclerotic coronary artery disease are at an increased risk for ischemic events (Lange and Hillis 2001). Additionally, cocaine may induce thrombus formation, enhance platelet aggregation, and decrease fibrinolysis by increasing the concentration of plasminogen-activator inhibitor (Kugelmass et al. 1993, Lee et al. 1995, Moliterno et al. 1994, Rezkalla et al. 1993, Rinder et al. 1994, Siegel et al. 1999). Postmortem as well as *in vitro* studies have suggested that cocaine may contribute to the pathogenesis of premature atherosclerotic formation by damaging the endothelial cell barrier, increasing its permeability to low-density lipoprotein and enhancing the expression of endothelial adhesion molecules and migration of leukocytes (Gan et al. 1999, Kolodgie et al. 1995, 1999, Lange and Hillis 2001). The American Heart Association treatment guidelines for emergency cardiovascular care indicate that nitroglycerin and benzodiazepines are first line agents and phentolamine

is a second line agent for patients with cocaine-related acute coronary syndrome. Propranolol is contraindicated as it exacerbates cocaine-induced vasoconstriction of coronary arteries. Fibrinolytics should be used with caution if at all, particularly in the presence of severe hypertension. Intracoronary fibrinolytic administration is preferred to peripheral administration. The use of labetalol is controversial because it blocks the peripheral signs of drug-induced sympathetic excess without affecting central nervous system effects such as seizures. Esmolol and metoprolol may induce hypotension (American Heart Association 2005).

Cocaine use is associated with a wide range of cardiac arrhythmias including sinus tachycardia, sinus bradycardia, supraventricular and ventricular tachycardia, ventricular premature contractions, ventricular tachycardia and fibrillation, torsades de pointes and asystole (Castro and Nacht 2000, Gamouras et al. 2000, Kerns et al. 1997, Perera et al. 1997, Singh et al. 2001). While the precise arrhythmogenic mechanism of cocaine is unclear, limited evidence suggests it may be due to cocaine's sodium-channel-blocking property similar to class I antiarrhythmic drugs that prolong the QRS and QT intervals on ECG (Brady and Chan 1999, Kerns et al. 1997). Life-threatening arrhythmia caused by cocaine in the absence of myocardial ischemia is rare. In many instances, cardiac arrhythmias have occurred in the context of profound hemodynamic or metabolic disturbances (Wang 1999). Patients with cocaine-induced ventricular arrhythmias and heart block should receive standard therapy including the treatment of ischemia if present, the correction of metabolic disturbances, and the administration of appropriate antiarrhythmic agents (Lange and Hillis 2001). Class IA antiarrhythmic drugs, such as quinidine, procainamide, and di-isopyramide, should be avoided since they may exacerbate prolongation of the QRS and QT intervals and slow the metabolism of cocaine.

Several cases of cardiomyopathy and left ventricular hypertrophy attributed to cocaine use have been reported (Fineschi et al. 1997, Missouris et al. 2001). The condition is often associated with chronic cocaine use and cocaine-related myocardial ischemia and infarction. While the exact underlying mechanisms of cocaine-induced cardiomyopathy and hypertrophy are still unclear, the process may involve repetitive sympathetic stimulation by cocaine with altered myocardial collagen and myosin composition in endothelial cells (Besse et al. 1997, He et al. 2000, 2001, Huang et al. 1997, Mao et al. 1997, Woolf et al. 1997, Xiao et al. 2000). A few cases of aortic dissection have also been reported in association with cocaine abuse (Baumgartner and Omari 1997, Madu et al. 1999, Perron and Gibbs 1997). This adverse event might be associated with sudden increase in blood pressure following cocaine use.

Intranasal abuse of cocaine has been associated with a number of medical complications including chronic sinusitis, septal perforation, subperiosteal abscess, pneumomediastinum, pneumothorax, and pulmonary edema (Gendeh et al. 1998). The presence of pulmonary edema in a young, otherwise healthy patient, without predisposing risk factors, should alert the physician to the possibility of cocaine abuse (Albertson et al. 1995, Bird and Markey 1997, Boghdadi and Henning 1997, Cuenca Carvajal et al. 1998).

Cerebrovascular accidents related to cocaine use have been well documented in the medical literature (Alves and Gomes 2000, Blanco et al. 1999, Daras et al. 2001, Kaufman et al. 1998, Kaufman et al. 2001, Neiman et al. 2000, Nwosu et al. 2001, Petitti et al. 1998, Qureshi et al. 2001, Tolat et al. 2000). Cerebral infarct, subarachnoid hemorrhage, intraparenchymal hemorrhage, and intraventricular hemorrhage have been observed as acute complications of cocaine use. The physiological etiology of these events appears to be related to adrenergic stimulation resulting in a sudden surge in blood pressure. Abrupt increases in blood pressure in otherwise normotensive individuals may precipitate spontaneous bleeding (Neiman et al. 2000, Strickland et al. 1998). Additional risk would be encountered by a cocaine user with an arteriovenous malformation or cerebral artery aneurysm.

Seizures were one of the earliest known complications of cocaine abuse (Chiarotti and Fucci 1999, Koppel et al. 1996, O'Connell and Heffron 2000, Steele et al. 2000, Winbery et al. 1998). Cocaine produces hyperpyrexia which in combination with its effects on neurotransmitters may contribute to the development of seizures (Boghdadi and Henning 1997, Winbery et al. 1998). Seizures may occur as a primary effect of cocaine owing to its ability to lower the seizure threshold or may be secondary to other central nervous system or cardiac events precipitated by cocaine use (Koppel et al. 1996). One study retrospectively analyzed 474 cases of cocaine-related seizures. Of these, 403 had no history of seizures. It was found that the majority of seizures were single, generalized, and induced by intravenous or "crack" cocaine abuse not associated with any lasting neurological deficits. Seizures that were focal, multiple, or occurred with nasal cocaine use were more frequently associated with an acute intracerebral complication or concurrent use of other drugs (Chiarotti and Fucci 1999, Koppel et al. 1996, Pascual-Leone et al. 1990). While anticonvulsants have not been helpful in preventing cocaine-related seizures, intravenous diazepam has been effective in acute management (Koppel et al. 1996). These findings imply that there is no clinical benefit to chronic anticonvulsant therapy in those who experience a cocaine-related seizure, rather substance abuse treatment for the cocaine use disorder is indicated.

Recently, acute renal failure as a result of rhabdomyolysis has been recognized as an important complication of cocaine abuse (Horowitz et al. 1997, Lampley et al. 1996, Ruttenber et al. 1999, Richards 2000, van der Woude 2000). Pregnancy may increase the risk of rhabdomyolysis and renal failure (Lampley et al. 1996). Renal failure may progress rapidly in the context of cocaine-induced rhabdomyolysis and dialysis may be necessary for some patients. The mechanism for this complication is unclear. Some possibilities include increased muscle activity, muscle compression, hyperthermia, and vasospasm with muscle ischemia (Richards 2000, Ruttenber et al. 1999, van der Woude 2000).

The major medical complications of cocaine abuse are summarized in Table 58–2.

## Treatment of Cocaine Use Disorders

Cocaine continues to be the most frequently mentioned illicit drug associated with medical adverse events, comprising 19% of all drug-related emergency department visits in 2004 with 46% of those with medical adverse events related to cocaine use seeking detoxification (DAWN 2004). Treatments for cocaine use disorders continue to evolve and have been shown to be effective. In a large outcome study,

**Table 58–2 Major Medical Complications Associated with Cocaine Abuse**

| |
|---|
| **Cardiovascular** |
| Myocardial infarct |
| Arrhythmias |
| Aortic dissection |
| Cardiomyopathy |
| Hypertension |
| **Respiratory** |
| Pneumonitis (associated with smoked cocaine) |
| Pulmonary edema |
| Nasal septal perforation, chronic sinusitis (associated with intranasal inhalation) |
| **Central nervous system** |
| Hyperpyrexia |
| Seizure |
| Cerebral infarct |
| Subarachnoid hemorrhage |
| Intraparenchymal hemorrhage |
| Intraventricular hemorrhage |
| **Renal** |
| Renal failure secondary to rhabdomyolysis |
| **Obstetrical** |
| Premature labor |
| Placental abruption |
| **Complications of Intravenous Use** |
| Infectious diseases (HIV, hepatitis) |
| Endocarditis |
| Cellulitis Abscesses |
| **Psychiatric** |
| Depression |
| Suicidality |
| Psychosis |

a comparison of short-term inpatient treatment programs, outpatient drug-free programs, and long-term residential programs specifically for those with cocaine use disorders was undertaken. Of those who received any treatment, 24% relapsed to weekly cocaine use, a large decrease over the 73% relapse rate in the year prior to treatment. Some required an additional treatment program (18%) in the year following treatment, which is not an uncommon scenario for this chronic, relapsing disorder. Those with high levels of psychosocial, medical, or psychiatric problems at intake or less than 90 days of treatment had higher cocaine use in the follow-up period. Treatment periods of 90 days or more were associated with better substance abuse outcomes (Crits-Christoph et al. 1999). In this section, the treatment process for cocaine abuse and dependence, including assessment and management of common problems, specific psychotherapies for cocaine use disorders, and pharmacotherapy will be reviewed.

## Assessment and Treatment Overview

The two primary goals of cocaine treatment are: (1) the initiation of abstinence through disruption of binge cycles and (2) the prevention of relapse. Treatment planning to achieve these goals must be considered in the context of the individual clinical presentation of the patient. Initial assessment to determine immediate needs is necessary to determine the most appropriate level of care (inpatient or outpatient treatment) as well as other psychiatric and medical considerations important to the development of the treatment plan.

The majority of those with cocaine use disorders are most appropriately treated in an outpatient setting. Outpatient treatment may vary by provider but generally includes multiple weekly contacts for the initial months of treatment because less frequent contact is not effective in the initiation or maintenance of abstinence (Coviello et al. 2001, Gottheil et al. 1998, Katz et al. 2001, Weinstein et al. 1997). These sessions consist of some combination of individual drug counseling, peer support groups, family or couples therapy, urine toxicology monitoring, education sessions, psychotherapy, and psychiatric treatment that may include pharmacotherapy for cocaine addiction and/or comorbid psychiatric disorders. Inpatient treatment is reserved for those who have been refractory to outpatient treatment, whose compulsive use of cocaine represents an imminent danger (e.g., suicidality associated with cocaine toxicity or acute abstinence), who have other comorbid psychiatric or medical disorders complicating their treatment, or who are dependent on more than one substance and require monitored detoxification.

## Cocaine Use Disorders: Clinical Course

Cocaine use is characterized by binge use that can occur over extended periods of time and is limited only by the supply of drug or money to purchase the drug. Cocaine toxicity may occur with repeated use of the drug over the course of a binge. Symptoms can include hypervigilance, psychomotor agitation, hyperawareness, and psychosis. While these symptoms generally resolve within 24 hours of cessation of cocaine use, prolonged symptoms may be indicative of an underlying bipolar disorder or psychotic disorder that will need further assessment (Carroll et al. 1994a). Another facet of cocaine toxicity that may be manifested as psychiatric symptoms is that of a syndrome of hyperthermia and agitation resembling neuroleptic malignant syndrome (Daras et al. 1995, Kosten and Kleber 1988, Nolla-Salas et al. 1996, Ross 1998, Wetli et al. 1996). An additional serious complication of cocaine intoxication is that of stimulant delirium characterized by confusion, disorientation, and agitation. This should be treated as a medical emergency since such symptoms may be indicative of cocaine overdose. The medical complications of cocaine abuse have been reviewed (above) and presentation of delirium in a cocaine abuser should prompt a thorough medical evaluation and treatment of any toxic side effects.

Cocaine abstinence symptoms may occur with the cessation of binge use (Foltin and Fischman 1998, Margolin et al. 1996, Milby et al. 2000). The abstinence syndrome is characterized by extreme exhaustion after a binge. Initial depression, agitation, and anxiety are a common experience, followed by craving for sleep. Prolonged hypersomnolence and hyperphagia are usually followed by a return to normal mood, although some dysphoria may remain (Rosenblum et al. 1999, Uslaner et al. 1999, Westermeyer et al. 1997).

Cocaine abusers may present to urgent care settings in the context of cocaine toxicity or severe psychiatric symptoms associated with acute abstinence including anxiety, depression, or psychosis. Symptoms may be severe enough to require emergent use of benzodiazepines or antipsychotics. Lorazepam is a good choice for treatment of anxiety, agitation, or psychosis because it can be administered orally and it is also well absorbed by the intramuscular route. The use of benzodiazepines in the severely agitated patient may decrease the need to employ the use of restraints. Antipsychotics should be used sparingly because, like cocaine, these drugs may lower the seizure threshold. In considering the choice of an antipsychotic, low-potency antipsychotics may be more likely than high-potency neuroleptics to lower seizure threshold and therefore should be avoided. Psychiatric management must also include clinical observation because suicidal ideation is not uncommon. Symptoms resembling those of a major depressive episode occur frequently in newly abstinent cocaine abusers. The occurrence of major depressive disorder must be excluded by observation, ideally over several weeks following the initiation of abstinence.

Individuals with cocaine use disorders may experience a withdrawal syndrome upon cessation of binge cocaine abuse that can last for up to 10 weeks. Cocaine withdrawal is marked by decreased energy, lack of interest, and anhedonia. These symptoms fluctuate and are usually not severe enough to meet diagnostic criteria for a major depressive episode. However, this subjective state experienced by the cocaine abuser is contrasted with vivid memories of cocaine-induced euphoria and constitutes a strong inducement to resume cocaine use (i.e., craving). It is during this time that relapse is most likely. Withdrawal symptoms generally diminish over several weeks if abstinence is maintained.

The withdrawal phase is followed by what has been termed "extinction," an indefinite period during which evoked craving can occur, placing the individual at increased risk for relapse. Craving is evoked by memories of cocaine use, moods, people, locations, or objects associated with cocaine use (money, white powder, pipes, mirrors, syringes) that act as cues to conditioned associations with drug use and drug-induced euphoria (Childress et al. 1993, Ciccocioppo et al. 2001, Robbins et al. 1997). Animal models have shown that sensitivity to drug-associated environmental cues and craving lasting 60 days following discontinuation of cocaine administration (Weiss et al. 2000, 2001a, 2001b). Such findings underline the individual's vulnerability to cocaine relapse well beyond the acute withdrawal phase (Robbins et al. 1999). The documentation of the chronic course of cocaine use disorders has influenced the development of treatment modalities. For example, outpatient treatment is generally recommended to occur over at least three months in an intensive outpatient setting. Those with histories of more severe use problems or frequent relapses may require treatment for longer periods. Pharmacotherapy development has targeted acute abstinence symptoms in which medications would be administered for days and/or weeks and abstinence maintenance in which medication therapy might extend for the duration of the substance abuse treatment. Ongoing supportive groups may be recommended for an indefinite period to assist the cocaine-addicted person in establishing new relationships with peers that will provide support for ongoing sobriety because the experience of drug craving and risk for relapse when the individual is confronted with drug-associated cues can continue for years.

## Overview of Treatment for Cocaine Use Disorders

Substance abuse treatment for cocaine use disorders has been influenced by the known disease course. One of the greatest challenges in the early stages of cocaine treatment is to prevent drop out. It has been estimated that up to 80% of patients drop out of treatment programs (Higgins et al. 1994). Frequent clinical contacts especially in the early weeks of treatment can help to establish a therapeutic alliance that will assist in engaging the patient in the treatment process. Many programs offer 3–6 days per week of substance abuse treatment sessions within outpatient partial hospital programs or intensive outpatient chemical dependency programs. Assessments by the program physician and counseling staff can identify other areas requiring specific interventions (comorbid medical or psychiatric disorders) and can expedite the initiation of appropriate pharmacotherapies. These interventions will help to improve treatment retention. Often patients must be helped to realize that their drug use is having a significant and adverse impact on their lives. Many patients come to treatment because of family, legal, or social pressures. They may be ambivalent about the need for treatment and require education about their addiction and assistance in reviewing the consequences of cocaine use in their lives. This inventory should occur in the initial visits to the substance abuse treatment program.

Initial treatment should include the encouragement of abstinence from all drug and alcohol use. Patients who abuse alcohol and marijuana often do not perceive these drugs as problems. Education regarding the use of such drugs as conditioned stimuli to the use of cocaine should be emphasized. The "disease model" of chemical dependency may be used to assist in the initiation of abstinence. Emphasis is placed on the patient recognizing chemical dependency as a disease needing treatment to control symptoms, but one for which there is no cure. Comprehensive drug education should also be provided in the initial treatment phase. Frequent contact with a drug counselor is an important part of treatment. Individual, group, and (where clinically indicated) family or marital therapy should be available. Attendance at 12-step or other mutual-help groups is often a useful adjunct to treatment and can be particularly helpful during the early stages of treatment when support for sobriety is essential.

The early recovery phase of treatment varies in duration from 3–12 months and is characterized by multiple weekly contacts and participation in therapeutic modalities with the goal of initiation and maintenance of abstinence. The focus during early recovery should be on relapse prevention and development of new and more adaptive coping skills, healthy relationships, and lifestyle changes that will facilitate abstinence.

During early recovery patients may feel pleased about their progress in treatment, become overly confident about their ability to control use, and test themselves by deliberately encountering what they know to be a high-risk situation for their drug use. Experimentation with cocaine to prove that drug use can be controlled often results in relapse and is associated with guilt. Patients should be informed about the potential for relapse from the start of the treatment process.

Relapse should be reviewed with the patient in a supportive way with an emphasis on helping the patient to gain an understanding of the events leading to relapse. Relapse should, however, also trigger a review of the treatment plan and consideration of the need for additional interventions or whether a higher level of care is needed to assist the patient in the recovery process.

Success with initiating and maintaining abstinence over several months is followed by a reduced frequency of contact (e.g., a decrease to weekly group or individual therapy sessions). The focus should be on maintaining a commitment to abstinence, addressing renewed denial, and continued improvement of interpersonal skills. Participation in mutual-help groups should continue to be encouraged. Mutual-help groups (e.g., Cocaine Anonymous) based on 12-step principles encourage patients to continue to view themselves as addicts in recovery—a cognitive structuring that many recovering drug abusers find helpful in maintaining sobriety.

## Psychotherapies for Cocaine Use Disorders

A variety of psychotherapeutic strategies for the treatment of cocaine use disorders have been described (Barber et al. 1997, Barber et al. 2001, Carroll et al. 1994a, 1995b, Crits-Christoph et al. 1998, 1999, Crits-Christoph and Siqueland 1996, Higgins et al. 1993) (Table 58–3). In contrast to opiate addiction, for which psychotherapies alone are insufficient (Woody et al. 1995, Woody and Munoz 2000), there appear to be at least some subpopulations of cocaine abusers for whom psychotherapy alone may be adequate (Crits-Christoph et al. 1997, 1998, 1999). Behavioral therapies, in particular cognitive–behavioral therapy (Carroll 1998) and contingency management approaches have been demonstrated to be effective treatments for some cocaine-dependent patients (Elk et al. 1998, Higgins et al. 1991, Jones et al. 2001, Milby et al. 2000).

**Table 58–3 Psychotherapies Shown to be Effective for Treatment of Cocaine Use Disorders**

| |
|---|
| Interpersonal therapy |
| Supportive expressive therapy |
| Cognitive–behavioral therapy/Relapse prevention therapy |
| Voucher based treatment/Incentives |
| Individual and group drug counseling |
| Mutual-help groups (e.g., Cocaine Anonymous) |

The lack of a medically dangerous withdrawal syndrome from cocaine suggests that some cocaine abusers may respond to psychotherapy alone in an outpatient treatment setting, compared with opiate- or alcohol-dependent persons for whom hospitalization may be required for detoxification. Another important reason for the development of psychotherapies for the treatment of cocaine use disorders is that no medication is currently approved for the treatment of these disorders. Psychotherapies are also important platforms on which any pharmacological treatment may be supported. Furthermore, individuals not eligible for pharmacological treatment or who do not respond to pharmacological treatment require treatment alternatives such as psychotherapeutic interventions. The following sections discuss psychotherapies that have been used effectively for cocaine use disorders and those currently under investigation.

### Interpersonal Therapy

Interpersonal or psychodynamically oriented treatment approaches such as interpersonal psychotherapy (IPT) are based on the concept that many psychiatric disorders, including cocaine dependence, are integrally related to disorders in interpersonal functioning that may be associated with the genesis or perpetuation of the disorder. IPT, as adapted for cocaine use disorders treatment, includes four characteristics: (1) adherence to a medical model of psychiatric disorders, which views these illnesses as chronic relapsing disorders, (2) focus on patients' difficulties in current interpersonal functioning, (3) brevity and consistency of focus, and (4) use of an exploratory stance by the therapist in examining the difficulties being experienced currently by the patient and which may be related to the abuse of cocaine (Carroll and Rounsaville 1993).

### Supportive–Expressive Therapy

Supportive–expressive therapy is a time-limited, focused psychotherapy. The therapy has two main components: supportive techniques to help patients feel comfortable in discussing their personal experiences related to drug abuse and expressive techniques to help patients identify and work through difficulties in interpersonal relationships. Special attention is paid to the role of drugs in relation to problem feelings and behaviors, and how problems may be solved without recourse to drugs (NIDA 1999b). The efficacy of individual supportive–expressive psychotherapy has been studied with cocaine-abusing, opiate-dependent patients in methadone maintenance treatment who had comorbid psychiatric diagnoses (Woody et al. 1995). It was found that supportive–expressive psychotherapy, when added to drug counseling, improved substance abuse treatment outcomes. Those receiving supportive–expressive therapy had fewer cocaine-positive urine toxicologies and required lower doses of methadone.

### Cognitive–Behavioral Therapy

Cognitive–behavioral therapy (CBT) is a short-term, focused approach to help cocaine users become abstinent from cocaine and other substances. The underlying assumption is that learning processes play an important role in the development and continuation of maladaptive behaviors such as cocaine abuse. CBT techniques can be used to help cocaine abusers identify and correct behaviors associated with cocaine use (Carroll 1998). Relapse prevention therapy (RPT) is based on cognitive–behavioral principles and attempts to address the serious problem of relapse in substance use disorders through the development of self-control strategies (Carroll et al. 1994a, 1994b). RPT may be especially well-suited as a psychotherapeutic intervention for cocaine abusers because it encompasses several distinctive features important to treating this population. Relapse prevention is oriented toward symptom control. Although the name implies focus on the prevention of relapse, in fact this method employs several strategies intended to facilitate abstinence as well. Specific techniques in cocaine addiction treatment include exploring the positive and negative consequences of continued use, self-monitoring to recognize drug cravings early on and to identify high-risk situations for

use, and developing strategies for coping with and avoiding high-risk situations and the desire to use. Research indicates that the skills individuals learn through relapse prevention therapy remain after the completion of treatment. In two long-term outcome studies, most people receiving this cognitive–behavioral approach maintained the gains they made in treatment throughout the year following treatment and a proportion of study participants continued to make gains following the termination of the 12-week CBT treatment period (Carroll et al. 1994a, 2000).

Relapse prevention techniques are easily integrated into other treatment modalities. These techniques have been employed in the context of pharmacotherapy, group therapy, brief psychoeducational groups for individuals entering drug-free treatment programs, and intervention for persons at risk for HIV infection (NIDA 1999). RPT is effective given either in a group format or individually (Schmitz et al. 1997). Other studies have shown that CBT/RPT is an effective platform on which to base cocaine pharmacotherapy. In a double-blind, placebo-controlled, clinical trial examining the joint action of naltrexone (NTX) in combination with RPT, patients receiving the combination treatment had less cocaine use over time than those receiving pharmacotherapy or RPT alone (Schmitz et al. 2001b). In a study of the effectiveness of disulfiram alone, CBT or 12-Step Facilitation therapies alone, or disulfiram in combination with either psychotherapy, those assigned to medication plus a psychotherapy had better outcomes in terms of reduced cocaine use and longer periods of abstinence than did those receiving either medication or psychotherapy alone (Carroll et al. 1998).

## Voucher-Based/Incentive Treatment

Developed from the theory of alternative reinforcement, the voucher-based treatment approach is another example of behavioral therapy. A model that has been effective for the treatment of cocaine use disorders is that of community reinforcement plus vouchers. Using this model delivered over a 24-week outpatient period, two specific treatment goals are addressed. One goal is the achievement of cocaine abstinence for a period long enough to help patients learn new skills that will help sustain abstinence and the second is the reduction of alcohol consumption in those who consume cocaine and alcohol together. In 1–2 individual counseling sessions weekly, patients focus on improving family relations, learning skills to minimize drug abuse, receiving vocational counseling, and developing new sober social contacts and new recreational activities. Those who abuse alcohol also receive treatment with disulfiram (Antabuse). Urine samples for toxicology screen are submitted 2 to 3 times weekly and vouchers are received for cocaine-free urines. Vouchers can be exchanged for retail goods that would support a drug-free lifestyle (e.g., gift certificates to local stores). This approach has been shown to facilitate patient engagement in treatment and support abstinence both in urban and rural settings in which it has been used (Bickel et al. 1995, Higgins et al. 1994, Silverman et al. 1996).

## Motivational Interviewing

Motivational interviewing (MI) was first described by Miller (1983) and further detailed by Miller and Rollnick (1991). The focus of this method is to encourage behavior change by helping patients explore and resolve their uncertainties about which course to follow with regard to their substance use problem. Motivational interviewing is more of a goal-directed therapy when compared to traditional counseling, where the central purpose of MI is to examine and resolve ambivalence and the counselor is intentionally directive in pursuing this goal. A MI pilot study among drug users found that MI significantly increased retention rates six months after commencement of the treatment program (Secades-Villa et al. 2004). Additionally, a meta-analysis by Rubak et al. (2005) provides evidence that MI outperforms traditional advice giving in the treatment of a broad range of behavioral problems and diseases.

Motivational Enhancement Therapy (MET) and brief motivational intervention are adaptations of MI. Brief motivational intervention is the practice of using a single MI session in primary care settings with nonhelp-seeking substance abusing individuals while MET is typically limited to two to four sessions and serves as a prelude to other treatment approaches. These inteventions have been used successfully among alcoholics (Burke et al. 2003, Gentilello et al. 1999) and may be a promising adjunct therapy in other drug abuse treatment settings. However, one randomized study in 342 adolescent and young adult ecstasy and cocaine users found that brief motivational intervention was no more effective at inducing behavior change than the provision of information alone (Marsden et al. 2006). Another pilot study in methadone-maintained cocaine users also found no significant treatment benefit from brief motivational intervention, but did observe a modest impact on one crack cocaine measure, therefore supporting the undertaking of a larger trial (Mitcheson et al. 2007). Additional studies among cocaine users have shown that MET (Rohsenow et al. 2004) and brief motivational intervention (Stotts et al. 2001) were beneficial for patients with lower initial motivation. Peer-delivered (nonprofessional, race-matched, recovering cocaine users) MI may further enhance results as one study revealed cocaine levels in hair were reduced by 29% for those in the brief motivational intervention group compared to 4% in the control group at six months (Bernstein et al. 2005). Current literature suggests that MI is less effective than other psychotherapies for cocaine use disorders. MI may be useful in selected patients, but predictors of its success have yet to be identified.

## Individual and Group Drug Counseling

Psychotherapeutic approaches are often delivered in the context of multimodal treatment programs and nearly all substance abuse clinicians emphasize the importance of mutual-help groups such as Cocaine Anonymous. The efficacy of psychotherapy for drug abuse was initially established in several studies conducted in opiate-dependent patients receiving methadone maintenance treatment (Kleinman et al. 1990, Rounsaville et al. 1983, Woody et al. 1995, Woody and Munoz 2000). In one study cocaine and heroin using volunteers in three methadone community programs were randomly assigned to 24 weeks of drug counseling alone (control) or drug counseling plus supportive-expressive psychotherapy (treatment). While the treatment and control groups had similar rates of opiate-positive urine samples throughout the study, the treatment group had fewer cocaine-positive urine samples and required lower doses of methadone. Unlike the control group, the gains

associated with the treatment group persisted and in some cases strengthened for at least six months after the end of therapy (Woody et al. 1995). This study shows the effectiveness of combining two therapies, drug counseling plus supportive-expressive therapy, each individually shown to be effective for treatment of cocaine dependence. Many treatment programs combine elements of effective psychotherapies for cocaine dependence into an individualized program for patients. The Woody et al. (1995) provides evidence that such an approach can be effective.

Specific aspects of individual and group drug counseling focus directly on reducing or stopping the use of drugs. It also addresses related areas of impaired social and occupational function as well as the content and structure of the patient's individualized recovery program. Through its emphasis on short-term behavioral goals, drug counseling helps the patient develop coping strategies and tools for abstaining from drug use and then maintaining abstinence (McLellan et al. 1993).

This premise of increased efficacy of psychotherapy in drug abuse treatment was examined in a multicenter clinical trial, the Drug Abuse Collaborative Cocaine Treatment Study (CCTS), which compared the efficacy of four common psychosocial treatments for cocaine-dependent patients. Participants ($N$ = 487) were randomly assigned to one of the four manual-guided treatments: individual drug counseling + group drug counseling, cognitive–behavioral therapy + group drug counseling, supportive–expressive therapy + group drug counseling, or group drug counseling alone. In this study, those receiving individual drug counseling + group drug counseling showed the greatest improvement in substance use outcomes (Crits-Christoph et al. 1999). This study shows that comprehensive drug counseling treatments that provide both individual and group counseling can be effective for the treatment of cocaine use disorders.

## Systematic Cue Exposure and Coping Skills

One factor that may be an important precipitant to relapse to drug use is that of conditioned responses produced by repeated drug administration in the presence of specific stimuli. First described by Pavlov in 1927, this phenomenon has been reported for cocaine and other psychoactive drugs in animals and humans (Ehrman et al. 1992, O'Brien et al. 1993, Robbins et al. 1997, 1999). Neuroimaging studies have linked cue-induced craving to the limbic region involved in memory, learning, and pleasurable activities such as sex (Childress et al. 1999, Garavan et al. 2000). Research has shown that cocaine abusers exhibit increased limbic activation when watching videos containing cocaine-related scenes. Control subjects with no history of cocaine use show no limbic activation in response to these cues (Childress et al. 1999). Furthermore, while sexually explicit scenes activate the same brain structures in cocaine users and nonusers, the level of activation is less for the cocaine users (Garavan et al. 2000).

Cocaine abusers often report intense craving, arousal, and palpitations when they encounter objects, persons, or situations that remind them of cocaine use. Such cues often result in relapse. Systematic cue exposure and extinction has been studied as a treatment for cocaine addiction (Ehrman et al. 1992, Monti et al. 1997, Rohsenow et al. 2004). To reduce cue-triggered relapse, a treatment technique has been developed that links cue exposure in a clinical setting and teaches cocaine users to control drug use by recognizing these cues (also called triggers) and their responses. Cue exposure is combined with the teaching of coping skills to address high-risk situations. Patients develop skills for how to avoid or modify the trigger situation when possible. For unavoidable triggers, patients are helped to establish a repertoire of cognitive and behavioral skills to disrupt the behavioral chain leading to cocaine abuse. A controlled trial showed that patients in cue-exposure therapy who relapsed had significantly fewer cocaine-using days than did a control group (Monti et al. 1997).

## Physician–Patient Relationship Considerations

The treatment of cocaine use disorders should be undertaken in the context of a thorough understanding of the disease (Table 58–4). The physician should develop individual treatment plans for patients based on the presenting complaints and symptoms related to cocaine abuse and any abstinence syndrome. Treatment plans include assessment for psychiatric and medical illnesses, pharmacological interventions, psychotherapy and other psychosocial interventions. A working knowledge of the course of cocaine use disorders is helpful in educating patients with the goal of gaining insight as to what kinds of symptoms may occur and the temporal relationship of such symptoms (e.g., craving) to cocaine abstinence. Patients with an understanding of what to expect over the course of treatment may be better

**Table 58–4 Cocaine Use Disorders: Recovery and Treatment**

| Parameter | Acute abstinence | Withdrawal phase | Extinction phase |
|---|---|---|---|
| Duration | Several hours to 4 days | 1–10 weeks | 3–12 months |
| Treatment | Symptomatic may need hospitalization for medical or psychiatric care and assessment | Initiate psychotherapy<br>Individual/group therapy<br>Self-help groups, other therapies, e.g., family, marital, individual, as needed | Continue psychotherapy, decrease intensity with continued abstinence; self-help groups and additional interventions developed for individual patients as needed |
| Pharmacotherapy | Benzodiazepines for anxiety, agitation, paranoia<br>High potency antipsychotics (sparingly) for severe psychosis or agitation | None FDA approved specific for cocaine use disorders Consider disulfiram for cocaine dependence or cocaine dependence-alcohol abuse/dependence<br>Psychotropics as needed for comorbid psychiatric disorders or cocaine-related disorders | Unusual to initiate in this phase Taper and discontinue pharmacotherapy for cocaine abuse and monitor clinically |

able to maintain abstinence while acquiring the skills necessary to permanently stop cocaine abuse.

The physician is the provider who will make decisions regarding pharmacotherapy for cocaine dependence. This is an important consideration because there are currently no medications for cocaine use disorders that are approved by the US Food and Drug Administration (FDA). Therefore, any decision to provide medication to assist with the maintenance of abstinence from cocaine abuse must be carefully considered with documentation of the rationale for medication choice, risks, and benefits of treatment, and informed consent from the patient. In making a decision concerning pharmacotherapy, consideration of multiple factors is necessary. Whether the patient is a candidate for pharmacotherapy should be determined on the basis of the individual's substance abuse history and current presentation and whether the patient has another psychiatric diagnosis that requires pharmacotherapy. Equally important, the physician must consider the medical status of the patient and current medication treatments as well as any potential interactions between possible pharmacotherapies for cocaine dependence being considered. Finally, the physician must also consider the risk of relapse to cocaine use while the patient is being treated with the medication and potential adverse interactions with cocaine or other illicit drugs.

The physician must also make an assessment of the therapeutic relationship including the strength of the bond between clinician and patient and the degree of trust that exists. This is important to determining whether the cocaine abuser is likely to adhere to the medication as prescribed and whether the patient will be comfortable discussing and processing relapses and/or obstacles to adherence before initiating pharmacological treatment for cocaine dependence. An individualized treatment plan must be developed and include a plan for assessment of the effectiveness of the pharmacotherapy treatment. This would include continued frequent assessment for adherence, adverse events and effectiveness of the medication treatment, continued participation in psychotherapies for cocaine dependence, and frequent urine toxicology screens to monitor illicit drug use. When possible, plasma concentrations of the medication used for treatment of cocaine dependence should be obtained to monitor adherence and determine optimal dosage. Another consideration is whether to dose medication in the clinic as a means of adherence monitoring and emphasizing the importance of the pharmacotherapy to the treatment process as part of the treatment plan. This has been used in cocaine treatment programs with good effect. While specifically developed for the use of disulfiram in the treatment of cocaine dependence (Higgins et al. 1993, Higgins and Budney 1993), administration of medication in the clinic can be adapted to other pharmacotherapies for cocaine use disorders as well.

## Pharmacotherapies for Cocaine Use Disorders

The development of pharmacological treatments for cocaine abuse has been based on the premise that an altered neurochemical substrate underlies the chronic, high-intensity (binge) use and acute abstinence/withdrawal that follows binge use. This neuroadaptation model has also served as the hypothetical underpinnings for a number of studies that have evaluated the clinical utility of psychotropic agents that, according to their pharmacological profiles, might possess anticraving properties, block euphoria, or decrease cocaine abstinence symptoms. The following section briefly reviews various pharmacotherapies that have been used for the treatment of cocaine abuse. To date, no medication has emerged as a pharmacotherapy approved by the FDA for the treatment of cocaine dependence.

### Dopaminergic Agents

Dopaminergic agents have been evaluated to ameliorate early withdrawal symptoms associated with cocaine abstinence. The theoretical basis of this treatment is that habitual use of cocaine results in central dopamine depletion and dopamine receptor supersensitivity. This altered state of dopaminergic function (or hypofunction) could be related to drug craving and other withdrawal symptoms that lead to repeated drug use, but might be corrected by use of a medication that enhances dopaminergic function.

Dopaminergic medications that have been evaluated in clinical trials and found not to be effective for the treatment of cocaine use disorders include amantadine (Gawin et al. 1989b, Handelsman et al. 1995, Kampman et al. 1996, Perez de los Cobos et al. 2001), bromocriptine, (Preston et al. 1992, Eiler et al. 1995, Handelsman et al. 1997, McCance-Katz and Kosten 1998, Boyarsky and McCance-Katz 2000) methylphenidate (Roache et al. 2000), mazindol (Malison et al. 1998b, Margolin et al. 1995a, Stine et al. 1995), buproprion (Margolin et al. 1995b, Oliveto et al. 2001), flupenthixol (Evans et al. 2001, Gawin et al. 1996), haloperidol (Kosten 1997, Ohuoha et al. 1997), risperidone (Grabowski et al. 2000, 2004) selegiline (Elkashef et al. 2003) and the D1 antagonist ecopipam (Haney et al. 2001, McCance-Katz et al. 2001, Nann-Vernotica et al. 2001). Although preclinical studies implicate dopamine in the reinforcing effects of cocaine, the lack of efficacy in the many clinical trials conducted with dopaminergic agents provides indirect evidence that reinforcing effects are likely to be mediated by multiple neurotransmitters and/or intracellular processes. Indeed, cocaine is also a potent inhibitor of the reuptake of serotonin and norepinephrine (see above), either or both of which may play a role in reinforcement.

One study may indicate some utility for amantadine as a short-term initial treatment for cocaine-dependent patients with severe cocaine withdrawal symptoms (Kampman et al. 2000). In a double-blind, placebo-controlled, study of 61 cocaine-dependent individuals, those with more severe cocaine withdrawal symptoms at the beginning of the trial and who received amantadine showed greater reductions in the number of cocaine-positive urine toxicologies during treatment (Kampman et al. 2000). These results appear to be consistent with those from earlier studies indicating that amantadine might be effective in reduction of craving during the early stages of cocaine abstinence, however, the effectiveness of the medication diminishes after 3–4 weeks of treatment (Giannini et al. 1989, Kosten et al. 1992). Therefore, if this drug is to be used, the duration of pharmacotherapy treatment should not exceed 1 month. Replication of these findings would provide stronger evidence for amantadine as an initial and short-term pharmacotherapy for those with severe cocaine withdrawal.

The US National Institute on Drug Abuse (NIDA) has a medication development program for developing treatment

for cocaine abuse. One component of this effort is the Clinical Research Efficacy Screening Trial (CREST) whose goal is to rapidly identify potential treatments that should be further evaluated. Two dopaminergic agents, carbergoline (Shoptaw et al. 2005) and reserpine (Berger et al. 2005) have recently shown enough promise to undergo further clinical efficacy trials. These trials are still ongoing to date.

## Desipramine

Desipramine was one of the earliest drugs explored as a potential cocaine pharmacotherapy. The rationale of using this tricyclic antidepressant as a treatment for cocaine use disorders was that desipramine treatment might reverse cocaine-induced postsynaptic dopaminergic receptor supersensitivity (McCance-Katz and Kosten 1998). Rather than acting as a general antidepressant in cocaine abusers who do not have major affective disorders, desipramine could act as a specific antianhedonic agent in this population. Whereas the positive aspects of antidepressants such as desipramine for treatment of cocaine abuse include lack of abuse liability and acceptance by patients, a significant disadvantage lies in the delayed onset of effect (approximately two weeks).

Findings from controlled clinical trials with desipramine in cocaine abusers have been mixed. An early study of 72 cocaine-abusing participants yielded encouraging results (Gawin et al. 1989a). Desipramine at dosages of 200–250 mg/day significantly decreased cocaine use. However, other clinical trials reported mixed results that were overall negative in terms of desipramine's effectiveness for the treatment of cocaine dependence (Arndt et al. 1992, Levin and Lehman 1991). In a controlled clinical trial that examined the efficacy of desipramine and psychotherapy alone or in combination as a treatment for ambulatory cocaine abusers, all groups showed significant improvement in treatment retention and a reduction in cocaine use at 12 weeks. None of the treatments, desipramine versus psychotherapy or desipramine versus combined psychotherapy and medication were clearly superior (Carroll et al. 1994a). Desipramine was more effective for subjects with lower cocaine consumption (1–2.5 g/week) or depression, indicating possible subgroups for whom this treatment might be helpful (Carroll et al. 1995b).

## Serotonergic Agents

The rationale for the exploration of drugs with serotonergic properties as cocaine pharmacotherapies is multifold. The potency of cocaine as an inhibitor of serotonin (5-HT) uptake actually exceeds that of dopamine by twofold to fourfold (Ritz et al. 1989). Animal studies have shown that "knockout" mice lacking serotonin genes were more motivated to self-administer cocaine than normal mice and were also more sensitive to cocaine's effects (Sora et al. 1998). It has been speculated that 5-HT may exert a dampening effect on the euphoria associated with cocaine use. Selective serotonin reuptake inhibitors (SSRIs) have been shown to displace cocaine completely from serotonergic binding sites in the hippocampus and partially displace it in the basal ganglia and cortex (Biegon et al. 1992). Despite promising preclinical findings, SSRIs, have not proven useful for the treatment of cocaine use disorders (Gonsai et al. 2002, Grabowski et al. 1995, Schmitz et al. 2001a). Focus now is turning towards other serotenergic drugs like the 5-$HT_3$ receptor antagonist, odansetron which is currently marketed as an antiemetic. 5-$HT_3$ receptors are indirect inhibitors of cortico-mesolimbic dopamine release (Bloom and Morales 1998). A 10-week, controlled, clinical pilot trial among 63 treatment-seeking volunteers revealed that the group receiving odansetron 4 mg twice daily had the lowest dropout rate among all treatment groups (0, 0.25 mg, 1 mg, or 4 mg twice daily) and a greater improvement in percentage of participants with a cocaine-free week compared with the placebo group. However, the placebo group did better than the 1 mg twice daily odansetron group suggesting a nonlinear dose-response (Johnson et al. 2006). A larger scale study with balanced treatment groups needs to be performed to confirm these findings.

## GABAergic Agents

The neurotransmitter γ-aminobutyric acid (GABA) inhibits dopamine release and reduces the reinforcing effects of cocaine in animals (Brebner et al. 2002). Two GABAergic medications that have been evaluated in clinical trials and found not to be effective for the treatment of cocaine use disorders include gabapentin (Berger et al. 2005, Bisaga et al. 2006, Gonzalez et al. 2007, Hart et al. 2007) and valproate (Reid et al. 2005, Tennant et al. 1993. Baclofen, however, is showing some promise for the treatment of cocaine dependence. This agent is a $GABA_B$ receptor agonist marketed as a muscle relaxant and currently is the only specific $GABA_B$ compound available for human testing. Though baclofen's sedative properties complicate the interpretation of animal studies, it appears that baclofen may produce a specific attenuation of cocaine reinforcement that does not interfere will all appetitive behaviours (i.e. food-reinforced responding) (Roberts et al. 1996). It is postulated that the mechanism of inhibition of drug reinforcement is in part through modulation of forebrain dopamine. In human brain imaging studies (Childress et al. 1999, 2000), experienced cocaine users were given 7–10 days of baclofen 10–20 mg twice daily to allow a gradual induction and minimize the contribution of any initial sedative effects. When compared to placebo, baclofen reduced video cocaine cue-induced craving and cue-induced activation of anterior cingulate and amygdala brain regions. Clinical studies involving baclofen have also been promising. In an open-label trial ($n$=10), baclofen 20 mg three times daily reduced self-reported craving and cocaine use (verified by urine toxicology) in nine of the 10 volunteers for an average of five weeks (Ling et al. 1998). Reduction in cocaine use as indicated by urine drug screening has been reported in baclofen-treated (20 mg thrice daily) patients in a randomized, placebo-controlled trial (Shoptaw et al. 2003). Collectively, preclinical and preliminary clinical study results highlight the potential for baclofen or future $GABA_B$ receptor agonists to be utilized as anti-relapse agents. An adequately powered clinical study needs to be performed to confirm these findings.

Tiagabine is marketed as an antiepileptic medication and acts as an inhibitor of presynaptic reuptake of GABA to increase functional GABA activity in synapses. A human laboratory study was performed in which cocaine was given in the presence of tiagabine. Tiagabine treatment did not affect cocaine-induced cardiovascular measures, but attenuated the subjective ratings of "stimulated" and "crave cocaine" (Sofuoglu et al. 2005). Additionally, a

10-week, placebo controlled clinical trial in 76 methadone–maintained, cocaine abusers found that tiagabine 24 mg/day significantly increased the proportion of cocaine-free urine samples compared to gabapentin and placebo arms (Gonzalez et al. 2007). Further clinical trials in nonmethadone maintained patients would be useful in elucidating whether tiagabine has any clinical utility as a treatment for cocaine dependence.

Two other GABAergic agents display potential and require further study. Topiramate is an antiepileptic medication that enhances GABA activity by potentiating its effect on chloride ion channels and acting as a glutamate receptor antagonist. A pilot study in volunteers who were able to remain abstinent during a two-week baseline period and then started topiramate showed reduced cocaine relapse than those randomly assigned to placebo (Kampman et al. 2004). Vigabatrin is also marketed as an antiepileptic drug outside of the US, but has not been approved in the US because of concern over visual field defects that seems to occur after long term use (Kalviainen et al. 1999, Lawden et al. 1999, Manuchehri et al. 2000, Miller et al. 1999). This agent is a selective, irreversible inhibitor of GABA transamine, a main enzyme that metabolizes GABA. Though a nine-week, follow-up, ocular safety study in cocaine and methamphetamine users did not produce any visual field defects or alterations in visual acuity (Brodie et al. 2005, Fechtner et al. 2006), larger and longer term safety studies need to be performed and an understanding of the severity and reversibility of this adverse event needs to be established in order to determine the risk versus benefits of using vigabatrin to treat cocaine dependence. At this time, vigabatrin should not be used in the treatment of cocaine dependence.

## Miscellaneous Agents

### Naltrexone

Naltrexone is an opiate antagonist approved for the treatment of alcohol and opiate dependence. It has also been evaluated as a possible treatment for cocaine dependence. The rationale for use of naltrexone for cocaine addiction is that opiate pathways may be important to the euphoric effect of cocaine; antagonism of this pathway might decrease the reinforcing effects of cocaine and, therefore, cocaine use (Sofuoglu et al. 2003). Results from clinical trials have been mixed. Two double-blind, randomized, placebo-controlled trials ($N$=90) were conducted in subjects with comorbid alcohol and cocaine use disorders using naltrexone (50 mg/day) (Modesto-Lowe et al. 1997, Hersh et al. 1998). Naltrexone was found not to be effective in reducing cocaine use or craving. In contrast, a study undertaken in the same patient population higher naltrexone dose (150 mg/day) and a longer treatment period (12 weeks) was positive (Oslin et al. 1999). The study reported that both alcohol and cocaine use was significantly reduced among those who completed the study (8 out of 15 subjects). Similar results were reported from another controlled clinical trial examining the joint action of naltrexone in combination with relapse prevention therapy (RPT) (Schmitz et al. 2001b). In this study, 85 cocaine-dependent participants who achieved initial abstinence were randomized into one of four cells: naltrexone (0 or 50 mg) and RPT or drug counseling over 12-weeks of outpatient treatment. Those receiving the combination of naltrexone 50 mg and RPT had less cocaine use than those randomized to the other conditions. Yet, a follow-up trial in dually dependent cocaine and alcohol users failed to replicate these findings (Schmitz et al. 2004) and adds to growing evidence that standard doses of naltrexone (50 mg/day) in cocaine-alcohol-dependent patients are insufficient. These conflicting results also suggest that the effectiveness of naltrexone may depend on multiple factors including other substance comorbidity, length of treatment, and type of psychotherapeutic intervention. More research is necessary to examine these factors.

### Disulfiram

Numerous studies have reported results of the use of disulfiram as a treatment for cocaine dependence (Suh et al. 2006) and disulfiram has been noted as the most promising pharmacotherapy being developed for cocaine dependence (Vocci and Elkashef 2005). Disulfiram, a general inhibitor of aldehyde dehydrogenases, is currently approved as a treatment for alcohol dependence. Disulfiram prevents the metabolism of acetaldehyde, an intermediary in alcohol metabolism, whose buildup produces noxious reaction when alcohol is consumed. Because disulfiram prevents the ingestion of alcohol with cocaine, a common practice of cocaine users wanting to potentiate euphoria or alleviate dysphoric and stimulant effects of binge cocaine use, it was hypothesized to be a possible treatment for cocaine dependence by preventing concomitant alcohol use. Earlier pilot studies reported that disulfiram at 250 mg/day decreased both cocaine and alcohol use (Carroll et al. 1993, Higgins et al. 1993). Human laboratory studies were undertaken in which cocaine and disulfiram were administered in combination. These studies have shown some evidence that disulfiram increases unwanted effects of cocaine (e.g., anxiety) and that a significant interaction between these two drugs occurs when cocaine is administered nasally or intravenously (Baker et al. 2007, Hameedi et al. 1995, McCance-Katz et al. 1998b). At doses of 62.5, 250 and 500 mg/day, disulfiram treatment increased plasma cocaine concentrations significantly (McCance-Katz et al. 1998b, Baker et al. 2006). However, in one study, following intravenous cocaine administration, disulfiram significantly decreased cocaine subjective effects including "any high," "cocaine high" and 'rush' without significantly increasing cocaine-associated cardiovascular responses (Baker et al. 2006).

A controlled clinical trial examined disulfiram treatment alone and in combination with either cognitive–behavioral therapy or 12-step facilitation therapy. In this study of 122 patients with comorbid cocaine and alcohol dependence, disulfiram was found to be associated with better treatment retention and decreased cocaine and alcohol use (Carroll et al. 1998). The best outcomes occurred in those randomized to receive psychotherapy with disulfiram treatment. Subsequently, a 1-year follow-up evaluation was conducted with 96 participants in this study which showed that the effects of disulfiram on reductions in cocaine and alcohol use were sustained (Carroll et al. 2000). Though the number of participants that remained completely abstinent from cocaine use at 1-year follow-up were small (n = 14), 78% were receiving disulfiram. Another encouraging finding was that the initiation of abstinence for even brief periods of time within the initial treatment period was associated with significantly

better substance abuse treatment outcomes during follow-up (Carroll et al. 2000). A later study by the same researchers employed a more sophisticated design among 121 cocaine-abusing outpatients. Volunteers were randomized to one of four groups for 12 weeks for treatment: disulfiram 250 mg/day plus cognitive-behavior therapy (CBT), placebo plus CBT, disulfiram 250 mg/day plus interpersonal psychotherapy (IPT), and placebo plus IPT. Participants assigned to disulfiram reduced their cocaine use significantly more than those on placebo, and those assigned to CBT reduced their cocaine use significantly more than those assigned to IPT. Further, those who benefited the most from disulfiram plus CBT were not alcohol dependent at baseline or fully abstained from drinking during treatment (Carroll et al. 2004).

Disulfiram has also shown promise in treating opioid-dependent, cocaine abusers who are concomitantly treated with methadone or buprenorphine (Petrakis et al. 2000, George et al. 2000). In the first study, treatment medication (disulfiram 250 mg/day or placebo) for 67 volunteers was placed directly into methadone liquid daily for 12 weeks. Patients in the disulfiram group significantly reduced their frequency and quantity of cocaine use. The efficacy of disulfiram was not different between drinking and non-drinking groups, indicating a direct effect of disulfiram on cocaine intake (Petrakis et al. 2000). In 20 buprenorphine-maintained patients, treatment (disulfiram 250 mg/day or placebo) was dispensed at the same time as the buprenorphine daily for 12 weeks. Those on disulfiram achieved abstinence more quickly and remained abstinent for a greater number of weeks when compared to those on placebo. The number of cocaine-negative urine tests were also higher in the disulfiram group (George et al. 2000).

It was originally thought that disulfiram may exert its therapeutic effects by preventing alcohol use with cocaine. However, studies have shown that disulfiram efficacy between alcohol consumers and nonconsumers is similar (Carroll et al. 2004, Petrakis et al. 2000). Disulfiram may be decreasing cocaine use by inhibiting dopamine beta-hydroxylase (DßH), an enzyme that catalyzes the conversion of dopamine to norepinephrine in peripheral and central noradrenergic neurons (Vaccari et al. 1996). Inhibition of DßH results in a decrease in norepinephrine in selected areas of the brain (Goldstein and Nakajima 1967, Karamanakos et al. 2001) and leads to a corresponding increase in central levels of dopamine which may act synergistically with the unpleasant stimulant effects associated with cocaine use. This could produce an aversive response to cocaine (McCance-Katz et al. 1998b) and lead to a reduction in cocaine use. An alternative explanation for the decreased cocaine-associated effects with disulfiram treatment could lie in its effects on the serotonin system. Attenuation of positive subjective effects of cocaine with enhanced serotonin neurotransmission have been reported (Walsh et al. 1994). Cocaine alters serotonergic function by blockade of serotonin reuptake. Disulfiram might inhibit the conversion of serotonin to its principle metabolite, 5-hydroxyindoleacetic acid and lead to an increase in the metabolite 5-hydroxytryptohol (5-HTOL) (Beck et al. 1980, 1986, 1995). Increased 5-HTOL levels have been associated with adverse events including headache, fatigue and diarrhea (Helander and Some 2000). The effects of 5-HTOL in the context of cocaine ingestion might negatively impact the perception of cocaine effects and contribute to the reductions in "high" and "rush" that were observed in one human laboratory study (Baker et al. 2006). Other possible mechanisms may contribute to effects of disulfiram on cocaine responses but these have yet to be elucidated. Taken in total, these findings indicate considerable promise for the development of disulfiram in a dose range of 62.5–250 mg daily as a treatment for cocaine dependence. Further clinical trials with this medication appear warranted.

### Carbamazepine

Carbamazepine is an anticonvulsant medication hypothesized to have potential as a therapy for cocaine abuse because of its ability to reverse cocaine-induced seizure kindling in an animal model and to reverse the dopamine receptor supersensitivity that results from chronic cocaine use (Kosten 1998). However, a recent meta-analysis conducted on five, randomized, controlled, trials with a total of 455 subjects enrolled, reported that carbamazipine is not effective in reducing cocaine use (Lima et al. 2001).

## Agonist-like, Substitution Therapy

One approach to the treatment of drug dependence is to administer drugs that can substitute for the drug on which the patient is dependent. The best example of such treatment is that of methadone maintenance therapy for heroin/prescription opioid dependence where the physiological withdrawal associated with opioid dependence is prevented and the euphoria associated with illicit opioid administration is blocked with chronic treatment (Ling et al. 1994). This type of treatment for opioid dependence has had an important positive impact on public health. Methadone maintenance therapy has been shown to improve life functioning as well as to decrease criminal behavior and needle sharing which has been associated with increases human immunodeficiency virus risk (Ball et al. 1988, Simpson et al. 1982). As with other drugs of dependence, such as opioids and nicotine, the research of agonist-like therapy for cocaine dependence is undertaken with caution in the US where concern that this type of therapy could result in widespread abuse and pose health risks is a significant consideration. However, several substitution medications for stimulant dependence have been evaluated in preclinical and clinical trials (Grabowski et al. 2004).

Oral formulations of cocaine (i.e. tea infusions, tablets) have been studied in Peru for coca paste smokers with overall results showing a significant reduction in relapse to heavy use and cravings (Llosa 1994, 1996). Additionally, in a phase II clinical trial, oral cocaine was administered over a range of doses (0–100 mg/day) for ten days (Walsh et al. 2000). Researchers found that oral cocaine modestly attenuated subjective and physiological responses to intravenous cocaine challenges. Similar results were produced in another study in which intravenous cocaethylene, a pharmacologically active cocaine homolog formed by transesterfication of cocaine in the presence of alcohol, was given over 6 hours before a cocaine challenge was administered (Baker et al. 2006). No adverse cardiovascular effects were reported. Cocaethylene has been found to have a longer half-life relative to cocaine (Hart et al. 2000), an important factor in medications development since the drug might lend itself to

a formulation that might be administered conveniently (e.g., once daily or less frequently).

Dexamphetamine (also known as dextroamphetamine and d-amphetamine), a drug marketed for attention deficit hyperactivity disorder and narcolepsy has shown modest positive results for the treatment of cocaine dependence in three clinical trials. In one 14-week placebo-controlled study, 30 cocaine dependent participants were assigned 60 mg/day dexamphetamine or placebo (Shearer et al. 2003). Retention was equivalent between the two treatment groups. However, dexamphetamine reduced cocaine use, criminal activity, cocaine cravings and signs of dependence when compared to the placebo group. In another 13-week, double-blind, placebo-controlled, trial ($n = 114$), cocaine positive drug screens were reduced with increasing dexamphetamine doses (15 mg/day titrated to 30 mg/day versus 30 mg/day titrated to 60 mg/day), though results were not statistically significant (Grabowski et al. 2001). A later 26-week ($n = 94$) study by the same group treated cocaine- and heroin-dependent volunteers with methadone and varying doses of dexamphetamine (0–60 mg/day) and found that cocaine intake significantly declined in the 30–60 mg/day group compared to the lower dose and placebo groups (Grabowski et al. 2004). With the exception of one case of psychosis (Shearer et al. 2003) in a participant who concurrently used methamphetamine and who had not disclosed a history of drug induced psychotic episodes, there were no other reported cardiovascular or psychiatric adverse events in these three clinical trials.

Modafinil is a stimulant-like medication marketed for the treatment of excessive sleepiness. The mechanism of action of this agent is controversial and currently remains not fully understood. It has been shown that modafinil promotes feelings of well-being (Beusterien et al. 1999) and has stimulatory effects that are largely opposite to cocaine withdrawal symptoms. Abuse liability studies have shown that abuse potential is modest (Jasinski 2000, Rush et al. 2002, Warot et al. 1993), therefore making modafinil an important candidate as a substitution treatment for cocaine dependence. Case reports of stimulant abusers treated with modafinil have shown decreased craving for amphetamines and another one decreased craving and less use of cocaine (Malcolm et al. 2002). A double-blind, placebo-controlled, cocaine challenge study with modafinil 200 and 400 mg/day was performed in seven nontreatment seeking-cocaine-dependent volunteers (Dackis et al. 2003). No additive effects between cocaine and modafinil on cardiovascular parameters were noted and subjects reported attenuation of cocaine effects on the Addiction Research Center Inventory (ARCI) Amphetamine Scale (a measure of drug euphoria). Another cocaine challenge study in 12 cocaine-dependent individuals identified no harmful pharmacokinetic interaction between modafinil and cocaine (Donovan et al. 2005) and though this was an open-label study, found that modafinil significantly dampened Visual Analog Scale measures of cocaine effects (Malcolm et al. 2006). To date, one randomized, double-blind, placebo-controlled, pilot study examining the efficacy of modafinil among 62 cocaine-dependent outpatients has been published (Dackis et al. 2005). Patients receiving modafinil 400 mg/day for eight weeks provided significantly fewer urine samples positive for cocaine metabolite and were more likely to achieve a protracted period of cocaine abstinence when compared to those on placebo. However, the results from this trial are conflicted as there was no significant modafinil effect on the rate of patient-reported cocaine use. Possibilities for these findings might possibly include dilute urine samples that did not show the presence of cocaine metabolite or urine testing not coincident with participant drug use, as well as a problem with the assay itself. Further well-designed research is warranted in order to determine whether modafinil may have efficacy in the treatment of cocaine dependence.

## Ongoing Medications Development for Cocaine Use Disorders

Medications development continues for cocaine use disorders. Several novel approaches have been discussed in the literature and some clinical trials are ongoing. A cocaine vaccine is being developed that may reduce or halt cocaine abuse. The vaccine is structurally similar to cocaine, but is coupled to a carrier protein that prevents rapid metabolism, thus making it possible to mount an immune response to cocaine by sequestering cocaine molecules in the bloodstream and preventing cocaine entry to the brain, thus preventing cocaine-associated euphoria and reinforcement (Fox 1997, Martell et al. 2005). Animal studies have shown that the anti-cocaine vaccine effectively blocked physiological and behavioral effects of cocaine (Carrera et al. 2000, 2001, Fox et al. 1996, Kantak et al. 2000, 2001). Further, the efficacy of the vaccine in preventing cocaine self-administration was examined using a rat model for cocaine relapse (Carrera et al. 2000). As compared to controls, vaccinated animals did not reinstate cocaine self-administration behavior when given a noncontingent cocaine infusion on two consecutive days. Upon double and triple infusions, 38–62% of vaccinated animals did not reinstate cocaine self-administration as compared with cocaine self-administration reinstatement in all control animals (Carrera et al. 2000). Initial human studies have shown the cocaine vaccine to have no serious adverse effects during 12 months of follow-up and confirm that it does induce cocaine-specific IgG cocaine antibodies in a time and dose dependent manner (Kosten et al. 2002, Martell et al. 2005). The most recent human trial examined initial efficacy of the vaccine and found that the higher dose vaccine (2000 mcg) was more likely to maintain cocaine-free urines than the lower dose (400 mcg). Of those in both groups who used cocaine during a 14-week study interval, 100% reported diminution of cocaine's euphoric effects. At six months, 89% of the low dose and 43% of the high dose group had relapsed, but the majority of volunteers (> 60%) continued to report attenuation of cocaine's euphoric effects (Martell et al. 2005).

Unlike typical antibodies, catalytic antibodies can selectively catalyze cocaine molecules via a wide range of reactions, from hydrolysis of esters and amides to pericyclic reactions (Cashman et al. 2000, Lerner et al. 1991, and Schultz and Lerner 1995). In rodent studies, catalytic antibody administration blocked toxicity of cocaine in rats and blocked cocaine reinforcement (Mets et al. 1998). This approach could provide a new and effective treatment for acute cocaine intoxication, but no human studies have yet been performed.

Acupuncture is an ancient Chinese therapy that may hold promise for treatment of cocaine use disorders. Earlier studies of acupuncture in cocaine addiction treatment

suffered from the lack of a rigorous scientific design and were inconclusive. One well designed study with an active acupuncture control procedure found that the patients who received acupuncture were more likely to be free from cocaine use during an eight-week study period than were control subjects as measured by cocaine-negative urine toxicology samples (Avants et al. 2000). However, a very large follow-up study by these same researchers did not have encouraging results for the use of acupuncture alone to treat cocaine dependence. This study was performed throughout 6 community-based clinics in the US and enrolled 620 cocaine-dependent patients. Volunteers were randomly placed in one of three groups: acupuncture, a needle-insertion control, or a relaxation control. Treatments and concurrent counseling were offered five times weekly for eight weeks. Counseling sessions were poorly attended and there was no difference between conditions based on urine samples or treatment retention (Margolin et al. 2002). A subsequent smaller study did show that adding spirituality focused group therapy to acupuncture was more beneficial than acupuncture alone (Margolin et al. 2005). However, there was not a spirituality focused group therapy alone condition in this study. At this time there is no evidence to support the use of acupuncture alone for the treatment of cocaine dependence.

## Common Problems in Management

Several common problems are encountered in the treatment of patients with cocaine use disorders. These include (1) relapse to cocaine use, (2) comorbid psychiatric disorders, (3) comorbid substance use disorders, (4) premature treatment termination, and (5) treatment refractoriness.

### Relapse to Cocaine Use

The psychological addiction to cocaine is powerful and the risk for relapse to cocaine use is high during treatment. This is particularly true in outpatient treatment settings when patients are often subject to exposure to the persons, places, and things that remind them of their cocaine use which can induce strong craving. Patients who are recently abstinent are at high risk for relapse because they often experience dysphoria with the cocaine withdrawal syndrome and contrast that mood state with the memory of cocaine-induced euphoria, which can be overwhelming and precipitate a new cycle of cocaine abuse. Patients early in the treatment process have not developed the coping skills that might help them to overcome drug craving and have not experienced success in remaining abstinent which is also important to helping the patient to gain control over cocaine craving.

It is important to discuss the risk of relapse with patients in cocaine treatment in general terms and to specifically address the concerns of individual patients regarding their relapse potential. This can provide the basis for building a repertoire of coping skills and assist with processing a relapse, should it occur, in a therapeutic manner. For outpatients who are unable to initiate and maintain abstinence, consideration of a higher level of care such as a partial hospital program, day treatment program, or a long-term program (e.g., therapeutic community) is appropriate.

### Diagnosis of Other Mental Disorders

The diagnosis of comorbid mental disorders can be difficult in the presence of cocaine use disorders. Affective and psychotic symptoms are common during cocaine intoxication. Affective symptoms may continue for up to several weeks following the initiation of abstinence. In addition, abuse of and/or relapse to cocaine and/or other illicit drug use is common and can exacerbate psychiatric symptoms. It can be difficult to determine whether psychiatric symptoms represent a comorbid psychiatric disorder, an extended withdrawal syndrome, or the continuation of substance abuse. In general, affective and psychotic symptoms that occur during intoxication remit within hours to days of cessation of cocaine use and require limited use of psychotropic medication. Affective symptoms related to cocaine withdrawal may continue for weeks, but generally improve over time and are not severe enough to meet criteria for a specific Axis I disorder such as major depressive episode. The patient whose psychiatric symptoms worsen despite treatment for cocaine use disorders, and in whom regular (2–3 times weekly) urine toxicology screens reveal continued abstinence is likely to have a comorbid psychiatric disorder and should receive appropriate psychiatric treatment. Those with a history of a well-documented psychiatric disorder that has occurred in the absence of drug abuse or predated the substance use disorder should also be observed closely for the development of a comorbid psychiatric illness during treatment with psychiatric intervention as needed. It is important to note, however, that the previous diagnosis of a mental illness in a person with a cocaine use disorder (or other substance use disorders), may not be accurate. Previous diagnoses made in the context of recent cocaine abuse or during withdrawal may actually reflect psychiatric symptoms related to cocaine intoxication or withdrawal. Careful evaluation of the patient at the time of presentation is needed to determine the presence of a comorbid psychiatric disorder regardless of prior diagnoses unless the patient has well-characterized mental illness and/or is known to the clinician. Common misdiagnoses include bipolar disorder, major depression, schizoaffective disorder, attention deficit hyperactivity disorder, generalized anxiety disorder, and panic attacks. While these disorders can be present concomitantly in those with cocaine use disorders, the overlap of symptoms between these mental disorders and those related to cocaine abuse mandate the careful evaluation of every patient known to have a cocaine disorder prior to making the diagnosis of a comorbid mental illness.

### Comorbid Substance Use Disorders

Abuse of or dependence on other illicit drugs or alcohol is common in patients with cocaine use disorders. It has been reported that 62–90% of cocaine abusers are also alcohol abusers and simultaneous use of these substances is common (Brookoff et al. 1996, Grant and Harford 1990, Heil et al. 2001, McCance-Katz et al. 1993). Cocaine abusers report that simultaneous use of alcohol can prolong euphoric effects and relieve the negative effects of binge cocaine use including stimulant effects such as anxiety, agitation, and paranoia, or to decrease acute abstinence symptoms (Hart et al. 2000, McCance et al. 1995). Opiates and benzodiazepines serve this purpose for some with primary cocaine use disorders, but this is less common. However, cocaine abuse by opiate dependent persons is common and may enhance or alter opiate-induced euphoria (e.g., heroin and cocaine taken simultaneously is termed a "speedball")

or decrease the sedative effects of opiates (Grella et al. 1997, Mello and Negus 2001, Negus et al. 1998). It is important to establish whether patients presenting for treatment also abuse other substances such as alcohol or opiates because physical dependence on these substances is common and may require medical withdrawal. If there is dependence on other drugs or alcohol, the medical withdrawal process should proceed prior to initiation of cocaine abuse treatment to ensure medical safety and optimize the possibility of effective treatment of the cocaine use disorder.

Patients presenting for treatment of cocaine use disorders must have a full evaluation with urine drug screen to determine current use of other drugs. An alcohol breath test (Breathalyzer) can be used to detect recent alcohol use and a urine test for ethyl glucuronide is now available and shows evidence of alcohol use for up to four days (Wurst et al. 2003). Laboratory findings including liver function (ALT, AST) and mean corpuscular volume (MCV) and carbohydrate deficient transferrin (Bortolotti et al. 2006) can also be helpful in the assessment of alcohol abuse.

The treatment of comorbid substance use disorders is important because continued abuse of other substances is associated with relapse to cocaine abuse. Treatment of comorbid substance use disorders can be integrated into the treatment program for cocaine abuse. Psychotherapies effective for cocaine abuse are also effective for other abused substances and individuals with comorbid disorders can address multiple substance use problems in individual and group counseling formats. Pharmacotherapies for other substance use disorders can be undertaken in conjunction with cocaine abuse treatment as well. For example, nicotine replacement therapy or naltrexone or disulfiram for alcohol use disorders can be a part of the individualized treatment plan for patients with cocaine abuse and nicotine dependence or alcohol dependence, respectively.

## Cocaine–Alcohol Abuse and Cocaethylene

Simultaneous abuse of cocaine and alcohol occurs frequently. One consequence of the coabuse of these substances is the formation of cocaethylene. Cocaethylene is a pharmacologically active homolog and metabolite of cocaine, formed by transesterification of cocaine in the presence of ethanol. Cocaethylene and cocaine share pharmacological characteristics in blocking dopamine uptake, inhibiting ligand binding to the dopamine transporter, and increasing dopamine concentration in brain microdialysate. Cocaethylene has less effect on serotonin and norepinephrine transporters than does cocaine (Bradberry et al. 1993, Henning and Wilson 1996, Jatlow et al. 1991, McCance-Katz et al. 1993). Although cocaethylene is equipotent to cocaine as a reinforcer in animals, it is less potent than cocaine in humans and has a longer elimination half-life than cocaine (Hart et al. 2000, McCance et al. 1995). However, the effects of cocaine, alcohol, and cocaethylene in combination could produce increased toxicity in co-abusers of these substances (Jatlow et al. 1991, McCance-Katz et al. 1998a, 2001). Because of this, it is important to recognize and provide treatment for cocaine and alcohol abuse when they occur simultaneously.

## Premature Treatment Termination

Premature treatment termination or treatment dropout is common in patients with cocaine use disorders. The most common reason for this occurrence is relapse to cocaine use. Patients are at especially high risk for relapse in the early stages of treatment when craving is most severe and coping skills and support systems are poorly developed. Addressing this possibility from the initial contact with the patient can be helpful in that it provides the patient with an understanding of what difficulties to expect in the process of abstinence initiation. In addition, discussion of the possibility of relapse and the potential for leaving treatment can also be used to help the individual to develop a plan for preventing this occurrence, which will improve the chance that the patient will ultimately be successful in treatment. Processing previous treatments and reasons for failure early in treatment can be helpful in determination of what level of care is most appropriate for the patient.

## Treatment Refractoriness

The term "treatment refractoriness" sometimes implies a lack of response to a therapeutic trial of a pharmacotherapy. In the case of cocaine dependence, however, there is no FDA-approved, effective pharmacotherapy with which to treat the disorder, therefore, the term relates to a different set of occurrences in the treatment setting. Recidivism to cocaine use, treatment dropout, and multiple treatment experiences are common. Such problems are a reflection of the severity of illness and parameters of relative treatment refractoriness. Comorbid substance use and psychiatric disorders contribute to treatment refractoriness. Lack of accurate diagnosis and treatment contributes to relapse potential in the form of continued exposure to high-risk situations and lifestyle instability that are associated with ongoing substance abuse. Continued psychiatric symptoms that patients attempt to relieve through cocaine use contribute to poor treatment outcome.

The psychological addiction associated with cocaine abuse can be disabling. Because physiological dependence, if it does occur, generally does not require pharmacotherapy, treatment referrals for patients with primary cocaine dependence, and no other acute medical or psychiatric condition, are generally to an outpatient drug abuse treatment clinic. Those unable to initiate and maintain sobriety in an outpatient drug treatment program should be evaluated for more intensive forms of treatment. Management of these individuals should include consideration of a variety of options including pharmacotherapy (see the earlier section on pharmacotherapy for cocaine abuse) and programs that offer a graded increase in structure. Such patients may need initial detoxification from another drug or alcohol that could require several days of inpatient treatment. Those who need intensive outpatient treatment often attend 5 days a week initially, and sessions last an average of 4 hours. There is a gradual reduction in the number of sessions per week as the period of sobriety lengthens. Such programs are of flexible duration but a full program usually requires at least 12 weeks. This program can be followed with resumption of the outpatient treatment clinic level of care, which takes place fewer days per week and with shorter sessions. Those with comorbid psychiatric disorders should be referred to specialty treatment programs that address both substance use disorders and mental illness. These programs differ from traditional substance abuse treatment programs in that they have a dual treatment orientation, increased use

of psychotropic medications, longer lengths of stay, and greater tolerance for relapse and medication nonadherence. As compared to standard drug abuse treatment programs, they tend to have a more severe case mix, a higher 180-day readmission rate, and a higher rate of psychiatric aftercare in the 30 days after discharge (Swindle et al. 1995).

Patients who have failed other forms of treatment may be referred to residential programs. Residential programs vary in length and must be tailored to the needs of the patient. Such programs can be important to the initiation of abstinence. These programs allow sufficient time in a drug-free and supportive environment so that the recovery process can begin, as well as provide adequate time for reduction of drug craving and acquisition of effective relapse prevention skills.

## Psychiatric Comorbidity

Treatment-seeking cocaine abusers have significant rates of psychiatric disorders (Carroll et al. 1997). Cocaine abuse may adversely affect the psychiatric disorder, with the occurrence of symptoms of psychosis, depression, or suicidal ideation that worsen during the course of cocaine use (Dixon 1999, Roy 2001, Schmitz et al. 2000, Serper et al. 1999). Patients with underlying psychotic disorders may exhibit exacerbation of psychotic symptoms in response to stimulants at doses that would not be psychotogenic in those without psychotic disorders or vulnerability to psychotic disorders (Yui et al. 1999). Those with psychotic disorders need pharmacological management and often require hospitalization as a result of exacerbations of the mental disorder that occur with cocaine abuse (Buckley 1998). Furthermore, those with comorbid psychiatric disorders complicated by substance abuse often require increased doses of psychotropic medications to control symptoms.

The diagnosis of comorbid psychiatric disorders in cocaine abusers is often challenging because the onset of many such disorders occurs in adolescence or early adulthood, the same period as for the onset of cocaine addiction. This makes determination of primary versus secondary diagnosis difficult. However, careful developmental and family histories and attention to the presence or absence of psychiatric symptoms during periods of sobriety can be helpful and may assist in diagnostic accuracy which is essential to providing adequate treatment. Worsening psychiatric symptoms in the context of abstinence from cocaine is also an indication of the presence of a concomitant mental illness.

Symptoms associated with substance use disorders, including acute intoxication and withdrawal syndromes, may be mistaken for mental illness, resulting in misdiagnosis and inappropriate psychiatric treatment that usually includes psychotropic medication. This can foster denial in that substance abusers who sometimes attribute drug abuse to a psychiatric or emotional problem leading to resistance to treatment for the substance disorder. Denial of a substance disorder when it is, in fact, the correct underlying diagnosis, results in ineffective treatment and continued drug abuse. The pervasive nature of substance use disorders requires increased emphasis on substance abuse education for mental health providers, attention to substance abuse in the history taking and ongoing treatment, and urine drug screens as a routine part of treatment. It is important to understand that treating a mental illness in a patient with both a substance use disorder and mental illness will not provide effective treatment for the substance use disorder. Conversely, treatment of only the substance use disorder in a patient with comorbid disorders will not effectively treat the mental illness. Such patients must receive concurrent treatment for substance use disorders and mental disorders.

## Comorbid Mood Disorders or Attention Deficit Hyperactivity Disorder

Comorbid mood disorders and residual attention deficit hyperactivity disorder (ADHD) may occur in cocaine abusers (Biederman et al. 1999). Lifetime prevalence of mood and anxiety disorders among those with cocaine use disorders in treatment have been reported to be as high as 48% for men and 70% for women (Brady and Randall 1999). Depressive disorders have been some of the most commonly diagnosed comorbid disorders among those with cocaine use disorders (Brown et al. 1998, Compton et al. 2000). Those diagnosed with cocaine use disorders and depression have greater overall distress and poorer functioning than those without depression (Schmitz et al. 2000). Lifetime prevalence of major depressive disorder has been shown to be significantly correlated with suicide attempts in those with cocaine use disorders.

Several lines of evidence point to the integral relationship of depression to cocaine use disorders. First, the symptoms associated with the cocaine withdrawal syndrome are similar to those observed in depressive disorders (Uslaner et al. 1999). Second, lifetime years of cocaine use is one of the major predictors for depression among cocaine users (McMahon et al. 1999). Third, severity of depressive symptoms in treatment-seeking cocaine abusers is associated with poorer treatment retention, greater urge and craving, and more intensive response to cocaine effects (Brown et al. 1998, Sofuoglu et al. 2001, Uslaner et al. 1999). These findings support the need for more intensive treatment approaches for patients with comorbid disorders. Antidepressant treatment is an important component of treatment for those with comorbid disorders. While antidepressants provide effective treatment for reduction of depressive symptoms, they have little effect on cocaine use (Carroll et al. 1997, Schmitz et al. 2001a). It is also worth mentioning that while comorbid depression may complicate diagnosis and treatment regimen in this population, neither a diagnosis of depression nor severity of depressive symptoms predicts treatment outcome (Brown et al. 1998).

Children with ADHD have been shown to have an increased risk of developing cocaine and other substance use disorders (Clure et al. 1999, Levin et al. 1998a, Schubiner et al. 2000). While methylphenidate is the most effective treatment for ADHD (Jensen 2000, Smith et al. 2000), many clinicians fear that methylphenidate treatment for those with comorbid ADHD and substance use disorders may increase the risk of substance abuse, particularly stimulant abuse. However, a longitudinal study has shown that treating children diagnosed with ADHD with stimulant medications, including methylphenidate, reduced the risk of substance abuse and dependence by 84% (Biederman et al. 1999). In addition, clinical reports have indicated that methylphenidate is effective for treating ADHD in those with cocaine dependence (McCance-Katz and Schottenfeld

1995). Clinical trials, however, investigating the efficacy of methylphenidate for the treatment of cocaine dependence and ADHD have shown mixed results. A pilot study showed that methylphenidate treatment for those with comorbid ADHD and cocaine abuse reduced ADHD symptoms, cocaine use, craving, and positive urine toxicologies for cocaine (Levin et al. 1998b). A larger 14-week study by the same researchers involved 106 participants (Levin et al. 2007). This placebo-controlled, double-blinded study found no difference in retention rate and improvement in ADHD symptoms between treatment groups. Yet, further analyses revealed that among ADHD treatment responders, those receiving methylphenidate were associated with a reduction in cocaine use compared to those receiving placebo. Another placebo-controlled, double-blinded, study in 48 dually diagnosed volunteers found an improvement in ADHD symptoms in the methylphenidate group, but no between-group difference in cocaine use or cravings (Schubiner et al. 2002).

## Antisocial Personality Disorder

Another psychiatric disorder common in cocaine abusers is antisocial personality disorder (Compton et al. 2000). Identification of this disorder is important because it is associated with poor treatment outcome in those with cocaine use disorders. There is no clear indication for use of pharmacotherapy in patients with antisocial personality disorder. If pharmacotherapy for a cocaine use disorder were to be considered, it would be best to stabilize the patient for several weeks and monitor symptoms carefully to determine need for medication treatment.

## Psychotic Disorders

Cocaine abuse is widely recognized as a significant clinical problem in patients with schizophrenia with a reported prevalence of 15–60% (Buckley 1998, Dixon 1999, Mauri et al. 2006, Swartz et al. 2006). Cocaine use may hasten the onset of a psychotic disorder in a vulnerable patient and may exacerbate the course of the illness by precipitating psychotic relapse (Volkow 2001) or by causing depression, anxiety, insomnia, agitation, or aggressiveness (Buckley 1998, Serper et al. 1999). Comorbid substance use disorders in those with psychotic disorders are associated with a variety of poor outcomes, including increased psychotic symptoms, poor treatment compliance, violence, medical illness (e.g., HIV infection), and poor social function that result in a higher cost of medical/psychiatric care (Dixon 1999). These findings underscore the need to integrate substance abuse treatment and psychiatric care for this population. Cocaine and other substance abuse usually persist despite treatment with antipsychotic medications. The efficacy of newer atypical antipsychotic medications for reduction of substance abuse among the schizophrenic population is yet to be established, but clozapine has been shown to reduce alcohol, smoking, and cocaine use (Zimmet et al. 2000). However, clozapine has been associated with cardiovascular side effects including near-syncopy in those pretreated with clozapine and then administered cocaine in a laboratory setting (Farren et al. 2000, Zimmet et al. 2000). These findings contraindicate the use of clozapine in those with cocaine use disorders. Patients with schizophrenia who adhere to antipsychotic medications and remain in treatment have higher levels of abstinence and fewer days of hospitalization (Bennett et al. 2001, Dixon 1999, Krystal et al. 1999, Zimmet et al. 2000). Taken together, these findings highlight both the detrimental influence of cocaine abuse on the course of schizophrenia and the possibility that cocaine abuse may cause and/or perpetuate a psychotic disorder closely resembling schizophrenia. Specialized dual-diagnosis treatment programs that attend to both the psychiatric and substance use disorders in these patients have shown promising results and should be used when available for the treatment of these severely ill patients (Bennett et al. 2001, Krystal et al. 1999, Martino et al. 1995).

Clinical Vignette 1

Mr. A, a 22-year-old man, was admitted to an outpatient clinic for treatment of cocaine dependence. He reported a 3-year history of cocaine abuse and intranasal use of cocaine daily for several months before seeking treatment. The patient maintained abstinence during the initial weeks of treatment, but complained of difficulty sitting still in groups and of poor concentration. He also described a calming effect of cocaine on these chronic problems, which contributed to intensified drug craving. A psychiatric evaluation revealed a developmental history consistent with attention-deficit hyperactivity disorder (ADHD). The history of residual symptoms was also confirmed by the patient's significant other.

A trial of methylphenidate was initiated at 10 mg/day and increased to a dosage of 20 mg/day. Mr. A reported feeling calmer and better table to concentrate, with decreased cocaine craving. When methylphenidate was increased to 30 mg/day, Mr. A complained of abdominal discomfort and irritability in the evening, which reminded him of cocaine withdrawal symptoms. Although it was recommended that the dose be reduced to 20 mg/day, the patient was anxious about the occurrence of these symptoms and requested that the medication be discontinued because he feared relapse. Within several days of stopping the medication, the unwanted symptoms abated, but the ADHD symptoms returned. A trial of atomoxetine was initiated with titration to 80 mg/day with no reported side effects. The patient reported improvement in concentration and decreased motor activity. He continued outpatient treatment in a partial hospital program with a specialized track for those with mental illness and self-help groups.

**Final DSM-IV-TR Diagnoses**

Axis I: Cocaine dependence, Attention-Deficit/Hyperactivity Disorder
Axis II: Deferred
Axis III: None

Clinical Vignette 2

Mr. B is a 34-year-old divorced man with a 10-year history of freebase cocaine abuse characterized by weekly binge use of up to 6 g of cocaine and alcohol use reported as five beers several times per week with cocaine, but no other illicit drug use. He was admitted to the hospital emergency department with a chief complaint of visual hallucinations and paranoid ideation that developed

*(continues)*

Clinical Vignette 2 *continued*

during the course of several hours of binge cocaine use. On physical examination, he was noted to be agitated with mild tachycardia and hypertension, but there were no other concurrent medical illnesses.

Haloperidol 5 mg and lorazepam 2 mg were administered by intramuscular injection for treatment of psychosis and agitation, with rapid abatement in symptoms. The patient was transferred to an inpatient unit for further evaluation. Resolution of visual hallucinations and paranoia occurred within 24 hours. After two days of hypersomnia, intermittent anxiety, and mild depressive symptoms, he reported feeling better and began to engage in substance abuse treatment. He was discharged to an outpatient clinic for further treatment of cocaine and alcohol use disorders.

Final DSM-IV Diagnoses
Axis I: Cocaine dependence, alcohol abuse, cocaine intoxication, cocaine withdrawal
Axis II: Deferred
Axis III: None

Clinical Vignette 3

Ms. C. is a 25-year-old, single woman with a 2-year history of binge cocaine use by the smoked route of administration. In the past four months, she has increased her use of cocaine from once weekly to up to three binges weekly. Following a 12 hour binge, she presents to the emergency department complaining of depression, suicidal thoughts, poor concentration, and feelings of paranoia. She is agitated and tearful. She is admitted to the psychiatric inpatient unit for further evaluation and treatment. For the first two days, she is hypersomnolent and hyperphagic. She is isolative and appears depressed. By day five she is participating actively in unit therapies and is no longer suicidal. The treatment team refers her to ongoing outpatient substance abuse treatment. Final DSM-IV TR Diagnoses:

Axis I: Cocaine Dependence, Cocaine Withdrawal, Cocaine-Induced Mood Disorder
Axis II: Deferred
Axis III: None.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

The ICD-10 and DSM-IV-TR Criteria sets for Cocaine Intoxication and Withdrawal are similar except that the ICD-10 criteria set for Withdrawal includes drug-craving as an additional item.

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CHAPTER 59

# Substance Abuse: Phencyclidine Use Disorders

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## Phencyclidine Intoxication

Phencyclidine (1-(1-phenylcyclohexyl)piperidine) (PCP) was developed as a general anesthetic agent in the 1950s under the brand name Sernyl (Collins et al. 1960, Greifenstein et al. 1958, Johnstone et al. 1958). The drug was considered physiologically promising because of its lack of respiratory and cardiovascular depressant effects. In fact, patients under PCP anesthesia, rather than manifesting a state of relaxed sleep such as that induced by typical anesthetic agents, appeared semiconscious, with open eyes, fixed staring, flat facies, open mouth, rigid posturing, and waxy flexibility. Because of this apparent sharp dissociation from the environment without true unconsciousness, PCP and the related drug ketamine were classified as dissociative anesthetics (Corssen and Domino 1966).

Approximately 50% of patients anesthetized with PCP developed behavioral syndromes including agitation and hallucinations during emergence from anesthesia (Collins et al. 1960, Greifenstein et al. 1958, Johnstone et al. 1958). A substantial number of subjects developed postoperative psychotic reactions, which in some cases persisted up to 10 days (Greifenstein et al. 1958, Johnstone et al. 1958, Corssen and Domino 1966, Meyer et al. 1959). Trials of subanesthetic doses of PCP for treatment of chronic pain led to similar although less severe adverse reactions (Meyer et al. 1959). As a result, after 1965, PCP was limited to veterinary applications. Ketamine remains available for human anesthesia; side effects are less frequent and severe owing to the lower potency and shorter duration of action of ketamine compared with PCP.

Despite its well-documented aversive and disruptive behavioral effects, PCP emerged during the 1970s as a popular drug of abuse, increasing in popularity to the point that in 1979, 13% of high-school seniors had tried it (Johnston et al. 1994). Although PCP has never regained that remarkable level of popularity, it has remained a significant public health problem among certain populations and in certain geographical areas. Compared with most other drugs of abuse, PCP has more complex and potentially more harmful effects.

### Epidemiology

Illicit use of phencyclidine was first noted in 1965 in Los Angeles (Lerner and Burns 1978). The spread of the drug from California throughout the country was facilitated by its ease of synthesis compared with other drugs. At least six synthetic methods, some simple, are published in scientific journals (Allen et al, 1993). Surveys of street drug samples indicated that PCP was sold under many street names (Table 59–1) and frequently combined with or misrepresented as other substances (Lerner and Burns 1978, Siegel 1978). During the late 1970s and early 1980s, PCP gained considerable notoriety in the popular press not only as a leading drug of abuse but as one with particularly novel and devastating effects.

According to trends in emergency department visits, deaths, initiates entering drug treatment programs, and surveys, PCP abuse increased through the 1970s, peaked in 1978 to 1979, and then declined sharply through 1981, when indicators began to show a new increase through 1984 (Crider 1986). The decline in PCP use during the late 1970s and early 1980s may have resulted in part from a variety of public health and law enforcement activities, including a nationwide education campaign aimed at informing treatment programs, emergency departments health agencies, and medical examiner–coroner offices of PCP effects and treatment procedures. PCP was rescheduled from Schedule III to the much more restrictive Schedule II of the Controlled

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**Table 59–1 Street Names for Phencyclidine and Mixtures**

| Phencyclidine | Phencyclidine Mixtures and Analogues |
|---|---|
| Angel dust | Beam me up Scottie (crack dipped in PCP) |
| Animal trank | Blunt (marijuana and PCP in cigar wrapper) |
| Baby doll | Love boat (marijuana dipped in PCP) |
| Black whack | Peanut butter (PCP mixed in peanut butter) |
| Butt naked | Special K (ketamine) |
| Devil's dust | Tragic magic (crack dipped in PCP) |
| Elephant tranquilizer | Wet |
| Embalming fluid | Illy (marijuana treated with formaldehyde/formalin and PCP) |
| Gorilla biscuits | Hydro |
| Heaven | Fry |
| Hog | |
| Jet fuel | |
| Mad dog | |
| Peace pill | |
| Rocket fuel | |
| Talk to the angels | |
| Yellow fever | |
| Zombie weed | |

Substance Act on the basis of its limited legitimate uses and significant abuse potential. Several PCP analogues were placed in Schedule I. Required reporting of production of the precursor, piperidine, began in 1979; penalties for possession of PCP with intent to sell were increased at about the same time (Crider 1986).

In more recent years, indicators of PCP use have remained generally low; however, localized increases have been observed, in some cases associated with the use of new dosage forms (in particular, the use of "blunts," cigars filled with PCP-impregnated marijuana) (Community Epidemiology Work Group 1994).

As of 2006, the highest rates of PCP use during the past year were observed among 18−20-year-olds, followed by 12−17, 21−25, and 26−34-year-olds. 2.4% of high school seniors endorsed lifetime abuse and 0.7% endorsed past-year abuse (Johnson et al. xxxx). Rates were increased from 2004, but generally stable from rates since 1991. In 2005, among Americans aged 12 or older, it was estimated that 48,000 had used PCP within the past month, 164,000 within the past year, and 6,603,000 (2.7% of the population) within their lifetimes. These rates were stable from the year prior (Substance Abuse and Mental Health Services Administration 2001). In 2005, PCP misuse/abuse was detected in 7,535 Emergency Department visits, higher than the rate for LSD or other hallucinogens. This rate was also stable from the prior year (Substance Abuse and Mental Health Services Administration 2007). Related drugs included ketamine, which accounted for 275 visits and dextramethorphan, which accounted for over 12,000 visits. Both ketamine and mega-dose dextramethorphan (5−10x recommended dose) can produce clinical symptoms similar to that of PCP.

Clinical Vignette 1

A 22-year-old single man was brought to the emergency department by a friend who left without providing any information. The patient was severely agitated and hypervigilant, repeatedly looking over his shoulders and patrolling the examination room. Asked to explain, he said, "I'm scared. Something is after me. I can't say anything else." He was unable or unwilling to give any history. Vital signs and neurological examination findings were within normal limits. A urine sample was sent for qualitative toxicological analysis. The result, received 5 days later, was positive for PCP. His condition remained unchanged during 3 hr of observation in the emergency department. He spontaneously went to the telephone and called the friend who had brought him to the hospital but found himself unable to speak. He handed the telephone to the emergency department physician, who was able to obtain from the friend the information that the patient had smoked three PCP-impregnated marijuana cigarettes in a 12-hr period beginning 18 hr before admission. The friend stated that this had been the patient's first exposure to PCP: "He got scared and bummed out and begged me to take him to the hospital." A mental status examination revealed impaired attention and memory, with concrete interpretation of proverbs. He continued to complain of being frightened and to survey his surroundings continuously, saying, "I have to watch out or I could get hurt." He admitted to feeling in great danger from forces outside himself. He denied hallucinations. It was noted that the patient became more agitated after interviews or clinical interventions.

He was admitted to the psychiatry service, where treatment was initiated with haloperidol 2 mg three times a day, increasing to 5 mg three times daily by the third day. His mental status remained essentially unchanged from that observed in the emergency department until the end of the third week after admission, when he reported having intervals when he felt less agitated and free of his feelings of persecution. According to the staff, however, at times he was still observed looking back over his shoulder and muttering to himself. His nonpsychotic intervals gradually became more frequent. At the end of the fourth week, he began interacting with staff and visitors and participating in groups and other ward activities. At the beginning of the sixth week, mental status examination revealed no evidence of psychosis. Neuroleptic medication was discontinued without relapse. He gave a history of sporadic abuse of marijuana and cocaine during the previous 3 years. He contacted his parents, who traveled from the distant state in which they lived to participate in treatment and discharge planning. He was discharged directly to a long-term residential drug treatment program. Contacted 1 year later, he was living with his parents in the other state, participating in Narcotics Anonymous, and stated that he had been drug free since discharge from the hospital. He added, "Even if I ever use drugs again—and I hope I won't—I would never, ever use PCP."

**Comment**

This clinical vignette illustrates a purely psychiatric presentation of PCP psychosis, with no physical or neurological symptoms or signs 6 hr after the last dose of drug. Without the history obtained from the friend, the correct diagnosis would not have been made until the toxicology results were received. All of the patient's symptoms could have been accounted for by a non–drug-related psychiatric illness. The failure of the psychotic symptoms to respond to neuroleptic medication, and the patient's recovery by the sixth week, are typical of the prolonged PCP psychosis in an otherwise nonpsychotic individual.

In 1983, more than 66% of PCP-related deaths reported to the Drug Abuse Warning Network involved at least one other drug. Many of the PCP-related deaths were not the result of overdose or drug interaction or reaction, but the direct result of some external event facilitated by intoxication (e.g., homicides, accidents). The various manners of death (such as drowning and being shot by police) reported are consistent with the disorientation and violent aggressive behavior that can be stimulated by PCP (Crider 1986).

## Etiology and Pathophysiology

### Psychotomimetic Effects

The psychotomimetic effects of PCP result from its interaction with a unique high-affinity PCP receptor, demonstrated in 1979 (Zukin and Zukin 1979, Sircar et al. 1987), that selectively binds PCP-like drugs in rank order proportional to their behavioral potencies. By contrast, a wide variety of other drugs of abuse and neurotransmitters fail to bind to the PCP receptor at physiologically relevant concentrations (Zukin and Zukin 1979, Vincent et al. 1979, Sircar et al. 1987, Wong et al. 1988, Zukin et al. 1983). The PCP receptor is located within the ion channel gated by the N-methyl-d-aspartate (NMDA) receptor complex (Figure 59–1). When activated by binding of the major excitatory amino acid neurotransmitter of brain, l-glutamate, in the presence of the coagonist glycine, the cation channel gated by the NMDA receptor is activated, permitting influx of calcium ions. Binding of PCP-like drugs uncompetitively inhibits NMDA receptor activation by l-glutamate, thus disrupting NMDA receptor-mediated glutamatergic neurotransmission in a fashion that cannot be surmounted by increasing l-glutamate concentration. Such disruption of NMDA receptor function results in impairment of a number of mental functions including learning and memory (Handelman et al. 1987, Balster and Chait 197, Thompson et al. 1987, Butelman 1989, Moerschbaecher and Thompson 1983). In animals, exposure to PCP-type drugs has been shown to result in reversible microscopic changes, including vacuolization, in specific populations of brain neurons (Olney et al. 1989). The applicability of these findings to humans remains to be established.

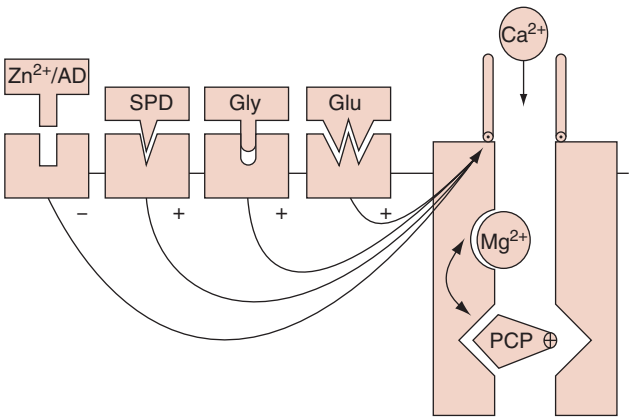



**Figure 59–1** *Schematic model of NMDA receptor functioning. After magnesium blockade is relieved by membrane depolarization, the cation channel gated by the NMDA receptor can be activated by binding of l-glutamate and glycine. Binding of PCP within the channel blocks ion flux. There are a number of other regulatory sites external to the channel, of which two are illustrated: A site at which polyamines such as spermidine (SPD) positively modulate activation induced by l-glutamate (Glu) and glycine (Gly); and a site at which zinc and tricyclic antidepressants (AD) negatively modulate activation.*

**Table 59–2 Single-Dose Effects of Intravenous Phencyclidine**

| |
|---|
| Withdrawal |
| Negativism |
| Catatonic posturing in some cases |
| Concrete, idiosyncratic, and bizarre thinking |
| Absence of significant physical or neurological findings |

The effects of low-dose PCP administration have been extensively studied in volunteers. In normal subjects (Table 59–2), single intravenous doses of 0.05−0.1 mg/Kg induced withdrawal, negativism, and in some cases catatonic posturing; thinking processes became concrete, idiosyncratic, and bizarre in the absence of significant physical or neurological findings; and drug effects persisted for 4−6 hr (Bakker and Amini 1961, Luby et al. 1959, Ban et al. 1961, Davies and Beech 1960, Domino and Luby 1981, Rodin et al. 1959). In contrast to lysergic acid diethylamide (LSD) or amphetamine (Domino and Luby 1981, Cohen et al 1961), PCP was noted to induce disturbances in symbolic thinking (Davies and Beech 1960, Cohen et al 1961), perception (Luby et al. 1959, Rosenbaum et al. 1959), and attention (Domino and Luby 1981) strikingly similar to those observed in schizophrenia. Administration of PCP to schizophrenic subjects caused exacerbation of illness-specific symptoms persisting up to several weeks (Luby et al. 1959, Domino and Luby 1981), suggesting that schizophrenic or preschizophrenic individuals may be at significantly increased risk of behavioral effects from PCP abuse. At the doses used in these studies, which were equivalent to the typical 5-mg street dose (Burns and Lerner 1976), serum PCP concentrations of 0.01−0.1 μM are attained. At such levels, the PCP receptor is the only target site that would be significantly occupied by the drug (Figure 59–2).

### Other Effects

Abusers often use PCP in higher or repeated doses leading to significantly higher serum concentrations than those associated selectively with psychotomimetic effects. In general, concentrations greater than 0.4 μM are associated with impairment of consciousness; at concentrations greater than 1.0 μM, coma, seizures, and respiratory arrest are common (Walberg et al. 1983, Pearce 1976). These neurological and metabolic effects result in part from interaction of PCP with sites other than the PCP-NMDA receptor, including catecholamine and indolamine reuptake sites (see Figure 59–2).

### Pharmacokinetics

PCP is extremely lipid soluble. As a result, it can reach its brain target sites after oral, parenteral, smoked, inhaled (McCarron et al. 1981), or topical administration. Another consequence of its lipophilicity is its tendency to accumulate in lipid tissues throughout the body, including the brain (James and Schnoll 1976, Misra et al. 1979). Flashbacks may result from mobilization of adipose stores, for example, by exercise (James and Schnoll 1976, Misra et al. 1979).

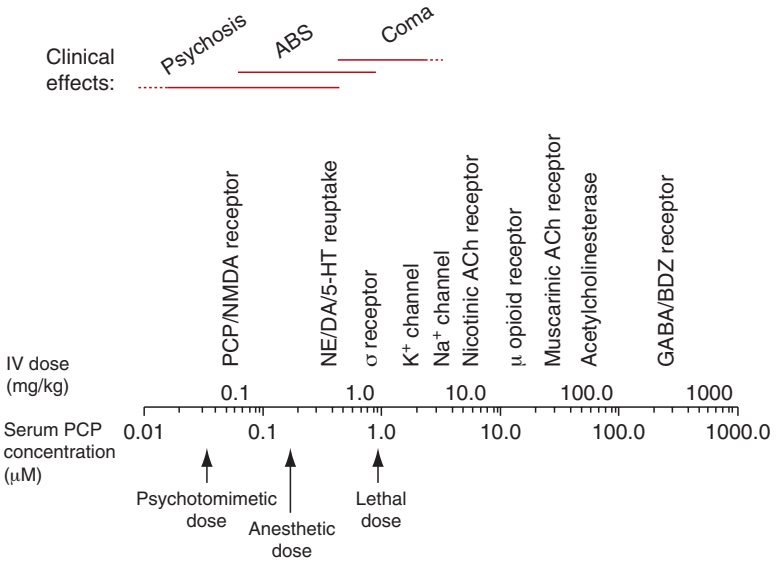



**Figure 59–2** *Dose range of PCP effects. Relationship of dose of PCP and PCP affinities for brain target sites to clinical effects is illustrated. Low psychotomimetic doses of PCP act selectively at the PCP site of the NMDA receptor–channel complex. ABS, Acute brain syndrome; ACh, acetylcholine; BDZ, benzodiazepine; DA, dopamine; GABA, (-aminobutyric acid; 5-HT, 5-hydroxytryptamine); NE, norepinephrine.*

Because of its p$K_a$ of 8.5, PCP is largely ionized in the stomach or urinary tract. However, in the nonacidic environment of the small intestine, PCP becomes nonionized and is readily reabsorbed across the intestinal mucosa; subsequent enterohepatic recirculation may account for the fluctuating clinical course often observed.

Metabolism of PCP occurs primarily in the liver. Both PCP (Cook et al. 1982) and hydroxylated metabolites (Wong and Biemann 1976) are excreted in the urine. The serum half-life of PCP has been reported to vary from 4−72 hr (Cook et al. 1982, Done et al. 1977). Its volume of distribution is 6.2 L/kg (Cook et al. 1982).

PCP can be detected in urine for approximately 7 days following single administration and 2−4 weeks following chronic use. Metabolism of PCP appears to be unaffected by alcohol, although its entry into CNS may be increased (Godley et al. 1991). In contrast, THC appears to inhibit PCP metabolism, leading to higher serum levels and prolonged serum half-life (Godley et al. 1991).

### Tolerance and Dependence

Tolerance to and dependence on PCP have not been formally investigated in humans. Clinical observations suggest that chronic PCP users are significantly less sensitive to a given dose than are casual users. In the case of ketamine, which shares the same fundamental mechanism of action as PCP, tolerance has been more formally observed in burn patients who require increased doses after a time to maintain the same level of analgesia (Carroll 1985). In laboratory animals, a twofold to fourfold shift to the right in the behavioral dose-response curve for PCP is observed in most studies, with indications that tolerance develops to a much greater extent with continuous administration (Balster 1986).

Signs of severe physical withdrawal have been noted in experimental animals when PCP is withdrawn after long-term administration (Balster 1986). In monkeys, even under circumstances in which physical withdrawal symptoms are minimal, normal behaviors are disrupted for a week or more after cessation of long-term PCP administration (Slifer et al. 1984). In humans, a single study indicated that one-third of 68 chronic PCP users had sought treatment to help them withdraw from PCP in the face of depressed mood, craving for the drug, and alterations in sleep and appetite that occurred when they attempted to cease drug use on their own (Tennant et al. 1981).

## Diagnosis and Differential Diagnosis

### Phenomenology and Variations in Presentation

Physicians must be alert to the wide spectrum of effects of PCP on multiple organ systems. Because fluctuations in serum levels may occur unpredictably, a patient being treated for apparently selective psychiatric or behavioral complications of PCP abuse may suddenly undergo radical alterations in medical status; emergency medical intervention may become necessary to avoid permanent organ damage or death. Any patient manifesting significant cardiovascular, respiratory, neurological, or metabolic derangement subsequent to PCP use should be evaluated and treated in a medical service; the psychiatrist plays a secondary role in diagnosis and treatment until physiological stability has been reached and sustained.

PCP-intoxicated patients may come to medical attention on the basis of alterations in mental status; bizarre or violent behavior; injuries sustained while intoxicated; or medical complications, such as rhabdomyolysis, hyperthermia, or seizures (Baldridge and Bessen 1990). As illicit ketamine use has increased significantly as part of the "club drug" phenomenon, it is important to remember that ketamine can induce the same spectrum of effects and complications, the chief difference from PCP being the much shorter duration of action of ketamine. In a series of 20 ketamine users presenting in Connecticut, the most frequent complications of ketamine abuse were severe agitation and rhabdomyolysis (Weiner et al. 2000).

### Psychiatric Presentation

The presenting symptoms may be predominantly or exclusively psychiatric, without significant alterations in level of consciousness, and may closely resemble an acute schizophrenic decompensation (Luisada 1978) with

concrete or illogical thinking, bizarre behavior, negativism, catatonic posturing, and echolalia. Subjective feelings and objective signs of "drunkenness" may or may not be present. Retrospective studies conducted during the period of widespread PCP abuse demonstrated that PCP psychosis could not reliably be distinguished from schizophrenia on the basis of presenting symptoms (Erard et al. 1980, Yesavage and Freeman 1978).

Studies of normal volunteers suggested that the acute psychosis induced by a single low dose of PCP usually lasts 4–6 hr (Javitt and Zukin 1991). However, in some PCP users, psychotic symptoms including hallucinations, delusions, paranoia, thought disorder, and catatonia, with intact consciousness, have been reported to persist from days to weeks after single doses (Burns and Lerner 1976, Allen and Young 1978, Rainey and Crowder 1975, McCarron et al. 1981). The frequency of such prolonged psychotic states after single doses has not been determined systematically. However, one study indicated that 25% of PCP-intoxicated patients required inpatient psychiatric admission (Allen and Young 1978). PCP psychosis can occur at undetectably low serum or urinary levels of the drug (Walberg et al. 1983, Pearce 1976). Sudden and impulsive violent and assaultive behaviors have been reported in PCP-intoxicated patients without previous histories of such conduct.

## Nonpsychiatric Presentation

In PCP intoxication, the central nervous, cardiovascular, respiratory, and peripheral autonomic systems are affected to degrees ranging from mild to catastrophic (Table 59–3).

The level of consciousness may vary from full alertness to coma. Coma of variable duration may occur spontaneously or after an episode of bizarre or violent behavior (McCarron et al. 1981). Prolonged coma due to continued drug absorption from ruptured ingested packages of PCP has been described (Jackson 1989).

Nystagmus (which may be horizontal, vertical, or rotatory) has been described in 57% of a series of 1,000 patients (McCarron et al. 1981). Consequences of PCP-induced central nervous system hyperexcitability may range from mildly increased deep tendon reflexes to grand mal seizures (observed in 31 of a series of 1,000 PCP-intoxicated patients) or status epilepticus (McCarron et al. 1981, Kessler et al. 1974). Seizures are usually generalized, but focal seizures or neurological deficits have been reported, probably on the basis of focal cerebral vasoconstriction (Crosley and Binet 1979). Other motor signs have been observed, such as generalized rigidity, localized dystonias, facial grimacing, and athetosis (McCarron et al. 1981).

**Table 59–3 Nonpsychiatric Findings in Phencyclidine Intoxication**

| |
|---|
| Altered level of consciousness |
| Central nervous system changes including nystagmus, hyperreflexia, and motor abnormalities |
| Hypertension |
| Cholinergic or anticholinergic signs |
| Hypothermia or hyperthermia |
| Myoglobinuria |

**DSM-IV-TR Criteria**

**Phencyclidine Intoxication**

A. Recent use of phencyclidine (or a related substance).
B. Clinically significant maladaptive behavioral changes (e.g., belligerence, assaultiveness, impulsiveness, unpredictability, psychomotor agitation, impaired judgment, or impaired social or occupational functioning) that developed during, or shortly after, phencyclidine use.
C. Within an hour (less when smoked, "snorted," or used intravenously), two (or more) of the following signs:
   (1) vertical or horizontal nystagmus
   (2) hypertension or tachycardia
   (3) numbness or diminished responsiveness to pain
   (4) ataxia
   (5) dysarthria
   (6) muscle rigidity
   (7) seizures or coma
   (8) hyperacusis
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

*Specify* if: With perceptual disturbances

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Hypertension, one of the most frequent physical findings, was described in 57% of 1,000 patients evaluated, and it was found to be usually mild and self-limiting, but 4% had severe hypertension, and some remained hypertensive for days (McCarron et al. 1981). One fatal case of hypertensive crisis late in the course of PCP intoxication has been described (Eastman and Cohen 1975). Tachycardia occurs in 30% of patients. PCP-induced tachypnea can progress to periodic breathing and respiratory arrest (Hurlbut 1991). Autonomic signs seen in PCP intoxication may be cholinergic (diaphoresis, bronchospasm, miosis, salivation, bronchorrhea) or anticholinergic (mydriasis, urinary retention) (McCarron et al. 1981).

Hypothermia and hyperthermia have been observed (McCarron et al. 1981). Hyperthermia may reach malignant proportions (Thompson 1979).

Rhabdomyolysis frequently results from a combination of PCP-induced muscle contractions and trauma occurring in relation to injuries sustained as a result of behavioral effects. Acute renal failure can result from myoglobinuria (Patel and Connor 1986).

In children, PCP intoxication may result from ingestion of remnants of used PCP-impregnated cigarettes or from inhalation of sidestream smoke (Karp et al. 1980, Schwartz and Einhorn 1986, Welch and Correa 1980). Young children often present with impaired consciousness, ataxia, nystagmus, staring (Karp et al. 1980, Schwartz and Einhorn

1986, Welch and Correa 1980), or apnea (Burns et al 1975). Aggressive or violent behavior is unusual in this population (Baldridge and Bessen 1990).

## Assessment

### Special Issues in Psychiatric Examination and History

The disruption of normal cognitive and memory function by PCP frequently renders patients unable to give an accurate history, including a history of having used PCP. Therefore, assay of urine or blood for drugs may be the only way to establish the diagnosis. PCP is frequently taken in forms in which it has been used to adulterate other drugs, such as marijuana and cocaine, often without the user's knowledge. One of the most alarming manifestations of this phenomenon is a preparation known variously as "illy," "hydro," "wet," or "fry." This mixture consists of a marijuana cigarette or blunt (sometimes tobacco) combined with embalming fluid (i.e., formaldehyde/formalin), but frequently also contains PCP, which may or may not be advertised to the user (Nelson 1999). "Fry" users are evidently aware that the combination may have extremely dangerous consequences, including impaired motor skills, incoherent behavior, paranoia, aggressive behaviors and long-term mental health problems (Peters et al. 2005), yet may not be fully aware of what is in the combination (Singer et al. 2005). Urine toxicological studies of individuals who use these mixtures frequently contain PCP, as well as other drugs (Singer et al. 2005). PCP precursors and synthesis by-products have been detected as well (Nelson 1999). In one recent study, use of frys was found in approximately 11% of substance abusing youths (Peters et al. 2003).

By disrupting sensory pathways, PCP frequently renders users hypersensitive to environmental stimuli to the extent that physical examination or psychiatric interview may cause severe agitation. If PCP intoxication is suspected, measures should be taken from the outset to minimize sensory input. The patient should be evaluated in a quiet, darkened room with the minimal necessary number of medical staff present. Assessments may need to be interrupted periodically.

### Relevant Physical Examination and Laboratory Findings

Vital signs should be obtained immediately on presentation. Temperature, blood pressure, and respiratory rate are dose-dependently increased by PCP and may be of a magnitude requiring emergency medical treatment to avoid the potentially fatal complications of malignant hyperthermia, hypertensive crisis, and respiratory arrest. In all cases, monitoring of vital signs should continue at 2–4-hr intervals throughout treatment, because serum PCP levels may increase spontaneously as a result of mobilization of drug from lipid stores or enterohepatic recirculation.

Analgesic and behavioral changes induced by PCP not only predispose patients to physical injury but also mask these injuries, which may be found only with careful physical examination (Baldridge and Bessen 1990).

On neurological examination, nystagmus and ataxia, although not conclusive, are strongly suggestive of PCP intoxication. Examination of deep tendon reflexes helps

Clinical Vignette 2

An 18-year-old high-school girl was transferred from the medical service to the psychiatric service 1 week after admission to the hospital. After friends had been unable to contact her for several days, the police were called and found the patient semiconscious on the floor of her apartment. While being transported to the hospital, the patient suddenly freed herself from restraints, assaulted one of the emergency medical personnel, and then lost consciousness. On presentation in the emergency department, blood pressure was noted to be 210/107 mm Hg, temperature was 104.1°F, and respiratory rate was 34/min. Extensive bruising was apparent on her back and lower extremities. While dehydration and electrolyte imbalances were being corrected, the patient had a grand mal seizure progressing to status epilepticus, which was treated with intravenous diazepam. Toxicological assays showed the presence of PCP in her urine; urinalysis was positive for heme.

She was admitted to the medical intensive care unit, where intensive measures to stabilize her condition were instituted. Vital and neurological signs fluctuated for the next 3 days as she slipped in and out of coma. On the fourth day, the patient regained consciousness but was delirious. She attempted to assault a nurse and was placed in four-point restraints. On transfer to the psychiatry service, temperature and blood pressure were within normal limits; deep tendon reflexes were mildly to moderately hyperactive. She was oriented to time and place, but cognitive functions were globally deficient. She refused neuroleptic medication. For the first 2 days on the service, she was mute. On the third day, she began stating repeatedly, "I was dead and I came back to life." On several occasions, staff reported that she appeared to be responding to internal stimuli, but she denied it. On the fifth day, she was able to give a history. She stated that PCP was her drug of choice and that she had used it for several years on a weekly basis. Before admission, she had obtained a new supply, in liquid form, from a source she had not previously used. She had dipped approximately 10 cigarettes in the liquid and had smoked an unknown number of them in a period of several hours. She "got high" but then "died and knew I was dead." She explained that she remembered suddenly falling to the floor and being unable to see, move, or hear for a long time. She recalled being aware of her condition and situation before being found but had no memory of events in the hospital until shortly before her transfer to the psychiatry service. She stated, "I'm a little crazy but that will clear up in another few days; it always has before. Dust [PCP] does that to a person." Mental status examination now revealed significant improvement in cognitive functioning. On the seventh day, she signed out against medical advice. During the discharge interview, she continued to maintain that she had literally died and come back to life. Three weeks after discharge, she was admitted to another hospital for treatment of PCP intoxication.

**Comment**

This clinical vignette illustrates the emergence of a purely psychotic picture after resolution of catastrophic medical complications of high-dose PCP intoxication. It also illustrates PCP dependence in a chronic user.

to establish the degree of nervous system hyperexcitability. Crossed or clonic deep tendon reflexes alert the physician to the possibility of subsequent seizures.

Because PCP is usually supplied in combination with other drugs and is often misrepresented, toxicological analysis of urine or blood is essential. However, there may be circumstances in which PCP may not be detected in urine even if it is present in the body, for example, when the urine is alkaline. On the other hand, in chronic PCP users, drug may be detected in urine up to 30 days after last use (Simpson et al. 1982). It must be kept in mind that false-positive PCP results can be caused by the presence of venlafaxine and O-desmethylvenlafaxine (Sena et al. 2002), or dextromethorphan (Shier et al. 2000). Urine should be tested for heme because of the possible complication of myoglobinuria.

Blood and urine samples should be sent for toxicological analysis. In addition, serum uric acid, creatine kinase, aspartate transaminase, and alanine transaminase elevations, common findings in PCP intoxication, were found to be associated with rhabdomyolysis in 22 of 1,000 cases (McCarron et al. 1981).

### Differential Diagnosis

The presence of nystagmus and hypertension with mental status changes should raise the possibility of PCP intoxication. Because of the close resemblance of both the acute and the prolonged forms of PCP psychosis to schizophrenia, and the increased sensitivity of patients with schizophrenia to the psychotomimetic effects of the drug, an underlying schizophrenia spectrum disorder should be considered, particularly if paranoia or thought disorder persists beyond 4–6 weeks after last use of PCP. PCP psychosis may also resemble mania or other mood disorders. Therefore, in all cases, a detailed psychiatric history should be obtained. Robust response of psychotic symptoms to treatment with neuroleptics would favor a diagnosis other than simple PCP psychosis.

PCP psychosis is readily distinguishable from LSD psychosis in normal as well as in individuals with schizophrenia by the lack of typical LSD effects, such as synesthesia. The cluster of psychotic symptoms, hypertension, and stereotypy may be seen in both PCP psychosis and chronic amphetamine psychosis; in such cases, accurate histories and toxicological analysis are particularly important.

In cases involving prominent PCP-induced neurological, cardiovascular, or metabolic derangement, encephalitis, head injury, postictal state, and primary metabolic disorders must be ruled out (Lerner and Burns 1978). Either intoxication with or withdrawal from sedative-hypnotics may be associated with nystagmus (Baldridge and Bessen 1990). Neuroleptic malignant syndrome should be ruled out in the differential diagnosis of PCP-induced hyperthermia and muscle rigidity (Baldridge and Bessen 1990).

### Course and Natural History

As drug levels decline, the clinical picture recedes in 5–21 days through periods of moderating neurological, autonomic, and metabolic impairments to a stage at which only psychiatric impairments are apparent. Once the physical symptoms and signs have cleared, the period of simple PCP psychosis may last 1 day to 6 weeks, whether or not neuroleptics are administered, during which the psychiatric symptoms and signs abate gradually and progressively. Even after complete recovery, flashbacks may occur if PCP sequestered in lipid stores is mobilized. Any underlying psychiatric disorders can be detected and evaluated only after complete resolution of the drug-induced psychosis. Although systematic studies in humans have not been carried out, clinical experience predicts a high likelihood of resumption of PCP use after recovery from PCP psychosis.

### Overall Goals of Treatment

The hierarchy of treatment goals begins with detection and treatment of physical manifestations of PCP intoxication. Equally important are measures to anticipate PCP-induced impulsive, violent behaviors and provide appropriate protection for the patient and others. The patient must then be closely observed during the period of PCP-induced psychosis, which may persist for weeks after resolution of physical symptoms and signs. Finally, the possibly dramatic medical and psychiatric presentation and its resolution must not divert the attention of the psychiatrist from full assessment and treatment of the patient's drug-seeking behavior.

## Standard Approach to Treatment

### Physician-Patient Relationship in Psychiatric Management

In contrast to psychotic states induced by drugs such as LSD, in which "talking the patient down" (by actively distracting the patient from his LSD-induced sensory distortions and convincing the patient that his or her distress stems from nothing more than the temporary effects of a drug that soon will wear off) may be highly effective, no such effort should be made in the case of PCP psychosis, particularly during the period of acute intoxication, because of the risk of sensory overload that can lead to dramatically increased agitation. The risk of sudden and unpredictable impulsive, violent behavior can also be increased by sensory stimulation.

### Somatic Treatments

There is no pharmacological competitive antagonist for PCP, in contrast to opiates and benzodiazepines. Any compound competing with PCP for binding to its recognition site within the NMDA receptor–gated ion channel would also block the channel and prevent ion flux, thus exerting PCP-like effects. Oral or intramuscular benzodiazepines are recommended for agitation. The degree to which PCP induced behavioral symptoms respond to antipsychotics remains controversial. Higher potency neuroleptics (e.g., haloperidol, pimozide) have been found to be superior to lower potency agents (e.g., chlorpromazine) (Giannini et al. 1984) and may also be effective against ketamine-induced psychosis (Giannini et al. 2000). Further low potency neuroleptics such as chlorpromazine may be more likely to decrease seizure threshold. However, such agents may also act as effective alpha-blocking agents, and may assist in the management of hypertension. Ascorbic acid has been reported to significantly augment the therapeutic effects of haloperidol (Giannini et al. 1987). Because of rela-

tively low rates of PCP induced psychosis, relatively little clinical literature is available concerning efficacy of atypical antipsychotics, relative to older high potency agents. Nevertheless, atypical antipsychotics, especially clozapine, have proven highly effective in animal models against both acute (Dunn et al. 2007, Geyer and Ellenbroek 2003, Linn et al. 2003,) and sustained (Abdul-Monim et al. 2006, Elsworth et al. 2007, Didriksen et al. 2007, Amitai et al. 2007, Dunn and Killcross 2006, Hashimoto et al. 2005) effects of phencyclidine administration.

In addition to antipsychotics, other classes of agent have been investigated. Meperidine was shown to be effective in one study (Giannini et al. 1985), although its use has not achieved widespread popularity. Benzodiazepines or other sedative /hypnotic are frequently employed for the management of agitation or excitation during acute PCP intoxication (Leikin et al. 1989), and have proven useful also in experimentally induced ketamine psychosis (Krystal et al. 1988). The antiepileptic drug lamotrigine has also proven effective against ketamine-induced psychosis (Anand et al. 2000), although clinical data are lacking. Diphenhydramine has been reported to be effective in the management of PCP-induced dystonias but not generalized rigidity (Leikin et al. 1989).

Because PCP is frequently taken in combination with other drugs, a toxicological analysis of urine and/or blood for other drugs besides PCP is essential. Urine should also be tested for heme because of the potential complication of myoglobinura. Serum uric acid, CPK and SGOT/SGPT elevations may also be associated with PCP-induced rhabdomyolysis.

Because of the large volume of distribution of PCP, dialysis is ineffective as a means of clearing the drug from circulation. Gastric lavage using activated charcoal may be effective in binding PCP and increasing its nonrenal clearance (Picchioni and Consroe 1979, Jones et al 1987). Cathartics, such as sorbitol or magnesium citrate, may also increase transit time and thus decrease intenstinal absorption. Because PCP is a weak base, urinary acidification is frequently recommended. Decreasing urinary pH from 7−5 and forcing diuresis may increase PCP clearance 100-fold. However, since 90% of PCP is metabolized by the liver, and only 10% is excreted unchanged in urine, the benefits of the increased renal clearance may not outweigh the risks (Tong et al. 1975). Further, because of the possibility of electrolyte imbalance and additional nephrotoxic effects, this should be considered a measure of last resort.

Recent drug development activities may produce more specific and effective pharmacotherapy of PCP-induced abnormalities. Large doses of oral glycine, which recently have been used safely and effectively in treatment of negative symptoms of schizophrenia in research studies in humans (Javitt 2006, Javitt et al. 2004), have been shown to reverse PCP-induced dopaminergic dysregulation in rodents (Toth and Lajtha 1986). Similar effects are seen with agents, such as the naturally occurring compound sarcosine, that increase glycine levels by blocking brain glycine transporters (Javitt 2006, Javitt et al. 2004, Toth and Lajtha 1986). Increased glycine concentrations at the NMDA receptor would increase channel activation and promote diffusion of PCP molecules from their binding sites within the channel. A single dose of a monoclonal anti-PCP IgG antibody has been found to produce profound reduction of the effects of daily PCP doses for two weeks or longer in rats (Hardin 2002). Hopefully such strategies will be tested and validated in humans.

## Special Features Influencing Treatment

### Psychiatric Comorbidity

PCP psychosis may be clinically indistinguishable from schizophrenia (Luby et al. 1959, Luisada 1978) or mania (Slavney et al. 1977). It has been suggested that some patients who remain psychotic for weeks after PCP ingestion may have an underlying predisposition to schizophrenia or mania. In some series, significant percentages of patients suffering prolonged PCP-induced psychosis are subsequently hospitalized with non–drug-induced schizophrenic disorders (Luisada 1978). In the case of a patient with schizophrenia, responsiveness to neuroleptic treatment may resume after recovery from prolonged PCP psychosis.

### General Medical Comorbidity

Patients with preexisting neurological, cardiovascular, respiratory, or renal disorders are at increased risk for complications of PCP intoxication, such as seizures, stroke, hypertensive crisis, respiratory arrest, or renal failure. Abusers of more than one drug may be at increased risk from the presence of other drugs exerting toxic effects on the same organ systems (e.g., cardiovascular effects of cocaine and amphetamine) or because of damage to specific organs secondary to infectious complications of parenteral drug use.

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CHAPTER

# 60 Substance Abuse: Hallucinogen- and MDMA-Related Disorders

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Hallucinogen Intoxication
Hallucinogen Abuse
Substance-Induced Psychotic Disorder
Hallucinogen Persisting Perception Disorder (Flashbacks)

## Introduction

Hallucinogenic agents have been used by humans for thousands of years. These agents, which derive from a variety of natural and synthetic sources, share the property of inducing a wide range of effects on perception, cognition, and affect in the absence of a delirium. They can induce depersonalization and derealization, and their use can result in intermittent or persistent recurrent perceptual alterations. Tolerance may develop with repeated use, but classical withdrawal symptoms usually do not occur. Many hallucinogens exist: they have essential general features but are different in the specific effects, use or abuse patterns, and propensity to induce psychosis.

The definition of an hallucinogenic drug has been a matter of controversy (Hollister 1968, Jarvik 1970, Brawley and Duffield 1972, LaBarre 1975, Martin and Sloan 1977, Grinspoon and Bakalar 1979, Schultes and Hofmann 1980). More than 90 species of hallucinogenic plants afford an ethnobotanical definition. Hundreds of substituted phenylethylamines and tryptamines lend themselves to chemical characterization. Because few have been systematically studied in humans, hallucinogens have been defined by their botanical or chemical rubrics rather than their psychophysiological effects. To address the problem of classification, one may define as hallucinogenic "any agent which has alterations in perception, cognition, or mood as its primary psychobiological action in the presence of an otherwise clear sensorium. Most commonly this includes indolealkylamines and phenethylamines, and excludes, *inter alia*, the anticholinergics, the arylcyclohexalamine dissociative anesthetics such as phencyclidine, stimulants such as amphetamine and cocaine, bromism and heavy metal intoxication" (Abraham et al. 1996). Instruments are now available which objectify the human factor in hallucinogenic responses (Hermle et al. 1994, Strassman et al. 1994). Future definitions may likely be refined based on neuroreceptor and second messenger drug effects.

## Ethnobotanical Hallucinogens

Human ingestion of hallucinogens can be traced back thousands of years. In the Americas, Europe, and Africa, hallucinogens were used for consecration during religious ceremonies, for divination, and as a tool for rites of passage and shamanic healing. It is possible that the soma of the 3500-year-old Hindu-Aryan Rig Veda (Smith 2000), the kykeon of the ancient Greek rites of the Eleusinian Mysteries (Wasson 1961) and the manna of the Judeo-Christian Old Testament (Merkur 2000) may have all been hallucinogen-containing substances.

The majority of these botanicals grow in the Americas. In South and North America, cacti containing the

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hallucinogen mescaline are still widely used by a number of Native peoples. In South America, boiled potions are made from *Trichocereus* species, a cactus containing about 1% mescaline. A much more potent mescaline-containing cactus, peyote (*Lophophora williamsii*), grows naturally in Northern Mexico and along the Texas–Mexico border. The Huichol of Mexico has used peyote as a religious sacrament continuously for 3000 years (Schaefer and Furst 1998), as have the Native American Church (NAC) of the United States (USA) and Canada. In the NAC, peyote is treasured as a holy sacrament from God to be ingested in all-night prayer ceremonies. Currently, the NAC has as many as 300,000 members and the ceremonial use of peyote is permitted by federal law (American Indian Religious Freedom Act of 1978 and successive Amendment of 1994). Several reports in the medical literature allude to participation in NAC meetings as a successful, culturally sensitive therapy for alcoholism and other drug addictions among Native Americans (Bergman 1971, Albaugh and Anderson 1974, Garrity 2000). In a study assessing neurocognitive performance and psychological well-being of 176 Native Americans, long-term peyote use was not associated with any degradation in neurocognition and, in fact, was associated with better mental health than nonusers (Halpern et al. 2005).

Hallucinogenic mushrooms containing psilocybin (4-phosphoryloxy-*N*, *N*-dimethyltryptamine) and psilocin (4-hydroxy-*N*, *N*-dimethyltryptamine), especially from the genus *Psilocybe*, are found throughout the Americas, Europe, and Asia. *P. cubensis* typically contains 1.6 mg psilocybin per gram of dried mushroom; a dose of 40 μg/kg induces a 3- to 4-h intoxication. The ancient cultures of Meso-America almost certainly venerated the *Psilocybe* experience (Wasson 1961), and some Native Americans of Oaxaca, Mexico continue to use these mushrooms in religious ceremonies to this day. Easily grown and indigenous to many parts of the USA (Halpern 2004), *Psilocybe* mushrooms are commonly trafficked as hallucinogens on the illicit market. Psilocybin can, in a carefully controlled research setting, reliably induce "deeply mystical" states (Griffiths et al. 2006), and has been postulated as offering important medical treatments for cancer-related anxiety (see www.canceranxietystudy.com), treatment-resistant obsessive-compulsive disorder (Moreno et al. 2006), and for cluster headache (Sewell et al. 2006).

Dimethyltryptamine (DMT), a short-acting hallucinogen, is also present in a wide variety of botanicals. Many indigenous peoples of the Amazon and elsewhere ingest potent DMT snuffs prepared from seeds of *Anadenanthera peregrina*, *A. columbrina*, and other botanicals (Schultes and Hofmann 1992). Originating in Brazil, two religions using an orally active form of DMT have evolved out of traditional practices and Christian beliefs in the 20th century, and are legally recognized in Brazil, Peru, Columbia, and the Netherlands. In 2006, the United States Supreme Court in a landmark unanimous decision (Gonzales v. UDV 2006) recognized that Americans also are afforded protection from religious persecution and legal sanction for membership in an ayahuasca-using religion. These religions, the União do Vegetal (UDV) and the Santo Daime, prepare a "tea" (*ayahuasca, hoasca, daime*) containing DMT from the leaves of *Psychotria viridis*, together with reversible monoamine oxidase inhibitors (MAOIs) derived from the vine *Banisteriopsis caapi*. Without inactivation of monoamine oxidase, DMT is not orally active. About 1–2 mg/kg of DMT, in the presence of sufficient MAOI, is a typical psychoactive dose. Subjective effects last 3–4 h and are frequently described as joyful and serene (Barbosa et al. 2005). Members of the ayahuasca-using religions often claim that it helps in treating drug addiction and "inoculating" teenage members from engaging in drug abuse (Doering-Silveira et al. 2005). Many strains of reed-canary grass (*Phalaris* sp.) found throughout North America contain appreciable amounts of DMT (Baxter and Slaytor 1972), but have apparently not been used by traditional societies.

One ceremonial drug that is no longer used traditionally is lysergic acid amide, a natural analog of lysergic acid diethylamide (LSD). This nonethylated amide was consumed by the ancient Aztecs in a drink called *Oliliuqui*, prepared from the seeds of the Tlilitzin plant (*Turbina corymbosa*). Lysergic acid amide is also found in the seeds of the morning glory (*Ipomoeo violacea*). In recent times, some individuals have attempted to use morning glory seeds for recreational intoxication, although other alkaloids in these seeds induce nausea and headache, and commercially obtained seeds are often coated with emetic chemicals or captan, a purple-colored fungicide and carcinogen that induces emesis, or with other emetic chemicals so as to discourage illicit consumption.

Less common natural hallucinogens include 5-methoxy-DMT, bufotenine (5-hydroxy-DMT), and salvinorin-A. Bufotenine and 5-methoxy-DMT can both be extracted from the venom of the American toad, *Bufo alvarius*, and then smoked for a powerful 15-min intoxication (Weil and Davis 1994). "Toad licking" or actual ingestion of the skin of the *Bufo alvarius* is poisonous. Salvinorin-A, a trans-neoclerodane diterpenoid, produces a 15–25 min intoxication when 200–500 μg are smoked. Unlike other hallucinogens, salvinorin A acts as a potent and selective κ-opioid receptor agonist without any action at 5-$HT_{2A}$ serotonin receptors, the molecular target thought to mediate the actions of the more commonly used and better known hallucinogens (Roth et al. 2002). It is extracted from the *Salvia divinorum* plant, and has been used as a religious sacrament by Mazatec shamans in Mexico for hundreds of years (Valdes 1994, Vorthermus and Roth 2006). Recently, it has been used as a recreational drug in America and elsewhere, largely through promotion on the Internet (Halpern and Sewell 2005).

One of the few Old World botanical hallucinogens still used for religious purposes is *Tabernanthe iboga*, a shrub that contains up to 6% of the indole alkaloid, ibogaine. In Western Aftrica, the Bwiti Cult and certain hunter-gatherer peoples of Gabon and the Congo continue to use a root-bark preparation from this plant (Fernandez and Fernandez 2001). Ibogaine induces intoxication for 6 h or more; the compound has been patented in the USA as a potential treatment for addiction.

In short, many hallucinogens are classical examples of drugs discovered by traditional societies and subsequently adopted for both licit and illicit use in industrialized countries. Unlike many other ethnobotanicals, however, hallucinogens continue to be widely used in their original religious settings, even as they are simultaneously used and abused in modern societies.

## Synthetic Hallucinogens

The dawn of modernity for hallucinogenic drugs can be placed to the moment in 1943 when Albert Hofmann, a Swiss chemist, discovered the potent psychological effects of LSD. Three days after an accidental exposure, Dr. Hofmann intentionally ingested 250 µg of LSD on April 19, 1943 and soon traveled home via bicycle as the pronounced psychological effects commenced. Within a decade, the drug was being tested as an agent of chemical warfare in the USA and Europe. Within 2 decades it assumed cult status among the ministry, academics, and students, culminating in an epidemic of abuse in its third decade—the late 1960s. Congress responded with the Drug Abuse Control Amendments of 1965 and 1968, which choked off drug supplies to researchers, and criminalized drug sale and use. The scientific impact of these laws was to retard the advance of knowledge in this field for a generation.

The development and chemical identification of additional agents causing LSD-like mental symptoms, however, proceeded apace. This work has both clarified aspects of their mechanisms of action and created a challenge to defining hallucinogens. Two classes of drugs appear to have commonalities with LSD. These include other substituted **indolealkylamines** (psilocybin, psilocin, ibogaine, DMT, and bufotenine, *inter alia*) and the **phenethylamines** (mescaline, 3,4-methylenedioxymethamphetamine [MDMA], methylenedioxyamphetamine [MDA], 4-brom-2,5-dimethoxyphenethylamine [2CB], and 2,5-dimethoxy-4-methamphetamine [DOM], *inter alia*) (Figure 60–1). The chemist Alexander Shulgin has synthesized and tested at least 179 phenethylamines (Shulgin and Shulgin 1991) and 55 indolealkylamines (Shulgin and Shulgin 1997) for hallucinogenic properties.

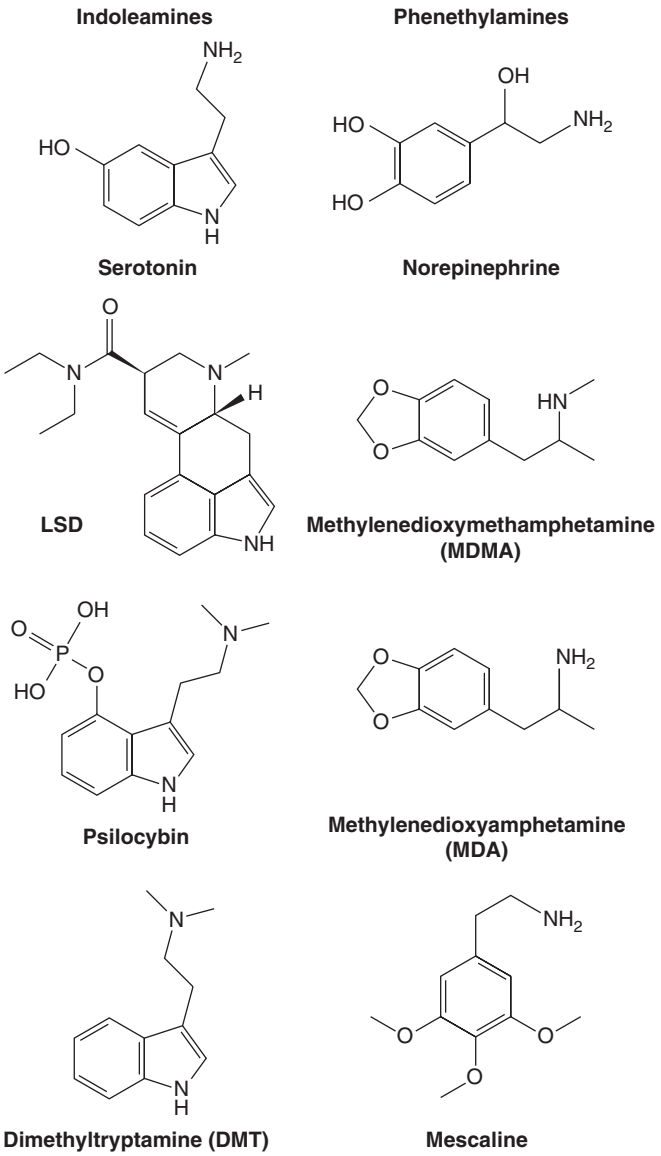



**Figure 60–1** *Representative substituted indoles and phenethylamine hallucinogens.*

## Human Experimentation with Hallucinogens

Abraham (2000) described a biphasic curve regarding enthusiasm and caution in publications on the hallucinogen, LSD, in the medical literature from 1960 to 1994 (Figure 60–2). Early in its history LSD spawned a flurry of positive reports regarding its clinical benefits, but following an epidemic of abuse, adverse reports predominated. Regulatory suppression of LSD research in the US then followed for several decades.

Recently, however, this unique class of drugs has inspired a new wave of research with selected hallucinogens with regulatory oversight of the issues of safety and efficacy. Studies have examined the safety of peyote in religious use (Halpern et al. 2005); the psychological effects of psilocybin, and dimethyltryptamine (Gouzoulis-Mayfrank et al. 2005); and possible therapeutic uses, such as ongoing studies for refractory anxiety in cancer patients and posttraumatic stress disorder (PTSD).

Hallucinogens have been used as experimental psychoses ("psychotomimetics"). A Swiss team has found increased metabolic activity in the frontal cortex of subjects on the dissociative anesthetic ketamine (Vollenweider et al. 1997), and in subjects during an experimental psychosis from psilocybin, increased serotonin-2 agonist activity (Vollenweider et al. 1998). Evidence is also emerging which supports the experimental use of hallucinogens for the treatment of psychiatric disorders. In a randomized trial of ketamine for depression, Zarate et al. found that the drug had benefits for a week following a single dose (Zarate et al. 2006).

## MDMA (Ecstasy)

3,4-Methylenedioxymethamphetamine (MDMA, commonly known as "ecstasy") is a synthetic amphetamine analog that is also similar to mescaline. It was originally synthesized by Dr. E. Merck in 1912 and patented in Germany in 1914 (Merck 1914, Freudenmann et al. 2006). It was never marketed and did not attract attention until the 1970s when it was described as an hallucinogen analog (Hardman et al. 1973). (This pre-clinical study (Hardman et al. 1973) was conducted in the early 1950s as part of the U.S. government's research into compounds for interrogation and warfare but wasn't declassified until 1973.) Anecdotal reports (Gaston and Rasmussen 1972, Shulgin and Shulgin 1991) suggest that a tiny minority may have used MDMA in the late 1960s, but the first verified illicit use of MDMA began in the 1970s or early 1980s. Recreational use of MDMA

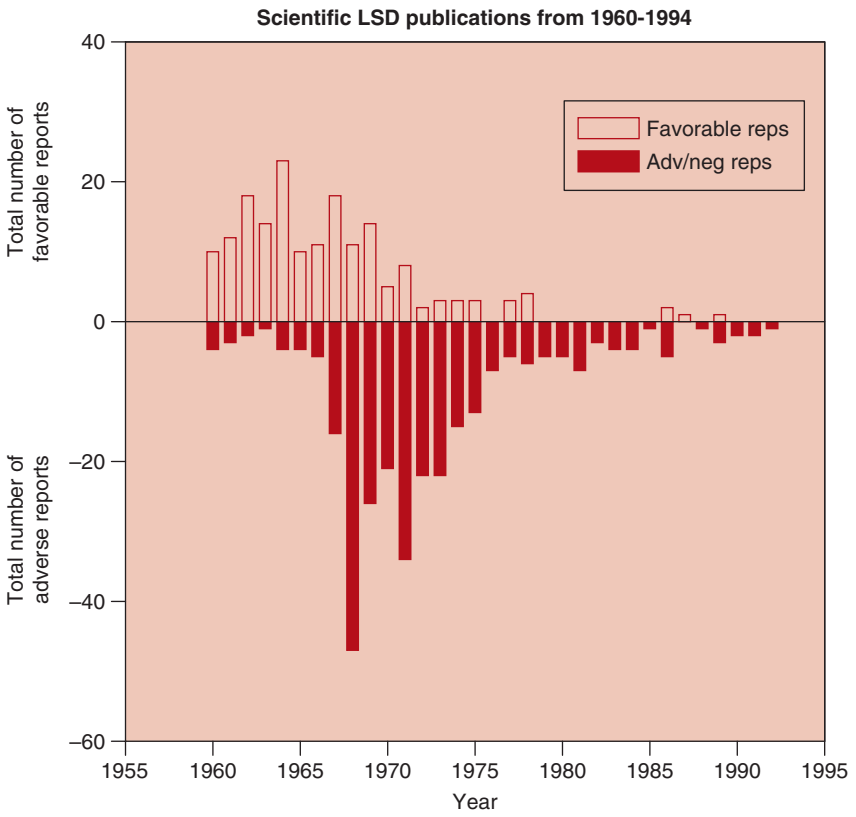



**Figure 60–2** *Scientific publications on LSD in* Index Medicus *1960–1994. For each year every human study was assigned a score of +1 for a favorable finding, or −1 for an adverse one. The scores for each year were summed and plotted. The curve shows a period of rising expectations followed by one of sober reconsideration. (Source: Reprinted with permission from Abraham HD (2000) Hallucinogen-related disorders. In Comprehensive Textbook of Psychiatry, 7th edition, Chapter 11.7, Kaplan HI and Sadock BJ (eds). Lippincott, Williams and Wilkins, Philadelphia, PA, USA, pp 1019.)*

took root due to its psychological effects and the fact that it was available legally, and was partially fueled by reports of the use of MDMA as a psychotherapeutic adjunct (Shulgin and Nichols 1978). In 1985, in response to the expanding recreational spread of MDMA in the dance club and "Rave" scene, the Drug Enforcement Administration (DEA) started the procedures to place MDMA into Schedule I. When evidence emerged that a structurally related congener, 3,4-methylenedioxyamphetamine (MDA) damages serotonergic neurons in rodents (Ricaurte et al. 1985), the DEA used this report to justify emergency Scheduling (Lawn 1986). Therapists who had used MDMA to assist psychotherapy challenged this placement before an Administrative Law Judge of the DEA who agreed with these petitioners and recommended MDMA be placed into Schedule III. This recommendation was not accepted by the DEA Administrator and MDMA in the United States has remained in Schedule I. MDMA may indeed induce 5-HT depletion (which may or may not reflect neurotoxicity) which may be associated with behavioral changes (Baumann et al. 2007). The actions of the DEA were supported by subsequent early reports that MDMA is toxic to animal (Stone et al. 1986, O'Hearn et al. 1988, Fischer et al. 1995, Hatzidimitriou et al. 1999) and possibly human brain (McCann et al. 1998—a study which has since been retracted, but found by others Semple et al. 1999, Reneman et al. 2002a, 2002b). High or frequently repeated doses of MDMA may be harmful to the brain. Heavy ecstasy users exhibit subtle but detectable impairments in memory and executive function, though the clinical significance of these findings remains unclear.

The publicity that followed the scheduling of MDMA only served to increase its popularity, particularly on college campuses (Peroutka 1987). Recognition of this trend let the National Institute of Drug Abuse (NIDA) and the Substance Abuse Mental Health Services Administration (SAMHSA) to begin formal collection of epidemiologic data in the mid to late 1980s. In the intervening years, the pattern of MDMA use has changed with use peaking among American teens in 2001. These factors have heightened public awareness of the drug through the years of reported increased use that has since leveled off in the later 2000s.

## Hallucinogen Intoxication

### Diagnosis

#### Definition and Diagnostic Features

Criteria for the diagnosis of acute hallucinogen intoxication are set forth in the following *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) (American Psychiatric Association 2000).

**DSM-IV-TR Criteria**

**Hallucinogen Intoxication**

A. Recent use of hallucinogen

B. Clinically significant maladaptive behavior or psychological changes (e.g., marked anxiety or depression, ideas of reference, fear of losing one's mind, paranoid ideation, impaired judgment, or

*(continues)*

impaired social or occupational function) that developed during or shortly after, hallucinogen use.

C. Perceptual changes occurring in a state of full wakefulness and alertness (e.g., subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) that developed during, or shortly after, hallucinogen use.

D. Two (or more) of the following signs, developing during, or shortly after, hallucinogen use:

(1) pupillary dilatation
(2) tachycardia
(3) sweating
(4) palpitations
(5) blurring vision
(6) tremors
(7) incoordination

E. The symptoms are not due to a general medical condition or are not better accounted for by another mental disorder.

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## Assessment and Differential Diagnosis

Chemical identification of hallucinogens in emergency specimens with methods such as gas chromatography-mass spectrometry remains costly and time consuming. Thus, clinicians in emergency settings must rely on a careful drug history, the social context of possible drug use, the information from the less drug-affected friends of the patient, the mental status examination, and signs apparent from the physical examination. The high potency of chemically pure LSD permits its distribution in single drops of solution. Thus, blotter paper (often marked with stamps of cartoon characters or New Age symbols) or a single sugar cube can easily carry more than the 50–100 μg of LSD necessary for the user to "trip" 6–12 h. Routes of administration other than by ingestion are rare. Autonomic arousal is the rule, with tachycardia, increased deep tendon reflexes, and dilated pupils present regardless of whether euphoria or panic is present. Hypersensitivity to visual and auditory stimuli is common, with atypical affective responses as the result.

Motor function is reduced, so patients seeking assistance in the emergency room are not likely to act out aggressively. "Bad trips" are drug-induced panic attacks in the context of an hallucinogenic experience, associated with feelings of unreality, confusion, and the flooding of the senses with unbidden imagery. Acute presentations of the proverbial "bad trip" have declined in conjunction with a decline in use in the last decade (SAMHSA's Drug Awareness Warning Network, DAWN; www.dawninfo.samhsa.gov, Substance Abuse Mental Health Services Administration, 2006). Reasons for the relative rarity of emergency room visits may be a reflection of increased awareness of safer procedures for managing the intoxication (many users report having a non-drug using "sitter" with extensive prior experience with hallucinogens) and the average dose of LSD sold on the street has decreased from 250 μg per perforated square of blotter paper in the late 1960s to 100–50 μg or less today, which may be a more "manageable" dosage for the inexperienced user to navigate when experiencing a profoundly dysphoric "bad trip."

## Differential Diagnosis

The differential diagnosis of an acute hallucinogenic intoxication includes intoxication by other agents (such as phencyclidine [PCP], cocaine, amphetamines, anticholinergics, and inhalants, among others). It also includes acute schizophrenia or affective disorder, panic disorder, head injury, sedative, hypnotic, anxiolytic, or alcohol withdrawal (including gamma-hydroxybutyrate [GHB]), metabolic disorders such as hypoglycemia and hyperthyroidism, seizure disorder, acute vascular events, release hallucinations of ophthalmologic disease, and the complications of central nervous system (CNS) tumors. Age, along with prior clinical history, the history of the current event, physical examination, and toxicology screen for suspected nonhallucinogenic agents usually reveal the diagnosis.

A patient presenting with a history of taking LSD may still, in fact, have ingested a different substance. The street practice of adulteration or mislabeling of the drug is common, though some 80% of street samples have been found to correctly contain LSD (Abraham 1983a). Psychosis following a smoked agent suggests PCP. Differentiating between PCP and LSD is clinically important, since LSD-induced panic responds well to oral benzodiazepines, while PCP delirium requires high potency antipsychotic medications such as haloperidol. A "palm test" can be employed to differentiate PCP from LSD toxicity (Abraham and Aldridge 1993). This is performed by the examiner holding an open palm in front of the patient, and asking "the names of all the colors you see in my palm." The LSD patient often ticks off a series of vivid colors and occasional images. The dissociated, aggressive PCP patient attempts to attack the hand.

## Epidemiology

Among hallucinogens, LSD remains the most popular in its class among American high school students. An annual drug survey of 45,000 students by the Monitoring the Future Program of the University of Michigan has been performed since 1975. There is a downward long-term trend of LSD lifetime use among American secondary school students. In 2001, 10.9% of seniors reported using LSD at least once. By 2006 that figure had fallen to 3.3%. Attitudes among seniors have relaxed regarding their perception of dangers from LSD use. In 1990, 44.7% of the students believed users were harming themselves from the drug if taken once or twice but by 2006 only some 36.1% held this view. Risk of harm from regular use of LSD was believed by 84.5% of seniors in 1990 and has similarly trended downward with 69.3% expressing this view in 2006. Disapproval of any use has remained fairly constant over the years with 88% of seniors disapproving of one or two uses of LSD and 99.5% disapproving of regular LSD use in 2006. While nearly half

of the seniors in 2000 (46.9%) reported that LSD is "fairly easy" or "very easy" to get, availability has trended downward to 29% in 2006 (Johnston et al. 2006). The price for a single dose of LSD has held fairly constant: DEA reports it retails for $2 to $5 in 2006 (Office of Diversion Control, 2006). Other hallucinogens are not well studied.

### Comorbidity Patterns

Individuals with antisocial personality disorder are more likely to have comorbid drug use including hallucinogens (Compton et al. 2005). The obverse is also true, that is, subjects with drug abuse are more likely to have antisocial personality disorder (Compton et al. 2000).

### Course

Acute intoxication with LSD generally lasts 6–12h.

## Etiology and Pathophysiology

### Genetic Factors

There are no known genetic factors in hallucinogen abuse.

### Neurobiological Factors

The acute effects of "tripping" on LSD-like (i.e., with similar psychic effects, e.g., psilocybin or mescaline) hallucinogens are variable and profound. Classic descriptions are offered by Albert Hofmann (1980) and Aldous Huxley (1954). Subjects given LSD without their knowledge suffer more anxiety, hypomotility, and speech disruption than those who take it knowingly. LSD is active within 30 min of ingestion of a 50–100 μg dose. Physically, the drug's autonomic arousal is associated with mydriasis which lasts for much of the trip. The flood of rapidly changing perceptual, affective, and cognitive effects is by alternate turns exhilarating, nerve wracking, and incapacitating. Table 60–1 illustrates a typical time course for the psychiatric effects of LSD.

The effective hallucinogenic dose varies widely between drugs in this class, and between individuals. Thus, a dose of 1 μg/kg of LSD is approximately equivalent to 150–200 μg/kg of psilocybin and 5–6 mg/kg of mescaline (Hollister 1984). Adverse reactions have been observed following 40 μg of LSD in some individuals, but absent in others taking as much as 2000 μg. The conventional explanation for this variability of response is instructional set, anticipation of drug effects due to previous experience, and environmental setting affect outcome (Zinberg 1984). Additionally, personality, preexisting mental illness, and genetic vulnerability to mental illness are also likely to be important.

**Table 60–1 Time Course for the Psychiatric Effects of LSD-Like Hallucinogens**

| Time | Psychiatric Effects |
|---|---|
| 0–30 min | Dizziness, nausea, weakness, anxiety |
| 30–60 min | Blurred vision, visual pseudohallucinations and hallucinations, illusions, afterimagery, geometric and imagistic imagery with eyes closed, decreased concentration, dissociation, depersonalization, out of body sensations, reduced coordination |
| 60–240 min | Intensified afterimagery, illusions, false perceptions of movement (walls appearing to breathe or melt), loss of rectilinearity of perceptions, a rapid flood of emotions which may include anxiety, euphoria, and oceanic unity, loss of the sense of time |
| 4–12 h | Gradual return to baseline mental state, but with continued arousal, headache, fatigue, contemplative frame of reference, sense of profundity |

Unlike the chronic use of stimulants, like amphetamine and cocaine, chronic use of hallucinogens does not lead to physiological dependence with only minor exceptions (Stone et al. 2006). On the other hand, tolerance to LSD rapidly builds in 4–7 days, and lasts 3 days (Abramson et al. 1956). LSD shows cross-tolerance with psilocybin, dimethyltryptamine, and mescaline, but not with amphetamines, or cannabis (Rosenberg et al. 1964). There is no withdrawal or documented fatalities from overdose. Homicide and suicide in the acute drug state have been reported (Cohen 1960, Reich and Hepps 1972) but are rare, ostensibly because of drug-induced hypomotility. The mechanism of action of hallucinogens is complex. Titeler et al. (1988) have shown that hallucinogenic potency of LSD and selected phenylisopropylamines correlates with the drug's ability to bind to the postsynaptic 5-$HT_{2A}$ receptor (Titeler et al. 1984, Nichols 2004) (see Figure 60–3).

Neurophysiologic studies in animals support the involvement of postsynaptic 5-$HT_{2A}$ for hallucinogenic activity (Abraham et al. 2002, Nichols 2004). Hallucinogens simultaneously decrease spontaneous activity in the locus coeruleus, considered a novelty detector in the midbrain, while enhancing sensory responses of the locus coeruleus by activating *N*-methyl-D-aspartate receptors. In the cerebral cortex, the drugs both inhibit and induce activity by exciting GABAergic and glutamatergic neurons respectively (see Figure 60–4). Stimulation of 5-$HT_{2A}$ by hallucinogenic compounds specifically activates the pertussis toxin-sensitive $G_{i/o}$ protein and Src kinases in cortical pathways. Interestingly, activation of 5-$HT_{2A}$ receptors by nonhallucinogenic compounds (e.g., lisuride) does not activate these proteins (González-Maeso et al. 2007). Hallucinogenic effects can be modeled when 5-$HT_{2A}$ are expressed only in the cortex, implying subcortical involvement is not needed for hallucinogenic actions (González-Maeso et al. 2007).

The presence of selective serotonin reuptake inhibitors blunts hallucinogenic effects, possibly through the activation of 5-$HT_1$ receptors (Aghajanian and Marek 1999, Bonson et al. 1996). $GABA_A$ anxiolytic agents (e.g., benzodiazepines) promptly bring the dysphoria of a "bad trip" to an end, presumably by inhibition of the locus coeruleus.

Several European groups have published neuroimaging studies of the acute effects of hallucinogens (Hermle et al. 1994, Vollenweider et al. 1997). Hermle and colleagues using single photon emission computed tomography (SPECT) in healthy volunteers found that mescaline resulted in increased metabolic activity in the temporofrontal cortex, in distinction to patients with schizophrenia, who show hypofrontality. Vollenweider and colleagues administered psilocybin to healthy volunteers who were then studied with $^{18}$F-deoxyglucose positron emission tomography (PET). This hallucinogen globally increased brain cingulate, frontal and medial temporal

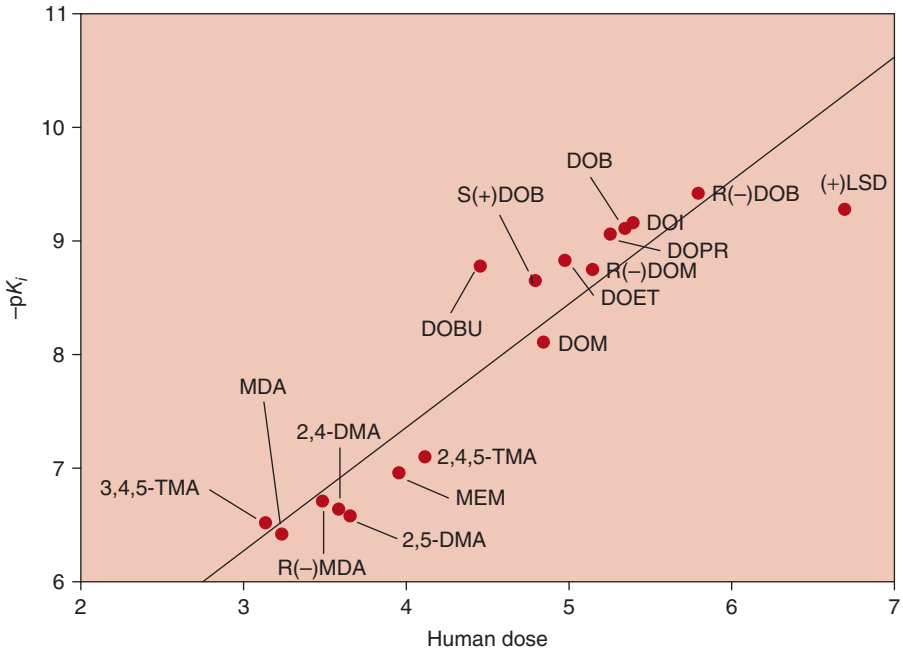



**Figure 60–3** *Affinity and potency of selected phenylisopropylamine hallucinogens and LSD at the 5-HT2 receptor. The 5-HT$_2$ receptors in rat frontal cortex were labeled with $^3$H-DOB (4-bromo-2,5-dimethoxyphenylisopropylamine). Sixteen phenylisopropylamine compounds and LSD were then assayed for affinity at these sites. Subjective human potencies were determined by Shulgin. Spearman's ranked correlation coefficient between 5-HT$_2$ affinities and hallucinogenic potencies is 0.09. A correlation between affinities and drug discrimination potencies in rats (data not shown) was 0.90 as well (Source: Reprinted with permission from Titeler M, Lyon RA, and Glennon RA (1988) Radioligand binding evidence implicates the brain 5-HT$_2$ receptor as a site of action for LSD and phenylisopropylamine hallucinogens. Psychopharmacology 94, 213–216.)*

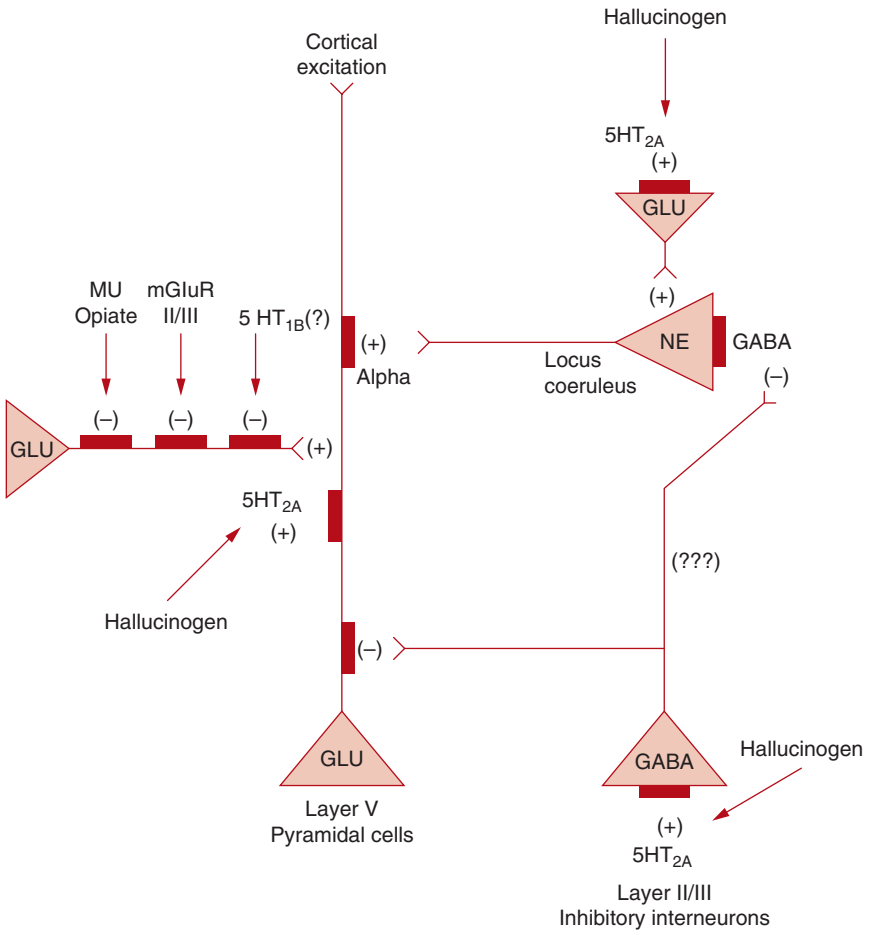



**Figure 60–4** *Schematic diagram of putative electrophysiological mechanism of action of hallucinogenic drugs. Depicted are serotonergic hallucinogenic inputs at the raphé nuclei and locus coeruleus, projecting to the vicinity of apical dendrites of layer V pyramidal cells in the neocortex. Hallucinogens, acting as partial agonists at 5-HT$_{2A}$ receptors, induce the release of glutamate from excitatory nerve terminals. Also shown are inhibitory modulators of 5-HT$_{2A}$-induced glutamate release: GABA, μ opiate, group II and III metabotropic glutamate, and possibly 5-HT$_{1B}$ receptors. NE, noradrenergic input; α1, alpha-1 adrenergic receptor; mGluR II/III, group II and III metabotropic glutamate receptor; GABA, γ-aminobutyrate. (Source: Adopted with permission from Abraham HD, McCann UD, and Ricaurte GA (2002) Psychedelic drugs. In Neuropsychopharmacology: The Fifth Generation of Progress, Davis KL, et al (eds). Lippincott, Williams & Wilkins, Philadelphia, PA, USA, pp 1545–1556.)*

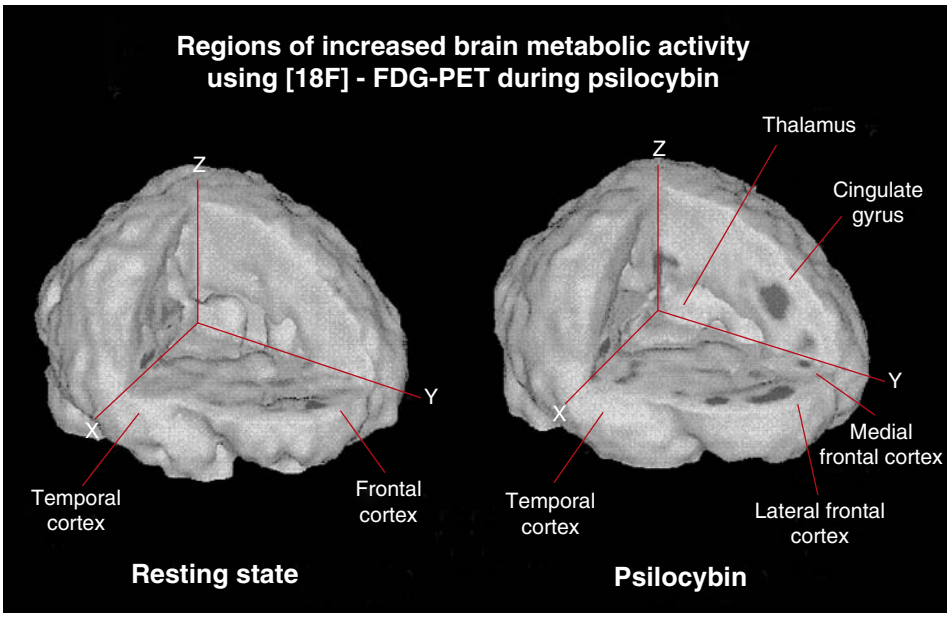



**Figure 60–5** *$^{18}$F-deoxyglucose positron emission tomography of health volunteers before and after the administration of psilocybin. In addition to a global increase in brain metabolic activity, note the increase in activation in the anterior cingulated and lateral and medial frontal cortex, and the medial temporal cortex. Metabolic activation correlated with the intensity of subjective symptoms. (Source: Adapted with permission from Hermle L, Spitzer M, and Gouzoulis E (1994) Arylalkanamine-induced 1 effects in normal volunteers: On the significance of research in hallucinogenic agents for psychiatry. In Fifty Years of LSD: Current Status and Perspectives of Hallucinogens, Pletscher A and Ladewig D (eds). Parthenon, New York, USA. Also, Vollenweider FX, Leenders KL, Scharfetter C, et al. (1997) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16, 257–272.) (See Color Plate XIII)*

cortex. Metabolic activation correlated with the intensity of subjective symptoms (see Figure 60–5).

### Psychosocial Factors

Psychosocial factors affecting the outcome of hallucinogen intoxication include the user's instructional set, the environmental setting, degree of suggestibility, and personality type. The most vulnerable person exposed to LSD, for example, would be one who slipped the drug without warning, with pre-existing psychiatric illness, rigid personality traits, in an excessively stimulating environment.

### Treatment

Treatment of hallucinogen intoxication with panic is easily managed with oral benzodiazepines (diazepam 20 mg or lorazepam 2 mg), which end dysphoric anxiety within 30 min. This knowledge, along with the availability of benzodiazepines in the environment, has reduced the need of psychiatric emergency interventions.

## Hallucinogen Abuse

### Diagnosis

The criteria for hallucinogen abuse as encoded in the DSM-IV-TR are shown below:

**DSM-IV-TR Criteria**

**Hallucinogen Abuse**

A. A maladaptive pattern of hallucinogen use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent hallucinogen use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to the substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

(2) recurrent hallucinogen use in situations in which it is physically hazardous

(3) recurrent hallucinogen-related legal problems

(4) continued hallucinogen use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

B. The symptoms have never met the criteria for Substance Dependence for this class of substance.

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### Assessment

The majority of patients abusing hallucinogens are diagnosed by clinical history. A mental status examination consistent with hallucinogen intoxication on more than one occasion supports the diagnosis. Unlike patients dependent on alcohol and other drugs, patients involved in hallucinogen abuse are not inclined to deny the behavior, though concurrent abuse of other drugs is not uncommon.

### Epidemiology

It is likely the prevalence of hallucinogen abuse has fallen steadily in the last 30 years. This is supported by a decline in published clinical studies, and a steady decrease in hallucinogen use in secondary schools (Johnston et al. 2006).

### Comorbidity
Clinical observations suggest that the habitual hallucinogen user is inclined to also abuse marijuana and psychostimulants, as opposed to opiates. Alcohol abuse is a risk since it is available as a layman's antianxiety agent. Depression and psychosis may appear independent of life hallucinogen exposures.

### Course
The natural history of hallucinogen abuse is a bell-shaped curve beginning in adolescence and declining by the midtwenties. This suggests that if hallucinogen dependence exists, it must be rare.

### Differential Diagnosis
The acute effects of hallucinogens are unique, but drugs sold as LSD, e.g., are often adulterated with a second drug, or contain an entirely different drug. Thus, PCP and amphetamine congeners must be considered. Not uncommonly, a patient with paranoid schizophrenia will describe being repeatedly poisoned with a hallucinogen, but the absence of a well-described drug experience and the presence of other psychotic symptoms make hallucinogens an unlikely diagnosis.

### Treatment
Clinical experience suggests that a chronic user of hallucinogens is a polydrug user. Conventional treatment of polydrug use involves an array, when indicated, of detoxification, individual and family therapy, 12-step abstinence programs, community treatment programs, pharmacotherapies, resolution of legal difficulties, and attention to comorbid illnesses.

## LSD-Related Psychotic Disorders

### Diagnosis

#### Definition and Diagnostic Features
Criteria for substance-induced psychotic disorders are noted below:

**DSM-IV-TR Criteria**

**Substance-Induced Psychotic Disorder**

A. Prominent hallucinations or delusions, Note: Do not include hallucinations if the person has insight that they are substance induced.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2)

(1) the symptoms in Criterion A developed during or within a month of substance intoxication or withdrawal

(2) substance use is etiologically related to the disturbance

C. The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following:

the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent nonsubstance related episodes).

D. The disturbance does not occur exclusively during the course of delirium.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Code specific substance-induced psychotic disorder.

292.11 amphetamine (or amphetamine-like substance), with delusions;

292.12 amphetamine (or amphetamine-like substance), with hallucinations;

292.11 hallucinogen, with delusions;

292.12 hallucinogen, with hallucinations.

Specify:

With onset during intoxication: if criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome.

With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome.

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Among the hallucinogens, LSD has been associated with the majority of, but not all, prolonged psychotic reactions following acute drug use. These have been reviewed extensively (Strassman 1984, Abraham and Aldridge 1993, Abraham et al. 1996). Psychoses are apparently rare with the abuse of botanical preparations, in all likelihood because such agents are of low potency (except for salvinorin-A), not widely abused, and often controlled by religious sanctions. By comparison, persisting psychoses have been seen following the administration of LSD to patients and experimental subjects, though this is uncommon as well (Opitz 1963, Leuner 1967, Baker 1967, McFarling 1980).

#### Assessment
Assessment for psychosis associated with hallucinogen use does not differ from that of acute intoxication. Other causes of psychosis should be ruled out with examination, toxicology studies to rule out other drug-induced psychosis, general

Clinical Vignette 1

A 19-year-old man used LSD for the fourth time. In the past, his trip on LSD ran an 8-hour course. Now, however, auditory and visual hallucinations persisted over the next week. At the same time his behavior became increasingly agitated and bizarre. His speech became rapid and incoherent. He was unable to sleep. His energy was increased though he talked of committing suicide. He expressed the delusion that he had sexual relations with a pet, and that he was androgynous. He was admitted to a psychiatric hospital where he showered with his clothes on and pulled a towel rack off the wall. Four-point restraints were required. His history was negative for prior psychosis. There was no history of drug dependency. His family history was positive for depression. The patient was treated at the onset with neuroleptics that were supplemented with lithium carbonate in the fourth week. He remained disoriented, delusional, and hallucinatory until the illness remitted 2 months after his last use of LSD.

**Comment**

This case illustrates the continuum between LSD use and an acute psychotic reaction. Salient are signs consistent with the positive symptoms of schizophrenia including multimodal hallucinations, bizarre delusions and behavior, and thought disorder. Like other patients in this class, without predisposing factors, this man had a relatively healthy premorbid adjustment and good outcome. The patient has avoided mind-altering drugs since discharge. There has been no relapse in a 20-year follow-up.

laboratory studies, and directed studies such as computed tomography of the brain. In addition to exhibiting positive signs of schizophrenia, patients with post-LSD psychoses show affective lability and the novel addition of visual hallucinations uncommon in non-drug-related psychoses (Abraham 1980). Patients with post-LSD psychosis in one study had healthier premorbid personalities and an earlier age of onset than non-drug-using schizophrenic subjects (Bowers 1972, Breakey et al. 1974). The uniqueness of post-LSD psychosis remains controversial. One comparison of post-LSD psychosis and non-drug-related schizophrenia found no essential clinical differences between the two (Vardy and Kay 1983). Bowers (1972) found that LSD-psychosis is associated with a reduced serotonin metabolite in cerebrospinal fluid (CSF), while Tsuang et al. (1982) found more visual hallucinations, depression, and families with affective disorder in drug-abusing psychotics than a drug-abstinent schizophrenia comparison group.

### Epidemiology

Rates for the development of psychosis following experimentally administered LSD range from 0.08% (Malleson 1971, Titeler et al. 1988) to 4.6% (Hollister 1984), with psychiatric patients being most at risk. Psychosis is associated with LSD use in two longitudinal studies (McLellan et al. 1979, Bowers 1977), 6 cross-sectional studies (Abraham 1980, Smart and Jones 1970, Breakey et al. 1974, Bowers 1972, Safer 1987, Vardy and Kay 1983), 13 case series (Cohen 1960, Anonymous 1966, Ungerleider et al. 1966, Smart and Bateman 1967, Tietz 1967, Blumenfield and Glickman 1967, Hekimian and Gershon 1968, Frosch 1969, Malleson 1971, Sanborn and Daniels 1971, Abruzzi 1977, McLellan and Druley 1977, Kornblith 1981), and 75 case reports (Cooper 1955, Cohen and Ditman 1963, Frosch et al. 1965, Metzner 1969, Hatrick and Dewhurst 1970, Muller 1971, Dewhurst and Hatrick 1972, Reich and Hepps 1972, Horowitz 1975, Lake et al. 1981, Abraham 1983b, Bowers 1987, Schwartz et al. 1987). The psychotogenic potency of LSD cannot be generalized to other agents in this class.

### Comorbidity Patterns

The diagnosis of hallucinogen psychosis is often confounded by preexisting mood and psychotic disorders, and the abuse of other drugs and alcohol. The dually diagnosed patient with psychosis and chronic drug abuse is more often the rule than the patient presenting de novo with psychosis following the recent ingestion of an hallucinogen. Comorbidity brings with it the added clinical challenges of more frequent psychotic episodes, poor medication compliance, poor self-care, aggression, prison, and the risk of suicide (Buckley 2006).

### Course

The natural history of post-hallucinogen psychoses appears to follow a highly variable course. On one end of a spectrum of severity, an individual may suffer an acute psychotic event following drug use which then resolves over a period of days or weeks. Further along this spectrum are those patients whose recovery occurs over months, or years. Finally, there are those smaller number of patients who descend into a painful state of psychotic chronicity, made all the more poignant because the illness tends to preserve insight as his peers progress through the life cycle.

### Differential Diagnosis

The differential diagnosis of post-hallucinogen psychosis is that for any acute psychotic disorder. This includes protracted psychoses following the use of the dissociative anesthetics PCP and ketamine, amphetamines, and cocaine, schizophrenia and affective disorders, migraine, deliria from CNS infections, closed head injuries, tumors, vascular events, and the toxic effects of bromine, heavy metals, and anticholinergic drugs. Central to diagnosis is a careful premorbid history, complemented by data from friends and family on the patient's recent medical history and behavior. Neurological examination, an acute urine for toxicological screening, and computed tomography or magnetic resonance imaging of the brain are helpful in ruling out treatable non-LSD-related psychotic disorders.

### Psychological Factors

Recent work by Bellack et al. (2006) has shown in a randomized clinical trial that behavioral treatment for dually diagnosed patients can be effective on measures of less drug use, reduced hospital stays, better retention in treatment, and quality of life.

## Treatment

Treatment of post-LSD psychoses has been described in 15 case series. Four case studies reported success with 1st generation neuroleptics (Cohen 1960, Reich and Hepps 1972, Hatrick and Dewhurst 1970, Dewhurst and Hatrick 1972), four with multiple treatments of bilateral electroconvulsive therapy (ECT) (Metzner 1969, Hatrick and Dewhurst 1970, Muller 1971, Fookes 1972), two with lithium (Horowitz

1975, Lake et al. 1981), and one with a controlled clinical trial of the serotonin precursor 5-hydroxytryptophan (Abraham 1983b).

## Hallucinogen Persisting Perception Disorder (HPPD)

### Diagnosis

#### Definition and Diagnostic Features

The definition of hallucinogen persisting perception disorder according to DSM-IV-TR is shown below:

**DSM-IV-TR Criteria**

**Hallucinogen Persisting Perception Disorder (Flashbacks)**

A. The reexperiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perception of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia).

B. The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (e.g., delirium, dementia, schizophrenia) or hypnopompic hallucinations.

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Clinical Vignette 2

A 40-year-old unemployed cook presented with a complaint of seeing lingering trails of moving objects in his visual field and unaccountable haloes around people. He reported "a career" of LSD use beginning at the age of 13 years and ending at the age of 20 years. He claimed use of the drug at least 400 times. On one trip he experienced a visual hallucination that his girlfriend sitting beside him in his moving vehicle had turned into a giant lizard. In terror, he attempted to kill her by steering the vehicle off the road and crashing it. His subsequent drug history involved daily use of marijuana for 5 years in his twenties, amphetamine and heroin dependence from the ages of 20 to 23 years, and alcohol dependence from the age of 28 years. Following an alcoholic binge at age 30 years, intermittent visual disturbances, which he first noticed in his twenties, became continuous, including hallucinations of patterns on walls, flashing lights, intensification of colors, and afterimages. After drinking caffeine, faces would appear to break into fragments. These symptoms persisted daily for the next 10 years.

**Comment**

This case illustrates two hallucinogen-related disorders: past history of acute intoxication with panic and current HPPD. This person's LSD-induced panic attack was nearly fatal, but his HPPD has been long-lived. Resolution of HPPD symptoms appears to occur in half of the patients, with the remainder learning to cope with a chronically altered perceptual apparatus. Comorbid disorders associated with HPPD include alcohol dependence (the effects of alcohol are reported to reduce the hallucinations), panic disorder, and major depressive disorder. One case in five develops a subsequent psychotic disorder. Common symptoms of HPPD include afterimagery of objects moving through the visual field ("trails"), imagistic and geometric hallucinations, aeropsia (myriad dots in the air), pareidolia (imagery within images), and difficulty reading.

Clinical Vignette 2 illustrates a number of features of HPPD.

#### Assessment

HPPD arises following the use of hallucinogenic drugs such as LSD. It may also arise following other hallucinogens, but not as commonly. The onset of symptoms occurs in the majority of cases within the first month following drug use, but spontaneous appearances of symptoms can occur months and years later. Visual symptoms predominate. They include afterimagery of objects moving through the visual field ("trails"), imagistic and geometric hallucinations, aeropsia (myriad dots in the air), pareidolia (imagery within images), and difficulty reading (Abraham 1983a). Figure 60–6 illustrates patient drawings of representative visual pseudohallucinations in HPPD. Such visual disturbances can vary in frequency from occasional to continuous. Symptoms can be acutely exacerbated by marijuana, stimulants, alcohol withdrawal, anxiety, or extreme physical activity. Other somatic symptoms difficult to characterize such as "a head feeling" and "depersonalization" are also commonly described.

#### Epidemiology

Overall, HPPD appears to occur only rarely in people who have had significant use of hallucinogens (Halpern and Pope 2003). HPPD is most likely to occur with prior LSD use, but may also occur following use of other hallucinogens.

#### Comorbidity Patterns

Clinical experience with HPPD suggests that three disorders are overrepresented comorbidly—panic disorder, major depressive disorder, and alcohol dependence—the last often being an ill-considered attempt at reducing visual disturbances. Although treatment of HPPD is often only palliative, alertness to reversible comorbid issues is crucial for a successful outcome.

#### Course

While at least 40% of LSD users report transient lingering visual effects following drug use, only a small percentage appear to develop HPPD. Among those, HPPD becomes

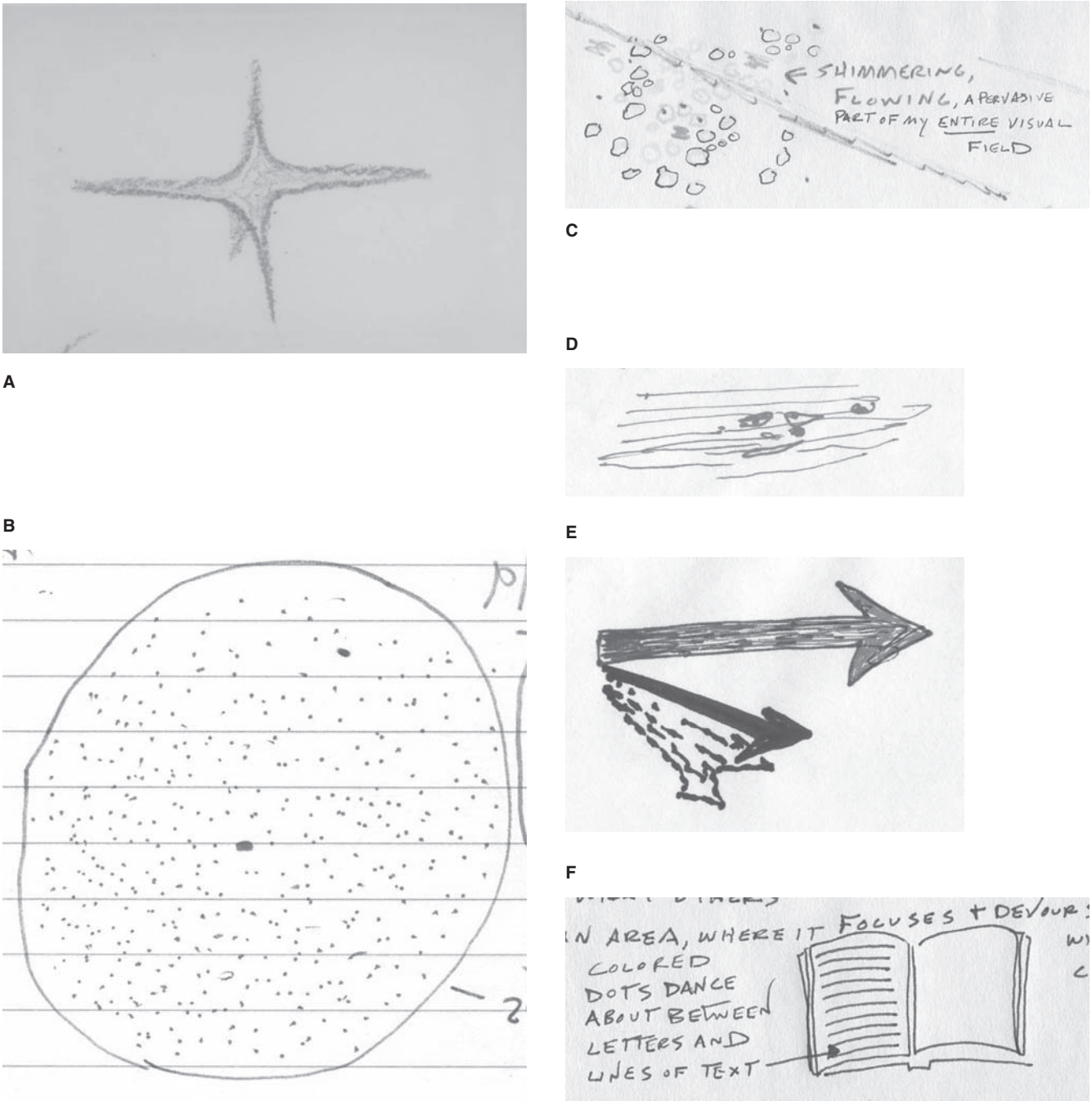



**Figure 60–6** *Drawings of hallucinations by patients with hallucinogen persisting perception disorder. These drawings of visual symptoms were made by actively symptomatic patients in a drug-free condition. Such imagery occurred to the patients on a daily basis. No patient was psychotic. Each knew that the visual disturbances were "not real." Image (A) the perception of flashes of light; (B) seeing countless dots moving in the air; (C) geometric shapes moving in swirling pattern; (D) pareidolia, in which the patient saw faces in the veneer of wood; (E) the trailing of afterimages as an arrow moved through the patient's visual field; (F) difficulty reading caused by moving afterimages of letters appearing on the paper suggesting an acquired dyslexia. (See Color Plate XIV)*

chronic in approximately half (Abraham 1983a). In the remainder, recovery tends to occur at a slow rate relatively impervious to pharmacological interventions.

## Differential Diagnosis

Although the typical HPPD patient tends to correctly diagnose the condition himself by consulting the DSM-IV-TR or internet sites devoted to HPPD, it is not uncommon for him to consult multiple clinicians for care before a clinical diagnosis is made. Because the symptoms are primarily perceptual, an HPPD subject may consult an ophthalmologist, neurologist, or psychologist before seeing a psychiatrist. Despite a patient's certainty about his diagnosis, the clinician is obligated to rule out other

sources of chronic organic hallucinosis, including other drug toxicities, neurodegenerative disorders, stroke, CNS tumors, infections, and head trauma. Magnetic resonance imaging of the brain is usually negative. Quantitative electroencephalography shows accelerated alpha and visual evoked potentials, especially in the posterior cerebrum.

## Etiology and Pathophysiology

### Early Studies

Sandison et al. (1954) first described LSD-like experiences recurring days to weeks following the ingestion of LSD. Subsequent clinical reports of this phenomenon adopted the street label of "flashbacks" to describe persisting imagery and LSD-associated affect (Rosenthal 1964, Robbins et al. 1967, Holsten 1976, Horowitz 1969, Shick and Smith 1970). Anderson and O'Malley (1972) first suggested that the term "flashback" was a misnomer, since many patients described not simply flashes of imagery, but continuous visual disturbances.

### Neurobiology

A series of studies of HPPD patients beginning in 1982 (Abraham 1982, Abraham and Wolf 1988, Abraham and Duffy 1996, 2001) provided evidence for the hypothesis that the visual symptoms in HPPD arise from chronic disinhibition of the visual apparatus (See Figure 60–7).

In a study of color perception (Abraham 1982) drug-free LSD users observing a white disk on a yellow background tended to see the disk as yellow. This suggested that in scanning the object the visual system saw yellow but could not inhibit the signal well enough to see white. A formal battery of psychophysical studies (Abraham and Wolf 1988) confirmed that drug free LSD users had poor dark adaptation and flicker perception—both manifestations of visual disinhibition. Finally, in controlled quantitative EEG studies with HPPD patients, neural correlates of visual hallucinations were found, including stable measures of cortical disinhibition (Abraham and Duffy 1996), as well as increased synchrony in the primary visual cortex (see Figure 60–8).

Pharmacological probes comparing an intravenous benzodiazepine to an antihistamine to inhibit visual symptoms in HPPD found that the former was superior even at the lowest doses (see Figure 60–9).

Further support for hallucinogen-mediated disinhibition of neurobehavioral systems comes from animal data, in which the hallucinogenic 5-$HT_{2A}$ agonist 2,5-dimethoxy-4-iodamphetamine (DOI) has been shown to disrupt sensory gating (Sipes and Geyer 1995).

## Treatment

### Treatment Goals

The goals of treatment are to reduce patients' unpleasant symptoms and improve function when possible. Since comorbid substance abuse is common, addressing that in a productive way is essential. Alcohol is reported by patients to reduce their symptoms, though in one study, 22 (65%) of "psychedelic drug users" reported alcohol or marijuana triggered flashbacks (Matefy et al. 1978). Benzodiazepines have been shown in case series to be helpful. These observations make symptom relief potentially difficult to balance with possible comorbid substance abuse.

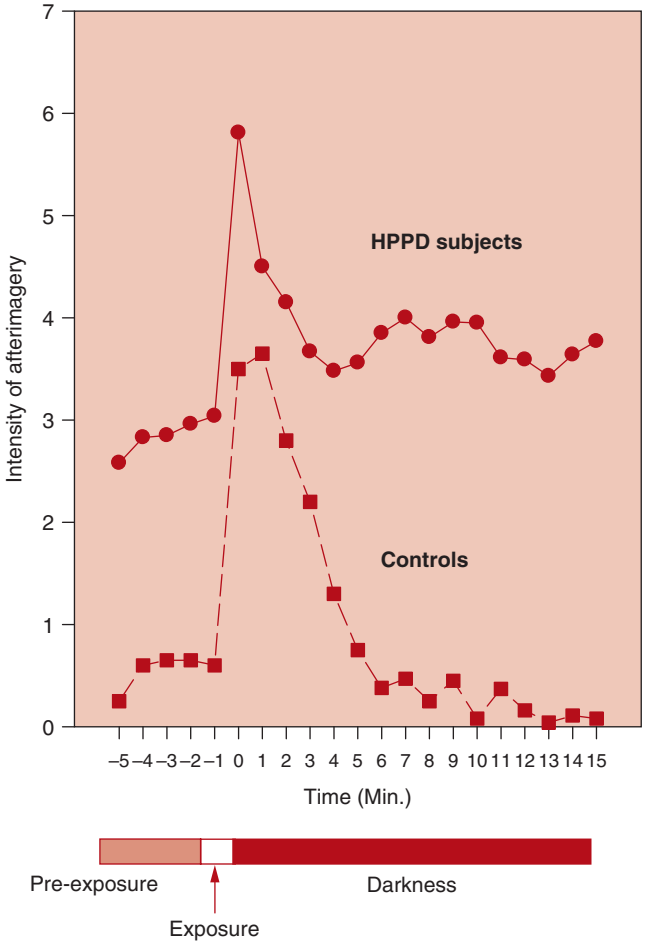



**Figure 60–7** *Persistence of afterimagery in HPPD and LSD-naïve controls. Twelve subjects with HPPD were compared to 12 nondrug controls on the persistence of experimentally induced afterimagery. For each minute of the study the subject was asked to score on a Likert scale from zero to seven the intensity of any afterimagery seen. Testing involved a 10 min preadaptation period, a 30 s fixation period at a light source, and a 15 min period in the dark. The intensity of afterimagery in HPPD SS exceeded that of controls at every point. At 15 min, image intensity persisted in the HPPD SS and exceeded their own pre-exposure baseline.*

### Somatic Treatments

Treatment is palliative. Benzodiazepines, olanzapine, sertraline, naltrexone, and clonidine have been reported to help in selected cases (Young 1997, Lerner et al. 1997, 1998, 2000, 2001, Aldurra and Crayton 2001, Alcantara 1998, Lauterback et al. 2000, for review see Halpern and Pope 2003). Benzodiazepines have been repeatedly recommended, though occasionally patients with HPPD will abuse them as a means of reducing these symptoms. One study of 16 patients receiving clonazepam 2 mg daily for 6 months showed significant and persistent improvement of HPPD symptoms (Lerner et al. 2003). Risperidone has been reported to exacerbate HPPD symptoms (Abraham and Mamen 1996). A single exposure to marijuana has been clinically observed to induce a prolonged exacerbation of HPPD. Because HPPD is also exacerbated by CNS arousal, affect, stress, and stimulants, these are to be reduced or avoided. HPPD is worse

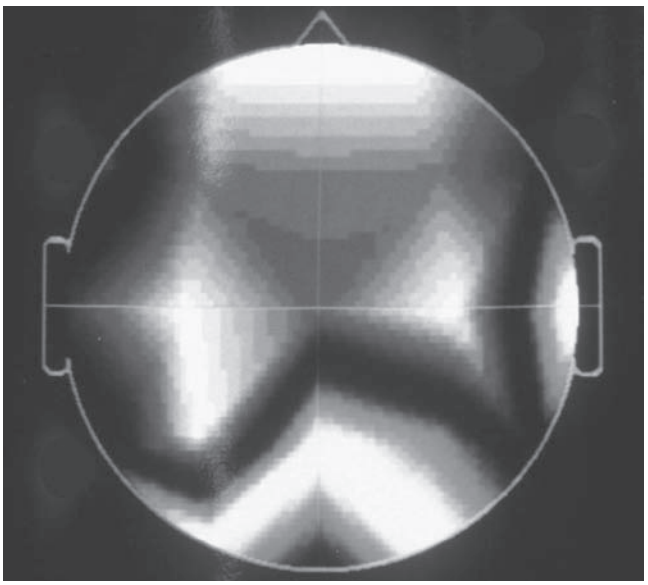


**Figure 60–8** *Increased EEG coherence in HPPD subjects between occipital electrodes. Thirty-eight actively symptomatic HPPD subjects and 33 controls were tested for electrical coherence, a measure of cortical coupling, between adjacent electrode pairs in the eyes open and closed states. The figure is a T-statistics Significance Probability Map of group differences in t-scores derived from mean coherence values at each pixel. Coherence is measured from the OZ electrode at 6 Hz. The view is top down, with the nose at the top. Increased coherence, denoted by a color gray scale, is increased occipitally denoted in white, and in the right temporal electrodes, in the HPPD sample with eyes closed, when visual hallucinations are reported to be more vivid. A global reduction in coherence is seen in HPPD between occipital and more distant electrodes, when compared to controls. (See the original publication for actual color values.) (Source: Reprinted with permission from Abraham HD and Duffy FH (2001) EEG coherence in post-LSD visual hallucinations. Journal of Psychiatric Research 107, 151–163 Copyright Elsevier (2001).) (See Color Plate XV)*

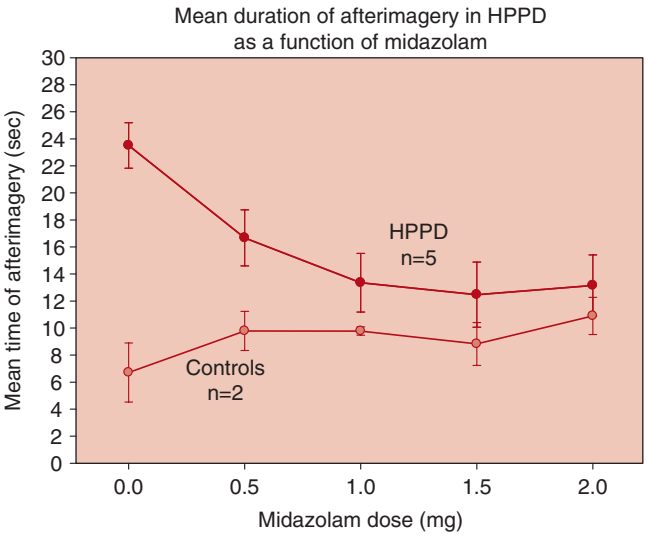



**Figure 60–9** *The effect of midazolam on HPPD afterimagery. Five HPPD subjects and two drug-naïve controls were studied over a 20 week period to test whether midazolam reduces visual symptoms of HPPD. Drug doses were given intravenously in a randomized, double-blind design every 2 weeks. Afterimages were generated by having a subject stare at a rotating black disk covered with random white dots, and then reporting image intensity on a 7-point Likert scale. Afterimages were reduced as a function of increasing doses of midazolam, but not doses of diphenhydramine (data not shown).*

with one's eyes closed, or when entering a dark environment. Thus, sunglasses, which serve to reduce the difference between outdoor and indoor luminance, may reduce HPPD symptoms when the patient enters an interior space.

### Psychosocial Treatments

Engaging patients with ongoing comorbid substance abuse into 12-step programs or other psychotherapeutic treatments aimed at reducing substance abuse is important for overall outcome (El-Mallakh 1998).

### Issues in the Clinician–Patient Relationship

Trust is essential in all clinical relationships. Trust is enhanced when the clinician is able to make the correct diagnosis quickly, takes the patient's reports seriously, and is able to prescribe effective treatments. In this regard, a careful history that allows the clinician to distinguish HPPD from primary psychoses is essential. Realizing that some antipsychotic agents, e.g., risperidone, may worsen the illness, clinicians should avoid such treatments. Similarly, reports of transient symptom relief from alcohol should not be written off as an excuse to continue to abuse alcohol, but should be recognized as a risk factor for alcohol dependence and possible benefit from a careful trial of GABA-A agonists (Abraham and Fava 1999). While alcohol acutely provides some measure of anxiolysis, rebound anxiety from pathologic overuse may hasten the reemergence or worsening of HPPD overall. Evidence, as noted above, exists that alcohol can trigger HPPD, despite patient self-reports of symptom amelioration with alcohol.

## Treatment Refractory Patients

There is a paucity of research in the area of treatment of HPPD (Halpern and Pope 2003). Although HPPD appears to be permanent in many cases, slow but steady recovery in some appears possible over a period of years. Beneficial factors appear to be avoidance of drugs and alcohol, enduring relationships and productive work. One of us (HDA) has followed a cohort of HPPD patients who have functioned well in their families and careers for three decades. It is common for a recovering HPPD patient to admit that visual disturbances are ever present but that involvement in meaningful tasks of daily life push the symptoms to the periphery of awareness.

# MDMA

## Diagnosis

### Definition and Diagnostic Features

The definition of hallucinogen abuse according to DSM-IV-TR is shown above.

### Assessment

A typical MDMA user is a college student (Pope et al. 2001, Peroutka et al. 1988). In a survey of 14,000 college students in 119 American colleges, MDMA users were more likely to use marijuana, smoke cigarettes, and engage in binge alcohol consumption (Strote et al. 2002). They were also more likely to have multiple sex partners (Strote et al. 2002). They considered arts and parties important, but they were not academic underachievers (Strote et al. 2002).

In a study of 132 pregnant MDMA users compared with 122 nonusers, several characteristics stood out. The MDMA-using women were younger (23.2 versus 31.2 years old, $P < 0.0001$), experienced more unplanned pregnancies (84.2 versus 54.3%, $P < 0.05$), and were more likely to be single parents (57.0 versus 18.3%, $P < 0.001$) (Ho et al. 2001). Over half abused alcohol (66.4% versus 37.3%, $P < 0.001$), and a greater fraction abused other drugs (not significant) (Ho et al. 2001). Over a third reported some psychiatric problem, but only 6.5% had a psychiatric diagnosis (Ho et al. 2001). While other drug use appears more common in subjects using MDMA, it is of interest to note that in over one third, their first exposure to illicit drugs is in the setting of MDMA use (Gervin et al. 2001).

## Epidemiology

Despite its existence for nearly 90 years, there was no significant nonmedical use of MDMA until the late 1970s. While there is some evidence that a very small number of people intentionally or unintentionally sampled MDMA during the 1960s (see Gaston and Rasmussen 1972, Shulgin and Shulgin 1991), MDMA use began in earnest during or shortly after therapists began experimenting with it as an adjunct to psychotherapy. Early use of MDMA was generally in small groups in private settings (Peroutka et al. 1988). Accurate epidemiologic data was not collected until 1983 when SAMHSA's Office of Applied Studies started to include specific questions about MDMA in their National Survey on Drug Use and Health and it wasn't until 1989 that the National Institute on Drug Abuse's Monitoring the Future survey also collected such data. By 1997, about 2.8% of a sample of college students reported using MDMA (Strote et al. 2002). College is the first time people are likely to begin use of MDMA (Randell 1992, Cuomo et al. 1994). In a survey of 14,000 college students at 119 American colleges by the Harvard School of Public Health College Alcohol Study, there was a 69% increase in use between 1997 and 1999 (from 2.8% to 4.7%) (Strote et al. 2002). Over the same time, the use of marijuana did not significantly change (38.5% in 1997 and 37.6% in 2000) (Strote et al. 2002). Use by all age groups has leveled off or declined in the intervening years. Use by 12$^{th}$ grade of high school remains substantial. Use by high school seniors peaked in 2001 with 11.7% reporting taking MDMA at least once in their lifetime contrasting with 6.5% in 2006. By 2006, 89% of high school seniors report disapproval of trying MDMA once or twice (Johnston et al. 2006). The popularity of MDMA is not just an American phenomenon, but is seen in Europe (Cregg and Traqcey 1993, Christophersen 2000), Australia (Topp et al. 1999) and Brazil (de Almeida and Silva 2005, Battisti et al. 2006).

In addition to increased popularity of MDMA, the pattern of use appears to have changed. Initial use was in small groups at doses ranging from 75 to 150 mg with an occasional booster of 50 to 100 mg (Downing 1986, Siegel 1986, Peroutka et al. 1988, Liester et al. 1992). The 1990s saw the onset of the rave phenomenon. These are generally large gatherings in warehouses or dance clubs. Dosages utilized in raves are much more variable ranging from 100 to 750 mg and as high as 1250 mg/night (Brown et al. 1995, Forsyth 1996). MDMA users are less likely to see the drug as harmful (Yacoubian et al. 2003). The introduction of testing services that ensure that illicit pills contain MDMA (e.g., DanceSafe) has removed an additional deterrent to some rave attendees (Dundes 2003) but such services are not accessed by a majority of users. Moerover, these services are not as readily known since passage of the Illicit Drug Anti-Proliferation Act of 2003. This U.S. federal law provides for serious criminal sanction against party promoters and club owners who knowingly host parties that encourage the use of drugs like MDMA. Because of concern that their presence may constitute "evidence" of violation of this Act, organizations, such as DanceSafe, are not typically invited anymore into clubs and rave events to offer their "harm reduction" education materials and pill testing for the presence of MDMA. Concomitant drug use is also more common in raves (Gerhard 2001, Gervin et al. 2001, Strote et al. 2002). These include alcohol, marijuana, and opiates. Furthermore, the term "ecstasy," which was originally used to refer specifically to MDMA (Hamid et al. 2005), has grown to refer to other related compounds such as MDA and 3,4-methylenedixoyethylamphetamine (MDE or "Eve") (Gerhard 2001) and to "club drugs" in general. The combination of multiple drug use increases the risks of adverse consequences associated with MDMA use (see below).

Prior to its placement on Schedule I by the DEA, MDMA was tested as an adjunct to psychotherapy (Shulgin and Nichols 1978, Greer and Tolbert 1986, 1998). In this setting, a dosage of 50–200 mg (with modal doses ranging from 100 to 150 mg), with a booster of 50–75 mg several hours later, was used. There are no published controlled studies of the use of MDMA in psychotherapy. However, there is one open study of 29 subjects in which the dosage used was 75–150 mg after a 6-h fast with an offered second dose of 50–75 mg. All subjects reported positive attitudinal and emotional changes (Greer and Tolbert 1986). Twenty-two felt that their insight into their own psychopathology was enhanced. Twenty-one subjects in couples treatment reported increased closeness and communication with their partner (Greer and Tolbert 1986). All subjects reported minor adverse consequences similar to those reported by recreational drug users. Two controlled experiments are ongoing in the United States with MDMA-assisted psychotherapy. One is examining this experimental treatment for refractory PTSD patients, the other is evaluating whether this may be helpful with advanced stage cancer patients struggling with treatment-refractory anxiety disorder secondary to a general medical condition.

## Comorbidity Patterns

Other drug use, particularly marijuana (98%) and alcohol (65%), is very common in subjects using MDMA (Wish et al. 2006, Breen et al. 2006). Tobacco use is also quite common (Boyd et al. 2003). Individuals who use high doses of MDMA are more likely to abuse other agents (Clatts et al. 2005). For approximately one-third of MDMA plus other substance users, MDMA was their initial illicit drug used in one study (Gervin et al. 2001). Tobacco and alcohol are the key "gateway" drugs to other intoxicant experimentatation.

Comorbid psychiatric conditions are also more common in MDMA users (Martins et al. 2006). Over half (55%) of MDMA users in one study had a comorbid psychiatric condition with 35.3 % experiencing at least one lifetime major depression and 25.4% with antisocial personality disorder (Flack et al. 2006). The majority of MDMA users

with mental illness report mental health problems prior to initiation of MDMA use (Lieb et al. 2002).

### Course

In general, people who use MDMA do not display a pattern of tolerance and increasing drug use. MDMA users generally limit the frequency of use of the drug. Most report limiting use of MDMA to twice per month or less. Fridays and Saturdays are the most common days for ingestion because users say they need one day to recover after use (Peroutka et al. 1988, Liester et al. 1992). More frequent use is associated with a loss of the desired effect of the drug (Gerhard 2001). Approximately 6 years after initiation of MDMA use, individuals begin to reassess their use pattern (Murphy et al. 2006). However, some individuals may use very high doses of MDMA or use it frequently. Such use, particularly when mixed with other drugs, may lead to adverse physical or cognitive consequences of MDMA use. Subjects with problematic MDMA use tend to use higher doses of the drug, including in binges, and are more likely to have both a personal and a family psychiatric history (Soar et al. 2006). While there is clearly an interplay between psychiatric problems and adverse consequences, most people who have been diagnosed with depression report having the depressive disorder diagnosis prior to MDMA use (Guillot and Greenway 2006, Huizink et al. 2006, Lieb et al. 2002).

### Differential Diagnosis

Other agents, such as MDA and alpha-ethyltryptamine (AET), may have similar effects to MDMA.

### Differences in Developmental, Gender, and Cultural Presentations

Females appear to be more sensitive to some of MDMA's acute effects compared to males (Liechti et al. 2001), an effect sometimes seen in rodents (Palenicek et al. 2005, Walker et al. 2007). Males are more likely to be heavy users of MDMA than females (Milani et al. 2004); however, women are more likely to experience psychopathology (Milani et al. 2004). Women using MDMA believe it reduces weight gain and increases their exercise duration, but do not use it primarily for weight control (Curran and Robjant 2006).

MDMA use is associated with increases in impulsivity. In heterosexual males, this is associated with an increase in the number of sex partners, in females it may contribute to significantly higher rate of unplanned pregnancies. In homosexual men, it may present with increased rate of unprotected anal sex (Ho et al. 2001, Clatts et al. 2005, Novoa et al. 2005). Homosexual subjects are also at greater risk for using "club drugs" which include MDMA (Lampinen et al. 2006).

## Etiology and Pathophysiology

### Neurobiological Factors

Former chronic ecstasy users (an average of 527 tablets) have higher self-reported depression as measured by the Beck Depression Inventory than non-drug-using controls (MacInnes et al. 2001). A meta-analysis of the small number of studies examining this issue also found a small depressogenic effect with prolonged MDMA use but noted that in most studies controlling for concomitant drug use was inadequate (Sumnall and Cole 2005). The predictors of developing this depressive syndrome are maximum quantity of pills consumed over a 12-h period and mild and frequent life stress (MacInnes et al. 2001). Pre-MDMA onset of a depressive disorder may contribute to and confuse the etiology of this depressive picture (Guillot and Greenway 2006, Huizink et al. 2006). Heavy MDMA use has also been associated with higher rates of psychopathology, including obsessive and compulsive behaviors, anxiety, somatization, and loss of libido (Parrott et al. 2001). The cause-and-effect relationship between MDMA use and these psychiatric syndromes is unclear, but since these syndromes involve serotonergic mechanisms, additional investigation into these potential long-term sequelae is warranted.

MDMA users have been noted to have problems with memory, attention, reasoning, and impulse control (Krystal and Price 1992, Allen et al. 1993, Parrott and Lasky 1998, McCann et al. 1999, Gouzoulis-Mayfrank et al. 2000, McGuire 2000, Reneman et al. 2000, 2001b, Bhattachary and Powell 2001, Verkes et al. 2001, Medina and Shear 2006). Heavy MDMA users (>55 life time tablets) suffered long-lived (after one year of abstinence) cognitive decline while moderate users (<55 life time tablets) did not have persisting cognitive sequelae (Reneman 2006a). Memory deficits can persist for at least 2 years after cessation of MDMA (Ward et al. 2006). In a study of 22 recent MDMA users, 16 ex-users (abstinent for over 1 year), and 13 normal controls who underwent the Rey Auditory Verbal Learning test, the immediate recall score (47, 48, and 60, respectively, $P = 0.001$) and the delayed recall score (9.8, 10.1, and 13.1, respectively, $P = 0.003$) were significantly less in recent and remote MDMA users than in normal controls, suggesting that the memory dysfunction persists for more than 1 year (Reneman et al. 2001b). The memory difficulties persisted despite recovery of serotonergic abnormalities on SPECT (Reneman et al. 2001b). Similarly, 15 MDMA users were tested initially after a 2-week abstinence, and again a year later (Zakzanis and Young 2001). The subjects who continued to use MDMA experienced a progressive decline of both immediate and delayed recall (Zakzanis and Young 2001). In 21 heavy users, 21 moderate users, and 20 nonusers, there was a "statistically significant but clinically small" decline in memory and prolongation of reaction time (Verkes et al. 2001). Heavy users were more affected than moderate users (Verkes et al. 2001).

In 80 subjects, which included novice users, regular users, and ex-users compared to nonusers, all MDMA subjects had decreased verbal fluency, decreased immediate prose recall, and decreased delayed prose recall, but no change in visual recall (Bhattachary and Powell 2001). The number of days since last MDMA use and total lifetime dose accounted for over 50% of the variance, suggesting both a dose–response effect and a possible recovery process (Bhattachary and Powell 2001). The relative sparing of visual recall is of interest since decline in 5-$HT_{2A}$ receptor density after MDMA use is a characteristic of all brain regions except the occipital cortex in rats and humans, where MDMA upregulates the receptor density (Reneman et al. 2002a). Nevertheless, studies of neurocognition and MDMA use, particularly studies that report verbal memory deficits, are often challenged by problems of statistical power and the confounds of demographics, comorbid drug use, and premorbid psychopathology.

MDMA is toxic to serotonergic neurons at high doses (10 mg/kg). This has been documented in several species including rats (Stone et al. 1986, Schmidt et al. 1986, Schmidt 1987, Cummins et al. 1987, O'Hearn et al. 1988, Slikker et al. 1988, 1989), mice (Stone et al. 1986), guinea pigs (Schmidt et al. 1986), and monkeys (Slikker et al. 1988, 1989, Ricaurte et al. 1988, 1992, Insel et al. 1989, Wilson et al. 1989, Fischer et al. 1995, Hatzidimitriou et al. 1999). Serotonergic loss is evident through several markers which include reduced brain serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and the serotonin transporter (Schmidt et al. 1986, Battaglia et al. 1987, Schmidt 1987, Commins et al. 1987, O'Hearn et al. 1988, Slikker et al. 1988, 1989, Acquas et al. 2001).

Immunocytochemical studies suggest that serotonergic neurons are damaged, but the cell bodies are preserved (O'Hearn et al. 1988, Wilson et al. 1989, Molliver et al. 1990). Recovery from MDMA-induced serotonergic damage occurs. While rodents appear to recover (Scanzello et al. 1993), in monkeys the damage persists at least 7 years (Ricaurte et al. 1992, Fischer et al. 1995, Hatzidimitriou et al. 1999).

In humans, serotonergic changes after repeated MDMA use are evident through several different types of studies. CSF 5-HIAA levels may be reduced in MDMA users (McCann et al. 1994). This effect is more pronounced in women than in men (McCann et al. 1994) and possibly represents changes in serotonergic turnover rather than persistent neurotoxicity (Mechan et al. 2005). *N*-acetyl aspartate (NAA, a marker of cellular health) was quantified with magnetic resonance spectroscopy in 15 MDMA users and 12 age-matched controls. NAA was significantly reduced in the frontal cortex, but not in the parietal or occipital cortex (Reneman et al. 2001c, 2002b). This effect appears to be dose related (Reneman et al. 2002b). In a prospective study of low dose MDMA, no decrease in the NAA signal was noted (de Win et al. 2007). The extent of previous MDMA use and frontal cortical neuronal loss were significantly associated, indicating that cortical damage is directly related to extent of MDMA use. McCann et al. (2005), utilizing PET methodology, found global reductions in serotonin transporter expression in some MDMA users. Semple et al. (1999) found similar results with SPECT in MDMA users compared to controls. Reneman et al. (2001a, 2001b) also used SPECT and [$^{123}$I]-2beta-carbomethoxy-3beta-(4-iodophenyl) tropane, which binds to both the serotonin and dopamine transporters with high affinity (Laruelle et al. 1994, Lew et al. 1996), and found that serotonin transporter binding was reduced in female heavy users but not male users (Reneman et al. 2001a, 2001b). This provides independent support to the finding that women are more susceptible to damage by MDMA. In subjects abstinent from MDMA for over 1 year, recovery of serotonin transporter density to normal levels was evident (Reneman et al. 2001a).

The confounding of human MDMA studies from other drugs presents an enduring difficulty in the literature. Croft et al. (2001) studied 18 pure cannabis abusers, 11 that use both cannabis and MDMA, and 31 subjects who use neither cannabis nor MDMA. They report that both cannabis and MDMA/cannabis users showed equal impairment in memory, learning, work fluency, speed of processing and manual dexterity compared to normal controls (Croft et al. 2001). This suggests that reports of cognitive decline attributed to MDMA use may be due to concomitant use of cannabis. Similar confounding has been observed in MDMA users with concomitant abuse of alcohol, marijuana, opioids, and inhalants (Medina and Shear 2006). Confounding is not supported as an explanation by animal or cellular studies (Krystal and Price 1992, Allen et al. 1993, Parrott and Lasky 1998, McCann et al. 1999, Gouzoulis-Mayfrank et al. 2000, McGuire 2000, Reneman et al. 2000a, 2000b, Bhattachary and Powell 2001, Zakzanis and Young 2001, Stone et al. 1986, Simantov and Tauber 1997, Hatzidimitriou et al. 1999, Taffe et al. 2001). A review of this question by Gouzoulis-Mayfrank and Daumann (2006) concluded that neural injury in humans can occur in heavy MDMA use, but that the evidence cannot be considered definite until preexisting traits and polydrug drug abuse are addressed. These very factors have been tackled in one study (Halpern et al. 2004) where neurocognitive testing was given to 23 MDMA users and 16 nonusers all of whom had little to no experience with other drugs (including alcohol) and in which premorbid functioning was sought through questions about parental education and employment and subject conduct in childhood. Overall, MDMA users did not differentiate in performance from the controls on any measure, but a post-hoc median split revealed that the heavy users ($N = 11$) did statistically worse on measures of impulsivity and mental processing speed. This study did not find the type or pattern of deficits as noted in the other studies above on polydrug MDMA users and is most suggestive that confounding has impacted human data collection on this issue of MDMA and neurocognitive health.

## Metabolism and Pharmacokinetics

MDMA is usually present in two optical isomers. The dextrorotary form, *S*-(+)-MDMA is more potent in the CNS than the levorotary form *R*-(-)-MDMA (Anderson et al. 1978). MDMA is broken down by *N*-demethylation, *O*-dealkylation, deamination, and conjugation. MDMA is metabolized into MDA (which itself is sometimes used recreationally), 4-hydroxy-3-methoxymethamphetamine (HMMA), and the main metabolite 3,4-dihydroxymethamphetamine (HHMA) (Helmlin et al. 1996, Fallon et al. 1999, Maurer et al. 2000, Pizarro et al. 2004). MDA can also be metabolized to HHMA and HMMA, which are either excreted unchanged in the urine or are glucuronidated prior to urinary excretion (Helmlin et al. 1996, Fallon et al. 1999, Maurer et al. 2000, de la Torre et al. 2004). HHMA plasma levels will peak at approximately the same concentration as the parent drug but ultimately accounts for only 17.7% of total drug recovered in a 24-h urine collection (Segura et al. 2001). The combination of MDMA and HHMA accounts for over 60% of total drug in the urine after 21 h (Helmlin et al. 1996).

The MDA metabolite peaks at around 2–6 h after an oral MDMA dose of 50–150 mg (Helmlin et al. 1996, de la Torre et al. 2000, Verebey et al. 1988). MDA accounts for less than 5 to 28% of MDMA (Helmlin et al. 1996, de la Torre et al. 2000, Verebey et al. 1988).

Maximum plasma MDMA concentrations are achieved 2–4 h after ingestion. In a study of two subjects who had previously used MDMA, the level peaked between 2 and 6 h at greater than 20 ng/mL (Pacifici et al. 2001). Mas et al. (1999)

found that the half-life of a lower dose (75 mg) was shorter (7.7 h) than a higher dose (125 mg at 8.6 h). Measured peak plasma concentrations were 130.9 ng/mL after 75 mg and 236.4 ng/mL after 125 mg (Mas et al. 1999). Similarly, de la Torre et al. (2000) found a dose-related peak plasma concentration in extensive metabolizer variants of CYP 2D6. (Extensive metabolizers possess enzymes that metabolize the drug at a faster rate than the general population.)

The peak MDMA concentration increases disproportionately in a nonlinear fashion compared to the metabolites. This suggests that the demethylating enzyme step is saturable with increasing MDMA dose (Figure ) (de la Torre et al. 2000).

The more active *S*-(+)-MDMA isomer is metabolized faster (Fallon et al. 1999, Cho et al. 1990) and more extensively (Fallon et al. 1999, Fitzgerald et al. 1989) than the levorotary form, so that the half-life of *S*-(+)-MDMA is 73.8 to 210 min while the half-life of *R*-(-)-MDMA is 100.7 to 350 min (Fallon et al. 1999, Verebey et al. 1988, Pacifici et al. 2001). The mean plasma concentration of the levorotary form is 2.4 times higher than the *S*-(+) isomer and a significantly greater amount is excreted unchanged in the urine (Fallon et al. 1999). MDMA in brain microsomes is metabolized primarily through *O*-dealkylation (Lin et al. 1992). Isomer-specific brain metabolism has not been studied.

Because MDMA is metabolized by CYP 2D6, some researchers expressed concern that MDMA might pose a risk in CYP 2D6 poor metabolizers (Schifano 2004). However, it appears that poor metabolizers are not greatly affected by MDMA (de la Torre et al. 2004, Segura et al. 2005). As well, Gilhooly and Daly (2002) failed to find higher numbers of poor metabolizers among ecstasy-related fatalities.

## Pharmacology

MDMA causes a calcium-independent release of serotonin (5-HT) from nerve endings (Johnson et al. 1986, McKenna and Peroutka 1990) with concomitant inhibition of serotonin reuptake (Steele et al. 1987). The dextrorotary enantiomer, *S*-(+)-MDMA, is more potent than the levorotary isoform (Johnson et al. 1986, Steele et al. 1987, Hiramatsu and Cho 1990). MDMA has a very low affinity for postsynaptic serotonin receptors (Lyon et al. 1986, Bettaglia et al. 1988). It also increases dopamine release (Yamamoto and Spanos 1988, Hiramatsu and Cho 1990, Nash et al. 1990) but this effect is less than the effect on serotonin (Johnson et al. 1986, Steele et al. 1987, McKenna and Peroutka 1990). There is also a dose-related increase in cortical acetylcholine (ACh) release (Acquas et al. 2001) but this may be mediated by serotonergic and dopaminergic mechanisms (Nair and Gudelsky 2006a) and may not have significant impact on ACh function (Nair and Gudelsky 2006b). The cortex is more sensitive to MDMA than the striatum: 3.2 mg/kg MDMA increases ACh release in the cortex some 141%, but only 32% in the striatum (Acquas et al. 2001). It is believed that the effects on 5-HT mediate most of the psychological effects of MDMA.

Indirect evidence of serotonergic involvement is found in neuroendocrine studies. In animals, MDMA treatment produces a profound increase in serum corticosterone and prolactin (Nash et al. 1988, Poland et al. 1997). This effect is attenuated or blocked by pretreatment with the serotonin neurotoxin, *p*-chlorophenylalanine (Nash et al. 1988), suggesting that the process is mediated by serotonin. MDMA at doses of 75 mg is associated with an increase in serum cortisol, while doses greater than 75 mg increase both cortisol and prolactin (Grob et al. 1996, Mas et al. 1999). The prolactin response to serotonin agonists, such as fenfluramine, is generally blunted in MDMA users compared to controls (Price et al. 1989, Verkes et al. 2001, Gerra et al. 1998, 2000, Gouzoulis-Mayfrank et al. 2002). However, since concomitant drug use, particularly marijuana, is so common in ecstasy users, all these studies are confounded by potential cannabis effects (Gouzoulis-Mayfrank et al. 2002). Consequently, this may be one of the reasons that studies using L-tryptophan as a neuroendocrine challenge have been negative (L-tryptophan is a serotonin precursor and increases brain serotonin levels) (Price et al. 1990, McCann et al. 1994). Alternatively, L-tryptophan challenge may be insufficiently sensitive. Many variables can influence neuroendocrine findings. In a naturalistic study of nightclub attendees, Wolff et al. (2006) found increased oxytocin only in people with detectable levels of MDMA, suggesting a role for this hormone both in increased feelings of affiliation and in changes in sodium regulation.

## Genetic Factors

Since MDMA has weak serotonin reuptake inhibitory action (Steele et al. 1987), the effect of serotonin transporter polymorphism has been investigated. Individuals with the short form of the serotonin transporter (homozygotes for the short form, ss) had reduced discrimination between between high and low probabilities of winning and a reduced reflection effect on gains-only/losses-only trials compared to short form homozygotes that do not use MDMA (Roiser et al. 2006). In other words, MDMA use may interact with serotonin transporter polymorphism to effect decision-making strategies (Roiser et al. 2006). However, serotonin transporter polymorphism did not predict the long-term cognitive decrements that can occur in heavy MDMA users (Reneman et al. 2006a).

## Acute Positive Psychological Effects

Subjects utilizing MDMA frequently report positive mood and emotional effects. They report increased self-esteem, high energy, relaxation, and joy (Cami et al. 2000, Liechti et al. 2001, Harris et al. 2002, Tancer and Johanson 2003). In the dose range of 1.75 to 4.18 mg/kg, most subjects report euphoria, increased physical and emotional energy, and a heightened sensual awareness (Downing 1986). In a double-blind, placebo-controlled study of 13 MDMA-naïve subjects given 1.7 mg/kg (about 119 to a 70 kg person), MDMA induced enhanced mood, a sense of improved well-being, increased emotional sensitivity, increased energy, and a heightened sensory awareness (Vollenweider et al. 1998). Similar findings were reported in another double-blind study (Grob et al. 1996). In a double-blind, placebo-controlled comparison study of MDMA 75 mg, MDMA 125 mg, and amphetamine 40 mg, all subjects reported an euphoria, but this feeling was greatest in the MDMA 125 mg group (Cami et al. 2000). In another blinded comparison of escalating MDMA doses and *m*-chlorophenylpeprazine (mCPP), a serotonin releasing agent, both drugs produced euphorogenic and hallucinogenic effects to a similar degree (Tancer and Johanson 2001). Participants reported feeling more talkative

and friendly after MDMA (Tancer and Johanson 2003, Vollenweider et al. 1998). The one attempt to assess feelings of empathy or closeness to others failed to detect it after 1.5 mg/kg MDMA (Harris et al. 2002), but the assessment consisted of two questions drawn from a larger questionnaire.

One of the most common reasons for using ecstasy is its effect on sexual drive. More than 90% of users report a moderate to profound increase in sexual desire and satisfaction (Zemishlany et al. 2001). Orgasm is reported as delayed but more intense (Zemishlany et al. 2001). However, in males, erection can be impaired in as many as 40% of subjects (Zemishlany et al. 2001).

## Acute Adverse Psychological Effects

Acute adverse effects include anxiety as well as alterations in perception, facilitated recall, and facilitated imagination (Cami et al. 2000, Vollenweider et al. 1998). MDMA acutely affects simple visual recall without affecting the ability to spot small changes in complex visual changes as noted in the first pharmacological challenge study involving change blindness (Ramaekers et al. 2006). As well as increasing positive mood, MDMA can increase anxiety and negatively experienced derealization (Cami et al. 2000, Harris et al. 2002, Liechti et al. 2001, Tancer and Johanson 2001), including anxiety related to feeling out of control. Altered perceptions (Siegel 1986, Vollenweider et al. 1998, Mas et al. 1999) may be experienced by some MDMA users as a negative consequence of the drug. In a double-blind, placebo-controlled study of 13 MDMA-naïve subjects, most reported anxiety, a mild depersonalization or derealization, a moderate thought disorder, and poor coordination (Vollenweider et al. 1998). In a study of 21 previous MDMA users given doses ranging from 1.75 to 4.18 mg/kg (an average of 175 mg for a 70 kg person), 40% reported impaired decision-making ability and 30% reported decreased mathematics performance (Downing 1986). When given as an adjunct for psychotherapy, all 29 subjects reported some adverse event (Greer and Tolbert 1986). Fatigue was the most common psychosomatic complaint (Greer and Tolbert 1986). Worsening or precipitation of panic attacks has been reported by several authors in different settings (Greer and Tolbert 1986). At least 49 cases of acute psychosis associated with MDMA use have been reported (Creighton et al. 1991, Cox 1993, Bone Pina et al. 2000, Milas 2000, Vaiva et al. 2001, Van Kampen and Katz 2001, Vecellio et al. 2003) including 32 in a 6-month follow-up study (Landabaso et al. 2002). In most of these cases there is use of concomitant substances. In several cases, the psychosis was long-lived for at least months. A wide range of impulsive or irrational behaviors have been associated with MDMA use (Dowling et al. 1987, Cadier and Clarke 1993, Hooft and Van der Voorde 1994, Cifasi and Long 1996). Most of these reports were published because they resulted in a major medical problem or death. MDMA use is associated with an increase in impulsive behaviors (Ho et al. 2001, Strote et al. 2002) and a reduced ability to measure risk when making risky decisions (Morgan et al. 2006).

## Physical Consequences of MDMA Use

MDMA increases blood pressure and heart rate (Grob et al. 1996, Lester et al. 2000, Mas et al. 1999, Vollenweider 1998). Chief side effects include decreased appetite, difficulty concentrating, impaired gait or balance, and tight jaw or jaw clenching (Harris et al. 2002, Liechti et al. 2001). Women more frequently reported experiencing side effects when compared with men (Liechti et al. 2001), while men showed a significantly greater increase in heart rate and body temperature. Humans exhibit complications that are related to both the sympathomimetic and serotonergic properties of MDMA. These include nausea, vomiting, anorexia, hypertension, palpitations, diaphoresis, headaches, difficulty walking, muscle aches and tension, hot and cold flashes, urinary urgency, nystagmus, blurred vision, insomnia, and dry mouth (Downing 1986, Greer and Tolbert 1986, Peroutka et al. 1988, Liester et al. 1992, Solowij et al. 1992, Topp et al. 1999). The common complaints of trismus and bruxism may reflect MDMA enhancement of serotonin activation of the 5-$HT_{1B}$ receptors of the trigeminal motor nuclei (Tancer and Johanson 2001).

In a survey study of 44 experienced MDMA users at an average dose of 120 mg (range 50–700 mg), all reported muscle tension, 91% reported diaphoresis, and 77% reported blurred vision and ataxia (Siegel 1986). Muscle tension in the form of trismus is a commonly reported adverse event (Downing 1986, Vollenweider et al. 1998). A transient gait disturbance was also common in a group of subjects who received MDMA as a psychotherapeutic adjunct, 21 MDMA users who received doses averaging 175 mg for a 70 kg subject, and 13 MDMA-naïve healthy controls (Downing 1986, Vollenweider et al. 1998). Other frequently reported acute physical consequences of MDMA use are hyperreflexia (Downing 1986), tachycardia, and hypertension (Grob et al. 1996).

Twenty-four hours after a single dose of MDMA averaging 119 mg in a 70 kg MDMA-naïve subject, a detailed evaluation revealed the presence of decreased energy, decreased appetite, restlessness, insomnia, and trismus (Vollenweider et al. 1998).

The acute motoric abnormalities have been related to driving impairment. A review of the literature noted at least 18 reports of driving impairment in people using MDMA (usually along with other drugs) (Logan and Couper 2001). These reports include six users stopped for speeding, eight for erratic driving, and five involved in collisions (Logan and Couper 2001). At least two MDMA-related deaths have been associated with automobiles (Hooft and Van der Voorde 1994, Cifasi and Long 1996). In a screen of intoxicated drivers in Norway, 2% of impaired drivers had MDMA in their blood, but 98% of these drivers had other drugs as well (Hausken et al. 2004). However, in a study of driving ability (using a simulator) after either MDMA alone or MDMA used with other drugs, MDMA alone was not associated with significant impairment, but combined drug use resulted in poor driving ability (Brookhuis et al. 2004). Notably, drivers with MDMA alone were unaware of taking increased risks while in the simulator (Brookhuis et al. 2004). A team in the Netherlands has performed a number of studies of effects of MDMA on driving skills (Kuypers et al. 2006, Lamers et al. 2003, Ramaekers et al. 2006). They found that 75 mg MDMA reduced weaving but impaired ability to estimate the time it took for an obscured object to move from one place to another, and they failed to find any effects of MDMA the day after drug administration (Ramaekers et al. 2006).

MDMA has been associated with a wide range of somatic toxic events. These include thrombotic or

hemorrhagic strokes (Harries and DeSilva 1992, Gledhill et al. 1993, Hughes et al. 1993, Manchanda and Connolly 1993, Rothwell and Grant 1993, Auer et al. 2002), leukoencephalopathy (Bertram et al. 1999), myocardial infarction (Qasim et al. 2001), arrhythmias (Dowling et al. 1987, Henry et al. 1992), and pneumothorax (Mazur and Hitchcock 2001). The wide range of manifestations suggests that most of these cases are either idiosyncratic or related to impurities remaining from the synthetic process. Since much of the MDMA supply is synthesized in small "basement" laboratories, the quality control of the manufacturing process may not be adequate. The results of weekly drug sampling in the Netherlands found that most (75% in 1996), but not all, "ecstasy" pills actually contained MDMA (Spruit 2001). The percentage dropped in 1997 and increased again in 1998 (Spruit 2001). About one-third of the pills contained amphetamine or other derivatives (Spruit 2001). These non-MDMA drugs might explain some of the heterogeneity of medical complications of "ecstasy" use. Certainly, the cases of hepatotoxicity (Henry et al. 1992, Shearman et al. 1992, Ijzermanset al. 1993, Khakoo et al. 1995, Ellis et al. 1996, Andreu et al. 1998, DeCarlis et al. 2001, Lawler et al. 2001, Brncic et al. 2006) and aplastic anemia (Marsh et al. 1994, Clark and Butt 1997) most likely are idiosyncratic or secondary to contaminants.

Cases of severe medical illness or death due to electrolyte and fluid abnormalities (Maxwell et al. 1993, Kessel 1994, Matthai et al. 1996, Hall 1997, Ajaelo et al. 1998, Magee et al. 1998, Holmes et al. 1999, O'Connor et al. 1999) and cases of multiple organ system failure (Henry et al. 1992, Brown and Osterloh 1987, Chadwick et al. 1991, Campkin and Davies 1992, Roberts and Wright 1993, Lehmann et al. 1995, Coore 1996, Demirkiran et al. 1996) are less likely due to MDMA use directly. These complications may be related to the specific environment in raves. In raves, people are exposed to hot, crowded environments with high-beat music invoking energetic dancing. In association with increased body temperature caused by MDMA (Liechti and Vollenweider 2000), dehydration and its consequences are increased at raves. Crowding has been shown to increase amphetamine toxicity in animals, a phenomenon labeled *aggregation toxicity* (Chance 1946, Hohn and Lasagna 1960). A similar phenomenon may occur in crowded raves in humans.

MDMA may also cause serotonergic hyperstimulation and produce a fatal serotonin syndrome-like (Sternback 1991) illness (Demirkiran et al. 1996, Mueller and Korey 1998).

### Social/Environmental Factors

Unlike many drugs of abuse, which are frequently used alone, MDMA is almost always used in the company of others. Most MDMA users report positive mood and emotional effects as they relate to others. In a survey of 44 experienced MDMA users, subjects reported a greater capacity for empathy, communication, and understanding (Downing 1986). MDMA use now is most common in large club gatherings.

## Treatment

There have been no studies examining the treatment of MDMA abuse or of its consequences. The issue of how a practitioner may help his/her patient discontinue MDMA abuse is never addressed in the literature. This is due to the rarity of presentation of subjects seeking treatment for MDMA addiction. Nonetheless, MDMA has abuse potential. Baboons will self-administer MDMA (Lamb and Griffiths 1987). Rhesus monkeys trained to self-administer cocaine, prefer MDMA (Beardsley et al. 1986). However, rhesus monkeys allowed to self-administer MDMA over an 18-month period reduce their administration over time (Fantegrossi et al. 2004). Also 50% of these animals will administer MDMA at a rate higher than they had administered cocaine. In several animal species that are trained to discriminate amphetamine from saline, MDMA easily substitutes for amphetamine (Glennon and Young 1984, Kamien et al. 1986). Animals treated with high-dose MDMA (40 mg/kg for 4 days) exhibit increased cocaine self-administration with rates twice those of saline-treated controls (Fletcher et al. 2001). Intracranial self-administration of MDMA lowers the threshold to a rewarding electrical stimulus to the medial forebrain bundle (Hubner et al. 1988). These data suggest that MDMA may facilitate the abuse of other substances. Indeed, humans who use MDMA rarely use the drug alone, and concomitant substance abuse then is likely (Wish et al. 2006, Breen et al. 2006). Thus, recommendation of 12-step programs and addressing other substance use is one reasonable approach.

### Treatment Goals

As with most issues regarding substance treatment, abstinence is generally the goal. "Controlled" MDMA use is actually possible (Peroutka et al. 1988, Liester et al. 1992), but MDMA abuse has led some users turn to heroin to "come down" (Gervin et al. 2001). In chronic users, drug education should reinforce the value of abstinence but also add information to reduce possible risks associated with future drug use.

### Somatic Treatments

There are no somatic treatments available that will reduce craving or MDMA abuse. However, somatic treatments are recommended for the consequences of MDMA abuse.

Psychosis secondary to MDMA has been treated with antipsychotic agents; one study suggests that olanzapine is effective (Landabaso et al. 2002). Second generation antipsychotic agents with significant 5-HT2C and 5-HT2A blockade (all atypicals with the exception of quetiapine) may be reasonable to use. Similarly, because of its ability to block postsynaptic 5-HT2C and 5-HT2A receptors (Sambunaris et al. 1997), mirtazepine has been recommended for depression associated with MDMA and used in at least one case (Fetter 2005). There have been no studies of anticholinergic agents or memantine in the treatment of cognitive dysfunction of MDMA.

### Special Factors Influencing Treatment

MDMA use during pregnancy may have consequences to the fetus. In studies with pregnant rats given MDMA, there is a documented entry of MDMA into the fetal compartment at significant levels (Campbell et al. 2006).

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CHAPTER

# 61 Substance Abuse: Inhalant-Related Disorders

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## Inhalant Intoxication

### Introduction

The term *inhalant abuse* is used to describe a variety of drug-using behaviors that cannot be classified by their pharmacology or toxicology but are grouped based on their primary mode of administration. Although other substances can be inhaled (e.g., tobacco, marijuana with or without phencyclidine, and even heroin or crack), volatilization is not the primary mode of administration; therefore, they do not fall into this classification. Solvent and propellant products vary by region and country, and also over time. With such a diverse group of substances included in a category, it is difficult to identify the chemical substances most prominently used by inhalant abusers. We will attempt to identify and classify abused chemical substances and the products containing them, characterize primary disorders and toxicities and discuss treatment issues. Types of products containing abused inhalants can be grouped as follows: (1) industrial or household cleaning and paint-type solvents including paint thinners or solvents, degreasers or dry cleaning solvents, solvents in glues, art or office supply solvents such as correction fluids, and solvents in magic markers (gasoline is similar to these products); (2) fluorocarbon propellant gases used in household or commercial products, in electronic (personal computer, office equipment) cleaners or as refrigerant gases; (3) butane/propane hydrocarbons are present in household aerosol sprays such as paint, hair, and fabric protector sprays, or in cigar lighters; (4) medical anesthetic gases such as ether, chloroform, halothane, and nitrous oxide (which is also available in whipped cream dispensers (e.g., whippets) and as octane boosters for car racing) and (5) aliphatic nitrites. Except for nitrites, the foregoing compounds affect the central nervous system (CNS) directly. As nitrites are mostly used as sexual enhancers rather than as mood alterants, the discussion of "inhalant abuse" will refer herein to the other volatile substances. Also, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) excludes anesthetics from the inhalant-related disorders section. Nationally, and in other surveys, anesthetics are included, as almost all of the inhalants act physiologically as would any anesthetic. With limited studies of the different issues, the authors do not limit their discussion to either category and try to discuss the issues utilizing the most current and available data.

### Substances Inhaled

Volatile substances (or inhalants) are ubiquitous. The practice of inhalation to produce euphoria can be traced to the ancient Greeks (Carroll 1977). At the turn of the 19th century, Humphrey Davy in England, experimenting with the newly discovered gas nitrous oxide, discovered its mind-altering effects (Bergman 1991). Ether and, later, chloroform parties occurred frequently; at one time, ether was suggested for treatment of alcohol addiction. These anesthetics are still abused (Hutchens and Kung 1985, Kringsholm 1980, Krenz et al. 2003). The 20th century brought the use of gasoline and along with it many other volatile mixtures including many solvents, cleaners, aerosols, degreasers, and glues. Table 61–1 enumerates many of the solvents (frequently noted on the labels) contained in products currently used for recreational purposes. Despite the widespread availability and inhalation of these substances, it was not

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**Table 61–1 Chemicals Commonly Found in Inhalants**

| Inhalant | Chemicals |
|---|---|
| **Adhesives** | |
| Airplane glue | Toluene, ethyl acetate |
| Rubber, household glues | Petroleum distillates, toluene, methyl chloride, acetone, methyl ethyl ketone, hexane, heptane |
| **Aerosols** | |
| Paint sprays | Butane, propane, fluorocarbons, toluene, xylene, hydrocarbons |
| Hair, deodorant sprays | Butane, propane |
| Air fresheners | Butane, propane |
| Analgesic, asthma sprays | Fluorocarbons |
| Fabric spray | Butane, trichloroethane |
| PC cleaners (AIR), dust removers | Dimethyl ether, hydrofluorocarbons |
| Head cleaner | Ethyl chloride |
| **Anesthetics** | |
| Gaseous | Nitrous oxide |
| Liquid | Halothane, enflurane |
| Local | Ethyl chloride |
| **Cleaning agents** | |
| Dry cleaners | Tetrachloroethylene, trichloroethane |
| Spot removers | Xylene, petroleum distillates, chlorohydrocarbons |
| Degreasers | Tetrachloroethylene, trichloroethane, trichloroethylene |
| Laquer thinners | Acetone, methanol, ethyl acetate, methyl chloride, toluene |
| **Solvents and gases** | |
| Nail polish remover | Acetone, ethyl acetate, (toluene rarely) |
| Paint remover | Toluene, methylene chloride, methanol, acetone, ethyl acetate |
| Paint thinners | Petroleum distillates, esters, acetone |
| Correction fluids and thinners | Trichloroethylene, trichloroethane |
| Cigar, charcoal lighter gases | Butane, isopropane |
| Cigar or cigarette lighter fluid | Petroleum distillates |
| Fire extinguisher propellant | Bromochlorodifluoromethane |
| **Food products** | |
| Whipped cream aerosols | Nitrous oxide |
| Whippets | Nitrous oxide |
| **Room odorizers** | |
| Poppers, fluids (rush, locker room) | Isoamyl, isobutyl, isopropyl, or butyl nitrite (now illegal) or cyclohexyl |

until the 1950s that reporters (Kerner 1988) and judicial action focused nationwide attention on "glue sniffing." Although this term is still used today, inhalant abuse has become the more common term used to describe the abuse of most of these substances. It is important to keep in mind that there are many different chemicals in many different products, most of which have dissimilar physiological effects and toxicities as well as unique chemical properties. Sometimes the substances are listed on the product label; however, many times the container lacks sufficient detail to identify all the potential toxin(s) and may even miss identifying the substance which induces abuse (see data in Kopstein 2006).

One of the greatest difficulties in evaluating "inhalants" as an abused or dependent substance is the criteria that define an inhalant's "reinforcing" effects. For most substances, a frequent use of that substance is a basic and reasonable approach. However, as inhalation is involved herein, there is a question as to what constitutes sufficient inhalation (e.g., a "dose") to get "high." Most importantly, the evaluator has an even greater problem of differentiating a response of "sniffing" for curiosity from those who are primarily inhaling to get a desired state of being, the ever elusive "high." Thus, questionaires are less helpful for these substances (in contrast to most "drugs of abuse") in determining any altered state of being. Determination of the "duration," "intensity" or "high frequency" of use by subject is necessary to establish a "dependent state" for these products. Nevertheless, with limited resources available, the authors are guided primarily by "ever use" data and firsthand knowledge to focus on which "volatile" products are being used to support dependence.

Another issue, for surveys and evaluation, unique for this "drug" is that the category of "inhalants" includes many different types of substances. Different subanalyses have helped to clarify the types of substances being abused. Thus, an analysis of questionnaire responses of lifetime use in surveys regarding the inhalation of various products (Table 61–2) indicate that gasoline and glue are the most popular for ages 12–17 years (Substance Abuse and Mental Health Services Administration 2001, 2006). In contrast, nitrous oxide is prominently used by college students. Although these numbers may not be accurate in defining the potential of these substances for producing dependencies/toxicities, the "lifetime" data (in contrast to frequent use) is the most statistically valid group for this analysis. Other surveys may vary somewhat in which products are most widely used. A recent study of incarcerated adolescents identified gasoline and PC duster sprays as the products most heavily abused (Howard et al. 2007). However, a common perception from the street name referring to the later products as "air" sprays, doesn't convey the potential hazard related to the presence of fluorocarbons.

It is difficult to identify which chemical in a product is the one which produces the "high" (may be more than one), or to quantitate the extent of abuse by collectively grouping all the products containing any one substance to evaluate the relative degree of that substance in inhalant dependency. With that caveat, a tentative order of preference of select chemicals will be delineated using historical human and animal reports and surveys. (1) Toluene is the most commonly used substance and is found in many commercial products. It is "often considered" to be nontoxic in spite of many studies/reports to the contrary. The use of pure toluene on the streets attests to it's popularity; this is enhanced by the availability of pure toluene, both in hardware stores and at warehouses. (2) If you group together cigarette lighter gases and all aerosols which contain butane propellants (most now do), the abuse of "butane-type" gases is very high (see below), especially the use of lighter-refill gas cartridges. (3) Gasoline for many reasons, mostly availability, has been and still is widely abused. (4) What has been most prevalent in the past, fluorocarbons, are not now widely used in the US as a propellant. However, with the manufacture of partly hydrogenated-fluorocarbons, this could increase their availability in many aerosol products (note as in PC sprays). Another related abuse is that asthma inhalers (containing fluorocarbons) have been used to get

**Table 61–2 Percentage in the US population reporting having used different types of inhalants in their lifetime (Percent), 2000, 2006 Data**

| Solvent or gas | Age 12–17 Year Life-1999 | Life-2005 | Age 18–25 Year Life-1999 | Life-2005 | Age 26–36 Year Life-1999 | Life-2005 |
|---|---|---|---|---|---|---|
| Gasoline, L. fluid | 3.4 | 3.6 | 2.7 | 2.5 | 0.9 | 1.3 |
| Spray paint | 2* | 3.0 | 1.3 | 1.2 | 0.3 | 0.5 |
| Glue or toluene | 3.8 | 4.3 | 2.4 | 2.0 | 1 | 1.2 |
| Correction fluids | 2.1 | 2.2 | 1.9 | 1.4 | 0.6 | 0.6 |
| Nitrous oxide | 2.0 | 1.6 | 9.5 | 9.2 | 2.8 | 4.6 |
| Aerosol sprays | 1.8 | 2.2 | 1.4 | 2.1 | 0.4 | 0.5 |
| Thinners | 1.7 | 1.7 | 1.5 | 1.1 | 0.5 | 0.5 |
| Butane, propane | 1.1 | 1.2 | 1.1 | 0.7 | 0.2 | 0.3 |
| Organic nitrites | 1.8 | 1.6 | 3.3 | 2.3 | 3.6 | 3.8 |

*Source*: Data from Substance Abuse and Mental Health Services Administration National Household Survey on Drug Abuse: Population Estimates 2000, 2006. US GovernmentPrinting Office, Washington DC; http://www.samhsa.gov.
*From 2000 survey.

"high" (Thompson et al. 1983, O'Callaghan and Milner 1988). (5) Nitrous oxide has been a favorite for many years in many situations, from the release of this gas from whipped cream aerosols to "whippets" (small compressed nitrous oxide "bombs") to commercial compressed tanks of $N_2O$; sold by the "balloon-full" to "college-age" groups. (6) Lastly, chlorohydrocarbons (nonfluoro) have been a problem in the past in the dry cleaning industry, as was the abuse of correction fluid products; they are now present in head cleaner products (the latter product reportedly produced a "mental status change" and walking instability in a subject [Finch and Lobo 2005]).

The practice of "sniffing," "snorting," "huffing," "bagging," or inhaling to get high describes various methods of inhalation (Sharp et al. 1992). These terms refer to the inhalation of volatile substances from (1) filled balloons, (2) bags, and (3) soaked rags and/or sprayed directly into oral orifices. Abusers can be identified by various telltale clues such as organic odors in the breath or clothes, stains on the clothes or around the mouth, empty spray paint or solvent containers, and other unusual paraphernalia. These clues may enable one to identify a serious problem of solvent abuse before it causes serious health problems or death.

It is now widely recommended that one should not mix alcohol and other sedatives. For example: "Degreaser's flush" (so described because of a flushing of the face) was observed when occupational workers left their degreasing vats to visit the local "pub" for alcohol (Pardys and Brotman 1974, Stewart et al. 1974). Also, heavy drinking has been associated with occupational toluene exposure (Antti-Poika et al. 1985). Both humans and rats have been noted to be thirsty when exposed to toluene and alcohol (Pryor et al. 1985, Kira et al. 1988). It is not yet been determined that either substance has the ability to encourage the use of the other.

Few studies have characterized the "high" produced by inhalants. Interestingly, a study by Evans and Raistrick (1987) summarized the "sniffer's" perceptive feelings when they inhaled two quite different substances, butane gas or toluene. Moods, thoughts, hallucinations (except tactile sensations), and colors appeared similar with either compound. However, time passed slowly with butane and more rapidly with toluene. This one study would indicate that these different chemical substances give similar-type reinforcements; this may be one reason why products containing them are widely abused. Also, different occupations from anesthesiologists to painters have a potential for abusing substances easily available to them (Yamashita et al. 1984, Nordin et al.1988, Jacob et al. 1989, Krause and McCarthy 1989). That inhalants are also abused by professionals, including medical personnel (Spencer et al. 1976, Jastak 1991, England and Jones 1992), and college students demonstrates a greater diversity of this dependency than is often appreciated. This may be indicative that a "typical" inhalant abuser pursues a high similar to the "lightheadedness" produced by early stage anesthesia. Many inhalants/solvents would produce anesthesia if sufficient amounts are inhaled with the proper amounts of oxygen present. As with any anesthetic, death is possible and too often occurs with these solvents/gases.

## Epidemiology

### Prevalence

Inhalant abuse is a worldwide problem. Many countries are now evaluating the abuse of solvents (Adelekan 1989, Alvarez et al. 1989, Pedersen et al. 1989, Kozel et al. 1995, Butt et al. 2004, Galduroz et al. 2005, Dell et al. 2005, Hedhili et al. 2005, Field-Smith et al. 2006, Carra et al. 2006). The extent of the international problem of inhalant abuse was discussed at a conference held in September 2005; synopses of the presentations are available on line at: http://international.drugabuse.gov/downloads/Inhalant_Summary.pdf. In the United States two longstanding surveys have tracked the rates and patterns of use. The Monitoring the Future (MTF) study (Johnston et al. 2006) employs anonymous surveys given in schools to 8th, 10th, and 12th graders while the National Survey on Drug Use and Health (NSDUH) conducts interviews with a sample of persons over the age of 12. The most current rates of inhalant use from these studies are shown in Table 61–3. The general trend is for inhalant use to decrease with increasing age reflecting the general perception that inhalants are a preferred drug by younger children. The MTF reports that approximately 1.5% of 8th graders have used inhalants on a weekly basis. There are no documented reasons why younger children use inhalants more often but it is likely

that accessibility and price are factors. The fact that lifetime prevalence decreases with grade level is somewhat anomalous since in any given population this number should increase or at least remain level as a cohort ages. A possible explanation for this is that, as described below, chronic inhalant users experience multiple personal and social problems, including dropping-out of school and are not present to be surveyed in the upper grades. Further, there may be problems with recall and the stigma attached to inhalant use; also there may be a realization as one matures that the earlier concept of what "high" means was not correct. Thus, older students negate in their minds the earlier report of inhalant abuse as a "high" experience.

**Table 61–3 Inhalant Use (Percent) Data**

| | High School* Year 2005 | | | Household† Year 2005 | | |
|---|---|---|---|---|---|---|
| | **8th Grade** | **10th Grade** | **12th Grade** | **Age 12–17 Yr (*n* = 23,360)** | **Age 18–25 Yr (*n* = 28,914)** | **Age 26–36 =and older Yr (*n* 170,656)** |
| Lifetime | 17.1 | 13.1 | 11.4 | 10.5 | 13.3 | 8.5 |
| Annual | 9.5 | 6.0 | 5.0 | 4.5 | 2.1 | 0.2 |
| 30-day | 4.2 | 2.2 | 2.0 | 1.2 | 0.5 | 0.1 |

*Source*: *,†Johnston et al. (2006); http://monitoringthefuture.org/.

The MTF data show a distinct pattern of inhalant use among adolescents over time. Using the lifetime prevalence measure as an indicator of overall exposure to inhalants, there was a gradual increase in use from 1975 through 1995, followed by a decline until 2003. Since 2003, there are signs that use may now be increasing again.

To establish the rates of diagnosable disorders, Wu et al. (2004) examined the results of the NSDUH. For adolescents ages 12–17 they found a 0.2% rate for DSM-IV-TR diagnoses of abuse and 0.2% rate for dependence. However, among the smaller cohort of youth who had used in the past year the rates were much higher at 6% and 4%, respectively. There were no differences by gender. Using the same procedures and database for adults, Wu and Ringwalt (2006) detected a 10% lifetime prevalence rate for inhalant use. Of the 0.5% who had used in the past year there was a diagnosis rate of 6.6% for abuse and 1.1% for dependence. Importantly, the patterns and correlates of inhalant use differed between adults and adolescents. The most commonly used inhalants by adults were nitrous oxide and poppers (amyl, other organic, nitrites) while adolescents preferred glue and gasoline. Further, adults did not use inhalants as often and there were fewer negative correlated behaviors or problems.

While the above percentages appear relatively small, the National Household Study on Drug Use and Health estimated that there were 178,000 persons in the US in 2000 with a diagnosis of inhalant abuse or dependence. (http://www.oas.samhsa.gov/Dependence/appendixc.htm). There is evidence to suggest that very few of these people are in treatment (Beauvais et al. 2002a). The lack of specific treatment protocols, the reluctance of abusers to present to treatment and a widespread attitude that inhalant abusers are refractory to treatment may account for this.

### Sociodemographic factors

Wu et al. (2004) examined the National Household survey for sociodemographic factors associated with past year inhalant abuse or dependence for 12–17-year-olds and concluded.

"Adolescents who met criteria for abuse or dependence reported coexisting delinquent behavior, multiple drug abuse and dependence and utilization of mental health services for other emotional problems. Thus, inhalant abuse and dependence may be a marker of general vulnerability rather than an isolated problem. This vulnerability may be influenced by individual as well as family factors, as evidenced by the association between foster care and inhalant use disorder."

They further found a strong relationship between disorders and early first use, prompting the recommendation that prevention activities must begin very early. Interestingly, while other studies have shown higher prevalence rates (particularly lifetime use) of inhalant use among certain minorities, specifically Mexican-Americans and American Indians, these differences did not show up for abuse and dependence diagnoses. With respect to American Indian adolescents, Beauvais et al. (2004) have demonstrated that while historically prevalence rates have been high, these rates have diminished over the past decade to where they are equivalent to non-Indian youth. African American adolescents have lower overall levels of drug use and, consistent with this, have the lowest levels of inhalant use.

Both for adults (Wu and Ringwalt 2006) and adolescents (Wu et al. 2004) few differences in inhalant use are found for family income, challenging the commonly held notion that inhalant use is restricted to lower income individuals. There is also some slight indication that, among adults, lifetime prevalence is higher among those with higher education. This finding must be viewed with caution since the questions asking about inhalant use included the use of nitrous oxide and nitrites, substances often excluded from the category of "inhalants." A further finding is that for adults inhalant use is more common in the urban areas while for adolescents it is more common in the small metro and rural areas. This may be due to lesser accessibility of other drugs in less populated areas, or alternately, as described above, the greater popularity of nitrous oxide and nitrites among adults in urban areas.

The disorders classified in this chapter are classified under the inhalant-related disorders section in DSM-IV-TR and are subdivided into two groups: inhalant use disorders and inhalant-induced disorders.

## Inhalant Use Disorders

The criteria of DSM-IV-TR has been recently studied and compared to DSM-III-R and *International Classification of Diseases,* Tenth Revision (ICD-10) (Howard et al. 2001). They identified certain inhalant abusers because, overall, these individuals are a very heterogeneous population that needs to be characterized and studied based on the type of inhalant. There are different ethnic groups associated with inhalant use as with any drug use, but there are also a variety of types of gases/solvents which are abused differently and are associated with different but yet unidentified disorders. Abusers of nitrous oxide or nitrites may have different dependencies than those abusing paint sprays. The groups studied by Howard et al. (2001) were predominately

solvent abusers. The conclusion from the above study was that the DSM-III-R was a better diagnostic system for inhalant abuse or dependence than is DSM-IV-TR.

### Inhalant Abuse

This diagnosis is probably more characteristic of children, adolescents, and industrial workers who occasionally intentionally inhale products they work with to get intoxicated. Inhalant use among younger people has been shown to be episodic and faddish. School surveys have shown wide differences from year to year within the same schools. It is characteristic of the imitative behavior of this developmental period that occurs when something "new" comes along and there is strong pressure to try it and be accepted. Much of this is minor experimentation that quickly wanes. However, as noted below, a single instance of inhalant use can be fatal, most often due to cardiac arrhythmia or anoxia. Those young people whose use is more extended can at times be diagnosed with abuse. School work can be disrupted and there may be absences from jobs. Because of their volatile and explosive nature, the use of inhalants is inherently dangerous and the physical and mental impairment can lead to a variety of injuries from accidents. Legal problems are usually rare because of the secretive nature of inhalant use and ambiguity over their legal status. Finally, use may continue despite frequent family disruption. It must be noted, however, that much use is surreptitious and the family may be unaware. Nonetheless, the impairment from abuse can disrupt family dynamics regardless of whether or not the family is aware. Older abusers who use products of their occupation are at primary risk from injury but clearly job performance and family dynamics can be affected.

### Inhalant Dependence

Evidence for the basis of inhalant dependence is slowly emerging. This is differentiated from the more extreme state of anesthesia related to the CNS depressant actions and the toxicity of these substances. Reinforcing actions of "inhalants" have been studied in humans exposed to anesthetics (Beckman et al. 2006); these actions were also critically reviewed by Balster (1998). A more recent study compared two different classes of anesthetics (isoflurane/sevoflurane and nitrous oxide) regarding subjective effects (Beckman et al. 2006). The "fluranes" were more sedative in action whereas nitrous oxide produced more pleasant, euphoric-like actions. More groups are beginning to focus on the cellular basis of dependence as contrasted/compared to anesthesia in humans. MacIver's group has examined the similarities between toluene and anesthetics, finding that both increase GABA-mediated inhibitory synaptic transmission in the hippocampus, and this likely contributes to a disruption of learning. In contrast, toluene did not depress glutamate synapses like anesthetics do (McDonald et al. 2003, MacIver 2006). Recent MRI studies in animals, given toluene acutely, have measured altered glucose uptake in the frontal cortex, as well as in other regions, including the hippocampus and thalamus (Schiffer et al. 2006). They stated that the cortical areas were more susceptible than striatal areas in altering place "preference" or "dependence" to toluene; Riegel et al. (2003) identified the nucleus accumbens involvement in locomotor hyperactivity. In these and other studies, GABAergic and/or dopaminergic (Schiffer et al. 2006, Riegel et al. 2003, Gerasimov et al. 2002) systems seem to be strongly involved in reward mechanisms. This correlates with the earlier studies of ataxia and pyramidal tract dysfunction described in humans by Rosenberg and colleagues. In addition the insula area of the brain has been linked to addiction (Naqvi et al. 2007); a recent case of butane exposure also identifies this area (Kile et al. 2007) in describing the patient's encephalopathy and relates this to his dependence on this inhalant. Which system and area of the brain is the primary, or important, reward system for these different states of dependence, as contrasted to the state of anesthesia, remains open to further study.

More recent studies, however, indicate that toluene (and other inhalants) acts rapidly due to the rapid absorption through the lungs, thus leading to a quick euphoria; all this makes it likely that they will produce a strong physical dependence. Thus a mild withdrawal syndrome often occurs in 10 to 24 hours after cessation of *heavy* use and lasts for several days. Symptoms include general disorientation, sleep disturbances, headaches, muscle spasms, irritability, nausea, and fleeting illusions. However, this is not an easily identified or a characteristic withdrawal syndrome that is useful for many practitioners in a clinical setting. The need to continue use is undeniably strong in many individuals. Specific treatments for inhalant dependence, other than the drug therapy and/or psychotherapy used for other drug dependencies, need to be developed.

Binging for extended periods of time is a common pattern among inhalant dependent individuals and it is likely that this is beyond their original intention. There are little data on whether the dependent patient will report attempts to stop or cut down their use. These people rarely voluntarily present for treatment of inhalant use and usually surface due to some other problem, usually public intoxication or accidents. Many adolescent users are identified by parents or other family members upon discovering a large number of containers containing inhalants (e.g., many empty hair spray cans found in a bedroom). Inhalants are readily available so it is unlikely that there is a great deal of time obtaining them; however, recovery from their effects can take an extended time. Clearly, long-term intoxication can interfere with social, occupational or recreational activities. Many inhalant dependent patients are well aware of the physical harm their use is causing but display an unusual sense of indifference.

## Inhalant-Induced Disorders

The primary disorder is inhalant intoxication, which is characterized by the presence of clinically significant maladaptive behavioral or psychological changes (e.g., belligerence, assaultiveness, apathy, impaired judgment, impaired social, or occupational functioning) that develop during the intentional short-term, high-dose exposure to volatile inhalants (diagnostic criteria A and B in DSM-IV-TR). The maladaptive changes occurring after intentional and unintentional exposure include disinhibition, excitedness, light-headedness, visual disturbances (blurred vision, nystagmus), incoordination, dysarthria, an unsteady gait, and euphoria. Higher doses of inhalants may lead to depressed reflexes, stupor, coma, and death, sometimes caused by cardiac arrhythmia. Lethargy, generalized muscle weakness, and headaches may occur some hours later depending on the dose.

**DSM-IV-TR Criteria**

**Inhalant Intoxication**

A. Recent intentional use or short-term, high-dose exposure to volatile inhalants (excluding anesthetic gases and short-acting vasodilators).

B. Clinically significant maladaptive behavioral or psychological changes (e.g., belligerence, assaultiveness, apathy, impaired judgment, impaired social or occupational functioning) that developed during, or shortly after, use of or exposure to volatile inhalants.

C. Two (or more) of the following signs developing during, or shortly after, inhalant use or exposure:

(1) dizziness
(2) nystagmus
(3) incoordination
(4) slurred speech
(5) unsteady gait
(6) lethargy
(7) depressed reflexes
(8) psychomotor retardation
(9) tremor
(10) generalized muscle weakness
(11) blurred vision or diplopia
(12) stupor or coma
(13) euphoria

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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## Psychiatric Disturbances Associated with Organic Solvent Abuse

Earlier studies were conflicting regarding the issue of comorbid psychiatric conditions among inhalant users. However, a series of larger and more recent studies have shown more consistency and conclude that generally inhalant users experience higher levels of psychiatric and social problems. In a nationally representative sample ($N = 73,396$) of adults, Wu and Ringwalt (2006) found significantly elevated levels of serious mental illness (including drug use and alcoholism) and higher levels of usage of treatment for these problems among those who had used inhalants in the past year. These findings were confirmed in another large national study by Wu and Howard (2006a). In this study the rates for women who had used inhalants were higher than for men. Earlier reports stated that inhalant users derived from psychiatric emergency room admittants differed significantly from matched other drug users in that they displayed significantly more self-directed destructive behavior, as well as some degree of recent suicidal and homicidal behavior (Korman et al. 1980). Cognitive measures of these and other inhalant abusers supported the antisocial and self-destructive nature of inhalant abusers (Korman et al. 1981, Oetting and Webb 1992). This is supported by another study of "autoerotic deaths" observed for inhalant abusers (Jackowski et al. 2005). Overall, there is accepted knowledge that long-term solvent abusers are among the most difficult to work with based on antisocial traits; also, it is likely that inhalants prevent their continued growth and development (Oetting et al. 1988, Oetting and Webb 1992). Another study identified child abuse occurred in those who extensively used inhalants (Fendrich et al. 1988). In an England study in a regional assessment center, solvent-abusing male adolescent delinquents were more depressed than other drug abusers (Jacobs and Ghodse 1988) and in a Turkish study, Evren et al. (2006) discovered significantly elevated rates of depression and anxiety disorders among adults diagnosed with inhalant dependency when compared to users of other drugs and nondrug users. In an earlier study, Dinwiddie et al. (1990) also found higher rates of depression, bipolar disorder, alcoholism and antisocial personality disorder among 130 inhalant users compared to nonusers. Underscoring the antisocial personality disorder association among inhalant users, 10 out of the 11 inhalant abusing patients examined by Dinwiddie et al. (1987) had such a diagnosis.

A similar pattern emerges among studies of adolescents. Using the NSDUH, Wu et al. (2004) found that 10.6% of adolescents (aged 12–17) who had used inhalants in the past year met the criteria for abuse or dependence with no gender difference. When compared to the remainder of the sample, these groups exhibited higher levels of treatment for mental problems, higher rates of abuse of other drugs and delinquency. Using the same database as above, Wu et al. (2004) examined the subgroup that had used both inhalants and marijuana and determined that this adolescent group had also used three or more other types of drugs (73%) and were diagnosed with abuse or dependence for alcohol (35%) and another drug (39%). Sakai et al. (2004) studied an inpatient and day care drug treatment population and compared patients diagnosed with inhalant abuse or dependence to (a) those who had used inhalants but did not have a diagnosis and (b) those adolescents who had never used inhalants. When compared to both groups, inhalant diagnosed adolescents had significantly more diagnoses for other drugs, higher levels of major depression, more suicide attempts and higher levels of abuse and neglect. In a study of incarcerated youth, similar results were reported by Howard et al. (2007). Two other studies show that diagnosed inhalant users have higher levels of conduct disorder (Sakai et al. 2006) and are more likely to use heroin and other injection drug use (Wu and Howard 2007).

## Etiology and Pathophysiology

### Toxicology of Inhalant Abuse

The majority of inhalant abusers are never seen in a hospital or outpatient facility. Some of the more common acute syndromes of the intoxicated state are listed in Table 61–4. Although many do not need medical attention related to their inhalant habit, of those who do, many often die before reaching the hospital as a result of asphyxia, cardiac

arrhythmia, or related overdose effects after inhaling fluorocarbons, low-molecular-weight hydrocarbon gases (butane, propane), nitrous oxide, gasoline or other solvents including toluene during either the first or a subsequent episode (Bass 1970, Wason et al. 1986, Al-Alousi 1989, Mathew et al. 1989a, Siegel and Wason 1990, Garriott 1992, Scerri et al. 1992, Fitzgerald et al. 1993, Groppi et al. 1994, Broussard et al. 1997, Rohrig 1997, Bowen et al. 1999, Hobara et al. 2000, Beauvais et al. 2002b, Martinez and Ballesteros 2005, Gaulier et al. 2003, Xiong et al. 2004, Field-Smith et al. 2006). Unusual reports of inhaling exhaust fumes for "pleasure" have even been noted; some result in death (Martinez and Ballesteros 2006). Death may also occur after inhalation of toluene-containing substances as a result of metabolic acidosis or related kidney failure if left untreated (Garriott 1992). Although it is not common, anesthetics abused by medical personnel or others have also been a cause of death; death related to nitrous oxide use is often due to asphyxia (Clark et al. 1985, Suruda and McGlothlin 1990, Wagner et al. 1992).

**Table 61–4 Symptoms Related to Solvent Abuse (Not All for Gases and Nitrites)**

| *Moderate Intoxication* |
|---|
| Dizziness |
| Headache |
| Lethargy |
| Disorientation, incoherence |
| Ataxia, gait (uncoordinated movement) |
| Odoriferous, foul breath (solvent vapors) |
| *Strong Intoxication* |
| Blurred vision |
| Belligerence |
| Nausea, vomiting |
| Irritability |
| Delirium |
| Slurred speech |
| *Severe (Rare)* |
| Seizures |
| Violent actions |

## Clinical Manifestations After Chronic Inhalant Abuse

Chronic high-level exposure to organic solvents occurs in the inhalant abuse setting at levels several thousand times higher than in the occupational setting and results in numerous irreversible disease states. Some toxicities have been validated through animal studies; others have been only tentatively correlated with certain substances. Table 61–5 describes several well-characterized disorders and identifies the solvent when corroborated by animal studies. Some substances have been strongly correlated with the development of a disorder through numerous case studies. The following discussion briefly describes these conditions and the important associated symptoms.

## Neurological Sequelae of Chronic Inhalant Abuse

The nervous system may be affected at many levels by organic solvents as well as other neurotoxic substances. Because of their nonfocal presentation, neurotoxic disorders may be confused with metabolic, degenerative, nutritional, or demyelinating diseases (Schaumburg and Spencer 1987). This is illustrated in the setting of chronic toluene abuse, which clinically may resemble the multifocal demyelinating disease, multiple sclerosis, in the findings on neurological examination (Lazar et al. 1983, Fornazzari et al. 1983, Hormes et al. 1986). In addition, neurotoxic syndromes rarely have specific identifying features on diagnostic tests such as computed tomography, magnetic resonance imaging (MRI), or nerve conduction studies (Schaumburg and Spencer 1987). As a result, subjects who only inhale for a limited time or to a limited extent may be difficult to diagnose. High-level chronic inhalant abuse, on the other hand, produces a specific MRI picture with a combination of diffuse white matter changes and low signal intensity in the basal ganglia and thalamus (Rosenberg et al. 1988a, Caldmeyer et al. 1993, Unger et al. 1994, Yamanouchi et al. 1995, 1997, Kamran and Bakshi 1998, Rosenberg et al. 2002).

Many organic solvents produce nonspecific effects (e.g., encephalopathy) after exposure to extremely high concentrations; a few produce relatively specific neurological syndromes with chronic administration. Two specific neurotoxic syndromes, a peripheral neuropathy and an ototoxicity, are well correlated with organic solvents. Most common, however, is a clinical syndrome consisting of cognitive impairment, cerebellar ataxia, and spasticity syndrome (Lazar et al. 1983, Fornazzari et al. 1983, Hormes et al. 1986). In addition, a myopathy may occur alone or in combination with any of these clinical syndromes.

### Central Nervous System Involvement (Encephalopathy)

Grabski (1961) first reported a case of persistent neurological consequences of chronic inhalation of toluene-containing solvents; this was further described by Knox and Nelson (1966). Other types of severe neurotoxicity were subsequently described, including cognitive dysfunction (Lazar et al. 1983, Fornazzari et al. 1983, Hormes et al. 1986, Kamran and Bakshi 1998, Kile et al. 2006) and cerebellar ataxia (Boor and Hurtig 1977, Malm and Lying-Tunell 1980, Streicher et al. 1981, Takeuchi et al. 1981, Lazar et al. 1983, Fornazzari et al. 1983). This encephalopathy was characterized using computed tomography (Schikler et al. 1982, Fornazzari et al. 1983) and, more extensively, MRI (Rosenberg et al. 1988b, Filley et al. 1990, Ikeda and Tsukagoshi 1990, Poungvarin 1991, Xiong et al. 1993, Caldmeyer et al. 1993, Kornfeld et al. 1994, Yamanouchi et al. 1995, 1997, Kamran and Bakshi 1998, Rosenberg et al. 2002, Aydin et al. 2003, Takebayashi et al. 2004). The most common syndrome is that of multifocal CNS involvement (Streicher et al. 1981, Metrick and Brenner 1982, Schikler et al. 1982, Fornazzari et al. 1983, Hormes et al. 1986, Rosenberg et al. 1988b, Poungvarin 1991, Xiong et al. 1993, Caldmeyer et al. 1993). Abstinence was first documented before clinical evaluation by Hormes et al. 1986; more recently by Takebayashi et al. (2004). Abstinence from solvent use is necessary to prevent intoxication symptoms interfering with neurologic

**Table 61–5 Diseases Observed in Humans After Chronic Inhalant Abuse**

| Condition | Syndrome | Substance | Animal Studies* |
|---|---|---|---|
| | Slowly Reversible and/or Irreversible Syndromes | | |
| Encephalopathy | Cognitive dysfunction | "Toluene,"† other solvents | — |
| Cerebellar syndrome | Limb dysmetria | "Toluene" | Rat |
| | Dysarthria | | — |
| Sensorineural otic | High-frequency hearing loss | TCE, toluene | Rat, mouse, |
| Sensorineural | | | |
| Optic nerve | Visual loss | "Toluene" | — |
| Oculomotor | Oculomotor disturbances (nystagmus) | Xylene, TCE | Rabbits |
| Myeloneuropathy | Sensory loss | Nitrous oxide | Rat,mouse, guinea pig |
| | Spasticity | | |
| Axonal neuropathy | Distal sensory loss, limb weakness | Hexane, methyl butyl ketone | Rat, monkey |
| Cardiotoxicity | Arrhythmia | Fluorocarbons, butanes/propanes | Mouse, rat, dog |
| Leukemia | Myelocytic | Benzene | Rat, mouse |
| Trigeminal neuropathy | Numbness, paresthesia | TCE and/or dichloroacetylene | Rat |
| Renal acidosis | Metabolic acidosis | "Toluene" | Rat |
| | Hypokalemia | | — |
| Carboxyhemoglobin | Hypoxia | Methylene chloride | Rat |
| Methemoglobinemia | Syncope, blue | Nitrites, organic | Rat |
| Neonatal syndrome | Retarded growth, development | "Toluene" | Rat |
| Hepatotoxicity | Fatty vacuoles, plasma liver enzymes | Chlorohydrocarbons | Rat |
| Immunomodulatory | Loss of immune cell function | Nitrites, organic | Rat |

*Symptoms observed in animal studies with these solvents.
†Quotation marks around substance indicates uncertainty about this solvent (alone) producing these symptoms.

measures. Microencephalopathy has emerged as a possible embryopathic syndrome in infants of women exposed during pregnancy to solvents containing toluene (Arnold et al. 1994, Pearson et al. 1994). Recently, encephalopathies have been observed following inhalation of butane-type products (a fluorocarbon-152A was also present in one case). The first study showed increasing cerebral atrophy by MRI after three weeks (Doring et al. 2002); the second was unremarkable as measured by MRI three days after admission (Harris and Mirza 2005).

Most reports emphasized the cerebellar and cognitive dysfunction, with most cases showing combined impairment of cerebral and cerebellar functions as well as pyramidal changes. Neurological abnormalities varied from mild cognitive impairment to severe dementia, associated with elemental neurological signs such as cerebellar ataxia, corticospinal tract dysfunction, oculomotor abnormalities, tremor, deafness, and hyposmia. Cognitive dysfunction was the most disabling and frequent feature of chronic toluene toxicity and may be the earliest sign of permanent damage. Dementia, when present, was typically associated with cerebellar ataxia and other signs (Hormes et al. 1986).

Rosenberg et al. (1988b, 2002) utilized MRI to study the brains of chronic abusers of toluene-containing substances and interpreted the encephalopathy as a diffuse CNS white matter change with the following abnormalities: (1) diffuse cerebral, cerebellar, and brain stem atrophy; (2) loss of differentiation of the gray and white matter throughout the CNS; and (3) increased periventricular white matter signal intensity on T2-weighted images (Filley et al. 1990). These MRI measures seemed to correlate with the extent of exposure and the impairment of the individual's capabilities as measured on several neuropsychological tests (Filley et al. 1990). Others (Xiong et al. 1993, Caldmeyer et al. 1993, Yamanouchi et al. 1995, 1997, Kamran and Bakshi 1998) corroborated these findings.

In a recent study, Rosenberg et al. (2002) extended their earlier observations on the MRI and cognitive abnormalities in both inhalant abusers and a comparison group of other drug abusers. Interestingly, both groups had significant and equally severe cognitive deficits, which did not demonstrate a dose–response relationship in the inhalant group, but abnormalities on MRI did reveal a strong dose–response relationship with inhalant abuse.

MRI results (Unger et al. 1994) may suggest a possible mechanism for the abnormalities in the basal ganglia and thalamus. The MRI analyses of eight chronic toluene abusers revealed diffuse white matter changes and marked hypointensity in the basal ganglia and thalamus, all seen on T2-weighted images (Figure 61–1). Thus, the hypointensity of the basal ganglia and thalamus on T2-weighted magnetic resonance images of brains of chronic toluene abusers may be related to partitioning of toluene into the lipid membranes in these areas. Recent MRI studies of these and other cortical areas (Aydin et al. 2003, Takebayashi et al. 2004) confirmed the above as well as observed changes in the ratios of choline/creatine in the basal ganglia in "toluene" abusers.

## Pathology

Few detailed pathological studies have been done (Escobar and Aruffo 1980, Rosenberg et al. 1988a, Kornfeld et al. 1994). The predominant feature in these studies is that of a leukoencephalopathy. A study of three cases (Kornfeld et al. 1994)—one of which was previously reported by Rosenberg et al. (1988a)—found pathological

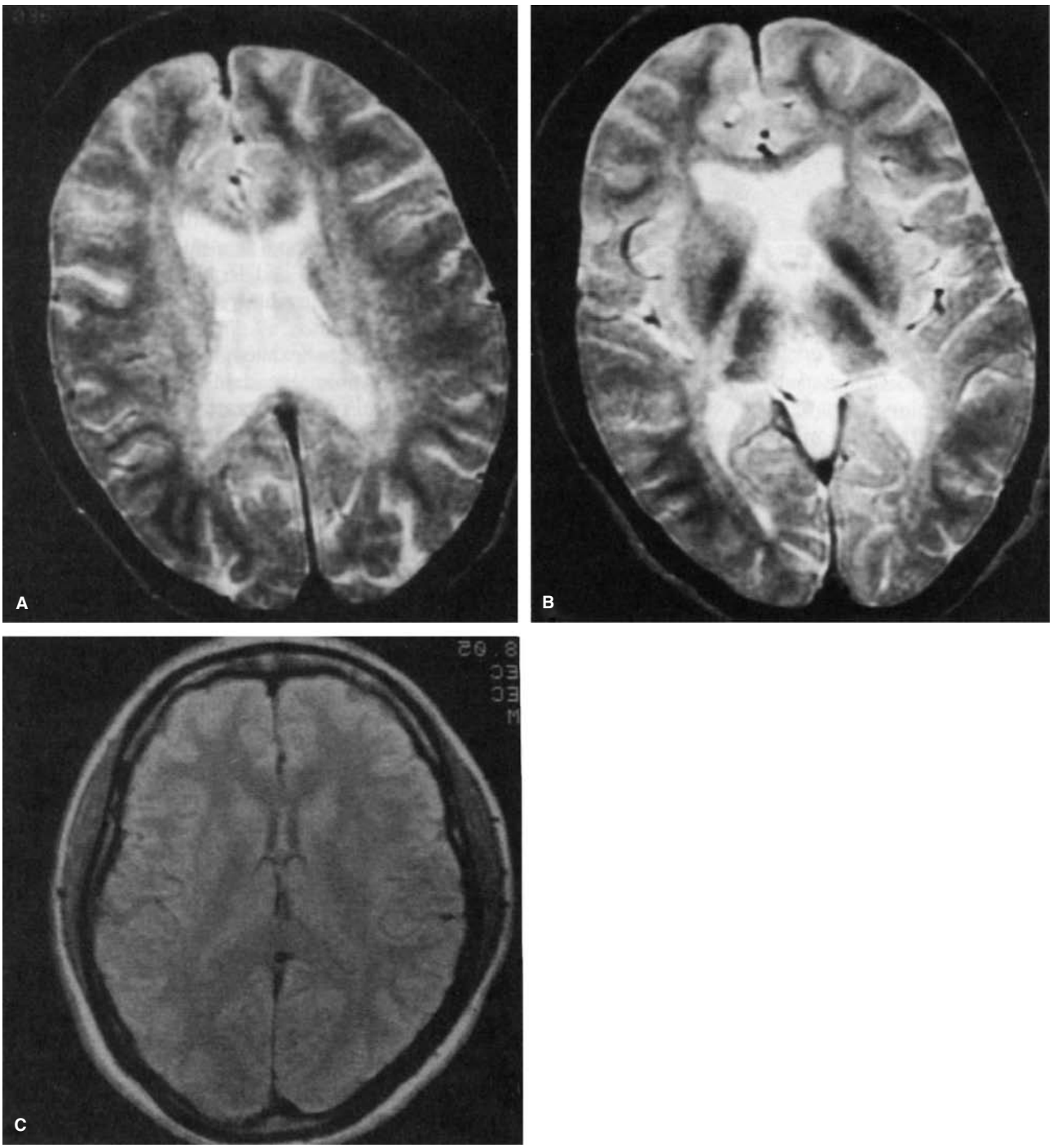



**Figure 61–1** *(a) Axial section of T2-weighted spin-echo MRI scan of a solvent abuser showing abnormally diffuse white matter changes and loss of gray–white differentiation; (b) Lower axial section of T2-weighted spin-echo MRI scan of a solvent abuser showing decreased signal intensity in the thalamus and global pallidus bilaterally, in addition to diffuse increased signal intensity in white matter; (c) Axial section of T2-weighted spin-echo MRI scan comparable to that of a normal subject. These are similar to those in studies reported by Rosenberg and colleagues [Reproduced from Rosenberg NL, Kleinschmidt-DeMasters BK, Davis KA, et al. (1988a) with permission of Wiley-Liss.].*

changes similar to those in adrenoleukodystrophy, a rare hereditary disorder affecting the white matter. Gross pathological study revealed a patchy loss of myelin (Figure 61–2). The overall pathological study revealed a demyelinating process grossly manifest as brain atrophy, including macrophages containing unusual cytoplasmic bodies with an increase of long-chain fatty acids similar to that seen in adrenoleukodystrophy (Kornfeld et al. 1994). These findings suggest that toluene is a white matter toxin (similar to that reported for multiple schlerosis by Filley 1999).

## Central Nervous System Involvement Possibly Related to Lead

Toxicities similar to those already noted may be caused by tetraethyllead (or its metabolite triethyllead) after prolonged or extensive inhalation of gasoline (Robinson 1978, Seshia

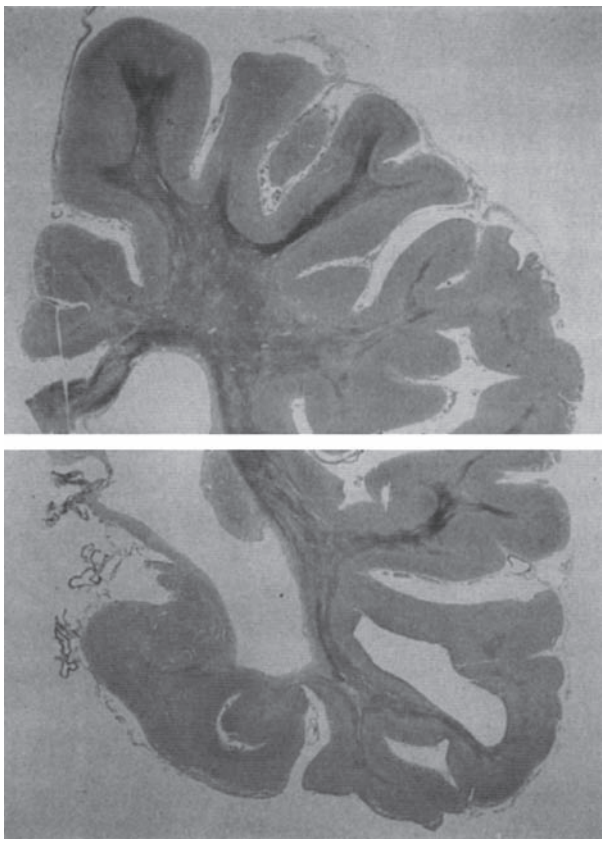


**Figure 61–2** *Patchy loss of myelin in central, convolutional, and callosal white matter. (Luxol fast blue–periodic acid–Schiff stain.) [Reproduced from Kornfeld M, Moser AB, Moser HW, et al. (1994) with permission of Lippincott Williams & Wilkins]*

et al. 1978, Valpey et al. 1978, Coodin et al. 1980, Prockop and Karampelas 1981, Goldings and Stewart 1982, Remington and Hoffman 1984, Eastwell 1985, Reese and Kimbrough 1993, Goodheart and Dunne 1994, Maruff et al. 1998, Cairney et al. 2004). The subject was reviewed well by Tenenbein (1997). Even with the elimination of lead products from gasoline in the US, the use of unleaded gasoline, which contains some of the previously described solvents, still produces similar encephalopathies. In cases in which high lead levels still may be observed, hallucinations and disorientation, dysarthria, chorea, and convulsions may be reported (Table 61–6). The symptoms have also included moderate to severe ataxia, insomnia, anorexia, slowed peripheral nerve conduction, limb tremors, dysmetria, and sometimes limb paralysis. In most cases the electroencephalogram is normal, but in severe states an abnormal to severely depressed cortical electroencephalogram is observed. Because many of these symptoms in the early stages of the disease can be reversed by chelation therapy with ethylenediaminetetraacetic acid, dimercaptol, or penicillamine, it is important to check the serum lead levels in any chronic inhalant abuser.

**Table 61–6 Mostly Irreversible Syndromes Caused by Chronic Inhalant Use Observed in Humans**

| Condition | Syndrome | Substance |
|---|---|---|
| Encephalopathy | Cognitive dysfunction, possible delirium, possible seizures | Lead (gasoline) |
| Cerebellar syndrome | Limb dysmetria, dysarthria, truncal ataxia, tremors | Lead (gasoline) |
| Sensorineural (optic) | Nystagmus | Lead (gasoline) |
| Peripheral nerves | Possible slower nerve conduction | |

## Ototoxicity

Sensorineural hearing loss (Rybak 1992) is one of the more commonly occurring clinical neurotoxic syndromes related to inhalant abuse, along with a related equilibrium disorder (Sasa et al. 1978). Neural conduction, most readily diagnosed by brain stem auditory evoked responses, was abnormal in several case studies (Biscaldi et al. 1981, Metrick and Brenner 1982, Lazar et al. 1983, Ehyai and Freemon 1983, Rosenberg et al. 1988b, Morrow et al. 1992). These studies suggest that brain stem auditory evoked responses would detect early CNS injury related to toluene or other solvent inhalation at a time when the neurological examination and MRI scans are normal. Brain stem auditory evoked responses may be a sensitive screening test for monitoring individuals at risk from toluene exposure and for early detection of CNS injury. Although specific in revealing abnormalities characteristic of CNS involvement in chronic inhalant abuse, brain stem auditory evoked responses revealed abnormalities in less than 10 individuals of a chronic inhalant abuse population (Levisohn et al. 1992).

The hearing loss was originally classified as one of high frequency (it probably still is for humans). It is now more clearly delineated as a midfrequency hearing loss when measured in rats (or guinea pigs) exposed to solvents (Crofton and Zhao 1993, Jaspers et al. 1993, Lataye et al. 2003). A recent study of rats observed no change in the outer hair cells after exposure to trichloroethylene (TCE) but revealed a loss of spiral ganglion cells in the middle turn of hair cells (Fechter et al. 1998). As hearing loss has been identified in humans exposed to high levels of toluene, inhalant abusers using these types of chemicals should be provided good auditory evaluations.

This neuropathy can be produced in days after high exposures of animals to specific solvents and is considered to originate with the destruction of cochlear cells, which contributes to a central conduction pathology as observed in the human studies noted earlier (Pryor et al. 1983, Rebert et al. 1983). Because of the quantitative animal model available, Pryor's group (Pryor 1995) has conducted a structure-activity study of many solvents in an effort to define the basic moiety responsible. Table 61–7 lists the different compounds and their activities. Niklasson et al. (1993) also analyzed the effects of some of these compounds on the vestibular function and correlated the changes with nystagmus in humans. A recent paper by Fuente and McPherson 2006 presents a thorough review of the human and animal literature on this.

## Other Cranial Nerve Involvement

A study of four subjects (Maas et al. 1991) supported earlier observations of pendular nystagmus and related eye

**Table 61–7 Auditory Response After Exposure to Different Solvents**

| Solvent | Hearing Loss |
|---|---|
| Benzene | No |
| Toluene | Yes |
| Ethylbenzene | Yes |
| *n*-Propylbenzene | Yes |
| Isopropylbenzene (cumene) | No |
| Methoxybenzene | Yes |
| 1,4-Dimethylbenzene (*p*-xylene) | Yes |
| 1,2-Dimethylbenzene (*o*-xylene) | No |
| 1,3-Dimethylbenzene (*m*-xylene) | No |
| Styrene | Yes |
| Monochlorobenzene | Yes |
| Carbon disulfide | Yes |
| Dichloromethane | No |
| Trichloroethane | No |
| TCE | Yes |
| Tetrachloroethylene | No |
| Acetone | No |
| Methyl ethyl ketone | No |
| Ethyl alcohol | No |
| *n*-Hexane | No |

movement disorders in sniffers of various solvents. Oculomotor dysfunction and tremor were seen only in severely affected individuals (Hormes et al. 1986). Optical neuropathy (Keane 1978, Takeuchi et al. 1981, Ehyai and Freemon 1983, Channer and Stanley 1983, Rosenberg et al. 1988a, Takeuchi 1988, Kiyokawa et al. 1999) and oculomotor dysfunction (Lazar et al. 1983, Maas et al. 1991, Poblano et al. 2000) have been observed after exposure to toluene-containing substances, pupillary damage after exposure to TCE (Feldman et al. 1985), and optical neuritis after methyl ethyl ketone (MEK) exposure (Berg 1971). Hollo and Varga (1992) suggested that visual function measures may be useful in detecting early toxic effects in solvent abusers. All of these neuropathies can be identified with specific cranial nerves (Table 61–8).

These changes have yet to be specifically correlated with TCE or other chemicals (Odkvist et al. 1980). Optic damage needs to be corroborated through animal studies. A study of the effects of TCE exposure in rabbits for 12 weeks measured a decreased amplitude of visual evoked responses; the responses slowly returned to normal 6 weeks after exposure (Blain et al. 1992).

Hexane is not usually considered a CNS toxin; however, some clinical studies have indicated that *n*-hexane affects the CNS. Also, experimental animal studies have shown that *n*-hexane causes axonal degeneration in the CNS (Schaumburg and Spencer 1976, Bruhn et al. 1981, Frontali et al. 1981). Clinically, cranial neuropathy, spasticity, and autonomic dysfunction occasionally occur (Altenkirch et al. 1982). Of all these possible actions, animal studies have demonstrated only the optical-toxic effects of 2,5-hexanedione, a toxic metabolite of hexane, in rats (Backstrom and Collins 1992). Until these issues are further clarified through human and animal studies, *n*-hexane should be primarily considered a peripheral nervous system toxin.

**Table 61–8 Cranial Nerve Abnormalities Noted in Inhalant Abuse**

| Cranial Nerve | Dysfunction |
|---|---|
| I | Hyposmia, anosmia |
| II | Optic neuropathy |
| III, IV, VI | Oculomotor disorders: nystagmus, opsoclonus, ocular dysmetria |
| VIII | Sensorineural hearing loss |

Anosmia is an often described syndrome of inhalant abuse. It would be expected that solvents would diminish the olfactory responses; however, it has seldom been studied. Mergler and Beauvais (1992) found that olfactory perception was reduced after 7 hours of exposure to toluene and returned to normal a couple of hours after cessation of exposure. Anosmia or hyposmia was detected on clinical examination utilizing simple bedside measures in chronic inhalant abusers (Hormes et al. 1986).

## Trigeminal Neuropathy

One neurological manifestation associated with TCE intoxication is a slowly reversible trigeminal neuropathy (Ruijten et al. 1991, Feldman et al. 1992). Cranial neuropathies were noted after general anesthesia with TCE more than 40 years ago. Individuals developed paresthesia around the lips, which then spread to involve the entire trigeminal distribution bilaterally. Motor weakness also occasionally occurred. Resolution of the trigeminal neuropathy occurs slowly, which is thought to indicate segmental or nuclear trigeminal involvement.

There has been a long-term controversy about whether or not unmetabolized TCE causes trigeminal neuralgia or the neurotoxicity is due to dichloroacetylene, an environmental breakdown product of TCE (Laureno 1993, Lash and Green 1993). The incidence of trigeminal neuralgia in humans can be disputed; however, animal studies do demonstrate the production of trigeminal neuralgia by TCE, as well as dichloroacetylene (Barret et al. 1992). There are no reports of trigeminal neuropathy noted for solvent abusers despite common inhalation of TCE from different products (Levy 1986).

## Myeloneuropathy

Nitrous oxide is not an organic solvent; however, it is widely abused by adolescents (Schwartz and Calihan 1984, Wagner et al. 1992), adults (Wagner et al. 1992, Brett 1997, Butzkueven and King 2000, Waters et al. 2005) and professional personnel (Jastak 1991, Vishnubhakat and Beresford 1991, Gillman 1992). Nitrous oxide is a common anesthetic widely used in dentistry; it is also used as a propellant for whipped cream. High levels of nitrous oxide exposure produce a myeloneuropathy with both central and peripheral components, even in the presence of adequate oxygen (Layzer 1978, Pema et al. 1998, Maze and Fujinaga 2000). The symptoms include numbness and weakness in the limbs, loss of dexterity, sensory loss, and loss of balance. The early neurological features indicate sensorimotor polyneuropathy; however, with persistent abuse, a myelopathy with severe spasticity may develop. There is also a combined degeneration of the posterior and lateral columns of the spinal cord resembling that in vitamin $B_{12}$ deficiency

(Layzer 1978). Studies focusing on the mechanism of this action indicate that cobalamins (vitamin $B_{12}$) are inactivated by nitrous oxide, primarily at the level of the enzyme methionine synthase, which needs vitamin $B_{12}$ to function (Nunn 1987). This enzyme is important in the maintenance of the myelin sheath (Flippo and Holder 1993). Flippo and Holder (1993) noted that paresthesia and other neuropathic symptoms resulting from spinal cord degeneration were produced after prolonged anesthesia in vitamin $B_{12}$-deficient patients. The relationship of vitamin $B_{12}$ and methionine has been recently reviewed (Toohey 2006). Administration of vitamin $B_{12}$ (or folinic acid) dramatically aids recovery of these surgical patients and may assist recovery in solvent abusers (Vishnubhakat and Beresford 1991), especially once the myelopathy appears. The use of methionine should also be considered (Fujinaga and Baden 1994). Recent studies have identified the role of GABA receptors in mediating these neurologic actions; thus, use of GABA agonists may be useful in some treatment regimens (Maze and Fujinaga 2000, Jevtovic-Todorovic et al. 2000).

In regard to dependence on nitrous oxide, studies of mice selectively bred for alcohol dependence showed a cross-dependence on nitrous oxide (Belknap et al. 1987). These studies also observed handling-induced convulsions shortly after cessation of nitrous oxide, which could be prevented by either alcohol or nitrous oxide. This might indicate a physical dependence on nitrous oxide that needs to be dealt with in treatment of this drug abuse state.

### Peripheral Neuropathy

Two organic solvents were identified as neurotoxins after an investigation of peripheral neuropathies in an industrial setting when the solvent methyl isobutyl ketone was replaced by methyl butyl ketone (MBK) (Allen et al. 1975). Cases of *n*-hexane polyneuropathy have been reported both after occupational exposure (Herskowitz et al. 1971, Mendell et al. 1974, Mallov 1976) and after deliberate inhalation of vapors from products containing *n*-hexane such as glues (Gonzalez and Downey 1972, Goto et al. 1974, Korobkin et al. 1975, Means et al. 1976, Oh and Kim 1976, Towfighi et al. 1976, King et al. 1985b, Dittmer et al. 1993, Takeuchi 1993), gasoline (Gallassi et al. 1980, Hall et al. 1986), and naphtha (Tenenbein et al. 1984). Both *n*-hexane and MBK (Menkes 1976) are metabolized to the same neurotoxin, 2,5-hexanedione, and produce a peripheral neuropathy. 2,5-Hexanedione is responsible for most, if not all, of the neurotoxic effects of exposure to *n*-hexane or MBK (Spencer et al. 1980, Graham et al. 1982). MEK alone produces neither clinical nor pathological evidence of a peripheral neuropathy in experimental animals (Spencer et al. 1980); however, it acts synergistically with MBK or *n*-hexane in experimental animals and probably in humans (Saida et al. 1976, Altenkirch et al. 1982, Ichihara et al. 1998). This potentiation of toxicity of one compound (MBK or *n*-hexane) by an otherwise nontoxic compound (MEK) underscores the difficulty in sorting out toxic effects of individual solvents contained in a mixture.

Clinically and pathologically, the neuropathy occurring with *n*-hexane or MBK is that of a distal axonopathy (Schaumburg and Spencer 1976). The clinical syndrome is an initially painless sensorimotor polyneuropathy, which begins after chronic exposure; weight loss may be an early symptom. Sensory and motor disturbances are noted initially in the hands and feet, and sensory loss involves primarily small fiber sensation (i.e., light touch, pin prick, temperature) with relative sparing of large fiber sensation (i.e., position and vibration). Electrophysiological studies reveal an axonal polyneuropathy and pathologically multifocal axonal degeneration, multiple axonal swellings, and neurofilamentous accumulation at paranodal areas (Spencer et al. 1975). Overlying the axonal swellings, thinning of the myelin sheath occurs. These findings are typical of a distal axonopathy or dying-back neuropathy described in relation to other toxic and metabolic causes of peripheral neuropathy.

Prognosis for recovery correlates directly with the intensity and duration of the toxic exposure and the severity of the neuropathy. Residual neuropathy is seen only in the most severely affected individuals with motor as well as sensory involvement, some of whom still continue to inhale despite warnings of further debilitation.

## Nonnervous System Toxicity of Inhalant Abuse

Most of the known adverse clinical effects of inhalant abuse relate to its effects on the nervous system. There are, however, other significant adverse effects on other organ systems including the kidney, liver, lung, heart, and hemopoietic systems.

### Renal Toxicity

Some time ago, Gabow (Streicher et al. 1981) and others (Bennett and Forman 1980, Will and McLaren 1981) described the effects of toluene-containing substances on the kidneys, which often result in hospitalization of inhalant abusers. Young people present most often, however, adults also present with renal disease after sniffing glue, spray paint, and other solvent products (Baerg and Kimberg 1970, Miller et al. 1985, Patel and Benjamin 1986, Batlle et al. 1988, Davidman and Schmitz 1988, Jone and Wu 1988, Marjot and McLeod 1989, Mizutani et al. 1989, Nelson et al. 1990, Carlisle et al. 1991, Gupta et al. 1991, Wilkins-Haug and Gabow 1991, Kaneko et al. 1992, Caravati 1997, Chang et al. 1999, Kao et al. 2000).

This dysfunction, which may rapidly reappear in individuals who return to their habit after release from the hospital, is characterized by hyperchloremic metabolic acidosis, hypokalemia, hypocalcemia, and other electrolyte imbalances. Solvents usually cause a unique distal-type tubular acidosis, but proximal tubules (Al-Ghamdi et al. 2003) are also affected (the distal tubule is responsible for the known electrolyte and metabolic imbalance; the proximal type is responsible for the wasting of amino acids and other proteins). These subjects often have associated gastrointestinal involvement, including nausea, vomiting, and severe abdominal cramps. On the basis of these reports, renal dysfunction appears to be one of the most common toxic effects noted for solvent abusers. Although this renal damage is usually reversible, other organs, particularly brain, are the target of repetitive acidosis and any depletion of important amino acids. This may be the basis for some of the observed neurological deficits (Yamamoto et al. 1992).

Of all the solvents, toluene is most often correlated with this disease (Al-Ghamdi et al. 2003); however, other solvents, including chlorinated hydrocarbons, are frequently the basis

for renal disease in these populations. Further animal studies are necessary to clarify specific solvent toxicities similar to those associated with nephrotic changes after exposure to halogenated hydrocarbons (Kimbrough et al. 1985, Lock 1989, 2006) and petroleum hydrocarbons (Short et al. 1987).

Clinicians especially need to be alert for pregnant women who abuse these solvents. Not only do they present to the clinic with renal tubular acidosis, but the fetuses may also be affected (Goodwin 1988, Lindemann 1991, Wilkins-Haug 1997). This condition places the mother at risk for hypokalemia and associated cardiac dysrhythmias and rhabdomyolysis (Wilkins-Haug 1997). Preterm labor therapy (β-mimetics and intravenous fluids) exacerbated the maternal and fetal problems. Fatty livers may also be observed in these pregnant subjects (Paraf et al. 1993). Treatment for their metabolic imbalance needs immediate attention.

### Treatment

For pregnant as well as other patients, electrolyte repletion usually restores the kidney function and eliminates the muscle spasms even in the more severely affected patients in a few days. Correction of salt and electrolyte imbalance, including potassium, calcium, magnesium, phosphate, and bicarbonate (Davidman and Schmitz 1988, Wilkins-Haug and Gabow 1991), is important and may be considered in the treatment of solvent abusers for muscle fatigue even in the absence of more severe kidney disorders. Caution about the use of bicarbonate early in the treatment of these subjects has been discussed by Lavoie and coworkers (1987).

### Pulmonary Toxicity

Solvents do irritate the lungs; however, few pulmonary problems have been reported (Devathasan et al. 1984). In two studies, mild pulmonary hypertension, acute respiratory distress, increased airway resistance and residual volume, and restricted ventilation were noted. Increased airway resistance or residual volume may be more clearly noted after an exercise challenge (Schikler et al. 1984, Reyes de la 1987). An increase in the frequency of respiratory (viral) illnesses, often noted in clinical reports, may be related to solvent exposure. In Australia (Currie et al. 1994), aspiration pneumonia was noted as a major cause of death in aboriginal sniffers. In sniffers in the US, aspiration pneumonia has not been a major cause of death. How to generalize the impact of dual exposure to solvent and infection is uncertain, but animal studies have measured decreased pulmonary bactericidal activity after exposure to solvents (e.g., dichloroethylene) (Sherwood et al. 1987). Animal studies have also measured pulmonary fibrosis in mice after solvent (TCE) (Forkert and Forkert 1994) exposure. A recent outbreak of respiratory illnesses has been associated with the leather treatment process where specific fluorocarbon aerosolized sprays are used (Hubbs et al. 1997).

Any pulmonary change may not be detected early on; it also may be enhanced by the other substances volatilized along with the solvent (e.g., polystyrenes, tars), utilized by the subject (e.g., tobacco and marijuana), or related to other conditions (Cartwright et al. 1983).

### Cardiotoxicity

One of the most common causes of solvent-induced deaths is cardiac arrhythmia, especially ventricular fibrillation and cardiac arrest (Wright and Strobl 1984, King et al. 1985a, Boon 1987, Cunningham et al. 1987, McLeod et al. 1987, Zakhari and Salem 1991, Ong et al. 1988, Bowen et al. 1999, Avella et al. 2006). Bass (1970) reported deaths related to fluorocarbons; fluorocarbons were also demonstrated to cause arrhythmias in animals (Taylor and Harris 1970). Fluorocarbon propellants have mostly been replaced by butanes and propane. However, similar arrhythmias were observed after the abuse of these newly designed aerosols (with butanes etc.), lighter gases, and cooking gases (Bass 1984, Siegel and Wason 1990, Roberts et al. 1990, Sugie et al. 2004, Pfeiffer et al. 2006). Chenoweth (1977) has shown that butane, hexane, heptanes, gasoline, some anesthetics, and toluene also produce these arrhythmias. Cruz and colleagues (2003) have recently related some of these actions to altered sodium currents. Although less common, sniffing glue (Cunningham et al. 1987, Knight et al. 1991, Wernisch et al. 1991) and TCE-containing stain removers (Wright and Strobl 1984, Hantson et al. 1990) have been linked to arrhythmias, myocarditis, and cardiac arrest. Organic nitrites have also been reported to produce bradycardia (Rosoff and Cohen 1986).

When arrhythmias are observed, antiarrhythmic therapy should be used (McLeod et al. 1987). Recovery from cardiopulmonary arrest is not common; however, a successful resuscitation from fluorocarbon overexposure has been reported (Brilliant and Grillo 1993). Cardiopulmonary resuscitation (mouth to mouth) followed by electrodefibrillation within 7 minutes was the primary emergency treatment. Exercise and epinephrine exacerbate these cardiotoxicities.

### Hematopoietic Toxicity

Of great concern are the incidences of neoplasm in solvent abusers. A common solvent, benzene, has long been identified as causing aplastic anemia and acute myelocytic leukemia (Austin et al. 1988, Yardley-Jones et al. 1991). Benzene is present in thinners, varnish removers and other solvents, and gasoline, which may lead to various neoplasms (Lauwerys et al. 1985, Knight et al. 1991). Based on the release of the nitrite ion in blood after the administration of organic nitrites, the ability to produce nitrosamines has fueled the speculation that nitrites are carcinogenic (Osterloh and Goldfield 1984, Yamamoto et al. 1987, Dunkel et al. 1989).

Most hematological changes can be overcome by the regenerative nature of red blood cells. Carbon monoxide, at high levels, produces cerebral hypoxia, which may subsequently have permanent neurological sequelae; it also produces carboxyhemoglobin. This occurs with exposure to a common solvent, methylene chloride (Horowitz 1986, Chang et al. 1999), as well as to cigarette smoke. The acute elevation of carboxyhemoglobin after exposure to methylene chloride has been studied in controlled experiments in humans (Stewart et al. 1972, Gamberale et al. 1975, Winneke 1981). The elevation is a result of the metabolism of the solvent methylene chloride to carbon monoxide (Stewart and Fisher 1972, Kubic et al. 1974, Ratney et al. 1974, Astrand et al. 1975), and therefore, the hypoxic effect of carbon monoxide as well as its narcotic actions must be taken into account in considering the actions of methylene chloride. The levels of carboxyhemoglobin may become

sufficiently high to cause brain damage (Barrowcliff and Knell 1979) or death (Manno et al. 1989).

One group of substances—the organic nitrites—produces a different hematological change, the formation of methemoglobin and hemolytic anemia (Wason et al. 1980, Brandes et al. 1989). This group of substances includes the volatile liquids amyl, butyl, isopropyl, and cyclohexyl organic nitrites. These drugs are not the typical solvents of most solvent abusers. A study could not correlate changes in regional blood flow with any psychological measures or somatic changes (Mathew et al. 1989b); also, isoamyl nitrite did not substitute for barbiturates as a reinforcing agent as do toluene and other solvents (Rees et al. 1987). These studies do not offer any explanation for why individuals become dependent on nitrites. However, the finding by Mathew and colleagues (1989b) that nitrites reduce anger, fatigue, and depression may offer a clue.

The nitrites are not usually considered toxic during inhalation because of syncope (fainting), and overdose is unlikely. However, Guss and coworkers (1985) noted a dangerously high methemoglobin level in a normal subject who had used isobutyl nitrite. Methemoglobinemia is the major identified toxicity of organic nitrites and is the cause of several deaths (Wood and Cox 1981). However, there is a specific treatment for nitrite overdose. The high and slowly reversible reduction of methemoglobin can be enhanced by the use of methylene blue (Smith et al. 1980).

Organic nitrites have also been reported to alter immune function as measured by direct lymphocytic actions (Soderberg and Barnett 1995) or in whole-animal studies (Gaworski et al. 1992). These effects are of special concern in the development of acquired immunodeficiency syndrome (AIDS). Haverkos and associates (1994) reviewed the possible link between the development of Kaposi's sarcoma and high amyl or butyl nitrite use. Seage and colleagues (1992); however, proposed that the link is related to enhancement of the accessibility of the human immunodeficiency virus.

Early studies did not show major effects of organic nitrites on isolated immune or bacterial cells (Lewis and Lynch 1988, Jacobs et al. 1983); however, studies by Soderberg's group (Soderberg and Barnett 1995) showed that isobutyl nitrite inhalation resulted in disruption of T-dependent immune mechanisms, including the induction of antibodies and cytotoxic T cells and of macrophage tumoricidal activity. This loss of immunity depended on habitual exposure and lasted for up to 5–7 days after exposures were terminated. The inhalant apparently produces this immunotoxicity by altering accessory cell functions, including diminished production of IL-1B in macrophage (Soderberg et al. 2004).

### Neonatal Syndrome

Newborns of mothers who chronically abuse solvents (Hersh 1989, Hersh et al. 1985, Goodwin 1988, Donald et al. 1991, Wilkins-Haug 1997) often present with abnormal growth similar to that described for the fetal alcohol syndrome. The mothers inhaled paint thinner and paint sprays and some also drank various quantities of alcohol. Thus, toluene may augment the fetal alcohol syndrome when alcohol is also consumed. It is also worth noting that the mothers of the infants in one (Hersh 1989) study showed ataxia, mild tremors, and slurred speech, and the mothers in the other studies presented with severe renal tubular acidosis. Newborns of these women showed growth retardation and some dysmorphic features including microcephaly and also distal acidosis and aminoaciduria (Wilkins-Haug 1997, Lindemann 1991). Some of these abnormalities were also observed in rodents exposed to toluene (Donald et al. 1991); however, the extent and severity of the effects are unclear. That solvents produce a "fetal syndrome" has been more comprehensively evaluated in a study of pregnant women who used toluene-based-solvents and/or alcohol (Tenenbein [2005], personal communication). In this study, only the babies of mothers who abused alcohol were observed to have a "fetal alcohol-t syndrome." However, some of the newborns of solvent abusers presented with renal acidosis.

Nitrous oxide has been shown to produce some "major visceral and minor skeletal (fetal) abnormalities" (Mazze et al. 1988). Also, animal studies demonstrated fetal toxicities of the liver caused by carbon tetrachloride (Cagen and Klaassen 1979) and malformations by chloroform (Murray et al. 1979). It is, thus, important that pregnant women not be exposed to very much of these substances. It is encouraging to know that a critical prospective study of female workers exposed to low levels of solvent showed no more fetal abnormalities than in the carefully matched control subjects (Eskenazi et al. 1988). This does not, however, diminish the need for pregnant women to avoid exposure to most solvents, especially at the high levels incurred through deliberate abuse.

## Treatment

Individuals need different treatments based on the severity of the dependence and medical complications. Primary care physicians should address the medical issues identified earlier as well as other medical concerns before dealing with the dependence on solvents and other drugs. During this period, sedatives, neuroleptics, and other forms of pharmacotherapy are not useful in the treatment of inhalant abusers and should be avoided in most cases as they are likely to exacerbate the depressed state and may complicate the problem of cardiac arrhythmia, especially in the acute intoxication stage.

Given the wide range of inhalants that are used, there are likely to be subpatterns of users (based on age and geographical regions, see Howard et al. 2007) for which treatment approaches might differ. Unfortunately the literature contains very little information about these categories. It is known that many users will gravitate toward certain products (e.g., toluene, nitrous oxide); these people may share common psychosocial backgrounds. Younger users may be more likely to use toluene-containing products whereas adults might prefer nitrous oxide (Wu and Ringwalt 2006). Another pattern might exist for professionals in the medical field who abuse anesthetics. Clearly, they would differ in multiple ways from abusers who prefer toluene, for instance. Until a better characterization of types of inhalant users is available, treatment planning would benefit from a complete history of inhalant use and a detailed psychosocial profile of individual users. Also, treatment of inhalant abuse at some drug treatment centers is often integrated with treatment for other types of drug use with no unique approaches identified for those with a primary inhalant disorder (Sakai et al. 2006); in contrast many heavily inhalant-dependent individuals (with inhalants as the major if not only drug

abuse disorder) are treated in an inhalant-unique treatment environment (Dinwiddie et al. 1987, Reidel et al. 1995).

Data on evidence-based treatment approaches for inhalant problems is extremely scarce and there is no accepted treatment protocol. Dinwiddie et al. (1987) reported a 100% relapse rate for young adult heavy-inhalant users 6 months after treatment. Sakai et al. (2006) found a reduction in inhalant use in a 2-year follow-up of adolescents admitted to a behavior modification, inpatient treatment program. Reidel et al. 1995 designed a program specifically for inhalant using adolescents employing education, neurocognitive retraining and cultural practices in a 90–120 day inpatient program. Six-month follow-up data revealed significant improvement in neurocognitive functioning and educational achievement and reductions in inhalant use. Given the design of the follow-up study it was not possible to tell what elements of the intervention were effective in producing the gains they found.

Most of what has been written on inhalant treatment derives from the nature of inhalants themselves and observations from those who have attempted to provide treatment. It is generally agreed that inhalants induce neurocognitive impairment that interferes with the usual treatment approaches (e.g., psychotherapy and educational interventions in the early stages of treatment). Since inhalants are lipophyllic, clearance from the body is very slow and the neurocognitive effects are longer lasting than may be found for other drugs. While there is little empirical evidence regarding the slope of the clearance curve, there is agreement that detoxification for heavy inhalant users requires an extended period and may take up to 1 month, and perhaps even longer depending on the history of use (Fornazzari 1988, Jumper-Thurman and Beauvais 1997). The recommendation for this period of time is to focus on basic life skills, hygiene, and dietary issues with minimal attention to therapeutic interventions. Neurocognitive testing may help in tracking the course of detoxification although there is question as to the utility of this during acute intoxication. Initial therapeutic interventions should be brief (15–20 minutes) and can be gradually extended depending on the cognitive clarity of the patient.

The evidence cited above for higher levels of psychiatric disorders, neurocognitive deficits and social dysfunction likely account for the intractableness inhalant users show toward treatment (Evren et al. 2006: Jumper-Thurman and Beauvais 1992). Further, these characteristics provide a distinctive profile that sets inhalant users sufficiently apart from other drug users. It is recommended that patients for whom inhalants are the *primary* drug of abuse be treated in programs specifically designed for inhalant abuse. Patients with a long history of abuse, and considering the lengthy detoxification period, usually require inpatient treatment. These findings also make it essential that screening for comorbid conditions be conducted before treatment planning commences. In particular, it is important to obtain a detailed history of use of other drugs of abuse, including alcohol, so that these conditions can also be addressed. It is not uncommon for patients to prefer drugs other than inhalants but will use inhalants when they are unable to afford other drugs. If the full range of comorbid conditions are not addressed, treatment is likely to fail.

A consequence of the manifold problems that inhalant users present is the need for increased intensity and length of treatment; the usual 14- to 30-day inpatient treatment is rarely sufficient to address the full range of issues. Some clinics report that a 6–12 month treatment regimen is required. Multiple resources are needed to attend to the various physical, neurological, social, and psychiatric problems that may be present. For younger patients it is important to involve family members in the process since family relationships have often deteriorated. (Dell et al. 2005, Howard and Jensn 1999). Given the high rates of relapse that have been observed among inhalant users, attention to follow-up care is essential (Reidel et al. 1995). Resources need to be identified in the community and close contact and coordination need to be maintained to reintegrate the patient back into a supportive environment. During treatment it is critical to restrict access to inhalable substances. This may be difficult given the ubiquity of inhalants. In inpatient settings maintenance and cleaning supplies should be carefully controlled. Drug screening would be useful in monitoring inhalant abusers. Routine urine screening for hippuric acid (the major metabolite of toluene) performed two or three times weekly can detect the high level of exposure to toluene commonly seen in inhalant abusers. More frequently performed expired breath analysis for toluene or other abused compounds is also available. As alcohol is a common secondary drug of abuse among inhalant abusers, alcohol abuse should be monitored and considered in the approach to treatment.

Taking a more global view of the treatment process, the following areas require consideration:

- Culture
- Family structure
- Living environment
- Peer interactions
- Individual's ability to learn and adapt
- Establishment of self-image
- Individual attitudes and behavioral characteristics
- Building basic life skills
- Social bonding

Clinical Vignette

A 15-year-old Native American boy was brought to the emergency department by the police after being arrested for vandalism and stealing. He was found with about a dozen butane cigarette lighters and some whippet canisters that he had stolen. When taken into custody, he was staggering and appeared confused. At the emergency department, he had a "gasoline-like" smell on his breath and was disoriented to time. On a brief neurological examination, he had nystagmus and cerebellar ataxia (wide-based gait, poor finger-to-nose pointing). A urine toxicology test for hippuric acid was positive. Because of his neurological findings an MRI scan was obtained. The scan showed multifocal white matter hypodensities consistent with demyelinating axonal degeneration. He was admitted to the hospital for observation and released 3 days later after a medical history could be obtained from him. He had run away from his home reservation a year earlier and had been abusing alcohol and a wide range of inhalants including butane, nitrous oxide, and toluene (glue sniffing) on an almost daily basis. The diagnosis was inhalant use disorder, dependence.

*Source:* Courtesy of Thomas R. Kosten.

Clinical Vignette

A 16-year-old male presented due to altered mental status. According to the history provided by his family, 1 day before admission he was observed to be confused and lethargic and also reported seeing hallucinations of spiders. These changes worsened with the patient becoming noncommunicative and intermittently agitated overnight. On examination, he was nonverbal, rarely nodded yes or no, and intermittently followed only simple commands. He had masked facies, appeared apathetic, and sat motionless. Examinations of cranial nerves, motor strength, tone, and reflexes were normal. Coordination testing was difficult; however, he seemed to have a mild degree of ataxia in both upper extremities. His gait was slow but otherwise normal. Sensory testing was limited owing to his mental status, but light touch and pain appeared intact. Routine urine toxicology was negative for amphetamines, cocaine, barbiturates, benzodiazepines, and opiates; this toxicology screen did not include testing for butane or other aromatic compounds that are abused via inhalation. Further history by a sibling revealed that the patient had inhaled a can of butane 2 days before his admission. This can, brought to the hospital by the parents, was a 300-mL empty can of butane lighter fluid. Laboratory confirmation of the butane exposure with gas chromatography was deemed futile as the urine collected was well over 24 hours postexposure. Laboratory studies did not indicate signs of infection, hepatic or renal dysfunction. An electroencephalogram recorded 2 days after admission demonstrated diffuse background slowing, intermittent bilateral frontal delta waves, and an abnormal arousal response pattern consistent with a toxic or metabolic encephalopathy. Magnetic resonance imaging demonstrated markedly abnormal increased signal in the thalami bilaterally on fluid-attenuated inversion recovery and other T2-weighted sequences. Signal abnormalities were also observed but to a lesser degree of severity in both insulae and right cerebellum. Diffusion-weighted imaging documented increased intensity in the thalami; however, the apparent diffusion coefficient maps did not indicate restricted diffusion consistent with infarction. Rather, the increased apparent diffusion coefficient values were indicative of edema and the diffusion-weighted imaging appearance that of "T2 shine through" of the edematous tissue. The neuroradiologic impression was that the imaging findings were consistent with a metabolic or toxic etiology, given the symmetry of the abnormalities. The patient remained hospitalized on the rehabilitation service, 3 months after admission, manifesting little change in his clinical symptoms. When he was last evaluated by the neurology service, he continued to exhibit a profound mutism and apathy.

*Source:* Courtesy of Kile et al. (2006).

Clinical Vignette

A 30-year-old male, ex-convict, came to counseling concerning a persistent "tingling" in his hands. He had consulted several physicians who could provide no plausible explanation and he was wondering if it was "something in his head." The man had a history of heavy use of multiple drugs of abuse, including inhalants. He maintained that he had been clean for several years. When queried about the types of inhalants used he produced an extensive list of substances but said he couldn't remember everything that he probably used. He said that of all the drugs he had used he preferred inhalants. When asked why he responded with: "You know the feeling of euphoria you feel when you are at the top of a roller coaster and are just starting to go down? That's how it is with inhalants, you can keep sniffing just enough at a time to keep that feeling going for a long time. It is such a rush and I have to be careful since I continue to have strong urges to go back to using." The counselor explained that the tingling sensation may well be the result of his use of an inhalant that contained *n*-hexane and that it may persist for some time. If he continued to be concerned about it he was encouraged to see a neurologist.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 and DSM-IV-TR criteria sets for Inhalant Intoxication are nearly equivalent (except that DSM-IV-TR lists additional symptoms).

## A Tribute to Dr. Neil Rosenberg

It was a tragic loss of Dr. Neil Rosenberg, an active neurologist, shortly after the publication of the second edition of this chapter. His findings, thoughts, and guidance are still a major part of this chapter. He was concerned about young people causing dementia prematurely not only through the voluntary overexposure of themselves to solvents but also through the use of other substances such as methamphetamine. He was a pioneer in the field of defining neurologic manifestations of solvent abuse and with his wife, Cathy, founded the International Institute on Inhalant Abuse. He devoted his energies through academic groups, including NIH and the American Academy of Neurology. More humbly he traveled throughout the United States and Central and South America, educating people about the dangers of inhaling chemicals and provided extensive humanitarian assistance to poor people in Peru and other countries in the latin Americas as well as Native Americans in the northern hemisphere, always with the prime goal of diminishing solvent- and other drug-dependent activities.

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CHAPTER

# 62 Substance Abuse: Nicotine Dependence

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Nicotine Dependence

Tobacco use is common throughout the world with there being about 1.25 billion smokers of which 1 billion are male and only 50 million live in the US (Lando et al. 2005, Warren et al. 2006). Even though only 4% of the world's smokers are from the US, nicotine dependence is the most common substance use disorder (SUD) in the US with 20.6% of the adult US population smoking cigarettes (Centers for Disease Control and Prevention 2006). Tobacco-caused diseases are the second most common cause of death in the world, including 5 million in 2005 and an estimate of 10 million in 2020 (Warren et al. 2006, The World Health Report 2002). Tobacco use and nicotine dependence has serious health consequences for the user, family members, and others who breathe environmental tobacco smoke or are exposed during pregnancy. Tobacco use and nicotine dependence increases morbidity and mortality. A large proportion of individuals with a current Axis I disorders (mental illness and/or other SUDs) are also nicotine dependent. In the US, the overall reduction in smoking rates in the general population has not been matched by proportional reductions amongst individuals with psychiatric disorders (Ziedonis and Williams 2003). As a result, about 44% of all the cigarettes consumed in the US are by individuals with psychiatric disorders (Lasser et al. 2000). The high rates of psychiatric disorders amongst smokers are common throughout the world (deLeon and Diaz 2005).

## Diagnosis

*Nicotine dependence* was first included as a SUD in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) in 1980 (American Psychiatric Association 1980). The nicotine withdrawal syndrome occurring after abstinence was also first classified as a disorder in DSM-III (American Psychiatric Association 1980). Of note, the DSM distinguishes nicotine from other substances by not including a diagnosis of nicotine abuse because most individuals transit quickly and directly from use to dependence (meeting criteria of tolerance and withdrawal).

## Definition and Diagnostic Features

The definition of Nicotine Dependence is similar to other SUDs and is listed in the Table of Diagnostic Criteria. In the DSM-IV-TR (American Psychiatric Association 1994), a specifier is used to designate the presence or absence of physiological dependence, depending on whether tolerance or withdrawal is present or whether both are absent. Further specifiers can be used to denote course (e.g., early full remission or sustained partial remission). Diagnostic features include the nicotine withdrawal syndrome and level of dependence severity.

The DSM-IV-TR nicotine withdrawal syndrome describes a characteristic set of symptoms that develops after abrupt cessation or a reduction in the use of nicotine products after at least several weeks of daily use and is accompanied by four of the following signs and symptoms: (1) dysphoria or depressed mood, (2) insomnia, (3) irritability, frustration, or anger, (4) anxiety, (5) difficulty concentrating, (6) restlessness or impatience, (7) decreased heart rate, and (8) increased appetite or weight gain (American Psychiatric Association 1994). The withdrawal symptoms must also cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and must not be secondary to a general medical condition or be accounted for by another mental disorder. Other symptoms that may be associated with nicotine withdrawal include craving for nicotine, a factor thought to be significant in relapse; a desire for sweets, and impaired performance on tasks requiring vigilance. The World Health Organization's

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ICD-10 criteria list also has craving, malaise, increased cough, and mouth ulceration and does not include the DSM decreased heart rate item.

To some extent, the degree of physiological dependence predicts severity of the withdrawal syndrome and difficulty in stopping smoking. The Fagerström Test for Nicotine Dependence (Heatherton et al. 1991) was developed to assess the degree of physical dependence on nicotine. Its two primary measures are number of cigarettes smoked per day and time in the morning until the first cigarette (see Section on "Assessment"). These two primary items are often used in isolation and called the Heaviness of Smoking Index (HSI) (Heatherton et al. 1989). A score of six or higher on the Fagerström Test for Nicotine Dependence (FTND) is indicative of higher severity of nicotine dependence (Fagerström et al. 1992), but does not constitute a definitive diagnosis. In addition to frank symptoms, other objective biological and physiological changes are associated with nicotine withdrawal, such as generalized slowing of electroencephalographic activity, decreases in catecholamine and cortisol levels, changes in rapid eye movement, impairment on neuropsychological testing, and decreased metabolic rate.

**DSM-IV-TR Criteria**

**Nicotine Dependence**

A pattern of nicotine use, leading to clinically significant impairment or distress, as manifested by at least three of seven criteria occurring at some time during a 12-month period:

(1) Tolerance
  (a) Absence of nausea, dizziness, and other characteristic symptoms of nicotine despite using substantial amounts or
  (b) A diminished effect with continued use of the same amount of nicotine

(2) Withdrawal
  (a) Presence of a characteristic withdrawal syndrome (see nicotine withdrawal) or
  (b) The use of the substance or related substances to relieve or avoid withdrawal symptoms, for example, smoking a cigarette immediately upon waking in the morning after a night of abstinence or immediately smoking a cigarette after disembarking from a long plane flight in order to relieve withdrawal symptoms

(3) Use of nicotine in larger amounts or over a longer period than was intended, for example, using up a package of cigarettes faster than originally intended

(4) Persistent desire or unsuccessful efforts to cut down or control nicotine use, for example, most smokers desire to stop smoking but numerous attempts are often required before successful cessation is achieved

(5) A great deal of time spent in activities necessary to obtain the substance, in use of the substance, or in recovery from its effects, for example, chain smokers who spend a good deal of the day in smoking activity or smokers with worksite smoking restrictions who interrupt their work repeatedly for cigarette "breaks"

(6) Important social occupational, or recreational activities given up or reduced because of substance use, for example, some smokers may have had to change jobs because of an inability to accommodate their smoking to workplace restrictions, although this would be uncommon

(7) Continued use despite having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by nicotine use, for example, continued smoking after the occurrence of a myocardial infarction or in the face of marital conflict related to the person's smoking

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## Assessment

The assessment of tobacco use and nicotine dependence (Table 62–1) often begins with an evaluation of the patterns of tobacco usage (number of cigarettes smoked per day, time to first cigarette in the morning, other times during the day, location, and circumstances). The severity of nicotine dependence can be assessed with the FTND (Heatherton et al. 1991). The FTND assesses factors such as the amount of time until the first cigarette in the morning, the number of cigarettes smoked in one day, smoking when ill, difficulty refraining from smoking, the degree to which the first cigarette of the day is the most difficult to give up, and smoking more in the morning than in the afternoon. The FTND, and its 2-item version, the HSI (Heatherton et al. 1989) are the most commonly used measures of severity of nicotine

**Table 62–1 Assessing Nicotine Use and Nicotine Dependence**

| |
|---|
| Current and past patterns of tobacco use (include multiple sources of nicotine) |
| Current motivation to quit |
| Objective measures: breath CO level or cotinine level (saliva, blood, urine) |
| Assess prior quit attempts (number and what happened in each attempt) |
| Why quit? How long abstinent? Why relapsed? |
| What treatment was used (how used and for how long) |
| Assess withdrawal symptoms and dependence criteria |
| Psychiatric and other substance use history |
| Medical conditions |
| Their common triggers (car, people, moods, home, phone calls, meals, etc.) |
| Perceived barriers against and supports for treatment success |
| Preference for treatment strategy |

dependence. It should be noted, however, that because some items assume that the smoker has primary control over their environments (e.g., the number of minutes after waking until first cigarette) these measures may be less relevant to those with serious mental illness or adolescents for whom the smoking environment is at least partially under the control of others (Steinberg et al. 2005).

In addition, the amount of tobacco usage can be assessed through cotinine levels or carbon monoxide (CO) levels. Cotinine levels can be obtained from the urine, blood, or saliva to assess the amount of nicotine ingested. Cotinine is a primary metabolite of nicotine and remains in the body for several weeks. Despite the advantage of this longer opportunity for detecting nicotine usage, the cotinine tests are costly and may require several days for a lab to report the results. In contrast, the expired-air test for a CO level is less costly and can be obtained within a min by any clinician with a CO meter. The CO meter is useful at intake and to monitor for relapse. Higher cotinine and CO levels are associated with a higher number of cigarettes per day and also severity of nicotine withdrawal. For the 20-cigarette-per-day smoker, expired-air CO levels are typically in the 10−30 parts per million (ppm) range and cotinine levels 250 to 300 ng/mL range.

A history of prior cessation attempts should include the nature of prior treatments, length of abstinence, timing of relapse, and factors specifically related to relapse (e.g., environmental or interpersonal triggers). An assessment should be made of the person's reasons for quitting, his or her motivation and commitment and self-efficacy (perceived ability to quit). The individual's stage of readiness (motivation) for stopping smoking is also important. One common model for conceptualizing motivation describes five stages: precontemplation, contemplation, preparation, action, and maintenance stages (Prochaska 1983). Clinicians determine whether the person is not yet seriously considering stopping smoking (precontemplation), is considering attempting to quit but not for several months (contemplation), is seriously considering quitting in the next month and has begun to think about the necessary steps to stop smoking (preparation), or is actually attempting to stop smoking (action) (Prochaska 1983). It is also important to assess the smoker's knowledge about smoking and nicotine dependence because deficits in knowledge and information can have a deleterious effect on smoking cessation attempts.

Assessing prior treatments includes assessing prior use of medications and psychosocial treatments. There are now seven Food and Drug Administration (FDA)-approved medications for nicotine dependence treatment, including five nicotine replacement therapies (NRT) (such as the patch, gum, spray, inhaler, and lozenge) and two non-nicotine pills bupropion (Zyban) and varenicline (Chantix). Non-FDA approved medications with some evidence supporting their use include nortriptyline and clonidine (Work Group on Substance Use Disorders, et al. 2006). Assessing about prior medication use includes asking about what dose of medications and how long it was taken; any side effects that developed; and how the patient actually took the medication (especially relevant for NRT). For example, the patient may report taking off the NRT patch prior to a shower and then replacing the same patch, rendering it ineffective. Prior psychosocial treatments might include group or individual treatment, American Lung Association and other community support groups, hypnosis, acupuncture, or Nicotine Anonymous. Understanding how long a patient was engaged in these approaches and whether the medications and psychosocial treatments were combined can be helpful in creating a new treatment plan. Evaluating potential triggers for tobacco use is important, including social context, time of day, and relationship to other activities, moods, people, and places. Triggers might include driving the car, speaking on the phone, meals, etc. In addition, the first two weeks of abstinence are a particularly vulnerable time period for withdrawal symptoms to be a trigger for use. A history of specific withdrawal symptoms and their severity and duration is critical, as is an assessment of the smoker's social and environmental contexts, for example, whether other household members smoke, and available family and social supports.

Assessment of the psychiatric history is also important. Numerous studies have shown the significance of current and past depression in relation to smoking, as well as the increased prevalence rates of cigarette smoking in patients with a variety of psychiatric disorders, such as MDD, schizophrenia, and alcohol and substance abuse (see Section on "Comorbidity Patterns"). The presence of these comorbid disorders may also make successful smoking cessation less likely (see section on special features influencing treatment), especially if undiagnosed and untreated.

Assessing the patient for a history of current alcohol or other substance abuse is also important, as the prevalence of smoking in persons with alcohol dependence as well as in other substance abusers is much higher than in the general population. It may also be more difficult for individuals with current or prior substance abuse or dependence to stop smoking, as there is evidence that persons with alcohol dependence and other substance abusers start smoking earlier and are more physiologically dependent on nicotine (Hughes 1993b). In addition, the use of alcohol or other substances may be intimately linked to smoking cigarettes and can serve as a strong trigger for craving and ultimate relapse.

A careful medical history should also be obtained. The presence of significant tobacco-related medical illness can sometimes serve as crucial leverage to help motivate the individual to attempt cessation. Current medications and medical conditions may also be important considerations in determining the approach to cessation, especially with regard to pharmacotherapy. For example, a history of seizures or an eating disorder is usually a contraindication to the use of bupropion/Zyban (nonnicotine pill medication). The individual should be assessed for pulmonary symptoms and signs (cough), and if there is a long history of significant nicotine use, pulmonary function tests should be considered. The presence of significant cardiovascular disease, especially a history of recent myocardial infarction, is especially relevant to planning psychopharmacological interventions. If the individual is already taking a psychiatric medication, consider it important to realize that quitting smoking may result in an increase in medication blood levels and side effects.

## Epidemiology

Tobacco use is very common throughout the world and there is great concern about the increase in tobacco-caused

diseases worldwide (Lando et al. 2005, Warren et al. 2006). Throughout the world, manufactured cigarettes is a very common way to use tobacco, however, there are high rates of other forms of tobacco in some countries, including high rates of chewing tobacco and water pipe use (Warren et al. 2006, The World Health Report 2002). Nicotine dependence is the most prevalent SUD in the US (Grant et al. 2004) with about 20.6% of the adult US population smoking cigarettes (Centers for Disease Control and Prevention 2006). World wide there ate about 5 million tobacco-caused deaths, and Cigarette smoking is the leading preventable cause of morbidity and mortality in the US, with an estimated 438,000 premature deaths occurring each year from tobacco-caused illnesses (Centers for Disease Control and Prevention 2005). Smoking is the cause of 90% of all lung cancers and nearly all cases of chronic obstructive pulmonary disease. It is associated with two times greater risk of death from stroke and coronary heart disease (U.S. Department of Health and Human Services 2004). It is also associated with an increased incidence of cancer at a number of other sites, including the larynx, oral cavity, esophagus, cervix, bladder, pancreas, and kidney and is associated with complications of pregnancy and negative effects on the fetus, including low birth weight (U.S. Department of Health and Human Services 2004). Detrimental effects on nonsmokers exposed to tobacco smoke have been demonstrated, particularly in children (U.S. Department of Health and Human Services 2006) Smoking causes 10 times the morbidity and mortality of all other substances of abuse combined and results in a total of $75.5 billion in direct medical costs for treating smoking-related illness (Centers for Disease Control and Prevention 2002) and $92 billion in lost productivity per year (Centers for Disease Control and Prevention 2005). The prevalence of smoking is increasing in most developing countries, whereas it is decreasing in most industrialized countries. In the US, there has been increasing societal pressure for individuals to stop smoking. Despite an increase in the proportion of smokers quitting, about 20% of the US population continues to smoke, with a lifetime prevalence of nicotine dependence of 24% (Breslau et al. 2001). Only 45% of the population has never smoked.

The prevalence of cigarette smoking is higher at lower socioeconomic levels. Slightly more males than females smoke, although more males than females are successful in stopping smoking. There is evidence that the number of cigarettes per smoker is increasing, leaving a more hardcore and potentially more dependent group of smokers. There has also been a recent increase in the rate of smoking among adolescents, particularly in the number of teenage girls smoking. This increased smoking rate amongst adolescents is particularly alarming, as smokers typically start smoking at an early age, with more than 60% of smokers beginning by age 14 years and nearly all by age 18 years. The Global Youth Tobacco Survey of 131 countries has found that about 8.9% of students were currently smoking and about 11.2% were currently using a tobacco product other than cigarettes (Warren et al. 2006). Of particular concern is that the rate of tobacco use amongst boys and girls is much more similar than the large difference between adult males and females, and this suggests an increase among women for the future (Warren et al. 2006).

## Comorbidity Patterns

Nicotine dependence and smoking are two to three times more common in individuals with psychiatric and other SUDs than in the general population (Hughes et al. 1986, Glassman 1993, Dierker et al. 2002). The high rates of psychiatric disorders amongst smokers are common throughout the world (deLeon and Diaz 2005, Lasser et al. 2004), Smoking-related illnesses are the primary cause of death among those in recovery from other substances. It is estimated that 55−90% of individuals with psychiatric disorders smoke versus the 20.6% of the general population. The prevalence of smoking is especially high in patients with schizophrenia (70–90%), generalized anxiety disorder (46%), alcohol abuse or dependence (43.5%), drug abuse or dependence (49%), and major depression (36.6%). Conversely, there is also evidence that affective, anxiety, and SUD may be more common in individuals who smoke than in those who do not or in those who have never smoked (Glassman 1993). Finally, there is evidence to suggest that in one study up to 75% of smokers with a history of MDD developed depressed mood during the first week of withdrawal versus only 30% of those with no depressive history, and that the withdrawal syndrome may be more severe in smokers with a history of depression (Covey et al. 1990). The presence of depressive symptoms during withdrawal is also associated with failed cessation attempts (West et al. 1989, Hughes 1992). Self-reported depressive symptoms during adolescence also predict later frequency and duration of smoking (Kandel and Davies 1986). Several studies suggest a genetic predisposition to both nicotine dependence and co-occurring depression (Carmelli et al. 1990, Kendler et al. 1993, Dierker et al. 2002, Glassman et al. 1990). It is interesting to note that a history of single-episode depression is not associated with reduced rates of smoking cessation, though a history of recurrent depression may be (Hitsman et al. 2003). ADHD decreases the age of onset of cigarette smoking and increases the overall risk for nicotine use in early adolescence (Millberger et al. 1997a, 1997c). Others have also found that adolescents with ADHD were three time more likely to smoke than adolescents without ADHD (Tercyak et al. 2002). Kollins et al. (2005) reported in a very large study including a cohort of 15, 197 eligible respondents between 15−22 years old that each reported inattention and hyperactivity/impulsivity symptom significantly increased the likelihood of regular smoking. There is also support for the idea that smoking may act as a gateway, increasing the risk for subsequent use of cannabis and other illicit drugs (Biederman et al. 2006). ADHD increases the risk for cigarette smoking and SUD) and is associated with greater SUD severity and chronicity (Wilens and Biederman 2006). A history of childhood ADHD is predictive of smoking cessation failure (Humfleet et al. 2005). Adult smokers with ADHD have more problems quitting than those without this condition (Pomerleau et al. 1995). The connection between ADHD and smoking is believed to be mediated by nicotine's enhancement on attention and concentration. Abstinence from nicotine can increase symptoms of inattention and hyperactivity-impulsivity and these symptoms are predictive of relapse (Rukstalis et al. 2005).

There is no simple reason why so many psychiatric patients smoke. As with other addictive disorders, a

combination of complex biological and psychosocial factors is likely. Potential biological factors in this group include a greater likelihood of susceptibility to nicotine dependence, with persons experiencing a greater sense of reward from nicotine. Other possibilities include using nicotine to reduce the side effects of psychiatric medications, both as a stimulant to counter sedation as well as a dopamine modulator that can diminish neuroleptic-induced parkinsonism. Subjectively, patients report that using nicotine improves their cognitive functioning and reduces stress, although research data is mixed in this regard (West and Hack 1991). In patients with schizophrenia, an abnormality in P50 gating, which is believed to relate clinically to the ability to filter out distracting auditory stimuli, is temporarily reversed with nicotine. Social and behavioral factors are also important in understanding nicotine dependence, and psychiatric and addictive comorbidity. Smoking has been ignored and is part of the pervasive culture in most mental health and substance abuse treatment centers and residential facilities. This is beginning to change. Historically, smoking was often used as a behavioral reward in psychiatric inpatient units and continues to serve as a social connector for many psychiatric patients. Patients who are coping with persistent psychiatric symptoms and reduced social and occupational functioning report smoking to fill the voids of boredom and disappointment (Ziedonis et al. 1994, Hall et al. 1991, Anda et al. 1990).

## Course

Nicotine dependence has been called a "pediatric disease" since most smokers started during adolescence. By the age of 18, 90% of those who will ever try a cigarette have done so, and age 18 years is the average age at which individuals become daily smokers. As with other SUD, the etiology of nicotine dependence is multifactorial and includes biological, psychological, and social factors, including genetic factors.

Nicotine is the primary psychoactive agent in tobacco smoke and smokeless tobacco and has powerful addictive properties (Benowitz 1988). As an indication of the addictive potential of this substance, one-third to one half of all children and adolescents who smoke one cigarette progress to become habitual users. Nicotine is considered to be the "gateway drug" to the use of other substances (Henningfield et al. 1990, Lai et al. 2000).

The National Health Interview Survey found that 70% of smokers interviewed reported they wanted to quit smoking at some point in their lifetime, and about 33% of smokers try to quit each year. Only about 3% of quit attempts without formal treatment are successful, and in recent years about 30% of smokers who want to quit are seeking treatment—including only 5% who seek counseling services (Zhu et al. 2000). Outcomes for nicotine dependence treatment vary by the type of treatment and the intensity of treatment with specific reports ranging from about 15−45% 1-year abstinence rates following treatment. Cessation attempts result in high relapse rates, with the relapse curve for smoking cessation paralleling that for opiates. Most individuals relapse trying to quit without treatment relapse within the first 8 days (Hughes et al. 2003). Recent data examining the natural time course of nicotine withdrawal indicates that different withdrawal symptoms reach their "peak" intensity at different times and that all withdrawals symptoms return to baseline within 10 days (Shiffman et al. 2006).

## Differential Diagnosis

Most tobacco users meet criteria for nicotine dependence, however, about 5% of tobacco smokers in the US are considered tobacco "chippers" and are not nicotine dependent. Chippers are occasional social smokers who may smoke up to five cigarettes in a day but do not smoke daily. They may smoke up to four days a week, however, they do not appear to suffer from nicotine withdrawal symptoms. Typically chippers use tobacco in a social context and not to "self-medicate." There appears to be a genetic link with chippers coming from a family of chippers; individuals from families of smokers who are nicotine dependent may appear to be occasional users initially, however, they usually progress rapidly to be nicotine dependent. Alcohol use can be a trigger for chippers to increase their tobacco use. Although these individuals are not nicotine dependent, they are still at risk for tobacco caused diseases since there is no safe dose of tobacco use (Work Group on Substance Use Disorders, et al. 2006).

## Differences in Developmental, Gender, and Cultural Presentation

Smoking is more common among white students (39.7%) than among Hispanic (34.0%) and black students (22.7%). The racial/ethnic differences are particularly striking among females; more than two times as many white females currently smoke (39.9%) as black females (17.4%), and almost five times as many white females are frequent smokers (20.1%) compared with black females (4.3%). Earlier data have shown high prevalence rates among American Indians and low prevalence rates among Asian-American and Pacific Islander youth, especially females. Smoking among black youth has shown the greatest increase since 1991, almost doubling from 12.6% in 1991 to 22.7% in 1997. Smoking was historically more common among men, but women are now almost as likely to smoke as are men; smoking among men has dropped, and women have caught up. This pattern is evident in several developed countries. In the developing world, sharp gender differences are still the norm. Even though prevalence has equalized, men still smoke more heavily than women. More than men, women report that they smoke in order to deal with stress and emotion. Despite their lighter smoking, women appear to be less successful at quitting smoking. Several avenues of research now indicate that men and women differ in their smoking behavior. For instance, women smoke fewer cigarettes per day, tend to use cigarettes with lower nicotine content, and do not inhale as deeply as men. However, it is unclear whether this is due to differences in sensitivity to nicotine or other factors that affect women differently, such as social factors or the sensory aspects of smoking.

## Etiology and Pathophysiology

### Genetic Factors

Family, adoption and twin studies strongly suggest the role of genetic factors in cigarette smoking. Comparing twins reared together and apart showed that in men the regular tobacco use has both genetic and rearing-environmental factor accounting for 61% and 20%, respectively

(Kendler et al. 2000). Another study looking at reared together monozygotic and dizygotic twins demonstrated that the liability for regular tobacco use breaks down as follows: 54% genetic, 24% familial-environmental and 20% individual-specific environmental risk factors (Sullivan and Kendler 1999). There is substantial overlap of the genetic factors predisposing to smoking initiation and the ones promoting the transition to nicotine dependence (Sullivan and Kendler 1999).The overall heritability of nicotine dependence is thought to be 60% (True et al. 1999, Kendler et al. 2000). In one study the genome-wide linkage scan analysis looking at the risk for nicotine dependence on the basis of the Fagerstrom Test demonstrated a significant association with a region on chromosome 5 in African Americans and on chromosome 7 for European American subjects (Gelernter et al. 2007). A different study assessing nicotine dependence with smoking quantity, HSI and the Fagerstrom Test showed a significant linkage to a region on chromosome 10q22 in African American subjects (Li et al. 2006). A number of other loci on chromosomes 6, 8, 16, and 19 were linked to various aspects of smoking behaviors (Swan et al. 2006). Smoking-induced dopamine release has also a genetic determinism. Smokers having genes associated with low-resting dopamine tone have been shown to have a greater smoking-induced dopamine release than those with alternate genotypes (Brody et al. 2006). Dopamine receptor and transporter genes have been associated to nicotine dependence (Batra et al. 2003). The catechol-O-methyltransferase (COMT) gene has an important role in dopaminergic circuits central to drug reward. Low COMT enzyme activity Met allele is associated with a decreased likelihood of becoming nicotine dependent (Beuten et al. 2006). There is evidence of a significant association between gamma amino butyric acid B2 (GABAB2) variants and nicotine dependence, implying that this gene might have role in the etiology of this drug addiction (Beuten et al. 2005). There is also genetic variability in the metabolism of nicotine that may help explain differences in both consumption and exposure. Metabolism of nicotine through the cytochrome P450 isozymes (CYP2A6 and CYP2D6) have displayed genetic polymorphisms and this will result in differences in nicotine metabolism. Both CYP2A6 and 2D6 genotype influences nicotine levels and smoking behavior. CYP2A6 slow metabolizers smoke fewer cigarettes per day compared to normal metabolizers and achieve higher levels of nicotine (Malaiyandi et al. 2006). Of note, the metabolism of the non-nicotine tobacco components is mostly through a different isoenzyme (will be discussed in more detail in the medication section of this chapter).

## Neurobiological Factors

Nicotine is readily absorbed in the lung from tobacco smoke or through the mucous membranes with smokeless tobacco. When smoking tobacco, nicotine enters the blood stream and is available to the brain within 7−9 s (even more quickly than with intravenous administration). Its peak effect occurs within 1 min, and effects are present after a single puff of smoke. With a half-life of approximately 2 hr, the level of nicotine in the blood stream gradually accumulates during the day, dropping but persisting overnight. Smokers, especially those with severe dependence, awaken in the morning in nicotine withdrawal and rapidly dose themselves. Nicotine receptors are ligand-gated ion channels with a variety of effects on the nervous, cardiovascular, immune and neuromuscular functioning (Changeux et al. 1998). The neuronal receptors are pentameric structures named on the basis of the $\alpha$ and $\beta$ subunits. There are 11 identified neuronal nAChR subunits, including 8 $\alpha$ ($\alpha$2–$\alpha$9) and 3 $\beta$ ($\beta$2–$\beta$4). Each subunit has 4 transmembrane spanning regions, M1−M4. The $\alpha4\beta2$ is proposed to have 2 $\alpha$4 and 3 $\beta$2 subunits.

As pointed out by Lloyd and Williams 2000 nicotine has a multiplicity of effects including "congnitive performace, vigilance, locomotor activiy, body temperature, respiration, cardiovascular and gastrointestinal tract function, electroencephalogram activity, cortical blood flow and pain perception." Most of these effects are also seen in humans. Nicotine is able to achieve the above by increasing the release of acetylcholine, dopamine, norepinephrine, serotonin, glutamate and gamma amino butyric acid (GABA) in the brain and the calcitonin and substance P in the spinal cord (Lloyd and Williams 2000). The beta2 nicotinic receptors are involved in the chronic, compulsive use of nicotine but not in the withdrawal syndrome (Besson et al. 2006).

Some of nicotine's effects are acute, while others appear only after chronic usage. It acts in two primary areas of the brain—the mesolimbic dopaminergic system (the brain reward pathway), which is related to the euphoriant effects of the drug, and the locus coeruleus, which mediates stress reactions and vigilance and relates to the higher mental and cognitive functions. There are specific nicotine receptor sites (the nicotinic cholinergic receptors) throughout the central nervous system in the hypothalamus, hippocampus, thalamus, midbrain, brain stem, and cerebral cortex. In addition, nicotine affects nearly all aspects of the endocrine–neuroendocrine system, including the catecholamine, serotonin, corticosteroid, and pituitary hormones. Its endocrine effects are mediated via the hypothalamic–pituitary axis and the adrenal medullary cortex. Centrally it causes release of acetylcholine, norepinephrine, serotonin, dopamine, vasopressin, growth hormone, corticotropin, cortisol, prolactin, and endorphins.

Nicotine has stimulant and depressive effects on both the central and the peripheral nervous systems. It also affects the cardiovascular system, the gastrointestinal system, and the skeletal motor system. Nicotine stimulates the cholinergic nervous system (sympathetic and parasympathetic).

Nicotine is a highly addictive substance that causes physical and psychological dependence that is similar to that of opiates and other substances of abuse (Office on Smoking and Health 1988, Henningfield 1984, Jarvik and Henningfield 1988). It is highly reinforcing, leading to compulsive use (Henningfield and Goldberg 1983). From a neurobiological perspective, there is strong evidence that the rewarding effects of smoking are mediated through the dopamine reward pathway, the mesolimbic dopamine (Balfour and Fagerstrom 1996). Nicotinic acetylcholine receptors, the site of action of nicotine, have been found on mesolimbic dopamine neurons (Clark and Pert 1985). Effects are related to dose, and tolerance to its actions develops rapidly, resulting in increased intake. Smokers adjust smoking behavior to regulate and maintain the level of nicotine in the blood stream. A withdrawal syndrome develops in response to reduced intake or total abstinence and involves both physiological and psychological symptoms (Benowitz

1988). Withdrawal symptoms overlap with those of alcohol and other substances of abuse (Hughes et al. 1994). The literature on the biology of the nicotine withdrawal state points to reduced dopaminergic, adrenergic, and norepinephrine function (Fung et al. 1996, Ward et al. 1991). In addition to the physiologically addictive aspects of nicotine, smoking is highly conditioned to cues in the environment.

Psychological Factors: Psychological dependence involves the perceived benefits/reasons a person smokes, such as a perception that they are able to improve mood and sense of well-being, to satisfy craving, and to provide stimulation and relaxation (Goldstein et al. 1991). Through this variety of central and peripheral actions, nicotine improves mood and decreases anxiety; decreases distress in response to stressful stimuli and decreases aggression; improves overall cognitive function and performance (improves reaction time, concentration, vigilance, and stimulus-processing capacity, increases attention, memory and learning, improves the ability to disregard irrelevant stimuli); and decreases the appetite for simple carbohydrates, decreases stress-induced eating, and increases resting metabolic rate. Many individuals soon become tolerant to these effects so that they smoke not to achieve them, but rather to avoid withdrawal symptoms. The direct beneficial effects of nicotine on mood and concentration become highly positive reinforcements, as do associated social context and behaviors linked with smoking, which then can act as powerful triggers for relapse during attempts at cessation. Individuals' expectations related to smoking are influential factors that counter the obvious health risks. For women these beliefs are also in the context of sociocultural attitudes that reinforce the belief that smoking helps to manage and control mood (anger, stress, depression), control weight gain, and increase an adolescent's sense of being independent and trendy.

### Social/Environmental Factors

The social component involves environmental and social cues that become associated with the behavior of smoking cigarettes, such as the association with drinking coffee or alcohol, talking on the telephone, taking a work break, or smoking at parties or social functions. In addition to genetic factors, smoking by family members normalizes this behavior, integrates tobacco use in daily activities, and also is a trigger for other's use. For adolescents and college age young adults, peer smoking and peer-group identification are also strong influencers of engaging in tobacco use, however, there are differences between ethnic groups. Family messages can moderate the effects of peer influence for some youth, and smoking can be perceived as "shaming" the family. Tobacco industry marketing and advertising strategies also try to promote psychological and social benefits of smoking in spite of the clear health risks. One strategy has been to engage celebrities and other public figures in being pro-smoking. The goal is to make smoking normal and to have youth see smoking everywhere (books, magazines, music, television, concerts, movies, sporting events, etc.).

## Treatment

Algorithms and primers for nicotine-dependence treatment have been developed, including from the American Psychiatric Association (1996) and Work Group on Substance Use Disorders, et al. (2006) and the US Public Health Service (Fiore et al. 2000). For smokers not yet ready to quit, use of interventions to increase motivation and presentation of information about treatment options are appropriate. Discussing reasons for the person to consider quitting—for example, health consequences specific to the individual—and the factors that may have prevented an attempt is important. Written materials and brief advice from the physician are methods of providing such information and increasing motivation. Preparation for quitting may include self-monitoring or keeping a diary of smoking, planning rewards for successful abstinence, and making a list of reasons for and potential benefits of quitting. Sources of social support should also be identified.

Formal treatment options have expanded rapidly in the past 30 years to include seven FDA-approved medications, a range of effective psychosocial interventions including internet and phone-line services. Unfortunately, few individuals receive combined medications and therapy treatment only 5% of smokers who make a 24-hr quit attempt receive counseling as part of their treatment (Zhu et al. 2000).

Nicotine dependence, like other SUD, can be thought of as a chronic relapsing illness with a course of intermittent episodes alternating with periods of remission for most smokers. Hughes et al. (2004) examined the relapse curves of untreated smokers to determine when smokers relapsed after trying to quit without treatment. Most smokers relapsed within the first 8 days with abstinence rates ranging from 24 to 51% at one week, 10% to 20% at one month, and 3−5% at six months. With treatment, however, the overall abstinence rate is 20−25% by one year. However, these reported lower outcome rates do not consider the additive effects over time related to multiple quit attempts, since about 40−50% of smokers in the US have been able to quit smoking in their lifetime. Less than 25% of the individuals who have quit smoking are successful on their first attempt. Repeated failures are common before successful abstinence, with the average smoker attempting to quit five or six times before success. Recent prior attempts at quitting do increase the odds that individuals will be able to quit smoking on a future attempt. Relapse can occur even after a long time of abstinence, with about 33% of former smokers who are abstinent for 1 year eventually relapsing 5−10 years after cessation.

### Treatment Goals

Nicotine dependence treatment targets severity of the problem, co-occurring disorders, and the different motivational levels to change. Treatment is provided in a range of levels of intensity of care (self-help, brief treatment, and once or twice per week outpatient treatment) and may include different modalities (self-help guides, internet resources, medications, and individual or group therapy). Treatment begins with an evaluation of the key biological, psychological, and social factors that are most significant for the individual in the initiation and maintenance of tobacco dependence. Several factors have been found to predict worse outcomes at smoking cessation (Kabat and Wynder 1987) (Table 62–2). Predictors include individual factors, manifestations of the addiction such as severity of withdrawal, and social and environmental circumstances. Treatment planning considers including biological and psychosocial treatment interventions.

**Table 62–2 Factors Predicting Worse Outcomes in Nicotine Dependence Treatment**

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| Physical reactivity (pulse, blood pressure, etc.) to smoking-related cues |
| Family and friends who are current smokers |
| Lack of social support from spouses, partners, family members, friends |
| Deficits in social skills and assertiveness |
| Higher severity of withdrawal symptoms |
| Limited ability to cope with effects occurring in response to cues or triggers |
| Depressed mood |

## Overall Approach to Treatment and Phases of Treatment

The general approach to the treatment of nicotine dependence considers three phases of treatment (engagement, quitting, and relapse prevention) (Table 62–3). Each phase of treatment includes consideration of three primary biological, psychological, and social factors effecting nicotine dependence outcomes. The importance of each of the biopsychosocial factors in initiating and maintaining smoking can vary considerably in different individuals. As a result, smoking cessation interventions should be tailored to the individual and his or her particular circumstances. This may be one reason why "one size fits all" generic treatment interventions have had such a low success rate. It must also be kept in mind that nicotine dependence is as complex in its components and determinants as other addictions and that more comprehensive multi-component treatment may be required.

When a smoker is ready for a cessation attempt, a "quit date" should be selected. After cessation, close monitoring should occur during the early period of abstinence. Before the quit date, the person should be encouraged to explore and organize social support for the self-attempt. Plans to minimize cues associated with smoking (e.g., avoiding circumstances likely to contribute to relapse) are important, as is considering alternative coping behaviors for situations with a higher potential for relapse. A telephone or face-to-face follow-up during the first few days after cessation is critical because this is the time that withdrawal symptoms are most severe, with 65% of patients relapsing by 1 week. A follow-up face-to-face meeting within 1−2 weeks allows a discussion of problems that have occurred (e.g., difficulties managing craving) and serves as an opportunity to provide reinforcement for ongoing abstinence. Even after the early period of abstinence, periodic telephone or face-to-face contacts can provide continued encouragement to maintain abstinence, allow problems with maintaining abstinence to be addressed, and provide feedback regarding the health benefits of abstinence. If a detoxification/quit attempt with pharmacotherapy alone fails, psychosocial treatments and the use of higher NRT dosages/multiple medications are possible clinical next steps. If pharmacotherapy is unacceptable or contraindicated, behavioral therapy (BT) alone should be provided. Failure with pharmacotherapy or BT alone suggests the need for more detailed in-depth assessment and more intensive and multimodal interventions.

**Table 62–3 Three Phases of Nicotine Dependence Treatment**

Engagement Phase

- Do a comprehensive evaluation of nicotine use and dependence
- Provide MET personalized feedback from the assessment
- Assess motivational level to quit and attempt to set a target quit date
- Explore previous quit attempts—what worked? What did not work? What triggered the return to tobacco use?
- Assess patient preference for treatment (medications, psychosocial treatments, group vs. individual, self-help, etc.) and provide education on treatment
- Create a treatment plan
- Strengthen and renew patient's motivation to quit smoking (MET orientation)
- Identify cues and triggers for usage
- Self-monitoring of smoking behavior (write down when use)
- Help patients gain understanding of their own tobacco use patterns
- Help increase knowledge about triggers and cues
- Help patients understand environmental influences on their smoking
- Begin education about tobacco, nicotine dependence, withdrawal symptoms, etc.
- Begin disconnecting smoking behavior and linked behaviors (no smoking while driving car, talking on phone, during meal time, etc.)
- Help them get medication evaluation and medications for the quitting phase

Quitting Phase

- Start medications on quit date (NRT) or before quit date (bupropion), sometimes begin NRT (gum, spray, inhaler, not patch) in small amounts and reduce tobacco usage in an equivalent or greater amount
- Teach specific coping techniques for handling withdrawal symptoms, cues/triggers, and how to enhance social support
- Help patient prepare emotionally, behaviorally, and physically for the quit date and the early abstinence period
- Help identify support systems, anticipate challenges, and address ways to handle people, places, things, and mood challenges
- Address nutrition and exercise components
- Address role of family/friends in supporting or sabotaging treatment
- Continue to strengthen client's resolve to quit
- Continue relapse prevention therapy approaches
- Assess triggers to craving and use and high-risk situations
- Coping with cravings, thoughts, and urges
- Problem solving
- Smoke refusal skills
- Planning for emergencies
- Seemingly irrelevant decisions
- Relapse analysis for slips

Relapse Prevention Phase

- Continue relapse prevention strategies for long-term abstinence
- Reinforce specific coping skills, including mood management and patient specific triggers
- Teach positive coping skills for dealing with frustration and anxiety
- Compliment success and provide encouragement
- Continue focus on maintaining motivation and commitment for abstinence
- Monitor progress
- Provide treatment within your discipline and make referrals when appropriate
- Encourage the use of peer support such as Nicotine Anonymous help the client gain personal insight and keep growing in their recovery
- Manage any relapses/slips to continue the course
- Continue medications as needed

## Treatment Benefits

Treatment of nicotine dependence with resultant abstinence can result in highly beneficial health effects (US Department of Health and Human Services 1990). In addition to nicotine being in tobacco, unprocessed tobacco smoke includes more than 2,500 compounds, and when manufactured additives and other compounds are taken into account, about 4,000 compounds are present (U.S. Department of Health and Human Services 1988). Research has demonstrated that the vast majority of harm associated with cigarettes is attributable to the byproducts of smoking rather than to the effects of nicotine (Slade 1999). Educating individuals and families about these benefits of abstinence from smoking can be helpful. Short-term effects (within 1 month) include a significant reduction in respiratory symptoms and respiratory infections such as influenza, pneumonia, and bronchitis. Excess risk of death from coronary heart disease is reduced after 1 year and continues to decline over time. In patients with coronary heart disease, smoking cessation decreases the risk of recurrent myocardial infarction and cardiovascular death by 50%. By 10−15 years of abstinence the mortality rate from all causes returns to that of a person who has never smoked. Pulmonary function can also return to normal if chronic obstructive changes have not already occurred at the time of cessation, and even with obstructive changes pulmonary function can improve with abstinence.

### Psychiatric Medication Management Issues with Abstinence

Tobacco (not nicotine) is metabolized by the P450/1a2 isoenzyme and enhances the metabolism of psychiatric medications that are also similarly metabolized by this isoenzyme (Lee and D'Alonzo 1993, Goldstein et al. 1991, Work Group on Substance Use Disorders, et al. 2006). Quitting smoking will eliminate tobacco's effects on the P450/1a2 isoenzyme, which will typically cause an increase in the blood levels of those medications also metabolized by that isoenzyme (including several psychiatric medications metabolized through 1A2), potentially resulting in increased side effects or other adverse events, including increased noncompliance due to the side effects (Lee and D'Alonzo 1993).

## Somatic Treatments

### Pharmacological Intervention

Pharmacological interventions have become an important component of treating nicotine dependence. Approaches used parallel other addictions in treating acute withdrawal (detoxification), protracted withdrawal, and even maintenance for harm reduction. The primary medications are NRT, bupropion, and varenicline. All seven of these modalities are FDA approved and have demonstrated efficacy (Table 62–4).

*Nicotine replacement therapy* (NRT) is the most widely used medication option and is available over-the-counter (patch, gum, and lozenge) or by prescription (patch, gum, spray, and inhaler). The principle behind nicotine replacement is that nicotine is the dependence producing constituent of cigarette smoking, and that smoking cessation and abstinence can be achieved by replacing nicotine without the harmful impurities in cigarette smoke. The abuse liability of nicotine replacement appears to be minimal. The intent is to substitute a safer, medically prescribed substance for nicotine and then to taper the substance in a manner that prevents or minimizes withdrawal. This agonist approach is similar to the use of benzodiazepines to treat acute alcohol withdrawal or methadone substitution and taper in the treatment of heroin addiction. The substituted nicotine initially prevents significant withdrawal symptoms that may lead to relapse during the early period of smoking cessation. The substituted nicotine is then gradually tapered and discontinued. Replacement produces a lower overall plasma level of nicotine than that experienced with smoking. Replacement not only avoids the strongly reinforcing peaks in plasma level but also prevents the emergence of withdrawal symptoms by maintaining the nicotine plasma level above a threshold. Typically, each cigarette contains about 13 mg of nicotine and about 2 mg is absorbed into the body.

**Table 62–4 Approaches to the Pharmacological Treatment of Nicotine Dependence**

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| Nicotine replacement or substitution (agonist administration) |
| FDA-approved nicotine patch, gum, spray, lozenge, and inhaler |
| Non-nicotine pill—bupropion/Zyban—FDA approved |
| Combinations of nicotine replacement types and/or bupropion |
| Non-FDA-approved experimental options: |
| Blockade therapy (antagonist administration) |
| Nonspecific attenuation therapy |
| Deterrent therapy |

*Nicotine gum*, approved in 1984, was the first NRT approved and it slowly releases nicotine from an ion exchange resin when chewed. The nicotine released is absorbed through the buccal mucous membranes. The NRT gum is available in doses of 2 and 4 mg, and the recommended dosing is in the range of 9−16 pieces/day. Peak blood nicotine levels achieved are low (approximately 10–15 ng/mL) compared with those in dependent smokers (15–100 ng/mL). Placebo-controlled studies of nicotine gum treatment in smoking cessation clinics show a doubling of abstinence rates (Lam et al. 1987) with the 4-mg dose possibly providing a better outcome than the 2-mg dose for persons who are highly nicotine dependent (Tonnesen et al. 1988). Nicotine gum is more effective when used in conjunction with some type of psychosocial intervention, particularly BT (Lam et al. 1987). Outcome is more positive when a definite schedule for gum use is prescribed—for example, one piece of gum per hour while awake—than when used on an as-needed basis (Fagerstrom and Melen 1985, Goldstein et al. 1989). Some studies suggest that it is also more effective when used for longer than 3 months (Fagerstrom and Melen 1985). Tapering may be necessary after 4−6 months of use, especially for individuals using higher total daily doses of gum. Nicotine gum is often not effectively utilized in patients with temporomandibular joint problems, dental problems, and dentures. Nicotine gum requires a highly motivated patient and a good deal of time in instructing the patient in proper use of the gum. Many individuals find the gum difficult to learn to use properly. Patients must be instructed that nicotine gum is not like bubble gum and that the gum is crunched a few times and "parked" between the gum and cheek. It should not be used soon after drinking acidic substances such as coffee,

soda, or orange juice because the acidic environment in the mouth interferes with its release and absorption. Specifics of the proper use of nicotine gum are provided by Schneider 1988. Side effects and adverse effects include local irritation in the mouth, tongue, and throat, mouth ulcers, hiccups, jaw ache, gastrointestinal symptoms (flatulence, indigestion, nausea), anorexia, and palpitations. About 6–9% continue to use nicotine gum for 1 year—this may reflect some risk for dependence. However, most individuals report that they still prefer the tobacco product and are using the nicotine gum only to avoid the tobacco usage (Hajek et al. 1988). The *nicotine lozenge* was FDA approved in 2002 and is similar in dosing to the nicotine gum and less complicated to use.

The *nicotine patch* transdermal delivery system provides continual sustained release of nicotine, which is absorbed through the skin. This form of nicotine replacement more than doubles the 1-year cessation rate (Hughes 1994b). There is a dose–response relationship, with patients receiving higher doses attaining higher cessation rates. The nicotine patch eliminates the conditioning of repeated nicotine use, which remains present with the use of other NRT products. Compliance rates are higher because it involves once-daily dosing and its administration is simple and discreet. The typical starting dose of NRT patch is 21 or 15 mg patch, however, in some cases multiple patches are used. Lower dose patches available at 7 and 14 mg are used to taper after smoking cessation. The patch delivers approximately 0.9 mg of nicotine/hr. Steady-state nicotine levels are 13–25 ng/mL and the highest levels are seen soon after patch application. The nicotine patch is often used for a total of 6–12 weeks but can be used for much longer (American Psychiatric Association 1996). The transdermal patch does not allow for self-titrated dosing, craving, and nicotine withdrawal symptoms like the other NRT routes (gum, spray, inhaler, lozenge), however, the nicotine blood levels are significantly less than with smoking. The patch can be used more discreetly and can be used despite dental or temporomandibular joint problems. Specifics on the proper use of transdermal nicotine are provided by Gourley (1994). Although the nicotine patch is well tolerated, about 25% of patients have significant local skin irritation or erythema and 10% discontinue the patch because of intolerable side effects. Other side effects include sleep problems with the 24-hr patches. In a few cases, nicotine toxicity developed when smokers continued their usual heavy cigarette smoking while using the transdermal nicotine patch. However, transdermal nicotine may cause less activation of blood coagulation and have less impact on the sympathetic nervous system than nicotine polacrilex gum; therefore, it may be preferable in the presence of cardiac disease (Rennard et al. 1991, Benowitz et al. 1993). One study found that it could be safely used in patients with stable coronary artery disease (Anonymous 1994, Gross et al. 1989, Hughes 1995).

Some experts suggest using nicotine gum concurrently with transdermal nicotine on an as-needed basis to cover emergent withdrawal symptoms or craving not controlled by replacement from the transdermal patch, whereas others suggest simply increasing the dose of the transdermal patch or using gum initially and then switching to the patch (Gourley 1994, Fagerstrom et al. 1993). The *nicotine nasal spray* is rapidly absorbed and produces a higher nicotine blood level than does transdermal nicotine or gum. A single dose of the spray delivers 0.5 mg to each nostril and it can be used one to three times/hr. It has been suggested that the effective daily dose in nicotine dependent smokers is 15–20 sprays (8–10 mg)/day (Balfour and Fagerstrom 1996). Onset of action of the spray is the most rapid of all nicotine replacements; nicotine levels in plasma reach 10–20 ng/mL (Balfour and Fagerstrom 1996). An initial concern about the nasal spray had been the potential for abuse because it has the most rapid absorption rate of the NRTs. It replicates repeated administration of nicotine in smoking, resulting in reinforcing peaks in the plasma level of the drug. Side effects of the spray include local airway irritation (i.e., coughing, rhinorrhea, lacrimation, nasal irritation), but tolerance to these local effects appears to develop. Systemic effects include nausea, headache, dizziness, tachycardia, and sweating (Balfour and Fagerstrom 1996, Sutherland et al. 1992).

The *nicotine inhaler* provides nicotine through a cartridge that must be "puffed." It mimics the upper airway stimulation experienced with smoking, however, absorption is primarily through the oropharyngeal mucosa. Although the blood level of nicotine is lower than with other forms of nicotine replacement (8–10 ng/mL), the inhaler has been shown to be effective (Tonneson et al. 1993). Controlled trials (Schneider 1996) indicate 1-year abstinence rates of 17% for the nicotine inhaler and 8% for placebo. Side effects of the inhaler and spray include local irritation, cough, headache, nausea, dyspepsia, the need for multiple dosing, and the impossibility of discreet use.

*Bupropion*, the non-nicotine pill FDA-approved medication option, is a heterocyclic, atypical antidepressant that blocks the reuptake of both dopamine and norepinephrine. Its efficacy as an aid to smoking cessation was first demonstrated in three double-blind placebo-controlled trials in nondepressed chronic cigarette smokers (Hurt 1997) (28% versus 4% abstinence at 12 weeks) (Ferry et al. 1992). It was well tolerated and did not produce weight gain. The effects in smoking cessation appear to be unrelated to its antidepressant properties (Hurt 1997). Smoking cessation rates appear to improve further when bupropion is combined with the nicotine patch (Nides 1997). In all studies, adverse events had a low incidence and included dry mouth, insomnia, nausea, and skin rash. There have been no reports of seizures in any smoking cessation studies to date, however, this agent should not be used in patients with a history of seizure disorders.

*Varenicline (Chantix:* In May 2006 the Food and Drug Administrartion approved Chantix (varenicline tartrate) for smoking cessation. Varenicline is an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist. The $\alpha 4\beta 2$ receptor is thought to mediate the rewarding properties of nicotine through the release of dopamine in the mesolimbic system, and in particular nucleus accumbens. The agonist effect on dopamine release is 35–60% that of nicotine, considered sufficient to reduce craving and withdrawal. Verenicline has also a competitive antagonist effects on nicotine due to the higher affinity for the $\alpha 4\beta 2$ receptor, which is thought to blunt the reinforcing effects of smoking (Keating and Siddiqui 2006). Varenicline's maximum plasma concentration is reached after 3–4 hr and following repeated oral doses the steady-state occurs within 4 days. The medication has a 20% plasma protein binding and a half-life of 24 hr. It is eliminated 92% unchanged in the urine. No meaningful clinical pharmacokinetic drug-drug interactions have been

identified. There were no pharmacokinetic differences due to age, race, gender, smoking status or use of other medications (Keating and Siddiqui 2006).The efficacy of Varenicline in smoking cessation was demonstrated in six clinical studies Gonzales et al. 2006, including several studies finding better outcomes with Varenicline compared to Bupropion (Jorenby et al. 2006, Nides et al. 2006). Varenicline should be started 1 week before the set date for patients to stop smoking. The approved course of treatment is 12 weeks. The recommended dose of 1 mg twice dailyshould be arrived at after a 1-week titration. For the first 3 days the patients should take 0.5 mg, followed by 0.5 mg twice a day for the next 4 days and then 1 mg twice a day for the rest of the therapeutic period. The adverse reactions leading to discontinuation include nausea, headache, insomnia and abnormal dreams. The most common adverse events occurring in more than 5% or twice the rate seen with placebo were nausea, sleep disturbance, constipation, flatulence and vomiting (Keating and Siddiqui 2006).

## Non-FDA Approved Medications

Several medications have been studied with some noted efficacy although not FDA approved. Clonidine has been evaluated in both oral (0.1 mg) and transdermal forms (0.1–1.3 mg) (Hughes 1994a). Clonidine, an antihypertensive drug with central neuroepinephrine/sympatholytic activity, is a presynaptic alpha-2-receptor agonist that has been used extensively in the management of opiate and alcohol withdrawal. It appears to be more effective in women than in men and may be less effective in patients with a history of MDD (Glassman et al. 1985 1988, Covey and Glassman 1991). Potential side effects and adverse effects include sedation, dry mouth, and hypotension. Buspirone, a nonsedative, nonaddictive, nonbenzodiazepine antianxiety agent, has been shown in some pilot studies to decrease craving, anxiety, and fatigue during withdrawal from nicotine, however, effects on cessation rate have been mixed and limited (Hughes 1994a). A few studies suggest that some of the traditional tricyclic antidepressants may help reduce nicotine withdrawal, craving, and relapse, including doxepin (Edwards et al. 1989), imipramine (Jacobs et al. 1971), and nortriptyline (Humfleet et al. 1996, Hall et al. 1998). However, the side effects of these tricyclic antidepressants can include increased appetite, weight gain, dry mouth, blurred vision, constipation, urinary hesitancy, and sedation.

Other medication strategies that have been evaluated include tiagabine, Rimonabant, Selegiline, and immunological approaches. The activation of nicotinic receptors is moderating the release of acetylcholine, dopamine, serotonin, noradrenaline, GABA and glutamate (Watkins et al. 2000). GABA inhibits and glutamate stimulates dopamine release (Mansvelder et al. 2002). Preclinical research suggests that medications enhancing GABA decreases the rewarding effects of stimulants like nicotine. Sofuoglu et al. (2004) showed that 8 mg of Tiagabine diminished the craving for cigarettes and increased the cognitive performance in the Classical Stroop test compared to placebo. Rimonabant is a selective cannabinoid CB1 receptor developed for the treatment of obesity, tobacco smoking and cardiometabolic risk factors. Three Studies with Rimonabant and Tobacco Use (the STRATUS trials) were done recruiting 6,500 patients in the USA and Europe looking at rimonabant in doses of 5 mg and 20 mg daily against placebo on smoking cessation at 10 and 50 weeks. In the STRATUS-US the quit rate was 26.7% in the 20 mg group as compared to 16.1% for placebo. STRATUS-Europe did not show significant differences. STRATUS-Worldwide demonstrated lower relapse rate after 1 year in the 20 mg group (41.5% vs. 32.5%) (Wierzbicki 2006, Siu and Tyndale 2007). Monoamine oxidase-B (MAO-B) is involved in the degradation of dopamine, tyramine and phenylethylamine. There is evidence from PET studies that MAO-B is reduced in the brain of smokers. After smoking cessation the enzyme activity returns to normal leading to a drop in the level of dopamine and resulting craving. Selegiline, a MAO-B inhibitor increasing the availability of dopamine, was shown to reduce craving and to mitigate the need for NRT (Biberman et al. 2003). It also improved the 52-week abstinence rate even though the result did not achieve statistical significance. The immunologic approach to treating nicotine dependence involves passive or active immunization against nicotine. The antibodies decrease the amount of unbound nicotine in the serum which is the fraction able to enter the brain and reach the receptors. As a consequence the rewarding and reinforcing effects of smoking are diminished. Also the bound fraction of nicotine is protected against rapid metabolism and excretion. The net results are prolonged nicotine effects and a reduced rate of nicotine intake in order to obtain the desired effects (LeSage et al. 2006). One of the several companies involved in the development of vaccines, Cytos Biotechnology, posted last year on the website http://www.cytos.com (accessed on January 10, 2007) the results of Phase II study regarding the efficacy of their product, CYT002-NicQb. The data showed that CYT002-NicQb promoted and sustained continuous abstinence from smoking from the week 8 to 52 after start of treatment in participants who achieved high antibody levels upon vaccination versus those participants who received only counseling and a placebo ($p = 0.012$).

## Combination Treatments

Combined NRTs/bupropion or serial pharmacotherapeutic approaches may also be beneficial, especially in more difficult to treat cases of nicotine dependence. For example, combining the patch with other nicotine replacement medications like nicotine gum or the spray allows for both more rapid onset of action and reduction of withdrawal symptoms through steady levels of nicotine released by the patch. Combining nicotine replacement with nonnicotine replacement strategies (e.g., bupropion and nicotine patch) has been beneficial in further improving outcomes in some studies and is common in clinical practice. The combination approach offers the advantage of multiple neurobiological mechanisms of actions. In addition, many researchers increasingly believe that periods of pharmacotherapy should be extended, although the issue of whether longer-term pharmacotherapy is beneficial in improving cessation rates remains unresolved. There may be some smokers who are unable to stop smoking without ongoing nicotine replacement, similar to individuals dependent on heroin who must be maintained on methadone. Although long-term/maintenance use of NRT requires further study, successful maintenance in smokers who have chronic relapses would potentially reduce a number of the serious health risks associated with smoking, in spite of individuals still being exposed to the effects of nicotine. Ongoing maintenance

antidepressant treatment may also be necessary for a time for some individuals with a history of serious depressive illness or for those who have had significant depressive symptoms emerge on cessation that do not improve with time.

## Psychosocial Treatments

In contrast with the treatment of other SUD, psychosocial treatment is underutilized and has not evolved to be the cornerstone of treatment. This limited utilization of psychosocial treatments does not match the very positive outcomes from either psychosocial treatments alone (25% 1-year abstinence with BT) or when combined with NRT or bupropion (50% improvement compared to NRT or bupropion alone), however, it does match the lack of health care coverage for this service. The underutilization of psychosocial treatment has become the cultural norm in nicotine dependence treatment. This may be due to several important considerations. These include: (1) Primary care practitioners most frequently attempt to address nicotine dependence and do not traditionally integrate BTs. (2) Nicotine dependence treatment is often not paid for by health care insurance companies. (3) Few behavioral health specialists have been formally trained in nicotine dependence treatments. (4) Mental health and addiction treatment programs have ignored addressing tobacco in those treatment settings, although this appears to be changing, and (5) Patients are unaware of this treatment modality and its success rates, and believe that medications or quitting cold turkey is all that is needed.

A great variety of psychosocial interventions have been developed to help in the treatment of nicotine dependence (Table 62–5). In general, the core psychotherapies in substance abuse treatment are motivational enhancement therapy (MET), cognitive–behavioral therapy (CBT), and 12-Step Facilitation. Psychosocial interventions, particularly Behavioral Therapy, have been shown to increase abstinence rates significantly (Ferry et al. 1992). However, only 7% of smokers attempting to quit smoking are willing to participate in BT (Ferry et al. 1992). In addition, it is more expensive than pharmacotherapy and more labor-intensive.

**Table 62–5 Psychosocial Interventions for the Treatment of Nicotine Dependence**

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| Self-help materials |
| Brief advice from the physician |
| Multiple component therapies |
| Motivational enhancement therapy |
| Cognitive–behavioral therapies/relapse prevention |
| Nicotine fading |
| Nicotine anonymous |
| Others used, but with limited empirical support: hypnosis and acupuncture |

## Brief or Minimal Medical Professional-Delivered Interventions/Advice

Even a brief face-to-face intervention by a physician or other medical staff can increase the likelihood of cessation 2−10-fold (Klesges et al. 1990). The impact of physician's brief advice to quit has received the most study relative to other disciplines such as nursing, however, clearly all disciplines have opportunity to make an impact. Physicians can inquire about a patient's smoking status, urge the patient to stop smoking, and spend a brief time counseling the patient about cessation strategies. Multiple follow-up interventions, even telephone contacts by other medical staff, can further improve the cessation rate. Resources are available to assist physicians in providing effective antismoking interventions, which can even be used by those not highly skilled in counseling. Physicians' advice appears to be most successful with patients with a serious medical problem or specific medical reason for quitting (e.g., pregnancy or congestive heart disease). In addition, because an estimated 70% of smokers in the US visit their physicians at least once a year, an important opportunity exists for providing this type of smoking cessation intervention.

MET is especially helpful for the smoker who continues to be ambivalent about quitting. MET strategies aim to enhance the smoker's commitment and motivation to quit smoking. The therapist maintains a patient-centered approach and is empathic and optimistic. The therapist adopts a focused but non-confrontational style while examining the effect of tobacco use on the smoker's life and collaborating with the smoker to develop and implement a treatment plan. MET is compatible with Prochaska and DiClemente's stages of change model, in which patients are assessed as being in the precontemplation, contemplation, preparation, action, or maintenance stage of change. This model also emphasizes the importance of tailoring interventions to the patient's motivational level (Prochaska et al. 1992). Interventions aimed at immediate cessation of tobacco are often ineffective for patients in the contemplation or pre-contemplation stage especially since there is usually not a powerful external motivator to maintain compliance. Without an external motivator, a confrontational approach is likely to provoke resistance and treatment dropout. Realistic goals for the poorly motivated patient are to simply increase awareness of the impact of tobacco and the possibility of change. Later interventions may involve creating a change plan and discussing feelings of ambivalence, including the patients' perceived benefits of using tobacco and reasons to stop using tobacco (Miller et al. 1995). An important initial component of MET is to provide personalized feedback on how tobacco may be affecting their lives and others. Feedback that has impact might include the cost of tobacco products during a year, negative health consequences, likelihood for health improvement in case of abstinence, social stigma toward smoking, CO levels, interaction of tobacco metabolism and specific medications, and other health consequences (wrinkles, impotence, etc.).

*Behavioral and CBT approaches* have been developed to be effective treatments for nicotine dependence, and as for any other addiction CBTs are one of the core therapy approaches. BTs often include a self-monitoring assessment phase that is linked with specific treatment interventions. The self-monitoring involves the identification of affective, cognitive, and environmental cues that trigger smoking behavior. Understanding the cues and triggers for usage are helpful in guiding the CBT approach of *relapse prevention*. Relapse prevention training helps clients develop problem-solving skills for coping with situations or emotions that might be likely to precipitate relapse, as well as alternative behaviors appropriate for high-risk situations. Individuals learn to manage an abstinence violation ("slip" or "lapse") in a way that prevents a relapse to smoking. Discussing ways

of managing withdrawal symptoms, such as sleep disturbance and irritability, can also be useful and, if performed in a group setting, can allow individuals to learn from others struggling with cessation. Stress management and relaxation training are often also used as adjunctive interventions, individually or in a group setting. Problems with the group format include a generally low compliance rate, lack of availability of groups in all geographical areas or at a given point in time, and patients' reluctance to participate. Problems with the individual format include higher cost and the need for a larger number of counselors per population (Hajek et al. 1985).

In relapse prevention coping skills training, patients are taught skills to manage situations without resorting to smoking. Cognitive approaches involve specific techniques such as reframing or restricting thoughts related to smoking or replacing thoughts about smoking with thoughts intended to enhance motivation or self-efficacy. Assertiveness training can contribute to improved coping by helping patients to ask for assistance from significant others and to request that others refrain from smoking in their presence. One controlled trial found that a cognitive intervention focused on enhancing the regulation of affect produced a better outcome in smokers with a history of MDD, suggesting some potential benefit of providing more expensive, time-intensive interventions to specific populations of patients (Hall et al. 1992). *Stimulus control strategies* involve removing or altering cues that have been strongly associated with smoking, for example, avoiding certain situations that are likely to increase craving or trigger smoking. Cue extinction involves repeated exposure of the individual to cues or triggers associated with smoking. Through repeated episodes of exposure that are not followed by smoking, these cues and triggers gradually lose their power to provoke craving. *Nicotine fading* contrasts with an abrupt discontinuation of tobacco. In some cases, this includes switching to a different brand of cigarettes with lower nicotine, and it usually also focuses on gradually reducing the number of cigarettes smoked on a schedule over time, usually several weeks. Nicotine fading sometimes helps to make the transition from several packs of cigarettes per day to the reduced amount of nicotine during NRT and other treatments. Nicotine fading may help any smoker try to quit, however, the research results are mixed and more research must be done in this area. Another nicotine fading strategy focuses on disconnecting specific triggers and tobacco usage, for example, helping patients not to smoke while in the car, on the phone, or during mealtime. Sometimes this reduces the overall nicotine consumption in the day, and it has the effect of increasing the individual's self-efficacy that they can begin to shape their behaviors and develop coping strategies to handle specific situations (American Psychiatric Association 1996). *Aversive techniques* include the use of rapid smoking and smoke holding. Rapid smoking involves inhaling cigarette smoke every 6 seconds until the smoker becomes ill. Several repetitions over several sessions are usually planned. Smoke holding involves holding smoke in the mouth and continuing to breathe. Both techniques have been found effective and safe even in patients with medical complications from smoking. A limiting factor in the use of these techniques is acceptability by the patient. In *contingency contracting* the patient participates in developing rewards for not smoking or punishment for smoking. As an example, a patient might give money to a friend or person overseeing the treatment. The money would be returned only if the patient successfully stopped smoking for a prescribed period.

Despite the fact that there has been little controlled research examining whether psychosocial intervention with spouses and significant others or families can increase abstinence rates, overall social support for individuals who are attempting to stop smoking appears to improve the outcome. Others in the smoker's immediate family or social circle can be involved in their treatment through education about appropriate supportive behaviors. Concerned others can also be engaged in treatment to provide assessment information or to help enhance patient motivation.

Hypnosis, acupuncture, and laser therapy are three approaches that some individuals believe have helped them in their efforts to quit smoking, however, the empirical evidence does not support their use as reported by the most recent Hajek et al. (2005). Hypnosis claims to reduce (or even ameliorate) the desire to smoke and/or to fortify resolve to quit. The results of nine randomized trials of hypnotherapy compared to 14 different control interventions did not show a greater effect for hypnosis as compared to control interventions or to no treatment (Abbot et al. 1998). Acupuncture is a traditional Chinese therapy aiming to reduce withdrawal symptoms associated with quitting smoking by inserting needles in specific areas of the body. Laser therapy purports to work the same mechanisms of action as acupuncture—only using low-level lasers rather than needles. A very recent Cochrane review (White et al. 2006) concluded that these therapies are unlikely to help smokers to quit although the authors note that it is difficult to make firm conclusions because of poor methodology used in the studies of these approaches.

## Self-Help

Many smokers have successfully quit smoking without participating in formal treatment (Fiore et al. 1990). Although only about 3−4% are successful during the past year, this success rate improves with multiple attempts and probable self-learning through trial and error and learning from others. Eventually about 50% of smokers are able to quit and more than 90% of successful quitters have been able to do so without the assistance of professionals or formal programs. These numbers reflect multiple factors including the limitations on access to treatment (nonexistent health insurance coverage and limited number of providers with expertise to help), the cumulative process of multiple attempts and learning from others and from self-help materials, and the severity of the nicotine dependence. The advantage of quitting without professional intervention is the decreased expense and time commitment, however, professional treatment may be necessary for higher severity cases that are often complicated by other behavioral health problems. The primary unassisted method of detoxification from nicotine dependence is precipitous cessation (cold turkey), which is used by more than 80% of smokers. This is followed by spontaneous strategies to handle cravings and triggers. Some smokers attempt to limit intake, taper the number of cigarettes smoked, or switch to a reduced tar or nicotine brand. Special filters and holders are also available to decrease the amount of smoke that is available from a cigarette. These methods are usually less successful because smokers have been shown to alter

smoking behavior by increasing the frequency, volume, or duration of the inhalation to ensure maintenance of blood levels of nicotine adequate to prevent withdrawal symptoms (Moss and Prue 1982, Russell 1987). Some smokers use nonprescription pills that are analogues of nicotine, such as lobeline, to help manage or prevent withdrawal symptoms. These agents have not been shown to be effective in controlled studies (Hughes 1994a).

### Nicotine Anonymous

Some geographical areas have Nicotine Anonymous groups that are structured similarly to Alcoholics Anonymous or Narcotics Anonymous groups. These groups are based on the 12-Step approach to recovery from addictions. Nicotine Anonymous is a relatively new organization (founded in 1985) and does not have the extensive network that other 12-Step programs like Alcoholics Anonymous or Narcotics Anonymous have developed. No formal controlled studies of the benefits of this intervention have been carried out. In addition, self-help written materials can play an important role in educating patients about the negative health effects of nicotine, the benefits of quitting, and the nature of the addiction. Self-help literature, internet resources, and Nicotine Anonymous can be effectively integrated into formal treatments of brief interventions, individual and group treatments. Even smokers with major health conditions, such as chronic obstructive pulmonary disease or cardiovascular disease, often have a difficult time attaining and maintaining abstinence. Numerous psychological and pharmacological treatments have been developed to assist with smoking cessation.

## Combined Psychosocial and Psychopharmacological Therapies

All nicotine dependence treatment practice guidelines recommend the integration of nicotine dependence treatment medications (NRT and bupropion or varenicline) with behavioral and supportive psychosocial treatment approaches. Empirical evidence supports the finding that medications double the quit rate compared to placebo, and face-to-face BT can double the quit rate compared to minimal psychosocial intervention. BT also can increase medication compliance. Integrated treatment further increases the quit rate by another 50% and triples the outcome rate compared to a control group (Fiore et al. 1990). Nicotine dependence treatment guidelines by the American Psychiatric Association (1996, 2006), Agency for Health Care Policy and Research (1996), and the US Public Health Service (Fiore et al. 2000) all support integrated treatment, and are excellent sources of clinical and research information. Recent reviews and meta-analyses by Hughes (1995), Fiore et al. (1990), Baille et al. (1994), and Ziedonis et al. (2001) also support integrated treatment.

Compared to treating other addictions, there is philosophical support among clinicians for integrated treatment for nicotine dependence. This support is probably due to the fact that there are effective medications for nicotine dependence and the absence of controversies that have plagued other fields of addiction, particularly with regard to abstinence versus controlled use and medical versus behavioral approaches. Unfortunately, few smokers use BT because of the added cost, lack of local expertise, waiting time for treatment, and preference against group therapy. Efforts are being made to make BT more acceptable to smokers and to triage smokers to more intensive therapies as needed.

Hughes (1995) performed a meta-analysis of existing studies of combined psychosocial and pharmacological treatments for smoking cessation and found that the addition of nicotine gum to psychosocial therapies resulted in a 60−80% increase in abstinence, whereas addition of transdermal nicotine produced a 40−80% increase in abstinence. Addition of psychosocial therapies to nicotine replacement (gum or transdermal) resulted in a 60−80% increase in abstinence with nicotine gum and an odds ratio of 3.1 for transdermal nicotine. Studies of combined nicotine gum and psychosocial treatment showed additive, possibly synergistic positive effects.

## Problems in Management

Repeated Relapse: Although generally effective treatments have been developed for nicotine dependence, research is limited on treatment matching and determining the timing and duration of interventions. Questions regarding treatment specificity become even more complicated when treating smokers who have experienced repeated relapses, those who have been unable to stop smoking, or those who are able to maintain abstinence for only brief periods (Table 62–6). Treatment algorithms applied to the general population of smokers may have little relevance to the smoker who suffers chronic relapses. At this time, the literature on any specific interventions designed to prevent relapse to smoking, is inconclusive (Hajek et al. 2005). The authors (Hajek et al. 2005) describe the current relapse prevention studies as insufficient for detecting small differences between interventions—whether due to low statistical power or less than ideal experimental designs. Given the lack of data regarding treatment specificity, the key to planning interventions with smokers who have had repeated relapses is a comprehensive reevaluation to determine the unique set of factors related to repeated relapse in a given individual. This analysis can serve as the basis for developing an individualized comprehensive treatment program. In approaching evaluation and treatment planning, it is important not to view the smoker as a "failure" but rather to understand how neglecting to adequately understand the illness of nicotile dependence as it presents in the particular patient has resulted in ineffective treatment with a poor outcome. It is also important to realize that even our "intensive" nicotine dependence treatments pale compared to the intensity of addiction treatment for other substances (residential treatment, intensive outpatient programs, partial hospitalizations, etc.). In some cases, the repeat relapsing smoker would appear to benefit from more intensive interventions, multiple-component interventions, or both. However, in some cases these smokers did not receive

**Table 62–6 Effectiveness of Nicotine Dependence Treatment Interventions**

| | |
|---|---|
| No professional or formal intervention | 5% |
| Physicians' advice | 10% |
| Nicotine polacrilex | 15–20% |
| Nicotine patch, gum, inhaler | 20–25% |
| Bupropion | 25% |
| Behavioral therapy | 25–30% |
| Medication and behavioral therapy | 40% |

an adequate single intervention and did not ever receive an adequate "dose" of treatment. In the latter case, treating with a previously used single therapy and ensuring the adequacy of all aspects of the treatment may be appropriate. For example, a patient may have relapsed despite being treated with NRT gum because an intermittent dosing schedule was prescribed or because of improper use of the gum, both of which resulted in an inadequate overall dose of nicotine replacement followed by withdrawal symptoms and relapse. Such a patient might be treated with NRT transdermal patch to improve compliance and ensure a stable plasma level of nicotine to prevent withdrawal symptoms. Alternatively, the dose of nicotine the patient was prescribed may have been too low and the withdrawal symptoms too substantial to refrain from relapsing. In some rarer cases, the dose may have been too high, leading to adverse effects, discontinuation of the transdermal patch, and subsequent relapse. Providing a lower dose that is tolerated may lead to successful cessation with a single previously used treatment. An inappropriate single treatment may also have been provided, as in the case of a male patient treated with one of the non-FDA-approved medications of clonidine for the management of nicotine withdrawal symptoms when research data show that clonidine is effective primarily in women. A single treatment may have been inappropriate in that it was focused on an area that is not critical, whereas an area critical to the maintenance of abstinence has been overlooked. A patient without a high degree of physiological dependence on nicotine may have been treated with nicotine replacement while the fact that her husband is a heavy smoker was not addressed. A future cessation attempt might be preceded by conjoint sessions with the spouse to motivate him also to stop smoking, to educate him about the psychological effects of smoking and the behavioral changes that may accompany cessation, and to enlist his aid in providing a more supportive environment for nicotine dependence treatment (e.g., not smoking at home or in the presence of the patient).

Even with multiple interventions, an important aspect of relapse may have been overlooked. For example, both nicotine replacement and group therapy may have been provided to a woman who then made a conscious decision to start smoking again to lose the weight gained during the cessation attempt. In this case, educating the woman about the effects of nicotine on metabolism, helping her develop a healthy diet and exercise plan, and providing her with a cognitive intervention to assist her in reframing and accepting the weight gain as a return to a normal weight that was abnormally lowered by nicotine might make a critical difference in the success of the cessation attempt. Planning to address weight loss at a future time after abstinence has been solidly established is an example of how serial treatment interventions might be used successfully. Alternative modalities might also be appropriate. For example, a group BT might have been prescribed for a person who was so anxious and uncomfortable in the presence of others that he or she avoided attending many of the sessions and was unable to participate even when present. Providing individual sessions in which key elements of the BT are presented and discussed might lead to more successful cessation. A history of depressive episodes or current depressive symptoms may have been overlooked. In such a case, or when significant depressive symptoms have emerged during the acute withdrawal period, pretreatment with antidepressant medication added to the prior treatment regimen may result in successful cessation.

The family and home environment should also be reassessed to determine if the smoker is receiving adequate support from the spouse, significant other, family, and general social circle. Conjoint marital or family sessions may be beneficial to educate family members about smoking cessation and the psychological, physiological, and behavioral changes that can occur with cessation. The family can also be counseled about what types of behaviors can undermine rather than support the nicotine dependence treatment effort. Family members can also assist and support the smoker in complying with treatment, for example, attending group meetings or encouraging the patient to call the physician, rather than discontinuing treatment, if adverse effects result from pharmacotherapy. The presence of one or more active smokers in the household may also need to be addressed, as this factor predicts relapse.

Some smokers may not be able to achieve successful abstinence with outpatient treatment despite intensive multiple interventions. Inpatient treatment represents a drastic intervention that should be reserved for the most treatment-resistant patients who have been completely unsuccessful despite repeated attempts and treatment with a variety of interventions. Inpatient treatment can provide the most intensive and aggressive program of treatment interventions coupled with close monitoring and prevention of access to nicotine. It requires a commitment of both time and money, however, as almost no insurance policies reimburse for such treatment. Inpatient nicotine dependence treatment is usually 1 week in duration. Follow-up data from the few programs in existence suggest that it may be effective for some highly treatment-resistant smokers (Hurt et al. 1992, Docherty 1991).

## Special Considerations in Treatment

### Co-occurring Mental Illness or Other Addictions

Individuals with nicotine dependence and either a co-occurring mental illness, another addiction, or all three are more likely to require some modifications in the traditional nicotine treatment approach. A critical issue in the treatment planning is the timing of the nicotine dependence treatment. There is literature supporting treating all together and also in delaying the nicotine dependence treatment until the other problems are stabilized. Successful nicotine dependence treatment in persons with active alcohol dependence is less likely than in individuals recovering from alcohol dependence, however, a few addiction treatment programs have addressed both problems simultaneously with success. Nicotine replacement appears to be especially beneficial in helping smokers with co-occurring mental illness and addiction. Appropriate treatment of the mental illness or other addiction is also important, including appropriate medications and therapy approaches. These individuals often benefit from clinicians beginning with a motivational enhancement approach that enhances the smoker's readiness to change and self-efficacy (Steinberg et al. 2004). Adding BT may address the social and other skills deficits that are often present in persons suffering from these co-occurring problems (Hughes 1993b). There is a growing literature supporting that treatment can

be effective with these harder to treat smokers when motivational enhancement, NRT medications, psychiatric medications, and BTs are integrated (Ziedonis et al. 1998, American Psychiatric Association 1996). Several authors summarize ways to modify and integrate medication and BT approaches for use among smokers with schizophrenia (Ziedonis and George 1997, Hughes and McHugh 1995), with depression (Hall et al. 1998), and with substance use disorders (Bobo 1989, Clemmey et al. 1997, Istvan and Matarazzo 1984). Successful nicotine dependence treatment has been shown in several studies to be associated with successful recovery from alcohol dependence (Friend and Pagano 2005, Hughes 1993a, 1993b, Burling and Ziff 1988, Budney et al. 1993, Sellers et al. 1987) although one notable study—inconsistent with the existing literature indicated that although offering tobacco and alcohol dependence treatment concurrently ensures that a greater number of patients are reached, this strategy may have an adverse effect on alcohol abstinence when compared to delaying nicotine dependence treatment (Joseph et al. 2004).

The dose of the transdermal patch was reduced from 21 mg during the first month to 14 mg during the second month and finally to 7 mg during the third month. Because he was apprehensive about discontinuing the 7 mg patch, he met with his physician to discuss his fears about relapse and ways of coping with situations he thought might be difficult. The patch was continued for an additional month, after which Mr. N was able to maintain successful abstinence. One year later, he called his physician after having relapsed. Because he had been smoking less than a pack of cigarettes per day for only 2 weeks, he was placed on 7 mg dose patch for only 2 weeks, after which the patch was discontinued. He discussed with his physician how a stressful family crisis had caused him to feel depressed and anxious, which he believed led to the relapse. He worked on coping skills and developing an alternative plan for handling bigger emotional triggers in the future. He was able to again successfully stop smoking and remained abstinent.

### Clinical Vignette 1

A 32-year-old married man, Mr. N, consulted his internist and stated that he wished to stop smoking but had been unable to do so on numerous prior attempts. During the last 2 years, he had twice tried to quit cold turkey and was able to abstain for only 2 days. During these periods of abstinence, he experienced severe nicotine withdrawal symptoms, including irritability, insomnia, restlessness, and trouble concentrating that interfered with his ability to perform his job. He reported that he started smoking again when his wife threatened to put him out of the house because she was so upset about his behavior, and when he found himself making extensive errors in his paperwork at the office. Mr. N was provided with literature about smoking and nicotine dependence, particularly about nicotine withdrawal. He was asked to read these materials with his wife. Because he smoked two packs of cigarettes per day and scored high on the Fagerstrom Tolerance Questionnaire, and because prior relapse appeared to be primarily the result of withdrawal symptoms, nicotine replacement was thought to be the treatment of choice. Because he frequently drank coffee during the day, the transdermal nicotine patch was chosen as the preferred route of administration. He was prescribed the transdermal nicotine patch (21 mg) and instructed in its use, its potential risks and benefits, and its potential side effects and adverse effects. He was told to select a quit date, notify the physician of this date, apply the patch, and stop smoking. He was instructed to call the physician 2 days after he stopped smoking and weekly thereafter for the first month for the purpose of monitoring and adjusting the dose of the patch when appropriate, and for encouragement and feedback on his progress. He was given self-help educational materials to help him learn to identify and manage the triggers to his smoking cigarettes. He was informed that there were support groups available and formal behavioral treatments in an individual or group format. Mr. N preferred this attempt to just taking the medication and self-help materials unless he relapsed. After stopping smoking, Mr. N experienced minimal withdrawal symptoms and was supported in his cessation effort by his wife. His work performance did not suffer significantly.

### Clinical Vignette 2

A 55 year-old married physician, Dr. X, decided to finally talk to his primary care provider about smoking cessation strategies. He had smoked up to 2 packs per day for more than 30 years. For a long time he thought he could "quit any time" and considered smoking "just a habit," making him "feel good, smart and more alert in the morning." He discarded the growing scientific evidence about the addictive properties of nicotine and appeared comfortable with the concept that "it did not apply to me." He also was slow to associate the reported negative health consequences of smoking to his own person. He ended up talking to his patients about smoking and increased risks for cardio-vascular disease, respiratory pathology and malignancies because the information in the professional literature that he regularly read was quite compelling. This fact did not seem to change his cigarette use though. His family became more assertive in pointing out to him his chain smoking, the fact that he would light the first cigarette in the morning even before getting out of bed and that would "have to do it" where ever he was, during his daily professional activities, at home or while on vacation. He started to finally cut down on smoking at home when his teenage son provided him with scientific evidence about the significance of second-hand exposure. He was caught off guard when realizing the increased anxiety, irritability, agitation, headache, fatigue and very poor concentration when "accidentally" running out of cigarettes even for half a day. His best friend, a psychiatrist, was quick to explain the above symptomatology as nicotine withdrawal and to talk about "obvious dependence after so many years of smoking." The veil of denial was beginning to tear but Dr. X, a proud, hard-working and highly respected medical professional decided to "try to beat this on my own." Asking for help from the substance abuse and mental health community seem hard due to his strongly moralistic views about addiction as "lack of will power." He switched to brands of low nicotine containing cigarettes; he tried cutting down on the number of daily cigarettes and he even applied aversive techniques, like smoke holding and rapid smoking. He was never able to achieve any sustained smoke-free periods of more than 3–4 weeks.

The withdrawal symptoms and intense cravings were instantaneously relived by relapse. He even attempted contingency management by making abstinence dependent on certain amounts of money given to his best friend; it again did not work. He was about to give up on fighting against the nicotine dependence when his recurring exercise-related chest discomfort and leg pain were diagnosed as ischemic coronary pathology and peripheral vascular disease. These 2 medical conditions were added to preexisting hypertension, "borderline" elevation in the cholesterol levels and frequent bouts of bronchitis. This is the moment when reluctantly Dr. X turned to his primary care physician and asked for help. Dr. X explained that based on his readings he identified himself as being in the action stage of change. He expressed his disbelief at motivational enhancement or cognitive-behavioral psychotherapeutic approaches as well as the usefulness of support groups but was willing to try nicotine-replacement therapy. He wanted the nicotine gum because he thought he would have more control over its use and as he put it "would have something to do with my hands and mouth as if I were smoking." He was instructed to choose a quit date when he would switch from smoking to the use of the gum. He was prescribed the 4-mg gums, presented their potential risks and benefits and explained the crunch and park procedure for their use. He was warned not to exceed 16 gums a day. He was also recommended to follow-up weekly for the first month after he stopped smoking to monitor for side effects, dose adjustments and overall progress. The withdrawal symptoms returned promptly following the quit date. Dr. X used the gums quite intensely exceeding "occasionally" the maximum number and reporting irritation in the mouth, nausea and dyspepsia. He admitted to "some benefit" but after 2–3 weeks he thought the cravings were "unbearable." Dr. X requested to be switched to the patch in the hope of minimizing the fluctuations in the nicotine level. He was started on 21 mg and to his surprise he started feeling "somewhat better." On occasion the urges to smoke were significant but overall he started noticing improvements in irritability, anxiety, fatigue and poor concentration. He surprised himself when he decided to ask his primary care physician for information on self help groups and relapse prevention techniques. He was still hoping to overcome the addiction on his own but seem to realize the need to extend the range of available skills and supports. It was around this time that during a business trip he developed prolonged precordial chest pain and collapsed. A massive inferior myocardial infarction was diagnosed complicated by treatment refractory arrhythmias. An emergent 5-vessel coronary artery bypass grafting was performed. The recovery period was prolonged. His cardiologist discontinued the nicotine patch during the attempts to stabilize the brittle cardiac rhythm abnormalities. After 6 weeks of rehabilitation efforts Dr. X returned home. He reported recurring cravings for cigarettes triggered by a multiplicity of factors. Buspar and Clonidine (the latter also added to control his fluctuating blood pressure) seem to do very little. Eventually he was prescribed Wellbutrin in a dose gradually increased to 300 mg daily. Over the following month Dr. X admitted to declining urges, irritability and "overall tension." Persistent initial insomnia responded to Ambien. His appetite for sweets increased gradually and to his dismay the weight started to go up. Six months later Dr. X returned to work. He was free of chest pain and hemodynamically stable. He was still taking Wellbutrin and proudly talking about "being smoke-free."

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CHAPTER

# 63 Substance Abuse: Opioid Use Disorders

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Opioid Intoxication
Opioid Withdrawal
Opioid Dependence
Opioid Abuse

## Introduction

The term *opioids* describes a class of controlled substances that act on opioid receptors, are widely used to control pain, and have significant abuse liability though some can also be used to treat opioid dependence. Numerous opioid receptors have been identified, but the physiologic and pharmacologic responses in man are best understood for the mu (μ) and kappa (κ) receptors. The μ receptor, for which morphine is a prototypical agonist, appears to be the one most closely related to opioid analgesic and euphorigenic effects. Opioids can be natural substances such as morphine, semisynthetics such as heroin, and synthetics with morphine-like effects such as meperidine. In addition to pain control, these drugs are prescribed as anesthetics, antidiarrheal agents, or cough suppressants. In addition to morphine and heroin, the opioids include codeine, hydromorphone, methadone, oxycodone, and fentanyl among others. Drugs such as buprenorphine, a partial agonist at the μ receptor, and pentazocine, an agonist–antagonist, are also included in this class because their physiologic and behavioral effects are mediated through opioid receptors. Their abuse liability is partly a function of potency and method of administration; these characteristics for some drugs of this class are summarized in Table 63–1.

The opioids approved for medical use with the greatest abuse potential are under Schedule II of the CSA; examples include fentanyl, hydromorphone, methadone, morphine, and oxycodone.

## Opioid-Related Disorders

As with other substances, there are two general categories of opioid-related disorders: opioid use disorders and opioid-induced disorders. Opioid use disorders include dependence and abuse (First and Pincus 2000). Opioid dependence, like other substance use disorders, has two sets of specifiers: the first being with physiologic features (i.e., tolerance and/or withdrawal), the second being with or without physiologic features. The second set describes course specifiers: early full remission, early partial remission, sustained full remission, sustained partial remission, on agonist therapy, and in a controlled environment. As of this writing, the agonist therapy category is used only with regard to the treatment of opioid dependence, and not in the treatment of other opioid-related disorders or substance dependencies.

Opioid-induced disorders include opioid intoxication, opioid withdrawal, opioid intoxication delirium, opioid intoxication psychotic disorders, opioid intoxication mood disorders, opioid intoxication sexual dysfunction, opioid intoxication sleep disorder, and opioid withdrawal sleep disorder. The defining features, according to DSM-IV-TR, for opioid dependence, abuse, intoxication, and withdrawal are similar to those for other substance use disorders. Essentially, opioid dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that the person is using high doses of opioids in a compulsive manner, for no legitimate medical reason, with loss of control over use and adverse medical or psychiatric consequences. Unlike

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**Table 63–1 Opioids**

| Drug | Active Metabolite | Route of Administration | Relative Potency | Medical Use | Plasma Half-Life (hr) | Duration of Action (hr) |
|---|---|---|---|---|---|---|
| Morphine | | IM, PO | 1 | Analgesia | 2 | 4–6 |
| Heroin | Morphine | IM | 1–2 | None | 0.5 | 3–5 |
| Codeine | | PO | 0.05 | Analgesia, antitussive | 2–4 | 4–6 |
| Fentanyl | | IM, IV | 40–100 | Analgesia | 3–4 | 1–2 |
| Hydromorphone | | IM, PO | 13 | Analgesia | 2–3 | 4–6 |
| Oxycodone | | PO | 0.5–1 | Analgesia | | 4–6 |
| Methadone | | IM, PO | 0.50 | Analgesia, opioid replacement pharmacotherapy | 15–40 | 18–30* |
| Buprenorphine | | IM, IV, SL | N/A (partial agonist) | Analgesia, opioid replacement pharmacotherapy | 6–12 | 4–6 (for analgesia) 12–48† |

*At steady state.
†Appears to be dose dependent.
IM, intramuscular; PO, by mouth; SL, sublingual; N/A, not applicable.

cocaine, hallucinogens, solvents, and other substances that do not always produce withdrawal signs and symptoms, opioid dependence is almost always accompanied by significant physiological tolerance and a defined withdrawal–abstinence syndrome. Opioid abuse is a less severe disorder that consists of intermittent use of one or more opioids, in the absence of compulsive use and significant tolerance and/or withdrawal, but resulting in recurrent social, legal, or personal problems, or in use that is physically hazardous. Opioid intoxication consists of clinically significant maladaptive behaviors or psychological changes that are associated with acute opioid effects. Opioid withdrawal is a syndrome associated with abrupt cessation or reduction of opioid use in persons who have been taking opioids regularly and have developed neuroadaptation to their agonist effects. Opioid withdrawal symptoms are generally opposite those of intoxication.

## Epidemiology of Opioid Abuse and Dependence

Heroin has traditionally been the subject of most attention within this class in western countries and has more recently emerged as a significant problem in Russia (Krupitsky et al. 2006a), Ukraine and other former Soviet States, Malaysia (Mazlan 2007), China, Iran (Mokri 2007), and Southeast Asia (Carrieri et al. 2006). In the US there has been a marked increase in prescription opioid abuse and dependence over the last 4–5 years such that it now has surpassed heroin. For example, the 2005 National Survey on Drug Use and Health (NSDUH; http://www.google.com/search?hl = en&ie = ISO-8859-1&q = nsduh; accessed on 2/24/07) found that abuse or dependence on unprescribed pain relievers was 6.81 times more prevalent among persons aged 12 or older than abuse and dependence on heroin (see Figure 7.2 in NSDUH report). The overall number of persons meeting criteria for abuse or dependence on pain relievers was estimated at 1.55 million as compared to 227,000 abusing or dependent on heroin. It is unclear if a similar problem has emerged in other countries. Marijuana continued to be the most often abused substance in many countries including the US, with an estimated 4 million individuals according to a very recent national survey. However, in that same survey, first-time initiates of unprescribed pain relievers surpassed first-time users of marijuana, and past-year initiates of unprescribed pain relievers were 20.3 times more common than past-year initiates of heroin.

Heroin addiction has traditionally been associated with large urban areas in the US, especially in northeast and mid-Atlantic states; however, the increase in prescription opioid use has been more concentrated in suburban and rural areas (Smith and Woody 2005). Oxycodone and hydrocodone containing products have traditionally been the main prescription opioids of abuse. Much attention has focused on Oxycontin®, a long-acting formulation of oxycodone that contains doses up to 80 mg/tablet. Though the slow absorption of this medication is unlikely to result in abuse when taken as prescribed, substance abusers have discovered that the tablets can be crushed, freeing much of the oxycodone that can then be inhaled or injected to produce a potent euphoria. Vigorous efforts to identify the scope of the prescription opioid abuse problem and reduce its prevalence have been underway. These efforts may be having an effect because the last 2 years have seen a leveling off in the growth of this problem (see Table 2.2 in NSDUH report).

In addition to treatment programs specifically designed for substance use disorders, patients with opioid-related disorders are seen throughout the medical treatment system including private practice, emergency rooms, and consultation and liaison settings. Physicians practicing in penal institutions see large numbers of persons with opioid use disorders due to their association with high levels of criminal activity. Accidents and injuries due to violence associated with buying or selling drugs are common and patients with opioid-related disorders are frequently seen on trauma and surgical services. In some areas violence accounts for more opioid-related deaths than overdose or HIV infection.

## Etiology and Pathophysiology of Opioid-Related Disorders

Opioid-related disorders, as in the case of other substance-related disorders, are felt to arise from a variety of social, psychological, and biological factors that interact to produce a "case." Among those identified as especially important are

opioid use within the individual's immediate social environment and peer group, availability of opioids, a history of childhood conduct disorder or adult antisocial personality disorder, and a family history of one or more substance use disorders. The families of persons with opioid dependence are likely to have higher levels of psychopathology, especially an increased incidence of alcohol and drug use disorders, and antisocial personality disorder (Rounsaville et al. 1982, Merikangas et al. 1998). These findings suggest that there is a genetic susceptibility to substance use disorders. Though many studies are underway to identify the nature and location of potential genetic factors for this susceptibility, the work is extremely complex (Mayer et al. 1997, Hoehe et al. 2000) and clear findings are not available at this time nor is information on the influence of psychological and environmental factors on the expression of a presumed genetic predisposition.

The exact mechanism or mix of factors that produce opioid dependence or abuse are unknown, as are the factors that contribute to the chronic relapsing pattern that is typically seen in many of these patients. Studies by Dole and others suggest that persons who have used opioids regularly over extended periods of time experience physiological alterations as a consequence of chronic use that are permanent and which contribute to an inability to achieve periods of sustained remission (Dole and Nyswander 1965, Kreek 1986). The exact nature of these physiological alterations has not yet been identified. Studies by Wikler and others have demonstrated the existence of conditioned drug responses that can persist for years and which may contribute to relapse in formerly dependent individuals (Wikler 1980, O'Brien et al. 1997).

**DSM-IV-TR Criteria**

**Opioid Intoxication**

A. The development of a reversible substance-specific syndrome due to recent ingestion of (or exposure to) a substance. **Note:** Different substances may produce similar or identical syndromes.

B. Clinically significant maladaptive behavioral or psychological changes that are due to the effect of the substance on the central nervous system (e.g., belligerence, mood lability, cognitive impairment, impaired judgment, impaired social or occupational functioning) and develop during or shortly after use of the substance.

C. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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## Clinical Picture of Opioid-Related Disorders

Heroin is usually taken by injection, though it can be smoked, inhaled ("snorted"), or taken orally. Smoking and inhalation are commonly seen only when very pure heroin is available, as has occurred in the parts of the US (particularly in the Northeast) and other countries where it is available. Opium smoking was the main way opioids were used in Iran and Southeast Asian countries for many years but that pattern is changing with the emergence of injecting use (Mokri 2007). Hydromorphone (Dilaudid®), morphine, and meperidine (Demerol®) are usually injected though they can be taken orally; fentanyl is almost always injected, as is buprenorphine in countries where it is being abused (Parfitt 2006). Codeine and other analgesics made for oral ingestion containing hydrocodone or oxycodone (such as Vicodin®, Percodan®, or Percocet®) are usually taken orally; Oxycontin is taken orally and injected, as discussed above. All of these drugs can cause intoxication, withdrawal, dependence, and are associated with abuse.

### Intoxication

Opioid intoxication is characterized by maladaptive and clinically significant behavioral changes developing within minutes to a few hours after opioid use (see DSM-IV-TR criteria for substance intoxication). Symptoms include an initial euphoria sometimes followed by dysphoria or apathy. Psychomotor retardation or agitation, impaired judgment, and impaired social or occupational functioning are commonly seen. Intoxication is accompanied by pupillary constriction unless there has been a severe overdose with consequent anoxia and pupillary dilatation. Persons with intoxication are often drowsy (described as being "on the nod") or even obtunded, have slurred speech, impaired memory, and demonstrate inattention to the environment to the point of ignoring potentially harmful events. Dryness of secretions in the mouth and nose, slowing of gastrointestinal activity, and constipation are associated with both acute and chronic opioid use. Visual acuity may be impaired as a result of pupillary constriction. The magnitude of the behavioral and physiologic changes depends on the dose as well as individual characteristics of the user such as rate of absorption, chronicity of use, and tolerance. Symptoms of opioid intoxication usually last for several hours, but are dependent on the half-life of the particular opioid that has been used. Severe intoxication following an opioid overdose can lead to coma, respiratory depression, pupillary dilatation, unconsciousness, and death (Table 63–2).

**Table 63–2 Signs and Symptoms of Opioid Intoxication**

| Symptoms |
|---|
| Euphoria, dysphoria, or apathy |
| Psychomotor retardation or agitation |
| Impaired judgment, social, or occupational functioning |
| **Signs** |
| Pupillary constriction |
| Drowsy or obtunded |
| Slurred speech, impaired memory, and inattention to environment |
| Dryness in mouth or nose |
| Slowed gastrointestinal activity and constipation |
| Severe intoxication can lead to coma, respiration depression, pupillary dilation, unconsciousness, and death. |

## Withdrawal

Opioid withdrawal is a clinically significant, maladaptive behavioral and physiological syndrome associated with cessation or reduction of opioid use that has been heavy and prolonged (see DSM-IV-TR criteria for substance withdrawal). It can also be precipitated by administration of an opioid antagonist such as naloxone or naltrexone. Patients in opioid withdrawal typically demonstrate a pattern of signs and symptoms that are opposite the acute agonist effects. The first of these are subjective and consist of complaints of anxiety, restlessness, and an "achy feeling" that is often located in the back and legs. These symptoms are accompanied by a wish to obtain opioids (sometimes called "craving") and drug-seeking behavior, along with irritability and increased sensitivity to pain. Additionally, patients typically demonstrate three or more of the following: dysphoric or depressed mood; nausea or vomiting; diarrhea; muscle aches; lacrimation or rhinorrhea; increased sweating; yawning; fever; insomnia; pupillary dilatation; fever; and piloerection. Piloerection and withdrawal-related fever are rarely seen in clinical settings (other than prison) as they are signs of advanced withdrawal in persons with a very significant degree of physiologic dependence; opioid-dependent persons with "habits" of that magnitude usually manage to obtain drugs before withdrawal becomes so far-advanced (Table 63–3).

**Table 63–3 Signs and Symptoms of Opioid Withdrawal**

| Symptoms |
|---|
| Anxiety, irritability, restlessness |
| Muscle aching |
| Craving for opioids |
| Increased pain sensitivity |
| **Signs** |
| Dysphoric or depressed mood |
| Nausea/vomiting/diarrhea |
| Lacrimation/rhinorrhea |
| Sweating |
| Yawning |
| Insomnia |
| Pupillary dilatation |
| Piloerection |
| Fever |

For short-acting drugs such as heroin, withdrawal symptoms occur within 6–24 hours after the last dose in most dependent persons, peak within 1–3 days, and gradually subside over a period of 5–7 days. Symptoms may take 2–4 days to emerge in the case of longer acting drugs such as methadone. Less acute withdrawal symptoms are sometimes present and can last for weeks to months. These more persistent symptoms can include anxiety, dysphoria, anhedonia, insomnia, and drug craving.

## Dependence

Opioid dependence is diagnosed by the signs and symptoms associated with compulsive, prolonged self-administration of opioids that are used for no legitimate medical purpose, or if a medical condition exists that requires opioid treatment, are used in doses that greatly exceed the amount needed for pain relief (see DSM-IV-TR criteria). Persons with opioid dependence typically demonstrate continued use in spite of adverse physical, behavioral, and psychological consequences. Almost all persons meeting criteria for opioid dependence have significant levels of tolerance and will experience withdrawal upon abrupt discontinuation of opioid drugs. Persons with opioid dependence tend to develop such regular patterns of compulsive use that daily activities are typically planned around obtaining and administering drugs.

Opioids are usually purchased on the illicit market, but they can also be obtained by forging prescriptions, faking or exaggerating medical problems, or by receiving simultaneous prescriptions from several physicians. Physicians and other health care professionals who are dependent will often obtain opioids by writing prescriptions or by diverting opioids that have been prescribed for patients.

**DSM-IV-TR Criteria**

**Opioid Withdrawal**

A. The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy and prolonged.

B. The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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## Abuse

Opioid abuse is a maladaptive pattern of intermittent use in hazardous situations (driving under the influence, being intoxicated while using heavy machinery, working in dangerous places, etc.), or periodic use resulting in adverse social, legal, or interpersonal problems (see DSM-IV-TR criteria). All of these signs and symptoms can also be seen in persons who are dependent; abuse is characterized by less regular use than dependence (i.e., compulsive use not present) and by the absence of significant tolerance or withdrawal. As with other substance use disorders, opioid abuse and dependence are hierarchical and thus persons diagnosed as having opioid abuse must never have met criteria for opioid dependence.

## Assessment and Clinical Picture

Opioid use disorders can occur at any age, including adolescence and the geriatric years, but most affected persons are between 20 and 45 years of age. There have been increasing numbers of reports of adolescents presenting for treatment with opioid problems, though good data are hard to find. Neonates whose mothers are addicted can experience opioid withdrawal, as will be discussed later. Rarely, young

**DSM-IV-TR Criteria**

**Opioid Dependence**

A maladaptive pattern of opioid use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
   (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:
   (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substance)
   (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) The substance is often taken in larger amounts or over a longer period than was intended

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance, or recover from its effects

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use

(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

*Specify* if:

With physiological dependence: evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)

Without physiological dependence: no evidence of tolerance or withdrawal (i.e., neither Item 1 nor 2 is present)

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children are affected with some cases of dependence having been reported in persons who are 8–10 years of age. Males are more commonly affected, with the male–female ratio typically being 3 or 4 to 1.

A nonjudgmental and supportive yet firm approach to these patients is especially important. They typically have engaged in antisocial or other forms of problematic behavior. They are often embarrassed or afraid to describe the extent of their behavior, and have extremely low self-esteem. At the same time, they are prone to be impulsive, manipulative, and to act out when frustrated. Communicating a feeling of nonjudgmental support in the context of setting limits, along with a clear and informed effort to provide appropriate help, will encourage optimum therapeutic opportunities.

**Physical Examination.** Sclerosed veins ("tracks") and puncture marks on the lower portions of the upper extremities are common in intravenous users. When these veins become unusable or otherwise unavailable, persons will usually switch to veins in the legs, neck, or groin. Veins sometimes become so badly sclerosed that peripheral edema develops. When intravenous access is no longer possible, persons will often inject directly into their subcutaneous tissue ("skin-popping") resulting in cellulitis, abscesses, and circular-appearing scars from healed skin lesions. Tetanus is a relatively rare but extremely serious consequence of injecting into the subcutaneous tissues. Infections also occur in other organ systems, including bacterial endocarditis, hepatitis B and C, and HIV infection.

Persons who "snort" heroin or other opioids or smoke opium often develop irritation of the nasal mucosa or respiratory tract. Difficulties in sexual function are common, as are a variety of sexually transmitted diseases. Males often experience premature ejaculation associated with opioid withdrawal, and impotence during intoxication or chronic

**DSM-IV-TR Criteria**

**Abuse**

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
   (1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
   (2) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
   (3) Recurrent substance-related legal problems
   (4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.

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use. Females commonly have disturbances of reproductive function and irregular menses.

**Laboratory Findings.** During dependence, routine urine toxicology tests are often positive for opioid drugs and remain positive for most opioids for 12–36 hours. Methadone, because it is longer acting, can be identified for several days. Fentanyl is not detected by standard urine tests but can be identified by more specialized procedures. Oxycodone, hydrocodone, and hydromorphone are often not routinely included on urine toxicology tests though they can be identified by some of these assays and by gas chromatography/mass spectrometry. Testing for fentanyl is not necessary in most programs, but needs to be performed in assessing and treating health care professionals such as anesthesiologists, persons working in intensive care or pain management units who have access to this drug. Concomitant laboratory evidence of other abuseable substances such as cocaine, marijuana, alcohol, amphetamines, and benzodiazepines is common.

Hepatitis screening tests are often positive, either for hepatitis B antigen (signifying active infection) or hepatitis B and/or C antibody (signifying past infection). Mild to moderate elevations of liver function tests are common, usually as a result of chronic infection with hepatitis C but also from toxic injury to the liver due to contaminants that have been mixed with injected opioids, or from heavy use of other hepatotoxic drugs such as alcohol. Low platelet count, anemia, or neutropenia, as well as positive HIV tests or low CD-4 cell counts are often signs of HIV infection. HIV is commonly acquired via the practice of sharing injection equipment, or by unprotected sexual activity that may be related to the substance use disorder, for example, exchanging sex for drugs or money to buy drugs.

**Differential Diagnosis.** Individuals who are dependent on "street" opioids are usually easy to diagnose due to the physical signs of intravenous use, drug-seeking behavior, reports from independent observers, the lack of medical justification for opioid use, urine test results, and the signs and symptoms of intoxication or withdrawal.

The signs and symptoms of opioid withdrawal are fairly specific, especially lacrimation and rhinorrhea, which are not associated with withdrawal from other abuseable substances. Other psychoactive substances with sedative properties such as alcohol, hypnotics, or anxiolytics can cause a clinical picture that resembles opioid intoxication. A diagnosis can usually be made by the absence of pupillary constriction, or by the lack of response to a naloxone challenge. In some cases, intoxication is due to opioids along with alcohol or other sedatives. In these cases, the naloxone challenge will not reverse all of the sedative drug effects.

Difficult diagnostic situations are seen among persons who fabricate or exaggerate the signs and symptoms of a painful illness (such as kidney stones, migraine headache, back pain, etc.). Because pain is subjective and difficult to measure, and because some of these individuals can be very skillful and deceptive, diagnosis can be difficult and time-consuming. Drugs that are obtained in such deceptions may be used by the individual in the service of his/her dependence or abuse, or may be sold on the illicit drug market for profit. These individuals cause problems not only for physicians, but also for patients with disorders that need opioids for pain relief. Patients who have pain that should be treated promptly with opioids are sometimes denied treatment or given inadequate amounts of opioids due to uncertainty or disbelief about the legitimacy of their complaints. Patients with cancer, kidney stones, or other painful conditions have sometimes suffered considerably from this type of "reverse discrimination." An example of an individual with drug-seeking behavior is given in Clinical Vignette 1.

Clinical Vignette 1

The medical director of a health care organization (HMO) referred a 43-year-old male for evaluation/treatment of pain. He had been receiving Percodan on a regular basis (4/day) for the last 2 years from an internist for chronic pain secondary to kidney problems. Prior to his referral, he had been in and out of emergency rooms over the past 6 years for treatment of renal pain. He had been prescribed narcotic analgesics on numerous occasions and his health plan had been billed for his care. As a result, the HMO had limited treatment to only his internist, and refused to pay for any care unless it was approved in advance.Review of his medical records revealed that he had been thoroughly worked-up for kidney disease on several occasions, and that he had an A-V malformation with periodic bleeding and clot formation; he had also passed kidney stones on at least two occasions. A cystoscopy done previously had showed evidence of traumatic lesions in the wall of the bladder that were secondary to instrumentation.

Social and occupational history showed that he had worked at two hospitals and on one occasion had impersonated a psychologist. During previous employment he had improperly used a company vehicle. When his supervisor attempted to have him fired, he turned the proceedings around and almost had the supervisor fired for failing to follow proper administrative procedures. Currently, he was working as an administrative aide for the city courts, and was in a hurry to "get his prescription filled" so that he could return to work. He described some of the problems he had experienced in attempting to obtain "proper treatment" from the HMO and expressed annoyance that he had been referred to the drug program for evaluation. He was very concerned about confidentiality, and felt that people he knew might see him entering the program and think that he had a drug problem. During the initial interview, he described his contacts in government, implying that he would not hesitate to complain if his treatment was inadequate or unsatisfactory. Upon examination he was well dressed, in no acute distress, and superficially friendly. There were no signs of anxiety, depression, loose associations, or of homicidal or suicidal ideas. His mood was in a normal range and his affect was appropriate, though it seemed as if he could become angered easily if frustrated or provoked. There were no overt signs or symptoms of opioid withdrawal or intoxication. After examination and based on the history, it was decided to give him a trial of methadone for pain and a dose of 20 mg was administered. Over the next hour the patient was observed to become sleepy with his speech slurred and rambling; respiratory and heart rates were mildly depressed and his pupils were constricted, all symptoms of opioid intoxication. Later, the patient admitted that he had not been using the Percocets; in fact, he had sold them for extra "spending money."

Persons with opioid dependence will often present with psychiatric signs and symptoms such as depression or anxiety. Such subjective distress often serves to motivate the patient to seek treatment and thus can be therapeutically useful. These symptoms can be the result of opioid intoxication or withdrawal, or they might result from the pharmacological effects of other substances that are also being abused such as cocaine, alcohol, or benzodiazepines. They may also represent independent, nonsubstance-induced psychiatric disorders that require long-term treatment. The correct attribution of psychiatric symptoms that occur in the context of opioid dependence or abuse follows the principles that are outlined in the substance-related section and other relevant parts of DSM-IV-TR.

Opioids are much less likely to produce psychopathology than most other drugs of abuse, and in some instances they reduce psychiatric symptoms such as anxiety and associated depression. In these cases, symptoms will emerge not during opioid use, but after it is discontinued. Clinicians have observed this problem in methadone maintenance patients who occasionally have an exacerbation of symptoms of schizophrenia, posttraumatic stress disorder (PTSD), or other problems during or following a methadone dose taper.

## Course and Natural History of Opioid Dependence

Opioid dependence can begin at any age, but problems associated with opioid use are most commonly first observed in the late teens or early 20s. Once dependence occurs it is usually continuous over a period of many years even though periods of abstinence are frequent. Reoccurrence is common even after many years of forced abstinence, such as occurs during incarceration. Increasing age appears to be associated with a decrease in prevalence. This tendency for dependence to remit generally begins after age 40 and has been called "maturing out." However, others remain opioid dependent into their 50s or 60s and beyond. Thus, though spontaneous remission can and does occur, most cases of untreated opioid dependence follow a chronic, relapsing course for many years.

## Treatment

There are currently a number of effective pharmacological and behavioral therapies for the treatment of opioid dependence, with these two approaches often combined to optimize outcome. There are also some newer options, which may take various forms. For example, methadone maintenance is an established treatment, while the use of buprenorphine and buprenorphine/naloxone in an office-based setting represents a relatively new variation on that theme. Clonidine has been used extensively to treat opioid withdrawal while lofexidine is a structural analog that appears to have less hypotensive and sedating effects. The depot dosage form of naltrexone, available in the US currently for the treatment of alcohol dependence and under development for opioid dependence treatment, may increase compliance with a medication that is a highly effective opioid antagonist but which has been underutilized due to poor acceptance by patients. In almost every treatment episode using pharmacotherapy, it is combined with some type of psychosocial or behavioral treatment. Recent research has documented the value of these additional treatments and provided insight into those that are the most effective, as discussed later in more detail.

### Detoxification: Long-Term, Short-Term, Rapid, and Ultra-Rapid

Detoxification from opioids, for most patients, is only the first phase of a longer treatment process. Most patients seeking treatment have been addicted to heroin or other opioids for 2–3 years, and some for 30 years or more. Thus, treatment usually involves changes in individuals' lifestyles. Though generally ineffective in achieving sustained remission unless combined with long-term pharmacological, psychosocial, or behavioral therapies, detoxification alone continues to be widely used. It is sometimes the only option available for individuals who do not meet criteria for, do not desire, or do not have access to agonist or partial agonist medications such as methadone or buprenorphine.

> Pharmacologic detoxification is generally ineffective in achieving sustained remission unless combined with long-term pharmacologic, psychosocial, or behavioral therapies.

The detoxification process may include use of opioid agonists (e.g., methadone), partial agonists (e.g., buprenorphine), antagonists (e.g., naloxone, naltrexone), or nonopioid alternatives such as clonidine, benzodiazepines, or nonsteroidal anti-inflammatory agents. In many cases, one or more medications are combined, such as naloxone with clonidine and a benzodiazepine (Table 63–4). The choice of detoxification medication and the duration of the process depend on numerous factors including patient preference, clinician expertise and experience, type of treatment facility, licensing, and available resources. Ultimately, however, the goal of detoxification is the achievement (and maintenance) of a drug-free state while minimizing withdrawal. Unfortunately, detoxification for some individuals appears to be used as an expedient means to achieve a drug-free state rapidly with no follow-up pharmacological or behavioral therapy.

**Table 63–4 Pharmacologic Agents in Opioid Detoxification**

| |
|---|
| Opioid agonists (methadone) |
| Partial agonists (buprenorphine) |
| Antagonists (naloxone, naltrexone) |
| Nonopioid alternatives (clonidine, benzodiazepines, nonsteroidal anti-inflammatory agents) |
| Combinations of some of the above medications |

Opioid detoxification paradigms are frequently categorized according to their duration: long-term (typically 180 days), short-term (up to 30 days), rapid (typically 3–10 days), and ultra-rapid (1–2 days). These temporal modifiers provide only a coarse description of the paradigm; they do not provide other important information such as the medications used or whether postdetoxification pharmacological, psychosocial, or behavioral therapy is provided. However, some general guidelines typically apply.

The most common detoxification protocols, and those for which the most data are available, are the long-term (typically 180 days) and short-term (up to 30 days) paradigms involving the use of methadone. Unfortunately, these strategies have not generally been associated with acceptable treatment response using relapse to opioid use as an outcome criterion. For example, one study (Banys et al. 1994) reported that more than half of the individuals participating in a 180-day detoxification program were using opioids illicitly during the medication taper phase. Six-month follow-up indicated that 38.5% of the urine samples ($n = 26$) tested negative for illicit opioids, only 3 of 31 patients reported remaining free of illicit opioids for the entire 6 months prior to follow-up, and 22 participated in some other form of treatment (Reilly et al. 1995). Results from more rapid detoxification using short- or even intermediate-term (up to 70 days) medication-tapering protocols are even less encouraging and have an unfortunately low success rate. It should be noted, however, that provision of additional services such as counseling, behavioral therapy, treatment of underlying psychopathologies, job skills training, and family therapy to address concomitant treatment needs can improve outcome though success rates remain low, even with these services (Kleber 1999).

Rapid detoxification involves the use of an opioid antagonist, typically naltrexone or naloxone, in combination with other medications (such as clonidine and benzodiazepines) to mitigate the precipitated withdrawal syndrome. The procedure is intended to expedite and compress withdrawal in order to minimize discomfort and decrease treatment time. Ultra-rapid detoxification also utilizes other medications, along with an opioid antagonist, to moderate withdrawal effects. However, rather than individuals being awake as they are during the rapid detoxification process, they are placed under general anesthesia or, alternatively, deeply sedated. A comprehensive review of the rapid and ultra-rapid detoxification literature has been published (O'Connor and Kosten 1998). Rapid detoxification studies were conducted in inpatient facilities, outpatient substance abuse treatment settings, and outpatient primary care facilities; ultra-rapid ones were confined to inpatient settings. Patients included those who were heroin dependent as well as those in methadone maintenance treatment. Only four of the ultra-rapid detoxification studies reviewed provided follow-up beyond the initial detoxification. Retention on postdetoxification naltrexone maintenance in one study was 53% at 1 month and 82% in another at 3 months. Only one of the ultra-rapid detoxification studies provided follow-up information indicating that all individuals were taking naltrexone 30 days post detoxification. Another study (Hensel and Kox 2000) in which ultra-rapid detoxification was followed by naltrexone maintenance and supportive psychotherapy, indicated that 49 of 72 patients were opioid abstinent 12 months following detoxification. All of these studies involved self-selected individuals, thus making it impossible to know the overall effectiveness of this type of intervention.

A major concern regarding ultra-rapid detoxification is the occurrence of potentially serious adverse effects, such as respiratory distress (San et al. 1995), or other pulmonary and renal complications (Pfab et al. 1999) during or immediately following the procedure. A high frequency of vomiting has also been reported (Cucchia et al. 1998). The degree to which serious adverse events occur has not yet been determined; however, there have been reports of sudden death occurring shortly after the procedure that were not caused by relapse to opioid use and overdose (O'Brien et al. [2001] personal communication).

In spite of the emerging evidence about serious adverse events, ultra-rapid detoxification may be appropriate for highly selected individuals based on considerations of previous treatment history, economic factors, and patient choice. However, patients seeking this treatment must be thoroughly informed that serious adverse events, including sudden unexpected deaths, have occurred in association with this procedure and its use should probably be limited to inpatient settings where monitoring by anesthesiologists and other highly trained staff is available.

Buprenorphine, a μ-opioid partial agonist, has also been used as a detoxification agent. Results from early inpatient studies have shown that it is safe, well tolerated, and mitigates opioid withdrawal signs and symptoms over a range of doses and detoxification schedules (Cheskin et al. 1994, Parran et al. 1994, Vignau 1998) and in outpatients (O'Connor et al. 1997, Diamant et al. 1998). More recent studies have confirmed and extended those findings. In particular, they have demonstrated the comparative efficacy of buprenorphine to clonidine or lofexidine, two alpha-adrenergic agonists (White et al. 2001, Oreskovich et al. 2005, Ponizovsky et al. 2006). One trial that utilized ancillary treatment medications and standard counseling procedures was conducted in community treatment programs (Ling et al. 2005). It involved both inpatient and outpatient participants and demonstrated a significant benefit of buprenorphine over clonidine with regard to the study's criterion for treatment success; the proportion of participants who were both retained in the study for its duration and provided an opioid-free urine sample on the last day of attendance. Another study, unique in that it compared buprenorphine to clonidine in a 28-day medical detoxification program for adolescents, found that buprenorphine was associated with better treatment retention and a greater percentage of opioid-negative urine samples (Marsch et al. 2005). Clonidine has been shown to suppress many of the autonomic signs and symptoms of opioid withdrawal. It can cause sedation and hypotension but has been used with few problems when appropriate monitoring is available. It does not suppress the subjective discomfort of withdrawal and probably for that reason is not well accepted by most patients.

Other alpha-2-adrenergic agonists have also been evaluated in order to find agents that are as or more effective, but less sedating and hypotensive than clonidine. Lofexidine, a medication that was originally promoted as an antihypertensive but was shown to lack clinically significant hypotensive effects, has been the most studied. When compared to clonidine, it has been found to equally suppress autonomic signs and symptoms of opioid withdrawal but with less sedation and hypotension (Kahn et al. 1997, Lin et al. 1997, Carnwath and Hardman 1998). When compared to methadone dose tapering, lofexidine detoxification was associated with opioid withdrawal effects that peaked sooner, but resolved to negligible levels more rapidly (Bearn et al. 1996). In another study (Bearn et al. 1998), an accelerated 5-day lofexidine treatment regimen attenuated opioid withdrawal symptoms more rapidly than 10 days of either lofexidine or methadone, with similar blood pressure responses observed

for the lofexidine groups. Data regarding the potential effectiveness of guanabenz and guanfacine have also been reported, but further studies are required to assess the potential utility of these medications. In summary, recent studies have shown that lofexidine is likely to be a useful opioid detoxification agent whose efficacy approximates that of clonidine but with fewer side effects.

## Opioid Agonist Pharmacotherapy

Methadone maintenance was developed by Dole and Nyswander (1968) and has become the most commonly used pharmacotherapy for opioid dependence. Methadone acts at the μ-opioid receptor and its ability to suppress opioid withdrawal for 24–36 hours following a single oral dose makes it an ideal medication for this purpose. Another μ-opioid agonist, LAAM, received approval in the US for maintenance treatment in 1993 and later in Europe. LAAM is a long-acting congener of methadone that suppresses withdrawal for 48–72 hours and thus has the advantage of requiring less frequent clinic visits than methadone, which must be taken daily. Though it has been shown effective, it was taken off the market in Europe because it was reported to have caused a few deaths due to prolongation of the QT interval. Only one company was manufacturing it and as a result of the European experience, the company stopped making it and it is no longer available, though it is still approved in the US. A third medication, buprenorphine (and a combination of buprenorphine with naloxone), received approval in the US for opioid dependence treatment in 2002 and has been used extensively in France. It has been mentioned previously as a detoxification agent and will be discussed later and in more detail as it has unique pharmacological properties compared to other therapeutic agents.

Both methadone and LAAM are Schedule II controlled substances and in the US can only be used for maintenance and detoxification in programs that are licensed by the Drug Enforcement Administration (DEA) and must pass periodic inspections to make certain that they are in compliance with national accrediting organizations and local requirements. The regulations in countries where methadone is allowed typically specify who is eligible for treatment, procedures that are required for its administration, the number of take-home doses permitted, and the type of medication storage security needed. Treatment programs in the US have been inspected at periodic intervals for the past 40 years and violations have resulted in sanctions ranging from administrative citations to, in a very limited number of cases, criminal prosecution in response to very serious problems. This combination of regulation by law enforcement and other agencies has resulted in a treatment system that is separated from the mainstream of other medical care and that consists almost entirely of specially licensed and inspected clinics in the US. Efforts were made to correct this problem in 2000 when the FDA transferred responsibility for inspecting methadone programs to State and other authorities. However, many clinics continue to be located in buildings that have been converted to comply with regulations but that were never intended for medical use. At the present time, it is estimated that approximately 240,000 patients are being maintained on methadone at 1,000 or more sites in the US (Parrino [2006] personal communication); this number represents 10–20% of all persons with opioid dependence based on data from the 2005 NHSDA, where 1.8 million persons were estimated to meet criteria for opioid abuse or dependence on prescription opioids or heroin. Use of methadone is also common in most European countries, Australia, and is rapidly expanding in Iran and China; buprenorphine is used more often than methadone in France (Carrieri et al. 2006).

The appropriate dose of agonist medication has been a subject of federal and local regulations in most countries, though there has been a gradual shift toward allowing more clinical judgment in its determination, especially in the US. A number of studies have been done during the last 35 years to determine the optimal dose and, although it is clear that some patients do well on low doses of methadone, studies have consistently shown that most individuals need higher doses if they are to achieve maximum benefit from agonist treatment (Ball and Ross 1991). The results of these comparison studies are generally supportive of the guidelines originally proposed by Dole and Nyswander, who recommended doses in the 80–120 mg/day range (Dole and Nyswander 1968). Clear relationships between methadone blood levels and clinical response have not been observed consistently. One study found significant correlations between oral dose and methadone concentration, but only among patients who complained of low dosing (Hiltunen et al. 1999). These findings suggest that some patients may be more sensitive to dose changes and that clinical response, including subjective complaints, is a more important guide to adequate dosing than blood levels. No controlled studies have been done examining doses above 120 mg even though they have become more common in the last several years due to the increased potency of heroin in many areas; thus the upper limits of dosing effectiveness are not well understood.

In addition to the transfer of regulatory oversight in the US from the FDA to State and other local authorities, there was another major paradigm shift in the way that opioid replacement pharmacotherapy can be provided, beginning with passage of the Drug Addiction Treatment Act of 2000 (DATA 2000). This legislation allowed for the use of CSA Schedule III, IV, and V medications for treatment of opioid dependence by physicians who have received a waiver from the Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration. Secondly, the FDA approved the use of buprenorphine and a buprenorphine/naloxone combination product for that indication. Thus, these two products can now be used outside the confines of traditional opioid treatment programs (OTPs) through what is commonly referred to as the office-based opioid treatment (OBOT) paradigm. Additionally, both buprenorphine and buprenorphine/naloxone may be used in OTPs as well. Initially, a limit of 30 patients per practice, and then 30 patients per prescriber, capped the maximum number of patients that a physician could treat at any one time in OBOT. Most recently, in December 2006, an amendment to the Controlled Substance Act enabling qualified physicians to treat up to 100 patients with buprenorphine and buprenorphine/naloxone was signed by the President (H.R. 6344 [2006]). It is anticipated that this recently passed legislation will enable more individuals to access treatment for opioid addiction.

To qualify for the waiver under DATA (2000) as described above, a physician must meet any one or more

of certain criteria (Substance Abuse and Mental Health Services Administration 2007). Some of these criteria include the following:

- Holding a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
- Holding an addiction certification from the American Society of Addiction Medicine.
- Holding a subspecialty board certification in addiction medicine from the American Osteopathic Association.
- Having, with respect to the treatment and management of opioid-addicted patients, completed not less than 8 hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or any other organization that the Secretary determines is appropriate for purposes of this subclause.

Although buprenorphine has been available internationally as an analgesic for approximately 30 years, it has only been available as an opioid addiction treatment medication for approximately 10 years, with approval first coming in France in 1996. Currently, over 40 countries have approved buprenorphine and/or buprenorphine/naloxone for the treatment of opioid dependence. Unlike methadone, which is a full opioid agonist at the μ receptor, buprenorphine is a partial μ agonist and also an antagonist at the κ receptor (Martin et al. 1976, Sadée et al. 1982). As such, buprenorphine administration is associated with effects that are dose dependent within a limited range, but that are submaximal at higher doses. This ceiling to the effects of buprenorphine provides for a greater margin of safety (e.g., with regard to respiratory depression) than that of full μ agonists. Additionally, buprenorphine has a high affinity for the μ-opioid receptor and dissociates slowly from it, thus attenuating the severity of withdrawal (Villiger and Taylor 1981, Rothman et al. 1995).

Since buprenorphine undergoes extensive first-pass metabolism after oral administration, it is administered sublingually as an opioid addiction pharmacotherapy. It is available in the US in both 2-mg and 8-mg dosage strengths. The buprenorphine/naloxone combination product, which was developed to reduce potential diversion and misuse, contains each component in a 4:1 ratio; 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets are available. Naloxone is only poorly absorbed when administered sublingually. Thus, if a buprenorphine/naloxone sublingual tablet is crushed and administered parenterally by an opioid-dependent individual, the naloxone component is likely to precipitate an opioid withdrawal syndrome, which potentially could serve as a deterrent to further abuse. Individuals may be inducted onto therapy with either buprenorphine or buprenorphine/naloxone, but the latter should be used for unsupervised (e.g., take-home) administration unless the combination product cannot be tolerated due to the above properties that are hoped to reduce its potential for abuse as compared to buprenorphine alone (the "mono product").

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome P-450 3A4 (Iribarne et al. 1997). Thus, the concomitant use of 3A4 inhibitors such as azole antifungal agents, macrolide antibiotics, and HIV protease inhibitors may potentially be associated with increases in buprenorphine plasma levels that could result in signs and symptoms of overmedication. Conversely, the concomitant use of 3A4 inducers (e.g., phenobarbital, phenytoin) has the potential to decrease plasma levels of buprenorphine to subtherapeutic levels, although this interaction has not been systematically evaluated. Given the relatively higher incidence of HIV disease in the addict population compared to the general one, it is fortuitous that there appear to be few potentially significant drug interactions between buprenorphine and HIV/AIDS treatment medications. For example, efavirenz has been associated with a pharmacokinetic, but not pharmacodynamic, interaction with buprenorphine when used clinically (McCance-Katz 2005). On the other hand, the combination of ritonavir and atazanavir with buprenorphine has been reported to be associated with an adverse event profile that has necessitated an adjustment to the buprenorphine dose, perhaps as a consequence of decreased metabolism of buprenorphine to norbuprenorphine and decreased formation of buprenorphine glucuronide (Bruce and Altice 2006).

It is likely that the most important potential interaction is the combination of buprenorphine with benzodiazepines, alcohol, and/or other CNS depressants. In a preclinical study (Nielsen and Taylor 2005), the combination of a benzodiazepine with buprenorphine was found to modify the ceiling effect observed when buprenorphine was administered alone, making buprenorphine appear to be more like a full agonist. Thus, the potential for severe respiratory depression may be increased when these medications are combined. Although the concomitant use of buprenorphine and benzodiazepines is not contraindicated, it is prudent to limit the prescribing of buprenorphine with CNS depressants generally. When the combination of buprenorphine and other CNS depressants cannot be avoided, it is important to monitor patients more closely for adverse events such as excessive sedation and respiratory depression.

## Antagonist Maintenance

Naltrexone is the prototypical opioid antagonist used in abstinence therapy, blocking the effects of heroin and other opioids through competitive receptor inhibition. Naltrexone has no opioid agonist effects and is a competitive opioid antagonist. It is orally effective and can block opioid effects for 24 hours when administered as a single daily oral dose of 50 mg; oral doses of 100–150 mg can block opioid effects for 48–72 hours (Lee et al. 1998). Opioid addicts in the US and most western countries have not favored naltrexone despite a favorable adverse event profile (nausea is typically the most common side effect), though interest and adherence have been much better in Russia (Krupitsky et al. 2006b) and in persons under significant legal pressure to stop opioid use (Cornish et al. 1998). Possible reasons for nonadherence and lack of interest are that unlike opioid agonists and partial agonists, it produces no positive, reinforcing effects nor does it attenuate the protracted opioid abstinence syndrome that can persist for several weeks after detoxification. Furthermore, it may precipitate an opioid withdrawal syndrome if

used too soon after opioid use stops, an effect that can be minimized by administering a naloxone challenge prior to giving the first dose of naltrexone.

While there is an extensive literature spanning more than 35 years on naltrexone treatment, work continues on increasing adherence and improving outcomes. One approach has been to combine it with family therapy and contingency management, which have improved adherence somewhat (Fals-Stewart and O'Farrell 2003), and contributed to the positive findings from studies in Russia where family members helped encourage adherence (Krupitsky et al. 2006b). Another has been to develop depot forms that block opioid effects for 14–28 days or longer. The only depot currently approved in the US is Vivitrol (http://www.vivitrol.com), which is injected once a month and approved for treatment of alcohol dependence. A naltrexone implant that blocks opioid effects for 6 months has been developed by Australian researchers and used with apparent success in several thousand opioid-dependent patients, though it has not completed the steps necessary for approval (http://www.staplefordcentre.co.uk/naltrexone-implants.htm). A Russian company has also developed an implant that blocks opioid effects for 2 months and is approved for use in that country (prodetoxon@mail.ru). These depot forms provide more time for patients to overcome their typical ambivalence about stopping opioid use and could result in more long-term success than has been the case with oral naltrexone. Another variant on antagonist treatment is nalmefene, an orally effective but somewhat longer acting (about 48 hours at dosages of 50–100 mg/day) opioid antagonist that has been effective for alcohol treatment (Mason et al. 1994) and shows promise as an alternative to naltrexone for opioid dependence (Jones et al. 2000).

## Psychosocial/Behavioral Treatments

Recent research has called attention to the fact that, as in other substance use disorders, most patients with opioid dependence and abuse are ambivalent about stopping use, as mentioned above (Miller and Rollnick 1991, Rollnick et al. 1999). This ambivalence presents a challenge as it contributes to varying levels of motivation to enter and remain in treatment, to early dropout, and to partial or (in some cases) nontreatment response. Studies have emphasized that clinicians must be aware of this "normal" ambivalence, and make reasonable efforts to resolve it in favor of sustained treatment participation and cessation of use (Rollnick et al. 1999). Suggestions that have been made regarding initial steps to maximize the chances for engagement in treatment and cessation of drug use include avoiding unnecessary delays in accessing treatment, expressing a hopeful and nonjudgmental attitude, performing a comprehensive evaluation, and developing a treatment plan that is responsive to patients' self-identified goals (Miller and Rollnick 1991).

In addition to challenges related to ambivalence, patients often have serious problems with nonopioid substance abuse and/or with medical, psychiatric, legal, employment, and family/social issues that preexist or result from the addiction. Research has found that addressing these additional problems can be helpful (McLellan et al. 1993), particularly if done on site (Umbricht-Schneiter et al. 1994); however, these approaches require coordination of services from multiple disciplines and are not always feasible.

### Individual Drug Counseling

The most common type of psychosocial treatment in opioid agonist maintenance is individual drug counseling. Counselors are typically persons at the masters or bachelors level who deliver a behaviorally focused treatment aimed to identify specific problems, help the patient access services that may not be provided in the clinic (e.g., medical, psychiatric, legal, family/social), stop substance use, reduce HIV risk, and improve overall adjustment. Functions that counselors perform include monitoring methadone doses and requesting changes when needed, reviewing urine test results, responding to requests for take-home medication, assisting with family problems, responding to crises, writing letters for court or social welfare agencies, recommending inpatient treatment when necessary, and providing support and encouragement for a drug-free lifestyle.

Counseling usually addresses both opioid and nonopioid use and their associated behaviors. Although nicotine (tobacco) use is not always included, the increased emphasis on adverse health effects of smoking has resulted in more attention to stop smoking at all levels within substance abuse treatment programs, including drug counseling. Counselors and patients typically have weekly, 30- to 60-minute sessions during the first weeks or months of treatment with reductions in frequency to biweekly or monthly depending on progress. The frequency of counseling can vary widely depending on the severity of the patient's problems, clinic requirements, and counselor workload.

The importance of regular counseling was clearly demonstrated in a study by McLellan et al. (1993) in which patients were randomly assigned to minimal counseling (one 5- to 10-minute session per month), standard counseling (one 45-minute session per week), or enhanced counseling (standard plus on-site referral to psychiatric, medical, and family/social services). Results showed a dose–response relationship with the minimal condition doing significantly worse than standard, and enhanced counseling doing the best overall; however, about 30% of patients did well with only minimal counseling. This study clearly demonstrated the positive benefits achieved by drug counseling and showed that, for most patients, counseling is necessary to maximize the benefits of agonist maintenance.

Though most counseling is individual, some programs use group therapy exclusively and others do not use it at all. Most agonist programs that use groups have them only for patients with focal problems such as HIV disease, PTSD, homelessness, or problems with grief following loss of close personal relationships. Many programs encourage patients to participate in self-help groups but advise them to select a group that accepts persons who are on agonist maintenance. Some programs have self-help groups that meet on site. Counselors, like psychotherapists, can vary widely in the results they achieve (McLellan et al. 1988). This variability seems more related to the ability to form a positive, helping relationship than to specific techniques (Luborsky et al. 1985).

Contingency management techniques are always included in drug counseling, if for nothing else but to fulfill regulations about requiring progress in treatment as a condition of providing take-home doses, and studies have shown that such contingencies can be helpful. For example, an opportunity to receive take-home doses in return for

drug-free urine tests is a powerful and practical motivator for many patients (Iguchi et al. 1996). More flexibility in dispensing take-homes for positive behavior could be an additionally useful result of the regulatory reforms that were described earlier. Another contingency that is easily applicable and which some programs have used with positive results is requiring a negative alcohol breath test prior to dispensing the daily dose of methadone.

Though counseling and other services are effective enhancements of agonist treatment, compliance is often an issue and clinics vary in the way they respond to this problem. Some remind patients of appointments, others do not permit patients to be medicated unless they keep appointments, and others suspend patients who miss appointments. For noncompliant patients, a powerful contingency is requiring certain behaviors for patients to remain on the program, a procedure that is often formalized in a "treatment contract." Here, the patient is given the option of stopping heroin and other drug use, keeping regular appointments, looking for work, or correcting other behaviors that need improvement as a condition for remaining in treatment. Patients who fail are administratively detoxified, suspended for months to years, and referred to another program, although the referrals are not always successful.

The long-term effects of this type of contingency management have not been well studied. For example, relatively little is known about negative effects on patients who might have improved with methadone and counseling, but not to the degree required by the contingency, and are subsequently discharged for failing a contract. A study done in Philadelphia (Zanis and Woody 1998) found that among 110 patients who were administratively discharged or dropped out of a Veterans Affairs maintenance program, 8.2% (9/110) died within the following year as compared to only 1% (4/397) who remained in treatment. Among the 43 patients (from the 110) who were discharged for failing a treatment contract, 5 (11.6%) died within a year. None of these five were in treatment at the time of death and all died as a result of overdoses. No overdose deaths occurred among patients remaining in treatment and, interestingly, there were no deaths in those who were suspended for violating program rules (mainly drug dealing or giving a false urine specimen). These results have been replicated in a later study (Woody et al. 2007) and are consistent with other studies showing higher rates of mortality among opioid-dependent individuals who are not in methadone treatment as compared to those who are on methadone. A representative of these studies was done in New South Wales, Australia, where it was found that only 3% of the 953 heroin-related fatalities occurred among patients receiving methadone maintenance (Darke et al. 1996). These data emphasize the dangers of suspension from maintenance treatment if the alternative is no treatment. These data, when considered along with studies showing a protective effect of maintenance on acquiring HIV infection (Metzger et al. 1998), have made some clinicians increasingly hesitant to suspend patients from maintenance treatment for positive urine test results alone. This caution may be especially relevant in environments where the potency of heroin is high and the risk of serious adverse events among those who are suspended is substantial unless they are enrolled in an alternative and meaningful treatment.

### Therapeutic Communities (TCs)

These programs are another approach that has been useful for treating persons with opioid dependence, especially those with a long history of addiction and a strong motivation to become drug free, either as a result of their own wish to recover, or from external pressures such as being given the choice of entering a TC or being incarcerated for a drug-related crime. These programs are very selective, self-governing, and long term (6–18 months), and take place in residential settings where patients share responsibilities for maintaining the milieu (cleaning, cooking, and leading group therapy). Confrontation of denial and behaviors such as lying and "conning," combined with group support for healthy, positive change, is used to restructure character and the addictive lifestyle. Medications such as methadone or naltrexone are rarely used, though many programs have adopted buprenorphine for detoxification. Medications for psychiatric or medical conditions are usually available after careful screening and evaluation. Many TCs have large numbers of individuals who have been referred by the criminal justice system including some who have not responded well to agonist maintenance on repeated occasions. Though dropout rates are high, studies have shown that over 80% of individuals who complete TCs have a sustained remission and demonstrate significant improvement in psychiatric symptoms, employment, and criminal behavior (Inciardi et al. 1997, DeLeon 1999).

## Addressing Comorbidity

Patients seeking treatment for opioid dependence are typically using one or more other substances (cocaine, alcohol, benzodiazepines, amphetamines, marijuana, nicotine), and have additional problems in the psychiatric, medical, family/social, employment, or legal areas. In fact, it is rare to find a person with only opioid dependence and no other substance use, or without a psychiatric, medical, or family/social problem. The presence of these problems, perhaps with the exception of nicotine dependence, tends to magnify the severity of the opioid dependence and makes the patient even more difficult to treat. An example of successful treatment of a difficult patient is given in Clinical Vignette 2.

Clinical Vignette 2

A 42-year-old male presented for treatment of opioid dependence; this was his sixth episode of methadone maintenance. The patient had a long history of alcoholism that interfered with treatment in the past and had begun using cocaine regularly. The patient had done fairly well in the past on methadone as far as illicit opioid use was concerned, but clinic attendance and his ability to comply with clinic rules, especially regarding take-home doses, had been severely compromised by alcohol abuse. The patient would typically remain in treatment for about a year, then become angry over his inability to obtain take-home doses due to ongoing positive breathalyzer readings, and drop out of treatment; relapse to opioid use always immediately followed. During previous treatment episodes, the patient had frequently been offered inpatient detoxification for alcoholism but always refused because (1) "alcohol was not his problem, heroin was the problem" and (2) he could not take time off work. When the patient presented for

treatment this time, he had severe social stressors; was unemployed (secondary to his alcohol problems) and living with his parents, who were threatening to put him out because of drug use.

He was told that this time, methadone would not be offered unless he first entered the hospital. After some discussion, he agreed that as part of his treatment plan he would first enter the hospital for 21–28 days of treatment including alcohol detoxification and stabilization on methadone and then be discharged to maintenance therapy. This approach worked. After inpatient discharge, the patient kept regular counseling appointments, continued to attend self-help meetings to which he had been introduced while on the inpatient unit, "requested" daily breathalyzer testing, and turned down an offer to return to his job in the liquor store. Over the past 3 years, his liver function tests returned to normal levels, he was stable on 65 mg of methadone/day with urine tests negative for opioids, although occasionally his urine was positive for cocaine.

## Psychiatric

Among the psychiatric disorders seen in persons with opioid dependence, antisocial personality is one of the most common (First and Pincus 2000). Diagnostic studies of persons with opioid dependence have typically found rates of antisocial personality disorder ranging from 20 to 50%, as compared to less than 5% in the general population. PTSD is also seen with increased frequency.

Opioid-dependent persons are especially at risk for the development of brief depressive symptoms, and for episodes of mild to moderate depression that meet symptomatic and duration criteria for major depression or dysthymia. These syndromes represent both substance-induced mood disorders as well as independent depressive illnesses. Brief periods of depression are especially common during chronic intoxication or withdrawal, or in association with psychosocial stressors that are related to the dependence. Insomnia is common, especially during withdrawal; sexual dysfunction, especially impotence, is common during intoxication. Delirium or brief, psychotic-like symptoms are occasionally seen during opioid intoxication (First and Pincus 2000).

The data on psychiatric comorbidity among opioid addicts and its negative effect on outcome (McLellan et al. 1983) have stimulated research on the effect of combining psychiatric and substance abuse treatment. Among these have been studies showing that tricyclic antidepressants can be useful for chronically depressed opioid-dependent persons who are treated with methadone maintenance (Nunes et al. 1998). Two other studies have shown that professional psychotherapy can be useful for psychiatrically impaired, methadone-maintained opioid addicts (Woody et al. 1984, 1999), although similar results were not found in a related study done in a different setting (Rounsaville et al. 1983). The main result in most pharmacotherapy and psychotherapy studies with methadone-maintained addicts has usually been a reduction in psychiatric symptoms such as depression, and a less consistent effect on reductions in substance use (Nunes et al. 1998, Woody et al. 1985, 1995).

Less than 5% of persons with opioid dependence have psychotic disorders such as bipolar illness or schizophrenia; however, these patients can present special problems since programs typically have few psychiatric staff. As a result, these patients are sometimes excluded from methadone treatment because they cannot be effectively managed within the constraints of the available resources. Others are treated with methadone, counseling, and the same medications used for nonaddicted patients with similar disorders. Though studies evaluating the outcome of combining opioid agonist treatment with antipsychotic or antimanic medications have not been done, there is little controversy that these medications are useful for persons with opioid dependence and psychotic disorders.

Women with opioid dependence can present special challenges because many have been sexually abused as children, have other psychiatric disorders, and are involved in difficult family/social situations (Blume 1999). Abusive relationships with addicted males are common, sometimes characterized by situations in which the male exerts control by providing drugs. These complex psychiatric and relationship issues have emphasized the need for comprehensive psychosocial services that include psychiatric assessment and treatment, and access to other medical, family, and social services. A promising treatment approach entitled "Seeking Safety" has been developed to address problems of substance abuse and PTSD (http://www.seekingsafety.org), and is being tested in a randomized trial in the National Institute on Drug Abuse Clinical Trials Network at the time this writing.

## Medical

Medical comorbidity is a major problem among persons with opioid dependence; HIV infection, AIDS, and hepatitis B and C have become some of the most serious and common problems, especially hepatitis C. Sharing injection equipment including "cookers" and rinse water, or engaging in high-risk sexual behaviors are the main routes of infection. Sexual transmission appears to be a more common route of HIV transmission among females than males because HIV is spread more readily from males to females than from females to males. Females who are intravenous drug users and engage in prostitution or other forms of high-risk sex are at extremely high risk for HIV infection (Blume 1999). Cocaine use has been found to be a significant risk factor as a single drug of abuse or when used in combination with heroin or other opioids (Booth et al. 2000).

After rising rapidly in the late 1970s and early 1980s, the incidence of new HIV infections among intravenous drug users, of whom opioid-dependent individuals constitute a large proportion, has decreased (Seage et al. 2001). However, as a result of high levels of needle sharing and other risky behavior in the early phases of the epidemic, HIV infection rates are as high as 60% in some areas of the US. Due to the long incubation period prior to the development of AIDS, it is expected that future years will continue to see high levels of morbidity and mortality associated with HIV, although the advent of new pharmacotherapies for HIV has extended many lives.

Studies have identified several important interactions between methadone and drugs to treat HIV. However, information is not complete and more studies are needed to map out the full extent of these interactions. One important interaction is that methadone increases plasma levels of zidovudine. The associated symptoms resemble methadone withdrawal and there have been instances in which

methadone doses have been increased in response to complaints of withdrawal, with the dose increases compounding the problem. Another important interaction involves decreased methadone levels secondary to nevirapine that may result in mild to moderate withdrawal. This interaction can be important if the patient is taken off either of these two drugs while on methadone, since the result may be a sudden rise in methadone levels with signs and symptoms of over medication (Altice et al. 1999, Otero et al. 1999).

As mentioned earlier, opioid-related mortality is high; studies have found annual death rates among opioid-dependent individuals of 10 per 1,000 or greater, which is substantially higher than demographically matched samples in the general population (Gronbladh et al. 1990). Common causes of death are overdose, accidents, injuries, and medical complications such as cellulitis, hepatitis, AIDS, tuberculosis, and endocarditis. The cocaine and alcohol dependence that is often seen among opioid-dependent persons contributes to cirrhosis, cardiomyopathy, myocardial infarction, and cardiac arrhythmias.

Tuberculosis is a particularly serious problem among intravenous drug users, especially heroin addicts. In most cases, infection is asymptomatic and evident only by the presence of a positive tuberculin skin test. However, many cases of active tuberculosis have been found, especially among those with HIV.

Other medical complications of heroin dependence are seen in children born to opioid-dependent women. Perhaps the most serious is premature delivery and low birthweight, a problem that can be reduced if the mother is on methadone maintenance and receiving prenatal care (Finnegan 1991). Another is physiological dependence on opioids, seen in about half the infants born to women maintained on methadone or dependent on heroin or other opioids. Effective treatments for neonatal withdrawal are available and long-term adverse effects of opioid withdrawal have not been demonstrated. Buprenorphine has theoretical advantages to methadone for treating neonatal withdrawal because of its partial agonist effects and relatively mild withdrawal syndrome, though it is not approved for that indication. Adverse neonatal effects associated with buprenorphine have not been observed when it has been used, and studies are currently underway to determine its safety and efficacy for use in pregnancy and neonatal withdrawal.

A recent study found that methadone is present in the breast milk of women maintained on doses as high as 180 mg but that the concentration is very low and no adverse effects were observed in the infants (McCarthy and Posey 2000). HIV infection is seen in about one-third of infants born to HIV-positive mothers, but can be reduced to about 10% if HIV-positive pregnant women are given zidovudine prior to delivery (Connor et al. 1994). HIV can also be transmitted by breast feeding, and thus formula is recommended for HIV-positive mothers with the exception of countries where it is unavailable or unaffordable. Thorough washing of infants born to HIV-infected mothers immediately after delivery also appears to reduce the incidence of HIV infection.

### Integrated Treatment

The comorbidity data have led to research that has demonstrated positive effects from integrating psychiatric and medical care within agonist and other substance abuse treatment programs, so-called one-stop shopping (Kessler et al. 1996). Clinical experience and National Institute on Drug Abuse demonstration projects have shown that integration of services can be done with very positive results on adherence to recommended medical treatments and evaluations (Umbricht-Schneiter et al. 1994). Related to this line of research are studies that have shown improved compliance with directly observed antituberculosis pharmacotherapy (Chaulk et al. 1995). These findings have important implications for tuberculosis control in methadone programs since intravenous drug users are at high risk for tuberculosis infection and because maintenance programs are settings where directly observed therapy can be easily applied. Similar principles apply to administration of psychotropic medication in noncompliant patients with schizophrenia or other major Axis I disorders.

## Harm Reduction

Harm reduction is concerned with minimizing negative consequences of addiction. As such, a focus is placed on the consequences of use and its attendant behaviors (Marlatt 1996). Examples of harm reduction include needle exchange programs, efforts directed at reducing drug-use-associated behaviors that may result in the transmission of HIV, and making changes in policies (including increasing treatment availability) that reduce heroin use and the criminal behavior associated with drug procurement. Harm reduction refers not only to reducing harm to the individual addict, but also to family, friends, and to society generally. Other terms sometimes used synonymously with harm reduction include harm minimization, risk reduction, and risk minimization (Riley et al. 1999).

A number of authors have identified the limitations of harm reduction when it is used as a sole strategy to combat the adverse effects of addiction. For example, Reuter and Caulkins (1995) point out the benefit of balancing drug use reduction and harm reduction components into a single framework, since reducing either component is likely to lower the chances for harm. Roche et al. (1997) have proposed a model for an integrated addiction treatment strategy that incorporates harm reduction and use reduction with abstinence and nonuse, in addition to other critical elements such as factors related to culture and gender. Additionally, MacCoun (1998) has provided a template for integrating harm reduction with prevalence reduction (discouraging the engagement in drug use) and quantity reduction (encouraging the reduction in frequency or extent of drug use).

With regard to opioids, much of the health-related harm from their improper or illicit use is secondary to elements other than the substances themselves (Kalant 1999). Sequelae from unhygienic methods of administration and poor injection technique are typically more serious than the constipation or other side effects of the drugs themselves, acute overdoses notwithstanding. At current levels of use, greater harm in the overall population of most countries is expected to result from the use of alcohol and tobacco rather than from opioids. With regard to opioid addiction treatment, maintenance on methadone or buprenorphine may be considered harm reduction measures. Both have the potential to reduce morbidity, mortality, and crime associated with drug use and the addict lifestyle and in this sense their outcomes

on target symptoms of opioid dependence bear a resemblance to the results of other medical therapies that control but do not cure the underlying problem, such as treatments used for hypertension, diabetes, or asthma.

Needle/syringe exchange has been one of the most controversial strategies for harm reduction. Research indicates that these programs may have beneficial effects in a number of areas, including a reduction in the spread of blood-borne infections such as hepatitis and HIV, and acting as a conduit to more comprehensive drug-abuse treatment services (Normand et al. 1995). In one study (Bluthenthal et al. 2000), the initiation and continuation of participation in a syringe exchange program by high-risk injection drug users was independently associated with a cessation of syringe sharing. In another (Strathdee et al. 1999), participation in a needle exchange program was associated with individuals entering detoxification treatment for both HIV-infected and noninfected groups. Not all findings have been positive, however. In a study designed to assess the association between risk behaviors and HIV infection among injection drug users, risk elevations for HIV associated with needle exchange programs were substantial and consistent despite adjustment for confounding factors (Bruneau et al. 1997). However, an examination of potential bias in nonrandomized comparisons (Hagan et al. 2000) suggested that injection drug users participating in needle exchange programs at a given point in time might include a high proportion of individuals whose pattern of drug use puts them at greater risk for blood-borne viral infections. Further, a prospective cohort study found no evidence of a causal association between needle exchange program participation and transmission of HIV (Schechter et al. 1999).

Harm reduction related to psychoactive substance abuse has gone through a number of stages. The current phase has been described as the development of an integrated public health perspective for all drugs in which a multifaceted, strategic approach is taken (Erickson 1999). Some of the most recent approaches have been the studies of daily, observed heroin administration for addicts who are unwilling to engage in the existing treatments or who have continued regular heroin use while on methadone maintenance. The first of these studies was done in Switzerland, followed by the Netherlands and Germany. Results have been positive (Blanken et al. 2005) and similar studies are now being considered or implemented in other countries. The direction of this approach will be guided, in part, by whether biases against a harm reduction philosophy can be overcome by those who see it as synonymous with acceptance of drug abuse or legalization, and how harm reduction objectives relate to an overall strategy to improve public health.

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CHAPTER

# 64 Substance Abuse: Sedative, Hypnotic, or Anxiolytic Use Disorders

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## Sedative, Hypnotic, or Anxiolytic Intoxication

## Introduction

Sedative–hypnotics include a chemically diverse group of medications primarily prescribed for treatment of anxiety, panic disorders, sleep disturbances and seizure disorders. They may be misused and their use can result in development of a substance use disorder abuse or dependence with physiological dependence. Inadequately treated, withdrawal of sedative–hypnotics may be life-threatening.

Considerations of sedative–hypnotic use disorders should reflect a sensible balance between their medical uses, and abuse and dependence. A discussion of the broad range of medical applications of sedative–hypnotics is beyond the scope of this chapter. This chapter focuses on adverse consequences of sedative–hypnotic use and the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) criteria of abuse and dependence.

Alcohol could be viewed as a sedative–hypnotic; however, alcohol, because of its widespread use and different cultural role in society is generally considered separately. Buspirone, although marketed for the treatment of anxiety, has a pharmacological profile sufficiently different that it is not usually included among the sedative–hypnotics. Antidepressant, anticonvulsants, and antihistamines have clinically useful antianxiety properties in some situations, but are not discussed here because they are not generally associated with abuse and dependence. Likewise Ramelteon, a hypnotic whose mechanism of action involves the melatoninergic system (Owen 2006), does not appear to be associated with abuse and dependence. The medications traditionally included in the category of sedative–hypnotics are listed in Table 64–1.

With the exception of the benzodiazepines and newer hypnotics (e.g., zaleplon, zopiclone, eszopiclone, and zolpidem), overdose with sedative–hypnotics can be lethal. Benzodiazepines and the newer hypnotics are rarely lethal if taken alone; in combination with alcohol or other drugs, however, they can be lethal.

When the benzodiazepines were introduced into clinical medicine in the early 1960s, their lack of lethality in overdose led physicians to believe that they were without harmful effects. Over time, it was recognized that the benzodiazepines could produce severe physiological dependence (American Psychiatric Association Task Force on Benzodiazepine Dependency 1990) and could be drugs of abuse. Nonetheless, their medical utility in treatment of disabling anxiety, episodic sleep disturbances, and seizures has made them indispensable to medical practice. The utility of this class of medication has led to the development of newer sedative–hypnotic drugs that are as clinically effective as benzodiazepines, but with a reduced dependence and tolerance liability.

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**Table 64–1 Sedative–Hypnotic Medications**

| Generic Name | Trade Names | Common Therapeutic Use | Therapeutic Dose Range (mg/d) |
|---|---|---|---|
| *Barbiturates* | | | |
| Amobarbital | Amytal | Sedative | 50–150 |
| Butabarbital | Butisol | Sedative | 45–120 |
| Butalbital | Fiorinal, Sedapap | Sedative/ analgesic | 100–300 |
| Pentobarbital | Nembutal | Hypnotic | 50–100 |
| Secobarbital | Seconal | Hypnotic | 50–100 |
| *Benzodiazepines* | | | |
| Alprazolam | Xanax | Antianxiety | 0.75–6 |
| Chlordiazepoxide | Librium | Antianxiety | 15–100 |
| Clonazepam | Klonopin | Anticonvulsant | 0.5–4 |
| Clorazepate | Tranxene | Antianxiety | 15–60 |
| Diazepam | Valium | Antianxiety | 5–40 |
| Estazolam | ProSom | Hypnotic | 1–2 |
| Flunitrazepam* | Rohypnol | Hypnotic | 1–2 |
| Flurazepam | Dalmane | Hypnotic | 15–30 |
| Halazepam | Paxipam | Antianxiety | 60–160 |
| Lorazepam | Ativan | Antianxiety | 1–16 |
| Midazolam | Versed | Anesthesia | – |
| Oxazepam | Serax | Antianxiety | 10–120 |
| Prazepam | Centrax | Antianxiety | 20–60 |
| Quazepam | Doral | Hypnotic | 15 |
| Temazepam | Restoril | Hypnotic | 7.5–30 |
| Triazolam | Halcion | Hypnotic | 0.125–0.5 |
| *Nonbenzodiazepine Hypnotics* | | | |
| Eszopiclone | Lunesta | Hypnotic | 1–3 |
| Zaleplon | Sonata, (Stilnox) | Hypnotic | 5–20 |
| Zolpidem | Ambien | Hypnotic | 5–10 |
| Zopiclone* | Imovane, Zimovane | Hypnotic | 3.75–7.5 |

*Flunitrazepam and zopiclone are not marketed in the US.

## Sedative–Hypnotic Related Disorders

Drug abuse, misuse, and addiction are deeply rooted in social values and attitudes. These social values in mainstream culture are reflected in drug abuse policy and drug control laws. For example, moderate use of alcohol is widely sanctioned for adults, but public intoxication or driving with an alcohol blood level above 80–100 mg/dL is not.

The term "misuse" is commonly applied to prescription sedative–hypnotics. The DSM-IV-TR does not provide criteria for misuse as it does for abuse and dependence. When medications are taken in higher doses, more frequently or for a longer period than prescribed, or taken by someone other than the person for whom the medication was prescribed, the behavior is generally considered misuse of the medication.

DSM-IV-TR defines abuse and dependence in terms of behavioral and physiological consequences to the person taking the medication. The criteria for abuse and dependence are intended to apply as uniformly as possible across classes of drugs, and the criteria do not distinguish the source of the medication or the intended purpose for which it was originally taken. Further, when most people, including physicians speak of drug dependence, they are referring to physical dependence, as characterized by aversive physiological consequences and symptoms that arise during withdrawal. DSM-IV-TR uses the term dependence to denote a more severe form of substance use disorder than abuse, and it uses specifiers[1] "with physiological dependence" or "without physiological dependence" to note the presence or absence of physical dependence. Physiological dependence is not required for a diagnosis of drug dependence. A diagnosis of substance dependence is made when a patient has dysfunctional behaviors that are a result of the drug use, and demonstrates an inability to modify or curb their use despite the often negative consequences of these behaviors.

Establishing whether or not the dysfunctional behavior is the "result" of drug use is extremely important. The patient may need to be observed medication-free to determine whether dysfunction is "caused" by drug use. The patient, the patient's family members and the treating psychiatrist may disagree about what is causing symptoms or behavioral dysfunction. Likewise, the underlying motivation for "drug-seeking" behavior may vary. For example, a patient whose panic attacks are ameliorated by a medication may exhibit what may be interpreted as drug-seeking behavior if access to the medication is threatened.

## Sedative–Hypnotics and GABA Receptors

GABA is the major inhibitory neurotransmitter in the central nervous system (CNS) mediating inhibition at three different classes of receptors designated as $GABA_A$, $GABA_B$, and $GABA_C$. (Loh and Ball 2003, Johnston et al. 2003). The $GABA_A$ receptor, a ligand-gated chloride ion channel or ionophore, contain binding sites for neurosteroids, benzodiazepines and barbiturates (Smith and Olsen 1995).

The opening or closing of the chloride channels affect the electrical polarization of a cell. Opening the chloride channel increases the inflow of chloride ions and increases the negative potential on the surface of the cell, thereby inhibiting firing of the cell.

The benzodiazepine receptor is allosterically coupled to the $GABA_A$ receptor: occupation of the benzodiazepine receptor by benzodiazepine agonists enhances the efficacy of GABA at the $GABA_A$ receptor. Likewise occupation of the $GABA_A$ receptor by GABA increases the affinity of benzodiazepines for the benzodiazepine receptor (Klein et al. 1994).

Substances that bind to the benzodiazepine site and facilitate the opening of chloride channels are designated agonists, those that decrease the chloride channel opening are inverse agonists, and those which occupy the site with no effect are antagonist. $GABA_A$ receptor composition can

[1]DSM-IV-TR page 195.

undergo significant changes in response to neurosteroids, barbiturates, benzodiazepines and alcohol, and to withdrawal of these substrates.

The benzodiazepine receptors, which are of primary concern here, are comprised of subunits, designated α, β, γ, and δ. Receptors have different ratios of subunits and different subunit composition designated, for example, $\alpha_1$ or $\alpha_4$ etc. These differences have physiological significance, for example, $\alpha_1$ subunits confer benzodiazepine sensitivity; $\alpha_4$ and $\alpha_6$ subunits confer benzodiazepine insensitivity (Smith 2001).

Chronic administration of and withdrawal from benzodiazepines appears to alter gene expression and function of the $GABA_A$ receptor, in vitro studies have found that benzodiazepine withdrawal can upregulate $\alpha_4$ subunits and downregulate $\alpha_1$ subunits making the $GABA_A$ receptors less responsive to benzodiazepine receptor agonists (Follesa et al. 2001). This may explain in part why over time benzodiazepines appear to become less effective in controlling symptoms in some patients, which gives them an impetus to increase dosage (Lader 1994). A similar shift towards an increase in $\alpha_4$ containing $GABA_A$ receptors and decreased benzodiazepine sensitivity has also been characterized as a component of ethanol withdrawal (Ma et al. 2004).

Hypnotic drugs such as zolpidem, zaleplon, eszopiclone, and zopiclone also bind to the benzodiazepine site on $GABA_A$ receptors.

## Abuse and Abuse Potential

Unlike drugs of abuse (e.g., methamphetamine or heroin) that are manufactured in clandestine laboratories and distributed through the street-drug black markets, sedative–hypnotics are exclusively manufactured by pharmaceutical companies. Sedative–hypnotics abused by addicts are acquired by Internet purchase, the drug black market, by robbery, or treatment subterfuge from physicians and pharmacies. Drug dependence may arise as an inadvertent consequence of medical treatment (iatrogenic) or through patient's self-abuse of sedative–hypnotics. The prevalence of abuse of a particular sedative–hypnotic is to some extent a reflection of its accessibility through medical channels.

The usual data sources for monitoring the prevalence of drug use in the US (e.g., the National Household Survey of Drug Use) are not valid measures of dependence. The Drug Abuse Warning Network (DAWN), which measures mentions of drugs occurring in emergency rooms, is limited because the mentions of drugs can be confounded by appropriate medical use.

The term "abuse" can have different meanings depending on its context of use. DSM-IV-TR provides specific behavioral criteria for diagnosis of "abuse" of a specified drug, abuse can also mean any nonmedical use, or use considered outside accepted medical practice. Recreational abuse of hypnotics is their use to produce intoxication or "a high" (Griffiths and Johnson 2005).

Some authors distinguish "recreational abuse" from "chronic quasi-therapeutic abuse," which is characterized by long-term use of a drug that is inconsistent with medical practice or against medical advice (Griffiths and Johnson 2005).

Until recently, studies of hypnotic efficacy were usually structured in terms of a few weeks. In clinical practice, many patients used them for months to years. Practice standards generally specify that they should be used for short-term treatment of insomnia. A 6-month placebo-controlled study of eszopiclone (Lunesta) (Krystal et al. 2003), discussed later in more detail, provided evidence that tolerance to the hypnotic effects did not develop.

Most people do not find the subjective effects of sedative–hypnotics pleasant or appealing beyond their therapeutic effects (e.g., relief of anxiety or facilitation of sleep). Many sedative–hypnotic abusers, on the other hand, have a subjectively different response to sedative–hypnotics. Addict's qualitative difference in subjective responses to medications is an important reason why medications that are safe and efficacious for nonaddicts cannot be safely prescribed for addicts. In addition, addicts may take doses of medications above recommended dosages, take them by injection or means other than prescribed (e.g., dissolving tablets and injecting them, crushing tablets and snorting them), or take them in combination with other prescription medications or street drugs such as heroin or cocaine, that put them at risk for adverse consequences.

Most individuals with sedative–hypnotic dependence are patients whose dependence evolved during a course of medical treatment, drug abusers (including alcohol) who also use sedative–hypnotics in addition to other drugs, or drug abusers who use sedative–hypnotics to self-medicate adverse effects of other drugs of abuse such as cocaine or methamphetamine.

The sedative–hypnotics discussed in this chapter all have some abuse potential, but there are differences in abuse potential between them. Some of the differences in abuse potential are mediated by their pharmacology, but often, access, current fashions, and availability all contribute.

Patients receiving methadone maintenance use benzodiazepines to "boost" (enhance) subjective effects of methadone. Some alcoholic patients use benzodiazepines either in combination with alcohol or as a second-choice intoxicant, if alcohol is unavailable. Fat-soluble benzodiazepines that enter the CNS quickly are usually the benzodiazepines preferred by addicts.

Addicts whose urine is being monitored for benzodiazepines prefer benzodiazepines with high milligram potency, such as alprazolam or clonazepam. These benzodiazepines are excreted in urine in such small amounts that they are often not detected in drug screens.

### Patterns of Abuse

Some sedative–hypnotics, such as the short-acting barbiturates, are primary drugs of abuse—that is, they are injected for the "rush" or are taken orally to produce a state of disinhibition similar to that achieved with alcohol. Oral methaqualone was commonly used as a recreational drug. Most abuse of benzodiazepines is in the context of a poly-drug use pattern in which they are taken in combination with other primary intoxicants, such as alcohol or heroin, to intensify the desired subjective effects.

Drug addicts may also use sedative–hypnotics to self-medicate withdrawal of drugs such as heroin. When the avowed intent is to stop the use of drugs such as heroin,

physicians may be lured into thinking that addicts' self-administration of sedative–hypnotics is not "abuse." While on occasion this may be the case, often it is not. Addicts' episodic attempts to stop using heroin by self-medicating opiate withdrawal symptoms with sedative–hypnotics without entering drug abuse treatment rarely results in opiate abstinence and may result in the secondary development of sedative–hypnotic dependence.

Addicts may also use sedative–hypnotics to reduce unpleasant side effects of stimulants, e.g., cocaine or methamphetamine. Impairment of judgment and memory produced by the sedative–hypnotic in combination with wakefulness of a stimulant may result in unpredictable behavior.

## Barbiturates

During the late 1960s and early 1970s, the short-acting barbiturates, secobarbital and pentobarbital, were common drugs of abuse. Addicts dissolved the tablets or the contents of capsules in water and injected the solution. The desired effect was the "rush," a dreamy, floating feeling lasting a few minutes after the injection. After the rush, the addict was intoxicated, but the primary appeal towards injection was the rush. The intoxication is not qualitatively different from that produced by oral ingestion of a short-acting barbiturate.

Injection of a barbiturate is associated with the usual infectious risk of injecting street drugs, but the barbiturates are particularly pernicious if inadvertently injected into an artery or if the solution is injected or leaked from a vein or artery into tissue surrounding the vessel. Barbiturates are irritating to tissue, and the affected tissue becomes indurated and may abscess. In addition, barbiturate solution injected into an artery produces intense vasoconstriction and blockage of the arterioles, resulting in gangrene of areas supplied by the artery.

## Methaqualone

Methaqualone (Quaalude) was removed from the US market in 1984 because of its abuse. In many countries it was marketed under the brand name of Mandrax, a formulation of methaqualone (250 mg) and diphenyldramine hydrochloride (25 mg). Although methaqualone and its isomers were removed from the legal market in South Africa in 1971, it remained a popular drug of abuse among South African drug abusers at least through 2002.[2] Detailed instructions for its synthesis are available on the Internet.[3]

## Benzodiazepines

For treatment of anxiety and insomnia, the benzodiazepines have largely supplanted the older sedative–hypnotics. The benzodiazepines have a major advantage over the older compounds. In an overdose, the older sedative–hypnotics are lethal at 10–15 times the usual therapeutic doses. Benzodiazepines, if taken alone, have a therapeutic ratio exceeding 100. In combination with alcohol or other drugs, the benzodiazepines may contribute to the lethality, but death from a benzodiazepine alone overdose is rare. Some atavistic uses of the older compounds remain driven primarily by economic considerations and misguided attempts to reduce abuse of benzodiazepines by addicts and perceived overprescription of benzodiazepines by physicians.

Benzodiazepines are often used or misused by addicts to self-medicate opiate withdrawal, to intensify the CNS effects of methadone, or to ameliorate the adverse effects of cocaine or methamphetamine.

Flunitrazepam, a potent benzodiazepine hypnotic never marketed in the US, is widely available by prescription in many other countries in 1- or 2-mg oral dosage forms and for injection. In the mid-1990s Rohypnol achieved notoriety as the date-rape drug.[4] Because of the media attention, considerable public debate ensued and the US Congress was prompted to pass legislation increasing penalties for rape when Rohypnol or other drugs were used to facilitate it.

Flunitrazepam has many street names, including rophies, ropies, roopies, roofies, ruffes, rofinol, loops, and wheels (Calhoun et al. 1996). Tablets of Rohypnol have the name of the manufacturer Roche engraved on them and a number indicating the milligram strength (either 1 or 2). Drug abusers usually prefer the 2-mg tablets, which are often called "Roche dos" or just "Roche" (usually pronounced "row-shay"). Although flunitrazepam is similar in many respects to other benzodiazepines in abuse potential (Woods and Winger 1997), flunitrazepam is among the benzodiazepines with the highest abuse potential (Farre et al. 1996, Bond et al. 1994) and has considerable appeal among heroin addicts (Thirion et al. 2002, Salvaggio et al. 2000).

Flunitrazepam and other benzodiazepines have also been associated with deaths among opiate addicts taking buprenorphine in France (Reynaud et al. 1998, Tracqui et al. 1998). Although buprenorphine alone or benzodiazepines alone are rarely fatal, the combination appears to increase the lethality, presumably having synergistic action in suppressing respiration (Gueye et al. 2002).

## Nonbenzodiazepine Hypnotics

The nonbenzodiazepine hypnotics, zolpidem, zaleplon, eszopiclone, and zopiclone are not chemically benzodiazepines but are similar in pharmacological profile. They bind to a portion of the benzodiazepine receptor site on the $GABA_A$ receptor (Byrnes et al. 1992). They are replacing the benzodiazepines as the most commonly prescribed hypnotics and, like the benzodiazepines, are relatively nonlethal if taken alone in an overdose. These medications are sometimes referred to as a class in professional and lay publications as the "Z" drugs, or "Z" hypnotics, to distinguish

[2]South African Police Service at www.saps.gov.za/drugs/meth.htm (accessed on 4/03/2007).

[3]Methaqualone (Quaalude) synthesis at www.designer-drug.com/pte/12.162.180.114/dcd/chemistry/quaalude.html (accessed on 4/30/2007).

[4]Subsequently, GHB (gamma-hydroxybutyric acid), which has some properties of a sedative–hypnotic, was also called a "date-rape drug."

them from the prebenzodiazepine hypnotics such as the barbiturates, chloral hydrate and methaqualone. The sedative effects (including respiratory depression) are reversed by the benzodiazepine antagonist flumazenil (Wesensten et al. 1995).

Like the benzodiazepines, the medications are remarkably safe from an overdose perspective. If taken alone, they are usually not lethal even when ingested at dosages many times the usual therapeutic dose. Their abuse potential appears less than benzodiazepines such as diazepam and flunitrazepam. Sudden cessation of therapeutic doses can produce in some individuals a period of rebound insomnia and increase in dream intensity, but not seizures. Case reports of dependence usually involve marked dose escalation and withdrawal may resemble high-dose benzodiazepine withdrawal.

### *Zolpidem*

Zolpidem (Ambien), an imidazopyridine hypnotic widely prescribed for treatment of insomnia, has been available for prescription since 1993 in the US and in Europe for several years before. It is commonly offered for sale by Internet pharmacies. A new product formulation, AmbienCR®, is widely advertised in professional journals and direct to consumer on TV and lay magazines. AmbienCR is a layered tablet with part of the tablet being rapidly released for sleep induction and a sustained release portion that is claimed to sustain sleep.

Case reports of abuse suggest that some patients increase the dosage many times above what is prescribed and that zolpidem produces a withdrawal syndrome similar to that of other sedative–hypnotics (Aragona 2000). The case histories also describe significant tolerance to the sedative effects of zolpidem.

Zolpidem is rapidly absorbed and has a short half-life (2.2 hours). Its sedative effects are additive with alcohol. Like triazolam, zolpidem decreases brain metabolism of glucose (Piercey et al. 1991).

The data concerning zolpidem's ability to produce tolerance and physical dependence have shown conflicting results. In some animal models, zolpidem does not produce tolerance or physical dependence (Perrault et al. 1992). Mice were administered zolpidem or midazolam (both 30 mg/kg) by gastric intubation for 10 days. Those treated with midazolam, but not zolpidem, showed tolerance to the drug's sedative effects and a lowered seizure threshold after the drug was stopped. Further, the benzodiazepine antagonist flumazenil precipitated withdrawal in the midazolam-treated animals but not in those treated with zolpidem.

Studies of baboons suggested that zolpidem is reinforcing and that it produces tolerance and physical dependence (Griffiths et al. 1992). In a free-choice paradigm, baboons consistently self-administered zolpidem intravenously at higher rates than either the vehicle solution alone or the triazolam. After 2 weeks of zolpidem self-administration, substitution of the vehicle solution alone resulted in suppression of food-pellet intake, which the investigators interpreted as zolpidem withdrawal. Baboons trained to discriminate oral doses of either phenobarbital (10 mg/kg) or lorazepam (1.8 mg/kg) from placebo responded to zolpidem as though it were an active drug more than 80% of the time. In another experiment, animals developed tolerance to zolpidem-induced ataxia and sedation during 7 days of drug administration. The investigators concluded that the rates of self-administration of zolpidem were similar to those of pentobarbital and higher than those maintained by 11 benzodiazepines that they had studied.

Case reports of psychosis have been described from therapeutic doses of zolpidem. A report from Belgium described two cases of transient psychosis after the first dose of 10 mg of zolpidem (Ansseau et al. 1992). Neither patient had a history of drug abuse or misuse nor were they using alcohol. Both patients experienced a transient psychosis with visual hallucinations beginning 20–30 minutes after 10 mg of zolpidem. Both patients had previously used benzodiazepines without difficulty and both were amnestic for the psychotic episode.

A report from Spain described a 20-year-old woman with severe anorexia who became terrified by visual hallucinations and illusions 20 minutes after taking a 10-mg dose of zolpidem (Iruela et al. 1993). She had full recall of the psychotic episode. A week later she took a 5-mg dose of zolpidem and experienced a similar episode of reduced intensity. A week later, she took 2.5 mg and again experienced visual distortions. Additional case reports of psychosis have been reported in the US (Markowitz and Brewerton 1996, Pitner et al. 1997).

### *Zaleplon*

Zaleplon (Sonata) is a pyrazolopyrimidine approved by the Food and Drug Administration (FDA) for marketing in the US in 1999. Like zolpidem it is chemically unrelated to the benzodiazepines, but binds on the same modulatory site on the $GABA_A$ receptor. Studies in baboons (Ator et al. 2000) and healthy volunteers with a history of drug abuse (Rush et al. 1999) suggest abuse potential similar to triazolam. Peak plasma concentration occurs about 1 hour following oral ingestion. It is rapidly metabolized with a half-life of about 1 hour. Impairment of short-term memory may occur at dosages of 10–20 mg.

### *Zopiclone*

Zopiclone is a racemic mixture of cyclopyrrolone stereoisomers usually marketed in a 7.5 mg dose. The S-isomer is active at the $GABA_A$ receptor, and the R-isomer has no hypnotic effect (Carlson Haskew et al. 2001). Zopiclone is not marketed in the US, but is available in Canada and many other countries under trade name of Imovane or Zimovane in a 7.5 mg dose. Eszopiclone and zopiclone also have abuse potential similar to triazolam (Griffiths and Johnson 2005). The report of the International Narcotics Control Board 2006 noted that zopiclone was being diverted and abused in Argentina (INCB 2006). Short-term use has not shown evidence of dependence or physiological withdrawal (Wadworth and McTavish 1993). In a report of four case histories, zopiclone was reported to show tolerance and withdrawal (Jones and Sullivan 1998). (Hajak et al. 2003 provide a review of abuse and dependence and case reports. Withdrawal seizures were reported in a 36-year-old male taking 60–90 mg/day (Aranko et al. 1991) and in more recent case reports (Flynn and Cox 2006).

### *Eszopiclone*

Eszopiclone (Lunesta) is the S-isomer of racemic zopiclone. Approved by the FDA for marketing in the US since 2005, it is widely advertised in direct to consumer advertising on TV and in lay magazines. Ads note that FDA-approval for long-term use is based on a 6-month, placebo-controlled trial of 3 mg nightly of eszopiclone (Krystal et al. 2003). Subjects with a history of substance abuse or dependence were excluded as were subjects who drank more than 2 alcoholic beverages per day or 14 per week. In the population studies, the study data are convincing for sustained efficacy in reduction of sleep latency, total sleep time, wake time after sleep onset, and number of awakenings over 6 months without evidence of dosage escalation. Abrupt discontinuation at end of the 6-month study had similar rates of "new" events in the placebo (10.7%) and eszopiclone (11.2%). An open-label, 6-month extension study was available to all patients (Roth et al. 2004). Eighty-six (86 of 111) placebo patients were switched to open-label eszopiclone and 296 of 360 patients received 3 mg of eszopiclone for 6 months. No evidence of tolerance was observed and no significant adverse events commonly associated with withdrawal occurred when the medication was discontinued.

From an addiction medicine viewpoint, the question of safety with patients with a previous history of drug-dependence remains unanswered.

## Polydrug Use/Abuse

For recreational purposes, benzodiazepines are rarely used alone. More commonly, they are used in combination with an opiate, alcohol or some combination of drugs. Benzodiazepines are commonly used by patients maintained on methadone or buprenorphine (Subutex, Suboxone) for treatment of opiate dependence.

While benzodiazepines are remarkably safe when taken in overdose alone, combination with alcohol or other sedative–hypnotics drugs can markedly increase the potential for lethality. The combination of a benzodiazepine with buprenorphine, a partial μ agonist, which by itself is also remarkably safe in overdose, can be lethal. Benzodiazepines are commonly misused and abused among methadone maintained patients, and are a contributing factor in many methadone-related overdose deaths.

## Acute Intoxication with Sedative–Hypnotics

The acute toxicity of sedative–hypnotics consists of slurred speech, incoordination, ataxia, sustained nystagmus, impaired judgment, and mood lability. When taken in large amounts sedative–hypnotics produce progressive respiratory depression and coma. The amount of respiratory depression produced by the benzodiazepines is much less than that produced by the barbiturates and other sedative–hypnotics. Consistent with its general approach, the DSM-IV-TR diagnosis of intoxication requires "clinically significant maladaptive behavioral or psychological changes" developing after drug use in addition to the signs and symptoms of acute toxicity. The DSM-IV-TR criteria for intoxication are shown above.

**DSM-IV-TR Criteria**

**Sedative, Hypnotic, or Anxiolytic Intoxication**

A. Recent use of a sedative, hypnotic, or anxiolytic.

B. Clinically significant maladaptive behavioral or psychological changes (e.g., inappropriate sexual or aggressive behavior, mood lability, impaired judgment, impaired social or occupational functioning) that developed during, or shortly after, sedative, hypnotic, or anxiolytic use.

C. One (or more) of the following signs, developing during, or shortly after, sedative, hypnotic, or anxiolytic use:
   (1) slurred speech
   (2) incoordination
   (3) unsteady gait
   (4) nystagmus
   (5) impairment in attention or memory
   (6) stupor or coma

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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## Dependence

Sedative–hypnotics can produce tolerance and physiological dependence. Physiological dependence can be induced within several days with continuous infusion of anesthetic doses. Patients who are taking barbiturates daily, for example, for a month or more above the upper therapeutic range listed in Table 64–1 should be presumed to be physically dependent and in need of medically managed detoxification.

## Withdrawal Syndrome

The withdrawal syndrome arising from the discontinuation of short-acting sedative–hypnotics is similar to that from stopping or cutting down on the use of alcohol. Signs and symptoms of sedative–hypnotic withdrawal include anxiety, tremors, nightmares, insomnia, anorexia, nausea, vomiting, postural hypotension, seizures, delirium, and hyperpyrexia. The syndrome is qualitatively similar for all sedative–hypnotics; however, the time course of symptoms depends on the particular drug. With short-acting sedative–hypnotics (e.g., pentobarbital, secobarbital, meprobamate, oxazepam, alprazolam, and triazolam), withdrawal symptoms typically begin 12–24 hours after the last dose and peak in intensity between 24 and 72 hours (symptoms may develop more slowly in patients with liver disease or in the elderly because of decreased drug metabolism). With long-acting drugs (e.g., phenobarbital,

diazepam, and chlordiazepoxide), withdrawal signs and symptoms peak on the fifth to eighth day.

During untreated sedative–hypnotic withdrawal, the electroencephalogram (EEG) may show paroxysmal bursts of high-voltage, low-frequency activity that precedes the development of seizures. The withdrawal delirium may include confusion, visual and auditory hallucinations. The delirium generally follows a period of insomnia. Some patients may have only delirium; others only seizures; and some may have both delirium and convulsions.

As is described in the later section on benzodiazepines, benzodiazepines may also produce a severe, protracted withdrawal syndrome, and withdrawal symptoms may be produced in some patients after cessation of long-term therapeutic dosing.

## Iatrogenic Dependence

Patients treated for months to years with benzodiazepines and other sedative–hypnotics may become physically dependent on sedative–hypnotics. The possibility of physical dependence should be discussed with the patient and, in some cases the patient's family before initiating long-term treatment. Physical dependence as a process of neuroadaptation should be explained. Patients should be advised against abruptly stopping the medication, particularly if doses beyond the usual recommended doses are prescribed, because of the possibility of developing severe withdrawal symptoms, including withdrawal seizures.

## Diagnosis and Differential Diagnosis

The diagnosis of sedative–hypnotic abuse and dependence is based primarily on drug-use history and the DSM-IV-TR criteria of behavior dysfunction caused by the drug. With dependence developing from prescribed use, the practical difficulty is determining when dysfunction is a result of the sedative–hypnotic use rather than the disorder for which the medication was prescribed. Clearly, intoxication on medications should be avoided; however, subtle memory dysfunction or emergence of symptoms (e.g., anxiety, insomnia) similar to those predating medication may be difficult to distinguish from rebound or withdrawal symptoms.

## Psychiatric Comorbidity

Numerous studies document a high rate of psychopathological conditions among alcohol and drug abusers. Although abuse of drugs can induce psychopathology, particularly depression, it is often impossible while a patient is using drugs or even in early recovery to assess whether the drug use is driving the psychopathology or the psychopathology is driving the drug abuse. Clearly, some drug abusers have severe underlying psychopathological conditions that must be treated if patients are to remain abstinent and functional.

Patients with severe underlying psychiatric disorders may have unrealistic hopes of becoming medication-free. Often the origin of request for benzodiazepine withdrawal comes from concerned friends or relatives. Patients' "problems" may be reframed as the use of "addictive medications" or "dependence" rather than the underlying psychopathology. As a practical matter, a trial of medication discontinuation may be undertaken with the understanding that return to a benzodiazepine or use of an antidepressant or other medications may be appropriate.

## Withdrawal Syndrome

Physiological dependence on sedative–hypnotics may occur after long-term use of amounts greater than normally prescribed or recommended, or, for some individuals, long-term use of therapeutic doses. The withdrawal syndrome manifests differently. With long-term therapeutic use, it is often difficult to differentiate a return of original symptoms (e.g., insomnia, panic attacks, generalized anxiety) from withdrawal signs and symptoms. For some patients, the symptoms of withdrawal continue months to years following discontinuation. Long-term symptoms following withdrawal that are attributed to withdrawal and not return of original symptoms is commonly characterized in the addiction medicine literature as a "protracted withdrawal syndrome." The evidence for protracted withdrawal evolves primarily from clinical observation.

Internet sites provide patients information and provide a forum where patients can exchange information about their experiences with dependence on benzodiazepine and the Z-drugs. TRAP, an acronym for the Tranquilliser Recover and Awareness Place, hosts several, Web sites[5] for people who are having difficulty discontinuing their drug use. Another organization, The Council for Information on Tranquillisers and Antidepressants (CITA) has a Web site offering support and information for people who have become "involuntarily addicted to their prescribed tranquillisers."[6] The premise of these sites is that most doctors are not aware of the addictive potential of benzodiazepines when prescribed for more than a few weeks and that they don't know that behavioral dysfunction and signs and symptoms that arise during medication discontinuation are actually protracted withdrawal symptoms. In this context, the terms "addiction" and "severe symptoms on discontinuation" are synonymous.

## High-Dose Withdrawal Syndrome

Studies of humans have established that large doses of chlordiazepoxide (Hollister et al. 1961) and diazepam (Hollister et al. 1963) taken for one month or more produce a withdrawal syndrome that is clinically similar to the withdrawal syndrome produced by high doses of barbiturates that had been previously described (Isbell 1950). Other benzodiazepines have not been studied under such precise conditions, but numerous case reports leave no doubt that they also produce a similar withdrawal syndrome when taken in excess of the upper therapeutic range.

Withdrawal symptoms can be systematically monitored with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ). Initially developed from clinical observations (Tyrer et al. 1990), its test-retest reliability, construct validity, and predictive validity have been demonstrated (Couvée and Zitman 2002). Low scores during the last phases of

[5]www.non-benzodiazepine.org.uk; www.Bcnc.org.uk, and www.Benzo.org.uk (accessed on 4/13/2007).

[6]www.citawithdrawal.org.uk (accessed on 4/13/2007).

tapering off predicted limited or no use of benzodiazepines during the year following discontinuation.

## Low-Dose Withdrawal Syndrome

Many people who have taken benzodiazepines in therapeutic doses for months to years can abruptly discontinue the drug without developing withdrawal symptoms. Others develop symptoms ranging from mild to severe when the benzodiazepine is discontinued. Characteristically, patients tolerate a gradual tapering of the benzodiazepine until they are at 10–20% of their peak dose. Further reductions in benzodiazepine dose then cause patients to become increasingly symptomatic. In addiction medicine literature, the low-dose withdrawal may be called therapeutic-dose withdrawal, normal-dose withdrawal, or benzodiazepine discontinuation syndrome. The symptoms can ultimately be categorized as symptom reemergence, symptom rebound, or a prolonged withdrawal syndrome.

Many patients experience a transient increase in symptoms for 1–2 weeks after benzodiazepine withdrawal. The symptoms are an intensified return of the symptoms for which the benzodiazepine was prescribed. This transient form of symptoms intensification is called *symptom rebound*. The term comes from sleep research in which rebound insomnia is commonly observed after sedative–hypnotic use. Symptom rebound lasts a few days to weeks after discontinuation (American Psychiatric Association Task Force on Benzodiazepine Dependency 1990). Symptom rebound is the most common withdrawal consequence of prolonged benzodiazepine use.

Following discontinuation the symptoms for which the sedative–hypnotic has been taken may return. This is referred to as symptom reemergence (or recrudescence). In other words, the patient's symptoms, such as anxiety, insomnia, or muscle tension, which had abated during benzodiazepine treatment return.

The reason for making a distinction between symptom rebound and symptom reemergence is that symptom reemergence suggests that the original symptoms are still present and must be treated. Symptom rebound is a transient withdrawal syndrome that will subside over time.

A few patients experience a severe, protracted withdrawal syndrome that includes symptoms (e.g., paresthesia and psychosis) that were not present before.

## Protracted Withdrawal Syndrome

Protracted benzodiazepine withdrawal may consist of relatively mild withdrawal symptoms such as anxiety, mood instability, and sleep disturbance similar to the protracted withdrawal syndrome described for alcohol and other drugs. In some patients, the protracted withdrawal syndrome from benzodiazepines can be severe and disabling and last many months.

There is considerable controversy surrounding even the existence of this syndrome, which evolves primarily from the addiction medicine literature. Many symptoms are nonspecific and often mimic an obsessive–compulsive disorder (OCD) with psychotic features. As a practical matter, it is often difficult in the clinical setting to separate symptom reemergence from protracted withdrawal. New symptoms, such as increased sensitivity to sound, light, and touch and paresthesia, are particularly suggestive of low-dose withdrawal.

The protracted benzodiazepine withdrawal has no pathognomonic signs or symptoms, and the broad range of nonspecific symptoms produced by the protracted benzodiazepine withdrawal syndrome could also be the result of agitated depression, GAD, panic disorder, partial complex seizures, and schizophrenia. The time course of symptom resolution is the primary differentiating feature between symptoms generated by withdrawal and symptom reemergence. Symptoms from withdrawal gradually subside with continued abstinence, whereas symptom reemergence and symptom sensitization do not.

The waxing and waning of symptom intensity are characteristic of the low-dose protracted benzodiazepine withdrawal syndrome. Patients are sometimes asymptomatic for several days, and then, without apparent reason they become acutely anxious. Often there are concomitant physiological signs (e.g., dilated pupils, increased resting heart rate, and increased blood pressure). The intense waxing and waning of symptoms are important in distinguishing low-dose withdrawal symptoms from symptom reemergence.

## Risk Factors for Low-Dose Withdrawal

Some drugs or medications may facilitate neuroadaptation by increasing the affinity of benzodiazepines for their receptors. Phenobarbital, for example, increases the affinity of diazepam to benzodiazepine receptors (Skolnick et al. 1981, Olsen and Loeb-Lundberg (1981) and prior treatment with phenobarbital increases the intensity of chlordiazepoxide (45 mg/day) withdrawal symptoms (Covi et al. 1973). A genetic component is likely. Patients at increased risk for development of the low-dose withdrawal syndrome are those with a family or personal history of alcoholism, those who use alcohol daily, and those who concomitantly use other sedatives. Case-control studies suggest that patients with a history of addiction, particularly to other sedative–hypnotics, are at high risk for low-dose benzodiazepine dependence. The short-acting, high-milligram-potency benzodiazepines appear to produce a more intense low-dose withdrawal syndrome (Rickels et al. 1990).

## Physical Dependence in Nondrug-Dependent Medical Patients

Long-term use of benzodiazepines can result in physical dependence in nondrug-dependent medical patients. Withdrawal symptoms "or" return of symptoms suppressed by the benzodiazepines may make discontinuation difficult.

Some patients who are physically dependent on or unable to discontinue a medication do not necessarily have a substance-use disorder. Physical dependence results from neuroadaptive changes resulting from long-term exposure to a medication. Inability to discontinue the medication may simply mean that patients are unwilling to tolerate the severity of postwithdrawal symptoms that develop. In the absence of medication-produced dysfunction, the continuation of the medication may be an appropriate choice. Patients who do not have a substance-use disorder take medications in the quantity prescribed. They follow

their physicians' recommendations, and they do not mix them with drugs of abuse.

### Presentation in Drug-Abusing Patients

Abusers of alcohol and other drugs rarely present for primary treatment of sedative–hypnotic dependency. From the drug-abusing patient's point of view, sedative–hypnotic use is an effort to self-medicate anxiety or insomnia, which is often the result of alcohol or stimulant abuse. Despite their assertion that the medication is being taken for symptom relief, they often take the medication in larger than physician-prescribed doses, combine the medication with intoxicating amounts of alcohol or other drugs, and purchase medications from street sources. They may also use the sedative–hypnotic as an intoxicant when other drugs are not available.

### Cultural and Minority Issues in Assessment and Treatment

There are marked class and ethnic differences in beliefs and values about the use of intoxicants and medications. The dominant culture in the US prohibits the use of any intoxicant other than alcohol and places limits on tolerated behaviors while intoxicated (e.g., public intoxication, driving an automobile while intoxicated).

Many patients view the distinction between medication and recreational drugs as arbitrary and pharmacologically irrational. For some, medications such as methaqualone simply extend the number of available intoxicants. A strength of the drug abuse and dependence criteria of DSM-IV-TR is that the diagnostic criteria for abuse and dependence are dysfunctional behaviors that most people would agree are pathological.

## Evaluation and Diagnosis

### Drug Use History

The patient's drug use history is usually the first source of information that is used in assessing sedative–hypnotic abuse or dependence. If the sedative–hypnotics were being used for treatment of insomnia or anxiety, the history is often best obtained as part of the history of the primary disorder and its response to treatment. A detailed history of use of all sedative–hypnotics, including alcohol, should be elicited from the patient. When framed in terms of the presenting disorder, patients are generally more candid about their drug use and their relationships with past treating physicians.

For many reasons, patients may minimize or exaggerate their drug use and not accurately report the behavioral consequences of their use. High doses of benzodiazepines or therapeutic doses of benzodiazepines in combination with alcohol may disrupt memory. Patients are likely to attribute impairment of function to the underlying disorder rather than to the medication use. Observations of patients' behavior by family members can be a source of valuable information. Whenever possible, the patient's history should be supplemented by medical and pharmacy records to help piece together as accurate a picture of drug use as possible. Pharmacy records may be helpful in establishing and verifying patient's drug use history, and urine testing can be useful in verifying recent drug use history.

Patients who are obtaining some or all of their medication from street sources may not know what they have been taking, as deception in the street-drug marketplace is common. For example, tablets sold as methaqualone have been found to contain phenobarbital or diazepam.

### Drug Abusers

Many abusers of alcohol or other drugs have symptoms that would reasonably indicate treatment with benzodiazepines or other sedatives if they were not drug abusers. Treating drug abusers with benzodiazepines or other sedatives, while they are still abusing drugs, is generally not helpful however. Such patients are at high risk of misusing or abusing the medications, and the medication may enable them to continue abuse of their primary drug. Drug abusers who are symptomatic because of drug toxicity need hospitalization and detoxification. In patients with drug dependence disorders, abstinence from all abusable medications is the preferred treatment goal, particularly during the first 6 months of abstinence. In patients who do not have a drug dependence disorder, return to benzodiazepine use after detoxification may have a different implication than among patients with a drug dependence disorder. The term *relapse*, which is clearly pejorative, could reasonably be applied to patients who self-administer a benzodiazepine when benzodiazepine abstinence is the agreed on goal of treatment. However, the term relapse should not be applied to patients without a substance abuse disorder who return to prescribed benzodiazepine use because emerging symptoms are not otherwise manageable.

Most patients who are being prescribed long-term benzodiazepine therapy have underlying major depressive disorder, panic disorder, or GAD. The clinical dilemma is deciding which patients are receiving appropriate maintenance therapy for a chronic psychiatric condition. Physical dependence on benzodiazepines may be acceptable if the patient's psychosocial function and disabling anxiety symptoms are ameliorated. The reason for the patient's request for benzodiazepine withdrawal from long-term, stable dosing should be carefully explored. Valid reasons to discontinue benzodiazepine treatment include: (1) breakthrough of symptoms that were previously well controlled; (2) impairment of memory or other neurocognitive function; and (3) abuse of alcohol, cocaine, or other medications.

### Physical Findings

Intoxication on sedative–hypnotics may produce slurred speech, unsteady gait, and sustained horizontal nystagmus. Sustained horizontal nystagmus is a reliable indicator of sedative–hypnotic intoxication. Onset of tremor, abnormal sweating, and blood pressure or pulse increase may be produced by sedative–hypnotic withdrawal.

### Laboratory Tests

Urine toxicology can be useful in monitoring patients' use of drugs and in confirming a history of drug or medication use. The detection time varies widely for benzodiazepines. Diazepam or chlordiazepoxide may be detected for weeks following chronic or high-dose use, whereas others, such as alprazolam or clonazepam, may not be detectable in routine toxicology urinalysis. Because of the variability in

laboratory cut-offs and detection time and different drugs included in the screening panel, the analytical laboratory should be asked about what they routinely screen for and the detection limits.

Definitive diagnosis of a psychiatric disorder during early abstinence is often not possible because protracted withdrawal symptoms may mimic anxiety disorders. Disruption of sleep architecture for days to months after drug withdrawal may occur. If the sedative–hypnotic dependence has developed secondary to stimulant or alcohol use, primary treatment of the chemical dependence should occur first. Often the symptoms that were driving the sedative–hypnotic use disappear after the patient is drug, abstinent.

## Treatment

Once a diagnosis of sedative–hypnotic dependence is manifested it is unlikely that a patient will be able to return to controlled, therapeutic use of sedative–hypnotics. All sedative–hypnotics, including alcohol, are cross-tolerant, and physical dependence and tolerance are quickly reestablished if a patient resumes use of sedative–hypnotics.

If after sedative–hypnotic withdrawal the patient has another primarily psychiatric disorder, such as generalized anxiety disorder (GAD), panic attacks, or insomnia, alternate treatment strategies other than sedative–hypnotics should be used if possible.

Treatment of sedative–hypnotic dependence that has developed as a result of treatment of an underlying psychiatric disorder is usually a lengthy undertaking. The goals of the first phase of treatment are to establish the diagnosis and, to the extent possible, delineate the comorbid psychiatric diagnoses and establish a therapeutic relationship with the patient. The art of treatment is knowing when the therapeutic alliance is sufficiently established to institute drug withdrawal, and knowing when outpatient treatment is not progressing adequately.

In the era of managed health care, it can be difficult, if not impossible, to get medical payors to authorize inpatient treatment of "low-dose" dependence. Although patients may experience intensely disturbing symptoms and may not be able to tolerate symptoms and comply with medication regimens, medical reviewers may deny hospitalization for treatment of dependence, and attribute symptoms arising during withdrawal as mismanagement of symptom reemergence.

### High-Dose Withdrawal

For discontinuation of benzodiazepines or nonbenzodiazepine hypnotics that are being used at dosages above those generally prescribed, one pharmacotherapy strategy is to substitute phenobarbital and stabilization period of 3–7 days, to taper the phenobarbital 30 mg/day. The phenobarbital withdrawal conversion equivalents are shown in Table 64–3. The dose conversions computed using Table 64–3 prevent the emergence of severe withdrawal of the classic sedative–hypnotic type. As discussed next, some patients who take high doses of benzodiazepines, or even therapeutic doses for months to years, may have prolonged withdrawal symptoms.

Three general strategies are used for withdrawing patients from sedative–hypnotics, including benzodiazepines. The first is to use decreasing doses of the agent of dependence. The second is to substitute phenobarbital or some other long-acting barbiturate for the addicting agent, and gradually withdraw the substitute medication (Smith and Wesson 1970, 1971). The third, used for patients with a dependence on both alcohol and a benzodiazepine, is to substitute a long-acting benzodiazepine, such as chlordiazepoxide, and taper it during 1–2 weeks.

Phenobarbital substitution has practical and pharmacological advantages for some patients. Phenobarbital is readily available and inexpensive. It is long acting and consequently there is little fluctuations in blood level between doses. During benzodiazepine withdrawal, the $GABA_A$ receptor may undergo changes that render an individual less sensitive to benzodiazepine agonists. Phenobarbital may owe its utility in benzodiazepine tolerant patients because barbiturates remain effective on benzodiazepine insensitive $GABA_A$ receptors (Akk 2004). Lethal doses of phenobarbital are many times higher than toxic doses, and the signs of toxicity (e.g., sustained nystagmus, slurred speech, and ataxia) are easy to observe. Finally, phenobarbital intoxication does not produce euphoria or behavioral disinhibition, so patients are more likely to view it as a medication.

The preferred withdrawal strategy depends on the particular benzodiazepine, the involvement of other drugs of dependence, and the clinical setting in which the detoxification program takes place. The gradual reduction of the benzodiazepine of dependence is used primarily in medical settings for dependence arising from treatment of an underlying condition. The patient must be cooperative, must be able to adhere to dosing regimens, and must not be abusing alcohol or other drugs.

Substitution of phenobarbital can also be used to withdraw patients who have lost control of their benzodiazepine use or who are polydrug dependent. Phenobarbital substitution has the broadest use for all sedative–hypnotic drug dependencies and is widely used in drug treatment programs. There has been growing support from the treatment community for the use of newer anticonvulsant medications such as gabapentin, oxcarbazepine, and tiagabine for management of substance abuse and abuse-related sleep disorders, as well as for relapse prevention, but their utility as a broad withdrawal substitution has not been demonstrated (Gentry et al. 2002).

#### Stabilization Phase

The patient's history of drug use during the month before treatment is used to compute the stabilization dose of phenobarbital. Although many addicts exaggerate the number of pills they are taking, the patient's history is the best guide to initiating pharmacotherapy for withdrawal. Patients who have overstated the amount of drug that they have taken will become intoxicated during the first day or two of treatment. Intoxication is easily managed by omitting one or more doses of phenobarbital and reducing the daily dose.

To compute the initial daily starting dose of phenobarbital, the patient's average daily use of each sedative–hypnotic is estimated. Next, the patient's average daily sedative–hypnotic dose for each drug is converted to its phenobarbital withdrawal equivalent by multiplying the average

**Table 64–2 Phenobarbital Withdrawal Equivalents of Nonbenzodiazepines***

| Generic Name | Trade Names | Dose Equal to 30 mg of Phenobarbital for Withdrawal† (mg) | Phenobarbital Conversion Constant |
|---|---|---|---|
| *Barbiturates* | | | |
| Amobarbital | Amytal | 100 | 0.33 |
| Butabarbital | Butisol | 100 | 0.33 |
| Butalbital‡ | Fiorinal | 100 | 0.33 |
| Pentobarbital | Nembutal | 100 | 0.33 |
| Secobarbital | Seconal | 100 | 0.33 |
| *Others* | | | |
| Eszopiclone | Lunesta | 2 | 15 |
| Zaleplon | Sonata | 10 | 3 |
| Zolpidem | Ambien | 5 | 6 |
| Zopiclone | Imovane, Zimovane | 4 | 7.5 |

*To estimate the starting dose of phenobarbital for withdrawal, multiply the mg of drug that the patient is taking per day with the phenobarbital conversion constant.

†Phenobarbital withdrawal conversion equivalence is not the same as therapeutic dose equivalence. The conversion equivalent is estimated from the hypnotic dose and has not been determined empirically.

‡Butalbital is in combination with opiate or nonopiate analgesics.

daily dose by the drug's phenobarbital conversion constant shown in Table 64–2 or Table 64–3. Finally, the phenobarbital withdrawal equivalences for each drug are added together. The maximum daily phenobarbital dose is limited to 500 mg/day. The total daily amount of phenobarbital is divided into three doses per day.

**Table 64–3 Phenobarbital Withdrawal Equivalents of Benzodiazepines**

| Generic Name | Trade Names | Dose Equal to 30 mg of Phenobarbital for Withdrawal* (mg) | Phenobarbital Conversion Constant |
|---|---|---|---|
| Alprazolam | Xanax | 1 | 30 |
| Chlordiazepoxide | Librium | 25 | 1.2 |
| Clonazepam | Klonopin | 2 | 15 |
| Clorazepate | Tranxene | 7.5 | 4 |
| Diazepam | Valium | 10 | 3 |
| Estazolam | ProSom | 1 | 30 |
| Flurazepam | Dalmane | 15 | 2 |
| Halazepam | Paxipam | 40 | 0.75 |
| Lorazepam | Ativan | 2 | 15 |
| Oxazepam | Serax | 10 | 3 |
| Prazepam | Centrax | 10 | 3 |
| Quazepam | Doral | 15 | 2 |
| Temazepam | Restoril | 15 | 2 |
| Triazolam | Halcion | 0.25 | 120 |

Phenobarbital withdrawal conversion equivalence is not the same as therapeutic dose equivalence.

Before receiving each dose of phenobarbital, the patient is checked for signs of phenobarbital toxicity: sustained nystagmus, slurred speech, or ataxia. Of these, sustained nystagmus is the most reliable. If nystagmus is present, the scheduled dose of phenobarbital is withheld. If all three signs are present the next two doses of phenobarbital are withheld, and the daily dosage of phenobarbital for the next day is halved.

If the patient is in acute withdrawal and has had or is in danger of having withdrawal seizures, the initial dose of phenobarbital is administered by intramuscular injection. If sustained horizontal nystagmus or other signs of intoxication develop after 1–2 hours after the intramuscular dose, the patient is in no immediate danger from barbiturate withdrawal. Patients are maintained with the initial dosing schedule of phenobarbital for 2 days. If the patient has neither signs of withdrawal nor phenobarbital toxicity (slurred speech, nystagmus, unsteady gait) phenobarbital withdrawal is begun.

## Withdrawal Phase

Unless the patient develops signs and symptoms of phenobarbital toxicity or sedative–hypnotic withdrawal, phenobarbital is decreased by 30 mg/day. Should signs of phenobarbital toxicity develop during withdrawal, the daily phenobarbital dose is decreased by 50% and the 30 mg/day withdrawal is continued from the reduced phenobarbital dose. Should the patient have objective signs of sedative–hypnotic withdrawal, the daily dose is increased by 50% and the patient is restabilized before continuing the withdrawal.

## Protracted Benzodiazepine Withdrawal

Phenobarbital conversions based on Table 64–3 are not adequate to suppress symptoms. For example, someone discontinuing 20 mg of diazepam would have a computed phenobarbital conversion of 60 mg. In managing low-dose withdrawal, an approach is to begin with about 200 mg/day of phenobarbital and then taper the phenobarbital, slowly as tolerated. If palpitations or other symptoms of autonomic hyperactivity are bothersome, beta-adrenergic blockers, such as propranolol or 2-adrenergic agonists, such as clonidine, may be useful adjuncts. Reports on the use of clonidine to reduce benzodiazepine withdrawal severity have yielded mixed results.

## Emerging Alternative Pharmacotherapy for Treatment of Benzodiazepine Dependence

Several small studies have explored the use of the benzodiazepine antagonist, flumazenil[7], for managing symptoms that emerged after benzodiazepine discontinuation. In an early, open-label pilot study, Lader and Morton (1992) used a single flumazenil injection administered by slow intravenous infusion of dosages between 0.2 and 2.0 mg) in 11 patients to assess the effect on persistent symptoms following withdrawal. Because of concern about precipitating benzodiazepine withdrawal, all patients had been off benzodiazepines from between 1 month to 5 years before flumazenil treatment. In an effort to assess placebo effects,

[7]In the older literature, flumazenil is known as Ro 15-1788.

a saline infusion preceded the first flumazenil infusion. They reported that symptoms were ameliorated for hours to days following flumazenil and suggested flumazenil as a potential treatment for the symptoms occurring after benzodiazepine discontinuation (Saxon et al. 1997, Gerra et al. 2002).

Current package inserts for flumazenil (generic and Roche) caution that insufficient data exist to support the use of flumazenil for treatment of benzodiazepine dependence.

## Low-Dose Withdrawal

Discontinuation of sedative hypnotics can present challenges to the patient and the physician. As previously discussed, determining whether symptoms that occur are the result of symptom reemergence, rebound, or physiological withdrawal can often not be objectively established with certainty. New symptoms such as paresthesias and unusual sensitivity to light or sound suggest a withdrawal syndrome whereas emergence of symptoms similar to those that the patient was having before sedative–hypnotic therapy suggests symptom reemergence.

The phenobarbital withdrawal equivalences that would be computed from Tables 64–2 and 64–3 will not be sufficient to manage *low-dose* withdrawal. For benzodiazepine withdrawal or the nonbenzodiazepine hypnotics, gabapentin 1200–2000 mg per day may provide symptom control. If phenobarbital is used, initial dosages of 200 mg/day may be required.

## Psychosocial Treatment

Psychosocial treatments are those services in addition to the medical management of withdrawal. When provided by psychiatrists, psychotherapy may be combined with medical management. Usually, in an inpatient drug abuse treatment setting, psychosocial services are groups and counseling provided by chemical dependence counselors, who may be in recovery from drug or alcohol dependence. While there are specific types of therapy, such as relapse prevention, motivational enhancement or cognitive behavioral therapy, most counselors use a blend of their own recovery experience, the aphorisms of 12-step recovery, and professional training.

### Psychotherapy

Insight-oriented psychotherapy and specifically psychoanalysis are much maligned as treatment of drug dependence. Two reasons deserve serious consideration: some psychotherapists approach treatment of drug dependence as though the drug use is a secondary symptom of neurosis that will cease if the underlying causes are understood. Additionally, insight-oriented psychotherapy itself may mobilize strong affect, memories, or emotions that patients in early or a fragile recovery are unable to tolerate, which may drive relapse to drug abuse.

The problem with drug dependence as a symptom of a neurosis model is that once drug abuse or dependence becomes established the drug use takes on a life of its own regardless of the underlying reason for initiation. Insight-oriented psychotherapy is rarely successful in stopping the drug use. During early recovery, most patients are coping with protracted withdrawal symptoms, repairing relationships, and learning to function without reliance on psychoactive drugs. Patients with underlying psychiatric disorders may have the additional burden of emergence of symptoms that had been ameliorated by their drug use. Psychotherapy during early recovery should be supportive and cognitive–behavioral and focused on coping with current life difficulties. Psychotherapists should remain vigilant for symptoms of panic attacks, generalized anxiety, depression, or sleep disturbances that interfere with function and be prepared to initiate appropriate psychopharmacological or somatic treatments when appropriate.

Psychotherapy can, however, have an important role in motivating a patient for primary treatment of drug dependency. Therapists can help break down patients' denial of their drug dependence by helping them see how drug use is interfering with relationships and undermining their ability to achieve their goals. In some instances, it is desirable to continue the psychotherapeutic relationship while the patient is undergoing treatment for chemical dependence. With some drug abusers, it is desirable to separate the medication management from psychotherapy to prevent the psychotherapy from becoming bogged down in discussions of medications and medication side effects.

### Twelve-Step Recovery

Alcoholics Anonymous, Narcotics Anonymous, and Cocaine Anonymous groups are important treatment adjuncts for many people recovering from alcohol and other forms of drug dependence. Although many groups are becoming more tolerant of appropriate use of pharmacotherapies, many individuals who attend 12-step recovery meetings are adamantly opposed to any form of psychotropic medication use and may counsel fellow members to stop their use. Strong opposition to medications is usually based on their own or friends' bad experience with medications. Some individuals recover without medications and believe that recovery is of better quality if not achieved with a pharmacological crutch.

Patients with underlying psychiatric disorders and the need for treatment with psychopharmacotherapeutic medications often require ongoing support from their psychotherapist if they must have medication.

**Clinical Vignette 1**

A 33-year-old woman was referred by her internist for treatment of alcohol dependence after an overdose of alprazolam (Xanax) and alcohol. The patient had ingested about 30 tablets of alprazolam (2 mg) and a bottle of wine after an argument with her husband. The patient and her husband were in the process of an acrimonious separation, and during the 3 months before her hospitalization, the patient had increased her alcohol consumption from one or two glasses of wine with the evening meal to 1.5 bottles of wine each night. The patient stated that she had wanted to die and that she had heard that the combination of alprazolam and alcohol was lethal. She had not previously made a suicide attempt; however, she was under the ongoing care of a psychiatrist because of panic attacks. A previous psychiatrist had started the patient with alprazolam about

*(continues)*

Clinical Vignette 1 *continued*

6 years before the overdose. Before treatment with alprazolam, her panic attacks had become disabling. While she was taking 4 mg/day of alprazolam, the panic attacks became infrequent, and much attenuated in intensity. She had resumed employment as a travel agent. As her alcohol use increased, the frequency and intensity of her panic attacked increased. Until the overdose, she took alprazolam exactly as prescribed, 2 mg twice a day at the same time each day. Her psychiatrist verified that her refills were consistent with her history. The patient was frightened by having overdosed and acknowledged that her alcohol use was excessive and that she needed treatment; however, she did not want to discontinue alprazolam because she feared worsening of the panic attacks.

**Discussion**

This patient presents a challenging clinical situation, often referred to in the chemical dependence treatment field as dual diagnosis: a major psychiatric disorder and chemical dependence. Alcohol and drug treatment programs generally want patients to discontinue all mood-altering medications, particularly those with abuse potential, when they enter treatment. Chemical dependence treatment staffs often observe that alcohol-abusing patients increase their use of prescription medication when they stop drinking.

Because the patient's panic attacks had been disabling, and because the alcohol abuse seemed a response to an acute situational stress, the patient began outpatient (4 nights/week) chemical dependence treatment, she and her husband began couples therapy, and the patient increased the frequency of visits with her psychiatrist. With the increased support, the patient completed the separation from her husband, remained abstinent from alcohol, and remained on a carefully monitored dose of alprazolam.

Clinical Vignette 2

A 45-year-old man entered inpatient treatment for alcohol dependence. He lived alone and acknowledged drinking up to a fifth of vodka per day. He made many attempts to stop drinking; however, each time, within 24 hours, he became tremulous, sweaty, and nauseous. During the past 10 years, he had had three inpatient detoxifications from alcohol, each followed by a year or more of abstinence. After treatment, he attended three to five Alcoholics Anonymous meetings per week. When asked about medication use, he said that he had been taking lorazepam (Ativan), but it did not help so he stopped it. He denied use of other medications. He denied ever having had a withdrawal seizure.

After admission to the hospital, the patient was treated with chlordiazepoxide (Librium), 25–50 mg every hour as needed, for alcohol withdrawal signs and symptoms. For the first 24 hours, he received 250 mg of chlordiazepoxide. He appeared comfortable and, on the second hospital day, participated in group therapy. While sitting in group therapy, he suddenly stood up, fell forward, and had a grand mal seizure lasting about 2 minutes. Subsequently, he revealed that he had been taking 6–12 mg/day of lorazepam up to the day before admission.

**Discussion**

For many reasons, patients may not reveal all their use of prescription medications or street drugs when they enter an alcohol or drug abuse treatment program. In some instances, patients may want to "protect" the prescribing physician or keep access to medications that would not be sanctioned by physicians working in an alcohol or drug treatment program. The psychotropic medication history is often best obtained as part of the general medical history, in which the patient is asked about any recent treatment of medical problems. Patients are often put at ease by overt assurances of confidentiality and by an explanation of why the drug use history is needed. Indirect questions may be productive—for example, "If we had tested your urine yesterday for all drugs and medications that you had taken during the 3 days just before you came in, what would the tests have shown?" This kind of questioning often provokes patients to ask about if, or how long, a particular drug or medication they are taking can be detected.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The DSM-IV-TR and *International Classification of Diseases,* 10th Revision (ICD-10) Criteria sets for Sedative, Hypnotic, or Anxiolytic Intoxication are almost equivalent (except that ICD-10 also includes "erythematous skin lesions or blisters." The 11 and ICD-10 symptom lists for Sedative, Hypnotic, or Anxiolytic Withdrawal include some different items: the ICD-10 list has craving, postural hypotension, headache, malaise or weakness, and paranoid ideation and do not include the DSM-IV-TR anxiety item.

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CHAPTER

# 65 Schizophrenia and Other Psychoses

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Schizophrenia, Paranoid Type
Schizophrenia, Disorganized Type
Schizophrenia, Catatonic Type
Schizophrenia, Undifferentiated Type
Schizophrenia, Residual Type
Schizoaffective Disorder
Brief Psychotic Disorder
Schizophreniform Disorder
Delusional Disorder
Shared Psychotic Disorder

*"Like a stone thrown onto the smooth surface of a peaceful pond, schizophrenia disrupts lives in ever-expanding concentric circles, so that many lives and many people suffer the pain that arises from a single case."*

Nancy Andreason, MD, Ph.D.

## Historical Overview

In prehistoric times, aberrant behavior was ascribed to magic and religious notions of evil forces that invaded and inhabited a human body. Many cultures treated deviant behavior with the practice of trephination, one of the earliest surgical procedures known (Figure 65–1). Trephining was performed by boring a hole into the skull of a living person to free the evil spirits. Trephined skulls have been found in Peruvian ruins and in parts of Africa, where the procedure may still be performed. In primitive cultures, shamans, who were seen as healers and spiritual leaders, sought to extricate the negative powers from the body with medicinal herbs or ritual chanting and dancing. Interestingly, those who were considered shamans or spiritual healers were often mentally ill themselves. Later, hallucinations and delusions were attributed to the work of the devil or witchcraft. Those found guilty of such sins could be burned at the stake, leading to the unfortunate death of many people who most likely were suffering from severe mental illnesses.

Despite these prevailing religious and spiritual views of mental illness, scientific theory, and medical hypotheses were also considered. In ancient Greece, Hippocrates explained aberrant behavior and madness by relating it to internal imbalances of the four body humors. He stated that our emotions, both joyous and sorrowful, come from the brain. He went further to posit that when a brain is diseased, madness may ensue. Galen, a prominent physician in the 1st century AD, also attributed mental illness to the disturbances of the humors, a theory he had derived from Hippocrates. He expanded on the Hippocratic and Aristotelian notion of mania and melancholia and described abnormalities in emotion and thought as a result of spirits and temperature alterations in the brain. Furthermore, he believed mental illnesses could be broken down into subtypes including aspects of paranoia and despair.

In the 18th century, Philippe Pinel, a prominent French physician, was one in a growing list of predecessors who believed that mental illness was a disease of the central nervous system and one that could be caused by hereditary or environmental factors. In his work with the mentally ill, he was known for his compassionate treatment of patients. He

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**Figure 65–1** *Extraction of the stone of madness by Saunders Memessen (1500–1566). (Source: Kales et al. (1990) Schizophrenia: Historical perspectives. In Recent Advances in Schizophrenia, Kales A, Stefanio CN, and Talbott JR [eds]. Springer-Verlag, New York, USA, p 5. Copyright 1990 Museo del Prado, Madrid.)*

believed that patients would benefit from being properly clothed and nourished and that, except in the most extreme circumstances, their chains should be removed, allowing them freedom within the hospital grounds. He offered instruction in how to handle patients who were potentially violent, with humane techniques that are used to this day. Pinel ended the common practice of viewing patients publicly for entertainment purposes. He implemented these humane changes in two French hospitals, Bicêtre and the Salpêtrière. Pinel was one of the early nosologists who categorized mental illness into subgroups and identified patients who had disturbances of intellect, emotion, or will. He also divided patients into those who had continuous symptoms and those who had signs of "intermittent madness" (Weiner 1992). These early concepts paved the way to our 21st century conceptualization of schizophrenia.

## Modern Concept of Schizophrenia

Our modern understanding of schizophrenia can begin with a look back to the 19th century. Although there were several influential contributors to early psychiatric nosology, there are a few leaders in psychiatry who are thought to have laid the foundation for current diagnostic criteria. To understand how the most recent diagnostic guidelines have been developed, one must place them in their historical context.

Emil Kraepelin (1856–1926) was a German psychiatrist who devoted his life's work to the task of describing and characterizing the symptoms his patients manifested. From these observations, he concluded that not all mental patients suffered from the same disease. He was one of the first to distinguish manic-depressive psychoses from other chronic psychotic illnesses (Kraepelin and Barclay 1919). Among the great contributions to the field of psychiatry are his insightful descriptions of the clinical presentation and course of these illnesses.

In naming the chronic illness he saw, Kraepelin borrowed from the French psychiatrist Benedict Augustin Morel, who in the 1850s had used the term *démence précoce* to describe a previously normal young boy who suddenly manifested symptoms of mental deterioration. Kraepelin, with a slightly different conception of the symptom presentation, used the Latin of Morel's term to label the more chronic illness "dementia praecox." In contrast to Morel, Kraepelin emphasized the outcome of the illness in his descriptions. He believed that dementia praecox was characterized by early onset of symptoms followed by a progressive course culminating in dementia. Later he came to believe that not all patients with dementia praecox ended up in a demented state and a few even recovered. Kraepelin observed, however, that a common theme for these patients was that they experienced a withdrawn state with concomitant hallucinations or bizarre delusions with no impairment of consciousness, sensorium, or memory.

For Kraepelin, the description of the symptoms was of paramount importance, and he published a detailed account of his patients' symptoms in a monograph entitled *Dementia Praecox and Paraphrenia*. He divided patients into three subtypes—hebephrenic, catatonic, and paranoid—and later described paraphrenia as being a separate clinical entity resembling paranoia with either systematized or nonsystematized beliefs and not characterized by the deterioration of personality as in dementia praecox.

Eugen Bleuler (1857–1939) was a Swiss psychiatrist who is known, among other things, for coining the term schizophrenia. Although erroneously defined at times as multiple personality disorder, this term means literally "splitting of the mind." Bleuler used the word to capture his belief that this mental illness was one in which different aspects of the psyche were split, which resulted in the classical symptoms he went on to describe. In his paper entitled "Dementia praecox and the group of schizophrenias," he put forth his theory that schizophrenia consisted of not just one illness with one etiological basis but a heterogeneous group of illnesses with distinguishing characteristics and clinical courses (Bleuler and Zinkin 1950). He differed from Kraepelin in believing that these illnesses were not as often characterized by an early onset and a terminal dementia. Bleuler expanded and modified earlier Kraepelinian concepts including the subdivisions of diagnoses and included the category of simple schizophrenia, which was eventually also adopted by Kraepelin.

Perhaps one of his most important contributions was Bleuler's emphasis on the content of symptom presentation. To Bleuler all patients had at least one fundamental or primary symptom, but other accessory or secondary symptoms were also manifested clinically. Bleuler's "four As," as they are now commonly called, consisted of primary symptoms: profound ambivalence, a looseness of associations, disturbance of affect (either excitation or withdrawal), and autism, which he described as living in an internal, unrealistic world, separated from normal social interaction. Bleuler attempted to describe negativism, which he thought was not only a result of motor disturbance but also had psychic meaning, which he thought was important to understand. Although his symptom descriptions are not used in their entirety in modern diagnostic classification systems because of their limited specificity, the remnants of these descriptions can be seen in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV-TR) (American Psychiatric Association 2000).

Kurt Schneider (1887–1967) has probably contributed to our current diagnostic classifications more than any other person. Schneider studied both Kraepelin's and Bleuler's ideas during his psychiatric training in Germany (Hoenig

1983). From his reading and his own clinical experience, he formulated a list of symptoms that he believed could be identified in his schizophrenia patients.

Without positing etiological theories, Schneider described symptoms of first and second rank, based on which were most likely to be found in a patient with schizophrenia. According to Schneider, the diagnosis of schizophrenia was appropriate if the patient experienced just one first-rank symptom; the second-rank symptoms, although common in schizophrenia, were not as specific. His first-rank symptoms included delusions of thoughts being broadcast; feelings of an external force inserting thoughts or withdrawing them from the mind; thought interference; and the sensation of forces influencing behavior, will, or body functions. The first-rank symptoms also include specific hallucinatory experiences, such as hearing voices, often two or more, commenting on the patient's behavior or criticizing the patient. The second-rank symptoms included paranoia, affective extremes, apathy or absence of emotions, and any hallucinatory experience other than those already described. Schneider's description of these symptoms paved the way to modern diagnostic criteria used today.

## Diagnosis

### Evolution of Structured Diagnostic Criteria for Schizophrenia

A specific "operationalized" set of diagnostic criteria for schizophrenia was first brought to light in a paper published by Feighner and colleagues (1972) of the St. Louis group. They presented a list of symptoms and signs that provided a reliable system for differentiating diagnostic groups. The St. Louis group emphasized the pattern and the duration of symptoms (requiring 6 months of symptoms to reach a diagnosis of schizophrenia) without regard to the etiology of the illness being observed. Feighner's group proposed that a set of consistent diagnostic criteria would facilitate and improve on research and clinical treatment of patients.

The research diagnostic criteria (RDC) were developed to improve diagnostic reliability in research, borrowing many of the concepts from the Feighner criteria and Schneiderian tradition. Unlike the Feighner criteria, the RDC diagnosis of schizophrenia does not require 6 months of active symptoms. Instead, schizophrenia is divided into three groups, based on temporal distinctions: acute (lasting 2 weeks to 6 months); intermediate, that is, subacute or subchronic (lasting 6 months to 2 years); and chronic (illness present for at least 2 years). This set of criteria excludes patients with a clear mood syndrome and assigns them to either an affective disorder or a schizoaffective disorder. For a diagnosis of schizophrenia, patients must have experienced two of nine symptoms listed, including delusions, thought disorder, hallucinations, or catatonic behavior. Many of these symptoms are derived directly from Schneiderian concepts. Diagnoses are assigned a degree of certainty (probable or definite) and are considered primary or secondary, based on the chronological presentation of concomitant illnesses. The RDC have remained essentially unchanged as other diagnostic classification system have been modified and revised, which allows homogeneously defined groups of patients to be compared over time.

Structured diagnostic aids made up of standardized questions were developed to increase the reliability of diagnostic assessments. Wing's present state examination (PSE) is an example. Like Schneider's description of first- and second-rank symptoms, it consists of a checklist of experiences covering a period of 1 month before the interview. This particular symptom algorithm has been widely used and validated around the world since its inception in 1970. The PSE was influential in the development of the RDC and, moreover, the structured interview that can be used with the RDC, the schedule for affective disorders and schizophrenia (SADS). Specifically, the SADS is a comprehensive list of questions that correspond to specific symptoms. The SADS and the RDC are similar to the PSE in their emphasis on the length of time in which symptoms are present and in the presence of psychosis, which are required for the diagnosis of schizophrenia.

The diagnostic schemata of the PSE, the Feighner criteria, and the RDC also had a profound impact on the development of the most commonly used guideline for psychiatric nosology in the US, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), developed by the American Psychiatric Association. This manual has gone through several revisions. DSM-I and DSM-II, now of more historical interest, postulated a somewhat broad, glossary-like definition of schizophrenia. Later versions have relied on field trials and consensus diagnoses of collaborating specialists to narrow the definition, making this manual an important resource for researchers, clinicians, politicians, attorneys, patients, family members, and even third-party payers.

DSM-III, developed in the 1970s and published by the American Psychiatric Association in 1980, viewed schizophrenia much more narrowly, and for the first time in the DSM specific criteria were required for a diagnosis of schizophrenia. These included a minimal duration of symptoms, at least 6 months, which had also been a requirement in the Feighner criteria. This decision stemmed from a debate about whether shorter (less than 6 months) psychotic episodes that resolved quickly were considered the same disease entity as the more chronic and unremitting type of illness. In addition, DSM-III diagnostic criteria placed emphasis on the more easily validated Schneiderian concepts and included a multiaxial system of diagnosis.

The revised edition of DSM-III (DSM-III-R) was published in 1987. It was arranged similarly to its predecessor, that is, with a lettered list of criteria, broken down into numbered lists of specific symptoms. It incorporated some important changes, including the exclusion of transient psychosis by adding a one-week minimal presence of symptoms in criteria A, unless these symptoms were eliminated by treatment during that period. DSM-III-R also eliminated the maximal age at onset (45 years) for schizophrenia. This major modification was based on a lack of compelling data supporting an age restriction. In fact, since this change was implemented, several studies have demonstrated that the index episode of schizophrenia can occur at any age (see Howard et al. 2000). Along the same lines, onset in childhood was considered, and wording was changed to allow for the possibility of differential prognoses.

### Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-IV was released in 1994, to coincide with the publication of the *International Statistical Classification of Diseases*

*and Related Health Problems*, 10th Revision (ICD-10), which was published by the World Health Organization in 1992. Many of the changes allow greater consistency between these two widely used classification systems. In DSM-IV the issue of brief psychotic episodes was revisited, and the minimal duration of active symptoms was extended from 1 week to 1 month, much as in ICD-10. With a slight swing of the pendulum back toward a Bleulerian conceptualization, criterion A now places greater emphasis on negative symptoms, including avolition, flattened affect, and alogia. The rest of the specific criteria, including criterion A and the criteria for the residual and prodromal syndromes, have been simplified from earlier versions.

In DSM-IV, criterion A of schizophrenia includes delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms. Two or more of these symptoms are required during the active phase of the illness. However, if the patient describes bizarre delusions or auditory hallucinations consisting of a voice commenting on the patient's behavior or voices conversing, only one of these symptoms is required to reach the diagnosis. It is important to distinguish negative symptoms, which are often difficult to appreciate, from the myriad factors that may contribute to the severity and serious morbidity associated with schizophrenia. Patients who are not motivated to attend to their personal hygiene or suffer from alogia and a flattened affect are sadly at a disadvantage in society. The addition of negative symptoms as a separate criterion in DSM-IV recognizes the prominence of these symptoms in patients with schizophrenia.

**DSM-IV-TR Criteria**

**Schizophrenia**

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g., frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behavior
   (5) negative symptoms, i.e., affective flattening, alogia, or avolition

***Note.*** Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

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Criterion B addresses loss of social and occupational functioning, not exclusively because of any one of the items in criterion A. Patients may have difficulties maintaining employment, relationships, or academic achievements. If the illness presents at an early age, rather than as a degeneration or reversal of function, there may be a break from continued academic and social gains that are developmentally appropriate so that the person never achieves what had been expected.

Criterion C eliminates patients with less than 6 months of continued disturbance and again requires at least 1 month of the symptoms from criterion A. Criterion C allows prodromal and residual periods to include only negative symptoms or a less severely manifested version of the other symptoms of the A criteria.

Criterion D excludes patients who have a more compelling mood aspect of their illness and therefore their symptoms might instead meet criteria for schizoaffective disorder or a mood disorder. Both of these restrictions force a narrower view of the diagnosis of schizophrenia, which lessens the tendency of psychiatrists to overdiagnose schizophrenia.

Criterion E clarifies the fact that patients with schizophrenia are not suffering from other medical illnesses or the physiological effects of substances that might mimic the symptoms of schizophrenia. Finally, criterion F acknowledges that schizophrenia can be diagnosed in patients with autistic disorder or developmental disorder, as long as there have been prominent delusions or hallucinations that have lasted at least 1 month.

## DSM-IV-TR Subtypes of Schizophrenia

In DSM-IV-TR, schizophrenia has been divided into clinical subtypes, based on field trials of the reliability of symptom clusters. The subtypes are divided by the most prominent symptoms, although it is acknowledged that the specific subtype may exist simultaneously with or change over the course of the illness. DSM-IV-TR also initiates an optional dimensional descriptor, which allows the condition to be characterized by the presence or absence of a psychotic, disorganized, or negative symptom dimension over the entire course of the illness.

### *Paranoid Type*

In DSM-IV-TR, paranoid-type schizophrenia is marked by hallucinations or delusions in the presence of a clear sensorium and unchanged cognition. Disorganized speech, disorganized behavior, and flat or inappropriate affect are not present to any significant degree. The delusions (usually of a persecutory or grandiose nature) and the hallucinations most often revolve around a particular theme or themes. Because of their delusions, these patients may attempt to keep the interviewer at bay, and thus they may appear hostile or angry during an interview. This type of schizophrenia may have a later age of onset and a better prognosis than the other subtypes.

**DSM-IV-TR Criteria**

**Paranoid Type**

A type of schizophrenia in which the following criteria are met:

A. Preoccupation with one or more delusions or frequent auditory hallucinations.
B. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect.

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### *Disorganized Type*

Disorganized schizophrenia, historically referred to as hebephrenic schizophrenia, presents with the hallmark symptoms of disorganized speech and/or behavior, along with flat or inappropriate (incongruent) affect. Any delusions or hallucinations, if present, also tend to be disorganized and are not related to a single theme. Furthermore, these patients would not be classified as having catatonic schizophrenia. These patients in general have more severe deficits on neuropsychological tests. According to DSM-IV-TR, these patients tend to have an earlier age at onset, an unremitting course, and a poor prognosis.

**DSM-IV-TR Criteria**

**Disorganized Type**

A type of schizophrenia in which the following criteria are met:

A. All of the following are prominent:
   (1) disorganized speech
   (2) disorganized behavior
   (3) flat or inappropriate affect
B. The criteria are not met for catatonic type.

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### *Catatonic Type*

Catatonic schizophrenia has unique features that distinguish it from other subtypes of schizophrenia in DSM-IV-TR. During the acute phase of this illness, patients may demonstrate marked negativism or mutism, profound psychomotor retardation or severe psychomotor agitation, echolalia (repetition of words or phrases in a nonsensical manner), echopraxia (mimicking the behaviors of others), or bizarreness of voluntary movements and mannerisms. Some patients demonstrate a waxy flexibility, which is seen when a limb is repositioned on examination and remains in that position as if the patient were made of wax. Patients with catatonic stupor must be protected against bodily harm resulting from the profound psychomotor retardation. They may remain in

**DSM-IV-TR Criteria**

**Catatonic Type**

A type of schizophrenia in which the clinical picture is dominated by at least two of the following:

(1) motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor;
(2) excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
(3) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism
(4) peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing
(5) echolalia or echopraxia

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the same position for weeks at a time. Because of extreme mutism or agitation, patients may not be able to report any difficulties. Some patients may experience extreme psychomotor agitation, with grimacing and bizarre postures. These patients may require careful monitoring to safeguard them from injury or deterioration in nutritional status or fluid balance.

### *Undifferentiated Type*

There is no hallmark symptom of undifferentiated schizophrenia; thus, it is the subtype that meets the criterion A for schizophrenia but does not fit the profile for paranoid, disorganized, or catatonic schizophrenia.

**DSM-IV-TR Criteria**

**Undifferentiated Type**

A type of schizophrenia in which symptoms that meet criterion A are present, but the criteria are not met for the paranoid, disorganized, or catatonic type.

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### *Residual Type*

The diagnosis of residual schizophrenia, according to DSM-IV-TR, is appropriately used when there is a past history of an acute episode of schizophrenia but at the time of presentation the patient does not manifest any of the associated psychotic or positive symptoms. However, there is continued evidence of schizophrenia manifested in either negative symptoms or low-grade symptoms of criterion A. These may include odd behavior, some abnormalities of thought processes, or delusions or hallucinations that exist in a minimal form. This type of schizophrenia has an unpredictable, variable course.

**DSM-IV-TR Criteria**

**Residual Type**

A type of schizophrenia in which the following criteria are met:

A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior.
B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in criterion A for schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

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## Cross-Cultural Definitions

Any diagnostic classification algorithm for an illness such as schizophrenia is necessarily limiting in its applicability to people of different cultures. Although its use allows some communication between mental health professionals internationally, there are bound to be distinct culturally acceptable definitions that may be more useful on a clinical level for a specific group of people. The ICD, now in its 10th revision, was developed by the World Health Organization to provide a means of collecting data regarding morbidity and mortality associated with health problems around the world. The chapter on mental illness, developed around the same time as DSM-IV, is easily understandable for those who are familiar with Western thinking. Yet the field of cross-cultural psychiatry is expanding. There is increased awareness of the need to work with patients within their own culturally diverse backgrounds. The classification schemes specific to local regions are often based on historical, religious, and traditional thinking unique to each setting.

As an example, in the psychiatric classification schemes in France, an important distinction has historically been made between transitory psychotic states (*bouffée délirante*) and what French psychiatry refers to as chronic delusional states. The latter are further subdivided into chronic interpretive psychosis, chronic hallucinatory psychosis, and chronic imaginative psychosis (Chabrol 2003). This has led to some confusion for those familiar with the ICD and DSM systems. Clinical differences are based on historical differences between the French and German Kraepelinian concepts, though more recent international classifications have reduced the discrepancies. The French characterization of a transitory psychosis has contributed in part to our conceptualization of brief psychotic disorder and schizophreniform psychosis (Chabrol 2003). As another example, Chinese psychiatric nosology and treatments based on a history dating back 3,000 years, are quite different from those in DSM and represent another example of cultural diagnostic differences. The original Chinese notions of mental illness were based, as in Western culture, on philosophy and religion. As Chinese medicine evolved, so did psychiatric concepts. The Chinese philosophy of yin and yang, or the opposing forces within all people, has predominated in the interpretation of psychiatric symptoms (Wig 1990). Other psychiatric traditions are based on mythological stories that have been passed from generation to generation.

One must avoid imposing Western definitions of psychosis on non-Western societies. Psychosis and delusions, by definition, must be beliefs or experiences that are incongruent with those of the patient's social or cultural background. An example of the difficulties in sorting through these matters is *koro*, which is the belief that one's genitals are shrinking into one's abdomen, based on Chinese mythology involving a fear of death. Although this is generally rare, there have been epidemics involving entire communities who have suffered from this condition. By Western standards, someone presenting with this symptom could be considered to have a psychotic or delusional disorder and even possibly be given a diagnosis of schizophrenia. A Western psychiatrist might fail to recognize that in some parts of Asia, this is within culture-bound limits and would be the equivalent of a neurosis as opposed to a psychosis.

In New Zealand, the Maori are well integrated with their European neighbors. While working in Westernized jobs, however, most continue to hold firmly to their Maori traditions. The differences in religious beliefs can lead to

difficult questions for mental health professionals, most of whom are of European descent. For example, Maoris who believe their relationship to the gods is unique, that they have been given special powers and messages from the gods to protect the Marae, or tribal community meeting place, may be within cultural norms and thus not meet any criteria for schizophrenia. In this context, the New Zealand government has long supported cross-cultural respect and communication and has created positions for cultural liaison specialists. These experts in Maori traditions are available to mental health teams to aid in decisions regarding diagnosis and treatment within a cultural context.

To determine where culture-bound beliefs end and delusions or inappropriate behaviors begin in a multicultural world is clearly not possible using only a written algorithm such as DSM-IV-TR. A critical step toward sound cross-cultural clinical care is developing an awareness of and a respect for diversity. Utilizing the expertise of persons familiar with a specific culture allows appropriate diagnosis and treatment of schizophrenia worldwide.

## Epidemiology

### World Health Organization Studies

Three major studies conducted by the World Health Organization (WHO) have provided clinicians and researchers with invaluable information regarding the epidemiology of schizophrenia. By utilizing consistent diagnostic criteria, having large sample sizes across several countries of diverse cultures and development, and including follow-up data, the WHO has collected a significant data set from which we can derive epidemiological information.

The first of these studies is known as the International Pilot Study of Schizophrenia and was conducted from 1969 to 1977. This study assessed 1,202 patients across nine countries (Taiwan, Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, US, and former USSR) utilizing Wing's Present State Examination, which was translated and back-translated to ensure consistency in diagnostic assessment across languages. A second major study, the Assessment and Reduction of Psychiatric Disability, examined social adjustment in 520 individuals with schizophrenia in seven countries: Bulgaria, Federal Republic of Germany, Netherlands, Sudan, Switzerland, Turkey, and Yugoslavia. From 1978 to 1986, the Determinants of Outcome of Severe Mental Disorders studied 1,379 patients in 10 countries who had sought help for mental illness and were diagnosed with probable schizophrenia (Jablensky et al. 1988). All three of these studies included long-term follow-up with assessments of the initial cohort for a period of up to 10 years. Although these studies were conducted with large sample sizes in different cultural settings, the methodology was consistent, with diagnostic assessments made by trained professionals, enhancing the reliability and validity of the conclusions.

### Epidemiological Catchment Area Program

One of the most comprehensive epidemiological undertakings in the US to date, the Epidemiological Catchment Area (ECA) program was planned as a result of a need for comprehensive data that would answer questions regarding the prevalence of mental disorders that could be utilized to implement services for those in need. Funded by the National Institute of Mental Health, the ECA program began in 1978 as a multisite program designed primarily to determine accurate prevalence rates of specific mental illnesses (Robins et al. 1984). Structured diagnostic interviews were administered to a population of almost 20,000 people residing in designated areas, and the corresponding DSM-III diagnoses were registered in a central data set.

### Epidemiological Findings: Incidence and Prevalence

The *incidence* of schizophrenia is defined as the number of new cases in a given population, usually per 1,000 persons, during a specific period of time (1 year by convention). In an illness with an insidious onset, such as schizophrenia, accurate incidence rates can be difficult to determine. Incidence rates are often calculated from first hospital admission data, which may not correspond to the time when the illness first presented. Incidence rates can also be calculated from retrospective interviews or chart reviews, which may misrepresent accurate incidence rates because of imperfect charting, unreliable historical information given by patients and their families, and nonvalidated retrospective diagnoses. In any case, the incidence varies depending on the methods and the diagnostic criteria used. For example, the US–UK study is often cited as an example of epidemiological variation based on different diagnostic criteria (Kramer 1969). This study, conducted in the 1960s, found a lower incidence of schizophrenia in the UK than in the US. It is now widely accepted that this difference was found because a broader definition of schizophrenia was being used in the US, and it did not reflect true differences in the incidence of schizophrenia in each country.

The data obtained from the WHO studies are important in part because the same diagnostic criteria were used in all countries studied. According to the results of the International Pilot Study of Schizophrenia, schizophrenia is found in all cultures and the incidence rates per 1,000 people annually ranged from 0.15 in Denmark to 0.42 in India. This finding is corroborated by a review of the literature, in which the incidence of schizophrenia across 13 studies representing seven countries is found to range between 0.11 (UK) and 0.54 (US) per 1,000 people per year (Eaton 1985). Small variations in these incidence rates, because they are so low, have little meaning epidemiologically. Furthermore, the range of incidence rates for schizophrenia decreases significantly when consistent, tightly defined diagnostic criteria are employed.

Because schizophrenia is a chronic illness, the incidence rates must, by definition, be much lower than the prevalence rates. *Prevalence* is defined as the number of cases present in a specified population at a given time or time interval (e.g., at a specific point in time, during a time period, or over a lifetime). Lifetime prevalence represents the proportion of persons who have ever had the illness at a given time.

Lifetime prevalence rates of schizophrenia, based on the ECA data, were approximately 1% (range across three sites, 1–1.9%) (Robins et al. 1984). Point prevalence rates based on International Pilot Study of Schizophrenia data showed no significant differences across study centers: schizophrenia was found universally with relatively equal frequencies in a wide variety of cultures, though newer data described

below challenge this. Eaton's review of the literature showed a range of point prevalence between 0.6 and 8.3 cases of schizophrenia per 1,000 persons in the population. The rate of schizophrenia per 1,000 persons fell within a similar range when looking at lifetime prevalence, point prevalence and period prevalence, which Eaton hypothesized was related to the fact that schizophrenia is a chronic but not fatal illness (Eaton 1985). In an update of Eaton's review, it was noted that methodological differences may have partly accounted for statistical outliers in studies examining the incidence and prevalence of schizophrenia in different countries regardless of the type of prevalence. Specific studies of smaller populations, such as Helgason's study of Iceland, found a 0.9% morbidity risk (which approximates point prevalence rates) of schizophrenia (Helgason 1964). This study has been highlighted because it examined 99% of patients in a closed population and supports the findings of the larger studies such as the ECA study.

Interestingly, smaller studies have found specific populations with either a higher or a lower prevalence of schizophrenia. For example, a higher rate of schizophrenia has been found in a specific community in the north of Sweden, in northeastern Finland, in northwestern Croatia, and in western Ireland. Lower rates of schizophrenia have been found in, for example, parts of Tonga, Papua New Guinea, Taiwan, and Micronesia. In the US, schizophrenia was almost nonexistent in the Hutterite community, a Protestant sect living in South Dakota. Epidemiologists generally agree that these communities may represent aberrant findings. However, if these differences in prevalence rates are accurate, several theories have been offered as explanations, including genetic preloading, differences in diet, or even differences in factors such as maternal age. The evidence for a suggestion raised that there might be a decline in the incidence of schizophrenia was inconsistent and conflicting.

Since these earlier reports, newer epidemiological data from excellent studies have been surprising. The lifetime prevalence of psychotic disorders in Finnish adults was 3.48% with 0.87% for schizophrenia. Data from a recent review of 1458 incidence rates from 33 countries found up to 5-fold variations in incidence of schizophrenia between sites and a skewed distribution of rates challenging the notion created by WHO studies that schizophrenia is equally distributed (McGrath 2007). A meta-analysis used 1721 prevalence estimates from 188 studies with original data published between 1965 and 2002 and drawn from 46 countries with an estimated 154,140 potentially overlapping prevalent cases in a systematic review. Point prevalence (median) was 4.6 persons per 1000; 3.3 for period prevalence and 4.0 for lifetime prevalence (0.4%) for schizophrenia. These numbers are significantly different than those reported by other studies and appears that 4–8 individuals per 1,000, rather than higher numbers reported previously develop schizophrenia during their lifetime. Schizophrenia prevalence ranges from 4 to 7 per 1,000 with countries from the developing world having a lower prevalence of schizophrenia. The authors also report that this study highlights that symptoms persist despite the interventions offered. Different types of prevalence estimates had from 3.4 fold for point to 4.6 fold for period variation (Saha et al. 2005). This group further analyzed data to explore the effect of latitude on prevalence rates. Incidence of schizophrenia in men was significantly higher at higher latitudes (60° or more) and congruent with another study where there were winter/spring excess schizophrenia births at higher latitudes suggesting that men may be more vulnerable to the exposures related to latitudes and schizophrenia. The prevalence estimates of schizophrenia were significantly higher at higher latitudes when compared with lower latitude bands. Lifetime morbid risk (LMR) was reported to be 7.2 per thousand. LMR attempts to include the entire lifetime of a birth cohort both past and future and includes those deceased at the time of survey. LMR is the probability of a person developing the disorder during a specified period of their life or up to a specified age. Based on cautious interpretation of the data, the prevalence of schizophrenia is reported to be lower in developing nations than in the developed ones. Questions are raised about the validity of the concept of equal incidence of schizophrenia across the world. Some but not all migrant groups have significantly higher rates of schizophrenia. There is an increased risk of schizophrenia associated with older paternal age, prenatal famine, winter/spring birth, higher latitude, prenatal infection, and pregnancy and birth complications.

## Sociodemographical Characteristics

### Age

One of the major changes from DSM-III to DSM-III-R was the abolition of the requirement for onset of symptoms before age 45 years for the diagnosis of schizophrenia. This led to more universal acceptance of the phenomenon of late-onset schizophrenia. DSM-IV and DSM-IV TR retained the revision made in DSM-III-R, and ICD-10 now includes paraphrenia (a term originally used by Kraepelin to signify a diagnosis distinct from dementia praecox in that the patients did not experience a deterioration) in a list of subtypes of schizophrenia instead of an independent diagnosis. Late paraphrenia subsequently came into favor to describe a paranoid delusional disorder with an onset usually after age 60 years. These changes in nomenclature and accepted nosological criteria have greatly affected epidemiological studies of schizophrenia and age at onset.

An investigation of late-onset schizophrenia found that 28% of patients had the onset of illness after age 44 years and 12% after age 63 years, based on 470 chart reviews of patients who had sought psychiatric help during a period of 20 years. Other studies have demonstrated that 23% of schizophrenia patients had an onset after their forties. The 1-year prevalence rate for schizophrenia in patients between 45 and 64 years of age was found to be 0.6% according to the ECA study. Furthermore, in a study of patients with onset after the age of 44 years, the majority of patients had symptoms that met all the criteria for schizophrenia found in DSM-III except for the age requirement, lending support to the need to discard the maximal age at onset limitation of DSM-III. Thus, although the majority of patients have an early age at onset, a certain subgroup of patients may have a disturbance that meets all the criteria of schizophrenia with onset in their forties or later.

The phenomenology of late-onset compared with early-onset schizophrenia may be distinct, with later-onset cases having a higher level of premorbid social functioning and exhibiting paranoid delusions and hallucinations more often than formal thought disorder, disorganization, and negative

symptoms. Studies have also shown a high comorbid risk of sensory deficits, such as loss of hearing or vision, in patients with late-onset schizophrenia. Specifically, late-onset patients are more likely to report visual, tactile, and olfactory hallucinations and are less likely to display affective flattening or blunting (Howard et al. 2000). For individuals over 65 years age, community prevalence estimates range from 0.1 to 0.5%. One of the most robust findings among the late-onset cases is the higher prevalence seen in women (Howard et al. 2000). This does not appear to be due to sex differences in seeking care, societal role expectations, or delay between emergence of symptoms and service contact. The International Late-onset Schizophrenia group has suggested a new classification system of *late-onset schizophrenia* (onset after the age of 44 years) and a *very late-onset schizophrenia-like psychosis* (onset after age 65) (Howard et al. 2000, Folsom et al. 2006). "Late-life" schizophrenia includes those individuals who had their onset during adolescent or early adulthood and are now middle-aged as well as the late-onset schizophrenia patients (Folsom et al. 2006). Future studies will clarify how meaningful these categories are.

## Sex

A large body of data suggests that although men and women have an equivalent lifetime risk, the age at onset varies with sex. Although some sites showed different prevalence rates of schizophrenia in men and women, the overall prevalence rates, as reported in the ECA survey, did not differ significantly between sexes. However, there is strong evidence that onset of schizophrenia is on average 3.5–6 years earlier in men than in women (Riecher-Rossler and Hafner 2000). The WHO 10-country study observed this phenomenon in most cultures studied. Therefore, incidence and prevalence rates of schizophrenia across sexes may vary according to age. Interestingly, in some cultural populations (e.g., West Ireland, Micronesia) the ratio of prevalence of schizophrenia for men could be as high as 2:1 (Myles-Worsley et al. 1999). Recent epidemiological reviews have reported that the male-female rate ratios were 1.4:1 (see McGrath 2007). However, data from another systematic review did not confirm this (Saha et al. 2005).

Many studies have used criteria for schizophrenia that require onset before the age of 45 years, which also has accounted for some of the discrepancy in findings. There is undoubtedly a subgroup of patients who have a later onset of illness (after age 45 years), and this subgroup is made up predominantly of women (Howard et al. 2000). Among these female schizophrenia patients, there is a higher incidence of comorbid affective symptoms. When the effects of gender, premorbid personality, marital status, and family history of psychosis on the age at onset were removed in a reanalysis of WHO 10-country study data, there was a significant attenuation of the sex differences (Jablensky and Cole 1997).

## Race

The ECA data have shown that there is no significant difference in the prevalence of schizophrenia between black and white persons when corrected for age, sex, socioeconomic status, and marital status. This finding is significant because it refutes prior studies that have shown the prevalence of schizophrenia to be much greater in the black population than in the white population. Adebimpe (1994) proposed several factors, including racial differences in help-seeking behavior, research populations, commitment status, and treatment, as explanations for some of these discrepancies. Efforts are being made to correct for some of these issues so that the epidemiological variables and heterogeneity of schizophrenia can be better understood in terms of race, whether black, white, Asian, or any other.

## Marital Status and Fertility

A study of marriage and fertility rates of individuals with schizophrenia compared with the general population showed that on average, by the age of 45 years, three times as many of those with schizophrenia as of the general population are still unmarried (40% of men and 30% of women with schizophrenia are still single by age 45). Studies have also shown that fertility rates are lower in patients with schizophrenia compared with the general population. These observations may be related, and further investigation of the role of premorbid function, negative symptoms, and fertility rates, including rates among unmarried patients, is warranted. With the advent of the newer and more effective antipsychotic medications, and their increased use in first episode patients, it is possible that we may witness improved fertility and marriage rates in patients with schizophrenia.

## Socioeconomic Status

For many years, epidemiological studies revealed a higher incidence and prevalence of schizophrenia in groups with lower socioeconomic status. With these findings came the hypothesis that lower social class could be considered a plausible risk factor for schizophrenia, possibly because of a higher risk of obstetrical complications, poorer nutrition, increased exposure to environmental toxins or infectious disease, or exposure to greater life stressors. In the past half century, studies have found that the actual incidence of schizophrenia does not vary with social class, based on first admission rates, adoption studies, and a series of studies examining the social class of the fathers of people with schizophrenia.

When these findings did not validate the original theory, it became clear that lower socioeconomic status was more a result than a cause of schizophrenia. This led to the acceptance of the downward drift hypothesis, which stated that because of the nature of schizophrenic symptoms, people who develop schizophrenia are unable to attain employment and positions in society that would allow them to achieve a higher social status. Thus, these patients drift down the socioeconomic ladder, and because of the illness itself they may become dependent on society for their well-being.

## Immigration

Epidemiological studies of immigrant populations in the early part of the 20th century led to the supposition that the stress of immigration increased the risk for psychosis. However, further investigations of acculturation as a risk factor for schizophrenia have yielded mixed results. The opposite idea, that having a mental illness increased the likelihood of emigrating, has also been reviewed (Eaton 1985). At this time, there is no conclusive evidence that emigration increases the risk of schizophrenia. Furthermore, immigration screening has become more rigorous since the earlier

studies, and legal immigrants may therefore be less likely to have an increased risk for developing schizophrenia.

The remarkably high incidence and prevalence rates of schizophrenia observed in second-generation Afro-Caribbean, and Suriname and Dutch Antilles migrants to the UK and Netherlands respectively are baffling. These findings have been replicated and data from 17 studies show a wide range of relative risk from 1.7 to 13.2 (Eaton and Harrison 2000). A recent systematic review suggests that migrants were more likely to develop schizophrenia than native-born individuals (median risk ratio = 4.6). These findings were confirmed by Saha et al. (2005) too. Diagnostic bias, misclassification, or biological risk factors do not account for these findings. Thus, environmental risk factor(s), currently unknown, have been proposed to underlie these phenomena. The relationship between migration and schizophrenia is complex and needs further clarification (Bhugra 2000).

## Industrialization

With the increasing presence of the mentally ill on the streets of modern urban locations, the question has often been raised of whether urban life, or industrialized society, is a risk factor for the development of schizophrenia. In fact, there seems to be data suggesting that people in urban areas have a higher relative risk for schizophrenia than those in rural areas or mixed urban/rural sites. However, in the larger study by the same group, prevalence did not differ according to urbanicity (Saha et al. 2005). Torrey and colleagues (1997) reanalyzed the US 1880 census data and found that urban residence was associated with a higher risk for psychosis. Marcelis and colleagues (1998) analyzed all first admissions for schizophrenia and other psychosis in Holland between 1942 and 1978 by place of birth and found a statistically significant relationship between size of urban areas and incidence of schizophrenia, affective, and other psychosis. Furthermore, in the WHO follow-up studies of the International Pilot Study of Schizophrenia, there was a significant difference in the course of schizophrenia between industrialized and developing nations, with individuals with schizophrenia in developing countries having a less severe and less chronic course of the illness.

Various explanations for these discrepancies have been postulated. For example, in industrialized areas the family structure may impose more social stresses on the ill relative, who is often unable to work and perform by society's standards, whereas in developing countries the family structure may be protective, with other relatives supporting the ill relative. Another possible explanation is a selection factor in developing countries resulting from the higher infant mortality in nonindustrialized societies. According to this hypothesis, children in less developed countries who would be at risk for schizophrenia would not be as likely to survive, thus skewing the prevalence rates of schizophrenia in these areas. However, some suggest that this risk factor of increase incidence of psychosis in urban areas is more ecological than genetic. Further investigation is needed to provide definitive answers as to why schizophrenia may have a higher prevalence and more severe course in industrialized nations.

## Season of Birth and Onset

That season of birth differs between individuals with schizophrenia and the general population has by now gained wide acceptance. This factor has been studied in the 20th century, with the predominant view that the birth rate of people with schizophrenia is highest in late winter (Eaton 1985). Torrey and colleagues (1997) confirmed this, reviewing approximately 250 studies and concluding that there is an excess of schizophrenia births during winter. In fact, there is approximately a 5–8% greater likelihood for individuals with schizophrenia to be born during winter months compared with the general population. This higher incidence of winter births has been found in both hemispheres, offering further evidence that this phenomenon is related to the colder months rather than specific calendar months.

It is clear that even though only a small proportion of all those with schizophrenia are born during winter months, the deviation from the seasonality of birth of the general population (the number of general births peaks in the spring) is a striking phenomenon. This finding is not unique to schizophrenia, and differences in seasonality of birth have been described for mania, diabetes mellitus, Down syndrome, congenital hip dislocation, and certain cardiovascular malformations. It is therefore debatable whether this observation has etiological significance unique to schizophrenia.

Season of onset has also been considered in epidemiological investigations of schizophrenia. A preponderance of data dating back to the early 1800s indicates that the summer season is associated with a higher incidence of the onset of symptoms. Suicide rates also vary according to season, with a spring peak, indicating that the interaction of environment and psychopathology may be of some significance. Recent reports of excess of summer births in patients who have deficit sub type of schizophrenia raises some interesting possibilities.

## Morbidity and Mortality

The economic costs of schizophrenia have been estimated to be six times the costs of myocardial infarction. The WHO has estimated that mental illness accounts for as much as two-fifths of all disability funding in the US. Amongst the homeless in New York City, a significant percentage of costs of hospital admissions were associated with schizophrenia patients. In the US, the cost of schizophrenia in 1994 was $44.9 billion and rising. In the UK, 5.4% of total National Health Service inpatient costs were attributed to schizophrenia. When all services were combined together, approximately £2.6 billion were spent annually taking care of schizophrenia patients. In Australia, it is estimated that schizophrenia costs approximately $3 billion for treatment and due to lost productivity (Mowry and Nancarrow 2001). Much of the cost of schizophrenia is due to the high morbidity of this chronic illness. Premorbid deficits, cognitive deficits, and negative symptoms account for much of the disability. Also, schizophrenia patients with more severe courses may require repeated hospitalizations and may not be capable of maintaining independent living or stable employment.

The mortality rate of schizophrenia is estimated to be twice that of the general population. Approximately 10% of the mortality is secondary to suicide. Young male patients with schizophrenia are most likely to complete suicide attempts, especially early in their illness. Degree of social isolation, agitation, depression, a sense of hopelessness, a

history of prior suicide attempts, and recent loss may be associated with increased risk of suicide among schizophrenia patients (Breier and Astrachan 1984). There is also some evidence that an increased number of relapses, rehospitalizations, and discharges lead to an increased risk of suicide. There have been observations that suicide rates of schizophrenia patients may be increasing in the era of shorter hospital stays and community treatment. However, with the advent of the Second Generation Antipsychotic (SGA) medications and especially with clozapine use, it is possible that this risk of suicide may even out or decrease due to their possible protective effects against suicide (Meltzer and Okayli 1995). Clozapine has an Food and Drug Administration (FDA) approval for treatment of patients who are at high risk for suicide. A recent meta-analysis by Lester (2006) suggests that suicide was significantly higher in males than females. Other factors leading to increased mortality rates in schizophrenia patients include an increased incidence of accidents as well as a more frequent association with other medical illnesses (including cardiovascular disease), comorbid substance abuse, a general neglect of health, an increased rate of damaging behaviors such as smoking and poor diet, decreased access to health services and depression. Results from a nationwide cohort of 2,230 patients from Finland suggest that mortality was 10 times higher in patients who were not taking medications compared to those who were. Suicides occurred in 26 cases who were not taking medications compared to one who was (Tiihonen et al. 2006).

In a study to examine rates of mortality in patients with severe mental illness (SMI), Osborn and associates (2007) used the United Kingdom's General Practice Research Database, which is a large community sample comprised of 46,136 people with SMI and 300,426 individuals without SMI. They found that patients with SMI have an increased risk of death from coronary heart disease and stroke that is not wholly explained by antipsychotic medication, smoking or social deprivation scores. Rates of nonrespiratory cancer mortality were not raised. These data confirm excess mortality in patients with SMI and suggest that increased focus on potential preventative measures, such as attention to diet and exercise, are particularly important for these individuals.

### Comorbidity with Other Illnesses

Schizophrenia is associated with an increased frequency of tuberculosis (not accounted for by institutionalization), celiac disease, myxedema, and arteriosclerotic heart disease. Patients who present with atypical psychoses have been noted to have an increased risk of ankylosing spondylitis and uroarthritis, which may indicate a relationship between the histocompatibility complex and schizophrenia.

Along these lines, there is a strikingly decreased risk for rheumatoid arthritis among patients with schizophrenia. Many of the studies supporting this observation were conducted before the use of phenothiazines, which eliminates any potential protective role of antipsychotics (Eaton 1985). Further investigation of this link may yield significant genetic or biological markers for both diseases.

Such studies of potential biological markers have yielded some interesting findings. Illnesses such as rheumatoid arthritis and ankylosing spondilitis are autoimmune disorders that are associated with human leukocyte antigens (HLA). The associated risks for these disorders and schizophrenia have led to speculation that some subgroup of patients with schizophrenia may be manifesting symptoms related to an autoimmune process. For example, studies have shown that there may be an association between HLA types and schizophrenia. In one recent study, the HLA frequency was increased for HLA A10, A11, and A29 and decreased for HLA A2 in patients with schizophrenia (Ozcan et al. 1996). Thus, although the presence of HLA is not universal among persons with schizophrenia, further investigation into this area may point to alternative hypothesis regarding etiology and treatment of a certain population of patients with schizophrenia.

Reversing the association, there are numerous medical illnesses with symptoms similar to those of schizophrenia. Among examples of these, the most common neurological disorder appearing clinically similar to schizophrenia is epilepsy, particularly of the temporal lobe. Other medical illnesses with symptoms similar to those of schizophrenia include basal ganglia calcifications and acute intermittent porphyria. Imbalances of endocrine function as well as certain infectious diseases can present with symptoms that mimic schizophrenic psychosis. Further investigation of these illnesses may lead to a greater understanding of the pathophysiology of schizophrenia.

## Etiology

The cause(s) of schizophrenia currently remain unknown. However, fast-paced developments in neuroscience combined with advances in psychiatric research have resulted in increased optimism about discovering the cause(s) and delineating the pathogenesis and pathophysiology of this mysterious illness. A leading view is that schizophrenia may be heterogeneous with respect to etiology. Thus, multiple causative mechanisms may give rise to distinct disease subtypes. If this is true, it is important for psychiatric researchers to differentiate the homogeneous subtypes of this illness. Moreover, it has been proposed that more than one causative mechanism might interact (the so-called double-hit hypothesis) to cause the illness in some individuals. Available data strongly indicate that the interactions between genetic and environmental factors may lie at the core of this illness. In this section, the main etiological theories of schizophrenia are examined.

### Genetics

Schizophrenia represents a daunting challenge for genetic researchers for several reasons: the paucity of extended multigenerational family histories containing large numbers of affected individuals; the increasing evidence of genetic heterogeneity, such as more than one phenotype or more than one genetic variant; a lack of agreement on the mode of transmission; and the genotype-phenotype relationship might be more symptom- than diagnosis-based. Following genetic modeling of epidemiological data and the results of several genome screens for susceptibility genes, the probability of schizophrenia being a single gene disorder is unlikely. The probability that several genes of large effects may confer vulnerability to schizophrenia is diminishing too. Thus, the focus has shifted to multiple genes of small to moderate effects which may compound their effects through interactions with each other and with other nongenetic risk factors

(see Mowry and Nancarrow 2001 and Maier et al. 2006 for more discussion). Thus, schizophrenia is a complex genetic disorder that does not show a simple Mandelian pattern of inheritance. Despite these formidable obstacles, enormous progress has been made in search of genetic basis for schizophrenia. Moreover, the proteins expressed by the genes (proteome) are equally important in understanding the working of the cells being studied.

## Family Prevalence Studies

Wide agreement now exists that the rate of schizophrenia among first-degree family members of persons with schizophrenia is higher than in control families. The chance of occurrence is approximately 10 times greater among these individuals than in individuals with no first-degree relatives with schizophrenia. There is approximately six times and two times greater chance of developing schizophrenia in second- and third-degree relatives of individuals with schizophrenia (Tsuang et al. 2001). In addition, the higher prevalence of schizophrenia spectrum disorders among family members of individuals with schizophrenia, such as schizoaffective disorder and schizoid and schizotypal personality disorders, provides support for a common genetic basis for this family of schizophrenia-like illnesses. Different studies have provided evidence for and against an increased prevalence of other psychotic disorders and nonpsychotic affective illnesses among relatives of persons with schizophrenia.

## Adoption Studies

Adoption studies constitute a powerful experimental strategy for examining the role of genetic versus environmental factors. In these studies, the rates of schizophrenia are compared in relatives of adoptees with and without schizophrenia. Danish adoption studies conducted in the 1960s and 1970s provided compelling evidence that adoptees with schizophrenia had higher rates of schizophrenia in their first-degree relatives than control adoptees (Kety 1987). A reanalysis of these data in the late 1980s confirmed the original finding that biological relatives of schizophrenia adoptees had significantly higher rates of schizophrenia (4.1%) than biological relatives of nonschizophrenia (control) adoptees (0.5%).

In Finland, a large study of adopted-away offspring of mothers with schizophrenia found that significantly more offspring of mothers with schizophrenia themselves developed schizophrenia (9.1%) than did control offspring (1.1%). An interesting aspect of the Finnish study was the examination of family environment in the adoptive families. A relationship was found between a disruptive family environment and occurrence of schizophrenia in adoptees. This suggests that environmental factors might play a role in the manifestation of the illness in genetically susceptible individuals. However, the study did not make clear whether the schizophrenia adoptee caused the disruptive home environment or the disruptive environment contributed to the manifestation of the illness. Longitudinal assessment of environmental conditions throughout childhood before the onset of illness will be important in resolving this issue.

Several methodological issues are important in interpreting the data from adoption studies, including the diagnostic status of biological fathers and levels of psychopathology in adoptive families. Additional factors to consider are the intrauterine environment, birth complications, and length of time from birth to adoptive placement.

## Twin Studies

Another approach to examining genetic contributions to schizophrenia involves concordance studies of dizygotic (nonidentical) and monozygotic (identical) twin pairs. Available data indicate that the concordance of schizophrenia among dizygotic twins is approximately 8–12%. This is much greater than the 1% rate found in the general population and comparable to the rate of concordance of schizophrenia among first-degree siblings. The concordance of schizophrenia among monozygotic twins is approximately 50%. Even though the high rate of concordance among monozygotic twin pairs is compelling evidence for genetic contributions, the fact that it is not higher than 50% suggests a role for additional, perhaps nongenetic, factors in the etiology of schizophrenia. Moreover, although monozygotic twins share the same genetic information, it is possible for a mutation to occur in one member of the twin pair and not the other. Birth order of twin pairs and different intrauterine effects are other factors to consider. An attractive and robust experimental design is provided by adoption away of monozygotic twin pairs, which effectively combines the strengths of both adoption and twin methodologies. The number of sets of adopted-away, monozygotic twin pairs affected with schizophrenia is relatively small. However, data available on the limited number of pairs meeting these criteria support the strong concordance of schizophrenia in monozygotic twins.

## Linkage and Association Studies

There was tremendous enthusiasm and hope riding on the two promising approaches to identify the faulty gene(s) responsible for schizophrenia: *linkage studies* and *association studies*. Linkage studies use polymorphic genetic markers to attempt to identify statistical agreement (known as a logarithm of the odds score) between the presence of the marker and illness in families under investigation. It should be noted that genetic markers mark a segment of DNA presumably where the gene of interest resides; they do not necessarily identify mutant genes themselves. Once linkage is established, the second stage of work begins, which entails searching the identified segment of DNA for the faulty gene. However, the linkage studies have a limited power to detect susceptibility genes of small effect, a most likely scenario in complex disease genetics such as schizophrenia. This can be overcome by association studies (Lichtermann et al. 2000).

Association studies actually use the candidate genes themselves and test the highly specific hypothesis that a mutation in the candidate gene occurs at a greater rate in the population of interest (in this case schizophrenia patients) than in nonaffected control populations. More recently, family based samples such as *trios* (consisting of the affected person and both parents, if available), are collected to avoid population stratification. One limitation of this approach is that it is all or none; that is, the candidate gene either is or is not associated with the illness. With enormous resources and efforts dedicated to uncover genetic underpinnings of schizophrenia and lack of commensurate progress, questions were being raised if schizophrenia's phenotypic variability has confounded the search for its causes. Specifically, the inconsistent and poorly replicated results of genetic linkage and association studies

using the current diagnostic category as the sole schizophrenia phenotype was disheartening. However, the Human Genome Project with its approximately 23,000 genes provided just the platform to search for schizophrenia genes. Recent discoveries of genes for schizophrenia were made possible through a successful genome-wide search using linkage analysis to map genes in broad candidate areas. This was followed by identification of susceptibility genes within this region by either systematic narrowing down or by trial and error. Three genes that emerged as strong candidates for susceptibility genes are the dysbindin gene on chromosome 6p (DTNBP1), the neuregulin-1 gene on chromosome 8p (NRG1), and DAOA (previously called G72/G30) gene on chromosome 13q. Remarkably, for each of these genes a majority of the studies have reported significant associations with markers and/or marker combinations (haplotypes). Linkage and association studies have now implicated these and several other loci in the genome that appear likely to harbor genes conferring risk for schizophrenia (see Table 65–1 and Figure 65–2).

These events have infused a new-found enthusiasm and optimism in the field. Thus, linkage strategy has proven to be ideal for finding regions containing major effect genes that follow identifiable inheritance patterns in families. What seemed difficult to do previously has now occurred with a sizeable set of confirmed linkage regions, some of which are strong enough to withstand rigorous correction for whole genome analysis (e.g. 1q, 6p, 6q, 15q) and others have been supported by meta-analysis (8p, 13q, 22q, etc.) (see Table 65–1 and Figure 65–2). Linkage has been partly successful because linked regions contain multiple susceptibility genes and thus, within a linkage sample, different genes segregating in different families can contribute to the linkage signal for that region. Additionally, linkage approach also benefited greatly from the presence of multiple susceptibility genes being present even up to 20 centimorgans apart. An example of this would be chromosome 6p22–24, where dysbindin MUTED and MRDS1 are located within 10 megabases of each other. Surprisingly, even among some of the most consistently replicated genes (e.g. dysbindin NRG1, DAOA), the associated alleles and haplotypes differ considerably across studies. Many believe that a unifying and simplifying approach, based on characterizing the functional state of the gene, is going to be one of the most productive ways to evaluate genetic effects (see Straub and Weinberger 2006 and Maier et al. 2006).

Neuregulin 1 (NRG1) was identified as a candidate gene via fine-mapping of a locus on chromosome 8p21–22 linked to schizophrenia in Iceland and replicated in other countries too. No functional polymorphisms have been identified yet. NRG1 signaling, via ErbB receptors and regulation of both NMDA receptors and postsynaptic density 95 (PSD-95), has been implicated in neuronal differentiation and migration. While the functional role of NRG1 in schizophrenia is not clear, postmortem studies suggest that NRG1 signaling may be enhanced in schizophrenia leading to suppression of NMDA receptor function consistent with the glutamate hypofunction hypothesis of schizophrenia (see below).

Dystrobrevin Binding Protein 1 or Dysbindin is linked to chromosome 6p and is widely distributed in brain and has been detected both pre and postsynaptically including in the synaptic terminal in the hippocampus. It is thought to influence glutamate neurotransmission. Dysbandin has also been connected with the glutamate hypofunction hypothesis. Dysbindin has been associated with negative symptoms of schizophrenia and also possibly prefrontal brain function.

D Amino Acid Oxidase Activator (DAOA) gene is located on chromosome 13. DAOA activates D Amino Acid Oxidase (DAO) which oxidizes D-Serine, which is a coagonist at NMDA glutamate receptors. Again, there may be a connection here with the Glutamate hypothesis (see Ross et al. 2006 for more details).

Using alternative strategies where cytogenic analyses in isolated families highly loaded with schizophrenia was pursued, a balanced (1:11) chromosomal translocation was detected to cosegregate. A specific gene which was not previously known on chromosome 1 was regularly disrupted and

**Table 65–1 Candidate Schizophrenia Susceptibility Genes and the Strength of Evidence in Four Domains**

| | | Strength of evidence (0 to 5+) | | | |
|---|---|---|---|---|---|
| | | Association with schizophrenia | Linkage to gene locus | Biological plausibility | Altered expression in schizophrenia |
| COMT | 22q11 | ++ | ++++ | +++ | yes, + |
| *DTNBP1* | 6p22 | +++++ | ++++ | ++ | yes, ++ |
| *NRG1* | 8p12-21 | +++++ | ++++ | +++ | yes, + |
| *RGS4* | 1q21-22 | +++ | +++ | ++ | yes, ++ |
| *GRM3* | 7q21-22 | +++ | + | ++ | no, ++ |
| *DISC1* | 1q42 | ++++ | ++ | ++++ | not known |
| *DAOA(G72/G30)* | 13q32-34 | +++ | ++ | ++ | not known |
| *DAAO* | 12q24 | ++ | + | ++++ | not known |
| *PPP3CC* | 8p21 | + | ++++ | ++++ | yes, + |
| *CHRNA7* | 15q13-14 | + | ++ | +++ | yes, +++ |
| *PRODH2* | 22q11 | + | ++++ | ++ | no, + |
| *AKT1* | 14q22-32 | + | + | ++ | yes, ++ |
| *GAD1* | 2q31.1 | ++ | | ++ | yes, +++ |
| *ERBB4* | 2q34 | ++ | | | yes, ++ |
| *FEZ1* | 11q24.2 | ++ | | +++ | yes, ++ |
| *MUTED* | 6p24.3 | ++++ | ++++ | +++ | yes |
| *MRDS1 (OFCC1)* | 6p24.3 | ++ | ++++ | + | not known |
| *NPAS3* | 9p34 | ++ | | ++ | not known |
| *GRIK4* | 11q23 | ++ | + | ++ | not known |

Adapted from Straub RE and Weinberger DR (2006) Schizophrenia—famine to feast. Biological Psychiatry 60(2), 81–83.

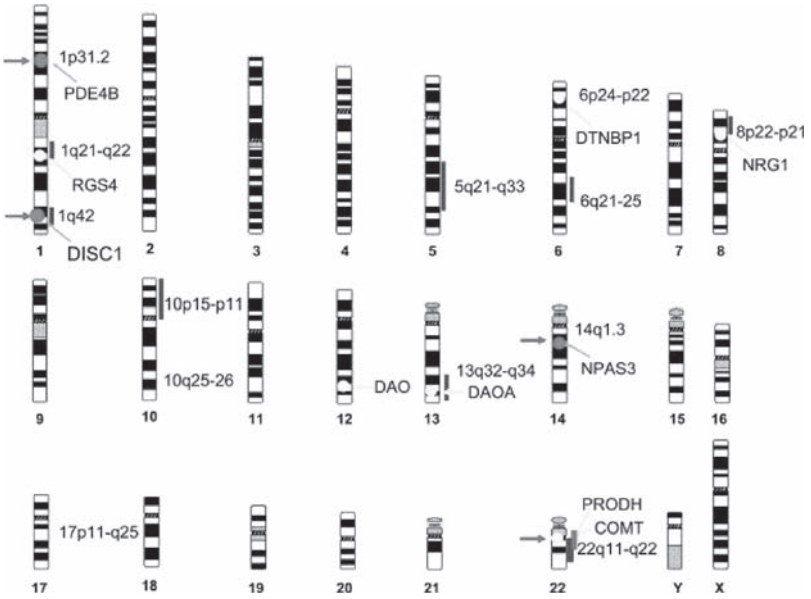



**Figure 65–2** *Locations of linkage findings and genes. (Source: Owen MJ, Craddock N, and O'Donovan MC [2005] Schizophrenia: Genes at last? Trends in Genetics 21(9), 518–525.)*

was named DISC1. Now, DISC1 is emerging as the best supported candidate gene for schizophrenia. DISC1 segregates with schizophrenia, bipolar disorder, and other major mental illnesses in a large pedigree in Scotland with LOD scores of 7. The translocation is between exons 8 and 9 of the DISC1 gene on chromosome 1. DISC1 appears to have roles in both brain development and adult neuronal functioning. Developmental roles include regulation of neuronal migration, neurite outgrowth and neuronal maturation. In adults it may modulate cytoskeletal function, synaptic transmission and plasticity. DISC1 interacts with several proteins implicated in neuropsychiatric diseases and possibly related to cortical development (see Ross et al. 2006, Maier et al. 2006).

Another successful alternative strategy is based on the principle that gene expression might guide to susceptibility genes. Abnormalities in synaptic and postsynaptic transmission are assumed to be a crucial feature of schizophrenia. Phosphokinases present as a family of candidate proteins involved in intracellular signal transmission and are coded by polymorphic genes; these have become 'hot' candidate genes. These DNA-sequence variants in the differentially expressed protein kinase B (AKT1) were found to be associated with schizophrenia (Maier et al. 2006).

Weinberger and colleagues (2001) suggested that the gene that encodes the postsynaptic enzyme catechol-*o*-methyl transferase (COMT) is preferentially involved in the metabolism of dopamine in frontal lobe and is located on chromosome 22q–11. Dopamine is hypothesized to underlie aspects of cognition in frontal lobe such as information processing. Based on animal studies, family-based association studies, and fMRI studies in schizophrenia patients and general population, Weinberger and colleagues proposed an interesting hypothesis that the COMT genotype with valenine allele (val/val type) may increase the risk of developing schizophrenia due to its effect on dopamine-mediated prefrontal information processing. However, a recent meta-analysis did not find an association between Val-variant of the COMT gene and schizophrenia. In the case of COMT, a gene has defied consistent association to its common functional coding val/met variant, likely because other functional variants in the gene have evolved to balance the effect of this polymorphism. The association between COMT alleles and schizophrenia appear to be less striking than the association between COMT and cognitive function. Variation at the COMT locus may provide the best studied example of the relationship between variation at the genetic locus and the endophenotype closely related to schizophrenia (Ross et al. 2006). The interaction between COMT val/met genotype and early adolescent cannabis use is interesting. While COMT genotype alone had no predictive effect on the emergence of schizophreniform illness by age 25, in combination with early marijuana use, the risk odds ratio for the val/val genotype was 10-fold greater than in the general population (Straub and Weinberger 2006).

A strong genetic association between schizophrenia and the chromosomal microdeletion syndrome, velocardiofacial syndrome (VCFS), caused by deletion of 1.5–3 Mb in chromosome 22q–11 has been postulated. Approximately 20–30% of patients with VCFS have schizophrenia or other major psychiatric disorder with psychosis. Patients with schizophrenia have increased frequency of the microdeletion compared with the general population. The VCFS region includes at least 27 genes including COMT. VCFS patients have facial dysmorphism and other features, and presumably are caused by loss of one copy of several or many genes in this region. The VCFS or Di George syndrome occurs with a frequency of approximately 1 in 6,000 births. Schizophrenia patients with VCFS have more severe cognitive deficits of spatial working memory, visual recognition, and attention than VCFS. Compared to matched normals, schizophrenia patients with VCFS have smaller total grey matter volume, larger lateral ventricles, and decreased gyrification in the frontal and parietal lobes (Jablensky 2006). The risk of schizophrenia is three times higher in people with learning disability than in the general population and chromosomal variants and abnormalities are increased. Structural MRI in these individuals reveals abnormalities of the hippocampus and amygdala that are more severe than in people with schizophrenia alone and very different from people with learning disability alone. VCFS is associated with learning

disability also. The associated phenotype is highly variable with congenital heart defects occurring in approximately 75% patients (Muir et al. 2006).

Modern functional genomic approaches such as DNA microarrays, based on the principles of nucleic acid hybridization, can check a tissue sample for presence of thousands of genes simultaneously. For example, Mirnics and colleagues (2000) employed cDNA microarrays and compared transcriptomes in schizophrenia and matched control subjects and found that only a few gene groups consistently differed between subjects and controls. In all subjects with schizophrenia, the most changed gene group was related to *presynaptic group secretory function* (PSYN) gene group and in particular the "mechanics" of neurotransmitter release. Thus, Mirnics and colleagues (2000) postulated that, as the most affected genes in the PSYN group varied across study subjects (suggesting that the illness has "distinct molecular signatures"), schizophrenia, therefore, may involve a combination of different sequence-related polygenic susceptibility factors and physiological adaptations that lead to impairment of the signaling between neurons. They found additional support for their hypothesis from reports of reduced expression of regulator of G-protein signaling 4 (RGS4) in individuals with schizophrenia. In the brain, RGS4 is one of the 30 or more RGS family members that serve as GTPase-activating proteins (GAPs), which reduce response duration of postsynaptic neurons after the release of presynaptic neurotransmitters that bind to G-protein coupled receptors. Thus, Mirnics et al. (2001) suggested that the deficits in PSYN and RGS4 expression may produce synaptic changes with pathophysiologic consequences relevant to schizophrenia. RGS4 is located on chromosomal region 1q21–22. Stress and other environmental factors appear to regulate this gene. Levitt et al. (2006) further suggests that RGS4 may be a molecule that may underlie increased vulnerability through genetic as well as environmental mechanisms.

It should not come as a surprise that many genes identified so far appear to impact biologically on some of the most basic processes of brain development, involving neuronal differentiation, synapse biology and various processes involved in neuronal plasticity. With the exception of DISC1, all known susceptibility genes code for synaptic proteins. This is not surprising as there is reduced dendritic spine density in the cortex and hippocampus of schizophrenia patients and diminished levels of synaptic markers such as synaptophysin and the complexin proteins have been observed consistently. Glutamate and GABA are fast transmitters. PRODH (Prolin Dehydrogenase) and DAOA code for proteins involved in glutamate signaling while the neuregulin-1 receptor ErbB forms a functionally important complex with glutamate NMDA receptors. Dysbindin is involved in the vesicular release of glutamate in the schizophrenic hippocampus, dysbindin immunoreactivity is diminished at glutamate terminals and mRNA and protein are decreased in schizophrenic prefrontal cortex (Morrison and Murray 2006). These are positive and hopeful developments. Clearly, faster, innovative, and sophisticated techniques have ushered genetic research into a new era with a renewed promise to explore genetic basis of mental illnesses.

Researchers are urgently searching for schizophrenia phenotypes for subgroups or dimensions that may define etiologically or genetically distinct subtypes. Similarly, the field is yearning for *endophenotypes* with simpler architecture than schizophrenia to possibly guide to newer leads in research (Mowry and Nancarrow 2001). Latent genetically influenced traits, which may be related only indirectly to the classic disease symptoms defined in major classification systems are known as "endophenotypes." They reflect an underlying susceptibility to the disease phenotype (or some form of it). In schizophrenia we are interested in endophenotypes that are measurable by neurophysiological or neuropsychological means. Crucial characteristics of any endophenotype include the fact that it can be measured before the explicit onset of the illness, and that it represents the genetic liability of nonaffected relatives of probands with the disorder. For example, in genetically complex disorder such as schizophrenia, could separate genetic loci contribute to distinct aspects of the illness phenotype (e.g., evoked potentials, aspects of cognition, etc.)?

Patients with schizophrenia have been shown to have deficits in sustained attention as measured by P50 and other information processing tests. Genome-wide linkage analysis showed that the P50 gating information processing deficit is heritable in families with schizophrenia and maximal linkage was at the chromosome 15q–14 locus of alpha-7 nicotinic acetylcholine receptor gene (Freedman et al. 2001). Polymorphisms in the gene and its nearby partial duplication are associated with diminished P50 inhibition and cognitive dysfunction. These data along with other converging lines of evidence including post mortem studies have strongly implicated the alpha-7 nicotinic receptor in the pathophysiology of schizophrenia and provides an intriguing potential target for novel therapeutics for this illness.

When the test for associations of at-risk haplotypes and at-risk alleles for schizophrenia were done in bipolar disorder, the DAOA and the NRG1 genes were found to be implicated in the etiology of bipolar disorder along with variants of dysbindin gene. Does this favor a common predisposing susceptibility allele? To answer this question, associations with the same haplotype/marker in schizophrenia and in bipolar disorder in the same population were done by Schumacher et al. (2004), and Green et al. (2005), and the data were able to support the possibility for the DAOA and the NRG1gene respectively. A similar pattern is emerging for DISC1. A refined analysis proposed 'persecutory delusions' to explain the association between the DAOA haplotype and bipolar disorder and NRG1 with mood incongruent psychotic features. Thus, questions are being raised as to what is the more appropriate clinical target for an involved susceptibility allele or haplotype, core symptoms or criteria driven diagnosis? Maier et al. (2006) observe that it is remarkable how all risk genes identified for schizophrenia and bipolar disorder involve glutamatergic transmission or development of neurons and glial cells. These observations point to cross-diagnostic communalities in glutamatergic transmission and neurodevelopment (see Maier et al. 2006). Furthermore, DTNBP1 at-risk haplotype is preferentially associated with negative symptoms. Although diagnostic categories are useful to detect susceptibility genes, the genotype-phenotype relationship might be more symptoms- than diagnosis-based. Thus, future developments in genetics are quite likely to have an impact on the nosology of schizophrenia and psychiatry.

## Viral Hypotheses

The suggestion that psychotic illnesses may be related to an infectious process has a long history. Jean Etienne Esquirol in 1845 noted that some forms of psychotic illness followed "epidemic" illness patterns. In the early part of this century, Karl Menninger observed an association between the onset of schizophrenia and influenza epidemics. In addition, it has long been known that clinical features of viral encephalitis may include psychosis and other features resembling those of schizophrenia.

Two lines of evidence that have provoked the most interest in the possibility that viral infections are causative of schizophrenia are an increase in birth during influenza epidemics of individuals who subsequently develop schizophrenia and an increase in winter births among patients with schizophrenia because of the higher rate of viral infections in winter months. Mednick and colleagues (1988) reported a strong association between pregnancies during the 1957 influenza epidemic in Helsinki, Finland, and subsequent development of schizophrenia. Moreover, it was learned that the relationship between viral exposure and schizophrenia appears strongest when exposure occurred during the second trimester of pregnancy. This is of interest because the second trimester is a critical period for cortical and limbic development. It was therefore reasoned that second-trimester viral exposure might disrupt neuronal development in key areas of the brain, such as the hippocampus and prefrontal cortex that have been implicated in this illness. In fact, there is some experimental evidence from animal models that viral exposure to these regions in the developing brain produces neuropathological changes resembling those observed in some postmortem studies of schizophrenia. However, reanalysis of previous data failed to detect significant association between *in utero* exposure to influenza epidemics and schizophrenia. Similarly, data from Australia failed to find an association between six influenza epidemics and schizophrenia (Morgan et al. 1997). These and other negative results have raised serious questions about this theory. Interestingly, in the North Finland birth cohort, a significant association was found with laboratory confirmed diagnosis of viral infection, especially Coxsackie B5 meningitis in the neonatal period and risk of schizophrenia later on.

As previously mentioned, several studies have demonstrated an excess of winter births among patients with schizophrenia. Although statistically significant, the association between winter births and schizophrenia appears relatively small, occurring in less than 10% of cases. Thus, season of birth remains an interesting (and unresolved) research issue but has little use as a risk factor for the illness from a clinical perspective. However, exposure to influenza *in utero* and excess winter births is interesting although indirect lines of evidence for a viral cause of schizophrenia. To date, there has been no direct confirmation for any viral agent causing this illness, such as viral isolates or consistent findings of specific viral antibodies. Advances in neurovirology, however, are providing new insights into the role of viruses in brain diseases, leading to new hypotheses about schizophrenia. One area involves the search for neurotropic retroviruses. For example, Borna virus is a naturally occurring neurotropic agent in horses and sheep. The development of a serological assay method to detect antibodies for Borna virus led to the discovery that its hosts also include humans and that it has relative tropism for the hippocampus. Moreover, its clinical manifestations range from asymptomatic infection to profound behavioral abnormalities that resemble some aspects of schizophrenia. An association between deficit symptoms, Borna virus antibodies and summer birth excess has been reported. There is now an active research effort to determine whether Borna and other neurotropic viruses are more common in schizophrenia. Torrey et al. (2006) are making a similar case for cytomegalovirus (CMV) to play an etiological role in schizophrenia using CMV antibodies in first episode patients. However, in infections that have been associated with schizophrenia such as rubella, influenza, Herpes Simplex Virus-1 and -2, cytomegalovirus, poliovirus, and toxoplasma gondii, it is not the virus itself that adversely affects fetal brain development, but rather the cytokine response from the infected mother. Moreover, infections during pregnancy can affect brain development by releasing stress hormones, producing hypoxia, hyperthermia or malnutrition or by triggering proinflammatory cascade of cytokine responses of the mother, placenta, or the fetus (Ross et al. 2006).

## Immune Dysfunction

Several research groups are exploring the possibility that schizophrenia may be associated with impaired immune function including alterations in autoimmunity. According to a recent report, a history of any autoimmune disease was associated with a 45% increase in schizophrenia, thyrotoxicosis, Sjogren's disease, celiac disease, acquired hemolytic anemia and interstitial cystitis (Eaton et al. 2006). Anticardiolipin antibody and antinuclear antibody, two autoantibodies that are used as markers of autoimmune vulnerability, have been shown to be increased in patients with schizophrenia in some but not all studies of this illness. Specific histocompatibility antigens (human leukocyte antigens) have also been linked to several autoimmune diseases and have been investigated in schizophrenia with conflicting results. Two other markers relevant to autoimmune function, impaired T lymphocyte proliferative response to the mitogen phytohemagglutinin and impaired interleukin-2 production, have shown more consistent alterations in patients with schizophrenia than in control populations. Interestingly, an inverse relationship exists between rheumatoid arthritis and schizophrenia. This has been explained by some as both illnesses sharing a common immune etiology such that once an individual is affected by one of the diseases, they become relatively immune to the other. Some of the most intriguing work in this area is focused on finding autoantibodies to brain tissue. Recent reports of atypical antipsychotic medications having immunomodulatory effects and selective COX-2 inhibitor (a nonsteroidal anti-inflammatory pain killer) having positive effects on schizophrenia symptoms are interesting and provide yet another avenue of research in understanding the complexity of schizophrenia. Immunological aberrations have been associated with clinical symptomatology in several studies with paranoid symptoms, negative symptoms, and acute symptomatology (Strous and Shoenfeld 2006).

## Birth Complications

Numerous studies have reported a higher rate of pregnancy and birth complications in patients with schizophrenia than in control populations (Cannon et al. 2002). The complication rates vary widely among studies, probably because

of the inherent difficulties in obtaining reliable and valid retrospective data in this area. In one study, two-thirds of schizophrenia patients and less than one-third of control subjects had histories of obstetrical complications. Hypoxia is one possible result of pregnancy and birth complications that has been shown to disrupt brain development. The hippocampus and some neocortical regions are particularly sensitive to shortfalls in oxygen. Thus, one proposed mechanism for a role of pregnancy and birth complications in the cause of schizophrenia involves hypoxia-mediated damage to these areas. While some investigators agree with this theory, others do not. Interestingly, some studies suggest that the rate of obstetric complications are higher in early-onset schizophrenia, occur more often in males, in people with prominent negative symptoms, and no family history of schizophrenia (Verdoux et al. 1997). Rhesus (Rh) factor incompatibility between mother and fetus leads to increase risk for schizophrenia (OR up to 2.6). It is not clear if this is due to hypoxia or increase in bilirubin levels or both.

A metaanalysis of data involving 854 individuals from 11 research groups (Verdoux et al. 1997) suggests that the relationship between birth complications and age at onset tend to be linear and may indicate a causal effect. Jones and colleagues (1998), using North Finland birth cohort involving 11,017 patients reported a sevenfold excess among schizophrenia patients of perinatal brain injury. In a historical and meta-analytic review by Cannon and colleagues (2002), complications of pregnancy, abnormal fetal growth and development and complications of delivery were significantly associated with developing schizophrenia but the effect sizes were generally small with odds ratios of less than 2. Diabetes in pregnancy (OR = 7.76), placental abruption (OR = 4.02) and birth weight of <2,000 gm (OR = 3.89) had higher odds ratios. They elaborate current methodological shortcomings and suggest need for newer and better approaches to inform our understanding of these important associations (Cannon et al. 2002). Recently, they proposed to group birth complications based on similar modes of action and suggested following categories: fetal growth retardation, fetal perinatal hypoxia and prenatal complications. They conceptualize fetal growth retardation as one of the earliest manifestations of the neurodevelopmental trajectory of schizophrenia that includes decrements in motor, language, and cognitive performance from infancy throughout childhood. Furthermore, based on work done by them and others, the intriguing interactions between fetal hypoxia and genetic risk for schizophrenia on brain structure leads them to postulate that reductions in gray matter volume in some cortical areas of the brain including hippocampus occur following gene-environmental interactions. Regarding prenatal complications, the list of risk factors continue to grow with effect size mentioned as an odds ratio of around 2.0 (Clarke et al. 2006).

The effects of both genes and environment on gene expression are called *epigenetics*. Environmental exposures, even stress and medication treatments, can affect gene expression. There may be critical periods in life when lifelong gene expression may be established such as during fetal life. The fetus receives signals about the health and environment of the mother through the placental circulation, including nutritional status, infection, and even stress. These exposures can determine the lifelong gene expression of the fetus through a process called *fetal programming*. The genotype of the individual may determine the developmental consequences of any fetal exposures or obstetric complications (Lieberman et al. 2006). However, according to Clarke et al. (2006), obstetric complications remain one of the best replicated "environmental" risk factors for schizophrenia but they are neither necessary nor sufficient causal factors for schizophrenia. Thus, further research in this area and with improved methodologies it is possible to have a stronger impact in decreasing the detrimental effects and interactions between genetic and environmental factors.

## Pathophysiology

Whereas *etiology* refers to the cause of an illness, *pathophysiology* refers to the abnormal processes that mediate the clinical manifestation of the illness. As was the case with etiology, the brain processes that give rise to schizophrenia are currently not known. However, rapidly converging bodies of neuroanatomical and neurochemical data appear to be closing in on defining the pathophysiology of this illness. In this section, these data are reviewed.

## Neuroanatomical Theories

The brains of patients with psychotic illnesses have been examined for hundreds of years. At the end of the 19th century, Alzheimer described loss of cortical neurons in patients with dementia praecox. In 1915 Southard noted cerebral atrophy in patients. Although these early reports were suggestive of a brain lesion in schizophrenia, only recently have the investigative tools become available to probe the human brain in enough detail to confirm cerebral abnormalities in this illness.

Advances in *in vivo* brain imaging and postmortem methodology have provided powerful new tools for neuroanatomical investigations of this illness. *In vivo* structural brain analysis began in earnest with computed tomography (CT), which provided the most compelling evidence for morphological abnormalities in this illness. CT has been replaced by magnetic resonance imaging (MRI) for morphological studies because of its superior anatomical resolution (1 mm or less in-plane resolution), ability to provide true volumetric and three-dimensional analysis of even minute brain regions, tissue segmentation capability and because it involves no radiation exposure. Positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional MRI (fMRI), and MR spectroscopy (MRS) are imaging tools used to assess the functional and neurochemical activity of specific brain regions. Magnetization transfer (MT) is a proton-weighted MRI image that can give information about the integrity of myelin. Diffusion Tensor Imaging (DTI) and Line Scan Diffusion Imaging (LSDI) are newer MRI approaches that can provide sophisticated information on the orientation and integrity of neuron fibers *in vivo*. DTI focuses on the diffusion of water in the brain and measures fractional anisotropy (FA) which measures the direction of flow or indirectly, lining up of neuronal fibers. Apparent diffusion coefficient (ADC) measures the water content, high or low. Advances in postmortem methodology include rapid access to brains after death, well-matched control groups, controls for antipsychotic exposure including studies of antipsychotic-naive populations, and application of new molecular biological techniques. The following

is an examination of the brain structures most often implicated in the pathophysiology of schizophrenia.

## Enlarged Ventricles

The ventricles are the fluid-filled spaces in the center of the brain. The most consistent morphological finding in the literature of schizophrenia is enlarged ventricles which have been confirmed by a large number of CT and MRI studies (McCarley et al. 1999). The effect size of ventriculomegaly has been reported to be 0.7. Seventy-nine percent of the well designed studies report enlargement of lateral ventricles. CT studies have tended to use ventricle–brain ratios to assess lateral ventricular size, and MRI studies have used more sophisticated quantifications. Lawrie and Abukmeil (1998), in a review report approximately 40% difference in volume between schizophrenia patients and controls across all volumetric MRI studies. It should be noted that although the ventricular increases are statistically significant, the ventricles are not grossly enlarged in most cases. In fact, radiologists most often read CT and MRI scans of patients with schizophrenia as normal. In addition, most studies of ventricular size demonstrate overlap between patients and normal control subjects, indicating that many patients have ventricles in the normal range. Nonetheless, enlargement of the ventricles is the first consistently reported finding confirming a brain abnormality in schizophrenia. Chronically ill patients are reported to have substantially more ventricular enlargement compared to those who are in their first episode. Increase in ventricular size with the progression of illness has been reported too. In a 10-year longitudinal study of brain changes in schizophrenia, ventricular enlargement was progressive, and not a developmentally static finding (see Figures 65–3 and 65–4). In first episode subjects, a meta-analysis showed that lateral ventricles are significantly larger and the volume tends to increase significantly longitudinally (Steen et al. 2006). Many have speculated that these changes may begin early and can be detected even before the onset of psychosis. However, two studies of patients in their prodrome did not show ventricular enlargement or its progression (see DeLisi et al. 2006). Using DTI, when comparisons were done in high risk adolescents

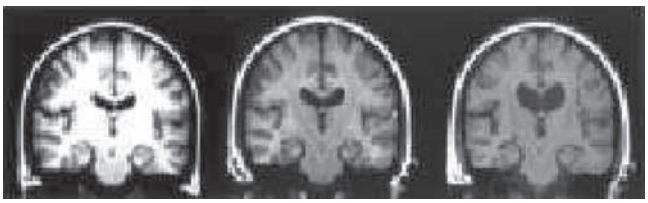


**Figure 65–3** *Magnetic resonance imaging (MRI) of a female patient who initially was scanned at the time of hospitalization for a first episode of schizophrenia. At the tenth year of follow-up, at age 34, she was an outpatient with a diagnosis of chronic schizophrenia stabilized with predominantly negative symptoms.*

for schizophrenia and controls, there was already elevated CSF content in the left parahippocampal gyrus and right superior temporal gyrus in this group compared to controls. However, this was a small sample. Some studies have reported displacements in the left posterior horn compared to controls and also disproportionately enlarged temporal horn of the left lateral ventricle in schizophrenia; these changes are in important areas such as caudate nucleus, hippocampus, amygdala etc, raising important etiological questions.

The pathophysiological significance of larger than normal ventricles is unclear (Lawrie and Abukmeil 1998). There have been reports that enlarged ventricles may be more prominent in more severely ill patients and related to poor response to neuroleptic medication, although these findings have not been consistently replicated. Ventricular enlargement, particularly third ventricle and temporal horn enlargement, has been found in first-episode patients with schizophrenia, which suggests that it is not secondary to chronic neuroleptic exposure or a progressive disease process. However, frontal horn enlargement is usually seen in chronic cases, suggesting possible progressive changes following onset of the illness. Enlarged ventricles are most likely a secondary manifestation of brain atrophy or some other process resulting in either focal or generalized reductions in brain mass. Indeed, there have been many reports of brain atrophy and reduced mass in the illness (Figure 65–5). Enlarged ventricles have also been reported in first-degree

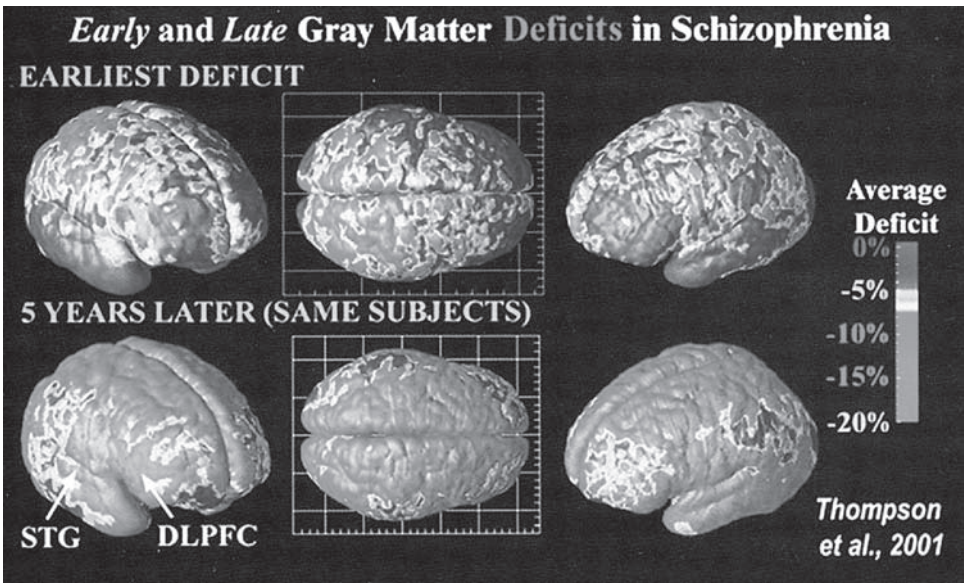



**Figure 65–4** *Structural abnor-malities in schizophrenia.*

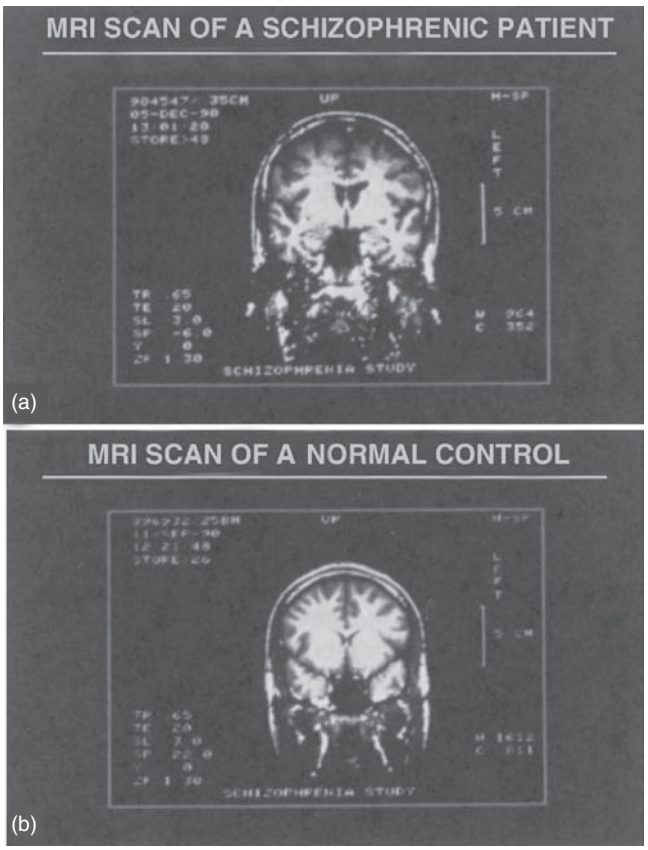



**Figure 65–5** *CT scans of a schizophrenic patient (a) and a healthy volunteer (b). Note enlarged ventricular spaces and brain atrophy in the scan of the patient with schizophrenia.*

relatives of subjects with schizophrenia and in persons suffering from schizotypal personality disorder raising interesting speculations of whether ventriculomegaly may be an indicator of neurodevelopmental risk for schizophrenia (Lencz et al. 2001).

## Limbic System

The limbic structures that have been implicated in schizophrenia are the hippocampus, entorhinal cortex, anterior cingulate, and amygdala. These structures have important functions for memory (hippocampus), attention (anterior cingulate), and emotional expression and social affiliation (amygdala). The entorhinal cortex serves as a "way station" between hippocampus and neocortex in that neurotransmissions between these regions synapse in the entorhinal cortex. The entorhinal cortex, hippocampus, and other components of the parahippocampal gyrus are often considered "mesiotemporal" structures because of their close anatomical and functional relationship.

There are more reports of abnormalities in hippocampal and related mesiotemporal structures than other limbic structures in schizophrenia. In fact, mesiotemporal pathology is consistently found in studies of schizophrenia and mesiotemporal structures are leading candidates for the neuroanatomical site of this illness. This region has been implicated by converging brain imaging and postmortem lines of evidence. One of the most consistent MRI morphological findings is reduction in size of the hippocampus (Breier et al. 1992). In addition, more than 25 postmortem studies have reported morphological and cytoarchitectural abnormalities in this structure. The findings have included reduced size and cellular number, white matter reductions, and abnormal cell arrangement. Nelson and colleagues (1998), conclude from a meta-analysis of 18 studies that there is a bilateral reduction of approximately 4% hippocampal volume in schizophrenia. However, reduced hippocampal volume is not reported by all studies. In another review, Lawrie and Abukmeil (1998) reported approximately 6% reduction in amygdala hippocampal complex. Reduction in the volume of amygdala is reported by some but not all. In a very interesting preliminary report from Australia, subjects who went on to develop schizophrenia had larger left hippocampal volumes compared to controls at baseline (during the prodrome) with subsequent reduction in volume after the onset of schizophrenia. The same group recently published findings involving 473 subjects, measuring hippocampal and amygdala volumes in patients with chronic schizophrenia ($n = 89$), first episode schizophrenia ($n = 162$), and those with ultrahigh risk for psychosis ($n = 135$), and controls (87). Patients with chronic schizophrenia had bilaterally smaller hippocampi, first episode schizophrenia patients had reduced left sided hippocampal volume but not in patients with schizophreniform psychosis, affective psychosis or other psychosis. Bilateral amygdala enlargement was present only in the first episode nonschizophrenia patients. The ultra high risk group (who did or did not develop psychosis) exhibited no hippocampal or amygdala volume changes compared to controls (Velakoulis et al. 2006).

The anterior cingulate has been implicated in schizophrenia largely because of postmortem findings of reduced gamma-amino butyric acid (GABA) interneurons. In addition, functional imaging studies have demonstrated altered metabolic activity both at rest and during selective attention tasks in the anterior cingulate in patients with schizophrenia. Data from many studies suggest possible neurodevelopmental abnormalities in anterior cingulate in patients with schizophrenia (Benes 2000). Bouras and colleagues (2001) reported mean total and laminar cortical thickness as well as mean pyramidal neuron size were significantly decreased in the dorsal and subgenual parts of anterior cingulate in schizophrenia patients. Thirty-one studies evaluated one or more of the medial temporal lobe structures—hippocampus, amygdala, parahippocampal gyrus, entorhinal cortex—with 77% reporting positive findings; this is one of the higher percentages of abnormalities reported in all regions of interest throughout the brain.

## Temporal Lobe

The superior temporal gyrus (STG) is involved in auditory processing and, with parts of the inferior parietal cortex, is a heteromodal association area that includes Wernicke's area, a language center. Because of the important role it plays in audition, it was hypothesized to be involved in auditory hallucinations. Indeed, MRI studies have found the STG to be reduced in size in schizophrenia and have found a significant relationship between these reductions and the presence of auditory hallucinations. Similarly, Wernicke's area, which is involved in the conception and organization of speech, has been hypothesized to mediate the thought disorder of schizophrenia, particularly conceptual disorganization. Support

for this hypothesis comes from a report of a patient with vascular and other lesions of this region that produce Wernicke's aphasia, a disruption in the organization of speech that resembles the thought disorder of schizophrenia. MRI studies have found a relationship between morphological abnormalities in this region and conceptual disorganization in schizophrenia (Shenton et al. 1992). McCarley and colleagues (1999) reviewed 118 MRI studies published from 1988 to 1998; 62% of the 37 studies of whole temporal lobe showed volume reduction and/or abnormal asymmetry. Of the 15 studies surveyed, 80% showed abnormalities in STG, the *highest* percentage of any cortical region of interest. This difference appears to be largely due to gray matter. Most studies, including those involving first episode patients, report abnormalities in *planum temporale* (area related to language) with specific reductions of left posterior STG gray matter. According to the authors, the higher percentage of abnormalities in specifically defined regions of interest of medial temporal lobe and STG suggests a nondiffuse distribution of temporal lobe structural changes. Reduced planum temporale volumes have been shown to be associated with positive symptoms. Narr et al. (2004) isolated regional volume deficits in patients experiencing their first episode of schizophrenia by using two novel and complimentary computerized surface-based image analysis techniques. Specifically, they compared hippocampal radial distances and perihippocampal cerebrospinal fluid distributions between diagnostic groups at thousands of homologous hippocampal surface locations allowing the identification of very large changes in hippocampal structure. They interpreted the results to suggest that volume reductions resulted from disturbed neurodevelopmental rather than neurodegenerative processes. Patients without prior antipsychotic exposure had smaller hippocampal volumes compared with the healthy group.

When DTI studies were done in adolescents at high risk for schizophrenia, there were changes already taking place in the left STG suggesting that perhaps, the atrophic changes occur early. The authors postulate that these changes are occurring early in the areas involved in language processing (DeLisi et al. 2006). Progressive volume reductions of the left STG in first episode of schizophrenia patients but not in bipolar patients was reported after 18 months. STG volume reductions have been documented in nonpsychotic offsprings of patients with schizophrenia, suggesting that STG volume reductions may be a marker of risk for schizophrenia.

## Prefrontal Cortex

The prefrontal cortex (PFC) is the most anterior portion of the neocortex, sitting behind the forehead. It has evolved through lower species to become one of the largest regions of the human brain, constituting approximately one-third of the cortex. It is responsible for some of the most sophisticated human functions. It contains a heteromodal association area that is responsible for integrating information from all other cortical areas as well as from several subcortical regions for the execution of purposeful behavior. Among its specific functions are working memory, which involves the temporary storage (seconds to minutes) of information, attention, and suppression of interference from internal and external sources. The most inferior portion of the PFC, termed the orbital frontal cortex (OFC), is involved in emotional expression. Given its unique role, it is not surprising that the PFC has been considered in the etiology of schizophrenia. Dorsolateral Prefrontal Cortex (DLPFC) is involved in working memory and other executive functions.

Indeed, several lines of evidence have implicated the PFC in schizophrenia. CT studies have provided evidence for prefrontal atrophy, and some, although not all, MRI studies have found evidence for decreased volume of this structure (Breier et al. 1992, McCarley et al. 1999). One of the earliest observations from functional imaging studies of schizophrenia was reduced perfusion of the frontal lobes. This finding was subsequently replicated by several PET studies suggesting decreased frontal glucose utilization and blood flow, which came to be known as *hypofrontality*. Subsequent functional imaging studies provided further support for hypofrontality by demonstrating that patients with schizophrenia failed to activate their frontal lobes to the same degree as normal control subjects when performing frontal cognitive tasks. This finding has been questioned because patients with schizophrenia typically perform poorly in many cognitive paradigms, so it is unclear whether their lack of frontal activation is a primary frontal deficit or secondary to poor cognitive task performance related to factors such as lack of motivation, inattention, or cognitive impairment stemming from nonfrontal regions. Functional Neuroimaging studies used CPT and working memory tasks and repeatedly found reduced activation in DLPFC (Ford et al. 2004). Moreover, PFC dysfunction became especially pronounced when the task complexity increased requiring greater effort to perform relatively simple tasks. There was a corresponding greater activation of DLPFC such that with greater task complexity, schizophrenia patients start failing. Context dependent response selection and execution deficits have been associated with DLPFC activation deficits. PFC dysfunction appears to be wide spread and disturbed over the DLPFC, ventral and medial prefrontal regions, each contributing to specific aspects of the clinical and cognitive domains. fMRI studies in high-risk individuals for schizophrenia (prodromal) have reported significant deficits in the recruitment of PFC regions with further deterioration prospectively during the course of illness (Morey et al. 2005). Auditory hallucinations were found to be associated with increases in Broca's area, a portion of the frontal cortex responsible for language production. This finding was of interest because it supported a hypothesis that auditory hallucinations were a form of abnormal "inner speech."

MRI studies employing diffusion tensor imaging have reported changes suggestive of an abnormality in white matter connectivity possibly due to reduced myelination of fiber tracts in patients with schizophrenia. Magnetic resonance spectroscopy (MRS) studies have reported reduced levels of neuronal membrane constituents (phosphomonoesters) and/or increased levels of their breakdown products (phosphodiesters) in patients with schizophrenia, primarily in the frontal cortex. Such abnormalities have been observed in treatment-naive first episode patients and have been correlated with trait-like negative symptoms and neurocognitive performance.

Though sometimes contradictory, the neuroimaging studies consistently report abnormalities in orbitofrontal region; often, these abnormalities tend to correlate with severity of schizophrenia symptomatology, show gender differences in relation to spatial localization and the gray matter

deficits may be more wide spread in chronic, as compared to medication-naive first episode patients (Lencz et al. 2001). Frontal lobe volumes were decreased in individuals with first episode of psychosis and showed progressive decline 30 months later. Increased cerebrospinal fluid volume in frontal lobes has been reported too. Additional support for PFC involvement in schizophrenia comes from postmortem studies with a range of findings. There have been reports of reduced cortical thickness, loss of pyramidal cells, malformed cellular architecture, loss of GABA interneurons, and evidence of failed neuronal migration. The Stanley Foundation Neuropathology Consortium is reported to be "the most extensively characterized collection of pathological specimens from patients with major mental illnesses." Their exploratory analyses of PFC from patients suffering from schizophrenia, bipolar disorder, and depression compared with samples from normal controls found the largest number of abnormalities in schizophrenia with an overlap with bipolar disorder. A majority of the abnormalities represented a decline in function suggesting a widespread failure of gene expression. Specifically, abnormalities involving the glycoprotein *Reelin* were observed in schizophrenia, a finding reported previously by other postmortem studies also. *Reelin*, an extracellular matrix glycoprotein secreted from different GABAergic interneurons during development and adult life, may be important for the transcription of specific genes necessary for synaptic plasticity and morphological changes associated with learning. Reelin is believed to play a key role in directing cortical neuronal migration. Mutations in reelin can cause lissencephaly. Future studies will clarify the role of *Reelin* in the pathology of schizophrenia.

Thus, a substantial body of evidence is converging on PFC as a site of pathophysiology in schizophrenia (Weinberger et al. 2001). The genetics of the prefrontal neurons, the cortical circuits and its underlying neurochemistry in the brains of individuals with schizophrenia is one the most intensely investigated area.

## Other Neocortical Regions

There are positive as well as negative reports of both parietal and occipital lobes showing differences between patients with schizophrenia and healthy controls. Abnormalities involving cerebellum have been reported too. At present, the significance of these findings are not clear (McCarley et al. 1999).

## Striatum

The striatum, consisting of the caudate, putamen, globus pallidus, substantia nigra, and accumbens, is an output center for the cortex and has been traditionally thought to have a primary role in the execution of motor programs. Subsequent studies have demonstrated an important cognitive role for this structure as well. Moreover, in primary diseases of the striatum, such as Parkinson's and Huntington's diseases, clinical manifestations include psychosis and other schizophrenia type behavior, which has contributed to interest in this region in the pathophysiology of schizophrenia.

Two related bodies of data are most frequently cited regarding the role of the striatum in schizophrenia; these concern the mechanism of antipsychotic drugs and postmortem studies of altered dopamine $D_2$ receptor numbers. The dorsal striatum (caudate and putamen) is the site of the vast majority of $D_2$ receptors in brain. All effective antipsychotic drugs antagonize this receptor and thus, by extrapolation, it was reasoned that this region might be central to the pathophysiology of schizophrenia. Moreover, the most consistent postmortem finding in the schizophrenia literature is an increased density of striatal $D_2$ receptors. However, antipsychotic exposure causes up-regulation of $D_2$ receptors, which may account for this postmortem finding. A current view of the antipsychotic mechanism is that the dorsal striatum is involved in mediating the extrapyramidal side effects of antipsychotic medications and, based on rodent studies of antipsychotic drug mechanisms, the ventral striatum (nucleus accumbens) may be involved in antipsychotic efficacy. Thus, attention has shifted toward the possible role of the accumbens in mediating the psychosis of schizophrenia.

Several MRI studies have found an increased volume of the caudate, putamen, and globus pallidus in schizophrenia (Breier et al. 1992). In all cases, the patients included in these studies had exposure to first generation antipsychotic (FGA) treatment, which raised the possibility that striatal enlargement may be secondary to antipsychotic exposure. In a longitudinal study of antipsychotic-naive patients who were subsequently treated with FGA, it was found that striatal size was not enlarged before antipsychotic drug treatment but increased after antipsychotic exposure, which supports the notion that FGA may account for this consistent morphological finding. This was further confirmed when increased size of caudate nucleus following long-term antipsychotic exposure normalized after switching to clozapine, a second generation antipsychotic drug which has significantly less activity in the striatal region.

## Thalamus

The thalamus is a nucleus that receives subcortical input and outputs it to the cortex. One theory posits that the thalamus provides a filtering function for sensory input to the cortex. A deficit in thalamic filtering was proposed to account in part for the experiential phenomena of being overwhelmed by sensory stimuli reported by many patients with schizophrenia. Preclinical studies have demonstrated that antipsychotic drugs modulate thalamic input to the cortex, which has been offered as a model for antipsychotic drug action. Several MRI studies have reported reduced volume and functional abnormalities of thalamus in patients with schizophrenia. A metaanalysis of data from first episode psychosis patients suggests that there are volumetric changes in thalamus at baseline but may not be progressive unlike other regions of interest (Steen et al. 2006). Postmortem studies have also found cell loss and reductions in tissue volume in thalamic nuclei. This thalamic tissue reduction is considered as a possible evidence of abnormal circuitry linking the cortex, thalamus, and cerebellum.

## Neural Circuits

Because of the large number of different neuroanatomical findings in studies of schizophrenia and the appreciation that brain function involves integration of several brain regions, current thinking about the neuroanatomy of this illness is centered on neural circuits. Thus, investigators are attempting to examine the integrity of a variety of cortical–cortical and cortical–subcortical neural networks that function together to execute behavioral programs. It is conceivable

that an isolated lesion anywhere in a neural circuit could result in dysfunction of the entire network, and therefore spurious conclusions could be drawn by investigating only one component of a neural network. Evidence suggests that schizophrenia may be associated with a decrease in synaptic connectivity of the dorsal PFC though this is not reported by all studies. McGlashan and Hoffman (2000) have proposed the Developmentally Reduced Synaptic Connectivity (DRSC) model which proposes that cortical gray matter deficits may arise from either reduced baseline synaptic density due to genetic and/or perinatal factors, or excessive pruning of synapses during adolescence and early adulthood or both. Margolis and colleagues (1994) propose that there could be graded apoptosis rather than a necrotic fulminant process. Apoptosis is a form of cell death that occurs in many neurodegenerative disorders in which intra- or extracellular physiologic events trigger a programmed sequence of cellular actions resulting in cell destruction and evacuation. According to Goldman-Rakic and Selemon (1997), there is regionally specific decreased neuronal size in cortical layer III with cytoplasmic atrophy and generally reduced neuropil. The reduced size and increased density of neurons or glia and decreased cortical thickness suggest that cell processes and synaptic connections are reduced in schizophrenia. This is consistent with reports of decreased concentrations of synaptic proteins (e.g., synaptophysin). This has been called "Reduced Neuropil Hypothesis." (Glantz et al. 2006) (See Figure 65–6). These cell processes and synapses could be lost as a consequence of a neurochemically mediated (through dopamine and or glutamate) synaptic apoptosis that would compromise cell function and alter brain morphology without, however, producing serious cell injury (and thus inducing glial reactions). However, McCarley and colleagues (1999) suggest that the main neural abnormality in schizophrenia involves neural connectivity (dendrite/neuropil/gray matter changes) rather than the number of neurons or network size. They suggest that a "failure of inhibition" on the cellular level is present in schizophrenia and may be linked to a "failure of inhibition" at the cognitive level. According to Lafargue and Brasic (2000) abnormalities involving the temporolimbic–prefrontal cerebral circuitry are postulated to underlie the organizational and memory deficits commonly observed in schizophrenia patients. Furthermore, as reviewed by these authors, a possible insult or injury to the mechanism of GABAergic and glutamatergic influence during early corticogenesis may largely contribute to the later manifestation of clinical schizophrenia. Malfunction of the cooperating sensory systems of excitation and inhibition during the early stages of development of the brain could result in the failure of "pioneer neurons" to properly differentiate and migrate to their appropriate cerebral locations. Consequently the later migrating projection neurons may fail to reach or invade their preselected area-specific brain sites. A disturbance of the proper GABAergic and glutamatergic influences would upset NMDA mechanisms and normal cortical development. If such disturbance is actively occurring from the onset of cerebral ontogeny, the affected individual may suffer from the signs and symptoms observed in schizophrenia. A challenge for the future is developing new approaches to examining the brain as an integrated and highly interactive system. An unanswered question is whether the morphological differences reflect hypoplasia (failure to develop) or atrophy (shrinkage).

## Electrophysiology

Electroencephalogram (EEG) records the electrical activity of brain, which may reflect the mental functions carried out by the neurons possibly in "real time." However, the precise localization of this event in the specific brain region is poor. Quantitive EEG (qEEG) involves computer assisted imaging and statistical analysis of the EEG for detecting abnormalities. A review of qEEG literature found that though 5–80% schizophrenia patients showed EEG abnormalities including increased slow activity in the delta and theta bands their significance is not clear. Clinically, individuals with schizophrenia often do not have EEG findings, and when they do, they are often of this nonspecific variety, unless there are other neurological disorders present.

When EEG activity from repeated presentations of a specific stimulus is summed across trials, some potentials

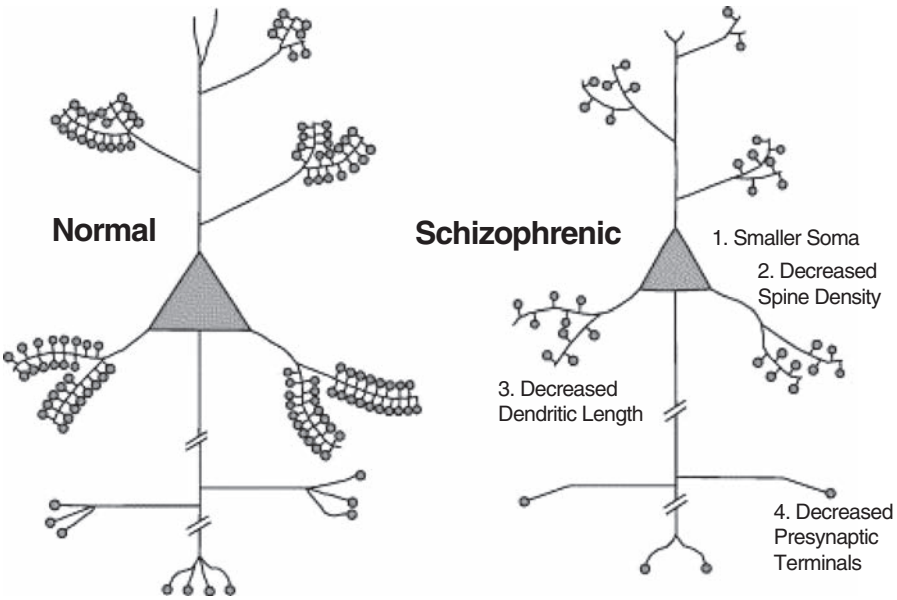



**Figure 65–6** *Cortical pyramidal neurons from subjects with schizophrenia exhibit: (1) smaller somal volume, (2) decreased spine density, (3) decreased dendritic length, and (4) decreased terminals (as demonstrated by decreased presynaptic markers) compared to healthy controls. These postmortem findings contribute to the hypothesis that schizophrenia stems from altered synaptic circuitry.*

related to the specific processing of the target stimulus can be extracted from the EEG and are referred as *event-related potentials* (ERPs). The P300 ERP, a positive deflection occurring approximately 300 milliseconds after the introduction of a stimulus, is regarded as a putative biological marker of risk for schizophrenia. The P300 amplitudes are smaller in patients with schizophrenia and is one of the most replicated electrophysiological findings. The P300 ERP is often elicited with an oddball paradigm, wherein two stimuli are presented in a random series such that one of them occurs relatively infrequently and subjects are instructed to respond to the infrequent target stimulus. Though the exact neural locations of the normal P300 generation are uncertain, it is thought that discriminating the target from a standard stimulus should involve frontal lobe. If the neuroelectric events that underlie P300 generation are related to an interaction between frontal lobe and hippocampal/temporal–parietal function, disease states that affect frontal and temporal/parietal lobe function should also affect P300 measures. This hypothesis has been supported by findings of smaller P300 amplitudes over left temporal scalp locations relative to the homologous right temporal locations for patients with schizophrenia compared to controls. Remarkably, reductions in the left posterior superior temporal gyrus gray matter volume (using MRI) correlated with the reduction in the temporal P300 amplitude in chronic and first episode schizophrenia. Even though the magnitude of P300 component differences between patients with schizophrenia and controls is highly reliable across individual studies (Jeon and Polich 2001), variation for the group effect size is systematically associated with disease definition, stimulus parameters, task conditions, and recording methods.

N400 is a negative deflection in the ERP occurring approximately 400 milliseconds after introduction of a stimulus, whose latency is thought to reflect the speed of linguistic operations related to semantic search. Abnormalities in the N400 amplitude in schizophrenia have been reported. Investigators suggest that individuals with schizophrenia do not use the context of the preceding portion of the sentence and fill-in responses to phrases based on the immediately preceding word rather than the whole sentence or passage.

Investigations using newer probes such as atypical antipsychotic agents and their effects on ERPs are interesting; clozapine, in a small sample using a double blind paradigm, improved the amplitude of the P300 but chlorpromazine did not. Thus, future studies promise interesting information in this area.

## Sensory and Sensorimotor Gating

An organism needs an internal mechanism to select from diverse sensory input the information that is necessary to function efficiently. This process is termed as *sensory* or *sensorimotor* gating. Thus, s*ensory gating* refers to the basic ability of the brain to suppress the response to repeated and possibly irrelevant environmental stimuli. Measures of sensory or sensorimotor gating are among the most widely studied physiological markers used in laboratory studies of schizophrenia. P50 and Prepulse Inhibition are important paradigms developed to quantify sensory and sensorimotor gating respectively.

P50 is an early positive component of an auditory averaged Event Related brain Potential (ERP), which is recorded at the vertex 50 ms after a click stimulus. In the P50 paradigm, when two identical auditory stimuli (clicks) are presented in close temporal proximity to each other (usually 500 ms), the amplitude of the P50 ERP to the first auditory stimulus is larger than the second stimulus. This P50 amplitude reduction or suppression seen with the second stimulus is a measure of sensory gating. When subjects fail to show a diminished response to the second stimulus, this suggests a failure of inhibitory mechanisms apparently due to reduction in short-term habituation. Numerous studies have now confirmed that individuals with schizophrenia exhibit less P50 suppression than healthy controls.

In the Prepulse Inhibition (PPI) of startle paradigm, PPI is defined as an inhibition of the startle response when a low-intensity stimulus (a prepulse) precedes an acoustic startle stimulus. As the prepulse stimulus reduces the effect of the startle-eliciting stimulus, the percentage of PPI provides a measure of the amount of sensorimotor gating (as it involves both sensory stimuli and motor responses). Like P50 suppression, numerous studies have now reported reduction of PPI in individuals with schizophrenia compared to healthy controls.

Although both paradigms are thought to measure gating of incoming information, they are based on different physiological phenomena. P50 suppression is measured by EEG while PPI is measured by electromyography. In contrast to P50 suppression, PPI is not a form of habituation. Though available evidence suggests that PPI and P50 suppression are only weakly related in either healthy volunteers or in individuals with schizophrenia, they could involve common brain mechanisms that regulate cortical and brain stem responsivity. PPI is subserved by cortico-striato-pallido-thalamic circuitry that has interacting and overlapping neural substrates with P50 generation circuitry, especially in mesial temporal lobe structures. Evidence supports decreased sensory gating in schizophrenia due to disruption in architecture, function, and neurotransmitters of hippocampus. Because of this defect, the schizophrenic hippocampus and amygdala (that are responsible for development of emotional significance and response to environmental and internal contexts) are bombarded by a large amount of auditory sensory data that overwhelms the defective limbic system and causes psychiatric symptoms.

Most antipsychotic agents with the possible exception of clozapine do not normalize gating difficulties. However, nicotine improves the gating difficulties. Furthermore, a genetic linkage for the occurrence of sensory gating defect to the $\alpha 7$ nicotinic acetylcholine receptor gene on chromosome 15q–14 has been suggested. Thus, the P50 ERP has been viewed as a promising candidate endophenotype of schizophrenia, a genetically influenced biobehavioral characteristic that will enhance the likelihood of identifying schizophrenia susceptibility. The relationship between abnormal sensory gating and clinical symptoms of schizophrenia is not fully understood especially because the P50 deficit is still present in medicated schizophrenia patients. Moreover, these abnormalities are not restricted to schizophrenia but also occur in other psychiatric as well as neurological conditions. The cross-species nature of both P50 and PPI enables the use of animal models of induced deficits to study pathophysiology as well as develop targeted treatments of schizophrenia. Specifically, in this era of the MATRICS program (see

page 1258), PPI models are likely to play an important role in developing pro-cognitive treatments.

## Mismatch Negativity

*Mismatch negativity* is a particular component of ERP that has a negative peak at 100–200 ms, and is generated by a mismatch process between the sensory input from a *deviant* stimulus and a neural sensory-memory trace (echoic memory) storing the physical features of a *standard* stimuli. MMN is elicited by infrequent variations (called *deviants*) in frequently presented stimuli called *standards* and is considered to reflect automatic, preattentive brain processes. MMN, considered to be one of the most important phenomena in cognitive and clinical electrophysiology, is attenuated in schizophrenia. It was not reduced in first episode schizophrenia patients suggesting that reductions in MMN amplitude might develop over time and thereby index the progression of the disorder. Some suggest that MMN is an index of the functioning of an automatic alerting mechanism designed to stimulate individuals to explore unexpected environmental events. The exact physiological underpinnings of memory traces are still unclear; a popular candidate is the phenomenon of long-term potentiation (LTP) which is mediated at the molecular level mostly by NMDA receptors to glutamate. LTP occurs when presynaptic depolarization originating from the environmental input is tightly linked (synchronized) in time with postsynaptic depolarization which often originates from the previous experience as part of the learning mechanism. Thus, LTP specific postsynaptic depolarization reflects predictive brain activity, a sort of a standard generated by the brain with which to compare inputs. Unexpected inputs are not synchronized with postsynaptic activity pretuned for the expected stimuli. One hypothesis is that the resulting desynchronization at the synaptic level in a group of neurons can cause MMN.

A meta-analysis failed to find a clear association between negative symptoms and MMN reduction. However, recent data suggest that deficits in MMN are associated with poor functional status in schizophrenia patients indicating that MMN deficits represent a core neurophysiological dysfunction. Thus, it is not surprising that researchers are focusing on the possible relationships of deficits in MMN to deficits in higher cognitive functions. Salisbury et al. (2007) associated progressive reductions in MMN amplitude and reductions in left Heschl's gyrus in a prospectively followed group of first episode schizophrenia patients providing support for involvement of auditory cortex in the pathogenesis of schizophrenia. However, simple volume loss does not account for the reduction in MMN. MMN reduction seems to stabilize following the first 1.5 years but that does not appear to be the case with the volumetric changes. Acute treatment with NMDA antagonists is also reported to lead to reduced MMN amplitude in both human as well as animal models leading to a possible explanation that alteration in subpopulation of cortical glutamatergic cells could trigger the sequences of events leading to reduced MMN generation.

## Gamma Band Activity

*Gamma band activity* (GBA) is fast cortical oscillatory activity in the γ-frequency band (30–100 Hz) as recorded in humans using EEG or magnetoencephalography (MEG). GBA is of particular interest in neuroscience research as it has been linked to a variety of perceptual or selective attention. Intra-cortical recordings in animals indicate that neurons encoding the same sensory stimulus synchronize their firing activity to form a cell assembly that underlies the cortical representation of the relevant object. This synchronization gives rise to fast cortical oscillations with frequencies in the γ-band range. While broadly distributed activity in the lower γ range found in EEG may reflect synchronization between cortical areas involved in a particular type of processing, activity in the higher *γ* range identified in MEG appears to represent local network activation. From a physiological perspective, there are strong arguments for synchronization in the γ-frequency band being important for neuronal communication. The hypothesis that synchronous firings of a group of cells increase their functional impact has been the corner stone of various theories of the role of oscillatory γ-frequency activity. It has been proposed that sustained neuronal firing in the γ-frequency is responsible for active maintenance of representations in working memory. A neuron receiving multiple synaptic inputs is more likely to fire if these inputs are synchronized. Synchronous firing has been reported to have stronger effect on receiving neurons in downstream areas. Attention relies on γ-band synchronization to integrate neural activities related to a specific sensory object into a stable, salient and coherent representation, which would then be available for further maintenance in short term memory or encoding into long-term memory. The synchronous assemblies mediating perception and the maintenance of memory do not necessarily belong to the same brain regions. Successful encoding and recall of long-term memory are associated with increased γ-frequency activity. During encoding, the increased γ-frequency activity provides a phasic drive to neurons that are already active. This might serve to entrain the γ activity in the receiving network and thus adjust the timing of neuronal firing to be optimal for synaptic plasticity. During recall, the increased γ-frequency activity might reflect reactivation of synaptically encoded representations. Thus, γ-band synchronization has been theorized to play a pivotal role in attention and memory with the suggestion that γ-frequency activity supports maintenance of working memory (Jensen et al. 2007).

Gamma-band responses of drug free schizophrenia patients during an auditory oddball paradigm have identified a reduced evoked γ response in a late-latency range. Gamma oscillations with late onset are associated with perceptual and associative learning, object representation and selective attention. Additionally, altered γ-band synchronization in schizophrenic patients has been demonstrated using other sensory modalities. The interconnected, inhibitory GABA neurons are postulated to play an important role in the generation of the neuronal-network oscillations with possible dysfunction of parvo albumin-containing GABA neurons. Activation of the α7 nicotinic acetylcholine receptors, which are present predominantly on GABA inter-neurons in the hippocampus, may enhance ongoing oscillations that might contribute to pro-cognitive effects of agonists at these receptors. It is presumed that neuronal synchrony and net-work oscillations share many common processes in human and animals providing a unique opportunity to develop translational biomarkers for drug discovery using animal models.

## Neurochemical Theories

### Dopamine

Dopamine is the most extensively investigated neurotransmitter system in schizophrenia. In 1973 it was proposed that schizophrenia is related to hyperactivity of dopamine. This proposition became the dominant pathophysiological hypothesis for the next 15 years. Its strongest support came from the fact that all commercially available antipsychotic agents have antagonistic effects on the dopamine $D_2$ receptor in relation to their clinical potencies (Creese et al. 1975). In addition, dopamine agonists, such as amphetamine and methylphenidate, exacerbate psychotic symptoms in a subgroup of patients with schizophrenia (Lieberman et al. 1987). Moreover, as noted earlier, the most consistently reported postmortem finding in the literature of schizophrenia is elevated $D_2$ receptors in the striatum.

The dopamine hyperactivity hypothesis and the primacy of $D_2$ antagonism for antipsychotic drug action were seriously questioned largely because of the advent of clozapine, an atypical or second generation antipsychotic (SGA) drug. Clozapine has proved to be the most efficacious treatment for chronic schizophrenia and yet it has one of the lowest levels of $D_2$ occupancy of all antipsychotic drugs. *In vivo* brain imaging studies demonstrated that clozapine $D_2$ occupancy levels were as low as 20% more than 12 hours after the last dose of medication in patients deriving excellent antipsychotic efficacy (compared with more than 80% $D_2$ occupancy for haloperidol) (Farde et al. 1988) (Figure 65–7). This started an extensive search for explanations underlying the extraordinary efficacy of clozapine. However, new information from PET studies has once again highlighted the central role that the dopaminergic system plays in treatment of psychosis. The first generation antipsychotics (FGA) and the SGA are effective only when their $D_2$ receptor occupancy exceeds 50%–65%, reinforcing the importance of $D_2$ antagonism in producing antipsychotic effects. However, an important difference between the FGA and SGA is in their affinity for the $D_2$ receptors. Medications like clozapine attach loosely to and dissociate rapidly from the dopamine $D_2$ receptors compared to typical antipsychotic agents (like haloperidol) which have strong affinity for and bind tightly to these receptors. Thus, Kapur and Seeman (2001) propose that this fast dissociation from the $D_2$ receptors and the low receptor affinity may explain the atypicality of clozapine (for more details see Chapter 102).

Five subtypes of dopamine receptor have now been discovered, $D_1$, $D_2$, $D_3$, $D_4$, and $D_5$, and interest in dopamine receptors other than the $D_2$ receptor has arisen. Reduced levels of $D_1$-like dopamine receptors (i.e. $D_1$ and $D_5$) in the prefrontal cortex of patients with schizophrenia including in those never exposed to antipsychotic agents have been reported. The $D_1$ receptors are expressed predominantly by pyramidal neurons on their dendritic spines, where they possibly modulate glutamate-mediated inputs to these neurons–inputs that mainly come from other pyramidal and thalamic neurons. Thus the reduced $D_1$-like receptors seen in the prefrontal cortex of schizophrenia patients may underlie aspects of cognitive dysfunction and severity of negative symptoms, a finding reported by PET studies too.

There was hope that $D_4$ receptor could be a possible pathophysiological candidate for schizophrenia as clozapine was initially reported to have differential affinity for this receptor. Contrary to initial expectations, $D_4$ receptors do not uniquely distinguish SGA from FGA. Short-term clinical trials involving a limited range of doses of at least two drugs with high $D_4$ potency failed to show antipsychotic effects.

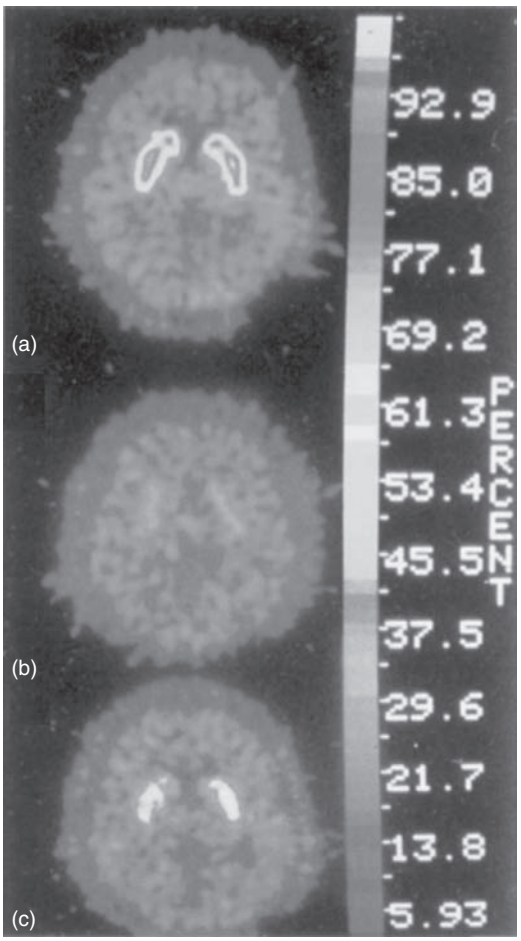



**Figure 65–7** *[$^{11}$C]Raclopride labeling of $D_2$ receptors in the striatum. (a) Medication-free healthy control subject. (b) Patient treated with 4 mg of haloperidol. (c) Patient treated with 500 mg of clozapine. (Source: Farde et al. (1988) Central $D_2$-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatr 45, 71–76. Copyright 1988 American Medical Association.) (See Color Plate XVI.)*

Clinical trials of dopamine agonists have resulted in improvements in the negative symptoms of schizophrenia. A revised model of dopamine dysfunction was proposed which stated that deficits in dopamine, perhaps in the prefrontal cortex, may result in negative and cognitive symptoms and that concomitant dopamine dysregulation causing dopamine increase in the striatum, perhaps related to faulty presynaptic control of dopamine release, and may be involved in positive symptoms. This bidirectional model is under investigation. Kapur (2003) proposed a link between dopamine hypothesis and clinical symptoms. He suggested that normally mesolimbic dopamine provides an external stimulus, or an internal thought with salience, which means that dopamine converts its mental representation from a neutral piece of information into one that 'grabs the attention' of the individual. During acute psychosis, where there is an

increased release of dopamine, salience is given (albeit inappropriately) to what would otherwise have been regarded as insignificant events and perceptions. This increased salience and overreaction to stimuli ultimately leads to paranoia and psychosis.

The DA hypothesis of schizophrenia has been critical in guiding schizophrenia research for several decades. Until recently, a main shortcoming of this hypothesis was absence of direct evidence linking DA dysfunction to schizophrenia. Sophisticated *in vivo* techniques have provided fascinating data directly implicating dopamine in developing psychosis. When the synthesis of dopamine in the brain was measured using PET scan following administration of radiolabeled fluro-L-DOPA, a dopamine precursor, an increase in dopamine was observed in drug-naïve schizophrenia patients compared to age matched controls. Similarly, dopamine release in the basal ganglia was elevated in drug-naïve schizophrenia patients compared to age matched controls when measured by PET and SPECT scans following an amphetamine challenge. This dopamine elevation correlated to the induction of positive symptoms of schizophrenia (Laruelle et al. 1996, Breier et al. 1997). Furthermore, SPECT studies using alpha-methyltyrosine showed that unchallenged release of dopamine was elevated in schizophrenia patients compared to controls (Laruelle et al. 1996). Arvid Carlsson, the Nobel Laureate, and his colleagues (Carlsson et al. 2001), whose work led to the original dopamine hypothesis, appreciate the significance of these data but observe that a wide scatter exists with some values of dopamine release being within normal range in patients with schizophrenia. They suggest that these findings may reflect heterogeneity where dopamine dysfunction may be limited to a subgroup of patients with schizophrenia. Furthermore, the observation that the elevated dopamine release correlates with a good clinical response to antipsychotic medications leads Carlsson and colleagues to suggest that DA release may be state dependent such that studies done in acute conditions may yield different results than in chronic remitted patient.

To complicate matters further, amisulpiride and remoxipride, two benzamide compounds, which are highly selective for $D_2$ and $D_3$ receptors but are atypical, meaning they belong to the SGA category. Sulpiride, on the other hand, is a benzamide but belongs to the FGA group. This raised the question of whether $D_2$ receptors were heterogeneous. PET studies were able to confirm the heterogeneity of $D_2$ receptors. When binding indices of select antipsychotics were determined in striatum and temporal cortex, there were markedly different profiles. These and other studies suggested that dopamine $D_2$ receptor populations in striatum and temporal cortex were not identical. The speculation is that in striatum, the $D_2$ population is dominated by synaptically located receptors whereas in temporal cortex the dominant receptor type is extrasynaptic. The dopamine $D_2$ autoreceptor is also extrasynaptic but located on the dopamine neuron itself. Extrasynaptic receptors are thought to be more responsive than postsynaptic receptors. Carlsson and Carlsson (2006) have recently proposed hypotheses involving heterogeneity of dopamine receptors, and the notion that schizophrenia is related to a "dopaminergic deficit" wherein compensatory extrasynaptic transmission of dopamine occurs as a result of feedback activation, and this increased transmission is partly responsible for positive psychotic symptoms. The authors further postulate that the SGAs efficacy may lie in their ability to both bolster synaptic transmission of dopamine but limit extrasynaptic transmission via their partial $D_2$ agonist properties. This hypothesis, though compelling, has yet to achieve widespread acceptance in the field. However, it has become increasingly clear that dopamine works closely with serotonin, glutamate, and other systems such that changes in one system affects the balance of the other systems too (see below).

## Serotonin

Interest in serotonin as a pathophysiological candidate in schizophrenia arose in 1956 with the discovery that the hallucinogen lysergic acid diethylamide (LSD) had primary effects on serotonin neurotransmission. Several studies were conducted to characterize its behavioral profile to determine whether LSD psychosis was a suitable model of schizophrenia. Indeed, LSD produces some features of schizophrenia, including a profound psychotic state, distractibility, social withdrawal, referential thinking, and delusions. However, the most prominent feature of LSD psychosis is visual hallucinations, and auditory hallucinations are exceedingly rare. Visual hallucinations are quite rare among patients with schizophrenia and auditory hallucinations are among the most common symptoms of the illness. Thus, because of the failure to mimic key features of schizophrenia and the growing interest in dopamine at that time, enthusiasm for serotonin's involvement in the pathophysiology of schizophrenia waned for some time.

Clozapine has a relatively high affinity for specific serotonin (5-hydroxytryptamine [5-HT]) receptors ($5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$) and risperidone, has even greater serotonin antagonistic properties. Most SGAs have a greater ratio of serotonin $5\text{-}HT_{2A}$ to dopamine $D_2$ binding affinity. This has led to the hypothesis that the balance between serotonin and dopamine may be altered in schizophrenia (Meltzer et al. 1989). Serotonin $5\text{-}HT_{2A}$ (and other serotonin) receptor occupancy by the antipsychotic drugs, depending on the areas of the brain involved, along with the synergistic effect of Dopamine $D_2$ and $5\text{-}HT_{2A}$ antagonism could be associated with improvement in cognition, depression, and $D_2$ receptor mediated EPS. This effect could be mediated by increase in prefrontal dopamine. Some have suggested that partial agonistic effects of some antipsychotics (e.g., aripiprazole, ziprasidone, etc) on $5\text{-}HT_{1A}$ receptor may also increase prefrontal dopamine.

In addition to the renewed interest in serotonin because of the action of new antipsychotic drugs, several postmortem studies have found elevations of serotonin and its metabolites in the striatum of patients with schizophrenia. Again, as was the case with striatal $D_2$ receptors, previous antipsychotic exposure may have contributed to this finding. Another common finding is decreased $5\text{-}HT_{2A}$ receptor densities in prefrontal cortex. Several postmortem studies and an *in vivo* PET study have shown elevation of $5\text{-}HT_{1A}$ receptor density in the cortex of patients with schizophrenia. The relevance of these findings are not clear. Some, but not all investigators, have reported that the partial serotonergic agonist *m*-chlorophenylpiperazine causes psychotic exacerbations in patients with schizophrenia but has no psychosis-inducing properties in normal control subjects.

There has been an explosion of new information about the structure and function of 5-HT receptors with identification of numerous serotonin receptor subtypes. 5-$HT_{1a}$, 5-$HT_{2c}$, 5-$HT_6$ and 5-$HT_7$, have been proposed as candidates for atypical drug action and are therefore reasonable targets for pathophysiological studies of schizophrenia. It is clear that the field is in the early stages of understanding the possible involvement of serotonin in schizophrenia.

## Glutamate and *N*-Methyl-D-aspartate Receptor

Glutamate is the primary brain excitatory amino acid neurotransmitter and is critically involved in learning, memory, and brain development. Approximately 60% of the neurons in the brain including all cortical pyramidal neurons and thalamic relay neurons use glutamate as their primary neurotransmitter. The glutamate receptors are divided into ionotropic and metabotropic receptors. The Ionotropic receptors are linked directly to ion channels and include *N*-methyl-D-aspartate (NMDA), AMPA, and kainate; metabotropic receptors are linked to second messenger systems and are divided into group I, II and III according to their functional activity. Interest in glutamate and the NMDA receptor in schizophrenia arose because of the similarity between phencyclidine (PCP) psychosis and the psychosis of schizophrenia (Javitt and Zukin 1991). PCP is a noncompetitive antagonist of the NMDA receptor and produces a psychotic state that includes conceptual disorganization, auditory hallucinations, delusions, and negative symptoms. PCP produces more symptoms that are similar to those of schizophrenia than most other pharmacological agents. It should be noted that PCP produces behaviors that are not commonly seen in schizophrenia as well, including spatial and temporal distortion, dreamlike states, and violence. Other findings that support a hypoglutamatergic function in schizophrenia are decreased glutamate levels in cerebrospinal fluid and increased NMDA receptor number and decreased glutamate binding in neocortex in postmortem studies. Olney and Farber (1995) further refined the "NMDA receptor hypofunction" hypothesis by demonstrating that glutamate, acting through NMDA receptors on GABAergic neurons, maintains tonic inhibitory control on numerous excitatory pathways including regulation of its own firing rates such that NMDA receptor hypofunction would abolish this inhibitory control resulting in chaotic, heightened discharges which may account for psychological dysfunction and eventual degeneration of these affected neurons observed in schizophrenia.

PCP and other highly potent NMDA receptor antagonists, such as MK-801, cause neuronal damage and therefore are not used as research tools in clinical populations. However, ketamine, a widely used dissociative anesthetic, is another noncompetitive NMDA antagonist and, at subanesthetic doses, produces a PCP-like psychosis resembling schizophrenia. In a PET study of healthy volunteers, subanesthetic ketamine administration produced a robust psychotic state and focal activation of the prefrontal cortex, suggesting that prefrontal NMDA receptors may mediate this schizophrenia-like behavioral syndrome. The Glutamate hypothesis of schizophrenia is one of the most active areas of research currently. Postmortem studies have reported alterations in NMDA receptor expression in certain brain areas of patients with schizophrenia (Gao et al. 2000). NMDA receptor is reported to play a critical role in guiding axons to their final destination during neurodevelopment. Also, abnormalities with glutamate transmission are reported in many areas of the brain such as frontal cortex, hippocampus, limbic cortex, striatum, and thalamus. Moreover, there are changes reported in the gene expression also in these areas. Some of the risk genes identified for schizophrenia also affect glutamatergic system. In animal models of NMDA receptor antagonists, SGA agents are more effective in ameliorating symptoms (Gainetdinov et al. 2001). Thus, hypoglutamatergia in schizophrenia may have very important downstream modulatory effects on catecholaminergic neurotransmission and play a critical role during neurodevelopment. It also plays an important role in synaptic pruning and underlies important aspects of neurocognition.

## GABA

GABA is the major inhibitory neurotransmitter in brain. Support for GABA's involvement in schizophrenia comes from two lines of investigation. First, clinical trials have demonstrated that benzodiazepines, administered both in conjunction with antipsychotic drugs and as the sole treatment, are effective at reducing symptoms in subgroups of schizophrenia patients. Benzodiazepines are agonists at $GABA_A$ receptors. Second, postmortem studies have consistently report reduced levels of the mRNA for the 67-kilodalton isoform of glutamic acid decarboxylase ($GAD_{67}$ encoded by GAD1), a major determinant of GABA levels in the DLPFC of schizophrenia subjects. Additional findings suggest that both the synthesis and the reuptake of GABA are reduced in a subset of DLPFC neurons in schizophrenia. The affected GABA neurons are the parvalbumin positive chandelier neurons whose exons synapse exclusively on the axons of pyramidal neurons. This results in decreased GABA synthesis and release, and induces compensatory response including decreased presynaptic GABA reuptake and upregulation of postsynaptic $GABA_A$ receptors. Reduced GABA signaling from chandelier cells to pyramidal neurons could contribute to the pathophysiology of working memory dysfunction (see Lewis and Gonzalez-Burgos 2006 for more details). A deficit in GABA interneurons in the anterior cingulum and prefrontal cortex and hippocampus of schizophrenia patients raise interesting possibilities underlying the etiology of schizophrenia (see Figure 65–7a). These interneurons are under control of neuronal patterning and associated genes and thus may represent a genetic vulnerability possibly contributing to the decreased regional brain size. Moreover, deficiency in GABA signaling may allow excitatory system to be overactive and resultant downstream effects. Also, GABAergic neurons are especially vulnerable to glucocorticoid hormones and also to glutamatergic excitotoxicity.

## Peptides

Several peptides have been hypothesized to play a pathophysiological role in schizophrenia. Interest in neurotensin arose because of the discovery that it is colocalized in some dopaminergic neurons and acts as a neuromodulator of this and other neurotransmitters. In preclinical studies, neurotensin was found to have effects that resembled those of antipsychotic drugs and antipsychotic drugs cause increases in neurotensin levels in rat brain. In addition, schizophrenia patients were found to have lower cerebrospinal

fluid neurotensin levels than healthy control subjects and other patients with neuropsychiatric disorders. It has been suggested as a novel target for treatment of psychosis (Caceda et al. 2006). Another peptide with neuromodulatory actions that was found to be colocalized with dopamine and was therefore of interest in relation to schizophrenia is cholecystokinin. Unlike the case of neurotensin, however, there has been a lack of consistent data from postmortem and cerebrospinal fluid studies of patients with schizophrenia. Moreover, a clinical trial of CCK-8, a cholecystokinin analogue, has failed to demonstrate antipsychotic efficacy. Other peptides that are under consideration for a pathophysiological role in schizophrenia are somatostatin, dynorphin, substance P, and neuropeptide Y.

### Norepinephrine

Heightened noradrenergic function has been implicated in psychotic relapse in subgroups of schizophrenia patients. In addition, clozapine, but not other antipsychotic drugs, consistently produces increases in central and peripheral indices of noradrenergic function, and one study found a significant relationship between increases in plasma norepinephrine and improvement in positive symptoms (Breier et al. 1994) (Figure 65–8).

## The Dopamine–Glutamate Theory

Carlsson and colleagues (2001) provide a multineurotransmitter theory of schizophrenia which improves upon previous biochemical theories of schizophrenia. Accumulating evidence suggests that hyperdopaminergia in schizophrenia is probably secondary to some other phenomena. The data involving glutamatergic system suggest that NMDA receptor antagonism enhances the spontaneous and amphetamine-induced release of dopamine and thus raises the possibility that *hypoglutamatergia* could be related to the *hyperdopaminergia*. Carlsson and colleagues (2001)

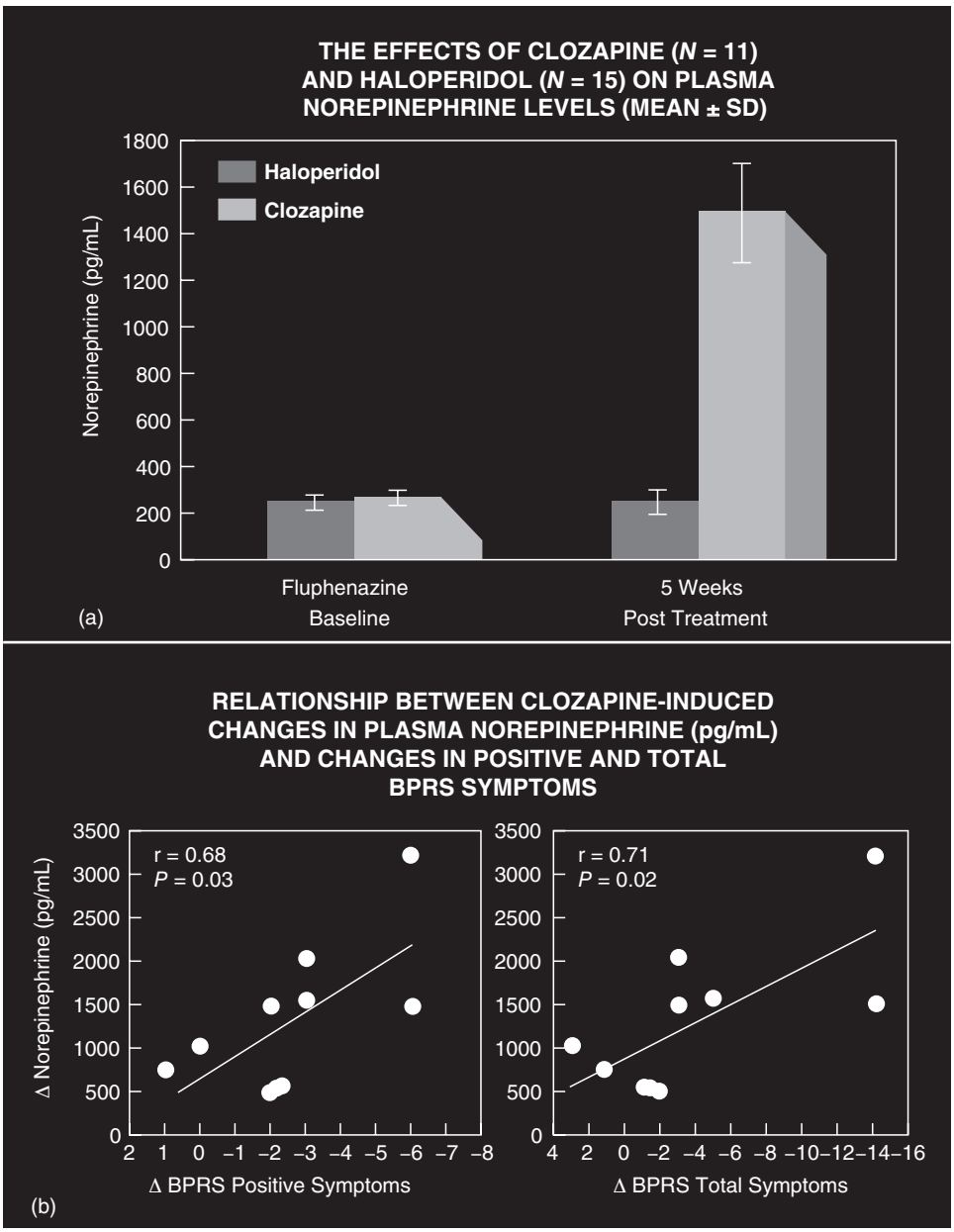



**Figure 65–8** *(a) Fivefold increase in plasma norepinephrine in patients with schizophrenia treated with clozapine for 5 weeks. (b) Significant relationship between improvement in symptoms and increases in plasma norepinephrine with clozapine. (Source: Breier A, Buchanan RW, Waltrip RW, et al. [1994] The effect of clozapine on plasma norepinephrine: Relationship to clinical efficacy. Neuropsychopharmacology 10, 1–7. Copyright 1994 American College of Neuropsychopharmacology. Reprinted with permission from Elsevier Science.)*

propose that psychotogenesis depends on an interaction between dopamine and glutamate pathways projecting to the striatum from the lower brain stem and cortex respectively. These neurotransmitters are predominantly antagonistic to each other, the former being inhibitory and the latter stimulatory when acting on striatal GABAergic projection neurons. These GABAergic neurons belong to striatothalamic pathways, which exert an inhibitory action on thalamocortical glutamatergic neurons, thereby filtering off part of the sensory input to the thalamus to protect the cortex from a sensory overload and hyperarousal. Hyperactivity of dopamine or hypofunction of the corticostriatal glutamate pathway should reduce this protective influence and could thus lead to confusion or psychosis. As a result, the indirect striatothalamic pathways have an inhibitory influence on the thalamus with the corresponding direct pathways exerting an opposite and excitatory influence. Both pathways are controlled by glutamatergic corticostriatal pathways enabling the cortex to regulate the thalamic gating in opposite directions. Thus, according to Carlsson and colleagues (2001), they appear to serve as *brakes* and *accelerators*.

It has been suggested that the activity of the direct pathways is predominantly phasic and of the indirect pathways is mainly tonic. This difference could have important consequences for a different responsiveness of the direct and indirect pathways to drugs. Thus the NMDA receptor antagonists are behavioral stimulants. AMPA receptor antagonists act in the same direction as NMDA antagonists in some and opposite direction in other experiments. Thus, the two most important animal models of psychosis are those induced by hyperfunction of dopamine and hypofunction of glutamate. The relationship between glutamate and serotonin is very important and interesting. Serotonin appears to play a more important role than dopamine in the behavioral stimulation induced by hypoglutamatergia. In two models of psychosis, haloperidol is quite powerful in alleviating the hyperdopaminergic stimulation induced by amphetamine but is least efficacious in the hypoglutamatergic behavioral stimulation induced by MK-801. However, M100907, a selective serotonin 5-$HT_{2A}$ antagonist is clearly more powerful in counteracting MK-801 than amphetamine-induced stimulation. These observations indicate that serotonin may play a more prominent role than dopamine in the behavioral stimulation induced by hypoglutamatergia. Schizophrenia is a syndrome of heterogeneous etiology and pathology. If one neurotransmitter is disturbed, it will inevitably have an impact on other neurotransmitters (Carlsson et al. 2001).

## Neurodevelopmental and Neurodegenerative Disease Processes and Neuroprotection

Neurodevelopmental hypotheses of schizophrenia posit that a disruption in normal development causes the illness (Cannon et al. 2000). Thus, the "lesion" occurs well before the onset of the illness and interacts with maturation events such as neuronal precursor, glial proliferation and migration; axonal and dendritic proliferation; myelination of axons; programmed cell death and synaptic pruning (Lieberman 1999a); and is in all likelihood a nonprogressive disease process. Support for the neurodevelopment hypothesis includes the fact that brain morphological abnormalities commonly found in this illness, such as enlarged ventricles and reduced mesolimbic structures, are present at the onset of the illness. Moreover, gliosis, which occurs during active pathological processes as part of the cellular reparative process in mature brains, is not commonly found in postmortem studies of schizophrenia.

That illness onset typically occurs in the teenage years and early twenties, as opposed to earlier in life when the proposed pathogenic insult occurs, has been explained by the fact that neural circuits implicated in this illness, are still undergoing myelination as well as synaptic "pruning" during the adolescent years and are therefore not fully functional until that time. Thus, an early lesion involving this region could remain silent until adolescence, when its normal functional capacity is expected to be realized. However, these assumptions have been questioned based on the MRI findings of changes in the volume of brain areas in patients with schizophrenia over a period of time (Lieberman 1999b, Weinberger and McClure 2002). This has generated interest in the "neurodegenerative hypothesis" of schizophrenia as originally proposed by Kraepelin and others. However, Weinberger and McClure have cautioned against overinterpretation of the MRI data without converging information from other areas.

More recent evidence supports both a degeneration process as well as developmental process. Thus, these are not mutually exclusive hypotheses, although they may be dominant at different stages of illness and have separate risk factors. Neurodevelopmental and neurodegenerative models could be conceptualized in one model. An individual's vulnerability genes may influence the development of a prodromal condition. Other exposures such as stress, substance abuse etc may further trigger the onset of psychosis, which may lead to deterioration. Psychosis may represent a tip of the iceberg of an underlying pathogenic process that is damaging the brain. However, psychosis may need to be treated promptly to prevent degeneration and/or deterioration. Prolonged psychosis or even residual positive symptoms may well create deficits that add to the severity beyond the level ultimately determined by the original brain pathophysiology. Whether these further deficits result from brain-damaging neurotoxicity or from attenuated synaptic plasticity secondary to withdrawal from daily routine, it is significantly related to a deteriorating course even when patients are on stable medications (Lieberman et al. 2006, McGlashan 2006).

Neuroprotection refers to an intervention that helps to maintain the functional integrity of the central nervous system. Progressive brain changes accompany the functional decline early in the course of illness. Neuroprotection strategies are potentially useful both as therapeutic interventions to improve actual loss of function, and as a prophylactic intervention to minimize anticipated loss of function. Functional deterioration follows the formal onset of psychosis in most patients. Patients with prodromal symptoms who were at high risk for conversion to psychosis were scanned by MRI at study entry and prospectively. Only those patients who actually went on to become psychotic demonstrated a significant loss of cortical gray matter in specific regions of the cortex such as orbito-frontal, medial and inferior temporal lobe, cingulate gyri, and the cerebellar cortex. Progressive brain changes were observed even at the very earliest stages of schizophrenia. Similarly, in patients with childhood-onset schizophrenia, regionally specific progressive loss of cortical

gray matter especially in the prefrontal cortex, the parietal cortex and the temporal lobe has been reported. The annual rate of loss was between 1 and 4% of cortical gray matter in these regions. These studies suggest that there was progressive loss of gray matter in early stages of the illness. Similar changes have been reported in first episode schizophrenia patients too. Thus, these observations have led to a hopeful conclusion that if the rate of progressive decline can be slowed both in gray matter loss and in overall level of function, then patients can have better long-term outcomes.

Amongst several underlying mechanisms, glutamate excitotoxicity appears more plausible. Hypofunction of the N-methyl-D-aspartate (NMDA) glutamatergic receptor may paradoxically lead to glutamatergic disinhibition associated with excess release of glutamate, resulting in excitotoxicity. This may account for both the clinical symptoms as well as the neuropathological deficits. While it has been difficult to demonstrate evidence of glutamatergic excitotoxicity, in patients with schizophrenia, significant reduction in the density of dendritic spines on pyramidal neurons in prefrontal cortex has been reported. This reduction of synaptic content, or neuropil, is consistent with the loss of cortical gray matter observed in neuroimaging studies. In a 2-year double blind randomized study, Lieberman and colleagues (2005) compared haloperidol and olanzapine in first episode psychosis patients. Almost 300 subjects participated. Olanzapine treated patients showed no significant change in whole brain gray volume over the course of the 2-year study. In comparison, the haloperidol patients showed a significant loss in whole brain gray volume starting at 12-week mark and continuing over the course of the 2-year period with significance being lost only at 2-year mark, likely because of considerable patient attrition by that time. This is the first randomized study demonstrating that the choice of antipsychotic treatment could affect progressive loss of gray matter occurs in first-episode psychosis. The total volume of gray matter is about 700 ccs and the average loss was 10–12 cc's. This may have a significant impact on cognitive and functional recovery. Neurocognitive composite scores indicated that for haloperidol-treated patients, less improvement in neurocognitive function was associated with greater decrease in gray-matter volume. Clinically, neurocognitive function has been identified as the most important measure determining functional outcome. Thus, findings from this study does suggest that treatment really can affect neurocognitive function and functional outcome and that these clinical measures appear to have important neurostructural correlates (see Lieberman et al. 2005 for more details).

## Clinical Manifestations and Phenomenology

The idea that schizophrenia can be divided into subgroups has been explored since the illness was first described. Attempts to subdivide schizophrenia have been based on multiple factors including symptom patterns, as in paranoid versus nonparanoid or reactive versus process schizophrenia, or outcome, such as the good versus poor prognosis subtypes. Biological and clinical factors, including platelet monoamine oxidase activity, amphetamine induction of psychosis, neurological soft signs, and perinatal complications, have also been considered in subgrouping this complex illness, although these classifications have generally not withstood the test of time as valid means of subdividing schizophrenia.

### Positive and Negative Symptoms

There has been an emphasis on positive and negative symptom clusters in some schizophrenia patients. Positive and negative symptoms were first described by Sir John Russell Reynolds, a British neurologist who had worked with epileptic patients. In 1857, in a presentation to a division of the London Medical Society, he proposed that physical signs could manifest themselves in positive and negative forms. The prominent neurologist Hughlings-Jackson expanded on Reynolds' statement by positing that negative symptoms could be thought of in terms of an upper motor neuron deficit that leads to the lower motor neuron hyperactivity, which he identified as a positive symptom. By definition, then, both negative and positive symptoms would be found in the same individual and there would be a causative relationship between them. In the psychiatric literature, positive symptoms have come to mean those that are actively expressed, such as hallucinations, thought disorder, delusions, and bizarre behavior, whereas negative symptoms reflect deficit states such as avolition, flattened affect, and alogia.

How these distinct symptom patterns are related in schizophrenia remains unresolved. Bleuler had conceptualized fundamental and accessory symptoms, and Schneider had divided symptoms into those of first and second rank, but neither specifically addressed positive and negative symptom subdivisions. Strauss and colleagues considered positive and negative symptoms as distinct symptom patterns associated with clinical course over time, with negative symptoms being more associated with poor long-term outcome. Subsequent hypotheses considered positive and negative symptoms to be either two end points of a spectrum of symptoms or a single disease process in which either the positive or negative symptoms are primary and the other symptoms become a secondary response.

Crow (1980) suggested that schizophrenia could be divided into a two-syndrome concept. According to his theory, type I schizophrenia patients are those who present, often more acutely, with a predominantly positive symptom profile and who have a good response to neuroleptics. In contrast, type II schizophrenia patients are those who have a more chronic illness, more frequent evidence of intellectual impairment and enlarged ventricular size and cortical atrophy as seen on CT or MRI scans, a poorer response to neuroleptics, and predominantly negative symptoms. Crow further postulated that type I schizophrenia may be secondary to a hyperdopaminergic state, whereas type II disease may be due to structural abnormality of the brain.

The idea that positive and negative symptoms may be overlapping end points along a single continuum of biological and clinical manifestations has been described by Andreasen and colleagues (1982). In their study of 52 schizophrenia patients, they found that negative symptoms correlated with the presence of ventricular enlargement and that patients with small ventricles were more likely to manifest positive symptoms. Furthermore, their group posited that negative and positive symptoms reflect opposite extremes of a spectrum and that a mixed symptom pattern can exist and may be present 30% of the time. Others have suggested that although the positive and negative characteristics may be part of a continuum, they may not be related to the presence or absence of structural brain abnormalities; rather,

there may be a relationship between the symptom pattern and outcome, depending on the clinical course.

A categorical scheme for differentiation of so-called primary and secondary negative symptoms was developed by Carpenter and colleagues (1985). This distinction is based in part on the fact that negative symptoms are not pathognomonic of schizophrenia. The negative symptoms that can be seen in a number of other illnesses, including depression and medical illness, and as a result of positive symptoms themselves or the side effects of medication, particularly extrapyramidal symptoms, are considered "secondary." The negative symptoms that are a core element of schizophrenia are deemed "primary" or "deficit" symptoms. This distinction enables further exploration of outcome variables and the heterogeneity of this illness and in many ways aids treatment decisions.

Because positive and negative symptoms may be seen differently by individual psychiatrists, valid psychometric scales have become important clinical and research tools. The Brief Psychiatric Rating Scale (BPRS), for example, includes subscales for positive and negative symptoms, as does the Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Others have more broadly defined negative symptoms. Crow proposed the use of a narrow definition, that is, flattened affect and poverty of speech, for negative symptoms, and Andreasen supported a broader definition in the widely used Scale for the Assessment of Negative Symptoms (SANS). This psychometric scale includes categories of alogia and flattened affect as well as items such as anhedonia, asociality, avolition, apathy, and deficits in attention.

Structured Clinical Interview for DSM-IV (SCID) is a semi-structured diagnostic interview designed to be administered by an experienced clinician. Though primarily used in research, a user-friendly clinician version (SCID-CV) is also available. It is a very helpful instrument for systematic evaluation in psychiatric patients.

## Symptom Cluster Analysis

Although the dichotomous positive–negative distinction has received clinical and research recognition, several reports suggest that this division is incomplete. Much of the interest in understanding the heterogeneity of schizophrenia has involved a more detailed look at the symptoms of schizophrenia. Sophisticated statistical techniques utilize factor analysis to reduce data to elucidate clusters of symptoms that are most likely to group together or be found independently.

An application of this approach found that there are three, rather than two, symptom dimensions that better subdivide schizophrenia. Correlational relationships between symptoms reveal that positive symptoms can be divided into two distinct groups. The first includes psychotic symptoms such as hallucinations and delusions, and the second includes symptoms of disorganization, consisting of thought disorder, bizarre behavior, and inappropriate affect. A third group is that of negative symptoms. Although these patterns of symptoms may be seen in different proportions in individuals and may change over time, they can be shown to have distinct clinical courses and may be related to independent neuropsychological deficits in a given individual.

In a 2-year follow-up study of these different symptom patterns, negative symptoms were found to remain stable and the other two dimensions were found to have a more fluctuating pattern. This study found that the three symptom dimensions changed independently.

An earlier report supporting three distinct symptom dimensions came from a study of neuropsychological and neurological findings in relation to schizophrenic symptoms. In this study, patients with a predominantly negative symptom dimension were shown to have cognitive deficits related to the frontal lobe, as were patients with thought disorder and inappropriate affect, but the specific deficits appeared to be related to different regions of the frontal lobe. Furthermore, patients who presented primarily with delusions and hallucinations appeared to have neuropsychological deficits associated with the temporal lobe.

Further investigation is warranted to understand the role of these three symptom dimensions in the onset, course, and treatment of schizophrenia. In addition, this factor analytical division of schizophrenic symptoms must be evaluated to understand their relationship to genetic and neurochemical mechanisms.

## Cognitive Impairment

In an attempt to describe schizophrenia in a way that was different from prevailing psychodynamic principles of the day, McGhie and Chapman (1961) reported that schizophrenia patients demonstrated profound deficits in selective attention. This idea had also been described earlier by both Kraepelin and Bleuler. At present, there is a growing body of literature supporting this observation. By now it is widely accepted that schizophrenia patients experience neuropsychological deficits that can be characterized by difficulties with working memory, attention/vigilance, information processing, executive function, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing and social cognition which leads to a generalized performance deficit. Typically, there is a wide variance with some aspects of performance being more impaired than others. Interestingly, small subgroups of the patients have cognitive functioning within the normal range. Most patients with schizophrenia have only modest reductions in their IQs with an average of 90, and about 0.67 standard deviation below that of the general population. In contrast, their performance is usually worse even in first episode patients. Usually patients with schizophrenia underperforms relative to estimates of their premorbid functioning (Harvey 2001). Cognitive impairments involving verbal learning, verbal delayed recall, working memory, vigilance and executive functioning have a significant negative impact on social and occupational functioning. Two meta-analysis of 24 and 9 studies respectively suggest that treatment with SGA agents improve cognitive function compared to FGA (Keefe et al. 1999, Harvey 2001).

The degree-of-cognitive deficit appears to be more strongly associated with severity of negative symptoms, symptoms of disorganization, and adaptive dysfunction than with positive symptoms. Verbal fluency is severely impaired in patients with psychotic disorders and the use of SGA result in significant improvement (Keefe et al. 1999). Motor functions (e.g., reaction time, motor and graphomotor speed) improve with clozapine, olanzapine, and risperidone. Olanzapine improves motor functions more than either haloperidol or risperidone. Furthermore,

motor functions are related to outcome, underscoring the importance of this domain. The symbol–digit and digit–symbol tests have been among the most responsive tests to SGA treatment (Keefe et al. 1999).

As a test of executive function, performance on the Wisconsin Card Sorting Test (WCST) improves with clozapine, risperidone, and olanzapine, although many negative findings have been reported. In Wisconsin Card Sorting Test, subjects sort a series of stimulus cards by matching them to four "key cards" that differ by form, color, and number. Successful performance on the WCST depends upon learning how to sort the cards and how to switch the sorting strategy when appropriate, since the "correct" sorting strategy changes after 10 consecutive correct responses.

Though the SGAs appear to have beneficial effects on cognition, much work still remains to eliminate biases; also, effect sizes of these improvements are modest (Harvey and Keefe 2001).

## Information Processing, Vigilance and Attention

The term *information processing* is used to describe the process of taking information and encoding it in such a way that it can be understood and recalled when appropriately cued. This construct is related to neural circuits and a stepwise logical spread of neurochemical messages, which may be impaired in schizophrenia. *Attention*, simply defined, is the ability to focus on a stimulus, either through conscious effort or passively. These two constructs are interrelated, and our understanding of their composite parts has increased in complexity in the past few decades. Vigilance refers to the ability to maintain attention over time.

Measures of attention were developed from the idea that patients with schizophrenia cannot block out unimportant stimuli in the way that those without schizophrenia can. This phenomenon has come to be called *gating*. Gating is usually seen, for example, when a weak stimulus is delivered before a real stimulus. Normally, the first stimulus would dampen or eliminate the response to the second. Two measures to assess gating function in patients with schizophrenia are the P50 event-related potential (related to sensory gating) and prepulse inhibition of the startle response (related to sensorimotor gating). As an example of these measures, the P50 event-related potential examines responses to auditory stimuli, and the amplitude of the P50 is indicative of a response change between two stimuli. The amplitude reduction of the P50 response from a first auditory click to a second auditory click is known as P50 suppression. Data suggest that patients with schizophrenia have significantly lower than normal levels of P50 suppression.

Specific methods employed in the assessment of information processing and attention are numerous and has been reviewed. The general principles behind each technique are related. Continuous performance tasks, for example, are tests of attention in which the subject must isolate a specific stimulus among repeated distracter stimuli. The stimulus can be in any sensory modality, such as a tone or a letter flashed on a screen. Another test of information processing is prepulse inhibition, which is the inhibition of a startle response by a weaker warning stimulus. Event-related potentials measure electrical brain activity after some sort of stimulus such as an auditory click.

Other information-processing measurements reported to be abnormal in some schizophrenia patients have included the skin conduction orienting response. This test involves habituation to a stimulus applied to the skin. Eye-tracking abnormalities such as smooth pursuit eye movements have also been found to be abnormal in schizophrenia patients.

In general, patients with schizophrenia have impairments in information processing, especially when they are exposed to increasing demands on their attentional capabilities, such as under timed conditions or in stressful situations. Therefore, these deficits not only are viewed as trait linked (i.e., a manifestation of the illness itself) but may be compounded when state linked (i.e., when there are increases in symptoms). The trait-linked disturbances in neuropsychological parameters are seen in those at high risk for developing schizophrenia, those who have schizophrenia, and relatives who appear clinically unaffected, which may indicate a genetic vulnerability.

Many of these tests of attention and information processing have been associated with specific symptoms and neuropsychological impairment in schizophrenia. For example, one study showed that impaired prepulse inhibition was related to increased perseveration on neuropsychological tests of higher executive function. Others have shown that deficits in attention and information processing may be associated with positive and/or negative symptoms. Specifically, deficits in visual processing and motor function (as seen with continuous performance tasks) have been linked to negative symptoms, whereas positive symptoms seem to be related to auditory-processing dysfunction. Deficits in vigilance can affect social interactions, community functions and acquisition of skills (Green 2006).Interestingly, abnormalities in these tests of information processing are not induced by FGAs; moreover, these medications may partially ameliorate the deficits. Attention has been reported to improve with SGAs. Because these deficits are seen more frequently in individuals with schizophrenia, their relatives, and those at risk of developing schizophrenia, the application of information-processing and sophisticated attention techniques may lead to more information about the heritability and genetics of schizophrenia. Further investigation regarding their correlation with specific symptom clusters, the effects of antipsychotic medications, and the relationship of these deficits to specific brain regions studied with PET and functional MRI should enhance our understanding of the neurocircuitry involved in these impairments.

## Learning and Memory

Although there are generally no consistent gross deficits of memory in schizophrenia patients, close examination of certain aspects of learning and memory has revealed striking abnormalities. Schizophrenia patients have been shown to be poorer in recall of word lists if the words are not grouped into categories. Furthermore, unlike normal control subjects, schizophrenia patients do not seem to show an improvement in memory when asked to recall words with latent positive emotional meaning. These findings have been attributed to poor cognitive organization in schizophrenia patients.

Others have reported that patients with chronic schizophrenia had impairment in new learning and short-term memory but not remote memory, possibly indicating temporal–hippocampal dysfunction. These may be more

likely in patients with a poor premorbid course and ventricular enlargement. In addition, in a long-term follow-up study of schizophrenia patients, those with memory impairment had a poorer outcome in terms of social and occupational function.

FGAs have not been shown to affect memory, unlike anticholinergic medications, which may decrease memory performance (Chakos et al. 2006). Despite these findings, some questions regarding the role of chronicity and FGA exposure in memory impairment has remained. It appears, however, that these deficits are inherent to schizophrenia itself, as impairment in verbal memory has been demonstrated even in antipsychotic-naive first-episode schizophrenia patients. Data from nine small sample studies did not suggest that SGAs significantly improved verbal memory. However, two recent small studies suggest that quetiapine may improve verbal memory.

Working memory is a cognitive system that stores and processes information needed for planning and reasoning for a brief duration. Some cognitive scientists refer to short-term memory as working memory. Working memory consists of verbal and visual memory subsystems with a central principle that manipulates and coordinates information stored in the two systems for problem solving, planning and organizing activities. Separate areas of the prefrontal cortex may underlie different aspects of the working memory. The workspace used for such memory is capacity-limited. Patients with schizophrenia have significant dysfunction in this area and are unable to change an ineffective strategy (i.e., shift sets) even when feedback is provided. This dysfunction occurs (albeit at a lower level) even in subjects with higher intelligence. FGAs do not appear to impair or improve working memory in patients with schizophrenia. There is limited evidence to support clozapine's role in enhancing working memory. Risperidone may improve aspects of working memory functions. Studies involving evaluation of working memory using neuroimaging, pharmacological models of schizophrenia, and neurochemical function should further our understanding of this manifestation of schizophrenia. Cognition in schizophrenia has become the new frontier with targets that may be amenable to psychopharmacological treatments. However, treatments studied thus far have failed to produce the magnitude of changes that would be clinically relevant.

### Social Cognition

Theory of mind (ToM) refers to the ability to represent the mental states of others and/or to make inferences about another's intentions. Overall, individuals with schizophrenia have impairments in ToM that appear to be independent from general cognitive abilities. Facial affect recognition deficits are stable in schizophrenia. ToM, attributional style and facial affect recognition are considered key domains of social cognition. These deficits in social cognition are in fact related to behavior. Changes in behavior that can be labeled as bizarre or deviant or abnormal precede the onset of psychosis and persist with significant variability and intensity throughout the course of illness. Recently there has been an increased recognition of social cognition and how it affects individuals with schizophrenia. Frith hypothesized that many symptoms typical of schizophrenia may be accounted for by a specific cognitive incapacity of schizophrenia patients to accurately attribute mental states to themselves or others, commonly referred to as 'having a theory of self and others' minds' leading to what Frith called 'disorders of willed action', disorders of self monitoring' and disorders of 'monitoring other persons' thoughts and intentions.' Schizophrenia patients show significant deficits in recognizing other people's emotions from facial expressions, gestures, or voices and inferring the mental states of others. Schizophrenia patients show problems in their ability to appreciate the mental states of others (emotion recognition). Some studies have shown that ToM had strong associations with executive functioning. Duration of illness had a fairly strong negative impact on the ToM performance but was unrelated to emotion recognition abilities. The evidence that the impairments in ToM skills are independent of general cognitive deficits is mixed. Facial affect recognition and social cue perception are two important areas in which there are significant and stable deficits (Brune and Brune-Cohrs 2006).

A number of studies suggest that there may be a decline in cognitive functioning around the prodrome with significant decline after the onset of psychosis. The FGA agents have minimal effect on the cognition. Longitudinally, improvements in psychotic symptoms do not correlate to improvement in cognition too. Some have found that over the course of a decade, in first episode patients, executive functions did not change but there was a decline in visual-spatial functioning. The course of neurocognitive impairment in elderly patients is uncertain, but this may also depend on the age of onset, chronicity of the illness, etc.

Cognitive dysfunction is not strongly correlated with severity of psychosis and positive symptoms, but does have significant correlation with various types of negative symptoms with modest effects. Thus, many believe that neurocognitive symptoms are not caused by psychosis. Thus changes in positive symptoms do not significantly improve cognition in schizophrenia. Some have blamed the side effects of the FGA on negatively affecting cognition. SGA agents were expected to improve cognition to a much better degree than the FGA. However, recent data from real world patients do not bear this out. If there are differences between FGAs and SGAs they are significantly small. Social and occupational functioning show strong association with cognitive functioning. Higher levels of cognitive impairments require greater amount of vocational support. Quality of life measures are also related to cognition.

## Differential Diagnosis

Making an accurate diagnosis of schizophrenia requires high levels of clinical acumen, extensive knowledge of schizophrenia, and sophisticated application of the principles of differential diagnosis. It is unfortunately common for patients with psychotic disorders to be misdiagnosed and consequently treated inappropriately. The importance of accurate diagnosis is underlined by an emerging database indicating that early detection and prompt pharmacological intervention may improve the long-term prognosis of the illness.

### Mental Status Examination

There is no specific laboratory test, neuroimaging study, or a diagnostic test that yields a definitive diagnosis of

schizophrenia. At present, the diagnosis of schizophrenia is made on a clinical basis. Schizophrenia can present with a wide variety of symptoms, and a longitudinal history of symptoms and comorbid clinical variables such as medical illness and a history of substance abuse must be evaluated before a diagnosis can be considered. The Mental Status Examination, much like the physical examination, is an additional clinical tool that aids the psychiatrist in generating a differential diagnosis and appropriate treatment recommendations.

## Appearance

Although a disheveled look is not pathognomonic for schizophrenia, patients with this disorder often present, especially acutely, with a disordered appearance. The description of a patient's appearance is an objective verbal sketch, much like the description of a heart murmur that can uniquely identify a particular patient.

A person with schizophrenia often has difficulty attending to activities of daily living, either because of negative symptoms (apathy, social withdrawal, or motor retardation) or because of the presence of positive symptoms, such as psychosis, disorganization, or catatonia, that interfere with the ability to maintain personal hygiene. Also, schizophrenia patients often present with odd or inappropriate attire, such as a coat and hat worn during the summer or dark sunglasses worn during an interview. It is generally thought that the inappropriate dress is a manifestation of symptoms such as disorganization or paranoid ideation. It should be noted that some patients present quite neatly groomed. Thus appearance is noted but is not diagnostic.

## Attitude

Individuals with schizophrenia may be friendly and cooperative, or they may be hostile, annoyed, and defensive during an interview. The latter may be secondary to paranoid symptoms, which can make patients quite cautious and guarded in their responses to questions.

## Behavior

Schizophrenia patients can have bizarre mannerisms or stereotyped movements that can make them look unusual. Patients with catatonia can stay in one position for weeks, even to the point of causing serious physical damage to their body; for example, a patient who stands in one place for days may develop stress fractures, peripheral edema, and even pulmonary emboli. Patients with catatonia may have waxy flexibility, maintaining a position after someone else has moved them into it. Patients with catatonic excitement exhibit odd posturing or purposeless, repetitive, and often strange movements.

Behaviors seen in schizophrenia patients include choreoathetoid movements, which may be related to antipsychotic exposure but have been reported in patients even before antipsychotic use. Other behaviors or movement disorders may be seen as parkinsonian features, such as a shuffling gait or a pill-rolling tremor.

Psychomotor retardation may be present and may be a manifestation of catatonia or negative symptoms. On close observation, it is usually characterized, in this group of patients, as a lack of motor movements rather than slowed movements.

Patients may present with agitation, ranging from minimal to extreme. This agitation is often seen in the acute state and may require immediate pharmacotherapy. However, agitation may be secondary to antipsychotic medications, as in akathisia, which is felt as an internal restlessness making it difficult for the person to sit still. Akathisia can manifest itself in limb shaking, pacing, or frequent shifting of position. Severely agitated patients may be unresponsive to verbal limits and may require measures to ensure their safety and the safety of others around them.

## Eye Contact

Paranoid patients may look hypervigilant, scanning a room or glancing suspiciously at an interviewer. Psychotic patients may make poor eye contact, looking away, or appear to stare vacuously at the interviewer, making a conversational connection seem distant. Characteristic responding to internal stimuli is seen when a patient appears to look toward a voice or an auditory hallucination, which the patient may hear. A nystagmus may also be observed. This clinical finding has a large differential diagnosis, including Wernicke-Korsakoff syndrome; alcohol, barbiturate, or phenytoin intoxication; viral labyrinthitis; or brain stem syndromes including infarctions or multiple sclerosis.

## Speech

In a Mental Status Examination, one usually comments on the rate, tone, and volume of a patient's speech, as well as any distinct dysarthrias that may be present. Pressured speech is usually thought of in conjunction with mania; however, it can be seen in schizophrenia patients, particularly on acute presentation. This is often difficult to assess, as it may be a normal variant or a cultural phenomenon, because some languages are spoken faster than others.

Tone refers to prosody, or the natural singsong quality of speech. Negative symptoms may include a lack of prosody, resulting in monotonous speech. Furthermore, odd tones may be consistent with neurological disorders or bizarre behavior.

Speech volume is important for a number of reasons. Loud speech can be a measure of agitation, it can occur in conjunction with psychosis, or it could even be an indication of hearing loss. Speech that is soft may be an indication of guardedness or anxiety.

Dysarthrias are notable because they can be idiopathic and long-standing, or they can be an indication of neurological disturbance. In patients who have been exposed to antipsychotics, orobuccal tardive dyskinesia should be considered when there is evidence of slurred speech.

## Mood and Affect

Affect, which is the observer's objective view of the patient's emotional state, is often constricted or flat in patients with schizophrenia. In fact, this is one of the hallmark negative symptoms. Flattened affect may also be a manifestation of pseudoparkinsonism, an extrapyramidal side effect of typical neuroleptics.

Inappropriate affect is commonly seen in patients with more predominant positive symptoms. A smile or a laugh while relating a sad tale is an example. Patients with catatonic excitement or hebephrenia may have bizarre presentations or affective lability, laughing and crying out of context

with the situation. Emotional reactivity must alert the clinician to the possibility of neurological impairment as well, as in the case of pseudobulbar palsy.

Mood is based on a patient's subjective report of how he or she feels, emotionally, at the time of the interview. It is not uncommon for patients with schizophrenia to be depressed (especially patients with history of higher premorbid functioning who may have some insight into the losses they are facing) or to be indifferent, with seemingly no emotional awareness of their situation.

### Thought Process

Because actual thoughts cannot be measured, thought processes are assessed by extrapolation from the organization of speech. Thought disorders can be more or less obvious, and a trained listener, much like a cardiologist who listens for heart murmurs or a neurologist who detects aphasias, is one who appreciates the normal logical pattern of flow of words and ideas in speech and can thus sense abnormalities.

There are many different versions of thought disorders: lack of logical connections of ideas (looseness of associations); shift of the original theme because of weak connections of ideas (tangentiality); overinclusiveness to the point of loss of the theme (circumstantiality); use of words and phrases with no relation to grammatical rules (word salad); repetition of words spoken by others (echolalia); use of sounds of other words, such as "yellow bellow, who is this fellow?" (clang associations); use of made-up words (neologisms); and repetition of a particular word or phrase, such as "this and that, this and that" (perseveration).

Other thought disorders are part of a constellation of negative symptoms. Examples would be thoughts that appear to stop abruptly, either because of interruption by an auditory hallucination or because the thought is lost (thought blocking); absence of thoughts (paucity of thought content); and a delayed response to questions (increased latency of response).

### Thought Content

Although not necessarily present in every patient, characteristic symptoms of schizophrenia include the belief that outside forces control a person's thought or actions. A patient might report that others can insert thoughts into her or his head (thought insertion), broadcast them to others (thought broadcasting), or take thoughts away (thought withdrawal). Other delusions, or fixed false beliefs, may also be prominent. Patients may describe ideas of reference, which is the phenomenon of feeling that some external event or report relates to oneself specifically; for example, a patient may infer special meaning from an image seen on television or a broadcast heard on the radio.

Paranoid ideation may be manifested as general suspiciousness or frank, well-systematized delusions. The themes may be considered bizarre, such as feeling convinced that aliens are sending signals through wires in the patient's ear, or nonbizarre, such as being watched by the Central Intelligence Agency or believing that one's spouse is having an affair. These symptoms can be quite debilitating and lead to a great deal of personal loss, which patients may not understand because the ideas are so real to them.

Patients with schizophrenia commonly express an abundance of vague somatic concerns, and a particular patient might develop a delusion around a real physiological abnormality. Therefore, somatic symptoms should be evaluated appropriately in their clinical context without automatically dismissing them as psychotic. Preoccupations and obsessions are also seen commonly in this population, and certain patients have comorbid obsessive–compulsive disorder.

The mortality rate for suicide in schizophrenia is approximately 10%. It is therefore imperative to evaluate a patient for both suicidal and homicidal ideation. Patients of all diagnoses, and particularly schizophrenia, may not spontaneously articulate suicidal or homicidal ideation and must therefore be asked directly about such feelings. Moreover, psychotic patients may feel compelled by an auditory hallucination telling them to hurt themselves.

### Perceptions

Perceptual disturbances involve illusions and hallucinations. Hallucinations may be olfactory, tactile, gustatory, visual, or auditory, although hallucinations of the auditory type are more typical of schizophrenia. Hallucinations in the other sensory modalities are more commonly seen in other medical or substance-induced conditions. Auditory hallucinations can resemble sounds, background noise, or human voices. Auditory hallucinations that consist of a running dialogue between two or more voices or a commentary on the patient's behavior are typical of schizophrenia. These hallucinations are distinct from verbalized thoughts that most humans experience. They are often described as originating from outside the patient's head, as if they were emanating from the walls or the radiators in the room. Less commonly, a patient with schizophrenia describes illusions or misperceptions of a real stimulus, such as seeing demons in a shadow.

### Consciousness and Orientation

One of the observations that struck Kraepelin in his first descriptions of dementia praecox was that patients did not have clouding of consciousness. Patients with schizophrenia most likely have a clear sensorium unless there is some comorbid medical illness or substance-related phenomenon. A schizophrenia patient may be disoriented, but this could be a result of inattentiveness to details or distraction secondary to psychotic preoccupation. In fact, there is some literature suggesting that a subgroup of patients may present as disoriented to temporal relations such as the date or their own age.

### Attention and Concentration

Studies utilizing continuous performance task paradigms have demonstrated repeatedly that schizophrenia patients have pervasive deficits in attention in both acute and residual phases. On a Mental Status Examination, these deficits may present themselves as the inability to perform mental exercises, such as spelling the word "earth" or "world" backward or performing serial subtractions.

### Memory

Careful assessment of memory in patients with schizophrenia may yield some deficits. Acquisition of new information, immediate recall, and recent and remote memory may be impaired in some individuals. Furthermore, answers to questions regarding memory may lead to idiosyncratic responses related to delusions, thought disorder, or other overriding

symptoms of the illness. In general, schizophrenia patients do not show gross deficits of memory such as may be seen in patients with dementia or head trauma.

### Fund of Knowledge

Schizophrenia is not the equivalent of mental retardation, although these syndromes can coexist in some patients. Patients with schizophrenia generally experience a slight shift in intellectual functioning after the onset of their illness, yet they typically demonstrate a fund of knowledge consistent with their premorbid level. Schizophrenia patients manifest a characteristic discrepancy on standardized tests of intelligence, with the nonverbal scores being lower than the verbal scores. Furthermore, some reports suggest that patients who have been chronically hospitalized or those with some cerebral atrophy may evidence diminished intellectual function.

### Abstraction

A classical aberration of mental function in a patient with schizophrenia involves the inability to utilize abstract reasoning, which is similar to metaphorical thinking, or the ability to conceptualize ideas beyond their literal meaning. For example, when the patient is asked what brought him or her to the hospital, a typical answer might be "an ambulance." On a Mental Status Examination, this concrete thinking is best elicited by asking a patient to interpret a proverb or state the similarities between two objects. For example, "a rolling stone gathers no moss" may mean, to the patient with schizophrenia, that "if a stone just stays in one place, the moss won't be able to collect." More profound difficulties in abstraction and executive function, often seen in schizophrenia, such as inability to shift cognitive focus or set, may be assessed by neuropsychological tests.

### Judgment and Insight

Individuals suffering from schizophrenia often display a lack of insight regarding their illness. Whether it is a reflection of a negative symptom, such as apathy, or a constricted display of emotion, patients often appear to be emotionally disconnected from their illness and may even deny that anything is wrong. Poor judgment, which is also characteristic and may be related to lack of insight, may lead to potentially dangerous behavior. For example, a patient walking barefoot in the snow because of the feeling that her or his shoes could be traced by surveillance cameras would be displaying both poor judgment and poor insight. On a formal Mental Status Examination, judgment is commonly assessed by asking patients what they would do if they saw a fire in a movie theater or if they saw a stamped, addressed envelope on the street. Insight can be ascertained by asking patients about their understanding of why they are being evaluated by a psychiatrist or why they are receiving a certain medication.

## Physical Examination

Although there are no pathognomonic physical signs of schizophrenia, some patients have neurological "soft" signs on physical examination. The neurological deficits include nonspecific abnormalities in reflexes, coordination (as seen in gait and finger-to-nose tests), graphesthesia (recognition of patterns marked out on the palm), and stereognosis (recognition of three-dimensional pictures). Other neurological findings include odd or awkward movements (possibly correlated with thought disorder), alterations in muscle tone, an increased blink rate, a slower habituation of the blink response to repetitive glabellar tap, and an abnormal pupillary response. The exact etiology of these abnormalities is unknown, but they have historically been associated with minimal brain dysfunction and may be more likely in patients with poor premorbid functioning and a chronic course. These neurological abnormalities have been seen in neuroleptic-naive patients as well as those with exposure to traditional antipsychotic medication. Overall, the literature suggests that these findings may be associated with the disease itself, although further research is needed to determine the role of neuroleptic exposure in the manifestation of neurological signs and the extent to which schizophrenia is itself associated with neurological abnormalities.

Neuro-ophthalmological investigations have shown that patients with schizophrenia have abnormalities in voluntary saccadic eye movements (rapid eye movement toward a stationary object) as well as in smooth pursuit eye movements. The influence of attention and distraction, neuroleptic exposure, and the specificity of smooth pursuit eye movements for schizophrenia have raised criticisms of this area of study, and further investigation is necessary to determine its potential as a putative genetic marker for schizophrenia.

### Additional Testing

The presentation of psychotic symptoms raises a broad differential diagnosis. Though a thorough history, mental status and physical examination are important, additional testing is utilized to help establish diagnoses of schizophrenia and other psychotic disorders. A thorough evaluation of psychotic symptoms would warrant baseline laboratory testing, including a toxicology screen, to rule out other conditions. In addition, EEG and MRI testing are useful to assess for underlying neurological disorders. Negative findings on EEG and MRI do not definitively rule out the possibility of other neurological conditions, though patients with schizophrenia and other psychotic disorders often do have essentially normal results on these tests. In addition, neuropsychological deficits seen in patients with schizophrenia can best be evaluated with neuropsychological testing. This type of testing can be quite useful in helping to establish diagnosis and baseline functioning, as well as in helping to assess for improvement over time.

## Other Conditions That Resemble Schizophrenia

### Schizoaffective Disorder

Possibly the most difficult diagnostic dilemma in cases in which a patient has both psychotic symptoms and affective symptoms are in the differentiation between schizophrenia and schizoaffective disorder. The term schizoaffective disorder was first coined by Kasanin (1933). Since then, there has been some controversy regarding this diagnostic entity. It has been included in studies of both affective disorder and schizophrenia and has at times been considered part of a continuum between the two, which has contributed to some of the diagnostic confusion.

In DSM-IV-TR, schizoaffective disorder is treated as a unique clinical syndrome. A patient with schizoaffective disorder must have an uninterrupted period of illness during which, at some time, they have symptoms that meet the diagnostic criteria for a major depressive episode, manic episode, or a mixed episode concurrently with the diagnostic criteria for the active phase of schizophrenia (criteria A for schizophrenia). Additionally, *the patient must have had delusions or hallucinations for at least 2 weeks in the absence of prominent mood disorder symptoms* during the same period of illness. The mood disorder symptoms must be present for a substantial part of the active and residual psychotic period. The essential features of schizoaffective disorder must occur within a single uninterrupted period of illness where the "period of illness" refers to the period of active or residual symptoms of psychotic illness and this can last for years and decades. The total duration of psychotic symptoms must be at least 1 month to meet the criteria A for schizophrenia and thus, the minimum duration of a schizoaffective episode is also 1 month.

The criteria for major depressive episode require a minimum duration of 2 weeks of either depressed mood or markedly diminished interest or pleasure. As the symptoms of loss of pleasure or interest commonly occur in nonaffective psychotic disorders, to meet the criteria for schizoaffective disorder criteria A, the major depressive episode must include pervasive depressed mood. Presence of markedly diminished interest or pleasure is not sufficient to make a diagnosis as it is possible that these symptoms may occur with other conditions too.

**DSM-IV-TR Criteria**

**Schizoaffective Disorder**

A. An uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia.

**Note:** The major depressive episode must include criterion A1: depressed mood.

B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.

C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify types:

**Bipolar type:** if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes)
**Depressive type:** if the disturbance only includes major depressive episodes

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## Brief Psychotic Disorder and Schizophreniform Disorder

The distinctions among brief psychotic disorder, schizophreniform disorder, and schizophrenia are based on duration of active symptoms. As discussed earlier, DSM-III adopted a 6-month rule from the St. Louis group criteria. DSM-IV has maintained the requirement of 6 months of active, prodromal, and/or residual symptoms for a diagnosis of schizophrenia. Brief psychotic disorder is a transient psychotic state, not caused by medical conditions or substance use, that lasts for at least 1 day and up to 1 month. Schizophreniform disorder falls in between and requires symptoms for at least 1 month and not exceeding 6 months, with no requirement for loss of functioning.

**DSM-IV-TR Criteria**

**Brief Psychotic Disorder**

A. Presence of one (or more) of the following symptoms:

(1) delusions
(2) hallucinations
(3) disorganized speech (e.g., frequent derailment or incoherence)
(4) grossly disorganized or catatonic behavior

**Note:** Do not include a symptom if it is a culturally sanctioned response pattern.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.

C. The disturbance is not better accounted for by a mood disorder with psychotic features, schizoaffective disorder, or schizophrenia and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

**With marked stressor(s)** (brief reactive psychosis): if symptoms occur shortly after and apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture
**Without marked stressor(s):** if psychotic symptoms do not occur shortly after, or are not apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture
**With postpartum onset:** if onset within four weeks postpartum

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**DSM-IV-TR Criteria**

**Schizophreniform Disorder**

A. Criteria A, D, and E of schizophrenia are met.
B. An episode of the disorder (including prodromal, active, and residual phases) lasts at least 1 month but less than 6 months. (When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional.")

Specify if:

**Without good prognostic features**

**With good prognostic features:** as evidenced by two (or more) of the following:

(1) onset of prominent psychotic symptoms within four weeks of the first noticeable change in usual behavior or functioning
(2) confusion or perplexity at the height of the psychotic episode
(3) good premorbid social and occupational functioning
(4) absence of blunted or flat affect

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## Delusional Disorder

If the delusions that a patient describes are not bizarre (e.g., examples of bizarre delusions include the belief that an outside force or person has taken over one's body or that radio signals are being sent through the caps in one's teeth), it is wise to consider delusional disorder in the differential diagnosis. Delusional disorder is usually characterized by specific types of false fixed beliefs such as erotomanic, grandiose, jealous, persecutory, or somatic types. Delusional disorder, unlike schizophrenia, is not associated with a marked social impairment or odd behavior. Moreover, patients with delusional disorder do not experience hallucinations or typically have negative symptoms.

**DSM-IV-TR Criteria**

**Delusional Disorder**

A. Nonbizarre delusions (i.e., involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration.
B. Criterion A for schizophrenia has never been met. *Note*. Tactile and olfactory hallucinations may be present in delusional disorder if they are related to the delusional theme.
C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre.
D. If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods.
E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type (the following types are assigned based on the predominant delusional theme):

**Erotomanic type:** delusions that another person, usually of higher status, is in love with the individual
**Grandiose type:** delusions of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person
**Jealous type:** delusions that the individual's sexual partner is unfaithful
**Persecutory type:** delusions that the person (or someone to whom the person is close) is being malevolently treated in some way
**Somatic type:** delusions that the person has some physical defect or general medical condition
**Mixed type:** delusions characteristic of more than one of the above types but no one theme predominates
**Unspecified type**

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## Affective Disorder with Psychotic Features

If the patient experiences psychotic symptoms solely during times when affective symptoms are present, the diagnosis is more likely to be mood disorder with psychotic features. If the mood disturbance involves both manic and depressive episodes, the diagnosis is bipolar disorder. According to DSM-IV-TR, affective disorders that are seen in patients with schizophrenia may fall in the category depressive disorder not otherwise specified or bipolar disorder not otherwise specified.

## Substance-Related Conditions

Psychotic disorders, delirium, and dementia that are caused by substance use, in DSM-IV-TR, are distinguished from schizophrenia by virtue of the fact that there is clear-cut evidence of substance use leading to symptoms. Examples of psychotomimetic properties of substances include a PCP psychosis that can resemble schizophrenia clinically, chronic alcohol intoxication (Korsakoff's psychosis), and chronic amphetamine administration, which can lead to paranoid states. Therefore, patients who have symptoms that meet criterion A of schizophrenia in the presence of substance use must be reevaluated after a significant period away from the suspected substance, and proper toxicology screens must be performed to rule out recent substance abuse.

## General Medical Conditions

General medical conditions ranging from vitamin $B_{12}$ deficiency to Cushing's syndrome have been associated with

**Table 65–2 Long-Term Follow-up Studies of Schizophrenia**

| Study | Location | Length of Follow-up (mean, year) | Sample Size (*N*) | Recovered or Significantly Improved (%) |
|---|---|---|---|---|
| DeSisto et al. (1995) | Maine | 36 | 117 | 45 |
| Harding et al. (1987b) | Vermont | 32 | 82 | 67 |
| Tsuang et al. (1979) | Iowa | 35 | 186 | 46 |
| Huber et al. (1980) | Bonn | 22 | 502 | 57 |
| Ciompi et al. (1980) | Lausanne | 37 | 289 | 53 |
| Bleuler (1972) | Zurich | 23 | 208 | 53 |

a clinical presentation resembling that of schizophrenia. Because the prognosis for the associated medical condition is better than that for schizophrenia and the stigma attached to schizophrenia is significant, it is imperative to provide patients with a thorough medical work-up before giving a diagnosis of schizophrenia. This includes a physical examination; laboratory analyses including thyroid function tests, syphilis screening, and folate and vitamin $B_{12}$ levels; a CT or MRI scan; and a lumbar puncture when indicated in new-onset cases.

## Course of Illness

The most influential model for the long-term course of schizophrenia was proposed by Kraepelin. Inherent in the term dementia praecox was the view that the course of this illness was similar to that of the dementias in that they were progressive with worsening over time. This downhill trajectory had profound clinical and research implications throughout the century. For example, if patients with schizophrenia recovered or even had a prolonged remission, it was generally considered that they had been erroneously diagnosed. Indeed, even in DSM-III, patients with schizophrenia were described as rarely recovering. Moreover, pathophysiological theories were influenced by this model in that disease processes that were progressive were given strong consideration.

The Kraepelinian model for this illness went essentially unchallenged for more than 50 years until well-designed epidemiological studies of schizophrenia were conducted. In long-term follow-up studies of 20 years or more, surprisingly favorable outcomes were observed: between 40 and 66% of patients had either recovered or were only mildly impaired at follow-up (Table 65–2). In the Vermont Longitudinal Study of Schizophrenia (Harding et al. 1987a, 1987b), 269 backward patients who were chronically institutionalized in the 1950s were followed up an average of 32 years later. The patients who met rigorously applied retrospective DSM-III diagnostic criteria for schizophrenia disorder ($N$ = 118) during their index admission in the 1950s were found on follow-up to have outcomes that varied widely; 82% were not hospitalized in the year of the follow-up, 68% displayed slight or no symptoms, 81% were able to meet their own basic needs, and more than 60% had good social functioning. Thus, these data indicate that the long-term outcome of schizophrenia is heterogeneous, with substantially larger numbers of patients having better outcomes than would have been predicted by the Kraepelinian model.

Based on current epidemiological data, a new model of the natural course of schizophrenia has been proposed (Breier et al. 1991). This model has three phases: an early phase marked by deterioration from premorbid levels of functioning; a middle phase characterized by a prolonged period of little change termed the stabilization phase; and the last period, which incorporates the long-term outcome data just cited, which is called the improving phase (Figure 65–9).

## First Episode Schizophrenia

An enormous clinical and research effort is directed internationally toward patients in very early stages of their illness and especially during their first psychotic break with a focus on early and effective intervention. First episode provides a unique opportunity to intervene early and effectively and possibly change the course of illness. It is well known that there is a delay of 1–2 years on an average between onset of psychosis and starting of treatment (Lieberman and Fenton 2000). This duration of untreated psychosis (DUP) has emerged as an independent predictor of likelihood and extent of recovery from a first episode of psychosis and possibly a modifiable prognostic factor. A large meta-analysis reported that shorter DUP was associated with greater improvement in severity of positive and negative symptoms as well as functional outcomes (Perkins et al. 2005). These associations were independent of the effect of other variables also associated with prognosis including premorbid functioning. In important and landmark studies done by the Norwegian Early Treatment and Intervention on Psychosis Program, they targeted general population, health professionals, schools and

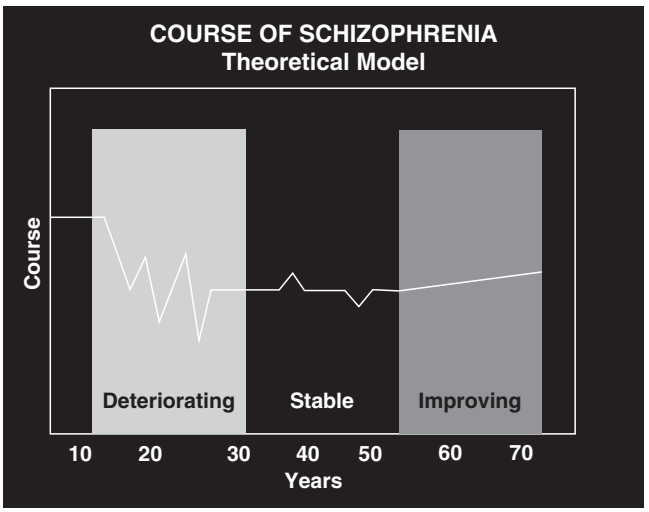



**Figure 65–9** *Model of the lifelong course of illness for schizophrenia. (Source: Breier A, Schreiber JL, Dyer J, et al. [1991] National Institute of Mental Health longitudinal study of chronic schizophrenia: Prognosis and prediction of outcome. Arch Gen Psychiatr 48, 239–246. Copyright 1991 American Medical Association.)*

other relevant establishment with a comprehensive multimedia educational program. Before the program, the DUP on an average was 114 weeks (median = 26 weeks). Following the program, the DUP was 26 weeks (median = 5 weeks) (Larsen et al. 2000). Emboldened by these findings, in a follow up study, they compared two areas in Norway with one receiving the intense community and professional education while the other did not. The median duration of DUP in the area with active educational program was 5 weeks and in the control area was 16 weeks implying that by mere spreading of information, psychoeducation and by having special programs, the DUP can be shortened with potential beneficial (possibly neuroprotective) effects on the course of illness. Additionally, the symptom severity and the 3-month clinical outcome were significantly better in the intervention program (Melle et al. 2004). These and other early and very early intervention programs are introducing the concept of "prevention" of morbidity related to schizophrenia, improving the course of schizophrenia and perhaps postponing the onset of illness significantly, a remarkably rare occurrence in the history of this devastating illness. Many such programs are now attempting innovative interventions (like the ones mentioned above) all over the world. The hope is that such programs will provide neuroprotection and eventually have an impact on suicidality too.

Larsen and colleagues (2000) examined 1-year outcome in 43 first episode patients and at 1-year follow-up 56% were in remission, 26% were still psychotic and 18% suffered multiple relapses. Both longer DUP and poor premorbid functioning predicted more negative symptoms and poor global functioning. Clinical deterioration appears to be correlated with the duration of psychosis and number of episodes of psychosis (Wyatt 1991). The deterioration usually occurs during the first 5 years after onset and then stabilize at a level where they have persistent symptoms and are impaired in their social and vocational function. After that point additional exacerbation may occur but they are not usually associated with further deterioration (Lieberman 1999a).

Long-term studies of schizophrenia suggest that negative symptoms tend to be less common and less severe in the early stages of the illness but increase in prevalence and severity in the later stages. Positive symptoms such as delusions and hallucinations are more common earlier on while thought disorganization, inappropriate affect, and motor symptoms occur more commonly in the later stages of illness. A possible decline in the prevalence of the hebephrenic and catatonic subtypes of schizophrenia may be attributed to effective treatment and possible arrest of the progression of illness. Thus with effective treatment, and with long-term compliance it is possible to produce favorable outcomes.

Following onset of the illness, patients experience substantial decline in cognitive functions from their premorbid levels. However, it is unclear whether, after the first episode, there is further cognitive decline due to the illness. Some studies even suggest a slight and gradual improvement. Increased number of episodes and the longer duration of untreated psychosis are associated with greater cognitive dysfunction.

Patients with first episode psychosis usually have excellent clinical response to antipsychotic treatment early in their course of illness when compared to chronic multiepisode patients. *Effective and early intervention does help achieve clinical remission and good outcome* (Lieberman 2006). Some suggest that SGAs should be used preferentially in the treatment of first episode patients with psychotic disorders (Lieberman 1996) as they are a highly treatment responsive group, and may be best able to optimize the outcome. In addition, first episode patients are sensitive to side effects, especially extrapyramidal and weight gain side effects. They require lower doses of medication to achieve therapeutic responses. The issue of treatment adherence is of critical importance in first episode patients. Although these patients respond very well with 1-year remission rates of greater than 80%, the 1-year attrition rates are as high as 60%. This important issue undermines management of first episode patients during this critical period of their illness.

According to Emsley et al. (2006), the most important factor by far in management of first episode patients is non and partial adherence to medication. Poor adherence is greatest early in the illness. Relapses and partial response result in accruing morbidity and enduring deficits in cognition and psychosocial function. In their 24-month study involving first episode patients with schizophrenia, schizophreniform and schizoaffective disorder, patients were treated with long acting risperidone every two weeks. Most patients showed clinical improvement with low relapse rates and low rates for treatment discontinuation for any reason. They had 86% retention rate. The authors suggest that rather than reserving the long-acting injectable antipsychotics for the chronic, difficult and poorly compliant patients, it is wiser to use it as a first line treatment whenever possible.

## Treatment

It could be argued that the successful treatment of schizophrenia requires a greater level of clinical knowledge and sophistication than the treatment of most other psychiatric and medical illnesses. It begins with the formation of a therapeutic psychiatrist–patient relationship and must combine the latest developments in pharmacological and psychosocial therapeutics and interventions.

## Psychiatrist–Patient Relationship

The psychiatrist–patient relationship is the foundation for treating patients with schizophrenia. Because of the clinical manifestations of the illness, the formation of this relationship is often difficult. Paranoid delusions may lead to mistrust of the psychiatrist. Conceptual disorganization and cognitive impairment make it difficult for patients to attend to what the psychiatrist is saying and to follow even the simplest directions. Negative symptoms result in lack of emotional expression and social withdrawal, which can be demoralizing for the psychiatrist who is attempting to "connect" with the patient.

It is important for the psychiatrist to understand the ways in which the psychopathology of the illness affects the therapeutic relationship. The psychiatrist should provide constancy to the patient, which helps "anchor" patients in their turbulent world. The qualities of the relationship should include consistency, acceptance, appropriate levels of warmth that respect the patient's needs for titrating emotional intensity, nonintrusiveness, and, most important, caring. "Old-fashioned" family doctors who know their patients well, are easily approachable, have a matter-of-fact style, attend to a broad range of needs, and are available and willing to reach out during crises provide a useful model

for the psychiatrist–patient relationship in the treatment of schizophrenia. With increasing medical morbidity secondary to lifestyle issues and side effects of medications, and recognition that persons with schizophrenia may be generally be at increased risk of medical morbidity, the psychiatrist also assumes more responsibilities of coordinating care across various disciplines, integrating discussions about 'wellness' along with illness management and heavily relying on this relationship to affect positive changes.

## Psychopharmacological Treatment

### Background

One hundred years ago, Philippe Pinel changed the philosophy of treating the mentally ill when he unchained patients and provided them with well-balanced diets in the hope that these interventions would ameliorate their symptoms (Weiner 1992). Attempts to treat these patients medically included interventions such as insulin shock, dialysis, and frontal lobotomies. These methods appeared effective at times, yet it was clear that something else was needed to help the poorly understood symptoms of schizophrenia.

It was mere serendipity when a surgeon in France, Henri Laborit, through his keen observations, recognized that chlorpromazine had unusual tranquilizing properties during its use as a preoperative anesthetic medication. This lead to its first successful use in the treatment of psychosis as described in the seminal work of Delay and Deniker in 1952 which provided a pharmacological strategy that would forever change the face of schizophrenia. The implementation of chlorpromazine became the turning point for psychopharmacology. Patients who had been institutionalized for years were able to receive treatment as outpatients and live in community settings. The road was paved for the deinstitutionalization movement, and scientific understanding of the pathophysiology of schizophrenia burgeoned.

The discovery of the first antipsychotic, chlorpromazine, a phenothiazine compound, led to the development of other phenothiazines and new classes of antipsychotic medications, now totaling 12 different classes available in the US today. The word neuroleptic, literally "nerve cutting," was used to describe the tranquilizing effects of these medications. The enormous efforts to understand the mechanism of action of these (typical) antipsychotics uncovered the intimate association of dopamine $D_2$ receptor blockade to the antipsychotic effects. This formed the basis of the original dopamine hypothesis suggesting that symptoms of schizophrenia were possibly related to the hyperactivity of the (mesolimbic and mesocortical) dopaminergic systems in the brain. Antipsychotics developed subsequent to chlorpromazine such as haloperidol, thiothixene, and so on, were modeled on the (misguided) belief that induction of EPS was an integral part of having an antipsychotic efficacy. Over the years another belief developed that all antipsychotics were similar in their efficacy and varied only in their side effects. However, the antipsychotic drug clozapine, which was available for clinical use since 1960s in Europe, challenged these beliefs by being significantly superior in efficacy than the existing antipsychotics and having minimal to no EPS! This started the era of antipsychotic agents being referred to as either "typical" (*conventional* or *traditional*) or "atypical" (or *novel*) antipsychotic drugs. If chlorpromazine started the first revolution in the psychopharmacological treatment of schizophrenia, then clozapine ushered in the second and more profound revolution whose impact is felt beyond schizophrenia and its full extent is yet to be realized. Moreover, clozapine invigorated the psychopharmacology of schizophrenia and rekindled one of the most ambitious searches for new antipsychotic compounds by the pharmaceutical industry. Following approval of clozapine in 1990, the FDA has already approved six new antipsychotics—risperidone (Risperdal 1994), olanzapine (Zyprexa 1996), quetiapine (Seroquel 1997), ziprasidone (Geodon 2001), aripiprazole (Abilify 2002), and paliperidone (Invega 2007)—and is on the verge of approving more, a remarkable progress indeed. Perhaps the best way to classify these medications would be to call the traditional, typical or conventional antipsychotics as *first generation antipsychotics (FGA)* and the atypical, novel or serotonin dopamine antagonists as *Second Generation Antipsychotics (SGA)*.

It is indeed hard to believe that FGAs were the only medications available in USA until 1994, with the exception of clozapine, for treatment of schizophrenia. Furthermore, it is equally amazing how dramatically the SGAs have replaced the FGAs in last decade. However, FGAs are still an important and sometimes the only choice in many parts of the world. Clinicians, educators as well as most among the research community firmly believed that the nonclozapine SGAs were *markedly* superior compared to the FGAs. When a number of meta-analyses and reviews failed to find meaningful or substantial differences between the FGAs and nonclozapine SGAs, it was puzzling and not quite believable. Actually, the psychiatry community was so enamored with these medications with remarkably better neurological adverse events that the spending increased from $1.4 billion in 1994 to more than $10 billion dollars annually toward antipsychotic medication costs. According to Rosenheck (2006), the high expectations from the SGAs combined with the enthusiasm with which each new medication was greeted is evident in increased annual sales every year after their approval such that they became "the most widely prescribed on-patent psychotropic drugs, and as much as 100 times the cost of some FGAs." Every new year saw SGAs eroding the market share of FGAs such that many believed it was only a matter of time before most of them would be out of use. However, data from two "practical clinical trials (discussed later, in Chapter 102)" and a study from VA medical center surprised the clinical and research community by failing to show meaningful differences in effectiveness, quality of life and other important outcome measures between FGAs and SGAs (excluding clozapine, aripiprazole and paliperidone) in nonrefractory patients (Lieberman et al. 2005, Jones et al. 2006, Rosenheck 2006, Lieberman 2006). When even treatment data from first episode studies failed to show substantial differences on efficacy and retention measures with some of the SGAs, the disappointment was palpable. Even the investigators of these studies were surprised by the results. These sobering results led Lieberman (2006) to conclude that the SGAs are not the "great breakthrough" in treatment as once thought but rather an "incremental advance" over the FGAs. However, there are others who do believe that the differences between the two groups of antipsychotic are sufficiently important to justify their preferential use.

Only time will tell if these data will lead to resurrection of FGAs clinically or a more gradual extinction. Many in the clinical and research community believe that both SGAs and FGAs have a place in the treatment of schizophrenia until we find dramatically better alternatives. There is no doubt that the FGAs are potent antipsychotic medications that play a major role in de-institutionalizing chronically ill schizophrenia patients and improving their quality of life; unfortunately, they also cause significant neurological side effects at therapeutic doses that are quite troubling. Increasingly, the opinions are converging on individualizing treatments for the patients that provide the most efficacy and least (or tolerable) side effects regardless of medication class utilized.

## First Generation Antipsychotic (FGA) Medications

There are seven major classes of FGAs currently available in USA. *Phenothiazines* were the first antipsychotics used in treatment of schizophrenia. These tricyclic compounds can be further classified into three subgroups. *Aliphatic* phenothiazines are low potency antipsychotics like chlorpromazine and triflupromazine which are likely to be quite sedating and have substantial hypotensive and anticholinergic side effects. *Piperidine* phenothiazines include thioridazine which also causes sedation, hypotension and anticholinergic side-effects. Moreover, it is likely to substantially prolong QTc interval such that it now carries a 'black box' warning requiring mandatory EKG monitoring. *Piperazine* phenothiazines are more likely to produce EPS but less likely to produce drowsiness, anticholinergic side effects and hypotension. These are also the most popular FGA phenothiazines with compounds like fluphenazine, perphenazine and procholorperazine.

Haloperidol, one of the most commonly used FGAs, belongs to *Butyrophenones* group. It is a potent dopamine $D_2$ receptor antagonist and thus more likely to cause acute dystonic reactions, EPS and TD. They do not cause anticholinergic and autonomic side effects. Haloperidol is also the most commonly used comparator antipsychotic drug in regulatory trials. Droperidol is another member of this group and was commonly used in ER to control agitation until it was reported to prolong QTc interval, cause *Torsades de Pointes* (ventricular arrhythmias), and sudden death. *Diphenylbutylpiperidines* share similarities with butyrophenones and pimozide is the only compound available from this group. Prolongation of QTc interval has emerged as a major concern limiting its use, though it is still popular in treatment of delusional disorders.

Chlorprothixene and thiothixene belong to *Thioxanthines* group and have side effects similar to the phenothiazines. Loxapine is the only *Dibenzoxapine* compound available in USA from this group; chemically it is a close cousin of clozapine but not clinically. Molindone, a representative *Dihydroindole* compound from this group, was widely used in individuals who gained weight on other antipsychotic medications.

## Clozapine and the Second Generation Antipsychotic (SGA) Medications

Though clozapine, a dibenzodiazepine compound, was approved for use in the US in 1990, it had been available in European markets during the 1970s but had been found to be associated with agranulocytosis, a potentially fatal side effect, which led to its removal from clinical trials. The need for improved treatment of schizophrenia, particularly for patients who do not respond to FGAs, generated interest in resuming investigations of clozapine's clinical efficacy.

Double–blind, controlled studies demonstrated the superior clinical efficacy of clozapine compared with FGAs, without the associated EPS (Kane et al. 1988, Breier et al. 1994). It is clearly superior to SGAs for psychosis. A summary of some of the US studies of patients with chronic and treatment-resistant schizophrenia suggests that approximately 50% of patients derive a better response from clozapine than from FGA (Table 65–3). Its effect on negative symptoms is controversial and has generated intense and passionate debates as to whether the efficacy of the medication is with primary or secondary negative symptoms or both. There is substantial evidence that clozapine decreases relapses, improves stability in the community, and diminishes suicidal behavior. It is the only antipsychotic that has received FDA approval for treating suicidal patients. There have also been reports that clozapine may cause a gradual reduction in preexisting tardive dyskinesia, improve tardive dystonia, decrease substance use, psychogenic polydipsia and cigarette smoking among schizophrenia patients.

Unfortunately, clozapine is associated with agranulocytosis, and because of this risk, it requires weekly to monthly white blood cell (WBC) testing. Approximately 0.8% of patients taking clozapine and receiving regular WBC monitoring develop agranulocytosis. Women and the elderly are at higher risk than other groups. The period of highest risk is the first 6 months of treatment. These data have led to monitoring of WBC counts less frequently after first 6 months to every other week if a person has a history of WBC counts within normal range in the preceding 6 months. After 1 year of WBC counts being in normal

**Table 65–3 Clozapine Responder Rates in Chronic Schizophrenia: US Studies**

| Study | Number of Inpatients | Illness Severity | Trial Duration | Responders (%) |
|---|---|---|---|---|
| Kane et al. (1988) | 126 | ++++ | 6 wk | 30 |
| Meltzer et al. (1990) | 51 | +++ | 6 mo | 61 |
| Davis et al. (1991) | 25 | ++++ | 1 yr | 60 |
| Wilson et al. (1992) | 37 | ++++ | 6 mo | 62 |
| Breier et al. (1993) | 30 | ++ | 1 yr | 60 |
| Zito et al. (1993) | 152 | ++++ | 1 yr | 43 |
| Pickar et al. (1994) | 40 | +++ | 4 mo | 50 |

range, the monitoring frequency decreases to once a month. Current guidelines state that the medication must be held back if the total WBC count is 3,000 $mm^{-3}$ or less or if the absolute polymorphonuclear cell count is 1,500 $mm^{-3}$ or less. Patients who discontinue clozapine treatment require blood monitoring for at least four weeks after the last dose. Other side effects of clozapine include orthostatic hypotension, tachycardia, sialorrhea, sedation, elevated temperature, weight gain, hyperglycemia, and hyperlipidemia. Furthermore, clozapine can lower the seizure threshold in a dose-dependent fashion, with a higher risk of seizures seen particularly at doses greater than 600 mg/day.

Clozapine has an affinity for dopamine receptors ($D_1$, $D_2$, $D_3$, $D_4$, and $D_5$), serotonin receptors (5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_6$, and 5-$HT_7$), alpha-1- and alpha-2-adrenergic receptors, nicotinic and muscarinic cholinergic receptors and $H_1$ histaminergic receptors. As clozapine has a relatively shorter half-life, it is usually administered twice a day.

The superior antipsychotic efficacy of clozapine has inspired an abundance of research in the field of modern psychopharmacology for the treatment of schizophrenia. Clozapine and the other SGAs have an array of biochemical profiles, with affinities to dopaminergic, serotoninergic, and noradrenergic receptors (Figure 65–10 [see Color Plate 000]) Research on the SGAs has led to a greater understanding of the biochemical effects of antipsychotic agents, leaving the basic dopamine hypothesis of schizophrenia insufficient to explain schizophrenia symptoms. Clozapine shows selectivity for mesolimbic neurons and does not increase the prolactin level. Binding studies have shown it to be a relatively weak $D_1$ and $D_2$ antagonist, compared with FGAs. Clozapine shares the property of higher serotonin 5-$HT_{2A}$ to dopamine $D_2$ blockade ratio reported to impart atypicality; thus, antipsychotics with this profile are often called serotonin dopamine antagonists. The noradrenergic system may also have a role in the mechanism of action of clozapine. Clozapine, but not FGAs, causes up to fivefold increases in plasma norepinephrine. Moreover, these increases in norepinephrine correlated with clinical response. Clozapine is available in tablet form only.

Following clozapine, risperidone was the first SGA approved by FDA in 1994. Risperidone is a benzisoxazole compound with a high affinity for 5-$HT_{2A}$ and $D_2$ receptors and has a high serotonin dopamine receptor antagonism ratio. It has high affinity for alpha-1-adrenergic and $H_1$ histaminergic receptors and moderate affinity for alpha-2-adrenergic receptors. Risperidone is devoid of significant activity against the cholinergic system and the $D_1$ receptors. The efficacy of this medication is equal to that of other first-line SGAs and is well tolerated and can be given once or twice a day. The most common side effects reported are drowsiness, orthostatic hypotension, lightheadedness, anxiety, akathisia, constipation, nausea, nasal congestion, prolactin elevation, and weight gain. At doses above 6 mg/day EPS can become a significant issue. The risk of tardive dyskinesia (TD) at the regular therapeutic doses is low. Risperidone is also available in a liquid form, rapidly disintegrating tablets called M tablets and as a long acting intramuscular preparation called Risperdal Consta which is given every two weeks. Risperidone will be the second SGA available in a generic form starting 2008.

Olanzapine, a thienobenzodiazepine compound approved in 1996, has antagonistic effects at dopamine $D_1$ through $D_5$ receptors and serotonin 5-$HT_{2A}$, 5-$HT_{2C}$, and 5-$HT_6$ receptors. The antiserotonergic activity is more potent than the antidopaminergic one. It also has affinity for alpha-1-adrenergic, $M_1$ muscarinic acetylcholinergic and $H_1$ histaminergic receptors. It differs from clozapine by not having high affinity for the 5-$HT_7$, alpha-2-adrenergic, and other cholinergic receptors. It has significant efficacy against positive and negative symptoms and may improve cognitive functions. EPS is minimal when used in the therapeutic range with the exception of mild akathisia. As the compound has a long half-life, it is used once a day and as it is well tolerated, it can be started at a higher dose or rapidly titrated to the most effective dose. It is available as a rapidly disintegrating wafer form (Zyprexa Zydis), which dissolves immediately in the mouth. A short acting intramuscular form has also been approved by FDA. The commonly observed adverse events include weight gain, hyperglycemia, hyperlipidemia,

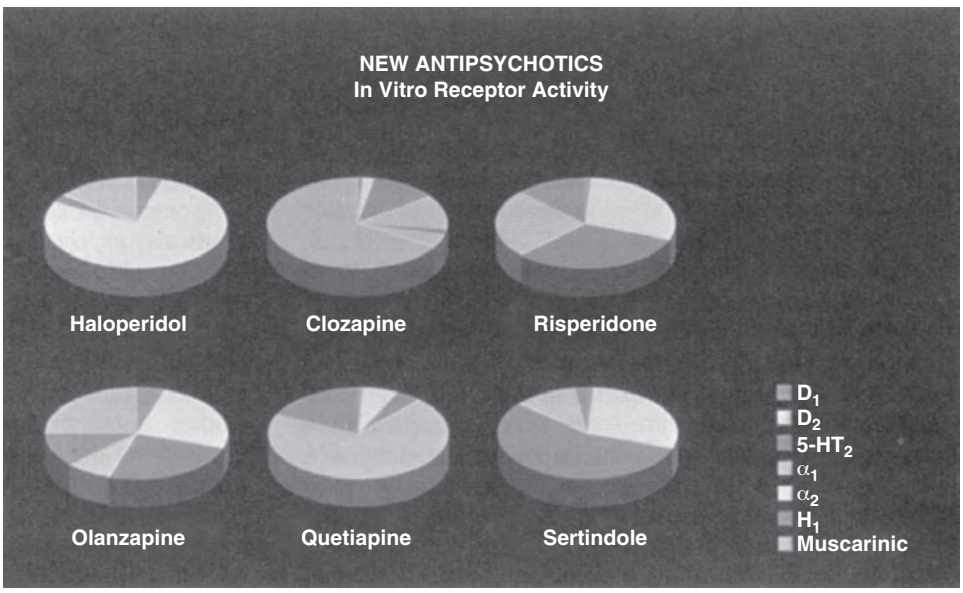



**Figure 65–10** In vitro *receptor affinity of new antipsychotic agents. (See Color Plate XVI.)*

sedation, dry mouth, nausea, lightheadedness, orthostatic hypotension, dizziness, constipation, headache, akathisia, and transient elevation of hepatic transaminases. The risk of TD and NMS is low. Though used as a once-a-day medication, it is often administered twice a day with the average dose of 15 to 20 mg/day. However, doses higher than 20 mg/day are often used clinically (Volavka et al. 2002). In the CATIE study, patients received olanzapine up to 30 mg/day (Lieberman et al. 2005).

Quetiapine, a dibenzothiazepine compound approved in 1997, has a greater affinity for serotonin 5-$HT_2$ receptors than for dopamine $D_2$ receptors; it has considerable activity at dopamine $D_1$, $D_5$, $D_3$, $D_4$, serotonin 5-$HT_{1A}$, and alpha-1-, alpha-2-adrenergic receptors. Unlike clozapine, it lacks affinity for the muscarinic cholinergic receptors. It is usually administered twice a day due to a short half-life. Quetiapine is as effective as FGAs and may improve cognitive function too. Among 2,035 patients enrolled in seven controlled studies, quetiapine at all doses used did not have an EPS rate greater than placebo. This is in contrast to olanzapine, risperidone, and ziprasidone, where there were dose related effects on EPS levels. The rate of treatment emergent EPS was very low even in high at-risk populations such as adolescent, parkinsonian patients with psychosis, and geriatric patients. There was no elevation of prolactin. Commonly observed adverse events include somnolence, postural hypotension, dizziness, agitation, dry mouth, and weight gain. Akathisia occurs on rare occasions. The package insert warns about developing lenticular opacity or cataracts and advises periodic eye examination based on data from animal studies. However, recent data suggest that this risk may be minimal. It is available as tablets and an extended release version is in development.

Ziprasidone, approved by FDA in 2001, has the strongest 5-$HT_{2A}$ receptor binding relative to $D_2$ binding amongst the SGA agents currently in use. Interestingly, ziprasidone has 5-$HT_{1A}$ agonist and 5-$HT_{1D}$ antagonist properties with a high affinity for 5-$HT_{1A}$, 5-$HT_{2C}$, and 5-$HT_{1D}$ receptors. As it does not interact with many other neurotransmitter systems, it does not cause anticholinergic side effects and produces little orthostatic hypotension and relatively little sedation. Just like some antidepressants, ziprasidone blocks presynaptic reuptake of serotonin and norepinephrine. Ziprasidone has a relatively short half-life and thus it should be administered twice a day and along with food for best absorption. Data for efficacy, side effects and dosing come from a number of studies. Ziprasidone at doses between 80 and 160 mg/day is probably the most effective for treating symptoms of schizophrenia. Ziprasidone pills should be taken with meals to obtain adequate blood levels. To assess the cardiac risk of ziprasidone and other antipsychotic agents, Pfizer and FDA designed a landmark study to evaluate the cardiac safety of the antipsychotic agents, given at high doses alone and with a known metabolic inhibitor in a randomized study involving patients with schizophrenia. This was done to replicate the possible worst-case scenario (overdose or dangerous combination treatment) in the real world. Some degree of QTc prolongation was observed with all antipsychotic agents. The least degree of QTc prolongation was observed with the oral form of haloperidol and the greatest degree with thioridazine (Figure 65–11). Commonly observed adverse events with the use of ziprasidone include somnolence, nausea, insomnia, dyspepsia, and prolongation of QTc interval. Dizziness, weakness, nasal discharge, orthostatic hypotension, and tachycardia occur less commonly.

Ziprasidone should not be used in combination with other drugs that cause *significant* prolongation of the QTc interval. It is also contraindicated for patients with a known history of significant QTc prolongation, recent myocardial infarction, or symptomatic heart failure. Ziprasidone has low EPS potential, does not elevate prolactin levels, and causes approximately 1 lb weight gain in short term studies (Allison et al. 1999). Ziprasidone is available in pill form and as a short-acting IM preparation.

When Arvid Carlsson, the Nobel Laureate and the original proponent of the dopamine theory of schizophrenia,

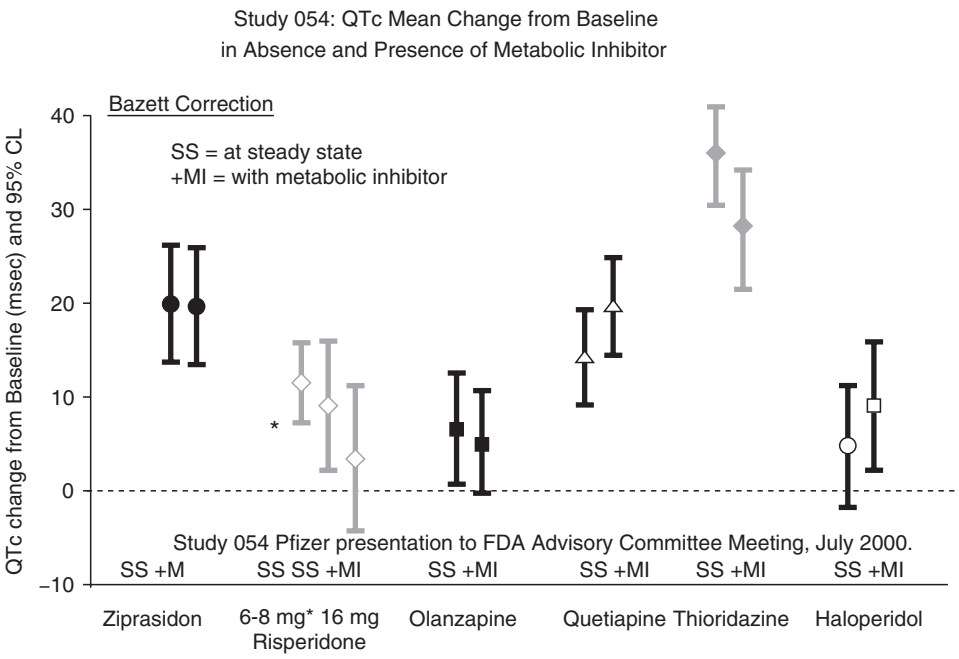



**Figure 65–11** *Study 054 was an open-label, parallel-group study in patients with schizophrenia to assess the effect of oral doses of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine and haloperidol on the QT interval of the EKG. EKGs were measured to correspond to Tmax of the given drug. There were 25 patients per group. The highest dose for each drug was reached based on US package insert. For Risperidone two different doses were used based on common practice of using lower than approved doses. Later in the study, a CYP 450 metabolism inhibitor was coadministered and EKGs were obtained. QTc was calculated using Bazett's correction. Data from this study resulted in "black box" warning from FDA for mesoridazine and thioridazine. (FDA Psychopharmacological Drugs Advisory Committee: Briefing documents for ziprasidone, July 2000.) (Source: Pfizer Pharmaceuticals and www.fda.gov)*

alluded to the possible advantages of a partial dopamine agonist at the Dopamine $D_2$ autoreceptor in treatment of schizophrenia, scientists at Otsuka Pharmaceutical Co, Japan focused their efforts and developed OPC 14597, a partial dopamine agonist. After years of clinical trials and in collaboration with Bristol-Myers Squibb, it was approved for marketing as Aripiprazole in 2002. In a refreshing departure from other antipsychotics, it has a different mechanism of action where, as a partial agonist at the Dopamine $D_2$ receptor, it behaves as a a functional dopamine $D_2$ antagonist in hyperdopaminergic environment and functional dopamine agonist in hypodopaminergic environment. This mechanism of action is thought to 'modulate' and 'stabilize' the dopaminergic system (see Figure 65–12). It is a serotonin 5-HT2A antagonist and partial agonist at 5HT1A receptor. It has moderate affinity for alpha 1 adrenergic and histaminergic H1 receptors with no significant effect at the anticholinergic receptors. Aripiprazole is a quinolinone compound and has a long half life of 75 hours. It is dosed once a day and is well absorbed orally and is not affected by administration of food. The advantages that aripiprazole offers as an antipsychotic medication are (a) it is perhaps the least sedating antipsychotic agent; (b) it does not increase prolactin levels, and may decrease the levels below baseline; (c) there is significantly less weight gain of 1 kg/year; (d) it does not elevate serum glucose levels; (e) it does not significantly elevate serum lipid levels; (f) it does not prolong QTc interval (g) and has relatively low rate of EPS. However, it does cause nausea during the early phase of the treatment and akathisia. As it is metabolized by CYP 3A4 and CYP 2D6, aripiprazole dose does require to be adjusted with CYP 3A4 inducers such as carbamazepine and CYP 3A4 and CYP 2D6 inhibitors such as fluoxetine. It is available in oral tablets, liquid and as short acting IM preparation.

Paliperidone or 9-hydroxy risperidone is an active metabolite of risperidone and was approved by FDA in 2006. It blocks the Dopamine $D_2$ receptors along with serotonin receptors like its parent compound risperidone. It was significantly efficacious in double-blind, placebo controlled studies involving 1,248 subjects and a comparator arm of olanzapine. There was a 22% relapse rate compared to 52% on placebo after 52 weeks treatment. The prolactin levels were four times as high among men and five times as high among women who received paliperidone at any dosage. EPS such as dystonia and hyperkinesis were more prevalent at 12 mg/day (10%) than 6 mg/day (5%). Tachycardia was more common than placebo. Paliperidone does not undergo hepatic metabolism thereby minimizing drug-drug interactions. Paliperidone ER is available using Osmotically controlled Release Oral-delivery System, or OROS formulation. There is an osmotic trilayer core, consisting of two distinct drug layers and an osmotic push layer. Good tolerance has been reported at 6, 9 and 12 mg/day.

The randomized controlled trials suggest that, on average, these antipsychotic agents are each associated with 20% improvement in symptoms. Recent studies and meta-analyses have given olanzapine an edge over the other SGAs except clozapine. However, treatment emergent weight gain and lipid elevations are the most commonly observed adverse events. Clozapine is the only antipsychotic agent that is more effective than most antipsychotics currently available in managing treatment resistant schizophrenia (Kane et al. 1988, McEvoy et al. 2006). Unfortunately, its potential for treatment-emergent agranulocytosis, seizures, and myocarditis, precludes its use as a first line agent for schizophrenia. A major difference amongst the newer antipsychotic agents is the side effect profile and its effect on the overall quality of life of the patient.

## Acute Treatment

Until recently, the FGAs were the mainstay of the treatment for acute episodes of psychosis. In last decade, the use of SGAs has surpassed the use of FGAs in the management of acute phase symptoms of schizophrenia, except for the use of parenteral form of antipsychotics where FGAs still hold an upper hand. Interestingly, this trend has not changed as dramatically even with the availability of three injectable preparations for acute use of SGAs namely olanzapine, ziprasidone and aripiprazole (Keith 2006). The primary

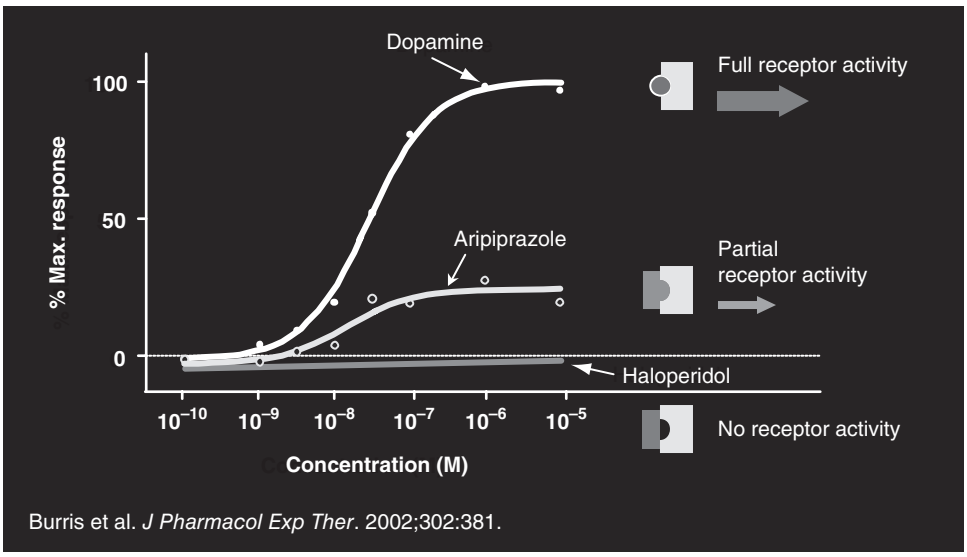



**Figure 65–12** *Aripirazale: activity at doned human $D_2$ receptors.*

goal of acute treatment is the amelioration of any behavioral disturbances that would put the patient or others at risk of harm. Acute symptom presentation or relapses are heralded by the recurrence of positive symptoms, including delusions, hallucinations, disorganized speech or behavior, severe negative symptoms, or catatonia. Quite frequently, a relapse is a result of antipsychotic discontinuation, and resumption of antipsychotic treatment aids in the resolution of symptoms. There is a high degree of variability in response rates among individuals. When pharmacotherapy is initiated, improvement in clinical symptoms can be seen over hours, days, or weeks of treatment.

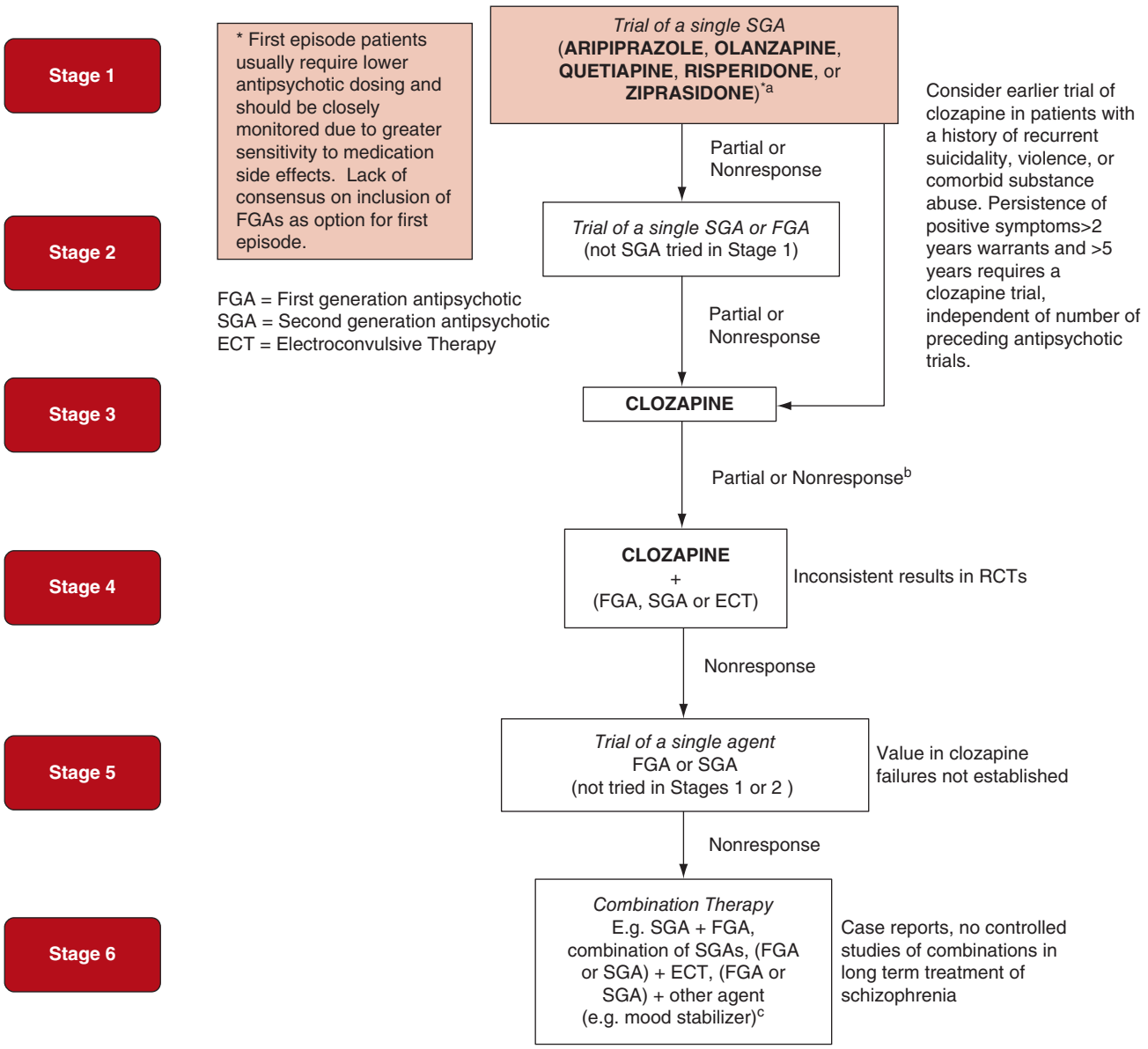
Studies have shown that although FGAs are undoubtedly effective, a significant percentage (between 20 and 40%) of patients show only a poor or partial response to these agents. Furthermore, there is no convincing evidence that one FGA is more efficacious as an antipsychotic than any other, although a given individual may respond better to a specific drug. Some have suggested that clinical efficacy of thioridazine is different and better than the other FGAs and perhaps having an atypical profile. With so many antipsychotics available, making an informed choice between using an FGA or an SGA by the patient and the clinician should be based on efficacy, side effect profile, history of prior response (or nonresponse) to a specific agent, or history of response of a family member to a certain antipsychotic agent. For a pharmacotherapy decision tree for the treatment of schizophrenia, management of treatment-emergent side effects and associated or coexisting symptoms in schizophrenia based on Texas Medication Algorithm Project, see Figure 65–13 and Table 65–4 and Table 65–5. Amongst the FGAs, low-potency, more sedating agents, such as chlorpromazine, were long thought to be more effective for agitated patients, yet there are no consistent data proving that high-potency agents are not equally useful in this context. The low-potency antipsychotics, however, are more associated with orthostatic hypotension and lowered seizure threshold and are often not as well tolerated at higher doses. Higher potency antipsychotics, such as haloperidol and fluphenazine, are safely used at higher doses and are effective in reducing psychotic agitation and psychosis itself. However, they are more likely to cause EPS than the low potency agents and SGAs.

The efficacy of SGAs on positive and negative symptoms is comparable to or even better than the FGAs (see e.g., Lieberman et al. [1993], Chakos et al. [2001], Geddes et al. [2000], Lieberman et al. [2005], Jones et al. [2006]). The significantly low potential to cause EPS or dystonic reaction and thus the decreased long-term consequences of TD has made the SGAs more tolerable and acceptable in acute treatment of schizophrenia. Other significant advantages adding to the popularity of some of the SGAs include their beneficial impact on mood symptoms, suicidal risk, and cognition. They are significantly easy to use, have rapid action depending on the type of preparation used (e.g. liquid, rapidly disintegrating forms, or IM), and may have better side effects profile for acute treatment depending on the SGA used and allows for individualizing treatment. Thus, the selection of the first line treatment with antipsychotic will depend on the circumstances under which the medications are started, for example, extremely agitated or incompetent patients who are refusing court-mandated treatments or catatonic patients would require intramuscular preparation, rapidly disintegrating oral tablets or liquid preparation of antipsychotics. Recent data suggest that SGA IM preparations such as ziprasidone, olanzapine and aripiprazole may hold significant advantages over the IM FGAs such as haloperidol. However they are also significantly more expensive. Except for clozapine, which is not considered first line treatment because of substantial and potentially life threatening side effects, there is no convincing data supporting the preference of one FGA/SGA over the other. However, if the patient does not respond to one, a trial with another antipsychotic is reasonable and may produce response. Once the decision is made to use an antipsychotic agent, an appropriate dose must be selected. Initially, higher doses or repeated dosing may be helpful in preventing grossly psychotic and agitated patients from doing harm. In an open trial, 80 schizophrenia inpatients were assigned to receive haloperidol at a dose of 5, 10, or 20 mg/day for 4 weeks. In this study, the patients receiving the highest dose of haloperidol initially demonstrated the most effective treatment of psychotic symptoms, but they were later found to have a higher incidence of EPS and emotional withdrawal. In general, studies indicate that doses of high-potency antipsychotics such as haloperidol can be maintained at a total of 10 mg/day in an acute setting, and that there is no generalizable benefit of using higher doses. Early adjuvant treatment with anticholinergic medication may facilitate compliance with medication by decreasing intolerable side effects.

Some patients who are extremely agitated or aggressive may benefit from concomitant administration of high-potency benzodiazepines such as lorazepam, at 1 to 2 mg, until they are stable. Benzodiazepines rapidly decrease anxiety, calm the person, and help with sedation to break the cycle of agitation. They also help decrease agitation due to akathisia. The use of these medications should be limited to the acute stages of the illness to prevent tachyphylaxis and dependency. Benzodiazepines are quite beneficial in treatment of catatonic or mute patients but the results are only temporary though of enough duration to help with body functions and nutrition.

## Maintenance Treatment

There is by now a great deal of evidence from long-term follow-up studies that patients have a higher risk of relapse and exacerbations if not maintained with adequate antipsychotic regimens (Hogarty et al. 1974). Noncompliance with medication, possibly because of intolerable antipsychotic side effects as well as other factors, may contribute to increased relapse rates. In a double-blind, placebo-controlled study of relapse rates, 50% of patients in a research ward demonstrated clinically significant exacerbation of their symptoms within 3 weeks of stopping antipsychotic treatment. Furthermore, in a comprehensive review of the literature on antipsychotic withdrawal examining 4,365 subjects, 53% of patients withdrawn from antipsychotics relapsed, compared with 16% of control subjects who were maintained with antipsychotic treatment. The length of follow-up was related to the risk of relapse. Unfortunately, in this review there were no clear demographical or clinical characteristics that consistently predicted relapse. Others have estimated that two-thirds of patients relapse after 9 to 12 months without antipsychotic medication, compared with 10 to 30%




[a]If patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate or fluphenazine decanoate.

[b]A treatment refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors Cognitive Behavioral Therapy (CBT) or Psychosocial augmentation should be considered.

[c]Whenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving **psychotic** symptoms, the patient is considered to be in Stage 6.

**Figure 65–13** *Selecting antipsychotic treatment, management of treatment-emergent side effects and associated or co-existing symptoms in schizophrenia using Texas Medication Algorithm for Schizophrenia. This project is a public-academic collaborative effort to develop, implement, and evaluate medication treatment algorithms for public sector patients. For more information or to view the most current version of the algorithm visit http://www.dshs.state.tx.us/mhprograms/TMAP.shtm. (Reproduced with permission from the Texas Department of State Health Services. Copyright 2007 Texas Department of State Health Services, all rights reserved).*

who relapse when FGAs are maintained. Long-term outcome studies showed that persistent symptoms that do not respond to FGA therapy are associated with a greater risk of rehospitalization (Breier et al. 1991). Nonpharmacological interventions may help decrease relapse rates (discussed later). CATIE study and others have shown that almost 50 to 75% of subjects will switch or discontinue antipsychotic medications within first 18 months or less. This occurs even in medications with more favorable EPS profiles. However, even with the SGAs, compliance rates are not substantially better (Keith 2006).

Long-term treatment of schizophrenia is a complex issue. It is clear that the majority of patients require maintenance medication. Some patients do well with stable doses of antipsychotics for years without any exacerbations. However, many patients who are maintained with a stable

**Table 65–4 Management of Treatment-Emergent Side Effects in Schizophrenia**

| Side Effect | Recommendations |
|---|---|
| GI Upset | – Nausea and diarrhea are usually transient side effects with antidepressants, and improvement should occur within 2–3 wk after initiation or dose increases.<br>– Administer medication with food and large quantities of liquid.<br>– Consider lowering dose, if possible, or slowing the dose titration.<br>– Persistent GI upset may require changing to an alternative medication or adding an adjunctive agent, such as an $H_2$ blocker (e.g., famotidine, ranitidine). |
| Tremor | – Enhanced physiologic tremor—A fine tremor of approximately 8–10 Hz; made worse with outstretched hands.<br>• Check blood levels of medication, if applicable.<br>• Decrease dose, divide dose, or change to slow release preparation of the medication.<br>• Propranolol can be given at 20–30 mg three times a day.<br>– Parkinsonian tremor—Coarse tremor at rest of approximately 4–6 Hz.<br>• See treatment recommendations under extrapyramidal symptoms (EPS) below. |
| Sedation | – A thorough evaluation of sleep behaviors should be performed, including a patient assessment of sleep quality.<br>– May try dosing medication at bedtime.<br>– Decrease dose if possible.<br>– Substitute a less sedating alternative medication.<br>– Adjunctive medications may be considered. However, in patients with psychosis, adjunctive treatment is not recommended as it may possibly worsen the course of the episode. |
| Extrapyramidal symptoms (EPS)—Parkinsonian tremor, akathisia, and dystonia | – Usually seen with typical antipsychotics or higher doses of risperidone.<br>– Parkinsonian tremor—coarse tremor at rest of approximately 4–6 Hz.<br>• Decrease dose, divide dosing, use bedtime dosing, or switch to alternate medication.<br>• Pharmacological treatments include benztropine 1–2 mg twice daily, diphenyhydramine 25–50 mg two or three times daily, or propranolol 20–30 mg three times daily.<br>– Akathisia may respond to propranolol 20–30 mg three times a day. If this is not effective, alternatives include clonidine 0.1 mg three times a day, lorazepam 1 mg two or three times a day, or clonazepam 0.5–1 mg twice a day.<br>– Dystonic reactions can often be prevented by benztropine 1 mg two or three times a day for the first few days of antipsychotic therapy. Acute dystonic reactions are generally managed with benztropine 1–2 mg IM or lorazepam 1–2 mg IM. |
| Tardive dyskinesia | – Prescribe typical antipsychotics in the lowest dose necessary for the shortest time possible. Mid-potency typical agents may be preferred if typical antipsychotic is selected.<br>– Use atypical antipsychotic medications.<br>– Consider clozapine which has an extremely low risk of TD.<br>– Consider other treatment modalities, including ECT. |
| Neuroleptic malignant syndrome (NMS) | – Patients with a history of NMS should be educated about the need to stay well hydrated and avoid strenuous physical activity when outside during hot weather.<br>– If the patient has been on a FGA, changing to a SGA is reasonable. |
| Sexual dysfunction | – May consider switching to an alternative medication with lower propensity to cause sexual dysfunction.<br>– If SSRI-induced sexual dysfunction, may consider adding bupropion 75–150 mg daily.<br>– Alternatives for the management of sexual dysfunction secondary to psychotropic medications is to add a selective phosphodiesterase (PDE) type 5 inhibitor. Use is contradicted with concurrent nitrates. Caution use with concomitant C4P3A4 inhibitors. Data available for use in females is limited to small, open label trials.<br>• Sildenafil 25–100 mg one-half to 1 hr before sexual activity.<br>• Tadalafil 10–20 mg one-half to 1 hr before sexual activity.<br>• Vardenafil 5–20 mg one-half to 1 hr before sexual activity.<br>– Other alternative is cyproheptadine 4–8 mg, given shortly before sexual intercourse. However, cyproheptadine is also a serotonin receptor antagonist, and frequent use in patients with affective symptoms should proceed with caution. |
| Insomnia | – Promote good sleep hygiene:<br>• Encourage regular aerobic exercise at least four hours before bedtime.<br>• Avoid alcoholic beverages.<br>• Encourage regular sleep cycles.<br>• Eliminate noises and distracting lights.<br>• Engage in relaxing activities before bed (reading, sex, meditation, etc).<br>• Try a glass of warm milk.<br>– If due to concomitant antidepressant use: reduce the dose of antidepressant, if possible.<br>– Try moving the dosing of the medication to the morning.<br>– Adjunctive medications:<br>• Zolpidem 5–10 mg once daily at bedtime.<br>• Zaleplon 5–20 mg (10 mg recommended dose) once daily at bedtime.<br>• Eszopiclone 2–3 mg once daily at bedtime.<br>• Benzodiazepine, such as temazepam 15–30 mg once daily at bedtime or lorazepam 0.5–2 mg once daily at bedtime.<br>• Trazodone 25–100 mg once daily at bedtime.<br>• Low-dose tricyclic antidepressant, such as amitriptyline 10–50 mg once daily at bedtime.<br>– Brief, targeted cognitive therapy. |

**Table 65–4 Management of Treatment-Emergent Side Effects in Schizophrenia *continued***

| Side Effect | Recommendations |
|---|---|
| Weight gain | – Exercise (walking, jogging, swimming) for at least 3 times weekly, and for at least 30 min each time.<br>– Diet:<br>• Eat smaller portions of 3 meals per day.<br>• Decrease excess fats (decrease fried foods, eat lean meats, increase vegetables, salads, and fruits).<br>• Decrease excessive low nutritional content carbohydrate (soft drinks, deserts, candy, gravies, potatoes, and white bread).<br>– Avoid snacking, and particularly, no evening snacks. |

In general, treatment emergent side effects should be addressed first by dose reduction or medication switching. Prescribing medications for side effects may lead to new side effects.
Benzodiazepines are best avoided in patients with prior history of substance abuse/dependence or who are at risk for substance abuse. Nonaddicting agents are preferred.

antipsychotic dose have episodic breakthroughs of their psychotic symptoms. In a study by Hogarty and associates (1974), 374 schizophrenia patients were followed for 2 years after hospitalization and randomized to receive placebo alone, placebo and sociotherapy, chlorpromazine alone, or chlorpromazine and sociotherapy. In this study, the placebo-only group had a relapse rate that was almost twice that of the chlorpromazine-treated group. Unfortunately, the difficulties in tolerating antipsychotic side effects often contribute to medication noncompliance. Furthermore, intensive case management and rehabilitation counseling did prevent relapse but only after a delayed period. Sociotherapy and drug treatment were found to have additive effects in preventing relapse.

Given the findings of Hogarty and colleagues, it would be prudent to assess patients for medication compliance when signs of relapse are suspected. Prodromal cues may be present before an exacerbation of psychotic symptoms. For example, any recent change in sleep, attention to activities of daily living, or disorganization may be a warning sign of an impending increase in psychosis.

With the increase use of SGAs the widely anticipated improvement in compliance due to significantly less neurological side effects and possible beneficial effects on negative symptoms and neurocognition did not pan out (Lieberman 2006, Lieberman et al. 2005, Jones et al. 2006). In a landmark study comparing risperidone to haloperidol for effects on maintenance treatment, at the end of 1 year, patients taking risperidone were significantly better clinically, more patients were compliant with it and fewer patients had relapses. In this double blind prospective study, 397 stable outpatients were randomized to receive either risperidone or haloperidol for a minimum of 1 year. The Kaplan-Meier estimate of the risk of relapse at the end of study was 34% for the risperidone group and 60% for the haloperidol group. Early discontinuation of treatment for any reason was more frequent among haloperidol treated patients. Risperidone group had greater reductions in the mean severity of both psychotic symptoms and extrapyramidal side effects than those in the haloperidol group (Csernansky et al. 2002). This led to an FDA indication for its use in maintenance treatment. Long-term use of olanzapine, quetiapine, aripiprazole and ziprasidone are also reported to have significant beneficial effects either in comparison to placebo or an FGA like haloperidol. Reviewing all the data would be beyond the scope of this chapter. However, some of the important studies are reviewed in Chapter 102. The data from treatment with clozapine suggest its significant superiority compared to other treatments. In the treatment refractory patients, long-term randomized trials found significant reduction in rehospitalization and suicide rates (Meltzer and Okayli 1995).

For patients for whom compliance is a problem, long acting preparation of antipsychotics are available in the US for fluphenazine, haloperidol and risperidone. The antipsychotic drug fluphenazine or haloperidol is esterified in an oily solution which is injected every 1 to 6 weeks to circumvent the need for daily oral antipsychotic medications in most cases (although some patients benefit from adjuvant oral medication). This form of medication delivery guarantees that the medication is in the system of the person taking it and eliminates the need to monitor daily compliance. This alternative should be considered if noncompliance with oral agents has led to relapses and rehospitalization. With these patients, maintenance treatment using long-acting preparations should begin as early as possible. In a meta analysis done by Adams and colleagues (2001), 3,348 patients were randomized in trials of fluphenazine decanoate. The study attrition rates were remarkably low at only 14% of those randomized compared to 40 to 60% in trials of oral SGA agents. Depot antipsychotic drugs are effective maintenance therapy for patients with schizophrenia. However, currently we only have esters of 2 FGAs and thus the significantly elevated risk of bothersome neurological side effects is an unfortunate limitation to their use. Fortunately, the recent approval of long acting risperidone (Risperdal Consta), the only long-acting SGA currently available should improve the situation. Unlike the decanoate compounds, here risperidone is encapsulated into microspheres made of biodegradable polymer suspended in an aqueous diluent. After injection, very little active moiety is released for up to three weeks and thus oral therapy should be continued during this period. With repeated administration every two weeks, steady state plasma levels are reached after 4th injection and are maintained for 4–6 weeks after last injection. Compared to the daily immediate–release oral therapy, treatment with risperidone consta is associated with reductions in peak blood levels of approximately 30% and also decreased plasma peak-to-trough ratios by 32–42% and may cause fewer adverse effects. Long term data report significant decrease in hospitalization rates from baseline to the end of the

**Table 65–5 Management of Associated or Coexisting Symptoms in Schizophrenia**

| Coexisting Symptom | Recommendations |
|---|---|
| Agitation/ excitement | – Consider adjunctive medications, including as needed use of oral and intramuscular medications including benzodiazepines, typical antipsychotics, and atypical antipsychotics:<br>• Lorazepam 1–4 mg or clonazepam 0.5–2 mg may be used in treating acute agitation. In emergent situations where rapid reduction of agitation is necessary, lorazapam 1–2 mg given intramuscularly may be preferable to oral dosing. The dose may be repeated every 1–2 hours as needed, and onset of effect is generally seen within 15–30 min.<br>• Haloperidol 5 mg orally or intramuscularly may be given every 30–60 min until patient is calm.<br>• Atypical antipsychotics in intramuscular or oral formulations may be given on an as needed basis to control acute agitation. If oral dosing is used, doses should be initiated at the low end of the dosing range. Intramuscular olanzapine, risperidone oral solution, and intramuscular ziprasidone act more rapidly than their oral counterparts and their use may be warranted in cases where the patient can not tolerate or does not respond to typical antipsychotic agents and/or benzodiazepines.<br>• Intramuscular olanzapine 2.5–10 mg, may repeat 2 hr after initial dose and 4 hr after second dose, with a maximum of 30 mg daily.<br>• Intramuscular ziprasidone 10–20 mg as needed to a maximum dose of 40 mg daily. The 10 mg dose may be given every 2 hr, and the 20 mg dose may be given every 4 hr.<br>• Intramuscular aripiprazole 5.25–9.75 mg as needed every 2 hr to a maximum of 30 mg daily.<br>• Risperidone oral solution is available in 1 mg/mL.<br>– Failure of the first trial of pharmacotherapy should be followed by a second trial of an alternative agent above.<br>– After failure of multiple trials of agents to control acute agitiation/excitement, consider moving treatment to the next algorithm stage. |
| Persistent symptoms of aggression/hostility/ mood lability | – Lithium, valproate and carbamazepine are all therapeutic options for the management of aggression and hostility associated with acute exacerbations in schizophrenia<br>– If there is no discernible change in the clinical picture after 1–3 wk, the clinician should discontinue the adjuvant mood stabilizer and consider switching the patient to clozapine. |
| Depression | – Medication treatments for depression in schizophrenia are the same as those used in major depressive disorder.<br>– SSRIs, venlafaxine XR, bupropion SR/XL, duloxetine and mirtazapine are recommended as first line treatments. |
| Insomnia | – Promote good sleep hygiene:<br>• Encourage regular aerobic exercise at least 4 hr before bedtime.<br>• Avoid alcoholic beverages.<br>• Encourage regular sleep cycles.<br>• Eliminate noises and distracting lights.<br>• Engage in relaxing activities before bed (reading, sex, meditation, etc.).<br>• Try a glass of milk.<br>– Adjunctive medications:<br>• Zolpidem 5–10 mg once daily at bedtime.<br>• Zaleplon 5–20 mg (10 mg recommended dose) once daily at bedtime.<br>• Eszopiclone 2–3 mg once daily at bedtime.<br>• Benzodiazepine, such as temazepam 15–30 mg once daily at bedtime or lorazepam 0.5–2mg once daily at bedtime.<br>• Trazodone 25–100 mg once daily at bedtime.<br>• Low-dose tricyclic antidepressant, such as amitriptyline 10–50 mg once daily at bedtime.<br>– Brief, targeted cognitive therapy. |

Benzodiazepines are best avoided in patients with prior history of substance abuse/dependence or who are at risk for substance abuse. Nonaddicting agents are preferred.

study with a better tolerability profile than the FGAs. There is likely to be significantly higher rates of compliance to this treatment.

Many studies have investigated appropriate maintenance doses of FGAs. Effective maintenance treatment is defined as that which prevents or minimizes the risks of symptom exacerbation, relapse and subsequent morbidity. A series of interesting dose-finding studies were performed to determine the minimal dosage required to prevent relapse and to reduce the risk of extrapyramidal symptoms and tardive dyskinesia. The relapse rate (56%) of patients treated with lower doses of fluphenazine decanoate (1.25–5 mg every 2 weeks) was significantly greater than the relapse rate (14%) of patients receiving standard doses (12.5–50 mg every 2 weeks). Other investigators have found that this low dosage range may appear to prevent relapse for a certain period but fails to do so if patients are followed up for more than 1 year. Unfortunately, no specific dosage reliably prevents relapse, and there is no way to predict future relapse. This is true for the SGAs as well.

Plasma drug levels and their correlation with clinical response have also been considered in determining dosage requirements. However, the results remain controversial. Some studies have found that levels that were in excess of a certain therapeutic window led to an exacerbation of symptoms. There is no strong evidence with which to sort out whether this finding was indeed a result of higher plasma levels, secondary to higher dosing for treatment-resistant patients, or due to the fact that the side effects associated with higher doses of antipsychotics may mimic exacerbations of

the primary illness. At this time, plasma drug levels are not recommended for dosage determination. They are clinically useful, however, for confirming compliance with medication and may provide information regarding toxicity or altered metabolism.

Thus the question comes up, are nonclozapine SGAs better than the FGAs in management of schizophrenia? There is no doubt of superiority of clozapine in patients who are (1) treatment refractory (2) hostile and aggressive (3) suicidal (4) concurrently using drugs and alcohol (5) having polydipsia and water intoxication and (6) intolerant to neurological side effects of other antipsychotic agents.

Some reviews of the literature comparing SGAs and FGAs have reported that they are generally equivalent in terms of efficacy against positive symptoms. Others have, using meta-analyses, raised concerns about the size and significance of the effects of SGA superiority over FGAs. Davis and Chen (2005) reviewed the data and divided the SGAs into three groups based on how effective they were. Amongst the antipsychotics available in USA, clozapine was in group one and clearly more effective than FGAs by about 0.5 effect size units. Risperidone and olanzapine were in the intermediate group as being more effective than FGAs. Aripiprazole, quetiapine and ziprasidone were in the third group which was not superior to FGAs. Furthermore, they suggest that these results were not likely due to higher and unfavorable doses of FGA. They report that the relapse rate on placebo is 10% per month. Based on the pooled results of long-term maintenance studies from approximately 50 randomized controls of FGA versus placebo, maintenance treatment reduced relapse quite substantially to one third. Again, they add that great majority of these relapses could have occurred because of poor compliance. As there are limited data of long term maintenance treatment they believe that even the limited data support that SGAs are better than FGAs in the maintenance treatment of schizophrenia as restoration of social functions, better efficacy against negative symptoms, depression and thought disorder may favor their use (Davis and Chen 2005).

Thus data from clinical trials provide confusing and inconsistent results. When 42 head-to-head studies of SGAs were analyzed, there appeared to be a bias in industry-sponsored studies where in 90% of the studies supported by pharmaceutical companies, the outcome favored the sponsoring company. To address such shortcomings including study design issues, NIMH embarked on its most ambitious and expensive project called clinical antipsychotic trials of intervention effectiveness (CATIE), see Chapter 102.

## Depression and Schizophrenia

Symptoms of depression occur in a substantial percentage of schizophrenia patients with a wide range of 7 to 75% and a modal rate of 25% and are associated with poor outcome, impaired functioning, suffering, higher rates of relapse or rehospitalization, and suicide (Siris 2000). It is important to distinguish depression as a symptom or as a syndrome when it occurs. There is an important overlap of symptoms of depression with the negative symptoms. Differentiating these states can sometimes be difficult especially in patients who lack the interpersonal communication skills to articulate their internal subjective states well. Studies have failed to find significant gender differences in prevalence of depression in schizophrenia. This is interesting as in affective disorders more women suffer from depression compared to men. In hospitalized patients with acute exacerbation, depression in women was closely associated with higher negative symptoms scores and younger age whereas in men, positive symptoms and shorter hospitalization were the main factors associated with depression. An increased risk of suicide has been reported for the period immediately after discharge from hospital especially in those patients who have comorbid depression. Survival times from last admission to suicide were significantly shorter in depressed males compared to depressed females with schizophrenia. However, survival times from last hospitalization to suicide between depressive and nondepressive male patients with schizophrenia was significant; this was not the case for females. Thus, hospitalization provides an important opportunity for implementing suicide prevention program that can be followed post discharge. A link between FGA use and depression has been suggested with some considering depression to be a form of medication induced akinesia. Specifically, during treatment with FGAs, less responsive depressive symptoms are revealed and appear to increase as the positive symptoms subside. The SGAs appear to have better efficacy in treating depressive symptoms when compared to placebo as well as FGAs; however, recent studies have failed to find significantly lower levels of depression during treatment with SGAs. Many patients have a reaction of disappointment, a sense of loss or powerlessness, or awareness of psychotic symptoms or psychological deficits that contributes to depression. Depression in schizophrenia is heterogeneous and requires careful diagnostic clarification. DSM-IV-TR suggests that the term "Post psychotic depression" be used to describe depression that occurs at any time after a psychotic episode of schizophrenia, even after a prolonged interval. However, a large number of patients still end up with a depression that will require treatment with an antidepressant, though results concerning combination treatment using antipsychotics and antidepressants are ambiguous. Clearly, optimizing antipsychotic treatment is a very important first step. SSRIs provide a safer and more tolerable profile compared to the tricyclic antidepressants. Combining cognitive behavioral therapy with pharmacotherapy may augment clinical response. In rare circumstances, ECT may be necessary especially if the patient is deemed to be a high suicide or self-harm risk.

### *Risks and Side Effects of FGAs*

Extrapyramidal symptoms are side effects more commonly associated with FGA medications that include dystonias, oculogyric crisis, pseudoparkinsonism, akinesia, and akathisia. They are referred to collectively as extrapyramidal symptoms or EPS because they are mediated at least in part by dopaminergic transmission in the extrapyramidal system (see Figure 65–14). Prevalence rates vary among the different types of extrapyramidal symptoms. When present, they can be uncomfortable for the patient and a reason for noncompliance.

Dystonias are involuntary muscular spasms that can be brief or sustained, involving any muscle group. They can occur with even a single dose of medication. When they develop suddenly, these spasms can be quite frightening to the patient and potentially dangerous, as in the case of laryngeal dystonias. They are more likely to be seen in

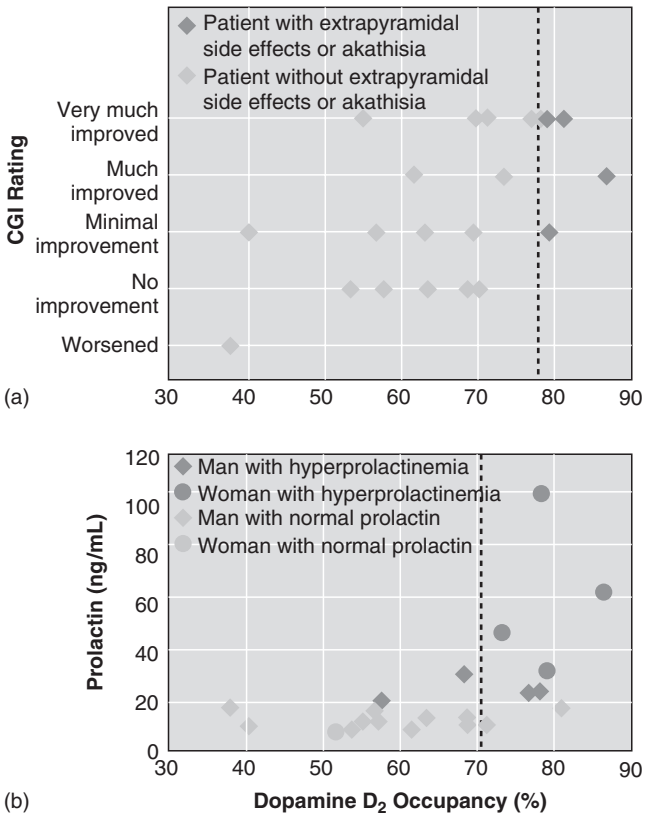



**Figure 65–14** *Relation of dopamine $D_2$ occupancy to CGI-rated clinical response (a) and prolactin level (b) among patients with first-episode schizophrenia receiving haloperidol. Dotted line in (a) indicates 78% of $D_2$ occupancy, which was associated with a significantly greater likelihood of extrapyramidal side effects or akathisia. Dotted line in (b) indicates 72% $D_2$ occupancy, which was associated with a significant greater liklelihood of hyperprolactinemia. (Source: Kapur S, Zipursky R, Jones C, et al. [2000] Relationship between $D_2$ occupancy, clinical reponse, and side effects: A double-blind PET study of first-episode schizophrenia. American Journal of Psychiatry 157, 514–520. Copyright 2000 American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.)*

young patients. Studies differ as to whether the prevalence is higher in males or females. Prevalence rates for dystonias secondary to FGA exposure range from 2 to 20%. They occur less commonly with SGAs.

Akathisia affects more than 20% of patients taking FGA medications. This clinical entity presents as motor restlessness or an internal sense of restlessness. Often patients experiencing akathisia are unable to sit still during an interview. Akathisia is difficult to differentiate from agitation. The tendency to treat agitation with antipsychotics may exacerbate akathisia, making treatment decisions challenging.

Treatment of acute dystonic reactions usually involves acute intramuscular administration of either an anticholinergic or diphenhydramine. Akathisia may not respond to anticholinergic medications. Both antipsychotic dosage reduction and the use of beta-blocking agents such as propranolol have been found to be efficacious in the treatment of akathisia.

Neuroleptic malignant syndrome (NMS) is a relatively rare but serious phenomenon seen in approximately 1% of patients taking FGAs. It can be fatal in 15% of cases if not properly recognized and treated. Because the symptoms of NMS may reflect multiple etiologies, making diagnosis difficult, Levenson has proposed clinical guidelines. According to Levenson, three major or two major and four minor manifestations are indicative of a high probability of NMS. Major manifestations of NMS comprise fever, rigidity, and increased creatine kinase levels, and minor manifestations include tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis. Others do not subscribe to the major-minor manifestation distinctions. In general, NMS is considered to be a constellation of symptoms that usually develops during 1–3 days. Although its pathogenesis is poorly understood, it has been associated with all antidopaminergic antipsychotic agents and presents at any time during treatment. It must be distinguished from other clinical entities, including lethal catatonia, malignant hyperthermia, and serotonin syndrome.

The mainstay of treatment of NMS is cessation of antipsychotic therapy and supportive care, including intravenous hydration, reversal of fever with antipyretics and cooling blankets, and careful monitoring of vital signs because of the risk of cardiac and respiratory disturbance. Rhabdomyolysis is one of the most serious sequelae of NMS; it can lead to renal failure unless patients are well hydrated. In some cases, dantrolene and bromocriptine have been reported to be effective pharmacological treatments. Though quite rare, NMS has been reported even with the use of SGAs. The decision to rechallenge the patient with antipsychotics after an episode of NMS must be made with caution. Given the potential risk involved, informed consent related to a rechallenge is important, and should be obtained unless there is a valid clinical or legal basis that it would not be required.

One of the major risks of antipsychotic treatment, especially with the FGAs is that of TD, a potentially irreversible syndrome of involuntary choreoathetoid movements and chronic dystonias associated with long-term antipsychotic exposure. These buccal, orofacial, truncal, or limb movements can be exacerbated by anxiety and disappear during sleep. They can present with a range of severity, from subtle tongue movements to truncal twisting and pelvic thrusting movements and even possible respiratory dyskinesias. The prevalence rates for this syndrome range from less than 10 to more than 50%, but it is generally accepted that the risk increases 3–5% per year for each year the patient is treated with FGAs. Older age is a considerable risk factor for TD, and there is some evidence that women are at increased risk for the development of this condition. Of note, a withdrawal dyskinesia that resembles TD may appear on cessation of the antipsychotic. The specific mechanism involved in TD remains unclear, although supersensitivity of dopaminergic receptors has been implicated.

All patients receiving FGA treatment should be monitored regularly for any signs of a movement disorder. DSM-IV TR now includes a diagnosis of antipsychotic-induced TD. If TD is suspected, the benefits of antipsychotic treatment must be carefully weighed against the risk of TD. This should be discussed with the patient, and the antipsychotic should be removed if clinically feasible or at least maintained at the lowest possible dose that provides antipsychotic effect. This would also be an indication to switch to an antipsychotic agent with significantly reduced risk

of TD or in the case of clozapine no risk of TD. In many instances, clozapine (and possibly quetiapine or olanzapine) may be the best treatment that can be offered for the TD itself. Unfortunately, there is no specific treatment of TD, although some investigators have proposed the use of adrenergic agents such as clonidine, calcium channel blockers, vitamin E, benzodiazepines, valproic acid, or reserpine to reduce the spontaneous movements.

## Side Effects of Second Generation Antipsychotic Agents

One of the most significant advantages of the newer antipsychotic agent is the relatively less risk of developing EPS and TD. However, treatment emergent substantial weight gain is a harbinger for long-term health consequences and frequently a commonly reported reason for noncompliance with medication. Accumulated data from multiple studies report that treatment emergent weight gain is observed mostly with clozapine and olanzapine, quetiapine, risperidone and paliperidone are intermediate and then ziprasidone and aripiprazole (see Figures 65–15 and 65–16). Patients with schizophrenia, independent of the use of antipsychotic agents are at higher risk of developing diabetes mellitus relative to the general population (Dixon et al. 2000, Thakore et al. 2002). The data from Patient Outcome Research Team (PORT) suggest that the rate of diabetes mellitus and obesity amongst patients with major mental illness was substantially higher even before the advent of the SGA. This was more so in women and nonwhite population (Dixon et al. 2000). Thakore and colleagues (2002) investigated visceral fat distribution in drug-naïve and drug-free patients with schizophrenia. Compared to controls, patients with schizophrenia had central obesity and significantly higher levels of plasma cortisol. Thus patients with schizophrenia are at a higher risk to develop major medical problems *even before they are exposed to antipsychotic medications*.

However, higher rates of diabetes have been reported from treatment with several SGAs, including clozapine (see Figure 65–17), olanzapine, risperidone and quetiapine (Lambert et al. 2006). In 2003, an FDA warning for hyperglycemia and diabetes mellitus was added to the package insert of all SGAs. It stated that "hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available." Additional guidance is provided to clinicians regarding monitoring and management of hyperglycemic related events. The potential risk of treatment emergent weight gain, diabetes (type II) and metabolic syndrome may result from changes in glucose metabolism and insulin resistance. In approximately 25–40% of the cases of hyperglycemia, insulin resistance appears to occur even in absence of significant weight gain raising some interesting questions about how these medications may interact with the insulinglycemic control. An alternative hypothesis that may account for some of these cases is that patients were prediabetic or undiagnosed with diabetes prior to SGA administration.

Hyperlipidemia is commonly observed with SGA treatment especially in women (Figure 65–18; Olfson et al. 2006); significant elevations of serum triglycerides are reported following SGA treatment. Baseline data from CATIE study suggest that the rate of DM was 12.5%, hyperlipidemia at 53% and hypertension at 37% but a significant number of these individuals were not receiving medical treatment for the same. At baseline, significantly large groups of subjects were already obese or over weight. Patients treated with olanzapine had the highest mean weight gain of 0.9 kg/month amongst all antipsychotic studied; about 30% subjects treated with olanzapine gained 7% or more weight from baseline compared with 7% to 16% with other treatment groups (Lieberman et al. 2005). Greater increases in glycosylated hemoglobin, total cholesterol and triglycerides were observed with olanzapine compared to other study drugs. Improvement in each metabolic variable was reported with ziprasidone treatment. In a subgroup of 689 subjects from CATIE study, 41% subjects met criteria for metabolic syndrome at baseline. Schizophrenia is already associated

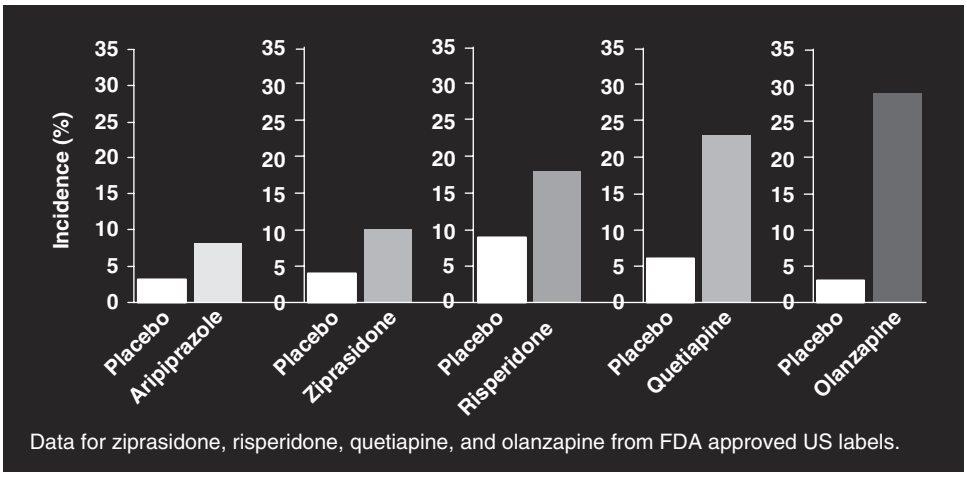



**Figure 65–15** *Clinically significant (≥ 7%) weight gain during antipsychotic treatment.*

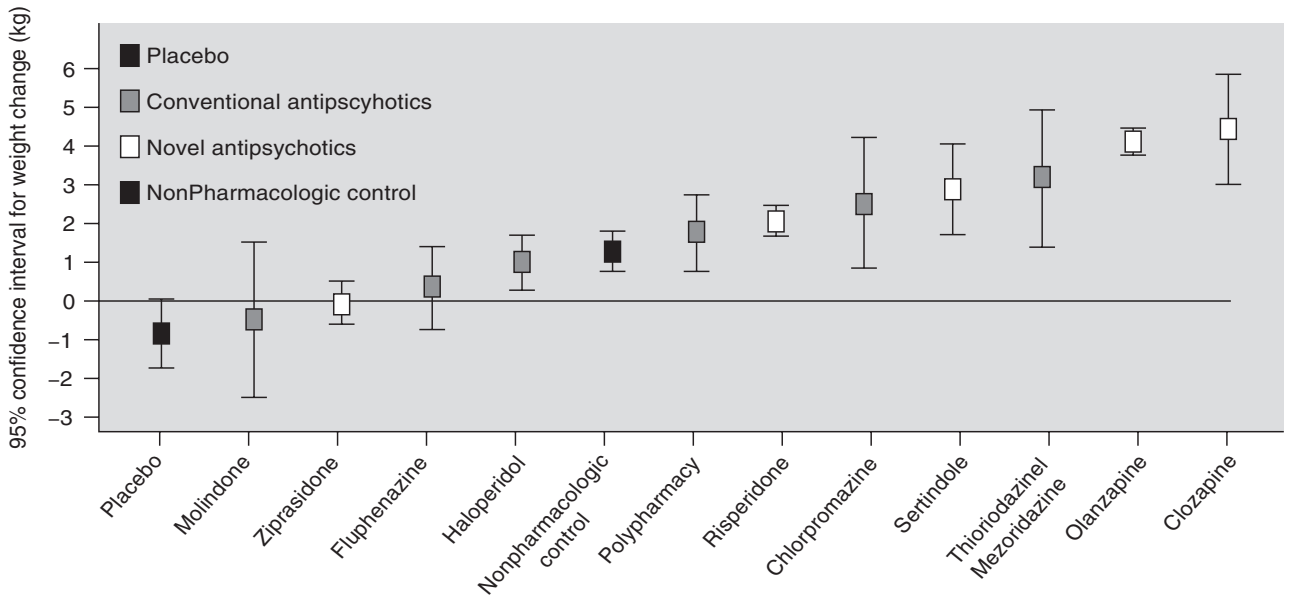



**Figure 65–16** *Ninety-five percent confidence intervals for weight changes after 10 weeks of standard drug doses, estimated from a random effects model. (Source: Allison DB, Mentore JL, Heo M, et al. [1999] Antipsychotic-induced weight gain: A comprehensive research synthesis. Am J Psychiatr 156, 1686–1696. Copyright 1999 American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.)*

with high mortality rate and this dramatic increase in obesity and metabolic syndrome in this group further increases risk of medical morbidity and mortality. Moreover, heavy smoking rates and unhealthy lifestyle only compounds the grim picture. Metabolic issues are also evident during treatment of first episode patient with SGAs. Sharing this concern, numerous monitoring guidelines have been recommended by various groups and countries (see Table 65–6) specifically suggesting assessments to be done at the time of starting antipsychotics especially SGAs and promoting ongoing assessments prospectively.

In the USA, a conference of experts in psychiatry and medicine was held at Mount Sinai in 2002 where specific recommendations were made regarding obesity, diabetes, hyperlipidemia and other health-related concerns regarding persons with schizophrenia (Marder et al. 2004). Similarly, American Diabetes Association, American

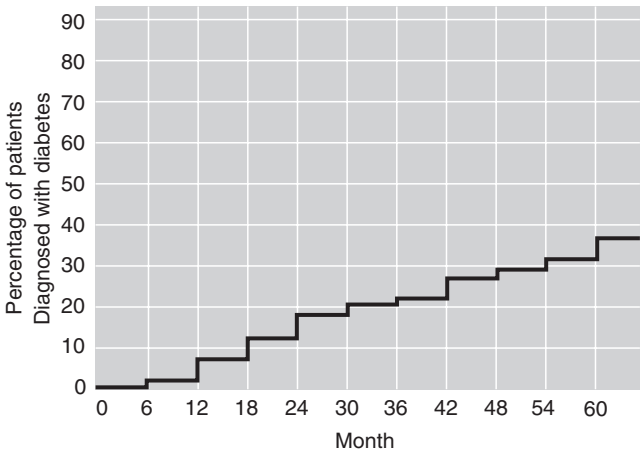



**Figure 65–17** *Comulative percentage of patients diagnosed with diabetes mellitus (N=30) over a 60-month period among 82 patients receiving clozapine. (Source: Henderson DC, Cagliero E, Gray C, et al. [2000] Clozapine, diabetes mellitus, weight gain and lipid abnormalities: A 5-year naturalistic study. American Journal of Psychiatry 157, 975–981. Copyright 2000 American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.)*

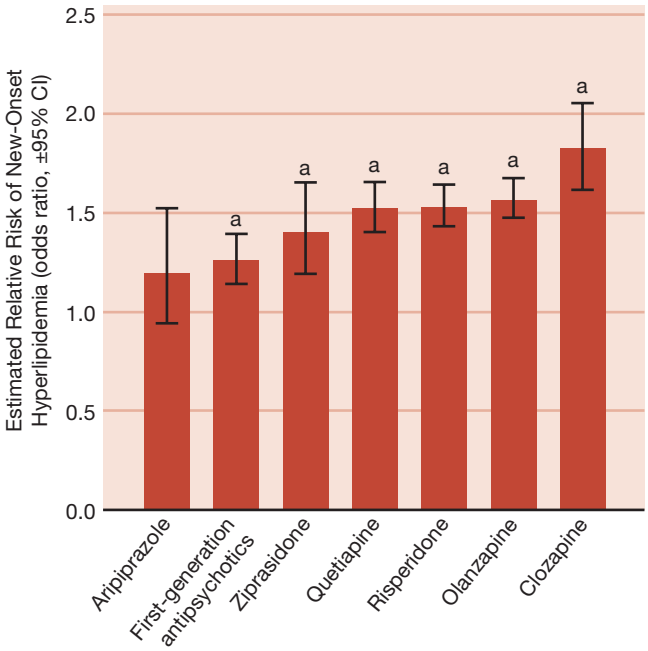



**Figure 65–18** *Association of antipsychotic medication treatment with new-onset hyperlipidemia in adults who were ages between 16–64 years and had a psychotic disorder. A matched case-control analysis was performed with pharmacy and claims data from the California Medicaid data set involving 13,133 incident cases of hyperlipidemia matched to 72,140 control subjects. (Source: Olfson M, Marcus SC, Corey-Lisle P, et al. [2006] Hyperlipidemia following treatment with antipsychotic medications. American Journal of Psychiatry 163, 1821–1825).*
*[a]Significantly different from no antipsychotic medication treatment $p < 0.05$.*

**Table 65–6 Recommended Groups to Monitor and Initial Workup**

| | Mount Sinai | Australia | ADA–APA | Belgium | United Kingdom | Canada |
|---|---|---|---|---|---|---|
| | Groups to monitor | | | | | |
| Workup | Schizophrenia, any antipsychotic | All patients, any antipsychotic | All patients, SGA | Schizophrenia, SGA | Schizophrenia, any antipsychotic | Schizophrenia |
| FPG | x | x | x | x | x | x |
| Random glucose | | x | | | x | |
| HbA1c | If FPG not feasible | | | No | In addition to FPG or random glucose | |
| OGTT | | | | x | | To follow up IFG |
| Lipids | x | x | x | x | | x |
| Weight | x | x | x | x | | x |
| Waist circumference | x | x | x | x | | x |
| Height | x | x | x | x | | x |
| Hip | | x | | | | |
| Blood pressure | | x | x | x | | x |
| Family history | x | x | x | x | | x |
| Medical history | x | x | x | x | | x |
| Ethnicity | x | x | | x | | |
| Tobacco | | | | x | | x |
| Diet–activity | | x | | x | | x |
| Signs and symptoms of diabetes | x | | x | x | x | x |

Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity also provided consensus guidelines (see Figure 65–19). Mount Sinai group also recommended interventions for management of weight gain and metabolic syndrome (see Figure 65–20; Covell et al. 2006). Many studies are indicating that these weight gains are reversible when switched to another antipsychotic. Mean weight reductions of approximately 10 kg with switch from olanzapine and 7 kg when switched from risperidone have been reported. However, switching medications is not always easy as it may result in relapse. When switching antipsychotic for management of side effects, the following table provides guidelines (Table 65–7; Weiden et al. 2006).

Amongst the SGAs, risperidone (and paliperidone), due to its potent dopamine D2 blockade, remove the inhibitory dopaminergic tone in the tuberoinfundibular neurons resulting in significant increase in prolactin levels. This increase in prolactin is significantly more than usually seen with the FGAs. It is likely that the serotonin system is also involved along with dopamine in raising the prolactin levels. Clozapine and quetiapine, on the other hand, are less potent at the D2 receptors and thus are less likely for treatment emergent prolactin elevations. In some individuals, these elevations of prolactin lead to amenorrhea, galactorrhea, gynecomastia, and may possibly decrease bone mineral density. Ziprasidone and olanzapine treatment emergent prolactin levels are not significantly increased within the therapeutic dose range. Aripiprazole, due to its unique effects on dopamine receptors, does not increase the prolactin levels and may in fact decrease them from baseline.

## Treatment Resistance and Negative Symptoms

The concept of treatment resistance has entered into common clinical judgment with the burgeoning interest in SGA, particularly clozapine. Treatment resistance was originally defined for research purposes (Kane et al. 1988). Patients who had failed to respond to or could not tolerate adequate

| | | Short-Term | | | Long-Term | | |
|---|---|---|---|---|---|---|---|
| | Baseline | 4 wk | 8 wk | 12 wk | Quarterly | Annually | Every 5 y |
| Personal/family history | X | | | | | X | |
| Weight (BMI) | X | X | X | X | X | | |
| Waist circumference | X | | | | | X | |
| Blood pressure | X | | | X | | X | |
| Fasting plasma glucose | X | | | X | | X | |
| Fasting lipid profile | X | | | X | | | X |

**Figure 65–19** *Consensus statement on antipsychotic drugs, obesity, and diabetes: Monitoring protocol for patients on second-generation antipsychotics (More frequent assessments may be warranted based on clinical status. Source: American Diabetes Association, et al. [2004] Diabetes Care 27, 596.)*

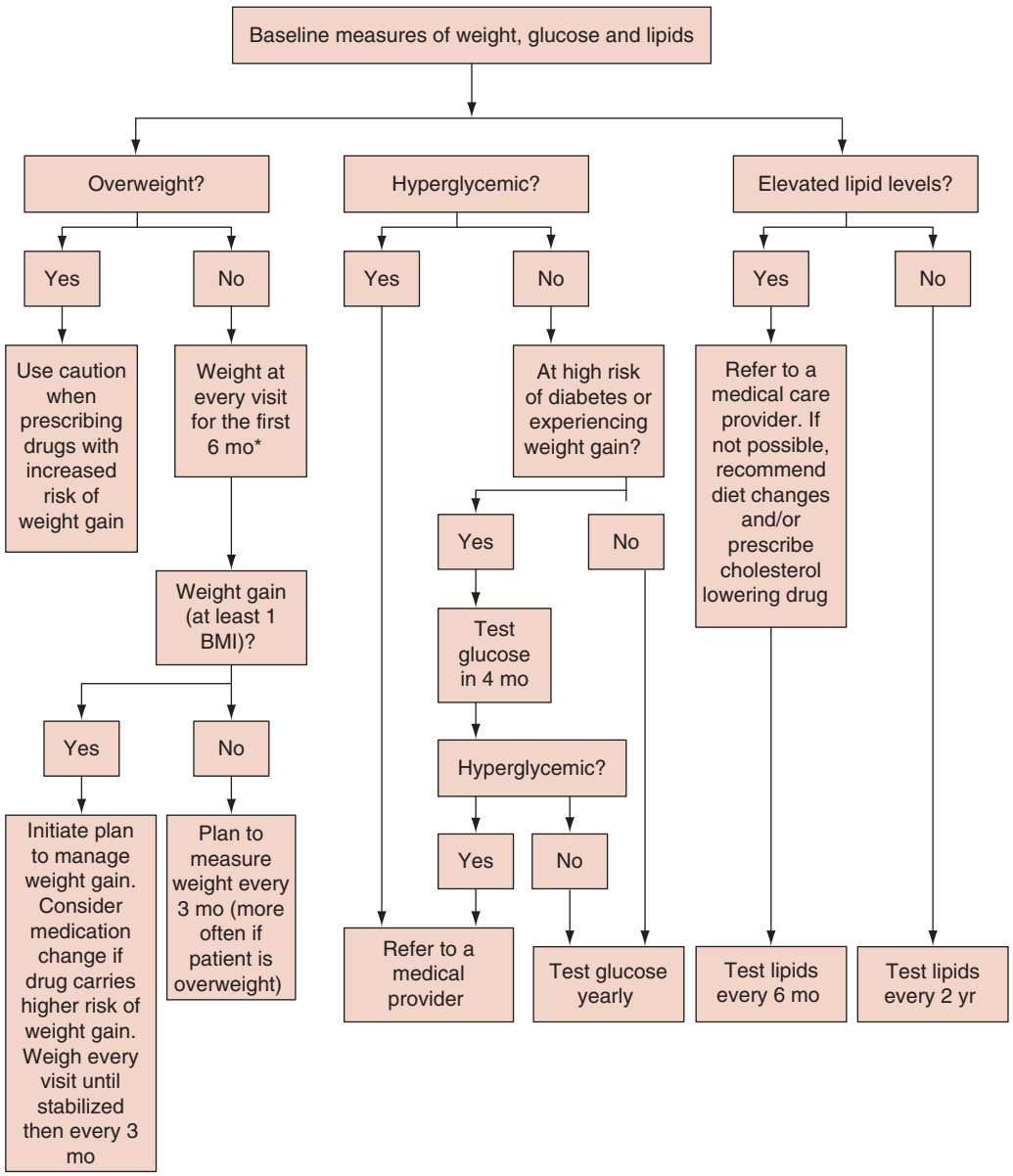



**Figure 65–20** *Flowchart for monitoring weight, glucose and lipid levels in patients with schizophrenia. All new patients with schizophrenia or patients starting a new medication should have a baseline measure of weight, fasting glucose ($HbA_{1C}$) and lipids (total, LDL and HDL cholesterol and triglycerides). *If visits infrequent, ask for pone reports of weight change.*

trials of FGA from three different biochemical classes and who had a clinically significant psychopathology rating based on the Brief Psychiatric Rating Scale qualified as treatment resistant. However, this research definition did not necessarily encompass patients who, by clinical standards, would meet the definition of treatment resistance. Marder and Van Putten (1988) suggested that backward schizophrenia patients, who are severely symptomatic or with severe TD or EPS, especially those with suboptimal responses to FGA agents, should be eligible for a trial of clozapine. One might also think of clinical treatment resistance as seen in patients who had an early age of illness onset with subsequent repeated hospitalizations and antipsychotic trials and who cannot achieve a level of social and occupational function commensurate with their age and level of education.

The concept of treatment resistance has undergone significant modification in recent years and is reviewed by Conley and Kelly (2001). The original concept of treatment refractory applied to the use of FGA agents. With the advent of the SGAs (which were generally thought to be more effective than the FGAs), the patient should fail at least one SGA agent before initiating a trial of clozapine mainly to avoid its side effects. The definition of the duration of a drug trial has also evolved over the years. It is increasingly appreciated that a 4–6 weeks duration of treatment with an antipsychotic agent at therapeutic doses can be considered an adequate trial. The recommended dosing has also undergone changes. The original recommendation considered a trial of 1,000 mg equivalent of chlorpromazine as a necessary minimum requirement but this threshold is now reduced to 400–600 mg/day equivalent based on the knowledge that these doses block enough dopamine $D_2$ receptors with higher doses providing no additional benefit. Thus, a 4–6 weeks trial of 400–600 mg

**Table 65–7 Potential Side Effect Benefits when Switching Between Antipsychotic Medications**

| Pre-switch antipsychotic | Post-switch antipsychotic: Aripiprazole | Olanzapine | Quetiapine | Risperidone | Ziprasidone |
|---|---|---|---|---|---|
| Haloperidol | ↓↓ EPS<br>↓↓ Prolactin<br>↓ Akathisia<br>↓ Sedation | ↓↓ Akathisia<br>↓↓ EPS<br>↓↓ Prolactin | ↓↓↓ Akathisia<br>↓↓↓ EPS<br>↓↓ Prolactin | ↓ Akathisia<br>↓ EPS | ↓↓ EPS<br>↓↓ Prolactin<br>↓ Akathisia<br>↓ Sedation |
| Aripiprazole | | ↓ Akathisia<br>↓ Insomnia | ↓↓ Akathisia<br>↓ EPS<br>↓ Insomnia | ↓ Insomnia | ↓ Akathisia<br>↓ Insomnia |
| Olanzapine | ↓↓↓ Dyslipidemia<br>↓↓↓ Weight<br>↓↓ Sedation<br>↓ Prolactin | | ↓ Akathisia<br>↓ Dyslipidemia<br>↓ EPS<br>↓ Prolactin<br>↓ Weight | ↓ Dyslipidemia<br>↓ Sedation<br>↓ Weight | ↓↓↓ Dyslipidemia<br>↓↓↓ Weight<br>↓↓ Sedation |
| Quetiapine | ↓↓ Sedation<br>↓ Dyslipidemia<br>↓ Orthostatic<br>↓ Weight | ↓ Orthostatic | | ↓ Sedation | ↓↓ Sedation<br>↓ Dyslipidemia<br>↓ Orthostatic<br>↓ Weight |
| Risperidone | ↓↓↓ Prolactin<br>↓ Dyslipidemia<br>↓ EPS<br>↓ Orthostatic<br>↓ Sedation<br>↓ Weight | ↓↓ Akathisia<br>↓↓ EPS<br>↓↓ Prolactin<br>↓ Orthostatic | ↓↓↓ Akathisia<br>↓↓↓ EPS<br>↓↓↓ Prolactin | | ↓↓ EPS<br>↓↓ Prolactin<br>↓↓ Weight<br>↓ Dyslipidemia<br>↓ Orthostatic<br>↓ Sedation |
| Ziprasidone | ↓ Prolactin<br>↓ Sedation | ↓ Akathisia<br>↓ Insomnia | ↓ Akathisia<br>↓ EPS<br>↓ Insomnia | ↓ Insomnia | |

EPS, extrapramidal symptoms; Orthostatic, orthostatic hypotension

EPS refers to Parkinsonism, including tremor, rigidity, and akinesia (bradykinesia), and does not refer to tardive dyskinesia or akathisia; Prolactin elevation is evident as amenorrhea and galactorrhea in women and should be considered in the differential diagnosis of sexual dysfunction in man. Dysllpidernia refers to elevated fasting triglyceride and cholesterol levels; the findings shown in this table have been documented to occur within 6 to 8 weeks of switching medications without other pharmacologic or dietary interventions.

↓ Benefits may be of clinical significance but does not represent the best switch choice for that specific side effect; ↓↓ Significant benefit that will effectively reverse side effect for majority of cases; ↓↓↓ Reserved for situations in which pre-switch antipsychotic is most associated with the side effect in question and the post-switch antipsychotic is likely to have the greatest magnitude of difference after a successful change in antipsychotic medication (ie, "top choice" for switching if that is the primary reason for making the switch).

*Note:* This table assumes that the problem in question has been established to be a result of the prior antipsychotic and is not caused by an unrelated process or exposure to another medication with a similar side effect problem.

of chlorpromazine equivalent is accepted as an adequate antipsychotic trial.

In treatment refractory patients, FGA use results in a less than 5% response rate (Kane et al. 1988). Clozapine is the only antipsychotic drug proven more efficacious in rigorously defined treatment refractory groups. Chakos and colleagues (2001) did a meta-analysis of 12 controlled studies involving 1,916 patients. Seven studies involved clozapine. The data showed that treatment resistant schizophrenia patients had more favorable outcomes when treated with clozapine rather than an FGA agent. However, monitoring of blood counts and fear of its side effects makes it one of most underused effective treatment for schizophrenia.

There is a dearth of good clinical data that indicates how effective risperidone is in this group. In one well-controlled double-blind study, risperidone was more effective and better tolerated than haloperidol though the efficacy was not comparable to clozapine. Two other studies have compared risperidone to clozapine in refractory patients and showed the efficacy of risperidone to be similar to clozapine but, the definition used of "treatment refractory" status and the study design are either not comparable or have limitations. From these and other open label-studies, risperidone appears to be superior to FGAs in treatment refractory patients but does not appear to be as efficacious as clozapine.

Olanzapine has been reported to have better outcome than haloperidol in the treatment-resistant schizophrenia group from a double-blind study. However, when olanzapine was compared to chlorpromazine in a treatment refractory group using a double-blind study design, the outcome with olanzapine was not comparable to what is typically seen with the use of clozapine. When patients refractory to olanzapine in this trial were subsequently treated with clozapine, the response rate was similar to what is seen with the use of clozapine in treatment-refractory group. Similar findings were reported from an open label study of olanzapine in a treatment refractory group. Thus, it appears that though olanzapine was better than FGAs it was not as efficacious as clozapine for treatment refractory patients. However,

these studies were conducted using the standard doses of olanzapine. Recent studies using higher doses of olanzapine up to 50 mg/day appear to be better and comparable to clozapine in efficacy (Volavka et al. 2002) suggesting that the treatment refractory group may need higher doses of olanzapine to have a meaningful outcome.

Negative symptoms, such as apathy, amotivational syndrome, flattened affect, and alogia, are often the most problematic for patients with schizophrenia, accounting for much of the morbidity associated with this illness. In addition, these symptoms are often the most difficult to treat and do not respond well to FGAs. The SGAs are perhaps more effective against the negative symptoms than the FGAs (Kane et al. 1988). However, the magnitude of the effect of these compounds on primary negative symptoms is not clear. Amisulpiride, an SGA that is not available in USA, has been extensively studied against core negative symptoms with a meta-analysis suggesting a small but significant effect size compared with placebo ($r = 0.26$; $p < 0.0001$) but not FGAs (Leucht et al. 2002). Clozapine has been extensively used in treatment of negative symptoms with significant impact on general negative symptoms though its effect on primary negative symptoms is disputed. Data about risperidone and olanzapine use are mixed. SSRIs in combination with antipsychotic medications have shown mixed but encouraging results (see Murphy et al. (2006)). They also observe that prevalence of deficits symptoms are lower in first episode patients compared to chronic patients suggesting progression of the underlying etiology and raising questions about the duration of negative symptoms also affecting the antipsychotic efficacy. Overall, they found the quality of studies done in this area poor and disappointing (Murphy et al. 2006). Clearly, one of the goals of psychopharmacological research is to develop new antipsychotic agents with low associated risk, a more effective treatment for negative and cognitive symptoms, a further reduction in positive symptoms, and an improvement in long-term relapse rate for patients with chronic schizophrenia.

## Use of Concomitant Psychotropic Medications (CPM) with Antipsychotics

Concomitant Psychotropic Medications or CPM use during treatment of schizophrenia has dramatically increased worldwide. However, CPM use can increase side effects, cause drug interactions, escalate treatment costs, and lead to nonadherence. CPM use has come under criticism especially when the data supporting their use are equivocal or limited. Multinational and large studies have reported 53–92% of subjects using CPM. In the NIMH sponsored CATIE study, the baseline mean CPM use was 2.03 + 1.10. Being anxious, depressed, female or using SGA were strongest predictors of taking multiple CPMs while African Americans or individuals with better neurocognitive functioning were less likely to take several CPMs at CATIE study baseline. Some studies reported higher CPM use with SGA while others had contradictory results. CPM use was lower in those who were employed. One study reported fewer adverse reactions, shorter length of hospital stay, increase discharges to community rather than to state hospitals with increase CPM use. However, when antidepressants and mood stabilizers were gradually tapered off at one center in stable patients, in most circumstances there were no untoward effects raising concern that CPM were either used for a duration longer than what was needed or they were not at all necessary in the first place. On the other hand, the number of CPM prescribed may closely relate to the severity of the patient's illness.

When data of each CPM class used are reviewed, sedative/anxiolytics (SA) were the most commonly used CPMs in most studies with inpatient use as high as 90% and outpatient use up to 47%. SA use varied with the antipsychotic used and was significantly greater with risperidone, quetiapine, and oral FGAs compared to olanzapine after 6 months of treatment in one study. However, SA dose was twice as high for olanzapine group compared to clozapine with suicide attempters receiving higher doses than non attempters in the InterSePT study. Women were significantly more often treated with SA than men. At an academic institution practicing evidence based medicine, SA use increased significantly from 76% in 1989 to 90% in 2001 and appeared to increase concurrently with the increase SGA use. SA use decreased from baseline to prospective study points in many studies indicating possible state specific short-term need for SA use. Benzodiazepines, when added to antipsychotic medications during acute treatment, were reported to be beneficial and additionally appeared to reduce anxiety, insomnia, agitation, and psychotic symptoms. Comorbid anxiety disorder and individuals with higher positive symptoms scores were more likely to receive sedative hypnotics. Higher number of depression symptoms also predicted higher benzodiazepine use.

The preferential use of SGA over FGA in last decade has resulted in significant decrease in anticholinergic (ACH) use. When evidence based medicine was practiced, ACH use decreased from 48% in 1989 to 14% in 2001 which was similar to baseline CATIE use of 15%. ACH use may worsen positive symptoms, as well as cognition but it does provide relief from parkinsonian symptoms.

Antipsychotic (AP) polypharmacy varies significantly based on stage of illness, severity and geographical location amongst other factors. At baseline, 5% subjects in CATIE study were receiving polypharmacy, while other studies reported a wide range from 7% to 90%. Males were associated with an increased likelihood of receiving long term AP polypharmacy. Lower neurocognitive scores were more likely to be associated with polypharmacy while older age, minority status, and comorbid depression or substance abuse were generally less likely to be associated with AP polypharmacy. Many recent studies have reported mixed results supporting concomitant use of two antipsychotic drugs.

Antidepressants (AD) were used in 9.5–25% subjects at baseline in the SOHO study with similar rates at 6 months across antipsychotic treatments. Female gender and presence of depressive symptoms was associated with greater use of AD. Although there is some evidence that FGAs themselves cause depression, there undoubtedly are schizophrenia patients who have primary depressive symptoms. Surprisingly, SGAs were significantly linked to AD use whereas FGAs were not. AD was more often prescribed to those who were unemployed, received more psychotropics and had milder positive symptoms. Comorbid conditions such as major depression, OCD and other anxiety disorder independently predicted adjunctive AD treatment at baseline in the CATIE study. Data from metaanalyses and review

of literature are not convincing that AD use in schizophrenia is helpful. AD medications have also been considered in the treatment of depression associated with schizophrenia. Negative symptoms are often difficult to distinguish from depression (both have features of amotivation, apathy, and social withdrawal), but those that are secondary to depression may respond to the addition of an antidepressant to the patient's medication regimen.

One study reported higher rates of mood stabilizer use in 2000 compared to 1995 even when there was corresponding increase in SGA use. Presence of depressive symptoms and hostility were associated with use of mood stabilizers in the SOHO study. Female gender predicted lithium use and higher positive symptoms predicted adjunctive mood stabilizer use at CATIE baseline. In a meta-analysis, lithium augmentation was found to be superior to placebo when added to an antipsychotic drug; however, the superiority of lithium augmentation was only of borderline statistical significance when participants with schizoaffective disorders were excluded. Depakote augmentation merely provided more rapid response to treatment with antipsychotic drug. There appeared no additional benefits.

When agonists of the glycine site of the NMDA receptor were added to FGAs in a placebo-controlled study, significant improvement were reported in negative symptoms and aspects of cognitive functioning. D-cycloserine, a partial agonist at the glycine site produced a selective improvement of negative symptoms at six weeks. Augmentation with another endogenous full agonist, d-serine was associated with significant improvement in negative, positive, and cognitive symptoms when added to conventional agents in an eight-week trial. Recently, a large study using ampakine CX 516 in some of the SGAs did not improve negative as well as cognitive symptoms in four weeks.

## Treatment Adherence

To achieve short and long-term goals of a treatment plan successfully in a patient suffering from schizophrenia, adherence to pharmacological as well as nonpharmacological interventions is pivotal. Data from 11 studies and 2,032 patients showed a relapse rate of 15% in people treated with SGA versus 23% in FGAs. Data from California Medicaid patients showed direct correlation between estimated partial adherence and hospitalization risk across a continuum of adherence behaviors from 1 to 10 days (Weiden 2006). Data from VA suggest that those with 100% compliance had significantly less hospitalization rates. In one study, poor adherence to antipsychotic treatment increased risk for suicide attempts up to 4 fold.

When patient's attitudes toward antipsychotic medications were assessed in 228 subjects, they highly correlated both with insight and positive relationships with staff. The quality of patient's relationships with clinicians during an acute admission was critical toward forming their attitudes toward their medication and adherence. Psychosocial interventions, especially psychoeducation for patients and family are effective avenues to improve adherence and reduce relapse and readmission rates. However, despite the effectiveness of psychoeducation, the number of family members and patients exploiting this approach is quite low (Kane 2006). In cases where there is a high risk of noncompliance or partial compliance, long-acting injectable antipsychotics can help improve adherence and reduce relapse and hospitalization rates. This mode of medication administration can detect noncompliance early, reliably and provide an opportunity to intervene when the medication is still in the person's system (Kane 2006), If schizophrenia is progressive and has neurodegenerative components and treatments for schizophrenia have neuroprotective effects (by arresting gray matter loss in important areas of the brain) either as a primary effect or secondary to prevention of relapses, then treatment adherence provides perhaps the most important opportunity to optimize these imperfect treatments. Otherwise, these losses may not be reversible.

## New Directions

Psychopharmacological research has focused on developing compounds with unique combinations of effects at these different neurotransmitter sites. Future strategies for the treatment of schizophrenia are based on novel constructs of its pathophysiology.

Neurocognitive impairments have now become the core feature of schizophrenia. In response to the identification of the bottleneck limiting the development of treatments specifically directed at the cognitive deficits in schizophrenia, NIMH developed Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. The MATRICS program is set out to develop a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might be best assessed and treated. Thus, there is a paradigm shift here such that the cognitive symptoms are treated separately from psychotic symptoms. MATRICS has identified domains of cognition deemed most relevant in schizophrenia. Experts from academia and industry met to identify the most intriguing molecular targets, promising compounds, relevant human test measures, and potentially predictive animal models for use in the discovery of treatments related to complex cognitive operations. Subsequently they developed a beta version of the MATRICS Consensus Cognitive Battery for Clinical Trials. The group had meetings focused on collaborations between the NIMH, FDA and industry. They have successfully addressed the obstacles to developing precognitive drugs. There is a lot of hope and promise invented in their efforts to develop a breakthrough in this area.

One area of interest involves the glutamatergic system. Glutamate, the major excitatory neurotransmitter in the brain, is implicated in information processing and memory, functions that are impaired in schizophrenia. PCP, an NMDA antagonist, causes a syndrome with symptoms clinically similar to those of schizophrenia. These observations have led to the hypothesis that the glutamatergic NMDA receptor is involved in the pathophysiology of schizophrenia. Investigation of compounds like CX516 that alter NMDA receptor activity is under way to learn more about the clinical significance of this neurotransmitter system.

Based on compelling evidence implicating the alpha-7 nicotinic receptor in the pathophysiology of schizophrenia, a proof of concept trial was conducted to determine if DMXB-A, a natural alkaloid derivative and partial alpha-7 nicotinic cholinergic agonist, was effective for cognitive impairment in patients with schizophrenia (Olincy et al. 2006). Significant cognitive improvement was reported

which provides preliminary support for the alpha-7 nicotinic receptor as a viable target for a novel treatment for schizophrenia. Replication in a larger sample of patients with longer treatment durations is needed to confirm these data.

In another area of drug development, researchers are studying G proteins, ubiquitous proteins found on cell membranes, where they play a critical role in second-messenger systems. These proteins have been found to be related to dopamine receptors in schizophrenic patients and to be involved in the mechanism of action of lithium in the treatment of bipolar disorder. Advanced genetic technology using techniques that could lead to altered receptor function "upstream" is also being explored. Given the enhanced understanding of influential biochemical, genetic, and neurodevelopmental interactions, there is promise of developing treatment strategies that would provide a more effective, safe means of ameliorating both the positive and negative symptoms of schizophrenia.

There is tremendous interest in early identification of potential subjects who may go on to develop schizophrenia. Attempts are underway to understand possible role for use of various treatment interventions before the onset of psychosis such that there can either be delay in onset of psychosis and possible change in the course of illness for the better.

## Nonpharmacological Treatment of Schizophrenia

### Background

Although psychopharmacological intervention has proved to be the foundation on which the treatment of schizophrenia depends, other approaches to the management of these patients serve a critical function. Studies have shown repeatedly that symptoms of schizophrenia have not only a genetic component but also an environmental aspect, and interactions with family and within the community can alter the course of the illness.

For many years, a dichotomous view of treatment options was tenaciously debated as dynamic psychiatry was challenged by developments in the neurosciences. A more unified view is now accepted, as it has become clear that psychopharmacological treatment strategies are most efficacious if combined with some type of psychosocial intervention and vice versa. It can be said that because of the chronic nature of schizophrenia, one or more treatments may be required throughout the illness and they are likely to have to be modified as symptoms change over time.

### Psychosocial Rehabilitation

Bachrach has defined psychosocial rehabilitation as "a therapeutic approach that encourages a mentally ill person to develop his or her fullest capacities through learning and environmental supports" (Bachrach 2000). According to the author, the rehabilitation process should appreciate the unique life circumstances of each person and respond to the individual's special needs while promoting both the treatment of the illness and the reduction of its attendant disabilities. The treatment should be provided in the context of the individual's unique environment taking into account social support network, access to transportation, housing, work opportunities, and so on. Rehabilitation should exploit the patient's strengths and improve his/her competencies. Ultimately, rehabilitation should focus on the positive concept of restoring hope to those who have suffered major setbacks in functional capacity and their self-esteem due to major mental illness. To have this hope grounded in reality, it requires promoting acceptance of one's illness and the limitations that come with it. While work offers the ultimate in sense of achievement and mastery, it must be defined more broadly for the mentally ill and should include prevocational and nonvocational activities along with independent employment. It is extremely important that work is individualized to the talents, skills, and abilities of the individual concerned. However, psychosocial rehabilitation has to transcend work to encompass medical, social, and recreational themes. Psychosocial treatment's basic principle is to provide comprehensive care through active involvement of the patient in his or her own treatment. Thus, it is important that a holding environment be created where patients can safely express their wishes, aspirations, frustrations, and reservations such that they ultimately mold the rehabilitation plan. Clearly, to achieve these goals, the intervention has to be ongoing.

Given the chronicity of the illness, the process of rehabilitation must be enduring to encounter future stresses and challenges. These goals cannot be achieved without a stable relationship between the patient and rehabilitation counselor, which is central to an effective treatment and positive outcome. Thus, psychosocial rehabilitation is intimately connected to the biological intervention and forms a core component of the biopsychosocial approach to the treatment of schizophrenia. In the real world, programs often deviate from the aforementioned principles and end up putting excessive and unrealistic expectations on patients, thus achieving exactly the opposite of the intended values of the program (see Bachrach (2000) for more details).

### Psychodynamic Approach

Many attempts have been made to understand the psychodynamic implications and meaning of schizophrenic symptoms. To mention all of the contributors who laid the foundations of psychodynamic theory is beyond the scope of this work. However, several names are important to put this vast field into historical perspective. Adolph Meyer (1866–1950), for example, contributed to our appreciation of a longitudinal, rather than a cross-sectional, perspective of the patient. He was one of the first to consider that maladjustment early on may have some influence on later psychotic development (Arieti 1955). In his work with patients, Sigmund Freud (1855–1939) thought that schizophrenia was an illness that represented a regression and a subsequent turning away from social supports because of unresolved conflicts. He observed that these patients had difficulties in developing transference, which was a necessary step to effective analysis. Freud concluded that patients with schizophrenia could not benefit from this treatment (Gabbard 1990). Carl Jung (1875–1960) concentrated specifically on the psychotic content, looking for symbolic meaning through word association tests while working with schizophrenia patients at the Bergozoli Hospital in Switzerland. He believed that humans shared images and mythological symbols or archetypes through a collective unconscious, which was reflected in the psychotic

processes of the individual with schizophrenia (Arieti 1955). Harry Stack Sullivan (1892–1949) focused his life's work on interpersonal therapy with schizophrenia patients. He thought that even the most severe schizophrenia patient was capable of a relational attachment (Arieti 1955, Gabbard 1990).

Psychotherapeutic technique held promise for many years as a potential for unraveling the mystery of individuals' symptoms, with the hope of improvement in course and symptoms and even cure. Based on derivations of the classical analytical school, symptoms of schizophrenia were thought of in terms of conflict and defense mechanisms. For example, when paranoid patients believe they are being preyed on, they are projecting onto others their own internal, unconscious wish to kill. Thus, unconscious conflicts became manifest as psychotic symptoms. To the psychodynamic therapist then, affectively laden material elicits an increase in thought disorder or psychotic responses, as it touches on the patient's unconscious feelings. These conceptualizations of schizophrenia influenced early work with these patients.

Although the psychodynamic understanding of intrapsychic events has been of historical interest, the application of traditional psychodynamic principles as primary treatment modalities is not recommended. One of the first studies that compared outcomes between medication-treated patients and psychotherapy-treated patients was conducted at the Camarillo State Hospital in 1968. This study found that the group of patients who received antipsychotic medication showed greater improvement than those who received psychotherapy alone. Subsequent studies have replicated these findings even when different types of therapy are examined. Evidence suggests that insight-oriented individual psychotherapy may not be as helpful for patients with schizophrenia as supportive, goal-directed individual therapy combined with medication treatment and social skills training.

## Individual Psychotherapy

Individual therapy in a nontraditional sense can begin on meeting a patient. Even the briefest of normalizing contacts with an agitated, acutely psychotic patient can have therapeutic value. Psychodynamic interpretations are not helpful during the acute stages of the illness and may actually agitate the patient further. The psychiatrist using individual psychotherapy should focus on forming and maintaining a therapeutic alliance (which is also a necessary part of psychopharmacological treatment) and providing a safe environment in which the patient is able to discuss symptoms openly. A sound psychotherapist provides clear structure about the therapeutic relationship and helps the patient to focus on personal goals.

Often, a patient is not aware of or does not have insight into the fact that some beliefs are part of a specific symptom. A psychotherapist helps a patient to check whether his or her reality coincides with that of the therapist. The therapeutic intervention then becomes a frank discussion of what schizophrenia is and how symptoms may feel to the patient. This objectifying of psychotic or negative symptoms can prove of enormous value in allowing the patient to feel more in control of the illness. A good analogy is to diabetic patients, who know they have a medical illness and are educated about the symptoms associated with exacerbation. Just as these patients can check blood glucose levels, schizophrenia patients can discuss with a therapist their sleep patterns, their interpersonal relationships, and their internal thoughts, which may lead to earlier detection of relapses.

Schizophrenia often strikes just as a person is leaving adolescence and entering young adulthood. The higher the premorbid level of social adjustment and functioning, the more devastating and confusing the onset of symptoms becomes. Young male patients with a high level of premorbid function are at increased risk of suicide, presumably in part because of the tremendous loss they face. These feelings can continue for years, with schizophrenia patients feeling isolated and robbed of a normal life. Therefore, a component of individual work (which can also be achieved to some degree in a group setting) with these patients is a focus on the impact schizophrenia has had on their lives. Helping patients to grieve for these losses is an important process that may ultimately help them achieve a better quality of life.

## Group Psychotherapy

Acutely psychotic patients do not benefit from group interaction. In fact, a quiet place with decreased social contact is most useful until medications have controlled acute symptoms. It is common in inpatient settings to slowly integrate patients into the ward community only as they appear less agitated and are able to remain in good behavioral control with improvement in psychotic symptoms. As their condition improves, inpatient group therapy prepares patients for interpersonal interactions in a controlled setting. After discharge, patients may benefit from day treatment programs and outpatient groups, which provide ongoing care for patients living in the community.

Because one of the most difficult challenges of schizophrenia is the inherent deficits in relatedness, group therapy is an important means of gathering patients together and providing them with a forum for mutual support. Insight-oriented groups may be disorganizing for patients with schizophrenia, but task-oriented, supportive groups provide structure and a decreased sense of isolation for this population of patients. Keeping group focus on structured topics, such as daily needs or getting the most out of community services, is useful for these patients (Gabbard 1990). In the era of community treatment and brief hospitalizations, many patients are being seen in medication groups, which they attend regularly to discuss any side effects or problems and to get prescriptions.

Cognitive behavioral group therapy (CBGT)is an important adaptation to provide CBT to a larger group when there are not many trained therapists. A systematic review on this topic was recently done. Out of 168 papers, 5 studies met the review criteria. CBGT was more effective than treatment as usual in reducing social anxiety and depression (Lawrence et al. 2006).

## Psychoeducational Treatment

One of the inherent deficits from which schizophrenia patients suffer is an inability to engage appropriately in social or occupational activities. This debilitating effect is often a lasting feature of the illness, despite adequate psychopharmacological intervention. This disability often isolates patients and makes it difficult for them to advocate appropriate social

support or community services. Furthermore, studies have found that there is a correlation between poor social functioning and incidence of relapse. One of the challenges of this area of study is the great deal of variability in individual patients. However, standardized measures have been developed to ascertain objective ratings of social deficits. These assessments have become important tools in the determination of effective nonpharmacological treatment strategies.

The literature suggests that schizophrenia patients can benefit from social skills training. This model is based on the idea that the course of schizophrenia is, in part, a product of the environment, which is inherently stressful because of the social deficits from which these patients suffer. The hypothesis is that if patients are able to monitor and reduce their stress, they could potentially decrease their risk of relapse.

For this intervention to be successful, patients must be aware of and set their own goals. Goals such as medication management, activities of daily living, and dealing with a roommate are achievable examples. Social skills and deficits can be assessed by patients' self-report, observation of behavioral patterns by trained professionals, or a measurement of physiological responses to specific situations (e.g., increased pulse when asking someone to dinner). Patients can then begin behavioral training in which appropriate social responses are shaped with the help of instructors.

One example of such a program, discussed by Liberman and colleagues (1986), is a highly structured curriculum that includes training manual, audiovisual aids, and role-playing exercises. Behaviors are broken down into small bits, such as learning how to maintain eye contact, monitor vocal volume, or ameliorate body language. The modules are learned one at a time, with role playing, homework, and feedback provided to the participants. In several studies, Liberman and coworkers have shown that patients who were treated with social skills training and medication spent less time hospitalized, with fewer relapses than those treated with holistic health measures (e.g., yoga, stress management) on 2-year follow-up. Research such as this in the field of social skills training is growing as the inherent deficits in information processing, executive function, and interpersonal skills are further elucidated.

Earlier studies have suggested that educational interventions influence both knowledge and drug use errors. Similarly, patient education improves compliance. Merinder (2000) reviewed patient education in seven randomized trials, four naturalistic studies and eight studies with mixed samples. The author concludes that knowledge and compliance can be improved by the interventions used and in some circumstances, relapse and symptomatology can be partly influenced. The didactic format influences knowledge more readily while interventions with behavioral contents influence compliance. Patient education programs tend to use more didactic interactive format, enabling a more thorough negotiation of illness attitudes.

### *Social Skills Training*

In large number of patients, deficits in social competence persist despite antipsychotic treatment. These deficits can lead to social distress whereas social competence can alleviate distress related to social discomfort. The "token economy" programs with operant conditioning paradigms were used in past to discourage undesirable behavior. However, nowadays there are better ways to deal with these behaviors. Paradigms using instruction, modeling, role-playing, and positive reinforcement are helpful. Controlled studies suggest that schizophrenia patients are able to acquire lasting social skills after attending such programs and apply these skills to everyday life. Besides reducing anxiety, social skills training also improve level of social activity and foster new social contacts. This in turn improves the quality of life and significantly shortens duration of inpatient care. However, their impact on symptom resolution and relapse rates is unclear.

### *Cognitive Remediation*

Patients with schizophrenia generally demonstrate poor performance in various aspects of information processing. Cognitive dysfunction can be a rate-limiting factor in learning and social functioning. Additionally, impaired information processing can lead to increased susceptibility to stress and thus to an increase risk of relapse. Practice appears to improve some of the cognitive dysfunction. Remediation of cognitive dysfunctions with social skills training has been reported to have positive impact. Mojtabai and colleagues (1998) performed a comprehensive metaanalysis of 106 controlled studies that were published between 1966 and 1994. They found that various types of cognitive behavioral therapies were particularly effective. Social skills training program, cognitive training program to improve neurocognitive functioning, and cognitive behavioral therapy approaches are oriented toward coping with symptoms, the disorder and everyday problems.

### *Cognitive Adaptation Training*

Cognitive adaptation training (CAT) is a novel approach to improve adaptive functioning and compensate for the cognitive impairments associated with schizophrenia. A thorough functional needs assessment is done to measure current adaptive functioning. Besides measuring adaptive functioning and quantifying apathy and disinhibition, a neurocognitive assessment using tests to measure executive function, attention, verbal and visual memory, and visual organization is also completed. Treatment plans are adapted to the patient's level of functioning, which includes patient's level of apathy. Interventions include removal of distracting stimuli, use of reminders such as checklists, signs, and labels. In a randomized trial, 45 patients were randomized to a standard medication plus CAT group; standard medication follow-up group and a control group which included standard medication plus a condition designed to control for therapist time. At 9 months there was a significant improvement in positive and negative symptoms in the CAT group compared with the two other groups, namely follow-up group and control group of standard medication plus controlled therapist time. The most consistent improvement was in favor of CAT group and involved motivation as measured by rating instruments. The GAF scores also differed significantly between the groups. The relapse rates for CAT, control, and follow-up groups were significantly different (13.33, 67.67, and 33.33%, respectively).

## Integrated Psychological Therapy (IPT)

IPT was one of the first clinically based cognitive rehabilitation programs that was specifically designed for persons

with schizophrenia. IPT is based on a building-block model that assumes that elementary, basic neurocognitive functions are necessary prerequisites for higher order complex social functions. Training is done in small groups in 30–60 mins sessions three times a week. There is training of abstraction, conceptual organization and basic perception and communications skills. The next level of training is behavioral level of social interaction and is similar to social skills discussed earlier. This is a structured, manual driven program for 6 months (Velligan et al. 2006).

## Family Therapy

A large body of literature explores the role of familial interactions and the clinical course of schizophrenia. Many of these studies have examined the outcome of schizophrenia in relation to the degree of expressed emotion (EE) in family members. EE is generally defined as excessive criticism and over-involvement of relatives. Schizophrenia patients have been found to have a higher risk of relapse if their relatives have high EE levels. Clearly, a patient's disturbing symptoms at the time of relapse may affect the level of criticism and over-involvement of family members, but evidence suggests that preexisting increased EE levels in relatives predict increased risk of schizophrenic relapse and that interventions that decrease EE levels can decrease relapse rates.

Specifically, studies have demonstrated effective strategies to lowering the risk of relapse with the use of family intervention and measurements of EE levels (Hogarty et al. 1986). For example, in a study by Falloon and colleagues (1985), 36 patients were randomly assigned to one of two treatment groups. One group received family therapy, the other individual therapy. In both groups the patients were maintained with appropriate antipsychotic doses. Family therapy was done in the home, with a focus on education about schizophrenia and ways in which families could achieve lowered stress levels and improved problem-solving skills. Specific problem-solving mechanisms were rehearsed and modeled by trained therapists. The individual treatment was supportive psychotherapy for the patient, which was conducted at the clinic. At the end of 9 months, family therapy was found to be a more effective means of preventing relapse (one relapsed out of 18) than individual therapy (eight relapsed out of 19). Moreover, the advantages of the family therapy persisted after a second year of less intensive follow-up (Falloon et al. 1985).

Hogarty and colleagues (1986) examined the effectiveness of antipsychotics alone, antipsychotics plus psychoeducational family treatment (based on addressing EE levels), social skills training for antipsychotic-treated patients with schizophrenia, and the combination of all three. Perhaps not surprisingly, they found a decreased relapse rate in the patients treated with medication and family therapy as well as in the group treated with antipsychotic and social skills training. The combination of the treatments had an additive effect and was far superior to medication treatment alone.

A controlled investigation of the effects of social intervention was also conducted. Patients were divided into groups, one that received routine outpatient treatment and one that underwent social intervention. In this study, one of the social interventions included reducing the time patients spent with their high-EE relatives. In addition, families received psychoeducational lectures about schizophrenia and its natural course and symptoms. Patients with schizophrenia received antipsychotics throughout the study. Relatives participated in group sessions that addressed coping mechanisms and familial interaction. As in the other studies, the patients who received the social interventions had a fivefold decrease in relapse rates that was sustained after 2-year follow-up.

Barbato and D'Avanzo (2000) critically reviewed family interventions in 25 randomized studies involving 1744 patients. Though the studies suffer from methodological limitations, the efficacy of family intervention on relapse rate is fairly well supported. This efficacy was particularly evident when contrasted with low quality or uncontrolled individual treatments. The addition of family intervention to standard treatment of schizophrenia has a positive impact on outcome to a moderate extent. Family intervention effectively reduces the short-term risk of clinical relapse after remission from an acute episode. There is evidence of effect on patient's mental state and social functioning, or on any family-related variables. The elements common to most effective interventions are inclusion of the patient in at least some phases of the treatment, long duration, and information and education about the illness provided within a supportive framework. There are sufficient data only for male chronic patients living with high EE parents. Evidence is limited for recent-onset patients, women, and people in different family arrangements and families with low EE. Research in family intervention is still a growing field. Thus, at present it is unclear if the effect seen with family therapy is due to family treatment or more intensive care.

Leff (2000) concluded from his review that family interventions reduced relapse rates by one -half over the first year of combined treatment with medications and family therapy. Medications and family therapy augment each other. Psychoeducation by itself is not enough. It also seems that multiple family groups are more efficacious than single family sessions. Attempts are being made to generalize training of mental health workers in effectively implementing these strategies. Pharoah et al. (2006) did a systematic review of literature involving 1765 participants and found that family intervention decreased the frequency of relapse, reduce hospital admission and may encourage compliance with treatment, it may prevent social impairment and the levels of expressed emotions.

Based on these findings, it is clear that there is a significant interaction between the level of emotional involvement and criticism of relatives of probands with schizophrenia and the outcome of their illness. Identifying the causative factors in familial stressors and educating involved family members about schizophrenia lead to long-term benefits for patients. Future work in this field must examine these interactions with an understanding of modern sociological and biological advances in genetics, looking at trait carriers, social skills assessments, positive and negative symptoms, and medication management with the SGAs.

## Case Management

Assertive Community Treatment (ACT) is a community care model with a caseload per worker of 15 patients or less in contrast to standard case management (SCM) with

a caseload of 30 to 35 patients. Intensive clinical case management (ICCM) differs from ACT by the case manager not sharing the caseload. In the ACT model, most services are provided in the community rather than in the office; the caseloads are shared across clinicians rather than individual separate caseloads. These are time unlimited services provided directly by the ACT team and not brokered out and 24-hour coverage is provided. Research on the ACT model confirms that it is successful in making patients comply with treatment and leads to less inpatient admissions. ACT also improves housing conditions (fewer homeless patients, more patients in stable housing), employment, quality of life, and patient satisfaction. No clear differences between ACT and standard or intensive clinical case management are reported with mental condition, social functioning, self-esteem, or number of deaths.

## Combining Pharmacological and Psychosocial Treatments

The combination of pharmacological and psychosocial interventions in schizophrenia can have complex interactions. For example, psychotherapies improve medication compliance on one hand but are more effective in the presence of antipsychotic treatment. Family psychoeducation has been reported to decrease the level of expressed emotion in the family resulting in better social adjustment and a need for lower dose of antipsychotic medications. Marder and colleagues, found in their study that pharmacological and psychosocial treatments affect different outcome dimensions. Medications affect relapse risk whereas skills training affect social adjustment. The VA cooperative study by Rosenheck and colleagues (2006), found that patients who received clozapine were more likely to participate in these treatments and led to improved quality of life. The qualitative differences in the interactions between the newer antipsychotic agents and psychotherapy suggest a hopeful trend of better utilization of psychosocial treatments.

## Access to Psychosocial Treatments

Though significant advances have been made in psychosocial treatments, not everyone suffering from schizophrenia is able to access all of the different treatments they could benefit from. Urban areas often provide more choices than rural ones. Funding for psychosocial services is a chronic issue. Moreover, clinicians are often not likely to refer their patients under the mistaken belief that patients will not engage in therapy. While countries like UK are providing more home based services as they shut down mental hospitals, in USA, home-based treatments are not common.

## Self-Directed Treatment

Groups such as the National Alliance for Mentally Ill (NAMI) and the Manic–Depressive Association offer tremendous resources to psychiatric patients and their relatives. They provide newsletters, neighborhood meetings, and support groups to interested persons. These nonprofessional self-help measures may feel less threatening to patients and their families and provide an important adjunct to professional settings.

Structured self-help clubs have also been effective means of bolstering patients' social, occupational, and living skills. The Fountain House was the first such club aimed at social rehabilitation. Patients who are involved are called members of the club, giving them a sense of belonging to a group. They are always made to feel welcome, useful, and productive members of the club community.

The clubhouse model has expanded to provide services such as transitional employment programs, apartment programs, outreach programs, and medication management and consultation services, to name a few. A self-supportive rehabilitation program for mentally ill patients is an important option for many schizophrenia patients who might otherwise feel isolated and out of reach.

## Stigma

Though tremendous progress has occurred in understanding and treatment of schizophrenia, stigmatizing attitudes still prevail; in a survey, schizophrenia elicited the most negative opinions and over 70% of those questioned thought that schizophrenia patients were dangerous and unpredictable. Thus, stigma surrounding schizophrenia can cause people suffering from the illness to develop low self-esteem, disrupt personal relationships, and decrease employment opportunities. The World Psychiatric Association (WPA), has initiated an international program aimed at developing tools to fight stigma and discrimination.

### Clinical Vignette 1

Mr. A first sought psychiatric help at the age of 19 years. During his first year of college he had a difficult adjustment. He had never had close friends, but at school he felt isolated from his family. Although he had always been a good student, averaging As and Bs in high school, he was unable to achieve the same level of academic performance. He became increasingly distressed by his sense of isolation and his inability to maintain an adequate grade point average. Around the middle of his first year of college he saw a psychiatrist, who thought he was having an adjustment reaction to his new surroundings. He was not given medication at the time but was referred for supportive psychotherapy. After two appointments with his therapist, he decided it was not helpful.

Shortly thereafter, he began to feel that the other students were staring at him and laughing at him behind his back. Then he began to feel as if they were playing tricks on him, sending secret messages to him over the radio to torment him. This experience lasted over 6 months. He also began hearing two voices, which he did not recognize. These voices would comment on his behavior and criticize his actions. They began to tell him to stay out of his dormitory room at night. The voices also warned him that the dormitory food was poisoned. One night, he was picked up by police for loitering and was brought to an emergency department.

The emergency department psychiatrist saw him as a disheveled, unshaven man who was agitated during the interview, pacing across the examining room. He was wearing dark sunglasses, although it was the middle of the night, and he said he did not want the examiner to read his mind by looking into his eyes, so he kept the sunglasses on throughout the interview. His speech was of normal rate and prosody, although there were long pauses in some of his responses. He was able to respond to questions clearly, and his thought processes were logical, although he

repeatedly spoke angrily as if responding to voices. He did say that the voices had been telling him to kill himself for the past two nights, although he said he was trying not to listen to them. The patient showed only some difficulty in concentration on a cognitive examination. His judgment was fair in that he recognized his need for some help, but he showed no insight into his symptoms.

The psychiatrist felt that the patient was potentially a risk of harm to himself because of the command auditory hallucinations and required hospitalization. Mr. A did not agree to come into the hospital, and the psychiatrist sought involuntary hospitalization through appropriate procedures. In the hospital, the patient was initially quite agitated, requiring intramuscular haloperidol and lorazepam. Almost immediately his behavior calmed, and he was able to agree to hospitalization and treatment. He was treated with risperidone, and the dose was titrated up to 3 mg/day by mouth at bedtime. After 1 week with this medication regimen, he began to experience a decrease in his auditory hallucinations and paranoid ideation. He was sleeping better and was no longer concerned about the foods he was eating.

Clinical Vignette 2

Ms. T, a 31-year-old woman, came to the US in her early twenties to study at a local university. Her family had sent her overseas after her mother was taken into a local psychiatric hospital in her native country. She had difficulty relating to her American classmates but was able to learn English and complete her coursework successfully. After graduation, she found a position working for a small company. Initially, she was punctual for work and her appearance was professional, although eccentric. Ms. T rarely socialized with her coworkers and generally spent her time alone. Several months after a prolonged visit from her previously estranged parents, she was notably more anxious. It became increasingly difficult for her to work closely with others. Ms. T gradually began to appear more disheveled and, at times, malodorous. Her supervisor grew concerned as she began to arrive late to work and seemed disorganized about her responsibilities. Her coworkers noted her bizarre behavior over several months. She began expressing concern about alien forces that would hide messages on her desk. She arrived at work one morning, speaking in rhymes that were partly in her native language and gesturing oddly, explaining that the day had arrived when the aliens would present themselves. Her concerned supervisor saw that she was unable to be shaken from this strange behavior and escorted her to a nearby emergency department for an evaluation.

The emergency department psychiatrist immediately made arrangements for admission, as Ms. T was not able to care for herself at that time. Results of her laboratory tests and physical examination were all within normal limits, and there was no evidence of substance abuse. Her brain MRI scan was also normal. With no identifiable organic cause, more than 1 month of active symptoms, and a 6-month prodromal period, Ms. T was given a presumptive diagnosis of schizophrenia, undifferentiated type.

In the hospital, she was given trifluoperazine at 10 mg twice daily. Her odd mannerisms gradually abated. In addition, her worries about the alien forces and her thought processes seemed to clear over the next few weeks. As her symptoms abated, she was able to participate in the structured group activities while in the hospital.

Eventually, Ms. T was moved to a day program. Her treatment team and Ms. T worked together and planned for her to move out of her apartment and into a psychiatric halfway house. She was not able to return to work, but during the next 6 months she adjusted well to participating in activities at her day program, helping in the clerical office. In the following 10 years, she was hospitalized three times because of noncompliance with medications. After her medication was changed to haloperidol decanoate, Ms. T remained stable and compliant with monthly appointments. Two years later, during her regular neurological examination looking for evidence of movement disorder, she exhibited mild tardive dyskinesia, which appeared to increase over time. On further evaluation, Ms. T had developed sustained insight into her illness and formed a strong alliance with her caseworker. After discussions with the patient and her team, a decision was made to switch her from haloperidol decanoate to oral olanzapine. The dose was titrated up to olanzapine 20 mg/day given at bedtime with weekly monitoring of compliance. She tolerated the switch well with further improvement in her clinical symptoms including symptoms of depression. One year later, her symptoms of tardive dyskinesia were in remission as well.

## Other Psychotic Disorders

## Schizoaffective Disorder

### Diagnosis

Kraepelin's landmark classification at the dawn of the 20th century could not accurately classify those patients who manifested both psychotic (schizophrenia-like) and affective symptoms and had a better course of illness than schizophrenia (Kraepelin 1919). It was Kasanin (1933), who coined the term *schizoaffective disorder* to describe some of these patients. However, over the decades, these patients were often classified as having atypical schizophrenia, good prognosis schizophrenia, remitting schizophrenia, or cycloid psychosis. Inherent within these diagnoses was the implication that they shared similarities to schizophrenia and also appeared to have a relatively better course of illness. With the advent of effective treatment of bipolar disorder with lithium salts, some of these patients started responding to lithium, and the term schizoaffective disorder gained further momentum. Unfortunately, this lack of diagnostic clarity has plagued the diagnosis of schizoaffective disorder such that there is much that is unknown about the illness.

Schizoaffective disorder criteria have evolved over the years and undergone major changes. According to the DSM-IV-TR, a patient with schizoaffective disorder must have an uninterrupted period of illness during which, at some time, they meet the diagnostic criteria for a major depressive episode, manic episode, or a mixed episode concurrently with the diagnostic criteria for the active phase of schizophrenia (criteria A for schizophrenia). Additionally, "the patient must have had delusions or hallucinations for at least 2 weeks in the absence of prominent mood disorder

symptoms" during the same period of illness. The mood disorder symptoms must be present for a substantial part of the active and residual psychotic period. The essential features of schizoaffective disorder must occur within a single uninterrupted period of illness where the "period of illness" refers to the period of active or residual symptoms of psychotic illness and this can last for years and decades. The total duration of psychotic symptoms must be at least 1 month to meet the criteria A for schizophrenia and thus, the minimum duration of a schizoaffective episode is also 1 month.

The criteria for major depressive episode require a minimum duration of 2 weeks of either depressed mood or markedly diminished interest or pleasure. As the symptoms of loss of pleasure or interest commonly occur in nonaffective psychotic disorders, to meet the criteria for schizoaffective disorder criteria A, the major depressive episode must include pervasive depressed mood. Presence of markedly diminished interest or pleasure is not sufficient to make a diagnosis as it is possible that these symptoms may occur with other conditions too.

The DSM-IV-TR diagnosis of schizoaffective disorder can be further classified as schizoaffective disorder *bipolar type* or schizoaffective disorder *depressive type*. For a person to be classified as having the bipolar subtype he/she must have a disorder that includes a manic or mixed episode with or without a history of major depressive episodes. Otherwise the person is classified as having depressive subtype having had symptoms that meet the criteria for a major depressive episode with no history of having had mania or mixed state.

## Clinical Features

The clinical signs and symptoms of schizoaffective disorder include all the signs and symptoms of schizophrenia, and a manic episode and/or a major depressive episode. The schizophrenia and mood symptoms may occur together or in an alternate sequence. The clinical course can vary from one of exacerbations and remissions to that of a long-term deterioration. Presence of mood-incongruent psychotic features—where the psychotic content of hallucinations or delusions is not consistent with the prevailing mood—more likely indicate a poor prognosis.

## Epidemiology

As discussed earlier, the diagnosis of schizoaffective disorder has undergone numerous changes through the decades making it difficult to get reliable epidemiology information. When data were pooled together from various clinical studies, approximately 2–29% of those patients diagnosed to have mental illness at the time of the study were suffering from schizoaffective disorder with women having a higher prevalence. This could possibly be explained by a higher rate of depression in women. Relatives of women suffering from schizoaffective disorder have a higher rate of schizophrenia and depressive disorders compared to relatives of male schizoaffective subjects. The estimated lifetime prevalence of schizoaffective disorder based on an elegant study done recently by Perala et al. (2007) is 0.32% (95% CI = 0.21–0.46) with men having 0.14% (95% CI = 0.06–0.34) which was statistically significantly different compared to women at 0.47% (95% CI = 0.30–0.72). In the inpatient settings of New York State psychiatric hospitals, approximately 19% of 6,000 patients had a diagnosis of schizoaffective disorder.

## Gender and Age

The depressive type of schizoaffective disorder appears to be more common in older people while the bipolar type probably occurs more commonly in younger adults. The higher prevalence of the disorder in women appears to occur particularly amongst those who are married. As in schizophrenia, the age of onset for women is later than that for men. Depression tends to occur more commonly in women.

## Course and Prognosis

Regarding the prognosis of schizoaffective disorder, to the extent that this illness has symptoms from both a major mood disorder and schizophrenia, theoretically one can confer a relatively better prognosis than schizophrenia and a relatively poorer prognosis than bipolar disorder. In one study where DSM-III and DSM-IV patients with schizoaffective disorder were followed for 8 years, the outcome of these patients more closely resembled schizophrenia than mood disorder with psychosis. Some data indicate that patients with a diagnosis of schizoaffective disorder bipolar type have a 2–5 years course similar to that of bipolar disorder, while patients diagnosed to have schizoaffective disorder depressive type have a course similar to schizophrenia on outcome measures such as occupational and social functioning after the index episode (Grossman et al. 1991). Regardless of the subtype, the following variables are harbingers of a poor prognosis:

a. a poor premorbid history
b. an insidious onset
c. absence of precipitating factors
d. a predominance of psychotic symptoms, especially deficit or negative ones
e. an early age of onset
f. an unremitting course, and
g. a family history of schizophrenia.

The corollary would be that the opposite of each of these characteristics would suggest a better prognosis. Interestingly, the presence or the absence of Schneiderian first-rank symptoms does not seem to predict the course of illness. The incidence of suicide in patients with schizoaffective disorder is at least 10%. Some data indicate that the suicidal behavior may be more common in women than men.

In a small sample comparing 27 schizoaffective disorder with 27 bipolar disorder patients, first rank symptoms and mood-incongruent psychosis did not differ between the two groups. Over 70% of the sample included unemployed or unskilled laborers. A few studies have reported that low socioeconomic status is a strong predictor of poor outcome.

In one study, 82% of those patients who were suffering from a first episode of schizoaffective disorder and had recovered, experienced psychotic relapse within 5 years. These patients had high rates of second and third relapses despite careful monitoring. Medication discontinuations in first episode patients who are stable for 1 year substantially increase relapse risks. Aside from medication status, premorbid social

adjustment was the only predictor of relapse in their study. Poor adaptation to school and premorbid social isolation predicted initial relapse independent of medication status. Thus, like schizophrenia, the risk of relapse is diminished by antipsychotic maintenance treatment.

## Differential Diagnosis

The possible differential diagnosis consists of bipolar disorder with psychotic features, major depressive disorder with psychotic features, and schizophrenia. Clearly, substance induced states and symptoms caused by coexisting medical conditions should be carefully ruled out. All conditions listed in differential diagnosis of schizophrenia, bipolar disorder, and major depressive disorder should be considered including but not limited to those patients undergoing treatment with steroids, those abusing substances such as PCP and medical conditions such as temporal lobe epilepsy. In circumstances where there is ambiguity, it may be prudent to delay making a final diagnosis until the most acute symptoms of psychosis have subsided and time is allowed to establish a course of illness and collect collateral information.

## Etiology

The etiology of schizoaffective disorder is unknown. There is a dearth of data relating to this illness. Studies involving families of schizoaffective probands suggest that they have significantly higher rates of relatives with mood disorder than families of schizophrenia probands. It is possible that some of the same environmental theories that apply to schizophrenia and bipolar disorder may also apply to schizoaffective disorder. Recent linkage studies have implicated the DISC1 gene locus for schizoaffective disorder.

Over the years, the concept of schizoaffective disorder has evolved such that many view it as either a type of schizophrenia or a type of mood disorder. Some have suggested that schizoaffective disorder represents a variant of schizophrenia in terms of clinical symptoms, family history and treatment. Moreover, in some studies schizophrenia patients did not differ from schizoaffective ones on cognitive impairment. Williams and associates suggested that the disorder represents a variant of either schizophrenia or mood disorder while others consider it to be on a continuum of illness intermediate between schizophrenia or mood disorder. One opinion is that schizoaffective disorder represents a phenotypic variation of either schizophrenia or mood disorder and over the long term becomes a subtype of either one. Alternatively, some view schizoaffective disorder as the simultaneous expression of schizophrenia and a mood disorder. However, Kendler and colleagues observe that schizoaffective patients differ significantly from both schizophrenia and mood disorder patients. Specifically, schizoaffective patients have more affective symptoms, fewer negative symptoms and a better course and outcome than schizophrenia. Bertelsen and Gottesman (1995) reviewed the literature relevant to genetic predisposition to schizoaffective disorder. Though variable, the results generally suggest that schizoaffective disorder is either a phenotypic variation or an expression of a genetic interform between schizophrenia and mood disorder, a position similar to Kendler. However, the possibility that schizoaffective disorder is distinct from schizophrenia and mood disorders is not supported by the observations that only a small percentage of the relatives of schizoaffective disorder probands have schizoaffective disorder.

It is most likely that schizoaffective disorder is a heterogeneous condition that includes all of the possibilities mentioned above. Thus, depending on the type of schizoaffective disorder studied an increased prevalence of either schizophrenia or mood disorders may be found in their relatives. As a group, patients with schizoaffective disorder have a prognosis intermediate between mood disorders and schizophrenia. Thus, on an average they have a better course than those suffering from schizophrenia, respond to mood stabilizers more often and tend to have a relatively nondeteriorating course.

## Treatment

With the shifting definitions of schizoaffective disorder, evaluating the treatment of schizoaffective disorder is not easy. Mood stabilizers, antidepressants, and antipsychotic medications clearly have a role in management of these patients. The presenting symptoms, their duration and intensity, and patient choices need to be incorporated into deciding what treatment(s) to choose.

## Antipsychotic Medications

Second Generation Antipsychotic medications (SGA) are reported to be more effective than the First Generation ones (FGA) in the treatment of schizoaffective disorder. They appear to have more broad-spectrum effects than the FGAs. Optimizing antipsychotic treatment, especially with the SGAs is more likely to be effective than the routine use of adjunctive antidepressants or mood stabilizers. However, when indicated, the use of antidepressants is well supported in schizoaffective patients who present with a full depressive syndrome after stabilization of psychosis.

Olanzapine is effective against symptoms of psychosis, mania, and depression. Tollefson and colleagues studied 300 patients with schizoaffective disorder bipolar type, one of the largest studies of its kind in schizoaffective disorder, and reported that olanzapine was significantly superior to haloperidol in treating affective and psychotic symptoms.

Ziprasidone was studied in 115 hospitalized patients with acute episode of schizoaffective disorder using a double blind randomized design. Ziprasidone was significantly superior to placebo and was well tolerated (Keck et al. 2001). Ziprasidone also has significant antidepressant effects at doses of 120 to 160 mg/day.

Vieta and colleagues studied 102 schizoaffective disorder bipolar type patients where risperidone was added to their existing regimen of mood stabilizers in the absence of an antipsychotic agent. Risperidone had significant clinical efficacy and a favorable safety profile when combined with mood stabilizers in patients with schizoaffective disorders. The response rate was comparatively better than what is typically observed in schizophrenia studies. Hillert and associates also reported that treatment with risperidone reduced both psychotic and mood symptoms in patients with schizoaffective disorder depressed type. However, a study with a small sample, did not find significant differences between haloperidol and risperidone in a

short-term 6-week double-blind randomized study. However, risperidone produced significantly greater responders in the patients with severe depression and also improved the sleep factor. Moreover, risperidone did not exacerbate manic symptoms, a prevailing concern at the time when this study was conducted. Furthermore, the risperidone group had less EPS compared to haloperidol. Efficacy of clozapine in schizoaffective disorder has been reported in several short term studies or chart reviews. Clozapine monotherapy has been reported to be effective in treatment up to 16 months in a small sample. Presence of affective symptoms predicted good response to clozapine. When clozapine use was compared in treatment refractory schizophrenia, bipolar disorder, and schizoaffective disorder the outcomes were significantly better in bipolar disorder and schizoaffective disorder. Persistent and enduring improvements with clozapine lasting 1 to 2 years have been reported. Clozapine also helps decrease suicidality. Thus, clozapine use may be beneficial in treatment refractory schizoaffective disorder as it has both mood stabilizing and antipsychotic properties, a substantial advantage.

### Mood Stabilizers

Two small open label studies suggest that valproic acid is effective in treating the manic symptoms associated with schizoaffective disorder, bipolar type with 65.2% reduction in manic episodes in 5 patients after 29 to 51 months. Similar results were reported by another study where 79% of the patients reported improvement after 1-year treatment with valproic acid. A study with small sample also reported 75% improvement in Clinical Global Impression scale.

Three double-blind, parallel-group studies examined the efficacy of lithium carbonate in schizoaffective mania. One study found that chlorpromazine alone was as effective as the combination of chlorpromazine and lithium. Another study, with a small sample found that the combination of lithium and haloperidol was more effective than haloperidol itself in patients with predominantly affective symptoms compared to those with predominantly psychotic symptoms. Reports of carbamazepine use are sparse and difficult to draw conclusions from. Lamotrigine was also reported to be useful in 3 cases of schizoaffective disorder. A comprehensive review by Cochrane Group has reported that concomitant use of lithium with antipsychotics was particularly efficacious in schizoaffective group.

**Antidepressants.** The SGAs are often efficacious against depression in patients who suffer from both depression and psychosis negating the need for routine use of antidepressants. However, there are patients who remain depressed even with optimal antipsychotic and mood stabilizer treatment. SSRIs are widely used in patients who present with schizoaffective disorder with depression. If the SSRIs and newer antidepressants do not show efficacy, tricyclic antidepressants do have a role. Interestingly, chlorpromazine in combination with amitriptyline was reported to be as effective as chlorpromazine alone. Many studies suggest that addition of antidepressants helps in effective treatment of depression in schizoaffective disorder. Occasionally, antidepressants may worsen the course. For patients suffering from depression where they are not responding adequately and are at risk for suicide, ECT is an effective alternative.

**Psychosocial Treatment.** To the extent that schizoaffective disorder shares symptoms with schizophrenia, most of the psychosocial treatments used in the treatment of schizophrenia are likely to be useful in the treatment of schizoaffective disorder. Specifically, patients benefit from individual supportive therapy, family therapy, group therapy, cognitive–behavioral therapy, and social skills training. Many patients would be suitable candidates for assertive community therapy (ACT). Depending on the level of recovery, some of the patients may need rehabilitation services to assist them with either developing skills for some form of employment or assistance to maintain a job. Family members benefit from support groups such as NAMI or MDA groups.

Clinical Vignette 3

Ms. Jones is a 29-year-old married woman with two children. She reported having problems with her sleep 9 months after the birth of her second child as marking the beginning of her illness. She was erratic, irritable, and gradually declined in her functioning. Her family noticed that she was unable to care for herself and her children. She was paranoid, suspicious of her neighbors, and felt that they were spying on her. She isolated herself in the house. Soon she was also noted to have euphoric mood with racing thoughts and grandiose delusions of being a very powerful person endowed with gifts from god. She was barely sleeping, only a few hours a day. After approximately 6 weeks of this behavior, she was brought to hospital after she got into a verbal altercation with her neighbor. There was no history of any medical problems, medication use, or any drug abuse. She was admitted to the hospital, started on valproic acid, and the dose was titrated up to 1,500 mg/day with blood levels of 80. Her symptoms of mania resolved within 2 weeks and she was discharged. However, on the follow-up visit, she reported being suspicious of her neighbor and felt that she was being watched. Her husband reported that patient kept the shades down on the side where the neighbors lived. She was started on ziprasidone 20 mg (QTc interval within normal range) twice a day and the dose was increased to 120 mg/day. Her symptoms resolved completely at the next visit. One year later, she was doing well on monotherapy of ziprasidone 120 mg/day and had started working part time.

## Brief Psychotic Disorder

### Diagnosis

Brief psychotic disorder is defined by DSM-IV-TR as a psychotic disorder that lasts more than 1 day and less than a month. Moreover, the disorder may develop in response to severe psychosocial stressors or group of stressors.

European and Scandinavian countries have traditionally diagnosed this type of psychosis as *psychogenic psychoses*, *reactive psychosis*, or *brief reactive psychosis*. Some have also referred to this condition as *hysterical psychosis*. These terms are probably more commonly used in Scandinavian countries due to Langfeldt and Leonhard's contributions to the classification of psychosis that does not have a course

like schizophrenia. In the US, brief reactive psychosis was formally included as a diagnostic category in DSM-III. Subsequently it has undergone a change in its name to *brief psychotic disorder*.

The DSM-IV-TR diagnostic criteria specify the presence of at least one clear psychotic symptom lasting a minimum of 1 day to a maximum of 1 month. Furthermore, DSM-IV-TR allows the specification of two additional features: the presence or the absence of one or more *marked stressors* and a *postpartum* onset starting within four weeks of postpartum period. DSM-IV-TR describes a continuum of diagnosis for psychotic disorder based primarily on duration of the symptoms. Once the duration criteria are met, other conditions such as etiological medical illnesses and substance-induced psychosis need to be excluded. In those cases where the duration of psychosis lasts more than 1 month, appropriate diagnosis to be considered are other psychotic conditions based on reevaluation of the clinical features, duration of psychosis, and presence of mood symptoms.

## Clinical Features

People suffering from this disorder usually present with an acute onset, manifest at least one major symptom of psychosis, and do not always include the entire symptom constellation seen in schizophrenia. Affective symptoms, confusion, and impaired attention may be more common in brief psychotic disorders than in chronic psychotic conditions. Some of the characteristic symptoms include emotional lability, outlandish behavior, screaming or muteness, and impaired memory for recent events. Some of the symptoms suggest a diagnosis of *delirium* and may warrant a more complete medical workup. The symptom patterns include acute paranoid reactions, reactive confusions, excitations, and depressions. In French psychiatry, *Bouffee delirante* is similar to brief psychotic disorder.

## Epidemiology

This illness is not uncommon, but, unfortunately, reliable estimates of the incidence, prevalence, sex ratio, and average age of onset are not available. Recently, using well defined measures in a nationally representative sample of 8028 subjects 30 years or older, Lifetime Prevalence was estimated at 0.05% (95% CI = 0.02–0.14) with rates in men were 0.08% (95% CI = 0.03–0.26) and in women 0,02% (95% CI = 0.00–0.17) making this a rare disorder (Perala et al. 2007). It is believed that this disorder is more common among young people with occasional cases involving older people. This disorder may be seen more commonly in patients from low socioeconomic classes and in those with personality disorders such as histrionic, paranoid, schizotypal, narcissistic, and borderline. Though immigrants and people who have experienced major disasters are reported to be at a higher risk, well-controlled studies have failed to show this.

### Precipitating Stressors

The precipitating stressors most commonly encountered are major life events that would cause any person significant emotional turmoil. Such events include the death of a close family member or severe accidents. Rarely, it could be accumulation of many smaller stresses.

### Course and Prognosis

As defined by DSM-IV-TR, the duration of the disorder is less than 1 month. Nonetheless, the development of such a significant psychiatric disorder may indicate a patient's mental vulnerability. An unknown percentage of patients who are first classified as having brief psychotic disorder later display chronic psychiatric syndromes such as schizophrenia and bipolar disorder. Patients with brief psychotic disorders generally have good prognosis, and European studies indicate that 50 to 80% of all patients have no further major psychiatric problems.

The length of the acute and residual symptoms is often just a few days. Occasionally, depressive symptoms follow the resolution of the psychosis. Suicide is a concern during both the psychotic phase and the postpsychotic depressive phase. Indicators of good prognosis are good premorbid adjustment, few premorbid schizoid traits, severe precipitating stressors, sudden onset of symptoms, confusion and perplexity during psychosis, little affective blunting, short duration of symptoms, and absence of family history of schizophrenia.

### Differential Diagnosis

Although the classical presentation may be short in duration and associated with stressors, a thorough and careful evaluation is necessary. Additional information is critical to rule out other major psychotic conditions as temporal association of stressors to the acute manifestation of symptoms may be coincidental and thus misleading. Other conditions to be ruled out include psychotic disorder due to a general medical condition, substance-induced psychosis, factitious disorder with predominantly psychological signs and symptoms, and malingering. Patients with epilepsy and delirium may also present with similar symptoms. Additional conditions to be considered are dissociative identity disorder and psychotic episodes associated with borderline and schizotypal personality disorder that may last for less than a day.

## Etiology

As with other psychotic illnesses, this condition appears to be heterogeneous; clearly, more research is necessary. The development of psychosis is an important indication of severity of this illness and may suggest either a breakdown of or inadequate coping mechanisms.

### Treatment

These patients may require short-term hospitalizations for a comprehensive evaluation and safety. Antipsychotic drugs are often most useful along with benzodiazepines. Long-term use of medication is often not necessary and should be avoided. If maintenance medications are necessary, the diagnoses may need to be revised. Clearly, the newer antipsychotic agents have a better neurological side effect profile and would be preferred over the typical agents.

Psychotherapy is necessary to help the person reintegrate the experience of psychosis and possibly the precipitating trauma. Individual, family, and group therapies may be necessary in some individuals. Many patients need help to cope with the loss of self-esteem and confidence.

Clinical Vignette 4

A 35-year-old recently separated immigrant woman was brought to the emergency room in an acutely agitated state with auditory hallucinations and confusion. She immigrated to the US 2 years ago to join her husband of 5 years. They separated 3 months ago; she lost her job a month later and had to bear significant financial hardship. Her father was medically ill and passed away unexpectedly 6 weeks previously. According to people close to her, she started having symptoms approximately 7 days before her admission. She was reported to be restless, pacing, and preoccupied with the recent stressors. On various occasions, her speech was tangential or incoherent. Her mood was labile and she appeared to be perplexed at times. Her attention and concentration was poor. She was paranoid of her husband (family members denied him being a threat to her) and often felt that her deceased father was communicating with her. She had passive suicidal thoughts. She was often upset about being hospitalized and demanded release from the hospital. She would get quite angry and throw tantrums if her request for discharge was denied. There was no history of alcohol or drug use. She was in good physical health. There was no history of similar or other episodes.

Admission work up was essentially normal. The urine toxicology screen, pregnancy test, and EEG were normal. Following admission, she was started on a low dose of benzodiazepine and an atypical antipsychotic agent. Her symptoms of agitation and psychosis responded rapidly within 1 week. Individual and group therapy sessions were very helpful in addressing her recent stressors and providing emotional support. Family therapy was offered but the patient and her family rejected it. With the help of individual and group therapy, she was able to develop some coping skills. Following discharge, she continued to respond to the low dose antipsychotic treatment and other therapies. She was not having any symptoms of psychosis and was able to deal with her stressors better. Approximately 3 weeks after discharge, though her stressors continued, she was responding well to the treatment, reached her baseline functioning, but due to significant weight gain and sedation, she decided to discontinue her medication. Six months later, she has continued with psychotherapy and group therapy, and has maintained her baseline functioning.

## Schizophreniform Disorder

### Diagnosis

Gabriel Langfeldt (1939) suggested the term *Schizophreniform Disorder* in 1937 for a heterogeneous group of patients characterized by the similarity of their symptoms to those of schizophrenia albeit with a good clinical outcome. Langfeldt observed that those patients whose diagnosis was questionable as schizophrenia had a much better outcome than those whose diagnosis was confirmed as schizophrenia; these patients were thus classified as having schizophreniform psychosis. Langfeldt also noted that these patients often had good premorbid adjustment, an abrupt onset of symptoms, frequent presence of psychosocial stressor(s), and a good prognosis.

Schizophreniform disorder shares a majority of the DSM-IV-TR diagnostic features with schizophrenia (see diagnostic criteria on page xxx) except the following two criteria: (a) the total duration of the illness which includes the prodrome, active, and residual phases is at least 1 month but less than 6 months in duration; (b) though impairment in social and occupational functioning may occur during the illness, it is not required or necessary. Thus, the duration of more than 1 month eliminates brief psychotic disorder as a possible diagnosis; if the illness lasts or has lasted for more than 6 months, the diagnosis has to be reevaluated for other possible conditions including schizophrenia. Therefore, the diagnosis of schizophreniform disorder is intermediate between brief psychotic disorder and schizophrenia. Hence, those patients whose duration of episode lasted more than a month and less than 6 months, and have recovered would be diagnosed as having schizophreniform disorder. On the other hand those patients who have not recovered from an episode, which is less than 6 months but more than 1 month in duration, and are likely to have schizophrenia would be diagnosed to have schizophreniform disorder until the 6 months criteria is met for schizophrenia. The diagnosis of 'provisional' schizophreniform disorder is made while the clinician monitors the evolving course of the illness, waits for the symptoms to resolve, or when the clinician cannot obtain a reliable history from a patient about the duration of the symptoms.

#### Specifiers for Prognostic Features

The DSM-IV-TR has specifiers for the presence or absence of good prognostic features. These features include a rapid onset (within four weeks) of prominent psychotic symptoms, presence of (psychogenic) confusion or perplexity at the height of the psychotic episode, good premorbid adjustment as evidenced by social and occupational functioning, and the absence of deficit symptoms such as blunted or flat affect.

#### Clinical Features

The clinical signs and symptoms and the Mental Status Examination of the patient with schizophreniform disorder are often similar to those with schizophrenia, but the presence of affective symptoms usually predict a favorable course. Alternatively, a flat or blunted affect may predict an unfavorable course.

### Epidemiology

Little is known about the incidence, prevalence, and sex ratio of schizophreniform disorder (Poulton et al. 2000). A strong linear relationship has been reported between self-reported psychotic symptoms in childhood at age 11 years and subsequent development of adult schizophreniform disorder. Those children with strong symptoms were 16 times more likely to have a schizophreniform diagnosis by age 26 years compared to control group. Forty-two percent of those who developed schizophreniform psychosis by age 26 years in the cohort had reported 1 or more psychotic symptoms at age 11 years. Interestingly, these psychotic symptoms which appeared at age 11 years did not predict mania or depression at age 26 years (Poulton et al. 2000). Over the years, schizophreniform psychosis has moved much closer to the diagnosis of schizophrenia. ECA studies indicate prevalence of 0.2% lifetime prevalence and 1-year prevalence of 0.1%. A well designed, elegant population survey of nationally representative sample of 8,028 subjects reported lifetime

prevalence rates of 0.07% (95% CI = 0.03–0.16) making it a rare condition (Perala et al. 2007).

## Family History

Several studies suggest that the relatives of patients with schizophreniform psychosis are at a high risk of having psychiatric disorders. The relatives of patients with schizophreniform psychosis are more likely to have mood disorders than are the relatives of patients with schizophrenia. In addition, the relatives of patients with schizophreniform disorder are more likely to have a diagnosis of a psychotic mood disorder than are the relatives of patients with bipolar disorders.

## Course and Prognosis

This is, as anticipated, variable. The DSM IV-TR specifiers "with good prognostic features" and "without good prognostic features" though helpful in guiding the clinician, require further validation. However, confusion or perplexity at the height of the psychotic episode is the feature best correlated with good outcome. Also, the shorter the period of illness, the better the prognosis is likely to be. There is a significant risk of suicide in these patients. Postpsychotic depression is quite likely and should be addressed in psychotherapy. Psychotherapy may help speed the recovery and improve the prognosis. By definition, schizophreniform disorder resolves within 6 months with a return to baseline mental functioning. With increased focus on first episode psychosis and early intervention, more studies will provide data regarding stability of diagnosis and longitudinal course. Those individuals who went on to develop schizophrenia had poorer premorbid functioning and longer duration of untreated psychosis, compared to those who did not.

### Differential Diagnosis

This is similar to schizophrenia. Psychotic disorder caused by a general medical condition and substance-induced psychotic disorder must be ruled out. General medical conditions to be considered are HIV infection, temporal lobe epilepsy, CNS tumors, and cerebrovascular disease, all of which can also be associated with relatively short-lived psychotic episodes. The increasing number of reports of psychosis associated with the use of anabolic steroids by young men who are attempting to build up their muscles to perform better in athletic activities require careful history. Factitious disorder with predominantly psychological signs and symptoms and malingering may need to be ruled out in some instances.

## Etiology

Schizophreniform psychosis, similar to other psychosis, is probably heterogeneous and due to an unknown cause. In general, some patients have a disorder similar to schizophrenia, whereas others have a disorder similar to mood disorders. Some data, however, indicate a close relation to schizophrenia. Several studies have shown that patients with schizophreniform disorder, as a group, have more affective symptoms (especially mania) and a better outcome than do patients with schizophrenia. In addition, the increased presence of mood disorders in the relatives of patients with schizophreniform disorder indicates a relation to mood disorders. Thus, the biological and epidemiological data are most consistent with the hypothesis that the current diagnostic category defines a group of patients, some of whom have a disorder similar to schizophrenia and others similar to a mood disorder.

## Brain Imaging

As in schizophrenia, a relative activation deficit in the inferior prefrontal region of the brain while the patient is performing Wisconsin Card Sorting Test is reported. One study showed that the deficit was limited to the left hemisphere indicating a similarity to schizophrenia. More studies are needed to determine the long-term course which is often variable and sometimes similar to schizophrenia but more often a shortened course quite different from schizophrenia. Some data indicate that patients with schizophreniform disorder may have enlarged ventricles, as seen on CT scans and MRI, while other data indicate that unlike the enlargement seen in schizophrenia, the ventricular enlargement in schizophreniform disorder is not correlated with outcome measures or other biological measures.

### Other Biological Measures

Although brain-imaging studies suggest a similarity between schizophreniform disorder and schizophrenia, one study of electrodermal activity has indicated a difference. Patients with schizophrenia born during the winter and spring months had hyporesponsive skin conductances, but this association was absent in patients with schizophreniform disorder. Though the significance of this one study would be difficult to interpret, the results do suggest caution in assuming similarity between patients with schizophrenia and those with schizophreniform disorder. Data from a study of eye tracking in the two groups also indicate that there are differences on some biological measures between schizophrenia and schizophreniform psychosis.

## Treatment

Hospitalization is often necessary and allows for effective assessment, treatment, and supervision of a patient's behavior. The psychotic symptoms, usually treated with a 3- to 6-month course of antipsychotic drugs, respond more rapidly than in patients with schizophrenia. One study found that 75% of the patients with schizophreniform psychosis compared to 20% of those with schizophrenia responded to antipsychotic agents within 8 days. ECT may be indicated for some patients, especially those with marked catatonic features or depression. If a patient has recurrent episodes, trials of lithium carbonate, valproic acid, or carbamazepine may be warranted for prophylaxis. Psychotherapy is usually necessary to help patients integrate the psychotic experience into their understanding of their minds, brains, and lives.

Clinical Vignette 5

Mr. A is a 25-year-old married white male who was brought to the emergency room by his family with complaints of paranoid thinking, agitation, auditory hallucinations, and insomnia. His family noticed that he was anxious, withdrawn, and had difficulty sleeping through the night 6 weeks previously. He reported to his wife that he was being harassed by his coworkers and felt that they were plotting against him. Mr. A reported hearing voices

*(continues)*

Clinical Vignette 5 *continued*

of a man and a woman with derogatory content. He did not leave the house for prolonged periods and complained of being under surveillance. He became quite agitated when his wife tried to have him visit a psychiatrist. When his family attempted to intervene, he threatened assault toward his brother. He did not report any precipitating factors except for a well-deserved promotion 6 months ago and his wife becoming pregnant 3 months ago. He was physically healthy and was not taking any medications. There was no past history of head injury or a seizure disorder. He did not consume any alcohol or drugs in the last 12 months. There was a history of occasional marijuana and alcohol use many years ago. He reported that his father had suffered from depression and was effectively treated for the same. He was described as a reliable and good worker and was with his current employer for 4 years. He had a few friends and was well adjusted with his wife. His admission laboratory workup and a head CT scan were within normal range, and his urine toxicology screen did not reveal any drugs. An atypical antipsychotic agent was initiated with benzodiazepines as needed for agitation, anxiety, and insomnia. He received individual and group therapy during the inpatient stay. He improved rapidly and was discharged 10 days later. He tolerated the medication well except for mild weight gain. He continued with individual therapy and had a few family counseling sessions. The patient decided to gradually discontinue his antipsychotic medications after 3 months of recovery. After one and a half years, he continues to work for the same firm, is back to his baseline, and does not have any residual symptoms.

## Delusional Disorder

Delusional disorder refers to a group of disorders, the chief feature of which is the presence of *nonbizarre* delusions. People suffering from this illness do not regard themselves as mentally ill and actively oppose psychiatric referral. Because they may experience little impairment, they generally remain outside hospital settings, appearing reclusive, eccentric, or odd, rather than ill. They are more likely to have contacts with professionals such as lawyers and other medical specialists for health concerns. The current shift in diagnosis from *paranoid* to *delusional* helps avoid the ambiguity around the term 'paranoid.' This also emphasizes that other delusions besides the paranoid ones are included in this diagnosis. It is important to understand the definition of nonbizarre delusion so as to reach an unambiguous diagnosis. Nonbizarre delusions typically involve situations or circumstances that can occur in real life (e.g., being followed, infected, or deceived by a lover) and are believable.

### History

The classical description of paranoia by Karl Ludwig Kahlbaum in 1863 paved the way for classification of paranoia. Kraepelin struggled with the concept of paranoia and his thinking finally evolved to define paranoia as an uncommon, insidious, chronic illness characterized by a fixed delusional system, an absence of hallucination, and a lack of deterioration of personality. Bleuler, on the other hand, viewed paranoia as a rare and milder version of schizophrenia and was not comfortable with a separate diagnosis. Freud used the autobiography of Daniel Paul Schreber, a jurist, and interpreted how unconscious homosexual tendencies were defended against by denial and projection in the form of delusions of persecution. His case study laid the basis for the psychodynamic understanding of paranoia.

### Diagnostic Criteria

According to DSM-IV-TR, the diagnosis of delusional disorder can be made when a person exhibits nonbizarre delusions of at least 1 month duration that cannot be attributed to other psychiatric disorders. Nonbizarre delusions must be about phenomena that, although not real, are within the realm of being possible. In general, the patient's delusions are well systematized and have been logically developed. If the person experiences auditory or visual hallucinations, they are not prominent except for tactile or olfactory hallucinations where they are tied in to the delusion (e.g., a person who believes that he emits a foul odor might experience an olfactory hallucination of that odor). The person's behavioral and emotional responses to the delusions appear to be appropriate. Usually the person's functioning and personality are well preserved and show minimal deterioration if at all.

### Subtypes

#### *Persecutory Type*

This is the most common form of delusional disorder (Yamada et al. 1998). Here the person affected believes that he or she is being followed, spied on, poisoned or drugged, harassed, or conspired against. The person affected may get preoccupied by small slights that can become incorporated into the delusional system. These individuals may resort to legal actions to remedy perceived injustice. Individuals suffering from these delusions often become resentful and angry with a potential to get violent against those believed to be against them.

#### *Jealous Type*

Individuals with this subtype have the delusional belief that their spouses/lovers are unfaithful. This is often wrongly inferred from small bits of benign evidence which is used to justify the delusion. Delusions of infidelity have also been called *conjugal paranoia*. The term *Othello syndrome* has been used to describe morbid jealousy. This delusion usually affects men, with no history of prior psychiatric problems. The condition is difficult to treat and may diminish only on separation, divorce, or death of the spouse. Marked jealousy (pathological jealousy or morbid jealousy) is a symptom of many disorders including schizophrenia and not unique to delusional disorder. Jealousy is a powerful emotion and when it occurs in delusional disorder or as part of another condition, it can be potentially dangerous and has been associated with violence including suicidal and homicidal behavior.

#### *Erotomanic Type*

Persons with delusional disorder of the erotomanic type have delusions of being loved by another. Most frequently, the patient is a woman, though men are also susceptible to these delusions. The patient believes that a perceived suitor, usually more socially prominent than herself, is in

love with her. This can become central focus of the patient's existence and the onset can be sudden. Erotomania shares many features with, is derived from, and is often referred to as *de Clerambault's syndrome*. Erotomanic delusions are not unique to delusional disorder, and can occur as part of other disorders too. Persons with erotomanic delusions often exhibit what has been called paradoxical conduct, the delusional phenomenon of interpreting all denials of love no matter how clear as secret affirmations of love. At times, it can manifest with more aggressive and possibly violent pursuit of love. Though the data are varied, one author has suggested that approximately 10% of stalkers have a primary diagnosis of erotomania. Recent data support that though they are less likely to be violent than other stalker types, stalkers with erotomanic delusions can become violent (Resnick 2007). Thus, such people are often in a forensic system. In a review by Meloy (1996), if violence occurred the object of love was the target at least 80% of the time, often related to resentment and rage in response to an absence of reaction from all forms of love communication or perceived jealousy. However, the object of aggression may also be companions or protectors of the love object who are viewed as trying to come between the lovers. Approaches to management can be difficult, as criminal sanctions alone may be inadequate. A combination of judicial interventions, and possible separation of victim and the person with erotomania, and treatment for the psychosis, may be needed in concert.

### Somatic Type

Delusional disorder with somatic delusions has been called *monosymptomatic hypochondriacal psychosis*. This disorder differs from other conditions with hypochondriacal symptoms in degree of reality impairment. Munro (1991) has described the largest series of cases and has used content of delusions to define three main types:

***Delusions of Infestations (Including Parasitosis).*** Delusional parasitosis is one of the most common presentations of monohypochondriacal psychosis, which occurs in absence of other psychiatric illness. In one study involving 52 patients, 88% of the cases were above 45 years of age. The prevalence of this condition is unknown. There appears to be a higher incidence of illness among middle-aged and elderly individuals. In the study mentioned above, 65% of the patients were females (Bhatia et al. 2000). This is similar to some reports but not all. The onset is insidious and chronic.

*Matchbox sign* describes the common phenomenon that occurred not so long ago in patients suffering from this condition. During their clinic visit, the patient would present with peeled skin, and other substances connected to delusional thinking in an empty old-fashioned matchbox as evidence that they were infested with insects. Delusional parasitosis has been described in association with many physical illnesses such as vitamin $B_{12}$ deficiency, pellagra, neurosyphilis, multiple sclerosis, thalamic dysfunction, hypophyseal tumors, diabetes mellitus, severe renal disease, hepatitis, hypothyroidism, mediastinal lymphoma, and leprosy. Use of cocaine and presence of dementia has also been reported.

Psychogenic parasitosis was also known as Ekbom's syndrome before being referred to as *delusional parasitosis*. Females experienced this disorder twice as often as males. Entomologists, pest control specialists, and dermatologists had often seen the patient before seen by a psychiatrist. All investigators have been impressed by the concurrent medical illnesses associated with this condition. Others have attempted to distinguish between delusional and nondelusional aspects of presentation to establish clearer diagnosis and thus management.

***Delusions of Dysmorphophobia.*** This condition includes delusions such as of misshapenness, personal ugliness, or exaggerated size of body parts.

***Delusions of Foul Body Odors or Halitosis.*** This is also called *olfactory reference syndrome*.

The frequency of these conditions is low, but they may be under diagnosed because patients present to dermatologists, plastic surgeons, and infectious disease specialists more often than to psychiatrists. Patients with these conditions do respond to pimozide, a first generation antipsychotic medication and also to SSRIs. Usually prognosis is poor without treatment. It affects both sexes equally. Suicide apparently motivated by anguish is not uncommon.

### Grandiose Type

This is also referred to as *megalomania*. In this subtype, the central theme of the delusion is the grandiosity of having made some important discovery or having great talent. Sometimes there may be a religious theme to the delusional thinking such that the person believes that he or she has a special message from god.

### Mixed Type

This subtype is reserved for those with two or more delusional themes. However, it should be used only where it is difficult to clearly discern one theme of delusion.

### Unspecified Type

This subtype is used for cases in which the predominant delusion cannot be subtyped within the above mentioned categories. A possible example is certain delusions of misidentification, for example, *Capgras's syndrome*, named after the French psychiatrist who described the 'illusions of doubles.' The delusion here is the belief that a familiar person has been replaced by an imposter. A variant of this is *Fregoli's syndrome* where the delusion is that the persecutors or familiar persons can assume the guise of strangers and the very rare delusion that familiar persons could change themselves into other persons at will (intermetamorphosis). Each disorder is not only a rare delusion but is highly associated with other conditions such as schizophrenia and dementia.

## Epidemiology

Though the existence of delusional disorder has been known for a long time, relatively little is known about the demographics, incidence, and prevalence. Unfortunately, people suffering from this illness function reasonably well in the community and lack insight resulting in minimal or no contact with the mental health system. However, the crude incidence is roughly 0.7 to 3.0 per 100,000 with a more frequent occurrence in females. A recent elegant epidemiological study reported Lifetime Prevalence of 0.18% (95%

CI = 0.11–0.30) using DSM-IV criteria (Perala et al. 2007). Some have associated this condition with widowhood, celibacy, and history of substance abuse. In one study, 1.2% of 4,144 consecutively attending subjects in an outpatient clinic were diagnosed to have delusional disorder. Half of the subjects were diagnosed to have *persecutory* type of delusional disorder. Females suffering from this disorder were significantly older than males. In a retrospective study from China, 0.83% of 10,418 outpatients met DSM-IV criteria of delusional disorder with equal gender distribution. The age range was 17–86 years with an average age of 42 ± 15 years. Women were significantly older than men at age of onset (46 versus 38.7). The mean duration of symptom onset to first psychiatry visit was 2.4 years and did not differ significantly between the sexes. Auditory hallucinations were reported in about 12%, tactile hallucinations in 6%, visual hallucinations in 2%, and olfactory hallucinations in 2%. The delusional disorder subtypes were persecutory type 71%, mixed 14%, jealous 8%, somatic 2%, unspecified 2%, erotomanic 1%, and grandiose 1% (Hsiao et al. 1999). Kendler reported a prevalence of 0.24 to 0.3% with a sex ratio of female to male of 1.18:1. Yamada and associates reported a 3:1 female-to-male ratio among their patients from Japan. Hwu and colleagues reported the lifetime prevalence of 0.48% in cities, 0.67% in townships, and 0.33% in rural villages. The gender ratios were not significantly different in their studies. Someya and colleagues reported that persecutory type of delusional disorder was more common (64%) followed by jealous type at (19%) in their cohort. Yamada and associates (1998) reported that persecutory type was most common at 51% followed by somatic type at 27.5% and jealous type at 147%. Both Yamada's and Hsiao's group did not find significant differences in the frequency of subtypes of delusional disorder between the sexes. Depressive symptomatology was present in 43% of the patients at their first visit (Hsiao et al. 1999). Higher frequency of depression has been reported by others at 51%. Both, depression before the onset of delusions and after the onset of delusions have been reported. The subgroup of patients who have hallucinations may have a poorer outcome depending on the intensity of the hallucinations.

## Course and Prognosis

Though the onset can occur in adolescence, generally it begins from middle to late adulthood with variable patterns of course, including lifelong disorder in some cases. Delusional disorder does not lead to severe impairment or change in personality, but rather to a gradual, progressive involvement with the delusional concern. Suicide has often been associated with this disorder. The base rate of spontaneous recovery may not be as low as previously thought, especially because only the more severely afflicted are referred for psychiatric treatment. Retterstol (Retterstol and Opjordsmoen 1991) has provided much information on this. The more chronic forms of the illness tend to have their onset early in the fifth decade. Onset is acute in nearly two-thirds of the cases and gradual in the remainder. In almost half of the cases the delusion disappears at follow-up, improves in 10%, and is unchanged in 31%. In the more acute forms of the illness, the age of onset is in the fourth decade, a lasting remission occurs in over half of the patients and a pattern of chronicity develops in only 10%; a relapsing course has been observed in 37%. Thus, the more acute and earlier the onset of the illness, the more favorable the prognosis. The presence of precipitating factors, married status and female gender are associated with better outcome. The persistence of delusional thinking is most favorable for cases with persecutory delusions and somewhat less favorable for delusions of grandeur and jealousy. However, the outcome in terms of overall functioning appears somewhat more favorable for the jealous subtype. Many believe that treatment nonadherence rather than lack of adequate response to medication is the main reason for persistent symptoms (Manschreck 2006). Some patients require hospitalization, often involuntarily, to prevent harm to themselves or others. Not uncommonly, they may get admitted through the legal system.

## Comorbidity

Depression occurs frequently and is often an independent disorder in these patients.

## Etiology

Etiology of the delusional disorder is unknown. Risk factors associated with the disorder include advanced age, sensory impairment/isolation, family history, social isolation, personality features (e.g. unusual interpersonal sensitivity), and recent immigration. Some have reported higher association of delusional disorder with widowhood, celibacy, and history of substance abuse. Age of onset is later than schizophrenia and earlier in men compared to women.

## Treatment

Though generally considered resistant to treatment and interventions, the management is focused on managing the morbidity of the disorder by reducing the impact of the delusion on the patient's (and family's) life. However, in recent years the outlook has been reported to be more optimistic (Manschreck 2006). An effective and therapeutic clinician–patient relationship is important but difficult to establish.

## Somatic Treatment

Overall, treatment results suggest that 81–90% of cases recover either fully or partially when treated with antipsychotic medications. However, limited psychopharmacological data exist regarding treatment of delusional disorder and more would be helpful. Treatment with pimozide was reported to produce full remission in 68% and partial recovery in 22% ($N = 143$). However, one double-blind, non placebo controlled study with only 7 subjects did not report pimozide to be beneficial. Recent reports suggest that with the introduction of the SGAs and possible concerns about cardiac side effects, pimozide use has dropped considerably. More patients are being treated with clozapine or antipsychotic combinations (Manschreck 2006). There are reports of treatment with FGA agents with variable success in small number of subjects. SSRIs have been used and reported to be helpful. Pimozide, fluoxetine, and amitriptyline were used in a study with pimozide showing good response. The SGAs showed comparable efficacy to other treatments.. In those individuals who do not comply with treatment or are likely to be at risk of hurting themselves or others due to their delusions, long acting antipsychotics administered intramuscularly would be helpful.

## Psychosocial Treatment

As mentioned earlier, developing a therapeutic relationship is very important and yet significantly difficult, and requires frank and supportive attitude. Supportive therapy is very helpful in dealing with emotions of anxiety and dysphoria generated because of delusional thinking. Cognitive therapy, when accepted and implemented, is helpful. Confrontation of the delusional thinking usually does not work and can further alienate the patient.

### Clinical Vignette 6

***Delusional Disorder—Somatic Type***

Ms. K is a 32-year-old woman who presented to a dermatology clinic with complaints of "bugs" infecting her fingers, lips, scalp, ears, nose, face, and genitals for the last 3 months. She believed that her husband was the source of infection as she had observed him frequently scratching his scalp. However, she stated her husband feels that "it (her condition) is all in her head." She noticed others scratching while around her and believed that they had become infested by her presence. She brought multiple samples of the "bugs" in plastic bags.

On physical examination, there were multiple superficial excoriations over her nose, forehead, ears, scalp, jaw, and upper trunk. The dermatologist believed that the patient was suffering from psychogenic parasitosis and reassured Ms. K that her symptoms would be taken seriously and that an entomologist would evaluate her samples. She was prescribed fluocinolone for scalp inflammation, and asked to return to clinic with her husband in 1 week.

Ms. K returned to the clinic with her husband, frantically claiming that "things were falling off" of her and that she always saw "red dots" at the outset of her symptoms. She denied pruritus, scratching, or seeing "bugs." Her speech was pressured and she was crying. She was upset at her husband for blaming her symptoms on "nerves." On examination, she demonstrated numerous, crusted bloody excoriations, and her pubis was shaved smooth. Her husband was also examined, and no suspicious lesions were noted. The dermatologist spoke to the husband and patient both alone and together. Her husband had excellent insight. Ms. K was reassured and asked to await the results from the entomologist. The entomologist's report contained skin debris and some incidental insect parts (Cullicoides species, which are not associated with dermatoses). Ms. K continued to worsen over the next several clinic visits, despite reassurance by the dermatologist. She also continued to bring in numerous samples and frequently stated that she believed that her husband is the "root of the problem." She was delusional and displayed poor insight. She refused psychiatric help but agreed to 50 mg intramuscular haloperidol decanoate. The dermatologist was hoping to control symptoms enough to allow psychiatric referral. She improved remarkably following injection and her skin was nearly clear. She did not feel that she was causing others to scratch around her. She also stopped bringing in samples of bugs. Though she demonstrated limited insight, she still felt that her illness was not due to psychiatric issues. She questioned taking medications when "all this started with my husband." Pimozide was started at 2 mg/day with a plan to gradually increase the dose upwards. Ms. K continued to show improvement in her symptoms but her insight had not improved much so her dose was doubled to 4 mg/day. Six weeks after starting pimozide, Ms. K's progress halted. She continued to state that her husband was scratching her scalp, which she believed to be the root of the problem. The dermatologist emphasized the success of haloperidol decanoate therapy and recommended it once more, but the patient refused it. Ms. K was instructed to increase the dose of pimozide to 6 mg/day. Numerous phone conversations over the next several weeks revealed that she was probably noncompliant with the prescribed oral medications. She reported a different dosage each conversation and was unable to give the name of her pharmacy on several occasions, nor could she describe the pills. Her delusions and complaints about her husband persisted. Meanwhile, she had seen another physician who treated her with lindane for pediculosis. She finally agreed to visit the psychosomatic clinic. She was seen by a psychiatrist and was diagnosed to have delusional disorder, somatic type. There were no symptoms of mania or depression noted. The anxiety and sleep disturbances associated with delusional thinking were treated with clonazepam. Four days later, Ms. K paged the dermatologist stating that she was much worse and needed to be seen immediately. She presented to the clinic with her hair matted down with calamine lotion, numerous superficial erosions, and various exogenous particles in her hair, but no parasites or nits were seen. There were serious concerns about her compliance. She refused the haloperidol decanoate injections due to side effects but agreed to visit the psychosomatic clinic again. She became quite erratic with her dermatology and psychosomatic clinic visits. She continued to have delusional thinking and other symptoms. After missing several clinic visits and with possible erratic compliance, she presented to the psychosomatic clinic with symptoms of anxiety and depression. As she was refusing haloperidol and was noncompliant with pimozide, she was switched to olanzapine 5 mg/day. During subsequent visits her husband reported past history of bouts of depression with neurovegetative symptoms possibly meeting the diagnosis of major depressive disorder with psychotic features. Her dose of olanzapine was meanwhile increased to 20 mg/day. She was started on an antidepressant the dose of which was gradually increased. Laboratory examinations for thyroid function tests, folate, and other chemistries were within normal range.

Unfortunately, Ms. K did not comply with medication recommendations, continued to seek the source of infestation, and resisted recommendations for either intramuscular (IM) medications or an inpatient admission. She was lost to follow-up. The last call for the patient came from her veterinarian. The patient had repeatedly brought her dog into the veterinarian's office, requesting evaluation of her pet for parasites, though the dog was not infested. The veterinarian was encouraged to refer the patient back to the psychosomatics clinic, but no further visits ensued.

*Source*: Adapted with permission from Slaughter et al. (1998). Copyright 1998 American Psychiatric Publishing.

### Clinical Vignette 7

***Delusional Disorder—Jealous Type***

A 35-year-old male janitor was admitted to a psychiatric hospital after violating a restraining order brought by his wife. The patient firmly believed (contrary to the facts in this case) that his wife was having an affair with someone for the last few years. He reported that he had often

*(continues)*

Clinical Vignette 7 *continued*

noticed his wife speaking softly and pleasantly with someone on the phone and would stop the conversation as soon as he entered the house. His attempts to trace the call were futile, further confirming his suspicion. He had noticed that his side of the bed was often ruffled as if someone had slept on it. He had also noticed that the bedroom window was on occasion open even when he had made sure that it was locked when he left for his night shift. His wife reported that she had caught him sniffing her undergarments and looking for evidence of recent sexual activity. When his wife confronted him, he angrily accused her of infidelity. Her attempts to reassure him by explaining the alleged evidence of infidelity made him even more suspicious. He started having his house under surveillance to detect the alleged lover. When no unusual activity was noticed, he concluded that she had become cautious.

He surprised her on a few occasions by coming home earlier than anticipated, and her not opening the door immediately resulted in further accusations and verbal arguments. He also went to her workplace unannounced. When his wife told him that he was losing his mind and reading too much into benign actions and events, he became infuriated and they had their first physical altercation resulting in police intervention. She refused to press charges the first time but when she was assaulted again, she brought a restraining order against him. She moved in with her mother. He started spying on her activities at her mother's place and confronted her at her work place with allegations of having an affair with someone there. She called the police when he assumed a threatening posture toward her resulting in his arrest and subsequent admission to a hospital by court order. He vehemently denied having any psychiatric illness, became very angry with his wife blaming her for his plight, and remained preoccupied with his wife's alleged infidelity. The psychiatrist interviewed the patient and his wife separately and then spoke with other family members. A diagnosis of delusional disorder, jealous type was reached and he was started on an atypical antipsychotic medication after much discussion about the alternatives to refusal of treatment. The patient's agitation and the intensity of the delusional thinking decreased but he remained convinced that his wife was having an affair with someone. The patient lacked insight into his illness. His wife started divorce proceedings, which was yet another proof of her scheme to get him out of the way so that she can marry her alleged lover. Following treatment with an antipsychotic agent and individual therapy, though
the patient still believed that his wife did have an affair,
he did not have thoughts of pursuing or hurting her.

## Shared Psychotic Disorder

### Diagnosis

Shared psychotic disorder is a rare disorder, which is also referred to as *shared paranoid disorder, induced psychotic disorder, folie a deux*, and *double insanity*. Jules Baillarger, in 1860, first described the syndrome and called it *folie a communiquee*, while Lasegue and Falret, in 1877, first described *folie a deux*. In this disorder, the transfer of delusions takes place from one person to another. Both persons are closely associated for a long time and typically live together in relative social isolation. In its more common form, *folie imposee*, the individual who first has the delusion is often chronically ill and typically is the influential member of the close relationship with another individual, who is more suggestible and who develops the delusion too. The second individual is frequently less intelligent, more gullible, more passive, or more lacking in self-esteem than the primary case. If the two people involved are separated, the second individual may abandon the delusion. However, this is not seen consistently. Other forms of shared psychotic disorder reported are *folie simultanee*, where similar delusional systems develop independently in two closely associated people. Occasionally more than two individuals are involved (e.g. *folie a trois*, *quatre*, *cinq*; also *folie a famille*) but such cases are very rare. The most common dyadic relationships who develop this disorder are sister–sister, husband–wife, and mother–child. Almost all cases involve members of a single family.

An important feature in the diagnosis is that the person with shared psychotic disorder does not have a preexisting psychotic disorder. The delusions arise in the context of a close relationship with a person who suffers from delusional thinking and resolve on separation from that person.

### Clinical Features

The key symptom of shared psychosis is the unquestioning acceptance of another person's delusions. The delusions themselves are often in the realm of possibility and usually not as bizarre as those seen in patients with schizophrenia. The content of the delusion is often persecutory or hypochondriacal. Symptoms of a coexisting personality disorder may be present, but signs and symptoms that meet criteria for schizophrenia, mood disorders, and delusional disorder are absent. The patient may have ideation about suicide or pacts about homicide; clinicians must elicit this information during the interview.

### Epidemiology

More than 95% of all cases of shared psychotic disorder involve two members of the same family. About a third of the cases involve two sisters, another one-third involve husband and wife or a mother and her child. The dominant person is usually affected by schizophrenia or a similar psychotic disorder. In 25% of all cases, the submissive person is usually affected with physical disabilities such as deafness, cerebrovascular diseases, or other disability that increases the submissive person's dependence on the dominant person. This condition is more common in people from low socioeconomic groups and in women.

### Course and Prognosis

Though separation of submissive person from the dominant person should resolve the psychosis, this probably occurs only in 10 to 40% of the cases. Unfortunately, when these individuals are discharged from hospital, they usually move back together.

### Differential Diagnosis

Malingering, factitious disorder with predominantly psychological sign and symptoms, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder must be considered.

### Etiology

There are some data that suggest that people suffering from shared psychotic disorder may have a family history

of schizophrenia. The dominant person suffering from this illness often has schizophrenia or a related psychotic illness. The dominant person is usually older, more intelligent, better educated, and has stronger personality traits than the submissive person, who is usually dependent on the dominant person. The affected individuals usually live together or have an extremely close personal relationship, associated with shared life experiences, common needs and hopes, and often, a deep emotional rapport with each other. The relationship between the people involved is usually somewhat or completely isolated from external societal cultural inputs. The submissive person may be predisposed to a mental disorder and may have a history of a personality disorder with dependent or suggestible qualities as well as a history of depression, suspiciousness, and social isolation. The dominant person's psychotic symptoms may develop in the submissive person through the process of identification. By adopting the psychotic symptoms of the dominant person, the submissive person gains acceptance by the other.

## Treatment

The initial step in treatment is to separate the affected person from the source of the delusions, the dominant individual. Antipsychotic agents may be used if the symptoms have not abated in a week after separation. Psychotherapy with the nondelusional members of the patient's family should be undertaken, and psychotherapy with both the patient and the person sharing the delusion may be indicated later in the course of treatment. To prevent redevelopment of the syndrome the family may need family therapy and social support to modify the family dynamics and to prevent redevelopment of the syndrome. Steps to decrease the social isolation may also help prevent the syndrome from reemerging.

Clinical Vignette 8

***Folie a Quatre***

Four members of a large Nigerian family presented with shared persecutory and religious delusions. The first to exhibit symptoms and therefore the presumptive inducer was a 25-year-old midwife (LM) with a 5-year history of persecutory delusions exacerbated in the year before presentation when her family refused to allow her marriage plans. She had become increasingly suspicious and accused others of being witches threatening her family. Attempts to help her with herbal medicines prescribed by a traditional healer, confirmed her delusions of being poisoned. She ate and slept little, and become socially isolated. She also became increasingly argumentative, verbally and physically aggressive, and preoccupied with religious observances. She was well dressed and covered her head with a white veil to signify purity. She held a Bible in her hand and gave "greeting in Jesus' name." Although calm and coherent, she frowned throughout the interview. She accused her relatives of planning with evil forces to eliminate her. She admitted seeing visions of her brother being anointed by the Holy Spirit.

Her brother (DM), older sister (TM) and 15-year-old niece (NM, TM's daughter) all gathered with other members of the family to pray for her. These three were subsequently noticed to be expressing the same persecutory and religious ideation. Their mother and other family members were extremely concerned to find appropriate treatment for the four. DM had worked intermittently as a schoolteacher and his presentation was very similar to LM. He also believed that his mother and older brother were witches who had collaborated with his wife to kill him by taking him to the traditional healer. He was argumentative, irrational but coherent, and expressed the belief that forces were pulling blood from his legs and other relatives were plotting to kill him. Both TM and NM expressed the same delusional thinking that others were planning to kill them all.

All four were admitted to their local psychiatric hospital but DM and LM failed to improve and were transferred to another hospital. Following their transfer, TM and NM made rapid recoveries and were discharged. DM and LM required higher doses of conventional antipsychotic agents and were commenced on depot injections. Attempts were made to separate LM from her brother. Despite this, they continued to meet and prayed incessantly together. They continued to express their shared persecutory beliefs, but after about 3 weeks of treatment their mental state had begun to improve and the pair spent less time together. After 8 weeks both were well enough for discharge and outpatient follow-up on depot medication. LM was subsequently able to return to work and DM enrolled for a course in a theological college.

*Source*: Adapted with permission from Mela et al. (1997).
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Clinical Vignette 9

***Folie Simultanee (Shared Psychotic Disorder)***

Twin A, a 30-year-old white female who had no previous psychiatric problems, was admitted to a psychiatric ward following a serious suicide attempt. Six months before admission, twin A and her husband found a sperm-filled condom in their bathroom after returning from an evening out. They were concerned that their babysitter had sexually abused their children, although there was no visible evidence.

Shortly thereafter, twin B, who lived in a neighboring city, sent twin A information on ritualistic sexual abuse by satanic cults. The twins then began meeting together and reading literature on satanic worship and ritualistic sexual abuse by satanic cults. Over time, the twins gradually reduced their social activities except for a few specific meetings. They attended support groups for parents of ritualistically sexually abused children and were convinced that increasingly more people were involved in satanic cults. Within the month before admission, they believed that the satanic cult involved their husbands, family members, neighborhood, church, and the police department. They believed that their children were forced to drink urine and to witness child sacrifice. They also believed that the children were ongoing victims of ritualistic sexual abuse and torture by means of having their feet dipped in hot water.

Several days before admission, the twins met together to view a four-part television series on satanic worship. This resulted in further "hysteria" between the two and the creation of a suicide pact. The evening prior to admission, twin B was brought for evaluation at the hospital. When twin A learned that twin B was at the hospital, she believed that the satanists had abducted her. This prompted a suicide attempt with her partially severing her carotid artery. She experienced a massive hemorrhage, requiring 10 units of packed red blood cells before surgical repair.

*(continues)*

Clinical Vignette 9 *continued*

Following stabilization, twin A was transferred to the inpatient ward and information was obtained through interviews with the twins and multiple family members. There was no evidence of mood disorders, substance abuse problems, or hallucinations in either twin. Both twins maintained the same delusional system at approximately the same intensity without one being dominant.

*Source*: Adapted with permission from White (1995). Copyright 1995 Canadian Psychiatric Association.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

The ICD-10 and DSM-IV-TR criteria sets for schizophrenia are similar in many important ways although not identical. The ICD-10 Diagnostic Criteria for Research provide two ways to satisfy the criteria for schizophrenia: having one Schneiderian first-rank symptom or having at least two of the other characteristic symptoms (hallucinations accompanied by delusions, thought disorder, catatonic symptoms, and negative symptoms). In contrast to DSM-IV-TR which requires 6 months of symptoms (including prodromal, active, and residual phases), the ICD-10 definition of schizophrenia requires only a 1-month duration thereby encompassing the DSM-IV-TR diagnostic categories of both schizophrenia and schizophreniform disorder. Thus, cases of DSM-IV-TR schizophreniform disorder are diagnosed in ICD-10 as schizophrenia.

The DSM-IV-TR and ICD-10 definitions of schizoaffective disorder differ with regard to the relationship of the schizoaffective disorder category with the category mood disorder with psychotic features. In DSM-IV-TR, the differentiation depends on the temporal relationship between the mood and psychotic symptoms (i.e., mood disorder with psychotic features is diagnosed whenever the psychotic symptoms occur only in the presence of a mood episode, regardless of the characteristics of the psychotic symptoms). In contrast, the ICD-10 definition of schizoaffective disorder is much broader. It includes situations in which certain specified psychotic symptoms (i.e., thought echo, insertion, withdrawal, or broadcasting; delusions of control or passivity; voices giving a running commentary; disorganized speech, catatonic behavior) occur even if they are confined to a mood episode. Therefore, many cases of DSM-IV-TR mood disorder with mood-incongruent psychotic features would be considered to be schizoaffective disorder in ICD-10. Furthermore, the ICD-10 definition suggests that there should be an "approximate balance between the number, severity, and duration of the schizophrenic and affective symptoms." For delusional disorder, the ICD-10 Diagnostic Criteria for Research specify a minimum 3-month duration in contrast to the 1-month minimum duration in DSM-IV-TR.

In contrast to the single DSM-IV-TR category brief psychotic disorder, ICD-10 has a much more complex way of handling brief psychotic disorders. It includes criteria sets for four specific brief psychotic disorders that differ based on types of symptoms (i.e., with or without symptoms of schizophrenia) and course (i.e., whether they change rapidly or not). Furthermore, the maximum duration of these brief psychotic episodes varies depending on the type of symptoms (i.e., 1 month for schizophrenia-like symptoms and 3 months for predominantly delusional). In contrast, DSM-IV-TR has a single criteria set and a maximum 1-month duration.

Finally, the ICD-10 and DSM-IV-TR definitions of shared psychotic disorder are almost identical.

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CHAPTER

# 66 Mood Disorders: Depression

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Major Depressive Episode
Major Depressive Disorder, Single Episode
Major Depressive Disorder, Recurrent

## Diagnosis

### Definition and Diagnostic Features

Depression conceptualizes a variety of psychic and somatic syndromes, and the diagnosis is derived from diligent clinical observation. Despite intensive biologically oriented psychiatric research the etiology of depressive disorders is still far from being fully understood, and a multifactorial genesis is assumed. Besides psychological and social factors, biological variables apparently play a prominent role, but to date there is not a single biological or genetic test for specifically establishing the diagnosis of depression.

Depression as a term in popular use is mostly considered to be synonymous with low mood or grief. Depression as a mental (and medical) disorder, however, is different, and, besides low mood, is characterized by a variety of additional symptoms. Different depressive syndromes are classified within diagnostic entities using operationalized diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000a) or the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) (World Health Organization 1992). According to DSM-IV-TR, five of nine symptoms, characteristic of depression, have to be present for a diagnosis of an episode of a major depressive disorder (MDD), see the DSM-IV criteria sets below. This term is often used synonymously with unipolar depression to distinguish it from a major depressive episode as part of bipolar disorder.

The first DSM-IV-TR core symptom is depressed mood during most of the day. This can be expressed by sadness, but may also be expressed as a feeling of emptiness or, in children or adolescents, as irritable mood. This draws a clear distinction between depression and grief or bereavement (characterized in DSM-IV-TR V62.82). As with the other core symptoms, this symptom counts toward the diagnosis of depression if it is indicated by patient's report or observation. The other psychological core symptoms are markedly diminished interest or pleasure in all or almost all activities, fatigue or loss of energy every day, and disorders of thought and thinking (both the formal aspects of thinking and the ability to concentrate and make decisions) as well as the content which is often characterized by feelings of worthlessness or inappropriate guilt, perhaps combined with hopelessness and recurrent suicidal thoughts. DSM-IV-TR also mentions three somatic or behavioral core symptoms: significant weight loss or decrease in appetite, insomnia or hyposomnia, and psychomotor agitation or retardation.

Both psychological and somatical consequences of MDD have to be taken into consideration when making a diagnosis and formulating a treatment plan. The diagnosis is not always obvious; many patients do not complain about bad mood but visit their general practitioner because of feeling unwell, poor appetite, feeling tired, or having difficulty concentrating on their work. These patients often undergo extensive somatic diagnostic procedures before depression is detected as the underlying cause.

Even if the depressive syndrome fails to fulfill DSM-IV-TR criteria for MDD, it regularly requires

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DSM-IV-TR Criteria (296.XX)

**Major Depressive Episode**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
4. Insomnia or hyposomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach of guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by bereavement , i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

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treatment. Recent guidelines recommend for minor depression a course of psychotherapy as first line treatment (National Institute for Health and Clinical Excellence 2004), but additional pharmacotherapy may be needed. Minor depression (also named "subthreshold" or "subsyndromal" depression) results often in substantial health care use, and constitutes a profoundly increased risk of developing major depression (Cuijpers et al. 2004). Community studies using DSM-IV-TR criteria for minor depression show point prevalence rates ranging from 5% to 10% (Kessler et al. 1997).

## Assessment

The diagnosis of depression is an observational, clinical diagnosis. Structured interviews, such as the Structured Clinical Interview for DSM-IV-TR Disorders (SCID), may be helpful to secure the diagnosis of an MDD but it is time consuming. The shorter Mini International Neuropsychiatric Interview (MINI) can help to generate reliable diagnoses.

However, almost by definition, these structured interviews which are designed for MDD overlook minor depression. Relying only on a structured interview for MDD and neglecting the overall clinical impression may thus drive the diagnostic procedure in the direction of somatic discomfort. In addition, patients often consult their family practitioner first for somatic complaints, unaware that these are part of a depressive syndrome. As a consequence, these patients are more likely referred (or refer themselves) to general practitioners or specialists in internal medicine rather than to psychiatrists. The majority of depressive patients can be diagnosed and treated by general practitioners. To enable primary care physicians to diagnose these patients correctly, the PRIME-MD Patient Health Questionnaire (PHQ-9) (Nease Jr. and Maloin 2003) or even more simplified screening questions may be used. A primary care physician may be in a better position than a psychiatrist to treat depression as he or she oversees the overall medical condition of the patient which may include other ongoing medical illness with the potential of drug–drug interactions. However, expert consultation should be mandatory when the depressive syndrome does not improve within 8 weeks of initial treatment or is very severe and complicated by suicidality.

After the diagnosis of depression has been secured, the level of symptom severity, functional impairment and the impact on quality of life should be assessed. Interviewing not only the patient but also the relatives is helpful to obtain a full clinical picture at the beginning of treatment. Recent

**DSM-IV-TR Criteria (296.2x)**

**Major Depressive Disorder, Single Episode**

A. Presence of a single Major Depressive Episode.

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

**Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance- or treatment-induced or are due to the direct physiological effects of a general medical condition.

If the full criteria are currently met for a Major Depressive Episode, specify its current clinical status and/or features:

**Mild, Moderate, Severe Without Psychotic Features/ Severe With Psychotic Features**
**Chronic**
**With Catatonic Features**
**With Melancholic Features**
**With Atypical Features**
**With Postpartum Onset**

If the full criteria are not currently met for a Major Depressive Episode, specify the current clinical status of the Major Depressive Disorder or features of the most recent episode:

**In Partial Remission, In Full Remission**
**Chronic**
**With Catatonic Features**
**With Melancholic Features**
**With Atypical Features**
**With Postpartum Onset**

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**DSM-IV-TR Criteria (296.3x)**

**Major Depressive Disorder, Recurrent**

A. Presence of two or more Major Depressive Episodes.

**Note:** To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

**Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance- or treatment-induced or are due to the direct physiological effects of a general medical condition.

If the full criteria are currently met for a Major Depressive Episode, specify its current clinical status and/or features:

**Mild, Moderate, Severe Without Psychotic Features/ Severe With Psychotic Features**
**Chronic**
**With Catatonic Features**
**With Melancholic Features**
**With Atypical Features**
**With Postpartum Onset**

If the full criteria are not currently met for a Major Depressive Episode, specify the current clinical status of the Major Depressive Disorder or features of the most recent episode:

**In Partial Remission, In Full Remission**
**Chronic**
**With Catatonic Features**
**With Melancholic Features**
**With Atypical Features**
**With Postpartum Onset**

*Specify:*

**Longitudinal Course Specifiers (With and Without Interepisode Recovery)**
**With Seasonal Pattern**

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life events causing psychosocial stress should be evaluated and may direct treatment towards early psychotherapeutic intervention. For choosing the appropriate setting of care, the presence of psychotic symptoms and of suicidal thoughts or plans must be assessed from the beginning and at every subsequent visit. Acute suicidality constitutes a medical emergency that calls for immediate and consequent action, and it may become necessary to retain the patient in a hospital setting.

Especially for those patients who do not respond to treatment, the correctness of diagnosis needs to be re-evaluated on a regular basis, and complicating factors identified. For example, treatment response could be confounded by ongoing, comorbid substance abuse, anxiety disorder or underlying personality disorders. In addition, patients and relatives should be carefully questioned for emerging (hypo)manic symptoms as the index episode of bipolar disorder is in the majority of cases a depressive episode. The emergence of (hypo)manic symptoms usually leads to changes in treatment plans, for example, discontinuing antidepressants and switching to mood stabilizer treatment.

## Epidemiology

Depression is probably the most common of psychiatric disorders and is among the most common of major biomedical conditions. MDD ranks high among the main causes of

illness-related disability. For the US, the National Comorbidity Survey found a lifetime prevalence of MDD, as defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) criteria, of 17% (Blazer et al. 1994). Globally, however, epidemiologic studies of depression show considerable variation across and within countries, to a large extent due to the cross-cultural unsuitability of assessment instruments. The International Consortium of Psychiatric Epidemiology interviewed 37,000 adults in 10 countries (in North America, South America, Europe, and Asia) using the WHO Composite International Diagnostic Interview (Kessler et al. 2003). The life time prevalence of depression for adults varied from 3% in Japan to 16.9% in the US, with most countries in the range between 8% and 12% (Andrade et al. 2003). For the US, the mean duration of depressive episodes was 16 weeks and about 90% of the patients were suffering from moderate to severe forms of depression causing marked role impairment (Kessler et al. 2003). Minor depression may be much more frequent: a South American study on the presence of depressive symptoms reported extremely high prevalence rates of up to 72.6% (Rodriguez and Puerta 1997). These numbers indicate not only the potential impact of psychosocial and cultural factors on the manifestation of depression but also the methodological difficulties in generating reliable statistics.

A family history of mood disorder is associated with a younger age at onset of depression (Nierenberg et al. 2007). Age and gender affect both the prevalence and the consequences of depression: women are twice as likely as men to be affected (Kessler 2003). Younger age at onset and female gender are positively correlated with suicidality including suicide attempts. Completed suicide, however, seems to be equally distributed between genders in most countries.

The importance of depression is heightened by the prediction that the prevalence of depressive disorder will increase in the years to come (Sartorius 2001). The WHO estimates that depressive disorders will be the second most frequent cause of disability in industrialized countries by the year 2020. The reasons include demographic factors (e.g., increased life expectancy at all ages), better chances of survival of people with chronic diseases often comorbid with depression, iatrogenic effects (e.g., use of medications likely to increase the rates of depression, e.g., corticosteroids), risks intrinsic to social changes (such as diminished family care and increasing numbers of people living alone) and increasing levels of stress due to growing occupational demands observable in many countries.

## Comorbidity Patterns

Frequently, depression does not stand by itself but occurs as a psychological or biological consequence of a somatic or psychiatric disorder. Here we deal only with the most frequent comorbidity patterns.

### Depressive Disorders with Comorbid Psychiatric Disorders

Comorbidity of depressive disorders with other psychiatric disorders is common and significantly affects treatment outcomes. Greater numbers of concurrent comorbid conditions are associated with increased severity, morbidity, and chronicity of depressive disorders (Rush et al. 2005).

#### *Anxiety Disorders*

A lifetime prevalence of more than 40% for comorbid anxiety disorders, namely panic disorder, phobias, and generalized anxiety disorder, has been reported in patients suffering from depressive disorders (Hasin et al. 2005), but it is not clear whether both diagnostic entities can be separated, or represent a mixed anxiety–depression syndrome. Patients with comorbid MDD and panic disorder show a greater severity of syndromes in comparison to patients suffering from MDD alone (Grunhaus et al. 1994).

Comorbid anxiety disorders may reduce the effectiveness of an antidepressant, as suggested by a small case series of patients treated with divergent tricyclic antidepressants (TCAs), most with imipramine or phenelzine (Grunhaus et al. 1986). Using antidepressants with proven efficacy in both MDD and anxiety disorders, for example, selective serotonin reuptake inhibitors (SSRIs) and some selective serotonin-noradrenalin reuptake inhibitors (SNRIs), together with concomitant specific psychotherapies seems to be a sensible strategy.

#### *Substance Abuse*

Abuse and addiction to alcohol, nicotine, and other drugs are often accompanied by depression, with a lifetime comorbidity of 40%, 30%, and 17%, respectively, in one survey (Hasin et al. 2005). Depressed patients with comorbid substance abuse are more likely to have an earlier age of onset of depression, more depressive symptoms, a greater functional impairment, and a history of more previous suicide attempts than patients with depression alone (Davis et al. 2006). Because pharmacokinetic and pharmacodynamic drug interactions, for example, between phenylpiperidine opioids and SSRIs (Ailawadhi et al. 2007), and the psychosocial consequences of drug abuse both have significant impact on response and recovery rates from depressive disorders, a combined therapeutic approach addressing the depression and any comorbid condition is mandatory. This is especially true for psychotherapeutic and psychosocial approaches, but is also relevant for pharmacotherapy, for example, by choosing antidepressants with lower pharmacological interaction potential, for example most SSRIs, or some selective noradrenalin reuptake inhibitors (NARI) and dual action antidepressants.

#### *Personality Disorders*

At least one-third of depressed patients fulfill the diagnostic criteria of a personality disorder, most commonly obsessive–compulsive (16%), paranoid (10%), and schizoid (7%) personality disorders (Hasin et al. 2005). It has been estimated that 6% of depressed patients also display features of Borderline Personality disorder (BPD) (Depression Guideline Panel 1993). Analyzing psychosocial and biological factors, Gunderson and Phillips (1991) concluded that BPD and depression coexist as independent disorders. For the other personality disorders, there is still uncertainty concerning their interdependency with depression.

Surprisingly, the occurrence of depression can be a positive prognostic factor for the treatment of borderline and antisocial personality disorders (Shea et al. 1992), although a higher risk of self-injury has been reported (Shea et al. 1987). However, antidepressant medication is usually less effective and treatment takes longer in patients with

personality disorders, and responsiveness to psychotherapy is often also low in these patients.

## Depressive Disorders with Comorbid General Medical Conditions

Depressive syndromes are frequently present in people with severe and chronic general medical conditions. Slow-progressing illnesses leading irrevocably to severe incapability show a high percentage of comorbid MDD, for example the prevalence of MDD among patients with age-related macular degeneration is approximately 30% (Casten et al. 2004). General medical conditions or their treatment may also be directly responsible for depressive symptoms (Patten and Barbui 2004). If depression is only mild to moderate, an organic factor is etiologically responsible for the depressive syndrome ("organic depression") and the organic disease can be treated sufficiently, treatment of the medical condition is mostly sufficient (e.g., substitution of thyroid hormones in case of hypothyroidism). However, with severe depression including suicidal ideation, additional symptomatic antidepressant treatment becomes mandatory. The same is true when the organic factor cannot be treated due to other conditions (e.g., discontinuation of immune system suppressors after transplantation). Possible organic causes for depressive syndromes are summarized in Table 66–1.

### *Cardiovascular Disorders*

A variety of studies confirm the interconnection between medical disorders and the risk for developing depressive symptoms either as adjustment disorder or MDD. An exceptionally high comorbidity of depressive symptoms and cardiovascular disease (CVD) has been described (Glassman et al. 2006, Purebl et al. 2006), but depression is rarely diagnosed in patients suffering from CVD in routine clinical settings. Comorbid MDD worsens the outcome of coronary heart disease or a myocardial infarction, especially in treatment-refractory depressed patients (Carney et al. 2004). Depression by itself, especially MDD, enhances cardiovascular mortality independently of other cardiovascular risk factors (Penninx et al. 2001). An important biological predictor of cardiac complications may be disinhibition of Hypothalamic-Pituitary-Adrenal (HPA) axis activity which occurs in the majority of MDD (Lederbogen et al. 1999).

Both a significantly lowered risk of death or myocardial re-infarction in patients taking SSRIs (Taylor et al. 2005) and a failure to lower cardiac risk by antidepressant treatment (Berkman et al. 2003, Shimbo et al. 2005) have been reported. Medications should have a drug–drug interaction risk as low as possible and should not interfere with cardiac conductance, rhythm, or output. Most modern antidepressants, including SSRI, NARI, and dual-action substances fulfill these criteria. In addition, $\Omega_3$ fatty acids have been described as having cardioprotective effects as well as potential antidepressant properties, (Frasure-Smith et al. 2004) and thus may be considered as an additional option in these patients.

### *Endocrinological Disorders and Diabetes Mellitus*

Depression is a risk factor for type II diabetes mellitus and a bidirectional positive association has been assumed (Evans et al. 2005). MDD may impact negatively on therapeutic adherence with a subsequent risk for vascular complications. Vice versa, hypercortisolism during MDD may facilitate the onset of diabetes. Antidepressant treatments show similar effectiveness in diabetic patients, however, some antidepressants and antipsychotics with sedating properties may facilitate weight gain. This may contribute to a metabolic syndrome worsening a preexisting diabetes mellitus or facilitating a switch from a prediabetic syndrome to diabetes (American Diabetes Association 2005).

**Table 66–1 Examples of Organic Factors Possibly Etiologically Responsible for Depressive Disorders***

| Category of Organic Disease | Organic Illness |
|---|---|
| Neurological disorders | • Stroke<br>• Dementia<br>• Epilepsy<br>• Huntington's chorea<br>• Hydrocephalus<br>• CNS infectious diseases<br>• CNS neoplasias<br>• PD<br>• Narcolepsy<br>• Sleep-apnea<br>• Trauma<br>• Wilson's disease |
| Endocrine disorders | • Adrenal disorders (Cushing's disease, Addison's disease)<br>• Hyperaldosteronism<br>• Hyper- or Hypoparathyroidism<br>• Hyper- or Hypothyroidism<br>• Postpartum hormonal changes |
| Other medical disorders | • Neoplasias and paraneoplastic syndromes<br>• Cardiopulmonary diseases<br>• Autoimmune disorders (e.g., lupus erythematodes)<br>• Porphyria<br>• Uremia<br>• Avitaminoses (vitamins B12, C, folate, niacin or thiamin) |
| Pharmacogenic depression | • Analgesics (ibuprofen, indomethacin, opiates, phenacetin)<br>• Antibiotics (streptomycin, sulfonamides, tetracyclines)<br>• Antihypertensives (reserpin, clonidine, digitalis)<br>• Chemotherapeutics (asparaginase, azathioprine, bleomycine, trimethoprime, vincristine)<br>• Hormones (high estrogen oral contraceptives)<br>• Immune system therapy / suppression (corticosteroids, interferons, mycophenolatmofetile, tacrolimus) |

*Evans et al. 2005, Katona 1997, World Psychiatric Association 2006.

### *Renal Disorders*

Having a severe acute or chronic renal disease predisposes to an adjustment disorder with marked depressive syndromes (Kimmel and Peterson 2005) or an MDD. Besides psychotherapeutic support, antidepressant pharmacotherapy may become necessary. Renal failure with consecutive diminished renal clearance may exaggerate the side effects and toxicity of antidepressants, necessitating a dose adjustment.

Half of the standard dose is usually recommended when starting treatment and the use of antidepressants with low potential to interact with other drugs via the cytochrome P-450 system, such as sertraline or citalopram. Frequent evaluation of side effects and blood level monitoring help prevent overdosing. If renal failure progresses and hemoperfusion or hemofiltration becomes necessary, antidepressant plasma levels may fall and dose adjustment may be required.

### *Hepatic Disorders*

Patients suffering from chronic hepatitis experience an enhanced risk for developing depression, especially those receiving interferon treatment. Patients with a history of depression may even require prophylactic antidepressant treatment when starting interferons (Schaefer et al. 2002). Treatment of comorbid depression and hepatic disorders requires specific precautions. Antidepressants rank fifth of drugs causing liver damage (Andrade et al. 2005). TCAs, irreversible inhibitors of monoaminooxidase inhibitor (MAOI) A and B and nefazodone seem to have higher hepatotoxicity than other agents, such as SSRIs (Lucena et al. 2003). SSRIs or other modern antidepressants still require a dose of adaptation in patients with hepatic disorders owing to reduced clearance of the drugs and their metabolites and, therefore, prolonged elimination times.

### *Infectious Disorders*

Viral or bacterial infections are often accompanied by psychiatric syndromes, frequently depression, which may require specific treatment. Infections of the nervous system, in particular, such as Lyme disease (Fallon and Nields 1994) or neurosyphilis (neurolues) (Pavlovic and Milovic 1999) may provoke psychiatric disorders including MDD. Infection with the human immune deficiency virus (HIV) is highly associated with depression and suicidal behavior (Jin et al. 2006, Porche and Willis 2006) and HIV risk behaviors endangering others occur more frequently with comorbid depression (Hutton et al. 2004).

Hepatitis C-infected patients are also more likely to have psychiatric comorbidities such as depressive disorders (Butt et al. 2006). Finally, treatments directed against infections such as interferons or antibiotics may increase the risk of developing depressive symptoms.

### *Neurological Disorders*

Depression is a relatively common psychiatric comorbidity of most neurological disorders, with prevalence rates ranging between 20% and 50% among patients with epilepsy, stroke, dementia, Parkinson's disease (PD), and multiple sclerosis (Kanner 2005b). In addition, some treatments of neurological disorders (e.g., corticosteroids) enhance the risk for depression as a treatment-related adverse event. Antidepressant pharmacotherapy becomes mandatory in most cases of medium to severe depression accompanying a neurological disorder, but may interfere with the underlying condition, for example, the TCA maprotililine, where a high risk of seizures has been described.

**Epilepsy** A bidirectional relationship between epilepsy and depression has been delineated (Kanner 2005a). For example, after temporal lobectomies in treatment-resistant epilepsy, patients often experience postsurgical depression and antidepressant pharmacotherapy may become necessary. On the other hand, Spencer et al. (2003) reported relief of depression after respective surgical treatment of epilepsy.

Because even low doses of antidepressants may trigger seizures in patients suffering from epilepsy, starting with the lowest efficacious doses, especially in the case of TCAs, is recommended. Fluoxetine and fluvoxamine exhibit the lowest risk for provoking seizures (Pisani et al. 1999). However, an interaction, especially with carbamazepine, may occur and therefore these combinations should be used cautiously, and be accompanied by monitoring for adverse events and carbamazepine serum levels.

**Stroke and Dementia** According to a large Danish registry study, severe depression is associated with cerebrovascular disorders as an independent risk factor ( Nilsson and Kessing et al. 2004). Conversely, after a stroke, patients often show depressed mood requiring treatment. In placebo-controlled studies, SSRI and NARI have confirmed efficacy in poststroke depression (Rickards 2005). SSRI or TCA treatment during the first 6 months after a stroke significantly increased survival both in depressed and, interestingly, also nondepressed patients (Jorge et al. 2003). Functional recovery and improvement of executive functioning following stroke also seem to be linked to antidepressant treatment (Narushima et al. 2007).

Prophylactic efficacy in preventing poststroke depression has been described particularly for the noradrenergic and selective serotonergic antidepressant (NaSSA) mirtazapine (Ween 2005).

Symptoms of depression in Alzheimer's disease and other forms of dementia are frequent, but virtually indistinguishable from somatic apathy, loss of drive and affective disturbances. In addition, depressive symptoms seem to be independent risk factors for the later development of Alzheimer's (Ownby et al. 2006) and a history of depression seems to be associated with a more rapid cognitive decline in patients with Alzheimer's and pronounced neuropathological changes in the hippocampus (Rapp et al. 2006).

When initiating antidepressants, SSRI, NARI, SNRI, and NaSSA seem to be more favorable than TCA due to their relative lack of anticholinergic side effects.

**PD** A high prevalence of depression in PD ranging from 20% to 40% (Lieberman 2006) has been described. Depression may frequently precede motor symptoms and the subsequent diagnosis of PD (Schuurman et al. 2002). No controlled studies have been published, but both SSRI and SNRI seems to be well tolerated and efficacious in most cases (Menza et al. 2004). A moderate association of SSRI use and extrapyramidal motor side effects in susceptible patients has been reported (Schillevoort et al. 2002), and an interaction between serotonergic and dopaminergic pathways has been assumed (Lambert et al. 1998). Using the MAO-B inhibitor selegiline (see Section, "MAOI") both PD symptoms and depression may improve. Although the anticholinergic effects of TCA may be beneficial in PD, other frequent somatic disorders such as concomitant heart disease, prostatic enlargement, or acute angle-closure glaucoma limit the usefulness of TCAs in this patient group (Cummings and Masterman 1999).

**Encephalitis Disseminata/Multiple Sclerosis** In addition to signs of behavioral disinhibition such as pathological laughing and crying, an association between multiple sclerosis and depression has been reported ( Patten and Metz 1997). Treatment with corticosteroids may additionally contribute to the emergence of a depressive syndrome, and at least in severe cases antidepressant pharmacotherapy may be needed.

**Migraine** Depression is one of the most frequent comorbid disorders in chronic migraine (Mercante et al. 2005). Vice versa, comorbid migraine has a devastating effect on the quality of life of depressed patients (Hung et al. 2006). When migraine is associated with a depressive disorder, antidepressant pharmacotherapy may not only ameliorate depressive symptoms but also prevent migraine attacks. Both TCA (amitriptyline) and SSRI (fluoxetine) have shown effectiveness in preventing migraine attacks using therapeutic antidepressant dosages (Campo-Arias 2004).

When using triptans for migraine treatment, one should be aware of a theoretically enhanced risk of a serotonin syndrome with concomitant use of SSRI, MAOI, or lithium. However, the reported rate of serotonin syndromes is very low; thus, the cautious use of triptans together with SSRI or lithium seems to be acceptable. MAOI, however, should be clearly avoided (Gardner and Lynd 1998).

### *Neoplasias and Paraneoplastic Syndromes*

Depression is frequent in patients suffering from cancer; rates of 19% for depressive symptoms and 8% for MDD have been reported (Wedding et al. 2007). In addition, most chemotherapeutics used in the treatment of cancer may provoke depression.

A comprehensive treatment plan should include all available pharmaco- and psychotherapeutic options and lead to a substantial improvement in quality of life (Miovic and Block 2007). Medications with low toxicity and interaction potential, for example, citalopram, sertraline, or venlafaxine may be advantageous considering other ongoing chemotherapies and potential liver and renal damage.

## Course and Subgroups

The average age of onset of depression is between 20 and 30 years (Ebmeier et al. 2006). A second peak of the age distribution is observed in the elderly. The course of the disorder may be restricted to one episode during one's lifetime, but in the majority of cases depression is a highly recurrent illness with an average of 8 lifetime episodes (Angst et al. 1995). However, approximately 20–25% of MDD patients experience a chronic, unremitting course and thus constitute a major challenge for treatment (Mueller and Leon 1996).

With the exception of recurrent brief depressive episodes as singled out in the ICD 10 (and included in the research appendix in DSM-IV-TR), the minimum duration threshold for an episode is at least 2 weeks. Shorter durations qualify for minor depression. The differences between MDD and minor depression may not always be very helpful for clinical decision making since it has been shown that minor depression can itself cause significant impairment in some individuals (Cuijpers et al. 2004)

### Severity of the Disease

Depression can be divided into mild, moderate, or severe. Besides clinical judgment and the diagnostic criteria according to DSM-IV-TR or ICD-10 or the Clinical Global Impression scale (CGI-S, Item I, severity of disease) (National Institute of Mental Health 1976), severity can be classified according to thresholds set using depression rating scales such as the Hamilton rating scale for depression (Hamilton 1960) or the Montgomery-Åsberg rating scale for depression (Montgomery et al. 1979).

This subdivision according to severity is of clinical importance because some guidelines recommend that mild depressive syndromes can be treated with psychotherapy only (National Institute for Health and Clinical Excellence 2004). This will change if there is a history of moderate to severe recurrent depression. In this instance, antidepressants will become a first line treatment in adults, alone or in combination with cognitive behavioral therapy (CBT) (Anderson et al. 2008). In moderate depression, most depressed patients do require the addition of antidepressant medication. In mild to moderate, but not in severe, depression there is a distinct probability of response using phytotherapeutics such as St. Johns wort (Kasper 2001) or benzodiazepines without antidepressants (Laakmann et al. 1996), even if this option is not recommended due to the inherent abuse potential. For severe depression, ECT, TCA, and dual-action substances such as venlafaxine, duloxetine, or mirtazapine may be especially advantageous.

### *Suicidality*

About two-thirds of people who commit suicide suffer from depression. Perhaps the most accurate prospective long-term, large cohort study on suicide risk in affective disorders was conducted by Angst et al. who followed up 406 patients with unipolar depression or bipolar disorder from 1963 to 2003 (Angst et al. 2005). By 2003, 11.1% of these patients had committed suicide. This underlines the prominent role of early diagnosis and treatment of depression for suicide prevention.

Dealing with suicidality is probably the greatest challenge in the treatment of depression, both for the psychiatrist and the patient (and, of course, the family). The topic of suicidal ideation needs to be addressed at every contact with severely depressed patients, and careful and sensible questioning is needed. Assessment of suicidality needs both experience and empathy, but proven predictors of an elevated suicide risk that may help guide decisions are severity of depression, history of suicide attempts, suicidal ideation, hopelessness, unemployment, comorbid psychotic disorders, substance abuse, personality disorder, a family history of mental disorders, male gender, and living single due to being widowed or divorced (Brown et al. 2000, Moscicki 1999). Suicide events are most common immediately before treatment initiation and during the interval until treatment becomes effective; during these early phases, doctors should plan frequent follow-up visits and also consider a possible supporting role for family members and caregivers. The short-term use of benzodiazepines, for example, lorazepam, to alleviate mood and lower possible restlessness and agitation, may be useful. In addition, doctors should give patients a realistic view about the duration until onset of improvement; overoptimistic expectations of patients and doctors may result in disappointment and consequently hopelessness and suicidality.

Over the past two decades, there has been controversy as to whether antidepressant treatment may put patients at

an increased risk of suicide, with conflicting claims being made, especially regarding SSRIs. Antidepressants may decrease suicide rates on a population basis ( Ludwig and Marcotte 2005), but at the same time they may increase suicidality (or even suicide events) in some individuals early in treatment (Healy and Whitaker 2003). As recently reviewed by Hall and Lucke (2006) and Möller (2006a, b), there is some supportive evidence for both views (see Section, "Treatment-Emerging Suicide and Suicidality").

## Depression with Psychotic Features

Psychotic features of depression such as hallucinations or delusions, for example, delusional hypochondria, feelings of guilt or nihilistic thoughts, are predominantly mood congruent, but may rarely be incongruent with the depressed mood. Psychotic symptoms are in most cases an indicator of the particular severity of depression, including suicide risk. In patients suffering from MDD with psychotic features, a combination of an antidepressant with an antipsychotic medication is usually recommended (Coryell 1996). However, this may not be best for all patients, for example, in elderly patients, the addition of perphenazine to the TCA nortriptyline did not improve efficacy of the treatment in comparison to the TCA monotherapy (Mulsant et al. 2001). ECT has also been recommended as a possible first line treatment in psychotic depression (American Psychiatric Association Committee on Electroconvulsive Therapy 2001).

### *Other Clinical Features with Possible Impact on the Course and Treatment Outcome*

**Catatonic Features** Severe psychomotor retardation, stupor, immobility, and, in contrast, severe agitation (sometimes labeled as catatonic features), can be observed in depressed patients (Taylor and Fink 2003). In routine clinical use, sedating antidepressants or combinations of nonsedating antidepressants with sedatives are used in agitated patients, whereas activating substances such as SSRIs or NARI are used in patients with predominant psychomotor inhibition. ECT may also have an excellent effect in these cases (Rohland et al. 1993).

**Melancholic Features** According to DSM-IV-TR, melancholia is characterized by a loss of the ability to feel pleasure and a variety of somatic symptoms and psychomotor alterations. Therapeutic consequences of melancholic features are similar to those for severe depression. Patients are frequently responsive to augmentative strategies, such as the combination with lithium or sleep deprivation.

**Atypical Features** There is no clear agreement about the features that should characterize atypical depression (Fountoulakis et al. 1999), for example, in French-speaking countries, the term "atypical" depression is used for a group of patients with psychotic features. According to DSM-IV-TR, atypical depression is characterized by the presence of at least two of the following criteria: increase in appetite and weight gain, hypersomnia, leaden paralysis, and long-standing pattern of interpersonal rejection sensitivity. The Inventory of Depressive Symptomatology-Clinician Rating (IDS-C30) is suitable for the diagnosis of atypical depression. Patients with atypical depression are more likely to have an earlier age at onset, a greater comorbidity with anxiety symptoms, and greater symptom severity compared with typical depression (Novick et al. 2005). Empirical data favor MAOI and SSRI as first-line treatment options (Henkel et al. 2006).

**Seasonal Pattern** Seasonal affective disorder (SAD), usually during autumn or winter often develops into bipolar disorder later and atypical symptoms as characterized in DSM-IV-TR may occur more frequently.

The strongest evidence for efficacy in SAD is for the SSRI citalopram. There is also preliminary evidence that citalopram prevents relapse while bupropion and CBT prevent recurrence the following season. Bright light therapy (phototherapy) can be used as an early augmentation strategy (see Section, "Nonpharmacological Treatment Strategies")

### *Depressive Syndromes in Pain Conditions*

Depressive syndromes and chronic pain are frequent comorbid conditions. Approximately 70% of patients with major depression present with physical complaints (Fava 2002, Simon et al. 1999). Somatization disorders, fibromyalgia, and similar conditions with predominant pain are often accompanied by depressed mood. In neuropathic pain accompanied by depression, antidepressants with a mixed serotonergic and noradrenergic mode of action such as the TCA amitriptyline used to be the treatment of choice. More recently, newer antidepressants, especially NARI, NaSSA, and SNRIs, and to a lesser extent SSRI, have shown efficacy in the treatment of pain conditions with and without comorbid depression (Jann and Slade 2007). Taken together, antidepressants with both serotonergic and noradrenergic properties appear to be particularly effective in the treatment of pain and painful physical symptoms, and antidepressants are now considered as an essential medication in therapeutic regimes for pain control.

## Adjustment Disorder with Depressed Mood/ Mixed Anxiety and Depressed Mood

In mild to moderate adjustment disorders (DSM-IV-TR V 309), psychotherapy alone may be sufficient, whereas with persisting and severe depressive symptoms additional pharmacotherapy may be needed. Although controlled efficacy trials of antidepressants in adjustment disorders are rare, both clinical experience and retrospective studies (Hameed et al. 2005) suggest no difference in response rates to treatment between depression and adjustment disorder with depressive symptoms.

## Dysthymic Disorder and MDD in Combination with Dysthymic Disorder

Diagnostic criteria for dysthymia and depressive disorders differ as far as the severity and duration of the symptoms are concerned. Dysthymic disorder is characterized by a period of at least 2 years with depressed mood, but having fewer than the five core symptoms of depression demanded by DSM-IV-TR for the diagnosis of MDD. In brief, dysthymic disorder is characterized by a chronic depressive syndrome of lower intensity of symptoms than in major depression, although it produces very similar levels of disability and loss of quality of life. A superimposing major depressive episode can occur in patients suffering from dysthymic disorder, named "double depression." The differential diagnosis of both disorders is difficult when dysthymic disorder

follows a depressive episode, because the symptoms of the former are then indistinguishable from MDD with incomplete remission. Only after achieving full remission for at least 6 months, can any subsequent dysthymic symptoms be diagnosed with some confidence as dysthymic disorder.

The acute efficacy of antidepressants in dysthymic disorder is comparable to MDD, although the probability of complete recovery is less (Judd et al. 1998). Early implementation of psychotherapy is therefore recommended.

### Recurrent Brief Depression[1]

Recurrent brief depression is characterized by at least monthly depressive episodes of short duration lasting only a few days (Pezawas et al. 2005). Except for the duration, all other criteria for MDD according to DSM-IV-TR are fulfilled, and cooccurrence of MDD and recurrent brief depression is relatively common. So far, there is little evidence supporting pharmacological treatment of recurrent brief depression; most published studies of acute and prophylactic SSRI treatment are negative (Montgomery et al. 1994).

## Differential Diagnosis

If organic factors can be ruled out, as the underlying cause for depressive symptoms MDD still needs to be separated from other mental disorders that show features and symptoms of depression, without fulfilling full DSM-IV-TR criteria for MDD. Dysthymic disorder and adjustment disorder with depressive symptoms have been discussed. The DSM-IV-TR heading "Depressive disorder not otherwise specified" summarizes further depressive syndromes which fall short of the threshold for MDD or dysthymic disorder. These syndromes include recurrent brief depression and minor depression, but also premenstrual dysphoric disorder, postnatal depression, and postpsychotic depressive disorder in schizophrenic patients. In those instances, depression can be conceived as secondary to another somatic condition or psychiatric illness. The treatment of postpsychotic depression has attracted little attention; however, the occurrence of depression after psychosis is frequent (in up to 40% of patients), constitutes one of the most worrisome predictors for a bad functional outcome (Conley et al. 2007) and therefore needs intense treatment. Although the quality of most studies is poor, a meta-analysis is supportive of the efficacy of antidepressants in postpsychotic depression (Whitehead et al. 2002). Furthermore, mood symptoms are common in substance abusers, and can usually be directly related to the intake of illegal drugs. In DSM-IV-TR, they are therefore classified as "organic mood syndrome, depressed type." They may be transient as a direct action of the substance, or lasting as a consequence of toxic brain impairment. Without knowing the causality, it is often impossible to distinguish mood symptoms due to substance abuse from MDD (Patten and Lamarre 1992). Substance–induced mood symptoms can also occur as a side effect of prescribed medication, for example, reserpine, beta blockers, oral contraceptives, corticosteroids, and some antibiotics.

A depressive episode, fulfilling MDD criteria, can also manifest itself as part of a bipolar or a schizoaffective disorder. It has been suggested that symptoms partially opposite to DSM-IV-TR criteria for MDD, such as increased appetite, weight gain, hypersomnia, or symptoms such as agitation and irritability can be observed more often in depression as part of bipolar disorder. However, a major depressive episode in unipolar, bipolar, and schizoaffective disorders can be virtually indistinguishable. This underlines the importance of having a reliable and detailed history of the patient, and diligent exploration for past (hypo)manic and/or psychotic episodes. If depression is then diagnosed as a part of bipolar or schizoaffective disorder, this might considerably change treatment regimens (see the respective chapters in this textbook).

## Differences in Developmental, Gender, and Cultural Presentations

### Developmental Presentations

#### *Depression in Children and Adolescents*

Depression in preschool children is rare (0.8% point prevalence, (Depression Guideline Panel 1993) but markedly increases during adolescence (4.7% point prevalence (Kashani et al. 1987). The clinical features of depressive disorders in young patients may differ substantially from those of adult patients. DSM-IV-TR explicitly mentions that irritable, not clearly depressed mood may dominate the clinical picture in young patients. In addition, instead of showing other typical depressive symptoms as defined by DSM-IV-TR or ICD-10, depressed children may exhibit mainly behavioral problems that cause difficulties in psychosocial functioning at home or at school. Identifying these behaviors as related to depression requires not only evaluating the patient but also talking to parents and teachers.

Gender differences in symptomatology are already apparent in adolescent depression. Bennett et al. (2005) interviewed 383 depressed adolescents using the Childhood Version of the Schedule for Affective Disorders and Schizophrenia and the Beck Depression Inventory. They found that within this sample, with a mean age of 15.8 years, depressed girls were more likely to exhibit guilt, body image dissatisfaction, self-blame, self-disappointment, feelings of failure, concentration problems, difficulties working, sadness, and depressed mood, fatigue, and health worries than depressed boys. In contrast, depressed boys had higher clinician ratings for anhedonia, depressed morning mood, and morning fatigue.

Treatment recommendations are based on relatively little evidence of efficacy and safety in children and adolescents. It is generally accepted that in mild to moderate depression a course of CBT should be considered as first line treatment for those not responding to initial structured supportive treatment (Anderson et al. 2008). In more severe depression, additional pharmacotherapy may become necessary. So far, 18 placebo-controlled RCTs of newer antidepressants have been conducted, but only 12 have been published. In summary, the evidence about safety and efficacy of SSRIs, except fluoxetine, is mixed. TCAs appear modestly more effective than placebo in adolescents but not to a clinically significant degree in children younger than 13 years (Hazell et al. 2002). Analysis of newer antidepressant studies in adolescents and younger children separately shows a significant benefit in the former (10 studies, 62% vs. 49% response, numbers needed to treat (NNT) 7–8) with no significant benefit in the latter (5 studies, 65% vs 58% response, NNT 14) (Bridge et al. 2007). However, studies of

fluoxetine did show similar significant benefit in both age groups (NNT 5). Fluoxetine is the only agent approved by regulatory agencies in the United States, United Kingdom, and Europe for use in depressed youth.

There is reasonable concern about the possibility of increased suicidal behavior in depressed youth treated with antidepressant medications (Leslie et al. 2005). Meta-analyses of RCTs imply that SSRIs increase suicide ideation compared with placebo, but observational studies suggest that SSRIs do not increase suicide risk more than older antidepressants (Hall and Lucke 2006) (see also Section, "Treatment-Emerging Suicide and Suicidality" for the inherent problems in using RCTs to evaluate suicide frequencies and suicidality). While there is no evidence of completed suicide from reported RCTs, compared with placebo, there is a higher incidence of self-harm and aggressive or impulsive actions, especially with paroxetine or venlafaxine treatment. The anxiolytic and activating properties of SSRIs may negatively superimpose on the patient's predisposition: A Finnish inpatient study showed that suicidal ideation was particularly prevalent among boy patients with conduct disorders who had previously manifested violent acts (Haavisto et al. 2003).

Therefore, when initiating medication, careful monitoring is advised. From a low start, children may be able to tolerate and sometimes require doses similar to those for adults. Particularly in the initial weeks, in addition to monitoring for suicidality, patients and families should be asked about medication compliance and changes in behavior.

### *Depression in the Elderly*

In adults, the prevalence of depression appears relatively independent of age (Patten et al. 2001) but a high rate of depressive symptoms requiring treatment in the elderly (Chopra et al. 2005) has been reported. Underdetection of minor depression, which shows a high prevalence in the old age (Horowitz et al. 2005) and requires treatment, constitutes a problem. Subsyndromal depression appears to be especially frequent in general medical treatment settings, for example, up to 30.5% in hospitals and long-term care (Parmelee et al. 1989).

The prevalence of suicidal ideation is relatively high in the elderly (Pfaff and Almeida 2005) and older patients tend to have more and longer major depressive episodes together with more general medical comorbidities (Husain et al. 2005). Finally, a considerable comorbidity exists with dementia, stroke, and PD, putting patients at additional risk for depression (see above).

The response to antidepressant treatment in the elderly may differ slightly from that in younger patients, as antidepressant-placebo differences in RCTs are significantly smaller than in younger adults (NNT 7–8 v 5) (Walsh and Sysko 2005). In addition, relapse rates are higher and the longitudinal outcome is less favorable than for middle-aged adults (Mitchell and Subramaniam 2005). The more adverse longitudinal course in old age may be more due to medical comorbidity, immobility, and psychosocial factors than to age itself.

An interesting question is whether a certain class of antidepressants is more favorable in old age. A Cochrane analysis (Mottram et al. 2006) of 14 RCTs detected no significant differences in efficacy between TCAs, TCA-related drugs, SSRIs, MAOIs, and atypical antidepressants, but more patients withdrew from the trials during treatment with TCAs compared to SSRI.

Thus, tolerability is an essential consideration when choosing an antidepressant in the elderly. Some side effects, which raise particular concerns in younger patients such as weight gain due to antihistaminergic effects, may even be beneficial for elderly patients often suffering from anorexia and weight loss. In addition, special attention must be paid to frequent medical comorbidities and potential drug–drug interactions.

Because of a reduced hepatic metabolism and renal elimination rate in the elderly, the appropriate dosages are lower than in younger patients (Chiu 1997). The Guidelines of the American Psychiatric Association emphasize that elderly patients typically require a lower dosage than younger patients to reach a particular blood level and tolerate a given serum concentration less well. However, the blood levels at which antidepressant medications are maximally effective appear to be the same as for younger patients (Wilson et al. 2001). Elderly depressed patients are particularly prone to the side effects of antidepressants, particularly cardiovascular side effects and treatment-related cognitive dysfunction (Moskowitz and Burns 1986). For patients with poor health, it is recommended to commence treatment with a low dosage and titrate gradually to the therapeutic dosage range ("*start low and go slow*"). But this caution can result in underdosing and suboptimal treatment regimes have been reported in up to 45% of elderly patients treated with antidepressants (Wang et al. 2005).

Older patients tend to take longer to recover from depression, recovery may have a later onset and improvement may continue up to 12 weeks, provided that there has been some earlier response. Currently at least 6 weeks of treatment is recommended to evaluate responsiveness (Wilson et al. 2001). After remission, maintenance treatment does not differ from what is recommended for adults in general (see Table 66–2) (Geddes et al. 2003).

ECT has been shown to be very effective. The use of modified ECT (a historical term which refers to the actual standard procedure of electroconvulsive treatment including anesthesia and muscle relaxation), which has fewer cognitive side effects, is now encouraged, especially in patients at particular medical risk for the use of antidepressants (Abrams 2002).

The empirically based psychotherapies, principally CBT and interpersonal psychotherapy (IPT) (Weissman et al. 2000), have demonstrated efficacy largely independent from age (et al. 2006). They may also be of special usefulness as sole treatment in minor depression to avoid the medical risks of pharmacological treatment.

## Gender-Related Differences

Gender differences in unipolar depression are a consistent finding in several longitudinal and cross-sectional studies (for a review: see Kuehner 2003). The lifetime prevalence shows an unadjusted mean female:male ratio of 2.1 whereas the point prevalence gender ratio is 1.7 (Angst et al. 2002b).

Several differences in comorbidities, symptomatology, and coping style between genders have been described.

**Table 66–2 Selected Guidelines for Duration of Antidepressant Treatment After Acute Treatment Response***

| Guidelines | Recommended Duration of Continuation After Medical Management of the Acute Episode (Months) | Number of Episodes That Would Indicate That Longer "Maintenance " Treatment Is Appropriate |
|---|---|---|
| US Agency for Health Care Policy and Research (Agency of Health Care Policy and Research 1993) | 4–9 | ≥ 2 |
| British Association for Psychopharmacology (Anderson et al. 2000) | 6 | ≥ 3 in the past 5 years (or ≥ 6 in total) |
| American Psychiatric Association (American Psychiatric Association 2000b) | 4–5 | Not specified |
| Australian and New Zealand Guidelines (Ellis 2004) | 12 | in recurrent depression: up to 3 years |
| Korean Guidelines (Lee et al. 2006) | 6–12 | 2 years up to indefinite for patients:<br>– with ≥ 3 episodes<br>– with 2 episodes + family history of mood disorder<br>– with comorbid dysthymia<br>– with a history of recurrence within 1 year after discontinuing medications<br>– with a severe depressive episode<br>– with a history of poor acute treatment response |

*Adapted from Geddes et al. (2003) and extended to more recent recommendations.

Disorders comorbid with depression and more frequent in females include anxiety, somatoform disorders, and eating disorders, especially bulimia, whereas men are more likely to suffer from comorbid alcohol and drug abuse (Marcus et al. 2005). In part, this may also reflect how men and women cope with depression, for example, Angst et al. (200b) found that depressed men were more likely to increase consumption of alcohol whereas women tried to cope through emotional release and religion.

The STAR*D study (Marcus et al. 2005) showed a significantly earlier age of onset of the first major depressive episode in women, and longer current major episodes in women compared to men. In the large Depression Research in European Society (DEPRES) I and II-study, women were significantly more likely to have five or more diagnostic symptoms of depression than men (female:male ratio 1.96) (Angst et al. 2002b).

A few features of depression appear more prevalent in men than in women, for example a tendency to overreact and anger attacks (Winkler et al. 2005).

Explanations for these gender differences are manifold and several factors may contribute, including, genetics, sex hormones, different endocrine stress reactivity, a higher incidence of thyroid axis abnormalities, prior anxiety disorders, personality traits, neuropsychological factors, gender role and psychosocial factors, and life events, for example, childhood sexual abuse (Kuehner 2003). So far, there are no consistent findings for gender differences in heritability (Kendler 1998), but gender-specific genetic polymorphism may play a role in different responsiveness and speed of onset of antidepressant action (Baghai et al. 2004).

Sex hormones may also modulate the manifestation and course of depression, and also treatment response. Specific vulnerabilities and complex interactions between the brain and gonadal hormones do exist (Halbreich and Kahn 2006). Thus, depressive symptomatology in vulnerable women seems to increase when their physiological estradiol levels decrease, for example, perimenstrually, in the postpartum period or during perimenopause. In addition, the efficacy of antidepressants seems to be influenced by estradiol levels (Pinto-Meza et al. 2006). Several, but not all, studies have shown estrogen treatment to be effective in postpartum as well as perimenopausal depression (for review: see Kahn and Halbreich 2005). Estrogens may enhance serotonergic activity and induce a better responsiveness to SSRIs (Stahl 2001). Estradiol may also be involved in the desensitization of the $5HT_{1A}$ receptor (Carrasco et al. 2004). Other neuroendocrine axes, such as the HPA and thyroid axis, may exhibit subtle differences between genders and thereby influence vulnerability to depression (Kornstein et al. 2002).

The apparently straightforward question of whether gender influences response to different types of antidepressant is complicated by age, menopausal status, and tolerability considerations. There is some evidence that younger women respond preferentially to SSRIs over noradrenaline reuptake inhibitors (TCAs, maprotiline, reboxetine) (Berlanga et al. 2006), respond better to SSRIs than men (Khan et al. 2005) and tololerate TCA less well than men (Baca et al. 2004, Kornstein et al. 2000), but no significant effects of gender were seen in studies comparing SSRIs with clomipramine in inpatients, with the SNRIs venlafaxine, and duloxetine or with bupropion (Anderson et al. 2008, Hildebrandt et al. 2003).

In summary, neither prevalence or symptomatology nor treatment response or consequences of depression are identical in men and women, and a gender-specific psychiatric approach, taking into account gender-specific risk- and influencing factors, including gender roles, is warranted.

### *Treatment of Depression During Pregnancy, Postpartum Depression, and Breast-Feeding*

The pregnancy and postpartum periods are considered to be relatively high risk times for the development of depressive symptoms or even MDD in women (for review see Cohen et al. 2004). Both acute and prophylactic treatment

of depressive disorders, during pregnancy, require an individual risk/benefit-analysis. For mild to moderate depression, psychotherapeutic counseling should be considered first, especially as depression may often be related to the changing role of the young mother. In severe MDD, however, this may not always be sufficient, and antidepressants need to be prescribed. Otherwise, if untreated, impaired feto-placental function, premature delivery, miscarriage, low fetal growth, and other perinatal complications may be the consequence. However, the use of antidepressant drugs in pregnancy might increase the risks of teratogenesis, neonatal toxicity, discontinuation symptoms, and neuropsychological and behavioral impairment (Bellantuono et al. 2006). After birth all available antidepressants are excreted into the milk at a concentration of approximately 1% of the corresponding plasma level (for review: see Burt et al. 2001). There is no ideal solution: the risk of an untreated depressive disorder causing maternal stress influencing also the fetus and birth outcome, and an enhanced risk for suicide, have to be weighed against a possibly enhanced, although rarely proven, risk for fetal malformations, growth impairment, fetal and neonatal toxicity, and behavioral aberrations caused by antidepressant treatments (Wisner et al. 2000).

The evidence for harmful effects of antidepressants is inconsistent. TCAs and fluoxetine or other SSRIs have been considered safe in pregnancy (Wisner et al. 1999). A meta-analysis reported that the use of newer antidepressants such as SSRI, SNRI, NARI, NaSSA, and Dopamine and Noradrenaline Reuptake Inhibitor (DNRI) is not associated with an increased risk of major malformations (Einarson and Einarson 2005), but recent studies observed a potentially increased risk for congenital malformations after paroxetine treatment (Cuzzell 2006). In addition, an arguable case-control study reported an association between the maternal use of SSRIs in late pregnancy and persistent pulmonary hypertension in newborns, probably causing a substantially enhanced infant mortality (Chambers et al. 2006).

For severe MDD, ECT can safely be administered during pregnancy and breast-feeding (Rabheru 2001). Sleep deprivation or bright light therapy might be suitable options for mild to moderate depression.

### Cultural Presentation and Ethnic Differences of Depression

The prevalence of depression worldwide varies greatly and appears to be relatively rare outside the western world. An extended WHO household survey using the WHO Composite International Diagnostic Interview of more than 60,000 adults in 14 countries (in North America, South America, Europe, Middle East, Africa, and Asia), gave 12-month prevalence rates of mood disorders ranging from 0.8% (Nigeria) to 9.6% (USA) (Demyttenaere et al. 2004).

A possible explanation for the discrepancy is that most diagnostic criteria for depression and the scales used in developed countries may not be appropriate for assessing functional impairment in rural developing country communities, and that many features of depression, for example, fatigue, could be misinterpreted as signs of HIV infection. But there may be also true differences, including a lower genetic vulnerability, dietary, and other environmental factors, for example, fish intake or sunlight exposure, less exposure to social or occupational stress, or better coping mechanisms. These remain unproven.

Within one country, many of the environmental factors should be equal, and differences in the rate of depression among groups of different ethnicity may be more likely due to biological (genetic) and psychosocial factors. When comparing ethnic groups within the US and controlling for confounding variables such as age, gender, marital, and socioeconomic status (Regier et al. 1993), the prevalence of major depression is similar but outcome varies considerably. As shown in the "Sequenced treatment alternatives to relieve depression" (STAR*D) study, patients of Afro-American or Hispanic origin are at a greater risk of developing chronic depression (Gilmer et al. 2005), but at the same time, they are less likely to receive adequate treatment. Fewer than half of the African Americans (45.0%) and only a quarter (24.3%) of the Caribbean blacks who met DSM-IV-TR MDD criteria received any form of therapy for depression (Williams et al. 2007). More public awareness and lowering thresholds to treatment in minorities is obviously required.

## Etiology and Pathophysiology

### Neurobiological Factors

Although the anatomical and physiological basis of depression is far from being completely understood, MDD most likely involves the limbic structures (in circuits involving the cingulate-hippocampus-mamillary bodies-anterior thalamus-cingulate), reward circuits (nucleus accumbens, sublenticular extended amygdala, amygdala, ventral tegmentum, cingulate, insula, thalamus, parahippocampal gyrus, and prefrontal cortex), hypothalamus, and anterior temporal cortex (Drevets 2000). Both deficiencies of neurotransmitters involved in these circuitries as well as damage to neurons and loss of connectivity, for example, by enduring hypercortisolemia, can underly what manifests clinically as depression.

### Monoamine Deficiency Hypothesis

#### *Noradrenaline and Serotonin*

Neurochemical dysfunction of central nervous neuromodulatory systems is a widely accepted hypothesis as the pathophysiologic correlate of depression. In 1965, Schildkraut developed the catecholamine/noradrenaline deficiency hypothesis (Schildkraut 1965) and in 1967, Coppen formulated the serotonin deficiency hypothesis (Coppen 1967). The basis of these theories was the discovery of depressiogenic properties of the alkaloid reserpine, a primarily antihypertensive agent, which causes depression due to depletion of monoaminergic synapses (Shore et al. 1955).

Additional support for this theory includes the finding that $\alpha$-methyltyrosine, an inhibitor of thyroxine hydroxylase, causes catecholamine depletion and transient depressive symptoms in remitted and euthymic, formerly depressed patients (Berman et al. 1999) and diminished concentrations of 3-methoxy-4-hydroxy-phenylglycole in cerebrospinal fluid, blood, and urine of depressed patients (Garlow et al. 1999).

Support for the serotonin deficiency hypothesis is provided by the tryptophan depletion test. The individual is instructed to restrict intake of the amino acid tryptophan.

which is an important precursor in the synthesis of serotonin (Delgado 2000). Although monoamine depletion does not decrease mood in healthy humans (Ruhe et al. 2007), it may reactivate depressive symptoms in remitted patients treated with SSRIs. Further evidence stems from the observation that the concentration of 5-hydroxyindole acetic acid (5-HIAA), which is a main metabolite of serotonin, is reduced in the cerebrospinal fluid of depressed patients in comparison to healthy controls (Cheetham et al. 1991). This deficiency has been associated with aggressive and suicidal behavior in depressed patients (Asberg et al. 1976). The observation that imipramine reduced the transport of noradrenaline and serotonin into rat brain slices in vitro, whereas iproniazid, the first clinically effective MAOI, inhibited the intraneuronal metabolism of biogenic amines, gave further support to the emerging monoamine hypothesis of depression (Ban 2001). But in spite of more than 40 years of research, these findings are able to explain only some, but not all aspects and symptoms of depressive disorders.

### *Dopamine*

It has been postulated that predominantly mesolimbic dopaminergic neurons which connect the ventral tegmentum with the ventral striatum (nucleus accumbens) may play a role in the pathogenesis of depressive disorders. They have a crucial role within the endogenous central nervous reward system, which is important for motivation, reinforcement of behavior, and reward (Berridge et al. 2003). Depressed patients suffering from psychomotor retardation show reduced dopamine turnover, reduced sensitivity of central dopamine receptors ,and a diminished intrasynaptic central nervous concentration of dopamine (Dunlop and Nemeroff 2007). Further evidence comprises the dopamine-depleting properties of reserpine (Goodwin et al. 1972) causing depressive syndromes with psychomotor retardation and the high comorbidity of depression with PD which is known to lead to a decline of dopaminergic neurons within the CNS. The efficacy of antidepressants enhancing dopaminergic neurotransmission such as bupropion or amineptine (Papakostas 2006) and the efficacy of dopamine receptor agonists such as bromocriptin, pramipexole, or ropinirole lend further support to this hypothesis (Dunlop and Nemeroff 2007).

### *Glutamate*

In depressed patients, enhanced glutamate concentrations in vivo within the occipital cortex have been shown using MRI spectroscopy (Sanacora et al. 2004) and postmortem in the frontal cortex. Probably due to enhanced glutamatergic neurotransmission, a compensatory downregulation of glutamatergic receptors may be responsible for a reduced binding capacity of MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist (Hashimoto et al. 2007) and of the glycine-binding sites of the NMDA receptor in suicide victims (Nowak et al. 1995). Drugs that target the NMDA receptor have shown antidepressant properties in both clinical and preclinical studies, for example, ketamine (Zarate, Jr. et al. 2006) and riluzole (Sanacora et al. 2007), and the mood stabilizing anticonvulsant lamotrigine, which blocks glutamate release, demonstrated antidepressant properties in bipolar depression (Calabrese et al. 1999) and as augmentative treatment in MDD.

Antidepressant properties in animal models (Robichaud et al. 2001) and in open trials in humans have been postulated for other NMDA antagonists such as MK-801 or amantadine (for review: see Muller and Schwarz 2007), but the cognitive side effects of these agents and their psychotomimetic properties complicate their use, so better tolerated agents would be needed.

Finally, interactions between the central nervous glutamatergic and the serotonergic system and their modulation via the immune system may be of importance (Muller and Schwarz 2007). In addition, the recent finding that genetic variation in a kainic acid-type glutamate receptor is reproducibly associated with response to the antidepressant citalopram, suggests that the glutamate system plays an important role in modulating response to selective SSRIs (Paddock et al. 2007).

### *γ-Aminobutyric Acid (GABA)*

A variety of altered functions of the inhibitor neurotransmitter GABA can be demonstrated in depressed patients (for review: see Brambilla et al. 2003). These include reduced concentrations of GABA in the CSF; a decreased number of GABAergic neurons within the orbitofrontal cortex; diminished cortical GABA concentrations in women suffering from postpartal depression; reduced growth–hormone stimulation after treatment with the GABA type B-agonist baclofen; and an imbalance of neuroactive steroids (allosteric modulators of specific neurotransmitter receptors such as GABA type A receptors). Patients suffering from depression may also have an imbalance of GABAergic neuroactive steroids. It has been shown that antidepressants are capable of changing the concentration of neuroactive steroids, which in turn impacts on GABAergic neurotransmission. This mechanism may contribute to their antidepressant action (Rupprecht 2003).

## Substance P and Neurokinin Receptors

Substance P is a neuropeptide within the family of tachykinins, which exert their biological effects via G-protein-coupled neurokinin (NK) receptors. It binds selectively to NK1 receptors, which are found within the CNS in regions important for affective behavior and stress reactions (Rigby et al. 2005). NK1-receptor knockout mice show a reduction of anxiety and stress-related behavior (Stout et al. 2001). Elevated serum concentrations of substance P in depressed patients, which can be diminished by antidepressant treatment, have been shown in several studies (Bondy et al. 2003, Lieb et al. 2004). Putative anxiolytic and antidepressant properties of NK1 antagonists have been postulated but a recent meta-analysis of five studies investigating the NK1 antagonist aprepitant failed to confirm antidepressant efficacy (Keller et al. 2006).

## Neuroendocrine Hypothesis

### *HPA-Axis*

Both hypo- and hyperthyroidism may influence depressive symptoms. A distinct proportion of depressed patients show diminished tri-iodothyronine (T3) levels (Linnoila et al. 1983). This "low-T3-syndrome" can also be induced by glucocorticoids (Rupprecht et al. 1989). About 25–30% of depressed patients show diminished secretion of thyroid

stimulating hormone (Loosen and Prange 1982), possibly due to chronic hypothalamic hypersecretion of thyrotropin-releasing hormone that downregulates its receptors in the pituitary. Although changes to the hypothalamic-pituitary-thyroid are nonspecific and can be shown only in a small proportion of depressed patients, both thyroxine (T4) and T3 augmentation of antidepressant treatments has been shown to be effective in treatment-resistant depression.

### *Growth Hormone (GH)*

GH stimulation tests have repeatedly shown diminished GH secretion in depressed patients (Dinan 1998). In addition, sleep polysomnography demonstrates reduced slow wave sleep and a shortened REM latency in depressed patients. It has been postulated that hypoactivity of the GH system together with hyperactivity of the HPA axis may be responsible for this phenomenon (Ehlers et al. 1987). Improved concentration, better memory functions, better mood, and relief of depression have been reported in GH-deficient adults treated with human GH (Mahajan et al. 2004).

### *Gonadal Steroids*

Estrogen may strongly influence the susceptibility for depressive disorders with the risk being higher in women during their reproductive phase which is characterized by cyclic fluctuations of gonadal steroid concentrations. The rapid decline of gonadal steroids in the postpartum period seems to be a risk factor for the development of depressive disorders (Payne 2003). Finally, estrogen concentrations are diminished in depressed female patients in comparison to healthy controls of the same age (Young et al. 2000).

Hormone replacement therapy in postmenopausal women showed antidepressant effects in some studies (see Section, "Gender-Related Differences"). Preclinical investigations indicate estrogen is capable of enhancing serotonergic neurotransmission (Amin et al. 2005) which may explain the reported higher responsiveness to SSRI treatment in women (Kornstein et al. 2000).

In depressed men, diminished testosterone levels have been found in comparison to healthy probands (Schweiger et al. 1999) and the incidence of depressive disorders correlates negatively with testosterone levels in elderly men (Shores et al. 2004). Testosterone replacement therapy shows antidepressant effects, but its clinical use is limited due to the enhanced risk of prostatic cancer (Pope Jr. et al. 2003).

### *HPA-Axis*

For a long time, dysregulation of the HPA system has been known as one of the major neuroendocrine abnormalities in MDD. This includes raised levels of corticotropin releasing factor (CRF) (Nemeroff et al. 1984), adrenocorticotropic hormone, and cortisol (Linkowski et al. 1987) during depressive episodes, which normalize after clinical remission. Enhanced HPA activity during the first weeks of antidepressant pharmacotherapy seems to be associated with lower rates of early treatment response (Hatzinger et al. 2002). Furthermore, persisting cortisol hypersecretion indicates a higher risk for the recurrence of depression, even if clinical remission has been achieved (Zobel et al. 1999). Long-term deterioration of the HPA system is highly correlated not only with the severity of disease, indicated by higher scores on measures of depression, but also with a greater number of episodes (Hatzinger et al. 2002).

Both in molecular investigations and animal studies, it has been shown that TCAs, MAOI, and some SSRIs modulate the regulation of the HPA system by enhancement of the expression of glucocorticoid receptors, thereby improving the feedback mechanism of the HPA system (Barden et al. 1995, Nemeroff et al. 2004).

Today, the HPA axis has become an important target for the development of new antidepressants. One approach has involved antagonists of CRF 1 receptors. Clinical studies have shown that the concentration of CRF is increased in the CSF of both suicide victims and depressed patients (Nemeroff 1996a). However, so far CRF antagonists have not shown efficacy in the treatment of depression in RCTs. More success has been reported in the development of glucocorticoid type-2 receptor antagonists. This approach was based on the observation that hypersecretion of cortisol is a frequent occurrence in patients with chronic depression in which melancholic features are prominent. There is preliminary clinical evidence that novel glucocorticoid receptor antagonists may be beneficial in such subgroups of depressed patients (Gallagher and Young 2006). For psychotic depression, there is preliminary evidence that antiprogesterone and glucocorticoid receptor antagonist mifepristone is effective both on mood symptoms and, even more, on psychotic features; however, these studies are not conclusive (Carroll and Rubin 2007). Finally, the steroid synthesis inhibitor metyrapone has shown acceleration of response to antidepressant treatment in one RCT (Jahn et al. 2004), but replication studies are still needed.

### *Disturbances of Sleep and Biological Rhythms*

Most patients with depression experience significant changes in sleep such as insomnia, hypersomnia, or excessive drowsiness which contribute greatly to the morbidity of the disorder, including reduced quality of life and diminished functioning (Krystal et al. 2007). Persistent sleep disturbance is a predictor of relapse and recurrence of depression. Ironically, sleep deprivation has been reported to reduce depressed mood, at least transiently. The reasons for this finding are not clear.

Sleep can be viewed as a part of the normal oscillating 24 hour biological cycle, or circadian rhythm. A variety of biological processes are influenced by circadian rhythms, including body temperature and secretion of various hormones, such as melatonin, growth hormone, prolactin, and cortisol. This rhythm is believed to be driven by several innate biological clocks, but is also influenced by the progression of the seasons and the changing photoperiod.

Sleep disturbances in depression can be divided into subjective complaints such as insomnia, hypersomnia, or excessive sleepiness and objective findings documented using polysomnography. Insomnia is the most common complaint and can include difficulty falling or staying asleep as well as early morning awakening, the classic finding in depression. Patients who experience insomnia often have daytime sleepiness. However, up to 20% of depressed patients report hypersomnia, especially those patients with atypical features. Many patients also report not feeling rested (nonrestorative sleep), decreased total sleep, and disturbing dreams (Krystal et al. 2007).

Abnormal polysomnography findings are common (although not universal) in depression. Total sleep time as well as the continuity of sleep is often decreased. Sleep is fragmented with frequent awakenings. Sleep efficiency (time actually asleep while in bed) is also reduced. Typically, there is a reduction in total duration as well as the percentage of nonrapid eye movement sleep (NREM). The duration of NREM prior to the first rapid eye movement sleep (REM) period, known as REM latency, is often decreased in depression. It is not clear whether depression-related sleep disturbances are trait markers for vulnerability to depression or are limited to periods of illness. Some evidence suggests that some sleep EEG findings may precede the onset of clinical depression. Indeed, some authors theorize that circadian rhythm disturbances are a core feature of affective disorders. These abnormalities in sleep and circadian rhythms are among the most consistent findings in biological psychiatry and successful treatment of depression often results in improved sleep. However, many other psychiatric and medical conditions which may be comorbid with depression, as well as alcohol, substance abuse, and medications, also affect sleep (Krystal et al. 2007, Thase 1999).

In addition to circadian rhythms, biological rhythms exert their effects over shorter and longer time lines. Ultradian rhythms oscillate more than once in a 24 hour period, while infradian rhythms operate over a much longer time period. These infradian cycles may entrain to seasonal changes in the photoperiod and it has been postulated that disturbances in infradian rhythms play a role in SADs (including winter depression). Light therapy (phototherapy) uses a full spectrum lamp to mimic the effects of sun exposure. It is usually given in the morning and believed to exert its therapeutic effect by resetting the biological clock (Terman 2007).

## Genetic Factors

Recent family studies have reported an approximately 3-fold increased risk for MDD in the first-degree relatives (parents, siblings, offspring) of individuals with MDD versus the general population, although there is some variation, due most likely to differences in diagnostic and sampling criteria (Sullivan et al. 2000). However, this finding is not specific: first-degree relatives of MDD patients also show a higher risk for developing anxiety disorders (Camp et al. 2005), eating disorders (Mangweth et al. 2003), substance abuse (Preisig et al. 2001), and other affective spectrum disorders (Hudson et al. 2003). Family studies alone do not allow one to distinguish the effects of genetic factors versus family environment. Complex disorders, of which MDD is a good example, are likely to involve a relatively large number of individual genes, none of which may themselves have a major impact on risk, as well as interactions with environmental factors.

Research has tended to focus on genes encoding neurotransmitter receptors and on the enzymes involved in monoaminergic transmission. The studies have used only small sample sizes and found only minor genetic effects, most of which could not be replicated. Nevertheless, meta-analysis has identified several genetic variants of candidate genes.

Several studies concentrated on promoter polymorphism in the serotonin transporter gene, which has a short allele that shows an association with depression and anxiety (Lesch et al. 1996), as well as enhanced susceptibility to stressful life events (Caspi et al. 2003). However, other investigations were not able to replicate this finding (Minov et al. 2001, Serretti et al. 1999). Polymorphisms of other receptors and enzymes of the biogenic amines have also been investigated. These include the tyrosine and tryptophan hydroxylase genes, the catechol-O-methyl transferase gene as well as genes for the serotonin and dopamine receptors (Kato 2001). But again, these studies have yielded inconclusive or negative results.

Functional polymorphisms in the angiotensin converting enzyme gene seem to influence the risk for developing depressive disorders (Arinami et al. 1996, Baghai et al. 2006a), HPA axis activity (Baghai et al. 2002), and the clinical effectiveness of antidepressant therapies (Bondy et al. 2005). Additionally, the glucocorticoid receptor-regulating cochaperone FKBP5 has been shown to influence both the susceptibility for depression and response to antidepressant treatment (Binder et al. 2004).

The conventional view that unipolar depression is evoked by the same genes irrespective of the age of onset of the disorder has been challenged by studies on late-onset depression. Hickie et al. (Hickie et al. 2001) demonstrated that late-onset depression is associated with a mutation in the methylene tetrahydrofolate reductase gene that encodes an important cofactor in monoamine biosynthesis; this mutation was not observed in patients with early-onset depression. It appears that the same mutation predisposes the patient to cerebrovascular disease and is associated with increased plasma homocysteine and folate deficiencies that frequently occur in late-onset depression.

There are only a few small studies published in which pharmacogenetics has been used to predict therapeutic response in individual patients. These studies have investigated variations in the genes for serotonin receptors and the serotonin transporter and their associations with a poor response to treatment with SSRI antidepressants (Joyce et al. 2003, Zanardi et al. 2001). Again, other investigators have been unable to replicate the observations (Kim et al. 2000). The STAR*D study found that homozygote carriers of the treatment-response-associated marker alleles of both the GRIK4 and HTR2A genes were 23% less likely to experience nonresponse to treatment with citalopram relative to participants who did not carry any of these marker alleles, suggesting the importance of interactions between serotonergic and glutamatergic transmission (Paddock et al. 2007). A more extensive update can be found in published reviews on pharmacogenetics and pharmacogenomics (Serretti et al. 2005).

## Neurotrophic Factors

A continuous accruement of neurons (neuroneogenesis) in the gyrus dentatus, a region within the hippocampus which is important for mood regulation, has been demonstrated (Eriksson et al. 1998). The neurotrophin hypothesis of depression and antidepressant effectiveness now postulates a depletion of neurotrophic factors such as brain-derived neurotrophic factor during depression, resulting in diminished neurogenesis and damage of predominantly hippocampal neurons, which can be counteracted by antidepressant treatments (Duman 2002). It has also been postulated that

stress and hypercortisolism in untreated depression results in hippocampal atrophy, including reduced synaptic plasticity due to a reduction in the length and numbers of dendritic branching (Sapolsky 2000). Neuroimaging supports this postulated enhanced neuronal degeneration within these regions in depressed patients (Frodl et al. 2002), and in healthy controls an association between hippocampal atrophy and cortisol levels has been reported (Lupien et al. 1998).

Chronic antidepressant treatment results in an enhanced expression of neurotrophic factors (Thome et al. 2002) and in an augmented neurogenesis within hippocampal regions (Malberg et al. 2000). This may explain the latency of several weeks before sufficient antidepressant action is observed in the treatment of MDD. In animal models nonpharmacological antidepressant treatment options such as sleep deprivation (Hairston et al. 2004), ECT (Stewart and Reid 1993), and repetitive transcranial magnetic stimulation (Muller et al. 2000) increased concentrations of brain-derived neurotrophic factor, whereas in depressed patients after ECT inconsistent results have been reported. Finally, effects on neurogenesis can not be the sole mechanism of antidepressants as their effectiveness is not always linked to action on neurotrophic factors (Coppell et al. 2003).

## Animal Models of Depression

There is presently great concern about the relevance and predictive validity of animal models of behavioral disorders (Winsky and Brady 2005), partially caused by the discrepancy between positive outcomes of candidate drugs in animal models followed by apparent lack of efficacy in humans. This raises the question whether an observed behavior in animals really resembles, at least in part, a depressive syndrome in humans. Depression presents as a heterogeneous entity made up of a variety of emotional, behavioral, and cognitive elements, and each component of the syndrome may involve different neurobiological substrates. It must be kept in mind that DSM-IV-TR and other classification systems simply provide diagnostic criteria based on changes in behavior and placing labels on the abnormal behaviors does not imply etiology.

When using animal models, we have to be aware that they can only model a very specific and limited facet of either behavior or neurochemical changes involved in depression. Animal models are used (1) to reproduce aspects of the behavioral disorder that can be studied, (2) as a test bed for discovering novel pharmaceuticals that may treat the disorder, and (3) as procedures through which new molecular targets can be identified for subsequent drug discovery and development.

Antagonism of the pharmacological effects of reserpine was the first model of abnormal monoaminergic function in depression where antidepressants were differentiated from other psychoactive drugs (Askew 1963). Reserpine nonselectively depletes synaptic stores of the monoamines noradrenaline, dopamine, and serotonin, and induces a syndrome of locomotor hypomotility and reduced body temperature. These behavioral symptoms can be reversed by different TCAs and MAOIs.

Similarly, hypothermia induced by high doses of the dopamine agonist apomorphine is reversed by antidepressant compounds (Puech et al. 1981), likely due to action on dopaminergic receptors on noradrenergic terminals, preventing noradrenaline release. Neither the reserpine nor amphetamine model attempts to mimic any of the behavioral symptoms of depression per se, they simply reveal activity of compounds in elevating synaptic concentrations of monoamines.

Neurochemical models were used to investigate receptors involved in the etiology of depression and thought to be a marker of the disorder. Changes in $\beta$-adrenergic receptor number and sensitivity, for example, have been associated with depression and suicide (Leonard 2000) and chronic treatment with TCAs could reduce the number of $\beta$-adrenergic receptors (McArthur and Borsini 2006).

An alternative approach in animal models was to induce behavioral changes not by drugs, but by negative environmental factors or stress, and then test the capability of potential antidepressants to prevent or reverse these behaviors. It is a very strong assumption in most models that depression can be viewed as a maladaptive response to stress (Wong and Licinio 2001).

The separation of infant monkeys from their mothers was one of the earliest models of the effects of social and environmental stress. Infant monkeys react to this separation initially by protesting and finally with behaviors resembling despair. Similar effects are observed following maternal separation in other animal species.

Chronic stress and depression in humans are often characterized by HPA axis dysfunction. Thus, stress-induced HPA dysfunction in animals may serve as a test bed for observing both subsequent anatomical and functional changes and their response to antidepressant treatment. Even brief periods of separation of a rat pup from its mother can induce endocrine responses related to stress such as increased corticotrophin-releasing factor and decreased glucocorticoids in various brain areas (Francis et al. 1999a). Rats that have experienced prolonged separation as pups show signs of HPA hyperactivation including decreased glucocorticoid receptor activation in the hippocampus, hypothalamus, and frontal cortex, and reduced negative feedback sensitivity. Similar to depressed patients, these animals show an early release from dexamethasone-induced suppression of basal adrenocorticotropic hormone (Nemeroff 1996b). Disruption of normal maternal care can not only cause sustained hyperactivity of the HPA system in response to adulthood stressors but also lead to increased anxiety- and depression-related behaviors in the adult offspring (Francis et al. 1999b).

Stress can also be induced by competition within a social milieu. A model of depression based on social hierarchy and subordination was proposed by Malatynska and Kostowski (1984). Pair-housed rats are forced to eat within a limited time, which means that the dominant member of the pair alone managed to eat sufficient food. Repeated treatment with an antidepressant helps the submissive animal to become more assertive and compete longer for food. Stress induced in socially housed rats alters neuroendocrine variables: subordinate animals showed not only increased defensiveness, increased ethanol consumption, and shorter lifespan than dominant rats but also had significantly elevated corticosterone levels and increased 5-HIAA/5-HT ratios, indicating a whole range of changes consistent with a depression-like profile (Blanchard et al. 1993). Interestingly, social hierarchy models can also be fitted in a way that they

may resemble manic behaviors (Malatynska and Knapp 2005).

Another example of an acute stress paradigm leading to lasting behavioral changes is the learned helplessness model which was proposed and developed during the 1960–1970s. A presumed state of depression is induced in animals by exposing them to an aversive stimulus like a weak electric shock under circumstances in which they cannot control or predict the onset or duration of the stimulus. Rats subjected to this procedure show long-lasting deficits in the motivation and ability to escape in subsequent trials where escape is possible, reduced locomotor activation and grooming, increased passivity, decreased appetite and decreased interest in sexual activity in a manner reminiscent of the anhedonic syndrome of depression in humans (Willner 1986). Helpless rats also develop alterations in sleep–wake patterns with modifications of the latency and amount of REM classically observed in depressed humans (Adrien et al. 1991). Pharmacological treatment with TCAs reduces these behavioral changes (McArthur and Borsini 2006). Nevertheless, the learned helplessness paradigm has shortcomings. Antidepressants work nonspecifically in a wide range of stress-related disorders and depression, thus, learned helplessness may be a better model of posttraumatic stress disorder and other conditions in which stress is a clear etiological factor than it is of depression.

The forced swimming test, also called behavioral despair, was first proposed as a simpler variation of the learned helplessness test, and is probably the most widely used screening test of antidepressant potential of novel compounds. Animals are forced to swim in a confined space. They become immobile following a phase of extensive swimming and climbing. Antidepressants from all classes reduce the immobility time when the rat is replaced in the water cylinder 24 h following the initial experience. Interestingly, different classes of medication may change different behaviors: SSRIs seem to prolong swimming time, whereas NARIs seem to increase climbing behavior (Nestler et al. 2002).

A variant of the forced swim test, used in mice, is the tail suspension test. Here, mice are suspended by their tails and the time it takes an animal to become immobile (to hang passively upside down) is measured. The major advantage of the forced swim or tail suspension test is its relatively high throughput and ease of use (Nestler et al. 2002). The test also provides a useful model in which to study the neurobiological and genetic mechanisms underlying stress and antidepressant responses (Lucki et al. 2001, Porsolt 2000).

One of the defining characteristics of MDD is, however, a persistence of depressed mood over a number of weeks. In addition, acute stress models do not allow for comparing the onset of action of compounds. A rapidly acting antidepressant would offer considerable advantages over existing therapies. Therefore, tests have been developed that require a prolonged period of treatment for the effects of antidepressant drugs to be observed. The most widely applied test is the olfactory bulbectomy model (Cairncross et al. 1977). Pheromone detection is very important in the psychosocial milieu of the rat. The olfactory bulbs receive incoming chemosensory information and relay this to limbic structures via an extensive network of neuronal connections. Bilateral aspiration of the olfactory bulbs thus deprives rats of this vital mediator with the external environment and results in dysregulation of the limbic–hypothalamic axis, increased sensitivity to stress, alterations in immune function, abnormal sleep patterns, agitation, weight loss, and changes in hedonic behavior (Song et al. 2005). The most notably behavioral change following olfactory bulbectomy is increased exploration and hyperactivity in an open field test that can be attenuated by chronic administration of antidepressants of various classes (Kelly et al. 1997). On a biochemical level, olfactory bulbectomy reduces concentrations and turnover of noradrenaline and serotonin in cortical forebrain regions and concentrations of noradrenaline in the frontal cortex. However, it may simply be that the chronic sensory deprivation caused by the destruction of the primary mode for receiving external sensory information constitutes a chronic stressor of high intensity.

## Psychological Factors

Depression is a multifactorial clinical phenomenon. In any case of depression, biological, environmental, and psychological factors may interact to varying degrees. Significant theoretical approaches to the psychology of depression to be considered include cognitive behavioral, interpersonal, social rhythm theory, and psychodynamic. The strength of these approaches has generally been in their utility rather than the power of their etiological theories, which have proven difficult to verify empirically.

Depression may be triggered by stressful life experiences in susceptible persons, but not everyone becomes depressed under similar stressful circumstances. The intensity and duration of the stressors, personality attributes, coping skills, and previous life experiences play a significant role in each individual's vulnerability to depression. Early life experiences shape how individuals experience the world and their place in it, including subsequent stressful life events. The availability and nature of a social support network is also a crucial variable. Different individuals may assign widely divergent meanings to similar stressful experiences, leading to very different affective and behavioral responses. This is why understanding the relationship between stressful life experiences and depression is not simple. Even seemingly advantageous life events, such as marriage can produce stress. Certain personality styles involving low self-esteem or pessimism may contribute to a difficulty in coping with change.

### Cognitive Theory

The cognitive or CBT approach to depression was originally developed by Beck (see Beck et al. 1979) and emphasizes a set of dysfunctional cognitions which are believed to contribute to depressive symptoms. From this perspective, cognitive distortions cause and maintain depression. However, the origins of cognitive distortions are not made explicit in CBT theory, which emphasizes a "here and now," immediate approach to understanding and treating depression. These cognitive distortions are believed to be relatively stable but dormant in asymptomatic individuals, apparently becoming more significant after a stressful life event serves as a trigger. Cognitive distortions are present moment to moment in the form of transient "negative automatic thoughts," which form a constant background of depressogenic thoughts in response to external events as well as internal experiences such as memories. These thoughts derive some of their power to influence mood through their repetitive nature, and tend

to remain unexamined unless made explicit through therapy. They typically exemplify certain characteristic types of cognitive distortions such as dichotomous ("black and white") thinking, overgeneralization, and personalization. They are not considered to be unconscious, as the individual is capable of recognizing them through introspection and self-examination. In addition to these transient phenomena, more stable, persistent, and deep seated ideas about one's self and the world known as "schemas" are important in cognitive theory. Schemas which contribute to depression tend to be somewhat inflexible, known in CBT terminology as "global and invariant." Beck also described a "negative cognitive triad" involving a negative view of one's self, one's world, and the future. Beck envisioned an interplay between cognition and behavior. Depressed patients respond to negative beliefs about themselves by developing self-defeating behavioral patterns, reducing opportunities to experience pleasurable or rewarding experiences.

Cognitive theory also reflects influences by learned helplessness models and hopelessness theory (Abramson et al. 1989, Seligman 1975). In hopelessness theory, "depressogenic attributional style" leads individuals to regard stressful events as permanent rather than temporary, and affecting most of one's life rather than being limited to specific areas. These attributional styles contribute to personal, internal rather than external explanations of depressive experiences.

### Interpersonal Theory

IPT was developed by Klerman and others (Klerman et al. 1984) and has played an important role in modern psychotherapy of depression; however, it does not present a thorough psychology of the etiology of depression. IPT focuses on difficulties in current interpersonal functioning. It involves a formal diagnostic assessment, inventory of important current and past relationships, and definition of the current problem area. In IPT, depression is held to relate to one or more of four functional areas: grief, interpersonal role disputes, role transitions, and interpersonal deficits. In IPT, the reciprocal relationship between one's mood and interpersonal events is explored. Stressful life events may overwhelm coping ability and produce a depressed mood, which then contributes to ongoing interpersonal difficulties. Once this relationship is identified, modifying it becomes the focus of treatment.

The relationship between psychological well being and one's interpersonal environment has long been a focus in psychiatry. Authors including Adolf Meyer, Frieda Fromm-Reichmann, and Harry Stack Sullivan emphasized adaptation to the social environment in understanding and treating psychiatric disorders, while Bowlby (1980) and others emphasized social attachment. IPT developed through an appreciation of these earlier thinkers. Numerous studies have shown a relationship between stressful life events (most of which have an interpersonal element) and depressed mood.

### Social Rhythm Theory

An attempt at integration of biological and psychosocial theories of depression has focused on the disruption of biological rhythms associated with psychosocial stressors. The loss of "social zeitgebers" (persons, social demands, or tasks which set the biological clock) has been proposed as a link between biological and psychosocial formulations (Ehlers et al. 1988). The loss of social rhythms is held to result in instability in biological rhythms, triggering a depressive episode in a person vulnerable to depression. The social zeitgebers theory suggests that external factors such as social relationships, interpersonal continuity, and work tasks entrain internal biological rhythms. Disruptions of these social rhythms due to loss of relationships interfere with biological rhythms that maintain homeostasis. This disruption leads to changes in neurobiologcal process including alterations in neurotransmitter functions, neuroendocrine regulation, and neurophysiologic control of sleep/wake cycle and other normal circadian oscillations.

### Psychodynamic Theories of Depression

Psychoanalytic thinking has explored depression since the early days of Freud's original work. Freud (1917) was interested in the distinction between normal grief and clinical depression. In his "Mourning and Melancholia," he suggested that depression involved a process of "turning aggression inward." This situation might arise when a close relationship ends through death, illness, conscious decision, or accident. The psychological process of grief, according to Freud, involves withdrawing the emotional attachment felt for the person no longer present. Sometimes, these emotions are ambivalent mixtures of loving and angry or hateful feelings. In such cases, the individual may be unable to resolve the aggressive feelings toward the lost loved one. Freud believed that such feelings have to be resolved, and that resolution in these cases involves the defense of introjection, a turning of the negative feelings inward, against the self. Clinically, this unconscious process would contribute to the guilt, self-criticism, and suicidal ideas which frequently complicate depression.

Later psychoanalytic theorists developed other views of depression. For example, Self Psychology, developed in the 1970s and 1980s, influenced by the work of the psychoanalyst Heinz Kohut (1971), emphasized the importance of maintaining psychological equilibrium. This equilibrium relies on a combination of regulatory capacities within the individual and resulting from important relationships. Kohut used the term "cohesive self" to describe the state in which adequate self awareness, self esteem, self regulation, and interpersonal awareness exist to allow the individual to function in an acceptable way. In this view, the loss of an important relationship with another person can produce a state of self fragmentation, leading to psychological symptoms such as depression. Treatment aims to reestablish a supportive environment, allowing the return of interpersonal and internal equilibrium. Also, a loss or blow to the individual's identity or sense of self may produce a narcissistic wound or injury. For instance, the loss of a job or significant relationship may play this role. The fragmentation of self in such a case may also contribute to depression. Treatment in these cases must involve reestablishment of one's sense of self, or even development of a new sense of self (Tasman, personal communication 2007).

## Social/Environmental Factors

As summarized by McLean and Link (1994), the two major conceptualizations of how life events affect mental health

are: (1) life events as disruptive experiences that necessitate changes and readjustment and (2) life events as meaningful experiences that arouse negative emotions.

A wide range of environmental adversities such as job loss, marital difficulties, major health problems, and loss of close personal relationships are associated with a substantial increase in risk for the onset of MDD (Kessler 1997). In childhood, a range of problems including physical and sexual abuse, poor parent-child relationships, and parental discord and divorce leave biological scars such as altered HPA axis function and increase the risk for MDD both in adolescence and later in life (Heim et al. 2001).

In the elderly, loss of loved ones constitutes a strong risk factor for depression following grief. Among longitudinal studies of population-based samples using diagnostic criteria, the risk of depression associated with the death of one's spouse is estimated as 24.3 during the first year, 9.0 during the first 2 years, and 3.1 during the first 3 years (Bruce 2002).

Social and environmental factors may have different effects depending on gender. In a large population–based sample, Kendler and colleagues (Kendler et al. 2001) found that women consistently reported higher exposure to housing problems, loss of confidant, crises and problems getting along with individuals in their proximal network, and illness of individuals in their distal network, whereas men consistently reported higher rates of other stressful life events, such as job loss, legal problems, robbery, and work problems. Consistent sex differences in the sensitivity to stressful life events were seen for only three categories: men were more sensitive to the effect of divorce or separation and work problems, and women were more sensitive to the impact of problems getting along with individuals in their proximal network.

In recurrent depression, social stressors and negative environmental factors may play a more pronounced role in the onset of early episodes, but may lose importance during the course of illness. Kendler and colleagues (Kendler et al. 2000) concluded from their study in the same sample of depressed women that the association between previous number of depressive episodes and the pathogenic impact of stressful life events on major depression is likely causal and biphasic. In patients with frequent relapses, the association between stressful life event exposure and risk of major depression progressively declines up to the ninth episode, but is then largely unchanged with further episodes. These results are consistent with the kindling hypothesis (Weiss and Post 1998), but suggest a threshold at which the brain is no longer additionally sensitized to the depressive state.

## Treatment

### Access to Mental Health Services

Ideally, patients and caregivers should have unrestricted access to mental health and complementary services when needed. According to WHO, however, fewer than 25% (in some countries even less than 10%) of depressed patients receive at least adequate minimal care. The reason is not always a lack of resources, but, other factors, for example, stigma, no insurance coverage or fear of losing one's job when missing time at work, may also create barriers to effective care. Even in highly industrialized countries, there is a large gap between the relatively high prevalence of depressive disorders and the delayed and relatively infrequent use of antidepressant treatments (Henkel et al. 2005), and reasons may include barriers to access mental health providers or underdiagnosis of depression and inadequate treatment.

### Treatment Goals: Response, Remission, and Recovery

Clinical trials focus on symptomatic relief measured by specific scales, for example, the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) or Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), and define response and remission in relation to these scores. The traditional definition of response in RCTs of antidepressants is a 50% improvement compared to baseline score. Remission is defined as the absence of depressive symptoms and a full return of functioning. Most RCTs use an absolute rating scale threshold to define remission, for example, HAM-D score $\leq 7$. When comparing across studies, however, effect sizes expressed as NNT may provide a better estimate of how effective a medication really is.

The goals of clinical management of MDD can be divided into acute, intermediate and long-term, corresponding to the different phases of treatment, namely acute, continuation and maintenance (prophylactic) treatment (Kupfer 2005) (see Figure 66–1). The ultimate goal of acute treatment is to achieve remission, meaning not only being asymptomatic (in the sense of not meeting the criteria for diagnosis of the disorder and having no or only minimal

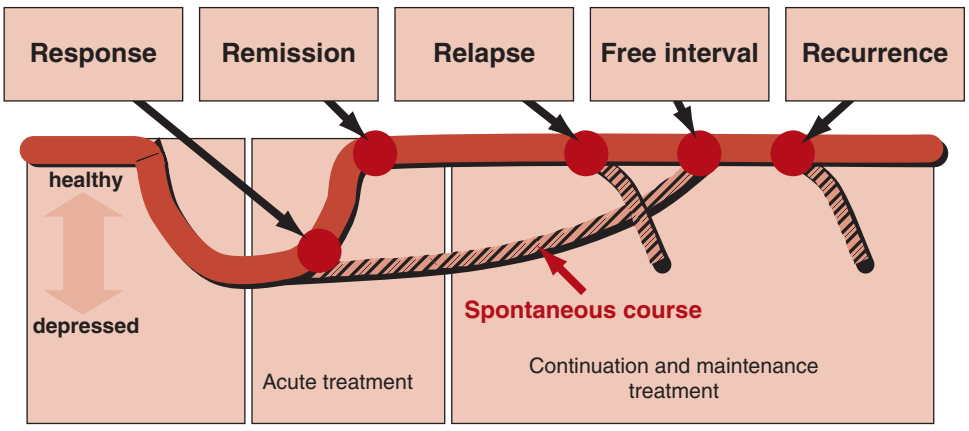



**Figure 66–1** *Long-term treatment of depression (modified from Kupfer 1991).*

residual symptoms), but also showing improvement in psychosocial and occupational functioning. From the patient's perspective, remission means the presence of features of positive mental health such as optimism and self-confidence, and a return to one's usual, normal self (Zimmerman et al. 2006). The intermediate goal of treatment is stabilization and prevention of a relapse, elimination of subsyndromal symptoms, and restoration of the prior level of functioning. The long-term goal is full recovery (Rush et al. 2006a), to prevent further episodes, maintain functioning, and ensure a satisfactory quality of life. In the following, the different stages of therapy will be elaborated, focussing on the pharmacological treatment.

## Acute Treatment

At least in severe depression and depression previously unresponsive to psychotherapy alone, initiation of antidepressant treatment is a regular part of the overall treatment plan. If not already ongoing, this treatment plan should also include psychotherapy, psychoeducation, and psychosocial support. The choice of medication depends on several factors including proven efficacy, tolerability and safety, previous experience, and preference of the patient.

Titrating medication usually starts with the lowest effective dose, derived from clinical studies, to ensure good tolerability. If side effects do not occur or fade within a few days, stepwise dosage increases up to the usual standard dose as recommended by the manufacturer (see Table 66–5) can be made until relief from depressive symptoms begins. Independent of the chosen drug, a delay of several weeks may occur until sufficient antidepressant effects can be observed. When switching from one medication to another, overlapping tapering is recommended unless a specific medication, for example, an irreversible MAO inhibitor or fluoxetine, demands a washout-phase (Larsen 1988); in this case, a washout-period of at least 2 weeks (up to 5 weeks, in case of a switch from fluoxetine to irreversible MAOIs) must be observed, especially when treatment with another serotonergic-acting medication is planned; otherwise, a potentially lethal serotonin syndrome may very rarely occur (Boyer et al. 2005). Between 1989 and 1999, 23 deaths caused by a serotonin syndrome were reported in the literature (Gillman 1999). A serotonin syndrome is not specific for SSRI, but may also happen with other serotonergic-acting substances, for example, venlafaxine in combination with MAOIs (Phillips and Ringo 1995). When switching to reversible MAO inhibitors, for example, moclobemide, a few (2–3) days of pausing medication appear to be enough (Dingemanse et al. 1998). For further details about MAOI tolerability see Section, "MAOI".

Expectations about the potential efficacy of a given treatment are not uniform across guidelines. It has been estimated that antidepressants currently in use achieve treatment response rates of 50–75% in moderately to severely depressed patients, which means that despite sufficient dosage up to half of patients do not respond sufficiently to the initial treatment choice. Concurrent pain and somatization indicate a longer time course until remission is achieved; especially the presence of bodily pain predicts difficulties in treating depression. These patients may require a more intense treatment right from the start, for example, the use of dual mechanism antidepressants that also address pain and thus increase the patient's chances of achieving remission (Karp et al. 2005).

The decision concerning whether a response is sufficient can be made clinically or, especially in research settings, be guided by the administration of established rating scales. Nonresponse is usually defined as a less than 25% decrease in baseline symptom severity, partial response as a 26–49% decrease in baseline symptom severity, and response as a greater than 50% decrease in baseline symptom severity (Bauer et al. 2002b). In case of nonresponse after 4 weeks of treatment, a switch of medication is usually recommended. Patients with a partial response after 6–8 weeks should receive a dose escalation, followed by augmentation or switching strategies (Hirschfeld et al. 2002, Quitkin et al. 2005). Recent results of the STAR*D study favor early augmentation, as the likelihood of response to monotherapy steadily declines with each medication switch (Rush 2007). However, there is reasonable evidence that especially in older patients it may take longer to achieve full response to antidepressant medication (up to 12 weeks) (Furukawa et al. 2000).

To bridge the time period until onset of symptomatic improvement and also for the acute relief of distressing symptoms, for example, agitation and sleep disturbances, short-term addition of benzodiazepines could be considered, as these may accelerate the response. A meta-analysis by Furukawa (Furukawa et al. 2001) showed that depressed patients receiving combination therapy were more likely to show a greater than 50% reduction from their baseline depressive severity than patients on antidepressant monotherapy (1.63 times at 1 week, falling to 1.06 times at 6–8 weeks). When benzodiazepines are given, the physician should check on a regular basis whether they are still needed, to prevent the risk of addiction (Clark et al. 2004). Additional early augmentation therapies such as sleep deprivation or light therapy may be considered, especially when the patient has been previously responsive to these modalities.

### *The Role of Therapeutic Drug Monitoring*

To establish true refractoriness or to check whether the previous treatment has been appropriate as far as dosage is concerned, therapeutic drug monitoring may be helpful. Serum levels should be measured under steady-state conditions (at least 5 half-lives, in most drugs after 1 week after dosage change) and at the time of minimal drug concentration (trough level). Therapeutic drug monitoring is based on the hypothesis that there is a well defined relationship between the drug plasma concentration and its clinical effects (therapeutic effects, adverse effects, and toxicity). This hypothesis is generally well accepted for lithium and for the TCAs nortriptyline, amitriptyline, desipramine, and imipramine (Baumann et al. 2005). However, results are inconsistent for other TCAs, SSRIs, and other more recently introduced antidepressants (Corruble and Guelfi 2000). Several factors may interfere with antidepressant serum concentrations, including absorption and excretion kinetics of the drug, bioavailability and binding properties to plasma proteins. In combination treatment regimens, various pharmacokinetic interactions between antidepressants and other medications may occur due to their common metabolism by cytochrome P-450 (CYP) enzyme isoforms and/or enzyme inhibition. Genetic polymorphisms of CYP2D6 and CYP2D19 are of high clinical relevance for antidepressants which are

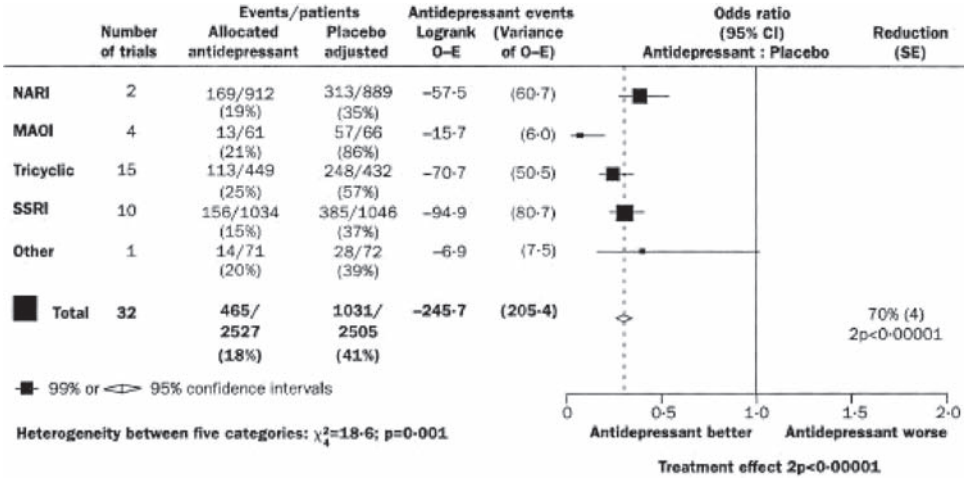



**Figure 66–2** *Cochrane meta-analysis of the efficacy of antidepressants in the prevention of recurrence of unipolar depression; risk of relapse, odds ratios by drug type (from Geddes et al. 2003).*

substrates of these enzymes, including TCAs, some SSRIs, venlafaxine, and mirtazapine. About 5–8% of the Caucasian population are considered as poor metabolizers and 1–7% as ultra-rapid metabolizers (Baumann et al. 2005); the fomer leads to increased serum levels and the latter to insufficient serum concentrations. In Asian populations, the poor metabolizer type may be less frequent (about 1% in Thai, Chinese, and Japanese populations, and up to 4.8% in Indians (Kitada 2003)).

Concomitant medication metabolized by the same enzymes influences the metabolic rate of other substances. For example, some SSRIs inhibit CYP2D6, especially fluoxetine and paroxetine, but also bupropion, with a consequent increase in serum levels of other substrates, for example, antiarrhythmics, beta-receptor antagonists such as propanolol or metoprolol, and opioids, for example, codeine. Other antidepressants, including imipramine, nefazodone, venlafaxine, and reboxetine[2], are metabolized by the CYP3A4 pathway, with some showing potent inhibition of this enzyme, for example norfluoxetine, the metabolite of fluoxetine and fluvoxamine (Baumann et al. 2005).

Owing to the costs of therapeutic drug monitoring (measuring plasma levels for a single psychoactive drug and its metabolites costs between $25 and $100), it should not be performed routinely, but only in cases with established serum concentration effectiveness/side effect relations and in conjunction with a clinical question, for example, insufficient treatment response, side effects due to overdosing.

## Continuation and Maintenance Treatment

### *General Principles of Maintenance Treatment*

The ultimate goal in any psychiatric disorder is to prevent recurrence of acute symptomatology and improve functionality and quality of life in patients.

Prophylactic treatment of unipolar depression is not restricted to pharmacotherapy. Psychotherapy, especially IPT and CBT, should be included in the overall treatment portfolio. Maintaining a good doctor-patient relationship, monitoring adherence and psychoeducation are important as well. To prepare patients and their relatives for long-term prophylactic treatment, they should be informed about topics such as expected course of illness, treatment options, medication efficacy and side effects, use of a daily self-reporting instruments for mood to detect early warning signs of relapse or recurrence, long-term perspectives, and, if applicable, projected end of treatment. Patients should also be trained to distinguish between spontaneous, short-lasting mood-fluctuations (blips), and true emergence of a new episode which should be treated as soon as possible (Rush 1999).

### *Continuation Treatment*

After initial remission from acute depression, continuation treatment should ensure stabilization, prevention of early relapses, and further improve functionality and promote reintegration. When antidepressant treatment has been effective and the primary goal of symptomatic remission has been achieved, it is usually recommended to continue the antidepressant in unchanged dosage for continuation treatment, unless side effects force tapering of the medication. The prophylactic effect of continuing antidepressant medication has been shown in a multitude of studies (Geddes et al. 2003) (see Figure 66–2). In a systematic review, Hirschfeld found that one-third to half of patients successfully stabilized in acute-phase treatment will relapse if medication is not sustained throughout the continuation period, whereas only 10–15% relapse if medication is continued (Hirschfeld 2001). It is also wise to continue the full dose during the maintenance treatment: patients who received only half of the acute phase dose of imipramine or paroxetine during maintenance therapy showed a significantly higher recurrence rate (Franchini et al. 1998, Frank et al. 1990). Thus, the often applied clinical practice of dose reduction during maintenance treatment lacks evidence and may put the patient at an increased risk of relapse. When full response is achieved with low dose acute antidepressant treatment, it may be justified to continue treatment in the lower dose range (Furukawa et al. 2003).

It is generally recommended to continue the effective antidepressant monotherapy or combination treatment for at least another 3–6 months (Hirschfeld 2000) (see Table 66–2) but at least until all symptoms have totally subsided, as residual symptoms are predictive for early relapse (Ramana et al. 1995). Patients with a history of previous long lasting episodes or several risk factors of recurrence (Nierenberg et al. 2003) (see Table 66–3) may be candidates for longer continuation treatment.

**Table 66–3 Risk Factors Influencing the Probability of the Recurrence of a Depressive Episode***

| Risk Factors for Depressive Recurrence |
|---|
| Residual symptoms |
| More than 3 prior depressive episodes |
| Chronic depression (episode > 2 years) |
| Family history of mood disorders |
| Comorbidities (e.g., anxiety disorder, substance abuse) |
| Late onset (age > 60 years) |
| Two or more acute medication trials to achieve remission |

*Modified from Nierenberg et al. (2003).

### *Prophylaxis of New Episodes*

If a decision for long-term maintenance treatment (prophylaxis against new depressive episodes) has been made, the transition from continuation to prophylaxis is not clear-cut. However, if there is no indication for prophylaxis or the patient refuses to continue on medication, a period of slow tapering off at the end of the continuation period is strongly advised. It has been suggested that the tapering phase should last at least 4–6 months (Bauer et al. 2002b).

Maintenance treatment is recommended for patients with recurrent episodes, especially when more than one episode (prior to the present one) has occurred during the last 5 years or when remission has been difficult to achieve. Other factors influencing the decision regarding maintenance treatment include both the number and severity of previous episodes, the duration of previous symptom-free intervals, the comorbid presence of other psychiatric or medical illnesses, as well as the presence of suicidal ideation. In patients with more than two or three relapses, year-long or sometimes life-long prophylactic treatment has been recommended, for example, the World Federation of Societies for Biological Psychiatry Guidelines recommend maintenance treatment of 5–10 years for patients with recurrent episodes not at special risk, for example, without genetic preposition, comorbidities or difficult psychosocial circumstances. They consider life-long maintenance in patients at greater risk, for example, with more severe episodes, and especially when two or three attempts to withdraw medication have been followed by another episode within a year (Bauer et al. 2003). Another apparent risk factor for recurrences is insufficient responsiveness during acute treatment trials: with two or more acute treatment trials needed to achieve remission, the average probability of a relapse within a 1 year follow-up increases, from 33.5% if only one to 50% if four treatment step were needed (Rush et al. 2006b).

Combining an antidepressant with lithium may not only improve relapse prevention (Sackeim et al. 2001) but also be more protective against suicide (Müller-Oerlinghausen et al. 2006). Once stabilized on this combination, it is not wise to withdraw lithium for at least a year (Bschor et al. 2002).

Where these recommendations are laid out for MDD, the advantages of continuation treatment may be less obvious in patients with long symptom-free intervals and/or only mild depression, and may not always outweigh the risks of some long–term pharmacotherapies, for example, hepatic or renal malfunction.

The chances of relapse decrease and the prognosis improves with time elapsed since discontinuing medication. The risk of a depressive relapse is 60% on placebo (compared to 29% on antidepressants) after 1 year. For the second and third year, the risk of relapse is reduced by 50% compared to the first year and may continue to decline (Geddes et al. 2003). Thus, decisions on long-term treatment must be made on an individual basis, taking into account the patient's past experience with longer medication-free intervals, if any.

For some patients, long-term treatment may lead to worse outcomes. A literature review by Fava (Fava 2003) raised the question of whether at least a substantial subgroup of depressed patients may not only have no benefit from maintenance medication, but even experience a worsening of the long-term course of the illness. According to Fava, the mechanism of this paradoxical effect may include tolerance to antidepressants in long-term treatment, onset of resistance upon each challenge with the same antidepressant, and withdrawal symptoms, with sudden discontinuation of antidepressants leading to destabilization. Fava speculates that continued drug treatment may initiate biological processes counteracting the initial acute effects of a drug and may result in loss of clinical effectiveness. With sudden drug discontinuation, these processes may operate unopposed at least for some time and increase vulnerability to relapse.

### *Alternatives to Antidepressants for Prophylactic Treatment: Lithium and Anticonvulsants*

If patients are not responsive to prophylactic antidepressant treatment or do not tolerate side effects, the first alternative is long-term lithium maintenance therapy. Although it may be even more efficacious in bipolar disorder and despite some negative published results in unipolar disorder (Burgess et al. 2001), the efficacy of lithium in preventing relapses in unipolar recurrent depression has been well established (Paykel 2001). Besides preventing new episodes, lithium has been demonstrated to normalize the mortality rates for cerebrovascular and cardiovascular disorders in affectively ill patients (Angst et al. 2002a). Combined lithium and antidepressant treatment reduces the risk of suicide to a significantly larger extent than antidepressants alone (Guzzetta et al. 2007). The usually recommended serum lithium levels for prophylaxis in unipolar recurrent depression are 0.5 to 0.8 mmol/L, but individual variations may occur.

Carbamazepine has been compared in two small double-blind trials with lithium in recurrent major depression, with results suggesting equal efficacy for lithium and carbamazepine (Blacker 1996). However, when using carbamazepine its capacity not only to induce its own hepatic metabolism, but also to accelerate metabolization of other drugs that are metabolized by CYP 3A4 needs consideration. Some antidepressants, for example, venlafaxine, nefazodone, reboxetine, and imipramine are substrates of CYP 3A4 and thus may not achieve sufficient plasma levels when used in combination with carbamazepine. CYP 1A2 and CYP2C9, which contribute also to carbamazepine metabolism, may also be inhibited by fluvoxamine. With these potential interactions and the limited scientific evidence from placebo-controlled studies, carbamazepine can only be recommended when other strategies have failed.

For other anticonvulsants only anecdotal reports and small case series have been published for prophylaxis in unipolar depression, but no controlled studies.

## Somatic Treatments

### Antidepressant Pharmacotherapy: General Considerations

The treatment portfolio in depression includes pharmacotherapy, psychotherapy, and sociotherapy. Pharmacotherapy is not always mandatory for less severe forms of depression, whereas severe depression usually requires pharmacotherapy or electroconvulsive therapy (ECT). In addition, a variety of other biological interventions such as sleep deprivation and bright light therapy may be effective in certain patient subgroups.

The discovery of TCAs was a milestone in the treatment of depression. However, despite their undoubted effectiveness, it soon became apparent that their anticholinergic and antihistaminergic side effects could cause problems. New antidepressants have been developed with a more selective mode of action to try to avoid these side effects. In the following section, we describe the modern antidepressants according their main mode of action, and subdivide the older tri- and tetracyclic substances according to their predominant action on serotonergic and noradrenergic neurotransmission.

Currently, TCAs and tetracyclic antidepressants with predominant serotonergic (e.g., clomipramine), noradrenergic (e.g., desipramine), or mixed serotonergic/noradrenergic (e.g., amitriptyline) action are available. In addition, selective and reversible inhibitors of monoaminooxidase A (RIMA, e.g., moclobemide), an irreversible MAO-B inhibitor (MAOBI, selegiline), nonselective and irreversible inhibitors of monoaminooxidase A and B (MAOI, e.g., tranylcypromine), selective SSRIs) (e.g., citalopram), selective (NARI) (e.g., reboxetine[3]), and antidepressants with a dual mode of action such as selective SNRI (e.g., venlafaxine), and NaSSA) (e.g., mirtazapine) acting via blockade of $\alpha_2$- and 5-$HT_2$-receptors are licensed. Furthermore, a dopamine and noradrenaline reuptake inhibitor (bupropion) and serotonin modulating antidepressants (e.g., trazodone) are available. The latest newly developed mechanism of action is the agonism at melatonergic $MT_1$ and $MT_2$ receptors and selective antagonism at serotonergic 5-$HT_{2c}$ receptors represented by the antidepressant agomelatine; FDA approval was still pending in late 2007. Other developments include the use of single enantiomers instead of racemic compounds, for example, escitalopram.

A summary of commonly used antidepressants including their primary mode of action and their influence on other receptor systems is shown in Table 66–4.

Despite the development of a variety of new antidepressants with different pharmacodynamic profiles, higher efficacy in comparison to older antidepressants has, so far, not been achieved. The latency of several weeks until the onset of sufficient therapeutic effects remains a serious and clinically relevant problem. A faster onset of response has been described in some publications for newer dual-action compounds, for example, mirtazapine and venlafaxine, but the clinical relevance is still controversial (Blier 2003). The only two methods for achieving more rapidly occurring, but in most cases unfortunately not sustained, antidepressant effects are sleep deprivation (Wu et al. 1990) and ECT (ECT Review Group 2003).

The usually recommended daily dosages for both starting and maintaining antidepressant treatments are presented in Table 66–5.

#### *Management of Medication Side Effects*

Minor side effects are common and associated with the majority of antidepressants, both old and new but the side effect profile differs. Patient complaints about side effects should always been taken seriously, otherwise nonadherence and unsupervised discontinuation will be the consequence. Patients do not always spontaneously report side effects, so active questioning is needed and somatic symptoms and concerns attributed to the medication by the patient need to be distinguished from symptoms of depression.

#### *Summary of Side Effects*

Antidepressant drugs can produce common side effects according to their receptor profiles. In addition, although rare, they may cause discontinuation symptoms, allergic reactions and blood dyscrasias.

Anticholinergic and antihistaminergic side effects may complicate the use of TCAs. In case of overdose, cardiovascular complications are more frequent then with other antidepressants, although they may also occur with newer antidepressants such as SSRIs (Pacher et al. 1999). Newer antidepressants have considerably fewer anticholinergic effects, but it is important to pay attention to their specific side effect profiles. In particular, the activating properties of NARI can cause tremor and restlessness together with sleep disturbances. SSRIs raise serotonin levels at multiple sites and at multiple receptors throughout the brain (Stahl 1998) and may cause nausea, headache, agitation, and a general activation syndrome, sexual dysfunction, and sometimes sleeplessness. Substances with additional antihistaminergic properties such as mianserin, mirtazapine, or doxepine may induce drowsiness at treatment onset, and later often increased appetite and weight gain (Kent 2000).

The specific side effect profiles of antidepressants are summarized in Table 66–6. In combination with Table 66–4 the specific side effect profile which can be expected using a specific antidepressant can be deduced.

The discontinuation of antidepressants may also elicit adverse events, sometimes mistaken as signs of dependence. A sudden stop of treatment may provoke discontinuation symptoms which have been described for numerous classes of antidepressant drugs (particularly frequent with MAO inhibitors, venlafaxine and SSRIs, especially paroxetine, and less frequent with fluoxetine and escitalopram) (Baboolal 2004, Haddad 1998, Rosenbaum et al. 1998, Schatzberg et al. 2006). Typical features of addiction, however, such as increasing tolerance and compulsive use, are missing with antidepressants[3]. Only bupropion, used as an antidepressant and for smoking cessation, has been a matter of controversy, but the compound is not amphetamine-like and an abuse potential is very unlikely in humans (Griffith et al. 1983, Miller and Griffith 1983).

A discontinuation syndrome manifests itself mostly as a "*Flu-like*" syndrome including agitation, sleep-disturbances, sweating, gastrointestinal discomfort, and headache. It may become particularly dramatic in newborns whose mothers

**Table 66–4 Commonly Used Antidepressants Including Their Primary Mode of Action and Their Additional Influence on Other Receptor Systems**

| Pharmacological group | Generic name | Primary pharmacodynamic mode of action | Secondary pharmacodynamic actions | Additional effects |
|---|---|---|---|---|
| SSRI | Citalopram | SRI | | |
| SSRI | Escitalopram[7] | SRI | | |
| SSRI | Fluoxetine | SRI | | |
| SSRI | Fluvoxamine | SRI | | |
| SSRI | Paroxetine | SRI | | ($M_1$) |
| SSRI | Sertraline | SRI | | DRI |
| SNRI | Venlafaxine | SRI/NRI | | |
| SNRI | Duloxetine | SRI/NRI | | |
| SNRI | Milnacipran | SRI/NRI | | |
| NARI | Reboxetine[2] | NRI | | ($M_1$) |
| (NARI) | Viloxazine | (NRI) | | |
| NaSSA | Mirtazapine | $\alpha_2$ | 5-$HT_{2,3}$; +5-$HT_1$ | $H_1$, $\alpha_1$, $\alpha_2$ |
| MT | Agomelatine[8] | MT1/MT2 | 5-$HT_{2c}$ | |
| RIMA | Moclobemide | MAI | | ($M_1$) |
| MAOI | Selegiline[9] | MBI | APD | |
| MAOI | Phenelzine | MAI | | |
| MAOI | Isocarboxacid | MAI/MBI | | |
| MAOI | Tranylcypromine | MAI/MBI | APD | |
| MAOI | Pirasidol[10] | MAI/MBI | | |
| SMA | Nefazodone[11] | SMA | 5-$HT_{2a}$, SRI | |
| SMA | Trazodone | SMA | 5-$HT_2$, SRI | $\alpha_1$ |
| DNRI | Bupropion | DNRI | NRI | |
| DA | Trimipramine | DA | 5-$HT_2$ | $H_1$, $M_1$, $\alpha_1$, $\alpha_2$ |
| GM | Tianeptine | GM | | |
| S-TCA | Clomipramine | SRI | NRI, $D_2$ | $M_1$, $\alpha_1$ |
| S/N-TCA | Amitriptyline | SRI/NRI | | $H_1$, $M_1$, $\alpha_1$, $\alpha_2$ |
| S/N-TCA | Amitriptylinoxid | SRI/NRI | | $H_1$, ($M_1$), $\alpha_1$, $\alpha_2$ |
| S/N-TCA | Dibenzepine | SRI/NRI | | |
| S/N-TCA | Dosulepine/Dothiepin | SRI/NRI | | |
| S/N-TCA | Doxepin | SRI/NRI | | $H_1$, $M_1$, $\alpha_1$ |
| S/N-TCA | Imipramine | SRI/NRI | | $M_1$, $\alpha_1$ |
| S/N-TCA | Melitracen[12] | SRI/NRI | | $M_1$ |
| S/N-TCA | Protriptyline | SRI/NRI | | |
| N-TCA | Desipramine | NRI | | ($M_1$) |
| N-TCA | Lofepramine | NRI | | $M_1$, $\alpha_1$ |
| N-TCA | Nortriptyline | NRI | SRI | $M_1$, $\alpha_1$ |
| S-TetraCA | Mianserin | SRI | NAR | $H_1$, $\alpha_1$, $\alpha_2$ |
| N-TetraCA | Amoxapine | NRI | | |
| N-TetraCA | Maprotiline | NRI | | $H_1$, ($M_1$), $\alpha_1$ |

+5-$HT_1$, serotonin 1 receptor stimulation; 5-$HT_2$, serotonin 2 receptor antagonism; 5- $HT_{2c}$, selective 5-$HT_{2c}$ receptor antagonist; 5-$HT_3$, serotonin 3 receptor antagonism; $\alpha_1$, $\alpha_1$ receptor antagonism; $\alpha_2$, $\alpha_2$ receptor antagonism; all. 5HTT, binding to the allosteric site of the serotonin transporter; APD, amphetamine prodrug; DA, dopamine ($D_2$) receptor antagonist; DNRI, dopamine and noradrenaline reuptake inhibitor; DRI, dopamine reuptake inhibition; GM, glutamatergic modulator; $H_1$, blockade of histamine 1 receptors; $M_1$, blockade of cholinergic muscarinic receptors; MAI, monoaminooxidase A inhibition; MBI, monoaminooxidase B inhibition; MAOI, irreversible inhibitor of monoaminooxidase A and B; MAOBI, irreversible inhibitor of monoaminooxidase B; MT, melatonergic antidepressant; MT1/MT2, melatonin 1 and melatonin 2 receptor agonist; NAR, noradrenaline releasing properties; NARI, selective noradrenaline (norepinephrine) reuptake inhibitor; NaSSA, noradrenergic and selective serotonergic antidepressant; NRI, noradrenaline (norepinephrine) reuptake inhibition; N-TCA, tricyclic antidepressant with primary noradrenergic effects; N-TetraCA, tetracyclic antidepressant with primary noradrenergic effects; RIMA, reversible inhibitor of monoaminooxidase A; SMA, serotonin modulating antidepressant; SNRI, selective serotonin and noradrenalin reuptake inhibitor; S/N-TCA, tricyclic antidepressant with similar serotonergic and noradrenergic effects; M-TCA, modified TCA with possible neuroprotective effects and effects on neuroplasticity; SRI, serotonin reuptake inhibition; SRS, serotonin reuptake stimulation; SSRI, selective serotonin reuptake inhibitor; S-TCA, tricyclic antidepressant with primary serotonergic effects; S-TetraCA, tetracyclic antidepressant with primary serotonergic effects.

were treated with serotonergic drugs until delivery (Wen et al. 2006). The onset of symptoms occurs within 2 days on average (Bogetto et al. 2002) and they may take up to 2 weeks to subside. Discernible effects are more likely with high doses and prolonged treatment. With less than 5 weeks of exposure, withdrawal effects are quite unusual and unexpected.

Besides the acute harassment, discontinuation symptoms may stress the therapeutic alliance by weakening confidence in the practitioner's advice (Garner et al. 1993), and put the patient at risk of an early relapse (Fava 2003, Harvey et al. 2003).

### *Consequences for Treatment*

If

- side effects are tolerable for the short, but not long term
- full or at least partial remission has been achieved
- and the patient is still willing to continue on the medication despite having experienced side effects, careful tapering down of the medication until side effects fade would be the first step. If side effects occur at low doses, therapeutic drug monitoring may be helpful. If side effects do not subside or efficacy is lost after tapering of

**Table 66–5 Commonly Used Antidepressants Including Dosage Recommendations[13]**

| Generic name | Recommended Starting Dose (mg) | Dosage Range Recommended by the Producer (mg/d) |
|---|---|---|
| Agomelatine | 25 | 25–50 |
| Amitriptyline | 25–75 | 150–300 |
| Amitriptylinoxid | 30–60 | 180–300 |
| Amoxapine | 50 | 100–400 |
| Bupropion | 100 | 200–300 |
| Citalopram | 20 | 20–60 |
| Clomipramine | 25–50 | 100–250 |
| Desipramine | 25–75 | 100–300 |
| Dibenzepine | 120–180 | 240–720 |
| Dosulepine / Dothiepin | 75 | 75–150 |
| Doxepine | 25–75 | 150–300 |
| Duloxetine | 40 / 60[14] | 60–120 |
| Escitalopram | 5–10 | 10–20 |
| Fluoxetine | 20 | 20–80 |
| Fluvoxamine | 50–100 | 100–300 |
| Imipramine | 25–75 | 150–300 |
| Isocarboxacid | 20 | 20–60 |
| Lofepramine | 70 | 140–210 |
| Maprotiline | 25–75 | 150–225 |
| Melitracen | 20 | 20–30 |
| Mianserin | 30 | 60–120 |
| Milnacipran | 50 | 100–200 |
| Mirtazapine | 15 | 30–45 |
| Moclobemide | 150–300 | 300–600 |
| Nefazodone | 100 | 300–600 |
| Nortriptyline | 25–50 | 75–300 |
| Paroxetine | 20 | 20–60 |
| Phenelzine | 15 | 30–90 |
| Protriptyline | 10 | 20–60 |
| Reboxetine | 4 | 8–12 |
| Selegiline | oral: 30<br>transdermal: 6 | oral: 30–60<br>transdermal: 6–12 |
| Sertraline | 50 | 50–200 |
| Tianeptine | 12.5 | 25–37.5 |
| Tranylcypromine | 10 | 20–40 |
| Trazodone | 50–100 | 200–600 |
| Trimipramine | 25–50 | 150–400 |
| Venlafaxine | 75 | 75–375 |
| Viloxazine | 100 | 200–500 |

medication, switching to an antidepressant in another class is advised.

If a discontinuation syndrome occurs, it can usually be abolished by re-starting the withdrawn drug followed by slow tapering off.

For the management of side effects, education of the patient plays an essential role. Experiencing side effects is less frightening if the patient is aware about their possibility. Especially with side effects that may subside after some days, such as increased sleepiness, informed patients may be more likely to tolerate them and to stay on the medication.

### *Blood Dyscrasias and Disturbance of Erythro- and Leucopoiesis During the Use of Antidepressants*

Neutropenia and thrombocytopenia[4] have been observed during treatment with mood stabilizers like carbamazepine, lamotrigine, or valproate. During antidepressant exposure with a variety of substances, including TCA or tetracyclic substances such as mianserin, neutropenia has also been reported. For the newer antidepressants, inconsistent case reports have been published for SSRI, venlafaxine, and mirtazapine.

### *Treatment-Emerging Suicide and Suicidality*

Evidence that a given antidepressant increases suicide rates can not be derived from a single randomized controlled trial. Fortunately, suicide is still such a rare event that it can not serve as a primary outcome criterion (besides the fact that such a prospective study would be unethical). Thus, less clearly defined parameters as "suicidality," including suicidal ideation, preparation for suicide, suicide attempts, but sometimes just the wish to be dead (which is a common symptom and indicative for the severity of depression, have to serve for detecting a potential suicide risk, As we do not know the exact relationship between what is, partially arbitrarily, defined as suicidality and completed suicide, the methodological basis for assessing suicide risk becomes weak.

Following several case reports in the 1990 on new-onset suicidality with fluoxetine, especially in children and adolescents, the FDA commissioned an independent group of investigators at Columbia University to review all untoward adverse events that suggested suicidal-like activity in controlled trials of SSRIs in children and adolescents. In 4,400 depressed children and adolescents in a total of 24 studies, there were no completed suicides; however, the risk of suicidal-like ideation or activity was 4% on active medication and 2% on placebo (US Food & Drug Administration 2005). The exact significance of this finding is not clear and the FDA did not make any conclusions regarding causality. A similar finding of increased risk of suicide attempts (OR: 2.28), but not of completed suicides has been reported in a recent meta-analysis of 702 RCTs primarily in adult patients (Fergusson et al. 2005). However, two other meta-analyses found no evidence that SSRIs increased the risk of suicide (Gunnell et al. 2005, Hammad et al. 2006).

Another source of information is naturalistic follow-up studies. Grunebaum et al. (Grunebaum et al. 2004) presented the results of a methodologically very sound analysis of US registries for the years between 1985 and 1999. Prescription rates for SSRIs and other newer antidepressants were both inversely associated with suicide rates. In a multivariable analysis adjusting for unemployment and alcoholic beverage consumption rates, SSRI antidepressant prescription rates remained inversely associated with the national suicide rate, suggesting an overall antisuicidal effect of medication. It is also of note that with the decline of antidepressant prescription in the US due to the FDA black box warning, suicide rates have increased again (Gibbons et al. 2007).

The effect of antidepressants on suicidality needs further evaluation. If at all, there may be more compelling evidence in adolescents than in adults. A potential explanation may be a higher rate of substance abuse or an undetected bipolar disorder with mixed symptomatology. Both underlying conditions may become harmful together with the activating, sometimes agitating effects, especially of SSRI and some SNRI. In adults, the more compelling evidence is for an antisuicidal effect of antidepressant treatment, generated

**Table 66–6 Modes of Action and Receptor Profiles, Direct and Indirect Effects of Antidepressants Possibly Associated with Clinically Relevant and Compliance Influencing Side Effects**

| Influenced receptors or neurotransmitters | Mode of action | Typical side effects (receptor)[15] |
|---|---|---|
| $M_1$ receptor | Antimuscarinic / Anticholinergic | • Dry mouth<br>• Accommodation disturbances<br>• Constipation<br>• Miction disturbances<br>• Worsening of angle-closure glaucoma<br>• Hyperhidrosis<br>• Cognitive disturbances<br>• Delirium<br>• Cardiac arrhythmias |
| $H_1$ receptor | Antihistaminergic | • Sedation<br>• Drowsiness<br>• Daytime tiredness<br>• Increased appetite<br>• Weight gain<br>• Metabolic syndrome |
| $\alpha_{1/2}$ receptor | Antiadrenergic | • Hypotension |
| NA transporter | Noradrenalin-Reuptake inhibition/ noradrenergic effects | • Tremor<br>• Dry mouth<br>• Tachycardia<br>• Restlessness<br>• Sleep disturbances<br>• Hypertonia |
| 5HT transporter blockade /5HT receptor agonism | Serotonin-Reuptake inhibition /serotonergic effects | • Headache ($5HT_{1D}$)<br>• Restlessness, agitation, akathisia ($5HT_2$)<br>• Anxiety, panic ($5HT_2$)<br>• Decreased appetite ($5HT_2$)<br>• Weight reduction ($5HT_2$)<br>• Sleep disturbances ($5HT_2$)<br>• Sexual dysfunction ($5HT_2$)<br>• Nausea ($5HT_3$)<br>• Diarrhea ($5HT_4$)<br>• Serotonin syndrome (all 5HT receptors; predominantly in combinations)<br>• Lack of emotion<br>• SIADH[16]<br>• Enhanced bleeding risk[17] |

mainly from large observational databases, but partially also from meta-analysis of RCTs (Goldney 2006).

## SSRIs

### *Efficacy*

SSRIs are the most frequently prescribed antidepressants as a first line treatment (Ostacher et al. 2005). Despite their similarities, some characteristics differ among SSRIs (see Table 66–7). Good efficacy has been described for each of the currently available substances, regardless of the etiology or severity of depression. Available data suggest that, within the group of SSRIs, escitalopram may be the most powerful (Llorca et al. 2005). A pooled analysis of all available study data found significant advantages of escitalopram in comparison to several SSRIs such as citalopram, fluoxetine, and sertraline and also in comparison to the SNRI venlafaxine (Kasper et al. 2006).

Some other antidepresants may be superior to SSRIs (venlafaxine (see e.g., Cipriani et al. 2006), milnacipran (see e.g., Puech et al. 1997), mirtazapine (see e.g., Thase et al. 2006a), but it is difficult to interpret the clinical meaning of these results. Compared to TCAs, the overall efficacy of SSRIs appears similar (Geddes et al. 2000), but MAOI may have an advantage over SSRI in treatment-resistant patients and those showing atypical features of depression (see Section, "Other Clinical Features with Possible Impact on the Course and Treatment Outcome").

### *Safety and Tolerability*

Most studies agree that the safety and tolerability profile of SSRIs as a pharmacological group of compounds is considerably better than that of TCAs (Cheeta et al. 2004, Mace and Taylor 2000). Since SSRIs have fewer anticholinergic effects, they have lower cardiovascular toxicity together with a lower risk for constipation and urinary retention. Other anticholinergic side effects, for example, effects on the visual system such as an enhanced risk for worsening of an angle-closure glaucoma and accommodation disturbances, are also rare using SSRIs[5]. The most frequent side effects

**Table 66–7 Clinical Highlights and Differences Between SSRIs***

| Generic Nname | Specific Cclinical Ffeatures of SSRIs |
|---|---|
| Citalopram (Bezchlibnyk-Butler et al. 2000) | One of the most selective SSRIs<br>Possibly lower incidence of sexual dysfunction<br>Possibly better tolerability in the elderly |
| Escitalopram (Baldwin 2002) | One of the most selective and best tolerated SSRIs<br>Possibly rapid onset of action and high effect size during antidepressant treatment, good effect in anxious depression and comorbid anxiety disorders |
| Fluoxetine (Calil 2001) | Good effect in atypical depression<br>Good effect in patients with fatigue and low energy<br>Long half life, weekly administration possible |
| Fluvoxamine (Ware 1997) | Good effect in anxious depression and comorbid anxiety disorders, potential advantages in psychotic depression<br>Possibly lower incidence of sexual dysfunction<br>Discontinuation effects after rapid tapering |
| Paroxetine (Green 2003) | Good effect in anxious depression and comorbid anxiety disorders<br>Mild anticholinergic action<br>Discontinuation effects more likely than for other SSRIs |
| Sertraline (Khouzam et al. 2003) | Good effect in atypical depression<br>Least selective over dopamine<br>More gastrointestinal side effects, but best documented cardiovascular safety |

*Modified according to Stahl (1997, 2006).

after short-term SSRI treatment are gastrointestinal discomfort such as nausea, diarrhea, or emesis. Also common are restlessness and agitation, sleep disturbances, dizziness, and headache. During long-term SSRI treatment sexual dysfunction such as loss of libido, anorgasmia, and in men disturbances of erectile or ejaculatory function may become a significant limitation. In long-term treatment, SSRI are also associated with discontinuation syndromes, especially paroxetine (Trenque et al. 2002).

Disorientation, restlessness, myocloni together with hyperreflexia, tremor, and pain-syndromes together with unstable vital signs are symptoms of the potentially fatal serotonin syndrome (Boyer et al. 2005). It occurs predominantly as an interaction of SSRIs with MAOIs or other serotonergic substances (e.g., S-TCAs or triptans used during acute therapy of migraine attacks), even before and after treatment with the SSRI, depending on the half-life of the other medication, but rarely during SSRI monotherapy.

Rare side effects of SSRIs are weight gain, anticholinergic effects or extrapyramidal motor side effects. A very rare adverse event during SSRI therapy of younger, but a not uncommon event in elderly patients, is an inappropriate secretion of antidiuretic hormone possibly causing an electrolyte imbalance and hyponatriemia with an increased risk for seizures (Degner et al. 2004) Finally, the combined use of SSRIs and substances increasing the risk of bleeding, for example, nonsteroidal anti-inflammatory agents or aspirin, is discouraged due to a blockade of serotonin reuptake in platelets and subsequent platelet dysfunction (Serebruany 2006).

## Selective Serotonin and Noradrenaline Reuptake Inhibitors

### *Efficacy*

SNRIs represent a group of antidepressants with a dual mode of action, on both serotonin and norepinephrine reuptake. Today, three substances of this group, venlafaxine, milnacipran, and duloxetine, are available. Response rates from clinical trials with venlafaxine and duloxetine are comparable, but venlafaxine has shown a trend to be more favorable in achieving remission (Vis et al. 2005). In comparison to SSRIs, venlafaxine appears equally effective as sertraline and escitalopram, but may be more potent than fluoxetine and paroxetine (Cipriani et al. 2006). For milnacipran, meta-analysis has shown an antidepressant efficacy similar to that of imipramine and significantly superior to that of SSRIs (Puech et al. 1997). Direct comparisons between duloxetine and paroxetine in RCTs displayed inconclusive results, and no significant difference was observed between duloxetine and escitalopram (Hirschfeld et al. 2004).

Direct comparisons between SNRIs (venlafaxine and milnacipran) and TCAs showed no significant or clinically relevant differences in efficacy (Samuelian and Hackett 1998, Van Amerongen et al. 2002).

### *Safety and Tolerability*

SNRI treatment shows a favorable tolerability profile when compared with TCAs, with most adverse events occurring early in treatment and tending to decrease or disappear with continued treatment (Stahl et al. 2005). For venlafaxine an extended release formulation is available that improves tolerability in comparison to the immediate release formulation. High dose therapy with venlafaxine may cause hypertension (Thase et al. 2006b). The risk of elevated blood pressure seems to be less prominent in newer SNRIs such as duloxetine and milnacipran (Stahl et al. 2005).

In case of overdose, the fatal toxicity index of venlafaxine seems to be in between SSRIs and TCAs (Koski et al. 2005), therefore some guidelines recommend to use SNRIs only as a second-line treatment after SSRIs have failed (Medicines and Healthcare products Regulatory Agency 2006, National Institute for Health and Clinical Excellence 2004).

## Selective Noradrenaline Reuptake Inhibitors

### *Efficacy*

The only marketed NARI, reboxetine, available in Europe and Australia, displays a similar efficacy as other new antidepressants. RCTS showed noninferiority to sertraline, fluoxetine, citalopram (Papakostas et al. 2007a) and imipramine (Montgomery 1998), but reboxetine may be more efficacious than SSRI in psychomotor retarded patients (Rampello et al. 2004).

### Safety and Tolerability

In all published studies, reboxetine displayed a good safety and tolerability profile (Burrows et al. 1998). Sexual dysfunction appears less common with reboxetine than with the SSRI fluoxetine (Clayton et al. 2003). Less frequent than with SSRI, reboxetine treated patients may also experience agitation and sleep disturbances. Due to $\alpha$-receptor agonistic effects reboxetine may cause hyperhidrosis and urinary retention despite its low anticholinergic activity.

## $\alpha$-Receptor Blocking Tetracyclic Antidepressants

### Efficacy

The structurally related TCAs mianserin and mirtazapine represent the $\alpha_2$-receptor blocking antidepressants. Mianserin was developed first and shows a higher affinity for the $\alpha_1$-adrenoceptor and higher noradrenaline reuptake compared to mirtazapine (Kelder et al. 1997). Mirtazapine is characterized in its own class with noradrenergic and specific serotonergic properties (NaSSA). The $\alpha_2$ antagonistic effect in the case of mirtazapine results in serotonergic activation, whereas with mianserin, the $\alpha_1$ antagonistic effect counteracts the $\alpha_2$ antagonistic effect.

Both mianserin and mirtazapine are at least as effective as TCAs and have some advantages in comparison to other newer antidepressants (Szegedi et al. 2005). Especially in the common case of insomnia accompanying a depressive disorder, mirtazapine significantly improves sleep quality in addition to its antidepressant effects (Thase 1999). Limited evidence suggests a more rapid onset of antidepressant action with mirtazapine in comparison to SSRIs (Blier 2003).

### Safety and Tolerability

In comparison to TCAs, NaSSAs exert a substantially better side effect profile (Tran et al. 2003). The safety in overdose is similar to that of SSRIs (Olver et al. 2001), but typical serotonergic side effects such as sexual dysfunction and gastrointestinal complaints are less frequent in mirtazapine-treated patients (Montgomery 1995). The most commonly reported adverse events during mirtazapine therapy are related to antihistaminergic properties, such as initial somnolence and dizziness, together with increased appetite and consecutive weight gain in the long run (Tran et al. 2003). Potentially fatal side effects are rare, but clinicians have to be aware of possible neutropenia both with mianserin and mirtazapine (Ozcanli et al. 2005). In addition, a rare risk of agranulocytosis has been reported for mianserin.

## Unselective Monoaminoreuptake-inhibitors/ TCAs

From the introduction of the first antidepressant, imipramine, tricyclics were the cornerstone in the treatment of depression for a long time. Over the last decade, however, tri- and tetracyclic antidepressants have lost their leading role, partly due to their tolerability problems, partly due to the emergence of new treatment alternatives.

Clinically, it can be useful to subdivide TCAs not only according to their sedating or activating properties, but also according to their effects on serotonergic, noradrenergic, and dopaminergic neurotransmission. In case of treatment failures and pharmacotherapy resistance, switching from serotonergic to noradrenergic or mixed acting TCAs seems plausible, but controlled studies supporting this approach are still lacking.

### Efficacy[6]

TCAs are still an effective treatment of depression independent of its severity. Controlled studies comparing TCAs with other classes of antidepressants were described above. Especially in severely depressed hospitalized patients, mixed serotonergic/noradrenergic tricyclics seem to perform better than SSRIs (Anderson et al. 2000) or the RIMA Moclobemide (Danish University Antidepressant Group 1993). Based on clinical experience, but without controlled evidence, TCAs with less significant sedating effects, such as clomipramine or desipramine, seem to be more suitable in retarded and anergic depression. TCAs with inherited strong antihistaminergic effects such as doxepine, amitriptyline or dosulepine may have advantages in agitated patients with significant sleep disturbances.

### Safety and Tolerability

The main concerns in using TCAs as a first line treatment are anticholinergic and antihistaminergic side effects. Sedating properties may be of use in the treatment of depression-related sleep disturbances, but daytime drowsiness and sedation often lead to discontinuation of treatment. In the long run, increased appetite, a consequent weight gain and in some cases the risk of metabolic syndrome becomes crucial.

Caution is warranted in suicidal patients due to the higher cardiotoxicity of tri- and tetracyclics in comparison with the more selective newer antidepressants.

## Glutamatergic Modulation/Other Modes of Action Not Directly Involving Monoamines—Tianeptine

Despite its modified tricyclic structure, initial studies showed that the modified TCA tianeptine did not share common pharmacological properties with other TCA, MAOI, or SSRI antidepressants (Wilde and Benfield 1995). Following chronic administration, tianeptine induces adaptive changes in cortical, but not hippocampal serotonin transporters (Pineyro et al. 1995a, Pineyro et al. 1995b) and has neuroprotective effects that contribute to antidepressant properties (McEwen et al. 2005). Tianeptine has been shown to change the neuronal architecture of the hippocampus and amygdala, the rate of apoptosis in the hippocampus and temporal cortex and to restore the hippocampal volume following exposure to chronic stress (McEwen et al. 2005). These effects have been explained in terms of modulation of glutamatergic transmission (Reagan et al. 2004).

### Efficacy

In published RCTs, the efficacy of tianeptine was comparable to SSRIs (Kasper and Olie 2002), amitriptyline (Invernizzi et al. 1994) and mianserin (Brion et al. 1996).

### Safety and Tolerabilhty

Tianeptine does not appear to be associated with severe anticholinergic or cardiovascular side effects (Loo and Deniker 1988). The overall tolerability profile is comparable to SSRIs in general and better than that of paroxetine (Kasper and Olie 2002).

## MAOIs

### *Efficacy*

A comparison of all available irreversible MAOIs reported similar efficacy to TCAs, but MAOI treatment may be especially efficacious in patients suffering from depression with anergic or atypical features (Henkel et al. 2006). In treatment-refractory depression, the use of supra-therapeutical doses of MAOI has been proposed, but only few clinical data support the effectiveness in refractory depression (Adli et al. 2005). Irreversible MAOIs are mostly considered as a subordinate treatment choice because of their potential to cause serious adverse events.

Selegiline, an MAO B inhibitor predominantly used in the therapy of PD, may exert significant antidepressant effects (Amsterdam 2003, Bodkin et al. 2002). A selegiline patch has been approved as an antidepressant by the FDA. This is the only antidepressant patch approved so far, and it may be a useful tool in patients who tend to forget to take medication.

Reversible inhibitors of monoaminooxidase A (RIMAs) are considered to be as effective as TCAs and SSRIs, but somewhat less effective than irreversible MAOIs (Bonnet 2003).

### *Safety and Tolerability*

MAOIs in combination with other sympathomimetic medications or tyramine-rich food may provoke a hypertensive crisis demanding, immediate treatment, for example, phentolamine, therefore dietary restrictions are necessary (Brown and Bryant 1988). These restrictions are not necessary when using RIMAs, however, at doses the risk of interactions with tyramine might again become clinically relevant (Bonnet 2003). In case of the selegiline transdermal patch, dietary modifications are necessary when using higher dose ranges (9 or 12mg/day).

Discontinuation symptoms including agitation, anxiety, sleeplessness or drowsiness, and even hallucinations and delirium have been described for MAOI (Dilsaver 1988). The risk for a serotonin syndrome due to the concomitant use of or accidental combination with other serotonin-enhancing antidepressants has to be kept in mind. Depending on the half-life of the substances, a drug-free interval of at least 2 weeks in case of a serotonergic medication before or after irreversible MAOIs is necessary to be on the safe side. In case of the prescription of MAOIs after fluoxetine, the interval has to be extended up to 5 weeks; in case of prescribing serotonergic substances after the RIMA moclobemide, it can be shortened to 3 days.

## Serotonin Modulating Antidepressants

### *Efficacy*

Nefazodone and its structural analog trazodone block 5-$HT_2$ receptors, but only modestly inhibit the reuptake of serotonin and noradrenaline (Blier et al. 2007). Both medications have proven antidepressant efficacy in RCTs and comparator trials (DeVane et al. 2002, Haria et al. 1994). Due to their sedating properties, nefazodone and trazodone appear particularly suitable for agitated patients and patients suffering from insomnia (Boerner and Möller 1999, Thase 1999).

### *Safety and Tolerability*

SMAs have a similar safety margin to TCAs, but are better tolerated (Lader 1996) due to lower anticholinergic and antihistaminergic activity. The most common side effects are sedation, dry mouth, nausea, somnolence, and dizziness (Cyr and Brown 1996). For trazodone, cases of priapism have also been reported, which led to it being investigated as an agent for erectile dysfunction (Fink et al. 2003).

However, several case reports of severe hepatotoxicity leading sometimes to fatal hepatic failure have been published for nefazodone, so that intensive clinical and laboratory monitoring is advised (Lucena et al. 2003). As a result, the original producer has withdrawn nefazodone from the market, but it is still available as a generic substance.

## DNRI

Currently, this class contains only one medication, bupropion; however, its mechanism of action is not as clear as the class name suggests. It is thought to be related to inhibition of presynaptic dopamine and noradrenaline reuptake transporters (Foley et al. 2006), but within the therapeutic dose range of bupropion, PET scan studies in humans found no effects on dopamine or noradrenaline transporters (Kugaya et al. 2003).

### *Efficacy*

In RCTs, bupropion showed significant antidepressant efficacy with an at least equal effect size in comparison to different SSRIs, namely sertraline, fluoxetine, and paroxetine, as well as in comparison with the TCAs amitriptyline, imipramine, and doxepine and the SNRI venlafaxine and the SMA trazodone (Foley et al. 2006).

### *Safety and Tolerability*

In comparison to the SSRIs sertraline and fluoxetine, bupropion-treated patients showed a lower rate of serotonergic side effects such as sexual dysfunction, gastrointestinal complaints, insomnia, and agitation (Hansen et al. 2005). Sexual dysfunction in male patients may be especially prominent but can be reduced by using an extended release formulation. Generalized seizures are considered to be a rare event in patients without risk factors (Montgomery 2005), but still more frequent than with other antidepressants, especially in conditions that increase the risk for seizures such as alcohol withdrawal, anorexia, or bulimia (Horne et al. 1988).

## Antidepressants Targeting Melatonergic Neurotransmission

A variety of animal studies and clinical trials in depressed patients suggest that agomelatine, a synthetic melatonergic $MT_1$ and $MT_2$ receptor agonist with serotonin $(5\text{-HT})_{2C}$ receptor antagonist properties within the central nervous system, has antidepressant effects. This has been confirmed together with a good tolerability profile in several trials (Montgomery and Kasper 2007) comparing agomelatine to established antidepressants such as paroxetine and venlafaxine. Sleep-related complaints were especially ameliorated without sedation during daytime.

A randomized, double-blind, multicenter study demonstrated the absence of discontinuation symptoms in sustained remitted patients when stopping agomelatine (Montgomery

et al. 2004). In summary, agomelatine represents a promising novel strategy in the treatment of depression, but its approval is still pending.

### Herbal preparations Used in the Treatment of Depression–-St. Johns wort

It is a matter of ongoing controversy whether herbal preparations used in the treatment of depression should be classified as antidepressants (Bauer et al. 2002b), although they make up a reasonable share of antidepressant prescriptions in several countries. The main reason is that RCTs could not prove that these medications are useful in severe MDD; another reason is their insufficiently defined mechanism of antidepressant action.

#### *Efficacy*

Most studies have concentrated on the use of St. John's wort (hypericum perforatum). Many different preparations of St. John's wort are available in over-the-counter packages that differ in the number and concentration of active and inactive, helpful and potentially harmful constituents. Both serotonergic mechanisms and MAO inhibition as antidepressant modes of action have been discussed (Deltito and Beyer 1998). Although promising in small RCTs against fluoxetine, sertraline, paroxetine, and imipramine, St John's wort did not separate from placebo in a sufficiently powered RCT (Shelton et al. 2001), and a recent meta-analysis also shows inconsistent results (Linde et al. 2005).

#### *Safety and Tolerability*

Comparative studies suggest a significantly better tolerability of St John's wort in comparison to SSRIs and TCAs. In particular, hypericum therapy was devoid of anticholinergic side effects, sedation, gastrointestinal disturbances, and sexual dysfunction (Trautmann-Sponsel and Dienel 2004). Because its mechanisms of action involve serotonergic mechanisms or monoamine-oxidase inhibition, concurrent use of St John's wort together with SSRIs and MAOIs should be avoided (Deltito and Beyer 1998) as a serotonin syndrome could theoretically occur.

### $\Omega_3$ Polyunsaturated Fatty Acids

#### *Efficacy*

After the publication of a potential epidemiological link between low fish intake and depression (Hibbeln 1998), low $\Omega_3$ fatty acid levels in depressed women during the perinatal period have been found (Rees et al. 2005). In four out of seven double-blind RCTs, a significant improvement of depressive symptoms could be seen after regular ingestion of eicosapentaenoic acid, an $\Omega_3$ fatty acid, as an adjunct to antidepressant treatment in comparison to placebo (Nemets et al. 2002, Peet and Horrobin 2002). A small study in postpartum depression established a dose range of 0.5 to 2.8 g/day as an effective dosage (Freeman et al. 2006).

However, other RCTs failed to show antidepressant effects of $\Omega_3$ fatty acids (see e.g., Silvers et al. 2005). Furthermore, it remains unknown whether $\Omega_3$ fatty acids substitution is effective only in patients with abnormally low $\Omega_3$ fatty acid levels or in all depressed patients.

#### *Safety*

The safety and tolerability profile of $\Omega_3$ fatty acid therapies seems to be unproblematic. Only diarrhea is a common side effect. As $\Omega_3$ fatty acids are considered cardioprotective, an additional benefit for depressed patients who have an elevated cardiovascular risk has been proposed and should be investigated further (Frasure-Smith et al. 2004).

## Treatment Refractory Depression

A general problem in pharmacotherapy of depression is the likelihood of nonresponse to the first antidepressant treatment (Rush 2007). Up to 50% of depressed patients do not respond sufficiently to a first course of an adequate antidepressant treatment (about 30% do not show sufficient improvement; about 20% drop out due to tolerability problems). Half of patients also fail to respond to a second antidepressant treatment trial. If several antidepressant treatment trials have been unsuccessful, response rates after switching to another drug are likely to decrease further (Fava et al. 2006) and long-term prognosis worsens (Rush et al. 2006b).

Patients who do not respond to at least two antidepressant monotherapies (in some wider definitions even one) are often defined as treatment resistant. However, reasons for such "treatment resistance" or "nonresponse to antidepressant treatment" may vary and often do not reflect true resistance to treatment. The definition by Ananth (Ananth 1998) as a "*failure to respond adequately to two successive courses of monotherapy with pharmacological different antidepressants given in adequate dose for sufficient length of time*" includes a number of prerequisites: correct diagnosis, adequate treatment in terms of dosage, duration, and compliance and unsuccessful previous therapy.

Biological hypotheses for therapy resistance are undiagnosed medical conditions maintaining depression or an abnormal drug metabolism (Rush et al. 2003). Other factors which may also lead to less favorable outcomes include alcohol- and substance abuse, personality disorders, and anxiety and panic disorder (Adli et al. 2005). Sharan and Saxena (1998) have identified several other factors predictive for poor response including a family history of affective disorders, severity of depression, suicide attempts, number of previous episodes, long duration of depression prior to treatment, negative life events, and poor social support. There is an obvious impact of social and environmental factors on chronicity of depression, specifically the interaction of cognitive and interpersonal factors and early adversity in maintaining and prolonging depressive episodes (Lara et al. 1999). For this reason, some experts point out that treatment with CBT and IPT needs to precede the decision that the condition is treatment resistant (Thase et al. 1997).

As described below, several pharmacological treatment strategies are suitable to deal with treatment refractoriness, including increase of dosage, switch to an antidepressant of the same class, switch to an antidepressant of another class, combination therapies with more than one antidepressant, and pharmacological and nonpharmacological augmentation strategies. However, it is impossible to predict the most effective treatment strategy for an individual patient. Strategies to enhance therapeutic effectiveness such as lithium

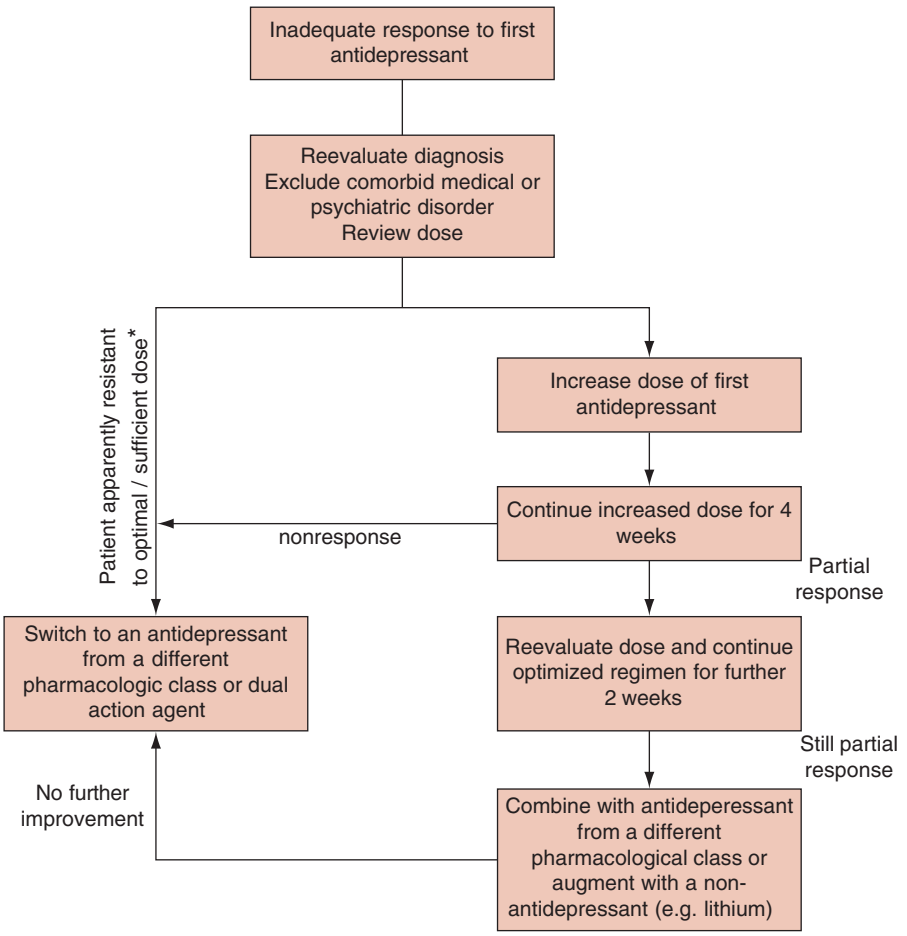



**Figure 66–3** *A step-wise approach to management of patients with inadequate response to antidepressant therapy (adapted from (Hirschfeld et al. (2002))* Therapeutic drug monitoring should be implemented in routine care (Mann et al. 2006); it is especially recommended in case of treatment failures.*

augmentation (Bauer et al. 2003, Zullino et al. 2001) or augmentation using thyroid hormones (Bauer et al. 1998) or other medications, for example, antipsychotics or mood stabilizers, are described in the following sections. Nevertheless, in case of further nonresponse the use of ECT may be clinically more effective than all of these strategies and is still the method of choice for treatment resistant depression (ECT review group 2003), although not all of these patients will respond to ECT.

## Psychopharmacological Strategies in Case of Nonresponsiveness to Antidepressant Treatments

### *Dose Escalation Strategies*

Before switching antidepressants, sufficient length of treatment and the adequacy of dosage should be considered. If in doubt, therapeutic drug monitoring may help ensure adequate blood levels of medication (Corruble and Guelfi 2000). Adli et al. ( 2005) conducted a systematic review of whether dose escalation may lead to additional benefit after a medium-dose treatment fails. They found some evidence that this may be true for TCA, but not for SSRI.

When the previous monotherapy was not efficacious at all, even at maximum dosage, the question arises which medication to test next. Whereas most guidelines recommend a switch to an antidepressant with another mode of action, this is not necessarly true. A recently published analysis of the Star*D trial pointed out that approximately 25% of patients non–responsive to citalopram may benefit from switching not only to bupropion or venlafaxine, but also sertraline (Rush et al. 2006c). Figure 66–3 summarizes a step-wise approach for management of nonresponsiveness to the first antidepressant.

### *General Introduction to Combination and Augmentation*

With a partial response it may often be unwise to discontinue the medication and risk worsening of symptoms. Thus, combination with another antidepressant or augmentation should be considered, and there is now sufficient evidence that combinations of antidepressants or augmentation strategies are more effective than monotherapy in some patients (Kennedy et al. 2001). Combination treatment is defined as the addition of another medication without expecting potentiation of efficacy of the previous drug. Benefits as well as side effects are additive. Usually, a medication with a different pharmacology or a drug with a dual mechanism of action is chosen for combination treatment. In contrast, augmentation means the addition of another agent which by itself may be not specifically helpful as a primary treatment of depression, but may enhance responsiveness to a given antidepressant. Such agents include lithium, thyroid hormones, pindolol, buspirone, and some atypical antipsychotics. Table 66–8 summarizes common augmentation strategies.

**Table 66–8 Biological Treatment Strategies for Partial and Nonresponding Patients with Mdds***

| Treatment Strategy | Mechanisms / Drug Classification |
|---|---|
| **Pharmacological Augmentation** | |
| Lithium | Mood stabilizer |
| Valproate, carbamazepine | Anticonvulsants / mood stabilizer |
| Amisulpride, Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone | Antipsychotic agents, 5-$HT_2$ antagonism |
| Pindolol Buspirone | 5 $HT_{1A}$ autoreceptor antagonist, $\beta$-receptor blocker 5 $HT_{1A}$ and $D_2$ receptor agonist |
| Stimulants | Dopamine and noradrenaline release and reuptake inhibition |
| Pergolide | Dopamine ($D_1$/$D_2$) agonist |
| Bromocriptine | Dopamine ($D_2$) agonist |
| Pramipexole | Dopamine ($D_2$/$D_3$) agonist |
| Reserpine | Reuptake inhibition of biogenic amines |
| **Hormone Augmentation** | |
| Triiodothyronine ($T_3$) | Thyroid hormone |
| L-Thyroxine ($T_4$) | Thyroid hormone |
| Estrogen (only women) | Ovarian steroid hormone |
| Dehydroepiandrosterone (DHEA) | Adrenal androgen hormone |
| **Miscellaneous** | |
| Ketokonazole, metyrapone | Peripheral cortisol suppression |
| L-Tryptophan, 5-Hydroxytryptophan | Essential amino acid, 5-H'I' precursor |
| $\Omega_3$ fatty acids | Food supplement |
| Folic acid (only women) | Vitamin |
| **Nonpharmacological** | |
| Electroconvulsive therapy (ECT) | Electric stimulation to elicit an epileptiform seizure in brain |
| [Repetitive transcranial magnetic stimulation (rTMS)] | Noninvasive stimulation of the cerebral cortex |
| [Vagus Nerve Stimulation (VNS)] | Autonomic signals to limbic and cortical function |
| Phototherapy (bright light therapy) | Chronotherapeutics |
| Sleep deprivation | Chronotherapeutics |

*Modified from WFSBP Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1 (Bauer et al. 2002b).

## Combination Treatment

### *Combination of Different Antidepressants*

*Efficacy*. Despite limited evidence, combination of antidepressants is a very common strategy. In a recent literature search, Dodd et al. (Dodd et al. 2005) identified only 8 randomized trials between 1978 and 2004 studying combinations of antidepressants, five of them including fluoxetine. Combining antidepressants with predominant serotonergic and noradrenergic properties, for example, SSRIs and SNRIs or SSRIs and NaSSA, is one of the most frequently used therapeutic options (de la Gandara et al. 2005). Alternatively, combination of two dual-action substances such as mirtazapine and venlafaxine may be useful in case of prior treatment resistance, but controlled evidence is still missing.

*Safety and Tolerability*. Combining two or even more antidepressants may enhance tolerability when both antidepressants are used in lower doses (King et al. 1994). As an example, sexual dysfunction caused by SSRI treatment may be reduced when using lower dosages within combination strategies, for example, with bupropion which causes a lower rate of sexual dysfunction than some SSRIs. With other combinations, however, a variety of possible pharmacokinetic interactions may enhance the risk for severe adverse events, for example, an increased TCA toxicity due to cytochrome P450 inhibition by fluoxetine or fluvoxamine. Thus, the tolerability profile of combinations depends on both the dosages and the metabolism of the substances used and their specific side effect profiles which may be additive or supplementary.

### *Combination of ECT and Antidepressants*

*Efficacy.* ECT as monotherapy may be sufficient to overcome treatment refractoriness (see Section, "Nonpharmacological Treatment Strategies)". The concomitant prescription of antidepressants during an ECT treatment course is quite frequent; typically either the patient was receiving medication prior to ECT, or it was introduced as pharmacological relapse prevention after ECT. In the first instance, the current recommendation is to maintain the antidepressant at a moderate dose during the entire course of ECT. There are reports of a putative acute benefit from combining ECT with TCAs, mirtazapine, or venlafaxine, but also of a lack of advantages with other concomitant medication like SSRIs (Baghai et al. 2006b).

*Safety and Tolerability.* The combination of ECT with therapeutic dosages of TCAs, SSRIs, and other modern antidepressants has been described as safe. The combination of ECT with MAOIs should be avoided, as lethal complications shortly after starting the pharmacological treatment have been described (Naguib et al. 2002). The combination of ECT with lithium may enhance somewhat the risks for anesthesia, prolonged seizures and transient cognitive impairment.

**Augmentation Treatment** Compared with switching antidepressants, augmentation strategies have some advantages. They eliminate the period of tapering out one antidepressant and introducing another, and usually build on a partial response. Consequently, if they work, augmentation strate-

gies can be rapidly effective; however, they may also raise tolerability and safety issues.

***Lithium***

Of all strategies listed in Table 66–8 which gives an overview on augmentation strategies, lithium augmentation has the best scientific evidence (Bschor et al. 2006). A multitude of open trials, 12 randomized, placebo-controlled trials, and a meta-analysis (Bauer et al. 2003) support the efficacy of lithium augmentation in the acute treatment of treatment-resistant unipolar depression. To allow full assessment of the patient's responsiveness, lithium augmentation should be administered for at least 4 weeks, ensuring serum levels of 0.6–0.8 mmol/L (Bauer et al. 2002b). Once stabilized on the combination, it is not wise to withdraw lithium for at least a year (Bschor et al. 2002).

The utility of lithium augmentation may be limited by side effects, for example, polyuria, muscular weakness, or tremor. Especially in older patients, lithium toxicity may occur even within therapeutic plasma levels and might present itself with a clinical syndrome which is not always easy to differentiate from an increase in depression severity.

*Thyroid Hormones.* At least 13 prospective trials (nine open and four controlled double-blind studies) support the usefulness of triiodothyronine (T3), with most studies employing 25–35.5 µg/day (Bauer et al. 2002b). Women especially seem to have a favorable response to thyroid hormone augmentation (Altshuler et al. 2001). A recently published STAR*D report confirmed the similar efficacy of T3 and lithium with lower rates of adverse events and slightly (but nonsignificant) higher remission rates in the T3 group (Nierenberg et al. 2006). Recently, augmentation with L-thyroxine (T4) has been postulated as an alternative to T3, and open studies and functional neuroimaging support the efficacy of this approach (Bauer et al. 2005), however, double-blind controlled studies are still missing.

***Anticonvulsants***

Although large randomized, placebo-controlled monotherapy trials failed (Hurley 2002), lamotrigine may be of interest for the treatment of refractory unipolar depression. Retrospective chart reviews, open, randomized open label (Schindler and Anghelescu 2007) and controlled augmentation studies (Barbosa et al. 2003, Normann et al. 2002) are supportive of an antidepressant effect of lamotrigine add-on in treatment resistant MDD.

For the older anticonvulsants, there is some evidence for augmentative efficacy of carbamazepine from open studies (Dietrich et al. 1998). However, studies also showed that carbamazepine augmentation stimulates the metabolism of venlafaxine and citalopram, therefore, it may be necessary to adapt the dose of the antidepressant accordingly (Ciusani et al. 2004, Steinacher et al. 2002).

Phenytoin showed some efficacy in a comparator study against fluoxetine in patients with nontreatment-resistant depression (Nemets et al. 2005), but not in an augmentation study in SSRI nonresponders (Kachkovskii and Kriukov 2006).

In summary, the evidence for the usefulness of augmentation with anticonvulsants remains weak.

***Pindolol***

A potential role of 5-$HT_{1A}$ agonists in treating depression and anxiety has been a major focus of research in the past decade (Blier et al. 2003). Pindolol is a $\beta$-adrenoreceptor antagonist. It also blocks 5-$HT_{1A}$ and 5-$HT_{1B/1D}$ receptors and, therefore, should prevent the negative feedback effect of increased somatodendritic serotonin (Dawson et al. 2000), which may accelerate the onset of antidepressant action (Artigas et al. 2001, Artigas et al. 2006).

However, despite positive open studies, three out of four controlled trials have failed to show advantages over placebo in treatment refractory patients and only one small study applying once-daily high dose pindolol (7.5 mg) demonstrated a significant advantage (Sokolski et al. 2004). Thus, pindolol augmentation in treatment-resistant depression remains an experimental approach.

***Buspirone and Tandospirone***

Buspirone and tandospirone are partial 5-$HT_{1A}$ agonists and are believed to activate postsynaptic 5-$HT_{1A}$ receptors and thus may enhance the action of SSRIs. Buspirone has affinity to $D_4$- and to a lesser extent $D_1$- and $D_2$-receptors in addition to $\alpha_1$- and $\alpha_2$-antagonistic activity (Millan et al. 2000). Recently, the STAR*D study investigated the efficacy of buspirone versus bupropion augmentation in SSRI nonresponders. In most outcomes, the rate of improvement was similar for both strategies, however, buspirone was associated with more tolerability problems (Trivedi et al. 2006).

For tandospirone, there is so far only preliminary and weak evidence for antidepressant efficacy (Yamada et al. 2003).

***Second Generation Antipsychotics***

First generation medium potent antipsychotics, such as sulpiride, accelerate and improve antidepressant (SSRI) treatment (Uchida et al. 2005). More recently, the use of different atypical antipsychotics (see Table 66–8) to augment antidepressants in nonpsychotic depressive disorder has been advocated. A recent meta-analysis (Papakostas et al. 2007b) extracted data from 10 clinical trial reports involving 1500 outpatients with treatment-resistant MDD. Patients randomized to adjunctive treatment with an atypical antipsychotic agent were more likely to experience remission or clinical response ($p = 0.001$) than patients who received adjunctive placebo. However, these results are largely driven by trials involving olanzapine (see e.g., Shelton et al. 2005) or risperidone (see e.g., Mahmoud et al. 2007), whereas the evidence for other atypical antipsychotics is very limited and comparator studies to established strategies such as lithium augmentation are lacking.

Other Augmentation Strategies:

The serotonin precursors L-tryptophan and 5-hydroxytryptophan have been studied in depressive disorders with equivocal results. Some smaller studies using L-tryptophan showed potentiation of MAOIs and augmentation of serotonergic antidepressants in treatment-resistant depression (for an overview: see Nelson 2000) and in seasonal depression refractory to light treatment (Lam et al. 1997). However, unambiguous controlled studies are still lacking.

Since an open pilot trial by Wharton with methylphenidate (Wharton et al. 1971), the efficacy of stimulants in treatment-resistant depression has been documented in case series and one larger retrospective chart review (Stotz

et al. 1999). However, the only randomized controlled study could not find a significant advantage over placebo (Zhang et al. 2000).

More recently, modafinil has been tested in two placebo-controlled studies in SSRI partial responders. A pooled analysis suggested that modafinil is both effective and well-tolerated as augmentation therapy, particularly when patients continue to experience fatigue and excessive sleepiness (Fava et al. 2007).

Also dopamine agonists such as pramipexole demonstrated antidepressant activities in open clinical trials. Their usefulness, however, is limited as they may provoke sleep attacks and thus interferes with safety in daily life, for example, driving.

Two RCTs suggest that the addition of folic acid improves antidepressant action, but as monotherapy folate failed to separate from placebo in another RCT (Taylor et al. 2004).

Besides acting against agitation and sleep disturbances, benzodiazepines may have other augmentative effects on antidepressant treatment (Furukawa et al. 2000, Furukawa et al. 2001); however, their long-term use is clearly discouraged due to their inherent risk of addiction.

In some instances, for example, perimenopausal depression, augmentation with estrogen has been recommended based on small pilot studies. A randomized, double-blind pilot study tested antidepressant augmentation with the selective estrogen receptor modulator raloxifene, showing good tolerability of raloxifene and a nonsignificant trend to higher remission rates after 8 weeks (Grigoriadis et al. 2005). Clearly, more controlled studies with adequate sample sizes are demanded.

### Summary

In summary, except for lithium and $T_3$, there is still a need for more controlled studies supporting pharmacological augmentation strategies. This area is receiving more scientific attention and ongoing studies like STAR*D or the *Texas Medication Algorithm Project* should supply further evidence for augmentation strategies in the near future, possibly leading to the development of evidence-based algorithms for treatment refractory patients.

## Nonpharmacological Treatment Strategies

### Electroconvulsive Therapy

ECT is defined as the induction of a series of generalized epileptic seizures for therapeutic purposes using brief-pulse stimulation techniques under anesthesia and muscle paralysis. The excellent therapeutic effectiveness of this method in the treatment of depression has been analysed in a variety of reviews and meta-analyses (Abrams 2002, Baghai et al. 2005, ECT review group 2003).

#### *ECT as First Line Treatment*

MDD accompanied by severe stupor as seen in melancholic, catatonic and/or psychotic depression may be a first line indication for ECT. If a rapid improvement is crucial for the patient, for example, in case of severe psychotic symptoms and/or high suicide risk, ECT should be considered earlier than other therapeutic options (American Psychiatric Association Committee on Electroconvulsive Therapy et al. 2001). In psychotic depression, remission rates for ECT of up to 90% have been reported, with relief experienced within 10–14 days (Petrides et al. 2001). The risk of suicide quickly declines under ECT, but the timely introduction of continuation treatments is essential to sustain the benefit (Kellner et al. 2005).

ECT also constitutes a first line alternative in conditions where antidepressants may be harmful, for example, during early pregnancy or the postpartum breast-feeding period, or in patients suffering from severe somatic diseases with the risk of worsening when exposed to antidepressants (Beliles and Stoudemire 1998, Franco-Bronson 1996, Rothschild 1996).

#### *ECT as Second Line Treatment*

The most common use of ECT is after failure of medication to achieve remission or when several medication trials provoked side effects which were not tolerable. ECT combined with ongoing pharmacotherapy enhances response rates significantly (Baghai et al. 2006b). Other reasons for initiating ECT may include newly emerging somatic comorbidities limiting pharmacological treatment or worsening of depressive symptoms, including severe suicidality while on antidepressant pharmacotherapy (American Psychiatric Association Committee on Electroconvulsive Therapy et al. 2001).

#### *Maintenance and Continuation ECT*

The term continuation ECT (C-ECT) is predominantly used to characterize the maintenance treatment after successful treatment of the acute phase to prevent an early relapse into the index episode. It is sometimes distinguished from maintenance ECT (M-ECT) (Sartorius and Henn 2005) which should characterize prophylactic treatment preventing a recurrent episode of depression. As one merges into the other without sharp boundaries, only the term C-ECT is used here.

ECT is considered as an efficacious prophylactic tool in selected patients, although the scientific evidence for the use of ECT as a maintenance treatment is limited. One recent RCT found comparable efficacy for C-ECT and maintenance antidepressant pharmacotherapy (Kellner et al. 2006). Therefore, C-ECT could be considered in cases of relapse or recurrence of depressive symptoms when adequate pharmacological and psychological therapy failed.

When switching from acute treatment to C-ECT, the usual clinical procedure is to slowly prolong the treatment intervals and continue C-ECT for at least 6 months. A frequently used alternative strategy (the so called *cafeteria style*) is to reestablish C-ECT treatment when the first signs of recurrence of depressive symptoms are reported (Abrams 2002, Fink et al. 1996). Regular weekly evaluations help to decide on an individual basis the adequate length of treatment-free intervals and when intervals need to be shortened.

#### *Side Effects*

According to the anesthetic used, the most frequent immediate side effects of ECT are headache, nausea, and vomiting. Due to predisposition or pharmacological interactions (e.g., lithium), prolongation of the action of muscle relaxants requiring longer assisted respiration may occur and on

rare occasions, prolonged seizures may need intervention with an anticonvulsant.

A typical side effect, more prominent in bilateral than in unilateral and in high than in low energy dose ECT, is transient cognitive impairment, consisting of short-term memory disturbances, a prolonged postictal reorientation period and memory disturbances including anterograde or retrograde amnesia (ECT review group 2003). Autobiographic long-term memory is very rarely affected (Lisanby et al. 2000). These effects are normally fully reversible; almost all patients report an amelioration of cognitive impairment after finishing the ECT treatment course (Devanand et al. 1991). However, some patients may experience lasting cognitive impairment, and more research is needed to characterize such patients a priori (Greenhalgh et al. 2005).

### *Safety*

In general ECT is one of the best tolerated antidepressant therapies with low risk for severe complications, even lower than that associated with the use of TCAs. The mortality rate during ECT varies between 1:50,000 and 1:25,000 treatments (Abrams 2002, American Psychiatric Association Committee on Electroconvulsive Therapy et al. 2001). Recent improvements in ECT include the development of methods which maintain good therapeutic efficacy, but display better tolerability with respect to cognitive disturbances. Modified ECT techniques, including unilateral or bifrontal pulse wave stimulation, anesthesia with muscle relaxation, and sufficient oxygenation, reduce adverse events substantially (Ghaziuddin et al. 2000).

## Total or Partial Sleep Deprivation

Total sleep deprivation is a nonpharmacological intervention, which exerts rapid antidepressant effects in about 60–70% of depressed patients who stayed awake for one night and the consecutive day (Benedetti et al. 2005, Wirz-Justice et al. 2005, Wu et al. 1990). Partial sleep deprivation means that patients get up between 1 and 2 AM and stay awake for the second half of the night and the consecutive day at least until 8 PM. This is as effective as total sleep deprivation and usually better accepted by depressed patients. Early night sleep deprivation is ineffective in the treatment of depression (Wu et al. 1990).

The clinical usefulness of total sleep deprivation is limited since relapse is observed in most patients when returning to a normal sleep pattern (Wu and Bunney 1990), or even after a short nap on the next day (Riemann et al. 1993). Strategies for relapse prevention are the combination with medication, bright light therapy, or the serial administration of partial sleep deprivation up to twice (or three times) a week (Kuhs et al. 1998). As another nonpharmacological method, a "*phase advance*" of the sleep period after sleep deprivation can be used to prevent relapse in about 60% of responders (Berger et al. 1997) meaning that after one night of total sleep deprivation, the patients starts a partial sleep deprivation schedule from 5:00 PM to 12:00 midnight, which then is shifted back by 1 hour each day until a "normal" sleep time of 11:00 PM to 6:00 AM has been reached. This gives patients 7 hours of sleep per night and makes it easier to cope with the sleep deprivation procedure. Nevertheless, due to its labor intensive procedures and the fact that additional (pharmacological) treatments for relapse prevention are needed anyway, sleep deprivation is used predominantly as an augmentation strategy to speed up relief from depression

## Bright Light Therapy (Phototherapy)

In SADs, bright white light therapy is effective in the treatment of depressive symptoms (Wirz-Justice et al. 2005). Recent studies support the use of phototherapy as an efficacious adjunctive treatment in nonseasonal unipolar and bipolar depression (Martiny et al. 2005, Terman et al. 2005). More randomized controlled trials, however, are needed to evaluate the therapeutic impact of phototherapy on nonseasonal depression (Golden et al. 2005). Currently, phototherapy should be considered in SADs as one first line therapy, and it can be tried in other forms of depression as one of several augmentation strategies (Craft and Perna 2004).

# Psychosocial Treatments

Several specific forms of psychotherapy have been developed for the treatment of depression, including CBT and IPT. In addition, various other forms of psychotherapy have been adapted for depression treatment. These include supportive psychotherapy, psychodynamic psychotherapy, and marital and family therapy.

In many psychiatric settings, combinations of psychotherapy and pharmacotherapy are provided. In this setting, supportive therapy is sometimes utilized (Winston et al. 2004). The psychiatrist focuses on establishing a positive therapeutic relationship with the patient. Ongoing education, collaboration with the patient, advice and encouragement are offered. The psychiatrist attempts to promote adherence to medication and other forms of therapy, combats hopelessness and helplessness, and remains alert for signs of suicidality. Such therapies are designed to address immediate needs for symptom reduction rather than primarily to achieve a deep level of psychological insight. Transference based interpretations are usually not a prominent part of such supportive therapy. Although often viewed as an eclectic form of therapy, some approaches to supportive therapy have been systematized (Novalis et al. 1993).

Combination pharmacotherapy and psychotherapy for depression has been studied but RCTs have not provided a clear answer to questions about when this is advantageous. In milder forms of depression, either pharmacotherapy or psychotherapy may be helpful; however, in more severe or complicated cases, combination therapy seems to confer a considerable advantage (Pampallona et al. 2004).

Marital and family conflicts are often significant factors in depression, in which cases, marital and family therapy may play a role in treatment. Several studies have shown effectiveness for marital therapy in relieving depressive symptoms as well as improving marital functioning (Beach 2003).

## CBT

CBT for depression is typically a short-term course of individual therapy, ranging from eight to twelve sessions. In CBT, the patient and therapist form a collaborative relationship designed to address problems and symptoms pragmatically in the present (the "here and now"). Usually, delving deeply into childhood conflicts is not emphasized; the focus is on identifying and modifying distorted cognitions

which are contributing to maintaining depressive symptoms and behaviors. The patient is helped to see the relationship between distorted, illogical thinking and depressed mood. CBT involves addressing the "negative cognitive triad": negative views of self, one's current world, and the future. Some type of behavioral activation strategy is often an important part of early therapy in CBT.

CBT is a structured therapy in which the therapist and patient develop explicit goals and an agenda for each session. Homework is typically given, which may involve reading assignments as well as monitoring thoughts, feelings, and behaviors, often using structured forms such as the "Daily Record of Dysfunctional Thoughts." Homework is discussed in the subsequent session. If the patient is unable to complete the assignment, the process itself is discussed and viewed as a therapeutic opportunity. Homework assignments often embody behavioral activation and other behavioral techniques as well as cognitive monitoring. The patient is guided to learn to monitor and modify their own thinking processes, thereby acquiring a skill which will continue to help them after the formal therapy is completed. In some therapies, underlying, persistent beliefs known as schemas become a focus of treatment. These schemas involve deep seated beliefs about one's self and the world, and are often inflexible. A typical schema involved in depression might be "I must please everyone" or "people would not like me if they knew what I'm really like." Schemas can be addressed using many of the same techniques which are used to identify and modify negative automatic thoughts, but typically are much more difficult to change.

A number of studies have demonstrated the efficacy of CBT for major depression (Thase 1997). CBT is a relatively standardized form of treatment and, in addition, a computerized form has been developed (Wright and Small 2005).

## Interpersonal Therapy

IPT is utilized primarily for outpatients with unipolar depression (Klerman et al. 1984). The focus is usually on four important interpersonal areas: interpersonal loss and grief (often following the loss or death of a loved one), role transitions involving difficulty adapting to changed life circumstances, interpersonal role disputes (usually with a loved one or close associate), and social deficits (limited social support networks). Interpersonal therapists believe that depression is maintained by problems in one or more of these four key areas. The therapy usually focuses on collaboratively identifying and correcting problems in one, or occasionally more than one, of these areas. The patient is encouraged to view depression as an illness involving problems to be solved rather than a personal weakness. Transference, exploration of the unconscious, dreams, defenses, and childhood experiences are usually not a part of IPT. The patient is educated about depression and its treatments, often including the use of medication. It is a pragmatic form of therapy that is designed to address symptoms in the present. It is usually a short-term therapy consisting of approximately 12–16 sessions.

IPT has been shown to be effective in clinical trials both alone and in combination with medication (de Mello et al. 2005). Continuation therapy with IPT has shown value in preventing relapse of depression (Frank 2007).

## Psychodynamic Therapy

Psychodynamic psychotherapies are designed to address unconscious, intrapsychic conflicts using psychoanalytic techniques such as free association, analysis of defense mechanisms, and interpretation of transference. These therapies were not designed as a specific form of therapy for depression or overt symptom suppression. Psychodynamic therapies are usually unstructured and the therapist is typically less active than their counterparts in CBT or IPT, which may present a problem for a demoralized depressed patient. Unlike CBT or IPT, there is no authoritative manual or handbook. Moreover, there are a variety of approaches to psychodynamic psychotherapy, making generalizations difficult. Although Freud's original contributions remain important, psychodynamic thinking has evolved enormously in recent decades, incorporating new insights from schools such as object relations and self psychology which may be applied to the treatment of depression. These observations focus on the nature of the self and its boundaries and relationships with others. Therapists may use these views in developing an empathic approach to the depressed patient very different to the traditional, reserved Freudian therapist. Psychodynamic therapy is usually open ended, but time limited approaches have been developed in recent decades. These brief dynamic therapies usually focus on current conflicts as manifestations of difficulty in early attachment and disruption of early object relations.

The efficacy of dynamic therapy has sometimes been controversial; however, recent studies have tended to show utility. Meta-analysis has suggested that longer durations of dynamic therapy may provide better outcomes than brief therapies (Leichsenring 2005, Leichsenring et al. 2006).

## Psychotherapy in Minor Depression

Minor depression has a considerable impact on the quality of life and carries a high risk of developing MDD (Cuijpers et al. 2004). A meta-analysis of randomized controlled studies examining the effects of psychological treatments for minor depression identified seven high-quality studies involving a total of 700 subjects. Five used CBT, one IPT and one problem-solving therapy (six problem-solving therapy sessions over the telephone (Lynch et al. 1997)). Significant effects on acute minor depression as well as protective effects against onset of major depression were observed (Cuijpers et al. 2007).

## Psychotherapy in Primary Care Settings

As a trained psychotherapist may not always be available, it is an interesting question whether psychosocial treatment can be successfully delivered by general practioners or community nurses. With a relative paucity of studies, evidence so far suggest that Problem-Solving Therapy for Primary Care (PST-PC) seems the most promising tool (Huibers et al. 2003). It typically involves an initial 60-minute session followed by five 30-minute sessions. PST-PC is largely based on the assumption that a range of life events or problems have a strong association with current psychological functioning (Nezu and Perri 1989). Besides MDD, PST-PC has also been shown to be an effective approach in minor depression and dysthymic disorder (Barrett et al. 2001). Techniques can be learned quite easily and PST-PC can be applied successfully by a trained community nurse (Wolf et al. 2007).

Another strategy for use in primary care settings is interpersonal counselling, developed by Klerman et al. (1987). It comprises a brief six-session intervention based on IPT, but designed to be administered by individuals who may not have mental health training, such as nurse practitioners. Especially in minor depression, IPC may be a useful and cost effective tool (Weissman et al. 2000).

CBT, and the abbreviated form, are effective in primary care, but involves psychotherapeutic expertise which makes them impractical (Teasdale et al. 1984). Psychosocial counseling can take different forms, such as Rogerian psychotherapy, supportive psychotherapy, or psychoeducational techniques without supplemental interventions. In primary care settings, it may be effective in the short-term, but still lacks proven efficacy in the long run (Bower and Rowland 2006).

### Recommendations

In general, empirically supported psychotherapies have demonstrated similar response and remission rates to pharmacotherapy for outpatients with depressive disorders, which, on average, may be less severely ill than inpatients. They treat mood and demoralization more quickly than neurovegetative symptoms of depression, the reverse of the pattern seen for most antidepressant medications. IPT and CBT also provide prophylaxis against relapse and recurrence when prescribed as less frequent (e.g., monthly) maintenance treatments (Frank et al. 2007).

However, the use of these psychotherapies clearly has its limitations. Some severely depressed patients may be too depleted to engage in psychotherapy effectively. They are also not intended to treat depression with psychotic features, nor as monotherapy for bipolar I depression (Frank et al. 2005, Miklowitz et al. 2003).

On the basis of their performance in controlled efficacy trials, IPT and CBT have already been included in some evidence-based professional and national treatment guidelines (Anderson et al. 2008, Karasu et al. 1993, National Institute for Health and Clinical Excellence 2004, Tylee 2006, van den Broek 2005).

For patients with chronic or severe depression, the combination of pharmacotherapy and one of these empirically validated psychotherapies may be preferable to monotherapy (Hollon et al. 2005). In a recent meta-analysis, the combined therapy outperformed psychotherapy, but only in moderate chronic depression, no differences were found in nonchronic depression (de Maat et al. 2007). Given health economics considerations, combined treatment may thus best be reserved for patients with chronic, highly comorbid, severe depressions, or those at high suicide risk.

## Issues in the Clinician–Patient Relationship

Throughout guidelines, there is a consensus that independent of the choice of the specific medical treatment intervention, general components of good psychiatric management, and psychotherapeutic support should be initiated and continued throughout the entire treatment (Bauer et al. 2002a, b). Elements of a good therapeutic alliance include the psychiatrist or physician taking full responsibility for diagnosis, conducting a physical examination, other investigations and explanation of the diagnosis and its consequences to the patient and relatives. The physician should listen to the patient's complaints and communicate clearly, in an understandable manner. The physician should determine together with the patient a treatment plan and the appropriate treatment setting and, in case of outpatients, ensure regular visits. During acute phase treatment, weekly or biweekly visits are recommended ; during the continuation phase and after syndromal recovery a frequency of once a month appears adequate (Bauer et al. 2002b). In the case of concurrent psychotherapy supplied by a psychotherapist, frequent communication between physician and therapist about the patient's status should go without saying.

There should be regularly scheduled follow-up, reviewing the accuracy of diagnosis and treatment success, and a strategy to enhance adherence to medication (Anderson et al. 2008). Some additional aspects need special attention when treating depressed patients (adapted from Goodwin 2003):

- Patients and relatives should be educated about potential symptoms that may raise questions about the original diagnosis, for example, the emergence of (hypo)manic symptoms.
- Patients and relatives should be informed about the possibility of enhanced drive before the onset of antidepressant action in the initial antidepressant treatment phase possibly leading to an enhanced suicide risk.
- Patients should be made aware of stressors, the impact of sleep disturbance, the importance of regular patterns of activity and early signs of relapse.
- Patients should be informed about the poor outcome associated with alcohol and substance abuse and, if needed, given appropriate advice and offered treatment.
- Functional impairment should be evaluated and managed: patients and familes should be given a realistic view about capacity to work and function within the family. Potential sources of psychosocial support in the community should be identified and the patient given help to contact them.

## Special Factors Influencing Treatment

Although standardization and guidance by treatment algorithms is a desirable goal in order to ensure quality of care, neither the pharmacological nor psychological treatment of depression will ever become uniform in all patients. Different needs and risk factors need careful consideration across age groups and gender. Psychiatric comorbidities and personality traits may have a large confounding influence on outcomes. Psychiatric comorbidities, as outlined above, negatively impact on treatment outcomes and long-term prognosis, and need to be treated simultaneously with the same effort as the depressive episode.

Medical comorbidity will affect both treatment responsiveness of depressive syndromes and the choice of medication, as both pharmacokinetic interactions with somatic medication and potential safety risks due to organ dysfunction have to be observed (see Section, "Depressive Disorders with Comorbid General Medical Conditions").

It goes almost without saying that enduring psychological factors, for example, low self esteem, lack of knowledge about the illness and hence an inappropriate concept of the illness, as well as an unfavorable social environment may

not only delay recovery, but also be risk factors for relapses. Thus, psychological counseling on an individual basis, psychoeducation, and intense social support are often needed for achieving treatment success.

Clinical Vignette 1

**Depression Dominated by Somatic Symptoms**

Mrs. D is a 62–year-old former teacher, living single, who retired from work 6 months ago. She presented to her GP complaining about loss of appetite, constipation, abdominal cramps, and a general feeling of weakness and loss of energy. Abdominal sonography and an abdominal CT scan were without pathological findings, but there were moderate signs of dehydration with an increase in creatinine and hematocrit as well as low serum iron and serum ferritin. She was prescribed a combined iron sulphate-folic acid preparation and advised to drink at least 1.5 L/day. No improvement in symptoms was observed after 1 month. Mrs. D now also complained of an increasing loss of pleasure. She was referred to a psychiatrist for a second opinion. At presentation she also reported low self esteem after retirement and difficulties structuring her daily routine also she didn't feel challenged by it. Diagnosis of a MDD was made and Mrs. D was started on fluoxetine 20 mg/day. She was sent to a CBT therapist. Her low self esteem after retirement and consecutive thoughts of being now worthless became the focus of the CBT. After having 12 sessions of CBT and fluoxetine at final dose of 40 mg for 8 weeks she started to improve slowly but constantly and reached full recovery after 3 months of treatment. For the next 2 years, CBT was continued on low frequency with one session per month and she continued to take fluoxetine for another year before it was tapered out over a 6-month period.

Clinical Vignette 2

**Treatment Refractory Depression**

Mr. J is a 51-year-old, married tax accountant. Soon after his 50th birthday, he experienced a temporary financial shortage and was not able to pay all bills in time. Thereafter he developed an increasing feeling of worthlessness, constant thoughts of guilt and shame, accompanied by hyposomnia and weight loss. He reported to his GP where diagnosis of an MDD was established. Mr. J was started on citalopram 20 mg for 2 weeks, then 40 mg for another 2 weeks and finally 60 mg/day but no improvement was observed after 8 weeks. Careful questioning by the GP revealed that he was now also suffering from increasing thoughts of death and as a consequence he was referred to a psychiatrist. The psychiatrist confirmed the diagnosis of MDD and switched citalopram to venlafaxine with a maximum dose of 225 mg after 4 weeks of treatment. However, Mr. J was not able to tolerate the high dose of venlafaxine; he developed increasing psychomotor agitation but showed no improvement of the depressive syndrome. In parallel with the switch of medication CBT was initiated but Mr. J felt overstrained by the therapy. Psychotherapy was cut back to an unchallenging, supportive level. Due to lack of improvement and side effects, venlafaxine was then tapered and mirtazapine started. Initially, mirtazapine lead to an improvement of sleep and a decrease of psychomotor agitation. But even with 60 mg of mirtazapine after 3 weeks the other depressive symptoms remained and thoughts of death became more intense leading to Mr. J's admission to in-patient care. In hospital mirtazapine was reduced to 45 mg and lithium augmentation was started. After 2 weeks a lithium serum level of 1.0 mmol/L was achieved, and the first signs of improvement were observed. With the constant medication of the lithium and mirtazapine, reduced to 45 mg/day, Mr. J was able to restart on CBT after 4 weeks and to gain profit from psychotherapy. Improvement continued and 3 months later Mr. J achieved full recovery. Due to the severity of the depressed episode, Mr. J and his psychiatrist decided on long-term prophylactic treatment with lithium and regular booster sessions of CBT.

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## End Notes

[1] Within DSM-IV recurrent brief depression can only be diagnosed as subthreshold major depressive disorder (MDD) although it is included in the research appendix. Within ICD-10 it is a diagnostic category of *recurrent depressive disorder*. The combination of severe depressive disorders and recurrent brief depression is sometimes also called "combined depression" (Pezawas et al. 2001).

[2] Reboxetine up to now is marketed in Europe, but not in the United States.

[3] In addition antidepressants do not have a market value to drug misusers, an authentic measure of abuse potential.

[4] Also antipsychotics such as clozapine or olanzapine (Duggal et al. 2004) used in augmentation therapies may cause leukopenia culminating to agranulocytosis.

[5] Comment on paroxetine: in case of acute angle-closure (closed-angle, narrow-angle) glaucoma contraindicated due to more anticholinergic side effects in comparison to other SSRIs (Bennett and Wyllie 1999).

[6] TCAs are available as oral and intravenous (i.v.) applicable medication. There is no scientific evidence for a differential efficacy profile of both pharmaceutical forms.

[7] In addition to the serotonin reuptake inhibiting properties escitalopram binds at the allosteric site on the serotonin transporter. The definition of a new class of SSRIs has been suggested (Allosteric Serotonin Reuptake Inhibitors (ASRI)).

[8] Not yet available, currently under review by European authorities (EMEA).

[9] Selegiline in some countries has been approved only as a drug against Parkinson's disease, not as an antidepressant.

[10] The use of pirasidol is limited to Russia and other eastern countries of the same geographical region. In the Russian literature it can be found under other names, such as pirlindol, pyrazidol, pirazidol or pirazidolum (for review: see Mosolov (1998)).

[11] Nefazodone has been withdrawn from the market in some countries.

[12] Melitracen has activating properties in low dosages and is predominantly used in Asian countries in a combined formulation (deanxit) with the antipsychotic drug fluoxetine.

[13] Different dosages are used in different countries (Patten et al. 2005, Sartorius 1986). For some populations, e.g., Japanese patients, the above mentioned dose recommendations are usually too high. Otherwise the definition of standard doses according to approval studies for authorities may cause recommendations which are lower than doses used more frequently in later clinical practice. Marketing aspects may influence dosage recommendations due to the calculation of the lowest possible daily

treatment costs. Also indication adjusted dose recommendations may be of importance. The indications for which antidepressant medications are used vary among countries.

[14] Recommended starting dose in the US 40mg, in Europe 60 mg.

[15] The sorting order represents grading from common and unperilous to more severe, but predominantly rare side effects.

[16] Syndrome of inadequate secretion of antidiuretic hormone, possibly resulting in hyponatremia and generalized epileptic convulsions.

[17] Due to decreased platelet concentration or diminished platelet aggregation.

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SECTION VI

Michael B. First, Section Editor

# *Disorders (continued)*

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CHAPTER

# 67 Mood Disorders: Bipolar (Manic–Depressive) Disorders

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Manic Disorder
Mixed Episode
Hypomanic Episode
Cyclothymic Disorder
Rapid Cycling

## Introduction

### Historical Background

Mania and depression have been recognized as far back as Western classical antiquity, and recognizable descriptions of bipolar (manic–depressive) disorder can be found in the writings of Galen's contemporary, Aretaeus of Cappadocia (c. 150–200 CE) (Porter 2002). Importantly, the debate regarding biological versus psychosocial etiologies of this and other mental illnesses can be traced forward from antiquity to the present day with impressive consistency: though the specific attributions and colorings may change, the tension between these two alternatives appears to be a consistent feature of Western thought about mental illness (Porter 2002, 2004).

The modern age of study of manic–depressive disorder can be considered to have begun with Emil Kraepelin, whose treatise *Manic–Depressive Insanity and Paranoia* (Kraepelin 1899, Kraepelin 1989, Berrios and Hauser 1988) is a classic in terms of both the importance of its scientific insights and the lucidity of its prose. Notably, this seminal work emphasized clinical description rather than pathogenesis, and emphasized both cross-sectional and longitudinal data. Kraepelin observed that patients who had symptoms of psychosis were of two main types: those whose illness followed a progressive downhill course and those whose illness remitted and recurred, frequently with return to their normal interepisode baseline. The former illness he termed *dementia praecox*, "early dementia," which we now call schizophrenia. The latter he called manic–depressive psychosis. This latter group included almost all severe mood disorders, grouping together persons with severe depressive episodes regardless of whether they experienced mania as well. Thus, he utilized not only cross-sectional data (the occurrence of mood episodes) but also longitudinal data (the tendency of mood episodes to remit and recur) to separate mood disorders from schizophrenia.

Later, Leonhard and Berman (1957) proposed the distinction between manic–depressive, or bipolar, disorder and pure depressive disorder, which has come to be called unipolar depression. Phenomenologically, Leonhard based this distinction on the occurrence of manic episodes in the former disorder but not in the latter, and supported this distinction by the observation that mania tended to occur more frequently in family members of patients with manic–depressive rather than unipolar disorder. This is an example of corroborating purely phenomenological distinctions with other types of empirical evidence, which was later codified in Robins and Guze's (1970) classic article on the definition of schizophrenia, which eventually served as the basis for evaluating most of the evidence for mood disorder validation for DSM-IV-TR.

This categorical approach to diagnosis, which clearly demarcates manic–depressive disorder from schizophrenia on the one hand and from unipolar depression on the other, is most successful when classic cases are considered. In reality,

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however, many boundary cases exist in which features of more than one syndrome exist and clear categorization is not possible. Recognizing this reality, Bleuler's classic *Textbook of Psychiatry* (Bleuler and Brill 1924) proposed that manic–depressive disorder and schizophrenia lie on a continuum that has no sharp border, with patients often exhibiting characteristics of both syndromes and evolving a course midway between the two. This presentation is indeed not uncommon and has been recognized in major diagnostic classification schemata as schizoaffective disorder (Levitt and Tsuang 1988, Blacker and Tsuang 1992). As discussed below, modern psychiatric genetics also provides some support for Bleuler's continuum approach (e.g., Craddock and Owen 2005).

The most recent roots of the atheoretical, phenomenological approach to diagnosis in the current DSM system lie in the St. Louis or Feighner criteria (Feighner et al. 1972), which specified explicit phenomenological criteria for the identification of various psychiatric disorders. The St. Louis criteria and the closely related Research Diagnostic Criteria (Spitzer et al. 1978) served as the diagnostic systems for most clinical psychiatric research in the 1970s and early 1980s, providing a common language for description of patients among investigators and increasing comparability of diagnostic samples across various sites. This phenomenological "technology" diffused into clinical practice and was codified for clinical use by the third edition of the DSM and its revision (American Psychiatric Association 1980, 1987). Currently, the DSM-IV-TR and the closely related *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10) (World Health Organization 1994) serve as the basis for the diagnosis of manic–depressive disorder both in clinical practice and in psychiatric research, although long-term psychiatric studies begun under the Research Diagnostic Criteria have continued to use that schema, which is fairly comparable (Williams and Spitzer 1982).

### A "Bipolar" Disorder?

In the first edition (Tasman et al. 1997), this chapter was entitled "Bipolar Disorders," yet beginning with the second edition the older term "manic–depressive disorder" has been included. Why?

Classically, mania has been considered to be the opposite of depression: manic individuals were said to be cheery, optimistic, and self-confident—hence the name bipolar disorder. However, in most descriptive studies, substantial proportions of hypomanic and manic patients actually exhibit dysphoric symptoms (e.g., Bauer et al. 1991, 1994c), while those with depressive episodes frequently exhibit manic symptoms (e.g., Benazzi 2004). In fact, admixtures of manic and depressive symptoms may be the modal mood state in unselected populations of individuals with this illness (Bauer et al. 2005b).

Further evidence that (hypo)mania is not the polar opposite of depression comes from investigation of self-reported quality of life in the various mood states of manic–depressive disorder (e.g., Vojta et al. 2001, Zhang et al. 2006). Although classically thought to be a desirable state, patients with mania or hypomania rate their preference for that state as equal to or less than their preference for euthymia, with depression and mixed states being rated less preferable.

Thus the term *manic–depressive* is less misleading than "*bipolar*," which implies that the two characteristic mood states are somehow polar opposites (see Section "Phenomenology"). This chapter therefore refers to the disorder by its older, but more accurate, name.

## Diagnosis

### Definition and Diagnostic Features

The phenomenological data for the diagnosis of manic–depressive disorder depend on both *cross-sectional* and *longitudinal* data. "Cross-sectional" refers to descriptive aspects of a syndrome that occur at a particular point in time, such as the number and type of symptoms that occur during an episode of depression. "Longitudinal" refers to the course of symptoms over time, such as the timing, duration, and recurrence of depressive episodes. It is not infrequent that diagnostic errors occur when longitudinal data are neglected as the psychiatrist focuses solely on cross-sectional presentation: "This must be manic–depressive disorder because the patient appears manic at the present time," or "this cannot be manic–depressive disorder because the patient is depressed now."

#### Episodes as the Basis for Diagnosis of Manic–Depressive Disorder

The DSM-based definition of manic–depressive disorder is built on the identification of individual mood *episodes* (Table 67–1). DSM-IV-TR criteria for individual mood episodes are summarized below for manic, mixed, and hypomanic episodes; criteria for major depressive episodes can be found in Chapter 66. Criteria for these episodes are reviewed in greater detail in the subsequent section on diagnosis. Most individuals with manic–depressive disorder have major depressive as well as mania or hypomanic episodes (Winokur et al. 1969, Solomon et al. 2003). Those who experience manic episodes are diagnosed with manic–depressive or bipolar *type I* disorder, and those with major depressive

**Table 67–1 Summary of Mood Episodes and Mood Disorders**

| Episode | Disorder |
|---|---|
| Major depressive episode | Major depressive disorder, single episode |
| Major depressive episode + major depressive episode | Major depressive disorder, recurrent |
| Major depressive episode + manic/mixed episode | Manic–depressive disorder, type I |
| Manic/mixed episode | Manic–depressive disorder, type I |
| Major depressive episode + hypomanic episode | Manic–depressive disorder, type II |
| Chronic subsyndromal depression | Dysthymic disorder |
| Chronic fluctuations between subsyndromal depression and hypomania | Cyclothymic disorder |

DSM-IV-TR Criteria

**Manic Episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a mixed episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

**Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of manic–depressive I disorder.

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and hypomanic (milder manic) episodes are diagnosed with manic–depressive or bipolar *type II* disorder.

Not surprisingly, most data regarding manic–depressive disorder come from the study of the more severe end of the spectrum, primarily type I disorder. Throughout this chapter, data on manic–depressive disorder derive from studies of type I disorder unless otherwise noted. DSM-IV-TR is the first version of the DSM series to include a specific category for type II disorder. Previously, persons with depressive and hypomanic episodes were grouped under the broad "bipolar disorder not otherwise specified," which included a variety of unusual presentations. On the basis of evidence reviewed by Dunner (1993), type II disorder was given separate categorical status.

This separation of type II from both type I and major depressive disorders is supported by several types of evidence. For instance, type II disorder occurs more frequently in families of persons with type II in comparison to families of persons with type I or major depressive disorder (Fieve et al. 1984, Coryell et al. 1984, Endicott et al. 1985). Study of the course over time of type II disorder indicated that persons with hypomania tended to have recurrent hypomanic episodes and did not convert into type I by developing mania (Coryell et al. 1995). In addition, persons with type II disorder may have more episodes over time than persons with type I (Dunner 1993). However, biological differences between these manic–depressive types have not been reliably demonstrated (Dunner 1993).

Nonetheless, as summarized in Section "Clinical Outcome," it should not be construed that type II disorder

DSM-IV-TR Criteria

**Mixed Episode**

A. The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period.

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

**Note:** Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of manic–depressive I disorder.

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is in all respects milder than type I, although hypomania is by definition less severe than mania. Specifically, the social and occupational function and quality of life for persons with type II disorder are similar to those for persons with type I disorder.

**DSM-IV-TR Criteria**

**Hypomanic Episode**

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

**Note:** Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of manic–depressive II disorder.

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Persons who experience subsyndromal manic–depressive mood fluctuations over an extended period without major mood episodes are diagnosed with *cyclothymic disorder*. Much less is known about this milder disorder because afflicted persons present for medical attention less frequently than those with full-blown manic–depressive disorder. Cyclothymic disorder has been considered at various times a temperament, a personality disorder, and a disorder at the milder end of the manic–depressive spectrum (Akiskal 1981). Available data clearly indicate that cyclothymic disorder is related to the more severe manic–depressive disorders (Akiskal et al. 1977, Goodwin and Jamison 1990). However, it is not clear to what degree such categorical disorders may be related to underlying dimensional characteristics such as temperament (Akiskal and Akiskal 2005). It is also not clear to what degree defining milder and milder categories for the disorder (e.g., "bipolar type 2.5" (Akiskal et al. 2003), "bipolar type 3" (Akiskal and Akiskal 1988), etc.) will have clinical utility.

## Phenomenology

Mood episodes are discrete periods of altered feeling, thought, and behavior. Typically they have a distinct onset and offset, beginning over days or weeks and eventually

**DSM-IV-TR Criteria**

**Cyclothymic Disorder**

A. For at least 2 years, the presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode.

**Note:** In children and adolescents, the duration must be at least 1 year.

B. During the above 2-year period (1 year in children and adolescents), the person has not been without the symptoms in criterion A for more than 2 months at a time.

C. No major depressive episode, manic episode, or mixed episode has been present during the first 2 years of the disturbance.

D. The symptoms in criterion A are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

F. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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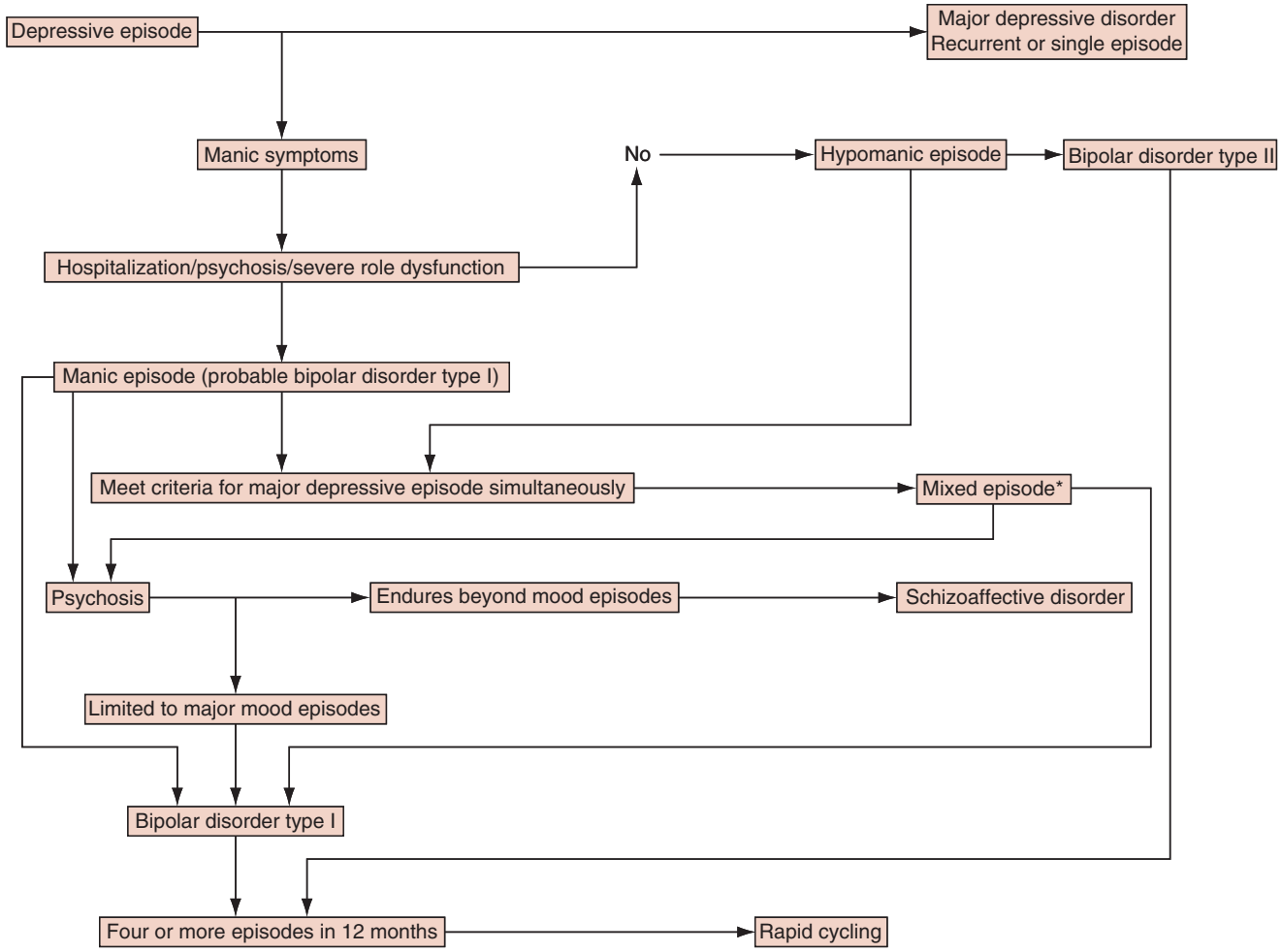



**Figure 67–1** *Diagnostic decision tree for manic–depressive disorder. The building blocks for a diagnosis of manic–depressive disorder are individual episodes and their characteristics, as summarized in Table 67–1.*

ending gradually after several weeks or months. As noted earlier, manic–depressive disorder is defined by the occurrence of depressive plus manic, hypomanic, or mixed episodes, or the occurrence of only manic or mixed episodes.

Major depressive episodes are defined by discrete periods of depressed or blue mood or loss of interest or pleasure in life that typically endures for weeks but must last for at least 2 weeks (see Chapter 66). These symptoms are often accompanied by changes in increase or decrease in sleep or appetite, decreased energy, and impaired cognition. Depressive episodes in manic–depressive disorder are indistinguishable from those in major depressive disorder (e.g., Abrams and Taylor 1980, Moller et al. 2001). About 75% of persons with manic–depressive disorder experience depressive episodes characterized by decreased sleep and appetite, while about 25% experience more "atypical" symptoms of increased sleep and appetite, rates that are indistinguishable from those in unipolar depression (Robertson et al. 1996, Posternak and Zimmerman 2002). Thus with regard to depressive episodes, the differential diagnosis between major depressive and manic–depressive disorders is made by longitudinal course not by cross-sectional symptom analysis. A diagnostic decision tree for manic–depressive disorder is given in Figure 67–1.

Manic episodes are defined by discrete periods of abnormally elevated, expansive, or irritable mood accompanied by marked impairment in judgment and social and occupational function. These symptoms are frequently accompanied by unrealistic grandiosity, excess energy, and increases in goal-directed activity that frequently have a high potenwtial for damaging consequences.

Hypomanic and manic symptoms may be identical, but hypomanic episodes are less severe. A person is "promoted" from hypomania to mania (type II to type I) by the presence of one of three features: psychosis during the episode, sufficient severity to warrant hospitalization, or marked social or occupational role impairment. This is an imperfect set of criteria, however, because the phenomenologic differentiation between hypomania and mania is not as cut-and-dried as one would hope. Of the three characteristics by which one is "promoted" from hypomania to mania, only the presence of psychosis is firmly grounded in the characteristics of the individual. The other two characteristics, marked social or occupational role impairment or hospitalization, clearly have components that are primarily external to the individual. If, for instance, one individual has relatively mild manic symptoms but is living with a family who is unable to tolerate the behavior, she/he is more likely to be hospitalized. Similarly, the comorbid presence of a severe disorder is more likely to result in hospitalization and a "promotion" from type II to type I disorder. Contrarily,

limited insurance benefits, or a more tolerant family increase the probability that a manic syndrome of a given severity will be managed without hospitalization and thus be diagnosed as "hypomania" rather than "mania." Overall, however, there is evidence that type II and type I manic–depressive disorders are separable (see Section "Episodes as the Basis for Diagnosis of Manic–Depressive Disorder"), though whether these represent separate categories versus different positions or a single continuum remains unclear.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 item set for a manic episode contains nine items, in contrast to the seven items in the DSM-IV-TR criteria set, the two additional items being marked sexual energy or indiscretions and loss of normal social inhibitions. However, the number of items required by ICD-10 Diagnostic Criteria for Research remains the same as the number in DSM-IV-TR (i.e., three items if mood is euphoric, four items if mood is irritable), which is likely to result in a more inclusive diagnosis of a manic episode in ICD-10. Furthermore, the duration of mixed episodes differs, with DSM-IV-TR requiring a duration of 1 week (as is the case for a manic episode), whereas the ICD-10 Diagnostic Criteria for Research require a duration of at least 2 weeks.

The criteria sets for hypomanic episode differ as well. The ICD-10 Diagnostic Criteria for Research contain several additional items (increased sexual energy and increased sociability) and does not include the DSM-IV-TR items inflated self-esteem and flight of ideas. Furthermore, ICD-10 does not require that the change in mood be observed by others.

Regarding the definition of type I disorder, in addition to differences in the diagnostic criteria for a manic and major depressive episode, the ICD-10 definition of "Bipolar Affective Disorder" (i.e., any combination of hypomanic, manic, or mixed with depressive episodes) does not distinguish between type I and type II disorder (i.e., cases of DSM-IV-TR Bipolar II Disorder are diagnosed as Bipolar Affective Disorder in ICD-10). However, ICD-10 Diagnostic Criteria for Research do include a diagnostic criteria set for type II in its appendix that is identical to the criteria set in DSM-IV-TR.

For cyclothymic disorder, the ICD-10 Diagnostic Criteria for Research provides list of symptoms that must be associated with the periods of depressed mood and hypomania, which differ from the ICD-10 item sets for dysthymic disorder and hypomania. In contrast, the DSM-IV-TR definition of cyclothymic disorder utilizes the same criteria for hypomania.

## Screening for Manic–Depressive Disorder

Since the last edition of this chapter, two brief instruments for screening for manic–depressive disorder have been developed and subjected to psychometric analysis. The Mood Disorders Questionnaire (Hirschfeld et al. 2000) consists of a yes/no checklist based on DSM-IV-TR criteria for mania. The second screener, the Bipolar Spectrum Diagnostic Scale (Ghaemi et al. 2005), consists of a text paragraph describing various symptoms that might occur during (hypo)mania followed by a single item with four choices: "This story fits me very well, or almost perfectly….This story fits me fairly well…. This story fits me to some degree, but not in most respects…. This story doesn't really describe me at all."

The sensitivity and specificity of the MDQ have been reported as, respectively, 0.28–0.73 and 0.67–0.90, and for the BSDS, respectively, 0.75 and 0.79 (Phelps and Ghaemi, 2006). The developers of one of these scales cogently conclude that each of these instruments could be useful as *screening* tools, but are *not* useful for diagnostic confirmation (Phelps and Ghaemi 2006). That is, a positive response merits further diagnostic evaluation but does not mean the individual has a manic–depressive spectrum disorder (low positive predictive value), while a negative response makes it unlikely that the individual has such a disorder (high negative predictive value).

## Additional Features: Psychosis and Rapid Cycling

Psychosis is an episode modifier and can occur in either depression or mania. If psychotic symptoms are limited to the major mood episode, the individual is considered to have manic–depressive disorder with psychotic features. On the other hand, if psychotic symptoms endure significantly into periods of normal mood, the diagnosis of schizoaffective disorder is made. For the formal DSM definition, 2 weeks of psychotic symptoms during normal mood is sufficient to convert a diagnosis of manic–depressive or major depressive disorder into schizoaffective disorder, because it is thought that such persons have a clinical course midway between individuals with mood disorders or schizophrenia. However, this cut-off point is fairly arbitrary, and its validity is not well established (Levitt and Tsuang 1988, Blacker and Tsuang 1992).

**DSM-IV-TR Criteria**

**Rapid-Cycling Specifier**

*Specify* if:

**With rapid cycling** (can be applied to manic–depressive I disorder or manic–depressive II disorder). At least four episodes of a mood disturbance in the previous 12 months that meet criteria for a major depressive, manic, mixed, or hypomanic episode.

**Note:** Episodes are demarcated by either partial or full remission for at least 2 months or a switch to an episode of opposite polarity (e.g., major depressive episode to manic episode).

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Rapid cycling a longitudinal course specifier is defined by DMS-IV-TR as the occurrence of four or more mood episodes within 12 months. Despite the name, the episodes are not necessarily or even commonly truly cyclical; the diagnosis is based simply on episode counting (American Psychiatric Association 2000). While some evidence supports four episodes (any combination of mania, hypomania, mixed,

or depressed) in 12 months as the cut-point (e.g., Bauer et al. 1994a), not all studies support a firm cut-off (e.g., Kupka et al. 2003), and here also it is likely that the phenomenon is part of a continuum rather than a set of discrete categories. Various studies have identified individuals with mood episodes of very brief, even 1 day, duration; such "ultra" or "truncated" rapid cycling shares many clinical features with DSM-defined rapid cycling, and in fact the vast majority of such individuals at some time also meet DSM criteria for rapid cycling (Bauer et al. 1994a).

Rapid cycling is of significance because it predicts a relatively poorer outcome and worse response to lithium and other treatments (e.g., Bauer and Whybrow 1993, Bauer et al. 1994b, Maj et al. 1994). Although rapid cycling was at one time considered by some to be an "end stage" of the disorder, empirical evidence indicates that it may have its onset at any time during the disorder (Bauer and Whybrow 1991, 1993, Bauer et al. 1994a) and may come and go during the course of illness (Coryell et al. 1992). Several specific risk factors may be associated with rapid cycling, each of which may give clues to its pathophysiology. These include female gender, antidepressant use, and prior or current hypothyroidism (Bauer and Whybrow 1993, Bauer et al. 1994b).

## Assessment

### Rationale for the Medical Assessment of Individuals with Manic–Depressive Disorder

Although the diagnosis of manic–depressive disorder is made on the basis of phenomenology, there are several reasons to conduct a thorough medical history and physical examination. First, there are several general medical or substance-related causes of manic depression that, if treated, may lead to the resolution of the mood episode. Second, medical evaluation is necessary before starting several types of medications used in the treatment of manic–depressive disorder. Third, ongoing medical assessment is required for tracking medication-induced side effects of several types of medications. Finally, for many patients with psychiatric illnesses, particularly chronic or severe illnesses, their first contact with medical care as an adult may be during the psychiatric interview—often under inpatient or even involuntary conditions. Because psychiatric illness is clearly not *protective* against medical illnesses, and since even common general medical illnesses may never have been screened for in the past, a thorough medical history and physical examination are necessary parts of the basic care of patients.

Many textbooks recommend a history, physical examination, and laboratory testing for the routine evaluation of persons with mood disorders. Although the history and physical examination are commonsense medical procedures, the use of laboratory testing, particularly routine screening batteries, is supported by few data (Bauer et al. 1993, Agency for Health Care Policy and Research 1993). For instance, using screening for thyroid abnormalities in individuals presenting with depressed mood as an example, Briggs et al. (1993) found no evidence that the prevalence of thyroid disorders among ambulatory patients with depression exceeds that in the general population. It has therefore been recommended to follow standard screening recommendations for the general population in individuals with depression (Agency for Health Care Policy and Research 1993).

The overall approach to evaluating persons with manic–depressive disorder for medical problems may be summarized as follows:

- Persons with psychiatric disorders, including manic–depressive disorder, should have regular screening for disease detection and health maintenance purposes as recommended for the general population.
- However, it should also be kept in mind that individuals with manic–depressive disorder, by virtue of having an often severe and disabling behavioral disorder, are less likely than the general population to have had adequate medical screening and treatment.
- Thus, special care must be made to ensure that health problems are not overlooked and that appropriate treatment or referral is effected.

If results of the history or physical examination reveal abnormalities, or if the psychiatric illness or treatment is associated with particular general medical conditions, more intensive testing is warranted. Examples of this latter are the use of lithium or some second generation antipsychotics, which are associated with, respectively, increased rates of thyroid and renal abnormalities or increased rates of obesity and type II diabetes.

### Medical Precipitants of Manic or Depressive Symptoms

Krauthammer and Klerman (1978) conceptualized secondary mania as mania occurring close on the heels of a specific known physiological insult, such as general medical illness or exposure to mania-inducing pharmacological agents. Most medical illnesses that affect brain function have been described in case reports or small case series to cause one or another psychiatric syndrome (Table 67–2), although none can be considered specific risk factors. Case reports or case series that propose that a putative causative medical illness is associated with manic–depressive disorder must be interpreted with caution. For instance, Josephson and MacKenzie (1979) described an association between hyperthyroidism and mania. However, almost all of these patients had additional factors that most likely contributed to the development of mania, such as a preexisting mood disorder due to a general medical condition or a prior history of mood disorders. Too much thyroid hormone in and of itself is not likely to cause mania (Bierwaltes and Ruff 1958). On the other hand, administration of medications has been

**Table 67–2 Medical Disorders Commonly Associated with Mania**

| Neurological Disorders | Endocrine Disorders |
|---|---|
| Stroke | Hyperthyroidism (in those with preexisting manic–depressive disorder) |
| Head trauma | Postpartum status |
| Dementia | |
| Brain tumors and metastases | |
| Paraneoplastic syndrome | |
| Infection (including HIV) | |
| Multiple sclerosis | |
| Huntington's disease | |

**Table 67–3 Treatments and Drugs Commonly Associated with Mania**

| Antidepressants | Dopaminergic Agents |
|---|---|
| Medications | Levodopa |
| Bright visible spectrum light treatment | |
| Electroconvulsive therapy | |
| **Adrenergic Agents** | **Drugs of Abuse** |
| Decongestants | Alcohol |
| Bronchodilators | Cocaine |
| Stimulants | Hallucinogens |
| | Amphetamines |
| | Caffeine |
| **Other Agents** | |
| Isoniazid | |
| Corticosteroids | |
| Anabolic steroids | |
| Disulfiram | |

observed frequently in clinical practice to be associated with the onset of mania, particularly in patients with preexisting depression. Such medications are listed in Table 67–3. Depressive symptoms may also be associated with certain medical conditions (Table 67–4) and medications or drugs (Table 67–5).

Some controversies have been hotly debated, particularly regarding the role of antidepressants in causing mania and rapid cycling (Prien et al. 1973b, Lewis and Winokur 1982, Wehr et al. 1993, Altshuler et al. 1995a; see also Section "Balancing Risks and Benefits of Antidepressant Treatment"). Of particular importance to psychiatric practice, all efficacious antidepressant treatments have been suspected to cause the induction of mania, with the exception of lithium, lamotrigine, and psychotherapy. Occasionally when a new antidepressant is developed, hope is raised that it will be the agent that will not induce mania. Clinical experience has not borne out these early hopes. This caveat for antidepressants also includes nonpharmacological antidepressants such as light and electroconvulsive therapy (ECT). The latter effect is paradoxical, as ECT is also used successfully to treat mania.

**Table 67–4 Medical Disorders Commonly Associated with Depression**

| Neurologic Disorders |
|---|
| Stroke |
| Head trauma |
| Dementia |
| Brain tumors |
| Infection (including HIV) |
| Multiple sclerosis |
| Parkinson's disease |
| Huntington's disease |
| **Endocrine** |
| Addison's disease |
| Cushing's disease |
| Hypothyroidism |
| Hyperthyroidism |
| Postpartum status |
| **Cancers** |
| Pancreatic |
| Paraneoplastic Syndromes |
| **Metabolic** |
| $B_{12}$, folate deficiencies |
| **Do Not Overlook** |
| Any medical disease that causes significant loss of function or self-esteem (e.g., cardiovascular disease, arthritis, chronic pulmonary disease) |

**Table 67–5 Treatments and Drugs Commonly Associated with Depression**

| High Blood Pressure Medications | Hormones |
|---|---|
| Alphamethyldopa | Corticosteroids |
| Clonidine | Oral contraceptives |
| | Anabolic steroids |
| **Ulcer Medications** | **Psychotropic Agents** |
| Cimetidine | Benzodiazepines (?) |
| Ranitidine | Neuroleptics (?) |
| **Drugs of Abuse** | |
| Alcohol | |
| Sedatives | |
| Amphetamine (withdrawal) | |
| Cocaine (withdrawal) | |
| Nicotine (withdrawal) | |

## Tracking Manic and Depressive Symptoms with Rating Scales

A plethora of rating scales is available for assessing manic and depressive symptoms, and associated features such as psychosis, functional status, and healthcare costs. For general information, the reader is referred to the compilation of rating scales by the APA (American Psychiatric Association Task Force for the Handbook of Psychiatric Measures 2000). For clinical usage, clinicians rating scales in general use for depression (see Chapter 66) can also be used for depressive episodes in manic–depressive disorder. Most share the shortcoming of tending to underrate hypersomnia, hyperphagia, and weight gain, "atypical" features that are common in manic–depressive disorder. Among mania scales, the Young Mania Rating Scale (Young et al. 1978, 1983) is well validated on outpatients as well as inpatients, and for hypomanic as well as manic episodes.

Self-report scales have the advantage of being brief (typically 5 minutes) and amenable to frequent, even daily, usage without undue burden. However, it is apparent that the simple single analog mood rating once widely used ("best" to "worst" mood) is of limited utility because of the high frequency of mixed symptoms (see Section "A 'Bipolar' Disorder?").

With the caveats noted regarding interview-based assessment of depression in this disorder, self-report instruments for unipolar depression can reasonably be used in manic–depressive disorder as well. Self-reports

for (hypo)manic symptoms have also been developed, and validation data indicate that insight sufficient for self-rating is preserved in most individuals in such episodes (e.g., Bauer et al. 1991, Sugar et al. 1992, Altman et al. 1997). Self-rating scales for (hypo)mania include the following: the Internal State Scale (ISS; Bauer et al. 1991, Glick et al. 2003), which also includes a rubric for diagnosing (hypo)manic, depressive, and mixed episodes as well as a depression symptom severity measure; the Self-Report Manic Inventory (Sugar et al. 1992); and the Altman Self-Rating Mania Scale (ASRS; Altman et al. 1997). The ASRS (Alvarez Mas et al. 2005) is available in Spanish, and the ISS is available in Castilian, Mexican, Caribbean Spanish, French, and German.

## Epidemiology

Epidemiological studies assess the *incidence* (onset frequency), *prevalence* (overall population load), and related characteristics in large samples of persons who are typically not preselected on the basis of presentation for clinical care. These studies are a valuable complement to clinic-based studies for several reasons. First, epidemiological studies avoid biases inherent in studying clinic-based samples. For example, clinical populations may underrepresent the milder (or most severe) variants of a disorder; further, willingness to request clinical care may be associated with sample characteristics that bias the sample in unknown ways. In addition, epidemiological studies may be helpful in determining overall population load for a particular disorder, which can be helpful in planning health services. On the other hand, the large sample size and required methodology for most epidemiological studies limit the extent to which any individual subject can be assessed.

Estimates of the lifetime risk for manic–depressive I disorder from epidemiological studies have ranged from 0.2 to 0.9% (Fremming 1951, Parsons 1965, James and Chapman 1975, Weissman and Myers 1978, Helgason 1979). The Epidemiological Catchment Area (ECA) study found a lifetime prevalence rate of 1.2% for combined type I and type II variants (Weissman et al. 1988); this agrees closely with the earlier study of Weissman and Myers (1978), which found 0.6% prevalence for each of the types individually. Little is known regarding the prevalence of cyclothymic disorder. The lifetime community prevalence rate of "bipolar spectrum" disorders has been estimated to be as high as 6%, based on at least two hypomanic symptoms lasting less than 1 week (Judd and Akiskal 2003).

Unlike major depressive disorder, manic–depressive disorder has an approximately equal gender distribution (Weissman et al. 1988). Few consistent data are available regarding differences in prevalence across ethnic, cultural, or rural–urban settings within the US, while there are some cross-national differences in mania (Sherazi et al. 2006). However, one of the more intriguing puzzles is the tendency of manic–depressive disorder to occur in higher socioeconomic strata than schizophrenia, which tends to aggregate in lower socioeconomic strata. Several theories have been advanced to explain this phenomenon (Goodwin and Jamison 1990, pp. 169–174), and some have questioned this association (Sherazi et al. 2006); however, several issues are clear. First, the finding is most likely not exclusively due to diagnostic bias (i.e., overdiagnosing persons of lower socioeconomic class with schizophrenia more frequently than manic–depressive disorder and the converse in persons of higher socioeconomic class). Second, the upward socioeconomic "drift" is not due to highly impaired patients "dragged" upward by higher functioning family members who are normal or who have adaptive subsyndromal manic–depressive spectrum characteristics; rather, patients themselves, at least those with type II disorder, are in many cases highly successful and occupy higher socioeconomic levels (Coryell et al. 1989a). Third, the findings are not limited to the US but have been replicated in European samples as well (Lenzi et al. 1993).

Of particular interest in regard to the epidemiology of manic–depressive disorder is that the incidence of manic–depressive disorder (and depressive disorders) appears to have increased since the 1940s (Gershon et al. 1987). Reasons for this are not clear, although environmental factors, either physiological or psychosocial, may be responsible. For instance, exposure to increasingly severe social stressors, or the breakdown of cultural supports that may buffer stresses, may contribute; increases in exposure to putative environmental toxins might also be considered. In addition, in those families afflicted with manic–depressive disorder across generations, those in later generations tend to have earlier onset; this phenomenon, called *anticipation*, may be due to changes in genetic loading across generations, instability of genetic material, or environmental factors either within the family or in the wider environment (Lange and McInnis, 2002, O'Donovan et al. 2003; see also Section "Postconceptual Congenital Factors"). Regardless of the cause, the increasing incidence and earlier onset of manic–depressive disorder indicate that this illness is not likely to decrease in importance as a clinical and public health issue.

## Comorbidity

Psychiatric and medical comorbidity in manic–depressive disorder has been increasingly recognized since the last edition of this textbook. At that time, only substance use disorders warranted specific summary. We now recognize that anxiety disorders are at least equally common among individuals with manic–depressive disorders, and that several other psychiatric disorders and many medical disorders are also common. In fact psychiatric comorbidity is the rule rather than the exception, with 57.3% (Bauer et al. 2005a) to 74.3% (Jacobi et al. 2004) having at least one active comorbidity, and 14.9% (Jacobi et al. 2004) to 29.8% (Bauer et al. 2005a) have two or more. Medical comorbidity rates are even higher, and both worsen outcome and constrain treatment (see Section "Medical Comorbidity").

### Substance Use Disorders

Some prevalence studies are conducted with community-based sampling, i.e., interviewing subjects regardless of whether or not they are receiving any kind of health care. Other studies are conducted on clinical samples whose members are, by definition, receiving healthcare services of some type. Whereas in the general population rates of alcohol abuse combined with alcohol dependence range from 3 to 13%, they are greater than 30% in persons with manic–depressive I disorder (Regier et al. 1990). Further, lifetime rates for drug dependence in individuals with manic–depressive I disorder are greater than 25%, and rates for any substance abuse or dependence are above 60%;

comparable rates for alcohol, drug, or any substance abuse or dependence in major depressive disorder in ECA data are, respectively, 12%, 11%, and 27% (Regier et al. 1990).

Substance use disorder comorbidity rates in clinical samples have recently been reviewed (Bauer et al. 2005a). Rates are high, but vary widely depending on whether the sample is inpatient or outpatient, and whether lifetime or current rates are ascertained (Table 67–6). Importantly, there is some evidence from large samples of individuals with manic–depressive disorder that rates of these disorders may vary depending on whether the samples reflect populations receiving health care in the public sector versus private institutions (Bauer et al. 2006a). For example, individuals recruited for a clinical trial of a care management intervention within the VA system ($n = 306$) had SCID-defined lifetime substance use disorder rate of 72% and current rate of 34%, similar to the screener-positive rate of substance use disorders of 55% in a clinical trial in a Texas community mental health setting ($n = 409$). In contrast, clinical trial or cohort samples of 261–1,000 subjects across three private sector studies revealed rates of 4–12% current substance use disorders. Thus these public sector rates more closely resemble community rates, raising the question of selection or barriers to entry into private sector health care for such dually diagnosed individuals.

**Table 67–6 Prevalence Rates (%) of Any Substance Use Disorder in Clinical Samples of Individuals with Manic–Depressive Disorder ()**

| | Inpatient | Outpatient |
|---|---|---|
| Current: any substance use disorder | 34–50% | 4–55% |
| Current alcohol | – | 2–46% |
| Current drug | 2–55% | 1–36% |
| Lifetime: any substance use disorder | 72% | 42–48% |
| Lifetime alcohol | 39–40 | <10–40% |
| Lifetime drug | 3–68% | 6–45% |

*Source:* From studies reviewed in Bauer et al. (2005a, 2006a).

## Anxiety Disorders

Community-based studies from several countries have investigated anxiety comorbidity in manic–depressive disorder. Lifetime anxiety disorder diagnosis in a Canadian sample of individuals with manic–depressive disorder was 51.8% (Schaffer et al. 2006), while lifetime rates for individual anxiety disorders in a Hungarian sample ranged from 12.5 to 22.1% (Rihmer et al. 2001). Among US individuals over 65 years of age, lifetime rates of panic and generalized anxiety disorders were, respectively, 19.0% and 20.5%, while current rates were, respectively, 11.9% and 9.5% (Goldstein et al. 2006). Anxiety disorders have been found in 33.3% of a community sample of adolescents with manic–depressive disorder as well (Lewinsohn et al. 1995).

Current anxiety rates in clinical samples (Table 67–7) match or exceed those for substance use disorders. As with substance use disorders, rates tend to be higher in inpatient samples than outpatients. Lifetime rates of all individual anxiety disorders appear to be substantial, while current rates are particularly notable in panic disorder (8–17%) and posttraumatic stress disorder (4–40%) (Bauer et al. 2005a, McIntyre et al. 2006c). Notably, there is less difference between current and lifetime rates than for substance use disorders suggesting that, from a population perspective, these disorders represent a chronic problem. Interestingly, comparison of anxiety disorder rates across large clinical cohorts recruited in the public versus private sector does not indicate the same disparity as for substance use disorders (Bauer et al. 2006a), suggesting that this comorbidity does not represent a barrier to private sector treatment.

**Table 67–7 Prevalence Rates (%) of Anxiety Disorders in Clinical Samples of Individuals with Manic–Depressive Disorder**

| | Inpatient | Outpatient |
|---|---|---|
| Current: individual anxiety disorders | 0–40% | 2–13% |
| Current: any anxiety disorder | 38% | 30–31% |
| Lifetime: individual anxiety disorders | 3–38% | 3–50% |
| Lifetime: any anxiety disorder | 16–43% | 18–79% |

*Source:* From studies reviewed in Bauer et al. (2005a, 2006a) and McIntyre et al. (2006c).

## Other Psychiatric Comorbidity

While attention-deficit hyperactivity disorder (ADHD) represents an alternative differential diagnostic possibility for manic–depressive disorder, there appears to be evidence that these distinct disorders also co-occur. In a predominantly adult clinical sample ADHD lifetime and current rates were found to be, respectively, 9% and 6% in youth (see Section "Treatment of Manic–Depressive Disorder Across the Life Cycle") and adults (Simon et al. 2004a).

In community samples of persons with manic–depressive disorder, lifetime rates of eating disorders range from 0 to 9% (McElroy et al. 2006a). In clinical samples, the lifetime rates of any eating disorder range from 8 to 27% (Simon et al. 2004a, McElroy et al. 2006a).

The relationship of manic–depressive disorder to borderline personality disorder has long been a subject of debate and scientific interest. Some have maintained that there is little to no relationship between the two (reviewed in Gunderson et al. 2006) while others have suggested that the two clinical syndromes are part of a single continuum (e.g., Akiskal 2004). Recent genetic studies suggest that there may be a link between manic–depressive disorder and personality or temperament (not necessarily borderline), yet much remains conjectural (e.g., Savitz and Ramesar 2006, Serretti et al. 2006). Perhaps the highest quality data to address the relationship of manic–depressive and borderline personality disorders come from the US National Institute of Mental Health (NIMH)-funded Collaborative Longitudinal Personality Disorders Study (Gunderson et al. 2000), in which subjects with a wide variety of personality disorders have been followed prospectively with standardized assessment tools. Four-year follow-up from this cohort supports a position between the above two poles. Specifically, compared to those with other personality disorders, individuals with borderline personality disorder have significantly higher rates of manic depression (19.4% vs. 7.9%), including both type I (11.7% vs. 5.5%) and type II (7.7% vs. 2.3%) disorder, and tend to have higher prospectively documented incidence rates ($p = 0.07$); however, manic-depression comorbidity rates are lower in borderline personality disorder than those

for major depression, PTSD, or substance use disorders (Gunderson et al. 2006).

### Medical Comorbidity

Evidence is accumulating that comorbid medical conditions are highly prevalent, worsen outcome, limit treatment options, and are induced or exacerbated by certain treatments. A variety of studies have documented high, or significantly increased, rates of medical comorbidity among individuals with manic–depressive disorder (Table 67–8; also recently reviewed in Newcomer, 2006). Over 80% have at least one active medical problem while 19–23% have two such conditions and 35–50% have three or more (Kilbourne et al. 2004, Fenn et al. 2005). In addition, several relatively low prevalence illnesses may be significantly increased in individuals with manic–depressive disorder compared to the population without this disorder, including chronic obstructive pulmonary disease, hepatitis C, and HIV (Kilbourne et al. 2004), migraine headaches (McIntyre et al. 2006b), and accidents and musculoskeletal trauma (Kilbourne et al. 2004, Beyer et al. 2005). Over half of those with manic–depressive disorder may be overweight, and 27% may be obese (Wang et al. 2006).

**Table 67–8 Prevalence Rates (%) of Selected Common Medical Disorders in Clinical Samples of Individuals with Manic–Depressive Disorder**

| | Inpatient | Outpatient |
|---|---|---|
| Tobacco use | 54–68% | – |
| Obesity | 20–49% | 3–50% |
| Cardiovascular disease and hypertension | 13–39% | 18–51% |
| Hyperlipidemia | 23–24% | 2–13% |
| Diabetes | 4–18% | 30–31% |

Increased rates of medical comorbidity have been associated with increased depression severity and worse treatment outcome (Thompson et al. 2006, McIntyre et al. 2006a), though not all studies have found this relationship (e.g., Beyer et al. 2005). Medical comorbidity has also been associated with worse function (McIntyre et al. 2006a) and physical quality of life (Fenn et al. 2005). One study has demonstrated reduced time to episode recurrence with obese individuals with manic–depressive disorder (Fagiolini et al. 2003), while another has found an increased rate of "natural death," which was associated with several medical findings including elevated liver transaminase levels and white blood cell counts (Tsai et al. 2005).

For decades clinicians have recognized that certain medical comorbidities limit the use of various psychotropic medications, for example, renal disease (lithium), liver disease (valproate, carbamazepine), cardiac arrhythmias (tricyclic antidepressants). More recently, clinicians have come to recognize that certain antipsychotic medications, particularly several of the second generation antipsychotics, are associated with weight gain, type II diabetes, and consequent increased cardiovascular risk (e.g., Correll et al. 2006, Guo et al. 2006, Olfson et al. 2006). Intriguingly, not all the risk of diabetes is attributable to psychotropic use, and manic–depressive disorder itself may be a significant risk factor (Regenold et al. 2002).

## Course

### Defining Outcome: Clinical, Functional, Quality of Life, and Economic Outcomes

Several developments in society at large, in biomedical treatment in general, and in mental health research in particular, have led to an expansion of the purview for mental health research beyond simple symptom reduction to include understanding the impact of illness and its care on a patient's overall quality of life and how to make the best use of available resources (Stewart et al. 1989, National Institute of Mental Health 1992, Leaf 1993). With this orientation, we can therefore conceptualize outcome in manic–depressive disorder according to three separate but interrelated domains: *clinical outcome, functional outcome and quality of life*, and *illness costs*. Clinical outcome consists of parameters that measure the illness itself, such as symptom severity, episode number, and duration. Functional outcome consists of social and occupational status and subjective quality of life. Illness costs consist of both direct (treatment) costs and indirect illness costs, which include lost productivity, necessary nontreatment social supports, and nontreatment interventions such as jail and the legal system. Each domain is reviewed below.

### Clinical Outcome

Manic–depressive disorder has its onset in most persons in adolescence and young adulthood, between the ages of 15 and 30. However, prepubertal mania and first-onset disease in the 9th decade of life are not unheard of. Once developed, multiple episodes are the rule. There is no typical pattern to episode recurrence, with some patients having isolated manic, hypomanic, or depressive episodes, others switching from one pole to the other in linked episodes, and still others switching continually from one pole to the other in quasicyclical fashion (Angst 1981). However, even among rapid-cycling patients, episodes are rarely periodic. Rather, the pattern is more accurately described by chaotic dynamics (Gottschalk et al. 1995).

Episode length typically ranges from 4 to 13 months, with depressive episodes typically longer than manic or hypomanic episodes (Goodwin and Jamison 1990, p 40). Women appear to have more depressive than manic episodes, whereas men have a more even distribution (Angst 1981). Also women predominate among rapid-cycling patients, representing 70–90% in most studies (Bauer and Whybrow 1993, Bauer et al. 1994b).

Manic–depressive disorder had been separated from *dementia praecox* (schizophrenia) by Kraepelin (1989) on the basis of relatively favorable outcome in terms of remitting versus chronic course of psychosis. However, this relatively optimistic view contrasts with the overall guarded prognosis described by most longitudinal studies in the last 3 decades, which have been less controlled but more inclusive than formal clinical trials. In the early studies, the majority had equivocal to poor outcome (Levinstein et al. 1966, Winokur et al. 1969) and almost half were chronically ill (Bratfos and Haug 1968). Although these studies include data from the prelithium era, studies since the development of modern psychopharmacology are not reassuring. Approximately 20–40% of patients with manic–depressive disorder do not respond well to lithium (Prien and Gelenberg 1989), and

that proportion may increase to as much as 80% for certain subgroups such as those with rapid-cycling (Dunner and Fieve 1974, Maj et al. 1989) or mixed episodes (Keller et al. 1986). Up to one-third of individuals remain chronically ill (Keller et al. 1986a), and one-quarter to one-third of hospitalized individuals go on to poor outcome or chronicity (Tohen et al. 1990, Harrow et al. 1990); further, 60% of an ambulatory sample of manic–depressive patients had fair to poor outcome based on a global outcome score after 1-year follow-up (O'Connell et al. 1991).

Since the last edition of this textbook, analyses of two large studies have provided a detailed look at prospective outcome. The NIMH Collaborative Study on the Psychobiology of Depression, begun in the 1970s, has now analyzed data from subjects for up to 20 years (Judd et al. 2002, 2003a–2003c). These data confirm the overall guarded prognosis for manic–depressive disorder. Individuals with type I disorder spent 46.6% of weeks with clinically significant symptoms, while those with type II disorder spent 55.8% of weeks symptomatic. Depressive weeks outnumbered manic weeks by 3:1 in both type I and type II though other analyses indicated more depressed weeks in type II. Notably, substantial amounts of time were spent with clinically significant symptoms that did not meet criteria for a full affective episode (Judd et al. 2003c), a finding in agreement with a large population-based cross-sectional study (Bauer et al. 2005a). Lack of a firm, categorical cut-off between DSM-defined episodes and subsyndromal symptoms is also supported by lack of difference between individuals with type II disorder who experienced 2–6 day hypomanic episodes versus those with longer hypomanias (Judd et al. 2003a). These data are consistent with earlier studies (e.g., Nilsson and Axelsson 1989, Harrow et al. 1990). These analyses extend our knowledge of type II disorder, but remain equivocal regarding whether type I and type II are distinct disorders. The NIMH Collaborative Study found no differences in baseline demographic or clinical characteristics or substance comorbidity between the types, though did find that type II was characterized by higher rates of anxiety comorbidity. Not surprisingly, intake episode severity was greater for type I (perhaps accounted for by manic compared to hypomanic severity), but those with type II received less intense pharmacotherapy (Judd et al. 2003c). The two types were found to have similar levels of social dysfunction (Coryell et al. 1989b, Judd et al. 2005). However, type II individuals appear to spend more time depressed than type I individuals (Judd et al. 2003b), while type I individuals appear to spend more time (hypo)manic than type II individuals (Judd et al. 2003b).

The second large study is the Systematic Treatment Enhancement Program for Bipolar Disorder (Sachs et al. 2003). This NIMH-funded program consisted of a long-term cohort follow-up study with several embedded randomized controlled trials. Cohort analyses indicated a predominance of depressive episodes in this mixed type I and II sample, with 29–41% of days depressed versus 19–20% of days "elevated" over 2 years of follow-up (Perlis et al. 2005). Notably, only 58.4% recovered from their index episode at study entry. In those who did recover, depressive relapses outnumbered (hypo)manic relapses by more than 2:1; the time for 25% of the sample to relapse was 21.4 weeks for depression, and 85.0 weeks for (hypo)mania (Perlis et al. 2006b). There are few predictors of recurrence that would not be expected a priori (Perlis et al. 2006b), such as more prior episodes, more chronicity of symptoms, and more residual symptoms each predict shorter time to relapse; although women apparently have shorter time to relapse than men, gender is not a significant predictor when these other factors are accounted for. Notably, current anxiety disorders predict shorter time to depressive relapse while current substance disorders predict shorter time to manic relapse.

## Functional Outcome and Health-Related Quality of Life

Substantial levels of functional impairment are characteristic of manic–depressive disorder, even when major clinical indices have improved. The book-length study of manic–depressive patients in the prelithium era by Winokur et al. (1969) documented their sample's functional impairment in detail. For instance, 79% of those employed before their index episode lost their jobs during that episode. Among those with incomplete remission during follow-up, 73% had long-term decrements in occupational status. Even more striking, 25% of those with complete remission or only infrequent episodes developed similar occupational decrements. In another early study, 60% had less than satisfactory social recovery (Hastings 1958).

In a study of persons with manic–depressive disorder treated at the NIMH, only 41% had returned to their jobs at 3 years of follow-up, and 15% were totally unemployed. Forty-five percent had normal family and social function, 21% evidenced "complete social withdrawal," and 11% "complete family disruption" (Carlson et al. 1974). On global outcome assessment, 57% were judged recovered, 10% had intermittent episodes, and 28% were functionally impaired with moderate to severe affective symptoms. In contrast, Dion et al. (1988) found that although 80% of their sample of manic–depressive patients became symptom free by 6 months after an index major affective episode, only 43% were employed and only 21% were employed at preepisode levels. Harrow et al. (1990) found at 1.7 years of prospective follow-up after an index manic episode that only 23% of patients were continuously unemployed, with 36% underemployed in comparison to preepisode levels. Occupational function was significantly worse than in a comparison group of depressive patients without history of mania. In addition, 36% showed at least moderate impairment in social function. These deficits were unrelated to the presence of symptoms, with the exception of psychosis, which was associated with profound impairment. Tohen et al. (1990) found 28% of subjects unemployed after index hospitalization for mania. Bauwens et al. (1991) found that levels of functional disability correlated both with number of prior episodes and with residual interepisode psychopathology.

Far and away the strongest predictor of functional deficits is ongoing depressive symptoms, even in mild degree (reviewed in Bauer et al. 2001b, Judd et al. 2005). The direction of causability is not clear, however. It is plausible that depressive symptoms render individuals less able to function in work and personal roles. It is equally plausible that unemployment, divorce, social isolation, and the like can cause or exacerbate depressive symptoms. In fact, both are likely. In any event, careful attention to functional deficits, depressive symptoms, and their

interplay is important to optimizing care and hopefully outcome.

Health-related quality of life—by definition a self-reported, subjective summary judgment regarding how one is functioning in the world—has been the subject of recent study in manic–depressive disorder. Mental quality of life in manic–depressive disorder is consistently well below population norms (e.g., Vojta et al. 2001, Zhang et al. 2006). As with social role function, the strongest predictor of poor quality of life is depressive symptoms (Vojta et al. 2001), even after control for numerous potential confounds (Zhang et al. 2006).

Manic–depressive disorder is characterized by high rates of suicidality. Suicide attempt rates may be as high as 2%/year (Baldessarini et al. 2001). Rates of completed suicide may be as high as 7–19% (Goodwin and Jamison 1990, Angst 2002), and may be 15-fold higher than in the general population (Harris and Barraclough 1997)

### Economic Outcome: Direct and Indirect Illness Costs

The Global Burden of Disease Study (GBDS) has ranked manic–depressive disorder sixth in disability worldwide (Murray and Lopez 1996, Lopez and Murray 1998). It is the most expensive mental disorder for US private behavioral health plans (Peele et al. 2003) and employers (Goetzel et al. 2003). Individuals with manic–depressive disorder receive care throughout the healthcare system (Simon and Unützer 1999, Das Gupta and Guest 2002), and up to 70% of direct treatment costs are generated outside the mental health sector (Begley et al. 2001, Bryant-Comstock et al. 2002). Lifetime total costs per patient exceed US $250,000 (Begley et al. 2001). If one can extrapolate to manic–depressive patients from the data for aggregate mental illness costs (McGuire 1991), 55% of treatment costs derive from public sector services and 45% from the private sector.

The high suicide rates in manic–depressive disorder place a substantial proportion at high risk of loss of life through this one cause alone, while excess mortality (see Section "Medical Comorbidity") adds to the economic cost of early loss of life. Without adequate treatment, a person with manic–depressive disorder from age 25 years can expect to lose 14 years of effective major activity (e.g., work, school, family role function) and 9 years of life (US Department of Health, Education, and Welfare 1979). The indirect costs of bipolar disorder are high as well, with substantial costs incurred by both work absence and reduced efficiency at work. For instance, a Dutch study indicates that yearly indirect costs due to bipolar disorder may total as much as $1.37 billion dollars, over three-fold the total direct treatment costs for the disorder (Hakkaart-van Roijen et al. 2004), underlining the substantial functional impact bipolar disorder can have on society.

## Differential Diagnosis

Differential diagnosis of manic–depressive disorder can be simplified by keeping in mind that the disorder, in classic form, consists of discrete episodes of (hypo)mania, depression, or their combination. Focus on discrete episodes is particularly important since a wide variety of behaviors can raise the suspicion of (hypo)mania, and since an unintended consequence of the appropriate attention to this disorder in the lay press has led in some quarters to its becoming a diagnosis du jour, too easily applied to chronic, aberrant behaviors that are not due to this illness.

As with all psychiatric disorders, underlying medical causes must be ruled out, as must untoward effects of medications. Illnesses and medications that have been associated with (hypo)manic episodes are found, respectively, in Tables 67–2 through 67–5. Recall that medication history should include not only those prescribed by physicians but also those that are self-prescribed (over-the-counter and herbal/supplements) and drugs of abuse (both illegal and legal). Similarly, medical and medication causes of depressive episodes can found in Chapter 66.

Individuals with recurrent major depressive disorder will often not recognize or report prior hypomanic or even manic episodes, so these must be queried for specifically. Several other Axis I disorders present with psychomotor hyperactivity or what appears to be decreased need for sleep (not just insomnia), such as, ADHD and PTSD; however, the former is typically chronic and the latter associated with prior trauma and trauma-related themes in the hyperactivity or sleeplessness (e.g., hypervigilance or fear of sleep).

Similarly, borderline personality disorder frequently involves mood lability, instability of interpersonal relationships, periodic feelings of emptiness or identity disturbance, and episodes of self-harm—all of which can be found in manic–depressive disorder, particularly the rapid-cycling variant. While psychodynamic formulation can frequently differentiate the former from the latter, even on purely descriptive grounds temporal course and relationship features clarify the diagnosis. Specifically, in manic–depressive disorder discrete several-day episodes are the rule, and they are not necessarily linked to discrete stressors such as interpersonal rejection; moreover, in this disorder history usually reveals that when the mood is stable the individual's patterns of interpersonal relationship often stabilize—though there is no question, as summarized above, that individuals with this disorder are often impoverished interpersonally due to their illness.

It should also be kept in mind that the differential diagnosis in individuals with possible manic–depressive disorder is often an issue of *and* rather than *or*. That is, since the majority of such individuals have some psychiatric comorbidity, anxiety, substance, and attention-deficit, and medical disorders are often present as concurrent comorbidities rather than alternative diagnoses (see Section "Comorbidity"). Comprehensive care depends on identifying and treating each of these.

Finally, it should also be noted that manic–depressive disorders likely represent part of a spectrum both with other mood disorders and perhaps other disorders (e.g., Perugi and Akiskal 2002) including schizophrenia (e.g., Craddock and Owen 2005, MacQueen et al. 2005, Potash 2006). Thus while classic textbook cases are readily identified, it is expectable that a variety of individuals will inhabit the boundaries of this disorder, which, as most psychiatric diagnoses, is likely best considered a "fuzzy set."

## Age, Gender, and Cultural Issues in Diagnosis and Assessment

Manic–depressive disorder is a worldwide problem, with manic–depressive disorder among the top 10 of all diseases

in terms of global burden worldwide, and sixth in terms of self-reported disability (Andrews et al. 1998). There are no major differences in the manifestations of manic–depressive disorder across gender, the adult lifespan, race/ethnicity, or culture. However, women appear to be at higher risk for rapid cycling (Bauer and Whybrow 1993, Bauer et al. 1994b), dysphoria during mania (McElroy et al. 1992, Bauer et al. 1994c), and comorbid disorders (Strakowski et al. 1992 and 1994). Note also that affective psychoses may be relatively underdiagnosed, and schizophrenia overdiagnosed, in African-Americans compared to Caucasians (Strakowski et al. 1993).

Among children and adolescents, the diagnosis of manic–depressive disorder is often complicated by less consistent mood and behavior baseline than occur in adults (Carlson and Kashani 1988). Little evidence is available regarding course and outcome in children. Available data indicate that, as with adults, mixed or cycling episodes predict more recurrences; unlike in adults, manic and mixed presentations may be associated with relatively shorter episodes compared with depressive presentations (Strober et al. 1995). Notably, attentional and executive cognitive deficits may remain in euthymic young adults who have experienced even one or two mood episodes as children (Kolur et al. 2006)

## Etiology and Pathophysiology

Review references outlining the various hypotheses of manic–depressive disorder are provided in Table 67–9. No single paradigm can explain the occurrence, and variability in course and severity of manic–depressive disorder. Rather, an integrative approach to understanding the causes of manic–depressive disorder is needed, which recognizes the contributions of a variety of biological, psychological, and social factors, as articulated in George Engel's biopsychosocial model (Engel 1977).

### Genetic and Congenital Hypotheses

#### Family, Twin, and Adoption Studies

Available evidence indicates that familial factors are important determinants of who will develop manic–depressive disorder. Numerous studies have shown that relatives of manic–depressive probands (identified cases) have higher rates of manic–depressive disorder than controls or unipolar probands (Table 67–10). Overall, rates of manic–depressive disorder in first-degree relatives (parents, siblings, children) of probands with manic–depressive disorder are elevated 5–10 times over rates found in the general population. In the latter group, the rates are 0.5–1.5%, while in the former group rates are 4–15% (Table 67–10). Polarity of first episode may also be familial (Kassem et al. 2006). Interestingly, rates of unipolar depression in first-degree relatives of individuals with manic–depressive disorder are elevated about twofold over those in the general population, or about 20–40%. Important for genetic counseling, this in turn means that the probability that a manic–depressive proband will have a unipolar child is greater than the probability that they will have a manic–depressive child; note that it is most likely that they will have neither.

Most genetic research has been done on type I disorder. However, type II also appears to have a familial

**Table 67–9 Major Hypotheses of the Pathophysiological Basis of Manic–Depressive Disorder***

| Hypotheses | Key Review References* |
|---|---|
| **Genetic** | Craddock and Jones (1999) |
| | Potash and DePaulo (2000) |
| | Shih et al. (2004) |
| | MacQueen et al. (2005) |
| | Potash (2006) |
| **Neurotransmitter** | |
| Norepinephrine | Prange (1964) |
| | Schildkraut (1965) |
| | Bunney et al. (1972a, 1972b, 1972c) |
| Dopamine | Goodwin and Sack (1974) |
| | Crow and Deakin (1981) |
| Serotonin | Coppen et al. (1972) |
| | Goodwin and Jamison (1990) |
| Acetylcholine | Janowsky et al. (1973) |
| Glutamine | Kugaya and Sanacora (2005) |
| **Second-Messenger Systems** | Stahl (2000) |
| | Sassi and Soares (2002) |
| | Bezchlibnyk and Young (2002) |
| | Coyle and Duman (2003) |
| **Neuroendocrine** | |
| Various | Amsterdam et al. (1983) |
| Thyroid | Bauer and Whybrow (1990) |
| | Sassi and Soares (2002) |
| **Neuroanatomic** | |
| | Brambilla et al. (2005) |
| | Strakowski et al. (2005) |
| | Manji and Lenox (2000) |
| **Cell Degeneration and Neuroprotection** | |
| | Manji and Duman (2001) |
| | Chen and Manji (2006) |
| **Complex Physiological Systems** | |
| Membrane, electrolytes | Goodwin and Jamison (1990) |
| Biological rhythms, annual | Faedda et al. (1993) |
| Biological rhythms, circadian | Wehr et al. (1982) |
| | Halaris (1987) |
| **Psychological** | |
| Cognitive | Rush and Hollon (1991) |
| Behavioral | Lewinsohn (1974) |
| Interpersonal | Weissman and Klerman (1991) |
| Psychoanalytic | Fenichel (1945) |
| | Cooper (1985) |
| | Kahn (1993) |
| | Hume et al. (1988) |
| **Psychobiological** | |
| | Frank et al. (1994) |
| | Johnson and Roberts (1995) |
| | Alloy et al. (2006) |
| | MacQueen et al. (2005) |
| **Neurocognitive** | Robinson et al. (2006) |
| **Social/Environmental** | |
| Psychosocial stress | Johnson (2005) |
| Physiologic stress | See "Biological rhythms," above |
| | Engel (1977) |
| **The Biopsychosocial Model** | |

*These key references are either reviews or well-referenced primary data articles that will provide the reader with an introduction to each area.

**Table 67–10 Rates of Manic–Depressive Disorder in First-Degree Relatives**

| Study | Proband is: | | |
|---|---|---|---|
| | Manic–Depressive | Unipolar | Control |
| Taylor et al. (1980) | 4.8 | 4.1 | – |
| Baron et al. (1982) | 14.5 | 3.1 | – |
| Gershon et al. (1982) | 8.0 | 2.2 | 0.5 |
| Coryell et al. (1985) | 7.0 | 2.8 | – |
| Tsuang et al. (1985) | 3.9 | 2.2 | 0.2 |

component. Type II probands have more type I disorder and more type II disorder than unipolar depressives and less type I disorder than type I probands (Endicott et al. 1985, Simpson et al. 1993).

Familial occurrence does not differentiate between inborn and environmental factors. Familial aggregation could be due to sharing genetic material, nongenetic congenital factors (e.g., similar inherited or acquired intrauterine factors, or exposure to similar perinatal risk factors), or physiologic or psychological environmental factors. Data from other types of studies indicate that at least part of this risk is due to biological, and likely genetic factors. Twin studies indicate that monozygotic twins (derived from a single egg and sperm and therefore having an identical genome) have higher concordance rates for manic–depressive disorder than do dizygotic twins (derived from fertilization of two eggs); 60–80% for monozygotic twins versus 20–30% for dizygotic twins (Price 1968, Bertelsen 1979). Further, one adoption study showed that rates of manic–depressive disorder in persons adopted away from their biological families are closer to those in the biological families than the adoptive families (Price 1968, Mendlewicz and Rainer 1977). Finally, linkage studies (see the next section) have suggested that in certain families manic–depressive disorder may be linked to specific genes. On the other hand, studies of monozygotic twins also indicate that only 40–70% are concordant for manic–depressive disorder. Thus, although there is clearly a genetic component to this illness, genetics is not destiny.

## Molecular Genetic Studies

Among the fastest growing areas of research since the last edition of this textbook has been psychiatric genetics. Most profoundly, there is a growing recognition that the factors that are transmitted genetically (endophenotypes) may not correspond well to preestablished DSM-defined disorders. In some cases, disorders previously considered quite distinct descriptively may be shown to share genetic diatheses (e.g., manic depression and schizophrenia; Craddock and Owen 2005, Potash 2006). In other cases, evidence suggests that what is transmitted genetically is not a discrete descriptively defined disorder, such as Huntington's disease, but rather a temperament (e.g., Serretti et al. 2006) or other characteristics (MacQueen et al. 2005). Some geneticists have argued cogently that large, simple genetic effects producing mental illness would have been eliminated from the population by natural selection, and that psychiatric genetics will reveal "genes with small interacting genetic effects, in conjunction with environmental factors" (Sanders et al. 2004), supporting Engel's biopsychosocial theory (Engel 1977). Thus psychiatric genetics may in some cases explain existing DSM-defined categories and in other cases require their complete rewriting. Importantly, some have suggested that psychiatric nosologists should not look exclusively or even primarily to geneticists in this task (Kendler 2006), and the search for endophenotypes would seem to support this view.

With these caveats, we note that several *genetic loci*, or locations on chromosomes, have been proposed to be associated with manic–depressive illness with two or more studies showing association with the chromosome sites 4p, 4q, 8q, 10q, 12q24, 13q, 18p, 18q, 21q, and 22q (Craddock and Jones 1999, Potash and DePaulo 2000, MacQueen et al. 2005, Potash 2006). A related approach to investigating genetic contributions to manic–depressive disorder is to look for differences in genes that code for components of systems thought to be involved in the pathophysiology of the disorder. Chief among such candidate genes have been those responsible for dopamine and serotonin receptors or metabolic enzymes (Potash and DePaulo 2000), the norepinephrine-metabolizing enzyme catechol-*O*-methyl transferase (COMT; Lachman et al. 1996, Kirov et al. 1998, Mynett-Johnson et al. 1998, Papolos et al. 1998), brain-derived neurotropic factor, which may be involved in stress response or antidepressant mechanisms (Neves-Pereira et al. 2002, Sklar et al. 2002), and the serotonin transporter (e.g., Mansour et al. 2005, Masoliver et al. 2006). Meanwhile, search is underway for the genetic basis of clinical characteristics that may represent relevant endophenotypes for manic–depressive disorder, including circadian rhythm and sleep parameters, electrophysiologic evoked potentials, response to stimulants, monocyte characteristics, and a series of neuroimaging and cognitive features (MacQueen et al. 2005).

In addition, it is possible that the expression of a psychiatric illness that is coded genetically may not be due simply to the presence or absence of specific genes, but rather to modifying pieces of DNA in close proximity to important genes. Specifically, small sections of DNA, three base-pairs in length (called *trinucleotide repeats*), appear to be overrepresented in genetic disorders with prominent psychiatric symptoms such as fragile X syndrome and Huntington's disease. The disproportionate number of trinucleotide repeats are hypothesized to be responsible for over- or underexpression of candidate genes, ultimately leading to neuropsychiatric symptoms (Petronis and Kennedy 1995). Recent evidence indicates that this mechanism may also be relevant to manic–depressive disorder (e.g., Lindblad et al. 1998, Lange and McInnis 2002, Swift-Scanlon et al. 2005), including the phenomenon of anticipation (see Section "Epidemiology"), although studies are far from conclusive for any genetic locus (Jones et al. 2002, O'Donovan et al. 2003).

## Postconceptual Congenital Factors

There has been little exploration of nongenetic congenital factors that may be responsible for manic–depressive disorder, although it is reasonable to suppose that intrauterine or perinatal factors that produce brain injury may lead to manic–depressive mood syndromes, just as head trauma during life may lead to mood disorders as well as cognitive impairment. Intriguingly, trinucleotide repeats may actually change over the postconceptual period (i.e., during development) leading

to changes in gene expression (Petronis and Kennedy 1995). This is contrary to classical Mendelian genetic theory, which assumes that genetic material is allocated during conception and cell division followed by the playing out of a genetically derived script, impervious to the impact of environmental factors. Rather, such data provide the basis for hypothesizing that environment may actually alter genetic expression and perhaps transmission on to the next generation.

## Neurobiologic Factors

A wide range of neurochemical, neuroendocrine, neuroanatomic, and neurophysiologic hypotheses have been put forward regarding the biological basis of manic–depressive disorder. The major hypotheses have been recounted in great detail in the excellent and still reasonably current review by Goodwin and Jamison (1990); Stahl (2000), and Sassi and Soares (2002) have reviewed these issues in detail using the methodologies more recently available. While each has something of value to contribute regarding the pathologic basis of manic–depressive disorder, it is by no means clear whether the disorder is basically a disorder of a particular neurochemical system, a particular neuroanatomic locus, or a particular physiologic system. Integration of these hypotheses awaits development of new methodologies for clinical neurobiologic investigations.

### Neurotransmitter Hypotheses

By extension from studies of depression and the actions of antidepressant medications, several neurotransmitter hypotheses have been proposed. Predominant among these has been the catecholamine hypothesis, articulated with regard to depression, by Prange (1964) and by Schildkraut (1965). Deficiency of norepinephrine or its effects was postulated to cause depression. A series of studies by Bunney et al. (1972a, 1972b, 1972c) explicitly extended these observations to manic–depressive disorder, proposing that changes in catecholamine function were responsible for the switch to mania.

Dopamine, which has been a prominent focus of schizophrenia research but relatively neglected in affective disorders until recently, has received attention specifically in the study of mania. Dopamine may underlie several of the prominent features of mania, including psychosis (Goodwin and Sack 1974), alterations in activity level (Goodwin and Sack 1974), and reward mechanisms (Crow and Deakin 1981). Subsequent demonstration of prominent dopaminergic effects of the antidepressants nomifensine and bupropion served to generate more attention for the role of dopamine in mood disorders (Kapur and Mann 1992). More recently, the surge of interest in neuroleptics in mania and perhaps prophylaxis in manic depression, occasioned by the development of the second generation antipsychotics (see Section "Somatic Treatments"), will likely rekindle interest in dopaminergic mechanisms.

Serotonin has received somewhat more sustained attention as a substrate of mood disorders, particularly in Europe (e.g., Coppen et al. 1972), and a "permissive hypothesis" whereby serotonin alterations permit instability of catechol systems leading to manic and depressive episodes has been articulated in broad strokes by Goodwin and Jamison (1990, pp 422–423) but has not been extensively developed. Implication of the serotonin transporter has enhanced interest further, although its relevance in manic–depressive disorder is not yet clear (e.g., Mansour et al. 2005, Masoliver et al. 2006).

Janowsky et al. (1973) proposed that acetylcholine deficits were associated with mania. As with the serotonin hypothesis, this theory posits that the cholinergic system also interacts with the catecholaminergic system to produce affective instability.

Recent evidence also suggests that gamma-aminobutyric acid (GABA) may also be involved in the pathophysiology of manic–depressive disorder (Post et al. 1992, Petty et al. 1993, 1996, Benes and Berretta 2001). Glutaminergic neurotransmission has also been a focus of more recent interest, based on in vitro data and in vivo neuroimaging studies; interestingly, this line of research requires broadening the focus of research from the neuron to include the glial cell as well (Kugaya and Sanacora 2005).

### Second-Messenger System Hypotheses

Since the first edition of this textbook, substantial research has focused on the role of postreceptor intracellular mechanisms known as second-messengers (and sometimes third- and fourth-messengers). This research is well summarized in several recent reviews (Stahl 2000, Sassi and Soares 2002, Bezchlibnyk and Young 2002, Coyle and Duman 2003). When neurotransmitters bind to postsynaptic neuronal receptors, a series of intracellular events are initiated that are mediated by chemical systems linked to those receptors. G-proteins link the receptors to second-messenger systems, which in turn are linked to protein kinases that control the synthesis and operation of cellular components (Sassi and Soares 2002).

The cyclic AMP and phosphatidyl inositol systems are the most extensively studied of these second-messenger systems. The phosphatidyl inositol system may mediate the clinical effects of lithium in manic–depressive disorder; particularly since this second-messenger system is linked to subtypes of adrenergic, serotonergic, dopaminergic, and cholinergic neurotransmitter systems. Specifically, lithium at therapeutically relevant concentrations has been demonstrated to inhibit phosphatidyl inositol turnover in cultured cell lines and animal studies (El-Mallakh and Li 1993, Lenox and Watson 1994). G-protein levels may be altered in individuals with manic–depressive disorder, and lithium modulates the efforts of several G-proteins (Bezchlibnyk and Young 2002). Lithium and valproate reduce phosphokinase activity (Manji and Lenox 2000). A variety of abnormalities of the cyclic AMP system have also been demonstrated in human and animal in vitro studies (Bezchlibnyk and Young 2002). These agents, and perhaps carbamazepine, ECT, and lamotrigine, also affect second-messenger systems involved in cellular growth and degeneration (Coyle and Duman 2003; see also Section "Cell Degeneration and Neuroprotective Effects of Medications"). Further, several preclinical and clinical studies suggest that manic depression may be associated with abnormalities in intracellular calcium metabolism, which is involved in signal transduction, synoptic plasticity, and cell death (Bezchlibnyk and Young 2002).

In clinical studies, persons with manic–depressive disorder have demonstrated alterations in platelet phosphatidyl inositol levels (Brown et al. 1993) and responsiveness of neutrophil phosphoinositol accumulation

(Greil et al. 1991). Cell lines derived from persons with manic–depressive disorder have been found to exhibit abnormalities of phosphatidyl inositol metabolism (Banks et al. 1990). In magnetic resonance spectroscopy studies of persons with manic–depressive disorder, phosphomonoester levels were found to be higher when in the manic state than in remission or in normal controls (Kato et al. 1994, Deicken et al. 1995).

## Neuroendocrine Hypotheses

Neuroendocrine hypotheses have sought to elucidate mechanisms in the production and maintenance of symptoms rather than identify a specific etiologic agent in manic–depressive or other mood disorders. These hypotheses were developed from the literature on stress response in otherwise normal subjects (Mason 1975). Typical neuroendocrine studies investigate peripheral or cerebrospinal fluid abnormalities of a particular system in persons with mood disorders and in controls and propose that either the neuroendocrine system itself or the neurotransmitter system that controls the hormone is in some way linked to the pathophysiology of the mood disorder of interest. Perhaps the most complete battery of neuroendocrine assessments in manic–depressive disorder was conducted by Amsterdam et al. (1983). Taken together, the literature does not identify specific endocrine findings as characteristic of manic–depressive disorder.

However, the thyroid axis may be of particular relevance since supplementation with high doses of the thyroid hormone thyroxine ($T_4$) may induce remission in individuals with rapid cycling who are refractory to standard pharmacotherapy, an effect that is independent of thyroid status or history (Bauer and Whybrow 1990). The mechanism for these effects has been the subject of much speculation. Various models posit that the brain is functionally hypothyroid either due to changes in hormone synthesis, transport, or metabolism, or due to increased demand; alternatively, other models propose that the brain has an excess of a thyroid-related substance, which administration of exogenous thyroid hormone diminishes (Bauer and Whybrow 1990, 2001, Joffe et al. 1993).

## Neuroanatomic Hypotheses

Two main types of studies have provided information on the possible neuroanatomic bases of manic–depressive disorder. First, persons with brain injuries who develop a phenomenologically manic–depressive picture have been analyzed, often neuropathologically, to determine sites of injury that may have produced the manic–depressive clinical picture. For example, lesions of the right side of the brain, particularly frontotemporal lesions, may be associated with manic-like syndromes (Starkstein et al. 1988).

Second, as recently reviewed by Strakowski et al. (2005), persons with manic–depressive disorder who do not have a known organic basis for their illness are studied either with *structural* (computerized tomography, magnetic resonance imaging [MRI]) or *functional* imaging (single photon [SPECT] or positron [PET] emission tomography, or functional MRI or spectroscopy [MRS]) to identify regions of abnormality. Although this area is rapidly growing, it is useful to keep in mind that few studies have compared individuals with manic–depressive disorder to those with other serious mental illnesses, so the specificity of findings is not clear. Further, few studies have assessed first-episode, untreated subjects, so the degree to which anatomic abnormalities reflect pathogenic factors, as opposed to end organ damage or effects of chronic medication usage, is unclear. Several structural imaging studies have demonstrated volume reductions in the subgenual prefrontal cortex (e.g., Drevets et al. 1997, Hirayasu et al. 1999, Brambilla et al. 2002), which may occur early in illness (Hirayasu et al. 1999). Increased volume of the corpus striatum has also been found in several studies, and may also be an early illness finding (e.g., Strakowski et al. 2002, Delbello et al. 2004). Several studies have also demonstrated enlargement of the amygdala (e.g., Strakowski et al. 1999, Altshuler et al. 2000, Brambilla et al. 2003).

There has been substantial interest in quantitating and localizing so-called "$T_2$ hyperintensities" found in MRI studies, thought to represent increased water content of microregions of the brain. These findings are nonspecific, and no consistency regarding prevalence or distribution in manic–depressive disorder has yet been demonstrated (Altshuler et al. 1995b, Yildiz et al. 2001).

A wide ranging and complex magnetic resonance spectroscopy literature suggests that individuals with manic–depressive disorder may have evidence for reduced cellular integrity in several prefrontal or striatal areas, though the degree to which these findings are specific to the pathogenesis of disorder, or are due to treatment or nonspecific damage, is not clear; similar concerns attend to findings of altered whole-brain energy metabolism (Strakowski et al. 2005).

A variety of functional imaging studies using PET or SPECT have demonstrated reduced blood flow or metabolism during bipolar depressive episodes (Strakowski et al. 2005), with some evidence that such parameters are increased during mania (Drevets et al. 1997, Blumberg et al. 2000), though the consisting of such findings will likely depend on the ability of imaging tools to identify specific prefrontal subregions. The strategy of combining functional imaging studies, such as FMRI, with cognitive activation tasks that depend on known neural circuitry represents an intriguing method to increase anatomical specificity of such findings (Strakowski et al. 2005).

Finally, it should be noted that a variety of PET studies have investigated serotonin receptor or transmitter binding and dopamine receptor binding in various brain regions (Strakowski et al. 2005). Though there is as yet little consistent evidence regarding abnormalities in manic–depressive disorder, development of higher resolution imaging techniques and multimodal strategies combing in vivo receptor binding with cognitive and/or pharmacologic challenges make this an area worth watching.

## Cell Degeneration and Neuroprotective Effects of Medications

One of the most exciting areas of recent research focuses on the possibility that lithium, and perhaps antidepressants and certain anticonvulsants such as valproate, may actually exert a *neuroprotective* effect in manic–depressive disorder. Evidence indicates that these agents may protect nerve cells by stimulating production of protective proteins, regulating a variety of protein kinases, or by stimulating nerve

growth (Manji and Duman, 2001, Chen and Manji, 2006). Such factors may differentiate manic–depressive disorder from schizophrenia (Benes et al. 2006, Dean et al. 2006). Interestingly, there is some MRI evidence that lithium treatment may be associated with normalization of the reduced volume of total gray matter in manic depression (Manji and Lenox 2000, Moore et al. 2000).

### Hypotheses Regarding Complex Physiologic Systems

Several complex systems, which for want of a better alternative are grouped together in this section as "physiologic" systems, have been postulated to play a pathogenic role in manic–depressive disorder. Classic theories of membrane and electrolyte imbalance (Goodwin and Jamison 1990, pp 467–481) have been extensively investigated in the past but appear, for the time being, to have passed out of favor. Similarly, kindling theory was once quite popular (e.g., Post et al. 1985, 1986a, 1986b), proposing an analogy between episodes in manic–depressive disorder and seizures in animal models of epilepsy, both of which were proposed to initially be stimulus driven but then to progress to autonomous occurrence. The theory provided an explanation for some effects of anticonvulsants in manic depression, but clinical data in support of the theory are scant (Bauer and Whybrow 1991).

A role for biological rhythms in the pathogenesis of manic–depressive disorder is suggested by two types of data. First, there are a large number of observational studies that have demonstrated seasonal peaks in the onset of affective episodes or hospitalizations for mood disorders. For manic–depressive disorder, the predominant seasons appear to be spring and fall (Goodwin and Jamison 1990, Kamo et al. 1993), although other patterns may occur with some consistency across years (Faedda et al. 1993). In addition, in seasonal affective disorder, codified in DSM-IV-TR as "seasonal pattern," a large proportion have manic–depressive disorder, and the clinical picture of winter depression is similar to the hypersomnolent, anergic, hyperphagic depression common in manic–depressive disorder (Bauer and Dunner 1993). Further, treatment with bright light has been shown to be efficacious in winter depression (Terman et al. 1989) and also appears to be an effective antidepressant in nonseasonal manic depression treated in the winter (Deltito et al. 1991) and perhaps in the summer (Bauer 1993); bright light also appears to be capable of inducing manic symptoms, as do other antidepressants (Bauer et al. 1994a).

The second type of data that suggest a biological rhythms mechanism is that persons with manic–depressive disorder often exhibit abnormalities of circadian (daily) rhythms. Many rhythmic parameters have been studied in persons with manic–depressive and other mood disorders, with various abnormalities found regarding the amplitude (height of the rhythm) and phase (timing of the rhythm) (Halaris 1987). Among the most promising findings is that light sensitivity to suppression of the hormone melatonin may be altered in persons with manic–depressive disorder (Lewy et al. 1980, 1985) and their relatives (Nurnberger et al. 1989). Further, one of the most striking findings in mania is the lack of need for sleep, and there is evidence that sleep deprivation may be both antidepressant and promanic (e.g., Wehr et al. 1982, Colombo et al. 1999).

## Psychological Factors

### Psychological Hypotheses

The psychological theories of mood disorders are wide ranging, including cognitive, behavioral, interpersonal, and psychoanalytic. Unfortunately, the bulk of theory regarding the psychological basis of mood disorders concerns depression, with little attention as yet to mania or manic–depressive disorder.

Cognitive theory regards depression as an affective response to negative beliefs (Beck et al. 1979, Rush and Hollon 1991). Attributions regarding events are based on unrealistically negative assumptions. When bad things happen, they happen because of one's inadequacy, they will always happen, and similar bad things will happen in other situations. Relatively stable patterns of attribution develop relatively early in life, and misinterpretations of events and maladaptive responses are triggered by proximate events (Abramson et al. 1978, Seligman et al. 1979). Behavior theory views depression as a consequence of a low rate of response-contingent positive reinforcement. The goal of behavior therapy is to increase positive reinforcement by participation in pleasant activities or building assertive skills needed to elicit social rewards. The learned helplessness model (Seligman 1975) and behavioral therapy for depression (Lewinsohn 1974) support the merit of these theoretical strategies. Similarly, cognitive–behavior therapy (CBT) represents perhaps the only treatment of any type with clear evidence for efficacy in bipolar depression (see Section "Psychotherapies")

The interpersonal theory of depression, which serves as the theoretical basis for interpersonal psychotherapy (IPT) (Klerman et al. 1984, Weissman and Klerman 1991), builds on the work of Adolph Meyer and Harry Stack Sullivan, who considered environment to play an important role in symptom development and protection from illness. Interpersonal theory proposes that depression develops most often in the context of adverse events, particularly interpersonal loss. IPT then aims at reducing symptoms by psychoeducation and subsequently by addressing problems in interpersonal relationships, primarily focusing on grief, role disputes, role transitions, and interpersonal deficits. Interpersonal factors, coupled with circadian rhythm disruption, have been hypothesized to play a role in manic–depressive disorder as well (see Section "Psychobiological Hypotheses")

Psychoanalytic theories regarding depression find perhaps their most concise and elegant formulation in Freud's classic *Mourning and Melancholia* (Freud 1924). Further development of his theories of depression is found throughout his *New Introductory Lectures in Psychoanalysis* (Freud 1933). For subsequent development of psychoanalytic theories of depression, the reader is referred in particular to Abraham (1927) and Fenichel (1945). As with schools of thought, psychoanalytic theory regarding mania has been much more limited than for depression. In general, psychoanalytic theories focus on mania as a less than completely successful defense against underlying depression. For instance, Dooley (1921) proposed that mania was a mechanism whereby one could ward off painful depressive thoughts. Schwartz (1961) suggested that mania, particularly its hyperactive and grandiose components, functioned as a defense against underlying emptiness and deprivation.

Fenichel (1945) also considered mania to be a response to depression. He proposed that in depression symptoms were caused by a battering superego punishing the self, while "the triumphant character of mania arises from the release of energy hitherto bound in the depressive struggle and now seeking discharge." Nonetheless, he succinctly remarks later in a discussion of cyclicity in manic–depressive and other mood disorders: "yet it is impossible to get rid of the impression that additional purely biological factors are involved"! More recent psychoanalytic theorists have emphasized the need for revision of traditional psychoanalytic theories in the face of accumulating evidence of a biological component to major mental illnesses, including manic–depressive disorder (Cooper 1985, Kahn 1993).

### Psychobiological Hypotheses

Successful treatment of manic–depressive disorder with medications has made the existence of a biological component of this disorder incontrovertible. Nonetheless, psychosocial factors may play prominent roles in the development of manic–depressive disorder and, once established, in its course. Several models that integrate psychological factors and biological mechanisms have been developed (Johnson and Roberts 1995).

Several examples illustrate the diversity of these proposals. As noted above, the kindling model proposed that discrete environmental stressors may be translated into enduring neurobiological changes that are responsible for mood episodes in manic–depressive disorder. Frank and colleagues (Ehlers et al. 1988, Frank et al. 1994, Swartz and Frank 2001) have proposed that the regulation of biological rhythms in persons with manic–depressive disorder may be disrupted by changes in interpersonal events. Depue (Depue et al. 1985, Depue and Iacono 1989) has proposed that mood disordered individuals, including those with manic–depressive spectrum disorders, have deficits in the regulation of biological responses to stress. Similar to cognitive theorists, Hume et al. (1988) have proposed another stress–vulnerability model specifically for manic–depressive disorder in which the threshold for commencement of mood symptoms, particularly in manic–depressive disorder, is influenced by a combination of the "perception" one has of stressful life events and a vulnerable biochemical mood regulatory system.

### Neurocognitive Factors

A variety of deficits in cognition have been demonstrated in manic–depressive disorder, though none of these has to date been proposed to play a pathogenic role. However, it is intriguing to speculate regarding how the cognitive deficits described below might make individuals more susceptible to psychosocial stressors that have been proposed to play a pathogenic role in the illness. Further, such deficits are important in understanding the clinical picture of the disorder, and in planning treatment. In this important last regard, if individuals with the disorder have clinically relevant cognitive compromise, despite not having a formal cognitive disorder diagnosis, it is likely that their ability to manage increasingly complex treatment regimens, navigate interpersonal relationships, and maintain optimal social role function will all be compromised. That said, the same *caveats* that apply to neuroimaging and other mechanism studies of manic–depressive disorder should be kept in mind, including the difficulty in differentiating among core pathogenic factors, nonspecific effects of illness progression, correlates of comorbid disorders, and effects of treatment.

A wide variety of cognitive deficits have been demonstrated in euthymic individuals with manic–depressive disorder, including sustained attention (Clark et al. 2002, Wilder-Willis et al. 2001), working memory (Ferrier et al. 1999), visuospatial memory (Rubinsztein et al. 2000), verbal memory (van Gorp et al. 1998, Altshuler et al. 2004), declarative memory (Thompson et al. 2001, van Gorp et al. 1999), problem-solving (Scott et al. 2000), processing speed (Tham et al. 1997), verbal learning (Zubieta et al. 2001), and executive function (Ferrier et al. 1999, El Badri et al. 2001, Altshuler et al. 2004). A recent meta-analysis of cognitive function in the euthymic phase of the disorder indicated that the most prominent abnormalities are found in executive function and verbal learning, with additional deficits in verbal memory, abstraction and set-shifting, sustained attention, response inhibition, and psychomotor speed (Robinson et al. 2006).

## Social/Environmental Factors

### Psychosocial Stressors

The possible association of stressful life events and the onset of depression has generated substantial interest among researchers from various theoretical backgrounds (e.g., Brown et al. 1977, Brown 1989, Beck et al. 1979, Klerman et al. 1984, Perris 1984a, 1984b, 1984c, Paykel and Cooper 1992, Frank et al. 1994, Johnson and Roberts 1995). Most of the literature regarding analysis of the relationship between stressful life events and manic–depressive disorder has focused on the precipitation of episodes in established manic–depressive disorder rather than the onset of the disorder de novo. However, recently Alloy et al. (2006) extensively and thoughtfully reviewed the literature on the relationship of parenting and maltreatment as risk factors for mood disorders. They found an association between depression and an "affectionless control" style of parenting, particularly with low levels of care, with suggestive evidence for an association with manic depression as well. They propose that the link is not specific, but rather increases risk of negative cognitive styles, which then lead to "a variety of forms of internalizing psychopathology."

There are several methodological problems that may make interpretation of life events studies difficult. Examples include recall bias in retrospective design, and in both retrospective and prospective studies include sample heterogeneity, length of time window for identification of relevant events, definition of onset of mood episode, and choice of signal event (e.g., hospitalization versus onset of episode). Further, in prospective studies, differences in attribution and recall can be significantly different depending on whether a person is interviewed for life events prior to or after the index episode has commenced.

Data on the relationship between life events and the course of manic–depressive disorder have recently been extensively reviewed by Johnson (2005). An association of episode onset with severe adverse life events, typically major losses, on symptoms or episodes has been fairly consistent across studies. This relationship appears to

obtain for depressive but not manic episodes, though many depressive episodes have no identifiable stressor. There is less evidence that schedule-disrupting events trigger either type of episode, aside from sleep disruption being associated with mania (e.g., Colombo et al. 1999). Intriguingly, there is a small literature indicating that goal attainment may be associated with manic episodes, consistent with the model that individuals with manic–depressive disorder have (at times) heightened response to environmental rewards.

### Integrating Assessment and Treatment: The Biopsychosocial Approach

While the evidence reviewed above in Section "Neurobiologic Factors" and below in Section "Antimanics, Antidepressants, and 'Mood Stabilizers'" indicates that there is a substantial biological substrate for manic–depressive disorder, we also know that the illness is not fully genetically determined, and that its etiology and course are not meaningfully explainable in solely biological terms. Moreover, astute clinicians realize that psychosocial factors must be taken into account when planning any type of chronic illness treatment. Therefore, a nonreductionistic and biopsychosocial approach to the disorder, as Engel (1977) proposed for all medical illnesses, will likely serve us best as clinicians, educators, and researchers. Accordingly, Section "Treatment" on treatment deals with an equal level of attention to both pharmacologic and psychosocial interventions for this illness.

## Treatment

## Treatment Goals

### General Considerations

Traditionally, treatment for manic–depressive disorder has been categorized as acute versus prophylaxis, or maintenance, i.e., treatment geared toward resolution of a specific episode versus continued treatment to prevent further symptoms.

In a complementary conceptualization, treatment can be focused on improving clinical outcome (episodes and symptoms) or functional outcome (social and occupational function and health-related quality of life). Although this categorization appears straightforward, clinical practice reveals many subtleties. For instance, it is erroneous to assume that clinical outcome is the domain of pharmacotherapy and that functional outcome is the domain of psychotherapy. In actuality, most psychotherapies by design focus on reducing symptoms. Likewise, pharmacotherapeutic stabilization of symptoms clearly contributes to improved role function. Further, treatments that improve one domain may cause decrements in another. For instance, effective maintenance treatment with lithium may come at the cost of hand tremor, which interferes with work function and causes embarrassment in social situations. Balancing the costs and benefits of various specific treatments—each somatic and psychotherapeutic treatment has both costs and benefits—requires active participation of the patients and, if available, the families.

What is the goal of treatment? As articulated in *The President's New Freedom Commission* for mental health, the goal of treatment is recovery, which is described as "a process of positive adaptation to illness and disability, linked strongly to self-awareness and a sense of empowerment" and, after Anthony (1993), "a way of living a satisfying, hopeful, and contributing life even with the limitations caused by illness" (Hogan 2003).

### Understanding Evidence-Based Medicine

One of the functions of a textbook is to synthesize and present relevant scientific data in a concise and easily accessible manner. Another is to provide the context and underpinnings of such data. In the service of this latter aim, this treatment section is introduced, as in the last edition, with a brief review of evidence-based methods of evaluating the available scientific data, including both the strengths and weaknesses of the evidence on which we base clinical and sometimes policy decision-making.

#### *Levels of Evidence*

A major advance in the last 20 years in medicine has been development of quantitative and qualitative tools to assess the quality of data that underlie our treatment decisions, typically considered under the rubric of "evidence-based medicine." For instance, quantitative techniques such as meta-analysis provide numeric conclusions with regard to significance of similar interventions in diverse studies (Irwig et al. 1994). More qualitative, yet standardized, techniques of evidence-based medicine (EBWG 1992, Chalmers 1993, ACC/AHA 1996) have been used in reviewing and summarizing treatment interventions in medicine and more recently in mental health. Briefly, these techniques consist in comprehensively identifying relevant data-based articles, summarizing their methods and conclusions, and then in a standardized quantitative or qualitative fashion rating the scientific quality of the evidence based on the rigor of their methodology.

In the 1980s, the US Agency for Healthcare Research and Quality (AHRQ) (formerly the Agency for Health Care Policy and Research; AHCPR) developed guidelines for a wide variety of medical, surgical, and mental health conditions including the identification and treatment of depression in primary care (AHCPR 1993). Similar evidence-based techniques of one type or another have also served as the basis for bipolar guidelines from a variety of professional groups including, for example, the American Psychiatric Association (2002), US Department of Veterans Affairs (VA) (e.g., VHA 1997, Bauer et al. 1999), the Canadian Psychiatric Association (Haslam et al. 1997), the Texas Department of Mental Health and Mental Retardation (Gilbert et al. 1998, Rush et al. 1999), the British Association for Psychopharmacology (Goodwin et al. 2003), the World Federation of Societies of Biological Psychiatry (e.g., Grunze et al. 2004) and the Canadian Network for Mood and Anxiety Treatments (Yatham et al. 2006). However, not all bipolar guidelines are evidence based in this sense, but rather are based on surveys of experts' opinions (e.g., Kahn et al. 1997, Sachs et al. 2000).

The AHCPR developed a hierarchical system for categorizing evidence according to the scientific quality (internal validity) of the studies (Table 67–11), a variant of which has been used by most guidelines for assessing evidence. Some guidelines also use a system by which the guideline authors utilize the evidence to arrive at a "strength of recommendation," which is also based implicitly on quality of the underlying evidence (e.g., American Psychiatric Association 2002).

**Table 67–11 HCPR/AHRQ Evidence Classification System**

| | |
|---|---|
| **Class A** | **Randomized or Other Controlled Trials**<br>Examples: Randomized controlled trials of intervention versus waiting list control or no added treatment; other controlled trials with treatment assignment independent of subject characteristic, time of presentation, etc. |
| **Class B** | **Well-Designed Clinical Studies**<br>Examples: Open studies with a priori design and follow-up period of designated endpoint; pre/post mirror-image studies with "post" period designed a priori. |
| **Class C** | **Case Series, Case Reports, Retrospective Chart Reviews**<br>Examples: Prospectively gathered data on a series of patients followed in treatment; retrospective chart review after implementation of an intervention. |

*Source*: Adapted from HCPR (1993).

### *Limitations: The "Pyramid" of Evidence Quality*

Understanding published data according to levels of quality is clearly a conceptual advance of great importance—data from a case series are clearly not the same as data from Class A randomized controlled trial (RCT). However, one of the limitations of the evidence base for manic–depressive disorder, and one suspects for disorders in general, is that the RCT "jewel in the crown" of evidence-based medicine represents only a small fraction of the available data—far more data derive from Class B and C studies (e.g., Bauer and Mitchner 2004).

### *Limitations: The Efficacy–Effectiveness Gap*

Moreover, the grading of evidence is based solely on characteristics related to internal validity, the scientific structure of the protocol itself. A complementary concern is that of external validity, the applicability of findings to a population of more general interest. The US Institute of Medicine recognized as long ago as 1985 (Institute of Medicine 1985) that there is a persistent gap between the impact of treatments predicted by highly controlled trials (efficacy) and the actual performance of such treatments in general practice (effectiveness). They proposed that this "efficacy–effectiveness gap" is in part due to the exclusion of "complicated" subjects from clinical trials (e.g., for manic–depressive disorder, those with substance abuse, personality disorders, or medical problems) and those unwilling to risk exposure to placebo. Another likely contributor is variation in provider attitudes and capabilities, and a third is system characteristics that support or impede optimal care in general practice. One can see that, in efficacy trials to establish the impact of a new intervention, it is reasonable to assess impact under optimal conditions; however this same exclusivity and careful control also limit the relevance of such studies in the general clinical setting. Recognizing this, a number of recent clinical trials, considered variously under the related concepts of "effectiveness trials" (Wells 1999, Bauer et al. 2001a) or "practical clinical trials" (e.g., March et al. 2005) have sought to address this gap, balancing issues of internal and external validity to more cogently inform clinical practice for manic–depressive disorder (e.g., Geddes et al. 2002, Sachs et al. 2003, Bauer et al. 2006a, 2006b, Simon et al. 2006), as is also being done for such other disorders as depression (e.g., Fava et al. 2003) and schizophrenia (e.g., Stroup et al. 2003).

### *Limitations: The Question of Bias in the Evidence Base*

"Bias" is a hot-button word that raises the specter of scientific misconduct, or worse. However, bias is best understood as a compromise in internal validity within or across studies, which may be purposeful or not. Several studies have demonstrated evidence of bias in several areas in peer-reviewed literature (e.g., Dickersin 1997, Montori and Guyatt 2000). While we are not aware of publication bias in the literature on treatment of manic–depressive disorder, there is such evidence in other areas of psychopharmacology. For instance, meta-analyses of antidepressant and anxiolytic efficacy, based on predominantly published data, are regularly positive (www.cochrane.org). However, analysis of the FDA Summary Basis of Approval Reports for approved antidepressants and anxiolytics—which reflect *all* studies, published and unpublished, submitted to the FDA—indicates that the majority of such studies are actually negative (Khan et al. 2002). Of additional concern, there appears to be a sponsorship bias in which industry-sponsored studies that show evidence for efficacy of a proprietary agent are more likely to be published than those that show no efficacy (Davidson 1986, Rochon et al. 1994, Djulbegovic et al. 2000), as has also been demonstrated in mental health treatment research (Kelly et al. 2006), pharmacoeconomic studies (Baker et al. 2003), and meta-analyses (Jorgensen et al. 2006).

The astute clinician will therefore bring neither uncritical enthusiasm nor undue cynicism to the evidence base for treatment of manic–depressive disorder. Rather, an awareness of the potential for circumstantial, and perhaps at times purposeful (e.g., Angell 2004), bias is in order—as has been formally recognized by leading journal editors (e.g., Lewis et al. 2006, Freedman et al. 2006). Given the complexities socioeconomic nexus from which scientific data derive, one might do well to adapt an old saying: *Caveat lector*—Let the reader beware (Bauer 2006).

## Somatic Treatments

### Antimanics, Antidepressants, and "Mood Stabilizers"

### *Mood Stabilizers: The "2 × 2" Definition*

The term "mood stabilizer" is not recognized by the US Food and Drug Administration (FDA). The term is used loosely among both clinicians and scientists, leading to some confusion. It stands to reason that an agent could be considered a mood stabilizer for manic–depressive disorder if it has efficacy in four key roles in its treatment: (a) treatment of acute manic symptoms, (b) treatment of acute depressive symptoms, (c) prophylaxis of manic symptoms, and (d) prophylaxis of depressive symptoms (alternative terms for prophylaxis include (prevention, maintenance treatment). We (Bauer and Mitchner 2004) and others (Calabrese et al. 1999) have proposed this definition, while at other times some have argued for a looser definition, which applies the term to any agent that has efficacy in any one of those roles while not worsening other aspects of the disorder (Sachs 1996, Bowden 1998, Ketter and Calabrese 2002).

Although it is clear that a single agent suffices to stabilize manic–depressive disorder in only a minority of individuals (e.g., Sachs et al. 1994b, Unützer et al. 1998), adopting the more stringent definition both focuses our search for new interventions on *all* phases of the disorder and also leads to a conceptual approach that clarifies our evaluation of evidence. This approach leads to arraying the evidence according to a conceptual 2 × 2 table (mania/depression, acute/prophylaxis), in which agents used in manic–depressive disorder can be listed in any or all of the four boxes in the table in which they have proven efficacy. According to this schema, an agent would be categorized as a mood stabilizer if it can be listed as having efficacy in each of the four boxes.

### *Summarizing the Class A Evidence*

We have conducted an exhaustive review of the literature on psychopharmacologic agents used in manic–depressive disorder and evaluated them against this "2 × 2" definition, as detailed elsewhere (Bauer and Mitchner 2004) and more recently updated to include combination treatments (Bauer 2005). Briefly, we identified all Class A double-blind controlled trials for acute (hypo)mania, acute depression, prevention of (hypo)mania, and prevention of depression. We considered an agent to be efficacious for each of these roles if it met the "FDA-like" criterion of having at least two published placebo-controlled trials indicating efficacy. Note that we reviewed only studies published in the peer-reviewed literature, not unpublished studies.

Tables 67–12 through 67–14 summarize this review, updated here with studies published through December 2006. These tables include only those agents with at least two double-blind controlled trials, using either placebo or an active comparator, either in a parallel groups design or a within-subjects, on–off–on (ABA) design. Note also that negative studies are also listed for these agents, with the study preceded by a "–."

In summary fashion, Table 67–15 summarizes these trials based on the 2 × 2 definition of a mood stabilizer. As can be seen, a substantial number of agents meet criteria as acute antimanic agents, while only lithium meets criteria for acute depression. The paucity of efficacious agents for bipolar depression is striking, though a pooled meta-analysis of 12 Class A antidepressant trials supports overall efficacy of the class, without difference among types of antidepressants (Gijsman et al. 2004). Lithium and lamotrigine meet criteria for prophylaxis. Note that most studies assessed relapse to any episode rather than specifically mania or depression, while lithium has also been shown in two studies to prevent relapse specifically to mania.

### *Some Additional Considerations*

The vast majority of studies of efficacy against manic symptoms comes from study of mania rather than hypomania. The latter is treated predominantly by logical extension.

Evidence is scarce concerning efficacy of specific agents for acute depressive episodes, which appears to be a particularly difficult syndrome to treat pharmacologically. Most treatment is undertaken by extension from treatment experience in unipolar depression. A comprehensive discussion of evidence for efficacy of various antidepressants in unipolar depression can be found in Chapter 101 in this book. The particularly important issue of how long and how aggressively to treat bipolar depression with antidepressants is of sufficient importance to address in a separate section (see Section "Balancing Beneficial and Unwanted Effects of Medications").

While lithium has the most extensive support for prophylaxis, it is also notable that strong case-control data across 10,000s of patient-years support an antisuicide effect (e.g., Baldessarini et al. 2003, Goodwin et al. 2003, Ernst and Goldberg 2004). Interestingly, this effect appears to be independent of lithium's effect on mood (e.g., Hanus and Zapletalek 1984, Lepkifker et al. 1985, Ahrens and Muller-Oerlinghausen 2001); moreover, lithium may also be associated with reduced all-cause mortality (Tsai et al. 2005).

Additional issues in prophylaxis of manic–depressive disorder deserve comment. When is lifetime, or at least long-term, prophylaxis warranted? After one manic episode? One hypomanic episode? One depressive episode with a strong family history of manic–depressive disorder? There is insufficient empirical evidence with which to make strong recommendations, although a creative study by Zarin and Pass (1987) using computer-based modeling investigated tradeoffs of treatment versus observation based on costs and benefits of recurrence risks and drug side effects under several strategies. In clinical practice without clear guidelines, such decisions need to take into account the capability of the patient and family in reporting symptoms, rapidity of onset of episodes, episode severity, and associated morbidity. Clearly, the risks of a wait-and-see strategy would be different in a person who had a psychotic manic episode than in a person who had mild hypomania.

Can maintenance, or prophylaxis, medications ever be discontinued? Again, there are no solid data on which to base this decision. However, if lithium discontinuation is contemplated, there is evidence that rapid discontinuation (in less than 2 weeks) is more likely to result in relapse than slow taper (2–4 weeks), with relapse rates higher in type I than in type II patients (Faedda et al. 1993, Suppes et al. 1993). In type I patients, relapse rates for rapid discontinuation versus slow taper were, respectively, 96 and 73%, whereas in type II patients they were 91 and 33% (Faedda et al. 1993).

## Combination Strategies

As noted above, combination strategies are the rule rather than the exception in clinical practice (e.g., Sachs et al. 1994b, Unützer et al. 1998). Table 67–16 summarizes the Class A placebo-controlled trials of combination strategies for manic–depressive disorder.

## A Simple Treatment Algorithm for Manic–Depressive Disorder

A treatment algorithm for refractory manic–depressive disorder, including strategies to deal with rapid cycling is found in Figure 67–2. It is derived from clinical practice guidelines from the USVA and used in a multisite collaborative care management trial for manic–depressive disorder (Bauer et al. 2006a, 2006b). By design, the algorithm primarily specifies drug classes rather than individual agents. This allows the choice of specific agent to be chosen collaboratively by the provider and the patient based on efficacy data combined with patient preference (see also Sections "Balancing Beneficial and Unwanted Effects of Medications" and "Treatment-Refractory Patients"). In a multisite proof-of-concept study, the use of the algorithm was significantly associated with

**Table 67–12 Summary of Acute Mania Agents with at Least Two Class A Trials***

| | Placebo Control | | Active Control | |
|---|---|---|---|---|
| | **Parallel Groups** | **ABA** | **Parallel Groups** | **ABA** |
| Lithium | Maggs (1963)<br>Bowden et al. (1994)<br>Bowden et al. (2005) | Stokes et al. (1971) | Johnson et al. (1968)<br>Platman (1970)<br>Spring et al. (1970)<br>Johnson et al. (1971)<br>Prien et al. (1972)<br>Takahashi et al. (1975)<br>Shopsin et al. (1975) | – |
| Chlorpromazine | | | Johnson et al. (1968)<br>Spring et al. (1970)<br>Johnson et al. (1971)<br>Prien et al. (1972)<br>Shopsin et al. (1975) | |
| Haloperidol | Garfinkel et al. (1980)<br>McIntyre et al. (2005) | | Shopsin et al. (1975)<br>Segal et al. (1998)<br>Shi et al. (2002) | |
| Carbamazepine | Weisler et al. (2004)<br>Weisler et al. (2005) | – | Okuma et al. (1979)<br>Lerer et al. (1987)<br>Lusznat et al. (1988)<br>Brown (1989)<br>Okuma et al. (1990)<br>Small et al. (1991) | – |
| Divalproex | Pope et al. (1991)<br>Bowden et al. (1994) | Emrich et al. (1980) | Freeman et al. (1992)<br>Vasudev et al. (2000)<br>−Tohen et al. (2002a)<br>Zajecka et al. (2002) | – |
| Olanzapine | Tohen et al. (1999)<br>Tohen et al. (2000) | – | Tohen et al. (2002a)<br>Shi et al. (2002)<br>Zajecka et al. (2002) | – |
| Risperidone | Hirschfeld et al. (2004)<br>Khanna et al. (2005)<br>Smulevich et al. (2005) | | Segal et al. (1998)<br>Perlis et al. (2006a) | |
| Ziprasidone | Keck et al. (2003)<br>Potkin et al. (2005) | | | |
| Quetiapine | Bowden et al. (2005)<br>McIntyre et al. (2005) | | | |
| Aripiprazole | Keck et al. (2006)<br>Sachs et al. (2006) | | Vieta et al. (2005) | |
| Verapamil | −Janicak et al. (1998) | Giannini et al. (1984)<br>Dubovsky et al. (1986) | Garza-Trevino et al. (1992)<br>Hoschl and Kozeny (1989)<br>−Walton et al. (1996) | |
| Clonazepam | Edwards et al. (1991) | – | Clark et al. (1997) | Chouinard et al. (1982) |
| Clonidine | – | – | – | −Giannini et al. (1985)<br>−Giannini et al. (1986) |

*Trials are positive if better than placebo or, if compared to an active agent, better than that comparator or similar plus both better than baseline; trials are negative (–) or equivocal (±) if the agent was no different from placebo or equaled the comparator but, no comparison to pretreatment baseline was available.

increased intensity of mood-specific pharmacotherapy (Bauer 2001a). The entry point for this algorithm is the occurrence of any major mood episode (depression, hypomania, mania, or mixed episode) in an unmedicated patient. Patients with recurrence on medications may enter the algorithm at the appropriate point along the flow diagram. For simplicity of presentation, only depressive and cycling outcomes are illustrated. This is because depressive episodes are more common than manic or hypomanic episodes, and all but the most refractory of the latter episodes are relatively easily treated by the addition (or resumption) of lithium or anticonvulsants or the use of neuroleptics, as summarized above.

## Balancing Beneficial and Unwanted Effects of Medications

All psychotropic medications have side effects. Some side effects may actually be desirable (e.g., sedation with some antidepressants in persons with prominent insomnia), and specific medications are often chosen on the basis of desired side effects. However, side effects usually represent factors that decrease a patient's quality of life and compromise adherence.

Extensive reviews of side effects of the agents most commonly encountered in the treatment of manic–depressive disorder are available elsewhere in this textbook (Chapters 101, 102, and 103), in a variety of texts

**Table 67–13 Summary of Acute Depression Agents with at Least Two Class A Trials***

| | Placebo Control | | Active Control | |
|---|---|---|---|---|
| | **Parallel Groups** | **ABA** | **Parallel Groups** | **ABA** |
| Lithium | – | Goodwin et al. (1972)<br>Baron et al. (1975)<br>Mendels (1976) | – | – |
| Fluoxetine | Cohn et al. (1989)<br>−Amsterdam and Shults (2005a)<br>−Amsterdam and Shults (2005b) | – | – | – |
| Tranylcypromine | – | – | Himmelhoch et al. (1991)<br>Thase et al. (1992) | – |
| ECT | – | – | Sackeim et al. (1987, 1993, 2000) | |

*Trials are positive if better than placebo or, if compared to an active agent, better than that comparator or similar plus both better than baseline; trials are negative (–) or equivocal (±) if the agent was no different from placebo or equaled the comparator but, no comparison to pretreatment baseline was available.

(e.g., Bauer 2003a, Schatzberg et al. 2003, Marangell and Martinez 2006), and in electronic references for desktop and hand-held computers. Several excellent review articles have summarized side effects of lithium (Gitlin et al. 1989, Goodwin and Jamison 1990, pp 701–709) and the various anticonvulsants (Swann 2001) including carbamazepine (Ketter and Post 1994) and divalproex (Keck et al. 1994), and lamotrigine (Botts and Raskind 1999).

A brief overview of the most frequent or important side effects of lithium, carbamazepine, and valproic acid is found in Tables 67–17a–c. Note that some side effects may be encountered at any serum level of the drug, even within the therapeutic range. Some side effects may be dose related even within that range and may respond to dosage reduction. Others are more idiosyncratic and require other management, as detailed in a subsequent section. Note that

**Table 67–14 Summary of Prophylaxis Agents with at Least Two Class A Trials***

| | Placebo Control | | Active Control | |
|---|---|---|---|---|
| | **Parallel Groups** | **ABA** | **Parallel Groups** | **ABA** |
| Lithium | Baastrup et al. (1970)<br>Coppen et al. (1971)<br>Cundall et al. (1972)<br>Prien et al. (1973a)<br>Prien et al. (1973b)<br>Stallone et al. (1973; M+/D+)<br>Kane et al. (1982)<br>Dunner et al. (1976; M+/D–)<br>Bowden et al. (2000; M–/D–)<br>Calabrese et al. (2003) | – | Gelenberg et al. (1989) | – |
| Carbamazepine | −Okuma et al. (1981) | – | –Coxhead et al. (1992)<br>±Simhandl et al. (1993) | – |
| Divalproex | Bowden et al. (2000; M–/D–) | | | |
| Lamotrigine | Calabrese et al. (2000, 2003)<br>Bowden et al. (2003) | Obrocea et al. (2002) | | |
| Olanzapine | Tohen et al. (2006; M+/D+) | | Tohen et al. (2005; M+) | |
| Imipramine | −Prien et al. (1973b)<br>−Kane et al. (1982) | | Prien et al. (1984; M–/D+) | |
| Nimodipine | | −Pazzaglia et al. (1993)<br>−Pazzaglia et al. (1998) | | |

*Study outcomes are for relapse to either manic or depressive episode or, when available, specifically to mania (M) or depression (D). Trials are positive if better than placebo or, if compared to an active agent, better than that comparator or similar plus both better than baseline; trials are negative (–) or equivocal (±) if the agent was no different from placebo or equaled the comparator but, no comparison to pretreatment baseline was available.

**Table 67–15 The "2×2" Mood Stabilizer Definition: Agents with at Least Two Placebo-Controlled Class A Trials for Each Treatment Need in Manic–Depressive Disorder**

| | Mania | Depression |
|---|---|---|
| Acute | Lithium | Lithium |
| | Haloperidol | |
| | Carbamazepine | |
| | Divalproex | |
| | Olanzapine | |
| | Risperidone | |
| | Quetiapine | |
| | Ziprasidone | |
| | Aripiprazole | |
| | Verapamil (±) | |
| Prophylaxis | Lithium (mania, any episode)* | |
| | Lamotrigine (any episode)* | |

*Both lithium and lamotrigine are supported by at least two placebo-controlled Class A trials for prophylaxis that measured time to relapse to either mania or depression. Lithium is also supported by two such trials for relapse specifically to mania and one for relapse specifically to depression plus one trial versus active comparator for relapse specifically to depression (see Table 67–12).

**Table 67–16 Positive Class A Placebo-Controlled Trials of Combination Treatment for Manic–Depressive Disorder**

| Combination Strategy | Reference |
|---|---|
| **Acute Mania** | |
| Haloperidol → lithium | Garfinkel et al. (1980) |
| Carbamazepine → lithium | Kramlinger and Post (1989) |
| Lithium → haloperidol | Chou et al. (1999) |
| Phenytoin → haloperidol | Mishory et al. (2000) |
| Divalproex → neuroleptic | Muller-Oerlinghausen et al. (2000) |
| Olanzapine → lithium or divalproex | Tohen et al. (2002b) |
| Risperidone or haloperidol → lithium or divalproex | Sachs et al. (2002) |
| Risperidone → lithium or divalproex | Yatham et al. (2003) |
| Quetiapine → lithium or divalproex | Sachs et al. (2004) |
| Quetiapine → lithium or divalproex | Yatham et al. (2004) |
| **Acute Depression** | |
| Olanzapine or olanzapine and fluoxetine → lithium, anticonvulsants and/or neuroleptics | Tohen et al. (2003b) |
| Pramipexole → lithium or divalproex | Zarate et al. (2004) |
| **Prophylaxis** | |
| Imipramine → lithium | Quitkin et al. (1981) |
| High-dose thyroxine → treatment as usual (in rapid cycling) | Bauer et al. (1990) |
| Divalproex → lithium | Solomon et al. (1997) |
| Omega-3 fatty acids → treatment as usual | Stoll et al. (1999) |
| Magnesium → verapamil | Giannini et al. (2000) |
| Gabapentin → lithium or divalproex or Carbamazepine | Vieta et al. (2006) |

not all laboratory findings represent pathological processes that are associated with or presage morbidity for the patient; that is, not all are clinically significant.

Note also that the concept of the "therapeutic level" is not as straightforward as we would like to assume. The lower limit is usually established by the lowest level necessary for therapeutic effect, whereas the upper limit is set by the lowest level associated with regular, significant toxicity. This range is never established with complete precision. For some medications such as lithium, the therapeutic window is actually quite narrow, with toxic effects developing with some regularity after the upper limit of the therapeutic range is surpassed and with serious toxicity developing at only modestly higher serum levels. As a further complication, for many persons the minimum level of lithium for good response may be substantially above the 0.5–0.8 mEq/L that is usually set as the lower therapeutic limit, but this is reached only at the cost of increased incidence of side effects (Gelenberg et al. 1989). On the other hand, for divalproex, the upper limit of the therapeutic range for mood stabilization may actually be 125 mg/dL rather than the listed range of 100 mg/dL usually accepted for antiepileptic effect, and this level is often reached without undue side effects (Keck et al. 1994).

Thus established therapeutic levels should be used as important guidelines, and exceeding therapeutic levels should be done only with careful monitoring. However, one must not be falsely reassured that reaching the lower level of a therapeutic range is equally effective for all patients, while taking with a grain of salt the upper limits of the therapeutic range for drugs with a wider therapeutic window.

Another important issue to consider is drug–drug interactions, which may lead to side effects (see Bauer [2003] for a comprehensive review). Most commonly the locus of such interactions is the hepatic microsomal P-450 metabolic system, which inactivates drugs and other exogenous substances, and for which psychotropic drugs are often substrates, inhibitors, or inducers. However, other drug interactions must also be kept in mind. For example, addition of thiazide diuretics, or nonsteroidal anti-inflammatory agents, the latter available over the counter, is a common reason for increase in lithium level and development of toxicity based on changes in renal handling of lithium. Note also that toxic drug–drug interactions may not be reflected in an increased serum level if the main interaction is displacement of protein-bound drug. Because free drug concentrations are usually 1–10% of total serum drug, a displacement of even 50% of bound drug may be associated with negligible if any changes in total serum level. However, since both therapeutic and toxic effects are due to free, not bound, drug, unwanted side effects may develop despite total drug levels measured in the therapeutic range.

## Balancing Risks and Benefits of Antidepressant Treatment

Traditionally over the past generation, the teaching has been to use antidepressants in bipolar depression gingerly, only for the shortest time and lowest dose possible; this is based on data indicating an association between antidepressant use and emergence of manic symptoms or rapid cycling (e.g., El-Mallakh and Karippot 2002). Estimate of the risk of antidepressant-induced (hypo)mania, typically defined as symptom emergence within 2 weeks of the initiation of antidepressants, range from 9 to 40% (e.g., Post et al. 2001, Goldberg and Whiteside 2002, Post et al. 2006), though a meta-analysis of 12 Class A trials found no difference in

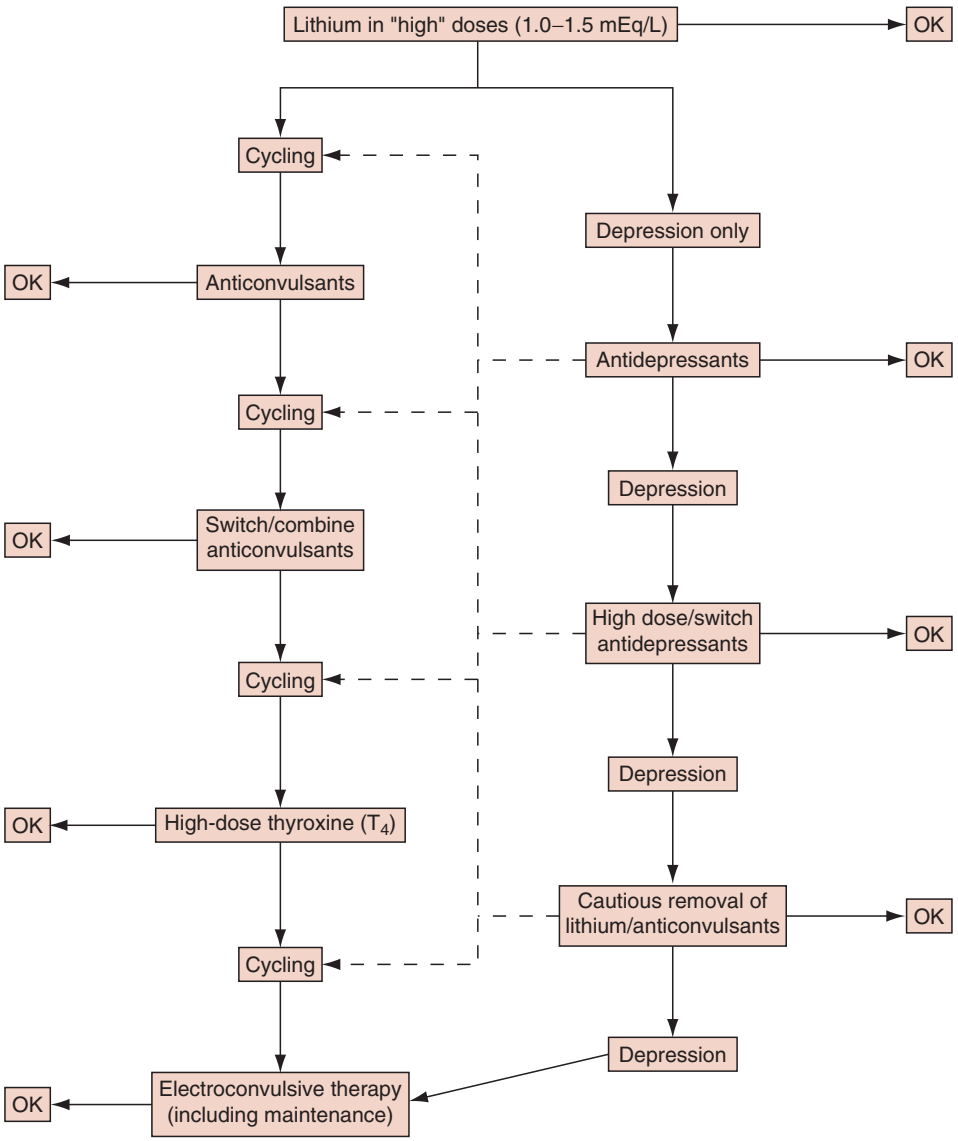



**Figure 67–2** *Pharmacologic treatment algorithm for depression and rapid cycling in manic–depressive disorder; for more complete discussion, and treatment strategies for (hypo)mania, see Section "A Simple Treatment Algorithm for Manic–Depressive Disorder." For details regarding how to use specific psychopharmacologic agents, see Bauer (2003b).*(Source: *Bauer 1994.*)

switch rate versus placebo (Gijsman et al. 2004). The risk appears to be higher with antidepressants that affect both catecholaminergic and serotonergic neurotransmission than those that affect only the latter (e.g., Peet 1994, Gijsman et al. 2004, Mundo et al. 2006, Post et al. 2006), while evidence is split regarding whether bupropion is relatively safer (Sachs et al. 1994a, Post et al. 2006) or not (Joffe et al. 2002). This risk is not fully counterbalanced by treatment with antimanic agents (e.g., Post et al. 2001) though such medications (Mundo et al. 2006), perhaps especially lithium (Henry et al. 2001), may provide added protection.

However, counterbalancing this risk is the robust finding across more than a dozen studies that continuing

**Table 67–17a Side Effects of Lithium and Commonly Used Anticonvulsants; I: Life Threatening**

| | At Therapeutic Levels | | At Toxic Levels |
|---|---|---|---|
| | **Idiopathic** | **Dose Related** | **Dose Related** |
| Lithium | | | Renal failure<br>Encephalopathy |
| Carbamazepine | Agranulocytosis*<br>Aplastic anemia*<br>Stevens–Johnson* | | |
| Divalproex | Hepatic necrosis | Thrombocytopenia | Thrombocytopenia |
| Lamotrigine | Stevens–Johnson* | | |

*Typically during first 1–6 months of treatment; for lamotrigine, related to rate of dose increase.

**Table 67–17b Side Effects of Lithium and Commonly Used Anticonvulsants; II: Clinically Significant Side Effects**

| | Lithium | Carbamazepine | Divalproex | Lamotrigine |
|---|---|---|---|---|
| Neurologic/muscular | Lethargy<br>Memory (anomia)<br>Tremor*<br>Myoclonus | Lethargy<br>Blurred vision<br>Ataxia* | Lethargy<br>Depression<br>Tremor*<br>Ataxia | Lethargy<br>Ataxia<br>Blurred vision<br>Headache |
| Endocrine/metabolic | Weight gain*<br>Hypothyroidism | | Weight gain* | |
| Hematologic | | | Thrombocytopenia to <20,000 | |
| Renal | Polyuria | | | |
| Hepatic | | Jaundice, Encephalopathy | Jaundice, Encephalopathy | |
| Gastrointestinal | Nausea*<br>Diarrhea* | Nausea* | Nausea* | Nausea* |
| Dermatologic | Maculopapular rash<br>rash<br>Psoriasis<br>Acne | Maculopapular rash<br>Alopecia | Maculopapular rash | Maculopapular rash |
| Other | | | Back pain | |

*Most common reasons in our experience for noncompliance.

**Table 67–17c Side Effects of Lithium and Commonly Used Anticonvulsants; III: Subclinical Laboratory Abnormalities**

| | Lithium | Carbamazepine | Divalproex | Lamotrigine |
|---|---|---|---|---|
| Neurologic/muscular | | | | |
| Endocrine/metabolic | Increased TSH | Decreased free thyroxine index | | |
| Cardiopulmonary | EKG T-wave flattening | | | |
| Hematologic | Leukocytosis (may exceed 20,000) | Leukopenia | Thrombocytopenia (to > 20,000) | |
| Renal | Decreased urine-specific gravity, glomerular filtration rate | | | |
| Hepatic | | Increased serum transaminases and ammonia | Increased serum transaminases and ammonia | |

depression is the strongest predictor of poor functional outcome (reviewed in Bauer et al. 2001a) and poor self-reported quality of life (e.g., Vojta et al. 2001, Zhang et al. 2006); not surprisingly, continued depression is also a risk factor for relapse (reviewed in Altman et al. 2006) and suicide. Moreover, in contrast to findings in adolescent depression and anxiety disorders, treatment with antidepressants does not appear to increase suicidality in individuals with manic–depressive disorder (Bauer et al. 2006c, McElroy et al. 2006b). In addition, there is an accumulating evidence base indicating that cessation of antidepressants increases risk for bipolar depressive relapse (e.g., Altshuler et al. 2003, Fu et al. 2006).

Thus prior practice must be reevaluated, and we should give renewed consideration to aggressive, long-term treatment of individuals with bipolar depression with antidepressants. Careful monitoring for the emergence of manic symptoms must, of course, be part of this treatment, and most guidelines recommend cotreatment with antimanic agents.

## Guiding Principles for Managing Side Effects

As noted previously, some side effects may be desirable. However, in many cases they are impediments to treatment, frequently of sufficient importance to lead to nonadherence (Jamison et al. 1979). As clinicians, however, we might reframe nonadherence not as a patient characteristic but rather as a characteristic of the clinician–patient dyad (Sajatovic et al. 2006); that is, nonadherence is most appropriately considered as an instance of "insufficient provider–patient cost-benefit analysis." Stressing adherence when a person suffers from significant side effects is usually much less effective than working to set appropriate expectations of the patient and to find a regimen of minimal toxicity. Goodwin and Jamison's (1990, p 672) point that managing side effects is as much psychotherapeutic as medical is well taken in this regard, and has been a key component of some psychosocial interventions for this disorder (e.g., Bauer and McBride 2003).

Nonetheless, the astute psychiatrist does have several strategies available to improve patients' tolerance of medications. First, dose reduction may be achieved without compromising efficacy in some patients. Some side effects, such as lithium-induced nausea, usually respond well to this, whereas others, such as lithium-induced memory loss, improve less reliably. Second, simple changes in preparation may be helpful, such as using enteric-coated lithium. Uncoated valproic acid causes nausea so frequently that only the coated forms are routinely used; however, the pediatric "sprinkle" preparation may be of some benefit in persons with nausea even with enteric-coated valproic acid. Third, changing the administration schedule may ameliorate side effects. Commonsense strategies such as taking

nausea-inducing medications after a meal should not be overlooked. Single daily dosing of lithium, carbamazepine, or valproic acid may decrease daytime sedation without compromising efficacy. For more obscure reasons, single daily dosing of lithium appears to decrease polyuria quite effectively (Bowen et al. 1991). Fourth, addition of medications to counteract side effects can sometimes be the only way to continue treatment. Addition of beta-blockers can reduce lithium- or valproic acid-induced tremors. Judicious use of thiazide diuretics, often in conjunction with potassium-sparing diuretics or potassium supplements, can reduce lithium-induced polyuria. Finally, change to another drug may be the only alternative. This is clearly indicated in the case of serious allergic reactions. Polypharmacy should be avoided wherever possible.

## Psychosocial Treatments

Since the first edition of this textbook one of the fastest moving areas of research in manic–depressive disorder has been the development of psychosocial interventions. Such interventions have been studied almost exclusively in the context of ongoing medication management, rather than as a substitute for psychopharmacology. The field has advanced quickly enough that now space allows review only of Class A controlled trials of such interventions, and the reader is referred to the prior edition for review of the breadth of interventions that have been studied under less controlled conditions (Bauer 2003b).

Another aspect of the dynamism of this area is the application of chronic care models to manic–depressive disorder. While there is some overlap conceptually and generationally with psychotherapy, the interventions are sufficiently distinct to warrant separate description.

### Psychotherapies

Class A studies of psychotherapy for manic–depressive disorder, all of which added psychotherapy to reasonable pharmacotherapeutic regimens, are summarized in Table 67–18. Several differences are evident in comparison to the pharmacotherapy studies reviewed above. Most psychotherapy studies investigated outcome or process measures over time, rather than response of acute episodes, so the table is divided into relatively shorter versus longer term studies rather than strictly acute versus prophylaxis as in medication trials. Such study designs reflect the expectation that psychotherapy acts via mechanisms that involve relearning and behavior change, and that such mechanisms take time. Additionally, the variety of outcome measures tends to be more heterogeneous, reflecting the breadth of outcomes hypothesized to be responsive to psychotherapeutic interventions. Studies also tend to reflect assessment of incremental or ongoing change over time rather than time to relapse, which some have proposed is more relevant to assessing treatment for chronic illnesses such as manic depression (e.g., Rea et al. 2003, Bauer et al. 2006a).

The major types of psychotherapy that have been investigated include cognitive or cognitive–behavioral therapy, single- or multifamily therapy, and group and individual psychoeducation. It should be kept in mind that there are often not firm lines between the types of therapy, with cognitive techniques including substantial psychoeducational components and vice versa (Colom and Vieta 2004).

It is notable from Table 67–18 that, in distinction to psychopharmacological studies, several interventions have demonstrated reduced time depressed or depressive relapse rate. Several interventions have also shown improvement in manic symptoms or relapse. Importantly, improved social role function has also been demonstrated with several psychotherapies.

Optimism for combined psychotherapy–pharmacotherapy is clearly warranted, but is tempered somewhat by evidence that more ill patients tend to do less well in at least cognitive psychotherapy than those who are higher functioning (Scott 2005, Scott 2006a, 2006b), and that family therapy cannot be done on those who do not have families. Thus efficacy versus effectiveness considerations (see Section "Understanding Evidence-Based Medicine") are at least as prominent with psychotherapy studies as with other interventions, and enhancing such treatments to engage and improve outcome for more severely ill individuals clearly must be a focus of future work. In this regard, the relatively short-term group intervention study of individuals with manic–depressive disorder and comorbid substance use disorders is promising (Weiss et al. 2007).

### Collaborative Chronic Care Models for Manic–Depressive Disorder

Chronic care models (CCMs) have been applied to management of chronic medical illnesses, addressing which are inadequately treated, despite the availability of efficacious medications (Von Korff et al. 1997, Wagner 2000, Bodenheimer et al. 2002a–2002c). The central focus of CCMs, which are based on principles of social learning and self-regulation theories (Von Korff et al. 1997), is to reorganize medical care to support an effective partnership between clinicians and patients to improve outcomes relevant to patients (Bodenheimer et al. 2002a). CCMs typically include components to enhance patient self-management skills, facilitate information flow to providers, support provider decision-making via expert guidance through guidelines or consultation, and redesign work roles to emphasize anticipatory rather than reactive care. They are clinic based without mobile treatment or community outreach components. Substantial evidence indicates that CCMs improve process and outcome measures for a variety of chronic medical illnesses (Bodenheimer et al. 2002b, 2002c) and for depression treated in primary care (Badamgarav et al. 2003) and may be cost-effective (Simon et al. 2001).

Recently, two multisite RCTs totaling over 700 subjects (Bauer et al. 2006a, 2006b, Simon et al. 2005, 2006) have shown that CCMs can also improve clinical and functional outcome and process measures in manic–depressive disorder, and at minimal to no net cost (see Table 67–18). Importantly, both these trials were constructed as effectiveness trials (see Section "General Considerations"), enrolling unselected or severely ill patients.

Thus CCMs likely have a role in optimizing outcome for individuals with manic–depressive disorder, including those with severe illness. Based on these studies, at least one major practice guideline has endorsed their use in this disorder (Yatham et al. 2006). Notably, CCMs involve psychotherapeutic components, and psychotherapeutic interventions involve some (usually implicit) care coordination; thus both may be considered along a continuum of psychosocial interventions.

**Table 67–18 Psychosocial Interventions for Manic–Depressive Disorder with Class A Evidence***

| Study | Intervention and Trial Structure | Primary and Other Major Clinical Outcome Measures | Primary and Other Major Functional Outcome Measures | Major Process Measures |
|---|---|---|---|---|
| | | **Shorter Term Studies (< 12-Month Outcomes)** | | |
| Cochran (1984) | • Individual psychoeducation/cognitive–behavioral therapy<br>• Weekly for 6 weeks<br>• vs. TAU<br>• Assessment at 6 weeks and 6 months | – | – | • Improved adherence at 6 weeks and 6 months |
| Peet and Harvey (1991) | • Educational videotape and fact sheet on lithium<br>• One session<br>• vs. TAU<br>• Assessment at 6 and 12 weeks | – | – | • Improved lithium knowledge at 6 and 12 weeks |
| Van Gent and Zwart (1991) | • Group psychoeducation for partners of individuals with bipolar disorder<br>• Five sessions<br>• vs. TAU<br>• Assessment at 6 months | – | – | • Improved illness and treatment knowledge at 6 months<br>• No difference in adherence or readmission rate |
| Clarkin et al. (1998) | • Marital therapy<br>• 25 weekly to bimonthly sessions<br>• vs. TAU<br>• Assessment at 11 months | • No change in symptoms | • Improvement in function | • Improved adherence at 11 months |
| Lam et al. (2000) | • Individual cognitive therapy<br>• 12–20 sessions over 6 months<br>• vs. TAU<br>• Assessment at 6 and 12 months | • Fewer total and hypomanic episodes over 12 months | • Improved social performance | • Improved adherence at 12 months |
| Scott et al. (2001) | • Individual cognitive therapy<br>• 25 sessions<br>• vs. waiting list control for 6 months followed by cognitive therapy<br>• Assessment at 6 months | • Reduced depressive, manic, and global psychopathology symptoms at 6 months | • No change in work or social adjustment | – |
| Weiss et al. (2007) | • Integrated group bipolar-substance treatment<br>• 20 weekly sessions plus TAU<br>• vs. 20 weekly sessions of group drug counseling plus TAU<br>• Assessment at 8 months | • Fewer days of substance use<br>• Fewer days of alcohol, but not drug, use<br>• No difference in weeks ill<br>• Increase in manic and depressive symptoms with integrated treatment | – | – |
| | | **Longer Term Studies (> 12-Month Outcomes)** | | |
| Clarkin et al. (1990) | • Single-family inpatient sessions<br>• At least 6 sessions during hospitalization<br>• vs. TAU<br>• Assessment at 6 and 18 months | • No significant difference at 6 or 18 months | • Overall role function improvement at 6 and 18 months | • No changes in family attitude at 6 or 18 months |
| Perry et al. (1999) | • Individual psychoeducation<br>• 7–12 sessions<br>• vs. TAU<br>• Assessment over 18 months | • Reduced number of manic relapses<br>• No difference in depressive relapses | • Improved social functioning at 18 months<br>• Improved employment at 18 months | – |
| Frank et al. (1999, 2005) | • Individual interpersonal/social rhythms therapy<br>• Weekly to monthly sessions<br>• vs. clinical management, cross-over at time of remission<br>• Assessment over 12 and 24 months | • No difference in time to remission<br>• No difference in time to relapse by 12 months<br>• Increased time to relapse over 24 months if given IPSRT initially | – | • Social rhythms more stable |
| Miklowitz et al. (2000, 2003) | • Single-family family-focused therapy<br>• 21 sessions weekly to monthly over 9 months<br>• vs. 2 educational sessions plus crisis management<br>• Assessment at 12 and 24 months | • Increased time to relapse<br>• Fewer total relapses at 12 and 24 months<br>• Reduced mean depressive symptoms by 12 and 24 months<br>• No difference in mean manic symptoms | – | • No effect on adherence at 12 months<br>• Improved adherence at 24 months |

*(continues)*

**Table 67–18 Psychosocial Interventions for Manic–Depressive Disorder with Class A Evidence* continued**

| Study | Intervention and Trial Structure | Primary and Other Major Clinical Outcome Measures | Primary and Other Major Functional Outcome Measures | Major Process Measures |
|---|---|---|---|---|
| | | **Longer Term Studies (> 12-Month Outcomes)** | | |
| Rea et al. (2003) | • Single-family family-focused therapy<br>• 21 sessions weekly to monthly over 9 months<br>• vs. 21 individual therapy sessions over 9 months<br>• Assessment at 24 months | • No difference in time to relapse<br>• Fewer total relapses | – | • Increased time to hospitalizations<br>• Decreased number of hospitalizations<br>• No difference in hospitalization rate |
| Colom et al. (2003a) | • Group psychoeducation<br>• 21 group sessions<br>• vs. 21 unstructured group sessions<br>• Assessment over 24 months | • Reduced percentage with relapses, increased time to depressive, manic, or mixed recurrence<br>• Reduced time to first relapse | – | • Reduced hospitalization rate at 12 and 24 months |
| Colom et al. (2003b) | • Group psychoeducation<br>• 21 group sessions<br>• vs. 21 unstructured group sessions<br>• Assessment over 24 months | • Reduced percentage with relapses and total number of relapses<br>• Reduced time to first relapse | – | • Reduced hospitalization rate |
| Lam et al. (2003, 2005a, 2005b) | • Individual cognitive therapy<br>• 16 sessions<br>• vs. TAU<br>• Assessment at 12 and 30 months | • Fewer episodes, days in episode at 12 and 30 months<br>• Longer time to relapse to any episode and depressive episodes, but not manic episodes | • Improved social function at 12 and 30 months | • Reduced hospitalization rate at 12 months<br>• Increased costs with cognitive therapy but judged cost-effective based on cost of days depressed |
| Miller et al. (2004) | • Single-family McMaster family therapy or multifamily group therapy<br>• 6–10 sessions<br>• vs. TAU<br>• Assessment at 28 months\ | • No difference in time to recovery from mania or depression across 3 groups | – | – |
| Simon et al. (2005, 2006) | • Collaborative chronic care model<br>• Ongoing patient/provider/access intervention including group psychoeducation<br>• vs. TAU<br>• Assessment at 24 months | • Reduced manic symptoms at 12 and 24 months<br>• No difference in depressive symptoms at 12 or 24 months | – | • Direct treatment cost increase of US$1251 over 24 months |
| Ball et al. (2006) | • Individual cognitive therapy with emotive techniques added<br>• 20 sessions over 6 months<br>• vs. TAU<br>• Assessment at 6 and 18 months | • No difference in number of episodes<br>• Trend to longer time to depressive relapse<br>• No difference in days depressed or manic | – | – |
| Bauer et al. (2006a, 2006b) | • Collaborative chronic care model<br>• Ongoing patient/provider/access intervention including group psychoeducation<br>• vs. TAU<br>• Assessment at 36 months | • Reduced weeks in episode and weeks manic, but not weeks depressed, over 36 months<br>• No difference in mean manic or depressive symptoms over 36 months | • Improved social role function over 36 months<br>• Improved mental quality of life over 36 months<br>• No difference in physical quality of life | • Improved patient satisfaction<br>• Cost-neutral<br>• No difference in medication intensity |
| Scott et al. (2006a) | • Individual cognitive–behavioral therapy<br>• 22 sessions<br>• vs. TAU<br>• Assessment at 18 months | • No difference in recurrence rates for depression, mania, or either episode type<br>• No difference in mean manic or depressive symptoms | – | – |

*Each row reflects a single study, sometimes reported in more than one article in which case multiple citations are listed for that row; TAU, treatment as usual.

CCMs provide a care-organization platform through which medications and psychotherapies may be more effectively delivered.

## Issues in the Clinician–Patient Relationship

The most critical issue in establishing the clinician–patient relationship is coming to a shared understanding that manic–depressive disorder is a chronic condition that will require ongoing, anticipatory, and collaborative management. This is a key tenet of CCMs for medical illnesses (e.g., Von Korff et al. 1997, Wagner et al. 1996), and has also been a critical component of such models for manic–depressive disorder (e.g., Bauer and McBride 2003, Bauer et al. 2006a). As detailed in these resources, the clinician–patient relationship must include education to enhance self-management skills and adequate access and continuity of care—timely access can often prevent hospitalization for mania if new onset symptoms can be treated early, and can minimize nonadherence due to medication side effects.

The collaborative stance that this approach entails goes beyond paternalistic ("Do as I say and you'll get better") and maternalistic ("I can fix your problems with…support/psychotherapy/pills/etc.") approaches to care. Rather, the collaborative stance is better illustrated as a "coach–athlete" relationship in which the patient is the one in competition with the illness and the clinician, standing on the sidelines of the illness, provides specific technical assistance. Some have cast this as "The patient is the values expert, the clinician is the technical expert," or "The clinician is the expert in disease in general and the patient is the expert in their specific case." Regardless of analogy, the collaborative approach stresses activation of patient motivations, priorities, and skills in the service of identifying needs and priorities that can be addressed by the clinician's technical skill. There is empirical evidence that individuals with manic depression prefer such approaches (e.g., Ludman et al. 2002, Berk et al. 2004) and such patient-activating approaches have begun to be incorporated into clinical practice guidelines (e.g., Yatham and Kennedy 2005).

It should also be noted that patients often come to treatment ambivalent about recognizing their illness or accepting appropriate treatment. This should be treated as the norm rather than the exception, as it is for most illnesses and behavioral medicine situations; that is, among "stages of change," few individuals are consistently at the action stage; most are contemplative or even precontemplative. In such common situations we have found motivational interviewing techniques, which have evidence-based support for substance use disorders and behavioral medicine (e.g., Miller and Rollnick 2002, Rubak et al. 2005), also to be helpful in resolving ambivalence in manic–depressive disorder as well.

## Treatment-Refractory Patients

In a disorder that is characterized by a relapsing course, often with interepisode residual symptoms, typically with ongoing functional deficits, and usually requiring multiple medications to achieve even this status, what is the meaning of "refractory"? There is no widely accepted definition, as there is for individual major depressive episodes. Accordingly, while there have been a large number of combination studies after individuals failed to respond to mono- or dual therapy (see Section "Combination Strategies"), there have been only a few studies that investigated individuals judged a priori to be "refractory." Refractory bipolar depressive episodes had very low response rates in a RCT of added lamotrigine, risperidone, or inositol (Nierenberg et al. 2006). Among those with rapid cycling, a parallel group placebo-controlled trial of lamotrigine revealed mixed results (Calabrese et al. 2000), while a case series and very small on/off/on placebo-controlled trial of high-dose thyroxine revealed some improvement in refractory rapid cycling (Bauer and Whybrow 1990). A controlled trial of added clozapine versus maintenance treatment as usual indicated some benefit in those with a recurring course and a history of mania (Suppes et al. 1999).

A complementary approach to understanding refractoriness is to consider characteristics that coexist with the illness that increase difficulty in treatment. Such contributors include comorbid psychiatric disorders, comorbid medical disorders that limit treatment choice or contribute to depressive symptoms and functional deficits, and nonadherence. Additionally, when an individual does not respond to a variety of treatments, the diagnosis itself should be reconsidered, and investigation undertaken in particular for medical and substance-related causes of the symptoms.

## Special Features Influencing Treatment

### Treatment of Comorbid Disorders

As noted in Sections "Medical Precipitants of Manic or Depressive Symptoms" and "Medical Comorbidity," medical disorders or treatments may cause mood episodes, either de novo or in the course of already established manic–depressive disorder. Regarding comorbid psychiatric disorders, the choice of approach to management may be driven by a variety of implicit assumptions. Psychiatrists may assume that the comorbid disorder is caused by manic–depressive disorder and consequently believe that treatment of the manic–depressive disorder will lead to resolution of the comorbidity. Others may assume that the mood instability of manic–depressive disorder is due to the comorbid illness, such as alcohol or drug intoxication or withdrawal, or intrapsychic or psychophysiological effects of prior trauma.

It stands to reason, rather, that *parallel* (simultaneous) treatment is preferable to *sequential* treatment (treating one disorder until resolution and then attending to the other), as the prognosis of manic–depressive disorder is worse when complicated by substance use (Himmelhoch et al. 1976, Himmelhoch 1979) and the course of alcoholism is worse when complicated by mood disorders (Rounsaville et al. 1987).

It is also likely that the highly confrontative approaches of some traditional substance dependence treatment programs will not likely serve the needs of often highly impaired depressed or manic persons. Similarly, the presence of anxiety disorders is associated with worse outcome (e.g., Simon et al. 2004b, Bauer et al. 2005a). Among RCTs for those with comorbid substance disorders, we are aware only of the integrated group psychotherapy intervention of Weiss et al. (2007), and a placebo-controlled trial of divalproex in those with comorbid alcohol dependence (Salloum et al. 2005); in this latter study divalproex reduced alcohol consumption but had no mood effects over 24 weeks. We are as yet aware of no interventions developed specifically for individuals with comorbid anxiety disorders.

## Treatment of Manic–Depressive Disorder Across the Life Cycle

### *Childhood and Adolescence*

Childhood and adolescence represent particular challenges for assessment, and several recent detailed reviews have recently appeared (e.g., Danielyan and Kowatch 2005, Axelson et al. 2006, Kyte et al. 2006, Strober et al. 2006). Diagnostic criteria from adults have been applied to children and adolescents, though the degree to which the syndrome is the same across ages is open to question (e.g., Biederman et al. 2004, Kowatch et al. 2005); interestingly, over 80% of youth may present with elevated rather than irritable mood. Moreover, assessment is made more difficult by overlap or comorbidity with ADHD (Kim and Miklowitz 2002, Biederman et al. 2004), anxiety disorders (Dineen Wagner 2006) and conduct disorder (Kim and Miklowitz 2002, Kyte et al. 2006). Rates of ADHD as high as 87% have been described (e.g., Biederman et al. 1999, Geller et al. 2000, Singh et al. 2006), though much lower lifetime rates in community samples of adolescents with manic–depressive disorder have been reported (11%; Lewinsohn et al. 1995). Rates of anxiety disorder range from 14 to 54% (Biederman et al. 1999, Findling et al. 2001) Rates of conduct disorder (12–41%) and oppositional-defiant disorder (46–86%) are also substantial (Biederman et al. 1999, Findling et al. 2001, Tillman et al. 2003, Axelson et al. 2006). Little is known about long-term course or outcome of manic–depressive disorder in youth (Strober et al. 2006).

Treatment is undertaken mainly by extension from treatment of adults, substantiated with open trials in youth of, for example, lithium (Kowatch et al. 2000, Kafantaris et al. 2003), carbamazepine (Kowatch et al. 2000), divalproex (Kowatch et al. 2000, Wagner et al. 2002), various antipsychotics (e.g., Frazier et al. 2001, Kafantaris et al. 2001), and cognitive–behavioral therapy (Feeny et al. 2006). Combination treatment appears to be common, as it is in adults (Kowatch et al. 2003).

Not surprisingly, there are far fewer RCTs than in adults, though some data support the utility of lithium (Kafantaris et al. 2004), divalproex (Findling et al. 2005), and quetiapine (Delbello et al. 2002 and 2006). Oxcarbazepine was found to be no different than placebo (Wagner et al. 2006), and data on topiramate are inconclusive (Delbello et al. 2005). Use of amphetamine in children with comorbid ADHD improved ADHD without worsening manic symptoms (Scheffer et al. 2005). Among psychosocial interventions, RCT data support the use of multi-family group and individual family psychoeducation (Fristad 2006) in children as well as family-focused therapy for adolescents (Miklowitz et al. 2004).

### *Pregnancy*

The complexities of treating manic–depressive disorder during pregnancy and breastfeeding have recently been extensively reviewed (e.g., Yonkers et al. 2004, Gentile 2006). There is some evidence that lithium may be teratogenic, associated with increased rates of cardiac abnormalities (Weinstein and Goldfield 1975) although this risk may be overestimated (Cohen et al. 1994). Divalproex and perhaps carbamazepine (Robert and Guiband 1983, Delgado-Escueta and Janz 1992, Scolnik et al. 1994) have been associated with neural tube defects (Robert and Guiband 1983), leaving the neuroleptics, antidepressants, and ECT as the preferable management strategies during pregnancy, particularly during the first trimester. It should be kept in mind, however, that treatment decisions are based on *risk*, not *certainty*. Risk of fetal malformation, parental attitude toward raising children with birth defects, severity of illness, and ease of management with alternative therapies all need to be considered in conjunction with the woman and her partner.

It should also be noted that there may be some relationship between manic–depressive disorder and both postpartum depression and postpartum psychosis. These syndromes are reviewed in Chapter 119.

### *Older Adults*

Aging also presents certain treatment complexities. Several extensive references have recently appeared reviewing issues in clinical assessment and treatment of manic–depressive disorder in later life (e.g., Depp and Jeste 2004, Young et al. 2004, Sajatovic et al. 2005, Blow and Sajatovic 2007).

Older individuals with manic–depressive disorders can be considered of two types: those with later age of onset (usually at 40 or 50 years of age or older), and those with more typical younger onset. Evidence indicates that the former probably represent a subpopulation enriched with identifiable medical factors that may be the cause of mania, in particular neurological disorders, identified in 12–38%; however, the degree to which such factors are pathogenic is not clear (Depp et al. 2004), and there are insufficient grounds for considering late-onset manic–depressive disorder a separate subtype (Depp et al. 2004). Interestingly, manic–depressive disorder does not appear to worsen with age (Fenn et al. 2005), and the prevalence may decrease (Depp et al. 2004), though the extent to which each of these findings is due to selective mortality of the more severely ill at an earlier age is not clear.

Perhaps the key characteristic differentiating older from younger individuals, regardless of age of onset, is the increasing prevalence of medical comorbidity (Fenn et al. 2005); this study of inpatients indicated that those over 50 years of age had a median of 4 or more medical comorbidities requiring treatment, while another reported that 20% had 7 or more medical comorbidities (Brown 1998). Notably, while measures of physical quality of life decline with age, this trend is due to increasing prevalence of medical comorbidity, not age per se; thus attention to these comorbidities may improve quality of life (Fenn et al. 2005).

Unfortunately, no RCTs have yet been published specifically in older adults, and treatment is implemented based on data from all-age samples. Both early- and late-onset individuals of older age represent similar basic assessment and treatment issues, including the need to identify reversible causes and, especially in older individuals, the need to identify medical comorbidities and manage psychotropic medications accordingly. Several such management issues are highlighted in the following paragraphs.

As discussed in Chapters 101 and 123, tricyclic antidepressants may be associated with clinically significant cardiac conduction abnormalities, hypotension, sedation, glaucoma, and urinary retention particularly in the presence of prostatic hypertrophy. These are of even greater concern in the elderly. The risk of sedation due to neuroleptics and

benzodiazepines and of hypotension due to low-potency neuroleptics can also complicate treatment. Subsequent complications such as hip fracture (Ray et al. 1987) are not infrequently the initial event in a cascade of complications that can be terminal.

By contrast, lithium, carbamazepine, and valproic acid are relatively well tolerated in the elderly. However, careful attention must be given to three mechanisms of drug toxicity in this population: reduced renal clearance, multidrug protein-binding competition, and hepatic P-450 drug interactions. Second generation, and perhaps some first generation antipsychotics, have been associated with increased risk of cerebrovascular events, while agent-specific side effects ranging from sedation and hypertension to akathisia to metabolic syndrome must be considered (see Chapter 102). The risk of clinically significant renal toxicity with appropriately dosed lithium is not great (Schou 1988, Gitlin 1993, Kehoe 1994). Although glomerular filtration rate decreases with age in persons treated with lithium, the rate of decline does not appear to be accelerated by lithium treatment (Lokkegaard et al. 1985, Vaamonde et al. 1986). Nonetheless, careful monitoring of renal function is needed in the elderly, especially those with additional risk factors for renal disease such as hypertension or diabetes. In addition, increasing age is a risk factor for hypothyroidism (Bauer et al. 1993), as is lithium use (Bauer et al. 1990). Thus, elderly persons taking lithium should be followed up carefully for decrements in thyroid function; however, hypothyroidism is not necessarily an indication for lithium discontinuation, as thyroid supplementation is straightforward. Treatment choice requires careful risk-benefit assessment in all patients, and in older individuals particularly, careful attention to the variety of increased medical risks that come with age is essential.

Clinical Vignette

Ms. B, a 59-year-old separated woman with type I disorder enrolled in a collaborative chronic care model (CCM; see Sections "Collaborative Chronic Care Models for Manic–Depressive Disorder" and "Issues in the Clinician–Patient Relationship") after hospitalization for an acute manic episode with psychotic features. She was retired, separated, and had few social contacts. Although diagnosed with manic–depressive disorder 19 years earlier, she had had inconsistent mental health treatment. Episodes had been dramatic for her, often involving police bringing her to the hospital. Medical records documented that her denial of illness was the greatest barrier to treatment. Initially, she presented as distrustful and engaged in only limited discussion of her mood disorder. Gradually, psychoeducation group participation provided her with a sense of support and an ability to identify her own illness characteristics. She became proficient in identifying early warning symptoms of mood episodes and the benefits of consistency in taking medications. She utilized personal cost-benefit analysis (Bauer and McBride 2003) to address medication side effects, and utilized easy access CCM appointments to remain in treatment rather than stopping medications as she had in the past. Although she had two more hospitalizations over the next 3 years, her daughter reported to the CCM staff, saying: "This program is the best thing that has happened to her…she has been so much better."

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CHAPTER

# 68 Mood Disorders: Premenstrual Dysphoric Disorder

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## Diagnostic Criteria for PMDD

### Definition and Diagnostic Features

Premenstrual syndrome (PMS) is a combination of emotional, behavioral, and physical symptoms that occur in the premenstrual or luteal phase of the menstrual cycle. The term "premenstrual tension" appeared in the medical literature 70 years ago (Frank 1931), but widely accepted diagnostic criteria for PMS do not exist. Diagnostic criteria for PMS often require a minimum of one premenstrual symptom, such as the criteria proposed in the *American College of Obstetrics and Gynecology Practice Guidelines* (American College of Obstetrics and Gynecology 2000) or in the *International Classification of Diseases, 10th Revision* (World Health Organization 1993). Approximately 80% of women report at least mild premenstrual symptoms, 20–50% report moderate to severe premenstrual symptoms, and approximately 5% of women report severe symptoms for several days with impairment of role and social functioning (American Psychiatric Association 2000). The 5% of women with the severest form of PMS generally have symptoms that meet the diagnostic criteria for premenstrual dysphoric disorder (PMDD).

The diagnostic criteria for PMDD are listed in the appendix of DSM-IV-TR (American Psychiatric Association 2000), and they are an updated version of the older DSM-III-R criteria for late luteal phase dysphoric disorder. A clinician can indicate that a woman has symptoms that meet the diagnostic criteria for PMDD by using the DSM-IV-TR diagnosis 311, depressive disorder not otherwise specified. To meet the PMDD criteria, at least five out of 11 possible symptoms must be present in the premenstrual phase; these symptoms should be absent shortly following the onset of menses; and at least one of the five symptoms must be depressed mood, anxiety, lability, or irritability. The PMDD criteria require that role functioning be impaired as a result of the premenstrual symptoms. The functional impairment reported by women with PMDD is similar in severity to the impairment reported in major depressive disorder (MDD) and dysthymic disorder (Pearlstein et al. 2000, Halbreich et al. 2003). Women with severe PMS and PMDD have reported disruption in their social relationships, parenting roles, and work productivity as well as increased health-care utilization (Pearlstein et al. 2000, Chawla et al. 2002, Borenstein et al. 2003, Halbreich et al. 2003, Borenstein et al. 2005).

The PMDD criteria require that a woman prospectively rate her emotional, behavioral, and physical symptoms over two menstrual cycles to confirm the diagnosis. Several studies have reported that retrospective reports of premenstrual symptoms may inaccurately identify the timing or amplify the severity of symptoms compared to prospective reporting (Schnurr et al. 1994). Charting two menstrual cycles is advantageous, since some women have variability of symptom severity from cycle to cycle due to factors such as seasonal worsening, or a woman might have the unusual presence of follicular phase psychological symptoms due to a transient stressor. Studies conducted over the past two decades have used different instruments for daily ratings and various scoring methods to measure the premenstrual increase of symptoms (Schnurr et al. 1994). Recent studies utilize visual analog scales (Steiner et al. 1999) and Likert scale daily rating forms such as the Daily Record of Severity of Problems (Endicott et al. 2006) or Penn Daily Symptom Report (Freeman et al. 1996), with a scoring method that compares the average of symptom scores during the premenstrual days to the average of symptom scores postmenses.

A woman presenting with PMS should ideally bring to her clinician two cycles of an established daily rating form, or alternatively ratings of her most problematic symptoms, rated with anchor points ranging from "not present" to "severe." The clinician should review the daily ratings to

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confirm that the symptoms are in fact confined largely to the premenstrual phase, with the relative absence of symptoms in the follicular phase, and the clinician should also assess premenstrual functional impairment (Figure 68–1). Ratings that demonstrate follicular symptoms with increased symptom severity in the premenstrual phase suggest "premenstrual exacerbation" of an underlying disorder rather than PMDD. The DSM-IV-TR PMDD criteria state that the premenstrual symptoms should not be an exacerbation of an underlying disorder, but that PMDD could be superimposed on another disorder, like panic disorder. No formal guidelines exist for how to apply this criterion clinically.

**DSM-IV-TR Criteria**

**Diagnostic Criteria for PMDD**

Research Criteria for Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, 5 (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   (1) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   (2) marked anxiety, tension, feelings of being "keyed up," or "on edge"
   (3) marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
   (4) persistent and marked anger or irritability or increased interpersonal conflicts
   (5) decreased interest in usual activities (e.g., work, school, friends, hobbies)
   (6) subjective sense of difficulty in concentrating
   (7) lethargy, easy fatigability, or marked lack of energy
   (8) marked change in appetite, overeating, or specific food cravings
   (9) hypersomnia or insomnia
   (10) a subjective sense of being overwhelmed or out of control
   (11) other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

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## Differential Diagnosis

Depression and anxiety disorders are the most common Axis I psychiatric disorders that may be concurrent and exacerbated premenstrually, with less clear evidence for bipolar disorder, post-traumatic stress disorder, eating disorders, and substance abuse (Endicott 1994, Hendrick et al. 1996, Pearlstein and Stone 1998, Kim et al. 2004). Since most PMDD symptoms are affective or anxiety related, "pure PMS" or PMDD is generally not diagnosed when an underlying depression or anxiety disorder is present; these women would be considered to have premenstrual exacerbation of their underlying depression or anxiety disorder. A recent study reported that 64% of the first 1500 women with MDD enrolled in the STAR*D study endorsed premenstrual exacerbation of their depressive symptoms by retrospective report (Kornstein et al. 2005). Another recent study reported that 68.5% of 1747 women with MDD and 65.1% of 665 women with bipolar I disorder retrospectively reported premenstrual mood symptoms (Payne et al. 2006). Personality disorders are not elevated in prevalence in women with PMDD (Critchlow et al. 2001), but women with PMDD and a personality disorder may demonstrate premenstrual phase amplification of personality dysfunction (Berlin et al. 2001). Schizophrenia may be an example of a disorder that does not have premenstrual exacerbation of psychotic symptoms but may have the superimposition of affective and anxiety symptoms of PMDD (Choi et al. 2001). The prevalence of premenstrually exacerbated disorders is unknown, and women with these conditions present frequently to their primary care clinician or gynecologist. The general guideline is to treat the underlying disorder first and see if subsequent daily ratings suggest persistence of premenstrual symptoms that might meet criteria for PMDD. Since most recent treatment studies have been conducted on women with PMS and PMDD without follicular symptomatology, this literature is not particularly informative on how to treat women with premenstrually exacerbated disorders.

Several medical conditions should also be considered when evaluating a woman with premenstrual complaints. Symptoms of endometriosis, polycystic ovary disease, thyroid disorders, adrenal system disorders, hyperprolactinemia, and panhypopituitarism may mimic symptoms of PMS. Several medical disorders may demonstrate a premenstrual increase in symptoms without accompanying emotional symptoms,

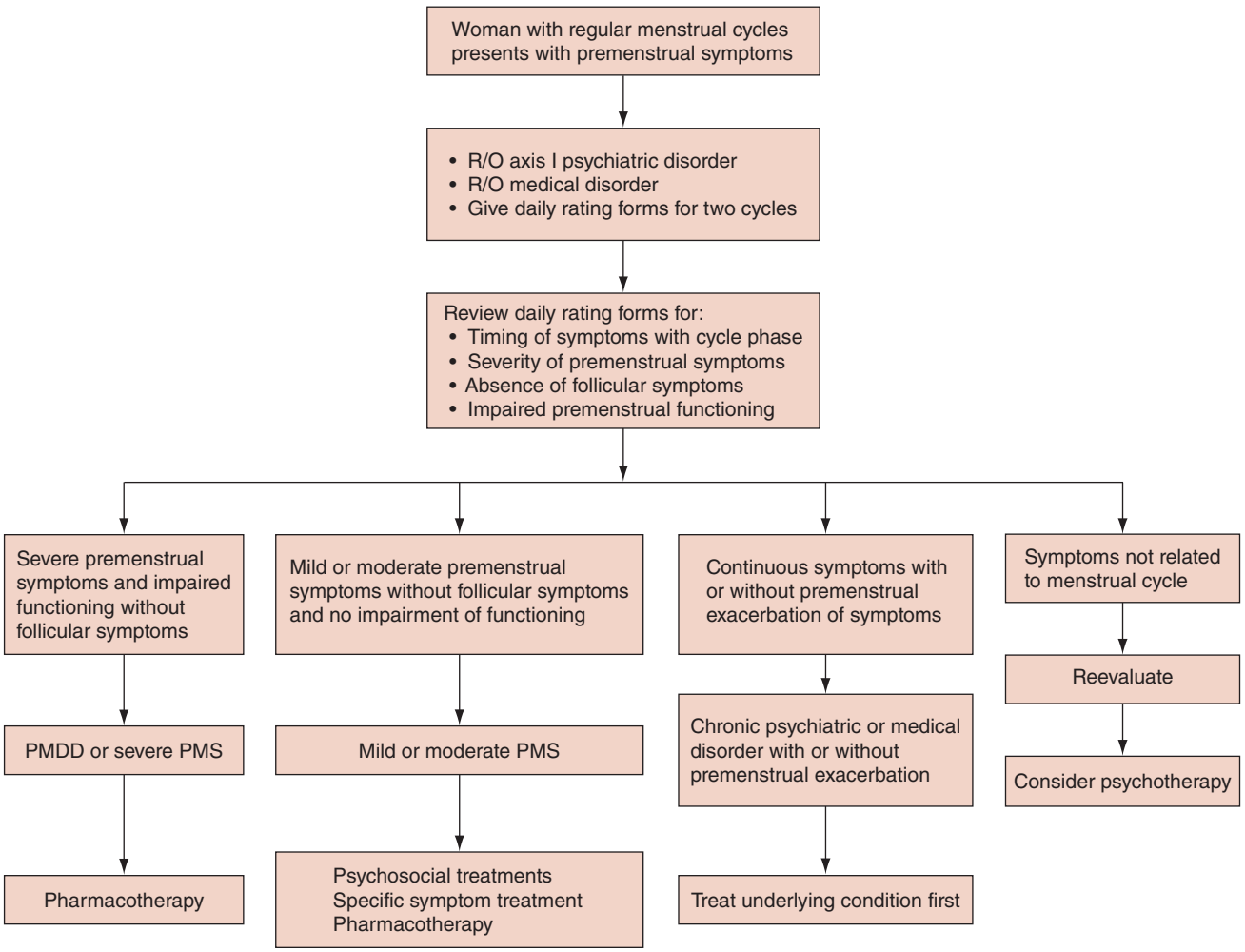



**Figure 68–1** *Diagnosis and initial treatment algorithm of premenstrual symptoms.*

such as migraines, asthma, epilepsy, irritable bowel syndrome, diabetes, allergies, and autoimmune disorders (Pearlstein and Stone 1998, Case and Reid 2001). It is presumed that the menstrual cycle fluctuations of gonadal hormones influence some of the symptoms of these medical conditions.

## Course

Premenstrual symptoms have been reported in women from menarche through perimenopause. Anecdotally many women report increasing severity of symptoms with advancing age and parity, but few longitudinal studies have been conducted evaluating the frequency and severity of premenstrual symptoms (Endicott et al. 1999). A 4-year longitudinal study of 1251 women 14–24 years of age in Munich, Germany, reported that both threshold and subthreshold PMS were relatively stable conditions (Wittchen et al. 2002). Mood lability, irritability, and anxiety have been reported to be the most stable premenstrual symptoms across cycles (Bloch et al. 1997). It has been hypothesized that women with PMDD are vulnerable to the development of affective disorders at other times of hormonal fluctuation across the reproductive years, such as the postpartum period and perimenopause. Retrospectively reported premenstrual symptoms have been identified as a predictor for perimenopausal depression in clinic and community samples (Richards et al. 2006). A study of perimenopausal women reported that prospectively rated premenstrual dysphoria and other premenstrual symptoms were significantly higher in women with perimenopausal depression compared to perimenopausal women without depression (Richards et al. 2006).

## Epidemiology

The prevalence of PMDD has ranged from 4.6% to 6.4% in studies of women who prospectively rated their symptoms for at least one menstrual cycle (Rivera-Tovar and Frank 1990, Cohen et al. 2002b, Sternfeld et al. 2002). Approximately 20% of women have "subthreshold PMDD," or severe PMS, due to having fewer and less severe symptoms or a lack of the functional impairment required to meet the PMDD criteria (Wittchen et al. 2002, Steiner et al. 2003). Studies with the prospective confirmation of diagnosis have not been conducted in adolescent girls younger than age 18 years, but studies with retrospective reports of premenstrual symptoms suggest possible higher prevalence rates of severe PMS in adolescents and association with symptoms of dysmenorrhea (Derman et al. 2004, Vichnin et al. 2006). Irritability has been identified as the most common premenstrual symptom in the United States and European samples (Endicott et al. 1999, Angst et al. 2001, Pearlstein et al. 2005c). A few studies have examined the prevalence of premenstrual symptoms with prospective ratings in non-United States or European countries. Prevalence rates of

severe PMS or PMDD have been reported to be 18.2% of 384 college students in Pakistan (Tabassum et al. 2005), 6.4% of 52 volunteer women in India (Banerjee et al. 2000), 12% of 150 women in a PMS clinic in Taiwan (Hsiao et al. 2002), and 2.4% of 83 women in a population cohort in Iceland (Sveindottir 1998). Some cultures and cultural subgroups describe more somatic than emotional symptoms (Hasin et al. 1998, van den Akker et al. 1995). Studies have failed to consistently identify predictors of PMDD such as age, parity, socioeconomic status, and menstrual cycle characteristics such as heavy bleeding or dysmenorrhea (Endicott et al. 1999, Steiner and Born 2000). Elevated lifetime prevalence of MDD in women with PMDD has been reported in several studies (Endicott 1994), as well as an elevated lifetime prevalence of postpartum depression (Critchlow et al. 2001).

## Etiology and Pathophysiology

### Genetic Factors

Studies of twin samples have suggested heritability of premenstrual symptoms (Condon 1993, Kendler et al. 1998, Treloar et al. 2002). The overlap with genetic liability for PMS with MDD, seasonal affective disorder, and personality characteristics is unclear (Kendler et al. 1998, Praschak-Rieder et al. 2002, Treloar et al. 2002). PMDD has been associated with multiple polymorphic alleles on the ESR1 gene (Rubinow and Schmidt 2006), but studies have failed to identify gene polymorphism differences between women with PMDD and controls on the serotonin transporter (Melke et al. 2003, Magnay et al. 2006), transcription factor activating protein-2 (Damberg et al. 2005), tryptophan hydroxylase, and monomine oxidase A promoter (Magnay et al. 2006) genes.

### Neurobiological Factors

There are several reviews of pathophysiologic hypotheses of PMS and PMDD and their evidence (Parry 1997, Steiner and Pearlstein 2000, Backstrom et al. 2003, Halbreich 2003, Sundstrom-Poromaa et al. 2003). The majority of studies do not identify consistent abnormalities of hormones of the hypothalamic–pituitary–gonadal (HPG) axis, although a few studies have suggested altered luteinizing hormone (LH) pulse (Eriksson et al. 2006a). Data demonstrating consistent abnormalities of thyroid hormones, cortisol, prolactin, glucose, prostaglandins, beta-endorphins, vitamins, or electrolytes are lacking (Parry 1997, Halbreich 2003). Women with PMDD are more sensitive to the anxiolytic properties of carbon dioxide inhalation, lactate infusion, cholecystokinin tetrapeptide, and flumazenil, and increased adrenergic receptor binding may reflect abnormal noradrenergic function (Halbreich 2003). Women with PMDD have abnormal melatonin secretion and other circadian system abnormalities (Parry and Newton 2001).

Since consistent abnormalities in the HPG axis have not been identified, it is thought that premenstrual symptoms may occur due to a differential sensitivity to mood-perturbing effects of gonadal steroid fluctuations in women with PMS and PMDD (Schmidt et al. 1998). It is probable that the etiology of the "differential sensitivity" is multifactorial and in part genetically determined (Rubinow and Schmidt 2006). The specific neurotransmitter and neurosteroid abnormalities in women with PMS and PMDD are not known, but serotonin, norepinephrine, gamma-aminobutyric acid (GABA), allopregnanolone (ALLO, an anxiolytic metabolite of progesterone that acts at the $GABA_A$ receptor), endorphins, and factors involved in calcium homeostasis may all possibly be involved. It has been proposed that women with PMDD have altered affective information processing and regulation during the luteal phase with abnormal activation patterns in specific brain regions (Rubinow and Schmidt 2006). Imaging studies have suggested altered serotonin function (Eriksson et al. 2006b, Jovanovic et al. 2006) and altered GABAergic function (Epperson et al. 2002, Smith et al. 2003) in women with PMDD compared to healthy controls.

A large number of studies have reported abnormalities in the serotonin system in women with PMS and PMDD. These include abnormal levels of whole blood serotonin, serotonin platelet uptake, and platelet tritiated imipramine binding; abnormal responses to serotonergic probes such as L-tryptophan, buspirone, meta-chlorophenylpiperazine, and fenfluramine; and exacerbation of premenstrual symptoms after tryptophan depletion (Steiner and Pearlstein 2000, Parry 2001, Halbreich 2003). Several studies have also suggested that women with PMDD have decreased luteal phase levels of GABA, abnormal ALLO levels, and decreased luteal phase sensitivity of the $GABA_A$ receptor as shown by flumazenil challenge, and the sedative and saccadic eye velocity responses to benzodiazepines and alcohol (Backstrom et al. 2003, Halbreich 2003, Sundstrom-Poromaa et al. 2003). It is possible that the rapid efficacy of selective serotonin reuptake inhibitors (SSRIs) in PMDD may be due in part to their ability to increase ALLO levels in the brain and enhance $GABA_A$ receptor function (Eser et al. 2006). Alternative hypotheses for the fast action of SSRIs in PMDD include enhanced function of $5\text{-}HT_{2C}$ receptors (Landen and Thase 2006) and inhibition of the serotonin transporter with resulting decreased LH production (Clayton et al. 2006).

Several factors that influence calcium and bone homeostasis fluctuate with the menstrual cycle, and it is possible that some of these factors are abnormal in women with PMS and PMDD (Thys-Jacobs 2000). A recent case–control study reported that a high intake of calcium and vitamin D was associated with a lower risk of PMS by women's retrospective self-report (Bertone-Johnson et al. 2005). One study reported decreased bone mineral density in women with prospectively confirmed PMS (Thys-Jacobs et al. 1995); however, a later study in women with PMDD failed to find decreased bone mineral density compared to controls (Halbreich and Kahn 2001). It has been reported that women with PMS had reduced periovulatory calcium levels and elevated parathyroid hormone levels compared to controls, perhaps secondary to elevated preovulatory estrogen levels (Thys-Jacobs and Alvir 1995). It is possible that the administration of supplemental calcium normalizes the periovulatory fluctuations in calcium and parathyroid hormone, thus regulating calcium effects on neurotransmitter synthesis and release leading to affective symptom relief in women with PMS (Thys-Jacobs 2000).

### Psychological and Social/Environmental Factors

Studies have suggested an association between stressful life events and daily stressors with PMS (Ross and Steiner

2003). It has been proposed that PMS is specific to Western cultures due to family, society, and media influences that promote negative expectations and attitudes about the menstrual cycle (Anson 1999, Ross and Steiner 2003, Di Giulio and Reissing 2006). The attitude toward menstruation that develops with socialization is also influenced by cognitive processes. PMS has been reported to be more common in women who assign negative attributions to premenstrual symptoms, have poor coping strategies and problem-solving abilities, and feel that their symptoms are not in their control (Reading 1992, Di Giulio and Reissing 2006). In spite of possible altered cognitive processes in women with PMS or PMDD, cognitive performance is not abnormal in women with PMDD compared to controls (Resnick et al. 1998, Morgan and Rapkin 2002).

# Treatment

## Treatment Goals

Treatment strategies have largely followed the etiologic theories. The most systematically studied treatments have been the "correction" of neurotransmitter dysregulation with antidepressant or anxiolytic medications, or the elimination of hormonal fluctuations with ovulation suppression treatments. Different treatment modalities may differentially treat specific symptom profiles, but treatment studies have rarely reported efficacy for specific anxiety, mood, and behavioral and somatic symptom profiles (Halbreich et al. 2006).

## Somatic Treatments

### Antidepressant Treatment

The treatment studies of SSRIs in PMDD have suggested similar efficacy rates to treatment studies of SSRIs in MDD, with 60–70% of women responding to SSRIs compared to approximately 30% of women responding to placebo, depending on how response is defined (Halbreich et al. 2006). In general, the effective SSRI doses are similar to the doses recommended for the treatment of MDD (Figure 68–2). A systematic review of randomized controlled trials (RCTs) of SSRIs reported that women with severe PMS or PMDD were approximately seven times more likely to respond to SSRIs compared to placebo (Dimmock et al. 2000, Wyatt et al. 2002). This review included 12 trials with continuous (daily) dosing of fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine and four trials with intermittent dosing (SSRI administered during the luteal phase only from ovulation to menses) of sertraline and citalopram. The efficacy of continuous and intermittent dosing was equivalent based on the RCTs evaluated (Dimmock et al. 2000). Since this systematic review, one study of 167 women with severe PMS and PMDD reported that continuous and intermittent dosing of sertraline were equivalent in efficacy and both were superior to placebo (Freeman et al. 2004). However, another study has suggested that while both continuous and intermittent paroxetine were superior to placebo for irritability, affect lability, and mood swings, intermittent paroxetine was less

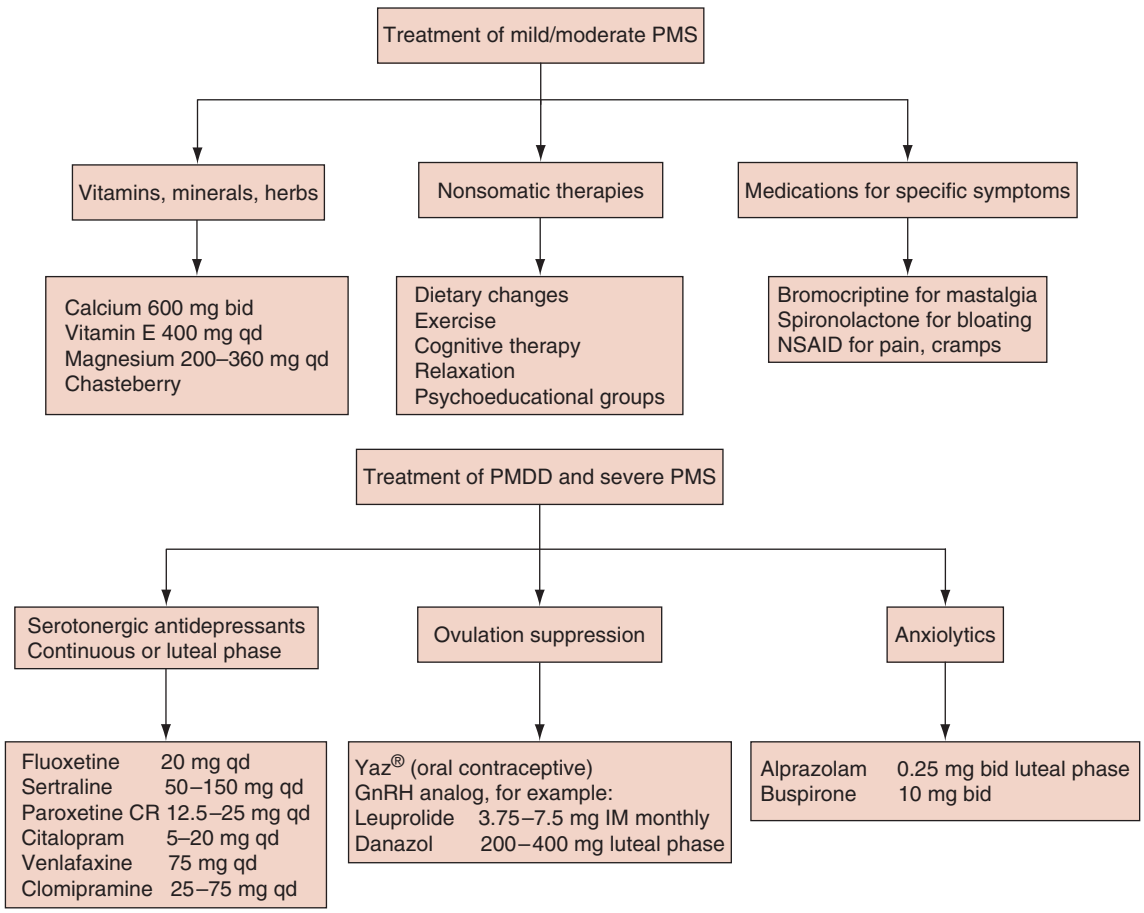



**Figure 68–2** *Treatment algorithm of premenstrual symptoms.*

effective than continuous paroxetine for depressed mood, low energy, food cravings, and somatic premenstrual symptoms in 167 women with PMDD (Landen et al. 2007). Thus, it remains a possibility that continuous SSRI dosing may be more effective than intermittent SSRI dosing for women with more severe and varied symptoms.

Two of the RCTs with continuous dosing included in the Dimmock and colleagues' review involved samples of more than 200 women. One RCT compared fluoxetine 20 mg/day, 60 mg/day, and placebo over 6 months in 277 women with PMS (Steiner et al. 1995). Fluoxetine 20 mg/day was better tolerated than 60 mg/day, although both dosages were more efficacious than placebo in reducing premenstrual emotional, behavioral, and physical symptoms. Surprising results from this study included the fast onset of action of fluoxetine and the improvement of physical premenstrual symptoms (Steiner et al. 1995). The other large RCT involved daily flexible-dose sertraline over 3 months, and the average dose of 110 mg/day was more effective than placebo in reducing premenstrual symptoms (Yonkers et al. 1997) and improving psychosocial functioning in 243 women (Pearlstein et al. 2000). Since this review, two large RCTs have demonstrated superior efficacy of continuous dosing of paroxetine CR 12.5 and 25 mg/day compared to placebo over 3 months in reducing premenstrual mood and physical symptoms in 313 (Cohen et al. 2004) and 359 (Pearlstein et al. 2005b) women with PMDD. In both studies, the 25-mg daily dose of paroxetine CR was more effective than the 12.5-mg daily dose in the improvement of premenstrual functioning and the reduction of premenstrual physical symptoms.

Since the review of Dimmock and colleagues, RCTs have also further established the efficacy of intermittent dosing, or luteal phase dosing, from ovulation to menses of fluoxetine, sertraline, and paroxetine CR. Fluoxetine 20 mg/day during the luteal phase only was superior to placebo in reducing premenstrual emotional and physical symptoms in 252 women with PMDD, while fluoxetine 10 mg/day during the luteal phase only was superior to placebo in reducing emotional symptoms but not physical symptoms (Cohen et al. 2002a). Sertraline 50–100 mg/day during the luteal phase only was superior to placebo for improving premenstrual emotional symptoms and impaired functioning, but not premenstrual physical symptoms in 200 women with PMDD (Halbreich et al. 2002). Another RCT reported that luteal phase dosing of paroxetine CR 12.5 and 25 mg/day were superior to placebo in reducing premenstrual symptoms in 366 women with PMDD (Steiner et al. 2005). Studies involving intermittent dosing have reported the absence of discontinuation symptoms when fluoxetine, sertraline, and paroxetine CR at the given doses were abruptly stopped the first day of menses. Intermittent dosing continues to be effective for symptoms that continue into the first few days of menses even when the antidepressant is discontinued on the first day of menses (Yonkers et al. 2005b). The United States Food and Drug Administration (FDA) has approved the use of continuous and intermittent dosing of fluoxetine, sertraline, and paroxetine CR for women with PMDD with specific dosage recommendations (see Figure 68–2).

The efficacy of intermittent dosing, as well as the finding from most continuous dosing SSRI trials that efficacy is achieved by the first treatment cycle, has suggested a more rapid and different mechanism of action of SSRIs in PMDD compared to its effect in MDD, which typically takes 3–6 weeks. As mentioned above, one hypothesis explaining the rapid improvement of premenstrual symptoms by SSRIs may be an increase in ALLO. This hypothesis suggests that it may not be necessary to begin the SSRI by ovulation. Some studies have evaluated the efficacy of SSRIs for "symptom onset" dosing of SSRIs, i.e., administering SSRIs from the postovulatory day that premenstrual symptoms appear until menses. Interestingly, weekly fluoxetine 90 mg administered just 1 week prior to the expected onset of menses was not superior to placebo, but fluoxetine 90 mg administered 2 weeks and 1 week prior to the expected onset of menses in 257 women with PMDD was reported to be superior to placebo in reducing premenstrual emotional symptoms and improving premenstrual functioning, but not premenstrual physical symptoms (Miner et al. 2002). Symptom-onset dosing of low-dose sertraline (25–50 mg/day) was reported to be superior to placebo in reducing premenstrual symptoms in 296 women with prospectively confirmed PMS (Kornstein et al. 2006). Preliminary studies in women with PMDD have suggested superiority of symptom-onset paroxetine compared to placebo (Yonkers et al. 2006) and efficacy with both symptom-onset and luteal phase escitalopram dosing, although luteal phase dosing was more effective for women with severe symptoms (Freeman et al. 2005).

Daily dosing of immediate release venlafaxine, an antidepressant with both serotonergic and noradrenergic action, was reported to be superior to placebo in the reduction of emotional and physical symptoms of PMDD in 157 women (Freeman et al. 2001b). Smaller RCTs have reported efficacy with clomipramine, a tricyclic antidepressant with largely serotonergic action, in daily dosing (Sundblad et al. 1992) and luteal phase dosing (Sundblad et al. 1993). The doses of clomipramine reported to be effective for PMS (25–75 mg/day) are lower than expected effective doses for MDD (see Figure 68–2). One RCT reported that nefazodone was not superior to placebo in PMS (Landen et al. 2001); however, increasing nefazodone in the luteal phase was reported to improve premenstrual exacerbation of MDD in a small crossover study (Miller et al. 2002). Three RCTs have compared SSRIs to nonserotonergic antidepressants and placebo, and each has reported specific efficacy of the SSRI over placebo and the nonserotonergic antidepressant. A large study compared sertraline to desipramine and placebo (Freeman et al. 1999), and two smaller studies compared paroxetine to maprotiline and placebo (Eriksson et al. 1995), and fluoxetine to bupropion and placebo (Pearlstein et al. 1997). The differential superiority of serotonergic antidepressants compared to noradrenergic antidepressants is compatible with the proposed serotonin dysfunction in PMDD.

Most SSRI trials have been 3 months or less in duration, and although a few open studies suggest maintenance of SSRI efficacy over 1–2 years, evidence-based long-term treatment recommendations do not exist. Clinically, many women note the recurrence of premenstrual symptoms after SSRI discontinuation and many women choose to take SSRIs over a long period of time. Studies are needed to identify whether or not some women develop tolerance to the SSRI and need a higher dose over time and whether or not some women stay in remission for a period of time

following SSRI discontinuation. Future studies also need to systematically compare the efficacy and predictors of response to symptom-onset, luteal phase, and continuous daily SSRI dosing in women with PMDD. In addition, systematic studies are needed of the "bumping up," or semi-intermittent dosing, of SSRIs in women with premenstrual exacerbation of an underlying depressive or anxiety disorder. In these women, SSRI dose is increased during the luteal phase and decreased back to the usual dose at menses (Steiner et al. 2006).

## Oral Contraceptives

Even though oral contraceptives (OCs) have been commonly prescribed by gynecologic and medical clinicians for the treatment of PMS, until recently there was minimal literature endorsing their efficacy. Surveys of population cohorts without defined PMS or PMDD have reported that OCs do not alter mood in most women, but a subset of women reports improvement of premenstrual symptoms, and another subset reports the production of adverse premenstrual symptoms (Sanders et al. 2001, Joffe et al. 2003). Two older RCTs in samples with confirmed PMS reported a lack of efficacy with monophasic or triphasic OCs (Backstrom et al. 1992, Graham and Sherwin 1992). A more recent RCT compared an OC containing ethinyl estradiol 30 μg and drospirenone 3 mg to placebo in 82 women with PMDD (Freeman et al. 2001a). Both the OC and placebo improved most premenstrual symptoms, and the OC was significantly more efficacious than placebo only in decreasing food cravings, increased appetite, and acne. However, an OC containing ethinyl estradiol 20 μg and drospirenone 3 mg, Yaz®, administered as 24 days of active pills followed by a 4-day hormone-free interval, has been reported to be superior to placebo in reducing premenstrual emotional and physical symptoms in a 3-month parallel study in 450 women with PMDD (Yonkers et al. 2005a) and in a crossover design study in 64 women with PMDD (Pearlstein et al. 2005a). In addition to the improvement noted on the daily symptom self-ratings, clinician ratings of PMDD demonstrated improvement, and self-ratings of quality of life improved with Yaz® compared to placebo. The efficacy of this particular OC may be due to its administration in a 24/4 regimen, which provides more stable hormone levels and reduces adverse symptoms that can occur during withdrawal bleeding, and may also be due to the unique antimineralocorticoid and anti-androgenic properties of drospirenone (Pearlstein et al. 2005a, Yonkers et al. 2005a). In 2006, Yaz® received FDA approval for the treatment of PMDD in women desiring oral contraception.

## Other Ovulation Suppression Treatments

Gonadotropin-releasing hormone (GnRH) agonists suppress ovulation by downregulating GnRH receptors in the hypothalamus, leading to decreased follicle-stimulating hormone (FSH) and LH release from the pituitary, resulting in decreased estrogen and progesterone levels. GnRH agonists are administered parenterally (e.g., subcutaneous monthly injections of goserelin, intramuscular monthly injections of leuprolide, and daily intranasal buserelin) (see Figure 68–2). Ten double-blind, placebo-controlled studies of GnRH agonists in PMS and PMDD have been published to date, and GnRH agonists are reported to be superior to placebo in eight of these studies (Backstrom et al. 2003, Pearlstein 2004). A meta-analysis of five of these published studies suggested an odds ratio of 8.66 that GnRH agonists will lead to improvement in premenstrual emotional and physical symptoms compared to placebo (Wyatt et al. 2004). After relief of PMS is achieved with a GnRH agonist, "add-back" hormone strategies have been investigated due to the undesirable medical consequences of the hypoestrogenic state resulting from prolonged anovulation. Although the "add-back" of estrogen and progesterone to goserelin (Leather et al. 1999) and leuprolide (Schmidt et al. 1998) has been reported to cause the reappearance of mood and anxiety symptoms, the meta-analysis concluded that "add-back" hormones did not reduce the efficacy of GnRH agonists (Wyatt et al. 2004). Since women with severe PMS and PMDD have an abnormal response to normal hormonal fluctuations (Schmidt et al. 1998), it is not surprising that some women may have the induction of mood and anxiety symptoms from the addition of gonadal steroids, reducing the benefit of the replacement strategy. Other suggested replacement strategies have included low-dose pulsed progesterone (Mitwally et al. 2002) and tibolone, a synthetic steroid with estrogenic, androgenic, and progestogenic properties (Di Carlo et al. 2001). More research is needed to evaluate the safety of long-term use of GnRH agonists and replacement hormonal treatments.

Danazol, a synthetic steroid, alleviates premenstrual symptoms when administered at 200–400 mg q.d. doses that induce anovulation (Hahn et al. 1995). A study with danazol 200 mg/day administered during the luteal phase only, not causing anovulation, reported that breast tenderness but not other premenstrual symptoms were reduced (O'Brien and Abukhalil 1999). Anovulation due to the administration of estrogen or progesterone throughout the cycle or from oophorectomy is not common treatment, largely due to the medical risks from the prolonged anovulatory state, leading to the same long-term health issues as with GnRH agonists. The small literature with estrogen or progesterone administered most of the cycle has yielded mixed reports (Epperson et al. 1999, Backstrom et al. 2003). Two small studies reported relief of intractable PMS with hysterectomy and bilateral oophorectomy (Casper and Hearn 1990, Casson et al. 1990). Hysterectomy with oophorectomy is considered a last-resort treatment option for women with severe PMDD who do not respond to more conventional treatments (Cronje et al. 2004, Studd 2006).

## Progesterone

The early assumption that PMS was due to a progesterone deficiency, which has never been substantiated, led to luteal phase progesterone being one of the earliest treatments of PMS in the literature. A systematic review of published double-blind, placebo-controlled randomized studies of luteal phase progesterone (given as vaginal suppositories or oral micronized tablets) and progestogens reported that there was no clinically meaningful difference between all progesterone forms and placebo, although there was a small statistically significant superiority of progesterone over placebo (Wyatt et al. 2001). There was a slight advantage for oral micronized progesterone, and the authors postulated that this may be due to the increase in ALLO levels derived from this form of progesterone. A more recent systematic

review concluded that due to the methodological shortcomings of previous studies, it is not possible to establish whether or not progesterone is helpful for PMS or PMDD (Ford et al. 2006).

### Other Medications

Alprazolam (administered during the luteal phase) has been reported to be superior to placebo in most studies (Smith et al. 1987, Harrison et al. 1990, Berger and Presser 1994, Freeman et al. 1995) but not all (Schmidt et al. 1993), and although it has a lower efficacy rate than SSRIs, it is effective for premenstrual emotional symptoms. Alprazolam should be tapered over the first few days of menses each cycle. An early (Rickels et al. 1989) and a more recent (Landen et al. 2001) study of buspirone 25 mg/day during the luteal weeks indicated some efficacy. Spironolactone has been reported to decrease premenstrual emotional and physical symptoms (Wang et al. 1995). Bromocriptine has been reported to decrease premenstrual breast tenderness (Andersch 1983). Previous studies reporting efficacy that deserve further study include nonsteroidal anti-inflammatory drugs (Mira et al. 1986), doxycycline (Toth et al. 1988), naltrexone (Chuong et al. 1988), and atenolol (Rausch et al. 1988).

### Herbal and Complementary Treatments

Evidence-based reviews of complementary treatments have reported that the strongest evidence exists for benefit with chasteberry, or *vitex agnus castus* (Stevinson and Ernst 2001, Domoney et al. 2003, Fugh-Berman and Kronenberg 2003, Girman et al. 2003, Dennehy 2006). In addition to the studies cited in these reviews, chasteberry has been reported to reduce premenstrual symptoms in an open study of 118 women with PMDD (Prilepskaya et al. 2006). Chasteberry and fluoxetine were compared in an RCT involving 41 women with PMDD, and although both treatments were effective, fluoxetine was better for emotional symptoms and chasteberry was better for physical symptoms (Atmaca et al. 2003). It is hypothesized that the benefit of chasteberry for premenstrual symptoms could be due to its being a dopamine agonist with possible reductions of FSH or prolactin levels (Girman et al. 2003). The evidence-based reviews concluded that RCTs have not suggested consistent benefit for *ginkgo biloba*, evening primrose oil, and homeopathic treatments but that initial positive RCTs suggest further study of massage, reflexology, biofeedback, and chiropractic manipulation. *Qi* therapy (an oriental complementary mind–body therapy involving energy flows) was reported to be superior to placebo in 36 women with prospectively confirmed PMS (Jang and Lee 2004). There have been positive open reports, but no RCTs, with acupuncture, yoga, guided imagery, photic stimulation, and hypericum (Pearlstein 2004).

### Dietary Supplementation

A large RCT compared calcium 600 mg b.i.d. and placebo in 466 women with PMDD (Thys-Jacobs et al. 1998). Calcium was reported to have a 48% efficacy rate for reducing the emotional and physical symptoms of the PMDD diagnostic criteria, except for fatigue and insomnia, compared to 30% for placebo. However, women with concurrent psychiatric illness were not clearly excluded, and other treatments except for analgesics were allowed. The efficacy of calcium was somewhat less in women who were also taking OCs. The results of this study were notable, and calcium deserves further study.

Several early studies were conducted with vitamin $B_6$ for the treatment of PMS, and a review of the early studies reported a lack of efficacy (Kleijnen et al. 1990). A meta-analysis of nine controlled trials including 940 women with PMS indicated only weak support for vitamin $B_6$ (50–100 mg/day) in reducing premenstrual symptoms (Wyatt et al. 1999). Two small RCTs have suggested efficacy with magnesium (Facchinetti et al. 1991, Walker et al. 1998), but other studies have failed to document magnesium deficiency in women with PMDD or superior efficacy of supplemental magnesium in reducing premenstrual mood symptoms compared to placebo (Khine et al. 2006). An RCT reported superior efficacy with trytophan compared to placebo in women with PMDD (Steinberg et al. 1999) and an early study that suggested efficacy for vitamin E deserves replication (London et al. 1987). An initial study evaluating the effect of fish oil on premenstrual symptoms suggested promise (Sampalis et al. 2003). Several trials have been conducted with multinutrients containing several vitamin and mineral components. As reviewed, results from these studies have been mixed and several of the supplements studied contained quantities of vitamins that exceeded daily recommended levels (Bendich 2000, Stevinson and Ernst 2001).

## Lifestyle Modifications and Psychosocial Treatments

Many lifestyle modifications and psychosocial treatments have been suggested for PMS. Lifestyle modifications are often suggested through self-help materials or in an individual or group psychoeducation format. One study reported that a weekly peer support and professional guidance group for four sessions was superior to waitlist control in terms of reducing premenstrual symptoms. The treatment consisted of diet and exercise regimens, self-monitoring and other cognitive techniques, and environment modification (Taylor 1999). Another study reported that a four-session group intervention over 18 weeks emphasizing diet, exercise, and a positive reframing of a woman's perceptions of her menstrual cycle experiences was superior to a control condition for reducing premenstrual symptoms (Morse 1999). Few studies have been conducted on individual lifestyle or psychosocial treatments to identify which components are most efficacious.

Dietary recommendations include decreased caffeine, frequent snacks or meals, reduction of refined sugar and artificial sweeteners, and increase in complex carbohydrates. Reduction of salt, foods with high saturated fat, and red meat has also been suggested. It is hypothesized that the maintenance of a steady serum glucose level through the ingestion of complex carbohydrates may decrease premenstrual food cravings and increase the availability of tryptophan in the brain for serotonin synthesis (Pearlstein 2004). To date, only two RCTs have examined a specific dietary regimen. Both RCTs compared a beverage containing simple and complex carbohydrates to an isocaloric placebo beverage that did not increase tryptophan availability. Both studies reported that the beverage containing simple

and complex carbohydrates was superior for reducing premenstrual dysphoria and other symptoms (Sayegh et al. 1995, Freeman et al. 2002).

Exercise is a frequently recommended treatment for PMS that has yet to be tested in a sample of women with prospectively confirmed PMS or PMDD. As reviewed, negative affect and other premenstrual symptoms improve with regular exercise in women in general (Pearlstein 1996, Scully et al. 1998). It is not clear if aerobic exercise is superior to nonaerobic exercise in terms of symptom relief. Relaxation has likewise had little systematic study in PMS; one RCT reported that relaxation therapy was superior to both symptom charting and leisure reading (Goodale et al. 1990). Cognitive therapy (CT) is consistently reported to be an effective treatment for women with PMS. Two studies in women with prospectively confirmed PMS reported superiority of individual CT over a waitlist control (Blake et al. 1998) and superiority of group CT over information-focused therapy (Christensen and Oei 1995) for reducing premenstrual symptoms. A more recent RCT examined the relative efficacy of fluoxetine 20 mg/day, 10 individual CT sessions, or their combination, in women with PMDD (Hunter et al. 2002a, 2002b). Efficacy rates at 6 months were comparable between the three treatments; however, at 1 year, women who had received CT were coping better than those who had received fluoxetine alone.

### Other Treatments

Although a crossover study reported that evening bright light for two premenstrual weeks decreased depression and tension (Lam et al. 1999), a meta-analysis of the few existent trials suggested a small effect size for bright light therapy (Krasnik et al. 2005). As reviewed, both light therapy and sleep deprivation may decrease premenstrual dysphoria by correcting abnormal circadian rhythms found in women with PMDD (Parry and Newton 2001).

### Special Factors Influencing Treatment

One of the unique aspects of treating women with severe PMS and PMDD is that symptoms, although cyclical, may be present for 40 years of a woman's life. Even though evidence-based long-term studies of efficacy and adverse effects are lacking, many women receive pharmacotherapy for PMDD for many years. One issue that arises with long-term antidepressant use is planned or inadvertent conception. Women and their partners need to have the risks of fetal exposure to the SSRIs, anxiolytics, and other pharmacologic treatments be part of the informed consent process. Some women with PMDD will discontinue medications prior to trying to conceive, other women will choose to stay on the medication with discontinuation once pregnancy occurs. Pharmacotherapy is often started postpartum when menses resume, and the risks of psychotropic medications with breastfeeding may need to be considered. Adverse effects are another issue that arises with long-term pharmacotherapy treatment for PMDD. Although many women are satisfied with the improvement of their premenstrual emotional and physical symptoms with SSRI use, they may have accompanying weight gain, decreased libido and delayed orgasm. Women may try different SSRIs and different dosing regimens in search of the long-term treatment option with the fewest adverse effects, but many women continue to have long-term adverse effects.

## Conclusion

Women with severe PMS and PMDD comprise a substantial proportion of menstruating women. These women have several symptomatic days each month that lead to disrupted relationships and decreased quality of life. Women presenting with premenstrual complaints should prospectively rate their symptoms for two menstrual cycles to rule out the presence of a concurrent psychiatric or medical disorder. Once the diagnosis of severe PMS or PMDD is confirmed, SSRI medication is considered the first-line treatment (American College of Obstetrics and Gynecology 2000, Altshuler et al. 2001, Steiner et al. 2006). SSRI medication may be effective when administered daily or intermittently (from ovulation to menses). Nutritional approaches, exercise, calcium, chasteberry, and CT may be appropriate as first treatments in mild cases, otherwise they may accompany medication treatment (Altshuler et al. 2001). Prior to the FDA approval of the first OC for PMDD, second-line treatment options included changing to a second SSRI, hormone therapy (such as GnRH agonists), or adding adjunctive anxiolytics or other medications targeted to specific symptoms (American College of Obstetrics and Gynecology 2000, Altshuler et al. 2001). Now the OC, Yaz®, containing 20 μg of ethinyl estradiol and 3 mg of dropsirenone, could be considered an alternative first-line treatment in women with PMDD desiring contraception. Future studies are still needed for women with severe PMS and PMDD, such as to identify predictors for which women may benefit from SSRIs versus hormonal strategies, to examine the possible benefit of SSRIs and a hormonal treatment, and to determine the optimal duration for medication treatment.

Clinical Vignette

Ms. A is a 34-year-old married woman who presents to her gynecologist for her first annual examination since giving birth to her third child 6 months before. Ms. A had always noted 2–3 days of irritability, mood swings, and cravings for chocolate before her menses prior to conceiving her third child, but she did not feel that these symptoms had interfered with her functioning. Since her menses has resumed in the past year, Ms. A has noted 10–14 days of tension, lack of patience, yelling at her husband and children, feeling more sensitive and overwhelmed, low energy, feeling more clumsy, increased appetite and cravings for sweets, desire to be alone, abdominal bloating, and breast tenderness. Ms. A tells her gynecologist that now the symptoms are interfering with her quality of life and her functioning as a homemaker and she requests medication for her symptoms. Ms. A has an unremarkable psychiatric or medical history.

Ms. A is given a self-help pamphlet that details the recommended dietary, exercise, and lifestyle modifications. She is also encouraged to chart her most troublesome symptoms daily. The gynecologist discusses pharmacological treatment options that Ms. A should consider once the daily charting is reviewed and the diagnosis of PMS or PMDD is confirmed, including SSRIs, an OC, and dietary supplements.

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CHAPTER

# 69 Anxiety Disorders: Panic Disorder With and Without Agoraphobia

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Panic Disorder with Agoraphobia
Panic Disorder without Agoraphobia

## Introduction

Descriptions of cases resembling agoraphobia date back thousands of years, appearing in the writings of Hippocrates and others. The term agoraphobia was, however, coined less than 150 years ago by Westphal (1871) to describe patients who appeared to be experiencing panic attacks accompanied by anticipatory anxiety and functional incapacitation when walking the streets of their neighborhoods. Westphal wrote that "it is not possible for them to walk across open spaces and through certain streets . . . they are troubled in their freedom and movement . . . they absolutely do not know the reasons for this fear . . . it comes by itself; a sudden occurrence, strange thing . . . [and] stimulation of alcohol makes it easier to overcome" (translated by Knapp and Schumacher 1988). Although this description alludes to a panic-like occurrence, Westphal did not make an association between panic attacks and agoraphobia. Freud (1894/1949), whose description of anxiety attacks holds many similarities (but also some notable differences) to contemporary descriptions of panic disorder, was the first to explicate this association. In describing agoraphobia, he specifically mentioned the role of panic, anticipatory anxiety, and escape concerns as central to the condition (Freud 1895/1949). Interestingly, the writings of

Clinical Vignette 1

Sandra B. was a 20-year-old college student who presented to a student health clinic reporting recurrent panic attacks. Her first attack occurred seven months earlier while smoking marijuana at an end-of-term party. At the time she felt depersonalized, dizzy, short of breath, and her heart was beating wildly. Sandra had an overwhelming fear that she was going crazy. Friends took her to a nearby hospital emergency department where she was given a brief medical evaluation, reassured that she was simply experiencing anxiety, and given a prescription for lorazepam. In the following months, Sandra continued to experience unexpected panic attacks and became increasingly convinced that she was losing control of her mind. Most of her panics occurred unexpectedly during the day, although they sometimes also occurred at night, violently wrenching her from a deep, dreamless sleep. Sandra began avoiding a variety of substances (e.g., alcohol, marijuana, coffee) and activities (e.g., aerobics classes) because they produced bodily sensations, such as palpitations and dizziness, which she feared. She believed that if these sensations became too intense then she might "tip over the edge" into insanity. Increasingly, Sandra also began to avoid shopping malls, lecture halls, and other public places for fear that she would have a panic attack and lose control. Whenever she contemplated entering these situations, she became highly anxious and sometimes panicked if she actually entered them. As a result of avoiding lectures, her grades began to fall and she was at risk for failing her courses. She became increasingly depressed and, at times, contemplated suicide as a way of ending her misery. At the urging of a roommate, she eventually sought help from the student health clinic.

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both Westphal and Freud allude to mechanisms and processes that today comprise part of modern psychological and biological models of panic disorder. These models are discussed in detail in the sections that follow below.

Reference to panic-like symptoms can also be found in the writings about popular historical figures such as Darwin and in the cardiology literature. Some of the terms used in this literature began to appear in conjunction with DaCosta's work on American Civil War soldiers (e.g., irritable heart, DaCosta's syndrome, soldiers heart) and subsequent observations of those participating in World Wars I and II (e.g., effort syndrome, neurocirculatory asthenia, cardiac neurosis). The early cardiology literature is replete with attempts to link panic-like symptoms to some form of cardiac pathology, most notably mitral valve prolapse. Research has for the most part failed to support this hypothesis (Sivaramakrishnan et al. 1994).

The origin of the panic disorder construct as a separate diagnostic entity was influenced by the work of a number of researchers but none so much as Donald Klein in the late 1950s and early 1960s (Klein 1980). Klein observed that, contrary to expectation, a subgroup of patients with anxiety neurosis did not improve on chlorpromazine (an antipsychotic sedative) and in some cases became worse. When he gave this subgroup imipramine, a compound newly introduced in the 1950s, which was derived from modifications to chlorpromazine, marked improvements were observed. Prior to taking imipramine these patients, unlike those who were responsive to chlorpromazine, had been experiencing rapid rushes of terror, racing hearts, and other physical sensations, which prompted them to rush to the nurses station with reports that they were about to die. On the basis of this differential drug response, Klein concluded that imipramine was effective against these seemingly spontaneous episodes of panic and, importantly, that these attacks were distinct from other forms of anxiety. He also suggested that agoraphobia was a consequence of spontaneous panic attacks.

Due in large part to the pioneering work of Klein and his colleagues, anxiety neurosis was later divided in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) (American Psychiatric Association 1980) into generalized anxiety disorder and panic disorder. Diagnosis of panic disorder required a minimum of three panic attacks that were of sudden onset, involved at least 4 of 12 symptoms, and occurred within a three-week period. Phobic neurosis was divided into simple phobia, social phobia, and agoraphobia. Agoraphobia without panic attacks was considered to be conceptually distinct from agoraphobia with panic attacks.

The distinction between agoraphobia with and without panic was dropped in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (American Psychiatric Association 1987). Despite evidence that it is rare (Grant et al. 2006, Kessler et al. 2006), agoraphobia without a history of panic disorder remained a separate codable diagnosis. The DSM-III-R was restructured to include separate diagnoses for panic disorder without agoraphobia and panic disorder with agoraphobia. Diagnosis of panic disorder required (1) at least 4 panic attacks (of sudden onset and comprising at least four of 13 symptoms) in a four-week period or (2) one or more unexpected attacks followed by at least one month of persistent worry over subsequent attacks. Changes in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (American Psychiatric Association 1994) and Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), as described in detail below, involved removal of the criteria sets for panic attacks and agoraphobia from the criteria set for panic disorder and refinements to the definition of panic disorder necessitating both recurrent unexpected attacks and associated persistent worry or behavioral change.

## Diagnosis

### Definition and Diagnostic Features

#### DSM-IV-TR Definition and Diagnostic Criteria

According to DSM-IV-TR, panic disorder is defined by recurrent and unexpected panic attacks. At least one of these attacks must be followed by one month or more of

1. persistent concern about having more attacks,
2. worry about the implications or consequences of the attack, or
3. changes to typical behavioral patterns (e.g., avoidance of work or school activities) as a result of the attack.

In addition, the panic attacks must not stem solely from the direct effects of illicit substance use, medication, or a general medical condition (e.g., hyperthyroidism, vestibular dysfunction) and are not better explained by another mental disorder (e.g., such as social phobia for attacks that occur only in social situations). A diagnosis of panic disorder with agoraphobia is warranted when the criteria for panic disorder are satisfied and accompanied by agoraphobia (i.e., anxiety about being in a place or a situation that is not easily escaped or where help is not easily accessible if panic occurs).

Although panic attacks are a cardinal feature of panic disorder and, in combination with agoraphobia, are essential to a diagnosis of panic disorder with agoraphobia, the criteria sets for panic attacks and for agoraphobia are listed separately as standalone noncodable conditions that are referred to by the diagnostic criteria for panic disorder and agoraphobia without history of panic disorder. Notwithstanding, accurate diagnosis is difficult without a sufficient understanding of these features. Tables 69–1 and 69–2 show the DSM-IV-TR criteria for panic attack and agoraphobia, respectively. While the criteria for agoraphobia are generally straightforward, panic attacks can be difficult to understand.

Several studies have shown that people report having what they consider to be a panic attack during or in association with actual physical threat (i.e., a true alarm situation; Barlow 2004). It is, however, important to distinguish between a fear reaction in response to actual threat and a panic attack. In an attempt to do so, the DSM-IV-TR has clarified that panic attacks occur "in the absence of real danger" (Barlow 2004, p 430). Such attacks involve a paroxysmal occurrence of intense fear or discomfort accompanied by a minimum of 4 of the 13 symptoms shown in Table 69–1. The DSM-IV-TR recognizes three characteristic types of panic attacks, including those that are *unexpected* (i.e., not associated with an identifiable internal or external trigger and appear to occur "out of

**Table 69–1 Definition and Criteria for Panic Attack**

A panic attack is a discrete period of intense fear or discomfort in the absence of real danger that develops abruptly, reaches a peak within 10 min, and is accompanied by four (or more) of the following symptoms:

(1) Palpitations, pounding heart, or accelerated heart rate
(2) Sweating
(3) Trembling or shaking
(4) Sensations of shortness of breath or smothering
(5) Feeling of choking
(6) Chest pain or discomfort
(7) Nausea or abdominal distress
(8) Feeling dizzy, unsteady, light-headed, or faint
(9) Derealization (feelings of unreality) or depersonalization (being detached from oneself)
(10) Fear of losing control or going crazy
(11) Fear of dying
(12) Paresthesias (numbness or tingling sensations)
(13) Chills or hot flushes

Adapted from American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. American Psychiatric Association, Washington DC.

**Table 69–2 Criteria for Agoraphobia**

A. Agoraphobia is characterized by anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations, such as being outside the home alone, being in a crowd, standing in a line, being on a bridge, or traveling in a motor vehicle.
B. The situations are avoided or are endured with marked distress or worry about having a panic attack or panic-like symptoms. Confronting situations is aided by the presence of a companion.
C. The anxiety or avoidance is not better accounted for by another mental disorder.

Adapted from American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. American Psychiatric Association, Washington DC.

the blue"), *situationally bound* (i.e., almost invariably occur when exposed to a situational trigger or when anticipating it), and *situationally predisposed* (i.e., usually, but not necessarily, occur when exposed to a situational trigger or when anticipating it). The term *limited symptom attacks* is used to refer to panic-like episodes comprising fewer than four symptoms.

Although unexpected panic attacks are required for a diagnosis of panic disorder, not all panic attacks that occur in panic disorder are unexpected. The occurrence of unexpected attacks can wax and wane and over the developmental course of the disorder they tend to become situationally bound or predisposed. Moreover, unexpected panic attacks as well as those that are situationally bound or predisposed can occur in the context of other psychiatric disorders, including all of the other anxiety disorders (e.g., a person with social phobia might have an occasional unexpected panic attack without the other features required to diagnose panic disorder; a dog phobic might panic whenever a large dog is encountered) (Barlow 2004) and some general medical conditions. A clear understanding of the distinction between types of panic attacks outlined in the DSM-IV-TR provides a foundation for diagnosis and differential diagnosis (discussed below). As described by Taylor (2000), however, consideration of other characteristics of panic—including duration of attacks, frequency of attacks, number and intensity of symptoms, nature of catastrophic thinking, and mechanism responsible for termination of an attack—can be important in identifying exacerbating and controlling factors.

**DSM-IV-TR Criteria**

**Panic Disorder with Agoraphobia**

A. Both (1) and (2):
  (1) recurrent unexpected panic attacks
  (2) at least one of the attacks has been followed by one month (or more) of one (or more) of the following:
    (a) persistent concern about having additional attacks
    (b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, going crazy)
B. The presence of agoraphobia.
C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive–compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

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**DSM-IV-TR Criteria**

**Panic Disorder without Agoraphobia**

A. Both (1) and (2):
  (1) recurrent unexpected panic attacks

(2) at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
  (a) persistent concern about having additional attacks
  (b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, going crazy)

B. Absence of agoraphobia.

C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive–compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

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## Assessment

The most comprehensive and accurate diagnostic information emerges when the clinician uses open ended questions and empathic listening, combined with structured inquiry about specific events and symptoms (American Psychiatric Association 1995). Useful structured interviews include the *Structured Clinical Interview for DSM-IV-TR* (SCID-IV) (First et al. 1996) and the *Anxiety Disorders Interview Schedule for DSM-IV-TR* (ADIS-IV; Di Nardo et al. 1994). A complete assessment for panic disorder also includes a general medical evaluation (American Psychiatric Association 1995), consisting of a medical history, review of organ systems, physical examination, and blood tests. A general medical evaluation is important for identifying general medical conditions that mimic or exacerbate panic attacks or panic-like symptoms (e.g., seizure disorders, cardiac conditions, pheochromocytoma). These disorders should be investigated and treated before contemplating a course of panic disorder treatment. It is also important to rule out the other anxiety disorders and major depressive disorder as primary factors in the person's panic attacks and avoidance prior to initiating treatment for panic disorder. A decision tree for assessment and differential diagnosis of patients presenting with panic attacks is presented in Figure 69–1.

Diagnostic information can be usefully supplemented by short self-report questionnaires to assess the severity of symptoms and other variables (Taylor 2000). The *Beck Depression Inventory* (Beck and Steer 1987) and *Beck Anxiety Inventory* (Beck and Steer 1993) are quick, reliable, and valid measures that can be administered at the start of each treatment session to assess the severity of past-week general anxiety and depression. The *Anxiety Sensitivity Index* (Peterson and Reiss 1992) is another useful short questionnaire that can be used to gauge the severity of the patient's fear of bodily sensations. Scores on this scale can be used to assess whether treatment is altering the patient's tendency to catastrophically misinterpret bodily sensations. This scale has good reliability and validity, is sensitive to treatment-related effects, and its posttreatment scores predict who is likely to relapse after panic treatment (Taylor 1999).

Another useful questionnaire to monitor treatment progress is the *Panic and Agoraphobia Scale* (Bandelow et al. 2000). This 13-item scale was designed as a short, sensitive measure for treatment outcome studies. The patient is asked to rate the past-week frequency and/or severity of the following: (1) panic attacks, (2) agoraphobia, (3) anticipatory anxiety (i.e., worry about having a panic attack), (4) panic-related disability in various areas of functioning, and (5) worry about the health-related implications of panic (e.g., worry that panic attacks will lead to a heart attack). The Panic and Agoraphobia Scale has good reliability and validity and is sensitive in detecting treatment-related change (Bandelow et al. 2000). It has the advantage of providing a broad assessment of many features of panic disorder and agoraphobia. A limitation is that it does not distinguish between full and limited symptom panic attacks or among the types of panics (i.e., unexpected, situationally bound, situationally predisposed). When asked to recall their attacks, patients may have difficulty making these distinctions. A clinical interview is needed to provide this information.

To gain more detailed information on panic attacks, clinicians and clinical researchers are increasingly including some form of prospective monitoring in their assessment batteries. The most widely used are the *panic attack records*. The patient is provided with a definition of a panic attack and then given a pad of panic attack records that can be readily carried in a purse or pocket. The patient is instructed to carry the records at all times and to complete one record (sheet) for each full-blown or limited symptom attack, soon after the attack occurs. Variants on the panic diaries developed by Barlow and colleagues (e.g., Rapee et al. 1990) are among the most informative and easy to use. A version is shown in Figure 69–2, which shows details of one of Sandra's panic attacks. These records are then reviewed during treatment sessions to glean information about the links among beliefs, bodily sensations, and safety behaviors, and to assess treatment progress.

Sandra reported that the panic attack summarized in Figure 69–2 occurred when she was in a neighborhood supermarket. As she walked down the aisle she looked at the long rows of fluorescent lights and then began to feel mildly depersonalized (see Taylor 2000, Chapter 4, for a discussion of the effects of fluorescent lighting and other environmental triggers on depersonalization). Upon noticing this

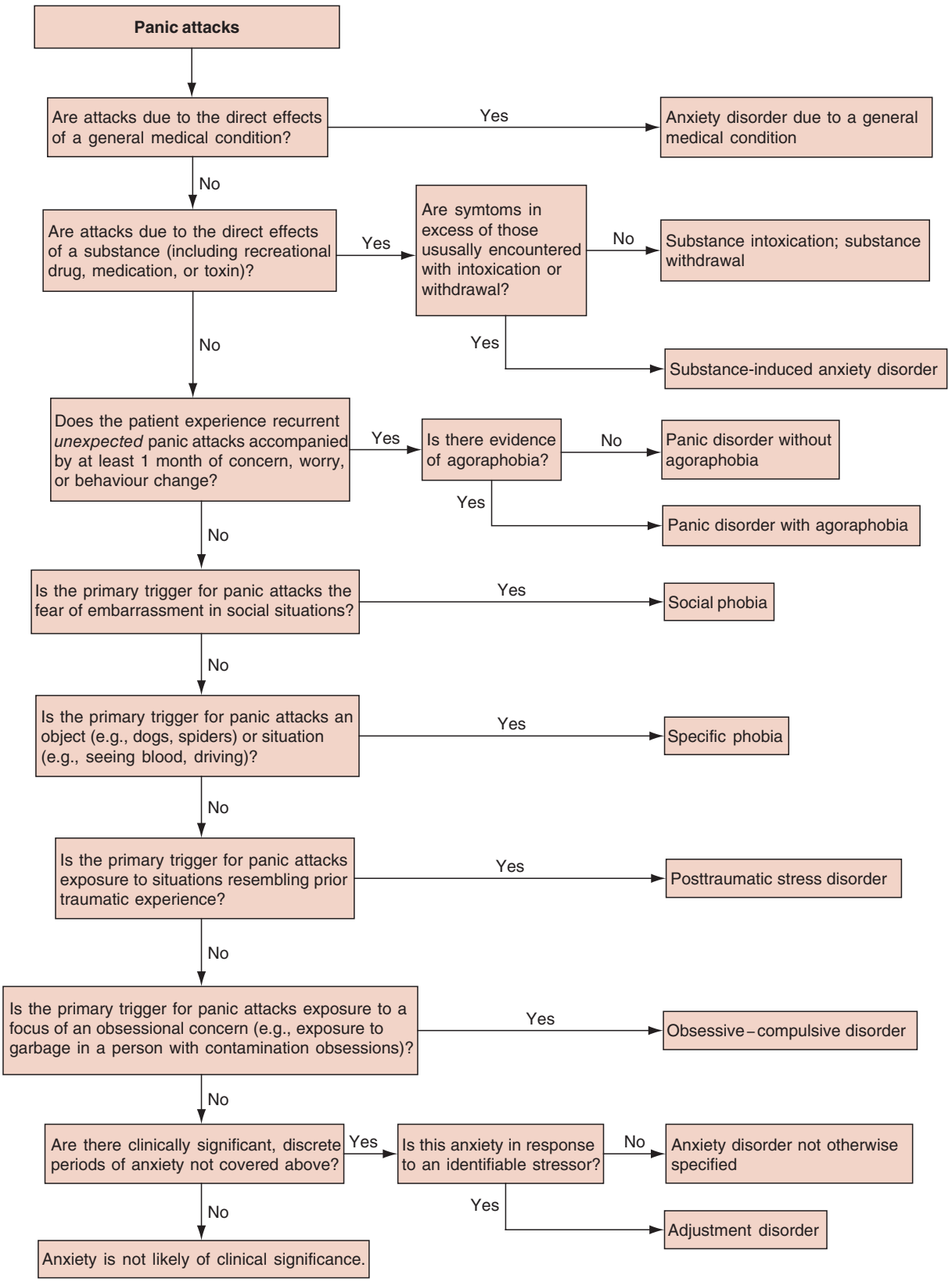



**Figure 69–1** *A decision tree for assessment of patients presenting with panic attacks.*

sensation, she began to increasingly worry that the depersonalization might become so intense that she would lose all contact with reality, to the point that she would be permanently insane. This greatly frightened her and led to an increase in the intensity of arousal sensations. In an effort to reduce the intensity of the feared depersonalization she averted her gaze from the lights and began studying the list of ingredients on cereal boxes. This distracting safety

PANIC ATTACK RECORD

NAME: **Sandra.B.**

DATE: **Oct 2** TIME: **4pm** DURATION (min): **15**

WITH: SPOUSE _____ FRIEND _____ STRANGER _____ ALONE ✓

STRESSFUL SITUATION: YES / NO EXPECTED: YES / NO

MAXIMUM ANXIETY (CIRCLE)

0 -------- 1 -------- 2 -------- 3 -------- 4 -------- 5 -------- 6 -------- 7 -------- 8
NONE MODERATE EXTREME

SENSATIONS (CHECK):

| | | | | | |
|---|---|---|---|---|---|
| POUNDING HEART | ✓ | SWEATING | ✓ | HOT/COLD FLASH | ✓ |
| TIGHT/PAINFUL CHEST | ✓ | CHOKING | ____ | FEAR OF DYING | ____ |
| BREATHLESS | ✓ | NAUSEA | ____ | FEAR OF GOING CRAZY | ✓ |
| DIZZY | ✓ | UNREALITY | ✓ | FEAR OF LOSING CONTROL | ✓ |
| TREMBLING | ____ | NUMB/TINGLE | ✓ | | |

THOUGHTS OR MENTAL IMAGES AT THE TIME (DESCRIBE):

**I'm losing contact with reality**

**Figure 69–2** *A completed panic attack record for Sandra.*

behavior calmed her down and reduced the feared depersonalization to the point that she was able to make her way to the express checkout counter and leave with the grocery items she had collected.

Note that the panic attack record serves as a useful memory aid to help patients recall the details and circumstances of their panic attacks. This example shows how the panic attack record helped Sandra recall that she used distraction as a safety behavior. Armed with this information, the therapist could set up exposure exercises to help Sandra learn whether distraction was essential to protecting her from the effects of depersonalization.

## Epidemiology

The lifetime prevalence rate for unexpected panic attacks in the general population ranges between 4 and 12% (Kessler et al. 2006). Investigations of unexpected panic attacks in college student samples using self-report methodology have revealed similar rates, ranging from approximately 5-11% (Asmundson and Norton 1993). The most recent general population estimate of the lifetime prevalence rate for any panic attack, whether unexpected or situationally cued, is 28% (Kessler et al. 2006). The one-year prevalence for any panic attack, as measured in college student samples, is also 28% (Norton et al. 1992). Agoraphobia has a lifetime prevalence of approximately 2%, and rarely occurs without a history of panic disorder (Grant et al. 2006, Kessler et al. 2006).

Estimates of the lifetime prevalence of panic disorder (with or without agoraphobia) range between approximately 1 and 5% in the general population (Grant et al. 2006, Kessler et al. 2006). Weissman et al. (1997) have demonstrated that despite some minor variation, lifetime prevalence rates are generally consistent around the world. One-year prevalence rates in the general community also vary slightly from lifetime rates, being between 0.2 and 2.1% (Grant et al. 2006, Weissman et al. 1997). In treatment seeking individuals, the prevalence of panic disorder is considerably higher. Approximately 10% of patients in mental health clinics and between 10 and 60% in various medical specialty clinics (e.g., cardiology, respiratory, vestibular) have panic disorder (e.g., Katon 2006). Panic disorder with agoraphobia is more common than panic disorder without agoraphobia in clinical samples (American Psychiatric Association 2000).

## Comorbidity Patterns

Lifetime comorbidity (i.e., the co-occurrence of two or more disorders at any point in a person's life, regardless of whether or not they overlap) in panic disorder is common, with over 80% of community-dwelling and treatment-seeking patients having had symptoms meeting diagnostic

threshold for at least one other disorder (Kessler et al. 2006). Recent data suggest that the prevalence of lifetime comorbidity in panic disorder with agoraphobia is 100% (Kessler et al. 2006). Comorbidity can pose considerable challenge to treatment. Below, we provide a summary review of the conditions that most often co-occur with panic disorder (also see Table 69–3). The reader is referred to Taylor (2000) for detailed discussion of the various comorbidity models and how they account for the co-occurrence of other disorders with panic disorder.

**Table 69–3 Comorbidity Data**

| | |
|---|---|
| Lifetime comorbidity rate | > 80% |
| Common comorbid conditions | Other anxiety disorders |
| | Major depression |
| | Somatoform disorders |
| | Pain-related disorders |
| | Substance use disorders |
| | Personality disorders |

### Other Anxiety Disorders

The rates of lifetime comorbidity between panic disorder and other anxiety disorders, although variable across epidemiological studies, are high. The most common comorbid anxiety disorders are social phobia and generalized anxiety disorder (15–30%), specific phobia (2–20%), obsessive compulsive disorder (10%), and posttraumatic stress disorder (2–10%) (American Psychiatric Association 2000). To date, there are no studies that have reported comorbid panic disorder and acute stress disorder. The most parsimonious explanation of high comorbidity between panic disorder and the other anxiety disorders is that they share a common diathesis.

### Major Depressive Disorder

Epidemiological studies indicate that major depressive disorder occurs in up to 65% of patients with panic disorder at some point in their lives. In approximately two-thirds of these cases, the symptoms of depression develop along with, or secondary to, panic disorder (American Psychiatric Association 2000). However, since depression precedes panic disorder in the remaining third (Breier et al. 1984), depressive symptoms co-occurring with panic disorder cannot be considered simply as a demoralized response to paroxysms of anxiety. While the risk of developing secondary depression appears to be more closely associated with the severity of agoraphobia than with the severity or frequency of panic attacks, this may be a confound of misdiagnosing some behavioral manifestations of depression as agoraphobia (Taylor 2000). Panic disorder and depression do not appear to be identical disorders (Stein and Uhde 1990) and their co-occurrence may be due to a shared diathesis or mutual exacerbation of symptoms.

### Somatoform and Pain-Related Disorders

Somatoform and pain-related disorders are frequently comorbid with panic disorder. For example, hypochondriasis has been diagnosed in approximately 20% of panic disorder patients attending general medical clinics and in almost 50% of those attending anxiety disorders clinics (Noyes 2001). Acute and chronic musculoskeletal pain (i.e., pain that persists for six months or longer), respectively, are reported by approximately 85 and 40% of panic disorder patients attending anxiety disorders clinics (Asmundson et al. 2001). Irritable bowel syndrome, a condition characterized persistent abdominal pain and defecation difficulties, co-occurs in 17-41% of treatment seeking panic disorder patients (Lydiard et al. 1994; Noyes et al. 1990). Emerging evidence suggests that comorbidity between panic disorder and both somatoform and pain-related disorders may be best explained by a shared diathesis model (e.g., Asmundson et al., in press).

### Substance Use Disorders

As illustrated in the case of Sandra, panic disorder can be precipitated by the use of psychotropic drugs, with the risk of developing panic disorder increasing with chronic drug use (Louie et al. 1996). Alcohol has been identified as playing a precipitating, maintaining, and aggravating role in panic disorder. The 6-month prevalence of alcohol abuse or dependence in panic disorder has been reported to be 40% in men and 13% in women (Leon et al. 1995). These rates are higher than those observed in people with other anxiety disorders and those with no anxiety disorder (Leon et al. 1995). Although alcohol problems have been reported to precede panic disorder in a majority of cases (Otto et al. 1992), most reports indicate that alcohol problems develop secondary to panic disorder, often as a means of self-medication (Bibb and Chambless 1986). Those having panic disorder with agoraphobia appear to be at greater risk for comorbid alcohol abuse or dependence than those without agoraphobia (Thyer et al. 1986).

### Personality Disorders

Lack of reliable assessment instruments for personality disorders as well as overlapping diagnostic criteria necessarily limit the degree of confidence in reports of comorbidity with panic disorder. Notwithstanding, 40-50% of panic disorder patients have been reported to qualify for one or more personality disorders (American Psychiatric Association 1998), a rate which exceeds that of approximately 10% observed in community control samples (Lenzenweger et al. 2007). The most commonly reported co-occurring personality disorders are avoidant, dependant, and histrionic personality disorders (Taylor and Livesley 1995). These disorders do not co-occur uniquely with panic, also being common in patients with depression and other anxiety disorders, and they often persist despite remission of panic symptoms (Mavissakalian and Hamann 1992). Reasons for comorbidity between panic and personality disorders currently remain unclear.

## Course

Panic disorder symptoms may wax and wane but, if left untreated, the typical course is chronic (American Psychiatric Association 2000). Data from a sample of patients assessed and treated through the Harvard/Brown Anxiety Disorders Research Program and followed prospectively over a 5-year period indicated remission rates in both men and women to be 39% (Yonkers et al. 1998). In general, among those receiving tertiary treatment, approximately 30% of

patients have symptoms that are in remission, 40–50% are improved but still have significant symptoms, and 20–30% are unimproved or worse at 6–10 years follow-up (American Psychiatric Association 2000).

### Costs

Panic disorder with or without agoraphobia is associated with impaired occupational and social functioning and poor overall quality of life (Kessler et al., 2006, Leon et al. 1995). People with panic disorder, compared to people in the general population, report poorer physical health (Markowitz et al. 1989). Panic disorder is a leading reason for seeking emergency department consultations (Weissman 1991) and a leading cause for seeking mental health services, surpassing both schizophrenia and mood disorders (Boyd 1986). Panic disorder exceeds the economic costs associated with many other anxiety disorders such as social phobia, generalized anxiety disorder, and obsessive–compulsive disorder (Greenberg et al. 1999). The high medical costs are partly because panic disorder patients quite often present to their primary care physician or hospital emergency departments, thinking they are in imminent danger of dying or "going crazy" (Katerndahl and Realini 1995). In these settings, patients may undergo a series of extensive medical tests before panic disorder is, if ever, finally diagnosed. Ruling out general medical conditions is good clinical practice but the process contributes substantially to the costs that panic disorder places on health care systems.

### Differential Diagnosis

Panic disorder is not diagnosed under several conditions, despite the occurrence of panic attacks. Panic disorder is not diagnosed if panic attacks present only as a feature of other mental disorders; for example, as in situationally bound or situationally predisposed panic attacks that often occur in the other anxiety disorders. When it can be established that panic attacks occur only in situations associated with another anxiety disorder, such as in social phobia when cued by social situations or in posttraumatic stress disorder when cued by trauma-related reminders, then the panic attacks should be attributed to the other disorder. Likewise, if panic attacks are determined to occur as the result of physiological consequences of a general medical condition (e.g., hyperthyroidism, pheochromocytoma, vestibular dysfunction, cardiac conditions) or of illicit substance use, then panic disorder is not diagnosed (American Psychiatric Association 2000). Instead, diagnoses of anxiety disorder due to a general medical condition, in case of the former, or substance-induced anxiety disorder, in case of the latter, may be appropriate. Because substances are often used as a means of self-medicating for panic attacks, a detailed history can aid in determining whether panic attacks preceded excessive uses of substances, in which case diagnoses of both panic disorder and substance dependence or abuse may be appropriate.

### Differences in Developmental, Gender, and Cultural Presentations

Age of onset for panic disorder is distributed bimodally, typically developing between 15 and 19 or 25 and 30 years (Ballenger and Fyer 1996). The clinical features of panic disorder, such as number and severity of symptoms, are much the same across the sexes (Oei et al. 1990). However, women are diagnosed with panic disorder more than twice as often as men (Kessler et al. 2006; Weissman et al. 1997). Recent research indicates that women are more likely to have panic disorder with agoraphobia and that they are more likely to have recurrence of symptoms after remission of their panic attacks than are men (Yonkers et al. 1998). Men, on the other hand, are more likely to have panic disorder without agoraphobia (Yonkers et al. 1998) and are more likely to self medicate with alcohol than are women (Cox et al. 1993). The literature remains unclear as to why these sex differences exist but alludes to the possible role of biological and/or socialization factors (Bekker 1996, Yonkers 1994). Socially prescribed gender roles may be important, such as the widely held social expectation that women should assume the role of homemaker. Consistent with this, agoraphobia is most likely to develop in people who do not need to leave the house in order to work (Mineka and Zinbarg 2006). This may encourage or perpetuate agoraphobic fear and avoidance because the person is not required to confront and thereby overcome their fears.

Panic disorder has been identified across many different cultures, although the expression of the disorder may vary from culture to culture. For example, people with panic disorder in some cultures may be more likely to emphasize the somatic symptoms of their panic attacks, while being reluctant to report cognitive symptoms such as fears of going mad or of losing control. Recent findings suggest that being Native American increases risk, while being Asian, Hispanic, or black decreases risk (Grant et al. 2006).

## Etiology and Pathophysiology

### Psychological Factors

#### Cognitive Model—The Vicious Cycle

There are several contemporary cognitive models of panic disorder, which for the most part, are based on variations of the "fear of anxiety" construct. Goldstein and Chambless (1978) proposed that fear of anxiety arises through the association of interoceptive cues with panic attacks. In other words, people with panic disorder are thought to learn to fear the recurrence of aversive panic episodes and thereby develop a fear of panic-related symptoms. Refuting the premise that fear of anxiety develops from the experience of panic attacks, Clark (1986) posited that panic attacks are the product of a tendency to *catastrophically misinterpret* autonomic arousal sensations that occur in the context of nonpathological anxiety (as well as physical illness, exercise, and ingestion of certain substances). Reiss et al. (1991), incorporating components of the Goldstein and Chambless and Clark models, proposed that panic attacks arise as a consequence of both

1. a predispositional tendency to catastrophically misinterpret and respond with fear to the benign arousal sensations, and
2. a learned fear of anxiety that is maintained by the experience of panic episodes.

More recently, Bouton et al. (2001) have described a variant of the original fear of anxiety model, suggesting that panic disorder develops when exposure to panic attacks

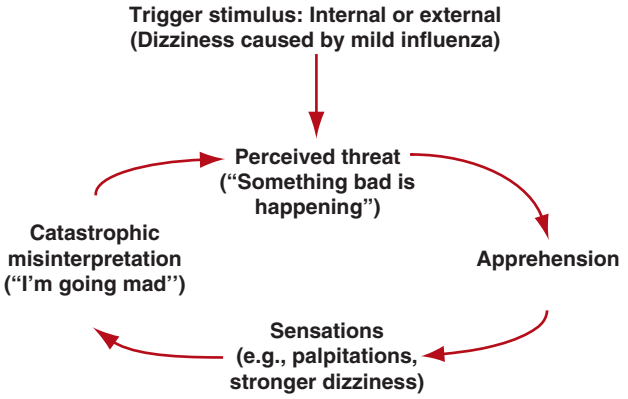



**Figure 69–3** *Application of the cognitive model to illustrate one of Sandra's panic attacks.*

conditions a person to respond with anticipatory anxiety (and sometimes with panic) to internal arousal and contextual cues. While each of these models has proven fruitful in research and treatment contexts, we focus below on the model of Clark (1986).

As described above, Clark (1986) proposes that panic attacks arise from the catastrophic misinterpretation of benign arousal sensations. To illustrate the cognitive processes proposed to underlie panic attacks, consider Sandra's experience during one of her many attacks. In this instance, she had dizziness sensations stemming from influenza, perceived them as threatening, became aroused, misinterpreted the sensations as being indicative that she was losing her mind, became further aroused with increasing dizziness, had further thoughts of going mad, and spiraled into panic. This vicious cycle is shown in Figure 69–3.

The vicious cycle model makes several assumptions. First, while recognizing that initial panic attacks may be caused by other factors (e.g., drug-related autonomic surges), it assumes that people prone to panic disorder have an enduring tendency to catastrophically misinterpret benign arousal sensations. Second, it assumes that misinterpretations can occur at the conscious and unconscious level (Clark 1988). Third, the cycle can be entered into at any point. For example, the cycle can be initiated by a contextual trigger, such as influenza-related dizziness in the case of Sandra, or simply by having catastrophic thoughts about bodily sensations. Fourth, physiological changes are viewed as one of the several components in a process, rather than as a pathogenic mechanism.

Cognitive models can also account for agoraphobia. Agoraphobia has long been regarded as a product of operant conditioning (Marks 1987). As noted above, it most often develops as a consequence of panic attacks. These attacks typically occur in particular situations (e.g., when in line at a shopping mall, when driving) and motivate the person to avoid or escape these situations. The avoidance and escape behaviors are negatively reinforced by the reduction of aversive autonomic arousal and other anxiety-related sensations. Cognitive factors such as expectations that an attack will be imminent and harmful and that coping will be ineffective play a significant role by influencing and maintaining avoidance behavior (Taylor and Rachman 1994).

A growing body of literature supports the vicious cycle model. Thoughts of imminent catastrophe have been identified as triggers of panic attacks (Taylor 2000). Patients with panic disorder relative to healthy and patient controls have been shown to be

1. characterized by strategic and automatic information processing (i.e., memory, attention) biases for physical threat cues (Mathews and MacLeod 2005),
2. more accurate, in some instances, at detecting body sensations (Zoellner and Craske 1999),
3. more likely to report fear of somatic sensations and beliefs in their harmful consequences (Taylor 1999), and
4. more susceptible to the influence of instructional manipulations of control in response to pharmacological panic provocation challenges, panicking less often under the illusion of greater control in some but not all cases (Barlow 2004).

Research shows that treatments stemming from the cognitive model (reviewed later in this chapter) are effective.

### Psychodynamic Models

The most promising psychodynamic models for understanding panic disorder are those that focus specifically on this disorder. Rather than reviewing all the models, we will summarize the model developed by the Cornell Panic-Anxiety Study Group (Milrod et al. 1997, Shear et al. 1993) because it has led to a promising treatment. According to the Cornell group, people at risk for panic disorder have (1) a neurophysiological vulnerability to panic attacks and/or (2) multiple experiences of developmental trauma. These factors lead the child to become frightened of unfamiliar situations and to become excessively dependent on the primary caregiver to provide a sense of safety. The caregiver is unable to provide support always, so the child develops a fearful dependency. This leads, in turn, to the development of unconscious conflicts about dependency (independence versus reliance on others) and anger (expression versus inhibition). The dependency conflict is said to express itself in a number of ways. Some panic-vulnerable people are sensitive to separation and overly reliant on others, while others are sensitive to suffocation and overly reliant on a sense of independence. These conflicts can activate conscious or unconscious fantasies of catastrophic danger, which can trigger panic attacks. In addition, the conflicts evoke aversive emotions, such as anxiety, anger, and guilt. The otherwise benign arousal sensations accompanying these emotions can become the focus of "conscious as well as unconscious cognitive catastrophizing" (Shear et al. 1993, p 862), thereby leading to panic attacks.

## Neurobiological Factors

Evidence suggests that several neurotransmitter systems, involving neurotransmitters or neuromodulators such as serotonin, noradrenalin, adenosine, gamma-aminobutyric acid, and cholecystokinin-4, play a role in panic disorder (Baldwin 2006). Various brain structures in the limbic system and associated regions have also been implicated. Contemporary biological models of panic, beginning with the pioneering work of Klein (1980), have grown in number and complexity in recent years in an effort to integrate and explain these findings. Recent emphasis has focused on the amygdala, a limbic structure that appears to be involved in coordinating

the different neurotransmitters involved in anxiety disorders (Goddard and Charney 1997). Today, there is no single, leading biological model of panic. However, there are a number of useful models that guide research and clinical practice (Gorman et al. 2000, Klein 1993). Among the most promising is the neuroanatomical hypothesis recently revised by Gorman et al. (2000). This hypothesis is useful for several reasons. First, it integrates a wide range of findings, including animal research and studies of humans. Second, it provides a unifying framework for understanding why panic disorder is associated with so many biological dysregularities such as abnormalities in neurotransmitter systems and irregularities on various indices of autonomic functioning (e.g., Abelson et al. 2001, Cohen et al. 2000). Third, the model accounts for treatment-outcome data, which show that both pharmacological and psychological therapies are effective treatments for panic disorder (as reviewed later in this chapter).

## Neuroanatomical Hypothesis

Gorman et al. (2000) begin with the observation that there is a remarkable similarity between the physiological and behavioral consequences of panic attacks in humans and conditioned fear responses in animals. Similarities include autonomic arousal, fear evoked by specific cues (i.e., contextual fear), and avoidance of these cues. Animal research indicates that conditioned fear responses are mediated by a "fear network" in the brain, consisting of the amygdala and its afferent and efferent projections, particularly its connections with the hippocampus, medial prefrontal cortex, hypothalamus, and brainstem. Animal studies also show that activation of this network produces biological and behavioral reactions that are similar to those associated with panic attacks. Thus, Gorman et al. (2000) posit that a similar network is involved in panic disorder.

The fear network consists of a complex matrix of interconnections, implicating a number of brain structures and neurotransmitter systems. Sensory input passes through the anterior thalamus to the lateral nucleus of the amygdala. Input is then transferred to the central nucleus of the amygdala, which coordinates autonomic and behavioral responses (LeDoux 2000). Direct sensory input to the amygdala from brainstem structures and the sensory thalamus enables a rapid response to potentially threatening stimuli. The central nucleus of the amygdala projects to the following structures:

1. the parabrachial nucleus, producing an increase in respiratory rate,
2. the lateral nucleus of the hypothalamus, causing autonomic arousal and sympathetic discharge,
3. the locus coeruleus, leading to an increase in norepinephrine and to increases in blood pressure, heart rate, and behavioral fear responses (e.g., freezing),
4. the paraventricular nucleus of the hypothalamus, resulting in an increase in the release of adrenocorticoids, and
5. the periaqueductal gray region, leading to avoidance behaviors (Davis and Whalen 2001, LeDoux 2000).

In addition, there are reciprocal connections between the amygdala and the sensory thalamus, prefrontal cortex, insula, and primary somatosensory cortex (Davis and Whalen 2001, LeDoux 2000).

According to Gorman et al. (2000), panic attacks arise from excessive activation of the fear network. In other words, the fear network becomes sensitized (conditioned) to respond to noxious stimuli such as internal bodily sensations and external contexts or situations that the person associates with panic. Sensitization of the network may be manifested by the strengthening of various projections from the central nucleus of the amygdala to brainstem sites (such as the locus ceruleus, periaqueductal gray region, and hypothalamus). The network could be over activated if brainstem inputs to the amygdala are dysregulated. However, autonomic activation (e.g., increased respiration and heart rate) and neuroendocrine activation (e.g., increased cortisol secretion) does not occur in all panic attacks. Moreover, a variety of biological agents with diverse physiological properties can trigger panic attacks in people with panic disorder (e.g., sodium lactate, yohimbine, CO2, caffeine, cholecystokinin-4) (McNally 1994). It is, therefore, unlikely that a single brainstem dysregulation is responsible for panic or, in turn, that brainstem dysregulation is the only way of producing an over-active fear network (Gorman et al. 2000).

Gorman et al. (2000) identify various other ways of activating the fear network. For example, the amygdala receives input from cortical regions involved in the processing and evaluation of sensory information. Therefore, a neurocognitive deficit in these cortico-amygdala pathways could result in the catastrophic misinterpretation of sensory information (i.e., misinterpretation of bodily sensations), leading to an inappropriate activation of the fear network. Notice that this pathway resembles the cognitive model of panic described earlier in this chapter. Thus, the Gorman et al. (2000) model integrates the cognitive model and places it in a neuroanatomical context.

In addition to playing a role in panic disorder, the fear network is thought to play a role in other anxiety disorders and in mood disorders. This is consistent with the comorbidity between panic disorder and these disorders. Abnormalities in the fear network may vary from disorder to disorder. For example, the strength of various connections between components of the network may distinguish various disorders.

Medications, particularly selective serotonin reuptake inhibitors (SSRIs), are thought to desensitize the fear network. This may happen in a number of ways. SSRIs increase serotonergic transmission in the brain (Baldwin 2006). Serotonergic neurons originate in the brainstem raphe and project throughout the central nervous system. Some of these projections have inhibitory influences. For example, the greater the activity in the raphe, the greater the inhibition of noradrenergic neurons in the locus ceruleus, resulting in a reduction of cardiovascular symptoms associated with panic attacks, such as tachycardia (Aston-Jones et al. 1991). Similarly, the greater the activity in the raphe, the greater inhibition in the periaqueductal gray region, resulting in a reduction in avoidance behavior (Viana et al. 1997). Increased serotonergic activity also may reduce hypothalamic release of corticotropin-releasing factor, thereby resulting in a reduction of cortisol (Brady et al. 1992) and a reduction in activity of the locus ceruleus (Butler et al. 1990), thereby leading to a reduction in fear. SSRIs may also directly inhibit activity of the lateral nucleus of the amygdala (Stutzman and LeDoux 1999).

Thus, there appear to be several ways in which SSRIs could desensitize the fear network. Effective psychological therapies are thought to reduce contextual fear and catastrophic misinterpretations at the level of the medial prefrontal cortex and hippocampus.

Given that other neurotransmitter systems have been implicated in panic disorder, it is quite likely that other pharmacologic agents should facilitate the desensitization of the fear network, particularly agents that target more than one of the neurotransmitter systems associated with panic disorder. Consistent with this, there is growing evidence that serotonin noradrenaline reuptake inhibitors (SNRIs) are effective in treating panic disorder (Bradwejn et al. 2005).

Gorman et al.'s (2000) neuroanatomical hypothesis is elegant and comprehensive. However, it is a work in progress and will need to be modified as new findings emerge. Additional brain structures may need to be included in the fear network. For example, a growing body of research suggests that the bed nucleus of the stria terminalis (which is associated with the amygdala) plays an important role in fear (Rosen and Schulkin 1998) and, therefore, should also be included in the fear network.

### Genetic Factors

The fear network is thought to be influenced by genetic factors and stressful life events, particularly events in early childhood (Gorman et al. 2000). Genetic variants of several candidate genes of neurotransmitter or neurohormonal systems, each with a small individual effect, may contribute to the susceptibility to panic disorder and other anxiety and mood disorders (Leonardo and Hen 2006). Research with monozygotic and dizygotic twins shows that panic disorder is moderately heritable, with 23–43% of variance in liability for panic being attributed to genetic factors (Kendler and Prescott, 2006).

Vulnerability to panic disorder appears to result from a combination of disorder-specific and disorder-nonspecific factors (Kendler and Prescott 2006). The importance of nonspecific genetic factors is consistent with observation that panic disorder is often comorbid with other disorders. Twin studies suggest that nonspecific factors influence the vulnerability to several disorders, including panic disorder, bulimia nervosa, generalized anxiety disorder, and alcohol dependence (Kendler and Prescott 2006). Genetic factors specific to panic disorder may be those that influence the tendency to catastrophically misinterpret bodily sensations. This cognitive tendency is a distinguishing feature of panic disorder, as described above. Recent twin research indicates that it is moderately heritable in women but not men (Jang et al. 1999). Thus, some specific genetic factors in panic disorder appear to be sex-linked.

Molecular genetic studies have suggested possible candidates genes for conferring risk for panic disorder and other emotional disorders (e.g., genes involves in the regulation of serotonin; Hariri et al. 2006). However, the process of "gene hunting" is slow and laborious, and many of the initial findings have not been replicated in later research (Leonardo and Hen 2006). To complicate matters, a growing body of research suggests that it is not genes per se that are most important, but rather the interaction of particular genes with particular types of environmental events (Moffitt et al. 2006). For example, people possessing one or more copies of the short allele of the serotonin transporter gene, compared to people with two copies of the long allele, are more likely to develop symptoms of anxiety and depression in response to stressful life events (Leonardo and Hen 2006, Moffitt et al. 2006). Further research is required to investigate the possible role of such gene-environment interactions in panic disorder.

### Social and Environmental Factors

Environmental events occurring during particular developmental phases such as separation from the primary caregiver during early childhood may activate the genes that modulate the fear network, thereby creating a vulnerability to panic disorder. Research suggests that later events, occurring during adolescence or early adulthood, then precipitate panic disorder in vulnerable individuals. These events may stress the individual at a psychological or physiological level. Events commonly associated with the onset of panic disorder include

1. separation, loss, or illness of a significant other disorder,
2. being the victim of sexual assault or other forms of interpersonal violence,
3. financial or occupational stressors, and
4. intoxication with, or withdrawal from, a psychoactive substance such as marijuana, cocaine, or anesthetic (Taylor 2000).

## Treatment

### Treatment Goals

Treatment goals as they pertain to panic disorder with and without agoraphobia are, in general, to reduce the frequency and severity of panic attacks, avoidance behavior, and panic-related disability in social and occupational functioning. There are a number of approaches that can be taken in treating panic disorder with and without agoraphobia. Both single and combined treatment modalities are presented in Figure 69–4. According to guidelines from the National Institute for Clinical Excellence (McIntosh et al. 2004), the interventions with the most enduring treatment effects include cognitive-behavioral therapy and particular pharmacotherapies (e.g., SSRIs, imipramine, clomipramine). As noted earlier, SNRIs are also promising treatments. Of the various treatments for panic disorder, high potency benzodiazepines are effective in the short term but are less effective in producing long-term remission of panic disorder (Cloos 2005, McIntosh et al. 2004).

### Psychosocial Treatments

#### Cognitive–Behavioral Therapy (CBT)

CBT treatment packages include a number of components, such as psychoeducation (e.g., information about the cognitive model of panic), breathing retraining, cognitive restructuring, relaxation exercises, interoceptive exposure, and situational exposure (Taylor 2000). Breathing retraining involves teaching the patient to breathe with the diaphragm rather than with the chest muscles. Cognitive restructuring focuses on challenging patient's beliefs about the dangerousness of bodily sensations (e.g., challenging the belief that palpitations lead to heart attacks).

Interoceptive exposure involves inducing feared bodily sensations to further teach patients that the sensations are

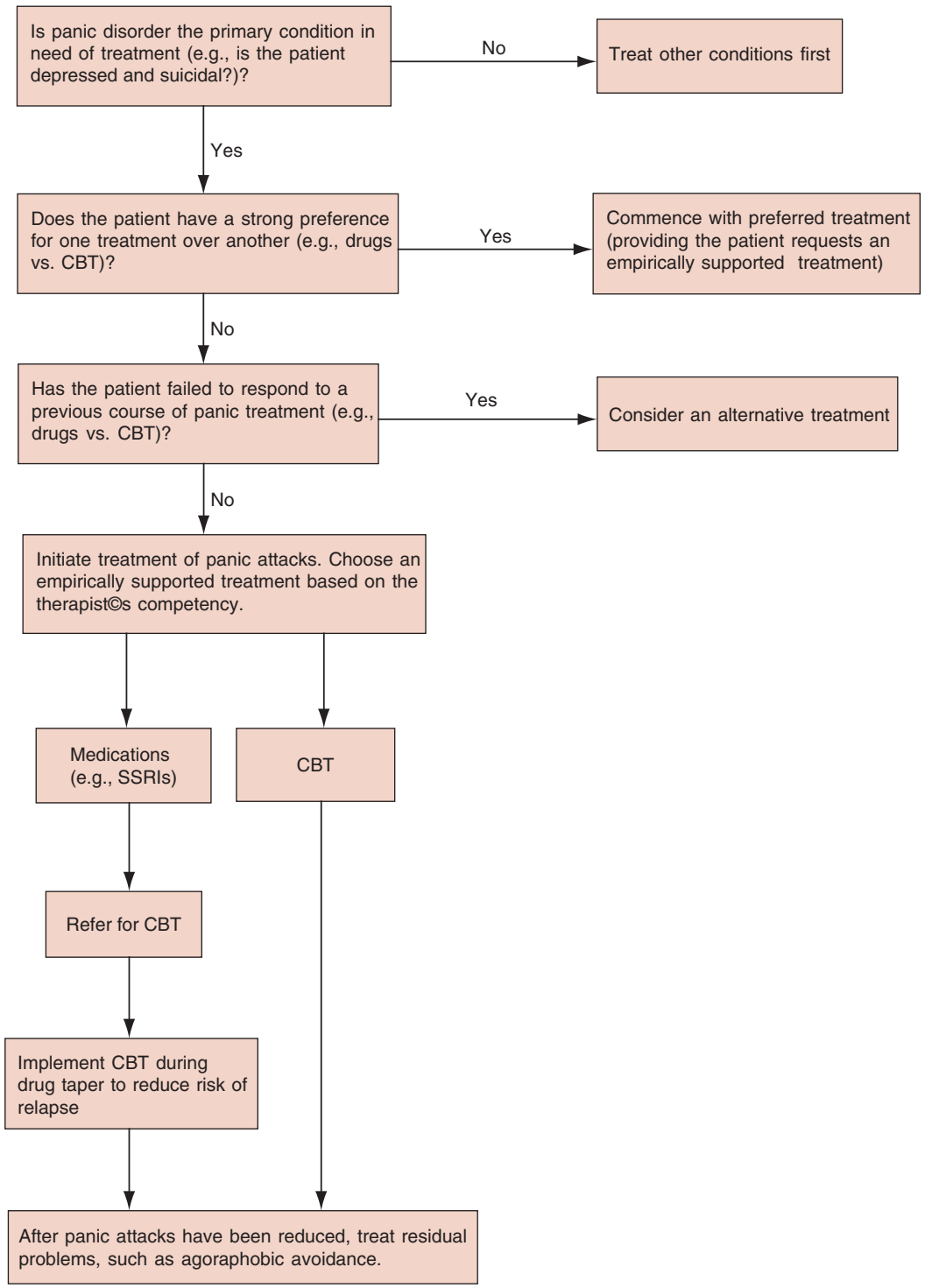



**Figure 69–4** *A decision tree for treating panic disorder.*

harmless. For example, Sandra's treatment involved interoceptive exposure exercises that induced depersonalization. Several tasks were used, including (1) staring at a ceiling fluorescent light for 1 minute, (2) staring at her reflection in the mirror for 2 minutes, and (3) staring at a spot on the wall for 3 minutes. Multiple tasks were used in order to promote the generalization of treatment effects (i.e., to help her learn that depersonalization was harmless regardless of how it arises).

Situational exposure involves activities that bring the patient into feared situations such as shopping malls, bridges, or tunnels. In Sandra's case, situational and interoceptive exposure were combined. She was asked to visit a lighting store to spend time inspecting the various fluorescent lamps. Exposure exercises are often framed as "behavioral experiments" to test patients' beliefs about the catastrophic consequences of arousal-related sensations. Sandra's exposure exercises helped her test the belief that depersonalization leads to permanent insanity. The exercises were also used to help her test the alternative, noncatastrophic belief that depersonalization is an unpleasant but harmless experience.

A common practice in CBT is to encourage patients to refrain from engaging in safety behaviors. Prior to treatment, Sandra typically engaged in distraction whenever she was exposed to depersonalization-inducing stimuli such as fluorescent lights. The CBT therapist encouraged her to refrain from distraction so she could learn that depersonalization is harmless, even when it becomes intense. Evidence suggests that reducing safety behaviors improves treatment efficacy (Taylor 2000). Despite the advantages of exposure exercises, they are medically contraindicated in some cases. For example, a hyperventilation exercise would not be used in a patient with severe asthma (Taylor 2000).

A large body of evidence shows that CBT is effective in reducing panic attacks, agoraphobia, and associated symptoms such as depression (Barlow 2004, Taylor 2000). However, not all CBT interventions may be necessary. Interoceptive exposure, situational exposure, and cognitive restructuring are the most widely used and supported interventions. Several studies suggest that breathing retraining reduces panic frequency. However, recent research casts doubt about the importance of hyperventilation in producing panic attacks. This suggests that breathing retraining may only be useful for a minority of patients, for which chest breathing or hyperventilation plays a role in producing panic symptoms. Breathing retraining may be counterproductive if it prevents patients from learning that their catastrophic beliefs are unfounded. Given these concerns, breathing retraining should be used sparingly in the treatment of panic disorder. If used at all, the clinician should ensure that the patient understands that breathing exercises are used to remove unpleasant but harmless sensations. Interoceptive exposure and cognitive restructuring are important for helping patients learn that the sensations are not dangerous.

How effective is CBT compared to other therapies? A small but growing literature suggests that the efficacy of CBT is equal to or greater than that of alprazolam and imipramine at posttreatment (Barlow 2004, Taylor 2000). Future research is needed to compare CBT to other pharmacotherapies, such as SSRIs. Preliminary evidence suggests that CBT is effective in treating patients who have failed to respond to pharmacotherapies (e.g., Heldt et al. 2006). Follow-up studies suggest that CBT is effective in the long term and is likely to be more effective than short-term pharmacological treatment. It is not known whether drug treatments would be as effective as CBT if patients remained on their medications. Any conclusions about the long-term efficacy of panic treatments are necessarily tentative because patients sometimes seek additional treatment during the follow-up interval.

### Other Psychosocial Interventions

Several other approaches have been used in the treatment of panic disorder, including psychodynamic psychotherapies (e.g., Milrod et al. 2000), hypnosis (e.g., Delmonte 1995), Eye Movement Desensitization and Reprocessing (EMDR) (Shapiro 1995), and mindfulness meditation (Miller et al. 1995). Support for these treatments is limited, largely to case studies and uncontrolled trials. Controlled studies (Feske and Goldstein 1997), although few in number, indicate that hypnosis and EMDR are of limited value in treating panic disorder. When used to treat this disorder, these treatments may be no better than placebo (Taylor 2000). Interventions that look more promising are mindfulness meditation (Miller et al. 1995) and psychodynamic psychotherapies modified to specifically focus on panic symptoms (Milrod et al. 2000). However, none have been extensively evaluated as panic treatments and none have been compared to empirically-supported treatments such as CBT or SSRIs.

## Pharmacological Treatments

Controlled studies show that effective anti-panic medications include tricyclic antidepressants (e.g., imipramine), monoamine oxidase inhibitors (MAOIs; e.g., phenelzine), high-potency benzodiazepines (e.g., alprazolam), SSRIs (e.g., fluvoxamine), and SNRIs (e.g., venlafaxine). According to the available research, these treatments seem to have broadly similar efficacy, at least in the short term, although there is some evidence that SSRIs tend to be most effective (Boyer 1995, Taylor 2000). The classes of medication differ in their side effects and their contraindications. Anticholinergic effects (e.g., blurred vision, dry mouth) are common problems with tricyclics. They are also contraindicated in patients with particular comorbid cardiac disorders. Dietary restrictions (i.e., abstaining from foods containing tyramine) are a limitation of many MAOIs. Sedation, impaired motor coordination, and addiction are concerns with benzodiazepines (Taylor 2000).

When efficacy and side effects are considered together, SSRIs (and possibly SNRIs) emerge as the most promising drug treatments for panic disorder. However, even SSRIs have side effects, with the most problematic being a short-term increase in arousal-related sensations (Pohl et al. 1988). To overcome this problem, SSRIs can be started at a low dose (e.g., 5–10 mg/d for paroxetine; 12.5–25 mg/d for sertraline) and then increased gradually (e.g., up to 10–50 mg/d for paroxetine; up to 25–200 mg/d for sertraline). The choice of SSRI is determined on the basis of several factors, including side effects, patient preference, and the patient's history of responding (or not responding) to particular agents.

For drug refractory patients, or patients who are unable to tolerate SSRI side effects, combination medications are sometimes used. For example, SSRIs can be augmented with benzodiazepines or other agents (Bandelow and Eckart 2004). Benzodiazepines can be used to dampen the side effects of SSRIs. Despite some positive preliminary reports supporting this strategy, its value in the treatment of panic disorder remains to be properly evaluated. An alternative strategy is to change the patient's medication. Another approach to the drug refractory patient is to use a psychosocial treatment such as CBT, as an alternative or adjunctive intervention. These approaches are discussed in more detail later in this chapter.

## Combined Treatments

### Simultaneous Treatments

Many clinicians believe the optimal treatment consists of drugs combined with some form of psychosocial intervention (Black 2006). This view arose from observations that even the most effective drugs and the most effective psychosocial interventions do not eliminate panic disorder in all cases. It was thought that combination treatments might be a way to improve treatment outcome. The available evidence provides mixed support for this view, and currently

it is unclear whether combining CBT with medication is more effective than either treatment alone (Pull 2007). In fact, there is evidence that combined treatment might lead to worse outcome (Black 2006).

To illustrate these findings, several studies have compared CBT to CBT combined with imipramine. These results have been mixed. Adding imipramine in the range of 150–300 mg/day to either situational exposure or CBT sometimes improves treatment outcome in the short-term, provided that patients are able to tolerate the dose (Barlow 2004, Taylor 2000). Any advantage of combined treatment tends to be lost at follow-up. Similarly, studies of combining CBT with SSRIs (fluvoxamine or paroxetine) have produced mixed results, with some studies finding the combination is no better than CBT alone, others finding that the combination is most effective, and yet others finding the combination to be most effective for some symptoms but not others. Methodological limitations of these studies might account for the inconsistent findings, and more research is needed on this important topic (Black 2006, Taylor 2000).

The neuroanatomical model (Gorman et al. 2000), with its dual emphasis on cognitive and serotonergic mechanisms, suggests that this combined treatment might be superior to CBT alone and to SSRIs alone. Yet pharmacotherapies such as SSRIs might undermine the patient's confidence in implementing CBT, particularly if they attribute their gains to medications rather than to their own efforts at using the skills learned in CBT. Large, well-designed studies are needed to explore these important issues.

### Sequential Treatments

A more promising type of combined therapy is a sequential approach, where patients are treated with pharmacotherapy during the acute phase, and then are treated with CBT as the medication is phased out. Several studies have shown that adding CBT during the tapering period for alprazolam and clonazepam reduces the relapse rate associated with these drugs (see Taylor 2000, for a review). It remains to be demonstrated that CBT can reduce relapse when patients are tapered off other antipanic drugs such as SSRIs. However, there is no reason to expect that CBT would not be helpful in these cases.

## Issues in Clinician–Patient Relationship

Regardless of whether the patient is treated with a psychosocial intervention or with medication, it is important to develop a sound clinician-patient relationship. A thorough assessment of the patient's problems is an important first step to establishing such a relationship, because a good assessment (combined with feedback of the results) gives the patient confidence that the clinician has a good understanding of the presenting problems. A sound working relationship is also facilitated when the clinician exhibits interpersonal warmth and is nonjudgmental. Patients with panic disorder are sometimes ashamed or embarrassed about their symptoms, especially if the patient views anxiety as a sign of personal weakness (Taylor, 2000). To this end it can be important for the clinician to point out that the patient has been exhibiting courage in all of his or her attempts to enter feared situations. The important message to convey is that courage is defined as persistence in the face of fear, regardless of whether or not the fears are excessive.

Patients with panic disorder may also be ashamed of the catastrophic beliefs (or images) they experience during their panic attacks. Typically, there is a state-dependency in the strength of these beliefs; during a panic attack the patient may be completely convinced in the veracity of the belief (e.g., "My heart is beating so rapidly that I'm bound to have a heart attack"), whereas in the calmer moments the patient may seriously question the veracity of the belief (e.g., "As I sit here in your office, it seems silly to think that palpitations will harm my heart, because my cardiologist has told me that my heart is fine"). Thus, when the patient is relatively calm in the clinician's office, the patient may be reluctant to discuss panic-related catastrophic beliefs because he or she currently views the beliefs as foolish or embarrassing. To circumvent this problem the clinician can educate the patient about the state-dependency of beliefs, and point out that sometimes even highly implausible beliefs can seem very convincing when the person is in the midst of panic. Such information conveys acceptance to the patient, thereby strengthening the therapeutic relationship and encouraging the patient to be more open about revealing catastrophic beliefs. In turn, this can facilitate treatment, especially CBT in which it is important to identify catastrophic beliefs. To illustrate, once this state-dependency in belief strength had been explained, and the clinician had provided information about the sometimes bizarre nature of panic-related catastrophic beliefs, one of our patients was able to reveal that many of her panic attacks were triggered by feelings of sexual arousal, accompanied by the terrifying belief that the arousal would never end and she would become permanently incapacitated.

A sound therapeutic relationship is also important for maximizing adherence to pharmacologic treatments. If the patient trusts the clinician, and is provided with relevant information about the benefits and likely side effects of a given drug, then the patient is likely to persist with taking the medication, even when unpleasant, temporary side effects are experienced. Although a sound therapeutic relationship is important for medication adherence, it may not be enough. It is often important for the clinician to identify any erroneous or unrealistic beliefs that the patient might have about taking psychotropic medication (e.g., "Drugs will turn me into an emotional automaton," or "Psychiatric drugs are a form of brain washing"). Cognitive restructuring, as used in CBT, can be applied to such beliefs in order to facilitate treatment adherence (Taylor, 2000).

## Treatment Refractory Patients

In the previous sections of this chapter, we noted that one useful strategy for treatment refractory panic disorder is to try an alternative treatment, such as switching from pharmacotherapy to CBT (Heldt et al. 2006) or switching from one drug to another. There are several other important strategies for improving treatment response. If the patient has received an adequate course of treatment—such as a drug at an adequate dose for a sufficient period of time, or CBT for a sufficient number of sessions—then treatment failure might be the result of an erroneous or inadequate case formulation. The clinician might have misdiagnosed panic disorder and implemented panic treatment in a case in which the panic-like symptoms were actually due to a general medical condition. For example, one of us (ST)

learned of a case in which a psychiatric resident was using CBT to treat a patient who appeared to have panic disorder with agoraphobia. Over the course of treatment, the patient became somewhat less concerned about the dangerousness of her symptoms, and became less avoidant, but her panic-like symptoms persisted unabated. The unsatisfactory response to treatment led the resident and supervisor to reassess the patient in order to identify the source of the problem. It turned out that the patient actually did not have panic disorder; she was suffering from the effects of a pheochromocytoma.

For cases of genuine panic disorder in which there is an unsatisfactory treatment response, treatment outcome may be improved by using more than one treatment. As noted earlier in this chapter, it is currently unclear whether combining medications with CBT improves outcome for the average patient, although this strategy may possibly be useful in particular cases. Drug augmentation strategies could also be used, such as combining an SSRI or tricylic antidepressant with a high potency benzodiazepine such as alprazolam or clonazepam (Bandelow and Eckart, 2004).

## Special Factors Influencing Treatment

In addition to the issues discussed above, patient preference is an important factor in determining treatment success; if a patient strongly prefers one particular treatment (e.g., CBT) and is given a non-preferred treatment (e.g., an SSRI), then treatment refusal, treatment non-adherence, or dropout may occur (Taylor, 2000). Also, given the fact that panic disorder is commonly comorbid with other disorders, there may be cases in which it is more important to treat one of the co-occurring disorders (e.g., a comorbid substance use disorder, a mood disorder associated with significant suicide risk, or personality disorder associated with self-harming behaviors) before a course of panic treatment should be contemplated.

Comorbid general medical conditions can also influence the selection and nature of panic treatment. For example, some cardiac conditions may contraindicate the use of particular medications (e.g., tricyclics). Patients with particular general medical conditions may be unable to safely complete some of the exercises used in CBT. For instance, some forms of interoceptive exposure (e.g., voluntary hyperventilation) may be contraindicated for panic patients who also have particular general medical conditions (e.g., poorly controlled epilepsy or severe asthma). These issues in treatment selection are discussed in more detail in Taylor (2000).

Finally, one of the most important issues influencing treatment selection concerns the problem of availability of suitably qualified clinicians. In many countries, or regions of countries, there is a dearth of clinicians with CBT expertise (typically psychologists) and a shortage of clinicians with psychopharmacology expertise (typically psychiatrists). Under such circumstances the burden of treating panic disorder typically falls upon the shoulders of the general practitioner or primary care physician. Here, treatment options typically consist of pharmacotherapy, combined with a few simple CBT exercises (e.g., graded exposure to feared situations). Such treatments may be beneficial for many patients with panic disorder, although a substantial proportion of patients will require specialist treatment (Bandelow and Eckart 2004, Taylor 2000). While in-person access to a specialist is not feasible, telephone and Internet administered CBT is a promising, empirically-supported option (e.g., Calbring et al. 2005).

## Comparison of DSM-IV-TR and International Classification of Diseases, Tenth Revision (ICD-10) Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research for a panic attack are identical to the DSM-IV-TR criteria set except that ICD-10 includes an additional symptom (dry mouth). In contrast to the DSM-IV-TR algorithm, which does not give special weight to any particular symptom, the ICD-10 algorithm requires that at least one of the symptoms be palpitations, sweating, trembling, or dry mouth. Like DSM-IV-TR, ICD-10 requires recurrent panic attacks but, in contrast to DSM-IV-TR, it does not include a criterion requiring that the panic attacks be clinically significant.

The ICD-10 Diagnostic Criteria for Research for Agoraphobia differ markedly from the DSM-IV-TR criteria. The ICD-10 specifies that there can be fear or avoidance of at least two of the following situations: crowds, public places, traveling alone, or traveling away from home. Furthermore, ICD-10 requires that at least two symptoms of anxiety (from the list of 14 panic symptoms) be present together on at least one occasion and that these anxiety symptoms be "restricted to, or predominate in, the feared situations or contemplation of the feared situations." In contrast, DSM-IV-TR Agoraphobia is defined in terms of "anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack." No specific avoided situations or specific types of anxiety symptoms are required for a diagnosis.

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CHAPTER

# 70 Anxiety Disorders: Social and Specific Phobias

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Social Phobia (Social Anxiety Disorder)
Specific Phobia

## Introduction

The experience of fear and the related emotion of anxiety are universal and familiar to everyone. Fear exists in all cultures and appears to exist across species. Presumably, the purpose of fear is to protect an organism from immediate threat and to mobilize the body for quick action to avoid danger. Emotion theorists consider fear to be an alarm response that fires in the presence of imminent threat or danger. The function of the primarily noradrenergic-mediated fear response is to facilitate immediate escape from threat (flight) or attack on the source of threat (fight) (Barlow 1991, 2002). Therefore, fear is often referred to as a fight-or-flight response (Cannon 1929). All the manifestations of fear are consistent with its protective function. For example, heart rate and breathing rate increase to meet the increased oxygen needs of the body, increased perspiration helps to cool the body to facilitate escape, and pupils dilate to enhance visual acuity.

Anxiety, on the other hand, is a future-oriented mood state in which the individual anticipates the possibility of threat and experiences a sense of uncontrollability focused on the upcoming negative event. In the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), anxiety is defined as "the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension" (p. 820). If one were to put anxiety into words, one might say, "Something bad might happen soon. I am not sure I can cope with it but I have to be ready to try." Anxiety is primarily mediated by the gamma-aminobutyric acid-benzodiazepine system (Barlow 1991, 2002).

Despite evidence that fear and anxiety are mediated by different brain systems, anxiety and fear are related, which makes sense ethologically. Experiencing anxiety after encountering signals of impending danger seems to lower the threshold for fear that is triggered when danger actually occurs (e.g., being attacked by a mugger or almost being hit by an automobile). Anxiety leads to a shift in attention toward the source of danger so that individuals become more vigilant for relevant threat cues and therefore are more likely to experience fear in the face of perceived immediate threat.

Fear and anxiety are not always adaptive. At times, the responses can occur in the absence of any realistic threat or out of proportion to the actual danger. Almost everyone has situations that arouse anxiety and fear despite the fact that the actual risk is minimal. It is not unusual to become anxious before a job interview or a speech. Many individuals feel fearful when exposed to situations such as dental visits, seeing certain animals, or being at certain heights. For some people, these fears reach extreme levels and may cause significant distress or impairment in functioning. It is at this point that what we typically refer to as shyness and fearfulness might meet diagnostic criteria for social phobia or specific phobia, respectively (see DSM-IV-TR Criteria 300.23 and 300.29).

As discussed later in this chapter, phobias are the most common of the anxiety disorders and are among the most common of all mental disorders. However, despite the frequency with which phobias occur in the general population, they have tended to be relatively ignored by clinicians and researchers. In the case of social phobia, it was not until the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) (American Psychiatric Association 1980) that the diagnostic category was created. The introduction of social phobia to the diagnostic nomenclature has led to a slow but steady increase in research on the disorder, so that social phobia

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has now become a popular topic of study among researchers on anxiety disorders. In addition to being widespread, social phobia is associated with significant functional impairment. Individuals with social phobia experience impairment in their work, home, and social relationships (Antony et al. 1998b). Also, social phobia often presents comorbidly with other mental disorders. Despite the high prevalence rate and significant impairment, generalized social phobia is rarely diagnosed or treated in a primary care setting and is often dismissed as extreme shyness (Heimberg 2003). For example, Katzelnick et al. (2001) found that only 0.5% of patients with generalized social phobia were accurately diagnosed even though over 44% had made a visit to a mental health specialist or had been prescribed antidepressants.

With respect to specific phobias, the lack of attention is probably due to several factors. First, many physicians and researchers may view specific phobias to be less severe than other disorders, therefore warranting less attention. In addition, few individuals with specific phobias present for treatment, and the ones who do seek help tend to differ from untreated individuals with phobias with respect to the number and types of specific phobias (Chapman et al. 1993). As with social phobia, there has been an increase in attention paid to specific phobias, along with increased recognition that these phobias can interfere seriously with an individual's ability to function. It is not unusual for flying phobias to lead individuals to refuse job promotions that involve travel or to avoid visiting distant family members. Likewise, individuals with insect phobias may avoid being outside during the summer.

## Diagnosis

Social phobia and specific phobias have both overlapping and distinguishing diagnostic and clinical features. The next section reviews the definitions and diagnostic features of the disorders as well as assessment methods. An overview of the clinical features of the disorders includes their epidemiology, comorbidity patterns, and course. Issues related to establishing a differential diagnosis are considered followed by an examination of differences in developmental, gender, and cultural presentations.

## Definition and Diagnostic Features

In the DSM-IV-TR (American Psychiatric Association 2000), social phobia (also known as social anxiety disorder) is defined as a "marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny of others." Typical situations feared by individuals with social phobia include meeting new people, interacting with others, attending parties or meetings, speaking formally, eating or writing in front of others, dealing with people in authority, and being assertive. Specific phobia is defined as a "marked and persistent fear that is excessive or

**DSM-IV-TR Diagnostic Criteria** for 300.23

**Social Phobia (Social Anxiety Disorder)**

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.

B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking away from social situations with unfamiliar people.

C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.

D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).

H. If a general medical condition or another mental disorder is present, the fear in criterion A is unrelated to it, e.g., the fear is not of stuttering, trembling in Parkinson's disease, exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa.

*Specify if:*

**Generalized:** if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder)

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**DSM-IV-TR Diagnostic Criteria** for 300.29

**Specific Phobia**

A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging.

C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.

D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The anxiety, panic attacks, and phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as obsessive-compulsive disorder (e.g., fear of dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., avoidance of stimuli associated with a severe stressor), separation anxiety disorder (e.g., avoidance of school), social phobia (e.g., avoidance of social situations because of fear of embarrassment), panic disorder with agoraphobia, or agoraphobia without history of panic disorder.

*Specify type:*

**Animal type**

**Natural environment type** (e.g., heights, storms, water)

**Blood-injection-injury type**

Situational type (e.g., airplanes, elevators, enclosed places)

**Other type** (e.g., fear of choking, vomiting, or contracting an illness; in children, fear of loud sounds or costumed characters)

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unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood)."

The diagnostic criteria for specific and social phobias share many features (see DSM-IV-TR Criteria 300.23 and 300.29). For both disorders, the phobic situation must almost invariably lead to an anxiety response (immediately, in the case of specific phobias), which may take the form of a panic attack. In addition, the individual must recognize that the fear is excessive or unreasonable (although this feature may be absent in children), avoid the phobic situation or endure it with intense distress, and experience marked distress or functional impairment as a result of the phobia. In the case of social phobia, the fear must not be related to another mental disorder or medical condition. For example, if an individual develops difficulties communicating after suffering a stroke, the fear must be unrelated to having other people notice one's problems in speaking. However, if the psychiatrist judges that social anxiety is substantially in excess of what most individuals with this disability would experience, a diagnosis of anxiety disorder not otherwise specified may be appropriate.

Finally, for both disorders the fear must not be better accounted for by another problem. For example, an individual with obsessive–compulsive disorder who fears contamination from contact with injections would not receive an additional diagnosis of specific phobia unless there were additional concerns about injections that were unrelated to contamination (e.g., fear of fainting during an injection, fear of pain from the needle). Each diagnosis has specifiers or subtypes to allow for the provision of more specific diagnostic information. For social phobia, the psychiatrist can specify whether the phobia is generalized (i.e., includes most social situations). For specific phobias, the psychiatrist can indicate which one of five types best describes the focus of the phobia: animal, natural environment, blood—injection–injury, situational, or other.

## Specific Phobia Phenomenology and Subtypes

As discussed earlier, DSM-IV-TR defines five main types of specific phobia: animal, natural environment, blood–injection–injury, situational, and other. These types were introduced on the basis of a series of reports to the DSM-IV-TR Anxiety Disorders Work Group (Curtis et al. 1990) showing that specific phobia types tend to differ on a variety of dimensions including age at onset, sex composition, patterns of covariation among phobias, focus of apprehension, timing and predictability of the phobic response, and type of physiological reaction during exposure to the phobic situation.

Although anxiety about physical sensations and the occurrence of panic is a feature typically associated with panic disorder, several studies have shown that panic-focused and symptom-focused apprehensions are not unique to panic disorder and agoraphobia. In fact, individuals with specific

phobias score a full standard deviation above the mean for normal persons on the Anxiety Sensitivity Index (Reiss et al. 1986), a questionnaire that measures anxiety related to experiencing the physical sensations of fear. In other words, individuals with specific phobias may report anxiety about the sensations (e.g., racing heart, breathlessness, dizziness) typically associated with their fear. Also, there is evidence that in addition to fearing danger from the phobic object (e.g., a plane crash, being bitten by a dog) many individuals with specific phobias fear danger or negative consequences as a result of their reaction in the phobic situation such as crashing the car in response to panic symptoms or being embarrassed by others noticing their anxiety symptoms (McNally and Steketee 1985). Also, the few relevant studies that have been conducted suggest that there may be differences in sensation-focused apprehension across specific phobia types.

Data are converging to indicate that individuals with phobias from the situational (e.g., claustrophobia) and blood–injury–injection types may be especially internally focused on their fear (Antony et al. 1997a). Whereas individuals with situational phobias tend to fear the possible consequences of panic, those with blood–injury–injection phobias seem uniquely concerned about sensations that indicate that fainting is imminent (e.g., lightheadedness, hot flashes).

Specific phobia types may differ with respect to timing and predictability of the phobic response as well. One study based on retrospective self-reports found that individuals with phobias of driving, enclosed places, and blood–injury were more likely to report that their fear was delayed in the phobic situation than were those with animal phobias (Craske et al. 1993). These data suggest that delayed and unpredictable panic attacks may be more characteristic of situational phobias than of other phobia types, consistent with the argument that situational phobias share more features with agoraphobia than do other specific phobia types. This is supported by the finding that individuals with situational phobias report more unexpected panic attacks than do individuals with other specific phobia types (Lipsitz et al. 2002).

Perhaps the most consistent difference among specific phobia types is the tendency for individuals with blood–injury–injection phobias to report a history of fainting in the phobic situation. Although all phobia types are associated with panic attacks in the phobic situation, only patients with blood and injection phobias report fainting (Antony et al. 1997b). Specifically, individuals with blood–injury–injection phobias experience a diphasic physiological response, which includes an initial increase in arousal followed by a sharp drop in heart rate and blood pressure that can lead to fainting. This response occurs at times in approximately 70% of people with blood phobias and 56% of those with injection phobias and seems to be unique to situations involving blood and medical procedures (Öst 1992). In other words, people who faint in these situations still show the usual type of response (i.e., increased arousal) in other situations that they fear (e.g., heights, flying, etc.). Disgust has been identified as a potential mediator of faintness associated with blood–injury–injection stimuli (Exeter-Kent and Page 2006).

The different responses experienced in different phobias have been explained from an evolutionary perspective. As mentioned earlier, the typical phobic responses of fear and panic are adaptive in that the increased arousal facilitates escape. In contrast, the most adaptive response during serious injury may be a drop in blood pressure to prevent excessive bleeding. It has been suggested that this response is mediated by an overactive sinoaortic baroreflex that is triggered by heightened arousal in situations involving blood or needles (Adler et al. 1991). Of course, in people with blood and injection phobias, the response is excessive and unwarranted, as there is typically no danger of excessive blood loss.

## Social Phobia Phenomenology and Subtypes

Many researchers in the area of social phobia tend to classify the disorder into two main subtypes. DSM-IV-TR requires that diagnosticians specify whether a social phobia diagnosis is "generalized," or includes most social situations. In addition, a "discrete or circumscribed" subtype is often used by investigators to describe patients with only one domain of social anxiety, usually involving performance-related situations (e.g., public speaking).

Several studies have examined differences among these subtypes. Specifically, patients with generalized social phobia tend to be younger, less educated, and less likely to be employed than are patients with discrete social phobia. In addition, generalized social phobia is associated with more depression, anxiety, general distress, and concerns about negative evaluation from others (Heimberg et al. 1990a, Turner et al. 1992). Discrete social phobias appears to be associated with greater cardiac reactivity.

Heimberg et al. (1993a) have suggested that a third subtype, called "nongeneralized" social phobia, be added to describe patients who (1) may or may not have discrete social fears, (2) report significant anxiety in situations involving social interaction, and (3) have at least one social domain in which they do not experience significant anxiety. An example of an individual with nongeneralized social phobia would be a person who functions well at work but feels anxious when meeting new people at casual parties and other situations outside of work. Although the nongeneralized subtype was not adopted in DSM-IV-TR, it has been evaluated in several research studies. In studies comparing generalized and nongeneralized social phobia, individuals with generalized social phobia tend to be more likely to have additional psychiatric diagnoses, poorer social skills, more functional impairment, poorer performance on a social interaction role play test, earlier age at onset, and more social avoidance than those with nongeneralized social phobia (Herbert et al. 1992). In addition, patients with generalized social phobia describe themselves as more shy and describe their families as more overprotective and less likely to socialize with others, compared to people with nongeneralized social phobia (Bruch and Heimberg 1994).

Several other methods of subtyping social phobia have been attempted as well (e.g., Holt et al. 1992). Overall, it appears that social phobia can take a variety of different forms. Further research is needed to determine if the DSM-IV-TR method of classifying the subtypes of social phobia can be improved. In a move away from subtyping social phobia, Hofmann et al. (2004) recently proposed a dimensional model based on the finding that individuals with social phobia are actually a heterogeneous group. According to this model, individuals with social phobia

may be best characterized along a dimensional continuum of emotional response and behavioral tendencies. Proposed dimensions include fearfulness, anxiousness, shyness, self-consciousness, submissiveness, and anger. Further work is necessary to investigate the utility of this dimensional approach.

## Assessment

As is the case with most disorders, a comprehensive assessment is important in helping the psychiatrist to decide which treatment approach is most appropriate for a given patient. In the case of specific and social phobias, a thorough evaluation should include a structured or semistructured interview, self-report measures, and a behavioral assessment. Each of these measures provides different types of information that may be relevant to later treatment decisions. This section provides an overview of relevant assessment issues. Additional comprehensive reviews may be found elsewhere (McCabe and Antony 2002, Rowa et al. in press).

During all parts of the initial evaluation, the psychiatrist should be sensitive to several issues. First, for many patients with phobias, even discussing the phobic object can provoke anxiety. For example, some patients with spider phobias experience panic attacks when they discuss spiders. Some patients with blood phobias faint when they discuss surgical procedures. Therefore, the psychiatrist should ask the patient whether discussing the phobic object or situation will provoke anxiety. If the interview is likely to be a source of stress, the psychiatrist should emphasize the importance of the information that is being collected, as well as the potential therapeutic value of discussing the feared object. As described in a later section, exposure to the feared stimulus is an essential component of the treatment of most specific phobias. Of course, the psychiatrist should use his or her judgment when deciding how much to push the patient in the first session. For treatment to be effective, establishing a trusting therapeutic relationship early in the course of treatment is essential.

With respect to social phobia, the assessment itself may be considered a phobic stimulus. Because individuals with social phobia fear the evaluation of others, a psychiatric interview may be especially frightening. Even completing self-report questionnaires in the waiting room may be difficult for patients who fear writing in front of others. The psychiatrist should be sensitive to this possibility and provide reassurance when appropriate.

Both specific phobia and social phobia may be associated with skills deficits that may have an impact on treatment. For example, social phobia is often associated with impairment in social skills such as poor eye contact (e.g., Spence et al. 1999). Individuals with a specific phobia of driving may lack basic driving skills and would benefit from driving lessons. Thus, a comprehensive assessment should include assessment of skills deficits relevant to the disorder so that treatment planning can include a skills training component.

### Structured and Semistructured Interviews

Although there are numerous structured and semistructured interviews available (Summerfeldt and Antony 2002), two of the most commonly used interviews for diagnosing anxiety disorders are the Anxiety Disorders Interview Schedule for DSM-IV-TR (ADIS-IV) (Brown et al. 1994) and the Structured Clinical Interview for Axis I DSM-IV-TR Disorders—Patient Edition (SCID-I/P for DSM-IV-TR) (First et al. 2001). Current and lifetime diagnoses of specific phobia and social phobia based on the ADIS-IV have been shown to have good to excellent reliability for the specific phobia types and the generalized type of social phobia (Brown et al. 2001b). To date, there are few published studies on the psychometric properties of the SCID-I for DSM-IV-TR. One study (Zanarini et al. 2000) found that the reliability (both interrater and test–retest) for social phobia was in the fair to good range and the reliability for other Axis I disorders was also good. Previous versions of the SCID-I for the DSM-III-R have been shown to be reliable, especially for phobic disorders (Antony and Swinson 2000a, Summerfeldt and Antony 2002). Each interview has advantages and disadvantages. Although the SCID-I provides detailed assessment of a broader range of disorders relative to the ADIS-IV (including eating disorders and psychotic disorders), the ADIS-IV provides more detailed information on each of the anxiety disorders and, like the SCID-I, includes sections to provide DSM-IV-TR diagnoses for the mood disorders and other disorders that are typically associated with the anxiety disorders (e.g., substance use and somatoform disorders). In addition, the ADIS-IV includes more questions to help differentiate specific and social phobias from other disorders with which they share features. Both the SCID-IV and ADIS-IV are available in versions for use with children, adolescents, and their parents (for review, see Grills and Ollendick 2002).

### Self-Report Measures

Numerous self-report measures have been created for the assessment of specific phobias and social anxiety. The main advantage of self-report measures is the time that they save for the psychiatrist. Relevant self-report measures are recommended before the clinical interview if possible. This will allow the interviewer to follow up specific responses during the interview. Measures can be administered again, periodically, to assess progress and outcome. It should be noted that questionnaire measures do not always correlate highly with performance on behavioral measures (Klieger and Franklin 1993). Furthermore, there is evidence that men are more likely than women to underestimate their fear on specific phobia measures (Pierce and Kirkpatrick 1992). The Fear Survey Schedule (Geer 1965, Wolpe and Lang 1964) is a commonly used measure for screening for various specific phobia types. However, the more recently developed Phobic Stimuli Response Scales (Cutshall and Watson 2004) may be more psychometrically sound, especially for assessing fears of blood–injury, animals, and physical confinement, as well as fears of social situations. In addition, a variety of measures exist to assess fear of specific objects and situations. For example, the Mutilation Questionnaire (Klorman et al. 1974) is a popular test for assessing fear of situations involving blood and medical procedures. Self-report measures for assessing both specific phobia and social anxiety are listed in Table 70–1. Detailed reviews of these and other measures are available (Antony et al. 2001b, McCabe and Antony 2002, Rowa et al. in press). For a review of child measures, see Ollendick et al. 2004).

**Table 70–1 Common Measures for Specific and Social Phobias**

| Specific Phobia |
|---|
| Acrophobia Questionnaire (AQ; Cohen 1977) |
| Claustrophobia Questionnaire (CLQ; Radomsky et al. 2001) |
| Dental Anxiety Inventory (DAI; Stouthard et al. 1993) |
| Fear of Flying Scale (FFS; Haug et al. 1987) |
| Fear Questionnaire (FQ; Marks and Mathews 1979) |
| Fear Survey Schedule (FSS; Geer 1965, Wolpe and Lang 1964, 1969, 1977) |
| Medical Fear Survey (MFS; Kleinknecht et al. 1996) |
| Mutilation Questionnaire (MQ; Klorman et al. 1974) |
| Phobic Stimuli Response Scales (PSRS; Cutshall and Watson 2004) |
| **Social Phobia** |
| Brief Social Phobia Scale (BSPS; Davidson et al. 1991b) |
| Liebowitz Social Phobia Scale (LSAS; Liebowitz 1987) |
| Mini-Social Phobia Inventory (Mini-SPIN; Connor et al. 2001) |
| Social Interaction Anxiety Scale (SIAS; Mattick and Clarke 1998) |
| Social Phobia and Anxiety Inventory (SPAI; Turner et al. 1989) |
| Social Phobia Inventory (SPIN; Connor et al. 2000, Davidson 1998) |
| Social Phobia Scale (SPS; Mattick and Clarke 1998) |
| Social Thoughts and Beliefs Scale (STABS; Turner et al. 2003) |

## Behavioral Tests

Behavioral testing is an important part of any comprehensive evaluation for a phobic disorder. This is particularly the case if behavioral or cognitive–behavioral treatment will be used. Because most individuals with phobias avoid the objects and situations that they fear, patients may find it difficult to describe the subtle cues that affect their fear in the situation. In addition, it is not unusual for patients to misjudge the amount of fear that they typically experience in the phobic situation. A behavioral approach test can be useful for identifying specific fear triggers as well as for assessing the intensity of the patient's fear in the actual situation.

To conduct a behavioral approach test, patients should be instructed to enter the phobic situation for several minutes. For example, an individual with a snake phobia should be instructed to stand as close as possible to a live snake and note the specific cues that affect his or her fear (e.g., size of snake, color, movement) and the intensity of the fear (perhaps rating it on a 0- to 100-point scale). Patients should pay special attention to their physical sensations (e.g., palpitations, sweating, blushing), negative thoughts (e.g., "I will fall from this balcony"), and anxious coping strategies (e.g., escape, avoidance, distraction).

The behavioral approach test will help in the development of a specific treatment plan. However, before treatment patients will often be reluctant to enter the feared situation. If this is the case, the information collected during the behavioral approach test may be elicited during the early part of behavioral treatment.

## Epidemiology

As discussed earlier, specific phobia and social phobia are among the most common psychiatric disorders and the most common of the anxiety disorders. Data from the National Comorbidity Survey Replication (NCS-R) (Kessler et al. 2005b) yielded lifetime prevalence estimates of 12.5% for specific phobias and 12.1% for social phobia in an epidemiological survey of over 9000 individuals aged 18 years and older from across the United States, based on DSM-IV-TR diagnostic criteria. The original NCS study (Kessler et al. 1994) reported similar findings based on DSM-III-R criteria with lifetime prevalence rates of 11.3% for specific phobias and 13.3% for social phobia. Table 70–2 lists lifetime prevalence rates for particular specific fears and phobias based on findings of the original NCS (Curtis et al. 1998), with phobias of animals and heights being the most frequently diagnosed specific phobias.

Results from epidemiological studies (Bourdon et al. 1988, Curtis et al. 1998) show that most specific phobias are more common in women than in men, although there are differences in sex ratio among phobia types. Specifically, the ratio of females to males is smaller for height phobias than for other specific phobia types. For social phobia situations, sex differences are less pronounced than for most specific

**Table 70–2 Lifetime Prevalence of Specific Fears with and without Specific Phobia**

| | Lifetime Fears* | | Lifetime Phobia Given Fear† | | Lifetime Phobia with Specific Fear in Total Sample‡ | |
|---|---|---|---|---|---|---|
| Specific Fear | % | s.e. | % | s.e. | % | s.e. |
| Height | 20.4 | 0.7 | 26.2 | 1.8 | 5.3 | 0.5 |
| Flying | 13.2 | 0.7 | 26.9 | 2.4 | 3.5 | 0.3 |
| Closed spaces | 11.9 | 0.6 | 35.1 | 2.5 | 4.2 | 0.4 |
| Being alone | 7.3 | 0.6 | 40.7 | 3.3 | 3.1 | 0.4 |
| Storms | 8.7 | 0.5 | 33.1 | 3.4 | 2.9 | 0.4 |
| Animals | 22.2 | 1.1 | 25.8 | 1.2 | 5.7 | 0.4 |
| Blood | 13.9 | 0.7 | 32.8 | 2.1 | 4.5 | 0.3 |
| Water | 9.4 | 0.6 | 35.8 | 2.8 | 3.4 | 0.3 |
| Any | 49.5 | 1.2 | 22.7 | 1.1 | 11.3 | 0.6 |

*Prevalence of lifetime fears in the total sample.

†Probability of specific phobia diagnosis in people endorsing each fear.

‡Percentage of people in total sample with specific phobia and each lifetime fear (i.e., 5.3% of total sample have lifetime-specific phobia and a height fear).

*Source*: Curtis et al. 1998. Specific fears and phobias: Epidemiology and classification Br J Psychiatr 173, 212–217. Reproduced with permission from The Royal College of Psychiatrists.

phobia types. In the NCS (Kessler et al. 1994), relatively small sex differences in social phobia prevalence were confirmed, with lifetime estimates of 11.1% for males and 15.5% for females. In addition, the relatively equal numbers of men and women with social phobia in epidemiological studies is consistent with findings from samples of individuals presenting for treatment (Hofmann and Barlow 2002).

The onset of social phobia is typically during childhood and adolescence, with a range of 13–24 years in clinical studies and 10–16.6 years in epidemiological studies (Wittchen and Fehm 2003). Although later onset (after age 25) does occur, it is rare, and most often secondary to a separate Axis I disorder such as depression or an eating disorder (Wittchen and Fehm 2003). The NCS-R survey yielded a median age of onset for social phobia of 13 years with 50% of the sample reporting onset between age 8 and age 15 (Kessler et al. 2005a). This is supported by research findings that social phobia is common in children and is diagnosed in a significant percentage of children referred to a specialty anxiety disorders clinic (Albano et al. 1995). A history of childhood anxiety has been associated with an earlier age of onset of social phobia as well as greater severity and comorbidity (Otto et al. 2001).

Mean age at onset for specific phobias appears to differ depending on the type of phobia. Phobias of animals, blood, storms, and water tend to begin in early childhood whereas phobias of heights tend to begin in the teens (Curtis et al. 1990), and phobias of the situational type (e.g., claustrophobia) begin even later, with mean ages at onset in the late teens to middle twenties (Curtis et al. 1990, Lipsitz et al. 2002). The NCS-R survey yielded a median age of onset for specific phobia of 7 years with 50% of the sample reporting onset between age 5 and age 12 (Kessler et al. 2005a).

## Comorbidity Patterns

The issue of comorbidity has received increasing attention in the years since the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (American Psychiatric Association 1987), was published. Before that time, the diagnostic decision rules in DSM-III were arranged hierarchically, such that having one diagnosis precluded the assignment of other diagnoses lower on the hierarchy. According to DSM-III-R and DSM-IV-TR, patients may receive multiple diagnoses. The issue of comorbidity is important for several reasons. First, covariation among disorders provides valuable information about the nature of specific disorders as well as the utility of current diagnostic nomenclature. For example, high rates of co-occurrence between two disorders could reflect overlap in the definitions of two disorders (as may be the case with social phobia and avoidant personality disorder) or shared etiological pathways. In addition, comorbidity may have implications for treatment. For example, an individual with social phobia who abuses alcohol might be less likely to benefit from treatment for social phobia if the alcohol abuse affects compliance with the social phobia treatment.

### Specific Phobia

One of the variables considered by the DSM-IV-TR Anxiety Disorders Work Group in its decision to classify specific phobias by types was the pattern of covariation observed among specific phobias within each of the four main types (Curtis et al. 1990). For example, about 70% of individuals with blood phobias tend to have injection phobias as well (Öst 1992). In addition, numerous factor analytical studies have found that blood–injection–injury phobias tend to cluster together as do animal phobias, natural environment phobias, and situational phobias (e.g., Liddell et al. 1991). In other words, having a phobia of one specific phobia type makes an individual more likely to have additional phobias of the same type than of other types. However, the clustering is not perfect; many studies show exceptions to this pattern (Curtis et al. 1998) and it has been argued that assigning specific phobias to types may not be diagnostically useful for a number of reasons (Antony et al. 1997b). Research on the classification of specific phobia types is inconsistent. For example, in several of these studies, height phobias tend to be associated with situational phobias (e.g., claustrophobia), despite height phobias being listed as an example of the natural environment type in DSM-IV-TR (Muris et al. 1999). Furthermore, it is not always clear where a particular phobia should be assigned. Is a phobia of dentists an example of a blood–injection–injury phobia or does it fall into the "other" type? Finally, it has been argued (Antony et al. 1997b) that simply naming the phobia (e.g., specific phobia, choking) is more informative and clinically useful than using the type classification "specific phobia, other type."

Specific phobias tend to co-occur with other specific phobias. One study found that 76% of a sample of 915 individuals with a lifetime history of specific phobias had at least one or more additional specific phobias (Curtis et al. 1998). This finding is consistent with research showing that individuals with specific phobias often report multiple fears on a fear survey (Hofmann et al. 1997). However, other research indicates that comorbid phobias may not be as prevalent (Fredrikson et al. 1996) and that numbers in previous studies may have been inflated by a lack of discrimination between multiple phobias and fears of multiple situations that are accounted for by a single phobia. For example, an individual may fear bridges, elevators, and flying due to a fear of heights. In this case, the multiple situations represent one specific phobia rather than multiple phobias. A recent methodologically rigorous study found that 15% of patients with a principal diagnosis of specific phobia also met criteria for another type of specific phobia (Brown et al. 2001a).

In addition, specific phobias often co-occur with other DSM-IV-TR disorders. A recent study found that 33% of patients presenting with a principal diagnosis of specific phobia had additional symptoms that met criteria for an Axis I anxiety or mood disorder (Brown et al. 2001a). However, compared with individuals who have other anxiety disorders, individuals with principal diagnoses of a specific phobia are less likely to have additional diagnoses. Rather, specific phobias typically occur on their own or as additional diagnoses of lesser severity than the principal diagnosis. For example, in one study, specific phobias occurred in about 27% of individuals with panic disorder and agoraphobia, in 16% of individuals with generalized anxiety disorder, and in 3–9% of individuals with other DSM-III-R disorders (Moras et al. 1995). Other studies confirm that specific phobias are a frequently occurring additional diagnosis, particularly with other anxiety disorders (Curtis et al.

1998, Goisman et al. 1995). However, specific phobias tend to occur less frequently in the context of other disorders such as depression (Schatzberg et al. 1998) and alcohol use disorders (Lehman et al. 1998).

Whereas the above-mentioned studies reflect "syndrome" comorbidity, one can also discuss comorbidity at the "symptom" level. In other words, one can examine the frequency with which specific fears are associated with disorders regardless of whether they meet criteria for specific phobia. One study examined the rate of subclinical specific fears (i.e., those not meeting a clinical threshold for distress or functional impairment) in a sample of patients with anxiety disorders (Antony et al. 1994). In this study, specific fears were the most frequently assigned subclinical diagnoses, with 28% of these patients reporting subclinical fears. In fact, almost half of all subclinical diagnoses assigned were specific fears. In summary, it appears that specific phobias commonly occur as additional diagnoses, at both clinical and subclinical levels.

## Social Phobia

Social anxiety is a feature of many disorders. Individuals with panic disorder, obsessive–compulsive disorder, or eating disorders often avoid social situations because of the possibility of being judged negatively if their symptoms are noticed by others. However, to meet diagnostic criteria for social phobia, one's concerns must not be exclusively related to the symptoms of another disorder. With this criterion in mind, social phobia still tends to be associated with a variety of other DSM-IV-TR disorders. Furthermore, unlike specific phobias, social phobia is frequently associated with additional disorders of lesser severity. It is estimated that 50–80% of patients with social phobia have at least one other mental disorder, most commonly other anxiety disorders, major depressive disorder, and substance abuse disorders (Fehm et al. 2005, Wittchen and Fehm 2003). The presence of comorbid mood disorders has been associated with a greater duration of social phobia as well as more severe impairment (Erwin et al. 2002). Other studies have found that panic disorder with or without agoraphobia, generalized anxiety disorder, posttraumatic stress disorder, major depressive disorder, and substance abuse are common additional diagnoses as well (Brown et al. 2001a, Kessler et al. 2005b, Mennin et al. 2000, Van Ameringen et al. 1991). In one prospective study, an estimated relative risk ratio of 2.30 for alcohol abuse or dependence was found in individuals with subclinical social phobia relative to individuals without social phobia or subclinical social fears, suggesting that individuals with subclinical social phobia were more than twice as likely to develop alcohol use disorders than were individuals without social phobia or subclinical social anxiety (Crum and Pratt 2001).

As an additional diagnosis, social phobia is often assigned in patients with panic disorder with agoraphobia, generalized anxiety disorder, obsessive–compulsive disorder, and major depressive disorder (Brown et al. 2001a). Social phobia is also common among patients with eating disorders (Schwalberg et al. 1992) and alcohol abuse (Riemann 1993) as well. In a study examining comorbidity in eating disorders, 20% of the sample had a lifetime diagnosis of social phobia (Kaye et al. 2004). When social phobia coexists with a mood disorder, substance abuse disorder, or another anxiety disorder, the social phobia tends to predate the other disorder (Van Ameringen et al. 1991). Treatment of these disorders should include components that address the social phobia when both disorders occur together.

## Course

As discussed earlier, the mean age at onset of social phobia is in the middle teens. The age at onset of specific phobias varies depending on the phobia type, with phobias of animals, blood, storms, and water tending to begin in early childhood, phobias of heights beginning in the teens, and situational phobias beginning in the late teens to middle twenties. Although childhood fears are often transient (e.g., most children outgrow fear of the dark without treatment), fears that persist into adulthood usually have a chronic course unless treated.

Although many phobias begin after a traumatic event, many patients do not recall the specific onset of their fear, and few empirical data exist regarding the initial period after the fear onset. Clinically, however, some patients report a sudden onset of fear, whereas others report a more gradual onset. Studies examining the onset of phobias have tended to assess the onset of the *fear* rather than the onset of the *phobia* (i.e., the point at which the fear creates significant distress or functional impairment). A study by Antony et al. (1997b) suggests that the fear and phobia onset are often not the same. Patients with specific phobias of heights, animals, blood–injection, or driving were asked to estimate the earliest age at which they could recall having their fear and the earliest age at which they could recall experiencing distress or functional impairment due to their fear. As shown in Table 70–3, phobias began at an average of 9 years after the fear onset. Anecdotally, the types of factors leading to the transition from fear to phobia included gradual increases in the intensity of fear, additional traumatic events (e.g., panic attacks, car accidents), increased life stress, and changes in living situation (e.g., starting a job that requires exposure to heights). Similarly, it is not unusual for individuals with social phobia to report having been shy as children, although their anxiety may not have reached phobic proportions until later.

The impact of specific phobia on quality of life has received little attention (Mogotsi et al. 2000). However, evidence suggests that specific phobia may be associated with significant psychosocial impairment (Essau et al. 2000). Social phobia is associated with a high degree of impairment and disability that increases over time (Fehm et al. 2005, Wittchen and Fehm 2003). For example, in one study, one fifth of patients with social phobia had clinically severe impairment in quality of life defined as being two more standard deviations below the community norm (Rapaport et al. 2005). One factor that may contribute to impairment in social performance for individuals with social phobia is the use of safety behaviors (Stangier et al. 2006).

## Differential Diagnosis

Social anxiety is associated with a variety of DSM-IV-TR disorders. Similarly, several disorders other than specific phobia are associated with fear and avoidance of circumscribed stimuli. Therefore, accurate diagnosis of specific and social phobias depends on a thorough understanding of the DSM-IV-TR criteria and knowledge of how to distinguish these disorders from related conditions. Correct

**Table 70–3 Mean Age of Onset (and Standard Deviations) for Specific Fears and Phobias and Agoraphobia**

| | Earliest Age of Recall (by Group) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Heights ($n$ = 15) | Animals ($n$ = 15) | Blood/Injection ($n$ = 15) | Driving ($n$ = 15) | PDA ($n$ = 15) | $F$ | $\eta^2$ |
| Fear | $20.47^{ac}$ (17.53) | $10.80^{ab}$ (8.37) | $7.93^{b}$ (3.71) | $25.67^{c}$ (11.84) | $28.14^{c}$ (11.95) | $8.78^{***}$ | 0.34 |
| Phobia | $34.13^{a}$ (16.36) | $20.00^{bcd}$ (10.21) | $14.50^{b}$ (8.30) | $32.20^{acd}$ (12.49) | $29.07^{ac}$ (11.52) | $6.95^{***}$ | 0.29 |
| Difference | $13.66^{a}$ (11.66) | $9.2^{ab}$ (10.64) | $6.50^{ab}$ (7.53) | $6.53^{ab}$ (8.17) | $0.93^{b}$ (1.73) | $4.08^{**}$ | 0.19 |

*Note*: PDA, panic disorder with agoraphobia. "Fear" refers to the age at which the fear began for individuals with specific phobias or the age at which panic attacks began for individuals in the panic disorder with agoraphobia (PDA) group. "Phobia" refers to the age at which the fear began to cause significant distress or functional impairment for the specific phobia groups or the age at which the individuals with PDA met full criteria for the disorder. "Difference" was calculated by subtracting ages of onset for the *fear* from those for the *phobia*. Group means (across rows) sharing superscript letters do not differ at $p < 0.05$. $^{**}P < .01$; $^{***}P < .001$.

*Source*: Antony et al. 1997b. Copyright 1997 Elsevier Science..

diagnosis depends on being able to evaluate the patient's focus of apprehension, reasons for avoidance, and range of situations feared.

Panic disorder with agoraphobia may easily be misdiagnosed as social phobia or a specific phobia (especially the situational type). For example, many patients with panic disorder avoid a variety of social situations because of anxiety about having others notice their symptoms. In addition, some individuals with panic disorder may avoid circumscribed situations, such as flying, despite reporting no other significant avoidance. Four variables should be considered in making the differential diagnosis: (1) type and number of panic attacks, (2) focus of apprehension, (3) number of situations avoided, and (4) level of anxiety outside of the phobic situation.

Patients with panic disorder experience unexpected panic attacks and heightened anxiety outside of the phobic situation, whereas those with specific and social phobias typically do not. In addition, individuals with panic disorder are more likely than those with specific and social phobias to report fear and avoidance of a broad range of situations typically associated with agoraphobia (e.g., flying, enclosed places, crowds, being alone, shopping malls). Finally, patients with panic disorder are typically concerned only about the possibility of panicking in the phobic situation or about the consequences of panicking (e.g., being embarrassed by one's panic symptoms). In contrast, individuals with specific and social phobias are usually concerned about other aspects of the situation as well (e.g., being hit by another driver, saying something foolish).

Consider two examples in which the differential diagnosis with panic disorder might be especially difficult. First, individuals with claustrophobia are typically extremely concerned about being unable to escape from the phobic situation as well as being unable to breathe in the situation. Therefore, like patients with panic disorder and agoraphobia, they usually report heightened anxiety about the possibility of panicking. The main variable to consider in such a case is the presence of panic attacks outside of claustrophobic situations. If panic attacks occur exclusively in enclosed places, a diagnosis of specific phobia might best describe the problem. In contrast, if the patient has unexpected or uncued panic attacks as well, a diagnosis of panic disorder might be more appropriate.

A second example is a patient who avoids a broad range ing on busy streets, and various social situations including parties, meetings, and public speaking. Without more information, this patient's problem might appear to meet criteria for social phobia, panic disorder with agoraphobia, or both diagnoses. As mentioned earlier, patients with panic disorder often avoid social situations because of anxiety about panicking in public. In addition, patients with social phobia might avoid situations that are typically avoided by individuals with agoraphobia for fear of seeing someone that they know or of being observed by strangers. To make the diagnosis in this case, it is necessary to assess the reasons for avoidance.

It may be difficult to distinguish among types of specific phobias. For example, is a bridge phobia best considered a situational type (i.e., driving) or a natural environment type (i.e., heights)? This decision should be based on the context of the bridge phobia. If the individual fears falling or fears other high places, a height phobia may be the appropriate diagnosis. In contrast, if bridges are one of many driving-related situations that the person fears, a driving phobia might be more appropriate.

Other diagnoses that should be considered before a diagnosis of specific phobia is assigned include posttraumatic stress disorder (PTSD) (if the fear follows a life-threatening trauma and is accompanied by other PTSD symptoms such as reexperiencing the trauma), obsessive–compulsive disorder (if the fear is related to an obsession, e.g., contamination), hypochondriasis (if the fear is related to a belief that he or she has some serious illness), separation–anxiety disorder (if the fear is of situations that might lead to separation from the family, e.g., traveling on an airplane without one's parents), eating disorders (if the fear is of eating certain foods but not related to a fear of choking), and psychotic disorders (if the fear is related to a delusion).

Social phobia should not be diagnosed if the fear is related entirely to another disorder. For example, if an individual with obsessive–compulsive disorder avoids social situations only because of the embarrassment of having others notice her or his excessive hand washing, a diagnosis of social phobia would not be given. Furthermore, individuals with depression, schizoid personality disorder, or a pervasive developmental disorder may avoid social situations because of a lack of interest in spending time with

others. To be considered social phobia, an individual must avoid these situations specifically because of anxiety about being evaluated negatively.

In the case of generalized social phobia, the diagnosis of avoidant personality disorder may be considered. However, most studies suggest that the differences between avoidant personality disorder and social phobia are more quantitative than qualitative and that the former may simply be a more severe form of the latter (Ralevski et al. 2005, Widiger 1992). Therefore, most patients who meet criteria for avoidant personality disorder will meet criteria for social phobia as well. Some researchers have proposed that the diagnosis of social phobia is preferred to that of avoidant personality disorder given that a personality disorder diagnosis should be ruled out when it includes significant features of an Axis I disorder (Wittchen and Fehm 2003).

Finally, social and specific phobias should be distinguished from normal states of fear and anxiety. Many individuals report mild fears of circumscribed situations or mild shyness in certain social situations. Others may report intense fears of public speaking or heights but insist that these situations rarely arise and that they have no interest in being in these situations. For the criteria for a specific or social phobia to be met, the individual must report significant distress about having the fear or must report significant impairment in functioning.

A variety of factors should be considered in deciding whether a patient's fear exceeds the threshold necessary for a diagnosis of specific or social phobia. To make the differential diagnosis between normal fears and clinical phobias, the psychiatrist should consider the extent of the individual's avoidance, the frequency with which the phobic stimulus is encountered, and the degree to which the individual is bothered by having the fear. For example, an individual who fears seeing snakes in the wild but who lives in the city, never encounters snakes, and never even thinks about snakes would probably not be diagnosed with a specific phobia. In contrast, when an individual's fear of snakes leads to avoidance of walking through parks, camping, swimming, and watching certain television programs, despite having an interest in doing these things, a diagnosis of specific phobia would be appropriate.

Similar factors should be considered in deciding at what point normal shyness reaches an intensity that warrants a diagnosis of social phobia. An individual who is somewhat quiet in groups or when meeting new people but does not avoid these situations and is not especially distressed by his or her shyness would probably not receive a diagnosis of social phobia. In contrast, an individual who frequently refuses invitations to socialize because of anxiety, quits a job because of anxiety about having to talk to customers, or is distressed about her or his social anxiety would be likely to receive a diagnosis of social phobia.

Diagnostic decision trees for social and specific phobias are presented in Figures 70–1 and 70–2.

## Differences in Developmental, Gender, and Cultural Presentations

For both assessment and treatment planning, it is important to consider variations in disorder features and phenomenology across developmental stages, gender, and cultural background.

### Developmental Differences

Several studies have begun to look at the prevalence of phobias across the life span. Little is known about the prevalence of phobias among elderly persons, although there is some evidence that the prevalence of phobic disorders may decrease slightly after age 65 years (Eaton et al. 1991).

Among children, specific and social fears are common (Straus and Last 1993). Because these fears may be transient, DSM-IV-TR has included a provision that social and specific phobias not be assigned in children unless they are present for more than 6 months. In addition, children may be less likely than adults to recognize that their phobia is excessive or unrealistic. The specific objects feared by children are often similar to those feared by adults, although children may be more likely to fear objects and situations that are not easily classified in the four main specific phobia types in DSM-IV-TR (e.g., balloons or costumed characters). In addition, children often report specific and social phobias having to do with school. Children with social phobia tend to avoid changing for gym class in front of others, eating in the cafeteria, or speaking in front of the class. They may stay home sick on days when frightening situations arise or may make frequent trips to the school nurse. Whereas some investigators have found that boys and girls are equally likely to present for treatment of phobias (Straus and Last 1993), others have found social phobia to be more common among girls than boys (Anderson et al. 1987). In one prospective study of childhood anxiety disorders, Last et al. (1996) found that almost 70% of children with a specific phobia were recovered over a 3- to 4-year period compared to a recovery rate of 86% for social phobia. Thus, almost a third of the clinical sample with specific phobia had symptoms that still met clinical criteria for specific phobia at the end of the follow-up period. This was the lowest recovery rate among the anxiety disorders that were studied. However, those in the clinical sample with specific phobia had the lowest rate of development of new psychiatric disorders (15%) compared to the other anxiety disorders studied (e.g., the rate of development for new psychiatric disorders was 22% for those in the clinical sample with social phobia).

### Gender Differences

As mentioned earlier, specific phobias tend to be more common among women than men (e.g., Curtis et al. 1998). This finding seems to be strongest for phobias from the animal type, whereas sex differences are smaller for height phobias and blood–injury–injection phobias. In addition, social phobia tends to be slightly more prevalent among women than men, although these differences are relatively small (Antony and Swinson 2000a, Fehm et al. 2005).

There are several reasons why women may be more likely than men to report specific phobias. First, as discussed earlier, there is evidence that men tend to underreport their fear (Pierce and Kirkpatrick 1992). Also, women may be more likely than men to seek treatment for their difficulties, which would account for the fact that sex differences are often larger in treatment samples compared with epidemiological samples. In addition, as discussed later, sex ratios for phobias differ across cultures, which may be explained by cultural differences in treatment seeking. Finally, the sex difference in prevalence may reflect actual differences between men and women in susceptibility to develop phobias.

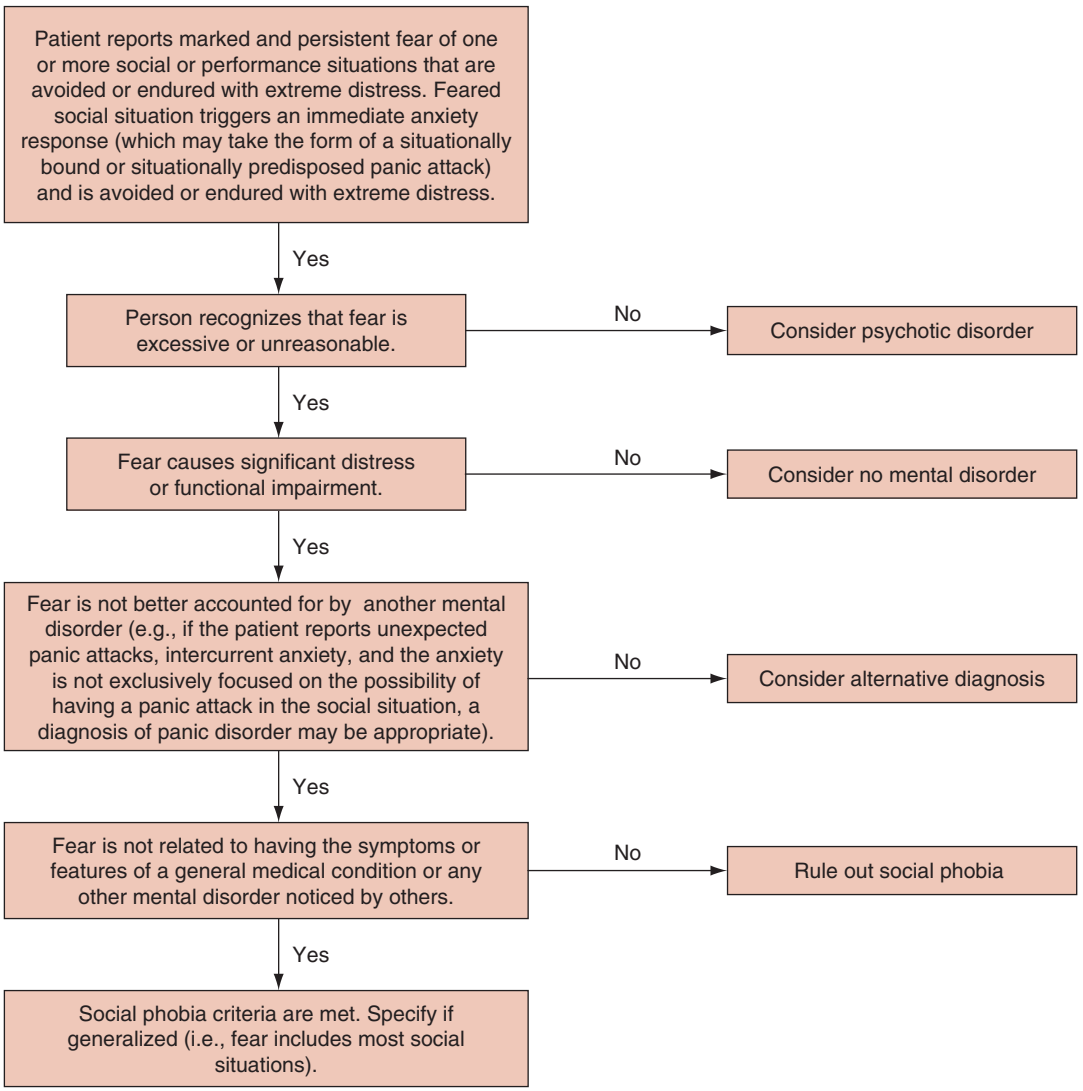



**Figure 70–1** *Social phobia: diagnostic decision tree.*

Women and men are taught to deal differently with typical phobic stimuli. Traditionally, boys more than girls are often encouraged to play with spiders and toy snakes and to engage in more adventurous activities (e.g., hiking in high places). In addition, women may have more role models for the development of fear than men do. Images of women standing on chairs when they see a mouse or running away from spiders are common in children's cartoons and other media, but men are rarely depicted as being frightened by these objects. Therefore, it is possible that in Western cultures women learn to fear certain situations more strongly than do men. Of course, it is difficult to know whether culture and the media are responsible for sex differences or whether they simply reflect differences that exist for other reasons (e.g., different predisposing factors). It will be interesting to see whether sex ratios for phobias change as traditional gender roles continue to evolve.

One study examining sex differences and social phobia found significant gender differences in the presentation of social phobia (Turk et al. 1998). Whereas men were more fearful than women of urinating in public bathrooms and returning items to a store, women were more fearful than men of a number of situations including talking to people in authority, public speaking, being the center of attention, expressing disagreement, and throwing a party. Sex differences were not found in terms of comorbidity, social phobia subtypes, or duration of illness.

## Cultural Differences

Little is known about cultural differences in specific and social phobias. Several reasons have been suggested for this lack of relevant data. First, individuals from minority cultures in the United States tend to underuse traditional mental health facilities and are more likely than other groups to terminate treatment after one session (Sue 1990). When African-Americans seek mental health services, they may be more likely to present to a physician, minister, or community mental health clinic than a university hospital, which is where much of the research tends to take place (Neal and Turner 1991). In addition, certain minority groups may be less likely to participate in psychological research because of the negative ways in which research data have historically

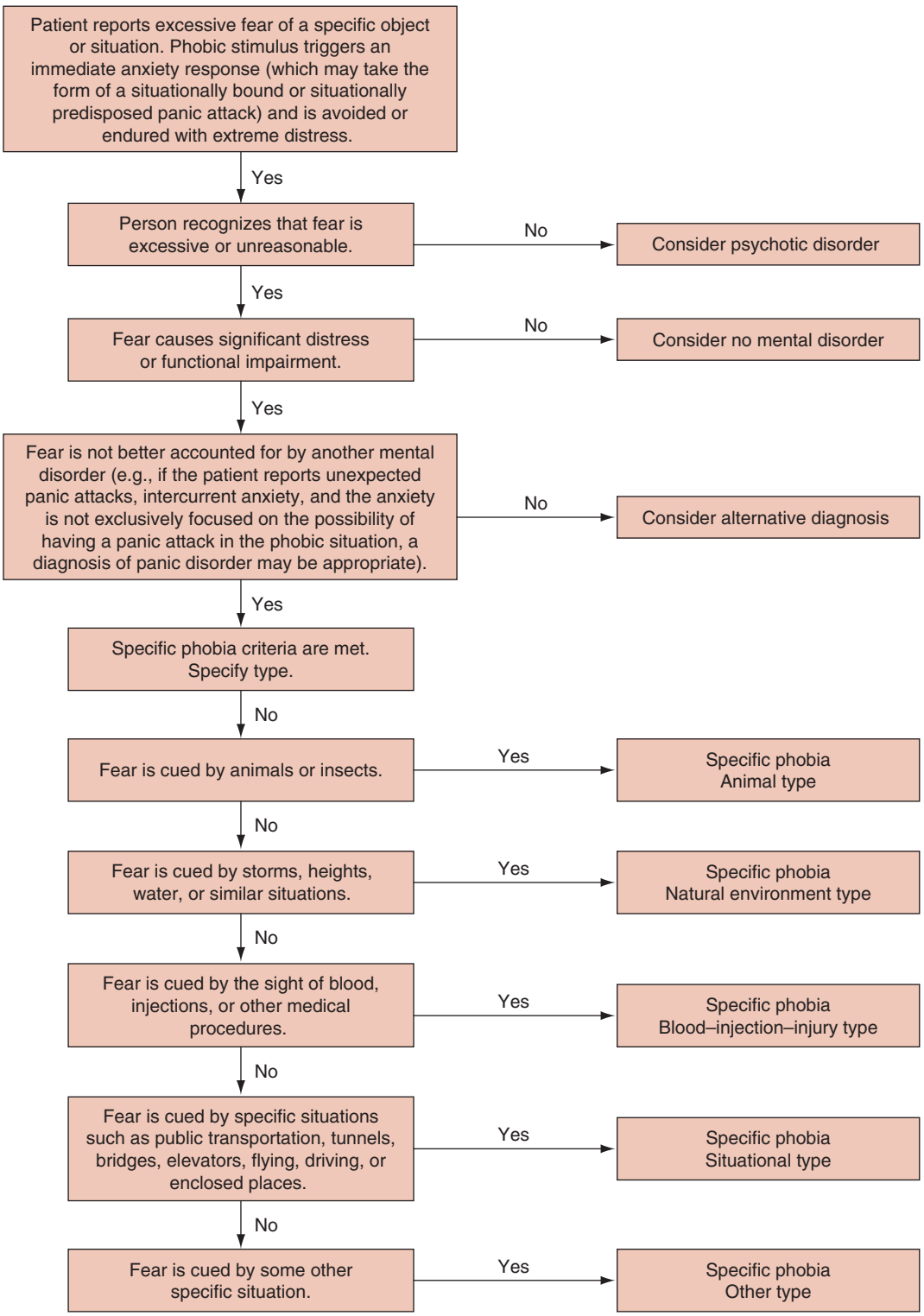



**Figure 70–2** *Specific phobia: diagnostic decision tree.*

been used to affect government policies toward minority groups (Neal and Turner 1991).

Nevertheless, a few studies bear on the issue of cultural differences in phobias. For example, there is evidence from epidemiological studies that African-Americans are 1.5–3 times as likely as whites to report phobic disorders, even after controlling for education and socioeconomic status (Brown et al. 1990, Curtis et al. 1998, Warheit et al. 1975). Several explanations for this finding have been provided. For example, some of the fears reported by African-American individuals may reflect realistic concerns that were misdiagnosed as phobias. For example, African-American persons in inner city communities may have more realistic reasons to fear violence (Warheit et al. 1975). Furthermore,

African-Americans experience more negative evaluation from others, and some of their social concerns may be realistic. Another possibility is that African-Americans experience more chronic stress than do whites and therefore may be more susceptible to the development of phobias and other problems. Finally, there may be cultural differences in response biases on questionnaire measures of fear and during interviews (Brown et al. 1990).

Other research has found that specific phobias are more common among US-born Mexican-Americans than in US-born whites or immigrant Mexican-Americans, after controlling for sex, age, socioeconomic status, and various other variables (Karno et al. 1989, Vega et al. 1998). No group differences emerged for the prevalence of social phobia across these groups (Karno et al. 1989). Some of the factors mentioned (e.g., differences in stress and response biases) may explain the differences between whites and Mexican-Americans born in the United States. In addition, it has been suggested that "selective migration" may account for the relatively low rate of phobias in immigrant Mexican-Americans. In other words, individuals with specific phobias may be less likely to emigrate.

A variety of studies have shown that specific phobias, social phobia, and related conditions exist across cultures. For example, in Japan, a condition exists called *taijin kyôfu* in which individuals have an "obsession of shame." This condition has much overlap with social phobia in that it is often accompanied by fears of blushing, having improper facial expressions in the presence of others, looking at others, shaking, and perspiring in front of others (Takahashi 1989). In addition, studies have identified individuals with social and specific phobias in a variety of other non-Western countries including Saudi Arabia (Bassiony 2005, Chaleby 1987), Israel (Iancu et al. 2006), India (Raguram and Bhide 1985), Japan (Kleinknecht et al. 1997, Sakurai et al. 2005), and other East Asian countries (Chang 1997, Lee and Oh 1999). Interestingly, in some other cultures, the sex ratio for phobias tends to be reversed. For example, in studies from Saudi Arabia and India, up to 80% of individuals reporting for treatment of phobias were male. Similarly, in Japan about 60% of patients with *taijin kyôfu* are male. In the case of phobias in India, it has been suggested that traditional gender roles may account for the difference in treatment seeking in Indian men and women (Raguram and Bhide 1985). Specifically, Indian women are often discouraged from leaving the house alone or conversing with others without the husband's permission. It is difficult to know how cultural expectations affect sex differences in phobias in other cultures.

Psychiatrists treating patients from different cultures should be aware of cultural differences in presentation and response to treatment. For example, there is some evidence that although Asian Americans and European Americans report a similar number of events that evoke anxiety in social situations, Asian Americans report more negative emotions in social situations than do European Americans (Lee et al. 2006). In a review of culture-specific strategies in counseling, Sue (1990) summarized data on cultural differences in verbal communication styles, proxemics (i.e., use of interpersonal space), nonverbal communication, and other verbal cues (e.g., tone and loudness). Many cues that a psychiatrist might use to aid in the diagnosis of social phobia in white Americans may not be useful for diagnosing the condition in other cultures. For example, although many psychiatrists interpret a lack of eye contact as indicating shyness or a lack of assertiveness, avoidance of eye contact among Japanese and Mexican-Americans is often viewed as a sign of respect, according to Sue (1990). In contrast to white Americans, Japanese are apparently more likely to view smiling as a sign of embarrassment or discomfort. Furthermore, cultural differences in tone and volume of speech may lead psychiatrists to misinterpret their patients. For example, whereas white Americans often are uncomfortable with silence in a conversation, British and Arab individuals may be more likely to use silence for privacy and other cultures use silence to indicate agreement among the parties or a sign of respect. In addition, Asian individuals have been reported to speak more quietly than white Americans, who in turn speak more quietly than those from Arab countries. Therefore, differences in the volume of speech should not be taken to imply differences in assertiveness or other indicators of social anxiety.

Treatment methods may have to be adapted for different cultures. For example, the direct style of many cognitive and behavioral therapists may be more likely to be perceived as rude or insensitive by individuals with certain cultural backgrounds than those with other backgrounds. It should be noted that individuals within a culture differ on these variables just as individuals across cultures differ. Therefore, although psychiatrists should be aware of cultural differences, these differences should not blind the psychiatrist to relevant factors that are unique to each individual patient.

## Etiology and Pathophysiology

The etiology of both social and specific phobia is complex and involves an interaction of biological, psychological, and social/environmental factors. This next section provides a review of etiological pathways and pathophysiology.

## Genetic Factors

Specific phobia and social phobia tend to run in families. It appears that being a first-degree relative of an individual with a specific phobia puts one at a greater risk for a specific phobia compared with first-degree relatives of never mentally ill controls (31% versus 11%). However, the particular phobia that is transmitted is usually different from that in the relative, although it is often from the same general type (e.g., animal, situational). Furthermore, relatives of people with specific phobias are not at increased risk for other types of anxiety disorders (including social phobia) or subclinical fears (Fyer et al. 1990). The results of studies examining genetic transmission of different phobia subtypes have been mixed. In one twin study, Kendler et al. (1999) found heritability estimates of 47% for animal phobias, 59% for blood–injection–injury phobias, and 46% for situational phobias. Others studies have not supported a genetic component in the development of natural environment and situational fears (e.g., Skre et al. 2000). The heritability of blood and injection phobias may be even greater than that for other phobias. One study found that 61% of individuals with blood phobia and 29% of those with injection phobias reported having a first-degree relative with the same fear (Öst 1992). However, these findings should be interpreted

with caution because relatives did not undergo independent interviews.

Findings for individuals with social phobia and their families show a similar pattern. In one study, 16% of first-degree relatives of individuals with social phobia had symptoms that met criteria for social phobia, whereas only 5% of first-degree relatives of never mentally ill control individuals had social phobia (Fyer et al. 1993). Other research has found that the relative risk for generalized social phobia is approximately ten times higher in first-degree relatives of individuals with generalized social phobia than in first-degree relatives of a control group without social phobia (Stein et al. 1998a).

Of course, the existence of a disorder in multiple family members does not necessarily imply genetic transmission. Family members often share learning experiences and other environmental factors. To establish a genetic relationship among family members with a particular disorder, twin studies, adoption studies, and molecular genetics studies are typically conducted. Currently, there are no adoption or molecular genetics studies of social or specific phobias, and twin studies have yielded conflicting results.

A twin study by Skre et al. (1993) found that although many of the anxiety disorders have a strong genetic component, in the case of specific and social phobias, environmental influences seem to be most important. In contrast, Andrews et al. (1990) found a genetic contribution to the development of neurotic traits and symptoms that may predispose individuals to develop anxiety disorders in general, but not a particular anxiety disorder. This study included individuals with social phobia but not specific phobias. Another twin study examining genetic transmission of both specific and social phobias found heritability estimates of 51% for social phobia, 47% for animal phobias, 59% for blood–injection–injury phobias, and 46% for situational phobias (Kendler et al. 1999). Consistent with previous research (Page and Martin 1998), individual-specific environmental influences (e.g., experiencing a traumatic event in the phobic situation) were found to be etiologically significant in the development of both social and specific phobias but family-specific environmental influences (e.g., shared environment) were not (Kendler et al. 1999). In another genetic study of specific and social phobias conducted by Kendler et al. (1992), both genetic and individual-specific environmental factors (e.g., phobia-specific traumatic event) were influential in the development of specific phobia, whereas for social phobia, both genetic and nonspecific environmental factors have an etiological role. More recently, Hettema et al. (2005) found that social phobia loaded on to a genetic factor shared with generalized anxiety disorder, panic, and agoraphobia whereas specific phobias loaded onto a separate uncorrelated genetic factor.

Although there are conflicting findings on whether there is a general genetic factor (influencing risk for any anxiety disorder) or a specific genetic factor (influencing risk for specific anxiety disorders such as specific and social phobias), some general conclusions can be made. In the case of social phobia, there seems to be a moderate (based on the strength of the correlations from twin studies) disorder-specific genetic influence combined with specific and nonspecific environmental influences. In the case of specific phobia, evidence supports a disorder-specific genetic contribution combined with disorder-specific environmental influences (e.g., traumatic conditioning experiences involving the phobic object or situation). The underlying structure of the genetic and environmental risk factors is similar between men and women for both social phobia and specific phobia (Hettema et al. 2005).

Although the nature of the genetic contribution has yet to be specified (a low threshold for alarm reactions or vasovagal responses is one possibility), specific and social phobias may be related to personality factors that have been found to be highly heritable. For example, fear of negative evaluation, a cognitive construct central to the phenomenology of social phobia, has been found to be moderately heritable (48%) in a twin study conducted by Stein et al. (2002). Two broader personality traits that may be relevant are neuroticism (or emotionality) and extroversion (or sociability) (Plomin 1989). Average heritability estimates for these traits are about 50% across a wide range of genetic studies. Emotionality probably predisposes individuals to develop a range of anxiety and mood disorders whereas sociability may be most relevant to social phobia. Furthermore, certain phobias may have other specific genetic contributions. Up to 70% of individuals with blood phobia report a history of fainting on exposure to blood (Öst 1992). It has been suggested that an inherited overactive baroreflex may contribute to the high rate of familial transmission of blood phobias (Adler et al. 1991).

## Neurobiological Factors

In contrast to the situation with other anxiety disorders, little is known about the physiological correlates of specific and social phobias. Only a few studies have examined physiological correlates of specific phobia. Research examining brain activity during the experience of phobic fear using positron emission tomography has yielded inconsistent results (Rauch et al. 1995, Wik et al. 1997), with some studies finding changes in cerebral blood flow associated with viewing phobia-relevant scenes and some studies finding no differences in cerebral blood flow between participants with and without phobias. In social phobia, decreased regional cerebral blood flow response to an anxiogenic public speaking task has been found bilaterally in the amygdala, hippocampus, and the periamygdaloid, rhinal, and parahippocampal cortices in individuals treated with citalopram or cognitive–behavioral group therapy, but not in those assigned to a waiting list control (Furmark et al. 2002). In addition, the degree of amygdalar–limbic attenuation was associated with clinical improvement in 1-year follow-up. Specific phobia may have been of less interest to researchers because no effective pharmacological treatments exist for this disorder. However, effective drug treatments have been identified for social phobia, leading to an increased interest in the biological factors underlying this disorder (Mathew et al. 2001).

Studies on the relationship between serotonin and social phobia have been mixed. Selective serotonin reuptake inhibitors (SSRIs) have been shown to be very effective in the treatment of social phobia. In addition, there is evidence of augmented cortisol response to fenfluramine in patients with social phobia, suggesting an association between social phobia and selective supersensitivity in the serotonergic system (Tancer et al. 1994, 1995). However,

there is research showing that [$^3$H] paroxetine binding (an indicator of serotonergic functioning) does not differ between social phobia patients and nonanxious controls (Stein et al. 1995).

There has also been some evidence to suggest a relationship between dopamine and social phobia. Unlike panic disorder, which responds well to a variety of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) (e.g., Schweizer et al. 1993), social phobia tends to have a positive response to MAOIs and show little response to tricyclic antidepressants (Levin et al. 1989). Whereas tricyclic antidepressants tend to act on noradrenergic and serotonergic systems, MAOIs affect noradrenergic, serotonergic, and dopaminergic systems (Cooper et al. 1983). This finding has led some investigators to suggest that the dopamine system is primarily involved in social phobia (Levin et al. 1989), which would explain why biological challenges that appear to affect noradrenergic activity (e.g., sodium lactate infusion, carbon dioxide inhalation) have little effect on patients with social phobia, despite having panicogenic effects in patients with panic disorder (Rapee et al. 1992). The dopamine hypothesis is consistent with findings that dopamine metabolite levels correlate with measures of extroversion (King et al. 1986) as well as findings that mice bred to be timid have been shown to be deficient in brain dopamine concentration (Lewis et al. 1989). In addition, a neuroimaging study found that striatal dopamine reuptake site densities were significantly lower in patients with social phobia as compared to controls (Tiihonen et al. 1997).

With respect to neuroendocrine correlates in social phobia, studies of the hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes in social phobia have found few differences between patients with social phobia and control persons. For example, research has found that patients with social phobia and controls did not differ on tests of thyroid function (Tancer et al. 1990) or levels of urinary free cortisol (Potts et al. 1991). However, more recent studies have found evidence of cortisol differences associated with social anxiety. Some research has found that shy children have higher salivary cortisol than nonshy children (Schmidt et al. 1997), whereas other studies have found evidence of lower salivary cortisol in socially anxious undergraduate students than in non-anxious students (Beaton et al. 2006). In comparison to control volunteers, social phobia patients have also been found to show dichotomies in the distribution and magnitude of their cortisol response to a speech task (social phobia-related stress task), but not a physical exercise task (nonsocial phobia-related stress task) (Furlan et al. 2001).

Imaging studies have found a number of differences between social phobia patients and controls. One study using functional magnetic resonance imaging (fMRI) found that conditioned aversive stimuli were associated with increased activation in the amygdala and hippocampus of social phobia patients, whereas decreased activation in these areas was observed in normal controls (Schneider et al. 1999). Other research using repeat proton magnetic resonance spectroscopy has found significant differences between individuals with social phobia and controls in cortical gray matter. Specifically, Tupler et al. (1997) found that social phobia is associated with specific choline and myoinositol abnormalities in cortical and subcortical gray areas of the brain. Another study using single photon emission computer tomography (SPECT) found that after an 8-week trial of citalopram there was significantly decreased activity in the anterior and lateral part of the left temporal cortex, the left cingulum, and the anterior, lateral, and posterior part of the left midfrontal cortex in a small ($N$ = 15) sample of social phobia patients (Van der Linden et al. 2000a). Compared to treatment responders, treatment nonresponders had higher activity at baseline in the lateral left temporal cortex and the lateral left midfrontal regions. Further research is necessary to understand the significance of these imaging findings as well as their specificity to social phobia.

A few studies have examined patterns of brain activity associated with shyness. In a study on high and low shyness (anxious self-preoccupation and avoidance of social situations) and sociability (preference to be socially active and seek out social situations) in college students, Schmidt (1999) found that shyness was associated with greater relative right frontal electroencephalogram (EEG) activity, whereas sociability was associated with greater relative left frontal EEG. In addition, Schmidt (1999) found the pattern of absolute EEG power in each frontal hemisphere differed for high shy/high social participants and high shy/low social participants.

Finally, there may be good reason to consider different underlying mechanisms in patients with performance-related phobias (e.g., public speaking) than in patients with generalized social phobia (i.e., those who fear most social situations). Individuals with performance-related phobias tend to show more autonomic reactivity (e.g., rapid heart beat) in the phobic situation than do patients with generalized social phobia (Levin et al. 1993). In addition, beta-blockers such as atenolol may be useful for decreasing performance anxiety in normal individuals (Gorman and Gorman 1987), although they have little effect on patients with generalized social phobia (Liebowitz et al. 1992). These facts have led some investigators to suggest that adrenergic hyperactivity may be involved in performance anxiety but not in generalized social phobia (Levin et al. 1989). However, it should be noted that despite limited evidence for the use of beta-blockers in normal groups (e.g., musicians with performance anxiety), their utility for treating patients with a diagnosis of social phobia (e.g., performance fears that lead to significant distress or impairment) has not been established.

## Psychological and Social/Environmental Factors

### Psychoanalytic Perspectives

Historically, the etiology of phobic disorders was typically explained from a psychoanalytic perspective. Freud postulated that phobias may often stem from an unresolved oedipal conflict. Specifically, incestuous sexual desire is proposed to lead to anxiety associated with being attacked and castrated. Although the defense mechanism of repression is typically used to protect the individual from experiencing the anxiety (and the underlying conflict), when repression is insufficient the ego must use additional defense mechanisms. In the case of individuals with phobias, Freud proposed that displacement of the anxiety to a less relevant object or situation occurs (such as a dog or some other animal),

so that the feared object is used to symbolize the primary source of the conflict. Patients with phobias use avoidance to further escape the effects of the anxiety (Nemiah and Uhde 1989). Although Freud's theory was once influential, its impact on current thinking among researchers has waned. Rather, most current research on psychological factors in the development of phobias has tended to focus on conditioning and information-processing theories and their interaction with neurobiological processes and environmental factors.

## Learning and Conditioning Perspectives

Emotions are "contagious." That is, we learn to respond to stimuli, in part, by observing other people's responses and also by our own experiences in these situations. In other words, we come to fear dangerous situations easily. This is important from an ethological perspective because our ancestors who could learn to fear threatening objects or situations easily were more likely to survive and pass these genes to their offspring. This inherited tendency to learn to experience fear in particular situations is the basis of conditioning models of phobia development.

## Mowrer's Two-Stage Model

The two-stage model of Mowrer (1939) was a precursor to current conditioning models for phobia development. According to Mowrer, the first stage in the development of fear involves a classical conditioning process by which a previously neutral stimulus is associated with an aversive stimulus so that the neutral stimulus becomes a trigger for fear. For example, a fear of dogs might develop after an individual is bitten (an aversive stimulus) by a dog (a neutral stimulus). Mowrer's second stage relies on operant conditioning principles to explain the maintenance of phobias. According to Mowrer, phobias are maintained by negative reinforcement resulting from avoidance of the phobic object. In other words, avoidance prevents the uncomfortable symptoms that occur when one is frightened and thereby maintains the desire to avoid the phobic object and situation.

Despite the research interest generated by Mowrer's model, the model suffers from several problems. First, many individuals report no specific conditioning experiences that trigger their phobias. In fact, many individuals report having fears despite never even having encountered the phobic situation, let alone having experienced a trauma in the phobic situation. Second, Mowrer's theory does not explain why many individuals experience traumas but never develop fears. For example, one study found that although traumatic events were reported to be the cause of fear among 56% of individuals with fears of dogs, 66% of nonfearful subjects reported a history of traumatic experiences with dogs that did not lead to the development of fear (Di Nardo et al. 1988).

## Rachman's Pathways to Fear Development

In response to these and other concerns with Mowrer's model, Rachman (1977) proposed three pathways to the development of fear. The first of these is *direct conditioning*, which typically involves the experience of being hurt or frightened by the phobic object or situation. Examples include being involved in an automobile accident, being humiliated in front of a group, falling or almost falling from a high place, or fainting at the sight of blood. Rachman's second pathway is called *vicarious acquisition*, which involves witnessing some traumatic event or seeing someone behave fearfully in the presence of a phobic situation. For example, a child might develop a fear of snakes after seeing her father behave fearfully around snakes, or someone might develop a fear of public speaking after seeing another individual heckled by the audience during a presentation. For the third pathway, Rachman proposed that fears can develop through *informational and instructional pathways*, which refer to the processes of learning through information obtained verbally from other people, the media, or various other sources. It is not surprising that individuals might develop flying phobias, given the frequency with which plane crashes are reported in the news. Similarly, a child might develop a fear of heights if his parents frequently warned him of the dangers of being near high places.

In addition to these pathways, Rachman acknowledged the role of biological constraints on the development of fear. Of particular relevance is the fact that fears are not randomly distributed. To explain this observation, Seligman (1971) proposed that organisms are predisposed to learn certain associations and not others. Seligman called his theory "preparedness" and hypothesized that individuals are "prepared" to develop some associations that lead to fear and not others. For example, an individual might be more likely to develop a fear of dogs after being bitten than to develop a fear of flowers after being pricked by a thorn. Seligman proposed that these associations evolved through natural selection processes to facilitate survival.

Evidence for the theory of preparedness is mixed. Although some authors have concluded that the studies to date do not support preparedness (McNally 1987), it may be argued that these studies have not adequately tested the theory. Most studies examining preparedness have attempted to associate dangerous objects (e.g., snakes) and nondangerous objects (e.g., flowers) with an aversive electrical shock and have found few differences in the subsequent development of fear. However, preparedness predicts that some "associations" are more difficult to establish than others, not that some "objects" are more easily feared than others. The theory does not necessarily predict that shock should be more easily associated with snakes than with flowers. A more appropriate experiment might be to compare the effects of a minor snakebite to the effects of being pricked by a thorny flower on the development of fear of each object.

Though the effects of preparedness have not been completely established, there remains strong evidence that conditioning processes can play an important role in the development of phobic disorders (Bouton et al. 2001). Numerous studies have examined the frequency with which Rachman's three pathways lead to fear development, as illustrated in Table 70–4. Most of these studies have focused on the development of specific phobias, although a few studies included social phobia groups. The majority of studies have found support for the model, indicating that both direct and indirect forms of phobia acquisition occur frequently across a wide range of phobia types (e.g., Merckelbach and Muris 1997, Muris et al. 1997, Townend et al. 2000). However, numerous people report onsets that are unrelated to these pathways (e.g., "I have had this fear

**Table 70–4 Percentage of Individuals with Phobias Reporting Varions Types of Onset***

| Study | Type of Fear | Direct Conditioning | Vicarious Conditioning | Information |
|---|---|---|---|---|
| McNally and Steketee (1985) | Animals | 23 | 0 | 4 |
| Menzies and Parker (2001) | Heights | 19 | 15 | 7 |
| Di Nardo et al. (1988) | Dogs | 56 | – | – |
| Merckelbach and Muris (1997) | Spiders | 23 | 15 | 4 |
| Merckelbach et al. (1992) | Spiders | 66 | 59 | 34 |
| Ehlers et al. (1994) | Driving | 36 | 12 | 16 |
| Merckelbach et al. (1996) | Spiders | 41 | 18 | 5 |
| Menzies and Clarke (1993b) | Heights | 18 | 20 | 8 |
| Öst (1991) | Blood | 49 | 26 | 7 |
| | Injection | 57 | 21 | 5 |
| Öst and Hugdahl (1985) | Blood | 46 | 32 | 9 |
| | Dentists | 69 | 12 | 6 |
| Kleinknecht (1994) | Blood–injury | 76 | 20 | 3 |
| Hofmann et al. (1995a) | Public speaking | 89 | 57 | 54 |
| Muris et al. (1997) | Animals | 45 | 0 | 29 |
| | Medical | 44 | 0 | 11 |
| | Spiders | 42 | 0 | 13 |
| | Social | 50 | 0 | 0 |
| | All fears | 40 | 1 | 27 |
| Öst (1985) | Blood | 50 | 25 | 2 |
| | Animals | 50 | 22 | 20 |
| | Dentists | 66 | 16 | 0 |
| | Enclosed places | 68 | 7 | 13 |
| | Social | 56 | 16 | 3 |
| Antony (1994) | Heights | 20 | 0 | 0 |
| | Animals | 20 | 7 | 7 |
| | Blood–injections | 27 | 0 | 7 |
| | Driving | 33 | 13 | 13 |

* Figures are rounded off to the nearest percent.

for as long as I can remember" or "I have always had this fear"). Overall, it appears that direct and indirect methods of fear development are relatively common, although the frequency of these onsets varies greatly across studies for a variety of reasons. First, studies have been inconsistent with respect to the populations studied (e.g., clinical groups, nonclinical participants such as college students, individuals recruited through advertisements). In addition, some studies included mixed groups of patients who have a similar fear, but for very different reasons (e.g., flying fears can be due to a specific phobia of flying, claustrophobia, or agoraphobia). Third, studies differed in the ways in which each pathway was defined. For example, an onset that followed an unexpected panic attack was included among the traumatic onsets in some studies but not others. Finally, some studies allowed participants to list multiple causes, whereas other studies had participants rate only the primary cause.

In addition to methodological differences, the inconsistency across studies may be partly explained by the lack of reliability of retrospective self-report. More recent studies have examined onset of phobias in children and included parental interviews to avoid problems associated with retrospective report (Merckelbach and Muris 1997, Poulton et al. 1999).

Despite the high frequency of direct and indirect conditioning events and informational onsets, it appears that they are not the whole story. In fact, studies have begun to include normal comparison groups and have found that these events are equally common in individuals who do not have phobias (e.g., Hofmann et al. 1995a, Menzies and Parker 2001, Merckelbach et al. 1992). Ultimately, to answer the question of how phobias begin, we must discover the variables that lead only certain individuals to develop phobias after experiencing conditioning events or receiving information that leads to fear. For example, several investigators have found that a tendency to feel "disgust" in response to certain stimuli may be important in the development of some animal phobias and blood phobias (Sawchuk et al. 2000, Woody and Teachman 2000). In addition, heightened disgust sensitivity in parents has been found to predict fear of disgust-relevant animals (e.g., snakes, mice, slugs, and cockroaches) in children (de Jong et al. 1997).

Several other variables have also been suggested as mediating factors in the development of fear. Stress at the time of the event may make individuals more likely to react fearfully. In addition, previous and subsequent exposure to the phobic object may protect an individual from the development of a phobia. For example, someone who grew up around dogs may be less likely to develop a phobia after being bitten than someone who has spent little time around dogs. The context of the event may also influence the reaction. For example, being with another supportive individual at the time of the trauma may protect an individual from developing fear. Finally, a number of individual difference variables such as perceived control, trait anxiety, and various

personality factors may influence an individual's likelihood of developing a phobia after a conditioning event. In fact, there is evidence that personality factors and parenting styles may be especially relevant to the development of social phobia. Familial environment including parental style (overprotective or rejecting), parental modeling, and degree of exposure to social situations are specific risk factors that have been associated with increased vulnerability for the development of social phobia (Wittchen and Fehm 2003).

It has been proposed that a fourth nonassociative pathway be added to Rachman's three associative pathways to fear development (Poulton and Menzies 2002). Nonassociative fear models (Menzies and Clarke 1995) propose that a limited number of fears are not acquired by conditioning or other learning processes. Rather, these evolutionary adaptive fears are proposed to be innate or biologically determined. This is similar to preparedness theory, however, it maintains that fears are acquired through a learning or conditioning process and that some fears are more easily learned than others. According to Poulton and Menzies (2002), the nonassociative pathway to fear acquisition helps to explain a number of research findings that run counter to associative models of fear development including the nonrandom distribution of common fears, and the emergence of some fears without any prior specific associative learning experiences (i.e., direct conditioning, vicarious conditioning, or informational transmission).

Based on current evidence, Rapee and Spence (2004) proposed an etiological model of social phobia in an attempt to capture the complexity of the disorder. According to their model, individuals have a "*set point*" level of social anxiety that is somewhat stable and consistent, and is directed by broad genetic factors (e.g., general emotionality, sociability). This *set point* may become altered up or down in response to primarily environmental factors (e.g., parents, peers, negative life events, culture, interrupted social performance, poor social skill). These environmental events may exert a powerful influence due to timing (critical stage of vulnerability), impact (intensity or meaning of the event), or chronicity. For example, a significant proportion of individuals with social phobia report having been severely teased or bullied during childhood (McCabe et al. 2003).

## Personality Variables

The work of Kagan and others (Kagan et al. 1984, Rosenbaum et al. 1991) has suggested that as early as 18 months of age, children differ with respect to their tendency to interact with other individuals, toys, and objects. Although about 70% of children are somewhat exploratory in these situations, about 15% of children are extremely exploratory, and the remaining 15% are quite shy and withdrawn. The behavior exhibited by the shy and withdrawn children has been called "behavioral inhibition" and has been proposed to be a predisposing factor in the development of social phobia and other anxiety disorders (Turner et al. 1996). One study found that the prevalence of social phobia was significantly greater (17%; $N = 64$) in children with behavioral inhibition than without (5%; $N = 152$) (Biederman et al. 2001). In addition, compared with nonanxious individuals, patients with social phobia describe their parents as having (1) discouraged them from socializing, (2) placed undue importance on the opinions of others, and (3) used shame as a means of discipline (Bruch and Heimberg 1994). Other predictors of the development of social phobia include a childhood history of separation anxiety, self-consciousness or shyness in childhood and adolescence, and a low frequency of dating in adolescence (Bruch 1989, Bruch and Heimberg 1994).

Perfectionism is another personality variable that has been associated with social phobia (Antony et al. 1998a). Although several other anxiety disorders have also been associated with perfectionism, concern about making mistakes and a perception of having critical parents are highest among individuals with social phobia compared to individuals with other anxiety disorders (e.g., panic disorder, obsessive–compulsive disorder, or specific phobia).

## Cognitive Variables

Numerous studies have examined the role of cognitive variables in social and specific phobias and have consistently found that individuals with these disorders exhibit attentional and attributional biases regarding the phobic object or situation. In studies of information processing, people with social and specific phobias devote more attention to threat-related information than do nonphobic individuals (Kindt and Brosschot 1999, Mattia et al. 1993). They also show perceptual and cognitive distortions consistent with their phobias (Jones and Menzies 2000, Pauli et al. 1998, Purdon et al. 2001, Rapee 1997, Roth et al. 2001). For example, individuals with snake or spider phobias tend to overestimate the degree of activity in the feared animal before treatment but not after treatment (Rachman and Cuk 1992). Likewise, people with social phobia tend to rate their own performance during public speaking more critically than do nonphobic control subjects (Rapee and Lim 1992). Furthermore, the discrepancy between self-ratings and observer ratings is greater for people with social phobia than control subjects (Norton and Hope 2001). In addition, individuals with social phobia tend to report more negative self-evaluative thoughts and underestimate their performance when interacting with others relative to nonanxious subjects (Stopa and Clark 1993). More recent research has found that compared to nonanxious individuals, individuals with social phobia are more likely to experience negative imagery and to take an observer's point of view (i.e., see themselves from an external perspective) when exposed to feared social situations (Hackmann et al. 1998, Wells and Papageorgiou 1999). Other research has found that social phobia is associated with impaired thought suppression affecting both social phobia-related stimuli as well as nonsocial phobia-related stimuli (Fehm and Margraf 2002).

Although it is clear that cognitive biases exist in individuals with phobias and that attentional and attributional biases improve after effective treatment, it is not known whether the cognitive biases exhibited by patients contribute to the development of the fear or whether they are simply a manifestation of the fear. However, there is evidence that symptomatic improvement in social phobia is associated with reductions in interpretive biases and self-focused attention (for review, see Clark and McManus 2002).

# Treatment

Following a discussion of treatment goals, this next section provides an empirical review of somatic and psychosocial treatments for social phobia and specific phobia. Effective

treatments fall into two main categories: pharmacological treatment and cognitive behavioral treatment (CBT). Pharmacological treatments have been used effectively for treating social phobia, although it is generally accepted that they are of limited utility for treating specific phobias. In contrast, CBT has been used with success for the treatment of specific and social phobias. Despite the existence of effective treatments, fewer than half of those who seek treatment in an anxiety disorders specialty clinic have previously received evidence-based treatments for their social anxiety (Rowa et al. 2000). Tables 70–5 and 70–6 summarize various treatments for social and specific phobias. See Swinson et al. (2006) for a comprehensive review of treatment guidelines for social and specific phobias, as well as other anxiety disorders.

## Treatment Goals

The main goal of treatment is to decrease fear and phobic avoidance to a level that no longer causes significant distress or functional impairment. In some cases, treatment includes strategies for improving specific skill deficits as well. For example, individuals with social phobia may lack adequate social skills and can sometimes benefit from social skills training. Likewise, some individuals with specific phobias of driving may have poor driving skills if their fear has prevented them from learning how to drive properly. Typically, effective treatment for social phobia lasts several months, although treatment of discrete social phobias (e.g., public speaking) may take less time. Specific phobias can usually be treated relatively quickly. In fact, for certain phobias (e.g., animals, blood, injections), the vast majority of individuals are able to achieve clinically significant, long-lasting improvement in as little as one session of behavioral treatment (Öst et al. 2001).

## Somatic Treatments

### Specific Phobia

As discussed earlier, pharmacotherapy is generally thought to be ineffective for specific phobias. However, little research has been conducted to assess the utility of medications for

**Table 70–5 Treatments for Social Phobia**

| Treatment | Advantages | Disadvantages | Rating |
|---|---|---|---|
| Cognitive–behavioral therapy (CBT) (e.g., exposure, cognitive restructuring, social skills training, education) | • Good treatment response<br>• Brief course of treatment<br>• Treatment gains maintained at follow-up<br>• Considered first line | • May lead to temporary increases in discomfort or fear | ++++ |
| SSRIs (e.g., escitalopram, fluvoxamine, paroxetine, sertraline) | • Good treatment response<br>• Early response, relative to CBT<br>• Effective for common comorbid disorders (e.g., depression)<br>• Lack of abuse potential<br>• Considered first line | • Side effects are common<br>• Risk of relapse after discontinuation | +++ |
| Venlafaxine | • Good treatment response<br>• Effective for common comorbid disorders (e.g., depression)<br>• Lack of abuse potential<br>• Considered first line | • Side effects are common.<br>• Potential exists for relapse after discontinuation | +++ |
| Moclobemide | • Good treatment response in some studies<br>• Fewer side effects than phenelzine<br>• Effective for common comorbid disorders (e.g., depression)<br>• Considered second line | • Side effects are common<br>• Does not separate from placebo in some studies<br>• Potential exists for relapse after discontinuation | ++ |
| Benzodiazepines (e.g., clonazepam) | • Good treatment response<br>• Considered adjunctive or second line | • Side effects are common<br>• Withdrawal symptoms and risk of relapse following discontinuation<br>• Potential for abuse<br>• Does not treat certain comorbid conditions (i.e., depression) | ++ |
| MAOIs (e.g., phenelzine) | • Good treatment response<br>• Early response<br>• Considered third line | • Relatively high rate of adverse effects<br>• Dietary restrictions must be followed<br>• Numerous drug interactions<br>• Potential exists for relapse after discontinuation | ++ |
| Gabapentin, pregabalin | • Good treatment response<br>• Considered third line | • Side effects are common<br>• More research is needed | ++ |
| β-Blockers (e.g., atenolol) | • Appears to be useful for "stage fright" in actors, musicians, and other performers | • Not effective for generalized social phobia<br>• Side effects are common<br>• Potential exists for relapse after discontinuation | + |

++++ First treatment of choice. Helpful for most patients, with few side effects. Good long-term benefits.

+++ Helpful for most patients. Potential for relapse after treatment is discontinued.

++ Second-line or third-line treatment due to a need for additional research, mixed evidence, or other issues (e.g., significant side effects).

+ Not especially effective for generalized social phobia.

**Table 70–6 Treatments for Specific Phobias**

| Treatment | Advantages | Disadvantages | Rating |
|---|---|---|---|
| In vivo exposure | • Highly effective<br>• Early response<br>• Treatment gains maintained at follow-up | • May lead to temporary increases in discomfort or fear | ++++ |
| Applied tension | • Highly effective for patients with blood–injection phobias who faint<br>• Early response<br>• Treatment gains maintained at follow-up | • Treatment is relevant only for one particular type of specific phobia | +++ |
| Applied relaxation | • May be effective for some patients | • Treatment has not been extensively researched for specific phobias | ++ |
| Cognitive therapy | • May help to reduce anxiety about conducting exposure exercises<br>• Preliminary evidence for reducing relapse rates when combined with exposure | • Treatment has not been extensively researched for specific phobias<br>• Treatment is probably not effective alone | ++ |
| Benzodiazepines | • May reduce anticipatory anxiety before patient enters phobic situation, and may reduce fear, particularly in situational specific phobias | • Treatment has not been extensively researched for specific phobias<br>• Treatment is probably not effective alone<br>• Side effects are common<br>• Discontinuation of symptoms may undermine benefits of treatment | ++ |
| SSRIs | • May reduce panic sensations for individuals with situational phobias that are similar to panic disorder (e.g., claustrophobia) | • Treatment has not been extensively researched for specific phobias<br>• There are a few studies (primarily case reports) with promising results.<br>• Discontinuation of medication may result in a return of fear | ++ |

++++Treatment of choice. Effective for almost all patients.

+++Very effective for a subset of patients.

++May be helpful for some patients. More research needed.

specific phobias, and it is not uncommon for phobic patients occasionally to be prescribed low dosages of benzodiazepines to be taken in the phobic situation (e.g., while flying). The few relevant studies that have been conducted have examined the use of benzodiazepines and beta-blockers alone or in combination with behavioral treatments for specific phobias and in general have found that drugs do not contribute much to the treatment of specific phobias (Antony and Barlow 2002). However, one problem with the research to date is that it has not taken into account differences among specific phobia types. For example, claustrophobia and other phobias of the situational type appear to share more features with panic disorder than with the other specific phobia types (Antony et al. 1997a). Therefore, medications that are effective for panic disorder (e.g., imipramine, alprazolam) may prove to be effective for situational phobias. Although there are few studies examining this hypothesis, preliminary data suggest that benzodiazepines may be helpful in the short-term but lead to greater relapse in the long-term and possibly interfere with the therapeutic effects of exposure across sessions (Wilhelm and Roth 1996). For example, one study found that CBT and benzodiazepines both led to fear reduction during dental surgery; however, whereas benzodiazepine treatment was associated with greater relapse during follow-up, CBT was associated with further improvements (Thom et al. 2000).

There have been very few controlled studies to date examining the effectiveness of antidepressants for specific phobia. One placebo-controlled, double-blind pilot study found that paroxetine was superior to placebo in reducing anxiety and fear levels in individuals with different types of specific phobia (Benjamin et al. 2000). There have also been several case study reports indicating the usefulness of selective serotonin reuptake inhibitors in the treatment of specific phobia. For example, one single-case study found fluvoxamine to be effective in the treatment of a specific phobia of storms in an 11-year-old boy who also had depression, school phobia, and obsessive–compulsive symptoms (Balon 1999). Another single-case study found that fluoxetine led to a reduction in flying phobia in two patients being treated for depression (Abene and Hamilton 1998).

## Social Phobia

In contrast to specific phobias, social phobia has been treated successfully with a variety of pharmacological interventions including SSRIs such as sertraline (Blomhoff et al. 2001, Van Ameringen et al. 2001), fluvoxamine (Stein et al. 1999, van Vliet et al. ), fluvoxamine CR (Stein et al. 2003), fluoxetine (Davidson et al. 2004), citalopram (Furmark et al. 2002), escitalopram (Kasper et al. 2005), and paroxetine (Allgulander and Nilsson 2001, Liebowitz et al. 2002, Stein et al. 1998b), benzodiazepines such as clonazepam (Davidson et al. 1993) and alprazolam (Reich and Yates 1988), traditional monoamine oxidase inhibitors (MAOIs) such as phenelzine (Heimberg et al. 1998), serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Liebowitz et al. 2005), and reversible inhibitors of monoamine oxidase A (RIMA) such as moclobemide (Versiani et al. 1996) and brofaromine (Lott et al. 1997).

Numerous controlled trials across a range of SSRIs including sertraline, fluvoxamine, and paroxetine have demonstrated their efficacy in the treatment of social

phobia, such that the SSRIs are currently considered the first-line medication treatment (for a meta-analysis of randomized controlled trials, see Van der Linden et al. 2000b). Preliminary research indicates that paroxetine may be useful in the treatment of individuals with comorbid social phobia and alcohol use disorder (Randall et al. 2001). Due to their tolerability and efficacy, the SSRIs have been referred to as "the new gold standard" in pharmacological treatment for social phobia (Van Ameringen et al. 1999, 2000). Another benefit of SSRIs is their broad spectrum efficacy for common comorbid disorders such as depression and panic disorder. Interestingly, despite the evidence for SSRIs as a first-line treatment for social phobia, examination of prescribing practices over a 12-year period in 232 patients with social phobia reflect that benzodiazepines continue to be more commonly prescribed over SSRIs and use of SSRIs as stand-alone medication remains low (Vasile et al. 2005).

Research on the use of anxiolytics for the treatment of social phobia has focused on high potency benzodiazepines (e.g., clonazepam, alprazolam) and the nonbenzodiazepine buspirone. Several studies have examined the utility of clonazepam for treating social phobia. In a placebo-controlled study, Davidson et al. (1993) found that 78% of patients responded to clonazepam (mean dosage, 2.4 mg/day), whereas only 20% responded to placebo. One study comparing clonazepam to cognitive–behavioral group therapy found that patients in both conditions improved significantly and no differences between treatment conditions were observed aside from greater improvement in the clonazepam group at 12 weeks of treatment (Otto et al. 2000). These results confirmed findings from smaller open trials and case studies supporting the use of clonazepam for social phobia (mean dosages, 2.1–2.75 mg/day) (Davidson et al. 1991a, Munjack et al. 1990). In addition, uncontrolled pilot studies have suggested that alprazolam (mean dosage, 2.9 mg/day) (Lydiard et al. 1988, Reich and Yates 1988) may be effective for social phobia, although more controlled clinical trials are needed. The findings from controlled trials on buspirone have found no significant advantage of buspirone over placebo (Clark and Agras 1991, van Vliet et al. 1997), though previous uncontrolled studies had found some benefit following treatment with buspirone (Munjack et al. 1991, Schneier et al. 1993).

Due to the potentially severe side effects of MAOIs as well as the necessity for certain dietary restrictions, they are not recommended as a first-line treatment. The findings from more recent trials involving RIMAs have been less encouraging than those from earlier studies. For example, a fixed dose study conducted over 12 weeks found that moclobemide did not have a significant benefit over placebo at five dosages ranging from 75 to 900 mg/day (Noyes et al. 1997). Other studies have also found poor responses to moclobemide (Oosterbaan et al. 2001, Schneier et al. 1998). Discontinuation of MAOIs and RIMAs has been associated with a tendency to relapse.

Research on beta-blockers indicates that they are no better than placebo for most patients with generalized social phobia (Liebowitz et al. 1992). Although beta-blockers have been used to treat individuals from nonpatient samples with heightened performance anxiety (e.g., people with public speaking anxiety, musicians with stage fright) (Hartley et al. 1983), their efficacy for treating individuals with clinically diagnosed discrete social phobia has not been established. Nevertheless, beta-blockers are often prescribed for discrete performance-related social phobias.

Preliminary findings suggest that medications such as gabapentin and pregabalin, typically used in the treatment of partial seizures, may be effective in the treatment of social phobia. Placebo-controlled trials have found that patients taking gabapentin and pregabalin had significant reductions in social anxiety compared to patients in the placebo groups (Pande et al. 1999, 2004). However, further research is needed to confirm these findings.

## Psychosocial Treatments

### Specific Phobias

Numerous studies have shown that exposure-based treatments are effective for helping patients to overcome a variety of specific phobias including fears of blood (Öst et al. 1991), injections (Öst 1989), dentists (Moore and Brødsgaard 1994), spiders (Muris et al. 1998, Öst 1996a), snakes (Gauthier and Marshall 1977), rats (Foa et al. 1977), enclosed places (Craske et al. 1995), thunder and lightning (Öst 1978), water (Menzies and Clarke 1993a), flying (Öst et al. 1997), heights (Baker et al. 1973), choking (McNally 1986), and balloons (Houlihan et al. 1993).

The way in which exposure is conducted appears to make a difference. Exposure-based treatments can vary on a variety of dimensions including the degree of therapist involvement, duration and intensity of exposure, frequency and number of sessions, and the degree to which the feared situation is confronted in imagination versus in real life. In addition, because individuals with certain specific phobias often report a fear of panicking in the feared situation, some investigators (Antony and Swinson 2000a) have suggested that adding various panic management strategies (e.g., cognitive restructuring, exposure to feared sensations) may help to increase the efficacy of behavioral treatments for certain specific phobias. It remains to be shown whether the addition of these strategies will improve upon the efficacy of treatments that include only exposure.

Several reviews have summarized the effects of the above mentioned variables on exposure-based treatments (Antony and Barlow 2002, Antony and Swinson 2000a). Although some studies have led to contradictory results, the following generalizations are more or less accepted by the majority of investigators. First, exposure seems to work best when sessions are spaced close together. Second, prolonged exposure seems to be more effective than exposure of shorter duration. Third, during exposure sessions, patients should be discouraged from engaging in subtle avoidance strategies (e.g., distraction) and overreliance on safety signals (e.g., being accompanied by one's spouse during exposure). Fourth, real-life exposure is more effective than exposure in imagination. Fifth, exposure with some degree of therapist involvement seems to be more effective than exposure that is exclusively conducted without the therapist present (Park et al. 2001). Exposure may be conducted gradually or quickly. Both approaches seem to work equally well, although patients may be more compliant with a gradual approach. Finally, in the case of blood and injection phobias, the technique called applied muscle tension (Öst and Sterner

1987) should be considered as an alternative or addition to exposure therapy. Applied muscle tension involves having patients repeatedly tense their muscles, which leads to a temporary increase in blood pressure and prevents fainting upon exposure to blood or medical procedures.

Cognitive strategies have also been used either alone or in conjunction with exposure for treating specific phobias (Craske and Rowe 1997). The evidence suggests that the addition of cognitive strategies to exposure may provide added benefit (Craske et al. 1995) for some individuals. For a detailed guide to integrating cognitive strategies with exposure see Antony and Swinson (2000a).

Specific phobias are among the most treatable of the anxiety disorders. For example, in as little as one session of guided exposure lasting 2–3 hours, the majority of individuals with animal or injection phobias are judged much improved or completely recovered (Antony et al. 2001a, Öst 1989, Öst et al. 1997). One study demonstrated that one session of exposure treatment was effective in the treatment of children and adolescents with various specific phobias (Öst et al. 2001). Moreover, exposure conducted with a parent present was equally effective as exposure treatment conducted alone (Öst et al. 2001). However, despite how straightforward the concept of exposure may seem, many subtle clinical issues can lead to problems in implementing exposure-based treatments. For example, although a patient might be compliant with therapist-assisted exposure practices, he or she may refuse to attempt exposure practices alone between sessions. In such cases, involving a spouse or other family member as a coach during practices at home may help. In addition, gradually increasing the distance between therapist and patient during the therapist-assisted exposures will help the patient to feel comfortable when practicing alone. However, to maintain the patient's trust and to maximize the effectiveness of behavioral interventions, it is important that exposure practices proceed in a predictable way, so that the patient is not surprised by unexpected events. Several self-help books and manuals for treating a range of specific phobias have been published in the past decade. Whereas some of these manuals were developed to be used with the assistance of a therapist (Antony et al. 2006, Craske et al. 2006), others were developed for self-administration (Antony and McCabe 2005, Antony and Rowa 2007, Antony and Watling 2006).

Recent developments in technology have started to have an impact on the treatment of specific phobias. Videotapes are commonly used to show feared stimuli to patients during exposure. Computer administered or assisted behavioral treatments such as computer-guided self-exposure have also been used (Marks et al. 2004, Smith et al. 1997). More recent is the use of virtual reality to expose patients to simulated situations that are more difficult to replicate in vivo such as flying (Kahan et al. 2000) and heights (Rothbaum et al. 1995) as shown in Figure 70–3. Emerging data on the effectiveness of virtual reality is encouraging (Rothbaum et al. 2000). Controlled studies have found virtual reality treatment to be more efficacious then wait-list control for height fears (Krijn et al. 2004) and fear of flying (Rothbaum et al. 2000). Some studies suggest that in vivo exposure is still superior (Dewis et al. 2001) whereas other studies have found the two approaches to be equivalent (e.g., Emmelkamp et al. 2002, Rothbaum et al. 2002).

## Social Phobia

Empirically validated psychosocial interventions for social phobia have primarily come from a cognitive–behavioral perspective and include four main types of treatment: (1) exposure-based strategies, (2) cognitive therapy, (3) social skills training, and (4) applied relaxation (Antony and Swinson 2000a, Turk et al. 1999). Exposure-based treatments involve repeatedly approaching fear-provoking situations until they no longer elicit fear. Through repeated exposure, patients learn that their fearful predictions do not come true despite their having confronted the situation. Table 70–7 illustrates an example of an exposure hierarchy that might be used to structure a patient's exposure practices. An exposure hierarchy is a list of feared situations that are rank ordered by difficulty and used to guide exposure practices for phobic disorders including social phobia and specific phobia. The patient and therapist generate a list of situations that the patient finds anxiety provoking. Items are placed in descending order from most anxiety provoking to least anxiety provoking, and each item is rated with respect to how anxious the patient might be to practice the item. Exposure practices are designed to help the patient become more comfortable engaging in the activities from the hierarchy. Cognitive therapy helps patients identify and change anxious thoughts (e.g., "Others will think I am stupid if I participate in a conversation at work") by teaching them to consider alternative ways of interpreting situations and to examine the evidence for their anxious beliefs. Social skills training is designed to help patients to become more socially competent when they interact with others. Treatment strategies may include modeling, behavioral rehearsal, corrective feedback, social reinforcement, and homework assignments. Finally, applied relaxation has been studied primarily by Öst et al. (1984) and involves learning to relax one's muscles during rest, during movement, and eventually in anxiety-provoking social situations.

Although these methods are presented as four distinct treatment approaches, there is often overlap among the various treatments. Social skills training typically requires exposure to the phobic situation so that new skills may be practiced (e.g., behavioral rehearsal). The same may be said of applied relaxation, which includes learning to conduct relaxation exercises in the phobic situation. In fact, most treatments for social phobia involve some type of exposure to anxiety-provoking social interactions and performance-related tasks. Furthermore, many cognitive–behavioral therapists treat patients using several different strategies delivered in a comprehensive package.

Studies demonstrating the efficacy of CBT for social phobia are too numerous to describe in detail, although several representative studies are reviewed here. In addition, studies that specifically compare cognitive–behavioral and medication treatments are described. For interested readers, more comprehensive reviews on CBT for social phobia have been written by Rowa and Antony (2005) and Fresco and Heimberg (2001). Also, a clinical description of a cognitive–behavioral group treatment (CBGT) for social phobia is provided by Turk et al. (2001) and by Heimberg and Becker (2002).

Several studies have compared various cognitive–behavioral strategies and their combinations for treating social phobia. For example, Wlazlo et al. (1990) compared



**Figure 70–3** *Virtual reality exposure is an emerging treatment for specific phobias related to situations that are difficult to replicate in vivo such as flying.*

**Table 70–7 Exposure Hierarchy for Generalized Social Phobia**

| Item | Fear Rating (0–100) |
|---|---|
| Have a party and invite everyone from work. | 99 |
| Go to work Christmas party for 1 hour without drinking. | 90 |
| Invite Cindy to have dinner and see a movie. | 85 |
| Go for a job interview. | 80 |
| Ask boss for a day off from work. | 65 |
| Ask questions in a meeting at work. | 65 |
| Eat lunch with coworkers. | 60 |
| Talk to a stranger on the bus. | 50 |
| Talk to cousin on the telephone for 10 minutes. | 40 |
| Ask for directions at the gas station. | 35 |

social skills training to exposure therapy conducted either individually or in groups. All three treatments led to significant improvements and there were no differences between treatments. However, exposure therapy conducted in groups tended to be more effective for the subset of patients with social skills deficits, most likely by enabling those individuals with deficits to develop their skills through exposure to social situations and interactions in the group. Mattick and Peters (1988) found that guided exposure was more effective when cognitive therapy was included than when exposure was conducted without cognitive therapy. Scholing and Emmelkamp (1993) failed to replicate this finding and found that treatment was equally effective when exposure was conducted alone, it followed several sessions of cognitive therapy, or was integrated with cognitive therapy from the first session.

Whereas these studies examined the use of specific cognitive–behavioral strategies, other studies have examined the use of comprehensive treatments that include several therapeutic components. For example, Turner et al. (1994) evaluated their multicomponent social phobia treatment that included education, social skills training, exposure, and programmed practice between sessions. All patients had the generalized subtype of social phobia and were judged to be severely disabled by their symptoms. On a comprehensive measure of end-state functioning, 85% of patients met moderate to high end-state functioning criteria by the end of treatment. Unfortunately, this study did not include a comparison treatment group.

Heimberg et al. (1990b) compared supportive psychotherapy with a comprehensive CBGT package that

included exposure to simulated and real social situations as well as cognitive restructuring for the treatment of social phobia. Although both groups improved on most measures, patients receiving CBGT were significantly more improved immediately after treatment and at 3- and 6-month follow-up. CBGT was more effective despite the fact that patient ratings of treatment credibility and expectations for improvement were equal for both treatments. Patients receiving CBGT continued to be more improved at 5-year follow-up (Heimberg et al. 1993b), although only 41% of the original sample participated in the follow-up study, which limited the validity of these findings. Other research has confirmed that cognitive–behavioral therapy is superior to supportive therapy (Cottraux et al. 2000).

Heimberg et al. (1998) compared four treatments for social phobia: (1) CBGT, (2) phenelzine, (3) supportive psychotherapy, and (4) placebo. Overall, both phenelzine and CBGT were equally effective after 12 weeks of treatment and were significantly more effective than placebo or supportive psychotherapy. Phenelzine tended to work more quickly than CBGT and appeared to be more effective on a few measures. However, preliminary analyses of long-term outcome showed that after discontinuing treatment, patients receiving CBGT were more likely than patients who received phenelzine to maintain their gains, with approximately half of patients taking phenelzine relapsing, compared to none of the patients that responded to CBGT (Liebowitz et al. 1999).

In a randomized clinical trial comparing cognitive therapy to moclobemide for social phobia, Oosterbaan et al. (2001) found that cognitive therapy was significantly better than moclobemide, but not placebo, after 15 weeks of active treatment. After a 2-month follow-up period, cognitive therapy was significantly better than both moclobemide and placebo. In addition, treatment gains in the cognitive therapy group were maintained over a 15-month follow-up period.

A study by Haug et al. (2000) examined the effect of exposure therapy alone or in combination with sertraline for generalized social phobia in a primary care setting. Family physicians were trained for 30 hours in assessment of social phobia and in the application of exposure therapy. Family physicians reported satisfaction with the training program and found that the exposure treatment was also useful for treating patients with other conditions. Although exposure therapy and sertraline were effective alone, the combination of exposure therapy and sertraline appeared to confer added benefit.

In the most comprehensive study to date examining the relative and combined effects of CBT and medication, Davidson et al. (2004) compared CBT alone to fluoxetine alone, placebo, CBT plus fluoxetine, and CBT plus placebo. By the end of treatment, all four active treatments were more effective then placebo, and there were no differences between them. In this study, combined treatment was no more effective than either medication or CBT alone.

According to cognitive models of social phobia, one of the mechanisms by which CBT works is by causing a positive shift in an individual's self-representation (e.g., decreased negative self-focused thoughts and increased task-focused thoughts and positive self-focused thoughts). Indeed, there is evidence that following CBT, individuals report significantly fewer negative self-focused thoughts (Hofmann 2000). Similarly, cognitive biases are reduced following successful pharmacotherapy treatment as well and are related to the degree of symptomatic improvement in both psychological and pharmacological treatments (McManus et al. 2000).

In summary, it seems clear that effective psychosocial treatments and medications for social phobia exist. Although both types of treatments appear to be equally effective, each has advantages and disadvantages. Medication treatments may work more quickly and are less time-consuming for the patient and therapist. In contrast, improvement after CBT appears to last longer. Due to medication side effects, CBT may be more appropriate for some individuals. More studies are needed to examine the efficacy of combined medication and psychosocial treatments for social phobia. A meta-analysis of 24 studies examining cognitive–behavioral and medication treatments for social phobia found that both treatments were more effective than control conditions (Gould et al. 1997). In this study, the SSRIs and benzodiazepines tended to have the largest effect sizes among medications and treatments involving exposure either alone or with cognitive therapy had the largest effect sizes among CBT. Another meta-analytic study of 108 psychological and pharmacological treatment–outcome trials found that the pharmacotherapies (SSRIs, benzodiazepines, MAO inhibitors) were the most consistently effective treatments, with both SSRIs and benzodiazepine treatments equally effective and more effective than control groups (Fedoroff and Taylor 2001). Further, maintenance of treatment gains for CBT was moderate and continued during follow-up intervals. In comparison, it is not known the extent to which treatment gains for medication treatments are maintained following discontinuation. Reviews of the efficacy of pharmacological and cognitive–behavioral treatments suggest that successful treatments may involve medication, CBT, or a combination of both (Scott and Heimberg 2000). Detailed descriptions of cognitive–behavioral therapy for social phobia are available in a self-help format (e.g., Antony and Swinson 2000b). Self-help manuals may be used on their own or in conjunction with therapy.

Treatment decision trees for social and specific phobias are presented in Figures 70–4 and 70–5.

## Treatment Refractory Patients

Several variables may lead to an initially poor treatment response. Anticipating potential difficulties will help increase treatment efficacy. Possible reasons for a worse outcome include poor compliance, poor motivation, and poor understanding of the treatment procedures. In addition, interpersonal issues and other possible conflicts may interfere with the successful treatment of specific and social phobias.

Patients fail to comply with treatment procedures for a variety of reasons. In the case of pharmacological treatments, patients may avoid taking medications because of side effects, lack of confidence in efficacy, or preference for an alternative type of treatment. If patients are not compliant with medications, the physician should attempt to identify the reasons for poor compliance and to suggest methods of increasing compliance or changing to another type of treatment.

In the case of CBT, common reasons for poor compliance are anxiety about the treatment procedures, lack of time, and lack of motivation to conduct the treatment

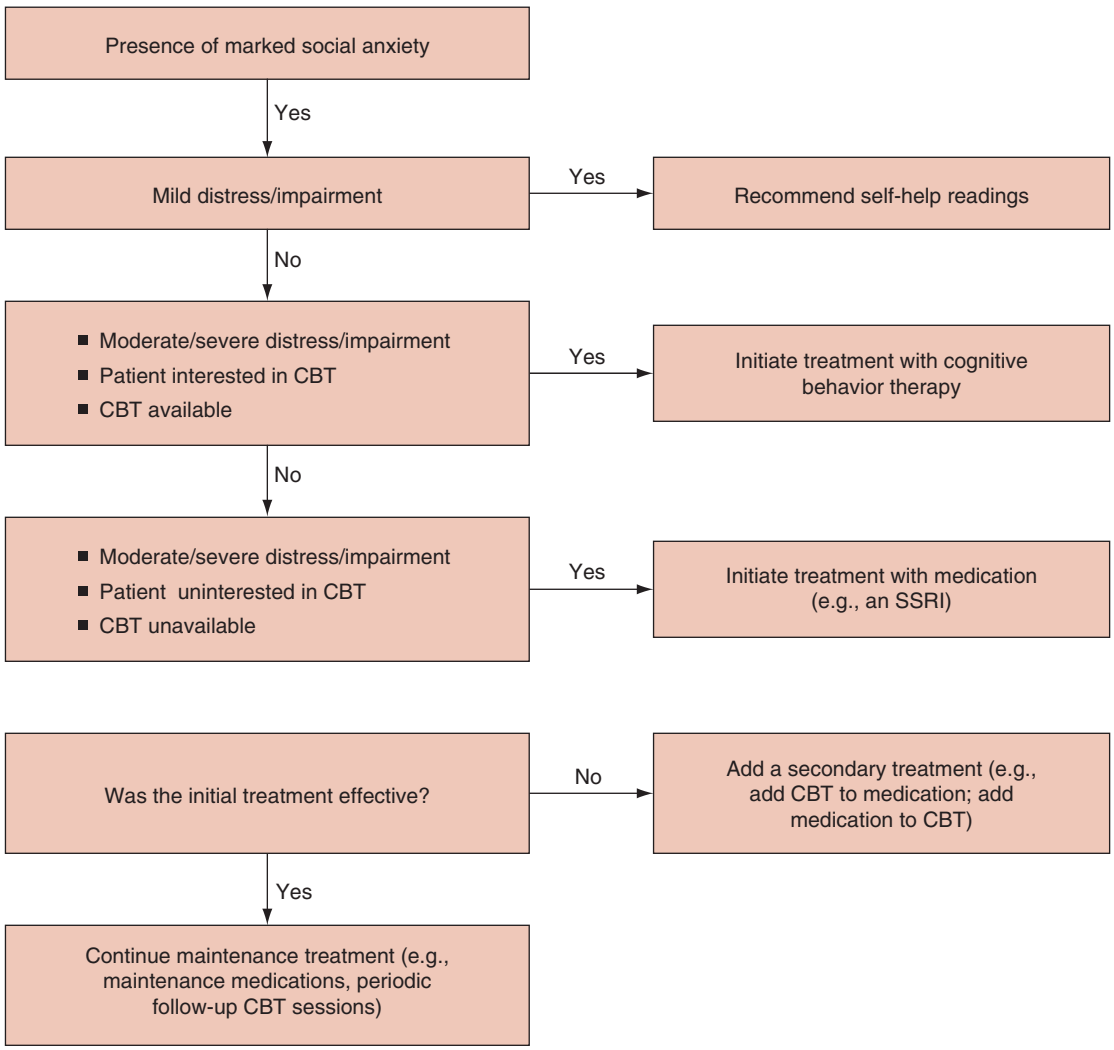



**Figure 70–4** *Social phobia: treatment decision tree.*

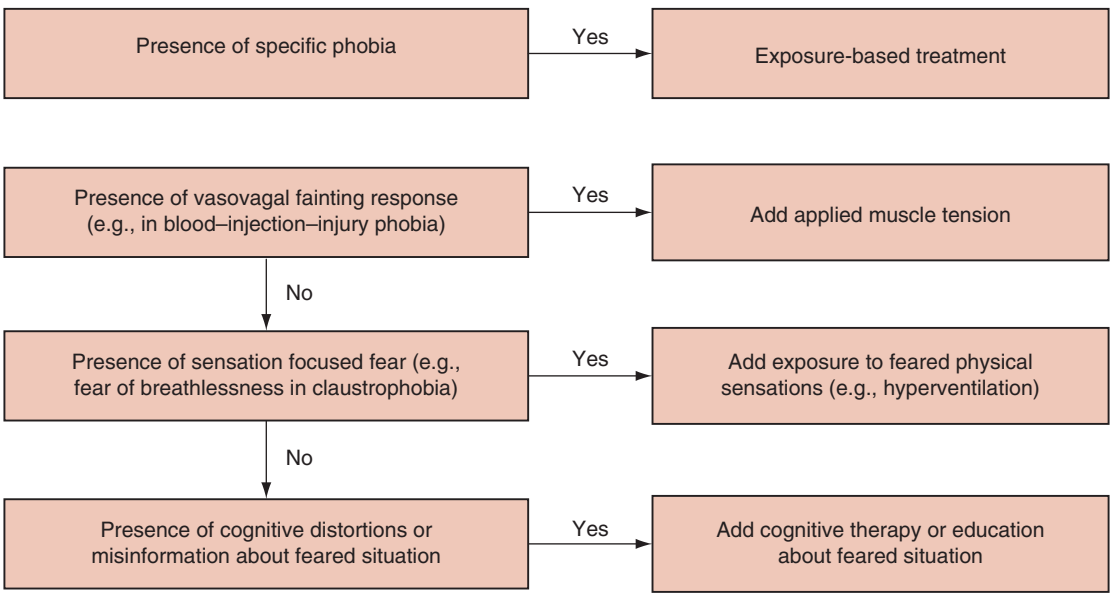



**Figure 70–5** *Specific phobia: treatment decision tree.*

properly. Because CBT requires patients to confront the situations they fear most, patients often feel extreme anxiety about participating in the treatment. Patients should be reassured that their anxiety is normal and that they will never be forced to do anything that they are unwilling to try. Furthermore, the difficulty of exposure tasks should be increased gradually to maximize treatment compliance. If patients do not have the time or motivation to conduct treatment as suggested, therapists should be willing to find ways to make the treatment more accessible to the patient. For example, involvement of a friend or relative of the patient as a coach may allow the patient to conduct more practices without the therapist's assistance. The therapist could also explore the possibility that the patient consider beginning treatment later, when more time is available.

Poor motivation can lead to poor compliance with the treatment procedures. If a patient's symptoms are not especially severe, the distress and impairment created by the disorder may not be enough to motivate the patient to take medications regularly or to confront the phobic situation in a systematic way. Furthermore, as a patient improves in treatment, she or he may experience a decrease in motivation. Patients should be encouraged to continue with treatment assignments even after improvement. More complete improvements may protect against a return of symptoms.

Finally, treatment procedures may be complicated for some patients. This is especially the case for CBT. Patients may fail to complete homework assignments (e.g., monitoring anxious cognitions) simply because the treatment rationale and the specifics of how to conduct the treatment procedures were not made clear. Therefore, therapists should continually assess the patient's understanding of the treatment procedures.

## Special Factors Influencing Treatment

### Predictors of Treatment Outcome

A number of studies have examined predictors of outcome for treatment of specific and social phobias. These studies tend to fall into two main categories. First, several investigators have attempted to match treatment strategies to specific characteristics of patients. Second, several studies have examined the relationship between individual differences (e.g., duration and severity of illness, personality factors) and response to treatment.

Öst and colleagues conducted a series of studies to investigate whether specific types of individuals might benefit from particular types of treatment. For example, Öst et al. (1982) identified a group of individuals with claustrophobia who were primarily *behavioral responders* (i.e., for whom avoidance was the principal mode of responding) and another who were primarily *physiological responders* (i.e., for whom the principal response was increased arousal in the phobic situation). In this study, behavioral responders benefited more from exposure than from applied relaxation, whereas physiological responders benefited most from applied relaxation. Similar findings were found for behavioral and physiological responders with social phobia (Öst et al. 1981). However, despite small differences in treatment efficacy for different types of patients, the majority of patients seem to do well with either type of behavioral treatment. Furthermore, many patients do not fall neatly into one category of responders but rather show features of both avoidance and physiological responding. Finally, several studies have failed to show differences in treatment efficacy for individuals with dental phobia (Jerremalm et al. 1986) and social phobia (Mersch et al. 1989) who have different response styles, which raises questions about the reliability of previous findings.

Heimberg and Juster (1995) reviewed some other predictors of response to CBT for social phobia. Subtype of social phobia seems to predict outcome (with generalized social phobia being associated with a worse treatment outcome than nongeneralized social phobia), but not when severity of symptoms is controlled. In other words, individuals with more severe symptoms before treatment can be expected to have more severe symptoms after treatment. With respect to comorbidity on outcome, findings have been mixed. Some research has found that the presence of comorbidity (additional personality, mood, or anxiety disorders) did not affect outcome following CBT for social phobia (Brown et al. 1995, Hofmann et al. 1995b, Van Velzen et al. 1997). However, other research has found that the presence of depression and avoidant personality traits were associated with a poorer outcome (Chambless et al. 1997, Scholing and Emmelkamp 1999).

Most pharmacological studies have failed to examine predictors of outcome. One exception was a study by Van Ameringen et al. (1993), who found that a shorter duration of symptoms and older age at onset were associated with more positive outcomes after treatment of social phobia with fluoxetine.

Several studies have examined characteristics of individual subjects that predict outcome in the behavioral treatment of specific phobias. Two studies have found that coping style predicts outcome. In one study, "monitors" (those who cope with fear by seeking fear-relevant information, e.g., scanning a room for spiders in the case of an individual with spider phobia) responded more poorly to behavioral treatment and relapsed more often compared with "blunters" (those who cope with fear by avoiding fear-relevant information, e.g., avoiding looking around for spiders for fear of seeing them) (Muris et al. 1993). However, another study led to opposite findings, with monitors responding most (Steketee et al. 1989). Finally, a study by Antony et al. (2001a) found no relationship between coping style and treatment outcome in a group of patients with spider phobia.

Other patient-related variables that may be associated with treatment outcome for specific phobias include symptom severity, level of generalized anxiety, previous experience with the phobic stimulus, and reliance on safety behavior during exposure. Specifically, patients with more severe height phobias have been shown to demonstrate greater change after treatment than did patients with less severe phobias (Baker et al. 1973), although that does not imply that their posttreatment symptoms are less severe. In addition, elevated generalized anxiety has been shown to be associated with poorer outcome in patients with height phobia (Baker et al. 1973). Moreover, extensive prior experience with flying has been shown to be associated with a worse outcome after behavioral treatment for flying phobia (Solyom et al. 1973). Allowing individuals to engage

in safety behaviors during exposure treatment, such as use of medication or distraction, has been found to interfere with fear reduction (Sloan and Telch 2002). Further research suggests that just the perception of the availability of safety aids rather than their actual use interferes with fear reduction during exposure (Powers et al. 2004). Despite these findings, other research examining potential predictors of outcome in the treatment of specific phobia (e.g., age of onset, duration of phobia, method of onset, family history, anxiety, depression, heart rate, severity, and blood pressure) failed to find a stable predictor of outcome (Hellström and Öst 1996).

It should be noted that none of these findings has been replicated and they should therefore be interpreted with caution. Much more research is needed to identify predictors of outcome with CBT and especially with pharmacological treatment. For example, little is known about the efficacy and effectiveness of treatments for specific and social phobias in special populations (e.g., elderly persons, culturally diverse groups). There has also been a lack of research on the impact of comorbidity on success of treatment with specific phobias.

## Relapse and Return of Fear

With respect to specific phobia, it is common for some return of fear to occur in the presence of the phobic stimulus (Craske 1999). Although relapse following treatment of a specific phobia is believed to be rare (Öst 1996b), one study found a considerable proportion of individuals experienced a clinically significant return of symptoms over an average 12-year follow-up period (Lipsitz et al. 1999). A number of variables have been identified that predict return of fear including distraction during exposure, a relatively quick reduction in fear during exposure (Rose and McGlynn 1997), a relatively slow reduction in fear during exposure (Rachman and Whittal 1989), higher initial heart rate (Craske and Rachman 1987), spacing of exposure sessions and the degree to which the exposure stimuli are varied (Rowe and Craske 1998a, 1998b), the tendency to overassociate fear-relevant stimuli with aversive outcomes (de Jong et al. 1995), and depression (Salkovskis and Mills 1994). In addition, being challenged by the phobic stimulus in a context that is different from the context in which treatment took place may also increase the likelihood that fear will return (Mineka et al. 1999).

**Clinical Vignette 1 • Social Phobia**

Ms. K is a 29-year-old student who presented with social phobia. She reported being shy as a child and could remember pretending to be ill to stay home from school. As she got older, she met more children and by high school was quite comfortable with her friends at school. Meeting new people was still difficult, as was public speaking in class. Fortunately, neither situation came up often.

In college, Ms. K's problem became worse. Several of her classes required her to make presentations. In addition, because she lived off campus, she found it particularly difficult to meet friends. The few times she tried to talk to people in class, she felt as though she had nothing to say. Before long, she stopped trying. Ms. K did not avoid her class presentations at first. Rather, she tended to overprepare for them and tried to use overheads when possible because the dark room helped to decrease her anxiety. Still during presentations she could feel her heart pounding and she tended to have difficulty breathing. Her mouth became dry and she was sure that her classmates could see her shaking and perspiring.

After her first year of college, Ms. K began to avoid any class that required presentations. In addition, she found herself avoiding other situations in which people might notice her shaking. Specifically, she avoided writing in front of others, holding drinking glasses, and other situations that might focus other people's attention on her hands. She also avoided engaging in conversation with others and when people approached her, she tried to end the conversation as quickly as possible. In addition to fearing that others would notice her anxiety, Ms. K felt that others might see her as weak, unattractive, or foolish.

During a diagnostic interview, it was found that Ms. K was suffering from social phobia. She seemed bright and motivated, and it was decided that she might benefit from CBGT for social phobia. However, the patient initially rejected this option because of anxiety about participating in a group. Therefore, she started 10 mg of paroxetine and gradually increased the dosage to 50 mg. Because of difficulties due to sexual dysfunction, the dosage was decreased to 40 mg and her sexual symptoms subsided.

During a period of 6 weeks, Ms. K felt more comfortable around people and decided that she was willing to participate in a 12-session CBGT program. Treatment included a variety of components, including information about the nature of anxiety and social phobia, cognitive restructuring, role-play exposures to anxiety-provoking situations (e.g., group presentations), and homework assignments to enter feared situations. In addition, Ms. K practiced purposely shaking in front of others, until the symptom was no longer frightening to her. Over the course of the CBGT, Ms. K's medication was gradually discontinued.

By the end of treatment, Ms. K was essentially symptom free and criteria for social phobia were no longer met. Furthermore, she had met several new friends and had enrolled in a few classes that required her to make presentations. Although she still became nervous before speaking in public, she looked forward to the presentations. She rarely experienced shaking in front of others and was no longer particularly concerned about shaking.

**Clinical Vignette 2 • Specific Phobia**

Mr. D, a 38-year-old attorney, presented for treatment of snake phobia. Growing up in New York City he rarely saw snakes, although he reported fearing toy snakes even as a child. In his late twenties, he relocated to a rural area where he encountered snakes every few weeks. Mr. D began to avoid entering his backyard and walking in his neighborhood, even with his family. Before he drove to work his wife checked the area around his car for snakes. His fear became worse over time so that even seeing a photograph of a snake induced a panic attack.

When Mr. D did see a snake he tended to have an intense panic attack, including breathlessness, dizziness, palpitations, and a feeling that he might lose control and embarrass himself. He was not sure how the fear

*(continues)*

Clinical Vignette 2 *continued*

developed, nor could he identify what bothered him about snakes, except perhaps something about their movement. Mr. D decided to move back to the city and had just put his house up for sale when he presented for treatment.

Mr. D had a specific phobia of snakes and reported no other significant problems with anxiety. Before he began behavioral treatment, a full assessment of his fear was conducted. A hierarchy of feared situations was generated ranging from moderately anxiety provoking tasks (e.g., looking at a photograph of a snake) to extremely difficult tasks (e.g., touching a snake). In addition, a behavioral approach test was conducted during which it was discovered that Mr. D could stand no closer than 10 feet from a live snake in an aquarium. In addition, during the behavioral approach test he became aware that his main anxious thought was that the snake would touch him and perhaps bite him. His fear tended to increase when the snake looked in his direction or moved in the aquarium.

Mr. D was treated during two sessions of therapist-assisted exposure, each lasting 120 minutes. During the sessions, he practiced the various tasks on his hierarchy and continued to do so even when his fear was overwhelming. Each step was first demonstrated by the therapist. By the end of two sessions, Mr. D was able to look at, touch, and hold a snake with minimal anxiety. At 1-month follow-up, he reported that he no longer avoided situations in which he might see snakes and had decided to continue living in his house.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research for Social Phobia specify that at least two symptoms of anxiety (i.e., from the list of 14 panic symptoms) be present together on at least one occasion along with at least one of the following anxiety symptoms: blushing or shaking, fear of vomiting, and urgency or fear of micturition or defecation. Furthermore, these anxiety symptoms must be "restricted to, or predominated in, the feared situations or contemplation of the feared situations." In contrast, the DSM-IV-TR criteria do not specify any particular types of anxiety symptoms nor is any restriction placed on whether anxiety can occur in situations other than social situations.

For specific phobia, the ICD-10 Diagnostic Criteria for Research also specify that the anxiety symptoms be "restricted to, or predominated in, the feared situations or contemplation of the feared situation." DSM-IV-TR again does not impose any such restriction.

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CHAPTER 71

# Anxiety Disorders: Obsessive–Compulsive Disorder

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## Obsessive–Compulsive Disorder

### Definition and Diagnostic Features

Obsessive–compulsive disorder (OCD) is an intriguing and often debilitating syndrome characterized by the presence of two distinct phenomena: obsessions and compulsions. Obsessions are intrusive, recurrent, unwanted ideas, thoughts, or impulses that are difficult to dismiss despite their disturbing nature. Compulsions are repetitive behaviors, either observable or mental, that are intended to reduce the anxiety engendered by obsessions. Obsessions or compulsions that clearly interfere with functioning and/or cause significant distress are the hallmark of OCD.

Although OCD was originally considered rare, findings from the Epidemiologic Catchment Area (ECA) survey in 1984 demonstrated that OCD was 50–100 times more common than had been previously believed (Myers et al. 1984). With increasing recognition of OCD, both in the mental health field and in the media, many individuals with OCD have pursued treatment for this disorder. This has led to systematic investigation of clinical features such as symptom subtype, course, comorbidity, and the role of insight both descriptively and as moderators of treatment response.

These studies, conducted over the two decades, have greatly furthered our understanding of the clinical characteristics of this disorder. OCD is now considered a relatively common disorder that usually has its onset during puberty, although it may begin as early as age 2 years and infrequently begins after age 35 years. Women develop OCD slightly more often than men. Earlier studies found that the course of OCD is usually chronic, with symptom severity waxing and waning over time. However, those studies, which had a number of methodological limitations, were conducted prior to the availability of effective treatments for this disorder. More recent evidence suggests that some individuals have a more episodic and favorable course.

Several large studies have found that the most common obsession is contamination, and the most common compulsion is checking. However, most individuals with this disorder have multiple obsessions and compulsions over time. A number of psychiatric disorders co-occur with OCD, major depressive disorder being most frequent. Comorbidity with tic disorders is well established. That association plus a familial relationship between OCD and tic disorders has led to suggestions that OCD has a specific-tic–related phenotype. There has been considerable interest in the role of insight, or awareness, in OCD. An ability to recognize the senselessness of the obsessions and the ability to resist obsessional ideas have been considered fundamental components of OCD. However, research findings from the past two decades have demonstrated a continuum of insight in this disorder, which ranges from excellent (i.e., complete awareness of the senselessness of the content of the obsessions), through poor insight, to delusional thinking (i.e., the obsessions are held with delusional conviction) (Eisen and Rasmussen 1993, Lelliot et al. 1988, Foa and Kozak 1995). To reflect these findings, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) established a specifier—with poor insight—and also noted that, in cases of delusional OCD, an additional diagnosis of delusional disorder or psychotic disorder not otherwise specified may be appropriate (American Psychiatric Association 1994).

OCD's clinical presentation is characterized by phenomenological subtypes based on the content of the obsessions and corresponding compulsions. The list of subtypes in the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS)

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**Table 71–1 Yale–Brown Obsessive–Compulsive Scale Symptom Checklist**

- Aggressive obsessions
  - Fear might harm others
  - Fear might harm self
  - Violent or horrific images
  - Fear of blurting out obsessions or insults
  - Fear of doing something embarrassing
  - Fear of acting on other impulses (e.g., robbing a bank, stealing groceries, overeating)
  - Fear of being responsible for things going wrong (e.g., others will lose their job because of patient)
  - Fear something terrible might happen (e.g., fire, burglary)
  - Other
- Contamination obsessions
  - Concerns or disgust with bodily waste (e.g., urine, feces, saliva)
  - Concern with dirt or germs
  - Excessive concern with environmental contaminants (e.g., asbestos, radiation, toxic wastes)
  - Excessive concern with household items (e.g., cleansers, solvents, pets)
  - Concerned will become ill
  - Concerned will become ill (aggressive)
  - Other
- Sexual obsessions
  - Forbidden or perverse sexual thoughts, images, or impulses
  - Content involves children
  - Content involves animals
  - Content involves incest
  - Content involves homosexuality
  - Sexual behavior toward others (aggressive)
  - Other
- Hoarding or collecting obsessions
- Religious obsessions
- Obsession with need for symmetry or exactness
- Miscellaneous obsessions
  - Need to know or remember
  - Fear of saying certain things
  - Fear of not saying things just right
  - Intrusive (neutral) images
  - Intrusive nonsense sounds, words, or music
  - Other
- Somatic obsession–compulsion
- Cleaning or washing compulsions
  - Excessive or ritualized hand washing
  - Excessive or ritualized showering, bathing, brushing the teeth, or grooming
  - Involves cleaning of household items or inanimate objects
  - Other measures to prevent contact with contaminants
- Counting compulsions
- Checking compulsions
  - Checking that did not or will not harm others
  - Checking that did not or will not harm self
  - Checking that nothing terrible did or will happen
  - Checking for contaminants
  - Other
- Repeating rituals
- Ordering or arranging compulsions
- Miscellaneous compulsions
  - Mental rituals (other than checking or counting)
  - Need to tell, ask, or confess
  - Need to touch
- Measures to prevent
  - Harm to self
  - Harm to others
  - Terrible consequences
- Other

(Table 71–1) was generated on the basis of clinical interviews with OCD patients in the 1980s (Goodman et al. 1989a). These subtypes are remarkably consistent with phenomenological descriptions in the psychiatric literature beginning with scrupulosity in the 15th century:

> William of Oseney . . . read two or three books of Religion and devotion very often . . . (he) had read over those books 3 hours every day. In a short time he had read over those books three times more help; (He) began to think . . . that now he was to spend 6 hours every day in reading those books, because he had now read them over six times. He presently considered that . . . he must be tied to 12 hours every day (Hunter and Macalpine 1982).

The basic types of obsessions and compulsions seem to be consistent across cultures (Rasmussen and Eisen 1992). The most common obsession is fear of contamination, followed by pathological doubt, a need for symmetry, and aggressive obsessions (Figure 71–1). The most common compulsion is checking, which is followed by washing, the need to maintain symmetry, the need to ask or confess, and counting (Figure 71–2). Children with OCD present most commonly with washing compulsions, which are followed by repeating rituals (Swedo et al. 1989).

Most patients have multiple obsessions and compulsions over time, with a particular fear or concern dominating the clinical picture at any one time. The presence of obsessions without compulsions, or compulsions without obsessions, is unusual. In the DSM-IV OCD field trial of 431 patients, only 2% had only obsessions and 2% had only compulsions; the remaining 96% endorsed both obsessions and compulsions (Foa and Kozak 1995). Patients who appear to have obsessions without compulsions frequently have unrecognized reassurance rituals or mental compulsions, such as repetitive, ritualized praying, in addition to their obsessions. Pure compulsions are also unusual in adults, although they do occur in children, especially in the young (e.g., 6–8 years of age; Swedo et al. 1989). Most people have both mental and behavioral compulsions; in the DSM-IV field trial 79.5% reported having both mental and behavioral compulsions, 20.3% had behavioral compulsions only, and 0.2% had only mental compulsions.

The search for whether specific obsessions and compulsions have predictive value in terms of treatment response, biologic markers, or genetic transmission has not been particularly fruitful. There has been considerable interest in

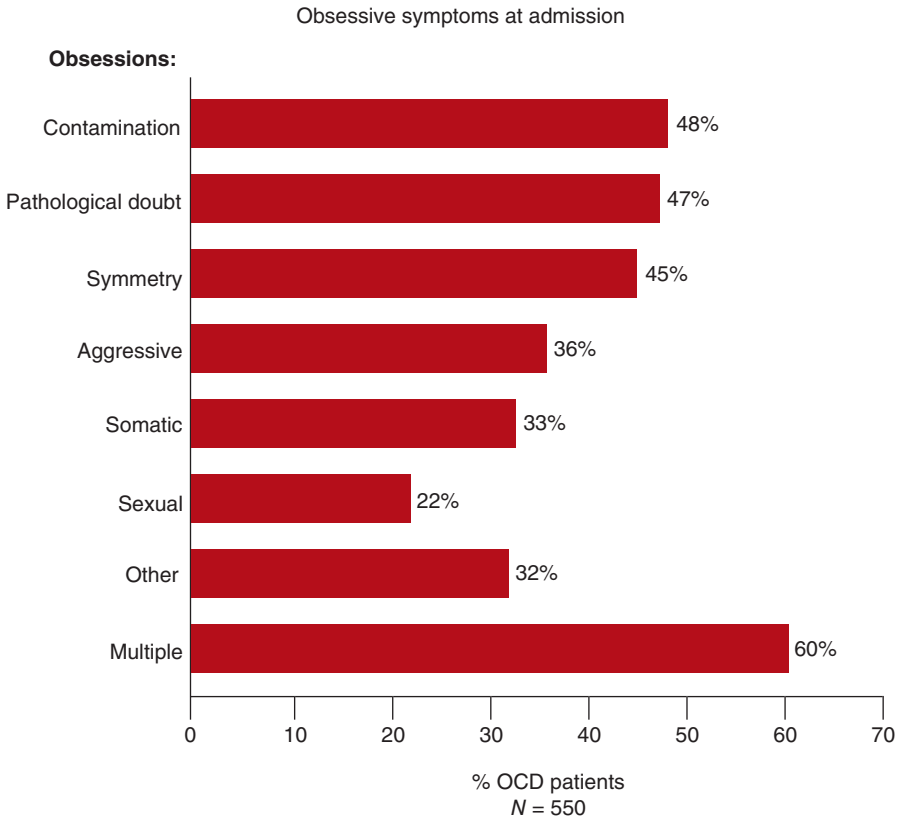



**Figure 71–1** *Obsessive symptoms at the time of initial evaluation in 550 patients with OCD.*

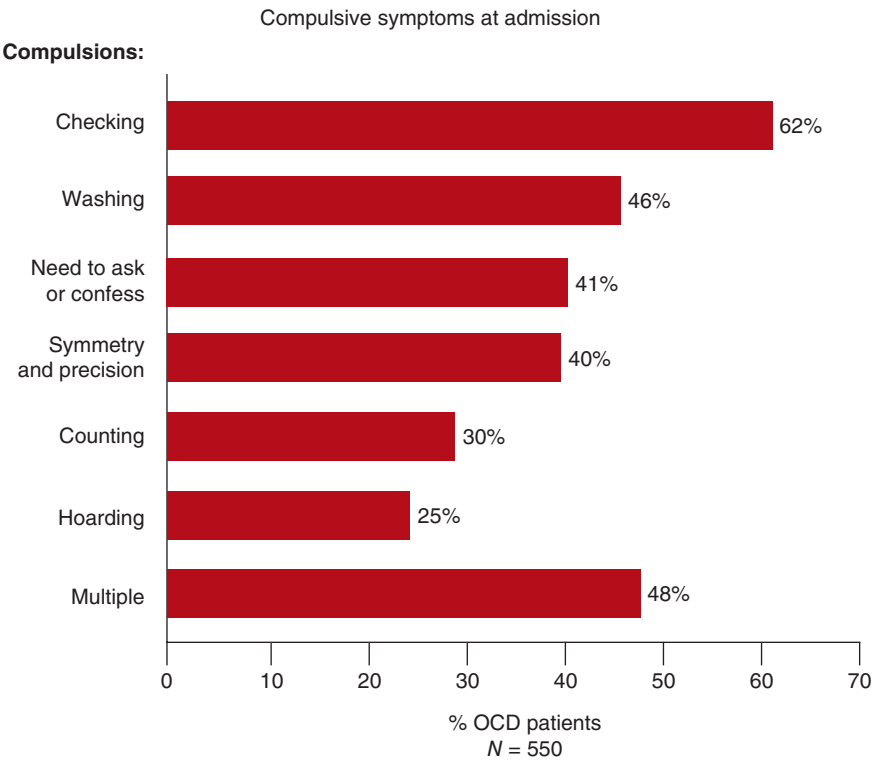



**Figure 71–2** *Compulsive symptoms at the time of initial evaluation in 550 patients.*

exploring whether certain clusters of obsessions and compulsions represent specific OCD phenotypes. A number of studies have addressed this question systematically using the Y-BOCS Symptom Checklist to identify groups of obsessions and compulsions that cluster together on factor analysis. Several studies have found between 3 and 5 such symptom dimensions: symmetry/ordering, hoarding, contamination/cleaning, aggressive obsessions/checking, and sexual/religious obsessions (reviewed by Mataix-Cols et al. 2005). The symmetry dimension has been associated with comorbid tic disorder; in one study, patients who scored high on this dimension had a relative risk for chronic tic disorder that was 8.5 times higher than those scoring low on this factor (Leckman et al., reviewed in Mataix-Cols et al. 2005). It appears that these symptom dimensions are stable over time; that is, although a patient's specific obsessions and compulsions may change over time, new obsessions and compulsions that develop are often within the same symptom dimension as the previous symptoms (Mataix-Cols et al. 2005). A study using positron emission tomography (PET scans) to evaluate neural correlates to specific areas of the brain for various symptom dimensions suggests that dysfunction in separate regions of the brain, such as the striatum and prefrontal cortex, may mediate different symptom dimensions. (Rauch et al., reviewed in Mataix-Cols et al. 2005).

Data were analyzed from a number of placebo-controlled serotonin reuptake inhibitor (SRI) treatment studies to assess whether symptom factors or dimensions were associated with treatment response (Mataix-Cols et al. 2005). No clear pattern emerged except that patients with hoarding obsession had a significantly poorer response to SRIs. Whether these identified dimensions are associated with response to behavioral treatment, biological markers, or genetic transmission has only begun to be investigated.

The following descriptions of some common obsessions and compulsions illustrate the clinical presentation of these symptoms. In some cases, a particular symptom may belong to more than one "type" of obsessive or compulsive grouping. For instance, a patient who has concerns about cancer may have hand washing as a compulsion related to her somatic obsession. However, if the patient also washes repeatedly to avoid contamination in general, not just for cancer, she would have both contamination and somatic obsessions and compulsions.

## Contamination

Contamination obsessions are the most frequently encountered obsessions in OCD. Such obsessions are usually characterized by a fear of dirt or germs. For example, a 38-year-old computer programmer was excessively preoccupied with the thought that her apartment would become dirty. She had never allowed a visitor into her apartment or worn a coat during the winter, because she feared that she would be unable to protect her apartment from dirt brought inside by either a visitor or a coat. To avoid contamination, she washed her clothes and showered immediately on entering her home.

Contamination fears may also involve toxins or environmental hazards (e.g., asbestos or lead) or bodily waste or secretions. Patients usually describe a feared consequence of contacting a contaminated object, such as spreading a disease or contracting an illness themselves. Occasionally, however, the fear is based not on a fear of disease but on a fear of the sensory experience of not being clean. The content of the contamination obsession and the feared consequence commonly changes over time; for example, a fear of cancer may be replaced by a fear of a sexually transmitted disease.

Many patients with contamination fears use avoidance to prevent contact with contaminants, as is illustrated by a 58-year-old housewife who spent the entire day sitting in a chair to avoid touching anything in the house that might be dirty. In some cases, a specific feared object and associated avoidance become more generalized. For example, a woman with a fear of acquired immunodeficiency syndrome (AIDS) initially avoided anything that looked like dried blood but eventually avoided anything red.

Excessive washing is the compulsion most commonly associated with contamination obsessions. This behavior usually occurs after contact with the feared object; however, proximity to the feared stimulus is often sufficient to engender severe anxiety and washing compulsions, even though the contaminated object has not been touched. Most patients with washing compulsions perform these rituals in response to a fear of contamination, but these behaviors occasionally occur in response to a drive for perfection or a need for symmetry. Some patients, for example, repeatedly wash themselves in the shower until they feel "right" or must wash their right arm and then their left arm the same number of times.

## Need for Symmetry

Need for symmetry is a term that describes a drive to order or arrange things perfectly or to perform certain behaviors symmetrically or in a balanced way. Patients describe an urge to repeat motor acts until they achieve a "just right" feeling that the act has been completed perfectly. Patients with a prominent need for symmetry may have little anxiety but rather describe feeling unsettled or uneasy if they cannot repeat actions or order things to their satisfaction. In addition to a need for perfection, the drive to achieve balance or symmetry may be connected with magical thinking. For example, a 22-year-old college student felt compelled to walk across doorway thresholds exactly in the center to prevent something terrible from happening to his parents. The desire to "even up" or balance movements may be present in patients with tapping or touching rituals. Such a patient may, for example, feel that the right side of the chair must be tapped after the left side has been tapped. Such urges and behaviors are frequently seen in patients with comorbid tic disorders (Leckman et al. 1994, reviewed in Mataix-Cols et al. 2005), who may, for example, describe an urge to tic on the right side of their body after experiencing a tic on the left side.

Patients with a need for symmetry frequently present with obsessional slowness, taking hours to perform acts such as grooming or brushing their teeth. A 23-year-old cook spent 2 hours a day brushing his teeth in a symmetrical fashion and as a result developed gingival erosion. He reported being exquisitely aware of exactly how the toothbrush touched each surface of each tooth and of how he placed the toothbrush and cup down after finishing. He was unable to describe any obsession or fear about not performing this task adequately but rather felt unable to stop until he had brushed completely, despite warnings from his dentist about the harm he was causing.

## Somatic Obsessions

Patients with somatic obsessions are worried about the possibility that they have or will contract an illness or disease. In the past, the most common somatic obsessions consisted of fears of cancer or venereal diseases. However, a fear of developing AIDS has become increasingly common. Checking compulsions consisting of checking and rechecking the body part of concern, as well as reassurance seeking, are commonly associated with this fear. For example, a 29-year-old firefighter spent 3 hours a day examining his throat in the mirror and palpating his lymph nodes to determine whether he had throat cancer. He also repeatedly asked his wife whether she thought his throat looked normal. While it may be difficult to distinguish the somatic obsessions of OCD from those of hypochondriasis, somatic obsessions in OCD usually involve compulsive behaviors of some sort done by the patient, not necessarily seeking medical opinions about the feared illness (see below for more elaboration).

## Sexual and Aggressive Obsessions

People with sexual or aggressive obsessions are plagued by fears that they might harm others or commit a sexually unacceptable act such as molestation. Often, they are fearful not only that they will commit a dreadful act in the future but also that they have already committed the act. Patients are usually horrified by the content of their obsessions and are reluctant to divulge them. It is striking that the content of these obsessions tends to consist of ideas that patients find particularly abhorrent. A 32-year-old librarian who wanted to be a good mother had intrusive thoughts of stabbing her daughter. The horror and revulsion that she experienced in response to this image is typical of patients' reactions to their aggressive and sexual thoughts.

Patients with these highly distressing obsessions frequently have checking and confession or reassurance rituals. They may report themselves to the police or repeatedly seek out priests to confess their imagined crimes. For example, a 63-year-old mother of five children and seven grandchildren felt compelled to confess to her priest that she might have had a sexual thought or feeling while drying herself after showering. A 29-year-old secretary constantly checked the local news to be certain that she had not murdered someone. An unsolved murder case caused her tremendous anxiety and led to extensive reassurance rituals.

## Pathological Doubt

Pathological doubt is a common feature of patients with OCD who have a variety of different obsessions and compulsions. Individuals with pathological doubt are plagued by the concern that, as a result of their carelessness, they will be responsible for a dire event. They may worry, for example, that they will start a fire because they neglected to turn off the stove before leaving the house. Although many patients report being fairly certain that they performed the act in question (e.g., locking the door, unplugging the hair-dryer, paying the correct amount on a bill), they cannot dismiss the nagging doubt "What if?"

Such patients often describe doubting their own perceptions. A 42-year-old man felt incapable of throwing grocery bags away because he feared he might not have completely emptied them. Immediately after staring into an empty bag, he inevitably thought, "What if I missed something important in there?" A 33-year-old lawyer was unable to mail anything because she feared she had inadvertently placed written misinformation inside the envelope.

Excessive doubt and associated feelings of excessive responsibility frequently lead to checking rituals. For example, individuals may spend several hours checking their home before they leave. As with contamination obsessions, pathological doubt can lead to marked avoidance behavior. Some patients become housebound to avoid the responsibility of potentially leaving the house unlocked.

Pathological doubt is also embedded in the cognitive framework of a number of other obsessions. Patients with aggressive obsessions may be plagued by the doubt that they inadvertently harmed someone without knowing that they did so. For example, a young mother did not allow her children to have friends sleep at her house because she feared she might harm them during the night. Although she agreed that it was preposterous to think that she might commit a violent act without being aware of it, she nonetheless stated that she "did not want to take a chance," and she was unable to dismiss her nagging worry and doubt.

## Insight

An awareness of the senselessness or unreasonableness of obsessions (often referred to as insight) and the accompanying struggle against the obsessions (referred to as resistance) have generally been considered fundamental components of OCD. However, during the past century there have been numerous descriptions of patients with OCD who are completely convinced of the reasonableness of their obsessions and need to perform compulsions. Patients with OCD may have varying degrees of insight and resistance, with obsessive–compulsive psychosis at one extreme of a hypothesized continuum.

One study that investigated the range of insight in OCD used an interview that evaluated several insight-related parameters, including the fixity of beliefs underlying the obsession, bizarreness, resistance, and degree of control (Lelliot et al. 1988). The fixity dimension included several constructs: strength of the belief in the feared situation, how the patient thought others viewed the belief, and the patient's response to evidence that contradicted the belief. A full range of responses was found in the 43 patients assessed, which led the authors to conclude that good insight is not necessarily present and that insight spans a spectrum from good to absent (i.e., delusional thinking).

More recently, degree of insight in OCD was addressed during the DSM-IV field trial in which patients were asked if they feared consequences other than anxiety if they did not perform their compulsions (Foa and Kozak 1995). Fifty-eight percent believed that harmful consequences would occur. The degree of certainty that their obsessions were reasonable ranged across the entire spectrum of insight: 30% were uncertain whether they actually needed to perform their compulsions to avoid harm; however, 4% were certain, and 26% were mostly certain. Again, this finding supports the notion that patients with OCD do not always maintain good insight but rather have varying degrees of insight. Although patients may be aware that their obsessions are excessive—that is, recognizing that they spend too much time thinking about them—they may have little insight into the fact that the belief underlying their obsession (e.g., that

they will get cancer from stepping on a chemically treated lawn) is senseless, unreasonable, or unrealistic.

To reflect these findings, DSM-IV-TR established a new OCD specifier, with poor insight. This specifier applies to "an individual who, for most of the time in the current episode, does not recognize that the obsessions or compulsions are excessive or unreasonable." DSM-IV-TR also acknowledges that the beliefs that underlie OCD obsessions can be delusional and notes that in such cases an additional diagnosis of delusional disorder or psychotic disorder not otherwise specified may be appropriate.

Despite these changes, there was no generally accepted, reliable, and valid method to assess degree of insight. To address the need for a scale that measures insight in OCD and other psychiatric disorders, Eisen and Phillips developed the Brown Assessment of Beliefs Scale, a semistructured clinician-administered interview with specific probes and anchors that measure various dimensions of delusionality (Eisen et al. 1998). Items assess dimensions such as conviction, perception of others' views of the belief, fixity, and insight (awareness that obsessions and compulsions are caused by a psychiatric illness). Combining data from a number of studies, 20–25% of individuals with OCD at some point during their illness are fairly convinced that their obsessions are realistic and that consequences other than anxiety would occur if they did not perform their compulsions. Nonetheless, most people with OCD are aware that other people think their symptoms are unrealistic and that the obsessions are caused by a psychiatric illness.

Whether insight is an important predictor of prognosis and treatment response is an intriguing issue that has received little investigation. However, it appears that patients with poor insight or overvalued ideas may not respond as well to behavioral therapy as patients with good insight. In the only study that has, to our knowledge, assessed whether insight predicts medication response, patients with poor insight at study baseline were just as likely to have a response of OCD symptoms to open-label sertraline as those with good to excellent insight. In addition, insight improved with sertraline treatment during this 16-week study (Eisen et al. 2001).

More studies are needed to determine the effect of insight on treatment response. For example, to our knowledge no studies have assessed whether adding an antipsychotic to an SRI is more effective in patients with poor insight than in those with good insight. Studies that assess the impact of insight on compliance, refusal of, and response to behavioral therapy are also needed.

### Demographics—Marital Status

In a study of 250 subjects with OCD 52% were married, 43% were never married, and 5% were divorced (Rasmussen and Eisen 1992). The percentage of patients who had never married was significantly higher than that of age-matched controls. In the BNPMS, 36% of subjects with OCD lived alone, which was more than twice the rate of nonneurotic controls (Torres et al. 2006a). However, a study comparing marital status in probands with OCD and an age-matched group of patients with major depressive disorder found no significant differences between the two groups (Coryell 1981). Although marital status was not found to be a predictor of course in a number of follow-up studies, a prospective study of 107 subjects with OCD found that being married significantly increased the probability of partial remission, with married patients more than twice as likely to remit as unmarried ones (Steketee et al. 1999). Furthermore, rehospitalization after 6–8 years of follow-up after cognitive–behavioral therapy (CBT) combined with either fluvoxamine or placebo was associated with living without a partner (Rufer et al. 2005).

## Epidemiology

Since the 15th century, the psychiatric literature has contained striking descriptions of patients with debilitating obsessions and compulsions. Until the mid-1980s, however, OCD was considered extremely rare. This perception was based on studies from the 1950s and 1960s that examined the frequency of psychiatric diagnoses in inpatient and outpatient settings. The results of a large psychiatric epidemiological study, the national ECA survey, conducted in the US in 1984, painted a different picture of OCD's prevalence. This study found that OCD was the fourth most common psychiatric disorder (after the phobias, substance use disorders, and major depressive disorder), with a prevalence of 1.6% over 6 months and a lifetime prevalence of 2.5% (Myers et al. 1984). Although the ECA survey has been criticized as overestimating OCD's prevalence, a subsequent study in the US and several epidemiological studies in other countries have supported its findings. Using the same instrument as the ECA, studies have been done in diverse cultures, including Puerto Rico, Canada, Germany, Taiwan, New Zealand, and Korea, as part of the Cross National Collaborative Group (Weissman et al. 1994). The lifetime (range 1.9–2.5%) and annual (range 1.1–1.8%) prevalence rates of OCD were remarkably consistent across countries with the exception of Taiwan. The rates in Taiwan were substantially lower than in all the other sites, paralleling Taiwan's low rates of other psychiatric disorders. A recent epidemiological study in the UK, the British National Psychiatric Morbidity Survey of 2000 (BNPMS), used the Clinical Interview Schedule—Revised and ICD-10 criteria.

**ICD-10 Criteria for Obsessive-Compulsive Disorder**

**F42 Obsessive-compulsive disorder**

The essential feature is recurrent obsessional thoughts or compulsive acts. Obsessional thoughts are ideas, images, or impulses that enter the patient's mind again and again in a stereotyped form. They are almost invariably distressing and the patient often tries, unsuccessfully, to resist them. They are, however, recognized as his or her own thoughts, even though they are involuntary and often repugnant. Compulsive acts or rituals are stereotyped behaviours that are repeated again and again. They are not inherently enjoyable, nor do they result in the completion of inherently useful tasks. Their function is to prevent some objectively unlikely event, often involving harm to or caused by the patient, which he or she fears might otherwise occur. Usually, this behaviour is recognized by the patient as pointless or ineffectual and repeated attempts are made to resist.

Anxiety is almost invariably present. If compulsive acts are resisted the anxiety gets worse.

***Includes:*** anankastic neurosis, obsessive-compulsive neurosis

***Excludes:*** obsessive-compulsive personality (disorder)

**F42.0 Predominantly obsessional thoughts or ruminations**

These may take the form of ideas, mental images, or impulses to act, which are nearly always distressing to the subject. Sometimes the ideas are an indecisive, endless consideration of alternatives, associated with an inability to make trivial but necessary decisions in day-to-day living. The relationship between obsessional ruminations and depression is particularly close and a diagnosis of obsessive-compulsive disorder should be preferred only if ruminations arise or persist in the absence of a depressive episode.

**F42.1 Predominantly compulsive acts [obsessional rituals]**

The majority of compulsive acts are concerned with cleaning (particularly handwashing), repeated checking to ensure that a potentially dangerous situation has not been allowed to develop, or orderliness and tidiness. Underlying the overt behaviour is a fear, usually of danger either to or caused by the patient, and the ritual is an ineffectual or symbolic attempt to avert that danger.

**F42.2 Mixed obsessional thoughts and acts**

**F42.8 Other obsessive-compulsive disorders**

**F42.9 Obsessive-compulsive disorder, unspecified**

In this sample, the weighted prevalence of OCD was 1.1% (Torres et al. 2006a).

## Comorbidity

### Major Depression

OCD frequently occurs in association with other Axis I disorders. In a study of 100 patients with primary OCD, 67 had a lifetime history of major depressive disorder, and 31 had symptoms that met criteria for current major depressive disorder (Rasmussen and Eisen 1991). In the BNPMS, 36% of subjects with OCD met criteria for depressive episode (Torres et al. 2006a). Although it may be difficult to distinguish a primary from a secondary diagnosis, some individuals with OCD view their depressive symptoms as occurring secondary to the demoralization and hopelessness accompanying their OCD and report that they would not be depressed if they did not have OCD. However, others view their major depressive symptoms as occurring independently of their OCD symptoms, which may be less severe when they cycle into an episode of major depression, because they feel too apathetic to be as concerned with their obsessions and too fatigued to perform compulsions. Conversely, OCD symptoms may intensify during depressive episodes.

### Tic Disorders

Although findings have varied, the generally accepted frequency of tic disorders in patients with OCD is far higher than in the general population, with a rate of approximately 5–10% for Tourette's Disorder and 20% for any tic disorder (Leonard et al. 1992). Conversely, patients with Tourette's disorder have a high rate of comorbid OCD, with 30–40% reporting obsessive–compulsive symptoms (Lees et al. 1984, Robertson et al. 1988). The likelihood of childhood onset of OCD is greater in this group, and the presence of tics is associated with more severe OCD symptoms in children (Leonard et al. 1992). There is an increased rate of both OCD and tic disorders in the first-degree relatives of OCD probands with a family lifetime history of tics (Nestadt et al. 2000b), and an increased frequency of tic disorders in the first-degree relatives of OCD probands compared to controls (Grados et al. 2001). There are also phenomenologic observations that link OCD and tic disorders. Individuals with both OCD and tics have several features that distinguish them from individuals with OCD alone. They more frequently have symmetry, ordering and arranging, and hoarding compulsions, and they more frequently try to attain a "just right" feeling. These data strengthen the notion that tic disorders and OCD are highly related. In fact, it has been suggested that tic disorders are an alternative expression or phenotype of the familial OCD subtype (Grados et al. 2001).

### Anxiety Disorders

Anxiety disorders frequently coexist with OCD, with relatively high lifetime rates of specific phobia (22%), social phobia (18%), and panic disorder (12%) in patients with OCD (Rasmussen and Eisen 1991). In one study, 17 of 100 subjects with OCD had a lifetime history of an eating disorder (Rasmussen and Eisen 1991). Conversely, in 93 subjects with an eating disorder, 37 had symptoms that met criteria for comorbid OCD (Rubenstein et al. 1992). In 114 epidemiologically ascertained subjects from the UK BNPMS study, subjects with OCD had significantly more comorbid conditions than subjects with other neuroses. These included generalized anxiety disorder (31.4%), agoraphobia or panic disorder (22.1%), social phobia (17.3%), and specific phobia (15.1%). There were no significant gender differences in either overall comorbidity or the comorbid prevalence of individual neurotic disorders (Torres et al. 2006a).

### Psychotic Disorders

It has long been noted that the co-occurrence of OCD symptoms in patients with psychotic disorders is more than would be expected by chance. Furthermore, it has more recently been suggested that the admixture of psychotic and OCD symptoms may represent a "schizo-obsessive" subtype. One of the complications in studying this issue is that it is often difficult to differentiate delusions from obsessions with poor insight (reviewed by Bottas et al. 2005). In the BNPMS, 15 of 114 OCD subjects screened positive for possible psychosis (12.7%). Of these, 3 (15.8%) or 2.6% of all OCD subjects met ICD-10 criteria for schizophrenia in the past year (Torres et al. 2006a). This is consistent with a previous study, in which 14% ($N = 67$) of 475 OCD subjects had psychotic or psychotic-like symptoms (Eisen and Rasmussen 1993). These 67 subjects were quite heterogeneous: 18 (4% of the larger cohort) had comorbid schizophrenia, 8 (2%)

had comorbid delusional disorder unrelated to OCD, and 14 (3%) had comorbid schizotypal personality disorder. In the remaining 27 patients (6% of the larger cohort), the only psychotic symptom was a delusional conviction about the reasonableness of the obsessions (i.e., delusional OCD or OCD without insight). Of interest, the 27 subjects without insight regarding their OCD symptoms were similar to the subjects without any psychotic symptoms (i.e., OCD with insight) in terms of epidemiological and clinical features, such as course of illness. More recently, a longitudinal study of 293 adults with primary OCD reported a lower frequency of comorbid psychotic symptoms at intake with a lifetime frequency of 2.7% ($n$ = 8) and a current frequency of 2% ($n$ = 6) (Pinto et al. 2006).

In contrast, several studies of OCD and comorbid schizophrenia found that compared to subjects with OCD alone, those with comorbid schizophrenia have a worse prognosis in terms of long-term outcome (social relations, employment, psychopathology, and global functioning; Fenton and McGlashan 1986). Similarly, treatment studies of patients with OCD and comorbid schizotypal personality disorder have shown a poorer prognosis and poorer response to psychotropic medications for the comorbid group (Jenike et al. 1986). Thus, it appears important to differentiate OCD plus a comorbid psychotic disorder, which may have a relatively poor outcome, from delusional OCD, which may be more similar to OCD with insight and without comorbid psychosis.

Retrospective follow-up studies that have examined the subsequent development of schizophrenia in patients with OCD have had varying results, with rates ranging from 0.7% to as high as 12.3% (reviewed by Goodwin et al. 1969). These studies were, however, methodologically limited in that none were prospective, diagnoses were made by chart review, and standardized diagnostic criteria were not used, which probably resulted in the inclusion of affective psychoses. In reviewing this literature, Goodwin et al. (1969) concluded that people with OCD were at no greater risk for developing schizophrenia than the general population. Conversely, studies of patients with schizophrenia or schizoaffective disorder have found rates of OCD ranging from 8 to 46%. This strikingly large range is most likely due to the OCD criteria used (i.e., subclinical OCD symptoms vs. OCD symptoms severe enough to cause significant impairment or distress) (Eisen et al. 1997, Porto et al. 1997, Berman et al. 1995). Regardless, it is clear that a significant number of people with schizophrenia have OCD symptoms that require assessment and may benefit from treatment.

## Personality Disorders

The relationship between OCD and personality disorders, particularly obsessive–compulsive personality disorder (OCPD), has received considerable attention. Early observations noted the presence of OCPD traits in patients with OCD. Systematic studies have yielded inconsistent findings. In the British BNPMS, 76% of all OCD subjects screened positive for any personality disorder (Torres et al. 2006b). In a study of 96 subjects with OCD that used the Structured Clinical Interview for DSM-III personality disorders (SCID-II), 36 had a personality disturbance that met criteria for one or more personality disorders (Baer et al. 1990a). Dependent ($N$ = 12), histrionic ($N$ = 9), and obsessive–compulsive ($N$ = 6) personality disorders were most frequent. However, a study that used the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) criteria found that OCPD was present in 25 of 59 subjects with OCD; the higher rate of OCPD found with the DSM-III-R criteria may reflect changes in the criteria set between DSM-III and DSM-III-R. Another study of the rate of OCPD in first-degree relatives of OCD probands found a similar frequency of OCPD in people with OCD. OCPD occurred in 32% of the probands and was twice as frequent in the relatives of OCD probands as in relatives of control probands (Samuels et al. 2000), suggesting that OCPD may share a common familial etiology with OCD. Regarding the converse, in a recent study of 629 subjects with personality disorders, 20% of patients with OCPD met DSM-IV-TR criteria for OCD, which was more frequent than any other personality disorder (Eisen et al. 2006).

Although personality disorders are considered to be stable over time, one study found that of 17 OCD patients with a personality disorder, 9 of the 10 treatment responders no longer met criteria for either avoidant or dependent personality disorder after successful pharmacotherapy, raising the question of whether these personality disorders actually represented a coping style in response to OCD (Ricciardi et al. 1992). And an alternative explanation is that pharmacotherapy may have the potential of ameliorating certain aspects of the personality disorder.

## Course

Age at onset usually refers to the age when OCD symptoms (obsessions and compulsions) reach a severity level wherein they lead to impaired functioning or significant distress or are time-consuming (i.e., meet DSM-IV-TR criteria for the disorder). Reported age at onset is usually during late adolescence. In one study drawn from an OCD clinic sample ($N$ = 560), the onset for males occurred significantly earlier than for females (19.5 ± 9.2 years vs. 22.0 ± 9.8 years). In this study, 83% of patients experienced the onset of significant symptoms between ages 10 and 24 years, whereas less than 15% experienced onset after age 35 years (Rasmussen and Eisen 1998). People with OCD, however, usually describe the onset of minor symptoms in childhood, well before the onset of symptoms meeting full criteria for the disorder.

Earlier age at onset has been associated with an increased rate of OCD in first-degree relatives (Nestadt et al. 2000a). These data suggest that there is a familial type of OCD characterized by early onset. Age at onset of OCD may also be a predictor of course. The vast majority of patients report a gradual worsening of obsessions and compulsions prior to the onset of full-criteria OCD, which is followed by a chronic course (see later). However, Swedo and colleagues have described a subtype of OCD that begins before puberty and is characterized by an episodic course with intense exacerbations. Exacerbations of OCD symptoms in this subtype have been linked with group A beta-hemolytic streptococcal infections, which has led to the subtype designation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). In their study of 50 children with PANDAS, the average age of onset was 7.4 years. Whether the course of illness in patients with PANDAS continues to be episodic into adulthood, or, as is the case with postpubertal onset,

tends to be chronic, is not known (reviewed by Snider and Swedo 2004).

Earlier phenomenological and follow-up studies consistently showed the course of OCD to be continuous and chronic in which patients were rarely symptom-free at follow-up. However, these studies had a number of methodological limitations, including a lack of standardized criteria to determine the diagnosis, diagnoses based on chart review, a lack of structured interviews, a retrospective study design, and a lack of consensus on definitions of relapse, remission, and recovery. In keeping with the older literature, a more recent study showed that the course of OCD is usually waxing and waning; that is, once a patient acquires OCD, obsessions or compulsions, or both, are present continuously, with varying degrees of intensity over time. Relatively few patients had either a progressively deteriorating course or a truly episodic course (Rasmussen and Eisen 1991). Although this study had some methodological advantages over previous studies, it was not prospective, and the effect of treatment on the course of illness was not addressed.

A recent 3-year naturalistic prospective study of 79 adults with OCD, in which the effect of treatment was assessed, supported earlier findings that OCD is usually chronic with fluctuations in symptom intensity and high rate of relapse; it is notable that this course was most common even during an era when effective treatments were available. Although 50% of the subjects achieved partial remission in the first year of the study, the probability of subsequent relapse was 60%. Thirty-eight percent achieved full remission (Catapano et al. 2006). In a follow-up study of 144 people with OCD assessed in the 1950s and again in the 1990s, mean length of follow-up from illness onset was 47 years. Most subjects reported a significant decrease in OCD symptom severity, which varied from complete recovery (20%) to recovery with continued subclinical symptoms (28%) to continued OCD but with clear improvement (35%). Worse outcome was associated with early age of onset, chronic course, and low social functioning at baseline (Skoog and Skoog 1999).

A recent meta-analysis pooled 16 study samples comprising 521 children followed between 1 and 15.6 years (Stewart et al. 2004). The persistence of OCD was lower than previously believed. The authors reported that two-thirds of studies showed that OCD did not persist as a full clinical syndrome in the majority of subjects. The pooled mean rate of persistence of full threshold OCD was 41%. The persistence of OCD was predicted by inpatient treatment, longer duration of illness at baseline, and an earlier age at onset of OCD. However, gender, age at assessment, and length of follow-up may also be related to the persistence of OCD.

## Differential Diagnosis

OCD is sometimes difficult to distinguish from certain other disorders. Obsessions and compulsions may appear in the context of other syndromes, which can raise the question whether the obsessions and compulsions are a symptom of another disorder or whether both OCD and another disorder are present (see section on comorbidity). A general guideline is that if the content of the obsessions is not limited to the focus of concern of another disorder (e.g., an appearance concern, as in body dysmorphic disorder, or food concerns, as in an eating disorder) and if the obsessions or compulsions are preoccupying as well as distressing or impairing, OCD should generally be diagnosed.

Diagnostic dilemmas may also arise when it is unclear whether certain thoughts are obsessions or whether, instead, they are ordinary worries, ruminations, overvalued ideas, or delusions. In a similar vein, questions may develop about whether certain behaviors constitute true compulsions or whether they should instead be conceptualized as impulses, tics, or addictive behaviors.

### Obsessive–Compulsive Disorder Versus Other Anxiety Disorders

Both OCD and the other anxiety disorders are characterized by the use of avoidance to manage anxiety. However, OCD is distinguished from these disorders by the presence of compulsions. For OCD patients with preoccupying fears or worries but no rituals, several other features may be useful in establishing the diagnosis of OCD. In social phobia and specific phobia, fears are circumscribed and related to specific triggers (in specific phobia) or social situations (in social phobia). Although circumscribed situations may initially trigger obsessions and compulsions in OCD, triggers in OCD become more generalized over time, unlike the triggers in social and specific phobias, in which the evoking situations remain circumscribed.

As many as 60% of people with OCD experience full-blown panic symptoms. However, unlike panic disorder, in which panic attacks occur spontaneously, panic symptoms occur in OCD only during exposure to specific feared triggers such as contaminated objects. The worries that are present in generalized anxiety disorder (GAD) are more ego syntonic and involve an exaggeration of ordinary concerns, whereas the obsessional thinking of OCD is more intrusive and is limited to a specific obsessions (e.g., contamination, blasphemy), and usually has an irrational, senseless, or unreasonable quality. Also, whereas the worry of GAD is considered primarily "thought-like" in nature, obsessional symptoms may consist of thoughts, impulses, or images.

### Obsessive–Compulsive Disorder Versus Psychotic Disorders

One question is how to differentiate OCD from psychotic disorders such as schizophrenia and delusional disorder. Another question is how to distinguish OCD with insight from OCD without insight (delusional OCD). One distinguishing feature between OCD and the psychotic disorders is that the latter are not characterized by prominent ritualistic behaviors. If compulsions are present in a patient with prominent psychotic symptoms, the possibility of a comorbid OCD diagnosis should be considered. Furthermore, although schizophrenia may be characterized by obsessional thinking, other characteristic features of the disorder, such as prominent hallucinations or thought disorder, are also present. With regard to delusional disorder, paranoid and grandiose concerns are generally not considered to fall under the OCD rubric. However, some other types of delusional disorders, such as the somatic and jealous types, seem to bear a close resemblance to OCD and are not always easily distinguished from it. It will be interesting to see whether future research indicates that certain types of somatic delusional disorders (e.g., the delusional variant of hypochondriasis) and the jealous type of delusional

disorder (also referred to as pathological jealousy) are actually variants of OCD.

The second issue noted above—how to distinguish OCD with insight from OCD without insight—is complex. As previously discussed, insight in OCD is increasingly being recognized as spanning a spectrum from good to poor to absent. Both clinical observations and research findings indicate that some individuals hold their obsessional concerns with delusional intensity and believe that their concerns are reasonable. In DSM-IV-TR, delusional OCD may be double coded as both OCD and delusional disorder or as both OCD and psychotic disorder not otherwise specified; in other words, patients with delusional OCD would receive both diagnoses. This double coding reflects the fact that it is unclear whether OCD with insight and OCD without insight constitute the same or different disorders. Further research using validated scales to assess insight in OCD is needed to shed light on this question.

## Obsessive–Compulsive Disorder Versus Impulse Control Disorders

Differential diagnosis questions have been raised with regard to kleptomania, trichotillomania, pathological gambling, and other disorders involving impulsive behaviors. Several features have been said to distinguish these disorders from OCD. For example, OCD compulsions generally have no gratifying element, although they do diminish anxiety. In contrast, behaviors of the impulse control disorders are usually gratifying, pleasurable, and rewarding. In addition, the affective state that drives the behaviors associated with these disorders may differ. In OCD, fear is frequently the underlying drive that leads to compulsions, which, in turn, decrease anxiety. In the impulse control disorders, patients frequently describe heightened tension, but not fear, preceding an impulsive behavior. However, OCD and the impulse control disorders have some features in common. Research is ongoing to explore the relationship between OCD and the impulse control disorders by examining similarities and differences in treatment response, biological markers, familial transmission, and other external validators (Dell'Osso et al. 2006).

## Obsessive–Compulsive Disorder Versus Tourette's Disorder

Complex motor tics of Tourette's disorder may be difficult to distinguish from OCD compulsions. Both tics and compulsions are preceded by an intrusive urge and are followed by feelings of relief. However, OCD compulsions are usually preceded by both anxiety and obsessional concerns, whereas, in Tourette's disorder, the urge to perform a tic is not preceded by an obsessional fear. This distinction breaks down to some extent when considering the "just right" perceptions of some patients with OCD. The "just right" perception refers to the need to perform a certain motor action, such as touching, tapping, checking, ordering, arranging, or counting, until it feels right. Determining when an action has been performed enough or perfectly may depend on tactile, visual, or auditory perceptions. In a study of patients with Tourette's disorder and OCD symptoms, most patients could distinguish between the mental urge to do something repeatedly until it felt right and a physical urge to perform a motor tic. However, it is sometimes difficult for psychiatrists to distinguish between complex tics and compulsions, especially when a patient has both disorders (Miguel et al. 1995).

## Obsessive–Compulsive Disorder Versus Hypochondriasis

Fears of illness that occur in OCD, referred to as somatic obsessions, may be difficult to distinguish from hypochondriasis. Usually, however, patients with somatic obsessions have other current or past classic OCD obsessions unrelated to illness concerns. Patients with OCD also often engage in classic OCD rituals, such as checking or reassurance seeking, in an attempt to diminish their illness concerns. Unlike patients with OCD, patients with hypochondriasis experience somatic and visceral sensations. Although insight and resistance have been used to distinguish OCD from hypochondriasis, with the concern in hypochondriasis being said to be ego syntonic (realistic and justified) and that of OCD to be ego dystonic (unacceptable and undesirable thoughts, actions, or both), studies have demonstrated a range of insight in OCD. Attempting to differentiate these disorders by degree of insight or ego syntonicity may, therefore, be of limited usefulness.

## Obsessive–Compulsive Disorder Versus Body Dysmorphic Disorder

Body dysmorphic Disorder (BDD), a preoccupation with an imagined or slight defect in appearance (e.g., thinning hair, facial scarring, or a large nose), has many similarities to OCD (Phillips 1991). Patients with BDD experience obsessional thinking about the supposed defect and usually engage in associated repetitive ritualistic behaviors, such as mirror checking and reassurance seeking. BDD also appears similar to OCD in terms of age of onset, course of illness, and other variables (Phillips et al. 2006). Nonetheless, emerging data suggest that there are some important differences between the two disorders, and they are currently classified separately in DSM-IV-TR. Insight, for example, is more frequently impaired in BDD than in OCD. Furthermore, there is a greater prevalence of major depression, suicidality, and substance abuse in BDD (Phillips et al. 2006). If the content of a patient's obsessions involves a concern about a supposed defect in appearance, BDD, rather than OCD, is the diagnosis that should be given.

## Obsessive–Compulsive Disorder Versus Obsessive–Compulsive Personality Disorder

OCPD is a lifelong maladaptive personality style characterized by perfectionism, excessive attention to detail, indecisiveness, rigidity, excessive devotion to work, restricted affect, lack of generosity, and hoarding. OCD and OCPD have historically been considered variants of the same disorder on a continuum of severity, with OCD viewed as the more severe manifestation of illness. Contrary to this notion, studies using structured interviews to establish diagnosis have found that not all patients with OCD also have OCPD. One reason for the perception that these disorders are linked lies in the frequency of several OCPD traits in patients with OCD. In one study, the majority of 114 patients with OCD had perfectionism and indecisiveness (82 and 70, respectively). In contrast, other OCPD traits, such as restricted affect, excessive devotion to work, and rigidity, were seen infrequently.

Although perfectionism and indecisiveness are relatively common traits in patients with OCD, the distinction between OCD and OCPD is important, and several guidelines may be useful in distinguishing them. Unlike OCPD, OCD is characterized by distressing, time-consuming ego-dystonic obsessions and repetitive rituals aimed at diminishing the distress engendered by obsessional thinking. One of the hallmarks that traditionally has been used to distinguish OCD from OCPD is that, in contrast, OCPD features are considered ego syntonic. In addition, as previously noted, the traits of restricted affect, excessive devotion to work, and rigidity are generally characteristic of OCPD but not OCD. Although useful, these guidelines are not absolute, and some patients defy easy categorization. Some patients, for example, spend hours each day engaged in ego-syntonic behaviors such as excessive cleaning; such patients may seek treatment not because they are disturbed by their behaviors but because the behaviors cause problems in functioning or family friction. It is unclear whether some of these patients should be diagnosed with OCPD or subthreshold OCD.

## Obsessive–Compulsive Spectrum Disorders

Certain disorders other than OCD—such as BDD, hypochondriasis, and eating disorders—are characterized by obsessional thinking and/or ritualistic behaviors. On the basis of these apparent similarities with OCD, the concept of OCD spectrum disorders has been developed. They have been defined as disorders that share features with OCD (Hollander et al. 2007) and are posited to have "spectrum membership" on the basis of their similarities with OCD across multiple domains. These domains include not only symptoms but also treatment response, comorbidity, joint familial loading, sex ratio, age at onset, course, premorbid personality characteristics, and presumed cause. Cause is inferred from characteristics such as neurological deficits, response to biological challenges, biochemical indices, brain imaging patterns (functional and anatomical), and environmental risk factors. It is worth noting that there are currently no operational criteria for what constitutes an OCD spectrum disorder; for example, in which of the preceding domains must similarities be documented, and how similar in each domain must the disorder be to OCD?

Disorders postulated to be OCD spectrum disorders include BDD, hypochondriasis, tic disorders, eating disorders, "grooming" disorders such as nail-biting and trichotillomania, and the impulse disorders (Hollander et al. 2007, see Figure 71–3). Of interest is a recent study investigating the frequency of these disorders in first-degree relatives of people with OCD. BDD, hypochondriasis, any eating disorder (although not anorexia or bulimia individually), and grooming disorders (but not the impulse control disorders) were found more frequently in probands with OCD than in general population controls. In addition, BDD and grooming disorders (although not the other disorders) were significantly more common in the first-degree relatives of OCD probands than in relatives of controls (reviewed in Hollander et al. 2007). This finding suggests that certain of the proposed OCD spectrum disorders may have a familial link to OCD. The relationship of these disorders with OCD is an area in which exciting research will be conducted in coming years.

## Differences in Gender Presentation

Women appear to develop OCD slightly more frequently than do men. The BNPMS study reported a female-to-male ratio of 1.44:1 (Torres et al. 2006a). However, a study that assessed the presence of comorbid disorders characterized

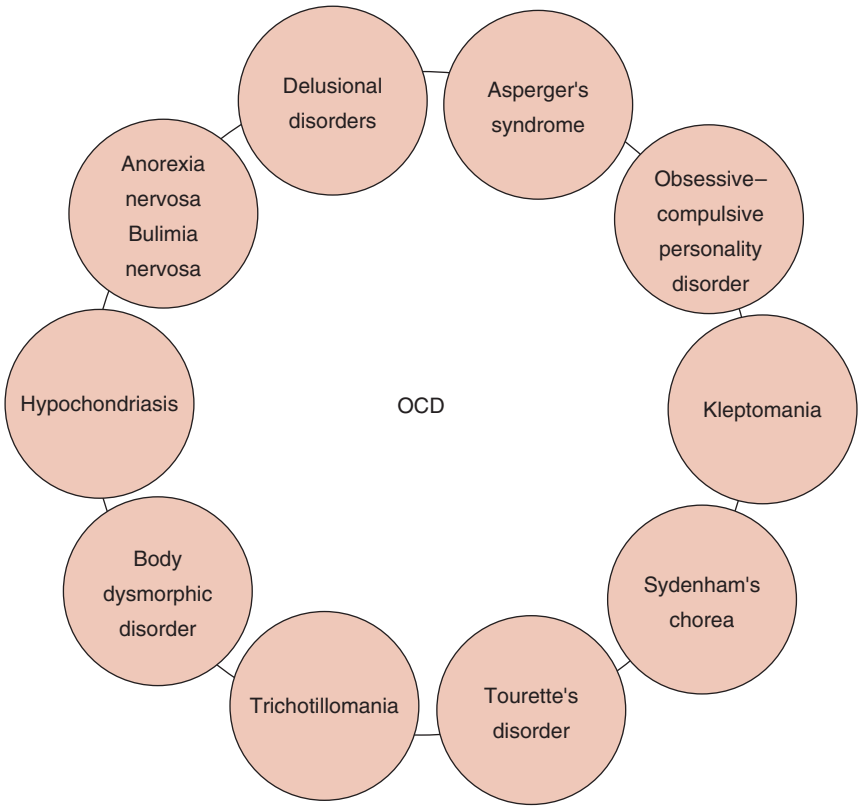



**Figure 71–3** *OCD spectrum disorders.*

by psychosis (schizophrenia, delusional disorder) or psychosis-like features (schizotypal personality disorder) in 475 patients with OCD found a different sex ratio. Fifty-six percent of the patients with OCD who did not have one of these comorbid disorders were women, whereas 85% of those with one of these comorbid disorders were men (Eisen and Rasmussen 1993).

A predominance of males has also been observed in child and adolescent OCD populations. In a study of 70 probands with OCD who were aged 6–18 years, 67% were males (Leonard et al. 1989). This finding may be due to the fact that males develop OCD at a younger age than do females. Evidence for sex differences in the genetic etiology of OCD have come from both a segregation analysis of a family sample (Nestadt et al. 2000b), as well as an association study of a polymorphism in the MAOA gene (Lochner et al. 2004).

## Etiology and Pathophysiology

A number of intriguing avenues have been investigated to determine the etiology and pathophysiology of OCD. Although our understanding of what causes this disorder has continued to grow, there is still much to learn. It is likely that OCD is caused by a complex interaction of factors rather than a single defect. However, for the purpose of clarity, these factors are described separately.

### Genetic Factors

#### Twin and Family Studies

A number of approaches have been used to evaluate the role of heredity in OCD. Twin studies have examined rates of concordant monozygotic twins versus discordant monozygotic twins with OCD. Although these studies have methodological limitations (e.g., a lack of a comparison group consisting of dizygotic twins), the data do support the notion that genetic factors are implicated in the etiology of OCD. However, given that the concordance rate of less than 100% even in monozygotic twins, it is clear that environment also plays a role in the development of OCD. A recent review by van Grootheest et al. (2005) reported heritability estimates of OCD symptoms ranging from 27 to 47%.

A second approach to examining the role of genetics in OCD has been to investigate the rate of OCD in family members of OCD probands. In a recent review and meta-analysis of the genetic epidemiology of OCD, Hettema et al. (2001) analyzed four studies that met their stringent criteria of including (1) operationalized diagnostic criteria, (2) systematic ascertainment of probands and relatives, (3) direct interviews with the majority of subjects, (4) blind diagnostic assessment of relatives, and (5) inclusion of a comparison group. They reported an aggregate odds ratio of 4.0, supporting the familial aggregation of OCD.

Further evidence supporting familial transmission of OCD has been obtained by studying the frequency of OCD in relatives of patients with Gilles de la Tourette's syndrome (TS). Family studies have found higher rates of OCD symptoms among family members of TS patients (Pauls et al. 1986) as well as higher rates of Tourette's disorder and tics in first-degree relatives of children with OCD (Leonard et al. 1992). In addition, as previously noted, there are differences in the types of OCD symptoms seen in patients with TS plus OCD versus those with OCD alone. Moreover, it has been found that even among those OCD patients who do not have TS, if they share the TS/OCD symptom cluster (checking and ordering), they are more likely to have a positive family history for OCD (Pauls et al. 1986). This may imply that there are distinct subtypes of OCD, some of which are familial and some of which are not. Taken together, available data support familial transmission in some cases of OCD and suggest that genetic factors play an important role in its etiology, particularly in patients with comorbid tic disorder.

#### Linkage and Association Studies

As with other complex diseases, it is unlikely that OCD is a single-gene disease. Association studies with candidate genes have focused mostly on the serotonin and dopamine systems, since medications treating OCD and TS are known to involve these systems. These genes have included the serotonin transporter, serotonin 1D, 2A, and 2C receptors, tryptophan hydroxylase, dopamine D2, D3, and D4 receptors, dopamine transporter, monoamine oxidase A, and catechol-o-methyltransferase. However, these studies have been equivocal, yielding positive as well as numerous negative results (Pato et al. 2002, Hemmings and Stein 2006). A major drawback to candidate gene studies is that they require a considerably detailed understanding of the pathophysiology of the disease in question in order to generate genetic candidates with substantive a priori support. As is the case with most psychiatric illnesses, the pathophysiology of OCD is poorly understood. Therefore, approaches based on gene discovery rather than the testing of candidates could be beneficial in identifying susceptibility genes as well uncovering previously unknown pathophysiological processes.

Linkage studies attempt to identify chromosomal regions where genetic markers cosegregate with the disease. The first genome-wide study implicated chromosome 9p24 (Hanna et al. 2002). A second study produced evidence supporting chromosomes 3q, 7p, 1q, 15q, and 6q (Shugart et al. 2006). The 9p24 linkage was followed up by testing the glutamate transporter gene, SLC1A1. This gene has now been positively associated in two independent samples (Dickel et al. 2006, Arnold et al. 2006).

In the last few years, genome-wide association has been heralded as a powerful means of discovering susceptibility alleles. This method tests hundreds of thousands of markers across the genome for association with the disease. This approach has yet to be implemented in OCD, but promises to overcome limitations of both linkage and candidate gene studies. Future directions in the genetics of OCD will also likely include whole-genome gene expression analysis using microarrays and analysis of copy number variation, as well as studies of epigenetic factors such as DNA methylation.

### Neurobiological Factors

#### Neuroanatomical Aspects

Brain imaging techniques have advanced the search for abnormalities in brain functioning and/or structure in patients with OCD. Numerous studies have now been done with both structural imaging—CT (computed tomography) and MRI (magnetic resonance imaging) (Szeszko et al.

1999)—and functional imaging—PET (positron emission tomography), SPECT (single photon emission computed tomography), fMRI (functional magnetic resonance imaging), and MRS (magnetic resonance spectroscopy), and most recently, diffusion tensor imaging. These techniques have demonstrated abnormalities in OCD patients (Saxena et al. 1998). These abnormalities occur at rest and with symptom provocation (Baxter et al. 1992, Rauch et al. 1994), and they are "normalized" with effective treatment (Saxena et al. 2002, Nakao et al. 2005).

While not all results are in agreement, a majority of these studies have implicated abnormalities in the orbitofrontal cortex, anterior cingulate cortex, and structures of the basal ganglia and thalamus. These structures are proposed to be linked in neuroanatomical circuits (Baxter 1992). One well-articulated model by Saxena et al. (1998) proposes that OCD symptoms are mediated by hyperactivity in orbitofrontal–subcortical circuits, which might be due to an imbalance in tone between direct and indirect striato–pallidal pathways (Saxena et al. 1998, Lacerda et al. 2003, Szeszko et al. 2005) (see Figure 71–4). Some studies have implicated a preferential role for right anterolateral orbitofrontal cortex in both OCD symptoms and symptom response. This view has neurocognitive implications because studies of executive function in OCD patients have shown that patients have difficulty with alternation tasks and tasks that involve making choices (Cavedini et al. 2001), which may in fact be mediated by inappropriate activation of frontal striatal regions (Maltby et al. 2005). Successful treatment of OCD symptoms may lead to normalization of frontal cortical activation (Saxena et al. 2002, Nakao et al. 2005).

Further indirect evidence implicating a role for basal ganglia dysfunction in OCD lies in the clinical relationship between neurological insults to the basal ganglia and the subsequent development of obsessions and compulsions. There is an association between OCD and Tourette's disorder, Sydenham's chorea, bilateral necrosis of the globus pallidus, and postencephalitic parkinsonian symptoms.

## Neurochemical Aspects

The hypothesis that OCD involves an abnormality in the serotonin neurotransmitter system has been called the serotonin hypothesis. Several different lines of investigation support this hypothesis: (1) therapeutic response of patients to chronic administration of certain types of medication, (2) measurements of central and peripheral neurotransmitter or metabolite concentration, and (3) pharmacologic challenge paradigms that measure behavioral and neuroendocrine effects produced by acute administration of selective pharmacologic agents, and (4) measurement of receptor binding using radioligands (reviewed by Mataix-Cols and van den Heuvel 2006, Westenberg et al. 2007).

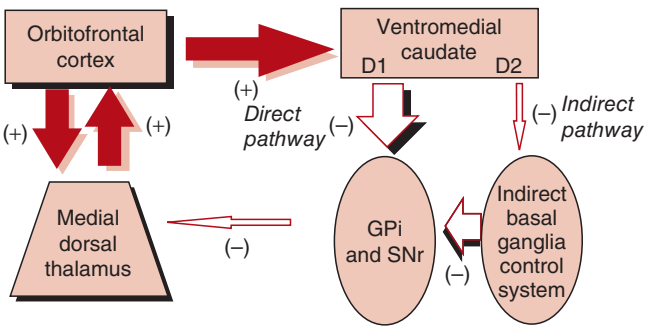



**Figure 71–4** *Model of OCD pathophysiology: Imbalance of direct >> indirect pathway "tone" in orbitofrontal–subcortical circuit. Gpi, globus pallidus interna; SNr, substantia nigra. (Source: Saxena et al. 1998.)*

All the evidence from treatment studies points to a role for serotonin and indicates a need for prolonged administration to see a positive effect. All of the antidepressants that effectively treat OCD affect serotonin (Westenberg et al. 2007). These antidepressants are potent inhibitors of the presynaptic reuptake of serotonin (i.e., SRIs). Those antidepressants that primarily affect the noradrenergic system have not been found to have antiobsessional properties. Exactly how the SRIs improve OCD symptoms remains unclear; while the immediate action of these agents may be to increase serotonin in the synapse, they undoubtedly cause a cascade of changes, both presynaptically and postsynaptically. A number of studies have examined the relationship between SRI blood levels and improvement in OCD, with inconsistent results (reviewed by Westenberg et al. 2007).

Decreased levels of cerebrospinal 5-hydroxyindoleacetic acid, a serotonin metabolite that is reduced with serotonin reuptake inhibition, have been correlated with clinical improvement after clomipramine treatment. A decrease in platelet serotonin levels—an indirect measure of neuronal reuptake—has been highly correlated with clinical improvement with clomipramine (reviewed in Westenberg et al. 2007); higher whole-blood 5-HT levels have been associated with clinical improvement with SRIs (Delorme et al. 2004). These various studies generally support the association between improvement of OCD with an SRI and acute alterations of serotonin in the brain and, in turn, support the serotonin hypothesis.

More compelling have been recent in vivo studies quantifying the density of cerebral serotonin receptors as well as the serotonin transporter. Using the radioligand [$^{18}$F]altanserin, Adams et al. (2005) reported increased density of serotonin 2A receptors in the caudate nuclei of OCD patient. This was interpreted as an upregulation of receptors in response to reduced synaptic concentrations of serotonin. Additionally, as revealed using SPECT, higher occupancy of the serotonin transporter by [123-beta] citalopram was associated with better citalopram response, further supporting the hypothesis (Stengler-Wenzke et al. 2006). These findings, however, have yet to be replicated. Furthermore, there is a relative paucity of such studies in OCD compared to, for example, Major Depressive Disorder. Additional methods such as postmortem brain studies, moreover, have yet to be employed in OCD.

Figure 71–5 shows a serotonin synapse with several of the possible sites of action for drugs that alter OCD symptoms.

Pharmacologic challenge studies constitute yet another line of evidence supporting the role of serotonin in the pathophysiology of OCD. The serotonin receptor partial agonist *m*-chlorophenylpiperazine, and more recently, the serotonin 1B agonist sumatriptan have been shown to increase symptoms of OCD and anxiety in patients with OCD but to have no effect in normal control subjects (Hollander et al.

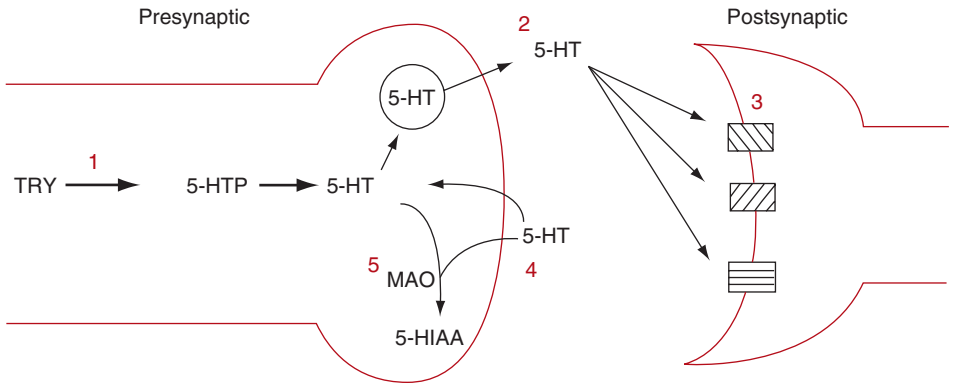



**Figure 71–5** *Diagram of a serotonin (5-HT) synapse describing several of the possible sites of action for drugs that alter OCD symptoms. At (1) the rate-limiting step in serotonin synthesis, L-tryptophan (TRY) is hydroxylated to 5-hydroxytryptophan (5-HTP). After serotonin is formed, it is sequestered into vesicles that are released at the presynaptic cell membrane (2). Fenfluramine increases this release. Once released, serotonin can interact with a number of different postsynaptic receptors (3). Several selective agonists (buspirone, m-chlorophenylpiperazine) have been developed to activate each of these serotonin receptor subtypes. Metergoline is a nonselective antagonist, blocking serotonin effects at each of these sites. The inactivation of serotonin is mediated by reuptake (4), the step inhibited by clomipramine, fluvoxamine, and fluoxetine. Finally (5), serotonin is either metabolized to its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), by the enzyme monoamine oxidase (MAO), or recycled back into vesicles for release. (Source: Insel and Winslow 1990.)*

1992, Gross-Isseroff et al. 2004). The increase in obsessions can be blocked with pretreatment by the serotonin receptor antagonist metergoline or by chronic treatment with clomipramine. However, results with *m*-chlorophenylpiperazine have been contradictory, which may reflect methodological issues or the fact that this agent has complex effects on multiple receptors. Challenge studies with other serotonergic agents have not implicated serotonin in the pathophysiology of OCD. For example, no behavioral or neuroendocrine changes were found after administration of fenfluramine, a serotonin-releasing and reuptake-blocking agent, or after administration of tryptophan, a serotonin precursor that increases serotonin synthesis, which differs from findings in depression. It is unclear whether these negative findings are attributable to methodological limitations or constitute evidence against the serotonin hypothesis (reviewed in Westenberg et al. 2007). Although available data are not entirely consistent, on balance there is now substantial evidence implicating serotonin in the pathophysiology of OCD. However, the exact role of this neurotransmitter and whether it is involved in the etiology, or is instead part of a final common pathway, of this disorder remains unclear.

The role of the dopamine system in OCD's pathophysiology has also been investigated (reviewed by Mataix-Cols and van den Heuvel 2006, Westenberg et al. 2007). When added to the SRIs, dopamine antagonists (neuroleptic agents) decrease symptoms of OCD in patients with OCD and comorbid tics, as well as in patients with OCD and comorbid schizotypal personality disorder. More recently, the addition of low-dose antipsychotics as an augmentation strategy in treatment-refractory OCD has been demonstrated to be successful in several double-blind, placebo-controlled studies (Bloch et al. 2006), and will be further discussed below. It has been hypothesized that some forms of OCD, particularly OCD plus Tourette's disorder, may involve an imbalance in activity between serotonergic and dopaminergic systems (reviewed in Westenberg et al. 2007).

Given the complex interactions and overlap among monoaminergic and other receptors in the brain, it is likely that a number of neurotransmitters are involved in OCD's pathophysiology and etiology. Drawing from these rather conflicting results, Mataix-Cols and van den Heuvel (2006) describe the currently accepted pathophysiological model of OCD as involving two neuroanatomical pathways. A direct pathway involves an inhibitory GABAergic signal from the striatum to the internal part of the globus pallidus, which causes disinhibition of the thalamus, resulting in an excitatory effect on the prefrontal cortex. Additionally, an indirect pathway involves an excitatory signal to the internal part of the globus pallidus resulting from an inhibitory signal from the striatum to the external part of the globus pallidus and subthalamic nucleus. This in turn causes inhibition of the thalamus, and thereby, *decreased* excitation of the prefrontal cortex. The effects of long-term treatment with SRIs are probably several: to change the ratio of dopamine to serotonin turnover, alter the gene expression of target neurons to stress-related neuropeptides, and decrease the sensitivity of subtypes of presynaptic serotonin auto- and heteroreceptors belonging to the $5\text{-HT}_1$ receptor family. Ongoing research is expected to elucidate further the likely role of serotonin and the possible role of other neurotransmitters in OCD.

## Animal Models

Animal models may provide an important window on treatment efficacy and the influence of environmental and genetic factors in OCD. Because of the inherent difficulties in studying cognitive aspects of OCD (such as guilt, overresponsibility, and doubt) in animals, attention has focused on repetitive motor actions that are similar to compulsions. Ethologists have observed that when specific, goal-directed actions are thwarted, animals may substitute unrelated behaviors, known as displacement behaviors, which frequently involve digging, pecking, or grooming (Tinbergen 1953). These motor actions have several elements: they are triggered by conflict over territory or by frustration, they continue in a stereotyped fashion, and they are excessive and/or inappropriate to the context in which they are performed. Thus, they are similar to the compulsive behaviors

of OCD and may also relate to compulsive grooming behaviors in BDD. Animal models offer the advantage of accessibility and ease of manipulation for controlled trials and as such can play a valuable role in understanding OCD's etiology.

Most of the earlier animal models relied on such naturally occurring behaviors, called behavioral models, along with tail chasing, fur chewing, and weaving. As reviewed by Joel, the behavioral animal models currently in use comprise barbering and marble burying in mice, along with signal attenuation in mice, which was developed by Joel and colleagues (Joel 2006). The latter is based on the hypothesis that compulsive behaviors result from a deficit in the feedback associated with the performance of normal goal-directed responses. An example would include repetitive lever-pressing in mice in the absence of a conditioned stimulus, which would be analogous to compulsive behavior in humans. It has been shown that SSRIs, as well as D1-antagonists, may inhibit compulsion-like lever-pressing (Joel 2006). This may both validate the model as well as suggest a new treatment strategy for OCD (dopamine D1 receptor antagonism).

There are two additional types of animal models in OCD: those in which compulsion-like behaviors are induced by either genetic manipulations (genetic models) or pharmacological manipulations (pharmacological models). Examples of genetic models include the induction of excessive grooming by disruption of Hoxb8 (Greer and Capecchi 2002), a transcription factor involved in development; as well as "neat" repetitive chewing associated with knockout of the 5-HT2c receptor (Chou-Green et al. 2003). Examples of pharmacological models include "indecision" (i.e., a decrease in spontaneous alternation, or the tendency of rats to explore novel places sequentially) induced by 5-HT agonists (Yadin et al. 1991, Fernandez-Guasti et al. 2003), as well as "compulsive checking" (i.e., a short return time to certain locales) induced by the dopamine D2/D3 agonist quinpirole (Eilam and Szechtman 2005, Szechtman et al. 1998).

## Psychological and Environmental Factors

### Learning Theory

A model based on the psychological concept of conditioning has been used to understand the development of obsessions and compulsions (Baer and Minichiello 1990). Compulsions, whether mental or observable, usually decrease the anxiety engendered by obsessional thoughts. Thus, if a person is preoccupied with fears of contamination from germs, repetitive hand washing usually decreases the anxiety caused by these fears. The compulsion becomes a conditioned response to anxiety. Because of the tension-reducing aspect of the compulsion, this learned behavior becomes reinforced and eventually fixed (Rachman and Hodgson 1980). Compulsions, in turn, actually reinforce anxiety because they prevent habituation from occurring; that is, by performing a compulsion, contact with the fear-evoking stimulus (e.g., dirt) is not maintained, and habituation (a decrease in fear associated with the stimulus) does not occur. Thus, the vicious circle linking obsessions and compulsions is maintained (Figure 71–6). This learning theory model of OCD has had a major influence on the way behavioral therapy is used in its treatment.

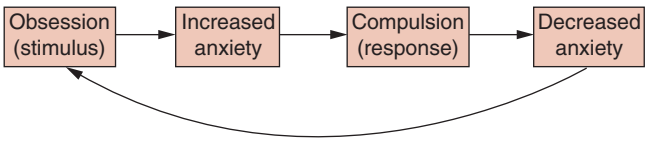



**Figure 71–6** *Learning theory of OCD.*

### Psychoanalytic Theory

Psychoanalytic theory is based on the concept that psychiatric symptoms have psychological meaning stemming from unconscious conflicts. In Freud's theory, themes of control, aggression, and autonomy are dominant during the anal period of development, which occurs during toilet training. Poorly resolved childhood struggles over control can result in conflicts over obedience and defiance. The unconscious conflict between passivity and aggression, or obedience and defiance, may lead to anxiety. The anxiety produced by these conflicts is hypothesized to lead to the formation of obsessions and compulsions as well as the defenses of reaction formation, isolation, and undoing.

Much of the psychoanalytic literature on OCD does not distinguish between the phenomena observed in OCD (obsessions and compulsions) and the traits of OCPD (MacKinnon and Michels 1971). This distinction has relevance because of treatment implications. Although the clinical observations of earlier psychoanalysts, such as Freud's famous Ratman case (Freud 1963), reflect current clinical presentations of Axis I OCD, understanding symptoms from the psychoanalytic perspective have not yielded improvement in this disorder's symptoms. Conversely, characterologic problems such as perfectionism, indecisiveness, and rigidity, seen in OCPD, may benefit from a psychoanalytic orientation that focuses on the meaning of these symptoms or traits; such traits have typically not responded well to medications alone, although further investigation of this question is needed.

## Phylogenetic Model

Recent theory has attempted to integrate the biology of OCD with psychological models by proposing a phylogenetic model based on systems theory. In this model, behavioral inhibition and harm-assessment systems, which develop early in human phylogeny, are disrupted. This disruption can occur at a hierarchically primary level of biological organization, resulting in neurobiologic disturbance, or at a hierarchically higher level of organization, leading to psychological disturbances. Such a model can help to explain the diversity of symptoms seen in OCD, from the more primitive biologically based behaviors based on fight/flight and risk to more psychologically sophisticated behaviors involving morality and guilt. This model might also explain why neither biological nor psychological treatments alone always lead to complete remission of symptoms (Cohen et al. 1997).

# Treatment Goals

## General Considerations

Both pharmacologic and behavioral therapies have proved effective for OCD. The majority of controlled treatment trials have been performed with adults aged 18–65 years. However, these therapies have been shown effective for patients

of all ages. In general, children and the elderly tolerate most of these medications well. For children, lower doses are indicated because of lower body mass. For instance, the recommended dose for clomipramine in children is up to 150 mg/day (3 mg/kg/day) versus 250 mg/day in adults. Use of lower doses should also be considered in the elderly because their decreased ability to metabolize medications can increase the risk of side effects and toxicity (Pato and Zohar 2001). Behavioral therapy has also been used successfully in all age groups, although when treating children with this modality it is usually advisable to use a parent as a cotherapist. A flowchart that outlines treatment options for OCD is shown in Figure 71–7.

In general, the goals of treatment are to reduce the frequency and intensity of symptoms as much as possible and to minimize the amount of interference the symptoms cause. It should be noted that few patients experience a cure or complete remission of symptoms. Instead, OCD should be viewed as a chronic illness with a waxing and waning course. Symptoms are often worse during times of psychosocial stress. Even when on medication, individuals with OCD are often upset when they experience even a mild symptom exacerbation, anticipating that their symptoms will revert to their worst, which is rarely the case. Anticipating with the patient that stress may make the symptoms worse can often be helpful in long-term treatment. Expert consensus guidelines, based on completion of a survey by 79 experts in the field, provide a reasonable approach to clinical practice in treating patients with OCD. However, like any consensus report based on clinical practice, not all of the recommendations are supported by empirical data. Further work in neurosurgical techniques, particularly less invasive approaches like gamma knife and possibly transmagnetic stimulation, may offer other options in the future for treating OCD (Greenberg et al. 1997) (see later).

## Somatic Treatments

The most extensively studied agents for OCD are medications that affect the serotonin system (see Figure 71–5). Many studies implicate the serotonin system in OCD's pathophysiology, although comparative studies also seem to implicate other neurotransmitter systems, including

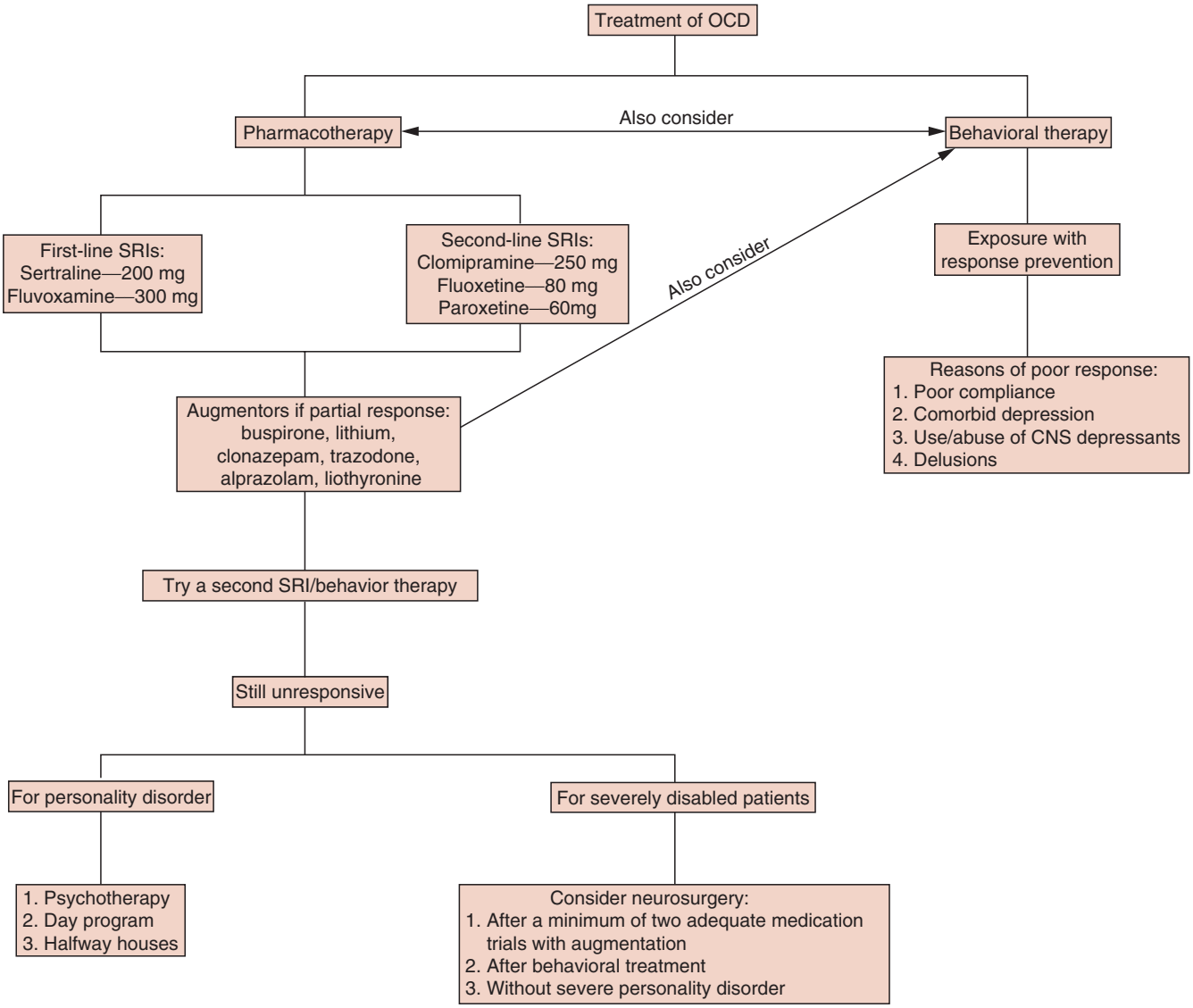



**Figure 71–7** *Flowchart of treatment options for OCD.*

the dopaminergic system, in treatment response (reviewed by Westenberg et al. 2007). The principal pharmacologic agents used to treat OCD are the SRIs, which include clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram, and escitalopram.

Outcome measures in OCD treatment trials generally include the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b), a reliable and valid 10-item, 40-point semistructured instrument that assesses the severity of obsessions and rituals during the preceding week. Studies conducted since 1989 have generally used the Y-BOCS as one of the major outcome measures. Most studies have used Y-BOCS scores of 16–20 as a study entry criterion, although it has been argued that higher scores (e.g., 20–21) might reduce the increasing placebo response rates being obtained in OCD studies (Greist et al. 1995). Treatment response is generally considered to constitute at least a 25–35% reduction in OCD symptoms as measured by the Y-BOCS (Goodman et al. 1993). Another frequently used global outcome measure is the National Institute of Mental Health Global Obsessive–Compulsive Scale (NIMH-OC) (Pato et al. 1994) (Clinical Vignette 1).

**Clinical Vignette 1: Pharmacotherapy**

Ms. M was a 38-year-old married teacher who had experienced OCD symptoms since age 10 years. At that time, she had a need to reread sentences, as well as a need to check things like doors and faucets to guard against something bad happening. Her symptoms subsided somewhat during her teenage years but resurfaced during her early 20s. She sought treatment from a hypnotherapist in her late 20s and subsequently did relatively well, with only minimal symptoms, for the next 10 years. She noted, however, that during that time she continued to be a nervous person who worried about everything.

At the time of her initial visit, she reported a significant worsening of her OCD symptoms during the previous weeks. In particular, she began to have trouble driving her car. She often found herself retracing her route to ascertain that she had not hit something or to pick up road debris that she was worried might get in her way. This behavior greatly lengthened her driving time and, as a result, Ms. M began to drive less and to avoid unnecessary trips like driving to stores to shop. As her symptoms worsened, she began to avoid driving at night because she worried that she would not see debris and other objects in the road. In addition, much to her chagrin, she began to involve her husband in her rituals by asking him to drive back with her to make sure that nothing was wrong. She also experienced increased checking behavior, for example, rechecking how she had written a check or retracing her steps at school to ascertain that she had not kicked something down the stairs. Overall, she estimated that her symptoms were moderately severe and taking about 3 hours per day. Ms. M had also begun to experience prominent neurovegetative symptoms of depression, including early morning awakening, decreased energy and initiative, psychomotor slowing, and a 10-pound weight loss.

Ms. M was entered in a 10-week placebo-controlled blinded clomipramine trial and received clomipramine 250 mg/day. Within 3 weeks of starting treatment, she began to show some signs of improvement. She reported less frequent episodes of driving back and less avoidance of driving to go shopping; however, she did not experience much change in other checking behaviors. After 5–6 weeks at 250 mg/day of clomipramine, Ms. M noted marked improvement (approximately 85%) in her symptoms. She had only transient episodes of needing to drive back, which lasted less than 5 minutes, and no avoidance of driving; her checking had also improved. She began to have some symptom-free days. Ms. M also had no depressive symptoms and experienced a general sense of well-being, which was a significant improvement from her baseline. However, she began to complain of significant drowsiness and fatigue, despite adequate sleep, as well as dry mouth and tremor.

Within 10 weeks of beginning treatment, Ms. M was virtually free of OCD symptoms, experiencing only a few mild and transient episodes. Because she was at the end of the blinded medication period, her clomipramine dose was decreased from 250 to 150 mg/day. Within 1 week, she reported that she had started retracing her route while driving and had other symptoms of OCD that occupied about 1 hour per day. Her dose was increased to 200 mg/day, but in 1 week she called her physician to say that she was distressed because her OCD symptoms had interfered with her ability to pick up her child and that her symptoms had increased to 3 hours per day. Her clomipramine was increased to 250 mg/day. Within 8 weeks, Ms. M had returned to her previous level of good health. She was driving normally, was not checking or engaging in avoidance behavior, and had no obsessional fear of harm coming to others. Although on some days she experienced about 45 minutes of fleeting symptoms, on other days she was totally symptom-free. However, she was experiencing some side effects, such as dry mouth, tremor, weight gain, and fatigue. Her fatigue became marked to the point that she came home from her job as a school teacher exhausted and slept 16 hours a day on the weekend.

After 1 year at 250 mg/day of clomipramine, a taper was again attempted, and the medication was discontinued within a month. Before the taper, Ms. M's Y-BOCS score was 4 (out of a possible total score of 40), but after 2 weeks without medication it rose to 6, indicating an increased effort on her part to resist her obsessions and compulsions. After 7 weeks of not taking medication, her Y-BOCS score rose to 10, and after 15 weeks it rose to 16, indicating moderate symptom severity. She noted that she had 1–3 hours of obsessions and 1 hour of compulsions per day, with increasing effort needed to resist symptoms. In addition, she noted the return of her nervousness and tendency to worry. However, Ms. M also had a lessening of her fatigue and lost 5 of the 10 pounds she had gained on the medication.

The return of symptoms was distressing to Ms. M, and she decided to try another medication. Sertraline was begun, and after only 6–8 weeks of treatment, at 200 mg/day, she had a remission of all OCD symptoms and the return of a sense of well-being. She had no side effects. At 5 months of follow-up she remained symptom-free, and her Y-BOCS score had decreased to 1, with only 15 minutes of symptoms per week.

## Clomipramine

The tricyclic antidepressant clomipramine is among the most extensively studied pharmacological agents in OCD. This drug is unique among the antiobsessional agents in that, in

addition to its potency as an SRI, it has significant affinity for noradrenergic, dopaminergic, muscarinic, and histaminic receptors. The largest double-blind, placebo-controlled trial of clomipramine in OCD was conducted in a collaborative sample of 520 patients at 21 sites (The Clomipramine Collaborative Study Group 1991). Both outcome measures, the Y-BOCS and the NIMH-OC, demonstrated a significant decrease in the severity of OCD symptoms in the group receiving clomipramine compared to the placebo group. Duration of treatment was 10 weeks, and the mean dose was approximately 200 mg/day, with 69% of patients taking 150–250 mg/day. About half (51–60%) of the patients receiving clomipramine experienced a 35% or greater reduction in symptoms as measured by the Y-BOCS, whereas only 7–7.5% of the placebo group had a similar response. The most common side effects were those typical of the tricyclic antidepressants, including dry mouth, dizziness, tremor, fatigue, somnolence, constipation, nausea, increased sweating, headache, mental cloudiness, and sexual dysfunction. In a meta-analysis of seven double-blind, placebo-controlled trials, there was a net improvement of 8.19 in Y-BOCS scores in patients treated with clomipramine (Ackerman and Greenland 2002). In this analysis, clomipramine outperformed fluvoxamine, fluoxetine, and sertraline. Previous data have indicated that at doses of 300 mg/day or more, the risk of seizures is 2.1%, but at doses of 250 mg/day or less, the risk of seizures is low (0.48%) and comparable to that of other tricyclic antidepressants. It is therefore recommended that doses of 250 mg/day or less be used. Elderly patients may be more prone to tricyclic side effects, such as orthostatic hypotension, constipation (which may lead to fecal impaction), forgetfulness, and mental cloudiness, which might be confused with dementia. Most of these side effects can be treated by simply lowering the dose, although the cardiac conduction effects of tricyclic antidepressants may preclude the use of clomipramine in patients with preexisting cardiac conduction problems, especially atrioventricular block.

Several studies of IV clomipramine were promising as they demonstrated quicker onset of action and fewer side effects than the oral form, and it may be effective even in patients who do not respond to oral clomipramine. Oral clomipramine, like other SRIs, usually takes a minimum of 4–6 weeks to produce a clinically significant clinical response, but in at least one study by Koran et al. (1997), in which they used IV pulse dosing, patients showed a response within 4.5 days (Koran et al. 1997). The reasons for this unique response are not fully understood, but it is postulated that the IV preparation avoids first-pass hepatoenteric metabolism, leading to increased bioavailability of the parent compound clomipramine. This in turn may play a role in rapidly desensitizing serotonergic receptors or initiating changes in postsynaptic serotonergic neurons. However, in a recent randomized, double-blind, placebo-controlled double-dummy study by Koran et al., oral pulse-loading (simply giving these large doses orally rather than intravenously) of clomipramine resulted in a response that was equally rapid as that to the intravenous pulse-loaded formulation (Koran et al. 2006), but this has yet to be replicated. Although IV clomipramine for obsessional states has been studied as far back as 1973, this preparation is still not FDA-approved for clinical use in the US. Cardiac monitoring is recommended during the use of IV clomipramine.

## Fluoxetine

Fluoxetine (as well as fluvoxamine, sertraline, paroxetine, and citalopram) is often referred to as a selective serotonin reuptake inhibitor (SSRI) and sometimes as serotonin transport inhibitor (STI) because they have a far more potent effect on serotonergic than on noradrenergic or other neurotransmitter systems. Despite their different chemical structures, all of the SSRIs appear to have similar efficacy in treating OCD (Denys 2006).

Fluoxetine was first marketed in the US in 1987 for the treatment of depression, and was the first available SSRI in this country. Initially, on the basis of fluoxetine's selectivity for serotonin receptors, researchers were hopeful that this medication would be more efficacious than clomipramine, which has affinity for cholinergic, adrenergic, and histaminic receptors in addition to serotonergic ones. It has been demonstrated to be effective in three double-blind, placebo-controlled trials in a meta-analysis, demonstrating an improvement in Y-BOCS score of 1.6 points (Ackerman and Greenland 2002). Furthermore, it has been shown to be equally effective as clomipramine, although in meta-analysis the effect size of clomipramine was greater.

The fixed-dose trials of fluoxetine are particularly noteworthy (Tollefson et al. 1994a 1994b). Although these studies indicated that doses of 20, 40, and 60 mg/day were all effective when compared with placebo, there was a trend toward 60 mg/day being more effective. Some patients who did not respond at lower doses responded at higher doses, and others who responded at lower doses showed increased improvement at a higher dose (Tollefson et al. 1994a). In addition, patients maintained their improvement or experienced increased improvement during the 5- to 6-month follow-up period (Tollefson et al. 1994a). Another study reported that only a dose of 60 mg/day, and not less, was sufficient to prevent relapse at 1 year (Romano et al. 2001). Anecdotal clinical experience suggests that even larger doses, perhaps 80 mg/day and above, may be needed in some patients.

Fluoxetine has fewer side effects than clomipramine, reflecting its more selective mechanism of action. The most common side effects are headache, sexual dysfunction, nausea, insomnia, anorexia, dry mouth, somnolence, nervousness, tremor, and diarrhea. Side effects occur more frequently at higher doses (Tollefson et al. 1994b). Fluoxetine's long half-life, which is unique among the SRIs, is 2–4 days for the parent compound and 4–16 days for its active metabolite (Pato et al. 1991a). This long half-life can be beneficial for patients who do not comply with treatment, because relatively high steady-state levels are maintained even when several doses are missed. However, the long half-life can present problems when switching or discontinuing fluoxetine, because 5 weeks or more may be required for the medication to be completely cleared from the body. Hence the added delay, 5 weeks rather than 2 weeks for the other SRIs, is required when switching from fluoxetine to an MAOI.

## Fluvoxamine

Fluvoxamine became available for the treatment of OCD in the US in 1995. It is a unicyclic agent that differs from the other SSRIs in that it does not have an active metabolite. A meta-analysis of four double-blind, placebo-controlled trials demonstrated a net improvement in Y-BOCS score of 4.84

(Ackerman and Greenland 2002). In head-to-head studies with clomipramine, it may be as effective, but with fewer adverse effects (Mundo et al. 2001). As has been demonstrated for the other SSRIs, relatively long treatment trials are indicated before concluding that it is ineffective in OCD.

The largest fluvoxamine study (reviewed in Ackerman and Greenland 2002) was a 10-week multicenter double-blind, placebo-controlled study of 320 patients. The mean dose of fluvoxamine was 249 mg/day. As in the other studies, the fluvoxamine-treated patients had a significant reduction in OCD symptoms; however, unlike most of the earlier medication trials there was a relatively high placebo response rate of 11%. One of the important conclusions from this study was that prior failure to respond to another SSRI was associated with a lower likelihood of responding to fluvoxamine. Nonetheless, six of 31 patients in whom a previous trial of clomipramine or fluoxetine had failed did respond to fluvoxamine. Lack of response at 4 and 6 weeks did not predict response at 10 weeks, and the authors concluded that a full 10 weeks of treatment was needed to assess treatment response. All of the fluvoxamine studies showed a similar side effect profile, which included insomnia, nervousness, fatigue, somnolence, nausea, headache, and sexual dysfunction. Insomnia and nervousness tended to occur early in treatment, whereas fatigue and somnolence occurred later. Overall, the medication was well tolerated, with only 10–15% of patients dropping out of treatment because of side effects.

### Sertraline

Sertraline is a naphthalenamine derivative with an active metabolite, *n*-desmethylsertraline. Meta-analysis of four double-blind, placebo-controlled studies, including one fixed-dose study of 325 patients, demonstrated that sertraline was significantly more effective than placebo, with efficacy similar to that of clomipramine (Ackerman and Greenland 2002). In the fixed-dose study, there was a trend toward 200 mg/day being more effective than 50 mg/day or 100 mg/day. Similar to other SSRI trials, the dropout rate from adverse side effects was only 10%. Typical side effects included nausea, sexual dysfunction, headache, diarrhea, insomnia, and dry mouth (Greist et al. 1995).

In patients with OCD and comorbid depression, sertraline was more effective for OCD symptoms than the non-SRI desipramine. Furthermore, even though desipramine did improve depressive symptoms, a significantly greater number of patients treated with sertraline achieved remission from depression (Hoehn-Saric et al. 2000). A more recent study compared sertraline to fluoxetine. Although these SRIs were similar in efficacy, sertraline was associated with earlier improvement and a possibly greater chance of remission (Bergeron et al. 2002).

### Paroxetine

Paroxetine is another SSRI that differs in structure from those previously discussed. It is a phenylpiperidine compound that is marketed as an antidepressant and that, like sertraline, shows promise in the treatment of OCD. Its efficacy, as noted below, is comparable to that of other SRIs (Ackerman and Greenland 2002, Denys 2006). Side effects are similar to those of other SSRIs and include lethargy, dry mouth, nausea, insomnia, somnolence, tremor, sexual dysfunction, and decreased appetite. Reports of an acute discontinuation syndrome, which can include general malaise, asthenia, dizziness, vertigo, headache, myalgia, loss of appetite, nausea, diarrhea, and abdominal cramps, warrant a gradual reduction in dose if this medication is to be discontinued (reviewed in Baldwin et al. 2007).

### Citalopram/Escitalopram

Citalopram is a cyclic phthalin derivative with S (active) and R (inactive) enantiomers; it is unique in its selectivity for serotonin reuptake compared to the other SRIs. It has few significant secondary binding properties, and its minimal effect on hepatic metabolism probably makes it safer to combine with other medications. A multicenter fixed-dose-placebo-controlled trial with 401 patients showed that 52–65% of patients responded in the three dosage groups compared to a 37% response rate in the placebo group. While there was a trend for a higher dose to lead to a higher response rate, as with other SRIs, there was no statistical difference between the three doses used (20, 40, and 60 mg/day). Typical side effects included fatigue, sweating, dry mouth, ejaculation failure, nausea, and insomnia, although many patients habituated to these side effects in 4–6 weeks. Thus, citalopram is a good choice for OCD treatment because of its side effect profile and low probability of causing drug–drug interactions (Richter 2001). At the current time, however, OCD remains an off-label indication for citalopram. Escitalopram, the more potent S enantiomer of citalopram, was introduced in 2001, and was initially FDA approved for the treatment of GAD. A recent randomized double-blind, placebo-controlled trial demonstrated that at the 20 mg dose, there were higher response and remission rates, improved functioning, and better tolerability than paroxetine (Stein et al. 2007).

### Other Agents

Several open-label trials of venlafaxine suggest that this serotonin–norepinephrine reuptake inhibitor (SNRI) may be as effective as SRIs, but this has yet to be confirmed in double-blind, placebo-controlled trials (Denys 2006). Other agents that are potentially effective as monotherapy include aripiprazole, mirtazapine, and St. John's Wort (*Hypericum perforatum*) (reviewed in Denys 2006). However, these have also yet to be supported by double-blind, placebo-controlled studies. Although OCD is classified as an anxiety disorder, it tends to differ from the other anxiety disorders in that it has obsessions and compulsions as its hallmark, and these OCD symptoms usually require some regulation of serotonin to achieve symptomatic improvement. However, like other anxiety disorders, patient wi th OCD can have anxiety symptoms or comorbid panic attacks and may benefit from the addition of a benzodiazepine during the course of treatment.

### Which SRI to Choose?

The efficacy of each SRI—clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram—is supported by existing data. During the last 10 years at least seven head-to-head SRI comparison studies have been done; six of which compared clomipramine to fluoxetine, fluvoxamine, paroxetine, or sertraline, and one study compared fluvoxamine to both paroxetine and citalopram (reviewed

by Baer et al. 1990b, Ackerman and Greenland 2002, Denys 2006). In general, sample sizes have been small, usually with 10–30 patients per group. All of the studies found that the agents studied were equally efficacious, although they may have been underpowered to detect differences among medications.

However, several meta-analyses (Jenike et al. 1990, Greist et al. 1995, Greist and Jefferson 1998, Ackerman and Greenland 2002) of OCD trials, which compared SRIs across large placebo-controlled multicenter trials, lend some support to the notion that clomipramine might be more effective than the more selective agents. In a four-way (clomipramine, fluoxetine, fluvoxamine, and sertraline) meta-analysis, effect sizes were computed by comparing the average change in Y-BOCS scores pooled over various studies with different medications (Ackerman and Greenland 2002). Clomipramine led to the largest effect sizes. However, like most meta-analyses, these studies are flawed by factors that include variations in the study protocol, sample size, and the number of treatment-resistant and treatment-naive subjects. Nonetheless, as Greist et al. (1995) point out, these differences cannot explain the fact that the clomipramine trial had a lower dropout rate (12% overall) (Greist and Jefferson 1998, Greist et al. 1995) than other trials, despite a higher rate of side effects. In conclusion, these meta-analyses support a trial of clomipramine in all patients who do not respond to SRIs, even though clomipramine tends to cause more side effects and has greater toxicity in overdose.

A number of studies have assessed predictors of medication response. Predictors of poor response have included failure to respond to a previous SRI, early age of OCD onset, presence of schizotypal personality disorder, and the presence of hoarding and washing compulsions, as well as of religious and sexual obsessions. However, not all studies have had consistent findings, and more investigation of this issue is needed using larger and more narrowly defined samples (reviewed in Tukel et al. 2006).

It is worth noting that the SSRIs, via their effect on the liver cytochrome system enzymes, in particular CYP2D6, can inhibit the metabolism of certain other drugs. They can therefore elevate blood levels of a variety of coadministered drugs, including tricyclic antidepressants (such as clomipramine), carbamazepine, phenytoin, and trazodone. Although all SSRIs (with the exception of citalopram and escitalopram) share this property, fluoxetine may have the greatest effect (Liston et al. 2002). Some clinicians have taken advantage of these interactions by carefully combining fluvoxamine with clomipramine in order to block clomipramine's metabolism to desmethylclomipramine; this in turn favors serotonin reuptake inhibition provided by the parent compound rather than the norepinephrine reuptake inhibition provided by the metabolite. However, caution should be used with this approach since the elevation in clomipramine levels, and perhaps other compounds, can be nonlinear and quickly lead to dangerous toxicity (Szegedi et al. 1996); at the very least, clomipramine levels should be carefully monitored and clomipramine must generally be used at much lower doses than usual when it is combined with an SSRI.

All of the SSRIs are generally well tolerated, with a relatively low percentage of patients experiencing notable side effects or discontinuing them because of side effects. In addition, these compounds are unlikely to be lethal in overdose, except for clomipramine, which can lead to cardiac arrhythmias and death. All these agents can cause sexual side effects, ranging from anorgasmia to difficultly with ejaculatory function. However, such symptoms are not readily volunteered by the patient; thus it is important to ask. Should such symptoms be experienced, conservative measures may include dosage reduction, transient drug holidays for a special weekend or occasion, or switching to another SRI since patients may not have the same degree of dysfunction with a different agent. However, if the clinician feels that it is critical to continue the same agent, a number of treatments have been reported in the literature. Among those that have been tried are yohimbine, buspirone, cyproheptadine, bupropion, dextroamphetamine, methylphenidate, amantidine, nefazodone, and sildenafil, to name a few (reviewed by Taylor et al. 2005) (Clinical Vignette 1).

## Assessing Treatment Resistance

Before concluding that a patient is treatment resistant, the adequacy of previous treatment trials must be assessed (Table 71–2). In particular, it is critical to know both the duration and dose of every medication that has been used. Typically, patients who appear treatment resistant have received an inadequate duration of treatment, which should be a minimum of 10–12 weeks, or an inadequate medication dose, which should be the maximum dose for any particular agent. Some psychiatrists consider patients truly treatment resistant only if they have failed several adequate pharmacologic trials, including one with clomipramine, and several augmentation strategies including behavioral therapy. With this kind of aggressive treatment, the vast majority of patients usually experience some improvement, although few patients become symptom-free (Denys 2006).

When inadequate treatment is not the reason for poor treatment response, it is important to assess the accuracy of the diagnosis. Schizotypal personality disorder, borderline personality disorder, avoidant personality disorder, and OCPD seem to be associated with poorer response to

**Table 71–2 Things to Consider in Patients with Obsessive–Compulsive Disorder in Whom Initial Treatment Fails**

| |
|---|
| **Was the diagnosis correct?** |
| Is there an Axis II disorder, especially schizotypal or obsessive–compulsive personality disorder? |
| Are there comorbid diagnoses that could interfere with treatment response? |
| Is a major depressive disorder present? |
| Are there obsessive thoughts, overvalued ideas, or delusions? |
| **Was the pharmacotherapy trial adequate?** |
| Was a known effective agent used? |
| Was the dose adequate? |
| Was the duration of treatment long enough? |
| **Was behavioral therapy performed?** |
| Were an adequate number of sessions attended? |
| Did the patient comply with homework assignment? |
| Was there cognitive impairment inhibiting the ability to implement treatment? |
| Was there concurrent use of central nervous system depressants that affect ability to attend to evoked anxiety? |

pharmacotherapy; particularly if the personality disorder is the primary diagnosis (Jenike et al. 1986, Goodman et al. 1993).

As above, there is anecdotal evidence that up to 80 mg/day of fluoxetine is necessary for response in some patients. At the current time, there is only limited evidence suggesting that using doses higher than those recommended on package labeling are effective in the SRI treatment of OCD. Ninan et al. (2006) recently reported greater symptom improvement in patients receiving 250–400 mg/day sertraline compared to a 200 mg/day group in a multicenter double-blind trial. Systematic studies using other SRIs at doses higher than the maximum recommended by the pharmaceutical company have not been done to our knowledge. However, in our experience some patients benefit from higher doses but it must be done with strict monitoring and caution. Furthermore, there have been no studies supporting higher plasma levels as predictors of response. Switching agents from one SRI to another may be effective in some patients, but very few studies have examined this (reviewed in Denys 2006).

Behavioral therapy (see later) seems less effective in patients with comorbid major depressive disorder. Comorbid depression may inhibit the ability to learn and to habituate to anxiety. Initial pharmacotherapy sometimes improves depression, as well as OCD symptoms, and may increase the likelihood of success with behavioral treatment.

### Augmentation Strategies

If a patient has had only a partial response to an antiobsessional agent of adequate dose and duration, the next question is whether to change the SRI or add an augmenting agent. Current clinical practice suggests that if there is no response at all to an SRI, it may be best to change to another SRI. However, if there has been some response to treatment, an augmentation trial of at least 2–8 weeks may be warranted. The drug class with by far the greatest support as effective, augmenting agents are low-dose atypical antipsychotics. Nine double-blind, placebo-controlled trials of antipsychotic augmentation have recently been included in a meta-analysis (Bloch et al. 2006) that reported a lack of evidence of publication bias in published studies. This study reported that nearly a third of treatment-refractory OCD patients responded to this strategy, using a 35% reduction of Y-BOCS score as the definition of response. The agents with the most compelling evidence of efficacy were risperidone (three studies) and haloperidol (one study). The evidence for newer agents such as olanzapine and quetiapine was equivocal, necessitating additional studies of these agents. The results also suggest that given the good response to SSRIs alone, antipsychotic augmentation should only be considered after a full trial of 3 months of an SSRI alone. Patients with comorbid tics were especially likely to respond. The use of an antipsychotic agent should be considered carefully in light of the risk of extrapyramidal symptoms and side effects such as weight gain, lethargy, and tardive dyskinesia. Thus, when a neuroleptic drug is used, target symptoms should be established before beginning treatment, and the medication discontinued within several months if target symptoms do not improve.

As reviewed by Denys (2006), augmenting agents that have been supported in at least one open-label trial have included morphine, the beta-blocker pindolol, venlafaxine, amisulpride, the glutamate-modulating agent riluzole, and topiramate. The use of lithium (300–600 mg/day) and buspirone (up to 60 mg/day) as augmentation agents has also been explored. Both agents looked promising in open-label trials but failed to be effective in more systematic trials. Augmentation with fenfluramine (up to 60 mg/day), clonazepam (up to 5 mg/day), clonidine (0.1–0.6 mg/day), and trazodone (100–200 mg/day), as well as the combination of clomipramine with any of the SSRIs, has had anecdotal success but has not been evaluated in methodologically rigorous studies. Support for these agents remains modest at best, however, and they should clearly be considered second- or third-line alternatives.

## Behavioral Therapy

Behavioral therapy is effective for OCD both as a primary treatment and as an SRI augmentation agent (Marks et al. 1988, Foa et al. 1985, Greist 1994, Neziroglu et al. 2006). This form of therapy is based on the principle of exposure and response prevention. The patient is asked to endure, in a graduated manner, the anxiety that a specific obsessional fear provokes while refraining from compulsions that allay that anxiety. The principles behind the efficacy of behavioral treatment are explained to the patient in the following way. Although compulsions, either covert or overt, usually immediately relieve anxiety, this is only a short-term solution; the anxiety will ultimately return, requiring the performance of another compulsion. However, if the patient resists the anxiety and urge to ritualize, the anxiety will eventually decrease on its own (i.e., habituation will occur), and the need to perform the ritual will eventually disappear. Thus, behavioral therapy helps the patient habituate to the anxiety and extinguish the compulsions.

Compulsions, especially overt behaviors like washing rituals, are more successfully treated by behavioral therapy than are obsessions alone or covert rituals like mental checking. This is because covert rituals are harder to physically resist than are rituals like hand washing and checking a door. In fact, washing rituals are the most amenable to behavioral treatment, followed by checking rituals and then mental rituals.

In the early stages of treatment, a behavioral assessment is performed. During this assessment, the content, frequency, duration, amount of interference and distress, and attempts to resist or ignore the obsessions and compulsions are catalogued. An attempt is made to clarify the types of symptoms, any triggers that bring on the obsessions and compulsions, and the amount and type of avoidance used to deal with the symptoms. For instance, in the clinical vignette described later, the fact that Ms. Z stopped preparing meals to deal with her obsessional concerns about contamination was carefully documented. The patient, usually with the help of a therapist, then develops a hierarchy of situations according to the amount of anxiety they provoke. During treatment, patients gradually engage in the anxiety-provoking situations included in their hierarchy without performing anxiety-reducing rituals (see Clinical Vignette 2).

Behavioral therapy can be used with patients of any age and has been used in young children, often with the help of a parent as a cotherapist. However, not many systematic

trials of behavioral treatment in children have been performed. More recently, behavioral therapy in a group setting has been explored and found as effective as, and perhaps even more effective than, individual behavioral treatment (Braga et al. 2005). The group seems to act as a catalyst for change by promoting group cohesion, support, and encouragement. Groups can include patients with different symptoms, though each has a personalized hierarchy. Because family members are often affected by the patient's rituals and often function as unwilling participants in rituals, as members of the group, they not only gain knowledge and understanding about OCD but can be cotherapists at home for homework assignments.

### Clinical Vignette 2: Behavioral Therapy

Ms. Z was a married woman in her late 20s whose primary OCD symptom consisted of severe contamination obsessions. She feared that she would contract cancer from various substances, such as detergents, chemical lawn treatments, foods, asbestos, gasoline, oil spills on beaches, and batteries. She also had aggressive obsessions that if she did not do certain things, harm would come to her family members. In response to these fears, Ms. Z washed more than 100 times per day, avoided situations that might lead to contamination, checked items repeatedly for evidence of contamination, and sought reassurance from others more than 50 times a day.

Ms. Z's symptoms dated back to age 8 years when she had aggressive obsessions and felt that she had to touch certain things in her room. Her life had been riddled with magical thinking; to combat fears of dying or to prevent bad things from happening to others, she had to open and close the refrigerator in a certain way, had to close lids a certain way, had to touch the floor, and had to touch both of her eyes. She kept most of these rituals hidden from others.

Around the time she became pregnant in her late 20s, Ms. Z's symptoms worsened. Her contamination fears heightened to the point that she avoided contact with family members and relatives who might be contaminated with cancer or contaminated because of where they lived. Her husband was drawn into her rituals, often giving her reassurance. She eventually stopped cooking because of her fears of insecticides, bacteria, and chemicals on food, and her son and husband ate meals at a relative's house.

At initial evaluation, Ms. Z spoke of the distress and impairment she experienced from her symptoms and of her desire to stop her "strange" behavior. Ms. Z decided to pursue insight-oriented psychotherapy first for 6 months and only when this was not bringing improvement of her OCD symptoms did she finally agree to a more empirically established treatment for OCD, combined behavioral therapy and pharmacotherapy consisting of clomipramine, which was gradually increased from 50 to 250 mg/day. (Although it may appear obvious, it may be helpful to clarify that the clomipramine doses started low, perhaps 50 mg/day, and was raised gradually to 250 mg.)

Behavioral therapy was initially begun on an individual basis. During the first sessions, psychoeducation and exposure and response prevention techniques were discussed. One of the first homework assignments included keeping a daily record of how many times Ms. Z washed her hands. When she returned for the next session, she reported that the frequency had decreased; as she stated, "Knowing I had to write down when I had the urge prevented me from washing. Having to stop and think about why I was doing the ritual helped me to resist." (In 10% of patients, record keeping alone results in a decrease in target behaviors.) Sessions continued, with the therapist modeling exposure and response prevention. For example, the therapist asked Ms. Z to join her in touching doorknobs, floors, shoes, batteries, paint chips, and plant soil while continually reassuring her, identifying the cancer fear as OCD, and pushing her to understand that her initial urge to avoid or wash could easily become a command if she did not challenge the feeling. After every session, a specific homework assignment was negotiated that Ms. Z could practice daily. She was instructed to call the therapist if she had trouble with the homework assignments. Ms. Z reported compliance with homework assignments as well as a decrease in anxiety, but she continued to experience severe fear of contamination.

Ms. Z then entered a 10-session behavioral therapy group that strengthened her confidence and encouraged her to participate in group exercises (touching objects and resisting washing). By allowing her to share her experiences with other group members, the group also validated her feelings of frustration and isolation. Independently, Ms. Z began to choose goals such as allowing her son to have a toy that she had taken away because it was "contaminated," resisting washing his hands, and making herself lunch for work.

However, it became apparent that as certain symptoms improved, Ms. Z continued to engage in many elaborate rituals at home. To address this problem, home visits were planned. While in the home, the therapist encouraged Ms. Z to touch and clean avoided articles of clothing, throw away rubber gloves that were used to prevent contamination, and even share feared contaminated foods like grapes and celery that Ms. Z had been avoiding because they could not be adequately washed or peeled.

Eventually, Ms. Z also enrolled with her husband in a second eight-session group behavioral treatment that included family members. This gave her husband the ability to observe participant modeling of exposure and response prevention with the support and validation of other family members.

During the next 18–24 months of treatment, Ms. Z began to set more challenging behavioral goals and decreased treatment from as many as three individual therapy sessions and two group and family behavioral group sessions per week to one individual behavioral session per week, with sustained improvement between sessions. She eventually contracted to cook meals, do laundry, and buy groceries and was able to have guests come to her house without experiencing excessive contamination concerns.

Despite its efficacy, behavioral therapy has limitations. To begin with, about 15–25% of patients refuse to engage in behavioral treatment initially or drop out early in treatment because it is so anxiety provoking (Greist 1994; see Figure 71–8). Behavioral treatment fails in another 25% of patients for a variety of other reasons (Greist 1994, Foa et al. 1983), including the following: concomitant depression; the use of central nervous system depressants, which may inhibit the ability to habituate to anxiety; lack of insight; poor compliance with homework, resulting in inadequate exposure; and poor compliance on the part of the therapist in enforcing

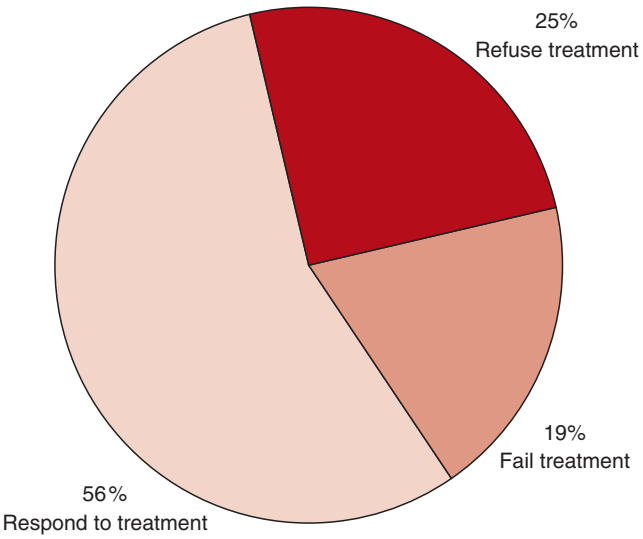



**Figure 71–8** *Diagram of behavioral therapy results.*

the behavioral paradigm (Greist 1994). Thus, overall, 50–70% of patients are helped by this form of therapy.

One of the issues that has emerged in treating OCD with CBT is the lack of trained therapists and the cost of repeated individual exposure sessions. Thus, in addition to developing group treatments, which allow therapists to treat a number of patients simultaneously, researchers have begun to develop computer-guided behavior therapy. Several recent reports have shown that while this modality is not as effective as individual behavior therapy, it does allow for significant improvement in symptoms over a control condition like relaxation therapy (Greist et al. 2002). In our clinical experience such treatment is more suitable for patients whose illness is less severe and less complex (e.g., without problems of comorbidity).

Behavior therapy can be used as the sole treatment of OCD; particularly with patients whose contamination fears or somatic obsessions make them resistant to taking medications. Behavioral treatment is also a powerful adjunct to pharmacotherapy. A meta-analysis has demonstrated that combined behavioral therapy and SRI treatment is superior to either behavioral therapy or pharmacotherapy alone (Eddy et al. 2004). From a clinical perspective, it may be useful to have patients begin treatment with medication to reduce the intensity of their symptoms or comorbid depressive symptoms if present; patients may then be more amenable to participating in behavioral therapy and experiencing the anxiety that will be evoked by the behavioral challenges they perform (see Chapter 91 for further discussion).

Work by Baxter et al. (1992) has illustrated some interesting correlations between treatment response and changes in neurophysiology. These investigators studied two groups of nine patients each, with one group treated with medication only (fluoxetine up to 80 mg/day for 10 weeks) and the other group treated with individual behavioral therapy only (exposure and response prevention for 10 weeks). Positron emission tomography scans with $^{18}$F-fluorodeoxyglucose were performed on all patients before and after treatment. Compared with nonresponders and control subjects, responders in both the medication and the behavioral treatment groups showed a decrease in activity in the right head of the caudate nucleus. This finding seems to support the notion that both forms of treatment bring about similar changes in neurophysiology, which lead to improvement in symptoms. These results also provide important theoretical links with the serotonin hypothesis described earlier in this chapter, as basal ganglion structures like the caudate nucleus have been postulated to mediate serotonin function.

## Other types of Psychotherapy

The use of psychotherapeutic techniques of either a psychoanalytic or a supportive nature has not been proved successful in treating the specific obsessions and compulsions that are a hallmark of OCD. However, the more characterological aspects that are part of OCPD may potentially be helped by a more psychoanalytically oriented approach. As noted earlier, the defense mechanisms of reaction formation, isolation, and undoing, as well as a pervasive sense of doubt and need to be in control, are hallmarks of the obsessive–compulsive character. Salzman (1983) and MacKinnon and Michels (1971) have written elegantly on how to approach the maladaptive aspects of this character style in therapy. In essence, the patient must be encouraged to take risks and learn to feel comfortable with, or at least less anxious about, making mistakes and to accept anxiety as a natural and normal part of human experience. Techniques for meeting such goals in treatment may include the psychiatrist's being relatively active in therapy to ensure that the patient focuses on the present rather than getting lost in perfectly recounting the past, as well as the psychiatrist's being willing to take risks and present herself or himself as less than perfect.

## Neurosurgery

Occasionally, even after receiving adequate pharmacotherapy (including augmentation), adequate behavioral therapy, and a combination of behavioral therapy and pharmacotherapy, patients may still experience intractable OCD symptoms. Such patients may be candidates for neurosurgery. Although criteria for who should receive neurosurgery vary, it has been suggested that failure to respond to at least 5 years of systematic and clearly adequate treatment is a reasonable criterion. Frequently used criteria are the following: a minimum of two adequate medication trials with augmentation plus adequate behavioral therapy in the absence of severe personality disorder.

The procedures that have been most successful interrupt tracts involved in the serotonin system. The surgical procedures used—anterior capsulotomy, cingulotomy, and limbic leukotomy—all aim to interrupt the connection between the cortex and the basal ganglia and related structures. Current stereotactic surgical techniques involve the creation of precise lesions, which are often only 10–20 mm, to specific tracts. These procedures have often been done with radio-frequency heated electrodes and more recently with gamma knife techniques. Postsurgical risks have been minimized, and in some cases cognitive function and personality traits improve along with symptoms of OCD.

Data compiled from a number of small studies have yielded success rates of 25–84% after cingulotomy (Cosgrove and Rauch 2003). However, most samples are small and the procedures have often differed in both lesion location and size, making it difficult to compare them. However, in a

recent prospective long-term follow-up study, all 44 patients received the same procedure (cingulotomy), although some had single procedures and others multiple procedures (Dougherty et al., reviewed in Cosgrove and Rauch 2003). This study had several important findings. Clinical improvement occurred in 32–45% of patients, depending on the criteria used to rate full or partial response, and the average effect size was 1.27, comparable to that seen in pharmacologic trials (1.09–1.53). However, these changes were not immediately apparent postoperatively, and most patients were encouraged to engage in pharmacotherapy and/or behavior therapy postoperatively. The longitudinal follow-up component of the study, which was a mean duration of 32 months, allowed the researchers to assess the longer term impact of the procedure in ways other studies could not. Of particular note, patients continued to show improvement for up to 29 months after surgery without receiving further procedures. As a result, the authors noted that the typical 6-month wait before deciding whether to repeat and extend the lesion may be too brief. A recent study reported a 48% mean improvement rate in the Y-BOCS, as well as no significant incidence of adverse events in Korean patients followed for up to 24 months (Jung et al. 2006).

Deep brain stimulation, which involves stimulation with an electrical current at sites deep in the brain rather than on the surface, is a more recent technique that is currently under investigation. Psychiatric neurosurgery teams in the US and Europe have studied deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) for severe and highly treatment-resistant obsessive–compulsive disorder (OCD). Long-term data show that the procedure can be successfully implemented by dedicated interdisciplinary teams, and support its therapeutic promise (Greenberg et al. 2006). In conclusion, neurosurgical treatments offer hope to some of the most severely ill and treatment-resistant patients and should therefore be considered. However, which surgical lesions are most effective in which patients still needs much more study (see other chapters for further discussion).

## Issues in the Physician–Patient Relationship

Treatment for OCD is often effective, leading to at least some response in a majority of patients. However, treatment adherence is difficult for some patients, which may interfere with treatment efficacy. Short- and long-term compliance with treatment can be greatly facilitated by considering how the nature of the illness affects the treatment modalities used.

At the core of OCD are the concepts of obsessional doubt, risk aversion, and a need to feel in control of one's environment. These three concepts affect behavioral and pharmacological treatment. In the initial phases of behavioral treatment, it may be difficult to engage the patient in treatment because of his or her doubt that the treatment will be effective and an unwillingness to experience the anxiety that results from exposure to feared stimuli. Extra time often must be spent convincing patients of the potential efficacy of treatment and lack of serious side effects from behavioral treatment. Unlike pharmacological treatment, in which the side effects can be quantified in medical terms, the side effects that patients fear from behavioral treatment are related to their cognitive distortions. For instance, those with contamination fears may be thoroughly convinced that simply walking by an AIDS clinic will put them at risk of contracting AIDS or that simply using a public bathroom will give them a communicable disease. Thus, reassurance that this is not the case and that it is safe to engage in behavioral treatment may first involve playing out the catastrophic consequences in their mind or role-playing and discussing the irrational nature of the fear to the fullest extent possible.

When behavioral treatment is started, it is customary to develop a hierarchy of subjective units of distress, which rate particular events according to how much anxiety they produce. For some patients, the ability to develop this hierarchy and thereby obtain a sense of control over their fears, and the ability to begin with the least stressful challenges, can allow them to engage in behavioral treatment. Emphasizing that the patient and therapist are a team and that the patient and therapist will design exposures together may be helpful.

Similar concerns related to doubt, risk aversion, and control must also be addressed when pharmacological treatment is undertaken. In the initial treatment phases, the major task is getting the patient to engage in treatment. Patients with OCD, particularly those with contamination and somatic obsessions, often have numerous questions about medication safety and may be hesitant to take them. Patients with contamination and somatic obsessions may be more likely to engage in behavioral treatment initially.

Although it is important that patients have a thorough understanding of side effects, the psychiatrist should not be thorough to an obsessional degree. Many patients with OCD want a detailed understanding of every side effect and have difficulty differentiating which side effects are of concern and which are not. Thus, it is critical when discussing side effects to present an objective assessment of the relative frequency and severity of various side effects. It is important to emphasize that even though some of the rare side effects are more serious than the more common side effects, they are unlikely to occur. It is also worth keeping in mind that the patient's concerns about a particular side effect may be different from the psychiatrist's. Again, it may help to elicit the catastrophic fears that the patient has and address the irrational obsessional qualities of those fears.

The initial phase of treatment is often the most difficult. This has to do with both risk aversion and a need to be in control. With pharmacologic treatment, patients may occasionally experience an initial worsening of symptoms in addition to side effects. This can be terrifying to the patient and can lead to an abrupt discontinuation of the medication. Warning the patient before treatment that this might occur increases the patient's sense of control. Similarly, the antiobsessional effects of treatment often take 6–10 weeks to be seen and are often gradual in onset. This gradual response is often delayed until after the patient experiences some side effects. Thus, the early phase of treatment may need to focus on encouraging the patient to stay on medication despite side effects and no improvement. Side effects can often be framed as a good sign that the medication is being actively absorbed by the body. Again, preparing patients in advance helps them feel in control and able to continue treatment. The gradual onset of improvement, although in some cases

frustrating, is also reassuring to patients who might feel out of control if improvement occurred too rapidly.

Unlike many patients with mood disorders, most patients with OCD do not have full recovery from their symptoms. Although the majority of patients, perhaps as many as 85%, experience some improvement, most tend to remain symptomatic to some degree (The Clomipramine Collaborative Study Group 1991), and even if treated with CBT and medications, when followed for up to 8 years (Rufer et al. 2005). Nonetheless, symptom improvement of even 10–15% can have a dramatic positive effect on their lives.

## Duration and Discontinuation of Treatment

Little systematic research has been performed to guide decisions about continuation, maintenance, and discontinuation of treatment. The largest study of extended pharmacologic treatment involved fluoxetine (Tollefson et al. 1994b). In this study, 70 patients who had responded to fluoxetine and 198 patients who had not responded during an acute 13-week trial were given the opportunity to continue on medication for another 6 months. At the end of the 6 months, 74.3% of those who had responded initially experienced further improvement. In the nonresponder group, 91.7% experienced a decrease in symptoms when the medication dose was increased from the previous unsuccessful dose. Only 19% of patients ($N$ = 13) experienced a significant worsening of symptoms during the follow-up period. Similar to previous reports on fluoxetine, this study suggested that symptom improvement was maintained over time. Even more important, further improvement occurred in responders with longer treatment and in nonresponders with continued treatment at higher doses.

In another study, 85 patients who had been treated with a variety of antiobsessional medications were followed up 1–3.5 years after initial treatment (Orloff et al. 1994). Ninety-four percent of the patients were still taking medication, and 87% had maintained previous gains or achieved further improvement. Thus, from a clinical point of view, it seems wise to continue medication for an extended period, perhaps for 6 months to a year after initiating treatment, because during this period improvement is maintained and some patients experience further improvement. Overall, this extended duration of treatment did not result in worsening side effects; in fact, in most cases patients habituated to side effects. In general, the most bothersome side effects that persist with SRI treatment appear to be fatigue, weight gain, and sexual dysfunction.

In recent years a number of studies of long-term efficacy have emerged. One study that included a follow-up period of 2 years for 38 OCD patients on sertraline showed continued efficacy with fewer side effects with longer term treatment (Rasmussen et al. 1997). Other studies have attempted to answer important clinical questions not only about long-term efficacy but also about the effects of medication discontinuation after 1 year of treatment (Kordon et al. 2005). The latter is an important question because few studies of systematic discontinuation have been done, and in those that have been done relapse rates were quite high, above 90% (Pato et al. 1988, Leonard et al. 1991). One such study (Koran et al. 2002) involved 223 patients who had been successfully treated with single-blind sertraline for 52 weeks who were then randomized in a double-blind manner to continue treatment for another 6 months or placebo. One-third of the patients in the placebo group relapsed; this was surprisingly lower than the percentage found in earlier studies. The authors offered several plausible explanations for this, which included the possibility that 1 year of effective treatment may provide sustained benefit for patients, and that patients may have engaged in self-directed behavior therapy, something that was not readily available at the time of the previous discontinuation studies. They also noted that while OCD symptom ratings did not worsen in the placebo-treated group as a whole, quality of life did significantly deteriorate. This finding points to the need for more sensitive measures of patient improvement and for further studies of long-term treatment efficacy.

Some preliminary data have suggested that in treatment responders it may be possible to decrease the dose of clomipramine over the longer term without subsequent relapse (Pato et al. 1990). Two studies have more systematically addressed this issue. In one study (Mundo et al. 1997), patients were treated with one-third or two-thirds of their effective doses of clomipramine or fluvoxamine, without experience a worsening of symptoms over 102 days. In another study (Ravizza et al. 1996), doses of clomipramine, fluoxetine, or fluvoxamine were halved, without worsening of symptoms over the next 3 months. Thus it may be possible to decrease the SRI dose in longer term treatment, although this important issue needs further investigation.

The data on discontinuation of behavioral therapy are also encouraging. In summarizing data from several 1- to 6-year follow-up studies of behavioral therapy, O'Sullivan and Marks (1991) noted that overall about 75% of patients continued to do well at follow-up. However, most studies also noted that few patients were symptom-free. A recent study followed up 102 patients who had received fluvoxamine with or without CBT (defined as either cognitive therapy or exposure in vivo with response prevention) for 5 years. Fifty-four percent of patients no longer met criteria for OCD. Furthermore, the type of treatment received did not predict patient outcome (van Oppen et al. 2005).

## Conclusion

For many patients with OCD the illness is lifelong, starting in early childhood and extending into adulthood. It is often familial and accompanied by comorbid conditions including, depression, other anxiety disorders, Tourette's syndrome and even psychosis. However, with a combination of pharmacologic and behavioral treatment, at adequate dose and duration, patients can often have significant improvement in symptoms and overall function.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research for Obsessive–Compulsive Disorder differentiate between obsessions and compulsions based on whether they are thoughts, ideas, or images (obsessions) or acts (compulsions). In contrast, DSM-IV-TR distinguishes between obsessions and compulsions based on whether the thought, idea, or image causes anxiety or distress or prevents or reduces it. Thus, in DSM-IV-TR, there can be cognitive compulsions that would be considered obsessions in ICD-10. In addition, ICD-10 sets a

minimum duration of at least 2 weeks whereas DSM-IV-TR has no minimum duration.

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CHAPTER

# 72 Anxiety Disorders: Traumatic Stress Disorders

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Posttraumatic Stress Disorder
Acute Stress Disorder

This chapter reviews posttraumatic stress disorder (PTSD) and the relatively new diagnosis of acute stress disorder (ASD). We provide definitions and summarize epidemiology, etiology, pathophysiology, diagnosis, differential diagnosis, and comorbidity. We also review the course and natural history of these disorders. Finally, we review overall goals of treatment and discuss specific treatment approaches and factors influencing response.

## POSTTRAUMATIC STRESS DISORDER

### Diagnosis

#### Definition and Diagnostic Features

PTSD is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) by six different criteria (American Psychiatric Association 2000). First, the disorder arises in a person who has been exposed to a traumatic event in which he or she experienced, witnessed, or was confronted with actual or threatened death or serious injury or a threat to the physical integrity of self or others. A wide range of traumatic events may meet this criteria, including military combat exposure; natural disasters; serious accidents; childhood physical, sexual, or emotional abuse; adult physical and sexual assault; domestic violence; and terrorist incidents. Furthermore, the emotional response to this traumatic event must have involved intense fear, helplessness, or horror. In children, the response may take the form of disorganized or agitated behavior.

Second, there must have been at least one of five possible intrusive symptoms focused on the reexperiencing or recollection of the trauma. The first includes distressing recollections, images, thoughts, or perceptions of the traumatic event. For instance, a rape survivor may have disturbing recollections of details of the assault that come to mind unexpectedly when she does not expect to think about the event; these memories may evoke similar feelings of fear and helplessness as when the event occurred. A second reexperiencing symptom may include recurrent distressing nightmares, where trauma survivors may struggle at night reliving the trauma in their dreams. Third, trauma survivors may act or feel as if the trauma were recurring, also known as "flashbacks." These are very vivid reliving experiences in which they may have sensory experiences, including sights, sounds, and smells, related to the trauma. Fourth, trauma survivors may have intense psychological distress when exposed to internal or external cues resembling the trauma (e.g., rape survivor acutely distressed when seeing a man that looks like the perpetrator). The last intrusive symptom includes physiological reactivity (e.g., increased heart rate (HR) and sweating) when exposed to trauma-related cues. Allowance is made for a different set of reactions in children, in whom reexperiencing symptoms may take the form of repetitive play, frightening dreams without recognizable content, or reenactment of the trauma.

Third, persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness must occur as evidenced by at least three out of seven symptoms. Although grouped together as one criterion, it is likely that phobic avoidance, emotional numbing, and withdrawal do not reflect the same underlying phenomenon. These seven symptoms include avoidance of thoughts, feelings,

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**DSM-IV-TR Criteria 309.81**

**Posttraumatic Stress Disorder**

A. The person has been exposed to a traumatic event in which both of the following were present:
   (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   (2) the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   (1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed
   (2) recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content
   (3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur
   (4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
   (5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
   (1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
   (2) efforts to avoid activities, places, or people that arouse recollections of the trauma
   (3) inability to recall an important aspect of the trauma
   (4) markedly diminished interest or participation in significant activities
   (5) feeling of detachment or estrangement from others
   (6) restricted range of affect (e.g., unable to have loving feelings)
   (7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   (1) difficulty falling or staying asleep
   (2) irritability or outbursts of anger
   (3) difficulty concentrating
   (4) hypervigilance
   (5) exaggerated startle response

E. Duration of the disturbance (symptoms in criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Specify** if:

**Acute:** if duration of symptoms is less than 3 months

**Chronic:** if duration of symptoms is 3 months or more

**Specify** if:

**With delayed onset:** if onset of symptoms is at least 6 months after the stressor

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or conversations about the trauma; avoidance of activities, places, or people that cause remembrance of the trauma; difficulty recalling important details of the traumatic stressor; decreased interest in significant life activities; feeling detached or distant from others; a restricted range of affect; and sense of a foreshortened future.

Fourth, there must be at least two out of five symptoms of increased arousal following exposure to the traumatic event. Arousal symptoms may include sleep disruption, irritability or anger outbursts, problems concentrating, hypervigilance, and exaggerated startle responses. Diagnostically, all of these symptoms should have an onset temporally related to the traumatic event.

Symptoms of PTSD should last at least 1 month, and it is necessary that the symptoms cause clinically significant distress or impairment in social, occupational, or other areas of functioning. PTSD is considered to be "acute" if the duration of symptoms is between 1 and 3 months or "chronic" if the symptoms persist for 3 months or longer. If symptoms do not occur until at least 6 months have passed since the stressor occurred, the delayed onset subtype is given. Please refer to the above table which outlines

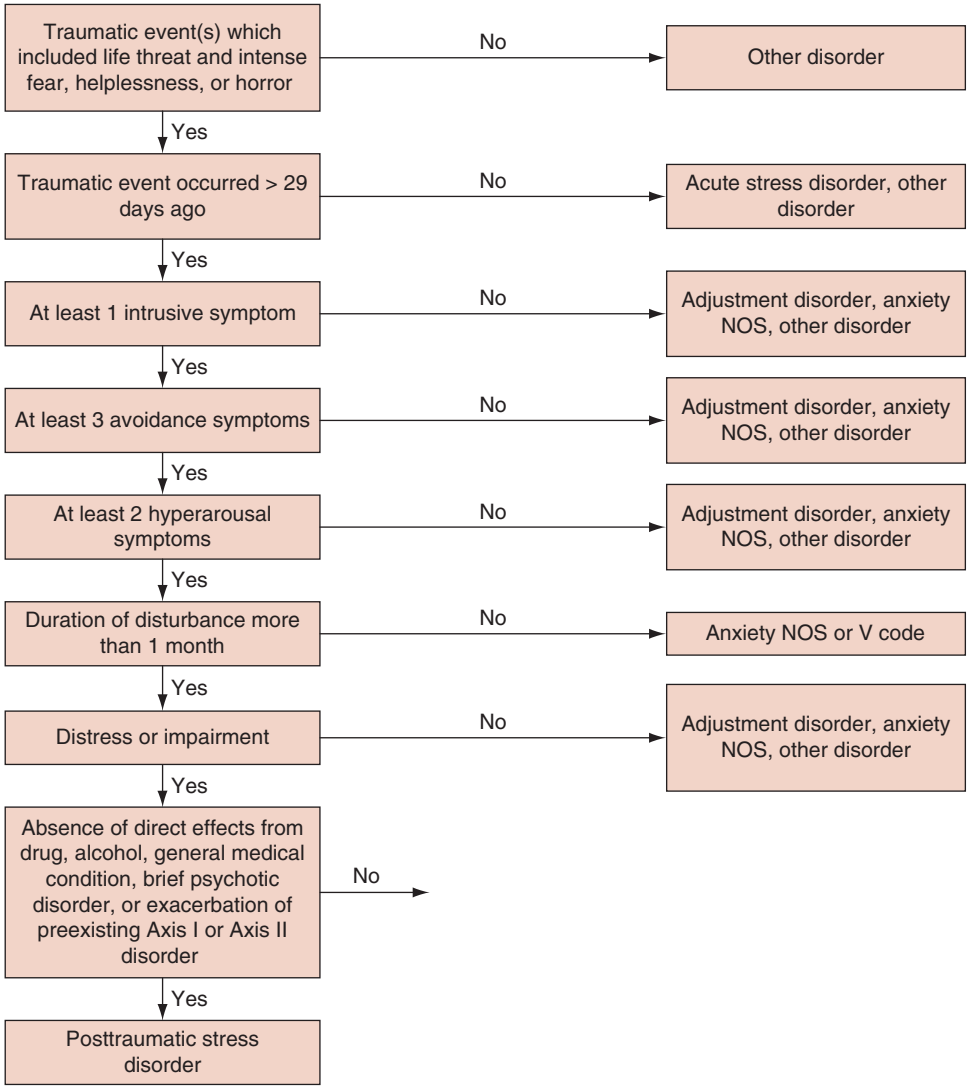



**Figure 72–1** *Diagnostic decision tree for posttraumatic stress disorder.*

the specific DSM-IV-TR PTSD symptomatology and Figure 72–1 for a PTSD diagnostic decision tree.

## Assessment

PTSD assessment experts have suggested that the comprehensive evaluation of PTSD should include information from the traumatized individual, collaterals, and psychometric indices, such as self-report questionnaires and personality assessment (Wilson and Keane 2004). The standard for diagnosis in clinical research studies is always to use a structured clinical interview. The administration of self-report instruments can be used to corroborate information obtained in the clinical interview or can be used as a screening assessment prior to a clinical interview. All information would then be integrated on the basis of clinical judgment, especially if discrepancies existed. A number of structured interviews and self-rating scales are available. The "gold standard" of structured clinical interviews is the Clinician-Administered PTSD Scale (CAPS; Blake et al. 1990). Other instruments that have been used to evaluate PTSD are the Structured Clinical Interview for DSM-IV-TR (First et al. 1996), the Diagnostic Interview Schedule (Robins et al. 1981), and the Structured Interview for PTSD (Davidson et al. 1989). Self-rated measures include the Davidson Trauma Scale (Davidson et al. 1997), the Short PTSD Rating Instrument (Connor and Davidson ), the PTSD Checklist (Weathers et al. 1979), the PK scale on the Minnesota Multiphasic Personality Inventory (Keane et al. 1984), the Mississippi Scale for Combat-Related PTSD (Keane et al. 1988), the Impact of Events Scale (Horowitz et al. 1979), and the PTSD Scale (Foa et al. 1993, 1995).

Similar to adult assessment, a comprehensive evaluation of PTSD in children and adolescents should include direct observation, structured interview, self-report measures, collateral informants (e.g., parent and teacher reports), and behavioral analysis of pre- and posttrauma functioning. Structured interviews and psychometric measures are available for children with PTSD but are less well developed with regard to having established validity and reliability data (Stallings and March 1995). Nader et al. (1994), for instance, have developed a version of the CAPS for children and adolescents. This scale allows for current and lifetime diagnoses

as well as the dimensional assessment of PTSD symptoms and related psychopathology. It has also been suggested (Costello 1989) that the uses of additional measures such as the Conners Parent Rating Scale and Conners Teacher Rating Scale (Conners 1985) are important adjuncts to assess externalizing comorbid symptoms, whereas the Children's Depression Inventory (Kovacs 1985) can be used to assess internalizing symptoms found in PTSD.

## Epidemiology

Community-based studies conducted in the United States have documented a lifetime prevalence rate for PTSD of approximately 6.8–8.0% of the adult population (Kessler et al. 1995, 2005). General population female-to-male lifetime prevalence ratio is 2:1 (Breslau 2001). General population prevalence rates from other countries indicate variation based on levels of economic development (Keane et al. 2006); that is, PTSD prevalence tends to be higher in less economically developed, non-Western countries, with reported ranges from 1.5% in an Australian sample to 37.4% in an Algerian sample (Keane et al. 2006). The highest rates of PTSD occurrence associated with particular traumatic exposures (i.e., occurring in one third to three fourths of those exposed) are among survivors of rape, those exposed to military combat and captivity, those involved in graves registration (i.e., registering dead bodies through the morgue), and survivors of ethnically or politically motivated internment and genocide (Breslau 2001).

Epidemiological studies show that PTSD often remains chronic, with a significant number of people remaining symptomatic several years after the initial event. In support of this view are epidemiological data that show that recovery frequently does not occur. For example, the National Vietnam Veterans Readjustment Study (Kulka et al. 1990) found lifetime and current prevalence rates of PTSD to be, respectively, 30.9 and 15.2%. These data have recently been reanalyzed using more stringent inclusion criteria (Dohrenwend et al. 2006) and suggest slightly more conservative lifetime and current prevalence rates of 18.7 and 9.1%. However, this study is controversial and some experts suggest this may underestimate the actual prevalence rates among Vietnam veterans. In a nationally representative sample of rape victims, Kilpatrick et al. (1992) found a lifetime prevalence rate of 32% and a current prevalence rate of 12%. In children, studies by Pynoos et al. (1987, 1993) revealed prevalence rates of 58.4% in children exposed to sniper attacks in the United States and 70.2% in those exposed to an earthquake in Armenia. In two of the epidemiological catchment area (ECA) sites, Davidson et al. (1991) and Helzer et al. (1987) found that 47 and 33%, respectively, retained the diagnosis of PTSD for more than 1 year. Kessler et al. (1995) documented that one third of those diagnosed with PTSD fail to recover even after many years. Therefore, chronicity of PTSD is not limited to the more severe treatment-seeking samples.

## Comorbidity Patterns

The wealth of clinical literature describes the complexity of PTSD and the fact that PTSD is unlikely to occur in isolation. Psychiatric comorbidity is the rule rather than the exception, and a number of studies have demonstrated this in both clinical and epidemiological populations (e.g., Davidson et al. 1985, 1991, Kessler et al. 1995). In these studies, a wide range of disorders is likely to occur at an increased probability. These include major depressive disorder, all of the anxiety disorders, alcohol and other substance use disorders, somatization disorder, and schizophrenia and schizophreniform disorder. A few studies have documented the course of comorbid conditions. For example, Shalev et al. (1990) have shown that major depressive disorder co-occurs with PTSD, but can take a separate course. Several researchers have provided evidence that comorbid substance abuse tends to be a consequence rather than a precursor of PTSD (Bremner et al. 1996, Breslau et al. 1991).

## Course

Immediately following traumatic exposure, a high percentage of individuals develop a mixed symptom picture, which includes disorganized behavior, dissociative symptoms, psychomotor change, and sometimes, paranoia. The diagnosis of ASD, as described later in this chapter, accounts for many of these reactions (American Psychiatric Association 2000). These reactions are generally short lived, although by 1 month the symptom picture often settles into a more classic PTSD presentation, such that after rape; for example, as many as 90% of individuals may qualify for the diagnosis of PTSD. Approximately 50% of people with PTSD recover, and approximately 50% develop a persistent, chronic form of the illness still present 1 year following the traumatic event.

The longitudinal course of PTSD is variable (Davidson et al. 2004) in both child and adult samples. Permanent recovery occurs in some people, whereas others show a relatively unchanging course with only mild fluctuation. Still others show a more obvious fluctuation with intermittent periods of well-being and recurrences of major symptoms. In a limited number of cases, the passage of time does not bring a resolution of symptoms, and the patient's condition tends to deteriorate with age. Particular symptoms that have been noted to increase with time in many people include startle response, nightmares, irritability, and depression. One recent longitudinal study (Solomon and Mikulincer 2006) highlighted this variable course of PTSD among veterans over a 20-year period. They assessed Israeli soldiers who fought in the Lebanon War at 1, 2, 3, and 20 years after combat and discovered that many of the participants displayed temporal differences in their symptom profiles, with reactivation of symptoms and relapse occurring frequently and the lowest rate of symptom endorsement at the third time point. They speculate how aging and exposure to ongoing trauma in the region might have affected the course of PTSD. In children and adolescents, PTSD symptoms may present differently depending on developmental stage and severity of traumatic exposure (American Academy of Child and Adolescent Psychiatry 1998).

General medical conditions may occur as a direct consequence of the trauma (e.g., head injury and burns). In addition, chronic PTSD may be associated with increased rates of adverse physical outcomes, including musculoskeletal problems and cardiovascular morbidity (Beckham et al. 1997, 1998, Schnurr and Green 2003).

## Differential Diagnosis

PTSD symptoms may overlap with symptoms of a number of other disorders in the DSM-IV-TR. Both PTSD and adjustment disorder are etiologically related to stress exposure.

PTSD may be distinguished from adjustment disorder by assessing whether the traumatic stress meets the severity criteria described earlier. Also, if there are an insufficient number of symptoms to qualify for the diagnosis, this might merit a diagnosis of adjustment disorder.

Specific phobias may arise after traumatic exposure. For example, after an automobile accident, victims may develop phobic avoidance of traveling, but without the intrusive or hyperarousal symptoms. In such cases, a diagnosis of specific phobia should be given instead of a diagnosis of PTSD.

The criteria set for generalized anxiety disorder include a list of six symptoms of hyperarousal, of which four are common to PTSD: being on edge, poor concentration, irritability, and sleep disturbance. PTSD requires both reexperiencing symptoms and avoidance symptoms, and the worry in PTSD is focused on concerns about reexperiencing the trauma. In contrast, the worry in generalized anxiety disorder is about a number of different situations and concerns. However, it is possible for the two conditions to co-occur.

In obsessive–compulsive disorder (OCD), recurring and intrusive thoughts occur, but the patient recognizes these to be inappropriate and unrelated to any particular life experience. OCD is a common comorbid condition in PTSD and may develop with generalization (e.g., compulsive washing for months after a rape to reduce contamination feelings). It may also develop by activation of an underlying OCD diathesis. If the content of the ruminative thinking is focused solely on the traumatic event, this may indicate intrusive reexperiencing symptoms and be better accounted for by PTSD than OCD.

Autonomic hyperarousal is a cardinal part of panic attack, which may indicate a diagnosis of panic disorder. To distinguish between panic disorder and PTSD, the therapist needs to assess whether panic attacks are related to the trauma or reminders of the same (in which case they would be subsumed under a diagnosis of PTSD) or whether they occur unexpectedly and spontaneously (in which case a diagnosis of panic disorder would be justified).

Depression and PTSD share a significant overlap, including four of the criterion C cluster symptoms and three of the criterion D cluster symptoms. Thus, an individual who presents with reduced interest, estrangement, numbing, impaired concentration, insomnia, irritability, and sense of a foreshortened future may manifest either disorder. PTSD may give rise to depression as well, and it is possible for the two conditions to coexist. In a few instances, a patient with prior depression may be more vulnerable to developing PTSD. Reexperiencing symptoms are present only in PTSD.

Dissociative disorders also overlap with PTSD. In the early aftermath of serious trauma, the clinical picture may be predominantly one of the dissociative states (see the section on ASD). ASD differs from PTSD in that the symptom pattern occurs within the first few days after exposure to the trauma, lasts no longer than 4 weeks, and is typically accompanied by prominent dissociative symptoms.

More rarely, PTSD must be distinguished from other disorders producing perceptual alterations, such as schizophrenia and other psychotic disorders, delirium, substance use disorders, and general medical conditions producing psychosis (e.g., brain tumors).

## Differences in Developmental, Gender, and Cultural Presentations

There are some age-specific developmental differences in how children and adolescents present with PTSD compared to adults with PTSD. For instance, there are documented differences in arousal modulation, cause-and-effect reasoning, language and conceptual skills, and social information processing; these skills may cause different manifestation of PTSD symptoms in children and adolescents, particularly in how children process and understand the traumatic stressor (Vernberg and Johnston 2001). There are also differences in symptom presentation between children and adults, as noted in DSM-IV-TR criteria. Gender differences have been extensively studied in adult trauma populations, with the preponderance of evidence suggesting that men are more likely to be exposed to trauma but women are significantly more likely to develop PTSD from trauma exposure and to have a longer persistence of symptoms (Breslau 2001). Some researchers argue that this increased risk of PTSD in women is due to the types of traumatic experiences experienced by women, including sexual victimization histories (Cortina and Kubiak 2006). There may also be differences in the set of symptoms endorsed by gender, with a recent study finding that women were more likely to endorse reexperiencing and arousal symptoms, while men were more likely to report detachment and numbing (Peters et al. 2006), a finding that is consistent with prior research. Finally, it appears that PTSD is represented similarly across diverse ethnic and cultural backgrounds; however, the disclosure of trauma, level of social support, and interpretations of suffering and traumatic exposure may significantly vary across cultures and should be considered in the context of assessment and treatment for PTSD (Keane et al. 2006).

## Etiology and Pathophysiology

### The Event

PTSD is defined in terms of etiology as much as phenomenology. The disorder cannot exist unless the individual has been exposed to a traumatic event with a particular set of properties. Community-based epidemiological studies suggest that up to 70% of individuals will experience at least one traumatic event meeting criterion A(1) over the course of their lifetime (Breslau et al. 1991, Kessler et al. 1995, Norris 1992). The relative severity of the traumatic event, predisposing factors, and peritraumatic environmental factors must all be considered in understanding the etiology of PTSD. In most instances, occurrence of the disorder represents the outcome of an interaction among these three groups of factors.

The likelihood of developing PTSD with regard to the nature of the event was reviewed by March (1990, 1993). A consistent relationship occurred between magnitude of stress exposure and risk of developing PTSD. This association held up in many different trauma populations in adults and children. A more recent meta-analysis across 49 studies (Brewin et al. 2000) found an average weighted effect size of $r = 0.23$ between severity of trauma exposure and PTSD severity, suggesting a modest but statistically significant relationship between these two variables of interest. A dose–response model of PTSD has largely been adopted, in which symptom severity is a function of trauma severity (Keane et al. 2006).

To provide further context for this relationship, here are some examples of these findings across some representative studies. In the St. Louis ECA study, PTSD rates were three times higher in wounded Vietnam veterans than in non-wounded veterans (Helzer et al. 1987). In the North Carolina ECA study, PTSD was much more likely to occur in sexual assault victims who were physically injured than in those who were noninjured (Winfield et al. 1990). Other studies have shown similar results in Vietnam veterans (Kulka et al. 1990) and victims of a volcanic eruption (Shore et al. 1986). In children, Pynoos et al. (1987, 1993) showed that physical proximity to the stressful event was linearly related to the risk of PTSD symptoms in two different populations.

March (1993) concluded that besides the objective event characteristics—namely, actual or threatened death or injury or threat to physical integrity—cognitive and affective responses to the stressor are also important in determining the likelihood that PTSD will develop. In particular, the experience of intense fear, helplessness, or horror is a determinant of a person's likelihood to develop PTSD. The range of identified events that may be considered traumatic has increased over the years, which is likely due to a change in definition from the DSM-III-R to the DSM-IV-TR. In DSM-III-R, a traumatic event was considered to be an event "outside the range of human experience." This definition was modified in DSM-IV-TR to indicate that a traumatic event is defined as an event that involves experiencing or witnessing actual or threatened death or serious injury or learning about an unexpected or violent death and having a response that involves intense fear, helplessness, or horror. There are medical/surgical events (Shalev 1990), such as a cancer diagnosis or open-heart surgery that have been documented to meet criterion A (DSM-IV-TR criteria for PTSD) in some cases; however, inclusion of such traumatic stressors is somewhat controversial and the range of inclusion varies across studies.

## Genetic Factors

The field of genetics has begun to explore complex mental health diagnoses and what genes are necessary and sufficient for the development of these disorders (Koenen 2003, Roberts et al. 2006). Although there is limited research conducted thus far on the genetics of PTSD, it is presumed that many different genes may contribute to inherited liability for PTSD. Several reviews have been conducted to examine genetic factors, such as familial psychopathology to the development of PTSD. For instance, Connor and Davidson (1997) reviewed many of the complexities involved in studying familial risk factors of PTSD. From the available literature, which is based on male combat veterans, general population surveys and rape-trauma-related PTSD, there is evidence to suggest that anxiety and depression in families is a risk factor for PTSD (Davidson et al. 1998). Another meta-analytic review of risk factors suggested an effect size of 0.17 for family of origin psychopathology (Ozer et al. 2003). This is a small but significant effect size which suggests that those who reported a family history had higher rates of PTSD than those without such a family history.

Genetic heritability of PTSD can also be considered through examination of twin studies. For instance, a twin study of Vietnam veterans concordant and discordant for combat exposure has shown that a significant part of the variance is explained on the basis of genetic factors with respect to all three symptom clusters (i.e., intrusive, avoidant, and hyperarousal symptoms) (True et al. 1993). McLeod et al. (2001) examined the role of genetic and environmental influences on the relationship between combat exposure, PTSD symptoms, and alcohol use in 4072 male–male twin pairs; the authors tested three hypotheses: (1) alcohol use and PTSD may share an environmental risk factor (i.e., combat) that increases the possibility that they will occur together; (2) the relationship between PTSD and alcohol problems is that one may develop as a consequence of the other; and (3) PTSD and alcohol problems occur together because of a shared vulnerability that increases risk for both disorders. Their analyses supported hypothesis (3); the same additive genetic influences that affect the environmental influences of combat exposure also include the level of alcohol use and level of PTSD symptoms. It is important to note, however, that specific unique environmental factors the twins did not share were more important than were genetic factors for combat exposure and PTSD symptoms, whereas environmental influences appeared about equally important as genetic influences on alcohol use. These results were consistent with previous findings by this group (McLeod et al. 2001). Overall, the evidence suggests that psychiatric history, both personal or in family members, increases the likelihood of being exposed to a trauma and developing PTSD once exposed (Hidalgo and Davidson , True and Lyons 1999).

King et al. (2001) have developed a congenital learned helplessness animal model, in which rats genetically bred for learned helplessness behavior, exhibited physiologic symptoms of analgesia, learning deficits, and hyporesponsivity of the hypothalamic–pituitary–adrenal (HPA) axis similar to those observed in humans with PTSD. HPA axis hypofunction, physiologic markers of increased arousal, and increased acoustic startle response are all potential PTSD-associated traits that might be susceptible to genetic analysis. However, the capacity of these traits to distinguish PTSD from non-PTSD patients and their familial pattern must be better defined before they can be employed in genetic studies.

## Neurobiological Factors

Identification of biological changes related to PTSD has provided hypotheses for understanding how some individuals develop PTSD in response to a traumatic event, whereas others do not (Yehuda 2002). As summarized by Yehuda (2002), patients with chronic PTSD have increased circulating levels of norepinephrine (Yehuda et al. 1998) and increased reactivity of the alpha-2-adrenergic receptors (Southwick et al. 1993). These changes have been hypothesized to possibly account for some of the somatic symptoms that occur in individuals with PTSD. Neuroanatomical studies have implicated alterations in the amygdala and hippocampus in patients with PTSD (Rauch et al. 2000). Functional magnetic resonance imaging and positron-emission tomography have demonstrated increased reactivity of the amygdala and anterior paralimbic region to trauma-related stimuli (Lieberzon et al. 1999). Furthermore, in response to trauma-related stimuli, there is decreased reactivity of the anterior cingulate and orbitofrontal areas (Shin et al. 1999). These biological alterations suggest that there may be a neuroanatomical substrate for symptoms (intrusive recollections and

other cognitive problems) that characterize PTSD (Schnuff et al. 2001, Vasterling et al. 1998). However, it is unknown whether these changes are preexisting, a result of traumatic exposure, or a result of having PTSD (Pitman 2001).

## Sympathetic Nervous System Alterations

A meta-analytic review found a positive association between the diagnosis of PTSD and basal cardiovascular activity (Buckley et al. 2001). Particularly, individuals with a current PTSD diagnosis had a higher resting HR relative to both trauma-exposed individuals without a PTSD diagnosis and nontrauma-exposed controls. An additional analysis revealed that differences were greatest in studies with the most chronic PTSD samples (Buckley and Kaloupek 2001). A more recent investigation of basal cardiovascular activity (Buckley et al. 2004) and ambulatory activity (Beckham et al. 2002, 2006) found similar results. In addition, there are two recent studies suggesting that parasympathetic activity (i.e., baroreceptor sensitivity) may also be impaired among those with PTSD (Hughes et al. 2006, in press). Along with increased 24-hour urinary catecholamines, results suggest dysregulation in sympathetic tone and parasympathetic tone (Pitman 1993). There has been repeated demonstration that there is heightened sympathetic arousal in PTSD patients when reexposed to the original trauma in controlled settings (Buckley et al. 2001).

Although a conditioning model provides a viable explanation of the process through which trauma-related cues may generate the heightened physiological responses characteristic of PTSD, it does not explain why some individuals develop PTSD when exposed to traumatic events, while others do not. It has been hypothesized that differential susceptibility to developing PTSD might be attributable in part to individual differences in conditionability, such that some individuals more readily acquire and maintain a conditioned response compared with others, and thus may be more likely to develop PTSD after a traumatic event (Keane et al. 2006). A single study has provided support for this hypothesis, finding greater conditionability in individuals with PTSD (Orr et al. 2000). However, further study is needed to evaluate whether this conditionability is a precursor or consequence of PTSD.

There is evidence of brain dysfunction in individuals with PTSD, as evidenced by abnormalities in evoked potentials. For example, as reported by Pitman et al. (1999), electroencephalographic event-related potential (ERP) response abnormalities in PTSD include reduced P2 amplitude at high stimulus intensities, impaired P1 habituation, and attenuated P3 amplitude to target auditory stimuli. Larger P3 and N1 amplitude responses and shorter P3 and N1 latencies have been reported in PTSD subjects in response to trauma-related stimuli. Based on a review of these studies (Pitman et al. 1999), these ERP findings suggest that PTSD patients have increased cortical inhibition to high-intensity stimuli, impairments in memory and concentration, auditory gating deficits, and heightened selective attention to trauma-related stimuli. These findings are fairly consistent across studies, with a recent meta-analysis suggesting similar changes in information processing following development of PTSD (Karl et al. 2006).

Further, there is some evidence that psychophysiological response to acute trauma exposure may predict the development of PTSD. Shalev et al. (1998) demonstrated that on arrival to the emergency department, regardless of whether PTSD ultimately developed, survivors of traumatic events showed elevated HRs, which were normal at later assessment occasions. However, those who subsequently developed PTSD showed higher emergency department and 1-week HRs than those who did not.

## Neuroendocrine Factors

The HPA axis has been the most extensively studied neuroendocrine system in PTSD (Southwick et al. 2005, Yehuda 2002, Yehuda et al. 1991). These studies have summarized the principal findings in the literature as follows: reduced 24-hour urinary cortisol excretion, supersuppression of cortisol after low-dose dexamethasone administration, blunting of corticotropin in response to corticotropin-releasing hormone, and increased numbers of glucocorticoid receptors. Their interpretation of these findings suggest that chronic PTSD is accompanied by supersuppression of the emergency HPA response to acute stress. The authors speculate that this may result from the organism's attempt to protect itself from the potentially toxic effect of high levels of corticosteroids that might occur with repeated exposure to stress or from reminders of the trauma. In further support of the importance of HPA axis alteration in PTSD is the finding (Yehuda et al. 1991) that glucocorticoid receptor changes also correlate with the severity of PTSD symptoms, but not with the less specific anxiety and depressive symptoms measured on other rating scales. In a large sample of Vietnam veterans, combat-exposed veterans with current PTSD had lower cortisol compared to noncombat-exposed veterans without PTSD or combat-exposed veterans with lifetime PTSD but without current PTSD (Boscarino 1996). Lower levels of circulating cortisol and blunted HPA axis response have been demonstrated in both human and other animal models (e.g., Cohen et al. 2006, Santa Ana et al. 2006).

Further evidence for abnormalities in neurotransmitter regulation comes from provocation studies conducted with Vietnam veterans. Administration of yohimbine, an alpha-2-adrenergic antagonist, provoked symptoms of PTSD in combat veterans who had PTSD, as did the serotoninergic challenge with *m*-chlorophenylpiperazine. Of considerable interest is that there was no overlap between these two groups, suggesting some selectivity in the way in which neurotransmitter systems can be affected between individuals (Krystal et al. 1989, Southwick et al. 1993). Finally, evidence to support alteration of noradrenergic and serotoninergic pathways in PTSD comes from the clinical effects of medications that are selective for these neurotransmitter systems, as discussed later. The opioid system has also been investigated, but less extensively and without any consensus being obtained. One early study (Pitman et al. 1990) found the existence of a naloxone-reversible analgesia in combat veterans exposed to the reminders of the trauma.

## Sleep Studies

Studies support that there are two distinct, but possibly interrelated, types of sleep complaints in individuals with PTSD: nightmares that replicate traumatic events and impairment in initiating and maintaining sleep (Harvey et al. 2003, Neylan et al. 1998). Data further suggest that sleep problems in PTSD can also include excessive motor activity

and awakenings with somatic anxiety symptoms (Inman et al. 1990, Mellman et al. 1995). There is support for these complaints, using polysomnography studies, particularly in reduced sleep time or efficiency and increased awakenings in the PTSD patients (Mellman in press). There has also been documentation of PTSD subgroups with breathing-related sleep disorders. Although most studies have involved combat veterans, more recent studies have included civilian PTSD populations (Krakow et al. 2001). Initial data indicate that for up to 2 months following exposure to trauma, development of PTSD is associated with a more fragmented rapid-eye-movement sleep (Harvey et al. 2003, Mellman et al. 2001). Occasionally, a discrepancy is noted between subjective accounts of sleep and objective findings, with individuals with PTSD perceiving poorer sleep than what is reflected in sleep studies (Harvey et al. 2003). However, sleep disruption, whether based on subjective or objective measures, is a biological factor that contributes to distress and increases functional impairment in trauma-exposed individuals.

## Psychological Factors

### Behavioral Models

Conditioning theory has been helpful in explaining the process through which stimuli that are associated with a traumatic event can alone elicit intense emotional responses in individuals who have PTSD (Guthrie and Bryant 2006). Cues (i.e., conditioned stimuli) that are present at the time of the trauma (the unconditioned stimulus) become associated with the unconditioned emotional response (fear, helplessness, or horror). Following the traumatic event, these cues alone can then repeatedly elicit the strong emotional response. For example, a woman who has been raped (unconditioned stimulus) in a dark alley (conditioned stimulus) by a man (conditioned stimulus) and has an intense fear response (unconditioned response) may demonstrate a fear response (now the conditioned response) when she sees a dark alley (conditioned stimulus) or is in the presence of a man (conditioned stimulus). Avoidance behaviors develop to decrease anxiety associated with the conditioned stimuli. For example, the woman who has been raped may avoid going outside when it is dark and also avoid being in the company of men. Behavioral treatments using exposure principles require confrontation with the feared situation and may ultimately lead to reduction of anxiety (Nemeroff et al. 2006).

### Cognitive Models

Exposure to a severe or unexpected event may result in an inability to process and assimilate the experience adequately or to deal effectively with its impact (Resick and Schnicke 1992, 1996). A period of prolonged, difficult, and often incomplete assimilation occurs. The experience is kept alive in active memory, intruding itself into awareness either during the day or at night. The pain of the unbidden experience is followed by active attempts to avoid reminders of the trauma. These intrusive and avoidance phases often alternate. In general, the assumption of these cognitive theories is that exposure to trauma disrupts previously held beliefs about the world and that maladaptive belief changes may contribute to distress and functional impairment among trauma survivors (Boeschen et al. 2001).

Foa and Kozak (1986) proposed that fear can be considered a cognitive structure with three elements: stimulus, response, and meaning. To reduce fear, the fear memory must first be activated and then new information provided to modify the fear structure. Cognitive interventions can be used to recognize and change maladaptive cognitions and to replace interpretations of danger by realistic or safer interpretations, with the ultimate hope that the patient will integrate the new information into the fear structure, leading to a more realistic appraisal of the degree of danger.

## Social/Environmental Factors

Although systematic research is scant, it may be that individuals exposed to repeated or continuous trauma, particularly of an interpersonal nature, may be more likely to develop PTSD. Trauma involving loss of community or support structures is likely to be particularly damaging. Because social support has been held to produce a buffering effect, lack of support might be considered an additional vulnerability factor. Women are at more risk than men for PTSD.

# Treatment

## Treatment Goals

General principles of treating PTSD involve explanation and destigmatization, which can be provided to both the patient and the family members. This often includes psychoeducation about basic PTSD symptoms and the way in which it can affect behaviors and relationships. Information can be given about general treatment principles, pointing out that sometimes cure is attainable but that at other times symptom containment is a more realistic treatment goal, particularly in chronic and severe PTSD. Regaining self-esteem and attaining greater control over impulses and affect are also desired in many instances. Information can be provided as to appropriate literature, local support groups and resources, and names and addresses of national advocacy organizations. If the therapist attends to these important issues early in treatment, the patient is able to more readily build trust and also to appreciate that the therapist shows a good understanding of both the condition and the patient.

PTSD is sometimes comparatively straightforward to treat and at other times, it is more complicated. Treatment by a mental health provider is often warranted to address the problematic symptoms of PTSD. There has also been recent interest in integrating PTSD assessment and intervention in primary care settings, as traumatized individuals are often more comfortable seeking assistance from their primary care provider. Therefore, primary care may be a useful avenue to reach a larger population of trauma survivors that may need mental health assistance. Once the individual is identified and a provider is involved, the initial history taking can evoke strong affect to a greater degree than is customarily found in other disorders. In fact, it may take several interviews for the details to emerge. A sensitive yet persistent approach is needed on the part of the interviewer. During treatment, although the mental health care provider will clearly want to impart a sense of optimism to the patient, it is also a reflection of reality to point out early that recovery may be a slow process and that some symptoms (e.g., phobic avoidance and startle response) may persist. It is important for the mental health care provider to be comfortable in hearing

and tolerating unpleasant affect and sometimes horrifying stories from trauma survivors, responding in a noncritical and accepting manner. In addition, providers need to pay attention to secondary traumatization issues; this refers to the impact on mental health professionals being repeatedly exposed to the disturbing details of traumas and the often dramatic emotional impact felt by the trauma survivor. It is important for providers to carefully monitor their emotional responses to this exposure and how this may affect the therapeutic relationship (Adams et al. 2006).

There are times when decompensation occurs to such an extent that the provider will have to judge whether hospitalization is indicated. Denial of particularly painful issues can lead to avoidance of therapy and missed appointments. Similarly, the emergence of unpleasant or troubling side effects with medication may also lead to treatment discontinuation. At all times, it is advisable for the therapist to remind the patient that difficult issues will arise periodically and that, rather than the patient taking unilateral action to drop out of treatment, these issues are best discussed with the therapist, with the hope that they can be resolved and further treatment progress can be made.

At times, it is helpful to engage the spouse or significant family member in treatment because of the difficulties and stresses to which they may be subjected. Furthermore, they can provide information that might help the therapist to acquire a better grasp of the severity of symptoms as well as their effects on the lives of others. For example, sleeping partners can give a more graphic account of the nocturnal disturbances that may occur in symptomatic patients with PTSD. They may also provide important supplementary information as to the effects of poor impulse regulation or impaired memory or concentration on daytime behaviors in an individual.

Given that many patients with PTSD are receiving more than one treatment, coordination of effort between providers is important. At times, different philosophical persuasions may result in one provider being somewhat less supportive of another's efforts, a situation in which everybody loses. Mutual respect for each other's efforts is essential if optimal progress is to be made by the patient.

Specific treatment approaches include the use of pharmacotherapy, psychotherapy, anxiety management, and attention to the general issues described earlier.

## Pharmacotherapy

PTSD may be accompanied by enduring neurochemical and psychophysiological changes and can lead to substantial impairment and distress. Sometimes the intensity of symptoms is severe enough to preclude the effective use of trauma-focused psychotherapy. In these situations, among others, the use of medication should not be delayed unnecessarily. Initial studies showed benefit for the tricyclic antidepressant and monoamine oxidase inhibitor medications. However, the selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRI) have now replaced these as first-line agents (Davidson 2006). SSRIs have demonstrated superiority over placebo in multiple well-controlled, double-blind trials in the past decade, and sertraline and paroxetine are two SSRIs officially indicated for the treatment of PTSD in the United States and elsewhere (Davidson 2006). Two large trials have more recently demonstrated superior efficacy of the SNRI drug, venlafaxine-extended release, relative to placebo in PTSD (Davidson et al. 2006a, 2006b). Although serotonin reuptake inhibitors are the pharmacotherapy of first choice for PTSD, other medications have also demonstrated some efficacy in managing symptoms in trauma populations, but only in small samples, or in uncontrolled trials. The main groups of medications relevant to the treatment of PTSD along with dose ranges and dose increment recommendations can be found in Table 72–1. These recommendations are from the International Psychopharmacology Algorithm project and adapted from a previously published paper (Connor and Butterfield 2003). Please note that these specific medications were included due to the empirical support found for their use within the PTSD literature and the dosages are different than what might be recommended for other mental health conditions. A suggested sequencing of treatment is outlined in Figure 72–2.

Two double-blind clinical trials in a combined total of more than 100 patients support the efficacy of amitriptyline and imipramine in combat veterans with PTSD (Davidson et al. 1990, Frank et al. 1988). In both studies, the medication was effective on intrusive PTSD symptoms and, to a weaker extent, on avoidant symptoms. Of importance was that clinical efficacy occurred in patients who did not suffer from depressive illness, suggesting that the effect of tricyclic agents in PTSD is independent of antidepressant properties. In fact, Davidson et al. (1993) found that response was inversely correlated with baseline depression level.

Phenelzine has been found to be effective in symptom reduction based on Kosten et al. (1991). Of note was the finding that avoidant symptoms improved to a much greater degree with phenelzine than with the tricyclic agents. However, the side effects of phenelzine limit its use to a third- or fourth-line drug to be used only when other, safer medications have failed to work. Several placebo-controlled trials have shown positive effects for the SSRI medications, specifically fluoxetine (Connor et al. 1999, Martenyi et al. 2002, 2003, van der Kolk et al. 1994), sertraline (Brady et al. 2000, Davidson et al. 2001), and paroxetine (Marshall et al. 1998, Tucker et al. 2001). Two trials have shown benefit for venlafaxine-extended release, one of which was a 6-month trial, demonstrating sustained efficacy, with high rates of remission at study end point (Davidson et al. 2006a, b). One novel and important finding from the 6-month study was the ability of medication to increase personal resiliency to a greater degree than placebo, the first time this has been demonstrated, to our knowledge. It is possible that optimal response to an SSRI takes over 6 months (Londborg et al. 2001). Data support positive effects for SSRI in men and women and in adults who have survived all major classes of trauma (e.g., combat, sexual violence, nonsexual violence, and accident). Each of these medications has broad-spectrum properties across the full symptom range of the disorder, as well as improving function and, perhaps, resilience, or stress coping (Connor et al. 1999, Davidson 2006). They also support the benefit of SSRI drugs in those with and without comorbid major depression (Brady et al. 2000, Connor et al. 1999, Davidson et al. 2001, in press, Marshall et al. 1998, van der Kolk et al. 1994).

Because PTSD is a chronic disorder, there is a significant risk of relapse, especially if treatment is discontinued prematurely. Bearing this out are three studies that report higher rates of relapse when an SSRI is replaced by a placebo,

**Table 72–1 Medications in Posttraumatic Stress Disorder: Dose Ranges and Side Effects**

| Drug | Starting Dose (mg/d)* | Maximum Dose (mg/d)* | Dose Increments* |
|---|---|---|---|
| SSRI/SNRI | | | |
| Citalopram | 20 | 60 | 20 mg every 2 weeks |
| Escitalopram | 5 or 10 | 20 | 5 or 10 mg every 2 weeks |
| Fluoxetine | 10 | 60 | 10 or 20 mg every 2 weeks |
| Fluvoxamine | 50 | 300 | 50 or 100 mg every 2–4 weeks |
| Paroxetine | 10–20 | 50 | 10–20 mg every 2 weeks |
| Sertraline | 25 | 200 | Increase to 50 mg within a week, then 25 or 50 mg every 1–2 weeks thereafter |
| Venlafaxine | 37.5 | 300 | Increase to 75 mg within 1 week, then 37.5 or 75 mg. every 2 weeks thereafter |
| Tricyclic antidepressants | | | |
| Amitriptyline | 25 or 50 | 300 | 50 mg by 1 week, then 25 or 50 every 1–2 weeks thereafter |
| Imipramine | 25 or 50 | 300 | 50 mg by 1 week, then 25 or 50 mg every 1–2 weeks thereafter |
| Other antidepressants | | | |
| Mirtazapine | 15 | 60 | 15 mg every 2 weeks |
| Trazadone | 50 or 100 | 400 | 100 mg after 1 week, then 50 or 100 mg every 2 weeks thereafter |
| Phenelzine | 30 | 90 | 45 mg after 1 week, then 15 mg every 2 weeks thereafter |
| Mood stabilizers | | | |
| Carbamazepine | 400 | 1600 | 200 mg every 2 weeks and by plasma level where available |
| Lamotrigine | 25 | 400 | 50 mg after 2 weeks, then 50 mg every 2 weeks thereafter (see product label for recommended schedule in presence of valproic acid and other anticonvulsants) |
| Topiramate | 12.5 or 25 | 500 | 25 mg every 2 weeks (or 50 mg at the upper dose ranges) |
| Valproic acid and divalporex | 500 | 2000 | 500 mg every 2 weeks according to toxicity or, where available, plasma level |
| Atypical antipsychotics | | | |
| Olanzapine | 2.5 or 5 | 20 | 2.5 or 5 mg every 1–2 weeks |
| Quetiapine | 25 | 300 | 25 or 50 mg every 1–2 weeks |
| Risperidone | 0.5 | 3 | 0.25 or 0.5 every 1–2 weeks |
| Adrenergic inhibitors | | | |
| Clonidine | 0.1 | 0.6 | 0.1 or 0.2 every 1–2 weeks |
| Guanfacine | 1 | 3 | 1 mg every 2 weeks |
| Prazosin | 1–2 | | |
| Propranolol | 20–40 | 160 | 20–40 mg every 3–4 days |

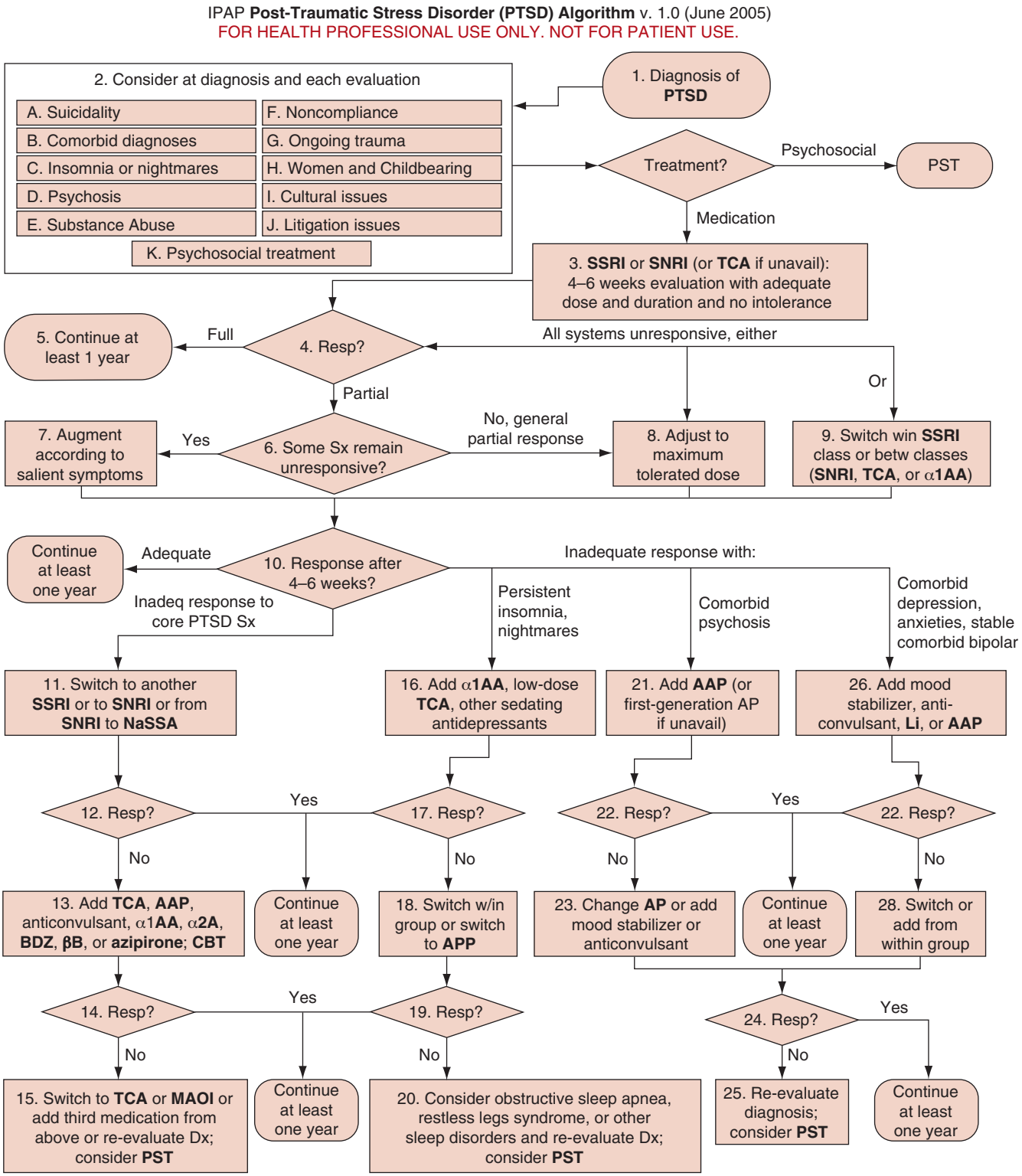
* See elsewhere for available levels of evidence to support use of each medication. Dose increments to proceed unless clinical response of at least 50% reduction in symptom severity or due to problematic side effects. Issues of drug interactions are clinically important but not addressed in this particular table. Adequacy of treatment trial suggested is 12 weeks at the maximum tolerated dose for all of the above medications.

as compared to groups who remained on their drug, over a period of 1 year or more (Davidson et al. 2001a, 2005, Martenyi et al. 2003).

There have been a number of open studies, suggesting benefit of carbamazepine, propranolol, clonidine, and valproic acid. There have also been two negative double-blind placebo-controlled trials of desipramine and phenelzine (Davidson 1992); however, treatment length in these two studies may have been too short because in the study by Davidson et al. (1990) it was not until week 8 that amitriptyline became superior to placebo.

At this point, the indications for antipsychotic and mood-stabilizing drugs are poorly defined, but clinical experience suggests that they continue to have a role in the pharmacologic treatment of PTSD. It is encouraging to know that five double-blind, placebo-controlled, augmentation studies of either olanzapine or risperidone have shown positive benefits for the drug, in combat veterans and noncombat veterans, with PTSD. Almost all patients were already taking an SSRI, to which they had shown partial response (Bartzokis et al. 2005, Hamner et al. 2004, Monnelly and Ciraulo 1999, Reich et al. 2004, Stein et al. 2003). Antipsychotic medications appear to be useful in enhancing sleep, reducing aggression, and otherwise treating different aspects of PTSD. We do not have adequate data to suggest in what ways, if any, anticonvulsants, mood stabilizers, or other drugs are helpful. One exception may be prazosin, the alpha-1-adrenergic antagonist, for which there is some evidence that, in augmentation to an antidepressant, it leads to improvement in nightmares (Raskind et al. 2003). The appropriate role for the use of benzodiazepines is not well defined. The antiphobic and antiarousal effects of the benzodiazepines should, in theory, be helpful in PTSD. However, withdrawal from short-acting benzodiazepines may also introduce an additional set of problems with intense symptom rebound. In patients who have a propensity to abuse alcohol and other substances, benzodiazepines are not recommended.

Overall, the antidepressants and, to a lesser extent, the atypical antipsychotics are the most useful, and best studied, medication groups in treating PTSD. Mood stabilizers, hypnotics, beta- blockers, alpha-2-agonists, alpha-1-antagonists, and anxiolytics have a less clearly defined place. Preliminary research regarding the use of beta-blockers, specifically taking propranolol immediately after trauma exposure, may prevent some symptoms of PTSD and reduce




**Key**: α**1AA**=$\alpha_1$–adrenergic antagonist; α**2A**=α2–agonist; **AP**=antipsychotic; **AAP**=atypical antipsychotic; **βB**=beta-blocker; **BDZ**=benzodiazepine; **CBT**=cognitive behavioral therapy; **Dx**=diagnosis; **Li**=lithium; **MAOI**=monamine axidase inhibitor; **NaSSA**=noradrenergic and selective serotonergic antidepressant; **PST**=psychosocial treatment; Resp=response; **SNRI**=serotonin and noradrenaline reuptake inhibitor, **SSRI**=selective serotonin reuptake inhibitor, **Sx**=Symptoms; **TCA** = tricyclic antidepressant.

**Figure 72–2** *Pharmacotherapy steps for posttraumatic stress disorder. Reprinted with permission from Dr. Kenneth Jobson, International Pharmacotherapy Algorithm Project.*

the memory-enhancing effects of the autonomic response (Pitman et al. 2002, Vaiva et al. 2003).

Often, patients need a combination of drugs but polypharmacy should be utilized in a carefully planned fashion. Also, since the time course of response may be slow, it is advisable to persist with a particular course of action for at least 8 weeks before deciding that it has been unhelpful. Partial response can be converted into full remission as long as 6–9 months into treatment. Three relapse-prevention studies have shown the ability of fluoxetine and sertraline to protect against relapse over a 1-year or greater length of treatment.

## Psychosocial Treatments

Despite theoretical differences, most schools of psychotherapy recognize that cognitively oriented approaches to the treatment of anxiety must include an element of exposure (Foa et al. 2000). Because PTSD avoidance of danger that is conditioned by real experience, correction of these "fear structures" requires exposure to ensure habituation. Although a range of possible PTSD interventions has recently been reviewed (Foa et al. 2000), including group therapy, cognitive–behavioral therapy (CBT), eye movement desensitization and reprocessing (EMDR), and psychodynamic therapy, the preponderance of current evidence suggests that the primary effective component of PTSD treatment is prolonged exposure (Rothbaum et al. 2000). Prolonged exposure depends on the fact that anxiety will be extinguished in the absence of real threat, given a sufficient duration of exposure in vivo or in imagination to traumatic stimuli. When using in vivo exposure techniques, patients are asked to confront real-life situations that trigger anxiety (e.g., street where car accident happened or room where assault occurred) and remain in these situations until their anxiety begins to decrease. In imaginal exposure, the patient retells the traumatic experience as if it were happening again, until doing so becomes a pedestrian exercise and anxiety decreases. Between sessions, patients perform exposure homework, including listening to tapes of the flooding sessions and limited exposure in vivo. A review of 12 studies suggests that prolonged exposure is a component of the most well controlled study designs and is associated with positive results (Rothbaum et al. 2000). However, not every patient may be a candidate for exposure. Due to the high anxiety and temporarily increased symptoms associated with prolonged exposure, there are patients who will be reluctant to confront traumatic reminders. Patients in whom guilt or anger are primary emotional responses to the traumatic event (as opposed to anxiety) may not profit from prolonged exposure (Foa et al. 1995, Pitman et al. 1991). More empirical research is needed to evaluate how this efficacious treatment can be most effectively implemented in trauma populations. Additional research is also needed to identify methods to increase patient tolerability of the treatment.

In addition to exposure therapy, the use of EMDR has been empirically supported within PTSD patient populations. According to its creator, EMDR facilitates the accessing and processing of traumatic memories to bring closure and resolution (Shapiro 2001). Patients are asked to identify the most disturbing images of their trauma, including body sensations and a negative cognition about what they learned from the trauma. They are also asked to create a positive cognition that they wish could replace the negative cognition about the trauma. During active treatment, patients are asked to bring to mind the disturbing image, sensations, and the negative cognition while tracking the clinician's moving finger back and forth in front of their visual field. These tracking sessions continue in order for the patient to focus on whatever changes or new associations have occurred. Tracking is repeated in future sessions until the patient has no further changes; then, more tracking is implemented to reinforce the positive cognition. Although EMDR has been empirically supported in the literature, there is some controversy about the "active ingredient" in EMDR and the restricted access to this treatment protocol through a proprietary company.

Anxiety management techniques are designed to reduce anxiety by providing patients with better skills for controlling worry and fear. Among such techniques are muscle relaxation, self-distraction (thought stopping), control of breathing and diaphragmatic breathing, guided self-dialogue, and stress inoculation training. These techniques focus on enhancing a trauma survivor's ability to manage negative effect, especially anxiety and anger, and increase their everyday functioning. Although these interventions have less empirical evidence regarding treatment efficacy for PTSD, generally the results are positive and further controlled evaluation across trauma population samples is needed (Rothbaum et al. 2000).

Further, cognitive approaches to the treatment of PTSD have also gained empirical support (Resick and Schnicke 1992, Rothbaum et al. 2000). Overall, cognitive therapy for PTSD focuses on challenging dysfunctional, automatic thoughts that may develop following trauma exposure. (For example, the world is a dangerous place.) This is particularly important because dysfunctional interpretation of the traumatic event may lead to negative mood states, such as anxiety, generalized fear, and self-blame. In a recent comparison of cognitive therapy to imaginal exposure in the treatment of chronic PTSD, both treatments were associated with positive improvements at posttreatment and follow-up, with no differences in outcome between treatments (Tarrier et al. 1999). However, patients who received imaginal exposure were more likely to experience an increase in PTSD symptoms during the treatment course, and those who did were more likely to miss treatment sessions, rate the therapy as less credible, and be rated as less motivated by the therapist.

Other recent approaches have focused on efficaciously treating one aspect of PTSD symptomatology, such as anger (Yehuda 1999) and nightmares (Krakow et al. 2001). Some approaches have focused on specific interpersonal difficulties, such as difficulty dealing with authority figures following combat trauma (Lubin and Johnson 2000). There has also been a recent report of positive results, using interventions to target both PTSD and a comorbid disorder. For example, Triffleman et al. (1999) reported patient improvement using a group intervention to simultaneously treat co-occurring substance abuse and PTSD. Similar support has been found with data from the Seeking Safety Protocol for comorbid PTSD and substance abuse (Najavits 2006). Falsetti et al. (2001) have reported an intervention entitled multiple channel exposure therapy to treat comorbid panic attacks and PTSD.

In contrast to the treatment-efficacy literature for adults with PTSD, the child-focused PTSD literature is primarily

limited to open trials and case reports (Ruggiero et al. 2001). Ruggiero et al. (2001) underscore that adult treatment approaches need to be empirically evaluated for use in children with PTSD. Although the literature is fairly limited thus far, one recent randomized clinical trial (Cohen et al. 2004, 2005) found trauma-focused CBT to be more effective than conventional child-centered therapy among childhood sexual abuse survivors. The trauma-focused CBT included skills such as expressing feelings; learning basic coping skills; recognizing the relationship between thoughts, feelings, and behaviors; gradual exposure; cognitive processing of the trauma; joint child–parent sessions; psychoeducation about body safety and child sexual abuse; and parent management skills. The child-centered therapy included active listening, reflection, accurate empathy, encouragement to talk about feelings, and limited interpretations when clinically appropriate. Similar research needs to be conducted to determine evidence-based practices for the treatment of child and adolescent PTSD.

As no single treatment for PTSD has been shown to be curative, patient characteristics, characterization of the nature and range of stress responses of trauma victims (McFarlane and Yehuda 2000), partial response (Taylor et al. 2001), treatment combinations, sequencing of treatment approaches, and further well-controlled investigations of current approaches are all important empirical topics to be addressed. For example, in patients unwilling to undergo exposure therapy, teaching of affect management skills may be helpful (Wolfsdorf and Zlotnick 2001).

### Psychodynamic Therapy

Psychodynamically based approaches emphasize the interpretation of the traumatic event as being a critical determinant of symptoms. Treatment is geared to alter attributions, usually by means of slow exposure and through confrontation and awareness of the negative affect that have been generated by the trauma. Conflictual meanings begin to appear, and it is the task of treatment to reinterpret the experience in a more realistic and adaptive fashion. During such treatment, it is important to ensure that the affect intensity is not overwhelming or disorganizing. Obviously, support needs to be provided throughout, and sometimes other treatment approaches are used adjunctively. Excessive and maladaptive behaviors such as avoidance, use of alcohol or working excessively, or risk taking may occur as a means of coping with the experience and need to be identified and addressed.

Using psychodynamic concepts, Horowitz (1973) developed a trauma-focused, time-limited, psychotherapeutic approach. Periods of intrusion are considered an attempt at mastery rather than a failure in defenses, whereas emotional numbness is seen as a result of defensive overcontrol. Overwhelmingly intrusive symptoms are counteracted by means of structuring, and avoidance and numbing are met with procedures to minimize such behavior. With this approach, as with any psychotherapeutic approach, the establishment of a safe therapeutic alliance is essential and medications are used sparingly. The goal of such trauma-focused therapy is to achieve an end point in which the trauma is meaningfully integrated into the survivor's life schema, with reduction of intensity and frequency of the intrusive and avoidant phases of PTSD. Although this and other psychodynamic approaches await controlled testing, they aspire to reduce all aspects of PTSD symptoms (Kudler et al. 2000).

Roth and Newman (1991) presented a conceptual framework for understanding the emotional impact of sexual trauma. The survivor must come to understand the affective impact of the event so that she or he is no longer preoccupied or driven by negative feelings or self-defeating behaviors. It is also important for the survivor to grapple with the meaning of the trauma so as to reach adaptive resolution. Preliminary studies utilizing this approach show promise of efficacy.

## Special Factors Influencing Treatment

### Psychiatric Comorbidity

Several important issues of comorbidity need to be considered in the treatment of PTSD. These may suggest either a contraindication to a particular treatment or the need to first treat the comorbid state before embarking energetically on the PTSD problems. Thus, comorbid depression needs to be treated, as it is likely to interfere with the benefits of behavioral therapy or other psychotherapies (Davidson et al. 2004). In fact, as mentioned earlier, in some instances guilt-bound issues may worsen with exposure. A suicidally depressive individual with PTSD needs to be adequately treated before dealing with issues of PTSD, which may in fact worsen suicidality in some instances.

Occasionally, severe depression comorbid with PTSD may need to be treated with electroconvulsive therapy. Although this form of treatment has no proven place as a major intervention for PTSD per se, in comorbid cases it has been noted that PTSD symptoms may also abate when they are tied to the presence of depression. Davidson and Fairbank (1993) reported that amitriptyline is less likely to help combat veterans with PTSD if they have been exposed to more severe forms of combat trauma and also if they have more severe symptoms of depression, anxiety, and PTSD.

### General Medical Comorbidity

PTSD patients have been shown to have an increased risk of medical conditions, with particular conditions perhaps being more prevalent (gastrointestinal disease and cardiovascular disease) (Beckham et al. 1998, Boscarino 1997, Schnurr and Green 2003, Schnurr and Janowski 1999). There is also evidence that chronic pain and PTSD are commonly associated, even when PTSD has not followed serious physical injury (Beckham et al. 1997). With a focus on the mind–body connection, these medical conditions and bodily symptoms should be addressed concurrently with PTSD treatment.

### Demographic Factors

It is not known to what extent sex or age is likely to determine treatment outcome. However, it is generally believed that lack of psychosocial supports can interfere with successful adaptation to trauma and response to treatment (Keane et al. 2006).

**Nonresponse to Treatment**. A stepwise sequence of approaches may be used in the treatment of PTSD but it must be said that there are no definitive guidelines currently in place. As a result, the particular order in which treatments are considered varies based on individual circumstances.

Also, no uniform definition exists as to what constitutes a good or poor response to treatment. In general, some symptoms of chronic PTSD persist, albeit at a considerably reduced level, in people who have undergone treatment. A summary of the limited information available for predicting response to pharmacotherapy and behavioral therapy in PTSD arising from combat trauma is given elsewhere (Davidson and Fairbank 1993).

### Summary of Treatment

Whatever the type of treatment administered, a number of goals are common to all and can be summarized as follows: (1) to reduce intrusive symptoms, (2) to reduce avoidance symptoms, (3) to reduce numbing and withdrawal, (4) to dampen hyperarousal, (5) to reduce psychotic symptoms when present, and (6) to improve impulse control when this is a problem.

By reducing troublesome symptoms, a number of other important goals can also be accomplished as well: (1) to develop the capacity to interpret events more realistically with respect to their threat content; (2) to improve interpersonal work and leisure functioning; (3) to promote self-esteem, trust, and feelings of safety; (4) to explore and clarify meanings attributed to the event; (5) to promote access to memories that have been dissociated or repressed when judged to be clinically appropriate; (6) to strengthen social support systems; and (7) to move from identification as a victim to that of a survivor.

The three major treatment approaches, pharmacotherapeutic, cognitive–behavioral, and psychodynamic, all emphasize different aspects of the problem. Pharmacotherapy targets the underlying neurobiological alterations found in PTSD and attempts to control symptoms so that the above treatment goals can be more effectively accomplished. Cognitive–behavioral treatments emphasize confronting traumatic memories through exposure as well as identifying and challenging dysfunctional beliefs about the trauma. The psychodynamic approach emphasizes the associations that arise from the trauma experience and that lead to unconscious and conscious representations. Defense mechanisms that lead to lack of memory, and the contributions from early development, are also brought into play in psychodynamic therapy.

### Issues in the Doctor–Patient Relationship

Management problems are likely to occur as a result of both therapist-related factors and patient-related factors. With regard to the therapist, it must be recognized that much of the material offered by the patient is charged with affect and, at times, may strain credibility and lead to high levels of doubt. The therapist may fall into the error of being unable to accept such an emotionally charged experience and thus rejecting or denying its validity. Equally, the therapist may fall into the error of overidentification with the patient such that impartiality is lost. It is important for therapists not to become overinvolved with rescue fantasies or to break down customary therapist–patient boundaries.

Although not unique to PTSD, powerful violent urges may arise in the patient during treatment, which may challenge the therapist's feeling of safety. Simple strategies, such as considering where the patient and therapist sit with respect to proximity of escape, merit attention. For example, a female therapist dealing with a highly hostile and threatening male patient would do well to be sure that she can exit the room quickly if necessary and not be trapped behind a desk with the patient having control of the exit. Another simple yet important issue calling for attention is whether there is an available alarm if the therapist is dealing regularly with violent or threatening patients.

## ACUTE STRESS DISORDER

### Diagnosis

#### Definition and Diagnostic Features

It has long been recognized that clinically significant dissociative states are seen in the immediate aftermath of overwhelming trauma. In addition, many individuals may experience less clinically severe dissociative symptoms or alterations of attention and time sense. Because such syndromes, even when short lasting, can produce major disruption of everyday activities, they may require clinical attention. During triage situations after a disaster, it can be important to recognize this clinical picture, which may require treatment intervention and may also be predictive of later PTSD. As a result of these considerations, a decision was made to include in a new entity, ASD, grouped together with PTSD in the anxiety disorders section. This definition describes stress reactions that occur within the initial month after a trauma has occurred. Essentially, the definition parallels the diagnostic features of PTSD, with identical criterion A requirements for a traumatic stressor(s) and a clinical presentation that includes symptoms of reexperiencing, avoidance, and hyperarousal. One significant difference in diagnostic criteria for ASD is an emphasis on conspicuous dissociative symptoms, of which at least three must be present, as a hallmark feature of ASD. The possible dissociative symptoms in ASD are a subjective sense of numbing, detachment or absence of emotional response, reduced awareness of one's surroundings, derealization, depersonalization, and dissociative amnesia.

There has been a call for empirical evidence of acutely traumatized individuals to address the inclusion of ASD as a separate diagnostic category from PTSD (Bryant 2003, Bryant and Harvey 1997). The current emphasis placed on acute dissociative responses may be flawed in that there are multiple pathways to PTSD, and trauma survivors who display severe acute stress reactions without dissociation can develop PTSD (Harvey and Bryant 1999). Other criticisms include the fact that the primary role of ASD is to predict another diagnosis, making it repetitive to have two separate diagnoses; that distinguishing between ASD and PTSD primarily based on duration of symptoms may not be warranted; and that inclusion of ASD in the DSM-IV-TR was made without meeting the same critical review and criteria normally followed for inclusion of other diagnoses. Review of these conceptual issues have recently been published (Bryant 2003).

### Assessment

Recommendations for assessment of ASD largely follow the general principles addressed above in the PTSD assessment section. It is important to collect clinically relevant information through clinical interview, self-report questionnaires,

**DSM-IV-TR Criteria** 308.3

**Acute Stress Disorder**

A. The person has been exposed to a traumatic event in which both of the following were present:
   (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   (2) the person's response involved intense fear, helplessness, or horror

B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
   (1) a subjective sense of numbing, detachment, or absence of emotional responsiveness
   (2) a reduction in awareness of his or her surroundings (e.g., "being in a daze")
   (3) derealization
   (4) depersonalization
   (5) dissociative amnesia (i.e., inability to recall an important aspect of the trauma)

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience.

G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.

H. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition is not better accounted for by brief psychotic disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

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collateral informants, and psychophysiological measurement to obtain a thorough assessment of symptom presentation. Two useful assessment tools described in the literature are the Acute Stress Disorder Interview (ASDI; Bryant et al. 1998) and the Acute Stress Disorder Scale (ASDS; Bryant et al. 2000). The ASDI is a structured interview based on DSM-IV-TR diagnostic criteria and appears to have good internal consistency, test–retest reliability, and construct validity. The ASDS is a self-report measure with good reliability and validity data and correlates highly with the symptom clusters on the ASDI. Recently, a self-report scale of ASD has been developed, the ASDS. The scale has demonstrated good test–retest reliability ($r$ = 0.94), and in one sample (bushfire survivors), the ASDS predicted 91% of survivors.

## Epidemiology

Little is known about the epidemiology of ASD as defined in DSM-IV-TR, but some preliminary studies on the prevalence rates of acute PTSD have been published. The following are rates for a representational sample of such studies: 9% among Manhattan residents after the September 11 terrorist attacks (Galea et al. 2002), 13–25% for motor vehicle accident survivors (Harvey and Bryant 1999), 19% for physical assault survivors (Brewin et al. 1999), 24% for survivors of terrorist attack in Israel (Kutz and Dekel 2006), 33% for those who witnessed community violence (Classen et al. 1998), and 94% among a sample of rape victims (Rothbaum et al. 1992). One problem of some postdisaster surveys is that they evaluate subjects at points several months or years after the event. This makes any meaningful assessment of acute stress syndromes difficult. One exception was the self-report-based assessment of morbidity 2 months after an earthquake in Ecuador, which found a 45% rate of acute stress reactions, with the most prominent symptoms being fear, nervousness, tenseness, worry, insomnia, and fatigue (Lima et al. 1989). Other common acute stress reactions include high rates of numbing, dissociative symptoms, intrusive thoughts, avoidance behaviors, insomnia, concentration problems, irritability, and autonomic arousal (Bryant 2003). It is normative to have at least some levels of distress within the initial month of trauma exposure.

In a study by Koopman et al. (1994) of individuals who had been exposed to a firestorm, the participants showed a high incidence of dissociative symptoms, including time distortions, alterations in cognition and memory, and derealization. Most of these symptoms had lessened by a 4-month follow-up. A study by Bryant and Panasetis (2001) reported that 53% of participants reported panic attacks during their trauma, and those who had symptoms that met criteria for

ASD reported more peritraumatic panic symptoms. These data suggest that peritraumatic panic may be related to subsequent PTSD.

Retrospective reports of acute stress symptoms should be interpreted cautiously because of the influence of current symptoms on recall of acute symptoms. In a longitudinal study evaluating report of acute stress symptoms at 1 month and 2 years posttrauma, at least one of the four ASD diagnostic clusters was recalled inaccurately by 75% of patients (Harvey and Bryant 2000).

## Course

A recent review of prospective studies of ASD suggests that approximately three quarters of individuals who meet criteria for ASD will later develop full-blown PTSD (Bryant 2003). Therefore, the ASD diagnosis is strongly predictive of the development of PTSD over time. However, it also appears from this review that of those who develop PTSD, only 50% met criteria for ASD within the initial month. This suggests that although ASD may be predictive of later PTSD, there are still a significant group of individuals who develop PTSD without initially meeting criteria for ASD. The emphasis on dissociative symptoms as a requirement for ASD diagnosis may account for this discrepancy (Bryant 2003).

Specific symptoms may affect the course of the disorder and development of subsequent PTSD. For instance, Koopman et al. (1994) indicated that dissociative and cognitive symptoms, which are so common in the immediate wake of trauma, improve spontaneously with time. However, they also found that the likelihood of developing PTSD symptoms at 7-month follow-up was more strongly related to the occurrence of dissociative symptoms than to anxiety symptoms immediately after exposure to the trauma.

## Differential Diagnosis

ASD may need to be distinguished from several related disorders (Figure 72–3). Brief psychotic disorder may be a more appropriate diagnosis if the predominant symptoms are psychotic. It is possible that major depressive disorder can develop following trauma and that there may be some overlap with ASD, in which case both disorders are appropriately diagnosed. When ASD-like symptoms are caused by direct physiological perturbation, the symptoms may be more appropriately diagnosed with reference to the etiological agent. Thus, an ASD-like picture that develops secondary to head injury is more appropriately diagnosed as mental disorder due to a general medical condition, whereas a clinical picture related to substance use (e.g., alcohol intoxication) is appropriately diagnosed as substance-induced disorder. Substance-induced symptoms are confined to the period of intoxication or withdrawal. The fact that the symptoms are due to the physiological consequences of head injury needs substantiating by evidence from the history, physical examination, and laboratory testing that the symptoms are a direct physiological consequence of head trauma.

Because ASD by definition cannot last longer than 1 month, if the clinical picture persists, a diagnosis of PTSD is appropriate. Some increased symptoms are expected in the great majority of subjects after exposure to major stress. These remit in most cases and reach the level of clinical diagnosis only if they are prolonged, exceed a tolerable quality, or interfere with everyday function. Resolution may be more difficult if there has been previous psychiatric morbidity, subsequent stress, and lack of social support.

## Etiology and Pathophysiology

Little is known about the etiology of ASD specifically, but it is likely that many of the same factors that apply to PTSD are relevant for ASD; that is, trauma intensity, preexisting psychopathology, family and genetic vulnerability, abnormal personality, lack of social supports at the time of the trauma, and physical injury are all likely to increase vulnerability for ASD.

The role of acute arousal in the development of PTSD has been evaluated in one study (Bryant and Harvey 2000). Resting HR and ASD symptoms together were found to account for 36% of the variance in PTSD prediction (Bryant and Harvey 2000). Further, a formula using resting HR following the trauma exposure (HR > 90 beats/minute) and the diagnosis of ASD to predict PTSD development possessed strong sensitivity (88%) and specificity (85%) (Bryant and Harvey 2000).

## Treatment

Lundin (1994) reviewed the treatment of acute traumatic stress states and pointed out the six general principles involved in administering any treatment immediately after trauma. These include principles of brevity, immediacy, centrality, expectancy, proximity, and simplicity. That is, treatment of acute trauma is generally aimed at being brief, provided immediately after the trauma whenever possible, administered in a centralized and coordinated fashion with the expectation of the person's return to normal function and as proximately as possible to the scene of the trauma, and not directed at any uncovering or explorative procedures but rather at maintaining a superficial, reintegrating approach.

People most highly at risk, and therefore perhaps most in need of treatment, are as follows: survivors with psychiatric disorders; traumatically bereaved people; children, especially when separated from their parents; individuals who are particularly dependent on psychosocial supports, such as the elderly, handicapped, and mentally retarded individuals; and traumatized survivors and body handlers.

Different components of treatment include providing information, psychological support, crisis intervention, and emotional first aid. Providing information about the trauma is important, as it can enable the survivor to fully recognize and accept all the details of what happened. Information needs to be given in a way that conveys hope and the possibility that psychological pain and threat of loss may be coped with. Unrealistic hope needs to be balanced by the provision of realistic explanations as to what happened. Psychological support helps to strengthen coping mechanisms and promotes adaptive defenses. The survivor benefits if he or she recognizes the need to take responsibility for a successful outcome and is as actively involved with this as possible. Crisis intervention is often used after disasters and acts of violence or other serious traumas. Emotional first aid has been described by Caplan (1984) using the six principles presented earlier and is used to achieve any of the following: acceptance of feelings, symptoms, reality, and the need for help; recognition of psychologically distressing issues; identification of available resources; acceptance of responsibility and absence

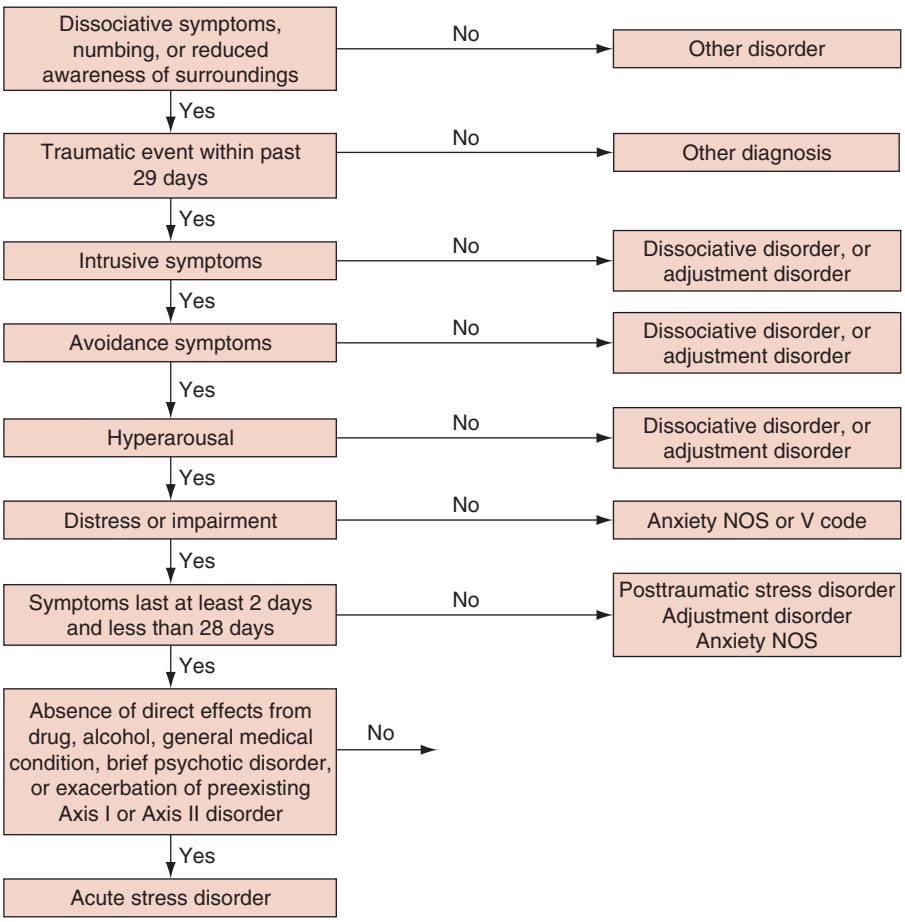



**Figure 72–3** *Diagnostic decision tree for acute stress disorder.*

of blame; cultivation of an optimistic attitude; and efforts to resume activities of daily life as much as possible.

Civilian trauma survivors with ASD were found to engage in the cognitive strategies of punishment and worry more than survivors without ASD (Warda and Bryant 1998), and CBT has been shown to reduce these strategies and increase the use of reappraisal and social control strategies (Bryant et al. 2001). Social control strategies allow for thought control as a means of managing intrusive thoughts about the trauma in a social context. Reappraisal allows a trauma survivor to functionally manage unwanted thoughts and interpret their trauma in a more adaptive manner. As has been found in treatment outcome research with PTSD, there is evidence that CBT for acute symptoms following trauma exposure has had positive results in reducing the frequency and intensity of problematic symptoms. When examining published randomized clinical trials, four out of five found that individuals receiving CBT experienced greater reduction in acute PTSD symptoms than their comparison groups (Brom et al. 1993, Bryant et al. 1998, 1999, Echeburua et al. 1996, Gidron et al. 2001). In a more recent longitudinal outcome study (Bryant et al. 2006), researchers found that CBT reduced reexperiencing and avoidance symptoms at a 3-year follow-up more so than supportive counseling, suggesting the long-term benefits of early CBT for trauma survivors.

There is sparse investigation as to whether early recognition and effective treatment of acute stress reactions prevent the development of PTSD, although it is safe to assume that they are likely to have beneficial effects in this regard. There was one study reviewed with motor vehicle accident survivors that suggested exposure therapy, and exposure therapy with anxiety management training may be effective in preventing PTSD (Bryant et al. 1999). A more recent technique, critical incident stress debriefing (Mitchell and Everly 2000), has been described as an intervention designed to prevent the development of PTSD but has been found to be ineffective (Carlier 2000, Carlier et al. 2000). Psychological debriefing has been a controversial topic within the trauma literature and has yielded inconsistent efficacy findings. A recent review of randomized clinical trials using debriefing found that there is no conclusive evidence to support using this intervention with acute trauma cases (Litz et al. 2002).

Clinical Vignette 1

Ben, a 9-year-old third grader, developed PTSD when a drunken driver struck a car in which Ben was riding. Ben's mother was severely injured, and Ben broke his left arm and left lower leg. He recalled being extremely frightened as the car careened out of control, coming to rest upside down. However, his worst moments came when he saw the emergency helicopter taking his unconscious mother to the hospital. Ben believed that she was dead or would die and thought that he too might die without her there to help him.

Despite an excellent medical outcome and full recovery for both Ben and his mother, he developed characteristic

Clinical Vignette 1 *continued*

PTSD symptoms, including intrusive images, dreams, and traumatic play; avoidance of being driven in cars and compulsive reassurance seeking; affective constriction; and mild hyperarousal. (Ben's mother had no memory of the event and was free of emotional sequelae.) Because of significant disturbances in memory and concentration and worsening school performance, Ben's teacher entertained the possibility of attention-deficit hyperactivity disorder. However, the consulting psychologist, recognizing the absence of hyperactivity symptoms before age 7 and the relationship between Ben's school problems and the life-threatening accident, made the correct diagnosis of PTSD.

Treatment consisted of cognitive–behavioral psychotherapy, including psychoeducation, anxiety management training, and exposure. The family members and Ben's teacher were involved in all steps of the treatment program; Ben was symptom free after 12 weekly treatment sessions and remained in remission 1 year later.

Clinical Vignette 2

Mr. R, a 34-year-old married man, was referred for medication management by his counselor. He had been healthy until a life-endangering airplane accident 2 years earlier, in which all passengers were killed except for him. He was still experiencing intrusive memories and reliving of the event when seen, despite having had helpful individual counseling. The events of the accident were engraved in his memory with much clarity, and he could not understand how he survived. He was physically injured, with a broken ankle, severe lacerations of his arm, and damage to his back and face. Whenever he saw a plane, he experienced a resurgence of symptoms, and he was unable to take airplane trips. Whenever he rode in an elevator, the sensations he experienced while ascending or descending reminded him of the incident, and he became upset. He experienced hundreds of nightmares relating to the accident, felt as if he were constantly waiting for something bad to happen, and often found it impossible to direct his attention and his mind away from trauma images and memories. He had become fearful of even going to sleep. There was a general reduction of interest in things, and many of his former hobbies no longer gave him any pleasure. He found doing his job to be extremely difficult and thought about quitting. He revisited the site of the accident on each anniversary.

The initial treatment plan recognized that he had already received helpful individual counseling, the focus of which had been on reliving and retelling the story, accepting the painful consequences, and dealing with feelings of guilt because of his survival. Although he recognized the usefulness of these approaches, the intensity of his symptoms continued to be distressing and troublesome. As a result, it was agreed to initiate treatment with sertraline (25 mg), increasing upward to 50 mg after a week, supplemented by clonazepam (0.25 mg) at night, largely to facilitate sleep and reduce hyperarousal and startle response. It was explained to Mr. R that the sertraline would be expected to help more with the intrusive and avoidant and numbing symptoms. He also completed two self-rating scales for PTSD, the Impact of Events Scale (IES) (Keane et al. 1988) and the Davidson Trauma Scale (DTS) (Davidson et al. 1997). The baseline IES score was 47 (range of scores is 0–88), and the baseline DTS score was 101 (range of scores is 0–136). After 5 weeks, the dose of sertraline was increased to 100 mg/day and the dose of clonazepam remained at 0.25 mg. By the sixth week, his symptom distress was much less, with an IES score of 22 and a DTS score of 49. In other words, there was a greater than 50% reduction of symptoms. On an everyday level, he noticed much less avoidance of going into situations reminding him of the trauma, reduced frequency and severity of nightmares and daytime recollections, and greater ability to focus on important tasks related to his work and family. However, he continued to describe persistent startle response.

Mr. R did not continue his individual therapy, feeling that he had maximal benefit after receiving this form of treatment for more than a year. He continued with his medication for another year and noticed improved ability to deal with situations that might have been extremely distressing to him, including being a direct witness to a fatal traffic accident. He was still unable to take airplane trips. At one point during his medication management, he unilaterally opted to discontinue his medication without discussing it because he experienced sexual difficulties, including a loss of sex drive, which was particularly vexing to him, as he and his wife were attempting to start a family. The use of cyproheptadine proved to be helpful in counteracting this side effect. He was also involved in litigation after the accident and recognized that it was going to be extremely protracted. The litigation also brought with it a whole new set of problems, in which he felt himself being put in the victim position. He acknowledged that, although much progress had been made and he was much more highly functional, "nothing is quick with this condition" and that he still had a number of symptoms. He was willing to consider the possibility of additional treatment focused on his fear of flying. He also recognized that when he had stopped his medicine, the symptoms came back with a vengeance, and at present he became more compliant in taking his antidepressant and anxiolytic medications.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 diagnostic criteria for research for PSTD provides a different stressor criterion: a situation or event "of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost everyone," which is similar to the DSM-III-R definition of a traumatic stressor. DSM-IV-TR instead defines a traumatic stressor as "an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others." Furthermore, the ICD-10 diagnostic algorithm differs from that specified in DSM-IV-TR in that the DSM-IV-TR criterion D (i.e., symptoms of increased arousal) is not required. In contrast to DSM-IV-TR, which requires that the symptoms persist for more than 1 month, the ICD-10 diagnostic criteria for research do not specify a minimum duration.

For ASD, the ICD-10 diagnostic criteria for research differs in several ways from the DSM-IV-TR criteria: (1) primarily anxiety symptoms are included; (2) it is required that the onset of the symptoms be within 1 hour of the stressor; and (3) the symptoms must begin to diminish after not more than 8 hours (for transient stressors) or 48 hours (for

extended stressors). In contrast to DSM-IV-TR, the ICD-10 diagnostic criteria for research does not require dissociative symptoms or that the event be persistently reexperienced.

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CHAPTER 73

# Anxiety Disorders: Generalized Anxiety Disorder

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## Diagnosis

### Definition and Diagnostic Features

Generalized anxiety disorder (GAD) was first defined in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association (APA) 1980). Introduced as a residual category, GAD was diagnosed only if a patient failed to meet criteria for any other Axis I disorder. The diagnostic criteria were revised substantially in DSM-III-R and DSM-IV-TR to define patients' worries as "excessive" and "uncontrollable" and to stipulate that worry must be present more days than not for at least 6 months (APA 1987, 1994). The DSM-IV-TR definition of GAD also requires three of six associated symptoms: sleep disturbance, difficulty concentrating, restlessness, irritability, fatigue, and muscle tension. At least some of these symptoms must be present more days than not for 6 months. To warrant a diagnosis of GAD, an individual's worry and associated symptoms must result in clinically significant impairment or distress. Although no longer a residual diagnosis, GAD is not diagnosed if the patient's symptoms occur exclusively during a mood disorder, psychotic disorder, posttraumatic stress disorder (PTSD), or pervasive developmental disorder.

#### Revisions to Diagnostic Criteria

Despite several revisions to the diagnostic criteria, GAD remains among the least reliably diagnosed anxiety or mood disorders (Brown et al. 2001b). This diagnostic unreliability has prompted criticism of the definition of GAD and proposals for revisions to the diagnostic criteria. Although there is consensus that the core feature of GAD is worry or anxious apprehension, debate about the validity and clinical utility of the DSM-IV-TR criteria continues.

##### *Worry Criterion*

The GAD worry criterion has elicited numerous criticisms and undergone extensive revisions. In DSM-III-R, the key feature of GAD was defined as excessive and/or unrealistic worry in two or more spheres unrelated to another Axis I disorder. The minimum duration of the symptoms was also lengthened from 1 to 6 months in DSM-III-R, thereby clarifying the boundary between GAD and nonpathological worry or adjustment disorders. Recently, however, Kessler et al. (2006) argued that there is little empirical basis for the current duration criterion. The requirement that worries be "unrealistic" was removed in response to arguments that this criterion was difficult to assess (Abel and Borkovec 1995). The DSM-IV-TR definition of GAD specifies that worries must be "excessive," pervasive (i.e., occurring more days than not for at least 6 months), and uncontrollable. There is, however, considerable variability in how clinicians determine if a worry is excessive, leading Ruscio et al. (2005) to argue that individuals with nonexcessive worry may warrant a diagnosis of GAD.

##### *Associated Symptoms Criterion*

The current associated symptoms criterion represents a substantial shift from previous editions of the DSM. The DSM-III criteria required that four major symptom groups accompany worry: motor tension, autonomic hyperactivity, apprehensive expectation, and vigilance and scanning (APA 1980). In DSM-III-R, a diagnosis of GAD required the presence of at least six of 18 associated symptoms, which formed three clusters (autonomic hyperactivity, motor tension, and vigilance and scanning). In diagnostic interviews, however, patients with GAD endorsed symptoms of autonomic hyperactivity less frequently than symptoms from the other clusters (Brawman-Mintzer et al. 1994). In DSM-IV-TR, only the six most commonly endorsed symptoms from the motor tension and vigilance and scanning clusters were retained (Marten et al. 1993). Despite these empirically driven revisions, both the DSM-III-R and the DSM-IV-TR associated symptoms criteria lack specificity and fail to adequately discriminate patients with GAD from those with depressive disorders (Brown et al. 1995). Indeed, several of the associated symptoms of GAD, including sleep

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disturbance, difficulty concentrating, and fatigue, are identical to symptoms of major depressive disorder (MDD) and dysthymic disorder. There is, however, evidence that certain symptoms may be differentially associated with worry and depression, with muscle tension exhibiting perhaps the clearest relationship with GAD (Joormann and Stöber 1999).

### Discriminant Validity

Debate over the diagnostic criteria for GAD reflects the conceptual confusion surrounding the disorder. GAD was retained as a formal diagnosis in DSM-IV-TR despite arguments that it did not constitute a separate disorder but consisted of symptoms that could be subsumed under other diagnostic categories (Brown et al. 1994). There is evidence of GAD's poor discriminant validity, which is perhaps not surprising, given the extensive overlap of GAD's diagnostic criteria with those of other anxiety and mood disorders. In a study conducted with a large clinical sample, 65% of patients diagnosed with GAD met criteria for an additional mood or anxiety disorder diagnosis (Brown et al. 2001a). This finding lends support to the argument that GAD represents the "basic" anxiety disorder in that its core feature, anxious apprehension, is present in all anxiety disorders (Barlow et al. 1996). GAD features, which overlap significantly with the higher-order trait of negative affect, may also be conceptualized as vulnerability dimensions for other emotional disorders (Brown et al. 1998). In light of the extensive comorbidity among anxiety and mood disorders, some have argued in favor of a "general neurotic syndrome" that assumes a homogenous diathesis for a heterogeneous expression of symptoms and collapses the spectrum of anxiety and mood disorders into a single entity (Andrews 1996, Andrews et al. 1990). The results of a large-scale study, however, have clarified the distinction between GAD and depression (Brown et al. 1998). In this study of a mixed clinical sample, five DSM-IV-TR constructs (mood disorders, GAD, panic disorder/agoraphobia, obsessive-compulsive disorder (OCD), and social phobia) were defined by questionnaires and clinical interview ratings. The outcome of confirmatory factor analysis supported a five-factor model, rather than a model in which features of GAD and mood disorders were collapsed under a single factor. Correlations among the five factors did suggest areas of overlap. The GAD factor, for example, was most strongly associated with the mood disorder factor, and the OCD factor was most highly correlated with the GAD factor. These patterns of associations are not surprising, given the overlap between GAD and depression and GAD and OCD, as discussed below.

### Structural Relationships among Dimensions of Anxiety and Mood Disorders

The aforementioned study examined relationships of dimensional features of DSM-IV-TR disorders and features of the tripartite model of anxiety and depression (Clark and Watson 1991). This model proposes a structure of anxiety and depression consisting of negative affect (or general distress), which is associated with both anxiety and mood disorders; physiological hyperarousal, which is specific to anxiety disorders; and low positive affect (or anhedonia), which is specific to mood disorders. Consistent with theoretical predictions about the nature of anxiety and mood disorders (Clark et al. 1994), the negative affect factor was significantly related to all five disorder constructs (most strongly with GAD and depression), whereas positive affect was significantly inversely related to depression and social phobia only (Brown et al. 1998). In longitudinal analyses, temporal variance in a neuroticism/behavioral inhibition factor fully explained temporal covariance in selected DSM-IV-TR disorder constructs, including GAD (Brown 2007). Consistent with cross-sectional findings, positive affect/behavioral activation predicted significant additional variance in the depression and social phobia latent factors, but not in the GAD factor. Contrary to the predictions of the tripartite model, autonomic arousal in cross-sectional analyses was significantly associated only with the panic disorder/agoraphobia factor (Brown et al. 1998). When negative affect was held constant, the GAD and autonomic arousal factors were inversely related (such that higher levels of worry were associated with lower levels of autonomic arousal). This finding is consistent with laboratory studies of GAD (e.g., Thayer et al. 1996) that indicate an association between worry and autonomic suppression. In summary, negative affect is significantly related to both anxiety and depression, whereas low positive affect is uniquely associated with depression and social phobia. These data suggest a hierarchical relationship between dimensions of temperament and disorder constructs, with neuroticism perhaps serving as a vulnerability factor for several emotional disorders. Despite their phenomenological similarities, GAD and depression may be distinguished by their differential associations with positive affect. Furthermore, GAD is not associated with heightened physiological arousal (after controlling for general distress/negative affect), a finding consistent with the removal of symptoms of physiological arousal from the DSM-IV-TR associated symptoms criterion.

## Assessment

### Diagnostic Reliability

Several large-scale studies have examined the diagnostic reliability of GAD using semistructured clinical interviews. Based on two independent administrations of the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (ADIS-IV-L), one study indicated that GAD possessed only fair diagnostic reliability (kappa = 0.65) (Brown et al. 2001b). Many cases of inter-rater disagreement involved boundaries between GAD and other disorders, particularly MDD, dysthymic disorder, and anxiety disorder not otherwise specified (NOS). In disagreements involving an anxiety disorder NOS diagnosis, both interviewers agreed that clinically significant symptoms were present, but one did not assign a formal diagnosis of GAD because the number, duration, or severity of symptoms did not meet diagnostic threshold. The most common source of diagnostic disagreement (55%) was difference in patient report, suggesting that the DSM-IV-TR criteria are vague or lack clear, behavioral anchors. Although revisions to the DSM criteria have resulted in improved diagnostic reliability for GAD (Di Nardo et al. 1993), the disorder remains among the least reliably diagnosed anxiety or mood disorders.

#### *Self-Report Measures*

Scores on self-report measures may assist clinicians in distinguishing patients with GAD from those with other emotional disorders (see Table 73–1). Individuals with GAD receive significantly higher scores on the Penn State Worry

**Table 73–1 Assessment Instruments for GAD in Adults**

| Method of Assessment | Measure |
|---|---|
| • Self-report measures | Penn State Worry Questionnaire (PSWQ, Meyer et al. 1990) |
| | Worry Domains Questionnaire (Tallis et al. 1992) |
| | Worry Scale for Older Adults (Wisocki 1988) |
| | Generalized Anxiety Disorder Questionnaire-IV (GADQ-IV, Newman et al. 2002) |
| | Depression Anxiety Stress Scales (Lovibond and Lovibond 1995) |
| | Anxious Thoughts Inventory (Wells 1994) |
| | Intolerance of Uncertainty Scale (IUS, Buhr and Dugas 2002) |
| • Self-monitoring forms | Worry records/diaries in which client records intensity and content of worry, thoughts and physical sensations experienced during worry episodes, and behavioral responses to worry |
| • Structured interviews | Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (ADIS-IV-L, Di Nardo et al. 1994) |
| | Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-IV, First et al. 1997) |
| | World Health Organization Composite International Diagnostic Interview (WHO-CIDI, Kessler et al. 2004) |

Questionnaire (PSWQ), a psychometrically valid measure of trait worry (Meyer et al. 1990). The PSWQ also differentiates patients with GAD from those with OCD (Brown et al. 1992, 1993). Other self-report measures designed to assess worry include the Worry Domains Questionnaire (Tallis et al. 1992) and the Worry Scale for Older Adults (Wisocki 1988). The Depression Anxiety Stress Scales (DASS, Lovibond and Lovibond 1995) are useful in the assessment of GAD as well as other emotional disorders. The DASS is a 42-item questionnaire consisting of three distinct subscales. The stress subscale, which assesses general negative affect and tension, is strongly correlated with the PSWQ (Brown et al. 1995). The Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV, Newman et al. 2002) is a brief screening measure based on DSM-IV-TR criteria. Although GAD-Q-IV scores evidence moderate concordance with the results of structured interviews (kappa = 0.67), clinicians should not diagnose GAD on the basis of self-report scores alone.

## Structured Interviews

The ADIS-IV-L (Di Nardo et al. 1994) is the most widely used interview measure of GAD. Designed to assess both current and lifetime anxiety and mood disorders, the ADIS-IV-L also enables dimensional assessment of GAD symptoms, regardless of whether a formal diagnosis is under consideration. The clinician rates the excessiveness and controllability of several domains of worry and the associated symptoms on a zero to eight scale, with zero indicating the absence of a symptom and eight indicating the most severely interfering and distressing manifestation of the symptom. The assessment of these disorder features along continua allows for the determination of disorder severity and the presence of subthreshold symptoms. Dimensional data may also be more useful than categorical, presence–absence ratings in measuring outcomes of clinical trials (e.g., Brown and Barlow 2005) and as dimensional indicators in studies of latent structure (e.g., Brown et al. 1998). The Structured Clinical Interview for DSM-IV-TR Axis I Disorders also contains a diagnostic section on GAD and has good psychometric properties (SCID-IV, First et al. 1996). The Hamilton Anxiety Rating Scale (HARS; Hamilton 1959) is a 14-item clinician-administered interview designed to assess the severity of anxiety symptoms. Although not designed to assess GAD symptoms in particular, the HARS is frequently used as an outcome measure in treatment trials (e.g., Rickels et al. 2003, Stanley et al. 2003). The HARS contains two subscales that assess psychological and somatic symptoms of anxiety. Unfortunately, the HARS may fail to adequately discriminate between anxiety and depression (Moras et al. 1992). The World Health Organization (WHO) Composite International Diagnostic Interview (WHO-CIDI, Kessler et al. 2004) is a fully structured lay-administered interview that may be used to assign both DSM-IV-TR and *International Classification of Diseases* (10th ed, ICD-10) diagnoses. The WHO-CIDI, which has demonstrated adequate inter-rater and test–retest reliability, is often used in epidemiological research (Andrews and Peters 1998).

## ICD-10 Criteria

Although the diagnostic criteria for GAD found in the WHO's ICD-10 are similar to the DSM-IV-TR criteria, the differences may be substantial enough to affect prevalence estimates. The ICD-10 definition of GAD, for example, requires at least 6 months of "prominent" tension and worry accompanied by at least four of 22 associated symptoms (see Table 73–2). Notably, the ICD-10 definition does not require that worry be "uncontrollable," that the symptoms of GAD occur outside the context of a mood disorder, or that they

**Table 73–2 Comparison of DSM-IV-TR and ICD-10 Criteria for GAD**

| DSM-IV-TR | ICD-10 |
|---|---|
| • 6 months of "excessive" and "uncontrollable" worry | • 6 months of "prominent" tension and worry |
| • Three of six associated symptoms | • Four of 22 associated symptoms, at least one of which must be indicative of autonomic arousal (e.g., heart palpitations, sweating, trembling or shaking, or dry mouth) |
| • Symptoms cause "clinically significant" impairment or distress | • No clinical significance criterion |
| • Diagnosis not assigned if symptoms occur during the course of major depressive disorder or dysthymic disorder | • Diagnosis not assigned if symptoms occur during course of phobic anxiety disorder, panic disorder, or hypochondriacal disorder |

meet a "clinical significance" criterion. Differences in the two criterion sets resulted in poor inter-rater agreement on large, epidemiological study (Slade and Andrews 2001). Of the 151 people diagnosed with DSM-only GAD, 72 did not meet criteria for the ICD-10 diagnosis because they did not experience one of the four symptoms of autonomic arousal. The remaining 79 individuals did not receive the ICD-10 diagnosis because they also met criteria for panic disorder, phobic anxiety disorder, or OCD. Of the 201 individuals with ICD-only GAD, 144 failed to meet the DSM-IV-TR requirement that worries be excessive and 70 failed to meet the interference/distress criterion. Importantly, individuals with DSM-only diagnoses reported more functional impairment than individuals with ICD-only diagnoses, suggesting that the two criteria sets describe somewhat different syndromes.

## Epidemiology

Prevalence estimates of GAD vary widely, depending on the diagnostic criteria used and the population examined. The National Comorbidity Survey Replication (NCS-R), which entailed structured interviews of over 9000 individuals in the United States, obtained prevalence estimates of 3.1% and 5.7% for 12-month and lifetime GAD, respectively, using DSM-IV-TR criteria (Kessler et al. 2005a, 2005b). Lifetime prevalence rates were lowest among 18–29-year olds (4.1%) and individuals 60 years or older (3.65%), with the highest rates found among 45–59-year-olds (7.7%). Of those diagnosed with 12-month GAD, 32.3% experienced a "serious" degree of disability, characterized by a suicide attempt, impairment in multiple roles, bipolar I or II disorder, affective psychosis, violent behavior, or significantly impairing substance dependence. Another large-scale study found a 12-month prevalence rate of 2.07%, with the estimate substantially higher (4.2%) among those also meeting criteria for a 12-month substance abuse disorder (Grant et al. 2004). The lifetime prevalence rate was estimated at 4.1%. Sociodemographic factors associated with increased risk included being female, middle aged, unmarried, and with low income, whereas being black, Asian, or Hispanic decreased risk (Grant et al. 2005).

Prevalence estimates of GAD have been significantly affected by changes in the diagnostic criteria. For example, the lifetime prevalence for DSM-III GAD was estimated as high as 45%, but this figure dropped to 9% under the more stringent DSM-III-R criteria (Breslau and Davis 1985). More recently, researchers have noted that alterations in the DSM-IV-TR criteria for GAD may dramatically affect prevalence rates. Ruscio et al. (2005) found that disregarding the excessiveness criterion resulted in a 40% increase in prevalence estimates. Although GAD with excessive worry was associated with an earlier onset, more chronic course, and greater comorbidity, GAD patients with nonexcessive worry exhibited significant impairment and high rates of treatment seeking. Subthreshold cases of GAD that failed to meet the duration, excessiveness, and associated symptoms criteria were associated with significantly elevated risk for subsequent psychopathology (Ruscio et al. 2007). Although the diagnostic criteria for GAD have been revised substantially, questions remain about their sensitivity and specificity. Revisions to the criteria may not only alter our understanding of GAD's clinical features, but also dramatically affect the prevalence of the disorder.

### Comorbidity Patterns

Large-scale studies have indicated that most individuals diagnosed with GAD meet criteria for at least one additional diagnosis. In one study using a large clinical sample, 68% of individuals with a principal diagnosis of GAD met criteria for another Axis I disorder, most frequently MDD, social phobia, or panic disorder with or without agoraphobia (Brown et al. 2001a). Ninety-two percent of individuals with principal GAD met criteria for another lifetime disorder, with 64% meeting criteria for MDD. Notably, adherence to the DSM-IV-TR diagnostic hierarchy rules may lead to significant underestimates of comorbidity. For example, when following these rules, which stipulate that GAD is not diagnosed if its symptoms occur in the context of a mood disorder, only 5% of patients with a principal diagnosis of dysthymic disorder or MDD were also diagnosed with GAD. When the hierarchy rule was ignored, 90% of patients with dysthymia and 67% of patients with MDD also met criteria for GAD. Epidemiological studies have found similar patterns of comorbidity, with GAD most often associated with mood disorders and panic disorder (Wittchen et al. 1994).

GAD is also associated with elevated rates of alcohol and substance use disorders. In one epidemiological study, the prevalence of substance use disorders among individuals with GAD was 19.02%, and the prevalence of an alcohol use disorder was 14.82% (Grant et al. 2005). In another study, 18% of individuals with current principal GAD met criteria for a lifetime alcohol or drug use disorder (Brown et al. 2001a).

Several studies have indicated that GAD is frequently comorbid with irritable bowel syndrome (IBS), a disorder characterized by abdominal pain and abnormal bowel habits (constipation and/or diarrhea) (Blanchard et al. 1990, Sykes et al. 2003). No structural, physiological, or biochemical abnormalities have been found to account for the symptoms, and many studies have indicated that patients with IBS are more likely than healthy controls to have psychiatric illnesses, particularly anxiety and depression (Blanchard et al. 1990). In one study of treatment-seeking IBS patients, 60% also met criteria for GAD (Sykes et al. 2003).

The high rates of comorbidity associated with GAD have important implications for treatment. Higher rates of comorbidity are associated with lower rates of remission and greater likelihood of relapse over 12-year follow-up (Bruce et al. 2005). Nevertheless, Borkovec et al. (1995) demonstrated that treatment of GAD may produce significant improvement in comorbid conditions.

### Course

Many patients with GAD have difficulty pinpointing a clear age of onset or report that their symptoms began in childhood, suggesting a chronic course similar to that observed in personality disorders (Barlow et al. 1986, Sanderson and Wetzler 1991). Several studies, however, have indicated that GAD often begins in adulthood. In one large study with a clinical sample, the mean age of onset was 20.57 years (Brown et al. 2001a). There is some evidence for a bimodal distribution of age of onset in GAD, with earlier-onset GAD associated with higher levels of neuroticism and greater severity and comorbidity (Campbell et al. 2003). In this study, cases of GAD that were not associated with a precipitating stressor were more likely to be of earlier onset, whereas symptoms emerging in adulthood typically

began in the context of mild-to-moderate stress. A longitudinal study of patients with GAD indicated that many patients (46% of women and 56% of men) experienced episodes of full remission, with symptom-free periods lasting longer in women (Yonkers et al. 2003). The perception of GAD as a chronic, unremitting illness may not, therefore, be entirely accurate. Rather, chronic cases may represent a subgroup characterized by greater comorbidity. Notably, in 66% cases of comorbid GAD and MDD, the symptoms of GAD predated the onset of depression, which lends some support to the argument that GAD represents a prodrome of MDD (Brown et al. 2001a). On average, however, GAD onset is over 7 years prior to the onset of MDD, indicating that patients may experience long periods of clinically interfering worry well before they suffer from an episode of depression.

## Differential Diagnosis

Because anxious apprehension is, to some degree, characteristic of all anxiety disorders, assessment of GAD is particularly challenging. Guidelines for differentiating GAD from normal worry and from other emotional disorders are discussed below and in the decision tree presented in Figure 73–1.

### *Nonpathological Worry*

The clinician must determine whether an individual's worry warrants a diagnosis of GAD or whether it constitutes a normal reaction to a stressor. There is evidence that patients with GAD and nonanxious controls differ in the controllability of their worry rather than its content (Borkovec 1994). In one study, 100% of those diagnosed with GAD using DSM-III-R reported difficulty controlling their worry, compared to only 5.6% of the nonanxious comparison group (Abel and Borkovec 1995). Individuals with GAD are more likely than control participants to report that they worry a large percentage of every day, frequently experience untriggered worry, perceive their worry as difficult to control, and have a larger number of worry spheres. Furthermore, those diagnosed with GAD are more likely than controls to report worry about minor matters (Sanderson and Barlow 1990).

### *MDD and Dysthymic Disorder*

GAD shares several diagnostic features with both MDD and dysthymic disorder, including impaired concentration and sleep disturbance. Because of the substantial overlap between GAD and depression, a DSM-IV-TR hierarchy rule stipulates that GAD is not diagnosed if the symptoms have

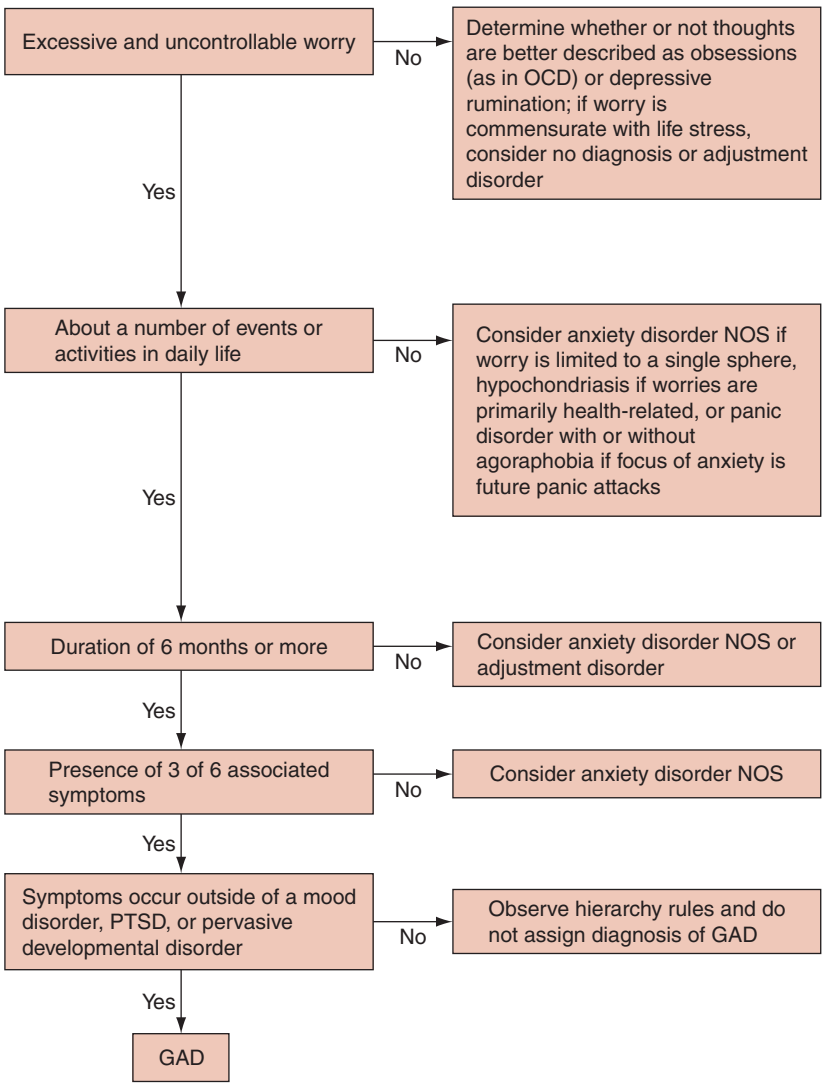



**Figure 73–1** *Diagnostic decision tree.*

occurred within the context of a mood disorder. Therefore, the assessor must determine when the symptoms of GAD onset relative to depression in order to make an accurate diagnosis. Measures of worry and the associated symptoms of GAD have not been effective at differentiating GAD from depression (Brown et al. 1995). The poor discriminability of these questionnaire measures is consistent with the hierarchical model of anxiety and depression, which proposes that negative affect is associated with both anxiety and mood disorders (Brown et al. 1998).

### *Panic Disorder with or without Agoraphobia*

Unlike GAD, panic disorder is characterized by the presence of recurrent, unexpected panic attacks and anxiety about future attacks. Although individuals with GAD may experience panic attacks, the attacks themselves are typically not the focus of their anxiety. Rather, the apprehension is often more diffuse. Patients with GAD are also more likely to experience chronic somatic symptoms rather than the discrete episodes of intense autonomic arousal associated with panic disorder. Although the ICD-10 prohibits diagnosing GAD if its symptoms occur during the course of panic disorder, the DSM-IV-TR does not impose this restriction. A patient experiencing anxiety about future panic attacks as well as excessive, uncontrollable worry about school, family, and minor matters may warrant both diagnoses. One study found that 18% of patients with a current principal diagnosis of GAD also met criteria for an additional diagnosis of panic disorder with or without agoraphobia (Brown et al. 2001a).

### *OCD*

Although OCD is a highly reliable diagnostic category (kappa = 0.75; Brown et al. 2001b), the disorder's phenomenological similarity to GAD has been noted (e.g., Craske et al. 1989). Worry and obsessions may appear similar, as might compulsions and reassurance-seeking behavior. In a review of the literature on obsessions and worry, Turner et al. (1992) concluded that existing data could not point to whether they were distinct phenomena. They noted that obsessions and worry are present to some degree in both clinical and nonclinical populations, often appear similar in form and content, are more frequent and less controllable in clinical populations, are both accompanied by negative affect, and appear to have a shared genetic vulnerability. The DSM-IV-TR offers some guidelines for differentiating obsessions and worry. The definition of OCD, for example, specifies that obsessions are not simply excessive worries about real-life problems. Rather, OCD is characterized by preoccupations that are intrusive and often ego-dystonic, or bizarre and alien to the individual (Rachman 1973). Furthermore, intrusive thoughts in OCD may elicit a phobic or panic reaction and are typically avoided or resisted, whereas worry thoughts, even if intrusive or repetitive, are typically not resisted (Steketee and Barlow 2002). Worry and obsessions may also exhibit differences in form. Worry is a predominantly verbal/linguistic process, whereas obsessions may take the form of impulses or images.

A large-scale study of the structural relationships among disorder features supports the notion that GAD and OCD overlap significantly (Brown et al. 1998). In this study, GAD exhibited the highest degree of overlap with other DSM-IV-TR diagnosis factors, as well as significant overlap with a nonspecific negative affect factor. The OCD latent factor was most strongly correlated with the GAD factor ($r = 0.52$), a finding perhaps attributable to similarity between chronic worry and obsessions, which both may be conceptualized as excessive and/or uncontrollable cognitive processes associated with negative affect.

Despite the similarity between chronic worry and obsessions and the structural relationships between the disorder constructs, a low rate of co-occurrence has been observed between OCD and GAD in some clinical studies (Brown et al. 2001b, 1993), whereas others have reported that over 30% of adults with OCD have a lifetime history of GAD (Andrews et al. 1990, Crino and Andrews 1996). In a sample consisting of 31 patients with a principal diagnosis of OCD and 46 with a principal diagnosis of GAD, patients with GAD were more likely to describe themselves as worriers and/or worry about minor matters than were patients with OCD, and patients ultimately diagnosed with OCD were more likely to respond affirmatively to interview screening questions for obsessions and compulsions (Brown et al. 1993). In addition, patients with OCD received significantly higher scores on a self-report measure of obsessions than did patients diagnosed with GAD, although significant correlations between scores on measures of obsessions and compulsions and worry were observed. Other studies have also indicated similarities between compulsions in OCD and worry-driven behaviors in GAD. In one sample, over half of the patients with GAD reported engaging in some "corrective, preventative, or ritualistic" act in response to their worry (Craske et al. 1989). A measure of thought–action fusion, or the tendency to assume causal relationships between one's own thoughts and the external world (Rachman 1993), has been used to differentiate obsessions from worry in an undergraduate sample, although this finding has not been replicated in a clinical sample (Coles et al. 2001). Studies on nonclinical samples have also indicated that individuals are more aware of the triggers of worry than of obsessions and that they consider obsessions less voluntary, although worry content and the presence of worry are more distressing than obsessions (Langlois et al. 2000).

Despite the shared variance between worry and obsessions and compulsions, the diagnoses can be reliably distinguished from another by trained interviewers. In a large-scale reliability study, diagnostic disagreements involving OCD were relatively uncommon; in the two disagreements involving another disorder, the other disorder involved was anxiety disorder NOS (Brown et al. 2001a). The low rate of co-occurrence of GAD and OCD and the high diagnostic reliability for OCD observed in these samples may indicate that interviewers observed features of both disorders in patients but subsumed the features of one under the principal diagnosis. This interpretation is unlikely, however, given the absence of diagnostic disagreements involving principal diagnoses of OCD and GAD. Although worry and obsessions are phenomenologically similar, this study indicates that OCD and GAD may be reliably differentiated. Nevertheless, there remains no definitive method by which to distinguish worries from obsessions.

### *Hypochondriasis*

Patients with GAD often report worrying about their own health and the health of significant others. A diagnosis of hypochondriasis may be considered, however, if a patient's

worry is predominantly about his or her health, rather than about a variety of topics. Hypochondriasis is also characterized by strong belief conviction, even in the face of contrary evidence, that one has a physical illness. Although patients with GAD may exhibit future-oriented worry about contracting or developing a disease, they are less likely than individuals with hypochondriasis to believe that they currently have an illness.

### *Anxiety Disorder Due to a Medical Condition*

Several medical conditions are associated with prominent symptoms of anxiety. Self-reported anxiety is a significant predictor of functional impairment in a variety of medical conditions, although is most common in individuals with digestive ailments (Marcus et al. 1997). Thyroid dysfunction, particularly hyperthyroidism, has long been associated with increased risk of generalized anxiety and panic attacks (Denicoff et al. 1990, Greer et al. 1973). Although the magnitude of this increased risk is unclear, practitioners may consider thyroid function testing in previously unscreened patients (Simon et al. 2002).

## Differences in Gender and Cultural Presentations

A robust finding of epidemiological studies is that GAD is approximately twice as common among women as among men (e.g., Wittchen et al. 1994). Few studies have examined cross-cultural differences in GAD, and there has been little indication that the prevalence or expression of symptoms differs reliably between cultural groups. In the National Comorbidity Survey, race, education, income level, and urbanicity were not unique predictors of risk for GAD (Wittchen et al. 1994). Another large epidemiological study, the National Epidemiologic Survey on Alcohol and Related Conditions, found that being female, unmarried (widowed, separated, or divorced), and having low income increased risk of GAD, whereas being black, Asian, or Hispanic decreased risk (Grant et al. 2005). There is some evidence that the lower risk for GAD may be found only among younger cohorts and be more pronounced among groups with less education (Breslau et al. 2005). In a large, nonclinical sample, African Americans, Asian Americans, and Caucasians did not differ in their scores on several measures of worry severity, although there were group differences on a questionnaire examining worry in particular domains (Scott et al. 2002). African Americans reported less worry than both other groups regarding relationships, self-confidence, and work. It is possible that more culturally relevant measures of worry may tap domains not assessed by commonly used self-report measures. Several epidemiological studies have examined the prevalence of GAD in various cultural groups. Studies in non-US populations have found lifetime prevalence rates of 0.8% in Germany (Wittchen et al. 1998), 3.7% in South Africa (Bhagwanjee et al. 1998), and 3.3% in Singapore (Lim et al. 2005).

# Etiology and Pathophysiology

Evidence from genetics, neurobiology, and psychology suggests a multifactorial etiology for GAD, consistent with Barlow's (2000) proposed triple vulnerabilities model. This model posits that anxiety disorders result from the combination of a general biological vulnerability, a general psychological vulnerability, and a specific psychological vulnerability. Evidence for each of these vulnerabilities is discussed further below.

## Genetic Factors

Studies examining genetic vulnerabilities for mental disorders have generally supported the notion that a shared vulnerability underlies anxiety disorders (Hettema et al. 2005). A meta-analysis of genetic epidemiology studies has also indicated that several anxiety disorders (including panic disorder, GAD, phobias, and OCD) aggregate in families and that the major source of familial risk is genetic (Hettema et al. 2001). Family and twin studies have also indicated a modest contribution of genetic factors to the development of both GAD and neuroticism. Notably, a large-scale twin study found that the genetic factors associated with neuroticism were indistinguishable from those conferring risk for GAD (Hettema et al. 2004), consistent with the high degree of overlap between neuroticism and GAD that has been observed in structural analyses (Brown et al. 1998). GAD and neuroticism shared only a modest proportion of individual environmental risk factors. Twin studies have also indicated substantial overlap in the genetic factors conferring risk for neuroticism and a variety of other internalizing disorders (Hettema et al. 2006), which is perhaps not surprising given the structural relationships observed between neuroticism and depression, GAD, social phobia, and OCD. Twin studies have also pointed to a shared genetic diathesis for depression and GAD. In a large-scale study of female twins, Kendler et al. (1992) found evidence of a completely shared genetic vulnerability for GAD and MDD. In contrast, the two disorders shared only some environmental risk factors, suggesting that nonfamilial environmental factors (e.g., stressful life events) determine whether an individual develops symptoms of depression or chronic anxiety.

Extant genetic research has focused on identifying shared genetic vulnerabilities for emotional disorders through twin studies, although researchers have begun to look more specifically at the genes associated with these disorders. Linkage studies have identified several genes that may confer risk for anxiety disorders (e.g., Thorgeirrson et al. 2003), but more studies are necessary to link particular genes with symptoms of emotional disorders.

## Neurobiological Factors

### *Autonomic Function*

An association between chronic anxiety and autonomic inflexibility, or an apparent restriction of sympathetic activation, has been demonstrated in several physiological studies (Hoehn-Saric et al. 2004, Thayer et al. 1996). Although it has been associated with a variety of emotional disorders, including panic disorder, autonomic inflexibility may be particularly relevant to GAD due to its association with the worry process (Friedman and Thayer 1998, Hoehn-Saric et al. 2004). Borkovec (1994) has proposed that worry is a verbal/linguistic process that serves to modulate the experience of anxiety and prevent the full processing of emotionally charged stimuli. In accordance with this view, psychophysiological studies have shown that worry is associated with restricted sympathetic arousal and low vagal tone

(Thayer et al. 1996). Even among control participants, worry is associated with decreased parasympathetic variability relative to baseline and relaxation conditions. In contrast, patients with GAD show greater muscle tension at baseline and in response to psychological challenge than control participants (Hazlett et al. 1994, Hoehn-Saric et al. 1989). These findings are consistent with structural analyses indicating that GAD, unlike other anxiety disorders, is not associated with autonomic hyperarousal when levels of negative affect are held constant (Brown et al. 1998).

### *Neurotransmitter Abnormalities*

Several neurotransmitter systems have been implicated in the etiology and maintenance of GAD. Because benzodiazepines are effective in reducing some symptoms of anxiety, researchers have speculated that individuals with GAD exhibit abnormalities in benzodiazepine receptor binding and distribution. One study has found decreased binding in the left temporal lobe of patients with GAD (Tiihonen et al. 1997). Results from studies examining plasma levels of norepinephrine in patients with GAD have been equivocal (Kelly and Cooper 1998, Mathew et al. 1982). GAD has been associated, however, with blunted growth hormone response to clonidine challenge tests, which assess noradrenergic receptor sensitivity (Abelson et al. 1991). Although selective serotonin-reuptake inhibitors (SSRIs) are widely used in the treatment of GAD, there is modest evidence of serotonin abnormalities in patients with GAD. Germine et al. (1992) examined emotional response to *m*-chlorophenylpiperazine, a serotonin agonist, in patients with GAD and depression. The depressed patients did not exhibit behavioral changes, but those with GAD experienced increased anxiety and anger. Like other emotional disorders, GAD appears to be associated with alterations in several neurotransmitter symptoms.

### *Neurmoimaging Studies*

Few neuroimaging studies have examined patients with GAD. An early positron emission tomography (PET) study indicated hypermetabolism in the right prefrontal cortex, right posterior temporal lobe, and a portion of the left occipital lobe, and lower metabolic rates in the basal ganglia in patients with GAD compared to control participants (Wu et al. 1991). In a small structural magnetic resonance imaging (MRI) study of children and adolescents, patients with GAD exhibited increased total and right amygdala volume compared to nonanxious controls (DeBellis et al. 2000). Abnormalities in fear circuitry, particularly hyperactivation in the right amygdala, have been observed in adolescents with GAD (McClure et al. 2007). Although suggestive of structural or metabolic abnormalities in patients with GAD, most extant studies have compared individuals with GAD to normal controls, not to patients with other anxiety disorders. It remains unclear, therefore, if the aforementioned findings are specific to GAD or characteristic of all anxiety disorders.

## Psychological Factors

### *Pathological Worry*

Borkovec (1994) has proposed that worry is a verbal–linguistic attempt to avoid future negative events. Worry provides short-term relief from intense levels of anxiety by allowing individuals to escape from aversive cognitions and images but may inhibit processing of anxiety-producing stimuli. Worry, therefore, is akin to situational avoidance in panic disorder; although it alleviates short-term discomfort, it ultimately serves to maintain anxiety through negative reinforcement. For example, a student worrying about an upcoming test might think in abstract terms (e.g., "This is going to be terrible") rather than invoke concrete images of the feared experience. Worry may prevent the complete activation of fear structures in memory, which may be necessary for long-term anxiety reduction (Borkovec and Hu 1990, Foa and Kozak 1986). Worry may also preclude effective problem solving because worry content often skips from one topic to another without resolution of particular problems.

### *Perceived Lack of Control*

Barlow (2002) has proposed that early experiences of uncontrollability may serve as a psychological vulnerability for emotional disorders. In studies with nonclinical samples, social psychologists have demonstrated that maintaining the illusion of control (i.e., the belief that one can affect and cope with events in one's environment) is adaptive (Alloy and Clements 1992, Taylor and Brown 1994, Taylor et al. 2000). Individuals with clinical disorders, including people diagnosed with anxiety disorders, sexual dysfunctions, and depression, often perceive themselves as having little control over their experiences (e.g., Cole and Turner 1993, Ladouceur et al. 1999, Weisberg et al. 2001). Patients with GAD are more likely than controls to perceive a lack of control over threatening events and to regard ambiguous information as threatening (Rapee 1991). This perceived lack of control may result from a variety of events, including trauma and insecure attachment to primary caregivers (Borkovec 1994). In patients with GAD, worry may be an ineffective attempt to assert control over uncertain future events. Intolerance of uncertainty, a construct related to perceived lack of control, has emerged as an important variable in the study of anxiety disorders (Dugas et al. 1998). Defined as the inability to accept that future negative events may occur, intolerance of uncertainty has been associated with symptoms of several anxiety disorders but is greater in individuals with GAD than in patients from a mixed anxiety disorder sample (Ladouceur et al. 1999). There is some evidence that treatment designed to specifically address intolerance of uncertainty is more efficacious than a wait-list control condition in alleviating symptoms of GAD (Ladouceur et al. 2000).

## Social/Environmental Factors

Barlow's (2000, 2002) model of the etiology of anxiety disorders posits that psychological and biological vulnerabilities may interact with stressful life events to produce clinical-level anxiety symptoms. As previously mentioned, stressful life events may play a differential role in the onset of early- and late-onset GAD (Campbell et al. 2003). Twin studies have suggested that GAD is only modestly heritable and largely determined by environmental influences (Hettema et al. 2001). Furthermore, although the genetic factors conferring risk for GAD and neuroticism overlap almost entirely, there is only modest overlap between the environmental risk factors (Hettema et al. 2004). The nature of the stressors that precipitate the onset of GAD remains unclear. In one study, 52% of individuals diagnosed with GAD reported

experiencing at least one past traumatic event (i.e., an event that would satisfy criterion A of the DSM-IV-TR definition of PTSD), whereas only 21% of nonanxious controls did, although it is unclear if the events occurred prior to the onset of the GAD (Roemer et al. 1996).

In summary, current etiological models of GAD propose that the disorder results from a combination of genetic, neurobiological, and psychological factors. Like most mental disorders, GAD is best described by a diathesis-stress model in which biological and psychological vulnerabilities interact with life stress to produce the onset of symptoms.

## Treatment

Many patients with GAD present to their primary-care physicians (PCPs) for treatment of somatic problems, which may include headache, muscle tension, gastrointestinal problems, and fatigue (Roy-Byrne and Wagner 2004, Wittchen 2002). Unfortunately, PCPs infrequently recognize GAD and rarely prescribe psychotherapy or pharmacotherapy (Wittchen 2002), although empirically supported treatments are available.

### Somatic Treatments

The most common pharmacological treatments for GAD include benzodiazepines, azapirones, and SSRIs. Benzodiazepines, which produce short-term sedation, muscle relaxation, and decreased physiological arousal, may provide relief from the somatic symptoms of GAD (Hoehn-Saric et al. 1988). Concerns have emerged, however, about the long-term use of benzodiazepines, which may lead to dependence (Ballenger et al. 2001). Azapirones, which include buspirone, are associated with less risk of dependence than benzodiazepines, although evidence for their efficacy in the treatment of GAD is equivocal (Davidson et al. 1999, Gammans et al. 1992). It is also noteworthy that the use of fast-acting drugs such as benzodiazepines and azapirones may be contraindicated by cognitive-behavioral approaches to GAD, which emphasize the importance of tolerating rather than avoiding the experience of anxiety.

Numerous antidepressants have been evaluated in the treatment of GAD. Two older drugs, trazodone and imipramine, were shown to be as effective as diazepam, although were less effective at alleviating somatic symptoms than psychological symptoms (Rickels et al. 1993). Several trials with newer antidepressants, including SSRIs and serotonin and norepinephrine-reuptake inhibitors (SNRIs), have produced promising findings. In a placebo-controlled trial of paroxetine, an SSRI, 62% and 68% of patients receiving 20 and 40 mg of paroxetine experienced significant symptom reduction, compared to only 46% in the placebo group (Rickels et al. 2003). Venlafaxine, an SNRI, was the first antidepressant approved by the Federal Drug Administration (FDA) for the treatment of GAD based on the results of several large, placebo-controlled trials (Sheehan 1999, Davidson et al. 1999). Unfortunately, there have been no large trials comparing the efficacy of two or more antidepressants in the treatment of GAD.

### Psychosocial Treatments

Cognitive-behavioral conceptualizations of GAD assume that individuals' thoughts and behaviors play a primary role in maintaining their symptoms. Several randomized controlled trials have examined the efficacy of cognitive-behavioral treatment (CBT) packages in individuals with GAD. In general, these studies have indicated that CBT for GAD, although it results in clinically significant improvement, is associated with lower rates of high end-state functioning than CBT for panic disorder (Barlow et al. 2000). Studies typically examine the effects of a CBT package rather than individual components of treatment. Most CBT packages consist of psychoeducation about the nature of anxiety, symptom monitoring, relaxation training, exposure (imaginal and in vivo), and cognitive restructuring. To date, the majority of treatment trials have compared CBT to no-treatment control groups. Those that have compared two or more active treatments have often found no clear evidence of differential efficacy (e.g., Barlow et al. 1992, Borkovec and Mathews 1988), although Borkovec and Costello (1993) found that CBT was associated with higher end-state functioning at follow-up than either applied relaxation training or nondirective treatment. Other studies have indicated that CBT is no more efficacious than nondirective treatments (e.g., Blowers et al. 1987). In an effort to identify active components of treatment, Borkovec et al. (2002) compared groups receiving either applied relaxation or self-control desensitization (i.e., rehearsing relaxation and coping statements in imaginal exercises), cognitive therapy, or a combination of these elements. No group differences were found, suggesting that each component was beneficial. Nevertheless, by 24 months posttreatment, only 52% of individuals in the cognitive therapy condition, 48% in the relaxation/self-control desensitization condition, and 38% in the combined condition met criteria for high end-state functioning.

In a recent meta-analysis of CBT for GAD, Mitte (2005) found that CBT was more efficacious than control conditions, yielding medium to large effect sizes when compared to pill or psychological placebo. In studies directly comparing CBT with pharmacotherapy (most often benzodiazepines), there was no difference in effect sizes between the two treatments. In contrast, an indirect comparison of CBT and pharmacotherapy (which included studies comparing each treatment to a control condition) suggested the superiority of drug treatment. However, attrition was lower for individuals receiving CBT (9%) than for those receiving pharmacotherapy (25%). Currently, neither mode of treatment is unequivocally superior to the other, and there are no large trials comparing combination therapy to either CBT or pharmacotherapy alone. Although elements of CBT packages vary, some common CBT components are discussed below.

#### *Self-Monitoring*

Self-monitoring of symptoms is a component of most cognitive-behavioral approaches. Data obtained by the patient are useful for conducting functional analyses of the patient's anxiety and worry episodes (i.e., determining the situational, psychological, and behavioral antecedents of worry; the methods used by the patient to alleviate anxiety; and the consequences of these actions). An example of a weekly record of mood and anxiety is shown as Figure 73–2. Routine self-monitoring not only allows the patient to gain experience observing and describing his or her symptoms, but also allows the clinician to track the patient's progress over time. Self-monitoring forms may be tailored to the individual

**WEEKLY RECORD OF ANXIETY AND DEPRESSION**

**Each evening, please rate how anxious and depressed you felt that day, as well as how good your day was.**

**Level of Anxiety/Depression/Pleasant Feelings**

**0----------1----------2----------3----------4----------5----------6----------7----------8**

**None A Little Some A Lot As Much as I Can Imagine**

| Date | Average Anxiety | Maximum Anxiety | Average Depression | Average Pleasantness | Percentage of Day Worried |
|---|---|---|---|---|---|
| 1/16 | 3 | 5 | 3 | 3 | 50 |
| 1/17 | 4 | 6 | 4 | 3 | 55 |
| 1/18 | 5 | 6 | 4 | 3 | 70 |
| 1/19 | 6 | 8 | 5 | 2 | 90 |
| 1/20 | 5 | 6 | 4 | 3 | 80 |
| 1/21 | 4 | 6 | 3 | 4 | 70 |
| 1/22 | 5 | 7 | 4 | 4 | 75 |

**Figure 73–2** *Mood and anxiety monitoring form.*

patient and used to track a variety of behaviors (e.g., benzodiazepine use and reassurance-seeking behavior).

### *Psychoeducation*

The nature of anxiety is discussed in order to normalize the patient's experience and distinguish between adaptive and maladaptive anxiety. The clinician and patient discuss biological and psychological factors related to the experience of anxiety, as well as the interaction between the three components of anxiety (i.e., thoughts, physical sensations, and behaviors). The concept of avoidance, or an individual's refusal or hesitation to enter situations or tolerate certain experiences, is introduced, and the clinician explains the role of avoidance in perpetuating the cycle of maladaptive anxiety. The clinician discusses worry as an avoidance strategy that prevents adequate processing of anxiety-provoking stimuli.

### *Cognitive Restructuring*

Cognitive therapy as outlined by Beck and colleagues (1985) is a component of many cognitive-behavioral protocols. Cognitive therapy entails the elicitation of automatic thoughts that serve to maintain patients' anxiety. After automatic thoughts are identified, the therapist and patient work together to evaluate the accuracy and utility of these thoughts. For example, anxious patients often think catastrophically (i.e., focus on the worst possible scenario) and overestimate the probability of negative events. Once the distorted thoughts are identified, patients develop alternative, rational thoughts. For example, a woman with GAD may assume that her husband has gotten into a car accident if he does not arrive home on time. An alternative thought may take into consideration her husband's long commute, the heavy traffic, or the possibility that he stayed late at work. Focusing on distorted cognitions may seem particularly relevant to the treatment of excessive and uncontrollable worry. As discussed below, however, some have questioned the utility of traditional cognitive restructuring in the treatment of GAD.

### *Exposure*

Situational exposures are an important component of CBTs for specific phobias, social phobias, OCD, and PTSD. Although GAD patients may also avoid anxiety-provoking situations, their primary mode of avoidance is worry (Borkovec 1994). Due to the difficulty of planning situational exposures in the absence of a clear phobic target, several CBT protocols for GAD (e.g., Craske et al. 2000) include worry exposures, during which the patient undergoes graded, imaginal exposures to the worst possible outcomes of various worries. During these exposures, the patient holds distressing images in mind for at least 25–30 minutes and then generates alternatives to the worst possible outcome. Throughout the exposure, the patient is asked to provide subjective ratings of their anxiety. After the worry exposure technique is introduced in session, the patient is assigned exposure homework throughout treatment. Even if the patient denies engaging in overt situational avoidance, the clinician should also assess for subtle behavioral avoidance. Patients, for example, may restrict their range of experience due to their excessive worry. Roemer et al. (2002) suggest asking patients what activities they would engage in if they worried less. Clinicians must work with patients to gradually eliminate these forms of avoidance, with the aim of demonstrating that they do not serve any protective function. Because GAD is so frequently comorbid with depression, some treatment protocols also include pleasant events scheduling, an approach intended to increase engagement in enjoyable activities.

### *Relaxation Training*

A traditional component of many anxiety treatment protocols is progressive muscle relaxation (PMR), as described by Bernstein and Borkovec (1973). PMR entails the tensing and relaxing of various muscle groups, with the goal of alleviating physiological symptoms of anxiety. A full, 16-muscle-group PMR session typically lasts 30 minutes, although time spent on PMR is reduced over the course of treatment,

in order to make the exercise more "portable." PMR may be particularly useful in addressing anxiety-related muscle tension. Notably, PMR has also been used in the treatment of IBS, a condition commonly found among GAD patients (Toner et al. 2000).

### *Worry Behavior Prevention*

As previously mentioned, many patients with GAD engage in corrective, preventative, or ritualistic behaviors that resemble the compulsions observed in OCD (Craske et al. 1989). These worry behaviors, which may include frequent telephone calls to family members for reassurance and avoidance of negative news stories, may result in the temporary reduction of anxiety, but also in its long-term maintenance. Once the patient and therapist have identified and monitored these behaviors, the patient will practice refraining from them and observing the consequences of behavior prevention. Often the patient's predictions regarding response prevention are inconsistent with the outcome of the exercise (i.e., the feared outcome does not occur). Gradual reduction of benzodiazepine use may be a target of CBT for anxiety disorders, as some patients use these drugs as avoidance strategies.

### *Additional Components*

Because patients with GAD often report feeling overwhelmed by their obligations, the therapist may introduce basic time management skills (e.g., delegating responsibilities, saying "no" to additional obligations, and adhering to an agenda). Training in problem solving may be included if patients tend to view problems catastrophically or if they have difficulty generating solutions to problems. Although individuals with GAD do not exhibit deficits in problem-solving skills, they may have more difficulty applying these skills than those with less severe worry (Dugas et al. 1998, Ladouceur et al. 1998). Approaches to problem-solving training vary, although Meichenbaum recommends teaching patients to conceptualize problems in specific terms and break them down into small, manageable segments (e.g., Meichenbaum and Jaremko 1983). Once the problem is defined, the patient is taught to brainstorm possible solutions, even those that initially sound unreasonable. Once a list of potential solutions has been generated, the patient selects and acts on the best possible option. These techniques allow patients to focus on real problems rather than imagined catastrophes and prompt them to think differently about difficult situations in their lives.

### *Recent Developments in Psychosocial Treatments*

Newer psychosocial treatments for GAD have integrated acceptance and mindfulness approaches into traditional CBT (Orsillo et al. 2003). These approaches, which include Hayes et al.'s (1999) Acceptance and Commitment Therapy, posit that individuals' efforts to control their internal experience often backfire, resulting in increased anxiety and dissatisfaction. Hayes argues that individuals' reluctance or unwillingness to remain "in contact" with their internal experience (thoughts, sensations, and emotions) may underlie many forms of psychopathology. Newer approaches to GAD treatment also draw from Wells' metacognitive theory, which hypothesizes that individuals with GAD tend to appraise their worry as more threatening and uncontrollable than do normal controls (and yet, paradoxically, believe that it is functional and adaptive) (Borkovec et al. 1999, Wells 2002). Notably, cognitive restructuring may be incompatible with these approaches, which emphasize the acceptance of anxious thoughts and place less importance on active attempts to change them. Elements of acceptance-based approaches may include experiential exercises, mindfulness training, identification of the patient's overriding values, and exploration of the incompatibility of experiential avoidance with these values (e.g., Orsillo et al. 2001). The efficacy of these newer approaches compared to extant CBT is yet to be determined by controlled trials (Figure 73–3).

## Treatment of Special Populations

### *Children*

Because GAD was not considered a childhood/adolescent disorder prior to the publication of DSM-IV, there is a paucity of treatment trials in this population. The precursor to childhood GAD in DSM-III and DSM-III-R was overanxious disorder, a category prone to overdiagnosis (e.g., Beidel et al. 1996) and low diagnostic reliability relative to other anxiety disorders (e.g., Silverman and Eisen 1992). Several small studies have demonstrated the efficacy of CBT in the treatment of overanxious disorder or GAD (e.g., Eisen and Silverman 1998, Kane and Kendall 1989). In randomized controlled trials with mixed anxiety samples, CBT has produced greater symptom reduction than wait-list control conditions immediately posttreatment and at long-term follow-up (Kendall 1994, Kendall et al. 1997, Flannery-Schroeder and Kendall 2000), although additional research is needed to assess differential treatment response across anxiety disorders. Other promising interventions incorporate family-management components into existing CBT protocols (e.g., Barrett et al. 1996). Few studies have examined the use of pharmacotherapy in childhood GAD, although one small,

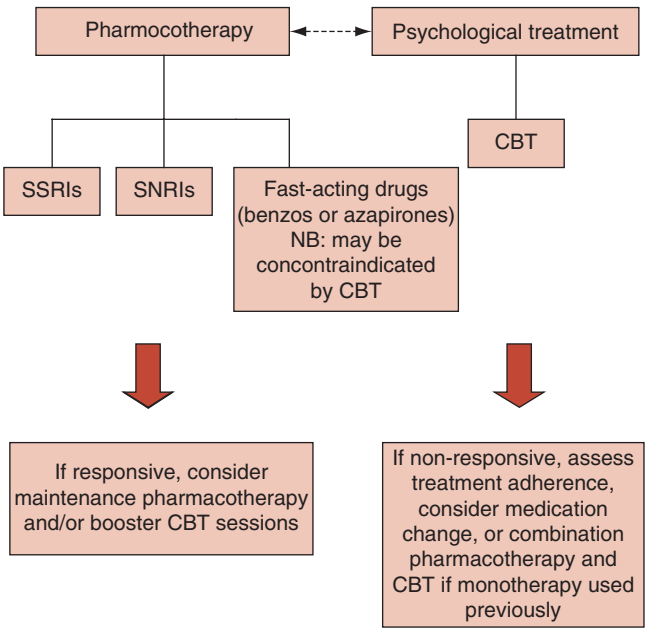



**Figure 73–3** *Treatment algorithm for GAD.*

placebo-controlled trial has supported the efficacy of sertraline (50 mg) in children and adolescents (ages 5–17 years) (Rynn et al. 2001).

### *Elderly*

Although the most recent data from the NCS-R suggest that GAD is not prevalent among older individuals (Kessler et al. 2005b), it has been estimated that 17% of elderly men and 21.5% of elderly women have sufficiently severe symptoms to warrant treatment (Himmelfarb and Murrell 1984). Moreover, a larger proportion of elderly individuals may not meet full criteria for GAD but, nevertheless, experience clinically significant distress or impairment as a result of their symptoms (Diefenbach et al. 2003). At least one randomized controlled trial has indicated that CBT is efficacious relative to no treatment in older adults, although only a minority of patients receiving CBT (45%) were classified as responders and those receiving CBT did not return to their premorbid level of functioning following treatment (Stanley et al. 2003).

## Treatment Refractory Patients

Randomized controlled trials of CBT and pharmacotherapy have identified several factors, predicting poor outcome in the treatment of GAD. Patients with interpersonal problems, defined as vindictive, intrusive, and domineering relationships, demonstrated poorer outcomes immediately posttreatment and at 2-year follow-up in CBT trial (Borkovec et al. 2002). Comorbidity has been associated with poorer outcomes among untreated GAD patients (Yonkers et al. 2003), underscoring the importance of including comorbid patients in treatment trials and reporting both initial and posttreatment levels of comorbidity. There is evidence that comorbidity decreases during psychosocial treatment of GAD (e.g., Ladouceur et al. 2000), although additional research is necessary to understand the relationship between pretreatment comorbidity and treatment outcome.

## Special Factors Influencing Treatment

Patients' belief in the functionality of worry may serve as a barrier to treatment progress, although this hypothesis requires empirical examination. Individuals with GAD often believe that their worry will help them prepare for, or help them avoid, future negative events (Borkovec and Roemer 1995), despite evidence to the contrary (Borkovec et al. 1999). Because individuals with GAD often fear low-frequency events, their worry may be reinforced by the nonoccurrence of their feared outcomes (Borkovec et al. 1999). Effective treatment of GAD requires that patients understand that their worry, although it may feel functional, is not an effective problem-solving strategy.

Case Vignette 1

Cindy was a 23-year-old, single Caucasian woman who had recently graduated from college. She reported that she was a lifelong "worrier" but that her anxiety had gotten worse after graduation. Cindy had a history of panic disorder, which had been successfully treated 5 years previously, multiple episodes of depression, and IBS. Although she had visited several gastroenterologists in the previous year, her bowel symptoms and pervasive anxiety persisted. Cindy reported frequent "breakdowns," during which she would become overwhelmed by daily tasks and begin crying uncontrollably. She worried frequently about her own health and became anxious when she saw news stories about epidemics. In addition, she was preoccupied with the future and had imagined various bleak possibilities (e.g., failing to "live up to [her] potential" and "wasting" her education). She was dissatisfied with her job and frequently went outside during the day to smoke cigarettes and pace. Cindy also experienced frequent muscle tension and had signed up for a yoga class but was too "impatient" to attend regularly. She noted that she could only relax when she was home watching television. She said her ideal day was one during which she had no obligations. Although her family was supportive of her, they were becoming increasingly frustrated by her tearful phone calls. Once a very social woman, Cindy had become increasingly withdrawn, insisting that she was unable to relax when she went out with friends. Her gastrointestinal symptoms had gradually worsened, and she had missed several days of work due to diarrhea. She was referred to an anxiety clinic by her gastroenterologist and was treated with a combination of sertraline and CBT. She attended approximately 20 sessions of CBT, which included thought monitoring and cognitive reappraisal, relaxation training, and worry exposure. Additional situational exposures (e.g., riding the subway) were included to address Cindy's avoidance of situations in which she might experience IBS symptoms. At posttreatment, Cindy demonstrated significant improvements on questionnaire measures of GAD symptoms, as well as fewer crying spells, more frequent social contact, and less reassurance seeking.

Case Vignette 2

Michael was a 67-year-old Caucasian man who sought treatment after decades of excessive anxiety. He described himself as "high-strung" but noted that this quality was an asset during his career in business. Following his retirement, however, he found himself unable to relax. Michael often awoke several hours early and was unable to return to sleep. He kept a "mental checklist" of tasks he wished to complete that day but often procrastinated. Consequently, his checklist became longer and more overwhelming. Michael's anxiety led to frequent interpersonal difficulties, particularly with romantic partners. Married and divorced twice, Michael acknowledged that he was "hard to live with" as a result of his intense irritability. His current partner often complained that he was so preoccupied with his worries that he no longer listened to her when she spoke. Michael initially had difficulty describing the content of his worry. Through self-monitoring, however, he discovered that his primary areas of concern were minor matters and personal finances. He frequently worried about trivial errands and stated that financial worries were on his mind "all day long," even though he was financially secure. Michael sought treatment after coming to the realization that he was "wasting' his retirement by worrying excessively. He was reluctant to take medication and therefore sought CBT for his anxiety. Treatment included standard components of CBT for GAD (e.g., cognitive reappraisal, worry exposure, and problem-solving training), as well as mindfulness training to help Michael focus his attention on the present rather than on future-oriented worries.

## Summary

Once a residual category in the DSM, GAD did not achieve the status of a full disorder until the publication of DSM-III-R in 1987. Since then, its definition has been revised substantially and now consists of excessive and uncontrollable worry accompanied by symptoms associated with negative affect. In light of the disorder's poor diagnostic reliability, many revisions to the diagnostic criteria have been proposed. As it is currently defined, GAD is associated with high rates of comorbidity and substantial overlap with depression and other anxiety disorders. Like most mental disorders, the etiology of GAD is complex. There is evidence that GAD is at least partially heritable and associated with abnormalities in neurotransmitter systems and autonomic function, as well as psychological vulnerabilities. Although several empirically supported treatments for GAD have been identified (including pharmacological and psychosocial approaches), treatment for GAD has lagged behind that of some other anxiety disorders.

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CHAPTER

# 74 Somatoform Disorders

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Somatization Disorder
Undifferentiated Somatoform Disorder
Conversion Disorder
Pain Disorder
Hypochondriasis
Body Dysmorphic Disorder
Somatoform Disorder Not Otherwise Specified

## Introduction

The somatoform disorders are a major diagnostic class in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) that groups together conditions characterized by physical symptoms suggestive of, but not fully explained by, a general medical condition or the direct effects of a substance. In this class, symptoms are not intentionally produced and are not attributable to another mental disorder. To warrant a diagnosis, symptoms must be clinically significant in terms of causing distress or impairment in important areas of functioning. The disorders included in this class are somatization disorder, undifferentiated somatoform disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, and somatoform disorder not otherwise specified (NOS).

Historically, the somatoform disorders were first officially grouped together in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) (American Psychiatric Association 1980). The class was characterized by the presence of physical (somatic) symptoms that were not fully explained by physical conditions. In DSM-IV-TR, the phrase "general medical condition or the direct effects of a substance" corresponds to the "physical disorders" of DSM-III and the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (American Psychiatric Association 1987). By definition, a general medical condition includes any medical condition not considered mental or psychiatric. Substances include any drugs of abuse (including alcohol), medications, or toxins. By "direct effect" we mean the actual physiological effects of a substance, such as intoxication or withdrawal, rather than indirect effects, such as the psychosocial consequences of abuse or dependence. This cumbersome terminology was adopted to avoid the designation of certain conditions as physical, organic, or biological, which could be interpreted to imply that such factors did not contribute to conditions identified as mental, functional, or psychiatric. In essence, general medical condition refers to any nonpsychiatric medical condition, which includes any medical condition not listed in the mental disorders section of the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10) (World Health Organization 1992). Examples include virtually all infectious and parasitic, endocrine, nutritional, metabolic, immunity, and congenital disorders of any organ system (including the nervous system). DSM-III and DSM-III-R (American Psychiatric Association 1987) required that "no demonstrable organic findings or known physiologic mechanisms" be present, whereas DSM-IV-TR specifies only that the physical symptoms not be *fully* accounted for by a general medical condition or the direct effects of a substance.

The somatoform disorders class was created for clinical utility, not on the basis of an assumed common etiology or mechanism. In DSM-IV-TR terms, it was designed to facilitate the differential diagnosis of conditions in which the first diagnostic concern is the need to "exclude occult general

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medical conditions or substance-induced etiologies for the bodily symptoms." As shown in Figure 74–1, only after such explanations are reasonably excluded should somatoform disorders be considered.

Many criticisms of the somatoform disorder category have been raised, and the disbanding of the class with reassignment of several of the disorders to other diagnostic classes has been considered (Hales 1996, Mayou et al. 2005). As summarized by Murphy (1990), criticisms include contentions that because the category is delineated on the basis of presenting symptoms, it is "superficial", that the individual disorders are not qualitatively distinct from one another or from "normality" and hence would be better described dimensionally rather than differentiated categorically, that the disorders are derived from hospital rather than community- or primary care-based populations, and, perhaps the most serious challenge, that the grouping "gives the spurious impression of understanding." On the other hand, proponents maintain that the somatoform grouping represents a major advance over previous systems and that segregation of such disorders into a class has helped clarify the conceptualization of the "mind–body" distinction, promoted greater consistency in terminology, and led to better descriptive distinctions between specific disorders (Cloninger 1987, Cloninger and Yutzy 1993). Supporters contend that maintaining this diagnostic class will foster more generalizable and thereby more clinically applicable research; an intent that appears to be supported when the literature before and after DSM-III is compared (Martin 1996). In the end, DSM-IV-TR left the class virtually intact from DSM-III-R.

A somatoform disorder category similar to the DSM-IV-TR class is included in ICD-10, perhaps demonstrating growing international acceptance for the grouping (Martin 1995). The ICD-10 category differs from the DSM-IV-TR class in that it requires "persistent requests for medical investigations" and resistance to consideration of "psychological causation" despite "repeated negative findings and reassurances by doctors that the symptoms have no physical basis." In DSM-IV-TR, such elements are required only in hypochondriasis and body dysmorphic disorder. The ICD-10 grouping also encompasses different disorders: somatization disorder, undifferentiated somatoform disorder, hypochondriacal disorder (of which body dysmorphic disorder is a subtype), somatoform autonomic dysfunction (a disorder not included in DSM-IV-TR), persistent somatoform pain disorder, other somatoform disorders, and somatoform disorder, unspecified. Somatoform autonomic dysfunction approximates the psychophysiological "reactions" or "disorders" of the *Diagnostic and Statistical Manual of Mental Disorders*, First Edition (DSM-I) and the *Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (DSM-II), respectively, encompassing syndromes involving organ systems under autonomic nervous system control (e.g., paroxysmal tachycardia, functional dyspepsia, and irritable bowel syndrome). In the DSM-IV-TR, many such syndromes are included under psychological factors affecting medical condition. Conversion disorder is not included as a distinct somatoform disorder in ICD-10 but is subsumed under dissociative (conversion) disorder. Also of note, there is no ICD-10 condition corresponding to pain disorders specified as acute in DSM-IV-TR; ICD-10 includes only persistent pain disorders.

The somatoform disorder concept should be distinguished from traditional concepts of "psychosomatic illness" and "somatization." The psychosomatic illnesses involved structural or physiological changes hypothesized as deriving from psychological factors. In the DSM-III, DSM-III-R, and DSM-IV-TR somatoform disorders, such objective changes are generally not evident. The "classic" psychosomatic illnesses of Alexander (1950) included bronchial asthma, ulcerative colitis, thyrotoxicosis, essential hypertension, rheumatoid arthritis, neurodermatitis, and peptic ulcer. In DSM-IV-TR, most of these illnesses would be diagnosed as a general medical condition on Axis III, and in some cases with an additional designation of psychological factors affecting medical condition on Axis I. By definition, the diagnosis of "psychological factors affecting medical condition" is not a psychiatric disorder, but it is included in DSM-IV-TR in the section for other conditions that may be a focus of clinical attention; it involves the presence of one or more specific psychological or behavioral factors that adversely affect a general medical condition.

The descriptive use of the term "somatization" in somatization disorder is not to be confused with theories that generally postulate a somatic expression of psychological distress (Lipowski 1988, Kellner 1990, Malt 1991). Steckel et al. (1943), who coined the term, defined somatization in 1943 as the process of a "bodily disorder" occurring as the expression of a "deep-seated neurosis." However, as argued by Kellner (1990), "empirical studies . . . suggest that there is no single theory that can adequately explain somatization, which is not only multifactorially determined but is an exceedingly complex phenomenon." Furthermore, treatment strategies derived from somatization theories have not proven effective. For example, the postulation that patients with somatoform disorders are alexithymic, that is, are unable to process emotions and psychological conflicts verbally and therefore do so somatically, suggested that teaching such patients to "appreciate" and "verbalize" their emotions would circumvent the need to "somatize" them. Such treatment approaches have been ineffective (Cloninger 1987).

## Differential Diagnosis

As shown in Figure 74–1, after it is determined that physical symptoms are not fully explained by a general medical condition or the direct effect of a substance, somatoform disorders must be differentiated from other mental conditions with physical symptoms.

In contrast to malingering and factitious disorder, symptoms in somatoform disorders are not under voluntary control, that is, they are not intentionally produced or feigned. Determination of intentionality may be difficult and must be inferred from the context in which symptoms present. Somatic symptoms may also be involved in disorders in other diagnostic classes. However, in such instances, the overriding focus is on the primary symptom complex (i.e., anxiety, mood, or psychotic symptoms) rather than the physical symptoms. In panic disorder and in generalized anxiety disorder, physical symptoms such as chest pain, shortness of breath, palpitations, sweating, and tremulousness may occur. However, such somatic symptoms occur only in the context of fear or anxious foreboding. In general, there is a lack of a consistent physical focus. In mood

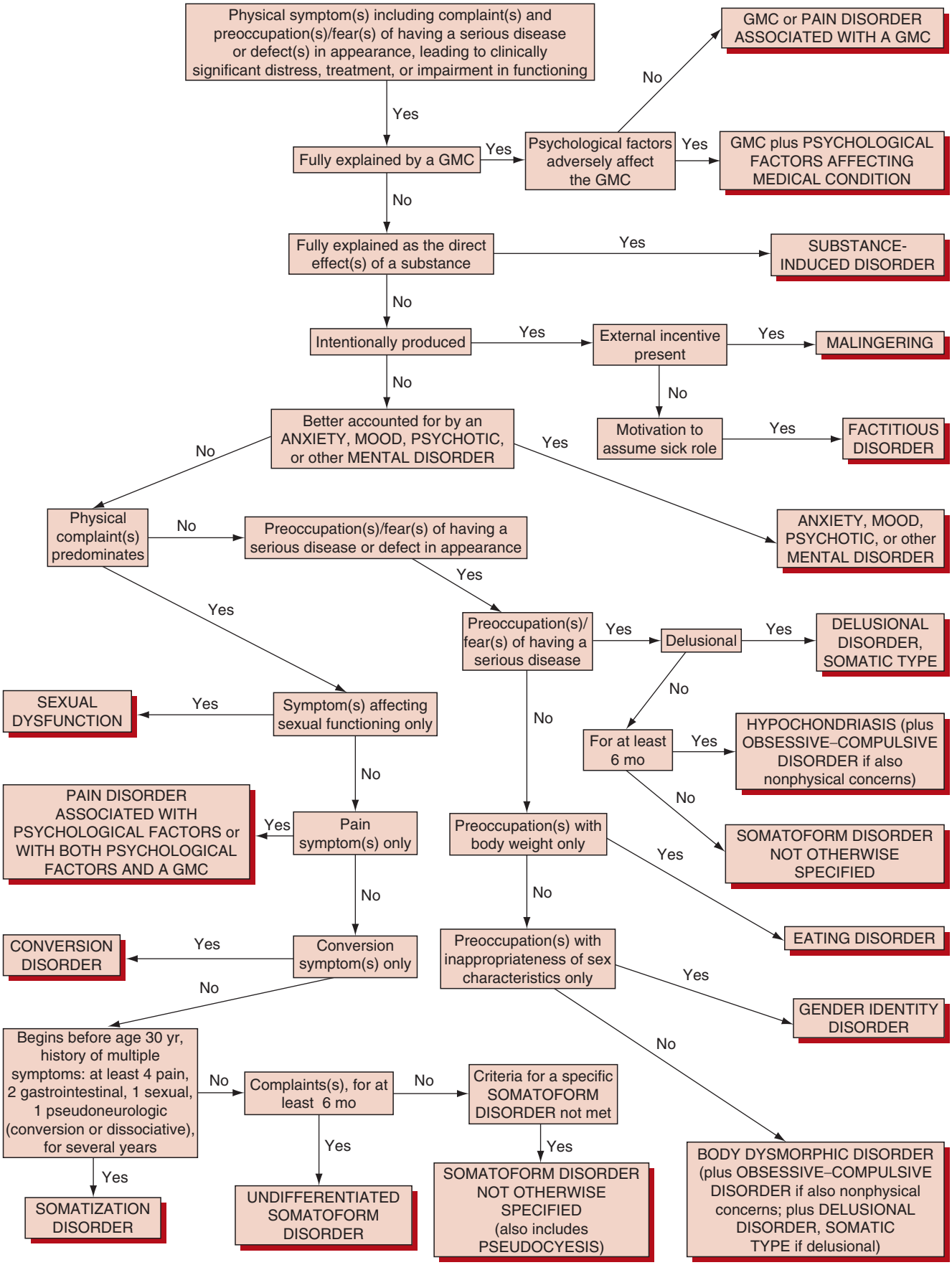



**Figure 74–1** *Somatic symptom diagnostic exploration and treatment algorithm. Differential diagnosis of clinically significant physical symptoms. Shadowed boxes represent diagnostic categories; GMC, general medical condition.*

disorders (particularly major depressive disorder) and in schizophrenia and other psychotic disorders, somatic preoccupations, fears, and even delusions and false perceptions may be evident. In the mood disorders, these are generally mood congruent (e.g., "I'm so worthless not even my organs work anymore"), whereas in the psychoses, bizarre and mood-incongruent beliefs are typical (e.g., "Half of my brain was removed by psychic neurosurgery").

### Differentiation Among the Various Somatoform Disorders

Whereas it is assumed that the specific disorders in the somatoform grouping are heterogeneous in terms of pathogenesis and pathophysiology, they are also phenomenologically diverse (see Figure 74–1). In somatization disorder, undifferentiated somatoform disorder, conversion disorder, and pain disorder, the focus is on the physical complaints themselves, and thus on perceptions. In hypochondriasis and body dysmorphic disorder, emphasis is on physically related preoccupations or fears, and thus on cognitions. Somatization disorder and, to a lesser extent, undifferentiated somatoform disorder are characterized by multiple symptoms of different types; conversion disorder, pain disorder, hypochondriasis, and body dysmorphic disorder are defined on the basis of a single symptom or a few symptoms of a certain type (see Figure 74–1). Whereas somatization disorder, undifferentiated somatoform disorder, and hypochondriasis are, by definition, at least 6 months in duration, conversion disorder, pain disorder, body dysmorphic disorder, and somatoform disorder NOS may be of short duration as long as they are associated with clinically significant distress or impairment.

### Epidemiology

In view of the vicissitudes of diagnostic approaches and the recency of the current somatoform disorder grouping, it is not surprising that estimates of the frequency of this group of disorders in the general population as well as in clinical settings are inconsistent if not nonexistent. Yet, existing data seem to indicate that such problems are indeed common and account for a major proportion of clinical services, especially in primary care settings. A World Health Organization study reported ICD-10 diagnoses of hypochondriasis in nearly 1% and of somatization disorder in nearly 3% of patients in primary care clinics in 14 countries (Ormel et al. 1994). Another study using primary care sites found 14% of 1,000 patients to be suffering from some somatoform disorder: 8% with "multisomatoform disorder" (see the undifferentiated somatoform disorder section), 4% with somatoform disorder NOS, 2% with hypochondriasis, and 1% with somatoform pain disorder (Spitzer et al. 1994).

Considering prevalence in nonclinic, community populations, Escobar et al. (1989) reported that nearly 20% of community respondents in Puerto Rico and 4.4% of comparable non-Hispanic Los Angeles residents fulfilled criteria for an "abridged somatization disorder," a construct with a lower threshold than somatization disorder that would generally correspond to a DSM-IV-TR diagnosis of either undifferentiated somatoform disorder or somatoform disorder NOS. In the Epidemiological Catchment Area community study (Robins et al. 1984), a low estimate of the frequency of somatization disorder (0.06–0.6%) was reported. Methodological problems may have led to a falsely low rate, as discussed in the somatization disorder section. Other studies have estimated much greater frequency, at least among women (Table 74–1).

In consideration of the substantial frequency of somatoform disorders in nonpsychiatric settings, instruments have been designed to aid primary care physicians in diagnosing psychiatric conditions. The Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al. 1994) includes somatoform items in its screening questionnaire and in its physician education guide. The DSM-IV Primary Care Edition (DSM-IV-PC) includes an "unexplained physical symptoms" algorithm among the nine it included to address the most common psychiatric symptom groups presenting in primary care settings (American Psychiatric Association 1995).

The epidemiology of the specific somatoform disorders is discussed individually in the following sections.

### Treatment

Whereas specific somatoform disorders indicate specific treatment approaches, some general guidelines apply to the somatoform disorders as a whole (Figure 74–2 and Table 74–2). By reorganizing and synthesizing the recommendations of Stoudemire (1988) and Kellner (1991) into three goals and three general strategies, the therapeutic goals include (1) as an overriding goal, prevention of the adoption of the sick role and chronic invalidism, (2) minimization of unnecessary costs and complications by avoiding unwarranted hospitalizations, diagnostic and treatment procedures, and medications (especially those of an addictive potential), and (3) effective treatment of comorbid psychiatric disorders, such as depressive and anxiety syndromes. The three general treatment strategies include (1) consistent treatment, generally by the same physician, with careful coordination if multiple physicians are involved, (2) supportive office visits, scheduled at regular intervals rather than in response to symptoms, and (3) a gradual shift in focus from symptoms to an emphasis on personal and interpersonal problems.

## SOMATIZATION DISORDER

### Definition and Diagnostic Features

As defined in DSM-IV-TR, somatization disorder is a polysymptomatic somatoform disorder characterized by multiple recurring pains and gastrointestinal, sexual, and pseudoneurological symptoms occurring for a period of years with onset before age 30 years. The physical complaints are not intentionally produced and are not fully explained by a general medical condition or the direct effects of a substance. To warrant diagnosis, they must result in medical attention or significant impairment in social, occupational, or other important areas of functioning.

The concept and criteria for somatization disorder (historically referred to as hysteria or Briquet's syndrome) embraced by DSM-IV-TR are the distillation of a long and convoluted struggle to describe this complex, multifaceted syndrome (Martin 1988). As reviewed by Veith (1965), the origins of the concept can be traced to descriptions in the medical literature of the pre-Hippocratic Egyptians, who attributed otherwise unexplained physical symptoms to peregrinations of the uterus; this hypothesis probably

**Table 74–1 Epidemiology and Natural History of the Somatoform Disorders**

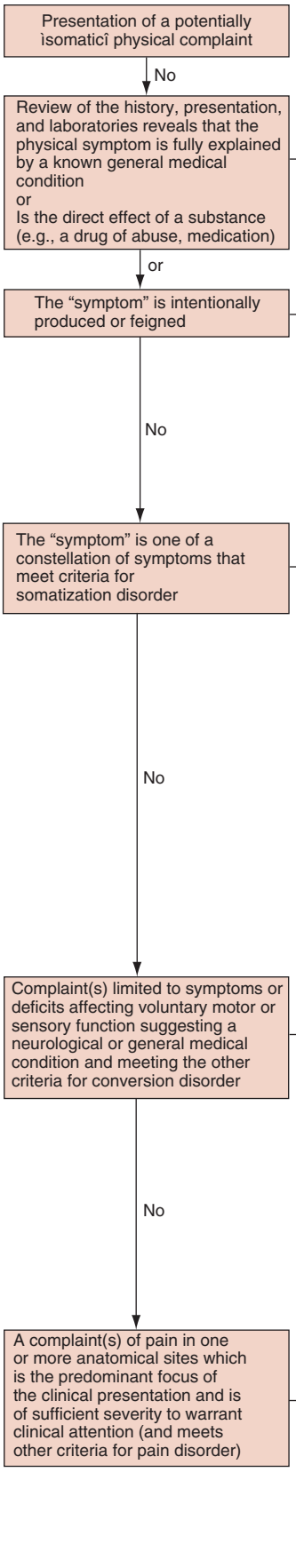
| Somatoform Disorder | Prevalence and Incidence | Age at Onset | Course and Progress |
|---|---|---|---|
| Somatization disorder | US women 0.2–2%; women/men = 10:1 | First symptoms by adolescence, full criteria met by mid-20s, not after 30 yr by definition | Chronic with fluctuations in severity Most active in early adulthood<br>Full remissions rare |
| Undifferentiated somatoform disorder | "Abridged somatization disorder" type estimated as 11–15% of US adults, 20% in Puerto Rico Preponderance of women in US but not Puerto Rico | Variable | Variable conversion disorder |
| Conversion disorder | Conversion symptoms common, as high as 25% Treated conversion symptoms: 11–500 per 100,000 5–14% of general hospital admissions 5–24% of psychiatric outpatients 1–3% of psychiatric outpatient referrals 4% of neurological outpatient referrals 1% of neurological admissions | Late childhood to early adulthood, most before age 35 yr<br>If onset in middle or late life, neurological or general medical condition more likely | Individual conversion symptoms generally remit within days to weeks Relapse within 1 yr in 20–25% |
| Pain disorder | 10–15% of US adults with work disability owing to back pain yearly A predominant symptom in more than half of general hospital admissions Present in as many as 38% of psychiatric admissions, 18% of psychiatric outpatients | Any age | Good if less than 6 mo in duration<br>Unemployment, personality disorder, potential for compensation, and habituation to addictive drugs associated with poorer prognosis |
| Hypochondriasis | Perhaps 4–9% in general medical settings, but unclear whether full syndrome criteria are met Equal in both sexes | Early adulthood typical | 10% recovery, two-thirds a chronic but fluctuating course, 25% do poorly<br>Better prognosis if acute onset, absence of personality disorder, absence of secondary gain |
| Body dysmorphic disorder | Not routinely screened for in psychiatric or general population studies<br>Perhaps 2% of patients seeking corrective cosmetic surgery | Adolescence or early adulthood<br>Perhaps in women at menopause | Generally chronic, fluctuating severity<br>In a lifetime, multiple defects perceived<br>Incapacitating: one-third housebound |
| Somatoform disorder NOS | Unknown | Variable | Variable |

derived from observations that such presentations were predominantly seen in women with onset during the reproductive years. In the 5th century AD, the Hippocratic literature formalized the concept, adopting the term *hysteria* from the Greek word for uterus. In time, belief in a uterine cause was abandoned, but use of the term hysteria continued.

In the mid-19th century, Paul Briquet (1859) adopted the term hysteria for the syndrome he described in his monograph, *Traité Clinique et Thérapeutique à l'Hystérie*, as characterized by dramatic and excessive medical complaints without evidence of an organic cause. Ultimately, such a description would constitute the basis for somatization disorder, yet the medical complaint aspect of hysteria was overshadowed for many years by psychodynamic interpretations originating with observations by Breuer and Freud (1955). In fact, much of Freud's theory of the unconscious can be traced to his work with hysteria. According to psychodynamic theory, "psychic energy" was converted into physical symptoms, thereby the term *conversion.* Although conversion symptoms were eventually reserved for pseudoneurological complaints, the more general term somatization came to be used for any body symptoms explained as an expression of a neurosis (Lipowski 1988, Steckel et al. 1943).

In time, the physical complaint aspect of hysteria was de-emphasized, with increased attention to intrapsychic, personality, or characterological features of hysteria. Meanwhile, in lay usage, hysteria came to signify excessive or histrionic emotional displays regardless of whether physical symptoms were involved. By the 1950s, the meaning had become so diffuse that the term hysteria, as attacked by Chodoff and Lyons (1958), had at least five connotations, only one of which related to physical complaints.

In 1951, Purtell et al. (1951) resurrected Briquet's formulation of a syndrome characterized by multiple medically unexplained somatic complaints, adding a quantitative perspective that required a given number of symptoms from a specified list for a diagnosis. This approach was refined in 1962 by Perley and Guze (1962) and again in 1972 by Feighner et al. (1972), who included hysteria among the 13 psychiatric diagnoses "canonized" as sufficiently studied to be considered valid and reliable psychiatric disorders. As




| Treatment Goals | Psychotherapy and Psychosocial Strategies and Techniques | Pharmacological and Physical Strategies and Techniques |
|---|---|---|
| 1. Prevent adoption of the sick role and chronic invalidism | 1. Consistent treatment, generally by same physician, coordinated if multiple | 1. Only as clearly indicated, or as time-limited empirical trial |
| 2. Minimize unnecessary costs and complications by avoiding unwarranted hospitalizations, diagnostic and treatment procedures, and medications | 2. Establish firm therapeutic alliance | 2. Antianxiety and antidepressant drugs for comorbid anxiety or depressive disorders; if diagnosis unclear, consider empirical trial |
| 3. Pharmacological control of comorbid syndromes | 3. Supportive office visits, scheduled at regular intervals | 3. Avoid drugs with abuse or addictive potential |
| 4. Instill, whenever possible, insight regarding temporal association between symptoms and personal, interpersonal, and situational problems | 4. Educate patient regarding manifestations of somatization disorder (psychoeducative approach) | |
| | 5. Focus gradually shifted from symptoms to personal and social problems | |
| 1, 2, and 3 (above) under treatment goals | Acute | 1 and 3 (above) under pharmacological and physical strategies and techniques |
| Prompt removal of symptoms | Reassurance, suggestion to remove symptom | Consider narcoanalysis as an interviewing or psychotherapy adjunct |
| | Consider narcoanalysis (interview after drowsiness from amobarbital or other sedative hypnotic, sometimes followed by methylphenidate or other stimulant), hypnotherapy, or behavioral therapy | |
| | Chronic | |
| | 1, 3, and 5 (above) under psychotherapy and psychosocial strategies and techniques | |
| Exploration | Exploration of various conflict areas, particularly interpersonal relationships | |
| Long-term | Long-term, intensive, insight-oriented, dynamic psychotherapy recommended by some | |
| 1, 2, and 3 (above) under treatment goals; also | 1, 3, and 5 (above) under psychotherapy and psychosocial strategies and techniques; also | 1 and 3 (above) under pharmacological and physical strategies and techniques; also |
| Acute pain: relieve symptom | Chronic pain: consider physical and occupational therapy, operant conditioning, cognitive?behavioral therapy | Acute: acetaminophen and NSAIDs alone or as adjuncts to opioids (if necessary) |
| Chronic pain: maintain function and motility rather than focus on total pain relief | | Chronic: tricyclic antidepressants, acetaminophen, and NSAIDs; if necessary, milder opioids orpure opioid agonists, but these only if tied to non pain objectives (such as increasing activity) |
| | | Consider acupunture, transcutaneous electrical nerve stimulation |

**Figure 74–2** *Diagnostic decision tree and treatment algorithm for somatoform disorders.*

**Table 74–2 Treatment of DSM-IV-TR Somatoform Disorders**

| Somatoform Disorder | Treatment Goals | Psychotherapy and Psychosocial Strategies and Techniques | Pharmacological and Physical Strategies and Techniques* |
|---|---|---|---|
| Somatoform disorders, as a group | 1. Prevent adoption of the sick role and chronic invalidism<br>2. Minimize unnecessary costs and complications by avoiding unwarranted hospitalizations, diagnostic and treatment procedures, and medications<br>3. Pharmacological control of comorbid syndromes | 1. Consistent treatment, generally by same physician, coordinated if multiple<br>2. Supportive office visits, scheduled at regular intervals<br>3. Focus gradually shifted from symptoms to personal and social problems | 1. Only as clearly indicated, or as time-limited empirical trial<br>2. Avoid drugs with abuse or addictive potential |
| Somatization disorder | 1, 2, and 3; also<br>• Instill, whenever possible, insight regarding temporal association between symptoms and personal, interpersonal, and situational problems | 1, 2, and 3; also<br>• Establish firm therapeutic alliance<br>• Educate patient regarding manifestations of somatization disorder (psychoeducative approach)<br>• Consistent reassurance | 1 and 2, also<br>• Antianxiety and antidepressant drugs for comorbid anxiety or depressive disorders; if diagnosis unclear, consider empirical trial |
| Undifferentiated somatoform disorder | 1, 2, and 3 | 1, 2, and 3 | 1 and 2 |
| Conversion disorder | 1, 2, and 3; also<br>• Prompt removal of symptoms | Acute:<br>• Reassurance, suggestion to remove symptom<br>• Consider narcoanalysis (interview after drowsiness from amobarbital or other sedative–hypnotic, sometimes followed by methylphenidate or other stimulant), hypnotherapy, or behavioral therapy<br>Chronic:<br>1, 2, and 3<br>• Exploration of various conflict areas, particularly interpersonal relationships<br>• Long-term, intensive, insight-oriented dynamic psychotherapy recommended by some | 1 and 2; also<br>• Consider narcoanalysis as an interviewing or psychotherapy adjunct |
| Pain disorder | 1, 2, and 3; also<br>• Acute pain: Relieve symptom<br>• Chronic pain: Maintain function and motility rather than focus on total pain relief | 1, 2, and 3; also<br>• Chronic pain: Consider physical and occupational therapy, operant conditioning, cognitive–behavioral therapy | 1 and 2; also<br>• Acute: Acetaminophen and NSAIDs alone or as adjuncts to opioids (if necessary)<br>• Chronic: Tricyclic antidepressants, acetaminophen, and NSAIDs; if necessary, milder opioids or pure opioid agonists, but these only if tied to nonpain objectives (such as increasing activity)<br>• Consider acupuncture, transcutaneous electrical nerve stimulation |
| Hypochondriasis | 1, 2, and 3; also<br>• Pharmacological control of central syndrome itself | 1, 2, and 3; also<br>• Cognitive–behavioral therapy involving prevention of checking rituals and reassurance seeking | 2; also<br>• Attempt to decrease hypochondriacal symptoms with SSRIs at higher than antidepressant doses or clomipramine |

**Table 74–2 Treatment of DSM-IV-TR Somatoform Disorders**

| Somatoform Disorder | Treatment Goals | Psychotherapy and Psychosocial Strategies and Techniques | Pharmacological and Physical Strategies and Techniques* |
|---|---|---|---|
| Body dysmorphic disorder | 1, 2, and 3, especially avoiding corrective surgery; also<br>• Pharmacological control of central syndrome itself | 1, 2, and 3; also<br>• Cognitive–behavioral therapy involving prevention of checking rituals and reassurance seeking | 2; also<br>• Attempt to decrease hypochondriacal symptoms with SSRIs at higher than antidepressant doses or clomipramine |
| Somatoform disorder NOS | 1, 2, and 3; also<br>• Evaluate carefully for alternative general medical or other psychiatric disorder to which the symptoms can be attributed | 1, 2, and 3 | 1 and 2 |

*NSAIDs, nonsteroidal antiinflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

summarized by Barsky (1989), the validity, reliability, and internal consistency of the Feighner criteria for hysteria were supported in clinical, epidemiological, and follow-up studies. In particular, the syndrome was stable, with an 80–90% probability that 6–8 years after the diagnosis was made the clinical picture would be essentially the same and no new medical or mental disorder would develop as an explanation for the original complaints.

Unfortunately, although feasible in research settings, the Feighner hysteria criteria were cumbersome clinically. Twenty-five medically unexplained symptoms from a specified list of 59 symptoms organized into 10 groups were required for a "definite" diagnosis, 20 for a "probable" diagnosis. Dissemination to different functions and organ systems was considered an essential aspect of the syndrome, a diagnosis requiring symptoms from 9 of the 10 groups.

**DSM-IV-TR Criteria** 300.81

**Somatization Disorder**

A. A history of many physical complaints beginning before age 30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.

B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:

(1) *four pain symptoms*: a history of pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination)

(2) *two gastrointestinal symptoms*: a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods)

(3) *one sexual symptom*: a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy)

(4) *one pseudoneurological symptom*: a history of at least one symptom or deficit suggesting a neurological condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting)

C. Either (1) or (2):

(1) after appropriate investigation, each of the symptoms in criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication)

(2) when there is a related general medical condition, the physical complaints or resulting social or occupational impairment is in excess of what would be expected from the history, physical examination, or laboratory findings

D. The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).

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DSM-I and DSM-II mentioned only conversion and dissociative reactions (hysterical neurosis: conversion and dissociative types in DSM-II), virtually ignoring a polysymptomatic disorder. ICD-9 listed somatization disorder and Briquet's disorder under other neurotic disorders. DSM-III recognized the need for inclusion of the syndrome characterized in the Feighner criteria but sought to make the diagnosis more usable. Somatization disorder was the term coined to escape the pejorative connotation of hysteria, yet avoiding the use of eponyms such as Briquet's syndrome. It also attempted to simplify the criteria of Feighner and colleagues by reducing the required number of symptoms to 14 in women and 12 (to prevent a possible sex bias) in men, from a list of 37 potential symptoms, and abolishing the requirement that symptoms came from multiple symptom groups. Whereas the Feighner criteria approach and its predecessors included anxiety and depressive symptoms, DSM-III did not, allowing diagnoses of comorbid anxiety and mood disorders. DSM-III-R incorporated minor changes, including elimination of the sex differential; it required 13 symptoms in both men and women and shortened the list of potential symptoms to 35.

Despite such efforts to simplify, the somatization disorder construct remained cumbersome, which undoubtedly contributed to underuse (Cloninger 1996). As a result, a new diagnostic algorithm was developed by Cloninger and colleagues from a reanalysis of an existing data set requiring four pain, two nonpain gastrointestinal, one sexual or reproductive, and one pseudoneurological symptom (either conversion or dissociative) (Cloninger and Yutzy 1993, Yutzy et al. 1992). In a multisite field trial study, these criteria were shown to identify a syndrome with good correspondence to hysteria as defined by Feighner and colleagues (because of demonstrated reliability and validity of the "diagnostic gold standard") (Yutzy et al. 1995), as well as with DSM-III and DSM-III-R criteria. The ICD-10 also includes somatization disorder within a somatoform disorder grouping. However, in addition to multiple unexplained somatic symptoms, ICD-10 requires "persistent refusal to accept medical reassurance that there is no adequate physical cause for the physical symptoms." Attributable in part to this requirement, DSM-IV and (TR/2000), Feighner, DSM-III, and DSM-III-R criteria all showed poor agreement with the ICD-10 criteria in the multisite field trial (Yutzy et al. 1995).

Changes in the diagnosis for DSM-IV-TR appeared to have facilitated a somewhat wider acceptance. Unfortunately, a number of problems with the diagnosis have remained, including the diagnostic complexity of the criteria set; the fact that the term "somatization" has acquired a pejorative connotation, a tendency for clinicians to diagnose more readily treatable symptoms such as anxiety and depressive syndromes without considering the underlying illness, and the fact that authorization and reimbursement for treatment of this chronic condition are often challenged or denied.

It is relatively easier to obtain approval for an intervention on the basis of major depressive disorder, for example, than on the basis of a disorder that is much more likely to be poorly understood by case reviewers.

Thus, whereas somatization disorder as currently defined in DSM-IV-TR is not entirely equivalent to the many previous definitions, it has a common conceptual core and appears to identify populations of patients similar to those defined by the Purtell–Robins, Perley–Guze, DSM-III, and DSM-III-R criteria. Thus, subsequent discussions in this chapter use the term somatization disorder, even in reviewing findings ascertained by these other various criteria.

## Epidemiology

In the US, somatization disorder is found predominantly in women, with a female/male ratio of approximately 10:1 (see Table 74–1). This ratio is not as large in some other cultures (e.g., in Greeks and Puerto Ricans). Thus, gender- and culture-specific rates are more meaningful than generalized figures. The lifetime prevalence of somatization disorder in US women has been estimated to be between 0.2 and 2%. The magnitude of this discrepancy is attributable, at least in part, to methodological differences. The Epidemiological Catchment Area study (Robins et al. 1984), the most recent large-scale general population study in the US to include an assessment for somatization disorder, found a lifetime risk of somatization disorder of only 0.2–0.3% in US women. However, this study may have underestimated the prevalence of somatization disorder because nonphysician interviewers were used. It is argued that it is difficult for lay interviewers to critically assess whether somatic symptoms are fully explained by physical conditions. As a result, they may more readily accept patients' general medical explanations of symptoms, resulting in fewer diagnoses of somatization disorder. With age and method of assessment taken into account, the lifetime risk for somatization disorder has been estimated to be 2% in US women (Cloninger et al. 1975).

## Course

Somatization disorder is rare in children younger than 9 years of age (Robins and O'Neal 1953) (see Table 74–1). Characteristic symptoms of somatization disorder usually begin during adolescence, and the criteria are met by the mid-20s (Guze and Perley 1963). Somatization disorder is a chronic illness characterized by fluctuations in the frequency and diversity of symptoms (Guze et al. 1986). Full remissions occur rarely, if ever. Whereas the most active symptomatic phase is in early adulthood, aging does not appear to lead to total remission (Goodwin and Guze 1989). Pribor et al. (1994) found that women with somatization disorder older than 55 years did not differ from younger somatization patients in the number of somatic symptoms. Longitudinal follow-up studies have confirmed that 80–90% of patients initially diagnosed with somatization disorder will maintain a consistent clinical picture and be rediagnosed similarly after 6–8 years (Cloninger 1993, Cloninger et al. 1986). Women with somatization disorder seen in psychiatric settings are at increased risk for attempted suicide, although such attempts are usually unsuccessful and may reflect manipulative gestures more than intent to die (Martin et al. 1985). It is not clear whether such risk is true for patients with somatization disorder seen only in general medical settings.

## Differential Diagnosis

As defined in DSM-IV-TR, somatization disorder is characterized by multiple recurring physical symptoms and, as will be described, often multiple psychiatric complaints (Wetzel et al. 1994). Thus, it is not surprising that somatization disorder may present in a manner suggestive of multiple general medical and, although too often forgotten, psychiatric

disorders (Table 74–3). Indeed, it can be said that an essential aspect of somatization disorder is its simulation of other syndromes. As described by Preskorn (1995), "Briquet's syndrome (i.e., somatization disorder) is fundamentally a syndrome of apparent syndromes" (see Table 74–3). Thus, the first task in the diagnosis of somatization disorder is the exclusion of other suggested medical and psychiatric conditions.

To help in this, Cloninger (1986) identified three features that generally characterize somatization disorder but rarely general medical conditions. Slightly restated, these are (1) involvement of multiple organ systems, (2) early onset and chronic course without development of physical signs or structural abnormalities, and (3) absence of laboratory abnormalities characteristic of the suggested physical disorders (Table 74–4). Another way of characterizing the distinction is the "reverse funnel effect" (Pinta 1995, personal communication). With most general medical conditions, the process of investigation "funnels down" to fewer and fewer specific diagnostic possibilities; in somatization disorder, the more extensive the investigation, the greater the number of suggested disorders.

Several general medical conditions may also fit this pattern and may be confused with somatization disorder. These include multiple sclerosis, other neuropathies, systemic lupus erythematosus, acute intermittent porphyria, other hepatic and hematopoietic porphyrias, hypercalcemia, certain chronic systemic infections such as brucellosis and trypanosomiasis, myopathies, and vasculitides. In general, such conditions begin with disseminated, nonspecific subjective symptoms and transient or equivocal physical signs or laboratory abnormalities.

**Table 74–3 Somatoform Disorders: A Syndrome of Simulated Syndromes**

| Symptom Examples | Examples of Simulated Neurological Conditions | Examples of Simulated Nonneurological General Medical Conditions | Examples of Simulated Psychiatric Conditions |
|---|---|---|---|
| Symptoms* of somatization disorder | | | |
| Pain | | | |
| Headache | Migraine | Temporal arteritis | Pain disorder |
| Abdomen | "Abdominal epilepsy" | Peptic ulcer disease | Pain disorder |
| Back | Lumbosacral radiculopathy | Ruptured disk | Pain disorder |
| Joints or extremities | | Fibromyalgia | Pain disorder |
| Chest | | Angina | Panic disorder |
| Menstruation, intercourse | | Endometriosis | Dyspareunia, vaginismus |
| Urination | Neurogenic bladder | Urinary tract infection | |
| Gastrointestinal (nonpain) | | | |
| Difficulty swallowing | Myasthenia gravis | Esophageal motility disorder | Eating disorder |
| Nausea | Raised intracranial pressure | Meniere's disease | Eating disorder |
| Bloating | | Galactose deficiency | Eating disorder |
| Vomiting (nonpregnancy) | | Raised intracranial pressure | Eating disorder |
| Diarrhea | | Irritable bowel syndrome | Eating disorder |
| Intolerance to several foods | | Food allergy | Eating disorder |
| Sexual (nonpain) | | | |
| Loss of interest | | | Major depressive episode |
| Erectile–ejaculatory dysfunction | Diabetic neuropathy | Antihypertensive drug effect | |
| Menorrhagia | | Leiomyofibroma | |
| Vomiting throughout pregnancy | | Preeclampsia, eclampsia | |
| Pseudoneurological | | | |
| Conversion | | | |
| Sensory | Stroke (hemianesthesia) | | Schizophrenia/(hallucinations) |
| Motor | Huntington's disease | Myopathy | Catatonia |
| Seizures | Epilepsy | Electrolyte imbalance | Catatonia |
| Mixed | Multiple sclerosis | Electrolyte imbalance | Catatonia |
| Dissociative | | | |
| Amnesia | Amnestic disorder | Anticholinergic drug effects | Dissociative identity disorder |
| Loss of consciousness (nonfainting) | Coma | Metabolic encephalopathy | Catatonia |
| Symptoms* often associated with somatization disorder | | | |
| Anxiety, panic | | Pheochromocytoma | Generalized anxiety and panic disorders |
| Dysphoria, affective lability | Frontal lobe syndrome | Endocrinopathy | Major mood disorders |
| Cluster B personality features | Frontal lobe syndrome | Acute intermittent porphyria | Brief psychotic disorder |

*All of these symptoms may be reported by patients with somatization disorder, without the clinical consistency and pathological findings to support the diagnosis of neurological, general medical, or psychiatric conditions separate from somatization disorder.

*Source*: Table originally developed by Ron L. Martin in conjunction with Sheldon H. Preskorn.

**Table 74–4 Discrimination of Somatization Disorder from General Medical Conditions**

| Features Suggesting Somatization Disorder | Features Suggesting a General Medical Condition |
|---|---|
| Involvement of multiple organ systems | Involvement of single or few organ systems |
| Early onset and chronic course without development of physical signs or structural abnormalities | If early onset and chronic course, development of physical signs and structural abnormalities |
| Absence of laboratory abnormalities characteristic of the suggested general medical condition | Laboratory abnormalities evident |

*Source:* Martin RL and Yutzy SH (1994) Somatoform disorders. In The American Psychiatric Press Textbook of Psychiatry, 2nd edition, Hales RE, Yudofsky SC, and Talbott JA (eds). American Psychiatric Press, Washington, DC, USA, p 600.

Somatization disorder is characterized by excessive psychiatric as well as physical complaints (Wetzel et al. 1994). Thus, other psychiatric disorders, including anxiety and mood disorders and schizophrenia, may be suggested. Although no specific exclusion criteria regarding other psychiatric disorders are given, one must be careful in accepting "comorbidity" and critically evaluate whether suggested syndromes are truly additional syndromes or simply manifestations of somatization disorder (Preskorn 1995).

The overlap between somatization disorder and anxiety disorders may be a particular problem. Patients with somatization disorder frequently complain of many of the same somatic symptoms as patients with anxiety disorders, such as increased muscle tension, features of autonomic hyperactivity, and even discrete panic attacks. Likewise, anxiety disorder patients may report irrational disease concerns and such somatic complaints as those involving gastrointestinal function that are commonly seen in somatization disorder. However, patients with anxiety disorders neither typically report sexual and menstrual complaints or conversion or dissociative symptoms as in somatization disorder, nor do they have the associated histrionic presentation and personal, marital, and social maladjustment common in patients with somatization disorder (Cloninger 1993).

It must be remembered that an anxiety disorder may be comorbid with somatization disorder. Here, objective observation of the patient rather than reliance on the patient's report may facilitate an additional diagnosis. For example, patients with somatization disorder may report that they are presently overwhelmed by anxiety while speaking calmly or even cheerfully about their symptoms, or they may be redirectable while in the midst of a reported panic attack.

Mood disorders (in particular depression) frequently present with multiple somatic complaints; especially in certain cultures such as in India, where somatic but not mental complaints are acceptable. A longitudinal history identifying age at onset and course of illness may facilitate discrimination of a mood disorder from somatization disorder. In mood disorders, the age at onset of the somatic symptoms is generally later than in somatization disorder; their first appearance generally correlates discretely with the onset of mood symptoms, and a lengthy pattern of multiple recurring somatic complaints is not seen. Also, resolution of the underlying mood disorder will generally result in disappearance of the somatic complaints.

From the other perspective, patients with somatization disorder often present with depressive complaints. In somatization disorder, a thorough investigation will reveal a multitude of somatic as well as "depressive" symptoms. Interestingly, somatization disorder patients complaining of depression have been found to proffer greater depressive symptoms than individuals with major depression (DeSouza et al. 1988). As in anxiety disorders, major depressive episodes may occur in patients with somatization disorder and must be differentiated from the tendency to have multiple complaints, which is characteristic of somatization disorder. As with anxiety disorders, in considering comorbidity with a depressive disorder, the patient's reports should be corroborated by collateral information or by direct observation. Thus, the veracity of the self-report of overwhelming depression and suicidal ideation should be doubted if the patient appears cheerful and charming, at least at times, when interviewed, or if the patient is reported to be actively involved in social activities on an inpatient psychiatric service.

Schizophrenia may present with generally single but occasionally multiple unexplained somatic complaints. Interview usually uncovers psychotic symptoms such as delusions, hallucinations, or disorganized thought. In some cases, the underlying psychosis cannot be identified initially, but in time, schizophrenia will become manifest (Goodwin and Guze 1989). Hallucinations are included as examples of conversion symptoms in DSM-IV-TR, as they were in the Purtell, Perley–Guze, and Feighner criteria, which may lead to diagnostic problems (Martin 1996). As discussed in the conversion disorder section, careful analysis of this symptom is warranted so that a misdiagnosis is not made, relegating a patient to long-term neuroleptic treatment on the basis of conversion hallucinations.

Patients with histrionic, borderline, and antisocial personality disorders frequently have an excess of somatic complaints, at times presenting with somatization disorder. Cloninger and Guze (1979) and Cloninger et al. (1975) have identified that antisocial personality disorder and somatization disorder cluster in individuals and within families and may share common causes. Dissociative phenomena, in particular dissociative identity disorder, are commonly associated with somatization disorder (Martin 1996). Because dissociative symptoms are included in the diagnostic criteria for somatization, a separate diagnosis of a dissociative disorder is not made if such symptoms occur only in the course of somatization disorder.

Unlike in hypochondriasis and body dysmorphic disorder, in which preoccupations and fears concerning the interpretation of symptoms predominate, the focus in somatization disorder is on the physical complaints themselves. Unlike in pain disorder and conversion disorder, multiple complaints of different types are reported; by definition in DSM-IV-TR, the history is of pain in at least four sites or functions (e.g., pain with intercourse, pain in swallowing), at least two nonpain gastrointestinal symptoms, at least one nonpain sexual or reproductive symptom, and at least one conversion or dissociative (i.e., pseudoneurological) symptom.

Whereas criteria require the onset of symptoms before the age of 30 years, most patients will have had some symptoms at least by adolescence or early adulthood. Symptoms are often described in a dramatic yet imprecise way and may be reported inconsistently from interview to interview (Martin et al. 1979). The medical history is usually complicated with multiple medical investigations, procedures, and medication trials. If there have been symptoms for at least 6 months but the onset is later than at age 30 years, or if the required number and distribution of symptoms are not evident, undifferentiated somatoform disorder is diagnosed. If the duration has been less than 6 months, somatoform disorder NOS applies. In general, the greater the number and diversity of symptoms, and the longer they have been present without development of signs of an underlying general medical condition, the greater can be the confidence that a diagnosis of somatization disorder is correct.

## Etiology and Pathophysiology

Many theories on the cause of somatization disorder have been proposed since the early uterine hypothesis was dismissed. Yet, etiology remains unknown. Psychodynamic hypotheses regarding the physical expression of unconscious conflict by conversion or somatization have been influential. Even Freud assumed a "constitutional diathesis," as had Charcot before him. Evidence exists for both biological and psychosocial contributions.

Somatization disorder has been shown to be familial. It is observed that in 10–20% of female relatives of patients affected by somatization disorder there is a lifetime risk in US women 10–20 times greater than that in the general population (Guze et al. 1986). Yet, aggregation in families may be attributable to both genetic and environmental factors. A cross-fostering study of a Swedish population demonstrated that genetic background and postnatal influences contribute to the risk of somatization disorder independently (Bohman et al. 1984, Cloninger et al. 1984). Of additional interest are observations that male relatives of patients with somatization disorder show increased rates of antisocial personality and alcoholism, suggesting an etiological link (Cloninger 1993).

Certain promising theories have focused on learning principles with possible organic underpinnings. Ford (1983) and later Quill (1985) postulated a social communication model based on learning theory to explain somatization disorder. Both hypothesized that individuals learn to somatize as a means of expressing their wants and needs and evoking care, nurturance, and support from family and caregivers. That different sex ratios may exist in different cultures suggests that such learning differs from culture to culture.

In the 1970s, impaired information-processing problems involving attention and memory were identified in experimental neuropsychological testing (Ludwig 1972, Bendefeldt et al. 1976). Such deficits may result in vague, nonspecific, and impressionistic description for experience. These may underlie a tendency for excessive somatic complaints and, together with tendencies for impulsiveness and monotony intolerance, may contribute to the often associated multiple personal and social problems (Cloninger 1993). In 1981, Flor-Henry et al. (1981) reported that the pattern of neuropsychological defects found in subjects with somatization disorder differed from that in normal control, schizophrenic, and psychotic depression comparison groups. Subjects with somatization disorder had greater bilateral, symmetrical patterns of frontal lobe dysfunction in comparison with normal control subjects and greater dominant hemisphere impairment than control and depressive subjects. Nondominant hemisphere dysfunction was also identified, with greater impairment in the anterior as opposed to posterior regions. However, subjects with somatization disorder had less nondominant hemisphere disorganization than schizophrenic subjects. Of interest, these findings were similar to findings in male patients with antisocial personality disorder, giving further support to an etiological link with this disorder.

## Treatment

First, a "management" rather than a "curative" strategy is recommended for somatization disorder. With the current absence of an identified definitive treatment, a modest, practical, empirical approach should be taken. This should include efforts to minimize distress and functional impairments associated with the multiple somatic complaints, to avoid unwarranted diagnostic and therapeutic procedures and medications, and to prevent potential complications including chronic invalidism and drug dependence.

In such regard, the general recommendations outlined for somatoform disorders should be followed (see Table 74–2). Consistent with these guidelines, Ford (1983) and Quill (1985) recommended that the patient be encouraged to see a single physician with an understanding of and, preferably, experience in treating somatization disorder. This helps limit the number of unnecessary evaluations and treatments. Both Smith et al. (1986) and Murphy (1982) advocated routine, brief, supportive office visits scheduled at regular intervals to provide reassurance and prevent patients from "needing to develop" symptoms to obtain care and attention. This "medical" management can well be provided by a primary care physician, perhaps with consultation with a psychiatrist. The study by Smith et al. (1986) demonstrated that such a regimen led to markedly decreased health care costs, with no apparent decrements in health or satisfaction of patients.

More ambitious goals have been proposed with the recommendation for multiple approaches including individual psychotherapy, nonfocused group therapy, and electroconvulsive therapy (Martin and Yutzy 1994). Whereas early observations indicated some promise with each of these approaches, studies have been generally uncontrolled and used small samples. Subsequent investigations have rarely attempted to replicate reported findings using sophisticated methodology.

Of note in the treatment of somatization disorder was the identification in 1935 by Luff and Garrod (1935) of a three-part approach. Scallet et al. (1976) subsequently endorsed this approach, which they called eclectic, recommending "reeducation, reassurance, and suggestion." This approach was further developed by multiple authors, such as Quill (1985), Cloninger (1986), Smith et al. (1986), and Murphy (1982), from whom three interrelated components emerge: (1) establishment of a strong physician–patient relationship or bond, (2) education of the patient regarding the nature of the psychiatric condition, and (3) provision of support and reassurance.

The first component, establishing a strong therapeutic bond, is important in the treatment of somatization disorder. Without this, it will be difficult for the patient to overcome skepticism deriving from past experience with many physicians and other therapists who "never seemed to help." In addition, trust must be strong enough to withstand the stress of withholding unwarranted diagnostic and therapeutic procedures that the patient may feel are indicated. The cornerstone of establishing a therapeutic relationship is laid when the psychiatrist indicates an understanding of the patient's pain and suffering, legitimizing the symptoms as real. This demonstrates a willingness to provide direct compassionate assistance. A full investigation of the medical and psychosocial histories, including extensive record review, will illustrate to patients the willingness of the psychiatrist to gain the fullest understanding of them and their plight. This also provides another opportunity to evaluate for the presence of an underlying medical condition and to obtain a fuller picture of psychosocial difficulties that may relate temporally to somatic symptoms.

Only after the diagnosis has been clearly established and the therapeutic alliance is firmly in place can the psychiatrist confidently limit diagnostic evaluations and therapies to those performed on the basis of objective findings as opposed to merely subjective complaints. Of course, the psychiatrist should remain aware that patients with somatization disorder are still at risk for development of general medical illnesses so that a vigilant perspective should always be maintained.

The second component is education. This involves advising patients that they suffer from a "medically sanctioned illness," that is, a condition recognized by the medical community and one about which a good deal is known. Ultimately, it may be possible to introduce the concept of somatization disorder, which can be described in a positive light (i.e., the patient does not have a progressive, deteriorating, or potentially fatal medical condition, and the patient is not "going crazy" but has a condition by which many symptoms will be experienced). A realistic discussion of prognosis and treatment options can then follow.

The third component is reassurance. Patients with somatization disorder often have control and insecurity issues, which often come to the forefront when they perceive that a particular physical complaint is not being adequately addressed. Explicit reassurance should be given that the appropriate inquiries and investigations are being performed and that the possibility of an underlying physical disorder as the explanation for symptoms is being reasonably considered.

In time, it may be appropriate to gradually shift emphasis away from somatic symptoms to consideration of personal and interpersonal issues. In some patients, it may be appropriate to posit a causal theory between somatic symptoms and "stress," that is, there may be a temporal association between symptoms and personal, interpersonal, and even occupational problems. In patients for whom such "insight" is difficult, behavioral techniques may be useful.

Even following such therapeutic guidelines, patients with somatization disorder are often difficult to treat. Attention-seeking behavior, demands, and manipulation are common, necessitating firm limits and careful attention to boundary issues. This, again, is a management rather than a curative approach. Thus, such behaviors should generally be dealt with directively rather than interpreted to the patient.

During the 1990s cognitive behavior therapy (CBT) began to yield positive preliminary results (Speckens et al. 1995, Lidbeck 1997). Kroenke and Swindle (2000) reported while CBT studies were problematic because of lack of controls, small sample size of imprecise diagnosis (somatization

Clinical Vignette 1

A 35-year-old, separated, employed woman was admitted to a psychiatric unit after presenting to the emergency department reporting suicidal feelings that followed a series of arguments with her most recent common-law husband. She reported having been depressed nearly continuously for the past 4 years but had never responded well to antidepressant medications, which often had an "opposite" effect on her. She endorsed virtually all symptoms of a major depressive episode as outlined in DSM-IV-TR. However, she did not appear to be depressed in the interview. In addition to problems with depression, she reported problems with anxiety, complaining of episodes of shortness of breath, chest pain, palpitations, tremulousness, and a feeling of impending doom. At times, she would have prolonged periods with some or all of these symptoms. She reported that she had had a great number of medical problems, but "the doctors keep telling me there's nothing really wrong with me." She reported extreme headaches, "like a knife being stuck through the back of my head into my eye," as well as other headaches virtually every day; other pains including abdominal pain, associated at times with nausea and vomiting; periods of constipation, followed by diarrhea, which had resulted in evaluation for gallbladder and peptic ulcer disease with no significant findings; and pain "in all of my joints," but particularly in her knees and her back, that she said had been diagnosed as degenerative arthritis at age 27 years, yet no deformities had developed since. She had menstrual problems since menarche, with pain that put her to bed and excessive flow with "big, blue clots," which resolved only after a hysterectomy 2 years earlier at age 33 years. The mother of four, she reported a long history of sexual problems including pain with intercourse. She had been told that she had a "tipped uterus." Throughout her life, she was seldom orgasmic and had not enjoyed sex "for years." She reported episodes of blurred vision with "spots" in front of her eyes, which caused her to stop work. She would also have periods when she just could not hear anything, "like someone put their hands over my ears." She also reported periods of uncontrollable shaking and a feeling that she was losing control of her body, for which she had been evaluated for seizures. She reported that, at times, she had feared having some serious medical disease, but "with all the workups I have had, I am sure they would have found something by now." She did relate that she found group therapy with "other people with problems like mine" beneficial.

The patient was diagnosed with somatization disorder and comorbid panic disorder. Panic attacks have ceased since institution of buspirone, but she continues to have multiple somatic complaints. After several months of weekly supportive psychotherapy emphasizing education and reassurance, she is beginning to acknowledge that it is unlikely that physical explanations for her symptoms will be identified. She is also showing progress in dealing more constructively with interpersonal and occupational issues.

disorders vs. "somatization"). There were clear trends toward a reduction in physical complaints and medical utilization. Allen et al. (2006) published a randomized clinical study that compared CBT and psychiatric consultation (with the primary care physician) with psychiatric consultation with the primary care physician alone. The CBT plus psychiatric consultation group was found to have a significant greater improvement in symptoms and functioning. However, it remains to be seen whether CBT will gain wide acceptance in the treatment of somtization disorder.

### Pharmacological Treatment

No effective somatic treatments for somatization disorder itself have been identified. In the 1960s, Wheatley (1962) reported that low doses of anxiolytic drugs provided symptom amelioration in double-blind clinical trials using general practitioners. He also noted that whereas chlordiazepoxide was recommended for reasons of effectiveness, preference by patients, safety, and symptom relief, the best results were obtained by optimistic physicians using low doses of any anxiolytic medication. Surprisingly little systematic study of the pharmacological management of somatization disorder has been done since.

Patients with somatization disorder may complain of anxiety and depression, suggesting readily treatable comorbid psychiatric disorders. As previously discussed, it is often difficult to distinguish actual comorbid conditions from aspects of somatoform disorder itself. Pharmacological interventions are likely to be helpful in the former but not in the latter. At times, such discrimination will be impossible, and an empirical trial of such treatments may be indicated. Patients with somatization disorder are often inconsistent and erratic in their use of medications. They will often report unusual side effects that may not be explained pharmacologically. This makes evaluation of treatment response difficult. In addition, drug dependence and suicide gestures and attempts are not uncommon.

## UNDIFFERENTIATED SOMATOFORM DISORDER

### Definition and Diagnostic Features

As defined in DSM-IV-TR, this category includes disturbances of at least 6 months' duration, with one or more unintentional, clinically significant, medically unexplained physical complaints. In a sense, it is a residual category, subsuming syndromes with somatic complaints that do not meet criteria for any of the "differentiated" somatoform disorders yet are not better accounted for by any other mental disorder. On the other hand, it is a less residual category than somatoform disorder NOS, in that the disturbance must last at least 6 months (see Figure 74–1). Virtually any unintentional, medically unexplained physical symptoms causing clinically significant distress or impairment can be considered. In effect, this category serves to capture syndromes that resemble somatization disorder but do not meet full criteria.

The term undifferentiated somatoform disorder was introduced in 1987 with DSM-III-R, replacing the atypical somatoform disorder of DSM-III. However, the category has not been well used, not only by psychiatrists but also by primary care physicians for whom identification of such a syndrome could be useful. Terms that have been used in a similar manner include *subsyndromal*, *forme fruste*, or *abridged* somatization disorder (Kirmayer and Robbins 1991). Escobar et al. (1989), defining an abridged syndrome as requiring at least six significant unexplained somatic symptoms for women and four for men, argued that especially in primary care settings, such a condition was much more common than a full somatization disorder and it predicted disability and future use of medical services. This group also argued that this construct met many of the suggested requirements for validity as a psychiatric disorder, although adequate follow-up and family studies have not yet been done.

Due to this as well as the underuse of such a construct, perhaps attributable, at least in part, to the ambiguity of designation as undifferentiated, consideration was given to differentiating an abridged somatization syndrome as "multisomatoform disorder" in DSM-IV-TR. However, owing to uncertainties about the nature of such an entity, especially as to overlap with other syndromes such as anxiety and depressive disorders, and because the few data available suggested a variable course (Cloninger 1996), unlike somatization disorder, such a syndrome was left under the undifferentiated somatoform disorder rubric in DSM-IV-TR. A more specific designation could have proved misleading clinically, promoting a false sense of security, with a tendency to preclude

**DSM-IV-TR Criteria** 300.81

**Undifferentiated Somatoform Disorder**

A. One or more physical complaints (e.g., fatigue, loss of appetite, gastrointestinal or urinary complaints).

B. Either (1) or (2):

(1) after appropriate investigation, the symptoms cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication)

(2) when there is a related general medical condition, the physical complaints or resulting social or occupational impairment is in excess of what would be expected from the history, physical examination, or laboratory findings

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. Duration of the disturbance is at least 6 months.

E. The disturbance is not better accounted for by another mental disorder (e.g., another somatoform disorder, sexual dysfunction, mood disorder, anxiety disorder, sleep disorder, or psychotic disorder).

F. The symptom is not intentionally produced or feigned (as in factitious disorder or malingering).

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efforts to uncover a general medical or substance-related explanation for symptoms or to identify another psychiatric condition better accounting for the symptoms.

The DSM-IV-TR undifferentiated somatoform disorder category is little changed from DSM-III-R. Exclusion occurs on the basis of symptoms not better accounted for by another mental disorder rather than by occurrence exclusively during the course of another mental disorder.

## Epidemiology

Some have argued that undifferentiated somatoform disorder is the most common somatoform disorder. Escobar et al. (1991), using an abridged somatization disorder construct requiring six somatic symptoms for women and four for men, reported that 11% of non-Hispanic US whites and Hispanics, 15% of US blacks, and 20% of Puerto Ricans in Puerto Rico fulfilled criteria. A preponderance of women was evident in all groups except the Puerto Rican sample (see Table 74–1). According to Escobar, such an abridged somatoform syndrome is 100 times more prevalent than a full somatization disorder.

## Course

As shown in, it appears that the course and prognosis of undifferentiated somatoform disorder are highly variable. This is not surprising, because the definition of this disorder allows a great deal of heterogeneity.

## Differential Diagnosis

In comparison to when the full criteria for the well-validated somatization disorder are met, exclusion of an as yet undiscovered general medical or substance-induced explanation for physical symptoms is far less certain when the less stringent criteria for undifferentiated somatoform disorder are met. Thus, the diagnosis of undifferentiated somatoform disorder should remain tentative, and new symptoms should be carefully investigated.

Because undifferentiated somatoform disorder represents somewhat of a residual category, the major diagnostic process, once occult general medical conditions and substance-induced explanations have been considered, is one of exclusion. As shown in Figure 74–1, whether the somatic symptoms are intentionally produced as in malingering and factitious disorder must be addressed. Here, motivation for external rewards (for malingering) and a pervasive intent to assume the sick role (for factitious disorder) must be assessed. The next consideration is whether the somatic symptoms are the manifestation of another psychiatric disorder. Anxiety and mood disorders commonly present with somatic symptoms; high rates of anxiety and major depressive disorders are reported in patients with somatic complaints attending family medicine clinics (Kirmayer et al. 1993). Of course, undifferentiated somatoform disorder could be diagnosed in addition to one of these disorders, so long as the symptoms are not accounted for by the other psychiatric disorder. Crucial in this determination is whether the symptoms are present during periods in which the anxiety or mood disorders are not actively present.

Next, other somatoform disorders must be considered. In general, undifferentiated somatoform disorders are characterized by unexplained somatic complaints; the most common according to Escobar et al. (1989) are female reproductive symptoms, excessive gas, abdominal pain, chest pain, joint pain, palpitations, and fainting, rather than preoccupations or fears as in hypochondriasis or body dysmorphic disorder. However, a patient with some manifestations of these two disorders but not meeting full criteria could conceivably receive a diagnosis of undifferentiated somatoform disorder. An example is a patient with recurrent yet shifting hypochondriacal concerns that do respond to medical reassurance. If symptoms are restricted to those affecting the domains of sexual dysfunction, pain, or pseudoneurological symptoms, and the specific criteria for a sexual dysfunction, pain disorder, and/or conversion disorder are met, the specific disorder or disorders should be diagnosed. If other types of symptoms or symptoms of more than one of these disorders have been present for at least 6 months, yet criteria for somatization disorder are not met, undifferentiated somatoform disorder should be diagnosed. By definition, undifferentiated somatoform disorder requires a duration of 6 months. If this criterion is not met, a diagnosis of somatoform disorder NOS should be considered.

Patients with an apparent undifferentiated somatoform disorder should be carefully evaluated for somatization disorder. Typically, patients with somatization disorder are inconsistent historians, at one evaluation reporting a large number of symptoms fulfilling criteria for the full syndrome, at another time endorsing fewer symptoms (Martin et al. 1979). In addition, with follow-up, additional symptoms may become evident, and criteria for somatization disorder will be satisfied. Patients with multiple somatic complaints not diagnosed with somatization disorder because of a reported onset later than 30 years of age may be inaccurately reporting a later age at onset. If the late age at onset is accurate, the patient should be carefully scrutinized for an occult general medical condition.

In addition to the range of symptoms specified in the other somatoform disorders, patients complaining primarily of fatigue (chronic fatigue syndrome), bowel problems (irritable bowel syndrome), or multiple muscle aches/weakness (fibromyalgia) can be considered for undifferentiated somatoform disorder. Substantial controversy exists regarding the etiology of such syndromes. Even if an explanation on the basis of a known pathophysiological mechanism cannot be established, many argue that the syndromes should be considered general medical conditions. However, for the time being, these syndromes could be considered in a highly tentative manner under the undifferentiated somatoform disorder rubric. Careful reconsideration of the psychiatric label should be undertaken at regular intervals if the symptoms persist. The psychiatrist should remain ever vigilant to the emergence of another general medical or psychiatric condition. Noteworthy is also the fact, when patients are diagnosed with chronic fatigue syndrome, careful evaluation procedures as recommended by an international study group should be followed (Fukuda et al. 1994).

## Etiology and Pathophysiology

Theories of etiology involving the concept of somatization have been posited by some. As reviewed by Kirmayer and Robbins (1991), somatization can be viewed as "a pattern of illness behavior by which bodily idioms of distress may serve as symbolic means of social regulation as well as protest

or contestation." However, as previously discussed, such hypotheses have defied verification.

Clinical Vignette 2

A 34-year-old woman was referred for psychiatric evaluation of "possible depression and anxiety" by her primary care physician. For at least the past 2 years, she complained of painful, prolonged menstruation with excessive flow, abdominal cramping even when not menstruating, fatigue, and headaches. Medical investigation including extensive blood work, gynecological examination, and gastrointestinal evaluations did not establish any objective findings. Despite her reports of excessive menstruation, she had never been anemic and had not lost any weight. Her headaches varied. Some were preceded by an aura and were associated with nausea, vomiting, and photophobia, but most were consistent with "tension headaches" and relieved by acetaminophen. When discussing her personal life, the patient became tearful. Although she remained married, she reported little support from her husband of 9 years who was dedicated to his work, spending excessive hours at the office and on the road, leaving the patient with much of the responsibility for the household and their three young children aged 8, 6, and 3 years. She felt that she could not tolerate the situation much longer. She was sad but thought that if her home situation improved, she would have hope. She felt exhausted from the time she awoke in the morning to when she went to bed, had some loss of appetite but no weight loss, remained interested in things, but "just didn't have the time." She reported trouble concentrating but attributed it to being interrupted every 5 minutes with some "kid problem." She felt down on herself and that she was "wasting all the potential I have" taking care of the home and her children. She denied any suicidal ideation but believed that "if I died everyone would see how much I do around here!" She denied feeling tense or anxious or any episodes of apprehension.

She had no prior history of psychiatric problems, and before the onset of her menstrual and abdominal problems, she had been in good health. However, on further exploration, she reported that she had a period in her teens when she had similar problems after breaking up with a boyfriend and experiencing some academic problems. She also later reported occasional miscellaneous medical problems for which she sought medical attention; these were generally associated with "something that was going around."

The psychiatric impression was (1) possible undifferentiated somatoform disorder but rule out depressive disorder NOS or dysthymic disorder; (2) rule out somatization disorder; although the patient's history as presently obtained did not fulfill criteria, it was noted that she was an inconsistent historian, and thus a thorough review of her medical records was indicated; (3) possible unidentified general medical condition; and (4) partner relational problem. Recommendations included that (1) the patient's home situation be assessed for possible redistribution of the work and responsibility load; (2) the patient and her husband be referred for marital counseling; (3) while the patient's psychiatric history was being further assessed, an antidepressant medication with a low sedation side effect profile should be started on a trial basis; and (4) the primary care physician should be advised to be vigilant for a possible unidentified underlying general medical condition, given the ambiguity of the patient's psychiatric status.

If it is assumed that undifferentiated somatoform disorder is simply an abridged form of somatization disorder, etiological theories reviewed under that diagnosis should apply. An intriguing research question is why the syndrome is fully expressed in some and only partially expressed in others.

### Treatment

In view of the broad inclusion and minimal exclusion criteria for undifferentiated somatoform disorder, it is difficult to make treatment recommendations beyond the generic guidelines outlined for the somatoform disorders in general. More definitive recommendations await a more extensive empirical database. A substantial proportion of patients with undifferentiated somatoform disorders improve or recover with no formal therapy. However, appropriate psychotherapy and pharmacological intervention may accelerate the process.

Kellner (1991) outlined some recommendations for patients with symptoms of headache, fibromyalgia, and chronic fatigue syndrome, conditions that some would include under undifferentiated somatoform disorder. Generally recommended are brief psychotherapy of a supportive and educative nature. As with somatization disorder, the physician–patient relationship is of great importance. Judicious use of pharmacotherapy may also be of benefit; particularly if the somatoform syndrome is intertwined with an anxiety or depressive syndrome. Here, usual antianxiety and antidepressant medications are recommended. Patients with unexplained pains may benefit from pain management strategies as outlined in the pain disorder section.

## CONVERSION DISORDER

### Definition and Diagnostic Features

As defined in DSM-IV-TR, conversion disorders are characterized by symptoms or deficits affecting voluntary motor or sensory function that suggest yet are not fully explained by a neurological or other general medical condition or the direct effects of a substance. The diagnosis is not made if the presentation is explained as a culturally sanctioned behavior or experience, such as bizarre behaviors resembling a seizure during a religious ceremony. Symptoms are not intentionally produced or feigned, that is, the person does not consciously contrive a symptom for external rewards, as in malingering, or for the intrapsychic rewards of assuming the sick role, as in factitious disorder.

Four subtypes with specific examples of symptoms are defined: with motor symptom or deficit (e.g., impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, and urinary retention); with sensory symptom or deficit (e.g., loss of touch or pain sensation, double vision, blindness, deafness, and hallucinations); with seizures or convulsions; and with mixed presentation (i.e., has symptoms of more than one of the other subtypes). The list of examples is also contained among the pseudoneurological symptoms listed in the diagnostic criteria for somatization disorder. Although determination is highly subjective and of questionable reliability and validity, association with psychological factors is required.

To a great extent, the concept of a conversion disorder derived from the work of neurologists such as Charcot,

**DSM-IV-TR Criteria** 300.11

**Conversion Disorder**

A. One or more symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general medical condition.

B. Psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors.

C. The symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering).

D. The symptom or deficit cannot, after appropriate investigation, be fully explained by a general medical condition, or by the direct effects of a substance, or as a culturally sanctioned behavior or experience.

E. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

F. The symptom or deficit is not limited to pain or sexual dysfunction, does not occur exclusively during the course of somatization disorder, and is not better accounted for by another mental disorder.

*Specify* type of symptom or deficit:

**With motor symptom or deficit** (e.g., impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, and urinary retention)

**With sensory symptom or deficit** (e.g., loss of touch or pain sensation, double vision, blindness, deafness, and hallucinations)

**With seizures or convulsions** (includes seizures or convulsions with voluntary sensory components)

**With mixed presentation** (if symptoms of more than one category are evident)

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Breuer, and Freud (1893–1895) in the late 19th and early 20th centuries and more recently of Ziegler and Paul (1954) and Marsden (1986). Conversion disorder was called conversion reaction in DSM-I and hysterical neurosis, conversion type in DSM-II. In both DSM-I and DSM-II, the conversion process was restricted to symptoms affecting the voluntary motor and sensory nervous systems. Symptoms for which there was some physiological understanding (generally involving the autonomic nervous system) were subsumed under the psychophysiological disorders.

Unfortunately, conversion disorder or conversion hysteria came to be equated, at least by some, with hysteria, a term used by others to describe a more pervasive, chronic, and polysymptomatic disorder, denoted as somatization disorder in DSM-III, DSM-III-R, and DSM-IV-TR. Whereas conversion symptoms are among its most dramatic symptoms, somatization disorder is characterized by multiple unexplained symptoms in many organ systems; in conversion disorder, even a single symptom affecting voluntary motor or sensory function may suffice. Such nosological inconsistencies have resulted in a great deal of confusion, both in research and in clinical practice.

To add to the confusion, DSM-III and DSM-III-R used a broadened definition of conversion, including disorders characterized by symptoms involving any "loss or alteration in physical functioning suggesting a physical disorder," as long as the mechanism of conversion was evident, that is, the symptom was "an expression of a psychological conflict or need." Thus, disparate symptoms, including those involving primarily the autonomic or endocrine system, for example, "psychogenic" vomiting (assumedly expressing revulsion and disgust) and "pseudocyesis" (interpreted as representing unconscious conflict regarding pregnancy), were included as examples of conversion symptoms. In DSM-IV-TR, conversion disorder was again restricted to symptoms affecting the voluntary motor and sensory systems. This change was consistent with the symptomatic, epidemiological, and prognostic differences between the pseudoneurological conversion symptoms and other types of symptoms involving "function."

The relationship of conversion disorder to the dissociative disorders warrants comment (Martin 1996). Long recognized as related, they were subsumed as subtypes of hysterical neurosis in DSM-II: conversion involving voluntary motor and sensory functioning, and dissociation affecting memory and identity. They are unified in one category in ICD-10: dissociative (conversion) disorders. DSM-IV-TR retained the basic organization of DSM-III and, DSM-III-R, classifying conversion disorder with the somatoform disorders; the dissociative disorders compose their own major grouping. However, the DSM-IV-TR text acknowledges the symptomatic, epidemiological, and probable pathogenetic similarities between conversion and dissociative symptoms. Such symptoms have been attributed to similar psychological mechanisms, and they often occur in the same individual, sometimes during the same episode of illness. DSM-IV-TR does suggest that patients with conversion disorder be carefully scrutinized for dissociative symptoms.

Hallucinations are included among the sensory nervous symptoms in DSM-IV-TR. Whereas the concept of conversion hallucinations has a long tradition (Martin 1996), DSM-III and DSM-III-R noted hallucinations as a manifestation of only two nonpsychotic disorders: posttraumatic stress disorder, in which a traumatic event is reexperienced, and multiple personality disorder (dissociative identity disorder in DSM-IV-TR), wherein one or more personalities hear the voice of, talk with, or engage in activities with one or more of the other personalities. Inclusion of hallucinations as a conversion symptom was supported by the somatization disorder field trial, in which one-third of a large sample of nonpsychotic women with evidence of unexplained somatic complaints reported a history of hallucinations. Among the 40% who had symptoms that met criteria for somatization

disorder, more than half reported hallucinations (Martin 1995, unpublished data). Women with other conversion symptoms were more likely to report hallucinations than were those with no other conversion symptoms.

In general, conversion hallucinations (referred to by some as pseudohallucinations) differ in several ways from those in psychotic conditions. Conversion hallucinations typically occur in the absence of other psychotic symptoms, insight that the hallucinations are not real may be retained, and they often involve more than one sensory modality, whereas hallucinations in psychoses generally involve a single sensory modality, usually auditory. Conversion hallucinations also often have a naive, fantastic, or childish content, as if they are part of a fairy tale, and are described eagerly, sometimes even provocatively, as an interesting story (e.g., "I was driving downtown and a flying saucer flew over my car and I saw you [the psychiatrist] in a window and I heard your voice calling to me"). They often bear some understandable psychological purpose, although the patient may not be aware of intent. In the example given, the "sighting" was reported at the time that no further sessions were scheduled.

## Epidemiology

Vastly different estimates of the incidence and prevalence of conversion disorder have been reported. Much of this difference may be attributable to methodological differences from study to study, including the changing definition of conversion disorder, ascertainment procedures, and populations studied. General population estimates have generally been derived indirectly, extrapolating from clinic or hospital samples.

Conversion symptoms themselves may be common; it was reported that 25% of normal postpartum and medically ill women had a history of conversion symptoms at some time during their life (Cloninger 1993), yet in some instances, there may have been no resulting clinically significant distress or impairment. Lifetime prevalence rates of treated conversion symptoms in general populations are much more modest, ranging from 11 to 500 per 100,000 (Martin 1996) (see Table 74–1). About 5–24% of psychiatric outpatients, 5–14% of general hospital patients, and 1–3% of outpatient psychiatric referrals reported a history of conversion symptoms (Cloninger 1993, Ford and Folks 1985, Toone 1990), although their current treatment was not necessarily for conversion symptoms. A rate of nearly 4% of outpatient neurological referrals (Perkin 1989) and 1% of neurological admissions (Ziegler and Paul 1954) involved conversion disorder. In virtually all studies, an excess (to the extent of 2:1 to 10:1) of women reported conversion symptoms relative to men (Ljunberg 1957, Stefansson et al. 1976, Raskin et al. 1966). In part, this may relate to the simple fact that women seek medical evaluation more often than men do, but it is unlikely that this fully accounts for the sex difference. There is a predilection for lower socioeconomic status; less educated, less psychologically sophisticated, and rural populations are overrepresented (Veith 1965, Weinstein et al. 1969, Lazare 1981, Folks et al. 1984). Consistent with this, higher rates (nearly 10%) of outpatient psychiatric referrals are for conversion symptoms in "developing" countries (Stafanis et al. 1976). As countries develop, there may be a declining incidence in time, which may relate to increasing levels of education, and medical and psychological sophistication (Nandi et al. 1992).

## Course

Age at onset is typically from late childhood to early adulthood. Onset is rare before the age of 10 years (Maloney 1980) and after 35 years, but cases with an onset as late as the ninth decade have been reported (Weddington 1979). The likelihood of a neurological or other medical condition is increased when the age at onset is in middle or late life. Development is generally acute, but symptoms may develop gradually as well. The course of individual conversion symptoms is generally short; half (Folks et al. 1984) to nearly all (Carter 1949) symptoms remit by the time of hospital discharge. However, symptoms relapse within 1 year in one-fifth to one-fourth of patients. Typically, one symptom is present in a single episode, but multiple symptoms are generally involved longitudinally. Factors associated with good prognosis include acute onset, clearly identifiable precipitants, a short interval between onset and institution of treatment, and good intelligence (Toone 1990). Conversion blindness, aphonia, and paralysis are associated with relatively good prognosis, whereas patients with seizures and tremor do more poorly. Some patients diagnosed initially with conversion disorder will have a presentation that meets criteria for somatization disorder when they are observed longitudinally (Kent et al. 1995).

Individual conversion symptoms are generally self-limited and do not lead to physical changes or disabilities. Rarely, physical sequelae such as atrophy may occur. Marital and occupational problems are not as frequent in patients with conversion disorder as they are in those with somatization disorder (Tomasson et al. 1991, Coryell and House 1984). In a long-term follow-up study, excess mortality by unnatural causes was observed (Coryell and House 1984). However, the reason for this was unclear in that none of the deaths was by suicide.

## Differential Diagnosis

As shown in Figure 74–1, the first consideration is whether the conversion symptoms are explained on the basis of a general medical condition. Because conversion symptoms by definition affect voluntary motor or sensory function (thus pseudoneurological), neurological conditions are usually suggested, but other general medical conditions may be implicated as well. Neurologists are generally first consulted by primary care physicians for conversion symptoms; psychiatrists become involved only after neurological or general medical conditions have been reasonably excluded. Nonetheless, psychiatrists should have a good appreciation of the process of making such exclusions. More than 13% of actual neurological cases are diagnosed as functional before the elucidation of a neurological illness (Perkin 1989). Even after referral, vigilance for an emerging general medical condition should continue. A significant percentage—21% (Gatfield and Guze 1962) to 50% (Slater and Glithero 1965)—of patients diagnosed with conversion symptoms are found to have neurological illness on follow-up.

Apparent conversion symptoms mandate a thorough evaluation for possible underlying physical explanation. This evaluation must include a thorough medical history, physical

(especially neurological) examination, and radiographical, blood, urine, and other tests as clinically indicated. Reliance should not be placed on determination of whether psychological factors explain the symptom. As reviewed by Cloninger (1987), such determinations are unreliable except, perhaps, in the cases in which there is a clear and immediate temporal relationship between a psychosocial stressor and the symptom, or in the cases in which similar situations led to conversion symptoms in the past. A history of previous conversion or other unexplained symptoms, particularly if somatization disorder is diagnosable, lessens the probability that an occult medical condition will be identified (Cloninger 1993). Although conversion symptoms may occur at any age, symptoms are most often first manifested in late adolescence or early adulthood. Conversion symptoms first occurring in middle age or later should increase suspicion of an occult physical illness.

Symptoms of many neurological illnesses may appear inconsistent with known neurophysiological or neuropathological processes, suggesting conversion and posing diagnostic problems. These illnesses include multiple sclerosis, in which blindness due to optic neuritis may initially present with normal fundi; myasthenia gravis, periodic paralysis, myoglobinuric myopathy, polymyositis, and other acquired myopathies, in which marked weakness in the presence of normal deep tendon reflexes may occur; and Guillain–Barré syndrome, in which early extremity weakness may be inconsistent (Cloninger 1993).

Complicating diagnosis is the fact that physical illness and conversion or other apparent psychiatric overlay are not mutually exclusive. Patients with physical illnesses that are incapacitating and frightening may appear to be exaggerating symptoms. Also, patients with actual neurological illness will also have "pseudo" symptoms. For example, patients with actual seizures may have pseudoseizures as well (Desai et al. 1982). Considering these observations, psychiatrists should avoid a rash and hasty diagnosis of conversion disorder when faced with symptoms that are difficult to interpret.

As with the other somatoform disorders, symptoms of conversion disorder are not intentionally produced, in distinction to malingering or factitious disorder. To a large part, this determination is based on assessment of the motivation for external rewards (as in malingering) or for the assumption of the sick role (as in factitious disorder). The setting is often an important consideration. For example, conversion-like symptoms are frequent in military or forensic settings, in which obvious potential rewards make malingering a serious consideration.

A diagnosis of conversion disorder should not be made if a conversion symptom is fully accounted for by a mood disorder or by schizophrenia (e.g., disordered motility as part of a catatonic syndrome of a psychotic mood disorder or schizophrenia). If the symptom is a hallucination, it must be remembered that the descriptors differentiating conversion from psychotic hallucinations should be seen only as rules of thumb. Differentiation should be based on a comprehensive assessment of the illness. In the case of hallucinations, posttraumatic stress disorder and dissociative identity disorder (multiple personality disorder) must also be excluded. If the conversion symptom cannot be fully accounted for by the other psychiatric illness, conversion disorder should be diagnosed in addition to the other disorder if it meets criteria (e.g., an episode of unexplained blindness in a patient with a major depressive episode). In hypochondriasis, neurological illness may be feared ("I have strange feelings in my head; it must be a brain tumor"), but the focus here is on preoccupation with fear of having the illness rather than on the symptom itself as in conversion disorder.

By definition, if symptoms are limited to sexual dysfunction or pain, conversion disorder is not diagnosed. Criteria for somatization disorder require multiple symptoms in multiple organ systems and functions, including symptoms affecting motor or sensory function (conversion symptoms) or memory or identity (dissociative symptoms). Thus, it would be superfluous to make an additional diagnosis of conversion disorder in the context of a somatization disorder.

A last consideration is whether the symptom is a culturally sanctioned behavior or experience. Conversion disorder should not be diagnosed if symptoms are clearly sanctioned or even expected, are appropriate to the sociocultural context, and are not associated with distress or impairment. Seizure-like episodes, such as those that occur in conjunction with certain religious ceremonies, and culturally expected responses, such as women "swooning" in response to excitement in Victorian times, qualify as examples of these symptoms.

## Etiology and Pathophysiology

The term conversion implies etiology because it is derived from a hypothesized mechanism of converting psychological conflicts into somatic symptoms, often symbolically (e.g., repressed rage is converted into paralysis of an arm that could be used to strike). A number of psychological factors have been promoted as part of such an etiological process, but evidence for their essential involvement is scanty at best. Theoretically, anxiety is reduced by keeping an internal conflict or need out of awareness by symbolic expression of an unconscious wish as a conversion symptom (primary gain). However, individuals with active conversion symptoms often continue to show marked anxiety, especially on psychological tests (Lader and Sartorious 1968, Mears and Horvath 1972). Symbolism is infrequently evident, and its evaluation involves highly inferential and unreliable judgments (Raskin et al. 1966). Overinterpretation of symbolism in persons with occult medical condition may contribute to misdiagnosis. Secondary gain, whereby conversion symptoms allow avoidance of noxious activities or the procurement of otherwise unavailable support, may also occur in persons with medical conditions, who may take advantage of such benefits (Raskin et al. 1966, Watson and Buranen 1979).

Individuals with conversion disorder may show a lack of concern out of keeping with the nature or implications of the symptom (the so-called *la belle indifférence*). However, indifference to symptoms is not invariably present in conversion disorder (Lewis and Berman 1965) and is also seen in individuals with general medical conditions (Weinstein et al. 1969), on the basis of denial or stoicism (Pincus 1982). Conversion symptoms may present in a dramatic or histrionic fashion and may be highly suggestible. A dramatic presentation is also seen in distressed individuals with medical

conditions. Even symptoms based on an underlying medical condition may respond to suggestion, at least temporarily (Gatfield and Guze 1962). In many instances, preexisting personality disorders (in particular histrionic personality disorder) are evident and may predispose to conversion disorder. Persons with conversion disorder may often have a history of confused sexuality (Lewis 1974) many (one-third) report a history of sexual abuse, especially incestuous. Thus, two-thirds may not report such a history. Individuals with conversion disorder are often reported to be the youngest or the youngest of a sex in sibling order, but this is not a consistent finding (Ziegler et al. 1960, Stephens and Kamp 1962).

If not directly etiological, many psychosocial factors have been suggested as predisposing to conversion disorder. At a minimum, many persons with conversion disorder are in chaotic domestic and occupational situations. As previously mentioned, individuals from rural backgrounds and those who are psychologically and medically unsophisticated appear to be predisposed, as are those with existing neurological disorders. In the last case, a tendency to conversion symptoms has been attributed to "modeling," that is, patients with neurological disorders are likely to have observed in others, as well as in themselves, various neurological symptoms, which they then may simulate as conversion symptoms.

Available data suggest a genetic contribution. Conversion symptoms are more frequent in relatives of individuals with conversion disorder (Toone 1990). In a nonblinded study, rates of conversion disorder were found to be elevated tenfold in female (fivefold in male) relatives of patients with conversion disorder (Ljunberg 1957). Accumulated data from available twin studies show 9 concordant and 33 discordant monozygotic pairs and no concordant but 43 discordant dizygotic pairs (Inouye 1972). Nongenetic familial factors, particularly incestuous childhood sexual abuse, may also be involved in some. Nearly one-third of individuals with medically unexplained seizures reported childhood sexual abuse, compared with less than 10% of those with complex partial epilepsy (Alper et al. 1993). Data looking specifically at abuse history in other well-defined conversion disorder cases are not available.

## Treatment

Reports of the treatment of conversion disorder date from those of Charcot, which generally involved symptom removal by suggestion or hypnosis. Breuer and Freud, using such psychoanalytic techniques as free association and abreaction of repressed affects, had more ambitious objectives in their treatment of Anna O., including the resolution of unconscious conflicts. To date, whereas some recommend long-term, intensive, insight-oriented psychodynamic psychotherapy in pursuit of such goals (Ford 1995), most psychiatrists advocate a more pragmatic approach, especially for acute cases.

Therapeutic approaches vary according to whether the conversion symptom is acute or chronic. Whichever the case, direct confrontation is not recommended. Such a communication may cause a patient to feel even more isolated. An undiscovered physical illness may also underlie the presentation.

In acute cases, the most frequent initial aim is removal of the symptom. The pressure behind accomplishing this depends on the distress and disability associated with the symptom (Ford 1995). If the patient is not in great distress and the need to regain function is not immediate, a conservative approach of reassurance, relaxation, and suggestion is recommended (Ford 1983). With this technique, the patient is reassured that on the basis of evaluation the symptom will disappear completely and, in fact, is already beginning to do so. The patient can then be encouraged to ventilate about recent events and feelings, without any causal relationships being suggested. This is in contrast to attempts at abreaction, by which repressed material, particularly regarding a painful experience or a conflict, is brought back to consciousness.

If symptoms do not resolve with such conservative approaches, a number of other techniques for symptom resolution may be instituted. It does appear that prompt resolution of conversion symptoms is important because the duration of conversion symptoms is associated with a greater risk of recurrence and chronic disability (Cloninger 1993). The other techniques include narcoanalysis (e.g., amobarbital interview), hypnosis, and behavioral therapy (Ford 1995). In narcoanalysis, amobarbital or another sedative–hypnotic medication such as lorazepam is given intravenously to the point of drowsiness. Sometimes this is followed by administration of a stimulant medication, such as methamphetamine. The patient is then encouraged to discuss stressors and conflicts. This technique may be effective acutely, leading to at least temporary symptom relief as well as expansion of the information known about the patient. This technique has not been shown to be especially effective with more chronic conversion symptoms. In hypnotherapy, symptoms may be removed with the suggestion that the symptoms will gradually improve posthypnotically. Information regarding stressors and conflicts may be explored as well. Formal behavioral therapy, including relaxation training and even aversive therapy, has been proposed and reported by some to be effective. In addition, simply manipulating the environment to interrupt reinforcement of the conversion symptom is recommended.

Anecdotally, somatic treatments including phenothiazines, lithium, and electroconvulsive therapy have been reported effective. However, in many cases, this may be attributable to simple suggestion. In other cases, resolution of another psychiatric disorder, such as a psychotic disorder or a mood disorder, may have led to the symptom's removal. It should be evident from the preceding discussion that in acute conversion disorders, it may be not the particular technique but the influence of suggestion that is specifically associated with symptom relief. It is likely that in various rituals, such as exorcism and other religious ceremonies, immediate "cures" are based on suggestion. Suggestion seems to play a major role in the resolution of "mass hysteria," in which a group of individuals who believe that they have been exposed to some noxious influence such as a "toxin" or even a "spell" experience similar symptoms that do not appear to have any organic basis. Often, the epidemic can be contained if affected individuals are segregated. Simple announcements that no such factor has been identified and that symptoms experienced by the group have been linked to mass hysteria have been effective.

Thus far, this discussion has centered on acute treatment primarily for symptom removal. Longer term

approaches include strategies previously discussed for somatization disorder—a pragmatic, conservative approach involving support and exploration of various conflict areas, particularly of interpersonal relationships. A certain degree of insight may be attained, at least in terms of appreciating relationships between various conflicts and stressors and the development of symptoms. Others advocate long-term, intensive, insight-oriented dynamic psychotherapy.

Clinical Vignette 3

A 47-year-old woman was referred for psychiatric consultation by her primary care physician at the recommendation of a neurologist. She had been admitted to the hospital 2 days earlier, after presenting with mild acidosis attributed to poor control of her insulin-dependent diabetes mellitus. She had become concerned that insulin was "making me fat" and had been taking it erratically for several weeks. On admission, she also complained of generalized muscle weakness, more pronounced on the left side, especially in the arm, and reported that she had had a "stroke" affecting the right side 1 year before, for which she was not hospitalized. On examination, the neurologist observed that the patient showed no atrophy or spasticity and that deep tendon reflexes were decreased but equal bilaterally. On testing of the left upper extremity, the patient was observed to show weakness in extending and flexing the arm against resistance, yet more careful examination revealed residual strength inconsistent with that shown in these tests. Her primary care physician reported some question of a stroke 1 year before, which was never clearly ascertained. A "hysterical component to the neurological symptoms" was considered. Nonetheless, diagnostic procedures were instituted, including magnetic resonance imaging. No abnormalities were seen by this test. Two days later, it was concluded that a stroke was improbable, and noting reports of depressed mood, the neurologist recommended psychiatric consultation.

When seen by the psychiatric consultant, she still complained of the weakness, although it was somewhat improved and not so clearly localized to the left side. She also mentioned that she had been depressed for several weeks before admission and that she had been treated with some success with fluoxetine in the past. She reported multiple conflicts concerning her living situation. She was living with her married son and felt that his wife resented her presence. She felt "trapped" in that she could not afford to live independently. Medical records indicated that diabetes mellitus had been diagnosed at age 36 years and was treated with oral hypoglycemic agents until age 41 years, when insulin became necessary for adequate control. The record also revealed several episodes of transient unexplained weakness as well as occasional problems with headaches and joint pain going back to age 26 years, with several mentions of temporal proximity of such symptoms to marital and occupational difficulties. Yet, criteria for somatization disorder were not fulfilled.

The psychiatrist's provisional diagnoses were (1) psychological factors affecting medical condition (noncompliance with insulin regimen); (2) conversion disorder, with motor symptom or deficit; and (3) possible major depressive disorder, recurrent. Treatment with sertraline, 50 mg at bedtime, was recommended. It was also suggested to the patient that her tests were now completed and that it was expected that her weakness would continue to improve. When the psychiatrist visited her the next day, she reported that her weakness was better and that she was also beginning to feel less depressed. The patient was encouraged to continue to see her primary care physician and to comply with his recommendations, and she was referred to social work for assistance with her living situation. Referral for outpatient psychiatric care was also recommended.

This clinical vignette illustrates several important aspects concerning the diagnosis, course, and treatment of conversion disorder. As is not uncommon, the patient does suffer from a medical illness to which many symptoms can ordinarily be attributed. However, the extent of her complaints, the lack of neuroanatomical verification, and inconsistencies of her report and the documented history suggested a possibility that her motor symptoms were not fully attributable to a general medical condition. This interpretation was supported by her past history of apparent conversion symptoms as well as some other somatic complaints. Although she was also complaining of depression, her history was vague, and her "response" to 1 day of treatment with an antidepressant drug was unlikely to be pharmacological. Her motor symptoms were resolving with reassurance and suggestion, such that the short-term prognosis for her motor symptoms was good. However, her history of noncompliance with medical treatment, and multiple situational and interpersonal problems indicated the advisability of continued psychosocial if not psychiatric intervention.

## PAIN DISORDER

### Definition and Diagnostic Features

The term "pain disorder" was new to DSM-IV-TR. It replaced the DSM-III-R designation somatoform pain disorder. Because the disorder was already included in the somatoform grouping, somatoform was redundant. In addition, whereas the DSM-III-R somatoform pain disorder was more neutral than the DSM-III psychogenic pain disorder, it maintained differentiation between imaginary or exaggerated and real pain, following a dualistic dichotomy of separating mind and body. The matter of determining psychogenicity was always a problem (Williams and Spitzer 1982). As reviewed by Cloninger (1993), raters show only moderate agreement on such questions even when they are given the same information. Yet, both DSM-III psychogenic pain disorder and DSM-III-R somatoform pain disorder required that the pain not have an organic or pathophysiological explanation and that the complaint or impairment be greatly in excess of what would be expected from the physical findings.

As defined in DSM-IV-TR, the essential feature of pain disorder is pain with which psychological factors "have an important role in the onset, severity, exacerbation, or maintenance". Pain disorder is subtyped as pain disorder associated with psychological factors and pain disorder associated with both psychological factors and a general medical condition. The third possibility, pain disorder associated with a general medical condition, is not considered to be a mental disorder, because the requirement is not met that psychological factors play an important role. Thus, the DSM-IV-TR concept of pain disorder as a mental disorder

**DSM-IV-TR Criteria** 307.xx

**Diagnostic Criteria for Pain Disorder**

A. Pain in one or more anatomical sites is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention.

B. The pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain.

D. The symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering).

E. The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for dyspareunia.

*Code* as follows:

**307.80 Pain disorder associated with psychological factors:** Psychological factors are judged to have the major role in the onset, severity, exacerbation, or maintenance of the pain. (If a general medical condition is present, it does not have a major role in the onset, severity, exacerbation, or maintenance of the pain.) This type of pain disorder is not diagnosed if criteria are also met for somatization disorder.

*Specify* if:

**Acute**: Duration of less than 6 months

**Chronic**: Duration of 6 months or longer

**307.89 Pain disorder associated with both psychological factors and a general medical condition:** Both psychological factors and a general medical condition are judged to have important roles in the onset, severity, exacerbation, or maintenance of the pain. The associated general medical condition or anatomical site of the pain (see below) is coded on Axis III.

*Specify* if:

**Acute:** Duration of less than 6 months

**Chronic:** Duration of 6 months or longer

**Note:** The following is not considered to be a mental disorder and is included here to facilitate differential diagnosis.

**Pain disorder associated with a general medical condition:** A general medical condition has a major role in the onset, severity, exacerbation, or maintenance of the pain. (If psychological factors are present, they are not judged to have a major role in the onset, severity, exacerbation, or maintenance of the pain.) The diagnostic code for the pain is selected based on the associated general medical condition if one has been established or on the anatomical location of the pain if the underlying general medical condition is not yet clearly established—for example, low back (724.2), sciatic (724.3), pelvic (625.9), headache (784.0), facial (784.0), chest (786.50), joint (719.4), bone (733.90), abdominal (789.0), breast (611.71), renal (788.0), ear (388.70), eye (379.91), throat (784.1), tooth (525.9), and urinary (788.0).

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was broadened and allowed the psychiatrist much greater specificity in considering etiological factors and a more useful schema for differential diagnosis. The focus is placed on the presence of psychological factors rather than the exasperating determination of whether the pain is attributable to organic disease.

In addition, DSM-IV-TR requires that pain be the predominant focus of the clinical presentation and that it cause clinically significant distress or impairment. Specifiers of acute (duration of less than 6 months) and chronic (duration of 6 months or longer) are provided. Both DSM-III and DSM-III-R required chronicity: prolonged in DSM-III, for at least 6 months in DSM-III-R. This left no place for clinically significant syndromes of recent onset or limited duration and undoubtedly contributed to the fact that DSM-III and DSM-III-R pain diagnoses were little used.

With the changes outlined, the DSM-IV-TR-defined pain disorder is compatible with current theories of pain and should be more clinically applicable.

## Epidemiology

Given the tortuous course of changing diagnostic criteria, only estimates can be made for the epidemiological parameters of pain disorder. As to pain itself, some empirical studies suggest that it is common. Perhaps an indirect evidence of this is the proliferation of pain clinics nationally. Of course, many patients attending these clinics fall into the category of pain disorder associated with a general medical condition, but undoubtedly, some also have involvement of psychological factors as required for a diagnosis of pain disorder as a mental disorder. The same would apply to the 10–15% of adults in the US in any given year who have work disability because of back pain (Osterweis et al. 1987). Pain has been found to be a predominant symptom in 75% of consecutive general medical patients, with 75% of these (thus 50% overall) judged as having no identifiable physical cause (King 1994). As reviewed by Stoudemire (1988), no apparent physical basis is found in 40–50% of patients presenting with nonspecific abdominal pain. At least half of such patients show major personality problems in addition,

with such aberrations associated with poor outcome. Whereas primary care and other nonpsychiatric physicians probably see most pain patients, 38% of psychiatric inpatient admissions (Delaplaine et al. 1978) and 18% attending a psychiatric outpatient clinic (Chaturvedi 1987) report pain as a significant problem.

## Course

Given the heterogeneity of conditions subsumed under the pain disorder rubric, course, and prognosis vary widely. The subtyping at 6 months is of significance. The prognosis for total remission is good for pain disorders of less than 6 months' duration. However, for syndromes of greater than 6 months' duration, chronicity is common. The site of the pain may be another factor. As described by Stoudemire and Sandhu (1987), certain anatomically differentiated pain syndromes can be distinguished, and each has its own characteristic pattern. These include syndromes characterized primarily by headache, facial pain, chest pain, abdominal pain, and pelvic pain. In such syndromes, symptoms tend to be recurrent, with relapses occurring in association with stress. A high rate of depression has been observed among patients with unexplained facial pain. Facial pain is often alleviated by antidepressant medication. This effect has been observed in both patients with depressive symptoms and those without.

Other factors affecting course and prognosis include associated psychiatric illness and external reinforcement. Employment at the outset of treatment predicts improvement (Martin 1995). Chronicity is more likely in the presence of certain personality diagnoses or traits, such as pronounced passivity and dependency. External reinforcement includes litigation involving potential financial compensation or disability. Continuation of the pain disorder may prove more lucrative than its resolution and return to work. Level of activity, which is generally associated with improvement, is discouraged by fears of losing compensation. Thus, although outright malingering may be rare (Leavitt and Sweet 1986), pain behaviors are often reinforced and maintained. Habituation with addictive drugs is associated with greater chronicity.

## Differential Diagnosis

As shown in Figure 74–1, the diagnostic approach begins with assessment of whether the presentation is fully explained by a general medical condition. If not, it may be assumed that psychological factors play a major role. If it is judged that psychological factors do not play a major role, a diagnosis of pain disorder associated with a general medical condition may apply. As previously mentioned, this does not have a mental disorder code.

If psychological factors are involved, the first consideration is whether the pain is feigned. If so, either malingering or factitious disorder is diagnosed, depending on whether external incentives or assumption of the sick role is the motivation. Evidence of malingering includes consideration of external rewards relative to the chronology of the development and maintenance of the pain. In factitious disorder, a pattern of successive hospitalizations and medical evaluations is evident. Inconsistency in presentation, lack of correspondence to known anatomical pathways or disease patterns, and lack of associated sensory or motor function changes suggest malingering or factitious disorder, but pain disorder associated with psychological factors may show this pattern as well. The key question is whether the patient is experiencing rather than feigning the pain.

Determination of the relative contributions of psychological and general medical factors is difficult. Of course, careful assessment of the nature and severity of the potential underlying medical condition and the nature and degree of pain that would be expected should be made. Traditionally, the so-called conversion V or neurotic triad (consisting of elevation of the hypochondriasis and hysteria scales with a lower score on the depression scale) on the Minnesota Multiphasic Personality Inventory has been purported to indicate emotional indifference to the somatic concerns as might be expected if the symptom is attributable to psychological factors rather than organic disease. However, evidence indicates that this configuration may also occur as an adjustment to chronic illness.

A diagnosis of pain disorder requires that the pain be of sufficient severity to warrant clinical attention, that is, it causes clinically significant distress or impairment. A number of instruments have been developed to assess the degree of distress associated with the pain. Such measures include the numerical rating scale and visual analog scale as described by Scott and Huskisson (1976), the McGill Pain Questionnaire, and the West Haven-Yale Multidimensional Pain Inventory (Osterweis et al. 1987).

DSM-IV-TR includes a number of exclusionary conventions. By definition, if pain is restricted to pain with sexual intercourse, the sexual disorder, dyspareunia, not pain disorder, is diagnosed. If pain occurs in the context of a mood, anxiety, or psychotic disorder, pain disorder is diagnosed only if it is an independent focus of clinical attention and is not better accounted for by the other disorder, a highly subjective judgment.

If pain occurs exclusively during the course of somatization disorder, pain disorder is not diagnosed because pain symptoms are part of the criteria for somatization disorder and are thereby subsumed under the more comprehensive diagnosis. Because somatization disorder is a lifelong condition, this exclusion generally applies in someone with somatization disorder by history. Important here is that in addition to pain, somatization disorder involves multiple symptoms of the gastrointestinal system, the reproductive system, and the central and peripheral nervous systems; whereas in pain disorder, the focus is on pain symptoms only.

Specification of acute versus chronic pain disorder on the basis of whether the duration is less than or greater than 6 months is an important distinction. Whereas acute pain, in most cases, will be linked with physical disorders, when pain remains unexplained after 6 months, psychological factors are often involved (Cloninger 1993). However, the psychiatrist must remember that a significant minority (in one study 19%) of patients with chronic pain of no apparent physical origin will ultimately be found to have occult organic disease (Cloninger 1993).

In patients with unexplained pelvic pain, psychiatrists should be warned about cavalier conclusions regarding the absence of physical disease. With laparoscopy, a high frequency of occult organic disease has been identified in several studies. Thus, laparoscopy may be indicated in patients with pelvic pain. Electromyography may be helpful

in distinguishing muscle contraction headaches. Failure to show coronary artery spasm with provocative procedures and failure to respond to nitroglycerin may be useful in distinguishing patients with pain disorder from those in whom the pain is attributable to coronary artery disease.

## Etiology and Pathophysiology

In considering the etiology of pain disorder, possible mechanisms of pain itself must be considered. As reviewed by King (1994), the definition of pain sanctioned by the International Association for the Study of Pain Subcommittee on Taxonomy is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." It goes on to acknowledge that pain is not simply "activity induced in the nociceptor and nociceptive pathways by a noxious stimulus" but "is always a psychological state." Thus, it accepts the hypothesis that pain involves psychological as well as physical factors.

Many theories of the etiology and pathophysiology of pain involving both biological and psychological factors have been proposed. It is known that a neuropathway descends from the cerebral cortex and medulla, which inhibits the firing of pain transmission neurons when it is activated (Cloninger 1993). This system is apparently mediated by the endogenous opiate-like compounds, endorphins, and by serotonin. Indeed, metabolites of both of these neurotransmitters may be reduced in the cerebrospinal fluid of chronic pain patients (von Knorring and Attkisson 1979).

The gate control theory developed by Melzack and Wall (1983), as reviewed by King (1994), links biological and psychological factors. It hypothesizes a gate-like mechanism involving the dorsal horn of the spinal cord by which large A-beta fibers as well as small A-delta and C fibers carry impulses from the periphery to the substantia gelatinosa and T-cells in the spinal cord. Activation of the large fibers inhibits whereas activation of the small fibers facilitates transmission to the T-cells. In addition, impulses descending from the brain, influenced by cognitive processes, may either inhibit or facilitate transmission of pain impulses. Such a mechanism may explain how psychological processes affect pain perception.

By definition, both pain disorder associated with psychological factors and pain disorder associated with both psychological factors and a general medical condition involve psychological factors. In the case of the former, it is presumed that there is little contribution from general medical conditions; in the latter, both physical and psychological factors contribute. A plethora of not necessarily mutually exclusive theories has been proposed to explain how this takes place.

As reviewed by Cloninger (1993), psychological constructs involving learning theories, both operant and classical conditioning, may apply. In operant paradigms, pain-related complaints are reinforced by increased attention, relief from obligations, monetary compensation, and the pleasurable effects of analgesics. In classical conditioning, originally neutral settings such as a workplace or bedroom where pain was experienced come to evoke pain-related behavior. Social and cultural attitudes may also have effects. Patients with unexplained pain are more likely than others to have close relatives with chronic pain. Although findings have differed from study to study, ethnic differences may also have effects, such as greater pain tolerance in Irish and Anglo-Saxon groups in comparison to southern Mediterranean groups.

## Treatment

### Psychosocial and Somatic Treatments

Treatment of pain overall has been well summarized by King (1994). An overriding guideline is that the psychiatrist not do anything that will actually perpetuate and even promote "pain-related behavior." Thus, a major goal is to encourage activity. Other guidelines include avoidance of sedative–antianxiety drugs, judicious use of analgesics on a fixed interval schedule so as not to reinforce pain-related behaviors, avoidance of opioids, and consideration of alternative treatment approaches such as relaxation therapy. Depression should be treated with appropriate antidepressant drugs, not sedative–antianxiety medications. The difficulties in managing pain disorder patients have resulted in the establishment of many clinics and programs especially designed for pain. Referral to such a service may be indicated. Intervention should best be provided early in the course of the syndrome, before pain-related behaviors become entrenched. Once continuing disability compensation is established, therapeutic efforts become much more difficult.

The preceding general guidelines apply whether or not a general medical basis for the pain is involved. Of course, if only pain disorder associated with psychological factors is involved, psychological management will be the mainstay. For patients with pain associated with general medical factors (not a mental disorder) in which psychological factors do not play a major role, efforts should be made to prevent the development of psychological problems in response to the resulting distress, isolation and loss of function, and iatrogenic effects such as exposure to potentially addicting drugs.

In acute pain, the major goal is to relieve the pain (Osterweis et al. 1987). Thus, pharmacological agents generally play a more significant role than in chronic syndromes. Whereas the risk of developing opioid dependence appears to be surprisingly low (4 per 12,000) among patients without a prior history of dependence (Porter and Jick 1980), nonopioid agents should be used whenever they can be expected to be effective. As discussed for chronic pain, these include particularly acetaminophen and the nonsteroidal antiinflammatory drugs (NSAIDs), of which aspirin is considered a member. Even if an opioid analgesic is employed, these drugs should be continued as adjuncts; often, they lessen the required dose of the opioid.

It is with the chronic syndromes that proper management is crucial to ease distress and prevent the development of additional problems. As advised by King (1994), the overriding goal is to maintain function, because total relief of the pain may not be possible. Physical and occupational therapy may play a major role. There may be resistance to the involvement of a psychiatrist as an indication that the pain is not seen as real. Such issues must first be resolved. An attempt should be made to ascertain the roles that psychological and general medical factors play in the maintenance of the pain.

A large variety of psychotherapies including individual, group, and family strategies have been employed.

Two techniques that warrant special attention are operant conditioning and CBT. In operant conditioning, the pattern of reinforcement of pain behavior by medication, attention, and excuse from responsibilities is to be interrupted and reinforcement shifted to usual daily activities. To assess the role of operant conditioning, it may be necessary to have patients keep a diary and to interview family members to identify any conditioning patterns. In CBTs, the goal is the identification and correction of attitudes, beliefs, and expectations. Biofeedback and relaxation techniques may be used to minimize muscle tension that may aggravate if not cause pain. Hypnosis may also be used to achieve muscle relaxation and to help the patient "dissociate" from the pain.

Pharmacological intervention may also be useful in chronic syndromes. Effort should be made to avoid opioids if possible. Agents to be tried first include antidepressants, acetaminophen, NSAIDs (including aspirin), and anticonvulsants such as carbamazepine. Antidepressants seem particularly useful for neuropathic pain, headache, facial pain, fibrositis, and arthritis (including rheumatoid arthritis). Analgesic action seems to be independent of antidepressant effects. Most work has been done with the tricyclic antidepressants; other classes, such as the monoamine oxidase inhibitors (MAOIs) and the selective serotonin reuptake inhibitors (SSRIs), may be effective as well. Although it was thought that the action is mediated by serotoninergic effects, agents such as desipramine with predominantly noradrenergic activity seem to be effective as well. NSAIDs, of which aspirin, ibuprofen, naproxen, and piroxicam are commonly used examples, may alleviate pain through inhibition of prostaglandin synthesis. Unfortunately, this effect may also contribute to side effects, such as aggravation of peptic or duodenal ulcers and interference with renal function. For patients unable to tolerate NSAIDs, acetaminophen should be tried.

If opioid analgesics are used, it is recommended that use be tied to objectives such as increasing level of activity rather than simply pain alleviation (King 1994). Milder opioids, such as codeine, oxycodone, and hydrocodone, should be implemented first. The once widely used propoxyphene has less analgesic effect than these drugs; it is not devoid of abuse potential as once thought and is not recommended. Pure opioid agonists such as morphine, methadone, and hydromorphone should be tried next. Meperdine, also in this class, is no longer recommended for chronic pain because prolonged use allows accumulation of a toxic metabolite, normeperdine, a cerebral irritant, which may cause anxiety, psychosis, or seizures. Meperidine may also have a lethal interaction with MAOIs.

There are no advantages to mixed opioid agonist–antagonists. The once commonly used pentazocine should be avoided because it has abuse potential and psychotomimetic effects in some patients. It remains to be seen whether newer agents (buprenorphine, butonphanol, and nalbuphine) have lower abuse potential as claimed. Above all, psychiatrists should be judicious in the use of opioid analgesics, considering not only their abuse potential but their large number of side effects including constipation, nausea and vomiting, excessive sedation, and, in higher doses, respiratory depression that may be fatal (King 1994).

In addition to pharmacotherapy, a number of other "physical" techniques have been used, such as acupuncture and transcutaneous electrical nerve stimulation. These carry little risk of adverse effects or aggravation of the pain disorder. Other procedures such as trigger point injections, nerve blocks, and surgical ablation may be recommended if specifically indicated by an underlying general medical condition.

As can be seen in the preceding discussion, the management of pain disorders is not monomodal. A great number of psychological and physical factors and interventions may be considered.

Clinical Vignette 4

A 60-year-old dentist was referred to a psychiatrist for an evaluation by an insurance company from which the patient was receiving $2,000 per month on the basis of disability resulting from "groin" pain. The pain began suddenly nearly 5 years before while he was working at his office. He described it as a burning pain most severe in his left scrotum and perianal area and radiating down his left leg. The pain was not aggravated by urination, defecation, sexual intercourse, or activity. Thus began a series of diagnostic and treatment procedures including a radical prostatectomy with vascular sparing, a partial colonectomy, a lumbar laminectomy, and intrathecal anesthetic injection of vertebral facets. Whereas objective indications for each surgery were present, including chronic prostatitis and seminal vesiculitis, diverticulitis and hemorrhagic dysplasia of the colon, and probable compression of a lumbar vertebra, none of these procedures appreciably relieved his pain. A working diagnosis of lumbosacral plexopathy was given by the neurologist who had assumed his care. The patient was receiving oxycodone (5 mg) and acetaminophen (325 mg) (Percocet) three to four times daily, naproxen (Naprosyn) (250 mg three times daily), and carbamazepine (Tegretol) (100 mg/day). The patient took medications religiously and never took more than prescribed. He reported that with this regimen, "the edge was taken off the pain," but he did not have adequate relief. Yet, when attempts were made to discontinue the Percocet, "it became intolerable." After the onset of the pain, the patient was not able to maintain his practice, leaving it in the hands of his son who was also a dentist; "Even if I could stand the pain, I couldn't concentrate on my work well enough to do justice to my patients." He worked only occasionally, performing some simple procedures. "I wish I could return to work because I certainly can't support myself on my disability check. Besides, I'm like an adult hyperactive child. I need to stay busy."

At the time of the onset of the pain, the patient was in the midst of highly contested divorce settlement proceedings. The divorce from his wife of 12 years had resulted from the wife's long-standing infidelity, which had come as a total surprise to the patient when he discovered it. He previously divorced a wife of 26 years after she had become unfaithful. The patient had a successful dental practice. Throughout his life, he had been a hard worker, a workaholic, supporting himself through dental school; subsequently, he put his children through college and graduate or professional school. He had no history of alcohol or drug abuse. He had an episode of depression and "bizarre behavior" at the time of his first divorce, was hospitalized and treated with medications, but did not follow through with recommended outpatient care. With the current episode of pain, he also had a depressive syndrome, initially with ideas that other family members had

Clinical Vignette 4 *continued*

been involved in a conspiracy with his wife and that he himself was being investigated by the Central Intelligence Agency. He was again briefly hospitalized and treated with haloperidol and fluoxetine; he was prescribed fluoxetine and lithium on discharge. For follow-up care, he chose an old professional friend as his psychiatrist, who maintained him with fluoxetine (20 mg/day) and saw the patient sporadically for supportive psychotherapy, which according to the patient "didn't amount to much." Lithium had been discontinued on the insistence of the patient, who reported that it made him "dopey." The patient now minimized the episode leading to hospitalization, saying that he was "upset and hurt" by his wife's infidelity. He reported that he still felt depressed but was much better. "Who wouldn't be depressed if they were in pain all the time and couldn't work!"

Psychiatric diagnoses included (1) pain disorder associated with psychological and general medical features, and (2) major depressive disorder, recurrent, with psychotic features in the past. It was also concluded that the patient was disabled from performing the duties of his occupation. Recommendations included (1) that the patient be considered temporarily disabled and be given compensation, (2) referral to a regional pain clinic for more thorough evaluation of pain management, and (3) referral to a psychiatrist (preferably incorporated in the pain clinic referral) with whom the patient does not have a friendship such that objectivity could be maintained.

This clinical vignette illustrates a number of factors important in consideration of pain disorders. First, in this case, it is virtually impossible to dissect the pain complaint as either wholly physically or psychologically based. In all likelihood, the two are intertwined here. Malingering is unlikely. The patient, at least consciously, is motivated to return to work because of both interest and financial incentive. The level of disability compensation is not adequate to maintain his customary style of living. It does not appear that the patient is simply drug seeking, because he has no history of substance abuse and has never overused his opioid medication. Second, the patient fits one stereotype of a person vulnerable to a pain disorder, considering his strong work ethic and reluctance to see things on a psychological or emotional level. Third, despite many evaluations, it does not appear that the patient is yet receiving optimal pain management. He is continued on an opioid analgesic. Whereas treatment with an NSAID and carbamazepine may be appropriate, the carbamazepine is dosed such that it is unlikely to be at a therapeutic plasma level, and a tricyclic antidepressant, which would be the treatment of choice, has not been tried. Last, the psychiatrist is faced with the dilemma of either recommending disability compensation, which may work to reinforce the pain behavior and prolong it, or not recommending compensation to which the patient is legitimately entitled.

**DSM-IV-TR Criteria** 300.7

**Hypochondriasis**

A. Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.

B. The preoccupation persists despite appropriate medical evaluation and reassurance.

C. The belief in criterion A is not of delusional intensity (as in delusional disorder, somatic type) and is not restricted to a circumscribed concern about appearance (as in body dysmorphic disorder).

D. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The duration of the disturbance is at least 6 months.

F. The preoccupation is not better accounted for by generalized anxiety disorder, obsessive–compulsive disorder, panic disorder, a major depressive episode, separation anxiety, or another somatoform disorder.

*Specify* if:

**With poor insight:** If, for most of the time during the current episode, the person does not recognize that the concern about having a serious illness is excessive or unreasonable

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## HYPOCHONDRIASIS

### Definition and Diagnostic Features

As defined in DSM-IV-TR, the essential feature in hypochondriasis is preoccupation with fears or the idea of having a serious disease based on the "misinterpretation of bodily symptoms." This is in contrast to somatization disorder, conversion disorder, and pain disorder, in which the symptoms themselves are the predominant focus. There was some debate in the development of DSM-IV-TR as to whether it was necessary that a body complaint be present. On the basis of empirical data, however, it was determined that this requirement was a valid one and helped to distinguish the "disease conviction" of hypochondriasis from "disease fear" as in phobic disorder (Cote et al. 1996). Bodily symptoms may be interpreted broadly to include misinterpretation of normal body functions. In hypochondriasis, the preoccupation persists despite reassurance from physicians and the accumulation of evidence to the contrary. As in the other somatoform disorders, symptoms must result in clinically significant distress or impairment in important areas of functioning. The duration must be at least 6 months. Hypochondriasis is not diagnosed if the hypochondriacal concerns are better accounted for by another psychiatric disorder, such as major depressive episodes or various psychotic disorders with somatic delusions.

Clinical descriptions of a syndrome characterized by preoccupation with body function are found in the writings of the Hippocratic era (Stoudemire 1988). The Greeks attributed the syndrome to disturbances of viscera below the xiphoid cartilage (i.e., hypochondria). Even into the 19th century, hypochondriasis was applied specifically to

somatic complaints below the diaphragm, rather than the topographically nonspecific concept of more recent usage (Cloninger 1993). As reviewed by Murphy (1990), Gillespie in 1928 encapsulated a concept of hypochondriasis consistent with the current concept, emphasizing preoccupation with a disease conviction "far in excess of what is justified," which showed "an indifference to the opinion of the environment, including irresponsiveness to persuasion." Gillespie considered hypochondriasis a discrete disease entity. DSM-I did not include hypochondriasis as a separate illness. Hypochondriacal preoccupation was mentioned as one of the malignant symptoms observed in psychotic but not reactive depression. DSM-II included hypochondriacal neurosis. In DSM-III, DSM-III-R, and DSM-IV-TR, hypochondriasis is included as one of the somatoform disorders.

Throughout the modern period, there has been controversy as to whether hypochondriasis represented an independent, discrete disease entity as was proposed by Gillespie. Some maintain that hypochondriasis is virtually always secondary to another psychiatric disorder, usually depression (Kenyon 1976). A number of studies suggested that of the many patients with hypochondriacal complaints few meet criteria for the full diagnosis (Barsky et al. 1993). Moreover, the lack of bimodality to the complaints suggests a continuum rather than a discrete entity (Noyes et al. 1993).

In the development of DSM-IV-TR, owing to observations that the disease conviction resembled disease phobia or the incorrigible ideas of obsessive–compulsive disorder, placement of hypochondriasis with the anxiety disorders was considered (Cote et al. 1996). Similarly, a case can be made that disease conviction is on a continuum with somatic delusions of disease, suggesting inclusion with the delusional disorders. In the end, such considerations were resolved by keeping hypochondriasis with the somatoform disorders, defining it in terms of an idea that one already has a particular illness rather than fears of acquiring one to distinguish it from a disease phobia, and by excluding cases in which the idea was of delusional proportions to differentiate hypochondriasis from delusional disorder, somatic type.

## Epidemiology

Some degree of preoccupation with disease is apparently common. As reviewed by Kellner (1991), 10–20% of "normal" and 45% of "neurotic" persons have intermittent unfounded worries about illness, with 9% of patients doubting reassurances given by physicians. In another review, Kellner (1985) estimated that 50% of all patients attending physicians' offices "suffer either primary hypochondriacal symptoms or have minor somatic disorders with hypochondriacal overlay." How these relate to hypochondriasis as a disorder is difficult to assess because these estimates do not appear to distinguish between a focus on the symptoms themselves (as in somatization disorder) and preoccupation with the implications of the symptoms (as in hypochondriasis). The Epidemiological Catchment Area study (Robins et al. 1984) did not assess for hypochondriasis. A 1965 study reported prevalence figures ranging from 3 to 13% in different cultures (Kenyon 1965), but it is not clear whether this represents a syndrome comparable to the current definition or just hypochondriacal symptoms. As already noted, many patients manifest some hypochondriacal symptoms as part of other psychiatric disorders, and others have transient hypochondriacal symptoms in response to stresses such as serious physical illness yet never fulfill the inclusion criteria for DSM-IV-TR hypochondriasis. Assessment of the incidence and prevalence of hypochondriasis undoubtedly requires study of general or primary care rather than psychiatric populations, because patients with hypochondriasis are convinced that they suffer from some physical illness. To date, study of such populations suggests that 4–9% of patients in general medical settings suffer from hypochondriasis (Fallon et al. 1993).

Of note, similar subsequent studies by Gureje et al. (1997), Escobar et al. (1998), and Noyes et al. (2000) all reported frequencies in the same general range (2.2–10.6).

It does appear that hypochondriasis is equally common in males and females. Data concerning socioeconomic class are conflicting.

## Course

Data are conflicting, but it appears that the most common age at onset is in early adulthood. Available data suggest that approximately 25% of patients with a diagnosis of hypochondriasis do poorly, 65% show a chronic but fluctuating course, and 10% recover. This pertains to the full syndrome. A much more variable course is seen in patients with just some hypochondriacal concerns. It appears that acute onset, absence of a personality disorder, and absence of secondary gain are favorable prognostically.

## Differential Diagnosis

As shown in Figure 74–1, the first step in approaching patients with distressing or impairing preoccupation with or fears of having a serious disease is to exclude the possibility of explanation on the basis of a general medical condition. Fears that may seem excessive may also occur in patients with general medical conditions with vague and subjective symptoms early in their disease course. These include neurological diseases, such as myasthenia gravis and multiple sclerosis, endocrine diseases, systemic diseases that affect several organ systems, such as systemic lupus erythematosus, and occult malignant neoplasms (Kellner 1991). The disease conviction of hypochondriasis may actually be less amenable to medical reassurance than the fears of patients, with general medical illnesses, who may at least temporally accept such encouragement. Hypochondriacal complaints are not often intentionally produced such that differentiation from malingering and factitious disorder is seldom a problem.

Exclusion is made if the preoccupation is better accounted for by another psychiatric disorder. DSM-IV-TR lists generalized anxiety disorder, obsessive–compulsive disorder, panic disorder, a major depressive episode, separation anxiety, or another somatoform disorder as candidates. Chronology will be of utmost importance in such discriminations. Hypochondriacal concerns occurring exclusively during episodes of another disturbance, such as an anxiety or depressive disorder, do not warrant an additional diagnosis of hypochondriasis. The presence of other psychiatric symptoms will also be helpful. For example, a patient with hypochondriacal complaints as part of a major depressive episode will show other symptoms of depression, such as sleep and appetite disturbance, feelings of worthlessness, and self-reproach, although depressed elderly patients may

deny sadness or other expressions of depressed mood. A confounding factor is that patients with hypochondriasis often have comorbid anxiety or depressive syndromes (Kenyon 1965). Again, characterizing the symptoms by chronology will be useful. Treatment trials may also have diagnostic significance. Depressed patients who are hypochondriacal may respond to non-SSRI antidepressant medications or electroconvulsive therapy (often necessary to reverse a depressive state of sufficient severity to lead to such profound symptoms), with resolution of the hypochondriacal as well as the depressive symptoms.

Hypochondriasis is differentiated from other somatoform disorders such as pain, conversion, and somatization disorders by its predominant feature of preoccupation with and fears of having an underlying illness based on the misinterpretation of body symptoms, rather than the physical symptoms themselves. Patients with these other somatoform disorders at times are concerned with the possibility of underlying illness, but this will generally be overshadowed by a focus on the symptoms themselves.

The next consideration is whether the belief is of delusional proportions. Patients with hypochondriasis, although preoccupied, generally acknowledge the possibility that their concerns are unfounded. Delusional patients do not. Somatic delusions of serious illness are seen in some cases of schizophrenia and in delusional disorder, somatic type. In general, patients with schizophrenia who have such delusions also show other signs of schizophrenia, such as disorganized speech, peculiarities of thought and behavior, hallucinations, and other delusions. Belief that an underlying illness is being caused by some bizarre process may also be seen (e.g., "I'm trying not to defecate because it will cause my brain to turn to jelly"). Patients with schizophrenia may also show improvement with neuroleptic treatment, at least in the "active" symptoms of their illness, under which somatic delusions are included.

Differentiation from delusional disorder, somatic type, may be more difficult. It is often a thin line between preoccupation and fear that is a conviction and that which is a delusion. Often, the distinction is made on the basis of whether the patient can consider the possibility that the conviction is erroneous. Yet, patients with hypochondriasis vary in the extent to which they can do this. DSM-IV-TR acknowledges this by its inclusion of the specifier with poor insight. In the past, some argued that differentiation could be made on the basis of response to neuroleptics, especially pimozide; patients with delusional disorder, but not hypochondriasis, respond. Interestingly, there is now at least one case report of successful treatment of a syndrome corresponding to delusional disorder, somatic type, in a nondepressed patient with the SSRI paroxetine (Brophy 1994). As with hypochondriasis, response was obtained only when the dose was raised beyond an antidepressant dose (to 60 mg/day).

If it is concluded that the preoccupations are not delusional, the next consideration is whether the duration requirement of 6 months has been met (see Figure 74–1). Syndromes of less than 6 months' duration are diagnosed under either somatoform disorder NOS or adjustment disorder if the symptoms are an abnormal response to a stressful life event. The reason to make such a distinction is to distinguish hypochondriasis from transient syndromes, the longitudinal course of which has been shown to be more variable, suggesting heterogeneity (Barsky et al. 1993).

Other diagnostic considerations include whether the preoccupations or fears are restricted to preoccupations with being overweight, as in anorexia nervosa, with the inappropriateness of one's sex characteristics, as in a gender identity disorder, or with defects in appearance, as in body dysmorphic disorder. The preoccupations of hypochondriasis resemble the obsessions, and the health checking and efforts to obtain reassurance resemble the compulsions of obsessive–compulsive disorder. However, if such manifestations are health centered only, obsessive–compulsive disorder is not diagnosed. If, on the other hand, nonhealth-related obsessions and compulsions are present, obsessive–compulsive disorder may be diagnosed in addition to hypochondriasis.

## Etiology and Pathophysiology

Until recently, psychoanalytic hypotheses of etiology predominated. Freud hypothesized that hypochondriasis represented "the return of object libido onto the ego with cathexis of the body" (Viederman 1985). Subsequently, the cathexis to the body hypothesis was elaborated on to include interpretations involving disturbed object relations—displacement of repressed hostility to the body to communicate anger indirectly to others. Dynamic mechanisms involving masochism, guilt, conflicted dependency needs, and a need to suffer and be loved at the same time have also been suggested (Stoudemire 1988). The presence of such "narcissistic" mechanisms has been suggested as the reason that patients with hypochondriasis were "unanalyzable." Other psychological theories involve defense against feelings of low self-esteem and inadequacy, perceptual and cognitive abnormalities, and operant conditioning involving reinforcement for assumption of the sick role.

Biological theories have been suggested as well. Hypochondriacal ideas have been attributed to a hypervigilance to insult, including overperception of physical problems (Barsky and Klerman 1983). This has been posited in particular in reference to hypochondriasis as an aspect of depression or anxiety disorders. Hypochondriasis has been included by some in the posited obsessive–compulsive spectrum disorders along with obsessive–compulsive and body dysmorphic disorders, anorexia nervosa, Tourette's disorder, trichotillomania, pathological gambling, and other impulsive disorders (Hollander 1993). All these disorders involve repetitive thoughts or behaviors that patients are unable to delay or inhibit without great difficulty. Evidence for this clustering includes observations of clinical improvement with SSRIs such as fluoxetine even in nondepressed patients with hypochondriasis, body dysmorphic disorder, obsessive–compulsive disorder, and anorexia nervosa. Because such a response is not evident with non-SSRI antidepressants, some type of common serotonin dysregulation is suggested for these disorders.

## Treatment

### Psychosocial and Somatic Treatments

Until recently, it appeared that patients with hypochondriasis as a primary condition benefited, but only modestly, from psychiatric intervention. Patients referred early for psychiatric evaluation and treatment showed a slightly better

prognosis than those continuing with only medical evaluations and treatments (Kellner 1983). Of course, the first step in treatment is getting the patient to a psychiatrist. Patients with hypochondriasis generally present initially to nonpsychiatric physicians and are often reluctant to see a psychiatrist. Referral should be done sensitively, with the referring physician stressing to the patient that his or her distress is real and that psychiatric evaluation will be a supplement to, not a replacement for, continued medical care.

Initially, the generic psychotherapeutic techniques outlined for the somatoform disorders in general should be followed. As reviewed by Fallon et al. (1993), dynamic psychotherapy is of minimal effectiveness, supportive–educative psychotherapy as described by Kellner (1991) is only somewhat helpful, and primarily for those with syndromes of less than 3 years' duration, and CBT, especially response prevention of checking rituals and reassurance seeking, was seen only as moderately effective at best. Interestingly, more recent studies by Warwick et al. (1996), Clark et al. (1990), and Barsky and Ahern (2004) have all strongly suggested that the specific procedures of CBT including psychoeducation, cognition restructuring, and exposure-response prevention are all active components in improving hypochondriacal symptoms (e.g., reducing anxiety, health concerns, functional impairment). These studies and others lead Taylor et al. (2005) to conclude that there is now clear evidence that hypochondriasis can be effectively managed using CBT. Time will tell whether CBT will gain wide acceptance.

Pharmacotherapy of comorbid depressive or anxiety syndromes was often effective, and control of such syndromes aided in general management, yet hypochondriasis itself was not ameliorated. Although controlled trials are lacking, anecdotal and open-label studies suggest that serotoninergic agents such as clomipramine and the SSRI fluoxetine may be effective in ameliorating hypochondriasis. Similar effects have been reported with the other SSRIs. Response to fluoxetine has been reported with doses recommended for obsessive–compulsive disorder, rather than usual antidepressant doses (i.e., 60–80 mg/day rather than 20–40 mg/day). Several problems with medications have been reported including relapse at discontinuation (Viswnathan and Paradis 1991), worsening of symptomology because of side effects (Fallon 2001) and significant placebo effect (Fallon et al. 1996). It is also noteworthy that there have been scattered case reports over the years describing a reduction in hypochondriacal symptoms as a result of antipsychotics including pimozide and the newer atypicals including olanzepine. Pharmacotherapy is best combined with the generic psychotherapy recommendations for somatoform disorders, as well as with cognitive–behavioral techniques to disrupt the counterproductive checking and reassurance-seeking behaviors.

Clinical Vignette 5

A 26-year-old single man presented for psychiatric evaluation at the insistence of his job supervisor, who was concerned that the patient was not keeping up with his assignments at work. The patient reported that he could not concentrate on his work because for the past 4 years he had been constantly preoccupied with the thought that there was something seriously wrong with his arms resulting from a "strain" while he moved furniture. Although there was minimal pain associated, he was convinced that the problem would progress and he would lose the use of his arms. Multiple consultations with orthopedic surgeons and neurologists had not identified any underlying physical problem. He rejected physical therapy for fear that it would only aggravate the underlying problem. Physical activity involving his arms was avoided as much as possible. Not able to avoid driving to work, he wore a prosthesis that he had constructed from various elastic bandages "to prevent any strain." He arrived at work early to be ensured a parking space that was easy to enter.

In addition to this preoccupation, he also feared that ulcerative colitis was developing. This began after his father died of a gastrointestinal hemorrhage when the patient was 16 years old. Initially diagnosed as possible ulcerative colitis, it was found at postmortem examination to be due to a ruptured abdominal aneurysm. The patient fully accepted this diagnosis, yet he could not stop thinking that he was at risk for ulcerative colitis despite multiple gastrointestinal evaluations that failed to find any signs of the illness in him. He adhered to a strict diet, avoiding any "roughage," and was concerned about "regularity." He would awaken every day 2 hours earlier than necessary to have enough time for a bowel movement before going to work. The slightest gastrointestinal sensation would aggravate his concern, and he would carefully examine his stool for any signs of blood or mucus. He reported that his work attendance was excellent but that most of the time he would just sit at his desk and move papers around to look busy while thinking about his health problems. "I have a civil service job and until now I got away with it." The patient had no prior psychiatric evaluations. For both of his health concerns, he was able to consider the possibility that there was no underlying physical cause, "but I can't stop thinking about them. What if all the doctors are wrong?"

The psychiatrist's diagnosis was hypochondriasis, with poor insight. The patient was to be further evaluated for a concurrent major depressive episode and also for nonhealth preoccupations that would suggest an additional diagnosis of obsessive–compulsive disorder. The psychiatrist's recommendations included (1) a trial of fluoxetine to be increased to 60 mg/day if tolerated, (2) supportive–educative psychotherapy to ensure compliance and for support, and (3) cognitive–behavioral therapy to reinforce use of his arms, to extinguish assumptions that he needed a special diet, and to reassure him that dire consequences would not occur if his bowel movements were not absolutely punctual.

This clinical vignette illustrates several important typical aspects of hypochondriasis. First, the onset of the disorder was early, in the late teens, with consolidation of symptoms by early adulthood. Second, a chronic course was observed, with some fluctuation in severity. The physical complaints themselves were minimal. It was the preoccupation with fears of underlying illness that predominated and led to distress and impairment.

## BODY DYSMORPHIC DISORDER

### Definition and Diagnostic Features

As defined in DSM-IV-TR, the essential feature of this disorder is preoccupation with an imagined defect in appearance or a markedly excessive concern with a minor anomaly.

**DSM-IV-TR Criteria** 300.7

**Body Dysmorphic Disorder**

A. Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive.

B. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in anorexia nervosa).

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DSM-III-R dictated "in a normal-appearing person," but this phrase was eliminated from the definition as nonessential, redundant, and inaccurate. In body dysmorphic disorder, a person could be preoccupied with an imagined defect while she or he actually had some other anomaly and was not normal appearing. To exclude conditions with trivial or minor symptoms, the preoccupation must cause clinically significant distress or impairment. By definition, body dysmorphic disorder is not diagnosed if symptoms are limited to preoccupation with body weight, as in anorexia nervosa or bulimia nervosa, or to perceived inappropriateness of sex characteristics, as in gender identity disorder.

According to de Leon et al. (1989), preoccupations most often involve the nose, ears, face, or sexual organs. Common complaints include a diversity of imagined flaws of the face or head, including defects in the hair (e.g., too much or too little), skin (e.g., blemishes), and shape or symmetry of the face or facial features (e.g., nose is too large and deformed). However, any body part may be the focus, including genitals, breasts, buttocks, extremities, shoulders, and even overall body size.

Body dysmorphic disorder has been well described in the European and Japanese literature, generally designated dysmorphophobia, often under the rubric of the monosymptomatic hypochondriacal psychoses (Munro 1980). Until relatively recently, it had been virtually ignored in the US literature as well as clinically. Such a disorder was not mentioned in DSM-I or DSM-II (Andreasen and Bardach 1977). Dysmorphophobia was included parenthetically as an example of an atypical somatoform disorder in DSM-III. It was renamed body dysmorphic disorder when included in DSM-III-R. This term was retained in DSM-IV-TR and DSM-IV-TR. ICD-10 lists body dysmorphic disorder as a type of hypochondriacal disorder. Since inclusion in DSM-III, increased study has led to a better characterization of the disorder, which has promoted better detection clinically. Since 1996, it has been included in the Structured Clinical Interview for DSM-IV-Axis I disorders (SCID-I) (First et al. 1996) designed for research purposes. However, the clinical version of this instrument, the Structured Clinical Interview for DSM-IV-Clinical Version (SCID-CV) (First et al. 1997), only includes a single screening question and not the full criteria for the condition.

The definition of the disorder was reexamined for DSM-IV-TR on several counts, but especially as to its relationship to other psychiatric disorders (Phillips and Hollander 1996). After much deliberation, it was determined that body dysmorphic disorder, although often comorbid with anxiety and mood disorders, was sufficiently discrete to be maintained as a separate disorder. As discussed in the differential diagnosis section, it can be distinguished from depressive disorders and from most anxiety disorders, although it resembles obsessive–compulsive disorder in phenomenology, course, and even response to treatment. It was also decided to keep it with the somatoform disorders grouping, although it does not share much with the other disorders in this grouping (with the exception of hypochondriasis), beyond the fact that affected patients are generally referred to psychiatrists from other physicians and that they also present with medically unexplained physical complaints (defects in appearance in body dysmorphic disorder).

In terms of its relationship to the psychotic disorders, DSM-IV-TR dropped the DSM-III-R exclusionary rule that body dysmorphic disorder not be diagnosed if the preoccupation was of delusional intensity (i.e., the patient totally lacked insight or the ability to consider the possibility that the concern was unjustified). This exclusion remains in ICD-10. As de Leon et al. (1989) pointed out, it is extremely difficult to determine whether a dysmorphic concern is delusional in that with body dysmorphic disorder a continuum exists from clearly nondelusional preoccupations to unequivocal delusions such that defining a discrete boundary between the two ends of the spectrum would be artificial. Furthermore, individual patients seem to move back and forth along this continuum. Support for rejecting the exclusion is preliminary evidence that dysmorphic preoccupations may respond to the same pharmacotherapy (SSRIs), regardless of whether the concerns are delusional (Hollander et al. 1993). Perhaps as a reflection of the state of knowledge at this point, both body dysmorphic disorder and delusional disorder, somatic type, can be diagnosed on the basis of the same symptoms, in the same individual, at the same time. Thus, the definition of body dysmorphic disorder differs from hypochondriasis, which is not diagnosed if hypochondriacal concerns are determined to be delusional.

## Epidemiology

Knowledge of such parameters is still incomplete. In general, patients with body dysmorphic disorder first present to nonpsychiatrists such as plastic surgeons, dermatologists, and internists because of the nature of their complaints and are not seen psychiatrically until they are referred (de Leon et al. 1989). Many resist or refuse referral because they do not see their problem as psychiatric; thus, study of psychiatric clinic populations may underestimate the prevalence of the disorder. It has been estimated that 2% of patients seeking corrective cosmetic surgery suffer from this disorder (Andreasen and Bardach 1977). General population studies have identified rates of occurrence from 0.7 to 2.3% (Faravelli et al. 1997, Otto et al. 2001, Mayville et al. 1999).

## Course

Age at onset appears to peak in adolescence or early adulthood (Phillips 1991). Body dysmorphic disorder is generally a chronic condition, with a waxing and waning of intensity but rarely full remission (Phillips et al. 1993). In a lifetime, multiple preoccupations are typical; in one study, the average was four (Phillips et al. 1993). In some, the same preoccupation remains unchanged. In others, new perceived defects are added to the original ones. In others still, symptoms remit, only to be replaced by others. The disorder is often highly incapacitating, with many patients showing marked impairment in social and occupational activities. Perhaps a third becomes housebound. Most attribute their limitations to embarrassment concerning their perceived defect, but the attention and time-consuming nature of the preoccupations and attempts to investigate and rectify defects also contribute. The extent to which patients with body dysmorphic disorder receive surgery or medical treatments is unknown. Superimposed depressive episodes are common, as are suicidal ideation and suicide attempts. Actual suicide risk is unknown.

In view of the nature of the defects with which patients are preoccupied, it is not surprising that they are found most commonly among patients seeking cosmetic surgery. Preoccupations persist despite reassurance that there is no defect to surgically correct. Surgery or other corrective procedures rarely if ever lead to satisfaction and may even lead to greater distress with the perception of new defects attributed to the surgery.

## Differential Diagnosis

The preoccupations of body dysmorphic disorder must first be differentiated from usual concerns with grooming and appearance. Attention to appearance and grooming is universal and socially sanctioned. However, diagnosis of body dysmorphic disorder requires that the preoccupation cause clinically significant distress or impairment. In addition, in body dysmorphic disorder, concerns focus on an imaginary or exaggerated defect, often of something, such as a small blemish, that would warrant scant attention even if it were present. Persons with histrionic personality disorder may be vain and excessively concerned with appearance. However, the focus in this disorder is on maintaining a good or even exceptional appearance, rather than preoccupation with a defect. Such concerns are probably unrelated to body dysmorphic disorder. In addition, by nature, the preoccupations in body dysmorphic disorder are essentially unamenable to reassurance from friends or family or consultation with physicians, cosmetologists, or other professionals.

Next, the possibility of an explanation by a general medical condition must be considered (see Figure 74–1). As mentioned, patients with this disorder often first present to plastic surgeons, oral surgeons, and others, seeking correction of defects. By the time a mental health professional is consulted, it has generally been ascertained that there is no physical basis for the degree of concern. As with other syndromes involving somatic preoccupations (or delusions), such as olfactory reference syndrome and delusional parasitosis (both included under delusional disorder, somatic type), occult medical conditions, such as an endocrine disturbance or a brain tumor, must be excluded.

In terms of explanation on the basis of another psychiatric disorder, there is little likelihood that symptoms of body dysmorphic disorder will be intentionally produced as in malingering or factitious disorder. Unlike in other somatoform disorders, such as pain, conversion, and somatization disorders, preoccupation with appearance predominates. Somatic preoccupations may occur as part of an anxiety or mood disorder. However, these preoccupations are generally not the predominant focus and lack the specificity of dysmorphic symptoms. Because patients with body dysmorphic disorder often become isolative, social phobia may be suspected. However, in social phobia, the person may feel self-conscious generally but will not focus on a specific imagined defect. Indeed, the two conditions may coexist, warranting both diagnoses. Diagnostic problems may present with the mood-congruent ruminations of major depression, which sometimes involve concern with an unattractive appearance in association with poor self-esteem. Such preoccupations generally lack the focus on a particular body part that is seen in body dysmorphic disorder. On the other hand, patients with body dysmorphic disorder commonly have dysphoric affects described by them variously as anxiety or depression. In some cases, these affects can be subsumed under body dysmorphic disorder; but in other instances, comorbid diagnoses of anxiety or mood disorders are warranted.

Differentiation from schizophrenia must also be made. At times, a dysmorphic concern will seem so unusual that such a psychosis may be considered. Furthermore, patients with this disorder may show ideas of reference in regard to defects in their appearance, which may lead to the consideration of schizophrenia. However, other bizarre delusions, particularly of persecution or grandiosity, and prominent hallucinations are not seen in body dysmorphic disorder. From the other perspective, schizophrenia with somatic delusions generally lacks the focus on a particular body part and defect. Also in schizophrenia, bizarre interpretations and explanations for symptoms are often present, such as "this blemish was a sign from Jesus that I am to protect the world from Satan." Other signs of schizophrenia, such as hallucinations and disorganization of thought, are also absent in body dysmorphic disorder. As previously mentioned, the preoccupations in body dysmorphic disorder appear to be on a continuum from full insight to delusional intensity whereby the patient cannot even consider the possibility that the preoccupation is groundless. In such instances, both body dysmorphic disorder and delusional disorder, somatic type, are to be diagnosed.

Body dysmorphic disorder is not to be diagnosed if the concern with appearance is better accounted for by another psychiatric disorder. Anorexia nervosa, in which there is dissatisfaction with body shape and size, is specifically mentioned in the criteria as an example of such an exclusion. DSM-III-R also mentioned transsexualism (gender identity disorder in DSM-IV-TR) as such a disorder. Although not specifically mentioned in DSM-IV-TR, if a preoccupation is limited to discomfort or a sense of inappropriateness of one's primary and secondary sex characteristics, coupled with a strong and persistent cross-gender identification, body dysmorphic disorder is not diagnosed.

The preoccupations of body dysmorphic disorder may resemble obsessions and ruminations as seen in obsessive–compulsive disorder. Unlike the obsessions of

obsessive–compulsive disorder, the preoccupations of body dysmorphic disorder focus on concerns with appearance. Compulsions are limited to checking and investigating the perceived physical defect and attempting to obtain reassurance from others regarding it. Still, the phenomenology is similar, and the two disorders are often comorbid. If additional obsessions and compulsions not related to the defect are present, obsessive–compulsive disorder can be diagnosed in addition to body dysmorphic disorder.

## Etiology and Pathophysiology

A number of sociological, psychological, and neurobiological theories have been proposed. Body dysmorphic disorder has been explained, at least in part, as an exaggerated incorporation of societal ideals of physical perfection and acceptance of cosmetic plastic surgery to attain such goals. A high frequency of insecure, sensitive, obsessional, schizoid, anxious, narcissistic, introverted, and hypochondriacal personality traits in body dysmorphic patients have been described (Phillips 1991). Various psychodynamic mechanisms and symbolic meanings of dysmorphic symptoms have been suggested (Phillips 1991), going back to Freud's case of the Wolfman who had dysmorphic preoccupations regarding his nose.

Some interesting neurobiological possibilities have emerged, particularly concerning observations that hypochondriasis, body dysmorphic disorder, and a number of other conditions involving compelling repetitive thoughts or behaviors may respond preferentially to SSRIs, not to other antidepressant drugs. An obsessive–compulsive spectrum disorders grouping, the pathological process of which is mediated by serotoninergic dysregulation, has been suggested. As further evidence, symptoms of body dysmorphic disorder as well as those of obsessive–compulsive disorder may be aggravated by the partial serotonin agonist *m*-chlorophenylpiperazine (Hollander et al. 1992).

## Treatment

### Psychosocial and Somatic Treatments

First, the generic goals and treatments as outlined for the somatoform disorders overall should be instituted. These are beneficial in interrupting an unending procession of repeated evaluations and the possibility of needless surgery, which may lead to additional perceptions that surgery has resulted in further disfigurement. Phillips and Diaz (1997) reported that 83% (of 139 patients) who received surgical, dermatological, or other nonpsychiatric treatment reported worsening or no change in symptoms.

Traditional insight-oriented therapies have not generally proved to be effective. Results with traditional behavioral techniques, such as systematic desensitization and exposure therapy, have been mixed. At least without amelioration with effective pharmacotherapy, the preoccupations do not extinguish as would be expected with phobias. A cognitive–behavioral approach similar to what was recommended for hypochondriasis may be more effective. This includes response prevention techniques whereby the patient is not permitted to repetitively check the perceived defect in mirrors. In addition, patients are advised not to seek reassurance from family and friends, and these persons are instructed not to respond to such inquiries. Some patients adopt such behaviors spontaneously, avoiding mirrors and other reflecting surfaces, refusing even to allude to their perceived defects to others. Such "self-techniques" may be encouraged and refined. There remains a paucity of randomized controlled trials, particularly directly comparing treatments.

Biological treatments have long been used but until recently were of limited benefit to patients with body dysmorphic disorder. Approaches have included electroconvulsive therapy, tricyclic and MAOI antidepressants, and neuroleptics (particularly pimozide) (Andreasen and Bardach 1977). In most reports of positive response to tricyclic or MAOI antidepressant drugs, it is unclear whether response was truly in terms of the dysmorphic syndrome or simply represented improvement in comorbid depressive or anxiety syndromes. Response to neuroleptic treatment has been suggested as a diagnostic test to distinguish body dysmorphic disorder from delusional disorder, somatic type (Riding and Munro 1975). The delusional syndromes often respond to neuroleptics; body dysmorphic disorders, even when the body preoccupations are psychotic, generally do not. Pimozide has been singled out as a neuroleptic with specific effectiveness for somatic delusions, but this specificity does not appear to apply to body dysmorphic disorder.

An exception to this uninspiring picture is the observation of a possible preferential response to antidepressant drugs with serotonin reuptake blocking effects, such as clomipramine, or SSRIs, such as fluoxetine and fluvoxamine (Hollander et al. 1992, Hollander et al. 1999). Phillips et al. (1993) reported that more than 50% of patients with body dysmorphic disorder showed a partial or complete remission with either clomipramine or fluoxetine, a response not predicted on the basis of coexisting major depressive or obsessive–compulsive disorder. As with hypochondriasis, effectiveness is generally achieved at levels recommended for obsessive–compulsive disorder rather than for depression (e.g., 60–80 mg/day rather than 20–40 mg/day of fluoxetine). The SSRIs appear to ameliorate delusional as well as nondelusional dysmorphic preoccupations. Successful augmentation of clomipramine or SSRI therapy has been suggested with buspirone, another drug with serotoninergic effects. Neuroleptics, particularly pimozide, may also be helpful adjuncts, particularly if delusions of reference are present. Little seems to be gained with the addition of anticonvulsants, or benzodiazepines to the SSRI therapy.

As yet, rigorous studies have not been conducted, but anecdotal observations and open-label studies show promise for effective treatment with SSRIs and other serotoninergic agents for this, until now, therapeutically exasperating disorder. If such approaches fulfill their initial promise, integrated approaches using pharmacotherapy and other modalities such as CBT may provide effective treatment options.

Clinical Vignette 6

A 22-year-old single woman who lived with her parents was referred for psychiatric consultation because of preoccupations of 4 years that there was something wrong with the way her teeth were situated in her jaw. She could not specify what exactly was wrong but insisted that her teeth felt "funny" and at times would actually relocate,

especially while she was eating. She spent "hours" each day in front of a mirror examining her teeth from various angles. With the exception of her parents, she had become essentially a recluse in that people avoided her because she would repeatedly ask their opinion as to whether they thought her teeth were abnormally placed. At one family function, she showed her mouth full of food to a relative, asking if her teeth could be seen moving, disgusting the relative, who insisted the parents arrange for a psychiatric evaluation. By the time of referral, she had received multiple dental, orthodontic, and oral surgery evaluations, none of which indicated any abnormality. Despite this, she was "absolutely sure" that there was something wrong with her teeth or mouth. She would not even consider hypothetically that her concerns were unfounded and might be the consequence of a misinterpretation or of a psychiatric disturbance. As described by her parents, their family physician had tried treatment with alprazolam ("to calm her down"), imipramine ("in case she's depressed and it might help any pain"), and low-dose haloperidol ("she might be schizophrenic").

The psychiatrist diagnosed body dysmorphic disorder and delusional disorder, somatic type. He recommended (1) continued psychiatric care with the institution of pharmacotherapy with sertraline, 50 mg/day to be increased to 150 mg as tolerated, (2) preventing the patient from self-checking by removing all mirrors from her living space, and (3) that no response be given to any questions about the appearance of her mouth or teeth. The patient was carefully advised that the last two measures were being instituted. The rationale was explained to reassure her that they were not being instituted punitively. The patient showed little comprehension of these explanations.

This clinical vignette illustrates several important aspects of body dysmorphic disorder. The age at onset of the disorder in this patient is typical at 18 years. Although her perception that her teeth were relocating was atypical, the locale of her preoccupation (the teeth) is fairly common. Her pattern of seeking reassurance from self-examination and soliciting the opinion of others is also common in these patients. The patient's actual physical complaints were minimal. She reported no pain and no actual physical discomfort in her mouth; it was "how they looked." The patient gave no evidence of even partial insight that her perceptions regarding her mouth and teeth were erroneous. Thus, she qualified for a diagnosis of delusional disorder, somatic type, as well as body dysmorphic disorder, as is allowed in the DSM-IV-TR criteria. Last, the patient was appropriately prescribed an SSRI with the expectation of reaching a dose higher than that recommended for depression. Because this patient was also delusional, the neuroleptic pimozide was also considered as an adjunct. The behavioral manipulations of preventing self-checking and seeking reassurance from others were also recommended.

**DSM-IV-TR Criteria** 300.81

**Somatoform Disorder Not Otherwise Specified**

This category includes disorders with somatoform symptoms that do not meet criteria for any specific somatoform disorder. Examples include:

1. Pseudocyesis: a false belief of being pregnant that is associated with objective signs of pregnancy, which may include abdominal enlargement (although the umbilicus does not become everted), reduced menstrual flow, amenorrhea, subjective sensation of fetal movement, nausea, breast engorgement and secretions, and labor pains at the expected date of delivery. Endocrine changes may be present, but the syndrome cannot be explained by a general medical condition that causes endocrine changes (e.g., a hormone-secreting tumor).
2. A disorder involving nonpsychotic hypochondriacal symptoms of less than 6 months' duration.
3. A disorder involving unexplained physical symptoms (e.g., fatigue or body weakness) of less than 6 months' duration that are not due to another mental disorder.

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## SOMATOFORM DISORDER NOS

### Definition and Diagnostic Features

Somatoform disorder NOS is the true residual category for this group of disorders. By definition, disorders considered under this category are characterized by somatic symptoms, but criteria for any of the specific somatoform disorders are not met. Several examples are given, but syndromes potentially included under this category are not limited to these. Unlike for undifferentiated somatoform disorder, no minimal duration is required. This category was incorporated into DSM-III-R, replacing the DSM-III atypical somatoform disorder, a residual category requiring that physical symptoms and complaints not be explained on the basis of demonstrable organic findings or a known pathophysiological mechanism and that they were "apparently linked to psychological factors." The only example given was dysmorphophobia. DSM-III-R similarly required that criteria for any specific somatoform or adjustment disorder with physical symptoms not be met. Examples given were nonpsychotic hypochondriacal symptoms and non–stress-related physical complaints of less than 6 months' duration. DSM-IV-TR lists as examples pseudocyesis, disorders involving hypochondriacal complaints but of less than 6 months' duration, and disorders involving unexplained physical complaints such as fatigue or body weakness not due to another mental disorder and again of less than 6 months' duration. This last syndrome would seem to resemble neurasthenia of short duration, a syndrome with a long historical tradition with inclusion in DSM-II, ICD-9, and ICD-10. Neurasthenia was considered for inclusion as a separate DSM-IV-TR somatoform disorder. Reasons that it was not included in DSM-IV-TR include difficulties in delineating it from depressive and anxiety disorders and from other somatoform disorders. If included, neurasthenia could have become a clinical "wastebasket" that could facilitate premature closure of diagnostic inquiry, such that

underlying general medical conditions as well as other mental disorders would more likely be overlooked.

Inclusion of pseudocyesis deserves special mention. This syndrome, not mentioned at all in DSM-II, was included in DSM-III and DSM-III-R as an example of a conversion symptom under the broadened definition of conversion, on the basis that it represented a somatic expression of a psychological conflict or need, in this case involving ambivalence toward pregnancy. The resulting conflict was resolved somatically as a false pregnancy, lessening anxiety (primary gain) and leading to unconsciously needed environmental support (secondary gain). With the restriction of conversion in DSM-IV-TR to include only symptoms affecting voluntary motor and sensory function, pseudocyesis was excluded from the conversion disorder definition. In a sense, it is placed in the somatoform disorder NOS category for lack of a more appropriate place. Pseudocyesis is a reasonably discrete syndrome for which specific criteria as listed in DSM-IV-TR can be delineated. These criteria were derived from a review of the existing literature (Lipowski 1988). However, given its rarity, it is not listed as a specified somatoform disorder. Whelan and Stewart (1990) reported six cases in 20 years of consulting to a unit in which 2,500 women delivered per year. It could also be described as a psychophysiological endocrine disorder. On the basis of a literature review (Lipowski 1988), in many cases, a neuroendocrine change accompanies and at times may antedate the false belief of pregnancy. This approaches inclusion as a medical condition, which would lend itself to consideration of psychological factors affecting medical condition. However, in most instances, a discrete general medical condition (such as a hormone-secreting tumor) cannot be identified.

## Differential Diagnosis

As a residual category, somatoform disorder NOS is to be diagnosed after all other possibilities are excluded (see Figure 74–1). After it is determined that a syndrome with somatoform symptoms is not attributable to a nonsomatoform psychiatric disorder and does not meet criteria for any of the specific somatoform disorders (including, on the symptom-focused side, pain, conversion, and somatization disorders and, on the preoccupation-focused side, hypochondriasis or body dysmorphic disorder), the two diagnostic possibilities that remain are undifferentiated somatoform disorder and somatoform disorder NOS. Except in the case of pseudocyesis, these two are differentiated on the basis of whether the disturbance is of 6 months' duration. If symptoms last more than 6 months, undifferentiated somatoform disorder is diagnosed; if less than 6 months, somatoform disorder NOS.

Clinical Vignette 7

A 64-year-old man was referred for psychiatric consultation by a gastroenterologist because of the patient's uncompromising preoccupation of 4 months that he suffered from colon cancer. This fear developed after the patient underwent lower bowel radiography to evaluate complaints of constipation unimproved with dietary changes, stool softeners, and laxatives. He was allowed to view his radiographs, and he noted a "shadow" that he was convinced represented a cancer mass. The patient was reshown the film with explicit explanation. He was satisfied temporarily, but he soon became concerned that if it was not cancer, a rubber tube may have been left in his colon from the barium enema examination and, if left there, would eventually cause cancer. The patient could consider that his concern might be unfounded, yet "I just can't shake the idea that I have cancer." The patient had no other unusual ideas or prominent symptoms. He denied feeling sad and was not worried about other things. He did feel that "this is draining all my energy" and had difficulty in concentrating on any of his usual interests or hobbies. He did not feel guilty about anything and was not contemplating suicide or wishing to be dead, but "I just know this thing is going to kill me!" He had no prior history of excessive health concerns and had never felt any need for psychiatric treatment.

The psychiatrist's diagnosis was (1) possible somatoform disorder NOS, consider hypochondriasis early in its course, but ruled out major depressive disorder or delusional disorder, somatic type, as alternative explanations; (2) ruled out occult general medical condition underlying his complaints: a gastrointestinal disorder with subtle symptoms and no objective findings; depressive disorder NOS; delusional disorder, somatic type; or mental disorder NOS due to a general medical condition. It was recommended that the patient be (1) thoroughly evaluated for a general medical condition, including endocrine studies, and (2) empirically started on an SSRI.

This clinical vignette illustrates an important aspect of somatoform disorder NOS. In using this diagnosis, the psychiatrist must remain cognizant that it is a residual category, and vigilance must be maintained for the emergence of a previously undetected general medical or psychiatric condition.

# CONCLUSION

As a group, the syndromes now subsumed under the rubric of somatoform disorders are relatively common and are associated with great direct and indirect costs to society. Yet, they have remained a "stepchild" of psychiatry, underdiagnosed and underresearched. Perhaps the first step in bringing these conditions into the light was the formalization of criteria and nomenclature and their aggregation into a group in DSM-III. This has allowed a practical approach to the differential diagnosis of conditions with physical symptoms suggestive of underlying general medical conditions (see Figure 74–1). Moreover, the definition of this group has been conducive to more coordinated research in which findings are more comparable from one investigation to another. With this, therapeutic direction is emerging, with some general guidelines for all of these disorders, some specific ways of managing patients with somatization disorder, undifferentiated somatoform disorder, and conversion disorder, and a more utilitarian approach to management of patients with pain disorders.

It appears that pharmacological inroads are being made in the treatment of hypochondriasis and body dysmorphic disorder in terms of the possible efficacy of SSRIs. This pharmacological "probe" suggests that these disorders may be more closely linked with the so-called obsessive–compulsive spectrum disorders (Hollander 1993) than with the other somatoform disorders, a linkage that may be reflected in future diagnostic systems. Even if this turns out to be the case, the somatoform disorder concept will have served its purpose in stimulating and making possible research leading to a better understanding and ultimately more effective treatments for these complex conditions.

Much work remains to be done before the knowledge concerning the somatoform disorders and their treatment catch up with the understanding of other groupings of psychiatric disorders.

## Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research for Somatization Disorder has both a different item set and algorithm. Six symptoms are required out of a list of 14 symptoms, which are broken down into the following groups: 6 gastrointestinal symptoms, 2 cardiovascular symptoms, 3 genitourinary symptoms, and 3 "skin and pain" symptoms. It is specified that the symptoms occur in at least two groups. In contrast, DSM-IV-TR requires 4 pain symptoms, 2 gastrointestinal symptoms, 1 sexual symptom, and 1 pseudoneurological symptom. Furthermore, the ICD-10 Diagnostic Criteria for Research specify that there must be "persistent refusal to accept medical reassurance that there is no adequate physical cause for the physical symptoms." DSM-IV-TR only requires that the symptoms result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning and that the symptoms cannot be fully explained by a known general medical condition or substance. For Undifferentiated Somatoform Disorder, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are almost identical.

Regarding conversion disorder, ICD-10 considers conversion a type of dissociative disorder and includes separate criteria sets for dissociative motor disorders, dissociative convulsions, and dissociative anesthesia and sensory loss in a section that also includes dissociative amnesia and dissociative fugue.

For pain disorder, the ICD-10 Diagnostic Criteria for Research require that the pain last at least 6 months and that it not be "explained adequately by evidence of a physiological process or a physical disorder." In contrast, DSM-IV-TR does not force the clinician to make this inherently impossible judgment and instead requires the contribution of psychological factors. Furthermore, DSM-IV-TR includes both acute (duration less than 6 months) and chronic pain (more than 6 months). This disorder is referred to in ICD-10 as "Persistent Somatoform Pain Disorder."

ICD-10 provides a single criteria set that applies to both the DSM-IV-TR categories of hypochondriasis and body dysmorphic disorder. The ICD-10 Diagnostic Criteria for Research for Hypochondriasis specifies that the belief is of a "maximum of two serious physical diseases" and requires that at least one be specifically named by the individual with the disorder. The DSM-IV-TR has no such requirement.

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CHAPTER

# 75 Factitious Disorders

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Factitious Disorder
Factitious Disorder by Proxy

## Introduction

Patients with factitious disorder consciously induce or feign illness in order to obtain a psychological benefit from being in the sick role. They usually have little insight into the motivations of their behaviors but are still powerfully driven to appear ill to others. In many cases, they endanger their own health and life in their desire to appear sick. Patients with this disorder will often induce serious illness or undergo numerous unnecessary, invasive procedures. As most people avoid sickness, the actions of these patients appear to run counter to human nature. Also, since entry into the "sick role" requires that the sick person should try to get better, patients with factitious disorder must conceal the voluntary origin of their symptoms. The inexplicability of their actions combined with their deceptive behavior stir up both intense interest and intense (usually negative) countertransference in health care providers.

Parsons (1951) described the "sick role" and noted that in our society there are four aspects of this role. First, the patient is not able to will himself or herself back to health but instead must "be taken care of." Second, the patient in the sick role must regard the sickness as undesirable and want to get better. Third, the sick patient is obliged to seek medical care and cooperate with his or her medical treatment. Finally, the sick patient is exempted from the normal responsibilities of his or her social role.

It is the conscious awareness of the production of symptoms that differentiates factitious disorder from the somatoform disorders. Patients with somatoform disorders are unaware of the psychological origins of their symptoms, and they genuinely believe themselves to be ill. In contrast, it is the underlying motivation to produce symptoms that separates factitious disorders from malingering. Patients who malinger consciously feign or induce illness in order to obtain some external benefit (such as money, narcotics, or excuse from duties) as opposed to the internal, psychological motivation of a patient with factitious disorder. While the distinctions among these disorders appear satisfyingly clear, in practice, patients often blur the boundaries. Patients with somatoform disorders will sometimes consciously exaggerate symptoms which they have unconsciously produced, and it is a rare patient who consciously creates illness and yet receives no external gain at all, be it disability benefits, excuse from work, or even food and shelter.

While physicians have known about the feigning of illness since at least ancient Greece (Feldman 2000), it is likely that Asher's (1951) article brought the concept of factitious illness into general medical knowledge. Asher coined the term Munchausen's syndrome referring to the Baron von Munchausen, a character in German literature who was known for greatly exaggerating the tales of his exploits. (The use of this term may be somewhat unfair to the baron. Apparently, Rudolf Raspe, his unauthorized biographer, may have greatly overstated both the Baron's exploits and his tendency to exaggerate (Guziec et al. 1994)). Asher described Munchausen's syndrome as severe, chronic factitious disorder combined with antisocial behavior including wandering from hospital to hospital (peregrination). However, his memorable term has often been used interchangeably with "factitious disorder" and incorrectly applied to patients with less severe forms of the disease.

Patients have been known to create or feign numerous illnesses, both acute and chronic, in all of the medical specialties. It appears that the only limit is the creativity and knowledge of a given patient. In fact, there is at least one case report of a patient who feigned factitious disorder itself (Gurwith and Langston 1980). The patient claimed to have Munchausen's syndrome, to have undergone numerous unnecessary procedures and operations, and as a result, to need immediate hospitalization. He displayed his abdomen, which appeared to have numerous surgical scars and hinted that searches of his hospital room would be fruitful. However, collateral information revealed that the physicians and hospitals he had reported had never treated the patient, and his "scars" washed off with soap and water. Patients with factitious disorder are often quite medically sophisticated. Even though acquired immune deficiency syndrome was not described until the early 1980s, the first factitious cases

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followed shortly thereafter, at least as early as 1986 (Miller et al. 1986). Some individuals pursue the sick role not by feigning illness in themselves, but instead by creating it in another person, usually someone dependent on the perpetrator. They seek the role of caring for an ill individual and are diagnosed with factitious disorder by proxy.

## Factitious Disorder

### Diagnosis

#### Definition and Diagnostic Features

For a diagnosis of factitious disorder (see *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria for factitious disorder) to be justified, a person must be intentionally producing illness; his or her motivation is to occupy the sick role, and there must not be external incentives for the behavior. While the DSM is clear that no external incentives can be present to meet the criteria for the diagnosis, it is rarely the case that there is absolutely no secondary gain for a patient (as the sick role automatically conveys some external benefits such as release from usual duties). In practice, clinicians will often diagnose patients with factitious disorder in the presence of some external gain as long as the external benefits do not appear to be a major motivation for the production of symptoms. Of course, some patients muddy the distinction between factitious disorder and malingering, as they appear to be motivated both by seeking the sick role and by powerful external motivations. For example, Eisendrath and McNeil (2004) reported four cases of patients involved in civil litigation (an external incentive in the form of a monetary reward), yet their factitious illnesses continued after the litigation was complete and resulted in the patients' deaths. Some authors have complained about the inherent subjectivity in defining a diagnosis in part by the patient's motivation (and therefore involving some speculation by the clinician) (Turner 2006), however, as the distinction between malingering and factitious disorder rests on the internal motivation of the patient, it is impossible to escape this subjectivity, at least with the current definitions. Patients who readily admit to inducing symptoms, such as self-mutilating patients, are not diagnosed with factitious disorder as they are not creating their symptoms to occupy the sick role. The diagnosis of factitious disorder (Figure 75–1) is subclassified, depending on whether the factitious symptoms are predominantly physical, psychological, or a combination of both.

Due to the inherently deceptive nature of patients with factitious disorder, the literature is largely confined to case reports and case series. It is likely that many patients with less severe forms of the disease escape detection, and their clinical characteristics might be quite different.

##### *Factitious Disorder with Predominant Physical Signs and Symptoms*

Patients with this subtype of factitious disorder present with physical signs and symptoms. The three main methods patients use to create illness are: (1) giving a false history, (2) faking clinical and laboratory findings, and (3) inducing illness (e.g., by surreptitious medication use, inducing infection, or preventing wound healing) (Eisendrath 1994). There are reports of factitious illnesses in all of the medical specialties. Particularly common presentations include fever, self-induced infection, gastrointestinal symptoms, impaired wound healing, cancer, renal disease (especially hematuria and nephrolithiasis), endocrine diseases, anemia, bleeding disorders, and epilepsy (Wise and Ford 1999). True Munchausen's syndrome fits within this subclass and is the most severe form of the illness. According to the DSM-IV-TR, patients with Munchausen's syndrome have chronic factitious disorder with physical signs and symptoms, and in addition, have a history of recurrent hospitalization, peregrination, and *pseudologia fantastica*—dramatic, untrue, and extremely improbable tales of their past experiences (American Psychiatric Association 2000). They are often very familiar with hospital procedure and use this knowledge to present dramatically during off-hours or at house officer transition times when the factitious nature of their symptoms is least likely to be discovered.

**DSM-IV-TR Criteria**

**Factitious Disorder**

A. Intentional production or feigning of physical or psychological signs or symptoms.

B. The motivation for the behavior is to assume the sick role.

C. External incentives for the behavior (such as economic gain, avoiding legal responsibility, or improving physical well-being, as in malingering) are absent.

**Code based on type**

300.16 With Predominantly Psychological Signs and Symptoms: if psychological signs and symptoms predominate in the clinical presentation 300.19 With Predominantly Physical Signs and Symptoms: if physical signs and symptoms predominate in the clinical presentation 300.19 With Combined Psychological and Physical Signs and Symptoms: if both psychological and physical signs and symptoms are present and neither predominates in the clinical presentation

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##### *Factitious Disorder with Predominantly Psychological Signs and Symptoms*

Another subtype of factitious disorder includes patients who present feigning psychological illness. They both report and mimic psychiatric symptoms. There are reports of factitious psychosis, posttraumatic stress disorder, homicidal ideation, and alcohol dependence (Pope et al. 1982, Sparr and Pankratz 1983, Mitchell and Francis 2003, Thompson and Beckson 2004), and it is likely that patients feign psychiatric disorders across the full spectrum of mental illness. In addition, there are reports of false claims of being a victim of stalking or rape (Pathe et al. 1999, Feldman et al. 1994), and these cases are often diagnosed with a factitious psychological disorder such as posttraumatic stress disorder.

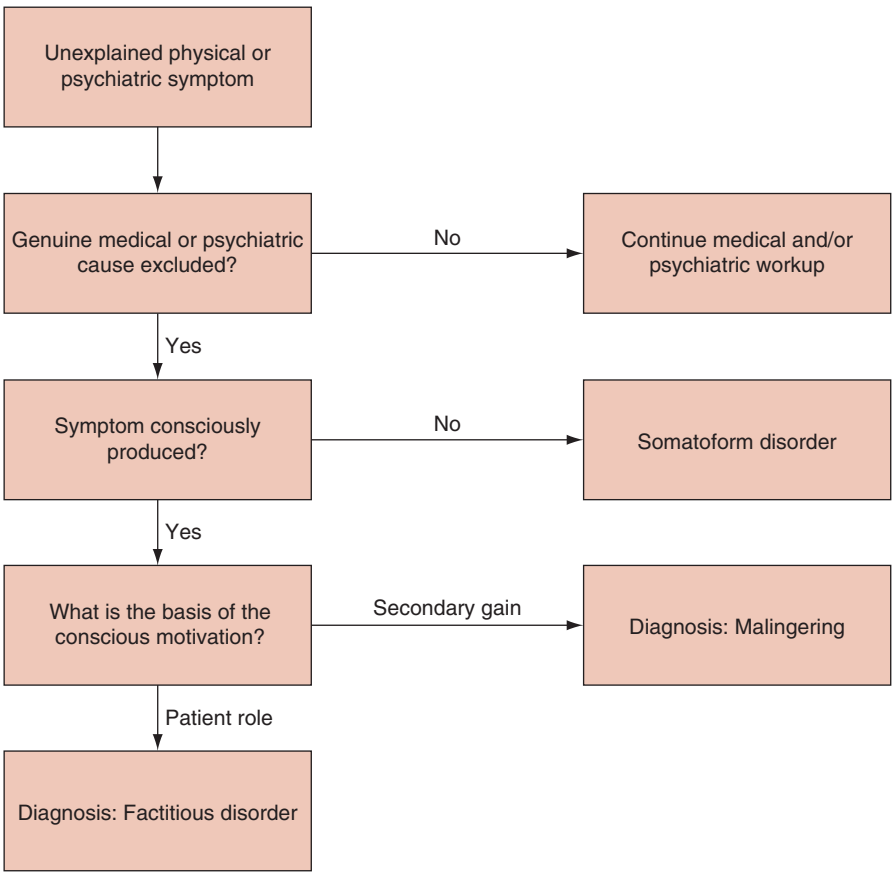



**Figure 75–1** *Diagnostic decision tree for factitious disorder.*

While patients with factitious psychological symptoms feign psychiatric illness, they also often suffer from true comorbid psychiatric disorders, particularly Axis II disorders and substance abuse, and case reports suggest that patients with psychological factitious disorder have a high rate of suicide and a poor prognosis (Eisendrath 2001, Pope et al. 1982, Popli et al. 1992). While Munchausen's syndrome is considered a subset of physical factitious disorder, there are case reports of patients presenting with psychological symptoms who also have some of the key features of Munchausen's (pathological lying, wandering, and recurrent hospitalizations) (Merrin et al. 1986, Popli et al. 1992).

### *Factitious Disorder with Combined Psychological and Physical Signs and Symptoms*

DSM-III separated factitious disorder into two disorders, based on whether the symptoms were physical or psychological. However, case reports clarified that this distinction was often artificial (Merrin et al. 1986, Parker 1993). Some patients present with simultaneous psychological and physical factitious symptoms, and some patients move between physical and psychological presentations over time. DSM-IV-TR was revised to account for patients who present with both psychological signs and symptoms, though this category of patients is the least well studied.

Clinical Vignette 1

**Munchausen's Syndrome**

A 42-year-old man was brought in by ambulance from a public park after complaining of shortness of breath and collapsing. Onlookers called 911. In the emergency room, the patient complained of shortness of breath and chest pain. He reported that he had a history of multiple pulmonary emboli necessitating Greenfield filter placement. He seemed to be very familiar with the medical terminology and clinical findings in pulmonary emboli. The patient had an extensive workup including a high resolution CT scan, but all studies were normal. The medical team noted that the patient appeared to be holding his breath when his oxygen saturation was being measured, and in addition, was performing a Valsalva maneuver during his ECGs. The medical resident attempted to clarify the patient's history by obtaining collateral information. The hospitals contacted reported that the patient had presented numerous times with the same complaints, and there had been suspicion of a factitious disorder. The medical resident informed the patient of the conflicting information, at which point the patient became very angry and immediately left the hospital. He was lost to follow up.

Clinical Vignette 2

**Factitious Disorder with Psychological Features**

A 46-year-old man presented complaining of symptoms of posttraumatic stress disorder (PTSD). He reported intense flashbacks, numbing and avoidance, and irritability resulting from his experience as a combat veteran. He began intensive treatment for PTSD including support groups, individual therapy, and medication management. He was an extremely active participant in the support groups and would recount detailed horrors of his time in combat. A staff member verifying the patient's history learned the patient had served in the military but was not a combat veteran. The patient was confronted in a supportive manner, and he admitted that he had fabricated his history. It was recommended that the patient would continue in psychiatric treatment, and he agreed to do so.

## Assessment

The diagnosis of factitious disorder is made in several ways. Factitious disorder is occasionally diagnosed accidentally when the patient is discovered in the act of creating symptoms. A history of inconsistent or unexplainable signs and symptoms or failure to respond to appropriate treatment can prompt health care providers to probe for evidence of the disorder, as can evidence of peregrination or pathological lying. In some cases, it is a diagnosis of exclusion in an otherwise inexplicable case. In order to make the diagnosis, it is necessary to consider it in the differential of the patient's illness; however, physicians are often hesitant to suspect that their patients may be deceiving them. Given that the prevalence of factitious disorder may be over 1% of the inpatient population, physicians should probably include it on the differential in medically complex cases more frequently than is now done, as this would allow for a careful investigation of the possibility of factitious disorder along with the other possible diagnoses. However, it would be important to clarify to other members of the treatment team that it is just one diagnosis of several that is being considered given the significant countertransference issues that can arise in dealing with factitious disorder.

If there is suspicion of factitious disorder, confirmation can be difficult. Laboratory examination can confirm some factitious diagnoses such as exogenous insulin or thyroid hormone administration. Collateral information from family members or previous health care providers is often extremely helpful. Factitious disorder with psychological signs and symptoms can be particularly difficult to diagnose, as so much of psychiatric diagnosis relies on the patient's report. However, there is some evidence that neuropsychological testing may be helpful in making the diagnosis. Both McCaffrey and Bellamy-Campbell (1989) and Fairbank et al. (1985) report the ability to detect over 90% of cases of factitious PTSD using the Minnesota multiphasic personality inventory (MMPI). However, Perconte and Goreczny (1990) were unsuccessful in attempting to replicate the findings. In addition, there is a report of MMPI-test-results being used to support a diagnosis of factitious disorder with psychological features in a woman thought to be feigning symptoms of multiple personality disorder (Coons 1993).

## Epidemiology

The nature of factitious disorder makes it difficult to determine how common it is within the general population. Patients attempt to conceal themselves, thereby artificially lowering the prevalence. The tendency of patients to present several times at different facilities, however, may artificially raise the prevalence. Most estimates of the prevalence of the disease, therefore, rely on the number of factitious patients within a given inpatient population. Such attempts have generated estimates that 0.5−3% of medical and psychiatric inpatients suffer from factitious disorder. Of 1,288 patients referred for psychiatric consultation at a Toronto general hospital, 10 (0.8%) were diagnosed with factitious disorder (Sutherland and Rodin 1990). A prospective examination of all 1,538 patients hospitalized in a Berlin neurology department over 5 years found five (0.3%) cases of factitious disorder (Bauer and Boegner 1996). An examination of 506 patients with fever of unknown origin (FUO) revealed that 2.2% of the fevers were of factitious origin (Rumans and Vosti 1978), and a review of 199 Belgian patients with FUO found 7 of 199 (3.5%) to be factitious (Knockaert et al. 1992). A similar study of patients with FUO at the National Institutes of Health (NIH) revealed that 9.3% of the fevers were factitious (Aduan et al. 1979). The increased prevalence found at the NIH may be due to the fact that the study was undertaken in a more tertiary setting, and it is a reminder that the prevalence of factitious disorder likely varies widely depending on the population and the setting. Gault et al. (1988) examined 3,300 renal stones brought in by patients and found that 2.6% of these stones were mineral and felt to be submitted by factitious or malingering patients. There is much less data on the prevalence of factitious disorder with psychological features. A study of psychiatric inpatients showed a prevalence of 0.5% of admissions determined to be a result of a factitious psychological condition (Bhugra 1988). There are few data about the prevalence of factitious disorder in an outpatient population. Because factitious patients do not readily identify themselves in large community surveys, it is not currently possible to determine the prevalence of the disorder in the general population.

## Comorbidity Patterns

All types of factitious disease show a strong association with substance abuse (Kent 1994) as well as borderline and narcissistic personality disorders. In a case series by Ehlers and Plassman (1994), 9 of 18 patients had personality features that met criteria for borderline personality disorder, and another 6 of 18 had personality features that met criteria for narcissistic personality disorder. In a series of 93 patients with factitious disorder, Krahn et al. (2003) found that 32% of the patients had a second DSM-IV-TR diagnosis and that 33% had a chemical dependency. Analyses of reported cases of patients with factitious disorder by proxy have found a high incidence (approximately one-fourth to one-third) of comorbidity with personal factitious disorder or factitious features (Sheridan 2003, Rosenberg 1987). There is not any data on the reverse, that is, how many patients with factitious disorder also have factitious disorder by proxy, but it is worth being alert to the possibility that a patient with factitious disorder might also be inducing illness in a dependent.

### Course

Numerous reports (Carney and Brown 1983, Reich and Gottfried 1983, Wise and Ford 1999) in the literature describe two different subclasses of factitious patients, and the course for each subclass is quite different. The first type fits with the classic Munchausen's syndrome diagnosis: they have chronic factitious symptoms associated with antisocial traits, pathological lying, minimal social supports, wandering from hospital to hospital, and very poor work and relationship functioning. Patients with Munchausen's syndrome appear of having an extremely poor prognosis (Eisendrath 2001, Carney and Brown 1983). Fortunately, this most severe class of patients makes up the minority of factitious patients, probably fewer than 10%.

The second and more typical type of patient does not display pathological lying or wandering. Their recurrent presentations are usually within the same community, and they become well known within the local health care system. They often have stable social supports and employment, and a history of a medically related job. This larger class of factitious patients is more likely to accept psychiatric treatment and to show improvement. There are individuals who may have an episode of factitious disorder in reaction to a life stressor, but may return to premorbid functioning after the stressor is resolved (Goldstein 1998).

The course of untreated factitious disorder is variable. Patients with factitious disorder commonly suffer a great deal of morbidity, both physical and psychological, and some cases can be fatal. One survey of 41 cases noted only one fatality, though many of the other cases were life-threatening (Reich and Gottfried 1983). Another retrospective report noted two fatalities out of 28 patients for whom they had the follow-up data (out of 93 total patients)—though they did not report if it was thought that these deaths were due to the factitious illness (Krahn et al. 2003). Eisendrath and McNeil (2002 and 2004) reported that of a series of 20 factitious patients who were involved with civil litigation, there were four deaths, all of which occurred as a direct result of the factitious illness. Patients with psychological signs and symptoms are reported to have a high rate of suicide and a poor prognosis (Pope et al. 1982, Popli et al. 1992).

### Differential Diagnosis

The differential diagnosis of factitious disorder includes rare or complex physical illnesses, somatoform disorders, malingering, other psychiatric disorders, and substance abuse (McKane and Anderson 1997). It is especially important to rule out genuine physical illness since complex medical illnesses can be mistaken for factitious disorder, and because patients with factitious disorder often induce real physical illness.

### Differences in Developmental, Gender, and Cultural Presentations

Factitious patients span a broad age-range. Reports in the literature show patients ranging from 8 to 85 years (Absolut de la Gastine et al. 1998, Davis and Small 1985). Of note, there is a report of a 4-year-old patient thought to have factitious disorder but who reported that he had been coached by his mother and may be better diagnosed as a victim of factitious disorder by proxy (Croft and Jervis 1989). Case series suggest that the majority of people with factitious disorder are women—one case series found 78% of patient to be women (Plassmann 1994a) and another 72% (Krahn et al. 2003) while the majority of patients with the more severe Munchausen's variant are men. A case series of patients with cardiac Munchausen's syndrome (who had an average of six hospitalizations) found that 54% were men (Mehta and Kahn 2002). Ethnicity is frequently not reported in case studies and series, so it is difficult to determine if there are any ethnic differences in the prevalence or presentation of factitious disorder. In Krahn et al.'s (2003) review of 93 patients with factitious disorder who presented to the Mayo Clinic, 84% were Caucasian and 2% were African-American with the remaining 7% of other races (Krahn et al. 2003). However, as these patients were drawn from a population that presented to a tertiary care center in Minnesota, it is not likely the representative of the general population. While cases of factitious disorder have been reported worldwide, it is not known if the presentation varies from culture to culture (though it would not be surprising as the construct of the sick role does very culturally).

## Etiology and Pathophysiology

### Genetic Factors

While factitious disorder appears to run in families, it is not known if this is explainable by genetic factors, environmental factors or both.

### Neurobiological Factors

The presence of central nervous system (CNS) abnormalities in some patients with factitious disorders have led some to hypothesize that underlying brain dysfunction contributes to factitious disorder. One review of factitious patients with *pseudologia fantastica* found CNS abnormalities (such as EEG abnormality, head injury, imaging abnormalities, or neurological findings) in 40% of the patients (King and Ford 1988). There have been case reports of magnetic resonance imaging (MRI) (Fenelon et al. 1991) and single photon emission computed tomography (SPECT) (Mountz et al. 1996) abnormalities, but it is unknown if these abnormalities were related to the disorder.

### Psychological Factors

Patients with factitious disorder create illness in pursuit of the sick role. For these patients, being in the sick role may allow them to compensate for an underlying psychological deficit. Most authors identify several common psychodynamic motivations for factitious disorder (Feldman 2000, Eisendrath 2001, Guziec et al. 1994, Folks 1995, Hyler and Sussman 1981). First, patients with little sense of self may seek the sick role in order to provide a well-defined identity around which to structure themselves. Others may seek the sick role in order to meet dependency needs which have gone unmet elsewhere. As a patient, they receive the attention, caring, and nurturing of the health care environment and are relieved of many of their responsibilities. In addition, some patients may engage in factitious behaviors for masochistic reasons. They feel that they deserve punishment for some forbidden feelings and thus they should suffer at the hands of their physicians. Other patients may be motivated by anger at physicians and dupe them in retaliation. Patients with a history of childhood illness or abuse may attempt to master

past traumas by creating a situation over which they have control. Finally, some authors have speculated that some patients may be enacting suicidal wishes through their factitious behavior (Schoenfeld et al. 1987, Roy and Roy 1995).

### Social and Environmental Factors

In addition, childhood developmental disturbances are thought to contribute to factitious disorder. Predisposing factors are thought to include (1) serious childhood illness or illness in a family member during childhood, especially if the illness was associated with attention and nurturing in an otherwise distant family, (2) past anger with the medical profession, (3) past significant relationship with a health care provider, and (4) factitious disorder (especially factitious disorder by proxy) in a parent (McKane and Anderson 1997). It is thought that factitious disorder is more common in people in the health care professions, though it is not known if working in health care increases the risk for developing factitious disorder or if people with factitious disorder are drawn to health care work.

## Treatment

### Treatment Goals

The goals in treating patients with factitious disorder are twofold: first to minimize the damage done by the disorder to both the patient's own health and the health care system, and second, to help patients recover, at least partially, from the disorder. These goals are furthered by treating comorbid medical illnesses, avoiding unnecessary procedures, encouraging patients to seek psychiatric treatment, and providing support for health care clinicians. As mentioned before, patients with true Munchausen's syndrome (including antisocial traits, pathological lying, wandering, and poor social support) are felt to be refractory to treatment. While factitious disorder is extremely difficult to cure, effective techniques exist to minimize morbidity, and some patients are able to benefit greatly from psychiatric intervention.

### Somatic Treatments

It is extremely important to treat any comorbid medical illnesses as patients with factitious disorder often induce genuine medical illness, and patients with factitious disorder are not immune to the physical illnesses that plague the general population. As much as possible, providers should base medical treatment on objective physical and laboratory signs and avoid unnecessary procedures. There are no clear data supporting the effectiveness of medications in treating factitious disorder. There is a case report of effective pimozide treatment in a patient thought to have delusional symptoms (Prior and Gordon 1997) as well as a case report of a factitious patient with comorbid depression improving when treated with an antidepressant in addition to intensive psychotherapy (Earle and Folks 1986).

### Psychosocial Treatments

Soon after Asher's (1951) article was published, many patients with factitious disorder were vigorously confronted once the nature of their illness was discovered. Unfortunately, most patients would deny their involvement and seek another provider who was unaware of their diagnosis (Eisendrath 2001). In addition, the idea of "blacklists" was proposed in order to aid detection of these patients. However, issues regarding patient confidentiality, as well as concerns about cursory medical evaluations that might miss genuine physical illness, prevented this idea from being adopted (Eisendrath 2001). Although aggressive confrontation is usually unsuccessful, supportive, nonpunitive confrontation may be helpful for some. In one case series, 33 patients were confronted with the factitious nature of their illness. While only 13 admitted feigning illness, most of the patients' illnesses subsequently improved, at least in the short term (Reich and Gottfried 1983).

Eisendrath suggested three alternatives to confrontation that he found effective. First is inexact interpretation, in which the psychiatrist interprets the psychodynamics thought to be underlying the patient's behavior without explicitly identifying the factitious behavior. He gave the example of a patient suspected of having factitious disorder who developed septicemia after her boyfriend proposed marriage. The consultant suggested that the patient might feel a need to punish herself when good things happened to her. She agreed, and soon after, admitted that she had injected a contaminant intravenously (Eisendrath 2001). The second technique is the therapeutic double bind. The physician presents the patient with a new medical intervention to treat his or her illness. The patient is told that one possibility is that the patient's illness has a factitious origin, and that, if so, the treatment would not be expected to work while, if the illness is biological, the treatment will work and the patient will improve. The patient must decide to give up the factitious illness or admit it. A third technique is to provide the patient with a face-saving way, such as hypnosis or biofeedback, of giving up his or her symptoms without admitting that they are not genuine. Eisendrath (2001) points out that in emergent situations, there may not be time for nonconfrontational techniques, and more directly confrontational means may be necessary.

While many patients with factitious disorder are hesitant to pursue psychiatric treatment, there are numerous case reports of successful treatment of the disorder with long-term psychotherapy. In many of these cases, the therapy lasted several years, though Cohen and Chang (2004) reported a patient with significant improvement after 5 months of treatment (2004). Plassmann (1994b) reports a case series of 24 factitious patients. Twelve of these patients accepted psychotherapy and 10 continued with long-term treatment, lasting up to 4.5 years. He reports "significant, or at least marked, improvement" in those 10 patients. These case reports support the idea that treatment of patients with factitious disorder is not impossible, and these patients can improve. However, expectations must be realistic as improvement in the disorder can take several years (Figure 75–2).

### Issues in the Clinician–Patient Relationship

Patients with factitious disorder frequently stir intense countertransference reactions in the health care team. These reactions frequently include anger at having been duped or deceived as well as powerlessness both at the inability to know with certainty the medical reality of the situation and also to definitively treat the patient. These reactions can interfere with compassionate care of the person with factitious disorder, leading to complete dismissal of all of the patient's complaints and even to punitive retaliation on the

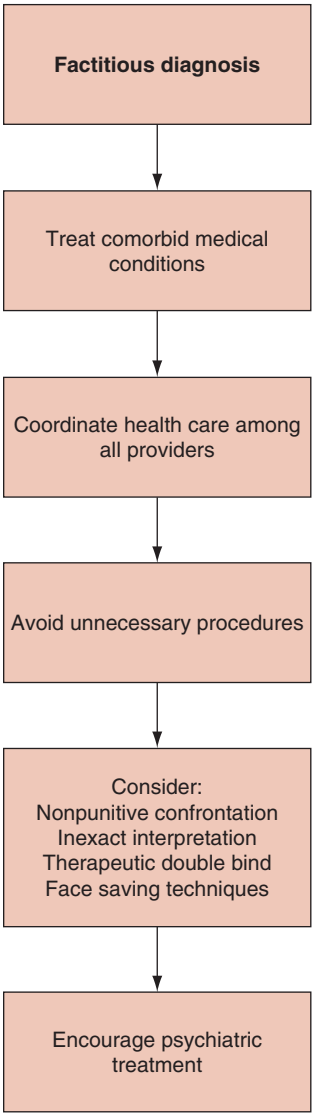



**Figure 75–2** *Treatment flowchart for factitious disorder.*

part of the treating team. An important component in the treatment of patients with factitious disorder is the coordination of health care among all providers. This allows for fewer unnecessary interventions, minimizes splitting among the health care team, and allows the health care team to vent and process the strong emotions that arise when caring for factitious patients. It can be helpful to remind ourselves and other members of the treatment team that, while the presenting complaint is factitious, the patient still suffers from a life-threatening illness, and that, despite the havoc these patients can wreck in the treatment setting, they are still usually the greatest victim of their illness.

### Special Factors Influencing Treatment

#### *Ethical Considerations*

Treating patients with factitious disorder often raises ethical questions regarding confidentiality, privacy, and medical decision-making, and it is important to be alert to these issues. Often, patients with factitious disorder will want to keep their diagnosis confidential, even when to do so may harm the patient or others. For example, although a consulting physician may diagnose a patient with factitious disorder, the patient may refuse consent to reveal this information to the referring physician. If the consultant does inform the referring physician, she has violated the patient's confidentiality, but if she does not, the referring physician is likely to continue to treat the patient for the incorrect diagnosis. Dilemmas regarding patient privacy also arise with factitious patients. For example, hospital room searches could often help clarify the diagnosis or remove materials the patient is using to harm himself, but these searches also violate the patient's privacy. Dilemmas surrounding medical decision-making can arise when a patient with factitious disorder refuses treatment or requests potentially harmful treatments. It can often be difficult to resolve these ethical dilemmas. In general, even though the factitious patient is deceptive within the doctor–patient relationship, the physician is not released from his or her responsibilities within that relationship, and the patient retains his or her rights of confidentiality, privacy, and autonomy. As with all the patients, emergency situations require different ethical guidelines. Often, ethics and legal consultations can be very helpful in sorting through the difficult issues of patient care in the setting of factitious disorder.

## Factitious Disorder by Proxy

Some individuals pursue the sick role not by feigning illness in themselves, but by creating it in another person, usually someone dependent on the perpetrator. They seek the role of caring for an ill individual (the sick role by proxy). In this disorder, there are two patients, the individual with the diagnosis, and his or her victim. While people who suffer from factitious disorder by proxy have a mental illness, they often also commit criminal acts, usually dependent or child abuse, and the criminal justice and child protective systems are often involved.

## Diagnosis

### Definition and Diagnostic Features

In factitious disorder by proxy, one person creates or feigns illness in another person, usually a child, though occasionally

**DSM-IV-TR Criteria**

**Factitious Disorder by Proxy**

A. Intentional production of or feigning of physical or psychological signs or symptoms in another person who is under the individual's care.

B. The motivation for the perpetrator's behavior is to assume the sick role by proxy.

C. External incentives for the behavior (such as economic gain) are absent.

D. The behavior is not better accounted for by another mental disorder.

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the victim is an elder or developmentally delayed adult. The veterinary literature even reports cases of factitious disorder by proxy in which the victim is a pet (Munro and Thrusfield 2001). Factitious disorder by proxy is not defined as a specific disorder in DSM-IV-TR but instead is listed under the "not otherwise specified" heading with research criteria included. The diagnostic criteria for factitious disorder by proxy are similar to that of factitious disorder itself, with the exception of the victim of the feigned or induced illness. While numerous symptoms have been reported, common presentations include apnea, seizures, and gastrointestinal problems. The perpetrators appear extremely caring and attentive when observed, but appear indifferent to the child when they are not aware of being observed (Eisendrath 2001).

### Assessment

The diagnosis of factitious disorder by proxy is usually made by having an index of suspicion in a child with unexplained illnesses. Laboratory findings can occasionally confirm the diagnosis, and collateral information from multiple family members can be very useful. In addition, the diagnosis is supported if symptoms occur only in the parent's presence and resolve with separation. Covert video surveillance has been used to diagnose this condition, though it raises questions of invasion of privacy. In general, it has been felt that the welfare of the child overrides the parent's right to privacy.

### Epidemiology

As in factitious disorder, the exact prevalence of factitious disorder by proxy is unknown. There have been studies of the annual incidence of factitious disorder by proxy in the general population in both the United Kingdom and New Zealand. In New Zealand, the annual incidence of factitious disorder by proxy in children less than 16 years was found to be 2.0/100,000 (18 total cases) (Denny et al. 2001). In the United Kingdom, the annual incidence in children under 16 was 0.5/100,000 (128 total cases) (McClure et al. 1996). As for the incidence within clinical populations, an Argentinean survey of 113 children with FUO found four (3.5%) cases of factitious fever (Chantada et al. 1994). A survey of 20,090 children brought in with apnea found 54 (0.27%) to be victims of factitious disorder by proxy (Kravitz and Willmott 1990). Finally, a review of children brought in for treatment of acute, life threatening episodes of diverse etiologies ranging from seizure disorders to electrolyte abnormalities found 1.5% to be factitious (Rahilly 1991).

### Comorbidity Patterns

There is high psychiatric morbidity in the children—many go on to develop factitious disorder or other psychiatric illnesses themselves (McGuire and Feldman 1989). For the adults with factitious by proxy, there is high comorbidity with other psychiatric disorders and a history of abuse. In a review of 451 reported cases of factitious by proxy, Sheridan (2003) found that 23% had another psychiatric disorder, usually depression or a personality disorder, and 22% had a history of abuse. In addition, in reported cases, there is an increased rate (~25–30%) of personal factitious disorder in patients with factitious disorder by proxy (Sheridan 2003, Rosenberg 1987).

### Course

Factitious disorder by proxy appears to have a much higher mortality rate than self-inflicted factitious disorder. In Rosenberg's (1987), survey of 117 victims, there was a 9% mortality rate, and of the 54 victims of the disorder in the apnea survey, three index cases and five siblings were dead at the follow-up (Kravitz and Wilmott 1990). McClure et al. (1996) found that eight of 128 index cases in the UK were fatal (6.25%) while Denny et al. (2001) reported no fatalities in 18 index cases. Sheridan (2003) reviewed 451 reported cases of factitious disorder by proxy and found a 6% mortality rate and 7% rate of long-term or permanent disability. In addition, she found 25% of the known siblings of the victims were known to be dead.

### Differential Diagnosis

As with factitious disorder, the differential includes complex medical illness. In addition, in an older child, the differential might include personal factitious disorder in the child. As yet, there are no reports of personal factitious disorder in a child under 8, whereas the victim in factitious by proxy is usually a younger child.

### Differences in Developmental, Gender and Cultural Presentations

Boys and girls appear to be victims of factitious disorder by proxy in equal numbers (Rosenberg 1987, Sheridan 2003). However, the perpetrators are usually the mothers. In Rosenberg's (1987) review of 117 cases, all of the perpetrators were mothers. In Sheridan's (2003), subsequent review of 451 cases, 77% of the perpetrators were the birth mothers and 7% were the fathers. The average age of the victim in these two reviews was 49 months (Sheridan 2003) and 40 months (Rosenberg 1987).

## Etiology and Pathophysiology

### Psychological Factors

As counterintuitive as it is to comprehend why anyone would induce illness in oneself, it can be even more difficult to understand inducing illness in one's own child. The perpetrator in factitious disorder by proxy appears to seek not the "sick role" but the "parent to the sick child" role. This role is similar to the sick role in that it provides structure, attention from others, caring, and relief from usual responsibilities. In addition, the psychological factors that play a role in other forms of child abuse may also be present.

### Social/Environmental Factors

Childhood developmental disturbances are thought to contribute to the development of factitious disorder by proxy. Based on case reports, the perpetrator often has a history of family dysfunction (Bools et al. 1994). In Sheridan's (2003) review, 22% of perpetrators reported a personal history of either childhood or domestic abuse. In addition, a background in health care was also associated with the disorder: in Rosenberg's (1987) review, 30% of the perpetrators had a health care background (1987), and in Sheridan's (2003) review, 14% has a health care background.

## Treatment

Due to the high morbidity and mortality, treatment requires at least temporary separation from the parent and

Clinical Vignette 3

**Factitious Disorder by Proxy**

A 6-month-old infant presented to the emergency room after a seizure. The family reported no significant past medical history. The infant was resuscitated. There was no evidence of infection, the patient had a normal blood glucose, and the urine toxicology screen was negative. After 5 hours, the child recovered. The infant presented again 5 days later with another seizure. The infant's blood glucose was low, and continued to fall below normal levels despite administration of dextrose. A blood insulin level was elevated and a c-peptide level suggested endogenous hyperinsulinism. The workup (including CT scan) was otherwise normal. Further history revealed that both grandmothers had Type II diabetes and took oral hypoglycemic agents. A blood test on the infant was positive for sulfonylurea. A case conference was held, and it was discovered that the mother's first child had been removed from the home due to some charges of abuse. It was recommended that the infant be placed in foster care while the police investigated the case (Owen et al. 2000).

notification of local child protective agencies. The perpetrators often face criminal charges of child abuse. There is high psychiatric morbidity in the children—many go on to develop factitious disorder or other psychiatric illnesses themselves. Psychiatric intervention is necessary to ameliorate this morbidity as much as possible in these children (McGuire and Feldman 1989). There are some case reports of successful psychotherapeutic treatments of the parents in this disorder (Rand and Feldman 2001).

## Summary

Patients with factitious disorder seek, often desperately, the sick role. Due to the nature of the disorder, the literature on factitious disorder is largely confined to case reports and case series, limiting the information available. Patients with factitious disorder present with a broad spectrum of signs and symptoms, and effective diagnosis often requires a high index of suspicion. The differential diagnosis of factitious disorder includes physical illness, somatoform disorders, malingering, psychiatric illness, and substance abuse. While factitious disorder is extremely difficult to cure, effective techniques exist to minimize morbidity, and some patients are able to benefit greatly from psychiatric intervention.

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CHAPTER

# 76 Dissociative Disorders

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Dissociative Amnesia
Dissociative Fugue
Depersonalization Disorder
Dissociative Identity Disorder
Dissociative Trance Disorder
Acute Stress Disorder

Dissociative phenomena are best understood through the term *désagrégation* (disaggregation) originally given by Janet (1920). Events normally experienced as connected to one another on a smooth continuum are isolated from the other mental processes with which they would ordinarily be associated. The dissociative disorders are a disturbance in the organization of identity, memory, perception, or consciousness. When memories are separated from access to consciousness, the disorder is dissociative amnesia. Fragmentation of identity results in dissociative fugue or dissociative identity disorder (DID; formerly multiple personality disorder). Disintegrated perception is characteristic of depersonalization disorder. Dissociation of aspects of consciousness produces acute stress disorder and various dissociative trance and possession states. Numbing and amnesia are diagnostic components of posttraumatic stress disorder (PTSD). These dissociative and related disorders are more a disturbance in the organization or structure of mental contents than in the contents themselves. Memories in dissociative amnesia are not so much distorted or bizarre as they are segregated from one another. The identities lost in dissociative fugue or fragmented in DID are two-dimensional aspects of an overall personality structure. In this sense, patients with DID suffer not from having more than one personality but rather from having less than one personality. The problem involves information processing: the failure of integration of elements rather than the contents of the fragments.

The dissociative disorders have a long history in classical psychopathology, being the foundation on which Freud began his explorations of the unconscious (Breuer and Freud 1955) and Janet (1920) developed his dissociation theory. Although much attention in psychiatry has shifted to diagnosis and treatment of mood, anxiety, and thought disorders, dissociative phenomena are sufficiently persistent and interesting that they have elicited growing attention from both professionals and the public. There are at least four reasons for this:

1. They are fascinating phenomena in and of themselves, involving the loss of or change in identity, or memory, or a feeling of detachment from extreme and traumatic physical events.
2. Dissociative disorders have their genesis in traumatic stress, a phenomena which seems to be ever more present in our society.
3. Dissociative disorders remain an area of psychopathology for which the best treatment is psychotherapy. No pharmacological treatment has been found to effectively treat these disorders, although adjunctive pharmacological interventions can be symptomatically helpful in some cases.
4. Dissociation as a phenomenon has much to teach us about information processing in the brain.

## Development of the Concept

The French philosopher and psychologist Pierre Janet (1920) is credited with the initial description of the disorder, *désagrégation mentale.* The French term *désagrégation* carries with it a different nuance than the English translation, dissociation. It implies a separation of mental contents despite their general tendency to aggregate or be processed together. Janet described hysteria as "a malady of the personal synthesis" (Janet 1920, p 332). The problem is a difficulty in integration rather than a proliferation of components of consciousness, memory, identity, or perception. Janet viewed dissociation as a purely pathological process.

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Jean-Martin Charcot (1890), the well-known neurologist and fellow countryman of Janet, was interested in hypnosis and taught the technique to Freud. He believed that even a normal process such as hypnosis, which could be used to access disaggregated mental contents, was itself evidence of dissociative pathology (*un état nerveux artificiel ou expérimental*, "an artificial or experimental nervous state" [Charcot 1890]). Charcot taught, for example, that once patients were cured of hysteria, they would no longer be hypnotizable. This hypothesis has been proven erroneous. Indeed, many normal individuals are highly hypnotizable and suffer of no psychopathology (Hilgard 1965, Spiegel and Spiegel 2004).

The dissociative disorders might have been studied more intensively during the 20th century had not Janet's and Charcot's work been so thoroughly eclipsed by Freud's psychoanalytic theory, emphasizing as it did repression rather than dissociation. In his early writings with Breuer, Freud explored the unconscious through an examination of similar dissociative phenomena. Cases in the studies on hysteria (Breuer and Freud 1955), such as that of Anna O., clearly involved dissociation. Indeed, Anna O. had many symptoms suggestive of DID. The fragmentation of identity and memory, typical of dissociative states, provided a natural stage for developing a theory involving the unconscious: the processing of information not readily available to conscious awareness. The vehicle they employed to explain this lack of integration was the concept of "hypnoid states." Breuer and Freud (1955) thought that dissociative symptoms could be attributed to the capacity of certain individuals to enter these hypnoid states, rather than the reverse, as Charcot had thought. To develop a more general theory of human psychopathology, Freud went on to study other kinds of patients, such as those with obsessive-compulsive disorder (Freud 1995) and schizophrenia (Freud 1958a). This shift in the population of patients he studied may well account for his increasing interest in repression rather than dissociation as a model of motivated forgetting. Much has been made of the fact that Freud abandoned the trauma theory of the etiology of the neuroses. What may have happened is that he abandoned the study of individuals for whom trauma could plausibly be applied as an etiological factor in their psychiatric disorder.

Hilgard (1977) developed a neodissociation theory that revived interest in Janet's psychological principles and dissociative psychopathology. Hilgard postulated divisions in mental structure that were horizontal rather than vertical, as in Freud's archeological model. The neodissociation model allowed for immediate access to consciousness of any of a variety of warded-off memories, which is not the case in Freud's system. In the dynamic unconscious model, repressed memories must first go through a process of transformation as they are accessed and lifted from the depths of the unconscious, for example, through the interpretation of dreams or slips of the tongue (Freud 1958b). In Hilgard's model, amnesia is a crucial mediating mechanism that creates barriers dividing one set of mental contents from another. Thus, flexible use of amnesia is conceptualized as a key defensive strategy. Therefore, reversal of amnesia is an important therapeutic tool.

Repression as a general model for keeping information out of conscious awareness differs from dissociation in four important ways:

1. In repression, information is disguised as well as hidden. Dissociated information is stored in a discrete and untransformed manner, whereas repressed information is usually disguised and fragmented. Even when repressed information becomes available to consciousness, its meaning remains hidden, as is the case of many dream content.
2. Retrieval of repressed information usually requires interpretation and translation. Retrieval of dissociated information can often be direct. Techniques such as hypnosis can be used to access warded-off memories. By contrast, uncovering of repressed information often requires repeated recall trials through intense questioning, psychotherapy, or psychoanalysis with subsequent interpretation (i.e., of dreams).
3. Repressed information is not discretely organized temporally. The information kept out of awareness in dissociation is often for a discrete and sharply delimited time, whereas repressed information may be for a type of encounter or experience scattered across times.
4. Repression is less specifically tied to trauma. Dissociation seems to be elicited as a defense most commonly after episodes of physical trauma, whereas repression is in response to warded-off fears, wishes, and other dynamic conflicts.

Whether dissociation is a subtype of repression or vice versa, both are important methods for managing complex and information charged with negative affect. Given the complexity of human information processing, the synthesis of perception, cognition, and affect is a major task. Mental function is composed of a variety of reasonably autonomous subsystems involving a perception, memory storage and retrieval, intention, and action (Spiegel 1991, Rumelhart and McClelland 1986, Cohen and Servain-Schreiber 1992a, 1992b, Baars 1988). Indeed, a sense of mental unity is an accomplishment, not an automatic consequence of consciousness (Spiegel 1990, Kihlstrom and Hoyt 1990). It is remarkable not that dissociative disorders occur at all, but rather that they do not occur more often.

Models of mental experience are presented in Table 76–1.

## Epidemiology

Dissociative disorders are not among the more common psychiatric illnesses but are not rare. Few good epidemiological studies have been performed. Some estimate the prevalence at only 1 per 10,000 in the population (Coons 1984), but far higher proportions are reported among psychiatric populations. In fact, the prevalence of the disorder seems to be associated to the specific population under study. For example, data from the general population suggest that the numbers are higher than initially described by Coons (Kluft 1991). In fact, some have found them to be as high as 1% (Ross 1991, Ross et al. 1991b, Vanderlinden et al. 1991). The data seem to indicate that the incidence may be even higher in some specialized inpatient populations, as high as 3% (Kluft 1991, Ross 1991, Ross et al. 1991a). More

**Table 76–1 Models of Mental Experience**

| Mental Function | Dissociation | Repression |
|---|---|---|
| Organization | Horizontal | Vertical |
| Barriers | Amnesia | Dynamic conflict |
| Etiology | Trauma | Developmental conflict over unacceptable wishes |
| Nature of contents | Untransformed: traumatic memories | Disguised, primary process: dreams, slips |
| Means of access | Hypnosis | Interpretation |
| Treatment | Psychotherapy emphasizing access, control, and working through traumatic memories | Psychotherapy emphasizing interpretation, transference |

recent studies (Foote and Smolin 2006) have that 29% of the patients of inner city, hospital-based outpatient psychiatric clinics have received a diagnosis of a dissociative disorder.

More recently, there has been a rise in reported cases of dissociation, which may be better attributed to greater awareness of the diagnosis among mental health professionals. Other factors that may contribute to the apparent increase includes the availability of more specific diagnostic criteria and the fact that some cases may have been previously misdiagnosed as schizophrenia or borderline personality disorder (BPD). Some dissociation experts attribute possible underdiagnosis to family disavowal of sexual and physical abuse. However, there is also controversy about possible overdiagnosis of the syndrome. Yet there are those who propose that the apparent increase is the result of hypnotic suggestion and inadequate handling by therapists (Brenner 1994, 1996, Frankel 1990, Ganaway 1989, 1995, McHugh 1995a, 1995b, Spanos et al. 1985, 1986). They claim that individuals who most commonly have been diagnosed with the disorder are highly hypnotizable and therefore especially sensitive to suggestion or cultural influences. Although psychiatrists' expectations amplified with hypnosis may account for some cases, they cannot account for many patients diagnosed without benefit of hypnosis or by "skeptical" psychiatrists.

Women make up the majority of cases, accounting for over 90% of the cases, in some studies (Putnam et al. 1986, Coons et al. 1988, Schultz et al. 1989). Researchers (Dominguez et al. 2004) have studied the relationship between exposure to traumatic events, post-traumatic suffering and dissociative symptoms, and the relationship between type of trauma and dissociation in a large sample of outpatient adults seeking treatment at an urban ambulatory mental health clinic in Jerusalem. They found that 83% of subjects reported high levels of intrusion and avoidance symptoms, while 15% reported high levels of dissociative phenomena. These results suggest an association between physical and sexual abuse and high levels of dissociation, particularly in subjects reporting a history of early childhood abuse and an increased prevalence of lifetime traumatic events.

The most commonly diagnosed dissociative disorder diagnosis is the "not otherwise specified" category, both in the US (Mezzich et al. 1989, Saxe et al. 1993) and in non-Western countries. In nondeveloped countries, dissociative trance and possession trance syndromes make the bulk of the cases of dissociative disorder (Adityanjee et al. 1989, Saxena and Prasad 1989). Despite the controversies, dissociative disorders are ubiquitous around the world, although the structure of the symptoms varies across cultures (Adityanjee et al. 1989, Berger et al. 1994, Boe et al. 1993, Brown et al. 1999, Coons and Milstein 1986, Draijer and Langeland 1999, Eriksson and Lundin 1996, Friedl and Draijer 2000, Horen et al. 1995, Modestin et al. 1996, Putnam 1989, Ronquillo 1991, Sar et al. 2000, Wittkower 1970). Not surprisingly, the symptomatology presented seem to reflect cultural norms and biases. For example, in Western cultures, where the importance of the individuality is emphasized dissociation often takes the form of dissociated elements of individual personality. On the contrary, in Eastern cultures where sociocentricity is emphasized, possession trance, in which patients feel themselves to be taken over by an outside entity or entities, is more common.

Te wildt (2004) theorized that the new digital media may adversely impact people's mental health, an effect that is widely underestimated. Maldonado et al. (2002) conducted a study to compare the effects in society of generic social events. They found that unrelated, consecutive societal events may have an additive effect on the development of trauma-related symptoms and that physical presence at the site of the trauma may not be needed for a person to be psychologically affected. They suggested that distant exposure to vicarious traumatic events (e.g., Internet, television, and media coverage) may somehow sensitize individuals to develop acute stress-like reactions when exposed to future traumatic events.

## Diagnostic Criteria and Treatment

Our discussion follows diagnostic criteria for the dissociative disorders as found in the *Diagnostic and Statistical*

**DSM-IV-TR Criteria 300.12**

**Dissociative Amnesia**

A. The predominant disturbance is one or more episodes of inability to recall important personal information, usually of a traumatic or stressful nature, that is too extensive to be explained by ordinary forgetfulness.

B. The disturbance does not occur exclusively during the course of dissociative identity disorder, dissociative fugue, posttraumatic stress disorder, acute stress disorder, or somatization disorder and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a neurological or other general medical condition (e.g., amnestic disorder due to head trauma).

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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*Manual of Mental Disorders*, Fourth-text-revised Edition (DSM-IV-TR; American Psychiatric Association 2000).

## Dissociative Amnesia

Dissociative amnesia represents the classical functional disorder of episodic memory. The disorder does not involve procedural memory or problems in memory storage, as in classic organic amnesia (e.g., Wernicke-Korsakoff syndrome). Furthermore, unlike dementing illnesses, dissociative amnesia is reversible (Janet 1920), for example, by using hypnosis or narcoanalysis. It usually involves one episode, but multiple periods of lost memory have been described (Coons and Milstein 1986). It has three primary characteristics:

1. Type of memory lost: The memory loss is episodic and usually involves the loss of first-person recollection of specific events and identity, rather than knowledge of procedures.
2. Temporal structure: The memory loss is for one or more discrete time periods, ranging from minutes to years. It is not vagueness or inefficient retrieval of memories but rather a dense unavailability of memories that were encoded and stored. Unlike the situation in amnestic disorders, for example, resulting from damage to the medial temporal lobe in surgery (the case of H.M. [Milner 1959]), in Wernicke-Korsakoff syndrome, or in Alzheimer's-type dementia, there is usually no difficulty in learning new episodic information. Thus, the amnesia of dissociative disorders is typically retrograde rather than anterograde (Loewenstein 1991). However, a dissociative syndrome of continuous difficulty incorporating new information that mimics organic amnestic syndromes has been observed (Schacter 1995).
3. Type of events forgotten: The memory loss is usually for events of a traumatic or stressful nature. This fact has been noted in the language of the DSM-IV diagnostic criteria. In one study (Coons and Milstein 1986), the majority of cases involved child abuse (60%), but disavowed behaviors such as marital problems, sexual activity, suicide attempts, criminal activity, and the death of a relative have also been reported as precipitants.

Dissociative amnesia most frequently occurs after an episode of trauma, and its onset may be gradual or sudden.

**Clinical Vignette 1**

A 30-year-old woman was beaten and raped by a man who drove her home from a party. She had refused his request to enter her apartment, but he returned a few minutes later claiming that he had to make a phone call. He then sexually assaulted her. She screamed and struggled and called the police immediately afterward. He was arrested when he returned to retrieve some jewelry she had pulled off his neck during the struggle. She had not suffered a concussion but began to lose memory of the rape in the ensuing week. By the end of the week she had no memory of the rape but became listless and depressed. Her psychotherapist used hypnosis to help retrieve her memory, which she was gradually able to do. Her recollections were consistent with her physical injuries and reports of neighbors who heard her screams.

**Clinical Vignette 2**

A 54-year-old man was involved in a motorcycle accident. He was wearing a helmet, which was damaged but did protect him during the accident. He was determined by the doctors in the emergency room to have suffered no significant head trauma. He did not lose consciousness, and he talked with a friend after the accident about it. However, he had no memory of the accident or of the 12 hours afterward. His first recollection was of a friend telling him, "You crashed my motorcycle." When he returned the next day to the hospital where he had been treated, he recognized a nurse as familiar, and she told him that he had been yelling when they treated his injured left knee. Yet, this visit did not stimulate any direct recollection of his time in the hospital. He had recovered no memory of the accident a month later.

Dissociative amnesia occurs most often in the third and fourth decades of life (Coons and Milstein 1986, Ross 1989, Putnam 1989). Recent studies suggest that the prevalence of dissociative amnesia in the general community is 1.8% (Johnson et al. 2006). Comorbidity with certain Axis I diagnoses, such as conversion disorder, bulimia nervosa, alcohol abuse, and depression are common. On the other hand, Axis II diagnoses of histrionic, dependent, or BPDs occur in a substantial minority of such patients (Coons and Milstein 1986). The typical course of dissociative amnesia is described in Clinical Vignette 2.

Such individuals typically demonstrate not vagueness or spotty memory but rather a complete loss of an episodic memory for a finite period. They may not initially be aware of the memory loss; that is, they do not remember that they do not remember. They often report being told that they have done or said things that they cannot remember.

Some individuals do suffer from episodes of selective amnesia, usually for specific traumatic incidents, which may be interwoven with periods of intact memory. In these cases, the amnesia is for a type of material remembered rather than for a discrete time period (Loewenstein 1991).

### Implicit Effects of Dissociated Memories

Although information is kept out of consciousness in dissociative amnesia, it may well exert an influence on conscious behavior: out of sight does not mean out of mind. For example, a rape victim with no conscious recollection of an assault nonetheless behaves like someone who has been sexually victimized. As noted in Clinical Vignette 1, such individuals often suffer detachment and demoralization, may be unable to enjoy intimate relationships, and show hyperarousal to stimuli or circumstances reminiscent of the trauma. This loss of explicit memory with retention of implicit knowledge is similar to priming in memory research. Individuals who have read a word in a list complete a word stem (a partial word such as "pre" for "present") remember more quickly if they have seen that word minutes or even hours earlier. This priming effect occurs despite the fact that they cannot consciously recall having read the word, or even the list in which it occurred. When asked in a free recall format to list the word they have seen, they cannot name it, yet they act as though they have seen it and do remember it. Similarly, individuals instructed in hypnosis to forget having seen a list of words nonetheless demonstrate priming effects

of the hypnotically suppressed list (Kihlstrom 1987). It is the essence of dissociative amnesia that material kept out of conscious awareness is nonetheless active and may influence consciousness indirectly (Van Der Hart 2001).

Individuals with dissociative amnesia generally do not suffer disturbances of identity, except to the extent that their identity is influenced by the warded-off memory. It is not uncommon for such individuals to develop depressive symptoms as well, especially when the amnesia occurs in the wake of a traumatic stressor.

### Treatment

To date, there are no controlled studies that have addressed the treatment of dissociative amnesia. Thus, no proven pharmacological treatments are available (Maldonado et al. 2000**).**

#### *Psychotherapy*

Often, patients suffering from dissociative amnesia experience spontaneous recovery when they are removed from the stressful or threatening situation, when they feel safe, and/or when exposed to personal cues from their past (i.e., home, pets, family members) (Kardiner and Spiegel 1947, Loewenstein 1991, Maldonado et al. 2000, Maldonado and Spiegel 2007, Reither and Stoudemire 1988). In cases where exposure to a safe environment is not enough to restore normal memory functioning, pharmacologically facilitated interviews may prove useful (Baron and Nagy 1988, Naples and Hackett 1978, Perry and Jacobs 1982).

#### *Hypnosis*

Most patients with dissociative disorders are highly hypnotizable on formal testing and are therefore easily able to make use of hypnotic techniques such as age regression (Spiegel and Spiegel 2004). Hypnosis can enable such patients to reorient temporally and therefore achieve access to otherwise dissociated and unavailable memories.

**Abreaction.** If there is traumatic content to the warded-off memory, patients may abreact, that is, express strong emotion as these memories are elicited. Such abreactions are rarely damaging in themselves but are not intrinsically therapeutic either. They may be experienced by the patient as a reinflicting of the traumatic stressor. Such patients need psychotherapeutic help in integrating these warded-off memories and the associated affect into consciousness, thereby gaining a sense of mastery over them.

**Screen Technique.** One technique that can help bring such memories into consciousness while modulating the affective response to them is a projective technique known as "the screen technique" (Spiegel 1981). While using hypnosis, such patients are taught to recall the traumatic event as if they were watching it on an imaginary movie or television screen. This technique is often helpful for individuals who are unable to remember the event as if it were occurring in the present, either because for some highly hypnotizable individuals that approach is too emotionally taxing, or in some case, because subjects are not sufficiently hypnotizable to be able to engage in such hypnotic age regression. The screen can be employed to facilitate cognitive restructuring of the traumatic memory, for example, by picturing on the left side of the screen some component of the traumatic experience, and on the right side something they did to protect themselves or someone else during it. This makes the memory both more complex and more bearable.

A particularly useful feature of this technique is that it allows for the recollection of traumatic events without triggering an uncontrolled reliving of the trauma, as is the case of traumatic flashbacks. The screen technique provides a "controlled dissociation" between the psychological and somatic aspects of memory retrieval. Individuals can be put into self-hypnosis and instructed to get their body into a state of floating comfort and safety. They can do this by imagining that they are somewhere safe and comfortable: "Imagine that you are floating in a bath, a lake, a hot tub, or just floating in space." They are reminded that no matter what they see on the screen their bodies are safe and comfortable: "Do the work on your imaginary screen, not in your body." In this way the tendency for physiological arousal to accompany and intensify the working through of traumatic memories can be controlled, facilitating the psychotherapeutic work.

The psychotherapy of dissociative amnesia involves accessing the dissociated memories, working through affectively loaded aspects of these memories, and supporting the patient through the process of integrating these memories into consciousness.

## Dissociative Fugue

Dissociative fugue combines failure of integration of certain aspects of personal memory with loss of customary identity and automatisms of motor behavior (American Psychiatric Association 2000). It involves one or more episodes of sudden, unexpected, purposeful travel away from home, coupled with an inability to recall portions or all of one's past, and a loss of identity or the assumption of a new identity. The onset is usually sudden, and it frequently occurs after a traumatic experience or bereavement. A single episode is not uncommon, and spontaneous remission of symptoms can occur without treatment.

It was originally thought that the assumption of a new identity, as in the classical case of the Reverend Ansel Bourne

Clinical Vignette 3

A victim of a violent attempted rape had developed a selective amnesia for much of the physical struggle itself. She had suffered a basilar skull fracture, although she had not been rendered unconscious. She had a generalized seizure shortly after the assault. She initially sought help with hypnosis in an attempt to improve her recollection of the assailant's face.

She was instructed in the screen technique and used it to relive the assault. She remembered two things she had not previously recalled. One was that she recognized that he intended not merely to rape her but to kill her. On the other side of the screen she came to the realization that the assailant was surprised at how hard she was fighting with him. She became convinced that had she let him drag her into her apartment, she probably would not have survived. She was tearful and frightened as she recalled this aspect of the attack, which had been previously unavailable to consciousness.

She was then instructed to divide the imaginary screen in half, on the left side picturing an image of the viciousness and intensity of the assault on her and on the right side recognizing what she had done to protect herself. She was instructed to concentrate on these two aspects of the assault and then, when she was ready, to bring herself out of the state of self-hypnosis. She was told that she could use this self-hypnosis exercise, several times a day if she wished, as a means of putting her memories of the rape into perspective. This cognitive and emotional restructuring of the traumatic memories made them more bearable in consciousness.

Before hypnosis-facilitated psychotherapy, she had blamed herself for having fought so hard that she was seriously injured. Afterward, she recognized that she may well have saved her life by fighting off the assailant so vigorously. This positive therapeutic outcome occurred despite the fact that she was unable to recall any new details about the assailant's physical appearance. Furthermore, she had brought into consciousness painful and frightening details of the attack involving recognition of the seriousness of the threat to her life. Seeing the seriousness of the danger, however, allowed her to acknowledge the magnitude of the threat and therefore give herself credit for the nature of her response to it.

**DSM-IV-TR Criteria 300.13**

**Dissociative Fugue**

A. The predominant disturbance is sudden, unexpected travel away from home or one's customary place of work, with inability to recall one's past.

B. Confusion about personal identity or assumption of new identity (partial or complete).

C. The disturbance does not occur exclusively during the course of dissociative identity disorder and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., temporal lobe epilepsy).

D. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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(James 1984), was typical of dissociative fugue. However, a review of the literature (Reither and Stoudemire 1988) shows that in the majority of cases there is loss of personal identity but no clear assumption of a new identity.

Not infrequently, fugue episodes represent dissociated but purposeful activity.

## Treatment

To date, there are no controlled studies that have addressed the treatment of dissociative fugue. Similarly there are proven pharmacological treatments available (Maldonado et al. 2000). Many cases of dissociative fugue remit spontaneously. Again, hypnosis can be useful in accessing dissociated material. The case in Clinical Vignette 4 was reported by Spiegel and Spiegel (2004).

Hypnosis can be helpful in treating dissociative fugue by accessing otherwise unavailable components of memory and identity. The approach used is similar to that for dissociative amnesia. Hypnotic age regression can be used as the framework for accessing information available at a previous time. Demonstrating to patients that such information can be made available to consciousness enhances their sense of control over this material and facilitates therapeutic working through of emotionally laden aspects of it.

Once reorientation is established and the overt identity and memory loss of the fugue have been resolved, it is important to work through interpersonal or intrapsychic issues that underlie the dissociative defenses. Such individuals are often relatively unaware of their reactions to stress because they can so effectively dissociate them (Spiegel 1974). Thus, effective psychotherapy is anticipatory, helping patients to recognize and modify their tendency to set aside their own feelings in favor of those of others.

Patients with dissociative fugue may be helped with a psychotherapeutic approach that facilitates conscious integration of dissociated memories and motivations for behavior previously experienced as automatic and unwilled. It is often helpful to address current psychosocial stressors, such as marital conflict, with the involved individuals, as in the case of the woman found on the army base. To the extent that current psychosocial stress triggers fugue, resolution of that stress can help resolve it and reduce the likelihood of recurrence. Highly hypnotizable individuals prone to these extreme dissociative symptoms often have great difficulty in asserting their own point of view in a personal relationship (Spiegel and Spiegel 2004, Spiegel 1974, Spiegel et al. 1988). Rather, they interact with others as though they were undergoing a spontaneous trance experience. One such individual described herself as a "disciple in search of a teacher." Psychotherapy can help such individuals recognize and modify their tendency to unthinking compliance with others and extreme sensitivity to rejection and disapproval.

Clinical Vignette 4

A woman who appeared dazed but physically unharmed was brought into an army hospital emergency department by the base guards because she had been found wandering nearby. She said that she did not know who she was, where she lived, or how she happened to be there. Initially, plans were made to admit her to the hospital for a full neurological and psychiatric evaluation. She proved to be highly hypnotizable, and hypnosis age regression was used to take her back to an earlier year. She then reported her name and that she lived some 500 miles away. The time was changed again to a period just before this apparent fugue episode. She reported having received unsigned letters from someone at that army base, where, it turned out, her husband was stationed. These letters suggested that her husband was having an affair. This had deeply upset her. She and her husband were reunited and reconciled, and the fugue episode ended.

Clinical Vignette 5

A businessman found himself on a transatlantic flight from California to London without recollecting who he was or how he had gotten on the airplane. In later psychotherapy, exploring these fugue episodes, it was determined that he had had an extremely conflicted relationship with a successful but neglectful father. The father had recently died, leaving him financially well-off but emotionally ambivalent. He had spent his boyhood years in London and he recognized in therapy that the travel to London seemed to represent an unconscious attempt to revisit his childhood years and "set his father straight," something he had never been able to do while his father was alive. In this case the dissociative fugue was a form of pathological grief reaction.

In the past, medication-facilitated interviews were used to reverse dissociative amnesia or fugue. However, such techniques offer no advantage over hypnosis and are not especially effective (Perry and Jacobs 1982). Not infrequently, the ceremony of injecting the drug elicits spontaneous hypnotic phenomena before the pharmacological effect is felt, and sedation, respiratory depression, and other side effects can be troublesome. It also promotes dependency on the therapist. On the contrary, when hypnosis is used, patients are trained on self-hypnotic techniques, promoting the use of hypnosis instead of spontaneous dissociation. This enhances the patients' level of control while enhancing a sense of mastery and self-control.

Clinical Vignette 6

A woman in a Veterans Administration hospital had lost all memory for the preceding 10 months and insisted that she was in another hospital where she had been the previous December. She proved on testing with the hypnotic induction profile (HIP; Spiegel and Spiegel 2004) to be highly hypnotizable (10 of 10 on the induction score). She was hypnotized with a simple rapid induction technique involving the following instruction: "On one, do one thing, look up. On two, do two things, slowly close your eyes and take a deep breath. On three, do three things, let the breath out, let your eyes relax but keep them closed, and let your body float. Then let one hand or the other float up into the air like a balloon and that is your signal to yourself that you are ready to concentrate."

When she did this, she was told that we would be changing times, counting backward in years, and that when her eyes opened she would be at an earlier time in her life. We agreed that when I touched her forehead, she would close her eyes and we would change times again. We then began counting several years back. When she opened her eyes, she spoke as though she were in a different location earlier in her life. She was reoriented to the time when she really was in the other psychiatric hospital in a different city, and she talked about that experience. She was then instructed to close her eyes again and count forward in months to the present month. She opened her eyes and was then properly oriented and had episodic memory for what had transpired in her life in recent months.

## Depersonalization Disorder

This dissociative disorder involves lack of integration of one or more components of perception. The essential feature of depersonalization disorder is the occurrence of persistent feelings of unreality, detachment, or estrangement from oneself or one's body, usually with the feeling that one is an outside observer of one's own mental processes (American Psychiatric Association 2000, Steinberg 1991). Individuals suffering depersonalization are distressed by it. They are aware of some distortion in their perceptual experience, and are not technically hallucinating or psychotic. Affected individuals often fear that they are "going crazy." The symptom is not infrequently transient. A recent study of community adults suggests the prevalence of depersonalization disorder is 0.8% (Johnson et al. 2006).

Derealization (i.e, an altered perception of their surroundings resulting in the world seeming unreal or dream like) occurs frequently in patients with depersonalization disorder. Such individuals often ruminate anxiously about this symptom and are preoccupied with their own somatic and mental functioning.

The symptom of depersonalization frequently co-occurs in a variety of other psychiatric disorders, such as in patients with anxiety disorders (e.g., panic, phobia). Depersonalization may be seen as a symptom of PTSD, and may also be present as a symptom of alcohol and drug abuse or withdrawal, a side effect of prescription medications, during periods of stress, and it may be elicited by sensory deprivation. The symptom of depersonalization is also commonly seen in the course of a number of other neurological and psychiatric disorders (Pies 1991). It is considered a disorder when it is a persistent and predominant symptom. The phenomenology of the disorder involves both the initial symptoms themselves and the reactive anxiety caused by them.

### Treatment

To date, there are no controlled studies (using either psychotherapy or pharmacological agents) that have demonstrated their usefulness in the treatment of depersonaliztion (Maldonado et al. 2000). Nevertheless, we know that depersonalization is most often transient and may remit without formal treatment. Recurrent or persistent depersonalization should be thought of both as a symptom in itself and as a component of other syndromes requiring treatment, such as anxiety disorders and schizophrenia.

The symptom of depersonalization may respond to training in self-hypnosis. Sometimes, a hypnotic induction by itself or the deliberate worsening of symptoms by the therapist may be used as a method to teach patients how to control these episodes. For example, a hypnotic induction may be used to induce transient depersonalization symptoms, such as a sense of detachment from part of the body. This is a useful exercise, in that by having a structure for inducing the symptoms, one provides the patient with a context for understanding and controlling them. Patients may be instructed on how these episodes, usually experienced by them as spontaneous and erratic, are similar to a form of hypnotic dissociation that can be modified and eventually controlled. Such individuals can be taught to induce a pleasant sense of floating lightness or heaviness in place of the anxiety-related somatic detachment. The use of an imaginary screen to picture problems in a

**DSM-IV-TR Criteria 300.6**

**Depersonalization Disorder**

A. Persistent or recurrent experiences of feeling detached from, and as if one is an outside observer of, one's mental processes or body (e.g., feeling like one is in a dream).

B. During the depersonalization experience, reality testing remains intact.

C. The depersonalization causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The depersonalization experience does not occur exclusively during the course of another mental disorder, such as schizophrenia, panic disorder, acute stress disorder, or another dissociative disorder, and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., temporal lobe epilepsy).

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Clinical Vignette 7

A 54-year-old businesswoman was referred for evaluation of lifelong depersonalization symptoms, episodes characterized by a feeling of detachment, alternating with eruptions of uncharacteristic anger, or childlike behavior. The episodes occurred more frequently after relationship problems or losses, dismissive or controlling treatment by others, and especially around important family holidays, such as Thanksgiving and her birthday. She had a history of parental physical abuse early in life. She was tested with the Hypnotic Induction Profile and scored 8.5/10 points, indicating moderate-to-high hypnotizability. She was taught a self-hypnosis exercise in which she felt her body to be floating comfortably while she pictured herself in a pleasant outdoor scene. She was then able to experience an emotion of anger as she thought about her last episode of depersonalization, and made an association to an earlier episode of parental mistreatment. She was instructed to practice this self-hypnosis exercise three times a day, and observe if she felt a depersonalization episode coming on. Follow-up 3 weeks later indicated that there was a decrease in the number of spontaneous depersonalization episodes, and she found that she could use the self-hypnosis to identify and work through feelings that she had previously been unaware of or that had created difficulties for her. She was, for example, able to recognize a feeling of hurt and rejection at the close of a prior therapy, cry over it, and "move beyond" it. She saw the hypnosis exercise as a means of understanding previously alien feelings and working through them, while increasing her ability to induce relaxation and handle stress.

way that detaches them from the typical somatic response is also helpful (Spiegel and Spiegel 2004). Other relaxation techniques such as systematic desensitization, progressive muscle relaxation, and biofeedback may also be of help. Psychotherapy aimed at working through emotional responses to any traumatic or other stressors that tend to elicit depersonalization may also be helpful.

Given the absence of proven pharmacological approaches, the treater must balance the potential therapeutic benefit and risk of any regimen used. Antianxiety medications are most commonly used and may be helpful in reducing the amplification of depersonalization caused by anxiety. However, because antianxiety drugs can themselves produce symptoms of depersonalization and derealization their use should be carefully monitored. Increasing dosage, a standard technique when there is lack of therapeutic response, may also increase symptom intensity, leading to a spiral of increasing symptoms and drug dosage but without therapeutic benefit. Appropriate pharmacological treatment for comorbid disorders is an important part of treatment. Consider the use of antianxiety medications for generalized anxiety or phobic disorders (Stein and Uhde 1989) or of antipsychotic medications (Nuller 1982) for psychotic disorders is often beneficial in conditions in which there is contributory comorbidity.

## Dissociative Identity Disorder (Multiple Personality Disorder)

DID is the most popular, widely discussed, and recognized of the dissociative disorders. By definition, the disorder involves the "presence of two or more distinct identities or personality states each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self. These identities or personality states recurrently take control of the person's behavior" (American Psychiatric Association 2000). Often amnesia is present:

**DSM-IV-TR Criteria 300.14**

**Dissociative Identity Disorder**

A. The presence of two or more distinct identities or personality states (each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self).

B. At least two of these identities or personality states recurrently take control of the person's behavior.

C. Inability to recall important personal information that is too extensive to be explained by ordinary forgetfulness.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., blackouts or chaotic behavior during alcohol intoxication) or a general medical condition (e.g., complex partial seizures).

**Note:** In children, the symptoms are not attributable to imaginary playmates or other fantasy play.

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"Inability to recall important personal information that is too extensive to be explained by ordinary forgetfulness" (American Psychiatric Association 2000). DID can better be understood as a failure of integration of various aspects of identity and personality structure. This allows for different relationship styles (dependent versus assertive/aggressive) and mood states (depressed versus hostile) to be segregated with different identities and personal memories, which leaves patients mystified by events that occurred in another "state," or by responses of others to them for behavior that occurred in a different "state."

As in most dissociative disorders, this degree of abnormal fragmentation of personality is often the sequelae of traumatic events in childhood. The development of dissociated experiences may be perceived by the patient as protective, allowing him or her to tolerate and partially evade the experience of chronic abuse.

Because of its "protective qualities" DID patients may view treatment as an attempt to deprive them of a defense against attack. They may have difficulty understanding other people's reactions to their behavior, given that others response to one aspect of their personality may not be remembered or understood by others. Some DID patients, for example, may be puzzled by comments made by friends and acquaintances regarding her behavior (likely a personality different from the core) for which she had no memory. Thus, their personality fragmentation renders them vulnerable to interpersonal problems yet gives them the belief that they are relatively protected from them.

## Prevalence

There are no definitive studies confirming the absolute prevalence of DID, although there is widespread agreement that the number of diagnosed cases has increased considerably in the US and some European countries in the past two decades (Boon and Draijer 1993). Several studies have estimated the prevalence as approximately 1% of psychiatric inpatients (Saxe et al. 1993, Ross et al. 1991a). On the other hand recent studies (Foote et al. 2006) suggest the incidence in a mental health clinic population may be as high as 5%. There are several factors that may account for the apparent increase in the number of reported cases including: (1) a more general awareness of the diagnosis among mental health professionals. (2) the availability of specific diagnostic criteria. (3) reduced incidence of misdiagnosis of DID patients as having other disorders with similar presentation (e.g., psychosis, BPD).

Some authors have attributed the increase in reported cases to a multitude of artificial factors including: social contagion, the result of hypnotic suggestion, and misdiagnosis (Frankel 1990, Ganaway 1995, McHugh 1995a, 1995b, Spanos et al. 1986). They argue that patients diagnosed with DID are highly hypnotizable, thus by definition quite suggestible and therefore especially vulnerable to direct or implicit hypnotic suggestion by overzealous therapists. They have noted that not infrequently a few specialist psychiatrists make the vast majority of diagnoses.

Counter to their arguments, the data suggest that the symptoms of patients diagnosed by specialists in dissociation do not differ from those of patients diagnosed by psychiatrists, psychologists, and physicians in more general practice who diagnose one or two cases a year. Also, DID patients have been noted to persist in presenting symptoms for an average of 6.5 years before acquiring the diagnosis (Putnam 1985). Similarly, they often encounter many psychiatrists and psychologists who are convinced that they do not have DID, but instead another disorder, such as schizophrenia. It is indeed true that these patients are highly hypnotizable and therefore suggestible (Spiegel 1974, Frischholz 1985). If the symptoms were to be created by suggestibility alone, it seems likely that they would accept a suggestion that they have some other disorders as well (e.g., schizophrenia or BPD). Because of this, care must be taken in the manner in which the illness is presented to them. However, it is unlikely that the increased number of cases currently reported is accounted for by suggestion alone. Reduction in previous misdiagnosis and increased recognition of the prevalence and sequelae of physical and sexual abuse in childhood (Kluft 1984a, 1991, Frischholz 1985, Spiegel 1984, Terr 1991, Herman et al. 1989) are also reasonable explanations.

## Course

The disorder may present in childhood, but more typically is recognized between adolescence and the third decade of life (Kluft 1984a). The symptoms rarely emerge after the age of 40 years. Nevertheless, there is often considerable delay between initial symptom presentation and diagnosis (Putnam et al. 1986). When the condition goes untreated, DID is a chronic and recurrent disorder. Available data suggest it rarely remits spontaneously.

Even after they begin to be manifested, the symptoms may not be evident for a certain period of time (Kluft 1985). Some have called DID "a disease of hiddenness" (Schacter 1995). The dissociation itself makes it difficult for the patients to effectively self-monitor and to accurately report their symptoms or the personal history that may trigger a suspicion of the diagnosis. Most patients suffering from DID are not fully aware of the extent of their dissociative symptology. When they do, they are usually reluctant to bring up symptoms because of confusion or shame about the illness or because of having experienced skepticism from mental health professionals in the past. Similarly, the shame associated with previous victimization and fear of retribution may also inhibit reporting of symptoms.

## Comorbidity

The most significant comorbid psychiatric conditions include depression, substance abuse, and BPD (Maldonado and Spiegel 2005). Sexual dysfunction, eating, and sleep disorders occur less frequently. Self-mutilative behavior, impulsivity, and labile interpersonal relationships are frequently exhibited by DID patients. In fact, nearly one-third of DID patients also meet diagnostic criteria for BPD. Patient exhibiting this interaction (i.e., DID plus BPD) also experience higher levels of depression (Horevitz and Braun 1984).

There may be a common etiological pathway to both DID and BPD. In fact, research shows a high incidence of dissociative symptomatology in many patients with BPD, especially those who report histories of physical and sexual abuse (Chu and Dill 1990, Ogata et al. 1990). By the same token, many DID and BPD patients also exhibit symptoms consistent with the diagnosis of PTSD (e.g., intrusive

flashbacks, anhedonia, recurrent nightmares of physical and sexual abuse, and symptoms of hyperarousal, especially when exposed to reminders of childhood trauma) (Breuer and Freud 1955, pp 463–468, Kluft 1985, 1991, Spiegel and Cardeña 1990).

Not only is the number of comorbid psychiatric problems lengthy, but also DID patients face the problem of misdiagnosis. As mentioned before, sometimes DID patients are misdiagnosed as having schizophrenia or some other psychotic disorder (Kluft 1987). The likely source of the misdiagnosis is the misinterpretation of the patient's report of having more than one person living inside them as a bizarre delusion rather than evidence of dissociation. Also, DID patients may report experiencing auditory hallucinations when one personality state speaks to or comments on the activities of another. DID patients may also be diagnosed as having conversion disorder (Ross et al. 1990) or some other somatoform disorder given the preponderance of psychosomatic complaints, such as migraine headaches and other ailments (Spiegel 1987). Practitioners must bear in mind that some studies have identified that approximately a third of DID patients may suffer from complex partial seizures (Schenk and Bear 1981). Therefore, newly diagnosed cases with DID should be evaluated for the possibility of a seizure disorder or some other medical conditions.

## Psychological Testing

At least three objective measures may help in the diagnosis of DID cases. First, DID patients score far higher than normal individuals on standard measures of hypnotizability, whereas psychotic patients tend to have lower than normal scores or the absence of high hypnotizability (Spiegel et al. 1982, Spiegel and Fink 1979, Lavoie and Sabourin 1980, Pettinati 1982, Pettinati et al. 1990, Van Der Hart and Spiegel 1993). Second DID patients score extremely high on scales of trait dissociation,(Bernstein and Putnam 1986, Ross 1989, Carlson et al. 1993). In contrast to normal populations and other groups of patients (Ross et al. 1990, Steinberg et al. 1990). Third, form level on the Rorschach test is usually within the normal range in DID patients, but there are frequent emotionally dramatic responses, often involving mutilation of a type that is often seen in histrionic personality disorder (Scroppo et al. 1998). Good form level is also useful in distinguishing patients with DID from those with schizophrenia, who have poor form level.

## Treatment

### *Psychotherapy*

**Therapeutic Direction.** DID patients may be aided in gaining control over the dissociative process underlying their symptoms in a number of ways (Maldonado et al. 2000, Maldonado and Spiegel 2007). The psychotherapy of DID should involve a form of structured empathy in which patients experiencing themselves as damaged and fragmented is acknowledged, while the therapist helps patients understand that the fundamental problem was a failure of integration of disparate memories and aspects of the self. Viewed in this way, DID patients suffer from having less than one personality rather than more than one. The ultimate goal in the therapy of DID is to facilitate integration of disparate elements. This can be done in a variety of ways.

Clinical Vignette 8

A 35-year-old woman with DID confided in her psychiatrist in one personality state that she planned to commit suicide. The psychiatrist noted that other parts of herself would be quite alarmed to learn of this plan and said that he planned to inform them. "You can't do that," she protested. "Why not?" inquired the psychiatrist. "Doctor-patient confidentiality," she replied. Tzhe psychiatrist was unmoved by this argument.

Clear limit setting and commitment on the part of the therapist to help all portions of the patient's personality structure learn about warded-off information is paramount. Given the nature of the genesis, secrets are frequently a problem with DID patients. Often, patients use their therapists to reinforce a dissociative strategy of withholding relevant information from certain personality states. Therefore, it is imperative that therapists clarify explicitly that they will not become involved in secret collusion. In fact, when important agreements are negotiated, such as commitments on the part of patients to contract for safety, it is useful to discuss that this is an "all-points bulletin," requiring attention from all the relevant personality states.

## Hypnosis

Hypnosis can be helpful in facilitating psychotherapy as well as establishing the diagnosis of DID (Spiegel and Spiegel 2004, Braun 1984, Kluft 1982, Maldonado et al. 2000). Hypnosis may be helpful in a variety of ways. First, mere structure of hypnotic induction may elicit dissociative phenomena. Second, hypnosis may help facilitate access to dissociated personalities. Dissociation may occur spontaneously during hypnotic induction, but it may be elicited formally by using a variety of therapeutic techniques, such as age regression, to reorient to a time when a different personality state was manifest. The process of hypnosis-mediated dissociation may become the means of teaching DID patients how to control the dissociative process. Third, entering the state of hypnosis may make it possible simply to address and elicit different identities or personality states at the therapist's suggestion. After some formal exercises such as this, it is often possible to ask the patient to speak with a given alter personality, without the formal use of hypnosis.

Clinical Vignette 9

A young woman with DID remembered a particularly painful episode in hypnosis. When she was 12 years old her stepfather smoked a good deal of marijuana and then forced her to have oral sex with him. She recalled being repelled by what he was forcing her to do and then remembered that she gagged and vomited all over him. "I spoiled his fun. He threw me up against a wall but it did not bother me a bit because I knew I ruined it for him." She was instructed to picture on one side of the screen what he had done to her and on the other what she had done to him.

**Memory Retrieval.** Because the loss of memory in DID is complex and chronic (Charcot 1890), its retrieval is likewise a more extended and integral part of the psychotherapeutic process. The therapy becomes an integrating experience of information sharing among disparate personality elements. By thinking of DID as a chronic form of PTSD, the focus of psychotherapy is concentrated on working through traumatic memories in addition to controlling the dissociation. The controlled access to dissociated memories greatly facilitates the process of psychotherapy. As discussed before (e.g., dissociative amnesia) a variety of strategies can be employed to help patients with DID break down amnesic barriers. Once memories of earlier traumatic experience have been brought into consciousness, it is crucial to help the patient work through the painful affect, inappropriate self-blame, and other reactions to these memories (Lindemann 1944, Spiegel et al. 1982). This therapeutic process can be thought of as a kind of grief work (Lindemann 1944) in which information retrieved from memory is reviewed, traumatic memories are put into perspective, and emotional expression is encouraged and worked through. This process makes it possible for patients to endure and helps them disseminate the information as widely as possible among various parts of the patient's personality structure. Instructions to other alter personalities to "listen" while a given one is talking and reviewing previously dissociated material can be helpful.

Projective techniques (e.g., screen technique) may help make the traumatic memories more bearable by placing them in a broader perspective, one in which trauma victims can also identify adaptive aspects of their response to the trauma. This approach may help DID patients work through traumatic memories, enabling patients to consciously bear the content of these recollections and reducing the need for dissociation as a means of keeping such memories and associated painful affect out of consciousness.

**The Rule of Thirds.** The rule of thirds (Kluft 1991, Schacter 1995) may help therapists pace the course of a treatment that otherwise can be emotionally taxing and time consuming. Kluft suggests that therapists spend the first-third of the psychotherapy session assessing the patient's current mental state and life problems. Carefully defining a problem area that might benefit from retrieval into conscious memory and working through. Then, therapists should spend the second-third of the session accessing and working through this memory. Finally, the last-third is used helping patients assimilate the information, regulate and modulate emotional responses, and discuss any responses to the therapist and plans for the immediate future. Appropriate limits must be set concerning self-destructive or threatening behavior, agreements must be made regarding physical safety and treatment compliance, and other matters must be presented to the patient in such a way that dissociative ignorance is not an acceptable explanation for failure to live up to the agreements.

**Integration.** The ultimate goal in the psychotherapy of DID is integration of the patient's multiple ego states. Therapists must be aware that often one or more of the personality states may exert considerable resistance to the process of integration, particularly early in the process of therapy. The reason for this resistance is the patient's fear that attempts at integration are part of the therapist plan to "eliminate" or "kill" personalities. These fears must be worked through the course of therapy and the patient needs to understand that the goal is to learn how to control the episodes of dissociation leading eventuallly to full integration of all parts, rather than the elimination of any. Done this way, patients develop a sense of gradually being able to control their dissociative processes in order to work through the traumatic memories. In order to enhance mastery and control, the process of the psychotherapy must help patients minimize rather than reinforce the content of traumatic memories, which often involves re-experiencing a sense of helplessness in a symbolic re-enactment of the trauma (Freud 1958a, Maldonado et al. 2000). Although there have been no controlled trials of the outcome of psychotherapy for this disorder, case series reports indicate a positive outcome in a majority of cases (Kluft 1984b, 1986, 1991). The stages of therapy are presented in Table 76–2.

**Table 76–2 Stages of Therapy**

| Stages | Techniques |
|---|---|
| Establishing treatment | Education; development of an atmosphere of safety; instill confidence |
| Preliminary interventions | Confirm diagnosis; set limits; access dissociation with hypnosis |
| History gathering | Explore components of dissociative structure |
| Working through trauma | Grief work |
| Move toward integration | Enhance communication across dissociative states |
| Integration-resolution | Encourage development of integrated self |
| Learning coping skills | Help with life decisions and relationships |
| Solidification of gains | Transference examination |
| Follow-up | Maintenance |

*Source*: Reproduced from Kluft RP (1991)with permission of American Psychiatry Press.

### *Traumatic Transference*

Transference applies with special meaning to patients who have been physically and sexually abused, especially in childhood. These patients have experienced individuals who are presumed to be caretakers acting instead in an exploitative and sometimes sadistic fashion. Although their reality testing is good enough that they can perceive genuine caring, they often unconsciously expect psychiatrists to exploit them. They may experience the process of working through of traumatic memories as a reinflicting of the trauma, and perceive the psychiatrist as taking sadistic pleasure in their suffering. Sometimes, patients may misattribute the passivity on the part of the psychiatrist with some uncaring family figure who knew that abuse was occurring but did little or nothing to stop it. It is important in managing the therapy of trauma victims to keep these issues in mind and make them frequent topics of discussion. This can diffuse, if not eliminate, such traumatic transference distortions of the therapeutic relationship (Spiegel 1988).

### *Psychopharmacology*

As with other dissociative disorders, there is little evidence that psychoactive drugs are of great help in reversing dissociative symptoms (Maldonado et al. 2000). In the past, short-acting barbiturates such as sodium amobarbital were used intravenously to reverse functional amnesia, but this technique is no longer employed, largely because of poor results (Perry and Jacobs 1982). Research data provide no evidence suggesting that any medication regimen has any significant therapeutic effect on the dissociative process manifested by DID patients (Loewenstein 1991, Markowitz and Gill 1996, Putnam 1989). To date, pharmacological treatment has been limited to symptom control (e.g., insomnia, panic attacks) or the management of comorbid conditions (e.g., depression).

Of all available classes of psychotropic agents, antidepressants are the most useful class for the treatment of patients with DID. That is because patients suffering from dissociation frequently experience comorbid dysthymic or major depressive disorder. Nevertheless, medication compliance may be a problem with dissociative patients because dissociated personality states may interfere with medication taking or may take excess medication in an overdose attempt. Because of this the newer agents—selective serotonin reuptake inhibitors (SSRIs)—are particularly useful, given their high level of effectiveness, lower side effect profile, and even lower danger in overdose, compared with tricyclic antidepressants and monoamine oxidase inhibitors.

Benzodiazepines have mostly been used to facilitate recall by controlling secondary anxiety associated with retrieval of traumatic memories (i.e., medication-facilitated interviews). All CNS-depressant agents may cause sudden mental state transitions, which may in turn increase rather than decrease amnesic barriers. Therefore, as useful as they could be on short-term basis (i.e., acute management of a panic attack), the long term of these agents may, in fact, contribute rather than treat dissociative episodes. Thus, the long-term use of these agents is not indicated.

Anticonvulsant agents may be useful in this patient population. As we discussed earlier, seizure disorders have a high rate of comorbidity with DID. As expected, anticonvulsant agents may help control the dissociation associated with epileptogenic activity. We also know that anticonvulsant agents have proven effective in the management of mood disorders that are prevalent in DID patients. Similarly, anticonvulsant agents have been found to be effective in the treatment of impulsive behaviors associated with personality disorders and brain injury. These agents may produce less amnestic side effects than the benzodiazepines and thus may be preferred in the treatment of certain psychiatric conditions such as impulse control and anxiety states. Due to potential problems such as neurological side effects, blood dyscrasias, and hepatotoxicity there is greater need for closer monitoring, making their use less desirable than the newer SSRIs.

Of all pharmacological agents available, antipsychotics may be the the least desirable. There is no evidence that they are useful in reducing dissociative symptoms. In fact, there have been reports of increased levels of dissociation and an increased incidence of side effects when used in patients suffering from dissociative disorders. Therefore, the use of these agents in DID is not recommended.

## Dissociative Trance Disorder

### Dissociative Trance

Dissociative trance disorder has been divided into two broad categories, dissociative trance and possession trance (American Psychiatric Association 2000). Dissociative trance phenomena are characterized by a sudden alteration in consciousness, not accompanied by distinct alternative

**DSM-IV-TR Criteria**

**Dissociative Trance Disorder**

A. Either (1) or (2):

(1) trance, i.e., temporary marked alteration in the state of consciousness or loss of customary sense of personal identity without replacement by an alternate identity, associated with at least one of the following:

(a) narrowing of awareness of immediate surroundings, or unusually narrow and selective focusing on environmental stimuli

(b) stereotyped behaviors or movements that are experienced as being beyond one's control

(2) possession trance, a single or episodic alteration in the state of consciousness characterized by the replacement of customary sense of personal identity by a new identity. This is attributed to the influence of a spirit, power, deity, or other person, as evidenced by one (or more) of the following:

(a) stereotyped and culturally determined behaviors or movements that are experienced as being controlled by the possessing agent

(b) full or partial amnesia for the event

B. The trance or possession trance state is not accepted as a normal part of a collective cultural or religious practice.

C. The trance or possession trance state causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The trance or possession trance state does not occur exclusively during the course of a psychotic disorder (including mood disorder with psychotic features and brief psychotic disorder) or dissociative identity disorder, and is not due to the direct physiological effects of a substance or a general medical condition.

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identities. In this form the dissociative symptom involves an alteration in consciousness rather than identity. Also, in dissociative trance, the activities performed are rather simple, usually involving sudden collapse, immobilization, dizziness, shrieking, screaming, or crying. Memory is rarely affected, and if there is amnesia, it is fragmented.

Dissociative trance phenomena frequently involve sudden, extreme changes in sensory and motor control. A classic example is the *ataque de nervios*, prevalent in Latin American countries. For example, this phenomenon is estimated to have a 12% lifetime prevalence rate in Puerto Rico (Lewis-Fernandez 1994). A typical episode involves a sudden feeling of anxiety, followed by total body shakes, which may mimic convulsions. This is then followed by hyperventilation, unintelligible screaming, agitation, and often violent bodily movements. Usually, this is followed by collapse and probably transient loss of consciousness. After the episode is over, subjects complain of fatigue and having been confused, although this behavior is dramatically different from classic postictal states. Some subjects may experience amnesia at least to some aspects of the event (Lewis-Fernandez 1994).

Other examples include *lata* and "falling out." Lata represents the Malay version of trance disorder. In these episodes, afflicted individuals usually experience a sudden vision, mostly of a threatening spirit. The observable behavior includes screaming or crying and physical manifestation of overtly violent behavior, which often requires the sufferer to be physically restrained. Patients often report episodes of amnesia, but there is no clear possession by the offending spirit (Lewis-Fernandez 1994). On the other hand, "falling out" more commonly occurs among African-Americans in the southern US. Similarly to other trance episodes, the affected individual may enter a trance state, followed by bodily collapse, the inability to see or speak, despite the fact that they are fully conscious. Temporary confusion may be observed, although subjects are not usually amnesic to what occurred during the episode (Lewis-Fernandez 1994).

## Possession Trance

In contrast to dissociative trance episodes, possession trance involves the assumption of a distinct alternative identity. The new identity is presumed to be that of a deity, ancestor, or spirit who has transiently taken possession of the subject's mind and body. Different from dissociative trance episodes, which are characterized by rather crude, simplistic, regressive-like behaviors, possession trance victims often exhibit rather complex behavior. During these episodes, subjects may, for example, express otherwise forbidden thoughts or needs, engage in unusually and uncharacteristic aggressive behavior (e.g., verbal or physical expressions of aggression), or may attempt to negotiate for change in family or social status. Also, in contrast to dissociative trance episodes, possession trance episodes often are followed by dense amnesia for a large portion of the episode during which the spirit identity was in control of the subject's behavior.

## Cultural Context

Dissociative-like phenomena have been described in virtually every culture (Lewis-Fernandez 1994, Katz 1982, Kirmayer 1994). Yet they appear to be more prevalent in the less heavily industrialized Second and Third World countries. Studies on the prevalence of dissociative disorders in India have suggested that the 1-year prevalence of dissociative trance disorder is approximately 3.5% of all psychiatric hospitalizations, making it a highly frequent mental disorder (Adityanjee et al. 1989, Saxena and Prasad 1989). Trance and possession syndromes are by far the most common type of dissociative disorders seen around the world. On the other hand, DID, which is relatively more common in the US, is virtually never diagnosed in underdeveloped countries. This difference in prevalence and distribution of dissociative disorder across different populations may be mediated by cultural, as well as biological factors. For example, Eastern culture is far more sociocentric than Western culture. Thus, being "possessed" by an outside entity would be more culturally comprehensible and acceptable in the East. On the other hand, an apparent proliferation of individual identities would fit better with the Western preoccupation with individualism. Nonetheless, the underlying dissociative mechanism inhibiting integration of perception, memory, and identity may suggest a common underlying mechanism amongst these dissociative syndromes.

Trance and possession episodes are usually understood as an idiom of distress and yet they are not viewed as normal. That is, they are not a generally accepted part of cultural and religious practice, which often does involve normal trance phenomena, such as trance dancing in the Balinese Hindu culture. Trance dancers enjoy the remarkable privilege of being the only portion of this socially rigid society able to elevate their social status. The way they are able to do that is by developing the ability to enter trance states. During these altered states of consciousness, which usually occur within the context of a socially acceptable ceremony setting, they dance over hot coals, hold a sword at their throat, or in other ways exhibit supernormal powers of concentration and physical prowess. The mechanism mediating these phenomena is not fully understood, but there is evidence of elevations in plasma noradrenaline, dopamine, and beta-endorphin among Balinese trance dancers during trance states. This form of trance is considered socially normal and even exalted.

By contrast, disordered trance and possession trance are viewed by the local community as an aberrant form of behavior that requires intervention. Such symptoms often arise in the context of family or social distress, for example, discomfort in a new family environment. Thus, cultural informants make it clear that people with dissociative trance disorder are abnormal.

Differences in culture clearly influence almost all mental disorders (Table 76–3). Delusional content of a schizophrenic patient is often dramatically different in a Hindu versus a Christian. Similarly, the manifestations of major depressive disorder may take a different form in China, where it looks more like what used to be called neurasthenia, where it may present with far more somatic symptoms, compared with predominantly guilty ruminations, seen in Western patients (Kleinman 1977). Similarly, variations in the form and presentation of the various dissociative disorders, depending on the population under study, only underscore the ubiquity of the mechanism of dissociation. The DSM-IV task force voted to include dissociative trance disorder in the appendix of the DSM-IV (American Psychiatric Association 2000) to stimulate further research on the question of whether it should be a separate Axis I disorder or whether it should

**Table 76–3 Characteristics of Dissociation in Western and Eastern Cultures**

| Dissociative Phenomenon | Western | Eastern |
|---|---|---|
| Splitting of consciousness | Depersonalization | Dissociative trance |
| Splitting of identity | DID (multiple personality disorder): multiple internal identities | Possession trance: control by external identities |
| Splitting of memory | Dissociative amnesia | Secondary in dissociative trance, more common in possession trance |
| Loss of somatic control | Conversion disorder | Dissociative trance, e.g., *lata, ataque de nervios* |
| Treatment | Therapist reduces dissociation in subject, often with hypnosis | Healer enters trance or dissociative state to take on offending spirit |

be included as a subtype in the category of dissociative disorders not otherwise specified.

## Treatment

Treatment of these disorders varies from culture to culture. Rubbing the body with special potions, negotiating to change the affected person's social circumstances, and physical restraint are often used. Ceremonies to remove or appease the invading spirit are also employed.

## Dissociation and Trauma

One of the important developments in the modern understanding of dissociative disorders is the establishment of a clearer link between trauma and dissociation (Spiegel and Cardeña 1991, Spiegel and Spiegel 2004). Although the role of traumatic stress in eliciting dissociative symptoms was a part of Janet's early thinking (Van Der Hart et al. 1989) as well as that of Breuer and Freud (1955), more attention was paid to the symptoms, developmental issues, and personality features than to the role of traumatic stressors themselves. Later work has examined in more detail the proximate role of trauma in eliciting dissociative symptoms.

Trauma can be understood as the experience of being made into an object, a thing, the victim of someone else's rage or of nature's indifference. Trauma represents the ultimate experience of helplessness: loss of control over one's own body. There is growing clinical evidence that dissociation occurs as a defense during traumatic experiences, constituting an attempt to maintain mental control at the moment when physical control has been lost (Spiegel et al. 1988, Putnam 1985, Kluft 1984a, Spiegel 1984). Many assault victims report floating above their body, feeling sorry for the person being assaulted beneath them. Patients, victims of childhood abuse, have reported "taking themselves elsewhere" where they could "safely play," by themselves or with imaginary friends, while their bodies were brutally abused by a perpetrator. In fact, there is evidence (Terr 1991) that children exposed to multiple traumas as opposed to single-blow traumas are more likely to use dissociative defense mechanisms, which include spontaneous trance episodes and amnesia.

As noted in the section on DID, there is an accumulating literature suggesting a connection between a history of childhood physical and sexual abuse and the development of dissociative symptoms (Coons and Milstein 1986, Kluft 1984a, 1985, Spiegel 1984). Similarly, dissociative symptoms have been found to be more prevalent in patients with Axis II disorders, such as BPD, when there has been a history of childhood abuse (Herman et al. 1989, Chu and Dill 1990).

Another means of examining the putative connection between dissociation and trauma is to look at the prevalence of dissociative symptoms after recent trauma (Spiegel and Cardeña 1991). If it is indeed the case that trauma seems to elicit dissociative symptoms, they should be observable in the immediate aftermath of trauma. In the early literature examining responses to trauma, Lindemann (1944), studying the aftermath of the Coconut Grove fire, observed that the individuals who acted as though little or nothing had happened had an extremely poor long-term prognosis. These were individuals who had been injured or had lost loved ones. Indeed, it was the absence of post-traumatic symptoms in this group, compared with the agitation, dysphoria, and restlessness that typified the majority of survivors, that led him to formulate the normal process of acute grief.

Several subsequent researchers have observed that psychic numbing is a predictor of later PTSD symptoms. In fact, Solomon and Mikulincer (1988) observed that psychic numbing accounted for 20% of the variance in later PTSD symptoms among Israeli combat soldiers. Similarly, McFarlane (1986) found that numbing in response to the Ash Wednesday bush fires in Australia was a strong predictor of later post-traumatic symptoms.

Research on survivors of other life-threatening events, including hostage taking, indicated that more than half have experienced a sense of detachment, feelings of unreality (i.e., depersonalization), lack of emotions, hyperalertness, and automatic movements (Noyes and Kletti 1977, Madakasira and O'Brien 1987, Sloan 1988, Noyes and Slymen 1978–1979). Numbing, anhedonia, and an inability to feel deeply about anything were reported in about a third of the survivors of the Hyatt Regency skywalk collapse (Wilkinson 1983) and in a similar proportion of survivors of the North Sea oil rig disaster (Holen 1993). These findings are consistent with our studies of survivors of the Loma Prieta earthquake (Cardeña and Spiegel 1993). One-quarter of this sample of normal students reported marked depersonalization during and immediately after the event.

Although these dissociative responses to traumatic stressors have been conceptualized as adaptive defenses to overwhelming situations, the thrust of the literature indicates that the presence of dissociative symptoms in the immediate aftermath of trauma is a strong predictor of the development of later PTSD (Solomon and Mikulincer 1988, McFarlane 1986, Freinkel et al. 1994, Koopman et al. 1994, Marmar et al. 1994, Birmes 2001). For example, victims of the Oakland-Berkeley firestorm who reported significant dissociative symptoms had suffered relatively greater exposure to the fire and also were more likely to have significant symptoms

of PTSD 7 months later (Koopman et al. 1994). Similarly, Marmar et al. (1994) found that peritraumatic dissociation was a strong predictor of later PTSD symptoms among Vietnam veterans. Thus, physical trauma seems to elicit dissociation, perhaps in individuals who are prone to the use of this defense by virtue of either previous traumatic experience or a constitutional tendency to dissociate. This dissociative reaction may, in some cases, resolve quickly. However, in others it may become the matrix for later posttraumatic symptoms, such as dissociative amnesia for the traumatic episode. Indeed, more extreme dissociative disorders, such as DID, have been conceptualized as chronic forms of PTSD (Kluft 1984b, 1991, Spiegel 1984, 1986b). Recollection of trauma tends to have an off-on quality involving either intrusion or avoidance (Horowitz 1976), in which victims either intensively relive the trauma as though it were recurring or have difficulty remembering it (Madakasira and O'Brien 1987, Cardeña and Spiegel 1993, Christianson and Loftus 1987). Thus, physical trauma seems to elicit dissociative responses, which, in turn, predispose to the development of later PTSD, perhaps by reducing the likelihood of working through the traumatic experiences afterward.

## Acute Stress Disorder

As a result of the line of research just reviewed, a new diagnostic category, acute stress disorder, was included in DSM-IV-TR (American Psychiatric Association 2000). There was an acute stress reaction category in the *Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (DSM-II), and the *International Classification of Diseases*, Ninth Revision (ICD-9) has a similar category. It was thought that the inclusion of this diagnosis would facilitate early detection and intervention and would also remedy a hole in the nosology: how to diagnose a substantial minority of victims of acute trauma who are quite symptomatic within the first month after the occurrence of the traumatic stressor.

Although acute stress disorder is classified among the anxiety disorders in DSM-IV-TR (American Psychiatric Association 2000), mention is made of it in this chapter because half of the symptoms of this disorder are dissociative in nature.

This diagnostic criteria would designate approximately a third of individuals exposed to serious trauma as symptomaatic. Dissociative symptoms occurring at the time of the trauma are strongly predictive of later development of PTSD (Koopman et al. 1994, Marmar et al. 1994, Classen et al. 1993, Freud 1995) and are associated with higher cortisol levels during exposure to uncontrollable stress (Freud 1958a). Similarly, the occurrence of later PTSD is predicted by the occurrence of symptoms of intrusion, avoidance, and hyperarousal in the immediate aftermath of

**DSM-IV-TR Criteria 308.3**

**Acute Stress Disorder**

A. The person has been exposed to a traumatic event in which both of the following have been present:
   (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   (2) the person's response involved intense fear, helplessness, or horror

B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
   (1) a subjective sense of numbing, detachment, or absence of emotional responsiveness
   (2) reduction in awareness of his or her surroundings (e.g., "being in a daze")
   (3) derealization
   (4) depersonalization
   (5) dissociative amnesia (i.e., inability to recall an important aspect of the trauma)

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience.

G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.

H. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by brief psychotic disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

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rape (Rothbaum and Foa 1993) and combat trauma (Blank 1993, Solomon et al. 1988). Although most individuals experiencing serious trauma are initially symptomatic, the majority recover without developing PTSD. Most studies demonstrate that 25% or less of those who experience serious trauma later become symptomatic.

This diagnostic category is useful not only for research on the normal and abnormal processes of adjusting to trauma, but also as a means of providing an important opportunity for early intervention, and thus, prevention of later psychopathology. Even though dissociation has a role at the time of trauma, if the defense persists too long it may interfere with the working through of traumatic material. Lindemann (1944) described the term "*grief work*," referring to process needed to put traumatic experience into perspective and reduce the likelihood of later symptoms. In this context, psychotherapy, aimed at helping individuals acknowledge, bear, and put into perspective a traumatic experience shortly after the trauma, should be helpful in reducing the incidence of later PTSD.

## Theoretical and Research Issues: Models and Mechanisms of Dissociation

### Dissociation and Information Processing

Dissociation may seem like a historical aberration, a throwback to earlier and more primitive models of the mind. Yet these disorders are surprisingly congruent with information processing-based theories of mental function. For example, connectionist and parallel distributed processing models (Rumelhart and McClelland 1986) take a bottom-up rather than a top-down approach to cognitive organization. Traditional models emphasize a supraordinate structure in which broad categories of information structure the processing of specific examples of those categories, that is, the category "sweet" must exist to make sense of "sugar," "candy," and "jelly." In the parallel distributed processing models, subunits or neural nets process information through patterns of co-occurrence of input stimuli that lead to activation patterns in these neural nets, which produce pattern recognition. The output of one neuronal system becomes the input to another, thereby gradually building up integrated and complex patterns of activation and inhibition. A bottom-up processing model system has the advantage of accounting for the processing of vast amounts of information and the ability to recognize patterns with approximate information. Nevertheless, such models make the classification and integration of information problematical.

Information seems to be processed on the basis of the co-occurrence of patterns of activation rather than its appearance in a predefined category. Therefore, in parallel distributed processing system models, failures in integration of mental contents are theoretically likely to occur. Inappropriate but apparent similarities may appear when activation patterns are similar, and conversely, no two pieces of information are necessarily connected. There have been models created to explain psychotic, dissociative, and mood disorders, based on abnormal or defective neuronal association network patterns (Li and Spiegel 1992, Hoffman 1987). These neural models assumed that when there are problems with the processing of input information (a model for traumatic input), the brain is more likely to have difficulty achieving a coherent and balanced output. This could then lead to the development of dissociation of information and data manifested in the subject's inability to process smoothly all of the incoming information.

From a more clinical perspective, dissociation may be explained by one of three models or combinations of these. The models proposed include the following: the neurological model, which suggests that some underlying neurological process, such as hemispheric disconnection or epilepsy, plays a role in promoting dissociative symptoms; the role enactment model or social role demand theory, which suggests that the symptoms are an artificial social construct rather than a true psychiatric disorder; and the autohypnotic model. This theory recognizes and reconciles the connection between traumatic events, dissociative experiences, and hypnotizability. These models have been discussed at length elsewhere (Maldonado 2007) and will not be discussed here.

### Dissociation and Biological Processes

A number of studies have found biological correlates to dissociative disorders. Yet, to date, it is difficult to determine whether these biological changes are the product of dissociative processes or what causes dissociative symptoms.

For example, Simeon et al. (2007) found that compared to normal controls, patients suffering from dissociative disorders exhibited significantly greater resistance to, and faster escape from, dexamethasone suppression. Similarly, the dissociative disorder (DD) group demonstrated a significant inverse correlation between dissociation severity and cortisol reactivity. This study demonstrated a distinct pattern of HPA-axis dysregulation in dissociative disorder (DD) and emphasized the importance of further study of stress-response systems in dissociative psychopathology.

Elzinga et al. (2007) used functional magnetic resonance imaging (fMRI) to assess the working memory in dissociative disorder (DDs) patients during performance of a parametric, verbal working-memory task and compared them to healthy control (HCs) subjects. Imaging data (fMRI) showed that both groups activated brain regions typically involved in working memory (i.e., anterior, dorsolateral and ventrolateral prefrontal cortex (PFC), and parietal cortex) but DDs showed more activation in these areas, particularly in the left anterior PFC, dorsolateral PFC and parietal cortex. As expected, given these findings, DDs also made fewer errors with increasing task load compared to HCs. This study replicated findings of previous studies in nonpathological high dissociative individuals; thus, suggesting that trait dissociation is associated with enhanced working-memory capacities. Similarly, this difference in working memory may help distinguish DDs from patients with PTSD who are generally characterized by impaired working memory.

### Dissociation and Memory Systems

There are two broad categories of memory known as explicit and implicit (Schacter 1992), declarative and procedural (Squire 1987), or episodic and semantic (Tulving 1983). These two basic memory systems serve different functions. Explicit or episodic memory involves recall of personal experience identified with the self, for example, "I went dancing last night." The second type is known as implicit or

procedural memory. This involves the execution of routine operations, such as driving a car, or typing on a keyboard. Most of these rather automatic operations could be carried out with little conscious awareness, but yet with a high degree of proficiency. These two types of memory seem to reside in different cerebral anatomical localizations. Episodic memory seems to be primarily associated with limbic system function, primarily involving the hippocampal formation and mamillary bodies. On the other hand, procedural memory appears to be a function of basal ganglia and cortical functioning (Kosslyn and Koenig 1992).

The fact that there are separate memory systems may account for certain types of dissociative phenomena (Spiegel et al. 1993). For example, the automaticity observed in certain types of dissociative disorders reflect the separation of self-identification associated with explicit memory from routine activity in implicit or procedural memory. It is thus not at all foreign to our mental processing to act in an automatic way devoid of explicit self-identification. Future research on the neurobiology of memory may well provide insights into the functional disintegration of memory, perception, identity, and consciousness seen in dissociative disorders (Zola-Morgan et al. 1982, Zola-Morgan and Squire 1985).

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research for dissociative amnesia specify that there be a "convincing association in time between the onset of symptoms of the disorder and stressful events, problems, or needs." In DSM-IV-TR, the criteria set notes that the forgotten information is usually of a stressful or traumatic nature.

For dissociative fugue, in contrast to DSM-IV-TR, the ICD-10 Diagnostic Criteria for Research specify "amnesia for the journey." Furthermore, in contrast to DSM-IV-TR, the ICD-10 Diagnostic Criteria for Research do not indicate that there is an inability to recall one's past during the fugue or that there be confusion about personal identity.

DID is included in ICD-10 as an example of an "other dissociative (conversion) disorder" under the rubric "multiple personality disorder." The ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are almost identical.

Finally, ICD-10 has a single category "depersonalization-derealization syndrome" for presentations characterized by either depersonalization or derealization. In contrast, the DSM-IV-TR category includes only depersonalization and mentions derealization as an associated feature. Furthermore, unlike DSM-IV-TR that includes this category in the dissociative disorders section, ICD-10 includes the category within the "other neurotic disorders" grouping.

## Conclusion

The dissociative disorders constitute a challenging and fascinating spectrum of psychiatric illnesses. The failure of integration of memory, identity, perception, and consciousness seen in these disorders results in symptoms that illustrate fundamental problems in the organization of mental processes. Dissociative phenomena often occur during and after physical trauma but may also represent transient or chronic defensive patterns. Dissociative disorders are generally treatable and are a domain in which psychotherapy is a primary modality, although pharmacological treatment of comorbid conditions such as depression can be quite helpful. The dissociative disorders are ubiquitous around the world, although they take a variety of forms. They represent a fascinating diagnostic, therapeutic, and investigative challenge.

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CHAPTER

# 77 Sexual Disorders

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Hypoactive Sexual Desire Disorder
Sexual Aversion Disorder
Sexual Dysfunction Due to a General Medical Condition
Substance-Induced Sexual Dysfunction
Female Sexual Arousal Disorder
Male Erectile Disorder
Female Orgasmic Disorder
Premature Ejaculation
Dyspareunia
Vaginismus
Gender Identity Disorder
Voyeurism
Sexual Sadism
Frotteurism
Fetishism
Sexual Masochism
Transvestic Fetishism

## Preface

To escape from the clinical significance of sexual matters, mental health professionals have to blind and deafen themselves to the importance of these topics:

- Teenage pregnancy, sexual abuse of children and minors, stranger and date rape, HIV infections and other sexually transmitted diseases.
- Abortion, extramarital affairs, commercial sex, sex between physicians and their patients.
- The appeal of Internet pornography and its impact on partner sexual behaviors.
- The consequences of substance abuse, medical illnesses, and psychiatric disorders on the ability to have sex.
- Minority status and unique developmental struggles of gay males, lesbian women, bisexual persons, and the transgendered.
- The sexual side effects of psychotropic medications.
- The role of masturbation in the life cycle.
- The search for an aphrodisiac.
- The regulation of sexual behaviors by religions and governments.

American mental health professionals have been educated within a conservative contradictory sexuality environment. Our personal sexual lives remain guarded even as we are immersed in sexual imagery of youth by various media. This public saturation is not particularly educational; personal sexual concerns remain ubiquitous. When patients look to clinicians for assistance with their sexual worries, they assume that we have a confident knowledgeable comfort with the subject. They are often wrong. For our professional learning to begin, we must allow ourselves to carefully listen to the patient and ask questions, which become more obvious with accumulating clinical experience. Eventually, we discover that some sexual issue lurks behind many psychiatric decompensations. (Figure 77–1)

It is remarkable how silent psychiatric training has been about sexual life since the early 1980s, a span of time during

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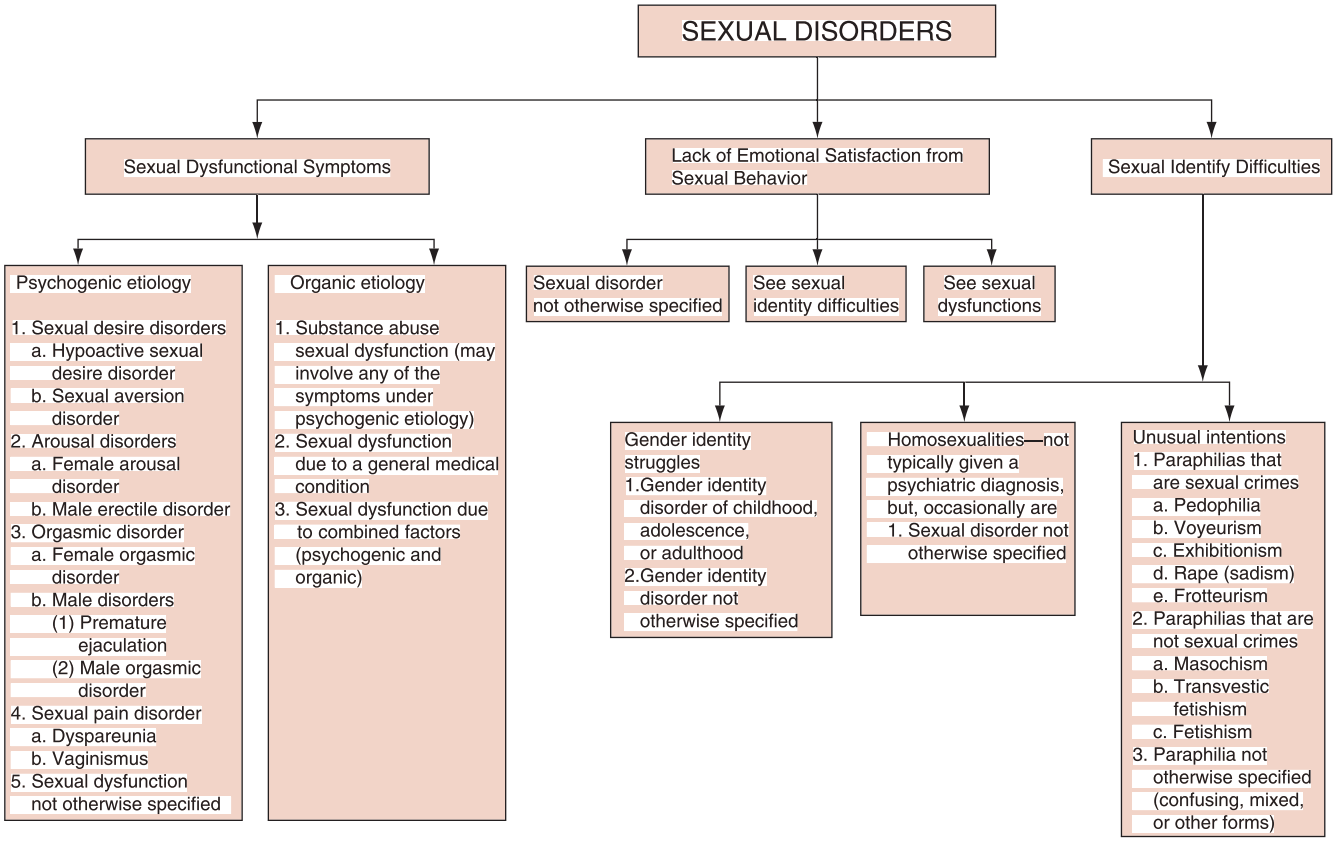



**Figure 77–1** *Diagnostic decision tree for sexual disorders.*

which the culture learned that sexuality has the potential to generate concerns from childhood to old age. Clinical sexuality thrives best on multiple perspectives. Its scope is too broad for any one scientific profession to master, for any branch of the humanities to have the last word, for any one government's policy to prevail, or for one religion's pronouncements to settle a contention.

Humans are not sexually static reproductively-driven mammals. All sexual behavior, solitary and partnered, normal and abnormal, is simultaneously influenced by biological, personal, interpersonal, and cultural forces. Sexual behavior is richly multidetermined. Every person's sexuality slowly evolves over decades and more rapidly oscillates during short periods of time. Biological maturation and psychological maturation inexorably create different sexual challenges at each life era. Young new couples, for instance, typically struggle to orchestrate mutually satisfying intercourse. Ten years later, many are struggling to find time for sex and arguing over its infrequency. Short-term fluctuations are brought about by the inevitable changeability of our biological, psychological, and interpersonal states. Each of us has a dynamic potential to change—from normal to dysfunctional, from dysfunctional to normal, and from ordinary to remarkable.

Despite aspirations to the contrary, medical treatments rest on biases. Urologists emphasize that erectile dysfunction is due to vascular disease. Gynecologists prefer to search for hormone deficiencies for women's complaints. Psychoanalysts find that early developmental conflicts are limiting adult sexual and love lives. Biological psychiatrists consider excursions of libido to be due to depression or hypomania. Addiction specialists invoke problematic sexual excesses as another symptom requiring a 12-step program. Systems theorists find interpersonal dynamics to be the usual cause of diverse sexual dysfunction. Social psychologists find multigenerational religious guilt a favorite culprit. There is little need for acrimonious debate about etiology of sexual disorders since biological, psychological, interpersonal, and cultural factors are operative in all individuals all the time.

Clinical sexuality has one major recent scientific breakthrough to claim: the new class of drugs for erectile dysfunction known as the PDE-5 inhibitors (Lue 2000). Generally, knowledge of the treatment of sexual disorders is more anecdotal than rigorously evidence based (Heiman 2002). Nonetheless, we seem to be able to provide helpful care for many patients. To be able to be helpful, the psychiatrist needs to be diagnostically competent and skillful with medications—which most are—and interested and willing to talk at length with their patients—which is often not the case.

## The Components of Sexuality

An adult's sexuality has seven components: gender identity, orientation, intention (what one wants to do with a partner's body and have done with one's body during sexual behavior), desire, arousal, orgasm, and emotional satisfaction (Levine 1998). The first three components constitute our sexual identity. The second three comprise our sexual function. The seventh, emotional satisfaction, is based on our personal reflections on the first six (Table 77–1: Section I). The DSM-IV-TR designates impairments of five of these components as pathologies. Concerns about orientation and the failure to find sexual behaviors emotionally satisfying

**Table 77–1 Mechanisms of Sexual Equilibrium**

I. Interplay of Each Person's Seven Sexual Components

| *Person A* | | *Person B* |
|---|---|---|
| Gender identity | € | Gender identity |
| Orientation | € | Orientation |
| Intention | € | Intention |
| Desire | € | Desire |
| Arousal | € | Arousal |
| Orgasm | € | Orgasm |
| Emotional satisfaction | € | Emotional satisfaction |

II. Regard That Each Person Has for the Partner's Component Characteristics

Positive regard leads to:
- Increased sensual abandon
- Positive attitudes toward self and partner
- Frequent sexual behavior

Negative regard leads to:
- Increased personal inhibition
- Hostile critical attitudes toward self and partner
- Limited motivation to engage in partner sexual behavior

are not officially considered to be sexual disorders in the DSM.

## Sexual Development Through the Life Cycle

While the psychological foundations for a healthy sexual life are laid down during childhood through parent–child relationships, each subsequent phase of life—adolescence, young adulthood, middle life, and older age—has inherent developmental challenges and potentials (Erikson 1963). The normal tasks of sexual development at each phase provide the clinician with an understanding of age-related etiologies of sexual disorders (Levine 1992). Adolescent sexual troubles often reflect difficulties consolidating a personally acceptable sexual identity (Savin-Williams and Cohen 2004). Young adult dysfunctions often indicate the presence of psychological obstacles to growing comfortable as a sexual pleasure-seeking, pleasure-giving person while integrating sex into the larger context of human attachment. Middle-life disorders often represent failures to maintain psychological intimacy and to diplomatically negotiate tensions within an increasingly complex interpersonal relationship. The dysfunctions of older persons often represent failures to preserve sexual function in the face of biological assaults of menopause, aging, illness, medications, radiation, and surgery. Most etiologic factors can operate in another epoch as well. For instance, a young person's new indifference to sexual behavior may be due to an SSRI or an older person's new marriage may expose previously avoided personal discomfort with receiving and giving sexual pleasure.

# THE SEXUAL DYSFUNCTIONS

## Significance of Sexual Dysfunction

Sex is recreation but it is also an important means of establishing and reaffirming emotional attachments. Sexual competence—the ability to desire a partner, become aroused, and attain orgasm in a cooperative manner when together—enables a person to experience the physical expressions and emotional complexities of love. Sexual behaviors occur more frequently among couples with mutually pleasurable sex than those with unilaterally satisfying behavior. Mutually pleasurable sexual behavior allows both partners to be comforted and stabilized by loving and feeling loved. However they are brought about, sexual dysfunctions limit the sense of competence, participation in one of life's heralded pleasures, and the sense of feeling stable in relationship to another.

## DSM-IV-TR Diagnoses

DSM-IV-TR specifies three criteria for each sexual dysfunction. The first criterion describes the psychophysiologic impairment; for example, absence of sexual desire, arousal, or orgasm. The second requires that the patient have marked distress or interpersonal difficulty as a result, while the third asks the clinician to ascertain that some other Axis I diagnosis, medical illness, medication, or substances of abuse does not best explain the problem. Table 77–2 lists the first criterion of each of the 12 sexual dysfunction diagnoses. DSM-IV-TR gives the clinician additional latitude for deciding when a person who meets the first criterion qualifies for a disorder. The doctor is asked to consider the effects of the individual's age, experience, ethnicity and cultural background, the degree of subjective distress, adequacy of sexual stimulation, and symptom frequency. No data exist to tell us how to exercise this judgment.

## Epidemiology

Numerous attempts to describe the prevalence of sexual dysfunction have been made in the previous 25 years. These range from attempts to define the frequency of a particular dysfunction, for instance, male erectile disorder, to attempts to estimate the prevalence of a series of separate dysfunctions; for example, desire, arousal, and orgasmic disorders of women. All such efforts quickly confront methodological influences of sampling, means of obtaining the information, definition of each dysfunction, purpose of the study, and perspective of its authors (Laumann and Michael 2001). These data not surprisingly, therefore, demonstrate a range of prevalence depending on the problem studied. Gender identity disorders are relatively rare (< 1–2%). Lifelong sexual desire disorders among women may involve up to 15%, but among young men involve up to 5%. Acquired desire disorders among older individuals are probably three times as common as lifelong ones. More than half of women at age 55 years have recognized a decline in their sexual function. Perhaps 25% of women in their 20s have difficulty having orgasm and approximately 33% of men less than age 40 claim to ejaculate too rapidly. The majority of men by age 70 years are likely to be having erection problems. The recent careful epidemiologic study, designed by sociologists, successfully assessed a representative sample of the US (Laumann et al. 1994). They interviewed men and women between age 18 and 59 years and found that sexual function is impaired in 35% of the population, particularly among young women and older men. This is noteworthy for psychiatrists because our studies of sexual dysfunction attributed to medications or new psychiatric disorders tend to assume that patients are generally functionally intact prior to becoming ill or taking medications. This assumption is not tenable. There is a vital distinction to be made, however,

**Table 77–2 Delineating Criteria of 12 Sexual Dysfunction Diagnoses**

| Sexual Desire Disorders | Sexual Arousal Disorders | Orgasmic Disorders | Sexual Pain Disorders |
|---|---|---|---|
| Hypoactive sexual desire disorder:<br>Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity | Female sexual arousal disorder:<br>Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement | Female orgasmic disorder:<br>Persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase | Dyspareunia<br>Recurrent or persistent genital pain associated with sexual intercourse in either a male or a female |
| Sexual aversion disorder:<br>Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner | Male erectile disorder:<br>Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection | Male orgasmic disorder:<br>Persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity | Vaginismus:<br>Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse |
| | | Premature ejaculation:<br>Persistent or recurrent ejaculation with a minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it | |

| Sexual Dysfunction Due to a General Medical Condition | Substance-Induced Sexual Dysfunction | Sexual Dysfunction Not Otherwise Specified |
|---|---|---|
| Any of the above-mentioned diagnoses must be judged to be exclusively due to the direct physiological effects of a medical condition | A sexual dysfunction that is fully explained by substance use in that it develops within a month of substance intoxication | For problems that do not meet the categories just described |

between current prevalence estimates for any dysfunction based only on the presence or absence of a particular problem. DSM-IV-TR asks that the diagnosis be based on the presence of distress or impairment and that the problem cannot be attributed to another disorder. Epidemiological data often ignore these criteria. For example, a study may show that 70% of 60-year-old women have diminished sexual desire but only 20% are currently distressed about it. In addition, there is considerable uncertainty whether erectile dysfunction can be entirely explained by depression or social anxiety disorder.

## Sexual Equilibrium

Etiologic ideas about one individual's sexual dysfunction are usually less complex than for couples because sexual dysfunction within a stable sexual partnership involves two individual psychologies and biologies, their interpersonal impact on one another, and their cultures. The clinician must be wary when one coupled person is presented as having a sexual dysfunction and the partner is presented as "normal." Sexual dysfunction in a couple is a two-person problem in terms of immediate effects and often in terms of cause as well (Table 77–1: Section II). How a partner regards the sexual characteristics of the other is a subtle ingredient of sexual comfort, competence, and dysfunction. For instance, a young woman's new inability to attain orgasm with her husband may be traced to her embarrassment at sharing her excitation with him because she perceives him to be generally critical of her. Similarly, the origin of a husband's erectile dysfunction may be traced to the emergence of his wife's negative regard for him, which stemmed from something other than his sexual behavior. This *ordinary* connectivity of a couple's sexual function is referred to as the couple's sexual equilibrium (Levine 1998). The sexual equilibrium explains five observations:

1. Improvement and deterioration of sexual function can rapidly occur.
2. When a couple's nonsexual relationship is good, their sexual life may not be.
3. Individual psychotherapy is often insufficient to help coupled patients improve their sexual life.
4. A negative attitude from the partner can block improvement in a couple's sexual life regardless of the therapy format and therapist skill.
5. A conversation with a therapist who is attuned to the emotional meanings of a couple's interaction can shift a dysfunctional equilibrium back to mutually satisfying sexual behavior.

## The Nature of Sexual Desire

We summarize many things under the rubric of sexual desire: erotic fantasies, sexual dreams, initiation of sexual behavior, receptivity to partner-initiated sexual behavior, masturbation, genital sensations, heightened responsivity to erotic environmental cues, and sincere statements about wanting to behave sexually. These are often referred to as manifestations of libido, but this historic term has created the illusion that libido was a homogeneous force. The diverse and changeable desire manifestations are produced by the intersection of three mental forces: drive (biology), motive (psychology), and values (culture) (Levine 2003).

**Drive.** By only partially understood psychoneuroendocrine mechanisms, the preoptic area of the anterior-medial hypothalamus and the limbic system periodically produce sexual drive in both sexes (Federman 2006). *Drive* is recognized by genital tingling, heightened responsivity to erotic environmental cues, plans for self or partner sexual behavior, nocturnal orgasm, and increased erotic preoccupations. These are spontaneous particularly among adolescents and young adults. Although people can become aroused and attain orgasm without evident drive, drive propels the sexual physiological process. Without drive, the sexual response system is less efficient. While men as a group seem to have significant more drive than women as a group, in both sexes, drive requires at least the presence of a modest amount of testosterone. Drive is frequently dampened by medications that act within the central nervous system, substances of abuse, psychiatric illness, systemic physical illness, despair, and aging. It is heightened by low doses of a few often-abused substances such as alcohol or amphetamine, manic mechanisms, falling in love, joy, and some drugs for Parkinson's disease.

**Motive.** The psychological aspect of desire is referred to as *motive* and is recognized by willingness to bring one's body to the partner for sexual behavior either through initiation or receptivity. Motive often directly stems from the person's perception of the context of the nonsexual and sexual relationship. Sexual desire diagnoses are made in persons who have adequate drive manifestations and those who apparently have none. Most sexual desire problems in physically healthy adults are generated by one partner's unwillingness to engage in sexual behavior. This is often kept secret, however, from the partner because the reason for the unwillingness would have to be explained; something that the patient may not be ready to do.

**Values.** Sexual motives are originally programmed by social and cultural experiences. Children and adolescents acquire values—beliefs, expectations, and rules—for sexual expression. Young people have to negotiate their way through the fact that their early motives to behave sexually frequently coexist with their motives *not* to engage in sexual behavior. Conflicted motives often persist throughout life but the reasons for the conflict evolve. A teenager possessed of considerable drive and motive to make love may inhibit all sexual activities because of religiously acquired moral considerations or the sense that he or she is just not ready yet.

Two practical dimensions of the values' contribution to sexual desire are embodied in the answers to two questions most people consider when sex is in the offing: "Is this sexual behavior with this person at this time morally acceptable to me?" and "Is this behavior normal?"

> An 80-year-old man who had no drive manifestations and had avoided all sexual contact with his wife for a decade because he could not get an erection, passionately answered a doctor's query about his sexual desire, "Of course, I have sexual desire! I am a red-blooded American male! Why do you think I am here?" He was only speaking about his wish to be sexually capable now that the PDE-5i medications exist. Scientific progress created for him a new definition of normality—potent at 80!

For a young teenager, "Is the behavior normal?" often refers to masturbation and the person may not be certain that it is normal. In a few years, however, he or she may learn that it is normal and then masturbation will commence without worry. An older person may state that he has no desire for extramarital sex when in fact he is sorely tempted and recurrently excited by a particular person. His statement reflects his sense that he does not wish to succumb to an act that he considers to be immoral.

The appearance and disappearance of sexual desire is often enigmatic to a patient, but its ebb and flow result from the ever-changing intensities of its components, biological *drive*, psychological *motive*, and socially acquired *values* (Table 77–3) (Levine 2003). In young and middle-aged men drive manifestations tend to lead to behaviors that cause arousal. In comparably aged partnered women, it is often the partners' initiations that occur first and then induce arousal, which leads to women's motives to behave sexually (Basson 2000).

**Table 77–3 Three Interactive Components of Sexual Desire**

| Sexual Drive = Biological Component |
|---|
| Evolves over time, decreasing with increasing age |
| Diminished by many psychotropic, antihypertensive, and antineoplastic medications |
| Manifested by the internally stimulated privately experienced genital sensations and thoughts of sexual behavior |
| **Sexual Motivation = Psychological Component** |
| Highly contextual in terms of relationship status |
| The most socially and psychologically responsive of the three components |
| Evolves over time but not predictably |
| Manifested by a person's willingness to bring his or her body to a specific person for sexual behavior |
| **Values = Social Component Manifested as Wishes to Have Sex in a Particular Context** |
| Expectations for sexual behavior based on membership in various subcultural groups such as family, religion, gender, region, and nation |
| These expectations begin as cognitions of what is right and wrong and what a person is entitled to sexually and are influenced by what people think others in their cohort are experiencing |
| Often clinically difficult to distinguish from motivation, which values influence |

Clinical Vignette 1

A 51-year-old secretary explained that she had had a wonderful sexual life with her husband until she humorously asked whether he had ever had an affair during their 20-year marriage. He shocked her by confessing a past "insignificant" one. As she thought about this over a week, she became increasingly enraged and asked him to leave the home. Several weeks later, he came back after constant phone contact and in response to her coming down with a flu-like illness. When their sexual behavior resumed 2 months later, she became the "ice queen"—unable to stand his touches. Her aversion lasted 6 months. Four years later when she discovered that he was having an affair, she redeveloped her aversion, adding that she felt that he was raping her when he touched her and that she could not

stand his saliva or semen. She did everything she could do to avoid sex. Her second period of aversion lasted 4 years before she was referred for psychotherapy. At that time, she saw no relationship between her discoveries of his infidelity and her sexual aversion state.

## Sexual Desire Diagnoses

Two official diagnoses are given to men and women whose desires for partner sexual behavior are deficient: hypoactive sexual desire disorder (HSDD) and sexual aversion disorder (SAD). The differences between the two revolve around the emotional intensity with which the patient avoids sexual behavior. When visceral anxiety, fear, or disgust is routinely felt as sexual behavior becomes a possibility, sexual aversion is diagnosed. HSDD is far more frequently encountered. It is present in at least twice as many women than men; female-to-male ratio for aversion is far higher. Like all sexual dysfunctions, the desire diagnoses may be lifelong or may have been acquired after a period of ordinary fluctuations of sexual desire. Acquired disorders may be partner specific ("situational") or may occur with all subsequent partners ("generalized").

DSM-IV-TR Criteria

**Hypoactive Sexual Desire Disorder**

A. Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person's life.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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DSM-IV-TR Criteria

**Sexual Aversion Disorder**

A. Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction).

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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When the psychiatrist concludes that the patient's acquired generalized HSDD is either due to a medical condition, a medication, or a substance of abuse, the diagnosis is further elaborated to sexual dysfunction due to general medical condition or substance-induced sexual dysfunction (e.g., HSDD due to multiple sclerosis). The frequency of the specific etiologies is heavily dependent on the clinical setting. In oncology settings, medical causes occur in high frequency; in drug rehabilitation programs, methadone maintenance will be a common cause. In marital therapy clinics, anger and loss of respect for the partner, hidden incompatibility of sexual identity between the self and the partner because of covert homosexuality or paraphilia, an affair, or childhood sexual abuse will commonly be the basis. In general psychiatry settings, medication side effects will often be the top layer of several causes. When a major depressive disorder is diagnosed, for instance, the desire disorder is often assumed to be a symptom of the depression. This usually is incorrect. The desire disorder often precedes the decompensation into depression.

## From a Desire Diagnosis to Dynamics

Those with *lifelong* deficiencies of sexual desire are often perceived to be struggling with either: (1) sexual identity issues involving gender identity, orientation, or a paraphilia; (2) having failed to grow comfortable as a sexual person due to extremely conservative cultural backgrounds, developmental misfortunes, or abuses. Occasionally, the etiology is enigmatic, raising the important question whether it is possible to never have any sexual drive manifestations on a biological basis. (Theoretically, the answer is yes.) Both acquired and lifelong desire disorders are often associated

with past or chronic mood disorders. Disorders of desire are often listed as "of unknown etiology" (Rosen and Leiblum 1995), but clinicians should be skeptical of this idea because

1. the patient may not tell the doctor the truth early in the doctor–patient relationship;
2. the patient may have strong defenses such as repression against knowing the truth;
3. the patient may not be able to speak freely in front of the partner;
4. the patient may be influenced by the unappreciated stresses in the partner;
5. the doctor may not realize the usual causes of the problem;
6. the doctor may not believe in developmental influences on the organization of adult sexual function.

A patient presenting with SAD should strongly suggest four possibilities to the clinician:

1. that a remote traumatic experience is being relived because of the partner's expression of interest in sexual behavior;
2. that without the symptom the patient feels powerless to say "no" to sexual advances;
3. the patient is angry at the partner but is too afraid to state why;
4. the patient feels guilty about his or her own sexual behavior with another person.

The doctor's attention should focus on the patient's sexual development as a child, adolescent, and young adult when the aversion is lifelong, whereas when it is *acquired*, the focus of the history should be on the period immediately prior to the onset of the symptom.

Desire disorders require the clinician to think both in terms of development and personal meanings of sex to their individual patients (Table 77–4). Because all explanations are speculative, they should at least make compelling sense of the patients' life experiences. Some explanations

DSM-IV-TR Criteria

**Sexual Dysfunction due to … [Indicate the General Medical Condition]**

A. Clinically significant sexual dysfunction that results in marked distress or interpersonal difficulty predominates in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the sexual dysfunction is fully explained by the direct physiological effects of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., major depressive disorder).

*Select* code and term based on the predominant sexual dysfunction:

625.8 Female hypoactive sexual desire disorder due to…[indicate the general medical condition]: if deficient or absent, sexual desire is the predominant feature

608.89 Male hypoactive sexual desire disorder due to … [indicate the general medical condition]: if deficient or absent, sexual desire is the predominant feature

607.84 Male erectile disorder due to … [indicate the general medical condition]: if male erectile dysfunction is the predominant feature

625.0 Female dyspareunia due to … [indicate the general medical condition]: if pain associated with intercourse is the predominant feature

608.89 Male dyspareunia due to … [indicate the general medical condition]: if pain associated with intercourse is the predominant feature

625.8 Other female sexual dysfunction due to … [indicate the general medical condition]: if some other feature is predominant (e.g., orgasmic disorder) or no feature predominates

608.89 Other male sexual dysfunction due to … [indicate the general medical condition]: if some other feature is predominant (e.g., orgasmic disorder) or no feature predominates

Coding note: Include the name of the general medical condition on Axis I, e.g., 607.84 male erectile disorder due to diabetes mellitus; also code the general medical condition on Axis III.

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**Table 77–4 Obstacles to Discovering the Psychological Contributants to a Sexual Desire Disorder**

| Obstacles That Reside in the Patient |
|---|
| The patient may not tell the psychiatrist the truth about life circumstances |
| The patient may have strong defenses against knowing the truth |
| The patient may be unable to tell the truth in front of the partner |
| The patient may not actually know what is occurring in the partner's life, although she or he is reactive to it |
| **Obstacles That Reside in the Psychiatrist** |
| The psychiatrist may not realize the psychological factors that usually cause these problems |
| The psychiatrist may not believe that developmental influences can organize an adult sexual function such as sexual motivation |
| The psychiatrist may not like to deal with the murky complexity of nonbiological developmental and interpersonal issues when thinking about etiology |

are based on the influence of remote developmental processes. The term *Madonna–whore complex* misleads us into thinking that this is only a male pattern. The syndrome is manifested by normal sexual capacity with anyone but the fiancé or spouse. Freud interpreted this as a sign of incomplete resolution of the oedipal complex (Freud 1912). The man was thought to be unable to sexually desire his beloved because he had unconsciously equated her with his mother. He withdrew his sexual interest from her to protect himself from symbolic incest. Some women are comparably unable to sexually enjoy their partners because they unconsciously confuse their beloved with their father. Another form can be seen among patients whose parents were grossly inadequate caregivers. When these men and women find a reliable, kind, supportive person to marry, they quickly discover a strong motive to avoid sexual behavior with their fiancé. The patient makes the partner into a good-enough parent, experiences anxiety as an unconscious threat of incest associated with the possibility of sex, and becomes skillful at avoiding sexual opportunities.

Most sexual desire disorders are difficult to quickly overcome in brief treatments. Serious individual or couple issues frequently underlie these diagnoses. They have to be afforded time to emerge and to be worked through. However, clinicians need not be pessimistic (Hall 2005). For example, helping a couple resolve a marital dispute may return them to their usual normal sexual desire manifestations. For many individuals and couples, therapy assists the couple to more calmly accept the profound implications of continuing marital discord, infidelity, homosexuality, or other contributing factors. Some treatment failures lead to divorce and the creation of a relationship with a new partner. There is then no further sign of the desire problem. Problems rooted in early developmental experiences are particularly difficult to overcome. While DSM-IV-TR asks the clinician to make many distinctions among the desire disorders, no follow-up study has been published in which either the subtypes (lifelong, acquired, situational, generalized) or etiologic organizers (relationship deterioration with and without extramarital affairs, sexual identity incompatibilities, parental, and medical) are separated into good and poor prognosis categories.

Developmental and identity matters are typically approached in long-term individual psychotherapy. In these sessions, women often discuss the development of their femininity from adolescence to young womanhood, focusing on issues of body image, beauty, social worth to others, moral sensibilities, social awkwardness, and whether they consider themselves deserving of personal physical pleasure. Men often discuss similar issues in terms of masculinity.

Anger, loss of respect, marital discord, and extramarital affairs may be approached in either individual or conjoint formats. In either setting, patients often formulate

**DSM-IV-TR Criteria**

**Substance-Induced Sexual Dysfunction**

A. Clinically significant sexual dysfunction that results in marked distress or interpersonal difficulty predominates in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the sexual dysfunction is fully explained by substance use as manifested by either (1) or (2):

(1) the symptoms in criterion A developed during, or within a month of, substance intoxication

(2) medication use is etiologically related to the disturbance

C. The disturbance is not better accounted for by a sexual dysfunction that is not substance induced. Evidence that the symptoms are better accounted for by a sexual dysfunction that is not substance induced might include the following: the symptoms precede the onset of the substance use or dependence (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced sexual dysfunction (e.g., a history of recurrent non-substance-related episodes).

Note: This diagnosis should be made instead of a diagnosis of substance intoxication only when the sexual dysfunction is in excess of that usually associated with the intoxication syndrome and when the dysfunction is sufficiently severe to warrant independent clinical attention.

*Code* [specific substance]-induced sexual dysfunction:

(291.8 Alcohol; 292.89 Amphetamine [or Amphetamine-like Substance]; 292.89 Cocaine; 292.89 Opioid; 292.89 Sedative, Hypnotic, or Anxiolytic; 292.89 Other [or Unknown] Substance)

*Specify* if:

With impaired desire

With impaired arousal

With impaired orgasm

With sexual pain

*Specify* if:

With onset during intoxication: if the criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome

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the etiology as having fallen out of love with the partner. Those whose cultural backgrounds limit their ease in being a sexual person are often encouraged in educational and cultural experiences that might help them outgrow their earliest notions about what is proper sexual behavior.

## The Problems of Sexual Arousal

The emotion interchangeably referred to as sexual arousal or sexual excitement generates changes in respiration, pulse, and muscular tension as well as an increased blood flow to the genitals. Genital vasocongestion creates vaginal lubrication, clitoral tumescence, labial color changes, penile erection, testicular elevation, and penile color changes (Masters and Johnson 1966). How arousal is centrally coordinated in either sex remains mysterious. During lovemaking, men and women do not necessarily maintain or progressively increase their arousal; rather often there is a fluctuating intensity of arousal, which is reflected in variations in vaginal wetness and penile turgidity and nongenital signs of arousal.

### Female Sexual Arousal Disorder (FSAD)

The specificity and validity of this disorder is unclear. In women, it is far more difficult to separate arousal and desire problems than in young men. New desire/arousal problems arise typically in the middle-to-late 40s in up to 50% of women as perimenopausal vaginal lubrication diminishes (Grady 2006). It is assumed to be endocrine in origin even though estrogen treatment only reliably improves the symptoms relating to vaginal moisture deficiency. The disorder is also seen among regularly menstruating women, who claim that they desire sex but simply do not become aroused with the same efficiency and intensity. Making the diagnosis of FSAD implies that drive and motivation are relatively intact. The disorder is typically an *acquired* one. The women focus on the lack of moisture in the vagina or their failure to be excited by the behaviors that previously reliably brought pleasure. Assuming that some mental factor distracts them from excitement during lovemaking, therapy focuses on identifying what this might be (Basson 2003).

In menopausal women, FSAD is more often focused on the body as a whole rather than just genital moisture deficiencies. Skin insensitivity, often a euphemism for decreased pleasure in response to oral and manual nipple, breast, and vulvar stimulation, is often initially treated as a symptom of "estrogen" deficiency. Early in the menopause, a small minority of women have an increase in drive due to changing testosterone–estrogen ratios. Yet, they may still subjectively experience arousal as subjectively different. Therapy often focuses on the women's concerns about estrogen replacement and the consequences of menopause in terms of body image, attractiveness, fear of partner infidelity, loss of health and vigor, and aging.

Aging of the female arousal mechanisms, whether simply due to shifts in ovarian steroid production or systemic aging mechanisms, occurs earlier than deterioration of orgasmic physiology. Women with decreasing arousal are often, therefore, still reliably orgasmic with the use of vaginal lubricants (Basson 2006). Women who have been treated with chemotherapy for various cancers are a particularly problematic group to offer assistance to for their new arousal problems. Fear of stimulating estrogen sensitive breast cancer cells, increasing the risk of thromboembolic phenomena, stroke, and myocardial infarction has dramatically limited the use of estrogen/progesterone replacement (WHI Writing Group 2002).

**DSM-IV-TR Criteria**

**Female Sexual Arousal Disorder**

A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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The use of PDE-5i drugs for erectile dysfunction stimulated an ongoing search for medications for HSSD and FSAD. Thus far, no single compound, including sildenafil, has been able to demonstrate effectiveness in placebo-controlled studies (Basson et al. 2002).

Here is a relatively simple case of an acquired arousal disorder that was most likely a combination of perimenopausal biological changes and more important psychological ones.

A regularly menstruating 50-year-old widow complained of difficulty with arousal with her new "good-enough" lover. She was motivated to behave sexually with him but something seemed to have happened to her since her husband developed a brain tumor and died and she spent 2 years without dating. Her body, which used to work well sexually, had ceased to be reliably sexually functional. She was intermittently vaginally dry despite using a lubricant, she had trouble sustaining excitement, and orgasm only occasionally occurred with great effort. She could masturbate efficiently when alone, but was not motivated to do it—"What good is it?" Not depressed clinically, she was baffled by her failure to adapt to her new situation. Her conversation with the therapist wove together

two themes: the unusually happy life she had with her husband who tragically died so young leaving her to grieve forever and her musings about the meaning of her new lover's wife's suicide. "Let's face it, as nice as he is, he is no George."

## Male Erectile Disorder (ED)

The mechanisms of sequestering and maintaining arterial blood within the corpora cavernosa involve both cAMP and cGMP biochemistry. The advent of the PDE-5i's has diminished the emphasis on psychogenic versus organic ED and the urological/psychological turf wars of the past. While it is widely recognized that young men more commonly have pure psychogenic ED and men over 50 often have significant organic contributants, some younger men have organic factors and some older men have significant psychological and interpersonal reasons for their inability to sustain potency. It is important for mental health professionals to realize that the PDE-5i class of medications, while capable of curing the problem in many individuals, often only slightly helps. Psychiatric attention is often still required because the sexual context can become in some subtle ways too dangerous, frightening, or otherwise unwanted for men to be potent with a particular partner.

The prevalence of ED rises dramatically in the sixth decade of life from less than 10 to 30%; it increases further during the seventh decade (Feldman et al. 1994). Aging, medical conditions such as diabetes, prostate cancer, hypertension, and cardiovascular risk factors predict the most common pattern of ED due to a medical condition in this age group. While medication-induced, neurological, endocrine, metabolic, radiation, and surgical causes of erectile dysfunction also exist, in population studies diabetes, hypertension, smoking, lipid abnormalities, obesity, and lack of exercise are correlated with the progressive deterioration of erectile functioning in the sixth and seventh decades. These factors are thought to create a relative penile anoxemia, which stimulates the conversion of corporal smooth muscle cells into fibrocytes. The gradual loss of elasticity of the corpora interferes with filling and sequestering of arterial blood (Carrier et al. 1993). Erections at first become unreliable and finally impossible to obtain or sustain.

At every age, *selectivity* of erectile failure is the single most important diagnostic feature of psychogenic erectile dysfunction. Clinicians should inquire about the relative firmness and duration of erections under each of these circumstances: masturbation, sex other than intercourse, sex with other female or male partners, upon stimulation with explicit media materials, in the middle of the night, and upon awakening. If under some circumstances the erection is firm and lasting, the clinician can usually assume that the man's neural, endocrine, and vascular physiology is sufficiently normal and that the problem is psychogenic in origin. This is true even for men in their 50s and older (Levine 2004). Clinicians often feel more certain about this diagnosis when no diseases thought to lead to erectile dysfunction are present.

**DSM-IV-TR Criteria**

**Male Erectile Disorder**

A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The erectile dysfunction is not better accounted for by another Axis I disorder (other than a sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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Clinical Vignette 2

A 35-year-old man who is potent reliably with his wife becomes sexually anxious when he attempts to have intercourse with a new partner. During foreplay with her, he has been lastingly erect. But when he attempts to penetrate he does so with a softening erection and it becomes a race between rapid ejaculation and loss of erection.

*Patient*: "What is going on here doctor?"
*Doctor*: "What is going on here?"
*Patient*: "I know there is nothing wrong with me physically."
*Doctor* "Me, too. So why did you spend so much time with the urologist?"
*Patient*: "I guess I did not want to face what I am doing about my wife and children and my resentment of being confined by marriage."

Lifelong male ED typically is psychogenic and involves either a sexual identity dilemma—such as, gender identity disorder, a hidden-from-wife homoerotic orientation, a paraphilia, or another diagnosis associated with the man's fear of being sexually close to a partner such as some instances of obsessive–compulsive disorder, schizoid personality, a psychotic disorder, or borderline personality disorder. Sexual identity problems are often initially denied unless the clinician is nonjudgmental and thorough during the inquiry. Occasionally, a reasonably normal young man with an unusually persistent fear of sexual intercourse seeks attention.

**Table 77–5 What the Psychiatrist Should Expect to Encounter Among Men Who Have Never Been Able to Have Intercourse with a Woman**

| Unconventional Sexual Identity |
|---|
| Gender identity problem |
| Wish to be a woman |
| A history of cross-dressing in women's clothing in private and/or public |
| Suspected by psychiatrist but information initially withheld |
| Homoeroticism |
| Without sexual behavior with men |
| With sexual behavior with men but not known to the female partner |
| With sexual behavior with men and known to the female partner |
| Paraphilia |
| One or more of a wide range of paraphilic patterns |
| Preference for prepubertal or young adolescents often initially denied unless thoroughly, systematically, and nonjudgmentally questioned |
| Compulsivity with or without obvious paraphilic imagery confined to masturbation with the help of pornographic images for stimulation |
| **Serious Character Disorders (Men Have Strong Fear of Closeness to Women)** |
| Obsessive–compulsive |
| Schizotypal |
| Schizoid |
| Avoidant |
| Rigidity that is associated with previous psychotic decompensation |
| **Anxious Beginners** |
| Psychiatrically normal young men with inordinate anxiety and shyness that quickly respond to psychiatrist's encouragement and optimism and partner warmth and patience |

These good prognosis cases are sometimes informally referred to as anxious beginners (Table 77–5). With that exception, men with lifelong ED, when taken into individual therapy, are usually perceived as having a strong motive to avoid sexual behavior and while dysfunctional with a partner during much of their therapy might also appropriately be diagnosed as having HSDD with normal drive but with a motive to avoid partner sex. The prognosis with older men with lifelong erectile dysfunction is poor even with modern erectogenic agents. Long-term therapy, even if it does not enable regular intercourse, may enable more emotional and sexual closeness to a partner. Some reasonably masculine appearing men with mild gender identity problems can quickly become potent if they can reveal their need during sexual relationship to cross-dress (use a fetish article of clothing) to a partner who calmly accepts his requirement. However, most of these men have inordinate fears of sexually bonding to any woman and, in therapy, become preoccupied with their resistance to psychological intimacy with the therapist. The skillful therapist may then be able to have the patient reveal early life attachment fears. Some of them marry and form companionate relationships that are rarely or never consummated.

In dramatic contrast, men with long-established good potency who have recently lost their erectile capacities with their partner—acquired psychogenic ED—have a far better prognosis (Table 77–6). They may be treated in individual or couples format, depending on the precipitants of the sexual problem and the status of their relationship with their partner. Many of these therapies become focused on resentments that have not been identified, discussed, and worked through by the couple. Such distressed couples are most efficiently helped in a conjoint format. When extramarital affairs are part of the relationship deterioration and cannot be discussed, most clinicians simply work with one spouse. Potency is frequently lost following a separation or divorce. Impaired potency after a spouse's death is usually about unresolved grief, but the clinician should be aware that some of these men had the same problem with their wives. Men also often get worried about their potency when their financial or vocational lives crumble, when they have a serious new physical illness such as a myocardial infarction or stroke, or when their wives become seriously ill. The esthetics of lovemaking requires a context of reasonable physical health; when one spouse becomes chronically ill or disfigured by illness or surgery, either one of the couple may lose their willingness to be sexual. This may be reflected in impaired erections or sexual avoidance.

Regardless of the precipitating factors, men with arousal disorders have performance anxiety. They anticipate erectile failure before sex begins and vigilantly monitor their state of tumescence during sex (Masters and Johnson 1970). Performance anxiety is present in almost all impotent men (and after any dysfunction gets established in men or women). Performance anxiety is efficiently therapeutically addressed by pointing it out to the patient and asking him to make love without trying intercourse on several occasions to demonstrate to himself how different lovemaking can feel for him when he is not risking failure. This enables some men to relax, concentrate on sensation, and return to previous states of sensual abandon during lovemaking. This technique is known as *sensate focus*.

The psychological treatment of acquired ED is often highly satisfying for the professional because many of the men are anxious for help. Motivation to behave sexually

**Table 77–6 Apparent Precipitants of Recently Acquired Psychogenic Erectile Dysfunction and Their Associated Private Emotions***

| |
|---|
| Deterioration of marital relationship: anger, guilt, disdain, sadness |
| Divorce: abandonment, anger, guilt, sadness, shame |
| Deterioration of personal or spousal health: sadness, anxiety, anger, shame |
| Death of spouse ("widower's impotence"): sadness, longing, guilt |
| Threat of or actual unemployment: anxiety, worthlessness, guilt, anger, shame |
| Financial reversal: shame, guilt, anxiety |
| Surreptitious extramarital affair: guilt |
| Reunited marriage after extramarital affair: shame, anxiety |

*These short lists of emotions are a mere introduction to what transpires within the man's mind as a result of the meanings that the sexual behavior has for him. Although incomplete and oversimplified, they are listed to remind the psychiatrist that what the man feels about his life competes with sexual arousal during sexual behavior to diminish the secretion of nitric oxide in the cavernosal endothelial cells, which in turn limits the amount of vasodilating cGMP.

is often present, fear can be allayed, and men can learn to appreciate the emotional complexity of their lives. They can be shown how their minds prevented intercourse until they could acknowledge what has been transpiring within and around them. Many recently separated men, for example, are grieving, angry, guilty, uncertain, and worried about their finances. Yet, they may propel themselves into a new relationship. Two characteristics seem to predispose to erectile problems at key life transitions: (1) the pursuit of the masculine standard that men ought to be able to perform intercourse with anyone, anywhere, under any circumstances; (2) the inability to readily grasp the nature and significance of his inner experiences. "Yes, my schizophrenic daughter became homeless in another city, my wife was depressed and began drinking to excess in response, and I had a financially costly affair with my secretary. What do these have to do with my loss of potency?" (Table 77–7.)

The phosphodiesterase type 5 inhibitors, sildenafil, vardenafil, and tadalafil maintain corporal vasodilation by preventing the degradation of cGMP. Sexual arousal is not generated by these medications. Arousal is brought about by fantasy, masturbation, anticipation, or partner interaction, and leads to the corporal secretion of nitric oxide, which is converted by an enzyme into cGMP, which relaxes the smooth muscle of the capillaries and decreases the resistance to blood flow. No PDE-5i should be used when any organic nitrate is being taken because it dangerously potentiates the hypotensive effect of the nitrates risking brain and myocardial infarction (Goldstein et al. 1998). The PDE-5i drugs are underutilized by psychiatrists for three major reasons: psychiatrists often have not been well trained in sexual history taking so they remain uncomfortable talking to their patients about sexual issues in detail, they needlessly fear cardiac side effects from these medications, and drug manufacturers have targeted primary care physicians and urologists with their educational efforts because they are men's first medical contacts for this symptom.

**Table 77–7 Pathogenesis Model for Acquired Psychogenic Erectile Dysfunction**

Assumptions that predispose to ED
- A normal (or real, adequate, or competent) man is able to have intercourse with anyone under any circumstances
- Feelings are a womanly intrusion on my reason; I am disinterested and relatively unaware of them

Precipitating events (see Table 77–6)
↓
One episode of erectile failure
↓
Performance anxiety
↓
Another episode of erectile failure
↓
More performance anxiety
↓
Decreased frequency of sexual initiation
↓
Changes in the sexual equilibrium
↓
Established pattern of impotence with partner

Three conditions have unique response profiles to PDE-5i's: after prostatectomy the response rate is approximately 34%, among diabetics it is approximately 43%, and among those with pure psychogenic ED it is approximately 80%. Other interventions are effective in varying degrees for largely organic erectile dysfunction: vacuum pump, the intracavernosal injection of vasodilating substances (cAMP mechanism), intraurethral alprostadil, the surgical implantation of a penile prostheses, and outside the US, sublingual apomorphine. Because the rate of improving erections is significantly higher than the restoration of a mutually satisfactory sexual equilibrium with the PDE-5i class of drugs, mental health professionals still have a role to play (Leiblum 2002, Levine 2006, Pallas et al. 2000)

## Problems with Orgasm

### Female Orgasmic Disorder

The attainment of reasonably regular orgasms with a partner is a crucial personal developmental step for young women. This task of adult sexual development rests upon a subtle interplay of physiology, individual psychology, and culture. Reliable orgasmic attainment is usually highly valued by the woman and is often reflected in enhanced self-esteem, confidence in her femininity, relationship satisfaction, and the motive to continue to behave sexually.

Orgasm is the reflexive culmination of arousal. It is manifested by rhythmic pelvic floor musculature contractions followed by the release of muscular tension and pelvic vasocongestion, accompanied by varying degrees of pleasurable body sensations. Its accomplishment requires (1) the physiologic apparatus to augment and sustain arousal, (2) the psychological willingness to be swept away by excitement, and (3) tenacious focus on the required physical work of augmenting arousal. The diagnosis of female orgasmic disorder is made when the woman's psychology persistently interferes with her body's natural progression through arousal (Meston et al. 2004).

Estimates of prevalence of both lifelong and acquired psychological FOD range from 10 to 30% (Laumann et al. 1999) but the most common estimate is ~25%. Some of this variability is due to the different definitions of anorgasmia. It remains a difficult scientific judgment, however, where to draw the line between dysfunction and normality; for example, is it normal to attain orgasms during one-third of partner sexual experiences? Few women are always orgasmic.

The biologic potential for orgasmic attainment is an inborn endowment of nearly all physically healthy women. The cultural and psychological factors that influence orgasmic attainment are usually fundamental to the etiology of this problem. Centuries-old beliefs that sexual knowledge, behavior, and sexual pleasure were not the prerogative of "good girls" powerfully affect some women's sexual adjustment. These beliefs cause young women to be uninformed about the location and role of their clitoris and ashamed of their erotic desires and sexual sensations. For women with FOD, modern concepts of equality of sexual expression are insufficient to overcome these traditional beliefs. These emotionally powerful beliefs often lay behind their classic dysfunctional pattern: the women can become aroused to a personal plateau beyond which they cannot progress;

**DSM-IV-TR Criteria**

**Female Orgasmic Disorder**

A. Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of female orgasmic disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The orgasmic dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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thereafter, their excitement dissipates. After numerous repetitions, they begin to lose motivation to participate in sex with their partner. They may eventually meet criteria for HSDD.

## Diagnosis

The doctor should know the answers to the following questions. Does the patient have orgasms under any of the following sexual circumstances: solitary masturbation, partner manual genital stimulation, oral–genital stimulation, vibratory stimulation, any other means? Does she have orgasms with a partner different than her significant other? How are they stimulated? Does a particular fantasy make orgasmic attainment easier or possible? Under what conditions has she ever been orgasmic? Has she had an orgasm during her sleep?

### *Lifelong Varieties*

The lifelong *generalized* variety of the disorder is recognized when a woman has never been able to attain orgasm alone or with a partner by any means, although she regularly is aroused. When a woman can only readily attain orgasm during masturbation, she is diagnosed as having a lifelong *situational* type. Women with any form of lifelong FOD more clearly have conflicts about personal sexual expression due to fear, guilt, ignorance, or obedience to tradition than those with the acquired variety. Women who can masturbate to orgasm often feel fear and embarrassment about sharing their private arousal with any other person.

### *Acquired Varieties*

The acquired varieties of this disorder are more common and may present as complete anorgasmia, too-infrequent orgasms, or too-difficult orgasmic attainment. The most common cause of this problem is serotonergic compounds. Prospective studies of various antidepressants have demonstrated up to 70% incidence of this disorder among those treated with serotonergic antidepressants. When medications are not the cause of an acquired FOD, the doctor needs to carefully assess the meaning of the changes in her life prior to the onset of the disorder. Some of these women are in the midst of making a transition to a new partner after many years in another relationship. Some seem to suffer from memories of earlier shame-ridden behaviors such as incest. But it is likely that psychotherapy with a number of patients will reveal a range of reasons for their inhibitions.

## Treatment

When a doctor applies a label of disorder to a relatively anorgasmic woman, the woman often privately interprets the diagnosis as meaning that she has a serious and difficult problem to overcome. Physicians need to be careful about this because some of these women are relatively easy to help. It must be realized that many women gradually undo the effects of their culture on their own and grow to be increasingly responsive sexually with time and growing trust of their partners. Clinicians can do many women a great service by offering education and reassurance. Giving an inhibited woman new-to-her information in an encouraging manner can subdue her anxiety and foster her optimism. On the other hand, some women with this disorder are profoundly entrenched in not being too excited and consequently treatments fail. The prognosis is better with younger adults than middle-aged women.

Four formats are known to be of help. Individual therapy is the most commonly employed. In lifelong varieties of the disorder, therapy focuses on the cultural sources of sexual inhibition and how and when they impacted upon the patient. In the situational varieties, the therapist focuses on the meaning of the life changes that preceded the onset of the disorder. Group therapy is highly effective in helping women to reliably masturbate to orgasm and moderately effective in overcoming partner inhibition. It is typically done with college and graduate students in campus settings, not older women. Couple therapy may be useful to assist the couple with the subtleties of their sexual equilibrium. The personal and interpersonal dimensions of orgasmic attainment can be stressed. Often other issues then come to the fore that initially seemed to have little to do with orgasmic attainment. The most cost-effective treatment is bibliotherapy. Female orgasmic attainment has been widely written about in the popular press since the early 1970s. It is widely believed that these articles and books, which

strongly encourage knowledge of her genital anatomy, masturbation, and active pursuit of orgasm, have enabled many women to grow more comfortable and competent in sexual expression. Only recently has the science behind orgasmic attainment been placed on firmer footing with PET and fMRI study (Kamisarek et al. 2006). They have discovered that multiple areas in the brain are activated during orgasm.

## Male Orgasmic Disorder

When a man can readily attain a lasting erection with a partner, yet is consistently unable to attain orgasm in the body of the partner, he is diagnosed with male orgasmic disorder (MOD). The disorder has three levels of severity: (1) the most common form is characterized by the *ability* to attain orgasm with a partner outside of her or his body, either through oral, manual, or personal masturbation; (2) the more severe form is characterized by the man's inability to ejaculate in his partner's presence; and (3) the rarest form is characterized by the inability to ejaculate when awake. All three forms are usually lifelong and not partner specific. These men cannot allow themselves to be swept away in arousal by another person. They are sexually vigilant to not allow themselves to be controlled by the partner's power to convey them to orgasm. Male orgasm is expected by their female partners. It provides the woman the pleasure and validation of being exciting to the man. While she may have felt that her new partner was a sexual superman during the first several experiences with him, ultimately she is disappointed and loses her sexual motivation to make love to him. Clinicians, therefore, need to remember that the loss of sexual desire may be induced by the presence of a partner's dysfunction. Both the partners and the therapists of these men tend to describe them as controlling, unemotional, untrusting, hostile, obsessive–compulsive, or paranoid. Some of these men get better with psychotherapy, others improve spontaneously with time, and, for others the dysfunction leads to the cessation of the aspiration for sex with a partner. Medication treatments have shown inconsistently disappointing results.

## Premature Ejaculation

Premature ejaculation is a high prevalence (25–40%) (Laumann et al. 1999) disorder seen primarily in heterosexuals characterized by an untameably low threshold for the reflex sequence of orgasm. The problem, a physiological *efficiency* of sperm delivery, causes social and psychological distress. In failing to develop a sense of control over the timing of his orgasm in the vagina, the man fails to meet his standards of being a satisfying sexual partner. However, if his partner does not object, his rapidity is not likely to cause him to seek medical attention. The range of intravaginal containment times among self-diagnosed patients extends from immediately before or upon vaginal entry (rare), to less than a minute (usual), to less than the man and his partner desire within ~5 minutes (not infrequent). Time alone is a misleading indicator, however. The essence of the self-diagnosis is an emotionally unsatisfying sexual equilibrium apparently due to the man's inability to temper his arousal and choose when he ejaculates. Most men sometimes ejaculate before they wish to, but not persistently.

**DSM-IV-TR Criteria**

**Premature Ejaculation**

A. Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The premature ejaculation is not due exclusively to the direct effects of a substance (e.g., withdrawal from opiods).

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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## Clinical Approach

The history should clarify the answers to the following questions. Why is he seeking therapy now? Is the patient a sexual beginner or a beginner with a particular partner? Does he have inordinately high expectations for intravaginal containment time for a man his age and experience? Is he desperate about losing the partner because of the rapid ejaculation? Is the relationship in jeopardy for another reason? Does his partner have a sexual dysfunction? Does she have orgasms with him other than through intercourse? Is he requesting help to support his wife's misperception that their sexual problems are his fault when in fact he does not have the problem with his lover? Is his partner now blaming the man's sexual inadequacy for her infidelity? Is his new symptom a reflection of his fear about having a serious physical problem during sex such as angina, a stroke, or another myocardial infarction? The answers will enable the doctor to classify the rapid ejaculation into an acquired or lifelong and specific or general pattern, to sense the larger context in which his sexual behavior is conducted, and to plan treatment.

Premature ejaculation reflects to the man's sense that his contribution to the sexual equilibrium is deficient. It implies that he considers that he is far behind most men in his vaginal containment time and that he wants to provide his partner with a better opportunity to be nurtured during lovemaking through prolonged intercourse. Typically, he

aspires to "bring" his partner to orgasm during intercourse. If anxiety lowers the ejaculatory threshold and keeps it from its natural evolution to a higher level over time, then premature ejaculation is a self-perpetuating pattern. Premature ejaculation may last a lifetime even though some men with premature ejaculation have sex with a variety of partners under a variety of circumstances and have no problems with any other phase of sexual physiology (Waldinger 2003).

### Therapy

There are three efficient approaches to this dysfunction. The first is simply to refuse to confirm the patient's self-diagnosis. Some anxious beginners, men with reasonable intravaginal containment times of 2 or more minutes, and those with exaggerated notions of sexual performance can be calmed down by a few visits. When they no longer think of themselves as dysfunctional their intravaginal containment times improve. The second is the use of serotonergic medications. In a study of 15 carefully selected stable couples, daily administration of clomipramine 25 and 50 mg increased intravaginal containment times on average of 249% and 517% over baseline observations (Althof et al. 1995). Numerous similar reports testify to the fact that various serotonergic reuptake inhibitors can lengthen the duration of intercourse and have led to a search for an ideal SSRI to treat premature ejaculation. Thus far, no compound has been approved by the FDA for this purpose. With this off-label use of serotonergic drugs, clinicians need to determine with each patient whether the medication can be taken within hours or days of anticipated intercourse. Improvement is not sustained after medication is stopped. Serotonergic medications are quickly effective in over 90% of men. The third approach is behaviorally oriented sex therapy that trains the man to focus his attention on his penile sensations during vaginal containment and to signal his partner to cease movement or to apply a firm squeeze of the glans/shaft area to interrupt the escalation of arousal. This requires an increase in communication and full cooperation of the partner, which in themselves can go a long way in improving the couple's sexual equilibrium.

Rapid ejaculation in some men reflects mere inexperience; for others it is stubborn physiological efficiency; for some others it reflects fear of personal harm, which is either related to physical illness or to unresolved fears of closeness to a woman; and yet for others it reflects a partnership with a profoundly inhibited blaming partner. If the psychodynamic question is asked of men with persistent rapid ejaculation "Why does this man want to finish intercourse so quickly?" the answers vary from, "It is not a relevant question!" to "I'm afraid of her!" to "I'm afraid of what will happen to me." For instance, a large percentage of men ejaculate quickly for the first months after a myocardial infarction.

The advantages of costlier couple psychotherapy are to allow the man and his partner to understand their lives better, to address both of their sexual anxieties, and to deal with other nonsexual issues in their relationship. Effective psychotherapy allows the man to become positioned to continue the usual biological evolution that occurs during the life cycle from rapid ejaculation, which is true for many young men, to occasional difficulty in ejaculating, which is true for many men in their 60s.

## Sexual Pain Disorders

Here are some pertinent questions to ask a young woman who reports painful intercourse. Does she have a gynecologic abnormality that is generally associated with pain, such as endometriosis? Does she know herself to have a low pain threshold? Does she have another pain disorder such as fibromyalgia? Did the pain or the aversion to sexual intercourse come first? Is it possible to actually deeply penetrate her vagina with a penis, a finger, a tampon, or a penis-shaped object? Does her partner's sexual style cause her physical or mental discomfort; for example, is he overly aggressive or does he stimulate memories of former abuse? What has been the partner's response to her pain? Does her pain actually start before penetration because of her dread of pain?

These example questions help the doctor and the patient get interested in the problem. A great deal has been learned about sexual pain disorders since the 1990s (Bergeron et al. 2003). Sex-limiting pain often is the result of the subtle interplay of personal and relational, cognitive and affective, and fundamental biological processes that are inherent in other human sexual struggles that operate to produce these confusing disorders (Binik 2005).

The DSM-IV-TR presents dyspareunia and vaginismus as distinct entities. However, they have been viewed as inextricably connected in much of the modern sexuality literature; vaginismus is known to create dyspareunia and dyspareunia has been known to create vaginismus.

### Dyspareunia

Recurrent uncomfortable or painful intercourse in either gender is known as dyspareunia. Women's dyspareunia varies from discomfort at intromission, to severe unsparing pain during penile thrusting, to vaginal irritation following intercourse. In both sexes, recurring coital pain leads to inhibited arousal and sexual avoidance. "Dyspareunia" is used as both a symptom and a diagnosis. When coital pain is caused solely by defined physical pathology, dyspareunia due to a medical condition is diagnosed. When coital pain is due to vaginismus, insufficient lubrication, or other presumably psychogenic factors, dyspareunia not due to a medical condition diagnosis is made. Psychogenic etiologies may include a CNS pain perception problem raising the question, "What do we mean by psychogenic?"

#### Psychogenic Sources of Dyspareunia

Pain associated with intercourse may have purely subjective or psychological origin. Couple dynamics are often relevant, but the pain may be seen as a means of not allowing painful memories of childhood sexual abuse into clear focus. Fear of or helplessness about negotiating interpersonal conflicts may eventually lead to pain becoming a solution for avoiding unwanted sexual behaviors. While physicians tend to assume that pain has unconscious origins, sometimes it is merely faked; more often the patient is quite aware of its developmental origins but is too embarrassed to quickly communicate it to the doctor.

Personal psychological origins of painful intercourse pass through the common denominator of anxiety. Such anxiety may take the forms of dread of physical damage, worry about the psychological dependence that might result from physical union, fear of a first or another pregnancy,

**DSM-IV-TR Criteria**

**Dyspareunia**

A. Recurrent or persistent genital pain associated with sexual intercourse in either a male or a female.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The disturbance is not caused exclusively by vaginismus or lack of lubrication, is not better accounted for by another Axis I disorder (except another sexual dysfunction), and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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or a sexually transmitted disease. As this symptom is commonly seen in young women who cannot consummate sex, the anxiety may reflect their emotional unreadiness for intercourse as well as their partner's fear of intercourse. The anxiety often leads to the involuntary contraction of vaginal muscles, which becomes the mechanical source of her pain. Thus, dyspareunia and vaginismus reinforce each other. Both situational and acquired dyspareunia may reflect a woman's conscious or unconscious motivation to avoid sex with a particular partner; it may be her only means to express her despair about their nonsexual relationship. *Lifelong* dyspareunia draws the clinician's attention to developmental experiences.

### Differential Diagnosis

Because the *symptom* dyspareunia is produced by numerous organic conditions, the psychiatrist should be certain that the patient has had a pelvic examination by a person equipped to assess a broad range of regional pathology. Vulvovestibulitis is diagnosed by pain in response to cotton swab touching in a normal appearing vulvar vestibule. A fundamental unanswered question is, "Is the disorder of local or central origin?" In these patients and some others, the pain cannot be classified with certainty as a *symptom* of a central pain processes disorder or as a specific sexual *disorder concerning only intercourse.* Pain upon penile or digital insertion may be due to an intact hymen or remnants of the hymenal ring, vaginitis, cervicitis, episiotomy scars, endometriosis, fibroids, ovarian cysts, and so on. Postcoital dyspareunia often begins at orgasm when uterine contractions occur. Fibroids, endometriosis, and pelvic inflammatory disease should be considered. Postmenopausal pain, particularly if the woman has had many years without intercourse, is often a result of thinning of the vaginal mucosa, loss of elasticity of the labia and vaginal outlet, and decreased lubrication. Normal menopause, however, is often associated with mild pain due to inadequate lubrication (in both partners).

> The brilliant younger daughter of an immigrant family who married an accomplished man of her age and educational attainment developed painful intercourse shortly after marriage. Each had refused parental wishes to arrange a marriage. Each family seemed quite pleased with this love union. Shortly after marriage, she had significant continuing pain on intercourse. They avoided sex. Her easy acceptance of this led the clinician to suspect and correctly diagnose a prolactin secreting pituitary tumor. When that was effectively treated with bromocriptine, they returned to intercourse only to find that she still had significant pain. They sought additional assistance because she was also despairing that she would never become pregnant. Her symptoms resolved in individual therapy after she spent several intense sessions discussing the shame of sexual molestation by her older sister. She could never bear to bring such news to her proud parents or her husband. She eventually did tell her husband.

Male dyspareunia is usually due to a medical condition. Herpes, gonorrhea, prostatitis, and Peyronie's disease cause pain during intercourse. Remote trauma to the penis may cause penile chordee or bowing, which makes intercourse mechanically difficult and sometimes painful. Pain experienced upon ejaculation can be a side effect of trazodone.

## Vaginismus

Vaginismus is an involuntary spasm of the musculature of the outer third layer of the vagina, which makes penile penetration difficult or impossible. The diagnosis is not made if an organic cause is known. Although a woman with vaginismus may wish to have intercourse, her symptom prevents the penis from entering her body. It is as though her vagina says, "No!" In lifelong vaginismus, the anticipation of pain at the first intercourse causes muscle spasm. Pain reinforces the fear and on occasion the partner's response gives her good reason to dread a second opportunity to have intercourse. Early episodic vaginismus may be common among women, but most of the cases that are brought to medical attention are chronic. Lifelong vaginismus is relatively rare. The clinician needs to focus attention on what may have made the idea of intercourse so overwhelming to her: parental intrusiveness, sexual trauma, childhood genital injury, illnesses whose therapy involved orifice penetration, and surgery.

The woman with lifelong vaginismus not only has a history of unsuccessful attempts at penetration but also displays an avoidance of finger and tampon penetration. The most

DSM-IV-TR Criteria

**Vaginismus**

A. Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse.

B. The disturbance causes marked distress or interpersonal difficulty.

C. The disturbance is not better accounted for by another Axis I disorder (e.g., somatization disorder) and is not due exclusively to the direct physiological effects of a general medical condition.

*Specify* type:

Lifelong type

Acquired type

*Specify* type:

Generalized type

Situational type

*Specify:*

Due to psychological factors

Due to combined factors

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dramatic aspect of her history, however, is her inability to endure a speculum examination of her vagina. Vaginismus is a phobia of vaginal entrance.

### Treatment of Dyspareunia and Vaginismus

While vaginismus has the reputation of being readily treatable by gynecologists by pairing relaxation techniques with progressively larger vaginal dilators, the mental health professional typically approaches the problem differently (Bergeron et al. 2003). The psychiatric approach to both vaginismus and dyspareunia is attuned to the role that her symptom plays in her life. The therapy, therefore, does not begin with a cavalier, optimistic attempt to remove the symptom, which only frightens some patients. Rather, it begins with a patient exploration of the developmental and interpersonal meanings of the need for the symptom. "I wonder how this problem originally got started? Can you tell me a bit more about your life?" In the course of assisting women with these problems a variety of techniques may be utilized including relaxation techniques, sensate focus, dilatation, marital therapy, and medication. Short-term therapies should not be expected to have lasting good results because once the symptom is relieved, other problematic aspects of the patient's sexual equilibrium and nonsexual relationship often come into focus. Clinicians have developed an impression that women with a diagnosis of dyspareunia are particularly difficult to help permanently. However, this is a largely unstudied topic.

### Sexual Dysfunction Not Otherwise Specified

This diagnosis is reserved for circumstances that leave the doctor uncertain as to how to diagnose the patient. This may occur when the patient has too many fluctuating dysfunctional symptoms without a clear pattern of prominence of any one of them. Sometimes the psychiatrist is unable to determine whether the dysfunction is the basic complaint or when the sexual complaints are secondary to marital dysfunction. At other times the etiology is the uncertain: psychogenic, due to a general medical condition, or substance induced. When the patient does not emphasize the dysfunction as the problem but emphasizes instead the lack of emotional satisfaction from sex, the psychiatrist may temporarily provide this NOS diagnosis. It is usually possible to find a better dysfunction diagnosis after therapy begins.

## GENDER IDENTITY DISORDERS

The organization of a stable gender identity is the first component of sexual identity to emerge during childhood. The processes that enable this accomplishment are so subtle that when a daughter consistently acts as though she realizes that "I am a girl and that is all right," or when a son's behavior makes a comparable announcement, families rarely even remember their children's temporary confusion and behaviors to the contrary. Adolescent and adult gender concerns are not rare. They are, however, commonly hidden from a perceptive view, sometimes long enough to developmentally evolve into other less dramatic forms of sexual identity such as periodic cross-dressing, wish for hysterectomy, body dysmorphia. Gender identity variations provoke fascination, scorn, and controversy. Some transgendered adolescents and adults and scholars of sexual minority status argue that the concept of a gender identity disorder is based on a profound cultural misunderstanding and intolerance of variations in gender identity. They assert that parental anxiety that their gender variant child will grow up to be homosexual has stimulated psychiatry to endorse a hormonal/surgical treatment that falsely promises to restore the child to a simple male or female form (Hill et al. 2007). Others argue that treatment of gender identity disorder is humane relief of suffering, which makes patients happy, and has little to do with culturally widespread homophobia; gender identity and orientation are separate but often confused phenomena (Zucker 2004).

### Extremely Feminine Young Boys

Although occasionally the parents of a feminine son have a convincing anecdote about persistent feminine interests dating from early in the second year of life, boyhood femininity is more typically only apparent by the third year. By the fourth year playmate preferences become obvious. Same-sex playmate preference is a typical characteristic of young children. Cross-gender–identified children consistently demonstrate the opposite-sex playmate preference (Maccoby and Jacklin 1987). The avoidance of other boys has serious consequences in terms of social rejection and loneliness throughout the school years. The peer problems of feminine boys cause some of their behavioral and emotional problems, which are in evidence by middle-to-late childhood (Zucker 1990). However, psychometric studies

support clinical impressions that feminine boys have emotional problems even before peer relationships become a factor; that is, something more basic about being cross-gender–identified creates problems. Young feminine boys have been shown to be depressed and have difficulties with separation anxiety (Coates and Person 1985).

Speculations about the origin of boyhood femininity generally suggest converging cumulative forces. Any child's cross-gender identifications are likely to involve a host of factors: constitutional forces, problematic interactions with parents, problematic internal processing of life experiences, and family misfortune—financial, reproductive, physical disease, emotional illness, or death of vital persons. These factors are sometimes restated as temperament, disturbed family functioning, separation–individuation problems, and trauma.

Temperament is a dual phenomenon being both the child's predisposition to respond to the world in a certain way and the aspects of the child to which others respond. The common temperamental factors of feminine boys have been described as follows: a sense of body fragility and vulnerability that leads to the avoidance of rough-and-tumble play; timidity and fearfulness in the face of new situations; a vulnerability to separation and loss; an unusual capacity for positive emotional connection to others; an ability to imitate; sensitivities to sound, color, texture, odor, temperature, and pain (Coates et al. 1992). This raises the issue whether some forms of this childhood disorder rest upon a more basic problem such as a pervasive developmental disorder. This matter of origin is often simplified by patients and professionals as "obviously biogenic," which only avoids confronting the challenging psychopathophysiological mechanisms

The development of boyhood femininity *may* occur within the mind of the toddler in response to a loss of emotional availability of a nurturing mother. The child creates a maternal (feminine) self through imitation and fantasy in order to make up for the mother's emotional unavailability. This occurs beyond the family's awareness and is left in place by the family either ignoring what has transpired in the son or valuing it. The problem for the feminine boy is that the social expectations of other people are unyielding; the adaptive early life solution becomes progressively more maladaptive with time. Only some children persist in their obstinate insistence of who they are in the face of increasing evidence to the contrary. The current answer to the question whether boyhood femininity is entirely constitutional, an adaptive solution that becomes maladaptive, or due to some other process is not known.

It is vital to remember that a large well-matched group of feminine boys were followed for over a decade. Undertaken to trace the evolution of early onset child gender identity disorder, this study demonstrated that gender identity disorder did not persist; rather boyhood effeminacy was a frequent precursor of adolescent homoeroticism and homosexual behavior (Green 1987). Feminine gender role behaviors give rise to more masculine behavioral styles as adolescence emerges.

## Masculine Girls: Tomboys

The masculinity of girls may become apparent as early as age 2 years. The number of girls brought to clinical attention for cross-gendered behaviors, self-statements, and aspirations is consistently less than boys by a factor of 1:5 at any age of childhood in Western countries. This may reflect a difference in incidence of childhood gender disorders, negative cultural perceptions of femininity in boys, a broader range of cross-gender expression permitted to girls, or an intuitive understanding that cross-gender identity more accurately predicts homosexuality in boys than girls.

The distinction between tomboys and gender-disordered girls is often difficult to make. Tomboys are thought of as not as deeply unhappy about their femaleness, not as impossible to occasionally dress in stereotypic female clothing, and not thought to have as profound aversion to their womanly physiologic transformations. Tomboys are able to enjoy some feminine activities along with their obvious pleasures in masculine-identified activities. Girls who are diagnosed as gender disordered generally seem to have a relentless intensity about their masculine preoccupations and an insistence about their future. The onset of their cross-gendered identifications is early in life. Although most lesbians have a history of tomboyish behaviors, most tomboys develop a heterosexual orientation.

## The Subjectivity of a Well-Developed Gender Disorder

Children, teenagers, and adults exist who rue the day they were born to their biological sex and who long for the opportunity to simply live their lives in a manner befitting the other gender. They repudiate the possibility of finding happiness within the broad framework of roles given to members of their sex by their society. Their repudiation seems to have nothing to do with social mores or political issues. They literally repudiate their gendered body, repudiate the self in that body, and reject performing roles expected of people with that body. They privately rebel against the need of others to designate them in terms of their biological sex.

The repudiation and rebellion may first occur as a subjective internal drama of fantasy, as behavioral expression in play, or a preference for the company of others. Regardless of when and how it is displayed, however, the drama involves the relentless feeling that "life would be better—easier, fuller, more enjoyable—if I and others could experience me as a member of the opposite sex."

By mid-adolescence, the extremely gender disordered have often envisioned the solution for their paralyzing limiting self-consciousness: to live as a member of the opposite gender, to transform their bodies to the extent possible by modern medicine, and to be accepted by all others as the opposite sex. Some of them go beyond the fantasy or private cross-dressing and come to psychiatric attention. When a clinician is called in, the family has one set of hopes, the patient another. The clinician has many tasks, one of which is to mediate between the ambitions of the gender-disordered person and the family and see what can be done to help the patient. When these patients first appeared 50 years ago, most psychiatrists presumed they were psychotic. But actual evaluations revealed that the vast majority of patients' sense of reality, apart from the gender issue, was not impaired. Even today, countertransference reactions can be quite aversive. Most patients self-refer or get referred to specialists in gender identity disorders, who, by and large, are not philosophically against sex/gender change. These therapists have discovered

**DSM-IV-TR Criteria**

**Gender Identity Disorder**

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following:

(1) repeatedly stated desire to be, or insistence that he or she is, the other sex

(2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing

(3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex

(4) intense desire to participate in the stereotypical games and pastimes of the other sex

(5) strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it

Would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

C. The disturbance is not concurrent with a physical intersex condition.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Code* based on current age:

302.6 Gender identity disorder in children

302.85 Gender identity disorder in adolescents or adults

*Specify* (for sexually mature individuals):

Sexually attracted to males

Sexually attracted to females

Sexually attracted to both

Sexually attracted to neither

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that these patients possess many of the ordinary aspects of life and one unusual ambition; they often want to be the opposite sex so badly that they are willing to make it a priority over family, friends, vocation, and material acquisition.

## Diagnostic Criteria of Gender Identity Disorder

Adults who permanently change their bodies to deal with their gender dilemmas represent the far end of the spectrum of adaptations to gender problems. Even the lives of those who reject bodily change, however, have considerable pain because the images of a better gendered self may recur throughout life, becoming more powerful whenever life becomes strained or disappointing.

The diagnosis of the extreme end of the gender identity disorder spectrum is clinically obvious. The challenging diagnostic task for clinicians is to suspect gender struggles when a patient's manner suggests a unisex or cross-gendered appearance, a dissociative identity disorder, severe forms of character pathology, and those who seem unusual based on a clinician's intuition.

To qualify for gender identity disorder (GID), four criteria must be met.

### Criterion 1: Strong, Persistent Cross-Gender Identification

Because young children may not verbalize enough about their inner experiences, for the clinician to be certain that this criterion is met, at least four of five manifestations of cross-gender identification must be present: (1) repeatedly stated desire to be, or insistence that he or she is, the opposite sex; (2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing stereotypical masculine clothing; (3) strong and persistent preferences for cross-gender roles in fantasy play or persistent fantasies of being the opposite sex; (4) intense desire to participate in the games and pastimes of the opposite sex; (5) strong preference for playmates of the opposite sex.

In adolescence and adulthood, this criterion is fulfilled when the patient states the desire to be the opposite sex, has frequent social forays into appearing as the opposite sex, desires to live or be treated as the opposite sex, or has the conviction that his or her feelings and reactions are those typical of the opposite sex.

### Criterion 2: Persistent Discomfort with One's Gender or the Sense of Inappropriateness in a Gender Role

This criterion is fulfilled in boys who assert that their penis or testicles are disgusting or will disappear or that it would be better not to have these organs; or who demonstrate an aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities. In girls, rejection of urinating in a sitting position or assertion that they do not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing fulfill this criterion.

Among adolescents and adults, this criterion is fulfilled by the patient's exhibiting the following characteristics: preoccupation with getting rid of primary and secondary sex characteristics; preoccupation with thoughts about hormones, surgery, or other alterations of the body to enhance the capacity to pass as a member of the opposite sex such as electrolysis for beard removal, cricoid cartilage shave to minimize the Adam's apple, breast augmentation; or preoccupation with the belief that one was born into the wrong sex.

### Criterion 3: Not Due to an Intersex Condition

In the vast majority of clinical circumstances, the patient possesses normal genital anatomy and sexual physiology. When a patient with a GID and an accompanying intersex condition such as congenital adrenal hyperplasia, an anomaly of the genitalia, or a chromosomal abnormality is encountered, the clinician will be uncertain whether the intersex condition is the cause of the GID because the vast majority of patients with intersex conditions do not meet criteria for GID (Diamond and Watson 2004). The clinician may either diagnose gender identity disorder not otherwise specified (GIDNOS) or list GID on Axis I and the intersex condition on Axis III.

### Criterion 4: Significant Distress and Impairment

It is likely that many children, adolescents, and adults struggle for a while to consolidate their gender identity but eventually find an adaptation that does not impair their capacities to function socially, academically, or vocationally as a member of their sex. These persons do *not* qualify for GID nor do those who simply are not stereotypic in how they portray their gender roles. Mental health professionals encounter parents who are disturbed by their adolescent child's gender roles. Parental distress is not the point of criterion 4; this criteion refers to patient distress.

## Diagnostic Criteria of GIDNOS

If an accurate community-based study of the gender-impaired could be conducted, most cases would be diagnosed as GIDNOS. The diagnostician needs to understand that gender identity development is a dynamic evolutionary process and clinicians get to see people at crisis points in their lives. At any given time, although it is clear that the patient has some form of GID, it may not be that which is described as GID. Here is one example: an adult female calls herself a "neuter." She wants her breasts removed because she hates to be perceived as a woman. For 2 years she has been exploring "neuterdom" and states that "I am definitely not interested in being a man!" She may be classified as GIDNOS.

GIDNOS is a large category designed to be inclusive of those with unusual genders who do not clearly fit the criteria of GID. There is no implication that if a patient is labeled GIDNOS his or her label cannot change. GIDNOS contains the many forms of transvestism: masculine-appearing boys and teenagers with persistent cross-dressing (former fetishistic transvestites) who are evolving toward GID, socially isolated men who want to become a woman shortly after their wives or mothers die (secondary transvestites) but express considerable ambivalence about the very matter they passionately desired at their last visit, extremely feminized homosexuals with careers as "drag queens" who seem to want to change their sex when depressed, and so on. GIDNOS would also capture men who want to be rid of their genitals without being feminized, unisexual females who imagine themselves as males but who are terrified of any social expression of their masculine gender identity, masculine lesbians in periodic turmoil over their gender, and those women who strongly identify with both male and female who want mastectomies. In using gender identity diagnoses, clinicians need to be mindful that the Axis I diagnosis is focused on gender identity/role not orientation. To dismiss a patient as merely homosexual is to not grasp the primacy of the patient's developmental problem.

Some patients with struggles over gender expression would not be either GID or GIDNOS. Some would diagnose this man as having a paraphilia.

**Clinical Vignette 3**

A couple married for 32 years sought help immediately after the wife unexpectedly returned home and discovered that her husband had been out in public dressed as a woman. She was certain that his public passing as a woman represented a worsening of his judgment. Thirty years before, he had revealed that he was sexually aroused by women's clothing and wanted to cross-dress for lovemaking. She adamantly refused to consider it. Since that incident, she never mentioned it again trying to act as though she was unaware of his "secret." Privately, she periodically worried that he was putting on her panty hose and bra to masturbate. Their sexual frequency declined after his initial request and, over the ensuing 20 years, she slowly developed an aversion to being touched by him. Sexual behavior ceased 10 years ago.

The 55-year-old masculine-appearing physical education teacher husband elected to enter individual therapy where he expressed his dilemma. He wanted to spare his wife pain. She believed that his "prurient" interest would go away if only he had more faith and prayed more, but he knew

*(continues)*

Clinical Vignette 3 *continued*

that nothing, including his fundamentalist religious patterns, diminished his periodic need to wear women's clothing. "If I tell her about my cross-dressing, she withdraws in anger. If I do not tell her about it, her imagination about how often I am doing it runs wild and she punishes me for cross-dressing that I don't do. If I stop cross-dressing, I deprive myself of unparalleled comfort and sumptuous pleasure and the desire eventually overtakes me. I lose either way. Should I honor my wife or my own identity?" His daily rate of masturbation has not changed much. He thinks he masturbates to cope with her refusal to have sexual behavior together. "My cross-dressing has actually kept me from having affairs with other women, thankfully."

Three factors point to the paraphilia Fetishistic Transvestism as a diagnosis: his arousal to female clothing was reported to have increased over time, he cross-dresses without a well-developed feminine identity, and he masturbates daily. Let us now add to this description his wife's new diagnoses of advanced ovarian cancer. As he copes with this bad news and helps her with the painful process of dying, within his privacy is stirring his need to increase his social presentation as a woman, his fantasies of having genital reconstruction, and his recognition that his grief is balanced by his opportunity to live as a woman soon. If the psychiatrist sees him after his wife's death, GIDNOS might appear to be the new diagnosis. Fetishistic Transvestism, GIDNOS, and GID can be evolutionary points in a person's life.

## The Relationship of GIDs to Orientation

The usual clarity of distinctions between heterosexual, bisexual, and homosexual orientations rests upon the assumption that the biological sex and psychological gender of the person and the partner are known. A woman who designates herself as a lesbian is understood to mean she is erotically attracted to other women. "Lesbian" loses its meaning if the woman says she feels she *is* a man and lives as one. She insists, "I am a heterosexual man; men are attracted to women as am I!" The clinician may erroneously think, "You are a female therefore you are a lesbian!" DSM-IV-TR suggests that adults with GID should be grouped according to which sex the patient is currently sexually attracted: males, females, both, or neither. This makes sense for most gender patients because it is their gender identity that is most important to them. Some are rigid about the sex of those to whom they are attracted because it supports their idea about their gender, others are bierotic and are not too concerned with their orientation, still others have not had enough experiences to overcome their uncertainty about their orientation. In the face of a gender identity diagnosis, orientation is more fluid than it usually is when gender identity is not an issue. Some gender patients find partners too complicated; they are only interested in themselves.

## Treatment Options for the GIDs

The treatment of these conditions, although not as based on rigorous scientific evidence, is scrutinized by multidisciplinary committees of specialists within the World Professional Association for Transgendered Health who periodically update their Standards of Care (Meyer et al. 2001). The treatment of any GID begins after a careful evaluation, including interviews with parents, other family members and spouses, psychometric testing, and occasionally physical and laboratory examination. The details will depend on the age of the patient. It is possible, of course, to have a GID as well as mental retardation, a psychosis, dysthymic disorder, severe character pathology, or any other psychiatric diagnosis (Table 77–8).

**Table 77–8 Steps in Evaluation of the Profoundly Gender Disordered***

Step One: Formal evaluation and diagnosis leads to either gender identity disorder or gender identity disorder NOS but effort should be made to assess whether another treatable psychiatric or physical disorder is present.

Step Two: Referral of patient for individual psychotherapy within the gender program or with an interested professional. Do the diagnoses remain the same? If yes, does the patient consistently want to:

- Discuss his (or her) situation but make no changes?
- Increase cross-dressing toward cross-living?
- Prepare the family for the real-life test?
- Obtain permission to proceed with hormones?

Step Three: Approval for hormones from a gender committee or on written recommendation from the psychiatrist to an endocrinologist. Individual or group psychotherapy should continue.

Step Four: Real-life test of living and working full time in the aspired-to-gender role for at least 1 year. Does the patient want to continue to surgery?

Step Five: Gender committee approval for surgery. Many patients have cosmetic surgery other than that listed with only ordinary patient–surgeon consent. This most often involves breast augmentation but may include numerous other attempts to improve ability to pass as opposite sex and be attractive.

- Men: genital reconstruction
- Women: mastectomy, hysterectomy, genital reconstruction

*Most patients will not complete all of these steps.

### Individual Psychotherapy

There is no psychotherapy technique to cure an adult's gender problem. People who have long lived with profound cross-gender identifications do not simply obtain insight, get behaviorally modified, or get medicated into a conventional gender identity. Psychotherapy can be useful, nonetheless. If the patient is able to trust a therapist, there can be much to talk about—family relationships are often painful, barriers to relationship intimacy are profound, work poses many difficult issues, and there is the matter of psychic reality. Perhaps gender change does not erase the psychic remnants of past history and characterologic features. Perhaps when the surgery is accomplished, loneliness will continue; particularly if family has been abandoned. What happens if the transsexual past causes others to avoid the patient? The patient naturally thinks about "How am I going to live my life if I don't go through with cross-gender living, hormone therapy, mastectomy, or genital surgery and if I do?" The therapist can help the patient recognize and respect previously unstated ambivalence. Completion of the gender transformation process usually takes longer than the patient

desires, and the therapist can be an important source of support during and after these changes. And then again, there are rare situations when psychotherapy seems to allow cross-gender preoccupations to disappear.

> Jim, a socially isolated 32-year-old chronically depressed homoerotic man, who was given numerous psychiatric diagnoses and many psychotropic regimens during his previous four impoverished years of near homelessness, sought help for his sometimes ego-alien, sometimes alluring, thoughts of becoming a woman. A high dose of clomipramine (Anafranil) and weekly psychotherapy enabled these thoughts to disappear and, thus far, not return in 4 years. The therapy focused on the death of his parents, the lack of a nurturing person in his life, and the fantasy that someone would love him—perhaps one of those unattainable attractive men he sees but cannot speak to. Now on lithium, alprazolam, and tranylcypromine, the patient is able to work productively and has lost his hostile paranoid attitude toward his few remaining relatives. He is no longer bothered by the presence of his penis, no longer dreams of being a woman, and no longer searches the Internet for transgendered information. He is by no means healthy. He hoards, his apartment is filled with garbage, he refuses access to everyone, and talks about moving to a new city where a male lover will be found.

## Group Therapy

Group therapy for gender-disordered people has the advantages of allowing patients to know others with gender problems, of decreasing their social isolation, and of being among people who do not experience their cross-gender aspirations and their past behaviors as weird. Group members can provide help with grooming and more convincing public appearances. The success of these groups depends on the therapist's skills. In recent years, the groups have morphed into self-help groups without a therapist.

## "Real-Life Experience or Test"

Living in the aspired-to-gender role—working, relating, conducting the activities of daily living—is a vital process that enables one of three decisions to be made: to abandon the quest, to simply live in this new role, or to proceed with breast or genital surgery (Petersen and Dickey 1995). Some clinicians use the real-life test as a criterion for recommending hormones but this varies because some patients' abilities to present themselves in a new way are definitely enhanced by prior administration of cross-sex hormones. The reason for the real-life experience is to give the patient, who created a transsexual solution in fantasy, an opportunity to experience the solution in reality. The real-life experience should improve the patient's psychological function. If it does not, the clinician and patient have to be wary of gender transition.

## Hormone Therapy

Ideally, hormones should be administered by endocrinologists who have a working relationship with a mental health team dealing with gender problems. The effects of administration of estrogen to a biological male are as follows: breast development, testicular atrophy, decreased sexual drive, decreased semen volume and fertility, softening of skin, fat redistribution in a female pattern, and decrease in spontaneous erections. Breast development is often the highest concern to the patient. Because hair growth is not affected by estrogens, electrolysis or laser treatments are used to remove beard growth. Side effects within recommended doses include hypertension, hyperglycemia, lipid abnormalities, thrombophlebitis, and hepatic dysfunction. Patients should therefore be monitored regularly. The most dramatic effect of hormones is on the sense of well-being, which is so quickly apparent through patients' reports of feeling calmer and happier knowing that their bodies are being demasculinized and feminized that clinicians have wondered what a placebo-controlled study might demonstrate.

The administration of androgen to females results in an increased sexual drive, clitoral tingling and growth, weight gain, and amenorrhea and hoarseness. An increase in muscle mass may be apparent if weight training is undertaken simultaneously. Hair growth depends on the patient's genetic potential. Androgens are administrated intramuscularly 200–300 mg/month. It is prudent to periodically monitor hepatic, lipid, and thyroid functioning. Most patients are delighted with their bodily changes. Breast size does not significantly regress on androgens.

## Surgical Therapy

Surgical intervention is the final external step. It should not occur without a mental health professional's input, even when the patient provides a heart-felt convincing set of reasons to bypass the real-life test, hormones, and psychotherapy. Genital surgery is expensive, time-consuming, at times painful, and has frequent anatomic complications and functional disappointments. Surgery has the potential to add further improvements in the lives of patients—more social activities with friends and family, more activity in sports, more partner sexual activity, and improved vocational status (Mate-Kole et al. 1990). Thousands of patients worldwide have received surgery. Following them systematically over time to ascertain their short-, medium-, and long-term adjustments have proven elusive, however. Nonetheless, there are specialists who are quite positive (Pfafflin 2003) and those who are more skeptical (Carroll 1999).

### Males

Surgery consists of penectomy, orchiectomy, vaginoplasty, and fashioning of labia. The procedures used for the creation of a neovagina have evolved over the years. Postoperatively, the patient must maintain the patency of the neovagina by initially constantly wearing and then periodically using a vaginal dilator. Vaginal stenosis or shortening is a frequent complication. The quest for an unmistakable feminine shape leads many young adult patients to augmentation mammoplasty and the shaving of the cricoid cartilage.

### Females

The creation of a male-appearing chest through mastectomies and contouring of the chest wall requires only a brief hospital stay. Patients are usually immediately delighted with their newfound freedom, but their fantasies of going shirtless are often not fulfilled due to the presence of two noticeable horizontal chest scars. The creation of a neophallus that

can become erect, contain a functional urethra throughout its length (enabling urination while standing), and pass as an unremarkable penis in a locker room has been a significant surgical challenge and is far from being perfected. The surgery is, however, the most time-consuming, technically difficult, and expensive of all the sex reassignment procedures. Erection is made possible by a penile prosthesis. Many prudent patients consider themselves reassigned when they have a hysterectomy, oophorectomy, and mastectomy. Some just have a mastectomy. They find a partner who understands the situation and supports the idea of living with, and loving with, female genitals.

Ongoing controversy about sex reassignment surgery is ultimately based on the overarching principle of medical ethics, "Above all, do not harm." The removal of healthy tissue, which GID specialists argue helps rather than harms the patient, creates a distinct countertransference avoidance of working with this community of patients. Negative countertransference needs to be recognized and its roots appreciated by both sides in the endless controversy about how to care for people who entertain bodily transformations for their distress over gender.

## THE PARAPHILIAS

A paraphilia is a disorder of intention, the final component of sexual identity to develop in children and adolescents. Intention refers to what individuals want to do with a sexual partner and what they want the partner to do with them during sexual behavior. Normally, the images and the behaviors of intention are characterized by peaceable mutuality. The disorders of intention are recognized by unusual eroticism (images) and often socially destructive behaviors such as sex with children, rape, exhibitionism, voyeurism, masochism, obscene phone calling, or sexual touching of strangers. Only about 5% of the diagnoses of paraphilia are given to women raising the question whether there are unrecognized forms of female paraphilia (Beier 2000). All etiologic speculations of paraphilia try to explain how male sexual development has gone awry. Accounts of paraphilic behaviors have been in general literatures for centuries, but they have been of psychiatric interest only since 1905 (Freud 1905). Freud thought of the paraphilias as deviations in the aim of the sexual instinct. He coined the term by combining the Greek words for "along the side" (*para*) and "love" (*philia*). In 1905, paraphilia denoted those fixed preferences for sexual behaviors that led to forms of orgasmic attainment other than the uniting of penis and vagina.

Now it is apparent that paraphilias occur among individuals of all orientations and among those with conventional and unconventional gender identities. A homosexual sadist is paraphilic only on the basis of sexual cruelty. A transsexual who desires to be beaten during arousal is paraphilic only on the basis of masochism.

### Three General Characteristics of the Paraphilias

#### A Long-standing, Unusual, Highly Arousing Erotic Preoccupation

Erotic intentions that are recent in origin, conventional, and somewhat exciting may be problematic in some way but they are typically *not* clearly paraphilic. The sine qua non of the diagnosis of paraphilia is unusual, often hostile or demeaning dehumanized eroticism, which has preoccupied the patient for most of his adolescent and adult life. The paraphilic fantasy is often associated with this preoccupying arousal when it occurs in daydreams and masturbation reveries or is encountered in explicit films or magazines. The specific imagery varies from one paraphilic patient to the next, but both the imagined behavior and its implied relationship to the partner are unusual. This often means that it is suffused with overt or subtle forms of aggression such as the wish to hurt a child the way he was hurt when he was at a particular age. Paraphilias may be unusual also in that the focus is not actually about a partner—it is about an inanimate thing such as clothing or about the image of the self as a woman. Images of rape, obscene phone calling, exhibitionism, and touching of strangers are rehearsals of victimization. In masochistic images, the aggression is directed at the self; for instance, autoerotic strangulation, slavery, torture, spanking. In others, the aggression is well disguised as *love* of children or teenagers. In some, however, aggression is absent. Aggression is so apparent in most paraphilic content, however, that when none seems to exist, the clinician needs to wonder whether it is actually absent or being hidden from the doctor. Paraphilic fantasies often rely heavily upon the image of a partner who does not possess "personhood." Some imagery in fact has no pretense of a human partner at all; clothing, animals, or excretory products are the focus. Other themes such as preoccupation with feet or hair combine both human and inanimate interests. Paraphilic images are usually devoid of any pretense of caring or human attachment. The hatred, anger, fear, vengeance, or worthlessness expressed in them requires no familiarity with the partner. Paraphilic images are conscious—clearly known to the individual. They should not be confused with speculations about "unconscious" aggression or sadomasochism that some assume are part of all sexual behavior. Clinicians should expect to occasionally see paraphilic patients whose preoccupations are not hostile to others.

An individual's paraphilic themes often change in intensity or seem to change in content from time to time. The stimuli for these changes often remain unclear. It is a moot point whether such changes should be considered a shift to a different disorder, a new paraphilia, or a natural evolution of the basic problem. The shifts from imagining talking "dirty" on the phone in order to scare a woman to imagining raping can be considered an intensification of sadism. Switches between sadism and masochism or voyeurism and exhibitionism are common. Changes from voyeurism to pedophilia or from pedophilia to rape, however, raise the question whether a new disorder has developed. The most socially significant shifts are from erotic imagery to sexual behavior. In most instances, it is reasonable to consider that paraphilia is a basic developmental disorder in which particular erotic and sexual manifestations are shaped by the individuality of the person's history.

Most paraphilic adults can trace their fantasy themes to puberty and many can remember these images from earlier years. When adolescent rapists or incest offenders are evaluated, they often are able to report prepubertal aggressive erotic preoccupations. Men who report periodic paraphilic imagery interspersed with more usual eroticism

have had their paraphilic themes from childhood or early adolescence. To make a diagnosis of paraphilia, the patient must evidence at least 6 months of the unusual erotic preoccupation. Duration is usually not in question, even among adolescents, however (Shaw 1999).

### Pressure to Act Out the Fantasy

To be paraphilic often means that the erotic imagery exerts a pressure to play out the often imagined scene. In its milder forms, the pressure results merely in a preoccupation with a behavior. For instance, a man who prefers to be spoken to harshly and dominated by his wife during sex thinks about his masochistic images primarily around their sexual behaviors. He does not spend hours daydreaming of his erotic preferences. In its more intense forms, paraphilias create a *drivenness* to act out the fantasy in sexual behavior—usually in masturbation while wearing panty hose, tying a ligature around his neck, or inserting a dildo into the rectum while spanking himself. Frequent masturbation, often more than once daily, continues long after adolescence and generally exceeds the rate found in most men his age. In the most severe situations, the need to attend to the fantasy and masturbate is so overpowering that life's ordinary activities cannot efficiently occur. Masturbation and sometimes partner-seeking behavior—such as finding a woman to shock through exhibiting an erection—is experienced as driven. The patient reports either that he cannot control his behavior or he controls it with such great effort that his work, study, parenting, and relationships are disrupted. This pressure to behave sexually often leads the man to believe he has a high sex drive. Some severe paraphilics describe their masturbation-to-orgasm frequencies as 10/day. Even when the patient's estimate of his frequency of orgasm strains credulity less, the return of sexual drive manifestations so soon after orgasm (Kafka 2000) suggests that either something is wrong with the patients' sexual drive generator, their satiety mechanisms, or that their existential anxiety overpowers their other defense mechanisms.

Paraphilic men often report collecting and viewing pornography, visiting sexual bookstores to see explicit videos or peep shows, frequenting prostitutes for their special sexual behaviors, downloading explicit images from the Internet, or extensively using telephone sex services or strip clubs. Victimization of others, while certainly a serious public health problem, is the least common form of sexual acting out but it is by no means rare (Abel et al. 1987). When the behavioral diagnosis of exhibitionism, pedophilia, or sadism is made in an individual charged with a sex offense, the clinician should assume that the numbers of victims far exceed the number stated in the criminal charges.

Two other diagnostic sounding terms, compulsive sexual behavior and sexual addiction, are informally and synonymously used to refer to heterosexual and homosexual men and women who display an intense drivenness to behave sexually without paraphilic imagery. The personal, interpersonal, and medical consequences of paraphilic and nonparaphilic sexual compulsivity seem indistinguishable as do their usual psychiatric comorbidities: depression, anxiety disorders, substance abuse, and attention deficit disorders (Kafka 1997). Legal consequences of nonparaphilic compulsivity may involve arrests for soliciting prostitution.

### Partner Sexual Dysfunction

A sexual dysfunction involving desire, arousal, or orgasm with a partner, although not invariably present among paraphilics, is common. The wives of paraphilics tell stories with these themes: "He is not interested in sex with me." "He never initiates." "He doesn't seem to enjoy our sexual life together except when…." "He is usually not potent." "Even when we do make love, he rarely ejaculates." Some paraphilic men, however, are able to function well without paraphilic fantasies but others are either able to primarily function when their partners are willing to meet their special requirements for arousal or when they fantasize about their paraphilic script.

## Speculations About the Underlying Problem

Paraphilia has been considered in 15 somewhat different ways, depending on era, ideology, and region: (1) an impairment in the bonding function of sexuality; (2) a courtship disorder; (3) the erotic form of hatred motivated by the need for revenge for childhood trauma; (4) a fixation to childhood misunderstandings that women had penises and that men could lose theirs during sex (castration anxiety); (5) the unsuccessful repair of early life passive, helpless experiences with a terrifying, malignant, malicious preoedipal mother; (6) a strategy to stabilize a conventional masculine or feminine gender identity; (7) a strategy to deny the differences between the sexes and the generations of child and parent; (8) an outcome of childhood sexual abuse; (9) a consequence of far less than ideal parent–child relationships; (10) a soft neurological sign of a neural wiring defect; (11) a released behavior due to cerebral pathology—for example, temporal lobe dysfunction, or substance abuse; (12) the sexual face of an addiction disorder; (13) an unusual manifestation of an affective disorder; (14) an obsessive–compulsive spectrum disorder; (15) a defective self-system requiring a patch—that is, a sexual preoccupation—to shore up the private, carefully-hidden-from-others sense of inadequate subjective masculinity.

Whatever its ultimate psychopathogenesis and nature, the paraphilias are sexual identity disorders that generally make normal erotic and sexual loving unattainable. Culture asks us to have some image of attachment, some ability to neutralize anger toward others, some ability to contain the anxiety over closeness, and some psychological motive to simultaneously enhance the self and the partner through sexual contact. Ordinary intentions aim for peaceable mutuality between real people; paraphilic ones aim at aggressive one-sidedness. Impaired masculinity is another phrase that conveys a persistent subjective sense of sexual identity. Some paraphilic men will acknowledge that they do not feel entirely masculine or that their paraphilic activities bolster their sense of masculinity. "I am far more reliably potent when I cross-dress…hurt a woman…think of myself as a woman receiving a penis in my vagina, etc." This sexual identity disorder could be referred to as a disorder of self, specifically of that part of the self that maintains a sense of masculinity. Paraphilics often bear an enigmatic paradox between what they want to be and what they are. They often hunger for a behavior that feels sick or uncontrollable and that robs them of autonomy. This is why the behaviors are often thought of as addictions and are often associated with other forms of substance abuse, obsessive–compulsive phenomena, and affective symptoms. Relative to the dynamic

fluctuations of sexual dysfunctions, intention disorders are tenacious throughout life.

Classic studies of psychiatric epidemiology have never investigated the prevalence of paraphilia. The rise of the Internet, which provides something for every erotic taste, has also helped some men to discover their intense excitement over images that they previously only dimly imagined. Thus, the Internet may subtly increase the prevalence of paraphilic eroticism.

## The Specific Paraphilias

### Criminal Sex Offending Behaviors

#### Exhibitionism

Exhibitionism generally involves teenagers and men displaying their penises so that the witness will be shocked or (in the paraphilic's fantasy) sexually interested. They may or may not masturbate during or immediately following this act of victimization. This diagnosis is not usually made when a man is arrested for "public indecency" and his penile exposures are motivated to arrange homosexual contact in a public place generally unseen by heterosexuals. Penile display in parks is one way to make anonymous contact. The presence or absence of exhibitionistic imagery allows the clinician to make the distinction between paraphilia and homosexual courting. Clinicians should not assume that men with homosexual orientations cannot suffer from exhibitionism.

Clinical Vignette 4

A 43-year-old married policeman was incarcerated after evidence linked him to six rapes. Five years prior to his arrest, he described to his psychotherapist the adolescent beginning of a lifelong erotic form of stalking. He masturbated to images of following woman years before he began to incorporate rape into the scenario. He spent much of his leisure time selecting women visually, finding out about them, and following them. The vast majority of his "victims" were never aware of his stalking behaviors, but these behaviors fuelled his more than daily masturbation. He claimed and his wife confirmed that for most of their marriage he had no apparent sexual interest in her. Superficially, he was a stalker, but the aim of stalking was sadistic dominance, fear-inducing rape.

#### Pedophilia

Pedophilia is the most widely and intensely socially repudiated of the paraphilias. Pedophiles are men who erotically and romantically prefer children or prepubertal adolescents. They are grouped into categories depending upon their erotic preferences for boys or girls and for infant, young, or pubertal children. There is some confusion between when a prepubertal child is an adolescent. Society, though not the DSM-IV-TR, thinks of a pedophile as a person who sexually targets a minor and therefore prosecutes under this term adults who target adolescents. Some pedophiles have highly age- and sex-specific tastes, others are less discriminating. Since the diagnosis of any paraphilia including pedophilia requires recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children over a period of at least 6 months, the disorder should not be expected to be present in every person who is guilty of child molestation. Some intrafamilial child abuse occurs over a shorter time interval and results from combinations of deteriorated marriages, sexual deprivation, sociopathy, and substance abuse. Child molestation, whether paraphilic or not, is a crime, however. Child molesters show several patterns of erectile responses to visual stimulation in the laboratory. Some have their largest arousal to children of a specific age and others respond to both children and adults (Marshall et al. 2006). These tests, however, cannot alone be relied upon for the diagnosis. Some recognized that pedophiles can pass phallometric and visual response time examinations—that is, appear to be interested in only adolescents and adults. (The ordinary heterosexual responds both to adolescents and adults.) Some pedophiles respond with their greatest arousal to aggressive cues.

#### Voyeurism

Men whose sexual life consists of watching homosexual or heterosexual videos in sexual bookstores occasionally come to psychiatric attention after being charged with a crime following a police raid. The voyeurs who are more problematic for society are those who watch women through windows or break into their dwellings for this purpose. Some of these crimes result in rape or nonsexual violence, but many are motivated by pure voyeuristic intent (which is subtly aggressive).

DSM-IV-TR Criteria

**Voyeurism**

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving the act of observing an unsuspecting person who is naked, in the process of disrobing, or engaging in sexual activity.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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#### Sexual Sadism

While rape is an extreme variety of sadism, paraphilic sadism is present only in a minority of rapists. It is defined by the rapist's prior use of erotic scripts that involve a partner's fear, pain, humiliation, and suffering. Rapists, whether paraphilic or not, are highly dangerous men whose antisocial behaviors are generally thought to be unresponsive to ordinary psychiatric methods. Their violence poten-

**DSM-IV-TR Criteria**

**Sexual Sadism**

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving acts (real, not simulated) in which the psychological or physical suffering (including humiliation) of the victim is sexually exciting to the person.
B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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tial often makes psychiatric therapy outside of institutions imprudent. Noncriminal paraphilic sadism—that is, arousal to images of harming another that has not crossed into the behavioral realm, can be treated in outpatient settings. The most common form of sexual sadism is found among those who enjoy sadomasochistic sexual practices. Some can enjoy either the dominant or the submissive role while others are exclusively controlling and pain or fear inducing. Those who study murderers have long recognized a subset of sadistic murderers who torture their victims prior to killing them.

## Frotteurism

Frotteurism, the need to touch and rub against nonconsenting persons, although delineated as a criminal act, is probably better understood as the most socially benign form of paraphilic sadism. Frotteurism often occurs in socially isolated men who become sexually driven to act out. They often are unaware of how frightening they can be.

**DSM-IV-TR Criteria**

**Frotteurism**

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving touching and rubbing against a nonconsenting person.
B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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## Stalking

Stalking is the latest erotic preoccupation to be criminalized. Forensic psychiatry has defined various motivations for arrested stalkers, including those who have made the transition from romantic to violent preoccupation with the victim. Stalking is particularly frightening because murder occasionally results. It is likely that stalking as a behavior is the product of further deterioration of an already compromised mind, although not necessarily a paraphilic one. Some stalkers are found to be sexual sadists.

Clinical Vignette 5

A 45-year-old married mustached corporate middle manager and father of four sons ages 16–25 years, sought help for 3 years of consistent, and a decade of episodic, erectile dysfunction with his wife. He often failed to find their sexual behavior deeply satisfying. What concerned him more immediately, however, were his "addictions" to masturbation and watching homosexual pornography and his preoccupations with providing fellatio and receiving anal intercourse, and thoughts of having intercourse with women entertainers of different races. Ever since he arranged for a man to perform fellatio on him 3 years ago and he found it to be the most thrilling sex of his life, he has been unable to get homosexual imagery out of his mind. His masturbation dramatically increased (he began to masturbate at work) and he began having images of receiving anal penetration (sometimes accompanied by inserting his finger into his anus). He began cruising bookstores looking for mustached, handsome, masculine men with whom to perform and receive fellatio. His participation in Sex and Love Addicts Anonymous meetings had become insincere; the stories he heard greatly excited him and he worried that his befriending others often just led to negotiations for sex. His sexual experiences with his wife now could only be maintained by the fantasy that he was with a man. He reported that a previous therapist, after hearing about his periodic adolescent homoerotic fantasies and his 3 years of cruising, told him during their first session, "Face it. You are simply gay." This greatly distressed the patient. When, during the second visit, he sensed that the therapist might have been trying to seduce him, he decided not to return.

Treatment with a serotonergic agent dramatically diminished his erotic preoccupations. After months of dramatic benefit from this "miracle," he began to periodically stop the medication so that his homoerotic thoughts would return and he could cruise for homosexual sex on business trips. His discussions in twice-monthly, half-hour therapy eventually led to more motivation to engage in sex with his wife and eventually his potency with her improved. He could not, however, dependably ejaculate in her vagina. He was able to masturbate to orgasm in her presence after he brought her to numerous orgasms during intercourse. He preferred not to recall his thwarted hunger for closeness to his mustached father, his two molestation experiences with a priest as a 16-year-old, and his feelings about his sons' emerging sexual expressions. When his and his wife's best male friend died from a malignancy within 6 weeks of initial diagnosis, he experienced an upsurge in compulsivity that kept him from thinking about his loss.

"I don't think I am simply gay. I don't like the gay lifestyle. I can't stand effeminacy in men! My good life with my family and in the corporation would be destroyed. I don't even think of me that way. I am some kind of bisexual. I just love homosexual sex. I want to suck and be sucked. I think it would be great to be screwed up the ass. But I'm too afraid of AIDS to do it. I'd like to screw a woman rock star or two, but that is probably not very likely." At various times, his mental state could accurately be described as largely depressed, anxious, paranoid, obsessive, compulsive, or dissociated. He feels that dishonesty with his wife is the best policy even when she inquires whether he is a homosexual. At various times, this man's sexual and other psychiatric diagnoses changed. His homosexual desire and his social repudiation of homosexual living put him in a profound lasting dilemma. Over time, he came to more clearly understand and accept the nature of his erectile dysfunction with his wife and its total absence with men. His life illustrates that there is more to a person's sexual life than can be captured by a diagnosis.

Here is an 8-year follow-up. Married still, a grandfather several times over, still working for the same corporation, he has come to recognize that he is far more homosexual than heterosexual, is disinterested in sex with his wife who still accuses him of being gay because of his sexual dysfunctions and his pleasures in traveling, and has had differential response to sildenafil. Sildenafil barely works with his wife who also takes it for her own inability to stay aroused with her husband. Sildenafil routinely enhances his sexual capacity with a man. He actually does not need it with a male partner but uses it with a sense of enhancement. Mustached men still excite him but he has sex with other men without disappointment. He loves anal sex and occasionally permits condomless contact. These invariably create months of obsession about getting AIDS and repeated HIV testing. "Let's face it," he recently told me, "I'm gay but I never want anyone in my family to ever discover it."

## Noncriminal Forms of Paraphilia

Because the individual manifestations of paraphilia depend on the particular individual life history of the affected, over 150 paraphilic categories have been identified. Most fall into variations of those listed in the DSM-IV-TR but there are relatively rare exceptions. All convey an unusual means of attaining arousal during masturbation or consenting partner behaviors. They range widely from the bizarre to the more "reasonable" and from the common to the unique. They often subtly combine elements of more than one paraphilia.

### Fetishism

Fetishism, the pairing of arousal with wearing or holding an article of clothing or inanimate object such as an inflatable doll, has a range of manifestations from infantilism in which a person dresses up in diapers to pretend he is a baby to the far more common use of a female undergarment for arousal purposes. Fetishism when confined to one garment for decades is classified as a paraphilia, but many cases involve more complex varieties of cross-dressing and overlap with GIDNOS. Transvestic fetishism is the diagnosis used when it is apparent that the urges to use the clothing of the opposite sex is part of a larger mental preoccupation with that sex.

### Sexual Masochism

Sexual masochism is diagnosed over a range of behaviors from the sometimes fatal need to nearly asphyxiate oneself to the request to be spanked by the partner in order to be excited. Masochism may be the most commonly reported or acknowledged form of female paraphilia, although it is more common among men. Sadists and masochists sometimes find one another and work out an arrangement to act out their fantasies and occasionally reverse roles. Large city coroners usually encounter a few deaths a year of males or females that seemed to have accidentally died of asphyxia. The males usually are found cross-dressed. When no paraphilic erotica or paraphernalia is found, they are left to speculate that the victim may have simply been experimenting with a ligature to see if the idea that orgasm can be intensified by anoxia is correct.

**DSM-IV-TR Criteria**

**Fetishism**

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving the use of nonliving objects (e.g., female undergarments).

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The fetish objects are not limited to articles of female clothing used in cross-dressing (as in transvestic fetishism) or devices designed for the purpose of tactile genital stimulation (e.g., a vibrator).

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### Paraphilia Not Otherwise Specified

Paraphilia not otherwise specified is a DSM-IV-TR category for other endpoints of abnormal sexual development that lead to preoccupations with other paraphilic stimuli, including amputees, feces, urine, sexualized enemas, sex with animals, sex with the dead, etc.

## Treatment

Four general approaches are employed to treat the paraphilias. The treatments are typically multimodal in application (Marshall et al. 2006).

**DSM-IV-TR Criteria**

**Sexual Masochism**

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving the act (real, not simulated) of being humiliated, beaten, bound, or otherwise made to suffer.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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**DSM-IV-TR Criteria**

**Transvestic Fetishism**

A. Over a period of at least 6 months, in a heterosexual male, recurrent intense sexually arousing fantasies, sexual urges, or behaviors involving cross-dressing.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* if:

With gender dysphoria: if the person has persistent discomfort with gender role or identity

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## Evaluation Only

Evaluation only is selected when the evaluator concludes that the paraphilia is benign in terms of society, the patient will be resistant to the other approaches, and does not suffer greatly in terms of social and vocational functioning in ways that might be improved. Often these are isolated men with private paraphilic sexual pleasures, such as telephone sex with a masochistic scenario.

## Psychotherapy

What constitutes psychotherapy for paraphilia heavily depends on the training of the therapist. Therapy can assist in changing, at least temporarily, the erotic script of a patient. There is great controversy about the ability of criminal paraphilic minds to be changed. All treatments over the years have tended to most strongly resemble cognitive–behavioral interventions. They can be highly useful in diminishing paraphilic intensifications and gradually teaching the t better management techniques of the situations that have triggered acting out. Treatment techniques often include attempting to interrupt paraphilic arousal via pairing masturbatory excitement with either aversive imagery or aversive stimuli, social skills training, assertiveness training, and confrontation with the rationalizations that are used to minimize awareness of the victims of sexual crimes, and marital therapy (Abel and Osborn 1995). The self-help movement has created 12-step programs for sexual addictions to which many individuals now belong. Group psychotherapy is offered by trained therapists as well. When the lives of paraphilics are illuminated in various therapies, it becomes apparent that the emotional pain of the patients is thought to be great; the sexual acting out is often perceived as a defense against recurrent unpleasant emotions from any source. These often, however, involve self-esteem and attachment anxiety or anxiety over closeness.

## Medications

In the early 1980s, depo-medroxy-progesterone (Provera) was first used to treat those who were constantly masturbating, seeking out personally dangerous sexual outlets, or committing sex crimes. The weekly 400–600 mg injections often led to the men being able to work, study, or participate in activities that were previously beyond them because of concentration or attention difficulties. In the late 1980s, the use of oral Provera, 20–120 mg/day led to similar results: the drug enabled these men to leave their former state in which their sexual needs took priority over other life demands, and they did not have depo-Provera's side effect profile—weight gain, hypertension, muscle cramps, and gynecomastia. Today, gonadotrophin-releasing blockers such as leuprolide acetate (Lupron) are occasionally used for this purpose (Kreuger and Kaplan 2001). The possible side effects are similar to oral Provera. Despite the fact that the clinical results are among the most powerfully effected by any psychopharmacologic treatment, many psychiatrists cannot overcome their disinclination to give a "female" hormone to a man or to work with patients who victimize others sexually. Serotonergic agents are now more commonly used as a first line of treatment and their administration, of course, creates fewer countertransference obstacles. While these studies are the result of open labeled series of cases without placebo control groups, the SSRIs are in widespread use for compulsive sexual behaviors and sexual obsessions. Their efficacy is the source of the speculation that some of the paraphilias may be an obsessive–compulsive spectrum disorder.

## External Controls

Sexual advantage-taking, whether it be by a paraphilic physician with his patients, by a pedophilic mentally retarded man in the neighborhood, or of a grandfather who has abused several generations of his offspring, can often be stopped by making it *impossible* for these behaviors to be unknown to most people in his life. The doctor's staff can be told, the neighbors can know, the family can meet to discuss the current crisis and review who has been abused over the years and plan to never allow grandfather alone with any child in or outside the family. The concept of external control is taken over by the judicial system when sex crimes are highly repugnant or heinous. The offender is removed from society for punishment and the protection of the public. This includes physicians who have sexually abused patients.

Psychiatrists need to be realistic about the limitations of various therapeutic ventures. Sexual acting out may readily continue during therapy beyond the awareness of the therapist. The more violent and destructive the paraphilic behavior is to others, the less the therapist should risk ambulatory treatment. Unfortunately, outside of a few forensic mental hospitals and occasion prisons, there are limited inpatient treatment program for sex offenders, paraphilic or not. Since paraphilia occurs in patients with other psychiatric conditions, the psychiatrist needs to remain vigilant that the treatment program is comprehensive and does not lose sight of the paraphilia just because the depressive or obsessive–compulsive symptoms are improved. Paraphilia may be improved by medications and psychotherapy but the clinician should expect that the intention disorder is the patient's lasting vulnerability.

## SEXUAL DISORDER NOT OTHERWISE SPECIFIED

If the clinician is uncertain about how to categorize a person's problem, it is more reasonable to use this diagnosis than one that does not encompass the range of the patient's suffering. Sexual disorder not otherwise specified can be used when the therapist perceives a dramatic interplay between issues of sexual identity and sexual dysfunction, or when "everything" seems to be amiss. DSM-IV-TR, however, encourages the clinician to make multiple sexual diagnoses involving, for instance, a GID, a desire disorder, erectile, and orgasmic disorder.

DSM-IV-TR provides three examples when it would be appropriate to use the diagnosis sexual disorder NOS: (1) nonparaphilic compulsive sexual behaviors—that is, relentless pursuit of masturbatory or heterosexual or homosexual partner experiences without evidence of paraphilic imagery; (2) distress about a pattern of repeated sexual relationships involving a succession of lovers who are experienced by the individual only as things to be used; (3) persistent and marked distress about sexual orientation. Despite the removal of homosexuality from the DSM in 1974, men (particularly) and women still generate symptoms in their struggle to balance the demands of their homoeroticism with their ambitions to participate in conventional family life. This ongoing struggle can generate a variety of anxiety, depressive, compulsive, substance abusing, and suicidal states.

Sexual addiction, sexual compulsivity, or the loss of control of sexual behavior is quite common clinically. Clinical contacts with this as a chief complaint have soared in the last decade in response to access to Internet pornography. Treatment for these patterns ranges from 30-day self-pay inpatient 12-stepped modeled programs to self-help groups. Psychiatrists should be cognizant of the relationship between other addictions and unrecognized hypomanic states among these patients.

### The Doctor–Patient Relationship and Sexual Disorders

The main task is to become comfortable listening to sexual stories. Sexual concerns are extremely common in the general population and are more prevalent among those burdened by psychiatric disorders (Dennerstein 2003, Figueira et al. 2001, Kennedy et al. 1999). Although psychiatrists are skillful in assessing individual patients with major psychiatric disorders, we are not nearly as relaxed and confident about our capacities to respond to sexual complaints. Society regards a person's sexuality as an intensely private subject—so private that most people do not have a sufficient vocabulary to describe their own sexual lives. Psychiatrists grow up with these characteristics as well. Most psychiatrists experience a conscious countertransference barrier to exploring sexual issues in detail. This barrier consists of

1. the fear of personal or patient sexual arousal while talking about sex,
2. the fear of not knowing what relevant questions to ask,
3. the fear of not knowing how to help with these problems,
4. the fear of the sudden appearance of awareness of one's own sexual concerns,
5. the fear of having one's moral repugnance show to the patient (Risen 2003).

Excellent training in biological psychiatry has come at the expense of psychotherapy training. This has created the illusion that professional comfort with sexual life is no longer a clinical requirement. Most psychiatrists have no experience with a mentor who has demonstrated that the ordinary fears about dealing with sexual topics can be readily mastered and many patients can be helped through calm perspective-giving psychotherapy.

## FINAL THOUGHTS

A specific diagnosis like vaginismus or GIDNOS does not, per se, dictate the type and course of therapy. The clinician is called upon to weigh many factors in planning treatment. Accurate diagnosis is a vital first step but it quickly gives way to other, more artful considerations. "What factors set up this problem and what forces maintain it? What is the essence of this situation? What does this diagnosis mean in ordinary human terms? Can medication play a useful role? How am I to help? What am I to say? When and how should I say it?" These are essentially psychotherapy considerations. The sexual disorders challenge the doctor to integrate the advances of modern psychiatry with the traditions of less biologically oriented psychiatry and the knowledge accumulating in forensic settings for the purpose of seeing if the patient's distress can be lastingly altered. In this challenge, clinical science inevitably gives way to clinical art. The art involves enabling the patient's distress to make sense so that the underlying struggle—the developmental task—can be successfully negotiated.

### Comparison of DSM-IV-TR/ICD-10 Diagnostic Criteria

For hypoactive sexual desire disorder, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are essentially identical except that ICD-10 specifies a minimum duration of at least 6 months (DSM-IV-TR has no minimum duration).

The ICD-10 Diagnostic Criteria for Research for Sexual Aversion Disorder differs from the DSM-IV-TR criteria in

several ways. In contrast to DSM-IV-TR, which restricts the condition to the aversion to, and avoidance of, sexual genital contact, ICD-10 also includes presentations characterized by sexual activity resulting in "strong negative feelings and an inability to experience any pleasure." Furthermore, ICD-10 excludes cases in which the aversion is due to performance anxiety. Finally, ICD-10 specifies a minimum duration of at least 6 month whereas DSM-IV-TR does not specify any minimum duration.

For female sexual arousal disorder and male erectile disorder, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are essentially equivalent except that ICD-10 specifies a minimum duration of at least 6 months. ICD-10 includes a single category ("Failure of Genital Response") with two separate criteria sets by gender. In contrast, DSM-IV-TR includes two separate categories.

For female and male orgasmic disorders, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are essentially equivalent except that ICD-10 specifies a minimum duration of at least 6 months. In contrast to DSM-IV-TR, which has male and female versions defined separately, ICD-10 has a single category that applies to both genders.

For premature ejaculation, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are essentially equivalent except that ICD-10 specifies a minimum duration of at least 6 months. Similarly, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria for dyspareunia and vaginismus are essentially equivalent except that ICD-10 specifies a minimum duration of at least 6 months. Furthermore, these conditions are referred to in ICD-10 as "Nonorganic Dyspareunia" and "Nonorganic Vaginismus."

The definition of a paraphilia is essentially the same in DSM-IV-TR and ICD-10. However, ICD-10 does not include a separate category for Frotteurism and has a combined "Sadomasochism" category.

For GID, ICD-10 defines three separate disorders: "Gender Identity Disorder of Childhood," "Dual-role Transvestism," and "Transsexualism" all of which are included under the single DSM-IV-TR category Gender Identity Disorder.

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CHAPTER

# 78 Eating Disorders

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Anorexia Nervosa
Bulimia Nervosa

## Introduction

In the current psychiatric nomenclature of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), the eating disorders consist of two clearly defined syndromes: anorexia nervosa and bulimia nervosa. Many individuals presenting for treatment of an eating disorder (Figure 78–1) fail to meet formal criteria for either anorexia nervosa or bulimia nervosa, which raises an important theoretical and practical question: What is an eating disorder? Although this topic has received surprisingly little attention, it has been suggested that a working definition of an eating disorder might be "a persistent disturbance of eating behavior or behavior intended to control weight, which significantly impairs physical health or psychosocial functioning" (Fairburn and Walsh 2002). This definition clearly encompasses the recognized disorders, anorexia nervosa and bulimia nervosa. In addition, it provides a basis for viewing eating disorders as clinically significant problems that may not meet criteria for anorexia nervosa or bulimia nervosa. The term atypical eating disorder is often applied to such problems, even though the number of individuals suffering from them may well outnumber those with "typical" eating disorders. One example of an atypical eating disorder is that of women who are overly concerned about their weight, have dieted to a below-normal weight, but have not ceased menstruating and, therefore, do not meet full criteria for anorexia nervosa. Another is that of individuals who binge and vomit regularly, but at less than the twice-a-week frequency required for bulimia nervosa.

An additional example of a clinically important atypical eating disorder is the occurrence of frequent binge-eating that is not followed by the self-induced vomiting or other inappropriate attempts to compensate, which are characteristic of bulimia nervosa. This disturbance, for which the name binge-eating disorder has been proposed (DSM-IV-TR appendix B) (Yanovski 1993), is a common behavioral pattern among obese individuals who present for treatment at weight loss clinics.

At present, obesity is not considered an eating disorder. Obesity refers to an excess of body fat and is viewed as a general medical, not a psychiatric, condition. Although there is increasing interest in the role of the brain in the development and persistence of obesity, at this stage of our knowledge, obesity is conceived as an etiologically heterogeneous condition, influenced by cultural, environmental, and innate biological factors. It seems appropriate to describe as having an eating disorder only those obese individuals who manifest a clear behavioral abnormality that impairs health or psychosocial functioning have an eating disorder (Devlin, in press).

## ANOREXIA NERVOSA

### Diagnosis

#### Definition and Diagnostic Features

##### History

The syndrome of anorexia nervosa was clearly recognized and, in fact, named in the late nineteenth century. Almost simultaneously, Sir William Gull in England and Charles Lasègue in France described series of cases of young women with impressive weight loss and psychological disturbance. Gull termed this illness "anorexia nervosa" and Lasègue—*anorexie hystérique*. The salient clinical features described more than 100 years ago are remarkably similar to those presented by patients in the opening years of the twenty-first century.

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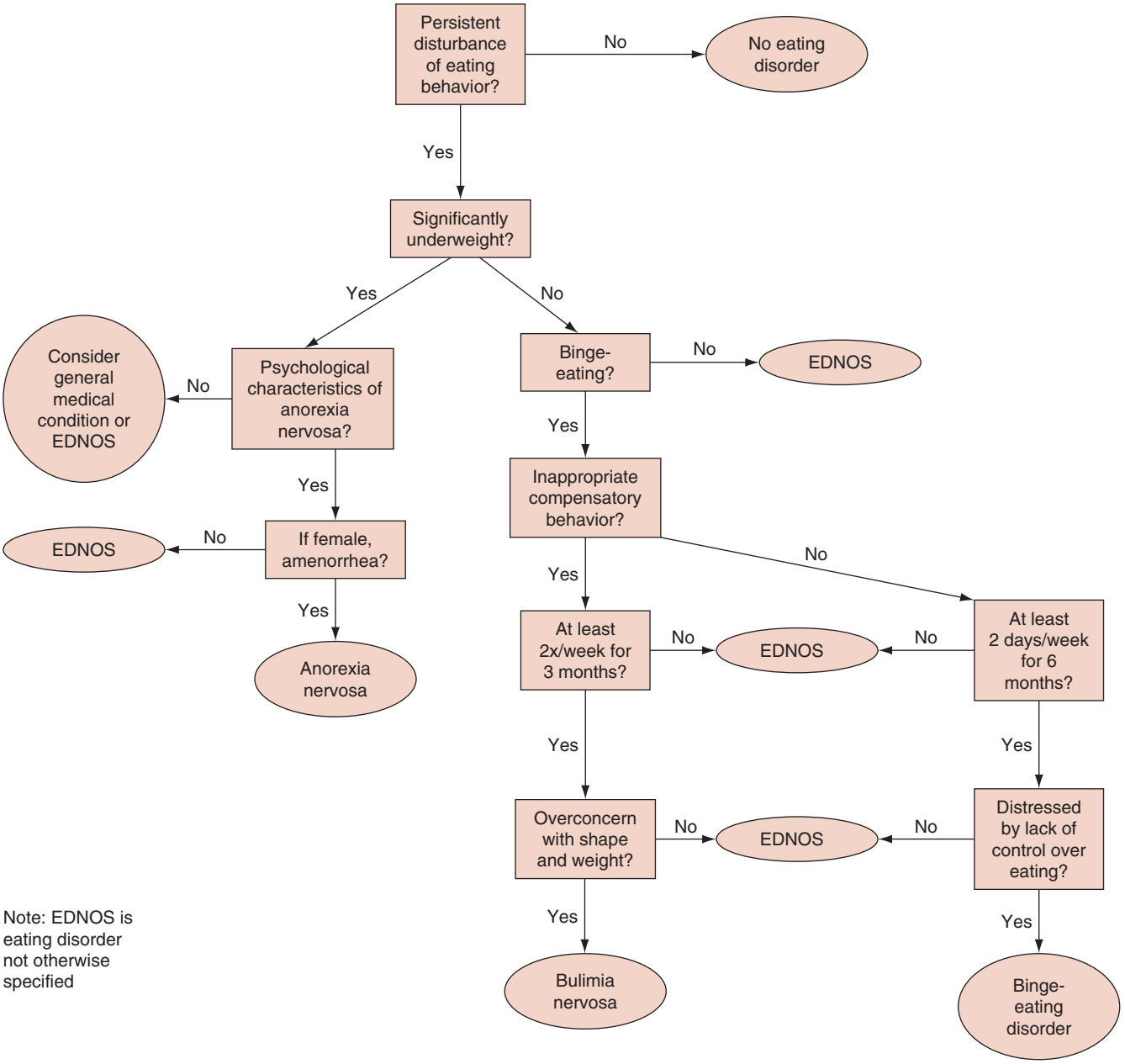



**Figure 78–1** *Algorithm for diagnosis of eating disorders.*

It is likely that cases of anorexia nervosa were also recognized well before the nineteenth century. In 1689, in a Treatise on Consumptions, Richard Morton (1689) described an 18-year-old girl with amenorrhea and self-imposed weight loss that he attributed to "a multitude of cares and passions of her mind"; this young woman eventually died of her illness, which Morton termed "nervous consumption" to emphasize its important psychological determinants. Bell (1985) has suggested that the fasting and asceticism of some medieval saints might today be viewed as manifestations of an eating disorder (Figure 78–2). Anorexia nervosa's long history suggests that although changing cultural norms for what is viewed as esthetically desirable may have played a role in increasing the frequency of anorexia nervosa, they do not fully explain the occurrence of the syndrome.

## Definition

The DSM-IV-TR criteria require the individual to be significantly underweight for age and height. Although it is not possible to set a single weight loss standard that applies equally to all individuals, DSM-IV-TR provides a benchmark of 85% of the weight considered normal for age and height as a guideline. Despite being of an abnormally low body weight, individuals with anorexia nervosa are intensely afraid of gaining weight and becoming fat, and remarkably, this fear typically intensifies as the weight falls.

DSM-IV-TR criterion C requires a disturbance in the person's judgment about his or her weight or shape. For example, despite being underweight, individuals with anorexia nervosa often view themselves or a part of their body as being too heavy. Typically, they deny the grave medical risks engendered by their semistarvation and place




**Figure 78–2** *Engraving of St. Catherine of Siena, whose religious practices bore some resemblance to anorexia nervosa. [Reproduced from Bedoyere (1947).]*

enormous psychological importance on whether they have gained or lost weight. For example, someone with anorexia nervosa may feel intensely distressed if her or his weight increases by half a pound. Finally, criterion D requires that women with anorexia nervosa be amenorrheic.

The DSM-IV-TR criteria for anorexia nervosa are generally consistent with recent definitions and descriptions of this illness. In addition, in DSM-IV-TR, a new subtyping scheme was introduced. DSM-IV-TR suggests that individuals with anorexia nervosa be classed as having one of two variants, either the binge-eating/purging type or the restricting type. Individuals with the restricting type of anorexia nervosa do not engage regularly in either binge-eating or purging and, compared with individuals with the binge-eating/purging form of the disorder, are not as likely to abuse alcohol and other drugs, exhibit less mood lability, and are less active sexually.

## Assessment

In assessing individuals who may have anorexia nervosa, it is important to obtain a weight history, including the individual's highest and lowest weights and the weight he or she would like to have now. For women, it is useful to know the weight at which menstruation last occurred, because it provides an indication of what weight is normal for that individual. The patient should be asked to describe a typical day's food intake and any food restrictions and dietary practices such as vegetarianism. The psychiatrist should ask whether the patient ever loses control over eating and engages in binge-eating and, if so, the amounts and types of food eaten during such episodes. The use of self-induced vomiting, laxatives, diuretics, enemas, diet pills, and syrup of ipecac to induce vomiting should also be queried.

**DSM-IV-TR Criteria**

**Anorexia Nervosa**

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).

B. Intense fear of gaining weight or becoming fat, even though underweight.

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)

*Specify* type:

**Restricting type:** during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

**Binge-eating/purging type:** during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

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Probably the greatest problem in the assessment of patients with anorexia nervosa is their denial of the illness and their reluctance to participate in an evaluation. A straightforward but supportive and nonconfrontational style is probably the most useful approach, but it is likely that the patient will not acknowledge significant difficulties in eating or with weight and will rationalize unusual eating or exercise habits. It is therefore helpful to obtain information from other sources such as the patient's family.

### Physiological Disturbances

An impressive array of physical disturbances has been documented in anorexia nervosa, and the physiological bases of many are understood (Walsh 2005) (Table 78–1). Most of these physical disturbances appear to be secondary consequences of starvation, and it is not clear whether or how the physiological disturbances described here contribute to the development and maintenance of the psychological and behavioral abnormalities characteristic of anorexia nervosa.

**Table 78–1 Medical Problems Commonly Associated with Anorexia Nervosa**

| |
|---|
| Skin |
| Lanugo |
| Cardiovascular system |
| Hypotension |
| Bradycardia |
| Arrhythmias |
| Hematopoietic system |
| Normochromic, normocytic anemia |
| Leukopenia |
| Diminished polymorphonuclear leukocytes |
| Fluid and electrolyte balance |
| Elevated blood urea nitrogen and creatinine concentrations |
| Hypokalemia |
| Hyponatremia |
| Hypochloremia |
| Alkalosis |
| Gastrointestinal system |
| Elevated serum concentration of liver enzymes |
| Delayed gastric emptying |
| Constipation |
| Endocrine system |
| Diminished thyroxine level with normal thyroid-stimulating hormone level |
| Elevated plasma cortisol level |
| Diminished secretion of luteinizing hormone, follicle-stimulating hormone, estrogen, or testosterone |
| Bone |
| Osteoporosis |

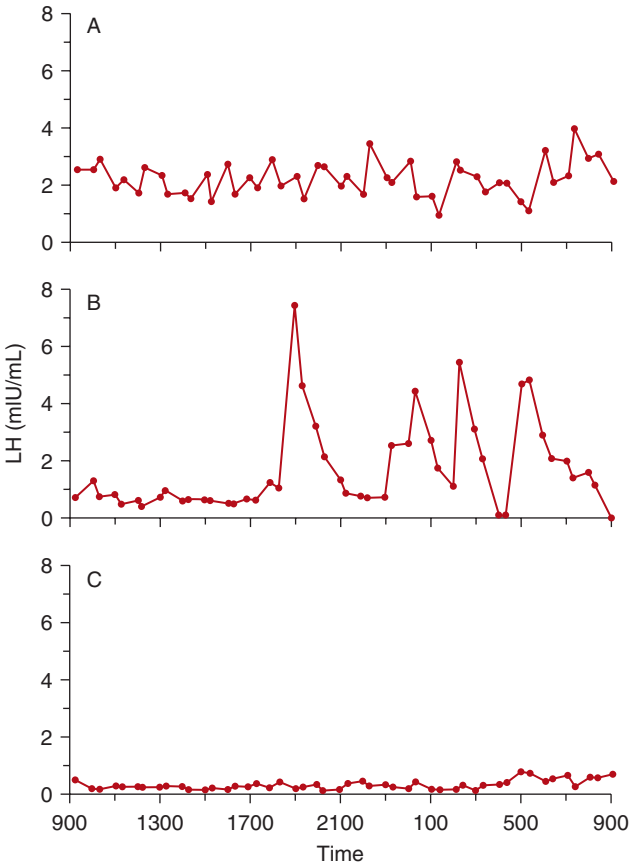



**Figure 78–3** *Patterns of 24-hour luteinizing hormone (LH) secretion of a normal adult woman (a), of a woman with anorexia nervosa showing a pattern normally seen in adolescence (b), and of a woman with anorexia nervosa showing a pattern normally seen before puberty (c).*

This section briefly describes the major physical abnormalities of anorexia nervosa and what is understood about their etiology.

The central nervous system is clearly affected. Computed tomography has demonstrated that individuals with anorexia nervosa have enlarged ventricles, an abnormality that improves with weight gain. It appears that disturbances in serotonergic pathways are present both in the underweight state and following recovery, suggesting that serotonergic abnormalities may play a role in predisposing individuals to the development of anorexia nervosa (Kaye et al. 2005).

Some of the most striking physiological alterations in anorexia nervosa are those of the hypothalamic–pituitary–gonadal axis. In women, estrogen secretion from the ovaries is markedly reduced, accounting for the occurrence of amenorrhea. In analogous fashion, testosterone production is diminished in men with anorexia nervosa. The decrease in gonadal steroid production is due to a reduction in the pituitary's secretion of the gonadotropins luteinizing hormone and follicle-stimulating hormone, which in turn is secondary to diminished release of gonadotropin-releasing hormone from the hypothalamus. Therefore, the amenorrhea of anorexia nervosa is properly viewed as a type of hypothalamic amenorrhea. These changes appear mediated to a substantial degree by marked reductions in the serum level of leptin, reflecting undernutrition and decreased body fat mass.

In an adult with anorexia nervosa, the status of the hypothalamic–pituitary–gonadal axis resembles that of a pubertal or prepubertal child—the secretion of estrogen or testosterone, of luteinizing hormone and follicle-stimulating hormone and of gonadotropin-releasing hormone, is reduced. This endocrinological picture may be contrasted with that of postmenopausal women who have a similar reduction in estrogen secretion but who, unlike women with anorexia nervosa, show increased pituitary gonadotropin secretion. Furthermore, even the circadian patterns of luteinizing hormone and follicle-stimulating hormone secretion in adult women with anorexia nervosa closely resemble the patterns normally seen in pubertal and prepubertal girls (Figure 78–3). Although similar abnormalities are also seen in other forms of hypothalamic amenorrhea and are therefore not specific to anorexia nervosa, it is nonetheless striking that this syndrome is accompanied by a physiological arrest or regression of the reproductive endocrine system.

The functioning of other hormonal systems is also disrupted in anorexia nervosa, although typically not as profoundly as is the reproductive axis. Presumably as part of the metabolic response to semistarvation, the activity of the thyroid gland is reduced. Plasma thyroxine levels are somewhat diminished, but the plasma level of the pituitary hormone and thyroid-stimulating hormone is not elevated. The activity of the hypothalamic–pituitary–adrenal axis is increased, as indicated by elevated plasma levels of cortisol and resistance to dexamethasone suppression. The regulation of vasopressin (antidiuretic hormone) secretion from the posterior pituitary is disturbed, contributing to the development of partial diabetes insipidus in some individuals.

Anorexia nervosa is often associated with the development of leukopenia and of a normochromic, normocytic anemia of mild-to-moderate severity. Surprisingly, leukopenia does not appear to result in a high vulnerability to infectious illnesses. Serum levels of liver enzymes are sometimes elevated, particularly during the early phases of refeeding, but the synthetic function of the liver is rarely seriously impaired so that the serum albumin concentration and the prothrombin time are usually within normal limits. Serum cholesterol levels are sometimes elevated in anorexia nervosa, although the basis of this abnormality remains obscure. In some patients, self-imposed fluid restriction and excessive exercise produce dehydration and elevations of serum creatinine and blood urea nitrogen. In others, water loading may lead to hyponatremia. The status of serum electrolytes is a reflection of the individual's salt and water intake and the nature and severity of the purging behavior. A common pattern is hypokalemia, hypochloremia, and mild alkalosis resulting from frequent and persistent self-induced vomiting.

It has become clear that individuals with anorexia nervosa have decreased bone density compared with age- and sex-matched peers and, as a result, are at increased risk of fractures. Low levels of estrogen, high levels of cortisol, and poor nutrition have been cited as risk factors for the development of reduced bone density in anorexia nervosa. Theoretically, estrogen treatment might reduce the risk of osteoporosis in women who are chronically amenorrheic because of anorexia nervosa, but controlled studies indicate that this intervention is of limited, if any, benefit.

Abnormalities of cardiac function include bradycardia and hypotension, which are occasionally symptomatic. The pump function of the heart is compromised, and congestive heart failure occasionally develops in individuals during overly rapid refeeding. The electrocardiogram shows sinus bradycardia and a number of nonspecific abnormalities. Arrhythmias may develop, often in association with fluid and electrolyte disturbances. It has been suggested that significant prolongation of the QT interval may be a harbinger of life-threatening arrhythmias in some individuals with anorexia nervosa, but this has not been conclusively demonstrated.

The motility of the gastrointestinal tract is diminished, leading to delayed gastric emptying and contributing to complaints of bloating and constipation. Rare cases of acute gastric dilatation or gastric rupture, which is often fatal, have been reported in individuals with anorexia nervosa who consumed large amounts of food when binge-eating.

As already noted, virtually all of the physiological abnormalities described in individuals with anorexia nervosa are also seen in other forms of starvation, and most improve or disappear as weight returns to normal. Therefore, weight restoration is essential for physiological recovery. More surprisingly, perhaps, weight restoration is believed to be essential for psychological recovery as well. Accounts of human starvation amply document the profound impact of starvation on mental health. Starving individuals lose their sense of humor and interest in friends and family fades, and mood generally becomes depressed. They may develop peculiar behavior similar to that of patients with anorexia nervosa, such as hoarding food or concocting bizarre food combinations. If starvation disrupts psychological and behavioral functioning in normal individuals, it presumably does so as well in those with anorexia nervosa. Thus, correction of starvation is a prerequisite for the restoration of both physical and psychological health.

### Physical Examination and Laboratory Findings

The patient should be weighed, or a current weight should be obtained from the patient's general physician. Blood pressure, pulse, and body temperature are often below the lower limit of normal. On physical examination, lanugo, a fine, downy hair normally seen in infants, may be present on the back or the face. The extremities are frequently cold and have a slight red-purple color (acrocyanosis). Edema is rarely observed at the initial presentation but may develop transiently during the initial stages of refeeding.

The basis for laboratory abnormalities is presented in the earlier section on physiological disturbances. Common findings are a mild-to-moderate normochromic, normocytic anemia and leukopenia, with a deficit in polymorphonuclear leukocytes leading to a relative lymphocytosis. Elevations of blood urea nitrogen and serum creatinine concentrations may occur because of dehydration, which can also artificially elevate the hemoglobin and hematocrit. A variety of electrolyte abnormalities may be observed, reflecting the state of hydration and the history of vomiting and diuretic and laxative abuse. Serum levels of liver enzymes are usually normal but may transiently increase during refeeding. Cholesterol levels may be elevated.

The electrocardiogram typically shows sinus bradycardia and, occasionally, low QRS voltage and a prolonged QT interval; a variety of arrhythmias have also been described.

## Epidemiology

Anorexia nervosa is a relatively rare illness. Even among high-risk groups, such as adolescent girls and young women, the point prevalence of strictly defined anorexia nervosa is only about 0.5%. The prevalence rates of partial syndromes are substantially higher (Van Hoeken et al. 1998). Some, but not all, studies suggest that its incidence has increased significantly during the last 50 years, a phenomenon usually attributed to changes in cultural norms regarding desirable body shape and weight.

Anorexia nervosa usually affects women; the ratio of men to women is approximately 1:10 to 1:20. Anorexia nervosa occurs primarily in industrialized and affluent countries, and some data suggest that, even within those countries, anorexia nervosa is more common among the higher socioeconomic classes. Some occupations, such as ballet dancing and fashion modeling, appear to confer a particularly high risk for the development of anorexia nervosa. Thus, anorexia nervosa appears more likely to develop in an environment in which food is readily available but in which, for women, being thin is somehow equated with higher or special achievement.

## Comorbidity Patterns

Symptoms of mood and anxiety disturbances, especially obsessive–compulsive disorder, are commonly observed among individuals with anorexia nervosa. These symptoms improve substantially with weight gain but often do not resolve completely. Some individuals, especially those with the binge/purge subtype, may also have problems with substance abuse.

## Course

### Onset

Anorexia nervosa often begins innocently. Typically, an adolescent girl or young woman who is of normal weight or, perhaps, a few pounds overweight decides to diet. This decision may be prompted by an important but not extraordinary life event, such as leaving home for camp, attending a new school, or a casual unflattering remark by a friend or family member. Initially, the dieting seems no different from that pursued by many young women, but as weight falls, the dieting intensifies. The restrictions become broader and more rigid; for example, desserts may first be eliminated, then meat, and then any food that is thought to contain fat. The person becomes increasingly uncomfortable if she is seen eating and avoids meals with others. Food seems to assume a moral quality so that vegetables are viewed as "good" and anything with fat is "bad." The individual has idiosyncratic rules about how much exercise she must do, and when, where, and how she can eat.

Food avoidance and weight loss are accompanied by a deep and reassuring sense of accomplishment, and weight gain is viewed as a failure and a sign of weakness. Physical activity, such as running or aerobic exercise, often increases as the dieting and weight loss develop. Inactivity and complaints of weakness usually occur only when emaciation has become extreme. The person becomes more serious and devotes little effort to anything but work, dieting, and exercise. She may become depressed and emotionally labile, socially withdrawn, and secretive, and she may lie about her eating and her weight. Despite the profound disturbances in her view of her weight and calorie needs, reality testing in other spheres is intact, and the person may continue to function well in school or at work. Symptoms usually persist for months or years until, typically at the insistence of friends or family, the person reluctantly agrees to see a professional.

### Natural History

The course of anorexia nervosa is enormously variable. Some individuals have mild and brief illnesses and either never come to medical attention or are seen only briefly by their pediatrician or general medical physician. It is difficult to estimate the frequency of this phenomenon because such individuals are rarely studied.

Most of the literature on course and outcome is based on individuals who have been hospitalized for anorexia nervosa. Although such individuals presumably have a relatively severe illness and adverse outcomes, a substantial fraction, probably between one-third and one-half, makes full and complete psychological and physical recoveries. On the other hand, anorexia nervosa is also associated with an impressive long-term mortality. The best data currently available suggest that 10–20% of patients who have been hospitalized for anorexia nervosa will, in the next 10–30 years, die as a result of their illness. Much of the mortality is due to severe and chronic starvation, which eventually terminates in sudden death. In addition, a significant fraction of patients commit suicide.

Between these two extremes are a large number of individuals whose lives are impaired by persistent difficulties with eating. Some are severely affected, maintaining a chronic state of semistarvation, bizarre eating rituals, and social isolation; others may gain weight but struggle with bulimia nervosa and strict rules about food and eating; and still others may recover initially but then relapse into another full episode. There is a high frequency of depression among individuals who have had anorexia nervosa and a significant frequency of drug and alcohol abuse, but psychotic disorders develop only rarely. Thus, in general, individuals either recover or continue to struggle with psychological and behavioral problems that are directly related to the eating disorder. It is of note that it is rare for individuals who have had anorexia nervosa to become obese.

It is difficult to specify factors that account for the variability of outcome in anorexia nervosa. A significant body of experience suggests that adolescents with a short duration of illness have the best prognosis, but there are also suggestions that prepubertal onset may portend a difficult course. It is likely that the severity of the illness (e.g., the lowest weight reached and the number of hospitalizations) and the presence of associated symptoms, such as binge-eating and purging, also contribute to poor outcome. However, it is impossible to predict course and outcome in an individual with any certainty.

## Differential Diagnosis

In general, anorexia nervosa is not difficult to recognize. Uncertainty surrounding the diagnosis sometimes occurs in young adolescents who may not clearly describe a drive for thinness and the fear of becoming fat. Rather, they may acknowledge only a vague concern about consuming certain foods and an intense desire to exercise. It can also be difficult to elicit the distorted view of shape and weight (criterion C) from patients who have had anorexia nervosa for many years. Such individuals may state that they realize they are too thin and may make superficial efforts to gain weight, but they do not seem particularly concerned about the physical risks or deeply committed to increasing their calorie consumption.

Although depression, schizophrenia, and obsessive–compulsive disorder may be associated with disturbed eating and weight loss, it is rarely difficult to differentiate these disorders from anorexia nervosa. Individuals with major depression may lose significant amounts of weight but do not exhibit the relentless drive for thinness characteristic of anorexia nervosa. In schizophrenia, starvation may occur because of delusions about food, for example, that it is poisoned. Individuals with obsessive–compulsive disorder may describe irrational concerns about food and develop rituals related to meal preparation and eating but do not describe the intense fear of gaining weight and the pervasive wish to be thin that characterize anorexia nervosa.

A wide variety of medical problems cause serious weight loss in young people and may at times be confused with anorexia nervosa. Examples of such problems include gastric outlet obstruction, Crohn's disease, and brain tumors. Individuals whose weight loss is due to a general medical illness generally do not show the drive for thinness, the fear of gaining weight, and the increased physical activity characteristic of anorexia nervosa. However, the psychiatrist is well advised to consider any chronic medical illness associated with weight loss, especially when evaluating individuals with unusual clinical presentations such as late age at onset or prominent physical complaints, for example, pain and gastrointestinal cramping while eating.

### Differences in Presentation

The symptoms of anorexia nervosa are remarkably homogeneous, and differences between patients in clinical manifestations are fewer than in most psychiatric illnesses. Younger patients may not express verbally the characteristic fear of fatness or the overconcern with shape and weight, and some patients with long-standing anorexia nervosa may express a desire to gain weight but be unable to make persistent changes in their behavior. It has been suggested that in other cultures, the rationale given by patients for losing weight differs from the fear of fatness characteristic of cases in North America. For example, the features of weight phobia, fear of fatness, and pursuit of thinness have been described as being absent in some patients in Hong Kong and India who, in other regards, present symptoms that closely resemble those of anorexia nervosa; reasons for food refusal given by such patients include lack of appetite and epigastric bloating (Keel and Klump 2003).

Men have anorexia nervosa far less frequently than women. However, when the syndrome does develop in a man, it is typical.

## Etiology and Pathophysiology

### Introduction

At present, the etiology of anorexia nervosa is fundamentally unknown. However, from several sources, it is possible to identify risk factors whose presence increases the likelihood of anorexia nervosa. It is also possible to describe the course and complications of the syndrome and to suggest interactions between features of the disorder, for example, between malnutrition and psychiatric illness. Thus, as indicated in Figure 78–4, the difficulties that lead to the development of anorexia nervosa may be distinct from the forces that intensify the symptoms and perpetuate the illness once it has begun.

### Genetic Factors

Anorexia nervosa occurs more frequently in biological relatives of patients who present with the disorder. The prevalence rate of anorexia nervosa among sisters of patients is estimated to be approximately 6%; the morbid risk among other relatives ranges from 2% to 4%. Some evidence for a genetic component in the etiology of anorexia nervosa comes from twin studies, which reported substantially higher concordance rates for monozygotic than for dizygotic twin pairs (Klump et al. 2001). However, conclusive data for genetic transmission of the disorder are not yet available.

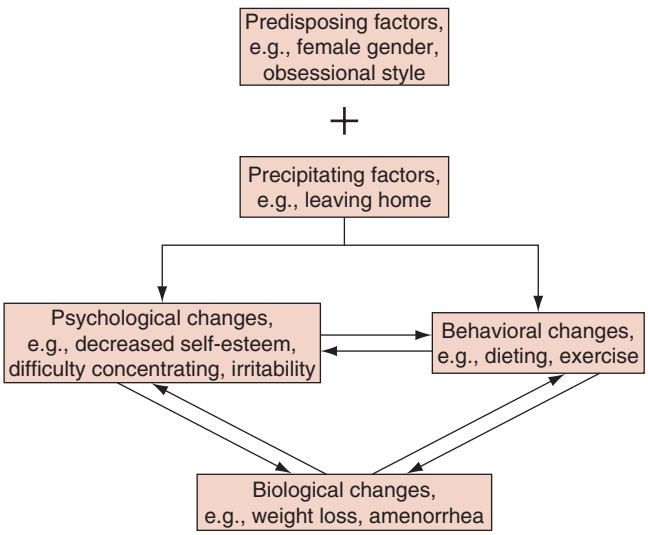



**Figure 78–4** *Schematic diagram illustrating how an interplay of factors may lead to the initiation and persistence of anorexia nervosa.*

### Developmental Factors

Because anorexia nervosa typically begins during adolescence, developmental issues are thought to play an important etiological role. Critical challenges at this time of life include the need to establish independence, a well-defined personal identity, fulfilling relationships, and clear values and principles to govern one's life. Family struggles, conflicts regarding sexuality, and pressures regarding increased heterosexual contact are also common. However, it is not clear that difficulties over these issues are more salient for individuals who will develop anorexia nervosa than for other adolescents. Depression has been implicated as a nonspecific risk factor, and higher levels of depressive symptoms as well as insecurity, anxiety, and self-consciousness have been documented in adolescent girls in comparison with adolescent boys. Similarly, the progression of physical and sexual maturation and the concomitant increase in women's percentage of body fat may have a substantial impact on the self-image of adolescent girls, particularly because the relationship between self-esteem and satisfaction with physical appearance and body characteristics is stronger in women than in men.

### Psychological Factors

#### Psychological Functioning

Various psychoanalytic theories have been postulated (e.g., defense against fantasies of oral impregnation, underlying deficits in the development of object relations, and deficits in self-structure), but such hypotheses are difficult to verify. Bruch (1973, 1982) suggested that anorexia nervosa stems from failures in early attachment, attempts to cope with underlying feelings of ineffectiveness and inadequacy, and an inability to meet the demands of adolescence and young adulthood. These ideas, as well as her conceptualization that the single-minded focus on losing weight in anorexia nervosa is the concrete manifestation of a struggle to achieve a sense of identity, purpose, specialness, and control, are compelling and clinically useful. Cognitive–behavioral theories emphasize the distortions and dysfunctional thoughts (e.g., dichotomous thinking) that may stem from various causal factors, all of which eventually focus on the belief that it is essential to be thin.

#### Personality Traits

Although the existence of a specific predisposing personality style has not been conclusively documented, certain traits have commonly been reported among women with anorexia nervosa. Women hospitalized for anorexia nervosa have greater self-discipline, conscientiousness, and emotional caution than women hospitalized for bulimia nervosa and women with no eating disorders (Casper et al. 1992). In addition, even after they have recovered from their illness, women who have had anorexia nervosa tend to avoid risks and to exhibit high levels of caution in emotional expression

and strong compliance with rules and moral standards (Srinivasagam et al. 1995).

### Familial Factors

Individual psychiatric disorders in parents, dysfunctional family relationships, and impaired family interaction patterns have been implicated in the etiology of anorexia nervosa. Mothers of individuals with anorexia nervosa are often described as overprotective, intrusive, perfectionistic, and fearful of separation; fathers are described as withdrawn, passive, emotionally constricted, obsessional, moody, and ineffectual. Family system theorists have suggested that impaired family interactions such as pathological enmeshment, rigidity, overprotectiveness, and difficulties confronting and resolving conflicts are central features of anorexic pathology (Minuchin et al. 1978). However, few empirical studies have been conducted to date, particularly studies that also examine psychiatrically or medically ill comparison groups. Therefore, the precise role of the family in the development and course of anorexia nervosa, although undoubtedly important, has not been clearly delineated.

## Social/Environmental Factors

It has been suggested that an increased prevalence of anorexia nervosa is related to the current emphasis in contemporary Western society on an unrealistically thin appearance in women. There is substantial evidence that a desire to be slim is common among middle- and upper-class white women and that this emphasis on slimness has increased significantly during the past several decades. In the USA, anorexia nervosa develops more frequently in white adolescents than in adolescents from other racial groups. A variety of characteristics may protect African-American girls from developing eating disorders, including more acceptance of being overweight, more satisfaction with their body image, and less social pressure regarding weight (Striegel-Moore et al. 2003).

It has also been suggested that the emphasis of contemporary Western society on achievement and performance in women, which is a shift from the more traditional emphasis on deference, compliance, and unassertiveness, has left many young women vulnerable to the development of eating disorders such as anorexia nervosa. These multiple and contradictory role demands are embodied within the modern concept of a superwoman who performs all of the expected roles (e.g., is competent, ambitious, and achieving, yet also feminine, nurturing, and sexual) and, in addition, devotes considerable attention to her appearance (Gordon 2000). Other authors have noted that the core features of anorexia nervosa have been described in other cultural settings, indicating that the current societal emphasis on thinness is not a necessary precondition for the development of this syndrome (Keel and Klump 2003).

# Treatment

## Goals of Treatment

The first goal of treatment is to engage the patient and her or his family. For most patients with anorexia nervosa, this is challenging. Patients usually minimize their symptoms and suggest that the concerns of the family and friends, who have often been instrumental in arranging the consultation, are greatly exaggerated. It is helpful to identify a problem that the patient can acknowledge, such as weakness, irritability, difficulty concentrating, or trouble with binge-eating. The psychiatrist may then attempt to educate the patient regarding the pervasive physical and psychological effects of semistarvation and about the need for weight gain if the acknowledged problem is to be successfully addressed.

A second goal of treatment is to assess and address acute medical problems, such as fluid and electrolyte disturbances and cardiac arrhythmias. Depending on the severity of illness, this may require the involvement of a general medical physician.

The additional but most difficult and time-consuming goals are the restoration of normal body weight, the normalization of eating, and the resolution of the associated psychological disturbances. The final goal is the prevention of relapse.

## Initiation of Treatment

A common major impediment to the treatment of patients with anorexia nervosa is their disagreement with the goals of treatment; many of the features of their illness are simply not viewed by patients as a problem. In addition, this may be compounded by a variety of concerns of the patient, such as basic mistrust of relationships, feelings of vulnerability and inferiority, and sensitivity to perceived coercion. Such concerns may be expressed through considerable resistance, defiance, or pseudocompliance with the psychiatrist's interventions and contribute to the power struggles that often characterize the treatment process. The psychiatrist must try to avoid colluding with the patient's attempts to minimize problems but at the same time allow the patient enough independence to maintain the alliance. Dealing with such dilemmas is challenging and requires an active approach on the part of the psychiatrist. In most instances, it is possible to preserve the alliance while, nonetheless, adhering to established limits and the need for change.

The initial stage of treatment should be aimed at reversing the nutritional and behavioral abnormalities (Figure 78–5). The intensity of the treatment required and the need for partial or full hospitalization should be determined by the current weight, the rapidity of weight loss, and the severity of associated medical and behavioral problems and other symptoms such as depression. In general, patients whose weights are less than 75% of expected should be viewed as medically precarious and require intensive treatment such as hospitalization.

## Weight Restoration

Most inpatient or day-treatment units experienced in the care of patients with anorexia nervosa use a structured treatment approach that relies heavily on supervision of calorie intake by the staff. Patients are initially expected to consume sufficient calories to maintain weight, usually requiring 1500–2000 kcal/day in four to six meals. After the initial medical assessment has been completed and weight has stabilized, calorie intake is gradually increased to an amount necessary to gain 2–5 lb/week. Because the consumption of approximately 4000 kcal beyond maintenance requirements is needed for each pound of weight gain, the daily calorie requirements become impressive, often in the range of 4000 kcal/day. Some eating disorder units provide only

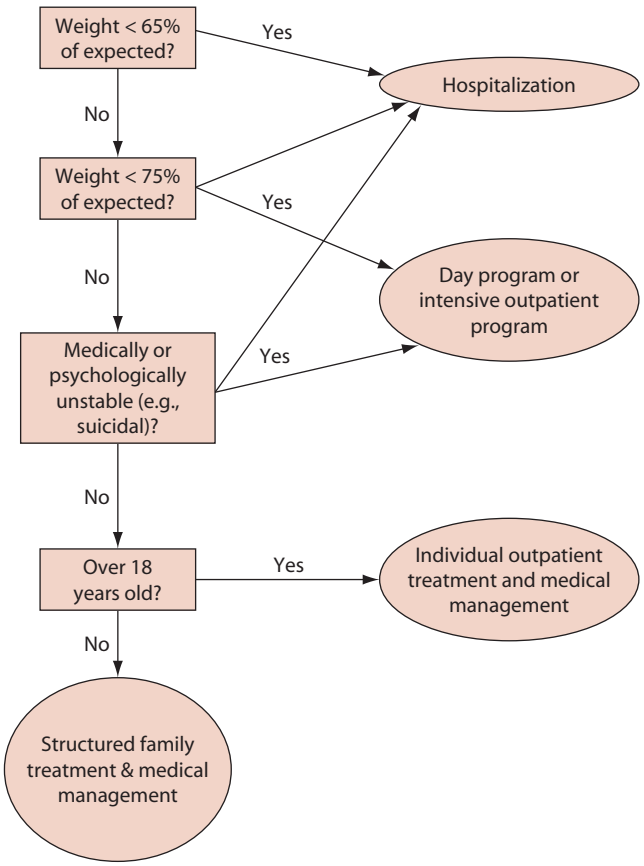



**Figure 78–5** *Algorithm for choice of initial treatment of anorexia nervosa.*

food, whereas others rely on nutritional supplements such as Ensure or Sustacal. During this phase of treatment, it is necessary to monitor patients carefully; many will resort to throwing food away or vomiting after meals. Careful supervision is also required to obtain accurate weights; patients may consume large amounts of fluid before being weighed or hide heavy articles under their clothing.

During the weight restoration phase of treatment, patients require substantial emotional support. It is probably best to address fears of weight gain with education about the dangers of semistarvation and the reassurance that patients will not be allowed to gain "too much" weight. Most eating disorder units impose behavioral restrictions, such as limits on physical activity, during the early phase of treatment. Some units use an explicit behavior modification regimen in which weight gain is tied to increased privileges and failure to gain weight results in bed rest.

A consistent and structured treatment approach, with or without an explicit behavior modification program, is generally successful in promoting weight recovery but requires substantial energy and coordination to maintain a supportive and nonpunitive treatment environment. In most experienced treatment units, parenteral methods of nutrition, such as nasogastric feeding or intravenous hyperalimentation, are only rarely needed. Nutritional counseling and behavioral approaches can also be effective in helping patients expand their dietary repertoire to include foods they have been frightened of consuming.

## Psychosocial Treatments

As weight increases, individual, group, and family psychotherapy can begin to address other issues in addition to the distress engendered by gaining weight (Garner and Garfinkel 1997). For example, it is typically important for patients to recognize that they have come to base much of their self-esteem on dieting and weight control and are likely to judge themselves according to harsh and unforgiving standards. Similarly, patients should be helped to see how the eating disorder has interfered with the achievement of personal goals such as education, sports, or making friends.

There is, at present, no general agreement about the most useful type of psychotherapy or the specific topics that need to be addressed. Most eating disorder programs employ a variety of psychotherapeutic interventions. A number of psychiatrists recommend the use of individual and group psychotherapy using cognitive–behavioral techniques to modify the irrational overemphasis on weight. Although most authorities see little role for traditional psychoanalytic therapy, individual and group psychodynamic therapy can address such problems as insecure attachment, separation and individuation, sexual relationships, and other interpersonal concerns.

## Family Treatment

There is good evidence supporting the involvement of the family in the treatment of younger patients with anorexia nervosa. Family therapy can be helpful in addressing family members' fears about the illness; interventions typically emphasize parental cooperation, mutual support and consistency, and establishing boundaries regarding the patient's symptoms and other aspects of his or her life.

In recent years, Lock et al. (2000) have described a novel approach that has come to be known as the "Maudsley method." In this family-based treatment, the parents are charged with the responsibility of refeeding, with the support and guidance of the therapist. This approach, which differs fundamentally from the traditional stance that encouraged parents to withdraw from the day-to-day management of eating, appears quite promising.

## Somatic Treatments

Despite the multiple physiological disturbances associated with anorexia nervosa, there is no clearly established role for medication (Zhu and Walsh 2002). The earliest systematic medication trials in anorexia nervosa focused on the use of neuroleptics. Theoretically, such agents might help to promote weight gain, reduce physical activity, and diminish the distorted thinking about shape and weight, which often reaches nearly delusional proportions. Early work in the late 1950s and 1960s using chlorpromazine led to substantial enthusiasm, but two placebo-controlled trials of the neuroleptics, sulpiride and pimozide, were unable to establish significant benefits. In recent years, interest has grown in taking advantage of the impressive weight gain associated with some atypical antipsychotics; however, no controlled data supporting this intervention have yet appeared.

Four controlled studies, three of tricyclic antidepressants and one of fluoxetine, have examined the use of antidepressants in the treatment of underweight patients with anorexia nervosa, and none has suggested substantial benefit from medication. Therefore, despite the frequency of

depressive symptoms among patients with anorexia nervosa, there is no good evidence supporting the use of antidepressant medication in their treatment.

### Prevention of Relapse

A large percentage of patients with anorexia nervosa remain chronically ill; 30–50% of patients successfully treated in the hospital require rehospitalization within 1 year of discharge. Therefore, posthospitalization outpatient treatments are recommended to prevent relapse and improve overall short- and long-term functioning. Cognitive–behavioral treatment appears to reduce the rate of relapse, but a recent study found that the addition of fluoxetine did not augment the utility of this psychological intervention (Walsh et al. 2006).

### Treatment-Refractory Patients

Some patients with anorexia nervosa refuse to accept treatment and thereby can raise difficult ethical issues. If weight is extremely low or there are acute medical problems, it may be appropriate to consider involuntary commitment. For patients who are ill but more stable, the psychiatrist must weigh the short-term utility of involuntary treatment against the disruption of a potential alliance with the patient.

The goals of treatment may need to be modified for patients with chronic illness who have failed multiple previous attempts at inpatient and outpatient care. Treatment may be appropriately aimed at preventing further medical, psychological, and social deterioration in the hope that the anorexia nervosa may eventually improve with time.

## BULIMIA NERVOSA

### Definition and Diagnostic Features

### History

Overeating has presumably been a problem for humans for millennia. However, interest in a disorder related to anorexia nervosa but characterized behaviorally by persistent binge-eating grew dramatically in the late 1970s and early 1980s, driven by the appearance of increasing numbers of patients with the chief complaint of binge-eating. In an article published in 1979, Russell (1979) clearly delineated the syndrome of bulimia nervosa, and in 1980, bulimia was formally recognized as a disorder in the newly published *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III). Although discussion continues about the best method of defining the syndrome, there have been no major changes in its conceptualization.

### Definition

The salient behavioral disturbance of bulimia nervosa is the occurrence of episodes of binge-eating. During these episodes, the individual consumes an amount of food that is unusually large, considering the circumstances under which it was eaten. Although this is a useful definition and is conceptually reasonably clear, it can be operationally difficult to distinguish normal overeating from a small episode of binge-eating. Indeed, the available data do not suggest that there is a sharp dividing line between the size of binge-eating episodes and the size of other meals. On the other hand, while the border between normal and abnormal eating may not be a sharp one, both patients' reports and laboratory studies of eating behavior clearly indicate that, when binge-eating, patients with bulimia nervosa do indeed consume larger than normal amounts of food (Walsh et al. 1992).

**DSM-IV-TR Criteria**

**Bulimia Nervosa**

A. Recurrent episodes of binge-eating. An episode of binge-eating is characterized by both of the following:

   (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.

   (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.

C. The binge-eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

*Specify* type:

**Purging type:** during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

**Nonpurging type:** during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

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Episodes of binge-eating are associated, by definition, with a sense of loss of control. Once the eating has begun, the individual feels unable to stop until an excessive amount has been consumed. This loss of control is only subjective, in that most individuals with bulimia nervosa will abruptly stop eating in the midst of a binge episode if interrupted, for example, by the unexpected arrival of a roommate.

After overeating, individuals with bulimia nervosa engage in some form of inappropriate behavior in an attempt

to avoid weight gain. Most patients who present to eating disorders clinics with this syndrome report self-induced vomiting or the abuse of laxatives. Other methods include misusing diuretics, fasting for long periods, and exercising extensively after eating binges.

The DSM-IV-TR criteria require that the overeating episodes and the compensatory behaviors both occur at least twice a week for 3 months to merit a diagnosis of bulimia nervosa. This criterion, although useful in preventing the diagnostic label from being applied to individuals who only rarely have difficulty with binge-eating, is clearly an arbitrary one.

Criterion D in the DSM-IV-TR definition of bulimia nervosa requires that individuals with bulimia nervosa exhibit an overconcern with body shape and weight. That is, they tend to base much of their self-esteem on how much they weigh and how slim they look.

Finally, in the DSM-IV-TR nomenclature, the diagnosis of bulimia nervosa is not given to individuals with anorexia nervosa. Individuals with anorexia nervosa who recurrently engage in binge-eating or purging behavior should be given the diagnosis of anorexia nervosa, binge-eating/purging subtype, rather than an additional diagnosis of bulimia nervosa. This is a change from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) system, in which both diagnoses could be given simultaneously.

In DSM-IV-TR, a subtyping scheme was introduced for bulimia nervosa in which patients are classed as having either the purging or the nonpurging type of bulimia nervosa. This scheme was introduced for several reasons. First, those individuals who purge are at greater risk of developing fluid and electrolyte disturbances such as hypokalemia. Second, data suggest that individuals with the nonpurging type of bulimia nervosa weigh more and have less psychiatric illness compared with those with the purging type. Finally, most of the published literature on the treatment of bulimia nervosa has been based on studies of individuals with the purging type of this disorder.

## Assessment

The assessment of individuals who may have bulimia nervosa is similar to that described for anorexia nervosa. The patient should be asked to describe a typical day's food intake and a typical binge, and the interviewer should assess whether the patient does indeed consume an unusually large amount of food, as required by the DSM-IV-TR definition of a binge. The interviewer should explicitly inquire about self-induced vomiting. The interviewer should ask about the use of laxatives, diuretics, diet pills, and enemas. A weight history should be obtained, so the interviewer can determine whether the binge-eating was preceded by anorexia nervosa, as is often the case, or by obesity. Because there is substantial comorbidity, the interviewer should ascertain whether there is a history of anxiety or mood disturbance or of substance abuse.

### Physiological Disturbances

In a small fraction of individuals, bulimia nervosa is associated with the development of fluid and electrolyte abnormalities that result from the self-induced vomiting or the misuse of laxatives or diuretics. The most common electrolyte disturbances are hypokalemia, hyponatremia, and hypochloremia. Patients who lose substantial amounts of stomach acid through vomiting may become slightly alkalotic; those who abuse laxatives may become slightly acidotic.



**Figure 78–6** *Dental erosion of upper front teeth of a patient with long-standing bulimia nervosa.*

There is an increased frequency of menstrual disturbances such as oligomenorrhea among women with bulimia nervosa. Several studies suggest that the hypothalamic–pituitary–gonadal axis is subject to the same type of disruption as is seen in anorexia nervosa but that the abnormalities are much less frequent and severe.

Patients who induce vomiting for many years may develop dental erosion, especially of the upper front teeth (Figure 78–6). The mechanism appears to be that stomach acid softens the enamel, which in time gradually disappears so that the teeth chip more easily and can become reduced in size. Some patients develop painless salivary gland enlargement, which is thought to represent hypertrophy resulting from the repeated episodes of binge-eating and vomiting. The serum level of amylase is sometimes mildly elevated in patients with bulimia nervosa because of increased amounts of salivary amylase.

Most patients with bulimia nervosa have surprisingly few gastrointestinal abnormalities. As indicated earlier, it appears that the disorder is associated with an enlarged gastric capacity and delayed gastric emptying, but these abnormalities are not so severe as to be detectable on routine clinical examination. Potentially life-threatening complications such as an esophageal tear or gastric rupture occur, but fortunately rarely.

The long-standing use of syrup of ipecac to induce vomiting can lead to absorption of some of the alkaloids and permanent damage to nerve and muscle, including clinically significant cardiomyopathy.

### Physical Examination and Laboratory Findings

The patient should be weighed and the presence of dental erosion noted. Routine laboratory testing reveals an abnormality of fluid and electrolyte balance such as those described in the section on physiological disturbances in 5–10% of patients with bulimia nervosa.

## Epidemiology

Soon after bulimia nervosa was recognized as a distinct disorder, surveys indicated that many young women reported problems with binge-eating, and it was suggested that the syndrome of bulimia nervosa was occurring in epidemic proportions. Later careful studies have found that

although binge-eating is frequent, the full-blown disorder of bulimia nervosa is much less common, with a lifetime prevalence of 1–2% among women in the USA (Hudson et al. 2007). Although the epidemiological data are limited, they suggest a significant increase in the incidence of bulimia nervosa in the last several decades (Keel and Klump 2003).

## Comorbidity Patterns

Among patients with bulimia nervosa who are seen at eating disorders clinics, there is an increased frequency of anxiety and mood disorders, especially major depressive disorder and dysthymic disorder; drug and alcohol abuse; and personality disorders. It is not certain whether this comorbidity is also observed in community samples or whether it is a characteristic of individuals who seek treatment.

## Course

### Onset

Bulimia nervosa typically begins after a young woman who sees herself as somewhat overweight starts a diet and, after some initial success, begins to overeat. Distressed by her lack of control and fear of gaining weight, she decides to compensate for the overeating by inducing vomiting or taking laxatives, methods she has heard about from friends or seen in media reports about eating disorders. After discovering that she can successfully purge, the individual may, for a time, feel pleased in that she can eat large amounts of food and not gain weight. However, the episodes of binge-eating usually increase in size and in frequency and occur after a variety of stimuli, such as transient depression or anxiety or a sense that she has begun to overeat. Patients often describe themselves as "numb" while they are binge-eating, suggesting that the eating may serve to avoid uncomfortable emotional states. Patients usually feel intensely ashamed of their "disgusting" habit and may become depressed by their lack of control over their eating.

Once established, the binge-eating tends to occur in the late afternoon or evening and almost always while the patient is alone. The typical patient presenting to eating disorders clinics has been binge-eating and inducing vomiting five to 10 times weekly for 3–10 years. Although there is substantial variation, binges tend to contain 1000 or more calories and to consist of sweet, high-fat foods that are normally consumed as dessert, such as ice cream, cookies, and cake. Although patients complain of "carbohydrate craving," they only rarely binge-eat foods that are pure carbohydrates, such as fruits. Patients usually induce vomiting or use their characteristic compensatory behavior immediately after the binge and feel substantial relief that the calories are "gone." In reality, it appears that vomiting is the only purging method capable of disposing of a significant number of ingested calories. The weight loss associated with the misuse of laxatives and diuretics is primarily due to the loss of fluid and electrolytes, not calories.

When not binge-eating, patients with bulimia nervosa tend to restrict their calorie intake and to avoid the foods usually consumed during episodes of binge-eating. Although there is phenomenological resemblance between binge-eating and substance abuse, there is no evidence that physiological addiction plays a role in bulimia nervosa. On the other hand, similar brain mechanisms mediate the reward both of eating and of abuse drugs, suggesting that a "final common pathway" may underlie the similarities in symptoms.

### Natural History

Over time, the symptoms of bulimia nervosa tend to improve, although a substantial fraction of individuals continue to engage in binge-eating and purging (Keel et al. 1999). Treatment intervention appears to reduce the length of illness. It is not clear what other factors are most predictive of good outcome, but those individuals who cease binge-eating and purging completely during treatment are least likely to relapse (Olmstead et al. 1994).

## Differential Diagnosis

Bulimia nervosa is not difficult to recognize if a full history is available. The binge-eating/purging type of anorexia nervosa has much in common with bulimia nervosa but is distinguished by the characteristic low body weight and, in women, amenorrhea. Some individuals with atypical forms of depression overeat when depressed; if the overeating meets the definition of a binge described previously (i.e., a large amount of food is consumed with a sense of loss of control), and if the binge-eating is followed by inappropriate compensatory behavior, occurs sufficiently frequently, and is associated with overconcern regarding body shape and weight, an additional diagnosis of bulimia nervosa may be warranted. Some individuals become nauseated and vomit when upset; this and similar problems are probably not closely related to bulimia nervosa and should be viewed as a somatoform disorder.

Many individuals who believe they have bulimia nervosa have a symptom pattern that fails to meet full diagnostic criteria because the frequency of their binge-eating is less than twice a week or because what they view as a binge does not contain an abnormally large amount of food. Individuals with these characteristics fall into the broad and heterogeneous category of atypical eating disorders. Binge-eating disorder (see section on binge-eating disorder), a category currently included in the DSM-IV-TR appendix B for categories that need additional research, is characterized by recurrent binge-eating similar to that seen in bulimia nervosa but without the regular occurrence of inappropriate compensatory behavior.

## Differences in Presentation

Probably the greatest difference in presentation is between those individuals who purge and those who do not. Individuals with the nonpurging form of bulimia nervosa are more likely to be overweight at the time of presentation and to exhibit less general psychiatric illness compared with individuals who induce vomiting.

# Etiology and Pathophysiology

As in the case of anorexia nervosa, the etiology of bulimia nervosa is uncertain. Several factors clearly predispose individuals to the development of bulimia nervosa, including being an adolescent girl or young adult woman. A personal or family history of obesity and of mood disturbance also appears to increase risk. Twin studies have suggested that inherited factors are related to the risk of developing bulimia nervosa, but what these factors are and how they operate are unclear.

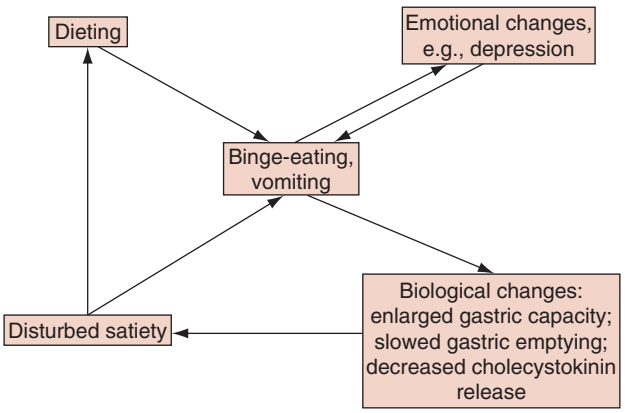



**Figure 78–7** *Diagram illustrating factors that may perpetuate bulimia nervosa.*

Many of the same psychosocial factors related to the development of anorexia nervosa are also applicable to bulimia nervosa, including the influence of cultural esthetic ideals of thinness and physical fitness. Similarly, bulimia nervosa primarily affects women; the ratio of men to women is approximately 1:10. It also occurs more frequently in certain occupations (e.g., modeling) and sports (e.g., wrestling, running).

### Psychological Factors

Although not proven, it seems likely that several factors serve to perpetuate the binge-eating once it has begun (Figure 78–7). First, most individuals with bulimia nervosa, because of both their concern regarding weight and their worry about the effect of the binge-eating, attempt to restrict their food intake when they are not binge-eating. The psychological and physiological restraint that is thereby entailed presumably makes additional binge-eating more likely. Second, even if mood disturbance is not present at the outset, individuals become distressed about their inability to control their eating, and the resultant lowering of self-esteem contributes to disturbances of mood and to a reduced ability to control impulses to overeat. In addition, cognitive–behavioral theories emphasize the role of rigid rules regarding food and eating, and the distorted and dysfunctional thoughts that are similar to those seen in anorexia nervosa. Interpersonal theories also implicate interpersonal stressors as a primary factor in triggering binge-eating. There is no evidence to suggest that a particular personality structure is characteristic of women with bulimia nervosa (Wonderlich 2002).

It has been suggested that childhood sexual abuse is a specific risk factor for the development of bulimia nervosa. Scientific support for this hypothesis is weak. The best studies to date have found that compared with women without psychiatric illness, women with bulimia nervosa do indeed report increased frequencies of sexual abuse. However, the rates of abuse are similar to those found in other psychiatric disorders and occur in a minority of women with bulimia nervosa. Thus, while early abuse may predispose an individual to psychiatric problems generally, it does not appear to lead specifically to an eating disorder, and most patients with bulimia nervosa do not have histories of sexual abuse (Welch and Fairburn 1994).

### Neurobiological Factors

There are also indications that bulimia nervosa is accompanied by physiological disturbances that disrupt the development of satiety during a meal and therefore increase the likelihood of binge-eating. These disturbances include an enlarged stomach capacity, a delay in stomach emptying, and a reduction in the release of cholecystokinin, a peptide hormone secreted by the small intestine during a meal that normally plays a role in terminating eating behavior (Klein and Walsh 2004). All these abnormalities appear to predispose the individual to overeat and therefore to perpetuate the cycle of binge-eating.

### Social/Environmental Factors

Evidence suggests an important role of sociocultural influences in the development of bulimia nervosa. For example, the frequency of the disorder appears to be very low in non-Western societies, and to have increased substantially in the last 50 years (Keel and Klump 2003).

## Treatment

### Treatment Goals

The goals of the treatment of bulimia nervosa are straightforward. The binge-eating and inappropriate compensatory behaviors should cease, and self-esteem should become more appropriately based on factors other than shape and weight.

The power struggles that often complicate the treatment process in anorexia nervosa occur much less frequently in the treatment of patients with bulimia nervosa. This is largely because the critical behavioral disturbances, binge-eating and purging, are less ego-syntonic and are more distressing to these patients. Most bulimia nervosa patients who pursue treatment agree with the primary treatment goals and wish to give up the core behavioral features of their illness.

### Psychosocial Treatments

The treatment of bulimia nervosa has received considerable attention in recent years, and the efficacies of both psychotherapy and medication have been explored in numerous controlled studies (Figure 78–8). The form of psychotherapy that has been examined most intensively is cognitive–behavioral therapy, modeled on the therapy of the same type for depression (Fairburn 2002). Cognitive–behavioral therapy for bulimia nervosa concentrates on the distorted ideas about weight and shape, on the rigid rules regarding food consumption and the pressure to diet, and on the events that trigger episodes of binge-eating. The therapy is focused and highly structured and is usually conducted in 3–6 months. Approximately 25–50% of patients with bulimia nervosa achieve abstinence from binge-eating and purging during a course of cognitive–behavioral therapy, and in most, this improvement appears to be sustained. The most common form of cognitive–behavioral therapy is individual treatment, although it can be given in either individual or group format. The effect of cognitive–behavioral therapy is greater than that of supportive psychotherapy and interpersonal therapy, indicating that cognitive–behavioral therapy should be the treatment of choice for bulimia nervosa.

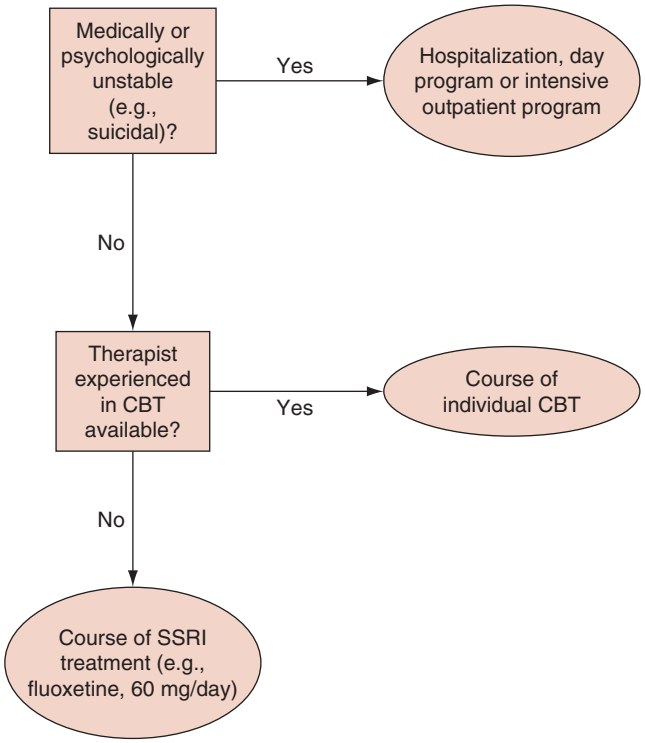



**Figure 78–8** *Algorithm for choice of initial treatment of bulimia nervosa.*

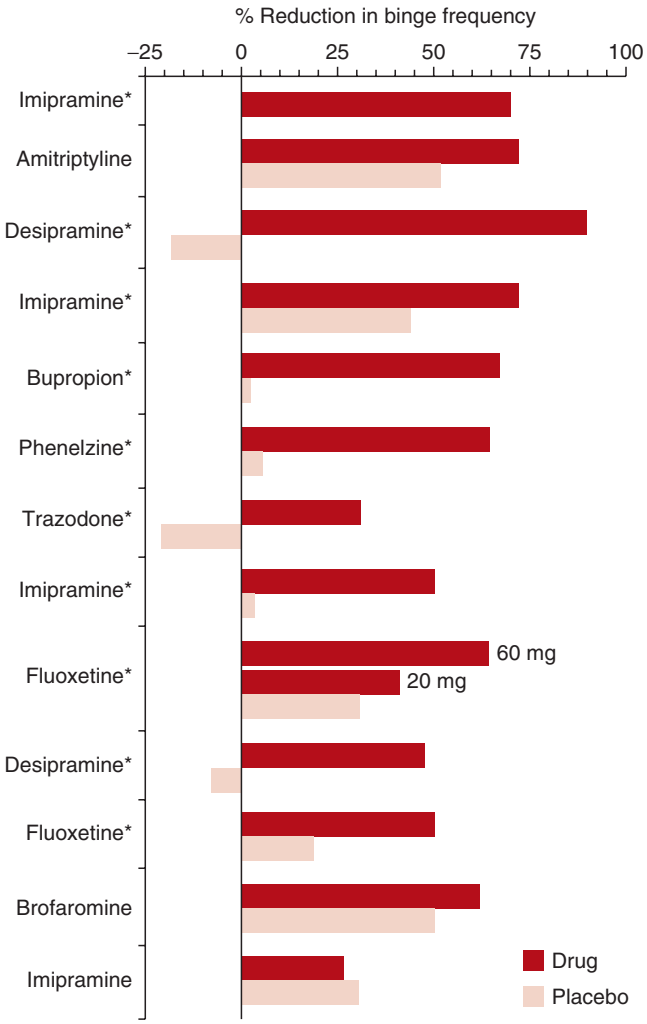



**Figure 78–9** *Results of controlled trials of antidepressants in bulimia nervosa. *indicates a statistically significant difference between the active medication and placebo. [Reproduced from Walsh and Devlin (1995) with permission from Elsevier.]*

## Somatic Treatments

The other commonly used mode of treatment that has been examined in bulimia nervosa is the use of antidepressant medication (Zhu and Walsh 2002). This intervention was initially prompted by the high rates of depression among patients with bulimia nervosa and has now been tested in more than a dozen double-blind, placebo-controlled studies, using a wide variety of antidepressant medications. Active medication has been consistently found to be superior to placebo, and, although there have been no large "head-to-head" comparisons between different antidepressants, most antidepressants appear to possess roughly similar antibulimic potency (Figure 78–9). Fluoxetine at a dose of 60 mg/day is favored by many investigators because it has been studied in several large trials and appears to be at least as effective as, and better tolerated than, most other alternatives. It is notable that it has not been possible to link the effectiveness of antidepressant treatment for bulimia nervosa to the pretreatment level of depression. Depressed and nondepressed patients with bulimia nervosa respond equally well in terms of their eating behavior to antidepressant medication.

Although antidepressant medication is clearly superior to placebo in the treatment of bulimia nervosa, several studies suggest that a course of a single antidepressant medication is generally inferior to a course of cognitive–behavioral therapy. However, patients who fail to respond adequately to, or who relapse following a trial of, psychotherapy may still respond to antidepressant medication.

## Treatment-Refractory Patients

Although psychotherapy and antidepressant medication are effective interventions for many patients with bulimia nervosa, some individuals have little or no response. There is no clearly established algorithm for the treatment of such refractory patients. Alternative interventions that may prove useful include other forms of psychotherapy and other medications such as SNRIs, sibutramine, and topiramate; these pharmacological agents have not been extensively studied, but anecdotal reports and a few controlled studies suggest that they can be of benefit. Hospitalization should also be considered as a way to normalize eating behavior, at least temporarily, and perhaps to initiate a more effective outpatient treatment.

## Special Factors Influencing Treatment

A major factor influencing the treatment of bulimia nervosa is the presence of other significant psychiatric or medical illness. For example, it can be difficult for individuals who are currently abusing drugs or alcohol to use the treatment methods described, and many psychiatrists suggest that the substance abuse needs to be addressed before the eating disorder can be effectively treated. Other examples include the treatment of individuals with bulimia nervosa and serious personality disturbance and those with insulin-dependent diabetes mellitus who "purge" by omitting insulin doses.

In treating such individuals, the psychiatrist must decide which of the multiple problems must be addressed first and may elect to tolerate a significant level of eating disorder to confront more pressing disturbances.

# BINGE-EATING DISORDER

## Diagnosis

### Definition and Diagnostic Features

#### History

As noted earlier, binge-eating disorder is a proposed diagnostic category related to, but quite distinct from, bulimia nervosa. Individuals with binge-eating disorder, like individuals with bulimia nervosa, repeatedly engage in episodes of binge-eating but, unlike patients with bulimia nervosa, do not regularly utilize inappropriate compensatory behaviors. The phenomenon of binge-eating without purging among the obese was clearly described by Stunkard (1959), 20 years before bulimia nervosa was recognized. Yet binge-eating disorder has been the focus of sustained attention only recently.

#### Definition

Suggested diagnostic criteria for binge-eating disorder are included in an appendix of DSM-IV-TR, which provides criteria sets for further study. These criteria require recurrent episodes of binge-eating, which are defined just as for bulimia nervosa. The major difference from bulimia nervosa is that individuals with binge-eating disorder do not regularly use inappropriate compensatory behavior, although the precise meaning of "regularly" is not specified. Other differences from the definition of bulimia nervosa relate to the frequency of binge-eating: individuals with bulimia nervosa must binge-eat, on average, at least two times per week over the last 3 months, whereas individuals with binge-eating disorder must binge-eat at least 2 days per week over the last 6 months. A major reason for the difference in the criteria is that the end of a binge episode in bulimia nervosa is usually clearly marked by the occurrence of inappropriate compensatory behavior, like purging, whereas in binge-eating disorder, the end of a binge episode may be more difficult to identify precisely. The criteria attempt to deal with this definitional difficulty by requiring the frequency of binge-eating to be measured in terms of the number of days per week on which episodes occur, and, because of the potential difficulty in distinguishing "normal" overeating from binge-eating, to require a 6-month duration, rather than 3 months for bulimia nervosa. In addition, the suggested DSM-IV-TR criteria for binge-eating disorder require that individuals report behavioral evidence of a sense of loss of control over eating, such as eating large amounts of food when not physically hungry. Finally, while there is some evidence that individuals with binge-eating disorder tend to be more concerned about body image than individuals of similar weight, the criteria for binge-eating disorder require only that there is marked distress over the binge-eating. Thus, the criteria for binge-eating disorder do not require that self-evaluation be overly influenced by concerns regarding body weight and shape, as is required for bulimia nervosa.

### Assessment

The assessment of individuals who may have binge-eating disorder parallels that of individuals who may have bulimia nervosa. It is important to obtain a clear understanding of daily food intake and of what the individual considers a binge. As in the assessment of bulimia nervosa, the interviewer should inquire about the use of purging and other inappropriate weight-control methods. Individuals who describe binge-eating disorder are likely to be obese, and it is important to obtain a history of changes in weight and of efforts to lose weight. The interviewer should also inquire about symptoms of mood disturbance and anxiety.

#### Physical Examination and Laboratory Findings

The salient general medical issue is that of obesity. Individuals with binge-eating disorder who are obese should be followed by a primary-care physician for assessment and treatment of the complications of obesity. There is no strong evidence at presence convincingly demonstrating that the behavioral disturbances characteristic of binge-eating disorder add to the physical risks of obesity. Whether the presence of binge-eating disorder affects the natural history of obesity is an intriguing but unanswered question.

### Epidemiology

The prevalence of binge-eating disorder is much greater than that of anorexia nervosa or bulimia nervosa. A recent study suggests a lifetime prevalence of 3.5% among women and 2% among men (Hudson et al. 2007). The prevalence among obese individuals who attend weight loss clinics is substantially higher, and the frequency of binge-eating disorder increases with the degree of obesity. In contrast to anorexia nervosa and bulimia nervosa, individuals with binge-eating disorder are more likely to be men (the female-to-male ratio is roughly 1.5:1, compared to approximately 10:1 for anorexia nervosa and bulimia nervosa), from minority ethnic groups, and middle aged.

### Comorbidity Patterns

Binge-eating disorder is frequently associated with symptoms of mood and anxiety disorder.

### Course

As the recognition of binge-eating disorder is relatively recent, there is little definitive information about the natural history of this disorder. However, recent data suggest that the symptoms tend to be stable over time (Pope et al. 2006).

### Differential Diagnosis

In theory, binge-eating disorder should be easy to recognize on the basis of patient self-report: the individual describes the frequent consumption of large amounts of food in a discrete period of time about which he or she feels distressed and unable to control. Difficulties arise, however, because of uncertainty about what precisely constitutes a "large amount of food," especially for an obese individual, and regarding what constitutes a discrete period of time. Many individuals describe eating continuously during the day or evening, thereby consuming a large amount of food, but it is not clear whether such behavior is best viewed as binge-eating.

Individuals who meet the proposed definition of binge-eating disorder clearly have increased complaints of depression and anxiety, compared to individuals of similar weight without binge-eating disorder.

As noted above, the most difficult issue in the diagnostic assessment of binge-eating disorder is determining whether the eating pattern of concern to the individual meets the proposed definition of binge-eating. There are numerous varieties of unhealthy eating, such as the consumption of high fat foods, and the nosology of these patterns of eating is not well worked out.

Some individuals with atypical depression binge-eat when depressed; if the individual meets criteria for both a binge-eating disorder and an atypical depression, both diagnoses should be made.

## Etiology and Pathophysiology

Little is known about the etiology of binge-eating disorder. Binge-eating disorder is clearly associated with obesity, but it is uncertain to what degree the binge-eating is a contributor to, and a consequence of, the obesity (Devlin, in press).

## Treatment

### Goals of Treatment

For most individuals with binge-eating disorder, there are three related goals. One is behavioral, to cease binge-eating. A second focuses on improving symptoms of mood and anxiety disturbance, which frequently are associated with binge-eating disorder. The third is weight loss for individuals who are also obese.

### Somatic and Psychosocial Treatments

Treatment approaches to binge-eating disorder are currently under active study. There is good evidence that both psychological (e.g., CBT) and pharmacological (e.g., SSRI) interventions, which are effective for bulimia nervosa, are also useful in reducing the binge frequency of individuals with binge-eating disorder and in alleviating mood disturbance. However, it is not clear how helpful these approaches are in facilitating weight loss. Standard behavioral weight loss interventions employing caloric restriction also appear useful in helping patients to control binge-eating, as do other forms of psychotherapy, such as interpersonal psychotherapy. Pharmacological approaches to weight loss, such as sibutramine and orlistat, may be able to address both binge-eating and weight loss. Definitive information about the best treatment algorithm for binge-eating disorder has not yet been developed.

Clinical Vignette 1

When Ms. A was first evaluated for admission to an inpatient eating disorders program, she had been restricting her food intake for approximately 5 years and had been amenorrheic for 4 years. At the time of her admission, this 24-year-old, single, white woman weighed 71 lb at a height of 5 feet 1.5 inches. In 12th grade, Ms. A menstruated for the first time and also developed "very large" breasts. She had a difficult first year at college, where she gained to her maximum weight of 120 lb. The following year, Ms. A transferred to a smaller college, became a vegetarian "for ethical reasons," and began to significantly restrict her food intake. She limited herself to a total of 700–800 cal/day, with a maximum of 200 calories per meal, and gradually lost weight in the next 5 years. Ms. A did not binge, vomit, abuse laxatives, or engage in excessive exercise. She considered herself to be "obsessed with calories" and observed a variety of rituals regarding food and food preparation (e.g., obsessively weighing her food).

Although Ms. A excelled academically, she had no close friends and had never been involved in a romantic relationship. She was quite close to her mother and sister and had always been dependent on her parents. After graduating (with honors) from college, Ms. A worked at a series of temporary jobs but was unemployed and living at home with her mother at the time of admission. She had been in outpatient psychotherapy with two different therapists during the previous 2 years. The first therapist did not address her eating disorder, and Ms. A continued to lose weight, from 90 to 80 lb. Although her second therapist confronted her about her anorexia nervosa and started her on desipramine at 20 mg/day for depressive symptoms, Ms. A continued to lose weight.

During her first 5-month hospitalization, Ms. A was treated with a multimodal program (behavioral weight gain protocol, individual and family therapy, fluoxetine at 60–80 mg for obsessive–compulsive traits, and depressive symptoms) and gained up to a weight of 98 lb. At discharge, she was maintaining her weight on food but remained concerned about her weight and was particularly frightened of reaching "the triple digits" (i.e., ≥100 lb). After leaving the hospital, Ms. A continued with outpatient psychotherapy and fluoxetine for several months. She was then seriously injured in a car accident and, during a prolonged convalescent period, discontinued treatment for her eating disorder. Ms. A remained unemployed, eventually moved in with her sister and her sister's family, and gradually lost weight.

About 3.5 years after discharge, at the age of 27 years, Ms. A again sought inpatient treatment. At admission, she weighed 83 lb but still felt "fat." During hospitalization, she steadily gained weight and was prescribed sertraline at 100 mg/day for feelings of low self-esteem, anxiety, and obsessional thinking. When she was discharged 5 months later, at a weight of 108 lb, she noted menstrual bleeding for the first time in more than 7 years. After leaving the hospital, Ms. A continued taking medication and began outpatient cognitive–behavioral psychotherapy. For the next year, she continued to struggle with eating and weight issues but managed to maintain her weight and successfully expand other aspects of her life by independently supporting herself with a full-time job, making new friends, and becoming involved in her first romantic relationship.

Clinical Vignette 2

When Ms. B, a 20-year-old white college student, was first evaluated for treatment at an outpatient eating disorders program, she had been binge-eating and purging for approximately 5 years. Each evening, she consumed large quantities of food, vomited three or four times, and took two to six laxatives. She also occasionally used herbal diuretics but had never abused diet pills or prescription diuretics. Ms. B's weight was well within the normal range (106 lb at a height of 5 ft 2 inches). She was extremely concerned about her shape and weight, was afraid of becoming

fat, and wanted to weigh no more than 100 lb ("the double digits are nice too … maybe 90 lb, but I don't think I could run at that weight").

Ms. B always binged alone in her dormitory room while watching television and flipping through magazines. A typical binge might consist of two packages of cookies, a half-gallon of ice cream, one box of cereal, one can of spaghetti, one bag of pretzels, one can of soup, one package of fishsticks, one bag of candy, and six bagels with butter, eaten during a 3–4-hour period. She would vomit every hour or so, each time making room for more food. Throughout the day, she would severely restrict her food intake, usually eating nothing but fruit, salad, oatmeal, diet hot chocolate, coffee, and chewing gum. She was an avid cross-country runner, totaling about 50 miles per week, but denied running to compensate for eating binges.

Ms. B was raised on the East Coast by her parents, who were college graduates, and had an older brother. She had a history of always being thin, and when she was in the sixth grade, she weighed 75 lb at a height of 4 ft 9 inches. She began binge-eating and purging at the age of 16 years, after her father was hospitalized for a suicide attempt. She read many books about eating disorders, because she "wanted to be anorexic," and within 2 months, she was binge-eating and purging every day. She had periodically been treated for her eating disorder, both with individual psychotherapy and with 20 mg of fluoxetine; none of these treatments was significantly helpful. She was also hospitalized for 7 weeks at the age of 17 years and stopped binge-eating and purging, but anorexia nervosa developed. Her weight dropped to 95 lb, which was 80% of her ideal body weight. She had not menstruated since she began binge-eating and purging, and she did not menstruate again until she was 19 years old.

Other than her father's depression, there was no family history of psychiatric illness or eating disorders. Ms. B had also had several major depressive episodes since she was 16 years old, during which she experienced depressed mood, lessened interest in her usual activities, tiredness, decreased concentration, and suicidal thoughts. She had never used drugs and drank only rarely.

Soon after she began a 4-month course of cognitive–behavioral therapy plus desipramine, 100 mg/day, Ms. B's eating disorder improved substantially. By the time she completed treatment, she was still binge-eating and vomiting occasionally, but she felt much more in control of her bulimia. Her self-esteem was greatly improved, and she was more aware of distortions in her thoughts about her eating and body shape and weight. She was optimistic yet realistic about maintaining the gains she had achieved. Ms. B was prescribed desipramine for 3 months more, and then for the following 9 months, she was treated with fluoxetine, 30 mg/day, and met occasionally with another therapist. Ms. B continued to be much improved, but not entirely well, binge-eating and purging once or twice a month.

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CHAPTER

# 79 Sleep and Sleep–Wake Disorders

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Primary Insomnia
Narcolepsy
Primary Hypersomnia
Breathing-Related Sleep Disorder
Circadian Rhythm Sleep Disorder
Nightmare Disorder
Sleep Terror Disorder
Sleepwalking Disorder
Substance-Induced Sleep Disorder

Clinicians, particularly psychiatrists and psychologists, need to master a general working knowledge of sleep and chronobiology, including the disorders of sleep and circadian rhythms, their clinical manifestations and differential diagnoses, and their clinical management. This chapter provides an overview of the most common topics in basic and clinical sciences of sleep.

## PHENOMENOLOGY AND ORGANIZATION OF SLEEP

### Physiological Regulation of Sleep and Wakefulness

#### Organization of Sleep

Sleep consists of two major states: (1) rapid eye movement (REM) sleep and (2) non-rapid eye movement (NREM) sleep, which alternate throughout the sleep period. In the adult, entry into sleep normally begins with NREM sleep and is followed after approximately 90 min by the first REM period. Thereafter, NREM sleep and REM sleep oscillate with a cycle length (the interval between onset of each NREM or REM period) of about 80−110 min (Figure 79–1). NREM sleep is predominant during the first third of the night while REM is predominant in the last third of the night.

On the basis of electroencephalographical (EEG) characteristics, NREM sleep in humans is further divided into stages: Stage 1, a brief transitional stage between wakefulness and sleep; Stage 2, which occupies the greatest amount of time during sleep; and Stages 3 and 4, often called delta sleep or slow wave sleep (SWS) because of the presence of characteristic high-amplitude slow EEG delta waves (Table 79–1). REM sleep is characterized by fast frequency EEG, REMs and inhibited muscle tone (atonia). Awakenings from REM sleep are commonly associated with reports of vivid dreaming, however, reports of dreams can also occur during NREM sleep, especially at sleep onset during stage 1 sleep.

#### Circadian Rhythm of Sleep and Wakefulness

Circadian rhythms are rhythms that fluctuate every 24 hr. The word 'circadian' comes from the Greek "circa" meaning "about" and "dies" meaning "day," thus circadian rhythms take about a day, or 24 hr. The rest–activity or sleep–wake cycle is an example of a circadian rhythm (Table 79–2). Circadian rhythms are also seen in hormonal secretions, gastric activity, and core body temperature, just to name a few. An example of the interaction between different circadian systems is the relationship between core body temperature and the sleep/wake cycle. Sleep initiation is associated with a drop in core body temperature with the nadir in the early

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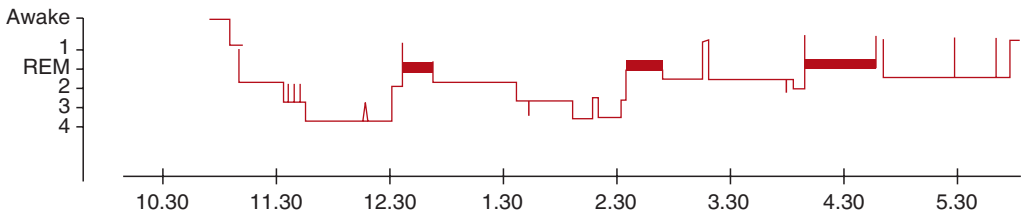



**Figure 79–1** *All-night polygraphic sleep stages in a normal young volunteer.*

morning hr, around 3–4 AM, while awakening from sleep is associated with core body temperature rising.

Circadian rhythms can be characterized by three different measures: (a) cycle length (*tau*) (e.g., the time between two peaks of the 24-hr temperature curve); (b) amplitude (e.g., the difference between the minimum value of the cycle (*nadir*) and maximum value, for example, the difference between the lowest and highest points in the 24-hr temperature curve); and (c) phase position of the rhythm (*acrophase*) (e.g., the time of day when the peak of the rhythm occurred).

**Table 79–1 Commonly Used Terms in Human Sleep Studies**

| Term | Definition |
|---|---|
| Delta wave | EEG pattern conventionally defined as ≤ 75 mV, ≤ 0.5 Hz (or cycles per second) wave; the amplitude tends to decrease with normal aging |
| NREM sleep | Stages 1, 2, 3, and 4 sleep |
| Total sleep time | NREM plus REM sleep time |
| REM latency | Time from onset of sleep to onset of REM sleep; declines from about 70–100 min in the 20s to 55–70 min in the elderly, short REM latency associated with narcolepsy, depression, and a variety of clinical conditions |
| REM sleep | REM sleep; characterized by low-voltage, relatively fast frequency EEG, bursts of REMs, and loss of tone (atonia) in the major antigravity muscles; associated with dreaming |
| Sleep efficiency | Percentage of time in bed spent in sleep; usually above 90% in the young, falls somewhat with age |
| Sleep latency | Time from "lights out" to onset of sleep |
| Stage 1 sleep | A brief transitional state of sleep between wakefulness and sleep, characterized by low-voltage, mixed-frequency EEG, and slow eye movements; about 5% of total sleep time |
| Stage 2 sleep | Characterized by K complexes and sleep spindles (12–14 per cycle rhythms) in the EEG; usually about 45–75% of total sleep time |
| Stages 3 and 4 sleep | Sometimes referred to as delta or slow wave sleep (SWS), based on amount of sleep delta waves in EEG, 20–50% of an epoch (i.e., 30 or 60 s) for Stage 3, more than 50% for Stage 4; amount per night declining from about 20–25% of total sleep time in the teens to nearly zero in the elderly |
| WASO | Wake time after sleep onset |
| REM density | A measure of amount of ocular activity per minute of REM sleep |

**Table 79–2 Commonly Used Terms in Chronobiology**

| Term | Definition |
|---|---|
| Acrophase | The time at which the maximal point of a circadian rhythm occurs, i.e., maximal secretion of cortisol normally occurs at midmorning in humans. |
| Circadian rhythm | Refers to biological rhythms having a cycle length of about 24 hr, derived from Latin *circa dies*, "about 1 d"; examples include the sleep–wake cycle in humans, temperature, cortisol, and psychological variation in the 24-hr day; characterized by exact cycle length (tau), amplitude, and phase position. |
| Constant routine | An experimental method used to estimate amplitude and phase position of circadian temperature and neuroendocrine rhythms; the subject remains awake for about 36 hr under dim light, with head elevated slightly, eating frequent equal-calorie meals, while blood samples are withdrawn unobtrusively every 20–30 min and rectal temperature is measured about once a minute. |
| Dim light MT onset (DLMO) | An experimental method for estimating the phase of MT onset; under dim light conditions starting in late afternoon, blood samples are withdrawn every 20–30 min to determine when MT secretion begins. |
| Nadir | Time when the minimal point of a circadian rhythm occurs. |
| Phase position | Temporal relationship between rhythms or between one rhythm and the environment; e.g., maximal daily temperature peak (acrophase) usually occurs in the late afternoon. |
| Phase-advanced rhythm | Phase position of biological rhythm occurs earlier than reference, i.e., the patient retires and arises early. |
| Phase-delayed rhythm | Phase position of biological rhythm occurs later than reference, i.e., the patient retires and arises late. |
| Phase-response curve | Graph showing the magnitude and direction of change in phase position of circadian rhythm depending upon timing of Zeitgeber with reference to the endogenous oscillator. |
| Tau | Cycle length, e.g., from one acrophase to the next. |
| Zeitgebers | Time cues, such as social activities, meals, and bright lights, that influence phase position of rhythm. |

The propensity for sleep and wakefulness varies in a circadian fashion, at least after infancy, and is modulated in part by one or more biological clocks. The suprachiasmatic nucleus (SCN) in the anterior hypothalamus plays a decisive role in the regulation of most circadian rhythms in humans and animals. The endogenous activity rhythms of the SCN are synchronized with the environment, primarily by ambient light. Information regarding light reaching the retina is conveyed to the SCN directly through the retinohypothalamic tract and indirectly through the intergeniculate leaflet of the lateral geniculate body. Changes in light intensity, especially at dawn and dusk, are particularly important in synchronizing endogenous oscillators controlling rhythms of sleep–wake, cortisol, melatonin (MT), and core body temperature with one another and with the outside world.

If humans are allowed to choose their sleep–wake cycles in the absence of time cues such as daily light–dark signals or clocks, they usually show, as most mammalian species do, a sleep–wake cycle longer than 24 hr. The self-selected rest–activity cycle is typically slightly longer, implying that neurons within the SCN have an inherent rhythmicity of approximately 24.2 hr. Subjects in a time-free environment are said to "free-run" because endogenous processes, such as a circadian oscillator, rather than environmental cues, determine their sleep–wake, endocrine, and other rhythms.

Exposure to light and darkness at appropriate times of the day can shift the circadian rhythms (Czeisler et al. 1989). Bright light at the beginning of the subjective evening in conjunction with dark during the subjective morning delays and resets the phase position of the temperature, cortisol, MT, and sleep–wake rhythms; dark in the subjective evening and bright light in the subjective morning have the opposite effect (i.e., advancing the rhythm). The magnitude and direction of the changes induced by bright light or other zeitgebers ("timegivers") at any particular time form the *phase-response curve* (Figure 79–2).

Animal research has demonstrated that lesions of the SCN abolish circadian rhythms of temperature, cortisol secretion, eating, drinking, or sleep–wakefulness. Sleep and wakefulness, for example, appear in brief bouts throughout the 24-hr day. Total sleep time, however, may increase under these circumstances.

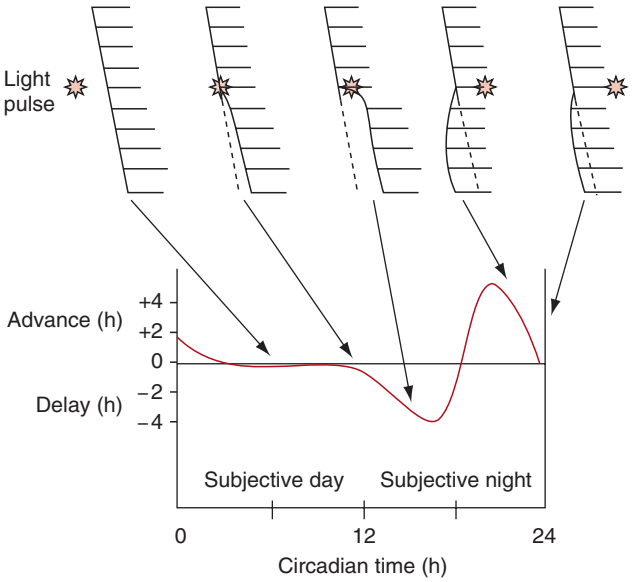



**Figure 79–2** *The phase-response curve in the hamster, demonstrating the magnitude and direction of phase-shifting properties of bright light, depending on when the light is presented with relationship to circadian time.*

## Homeostatic Regulation of Sleep–Wakefulness

Common experience suggests that the longer one is awake, the sleepier one feels. Conversely, sleep reverses sleepiness and other consequences of wakefulness. Thus, sleep serves a homeostatic function; it is a time of rest and restoration that overcomes the "ravages of wakefulness" (Daan et al. 1984). Consistent with the hypothesis, sleep deprivation usually decreases sleep latency and increases sleep efficiency and the amount of SWS on recovery nights.

The precise regulation of sleep and wakefulness remains an area of intense investigation and theory. Two current theories of sleep–wake regulation include the two-process model (Daan et al. 1984) and the opponent process model (Edgar et al. 1993). The first postulates that sleep and wakefulness are regulated by a circadian process (Process C), which sets the circadian thresholds for sleep and wakefulness, and a homeostatic process (Process S), in which sleep propensity builds up with wakefulness and dissipates during NREM sleep, especially SWS. The opponent process model postulates that the SCN promotes alertness and that duration of wakefulness facilitates sleep.

## Normal Age-Related Changes in Sleep and Wakefulness

The newborn spends nearly 50% of total sleep time in REM sleep. Because infants may sleep up to 16 hr a day, the infant may spend 8 hr in REM sleep per day. Newborns display a polyphasic sleep–wake pattern, with short bouts of sleep and wakefulness throughout the 24-hr day, until several months of age when the child eventually sleeps through the night. Daytime napping, however, often persists until the age of 4–6 years. SWS increases in the early years. Maximal "depth" of sleep may occur during the prepubertal period, when children are often difficult to awaken at night. Adolescents often still need at least 10 hr of sleep. Yet, during adolescence, Stages 3 and 4 sleep decline and daytime sleepiness increases, partially in association with the normal Tanner stages of pubertal development. Teenagers are also phase delayed which means that they may not get sleepy until the early morning hours (e.g., 2–3 AM) and do not naturally wake up until the later morning hours. Early school-start times and social pressures may produce mild sleep deprivation during weekdays, with some catch-up on weekends.

As adults enter middle age and old age, sleep often becomes more shallow, fragmented, and variable in duration and circadian timing compared with that of young adults. Stages 1 and 2 and the amount of time spent awake during the night tend to increase; REM latency and SWS decline. In a meta-analysis of 65 studies, examining over 3500 participants aged 5–102 years old, Ohayon concluded that most age-related sleep changes occur in early and mid-years of human life span, and in healthy older

adults, sleep remains fairly constant between the ages of 60 and 90 years (Ohayon et al. 2004).

Daytime sleepiness and napping usually increase with age, often as a function of disturbed nocturnal sleep. The elderly frequently choose an "early-to-bed, early-to-rise" pattern reflecting, in part, an apparent phase advance of the circadian clock. Even when they retire at the same time as when they were younger, they still tend to wake up early, thus sleep-depriving themselves. This can result in daytime sleepiness and napping. Psychiatrists should always consider the role of chronobiological factors when evaluating patients with sleep disorders, especially the elderly, who have more sleep–wake complaints than younger persons. The sleep–wake patterns of the early bedtimes of the elderly, short REM latency, sleep fragmentation at night, and napping during the day may reflect a phase-advance and reduced amplitude of the circadian oscillator.

Factors that could contribute to these age-related patterns include loss of influence from zeitgebers (light, work schedules, social demands, physical exercise) and a weaker signal from the circadian oscillator to effector systems. Indoor living conditions or loss of hearing and sight may deprive individuals of cues that synchronize the circadian system.

### Neurophysiology and Neurochemistry of Sleep

Certain homeostatic functions, particularly those regulated by circadian rhythms, will function most efficiently if they have a clear "on-off" cycle regulated by circadian pacemakers. Clearly, sleep is such an activity. For the brain to have the capacity to progress gradually from states of sleep to alertness (or vice versa) over a period of time would leave an individual at risk from predators and unable to function maximally for long periods during the day. Control for the capacity to shift between sleep and wake is now believed to reside in a "sleep switch", located within the hypothalamus. This model for regulation of sleep and wakefulness, incorporating the "two process model", has been explicated by Saper et al. (2005) and helps to explain how interactions between the homeostatic and circadian drives mentioned above are regulated. The model is based on observed reciprocal interactions between two hypothalamic areas, the ventrolateral preoptic area (VLPO) and the tuberomammalary nucleus (TMN). As the sun rises, when alertness is required, cells in the TMN are released from inhibitory control, leading to activation from the SCN. As the day progresses and homeostatic sleep drive grows, this activation prevents the "sleep debt" that has accumulated during hours of wakefulness from interfering with alertness required for daytime function.

After sunset, when initiation of sleep on a circadian basis is "programmed" to occur, the sleep switch promotes activation of the VLPO and inhibition of the TMN, facilitating sleep onset and promoting continuity of sleep over the night.

Another cycle of activity associated with sleep is alternation between the two states of sleep, REM and NREM. Lesion studies in cats have demonstrated that the NREM–REM sleep cycle is regulated within the brain stem (Steriade and McCarley 1990) (Figure 79–3). The isolated brain stem generates periodic episodes of REMs and muscle atonia, the physiological signatures of REM sleep. In contrast, the forebrain of this preparation generates alternating periods of EEG slow waves and EEG arousal, suggestive of NREM sleep and wakefulness, respectively.

Other research has demonstrated that lesions of the locus subcoeruleus in the cat result in REM sleep without atonia, in which the animal appears to act out dreams (i.e., fighting, stalking, or playing while still in REM sleep) (Hendricks et al. 1982). As described below, a clinical analogue of REM sleep without atonia is the REM sleep behavior disorder (RBD) (Schenck and Mahowald 2005). Patients with this disorder maintain muscle tone during REM sleep and act out the content of dreams (e.g., a man hits his wife sleeping in bed next to him believing he is fighting off pirates attacking his family).

No specific "sleep neurotransmitter" has been identified that is responsible for the induction or maintenance of sleep, but many different types of neurochemicals (neurotransmitters, neuromodulators, neuropeptides, immune modulators) have been implicated. Adenosine is a potential sleep promoting neurotransmitter; its concentration in basal forebrain increases with prolonged wakefulness. Caffeine probably promotes alertness by blocking the adenosine $A_1$ receptor. Histamine and glutamine also appear to play important roles in promoting alertness and brain activation. Of particular importance to psychiatry, acetylcholine, released from neurons originating in the dorsal tegmentum, induces REM sleep and cortical activation. Serotonin and norepinephrine, on the other hand, inhibit REM sleep, possibly by inhibition of cholinergic neurons responsible for REM sleep. These physiological mechanisms may be involved in both depression and the sleep disturbances associated with depression and other neuropsychiatric disorders, such as short REM latency (see below). For example, depression may be associated with a functional serotonin deficiency. The suppression of REM sleep during treatment with antidepressants may reflect either enhanced serotoninergic or noradrenergic neurotransmission or anticholinergic effects.

## SLEEP DISORDERS

This chapter attempts to provide a framework for psychiatrists and other mental health specialists to use in understanding the multiple causes of the sleep disorders, their diagnostic evaluation, and their treatment. Sleep disorders can be divided into four major categories: (1) insomnias, disorders associated with complaints of insufficient, disturbed, or nonrestorative sleep, (2) hypersomnias, disorders of excessive sleepiness, (3) disturbances of the circadian sleep–wake cycle, and (4) parasomnias, abnormal behaviors or abnormal physiological events in sleep. By definition, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) limits itself to chronic disorders (at least 1 month in duration) (American Psychiatric Association 2000). On the other hand, the *International Classification of Sleep Disorders* (ICSD) includes sleep disorders of short-term and intermediate duration, which in fact are more common than chronic disorders (American Academy of Sleep Medicine 2005).

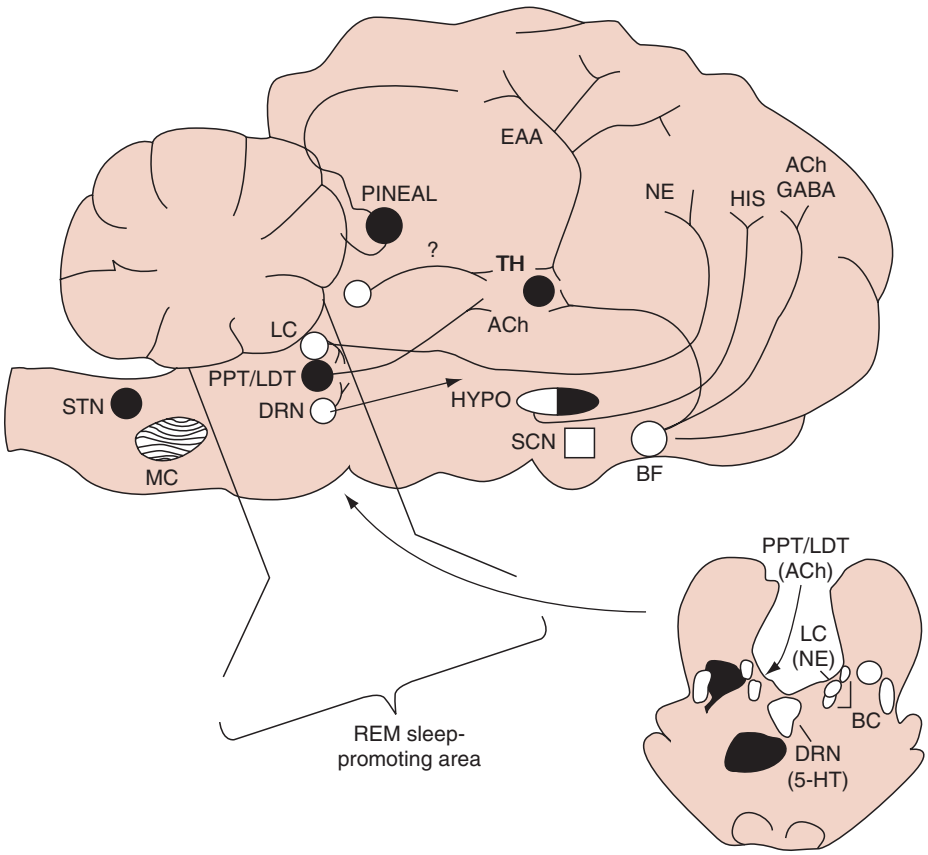



**Figure 79–3** *The neuroanatomy of sleep and wakefulness. ACh, acetylcholine; BC, brachium conjunctivum; BF, basal forebrain; DRN, dorsal raphe nucleus; EAA, excitatory amino acid; GABA, γ-aminobutyric acid; HIS, histamine; 5-HT, 5-hydroxytryptamine; HYPO, hypothalamus; LC, locus coeruleus; MC, magnocellular; NE, norepinephrine; PPT/LDT, pedunculopontine tegmental/lateral dorsal tegmental; SCN, suprachiasmatic nucleus; STN, solitary tract nucleus; TH, thalamus.*

## General Approach to the Patient with a Sleep Disorder

Disorders of sleep and wakefulness are common. Insomnia complaints are reported by about one-third of adult Americans during a 1-year period (Ancoli-Israel and Roth 1999); clinically significant obstructive sleep apnea may be seen in as many as 10% of working, middle-aged men (Young et al. 1993) and sleepiness is an under-recognized cause of dysphoria, automobile accidents, and mismanagement of patients by sleep-deprived physicians. All physicians hear complaints of sleep problems. Psychiatrists may be even more likely than other medical specialists to receive these complaints. Of particular importance for mental disorders, prospective epidemiological studies suggest that persistent complaints of either insomnia (Ford and Kamerow 1989, Livingston et al. 1993) or hypersomnia (Ford and Kamerow 1989) are risk factors for the later onset of depression, anxiety disorders, and substance abuse.

Clinicians treating patients with sleep complaints must have a diagnostic framework with which to obtain the information needed about both the patient as a person and his or her disorder. Two issues are particularly important: (i) How long has the patient had the sleep complaint? Transient insomnia and short-term insomnia, for example, usually occur in persons undergoing acute stress or other disruptions, such as admission to a hospital, jet lag, bereavement, or change in medications. Chronic sleep disorders, on the other hand, are often multidetermined and multifaceted. (ii) Does the patient suffer from any preexisting or comorbid disorders? Does another condition cause the sleep complaint, modify a sleep complaint, or affect possible treatments?

A detailed history of the complaint and attendant symptoms must be obtained (Tables 79–3 and 79–4). Special attention should be given to the timing of sleep and wakefulness; quantitative subjective measures of sleep and wakefulness, and when appropriate, qualitative measures of sleep; abnormal sleep-related behaviors; respiratory difficulties; medications or other substances affecting sleep, wakefulness, or arousal; expectations, concerns, attitudes about sleep, and efforts used by the patient to control symptoms; and the sleep–wake environment.

One approach to the differential diagnosis of persistent sleep disorders is suggested in the algorithm in Figure 79–4. First, determine whether the sleep complaint is comorbid with a medical, psychiatric, or substance use disorder. Second, consider the role of circadian rhythm disturbances and sleep disorders associated with abnormal events occurring predominantly during sleep (such as periodic limb movements, REM behavior disorder or parasomnias). Finally, evaluate in greater detail complaints of insomnia (difficulty initiating or maintaining sleep) and

**Table 79–3 Office Evaluation of Chronic Sleep Complaints**

- Detailed history and review of the sleep complaint: predisposing, precipitating, and perpetuating factors
- Review of difficulties falling asleep, maintaining sleep, and awakening early
- Timing of sleep and wakefulness in the 24-hr day
- Evidence of EDS and fatigue
- Bedtime routines, sleep setting, physical security, preoccupations, anxiety, beliefs about sleep and sleep loss, fears about consequences of sleep loss
- Medical and neurological history and physical examination, routine laboratory examinations: look for obesity, short fat neck, enlarged tonsils, narrow upper oral airway, foreshortened jaw (retrognathia), and hypertension
- Psychiatric history and examination
- Use of prescription and nonprescription medications, alcohol, stimulants, caffeine, toxins, insecticides, and other substances
- Evidence of sleep-related breathing disorders: snoring, orthopnea, dyspnea, headaches, falling out of bed, nocturia
- Abnormal movements or behaviors associated with sleep disorders: "jerky legs," leg movements, myoclonus, restless legs, leg cramps, nightmares, enuresis, sleepwalking, epilepsy, bruxism, sleep paralysis, hypnagogic hallucinations, cataplexy, night sweats, and so on
- Social and occupational history, marital status, living conditions, financial and security concerns, physical activity
- Sleep–wake diary for 2 weeks
- Interview with bed partners or persons who observe patient during sleep

excessive sleepiness. The possible role of sleep apnea as a disruptive factor in sleep continuity should be considered even if the principal complaint is one of insomnia.

## Role of the Sleep Laboratory in Clinical Sleep Disorders

Clinicians can successfully diagnose most sleep disorders by traditional clinical methods. Referral to a specialized sleep disorders center, however, should be considered in patients with symptoms of intractable insomnia or persistent excessive daytime sleepiness (EDS). Patients suspected of primary sleep disorders such as narcolepsy, RBD, sleep apnea, or periodic limb movements in sleep (PLMS) would also benefit from a referral to a sleep specialist. Specialists in sleep disorders medicine will evaluate the patient and, if necessary, arrange for sleep laboratory or ambulatory diagnostic procedures.

The most frequently utilized sleep laboratory evaluation is polysomnography (PSG), which typically records the EEG activity, eye movements with the electrooculogram (EOG), and muscle tone with the electromyogram (EMG) from the chin (submental) muscles. These measures are used to determine sleep stages. To evaluate sleep-related respiration and cardiovascular function, measures are made of nasal and oral air flow with a thermistor or cannula; of sounds of breathing and snoring with a small microphone on the neck or near the mouth; of respiratory movements of the chest and abdominal walls; of heart rate with the electrocardiogram; and of blood-oxygen saturation with finger oximetry. To evaluate PLMS, an EMG from the shin (anterior tibial) muscles is obtained. Other more specialized tests include intraesophageal pressures, which increase during the upper airway resistance syndrome if respiration is impeded and measures of gastroesophageal pH.

**Table 79–4 Selected Disorders and Terms Used in Clinical Sleep Disorders Medicine**

| Term | Definition |
|---|---|
| Apnea index | Number of apneic events per hour of sleep; usually is considered pathological if ≥ 5. |
| Cataplexy | Sudden, brief loss of muscle tone in the waking stage, usually triggered by emotional arousal (laughing, anger, surprise), involving either a few muscle groups (i.e., facial) or most of major antigravity muscles of the body; may be related to muscle atonia normally occurring during REM sleep; is associated with narcolepsy. |
| Hypopnea | 50% or more reduction in respiratory depth for 10 s or more during sleep. |
| MSLT | An objective method for determining daytime sleepiness; sleep latency and REM latency are determined for four or five naps (i.e., a 20-min opportunity to sleep every 2 hr between 10 am and 6 pm); normal mean values are above 15 min. |
| MWT | An objective method for determining daytime sleepiness; which measures the capacity to remain awake |
| PLMS index | Number of leg kicks per hour of sleep; usually is considered pathological if ≥ 5. |
| PSG | Describes detailed, sleep laboratory-based, clinical evaluation of patient with sleep disorder; may include EEG measures, eye movements, muscle tone at chin and limbs, respiratory movements of chest and abdomen, oxygen saturation, electrocardiogram, nocturnal penile tumescence, esophageal pH, as indicated. |
| Respiratory disturbance index | Number of apneas and hypopneas per hour of sleep; also called apnea-hypopnea index. |
| Sleep apnea | Sleep-related breathing disorder characterized by at least five episodes of apnea per hour of sleep, each longer than 10 s in duration. |

Daytime sleepiness can be evaluated in the sleep laboratory with the Multiple Sleep Latency Test (MSLT), which measures sleep latency during opportunities for napping during the day or with the Maintenance of Wakefulness Test (MWT), which measures the capacity to remain awake (see Table 79–4). Both tests consist of four or five recordings, typically obtained at 2-hr intervals over the course of a day. In the MSLT, the patient is asked to fall asleep while lying in bed in a dark, quiet room. In the MWT, the patient is asked to remain awake while sitting upright in a dimly lit room. In both tests, EEG measures are used to determine the appearance of sleep. In addition, subjective sleepiness can be assessed by questionnaires. One of the most widely used scales is the Epworth Sleepiness Scale (Johns 1994), in which the subject rates himself or herself from 0 (not sleepy) to 3 (very sleepy) in eight situations, for example, sitting quietly in a car, sitting and talking to someone, etc.

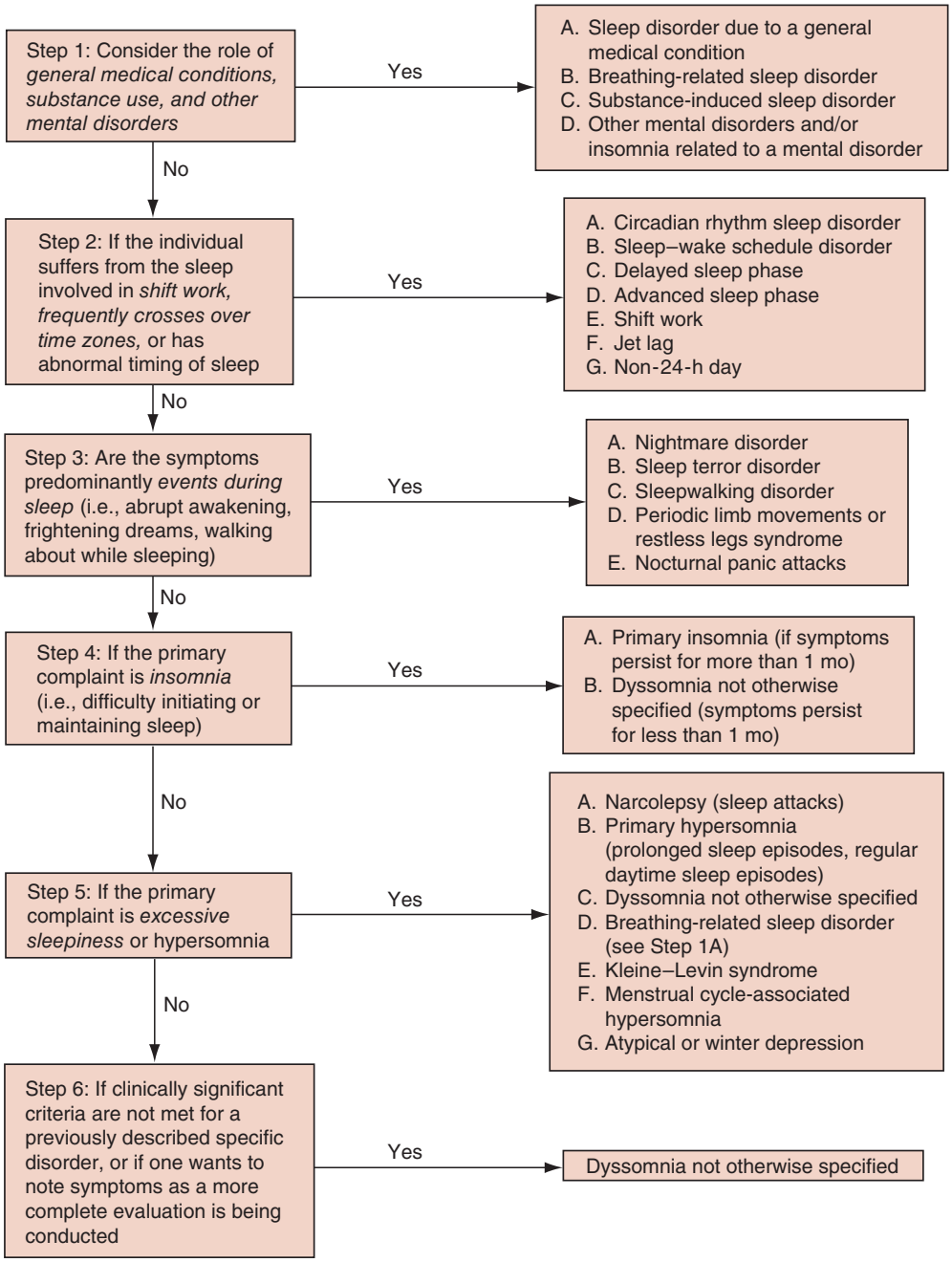



**Figure 79–4** *An algorithm for the differential diagnosis of persistent sleep disorder complaints.*

## Chronic Insomnia

### Diagnosis

#### Definition and Diagnostic Features

According to DSM-IV-TR criteria, insomnia is a subjective complaint of poor, insufficient, or nonrestorative sleep, given sufficient time in bed, lasting more than a month and associated with significant daytime distress or impairment. Insomnia can be primary (not associated with a medical or psychiatric condition or with substance abuse) or due to medical illness, psychiatric illness, or medication/substance use. The etiology of primary insomnia is unclear. Some patients may be genetically predisposed to insomnia, with reduced homeostatic sleep drive. Other predisposing factors, such as personality traits (e.g., anxious, obsessional, depressive, and avoidant personality traits), also put individuals at risk for developing insomnia. Precipitating and perpetuating factors can result in transient insomnia becoming chronic.

#### Assessment of Insomnia

Diagnosis and treatment of chronic insomnia are often challenging and difficult. PSG is rarely indicated as part of the routine evaluation of the insomnia patient. Both the clinician and the patient must be forbearing and realistic as they jointly explore the evolution, causes, manifestations,

and ramifications of the sleep complaint. Simple answers and simple solutions are rare. Even if insomnia is initially precipitated by a single event or condition, chronic insomnia is usually maintained by various predisposing and perpetuating factors. For example, a business woman in her early thirties had insomnia during a period of intense stress in her business, but it continued long after the stress had been satisfactorily resolved. Factors that contributed to chronicity included her lifelong somewhat obsessive, anxious personality structure and, after the onset of her insomnia, her gradually escalating concerns about her insomnia; these resulted in advanced sleep phase as she tried to spend more time in bed for "rest" and use of wine at bedtime to sleep. Her use of wine at bedtime absolutely contributed to her fragmented sleep. Properly sorting out and dealing with these factors led to resolution of her complaints.

### Epidemiology

In general surveys of the prevalence of insomnia in the population, about 1 in 3 people reported "insomnia" during the previous year, about 1 in 6 described it as "serious," and about 1 in 12 called it "chronic" (Ancoli-Israel and Roth 1999). The rates of insomnia are higher in women than in men, in the elderly than in the young, and in the lower than in the higher socioeconomic classes. In a survey conducted by the Gallup Poll for the National Sleep Foundation (Ancoli-Israel and Roth 1999, Roth and Ancoli-Israel 1999), the most common complaint of insomniacs was waking up feeling drowsy rather than specific complaints about sleep, implying that the sleepiness insomniacs experience could be associated with some morbidity. Compared with transient insomniacs or normal control subjects, chronic insomniacs reported greater difficulty enjoying family and social relationships, greater difficulty concentrating, more problems with memory, greater frequency of falling asleep while visiting friends, and more automobile accidents due to sleepiness. Nevertheless, only about 5% of patients with chronic insomnia ever sought medical attention specifically for insomnia. Only a minority of patients have ever used prescription sleeping pills. On the other hand, most psychiatrists do not routinely inquire about difficulties with sleep and wakefulness. If these patients with chronic or serious insomnia are to be helped, psychiatrists must be proactive and ask specific questions about sleep and its disorders.

**DSM-IV-TR Criteria**

**Primary Insomnia**

A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.

B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.

D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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### Comorbidity Patterns

A recent National Institutes of Health (NIH) (National Institutes of Health 2005) State-of-the-Science conference on insomnia focused extensively on comorbid insomnia, emphasizing the need to recognize how medical and psychiatric conditions interact and impact on insomnia complaints. The concept of comorbidity recognizes that two pathological states, for example, depression and insomnia, likely exist concurrently and will influence each other's course. Treating one does not mean necessarily that the other will improve; on the other hand, exacerbation in one may make the comorbid condition worse.

## Insomnia Comorbid with Psychiatric Disorders

As noted above, the DSM-IV-TR classification system has a specific category for Primary Insomnia, a disorder characterized as not being related to or caused by another sleep, mental, medical disorder or affects of a medication. Breathing-Related Sleep Disorder (BRSD) is a separate diagnosis, and is recognized as presenting at times with insomnia complaints.

A number of recent changes in the DSM-IV-TR have increased the utility of this instrument for the diagnosis of sleep disorders. These include codes for Insomnia due to specified Axis I and Axis II Disorder (e.g., Major Depressive Disorder and Generalized Anxiety Disorder) and Hypersomnia due to specified Axis I and Axis II Disorder (e.g., Major Depressive Disorder and Dysthymic Disorder). Also included is a code for Sleep Disorder due to a specified General Medical Condition, with the capacity to code this as Insomnia, a Hypersomnia, a Parasomnia, or a Mixed Type Disorder.

Circadian Rhythm Sleep Disorder is given a separate category, with separate coding for Delayed Sleep Phase, Jet Lag, and Shift Work Types. Substance-Induced Sleep Disorders also have specific codes based on the inducing agent (i.e., alcohol, opiods, amphetamines, etc.).

Although there is a specific category for "Primary Insomnia", there is no formal category for "Secondary Insomnia". Instead, many diagnoses reside within the broad "Dyssomnia Not Otherwise Specified" section for disturbances such as Restless Leg Syndrome (RLS) and Insomnia of Environmental Origin.

Subjective and objective disturbances of sleep are common features of many psychiatric disorders. Complaints may be of insomnia or hypersomnia, parasomnias (such as nightmares, night terrors, and nocturnal panic attacks), and circadian rhythm disturbances (early morning awakening). Before assuming that a significant sleep complaint invariably

signals a psychiatric diagnosis, mental health specialists should go through a careful differential diagnostic procedure to rule out medical, pharmacological, or other causes. Even if the sleep complaint is primarily related to an underlying psychiatric disorder, sleep disorders in the mentally ill may be exacerbated by many other factors, such as increasing age; comorbid psychiatric, sleep, and medical diagnoses; alcohol and substance abuse; effects of psychotropic or other medications; use of caffeinated beverages, nicotine, or other substances; lifestyle; past episodes of psychiatric illness (persisting "scars"); and cognitive, conditioned, and coping characteristics such as anticipatory anxiety about sleep as bedtime nears. Some features of these sleep disorders may persist during periods of clinical remission of the psychiatric disorder and may be influenced by genetic factors. Finally, even if the sleep complaint is precipitated by a nonpsychiatric factor, psychiatric and psychosocial skills may be useful in ferreting out predisposing and perpetuating factors involved in chronic sleep complaints.

Although signs and symptoms of sleep disturbance are common in most psychiatric disorders, an additional diagnosis of insomnia or hypersomnia related to another mental disorder is made according to DSM-IV-TR criteria only when the sleep disturbance is a predominant complaint and is sufficiently severe to warrant independent clinical attention. Many of the patients with this type of sleep disorder diagnosis focus on the sleep complaints to the exclusion of other symptoms related to the primary psychiatric disorder. For example, they may seek professional help with complaints of insomnia or oversleeping when they should be at work, excessive fatigue, or desire for sleeping pills, but initially, they minimize or strongly deny signs and symptoms related to poor mood, anxiety, obsessive rumination, alcohol abuse, or a personality disorder.

## Sleep Disturbances in Psychiatric Disorders: "Chicken or Egg?"

Chronic sleep disturbances may be risk factors for certain vulnerable individuals. For example, several longitudinal epidemiological studies reported that a persistent complaint of insomnia for a year was also a risk factor for the later onset of major depressive disorder, anxiety disorder, and substance abuse, for example, (Ford and Kamerow 1989, Livingston et al. 1993). One of these studies also assessed persistent hypersomnia and found that this complaint was a risk factor. Thus, specific sleep characteristics may predispose to, or be a risk factor for, later development of psychiatric or substance abuse disorders. Again, the complaint of chronic insomnia or hypersomnia or normal short sleep cannot always be equated with objective sleep abnormalities, but it should at least alert the psychiatrist to the possibility that the patient deserves careful monitoring for a time.

Sleep disruption may be particularly harmful to some persons, for example, bipolar disorder patients, whether euthymic or depressed, in whom sleep deprivation may precipitate a manic episode (Wehr 1992). Mania is not uncommon with jet lag or work-related sleep deprivation in bipolar disorder patients. Behavioral and apparent personality changes with sleep deprivation are probably common but more often ignored in everyday life. The irritability of sleep-deprived children is known to most parents; and who of us has not had a "bad day" after a "bad night"? Thus, the role of subjective insomnia and sleep loss in the prediction and prevention of mood disorders deserves further attention from psychiatrists and researchers.

Whereas insomnia is probably the most common sleep complaint in most psychiatric disorders, hypersomnia is not an infrequent complaint, especially in association with the following: bipolar mood disorder during depressed periods; major depressive disorder with atypical features (i.e., hypersomniac, hyperphagic patients with "leaden paralysis" and loss of energy); seasonal (winter) depression; stimulant abusers during withdrawal; some patients with personality disorders; and patients who are heavily sedated with anxiolytic, antipsychotic, or antidepressant medications, among other disorders.

More studies of sleep and sleep-related phenomenology have been conducted in *depression* than in any other disorder (Figure 79–5). Despite the common clinical impression that early morning wakefulness is a predominant symptom in depression, most of the objective measures in recent years have implicated abnormalities occurring at sleep onset and during the first NREM and REM periods: prolonged sleep latency; reduced Stages 3 and 4 sleep; increased duration and REM density of the first REM period; and associated neuroendocrine abnormalities, abnormalities in the HPA axis including increases in CRH and cortisol secretion, and abnormal dexamethasone suppression tests (Nestler et al. 2002). Furthermore, some studies have suggested that short REM latency or reduced delta sleep ratio (amount of delta waves in first NREM periods compared with second NREM periods) may predict relapse in depressed patients. Some of these sleep-related abnormalities appear to persist during periods of clinical remission, such as short REM latency, loss of Stages 3 and 4 sleep, and blunted nocturnal growth hormone release. Genetic factors may influence some of these measures, including short REM latency.

Given the prevalence of sleep disturbance in depression, one puzzle is the well-established observation that sleep deprivation and some other manipulations of sleep have antidepressant effects in about half of depressed patients. Total and partial sleep deprivation for one night has the best-documented benefits but, unfortunately, has not gained widespread clinical utility because most patients usually wake up depressed again after napping or sleeping. One exception may be premenstrual depression: partial sleep deprivation for one night at the onset of symptoms often aborts the symptoms for that month.

Even though the polygraphic sleep findings in depression do not appear to be diagnostically specific, they remain among the best-documented biological abnormalities of any psychiatric disorder at this time. One challenge is to understand their pathophysiological mechanism. Because of the shallow, fragmented sleep and response to sleep deprivation, the sleep of patients with depression has been described as "overaroused." For instance, the antidepressant response of sleep deprivation may "dampen down" an overly aroused limbic system in a subgroup of patients. Several studies have shown that responders to sleep deprivation differ from nonresponders at baseline assessment before sleep deprivation by having a higher level of metabolic activity in the cingulate gyrus and that this overactivity

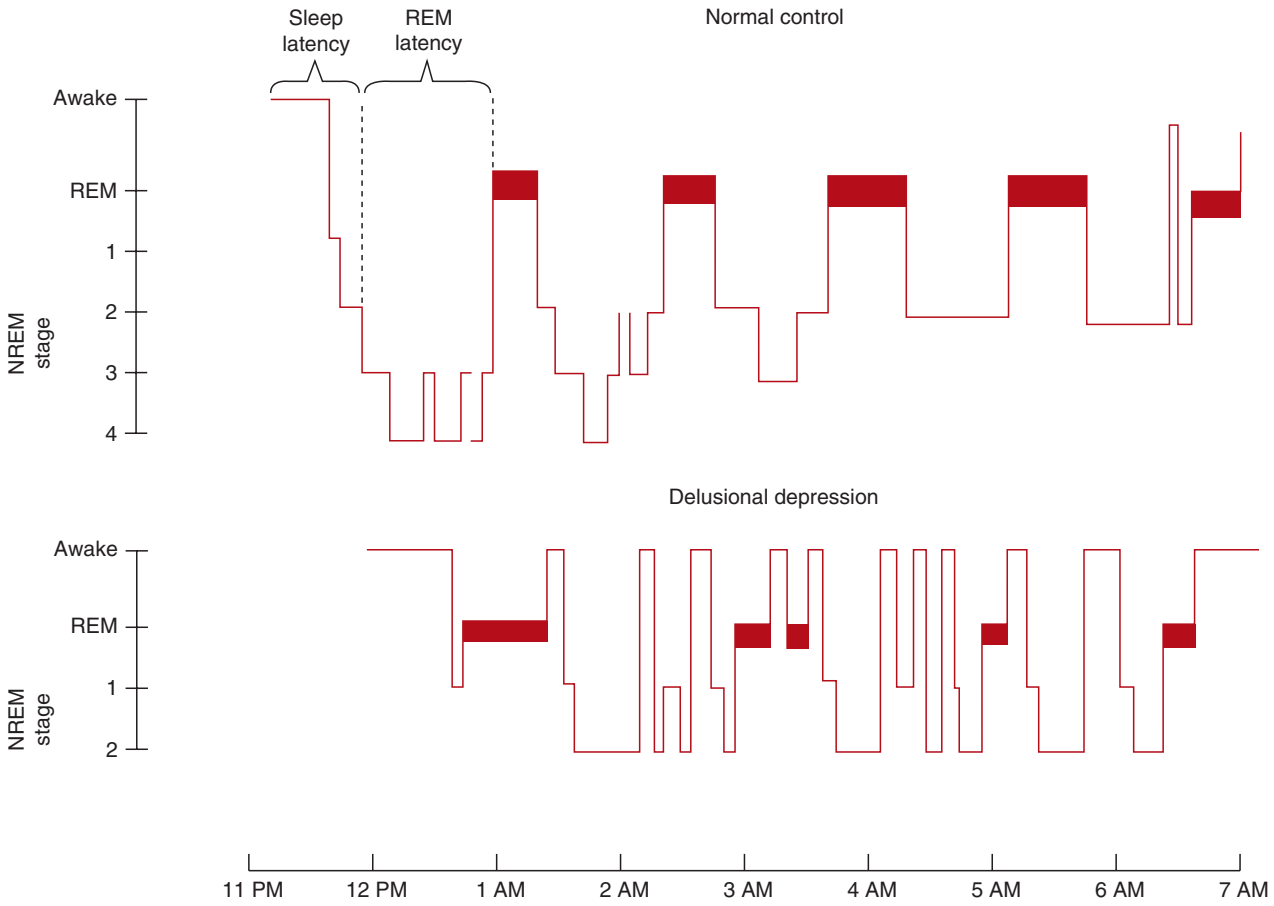



**Figure 79–5** *Polygraphic sleep characteristics of a patient with delusional depression compared with those of a normal control subject.*

approaches normality with clinical improvement (Ebert et al. 1994, Gillin et al. 2001).

## Treatment of Chronic Insomnia

Clinical management of insomnia is multidimensional, requiring behavioral and pharmacological approaches.

### Behavioral Treatments

Treatment of insomnia should, insofar as possible, be directed at identifiable causes, or those factors that perpetuate the disorders, such as temperament and lifestyle, ineffective coping and defense mechanisms, inappropriate use of alcohol or other substances, maladaptive sleep–wake schedules, and excessive worry about poor sleep. The harder these individuals try to sleep, the more elusive sleep becomes. They keep themselves awake by their apprehensions: "If I don't get to sleep right now, I won't be able to function tomorrow."

Table 79–5 lists the more common behavioral treatments. The most effective treatment for insomnia is cognitive–behavioral therapy (CBT), which as the name implies, is made up of both a cognitive and a behavioral component. The cognitive component reduces autonomic and cognitive arousal, targets maladaptive coping, challenges dysfunctional beliefs about sleep (e.g., "I must sleep 8 hr"), corrects unrealistic expectations (e.g., "I should never wake up at night"), reappraises perceptions of the insomnia consequences (e.g., "I can't work without 8 hr of sleep"), and recognizes maladaptive thoughts and associated catastrophic ideas that foster insomnia. Some of the common worries and catastrophic thoughts that patients with insomnia endorse include: "If I don't sleep well tonight I will…do poorly at work and get fired, be irritable with my husband who will divorce me, get sick and die, look unattractive and people will not want to be in my presence." The CBT challenges

**Table 79–5 Behavioral Techniques for the Treatment of Insomnia**

| Techniques | Goal |
|---|---|
| Sleep hygiene | Promote habits that help sleep; provide rationale for subsequent instructions |
| Stimulus control therapy | Strengthen bed and bedroom as sleep stimulus |
| Sleep restriction | Improve sleep continuity by limiting time spent in bed |
| Relaxation | Reduce arousal and decrease anxiety (progressive muscular relaxation, transcendental meditation, yoga, biofeedback) |
| CBT | Combines sleep reduction, stimulus control techniques, sleep restriction with cognitive therapy, challenge dysfunctional beliefs and misperceptions about sleep and insomnia |

**Table 79–6 Sleep Hygiene and Stimulus Control Rules**

| |
|---|
| Curtail time spent awake while in bed. |
| Go to bed only when sleepy. |
| Do not remain in bed for more than 20–30 min while awake. |
| Get up at the same time each day. |
| Avoid looking at the bedroom clock. |
| Avoid caffeine, alcohol, and tobacco near bedtime. |
| Exercise during the morning or afternoon. |
| Eat a light snack before bed. |
| Adjust sleeping environment for optimal temperature, sound, and darkness. |
| Do not worry right before and in bed. Use the bed for sleeping. |
| Do not nap during the day. |

black and white thinking, such as words like "always" (sleep poorly) or "never" (perform well) (Perlis et al. 2005).

The behavioral component of CBT identifies patient-specific perpetuating factors of insomnia and eliminates them behaviorally (e.g., use of alcohol to fall asleep, watching scary movies before going to bed). The patient is encouraged to create a relaxing before bedtime ritual (e.g., diary writing, hot bath, meditation) and not to try to compensate for a poor night's sleep by spending more time in bed in the morning or napping (Perlis et al. 2005). The behavioral component targets maladaptive coping (e.g., staying in bed for 12 hr), eliminates sleep incompatible behaviors (e.g., poor sleep hygiene), regularizes the sleep schedule, and educates patients about healthier sleep practices. The two behavioral treatments most commonly applied to accomplish these goals are stimulus-control therapy and sleep restriction therapy (Bootzin and Nicassio 1978, Morin et al. 1994, Spielman et al. 1987). The aim of stimulus control therapy is to break the negative associations of being in bed unable to sleep (Table 79–6). It is especially helpful for patients with sleep-onset insomnia and prolonged awakenings. Sleep restriction therapy (Table 79–7) is based on the observation that more time spent in bed leads to more fragmented sleep. Both therapies may take 3−4 weeks or longer to be effective.

CBT is effective for 70−80% of insomnia patients. It significantly reduces several measures of insomnia, including sleep-onset latency and wake-after-sleep onset. Aside from the clinically measurable changes, CBT enables many patients to regain a feeling of control over their sleep, thereby reducing the emotional distress that sleep disturbances cause (Morin et al. 1994).

**Table 79–7 Sleep Restriction Therapy**

| |
|---|
| Stay in bed for the amount of time you think you sleep each night, plus 15 min. |
| Get up at the same time each day. |
| Do not nap during the day. |
| When sleep efficiency is 85% (i.e., sleeping for 85% of the time in bed), go to bed 15 min earlier. |
| Repeat this process until you are sleeping for 8 hr or the desired amount of time. |
| Example: if you report sleeping only 5 hr a night and you normally get up at 6 AM, you are allowed to be in bed from 12:45 AM until 6 AM. |

**Table 79–8 Benzodiazepines**

| Drug | Trade Name | Half-life (hr) | Dose (mg) |
|---|---|---|---|
| Flurazepam HCL | Dalmane | 47−100* | 15 or 30 |
| Quazepam | Doral | 39−73* | 7.5 or 15 |
| Estazolam | Prosom | 10−24 | 0.5, 1 or 2 |
| Temazepam | Restoril | 3.5−18.4 | 7.5, 15 or 30 |
| Triazolam | Halcion | 1.5−5.5 | 0.125 or 0.25 |

*Includes active metabolites.

## Pharmacological Treatment

The ideal sleeping pill would shorten latency to sleep; maintain normal physiological sleep all night without blocking normal behavioral responses to the crying baby or the alarm clock; leave neither hangover nor withdrawal effects the next day; and be devoid of tolerance and side effects such as impairment of breathing, cognition, ambulation, and coordination. Furthermore, sleeping pills should not be habit-forming or addictive. Unfortunately, the ideal sleeping pill has yet to be developed.

There are numerous nonbehavioral, options for the treatment of insomnia. These include dietary supplements and herbal preparations, the over-the-counter medications such as antihistamines ($H_1$ receptor antagonists), off-label use of sedating antidepressants and other sedating medications, benzodiazepines receptor agonists (BzRAs) (Tables 79–8 and 79–9) and a MT receptor agonist (Table 79–9). In the NIH State-of-the-Science conference on insomnia (National Institutes of Health 2005), the panel concluded that there was very little evidence that dietary supplements and herbal remedies showed any benefit beyond placebo and that although MT was safe, there was little evidence for efficacy in the treatment of insomnia.

The NIH (National Institutes of Health 2005) also concluded that not only was there no systematic evidence for efficacy of antihistamines ($H_1$ receptor antagonists), but there were significant concerns about risks associated with the use of these agents. While the advantages of these drugs are their low cost and easy availability, the disadvantages are inconsistent efficacy, rapid development of tolerance to sedative effects, potential for residual effects, no well-defined effective dose and poorly defined half-life. The adverse effects of antihistamines can include dry mouth, blurred vision, urinary retention, constipation, risk of increased intraocular pressure in individuals with narrow angle glaucoma, residual daytime sedation, and anticholinergic effects which may lead to diminished cognitive function and delirium (which is of particular concern in the elderly) (Richardson et al. 2002).

Although the sedating antidepressants, such as trazodone or doxepin, are widely used off-label for the treatment of chronic insomnia, the NIH (National Institutes of Health 2005) concluded that all antidepressants have potentially significant adverse effects, raising concerns about the risk-benefit ratio. Trazodone, for example, has a 6.4-hr half-life in adults, and an 11.6-hr half-life in elderly. It is perceived to be safe, has generic availability, unscheduled status and lack of restrictions on prescription

**Table 79–9 Nonbenzodiazepines and MT Receptor Agonist**

| Drug | Trade Name | Indication | Half-life (hr) | Approved Doses (mg) | Required inactivity (hr) |
|---|---|---|---|---|---|
| Eszopiclone | Lunesta | Insomnia characterized by difficulties with sleep onset and/or sleep maintenance; approved for long-term treatment | 6 | 1, 2, 3 | 8 |
| Zaleplon | Sonata | Insomnia characterized by difficulties with sleep onset; approved for short-term treatment. | 1 | 5, 10, 20 | 4 |
| Zolpidem | Ambien | Insomnia characterized by difficulties with sleep onset; approved for short-term treatment. | 2.5 | 5, 10 | 7–8 |
| Zolpidem CR | Ambien CR | Insomnia characterized by difficulties with sleep onset and/or sleep maintenance; approved for long-term treatment. | 2.8 | 6.25, 12.5 | 7–8 |
| Ramelteon | Rozerem | Insomnia characterized by difficulty with sleep onset; approved for long-term treatment. | 1–2.6 | 8 | — |

duration. However, there are very few controlled studies of trazodone, with most trials usually consisting of less than 30 patients, of short duration (≤3 weeks), conducted in patients with comorbid depression or serotonin reuptake inhibitor (SSRI) -induced insomnia, and rely on solely on subjective measurements (Mendelson 2005). In a 2-week study comparing trazodone 50 mg to zolpidem 10 mg and placebo in 306 insomnia patients, both trazodone and zolpidem significantly improved subjective sleep latency, sleep duration, number of awakenings, and wake time after sleep onset (WASO) during the first week (although sleep latency was significantly shorter with zolpidem). By the second week, however, there was no difference between trazodone and placebo (Walsh et al. 1998). Adverse effects of trazodone include drowsiness, dizziness, dry mouth, priapism, orthostatic hypotension and other cardiovascular events (Mendelson 2005). While sedating anti-depressants may be potentially advantageous for patients experiencing chronic insomnia with depression, there are little data to suggest efficacy in nondepressed patients with insomnia.

Use of other off-label medication, such as anti-psychotics and anti-convulsants was also discouraged as studies demonstrating the usefulness of these medications for the treatment of insomnia are lacking (National Institutes of Health 2005). The panel also concluded that there were greater risks than benefits with these medications. The use of antipsychotic medications also raises the risk of tardive dyskinesia, weight gain and development of type II diabetes mellitus.

The only U.S. Food and Drug Administration (FDA) approved medications for insomnia are the benzodiazepine receptor agonists (the older benzodiazepines and the newer nonbenzodiazepines) and one MT receptor agonist (see Tables 79–7 and 79–8). The older benzodiazepines are non-selective agonists of BZD benzodiazepine receptors whose advantages are decreased sleep latency and increased total sleep time, but whose risks include daytime sedation, cognitive impairment, motor incoordination, dependence and abuse, tolerance development and rebound insomnia after withdrawal (Mendelson et al. 2004).

The newer nonbenzodiazepines, eszopiclone, zaleplon, and zolpidem preferentially bind to the benzodiazepine receptor, enhancing the effect of gamma-Aminobutyric acid (GABA) alpha subunits 1–3 on the ventrolateral preoptic nucleus, promoting sleep (Dawson et al. 2005). The newer, nonbenzodiazepine receptor agonists have fewer side effects as they act on selected alpha sub-units of the GABA receptors.

Ramelteon is a selective agonist of MT ($MT_1$ and $MT_2$) receptors, and appears to work exclusively through effects on the SCN activity (Dubocovich et al. 2003). It is believed that the activity of ramelteon is the result of inhibition of alertness in the SCN ($MT_1$) and entrainment of the sleep/wake rhythm ($MT_2$). Ramelteon is the only FDA-approved hypnotic that is not a controlled substance due to its lack of significant or clinically relevant residual effects such as abuse potential, dependence, development of tolerance, withdrawal syndrome/rebound insomnia in clinical trials (McGechan and Wellington 2005).

The NIH, in reviewing the benzodiazepine receptor agonists, concluded that short, intermediate and long-acting benzodiazepines are all efficacious, but that short-acting nonbenzodiazepine hypnotics are effective in initiating sleep and/or maintaining sleep and have superior safety/adverse event profile to older agents (National Institutes of Health 2005). It is important to note that at the time of the NIH conference held in June 2005, ramelteon had not yet been FDA-approved and therefore was not considered as part of the conference or its conclusions.

Patients should be educated about the anticipated benefits and limitations of sleeping pills, side effects, and appropriate use, and should be followed up by office visits or phone calls regularly if prescriptions are renewed. Treatment of these patients should focus on the lowest possible effective dose for the treatment of insomnia.

## General Approaches to the Clinical Management of Sleep Disorders in Psychiatric Patients

The sleep complaint in the patient with an apparent psychiatric disorder deserves the same careful diagnostic and therapeutic attention that it does in any patient. Just because a patient is depressed does not mean that the complaint of insomnia or hypersomnia can be explained away as a symptom of depression. Too many patients with depression have been found to have a breathing-related sleep disorder; too many patients with panic disorder to have insomnia secondary to caffeine. Chronic sleep complaints are multidetermined and multifaceted, even in many psychiatric patients. Differential diagnosis remains the first obligation of the psychiatrist before definitive treatment, which should be aimed at the underlying cause or causes.

Nonspecific treatments, such as use of sleep hygiene principles, are often helpful for both the sleep complaints and the underlying psychiatric disorders. In particular, bipolar disorder patients and patients whose daily activities are poorly organized (like patients with chronic schizophrenia and patients with certain personality disorders) may benefit from fairly rigid sleep–wake and light–dark schedules to synchronize circadian rhythms and impose structure on their behavior. Physical exercise, meditation, relaxation methods, sleep restriction therapy, and cognitive psychotherapy may help patients manage anxiety, rumination, and conditioned psychophysiological insomnia that often cause sleeplessness at night and fatigue during the day. Partial or total sleep deprivation may be like "paradoxical intention" therapy in the treatment of major depressive disorder or premenstrual dysphoric disorder but should probably be avoided in bipolar depression.

## Hypersomnia

The most recent version of the International Classification of Sleep Disorders (American Academy of Sleep Medicine 2005) devotes a section to Hypersomnia of Central Origin, differentiated from Sleep-Related Breathing Disorders, which are also likely causes of excessive sleepiness. Within the Hypersomnia category, three conditions are of particular interest and relevance to psychiatrist: Narcolepy, and Idiopathic and Recurrent Hypersomnia.

### Narcolepsy

#### Diagnosis

##### *Definition and Diagnostic Features*

Narcolepsy is associated with a pentad of symptoms: (1) EDS, characterized by irresistible "attacks" of sleep in inappropriate situations such as driving a car, talking to a supervisor, or social events, (2) cataplexy, a sudden bilateral loss of muscle tone, usually lasting seconds to minutes, generally precipitated by strong emotions such as laughter, anger, or surprise, (3) poor or disturbed nocturnal sleep, (4) hypnagogic hallucinations, varied dreams at sleep onset, and (5) sleep paralysis, a brief period of paralysis associated with the transitions into, and out of, sleep.

Narcolepsy is associated with significant social and financial impairment for affected individuals and their families. For example, automobile accidents may result from either sleepiness or cataplexy. Most states prohibit narcoleptic patients from driving, at least as long as they are symptomatic.

**DSM-IV-TR Criteria**

**Narcolepsy**

**A.** Irresistible attacks of unrefreshing sleep that occur daily for at least 3 months.

B. The presence of one or both of the following:

(1) cataplexy (i.e., brief episodes of sudden bilateral loss of muscle tone, most often in association with intense emotion)

(2) recurrent intrusions of elements of REM sleep into the transition between sleep and wakefulness, as manifested by either hypnopompic or hypnagogic hallucinations or sleep paralysis at the beginning or end of sleep episodes

C. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another general medical condition.

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##### *Epidemiology*

Narcolepsy is not a rare disease. The prevalence rate of 0.03−0.16% approximates that of multiple sclerosis.

##### *Course*

The disorder is lifelong. The first symptom is usually excessive sleepiness, typically developing during the late teens and early twenties. The full syndrome of cataplexy and other symptoms may be seen in association with the initial complaints of excessive sleepiness, but more often presents at a later date, typically within several years but at time delayed as long as 20 years. Once established, the disorder may progress to some degree with regard to development of additional symptoms (i.e., cataplexy and/ or other REM-intrusion symptoms), but patients typically do not experience a progression in the severity of their hypersomnia complaints.

##### *Differential Diagnosis*

Observers may mistake classic sleepiness in its mild form as withdrawal, poor motivation, negativism, and hostility. The hypnagogic imagery and sleep paralysis symptoms, alone and in combination, may resemble bizarre psychiatric illness. Like many medical disorders, narcolepsy presents a wide range of severity, from mild to cases so severe that employment is functionally impossible. Partial remissions and exacerbations occur. Sleep paralysis and hypnagogic imagery may be seen without cataplexy; cataplexy may present in isolation without other REM-associated phenomena. The presence of REM sleep onset at night or during daytime naps, an important sleep laboratory parameter, remains the most valid and reliable method available for diagnosing narcolepsy. Because of the seriousness of the disorder and likelihood that amphetamine or other stimulants will be used to treat the patient at some time, it is important that the diagnosis of narcolepsy be objectively verified as soon as possible. Furthermore, stimulant abusers have been known to feign symptoms of narcolepsy to obtain prescriptions.

##### *Etiology and Pathophysiology*

Narcolepsy is now understood as a physiological disturbance of REM sleep regulation, whose etiology is determined by both hereditary and autoimmune components (Lin et al. 1999, Nishino et al. 2000, Chemelli et al. 2005). It is also seen in dogs and other mammals. Genetic markers in humans (Nishino et al. 2000, Mignot et al. 1991, 1993) and basic neurochemical and neurophysiological studies in

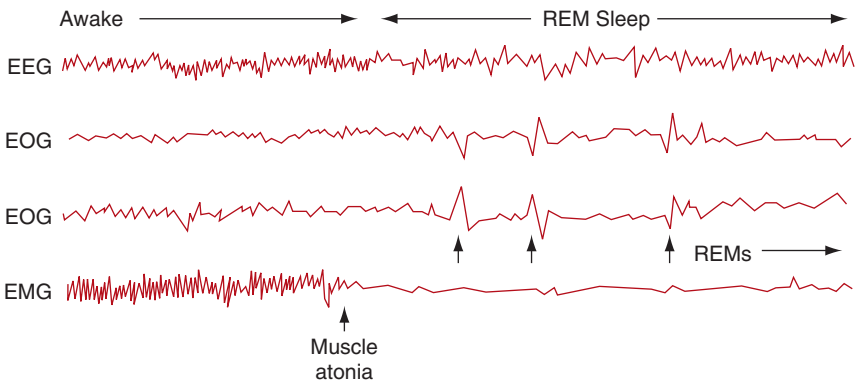



**Figure 79–6** *REM-onset sleep in a patient with narcolepsy. EEG, Electroencephalogram; EOG, electrooculogram; EMG, electromyogram; REMs, rapid eye movements.*

canine narcolepsy (Lin et al. 1999, Mignot et al. 1993, Siegel et al. 1992) may clarify the basic pathophysiological process of human narcolepsy.

Narcoleptic patients often enter REM sleep right after sleep onset ("sleep-onset REM periods"), reflecting an abnormally short or even nonexistent first NREM sleep period (Figure 79–6). Several of the core symptoms of narcolepsy can be understood as abnormal physiological representations of normal REM sleep. For example, cataplexy can be understood as an abrupt presentation during wakefulness of the paralysis normally seen in REM sleep. Cataplexy is usually triggered by an emotional stimulus. Sleep-onset REM periods may be subjectively appreciated as hypnagogic hallucinations, which may be accompanied by sleep paralysis. Dissociated REM sleep inhibition of the voluntary musculature may lead to complaints of cataplexy and sleep paralysis.

A strong association between narcolepsy and the human leukocyte antigen HLA-DR2 phenotype has been demonstrated (Rosenthal et al. 1991). Studies to date suggest that between 90 and 100% of Asian and white narcoleptics have the HLA-DR2 and DQwl phenotype, versus 20−40% of nonnarcoleptic control subjects. The frequent occurrence of this trait in "normal" populations limits the utility of this test for diagnostic purposes.

In recent years, a potential biochemical abnormality has been identified in both canine and human narcolepsy. Narcoleptic dogs appear to have a nonfunctional type 2 orexin receptor (OX2R) for orexin (hypocretin), a peptide neurotransmitter that has also been associated with feeding and energy metabolism. "Knockout" mice, which no longer make this peptide, appear to have a narcoleptic-like syndrome. Levels of orexin/hypocretin have been reported to be low in both autopsied brains and spinal fluid in human narcoleptics (Lin et al. 1999, Nishino et al. 2000, Chemelli et al. 2005).

### Treatment

#### *Treatment Goals*

The major goals of treatment of narcolepsy include: (a) to improve quality of life, (b) to reduce EDS, and (c) to prevent cataplectic attacks.

#### *Pharmacological Treatment*

The major wake-promoting medications are: modafinil, various formulations of amphetamines, and methylphenidate. Modafinil is preferred on grounds of efficacy, safety, availability, and low risk of abuse and diversion. SSRIs such as fluoxetine and citalopram and tricyclic antidepressants such as protriptyline and clomipramine have been used to treat cataplexy, sleep paralysis, and hypnogogic hallucinations. Relatively little research data exist supporting the use of these agents, whose therapeutic effects are presumed to be related to their REM-suppressant effects, which may partially or completely block the appearance of REM-related symptoms (i.e., cataplexy, sleep paralysis, and hypnagogic hallucinations).

Another new drug, sodium oxybate (Xyrem), has been approved by the FDA for treatment of narcolepsy. Xyrem is another name for Gamma Hydroxybutyrate (GHB), a potent CNS sedative which has been demonstrated to be effective for treatment of cataplexy and symptoms of sleepiness in patients with narcolepsy. (Littner et al. 2001). GHB has been widely abused as an intoxicant and has become notorious as a "date-rape" drug. As a consequence of its abuse potential, access to it is tightly-controlled and it is available only through a single central pharmacy.

Xyrem is taken as an oral solution, mixed with water. Xyrem is usually taken in two divided doses, the first administered at bedtime and the second 2.5–4 hr later. Daily dosages typically range from 5–9 g. Side effects are usually minor and related to the sedative properties of the compound, but can include headache, dizziness, weakness, enuresis, and encopresis.

## Primary Hypersomnia

### Idiopathic and Recurrent Hypersomnia

#### *Diagnosis*

**Definition and Diagnostic Features.** Idiopathic hypersomnia, also known as primary hypersomnia, has often been considered to be a "wastebasket" diagnosis, a condition diagnosed when excessive sleepiness was present but no other diagnosis (i.e., narcolepsy) would explain symptomatic complaints. Indeed, in the past this disorder was called "NREM Narcolepsy." However, specific diagnostic criteria for this condition are included in DSM-IV-TR, defining a disorder characterized by clinically significant excessive sleepiness of at least 1 month's duration, with significant distress or impairment. The hypersomnia is not caused by another

primary sleep disorder, a psychiatric disorder, a medical disorder, or a substance.

Patients with primary hypersomnia usually present with complaints of long and nonrestorative nocturnal sleep, difficulty awakening ("sleep drunkenness"), and daytime sleepiness and intellectual dysfunction; do not experience the accessory symptoms of narcolepsy such as cataplexy, sleep paralysis, and hypnagogic hallucinations; and often report frequent headaches and Raynaud's phenomena. Onset usually occurs before 25 years of age, and the condition is typically chronic once it has presented.

**Assessment.** A formal diagnosis requires polysomnographic confirmation of hypersomnia; based on objective levels of sleepiness in a formal MSLT, performed in a sleep laboratory setting following a night of nocturnal PSG that excludes the presence of other causes for excessive sleepiness (i.e., Sleep Apnea, Sleep Deprivation, PLMS, etc). Limited data obtained from normal subjects suggests that healthy normal individuals will demonstrate a MSLT sleep latency of about 10 min. It is to be expected that patients with narcolepsy will usually have a mean MSLT sleep latency of 8 min or less. At least one Sleep Onset REM Period (SOREMP) is expected in the patient with narcolepsy, but when strong clinical findings are present (i.e., observed cataplexy), the diagnosis may be made in the absence of a SOREMP. Subjective complaints of excessive sleepiness are not adequate. A family history of excessive sleepiness may be present, but is not needed to make the diagnosis.

Aside from associated medical and psychiatric disorders, the frequency and importance of hypersomnia and daytime sleepiness in otherwise healthy individuals have been increasingly recognized. Sleepiness, for example, as a result of sleep deprivation, disrupted sleep, or circadian dyssynchronization, probably plays a major role in mistakes and accidents in sleepy drivers, interns and medical staff, and industrial workers. Psychiatrists have an obligation to recognize and advise their patients about the dangers inherent in acute or chronic sleepiness.

**Epidemiology.** This is an uncommon disorder, representing 5−10% of patients presenting to sleep disorders centers for evaluation of hypersomnia. It is extremely rare in the general population, with a prevalence estimated to be as low as 20−50 per million.

Although usually seen as a persistent complaint, the DSM-IV-TR category for Primary Hypersomnia includes recurrent forms, conditions that are categorized separately in the *International Classification of Sleep Disorders* (American Academy of Sleep Medicine 2005). Patients with recurrent forms of hypersomnia present with well-defined periods of excessive sleepiness of at least 3 days' duration, occurring several times a year for at least 2 years. Among the recurrent or intermittent hypersomnia disorders are Kleine–Levin syndrome, usually seen in adolescent boys, and menstrual cycle-associated hypersomnia syndrome. In addition to hypersomnia (up to 18 hr per day), patients with Kleine–Levin syndrome often demonstrate aggressive or inappropriate sexuality, compulsive overeating, and other bizarre behaviors. The rare nature of this syndrome and its unusual behaviors may be mistaken for psychosis, malingering, or a personality disorder.

**DSM-IV-TR Criteria**

**Primary Hypersomnia**

A. The predominant complaint is excessive sleepiness for at least 1 month (or less if recurrent) as evidenced by either prolonged sleep episodes or daytime sleep episodes that occur almost daily.

B. The excessive sleepiness causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The excessive sleepiness is not better accounted for by insomnia and does not occur exclusively during the course of another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia) and cannot be accounted for by an inadequate amount of sleep.

D. The disturbance does not occur exclusively during the course of another mental disorder.

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* if:

**Recurrent**: if there are periods of excessive sleepiness that last at least 3 days occurring several times a year for at least 2 years

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**Differential Diagnosis.** This diagnosis is at times used "casually" to describe patients with sleepiness complaints without narcolepsy or sleep apnea.

**Etiology and Pathophysiology.** Little is known about the causes of this rare disorder. It has been observed in families with histories of narcolepsy, suggesting that (in some cases it may be a "forme-fruste" or variant of narcolepsy.

## *Treatment*

Clinical management is controversial, owing to the lack of controlled studies. As in narcolepsy, stimulants such as amphetamines or methylphenidate may be used, but use of these compounds is always complicated by risks of abuse and diversion, and by side effects including anxiety, agitation, elevation of blood pressure, and cardiac arrhythmias. Modafinil may also be used, although this use would be "off-label" as this is not an FDA-approved use for this compound.

However, some patients are intolerant of stimulants or report no significant therapeutic effects. For patients intolerant of, or insensitive to, stimulants, some success has been reported with the use of antidepressants, both of the monoamine oxidase inhibitors (MAOI) and the selective SSRI classes. Methysergide, a serotonin receptor antagonist, has been reported to be effective in some treatment-resistant

cases, but must be used with caution in view of the risk that retroperitoneal fibrosis may develop in association with persistent, uninterrupted use.

## Breathing Related Sleep Disturbances (BRSD)

The essential feature of BRSD is sleep disruption resulting from sleep apnea or alveolar hypoventilation, leading to complaints of insomnia or, more commonly, excessive sleepiness. The disorder is not accounted for by other medical or psychiatric disorders or by medications or other substances.

### Diagnosis

#### Definition and Diagnostic Features

The major diagnostic criterion for sleep apnea is cessation of breathing lasting at least 10 s. Hypopneas (50% decrease in respiratory effort) may also produce arousal or hypoxia even when complete apneas do not occur. An apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep; also called respiratory disturbance index or RDI) of 5 or more (Figure 79–7) is needed for a diagnosis. Most apneic episodes are terminated by transient arousals. Each time respiration ceases, the individual must awaken to start breathing again. Once the person goes back to sleep, breathing stops again. This pattern continues throughout the night. Clinically, however, it is not unusual to see patients who stop breathing for 60−120 s with each event and experience hundreds of events per night. Many individuals with BRSD cannot sleep and breathe at the same time and therefore spend most of the night not breathing and not sleeping.

Obstructive sleep apnea is characterized by repetitive episodes of upper airway obstruction that occur during sleep, resulting in numerous interruptions of sleep continuity, hypoxemia, hypercapnia, bradytachycardia, and pulmonary and systemic hypertension. It may be associated with snoring, morning headaches, dry mouth on awakening, excessive movements during the night, falling out of bed, enuresis, cognitive decline and personality changes, and complaints of either insomnia or, more frequently, hypersomnia and EDS. The typical patient with clinical sleep apnea is a middle-aged man who is overweight or who has anatomical conditions narrowing his upper airway.

There are three types of apnea. The first is obstructive sleep apnea, which involves the collapse of the pharyngeal airway during inspiration, with partial or complete blockage of airflow. The person still attempts to breathe and one can observe the diaphragm moving, but the airway is blocked and therefore there is no air exchange. It can be caused by bagginess or by excessive pharyngeal mucosa and a large uvula, fatty infiltration at the base of the tongue, or by collapse of the pharyngeal walls. The resulting decreased air passage

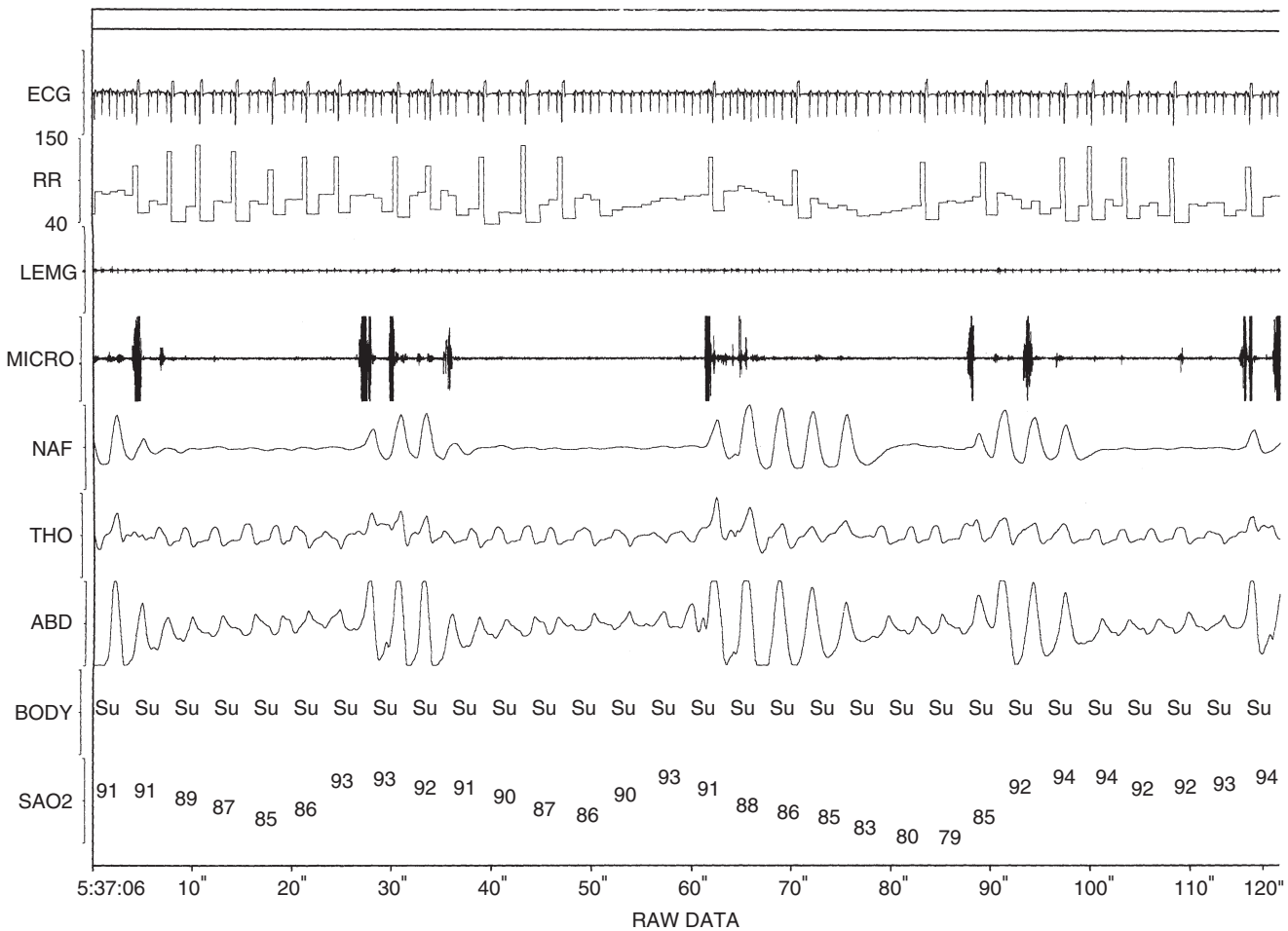



**Figure 79–7** *Mixed sleep apnea. EEG, Electroencephalogram; EOG, electrooculogram; EMG, electromyogram; ECG, electrocardiogram.*

**DSM-IV-TR Criteria**

**Breathing-Related Sleep Disorder**

A. Sleep disruption, leading to excessive sleepiness or insomnia that is judged to be due to a sleep-related breathing condition (e.g., obstructive or central sleep apnea syndrome or central alveolar hypoventilation syndrome).

B. The disturbance is not better accounted for by another mental disorder and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another general medical condition (other than a breathing-related disorder).

Coding note: Also code sleep-related breathing disorder on Axis III.

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compromises alveolar ventilation and causes blood-oxygen desaturation and strenuous attempts at inspiration through the narrowed airway, all of which lighten and disrupt sleep. Hypercapnia, which may occur in association with longstanding sleep apnea obstructive sleep apnea or chronic obstructive lung disease, may blunt ventilatory drive on chemical grounds without any obstruction of inspiratory efforts.

The second type is central sleep apnea, which results from failure of the respiratory neurons to activate the phrenic and intercostal motor neurons that mediate respiratory movements. There is no attempt to breathe, and although the airway is not collapsed, there is no respiration. This type of apnea is more commonly associated with heart disease.

The third type is mixed sleep apnea, which is a combination, generally beginning with a central component and ending with an obstructive component.

During apneas and hypopneas, the blood-oxygen level often drops to precarious levels. In addition, one often sees cardiac arrhythmias and nocturnal hypertension in association with the respiratory disturbances. The cardiac arrhythmias include bradycardia during the events and tachycardia after the end of the events. It is not unusual to see premature ventricular contractions, trigeminy and bigeminy, asystole, second-degree atrioventricular block, atrial tachycardia, sinus bradycardia, and ventricular tachycardia. However, the electrocardiogram taken during the waking state might be normal. It is only during the respiratory events during sleep that the abnormalities appear. Some of these rhythms may be lethal, and Caples et al. (Caples et al. 2007) has speculated that cardiac rhythm abnormalities associated with apnea may explain increased death rates in morning hours seen in sleep apnea patients. Health and longevity effects of apnea are usually assumed to relate primarily to increased risk of hypertension, heart disease and stroke.

The most common symptoms of BRSD include EDS and snoring. The EDS probably results from sleep fragmentation caused by the frequent nocturnal arousals occurring at the end of the apneas, and possibly from hypoxemia. The EDS is associated with lethargy, poor concentration, decreased motivation and performance, and inappropriate and inadvertent attacks of sleep. Sometimes the patients do not realize they have fallen asleep until they awaken.

The second complaint is loud snoring, sometimes noisy enough to be heard throughout or even outside the house. Often the bed-partner has complained for years about the snoring and has threatened to sleep elsewhere if she has not moved out already. Bed partners describe a characteristic pattern of loud snoring interrupted by periods of silence, which are then terminated by snorting sounds. Snoring results from a partial narrowing of the airway caused by multiple factors, such as inadequate muscle tone, large tonsils and adenoids, long soft palate, flaccid tissue, acromegaly, hypothyroidism, or congenital narrowing of the oral pharynx. Because the prevalence of snoring increases with age, especially in women, and because snoring can have serious medical consequences, the psychiatrist must give serious attention to complaints of loud snoring. Snoring is not always a symptom of BRSD. Approximately 25% of men and 15% of women are habitual snorers.

Patients with BRSD are frequently overweight. In some patients, a weight gain of 20 to 30 lb might bring on episodes of BRSD. The same fatty tissue seen on the outside is also present on the inside of the throat, making the airway even more narrow. Because obstructive sleep apnea is always caused by the collapse of the airway, in patients of normal weight, anatomical abnormalities (such as large tonsils, long uvula) must be considered.

Other symptoms of BRSD include unexplained morning headaches, nocturnal confusion, automatic behavior (i.e., behavior that is performed without conscious knowledge and that does not appear to be under conscious control) or night sweats. The severity of BRSD will depend on the severity of the cardiac arrhythmias, hypertension, EDS, respiratory disturbance index, amount of sleep fragmentation, and amount of oxygen desaturation.

Epidemiology: The lifetime prevalence of BRSD in adults has been estimated to be 9% in men and 4% in women (Young et al. 1993). The prevalence does increase with age, particularly in postmenopausal women. The prevalence in the elderly has been estimated to be 28% in men and 19% in women (Ancoli-Israel et al. 1991b).

Comorbidity Patterns: BRSD, especially central sleep apnea, is commonly seen in patients with congestive heart failure. Cor pulmonale may also be a consequence of longstanding BRSD and is seen in both sleep apnea syndrome and primary hypoventilation. Patients may present with unexplained respiratory failure, polycythemia, right ventricular failure, and nocturnal hypertension. About 50% of patients with BRSD have hypertension, and about one-third of all hypertensive patients have BRSD. The large cross-sectional Sleep Heart Health Study found that the increased risk for hypertension for those with severe sleep apnea, when compared to those with no sleep apnea, was significant at 1.37. In addition, associations of hypertension with measures of systolic and diastolic blood pressure (SDB) were seen in men and women, older and younger ages, all ethnic groups, and among normal-weight and overweight individuals (Nieto et al. 2000). It has also been shown that there is a dose–response association between SDB at baseline and

hypertension 4 years later suggesting that SDB may be a risk factor for hypertension and consequent cardiovascular morbidity (Peppard et al.).

Course: Mild-to-moderate sleep-related breathing disturbances increase with age, even in elderly subjects without major complaints about their sleep. The frequency is higher in men than in women, at least until the age of menopause, after which the rate in women increases and may approach that of men. In general, the severity of apnea in these older persons is mild compared with that seen in patients with clinical sleep apnea. However, older men and women with mild apnea have been reported to fall asleep at inappropriate times significantly more often than older persons without apnea. Furthermore, the frequency of sleep apnea and other BRSDs is higher in individuals with hypertension, congestive heart failure, obesity, dementia, and other medical conditions. Research studies have demonstrated that treatment with nasal continuous positive airway pressure (CPAP) can reduce blood pressure in patients with hypertension, prevent recurrence of atrial fibrillation, and even reverse atherosclerotic changes in patients with coronary artery disease (McNicholas 2007, Sanner et al. 2002).

The clinical significance of relatively mild "subclinical" sleep apneas is not fully understood yet. Psychiatrists should be aware, however, that such disturbances might be associated with either insomnia or EDS. Furthermore, for some patients with sleep apnea, administration of hypnotics, alcohol, or other sedating medications is relatively contraindicated. The risk is not yet known, but reports indicate that the older benzodiazepines (but not the newer nonbenzodiazepines) as well as alcohol may increase the severity of mild sleep apnea. Therefore, psychiatrists should inquire about snoring, gasping, and other signs and symptoms of sleep apnea before administering a sleeping pill. If patients have excessive sleepiness or morning hangover effects while taking benzodiazepines, major tranquilizers, or other sedating medications, the psychiatrist should consider the possibility of an iatrogenic BRSD due to medications.

### Differential Diagnosis

The diagnosis of BRSD must be differentiated from other disorders of excessive sleepiness such as narcolepsy (Table 79–10). Patients with BRSD will not have cataplexy, sleep-onset paralysis, or sleep-onset hallucination. Narcolepsy is not usually associated with loud snoring or sleep apneas. In laboratory recordings, patients with BRSD do not usually have sleep-onset REM periods either at night or in multiple naps on the MSLT. However, one must be aware that both BRSD and narcolepsy can be found in the same patient. BRSD must also be distinguished from other hypersomnias, such as those related to major depressive disorder or circadian rhythm disturbances.

**Table 79–10 Clinical Symptoms of BRSDs**

| Daytime Symptoms: | Nighttime Symptoms: |
|---|---|
| EDS | Loud snoring |
| Memory loss | Hypertension |
| Decreased mental function | Cardiac arrhythmias |
| Morning headache | Leg kicks |
| Automatic behavior | Confusion |
| Lethargy | Impotence |
| | Choking–gasping |

### Treatment of BRSD

#### *Treatment Goals*

The goal of treatment is to keep the airway open during sleep so the patient can breathe.

#### *Somatic Treatments*

Sleep apnea is sometimes alleviated by weight loss, avoidance of sedatives, use of oral airway dilation devices, and breathing air under positive pressure through a face mask (CPAP). Surgery may be helpful, for example, to correct enlarged tonsils, a long uvula, a short mandible, or bariatric surgery for morbid obesity. Surgical and laser pharyngoplasty may remove tissue and lead to localized scarring, tighten the pharyngeal mucosa and are intended to prevent collapse of the oropharynx. Radiofrequency and coblation techniques have also been used to "shrink tissue" in the oropharynx, but with generally less robust effects than those seen with more aggressive "standard" and laser approaches.

## Circadian Rhythm Sleep Disorder (Sleep–Wake Schedule Disorders)

### Diagnosis

Definition and Diagnostic Features: Circadian rhythm disturbances result from a mismatch between the internal or endogenous circadian sleep–wake system and the external or exogenous demands on the sleep–wake system. Thus, the individual's tendency to sleep–wakefulness does not match that of her or his social circumstances or of the light–dark cycle. Although some individuals do not find this mismatch to be a problem, for others the circadian rhythm disturbance interferes with the ability to function properly at times when alertness or sleepiness is desired or required. For those individuals, insomnia, hypersomnia, sleepiness, and fatigue result in significant discomfort and impairment. The more common circadian rhythm disturbances include delayed and advanced sleep phase, shift work and jet lag.

### Delayed and Advanced Sleep Phase Disorders

Delayed sleep phase refers to a delay in the circadian rhythm in the sleep–wake cycle. These individuals are generally not sleepy until several hours after "normal" bedtime (i.e., 2–3 AM). If allowed to sleep undisturbed, they will sleep for 7 or 8 hr, which means they awaken at 10–11 AM. People with delayed sleep phase are considered extreme "owls." They may or may not complain of sleep-onset insomnia. They usually enjoy their alertness in the evening and night and have little desire to sleep beginning at 10 PM or midnight. Their problem is trying to wake up at normal times (i.e., 6–7 AM). In essence, their rhythm is shifted to a later clock time relative to conventional rest–activity patterns.

**DSM-IV-TR Criteria**

**Circadian Rhythm Sleep Disorder**

A. A persistent or recurrent pattern of sleep disruption leading to excessive sleepiness or insomnia that is due to a mismatch between the sleep–wake schedule required by a person's environment and his or her circadian sleep–wake pattern.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The disturbance does not occur exclusively during the course of another sleep disorder or other mental disorder.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

*Specify* type:

**Delayed sleep phase type**: a persistent pattern of late sleep onset and late awakening times, with an inability to fall asleep and awaken at a desired earlier time

**Jet lag type**: sleepiness and alertness that occur at an inappropriate time of day relative to local time, occurring after repeated travel across more than one time zone

**Shift work type**: insomnia during the major sleep period or excessive sleepiness during the major awake period associated with night shift work or frequently changing shift work

**Unspecified type**

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Individuals with delayed sleep phase often choose careers that allow them to set their own schedules, such as freelance writers. Delayed sleep phase occurs commonly in late adolescence and young adulthood, such as in college students. As many of these individuals age, however, their endogenous sleep–wake rhythm advances and they eventually are able to conform themselves to a normal rest period at night.

As people age, the endogenous oscillator continues to advance resulting in an advanced sleep phase. In this condition, individuals become sleepy earlier in the evening (e.g., 7–8 PM). They will also sleep for 7 to 8 hr, but that means they awaken at 2 to 3 AM. These individuals are" "larks," being most alert in the morning. They complain of sleep maintenance insomnia, that is, they cannot stay asleep all night long.

## Assessment

The diagnosis of circadian rhythm disturbances is based on a careful review of the history and circadian patterns of sleep–wakefulness, napping, alertness, and behavior. According to DSM-IV-TR criteria, the diagnosis of circadian rhythm sleep disorder requires significant social or occupational impairment or marked distress related to the sleep disturbance. It is often useful for patients with chronic complaints to keep a sleep–wake diary covering the entire 24-hr day each day for several weeks. If possible, an ambulatory device that measures rest–activity, such as a wrist actigraph, might supplement the sleep–wake diary. Wrist actigraphs record acceleration of the wrist at frequent intervals, such as every minute, and save it for later display. Because the wrist is mostly at rest during sleep, the record of wrist rest–activity provides a fairly accurate estimate of the timing and duration of sleep–wakefulness. In addition, some commercial wrist activity devices have a built-in photometer, which provides a record of ambient light–darkness against which the rest–activity pattern can be compared.

## Epidemiology

Although formal epidemiologic data is not available, clinical experience suggests that delayed sleep phase is more common in adolescence, while advanced sleep phase is more prevalent in the elderly.

## Etiology and Pathophysiology

The etiology of extreme "night owls" and "larks" is probably multifaceted but, in at least some cases, appears to reflect genetic factors. Jones et al. (1999) described a family in which extreme phase advance (bedtime about 7 PM) appeared to be consistent with an autosomal dominant trait. One member of the family was studied in a temporal isolation facility; as predicted, her endogenous sleep–wake cycle averaged less than 24 hr, clearly different from most subjects who average about 24.2−24.5 hr. Members of this family appear to have a mutation of one of the "clock genes." Mignot et al. (1998) have also identified a single nucleotide polymorphism of the human CLOCK gene in people self-described as "night owls." In addition, Ancoli-Israel and colleagues (Ancoli-Israel et al. 2001) identified a pedigree of one family with phase delay.

## Treatment

### Treatment Goals

Clinical management includes strategies to shift the phase of the endogenous circadian clock in the appropriate direction.

### Somatic Treatments

Exposure to bright light in the morning advances the delayed sleep phase; that is, individuals will become sleepy earlier in the evening. On the other hand, administration of bright light in the evening acts to delay the circadian rhythm; that is, individuals will get sleepy later in the evening. For some individuals, spending more time outdoors in bright sunlight may be sufficient to treat the sleep phase. For example, individuals with delayed sleep phase should be encouraged to remove blinds and curtains from their windows, which would allow the sunlight to pour into their bedrooms in the morning when they should arise. When natural sunlight cannot be used to shift the circadian rhythm, light boxes can be

used, although the ideal intensity, duration, and wavelength are yet to be determined.

## Shift Work Sleep Disorder

### Diagnosis

#### Definition and Diagnostic Features

Shift work problems occur when the circadian sleep–wake rhythm is in conflict with the rest–activity cycle imposed by the externally determined work schedule. Different patterns include rotating schedules and more or less permanent evening and night schedules. Rotating schedules, particularly rapidly shifting schedules, are difficult because constant readjustment of the endogenous circadian oscillator to the imposed sleep–wake cycle is necessary. In both rotating and evening/night shift work schedules, further difficulties are encountered because the worker is usually expected to readjust to a normal sleep–wake cycle on weekends and holidays. Even if the worker can adjust his or her circadian system to the work schedule, he or she is then out of synchrony with the rhythm of family and friends during off-duty hours. These individuals, therefore, are constantly sleep deprived and constantly sleepy. They endure impaired performance and increased risk of accidents, somatic complaints, and poor morale; hypnotics, stimulants, and alcohol are often used excessively in relationship to unusual or shifting work schedules.

A specific disorder associated with shift work, Shift Work Sleep Disorder, has been defined and is included in the most recent International Classification of Sleep Disorders (American Academy of Sleep Medicine 2005). This condition is identified as Circadian Rhythm, Shift Work Type, in DSM-IV-TR. Based on research data showing symptomatic improvements in treated shift workers (Czeisler et al. 2005), the FDA has approved a specific pharmacological treatment (modafinil 200 mg, 1 hr before the start of shift work) for this disorder.

#### Epidemiology

Nearly a quarter of all American employees have jobs that require them to work outside the conventional 8 AM –5 PM schedule.

### Treatment

No totally satisfactory methods currently exist for managing shift work problems. Because people vary in their ability to adjust to these schedules, self-selection or survival of the fittest may be involved for those who cannot find other employment or work schedules. Older individuals appear to be less flexible than younger persons in adjusting to shift work. Some experiments suggest that the principles of chronobiology may be useful in reducing the human costs of shift work. For example, because the endogenous pacemaker has a cycle length (tau) longer than 24 hr, rotating shift workers do better when their schedules move in a clockwise direction (i.e., morning to evening to night) rather than in the other direction. Appropriate exposure to bright lights and darkness may push the circadian pacemaker in the correct direction and help stabilize its phase position, especially in association with the use of dark glasses outside and blackout curtains at home to maintain darkness at the appropriate times for promotion of sleep and shifting of the circadian pacemaker. Naps may also be useful in reducing sleep loss. Modest amounts of coffee may maintain alertness early in the shift but should be avoided near the end of the shift.

The FDA has approved the use of modafinil for the treatment of shift work sleep disorder. Recent research has demonstrated that subjects in performing shift work receiving modafinil, compared to placebo, demonstrated improved alertness, improved clinician ratings of well-being, improved quality of life and improved performance and alertness (Czeisler et al. 2005). Stimulants may also improve levels of alertness and performance of shift workers, but pose greater risks of side effects diversion and abuse, and not approved treatments for this disorder.

## Jet Lag

### Diagnosis

#### Definition and Diagnostic Features

Jet lag occurs when individuals travel across several time zones. Traveling east advances the sleep–wake cycle and is typically more difficult than traveling west (which delays the cycle). Jet lag may be associated with difficulty initiating or maintaining sleep or with daytime sleepiness, impaired performance, and gastrointestinal disturbance after rapid transmeridian flights. Individuals older than 50 years appear to be more vulnerable to jet lag than are younger persons.

### Treatment

Considerable research and theorizing are under way to better prevent and manage the problems associated with jet lag. Some efforts before departure may be useful to prevent or ameliorate these problems. For persons who plan to readjust their circadian clock to the new location, it may be possible to move the sleep–wake and light–dark schedules appropriately before departure. In addition, good sleep hygiene principles should be respected before, during, and after the trip. For example, many people are sleep deprived or in alcohol withdrawal when they step on the plane because of last-minute preparations or farewell parties. Whereas adequate fluid intake on the plane is necessary to avoid dehydration, alcohol consumption should be avoided or minimized because it causes diuresis and may disrupt sleep maintenance.

On arriving at the destination, it may be preferable to try to maintain a schedule coinciding with actual home time if the trip is going to be short. For example, the individual should try to sleep at times that correspond to the usual bedtime or with the normal mid-afternoon dip in alertness. If, on the other hand, the trip will be longer and it is desirable to synchronize the biological clock with local time, exposure to appropriate schedules of bright light and darkness may be helpful, at least theoretically.

Specific algorithms that may be helpful in resetting circadian rhythms are extremely complex, relating to the time hour of departure and arrival, times of sunrise and sunset, and the number of hours and direction that rhythms have been shifted (i.e., has the traveler advanced his or her clock by 8 hr, flying from San Diego to Paris, or delayed it by

15 hr, flying from New York City to Beijing). Some sleep hygiene suggestions are likely to be of benefit for all jet-lagged travelers. Obtaining light during the daylight hours at one's destination will help the brain recognize and adapt to local time; obtaining light exposure when one is sleepy during daylight hours will promote alertness and may help to speed entrainment to local time.

Although brief naps (i.e., of up to 20 min) may be restorative, longer naps (which may occur in response to timing of periods of sleep which would be occurring in one's home time zone) may interfere with adaptation to local time. Caffeine, if tolerated well and not contraindicated on medical grounds, will promote alertness and may help to minimize drowsy episodes during the "work" day at a time-shifted destination. Alcohol use, although helpful in promoting sleep and (perhaps) socially appropriate at a travel destination, will disrupt and fragment sleep in the hours after ingestion and should be avoided for the first few nights when jet lag is a problem.

In addition to synchronizing the clock with the new environment, sleep and rest should be promoted by good sleep hygiene principles, by avoidance of excessive caffeine and alcohol, and, when necessary, by administration of short-duration hypnotics. Because individual responses to sleeping pills vary considerably from person to person, it is often helpful to develop experience with specific compounds and doses before departure. Although use of MT to ameliorate effects of jet lag is often mentioned in suggestions for travelers, research data has not demonstrated clinical benefit. Preliminary studies have suggested that ramelteon may have circadian phase-shifting properties that might be of benefit; this is not yet an approved use for this medication.

## PLMS and Restless Legs Syndrome (RLS)

### Diagnosis

#### Definition and Diagnostic Features

PLMS is a disorder in which repetitive, brief, and stereotyped limb movements occur during sleep, often with a periodicity of about 20−40 s. Dorsiflexions of the big toe, ankle, knee, and sometimes the hip are involved (Table 79–11 and Figure 79–8). Most patients will demonstrate repetitive episodes of PLMS for periods of from a few minutes to an hour or more throughout the night. Rare patients will show continuous movements throughout the night.

**Table 79–11 Features of Periodic Limb Movementsin Sleep**

| |
|---|
| Leg kicks every 20–40 s |
| Duration of 0.5–5 s |
| Complaints of: |
| Insomnia |
| Excessive sleepiness |
| Restless legs |
| Uncomfortable sensations in legs |

A disturbance often comorbid with PLMS, RLS, is associated with disagreeable sensations in the lower legs, feet, or thighs that occur in a recumbent or resting position and cause an almost irresistible urge to move the legs (Walters et al. 1995). Patients with RLS describe the dysesthesias as aching, tingling, creeping, and crawling. Motor movement, such as walking, generally relieves the dysesthesias.

#### Assessment

##### *PLMS*

Questioning of the patient or bed partner often yields reports of restlessness, kicking, unusually cold or hot feet, disrupted and torn bedclothes, unrefreshing sleep, insomnia, or EDS. Patients may be unaware of these pathological leg movements or arousals, although their bed partners may be all too aware of the kicking, frequent movements, and restlessness. If these disorders are strongly suspected, the patient should probably be referred to a sleep disorders laboratory for evaluation and an overnight polysomnogram with tibial EMGs. These disorders are often associated with transient arousals in the EEG recording. Since diagnosis is made when the periodic limb movement index (number of leg jerks per hour of sleep) is 5 or greater, accompanied by arousals, an overnight sleep recording is necessary in order to count the number of leg jerks. The jerks occur primarily in the legs but may also appear in less severe forms in the arms. The movements can be bilateral or unilateral and occur in Stage 1 and Stage 2 sleep. Patients often have reduced deep sleep because the jerks continually awaken them.

##### *RLS*

Since the restlessness is a subjective symptom, the diagnosis of RLS is made upon history, with a standardized,

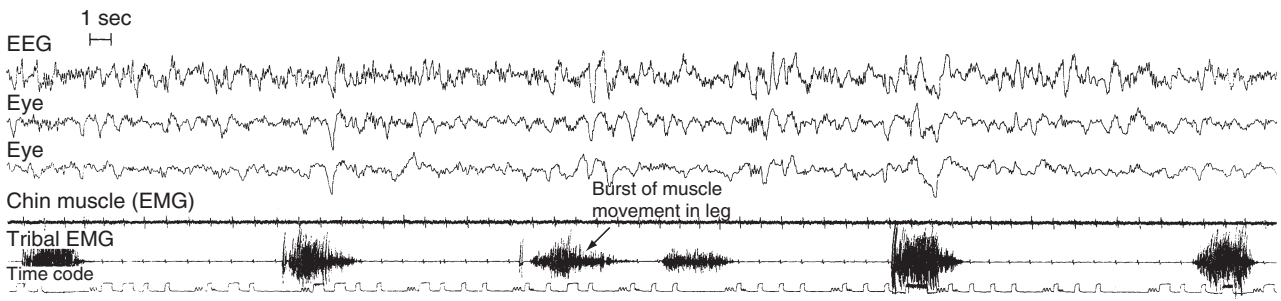



**Figure 79–8** *Periodic limb movements in sleep. Time scale: 1 cm = 1 s. EEG, Electroencephalogram; EMG, electromyogram.*

validated questionnaire (Walters et al. 2003). Mild RLS is defined as symptoms that occur episodically and are associated with mild sleep disruption. Moderate RLS is defined as symptoms that occur less than twice a week and cause moderate sleep disruption and mild daytime dysfunction. Severe RLS is defined as symptoms that occur more than twice a week and cause severe sleep disruption and daytime dysfunction.

Whereas almost close to 70% of patients with RLS have PLMS, only about 20% of patients with PLMS have RLS. RLS may be frequent in patients with uremia and rheumatoid arthritis or in pregnant women. Ferritin levels should be measured in patients with RLS.

### Epidemiology

Both PLMS and RLS usually occur in middle-aged people, but many patients report having had the same sensations as adolescents and even as children. In the older adult, the prevalence of PLMS has been estimated to be 45% (Ancoli-Israel et al. 1991a). The prevalence of RLS has been estimated to be between 2% and 15% of the general population (Berger and Kurth 2007).

### Comorbidity Patterns

PLMS and RLS may develop in association with sleep disordered breathing and narcolepsy. In addition, they are sometimes seen comorbid with medical conditions (e.g., congestive heart failure, arthritis, leukemia, venous insufficiency, chronic lung disease), neurological disorders (e.g., Parkinson's disease, low back pain, polio, peripheral neuropathy, chronic myelopathy), metabolic disorders (e.g., iron deficiency, anemia, uremia, hypothyroidism. Both conditions may be aggravated by tricyclic antidepressants, serotonin reuptake inhibitors, antihistamines, caffeine, and sleep deprivation.

### Etiology

It has been suggested that both conditions are familial, perhaps due to an autosomal dominant gene. It has been shown that PLMS activity in family members is significantly higher for those diagnosed with RLS compared to those without RLS (Birinyi et al. 2006). This difference was greater for older than younger subjects. In a search for sequence variants contributing to RLS, a genomewide association study with two replication studies were performed, focusing patients with RLS and PLMS. A genomewide significant association with a common variant in an intron of BTBD9 on chromosome 6p21.2 was found (Stefansson et al. 2007).

## Treatment

### Pharmacological Treatment

The treatment of choice for both RLS and PLMS are the dopamine agonists (Table 79–12). To date, only ropinirole and pramipexole have been approved by the FDA for the treatment of RLS. RLS patients with low ferritin levels should also be treated with ferrous sulphate.

Opiates, such as oxycodone and propoxyphene, have also been demonstrated to be somewhat effective in the treatment of PLMS and RLS. Anticonvulsants, such as carbamazepine and gabapentin, clonazepam (a benzodiazepine anticonvulsant) are also effective in the treatment of PLMS and possibly for RLS.

**Table 79–12 Pharmacologic Treatment Options in RLS/PLMS**

| Drug | Trade Name | Approved Dose (mg) | Comment |
|---|---|---|---|
| Ropinirole | Requip | 0.5–4 | Approved by FDA for RLS |
| Pramipexole | Mirapex | 0.125–5 | Approved by FDA for RLS |
| Levodopa/carbidopa* | Sinemet | 25/100 | Off-label use |

*This is off-label use; only ropinirole and pramipexole are FDA approved for the treatment of RLS.

# Parasomnias

The parasomnias are a group of disorders characterized by disturbances of either physiological processes or behavior associated with sleep, but not necessarily causing disturbances of sleep or wakefulness.

## Nightmare Disorder

### Diagnosis

#### *Definition and Diagnostic Features*

The essential feature of this disorder is the repeated occurrence of frightening dreams that lead to full awakenings from sleep. The dreams or awakenings cause the individual significant distress or dysfunction. This is clearly distinguished from the phenomenon of lucid dreaming, awareness of dreams while asleep that the "lucid dreamer" can direct and control and for which there is clear recall on awakening. These dreams are usually experienced by the "lucid dreamer" as a pleasant and at times enlightening experience. It has been reported that subjects can develop a greater capacity for lucid dreaming by cognitive preparation and efforts to control dream content prior to sleep onset.

#### *Differential Diagnosis*

By DSM-IV-TR definition, the disorder is excluded if the nightmare occurs in the course of another mental or medical disorder or as a direct result of a medication or substance. Most nightmares occur during REM sleep; REM nightmares take place most often during the last half of the night when REM sleep is most common.

#### *Epidemiology*

Although adults may experience occasional nightmares, nightmares are seen essentially universally at some point in time in children between the ages of 3 and 6 years. The exact prevalence in children is unknown, but figures of between 30% and 90% for nightmares occurring "at least sometimes" have been reported in children (Partinen and Hublin 2005). Individuals with a history of nightmare will typically experience increased frequencies of nightmares when they are under stress, or in withdrawal from

**DSM-IV-TR Criteria**

**Nightmare Disorder**

A. Repeated awakenings from the major sleep period or naps with detailed recall of extended and extremely frightening dreams, usually involving threats to survival, security, or self-esteem. The awakenings generally occur during the second half of the sleep period.

B. On awakening from the frightening dreams, the person rapidly becomes oriented and alert (in contrast to the confusion and disorientation seen in sleep terror disorder and some forms of epilepsy).

C. The dream experience, or the sleep disturbance resulting from the awakening, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The nightmares do not occur exclusively during the course of another mental disorder (e.g., a delirium, posttraumatic stress disorder) and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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REM-suppressant medications (e.g., alcohol, stimulants, most antidepressant medications).

Etiology is unknown. It has been reported that individuals under stress will have increases in REM duration and REM activity, perhaps in response to "problem solving" or emotional resolution which may occur in REM sleep. It has also been speculated that individuals with greater levels of creativity and "thinner boundaries" between conscious and unconscious brain processes may be at greater risk for experiencing nightmares (Hartmann et al. 1987).

### Treatment

The disorder is usually self-limited in children, and typically does not require formal therapeutic intervention. However, if nightmares persist in childhood or are present in adult life, treatment may be of benefit. Although psychotherapy is typically suggested as a treatment approach, little data supporting its use has been generated. Published data does support the use of several types of cognitive and behavioral interventions, including systematic desensitization, relaxation techniques and imagery rehearsal as methods effective in reducing the frequency and severity of nightmares (Nielsen and Zadra 2005). It is presumed that these interventions would function in a fashion analogous to preparation for lucid dreaming, that is that anticipation and efforts to alter distressing dream content may reduce the intensity of nightmare distress, if the nightmare occurs.

Medications used to reduce nightmare severity have included antidepressants and sedative hypnotic/anxiolytic agents. Although SSRIs do suppress REM activity, they also tend to lighten and fragment sleep. For this reason, sedating tricyclic and heterocyclic antidepressants (e.g., amitriptyline, doxepin, trazodone, etc.) may be used to try to reduce nightmare severity and promote sleep. Sedative hypnotic/anxiolytic agents do not suppress REM, but may prevent arousals in sleep caused by "anxious dreaming"/nightmares, and may reduce anxiety levels overall, reducing the probability that a nightmare will occur.

## Sleep Terror Disorder

### Diagnosis

#### *Definition and Diagnostic Features*

This disorder is defined as repeated abrupt awakenings from sleep characterized by intense fear, panicky screams, autonomic arousal (tachycardia, rapid breathing, and sweating), absence of detailed dream recall, amnesia for the episode, and relative unresponsiveness to attempts to comfort the person. Because sleep terrors occur primarily during delta sleep, they usually take place during the first third of the night. These episodes may cause distress or impairment, especially for caretakers who witness the event. Sleep terrors may also be called night terrors, *pavor nocturnus*, or incubus.

Sleep terrors do not appear to be associated with psychiatric illness in children. In adults, it is equally common in men and women, and may be associated with psychiatric disorders, such as posttraumatic stress disorder, generalized anxiety disorder, and borderline personality disorder. Stress and sleep deprivation may increase the occurrence of night terrors. An increased frequency of enuresis and somnambulism has been reported in the first-degree relatives of patients with night terrors.

#### *Epidemiology*

The prevalence of the disorder is estimated to be about 1–6% in children and less than 1% in adults. In children, it usually begins between the ages of 4 and 12 years and resolves spontaneously during adolescence. It is more common in boys than in girls. There is a strong genetic component, with high probability that one or both parents will have a history of sleep terrors, sleepwalking, or another parasomnia.

#### *Course*

In adults, sleep terrors usually begin between 20 and 30 years of age, with a chronic undulating course. The etiology of this disorder is unclear, but is presumed to relate to tendencies to spontaneous arousal from deep phases of nondreaming sleep.

### Treatment

Sleep hygiene, such as obtaining adequate sleep and avoiding sleep deprivation, and reduction of stress are all important in reducing the probability of sleep terrors occurring. Maintaining a "safe" sleep environment (i.e., removing sharp or pointed objects that the sleeper could run into, having these individuals sleep in ground-floor bedrooms) may reduce the risk of harm. Nocturnal administration of benzodiazepines has been reported to be beneficial, perhaps because these

**DSM-IV-TR Criteria**

**Sleep Terror Disorder**

A. Recurrent episodes of abrupt awakening from sleep, usually occurring during the first third of the major sleep episode and beginning with a panicky scream.

B. Intense fear and signs of autonomic arousal, such as tachycardia, rapid breathing, and sweating, during each episode.

C. Relative unresponsiveness to efforts of others to comfort the person during the episode.

D. No detailed dream is recalled and there is amnesia for the episode.

E. The episodes cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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drugs suppress delta sleep, the stage of sleep during which sleep terrors typically occur, and reduce arousal that may provoke the sleep terror.

## Sleepwalking Disorder

### Diagnosis

#### *Definition and Diagnostic Features*

This disorder is characterized by repeated episodes of motor behavior initiated in sleep, usually during delta sleep in the first third of the night. While sleepwalking, the patient has a blank staring face, is relatively unresponsive to others, and may initially be confused or disoriented on being aroused from the episode. Although sleepwalkers may be alert after several minutes of awakening, complete amnesia for the episode is common the next day. Sleepwalking may cause considerable distress, for example, if a child cannot sleep away from home or go to camp because of it. By DSM-IV-TR definition, pure sleepwalking is excluded if it occurs as a result of a medication or substance or is due to a general medical condition. However, sleepwalking may be an idiosyncratic reaction to specific drugs, including tranquilizers and sleeping pills.

Most behaviors during sleepwalking are routine and of low-level intensity, such as sitting up, picking the sheets, or walking around the bedroom. More complicated behaviors may also occur, however, such as urinating in a closet, leaving the house, running, eating, talking, or driving. A real danger is that the individual will be injured by going through a window or falling from a height.

**DSM-IV-TR Criteria**

**Sleepwalking Disorder**

A. Repeated episodes of rising from bed during sleep and walking about, usually occurring during the first third of the major sleep episode.

B. While sleepwalking, the person has a blank, staring face, is relatively unresponsive to the efforts of others to communicate with him or her, and can be awakened only with great difficulty.

C. On awakening (either from the sleepwalking episode or the next morning), the person has amnesia for the episode.

D. Within several minutes after awakening from the sleepwalking episode, there is no impairment of mental activity or behavior (although there may initially be a short period of confusion or disorientation).

E. The sleepwalking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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#### *Epidemiology*

Whereas about 10–30% of children have at least one sleepwalking episode, only about 1–5% have repeated episodes. The prevalence in adults is unknown.

#### *Course*

The disorder most commonly begins between the ages of 4 and 8 years and usually resolves spontaneously during adolescence.

#### *Etiology*

Genetic factors may be involved, because sleepwalkers are reported to have a higher than expected frequency of first-degree relatives with either sleepwalking or sleep terrors. Sleepwalking may be precipitated in affected patients by gently sitting them up during sleep, by fever, or by sleep deprivation. Adult onset of sleepwalking should prompt the search for possible medical, neurological, psychiatric, pharmacological, or other underlying causes such as nocturnal epilepsy.

### Treatment

No treatment for sleepwalking is established, but some patients respond to administration of benzodiazepines or sedating antidepressants at bedtime. The major concern should be the safety of the sleepwalker, who may injure herself or himself or someone else during an episode.

## REM Behavior Disorder

### Diagnosis

#### *Definition and Diagnostic Features*

First described in 1986, RBD, like sleepwalking, is associated with complicated behaviors during sleep such as walking, running, singing, and talking (Schenck and Mahowald 2005). In contrast to sleepwalking, which occurs during the first third of the night during delta sleep, RBD usually occurs during the second half of the night during REM sleep. It apparently occurs as a consequence of intermittent loss of the muscle atonia normally present in REM sleep, facilitating enacted dream motor activity. The movement activity that occurs is usually semi-purposeful, but may put the patient or bed partner at risk due to flailing or kicking arms or legs, or to the well-intentioned efforts of the sufferer to fight off assailants attacking in a dream.

Also, in contrast to sleepwalking, memory for the dream content is usually good in RBD. Furthermore, the idiopathic form typically occurs in men during the sixth or seventh decade of life. The cause or causes remain unknown. It has been reported in a variety of neurological disorders and during withdrawal from sedatives or alcohol; during treatment with tricyclic antidepressants or biperiden (Akineton); and in various neurological disorders including dementia, subarachnoid hemorrhage, and degenerative neurological disorders.

### Treatment

Nocturnal administration of clonazepam, typically in a dose of between 0.5−1 mg, is usually remarkably successful in controlling the symptoms of this disorder. Patients and their families should be educated about the nature of the disorder and warned to take precautions about injuring themselves or others. Extended follow-up of patients with this disorder has also demonstrated that those presenting with this condition are at high risk for later development of neurodegenerative disorders, including Parkinson's disease, multiple system atrophy, and dementia with Lewy body disease (Schenck and Mahowald 2005). Limited studies, typically performed open label in small case series, also suggests that MT in doses of between 3 and 12 mg at night may be effective for some patients who have not responded to treatment with clonazepam.

## Sleep-Related Eating Disorders

Changes in sleep patterns may occur in patients with eating disorders. Night bingeing and increased sleep after eating are commonly reported in bulimic patients, who are also reported to eat and shop for food while sleepwalking. The patient frequently does not remember these nocturnal episodes; they often become known from family or friends who have observed the behavior or from physical evidence of shopping or eating behaviors. Patients with anorexia nervosa are often hyperactive, needing little sleep. Given the degree of physical and psychic stress associated with eating disorders, it is surprising how limited are the objective sleep disturbances associated with these disorders.

Questions have been raised in both the lay and scientific press about the possibility that hypnotic medications could play a role in promoting unwanted, "automatic" behaviors in sleep. In response, the FDA has advised manufacturers of a broad range of sleeping pills to warn patients that use of these medications may increase the potential for "complex sleep-related behaviors" which may include "sleep-driving, making phone calls and preparing and eating food (while asleep)." This is a real concern, but events of this sort appear to occur infrequently, especially in view of the large numbers of patients using these medications on a regular basis.

## Sleep Disorders Due To a General Medical Condition

A sleep disorder due to a general medical condition is defined in DSM-IV-TR as a prominent disturbance in sleep severe enough to warrant independent clinical attention. Subtypes include insomnia, hypersomnia, parasomnia, and mixed types.

As a general rule, any disease or disorder that causes pain, discomfort, or a heightened state of arousal in the waking state is capable of disrupting or interfering with sleep (Sateia 2004). Examples of this phenomenon include pain syndromes of any sort, arthritic and other rheumatological disorders, prostatism and other causes of urinary frequency or urgency, chronic obstructive lung disease, and other pulmonary conditions. Many of these conditions increase in prevalence with advancing age, suggesting at least one reason that sleep disorders are more likely to be seen in senior populations. A few examples of sleep disorders due to general medical conditions follow.

## Rheumatological Disorders

Rheumatological disorders often cause disturbances of sleep depth and continuity (Sateia 2004). The pain and discomfort associated with flares of rheumatoid arthritis lead to markedly disrupted sleep, with complaints of increased pain and stiffness the following day. Similar (although somewhat less intense) complaints are seen in association with untreated (or insufficiently treated) osteoarthritis. In both disorders, normal movements associated with shifts in position and stage in sleep may trigger awakenings from which return to sleep may be difficult or impossible. Similar problems may be seen with injuries to, or inflammation of, the back or ribs, with a report of awakening with pain associated with all shifts of position while asleep.

## Fibromyalgia

Fibromyalgia is typically associated with complaints of chronic, relapsing fatigue with shallow, unrefreshing sleep and localized tenderness in different muscle groups ("trigger points"). No laboratory evidence of articular, nonarticular, musculoskeletal, or metabolic disease exists. Onset usually begins in young women. Although increased amounts of alpha-wave intrusion and disruption of other sleep stages have been described in some patients with fibromyalgia, this is not a uniform finding and is probably not important in the pathophysiological process (Sateia 2004).

## Gastrointestinal Conditions

Sleep disturbance is particularly associated with peptic ulcer disease and gastroesophageal reflux (Sateia 2004), and rectal urgency in patients with colitis or ileitis. Patients with

a colostomy may find sleep disrupted as a consequence of short transit time through remaining gut.

### Cerebral Degenerative Disorders

Sleep disturbances are common in patients with Parkinson's disease, Huntington's chorea, advanced Alzheimer's disease, hereditary progressive dystonia, and other similar disorders.

### Sleep in Elderly with Dementia

The sleep of older adults with dementia is extremely disturbed, with severely fragmented sleep, often to the extent that there is not a single hour in a 24-hr day that is spent fully awake or asleep (Pat-Horenczyk et al. 1998). Patients with mild to moderate dementia have extremely fragmented sleep at night, while those with severe dementia are extremely sleepy during both the day and night (Pat-Horenczyk et al. 1998). Sleep stages also change with dementia, with significantly lower amounts of Stages 3, 4, and REM sleep, and significantly more awakenings, as well as more time spent awake during the night. This results in increased Stage 1 sleep and decreased sleep efficiency (Ancoli-Israel et al. 2003a). It has also been shown that there is a high prevalence of sleep apnea in patients with dementia, with as many as 80% having symptoms that meet the criteria for diagnosis (Gehrman et al. 2003). The sleep changes and disruption seen are likely due to the neuronal degeneration found in Alzheimer's disease. Neuronal structures damaged in patients with dementia include the basal forebrain and the reticular formation of the brain stem, the same structures implicated in sleep regulation.

The nocturnal awakenings seen in dementia patients are often accompanied by agitation, confusion, and wandering. These behaviors have been referred to as "sundowning" as it was believed that they typically occurred as the sun set. It has been suggested that agitation or sundowning may be a circadian rhythm disorder (Bliwise et al. 1993, Martin et al. 2000). These authors found an association between circadian rhythms of activity, agitation and light exposure, indicating that sleep disruption in demented individuals may be amenable to treatment using bright light exposure. Others have tested this theory by exposing patients with dementia to bright light. The results have been mixed, but in general support the theory that increased light exposure, whether during the morning or evening, will improve both sleep and behavior to some extent (Ancoli-Israel et al. 2003b, McCurry and Ancoli-Israel 2003).

### Parkinson's Disease

Sleep difficulties are particularly common in patients with Parkinson's disease with over half complaining of difficulty falling asleep and almost 90% complaining of difficulty staying asleep. Sleep recordings confirm that these patients, in fact, do have a prolonged sleep latency and are awake about one-third of the night. The sleep disruption may be secondary to the Parkinson's disease itself or to the medication used to treat the disease. Neurochemical changes caused by the disease include reductions in serotonergic, noradrenergic, and cholinergic neurons, all of which are involved in sleep regulating mechanisms. Dopaminergic agonists used to treat the disease affect sleep–wake patterns. Motor activity, including tremors, muscle contractions, increased muscle tone, vocalizations, and PLMS all disrupt sleep. Respiratory disorders, most common in patients with autonomic disturbance, are likely to contribute to sleep fragmentation. Finally, sleep–wake schedules are easily disrupted, either due to the medications, or to circadian rhythm abnormalities such as advanced or delayed sleep phase. Sleep disruption often increases with the progression of the disease (Arnulf et al. 2002).

Sleep hygiene education may improve sleep in patients with Parkinson's disease. For example, since patients often complain of difficulty getting to the bathroom at night, having a commode available at the bedside may be extremely helpful. The spouse or bed partner might consider sleeping in a different bed since the patient's disrupted sleep may impact the sleep of the bed partner. Since the bed partner is often also the caregiver, this sleep disruption may lead to early institutionalization. In addition to behavioral treatment of sleep problems, adjusting the time and dose of the dopaminergic medications used for treating Parkinson's disease may improve the problem. Low doses in the evening may prevent insomnia but may not sufficiently control nocturnal rigidity. Higher evening doses will promote sleep by minimizing nocturnal rigidity, however, this may cause sleep-onset insomnia. Withdrawal from dopamine agonists may lead to severe akinesia, which is associated with sleep disruption. Some of the intermediate-acting sedative–hypnotics, such as clonazepam or temazepam, may improve the insomnia caused by nocturnal dyskinesia. The shorter-acting benzodiazepines, such as zolpidem or zaleplon, are also indicated to help stabilize the sleep–wake schedule. Sedating tricyclic antidepressants such as amitriptyline may improve both sleep-onset insomnia and some daytime parkinsonian symptoms. However, since they can cause nocturnal delirium, they are contraindicated for cognitively impaired patients.

Dopaminergic agents taken in the evening can cause sleep-onset insomnia. Chronic use of L-dopa causes vivid dreams, nightmares, and night terrors, particularly with demented patients. Therefore, for Parkinson's disease patients with dementia suffering from nocturnal hallucinations and confusion, only very small doses of L-dopa can be used, and the sleep disruption is particularly difficult to manage.

## Substance-Induced Sleep Disorder

An important aspect of the evaluation of any patient, particularly those with sleep disorders, is the review of medications and other substances (including prescription, over-the-counter and recreational drugs, as well as alcohol, stimulants, narcotics, coffee and caffeine, and nicotine) and exposure to toxins, heavy metals, and so forth (Gillin et al. 2005). These substances may affect sleep and wakefulness during either ingestion or withdrawal, causing most commonly insomnia, hypersomnia, or, less frequently, parasomnia or mixed types of difficulties. On the basis of DSM-IV-TR criteria, a diagnosis of substance-induced sleep disorder may be made if the disturbance of sleep is sufficiently severe to warrant independent clinical attention and is judged to result from the direct physiological effects of a substance. Substance-induced sleep disorder should only be diagnosed if the sleep disturbance is not better accounted for by a mental disorder and does not occur during delirium. If appropriate, the context for the development of sleep symptoms may be

**DSM-IV-TR Criteria**

**Substance-Induced Sleep Disorder**

A. A prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

(1) the symptoms in criterion A developed during, or within a month of, substance intoxication or withdrawal

(2) medication use is etiologically related to the sleep disturbance

C. The disturbance is not better accounted for by a sleep disorder that is not substance induced. Evidence that the symptoms are better accounted for by a sleep disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent nonsubstance-induced sleep disorder (e.g., a history of recurrent nonsubstance-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Note*: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the sleep symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome, and when the symptoms are sufficiently severe to warrant independent clinical attention.

*Code*

[specific substance]–induced sleep disorder:

(291.8 alcohol; 292.89 amphetamine; 292.89 caffeine; 292.89 cocaine; 292.89 opioid; 292.89 sedative, hypnotic, or anxiolytic; 292.89 other [or unknown] substance)

*Specify* type:

**Insomnia type**: if the predominant sleep disturbance is insomnia

**Hypersomnia type**: if the predominant sleep disturbance is hypersomnia

**Parasomnia type**: if the predominant sleep disturbance is a parasomnia

**Mixed type**: if more than one sleep disturbance is present and none predominates

*Specify* if:

With onset during intoxication: if criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome

With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome

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indicated by specifying with onset during intoxication or with onset during withdrawal.

The recognition of substance-related sleep disturbances usually depends on active searching by the psychiatrist, beginning with a careful history, physical examination, laboratory and toxicological testing, and information (with permission) from former health care providers or friends and relatives. Patients may not know what prescription medications they are taking or the doses, and may forget to mention over-the-counter medications, coffee, occupational or environmental toxins, and so forth. In the case of alcohol and drugs of abuse, they may deny to themselves and others their use, or quantity, or frequency of use. Substance dependence and abuse is often associated with other psychiatric diagnoses or symptoms. When comorbidity does exist, it is important to establish, if possible, whether the sleep disturbance is primary or secondary, that is, whether the sleep disturbance is substance-induced (secondary) or whether the substance use functions as a form of "self-medication" for sleep disturbance, in which the sleep disturbance would be considered primary. Many patients with alcoholism experience secondary depression during the first few weeks of withdrawal from alcohol and exhibit short REM latency and other sleep changes similar to those reported in primary depression. This secondary depression usually remits spontaneously. Likewise, about one-third of patients with unipolar depression and about three-fifths of patients with bipolar disorder, manic type, have a substance use pattern that meets diagnostic criteria for alcoholism or substance abuse at some point. Prognosis and treatment may be altered in comorbid states, depending on whether the sleep disturbance is primary or secondary. In general, treatment should be aimed at the primary diagnosis after management of any acute withdrawal condition that may exist.

## Alcohol

Alcohol is probably the most commonly self-administered "sleeping aid." Although it may be sedating, especially in middle-aged or elderly or sleep-deprived persons, its usefulness as a hypnotic is limited by potential disinhibiting and

arousing effects, gastric irritation, falling blood-alcohol levels in the early part of the night with mild withdrawal symptoms and sleep fragmentation at the end of the night, morning headaches and hangover effects, tolerance with repeated use, and exacerbation of BRSDs such as apnea.

Virtually any type of sleep disturbance has been attributed to the effects of alcohol or alcohol withdrawal in patients with alcohol abuse or dependence. Insomnia may occur during episodes of drinking and acute and chronic withdrawal. Complaints of insomnia and objective disruption of sleep continuity and Stages 3 and 4 sleep have been reported for up to several years in some abstinent patients. Hypersomnia may occur during heavy bouts of drinking, sometimes with peripheral compression neuropathies, or as "terminal hypersomnia" after delirium tremens. Circadian sleep disturbances may also occur during bouts of drinking, including periods of short polyphasic sleep–wake episodes. Parasomnias include sleepwalking and enuresis.

Because alcohol may temporarily improve the poor sleep of the chronic alcoholic individual, sleep disturbance may be a factor in relapse (Landolt and Gillin 2001). Treatment of the sleep disturbances of the chronic but abstinent alcoholic individual is difficult. Nonpharmacological approaches include sleep hygiene and sleep restriction, as well as attention to general nutrition, physical health, and psychosocial supports. Use of benzodiazepines or other hypnotics is not generally recommended because of cross-tolerance or deliberate or inadvertent overdose. It has been reported that increased REM percentage and short REM latency at admission to an inpatient alcohol treatment program are risk factors for relapse in primary alcoholic patients without depression (Gillin et al. 1994).

## Nicotine

Aside from medical complications, such as coughing that may interfere with sleep, smoking has been associated with both difficulties in falling asleep and getting up in the morning, suggesting that nicotine may phase delay the circadian oscillator. Furthermore, compared with nonsmokers, men who smoked reported more nightmares and women who smoked reported more daytime sleepiness. Furthermore, as blood-nicotine levels fall during the night, smokers go into relative withdrawal and start craving a cigarette. One of the best measures of nicotine dependence is how long the smoker can wait in the morning for the first smoke. Abstinence from smoking is associated with lighter and more fragmented sleep, daytime sleepiness on the MSLT, irritability, craving, and other subjective emotional distress.

## Amphetamines and Cocaine

Stimulants initially prolong sleep onset and reduce REM sleep, sleep continuity, and sleep duration, but tolerance usually develops. During acute withdrawal, hypersomnia and excessive REM sleep occur for the first week or so but may be followed by a few days of insomnia.

## Caffeine

Like the stimulants, caffeine usually promotes arousal and delays sleep, but withdrawal may be associated with hypersomnia. It is probably the most commonly self-administered stimulant, for example, the morning cup of coffee to "get going." Caffeine has some benefits as a mild stimulant to overcome sleepiness.

## Opiates

Short-term use of opiates may increase sleep and subjective sleep quality and reduce REM sleep, especially in patients who need an analgesic for relief of pain, but these drugs may also disrupt sleep. Tolerance usually develops with repeated administration. Withdrawal may be associated with hypersomnia or the "nods."

## Sedatives, Hypnotics, and Anxiolytics

Tolerance to the sedating effects of barbiturates, chloral hydrate, and even benzodiazepines usually develops with repeated administration. This is true especially with short half-life agents, with the possible exception of zaleplon. One or two days of withdrawal insomnia may occur after a few days of administration of short half-life benzodiazepines, such as triazolam, but not with the newer nonbenzodiazepine hypnotics, such as zolpidem and zaleplon.

**Sleep Societies and Associations: Resources for Professional and Patient Information**

| Name | Address | Phone | Website |
|---|---|---|---|
| American Academy of Sleep Medicine (AASM) | One Westbrook Corporate Center Suite 920 Westchester, IL 60154 USA | (708) 492-0930 | www.aasmnet.org |
| Academy of Dental Sleep Medicine (ADSM) | 10592 Perry Hwy, #220 Wexford, PA 15090-9244 USA | (724) 935-0836 | www.dentalsleepmed.org |
| Associated Professional Sleep Societies (APSS) | One Westbrook Corporate Center Suite 920 Westchester, IL 60154 USA | (708) 492-0930 | www.apss.org |
| American Sleep Apnea Association (ASAA) | 1424 K St. NW, Suite 302 Washington, DC 20005 USA | (202) 293-3650 | www.sleepapnea.org |
| Narcolepsy Network | 10921 Reed Hartman Hwy Cincinnati, OH 45242 USA | (513) 891-3522 | www.narcolepsynetwork.org |
| National Sleep Foundation (NSF) | 1522 K St. NW, Suite 500 Washington, DC 20005 USA | (202) 347-3471 | www.sleepfoundation.org |
| Sleep Research Society (SRS) | One Westbrook Corporate Center Suite 920 Westchester, IL 60154 USA | (708) 492-0930 | www.sleepresearchsociety.org |
| Society for Light Treatment and Biological Rhythms (SLTBR) | 4648 Main Street Chincoteague, VA 23336 USA | Fax: 757-336-5777 | www.sltbr.org |

Potential side effects associated with sedating medications during the sleep period include falls and fractures, difficulty arousing to the telephone or the crying infant, amnesia, impairment of cognitive and motor skills, drug-induced sleepwalking, and possibly, BRSDs.

## Other Substances

Many medications produce sleep disturbance, including those with central or autonomic nervous system effects, like adrenergic agonists and antagonists, dopamine agonists and antagonists, cholinergic agonists and antagonists, antihistamines, and steroids. Among the prescription drugs associated frequently with sleep disorders are the SSRIs, which have been connected with overarousal and insomnia in some patients and, more commonly, sedation in other patients. Additional sleep-related disturbances occasionally associated with the SSRIs include sleepwalking, RBD, and REMs during NREM sleep.

### Clinical Vignette 1

When first seen in evaluation, Mr. SV was a 48-year-old married male with a chief complaint of leg, arm, and occasional body jerking throughout the night, which caused awakenings and led to lightened and fragmented sleep. He also reported restlessness in his legs at sleep onset, interfering with his capacity to fall asleep. He reported that it typically took him 40 min to fall asleep, but that occasionally his initial sleep latency could be as long as 2 hr. He would typically awaken four to five times per night, then have difficulty falling back to sleep.

He reported that symptoms had been present for about 7 years, but had become much worse in the 2 months prior to his evaluation. He questioned whether this might have resulted from a more active exercise schedule that he had undertaken in an effort to lose weight.

Mr. SV reported that his sleep in recent weeks had been disrupted to the extent that he was sleeping only 4−5 hr per night. This reflected a significant decrease from his historic average of 7 hr of sleep per night. However, he denied any sleepiness as a consequence of his disturbed sleep, reporting an Epworth Sleepiness Scale Score of 0, consistent with no perceived hypersomnia tendencies.

He reported mild snoring but denied awareness of pauses in breathing. His wife confirmed the absence of any episodes of the "breath-holding" suggestive of sleep apnea. She confirmed the presence of "restless sleep," with frequent twitches and jerks of the arms and legs, which disrupted her sleep, as well as that of her husband.

Mr. SV reported a history of asthma, not requiring treatment with medication at that time. He denied any other significant health problems, specifically denying a history of anemia or of any type of kidney disease. Physical examination was normal, with a normal body mass index and neck circumference, and with a normal-appearing oral airway.

The presumptive diagnosis at this time was RLS and PLMS. A trial of L-dopa/carbidopa was initiated at a dose of 25/100 mg, with directions to increase the dose as needed.

Three weeks later, Mr. SV reported an excellent response at the initial dose of 25/100 taken 2 hr before bedtime, with a reported sleep latency of 5−10 min, and a reduction in awakenings to two to three times per night.

When he did wake up in the night, he reported that he could fall back to sleep without great difficulty.

Over the next 6 months, Mr. SV reported the need for a progressive increase in doses of L-dopa/carbidopa, to the point where he was taking 3 tablets of the 25/100 mg dose. He was beginning to experience an increase in sensations of restlessness prior to his evening dose of medication, as well as a return of movement symptoms in the early morning hours.

Rather than a further increase in medications, Mr. SV requested a trial of a different medication. He was instructed to discontinue the L-dopa/carbidopa and was started on pramipexole 0.125 mg, with instructions to begin with 1 tablet 1 hr before bedtime for 5 days, and to increase to up to 2 tablets as needed. He experienced initial benefit at the dose of 2 × 0.125 mg, with sustained sleep throughout the night and no complaints of restlessness at the start of the night.

He continued to do well with this regimen for 6 months. At that time he noted a return of some symptoms of restlessness and movement activity disrupting sleep. The dose was raised to 3 × 12.5 mg, (with good symptomatic relief). He has remained symptom-free at this dose, with no complaints of side effects or intolerance of the medication.

**Discussion**

Mr. SV presented with a typical RLS/PLMS history, although many patients with these complaints that have persisted over a longer period of time will also complain of daytime fatigue or sleepiness.

No sleep studies were performed. Although it would have been of interest to confirm the clinical diagnosis of RLS/PLMS with a polysomnographic study, there were no symptoms present suggestive of another disorder, such as sleep apnea, which could have caused his complaints and which could have been confirmed or excluded on the basis of PSG.

Had he not responded to a first or second course of pharmacologic therapy for his presumed RLS/PLMS, a sleep study could have been ordered to confirm the diagnosis.

From a historical perspective, the absence of anemia or of kidney disease were of importance to rule out treatable causes of RLS/PLMS (iron deficiency or renal failure). However, treatment for these conditions (iron replacement or dialysis) does not always lead to resolution of the RLS/PLMS complaints, particularly in early phases of treatment for iron deficiency anemia.

The history of loss of benefit from treatment with L-dopa/carbidopa is also not unusual. Patients taking this medication often experience a "breakthrough" of RLS symptoms over time, and may report that, as medication is given earlier in the evening to reduce symptoms of restlessness, symptoms begin to appear progressively earlier, frustrating efforts at effective treatment.

### Clinical Vignette 2

When seen in consultation, Ms. A was a 56-year-old married woman, the wife of a physician, referred by her rheumatologist for evaluation of long-standing sleep complaints. She described her sleep complaint as follows: "With the help of medications, I am able to sleep for 2−4 hr. When I wake up, I am fully awake no matter what the hour."

She stated that her sleep problems had been present for approximately 15 years. She described in great detail her severe problems with fibromyalgia, which had led to a substantial decline in functioning. She reported that she had experienced a significant degree of improvement under the care of her rheumatologist and noted that sedating antidepressants, particularly amitriptyline, had been helpful to her in controlling pain and improving her sleep. Other antidepressants that had been used singly or in combination included doxepin and nortriptyline. Cyclobenzaprine had been of some benefit but led to a complaint of mouth dryness. She had received various sedative medications in treatment of sleep complaints, including clonazepam, triazolam, temazepam, chloral hydrate, meprobamate, ethchlorvynol, and various barbiturates. In reviewing her history of hypnotic use, it became apparent that she had in fact used hypnotic medications on a nightly basis for more than 30 years. She had also used L-tryptophan in the past and had experienced a well-documented eosinophilia–myalgia syndrome, presumably associated with contaminants in L-tryptophan sold as a "food additive."

She reported that she took her sleep medication (at time of evaluation, temazepam at 30 mg) 2−2.5 hr before her regular hour of retiring of 11 PM. She awakened several hours later without awareness of any specific cause and reported difficulty in returning to sleep on a nightly basis. She listened to a tape recorder on a nightly basis, using self-help and relaxation tapes and keeping the recorder running throughout the night whether she was awake or asleep.

She reported that she "rested" for an hour at a time several times a day, although she denied feeling truly sleepy at any point in the daytime, acknowledging instead symptoms of fatigue and low energy. She acknowledged that "on rare occasions," she might briefly fall asleep during these periods of daytime rest.

A Minnesota Multiphasic Personality Inventory was performed a year before evaluation and demonstrated an elevation in the depression (D) scale. No formal psychiatric treatment had been recommended or obtained.

PSG was considered, but not obtained. PSG is typically not obtained as part of the initial evaluation of the insomnia patient. When the PSG demonstrates poor sleep- a low sleep efficiency- it confirms the patients subjective complaint but may not suggest a specific therapeutic intervention. When the PSG demonstrates relatively good sleep- a normal sleep efficiency- the patient is likely to report that this was a "better night than normal," unusual but occasionally experienced.

Although positive findings from a PSG are helpful for some patients, for example, when sleep apnea or leg movement activity is discovered, a PSG is usually reserved for patients who have atypical complaints, symptoms suggestive of a primary sleep disorder such as sleep apnea, and those who have failed multiple trials of pharmacotherapy, combined with behavioral and cognitive interventions.

Treatment for Ms. A was initiated to reduce reliance on medications, to improve sleep hygiene, and to improve nocturnal sleep continuity. Use of her tape recorder during the night was forbidden because it may have activated her, and her sleep medication was changed to zolpidem to allow more rapid onset of action and shorter duration of action. She was instructed to discontinue her periods of rest during the daytime, with the exception of a single 20-min period of rest or sleep in the afternoon. She was told not go to bed until she felt tired in the evening and to take her sleep medication at that time. She was instructed to avoid clock watching during the night and to read something relaxing or boring in another room until she felt sleepy, at which point she could return to bed. She was asked to complete a sleep diary on a daily basis. Her initial perception was of somewhat less sleep than she had previously been obtaining, with a further decline in daytime performance. In a period of 4 weeks, her reported sleep time at night climbed to 5 hr, with improvement in perceived daytime function. After a year of further support of behavioral interventions and good sleep hygiene, she was able to taper and discontinue use of hypnotics and antidepressants, reported a substantial improvement in her fibromyalgia complaint, and had essentially complete resolution of her sleep complaints.

## Clinical Vignette 3

When seen in consultation Mr. O was a 61-year-old married male attorney, seen alone, who presented for evaluation of complaints of snoring and observed pauses in breathing. His wife had reported to him her observation of very loud, continuous snoring and clear-cut sleep apnea episodes. On occasion, the snoring was loud enough that his wife needed to go sleep in a guest bedroom. Mr. O was aware, on occasion, of waking during the night due to snoring, but did not report awareness of any apneas. He had no difficulty initiating sleep at the start of the night, and would often fall asleep watching television in the evening.

Mr. O reported that he did not feel fully restored or refreshed upon awakening in the morning, and that he would wake up several times during the night, usually with the need to go to the restroom. He denied urinary frequency in the daytime,. He did report waking with a dry mouth during the night and in the morning, but not of a morning headache. He did report occasional problems with gastroesophageal reflux waking him during the night.

Mr. O acknowledged some reductions in concentration, memory, and attention during the day. He reported that he had experienced some increase in irritability and that he felt that his energy level was somewhat reduced relative to the past. He acknowledged some tendencies to excessive sleepiness when sedentary. He completed an Epworth Sleepiness Scale questionnaire which resulted in a score of 12, which was in the mildly elevated range. However, this likely reflected an underestimation of the severity of actual sleepiness.

Mr. O reported a benign medical history with no significant medical problems. However, his blood pressure had been observed to be "creeping up" when checked recently. He had a history of depression dating back many years, and was taking Wellbutrin with some benefit but without complete resolution of depressive symptoms. He denied taking any other medications on a regular basis. He did not smoke, and reported limited use of alcohol and caffeine containing beverages. He acknowledged that use of alcohol made his snoring worse, and that he occasionally used caffeine to increase alertness during the day.

He denied any history of injuries to or surgery involving the nose, throat, neck, or jaw, or any history of allergies. He noted that his father probably had sleep apnea, and that other relatives had been loud snorers.

On physical examination, Mr. O weighed 236 pounds fully clothed, carried on an approximate 5' 10" frame. Body habitus was obese (body mass index (BMI) = 34). The neck circumference was 18.5 inches, with a very full submandibular space. Nasal flow was equal bilaterally without obvious constriction. Facial structure was not noteworthy for a foreshortened jaw. Examination of the oropharynx demonstrated a crowded airway outlet.

Mr. O recognized that sleep apnea likely was present, but expressed concern about his ability to tolerate nasal CPAP if studies suggested that it would be appropriate therapy for him. PSG was performed. Mr. O demonstrated moderate obstructive sleep apnea-hypopneas, with an index of 24.8 events per hour for total sleep time, 11.9 events per hour in NREM sleep, and 49.2 events per hour in REM sleep. Apnea was also more severe in the supine position (Supine AHI = 32.5). ECG showed mild acceleration-decelerations with obstructive breathing events, but otherwise was unremarkable.

After a review of the study results, Mr. O agreed to a CPAP titration study, which documented that effective treatment of his sleep apnea could be attained at a CPAP pressure setting of 10 cm $H_2O$. He had little difficulty tolerating CPAP, indicated that the CPAP mask was properly fitted and that CPAP was comfortable, and stated that he would "absolutely" use it as therapy if prescribed. He rated his sleep quality with CPAP as much better than a normal night's sleep at home.

CPAP treatment was initiated, and Mr. O was quite successful with his adaptation to CPAP, as measured by records of hours of use obtained from his CPAP unit. He reported an immediate improvement in his perceptions of sleep quality, energy and cognitive function, and reported a progressive improvement in mood with functional absence of depressive symptoms.

He has continued to use nasal CPAP on a nightly basis for two years, with stability in mood, cognitive function and energy levels, and without continued in creases in blood pressure. He has expressed a desire to work on weight reduction, but has not attained any persistent weight loss.

## Comparison of DSM-IV-TR /ICD-10 Diagnostic Criteria

For primary insomnia, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are almost identical except that ICD-10 requires a frequency of at least three times a week for at least a month, whereas DSM-IV-TR does not specify a required frequency. For primary hypersomnia, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are almost identical except that ICD-10 also counts sleep drunkenness as a presenting symptom. Furthermore, ICD-10 requires that the problems occur nearly every day for at least 1 month (or recurrently for shorter periods of time).

Since narcolepsy and BRSD are included in chapter VI (Diseases of the Nervous System) in ICD-10, there are no diagnostic criteria provided for these conditions.

For circadian rhythm sleep disorder, the ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria are almost identical except that ICD-10 specifies that the problems occur nearly every day for at least 1 month (or recurrently for shorter periods of time) (DSM-IV-TR has no specified duration). This condition is referred to in ICD-10 as "Nonorganic disorder of the sleep–wake cycle."

The ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria for nightmare disorder and sleepwalking disorder are essentially identical. The ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria sets for sleep terror disorder are almost identical except that ICD-10 explicitly limits the duration of the episode to less than 10 min.

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CHAPTER

# 80 Impulse-Control Disorders

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Intermittent Explosive Disorder
Kleptomania
Pyromania
Pathological Gambling
Trichotillomania

## Introduction

Although dissimilar in behavioral expressions, the disorders in this chapter share the feature of impulse dyscontrol. Individuals who experience such dyscontrol are overwhelmed by the urge to commit certain acts that are often apparently illogical or harmful (McElroy et al. 1992). Whereas impulse-control disorders (ICDs) were once conceptualized as either addictive or compulsive behaviors, they are now classified within the DSM-IV-TR (American Psychiatric Association 2000) ICD category. These include intermittent explosive disorder (IED) (failure to resist aggressive impulses), kleptomania (failure to resist urges to steal items), pyromania (failure to resist urges to set fires), pathological gambling (failure to resist urges to gamble), and trichotillomania (failure to resist urges to pull one's hair). It should be noted that behaviors characteristic of these disorders may be notable in individuals as symptoms of another mental disorder. If the symptoms progress to such a point that they occur in distinct, frequent episodes and begin to interfere with the person's normal functioning, they may then be classified as a distinct ICD.

There are also a number of other disorders that are not included as a distinct category but are categorized as ICDs not otherwise specified in DSM-IV-TR. These include sexual compulsions (impulsive-compulsive sexual behavior), compulsive shopping (impulsive-compulsive buying disorder), skin picking (impulsive-compulsive psychogenic excoriation), and internet addiction (impulsive-compulsive computer usage disorder). These disorders are unique in that they share features of both impulsivity and compulsivity and might be labeled as ICDs. Patients with these disorders engage in the behavior to increase arousal. However, there is a compulsive component in which the patient continues to engage in the behavior to decrease dysphoria.

To properly conceptualize ICDs, it is helpful to understand the role of impulsivity within them. The trait of impulsivity has been the subject of increasing interest in psychiatry. Impulsivity is a defining characteristic of many psychiatric illnesses, even those not classified as ICDs, including Cluster B personality disorders like borderline personality disorder (BPD) and antisocial personality disorder (ASPD), neurological disorders characterized by disinhibited behavior, attention-deficit/hyperactivity disorder (ADHD), substance and alcohol abuse, conduct disorder, binge-eating, bulimia, and paraphilias. Impulsivity research has been conducted both in disorders characterized by impulsivity, like BPD, ASPD, and conduct disorder, and in traditional ICDs like IED. Clinicians should recognize that individuals who are prone to impulsivity and ICDs are often afflicted with a cluster of related conditions including sexual compulsions, substance use disorders, and posttraumatic stress disorder and to screen for comorbid conditions such as bipolar spectrum disorders and ADHD that contribute to impulsivity (Figure 80–1).

Impulsivity is the failure to resist an impulse, drive, or temptation that is potentially harmful to oneself (e.g. trichotillomania, pathological gambling) or others (e.g. IED, pyromania, kleptomania) is a common clinical problem and

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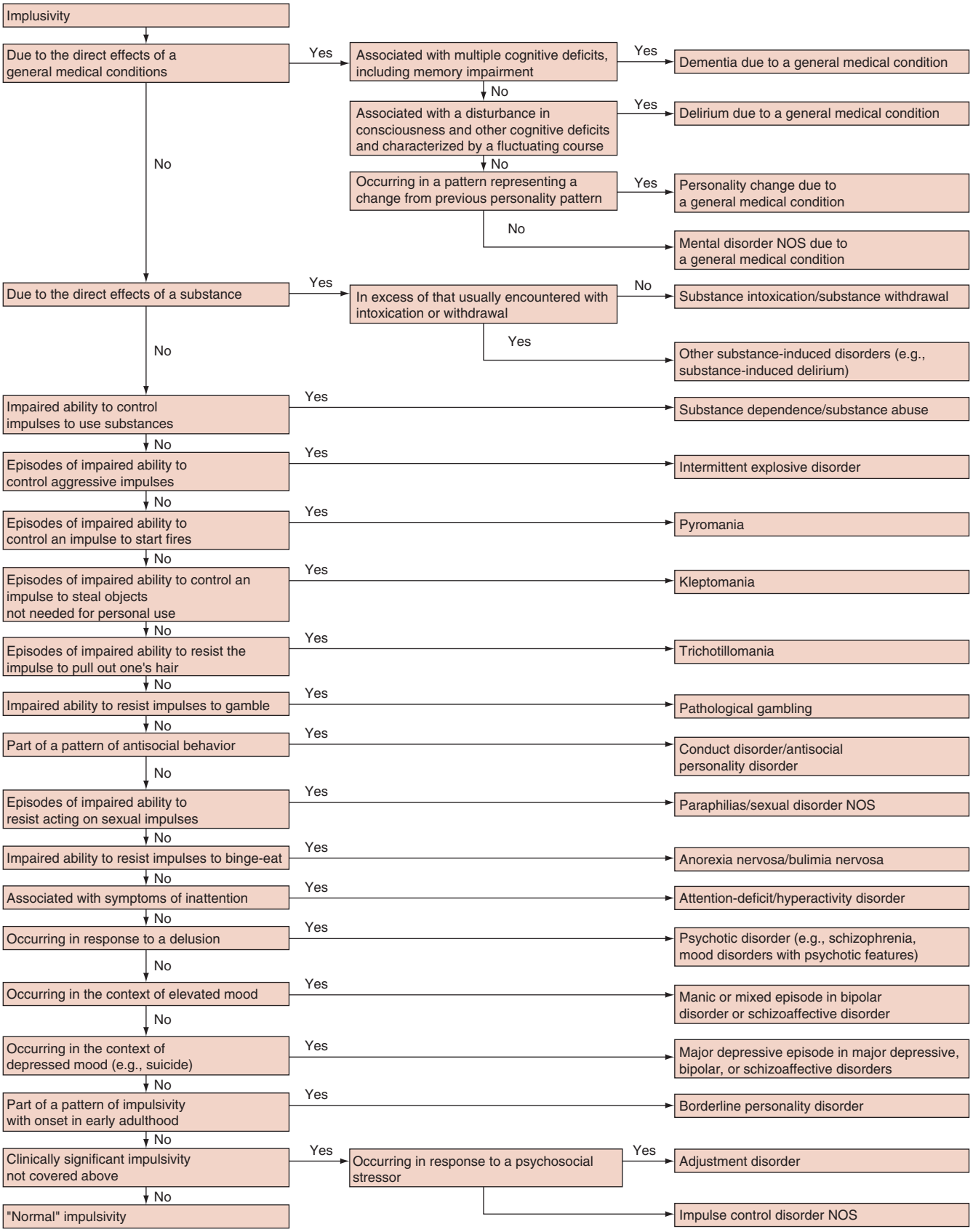



**Figure 80–1** *Differential diagnosis of impulsivity. Impulsivity is a tendency to act in a sudden, unpremeditated, and excessively spontaneous fashion. Other decision trees that should be considered are those for aggressive behavior, catatonia, delusions, depressed mood, euphoric or irritable mood, disorganized or unusual behavior, distractibility, eating behavior, self-mutilation, and suicide ideation or attempt. (NOS, not otherwise specified.)*

a core feature of human behavior. An impulse is rash and lacks deliberation. It may be sudden and ephemeral, or a steady rise in tension that may reach a climax in an explosive expression of the impulse, which may result in careless actions without regard to the consequences to self or others. Impulsivity is evidenced behaviorally as an underestimated sense of harm, carelessness, extroversion, impatience, including the inability to delay gratification, and a tendency toward risk taking, and sensation seeking (Hollander et al. 2002). What makes an impulse pathological is the person's inability to resist it and its expression.

New research findings associate various forms of impulsive behavior with biological markers of altered serotonergic function. These include impulsive suicidal behavior, impulsive aggression, and impulsive fire setting (Stein et al. 1993). In all these circumstances, impulsivity is conceived of as the rapid expression of unplanned behavior, occurring in response to a sudden thought. (This is seen by some as the polar opposite of obsessional behavior, in which deliberation over an act may seem never ending.) Although the sudden and unplanned aspect of the behavior may be present in the impulse disorders (such as in IED and kleptomania), the primary connotation of the word impulsivity, as used to describe these conditions, is the irresistibility of the urge to act. In DSM-IV-TR, ICDs are characterized by five stages of symptomatic behavior (Table 80–1). First is the increased sense of tension or arousal, followed by the failure to resist the urge to act. Third, there is a heightened sense of arousal. Once the act has been completed, there is a sense of relief from the urge. Finally, the patient experiences guilt and remorse at having committed the act. In conditions like trichotillomania, pyromania, and pathological gambling, the individual may spend considerable amounts of time fighting off the urge, trying not to carry out the impulse. The inability to resist the impulse is the common core of these disorders, rather than the rapid transduction of thought to action. A decision tree for the differential diagnosis of impulsive behaviors may be seen in Figure 80–1.

Other than sharing the essential feature of impulse dyscontrol, it is unclear whether the conditions in this chapter bear any relationship to each other. Emerging perspectives on the neurobiology of impulsivity suggest that impulsive behaviors, across diagnostic boundaries, may share an underlying pathophysiological diathesis. As noted earlier, markers of altered serotonergic neurotransmission have been associated with a variety of impulsive behaviors: suicidality, aggressive violence, pyromania, and conduct disorder. These observations have led to speculation that decreased serotonergic neurotransmission may result in decreased ability to control urges to act. In accord with this model, these disorders may be varying expressions of a single disturbance—or closely related disturbances—of serotonergic function. Although such markers of altered serotonergic function have been demonstrated among impulsive fire setters and impulsive violent offenders, there is, as yet, insufficient research on these conditions to accept or dismiss this theory.

It has been noted that these conditions are embedded in similar patterns of comorbidity with other psychiatric disorders. High rates of comorbid mood disorder and anxiety disorder appear typical of these disorders. This contextual similarity, combined with the common feature of impulsivity, may further support the notion that these conditions are—at the level of core diathesis—related to each other.

Although these conditions have historically been considered uncommon, later investigations suggest that some of them may be fairly common. Trichotillomania, for example, was once considered rare. However, surveys indicate that the lifetime prevalence of the condition may exceed 1% of the population. Pathological gambling may be present in up to 3% of the population. Extrapolation from the known incidence of comorbid conditions suggests that kleptomania may have a 0.6% incidence. It would seem reasonable to suspect that individuals with pyromania and kleptomania may seek to avoid detection and may therefore be underrepresented in research and clinical samples.

Few treatment studies of these specific conditions have been conducted. Attempts to treat these conditions are usually formulated by extrapolation from treatments that have been developed for other conditions. The treatment literature for most of these conditions reflects the general development of psychiatric theory. Papers from the early part of the 20th century are largely restricted to reports of the psychoanalytic treatment of individual cases or of small series. The aggressive quality of kleptomania, pyromania, and IED and the self-damaging nature of trichotillomania and pathological gambling have presented tempting substrates for the application of traditional analytical concepts. From this perspective, these behaviors have been seen as symptomatic expressions of unconscious conflict, often sexual in nature. Other formulations include desires for oral gratification and

**Table 80–1 Differential Diagnosis of Intermittent Explosive Disorder**

| IED Must Be Differentiated from Aggressive Behavior in | In Contrast to IED, the Other Condition |
|---|---|
| Substance intoxication or withdrawal | Is due to the direct physiological effects of a substance |
| Delirium or dementia (substance induced or due to a general medical condition) | Includes characteristic symptoms (e.g., memory impairment, impaired attention) |
| | Requires the presence of an etiological general medical condition or substance use |
| Personality change due to a general medical condition, aggressive type | Requires presence of an etiological general medical condition |
| Conduct disorder or ASPD | Is characterized by a more general pattern of antisocial behavior |
| Other mental disorders (schizophrenia, manic episode, oppositional defiant disorder, BPD) | Includes the characteristic symptoms of the other mental disorder |

*Source*: [Reproduced from First and Frances A (1995) with permission of American Psychiatric Press.]

masochistic wishes to be caught and punished, motivated by a harsh, guilt-inducing superego. The increasing influence of object relations theory was reflected in increasing emphasis on narcissistic psychopathology and histories of disturbed early parenting. As successful behavioral interventions were developed for other conditions, case reports of behavioral treatments for these conditions emerged. Reports of hypnotic treatments are also prominent in the literature.

As pharmacological treatments are applied to an increasing range of symptoms, the ICDs in this chapter present new opportunities to widen the application of thymoleptic and anxiolytic and, more recently, atypical neuroleptic medication. As part ongoing evolving theory, the very concept of impulsivity is still in ferment. Attempts to further refine the idea of impulsivity are reflected in a perspective offered by Van Ameringen et al. (1999).

Trichotillomania, IED, and pathological gambling have become the focus of increasing interest of late. However, kleptomania and pyromania remain stepchildren of research. Perhaps the legal implications of these behaviors and their entanglement with similar—but not impulsively motivated—behaviors complicate the availability of sufficient cases to facilitate research. Because of the limited body of systematically collected data, the following sections largely reflect accumulated clinical experience. Therefore, the practicing psychiatrist should be particularly careful to consider the exigencies of individual patients in applying treatment recommendations.

## Intermittent Explosive Disorder

### Diagnosis

#### Definition and Diagnostic Features

IED is a DSM diagnosis used to describe people with pathological impulsive aggression (see box for diagnostic criteria).

**DSM-IV-TR Criteria**

**Intermittent Explosive Disorder**

A. Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property.

B. The degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stressors.

C. The aggressive episodes are not better accounted for by another mental disorder (e.g., antisocial personality disorder, borderline personality disorder, a psychotic disorder, a manic episode, conduct disorder, or attention-deficit/hyperactivity disorder) and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., head trauma, Alzheimer's disease).

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Copyright 2000 American Psychiatric Association.

Impulsive aggression, however, is not specific to IED. It is a key feature of several psychiatric disorders and nonpsychiatric conditions and may emerge during the course of yet other psychiatric disorders. Therefore, the definition of IED as formulated in the DSM-IV-TR is essentially a diagnosis of exclusion. As described in criterion C, a diagnosis of IED is made only after other mental disorders that might account for episodes of aggressive behavior have been ruled out. The individual may describe the aggressive episodes as "spells" or "attacks." The symptoms appear within minutes to hours and, regardless of the duration of the episode, may remit almost as quickly. As in other ICDs, the explosive behavior may be preceded by a sense of tension or arousal and is followed immediately by a sense of relief or release of tension.

Although not explicitly stated in the DSM-IV-TR definition of IED, impulsive aggressive behavior may have many motivations that are not meant to be included within this diagnosis. IED should not be diagnosed when the purpose of the aggression is monetary gain, vengeance, self-defense, social dominance, or expressing a political statement or when it occurs as a part of gang behavior. Typically, the aggressive behavior is ego-dystonic to individuals with IED, who feel genuinely upset, remorseful, regretful, bewildered, or embarrassed about their impulsive aggressive acts. Because the essential feature of IED is the occurrence of serious assaultive acts or destruction of property, it is a diagnosis relevant to the interface between psychiatry and the law.

Many clinicians and researchers rarely consider the diagnosis of IED, although impulsive aggressive behavior is relatively common. In community surveys, 12-25% of men and women in the United States reported engaging in physical fights as adults, a frequent manifestation of impulsive aggression (Robins and Regier 1992). Impulsive aggressive behavior is usually pathological and causes substantial psychosocial distress/dysfunction (McElroy et al. 1998). Being the recipient of impulsive aggressive behavior can lead to similar behavior in children who grow up in this environment (Huesmann et al. 1984).

Violence is underreported in Western societies. As discussed by Lion (1992) although violence is commonly encountered in clinical psychiatric practice, its diagnostic acknowledgment within psychiatry has always been problematical (McElroy et al. 1992). To a large extent, this difficulty also reflects history: Freud himself never fully developed a theory of aggression and came to consider the existence of a "primary" destructive drive only late in his life, after the death and devastation of World War I (*Beyond the Pleasure Principle*, published in 1920) (Freud 1955).

Episodes of violent behavior appear in several common psychiatric disorders such as ASPD, BPD, and substance use disorders and need to be distinguished from the violent episodes of patients with IED, which are apparently rare. The study of Felthous et al. (1991) in which 15 men with rigorously diagnosed DSM-III-R IED were identified from among a group of 443 men who complained of violence, permitted some systematic observations about the "typical violent episode" as reported by patients with IED.

In the vast majority of instances, the subjects with IED identified their spouse, lover, or girl/boy friend as a provocateur of their violent episodes. Only one was provoked by a stranger. For most, the reactions occurred immediately and without a noticeable prodromal period. Only one subject

stated that the outburst occurred between 1 and 24 hours after the perceived provocation. All subjects with IED denied that they intended the outburst to occur in advance. Most subjects remained well oriented during the outbursts, although two claimed to lose track of where they were. None lost control of urine or bowel function during the episode. Subjects reported various degrees of subjective feelings of behavioral dyscontrol. Only four felt that they completely lost control. Six had good recollection of the event afterward, eight had partial recollection, and one lost memory of the event afterward. Most IED subjects tried to help or comfort the victim afterward.

## Assessment

### Psychiatric Examination and History

The DSM-IV-TR diagnosis of IED is essentially a diagnosis of exclusion, and the psychiatrist should evaluate and carefully rule out more common diagnoses that are associated with impulsive violence. The lifelong nonremitting history of impulsive aggression associated with ASPD and BPD, together with other features of antisocial behavior (in ASPD) or impulsive behaviors in other spheres (in BPD) may distinguish them from IED, in which baseline behavior and functioning are in marked contrast to the violent outbursts. Other features of BPD such as unstable and intense interpersonal relationships, frantic efforts to avoid abandonment, and identity disturbance may also be elicited by a careful history. More than in most psychiatric diagnoses, collateral information from an independent historian may be extremely helpful, especially in forensic settings. Of note, patients with IED are usually genuinely distressed by their impulsive aggressive outbursts and may voluntarily seek psychiatric help to control them. In contrast, patients with ASPD do not feel true remorse for their actions and view them as a problem only insofar as they suffer their consequences, such as incarceration and fines. Although patients with BPD, like patients with IED, are often distressed by their impulsive actions, the rapid development of intense and unstable transference toward the psychiatrist during the evaluation period of patients with BPD may be helpful in distinguishing it from IED.

Other causes of episodic impulsive aggression are substance use disorders, in particular alcohol abuse and intoxication. When the episodic impulsive aggression is associated only with intoxication, IED is ruled out. However, IED and alcohol abuse may be related, and the diagnosis of one should lead the psychiatrist to search for the other.

Neurological conditions such as dementias, focal frontal lesions, partial complex seizures, and postconcussion syndrome after recent head trauma may all present as episodic impulsive aggression and need to be differentiated from IED. Other neurological causes of impulsive aggression include encephalitis, brain abscess, normal-pressure hydrocephalus, subarachnoid hemorrhage, and stroke. In these instances, the diagnosis would be personality change due to a general medical condition, aggressive type, and it may be made with a careful history and the characteristic physical and laboratory findings.

Individuals with IED may have comorbid mood disorders. Although the diagnosis of a manic episode excludes IED, the evidence for serotonergic abnormalities in both major depressive disorder and ICDs supports the clinical observation that impulsive aggression may be increased in depressed patients, leading ultimately to completed suicide.

### Physical Examination and Laboratory Findings

The physical and laboratory findings relevant to the diagnosis of IED and the differential diagnosis of impulsive aggression may be divided into two main groups: those associated with episodic impulsive aggression but not diagnostic of a particular disorder and those, which suggest the diagnosis of a psychiatric or medical disorder other than IED. No laboratory or physical findings are specific for IED.

The first group of findings that are associated with impulsive aggression across a spectrum of disorders includes soft neurological signs such as subtle impairments in hand-eye coordination and minor reflex asymmetries. These signs may be elicited by a comprehensive neurological examination and simple pencil-and-paper tests such as parts A and B of the Trail Making Test. Measures of central serotonergic function such as cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) levels, the fenfluramine challenge test, and positron emission tomography (PET) of prefrontal metabolism also belong to this group. Although these measures advanced our neurobiological understanding of impulsive aggression, their utility in the diagnosis of individual cases of IED and other disorders with impulsive aggression is yet to be demonstrated.

The second group of physical and laboratory findings is useful in the diagnosis of causes of impulsive aggression other than IED. The smell of alcohol on a patient's breath or a positive alcohol reading with a Breathalyzer may help reveal alcohol intoxication. Blood and urine toxicology screens may reveal the use of other substances, and track marks on the forearms may suggest intravenous drug use. Partial complex seizures and focal brain lesions may be evaluated by EEG and brain imaging. In cases without a grossly abnormal neurological examination, magnetic resonance imaging may be more useful than computed tomography of the head. Magnetic resonance imaging can reveal mesiotemporal scarring, which may be the only evidence for a latent seizure disorder, sometimes in the presence of a normal or inconclusive EEG. Diffuse slowing on the EEG is a nonspecific finding that is probably more common in, but not diagnostic of, patients with impulsive aggression. Hypoglycemia, a rare cause of impulsive aggression, may be detected by blood chemistry screens.

## Epidemiology

IED has been subjected to little systematic study. As formulated in DSM-IV-TR, IED is probably a rare disorder. The exclusionary criterion in the DSM-IV-TR definition (criterion C) reflects an ongoing debate over the boundaries of this disorder. The current definition of IED is the result of a succession of attempts by researchers to classify syndromes associated with impulsive aggression. The diagnostic term "IED" first appeared in the 1980 *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III). The DSM-III and the revised third edition (DSM-III-R) definitions of IED required the absence of signs of generalized impulsivity or aggressiveness between episodes. Episodic behavioral disorders are quite common and exist across a continuum between ictal causes (excessive neuronal discharges) and purely motivational causes (psychogenic).

Temper proneness is a relatively common clinical syndrome that is associated with a wide variety of psychiatric disorders and is usually found in patients with central nervous system dysfunction, character disorders, and psychoactive substance abuse. "Pure" IED, on the other hand, was found to be a rare clinical entity.

A number of studies have looked at clinical populations, and one community survey has been done to determine the prevalence of IED. Numbers range between 1.1% and 6.3%. The evaluation of studies is complicated by the variety of defining criteria used, from DSM-III to current research criteria. Zimmerman et al. (1998) used the Structured Clinical Interview for DSM-IV to study current or lifetime IED in 411 psychiatric outpatients. They reported a rate of 3.8% for current IED and 6.2% for lifetime IED by DSM-IV criteria. A recent reanalysis of a much larger sample from the same population revealed similar rates of IED (Coccaro et al. 2005). Further, data from a pilot community sample study revealed a community rate of lifetime IED by DSM-IV-TR criteria at 4% and by IED-integrated research criteria at 5.1% (Coccaro et al. 2004). Considering the rates found in these more recent studies, IED could be as common as other major psychiatric disorders like schizophrenia or bipolar illness. In fact, the National Comorbidity Survey Replication (NCS-R) study found that IED is much more common than previously thought. Lifetime and 12-month prevalence estimates of DSM-IV IED were 7.3% and 3.9%, with a mean 43 lifetime attacks resulting in 1359 dollars in property damage. IED-related injuries occurred 180 times per 100 lifetime cases (Kessler et al. 2006).

In one study of the prevalence of DSM-III-R IED among violent men, Felthous et al. (1991) found that of 443 subjects who complained of violence, only 15 (3.4%) met criteria for IED. The DSM-III-R definition of IED was more restrictive than the current DSM-IV-TR diagnosis because it required the absence of signs of generalized impulsivity or aggressiveness between episodes. The EEGs of 13 of the men with IED were normal; two showed excessive slowing.

Most of the limited published data on gender differences suggest that males outnumber females with IED, and men with the disorder are more likely to be encountered in forensic settings, whereas women with the disorder are more likely to be found in psychiatric settings. This difference in presentation may reflect the reduced severity of the aggressive acts committed by women with IED. But, more recent data suggest that the male:female ratio is closer to 1:1 (Coccaro et al. 2005).

## Comorbidity Patterns

In contrast to the more restrictive DSM-III and DSM-III-R criteria, the DSM-IV-TR definition of IED allows signs of generalized impulsivity or aggressiveness to be present between episodes. It also allows the psychiatrist to give an additional diagnosis of IED in the presence of another disorder if the episodes are not better accounted for by the other disorder. These changes were deemed necessary because the clinical reality is that most individuals who have intermittent episodes of aggressive behavior also have some impulsivity between episodes and often present with other past or current psychiatric disorders.

Subjects with IED most frequently have other Axis I and II disorders. The most frequent Axis I diagnoses comorbid with IED lifetime include mood, anxiety, substance, eating, and other ICDs ranging in frequency from 7% to 89% (Coccaro et al. 1998b, McElroy et al. 1998). Such Axis I comorbidity rates raise the question of whether IED constitutes a separate disorder. However, recent data finding earlier onset of IED compared with all disorders, except for phobic-type anxiety disorders, suggest that IED is not secondary to these other disorders (Coccaro et al. 2005).

McElroy et al. (1998) and McElroy (1999) studied 27 individuals who had symptoms that met criteria for IED and reported: "Twenty-five (93%) subjects had lifetime DSM-IV-TR diagnoses of mood disorders; 13 (48%), substance use disorders; 13 (48%), anxiety disorders; 6 (22%), eating disorders; and 12 (44%), an ICD other than IED. Subjects also displayed high rates of comorbid migraine headaches. First-degree relatives displayed high rates of mood, substance use, and impulse-control disorders." McElroy et al. (1998) reported that the aggressive episodes observed in their subjects resembled "microdysphoric" manic episodes. Symptoms in common with both manic and IED episodes included irritability (79-92%), increased energy (83-96%), racing thoughts (62-67%), anxiety (21-42%), and depressed (dysphoric) mood (17-33%). However, this finding may not be surprising, because 56% of the subjects in question had a comorbid bipolar diagnosis of some type (bipolar I, 33%; bipolar II, 11%; and bipolar not otherwise specified or cyclothymia, 11%). The Rhode Island Hospital Study (Coccaro et al. 2005) suggests a much lower rate of comorbid bipolar illness, with a rate of 11% (bipolar I, 5%; bipolar II, 5%; and bipolar not otherwise specified, 1%). Regardless, clinicians should fully evaluate for bipolar disorder prior to determining treatment for IED, because mood stabilizers, rather than serotonin reuptake inhibitors (SSRIs), would be the first-line treatment for IED comorbid with bipolar disorder.

McElroy et al. (1998) reported that up to 44% of their IED subjects had another impulse-control–type disorder such as compulsive buying (37%) or kleptomania (19%). However, Coccaro et al. (1998b) found that IED subjects had a comorbid ICD, and only 5% of IED subjects had another ICD in the Rhode Island Hospital Study (Coccaro et al. 2005).

Some children with Tourette's disorder may be prone to rage attacks (Budman et al. 1998, 2000). The clinical manifestation of these attacks is similar to IED and may be more common among children with Tourette's who have comorbid mood disorders. On the basis of these observations, the rage attacks of these children may flow from an underlying dysregulation of brain function (Budman et al. 1998, 2000).

The limited literature on the comorbidity of impulsive aggressive episodes suggests that it often occurs with three classes of disorders:

1. Personality disorders, especially ASPD and BPD. By definition, ASPD and BPD are chronic and include impulsive aggression as an essential feature. Therefore, their diagnosis effectively excludes the diagnosis of IED (Figure 80–2). Coccaro et al. (1998b) reported the rate of BPD and/or ASPD in IED subjects to be 38%. However, rates of IED in subjects with BPD have been noted at 78% and in subjects with ASPD at 58% (Coccaro et al. 1998b). A review of unpublished data from the author's lab (Hollander 2007) (Hollander E [2007], personal communication) suggests that these rates are

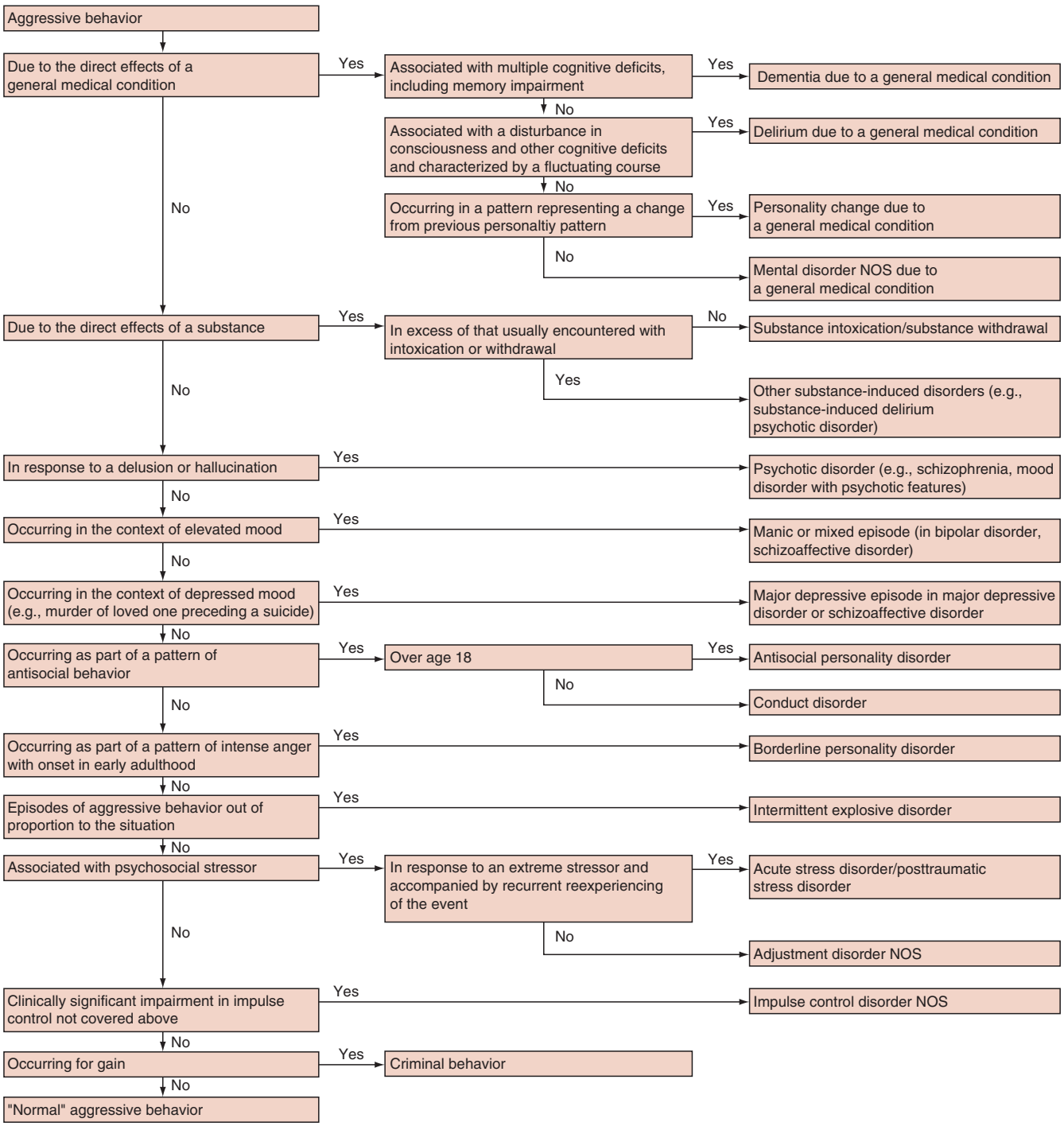



**Figure 80–2** *Differential diagnosis of aggression. The psychiatric nosology of aggression has not been well worked out and requires much additional study. This is a particularly unfortunate state of affairs because the attribution (or misattribution) of aggression to a mental disorder is a frequent focus of forensic attention and can mean the difference between a life term in prison or a promotional tour for a bestseller. Because of the inherent difficulties in making these determinations, psychiatric testimony in this regard should be interpreted with caution. Other decision trees that may be of interest include those for catatonia; delusions; euphoria or irritability; disorganized, agitated, or unusual behavior; impulsivity; hallucinations; substance use; and general medical condition.*

lower among subjects not seeking treatment and are lowest in the community (23% for BPD and/or ASPD; see also Coccaro et al. 2004). Regardless, BPD and ASPD subjects with a comorbid diagnosis of IED do appear to have higher scores for aggression and lower scores for general psychosocial function than do BPD/ASPD subjects without IED (Coccaro et al. 2005).

2. A history of substance use disorders, especially alcohol abuse. A concurrent diagnosis of substance intoxication excludes the diagnosis of IED. However, many patients with IED report past or family histories of substance abuse, and in particular alcohol abuse. In light of evidence linking personal and family history of alcohol abuse with impulsive aggression (Linnoila et al. 1989)

and linking both with low central serotonergic function (reviewed later), this connection may be clinically relevant. Thus, when there is evidence suggesting that alcohol abuse may be present, a systematic evaluation of IED is warranted, and vice versa.

3. Neurological disorders, especially severe head trauma, partial complex seizures, dementias, and inborn errors of metabolism. IED is not diagnosed if the aggressive episodes are a direct physiological consequence of a general medical condition. Such cases would be diagnosed as personality change due to a general medical condition, delirium, or dementia. However, individuals with IED often have nonspecific findings on neurological examination, such as reflex asymmetries, mild hand-eye coordination deficits, and childhood histories of head trauma with or without loss of consciousness. Their EEGs may show nonspecific changes. Such isolated findings are compatible with the diagnosis of IED and preempt the diagnosis only when they are indicative of a definitely diagnosable general medical or neurological condition. Such "soft" neurological signs may be diagnosed by a full neurological examination and neuropsychological testing.

## Course

Given the rarity of pure IED, limited research is available concerning the age at onset and natural course of IED. But, according to the DSM IV-TR (American Psychiatric Association 2000), and anecdotal case reports, the onset appears to be from childhood to the early 20s, and may be abrupt and without a prodromal period. The age of onset and course of IED distinguish it as separate from its comorbid diagnoses. The course of IED is variable, with an episodic course in some and a more chronic course in others. IED may persist well into middle life unless treated successfully. In some cases, it may decrease in severity or remit completely with old age. However, cognitive impairment caused by Alzheimer's disease and other age-related causes of dementia may result in the reappearance of impulsive aggressive behavior. A mean age at onset of 16 years and an average duration of about 20 years has been described (McElroy et al. 1998). Preliminary data (Coccaro et al. 2005) confirm these findings and indicate that onset of DSM-IV-TR IED occurs by the end of the first decade in 31%, by the end of the second decade in 44%, by the end of the third decade in 19%, and by the end of the fourth decade in only 6%. The mean age at onset in the NCS-R study was 14 years (Kessler et al. 2006).

Episodes typically last less than 30 minutes and involve one of or a combination of physical assault, verbal assault, or destruction of property. If provoked, it is usually from a known person and is seemingly minor in nature (McElroy et al. 1998). Many individuals frequently have minor aggressive episodes in the interim between severely aggressive/destructive episodes. Considerable distress, social, financial, occupational, or legal or impairments typically result from these episodes.

## Differential Diagnosis

The differential diagnosis of IED covers the differential diagnosis of impulsivity and aggressive behavior in general. Aggression is defined as forceful physical or verbal action, which may be appropriate and self-protective or inappropriate as in hostile or destructive behavior. It may be directed against another person or the environment, or toward the self. The psychiatric nosology of aggression is still preliminary. Impulsivity is defined as the tendency to act in a sudden, unpremeditated, and excessively spontaneous fashion. The IED diagnosis should be considered only after all other disorders associated with impulsivity and aggression have been ruled out. Chronic impulsivity and aggression may occur as part of a cluster B personality disorder (e.g. BPD and ASPD); during the course of substance use disorders and substance intoxication; in the setting of a general medical (usually neurological) condition; and as part of disorders first diagnosed during childhood and adolescence such as conduct disorder, oppositional defiant disorder, ADHD, and mental retardation. In addition, impulsive aggression may appear during the course of a mood disorder, especially during a manic episode, which precludes the diagnosis of IED, and during the course of an agitated depressive episode. Impulsive aggression may also be an associated feature of schizophrenia, in which it may occur in response to hallucinations or delusions. Impulsive aggression may also appear in variants of obsessive-compulsive disorder (OCD), which may present with concurrent impulsive and compulsive symptoms.

A special problem in the differential diagnosis of impulsive aggression, which may arise in forensic settings, is that it may represent purposeful behavior, which is distinguished from IED by the presence of motivation and gain in the aggressive act, such as monetary gain, vengeance, or social dominance. Another diagnostic problem in forensic settings is malingering, in which individuals may claim to have IED to avoid legal responsibility for their acts. Figure 80–2 presents the differential diagnosis of aggression.

Common disorders that should be excluded before IED is diagnosed and features that may be helpful in the differential diagnosis are summarized in Table 80–1.

## Differences in Gender and Cultural Presentations

Amok is an extremely rare culture-specific syndrome of episodic aggression first described in the Malay Peninsula but later found in Africa and Papua New Guinea. Amok is an episode of sudden, unprovoked rage in which the affected individual runs around with a weapon and attempts to kill a number of people or animals. Sometimes the perpetrator, typically a man, then kills himself. If captured alive, the individual with amok claims no memory of the acts. The etiology of amok and its relation to IED are unclear. Episodic violent behavior is more common in males than in females (DSM-IV-R).

## Etiology and Pathophysiology

Theories about the etiology of impulsive aggressive outbursts and IED have been part of psychiatry from its origins. Possession by spirits, humoral imbalances, and "moral weakness" were all suggested to play a role. Since the second-half of the 19th century, two main lines of explanation, which are to a large extent complementary, have been developed to account for the existence of individuals with episodic impulsive aggression. One line of explanation viewed the etiology of impulsive aggression as stemming from the effects of early childhood experiences and possibly

childhood trauma on the development of self-control, frustration tolerance, planning ability, and gratification delay, which are all important for self-prevention of impulsive aggressive outbursts. Early experiences with "good-enough" mothering that fosters phase-appropriate delay of gratification and the development of the potential for imitation and identification with the mother are considered important for normal development. Too much or too little frustration, as well as overgratification or undergratification, may impair the normal development of the ability to anticipate frustration and delay gratification (Khantzian and Mack 1983).

A second line of explanation, which has yielded numerous positive findings over the past 15 years, views impulsive aggression as the result of variations in brain mechanisms that mediate behavioral arousal and behavioral inhibition. A rapidly growing body of evidence has shown that impulsive aggression may be related to defects in the brain serotonergic system, which acts as an inhibitor of motor activity (Kavoussi et al. 1997, Staner and Mendlewicz 1998). Animal studies suggest that serotonergic neurons play a role in behavioral inhibition and thus provide an impetus to explore the role of serotonin in human impulsivity. Although the majority of the human studies involved patients who suffered from impulsive aggression in the context of disorders other than IED, their findings may be relevant to the behavioral dimension of impulsive aggression, of which IED is a "pure" form.

Measures examining central (and peripheral) serotonin function correlate inversely with life history, questionnaire, and laboratory measures of aggression. This relationship has been demonstrated by CSF 5-HIAA (Linnoila et al. 1983, Virkkunen et al. 1994), physiological responses to serotonin agonist probes (Coccaro et al. 1989, 1997b, Dolan et al. 2001, Manuck et al. 1998), and platelet measures of serotonin activity (Birmaher et al. 1990, Coccaro et al. 1996). The type of aggression associated with reduced central serotonin function appears to be *impulsive,* as opposed to *nonimpulsive,* aggression (Linnoila et al. 1983, Virkkunen et al. 1994). Linnoila et al. (1989) divided aggressive behaviors into impulsive and nonimpulsive forms and found that reduced CSF 5-HIAA was correlated with impulsive aggression only. These findings suggest that impulsive aggressive behavior can be distinguished biologically from nonimpulsive aggression. Interestingly, the inverse relationship between aggression and serotonin is not observed when catecholamine system function is impaired (Coccaro et al. 1989, Wetzler et al. 1991). Siever et al. (1991) and Stein et al. (1993) have confirmed a relationship between levels of 5-HIAA in the CSF and impulsive or aggressive behaviors. Pharmacological challenge studies have also demonstrated that low serotonergic responsiveness (measured by the neuroendocrine response to serotonergic agonists) correlates with scores of impulsive aggression. Studies of impulsive aggression among alcoholics have further defined a probable relationship between such behaviors and diminished serotonergic function (Virkkunen et al. 1995, Virkkunen and Linnoila 1993).

There is also evidence to support the role of nonserotonergic brain systems and modulators in impulsive aggression. These findings suggest a role for dopamine (Depue et al. 1994), norepinephrine (Coccaro et al. 1991), vasopressin (Coccaro et al. 1998a), brain-derived neurotrophic factor (Lyons et al. 1991), opiates (Post et al. 1984), and testosterone (Giammanco et al. 2005, Virkkunen et al. 1994) and an inhibitory interaction between neuronal nitric oxide synthase and testosterone in rodents (Kriegsfeld et al. 1997).

Another line of neurobiological evidence links impulsive aggression with dysfunction of the prefrontal cortex (PFC). Studies of neuropsychiatric patients with localized brain lesions have demonstrated that some bilateral lesions in the PFC may be specifically associated with a chronic pattern of impulsive aggressive behaviors. Neurological studies suggest that the PFC regions associated with impulsive aggression syndromes are involved in the processing of affective information and the inhibition of motor responsiveness, both of which are impaired in impulsive aggressive patients. Interictal episodes of aggression may occur among some people with epilepsy. In a quantitative MRI study of such episodes among people with temporal lobe epilepsy (TLE) (Woermann et al. 2000) three groups (24 TLE patients with aggressive behavior, 24 TLE patients without such behavior, and 35 nonpatient controls) were compared. The aggressive behavior was associated with a reduction of frontal neocortical gray matter.

Further evidence linking the PFC with the serotonergic system and impulsive aggression comes from postmortem and animal studies suggesting that the PFC is rich in excitatory 5-$HT_2$ receptors, whose number is increased in suicide victims and correlated with aggressive social behavior in primates. Lower levels of CSF 5-HIAA were found in neurological patients with frontal brain injuries than in patients with injuries in other brain regions. The fenfluramine challenge test, a neuroendocrine challenge to the serotonergic system, was found to increase cerebral prefrontal glucose metabolism in normal control subjects. PET studies have found selective reductions in glucose metabolism in the prefrontal and frontal cortex of patients with impulsive aggression. The regional reductions in glucose metabolism in impulsive aggressive patients were more significant during a continuous performance task, whose performance was impaired in neurological patients with frontal lesions and was found to increase frontal glucose metabolism in normal subjects (Raine et al. 1994). A visual-evoked potential and EEG study in a large group of aggressive children and adolescents also suggest that such behavior may be associated with altered innate characteristics of central nervous system function (Bars et al. 2001).

Thus, biological studies implicate the serotonergic system and the PFC in the pathogenesis of impulsive aggression. The diagnosis of IED is sometimes considered in forensic settings; the biological correlates of impulsive aggression focus attention on, but do not solve, the complicated problem of personal responsibility for impulsive violent acts that are correlated with objective biological findings.

## Family and Twin Studies

Clinical observation and family history data suggest that IED is familial. Familial aggregation of temper outbursts and IED has been reported in psychiatric patients with "temper problems" (Mattes and Fink 1987). McElroy et al. (1998) reported that nearly a third of first-degree relatives of IED probands had IED. A blinded, controlled, family history study using IED-integrated research criteria (Coccaro 1999) found a morbid risk of IED of 26% in relatives of IED-IR probands compared with 8% among the relatives of control probands, a significant difference. Although twin studies have

confirmed the hypothesis that both impulsivity (Seroczynski et al. 1999) and aggression (Coccaro et al. 1997a) are under substantial genetic influence, there are no twin studies of IED itself. Genetic influence for these two traits ranges from 28% to 47%, with nonshared environmental influences making up the lion's share of the remaining variance.

## Molecular Genetic Studies

Studies of particular genes in aggressive populations have used the candidate gene approach. Candidate genes are the genes for proteins with a suspected, or proven, biological association to a disorder [e.g., serotonin (5-HT) receptors in aggression]. The polymorphism HTR1B/G861C and short tandem repeat locus D6S284 are part of the gene for the 5-$HT_{1B}$ receptor for serotonin. These genetic sites were examined in 350 Finnish sibling pairs and 305 Southwestern American Indian sibling pairs, both with a high rate of alcoholism. The diagnoses of ASPD and IED were used to examine the traits of impulsivity and aggression. The rate of IED in relatives of ASPD probands was 15%, and the relatives of healthy control subjects had neither IED nor ASPD. Lappalainen et al. (1998) were able to discover that the gene predisposing to ASPD alcoholism resides close to the HTR1B version of the coding sequence. They concluded that impulsivity and aggression might be influenced, in part, by 5-$HT_{1B}$ receptors. Other candidate genes include the genes for tryptophan hydroxylase and MAO-A. Manuck et al. (1999, 2000) found an association of the traits of aggression, impulsivity, and serotonin activity (tested by *D,L-fenfluramine* challenge) with variations in both the tryptophan hydroxylase and the MAO-A genes in community samples.

## Imaging and Brain Localization

Few localization and functional studies have looked at impulsive aggression or IED. Using fluorodeoxyglucose positron emission tomography (FDG-PET), Siever et al. (1999) found blunted glucose utilization responses to serotonin stimulation in the orbitofrontal cortex (an area associated with impulsive aggression) of IED subjects with BPD. A similar finding was reported in the anterior cingulate and anteromedial orbital cortex of impulsive aggressive subjects after stimulation with the direct serotonin agonist *m*-chlorophenylpiperazine (New et al. 2002). Using PET with a 5-$HT_{1A}$ antagonist in healthy volunteers, Parsey et al. (2002) found a significant inverse correlation between lifetime aggression and serotonin receptor binding in the dorsal raphe, anterior cingulate cortex, amygdala, medial PFC, and orbital PFC. Using neuropsychological testing in impulsive aggressive subjects, Best et al.'s (2002) data supported a possible dysfunctional frontal circuit. More work is needed to reveal the specific functional brain abnormalities in impulsive aggressive individuals.

## Treatment

Given the rarity of pure IED, it is not surprising that few systematic data are available on its response to treatment and that some of the recommended treatment approaches to IED are based on treatment studies of impulsivity and aggression in the setting of other mental disorders and general medical conditions. Thus, no standard regimen for the treatment of IED can currently be recommended. Both psychological and somatic therapies have been utilized in the treatment of IED. A prerequisite for both modalities is the willingness of the individual to acknowledge some responsibility for the behavior and participate in attempts to control it.

### Psychological Treatment

Lion (1992) has described the major psychotherapeutic task of teaching individuals with IED how to recognize their own feeling states and especially the affective state of rage. Lack of awareness of their own mounting anger is presumed to lead to the buildup of intolerable rage that is then discharged suddenly and inappropriately in a temper outburst. Patients with IED are therefore taught how to first recognize and then verbalize their anger appropriately. In addition, during the course of insight-oriented psychotherapy, they are encouraged to identify and express the fantasies surrounding their rage. Group psychotherapy for temper-prone patients has also been described. The cognitive-behavioral model of psychological treatment may be usefully applied to problems with anger and rage management.

Anger treatment studies focus on treatment of anger as a component of other psychiatric illnesses, like substance abuse, post-traumatic stress disorder, depression, and domestic violence; and in forensic and mentally impaired populations. In a few rare cases, anger is addressed as the primary or only problem, and a limited number of treatments have been described. "Imaginational exposure therapy," used frequently in anxiety disorders, was studied in a noncontrolled pilot study of anger treatment (Grodnitzky and Tafrate 2000). Subjects habituated to anger-provoking scenarios, and the treatment was felt to be useful. In a controlled trial of high driving anger college students, Deffenbacher et al. (2000) compared pure relaxation training with relaxation training combined with cognitive therapy and an assessment-only control. Neither treatment condition improved general trait anger, but both treatments improved driving anger. When repeated in a new population of drivers with higher anger levels, both treatments lowered trait anger (Deffenbacher et al. 2002). Since relaxation training with cognitive therapy provided little gain over pure relaxation training, relaxation training in itself may be adequate treatment for driving anger.

Other versions of cognitive-behavioral therapy (CBT), like dialectical behavior therapy (DBT), have been studied in BPD patients. One study showed improvement in anger, global functioning, and social adjustment compared with a treatment-as-usual condition (Linehan et al. 1994). Improvement in anger and impulsivity has been shown with DBT across many disorders. There are no published double-blind, placebo-controlled studies on IED subjects in therapy, but studies of therapy in IED subjects are ongoing.

### Somatic Treatments

Several classes of medications have been used to treat IED and impulsive aggression in the context of other disorders. These included beta-blockers (propranolol and metoprolol), anticonvulsants (carbamazepine and valproic acid), lithium, antidepressants (tricyclic antidepressants and SSRIs), and antianxiety agents (lorazepam, alprazolam, and buspirone). Mattes (1990) compared the effectiveness of two commonly used agents, carbamazepine and propranolol, for the treatment of rage outbursts in a heterogeneous group of patients. He found that although carbamazepine and propranolol were overall equally effective, carbamazepine was

more effective in patients with IED and propranolol was more effective in patients with ADHD. A substantial body of evidence supports the use of propranolol—often in high doses—for impulsive aggression in patients with chronic psychotic disorders and mental retardation. Lithium has been shown to have antiaggressive properties and may be used to control temper outbursts. In patients with comorbid major depressive disorder, OCD, or cluster B and C personality disorders, SSRIs may be useful. Overall, in the absence of more controlled clinical trials, the best approach may be to tailor the psychopharmacological agent to coexisting psychiatric comorbidity. In the absence of comorbid disorders, carbamazepine, titrated to antiepileptic blood levels, may be used empirically.

Clinical Vignette 1

Mr. A is a 42-year-old separated man who works as a bank clerk. He came to seek outpatient psychiatric treatment after an angry outburst that led to the breakdown of his second marriage: his wife issued an order of protection against him after a rage attack in which he slapped her across the face and destroyed most of the kitchen and living room furniture. His rage was triggered by his wife's decision to buy a new microwave oven without consulting him. Mr. A, who remembered the episode clearly and with remorse, said that he realized how angry he was only after he actually struck at his wife.

During the course of his evaluation, Mr. A became tearful and admitted to several similar episodes during the course of his current and previous marriages. These episodes were rare, occurring once or twice a year. They were brief and apparently unpredictable and resulted in his separation from his first wife. Except during those episodes, Mr. A was a pleasant, rather timid man who deferred to his wife in most important decisions. There was no history suggestive of antisocial or borderline personality disorder. Mr. A, who described himself as a shy, withdrawn child, gave a history of head trauma at the age of 12 years, while he was ice skating, with loss of consciousness for 10 minutes. Other than this, his medical history was normal. There were no neurological or behavioral sequelae. Mr. A also described prolonged physical abuse by his alcoholic father. Mr. A himself denied a history of substance abuse, involvement with the criminal justice system, and prior psychiatric treatment. He denied a history of manic and depressive episodes. Mr. A had few friends and was not popular at his job. Although he had never lost his temper there, he believed that his boss and coworkers could sense his "stress" while dealing with clients.

Mr. A's physical and neurological examination was notable only for mild bilateral difficulty with rapid alternating hand movements. Except for his tearfulness while describing the episode, Mr. A's Mental Status Examination was unremarkable. Results of routine laboratory blood work and computed tomography of the head were within normal limits. An EEG was notable for diffuse slowing without an epileptic focus.

Mr. A's treatment was started with carbamazepine. at standard dosage. He also received a short course of psychotherapy that focused on recognizing his anger and venting it appropriately, on his memories of childhood physical abuse, and on his current sense of himself as a helpless person who was being controlled by his wife and boss. In addition, it was recommended that he transfer to a position that would not involve contact with clients. During a 2-year follow-up, Mr. A had no further rage episodes. He continued to have few friends but was able to maintain a long-term relationship with a woman he was planning to marry.

## Kleptomania

### Diagnosis

#### Definition and Diagnostic Features

Kleptomania shares with all other ICDs the recurrent failure to resist impulses. Unfortunately, in the absence of epidemiological studies, little is known about kleptomania. Clinical case series and case reports are limited. Family, neurobiological, and genetic investigations are not available. There are no established treatments of choice. Therefore, in reading this section the reader must keep in mind that much of what is described is based on limited data or on anecdotal information.

Kleptomania was designated a psychiatric disorder in 1980 in DSM-III (American Psychiatric Association 1980), and in DSM-III-R (American Psychiatric Association 1987) it was grouped under "disorders of impulse control not elsewhere classified." Kleptomania is currently classified in DSM-IV-TR (American Psychiatric Association 2000) as an ICD (see box below for criteria), but it is still poorly understood. Criterion A, which focuses on the senselessness of the items stolen, has often been considered the criterion that distinguishes kleptomania patients from ordinary shoplifters (Goldman 1991), but interpretation of this criterion is controversial. The archetype of the middle-aged female kleptomania patient who steals peculiar items may not adequately account for all people with kleptomania (Goldman 1991, McElroy et al. 1991a). Patients with kleptomania may in fact desire the items they steal and be able to use them, but do not need them. This may be particularly the case with kleptomania patients who hoard items (Goldman 1991), for which multiple versions of the same item are usually not needed, but the item itself may be desired and may be of practical use to the patient.

People with kleptomania often report amnesia surrounding the shoplifting act (Goldman 1991, Grant 2004), and deny feelings of tension or arousal prior to shoplifting and feelings of pleasure or relief after the thefts. They often recall entering and leaving a store but have no memory of events in the store, including the theft (Grant 2004). Others, who are not amnestic for the thefts, describe shoplifting as "automatic" or "a habit," and may also deny feelings of tension prior to a theft or pleasure after the act (DSM-IV-TR criterion B or C), although they report an inability to control their shoplifting (criterion A). Some report that they felt tension and pleasure when they started stealing, but it became a "habit" over time. Some speculate that patients who are amnestic for shoplifting or who do so "out of habit" represent two subtypes of kleptomania.

At presentation, the typical patient suffering from kleptomania is a 35-year-old woman who has been stealing for about 15 years and may not mention kleptomania as the presenting complaint or in the initial history (Goldman 1991, McElroy et al. 1991a). The patient may complain instead of anxiety, depression, lability, dysphoria, or manifestations of character pathology. There is often a history of a tumultuous

childhood and poor parenting, and in addition acute stressors may be present, such as marital or sexual conflicts. The patient experiences the urge to steal as irresistible, and the thefts are commonly associated with a thrill, a high, a sense of relief, or gratification. Generally, the behavior has been hard to control and has often gone undetected by others. The kleptomania may be restricted to specific settings or types of objects, and the patient may or may not be able to describe rationales for these preferences. Quite often, the objects taken are of inherently little financial value, or have meaningless financial value relative to the income of the person who has taken the object. Additionally, the object may never actually be used. These factors often help distinguish criminal theft from kleptomania. The theft is followed by feelings of guilt or shame and, sometimes, attempts at atonement. The frequency of stealing episodes may greatly fluctuate in concordance with the degree of depression, anxiety, or stress. There may be periods of complete abstinence. The patient may have a past history of psychiatric treatments including hospitalizations or of arrests and convictions, whose impact on future kleptomanic behavior can be variable.

**DSM-IV-TR Criteria**

**Kleptomania**

A. Recurrent failure to resist impulses to steal objects that are not needed for personal use or for their monetary value.

B. Increasing sense of tension immediately before committing the theft.

C. Pleasure, gratification, or relief at the time of committing the theft.

D. The stealing is not committed to express anger or vengeance and is not in response to a delusion or a hallucination.

E. The stealing is not better accounted for by conduct disorder, a manic episode, or antisocial personality disorder.

F. The stealing is not better accounted for by conduct disorder, a manic episode, or antisocial personality disorder.

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## Assessment

Generally, the diagnosis of kleptomania is not a complicated one to make. However, kleptomania may frequently go undetected because the patient may not mention it spontaneously and the psychiatrist may fail to inquire about it as part of the routine history. The index of suspicion should rise in the presence of commonly associated symptoms such as chronic depression, other impulsive or compulsive behaviors, tumultuous backgrounds, or unexplained legal troubles. It could convincingly be argued that a cursory review of compulsivity and impulsivity, citing multiple examples for the patient, should be a part of any thorough and complete psychiatric evaluation. In addition, it is important to do a careful differential diagnosis and pay attention to the various exclusion criteria before diagnosing theft as kleptomania. Possible diagnoses of sociopathy, mania, or psychosis should be carefully considered. In this regard, the psychiatrist must inquire about the affective state of the patient during the episodes, the presence of delusions or hallucinations associated with the occurrence of the behavior, the motivation behind the stealing, and the fate and subsequent use of the objects.

Although the typical patient may be a 35-year-old woman, it is important to remember that men, children, and elderly persons may present with or engage in kleptomania. Interestingly, Goldman's suggested that men may first present for evaluation 15 years later than women. Kleptomania occurs transculturally and has been described in various Western and Eastern cultures. Asian observers have also noted an overlap with eating disorders (Lee 1994). Atypical presentations should raise a greater suspicion of an organic etiology for whom a medical evaluation would then be indicated. Medical conditions that have been associated with kleptomania include cortical atrophy, dementia, intracranial mass lesions, encephalitis, normal-pressure hydrocephalus, benzodiazepine withdrawal, and TLE. A complete evaluation when such suspicions are present includes a physical and neurological examination, general serum chemistry and hematological panels, and an EEG with temporal leads or computed tomography of the brain (Chiswick 1976, Khan and Martin 1977, Mendez 1988, Wood and Garralda 1990, Coid 1984, McIntyre and Emsley 1990).

## Epidemiology

No epidemiological studies of kleptomania have been conducted, and thus its prevalence can be estimated only grossly and indirectly. In a thorough review of the existing literature, Goldman (1991) found that in a series of shoplifters, the estimate of kleptomania ranged from 0% to 24%. The frequency of kleptomania may be indirectly extrapolated from incidence rates of kleptomania in comorbid disorders with known prevalence, like bulimia nervosa. Such speculations suggest at least a 0.6% prevalence of kleptomania in the general population (Goldman 1991). However, given that people who shoplift are often not caught, this is almost certainly an underestimate. Also, the shame and embarrassment associated with stealing prevents most people from voluntarily reporting kleptomania symptoms (Grant and Kimm 2002c). In addition, studies examining comorbidity of other disorders may neglect to inquire about kleptomania. Studies of kleptomania in various clinical samples suggest a higher prevalence. A recent study of 204 adult psychiatric inpatients in the US, with multiple disorders, revealed that kleptomania may in fact be fairly common. The study found that 7.8% ($n = 16$) endorsed current symptoms consistent with a diagnosis of kleptomania and 9.3% ($n = 19$) had a lifetime diagnosis of kleptomania (Grant et al. 2005). Kleptomania appeared equally common in patients with mood, anxiety, substance use, or psychotic disorders. These findings are further supported by two French studies. One study of 107 depressed inpatients found that 4 (3.7%) had kleptomania (Lejoyeux et al. 2002); in another study of 79 alcohol-dependent inpatients, 3 (3.8%) reported symptoms consistent with kleptomania (Lejoyeux et al. 1999). In two studies examining comorbidity in pathological gamblers, rates of comorbid kleptomania ranged from 2.1% to 5% (Grant and

Kim 2003, Specker et al. 1995). A study of bulimia patients found that 24% met DSM-III (American Psychiatric Association 1980) criteria for kleptomania (Hudson et al. 1983).

The literature clearly suggests that the majority of patients with kleptomania are women (e.g. Grant and Kim 2002b, McElroy et al. 1991b, Presta et al. 2002). In a retrospective review of 56 cases that appeared to fulfill DSM-III-R criteria for kleptomania, McElroy et al. (1991b) found that 77% were women. Similarly, in a prospective series of 20 patients with DSM-III-R kleptomania, 75% were women (McElroy et al. 1991a). However, women generally seek psychiatric help more frequently than men, whereas men are more likely to become involved with the penal system (Goldman 1991). Consequently, this may not reflect true gender distribution. The severity of kleptomania symptoms and the clinical presentation of symptoms do not appear to differ based on gender (Grant and Kim 2002b).

## Comorbidity Patterns

High rates of other psychiatric disorders found in patients with kleptomania have sparked debate over the proper characterization of this disorder. Among those with kleptomania who present for treatment, there is a high incidence of comorbid mood, anxiety, and eating disorders, when compared with rates in the general population. Rates of lifetime comorbid affective disorders range from 59% (Grant and Kim 2002b) to 100% (McElroy et al. 1991b). The rate of lifetime comorbid bipolar disorder has been reported as ranging from 9% (Grant and Kim 2002b) to 27% (Bayle et al. 2003) to 60% (McElroy et al. 1991b). Studies have also found high lifetime rates of comorbid anxiety disorders (60–80%; McElroy et al. 1991b, 1992), ICDs (20-46%; Grant and Kim 2003), substance use disorders (23–50%; Grant and Kim 2002b, McElroy et al. 1991b), and eating disorders (60%; McElroy et al. 1991b). Personality disorders have been found in 43–55% of kleptomania patients, the most common being paranoid and histrionic personality disorder (Bayle et al. 2003, Grant 2004).

In reviewing 26 case reports of kleptomania, Goldman (1991) reported mention of histories of depression in 13 patients (50%), anxiety in 8 patients (31%), and bulimia nervosa in 3 patients (12%). Similar percentages are noted by McElroy et al. (1991b) in a review of 56 patients with probable kleptomania: 57% with mood disorder symptoms, 34% with anxiety disorder symptoms, and 11% with bulimic symptoms. Comorbidity patterns among those who present for treatment may be greater than among random samples. More reliable comorbidity rates can be found in a prospective study of 20 kleptomaniacs (McElroy et al. 1991a). Lifetime DSM-III-R comorbidity rates were 40% major depressive disorder, 50% substance abuse, 40% panic disorder, 40% social phobia, 45% OCD, 30% anorexia nervosa, 60% bulimia nervosa, and 40% other ICDs. Dissociative symptoms, significant character pathology, and trauma histories are commonly encountered among this group (Goldman 1991, McElroy et al. 1991b). Unfortunately, Axis I dissociative pathology and Axis II pathology have not yet been systematically investigated in these patients.

## Course

Kleptomania may begin in childhood, adolescence, or adulthood, and sometimes in late adulthood. However, most patients have an onset of symptoms before the age of 21 years, that is, by late adolescence (Goldman 1991, Grant and Kim 2002b, McElroy et al. 1991a, 1991b; Presta et al. 2002). In two separate studies, the mean age at onset was 20 years (Goldman 1991, McElroy et al. 1991a), and included people who had begun stealing as early as 5 to 7 years old. Onset beyond 50 years is unusual, and in some of these cases remote histories of past kleptomania can be elicited (Goldman 1991). Most clinical samples of kleptomaniacs report shoplifting for more than 10 years prior to entering treatment (Goldman 1991, Grant and Kim 2002c, McElroy et al. 1991b) and in some cases 15 or 16 years may elapse before treatment is sought (Goldman 1991, McElroy et al. 1991a).

The disorder appears to be chronic, but with varying intensity. At peak frequency, McElroy et al. (1991a) found a mean of 27 episodes a month, essentially daily stealing, with one patient reporting four acts daily. The majority of patients may eventually be apprehended for stealing once or more, and a minority may even be imprisoned; usually these repercussions do not result in more than a temporary remission of the behavior. People with kleptomania may also have extensive histories of psychiatric treatments, including hospitalization for other conditions, most commonly depression or eating disorders. Because of the unavailability of longitudinal studies, the prognosis is unknown. However, it appears that without treatment the behavior may be likely to persist for decades, sometimes with significant associated morbidity, despite multiple convictions for shoplifting (arrest or imprisonment), with transient periods of remission. Three typical courses have been described: sporadic with brief episodes and long periods of remission; episodic with protracted periods of stealing and periods of remission; and chronic with varying intensity (DSM-IV-TR, American Psychiatric Association 2000).

## Etiology and Pathophysiology

The etiology of kleptomania is essentially unknown, although various models have been proposed in an effort to conceptualize the disorder. At present, the available empirical data are insufficient to substantiate any of these models. With the exception of scant information on family history, data regarding possible familial or genetic transmission of a kleptomania diathesis are unavailable. One study found the risk for major mood disorders in first-degree relatives of probands with kleptomania to be 0.31; similar to the familial risk for probands with major depressive disorder (McElroy et al. 1991a). In the same study, 7% of first-degree relatives of kleptomania patients had histories of OCD. These findings, along with other lines of evidence, suggest that kleptomania shares a common biological diathesis with mood disorders or OCD. The affective spectrum model suggests that kleptomania and other ICDs may share a common underlying biological diathesis with other disorders like depression, panic disorder, OCD, and bulimia nervosa (McElroy et al. 1992, 1991b, Hudson and Pope 1990). The apparent high comorbidity of kleptomania with depression and bulimia nervosa has already been noted. As early as 1911, Janet (1911) recognized the alleviation of depressive symptoms on the commission of kleptomanic acts. Some individuals with kleptomania respond to treatment with thymoleptic agents or electroconvulsive therapy. These observations are cited as support for an affective spectrum model.

Although the affective spectrum has been claimed to encompass obsessive-compulsive pathology (Hudson and Pope 1990) there exists a more specific model conceptualizing kleptomania and other impulse disorders as obsessive-compulsive spectrum disorders (McElroy et al. 1993). Several lines of evidence support this model. First, there are phenomenological similarities between the classical obsessions and compulsions of OCD and the irresistible impulses and repetitive actions characteristic of kleptomania. Further, there appears to be a greater than chance occurrence of OCD in probands with kleptomania and in their relatives. In addition, both conditions have significant comorbidity with mood, anxiety, substance use, and eating disorders. However, OCD rituals are more clearly associated with relief of anxiety and harm avoidance, whereas kleptomania acts seem to be associated with gratification or pleasure. In addition, OCD is associated with a clear preferential response to SSRIs as opposed to general thymoleptics. The limited treatment literature (see later) does not support a similar response pattern in kleptomania. Unfortunately, the role of the serotonergic or of any other neurotransmitter system has not been sufficiently investigated in kleptomania. Interestingly, a large study found subjects with mixed anorexia and bulimia nervosa to have a higher lifetime prevalence of kleptomania than those with either anorexia or bulimia nervosa alone (Herzog et al. 1992). This could suggest a relationship between kleptomania and both the obsessive-compulsive (anorexic) and the affective (bulimic) spectrum.

Alternatively, kleptomania may be conceptualized as an addictive disorder. The irresistible impulse to steal is reminiscent of the urge and highly associated with drinking or drug use (McElroy et al. 1992). Marks (1990) proposed a constellation of behavioral (i.e., nonchemical) addictions encompassing OCD, compulsive spending, gambling, binging, hypersexuality, and kleptomania. This model postulates certain concepts thought to be common in all these disorders, like craving, mounting tension, "quick fixing," withdrawal, external cuing, and habituation. These components have not yet been well investigated in kleptomania.

## Biological Theories

### Serotonin and Inhibition

Compared with controls, kleptomania patients report significant elevations of impulsivity and risk taking (Bayle et al. 2003, Grant and Kim 2002d), and diminished inhibitory mechanisms may underlie the risk-taking behavior of kleptomania. The most well-studied inhibitory pathways involve serotonin and the PFC (Chambers et al. 2003). Decreased measures of serotonin have long been associated with a variety of adult risk-taking behaviors including alcoholism, fire setting, and pathological gambling (Moreno et al. 1991, Virkkunen et al. 1994). Blunted serotonergic responses in the ventromedial PFC have been seen in people with impulsive aggression (New et al. 2002), and this region has also been implicated in poor decision making (Bechara 2003), as seen in those with kleptomania. Although there are few biological studies of kleptomania, early evidence supports a theory of serotonergic involvement in the disorder. One study found a lower number of the platelet serotonin transporter in kleptomania patients versus healthy controls (Marazziti et al. 2000). Pharmacological case studies suggest that SSRIs like clomipramine and SSRIs (Lepkifker et al. 1999, McElroy et al. 1991b) may reduce the impulsive behavior associated with kleptomania.

### Dopamine and Reward Deficiency

Dopaminergic systems influencing rewarding and reinforcing behaviors have also been implicated in ICDs and may play a role in the pathogenesis of kleptomania. One proposed mechanism is "Reward deficiency syndrome," a hypothesized hypodopaminergic state involving multiple genes and environmental stimuli that puts an individual at high risk for multiple addictive impulsive and compulsive behaviors (Blum et al. 2000). Alterations in dopaminergic pathways have been proposed as underlying the seeking of rewards (e.g., shoplifting) that trigger the release of dopamine and produce feelings of pleasure (Blum et al. 2000). Further, dopamine release into the nucleus accumbens has been implicated in the translation of motivated drive into action, serving as a "go" signal (Chambers et al. 2003). Dopamine release into the nucleus accumbens seems maximal when reward probability is most uncertain, suggesting that it plays a central role in guiding behavior during risk-taking situations (Fiorillo et al. 2003). The structure and function of dopamine neurons within the nucleus accumbens, in conjunction with glutamatergic afferent and intrinsic GABAergic activities, appear to change in response to experiences that influence the function of the nucleus accumbens. So, future behavior may be determined in part by prior rewarding experiences via neuroplastic changes in the nucleus accumbens. This may explain why, over time, many kleptomania patients report shoplifting "out of habit" even without a pronounced urge or craving.

### Opioid System, Cravings, and Pleasure

Kleptomaniacs report frequent urges to steal, that result in theft twice weekly on average (Grant and Kim 2002b). Thus, urges linked to the experience of reward and pleasure may represent an important clinical target for treatment. Many indicate that the act of stealing reduces the urges or the tension these urges produce (McElroy et al. 1991b). While many report the urges as intrusive, the act of stealing is often a "thrill" for some, producing a pleasurable feeling (Goldman 1991, Grant and Kim 2002b). The μ-opioid system is thought to underlie urge regulation by processing reward, pleasure, and pain, in part through modulation of dopamine neurons in the mesolimbic pathway via γ-aminobutyric acid interneurons (Potenza and Hollander 2002). Studies of naltrexone, a μ-opioid antagonist, have shown its efficacy in reducing urges in those with kleptomania and other ICDs (Dannon et al. 1999, Grant and Kim 2002c, Kim et al. 2001).

In sum, repeated kleptomanic behavior may be a result of an imbalance between a pathologically increased urge and a pathologically decreased inhibition. The repeated shoplifting may therefore be due to increased activity of the mesocorticolimbic dopamine circuitry, indirectly enhanced through the opioid system, and decreased activity in the cortical inhibitor processes, largely influenced via serotonin.

Numerous psychological formulations of kleptomania have also been postulated over the years. A frequent theme reported by many authors and reviewed by Goldman (1991) and McElroy et al. (1991b) is that of kleptomania as an acting-out aimed at alleviating depressive symptoms. Fishbain

(1987) carefully described the case of a woman whose kleptomanic episodes were closely related to depressive bouts and who experienced an apparent antidepressant effect from the thrill and excitement of her risk-taking behavior. So kleptomania may result from an attempt to relieve feelings of depression through stimulation (Goldman 1991, McElroy et al. 1991a) and risk-taking behavior may produce an antidepressant effect for some patients (Fishbain 1987, Goldman 1991). Shoplifting may distract depressed patients from stressors and unpleasant cognitions. Ironically, problems resulting directly from shoplifting (e.g., embarrassment and shame from getting caught) may in turn lead to even more shoplifting as a misguided attempt of symptom management (Goldman 1991). Supporting the self-medication hypothesis of shoplifting, patients with kleptomania report high lifetime rates of depression (45-100%; Bayle et al. 2003, McElroy et al. 1991b) that usually (60% of cases) precedes the kleptomanic behavior (McElroy et al. 1991b). Further, several case studies report patients who described shoplifting as relief for their depressed moods (Fishbain 1987) and suggest that kleptomania symptoms improve with antidepressants (Lepkifker et al. 1999, McElroy et al. 1991b).

From a psychodynamic point of view, kleptomania has been viewed over the decades as a manifestation of a variety of unconscious conflicts, with sexual conflicts figuring prominently in the literature. Case reports have described conscious sexual gratification, sometimes accompanied by frank masturbation or orgasm during kleptomanic acts (Fishbain 1987, Fenichel 1945). Thus, it has been suggested that kleptomanic behavior serves to discharge a sexual drive that may have forbidden connotations similar to those of masturbation, and the stolen object itself may have unconscious symbolic or overt fetishistic significance. Although no systematic studies exist, there has long been an implication in the literature on kleptomania that those afflicted with kleptomania suffer disproportionately from a variety of sexual dysfunctions. Turnbull (1987) described six patients with a primary diagnosis of kleptomania, all of whom had dysfunctional sexual relationships with their partners, compulsive promiscuity, or anorgasmia.

Other cases of kleptomania have been understood as reflecting conflictual infantile needs and attempts at oral gratification, masochistic wishes to be caught and punished related to a harsh guilt-inducing superego or primitive aggressive strivings, penis envy or castration anxiety with the stolen object representing a penis, a defense against unwelcome passive homosexual longings, restitution of the self in the presence of narcissistic injuries, or the acquisition of transitional objects (Beldoch 1991). These various formulations are presented in detail in Goldman's review (1991). Psychodynamic interpretations associated with kleptomania should be carefully tailored to the individual. The literature on kleptomania has frequently implicated disturbed childhoods, inadequate parenting, and significant character disturbances in kleptomanic patients. From this perspective kleptomania can be more effectively understood in the context of an individual's overall character. Unfortunately, no clinical studies exist that systematically explore Axis II psychopathology in these patients.

Behavioral models also provide clues as to the pathogenesis of kleptomania. From an operant viewpoint, the positive reinforcer in kleptomania is the acquisition of items for nothing, and the intermittent reinforcement (e.g., not always being able to shoplift because of store security) of kleptomanic behavior may therefore be particularly resistant to extinction. Physiological arousal related to shoplifting (Goldman 1991) may be another reinforcer that initiates and perpetuates the behavior. Negative reinforcement (i.e., the removal of a punishing stimulus) hypothesizes that shoplifting is performed to experience relief from the aversive arousal of urges. The self-medication theory of kleptomania may represent a negative reinforcement. This could explain why kleptomaniac behavior continues despite the offender being frequently apprehended.

There may also be specific cognitive errors that are directly linked to kleptomanic behavior: (1) believing that only shoplifting will reduce the urge or the depressive state, (2) selective memory (e.g., remembering the thrill of shoplifting and ignoring the shame and embarrassment from being apprehended), and (3) erroneous self-assessment (e.g., that one deserves to be caught stealing because one is not intrinsically worth anything). A biopsychological perspective will most likely provide the most useful understanding for the treatment and prevention of kleptomania.

## Treatment

### Treatment Goals

The general goal of treatment is the eradication of kleptomanic behavior. Treatment typically occurs in the outpatient setting, unless comorbid conditions like severe depression, eating disturbances, or more dangerous impulsive behaviors dictate hospitalization. In the initial contact with the psychiatrist, as described earlier, it is important that the appropriate differential diagnoses be considered. The interview must be conducted in a respectful climate that ensures confidentiality. Patients may not only experience considerable guilt or shame for stealing, but also may be unrevealing because of the fear of legal repercussions. In the acute treatment phase, the aim is to decrease significantly or, ideally, eradicate episodes of stealing during a period of weeks to months. Concurrent conditions may compound the problem and require independently targeted treatment.

The acute treatment of kleptomania has not been, to date, systematically investigated. Recommendations are based on retrospective reviews, case reports, and small case series. Maintenance treatment for kleptomania has not been investigated either, and only anecdotal data exist for patients who have been followed up for significant periods after initial remission.

### Psychiatrist-Patient Relationship

As with any condition that may be associated with intense guilt or shame, kleptomania must be approached respectfully by the psychiatrist. Patients can be reassured and their negative feelings alleviated to some degree with proper initial psychoeducation. The treatment alliance can be strengthened by consistently maintaining a nonjudgmental and supportive stance. In addition, patients' fears regarding breaks of confidentiality and criminal repercussions must be addressed.

No treatments have been systematically shown to be effective for kleptomania. These treatment recommendations are supported by case reports and retrospective reviews

only. In general, it appears that thymoleptic medications and behavioral therapy may be the most efficacious treatments for the short term, while long-term psychodynamic psychotherapy may be indicated and have good results for selected patients.

## Somatic Treatments

No medication is currently approved by the US Food and Drug Administration for treating kleptomania. So, it is important to inform patients of "off-label" uses of medications for this disorder and the empirical basis for considering medication treatment.

Various medications—tricyclic antidepressants, SSRIs (Lepkifker et al. 1999), mood stabilizers, and opioid antagonists—have been examined for the treatment of kleptomania (Grant and Kim 2002c, McElroy et al. 1989) with mixed results. In a literature review of 56 kleptomania cases, McElroy et al. (1991a) noted that somatic treatments were described for 8 patients. Significant improvement was reported for seven of these. Treatment included antidepressants alone, antidepressants with antipsychotics or stimulants, electroconvulsive therapy alone, or electroconvulsive therapy with antidepressants. The medications most commonly used to treat kleptomania are the antidepressants. In a series of 20 patients fulfilling DSM-III-R criteria for kleptomania, McElroy et al. (1991b) found that 18 had received antidepressants and of those patients 10 had partial or complete remission of both kleptomanic urges and behavior. It has been suspected that kleptomania may respond selectively to SSRIs because of the anticompulsive and anti-impulsive properties of these compounds. Of these 18 patients, 10 were administered fluoxetine alone and only 2 had a full response and 1 had a partial response. These data are not suggestive of a high response rate to SSRIs, but dose and duration of treatment were not explicitly stated. In a report on three patients with concurrent DSM-III-R kleptomania and bulimia nervosa treated with serotonergic antidepressants, two received high-dose fluoxetine and one trazodone; all three showed significant improvement in kleptomania, independent of the course of bulimia nervosa and depression (McElroy et al. 1989). It is still unclear whether kleptomania responds preferentially to serotonergic antidepressants, and this question awaits further study. Other agents reported to have treated kleptomania successfully include nortriptyline (McElroy et al.1991b) and amitriptyline (Fishbain 1987). So, although little is known about maintenance pharmacological treatment for kleptomania, the literature suggests that symptoms tend to recur with cessation of thymoleptic treatment and again remit when treatment is reinstituted (McElroy et al.1991a, Fishbain 1987). But it remains unclear if the antikleptomanic effect of thymoleptics is dependent on or independent of their antidepressant effect.

A number of other medications have been employed to treat kleptomania. These include antipsychotics (McElroy et al.1991b, Fishbain 1987), stimulants (McElroy et al. 1991b), valproic acid (McElroy et al. 1991a), carbamazepine (McElroy et al. 1991a), clonazepam (McElroy et al. 1991a) and lithium (McElroy et al. 1991a, Monopolis and Lion 1983). Lithium augmentation may be of benefit when kleptomania does not respond to an antidepressant alone (Burstein 1992). Other agents used successfully as monotherapy for kleptomania include fluvoxamine (Chong and Low 1996) and paroxetine (Kraus 1999). Combinations of medications have also been effective in case reports: lithium plus fluoxetine (Burstein 1992), fluvoxamine plus buspirone (Durst et al. 1997), fluoxetine plus lithium, fluoxetine plus imipramine (McElroy et al. 1991b), and fluvoxamine plus valproate (Kmetz et al. 1997). Finally, there have been some reports of successful treatment of kleptomania with electroconvulsive therapy, which may have been administered for a concurrent mood disorder (McElroy et al. 1991b).

The findings from case reports have not been consistent. Seven cases of fluoxetine, three of imipramine, two of lithium as monotherapy, two of lithium augmentation, four of tranylcypromine, and one of carbamazepine combined with clomipramine all failed to reduce kleptomania symptoms (McElroy et al. 1991b). Some evidence suggests that SSRIs may even induce kleptomania symptoms (Kindler et al. 1997). A case series found that kleptomania symptoms respond to topiramate (Dannon 2003). In another case series, the two subjects treated with naltrexone responded (Dannon et al. 1999).

In the only open-label trial for kleptomania, naltrexone resulted in a significant decline in the intensity of urges to steal, stealing thoughts, and stealing behavior (Grant and Kim 2002c) (mean effective dosage 145 mg/day). A lower dosage, possibly 50 mg/day, may be effective in younger people with kleptomania (Grant and Kim 2002a). Opioid antagonists like naltrexone may be effective in reducing both the urges to shoplift and shoplifting behavior, by reducing the "thrill" associated with shoplifting and thus preventing the positive reinforcement of the behavior. Antidepressants, particularly those that influence serotonergic systems (e.g., SSRIs), may also be effective in reducing the symptoms of kleptomania, by targeting serotonergic systems implicated in impaired impulse regulation. If kleptomania represents both impaired urge regulation and inhibition of behavior, both opioid antagonists and antidepressants may play a role in controlling this behavior.

## Psychosocial Treatments

Formal studies of psychosocial interventions for kleptomania have not been performed. However, a number of clinical reports have supported behavioral therapy for kleptomania. Different behavioral techniques have been employed with some success, including aversive conditioning, systematic desensitization, covert sensitization, and behavior modification. In their review of 56 cases of kleptomania, McElroy et al. (1991a) noted that the 8 patients who were treated with behavioral therapy—mostly aversive conditioning—showed significant improvement. We give here some specific examples of behavioral techniques that have been successfully employed and described. One patient was taught to hold her breath as a negative reinforcer whenever she experienced an impulse to steal (Keutzer 1972). Another patient was taught to use systematic desensitization techniques to control the mounting anxiety associated with the impulse to steal (Marzagao 1972). A patient treated by covert sensitization learned to associate images of nausea and vomiting with the desire to steal (Glover 1985). A woman who experienced sexual excitement associated with shoplifting and would masturbate at the site of the act was instructed to practice masturbation at home, while fantasizing kleptomanic acts (Fishbain 1987). The literature suggests that these techniques

remain effective over the long term (Gauthier and Pellerin 1982, Glover 1985). In imaginal desensitization the patient imagines the steps of stealing and her ability to not steal in that context, while maintaining a relaxed state. Undergoing fourteen 15-minute sessions over 5 days, two patients reported complete remission of symptoms for a 2-year period (McConaghy and Blaszczynski 1988). Learning to substitute alternative sources of satisfaction and excitement when urges to steal occur has been successful in a woman treated weekly for 5 months, who reported 2 years of remitted symptoms (Gudjonsson 1987).

It appears that the most effective behavioral treatment of all may be complete abstinence, that is, the patient should no longer visit any of the stores or settings where kleptomanic acts occur. A number of patients who never come to psychiatric attention apparently employ this technique successfully, and it may be an appropriate treatment goal if it does not result in excessive restrictions of activity and lifestyle.

The clinical literature suggests that for most patients, behavioral therapy may be a more efficacious approach than insight-oriented psychotherapy. Insight-oriented psychotherapy, however, has been unsuccessful in treating this disorder in 11 published cases (McElroy et al. 1991b). Psychoanalysis has resulted in some limited success for kleptomania symptoms, but usually with the addition of medication (Fishbain 1988, Schwartz 1992). The psychodynamic treatment of kleptomania centers on the exploration and working through of the underlying conflict or conflicts. In a review of 26 case reports, McElroy et al. (1991a) reported that 4 of 5 patients had a good response to psychoanalysis or related therapy. However, in another review of 20 cases (meeting DSM-III-R criteria) McElroy et al. (1991b) reported that of 11 patients treated with psychotherapy, none showed improvement. There are case reports in the literature of successful psychodynamic treatment of kleptomania (Schwartz 1992). Such treatment, possibly in combination with other approaches, may be indicated for patients for whom a clear conflictual basis for the behavior can be formulated, who also have the needed insight and motivation to undertake this type of treatment. In proposing such treatments, which may be long term, the psychiatrist should consider whether there are immediate risks that must be addressed, such as a high risk of legal consequences.

As few empirical studies are available, research is needed to guide the selection of which psychotherapy to use, and to investigate of the combination of medication and psychotherapy in treating kleptomania.

### Special Treatment Considerations

Little is known about treating kleptomania and therefore special treatment considerations have not been elucidated. However, it is clear that comorbid conditions, like depression, bulimia nervosa, OCD, or substance abuse, must be addressed along with the kleptomania. In addition to the inherent suffering and morbidity of these other disorders, their course and severity could compound the kleptomanic behavior. In the rare cases of a precipitating or exacerbating organic etiology, the underlying organic cause must be treated. In addition, the treatment of particular groups such as children or the elderly should take into account special contributing life stage or situational factors. The involvement of family or others on whom the patient is dependent may be indicated.

### Refractoriness to Initial Treatment

There has not been sufficient study of the treatment of kleptomania to systematically delineate approaches to the refractory patient. However, general clinical principles can be applied. Medication trials should be maximized, predominantly employing antidepressants and mood stabilizers, alone or in combination. In addition, it is important that comorbid conditions such as depression or OCD be monitored and treated, because they complicate the course of kleptomania. For patients who have no response or a partial response to pharmacotherapy alone or who do not want medication treatment, behavioral therapy is indicated. Behavioral therapy can be used alone or in combination with medication. There are no systematic comparisons of medication, behavioral therapy, or combined treatments. Therefore, the initial treatment choice is based in the assessment of the particular circumstances of each presentation. The patient's past treatment history, comorbid diagnoses, and personal resources should be weighed in choosing a course of treatment. Finally, there may be refractory patients for whom a multiple combination approach is helpful. Fishbain (1987) described the treatment of a middle-aged woman with a long history of kleptomania, depression, and suicidality and extensive past psychiatric treatments who responded to a combination of supportive and insight-oriented therapy, medication, and behavior modification.

## Pyromania and Fire Setting Behavior

## Diagnosis

### Definition and Diagnostic Features

The primary characteristics of pyromania are recurrent, deliberate fire setting, the experience of tension or affective arousal before the fire setting, an attraction or fascination with fire and its contexts, and a feeling of gratification or relief associated with the fire setting or its aftermath. True pyromania is present in only a small subset of fire setters. Prins et al. (1985) have suggested the following motivations for intentional arson: financial reward, to conceal another crime, for political purposes, as a means of revenge, as a symptom of other (nonpyromania) psychiatric conditions (e.g., in response to a delusional belief), as attention-seeking behavior, as a means of deriving sexual satisfaction, and as an act of curiosity when committed by children. Revenge and anger appear to be the most common motivations for fire setting (O'Sullivan and Kelleher 1987). Fire setting may also be associated with other psychiatric diagnoses (see differential diagnosis section). Fire-setting behavior may be a focus of clinical attention, even when criteria for pyromania are not present. Because the large majority of fire-setting events are not associated with true pyromania (which is rare), this section also addresses fire-setting behavior in general. Recent diagnostic classifications include pyromania among the ICDs and fire setting is thought to result from a failure to resist an impulse. Although pyromaniacs may methodically prepare the fire and leave obvious clues of this preparation behind (Wise and Tierney 1999), pyromania is still considered an uncontrolled and often impulsive behavior.

The diagnosis of pyromania emphasizes the affective arousal, thrill, or tension preceding the act, as well as the feeling of tension relief or pleasure in witnessing the

**DSM-IV-TR Criteria**

**Pyromania**

A. Deliberate and purposeful fire-setting on more than one occasion.

B. Tension or affective arousal before the act.

C. Fascination with, interest in, curiosity about, or attraction to fire and its situational contexts (e.g., paraphernalia, uses, consequences).

D. Pleasure, gratification, or relief when setting fires, or when witnessing or participating in their aftermath.

E. The fire-setting is not done for monetary gain, as an expression of sociopathical ideology, to conceal criminal activity, to express anger or vengeance, to improve one's living circumstances, in response to a delusion or hallucination, or as a result of impaired judgment (e.g., in dementia, mental retardation, substance intoxication).

F. The fire-setting is not better accounted for by conduct disorder, a manic episode, or antisocial personality disorder

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outcome. This is useful in distinguishing between pyromania and fire-setting elicited by other motives (i.e., financial gain, concealment of other crimes, political, arson related to other mental illness, revenge, attention seeking, erotic pleasure, a component of conduct disorder). In children and adolescents, the most common elements are excitation caused by fires, enjoyment produced by fires, relief of frustration by fire setting, and expression of anger through fire setting (Brandford and Dimock 1986). The most frequent motives for arson by juveniles (RŠsŠnen et al. 1995) are revenge on parents or other authorities, the search for heroism or excitement, self-destructiveness, the craving for sensation, and an expression of outrage. There is also a lot of self-destructive behavior by juveniles before committing arson; 74% have suicidal thoughts and 44% have tried to commit suicide before committing their crimes. Females with pyromania frequently have a history of self-harm, sexual abuse, and psychosocial traumas (Noblett and Nelson 2001). Thus, pyromania could be a displacement of aggression in people with a history of sexual trauma. The channeling of aggression by their fire setting may be an attempt to influence their environment and improve their self-esteem where other means have failed. Fire setting may also be an attempt at communication by individuals with few social skills (Geller and Bertsch 1985).

Pyromania onset has been reported to occur as early as age of 3 years, but it may initially present in adulthood. Because of the legal implications of fire setting, individuals may not admit previous events, which may result in biased perceptions of the common age at onset. Men greatly outnumber women with the disorder. Further, nongeriatric state hospital inpatients who had engaged in fire-setting behavior were significantly more likely to have a history of nonlethal self-injurious behavior and had a significantly greater number of admissions to the state hospital (Geller and Bertsch 1985).

## Assessment

### The Psychiatric Interview

The interviewer must bear in mind that the circumstances of arson, whatever the motive, may pose legal and criminal problems for the individual. This may provide motivation to skew the reporting of events. Individuals who may be at risk for the legal consequences of fire setting may be motivated to represent themselves as victims of psychiatric illness, hoping that a presumed psychiatric basis of the behavior may attenuate legal penalties. Thus, the interviewer must maintain a guarded view of the information presented.

## Epidemiology

Most epidemiological studies have not directly focused on pyromania but instead on various populations of arsonists or fire setters. Most studies suggest that true pyromania is rare and reveal a preponderance of males with a history of fire fascination (Barker 1994). According to DSM-IV-TR, pyromania occurs more often in males, especially those with poorer social skills and learning difficulties. This notation confirms the Lewis and Yarnell (1951) data that only 14.8% of those with pyromania are female. Fire setting for profit or revenge or secondary to delusions or hallucinations is more frequent than "authentic" ICD. Although pyromania is a rare event, fire-setting behavior is common in the histories of psychiatric patients. Geller and Bertsch (1985) found that 50 (26%) of 191 nongeriatric state hospital patients had histories of some form of fire-setting behavior. Unlike pyromania, which is rare among women, fire-setting behavior was common in the histories of female patients (22%), as well as male patients (28.8%).

"True" pyromania in childhood is rare, but fire setting is frequent in children and in adolescents. Juvenile fire setting is most often associated with conduct disorder, ADHD, or adjustment disorder. Among children with psychiatric conditions, fire-setting behavior is quite common. Kolko and Kazdin (1988) found that among a sample of children attending an outpatient psychiatry clinic, approximately 20% had histories of fire setting. For a sample of inpatient children, the rate was approximately 35% (Kolko and Kazdin 1988).

The classic study *Pathological Fire-Setting (Pyromania)* by Lewis and Yarnell (1951) is one of the largest epidemiological studies of this topic and includes approximately 2000 records from the National Board of Fire Underwriters and cases provided from fire departments, psychiatric clinics and institutions, and police departments near New York City. Thirty-nine percent of the fire setters from the study received the diagnosis of pyromania. Twenty-two percent had borderline to dull normal intelligence, and 13% had between dull and low average intelligence. Fire setters were also described as driven by an irresistible impulse to set fires. The peak incidence of fire setting was between the ages of 16 and 18 years although. This observation has not been confirmed by more recent studies. The reported high prevalence rates of pyromania have not been confirmed by more recent studies. Koson and Dvoskin (1982) found no cases of pyromania in a population of 26 arsonists. Ritchie and Huff (1999) identified only 3 cases of pyromania in 283 cases of arson.

## Comorbidity Patterns

Limited data are available regarding individuals with pyromania. Reported data of comorbid diagnoses are generally derived from forensic samples and do not distinguish between criminally motivated fire setters and compulsive fire setters. Fire-setting behavior may be associated with other mental conditions like mental retardation, conduct disorder, alcohol and other substance use disorders, personality disorders, and schizophrenia. In most cases, fire-setting behavior is not directly related to pyromania. On the other hand, fire setting in subjects who do not have pyromania appears frequent and often underrecognized. Among psychiatric patients, Geller and Bertsch (1985) found that 26% of the patients had a history of fire-setting behavior, and 16% of these patients had actually set fires. Ritchie and Huff (1999) reviewed mental health records and prison files from 283 arsonists, 90% of whom had a recorded history of mental health problems. Thirty-six percent had schizophrenia or bipolar disorder, and 64% were misusing alcohol or drugs at the time of their fire setting.

Repo et al. (1997) examined the medical and criminal records of 282 arsonists in order to compare first time and repeat offenders. They found that alcohol dependence and ASPD were common among recidivist offenders, especially among those who committed violent crimes. Recidivist offenders commonly had a history of enuresis during their childhood, were younger than first time offenders at the time of their first offence, and were more often intoxicated with alcohol during the arson attempt. Psychosis was common among those with no record of recidivist criminal offences. Puri et al. (1995) examined a group of 36 forensically referred fire setters. They found that about one-third had no other evidence of mental illness, about a quarter were female, psychoactive substance abuse was common and interpersonal relationships were often disturbed. Lejoyeux et al. (2002) assessed ICDs, using the Minnesota Impulsive Disorders Interview, in 107 depressed inpatients who met DSM-IV-TR criteria for major depressive episodes. Thirty-one depressed patients met criteria for ICDs: 18 had IED, 3 had pathological gambling, 4 had kleptomania, 3 had pyromania, and 3 had trichotillomania. Patients with pyromania had a higher number of previous depressions (3.3 versus 1.3, $P = 0.01$). Bipolar disorders were more frequent in the ICD group than in the group without ICDs (19% versus 1.3%, $P = 0.002$).

Laubichler et al. (1996) compared the files of 103 criminal fire setters and subjects with pyromania. Subjects with pyromania were younger (average age 20 years) than criminal fire setters (average age 30 years). Seventy of the 103 subjects had consumed alcohol before setting a fire. Fifty-four presented with alcohol dependence. The authors suggested a correlation between the amount of alcohol consumed and the frequency of fire setting. RŠsŠnen et al. (1995) found that young arsonists have frequent alcohol problems: 82% had alcoholism and 82% were intoxicated at the time of committing the crime. The excessive consumption of alcohol had a close connection with the arson committed. Lejoyeux et al. (1999) searched for ICDs among consecutive admissions for detoxification of alcohol-dependent patients in a French department of psychiatry. They found 30 alcohol-dependent persons presenting with at least one ICD (19 with IED, 7 with pathological gambling, 3 with kleptomania, and 1 case of trichotillomania), but none of the patients presented with two or more ICDs, and no patient presented with pyromania. However, it cannot be concluded from such a limited population that pyromania is not associated with alcohol dependence. Further studies are needed.

## Course

According to the DSM-TR, there are insufficient data to establish a typical age at onset of pyromania and to predict the longitudinal course. However, the impulsive nature of the disorder suggests a repetitive pattern. Again, because legal consequences may occur, the individual may be motivated to represent the index episode as a unique event. Fire setting for nonpsychiatric reasons may be more likely to be a single event. In individuals with pyromania, fire-setting incidents are episodic and may wax and wane in frequency. Studies indicate that the recidivism rate for fire setters ranges from 4.5% (Mavromatis and Lion 1977) to 28% (Lewis and Yarnell 1951). In a cross-sectional and 10-year follow-up study Barnett et al. (1997, 1999) compared mentally ill and mentally "healthy" fire setters from trial records in Germany where a defendant with a psychiatric disorder can be found to be not responsible, to have diminished responsibility, or to be fully responsible. Mentally disordered arsonists were more likely than those with no disorder to have a history of arson before their trial, were more often convicted of arson again (11% relapse compared with 4%), had fewer registrations of common offenses like theft, traffic violations, and alcohol-related offenses, had a higher rate of recurrence, and committed fewer common offenses other than fire setting. Among all arsonists who committed crimes in addition to arson, those who were found to be partly responsible for their arson committed the highest number of offenses followed by those who were deemed not responsible for their actions and those who were fully responsible.

## Differential Diagnosis

Other causes of fire setting must be ruled out. Fire-setting behavior may be motivated by circumstances unrelated to mental disorders. Such motivations include profit, crime concealment, revenge, vandalism, and political statement or action (Geller 1987, Lowenstein 1989). Furthermore, fire setting may be a part of ritual, cultural, or religious practices in some cultures.

Fire setting may occur in the presence of other mental disorders. A diagnosis of fire setting is not made when the behavior occurs as a part of conduct disorder, ASPD, or a manic episode or if it occurs in response to a delusion or hallucination. The diagnosis is also not given if the individual suffers from impaired judgment associated with mental retardation, dementia, or substance intoxication.

## Etiology and Pathophysiology

Because pyromania is rare, there is little reliable scientific literature available regarding individuals who fit diagnostic criteria. But because of the morbid impact that arson has on society, fire-setting behavior (which often does not fulfill criteria for pyromania) has been the focus of scientific investigation and literature.

Arson has been the subject of several investigations of altered neuroamine function. These findings include the observation that platelet monoamine oxidase is negatively correlated with fire-setting behavior of adults who

had been diagnosed with attention-deficit disorder in childhood (Kuperman et al. 1988). Investigation of the function of serotonergic neurotransmission in individuals with aggressive and violent behaviors has included studies of CSF concentrations of 5-HIAA in individuals with a history of fire setting. 5-HIAA is the primary metabolite of serotonin, and its concentration in the CSF is a valid marker of serotonin function in the brain. Virkkunen et al. (1987, 1994) demonstrated that impulsive fire setting was associated with low CSF concentrations of 5-HIAA. This finding was consistent with other observations associating impulsive behaviors with low CSF 5-HIAA levels (like impulsive violence and impulsive suicidal behavior). A history of suicide attempt strongly predicts recidivism of arson (DeJong et al. 1992).

Impulse fire setters who are violent offenders are often dependent on alcohol and have an alcohol-dependent father (Linnoila et al. 1989). Virkkunen et al. (1996) investigated biochemical and family variables and predictors of recidivism among forensic psychiatric patients who had set fires. Male alcoholic patients and fire setters ($N = 114$) were followed for an average of 4.5 years after their release from prison. Low CSF 5-HIAA and homovanillic acid concentrations were associated with a family history of paternal alcoholism with violence. A low plasma cholesterol concentration was associated with a family history positive for paternal alcoholism without violence. Compared with nonrecidivists, the recidivists, who set fires during the follow-up period, had low CSF 5-HIAA and MHPG (a metabolite of norepinephrine) concentrations and early family environments characterized by paternal absence and the presence of brothers at home.

Psychodynamic models refer to the symbolism of fire which is complemented by "normal" human interest in fire. Fire interest starts between the ages of 2 and 3 years and was almost universal in a study of normal schoolboys at the ages of 6, 8, and 10 years (Kafry, 1980). The distinction between normal interest in fire and excessive interest leading to pyromania is not always clear among children. Playing with matches is not a symptom of pyromania. Kolko and Kazdin (1989) showed that "future" pyromaniacs had more curiosity about fire and liked to be exposured to people (parents/peers) who are involved with fire. According to Geller and Bertsch (1985), children at risk of pyromania were more often involved in fire setting, threatening to set a fire, sounding a false fire alarm, or calling the fire department with a false report of fire than were control subjects. Thus, there may be a continuum between excessive interest in fire and "pure" pyromania.

Since the first description of pyromania in 1833 by the French psychiatrist Marc, the symbolic sexual dimension of pyromania has been noted. Many pyromaniacs were later described as having fire fetishes. A "fire experience" may become a "fire fetish" via conditioning with positive feedback by for example imagining/recalling a fire fantasy just before orgasm (McGuire et al. 1965). Lewis and Yarnell (1951) suggest three main groups of fire setters: the accidental, the occasional, and the habitual.

## Treatment

### Treatment Goals

Because of the danger inherent in fire-setting behavior, the primary goal is elimination of the behavior. The treatment literature does not distinguish between pyromania and fire-setting behavior of other causes. Much of the literature is focused on controlling fire-setting behavior in children and adolescents.

### Psychiatrist-Patient Relationship

Because of the potential legal risks for people who acknowledge fire-setting behavior, the psychiatrist must take particular pains to ensure an environment of empathy and confidentiality. A corollary concern involves obligations that may be incumbent on the psychiatrist. Because of the legal implications of these behaviors and the potential for harm to another individual should fire setting recur, psychiatrists should consider both the ethical and the legal constraints that may follow from information learned in the course of treatment.

### Somatic Treatments

There are no reports of pharmacological treatment of pyromania. Because fire setting may be frequently embedded in other psychiatric illness, therapeutic attention may be directed primarily to the underlying disorder. However, the dangerous nature of fire setting requires that the behavior be controlled. Much in the same fashion that one would seek to educate impaired patients about the functional risks associated with their symptoms—and to establish boundaries of acceptable behavior—the fire-setting behavior must be directly addressed, even if it is not a core symptom of the associated disorder.

### Psychosocial Treatments

Treatment for fire setters is problematic because they frequently refuse to take responsibility for their acts, are in denial, have alcoholism, and lack insight (Mavromatis and Lion 1977). It has been estimated that up to 60% of childhood fire setting is motivated by curiosity. Such behavior often responds to direct educational efforts. In children and adolescents, focus on interpersonal problems in the family and clarification of events preceding the behavior may help to control the behavior (Lowenstein 1989). Principles of CBT have been also applied to childhood fire setting (Kolko 2001).

Treatments for fire setting are largely behavioral or focused on intervening in family or intrapersonal stresses that may precipitate episodes of fire setting. Behavioral treatments like aversive therapy have helped fire setters (McGrath and Marshall 1979, Koles and Jenson, 1985). Other treatment methods rely on positive reinforcement with threats of punishment an dstimulus satiation (Bumpass et al. 1983). Bumpass et al. (1983) treated 29 child fire setters and used a graphing technique that correlated external stress, behavior, and feelings on graph paper. After treatment (average follow-up, 2.5 years), only 2 of the 29 children continued to set fires. Relaxation training may also be used (or added to graphing techniques) to assist in the development of alternative modes of dealing with the stress that may precede fire setting. Another technique combines overcorrection, satiation, and negative practice with corrective consequences. The child is supervised in constructing a controlled, small fire in a safe location, which is then extinguished by the child. Throughout the process, the parent verbally instructs the child in safety techniques. Franklin et al. (2002b) confirmed the positive effect of a prevention program for pyromania. In

Clinical Vignette 2

A 34-year-old man came to a medical emergency department for the treatment of third-degree burns on his hands and face. He claimed to have been accidentally caught in a fire at a warehouse. Because of the patient's severe agitation and inability to explain the circumstances of the injury coherently, the treating surgeon asked that the patient be seen by a psychiatrist.

On meeting the psychiatrist the patient became even more severely agitated. He began to complain of the pain caused by his burns and was reluctant to speak with the psychiatrist. The patient insisted that he was in substantial pain and that he had no need to speak with "some shrink." Because the patient was going to be admitted for medical monitoring, the psychiatrist withdrew, planning to visit the patient again the next day in his hospital room. The next day the young man was more amenable to an interview. At this time he seemed sad and, although anxious, less visibly agitated than he was on the preceding day. He no longer questioned the psychiatrist's purpose in visiting him and participated in a brief discussion about his burns, the pain they caused, and the misfortune he suffered, having been caught in a fire. The psychiatrist again decided to withdraw after this brief conversation. Despite the passive cooperation the patient offered, the psychiatrist was still impressed with how guarded he seemed about the question of the events that led up to the fire. The psychiatrist concluded that the patient seemed to want to avoid discussing the details and decided that several visits might be necessary to engage the patient sufficiently to obtain an adequate history.

On the following day the patient seemed relieved when the psychiatrist entered the room. He said that he had something to tell the psychiatrist. He then proceeded to describe a history of fascination with fire since the age of 16 years. He had set a couple of small fires in wastebaskets at that age and found himself drawn to trade magazines that specialized in fire control equipment. He would often walk by the local firehouse and tried to follow the fire crews when they responded to a fire alarm. For a number of years he was aware of a growing urge to set fires. He worried about this compulsion and managed to avoid acting on it.

In the past 3 years his forbearance began to erode. In that period he had set several fires in isolated parts of the city. He was careful to do so in areas where he knew few people might be caught in the fire. He tried to arrange circumstances in which the fire would be quickly discovered. Indeed, he reported one of the fires himself—both because he was fearful of the harm that might occur and because he had a great urge to see the firefighters arrive and battle the flames. In a recent fire a firefighter had been mildly injured. At that point he realized the dangers of his compulsion. Several days ago he went out to set another fire. He did not realize how quickly the fire would progress and he was injured. After telling the psychiatrist this story he expressed great relief that he finally had shared his shame with someone. He also expressed the hope that it would be understood that he suffered from a compulsion and asked the psychiatrist if there might be some way to reduce or erase the need to set fires. He realized he faced criminal prosecution but felt relieved that his behavior had been interrupted before another person was seriously hurt. Eventually this patient committed to treatment and his pyromanic behavior remitted with a combination of cognitive–behavior therapy and medication treatment.

1999, they developed the Trauma Burn Outreach Prevention Program. All subjects arrested and convicted after setting a fire received 1 day of information. The program's interactive content focused on the medical, financial, legal, and societal impact of fire-setting behavior. The rate of recidivism was less than 1% in the group who attended the program, versus 36% in the control group.

## Pathological Gambling

### Diagnosis

#### Definition and Diagnostic Features

Pathological gambling has been considered a distinct diagnostic entity since 1980, when it was first included

DSM-IV-TR Criteria

**Pathological Gambling**

A. Persistent and recurrent maladaptive gambling behavior as indicated by five (or more) of the following
   1. is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)
   2. needs to gamble with increasing amounts of money in order to achieve the desired excitement
   3. has repeated unsuccessful efforts to control, cut back, or stop gambling
   4. is restless or irritable when attempting to cut down or stop gambling
   5. gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)
   6. after losing money gambling, often returns another day to get even ("chasing" one's losses)
   7. lies to family members, therapist, or others to conceal the extent of involvement with gambling
   8. has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling
   9. has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling
   10. relies on others to provide money to relieve a desperate financial situation caused by gambling

B. The gambling behavior is not better accounted for by a manic episode.

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in DSM-III (American Psychiatric Association 1980). DSM-IV-TR (American Psychiatric Association 2000) currently classifies pathological gambling as an ICD not elsewhere classified. Gambling as a behavior is common. Current estimates suggest that approximately 80% of the adult population in the US gamble. The amount of money wagered legally in the US grew from $17 to $210 billion in from 1974 to 1988, an increase of more than 1200%, making gambling the fastest growing industry in America at the time (Lesieur and Rosenthal 1991). DSM-IV-TR, like DSM-III-R before it, covertly recognized the ubiquity of gambling behavior and the desire to gamble by the careful wording of criterion A for pathological gambling: "Persistent and recurrent maladaptive gambling behavior as indicated by five (or more) of the following." This definition of pathological gambling differs from some other definitions of ICDs not elsewhere classified, which are worded as "Failure to resist an impulse to." This difference implies that neither gambling behavior nor failure to resist an impulse to engage in it is viewed as pathological in and of itself. Rather, the maladaptive nature of the gambling behavior is the essential feature of pathological gambling and defines it as a disorder.

## Assessment

The most established measure for pathological gambling is the South Oaks Gambling Screen (SOGS) (Lesieur and Blume 1987, 1993). It is a 20-item questionnaire, which assesses recurrent and maladaptive gambling behavior that disrupts personal, family, and vocational pursuits. However, the SOGS has some limitations in that it does not correspond exactly with the DSM-IV diagnosis of pathological gambling or take into account frequency of gambling behaviors. While the SOGS is a self-report screening measure for PG, the Pathological Gambling Modification of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS) (DeCaria et al. 1998b) is a clinician-rated outcome measure of PG. The PG-YBOCS consists of 10 questions that measure the severity and change in severity of pathological gambling symptoms over a recent time interval (usually within the past 1/2 week(s)). The first five questions assess urges and thoughts associated with pathological gambling, while the last five questions assess the behavioral component of the disorder. Although the PG-YBOCS is a relatively new measure of PG, it is one of the most widely used clinician-rated measures of PG. In addition to the SOGS and PG-YBOCS, the Gambling Symptom Assessment Scale (Kim et al. 2001) is a 12-item self-rated outcome measure designed to assess gambling symptom severity and change of gambling symptoms during treatment. It is an alternative pathological gambling measure that can be used in clinical studies.

It is not difficult to diagnose pathological gambling once one has the facts. It is much more of a challenge to elicit the facts, because the vast majority of patients with pathological gambling view their gambling behavior and gambling impulses as ego-syntonic and may often lie about the extent of their gambling (criterion A7). Patients with pathological gambling may first seek medical or psychological attention because of comorbid disorders. Given the high prevalence of addictive disorders in pathological gambling and the increased prevalence of pathological gambling in those with alcoholism and other substance abuse, an investigation of gambling patterns and their consequences is warranted for any patient who presents with a substance abuse problem. Likewise, the high rates of comorbidity with mood disorders suggest the utility of investigating gambling patterns of patients presenting with an affective episode.

The spouses and significant others of patients with pathological gambling deserve special attention. Individuals with pathological gambling usually feel entitled to their behavior and often rely on their families to bail them out (criterion A10). As a consequence, it is often the spouse of the patient with pathological gambling who first realizes the need for treatment and who bears the consequences of the disorder. Lorenz (1981) conducted a survey of 103 wives of pathological gamblers who attended Gam-Anon meetings (for family members of patients with pathological gambling). She found that most spouses had to borrow money and were harassed or threatened by bill collectors. Most spouses physically assaulted the gambler, verbally abused their children, and experienced murderous or destructive impulses toward the gambler. Although the gamblers themselves appeared less violent than the general population norms, their spouses were more violent, possibly because of desperation and anger. Eleven percent of the spouses of patients with pathological gambling admitted to having attempted suicide, and this result was replicated in a later study. These findings have two main implications for the assessment of pathological gambling: first, the spouse may be a valuable and motivated informant who should be questioned about the patient's behavior, and second, spouses should be specifically asked about the effects of the patient's illness on their own well-being and functioning and about suicidal ideation and attempts and the control of their own impulsivity.

## Epidemiology

Pathological gambling is considered to be the most common of the ICDs not elsewhere classified. The number of people whose gambling behavior meets criteria for pathological gambling in the US is estimated to be between 2 and 6 million (Volberg and Steadman 1988) . Surveys conducted between 1986 and 1990 in Maryland, Massachusetts, New York, New Jersey, and California estimated the prevalence of "probable pathological gamblers" among the adult population to be between 1.2% and 2.3%. These states have a broad range of legal wagering opportunities and a heterogeneous population. Similar surveys in Minnesota and Iowa, states with limited legal wagering opportunities and more homogeneous populations, yielded prevalence rates of 0.9% and 0.1%, respectively (Rosenthal 1992). Thus, availability of gambling opportunities and demographic makeup may influence the prevalence of pathological gambling. A 1998 study of national prevalence, using DSM-IV-TR criteria, determined that the prevalence of pathological gambling was 1.2% (1.7% for men and 0.8% for women). In addition to those who fulfilled DSM-IV-TR criteria, the researchers classified an additional 1.5% as "problem gamblers." The combined total of "pathological gamblers" and "problem gamblers" is 5.5 million adult Americans (Gerstein et al. 1999). During the past 20 years, many states have turned to lotteries as a way of increasing their revenues without increasing taxes. Currently, some form of gambling is legal in 47 of the 50 states,

as well as in more than 90 countries worldwide. From 1975 to 1999 revenues from legal gambling in the US has risen from $3 to 58 billion (Volberg 2002) thus the prevalence and incidence of pathological gambling are expected to increase. A meta-analysis of 120 published studies indicated that the lifetime prevalence of serious gambling (meeting DSM criteria for pathological gambling) among adults is 1.6% (Shaffer et al. 1999). Among those younger than 18 years, the prevalence is 3.9%, with past-year rates for adults and adolescents being 1.1% and 5.8%, respectively (Shaffer and Hall 1996). Although it is illegal for adolescents to gamble, this high rate may be due to illegal gambling of adolescents (e.g. via the internet or gambling with peers). Women make up about one-third of all Americans with pathological gambling. However, they are underrepresented in GA, in which only 2% to 4% of the members are women. This pattern is echoed in England and Australia, where women make up 7% and 10% of Gamblers Anonymous (GA) members, respectively. The reason for this discrepancy may be the greater social stigma attached to pathological gambling in women and their characteristic pattern of solitary gambling. Nonwhites and those with less than a high-school education are more highly represented among pathological gamblers than in the general population. The demographic makeup of patients in treatment for pathological gambling differs substantially from the demographics of all patients with pathological gambling. Jewish persons are overrepresented in treatment settings and in GA, while women, minorities, and those younger than the age of 30 years are underrepresented in GA and in treatment (Lesieur and Rosenthal 1991).

## Comorbidity Patterns

Overall, patients with pathological gambling have high rates of comorbidity with several other psychiatric disorders and conditions. Individuals presenting for clinical treatment of pathological gambling apparently have impressive rates of comorbidity. Ibanez et al. (2001) reported 62.3% of one group seeking treatment had a comorbid psychiatric disorder. The most frequent current comorbid disorders were personality disorders (42%), alcohol abuse or dependence (33.3%), adjustment disorders (17.4%), and mood disorders (8.7%) Lifetime comorbid diagnoses included alcohol abuse or dependence (34.8%), mood disorders (15.9%), and anxiety disorders (7.2%). The relatively low rate of comorbid mood disorders compared to the rates reported below may be due to the outpatient setting of this study.

### Mood Disorders

Pathological gambling is highly comorbid with affective disorders, among inpatient (McCormick et al. 1984) and outpatient samples (Linden et al. 1986). In several surveys, between 70% and 80% of all patients with pathological gambling also had mood symptoms that met criteria for a major depressive episode, a manic episode, or a hypomanic episode at some point in their life. More than 50% had recurrent major depressive episodes (Lesieur and Rosenthal 1991). A complicating factor is that recovering pathological gamblers may experience depressive episodes after cessation of gambling. In addition, some pathological gamblers may gamble to relieve feelings of depression (criterion A5). Despite criterion B for pathological gambling, which essentially precludes the diagnosis of pathological gambling if the behavior occurs exclusively during the course of a manic episode, many patients have a disturbance that meets criteria for both disorders because they gamble both during and between manic and hypomanic episodes. Between 32% and 46% of patients with pathological gambling were reported also to have mood symptoms that meet criteria for bipolar disorder, bipolar II disorder, or cyclothymic disorder (McElroy et al. 1992).

### Suicide

Although data are not yet conclusive, a meaningful association between problem gambling and suicidal behavior and/or ideation appears to exist. Phillips et al. (1997) conclude that "Las Vegas, the premier US gambling setting, displays the highest levels of suicide in the nation, both for residents of Las Vegas and for visitors to that setting. In general, visitors to and residents of major gaming communities experience significantly elevated suicide levels. In Atlantic City, abnormally high suicide levels for visitors and residents appeared only after gambling casinos were opened. The findings do not seem to result merely because gaming settings attract suicidal individuals." Others report that between 12% and 24% of pathological gamblers in various settings have had a history of at least one suicide attempt. In one study, 80% of pathological gamblers had a history of either suicide attempts or ideation (Lesieur and Rosenthal 1991).

### Substance Abuse and Dependence

There appears to be a strong relationship between pathological gambling and substance abuse as evidenced by the high rates of comorbid substance abuse and dependency with pathological gambling (Lesieur et al. 1986, McCormick et al. 1984, Linden et al. 1986, Lesieur 1988). Studies of prevalence of comorbid substance use disorders yield widely varying results; from 9.9% for alcohol and other substance dependence (Gerstein et al. 1999) to 44% for alcohol dependence and 40% for illicit drug dependence (Bland et al. 1993, Cunningham-Williams et al. 1998). Using a structured instrument, between 5% and 25% of substance-abusing patients in several settings were found to meet criteria for pathological gambling and an additional 10% to 15% were considered to have "gambling problems" (Lesieur and Rosenthal 1991). Among individuals with pathological gambling, individuals with higher socioeconomic status (SES) are more likely to have concurrent problems with alcohol abuse then are gamblers with lower SES (Welte et al. 2001). Failure to treat comorbid substance use disorders in gamblers may lead to higher relapse rates (Maccallum and Blaszczynski 2002).

### Other Disorders

Again, current data are inconclusive, but OCD, panic disorder, generalized anxiety disorder, and eating disorders have all been reported to be present in higher rates in patients with pathological gambling than in the general population. Pathological gambling has been described as being part of the obsessive-compulsive spectrum and sharing features with both OCD and impulsive cluster of obsessive-compulsive spectrum disorders (Dell'Osso et al. 2005, Bienvenu et al. 2000). The reported prevalence of OCD among pathological gamblers ranges from 0.9% (Cunningham-Williams et al. 1998) to 16% (Bland et al. 1993). Pathological gambling has

also been associated with ADHD (Carlton and Goldstein 1987). Retrospective studies suggest that many pathological gamblers have had symptoms that met criteria for ADHD as children (McElroy et al. 1992). Compulsive sexual behavior, compulsive buying disorder, and IED are relatively frequent in pathological gamblers, as are personality disorders. Murray (1993) found that pathological gamblers fit no particular personality profile, but several investigators have reported abnormal personality traits in pathological gamblers based on dimensional assessments (e.g., Roy et al. 1989). Taber et al. (1987) reported that 20% of 66 pathological gambling inpatients had personality disorders. Narcissistic and ASPD are believed to be overrepresented in these patients, and pathological narcissism is assumed by some psychoanalysts to underlie the entitlement displayed by many patients with pathological gambling. In addition to psychiatric disorders, patients with pathological gambling may manifest greater prevalence of stress-related medical conditions, like peptic ulcer disease, hypertension, and migraine.

## Course

The onset of pathological gambling is usually insidious, although some may be "hooked" by their first bet. There may be years of social gambling with minimal or no impairment followed by an abrupt onset of pathological gambling that may be precipitated by greater exposure to gambling or by a psychosocial stressor. The gambling pattern may be regular or episodic, and the course tends to be chronic. Over time, there is usually a progression in the frequency of gambling, the amounts wagered, and the preoccupation with gambling and with obtaining money with which to gamble. The urge to gamble and gambling activity generally increase during periods of stress or depression, as an attempted escape or relief (criterion A5).

Pathological gambling usually begins in adolescence in men (Hollander et al. 2000a) with gradual development of dependence, and may remain undiagnosed for years, they often present with a 20- to 30-year-gambling history. In contrast, onset in females is usually later in life. Prior to seeking treatment, the duration of pathological gambling is about 3 years. Thus, as a result of the differences in onset and duration, female pathological gamblers generally have a better prognosis than male pathological gamblers (Rosenthal 1992). Female pathological gamblers also tend to be depressed and may use gambling as an anesthetic, accompanied by excitement, to escape from life's problems (i.e., as in a dissociative state; Jacobs 1988).

Psychiatric disorders like major depression and alcohol or substance abuse and dependence, may develop from or be exacerbated by pathological gambling. There is also a mortality risk associated with the disorder. Estimates of suicide attempts in pathological gamblers range from 17% to 24% (Ciarrochi and Richardson 1989, 2000a). One study found that the suicide rate in cities where gambling is legalized is four times higher than in cities where it is not (Phillips et al. 1997). Younger patients are more likely to have suicidal tendencies and major depressive disorders (McCormick et al. 1984), and most pathological gambling begins during adolescence (Hollander et al. 2000a), thus early identification and intervention are crucial.

Rosenthal (1992) described four typical phases in the course of a typical male patient with pathological gambling: winning, losing, desperation, and hopelessness (Linnoila et al. 1989).

### Winning

Many male gamblers become involved with gambling because they are good at it and receive recognition for their early successes. Women with pathological gambling are less likely to have a winning phase. Traits that foster a winning phase and are typical of male patients with pathological gambling are competitiveness, high energy, ability with numbers, and interest in the strategy of games. The early winnings lead to a state in which a large proportion of the gambler's self-esteem derives from gambling, with accompanying fantasies of winning and spectacular success.

### Losing

A string of bad luck or a feeling that losing is intolerable may be the precipitant of chasing behavior; previous gambling strategies are abandoned as the gambler attempts to win back everything at once. The gambler experiences a state of urgency, and bets become more frequent and heavy. Debts accumulate, and only the most essential are paid. Covering up and lying about gambling become more frequent. As this is discovered, relationships with family members deteriorate. Losing gamblers use their own and their family's money, go through savings, take out loans, and finally exhaust all legitimate sources. Eventually, they cannot borrow any more, and faced with threats from creditors or loss of a job or marriage, they go to their family and finally confess. This results in the "bailout": debts are paid in return for a promise to stop or cut down gambling. Any remission, if achieved, is short lived. After the bailout there is an upsurge of omnipotence; the gambler believes it is possible to get away with anything, bets more heavily, and loses control altogether.

### Desperation

This stage is reached when the gambler begins to do things that would previously be inconceivable: writing bad checks, stealing from an employer, or other illegal activities. Done once, these behaviors are much more likely to be repeated. The behavior is rationalized as a short-term loan with an intention to pay it back as soon as the winning streak arrives. The gambler feels just one step away from winning and solving all the problems. Attention is increasingly taken up with illegal loans and various scams to make money. The gambler becomes irritable and quick tempered. When reminded of responsibilities or put in touch with guilt feelings, the gambler responds with anger and projective blame. Appetite and sleep deteriorate and life holds little pleasure. A common fantasy at this stage is of starting life over with a new name and identity, the ultimate "clean slate."

### Hopelessness

For some gamblers, there is a fourth stage in which they suddenly realize that they can never get even, but they no longer care. This is often a revelation, and the precise moment when it occurred is often remembered. From this point on, just playing is all that matters. Gamblers often acknowledge knowing in advance that they will lose and play sloppily so that they lose even if they have the right horse or a winning hand. They seek action or excitement for its own sake and gamble to the point of exhaustion.

Few gamblers seek help in the winning phase. Most do so only during the later phases and only after a friend, family member, or employer has intervened. Two-thirds of the gamblers have committed illegal activities by then, and the risk of suicide increases as they progress through the phases of the illness.

Without treatment, the prognosis of pathological gambling is poor. It tends to run a chronic course with increasing morbidity and comorbidity, gradual disruption of family and work roles and relationships, depletion of financial reserves, entanglement with criminals and the criminal justice system, and, often, suicide attempts. In the hands of an experienced psychiatrist, it is an "extremely treatable disorder" with a favorable prognosis (Rosenthal 1992). The difference between a poor and a good prognosis depends on treatment, and treatment depends on a diagnosis. As noted earlier, the diagnosis of pathological gambling is often missed in clinical settings because mental health professionals do not think to ask about it. Because most pathological gamblers do not see themselves as having a disorder and many of them do not even consider themselves as having a problem, collateral information from a family member may be very helpful.

## Differential Diagnosis

The differential diagnosis of pathological gambling is relatively straightforward (Table 80–2). Pathological gambling should be differentiated from professional gambling, social gambling, and a manic episode. Social gambling, engaged in by a majority of adult Americans, typically occurs with friends or colleagues, lasts for a specified time, and is limited by predetermined acceptable losses. Professional gambling is practiced by highly skilled and disciplined people and involves carefully limited risks. Many individuals with pathological gambling may feel that they are actually professional gamblers. Chasing behavior and unplanned losses distinguish pathological gamblers. Patients in a manic episode may exhibit a loss of judgment and excessive gambling resulting in financial disasters. A diagnosis of pathological gambling should be given only if a history of maladaptive gambling behavior exists at times other than during a manic episode. Problems with gambling may also occur in people with ASPD. If criteria are met for both disorders, both can be diagnosed.

## Differences in Gender and Cultural Presentations

An important and understudied area is the clinical presentation of pathological gambling in women. Women constitute a third of patients with pathological gambling in epidemiological studies. But, they are extremely underrepresented in treatment populations, and most psychoanalytic theories of pathological gambling ignore them completely. Part of this bias may be due to the fact that gambling carries a greater social stigma for women, women gamblers are more likely to live and to gamble alone, and treatment programs for pathological gambling in the US were first pioneered in Veterans Hospitals. Compared with men with pathological gambling, women with pathological gambling are more likely to be depressed and to gamble as an escape rather than because of a craving for action and excitement. Pathological gambling begins at a later age in female than in male gamblers, often after adult roles have been established. Big winning is usually less important than the need to impress. Women typically play less competitive forms of gambling in which luck is more important than skill, and they play alone. Their progression into the disorder is often more rapid, and the time between the onset of the disorder and the time they present for treatment is usually much shorter than for men (3 versus 20 years). The shorter duration makes for a better prognosis in treatment, but, unfortunately, few of the women with pathological gambling come to treatment.

The choice of gambling activities is dictated by local availability and cultural norms. Horseracing, cockfights, roulette, slot machines, casino card games, state-sponsored lotteries, and the stock market may all be used by the gambler. Likewise, the extent of gambling considered normal varies across cultures. DSM-IV-TR approaches this by concentrating on the consequences of gambling rather than on its frequency and type.

## Etiology and Pathophysiology

Pathological gambling has been included in DSM-III, DSM-III-R, and DSM-IV as a disorder of impulse control. Pathological gambling can also be viewed as an addictive disorder (Murray 1993), an affective spectrum disorder (McElroy et al. 1992) and an obsessive-compulsive spectrum disorder (Hollander et al. 1992b). DSM-IV-TR maintains a close relationship between pathological gambling and addictive disorders in that several of the diagnostic criteria for pathological gambling were intentionally made to resemble criteria for substance dependence (Table 80–3).

The parallels between pathological gambling and addictive disorders are manifold. Pathological gambling has been viewed as the "pure" addiction, because it involves several aspects of addictive behavior without the use of a chemical

**Table 80–2 Differential Diagnosis of Pathological Gambling**

| Pathological Gambling Must Be Differentiated From | In Contrast to Pathological Gambling, the Other Condition |
|---|---|
| Professional gambling | Is characterized by discipline and limited risk taking<br>Is intended to be a source of income |
| Social gambling | Usually occurs among friends |
| Is characterized by limited time spent on gambling and limited risk taking | |
| Manic episode | Involves episodes of characteristic symptoms (e.g., flight of ideas) |
| Is characterized by symptoms that persist at times when individual is not gambling | |

*Source:* [Reproduced from First and Frances A (1995) with permission of American Psychiatric Press.]

**Table 80–3 Comparison of DSM-IV-TR Criteria for Pathological Gambling and Substance Dependence**

| Pathological Gambling | Substance Dependence |
|---|---|
| A. Persistent and recurrent maladaptive gambling behavior as indicated by at least five (or more) of the following: | A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following: |
| A1. Is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble) | 1. A great deal of time is spent in activities necessary to obtain the substance or recover from its effects |
| A2. Needs to gamble with increasing amounts of money to achieve the desired excitement | 2. (Tolerance) (a). A need for markedly increased amounts of the substance to achieve intoxication or desired effect or (b). markedly diminished effect with continued use of the same amount of substance |
| A3. Has repeated unsuccessful efforts to control, cut back, or stop gambling | 3. There is a persistent desire or unsuccessful attempts to cut down or control substance use |
| A4. Is restless or irritable when attempting to cut down or stop gambling | 4. (Withdrawal) (a). The characteristic withdrawal syndrome for the substance |
| A5. Gambles as a way of escaping from problems or relieving a dysphoric mood | 5. (Withdrawal) (b). The same substance is taken to relieve or avoid withdrawal symptoms |
| A6. After losing money gambling, often returns another day to get even ("chasing" one's losses) | 6. The substance is often taken in larger amounts or over a longer period than was intended |
| A7. Lies to family members, therapist, or others to conceal the extent of involvement with gambling | |
| A8. Has committed illegal activities such as forgery, fraud, theft, or embezzlement to finance gambling | |
| A9. Has jeopardized or lost a significant relationship, job, or educational opportunity because of gambling | 7. Important social, occupational, or recreational activities are given up or reduced because of substance use |
| A10. Relies on others to provide money to relieve a desperate financial situation caused by gambling | |
| B. The gambling behavior is not better accounted for by a manic episode | 8. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance |

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substance. The parallels between substance dependence, in particular alcohol dependence, and pathological gambling have led to the successful adoption of the self-help group model of Alcoholics Anonymous (AA) to GA. Patterns of comorbidity also suggest a possible link between pathological gambling and addictions, in particular alcoholism. In addition to the comorbidity of pathological gambling and substance use disorders, family studies have demonstrated a familial clustering of alcoholism and pathological gambling. Ramirez et al. (1983) found that 50% of their patients with pathological gambling had a parent with alcoholism; other studies have also found high rates of a family history of substance dependence in patients with pathological gambling. There is also a greater prevalence of pathological gambling in parents of patients with pathological gambling.

The links between pathological gambling and affective disorders are also supported by family studies that demonstrate high rates of affective disorders in first-degree relatives of patients with pathological gambling (McElroy et al. 1992), as well as by high rates of comorbidity of pathological gambling and affective disorders. In addition, as noted by many authors and incorporated in the DSM-IV-TR criteria for pathological gambling, many patients with pathological gambling gamble as a way of relieving dysphoric moods (criterion A5), and cessation of gambling may be associated with depressive episodes in the majority of recovering gamblers (Linden et al. 1986).

The links between pathological gambling and obsessive spectrum disorders are less clear. Although a popular name for pathological gambling is compulsive gambling, the majority of people with pathological gambling do not experience the urge to gamble as ego-dystonic until late in the course of their illness, after they have suffered some of its consequences. The rates of comorbidity of pathological gambling and OCD and obsessive-compulsive personality disorder are not nearly as high as the rates of comorbidity of pathological gambling and affective and addictive disorders. Nevertheless, pathological gambling shares several characteristics with compulsions: it is repetitive, often has ritualized aspects, and is meant to relieve or reduce distress. Moreover, sporadic reports on the effectiveness of SSRIs in the treatment of pathological gambling suggest a possible link to obsessive spectrum disorders (Hollander et al. 1992b).

## Neurotransmitter Function

The association between altered function of the serotonin neurotransmitter system and impulsive behaviors has focused attention on a potential role for serotonin function in the neurophysiology of pathological gambling. Evidence of serotonergic dysfunction in pathological gamblers comes from neurobiological studies (Moreno et al. 1991, Carrasco et al. 1994, DeCaria et al. 1998a). These findings include: blunted prolactin response after intravenous administration

of the SSRI, clomipramine (Moreno et al. 1991), increased prolactin response after the administration of a serotonin agonist, m-CPP (DeCaria et al. 1996), and low platelet MAO-B activity (a correlate central nervous system concentrations of the serotonin metabolite 5-HIAA) (Blanco et al. 1996, Carrasco et al. 1994). However, direct measure of CSF 5-HIAA in pathological gamblers has yielded mixed results (Roy et al. 1988b, Bergh et al. 1997, Ibanez et al. 2002). Preliminary data support potential utility of SSRI medications in the treatment of pathological gambling (Hollander et al. 1998, 2000b, Ibanez et al. 2002). There is evidence of serotonergic dysfunction in depression (Coccaro et al. 1989), impulsivity (Linnoila et al. 1983), suicidality (Mann et al. 1992), and alcoholism (Tollefson 1991). This is of interest because pathological gambling is strongly associated with depression (Roy et al. 1988a, 1988b), impulsivity (Moreno et al. 1991), suicidality (Ciarrochi and Richardson 1989), and alcohol or drug abuse (Linden et al. 1986, McCormick et al. 1984). Thus, pathological gambling may also be associated with serotonergic dysfunction as it relates to these comorbid features.

Because of the "addictive" aspects of pathological gambling—and the role that dopaminergic function plays in chemical addictions—attention has been directed at dopamine function among pathological gamblers. Two available studies have yielded contradictory data (Roy et al. 1988b, Bergh et al. 1997). The role of noradrenergic function has also been explored. In support for such a role, pathological gamblers have been shown to have higher urinary and CSF concentrations of noradrenaline and metabolites (Roy et al. 1988b, Bergh et al. 1997). Measures of extroversion in pathological gamblers significantly correlate with indices of noradrenergic function (Roy et al. 1989). Further, increased noradrenergic function has been associated with arousal, irritability, and risk-taking behavior (Coccaro et al. 1991) and pathological gambling has been associated with increased arousal and tonic activity of the central noradrenergic system (Brown 1986, Dickerson et al. 1987, Roy et al. 1988b). In addition, increased growth hormone secretion, a measure of noradrenergic reactivity, was found in pathological gamblers in response to oral administration of clonidine, an alpha-2-adrenergic agonist (Ibanez et al. 2002).

## Genetic Contribution

The incidence of pathological gambling among first-degree family members of pathological gamblers appears to be approximately 20% (Ibanez et al. 2002). Inherited factors may explain 62% of variance in the diagnosis (Eisen et al. 1998) and some of these genetic factors may also contribute to the risk for conduct disorder, ASPD, and alcohol abuse (Eisen et al. 2001). Gambino et al. (1993) found that patients who perceived that their parents had gambling problems were three times more likely to score as probable pathological gamblers on the SOGS. Those who also perceived that their grandparents had gambling problems had a 12-fold increased risk compared with patients who did not perceive gambling problems in their parents and grandparents.

Serotonergic, noradrenergic, and dopaminergic genes have been investigated because of the putative role of these neurotransmitters in pathological gambling, and a number of molecular genetic studies performed to date have reported findings consistent with the involvement of these neurotransmitter systems in pathological gambling (e.g., Ibanez et al. 2001, Perez de Castro et al. 2002, Comings et al. 1996, 1997). However, some of the studies performed to date have not been adequately controlled for potential differences in racial and ethnic compositions, factors that could account for differences in allelic variant distributions. Thus, these studies should be regarded as preliminary.

At present, the main source of evidence for the genetic influence in the etiology of pathological gambling comes from a study of 3359 male twin pairs from the Vietnam Era Twin Registry cohort (Eisen et al. 1998, 2001, Slutske et al. 2000). These data suggest that gambling problems of increasing severity represent a single continuum of vulnerability rather than distinct entities (Eisen et al. 1998, 2001), a genetic susceptibility model in the pathogenesis of pathological gambling (Eisen et al. 1998), and indicates a common genetic vulnerability for pathological gambling and alcohol dependence in men (Slutske et al. 2000). In a smaller twin study, Winters and Rich (1999) found a significant heritability explaining "high action" gambling, like casinos and gambling slot machines, in 92 monozygotic and dizygotic male twin pairs. But, no significant differences in heritability were found among males for "low action" games and among 63 female monozygotic and dizygotic twin pairs for either "high action" or "low action" gambling.

## Neuropsychology

Clinical comorbidities and observations that pathological gambling involves strong motivations to engage in gambling and subjective feelings of reward, withdrawal, and craving for gambling, support the categorization of pathological gambling as "a nonpharmacological addiction" (Blanco et al. 2001, Holden 2001). This view is corroborated by neuroimaging findings that gambling-associated cognitive and motivational events, or responses of pathological gamblers to gambling-related stimuli, are associated with metabolic changes in brain regions implicated in studies of substance use disorders (Breiter et al. 2001, Holden 2001, Potenza et al. 2003). Using FDG-PET in unmedicated pathological gamblers without comorbid substance use disorders ($N = 7$), Hollander et al. (2001) found heightened limbic and sensory activation in a gambling-for-money condition, with increased emotional valence and greater risk and reward, which confirms the salience of monetary reward in the development of pathological gambling.

Some data support the notion that people with impaired impulse control exhibit abnormalities in risk-benefit decision making in both gambling and nongambling activities and that their cognitive or emotional sense of what distinguishes gambling from other decisions of daily living may be compromised (Crean et al. 2000, Petry 2001a, 2001b; Petry and Casarella 1999, Bechara 2001, Bechara et al. 2000, 2001, Potenza 2001). These deficits may produce an inability to inhibit motivated drives to gamble, leading to persistent gambling. Myopia for the future and insensitivity to punishment has also been shown in orbitofrontal and ventromedial PFC lesion patients (Bechara et al. 1994, Berlin et al. 2004) using gambling tasks. Cavedini et al. (2002) data suggest a link between pathological gambling and other disorders (i.e., OCD and drug addiction) all having diminished ability to evaluate future consequences, which may be explained in part by an abnormal functioning of the orbitofrontal cortex.

Attention problems and impulsivity in pathological gamblers could reflect deficits in executive functioning that are often a consequence of minimal brain damage with orbitofrontal cortex impairment (Rugle and Melamed 1993, Specker et al. 1995, Berlin et al. 2004).

### Psychodynamic Considerations

Psychoanalytic theories of gambling were the first systematic attempts to account for pathological gambling. Erotization of the fear, tension, and aggression involved in gambling behavior, as well as themes of grandiosity and exhibitionism, were explored by several authors during the first quarter of the 20th century. Freud (1961) in his influential essay on Dostoyevsky, suggested that the pathological gambler actually gambled to lose, not to win, and traced the roots of the disorder to the ambivalence felt by the young man toward his father. The father, the object of his love, is not only loved but also hated, and this results in unconscious guilt. The gambler then loses to punish himself, in what Freud labeled "moral masochism." Freud also spoke of "feminine masochism" in which losing is a way of gaining love from the father, who will somehow reward the loser for loyalty. To lose is to suffer, and for the feminine masochist, suffering equals love. Interestingly, in the later spirit of DSM-IV-TR, Freud also conceptualized pathological gambling as an addiction and included it in a triad with alcoholism and drug dependence. He saw all three as manifestations of that primary addiction, masturbation, or at least masturbatory fantasies. Like most researchers after him, Freud focused only on male gamblers.

Bergler, a psychoanalyst who treated many pathological gambling patients, expanded on Freud's idea that pathological gamblers gamble to lose (Lesieur and Rosenthal 1991). He traced the roots of this desire to lose to the rebellion of gamblers against the authority of their parents and the parents' intrusive introduction of the reality principle into their lives. The rebellion causes guilt, and the guilt creates the need for self-punishment. Bergler thought that the gambler's characteristic aggression is actually pseudoaggression, a craving for defeat and rejection. He saw the gambler as one who perpetuates an adversarial relationship with the world. The dealer in the casino, the gambler's opponents at the card table, the stock exchange, and the roulette wheel are all unconsciously identified with the refusing mother or the rejecting father. Overall, psychoanalytic approaches to pathological gambling (Lesieur and Rosenthal 1991) generally conceptualized it as either a compulsive neurosis (Freud, Bergler, and Rosenthal) or an impulse disorder (Fenichel). Fenichel (1945) focused on the gambler's entitlement and intense need to "get the stuff," an oral fixation. Several published case reports documented the successful treatment of pathological gambling by psychoanalysis.

Learning theories of pathological gambling focus on the learned and conditioned aspects of gambling and use the quantifiable nature of the behavior to test specific hypotheses. One hypothesis was that patients with pathological gambling crave the excitement and tension associated with their gambling, as evidenced by the fact that they are much more likely to place last-second wagers than are low-frequency gamblers, to prolong their excitement. Higher wagers placed by patients with pathological gambling also produce greater excitement, and greater amounts of money are required to achieve the same "buzz" over time, an observation incorporated in the diagnostic criteria for pathological gambling (criterion A2).

## Treatment

### Treatment Goals

The goals of treatment of an individual with pathological gambling are the achievement of abstinence from gambling, rehabilitation of the damaged family and work roles and relationships, treatment of comorbid disorders, and relapse prevention. This approach echoes the goals of treatment of an individual with substance dependence. There are many similarities and several important differences between the treatment of pathological gambling and the treatment of substance dependence. For most patients without severe acute psychiatric comorbidity, such as major depressive disorder with suicidal ideation or alcohol dependence with a history of delirium tremens, treatment may be given on an outpatient basis. Inpatient treatment in specialized programs may be considered if the gambler is unable to stop gambling, lacks significant family or peer support, or is suicidal, acutely depressed, multiply addicted, or contemplating some dangerous activity.

No standard treatment of pathological gambling has emerged. Despite many reports of behavioral and cognitive interventions for pathological gambling, there are minimal data available from well-designed or clearly detailed treatment studies (Petry 2002). Pharmacological treatments (see below) offer promise, but research-guided approaches are still insufficient to offer a standardized approach. Thus, general approaches, based in clinical experience and available resources (like GA or other support groups) should be considered. The treatment of pathological gambling may consist of participation in GA, individual therapy, family therapy, treatment of comorbid disorders, and medication treatment. Many treatment modalities of pathological gambling are similar to that of substance abuse disorders and were created based on the addiction model, like self-help groups, inpatient treatment programs, and rehabilitation programs. As is the case for substance dependence, the gambler needs to be abstinent to be accessible to any or all of these treatment modalities. Essential features of any therapeutic intervention for pathological gambling include the need to establish both a therapeutic alliance and network, address the underlying pathology, interrupt the behavior and maintain abstinence, problem solve, and improve quality of life.

The most popular intervention for problem gambling is GA, a 12-step group built on the same principles as AA, which utilizes empathic confrontation by peers who struggle with the same impulses. For many gamblers, participation in GA is sufficient, and it is an essential part of most treatment plans. Extensive data are lacking, but overall GA appears somewhat less effective than AA in achieving and maintaining abstinence. Evidence suggests that GA may not be very effective when used without other treatment modalities (Petry and Armentano 1999). Retrospective studies show a dropout rate of up to 70% within the first year (Stewart and Brown 1988), and overall dropout rates range from 75% to 90% (Moody 1990). Only 8% of GA members report total abstinence at 1-year follow-up and 7% at 2-year

follow-up (Brown 1985). Although participation in GA's spousal component, Gam-Anon, may be helpful for some family members, little evidence suggests that it reduces disordered gambling (Petry and Armentano 1999).

Individual therapy is often useful as an adjunct to GA. Rosenthal (1992) stressed that to maintain abstinence and use GA successfully, many gamblers need to understand why they gamble. Therapy involves confronting and teasing out the vicissitudes of the patient's sense of omnipotence and dealing with the various self-deceptions and the defensive aspects of the patient's lying, and problems involving magical thinking and reality. Relapse prevention involves knowledge and avoidance of specific triggers. In addition to psychodynamic therapy, behavioral treatment of pathological gambling has been proposed, with imagined desensitization achieving better rates of remission than aversive conditioning.

The greatest differences between the treatment of pathological gambling and other addictions are in the area of family therapy. Because relapse may be difficult to detect (no substance smelled on their breath, dilated or constricted pupils, or slurred speech or staggered gait) and because of a long history of exploitative behavior by the patient, the spouse and other family members tend to be more suspicious of, and angry at, the pathological gambling patient compared with families of alcoholic patients. Family sessions are often essential to offer the gambler an opportunity to make amends, learn communication skills, and deal with preexisting intimacy problems. The spouse and other family members often acquire their own psychiatric illnesses during the course of the patient's illness and may need individualized treatment to recover.

## Somatic Treatments

Although research reports of the pharmacological treatment of pathological gambling have reported some efficacy, there are still, as yet, insufficient data to come to any conclusions about the utility of medication. Pharmacological treatment studies of pathological gambling have demonstrated some promising results with the use of SSRIs (Hollander et al. 1992b, Hollander et al. 1998, 2000b, de la Gandara 1999, Zimmerman et al. 2002, Kim et al. 2002), serotonin reuptake inhibitors (Pallanti et al. 2002b), mood stabilizers (Haller and Hinterhuber 1994, Pallanti et al. 2002a, Hollander et al. 2002), opiate antagonists (Kim et al. 2001), and atypical antipsychotics (Potenza and Chambers 2001). Doses at the higher end of the usual treatment range should be considered with both SSRIs and opiate antagonists. Some studies have not reported significant findings, possibly due to high placebo response rates, high rates of discontinuation, as well as the possibility that different patients have differential responses to the various medication options based on endophenotypes that have yet to be elucidated (Blanco et al. 2002, Grant et al. 2003). At this time, pharmacological agent algorithms are still not definitive for the treatment of PG (Grant and Kim 2002e, Haller and Hinterhuber 1994, Hollander et al. 2000b, Kim and Grant 2001, Kim et al. 2001, Grant and Potenza 2004)). Treatment should ultimately target all symptom domains within the individual patient that contribute to compulsive gambling, including common comorbid conditions like bipolar spectrum disorder, ADHD, and substance abuse/dependence disorders.

## Psychotherapy

Inpatient programs for pathological gambling have included various combinations of individual and group psychotherapy and substance use treatment (Taber 1981), and most strongly encouraged or required attendance at GA meetings. Many patients improved in all programs, and outcome studies have shown 55% of patients reporting abstinence at 1-year follow-up (Russo et al. 1984, Taber et al. 1987). Although methodologically flawed, these reports suggest that professionally delivered multimodal therapy programs, given alone or in combination with GA, may be more effective than GA alone. Self-help manuals may also be useful for some (Dickerson et al. 1990), and studies comparing their effectiveness with professionally delivered CBT are ongoing (Petry and Armentano 1999).

Early psychoanalytic reports suggest that problem gambling is regressive and representative of various pregenital and genital instincts, unconscious conflicts, or painful affects. Most studies that report good outcome are based on single-case studies, and some authors believe that purely psychodynamic treatment of pathological gambling is difficult. Rosenthal and Rugle (1994) published a psychodynamic approach to pathological gambling treatment, which integrates traditional psychodynamic psychotherapy with an addiction model.

Behavioral, cognitive, and combined cognitive-behavioral methods have been used in treating pathological gambling. Aversive therapy has been employed to reach the goal of total abstinence of gambling, as have behavior monitoring, contingency management, contingency contracting, covert sensitization, systematic desensitization, imaginal desensitization, in vivo exposure, imaginal relaxation, psychoeducation, cognitive restructuring, problem-solving skills

Clinical Vignette 3

Mr. Z is a 44-year-old automobile mechanic who is married and has two adolescent children. He was referred for inpatient treatment from the emergency department of his local hospital after an overdose of a full bottle of over-the-counter sleeping pills taken as a suicide attempt. He took the pills in the setting of a major depressive episode without psychotic features. This was his first psychiatric contact. During his initial evaluation, Mr. Z admitted to several past depressive episodes for which he did not seek treatment and which resolved spontaneously. He also admitted to a history of alcohol abuse and stated that his drinking may have escalated recently. His family history was significant for a father with alcohol dependence and a mother with bipolar disorder. Mr. Z was treated as an inpatient with fluoxetine and improved rapidly, with full resolution of his suicidal ideation and other depressive symptoms.

Two days before his planned discharge from the hospital, a family meeting was held. During the meeting, his treatment team was surprised when his wife announced that she refused to let Mr. Z return home before "the other problem" was taken care of. At this point, a parallel history was taken and revealed that Mr. Z has had a problem with "excessive gambling" for the last 25 years. His wife meant that Mr. Z gambled with money that he did not have and went on gambling sprees that ended only when he lost all the money available to him and exhausted his current abilities to borrow money. During such episodes he had lost

the family home, was caught stealing spare parts from his job and was fired, and borrowed several thousand dollars from his in-laws and his sister, which he was unable to repay. More recently he became involved with loan sharks, who were now threatening him physically. His suicide attempt followed a threat to hurt him and his family if his debts were not paid.

Mr. Z began to gamble when he was 16 years old and stated that "there is nothing else like it." He frequented off-track-betting establishments and considered himself an expert in horseracing. His only social acquaintances were other gamblers, and he found other recreational activities dull and unsatisfying. When he was confronted with this history, Mr. Z felt that his wife was "being hysterical." He admitted that he loved to gamble but described himself as a professional gambler and cited several occasions on which he won significant amounts of money. He was not interested in any kind of treatment but agreed to attend GA if his extended family would help him out of his current financial problems.

During the course of a 2-year follow-up, Mr. Z continued to gamble and lose money. He stopped going to meetings. He was fired from his job again, discontinued his medication, became depressed, and started drinking. At that time, he came to treatment with his wife, who was attending Gam-Anon and began seeing a psychiatrist for the treatment of her own mild depression. Mr. Z agreed to an arrangement in which his wife would have complete power of attorney over his financial affairs. His participation in GA and AA became a prerequisite for his continued living at home. He was again given fluoxetine and began a course of individual psychotherapy with biweekly family sessions. For the first time in his adult life, Mr. Z was able to abstain from gambling for a period of 3 months.

training, social skills training, and relapse prevention. Use of cognitive restructuring facilitates a decrease in the frequency of gambling and irrational verbalizations associated with gambling (Ladouceur 1990).

## Trichotillomania

### Diagnosis

#### Definition and Diagnostic Features

The essential feature of trichotillomania is the recurrent failure to resist impulses to pull out one's own hair. Resulting hair loss may range in severity from mild (hair loss may be negligible) to severe (complete baldness and involving multiple sites on the scalp or body). Individuals with this condition do not want to engage in the behavior, but attempts to resist the urge result in great tension. Thus, hair pulling is motivated by a desire to reduce this dysphoric state. In some cases, the hair pulling results in a pleasurable sensation, in addition to the relief of tension. Tension may precede the act or may occur when attempting to stop. Distress over the symptom and the resultant hair loss may be severe.

Typically, the person complaining of unwanted hair pulling is a young adult or parent of a child who has been seen pulling out hair (Winchel 1992). Hair pulling tends to occur in small bursts that may last minutes to hours. Episodes may occur once or many times each day. Hairs are

**DSM-IV-TR Criteria**

**Trichotillomania**

A. Recurrent pulling out of one's hair resulting in noticeable hair loss.

B. An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior.

C. Pleasure, gratification, or relief when pulling out the hair.

D. The disturbance is not better accounted for by another mental disorder and is not due to a general medical condition (e.g., a dermatological condition).

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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pulled out individually and may be pulled out rapidly and indiscriminately. Often, however, the hand of the individual may roam the afflicted area of scalp or body, searching for a shaft of hair that may feel particularly coarse or thick. Satisfaction with having pulled out a complete hair (shaft and root) is often expressed. Occasionally the experience of hair pulling is described as quite pleasurable. Some experience an itch-like sensation in the scalp that is eased by the act of pulling. The person may then toss away the hair shaft or inspect it. A substantial number of people then chew or consume the hair (trichophagia). Hair-pulling is most commonly limited to the eyebrows and eyelashes. The scalp is the next most frequently afflicted site. However, hairs in any location of the body may be the focus of hair-pulling urges, including facial, axillary, chest, pubic, and even perineal hairs.

Anxiety is almost always associated with the act of hair pulling. Such anxiety may occur in advance of the hair-pulling behavior. A state of tension may occur spontaneously, driving the person to pull out hair in an attempt to reduce dysphoric feelings. Varying lengths of time must pass before the tension abates. Consequently, the amount of hair that may be extracted in an episode varies from episode to episode and from person to person. Frequently, hair pulling begins automatically and without conscious awareness. In such circumstances, individuals discover themselves pulling out hairs after some have already been pulled out. In these situations, dysphoric tension is associated with the attempt to stop the behavior.

Circumstances that seem to predispose to episodes of hair pulling include both states of stress and, paradoxically, moments of relaxation. Frequently, hair pulling occurs when at-risk individuals are engaged in a relaxing activity that promotes distraction and ease (e.g., watching television, reading, talking on the phone). It is common for hair pullers to report that the behavior does not occur in the presence of other people. A frequent exception may be that many pull hair in the presence of members of the nuclear family.

Some individuals have urges to pull hairs from other people and may sometimes try to find opportunities to do so surreptitiously (like initiating bouts of play fighting). There have been reports of individuals pulling hairs from pets, dolls, and other fibrous materials, like sweaters or carpets (Tabatabai and Salari-Lak 1981).

The distress that usually accompanies trichotillomania varies in severity. Concerns tend to focus on the social and vocational consequences of the behavior. Themes of worry include fear of exposure, feeling that "something is wrong with me," anxiety about intimate relationships, and sometimes inability to pursue a vocation. Because certain kinds of work, like reading and writing at a desk, seem to precipitate episodes of hair pulling, some individuals make career choices based on the avoidance of desk work. Leisure activities that may involve a risk of exposure (ranging from gymnastics class to sexual intimacy) may be avoided.

Patterns of hair-pulling behavior among children are less well described. Usually, the parent observes a child pulling out hair and may note patches of hair loss. Children may sometimes be unaware of the behavior or may, at times, deny it. Childhood trichotillomania has been reported to be frequently associated with thumb sucking or nail biting (Friman and Hove 1987). It has been suggested that trichotillomania with onset in early childhood may occur frequently with spontaneous remissions. Thus, some have recommended that trichotillomania in early childhood be considered a benign habit with a self-limited course. But, many people who present with chronic trichotillomania in adulthood report onset in early childhood (Reeve et al. 1992).

## Assessment

In general, the diagnosis of trichotillomania is not complicated. The essential symptom—recurrently pulling out hair in response to unwanted urges—is easily described by the patient. When the patient acknowledges the hair-pulling behavior and areas of patchy hair loss are evident, the diagnosis is not usually in doubt. Problems in diagnosis may arise when the diagnosis is suspected but the patient denies it. Such denial may occur in younger individuals and some adults. When the problem is suspected but denied by the patient, a skin biopsy from the affected area (see later) may aid in making the diagnosis.

### The Psychiatric Interview

The psychiatrist should carefully inquire into the nature of the distress and the patient's concerns. Although the cosmetic impact may appear slight, distress may be severe. Concerns about disclosure, anticipation of social rejection, and concerns about limitations in career choices are frequent and may result in chronic dysphoria. The psychiatrist should be aware of the embarrassment that may accompany inspection of the hair loss, particularly when located in regions of the body that are not usually accessible in the course of a standard psychiatric examination. Because of the apparent frequency of comorbid mood disorders (past or current), the interviewer should pay special attention to the presence of these features.

### Physical Examination and Laboratory Findings

Areas of hair loss can be marked by complete alopecia or can appear diffusely thinned or "ratty." Altered scalp appearance can range from small areas of thinned hair to complete baldness. For unclear reasons, several patterns of scalp loss are typical. Frequently, coin-sized areas of alopecia are noted at the vertex or at temporal or occipital regions. Among more severely afflicted people a peculiar pattern, the so-called tonsure trichotillomania, may appear: a completely bald head except for a narrow, circular fringe circumscribing the outer boundary of the scalp, producing a look reminiscent of medieval friars.

Despite the hair loss, most individuals with this condition have no overtly unusual appearance on cursory inspection. If the hair loss is not covered by clothing or accessories, artful combing of hair or use of eyeliner and false eyelashes may easily hide it. The ease with which the condition may often be hidden may explain the general underappreciation of its apparent frequency and potential associated distress.

### Associated Laboratory Findings

Histological findings are considered characteristic and may aid diagnosis when it is suspected despite denial by the individual. Biopsy samples from involved areas may have the following features. Short and broken hairs are present. The surface of the scalp usually shows no evidence of excoriation. On histological examination, normal and damaged follicles are found in the same area, as well as an increased number of catagen (i.e., nongrowing) hairs. Inflammation is usually minimal or absent. Some hair follicles may show signs of trauma (wrinkling of the outer root sheath). Involved follicles may be empty or contain a deeply pigmented keratinous material. The absence of inflammation distinguishes trichotillomania-induced alopecia from alopecia areata, the principal condition in the differential diagnosis (Mehregan 1970, Muller 1990).

## Epidemiology

Trichotillomania was long thought to be uncommon, often accompanied by other psychiatric conditions. Although definitive studies of frequency rates in the general population are still lacking, three surveys of nonclinical college-age samples support the emerging view that trichotillomania is more common than originally suggested. In two of these samples, totaling approximately 3000 undergraduate students, 10–13% of students reported hair pulling, with the prevalence of clinically significant pulling ranging between 1% and 3.5% (Christenson et al. 1991b, Rothbaum et al. 1993). A epidemiological study of trichotillomania and skin picking using self-report instruments (the Massachusetts General Hospital Hairpulling Scale and the Skin Picking Scale) in a sample of 1324 college freshmen found that 5.4% (72) endorsed relatively frequent hair pulling or skin picking (Hajcak et al. 2006). One epidemiological survey of 17-year-old adolescents in Israel suggests a prevalence rate of 1% for current or past hair pulling, with fewer reporting noticeable hair loss or distress from these symptoms (1995a).

These may be underestimates of the lifetime incidence of the disorder. Had these studies applied DSM-IV-TR criteria, which have become slightly less restrictive than DSM-III-R criteria, the rates might be higher. In addition, because onset may occur later in life than the mean ages of individuals in these groups, the true lifetime incidence would probably be higher. Moreover, these samples consist of a

selected population—largely first-year college students—and may not reflect the general population. Nonetheless, these studies indicate that the condition is likely to be far more common than previously assumed. But definitive, controlled studies of the prevalence of the condition have not yet been performed.

## Comorbidity Patterns

Many experts (e.g., Christenson and Mansueto 1999) have noted a common co-occurrence and formal similarities between trichotillomania and other body-focused ICDs like skin picking and severe nail biting. Nail biting and skin picking (excoriation) are often associated with trichotillomania and these three pathological behaviors often co-occur with each other and are thought to be related (Wilhelm and Margraf 1993, Bhatia et al. 1991, Simeon et al. 1997, O'Sullivan et al. 2000, Cohen et al. 1995, Wilhelm et al. 1999). If the skin-picking and nail-biting appear to be largely negatively reinforcing—that is, reducing anxiety associated with specific obsessional thoughts and/or reducing the likelihood of feared outcomes—they may be better conceptualized as OCD behaviors and addressed accordingly. However, Franklin et al. (2006) suggest, based on clinical experience, that these conditions are much more likely to formally resemble trichotillomania. In accordance, many trichotillomania patients have comorbid skin picking and nail biting (O'Sullivan et al. 2000, Lochner et al. 2002, Christenson et al. 1991a, Simeon et al. 1997).

Individuals with trichotillomania have increased risk for mood disorders (major depressive disorder, dysthymic disorder) and anxiety symptoms (Table 80–4). The frequency of specific anxiety disorders (like generalized anxiety and panic disorders and OCD) may be increased as well. Compared to controls, college students who reported frequent hair pulling or skin picking also reported significantly more symptoms of anxiety and stress reactivity, and had higher scores on a measure of obsessive-compulsive symptoms (Hajcak et al. 2006). Although it has been suggested that trichotillomania in childhood or adolescence is associated with schizophrenia or severe disruptions of the family system, no systematically collected data support such conclusions.

Christenson et al. (1991a) found that approximately 82% of an adult sample with trichotillomania met criteria for a past or current comorbid Axis I disorder, the most common being affective, anxiety, and addictive disorders. Of the patients with comorbid disorders, there was a lifetime prevalence rate of 65% for mood disorders, 57% for anxiety disorders, 22% for substance abuse disorders, 20% for eating disorders, and 42% for personality disorders. The most frequently cited comorbid personality disorders are histrionic, borderline, and obsessive-compulsive (Christenson et al. 1992, Schlosser et al. 1994, Swedo and Leonard 1992). In a larger sample of adults seeking treatment for trichotillomania, Christenson (1995) found comorbidity rates of 57% for major depression, 27% for generalized anxiety disorder, 20% for eating disorders, 19% for alcohol abuse, and 16% for other substance abuse. In a mixed sample of children, adolescents, and adults with trichotillomania, Swedo and Leonard (1992) found comorbidity rates of 39% for unipolar depression, 32% for generalized anxiety disorder, 16% for OCD, and 15% for substance abuse. Reeve et al. (1992) and King et al. (1995b) found that 7 of 10 and 9 of 15 children with trichotillomania had at least one comorbid Axis I disorder, respectively. Franklin et al. (2002a) and Tolin et al. (2002) reported little comorbidity in their pediatric treatment-seeking samples, suggesting that comorbidity may develop secondarily in the wake of trichotillomania. Sampling issues most likely underlie these observed differences. Nevertheless, if it is indeed the case that children and adolescents with trichotillomania are less comorbid than adults, early intervention in children and adolescents with trichotillomania may help reduce the rates and severity of later adult psychiatric comorbidity and functional impairment (Keuthen et al. 2002).

## Course

The age at onset typically ranges from early childhood to young adulthood. Peak ages at presentation may be bimodal, with an earlier peak about age 5 to 8 years among children in whom it has a self-limited course, whereas among patients who present to clinicians in adulthood the mean age at onset is approximately 13 years (Rothbaum et al. 1993, Winchel 1992, Swedo et al. 1989). Initial onset after young adulthood is apparently uncommon. There have been reports of onset as early as 14 months of age and as late as 61 years.

Trichotillomania may be one of the earliest occurring conditions in psychiatry. Some parents insist that their child began pulling hair before 1 year of age. When trichotillomania begins before age 6 years it tends to be a milder condition. It often responds to simple interventions and may be self-limited, with a duration of several weeks to several months, even if not treated. It often occurs in association with thumb sucking. In some cases it remits spontaneously when therapeutic attention is directed at concurrent, severe thumb -sucking (Watson and Allen 1993). It has been suggested that trichotillomania in childhood may be associated with severe intrapsychic or familial psychiatric conditions. But there is no reliable evidence that supports such a conclusion. Indeed, some have suggested that because it may be common and frequently self-limiting, it should be considered a normal behavior among young children.

Tricotillomania in adolescents and adults typically follows a chronic course, involves multiple hair sites, and

**Table 80–4 Lifetime Comorbidity and Trichotillomania**

| Reference | No Axis I | Anxiety Disorder | Mood Disorder | PSUD* | OCD | Eating Disorder |
|---|---|---|---|---|---|---|
| Christenson et al. (1991a) ($n$ = 60) | 18% | 57% | 65% | 22% | 15% | 20% |
| Winchel et al. (1992) ($n$ = 20) | 45% | 5% | 45% | 15% | 5% | 0% |
| Swedo et al. (1989) ($n$ = 14) | ? | 43% | 57% | 29% | † | 0% |

*PSUD, Psychoactive substance use disorder.

†Patients with OCD were excluded from this sample, as were patients with psychosis.

is associated with high rates of psychiatric comobidity (Christenson et al. 1991a). The chronic course may take one of two patterns: in one the frequency and severity of hair pulling waxes and wanes over months, without any true remissions; in the other, episodes are characterized by frequent hair pulling separated by long periods of remission (Moore and Jefferson, 2004). Some individuals have continuous symptoms for decades. For others, the disorder may come and go for weeks, months, or years at a time. Sites of hair pulling may vary over time. Circumscribed periods of hair pulling (weeks to months) followed by complete remission are reported among children. Progression of the condition appears to be unpredictable. It is not known which factors may predict a protracted and unremitting course.

Because of the unavailability of longitudinal studies of trichotillomania, generalizations about prognosis cannot be made. Patients who present in research clinics typically have histories of many years (up to decades) of hair pulling. Presentation after age 40 years appears to be far less common than in the previous three decades of life, suggesting that the condition may eventually remit spontaneously, even when untreated. It is likely that the persistent cases seen in research environments reflect the more severe end of the spectrum. As noted earlier, trichotillomania in children may often be a time-limited phenomenon.

## Differential Diagnosis

Among individuals presenting with alopecia who complain of hair-pulling urges, the diagnosis is not usually in doubt. When patients deny hair pulling, other (dermatological) causes of alopecia should be considered. These include alopecia areata, male pattern hair loss, chronic discoid lupus erythematosus, lichen planopilaris, folliculitis decalvans, pseudopelade, and alopecia mucinosa.

Trichotillomania is not diagnosed when hair pulling occurs in response to a delusion or hallucination. Many people twist and play with their hair. This may be exacerbated in states of heightened anxiety but does not qualify for a diagnosis of trichotillomania. Some may present with features of trichotillomania but hair damage may be so slight as to be virtually undetectable, even under close examination. In such conditions the disorder should be diagnosed only if it results in significant distress to the individual.

Trichotillomania may have a short, self-limited course among children and may be considered a temporary habit. Therefore, among children the diagnosis should be reserved for situations in which the behavior has persisted during several months.

## Differences in Gender and Cultural Presentations

Secondary avoidance of intimate relationships, which occurs among some individuals with trichotillomania, may be exacerbated for women in cultures in which physical appearance is weighted differently for men and women. Avoidance of sports activities, in which disguised hair loss can be revealed, may also have gender-related effects in cultures in which athletic participation has different social meanings for men and women. Although culture-based expectations regarding appearance may make hair loss a greater burden for women, women may have a greater opportunity to hide hair loss through the use of wigs, hats, and scarves.

Reliable data regarding sex ratio in the general population are not yet available. It has long been suggested that women greatly outnumber men. However, surveys of college students suggest that the true ratio may be near parity. The apparent preponderance of women presenting for treatment may alternatively reflect self-selection for presentation for treatment. Self-selection may reflect gender related, culturally based attitudes regarding appearance, as well as an acceptance of normative hair loss among men. Because such gender-related distinctions may not be made by parents who are concerned about hair-pulling habits in their children, the apparent equal presentation of male and female children may more accurately reflect the true sex ratio. For many women, hair pulling may worsen during the premenstrual phase (Keuthen et al. 1997).

## Etiology and Pathophysiology

The etiology of trichotillomania is unknown. The phenomenological similarities between trichotillomania and OCD have prompted speculations that the pathophysiology of the two conditions may be related. The apparent association between altered serotonergic function and OCD has guided attention toward the possible role of serotonergic function in the underlying cause of trichotillomania. Thus, interest has been spurred in examining serotonergic function in patients with trichotillomania.

Ninan et al. (1992) obtained CSF from eight individuals with trichotillomania and measured concentrations of the primary serotonin metabolite 5-HIAA. Baseline concentrations of 5-HIAA did not differ from those of control subjects, nor was there a relationship between the baseline 5-HIAA concentration and the severity of trichotillomania symptoms. But, seven of these patients were then treated with SSRIs (fluoxetine and clomipramine). The researchers found a negative correlation between baseline CSF 5-HIAA concentration and the degree of improvement after treatment. This observation does not, however, directly support a conclusion that altered serotonin function is etiologically related to trichotillomania.

Swedo et al. (1991) used PET to measure regional brain glucose in three groups: trichotillomania patients, OCD patients, and normal controls. Like OCD patients, those with trichotillomania had altered patterns of glucose utilization compared with normal controls. However, the regional patterns of altered glucose utilization differed between trichotillomania and OCD groups. In a morphometric MRI study, left putamen volume was found to be significantly smaller in 10 female trichotillomania subjects as compared with 10 normal matched controls (O'Sullivan et al. 1997).

Performance on neuropsychological tests may offer an additional basis for defining the underlying neuropathological process in people with trichotillomania. Because impaired performance on such tests may indicate altered function in particular brain regions, they may also help localize brain regions in which altered function may be associated with trichotillomania. On the basis of such tests, Rettew et al. (1991) suggested that trichotillomania patients may have deficits in spatial processing. Patterns of deficits on such tests may provide further support for a relationship between trichotillomania and other psychiatric conditions. Rettew et al. (1991) found similarities between trichotillomania and OCD subjects.

Keuthen et al. (1996) also speculated that people with trichotillomania would demonstrate alterations in neuropsychological function similar to individuals with OCD, who have been shown to have impairments in executive, visual-spatial and nonverbal memory function. In a study of 20 trichotillomania subjects and 20 matched healthy controls, they demonstrated the presence of impaired performance on two of these three parameters (nonverbal memory and executive function). These results were interpreted as supporting the presumed relationship between trichotillomania and OCD. However, Stanley et al. (1997a), in their study of 21 trichotillomania subjects versus 17 healthy controls, did not find evidence of deficits in visual-spatial ability, motor function, or executive function. But, differences were found on measures of divided attention, leading to the suggestion that trichotillomania might be more properly conceptualized as an affective or anxiety-based disorder, and that any demonstrated similarities with OCD may be related to their shared overlap with anxiety/affective disorders.

Additional support for a possible relationship between trichotillomania and OCD may come from family studies. In a preliminary investigation of psychiatric diagnoses among first-degree relatives of probands with trichotillomania, Lenane et al. (1992) found increased frequencies (compared with normal control subjects) of OCD, as well as mood and anxiety disorders. Bienvenu et al. (2000) examined 300 first-degree relatives of 343 OCD patients, and found increased rates of "grooming" conditions (e.g., nail-biting, skin-picking, trichotillomania), and other ICDs (e.g., kleptomania, pathological gambling, pyromania).

In sum, few data are available to support any particular model of the etiological pathophysiology of trichotillomania. Early studies point to some alteration of brain activity. There is inconsistent support in these studies for a relationship with OCD. Figure 80–2 shows a schematic diagram of a preliminary biopsychosocial model of trichotillomania (Franklin et al. 2006). This model is heuristic, not explanatory, but is hoped to stimulate new studies on the mechanisms of trichotillomania and to be modified as new data emerges.

## Treatment

### Treatment Goals

Treatment of trichotillomania typically occurs in an outpatient setting. Eradication of hair-pulling behavior is the general focus of treatment. Distress, avoidant behaviors, and cosmetic impairment are secondary to the hair-pulling behavior and would be likely to remit if the hair-pulling behavior is controlled. However, if sufficient control of hair pulling cannot be attained, treatment goals should emphasize these associated problems as well. Even if hair pulling persists, therapeutic interventions may be targeted at reducing secondary avoidance and diminishing distress. Treatment may be considered in three phases:

*Initial Contact*: The diagnosis is made and the patient and psychiatrist agree on a strategy that may incorporate both pharmacological and psychological interventions. If distress is severe, supportive interventions should be immediately considered in anticipation of incomplete treatment response or of a delay of weeks to months before interventions may be beneficial.

*Acute Treatment*: Even when treatment of hair-pulling behavior is optimally successful, there may be a delay of several weeks to months before adequate control is attained. So, the acute treatment phase may be prolonged.

*Maintenance*: It is not known how long patients must maintain active treatment interventions to prevent relapse. It should be anticipated that a substantial number of patients require ongoing treatment for an extended time. Pharmacological treatments may need to be maintained for open-ended periods. Behavioral or hypnotic intervention may require periodic "booster shots" to support continuation of benefits.

### Psychiatrist-Patient Relationship

It is important to bear in mind the particular nature of embarrassment that often accompanies this condition. Several factors contribute to feelings of shame for many with trichotillomania. When hair pulling has had its onset in childhood or adolescence, there is often a history of the hair pulling being treated as a family secret. Patients have been frequently castigated by parents or spouses for lack of self-control. There may also be a feeling that the problem is largely cosmetic, causing some individuals to fear they do not have the "right" to utilize health resources for its treatment. This may be manifest as fears of having their problem minimized or of being derided for seeking help. It is helpful for the clinician to share with patients an understanding that the problem pervades their daily life and may result in meaningful distress and functional inhibition.

A variety of treatment approaches have been advocated for trichotillomania. However, there have, as yet, been few controlled studies of the efficacy of any treatment approach. A review of the literature reveals that only eight randomized trials have been conducted thus far, seven of which included a control condition (see below). A number of investigations of the use of antidepressants with specific inhibition of serotonin reuptake (i.e., fluoxetine and clomipramine) have yielded mixed results (Rothbaum et al. 1993, Winchel et al. 1992, Swedo et al. 1989, Stein et al. 1997, Jaspers 1996). A multimodal approach, simultaneously utilizing several complementary treatment options, may turn out to be the most effective approach for most patients.

While a number of treatment options can be currently offered to individuals with trichotillomania, the durability of long-term outcomes is unclear. Keuthen et al. (1998, 2001) followed a group of hair pullers who had "naturalistic" treatment in the community. Treatments were pharmacological, behavioral or both. Among those who had benefits, improvements were often lost over time, and persistent treatment and ongoing treatment was common over the course of several years.

### Stress Management

Before embarking on a course of treatment, the psychiatrist and the patient should first consider the course and severity of the individual's condition. Because early remission may occur in cases of recent onset, mild trichotillomania of short duration does not necessarily require immediate intervention. In particular, if the hair pulling first occurred during a

period of stress, the behavior may spontaneously diminish as the stressful circumstances abate. In such circumstances, therapeutic attention may best be directed toward examining and seeking to diminish the basis for stress. Teaching alternative stress reduction methods may be useful in reducing recent-onset trichotillomania. However, when individuals with trichotillomania present to the psychiatrist, it is often likely to have been a persistent condition and may have been present for many years or decades. Among such patients, stress reduction may also be useful in reducing trichotillomania but complete remission is less likely.

## Somatic Treatments

The literature is generally made up of case studies, with progressively more controlled investigation in recent years. In general, knowledge about trichotillomania treatments is limited by small sample sizes, lack of specificity regarding sample characteristics, nonrandom assignment to treatment, dearth of long-term follow-up data, exclusive reliance on patient self-report measures, and lack of information regarding rates of treatment refusal and dropout.

A variety of medications have been used in the treatment of trichotillomania. In 1989, initial reports demonstrated the apparent benefits of fluoxetine and clomipramine. Clomipramine was found to be superior to desipramine (Swedo et al. 1989). Fluoxetine was reported beneficial in open treatment (Winchel et al. 1992). Although reports for more than 60 patients have subsequently added support for the use of these medications, the two double-blind studies in which fluoxetine has been compared with placebo did not demonstrate any improvement compared to placebo (Christenson et al. 1991b, Streichenwein and Thornby 1995). Fluvoxamine (Stanley et al.1997b), citalopram (Stein et al. 1997), escitalopram (Gadde et al. 2007), and venlafaxine (Ninan et al. 1998) have been reported to be efficacious in open trials. Although more controlled trials of SSRIs are needed, the use of such medications would be a prudent first step if a pharmacological approach has been agreed upon.

Of the six randomized, controlled trials evaluating the efficacy of pharmacotherapy conducted to date, five involved SSRIs. This may reflect the previously prevailing view that trichotillomania is a variant of OCD and thus ought to be responsive to the same pharmacological agents proven successful in for OCD. In sum, results from these controlled studies of SSRIs are equivocal at best, although in view of the small sample sizes more controlled research should be conducted to determine their efficacy (Swedo et al. 1989, 1993, Christenson et al. 1991c, Streichenwein and Thornby 1995, Ninan et al. 2000, van Minnen et al. 2003). Perhaps important differences between OCD and trichotillomania underlie this apparent difference in treatment response. However, several case studies indicated that augmentation of SSRIs with atypical neuroleptics may be beneficial (Epperson et al. 1999, Stein and Hollander 1992), and an open trial suggested that olanzapine may be efficacious as a monotherapy for trichotillomania (Stewart and Nejtek 2003). Interestingly, naltrexone, an opioid antagonist, thought to decrease positive reinforcement, has also been found superior to placebo in reducing trichotillomania symptoms (Christenson et al. 1994).

Although no double-blind discontinuation studies have been conducted in trichotillomania, evidence from open studies suggests that treatment response gained from pharmacotherapy may not be maintained in the long run (Pollard et al. 1991, Iancu et al. 1996). The absence of a single randomized, controlled trial in pediatric trichotillomania limits treatment recommendations for this population.

Initial evidence of improvement is usually first reported by the patient as greater awareness of the inclination to pull hair. This is usually followed by an ability to abort hair-pulling episodes more quickly than in the past. The ability to resist the urge follows. In cases with a good outcome, the inclination to pull diminishes and may eventually disappear. Patients who pull from several sites may find that the rate of improvement varies from site to site.

There have been conflicting reports of early relapse of symptoms in some patients treated with clomipramine or fluoxetine. Although good maintenance of benefit has been reported for some patients 6 months and longer after the initiation of treatment, early relapse after several weeks to months has also been reported. Keuthen et al. (2001) provided long-term data on maintenance of response over time. Following a group of people who had varying forms of treatment (pharmacological and psychological) for several years after an index evaluation, the authors concluded that initial improvement was common, but over time there was an increase in symptom scores and self-esteem scores worsened. This problem needs further exploration in long-term treatment studies. If early relapse turns out to be common, it would distinguish trichotillomania from depression and OCD, in which medication benefits are often well maintained as long as medication is continued. Optimal duration of treatment for well-treated individuals is still unknown. In accord with standards developed for the treatment of other conditions, it would be reasonable to continue medication for at least 6 months before tapering. Reinitiation of treatment may be needed.

In a 16-week open trial, the anticonvusant drug topiramate, which has shown promising results in the treatment of ICDs, significantly decreased the severity of hair pulling in adults with trichotillomania (Lochner et al. 2006). Christenson et al. (1991c) have reported successful treatment with lithium. This observation awaits replication. Because trichotillomania is often accompanied by other manifestations of anxiety—and for many individuals is exacerbated by stressful conditions—attempts at treatment with anxiolytic agents may be useful as well. There are no published reports of such treatments.

Adjunctive treatment with pimozide, a neuroleptic agent, has been advocated for some patients who are refractory to other medications (Stein and Hollander 1992). The potential benefits of neuroleptics have been reported now by several authors (Potenza et al. 1998, Gabriel 2001, Gupta and Gupta 2000, Epperson et al. 1999). Most of these reports describe individuals for whom SSRIs provided insufficient benefits. The addition of atypical neuroleptics much improved their outcomes. The greater margin of safety and tolerability associated with atypical neuroleptics may make this a more viable treatment option, but the potential side effects of atypicals should still be taken into consideration. Van Ameringen et al. (1999) found that eight of nine trichotillomania patients responded to haloperidol. Six previously failed treatment with SSRIs. The possible superiority of neuroleptics prompted these authors to speculate

that trichotillomania may be similar to Tourette's syndrome, which responds preferentially to neuroleptics.

## Psychosocial Treatments

### *Behavioral Treatment*

Various behavioral techniques have been tried (Diefenbach et al. 2000). The most successful technique, habit reversal, is based on designing competitive behaviors that should inhibit the hair-pulling behavior (Azrin and Nunn 1977, Azrin et al. 1980, Rosenbaum and Ayllon 1981). For example, if hair pulling requires raising the arm to the scalp and contracting the muscles of the hand to grasp a hair, the behaviorist may design a behavioral program in which the patient is taught to lower the arm and extend the muscles of the hand. As with most behavioral techniques, these interventions are most successful when the patient is strongly motivated and compliant. Also, the treating psychiatrist should be experienced in the use of such techniques. If necessary, a referral should be made to an experienced individual. Modified behavioral approaches have been described for children and adolescents (Vitulano et al. 1992, Rapp et al. 1998).

In a randomized, controlled trial (Diefenbach et al. 2006), patients completing group behavior therapy ($n = 12$) experienced significantly greater decreases in self-reported hair-pulling symptoms and clinician-rated hair loss severity than those in group supportive therapy ($n = 12$). In addition, a significantly higher percentage of those in the behavior therapy condition were rated as much improved or very much improved on the Clinical Global Impression scale at posttreatment. But, despite substantial symptom improvement, trichotillomania severity remained problematic at posttreatment, few patients in either treatment met criteria for clinically significant change at posttreatment, and relapse of symptoms occurred over the 6-month follow-up period. So these results provided support for the short-term efficacy of group behavior therapy.

### *Cognitive-Behavioral Therapy*

CBT has been developed for, and applied to, trichotillomania patients. A variety of techniques have been used, and although the current CBT literature justifies only cautious recommendations, habit reversal, awareness training, and stimulus control are generally purported as the core efficacious interventions. Successful outcome has been reported on several of these interventions. But, since most of the literature consists of uncontrolled case reports or small case series, confident conclusions cannot be drawn. This is evidenced by the three randomized trials with adults exploring CBT efficacy. Ninan et al. (2000) found CBT superior to clomipramine and placebo at post-treatment; the same pattern was reported by van Minnen et al. (2003) in their randomized, controlled trial of CBT, fluoxetine, and a wait-list condition. Azrin et al. (1980) found that habit reversal was more effective than negative practice, where subjects were told to act out the motions of hair pulling in front of a mirror, without doing any damage, for 30 seconds every hour, and then to maintain the exercises for 4 days after entirely breaking their habit and finally to gradually decrease the exercises over a 2-week time period. The treatment rationale involves the principles of satiation and heightened awareness. The problem of relapse following CBT has been highlighted in several studies (Lerner et al. 1998, Keuthen et al. 2001, Mouton and Stanley 1996). The limited and equivocal treatment literature suggests that there is neither a universal nor a complete response to any treatment for trichotillomania. Controlled studies of the efficacy of CBT treatments involving habit reversal, pharmacotherapy, and their combination are needed.

### *Hypnotherapy*

There are no formal studies of the use of hypnosis for trichotillomania, but there are many published reports of beneficial treatment (Barabasz 1987, Cohen et al. 1999, Fabbri and Dy 1974, Kohen 1996, Rowen 1981, Zalsman et al. 2001). Benefits may be variable. Some patients may have dramatic improvement. For some who improve, the benefits may be short-lived. As with behavioral interventions, the benefits of this approach are sometimes dependent on a highly motivated patient who can regularly carry out self-hypnotic measures as instructed by the psychiatrist. Some patients who have obtained partial benefits from either hypnosis or medication do well when both treatments are combined. Successful use of hypnotherapy for children with trichotillomania has also been reported (Cohen et al. 1999).

### *Dynamic Psychotherapy*

Many psychoanalytically oriented descriptions of people with trichotillomania have been published. These reports generally describe the psychodynamic formulations of individual cases and should not be the basis for generalizations about most individuals with trichotillomania. Although patients with trichotillomania may benefit from exploration and attempts to reduce intrapsychic conflict, the literature does not provide persuasive evidence of the efficacy of this approach in reducing hair pulling.

### *Self-help and Other Groups*

Self-help groups for patients with trichotillomania have appeared. Some are based in the structure of other 12-step programs. Some patients appear to experience meaningful reduction in hair-pulling symptoms after beginning participation in such a group. Although the efficacy of such groups in reducing symptoms remains to be established, most patients with trichotillomania can benefit from meeting other individuals with similar symptoms. Because of the lack of general awareness of trichotillomania, these individuals frequently believe that they are "oddball" individuals with a behavior that is unique. Many have experienced parental condemnation for the behavior and have been frequently castigated for a "habit" that may be viewed by others as under their voluntary control. The experience of meeting others with the condition is extremely supportive for such individuals and may help to reduce the attendant stress while supporting self-esteem. Where programs specifically oriented toward trichotillomania may not be generally available, these individuals may benefit from groups oriented toward OCD.

## Treatment of Comorbid Conditions

Depression, dysthymic disorder, and anxiety symptoms occur frequently in patients with trichotillomania. Successful treatment of depression may not be associated with reduction in trichotillomania. If depression or dysthymic disorder is present and independently provides an indication for medication, one of the antidepressants discussed earlier should be

chosen. If fluoxetine is used, the psychiatrist should be aware that a dose that is sufficient for reduction of the depressive symptoms may not be sufficient for reduction of trichotillomania. If panic disorder is present, either medication may still be used, but fluoxetine may initially exacerbate panic attacks in such patients and initiation of treatment at low doses (2.5–5 mg/day) should be considered. With slow titration upward, the patient should generally be able to tolerate usual doses with concomitant amelioration of the panic disorder. Combined treatment with anxiolytics may be useful for some and may contribute to the reduction in symptoms of trichotillomania. Other conditions that may be present, like OCD or eating disorders, may require special attention. Although fluoxetine may be useful for patients with eating disorders, medication treatment alone is unlikely to be adequate and the usual multimodal approaches for the treatment of bulimia nervosa or anorexia are appropriate. OCD may respond to treatment directed at trichotillomania, but adjunctive behavioral treatment of symptoms of OCD may be desirable.

## Age- and Cultural-Related Features

When trichotillomania presents in early childhood, as discussed earlier, the condition may be likely to be inherently self-limited. Often, all that may be necessary is to draw the child's attention to the behavior in some systematic way and to clarify for the child that the behavior is undesirable. Such methods include daily application of a nonmedicinal ointment to the affected region and reminding the child that the purpose is elimination of the hair-pulling habit. Some suggest that the child be given the responsibility of applying the ointment with parental supervision. Others suggest that parents should monitor the child as much as possible and respond with reminders that the hair should not be pulled and rewards with verbal encouragement for ceasing to pull hair. There have been no systematic studies of the benefits of such interventions, but dermatologists who specialize in the treatment of children have noted that hair-pulling behavior may frequently disappear within a few weeks of initiating such an approach. In circumstances in which childhood trichotillomania is more persistent, the parent and psychiatrist are faced with a dilemma. More elaborate behavioral interventions, such as habit reversal, should be tried. This, however, may be difficult with a child. Rosenbaum and Ayllon (1981) have described a modified version of habit reversal that may be employed with children. Hypnosis has been also used in the treatment of habit disorders in children. Medication should be cautiously considered when treating childhood trichotillomania. Although medication may be useful, the absence of data supporting the benefits of such treatments in children indicates a conservative approach. If medication is considered, its use in the treatment of childhood OCD should serve as a guideline.

Should the psychiatrist be presented with trichotillomania in a person of advanced age, special attention should be paid to usual concerns regarding the use of these medications in the elderly. Lower doses of medication should be considered because of potential altered pharmacokinetics in older persons. Medications with anticholinergic side effects (such as clomipramine) may present greater hazards for the older person. Sedative-hypnotic anxiolytics should be used sparingly because of greater vulnerability to cognitive side effects and the increased risk of falling. Women of childbearing potential (perhaps the majority of people who may present for treatment) should be advised regarding the potential risks of these medications to a developing fetus. If the patient is pregnant or considering pregnancy, behavioral treatments may be favored.

Clinicians should be sensitive to the interaction between cultural values and trichotillomania. Women of some cultures may be more prone to distress if trichotillomania is perceived as a hindrance to achieving valued goals, like marriage. Also, in some communities, wigs and other hair accessories are generally acceptable and may present a comfortable means of diminishing the cosmetic impact of hair loss. In other communities, such accoutrements may themselves draw undesired attention.

## Refractory Response or Nonresponse to Initial Treatment

Because research in the treatment of trichotillomania is still limited, it is not possible to recommend an initial best treatment for all patients. However, the decision is often determined by available resources. Support groups may not be easily found in many areas. Hypnotherapy and behavioral therapy may be more easily available, but psychiatrists with these skills may not be experienced in the specific techniques used in this condition. Pharmacological interventions may be more readily available. Wherever possible, simultaneous multimodal interventions should be considered. Pharmacological, behavioral, and hypnotic interventions, which may each be only partially useful, may be synergistic when used in combination.

If therapy with a single medication is not successful, the psychiatrist may consider augmenting one agent with another. Augmentation strategies in the treatment of trichotillomania have not been studied. General principles of augmentation used in the treatment of depression or OCD may be considered. There may be particular benefit in combining anxiolytic agents (such as buspirone or clonazepam) with an SSRI antidepressant. As noted above, the advent of atypical neuroleptics may offer a new and possibly efficacious treatment option. Despite the increasing safety of these medications, caution should be used in the introduction of a neuroleptic for the treatment of a persistent condition.

Clinical Vignette 4

Mr. G, a 32-year-old podiatrist, began pulling out hairs in his second year of college. He had always been a generally anxious person and thought of it as a nervous habit. Never particularly concerned about his appearance and noting the familial disposition to male pattern hair loss, he felt resigned to eventual baldness and thought little about it. He noted that his hair pulling tended to be worse in a variety of circumstances: before examinations, after a breakup with a girlfriend, while studying, and while watching television. He thought the last circumstance surprising. The others seemed to be situations of understandable stress, but television relaxed him. Indeed, at those times he was hardly aware of it until he would find his hands roaming searchingly through his scalp and would then find a small pile of hairs beside him on the sofa. Occasionally, an acquaintance would comment—with varying degrees of tact—on the ratty appearance of his hair, particularly

above the left temple. Nevertheless, he was still not too oncerned. He did note a progression of the habit until he was pulling from virtually every spot on his body where hair grew, including his perineum.

Despite Mr. G's relative lack of concern, his new wife was not so resigned to the habit. She could not deny the mild revulsion she felt when she saw the range of locations from which he pulled hair. (In the beginning of their courtship, she was aware of only the thinned scalp.) She insisted that he go to a psychiatrist.

Mr. G's new psychiatrist tried a variety of interventions. Noting Mr. G's general anxiety, the psychiatrist instructed him in relaxation techniques, while exploring with him the sources of stress in his life. This was not too helpful. They then embarked on a course of medication trials, including three different SSRIs. There was encouraging improvement at first, but a partial relapse occurred and the benefits were limited. The psychiatrist then heard about a local therapist who led a group therapy for people with trichotillomania and also practiced hypnotic techniques for the problem. With some hesitancy, Mr. G joined the group. He was initially uncomfortable, being the only man in the group, and he did not identify with many of the concerns expressed by the women. But he settled in, became an active participant, and was surprised to find that his hair-pulling diminished further. He found that he was pulling from fewer sites and was able to abort hair-pulling episodes more quickly. Fortified by the partial successes and encouraged by the other group members, he went to a behavioral psychologist, who used a technique called habit reversal to supply him with a repertoire of skills he could employ to control urges to pull his hair. Finally, with this multimodal approach (medication, hypnosis, and group and behavioral therapy) his hair pulling virtually disappeared. He had occasional relapses when under significant stress, but by and large he was relieved of his symptom. He and his wife thought the substantial efforts he had made to rid himself of the problem were worthwhile.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

The ICD-10 Diagnostic Criteria for Research do not include diagnostic criteria for IED. It is included in ICD-10 as an "other habit and Impulse-Control Disorder." The ICD-10 Diagnostic Criteria for Research and the DSM-IV-TR criteria for kleptomania, pyromania, and trichotillomania are essentially equivalent. Finally, the ICD-10 Diagnostic Criteria for Research for pathological gambling are monothetic (i.e., A plus B plus C plus D are required) whereas the DSM-IV-TR criteria set is polythetic (i.e., 5 out of 10 required) with different items. Furthermore, the ICD-10 criteria specify "two or more episodes of gambling over a period of at least 1 year," whereas DSM-IV-TR does not specify a duration.

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CHAPTER

# 81 Adjustment Disorders

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## Adjustment Disorders

### Definition

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) states that the essential feature of AD is the development of clinically significant emotional or behavioral symptoms in response to an identifiable psychosocial stressor (American Psychiatric Association 2000). The symptoms must develop within 3 months after the onset of the stressor (criterion A). The clinical significance of the reaction is indicated either by marked distress that is in excess of what would be expected given the nature of the stressor or by significant impairment in social or occupational (academic) functioning (criterion B). This disorder should not be used if the emotional and cognitive disturbances meet the criteria for *another* specific Axis I disorder (e.g., a specific anxiety or mood disorder) or are merely an exacerbation of a preexisting Axis I or Axis II disorder (criterion C). AD may be diagnosed if other Axis I or II disorders are present, but do not account for the pattern of symptoms that have occurred in response to the stressor. The diagnosis of AD does not apply when the symptoms represent bereavement (criterion D). By definition, AD must resolve within 6 months of termination of the stressor or its consequences (criterion E). However, the symptoms may persist for a prolonged period (i.e., longer than 6 months) if they occur in response to a chronic stressor (e.g., a chronic, disabling general medical condition) or to a stressor that has enduring consequences (e.g., the financial and emotional difficulties resulting from a divorce) (American Psychiatric Association 2000).

Although the above definition provides a certain structure for identifying and describing AD, there is still uncertainty as to when the impairment in functioning or the severity of the psychiatric symptoms that develop in response to a stressor are sufficient to warrant a diagnosis of AD. The DSM-IV-TR describes the boundary issues between conditions that may be a focus of clinical attention (V codes), *subthreshold* disorders [not otherwise specified (NOS) disorders], and the specific mental disorders (American Psychiatric Association 2000). A compelling literature documents that there is much "physical" in mental disorders and much "mental" in physical disorders (p. xxx). No definition adequately specifies precise boundaries for the concept of a "mental disorder." "The concept… lacks a consistent operational definition that covers all situations. …Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual" (p. xxxi). The issue of defining boundaries is especially problematic in the *subthreshold* diagnoses, for example, the AD, in which there are no symptom checklists, algorithms, or guidelines for the "quantification of attributes" (p. xxxii).

AD is *a subthreshold* diagnosis, which has undergone a major evolution since the original Diagnostic and Statistical Manual of the American Psychiatric Association 1952.

The symptoms of AD are defined in terms of their being a maladaptive response to a psychosocial stressor. There are, in fact, no specific symptoms of AD. The nature of the symptomatology is described by a variety of possible "subtypes" (Appendix 1). Mezzich et al. (1981) and Strain (1981) observed that many of the subtypes of AD were infrequently employed (e.g., "with mixed emotional features"), whereas "with physical complaints," a DSM-III-R category had insufficient time to be observed (American Psychiatric Association 1987). Both were deleted in DSM-IV-TR.

The lack of specific symptoms or quantifiable criteria of the AD permits the labeling of early or temporary mental states when the clinical picture is vague, and it does not meet full evidence for a specific mental disorder, but the morbid state is more than expected in a normal reaction, and treatment or an intervention may be indicated. ADs are an essential "linchpin" in the psychiatric–taxonomic spectrum-hierarchy: (1) disorders with specific diagnostic criteria; (2) disorders NOS; (3) ADs; (4) other conditions that may be a focus of clinical attention (V codes) (American Psychiatric Association 2000); and (5) normal fluctuations of mental states. Demoralization has been suggested as another V-code

*Psychiatry, Third Edition.* Edited by Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First and Mario Maj.
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category and should be distinguished from AD and other pathological conditions (Slavney 1999). Understandably, the ADs are a diagnostic group with a significant evolution since 1952 (Table 81–1). As the diagnosis of AD has evolved, the recognition of other stress-related disorders, for example, posttraumatic stress disorder (PTSD) has occurred. A new acute stress disorder diagnosis—those stress reactions that follow a disaster or cataclysmic personal event (e.g., acute stress disorder) (Spiegel 1994)—was introduced into DSM-IV-TR.

Disorders that do not fulfill the criteria for a specific mental disorder may be accorded a lesser interest by mental health care workers, research institutes, and third-party payers, even though they present with serious (or incipient) symptoms that require intervention or treatment. Given this

**DSM-IV-TR Criteria**

**Adjustment Disorders**

A. The development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).

B. These symptoms or behaviors are clinically significant as evidenced by either of the following:

(1) marked distress that is in excess of what would be expected from exposure to the stressor

(2) significant impairment in social or occupational (academic) functioning

C. The stress-related disturbance does not meet the criteria for another specific Axis I disorder and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

D. The symptoms do not represent bereavement.

E. Once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months.

*Specify* if:
**Acute**: if the disturbance lasts less than 6 months
**Chronic**: if the disturbance lasts for 6 months or longer
Adjustment disorders are coded based on the subtype, which is selected according to the predominant symptoms. The specific stressor(s) can be specified on Axis IV.

**309.0 With depressed mood**
**309.24 With anxiety**
**309.28 With mixed anxiety and depressed mood**
**309.3 With disturbance of conduct**
**309.4 With mixed disturbance of emotions and conduct**
**309.9 Unspecified**

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**Table 81–1 Diagnostic Categories of Adjustment Disorders**

| DSM-I (1952) Transient Situational Personality Disorder |
|---|
| Gross stress reactions |
| Adult situational reaction |
| Adjustment reaction of infancy |
| Adjustment reaction of childhood |
| Adjustment reaction of adolescence |
| Adjustment reaction of late life |
| Other transient situational personality disturbance |

| DSM-II (1968) Transient Situational Disturbance |
|---|
| Adjustment reaction of infancy |
| Adjustment reaction of childhood |
| Adjustment reaction of adolescence |
| Adjustment reaction of adult life |
| Adjustment reaction of late life |

| DSM-III (1980) Adjustment Disorder |
|---|
| Adjustment disorder with depressed mood |
| Adjustment disorder with anxious mood |
| Adjustment disorder with mixed emotional features |
| Adjustment disorder with disturbance of conduct |
| Adjustment disorder with mixed disturbance of emotions and conduct |
| Adjustment disorder with work (or academic) inhibition |
| Adjustment disorder with withdrawal |
| Adjustment disorder with atypical features |

| DSM-III-R (1987) Adjustment Disorder |
|---|
| Adjustment disorder with depressed mood |
| Adjustment disorder with anxious mood |
| Adjustment disorder with mixed emotional features |
| Adjustment disorder with disturbance of conduct |
| Adjustment disorder with mixed disturbance of emotions and conduct |
| Adjustment disorder with work (or academic) inhibition |
| Adjustment disorder with withdrawal |
| Adjustment disorder with physical complaints |
| Adjustment disorder not otherwise specified (NOS) |

| DSM-IV-TR (1994) Adjustment Disorder |
|---|
| Adjustment disorder with depressed mood |
| Adjustment disorder with anxiety |
| Adjustment disorder with mixed anxiety and depressed mood |
| Adjustment disorder with disturbance of conduct |
| Adjustment disorder with mixed disturbance of emotions and conduct |
| Adjustment disorder unspecified |
| **Acute:** This specifier can be used to indicate persistence of symptoms for less than 6 mo. |
| **Chronic:** This specifier can be used to indicate persistence of symptoms for 6 mo or longer. By definition, symptoms cannot persist for more than 6 mo after the termination of the stressor or its consequences. The chronic specifier therefore applies when the duration of the disturbance is longer than 6 mo in response to a chronic stressor or a stressor that has enduring consequences. |

concept, the ADs are formulated as a means of classifying psychiatric morbidity that is clinically significant; when the symptom profile is as yet insufficient to meet the more specifically operationalized criteria for another mental disorder; when the symptoms, disturbance of mood, and vocational or interpersonal dysfunction are in excess of a normal reaction to the stressors in question; and for which treatment is indicated. For example, a diagnosis of AD is not given when the clinical picture is a psychosocial problem (V code) requiring clinical attention, such as noncompliance, phase of life problem, bereavement, or occupational (academic) problem. Their etiological and dynamic attributes make the AD a fascinating group of disorders that serve as a fulcrum between normality and more specific mental disorders (Figure 81–1).

Attention to less severe mental symptoms (and psychiatric morbidity) may forestall the evolution to more serious disorders and allow remediation before relationships, work, and functioning are so impaired that they are disrupted or permanently sundered. Yet, in the gray area in which early diagnosis may have enormous value with modest therapeutic investment, guidelines are the most tenuous. It is the professionals at the "front door"—primary care physicians, triage personnel, emergency department staff, walk-in clinic staff—who need assistance in making this difficult call: Is there sufficient psychiatric morbidity to warrant mental health intervention?

Problems with the use of the AD diagnosis in clinical practice were highlighted in a survey of child and adolescent psychiatrists. Of those who responded, 55% indicated that they used AD to avoid the stigmatization of patients (in this case children and youth). More of those who favored the use of this category were psychodynamically oriented, not formally trained in the DSM-III-R, and not inclined to use NOS categories (American Psychiatric Association 1987, Setterberg et al. 1991). More than half of these psychiatrists did not consider the temporal onset criterion or the exclusionary criteria in applying this diagnosis. The survey results suggested that some psychiatrists, in part to protect their patients from the feared adversities of major psychiatric nomenclature, use the AD diagnosis excessively and incorrectly. Interestingly, the less stigmatizing nature of the mcondition when evaluating patients' risks (Katzman and Tamori 2005).

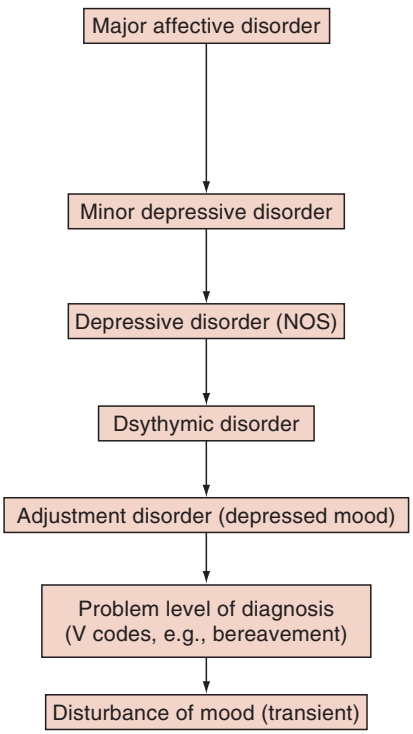



**Figure 81–1** *Descending order of depressive states, from most serious to least depressed mood, as a state of being for an occurrence of the moment.*

It is equally likely that the lack of specificity characterizing the AD diagnoses, make it difficult to truly separate them from other psychiatric syndromes. In a recent study, Casey et al. (2006) examined variables that might distinguish AD from other depressive episodes. The patients were screened for depression severity with the Beck Depression Inventory (BDI) and then interviewed with the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) which includes questions assessing the presence of AD. The authors were unable to find any independent variables that distinguished AD from other depressive episodes, including the severity of the BDI score at the outset.

Because AD is a nonpejorative psychiatric condition (Kovacs et al. 1993), it may also be overdiagnosed in youths (Kovacs et al. 1994). Andreasen and Wasek (1980) observed that 25% of a sample of adolescents with AD had attempted suicide and that 17% probably "would have met DSM-III criteria for major depressive disorder" because they had the required symptoms. Kovacs et al. (1993) stated, "Suicide attempts among clinically referred youths occur mostly in the context of specific psychiatric disorders, including major depressive and dysthymic disorders, and rarely in the context of AD, further suggesting that AD may have been incorrectly diagnosed in some cases." Reports that 5–12% of young inpatients with psychiatric disorders have been assigned a diagnosis of AD also raise the possibility of mislabeling (Andreasen and Wasek 1980, Faulstich et al. 1986). Nevertheless, in psychological autopsy studies of adolescent suicide completers, approximately 20% do not meet the criteria for any single psychiatric diagnosis, although they present with significant functional impairment and life-threatening behavior.

The problem of how to diagnose individuals with suicidal behavior who do *not* meet the criteria for a specific mental disorder has received considerable recent attention. De Leo et al. (1986aa, 1986bb) reported on the association of AD and suicidality. Runeson et al. (1996) observed from psychological autopsy methods that there was a very short median interval between first suicidal communication and suicide in AD (less than 1 month) compared to major depressive disorder (3 months), borderline personality disorder (30 months), or schizophrenia (47 months).

Recent life events, which would constitute an acute stress, were commonly found to correlate with suicidal behavior in a group that included those with AD (Isometsa et al. 1996). Spalletta et al. (1996) observed that assessment of suicidal behavior to be an important tool in differentiating major depressive disorder, dysthymic disorder, and AD. Furthermore, AD patients were observed to be among the most common recipients of a deliberate self-harm (DSH) diagnosis, with the majority involving self-poisoning (Vlachos et al. 1994). Thus, DSH with all its variants, for

example, reckless driving, is more common in AD patients (Vlachos et al. 1994), whereas the percentage of completed suicidal behavior per se was found to be higher in depressed patients (Spalletta et al. 1996). Of note, biological findings in suicidal patients with AD suggest characteristic patterns of monoamine oxidase (MAO) and noradrenaline turnover (Tripodianakis et al. 2000). Clearly, what is regarded, as a subthreshold diagnosis—AD—does not necessarily imply the presence of subthreshold symptomatology.

## Epidemiology

AD has principally been studied in clinical samples. Epidemiological data in adults are not available. The AD diagnosis was not included in the Epidemiologic Catchment Area Study conducted in five disparate sites throughout the United States, and there are only a few studies in children and adolescents. Andreasen and Wasek (1980) reported that 5% of an inpatient and outpatient sample were labeled AD. Fabrega et al. (1987) observed that 2.3% of a sample of patients presenting to a walk-in diagnostic and evaluation center clinic met criteria for AD with no other Axis I or Axis II diagnoses. When patients with other Axis I diagnoses (Axis I comorbidities) were also included, 20% had the diagnosis of AD. In a sample of more than 11,000 patients (all ages) 10% were found to have AD (Table 81–2), making it the second largest diagnostic category (Fabrega et al. 1986, 1987, Mezzich et al. 1989). In the Pittsburgh sample studied, 16% of the children and adolescents younger than 18 years were diagnosed with AD (Fabrega et al. 1986). In adults, women predominated over men by approximately 2:1. The sex ratio was more equal in children and adolescents, although there was still a slight excess of female patients.

Prevalence estimates of AD in other clinical populations have been characterized by considerable variability (see Table 81–2). In general, hospital inpatient and psychiatric consultation populations, AD was diagnosed in 21.5% and 11.5%, respectively (Popkin et al. 1988, Snyder and Strain 1990). Strain et al. (1998b) examined the consultation–liaison data from seven university teaching hospitals in the United States, Canada, and Australia. The sites had all used a common clinical database to examine 1,039 consecutive referrals. AD was diagnosed in 125 patients (12.0%); as the sole diagnosis in 81 (7.8%); and comorbidly with other Axis I and II diagnoses in 44 (4.2%) (Strain et al. 1998a). It had been considered as a "rule-out" diagnosis in an additional 110 (10.6%). AD with depressed mood, anxious mood, or mixed emotions were the most common subcategories used. AD was diagnosed comorbidly most frequently with personality disorder and organic mental disorder. Sixty-seven patients (6.4%) were assigned a V-code diagnosis only. Patients with AD compared to other diagnostic categories were referred significantly more often for problems of anxiety, coping, and depression; had less past psychiatric illness; and were rated as functioning better—all consistent with the construct of AD as a maladaptation to a psychosocial stressor. Interventions employed for this general hospital inpatient cohort were similar to those for other Axis I and II diagnoses, in particular, the prescription of antidepressant medications. Patients with AD required a similar amount of clinical time and resident supervision.

Oxman et al. (1994) observed that 50.7% of elderly patients (aged 55+ years) receiving elective surgery for coronary artery disease developed AD related to the stress of surgery. Thirty percent had symptomatic and functional impairment 6 months following surgery. It is reported that 27% of elderly patients examined 5–9 days following a cerebral vascular accident had symptoms that fulfilled the criteria for AD (Kellermann et al. 1999). Spiegel (1996) observed that half of all cancer patients have a psychiatric disorder, usually an AD with depression. Since patients treated for their mental states had longer survival time, treatment of depression in cancer patients should be considered integral to their medical treatment. AD is a frequently made diagnosis in patients with head and neck surgery (16.8%) (Kugaya et al. 2000), patients with HIV dementia (73%) (Pozzi et al. 1999), cancer patients from a multicenter survey of consultation–liaison psychiatry in oncology (27%) (Grassi et al. 2000), dermatology patients (29% of the 9% who had psychiatric diagnosis) (Pulimood et al. 1996), and

**Table 81–2 Prevalence of Adjustment Disorder**

| Study | Sample Type | Sample Size | Assessment Method | Prevalence |
|---|---|---|---|---|
| Bird et al. (1988) | Epidemiological, general population | Probability estimate of 2,036 households | Structured rating scales; clinical interview | 7.6% (CGAS* < Ld70) 4.2% (CGAS < Ld60) |
| Weiner and Del Gaudio (1976) | Epidemiological, clinical services | 1,344 | Clinical diagnosis | 27% of all cases |
| Mezzich et al. (1989) | Clinical screening evaluation (all services) | 11,282 | Semistructured assessment instrument | 10% (all ages) 16% (< Ld18 yr) |
| Faulstich et al. (1986) | Clinical (adolescent inpatient) | 392 | Chart review, clinical diagnosis | 12.5% |
| Hillard et al. (1987) | Clinical (emergency room department) | 100 adolescents 100 adults (random) | Chart review, clinical diagnosis | 42% of adolescents 13% of adults |
| Doan and Petti (1989) | Clinical (partial hospital) | 796 | Chart review, clinical diagnosis | 7% |
| Jacobson et al. (1980) | Clinical (four outpatient pediatric clinics) | 20,000 pediatric patients | Clinical diagnosis | 25–65% of cases with psychiatric diagnosis |

*CGAS, Children's Global Assessment Scale.

suicide attempters (22%) examined in an emergency room (Schnyder and Valach 1997). Other studies include diagnosis of AD in more than 60% of inpatients being treated for severe burns (Perez-Jimenzez et al. 1994), 20% of patients in early stages of multiple sclerosis (Sullivan et al. 1995), and 40% of poststroke patients (Shima et al. 1994).

In a study of emergency department visits, it was reported that 13% of adults and 42% of adolescents were diagnosed with AD (Hillard et al. 1987). Among adolescents in that study, AD was twice as common as any other diagnosis, including substance abuse. Faulstich et al. (1986) reported the prevalence of DSM-III conduct disorder and AD for adolescent psychiatric inpatients. Mezzich et al. (1981) and Fabrega et al. (1987) evaluated walk-in clinic patients (mainly adults) for the current presence of 64 symptoms in three diagnostic cohorts: (1) specific diagnoses, (2) AD, and (3) "not ill." Vegetative, substance use or abuse, and characterological symptoms were greatest in specific diagnoses, intermediate with the AD, and least in the "not ill." The symptoms of mood and affect, general appearance, behavior, disturbance in speech and thought pattern, and cognitive functioning had a similar distribution (specific diagnosis > AD > "not ill"). The patients with AD were significantly different from the "not ill" group with regard to more "depressed mood" and "low self-esteem" ($P < 0.0001$). The patients with AD and the "not ill" group had minimal disturbance of thought content and perception. Twenty-nine percent of the patients with AD versus 9.0% of the "not ill" patients had a positive response on the suicide indicators. The three cohorts did not differ on the kinds or amounts of general medical conditions.

Andreasen and Wasek (1980), using a chart review, reported that more inpatient adolescents experienced acting-out and behavioral symptoms than adults who were observed to have significant depressive symptoms (87.2% and 63.8%, respectively). Anxiety symptoms were frequent at all ages. They also observed that in their AD cohorts, 21.6% of the adolescents and 11.8% of the adults' fathers had problems with alcohol.

There are two published epidemiological studies in populations of children and adolescents that included AD. One, conducted in Puerto Rico, employed a two-stage screening process using standardized rating scales as well as structured and unstructured clinical interviews (Bird et al. 1988, 1989). The prevalence rate of AD was determined to be 7.6% if an upper limit of 70 on the Children's Global Assessment Scale (CGAS) is applied (Shaffer et al. 1983). However, if an upper limit of 60 is imposed (corresponding to "moderate" impairment on the CGAS), the prevalence of AD dropped to 4.2%. This indicates that up to 40% of AD diagnosed patients have only mild impairment, more than for any other diagnosis. A recent study conducted in a very large birth registry in Finland found that AD with mixed disturbance of emotions and conduct was the most frequent AD diagnosis, and occurred in 3.4% of the population at the time of the assessment (Almquist et al. 1999). Other studies conducted in pediatric patients who presented with psychiatric disturbance from four different clinics indicated rates of AD across the clinics ranging from 25 to 65% (Jacobson et al. 1980). The prevalence of AD in children and adolescents may be somewhat higher than it is in adults, but varies considerably according to the population studied.

The relationship between family functioning and AD was evaluated by administering the Family Assessment Devise (FAD) to families who had a member with one of seven mental disorders: schizophrenia, bipolar disorder, major depression, anxiety disorder, eating disorder, substance abuse, and AD (Friedmann et al. 1997). Regardless of which specific psychiatric diagnosis was present in the family member, having a family member in an acute phase of any of these psychiatric disorders—even a subthreshold diagnosis such as AD, was a risk factor for poor family functioning. AD in a family member was a significant family stressor.

## Etiology

By definition, the ADs are stress-related phenomena in which a psychosocial stressor results in the development of maladaptive states and psychiatric symptoms. The condition is presumed to be time limited, that is, a transitory reaction; symptoms recede when the stressor is removed or a new state of adaptation is defined. There are also other stress-related disorders in DSM-IV-TR, such as PTSD and acute stress disorder those stress reactions that follow a disaster or cataclysmic personal event (American Psychiatric Association 2000). These stress disorders are among the few conditions in DSM-IV-TR, along with substance-induced disorders and mental disorders due to a general medical condition, with a *known cause* and for which the etiological agent is *essential* to establishing the diagnosis. For the most part, the DSM-IV-TR is relatively atheoretical with regard to etiology and is instead phenomenologically driven in its definitions of disorders (Feighner et al. 1972). However, the DSM-IV-TR stress-induced disorders, including the AD, require the diagnostician to impute etiological significance to a life event—a stressor—and relate its effect in clinical terms to the patient, his/her symptoms, and his/her behavior.

That the relationship between stress and the occurrence of a psychiatric disorder is both complex and uncertain has caused many to question the theoretical basis of AD (Holmes and Rahe 1967, Rutter 1981, Weiner and Del Gaudio 1976). The linear model of stress–disease interaction, which serves as the model for AD has been questioned (Paykel et al. 1971, Woolston 1988). The linear model presupposes that a direct and clearly identifiable pathological reaction may follow a stressful event, a scenario that no doubt occurs in some individuals with AD but may not accurately characterize others. For example, there may be multiple stressors, insidious or chronic, as opposed to discrete events. Furthermore, relatively minor precipitating events may generate a disturbance in an individual who has previously been sensitized to stress.

Several authors have criticized the stressor criterion in AD because stressors are difficult to specify and measure, and their clinical implications and impact are uncertain (Fabrega and Mezzich 1987). Questions pertain to whether patients with AD are unusually sensitive to psychosocial events not likely to cause disturbance in others. Are there individuals who have been exposed to high levels of stress, the severity or accumulation of which would probably produce negative consequences in most people?

Diverse variables and modifiers are involved in the presentation of AD after exposure to a stress. Cohen (1981) argued that acute stresses are different from chronic ones in both psychological and physiological terms; that the meaning

of the stress is affected by "modifiers"—ego strengths, support systems, prior mastery—and that one must differentiate manifest and latent meaning of the stressors (e.g., loss of a job may be a relief or a catastrophe). An objectively overwhelming stress could have little impact on one individual, whereas another individual could regard a minor one as cataclysmic. A recent minor stress superimposed on a previous underlying (major) stress (which had no observable effect on its own) may have a significant impact, not operating independently but by its additive effect—the concatenation of events (Hamburg, personal communication).

Proper use of the AD diagnosis also requires a careful understanding of the timing of the stressor and the subsequent emotional or behavioral symptoms; by definition, this must occur within 3 months of the stressor. Until DSM-IV-TR, a time limit was also imposed regarding how long after the occurrence of the stressor this diagnosis could be employed. Before DSM-IV-TR, AD was a "transitory" diagnosis that, by definition, could not exceed 6 months; after 6 months, the diagnosis had to be changed to another psychiatric disorder. However, there are limited data with regard to the timing of symptoms following the occurrence of the stressor. Depue and Monroe (1986) and Rahe (1990) stated that the model of a single stressor impinging on an undisturbed individual to cause symptoms at a single point in time is insufficient to account for the many presentations of stress and illness in the clinical situation. Holmes and Rahe (1967) assigned relative values to specific stressors. Other life events scales have also been shown to be inconsistent in their ability to link stress and illness (Dohrenwend et al. 1978, Paykel et al. 1971, Tennant 1983). Depue and Monroe (1986) and Skodol et al. (1990) identified significant methodological problems in evaluating the quality, quantity, and timing of both stressors and symptoms. It was difficult to establish interrater reliability with regard to these three entities of a stressor. With regard to another attempt to assess and document stress in a multiaxial diagnostic schema, Axis IV of DSM-III, and DSM-III-R, was designed to allow the mental health worker to quantify the stress as a diagnostic attribute. Unfortunately, this measure was confounded by low reliability (Rey et al. 1988, Spitzer and Forman 1979, Zimmerman et al. 1987). As a result, the DSM-IV-TR Axis IV is now a qualitative list of psychosocial–circumstantial problems.

Andreasen and Wasek (1980) described the differences between the types of stressors found in adolescents and those of adults; respectively, 59 and 35% of the precipitants had been present for a year or more, and 9 and 39% for 3 months or less. Fabrega et al. (1987) reported that their group of patients with AD described stressors compared with the other cohorts: "specific psychiatric diagnoses" and "patients not ill." There was a significant difference in the amount of stressors reported relevant to the clinical request for evaluation; the group with AD, compared with the "specific diagnoses" and "not ill" patients, were overrepresented in the "higher stress" categories. Popkin et al. (1988) reported that in their general hospital inpatient consultation cohort, 68.6% of the patients were judged to have their medical illness as the primary psychosocial stressor. Snyder and Strain (1990) observed that the assessment of stressors on Axis IV was significantly more severe ($P = 0.0001$) for inpatient psychiatric consultation patients with AD compared with patients with other diagnostic disorders.

## Diagnosis and Differential Diagnosis

Each of the diagnostic constructs required for the diagnosis of AD is difficult to assess and measure: (1) the stressor, (2) the maladaptive reaction to the stressor, and (3) the time and relationship between the stressor and the psychological response. None of these three components has been operationalized for a diagnostic decision tree, which consequently plagues the AD diagnosis with limited reliability.

In contrast to other DSM-IV-TR disorders, the diagnostic criteria for AD include no clear and specific symptoms (or checklist) that collectively compose a psychiatric (medical) syndrome or disorder.

First, with regard to the maladaptive reaction, it is unclear how this concept can or should be operationalized. The social, vocational, and relationship dysfunctions, which are unspecified qualitatively or quantitatively, do not lend themselves to reliable or to valid assessment. The elements of culture (i.e., the expectable reactions within a specific cultural environment), differences in gender responses, developmental level differences, and differences in the "meaning" of events and reactions to them by a specific individual further confound it. Powell and McCone (2004) make this point in their case report of the treatment of a patient with AD secondary to the September 11th terrorist attacks. Since there has never before been a large-scale terrorist attack in America, how are clinicians to know what a "normal" response to such an event would be?

The concepts of "average expectable environment" (e.g., the expectation of adequate food in a household in an industrial society) and "patient's explanatory belief model" are examples of an attempt to weigh cultural and subjective differences in the assessment of an individual's mental state and reaction (Hartmann 1986, Klineman 1980). Such individual cultural–social considerations often require an understanding on the part of the psychiatrist and thereby often render the assessment of whether a reaction is excessive or maladaptive a judgment call.

Mixed anxiety–depressive disorder is another subthreshold diagnosis that is included as an unofficial category in the appendix of research criteria needing further study in DSM-IV-TR. This research category is similar to AD with mixed anxiety and depression that does not meet criteria for a specific mood or anxiety disorder, thus making it difficult to draw a boundary between the two disorders except that there is less emphasis on a stressor as a precipitating cause in the non-AD category. Furthermore, using the DSM-III-R definition of AD which limited the duration to 6 months, the main difference between the two diagnoses was the chronicity of the mixed anxiety–depressive disorder, as was noted in the mixed anxiety–depression field trial (Zinbarg et al. 1994). Now, with the change in criterion C for AD allowing for chronic forms of AD, the problem of differentiating the two subthreshold diagnoses remains difficult. This uncertainty is further complicated by the question of treatment. Is this an anxiety accompanied by depression that should be treated with anxiolytics, such as benzodiazepines or is this a depression accompanied by anxiety that should be treated with an antidepressant, such as a selective serotonin reuptake inhibitor (SSRI)?

The criterion and predictive validity of the diagnosis of AD in 92 children who had new onset insulin-dependent diabetes mellitus were examined (Kovacs et al. 1995). DSM-III

criteria were employed plus requiring four clinically significant signs or symptoms, and the time frame extended to 6 months (instead of the 3 months specified in the definition) after the diagnosis of diabetes. Thirty-three percent of the cohort developed AD (mean 29 days after the medical diagnosis) and the average episode length was 3 months with a recovery rate of 100%. The five-year cumulative probability of a new psychiatric disorder was 0.48 in comparison to 0.16 for the non-AD subjects. The findings support the criterion validity of the AD diagnosis using the criterion of predicting the future development of a psychiatric disorder.

## Maladaptation

Although the diagnosis of AD requires evidence of maladaptation, it is notable that no specific requirement for functional impairment has been included (e.g., there is no requirement for a certain decrement in the Global Assessment of Functioning Scale score in order to make the diagnosis). Fabrega et al. (1986) stated that both subjective symptoms and decrement in social function can be considered maladaptive and that the severity of either of these is subject to great individual variation. However, they could not conclude that the level of severity of psychiatric illness observed correlates with impaired functioning in three areas: occupational status, family, or with other individuals.

The psychiatrist needs to examine the patient's behavior to see whether it is beyond what is expected in a particular situation, and for that patient. In order to do this, the psychiatrist needs to take into account the patient's cultural beliefs and practices, his or her developmental age, and the transient nature of the behavior. If the behavior lasts a few moments or is an impulsive outburst, it would not qualify for a maladaptive response to justify the diagnosis of AD. The behavior in question should be maladaptive for that patient, in his/her culture, and sufficiently persistent to qualify for the maladaptation requirement for the AD diagnosis.

## Stresses

No criteria or guidelines are offered in DSM-IV-TR to quantify the degree of stress required for the diagnosis of AD or assess its effect or meaning for a particular individual at a given time. Many of the statements regarding the problem of assessing maladaptation described above apply equally well to the assessment of stressors (Woolston 1988, Zilberg et al. 1982). Mezzich et al. (1981) attempted to classify and quantify the psychosocial stressors in 13 domains (i.e., health, bereavement, love and marriage, parental, family stressors for children and adolescents, other familial relationships, work, school, financial, legal, housing, and miscellaneous). The measurement of the severity of the stressor and its temporal and causal relationship to demonstrable symptoms are often unclear.

According to DSM-IV-TR, even if a specific and presumably causal stressor is identified, if enough symptoms develop so that diagnostic criteria are met for a specific disorder, then that diagnosis should be employed instead of a diagnosis of AD (American Psychiatric Association 1980, 1987, 2000). Therefore, the presence of stressors does not automatically signify a diagnosis of AD, and conversely, a diagnosis of a specific disorder (e.g., major depressive or anxiety disorder) does not imply the absence of concomitant or concurrent stressful events (Setterberg et al. 1991).

The modifications introduced in DSM-IV-TR, which differentiate between acute and chronic forms of AD, solved the problem of a 6-month limitation in DSM-III-R's criteria. This change was validated by Despland et al. (1995), who observed that 16% of patients with AD required treatment for longer than 1 year, with the mean length exceeding the prior limitation of 6 months.

## Assessment of the Subtypes of Adjustment Disorder, Comorbidity, and Diagnostic Boundaries

The diagnostic criteria for AD define the contextual and temporal characteristics of a subthreshold response to a psychosocial stressor; while the specific quality and nature of the resultant psychological morbidity have been used as a means of subtyping.

DSM-IV-TR identifies six AD subtypes; two of the subtypes define discrete disturbances of mood (e.g., depressed, anxious); two describe mixed clinical presentations (e.g., mixed emotional features, mixed disturbance of emotions and conduct); one specifies disturbance of conduct; and the final subtype, unspecified, is a residual category.

Significant occurrence of comorbidity has been reported in studies of AD using structured diagnostic instruments. In a cohort of children, adolescents, and adults, approximately 70% of AD patients had at least one additional Axis I diagnosis (Fabrega et al. 1987). In the study of correlates of depressive disorders in children, 45% of those with AD with depressed mood had another disorder (Kovacs et al. 1984). However, comorbidity in AD was less than in dysthymic disorder or major depressive disorder, suggesting a "purer" or more encapsulated disturbance in AD.

Several studies reported an association of suicidal behavior in adolescents and young adults with AD. One study found that 56% of those hospitalized for suicidal behavior in an urban hospital setting met the DSM-II criteria for transient situational disturbance (an earlier diagnostic label for what came to be called AD) (Minnaar et al. 1980). A retrospective review of 325 consecutive hospital admissions for deliberate self-poisoning revealed that 58% of all cases met criteria for AD with depressed mood, the majority of whom were female patients aged 15–24 years (McGrath 1989). In a Scandinavian sample of 58 consecutive suicide victims aged 15–29 years, 14% were classified as AD with depressed mood (Runeson 1989); in a US population, 9% of suicide victims aged 10–29 years were reported to have AD (Fowler et al. 1986). These studies underscore the seriousness of AD in a subset of individuals and suggest that although the diagnosis may be *subthreshold*, its morbidity can be serious and at times even fatal.

The issue of boundaries between the specific mood and anxiety disorders, depressive disorder or anxiety disorder NOS, and the AD remains problematic. The specific mood and anxiety disorders are often associated with and, even precipitated by stress. Therefore, it is not always possible to say one group of diagnoses is accompanied by stress (the AD) and another (e.g., major depressive disorder) is not. Stress may accompany many of the psychiatric diagnoses, but it is not an essential etiological component required to make certain diagnoses (e.g., major depressive disorder).

More research is needed to carefully demarcate the boundaries among the problem-level, subthreshold, and

threshold disorders, in particular with regard to whether stressors are etiological precipitants, concomitants, or factors essentially unrelated to the occurrence of a particular psychiatric diagnosis. Furthermore, serial and ongoing observation of the clinical course is required to ascertain whether the AD is a transitory remitting event, the prodromal state of a more serious and developing disorder, or an intermittent chronic state of a low-level mood disorder. There is considerable evidence indicating that major depressive disorder is a highly recurrent, often chronic condition that is frequently associated with low-grade symptoms prior to, and between, major episodes (Keller et al. 1995). Thus, the differential diagnoses of depressed mood must be linked to ongoing assessment, not cross-sectional evaluation, which is so often the case; it is essential to maintain a longitudinal view of the subthreshold disorders to know their place in an individual's affective history. Keller et al. (1995) described the need for a longitudinal taxonomy, a "course-based classification system."

Boundary issues with subthreshold (i.e., so-called "minor") disorders of mood and anxiety were studied in the DSM-IV Field Trial for mixed anxiety and depression. Zinbarg et al. (1994) and Liebowitz (1993) reported that subsyndromal disorders were common and could be differentiated from other anxiety disorders. The "subdefinitional threshold" cases were often recurrent or chronic (of more than 6 months' duration) and thereby, according to DSM-III-R criteria used in the field trial, would not have been labeled AD. However, in DSM-IV-TR, AD can now also have a chronic form that persists longer than 6 months, so that the duration criterion does not help differentiate the subthreshold disorders, anxiety or depressive disorder NOS, and AD. Angst and Ernst (1993) argued that most diagnostic subgroups of depression are artificial and not diagnostic entities, but subtypes of the same spectrum disorder.

These data suggest that AD could be placed in an innovative category of "stress response syndromes," or for that matter, in several diverse locations within the DSM classification (Strain et al. 1993). However, evidence-based medicine does not offer data to support such alternative groupings at this time. In the extreme, AD could be eliminated altogether, with the advantage of maintaining the atheoretical approach of the DSM conceptual framework. This solution, however, does not seem warranted in view of the findings that demonstrate AD to be a valid diagnosis (Kovacs et al. 1994, 1995).

Construct validity was also observed in a retrospective data study comparing outpatients with single episode major depressive disorder, recurrent major depressive disorder, dysthymic disorder, depressive disorder NOS, and AD with depressed mood with or without mixed anxiety (Jones et al. 1999). The Medical Outcomes Study 36-item Short Form Health Status Survey (SF-36) was completed before and 6 months after treatment. The diagnostic categories were significantly different at baseline, but did not differ with regard to outcome at follow-up. Females were significantly more likely to be diagnosed with major depressive disorder or dysthymic disorder than with AD. Females were also more likely to score lower on the Mental Component Summary scales of the SF-36 scales at admission. AD patients scored higher on all SF-36 scales, as did the other diagnostic groups at baseline and again at follow-up. There was no significant difference among diagnostic groups with regard to treatment outcome. The authors concluded that the results support the construct validity of the AD diagnostic category (Jones et al. 1999).

In reviewing the diagnosis of AD for DSM-IV-TR, one issue emerges as fundamental: The effect of the imprecision of this diagnosis on reliability and validity, because of the lack of behavioral or operational criteria, must be determined. One study (Aoki et al. 1995), however, found three psychological tests, Zung's Self-Rating Anxiety Scale (Zung 1971), Zung's Self-Rating Depression Scale (Zung 1965), and Profile of Mood States (McNair et al. 1971), to be useful tools for AD diagnosis among physical rehabilitation patients. Although Aoki et al. (1995) succeeded in reliably differentiating patients with AD from healthy patients, they did not distinguish them from patients with major depression or PTSD.

In a recent study, Grassi et al. (2000) investigated psychosomatic symptoms in patients with AD in a hospital setting in order to further characterize the diagnosis of AD in the medically ill.

Results showed a considerable overlap between AD and abnormal illness behavior including health anxiety, somatization, conversion symptoms, and demoralization among others. Only 13 out of 100 AD patients interviewed did not present with psychosomatic symptoms.

## Course and Natural History

Andreasen and Hoenk (1982) demonstrated at a 5-year follow-up that there were important differences in adolescents and adults with regard to prognosis. It would be important to extend this long-term observation to cohorts of the elderly and the "old elderly" (those older than 75 years). Although the prognosis was favorable and most adult patients with AD were symptom free at 5 years (71% were completely well, 8% had an intervening problem, and 21% had a major depressive disorder or alcoholism), adolescents had a far different outcome. At a 5-year follow-up, 43% had a major psychiatric disorder (e.g., schizophrenia, schizoaffective disorder, major depressive disorder, substance abuse disorder, and personality disorder); 13% had an intervening psychiatric illness; and 44% had no psychiatric diagnosis (Andreasen and Hoenk 1982). In adolescents, behavioral symptoms and the chronicity of the morbidity were the major predictors for psychopathological disorders at the 5-year follow-up. This was not so with the adults in the study, and raises the question of whether these adolescents were diagnosed as having AD as part of a prodrome of another more serious disorder.

Kovacs et al. (1994) reported a much different set of findings. The authors report that children who were older at the time of onset of AD recovered faster, and there was a trend for subjects with the depressed mood subtype to recover faster than subjects with other symptoms. The researchers concluded that among young, school-aged, clinic-based patients, AD has clinical information value, and is associated with a favorable short-term prognosis, but is often associated with comorbid psychiatric disorders which complicates assessment. When effects of comorbidity were controlled for, there was no compelling evidence for a negative long-term prognosis during a follow-up period of 7–8 years specifically attributable to the earlier AD (Andreasen

and Hoenk 1982). A more recent report by Jones et al. (2002) looked at 10 years of readmission data for various psychiatric diagnoses including the AD. They found that admission diagnosis was a significant predictor of readmission and that AD had the lowest readmission rates. Furthermore, initial psychological recovery from an AD may in large part be attributable to removal of the stressor. This was found to be the case in prisoners who developed AD after being placed in solitary confinement and whose symptoms resolved shortly after their release (Andersen et al. 2000).

Thus, even if AD is properly diagnosed, the negative prognosis that has been reported could be attributable to comorbid disorders such as depressive, anxiety, or conduct disorders that were not recognized (Andreasen and Hoenk 1982). Kovacs et al. (1994), furthermore, reported that comorbid psychiatric disorders had no discernible effect on the speed of recovery from AD. Among both patients with AD and the control subjects, similar rates of dysfunction were detected during the follow-up, probably attributable to the specific psychiatric conditions that were present initially.

Snyder and Strain (1989) observed that in the acute care inpatient hospital setting, many of the psychiatric consultation patients initially thought to have an AD did not maintain that diagnosis at the time of discharge. These same authors also observed that many patients initially diagnosed as having major depressive disorder were reclassified to AD at discharge. It remains to be seen if either the major depressive disorder or the AD diagnosis is significantly altered at a 6-week follow-up and, in particular, when the patient has left the hospital. This evolution of psychiatric morbidity within the acute care general medical setting cautions the psychiatrist to go slowly with treatment until there is a level of certainty to justify an intervention, in particular, with a chemotherapeutic modality.

Attempting to diagnose disorders in an early state or before there is a full-blown syndrome or disorder often means that a patient will qualify for the AD criteria or the subsyndromal condition. Just as it is difficult to know when a patient has crossed the diagnostic line (threshold) from normal to disturbed behavior, it is difficult to know how quickly the symptoms will remit with a remission of the stressor, which for the general medical–surgical inpatient include (1) acute hospitalization, (2) uncertain medical diagnosis, (3) pain, (4) medications, (5) separation, and (6) lack of ability to function or contain emotions. The AD must be looked at as a *transitory state* for most patients, in that it may subside, respond with treatment, evolve to another diagnosis, or be maintained as the stressor continues.

Although most studies do point to a more benign prognosis for the AD, it is important to realize that the risk of serious morbidity and mortality still exists. Several recent studies investigating the association between suicide and AD underscore the importance of monitoring patients closely for suicidality, especially in younger populations. Portzky et al. (2005) conducted psychological autopsies on adolescents with AD who had committed suicide and found that suicidal thinking in these patients was brief and evolved rapidly and without warning. A slightly different profile was found in two other studies that looked at suicide attempters with a diagnosis of AD. These patients were more likely to have poor overall psychosocial functioning, prior psychiatric treatment, personality disorders, substance abuse histories, and a current "mixed" symptom profile of depressed mood and behavioral disturbances (Kryzhanovskaya and Canterbury 2001, Pelkonen et al. 2005). A study of the neurochemical variables of AD patients of all ages who had attempted suicide revealed biologic correlates consistent with the more major psychiatric disorders. Attempters were found to have lower platelet MAO activity, higher MHPG activity, and higher cortisol levels than controls. Though these finding differ from the lower MHPG and cortisol levels found in patients with major depression and suicidality, they are similar to findings in other major stress-related conditions (Tripodianakis et al. 2000).

## Treatment

There are few reported randomized controlled trials regarding the psychological, social, or pharmacological treatment of AD (Adams and Gelder 1994, Chalmers et al. 1992, Conte and Karasu 1992). In lieu of any substantive randomized controlled trials to guide treatment, the choice of intervention remains a clinical decision. The Institute of Medicine has developed *Guidelines for Clinical Practice: From Development to Use* (Field and Lohr 1992). A critical attribute of a guideline is the *strength of the evidence*. "Practice guidelines should be accompanied by descriptions of the strength of the evidence and the expert judgment behind them. [They] should be accompanied by estimates of the health and cost outcomes expected from the interventions in question, compared with alternative practice" (Field and Lohr 1992, p. 8). Therefore, with no evidence from randomized controlled trials, the treatment recommendations for the AD remain based on *consensus* rather than evidence. However, there has not been an official consensus conference on the optimal way to treat this disorder. Recommendations of clinical experts may differ from the results of meta-analyses of randomized controlled trials (Antman et al. 1992).

There are two clinical empirical approaches to treatment. One is based on the understanding that this disorder emanates from a psychological reaction to a stressor. The stressor needs to be identified, described, and shared with the patient; plans must be made to mitigate it, if possible. The abnormal response may be attenuated if the stressor can be eliminated or reduced. Popkin et al. (1990) have shown that in the medically ill, the most common stressor is the medical illness itself; and the AD may remit when the medical illness improves or a new level of adaptation is reached. The other approach to treatment is to provide intervention for the symptomatic presentation, despite the fact that it does not reach threshold level for a specific disorder, on the premise that it is associated with impairment and that treatments that are effective for more pronounced presentations of similar pathology are likely to be effective. This may include psychotherapy, pharmacotherapy, or a combination of the two (Schatzberg 1990).

### Psychotherapy

A psychotherapeutic intervention in AD is intended to reduce the effects of the stressor, enhance coping with the stressor that cannot be reduced or removed, and establishing a mental state and support system to maximize adaptation. Psychotherapy can involve any one of several approaches:

cognitive–behavioral treatment, interpersonal therapy, psychodynamic efforts, or counseling. Though brief therapeutic interventions are usually all that are needed, ongoing stressors or enduring character pathology that may make a patient vulnerable to stress intolerance may signal the need for lengthier treatments (Katzman and Tomori 2005).

The first goal of psychotherapy is to analyze the nature of the stressors affecting the patient to learn whether they may be avoided or minimized (e.g., assuming excessive responsibility out of keeping with realistic goals; putting oneself at risk, such as dietary indiscretions for a type I diabetic). It is necessary to clarify and interpret the meaning of the stressor for the patient. For example, an amputation of the leg may have devastated a patient's feelings about himself or herself, especially if the individual was a runner. It is necessary to clarify that the patient still has enormous residual capacity; that he or she can engage in much meaningful work, does not have to loose valued relationships, and can still be sexually active; and that it does not necessarily mean that further body parts will be lost. (However, it will also involve redirecting the physical activity to another pastime.) Otherwise, the patient's pernicious fantasies ("all is lost") may take over in response to the stressor (i.e., amputation), make the patient dysfunctional (at work, sex), and precipitate a painful dysphoria, anxiety reaction, or major depressive disorder.

Some stressors may elicit an overreaction (e.g., the patient's attempted suicide or homicide after the abandonment by a lover). In such instances of overreaction with feelings, emotions, or behaviors, the therapist would help the patient put his or her feelings and rage into words rather than into destructive actions and gain some perspective. The role of verbalization and the joining of affects and conflicts cannot be overestimated in an attempt to reduce the pressure of the stressor and enhance coping. Recreational drugs and alcohol are to be discouraged.

Psychotherapy, medical crisis counseling, crisis intervention, family therapy, group treatment, cognitive–behavioral treatment, and interpersonal therapy all encourage the patient to express affects, fears, anxiety, rage, helplessness, and hopelessness to the stressors imposed (Pollin and Holland 1992). They also assist the patient to reassess reality in the service of adaptation. Following the example given above, the loss of a leg is not the loss of one's life. But it is a major loss. Sifneos (1989) believed that patients with AD could profit most from brief psychotherapy. The psychotherapy should attempt to reframe the meaning of the stress, find ways to minimize it, and diminish the psychological deficit due to its occurrence. The treatment should expose the concerns and conflicts that the patient is experiencing; help the patient gain perspective on the adversity; and encourage the patient to establish relationships and to attend support groups or self-help groups for assistance in the management of the stressor and the self.

Wise (1988), drawing from his experience in military psychiatry, emphasized the variables of brevity, immediacy, centrality, expectance, proximity, and simplicity (BICEPS principles). The treatment structure encompasses a simple straightforward approach dealing with the immediate situation at hand which is troubling the patient. The treatment approach is brief, usually no more than 72 hours (True and Benway 1992).

In another sample, interpersonal psychotherapy was applied to depressed outpatients with human immunodeficiency virus (HIV) infection and found to be useful (Markowitz et al. 1992). Some of the attributes of interpersonal psychotherapy are psychoeducation regarding the sick role; using a here-and-now framework; formulation of the problems from an interpersonal perspective; exploration of options for changing dysfunctional behavior patterns; and identification of focused interpersonal problem areas. Lazarus (1992) described a seven-pronged approach in the treatment of minor depression. The therapy includes assertiveness training, enjoyable events, coping, imagery, time projection, cognitive disputation, role-playing, desensitization, family therapy, and biological prophylaxis.

Support groups have been demonstrated to help patients adjust and enhance their coping mechanisms, and they may enhance a sense of well being Spiegel et al. (1989). However, findings showing group psychological intervention and lessened mortality have not been confirmed in at least two replication trials reported to date (Cunningham et al. 1998, Goodwin et al. 2001). Group therapy in the form of support groups have also been used in patients with AD. These groups help patients enhance their coping mechanisms (Fawzy et al. 1993, Spiegel et al. 1989). Though studies looking at the survival benefits of psychosocial group interventions have been mixed and show at most modest benefits, improvements in mood, distress level, and overall quality of life in cancer patients who attend support groups are very well documented (Goodwin et al. 2001, Newell et al. 2002).

Another therapeutic modality, eye movement desensitization and reprocessing (EMDR) has been recently studied in patients with AD (Mihelich 2000). EMDR, a psychotherapeutic technique shown to be effective in the treatment of PTSD, was carried out on nine patients suffering from AD. Results showed significant improvement in patients with anxious or mixed features but not in those with depressed mood. Additionally, those with ongoing stressors did not show improvement.

Akechi et al. (2004) investigated associated and predictive factors in cancer patients with AD and major depression. Findings revealed that psychological distress in these patients was associated with a variety of factors including social supports, physical functioning and limitations, and existential issues. Though the findings are not surprising, they do highlight the necessity of a comprehensive care plan for the treatment of AD that includes physical, psychosocial, and existential components. Though studies have yet to evaluate the potential role of family and couples therapy as well as alternative therapies such as acupuncture and yoga, based on these findings, there may well be a role for these modalities in the future treatment of AD.

In terms of randomized controlled trials (RCTs), a search of the Cochrane Database revealed only two RCTs on the specific psychotherapeutic treatment of AD. Gonzalez-Jaimes and Turnbull-Plaza (2003) showed that "mirror psychotherapy" for patients suffering from AD with depressed mood secondary to a myocardial infarction was both an efficient and effective treatment. Mirror therapy is described as a type of therapy with psychocorporal, cognitive, and neurolinguistic components with a holistic focus. As part of the treatment, a mirror is used to

encourage patient acceptance of his/her physical condition that resulted from past self-care behaviors. In this study, mirror therapy was compared to two other treatments, Gestalt psychotherapy or medical conversation in addition to a control group. Depressive symptoms improved in all treatment groups compared with the control group, but mirror therapy appeared significantly more effective than other treatments in decreasing symptoms of AD at posttest evaluation.

In a second RCT, an "activating intervention" was carried out for the treatment of AD resulting in occupational dysfunction. One hundred ninety-two employees were randomized to receive either the intervention or care as usual (van der Klink et al. 2003). The intervention consisted of an individual cognitive behavioral approach to a graded activity, similar to stress inoculation training. Goals of treatment emphasized the acquisition of coping skills and the regaining of control. The treatment proved to be effective in decreasing sick leave duration and shortening long-term absenteeism when compared to the control group; both intervention and control groups, however, showed similar amounts of symptom reduction. This study formed the basis for the Dutch Practice Guidelines for the treatment of AD in primary and occupational health care (van der Klink and van Dijk 2003). These guidelines were prepared by a team of 21 occupational health physicians and one psychologist and subsequently reviewed and tested by 15 experts, including several psychiatrists and psychologists and 21 practicing occupational health physicians.

Though no other RCTs involving the psychotherapeutic treatment of pure cohorts of patients with AD could be found, many RCTs exist that studied an array of depressive and anxiety disorders and that included AD in their cohorts. For example, a recent trial comparing brief dynamic therapy (BDT) with brief supportive therapy (BSP) in patients with minor depressive disorders, including AD, was found in the Cochrane Database. Though both therapies proved efficacious in reducing symptoms, BDT was more effective at 6 months follow-up (Maina et al. 2005).

## Pharmacotherapy

Though psychotherapy has historically been the mainstay of treatment for the AD, Stewart et al. (1992) emphasized the need to consider psychopharmacological interventions as well as psychotherapy for the treatment of minor depression, and this recommendation might be extrapolated to other subthreshold disorders. This group recommends antidepressant therapy if there is no benefit from 3 months of psychotherapy or other supportive measures. Although psychotherapy is the first choice treatment, psychotherapy combined with benzodiazepines may be helpful, especially for patients with severe life stress(es) and a significant anxious component (Shaner 2000, Uhlenhuth et al. 1995). Tricyclic antidepressants or buspirone were recommended in place of benzodiazepines for patients with current or past heavy alcohol use because of the greater risk of dependence in these patients (Uhlenhuth et al. 1995).

Psychotropic medication has been used in the medically ill, in the terminally ill, and in patients who have been refractory to verbal therapies. Rosenberg et al. (1991) described in the medically ill with depressive disorders (the type of depression was unspecified) that 16 of 29 patients (55%) improved within 2 days of treatment with the maximal dose of amphetamine derivatives. The presence of delirium was associated with a decreased response. Whether methylphenidate is similarly useful in AD with depressed mood remains to be examined. Reynolds (1992), reviewing randomized controlled trials, concluded that bereavement-related syndromal depression also appears to respond to antidepressant medication. The medication chosen should reflect the nature of the predominant mood that accompanies the AD (e.g., benzodiazepines for AD with anxious mood; antidepressants for AD with depressed mood). For example, Schatzberg (1990) recommended that the therapist consider both psychotherapy and pharmacotherapy in the AD with anxious mood and that the psychiatrist prescribe anxiolytics as part of the treatment. Nguyen et al. conducted a double-blind randomized controlled trial to compare the efficacies of etifoxine, a nonbenzodiazepine anxiolytic drug, and lorazepam, a benzodiazepine, in the treatment of AD with anxiety in a primary care setting (Nguyen et al. 2006). Efficacy was evaluated on days 7 and 28 using the Hamilton Rating Scale for Anxiety (HAM-A). The two drugs were found to be equivalent in anxiolytics efficacy on day 28. However, overall more etifoxine recipients responded to the treatment. Moreover, 1 week after stopping treatment, fewer patients taking etifoxine experienced rebound anxiety, compared to lorazepam patients. The degree to which pharmacotherapy is used for AD has remained elusive. Olfson et al. (1998) report an increase in the use of antidepressants among less severely ill patients, including those with AD. However, Kaplan et al. (1994) suggest that those with less severe conditions are overall less likely to receive psychopharmacologic treatment.

Other authors have begun to examine the effect of homeopathic treatments. From a 25-week multicenter randomized placebo-controlled double-blind trial, a special extract from kava–kava was reported to be effective in AD with anxiety and without the adverse side effect profile associated with tricyclics and benzodiazepines (Volz and Kieser 1997). Tianeptine, alprazolam, and mianserin were found to be equally effective in symptom improvement in patients with AD and anxious mood (Ansseau et al. 1996). In a random double-blind study, trazodone was more effective than clorazepate in cancer patients for the relief of anxious and depressed symptoms (Razavi et al. 1999). Similar findings were observed in HIV-positive patients with AD (DeWit et al. 1999).

Hameed et al. (2005) in a retrospective chart review sought to determine if there was a difference in antidepressant efficacy in the treatment of major depressive disorder versus AD in a primary care setting. Patients had been prescribed mostly SSRIs. DSM-IV-TR symptoms, PHQ-9 depression rating scale scores, and functional disability reports were systematically used to assess the patient's response. Results showed that neither depressed, nor AD patients demonstrated a difference in clinical response to any particular antidepressant. Patients with a diagnosis of AD, however, were twice as likely to respond to standard antidepressant treatment as depressed patients. This study suggests that antidepressants are very effective in treating depression in the primary care setting and may be even more effective in the treatment for AD with depressed mood.

## Refractory Patients and Nonresponse to Initial Treatment

Those patients who do not respond to counseling or the various modes of psychotherapy that have been outlined and to a trial of antidepressant or anxiolytic medications should be regarded as treatment nonresponders. It is essential to reevaluate the patient to ensure that the diagnostic impression has not altered and, in particular, that the patient has not developed a major mental disorder, which would require a more aggressive treatment, often biological. The psychiatrist must also consider that an Axis II disorder might be interfering with the patient's resolution of the AD. Finally, if the stressor continues and cannot be removed (e.g., the continuation of a seriously impairing chronic illness), additional support and management strategies need to be employed to assist the patient in optimally adapting to the stressor that she or he is confronting (e.g., experiencing the progression of HIV infection).

DSM-IV-TR allows the use of the diagnosis of AD even after 6 months, and then it is described as AD, chronic. With such a contingency (e.g., AD lasting a few years), it is necessary to ensure that the patient is not experiencing dysthymic disorder or an unremitting depressive disorder. However, these diagnoses have a symptom profile that should distinguish them from the AD.

Clinical Vignette 1

A 35-year-old married woman, mother of three children, was desperate when she learned she had cancer and would need mastectomy followed by chemotherapy and radiation. She was convinced that she would not recover, that her body would be forever distorted and ugly, that her husband would no longer find her attractive, and that her children would be ashamed of her baldness and the fact that she had cancer. She wondered whether anyone would ever want to touch her again. Because her mother and sister had also experienced breast cancer, the patient felt she was fated to an empty future. Despite several sessions dealing with her feelings, the patient's dysphoria remained profound. It was decided to add antidepressant medication (fluoxetine, 20 mg/day) to her psychotherapy to decrease the patient's continuing unpleasant symptoms. Two weeks later, the patient reported that she was feeling less despondent and less concerned about the future and that she had a desire to start resuming her former activities with her family. As the patient came to terms with the overwhelming stressor and, assisted with antidepressant agents, her depressed mood improved, more adequate coping strategies to handle her serious medical illness were mobilized.

Although it is uncommon to use psychotropic medication for the majority of the ADs, this clinical vignette illustrates the effective use of antidepressant therapy in a patient who was not responding to counseling and psychotherapy; she never had symptoms that met the DSM-IV-TR criteria for a major depressive disorder. It has been found that the addition of a psychotropic medication in AD, on the basis of the mood disturbance, may assist those patients who continue to experience disordered mood and adjustment to the stressor despite treatment with verbal therapies. The antidepressant medications have also been found helpful in the terminally ill who exhibit AD with depressed mood and who have not responded to counseling alone.

## Conclusion

Appropriate and timely treatment is essential for patients with AD so that their symptoms do not worsen; do not further impair their important relationships; and do not compromise their capacity to work, study, or be active in their interpersonal pursuits. Treatment must attempt to forestall further erosion of the patient's capacity to function that could ultimately have grave and untoward consequences. Maladaptation may so impede the patient that irreversible losses in important sectors of his or her life may occur. Although this diagnosis lacks rigorous specificity, its treatment is no less challenging or less important. AD's lack of a designated symptom profile results in this diagnosis having insufficient specificity. However, it is this lack of specificity, which permits the psychiatrist to have a "diagnosis" to use when the patient is presenting with early, vague, nonconcrete symptomatology, which should be noted, identified, and followed. This is similar to the situation with early fever, or fever of unknown origin, which, by the way, may never go on to a specific medical diagnosis, but be at discharge simply diagnosed as a "fever of unknown origin." Unspecified chest pain is another example where the patient may never have a specific diagnosis even over time. Spitzer has described the ADs as a "wild card" in the psychiatric lexicon, that allows a place for an uncertain, early, not completely developed diagnosis to be housed until it develops into a full blown category, persists in a subsyndromal state, or disappears. As said above, this is not uncommon with physical or mental subsyndromal states.

DSM-III-R has been described as "medical illness and age unfair" (i.e., it does not sufficiently take into account the

Clinical Vignette 2

Mr. L, a 48-year-old laborer, had his right leg amputated below the knee as a result of vascular and neurological damage secondary to diabetes mellitus. He manifested both anxious and depressed moods, became difficult in his relationship with his wife, and refused to take care of himself even in those areas that he could despite his recent surgery. Mr. L complained that he could not function in his wheelchair without assistance, despite upper body capacity to both transfer and propel the chair on his own. Previous to the surgery, he had been independent and turned away assistance, maintaining that he could do it on his own. Despite his distress, he did not evidence the criteria for a major or minor depression (e.g., difficulties in eating, sleeping, guilt, hopelessness, or suicidal ideation). The stressor of his recent surgery had resulted in his maladaptation to his illness and his performance at home and in a depressed and anxious mood.

Mr. L illustrates the occurrence of an AD in response to the stressor of chronic illness and the loss of a body part essential to his usual occupational pursuit. Although bereavement is reserved for those patients who have lost a loved one, the loss of a body part or a body function constitutes a major stressor that can precipitate an AD. The patient's "giving in" and "giving up" were unlike his customary extreme independence and resulted in a maladaptation to the stressor, out of all keeping with the physical limitations imposed by the surgery. It was also out of keeping with his family and cultural ideals that they kept going the "best they could" and maintained responsibilities and self-care even if it meant discomfort and extra effort.

Clinical Vignette 3

A 38-year-old woman who had lost her sister 5 days before in the attack on the World Trade Center was convinced that she was responsible for the sister's death in that she did not stop by and have coffee with her that morning, thereby delaying her arrival at work which would have preserved her life. She was having difficulty sleeping, her diabetes was out of control, she found herself crying, unable to function at work, and having difficulty coping with her three children. She was anxious, depressed, and felt guilty that she was the only one who could have saved the sister, if she had not avoided her usual routine, which usually resulted in making the sister about 30 minutes late for her employment. The 30 minutes would have made the difference in arriving too late to enter the burning building. This patient did not have a posttraumatic stress response because it had not been 30 days since the stressor. She did not qualify for an acute stress disorder as she did not have derealization, depersonalization, or amnesia (i.e., at least 3 out of 5 symptoms are required). Could the patient be labeled as in bereavement? The patient has significant maladaptation to a major stressor characterized by a depressed and anxious mood. The degree of the patient's belief that she was responsible for the sister's death, and the degree of her nonfunctional capacity at work or to perform at home, does not support that bereavement would be a preferred diagnosis. Medications were prescribed to assist her with sleep and to reduce the daytime anxiety. What was the most appropriate diagnosis in the early days of this disaster, if the patient did not achieve the criteria for an acute stress response? It would seem that appropriate follow-up may highlight the trajectory of symptom development and whether the person goes on to develop other diagnoses or into a remission toward normalcy. Medications were temporarily prescribed to assist with the intense sleep and anxiety disturbances.

issues of age and/or medical illness) (L. George, personal communication, Strain 1981). DSM-IV-TR has tried to take this into consideration with much effort and thought placed on those psychological interface disorders that border between physical and mental phenomena, for example, the somatoform disorders, AD, dissociation, and so on. However, in addition to enhancing reliability and validity, the psychiatric taxonomy needs to consider the impact of developmental epochs (e.g., children and youth, adults, young elderly, and "old" elderly) and medical illness on symptomatology. With regard to the latter issue, Endicott (1984) has described replacing vegetative with ideational symptoms when evaluating depressed patients with medical illness. Rapp and Vrana (1989) confirmed Endicott's proposed changes in the diagnostic criteria for depression in medically ill elderly persons and observed maintenance of specificity and sensitivity, respectively, when substituting ideational for vegetative symptoms. Recent studies found AD patients to be significantly younger compared with patients who have a major psychiatric diagnosis (Despland et al. 1995, Mok and Walter 1995). Zarb's (1996) study suggests that cognitively impaired elderly, when evaluated using individual items of the Geriatric Depression Scale exhibited AD rather than major depressive disorder. In addition, Despland et al. (1995) reported that the patients' group with AD with depressive or mixed symptoms included more women, thus exhibiting a sex ratio resembling that for major depressive disorder or dysthymic disorder. Therefore, future editions of DSM may be able to take into account the differences encountered in symptom profiles for gender, various developmental epochs, and medical and psychiatric comorbidity.

Finally, longitudinal observations would describe the outcome of AD over time. Their resolution, evolution to another diagnosis, their response to a variety of treatments would augment our understanding and approach to this important subthreshold diagnosis.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

In contrast to DSM-IV-TR (which requires the onset of symptoms within 3 months of the stressor), the ICD-10 Diagnostic Criteria for Research specify an onset within 1 month. Furthermore, ICD-10 excludes stressors of "unusual or catastrophic type." In contrast, DSM-IV-TR allows extreme stressors so long as the criteria are not met for posttraumatic or acute stress disorder. ICD-10 also provides for several different subtypes, including "brief depressive reaction" (depressive state lasting 1 month or less), "prolonged depressive reaction" (depressive state lasting up to 2 years).

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CHAPTER

# 82 Personality Disorders

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Personality Disorder
Paranoid Personality Disorder
Schizoid Personality Disorder
Schizotypal Personality Disorder
Antisocial Personality Disorder
Borderline Personality Disorder
Histrionic Personality Disorder
Narcissistic Personality Disorder
Avoidant Personality Disorder
Dependent Personality Disorder
Obsessive–Compulsive Personality Disorder
Passive–Aggressive Personality Disorder
Depressive Personality Disorder

Everybody has a personality, or a characteristic manner of thinking, feeling, behaving, and relating to others. Some persons are typically introverted and withdrawn, while others are more extraverted and outgoing. Some persons are invariably conscientious and efficient, whereas others might be consistently undependable and negligent. Some persons are characteristically anxious and apprehensive, whereas others are typically relaxed and unconcerned. These personality traits are often felt to be integral to each person's sense of self, as they involve what persons value, what they do, and what they are like most every day throughout much of their lives.

Personality traits have long been the focus of considerable scientific research. Their heritability (Bouchard and Loehlin 2001), childhood antecedents (Caspi et al. 2005), temporal stability (Roberts and DelVecchio 2000), universality (Allik 2005) and functional relevance to work, well-being, marital stability, and even physical health (Ozer and Benet-Martinez 2006) have been well established across many studies. It is "when personality traits are inflexible and maladaptive and cause significant functional impairment or subjective distress [that] they constitute Personality Disorders" (American Psychiatric Association 2000, p 686). The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association 2000), provides the diagnostic criteria for 10 personality disorders. Two additional diagnoses are placed within an appendix to DSM-IV-TR for criterion sets provided for further study (passive–aggressive and depressive). We begin this chapter with a discussion of the diagnosis, etiology, and treatment of personality disorders in general, followed by a discussion of these points for the 12 individual personality disorders.

## Personality Disorder

### Definition

A personality disorder is defined in DSM-IV-TR as "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment" (American Psychiatric Association 2000, p 686). DSM-IV-TR Criteria: Personality Disorder provides the DSM-IV-TR general diagnostic criteria for a personality disorder.

Personality disorder is the only class of mental disorders in DSM-IV-TR for which an explicit definition and criterion set are provided. A general definition and criterion set can be useful to psychiatrists because one of the most common personality disorder diagnosis in clinical practice is often the diagnosis "not otherwise specified" (NOS) (Verheul and Widiger 2004). Psychiatrists provide the NOS diagnosis

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**DSM-IV-TR Criteria**

**General Diagnostic Criteria for Personality Disorder**

A. An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. This pattern is manifested in two (or more) of the following areas:
   1. cognition (i.e., ways of perceiving and interpreting self, other people, and events)
   2. affectivity (i.e., the range, intensity, lability, and appropriateness of emotional response)
   3. interpersonal functioning
   4. impulse control

B. The enduring pattern is inflexible and pervasive across a broad range of personal and social situations.

C. The enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The pattern is stable and of long duration and its onset can be traced back at least to adolescence or early adulthood.

E. The enduring pattern is not better accounted for as a manifestation or consequence of another mental disorder.

F. The enduring pattern is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., head trauma).

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when they determine that a personality disorder is present but the symptomatology fails to meet the criterion set for one of the ten specific personality disorders. A general definition of what is meant by a personality disorder is therefore helpful in determining whether the NOS diagnosis should in fact be provided. Points worth emphasizing with respect to the general criterion set provided in DSM-IV-TR Criteria: Personality Disorder are discussed in the following sections on the differential diagnosis, assessment, culture, epidemiology, and course of personality disorders.

## Differential Diagnosis

One of the innovations of DSM-III was the provision of a multiaxial system for clinical diagnosis (American Psychiatric Association 1980, Spitzer et al. 1980). Prior to DSM-III psychiatrists rarely diagnosed a personality disorder when a patient's symptoms met diagnostic criteria for an anxiety, mood, psychotic, or other mental disorder. In an extensive, widely cited, and historically influential study of psychiatric diagnosis, Ward et al. concluded that psychiatric diagnoses were excessively unreliable and that the greatest basis of disagreement was determining "whether the neurotic symptomatology or the characterological pathology is more extensive or 'basic'" (Ward et al. 1962, p 202). They criticized the assumption that a clinician must choose between a "neurotic condition" and a personality disorder when both in fact appeared to be present. A personality disorder will predate the onset of most other mental disorders and its presence is likely to have a considerable impact on the course, treatment, and even etiology of the other mental disorder (Dolan-Sewell et al. 2001, Millon et al. 1996). DSM-III, therefore, moved the personality disorders to a separate axis so that psychiatrists could diagnose both conditions "rather than being forced to arbitrarily and unreliably make a choice between them" (Frances 1980, p 1050). The multiaxial system does appear to have been successful in encouraging psychiatrists to no longer make arbitrary distinctions between personality disorders and other mental disorders (Loranger 1990). Ironically, however, the placement of the personality disorders on a separate axis may also have contributed to the development of false assumptions and exaggerated expectations concerning the distinctions between personality disorders and other mental disorders with respect to etiology, pathology, and treatment (Krueger 2005).

The second most frequently cited cause for unreliable clinical diagnosis identified by Ward et al. (1962) was the absence of specific, explicit diagnostic criteria. Another innovation of DSM-III (American Psychiatric Association 1980, Spitzer et al. 1980) was the provision of specific and explicit diagnostic criterion sets that have facilitated the obtainment of more reliable clinical diagnosis. This innovation, however, has been problematic for the personality disorders, as it is difficult to provide a brief list of specific diagnostic criteria for the broad and complex behavior patterns that constitute a personality disorder. The only personality disorder to be diagnosed reliably in general clinical practice has been antisocial (Widiger and Samuel 2005b) and the validity of this diagnosis has been questioned precisely because of its emphasis on overt and behaviorally specific acts of criminality, irresponsibility, and delinquency (Hare 2003).

## Assessment

There are assessment instruments, however, that will help psychiatrists obtain more reliable and valid personality disorder diagnoses. Semistructured interviews provide a researched set of required and recommended interview queries and observations to assess each of the personality disorder diagnostic criteria in a systematic, comprehensive, and replicable fashion. Semistructured interviews will obtain reliable diagnoses of personality disorders and are therefore the preferred method for their assessment in clinical research (McDermut and Zimmerman in press, Widiger in press). Psychiatrists can find the administration of semistructured interviews to be constraining (Westen 1997) but a major strength of semistructured interviews is their assurance through an explicit structure that each relevant diagnostic criterion has in fact been systematically assessed. Idiosyncratic and subjective interviewing techniques are much more likely to result in gender and culturally biased assessments (Garb 2005, Rogers 2003, Zimmerman 2003). The manuals that accompany a

semistructured interview also provide useful information for understanding the rationale of each diagnostic criterion, for interpreting vague or inconsistent symptomatology, and for resolving diagnostic ambiguities. There are currently five semistructured interviews for the assessment of the DSM-IV-TR (American Psychiatric Association 2000) personality disorders: (1) Diagnostic Interview for Personality Disorders (Zanarini et al. 1995), (2) International Personality Disorder Examination (Loranger 1999), (3) Personality Disorder Interview—IV (Widiger et al. 1995), (4) Structured Clinical Interview for DSM-IV-TR Axis II Personality Disorders (First and Gibbon 2004), and (5) Structured Interview for DSM-IV-TR Personality Disorders (Pfohl et al. 1997). Advantages and disadvantages of each particular interview have been discussed extensively (McDermut and Zimmerman 2005, in press, Widiger in press).

The Shedler-Westen Assessment Procedure—200 (SWAP-200) provides an additional alternative. The SWAP-200 is "a method for studying personality and personality pathology that strives to capture the richness and complexity of psychoanalytic constructs and formulations without forsaking the benefits of empirical rigor" (Shedler 2002, p 429). The SWAP-200 is a clinician rating form of 200 items, approximately half of which are equivalent to the existing DSM-IV-TR criterion sets. The rest were drawn from the psychoanalytic and personality disorder literature (Shedler 2002, Westen and Shedler 1999). SWAP-200 items are not ranked on the basis of an administration of a series of questions; instead, the SWAP-200 rating relies on "the empathically attuned and dynamically sophisticated clinician given free rein to practice his or her craft" (Shedler 2002, p 433). Quite a bit of research has been conducted using the SWAP-200 (Westen and Bradley 2005), although concerns have been raised regarding the validity of this research, particularly with respect to its use of a forced distribution of ratings (e.g., half of the items must be provided the lowest possible score and only a small minority can be provided the highest rating) that may artifactually compel the obtainment of improved convergent and discriminant validity (Clark 2007, Widiger and Samuel 2005b, Wood et al. in press).

The administration of an entire personality disorder semistructured interview can take 2 hours, an amount of time that is impractical in routine clinical practice. However, this time can be reduced substantially by first administering a self-report questionnaire that screens for the presence of the DSM-IV-TR personality disorders (Widiger et al. 2006). A psychiatrist can then confine the interview to the few personality disorders that the self-report inventory suggested would be present. Self-report inventories are useful in ensuring that all of the personality disorders are systematically considered and in alerting the clinician to the presence of maladaptive personality traits that might otherwise have been missed. There are a number of alternative self-report inventories that can be used, including (1) Minnesota Multiphasic Personality Inventory—2 personality disorder scales of Colligan et al. (1994), (2) Millon Clinical Multiaxial Inventory—III (Millon et al. 1997), (3) OMNI Personality Inventory (Loranger 2001), (4) Personality Diagnostic Questionnaire—4 (Bagby and Farvolden 2004), (5) Personality Assessment Inventory (Morey and Boggs 2004), (6) Schedule for Nonadaptive and Adaptive Personality Functioning (Clark et al. in press), (7) Wisconsin Personality Disorders Inventory (Klein et al. 1993), and (8) Coolidge Axis II Inventory (Coolidge and Merwin 1992). Advantages and disadvantages of each of them have also been discussed extensively (McDermut and Zimmerman 2005, in press, Millon et al. 1996, Widiger in press, Widiger et al. 2006).

## Culture

Cultural biases are one potential source of inaccurate personality disorder diagnosis that are worth noting in particular (Garb 2005, Lopez and Guarnaccia 2005, Morey et al. 2005). One of the general diagnostic criteria for personality disorder is that the personality trait must deviate markedly from the expectations of a person's culture (see DSM-IV-TR Criteria: Personality Disorder). The purpose of this cultural deviation requirement is to compel clinicians to consider the cultural background of the patient. A behavior pattern that appears to be aberrant from the perspective of one's own culture (e.g., submissiveness or emotionality) could be quite normative and adaptive within another culture. The cultural expectations or norms of the psychiatrist might not be relevant or applicable to a patient from a different cultural background. However, one should not infer from this requirement that a personality disorder is primarily or simply a deviation from a cultural norm. Deviation from the expectations of one's culture is not necessarily maladaptive, nor is conformity to one's culture necessarily healthy. Many of the personality disorders may even represent (in part) extreme or excessive variants of behavior patterns that are valued or encouraged within a particular culture. For example, it is usually adaptive to be confident but not to be arrogant, to be agreeable but not to be submissive, or to be conscientious but not to be perfectionist.

## Epidemiology

Virtually all patients will have had a characteristic manner of thinking, feeling, behaving, and relating to others prior to the onset of an Axis I disorder that could have an important impact on the course and treatment of the respective mental disorder (Dolan-Sewell et al. 2001, Mattia and Zimmerman 2001). Estimates of the prevalence of personality disorder within clinical settings are typically above 50% (Mattia and Zimmerman 2001). As many as 60% of inpatients within some clinical settings would be diagnosed with borderline personality disorder (BPD) (American Psychiatric Association 2000, Gunderson 2001) and as many as 50% of inmates within a correctional setting could be diagnosed with antisocial personality disorder (ASPD) (Derefinko and Widiger in press). Although the comorbid presence of a personality disorder is likely to have an important impact on the course and treatment of an Axis I disorder (Dolan-Sewell et al. 2001), the prevalence of personality disorder is generally underestimated in clinical practice, due in part to the failure to provide systematic or comprehensive assessments of personality disorder symptomatology and perhaps as well to the lack of funding for the treatment of personality disorders (Zimmerman and Mattia 1999).

Approximately 10–15% of the general population would be diagnosed with one of the ten DSM-IV-TR personality disorders, excluding personality disorder not otherwise specified (PDNOS) (Mattia and Zimmerman 2001, Torgersen et al. 2001). Table 82–1 provides prevalence

**Table 82–1 Epidemiology of Personality Disorders**

| | Sample | *N* | Int | DSM | PRN | SZD | STP | ATS | BDL | HST | NCS | AVD | DPD | OCP | PAG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Black et al. (1993) | R-HN | 127 | SIDP | III | 1.6 | 0.0 | 3.9 | 0.0 | 5.5 | 3.9 | 0.0 | 3.2 | 2.4 | 7.9 | 12.6 |
| Black et al. (1993) | R-OCD | 120 | SIDP | III | 1.7 | 0.0 | 2.5 | 0.8 | 0.8 | 2.5 | 0.0 | 0.8 | 0.8 | 10.8 | 8.3 |
| Coryell et al. (1989) | R-HN | 185 | SIDP | III | 0.5 | 1.6 | 2.2 | 1.6 | 1.1 | 1.6 | 0.0 | 1.6 | 0.5 | 3.2 | 2.2 |
| Drake et al. (1998) | Men(47) | 369 | Clinical | III | 1.1 | 4.1 | 2.4 | 0.8 | 0.5 | 3.8 | 3.5 | 1.6 | 10.3 | 0.5 | 7.8 |
| Jackson and Burgess (2000) | Comm | 10,641 | IPDE | IV | 1.3 | 1.9 | – | – | 1.0 | 0.5 | – | 2.3 | 1.0 | 3.1 | – |
| Klein et al. (1995) | R-DP | 258 | PDE | III-R | 1.7 | 0.9 | 0.0 | 2.2 | 1.7 | 1.7 | 3.9 | 5.2 | 0.4 | 2.6 | 1.7 |
| Lenzenweger et al. (1997) | Stdts | 1646 | PDE | III-R | 0.4 | 0.4 | 0.0 | 0.8 | 0.0 | 1.9 | 1.2 | 0.4 | 0.4 | 0.0 | 0.0 |
| Maier et al. (1992) | Comm | 452 | SCID-II | III-R | 1.8 | 0.4 | 0.7 | 0.2 | 1.1 | 1.3 | 0.0 | 1.1 | 1.5 | 2.2 | 1.8 |
| Moldin et al. (1994) | HN | 302 | PDE | III-R | 0.0 | 0.0 | 0.7 | 2.6 | 2.0 | 0.3 | 0.0 | 0.7 | 1.0 | 0.7 | 1.7 |
| Sammuels et al. (1994) | Comm | 762 | Clinical | III | 0.0 | 0.0 | 0.1 | 1.5 | 0.4 | 2.1 | 0.0 | 0.0 | 0.1 | 1.7 | 0.1 |
| Torgersen et al. (2001) | Comm | 2053 | SIDP-R | III-R | 2.4 | 1.7 | 0.6 | 0.7 | 0.7 | 2.0 | 0.8 | 5.0 | 1.5 | 2.0 | 1.7 |
| Median | | | | | 1.4 | 0.4 | 0.7 | 0.8 | 1.0 | 2.0 | 0.0 | 1.4 | 0.9 | 2.1 | 1.7 |
| DSM-IV-TR estimates | | | | | 0.5–2.5 | uncm | 3.0 | 2.0 | 2.0 | 2.0–3.0 | <1.0 | 0.5–1.0 | – | 1.0 | |

*Note: N*, number of persons in study; Int, interview that was used; DSM, edition of Diagnostic and Statistical Manual that was used (DSM-III or DSM-III-R); PRN, paranoid; SZD, schizoid; STP, schizotypal; ATS, antisocial; BDL, borderline; HST, histrionic; NCS, narcissistic; AVD, avoidant; DPD, dependent; OCP, obsessive–compulsive; PAG, passive–aggressive; R-HN, relatives of hypernormal (persons without history of mental disorder); R-OCD, relatives of persons with obsessive–compulsive anxiety disorder; Men(47), males of approximate age of 47 years; R-DP, relatives of persons with depression; Stdts, students; Comm, community; SIDP, Structured Interview for Personality Disorder (Pfohl et al. 1997); SCID-II, Structured Clinical Interview for DSM personality disorder (First et al. 1997); Clinical, unstructured or unspecified semistructured interview; PDE, personality disorder examination; uncm, uncommon.

data reported by the best available studies to date for estimating the prevalence of individual personality disorders within a community population. All of these studies have important limitations, though, that qualify their results. For example, many of the studies sampled persons who would probably have less personality disorder pathology than a randomly selected sample (e.g., some studies have sampled persons without any history of Axis I psychopathology) and studies have used either the DSM-III (American Psychiatric Association 1980) or DSM-III-R (American Psychiatric Association 1987) criterion sets rather than DSM-IV-TR (American Psychiatric Association 2000). Nevertheless, the prevalence estimates are generally close to those provided in DSM-IV-TR. Prevalence rates for individual personality disorders will be discussed later in this chapter.

## Comorbidity

There is also considerable personality disorder diagnostic co-occurrence (Bornstein 1998, Clark 2007, Livesley 2003). Patients who meet the DSM-IV-TR diagnostic criteria for one personality disorder are likely to meet the diagnostic criteria for another. Table 82–2 provides the co-occurrence among the DSM-III-R (American Psychiatric Association 1987) personality disorder diagnoses that were obtained for the development of DSM-IV-TR (American Psychiatric Association 1994). DSM-IV-TR instructs psychiatrists that all diagnoses should be recorded because it can be important to consider, for example, the presence of antisocial traits in someone with a BPD or the presence of paranoid traits in someone with a dependent personality disorder (DPD). However, the extent of diagnostic co-occurrence is at times so extensive that most researchers prefer a more dimensional description of personality (Cloninger 2000, Livesley 2003, Oldham and Skodol 2000, Widiger and Samuel 2005a). Diagnostic categories provide clear, vivid descriptions of discrete personality types but the personality structure of actual patients might be more accurately described by a constellation of maladaptive personality traits. Several studies

**Table 82–2 DSM-III-R Personality Disorder Diagnostic Co-Occurrence Aggregated Across Six Research Sites**

| | PRN | SZD | SZT | ATS | BDL | HST | NCS | AVD | DPD | OCP | PAG |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Paranoid (PRN) | | 8 | 19 | 15 | 41 | 28 | 26 | 44 | 23 | 21 | 30 |
| Schizoid (SZD) | 38 | | 39 | 8 | 22 | 8 | 22 | 55 | 11 | 20 | 9 |
| Schizotypal (SZT) | 43 | 32 | | 19 | 4 | 17 | 26 | 68 | 34 | 19 | 18 |
| Antisocial (ATS) | 30 | 8 | 15 | | 59 | 39 | 40 | 25 | 19 | 9 | 29 |
| Borderline (BDL) | 31 | 6 | 16 | 23 | | 30 | 19 | 39 | 36 | 12 | 21 |
| Histrionic (HST) | 29 | 2 | 7 | 17 | 41 | | 40 | 21 | 28 | 13 | 25 |
| Narcissistic (NCS) | 41 | 12 | 18 | 25 | 38 | 60 | | 32 | 24 | 21 | 38 |
| Avoidant (AVD) | 33 | 15 | 22 | 11 | 39 | 16 | 15 | | 43 | 16 | 19 |
| Dependent (DPD) | 26 | 3 | 16 | 16 | 48 | 24 | 14 | 57 | | 15 | 22 |
| Obsessive–Compulsive (OCP) | 31 | 10 | 11 | 4 | 25 | 21 | 19 | 37 | 27 | | 23 |
| Passive–Aggressive (PAG) | 39 | 6 | 12 | 25 | 44 | 36 | 39 | 41 | 34 | 23 | |

Sites used DSM-III-R criterion sets. Data obtained for purposes of informing the development of the DSM-IV-TR personality disorder diagnostic criteria.

*Source:* Widiger and Trull (1998).

have demonstrated that much of the personality disorder diagnostic co-occurrence is readily explained if they are understood as maladaptive variants of general personality structure (Lynam and Widiger 2001, O'Connor 2005).

In 1999, a DSM Research Planning Conference was held under joint sponsorship of the American Psychiatric Association and the National Institute of Mental Health, the purpose of which was to set research priorities that would optimally inform the authors of future editions of the diagnostic manual. A work group that concerned personality disorders focused its attention on the conceptual and empirical support for a dimensional model of classification (First et al. 2002). The Nomenclature Work Group also recommended that efforts toward a dimensional model of classification be developed for the personality disorders. "If a dimensional system of personality performs well and is acceptable to clinicians, it might then be appropriate to explore dimensional approaches in other domains" (Rounsaville et al. 2002, p 13). This conference was followed by a series of international conferences, each covering a particular domain of the diagnostic manual. The first of this series was devoted to setting a research agenda that would be most effective in leading the field toward a dimensional classification of personality disorder (Widiger et al. 2005).

A number of alternative dimensional models of personality disorder have been developed. Perhaps not surprisingly, as they are all attempting to do largely the same thing, it is evident that these alternative models can be well integrated within a common hierarchical structure defined at one level by four (or five) broad domains of general personality structure: extraversion versus introversion, antagonism versus agreeableness, constraint versus impulsivity, and emotional dysregulation versus emotional stability (Widiger and Simonsen 2005). These four broad domains correspond closely to four of the five domains of the five-factor model of general personality structure.

Five broad domains of personality functioning have been identified empirically through the study of the languages of a number of different cultures (Ashton and Lee 2001). Language can be understood as a sedimentary deposit of the observations of persons over the thousands of years of the language's development and transformation. The most important domains of personality functioning would be those with the greatest number of words to describe and differentiate their various manifestations and nuances, and the structure of personality will be evident by the empirical relationship among the trait terms. Such lexical analyses of languages have typically identified five fundamental dimensions of personality: extraversion (or positive emotionality), antagonism, conscientiousness, neuroticism (or negative affectivity), and openness (or unconventionality). Each of these five broad domains can be differentiated further in terms of underlying facets. For example, the facets of antagonism versus agreeableness include suspiciousness versus trusting gullibility, tough-mindedness versus tender-mindedness, confidence and arrogance versus modesty and meekness, exploitation versus altruism and sacrifice, oppositionalism and aggression versus compliance, and deception and manipulation versus straightforwardness and honesty (McCrae and Costa 1999). Perhaps most importantly for the purposes of this chapter, each of the DSM-IV-TR personality disorders can be understood as maladaptive variants of these personality traits that are evident in all persons to varying degrees (Clark 2007, Lynam and Widiger 2001, Mullins-Sweatt and Widiger 2006, Saulsman and Page 2004, Widiger et al. 2002).

Table 82–3 provides a description of the DSM-IV-TR personality disorders in terms of this five-factor model. For example, ASPD is primarily defined in terms of antagonism (i.e., aggressive, exploitative, callous, ruthless, and mistrustful) and low conscientiuosness (irresponsibile, negligent, and rash), but the five-factor model description goes beyond the DSM-IV-TR to include additional traits emphasized within the broader literature on psychopathy, including arrogance, glib charm (low self-consciousness), and fearlessness (low vulnerability), and lack of empathy (callousness) (Lynam and Widiger 2007). The five-factor description even includes the trait of low anxiousness that was emphasized by Cleckley (1941) but not included in either DSM-IV-TR (American Psychiatric Association 2000) or even most studies of psychopathy (Hare 2003). Advantages of understanding personality disorders in terms of this dimensional model are the provision of more specific descriptions of individual patients (including adaptive as well as maladaptive personality functioning), the avoidance of arbitrary categorical distinctions, and the ability to apply the extensive amount of research on the heritability, temperament, development, course, and cross-cultural validity of general personality functioning to an understanding of personality disorders (Widiger and Trull 2007).

## Course

Personality disorders must be evident since adolescence or young adulthood and have been relatively chronic and stable throughout adult life (see DSM-IV-TR Criteria: Personality Disorder). The World Health Organization (1992) International Classification of Diseases recognizes the existence of personality change secondary to catastrophic experiences and to brain injury or disease, but only the latter is included within DSM-IV-TR (American Psychiatric Association 2000). A 75-year-old man can be diagnosed with a DSM-IV-TR DPD but the symptoms must have been present throughout the entire duration of his adulthood (e.g., since the age of 18) unless the dependent behavior was a direct, explicit expression of a neurochemical disease or lesion.

The requirement that a personality disorder be evident since late adolescence and be relatively chronic thereafter has been a traditional means with which to distinguish a personality disorder from an Axis I disorder (Millon et al. 1996, Spitzer et al. 1980). Mood, anxiety, psychotic, sexual, and other mental disorders have traditionally been conceptualized as conditions that arise at some point during a person's life and that are relatively limited or circumscribed in their expression and duration. Personality disorders, in contrast, are conditions that are evident as early as late adolescence (and in some instances prior to that time), are evident in everyday functioning, and are stable throughout adulthood. However, the consistency of this distinction across disorders has been decreasing with each edition of the DSM, as early onset and chronic variants of Axis I disorders are being added to the diagnostic manual (e.g., early onset dysthymia and generalized social phobia). Some researchers have in fact suggested abandoning the concept of personality disorder and replacing it with early onset and chronic variants

**Table 82–3 DSM-IV-TR Personality Disorders from the Perspective of the Five-Factor Model of General Personality Functioning**

| | PRN | SZD | SZT | ATS | BDL | HST | NCS | AVD | DPD | OCP | PAPD | DPPD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Neuroticism (vs. emotional stability)* | | | | | | | | | | | | |
| Anxiousness (vs. unconcerned) | | | High | Low | High | | | High | High | High | | |
| Angry hostility (vs. dispassionate) | High | | | High | High | | High | | | | High | |
| Depressiveness (vs. optimistic) | | | | | High | | | | | | | High |
| Self-consciousness (vs. shameless) | | | High | Low | | Low | Low | High | High | | | High |
| Impulsivity (vs. restrained) | | | | High | High | High | | Low | | Low | | |
| Vulnerability (vs. fearless) | | | | Low | High | | | High | High | | | |
| *Extraversion (vs. introversion)* | | | | | | | | | | | | |
| Warmth (vs. coldness) | Low | Low | Low | | | | Low | | High | | Low | Low |
| Gregariousness (vs. withdrawal) | Low | Low | Low | | | High | | Low | | | | Low |
| Assertiveness (vs. submissiveness) | | | | High | | | High | Low | Low | | Low | |
| Activity (vs. passivity) | | Low | | High | | High | | | | | Low | |
| Excitement seeking (vs. lifeless) | | Low | | High | | High | High | Low | | Low | | Low |
| Positive emotionality (vs. anhedonia) | | Low | Low | | | High | | Low | | | | |
| Openness (vs. closedness) | | | | | | | | | | | | |
| Fantasy (vs. concrete) | | | High | | | High | | | | | | |
| Aesthetics (vs. disinterest) | | | | | | | | | | | | |
| Feelings (vs. alexithymia) | | Low | | | High | High | Low | | | Low | | |
| Actions (vs. predictable) | Low | Low | | High | High | High | High | Low | | Low | Low | |
| Ideas (vs. closed-minded) | Low | | High | | | | | | | Low | Low | Low |
| Values (vs. dogmatic) | Low | | | | | | | | | Low | | |
| *Agreeableness (vs. antagonism)* | | | | | | | | | | | | |
| Trust (vs. mistrust) | Low | | | Low | | High | Low | | High | | | Low |
| Straightforwardness (vs. deception) | Low | | | Low | | | Low | | | | Low | |
| Altruism (vs. exploitative) | Low | | | Low | | | Low | | High | | | |
| Compliance (vs. aggression) | Low | | | Low | | | Low | | High | | Low | |
| Modesty (vs. arrogance) | | | | Low | | | Low | High | High | | | High |
| Tender-mindedness (vs. tough-minded) | Low | | | Low | | | Low | | High | | | |
| *Conscientiousness (vs. disinhibition)* | | | | | | | | | | | | |
| Competence (vs. laxness) | | | | | | | | | | High | Low | |
| Order (vs. disorderly) | | | Low | | | | | | | High | Low | |
| Dutifulness (vs. irresponsibility) | | | | Low | | | | | | High | Low | High |
| Achievement striving (vs. lackadaisical) | | | | | | | | | | High | | |
| Self-discipline (vs. negligence) | | | | Low | | Low | | | | High | Low | |
| Deliberation (vs. rashness) | | | | Low | Low | Low | | | | High | | High |

of existing Axis I disorders (First et al. 2002). For example, avoidant personality disorder (AVPD) could become generalized social phobia and BPD could become an early onset and chronic mood dyscontrol. A precedent for this revision is that ICD-10 currently does not include a diagnosis of schizotypal personality disorder (STPD), including instead a diagnosis of schizotypal disorder that is an early onset and chronic variant of schizophrenia (World Health Organization 1992).

## Etiology and Pathophysiology

A primary purpose of a diagnosis is to lead to scientific knowledge concerning the etiology for a patient's condition and the identification of a specific pathology for which a particular treatment (e.g., medication) would ameliorate the condition (First and Tasman 2006). However, many of the mental disorders in DSM-IV-TR, including the personality disorders, may not in fact have single etiologies or even specific pathologies (Rutter 2003). The DSM-IV-TR personality disorders might be, for the most part, constellations of maladaptive personality traits that are the result of multiple genetic dispositions interacting with a variety of detrimental environmental experiences (Paris 2005, Widiger and Trull 2007).

## Treatment

One of the mistaken assumptions or expectations of Axis II is that personality disorders are untreatable. General personality structure is not itself set in stone. Temporal stability coefficients for personality are only about 0.31 in childhood (contributing to the reluctance to diagnose personality disorders in childhood), 0.54 during years of college, 0.64 at age 30 and leveling off at 0.74 between ages of 50 and 70 (Roberts and DelVecchio 2000). These temporal stability coefficients document the consistency of personality over time, but they also indicate that some change can occur. Temporal stability of maladaptive personality traits might be even lower (Skodol et al. 2005), as such traits are often the focus of clinical treatment (Beck et al. 1990, Gunderson and Gabbard 2000, Millon et al. 1996, Paris 1998, Stone 1993, Young et al. 2003). Personality disorders are among the more difficult of mental disorders to treat, as they

involve entrenched behavior patterns, some of which will be integral to a patient's self-image (Millon et al. 1996, Stone 1993). Nevertheless, there is compelling empirical support to indicate that meaningful responsivity to psychosocial and pharmacologic treatment does occur (Markovitz 2001, Perry et al. 1999, Sanislow and McGlashan 1998). Treatment of a personality disorder is unlikely to result in the development of a fully healthy or ideal personality structure, but clinically and socially meaningful change to personality structure and functioning does occur. In fact, given the considerable social, occupational, medical, and other costs that are engendered by such personality disorders as the antisocial and borderline, even marginal reductions in symptomatology can represent quite significant and meaningful public health care, social, and clinical benefits (Linehan 2001).

## The DSM-IV-TR Personality Disorders

DSM-IV-TR includes 10 individual personality disorder diagnoses that are organized into three clusters: (a) paranoid, schizoid, and schizotypal (placed within an odd–eccentric cluster); (b) antisocial, borderline, histrionic, and narcissistic (dramatic–emotional–erratic cluster); and (c) avoidant, dependent, and obsessive–compulsive (anxious–fearful cluster) (American Psychiatric Association 2000). Each of these personality disorders, along with the two that are included in the appendix to DSM-IV-TR for disorders needing further study (i.e., passive–aggressive and depressive), will be discussed in turn.

### Paranoid Personality Disorder

Paranoid personality disorder (PPD) is a personality disorder that has been in every edition of the American Psychiatric Association diagnostic manual. However, it has received limited empirical research (Blashfield and Intoccia 2000) due in part perhaps to attention of researchers shifting their interest from PPD to the STPD added to the 1980, third edition of the diagnostic manual (Parnas et al. 2005).

#### Definition

PPD involves a pervasive and continuous distrust and suspiciousness of the motives of others (American Psychiatric Association 2000) but the disorder is more than just suspiciousness. Persons with this disorder are also hypersensitive to criticism, they respond with anger to threats to their autonomy, they incessantly seek out confirmations of their suspicions, and they tend to be quite rigid in their beliefs and perceptions of others (Millon et al. 1996, Widiger et al. 1995). The presence of PPD is indicated by four or more of the seven diagnostic criteria presented in DSM-IV-TR Criteria 301.0.

#### Differential Diagnosis

PPD paranoid ideation is inconsistent with reality and is resistant to contrary evidence, but the ideation is not psychotic, absurd, inconceivable, or bizarre. PPD will also lack other features of psychotic and delusional disorders (e.g., hallucinations) and will be evident since early adulthood, whereas a psychotic disorder will become evident later within a person's life or will remit after a much briefer period of time. Persons with PPD can develop psychotic disorders but to diagnose PPD in such cases the paranoid personality traits must be evident prior to and persist after the psychotic episode. If PPD preceded the onset of schizophrenia, then it should be noted that it was premorbid to the schizophrenia (American Psychiatric Association 2000). However, it may not be meaningful to diagnose a person with both PPD and schizophrenia, as the premorbid paranoid traits may, in some cases, have simply represented a prodromal phase of the schizophrenic pathology.

**DSM-IV-TR Criteria** 301.0

**Paranoid Personality Disorder**

A. A pervasive distrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning by early adulthood, and present in a variety of contexts, as indicated by four (or more) of the following:

   (1) suspects, without sufficient basis, that others are exploiting, harming, or deceiving him or her

   (2) is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates

   (3) is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her

   (4) reads hidden demeaning or threatening meanings into benign remarks or events

   (5) persistently bears grudges, i.e. is unforgiving of insults, injuries, or slights

   (6) perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack

   (7) has recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, or another psychotic disorder, and is not due to the direct physiological effects of a general medical condition.

**Note:** if criteria are met prior to the onset of schizophrenia, add "premorbid," e.g., paranoid personality disorder (premorbid).

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#### Epidemiology and Comorbidity

Trust versus mistrust is a fundamental personality trait along which all persons vary (McCrae and Costa 1999). Thirteen percent of the adult male population and six percent of the adult female population may be characteristically mistrustful of others (Costa and McCrae 1992). However, only 0.5–2.5% of the population are likely to meet the DSM-IV-TR diagnostic criteria for PPD (see Table 82–1). It is suggested in DSM-IV-TR that approximately 10–30% of persons within inpatient settings and 2–10% within

outpatient settings will have this disorder (American Psychiatric Association 2000), but the lower end of these rates may represent the more accurate estimate. It does appear that more males than females have the disorder (American Psychiatric Association 2000).

Paranoid personality traits will be evident in other personality disorders. Persons with AVPD will be socially withdrawn and apprehensive of others; borderline, antisocial, and narcissistic persons may be impatient, irritable, and antagonistic; and schizotypal persons may display paranoid ideation. The diagnosis of PPD will often co-occur with these other personality disorder diagnoses (see Table 82–2). Persons with PPD are prone to develop a variety of Axis I disorders, including substance-related, obsessive–compulsive anxiety, agoraphobic, and depressive disorders (American Psychiatric Association 2000).

## Course

There is very limited research on the childhood antecedents and course of PPD. What is known is based largely on clinical experience. It is suggested that premorbid traits of PPD include social isolation, hypersensitivity, hypervigilance, social anxiety, peculiar thoughts, angry hostility, and idiosyncratic fantasies (American Psychiatric Association 2000). As children, they may appear odd and peculiar to their peers and they may not have achieved to their capacity in school. Their adjustment as adults would be particularly poor with respect to interpersonal relationships. They may become socially isolated or fanatic members of groups that encourage or at least accept their paranoid ideation. They might maintain a steady employment but will be difficult coworkers, as they will tend to be rigid, controlling, critical, blaming, and prejudicial. They are likely to become involved in lengthy, acrimonious, and litigious disputes that are difficult, if not impossible, to resolve (Millon et al. 1996, Stone 1993).

## Etiology and Pathophysiology

There is only limited research on the heritability of PPD (Torgersen et al. 2000), but quite a number of studies have indicated a genetic contribution to the development of suspiciousness and mistrust (Bouchard and Loehlin 2001, Jang et al. 1998, Nigg and Goldsmith 1994). There is some support for a genetic relationship of PPD with schizophrenia but these findings have not always been replicated and the findings may have been due to the overlap of PPD with the STPD (Siever 1992). There is only limited support for a genetic relationship with delusional disorder, persecutory type (Nigg and Goldsmith 1994).

There are no systematic studies on possible psychosocial contributions to the development of PPD. There is some support for the contribution of excessive parental criticism and rejection but there has not yet been adequate prospective longitudinal studies (Miller et al. 2001). Paranoid belief systems could develop through parental modeling, a history of discriminatory exploitation or abandonment, and the isolation of anger, resentment, and bitterness onto a group that is external to and distinct from oneself. Mistrust and suspicion is often evident in members of minority groups, immigrants, refugees, and other groups for whom such distrust can be a realistic and appropriate response to the social environment. It is conceivable that a comparably sustained experience through childhood and adolescence could contribute to the development of excessive paranoid beliefs that are eventually applied inflexibly and inappropriately to a wide variety of persons, but it can be very difficult to determine what is excessive or unrealistic suspicion and mistrust within a member of an oppressed minority (Alarcon 2005). Paranoid suspiciousness could in fact be more closely associated with prejudicial attitudes, wherein a particular minority group in society becomes the inappropriate target of one's anger, blame, and resentment.

There has been little consideration given to the neurophysiological concomitants of nonpsychotic paranoid personality traits. More attention has been given to cognitive, interpersonal, and object-relational models of pathology. Paranoid beliefs do appear to have a self-perpetuating tendency resulting from the narrow and limited focus on signs and evidence for malicious intentions (Young and Klosko 2005). The pathology of PPD, from this perspective, is inherent to the irrationality of the person's belief systems and is sustained by the biased information processing. There may also be an underlying motivation or need to perceive threats in others and to externalize blame that help to sustain the accusations and distortions (Gabbard 2000a, Millon et al. 1996).

## Treatment

There are no systematic studies on the treatment of PPD. Persons with PPD would rarely seek treatment for their feelings of suspiciousness and distrust. They will experience these traits as simply accurate perceptions of a malevolent and dangerous world (i.e., ego syntonic). They may not consider the paranoid attributions to be at all problematic, disruptive, or maladaptive. They will not be delusional, but they will also fail to be reflective, insightful, or self-critical. They may recognize only that they have difficulty controlling their anger and getting along with others. They might be in treatment for an anxiety, mood, or substance-related disorder or for various marital, familial, occupational, or social (or legal) conflicts that are secondary to their personality disorder, but they will also externalize the responsibility for their problems and will have substantial difficulty recognizing their own contribution to their internal dysphoria and external conflicts. They will consider their problems to be due to what others are doing to them, not to how they perceive, react, or relate to others.

The presence of paranoid personality traits will complicate the treatment of an Axis I disorder or a relationship problem (Dolan-Sewell et al. 2001). Trust is central to the development of an adequate therapeutic alliance, and yet it is precisely the absence of trust that is central to this disorder (Bender 2005). It can be tempting to be less than forthright and open in the treatment of excessively suspicious persons because they will distort, exaggerate, or escalate minor errors, misunderstandings, or inconsistent statements. However, therapists will find that they weave an increasingly tangled web as they walk gingerly around the truth. And, persons with PPD will seize upon any kernel of deception to confirm their suspicion that the therapist is not to be trusted. It is preferable to be especially forthright and precise with paranoid patients. Details that will be inconsequential and of no interest to most patients can be important to provide to persons with PPD so that they are ensured that nothing is being withheld or hidden from them.

Clinicians agree on several general principles in the treatment of paranoid personality traits (Beck et al. 1990, Gabbard 2000a, Millon et al. 1996, Stone 1993). It is usually pointless and often harmful to rapport to confront (or argue with) the paranoid beliefs. Such efforts may only alienate the patient and confirm his or her suspicions. The therapist should maintain a sincere and consistent respect for their autonomy and for their right to make their own decisions. However, one should not attempt to ingratiate oneself by being overly acquiescent and compliant. This can appear to be obviously patronizing, insincere, or manipulative. The goal is to develop, in a nonthreatening way, more self-reflection and self-awareness (e.g., recognition of the contribution of the paranoid traits and behaviors to the difficulties they are experiencing within their lives). A useful approach can be to communicate a sincere and respectful willingness to explore the implications, logic, and reality of the suspicions (Beck et al. 1990). Whenever one appears to be endangering rapport by moving too quickly, one should retreat to a more neutral and accepting position.

One must also be careful to avoid defensive reactions to the inevitable accusations. Any one of the conflicts they have had with others can develop within the therapeutic relationship (Gabbard 2000a) and their tendency to be contentious, rigid, accusatory, suspicious, and litigious can tax the empathy and patience of the therapist. One must attempt to maintain an empathic concern for their feelings of betrayal and reassure them in an understanding, forthright manner that is neither patronizing nor disrespectful. Termination of treatment may at times be necessary if continuation would only result in further acrimony.

The suspicions, accusations, and acrimony will often make the person with PPD a poor candidate for group therapies (Piper and Ogrodniczuk 2005). There is the potential to learn much about themselves within a group, but it is usually very difficult for them to develop the feelings of trust, respect, and security that are necessary for successful group therapy. Their propensity to make unfair hostile accusations will alienate them from other group members, and they may quickly become a scapegoat for difficulties and conflicts that develop within the group.

There have been a variety of studies on the pharmacologic treatment of psychotic paranoid ideation and schizotypal personality disorder (which often includes paranoid personality traits) but little to no research on the pharmacologic responsivity of the nonpsychotic suspiciousness and ego-syntonic paranoid ideation of PPD (Markovitz 2001, Perry et al. 1999, Soloff 2005). Persons with PPD may also perceive the use of a medication to represent an effort to simply suppress or control their accusations and suspicions rather than to respectfully consider and address them. However, they may be receptive and responsive to the benefits of a medication to help control feelings of anxiousness or depression that are secondary to their personality disorder.

## Schizoid Personality Disorder

Schizoid personality disorder (SZPD) has been in every edition of the American Psychiatric Association diagnostic manual. However, it has received limited empirical research (Blashfield and Intoccia 2000) due in part perhaps to attention of researchers shifting their interest from SZPD to the STPD added to the 1980, third edition of the diagnostic manual (Kalus et al. 1993, Parnas et al. 2005).

### Definition

SZPD is a pervasive pattern of social detachment and restricted emotional expression. Introversion (versus extraversion) is one of the fundamental dimensions of general personality functioning (McCrae and Costa 1999). Facets of introversion include low warmth (e.g., cold, detached, and impersonal), low gregariousness (socially isolated, withdrawn), and low positive emotions (reserved, constricted or flat affect, and anhedonic), which define well the central symptoms of SZPD (Widiger et al. 2002, see Table 82–3). The presence of SZPD is indicated by four or more of the seven diagnostic criteria presented in DSM-IV-TR Criteria 301.20.

### Differential Diagnosis

SZPD can be confused with the STPD and AVPD, as both involve social isolation and withdrawal (Kalus et al. 1993, Widiger et al. 1995). STPD, however, also includes an intense social anxiety and cognitive–perceptual aberrations.

**DSM-IV-TR Criteria** 301.20

**Schizoid Personality Disorder**

A. A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

   (1) neither desires nor enjoys close relationships, including being part of a family

   (2) almost always chooses solitary activities

   (3) has little, if any, interest in having sexual experiences with another person

   (4) takes pleasure in few, if any, activities

   (5) lacks close friends or confidants other than first-degree relatives

   (6) appears indifferent to the praise or criticism of others

   (7) emotional coldness, detachment, or flattened affectivity

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder, and is not due to the direct physiological effects of a general medical condition.

**Note:** if criteria are met prior to the onset of schizophrenia, add "premorbid," e.g., schizoid personality disorder (premorbid).

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The major distinction with AVPD is the absence of an intense desire for intimate social relationships. Both avoidant and schizoid persons are introverted, but the schizoid person is driven by an anhedonic disinterest in relationships (extremely low in positive emotionality) whereas the avoidant person is driven by a self-conscious neuroticism. Avoidant persons will exhibit substantial insecurity and inhibition (high neuroticism), whereas the schizoid person is largely indifferent toward the reactions or opinions of others (Widiger et al. 1995, 2002).

The presence of premorbid schizoid traits is considered to have prognostic significance for the course and treatment of schizophrenia (Siever 1992) but, more importantly, it might not be meaningful to suggest that a person has a schizoid personality disorder that is independent of or unrelated to a comorbid schizophrenia. The negative, prodromal, and residual symptoms of schizophrenia resemble closely the features of SZPD. Once a person develops schizophrenia, a diagnosis of SZPD can become rather pointless, as all of the schizoid symptoms can then be understood as (prodromal or residual) symptoms of schizophrenia.

## Epidemiology and Comorbidity

Approximately half of the general population will exhibit introversion within the normal range of functioning. However, only a small minority of the population would be diagnosed with a schizoid personality disorder (Mattia and Zimmerman 2001). Estimates of the prevalence of SZPD within the general population have been less than 1% (see Table 82–1) and SZPD is among the least frequently diagnosed personality disorders within clinical settings. Many of the persons who were diagnosed with SZPD prior to DSM-III are probably now diagnosed with either the avoidant or the STPD (Widiger et al. 1988) and prototypic (pure) cases of SZPD are likely to be quite rare within the population.

## Course

There are few systematic studies on the childhood antecedents of and adult course of SZPD. Persons with SZPD are likely to have been socially isolated and withdrawn as children. They may not have been accepted well by their peers and may have even been the brunt of some ostracism (American Psychiatric Association 2000). As adults, they will have few friendships (Stone 1993). The friendships that do occur are likely to have been initiated by their peers or colleagues. They will have had few sexual relationships and may never marry. Relationships will fail to the extent to which the other person desires or needs emotional support, warmth, and intimacy. Persons with SZPD may do well and even excel within an occupation, as long as substantial social interaction is not required. They would prefer to work in isolation. They may eventually find employment and a relationship that is relatively comfortable, but they could also drift from one job to another and remain isolated throughout much of their life. If they do eventually become a parent, they will have considerable difficulty providing warmth and emotional support, and they may appear neglectful, detached, and disinterested.

## Etiology and Pathophysiology

A fundamental distinction for schizophrenic symptomatology is between positive and negative symptoms (Walker et al. 2004). Positive symptoms include hallucinations, delusions, inappropriate affect, and loose associations; negative symptoms include flattened affect, alogia, anhedonia, and avolition. SZPD could be conceptualized as representing subthreshold negative symptoms, comparable to the subthreshold positive symptoms (cognitive–perceptual aberrations) that predominate STPD (Miller et al. 2001, Parnas et al. 2005). However, a genetic link of SZPD to schizophrenia that cannot be accounted for by comorbid STPD symptomatology has not been well established (Miller et al. 2001). There is only limited research on the heritability of SZPD (Torgersen et al. 2000) but quite a number of studies have indicated a genetic contribution for the personality dimension of introversion (Bouchard and Loehlin 2001, Jang et al. 1998, Jang and Vernon 2001). The pathology of SZPD is considered to be anhedonic deficits, or an excessively low ability to experience positive affect, which is also central to the general personality trait of introversion (Rothbart et al. 2000). Psychosocial models for the etiology of SZPD are lacking. It is possible that a sustained history of isolation during infancy and childhood, with an encouragement and modeling by parental figures of interpersonal withdrawal, indifference, and detachment, could contribute to the development of schizoid personality traits (Bernstein and Travaglini 1999).

## Treatment

There have been many studies on the pharmacologic treatment of the STPD but no comparable studies on SZPD (Markovitz 2001, Perry et al. 1999, Soloff 2005). The STPD and SZPD share many features, but the responsivity of the STPD to pharmacotherapy will usually reflect schizotypal social anxiety and cognitive–perceptual aberrations that are not seen in prototypic, pure cases of SZPD. Prototypic cases of SZPD would rarely present for treatment, whether it is for their schizoid traits or a concomitant Axis I disorder. They would feel little need for treatment, as their isolation will often be ego syntonic. Their social isolation will be of more concern to their relatives, colleagues, or friends than to themselves. Their disinterest in and withdrawal from intimate or intense interpersonal contact will also be a substantial barrier to treatment. They will at times appear depressed but one must be careful not to confuse their anhedonic detachment, withdrawal, and flat affect with symptoms of depression.

If persons with SZPD are seen for treatment for a concomitant Axis I disorder (e.g., a sexual arousal disorder or a substance dependence), it is advisable to work within the confines and limitations of the schizoid personality traits (Beck et al. 1990, Stone 1993). Charismatic, engaging, emotional, or intimate therapists can be very uncomfortable, foreign, and even threatening to persons with SZPD. A more businesslike approach can be more successful (Beck et al. 1990).

It is also important not to presume that persons with SZPD are simply inhibited, shy, or insecure. Such persons are more appropriately diagnosed with AVPD. Persons with SZPD are perhaps best treated with a supportive psychotherapy that emphasizes education and feedback concerning interpersonal skills and communication (Stone 1993). One may not be able to increase the desire for social involvements, but one can increase the ability to relate to, communicate with, and get along with others. Persons with SZPD may not want to develop intimate relationships, but they will

often want to interact and relate more effectively and comfortably with others. The use of role-playing and videotaped interactions can at times be useful in this respect. Persons with SZPD can have tremendous difficulty understanding how they are perceived by others or how their behavior is unresponsive to and perceived as rejecting by others.

Group therapy is often useful as a setting in which the patient can gradually develop self-disclosure, experience the interest of others, and practice social interactions with immediate and supportive feedback (Piper and Ogrodniczuk 2005). However, persons with SZPD are prone to being rejected by a group due to their detachment, flat affect, and indifference to the feelings of others. If the group is patient and accepting, they can benefit from the experience.

## Schizotypal Personality Disorder

STPD was a new addition to DSM-III (American Psychiatric Association 1980). It was developed through the process of constructing BPD, both being gleaned from a broad clinical and research literature discussing cases of "borderline schizophrenia," "borderline personality," "latent schizophrenia," and other similar constructs (Spitzer et al. 1979).

### Definition

STPD is a pervasive pattern of interpersonal deficits, cognitive–perceptual aberrations, and eccentricities of behavior (American Psychiatric Association 2000). The interpersonal deficits are characterized in large part by an acute discomfort with and reduced capacity for close relationships. The symptomatology of STPD has been differentiated further into components of positive (cognitive–perceptual aberrations) and negative (social aversion and withdrawal) symptoms comparable to the distinctions made for schizophrenia (Squires-Wheeler et al. 1997). The presence of STPD is indicated by five or more of the nine diagnostic criteria presented in DSM-IV-TR Criteria 301.22.

### Differential Diagnosis

AVPD and STPD share the features of social anxiety and introversion, but the social anxiety of STPD does not diminish with familiarity, whereas the anxiety of AVPD is concerned primarily with the initiation of a relationship (Widiger et al. 1995). STPD is also a more severe disorder that includes a variety of cognitive–perceptual aberrations that are not seen in persons with AVPD.

An initial concern of many clinicians when confronted with a person with STPD is whether the more appropriate diagnosis is schizophrenia. Persons with STPD closely resemble persons within the prodromal or residual phases of schizophrenia. This differentiation is determined largely by the absence of a deterioration in functioning. It is indicated in DSM-IV-TR that one should note that STPD is "premorbid" if the schizotypal symptoms were present prior to the onset of schizophrenia (American Psychiatric Association 2000). Premorbid schizotypal traits will have prognostic significance for the course and treatment of schizophrenia, and such traits should then be noted (Siever 1992). However, as discussed for SZPD, in most of these cases the STPD symptoms could then be readily understood as prodromal symptoms of schizophrenia. It should be emphasized, however, that only a very small minority of persons meeting criteria for STPD go on to develop schizophrenia (Raine 2006).

**DSM-IV-TR Criteria** 301.22

**Schizotypal Personality Disorder**

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood, and present in a variety of contexts, as indicated by five (or more) of the following:

   (1) ideas of reference (excluding delusions of reference)

   (2) odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations)

   (3) unusual perceptual experiences, including bodily illusions

   (4) odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped)

   (5) suspiciousness or paranoid ideation

   (6) inappropriate or constricted affect

   (7) behavior or appearance that is odd, eccentric, or peculiar

   (8) lacks close friends or confidants other than first-degree relatives

   (9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder.

**Note:** if criteria are met prior to the onset of schizophrenia, add "premorbid," e.g., schizotypal personality disorder (premorbid).

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### Epidemiology and Comorbidity

STPD may occur in as much as 3% of the general population, although most studies with semistructured interviews have suggested a somewhat lower percentage (see Table 82–1). STPD might occur somewhat more often in males (Parnas et al. 2005). STPD co-occurs most often with the schizoid, borderline, avoidant, and paranoid personality disorders (see Table 82–2). Common Axis I disorders are major depressive disorder and generalized social phobia (Miller et al. 2001).

## Course

There is insufficient research to describe the childhood precursors of adult STPD, although there are studies on infant and childhood neurodevelopmental abnormalities of persons with STPD (Parnas et al. 2005, Raine 2006). Persons with STPD would be expected to appear peculiar and odd to their peers during adolescence, and may have been teased or ostracized. Achievement in school might be impaired, and they may have been heavily involved in esoteric fantasies and peculiar interests. As adults, they may drift toward esoteric, fringe groups that support their magical thinking and aberrant beliefs. These activities can provide structure for some persons with STPD, but they can also contribute to a further loosening and deterioration if there is an encouragement of aberrant experiences. The symptomatology of STPD does not appear to remit with age (Miller et al. 2001, Raine 2006). The course appears to be relatively stable, with some proportion of schizotypal persons remaining marginally employed, withdrawn, and transient throughout their lives. As noted earlier, some persons meeting DSM-IV-TR criteria for STPD do eventually go on to develop schizophrenia (Walker et al. 2004) but the vast majority of cases do not (Raine 2006). Schizotypal symptomatology, as measured in scales assessing cognitive–perceptual aberrations, magical thinking, and social and physical anhedonia, has been studied longitudinally in a number of community samples, and the findings to date do not suggest any meaningful likelihood of the development of schizophrenia (Gooding et al. 2005).

## Etiology and Pathophysiology

There is compelling empirical support for a genetic association of STPD with schizophrenia (Fanous et al. 2001, Jang and Vernon 2001), which is not surprising given that the diagnostic criteria were obtained from the observations of biological relatives of persons with schizophrenia (Miller et al. 2001, Siever and Davis 2004). STPD is in fact classified within the World Health Organization (1992) International Classification as a form of schizophrenia rather than as a personality disorder. Inconsistent with this classification, however, is that STPD is much more comorbid with other personality disorders than with psychotic disorders and schizotypal symptomatology is evident within the general population with no apparent relationship to schizophrenia (Raine 2006).

A predominant model for the psychopathology of STPD is deficits or defects in the attention and selection processes that organize a person's cognitive–perceptual evaluation of and relatedness to his or her environment (Raine 2006). These defects may lead to discomfort within social situations, misperceptions, and suspicions, and to a coping strategy of social isolation. Correlates of central nervous system dysfunction seen in persons with schizophrenia have been observed in laboratory tests of persons with STPD, including performance on tests of visual and auditory attention (e.g., backward masking and sensory gating tests) and smooth pursuit eye movement (Parnas et al. 2005). This dysfunction may be the result of dysregulation along dopaminergic pathways, which could be serving to modulate the expression of an underlying schizotypal genotype (Raine 2006).

## Treatment

Persons with STPD may seek treatment for their feelings of anxiousness, perceptual disturbances, or depression. Treatment of persons with STPD should be cognitive, behavioral, supportive, and/or pharmacologic, as they will often find the intimacy and emotionality of reflective, exploratory psychotherapy to be too stressful and they have the potential for psychotic decompensation.

Persons with STPD will often fail to consider their social isolation and aberrant cognitions and perceptions to be particularly problematic or maladaptive. They may consider themselves to be simply eccentric, creative, or nonconformist. Rapport can be difficult to develop, as increasing familiarity and intimacy may only increase their level of discomfort and anxiety (Siever 1992). They are unlikely to be responsive to informality or playful humor. The sessions should be well structured to avoid loose and tangential ideation.

Practical advice is usually helpful and often necessary (Beck et al. 1990). The therapist should serve as the patient's counselor, guide, or "auxiliary ego" to more adaptive decisions with respect to everyday problems (e.g., finding an apartment, interviewing for a job, and personal appearance). Persons with STPD should also receive social skills training directed at their awkward and odd behavior, mannerisms, dress, and speech. Specific, concrete discussions on what to expect and do in various social situations (e.g., formal meetings, casual encounters, and dates) should be provided. The rate of progress will tend to be slow, and it

Clinical Vignette 1

LK was a 34-year-old male. He was referred to the Day Hospital Treatment Program by his parents. He had been living with them since his graduation from high school, with no apparent prospects of leaving home. They did not object to his staying at home, but they were now approaching retirement and they were worried that he might not be able to support himself. He was unemployed, had no close friends, and spent much of his time in his room with a computer.

LK was first diagnosed with schizotypal personality disorder at the age of 26. The diagnosis was influential in his obtainment of disability income. He had been unemployed since the age of 19. His career goal was to become a successful fortune-teller. He had no history of psychotic episodes, although he had at times become intensely involved in fringe belief systems. The only time he had left home for any significant period was to participate on a quest for a close encounter with an alien in the deserts of Arizona. No concrete, physical encounters occurred, but he did claim to have experienced a variety of signs of alien communication. He was also an active student of "numerology," or the study of the symbolic and spiritual significance of numbers. He described himself as a "3-8-4."

He did not complain of any clinical symptoms other than chronic feelings of anxiousness, which at times escalated to the point that he felt unable to leave the house. He was also rather odd in his appearance. For example, he would often wear thick red flannel shirts in the summer with lime green pants, and then switch to red pants and a green flannel shirt the next week. He cut his own hair, creating an erratic, peculiar appearance. He described a history of fleeting, superficial relationships. He would at times feel lonely but stated that he found most people to be "discomforting."

*(continues)*

His treatment consisted of group therapy, supportive psychotherapy, and a (low-dosage) neuroleptic. He found the group therapy to be helpful in providing feedback regarding his appearance and mannerisms, such as staring intently at persons and then exclaiming "what, what, what?!" when eye contact was made or drifting off into tangential topics during conversations. The supportive psychotherapy focused on improving his social judgment and awareness, including grooming, hygiene, and dress. Therapy also included discussions of his experiences, misperceptions, and difficulties with persons within the group and elsewhere. He was also referred to the Occupational Activities Program for counseling and guidance regarding employment. He eventually obtained a trainee position within a wholesale computer dealership. He found the job to be quite satisfying, as it allowed him to work with computers and required little contact with others.

is helpful if there remains a continuity in the therapeutic relationship (Stone 1993).

Most of the systematic empirical research on the treatment of STPD has been confined to pharmacologic interventions. Low doses of neuroleptic medications (e.g., thiothixene) have shown some effectiveness in the treatment of schizotypal symptoms, particularly the perceptual aberrations and social anxiousness (Markovitz 2001, Soloff 2005). Group therapy has also been recommended for persons with STPD but only when the group is highly structured and supportive (Piper and Ogrodniczuk 2005). The emotional intensity and intimacy of unstructured groups will usually be too stressful. Schizotypal patients with predominant paranoid symptoms may even have difficulty in highly structured groups.

## Antisocial Personality Disorder

ASPD has been included within every edition of the American Psychiatric Association's diagnostic manual. It is perhaps the prototypic personality disorder, as the term "psychopathy" originally referred to all cases of personality disorder (Schneider 1923). The term "psychopathy" now refers to a more severe variant of ASPD that predominates much of the current research literature on ASPD (Hare 2003).

### Definition

ASPD is a pervasive pattern of disregard for and violation of the rights of others (American Psychiatric Association 2000). Its primary diagnostic criteria include criminal activity, deceitfulness, impulsivity, recklessness, aggressiveness, irresponsibility, and indifference to the mistreatment of others (see DSM-IV-TR Criteria 301.7). DSM-IV-TR ASPD overlaps substantially with psychopathy, as it is assessed by the frequently used Psychopathy Checklist—Revised (PCL-R; Hare 2003). The primary differences are the inclusion of glib charm, arrogance, lack of empathy, and shallow affect within the PCL-R, and the requirement within DSM-IV-TR for evidence of conduct disorder within childhood (Widiger 2005b).

### Differential Diagnosis

The PCL-R is a checklist that is particularly well suited for the assessment of this disorder within settings that are heavily populated by persons with a criminal history (e.g., prison and forensic settings), as it includes psychopathic traits that are relatively more specific to ASPD within such settings, such as lack of empathy, glib charm, and arrogance (McDermut and Zimmerman in press, Widiger et al. 2002). The PCL-R, however, may not be used effectively within general clinical settings, as the assessment of much of its items depends heavily on a respondent's legal record and criminal history (Widiger 2005b).

ASPD will at times be difficult to differentiate from a substance-dependence disorder in young adults because many persons with ASPD develop a substance-related disorder and many persons with a substance dependence engage in antisocial acts. The requirement that the ASPD features be evident prior to the age of 15 though will usually assure the onset of ASPD prior to the onset of a substance-related disorder. If both are evident prior to the age of 15, then it is likely that both disorders are in fact present and both diagnoses should then be made (Widiger 2005b). ASPD and substance dependence will often interact, exacerbating and escalating each other's development (Sutker and Allain 2001).

**DSM-IV-TR Criteria** 301.7

**Antisocial Personality Disorder**

A. There is a pervasive pattern of disregard for and violation of the rights of others (occurring since age 15 years), as indicated by three (or more) of the following:
   (1) failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
   (2) deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
   (3) impulsivity or failure to plan ahead
   (4) irritability and aggressiveness, as indicated by repeated physical fights or assaults
   (5) reckless disregard for safety of self or others
   (6) consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
   (7) lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

B. The individual is at least age 18 years.

C. Evidence of conduct disorder with onset before age 15 years.

D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or a manic episode.

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## Epidemiology and Comorbidity

The National Institute of Mental Health Epidemiologic Catchment Area Study indicated that approximately 3% of males and 1% of females have ASPD (Robins et al. 1991). This rate has been replicated in subsequent studies, but it has also been suggested that the study may have underestimated the prevalence in males due to the failure to consider the full range of ASPD features. Other estimates have been as high as 6% in males (Kessler et al. 1994). The rate of ASPD within prison and forensic settings has been estimated at 50% (Hare 2003, Robins et al. 1991) but the ASPD criteria may exaggerate the rate within such settings due to the emphasis given to overt acts of criminality, delinquency, and irresponsibility that are common to the persons within these settings (Sutker and Allain 2001). More specific criteria for psychopathy provide a more conservative estimate of 20–30% of male prisoners with ASPD (Hare 2003).

ASPD is much more common in men than in women (Robins et al. 1991). A sociobiological explanation for the differential sex prevalence is the presence of a genetic advantage for social irresponsibility, infidelity, superficial charm, and deceit in males that contributes to a higher likelihood of developing features of ASPD (i.e., males with these traits are more likely to have offspring than males without these traits) (Sutker and Allain 2001). Persons with ASPD are likely to display borderline, narcissistic, and paranoid personality traits (see Table 82–2).

## Course

ASPD is one personality disorder for which much is known about childhood antecedents, as it is well documented that persons diagnosed with childhood-onset conduct disorder have a considerable risk of meeting the DSM-IV-TR criteria for ASPD as an adult (American Psychiatric Association 2000). The diagnosis of ASPD in fact requires an evidence of conduct disorder in childhood. There are also compelling data to indicate that ASPD is a relatively chronic disorder, although as the person reaches middle to older age research suggests that the frequency of criminal acts appears to decrease. Nevertheless, the core personality traits may remain largely stable (Harpur and Hare 1994).

As adults, persons with ASPD are unlikely to maintain steady employment, and they may even become impoverished, homeless, or spend years within penal institutions (Robins et al. 1991). However, some persons with ASPD characterized by high rather than low levels of conscientiousness may express their psychopathic tendencies within a socially acceptable or at least legitimate profession (Hare 2003). They may in fact be quite successful as long as their tendency to bend or violate the norms or rules of their profession and exploit, deceive, and manipulate others contribute to a career advancement. Their success, however, may at some point unravel when their psychopathic behaviors become problematic or evident to others. The same pattern may also occur within sexual and marital relationships. They may at first appear to be charming, engaging, and sincere, but most relationships will end due to a lack of empathy, responsibility, and fidelity. Persons with ASPD, however, are more likely than the general population to have died prematurely by violent means (e.g., accidents or homicides) and to engage in quite dangerous, high-risk behavior (Sutker and Allain 2001).

## Etiology and Pathophysiology

There is considerable support from twin, family, and adoption studies for a genetic contribution to the etiology of the criminal, delinquent tendencies of persons with ASPD (Waldman and Rhee 2006). Exactly what is inherited in ASPD, however, is not known. It could be impulsivity, an antagonistic callousness, or an abnormally low anxiousness, or all of these dispositions combined.

Numerous environmental factors have also been implicated in the etiology of antisocial behavior. Shared, or common, environmental influences account for 15–20% of variation in criminality or delinquency (Rhee and Waldman 2002). Not surprisingly, shared environmental factors such as low family income, inner city residence, poor parental supervision, single-parent households, rearing by antisocial parents, delinquent siblings, parental conflict, harsh discipline, neglect, large family size, and young mother have all been implicated as risk factors for antisocial behavior (Farrington 2006). The effects of these factors are not limited to learning. For instance, neglect and physical abuse can generate several possible avenues to the development of antisocial and aggressive behavior, such as desensitization to pain, impulsive coping styles, and early contact with the justice system (Sutker and Allain 2001). Nonshared environmental influences are also substantial contributors. Factors specific to the individual appear to account for fully 30% of antisocial behavior (Moffitt 2005). In short, this is the remaining variance not accounted for by genetic (50%) or shared environmental (20%) influences. Nonshared environmental factors may include delinquent peers, individual social and academic experiences, or sexual, physical abuse.

Considerable research effort has been focused on trying to isolate the primary pathology of antisocial behavior (Derefinko and Widiger in press). This extensive research base indicates that many deficits are involved in antisocial behavior, leading to a very complex picture of pathology. Historically, the individual with ASPD was said to suffer from a "superego lacunae" or deficits of the conscience, later modified in Cleckley's (1941) and Hare's (2003) descriptions of "semantic dementia," or a deficient processing of feelings and emotion. Laboratory research is now providing support for this theoretical model in studies assessing the psychopath's autonomic reaction to emotional words and fearful images.

The notorious failure of persons with ASPD to accurately anticipate negative consequences has often suggested a psychopathic cognitive deficit (Hiatt and Newman 2006). Existing literature indicates that the psychopathic person experiences stable deficits in the cognitive domains of attention and response modulation. According to this theory, persons with this disorder continue to engage in positively reinforcing behaviors even when they become substantially maladaptive (Newman and Lorenz 2003). Many psychophysiological deficits have also been associated with psychopathy, including an abnormally low physiological response (reduced skin conductance), suggesting that persons with ASPD may not develop the expected anticipatory arousal from threat of physical punishment. Additional autonomic arousal assessments include low resting heart rate levels and startle response deficits (Derefinko and Widiger in press). There is also the suggestion that persons with ASPD may have abnormally low levels of anxiousness. Some distress proneness (neuroticism) and attentional self-regulation

(constraint or conscientiousness) may be necessary in order to develop an adequate sense of guilt or conscience. Normal levels of neuroticism will promote the internalization of a conscience by associating wrongdoing or misbehavior with distress and anxiety, and the temperament of self-regulation will help modulate impulses into socially acceptable channels (Fowles and Kochanska 2000).

## Treatment

ASPD is considered to be the most difficult personality disorder to treat (Gunderson and Gabbard 2000, Stone 1993). Individuals with ASPD can be seductively charming and declare a commitment to change, but they often lack sufficient motivation. Their declarations of wanting to change might even be dishonest. They often fail to see the costs associated with antisocial acts (e.g., imprisonment, eventual impoverishment, and lack of meaningful interpersonal relationships) and may stay in treatment only as required by an external source, such as a parole. Residential programs that provide a carefully controlled environment of structure and supervision, combined with peer confrontation, have been recommended (Gunderson and Gabbard 2000). However, it is unknown what benefits may be sustained after the ASPD individual leaves this environment. When in inpatient treatment, individuals with ASPD may manipulate and exploit staff and fellow patients (Piper and Ogrodniczuk 2005). Studies have indicated that outpatient therapy is not likely to be successful, although the extent to which persons with ASPD are entirely unresponsive to treatment may have been somewhat exaggerated (Salekin 2001).

### Clinical Vignette 2

MF was a 24-year-old male, born in Miami, Florida. His biological mother died when he was 3 as the result of a stray bullet during a drug-related dispute. It was unclear whether his mother was herself involved in this dispute. He was taken from his biological father at the age of 6 due to a history of neglect and physical abuse. He then lived in a series of foster homes until the age of 10 when he was adopted by Mr. and Mrs. F.

Mr. and Mrs. F adopted M because they felt too old to raise a child from birth and wished to "give back to society what they had received." They were quite wealthy and wanted to provide a chance in life for a child from a disadvantaged background. However, they had difficulty from the beginning controlling M. He was first referred to treatment at the age of 13 for setting fire to the school. He was diagnosed with a conduct disorder but was described by his therapist as being tearful, remorseful, and ashamed. Treatment was said to be successful.

At the age of 16 he was remanded to treatment by a juvenile court for assaulting a police officer who had caught him trying to break into a neighbor's home. Mr. and Mrs. F acknowledged at his court hearing that he had a history of criminal behavior. Since his arrival within their home he had pawned expensive articles from the home and repeatedly vandalized the house. His parents, however, felt that he simply needed more patience, understanding, and love. They noted that after each "incident" he was always very remorseful. They characterized his various aggressive and criminal acts as "occasional setbacks" or "falling off the wagon."

Treatment at this time revealed an apparent history of sexual abuse by an older male sibling within one of the foster homes. MF tearfully recounted lurid episodes of sexual victimization and attributed his difficulty controlling his behavior to the abuse he had received from this sibling and his father. Treatment was terminated after 1.5 years of outpatient therapy with no apparent recurrence of criminal or aggressive acts.

MF, however, was again referred to treatment at the age of 24 when he was arrested for attempting to sexually abuse a neighbor's child. He presented as an intelligent, cultured young man who was ashamed, mortified, and distraught over his "inability" to control his sexual urges. He was diagnosed with pedophilia and referred to both individual and group treatment within a sexual offender's program. He discussed within his therapies of being sexually abused not only by a foster brother but also by his father.

However, his involvement within the program was questioned when he was discovered at night within the treatment center. He explained that he was simply trying to find his wallet that he left there after one of the group sessions. However, he had no explanation for how he had managed to enter the locked building. He claimed that the entry and office doors had not been locked. Members of his group spoke passionately on his behalf to be allowed to remain within the program. The staff was also painfully ambivalent. On the one hand, he was indeed the result of an abusive and neglectful history; on the other hand, he had committed a serious violation of the treatment program. The decision, however, became easier when it was discovered that he was sexually involved with a member of the staff, another program violation. He had stolen the keys from her. His motivation for treatment was also diminished substantially by the withdrawal of the sexual abuse charges by the neighbor's child and parents. MF's parents had apparently interceded on his behalf. The parents, however, continued to insist that he receive some form of treatment. He was then transferred to a summer residential program. After he left the sexual offenders program, group members acknowledged having been intimidated and threatened. Staff and patients concluded that he was in the building in order to obtain copies of the patients' confidential files.

The new treatment program was more actively confrontational and less tolerant. He eventually acknowledged that his past claims of being sexually abused were fraudulent. He had been physically abused by his biological father but he had not been sexually abused by him or anyone else. It was also discovered that he had gambled and lost a substantial amount of his parents' money, and had avoided a series of possible arrests by soliciting and obtaining the support of his parents and sympathetic victims.

MF proved to be very difficult to treat. It was never clear when he was being honestly remorseful and insightful, or simply saying what he believed the staff wanted to hear. His level of intelligence, verbal skills, and engaging charm were very compelling. He was indeed troubled by his past neglect and abuse. He would at times be able to acknowledge the bitterness, anger, and hurt from the past, and yet he would then use whatever sympathy or empathy this history elicited to attempt to manipulate the staff. When confronted with this disingenuous manipulation he would then confess, express regret and remorse, and attempt a new ploy. None of the staff felt that they were able to develop a really meaningful relationship. He completed the summer program but the staff was pessimistic regarding his future.

Therapists of individuals with ASPD should bear in mind that they may have considerable negative feelings toward clients with extensive histories of aggressive, exploitative, and abusive behaviors (Gunderson and Gabbard 2000). Rather than attempt to develop a sense of conscience in these individuals, therapeutic techniques should perhaps be focused on rational and utilitarian arguments against repeating past mistakes. These approaches would focus on the tangible, material value of prosocial behavior (Beck et al. 1990, Young et al. 2003). Some research has indicated that impulsive aggression might be treated with lithium, though its effect on other ASPD symptomatology remains to be seen (Markovitz 2001, Soloff 2005).

## Borderline Personality Disorder

BPD was a new edition to DSM-III (American Psychiatric Association 1980, Spitzer et al. 1979) and has since become the single most frequently diagnosed (Gunderson 2001) and studied (Blashfield and Intoccia 2000) personality disorder.

### Definition

BPD is a pervasive pattern of impulsivity and instability in interpersonal relationships, affect, and self-image (American Psychiatric Association 2000). Its primary diagnostic criteria include frantic efforts to avoid abandonment, unstable and intense relationships, impulsivity (e.g., substance abuse, binge eating, or sexual promiscuity), recurrent suicidal thoughts and gestures, self-mutilation, and episodes of rage and anger (see DSM-IV-TR Criteria 301.83).

### Differential Diagnosis

An instrument that is focused specifically on the assessment of BPD is the Diagnostic Interview for Borderlines—Revised (DIB-R; Zanarini et al. 1989). The DIB-R provides a more thorough assessment of components of BPD (e.g., impulsivity, affective dysregulation, and cognitive–perceptual aberrations) than is provided by more general DSM-IV-TR personality disorder semistructured interviews discussed earlier but psychiatrists might also find it impractical to devote up to 2 hours to assess one particular personality disorder, especially when it is likely that other maladaptive personality traits not covered by the DIB-R are also likely to be present (McDermut and Zimmerman in press, Widiger et al. 2006).

Most persons with BPD develop quite a number of Axis I mental disorders, including mood, dissociative, eating, substance-use, and anxiety disorders (Pfohl 2005). It can be difficult to differentiate BPD from these disorders if the assessment is confined to current symptomatology (Gunderson 2001). The diagnostic criteria for BPD require that the symptomatology be evident since adolescence, which should differentiate BPD from Axis I disorder in all cases other than a chronic mood disorder. If a chronic mood disorder is present, then the additional features of transient, stress-related paranoid ideation, dissociative experiences, impulsivity, and anger dyscontrol of BPD should be emphasized in the diagnosis (Gunderson 2001).

### Epidemiology

Approximately 1–2% of the general population would meet the DSM-IV-TR criteria for BPD (see Table 82–1). BPD is the most prevalent personality disorder within most clinical settings. Approximately 15% of all inpatients (51% of inpatients with a personality disorder) and 8% of all outpatients (27% of outpatients with a personality disorder) will have a BPD. Approximately 75% of persons with BPD will be female (Gunderson 2001).

**DSM-IV-TR Criteria** 301.83

**Borderline Personality Disorder**

A. A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

(1) frantic efforts to avoid real or imagined abandonment. **Note:** do not include suicidal or self-mutilating behavior covered in criterion 5

(2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation

(3) identity disturbance: markedly and persistently unstable self-image or sense of self

(4) impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). **Note:** do not include suicidal or self-mutilating behavior covered in criterion 5

(5) recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior

(6) affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)

(7) chronic feelings of emptiness

(8) inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)

(9) transient, stress-related paranoid ideation or severe dissociative symptoms

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### Course

Individuals with BPD are likely to have been emotionally unstable, impulsive, and hostile as children but there is in fact little longitudinal research on the childhood antecedents of BPD (Gunderson 2001, Silk et al. 2005). As adolescents, their intense affectivity and impulsivity may contribute to involvement with rebellious groups, along with a variety of Axis I disorders, including eating, substance, and mood disorders. BPD is at times diagnosed in children and adolescents but considerable caution should be used when doing so, as some of the symptoms of BPD (e.g., identity disturbance, hostility, and unstable relationships) could be confused with a normal adolescent rebellion or identity crisis (Ad-Dab'bagh and Greenfield 2001, Gunderson 2001).

As adults, persons with BPD may be repeatedly hospitalized, due to their affect and impulse dyscontrol, psychoticlike and dissociative symptomatology, and suicide attempts (Gunderson 2001, Stone 2005). The risk of suicide is increased with a comorbid mood disorder and substance-related disorder. It is estimated that 3–10% of persons with BPD will have committed suicide by the age of 30 (Gunderson 2001). Intimate relationships tend to be very unstable and explosive, and employment history is generally poor (Stone 2001). As the person reaches the age of 30, affective lability and impulsivity may begin to diminish. These symptoms may lessen earlier if the person becomes involved with a supportive and patient sexual partner (Stone 2001). Some, however, may obtain stability by abandoning the effort to obtain a relationship, opting instead for a lonelier but less volatile life. Occurrence of a severe stressor, however, can easily disrupt the lessening of symptomatology, resulting in a brief psychotic, dissociative, or mood disorder episode.

A controversy within the research literature is the rate of remission of BPD. Some longitudinal studies have provided high rates of remission (Skodol et al. 2005, Zanarini et al. 2005). However, some of these findings may simply represent errors during intake assessments (Widiger 2005a). Gunderson et al. (2003) provided details concerning the recent history for many of the persons diagnosed with BPD that were subsequently described as experiencing sudden, dramatic remissions. For one of the participants, the symptoms were attributed to the use of a stimulant for weight reduction during the year prior to the beginning of the study: "[T]he most dramatic improvement following a treatment intervention occurred when a subject discontinued a psychostimulant she had used the year prior to baseline for purposes of weight loss.…Discontinuation was followed by a dramatic reduction of her depression, panic, abandonment fears, and self-destructiveness" (Gunderson et al. 2003, p 116). The underlying general personality structure of the patients does appear to be relatively more stable (Warner et al. 2004).

## Etiology and Pathophysiology

There are studies supportive of BPD as a disorder with a distinct genetic disposition but many studies have also suggested a shared genetic association with mood and impulse control disorders (Torgersen 2005). There is also substantial empirical support for a childhood history of physical and/or sexual abuse, parental conflict, loss, and neglect (Silk et al. 2005). Past traumatic events are present in many (if not most) cases of BPD, contributing to the comorbidity with posttraumatic stress and dissociative disorders (Gunderson 2001, Hefferman and Cloitre 2000). BPD is perhaps best understood as an interaction of an emotionally unstable temperament with a cumulative and evolving series of intensely pathogenic relationships (Gunderson 2001, Widiger 2005d).

The pathogenic mechanisms of BPD are addressed in numerous theories (Stone 2005). Most concern issues of abandonment, separation, and/or exploitative abuse. Persons with BPD will often describe quite intense, disturbed, and/or abusive relationships with the significant persons of their past life (Gunderson 2001). The development of malevolent perceptions and expectations of others is not surprising (Ornduff 2000). These malevolent expectations and lingering feelings of bitterness and rage, along with an impairment in the ability to regulate affect (Chapman and Linehan 2005), may contribute to the perpetuation of intense, hostile, and unstable relationships.

## Treatment

Patients with BPD form relationships with therapists that are similar to their other significant relationships; that is, the therapeutic relationship can often be tremendously unstable, intense, and volatile (American Psychiatric Association 2001). Ongoing consultation with colleagues is recommended to address the therapist's negative reactions toward the client (e.g., distancing, rejecting, or abandoning the patient in response to feelings of anger or frustration) as well as positive reactions (e.g., fantasies of being the therapist who in fact rescues or cures the patient, or romantic, sexual feelings in response to a seductive patient). Sessions should emphasize the building of a strong therapeutic alliance, monitoring of self-destructive and suicidal behaviors, validation of suffering and abusive experience (but also helping the client take responsibility for actions), promotion of self-reflection rather than impulsive action, and setting of limits on self-destructive behavior (Gunderson 2001). The tendency of borderline patients to engage in "splitting" (polarization of an emotional response) should also be carefully monitored and addressed (e.g., devaluation of prior therapists, coupled with idealization of current therapist). The American Psychiatric Association (2001) has published practice guidelines for the psychotherapeutic and pharmacologic treatment of persons with BPD. Because borderline patients can present with significant suicide risk, a thorough evaluation of the potential for suicidal ideation and activity should have the initial priority. Also, many patients with BPD will have comorbid Axis I disorders, some of which might take priority (e.g., major depressive disorder, substance dependence, or dissociative disorder).

Dialectical behavior therapy (DBT; Chapman and Linehan 2005) has been shown empirically to be a particularly effective treatment of BPD (Lynch et al. 2007). The American Psychiatric Association (2001) also concluded that psychodynamic psychotherapy has obtained empirical support for the treatment of BPD that is equal to DBT (Bateman 2005, Gabbard 2000b), although this conclusion has been disputed (Sanderson et al. 2002). The dialectical component of DBT was derived largely from Zen Buddhist principles of overcoming suffering through acceptance. Mastery of conflict is achieved in part through no longer struggling or fighting adversity; pain is overcome when it is accepted as an inevitable, fundamental part of life. This principle is taught in part through the meditative technique of mindfulness, in which one attempts to empty one's mind of all thoughts, but accepts whenever and wherever the mind naturally travels. DBT initially focuses on reducing self-harm and parasuicidal behaviors that are disruptive to treatment. Contracts are at times used in which time with the therapist is limited secondary to treatment disruptive behavior. This can even go so far as to include suspension of treatment secondary to suicidal behavior. After mastery of treatment disruptive behavior, DBT teaches coping skills focused on emotional control and interpersonal relatedness. Individuals in DBT attend regular sessions with an individual therapist and discuss problems in applying the new skills. These sessions are augmented with a didactic skills-training group. Tables 82–4 and 82–5 provide a list of DBT treatment principles.

**Table 82–4 Dialectical Behavior Therapy Strategies**

| |
|---|
| Alternate between acceptance and change strategies |
| Balance nurturing with demands for self-help |
| Balance persistence and stability with flexibility |
| Balance capabilities with limitations and deficits |
| Move with speed, keeping the patient slightly off balance |
| Take positions whole heartedly |
| Look for what is not included in patient's own points of view |
| Provide developmental descriptions of change |
| Question intransigence of boundary conditions of the problem |
| Highlight importance of interrelationships in identity |
| Advocate a middle path |
| Highlight paradoxical contradictions in patient's own behavior, in the therapeutic process, and in life in general |
| Speak in metaphors and tell parables and stories |
| Play the devil's advocate |
| Extend the seriousness or implications of patient's statements |
| Add intuitive knowing to emotional experience and logical analysis |
| Turn problems into assets |
| Allow natural changes in therapy |
| Assess the patient, therapist, and process dialectically |

**Table 82–5 Basic Propositions of BPD Treatment from DBT**

| |
|---|
| 1. Patients are doing the best they can |
| 2. Patients want to improve |
| 3. Patients need to do better, try harder, and be more motivated to change |
| 4. Patients may not have caused all of their own problems, but they have to solve them anyway |
| 5. The lives of suicidal, borderline individuals are unbearable as they are currently being lived |
| 6. Patients must learn new behaviors in all relevant contexts |
| 7. Patients cannot fail in therapy |
| 8. Therapists treating borderline patients need support |

*Source*: Linehan (1993).

Clinical Vignette 3

SC was a 36-year-old female. She was referred to a Day Hospital Borderline Personality Disorders Treatment Program after her fourth hospitalization for depression and suicidality. SC had not known her father. She was raised by her mother who had a polysubstance dependence. Her relationship with her mother was described as negligent and distant. She had two brothers. The oldest brother abused her sexually for 3 years since she was 13 years old. The abuse ended when he was drafted into the army. She denied any feelings of anger or bitterness to him, and in fact described substantial feelings of fondness and affection. He died while serving in Vietnam.

She obtained good to excellent grades in school but had a history of indiscriminant sexual behavior, substance abuse, and bulimia. (Her common method for purging was to attempt to swallow a belt, thereby inducing vomiting.) Her first treatment was at the age of 19. She became significantly depressed when she discovered that her fiance was sexually involved with her best friend. Her hospitalization was precipitated by the ingestion of a lethal amount of drugs. Subsequent to this hospitalization she began to mutilate herself by scratching or cutting her arms with broken plates, dinner knives, or metal. The self-mutilation was usually precipitated by episodes of severe loneliness and feelings of emptiness.

She had a very active social life and a large network of friends. However, her relationships were very unstable. She could be quite supportive, engaging, and personable, but would overreact to common conflicts, disagreements, and difficulties. She would feel intensely hurt, depressed, angry, or enraged, and would hope that her friends would relieve her pain through some gesture. However, they would typically feel frustrated, annoyed, or overwhelmed by the intensity of her affect and her reactions.

Her sexual relationships were even more problematic. She would quickly develop intense feelings of attraction, involvement, and dependency. However, she would soon experience her lovers as disappointing and neglectful, which at times had more than a kernel of truth. Many were neglectful, unempathic, or abusive, but all of them found the intensity of the inevitable conflicts and her anger to be intolerable.

She was also questioning her sexual orientation. She had never been sexually involved with a woman, but she did have fantasies of an involvement with various women that she had known. It was conceivable that she might find a relationship with a woman to be more stable and satisfying, but it was likely that as much conflict would occur with women as had occurred with men.

She attended the Day Hospital BPD Program for 2 years. Treatment included group therapy, individual psychotherapy (using both cognitive–behavioral and insight), and antidepressant medication. The cognitive–behavioral treatment focused on daily management of problems, exploring alternative perceptions of and means for addressing conflicts with others, and gradually developing more effective coping strategies. The irrationality of her reactions became more apparent to her as their source within her past relationships was better understood. Treatment was successful in ending her reliance on self-mutilation and in decreasing the intensity of her interpersonal conflicts. She continued to have unstable relationships, but she was much more successful in acknowledging and resolving conflicts in ways that were more realistic and appropriate.

Pharmacologic treatment of patients with BPD is varied, as it depends primarily on the predominant Axis I symptomatology (Markovitz 2001, Soloff 2005). Persons with BPD can display a wide variety of Axis I symptoms, including anxiety, depression, hallucinations, delusions, and dissociations. It is important in their pharmacologic treatment not to be unduly influenced by transient symptoms or by symptoms that are readily addressed through exploratory or supportive techniques. On the other hand, it is equally important to be flexible in the use of medications and not to be unduly resistant to their use. Relying solely upon one's own psychotherapeutic skills can be unnecessary and even irresponsible.

## Histrionic Personality Disorder

HPD was not included within the first edition of the American Psychiatric Association's diagnostic manual. It was introduced in DSM-II (American Psychiatric Association 1968) and is perhaps one of the more controversial of the personality disorder diagnoses, given its close association with stereotypic feminine traits (Kaplan 1983, Ross et al. 1995, Widiger and First in press).

## Definition

HPD is a pervasive pattern of excessive emotionality and attention seeking (American Psychiatric Association 2000). Histrionic persons tend to be emotionally manipulative and intolerant of delayed gratification (Bornstein 1999, Stone 2005). HPD is indicated by the presence of five or more of the eight diagnostic criteria presented in DSM-IV-TR Criteria 301.50.

## Differential Diagnosis

HPD involves to some extent maladaptive variants of stereotypically feminine traits (Kaplan 1983). The DSM-IV-TR diagnostic criteria for HPD are sufficiently severe that a normal woman would not qualify, but studies have indicated that women are at times over diagnosed with the disorder (Widiger and First in press). Some self-report inventories are particularly prone to gender-biased assessments of HPD (Lindsay et al. 2000). It is therefore important to adhere closely to the DSM-IV-TR diagnostic criteria when confronted with histrionic symptoms in female patients.

Persons with HPD will often have borderline, dependent, or narcissistic personality traits (see Table 82–2). Prototypic cases of HPD can be distinguished from other personality disorders (Widiger et al. 1995). For example, the prototypic narcissistic person ultimately desires admiration, whereas the histrionic person desires whatever attention, interest, or concern can be obtained. As a result, the histrionic person will at times seek attention through melodramatic helplessness and emotional outbursts that could be experienced as denigrating and humiliating to the narcissistic person. However, most cases will not be prototypic and the most accurate description of a patient's constellation of maladaptive personality traits will be the provision of multiple diagnoses (Widiger and Trull 2007).

**DSM-IV-TR Criteria** 301.50

**Histrionic Personality Disorder**

A. A pervasive pattern of excessive emotionality and attention seeking, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

(1) is uncomfortable in situations in which he or she is not the center of attention

(2) interaction with others is often characterized by inappropriate sexually seductive or provocative behavior

(3) displays rapidly shifting and shallow expression of emotions

(4) consistently uses physical appearance to draw attention to self

(5) has a style of speech that is excessively impressionistic and lacking in detail

(6) shows self-dramatization, theatricality, and exaggerated expression of emotion

(7) is suggestible, i.e. easily influenced by others or circumstances

(8) considers relationships to be more intimate than they actually are

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## Epidemiology and Comorbidity

Approximately 1–3% of the general population may be diagnosed with HPD (see Table 82–1; Mattia and Zimmerman 2001, Torgersen et al. 2001). A controversial issue is its differential sex prevalence (Bornstein 1999, Stone 2005, Widiger and First in press). It is stated in DSM-IV-TR that the sex ratio for HPD is "not significantly different than the sex ratio of females within the respective clinical setting" (American Psychiatric Association 2000, p 712). However, this should not be interpreted as indicating that the prevalence is the same for males and females. It has typically been found that at least two thirds of persons with HPD are female, although there have been a few exceptions (Corbitt and Widiger 1995). Whether or not the rate will be significantly higher than the rate of women within a particular clinical setting depends upon many factors that are independent of the differential sex prevalence for HPD (Widiger 1998).

## Course

Little is known about the premorbid behavior pattern of persons with HPD (Bornstein 1999, Stone 2005). During adolescence they are likely to have been flamboyant, flirtatious, and attention seeking. As adults, persons with HPD will readily form new relationships but will have difficulty sustaining them. They may fall in love quite quickly, but just as rapidly become attracted to another person. They are unlikely to be reliable or responsible. Relationships with persons of the same sexual orientation will often be strained due to their competitive sexual flirtatiousness. Employment history is likely to be erratic and may be complicated by the tendency to become romantically or sexually involved with colleagues, by their affective instability, and by their suggestibility. Persons with HPD may become devoted converts to faddish belief systems. They have a tendency to make impulsive decisions that will have a dramatic (or melodramatic) effect on their lives. The severity of the symptomatology may diminish somewhat as the person ages.

## Etiology and Pathophysiology

There is little research on the etiology of HPD (Blashfield and Intoccia 2000, Stone 2005). There is a suggestion that HPD may share a genetic disposition toward impulsivity or sensation seeking with the ASPD (Lilienfeld and Hess 2001). It has also been suggested that HPD is (in part) a severe, maladaptive variant of the personality dimensions of extraversion and neuroticism (Widiger et al. 2002). Extraversion includes a disposition toward excitement seeking, gregariousness, and positive emotionality, and neuroticism includes the facets of angry hostility, self-consciousness, and vulnerability (Costa and McCrae 1992). There is considerable empirical support for the heritability of these personality dimensions (Bouchard and Loehlin 2001, Widiger and Trull 2007).

Environmental and social–cultural factors, however, may also play a significant role in the development of HPD

(Bornstein 1999, Stone 2005). Kernberg (1991), for example, speculated that the fathers of females with HPD combine early sexual seductiveness with subsequent authoritarian puritanical attitudes, while the mother tends to be domineering, controlling, and intrusive. Such a history may indeed occur in some cases of HPD but there is unlikely to be a specific, common pattern to all cases. The tendency of a family to emphasize, value, or reinforce attention seeking in a person with a genetic disposition toward emotionality may represent a more general pathway toward HPD (Cooper and Ronningstam 1992).

Affective instability is an important feature of HPD, which may be associated with a hyperresponsiveness of the noradrenergic system. This instability in the catecholamine functioning may contribute to a pronounced emotional reactivity to rejection and loss (Markovitz 2001). However, the attention seeking of HPD can be as important to the disorder as the emotionality. The purpose of the exaggerated emotionality is often to evoke the attention and maintain the interest of others (Bornstein 1999, Gunderson and Gabbard 2000, Stone 1993). Persons with HPD are intensely insecure regarding the extent to which others appreciate, desire, or want their company. They need to be the center of attention to reassure themselves that they are valued, desired, attractive, or wanted.

### Treatment

Persons with HPD will readily develop rapport but it will often be superficial and unreliable (Stone 2005). Therapists might also fail to appreciate the extent of influence they can have on the highly suggestible HPD patient (Bornstein 1999). Persons with HPD can readily become converts to whatever the therapist may suggest or encourage. The transformation to the theoretical model or belief system of the psychiatrist is unlikely to be sustained.

A key task in treating the patients with HPD is countering their global and diffuse cognitive style by insisting on attending to structure and detail within sessions and to the practical, immediate problems within daily life (Beck et al. 1990, Gunderson and Gabbard 2000, Stone 1993). It is also important to explore within treatment the historical source for their need for attention and involvement. Persons with HPD are prone to superficial and transient insights but they will benefit from a carefully reasoned and documented exploration of their current and past relationships.

Many clinicians recommend the use of group therapy for persons with HPD (Beck et al. 1990, Gabbard 2000a, Millon et al. 1996, Piper and Ogrodniczuk 2005). It is quite easy for them to become involved within a group, which may then be very useful in helping them recognize and explore their attention seeking, suggestibility, and manipulation, as well as develop alternative ways to develop more meaningful and sustained relationships. However, it is also important to closely monitor their involvements within the group, as they are prone to dominate and control sessions and they may escalate their attention seeking to the point of suicidal gestures. The intense affectivity of persons with HPD may also be responsive to antidepressant treatment, particularly those patients with substantial mood reactivity, hypersomnia, and rejection sensitivity (Markovitz 2001, Soloff 2005).

## Narcissistic Personality Disorder

NPD was new to the third edition of the American Psychiatric Association (1980) diagnostic manual. Its inclusion "was suggested by an increasing psychoanalytic literature and by the isolation of narcissism as a personality factor in a variety of psychological studies" (Frances 1980, p 1053). However, it is still not included within the World Health Organization (1992) International Classification of Diseases despite its presence since 1980 within DSM-III, as it has been perceived internationally as largely an American concept (Ronningstam 2005).

### Definition

NPD is a pervasive pattern of grandiosity, need for admiration, and lack of empathy (American Psychiatric Association 2000). Persons with NPD can be very vulnerable to threats to their self-esteem. They may react defensively with rage, disdain, or indifference but are in fact struggling with feelings of shock, humiliation, and shame. NPD is indicated by the presence of five or more of the nine diagnostic criteria presented in DSM-IV-TR Criteria 301.81.

**DSM-IV-TR Criteria** 301.81

**Narcissistic Personality Disorder**

A. A pervasive pattern of grandiosity (in fantasy or behavior), need for admiration, and lack of empathy, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

(1) has a grandiose sense of self-importance (e.g. exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements)

(2) is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love

(3) believes that he or she is "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions)

(4) requires excessive admiration

(5) has a sense of entitlement, i.e. unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations

(6) is interpersonally exploitative, i.e., takes advantage of others to achieve his or her own ends

(7) lacks empathy: is unwilling to recognize or identify with the feelings and needs of others

(8) is often envious of others or believes that others are envious of him or her

(9) shows arrogant, haughty behaviors or attitudes

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## Differential Diagnosis

NPD overlaps substantially with ASPD and particularly its more severe variant, psychopathy. Kernbeg (1998) considers the ASPD and NPD to lie along a common continuum of psychopathology. Both disorders include a disposition to dominate, humiliate, and manipulate others. Stone (1993) goes so far as to suggest, "all psychopathic persons are at the same time narcissistic persons" (Stone 1993, p 292). Hart and Hare (1998), psychopathy researchers, suggest alternatively, "psychopathy can be viewed as a higher-order construct with two distinct, albeit related facets, one of which is very similar to the clinical concept of narcissism" (p 429).

To help differentiate the NPD and ASPD, it has been suggested that "narcissists are usually more grandiose, while ASPD patients are exploitative, have a superficial value system, and are involved in recurrent antisocial activities" (Ronningstam 1999, p 681). It is also suggested that "exploitiveness in antisocial patients is probably more likely to be consciously and actively related to materialistic or sexual gain, while exploitive behavior in narcissistic patients is more passive, serving to enhance self-image by attaining praise or power" (Ronningstam 1999, p 681). Kernberg suggests, "the way to differentiate…narcissistic personality disorder from an antisocial personality disorder proper is the absence in the latter of the capacity for feeling guilt and remorse" (Kernberg 1998, pp 42–43). Narcissistic persons will feel guilty and remorseful when confronted with the negative effects of their exploitative use of others, whereas antisocial persons will not (Widiger et al. 1995). These speculations are compelling and have perhaps been beneficial in clinical practice, but they have not yet been empirically evaluated.

## Epidemiology and Comorbidity

NPD is among the least frequently diagnosed personality disorders within clinical settings (Gunderson et al. 1991), with estimates of prevalence as low as 2% (American Psychiatric Association 2000). A curious finding is that many community studies that have used a semistructured interview have not even been able to identify one single case (see Table 82–1), despite the substantial amount of research on maladaptive narcissistic personality traits within normal community and college samples (Morf and Rhodewalt 2001, Ronningstam 2005). It may be that the DSM-IV-TR diagnostic criteria do not fully capture the essential features of NPD (Gunderson et al. 1991). DSM-IV-TR NPD is diagnosed more frequently in males (American Psychiatric Association 2000), consistent with the finding within general personality research that men tend to be, on average, more arrogant than women (Costa et al. 2001). Persons with NPD are considered to be prone to mood disorders, as well as anorexia and substance-related disorders, especially cocaine (American Psychiatric Association 2000, Ronninstam 2005). Persons with NPD are likely to have comorbid antisocial (psychopathic), histrionic, paranoid, and borderline personality traits (see Table 82–2).

## Course

Little is known empirically about the course of narcissism. Clinical experience suggests that this disorder does not abate with age and may even become more evident into middle or older age (Kernberg 2004a). Persons with this disorder might be seemingly well adjusted and even successful as a young adult, having experienced substantial achievements in education, career, and perhaps even within relationships (Ronningstam 2005). However, their relationships with their colleagues, peers, and intimates might become strained over time as their lack of consideration for and even exploitative use of others becomes cumulatively evident. Successes might also become more infrequent, as their inability to accurately perceive or address criticism and setback contributes to a mounting number of failures. Persons with this disorder may at times not recognize their pathology until they have had a substantial number of setbacks, or they have finally recognized that the excessive importance they have given to achievement, success, and status has led to an emptiness and loneliness in their older age (Stone 1993). As a result, midlife and late-life transitions may be particularly difficult for persons with this disorder.

## Etiology and Pathophysiology

There has been little systematic research on the etiology of narcissism. Two twin studies have supported heritability for narcissistic personality traits (Jang et al. 1996, Torgersen et al. 2000), although given the complexity of narcissism (Fossati et al. 2005, Morf and Rhodewalt 2001, Raskin and Terry 1988, Ronningstam 2005), it is not entirely clear what precisely is being inherited. The predominant models for the etiology of narcissism have been largely social learning or psychodynamic (Ronningstam 2005). One model proposes that narcissism develops through an excessive idealization by parental figures, which is then incorporated by the child into his or her self-image (Millon et al. 1996). Narcissism may also develop through unempathic, neglectful, inconsistent, or even devaluing parental figures who have failed to adequately mirror a child's natural need for idealization (Kohut 1977). The child may find that the attention, interest, and perceived love of a parent are contingent largely on achievements or successes. They may fail to perceive the parents as valuing or loving them for their own sake, but may instead recognize that the love and attention are largely conditional on successful accomplishments. They might then develop the belief that their own feelings of self-worth are dependent upon a continued recognition of such achievements, status, or success by others. The character armor of arrogant self-confidence then masks a vulnerability and at times rage over the feeling of having been so neglected, and perhaps even mistreated and denigrated, as a child.

Conflicts and deficits with respect to self-esteem are central to the pathology of the disorder (Kernberg 1998, 2004a, Ronninstam 2005, Stone 1993), and there is considerable empirical support for this pathology in studies published within the general personality literature (Morf and Rhodewalt 2001). Narcissistic persons must continually seek and obtain signs and symbols of recognition to compensate for conscious or perhaps even unconscious feelings of inadequacy. Narcissism is not simply arrogant self-confidence, as it is more highly correlated with an instability in self-esteem rather than a consistently high self-confidence. Their feelings of insecurity will at times be evident but may also be masked by a disdainful indifference to criticism or even by overt expressions of anger and rage (Baumeister et al. 1996). Narcissistic persons may at times claim that it is not narcissism if they are in fact brilliant, talented, and successful. However, the pathology would still be evident by the excessive need for

the recognition of their achievements. They are uncomfortable when they are not being adequately appreciated for their accomplishments and they may in fact feel grossly insulted or enraged when they feel unjustly slighted (Stone 1993).

## Treatment

Persons rarely seek treatment for their narcissism. Individuals with NPD enter treatment-seeking assistance for another mental disorder, such as substance abuse (secondary to career stress), mood disorder (secondary to career setback), or even something quite specific, such as test anxiety. One may at times have narcissistic persons seeking treatment for a growing sense of discontent and futility with their lives (Ronningstam 2005). Once an individual with NPD is in treatment, he or she will have difficulty perceiving the relationship as collaborative and will likely attempt to dominate, impress, or devalue the therapist. They can idealize their therapists (to affirm that he or she is indeed of sufficient status or quality) but they may also devalue their therapist to affirm that they are of greater intelligence, capability, or quality, to reject the insights that they have failed to identify themselves, and to indicate that they warrant or deserve an even better therapist. How best to respond is often unclear as the establishment and maintenance of rapport will be an early and ongoing issue. It may at times be preferable to simply accept the praise or criticism, particularly when exploration will likely be unsuccessful, whereas at other times it is preferable to confront and discuss the motivation for the devaluation (or the idealization).

The optimal response to a narcissist's idealization has been a significant controversy within the psychoanalytic literature (Gabbard 2000a). Kohut (1977) had generally recommended a provision of empathy and a reflection (or mirroring) of positive regard and self-esteem, whereas Kernberg (2004b) generally recommended active confrontation of idealization, as early idealization would inevitably be followed by devaluation. Cognitive–behavioral approaches to NPD emphasize increasing awareness of the impact of narcissistic behaviors and statements on interpersonal relationships (Beck et al. 1990, Young et al. 2003). The idealization and devaluation can be responsive to role-playing and rational introspection, an intellectual approach that may itself be valued by some persons with NPD. Therapists must be careful not to become embroiled within intellectual conflicts and

### Clinical Vignette 4

RP was a well-regarded clinician with a good publication record and a successful private practice. However, one of his patients filed a complaint with the state board after their sexual relationship ended. He offered in his defense that his behavior was simply the result of marital stress. His license to practice was suspended indefinitely. One of the terms of his probation was to successfully complete 2 years of psychotherapy. RP agreed that treatment would be beneficial but questioned whether any clinician within his local community was sufficiently qualified, as he considered himself to be among the leading clinicians within this community.

Treatment was problematic from the very beginning. RP felt that their discussions should be quid pro quo: if he was going to reveal aspects of himself then the therapist should do likewise. When confronted with the understanding that he was the one in treatment, RP argued that the therapist must be having "narcissistic conflicts" if he is unwilling to accept the insight and guidance that he could offer. Some of the difficulty within the treatment was attributable to the situation (i.e., it would probably be difficult for most therapists to be mandated to receive therapy from a colleague) but as treatment progressed it became apparent that he had similar conflicts with other persons in his life.

RP's wife was threatening divorce in part because of a history of extramarital affairs. RP did not deny the existence of these affairs, but argued that his wife was exaggerating their importance: the other women meant little to him, why should they be of concern to her? He said that he did not keep his affairs secret from her prior to marriage (at least those that he was unable to keep secret), and therefore she knew from the beginning that extramarital affairs would occur. In addition, he felt that his affairs were only petty philandering and that his wife should tolerate them because she was "frankly lucky" to have him for a husband. He was good looking, wealthy, and professionally successful, and felt that if he had been more patient he might have found someone better than her.

RP was popular with women, at least at the beginning of relationships. He was charming, engaging, and verbally facile. However, he acknowledged during the course of therapy that some women eventually became unhappy, dissatisfied, and at times even angry with him. It is quite possible that his perception of his past relationships even understated the extent of the dissatisfaction. He attributed their dissatisfaction to "unrealistic and neurotic expectations." He stated that women would flirt with him because he is an "attractive catch" and that he was only fulfilling their fantasies by letting them become involved with him. He would soon lose interest though in the women with whom he became involved, and he acknowledged that it was not always easy to extricate himself from a relationship without any cost to himself.

He evidenced only a marginal insight into the potential harm he had caused the patient with whom he had the sexual relationship. He argued that the proscription against sexual involvements should not have been enforced in this instance because he had been very careful in determining that their relationship was not the intended target of the ethical guidelines: she was herself a "competent" professional who had "freely" entered the relationship and, in any case, no complaint would have been filed if he had been willing to continue the relationship. She was a well-known public figure. She testified to the state board that he repeatedly suggested to her that she accompany him on his business trips, and it was her impression that he wanted to show her off as a "trophy" to his colleagues. She stated that she ended the relationship when she discovered from her colleagues that he was bragging to others about their relationship and revealing details of their sexual activities.

Treatment was terminated by RP after 6 months of treatment upon reading the biannual report by his therapist to the state board regarding his progress. RP felt that he had been making substantial progress that was not being adequately appreciated by his therapist. He noted, for example, that his wife was no longer seeking a divorce and that his ex-patient was engaged to be married. He did indicate that he was dissatisfied with treatment, and felt that progress would be improved by "a more experienced and respected" clinician. He attributed the therapist's negative evaluation of his progress to professional jealousy.

competitions. Narcissistic persons can be acutely aware of the self-esteem conflicts of their therapist, and it is best for the therapist to model a comfortable indifference to losing disputes or conflicts.

Group therapy can be useful for increasing awareness of the grandiosity, lack of empathy, and devaluation of others (Piper and Ogrodniczuk 2005). However, these traits not only interfere with the narcissistic person's ability to sustain membership within groups (and within individual therapy), they may also become quite harmful and destructive to the rapport of the entire group. There is no accepted pharmacologic approach to the treatment of narcissism (Markovitz 2001, Soloff 2005).

## Avoidant Personality Disorder

AVPD was a new addition to DSM-III (American Psychiatric Association 1980). A criticism of its inclusion was that it had little prior recognition within the personality disorder literature (Gunderson 1983). However, it is now one of the more frequently diagnosed personality disorders (see Table 82–1), as timid, anxious, and insecure introversion is a common social and clinical problem (Millon et al. 1996).

### Definition

AVPD is a pervasive pattern of timidity, inhibition, inadequacy, and social hypersensitivity (American Psychiatric Association 2000). Persons with AVPD may have a strong desire to develop close, personal relationships but feel too insecure to approach others or to express their feelings. AVPD is indicated by the presence of four or more of the seven diagnostic criteria presented in DSM-IV-TR Criteria 301.82.

**DSM-IV-TR Criteria** 301.82

**Avoidant Personality Disorder**

A. A pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

(1) avoids occupational activities that involve significant interpersonal contact, because of fears of criticism, disapproval, or rejection

(2) is unwilling to get involved with people unless certain of being liked

(3) shows restraint within intimate relationships because of the fear of being shamed or ridiculed

(4) is preoccupied with thoughts of being criticized or rejected in social situations

(5) is inhibited in new interpersonal situations because of feelings of inadequacy

(6) views self as socially inept, personally unappealing, or inferior to others

(7) is unusually reluctant to take personal risks or to engage in any new activities because they may prove embarrassing

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### Differential Diagnosis

The most difficult differential diagnosis for AVPD is with generalized social phobia (Ralevski et al. 2005, Tillfors et al. 2004, Widiger 2005c). Both involve an avoidance of social situations, social anxiety, and timidity, and both are said to emerge from a childhood of shyness and introversion (American Psychiatric Association 2000). There is perhaps no meaningful distinction between them, as acknowledged in DSM-IV-TR. There are arguments to subsume all cases of AVPD into the diagnosis of generalized social phobia (First et al. 2002), as was done for introverted schizoid disorder of childhood in DSM-IV-TR. Support for the annexation of AVPD within generalized social phobia comes in part from the suggestion that insurance coverage will be easier to obtain for the treatment of an anxiety disorder than a personality disorder (Widiger 2005c). However, there is also considerable empirical support for the genetics, the neurophysiology, the childhood antecedents, the temporal stability, and the universality of the personality dimensions of introversion and neuroticism (Allik 2005, Bouchard and Loehlin 2001, Caspi et al. 2005, Depue and Lenzenweger 2001, Roberts and DelVecchio 2000).

Many persons with AVPD may also meet the criteria for DPD. This might at first glance seem unusual, given that AVPD involves social withdrawal whereas DPD involves excessive social attachment. However, once a person with AVPD is able to obtain a relationship, he or she will often cling to this relationship in a dependent manner. Both disorders include feelings of inadequacy, needs for reassurance, and hypersensitivity to criticism and neglect (i.e., abnormally high levels of anxiousness, self-consciousness, and vulnerability). A distinction between AVPD and DPD is best made when the person is seeking a relationship (Widiger et al. 1995). Avoidant persons tend to be very shy, inhibited, and timid (and are therefore slow to get involved with someone), whereas dependent persons urgently seek another relationship as soon as one ends (i.e., avoidant persons are high in introversion, whereas dependent persons are high in extraversion). Avoidant persons may also be reluctant to express their feelings, whereas dependent persons can drive others away by continuous expressions of neediness. The differentiation of AVPD from the SZPD and STPD was discussed in previous sections.

### Epidemiology and Comorbidity

Timidity, shyness, and social insecurity are not uncommon problems (Crozier and Alden 2005) and AVPD is one of the more prevalent personality disorders within clinical settings, occurring in 5–25% of all patients (American Psychiatric Association 2000, Mattia and Zimmerman 2001). However, AVPD may be diagnosed in only 1–2% of the general population (see Table 82–1). It appears to occur equally among males and females, with some studies reporting more males and others reporting more females (Corbitt and Widiger 1995). Persons with AVPD are likely to have symptoms that meet the DSM-IV-TR criteria for a generalized social phobia, and others may have a mood disorder.

## Course

Persons with AVPD will have been shy, timid, and anxious as children (Bernstein and Travaglini 1999, Millon et al. 1996). Some will have been diagnosed with a social phobia during childhood. Adolescence will have been a particularly difficult developmental period, due to the importance at this time of attractiveness, dating, and popularity. Occupational success may not be significantly impaired, as long as there is little demand for public performance. Persons with AVPD may in fact find considerable gratification and esteem through a job or career that they are unable to find within their relationships. The job may serve as a distraction from intense feelings of loneliness. Their avoidance of social situations will impair their ability to develop adequate social skills, and this will then further handicap any eventual efforts to develop relationships. As parents, they may be very responsible, empathic, and affectionate, but may unwittingly impart feelings of social anxiousness and awkwardness. Severity of the AVPD symptomatology diminishes as the person becomes older.

## Etiology and Pathophysiology

There is limited research on the etiology or pathology of DSM-IV-TR AVPD. However, AVPD is well understood as an extreme variant of the fundamental personality traits of introversion and neuroticism (Tyrer 2005, Widiger et al. 2002). Introversion includes such facets as passivity, social withdrawal, and inhibition, and neuroticism includes self-consciousness, vulnerability, and anxiousness (Costa and McCrae 1992). There is considerable empirical support for the etiology of these personality dimensions (McCrae and Costa 1999).

In childhood, neuroticism appears as a distress-prone or inhibited temperament (Rothbart et al. 2000). Shyness, timidity, and interpersonal insecurity might be exacerbated further in childhood through overprotection and excessive cautiousness (Schmidt et al. 2001). Parental behavior coupled with a distress-prone temperament has been shown to result in social inhibition and timidity (Burgess et al. 2001). Most children and adolescents will have many experiences of interpersonal embarrassment, rejection, or humiliation, but these will be particularly devastating to the person who is already lacking in self-confidence or is temperamentally passive, inhibited, or self-conscious.

AVPD may involve elevated peripheral sympathetic activity and adrenocortical responsiveness, resulting in excessive autonomic arousal, fearfulness, and inhibition (Siever and Davis 1991). Just as ASPD may involve deficits in the functioning of a behavioral inhibition system, AVPD may involve excessive functioning of this same system (Depue and Lenzenweger 2001). The pathology of AVPD, however, may be as much psychological as neurochemical, with the timidity, shyness, and insecurity being a natural result of a cumulative history of denigrating, embarrassing, and devaluing experiences (Schmidt et al. 2001). Underlying AVPD may be excessive self-consciousness, feelings of inadequacy or inferiority, and irrational cognitive schemas that perpetuate introverted, avoidant behavior (Beck et al. 1990).

## Treatment

Persons with AVPD will seek treatment for their avoidant personality traits, although many will initially seek treatment for symptoms of anxiety, particularly social phobia (generalized subtype). It is important in such cases to recognize that the shyness is not due simply to a dysregulation or dyscontrol of anxiousness. There is instead a more pervasive and fundamental psychopathology, involving feelings of interpersonal insecurity, low self-esteem, and inadequacy (Millon et al. 1996, Paris 1998, Stone 1993, Widiger 2001).

Social skills training, systematic desensitization, and a graded hierarchy of in vivo exposure to feared social situations have been shown to be useful in the treatment of AVPD (Beck et al. 1990, Millon et al. 1996). However, it is also important to discuss the underlying fears and insecurities regarding attractiveness, desirability, rejection, or intimacy (Gabbard 2000a, Gunderson and Gabbard 2000, Stone 1993). Persons with AVPD will at times be reluctant to discuss such feelings, as they may feel embarrassed, they may fear being ridiculed, or they may not want to "waste the time" of the therapist with such "foolish" insecurities. They may prefer a less revealing or involved form of treatment. It is important to be understanding, patient, and accepting, and to proceed at a pace that is comfortable for the patient. Insecurities and fears can at times be addressed through cognitive techniques, as the irrationality is usually readily apparent (Beck et al. 1990). It remains useful though to identify the historical source of their development, as this understanding will help the patient appreciate the irrationality or irrelevance of the patient's expectations and perceptions for his or her current relationships.

Persons with AVPD will often find group therapies to be helpful (Piper and Ogrodniczuk 2005). Exploratory and supportive groups can provide them with an understanding environment in which to discuss their social insecurities, to explore and practice more assertive behaviors, and to develop an increased self-confidence to approach others and to develop relationships outside of the group. Focused and specialized social-skills-training groups would be preferable to unstructured groups that might be predominated by much more assertive and extraverted members.

Many persons with AVPD will respond to anxiolytic medications and at times to antidepressants, particularly such monoamine oxidase inhibitors as phenelzine (Markovitz 2001, Soloff 2005). Normal and abnormal feelings of anxiousness can be suppressed or diminished through pharmacologic interventions (Widiger 2005c). This approach may in fact be necessary to overcome initial feelings of intense social anxiety that are markedly disruptive to current functioning (e.g., inability to give required presentations at work or to talk to new acquaintances). However, it is also important to closely monitor a reliance on medications. Persons with AVPD could be prone to rely excessively on substances to control their feelings of anxiousness, whereas their more

Clinical Vignette 5

LW was a 26-year-old female. She was first seen in treatment at the age of 19 when she entered an anxiety disorders treatment program. She was a music major (specializing in the flute) at a prominent university. However, she suffered from substantial feelings of anxiety to the point that she was unable to perform in front of an audience. She was diagnosed with a generalized social phobia when it was discovered that she was anxious within a wide variety of other social situations. She was generally timid, insecure, shy, and introverted. She was treated with phenelzine, and

(continues)

Clinical Vignette 5 *continued*

found substantial improvement within a few weeks in her more severe feelings of anxiety. She was able to complete the music program and graduated with honors.

However, she subsequently sought outpatient therapy at the age of 23 for feelings of depression. She complained of substantial feelings of inadequacy, worthlessness, and helplessness. She was currently married to a man who was sexually abusive and emotionally detached. She had in fact been involved in a series of disappointing and often exploitative relationships. She described herself as being undesirable, and yet she was in fact bright, attractive, responsible, and affectionate. Her past boyfriends had been either socially inadequate or domineering males who failed to provide her with much emotional support or meaningful involvement. Her current husband was attractive to her primarily because she perceived him as successful, strong, and protective. However, he was also continually critical, derogatory, and often required her to perform sexual acts that she found humiliating.

Her employment history was equally disappointing. She would rarely apply for any quality employment because she assumed that she would be rejected. When she did find employment, she would quit within just a few weeks because of feelings of tension and anxiety. Her feelings of anxiety were not confined to performing in front of others. She described a terror over the thought of disappointing any employer. She was in fact very capable, responsible, and even talented, but she was certain that she would eventually be shown to be inadequate and incompetent.

She described her mother as having been continually anxious and nervous, with a history of depression in her biological relatives. She described her father as being alcoholic, derogatory, and hostile. A typical example of his emotional abuse consisted of him interrogating at dinner each sibling in turn regarding his or her behavior (or failures) that day. Those that met with his disapproval were sent from the table. She performed very well in school because she was intensely afraid of his anger if she did less than excellent. She was cognitively aware that his criticisms were usually inappropriate and always excessive, but she could not help feeling fearful and hurt. He was her father and how he felt about her meant a great deal to her. In fact, she had largely incorporated his attitude to her as her own attitude toward herself.

She was treated with an antidepressant, group therapy for interpersonal assertiveness, and 3 years of outpatient psychotherapy that focused on her self-image. The therapist emphasized the irrationality and maladaptivity of her self-statements, and their development within her relationships within her family. In treatment, she gradually developed increasing feelings of self-confidence and assertion. Medication was terminated at the end of 6 months. By the end of the group and individual psychotherapy she had obtained employment within a department store and had been promoted to floor manager. She divorced her husband during treatment. She continued to suffer from feelings of anxiousness when dating, but the relationships were now more satisfying, meaningful, and promising.

general feelings of insecurity and inadequacy would require a more comprehensive treatment.

## Dependent Personality Disorder

DPD was, technically speaking, a new addition to DSM-III (American Psychiatric Association 1980) in that it had not been included within DSM-II (American Psychiatric Association 1968). However, a diagnosis of passive-dependent personality trait disturbance was included within the 1952 first edition of the American Psychiatric Association's diagnostic manual as a subtype to a passive–aggressive personality disorder, "characterized by helplessness, indecisiveness, and a tendency to cling to others as a dependent child to a supporting parent" (American Psychiatric Association 1952, p 37).

### Definition

DPD involves a pervasive and excessive need to be taken care of that leads to submissiveness, clinging, and fears of separation (American Psychiatric Association 2000, Bornstein 2005, Pincus 2002). Persons with DPD will also have low self-esteem, and will often be self-critical and self-denigrating. Its primary diagnostic criteria include extreme difficulty making decisions without others' input, need for others to assume responsibility for most aspects of daily life, extreme difficulty disagreeing with others, inability to initiate projects due to lack of self-confidence, and going to excessive lengths to obtain the approval of others (see DSM-IV-TR Criteria 301.6).

**DSM-IV-TR Criteria** 301.6

**Dependent Personality Disorder**

A. A pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

(1) has difficulty making everyday decisions without an excessive amount of advice and reassurance from others

(2) needs others to assume responsibility for most major areas of his or her life

(3) has difficulty expressing disagreement with others because of fear of loss of support or approval (**Note:** do not include realistic fears of retribution)

(4) has difficulty initiating projects or doing things on his or her own (because of a lack of self-confidence in judgment or abilities rather than to a lack of motivation or energy)

(5) goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant

(6) feels uncomfortable or helpless when alone, because of exaggerated fears of being unable to care for himself or herself

(7) urgently seeks another relationship as a source of care and support when a close relationship ends

(8) is unrealistically preoccupied with fears of being left to take care of himself or herself

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## Differential Diagnosis

Excessive dependency will often be seen in persons who have developed debilitating mental and general medical disorders, such as agoraphobia, schizophrenia, mental retardation, severe injuries, and dementia. However, a diagnosis of DPD requires the presence of the dependent traits since late childhood or adolescence (American Psychiatric Association 2000). One can diagnose the presence of a personality disorder at any age during a person's lifetime, but if, for example, a DPD diagnosis is given to a person at the age of 75, this presumes that the dependent behavior was evident since the age of approximately 18 (i.e., predates the onset of a comorbid mental or physical disorder).

Deference, politeness, and passivity will also vary substantially across cultural groups. It is important not to confuse differences in personality that are due to different cultural norms with the presence of a personality disorder (Millon and Grossman 2005). The diagnosis of DPD requires that the dependent behavior be maladaptive, resulting in clinically significant functional impairment or distress.

Many persons with DPD will also meet the criteria for HPD and BPD (see Table 82–2). Persons with both DPD and HPD may display strong needs for reassurance, attention, and approval. However, persons with DPD tend to be more self-effacing, docile, and altruistic, whereas persons with HPD tend to be more flamboyant, assertive, and self-centered, and persons with BPD will tend to be much more dysfunctional and emotionally dysregulated (Bornstein 2005, Widiger et al. 1995).

## Epidemiology and Comorbidity

DPD is among the most prevalent of the personality disorders (American Psychiatric Association 2000), occurring in 5–30% of patients and 2–4% of the general community (Mattia and Zimmerman 2001). A controversial issue is its differential sex prevalence (Bornstein 1995, Widiger 1998). DPD is diagnosed more frequently in females but there is some concern that there might be a failure to adequately recognize the extent of dependent personality traits within males (Bornstein 1995, Corbitt and Widiger 1995). Many studies have indicated that dependent personality traits provide a vulnerability to the development of depression in response to interpersonal loss (Blatt 2004, Bornstein 2005, Zuroff et al. 2004).

## Course

Persons with DPD are likely to have been excessively submissive as children and adolescents, and some may have had a chronic physical illness or a separation anxiety disorder during childhood (American Psychiatric Association 2000), but there is actually little systematic research on the etiology of excessive dependency. To the extent that independent responsibility and initiative are required, job functioning will be impaired or unsatisfactory. Individuals with DPD are prone to mood disorders throughout life, particularly major depression and dysthymia, and to anxiety disorders, particularly agoraphobia, social phobia, and panic disorder (Bornstein 2005). However, the severity of the symptomatology may tend to lessen with age, particularly if the person has obtained a reliable, empathic partner.

The self-esteem of a person with DPD is said to depend substantially on the maintenance of a supportive and nurturant relationship (Blatt 2004, Bornstein 2005), and yet these intense needs for reassurance can have the paradoxical effect of driving the needed person away. The dependent person's worst fears are then realized (i.e., he or she is abandoned and alone), and his or her sense of self-worth, -meaning, or -value is then furthered injured, perhaps even crushed by the rejection (Shahar et al. 2004). The dependent person might then indiscriminately select a readily available but unreliable, undependable, and perhaps even abusive person simply to be with someone. This partner would reaffirm the worst fears through the abuse, derogation, and denigration (i.e., conveying to the dependent person that he or she is indeed undesirable and unlovable, and that the relationship is again tenuous). In other words, a combination of evocative, reactive, and then proactive transactions with the environment are the means by which a dependent personality style can lead to depression.

Research on the relationship of dependency to depression, however, is not without fundamental concerns (Coyne et al. 2004). An important focus of future research will be a further articulation of the precise process or mechanism through which this association occurs. In theory, dependent personality traits contribute to the instability of intimate and supportive relationships through the expression of excessive needs for reassurance and/or pathogenic cognitions that contribute to intense feelings of helplessness and neediness. However, it is also possible that the emotional instability and pathologic attitudes are themselves the result of unstable interpersonal relationships. Dependency is a personality disposition that is seen much more often in women than in men (Bornstein 1996). A provocative reformulation of dependency in women is that the apparent feelings of insecurity may say less about the women than the persons with whom the women are involved. "Men and women may differ in what they seek from relationships, but they may also differ in what they provide to each other" (Coyne and Whiffen 1995, p 368). In other words, "Women might appear (and be) less dependent if they weren't involved with such undependable men" (Widiger and Anderson 2003, p 63).

## Etiology and Pathophysiology

There is very little systematic research on the etiology of dependency. Central to its etiology and pathology is considered to be an insecure interpersonal attachment (Bornstein 2005, Paris 1998, Pincus 2002, Stone 1993). Insecure attachment and helplessness may be generated through a parent–child relationship, perhaps by a clinging parent or a continued infantilization during a time in which individuation and separation normally occurs (Gabbard 2000a, Thompson and Zuroff 1998). However, DPD may also represent an interaction of an anxious-inhibited temperament with inconsistent or overprotective parenting (Bornstein 2005, Rothbart et al. 2000). Dependent persons may turn to a parental figure to provide a reassurance, security, and confidence that they are unable to generate for themselves. They may eventually believe that their self-worth is contingent upon the worth or importance they have to another person (Beck et al. 1990).

## Treatment

There are no empirically validated treatments for DPD. Treatment recommendations are essentially based on anecdotal

clinical experience. Persons with DPD will often be in treatment for one or more Axis I disorders, particularly a mood (depressive) or an anxiety disorder. These individuals will tend to be very agreeable, compliant, and grateful, at times to excess (Bornstein 2005). Many individuals with DPD will find that the therapeutic relationship itself satisfies their need for support and concern and may then desist from seeking a partner. The therapist can be perceived as the caring partner who will always be there. The dependent client might then even fear successful treatment, because termination may shortly follow (Gabbard 2000a). Thus, the client may remain excessively compliant and agreeable, in order to be a patient that the therapist would continue to treat. Therapists should be careful not to unwittingly encourage this submissiveness, nor to reject the client in order to be rid of their clinging dependency (Perry 2004).

An important component of treatment will often be a thorough exploration of the need for support and its root causes. Cognitive–behavioral techniques can be useful to address feelings of inadequacy and helplessness, and to provide training in assertiveness and problem-solving techniques (Beck et al. 1990, Young et al. 2003). Persons with DPD may also benefit from group therapy (Piper and Ogrodniczuk 2005). A supportive group is useful in diffusing the feelings of dependency onto a variety of persons, in providing feedback regarding their manner of relating to others, and in providing practice and role models for more assertive and autonomous interpersonal functioning. There is no known pharmacologic treatment for DPD (Markovitz 2001, Soloff 2005).

Clinical Vignette 6

LC was a 21-year-old college sophomore who unexpectedly returned home in the middle of the first semester, proclaiming that she could no longer suffer the anxiety and depression she felt at college. Neither she nor her parents felt that they had a clear understanding of what was making her feel so distraught. She was doing fine in her classes and was actively involved in a number of college organizations. Her mother called her academic advisor at college for advice and LC was referred to a clinician for consultation and treatment.

LC indicated at the initial session that she had been intensely ambivalent about attending college and had in fact delayed enrollment for 2 years in the hope that she could convince her parents that she would not have to leave home. She indicated that she felt overwhelmingly frightened and tearful away from home. She had been calling her parents three to five times each week, seeking their advice and reassurance but also simply to maintain regular contact. LC's level of anxiety decreased substantially when she returned home but quickly emerged at the thought of leaving home again.

LC's parents were concerned that she was returning home to be close to a boy that she had once dated. LC, however, denied this motivation, indicating that she had long abandoned any hope of a future in that particular relationship. LC was a popular young woman, generally considered to be quite amicable, modest, friendly, warm, attractive, bright, and engaging. However, she acknowledged that she often felt very insecure in her relationships, requiring reassurances from her girlfriends and boyfriends that she was not a burden to them, as she in fact grew increasingly burdensome in part from her need for their reassurance. She indicated that she had often fallen in love but had repeatedly felt crushed and devastated when the object of her love failed to become as attached. She said that one boyfriend broke up with her explicitly because he experienced her as being too "needy" and "clinging." She admitted that this was "not far from the truth" but had pleaded to him that she would no longer be so needy if only he would not leave her.

LC described her relationship with parents, particularly her mother, as being very close, supportive, and dependable. LC's childhood history, however, included many examples of failures to develop an independent self-confidence. For example, she felt unable to attend a summer camp attended by her best friends because of fears of separation from her parents; she did attend the following summer but taxed the patience of the camp counselors with her demands for attention and support. Her parents verbally encouraged her to develop greater independence and self-confidence but they also would repeatedly give in to her requests for protection and support. LC's mother in fact often appeared to be somewhat reluctant to let LC separate from her.

LC was seen in twice-weekly individual psychotherapy. Pharmacotherapy was provided for her anxious and depressive symptoms but was discontinued after 2 months due to complaints of side effects. Cognitive therapy focused on her self-denigrating beliefs of helplessness, behavioral therapy included a gradual shaping of independence from her parents, and insight therapy explored the relationship of her self-image with her relationships with her parents. Treatment was successful in developing sufficient independence and self-esteem for LC to feel comfortable and confident enough to return the following year to college. She successfully completed college although abandoned aspirations to pursue a social work career after she became married and had children of her own.

## Obsessive–Compulsive Personality Disorder

Obsessive–compulsive personality disorder (OCPD) has been included in every edition of the American Psychiatric Association's diagnostic manual, although there appears to have been "ruminative doubts" about its name, shifting from compulsive personality in DSM-I (American Psychiatric Association 1952), to obsessive–compulsive personality in DSM-II (American Psychiatric Association 1968), back to compulsive personality in DSM-III (American Psychiatric Association 1980), and back again to obsessive–compulsive in DSM-III-R (American Psychiatric Association 1987).

### Definition

OCPD includes a preoccupation with orderliness, perfectionism, and mental and interpersonal control (American Psychiatric Association 2000). OCPD is indicated by the presence of four or more of the eight diagnostic criteria presented in DSM-IV-TR Criteria 301.4.

### Differential Diagnosis

Devotion to work and productivity will vary substantially across cultural groups. One should be careful not to confuse normal cultural variation in conscientiousness with the presence of this personality disorder (Millon and Grossman 2005). A diagnosis of OCPD requires that the

**DSM-IV-TR Criteria** 301.04

**Obsessive–Compulsive Personality Disorder**

A. A pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

(1) is preoccupied with details, rules, lists, order, organization, or schedules to the extent that the major point of the activity is lost

(2) shows perfectionism that interferes with task completion (e.g., is unable to complete a project because his or her own overly strict standards are not met)

(3) excessive devotion to work and productivity to the exclusion of leisure activities and friendships (not accounted for by obvious economic necessity)

(4) is overconscientious, scrupulous, and inflexible about matters of morality, ethics, or values (not accounted for by cultural or religious identification)

(5) is unable to discard worn-out or worthless objects even when they have no sentimental value

(6) is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things

(7) adopts a miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes

(8) shows rigidity and stubbornness

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devotion to work be maladaptive or to the exclusion of leisure activities and friendships (American Psychiatric Association 2000).

OCPD resembles to some extent the obsessive–compulsive anxiety disorder (OCAD). However, many persons with OCPD fail to develop OCAD, and vice versa. There is in fact little empirical support for a close relationship of OCAD with OCPD (Costa et al. 2005). OCAD involves intrusive obsessions or circumscribed and repetitively performed rituals whose purpose is to reduce or control feelings of anxiety (American Psychiatric Association 2000). OCPD, in contrast, involves rigid, inhibited, and authoritarian behavior patterns that are more ego syntonic. If both behavior patterns are present, both diagnoses should be given, as these disorders are sufficiently distinct that it is likely that in such cases two different disorders are in fact present (Widiger et al. 1995).

OCPD may at times resemble NPD, as both disorders can involve assertiveness, domination, achievement, and a professed perfectionism. However, the emphasis in OCPD will be on work for its own sake, whereas narcissistic persons will work to achieve only status and recognition (Widiger et al. 1995). Persons with OCPD will also be troubled by doubts, worries, and self-criticism, whereas the narcissistic person will tend to be overly self-assured.

## Epidemiology and Comorbidity

Only 1–2% of the general community may meet the diagnostic criteria for the disorder (see Table 82–1) but this could be an underestimation (Costa et al. 2005). Up to 10% of the population has been estimated to be maladaptively stubborn, 4% excessively devoted to work, and 8% excessively perfectionistic (Nestadt et al. 1991). OCPD is one of the less frequently diagnosed personality disorders within inpatient settings, occurring in approximately 3–10% of patients (American Psychiatric Association 2000), but its prevalence may be much higher within private practice settings. This disorder does appear to occur more often in males than in females but exceptions to this finding have been reported (Corbitt and Widiger 1995).

## Course

There is little systematic research on the childhood antecedents or adult course of OCPD. As children, some persons with OCPD may have appeared to be relatively well behaved, responsible, and conscientious. However, they may have also been overly serious, rigid, and constrained (Rothbart et al. 2000). As adults, it is expected that many will obtain good to excellent success within a job or career. They can be excellent workers to the point of excess, sacrificing their social and leisure activities, marriage, and family for their job (Stone 1993). Relationships with spouse and children are likely to be strained due to their tendency to be detached and uninvolved, and yet authoritarian and domineering with respect to decisions. A spouse may complain of a lack of affection, tenderness, and warmth. Relationships with colleagues at work may be equally strained by the excessive perfectionism, domination, indecision, worrying, and anger. Jobs that require flexibility, openness, creativity, or diplomacy may be particularly difficult. Persons with OCPD may be prone to various anxiety and physical disorders that are secondary to their worrying, indecision, and stress. Those with concomitant traits of angry hostility and competitiveness may be prone to cardiovascular disorders. Mood disorders may not develop until the person recognizes the sacrifices that have been made by his or her devotion to work and productivity, which may at times not occur until middle age. However, most will experience early employment or career difficulties or even failures that may result in depression.

## Etiology and Pathophysiology

A variety of studies have indicated heritability for the trait of obsessionality (Nigg and Goldsmith 1994). OCPD relates closely to the general personality domain of conscientiousness or constraint (Costa et al. 2005, Widiger et al. 2002), which itself develops via a childhood temperament of attentional self-regulation (Caspi et al. 2005). This domain of general personality structure includes facets

of deliberation (rumination), self-discipline, achievement striving (workaholism), dutifulness (overconscientiousness and scrupulousness about matters of ethics and morality), order (preoccupation with details), and competence (perfectionism). There is considerable empirical support for the heritability of conscientiousness (Bouchard and Loehlin 2001).

Early psychoanalytic theories regarding OCPD concerned issues of unconscious guilt or shame (Gunderson and Gabbard 2000). A variety of underlying conflicts have since been proposed, including a need to maintain an illusion of infallibility to defend against feelings of insecurity, an identification with authoritarian parents, or an excessive, rigid control of feelings and impulses (Gabbard 2000a, Stone 1993). Any one or more of these conflicts might be relevant for a particular person with OCPD but there is quite limited empirical support for these particular models of etiology and pathology. OCPD includes personality traits that are highly valued within most cultures (e.g., conscientiousness) and some instances of OCPD may reflect exaggerated or excessive responses to the expectations of or pressures by parental figures.

### Treatment

Persons with OCPD may fail to seek treatment for the OCPD symptomatology. They may seek treatment instead for disorders and problems that are secondary to their OCPD traits, including anxiety disorders, health problems (e.g., cardiovascular disorders), and problems within various relationships (e.g., marital, familial, and occupational). Treatment will be complicated by their inability to appreciate the contribution of their personality to these problems and disorders (Gunderson and Gabbard 2000, Stone 1993). It is not unusual for persons with OCPD to perceive themselves as being simply conscientious, dutiful, moral, and responsible, rather than perfectionistic, stubborn, rigid, domineering, and unavailable. Their lack of insight is complicated further by the contribution of their traits to various achievements and successes (e.g., career advancement) and to the control of negative affect (e.g., ability to control feelings of dysphoria during a crisis). The OCPD traits are not invariably or always maladaptive, and persons with this disorder may not appreciate the disorder's cost to their physical health, psychological well-being, and personal relationships.

Cognitive–behavioral techniques that address the irrationality of excessive conscientiousness, moralism, perfectionism, devotion to work, and stubbornness can be effective in the treatment of OCPD (Beck et al. 1990, Young and Klosko 2005). Persons with OCPD may in fact appreciate the rational approach to treatment provided by cognitive–behavioral therapy. A common difficulty though is the tendency to drift into lengthy and unproductive ruminations and intellectualized speculations (Beck et al 1990, Gunderson and Gabbard 2000, Stone 1993). Therapeutic techniques that emphasize the acknowledgment, recognition, and acceptance of feelings will therefore be useful (Gabbard 2000a). Gestalt techniques that focus upon and confront feeling states will often feel threatening to persons with OCPD but precisely for this reason they can also be quite revealing and useful. Persons with OCPD will attempt to control therapeutic sessions, and techniques that encourage uncontrolled, freely expressed associations to explore historical motivations for control, perfectionism, and workaholism are often helpful.

Persons with OCPD can be problematic in groups (Piper and Ogrodniczuk 2005). They will tend to be domineering, constricted, and judgmental. There is no accepted pharmacologic treatment for OCPD (Markovitz 2001, Soloff 2005). Some persons with OCPD will benefit from anxiolytic or antidepressant medications, but this will typically reflect the presence of associated features or comorbid disorders. The core traits of OCPD might not be affected by pharmacologic interventions.

## Personality Disorder, Not Otherwise Specified

As indicated earlier, DSM-IV-TR includes a diagnostic category, PDNOS, for persons with a personality disorder who do not meet the diagnostic criteria for any one of the ten officially recognized diagnoses. PDNOS is one of the more commonly used personality disorder diagnoses in clinical practice (Verheul and Widiger 2004). It would not, of course, be possible to discuss the etiology, pathology, course, or treatment of the PDNOS disorder, as the diagnosis refers to a wide variety of personality types. However, one usage of PDNOS is for the two personality disorders presented in the appendix to DSM-IV-TR for criterion sets provided for further study, the passive–aggressive and the depressive (American Psychiatric Association 2000).

### Passive–Aggressive (Negativistic) Personality Disorder

PAPD had been included in all prior editions of the American Psychiatric Association's diagnostic manual. It was in fact the single most frequently used personality disorder diagnosis during the Second World War (Malinow 1981). However, its status has been controversial for quite some time. It was included within DSM-III (American Psychiatric Association 1980) only under the provision that it not be diagnosed if the patient met the criteria for any other personality disorder (Frances 1980, Gunderson 1983). A primary concern has been whether it is a situational reaction to authoritative control or in fact a temporally stable personality trait. There have been no longitudinal studies to address this concern. It was shifted to the appendix of DSM-IV-TR because there had been little research to support its validity (Widiger et al. 1995). Objections have been raised in response to the decision to downgrade the diagnosis (Wetzler and Morey 1999) and its broadened criterion set may eventually prove to have more validity and clinical utility than the DSM-III-R version (McCann 1988, Millon 1993) but, as yet, there have been only a few scattered studies (e.g., Bradley et al. 2006, Joiner and Rudd 2002), none of which appears to address the primary concerns regarding its validity.

#### *Definition*

PAPD is a pervasive pattern of negativistic attitudes and passive resistance to authority, demands, responsibilities, or obligations (American Psychiatric Association 2000). PAPD can be diagnosed by the presence of four or more of the seven criteria presented in DSM-IV-TR Criteria: Passive–Aggressive Personality Disorder.

**DSM-IV-TR Criteria**

**Passive–Aggressive Personality Disorder**

A. A pervasive pattern of negativistic attitudes and passive resistance to demands for adequate performance, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

(1) passively resists fulfilling routine social and occupational tasks

(2) complains of being misunderstood and unappreciated by others

(3) is sullen and argumentative

(4) unreasonably criticizes and scorns authority

(5) expresses envy and resentment toward those apparently more fortunate

(6) voices exaggerated and persistent complaints of personal misfortune

(7) alternates between hostile defiance and contrition

B. Does not occur exclusively during major depressive episodes and is not better accounted for by dysthymic disorder.

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### *Differential Diagnosis*

It is particularly important when assessing for PAPD to recognize that passive–aggressive behavior might be confined to settings in which persons have lost a freedom, responsibility, or decision-making authority that was previously available to them and overt expressions of assertiveness or opposition are being discouraged. For example, it would not be surprising to observe passive–aggressive behavior within the military, prison, or some inpatient hospitals. It is important in such settings to verify that the negativistic behavior was evident earlier and is currently evident within other situations.

### *Epidemiology and Comorbidity*

Approximately 1–2% of the community will meet the DSM-III-R criteria for PAPD (see Table 82–1). Up to 5% of patients were being diagnosed with PAPD (McCann 1988, Millon 1993, Wetzler and Morey 1999). The rate was higher when semistructured interviews were used but still low compared to most other personality disorders. The prevalence rate with the DSM-IV-TR criteria are likely to be higher, given the expansion of the disorder from simply a passive resistance to demands for adequate performance to a more general negativism (Millon 1993). An approximately equal prevalence of males and females has traits that meet the criteria for the disorder based upon the DSM-III and DSM-III-R criteria (Corbitt and Widiger 1995). However, the broader formulation of negativism resembles closely the general trait of oppositionalism, characterized by the tendency to be complaining, discontented, grumbling, whining, and argumentative, which does appear to occur more often in males than in females (Costa et al. 2001).

### *Course*

Many persons with PAPD may have met the criteria for an oppositional defiant disorder during childhood, which is also characterized by the tendency to be irritable, complaining, oppositional, argumentative, and negativistic. In DSM-III, PAPD was said to be the adult variant of oppositional defiant disorder, comparable to the relationship of ASPD to conduct disorder (American Psychiatric Association 1980). As adults, impairment is likely to be particularly evident with respect to employment. Persons with PAPD would be irresponsible, lax, and negligent employees, as well as resistant, oppositional, and even hostile. Resolution of interpersonal conflicts will be difficult, due to the tendency of the passive–aggressive person to blame others. They will be argumentative, sullen, and critical of their peers and friends, who may not tolerate their antagonism.

### *Etiology and Pathophysiology*

Central to the psychopathology of PAPD is considered to be bitter resentment (Millon et al. 1996). Passive–aggressive persons are said to have a hostile, angry, and bitter attitude toward the world. There are no data on its heritability or psychosocial etiology. However, the DSM-IV-TR diagnosis of PAPD appears to involve the general personality traits of oppositionalism, irresponsibility, and laxness (see Table 82–3), for which there is considerable empirical support for heritability (Widiger and Trull 2007). It has been suggested that passive–aggressive behavior is due in part to conflicts concerning dependency and resentment, or a history of mistreatment and neglect (McCann 1988). One might find a history of being exploited, neglected, mistreated, or abused by persons upon whom the person with PAPD relied. Negativistic traits may also be modeled by parental figures.

### *Treatment*

Persons with PAPD would rarely enter treatment to make effective changes to their personality or behavior. They are more likely to seek treatment for Axis I disorders (e.g., depression, anxiety, or somatoform disorder), or for marital, family, or occupational problems. The initiation of treatment is often at the insistence of a spouse, relative, or employer (Gabbard 2000a, Stone 1993). They can be very difficult patients to treat due to their tendency to be blaming, argumentative, pessimistic, and passively resistant (Millon et al. 1996). It is important for the therapist to remain supportive and empathic, carefully and benignly offering observations, suggestions, and reflections on their tendency to be their own worst enemy. Cognitive treatment can be useful to directly address the false perceptions, assumptions, and attributions (Beck et al. 1990) as long as the therapist is not drawn into unproductive disagreements and arguments. It is common for therapists to become frustrated, impatient, and defensive in response to the negativism, criticism, and complaints. Periodic consultation with colleagues is advisable. Group therapy is often helpful once the patient has developed a commitment to the group, as the various members can provide consistent and confirmatory feedback regarding the negativistic and passive–aggressive behavior. There is no known pharmacologic treatment for PAPD (Markovitz 2001, Soloff 2005).

## Depressive Personality Disorder

Depressive personality disorder (DPPD) was proposed for inclusion in DSM-III (American Psychiatric Association 1980) and DSM-III-R (American Psychiatric Association 1987), but there were concerns that it may not be adequately distinguished from the mood disorder of dysthymia (Klein 1999, Phillips et al. 1995, 1998, Ryder and Bagby 1999, Widiger 1999). This is somewhat ironic, as much of the research literature that guided the development of early onset dysthymia concerned research on depressive personality traits (Keller 1989, Keller and Russell 1996). A field trial by the DSM-IV-TR Mood Disorders Work Group indicated that many persons do meet diagnostic criteria for DPPD rather than early onset dysthymia (Phillips et al. 1995, Widiger 1999). Many persons diagnosed with early onset dysthymia may not be adequately described as having a disorder that is confined to the regulation or control of their mood (Klein 1999, Phillips et al. 1998). However, it was decided that the DSM-IV-TR diagnostic criteria for DPPD lacked sufficient empirical support to warrant full recognition (Gunderson 1998).

### Definition

DPPD is a pervasive pattern of depressive cognitions and behaviors that have been evident since adolescence and characteristic of everyday functioning (American Psychiatric Association 2000). These are persons who characteristically display a gloominess, cheerlessness, pessimism, brooding, rumination, and dejection. DPPD would be diagnosed by the presence of five or more of the seven criteria presented in DSM-IV-TR Criteria: Depressive Personality Disorder.

**DSM-IV-TR Criteria**

**Depressive Personality Disorder**

A. A pervasive pattern of depressive cognitions and behaviors beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

(1) usual mood is dominated by dejection, gloominess, cheerlessness, joylessness, unhappiness

(2) self-concept centers around beliefs of inadequacy, worthlessness, and low self-esteem

(3) is critical, blaming, and derogatory toward self

(4) is brooding and given to worry

(5) is negativistic, critical, and judgmental toward others

(6) is pessimistic

(7) is prone to feeling guilty or remorseful

B. Does not occur exclusively during major depressive episodes and is not better accounted for by dysthymic disorder.

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### Differential Diagnosis

There may be no meaningful distinction between DPPD and early onset dysthymia, as suggested within DSM-IV-TR (American Psychiatric Association 2000). The DSM-IV-TR Personality Disorders Work Group developed a criterion set for DPPD that placed particular emphasis on cognitive features as a means of distinguishing DPPD from a more vegetative dysthymia (Widiger et al. 1995). This criterion set was able to distinguish DPPD from cases of dysthymia within the mood disorders field trial (Phillips et al. 1995) but the criterion set for dysthymia was subsequently modified to include these cognitive features. The alternative criteria for dysthymia were placed in the appendix to DSM-IV-TR along with the criterion set for DPPD (Phillips et al. 1995, Widiger 1999). Some may prefer to use the diagnosis of early onset dysthymia, but a dysregulation in mood may not adequately explain why some persons are characterized by chronic attitudes of pessimism, negativism, hopelessness, and dejection. Quite a bit of research continues to be conducted on the validity of depressive personality and its distinction from dysthymia (e.g., Huprich et al. 2005, Pettit and Joiner 2006, Ryder et al. 2006a, 2006b).

### Epidemiology and Comorbidity

There are only limited data on the prevalence of DPPD within the general population. DPPD is likely to be comorbid with early onset dysthymia, although not all cases of DPPD will meet the DSM-IV-TR criteria for dysthymia (Klein 1999, Phillips et al. 1995). Many of the persons who meet the criteria for DPPD will also likely meet the DSM-IV-TR criteria for PAPD and BPD.

### Course

There is considerable research on the childhood antecedents (Caspi et al. 2005) and lifetime course (Roberts and Del Vecchio 2000) of depressive personality traits. As children, persons with DPPD will have been pessimistic, gloomy, passive, and withdrawn. Performance in school is often inadequate to poor. This behavior pattern continues essentially unchanged into and through adulthood. Some, however, may eventually become good workers, exhibiting tremendous discipline and devotion to their work (Phillips et al. 1995). Relationships with peers and sexual partners, however, are invariably problematic. They will be gloomy and irritable company, and will have difficulty finding pleasure, joy, or satisfaction in leisure activities (Millon et al. 1996). They may also be quite withdrawn and lonely, but lack an apparent motivation or energy to seek or maintain relationships.

### Etiology and Pathophysiology

Trait depression is a facet of the personality domain of neuroticism or negative affectivity, which has a well-documented heritability within the general population (Bouchard and Loehlin 2001, Jang et al. 1998, Jang and Vernon 2001). There are also data to indicate a shared genetic variance with mood disorder, consistent with the hypothesis that DPPD may involve a depressive temperament that pervades general personality functioning as well as providing a disposition toward mood disorders (Klein 1999). A characteristically low self-esteem, self-criticism, pessimism, brooding, and guilt could also result from continued, sustained criticism, derogation, and discouragement by a significant parental

figure that is accepted and incorporated by the child (Stone 1993).

### Treatment

Many persons with DPPD will be referred or seek treatment for a depressive mood disorder. It is important in such cases to recognize the extent to which the depressed mood reflects their fundamental view of themselves and the world. Their pessimism involves more than simply a dysregulation of mood. Cognitive–behavioral techniques have demonstrated efficacy in the treatment of depressive personality traits (Beck et al. 1990). The depressive individual's pessimistic view of themselves and their future should be systematically challenged. Explorations of the faulty reasoning, arbitrary inferences, selective perceptions, and misattributions can be influential in overcoming the pessimistic, gloomy, critical, and negativistic attitudes. Audio- or videotaped role-playing is useful in helping the person recognize the occurrence and pervasiveness of the depressive cognitions, and in generating, developing, and rehearsing more realistic and accurate reasoning. However, exploration of the source for and historical development of self-defeating behaviors may also be helpful, not only to undermine their credibility and validity within current relationships and situations but also to address any motivation for their perpetuation (Stone 1993). Persons with DPPD will also be responsive to antidepressant pharmacotherapy, particularly tricyclic antidepressants (Klein 1999, Markovitz 2001, Widiger 1999).

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CHAPTER 83

# Psychological Factors Affecting Medical Condition

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Psychological Factors Affecting Physical Condition
Psychological Factors Affecting Medical Condition

## Definition

This diagnostic category recognizes the variety of ways in which specific psychological or behavioral factors can adversely affect medical illnesses. Such factors may contribute to the initiation or the exacerbation of the illness, interfere with treatment and rehabilitation, or contribute to morbidity and mortality. Psychological factors may themselves constitute risks for medical diseases, or they may magnify the effects of nonpsychological risk factors. The effects may be mediated directly at a pathophysiological level (e.g., psychological stress inducing myocardial ischemia) or through the patient's behavior (e.g., noncompliance).

The criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) for this diagnosis were brief and emphasized the temporal relationship of psychological factors to the initiation or exacerbation of the medical condition. The criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) were expanded in two ways. The overall category was expanded to include situations in which psychological factors interfered with medical treatment, posed health risks, or caused stress-related pathophysiological changes. This diagnosis was also structured in DSM-IV-TR so that both the psychological factor and the general medical condition are to be specified. The psychological factor can be an Axis I or Axis II mental disorder (e.g., major depressive disorder aggravating coronary artery disease (CAD)), a psychological symptom (e.g., anxiety exacerbating asthma), a personality trait or coping style (e.g., type A behavior contributing to the development of CAD), maladaptive health behaviors (e.g., unsafe sex in a person with human immunodeficiency virus (HIV) infection), a stress-related physiological response (e.g., tension headache), or other or unspecified psychological factors. The medical condition is also noted on Axis III. The expansion and elaboration of diagnostic criteria in DSM-IV-TR were based on an extensive review of the literature by a DSM-IV-TR work group organized by organ system and medical specialty categories. Their work has been published and is a source of more detail for the interested reader. (Stoudemire 1995).

**DSM-III-R Diagnostic Criteria 316**

**Psychological Factors Affecting Physical Condition**

A. Psychologically meaningful environmental stimuli are temporally related to the initiation or exacerbation of a specific physical condition or disorder (recorded on Axis III).

B. The physical condition involves either demonstrable organic pathology (e.g., rheumatoid arthritis) or a know pathophysiological process (e.g., migraine headache).

C. The condition does not meet the criteria for a somatoform disorder.

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The subject of psychological factors affecting medical condition (PFAMC) has become the focus of intense research because of the illumination it may provide of basic disease mechanisms (e.g., psychoneuroimmunology) and because of the intense interest in improving both the outcomes and the efficiency of health care delivery. In epidemiological studies, several psychiatric disorders increase the likelihood of mortality (Bruce et al. 1994), especially depression, bipolar disorder, schizophrenia, and alcohol abuse or dependence. Psychiatric disorders may negatively affect outcome

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**DSM-IV-TR Criteria** 316

**Psychological Factors Affecting Medical Condition**

A. A general medical condition (coded on Axis III) is present.

B. Psychological factors adversely affect the general medical condition in one of the following ways:

(1) The factors have influenced the course of the general medical condition as shown by a close temporal associated between the psychological factors and the development or exacerbation of, or delayed recovery from, the general medical condition

(2) The factors interfere with the treatment of the general medical condition

(3) The factors constitute additional health risks for the individual

(4) Stress-related physiological responses precipitate or exacerbate symptoms of the general medical condition

Choose name based on the nature of the psychological factors (if more than one factor is present, indicate the most prominent):

**Mental disorder affecting…[indicate the general medical condition]** (e.g., an Axis I disorder such as major depressive disorder delaying recovery from a myocardial infarction)

**Psychological symptoms affecting…[indicate the general medical condition]** (e.g., depressive symptoms delaying recovery from surgery; anxiety exacerbating asthma)

**Personality traits or coping style affecting…[indicate the general medical condition]** (e.g., pathological denial of the need for surgery in a patient with cancer; hostile, pressured behavior contributing to cardiovascular disease)

**Maladaptive health behaviors affecting…[indicate the general medical condition]** (e.g., overeating; lack of exercise; unsafe sex)

**Stress-related physiological response affecting…[indicate the general medical condition]** (e.g., stress-related exacerbations of ulcer, hypertension, arrhythmia, or tension headache)

**Other or unspecified psychological factors affecting…[indicate the general medical condition]** (e.g., interpersonal, cultural, or religious factors)

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in medical illness, increasing adverse events, length of stay in general hospital patients, and health care costs (Saravay 2006, Walker et al. 2003, Daumit et al. 2006, Deykin et al. 2001). Interest has been further increased by intervention trials aimed at psychological factors or disorders that have demonstrated improvements in medical outcomes and in quality of life in patients with serious medical disorders.

It should be evident that this diagnosis is not really a discrete diagnostic category but rather a label for the interactive effects of psyche on soma. Mind–body interactions have long been a focus of interest, both in health and in disease. Psychiatric illness and medical disease frequently coexist. Psychiatrists and investigators of past eras were misled by this frequent comorbidity into premature conclusions that the psychological factors were preeminent in the causation of the medical disorders, and these were designated psychosomatic. A more modern approach has been to recognize that all medical illnesses are potentially affected by many different factors in the biological, psychological, and social realms. The earlier designation of certain disorders as psychosomatic (e.g., peptic ulcer disease) overvalued the contribution of psychological factors to those disorders and undervalued their contribution to other medical disorders (e.g., cancer). Furthermore, whereas labeling medical illnesses as psychosomatic drew attention to the importance of mind−body interactions, it unfortunately and falsely implied to many patients and physicians that the illness was basically psychogenic, that the symptoms were not "real," and that the illness was somehow the patient's fault.

The diagnosis of PFAMC focuses attention on one causal direction in the interactions between psyche and soma, that is, the effects of psychological factors on the medical condition (Figure 83–1). This represents a heuristic simplification, highlighting a particular process for further exploration, understanding, and intervention. In most patients, there are effects in the other direction as well (i.e., the effects of general medical illness on psychological function). Furthermore, both mind and body interact with social and environmental factors both dramatic (e.g., poverty, racism, war) and more subtle (e.g., employment status, neighborhood) (Roux et al. 2001), that affect the incidence and outcome of medical illness. Diagnosing PFAMC may help psychiatrist and patient address an important dimension of care, but the other "arrows" of Figure 83–1 often warrant attention too.

## Assessment and Diagnosis

The diagnosis of PFAMC differs from most other psychiatric diagnoses in its focus on the interaction between the mental and medical realms. As noted, the criteria require more than

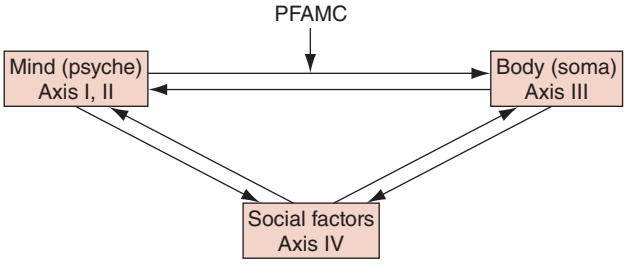



**Figure 83–1** *PFAMC: Interaction between psyche and soma. Social factors warrant attention as well.*

that the patient have both a medical illness and contemporaneous psychological factors, because their coexistence does not always include significant interactions between them. To make the diagnosis of PFAMC, either the factors must have influenced the course of the medical condition, interfered with its treatment, contributed to health risks, or physiologically aggravated the medical condition.

Let us consider each of these four ways of making the diagnosis of PFAMC in more detail. The psychological factor's influence on the course of a general medical condition can be inferred from a close temporal relationship between the factor and the development or exacerbation of the medical condition (or delayed recovery). For example, a 45-year-old male executive reports symptoms sounding like typical angina, but occurring only on weekends. Further questioning reveals that he is depressed over the deterioration of his marriage. During the week, he works late and has limited contact with his family, but he spends the weekend at home. The symptoms began after he and his wife started arguing every weekend. The temporal link between onset and recurrence of angina and marital arguments supports a diagnosis of PFAMC.

PFAMC can also be diagnosed when the psychological factor interferes with treatment, including not seeking medical care, not following up, nonadherence to prescribed drugs or other treatment, or maladaptive modifications in treatment made by the patient or family. The same 45-year-old executive with angina rejected his physician's recommendations for further assessment and treatment. He said, "I do get upset at home but I feel just fine at the office, so there couldn't be anything really wrong with me." The patient is able to acknowledge marital discord, but the defense of denial clouds his perception of his physical health and blocks appropriate medical care. This is another form of PFAMC.

PFAMC can also be diagnosed when the psychological factor contributes to health risks, exemplified by the same 45-year-old executive's increasing his smoking and drinking despite his physician's warnings. ("It's the only way I can cope with my wife.") Finally, PFAMC is an appropriate diagnosis when there are stress-related physiological responses precipitating or exacerbating symptoms of the medical condition. The same man observes that angina is most likely to occur after marital arguments during which he becomes irate, yelling, slamming doors, and throwing things.

When a patient's medical illness is faring worse than expected and not responding well to standard treatment, physicians should and often do consider whether a psychological factor may be responsible for the poorer than expected outcome. This is a far from trivial task. To ignore the possibility of PFAMC may miss the crucial barrier to the patient's recovery. On the other hand, premature or facile attribution to psychological factors may lead the physician to overlook medical or social explanations for "treatment-resistant disease" and unfairly blame the patient, with resultant further deterioration in health outcomes and the physician–patient relationship.

To illustrate, a common clinical problem is the brittle diabetic adolescent with labile blood glucose levels and frequent episodes of ketoacidosis and hypoglycemia, despite vigorous attempts by the physician to improve diabetic management and glucose control. The considerable difficulty in controlling such patients' diabetes is often attributed to adolescents' dislike of lifestyle restrictions, their tendency to act out and rebel against authority figures, their denial of vulnerability, their ambivalence about their need for nurturance, and their wish to be "normal". There are many adolescent (and some adult) diabetic patients for whom these psychological issues do play an important role in undermining diabetes management through noncompliance regarding medication, diet, visits to the physician, substance use, and activity limitations. However, psychological factors do not always account for brittleness and are sometimes incorrectly suspected. It has been demonstrated that much of the difficulty in achieving stable glucose control in adolescent diabetics is the result of the dramatically labile patterns of hormone secretion (cortisol, growth hormone) typical of adolescence, independent of psychological status.

PFAMC has descriptive names for subcategories described as follows.

### Mental Disorder Affecting a General Medical Condition

If the patient has a mental disorder meeting criteria for an Axis I or Axis II diagnosis, the diagnostic name is mental disorder affecting medical condition, with the particular medical condition specified. In addition to coding PFAMC, the specific mental disorder is also coded on Axis I or Axis II. Examples include major depressive disorder that reduces energy and compliance in a hemodialysis patient; panic disorder that makes an asthmatic patient hypersensitive to dyspnea; and schizophrenia in a patient with recurrent ventricular tachycardia who refuses placement of an automatic implantable defibrillator because he fears it will control his mind.

### Psychological Symptoms Affecting a General Medical Condition

Patients who have psychological symptoms that do not meet the threshold for an Axis I diagnosis may still experience important effects on their medical illness, and the diagnosis would be psychological symptoms affecting a medical condition. Examples include anxiety that aggravates irritable bowel syndrome (IBS); depressed mood that hinders recovery from hip replacement surgery; and anger that interferes with rehabilitation after spinal cord injury.

### Personality Traits or Coping Style Affecting a General Medical Condition

This may include personality traits or coping styles that do not meet criteria for an Axis II disorder and other patterns of response considered to be maladaptive because they may pose a risk for particular medical illnesses. An example is the competitive hostility component of the type A behavior pattern, and its impact on CAD. Maladaptive personality traits or coping styles are particularly likely to interfere with the physician–patient relationship as well as the patient's relationships with other caregivers.

### Maladaptive Health Behaviors Affecting a General Medical Condition

Many maladaptive health behaviors have significant effects on the course and treatment of many medical conditions. Examples include sedentary lifestyle, smoking, abuse of

alcohol or other substances, and unsafe sexual practices. If the maladaptive behaviors can be better accounted for by an Axis I or Axis II disorder, the first subcategory (mental disorder affecting a medical condition) should be used instead.

### Stress-Related Physiological Response Affecting a General Medical Condition

Examples of stress-related physiological responses affecting a medical condition include the precipitation by psychological stress of angina, cardiac arrhythmia, migraine, or attack of colitis in medically vulnerable individuals. In such cases, stress is not the cause of the illness or symptoms; the patient has an underlying medical condition (CAD, migraine, or ulcerative colitis), and the stressor instead represents a precipitating or aggravating factor.

### Other or Unspecified Psychological Factors Affecting a General Medical Condition

There are other psychological phenomena that may not fit within one of these subcategories. An interpersonal example is marital dysfunction. A cultural example is the extreme discomfort a woman from some cultures may experience being alone with a male physician, even while she is fully dressed. A religious example is a Jehovah's Witness who ambivalently refuses blood transfusion. These fall under the residual category of other or unspecified psychological factors affecting a medical condition.

## Differential Diagnosis

As noted before, the close temporal association between psychiatric symptoms and a medical condition does not always reflect PFAMC. If the two are considered merely coincidental, then separate psychiatric and medical diagnoses should be made. In some cases of coincident psychiatric and medical illness, the mental symptoms are actually the result of the medical condition (i.e., the causality is in a direction opposite from that of PFAMC). When a medical condition is judged to be pathophysiologically causing the mental disorder (e.g., hypothyroidism causing depression), the correct diagnosis is the appropriate mental disorder due to a general medical condition (e.g., mood disorder due to hypothyroidism, with depressive features). In PFAMC, the psychological or behavioral factors are judged to precipitate or aggravate the medical condition.

Substance use disorders may adversely affect many medical conditions, and this can be described through PFAMC. However, in some patients, all of the psychiatric and medical symptoms are direct consequences of substance abuse, and it is usually parsimonious to use just the substance use disorder diagnosis. For example, a patient with delirium tremens after alcohol withdrawal would receive a diagnosis of alcohol withdrawal delirium, not PFAMC, but a patient with alcohol dependence who repeatedly missed hemodialysis treatments because of intoxication would receive diagnoses of alcohol dependence and PFAMC (mental disorder affecting end stage renal disease).

Patients with somatoform disorders (e.g., somatization disorder, hypochondriasis) present with physical complaints which may mimic a medical illness, but the somatic symptoms are actually accounted for by the psychiatric disorder. In principle, it might seem that somatoform disorders are easily distinguished from PFAMC, because PFAMC requires the presence of a diagnosable medical condition. The distinction in practice is sometimes difficult because the patient may have both a somatoform disorder and one or more medical disorders. For example, a patient with seizures regularly precipitated by emotional stress might have true epilepsy aggravated by stress (PFAMC), pseudoseizures (conversion disorder), or both.

## Epidemiology and Comorbidity

Because this diagnosis describes a variety of possible interactions between the full range of psychiatric disorders (as well as symptoms and behaviors) on the one hand and the full range of medical diseases on the other, it is impossible to estimate overall rates of prevalence or incidence. We can start, however, by noting how frequently medical and psychiatric disorders coexist. Psychiatric problems are common in medical patients, although the measured frequency varies, depending on the criteria and method of measurement used. A reasonable estimate is that 25–30% of medical outpatients and 40–50% of general medical inpatients have diagnosable psychiatric disorders (Table 83–1). Most common in medical outpatients are depression, anxiety, and substance abuse; medical inpatients most often have cognitive impairment (delirium, dementia), depression, and substance abuse. Depression, both as a diagnosis and as a symptom has been better studied in the medically ill than any other psychiatric syndrome. Major depressive disorder occurs in 18–25% of patients with serious coronary disease, in 25% of those with cancer, and at three times the normal rate in diabetic patients. Individuals presenting with symptoms of chronic fatigue have a 50–75% lifetime prevalence of major depression (Sharpe and O'Malley 2005).

**Table 83–1 Prevalence of Selected Psychiatric Disorders**

| Disorder | Community | Primary Care Patients | Medical inpatients |
|---|---|---|---|
| All psychiatric Disorders | 15–20% | 25–30% | 40–50% |
| Depression | | | |
| Depressive symptoms | 10–15% | 10–30% | 20–35% |
| Major depressive Disorder | 2–4% | 5–10% | 5–25% |
| Anxiety | | | |
| Anxiety symptoms | 10–20% | 12–20% | 20–30% |
| Panic disorder | 1–2% | 2–15% | — |
| Cognitive disorders | | | |
| | 1% | — | 15–20% |
| | 5–10% (>65 yr) | — (>65 yr) | 30–50% |

*Source:* Levenson JL (1994) Common psychological reactions to medical illness and treatment. In Clinical Psychiatry for Medical Students, 2nd edition, Stoudemire A (ed). JB. Lippincott, Philadelphia, pp 580B–609.

Nonpsychiatric physicians underdiagnose and undertreat psychiatric disorders in the medically ill. Medical disorders are also common in patients seen for mental health treatment, and mental health specialists often underrecognize the presence and significance of coexisting medical disorders. Regardless of whether the patient has come seeking

medical care or mental health care, medical and psychiatric problems are often both present. Such coincidence by itself is not sufficient for the diagnosis of PFAMC. In some cases, the illnesses may coexist with little effect on each other; in other cases, the effects of the medical illness on the psychiatric condition may be more important. The diagnosis of PFAMC in DSM-IV-TR is reserved for patients in whom psychological factors adversely affect a medical condition in a specifiable way.

## Course

Given the wide range of psychiatric disorders and psychological factors that may affect medical illness and the large number of different medical disorders that may be influenced, there are no general rules about the course of the PFAMC interaction. Psychological factors may have minor or major effects at a particular point or throughout the course of a medical illness. We do know in general that patients with medical disorders who also have significant psychological symptoms have poorer outcomes and higher medical care costs than those patients with the same medical disorders but without psychological distress. A number of studies now document that psychological or psychiatric problems (particularly cognitive disorder, depression, and anxiety) in general medical inpatients are associated with significant increases in length of hospital stay (Saravay 2006). Psychosocial interventions have been able to improve outcomes in medical illness, sometimes with an attendant savings in health care costs (Saravay 2006).

The impact of psychological factors on the course and natural history of medical disorders is discussed further in this chapter in the context of specific diseases.

## Etiology and Pathophysiology

How do psychological factors affect medical illnesses? Physicians have long recognized that psychological factors seem to affect medical illnesses, and research elucidating the intervening causal mechanisms is now rapidly growing. From their clinical experience, physicians recognize many ways in which psychological factors affect the onset, progression, and outcome of their patients' illnesses. First, psychological factors may promote other known risks for medical illness. Smoking is a risk factor for heart disease, cancer, and pulmonary and many other diseases, and individuals with schizophrenia or depression are much more likely to smoke than the general population. A wide variety of psychiatric illnesses are associated with an increased likelihood of abuse of other substances. Depression and schizophrenia also are associated with a sedentary lifestyle. Patients with affective disorders often have chronic pain and chronically tend to overuse analgesics. Individuals with schizophrenia, bipolar disorder, and some personality disorders are more likely to engage in unsafe sex, which in turn increases the risk of sexually transmitted diseases, including HIV infection and hepatitis B. Depression, eating disorders, and other emotional and behavioral factors affect the pattern and content of diet.

In addition to promoting known risk factors for medical illness, psychological factors also have an impact on the course of illness by influencing how patients respond to their symptoms, including whether and how they seek care. For example, the defense mechanism of denial may lead an individual to ignore anginal chest pain, attribute it to indigestion, delay seeking medical attention, or minimize the pain when describing it to a physician. This tends to result in treatment delay after the acute onset of coronary symptoms, with consequently greater morbidity and mortality. Anxiety is also a common cause of avoidance or delay of health care; phobic fears of needles, sight of blood, surgery, and other health care phobias are common (Noyes et al. 2000). Patients may also neglect their symptoms and fail to promptly seek medical care because of depression, psychosis, or personality traits (e.g., procrastination).

Psychological factors also affect the course of illness through their effects on the physician–patient relationship, since they influence both patients' health behaviors and physicians' diagnostic and treatment decisions. A substantial proportion of the excess mortality experienced by individuals with mental disorders is explained by their receiving poorer quality medical care (Druss et al. 2001a). One explanation for the poorer quality and outcomes of medical care in patients with both serious medical and mental illnesses is the lack of integration between their medical and mental health care (Druss et al. 2001b). Psychological factors can also reduce a patient's compliance with diagnostic recommendations, treatment, and lifestyle change, and can interfere with rehabilitation through impairment of motivation, understanding, optimism, or tolerance. A meta-analysis found that patients with depression are three times as likely to be noncompliant with medical treatment than patients without (DiMatteo et al. 2000). In addition, many of the effects of psychological factors on medical illness appear to be mediated through a wide array of social factors, including social support, job strain, disadvantaged socioeconomic and educational status, and marital stress.

There is an increasing body of scientific evidence that psychological factors, in addition to their impact on classic (nonpsychological) risk factors, patient behaviors, and the physician−patient interaction, have direct effects on pathophysiological processes. For example, stress has been experimentally shown to cause myocardial ischemia in patients with coronary disease. Stress and depression are associated with a wide range of immunological effects (Graham et al. 2006, Schiepers et al. 2005). Many psychiatric disorders (especially mood disorders) are associated with disruptions in homeostasis, including sleep architecture, other circadian rhythms, and endocrine secretion and feedback. For example, depression causes increased bone remodeling and decreased bone density (Herran et al. 2000). That such effects occur is well established, but the magnitude of their clinical significance in medical disease is often unclear, and full explanatory causal linkages have for the most part not been demonstrated yet. Nevertheless, investigators have learned a great deal about changes in autonomic, hematologic, endocrine, immunologic, and sensory function, as well as gene expression that bring us closer to understanding how psychological factors may affect medical illness. These issues of pathophysiology are discussed later in this chapter for each organ system or specialty category.

## Treatment

Management of psychological factors affecting the patient's medical condition should be tailored both to the particular psychological factor of relevance and to the medical outcome of concern. Some general guidelines, however, can be

helpful. The physician, whether in primary care or a specialty, should not ignore apparent psychiatric illness. Unfortunately, this occurs all too often because of discomfort, stigma, lack of training, or disinterest. Referring the patient to a mental health specialist for evaluation is certainly better than ignoring the psychological problem but should not be regarded as "disposing" of it, because the physician must still attend to its potential impact on the patient's medical illness. Similarly, psychiatrists and other mental health practitioners should not ignore coincident medical disease and should not assume that referral to a nonpsychiatric physician absolves them of all responsibility for the patient's medical problem.

### Mental Disorder Affecting a Medical Condition

If the patient has a treatable Axis I disorder, treatment for it should be provided. Whereas this is obviously justified on the basis of providing relief from the Axis I disorder, psychiatric treatment is further supported by the myriad ways in which the psychiatric disorder may currently or in the future adversely affect the medical illness. The same psychopharmacological and psychotherapeutic treatments used for Axis I mental disorders are normally appropriate when an affected medical condition is also present. However, even well-established psychiatric treatments supported by randomized controlled trials have seldom been validated in the medically ill, who are typically excluded from the controlled trials. Thus, psychiatric treatments may not always be directly generalizable to, and often must be modified for, the medically ill.

When prescribing psychiatric medications for patients with significant medical comorbidity, the psychiatrist should keep in mind potential adverse effects on impaired organ systems (e.g., anticholinergic exacerbation of postoperative ileus; tricyclic antidepressant causing completion of heart block), changes in pharmacokinetics (absorption, protein binding, metabolism, and excretion), and drug–drug interactions. Psychotherapy may also require modification in patients with comorbid medical illness, including greater flexibility regarding the length and frequency of appointments, and deviations from standard therapeutic abstinence and neutrality (i.e., refraining from telling patients what to do and taking action on their behalf) (Perry and Viederman 1981). Psychotherapists treating patients with PFAMC should usually be much more active in communicating with other health care professionals caring for the patient (with the patient's consent) than is usually the case in psychotherapy.

If the patient has an Axis II personality disorder or other prominent personality or coping style, the psychiatrist should modify the patient's treatment accordingly, which is usually more easily accomplished than trying to change the patient's personality. For example, patients who tend to be paranoid or mistrustful should receive more careful explanations, particularly before invasive or anxiety-provoking procedures. With narcissistic patients, the psychiatrist should avoid relating in ways that may seem excessively paternalistic or authoritarian to the patient. With some dependent patients, it may be advisable to be more directive, without overdoing it and fostering excessive dependency.

### Psychological Symptoms Affecting a General Medical Condition

In some instances, psychiatric symptoms not meeting the threshold for an Axis I diagnosis will response positively to the same treatments used for the analogous Axis I psychiatric disorder, with appropriate modifications as noted before. There is not a great amount of treatment research on subsyndromal psychiatric symptoms, and even less in patients with comorbid medical illness, so this area of practice remains less evidence-based. Some psychiatric symptoms affecting a medical condition may be amenable to stress management and other behavioral techniques as well as appropriate reassurance.

Any intervention directed by the psychiatrist at a particular patient's psychological symptoms or behavior should be grounded in exploratory discussion with the patient. Interventions without such grounding tend to seem at best superficial and artificial and at worst are entirely off the mark. For example, if the psychiatrist wrongly presumes to know why a particular patient seems anxious without asking, the patient is likely to feel misunderstood. Facile, nonspecific reassurance can undermine the physician–patient relationship, because the patient is likely to feel that the psychiatrist is out of touch with and not really interested in the patient's experience. It is especially important with depressed patients that psychiatrists avoid premature or unrealistic reassurance or an overly cheerful attitude; this tends to alienate depressed patients, who feel that their psychiatrist is insensitive and either does not understand or does not want to hear about their sadness. Physicians *should* provide specific and realistic reassurance, emphasizing a constructive treatment plan, and mobilize the patient's support system.

### Personality Traits or Coping Style Affecting a General Medical Condition

As with Axis II disorders affecting a medical condition, psychiatrists should be aware of the personality style's effects on the physician–patient relationship and modify management to better fit the patient. For example, with type A "time urgent" patients, psychiatrists may need to be more sensitive to issues of appointment scheduling and waiting times. Group therapy interventions can enhance active coping with serious medical illnesses like cancer, heart disease, and renal failure but to date have usually been designed to be broadly generalizable rather than targeted to one particular trait or style (with the exception of type A behavior).

Another general guideline is not to attack or interfere with a patient's defensive style unless the defense is having an adverse impact on the medical illness or its management. Psychiatrists are particularly tempted to intervene when the defense is dramatic, breaks with reality, or makes the psychiatrist uncomfortable.

For example, denial is a defense mechanism that reduces anxiety and conflict by blocking conscious awareness of thoughts, feelings, or facts that an individual cannot face. Denial is common in the medically ill but varies in its timing, strength, and adaptive value. Some patients are aware of what is wrong with them but consciously suppress this knowledge by avoiding thinking about or discussing it. Others cope with the threat of being overwhelmed by their illness by unconsciously repressing it and thereby remain unaware of their illness. Marked denial, in which the patient emphatically refuses to accept the existence or significance of obvious symptoms and signs of the disease, may be seen by the psychiatrist as an indication that the patient is "crazy" because the patient seems impervious to rational

persuasion. In the absence of signs of another major psychiatric disorder (e.g., paranoid delusions), such denial is not often a sign of psychosis but rather represents a defense against overwhelming fear.

The adaptive value of denial may vary, depending on the nature or stage of illness. When a patient's denial does not preclude cooperation with treatment, the psychiatrist should leave it alone. The psychiatrist does have an ethical and professional obligation to ensure that the patient has been informed about the illness and treatment. After that, if the patient accepts treatment but persists with an irrationally optimistic outlook, the psychiatrist should respect the patient's need to use denial to cope. For some, the denial is fragile, and the psychiatrist must decide whether the defense should be supported and strengthened, or if the patient had better given up the denial to discuss fears directly and received reassurance from the psychiatrist. The psychiatrist should not support denial by giving the patient false information, but rather encourage hope and optimism. When denial is extreme, patients may refuse vital treatment or threaten to leave against medical advice. Here, the psychiatrist must try to help reduce denial but not by directly assaulting the patient's defenses. Because such desperate denial of reality usually reflects intense underlying anxiety, trying to scare the patient into cooperation will intensify denial and the impulse to flight. A better strategy for the psychiatrist is to avoid directly challenging the patient's claims while simultaneously reinforcing concern for the patient and maximizing the patient's sense of control.

### Maladaptive Health Behavior Affecting a General Medical Condition

This is an area of research with many promising approaches. To achieve smoking cessation, bupropion, varenicline, nicotine replacement, behavioral therapies, and other pharmacological strategies all warrant consideration. Behavioral strategies are also useful in promoting better dietary practices, sleep hygiene, safe sex, and exercise. For some patients, change can be achieved efficiently through support groups, whereas others change more effectively through a one-to-one relationship with a health care professional.

### Stress-Related Physiological Response Affecting a Medical Condition

Biofeedback, relaxation techniques, hypnosis, and other stress management interventions have been helpful in reducing stress-induced exacerbations of medical illness, including cardiac, gastrointestinal, headache, and other symptoms. Pharmacological interventions have also been useful (e.g., the widespread practice of prescribing benzodiazepines during acute myocardial infarction to prevent stress-induced increase in myocardial work).

### Psychological Factors in Specific Medical Disorders

In the remainder of this chapter, the effects of psychological factors on selected medical disorders are reviewed. The primary focus is on those effects for which there is reasonable evidence from controlled studies. Space considerations preclude inclusion of all valuable studies and all medical disorders.

Most of the early research suffers from serious methodological flaws, including use of small biased samples, limited or no statistical analysis, poor (if any) controls, and retrospective designs subject to recall and other biases (Levenson et al. 1990). This early work generated excitement and interest in psychosomatic medicine but also produced ideas that in retrospect were intellectually appealing but erroneous and simplistic regarding the special designation of certain diseases as psychosomatic.

Later research has shown improvements in methodology, but problems in design and interpretation continued. Several studies that seem to have shown significant effects of psychological factors on medical disease have been inconclusive because of nonequivalence in groups at baseline either in medical disease severity or in treatments received (many studies have not even monitored this possibility). Some studies failed to attend to important potential confounding factors such as smoking or diet. A number of studies have measured too many psychological variables and then overly emphasized the few "discovered" positive associations in the published results. Failure to standardize measures of initial psychological factors and measures of medical outcome has also been frequent. Despite these and other critiques, a large and growing body of disease-specific research has illuminated the full range of PFAMC.

## Psychological Factors in Oncology

Many health professionals and lay people believe that psychological factors play a major role in cancer onset and progression. The media have promoted popular ideas of overcoming cancer through "mind over body." Enthusiasm for these optimistic theories and practices should be tempered by the recognition that scientific evidence clarifying the relationship between psychological factors and cancer lags far behind. Nevertheless, there is an exciting frontier of exploration of immune and endocrine mechanisms that may provide a pathophysiological basis for some PFAMC in cancer (Spiegel and Sephton 2001). In this section, aspects of PFAMC in oncology that have received support in the research literature are reviewed.

### Mental Disorders and Psychological Symptoms Affecting Cancer

The most active area of study has been the linking of affective states, particularly depression (as a symptom or as a disorder), with the onset and course of cancer. An early large epidemiological study of more than 2000 employees of Western Electric reported that depressive symptoms were associated with a higher than normal frequency of cancer and twice as high a risk for death from cancer (Shekelle et al. 1981). Later epidemiological studies, however, have generally not found such associations (Vogt et al. 1994, Gallo et al. 2000). Recent prospective large cohort studies found no effect of depression on breast cancer risk in Finnish women (Aro et al. 2005) or of any cancer risk in Danes (Bergelt et al. 2005). The interpretation of epidemiologic studies is complex with many methodological problems, discussed in detail elsewhere (Levenson and McDonald 2002).

Besides epidemiologic studies, other research has focused on the impact of affective states on outcome in cancer patients. In the year after diagnosis of breast cancer, half of women have clinically significant depression, anxiety, or both (Burgess et al. 2005). Emotional distress may predict lower survival with lung cancer (Faller et al. 1999), as may

anger in metastatic melanoma patients (Butow et al. 1999). Other studies have found positive, negative or mixed associations between depression and mortality in cancer patients (Garssen and Goodkin 1999, Levenson and McDonald 2002, Watson et al. 2005). Besides survival, depression in cancer patients may result in poorer pain control (Glover et al. 1995), poorer compliance (Ayres et al. 1994), and less desire for life sustaining therapy (Lee and Ganzini 1992).

Bereavement is a significant stressor with a variety of psychological and physiological effects including immune functions, and has been often assumed to be a risk factor in cancer onset and progression. However, most studies have not supported this. A meta-analysis of 46 studies found only a modest association between separation and loss experiences and development of breast cancer (McKenna et al. 1999). A large prospective cohort study comparing cancer patients found no evidence that death of a child influences survival (Li et al. 2003). In another study, bereavement (death of a son) after, but not before, diagnosis of cancer was associated with accelerated demise (Levav et al. 2000). The evidence to date is that neither cancer onset nor progression have been clearly shown to be influenced by bereavement.

### Personality Traits or Coping Style Affecting Cancer

A large body of literature has described cancer patients' degree of emotional expressiveness and its purported effect on prognosis. Descriptive case reports began appearing in the 1950's, noting shorter survival in patients with depressed, resigning characteristics compared with patients who were able to express more negative emotions, such as anger. Using a variety of conceptualizations of the "expressive" versus "repressive" dichotomy, in an assortment of cancer types, several investigators have found reduced cancer risks in the more expressive subjects (Temoshok et al. 1985, Kune et al. 1991). Other clinical studies, again with varying definitions and study populations, have not supported an influence of this personality style (Cassileth et al. 1985, Buddeberg et al. 1991). While one recent cohort study study showed that neuroticism is negatively associated with cancer survival (Nakaya et al. 2006), most epidemiological studies have not supported a relationship between personality variables and cancer occurrence or mortality (Shekelle et al. 1981, Nakaya et al. 2005, Hansen et al. 2005).

Breast cancer patients who demonstrated a "fighting spirit" or who used denial, were found to have a higher survival rate than those with stoic acceptance or expressed hopelessness and helplessness (Greer et al. 1979). However, a recent study with longer follow-up indicated that a high fighting spirit confers no survival advantage (Watson et al. 2005). Fighting spirit did appear to predict longer survival after bone marrow transplantation for leukemia (Tschushke et al. 2001).

### Other Psychological Factors in Cancer

An enormous literature documents the adverse effects of maladaptive health behaviors as risk factors for the development of various cancers, especially smoking but also excessive alcohol use, unsafe sex, and dietary practices. Relatively less research has examined the effects of interpersonal variables on cancer, but there is some evidence that the quality of relationships may affect cancer onset and its course (Graves et al. 1991, Waxler-Morrison et al. 1991). Social relations and social support and their effects on cancer patients (as with other diseases) are complex phenomena and may vary with cancer site and extent of disease (Decker 2007).

A number of human studies have shown an increased frequency of stressful life events preceding the onset of cervical, pancreatic, gastric, lung, colorectal, and breast cancer (see Levenson and McDonald 2002 for review). Some research has tentatively linked life stressors with cancer recurrence or progression, although not unequivocally (Ramirez et al. 1989). Many other studies have failed to find any association between preceding stressful life events and cancer onset, relapse, or progression (Nielsen and Gronbaek 2006, Bergelt et al. 2006, Maunsell et al. 2001).

### Psychosocial Intervention and Cancer Outcome

A number of studies have shown improvement in the quality of life in cancer patients receiving group therapy, including improved mood and vigor, decreased pain, and better adjustment (Trijsburg et al. 1992, Andersen 1992, Fawzy et al. 1993, Spiegel et al. 1981, Goodwin et al. 2001). The possibility that a psychological intervention might improve longevity in metastatic breast cancer patients was exciting, supported initially by some studies (e.g., Spiegel et al. 1989, Cunningham et al. 1998), but not by the definitive replication study (Goodwin et al. 2001) as well as some others. Thus the evidence to date suggests that patients with cancer can be told that group therapy contributes to living better, not necessarily longer.

## Psychological Factors in Cardiology

### Coronary Disease

One of the most studied examples of PFAMC is the type A behavior pattern and its relationship to CAD. Type A is a complex set of traits including impatience, hostility, intense achievement drive, and time urgency, among others. Strong epidemiological evidence that type A behavior pattern was a risk factor for the development of CAD first appeared over 30 years ago (Rosenman et al. 1975). However, the relationship between type A behavior pattern and coronary disease has come under serious question. Later epidemiological studies have not strongly supported type A behavior pattern as a coronary risk factor, and most angiographic studies have failed to find an association between type A behavior and the extent of CAD (Dimsdale 1988). Whereas global type A behavior ratings are probably not reliable predictors of CAD outcome, a component may be. Of the type A traits, hostility has been the most consistently associated with increased cardiac events and mortality (Boyle et al. 2004). A number of relatively small, short-term studies have demonstrated that type A behavior can be targeted for structured treatment and can possibly be modified (Levenkron and Moore 1988). Only one large randomized study has been reported, in which men were assigned after myocardial infarction to receive cardiac group counseling with or without type A counseling. The CAD recurrence rate was 7.2% in the group that received type A behavior counseling and 13% in the control subjects, with no difference in mortality (Friedman et al. 1986).

Although it has received less media attention than type A, the evidence that depression is a risk factor affecting both

the onset and course of CAD is stronger than that for type A (Musselman et al. 1998, Glassman and Shapiro 1998). The weighting of depression as an independent risk factor in CAD has had to adjust for its interrelationships with other risk factors, especially smoking. Depression in CAD is associated with increased morbidity and mortality, which cannot be accounted for by other variables including severity of cardiac disease (Frasure-Smith et al. 1993, Carney et al. 2003). Frasure-Smith et al. (1993) reported a fourfold increase in mortality 6 months after myocardial infarction in patients with major depression compared to those without depression. In a large epidemiologic study, major depression tripled the relative risk of cardiac mortality in those without heart disease, and quadrupled it in those who did have heart disease (Penninx et al. 2001). Depression is also associated with an increased risk for serious arrhythmia. The severity of depressive symptoms has more impact on disability than does the number of stenosed coronary arteries (Sullivan et al. 1997). In the Heart and Soul Study of over 1000 outpatients with stable CAD, depressive symptoms strongly (negatively) contributed to health status, including symptom burden, physical limitation, quality of life, and overall health, but measures of ischemia and ejection fraction did not contribute (Ruo et al. 2003).

Patients with severe mental disorders have about twice the prevalence of the classic risk factors for CAD (Birkenaes et al. 2006). While the mechanisms by which depression increases morbidity and mortality in CAD has not been firmly established, evidence is mounting regarding depression's adverse effects on heart rate variability, autonomic imbalance and arrhythmia, and platelet activation (Carney et al. 2001, Musselman et al. 2000, Markovitz et al. 2000). Proinflammatory mediators associated with depression may also be a contributor to CAD (Parissis et al. 2004). In CAD, depression also reduces functional capacity (Wells et al. 1989), amplifies somatic symptoms (especially pain) (Light et al. 1991) and reduces motivation and compliance with medication, lifestyle change, and cardiac rehabilitation (Ziegelstein et al. 2000, Carney et al. 1995). Multicenter intervention studies have demonstrated the efficacy of treating depression in CAD but have not as yet shown that such treatment can improve medical outcomes (e.g., the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) (Glassman et al. 2002) and the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (Writing Committee for the ENRICHD Investigators 2003.

One specific mechanism by which psychological factors can affect CAD has been demonstrated experimentally. Silent myocardial ischemia (ischemic changes on the electrocardiogram without symptoms of angina) can be precipitated by acute mental stress (Rozanski et al. 1988). Those who experience it are twice as likely to have major cardiac events compared to those who do not (Jiang et al. 1996). Silent ischemia may be partly a consequence of cognitive or defensive traits such as denial, hyposensitivity to somatic sensation, or systematic misperception of angina (Barsky et al. 1990). Psychological stress also changes the balance between procoagulation and fibrinolysis (von Känel et al. 2001). Psychological factors may also affect outcome in CAD via differences in health care received. After myocardial infarction, patients with mental disorders are less likely to undergo cardiac catheterization and coronary revascularization than those without mental disorder (Druss et al. 2000).

Although the diagnosis and treatment of anxiety in patients with cardiac symptoms have received much attention, there has been less examination of anxiety as a risk factor affecting CAD. Increases in myocardial infarction and/or sudden death have been documented in epidemiologic studies of populations undergoing missile attacks, earthquakes, and other disasters (Krantz et al. 2000). Generalized anxiety disorder is associated with CAD risk factors even after controlling for depression (Barger and Sydeman 2005). Phobic anxiety predicts risk of ventricular arrhythmias and deaths from coronary heart disease (Kawachi and Berkman 2003, Watkins et al. 2006). The INTERHEART study of 11,000 patients with first myocardial infarction (MI), compared to 13,000 controls from 52 countries found higher rates of stress factors (work, home, financial, and major life events) associated with increased risk of MI (Rosengren et al. 2004). Anxiety following MI may lead to more frequent readmission for unstable angina and more MI recurrences (Frasure-Smith et al. 1995), as well as higher mortality (Moser and Dracup 1996). Anxiety's adverse effects on CAD outcome may occur via effects on heart rate variability, QT prolongation, or other autonomically-mediated phenomena, like the stress-induced silent ischemia described above (Januzzi et al. 2000).

Denial is another common and significant psychological factor in patients with coronary disease. Denial may prevent individuals from acknowledging acute cardiac symptoms and promptly seeking medical care. The length of delay between the onset of symptoms of a myocardial infarction and hospitalization is a powerful predictor of morbidity and mortality, so denial at the onset of symptoms has an adverse impact on acute coronary disease. In contrast, denial during hospitalization may have adaptive value, perhaps even reducing morbidity and mortality (Levenson et al. 1989, Levine et al. 1987).

There are other psychological factors deserving of study. Women with severe marital stress had triple the risk of recurrent coronary events than those without marital stress (Orth-Gomer et al. 2000). Many studies have also examined maladaptive health behaviors as risk factors in coronary disease, with the effects of smoking better established than those of sedentary lifestyle, obesity, or specific diet. The effects of psychopathology and of smoking on heart disease are easily confounded, as persons with psychiatric disorders are overall twice as highly to smoke as others, with the increased risk found with all the major anxiety, mood, and psychotic disorders (Lasser et al. 2000).

## Arrhythmias

There is evidence that psychological stressors can also play an important role in precipitating serious ventricular arrhythmias. Sudden cardiac death after psychological distress has been reported anecdotally for a long time but is difficult to study scientifically. There was an increase in life-threatening ventricular arrhythmias in New York City following the attack on the World Trade Center (Steinberg et al. 2005). A systematic review of published cases of ventricular fibrillation in patients without known cardiac disease could identify preceding psychological distress in 22% (Viskin and Belhassen 1990). A review of 96

published studies investigating psychosocial risk factors for arrhythmia found that 92% were positive (Hemingway et al. 2001).

### Congestive Heart Failure

Depression is especially common in patients with congestive heart failure (Koenig 1998, Jiang et al. 2001). In patients hospitalized for congestive heart failure, major depression is independently associated with increased mortality and readmission 3 and 12 months later (Jiang et al. 2001).

### Hypertension

The stress-related physiological response subcategory of PFAMC is particularly relevant to hypertension. There are some data suggesting that blood pressure reactivity to stress is a risk factor for the development of hypertension (Pickering and Gerin 1988) and may influence progression of disease as well (Shapiro 1988). Many studies have examined relationships between personality, coping style, blood pressure reactivity, and hypertension, but conflicting results and methodological limitations have precluded any consensus conclusions (Friedman et al. 2001). Findings regarding the effects of stress, anger, hostility, or anxiety on blood pressure in normotensive individuals are not necessarily relevant to clinical hypertension. Some epidemiologic studies have found depression and/or anxiety symptoms predictive of later development of hypertension even after controlling for confounding factors (Davidson et al. 2000, Jonas et al. 1997). A large prospective population-based study found a dose-response relationship between the Type A behavior factors of time urgency/impatience and hostility and increasing risk for hypertension (Yan et al. 2003). Several measures of occupational stress appear to be independent risk factors for hypertension in the general population (Levenstein et al. 2001). Some of the apparent association between psychological distress and hypertension is chiefly attributable to health risk behaviors (obesity, smoking, alcohol, and sedentary lifestyle). (Levenstein et al. 2001).

## Psychological Factors in Endocrinology

### Diabetes Mellitus

Despite some of the early psychosomatic literature, there is no unique diabetic personality, but physicians who take care of diabetic patients attest to a close interrelationship between psychological factors and glucose control. That psychological stress can adversely affect glucose control in diabetics seems expectable because the hormones of the stress response are part of the counterregulatory response to insulin. A number of studies have shown that glycemic control is poorer in those diabetic patients who have more perceived stress (Garay-Sevilla et al. 2000, Lloyd et al. 1999, Herpertz et al. 2000). As assessed by hemoglobin A1c, metabolic control was poorer in depressed children (Lernmark et al. 1999), and in adult depressed type 1 but not type 2 diabetics (De Groot et al. 1999, Van Tilburg et al. 2001). A meta-analysis of 24 studies concluded that depression consistently is associated with a small-to-moderate increase in hyperglycemia in both type 1 and type 2 diabetes (Lustman et al. 2000). Depression is associated with more diabetic complications (Lloyd et al. 1992, and De Groot et al. 2001). More recently, depressed diabetics have more severe diabetic symptoms (Ludman et al. 2004), more disability (Von Korff et al. 2005), greater mortality (Katon et al. 2005), and higher health care costs (Simon et al. 2005) than other diabetics. Most such research has been retrospective or cross-sectional, leaving it unclear which came first (poor metabolic control and complications or the psychological factor) and what is the relationship between them.

When psychiatric illness antedates and adversely affects the course of diabetes, it may be mediated by noncompliance (diet, medication, activity, visits to the physician, self-care) (Ciechanowski et al. 2000, Van Tilburge et al. 2001) or by neurohumoral mechanisms. The adverse effects in diabetic control cannot all be attributed to noncompliance. Psychological stress administered under laboratory conditions can impair glucose control in both insulin-dependent (Gonder-Frederick et al. 1990) and noninsulin-dependent diabetes (Goetsch et al. 1993). One potential explanation is that depression, anxiety, and stress are often associated with increases in cortisol and other counterregulatory hormones opposing the action of insulin.

Small randomized controlled trials have demonstrated improvements in glucose control in diabetics receiving psychological interventions (Delamater et al. 2001, Grey et al. 2000). The Pathways Study, the most comprehensive clinical trial of enhanced treatment for depression in diabetics, demonstrated that it improved the quality of care and outcomes for depression but did not result in improved glycemic control (Katon et al. 2004). Antidepressants are effective in the treatment of depression in diabetics, but can cause increases or decreases in blood glucose themselves. Deterioration in glucose control in schizophrenic diabetics can be due to atypical antipsychotic drugs, but diabetes was also a major problem for schizophrenics before their advent, presumably because of obesity (a side effect of almost every antipsychotic), unhealthy diet, and poorer health care (Dixon et al. 2000). Optimal management of diabetes requires a degree of organization very difficult for most patients with schizophrenia.

### Thyroid Disease

It is well established that too little or too much thyroid hormone can result in disturbances in mood and activity. In the other direction, the effects of emotion and stress on thyroid function, although long a focus of interest, are less well established. Parry's original report in 1825 described a woman who had hypothyroidism four months after she accidentally fell down stairs in a wheelchair. A number of classic studies reported a relationship between antecedent traumatic stress and the onset of thyrotoxicosis, particularly as part of Graves' disease. However, these studies were retrospective, uncontrolled, and too methodologically flawed by current standards to support the validity of such a link. Later studies have supported stressful life events as a risk factor for Graves' disease (e.g., Santos et al. 2002). Two prospective studies in patients newly diagnosed with Graves' disease found that after adjusting for confounding variables, psychological stress adversely affected the response to treatment and prognosis (Fukao et al. 2003, Yoshiuchi et al. 1998a). Psychological stress may also be a result of less optimal control of hyperthyroidism (Yoshiuchi et al. 1998b).

Whereas there has been little well-substantiated evidence of the impact of psychological factors on thyroid disease,

alterations in thyroid function or its hypothalamic-pituitary control have been demonstrated in relation to affective disorders, schizophrenia, and posttraumatic stress disorder (Mason et al. 1994). Depression has been most studied, revealing a variety of thyroid abnormalities, most frequently a relative increase in thyroxine without changes in the activated (triiodothyronine) and inactive (reverse triiodothyronine) forms and a blunting of the thyroid-stimulating hormone response to thyrotropin-releasing hormone (Goodwin and Jamison 1990). There is not agreement regarding the relationship between these endocrine changes and depressive pathophysiological processes, and it remains unknown whether depression modifies endocrine measures in clinical thyroid disease.

## Psychological Factors in Pulmonary Disease

Although asthma was once regarded as a classic psychosomatic disorder, it is currently viewed as a primary respiratory disease with varying immunological and autonomic pathophysiological changes. Many physicians still believe that psychological factors play an important role in the precipitation and aggravation of asthma, particularly anxiety. One must remember, however, that respiratory distress itself causes a wide array of anxiety symptoms (panic attacks, generalized and anticipatory anxiety, phobic avoidance), and most of the drugs used to treat asthma have anxiety as a potential side effect. Brittle asthmatic patients, like brittle diabetic patients, are more likely to have current or past psychiatric disorder (particularly anxiety disorders) than are other asthmatic individuals, but which came first has not been established. In a large population-based sample of adults, asthma was associated with a significantly increased likelihood of anxiety disorders (especially panic, generalized anxiety disorder, and phobias) and affective disorders (Goodwin et al. 2003). There is no typical personality type susceptible to development of asthma. Anxiety and depression are associated in asthmatic patients with more respiratory symptom complaints but no differences in objective measures of respiratory function (Rietveld et al. 1999). Asthma symptom severity increased in New York City following the terrorist attacks on September 11, 2001, and PTSD was a significant predictor of the increase (Fagan et al. 2003). Psychological factors and psychosocial problems in hospitalized asthmatics were a more powerful predictor of which ones required intubation than any other examined variable (e.g., smoking, infection, prior hospitalization, etc.) (Le Son and Gershwin 1996). Psychological morbidity is associated with high levels of denial and delays in seeking medical care, which may be life-threatening in severe asthma, (Miles et al. 1997), as well as less medication adherence and consequently poorer control of asthma (Cluley and Cochrane 2001). Not surprisingly then, psychopathology in severe asthmatics is associated with increased health care utilization, including hospitalizations, and outpatient and emergency room visits, independent of asthma severity (Ten Brinke et al. 2001).

Similar problems exist in interpreting relationships between anxiety or depression and other chronic obstructive pulmonary diseases (chronic bronchitis, emphysema). Depression and anxiety are common in chronic obstructive pulmonary disease (COPD) (Yohannes et al. 2000, Aydin and Ulusahin 2001), though this partly reflects their increased prevalence in past or current smokers. As in asthma, psychological distress in COPD amplifies dyspnea without usually causing changes in objective pulmonary functions. Depression and anxiety do lead to lower exercise tolerance (Withers et al. 1999), noncompliance with treatment (Bosley et al. 1996), poorer health status (Gudmundsson et al. 2006 and increased disability in COPD (Aydin and Ulusahin 2001). Anxious COPD patients are more likely to be hospitalized (Smoller et al. 1996) and rehospitalized (Gudmundsson et al. 2005), Depression in outpatients suffering from COPD may even be an independent predictor of mortality (Stage et al. 2005). Smoking is a well-established maladaptive health behavior causing and exacerbating chronic obstructive pulmonary disease, and its elimination is the most beneficial intervention available.

## Psychological Factors in Rheumatoid Arthritis

Rheumatoid arthritis (RA) was also once thought to be a psychosomatic disorder, but studies in the modern era have provided little or no support for this belief. There is no particular personality type susceptible to development of rheumatoid arthritis. Earlier research suggesting that stressful like events play a role in the development or onset of RA has not been supported by subsequent studies (e.g., Carette et al. 2000). Psychological factors and disease manifestations account for comparable proportions of disability in RA (Escalante and del Rincon 1999). Psychological morbidity in RA results in more pain, poorer quality of life, more joint surgery, lower compliance, and increased use of health care resources (Newman and Mulligan 2000, Wolfe 1999, Kroll et al. 1999).

Depression has been the most frequently studied psychological disturbance in rheumatoid arthritis; depression is very common, as in other chronic medical conditions (Soderlin et al. 2000). Depression appears to adversely affect outcome in rheumatoid arthritis, aggravating chronic pain, increasing health care use, and increasing social isolation (Dickens et al. 2007). A recent large longitudinal study found depression to be an independent risk factor for mortality in patients with RA (Ang et al. 2005). Randomized controlled trials of antidepressants in depressed RA patients demonstrate improvements in pain, morning stiffness, and disability in addition to depression (Bird and Broggini 2000, Ash et al. 1999).

Passive, avoidant, emotion-laden coping strategies (e.g., wish-fulfilling fantasy, self-blame) are associated with poorer adjustment to illness in RA compared with active, problem-focused coping (e.g., information seeking, cognitive restructuring) (Covic et al. 2000). RA patients with high helplessness are more likely to receive psychotropic, analgesic, and anti-inflammatory drugs and to be less adherent with treatment than those with low helplessness (Stein et al. 1988). Patients with RA may be more vulnerable to stress-induced increases in immune and endocrine function (Hirano et al. 2001). A randomized controlled trial of cognitive−behavioral therapy as an adjunct to standard treatment in recently diagnosed patients with RA showed it efficacious in reducing both psychological and physical morbidity (Sharpe et al. 2001).

## Psychological Factors in Neurology

Depression is frequent after stroke, particularly in the acute phase during hospitalization and the first few weeks after

stroke (Astrom et al. 1993). The presence of depression is associated with poorer outcome; including higher later mortality (House et al. 2001), and functional status is improved with treatment of depression after stroke (Lipsey et al. 1984). A negative attitude after stroke (i.e., feeling there is nothing one can do to help oneself) is associated with decreased survival (Dennis et al. 2000). Research has focused on depression as a complication of stroke but there is also evidence that depression and other psychological factors constitute risks for stroke, consistent with widespread lay and folk beliefs regarding stress and stroke. In a longitudinal prospective epidemiological study, depression appeared to significantly predict greater stroke frequency, but the finding disappeared when other significant predictors were taken into consideration (e.g., age, sex, smoking, hypertension, diabetes) (Colantonio et al. 1992). Later studies have found depressive symptoms increase the risk of stroke in older adults (Simons et al. 1998, Everson et al. 1998, Ostir et al. 2001). Depression appears to be an independent predictor of increased health care use after stroke (Jia et al. 2006) and is also associated with poorer functional recovery (Nannetti et al. 2005). As with many other major medical illnesses, stroke patients with extensive social support have better functional outcomes than those who do not have such support (Colantonio et al. 1993).

Depression is common in Parkinson's disease, may antedate the development of motor symptoms, and is associated with cognitive dysfunction (Holroyd et al. 2005, Errea and Ara 1999). Physicians observe that depression and other psychological factors interact to affect the course and outcome of Parkinson's disease, with depression resulting in impairment of functional capacity, but not motor function in Parkinson disease (Holroyd et al. 2005). Depression is also common and erodes quality of life in multiple sclerosis (MS) (Fruewald et al. 2001) and in epilepsy (Mensah et al. 2006, Barry et al. 2000). The study of depression as an independent risk factor affecting the onset or course of neurological diseases is challenging because depression may also be a direct physiologically-mediated consequence of the disease, a psychological reaction to the illness, or a complication of pharmacotherapy (Zorzon et al. 2001). In MS, depression may increase and its treatment decrease, production of proinflammatory cytokines (Gold and Irwin 2006, Mohr et al. 2001). Depression is especially difficult to study in MS because of its uncertain relationship to the MS-fatigue syndrome (Bakshi et al. 2001).

Patients with chronic migraine headaches have often been described as having a "typical" personality characterized as conscientious, perfectionistic, ambitious, rigid, tense, and resentful, but controlled studies have not supported any consistent conclusion. Specific personality traits in migraine appear more likely to be a consequence rather than a cause of suffering from recurrent headaches (Stronks et al. 1999). Migraine and depression are highly comorbid (Lipton et al. 2000). Migraine patients with anxiety and depression reported poorer treatment efficacy and satisfaction with treatment (Lanteri-Minet et al. 2005). A community-based survey found more personality disturbance and 2.5 times more psychological distress in migraine sufferers than in matched control subjects, but there was no relationship between headache frequency and the severity of psychological distress or personality abnormality (Brandt et al. 1990).

## Psychological Factors in End Stage Renal Disease

Studies of the influence of psychological factors upon the course of end-stage renal disease (ESRD) have nearly all focused on depression or noncompliance. There has been essentially no investigation of psychological factors in chronic renal failure before end stage.

Depression has been shown to be a better predictor of (shorter) survival than age or pathophysiological variables in dialysis patients (Burton et al. 1986, Shulman et al. 1989), although negative results have also appeared (Kutner et al. 1994). Depression is associated with smoking, alcoholism, and other forms of substance abuse that are highly prevalent in ESRD patients (Hegde et al. 2000). Subsequent studies have done a better job of controlling for ESRD severity and other potential confounds, and still find that depression predicts higher mortality (Kimmel et al. 2000). One prospective study in peritoneal dialysis patients found higher depressive symptoms associated with a greater risk of peritonitis, after controlling for other risk factors (Troidle et al. 2003). In hemodialysis patients, level of depression symptoms was a unique and significant predictive risk factor for the subsequent decision to withdraw from dialysis (McDade-Montez 2006).

Other outcome studies have focused on the impact of noncompliance in ESRD (Manley and Sweeney 1986). Compliance is a complex, multidimensional array of behaviors, and its relationship with health outcomes in dialysis patients is difficult to study. Thus, whereas effects of noncompliance on dialysis patients' outcomes are well recognized by physicians, they have not been adequately characterized empirically. Nevertheless, the widespread belief among physicians and nurses that noncompliance results in worse outcomes including higher mortality in ESRD is supported by a large multicenter study (Leggat et al. 1998). The chronic overuse of nonsteroidal antiimflammatory agents and analgesics is a maladaptive health behavior recognized as a fairly common contributing cause of chronic renal insufficiency (Fored et al. 2000). One psychosocial intervention outcome study in ESRD found that patients who participated in a support group lived longer than nonparticipants even after multiple psychosocial and psychological variables were controlled, but this was a naturalistic nonrandomized study (Friend et al. 1986).

## Psychological Factors in Gastroenterology

### Inflammatory Bowel Disease (IBD)

Ulcerative colitis is another disorder that was described in the early literature as a psychosomatic disease, but no specific psychogenic factor contributing to the development of ulcerative colitis or Crohn's disease has ever been substantiated. As with other chronic medical diseases, patients with more psychological distress tend to be those with more severe physical disease and poorer functional capacity, but the causal relationships are not clear (Sewitch et al. 2001). Psychological stress does appear to aggravate both symptom complaints and mucosal disease activity in ulcerative colitis (Levenstein et al. 1994). Depression may predict relapse in IBD (Mittermaier et al. 2004, Kurina et al. 2001). Disability and distress in patients with IBD are increased by the presence of a concurrent psychiatric disorder

(Walker et al. 1996). In fact, depression is a better predictor of subjective impairment in IBD than is inflammatory activity (Cuntz et al. 1999). Psychotherapy has the potential to improve outcomes in IBD, as suggested by controlled trials (Payne and Blanchard 1995, Jantschek et al. 1998).

### Peptic Ulcer Disease (PUD)

The direct effects of emotion on gastric secretion were first demonstrated in 1833 by William Beaumont, who made observations through a Canadian lumberjack's gastric fistula resulting from an injury. Early psychosomatic investigators studied the role of specific psychological risk factors for duodenal ulcer. In a classical empirical study, Weiner et al. (1957) successfully predicted which men in a large cohort of Army draftees would have duodenal ulcers by combining psychological criteria with the biological criterion of high baseline pepsinogen secretion. Since then, the central role of the bacterium Helicobacter pylori in the etiology of PUD has been clearly established. Many physicians have consequently discarded the longstanding belief that stress causes PUD, and concluded that PUD is an infectious disease, except when attributable to nonsteroidal anti-inflammatory drugs (NSAIDS). Nevertheless, psychological factors appear to be a significant part of the explanation for why only a fraction of those colonized by H. *pylorior* or taking NSAIDS develop ulcers. Psychological stress is an independent risk factor for the development (Rosenstock et al. 2003) and recurrence of duodenal ulcer (Levenstein et al. 1995aa). The frequency of peptic ulcer increases following catastrophic stressful events, including bombardment, earthquake, economic crisis, or being a prisoner of war or "boat people" refugee (Levenstein 2000). Overall, psychosocial factors contribute to 30−65% of peptic ulcers (Levenstein 2000), and are most likely to be present in patients with duodenal ulcers who do not have conventional medical risk factors (*H. pylori*, NSAIDS) (Levenstein et al. 1995bb). Occupational stress, family conflicts, depression, maladjustment and hostility also are prospectively associated with PUD (Levenstein et al. 1997).

Psychological factors appear to influence PUD through both health risk behaviors (smoking, alcohol abuse, overuse of NSAIDS, poor diet, poor sleep) and psychophysiologic mechanisms (pepsinogen and acid secretion, altered blood flow, impairment of mucosal defenses, and slowing of healing related to the action of cortisol) (Levenstein 2000).

### IBS

IBS is a heterogenous condition with a high frequency of comorbid anxiety (especially panic attacks), depression, and somatization. Whereas patients with IBS are psychologically more distressed than normal subjects, they do not have a common profile of psychological symptoms or personality traits (Walker et al. 1990). Patients with IBS are more likely to have a history of childhood sexual abuse than those with other gastrointestinal disorders in studies of patients seeking care at tertiary referral centers (Walker et al. 1993). In fact, almost all psychological characteristics and psychopathology thought to be more common in IBS are differentially increased only in those who seek medical care for their symptoms (Herschbach et al. 1999).

Both IBS patients and their physicians observe that their gastrointestinal symptoms seem aggravated by stress, but there is no clear evidence that stress causes a different gastrointestinal smooth muscle response than in control subjects (Camilleri and Neri 1989). Instead, psychological factors' effects on IBS appear predominantly on perception of pain and other somatic symptoms, and on health care seeking behaviors. After an acute episode of infectious gastroenteritis, individuals with more life stress, and who were more hypochondriacal, were the ones most likely to go on to develop IBS, without any differences in intestinal physiology (Gwee et al. 1999). In patients with severe IBS, concurrent psychiatric disorders are associated with significant impairment in health-related quality of life and higher health care costs (Creed et al. 2002, 2005).

## Psychological Factors in Dermatology

Dermatologists routinely observe the effect of psychological factors, especially anxiety, in the aggravation of a wide variety of dermatological conditions. There are few systematic studies, and perhaps the most important relationships are not uniquely related to particular dermatological disorders. Both anxiety and depression appear to worsen pruritus (itching). So-called neurotic excoriation complicates many dermatological disorders and is aggravated by anxiety, depression, and other behavioral factors (Gupta et al. 1996). That so many skin diseases appear to be precipitated or exacerbated by psychological stress also suggests a nonspecific impairment of cutaneous function. There is now evidence in both animals and humans that stress negatively affects skin's function as a permeability barrier (Garg et al. 2001).

Dermatologists clinically observe important relationships between psychological factors and urticaria, angioedema, atopic dermatitis, hyperhidrosis, acne, and psoriasis, (Arnold 2005) but controlled studies are lacking. Excessive sun exposure is a maladaptive health behavior contributing to skin cancer and various other dermatological conditions.

## Psychological Factors Affecting Infectious Diseases

HIV infection is the most destructive example of unsafe sexual practices as a maladaptive health behavior contributing to development and transmission of an infectious medical condition. Once contracted, HIV infection appeared to be a likely candidate for important effects of psychological factors, because of the work demonstrating changes in normal immune function after stress, bereavement, and depression. This has been a very active field of investigation with most but not all studies finding adverse effects of stress and depression on disease progression, immune function, and mortality in patients with HIV infection (Ironson et al. 2005, Leserman et al. 2002, Farinpour et al. 2003, Golub et al. 2003, Psychd et al. 2000, Sewell et al. 2000).

Psychological factors influence other infectious diseases as well, including the common cold (Cohen 2005), pneumonia (Mehr et al. 2001), genital herpes (Levenson et al. 1987), and recurrent urinary tract infections (Hunt and Waller 1992). A number of studies have convincingly shown that psychological stress suppresses the secondary (but not primary) antibody response to immunization (Cohen et al. 2001).

## Psychological Factors in Obstetrics

While much more attention has been paid to postpartum depression, antepartum depression also adversely affects pregnancy outcome. In a number of studies both antepartum anxiety and depression have been associated with growth retardation and premature birth (e.g., Neggers et al. 2006), resulting in lower birth weights, but potential confounding factors have often not been adequately controlled for, and not all studies have replicated these findings (e.g., Andersson et al. 2004). Whether depression and other psychological dysfunction cause poorer obstetric outcomes through poor nutrition, substance abuse (including tobacco), poor adherence or no prenatal care and/or, physiological (hormonal, vascular) effects require further investigation.

## Psychological Factors in Infertility

Psychological factors are likely to affect fertility because frequency and timing of sexual intercourse are important determinants of fertility. Nonconsummation, avoidance of intercourse, vaginismus, and psychogenic amenorrhea are attributable to psychological origins. Psychogenic causes do not account for most male impotence but do play a role in many cases (Schneid-Kofman and Sheiner 2005). In general, measures of stress, but not of psychopathology, have been associated with infertility (Greil 1997). This is a particularly complex subject for study because it involves potential psychological factors in both members of the couple and interactions between them as well as their effects on sexual behavior and fertility (Cwikel et al. 2004). Psychological factors have also been identified as predictors of drop out from infertility treatment (Smeenk et al. 2004). Most psychological distress seen in infertile couples is a result of, rather than a cause of, infertility.

### Clinical Vignette 1

Ms. A, a 46-year-old married attorney, was referred for psychiatric evaluation by her gastroenterologist, who follows her for long-standing IBS. She has had IBS since the age of 20 years, with complaints of intermittent constipation, diarrhea, crampy abdominal pain, and bloating. She feels that these symptoms have gradually worsened, particularly in the last month. She describes a highly pressured job and a stressful marriage. She has specifically noticed a precipitous increase in intestinal symptoms immediately after arguments with her husband and when facing deadlines at work. Three months ago, she developed depressed mood, early morning awakening, anorexia, fatigue, crying spells, impaired concentration, irritability, and preoccupation with thoughts of ill health. Her family physician diagnosed major depression and prescribed amitriptyline, which was discontinued after it caused worsening of her constipation. Her psychiatrist then tried fluoxetine (discontinued because of diarrhea) and trazodone (too sedating). She then responded well to nortriptyline with disappearance of the symptoms of depression and improvement in her IBS. However, severe IBS symptoms continued to follow the frequent marital arguments. The psychiatrist asked the patient to invite her husband to join one of their sessions so that marital issues could be further explored. He did so, resulting in the discovery that her husband was himself significantly depressed. He was referred to another psychiatrist for treatment, the marital discord abated, and her IBS symptoms returned to a manageable level.

In this clinical vignette, the patient had features of both mental disorder (major depressive disorder) affecting a general medical condition and stress-related physiological response affecting a general medical condition. Treatment included individual psychotherapy and antidepressant medication as well as marital assessment and intervention. Pharmacotherapy required modification because of gastrointestinal sensitivity to side effects.

### Clinical Vignette 2

Mr. B is a 60-year-old married judge with CAD. He was referred for psychiatric evaluation by his cardiologist because he declined coronary artery bypass surgery despite strong and repeated recommendations for surgery by the cardiologist. The cardiologist perceived that the patient's resistance to surgery was not due to lack of information or understanding.

Mr. B had no acute psychiatric symptoms, although he had several lifelong phobias including fear of cats, fear of being buried alive, and claustrophobia (recent episodes in the hospital elevator and during magnetic resonance imaging). His only previous psychiatric contact was some marital therapy 20 years earlier. His CAD was severe, with two myocardial infarctions and recurrent malignant arrhythmias. He continued to have recurrent angina despite maximal medical management; his pain occurred mainly at night as "a predictable consequence of pushing too hard at work" (he typically worked 12-hour days). He had also had a stroke 3 months ago, from which he had made a complete recovery with no sequelae. Twenty years earlier, he had surgery for a renal stone that was complicated postoperatively with five pulmonary emboli. He said that he has had "eight near-death experiences" amidst his various illnesses.

Mr. B was eager to discuss his reluctance to have coronary bypass surgery. He had not decided against the surgery but had been unable to reach a decision. He brought to the appointment with the psychiatrist a two-page list of arguments for and against surgery and other variables that could influence the decision and outcome. He was aware that he was approaching the question of surgery with the same style of carefully balanced consideration of all sides of an issue that he prided himself on in his occupation as a judge. He worked longer days than his colleagues because he believed it took more time to make fair, proper, and legally correct decisions. His analysis of the pros and cons of surgery, as well as intervening factors affecting and affected by the decision, appeared to the psychiatrist to be well informed, accurate, flexible, and appropriate. There was no evidence of rigidity in his thinking, premature closure, or distorted perceptions. Whereas the thought processes were logical, they had not enabled him to reach a decision, despite extensive discussions with the cardiologist over a period of months. He was aware that this was another decision in his life that was taking much longer than average, but he thought it could not be resolved any other way.

This case represents an example of personality trait or coping style affecting a general medical condition. His obsessional style was largely adaptive in his chosen occupation, although it reduced his efficiency. Now confronted with a major health care decision, and mindful of major complications he had suffered after surgery in the past, the need

to weigh all sides of an issue had paralyzed his decision-making. The presence of phobias in his history raised the possibility of these too affecting his decision-making, but he denied feeling fearful of the surgery, anesthesia, intubation, and the like. The anxiety he was experiencing was entirely focused around making the right decision.

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CHAPTER

# 84 Medication-Induced Movement Disorders

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Neuroleptic-Induced Acute Dystonia
Neuroleptic-Induced Parkinsonism
Neuroleptic-Induced Acute Akathisia
Neuroleptic-Induced Tardive Dyskinesia
Neuroleptic Malignant Syndrome
Medication-Induced Postural Tremor

## Introduction

The discovery of the antipsychotic effect of chlorpromazine in the early 1950s ushered in the modern age of psychopharmacology. Despite this milestone, optimism for treatment of schizophrenia was soon dampened by the realization that antipsychotic agents could produce significant side effects, most prominently movement disorders. Much of the subsequent research investigating new antipsychotic agents was thus motivated by a need to find effective agents with a lower propensity to cause movement disorders.

While antipsychotics may produce a variety of other side effects, movement disorders are particularly disturbing for a number of reasons. Acute movement disorders, such as dystonia and akathisia, may be excruciatingly uncomfortable. Patients in whom movement disorders develop may, in addition to experiencing subjective distress, be at increased risk for nonadherence to treatment (Diaz et al. 2004), suffer embarrassment that leads to social withdrawal, and even suffer occupational impairment in severe cases. Perhaps most disturbing is that antipsychotics can produce "tardive" or late-occurring movement disorders that may be persistent or even irreversible.

## Historical Background

The presence of so-called extrapyramidal motor reactions to drugs was first described in the 1940s with reserpine. It was, however, in the early 1950s that attention was first focused on the motor effects of antipsychotic drugs. In 1952, Delay and Deniker (1968) noticed extrapyramidal signs (EPS) after treatment with the antipsychotic medication chlorpromazine. Many of these EPS appeared similar to Parkinson's disease (PD), and some investigators proposed that the presence of EPS equated with the onset of antipsychotic benefit (Haase 1961).

Approximately 5 years after chlorpromazine proved effective for psychotic disorders, Schonecker (1957) noted the onset of orobuccal dyskinesias in patients with prolonged exposure to the drug. This condition lasted nearly 3 months after the chlorpromazine was stopped. This was in marked contrast to the Parkinsonian symptoms previously described, which had reversed upon discontinuation of antipsychotics. Similar reports soon followed in France, England, Denmark, and the US (Lohr and Jeste 1988a). The term *tardive dyskinesia* (TD) was first used in 1964 by Faurbye and coworkers (1964) to describe this condition. The number of reports grew rapidly in a period of years, and many of the cases were reported to be irreversible.

## Classification

There are different types of movement disorders that may result from treatment with antipsychotic medications. They are often categorized according to time of onset (acute or subacute vs. late-onset, i.e., tardive). For the purpose of this discussion, we group neuroleptic-induced movement disorders into the acute/subacute disorders (acute dystonia, parkinsonism, and akathisia), tardive disorders (prototypically TD), and neuroleptic malignant syndrome (NMS). It is important to note that patients often experience more than one type of medication-induced movement disorder either concurrently or sequentially (Casey 2004). We also devote a section to the discussion of medication-induced postural tremor that predominantly focuses on lithium-induced

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**Table 84–1 Time of Emergence of Neuroleptic-Induced Movement Disorders**

| Condition | Highest Risk of Emergence |
|---|---|
| Acute dystonia | Days 0–7 |
| Neuroleptic malignant syndrome | Days 0–7 (continues at lesser degree until end of first mo) |
| Akathisia | Days 7–14 (continues at lesser degree until 2.5 mo) |
| Parkinsonism | Days 14–30 (continues at lesser degree until 2.5 mo) |
| Tardive dyskinesia | Month 3* → onward (risk increases with increasing time on neuroleptic) |

*In patients older than 60 years, month 1 → onward.

tremor. This covers the major diagnostic groupings contained within the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) under the general title medication-induced movement disorders.

A typical time line for the emergence of the neuroleptic-induced movement disorders is provided in Table 84–1.

## Informed Consent/Medicolegal Issues

The possibility of irreversible neuroleptic-induced movement disorders places significant responsibility on the prescribing psychiatrist. Careful and reasoned thought must go into the analysis of whether the benefit of treatment with a medication exceeds the risk to the patient. In general, the more a patient is able to understand the nature of his or her illness and the reason that a particular medication is being prescribed, the more likely he or she is to be adherent to treatment. When the psychiatrist does not devote adequate time to informing and instructing the patient, this may damage the physician–patient rapport by engendering mistrust of the physician (by patients prone to paranoia), with subsequent adverse clinical and/or legal consequences. Unless declared incompetent by a court of law, a patient is considered to be legally competent to consent to or refuse psychotropic medications. The only exception to this rule is when an emergency situation exists and a patient must be medicated to prevent harm to self or others. The psychiatrist must provide information to the patient or the patient's decision-maker about the nature and purpose of the medication, its risks and benefits, alternatives to the proposed treatment, and prognosis without treatment. Obtaining a written informed consent is one way of documenting the consent process. Another way is noting in the chart a summary of the discussion with a patient (or caregiver) about the consent to neuroleptic treatment.

Physicians may hesitate to divulge the full range of medication-related risks out of fear that this will discourage adherence in patients often already averse to taking medications or that this will heighten patient anxiety about treatment. While this may happen in individual cases, a patient who has been prepared openly and honestly for possible side effects may view this discussion as evidence of the psychiatrist's knowledge and trustworthiness and may be more likely to respond to any side effects by consulting with the physician. Physicians may also choose to conduct the informed consent process over several meetings, based on the patient's ability to process information and his/her insight. On a final note, it may not be assumed that a patient already receiving antipsychotics prescribed by another physician has received an adequate informed consent. The process must begin anew with the new treating physician.

Although movement disorders are an important risk to weigh when choosing among antipsychotic medications (e.g., typical vs. atypical), there are many factors that make the overall risk–benefit profiles and treatment decisions less than straightforward. In general, the literature continues to expand with trials demonstrating reduced incidence of new onset neuroleptic-induced movement disorders with atypical antipsychotics and, in some cases, partial improvement of existing movement disorders caused by conventional antipsychotics. While atypical antipsychotics are not without a risk of movement disorders, their improved motor side effect profile suggests that they may be a better treatment choice in populations with increased risk for movement disorders.

Older adults represent such a population at risk for movement disorders; yet, the recent black-box warnings citing an association between atypical antipsychotics and death or cerebrovascular events in dementia patients make the safer motor side effect profiles with atypical agents less of a compelling reason to use these agents in older adults (Schneider et al. 2006). The risk of death or stroke in older adults with conventional antipsychotics is not clear. The issue is further complicated by recent evidence calling into question the relative benefits in efficacy of atypical antipsychotics versus typical agents (Lieberman et al. 2005), as well as the apparent higher risk of metabolic complications associated with some atypical antipsychotics compared to certain typical antipsychotics (Jin et al. 2004). The possibility of switching to an atypical agent should be discussed with patients maintained on a conventional agent who develop or have a high risk of movement disorders. Yet, this relative risk difference must be considered in the context of other potential adverse medication effects that may differentially occur with some atypical agents (e.g. metabolic disorders).

# ACUTE NEUROLEPTIC-INDUCED MOVEMENT DISORDERS

## Neuroleptic-Induced Acute Dystonia

### Definition

This long-lasting contraction or spasm of musculature develops in conjunction with the use of antipsychotic medication. Examples include torticollis (lateral neck rotation), retrocollis (neck extension), limb torsion, forced jaw closing (trismus) or opening, tongue protrusion, opisthotonus (extension of head, neck, and paraspinal muscles in an arch), and oculogyric crisis (forceful eye deviation).

### Etiology and Pathophysiology

The pathophysiological mechanism of neuroleptic-induced acute dystonia is largely unknown. Because no consistent pathological abnormality has been located in the brain, dystonia was often regarded in the past as a disorder of psychogenic origin. There is currently no evidence to support psychological factors as being the source of dystonia.

Abnormalities in dopamine–acetylcholine balance have been suggested as a possible mechanism because cholinergic antagonists and dopaminergic agonists seem to improve the dystonia in many patients, in contrast to

dopaminergic antagonists, which may exacerbate or cause dystonia (Stahl and Berger 1982).

## Epidemiology and Comorbidity

Acute dystonia is generally less common than most other extrapyramidal side effects of antipsychotics. Its frequency has been reported to range from 2 to 12% of patients taking conventional antipsychotic medication (Lohr and Jeste 1988a). For patients who receive high doses of high-potency conventional agents (e.g., haloperidol), however, the frequency may be as high as 50% (Swett 1975). Incidence of acute dystonia can probably be reduced if low-dose treatment strategies are employed. Furthermore, acute dystonia is considerably less likely to occur with atypical antipsychotic medications (i.e., less than 5% of individuals) (American Psychiatric Association 2000). However, cases of dystonia have been reported with atypical antipsychotics even in low doses (Alevizos et al. 2003, Brown 1997), so patients and clinicians should remain vigilant for this side effect even when using atypical agents.

Large doses of high-potency conventional antipsychotics (especially when administered parenterally) appear to be the most consistent risk factor reported for acute dystonia (Rupniak et al. 1986). Other factors that also predispose to dystonia are young age, male sex, and a prior dystonic reaction.

## Assessment and Differential Diagnosis

Neuroleptic-induced dystonia (sometimes referred to as a dystonic reaction) usually begins 12 to 36 hours after a new antipsychotic is started or the dosage of a preexisting one is increased. It is unusual to see a dystonia after 2 weeks of antipsychotic treatment, and probably 90% of all neuroleptic-induced dystonias occur within the first 5 days of antipsychotic treatment (Rupniak et al. 1986). Dystonias are also possible after the sudden discontinuation of anticholinergic medications (Sachdev 2005a). Patients may report a sense of tongue "thickness" or difficulty in swallowing in the 3 to 6 hours preceding the acute dystonia (Arana and Rosenbaum 2000). Others have reported a nonspecific prodromal anxiety/restlessness prior to fulminant dystonia (Sachdev 2005a).

Acute dystonia presents as a sustained, painful muscle spasm that produces twisting, squeezing, and pulling movements of the muscle groups involved. A notable feature of dystonias is their consistent directionality; even though there may be an accompanying tremor, the oscillations of a dystonic tremor are asymmetrically skewed in one direction. The most common muscle groups affected are the eyes, jaw, tongue, and neck, but any muscle group in the body can be involved. On occasion, the larynx or pharynx may be involved, and this can result in rapid respiratory compromise (American Psychiatric Association 2000).

Neuroleptic-induced acute dystonias are dramatic and usually easy to diagnose. There are, however, a number of other conditions that can present similarly and need to be ruled out. Spontaneously occurring focal or segmental dystonias may persist for days to weeks independent of medication. Neurological conditions such as temporal lobe seizures, infections, trauma, or tumors can produce symptoms similar to neuroleptic-induced acute dystonia. Several hereditary neurological disorders may cause psychiatric disturbance and dystonias (e.g., Wilson's disease, Huntington's disease, juvenile Parkinson's disease). Hypocalcemia may cause muscle spasms similar to dystonias. Other psychotropic medications (e.g., anticonvulsants and selective serotonin reuptake inhibitors) can cause dystonias, though less commonly than antipsychotics (American Psychiatric Association 2000).

Neuroleptic malignant syndrome (NMS) can produce muscle contractions that look similar to acute dystonia but can be distinguished by generalized "lead pipe" type of rigidity, fever, fluctuating consciousness, and unstable vital signs. Catatonia associated with an affective or psychotic disorder can be difficult to

**DSM-IV-TR Criteria**

**Neuroleptic-Induced Acute Dystonia**

A. One (or more) of the following signs or symptoms has developed in association with the use of neuroleptic medication:

(1) abnormal positioning of the head and neck in relation to the body (e.g., retrocollis, torticollis)
(2) spasms of the jaw muscles (trismus, gaping, grimacing)
(3) impaired swallowing (dysphagia), speaking, or breathing (laryngeal–pharyngeal spasm, dysphonia)
(4) thickened or slurred speech due to hypertonic or enlarged tongue (dysarthria, macroglossia) tongue protrusion or tongue dysfunction
(5) eyes deviated up, down, or sideward (oculogyric crisis)
(6) abnormal positioning of the distal limbs or trunk

B. The signs or symptoms in criterion A developed within 7 days of starting or rapidly raising the dose of neuroleptic medication, or of reducing a medication used to treat (or prevent) acute extrapyramidal symptoms (e.g., anticholinergic agents).

C. The symptoms in criterion A are not better accounted for by a mental disorder (e.g., catatonic symptoms in schizophrenia). Evidence that the symptoms are better accounted for by a mental disorder might include the following: the symptoms precede the exposure to neuroleptic medication or are not compatible with the pattern of pharmacological intervention (e.g., no improvement after neuroleptic lowering or anticholinergic administration).

D. The symptoms in criterion A are not due to a non-neuroleptic substance or to a neurological or other general medical condition. Evidence that the symptoms are due to a general medical condition might include the following: the symptoms precede the exposure to the neuroleptic medication, unexplained focal neurological signs are present, or the symptoms progress in the absence of change in medication.

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distinguish from dystonia clinically but does not respond to the administration of anticholinergic or antihistaminic medication. Furthermore, patients with catatonia are typically not concerned about their stiffness, whereas patients with dystonia are likely to be extremely distressed (American Psychiatric Association 2000).

On occasion, an acute dystonic reaction may resemble tardive dyskinesia (TD). This is easily clarified by administering anticholinergic medications, which rapidly clear dystonia and do not affect (or may worsen) TD. Making a differential diagnosis between an acute dystonia and tardive dystonia can be difficult. Tardive dystonia (similar to TD) is a diagnosis made late in the course of antipsychotic treatment and is generally a chronic condition compared with acute dystonia, which occurs early in the course of medication treatment and typically responds rapidly to pharmacological intervention.

### Course

A neuroleptic-induced acute dystonia typically subsides spontaneously within hours after onset. However, treatment should be started as soon as the dystonia is diagnosed because the experience is typically intensely distressing to the patient, and in rare cases can induce respiratory compromise.

### Treatment

It is important to note that there is no FDA-approved treatment for any medication-induced movement disorder, but a number of controlled trials, along with clinical experience, offer some guidance. The standard treatment approach for acute neuroleptic-induced dystonia is the immediate administration of an anticholinergic agent. In most cases, this medication may be administered orally, intramuscularly, or intravenously. The first dose of medication should be the equivalent of 2 mg of benztropine or 50 mg of diphenhydramine (an antihistamine with strong anticholinergic properties). This should be repeated if the first dose does not produce a robust response within 30 minutes (Lohr and Jeste 1988a). This standard approach is usually successful in resolving the dystonia. Educating patients about this side effect and the importance of seeking treatment may help to avert severe dystonias and the subsequent conditioning of patients to fear medication treatments.

In the unusual refractory case, intramuscular or intravenous anticholinergic or antihistaminic drugs should be used at more frequent dosing intervals, and consideration should be given to adding an intramuscular injection of lorazepam for additional sedation (Arana and Rosenbaum 2000). Since even milder dystonias respond much more quickly to intramuscular or intravenous medication, some clinicians advocate bypassing oral medication and going immediately to parenteral medications so as to avoid prolonging patient distress unnecessarily.

In cases of laryngeal or pharyngeal dystonias with airway compromise, repeated dosing of medication should occur at shorter intervals until resolution is achieved. Arana and Rosenbaum (2000) recommend that the patient receive 4 mg of intravenous benztropine within 10 minutes followed by 1 to 2 mg of intravenous lorazepam. If airway compromise continues for any appreciable amount of time, emergent support from an anesthesiologist should be obtained and the patient should receive general anesthesia with airway protection. Fortunately, the need for such measures is rare.

After a dystonia, a patient should be maintained with oral anticholinergic medication for at least 48 hours (or at least 2 weeks if there is a history of severe dystonias). Consideration should be given to decreasing the previous dose of the antipsychotic or possibly switching to a low-potency neuroleptic or atypical agent if the patient has been prescribed a conventional antipsychotic. The use of prophylactic anticholinergic medication (discussed in detail later) is not fully evidence-based and not without its own adverse effects.

## Neuroleptic-Induced Parkinsonism

### Definition

Neuroleptic-induced parkinsonism (NIP) is defined as parkinsonian signs or symptoms (resting tremor, muscle rigidity, and bradykinesia/akinesia) that develop in association with the use of an antipsychotic medication.

### Etiology and Pathophysiology

NIP is presumed to result from blockade of postsynaptic dopamine ($D_2$) receptors in the corpus striatum causing a pathological state functionally resembling the loss of dopaminergic cells in the striatum in idiopathic Parkinson's disease (PD). However, it is not clear whether nigrostriatal dopamine loss is adequate to explain the clinical symptoms seen in NIP or PD (Lohr and Jeste 1988a). It is possible that other neurochemical abnormalities may coexist with dopaminergic depletion to produce the syndrome. A model of the neurocircuitry involved in NIP was recently described by Ossowska (2002), essentially describing overactivation of the striatopallidal pathway and inhibition of the striatonigral pathway.

Interindividual factors may influence the risk of developing NIP. The finding that NIP was associated with echogenicity of the substantia nigra on transcranial ultrasound suggests that certain people may have a preexisting neuropathological diathesis to develop parkinsonism (Jabs et al. 2003). Familial factors (e.g., genetic traits) were implicated in a recent study showing that patients whose first-degree relatives had movement disorders were more likely to demonstrate EPS (including NIP) when treated with antipsychotics than patients without this family history (Lencer et al. 2004).

Positron emission tomography (PET) and other technologies have been utilized to examine the relationship between $D_2$ receptor blockade in the basal ganglia and both antipsychotic efficacy and NIP. Of note are findings that with conventional agents at least 60% occupancy of $D_2$ receptors is needed for satisfactory antipsychotic response but that NIP tends to occur with ≥80% occupancy (Farde et al. 1992). Interestingly, some clinicians using conventional antipsychotics expected efficacy at the dose where patients exhibited mild parkinsonism, such that causing mild EPS was considered by some to be a treatment goal.

With regard to atypical agents, there are several hypotheses about their decreased incidence of EPS, including NIP, compared to typical agents (Casey 2004). Most atypical antipsychotics have a high ratio of serotonin type 2 ($5HT_{2A}$, $5HT_{2C}$) -to- $D_2$ receptor blockade. Serotonin receptor blockade may have antipsychotic effects that are synergistic with $D_2$ blockade, allowing for therapeutic effects at relatively lower levels of $D_2$ blockade. Also, there are $5HT_{2A}$ and $5HT_{2C}$ receptors on striatal dopamine neurons, and their blockade appears to

**DSM-IV-TR Criteria**

**Neuroleptic-Induced Parkinsonism**

A. One (or more) of the following signs or symptoms has developed in association with the use of neuroleptic medication:

(1) parkinsonian tremor (i.e., a coarse, rhythmic, resting tremor with a frequency between 3 and 6 cycles per second, affecting the limbs, head, mouth, or tongue)

(2) parkinsonian muscular rigidity (i.e., cogwheel rigidity or continuous "lead-pipe" rigidity)

(3) akinesia (i.e., a decrease in spontaneous facial expressions, gestures, speech, or body movements)

B. The symptoms in criterion A developed within a few weeks of starting or raising the dose of a neuroleptic medication, or of reducing a medication used to treat (or prevent) acute extrapyramidal symptoms (e.g., anticholinergic agents).

C. The symptoms in criterion A are not better accounted for by a mental disorder (e.g., catatonic or negative symptoms in schizophrenia, psychomotor retardation in a major depressive episode). Evidence that the symptoms are better accounted for by a mental disorder might include the following: the symptoms precede the exposure to neuroleptic medication or are not compatible with the pattern of pharmacological intervention (e.g., no improvement after lowering the neuroleptic dose or administering anticholinergic medication).

D. The symptoms in criterion A are not due to a non-neuroleptic substance or to a neurological or other general medical condition (e.g., Parkinson's disease, Wilson's disease). Evidence that the symptoms are due to a general medical condition might include the following: the symptoms precede the exposure to neuroleptic medication, unexplained focal neurological signs are present, or the symptoms progress despite a stable medication regimen.

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promote dopamine release. Others have proposed that many atypicals exhibit more rapid dissociation from the receptors they block than typical drugs, and that this decreases propensity for EPS. Neurobiological studies have also indicated that atypical drugs may have a relative specificity for limbic dopamine receptors more so than striatal receptors. Given the heterogeneity of mechanisms of action among antipsychotics categorized as "atypical," these ideas remain speculative, and there are likely multiple pathways to increase or decrease NIP. Similar to conventional antipsychotics, higher doses of some atypical agents (particularly risperidone) also appear to be related to an increase in NIP, as $D_2$ receptor blockade may increase with the dose of the atypical drug (Glazer 2000).

## Epidemiology and Comorbidity

The reported frequency of NIP varies from 5 to 90%, depending on the study reviewed (Lohr and Jeste 1988a). This wide variation is due in part to inter-study differences in defining NIP (e.g., the inclusion of mild bradykinesia as NIP in some investigations). The incidence of "clinically significant" NIP with conventional antipsychotics has been reported as 10 to 15%. However, when high-potency conventional agents are used without anticholinergic drugs and signs of rigidity are carefully assessed, one is likely to find that the majority of patients have some NIP. Rates of parkinsonism induced by atypical antipsychotics are considerably lower (American Psychiatric Association 2000). The incidence of NIP appears age-related, with older adults at increased risk. A study of newly medicated older patients on low doses of conventional antipsychotics found 32% of patients met criteria for NIP (Caligiuri et al. 1999).

A number of other patient-related and medication-related risk factors have been proposed. A history of prior episodes of NIP and concomitant dementia or delirium may predispose to NIP (American Psychiatric Association 2000). In an investigation of EPS in patients with Alzheimer disease treated with very low dose conventional antipsychotics, 67% of patients met criteria for NIP at some time during the 9-month follow-up period (Caligiuri et al. 1998). Neuroleptic potency and preexisting extrapyramidal symptoms may also increase the risk of NIP (Chakos et al. 1992). Rapid increases in antipsychotic dosage, administration of higher absolute doses of antipsychotics, and absence of concurrent anticholinergic medication represent other risk factors for NIP (American Psychiatric Association 2000).

## Assessment and Differential Diagnosis

NIP symptoms may develop quickly after the initiation of an antipsychotic or insidiously during the course of treatment, with a typical onset being 2 to 4 weeks after antipsychotic initiation. The three cardinal symptoms of NIP are tremor, muscle rigidity, and akinesia.

Parkinsonian tremor is a steady, rhythmical, oscillatory motion generally at a frequency of 3–6 Hz. The most affected body area tends to be the upper extremities, but the tremor may spread to the head, neck, jaw, face, tongue, legs, and trunk. The tremor is typically most prominent at rest, suppressed during action, and increased during times of anxiety, stress, or fatigue (American Psychiatric Association 2000).

Parkinsonian muscle rigidity appears clinically as a firmness and spasm of muscles at rest that may affect all skeletal muscles or be confined to just a few specific muscle groups. It can appear as a continuous lead pipe-type rigidity that resists movement or a cogwheel-type rigidity that presents a "ratchet-like" resistance when a muscle is moved around a joint. The psychiatrist may diagnose cogwheel rigidity by placing his or her hand over the joint that is being passively moved (e.g., during forearm pronation/supination or wrist flexion/extension). Generalized muscle pain, body aches, and impaired coordination are features associated with NIP rigidity (American Psychiatric Association 2000).

Parkinsonian bradykinesia (or, if severe, akinesia) clinically manifests as decreased spontaneous motor activity and a global slowness in the initiation and execution of movements. It can be associated with drooling, neck flexion, decreased blinking, stooped shoulders, and blank facial expression ("masked facies") (American Psychiatric Association 2000). Formal tests of psychomotor speed (e.g., finger tapping) may be helpful in mild cases. Decreased arm swing during ambulation is often an early sign that may alert clinicians to NIP, and which patients themselves may fail to recognize. Objectively slowed movements may be accompanied by a subjective sense in patients that their mentation is slowed (bradyphrenia). Although not part of the parkinsonian "triad," postural instability may accompany NIP and predispose affected patients to falls.

Parkinsonism occurs in numerous medical and neurological conditions and can be caused by many medications (e.g., calcium channel blockers, amoxapine) or toxins. Other psychotropics (e.g., antidepressants, anticonvulsants, and lithium) have been reported to cause parkinsonism, though at much lower rates than neuroleptics. Idiopathic PD should be considered in the differential diagnoses of NIP; Mena and de Yebenes (2006) recently highlighted some general differences between PD and NIP, including the following: (1) more symmetry of symptoms in NIP than PD; (2) poor response of symptoms to L-DOPA in NIP compared to PD; and (3) higher levels of the dopamine metabolite homovanillic acid (HVA) in spinal fluid of patients with NIP compared to PD.

The tremor of NIP must be distinguished from tremor caused by other conditions. In general, nonparkinsonian tremors are finer, faster, and worse on intention. Tremor associated with substance withdrawal typically presents with associated hyperreflexia and increased autonomic signs. Cerebellar-associated tremors are usually coarse, action tremors and may present with associated nystagmus, ataxia, or scanning speech. Strokes and other central nervous system (CNS) lesions that cause parkinsonism usually have associated focal neurological symptoms. NMS can present with akinesia and lead pipe-type rigidity but also has other associated findings, such as fever, elevated creatine kinase, and fluctuating consciousness (American Psychiatric Association 2000).

A number of primary psychiatric illnesses may mimic symptoms of NIP, including major depressive disorder, catatonia (from mood or psychotic disorders), negative symptoms of schizophrenia, and certain conversion disorders (American Psychiatric Association 2000). Often, the diagnosis of NIP should be made provisionally and clarified by a dosage reduction of antipsychotic or trial of anticholinergic medication (American Psychiatric Association 2000).

## Course

NIP symptoms usually continue unchanged or diminish slowly in 2–3 months after onset. The signs and symptoms typically improve with a dose reduction, discontinuation of antipsychotic medication, or switch to an atypical antipsychotic in patients previously receiving a conventional antipsychotic. Improvement is also seen with the addition of antiparkinsonian medications. While typically reversible with medication discontinuation, NIP in a minority of patients (up to 20%) may persist or even progress in spite of drug discontinuation (Mena and de Yebenes 2006). Persistent NIP symptoms could occur when medications unmask latent parkinsonism in those with underlying diatheses. Alternatively, some studies have suggested that certain antispychotics (e.g., haloperidol) may be neurotoxic to striatal dopamine neurons through decreasing neurotrophic factors and/or generating free radical damage (Mena and de Yebenes 2006).

## Treatment

Many milder cases of NIP do not require treatment if they are not bothersome to the patient. A switch to an atypical agent should be strongly considered if troublesome NIP develops while on a conventional antipsychotic. Large randomized controlled trials have demonstrated reductions in parkinsonian symptoms in patients treated with atypical antipsychotics compared to typical drugs (Beasley et al. 1997, Chouinard et al. 1993). Clozapine and quetiapine may be particularly useful in patients prone to NIP, given their relative tolerability in the treatment of psychosis associated with idiopathic Parkinson's disease (Miyasaki et al. 2006). If symptoms become troublesome, the initial step should be to decrease the dose of antipsychotic to the lowest effective dose for the patient. The next step is to add a low dosage of an anticholinergic medication. The equivalent of 2 mg/day of benztropine generally represents a reasonable starting point. Periodic attempts should be made to wean the patient from the anticholinergic agent. As many as 90% of patients do not require anticholinergic medication at the end of 3 months (Johnson 1978). Anticholinergic medication should always be tapered slowly to avoid the rapid redevelopment of parkinsonian symptoms as well as the possibility of uncomfortable cholinergic rebound symptoms. Anticholinergic medications may not be a viable choice in older patients due to risks of cognitive impairment, urinary retention, and constipation. Clinicians should also be mindful of reports of anticholinergic abuse (especially trihexyphenidyl) among persons with serious mental illness, who report a "high" from such medications (Buhrich et al. 2000).

Refractory cases of NIP do occur and may require more aggressive management. Increasing the dose of the anticholinergic medication is one possibility because some patients may require high doses to achieve relief from NIP. If such high doses are to be employed, they should be used for the shortest possible time, and rigorous attention should be paid to the possibility of untoward anticholinergic effects (i.e., delirium, urinary retention, fecal impaction). Consideration may be given to starting a dopaminergic agent, such as amantadine or perhaps even levodopa. A major concern with this treatment approach is the possibility of exacerbating the psychosis for which the antipsychotic medication is being prescribed. Trials of dopaminergic agents are therefore best attempted in an inpatient setting or with careful outpatient observation and assessment. A number of experimental treatment strategies have been proposed for the treatment of refractory cases including vitamin E, calcium supplementation, electroconvulsive therapy, dehydroepiandrosterone (DHEA), and L-deprenyl (Osser 1992, Nachshoni et al. 2005).

Another treatment approach for the refractory case is to further lower the dose of the antipsychotic medication or even discontinue it until the NIP resolves, and then resume a different antipsychotic at a low dose. This treatment strategy

may also need to be carried out in an inpatient setting to monitor early emergence of psychotic symptoms.

## Neuroleptic-Induced Acute Akathisia

### Definition

Neuroleptic-induced acute akathisia is defined as a subjective feeling of restlessness and an intensely unpleasant need to move occurring secondary to antipsychotic treatment. The Greek origin of the word indicates "inability to sit."

### Etiology and Pathophysiology

The pathophysiological mechanism of akathisia remains unknown. Investigators have offered a number of theories, including akathisia as a subjective response to the rigidity and akinesia of NIP, as a primary sensory disturbance with secondary motor effects, and as a reaction to dopamine blockade in the mesocortical system. Mesocortical dopaminergic neurons that innervate the prefrontal cortex seem to be resistant to depolarization induced by long-term antipsychotic treatment, suggesting a possible explanation for why akathisia often does not improve with time (Lohr and Jeste 1988a).

The possibility that excessive noradrenergic activity plays a role in the pathogenesis of akathisia is supported by the efficacy of beta-adrenergic blockers in improving some cases of akathisia. A model implicating noradrenergic pathways from the locus coeruleus to limbic structures in movement disorders such as akathisia has been posited (Wilbur et al. 1988). The lower likelihood of akathisia with atypical antipsychotics and reports of selective serotonin reuptake inhibitors causing akathisia have implicated serotonin as having a possible role in akathisia; however, this is still under investigation (Miller and Fleischhacker 2000).

### Epidemiology and Comorbidity

Akathisia is a common side effect of antipsychotic treatment. It is estimated to occur in 20–75% of patients treated with conventional agents. The wide discrepancy in reported prevalence may result from a lack of consistency in the definition of akathisia, different prescribing practices, different study designs, and differences in population demographics (American Psychiatric Association 2000). While atypical antipsychotics are less likely to cause akathisia than typical agents, appreciable rates of akathisia are still reported with atypicals (Miller and Fleischhacker 2000). Clozapine-induced akathisia has ranged from 0 to 39% (Safferman et al. 1993) and a point prevalence of 13% was reported for risperidone (Miller et al. 1998). Akathisia may be a relatively common side effect of aripiprazole, which may be related to its relatively low rates of sedation and its partial agonist activity at dopamine receptors (Keck et al. 2006). Akathisia is thought by many psychiatrists to be a leading cause of nonadherence.

Higher doses of high-potency conventional antipsychotics appear to be most frequently associated with the appearance of akathisia (American Psychiatric Association 2000). Previous episodes of neuroleptic-induced akathisia increase the risk for future episodes if antipsychotics are restarted. Presence of NIP also appears to increase the risk of akathisia (Sachdev 2005a). As with other types of medication-induced movement disorders, structural brain disorders and mental retardation may also be risk factors (Sachdev 2005a).

**DSM-IV-TR Criteria**

**Neuroleptic-Induced Acute Akathisia**

A. The development of subjective complaints of restlessness after exposure to a neuroleptic medication.
B. At least one of the following is observed:
   (1) fidgety movements or swinging of the legs
   (2) rocking from foot to foot while standing
   (3) pacing to relieve restlessness
   (4) inability to sit or stand for at least several minutes
C. The onset of the symptoms in criteria A and B occurs within 4 weeks of initiating or increasing the dose of the neuroleptic, or of reducing medication used to treat (or prevent) acute extrapyramidal symptoms (e.g., anticholinergic agents).
D. The symptoms in criterion A are not better accounted for by a mental disorder (e.g., schizophrenia, substance withdrawal, agitation from a major depressive or manic episode, hyperactivity in attention-deficit/hyperactivity disorder). Evidence that symptoms may be better accounted for by a mental disorder might include the following: the onset of symptoms preceding the exposure to the neuroleptics, the absence of increasing restlessness with increasing neuroleptic doses, and the absence of relief with pharmacological interventions (e.g., no improvement after decreasing the neuroleptic dose or treatment with medication intended to treat the akathisia).
E. The symptoms in criterion A are not due to a non-neuroleptic substance or to a neurological or other general medical condition. Evidence that symptoms are due to a general medical condition might include the onset of the symptoms preceding the exposure to neuroleptics or the progression of symptoms in the absence of a change in medication.

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### Assessment and Differential Diagnosis

Akathisia tends to occur within the first 4 weeks of initiating or increasing the dose of antipsychotic medication. It can develop rapidly after the initiation or the dose increase of an antipsychotic. Patients with akathisia tend to have subjective complaints of "inner restlessness," most often in the legs. It may be difficult for the patients to describe their feelings. They feel that they must move, and this manifests as fidgeting, frequent changes in posture, crossing and uncrossing of the legs, rocking while sitting, marching in place, and shuffling when walking (American Psychiatric Association 2000). Some researchers have proposed subtypes of akathisia according to presence of objective, subjective, or both (mixed) symptoms (Sachdev 2005a), with mixed

presentations appearing most commonly and purely objective signs being relatively infrequent (Kim and Byun 2003).

Akathisia is often associated with dysphoria, anxiety, and irritability. When akathisia is severe, aggression or suicide attempts may result, although this causal link is controversial. Interestingly, akathisia has been proposed as a possible causal factor in the recently reported increase in "suicidality" associated with antidepressants in children, adolescents, and young adults (Muller-Oerlinghausen and Berghofer 1999). Akathisia in a psychotic patient can easily be mistaken for worsening of psychotic features, resulting in an increase in antipsychotic dose and an exacerbation of the akathisia.

The strange subjective discomfort associated with akathisia is the feature that seems to be most useful in making a differential diagnosis between neuroleptic-induced akathisia and other neuroleptic-induced movement disorders. TD is often associated with a lack of sensory perception of having a movement disorder. This contrasts with akathisia in which patients tend to be acutely aware of their distress. When patients with TD are uncomfortable, it is usually a result of social factors such as embarrassment and functional factors such as frustration over not being able to perform certain tasks. Another differentiating factor is that TD usually involves the face, mouth, and upper extremities, whereas akathisia more commonly involves the lower extremities. The rhythmical appearance of akathisia may sometimes suggest a tremorous condition. Thus, the tremor of NIP and idiopathic PD may be mistaken for akathisia, especially if the feet and legs are involved. Iron deficiency anemia can also present with symptoms similar to neuroleptic-induced akathisia. A number of other medications—particularly selective serotonin reuptake inhibitors—may produce akathisia clinically identical to that produced by antipsychotics (American Psychiatric Association 2000).

It is critical to differentiate akathisia from psychiatric disorders presenting with agitation, such as depression, mania, anxiety, schizophrenia, dementia, delirium, substance intoxication/withdrawal, and attention-deficit/hyperactivity disorder. Mistaking akathisia for a primary psychiatric disorder can result in an intervention that would be the exact opposite of what is appropriate (i.e., increasing the dose of an antipsychotic instead of decreasing it because akathisia is mistaken for worsening psychosis) (American Psychiatric Association 2000). Reports of "paradoxical worsening" with a neuroleptic should prompt consideration of akathisia as a side effect.

Akathisia symptoms also overlap with those of restless legs syndrome (RLS), although one study indicated less circadian variance and more "inner restlessness" with akathisia compared to RLS (Poewe and Hogl 2004). Interestingly, RLS is associated with dopamine abnormalities and responds to dopamine agonists (e.g., ropinirole). Both akathisia and RLS may occur in the course of idiopathic Parkinson's disease or iron deficiency.

### Course

Neuroleptic-induced akathisia typically lasts as long as antipsychotic treatment is continued but may have variable intensity over time (American Psychiatric Association 2000). Treatment of akathisia may or may not alter the course of the akathisia.

### Treatment

Akathisia may be difficult to treat effectively. The best initial approach is to try and reduce the chance of developing akathisia by minimizing the dosage of antipsychotic medication. The use of atypical antipsychotics should be considered because of their lower risk of akathisia. If using conventional antipsychotics, a switch to a low-potency agent such as thioridazine or chlorpromazine may prove helpful because these antipsychotics seem to have somewhat lower propensity to cause akathisia than high-potency conventional antipsychotics. After these initial steps, consideration should be given to initiation of an anti-akathisic drug regimen. A number of agents have been reported to be effective, including beta-adrenergic blockers, anticholinergic drugs, benzodiazepines, and clonidine (American Psychiatric Association 2000).

When using additional medications to treat akathisia, the beta-blocker propranolol is often considered first-line treatment, given the relative strength of evidence for its efficacy (Adler et al. 1993). To maximize anti-akathisic effects, beta-blockers may need to be lipophilic so as to cross the blood–brain barrier and also may need to have activity at the beta-2 receptor—both of which are characteristics of propranolol (Miller and Fleischhacker 2000). Benzodiazepines such as clonazepam and lorazepam have been shown to be efficacious in the treatment of akathisia and are also a reasonable therapeutic option, especially when anxiety is a prominent clinical feature; however, their side effects and abuse potential should be considered. Anticholinergic agents such as benztropine may also be tried, but less evidence exists to support their use. A limited number of studies have also shown possible roles for clonidine and amantadine in the treatment of akathisia (Miller and Fleischhacker 2000). Agents with $5HT_{2A}$ receptor blockade (e.g., mirtazapine, mianserin) have also been reported to be beneficial in akathisia. A small randomized, controlled trial found mirtazapine 15 mg/day and propranolol both improved akathisia more than placebo (Poyurovsky et al. 2006). Others have reported beneficial effects of vitamin B6 (600–1200 mg/day) in controlled trials (Miodownik et al. 2006).

## PROPHYLACTIC ANTICHOLINERGIC MEDICATION: PROS AND CONS

One issue that remains controversial among researchers and psychiatrists is whether preventive anticholinergic medication should be given to patients who are starting antipsychotics. Arguments against this practice include the risk of anticholinergic side effects such as dry mouth, blurry vision, constipation, and urinary retention. Further, anticholinergic medication is associated with cognitive side effects, such as memory impairment, confusion, and delirium. Additionally, polypharmacy increases health care costs, and risk for treatment nonadherence often increases along with the regimen complexity. Although some researchers have suggested anticholinergics may increase TD risk, the relationship between anticholinergics and TD is not definitive (Jeste and Caligiuri 1993).

Arguments in favor of initiating prophylactic anticholinergic therapy point to the decrease in the frequency of EPS (including dystonias, akathisia, and akinesia) when anticholinergic drugs are prescribed prophylactically (Winslow et al. 1986). Furthermore, medication nonadherence and

**Table 84–2 Treatment of Acute Neuroleptic-Induced Movement Disorders**

| Condition | First Choice | Second Choice | Third Choice |
|---|---|---|---|
| Acute dystonia | Anticholinergic medication, e.g., 2 mg benztropine PO, IM, or IV; 50 mg diphenhydramine PO, IM, or IV | Benzodiazepine, e.g., lorazepam 2 mg PO, IM, or IV | — |
| Parkinsonism | Decrease neuroleptic to lowest effective dose<br>Consider change to lower potency or atypical neuroleptic | Anticholinergic, e.g., benztropine at 2–4 mg/d divided b.i.d. | Consider high-dose anticholinergic<br>Consider discontinuation of neuroleptic<br>Consider amantadine (100–300 mg/d) |
| Akathisia | | | |
| with high-potency neuroleptic | β-blocker, e.g., propranolol 10–30 mg t.i.d. | Anticholinergic, e.g., 2 mg/d benztropine | Benzodiazepine, e.g., lorazepam, e.g., 1 mg t.i.d. |
| with low-potency neuroleptic | β-blocker | Benzodiazepine | Anticholinergic |
| with other extrapyramidal signs | Anticholinergic | Anticholinergic plus β-blocker | Anticholinergic plus benzodiazepine |

*Source*: Data adapted from Arana GW and Rosenbaum JF (2000) Handbook of Psychiatric Drug Therapy, 4th edition. Lippincott, Williams & Wilkins, Philadelphia, pp. 6–52.

decompensation may relate to inadequately treated EPS, especially akathisia and akinesia (Rifkin et al. 1975, Diaz et al. 2004). With the introduction and increased use of atypical antipsychotics, the risk of EPS has decreased, thus reducing the need for prophylactic anticholinergic medication for many patients prescribed atypical agents.

Although this complicated issue remains unresolved, some basic guidelines can be proposed. When high-potency conventional antipsychotics are prescribed for young to middle-aged adults, antipsychotic and anticholinergic medications may be administered concurrently, with the anticholinergic medication tapered slowly within the next few weeks. When psychosis is mild and antipsychotic medication may be gradually increased, it may be best to avoid anticholinergic medications until such time as they become clinically necessary. In patients with pre-existing cognitive impairment or those at high risk for developing such (e.g., older adults), anticholinergic medications are best avoided if possible. In general, long-term prophylactic use of anticholinergic medication is not recommended (Ungvari et al. 1999).

A summary of the treatment of acute neuroleptic-induced movement disorders is provided in Table 84–2.

# NEUROLEPTIC-INDUCED TARDIVE MOVEMENT DISORDERS

## Neuroleptic-Induced Tardive Dyskinesia

### Definition

Neuroleptic-induced tardive dyskinesia (TD) is a syndrome consisting of abnormal, involuntary movements caused by long-term treatment with antipsychotic medication. The movements are typically choreoathetoid in nature and principally involve the mouth, face, limbs, and trunk. TD, by definition, occurs late in the course of drug treatment.

### Etiology and Pathophysiology

Historically, striatal dopamine receptor supersensitivity (as a compensatory reaction to prolonged dopamine receptor blockade) has been the most prominent theory regarding the etiology of TD. Evidence in favor of this hypothesis includes increased striatal $D_2$ receptor binding using positron emission tomography among TD patients (Margolese et al. 2005). Yet, the $D_2$ supersensitivity seen in animal models of TD develops rapidly and almost invariably, whereas the clinical features of TD occur more slowly and only in a subset of patients (Jeste and Wyatt 1982, 2005a). It now seems more likely that a number of separate neurotransmitter systems are involved in the pathogenesis of TD. Some animal data implicate damage to gamma-aminobutyric acid (GABA)-containing striatal neurons as a causative factor in TD. There is also evidence that degeneration of striatal cholinergic interneurons and the resulting dopamine-acetylcholine imbalance play a role in TD pathogenesis (Jeste et al. 1992, Margolese et al. 2005). Lohr and Jeste (1988b) suggested that long-term antipsychotic use may produce toxic free radicals that damage striatal neurons and result in persistent TD. Antipsychotics may increase dopamine turnover, elevating levels of hydrogen peroxide and consequently free radicals, and antipsychotics may also generate free radicals via inhibition of the mitochondrial respiratory chain (Margolese et al. 2005). Other abnormalities reported to be associated with TD include reduced levels of brain-derived neurotrophic factor (BDNF) and elevated serum homocysteine (Lerner et al. 2005, Tan et al. 2005). Additionally, several candidate genes for increasing TD risk have been reported (e.g., serotonin receptors, dopamine receptors, cytochrome P450 enzymes) though none of these results are conclusive (Fernandez et al. 2003).

### Epidemiology and Comorbidity

The reported prevalence of TD has varied as a result of differences in study methodology (e.g., populations sampled, TD definitions, assessment measures) (Jeste and Wyatt 1981). Yassa and Jeste (1992) reviewed 76 studies of the prevalence of TD published from 1960 to 1990. In a total population of approximately 40,000 patients, the overall prevalence of

TD was 24.2%, although it was much higher (about 50%) in studies of elderly patients treated with antipsychotics. Children may also be at increased risk for the development of TD with antipsychotic treatment (Nasrallah 2006).

There have been relatively few studies of the incidence of TD. Kane and coworkers (1988) prospectively studied more than 850 patients (mean age 29 years) and found the incidence of TD after cumulative exposure to conventional antipsychotics to be 5% after 1 year, 18.5% after 4 years, and 40% after 8 years. Incidence in older populations has been found to be much higher. In fact, aging appears to be an important and consistent risk factor for the development of TD. The reasons for this increased risk of TD with aging are not known but may be related to the propensity of the nigrostriatal system to degenerate with age as well as pharmacokinetic and pharmacodynamic factors (Jeste and Caligiuri 1993). Jeste and coworkers (1995) evaluated 439 psychiatric patients with a mean age of 65 years and found that 28.8% of the sample met criteria for TD during the first 12 months of study treatment; 50.1% had TD by the end of 24 months, and 63.1% by the end of 36 months. The risk of severe TD has also been reported to be higher in older patients (Caligiuri et al. 1997).

Evidence supporting a reduced risk of TD with atypical antipsychotics is beginning to emerge. Although precise long-term rates remain unknown, preliminary 1-year incidence rates of TD with atypical antipsychotics have ranged from 0.4 to 2.6% (compared to 3–5% with typical agents) (Nasrallah 2006). The lower risk of EPS with atypical agents has led to the widespread opinion that these agents will also have reduced TD risk. The low risk of TD in clozapine-treated individuals has been well established (Lieberman et al. 1991). In addition, a lower incidence of TD has been reported in patients treated with risperidone (Chouinard et al. 1993, Jeste et al. 1999) and olanzapine (Tollefson et al. 1997). Another trial yielded significantly less TD with quetiapine compared to haloperidol (Emsley et al. 2004). In two studies comparing the rate of TD with typical vs. atypical antipsychotics in older adults, Jeste et al. (1999) and Dolder and Jeste (2003) found that the rate with atypical agents over 6–9 months was about 5 times lower than that with typical neuroleptics. Additionally, Jeste et al. (2000) reported that the one-year incidence of persistent TD with risperidone in elderly patients with dementia was less than 2%.

Gender (female) was thought to be a risk factor for TD. A meta-analysis of the published reports demonstrated a greater prevalence of TD in women (26.6%) compared with that in men (21.6%) (Yassa and Jeste 1992). Interestingly, studies of incidence of TD in older patients failed to confirm the reported propensity of women to have TD at a higher rate than men (Jeste et al. 1995). A possible interaction between gender, age of onset of schizophrenia, and severity of dyskinesia has been reported as women with late-onset schizophrenia (LOS) and men with early-onset schizophrenia (EOS) had more severe dyskinesia than men with LOS and women with EOS (Lindamer et al. 2001).

There are conflicting reports regarding ethnicity as a risk factor for TD. In a study of 491 chronic psychiatric patients, no significant differences in TD prevalence were found among blacks, whites, and Hispanics (Sramek et al. 1991). Higher incidence rates of TD in African-Americans than in whites, however, have been reported (Morgenstern and Glazer 1993). Wonodi et al. (2004) found less improvement among African-American patients with already established TD than among comparable Caucasian patients. Aside from genetic factors, possible explanations for higher rates of TD among African-Americans compared to whites include use of higher doses, a higher prevalence of slow metabolizers, and a high rate of misdiagnosis of mood disorders among African-Americans (Nasrallah 2006). There is some evidence that Asian patients may have the lowest prevalence rate of TD (Leung et al. 2003).

Total exposure to typical antipsychotic agents has been correlated with TD risk (Casey 1997) and, within elderly populations, cumulative amount of typical antipsychotics has also been associated with TD risk, especially with high-potency conventional agents (Jeste et al. 1995).

**DSM-IV-TR Criteria**

**Neuroleptic-Induced Tardive Dyskinesia**

A. Involuntary movements of the tongue, jaw, trunk, or extremities have developed in association with the use of neuroleptic medication.
B. The involuntary movements are present over a period of at least 4 weeks and occur in any of the following patterns:
   (1) choreiform movements (i.e., rapid, jerky, nonrepetitive)
   (2) athetoid movements (i.e., slow, sinuous, continual)
   (3) rhythmic movements (i.e., stereotypies)
C. The signs or symptoms in criteria A and B develop during exposure to a neuroleptic medication or within 4 weeks of withdrawal from an oral (or within 8 weeks of withdrawal from a depot) neuroleptic medication.
D. There has been exposure to neuroleptic medication for at least 3 months (1 month if age 60 years or older).
E. The symptoms are not due to a neurological or general medical condition (e.g., Huntington's disease, Sydenham's chorea, spontaneous dyskinesia, hyperthyroidism, Wilson's disease), ill-fitting dentures, or exposure to other medications that cause acute reversible dyskinesia (e.g., L-dopa, bromocriptine). Evidence that the symptoms are due to one of these etiologies might include the following: the symptoms precede the exposure to the neuroleptic medication or unexplained focal neurological signs are present.
F. The symptoms are not better accounted for by a neuroleptic-induced acute movement disorder (e.g., neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia).

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The observation that anticholinergic drugs exacerbate some symptoms of TD does not appear to indicate that the drugs promote the onset of the disorder (Jeste and Caligiuri 1993).

A wide variety of other TD risk factors have been investigated. People with diabetes mellitus may be at a higher risk for development of TD as well as spontaneous dyskinesias (Woerner et al. 1993). Caligiuri and Jeste (2004) demonstrated more prevalent and more severe TD among older adults with versus without diabetes mellitus, particularly among those taking atypical antipsychotics. The presence of dementia or delirium may or may not be a risk factor for TD. Mood disorders (especially unipolar depression) have been reported to increase risk for TD in a number of publications, although findings have been mixed (Casey 1988, Jeste et al. 1995). Yassa and coworkers (1984) determined central nervous system damage predisposed to TD, but other studies of older patients found organic diagnosis not to be associated with TD susceptibility (Jeste et al. 1995). Patients who experience an acute neuroleptic-induced movement disorder (especially parkinsonism or akathisia) are likely to be at a greater risk for development of TD if antipsychotic treatment is continued (Sachdev 2004). Other possible risk factors include negative symptoms, cognitive impairments, and comorbid substance abuse (Sachdev 2005a).

## Assessment and Differential Diagnosis

TD may develop at any age and typically has an insidious onset. It may develop during exposure to antipsychotic medication or within 4 weeks of withdrawal from an oral antipsychotic (or within 8 weeks of withdrawal from a depot neuroleptic). There must be a history of at least 3 months of antipsychotic use (or 1 month in the elderly) before TD may be diagnosed (American Psychiatric Association 2000).

The most common features of TD are involuntary movements of the tongue, face, and neck muscles. Less common are movements in the upper and lower extremities as well as in the trunk. Most rare of all are involuntary movements of the muscle groups involved with breathing and swallowing. The earliest symptoms typically involve buccolingual–masticatory movements. The movements of TD are choreiform (rapid, jerky), athetoid (slow, sinuous), or rhythmical (stereotypical) (American Psychiatric Association 2000).

Severe choreoathetoid dyskinesia differs from the milder forms mainly in the frequency and amplitude of the abnormal movements. Some cases of severe dyskinesia consist of generalized choreoathetosis of the face, trunk, and all four limbs (Casey and Rabins 1978). TD may be accompanied by dystonias, parkinsonism, and akathisia (Bitton and Melamed 1984).

TD is worsened by psychostimulants, short-term withdrawal of antipsychotic medication, anticholinergic medication, emotional arousal, stress, and voluntary movements of other parts of the body. It is improved by relaxation, voluntary movements of the involved parts of the body, sleep, and increased dose of antipsychotics (temporarily).

The differential diagnosis of TD is extensive. A number of nondyskinetic movement disorders are part of the differential diagnosis of TD. Tremor can be confused with TD, including the tremor of neuroleptic-induced parkinsonism, rabbit syndrome, Wilson's disease, and cerebellar disease. Furthermore, fine tremors of the fingers and hands are produced by anxiety states, alcoholism, hyperthyroidism, and drugs. Acute dystonias, myoclonus, tics, mannerisms, compulsions, and akathisia must be differentiated from TD. The differentiation is made on the basis of the clinical assessment. For further details, the reader is referred to Jeste and Wyatt (1982).

Once it has been established that the patient suffers from a dyskinesia, the main cause must be determined; a number of conditions may cause dyskinesia besides antipsychotic treatment. Certain prescription medications may cause TD, including metoclopramide, antiemetics, and amoxapine. The use of antiparkinsonian medications such as levodopa, amantadine, and bromocriptine can cause dyskinetic movements. Sydenham's chorea (a post-streptococcal complication) can produce choreiform movements in children. In the middle-aged or elderly patient, denture or dental problems may commonly mimic TD. Conversion disorder and malingering are conditions that can present with apparently involuntary movements. Hyperthyroidism and hypoparathyroidism are two endocrinological conditions that can produce dyskinesias similar to TD. Huntington's disease is a condition that can be difficult to distinguish clinically from TD, but certain features suggest a diagnosis of Huntington's disease, including (1) a family history of Huntington's disease, (2) the presence of dementia, (3) a slowly progressive downhill course, and (4) atrophy of the caudate nucleus on computed tomography scan. Focal lesions of the basal ganglia (e.g., tumor, stroke) may also result in dyskinesias.

Interestingly, the original descriptions of dementia praecox by Kraepelin (well preceding antipsychotic use) include the following: "Several patients continually carried out peculiar sprawling, irregular, choreiform, outspreading movements…" (Friedman 2004). Subsequent reports have indicated an increased rate of dyskinesias in neuroleptic-naïve persons with schizophrenia, as well as in their first degree relatives (Friedman 2004, Honer et al. 2005). Spontaneous dyskinesias may also occur in association with aging. While some have argued that TD thus represents a manifestation of schizophrenia itself rather than pharmacotherapy, antipsychotics clearly increase the risk for dyskinesias above any baseline rate in schizophrenia.

When it has been established that antipsychotics are responsible for the dyskinesia, it does not follow that the dyskinesia is necessarily TD. Acute dyskinesia occurring early in antipsychotic treatment may occur and responds well to anticholinergic medications. Withdrawal–emergent dyskinesia also occurs in a variable proportion of patients. This phenomenon refers to the appearance or worsening of dyskinetic movements on reduction or discontinuation of antipsychotic medication. Withdrawal–emergent dyskinesia is phenomenologically similar to TD and often has the full range of involuntary choreiform and athetoid movements. A typical case may begin within a few days after a sudden decrease in dosage and worsen as the antipsychotic is withdrawn. This phase is followed by rapid improvement in a period of weeks to months. A history of antipsychotic exposure and remission of dyskinetic symptoms within 3 months of antipsychotic withdrawal are suggestive of the diagnosis of withdrawal–emergent dyskinesia (Gerhard 1992).

Finally, tardive tics must be differentiated from TD. A number of cases of "tardive Tourette's disorder" have

been reported as a result of treatment with antipsychotics, emerging during treatment or after cessation of treatment (DeVaugh-Geiss 1980, Jeste and Wyatt 1982). Tardive tics present with symptoms similar to those of idiopathic Tourette's disorder. Motor tics are usually compulsive organized stereotypies that may, in certain cases, be difficult to distinguish from the choreoathetoid movements of TD. Vocal utterances (including barks, grunts, coughs, and yelps) often represent tardive tics, though vocal phenomena may also occur in TD. Tardive tics seem to show a pharmacological response similar to that of TD (i.e., masked by an increase in antipsychotics and exacerbated by withdrawal), possibly indicating this syndrome is simply a variant of TD (Jeste et al. 1986).

## Course

One-third of the TD patients experience remission within 3 months of discontinuation of antipsychotic medication, and approximately half have remission within 12 to 18 months of antipsychotic discontinuation (American Psychiatric Association 2000). Elderly patients are reported to have lower rates of remission, especially if antipsychotics are continued. When TD patients must be maintained with antipsychotics, TD seems to stabilize in 50%, worsen in 25%, and improve in 25%.

Time may be the most important factor in outcome of TD. In studies that have followed up patients for longer than 5 years, TD seems to improve in half of patients with or without antipsychotic treatment. Furthermore, TD may improve as slowly as it develops and may exist on a spectrum between resolution and persistence.

Severe TD may lead to numerous physical complications and psychosocial problems. Dental problems are common sequelae of severe oral dyskinesia, as are ulcerations of the tongue, cheeks, and lips (Yassa and Jones 1985). Hyperkinetic dysarthria and swallowing disorders have also been described in TD (Portnoy 1979). Respiratory disturbances, although fairly rare, have been reported by a number of investigators (Casey and Rabins 1978, Weiner et al. 1978). These disturbances are usually manifested by shortness of breath at rest, irregularities in respiration, and various grunts, snorts, and gasps. Respiratory alkalosis may be seen on laboratory tests. Gastrointestinal complications of severe TD may involve vomiting and dysphagia secondary to disruption of the normal activity of the esophagus (Yassa and Jones 1985).

Emotional distress may accompany severe dyskinesia. Suicidal ideation may result from distress over the dyskinesia, and there have been reports of some successful suicides. General impairment of functioning may be related to the severity of the dyskinetic disorder. Social embarrassment as a result of TD may represent a reason that some patients with TD tend to be reluctant to leave their homes. Even mild dyskinesia may lead to anxiety, guilt, shame, and anger. These symptoms can lead to depressive episodes (Yassa and Jones 1985). Alternatively, mild dyskinesias may not be noticed or spontaneously reported by patients, making clinical vigilance for early signs of TD important.

## Treatment

Despite intense effort, there is as yet no consistently reliable therapy for TD. As a result, the psychiatrist must focus primary efforts toward prevention of the disorder. Atypical antipsychotics appear to offer some advantage compared to older agents in terms of TD risk. Unnecessary antipsychotic use and excessive doses should be minimized. Patients with nonpsychotic mood or other disorders who need antipsychotics should receive the minimal necessary amounts of antipsychotic treatment and should have the medication tapered and then stopped once the clinical need is no longer present. In general, there must be enough clinical evidence to show that the benefits outweigh the potential risks of TD development. Antipsychotics should be used with particular caution in elderly patients because of their high risk for development of TD (Figure 84–1).

Gradual taper of the antipsychotic medication may be attempted as long as the risk/benefit ratio of antipsychotic maintenance versus withdrawal does not preclude such a

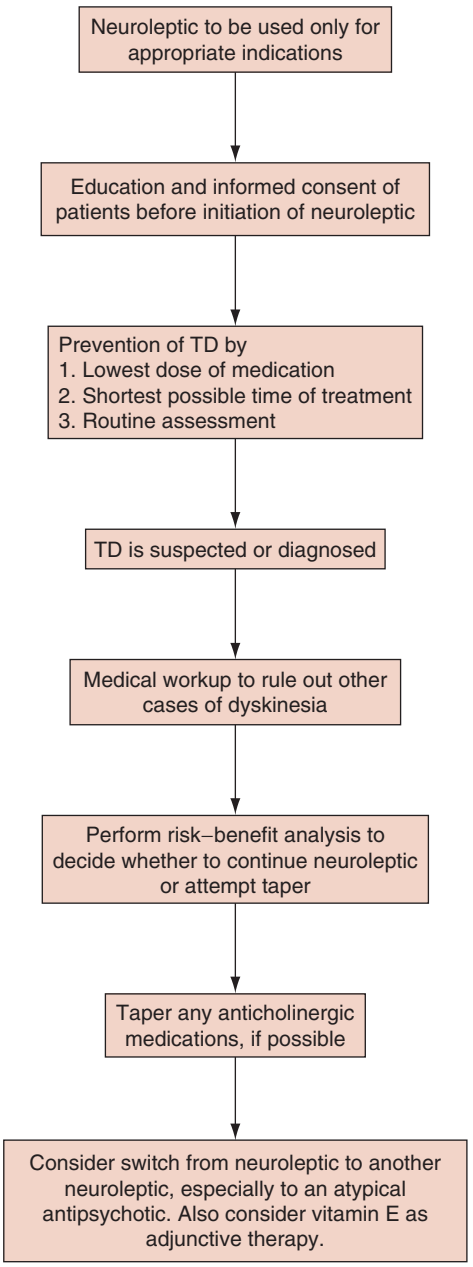



**Figure 84–1** *Management of tardive dyskinesia (TD).*

strategy. Using the lowest effective antipsychotic dose for long-term treatment of schizophrenia may help reduce TD risk. Paradoxically, antipsychotics themselves represent the most effective short-term treatment for TD. An increase in dosage of a conventional agent usually (in approximately 66% of patients) results in a clinically significant but temporary reduction in TD symptoms (Jeste et al. 1988). Atypical antipsychotics offer a means for reducing TD risk from treatment inception, though this advantage should be discussed with patients in the context of other possible side effects of atypical medications (e.g., metabolic effects). Clozapine may be effective in reducing TD in patients with existing TD (Lieberman et al. 1991, Small et al. 1987); however, side effects such as agranulocytosis, seizures, and anticholinergic symptoms limit its use. Additional studies have noted a beneficial effect of other atypical agents (i.e., risperidone and olanzapine) on preexisting TD (Jeste et al. 1997, Littrell et al. 1998). While some have argued that this could be a masking effect of atypicals on TD symptoms, Kinon et al. (2004) found open-label olanzapine reduced preexisting TD, and there was no rebound worsening in a blinded dose reduction phase.

A number of experimental studies have attempted to treat TD with alternative strategies. Jeste and coworkers (1988) reviewed these treatments and noted that they had variable and inconsistent degrees of success. One treatment that has demonstrated some efficacy is vitamin E (alpha-tocopherol). Lohr and Jeste (1988b) have proposed that antipsychotic treatment results in the production of free radicals that damage neurons. An antioxidant such as vitamin E might therefore, theoretically, result in improvement in the symptoms of TD. Zhang et al. (2004) showed an improvement in TD with vitamin E compared to placebo, which correlated with increased blood levels of superoxide dismutase (an enzyme that eliminates free radicals). A number of other studies of varying design have shown benefit of vitamin E in TD (Shriqui et al. 1992, Adler et al. 1998); however, a double-blind, placebo-controlled multicenter trial failed to show a difference between vitamin E and placebo after 1 year of treatment (Adler et al. 1999). The results are far from conclusive, but vitamin E has been used by some clinicians to treat TD because of its perceived benign nature. Yet, a recent meta-analysis demonstrating a slight increased risk of mortality with high dose vitamin E (largely in nonpsychiatric populations) compared to placebo makes the risk–benefit of this treatment in TD more difficult to interpret (Miller et al. 2005). Other previously mentioned theories of TD pathophysiology (e.g., damage to GABA and acetylcholine neurons) have led to other experimental treatments for TD, including benzodiazepines and cholinomimetics, but with inconsistent results. A recent small controlled trial of branched-chain amino acids led to improvement in TD compared to placebo, perhaps due to inhibition of CNS uptake of aromatic amino acid precursors of monoamines (Richardson et al. 2007). Damier and coworkers (2007) recently reported promising benefits of deep brain stimulation of the globus pallidus for recalcitrant TD.

Psychiatrists should regularly (e.g., every 3–6 months) assess for the presence and/or progression of TD and present the patient (or the patient's guardian) with information about the risks of treatment. The Abnormal Involuntary Movement Scale (AIMS) is a quick and common means for doing so (Fann et al. 1977). Psychiatrists may also give written information sheets, assess understanding by the patient or guardian, and accurately record evidence of the informed consent in the patient's record.

### Other Tardive Movement Disorders

Dyskinesia is not the only late-onset neuroleptic induced movement disorder. Tardive tics were discussed above in the differential diagnosis of TD. Other examples include tardive dystonia, tardive tremor, tardive myoclonus, and tardive akathisia. These are all less clearly characterized and less common than TD, and affected patients often also have TD. Tardive dystonia, like acute dystonia, may occur more often in young adults and males, and may respond to anticholinergics. Botulinum toxin may represent a treatment option for severe or persistent tardive dystonia (Brashear et al. 1998).

## OTHER NEUROLEPTIC-INDUCED DISORDERS

### Neuroleptic Malignant Syndrome

#### Definition

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal reaction to antipsychotic medications that is characterized clinically by muscle rigidity, fever, autonomic instability, and altered level of consciousness.

**DSM-IV-TR Criteria**

**Neuroleptic Malignant Syndrome**

**A.** The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.

B. Two (or more) of the following:

(1) diaphoresis
(2) dysphagia
(3) tremor
(4) incontinence
(5) changes in level of consciousness ranging from confusion to coma
(6) mutism
(7) tachycardia
(8) elevated or labile blood pressure
(9) leukocytosis
(10) laboratory evidence of muscle injury (e.g., elevated CPK [creatine kinase])

C. The symptoms in criteria A and B are not due to another substance (e.g., phencyclidine) or a neurological or other general medical condition (e.g., viral encephalitis).

D. The symptoms in criteria A and B are not better accounted for by a mental disorder (e.g., mood disorder with catatonic features).

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## Etiology and Pathophysiology

The pathophysiological mechanism of NMS remains unclear. The hypothesis of most interest is that of reduced dopaminergic activity secondary to neuroleptic-induced dopamine blockade. This reduced dopamine activity in different parts of the brain (hypothalamus, nigrostriatal system, and corticolimbic tracts) may serve to explain the various clinical features of NMS. Dopamine reduction in the hypothalamus may cause fever and autonomic instability; in the nigrostriatal system, dopamine reduction may lead to the rigidity; and the reduction in corticolimbic dopamine activity may explain the altered consciousness (Sewell and Jeste 1992). This hypothesis is based on the fact that antipsychotics are dopamine-blocking agents, whereas certain dopamine agonists are reported to help resolve NMS.

The dopaminergic blocking theory does not, however, explain why NMS may develop at a given time and in a given patient. There are probably other genetic, constitutional, environmental, and pharmacological factors that interact to produce the syndrome. Candidate genes identified as NMS risk factors in small studies include the $D_2$ receptor, $5HT_{2A}$ receptor, cytochrome P450 2D6, and the ryanodine receptor (involved in calcium regulation in muscles) (Kawanishi 2003). A number of investigators have proposed that other neurotransmitter abnormalities may be responsible for the syndrome, including serotonin, norepinephrine, and GABA changes. Gurrera (1999) proposed a comprehensive model in which sympathetic nervous system (SNS) dysregulation was posited to be the central mechanism of NMS, caused by neuroleptics' interruption of higher cortical tonic inhibition of the SNS (i.e., with resultant SNS hyperactivity).

## Epidemiology and Comorbidity

The exact frequency of NMS is unknown. A number of retrospective and prospective studies have found 0.02 to 3.2% of patients treated with antipsychotics to be affected with NMS. Several factors probably account for this large variability in frequency, including differences in study methods and diagnostic criteria for NMS (Adityanjee et al. 1999, Sewell and Jeste 1992).

A number of retrospective studies have attempted to isolate possible risk factors for the development of NMS. A prior episode of NMS appears to predispose to future episodes of NMS. Rosebush and coworkers (1989) found that the risk of recurrent NMS decreased as the time from an original NMS episode increased.

Preexisting medical problems, especially those associated with agitation or dehydration, may predispose neuroleptic-treated patients to develop NMS. Patients with a neurological condition and those with human immunodeficiency virus (HIV) may be at higher risk for development of NMS (Shalev et al. 1989). A number of potential risk factors related to antipsychotic treatment have been identified. Higher doses of antipsychotic, rapid increases in dosage (e.g., "rapid neuroleptization"), and intramuscular injections of high-potency conventional agents (e.g., haloperidol and fluphenazine) have been reported as risk factors for NMS (Keck et al. 1989). Coadministration of lithium with an antipsychotic has been proposed as a risk factor for NMS development, but the data regarding this are contradictory (Sewell and Jeste 1992). NMS has been reported with all of the atypical antipsychotics (including clozapine), and a recent review of atypical-induced NMS concluded that symptoms appear similar to NMS induced by conventional antipsychotics, though there was an inconclusive observation of lower mortality in NMS induced by atypicals compared to typicals (Ananth et al. 2004).

NMS is more frequently reported in men than in women and appears associated with younger age. A previous diagnosis of a mood disorder may place patients at a higher risk for NMS. Warm, humid climates may also predispose to the disorder (American Psychiatric Association 2000).

## Assessment and Differential Diagnosis

NMS usually presents in the first month of antipsychotic treatment but may develop at any time. Two-thirds of the cases manifest within the first week of treatment (American Psychiatric Association 2000). The two key diagnostic features for the disorder are severe muscle rigidity (classically referred to as lead pipe rigidity) and fever. A number of other features are also seen (see DSM-IV-TR criteria). For the psychiatrist, the most suggestive features are fluctuating consciousness (from confusion to coma), labile vital signs (tachycardia, unstable or elevated blood pressure), laboratory evidence of muscle injury (elevation of creatine kinase), and leukocytosis. Other features include diaphoresis, dysphagia, tremor, incontinence, and mutism (American Psychiatric Association 2000). The DSM-IV-TR criteria are broader than earlier criteria proposed by Pope and coworkers (1986), which require the following three items for a definite diagnosis: (1) oral temperature of at least 38°C in the absence of another known cause; (2) at least two extrapyramidal side effects from the following list: lead pipe-type muscle rigidity, cogwheeling, sialorrhea, oculogyric crisis, retrocollis, opisthotonos, trismus, dysphagia, choreiform movements, dyskinetic movements, festinating gait, and flexor–extensor posturing; and (3) autonomic dysfunction characterized by two or more of the following: hypertension, tachycardia, tachypnea, prominent diaphoresis, and incontinence. Sachdev (2005b) recently published reliability and validity data for a 36-point NMS rating scale that assesses a variety of the associated symptoms.

The differential diagnosis of NMS can be difficult (Table 84–3). The most important point is that the psychiatrist must start by suspecting NMS and then carefully rule out other possible organic problems. Because medical illness is a likely predisposing factor, it is important to consider that NMS may be present even if a definitive organic disease is found to explain the NMS-like symptoms.

Numerous general medical and neurological conditions can present with symptoms that resemble NMS, including CNS infection, status epilepticus, subcortical brain lesions, porphyria, and tetanus (American Psychiatric Association 2000). The presence of significantly elevated temperature and severe muscle rigidity makes the diagnosis of NMS more likely.

The syndrome of lethal catatonia (seen in patients with uncontrolled manic excitement or catatonic schizophrenia) can mimic NMS (with increased temperature, autonomic irregularities, and elevated creatine kinase), and

**Table 84–3 Differential Diagnosis of Neuroleptic Malignant Syndrome**

| Feature | Diagnosis | | | | |
|---|---|---|---|---|---|
| | Lethal Catatonia | Heat Stroke | Malignant Hyperthermia | Serotonin Syndrome | Neuroleptic Malignant Syndrome |
| Previous psychiatric illness | Yes | No | No | Yes | Yes |
| Onset of symptoms | + Prodromal psychotic symptoms | − Prodromal symptoms; development in several hours | − Prodromal symptoms; development after anesthesia | − Prodromal symptoms; development days to months after serotoninergic medication | − Prodromal symptoms; development hours to months after neuroleptic |
| Preceding anesthesia with muscle cell-depolarizing agents | No | No | Yes | No | No |
| Preceding neuroleptics | Maybe | Maybe | Maybe | Maybe | Yes |
| Preceding serotoninergic agents | Maybe | Maybe | Maybe | Yes | Maybe |
| Autonomic dysfunction | Maybe | No | No | Maybe | Yes |
| Episodes: stupor mixed with episodes of excitement | Yes | No | No | No | Maybe |
| Diaphoresis | Maybe | No | Maybe | Maybe | Yes |
| Rigidity | Fluctuating | No | Yes | Yes | Yes |

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the differential diagnosis can be difficult. It is obviously important to determine whether the patient is indeed being treated with an antipsychotic. Although NMS may clinically resemble catatonia, NMS does not typically have alternating periods of catatonic excitement and catatonic mutism. A past history of catatonic episodes is also important in making the differential diagnosis.

Heat stroke may also look like NMS but typically differs in that it presents with hypotension, dry skin, and limb flaccidity (American Psychiatric Association 2000). Malignant hyperthermia manifests similarly to NMS but generally occurs within the context of a patient's receiving halogenated anesthetic agents or succinylcholine. This condition typically begins immediately after administration of the anesthetic agent in genetically susceptible individuals (American Psychiatric Association 2000).

Medications can cause a number of conditions that may present as syndromes similar to NMS. Allergic drug reactions may produce fever and autonomic instability but not rigidity (Pelonero et al. 1998). Serotonin syndrome from serotonergic medications (e.g., antidepressants, triptans for migraine) also presents with confusion, fever, rigidity, and autonomic dysregulation (Birmes et al. 2003). A medication history can help distinguish between the two syndromes, but many patients receive concomitant antipsychotics and serotonergic antidepressants. Myoclonus, hyperreflexia, and diarrhea are more common in serotonin syndrome. Lithium intoxication and anticholinergic delirium can both resemble NMS, as can intoxication with amphetamines, cocaine, and phencyclidine. An NMS-like presentation has been described in Parkinson's patients with rapid discontinuation of dopaminergic drugs (Hashimoto et al. 2003).

## Course

The course of NMS is variable. Some cases may progress to death, whereas others may follow a mild self-limited course. Once the syndrome is recognized and the antipsychotic medication is discontinued, the syndrome usually resolves between 2 weeks and 1 month (American Psychiatric Association 2000).

Previous mortality rates were reported to be 4–25% (Sewell and Jeste 1992), though these appear to have declined in recent years to less than 10% with better recognition and treatment. The most common medical complications leading to morbidity and mortality are respiratory failure and renal failure. Shalev and coworkers (1989) reported that myoglobinemia and renal failure are the best predictors of mortality in NMS; the presence of either condition imparted a 50% mortality risk. In general, complications are a result of physiologic consequences of severe rigidity and immobilization such as deep vein thrombosis, pulmonary embolism, dehydration, and rhabdomyolysis (Pelonero et al. 1998). A small number of NMS cases have been reported to suffer long-term neuropsychiatric sequelae, such as motor and cognitive impairments (Adityanjee et al. 2005).

### Treatment

The most critical step in treatment (Table 84–4) is to recognize the clinical features of the syndrome and rapidly discontinue the antipsychotic. The importance of this initial step mandates that psychiatrists who use antipsychotics in their practice be cognizant of the early clinical features and recognize that the syndrome can occur at any time during the course of treatment. Shiloh et al. (2003) demonstrated that a protocol for monitoring motor, autonomic, and laboratory warning signs of NMS reduced the incidence to 0.2%, compared to 2.1% in treatment as usual.

Once NMS develops and the antipsychotic has been stopped, supportive care remains the core of treatment and often must be carried out in the context of a medical intensive care unit (Arana and Rosenbaum 2000). Each supportive intervention should be targeted to a specific symptom. Examples of interventions include cooling blankets for fever, cardiac monitoring for arrhythmias, and parenteral hydration for dehydration. Monitoring for urine output and renal function is important, and hemodialysis has been reported to reverse acute renal failure associated with myoglobinuria in NMS (Sanai et al. 2006).

Some specific treatments for NMS have been proposed, but their beneficial effects are unclear. The muscle relaxant dantrolene is thought by some investigators to be helpful in decreasing rigidity, hyperthermia, and tachycardia. Dantrolene was first shown beneficial in malignant hyperthermia and appears to block release of calcium from muscle sarcoplasmic reticulum, possibly by interacting with the ryanodine receptor. The usually recommended dose is 1 to 3 mg/kg/day orally or intravenously in four divided doses (Arana and Rosenbaum 2000). The dopamine agonist bromocriptine may also provide some relief of the symptoms, especially for muscle rigidity. Dosing is usually in the range of 5 to 10 mg orally three times a day (Arana and Rosenbaum 2000). The two medications can be administered together; however, a study by Rosebush and coworkers (1991) not only cast doubt on the benefit of the use of these agents in the treatment of NMS but also pointed to the possibility that these agents actually retard the course of improvement of NMS. In this study, 8 of 20 patients with presumed NMS received dantrolene, bromocriptine, or both along with supportive care, and 12 of 20 received supportive care only. There was a suggestion that the resolution of the NMS episodes took longer in the patients treated with the additional medications. The treatments in the investigation were not randomized or controlled (i.e., more severe cases may have received the medications more frequently).

At present, the appropriate course is to begin with antipsychotic discontinuation and supportive care and to consider antidote therapy only if improvement in symptoms is not seen within the first few days. Caroff and Mann (1998) suggested that treatment of NMS should be individualized for each patient based on clinical signs and symptoms. For example, supportive care may be sufficient in mild and early cases of NMS. Trials of bromocriptine, dantrolene, or amantadine may be helpful for patients with moderate–severe symptoms. Anticholinergics are generally best avoided (they may impair heat dissipation in febrile patients). Benzodiazepines may be useful for agitation and rigidity in NMS. Electroconvulsive therapy (ECT) is another treatment option in NMS. ECT's mechanism of action in alleviating NMS is unclear, though it does increase dopamine turnover in the brain. ECT is particularly useful when there is difficulty in distinguishing between NMS and lethal catatonia, when there is need for psychiatric treatment during a prolonged absence of antipsychotic pharmacotherapy, or when NMS symptoms are refractory. Some psychiatrists report rapid and dramatic success in use of electroconvulsive therapy for NMS.

A particular difficulty for the psychotic patient with NMS is that rechallenge with antipsychotics may cause NMS to recur. Successful rechallenge seems to be positively related to the length of time elapsed after resolution of NMS (Rosebush et al. 1989). Aside from avoiding the original offending agent, there are no absolute guidelines in choosing an alternative antipsychotic therapy after resolution of NMS in persistently psychotic patients. It is possible but not yet known definitively that atypical antipsychotics will prove to have a lower frequency of NMS. In general, it is recommended to switch to an agent in a different chemical class and with a lower $D_2$ affinity compared to the causal agent (Pelonero et al. 1998).

**Table 84–4 Treatment of Neuroleptic Malignant Syndrome**

| | |
|---|---|
| Step 1 | Assess medication regimen<br>• Stop dopamine antagonists<br>• Restart any recently stopped dopamine agonists |
| Step 2 | Supportive care<br>• Monitor vital signs<br>• Administer intravenous fluids<br>• Provide cooling blankets<br>• Administer antipyretics<br>• Consider dialysis for acute renal failure |
| Step 3 | No improvement within 24–28 h<br>• Administer oral bromocriptine 5 mg PO t.i.d. to be increased daily by 5 mg increments until positive response<br>• Continue bromocriptine for 10 d, then withdraw in period of 1 wk<br>• Monitor for relapse |
| Step 4 | If patient cannot tolerate bromocriptine or cannot take oral medications<br>• Administer intravenous dantrolene 1–3 mg/kg body weight/day, divided q.i.d.<br>• Gradually increase dose until positive response |
| Step 5 | Consider adding bromocriptine to dantrolene |
| Step 6 | Consider discontinuing all medications and giving supportive care only |
| Step 7 | Consider electroconvulsive therapy after 3–4 d, if no improvement |

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## Medication-Induced Postural Tremor

### Definition

This category refers to fine postural tremors that develop as a result of a medication. Medications that have been reported to cause such an effect are lithium, beta-adrenergic agonists, stimulants, dopaminergic medications, anticonvulsants, antipsychotics, antidepressants, and methylxanthines (e.g., caffeine) (American Psychiatric Association 2000). The psychotropic medication most typically associated with

such tremor is lithium, and most of the available information on medication-induced tremor relates to this drug.

## Etiology and Pathophysiology

Normal muscle contractions are accompanied by a generally imperceptible tremor during muscle fiber recruitment. This tremor is typically low in amplitude and is referred to as a physiological tremor. When these contractions are maintained, the amplitude of the tremor increases and it becomes visible. This is referred to as an enhanced physiological tremor (Young 1992). A number of medications, including lithium and bronchodilators, produce an enhanced physiological tremor. The pathophysiological mechanism of these tremors is not well understood but seems related to adrenergic-induced changes in the mechanical properties of the skeletal muscle (Young 1992). The response of these tremors to beta-adrenergic blocking agents and their exacerbation as a result of beta-adrenergic agonists lend support to the notion of adrenergic mediation.

## Epidemiology and Comorbidity

Estimates of the frequency of lithium-induced tremor vary widely across the literature and range between 4 and 65%. Lifetime incidence of tremor is estimated to be 25–50% of patients on lithium therapy (Price and Heninger 1994). A number of risk factors for the development of lithium-induced tremors have been proposed. These include older age, greater serum lithium levels, concomitant use of antidepressant or antipsychotic medication, high caffeine intake, history of tremor, alcohol dependence, and anxiety (American Psychiatric Association 2000).

## Assessment and Differential Diagnosis

Lithium-induced tremor may appear as soon as treatment is initiated. As the lithium level increases, the tremor becomes more severe and coarse and may have associated muscle twitching or fasciculations (American Psychiatric Association 2000). Complaints about the tremor are typically greatest at the beginning of therapy. There is disagreement as to whether the tremor typically remains stable or improves with time on lithium.

The lithium-induced tremor is reasonably easy to diagnose. It is a rhythmical tremor most prominent with sustained posture or movement. It commonly occurs in the hands or fingers but occasionally affects the head, mouth, or tongue (American Psychiatric Association 2000). The frequency of the tremor is typically 8–12 Hz and is similar in appearance to an essential tremor (Arana and Rosenbaum 2000). One can look for the tremor by asking the patient to hold the affected body part in a stable or outstretched position. The tremor is made worse by anxiety, stress, fatigue, hypoglycemia, thyrotoxicosis, pheochromocytoma, hypothermia, alcohol withdrawal, and performance of voluntary movements (American Psychiatric Association 2000, Arana and Rosenbaum 2000).

The most difficult differential diagnosis involves distinguishing a lithium-induced tremor from a preexisting tremor. To be classified as a medication-induced tremor, it must have a temporal relationship to the medication, it must relate to the serum level of the medication, and it must not persist after the medication is discontinued. A similar clinical condition is essential tremor, a common and sometimes familial illness, and differentiation between the two is nearly impossible clinically without the medication history.

Any of the factors listed that may exacerbate a medication-induced tremor can also cause a similar tremor in the absence of the medication. Medication-induced tremor may resemble NIP. NIP, however, is generally worse at rest, is lower in frequency, and has other associated features of parkinsonism (American Psychiatric Association 2000).

**DSM-IV-TR Criteria**

**Medication-Induced Postural Tremor**

A. A fine postural tremor that has developed in association with the use of a medication (e.g., lithium, antidepressant medication, valproic acid).
B. The tremor (i.e., a regular, rhythmic oscillation of the limbs, head, mouth, or tongue) has a frequency between 8 and 12 cycles per second.
C. The symptoms are not due to a preexisting nonpharmacologically induced tremor. Evidence that the symptoms are due to a preexisting tremor might include the following: the tremor was present prior to the introduction of the medication, the tremor does not correlate with serum levels of the medication, and the tremor persists after discontinuation of the medication.
D. The symptoms are not better accounted for by neuroleptic-induced parkinsonism.

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## Course

Tremors may be embarrassing for patients and at times impair activities that require delicate movements (e.g., buttoning, clothing, drawing) (Arana and Rosenbaum 2000). The actual percentage of patients who are bothered by their tremor is unknown but likely substantial. There do not appear to be any long-term sequelae as a result of having a medication-induced postural tremor. A sudden worsening of tremor may be indicative of the beginning of lithium intoxication.

## Treatment

Most treatment options have been described for treatment of lithium-induced tremor. Often the tremor is benign and not bothersome to the patient, in which case it requires no specific intervention. Patients with appreciable distress or functional impairment related to tremors, however, require treatment. Possible initial steps include reducing the lithium dose (if clinically feasible), changing to a one-time evening lithium dose, or changing the lithium preparation (e.g., to a sustained release formulation with possible reduced peak blood levels). Caffeine intake should be reduced or eliminated, and anxiety should be pharmacologically or behaviorally treated.

Beta-blockers represent the best-studied method for gaining pharmacological control of the tremor if the preliminary measures are ineffective. Arana and Rosenbaum

(2000) recommended starting propranolol on an as-needed basis. They suggested 10–20 mg a half-hour before the activity in which the tremor must not be present. If a patient requires chronic relief from the tremor, propranolol should be initiated at 10–20 mg b.i.d. and increased until adequate dose for suppression of the tremor is attained. Psychiatrists prescribing beta-blockers should be mindful of possible side effects, such as bradycardia, hypotension, asthma exacerbation, and worsening of preexisting heart failure.

Little information exists regarding the treatment of tremor induced by medications other than lithium and further investigations are needed.

### Clinical Vignette 1: Tardive Movement Disorders

Mrs. L, a 59-year-old divorced woman, was diagnosed with paranoid schizophrenia at the age of 33, though her symptoms predated the clinical diagnosis by several years. Mrs. L experienced intermittent paranoid delusions and command hallucinations for many years. After two hospitalizations and periods of treatment nonadherence, Mrs. L began to accept her diagnosis. She responded well to treatment with oral fluphenazine, with marked reduction and eventual remission of positive psychotic symptoms. She had relatively few negative symptoms, but residual cognitive impairments impeded her occupational functioning. Due to periods of past nonadherence, her treating psychiatrist suggested she switch to the decanoate form of fluphenazine. She did so and remained on fluphenazine decanoate 25 mg every two weeks.

Around 2 years after starting treatment with fluphenazine, Mrs. L developed orofacial dyskinesias consistent with TD. Over the subsequent 1–2 years, the dyskinesias in her orofacial muscles became somewhat more prominent and moderate in intensity. Also, she developed mild dyskinesias in her upper and lower extremities. Her truncal and respiratory muscles were never affected. Mrs. L. did not notice the dyskinesias initially and was never particularly bothered by them, even after her psychiatrist pointed them out to her, but she agreed that she did not want them to worsen. She discussed alternative treatments with her psychiatrist (e.g., oral low-potency antipsychotics, as atypical agents were not yet available), and decided to try lowering her fluphenazine dose by half. She soon experienced a temporary withdrawal-related increase in dyskinesias, which she found frightening (as she was not forewarned of this possibility), but which subsided. However, 4 months after lowering her fluphenazine dose she began to experience a relapse of hallucinations and paranoia. She and her treating psychiatrist decided to resume the original fluphenazine decanoate dose, with a short-term supplementation with oral fluphenazine. Her psychosis again resolved, and she did not wish to change treatments at that time despite the persistent dyskinesias.

Over the next several years, Mrs. L.'s TD symptoms waxed and waned but never disappeared or became significantly worse. Even with the advent of newer atypical agents, she preferred staying with a treatment which she knew had worked. At age 59, over the course of several weeks, Mrs. L. began to complain of a new symptom she had never experienced before, which she described as "nerves." Upon further questioning, it was difficult for Mrs. L. to convey the feelings she was experiencing, but she felt that "anxious" and "restless" were the best fits to describe her symptoms. She was noted to be fidgeting and rocking in her seat and to be marching in place with her feet. She did not have a history of comorbid mood or anxiety disorder, denied new psychosocial stressors, and had not changed her medications recently. Tardive akathisia was felt to be the most likely diagnosis. A thorough discussion of treatment alternatives (including atypical antipsychotics) ensued, but Mrs. L. preferred to find a way to treat the akathisia symptoms and remain on fluphenazine if possible. She was being treated by a primary care physician for osteoarthritis and hypertension, and was receiving acetaminophen and amlodipine (a calcium channel blocker). In consultation with her primary care physician, amlodipine was switched to propranolol, titrated to 20 mg three times daily. Mrs. L had a positive response to this change, with a significant reduction of her akathisia symptoms and good control of her blood pressure. Her TD symptoms remained largely unchanged, and she continued to have remission of psychosis with fluphenazine decanoate.

### Clinical Vignette 2: Acute EPS/dystonia

Mr. J, a 23-year-old single man, was psychiatrically hospitalized after attacking his brother in response to paranoid delusions. He believed his brother had been replaced by an imposter. He had complained of stress to a primary care physician 4 months earlier, and he began treatment with paroxetine for "anxiety." He noted some mild reduction in anxiety and thus continued to take the paroxetine. While in the emergency department prior to admission, the patient required emergent treatment for agitation and received haloperidol 5 mg intramuscularly. Upon his admission, the treating psychiatrist noted that he seemed tense primarily in reaction to paranoid beliefs, and the patient was started on risperidone 2 mg at bedtime. Mr. J later admitted to hearing the voice of a man commenting on his actions.

The following morning Mr. J began to complain that his tongue "felt funny" and was told dry mouth could be a side effect of the medication. Two hours later, he began moaning loudly and pointing to his throat. His neck was noted to be forcefully rotated to the right and his speech was somewhat difficult to understand. His vital signs were normal and his breathing was not yet compromised. Emergent treatment with benztropine 2 mg intramuscularly was ordered for a dystonic reaction. This resulted in partial relief of his torticollis and his speech improved, and the benztropine dose was repeated 40 minutes later. Within 1 hour after the second dose, the dystonia had resolved completely, but the patient was still distressed by the events and even more suspicious. The treating psychiatrist felt paroxetine might have decreased metabolism of both haloperidol and risperidone via inhibition of cytochrome P450 2D6 and thus increased the risk of EPS. The psychiatrist explained this to the patient and they agreed to switch to another antipsychotic agent with less $D_2$ receptor antagonism and with a different metabolic pathway, quetiapine. Prophylactic oral benztropine was also continued for 1 week and then tapered slowly.

## Comparison of DSM-IV/ICD-10 Diagnostic Criteria

Some of these categories are included in Chapter VI of ICD-10 (Diseases of the Nervous System) but no diagnostic criteria or definitions are provided.

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CHAPTER

# 85 Relational Problem Related to a Mental Disorder or General Medical Condition

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## Introduction

A relational problem is a situation in which two or more emotionally attached individuals (i.e., family members, romantic partners) engage in communication or behavior patterns that are destructive or unsatisfying, or both, to one or more of the individuals. Relational problems deserve clinical attention because, once initiated, they tend to be perpetuating and chronic, and are frequently contemporaneous with or followed by other serious problems, such as individual symptoms in the most vulnerable members of the family (e.g., depression) or social unit dissolution (e.g., divorce). They may be diagnosed either in the presence or *absence of individual Diagnostic and Statistical Manual of Mental Disorders* (DSM) disorders.

The strength and direction of causality between the individual and the relational problem are empirically undetermined. Few empirical investigations of the relational problems that are precursors to individual pathology have been conducted. Most of the existing research selects disturbed family units in which one member has an existing disorder (e.g., schizophrenia, depression) and examines the communication difficulties that accompany the disorder. Thus, cause-and-effect relations between individual disorders and relational difficulties often are not clearly specified. In some circumstances, individual psychopathology may lay the groundwork for relational difficulties, as when maternal depression disrupts the development of infant attachment processes (e.g., Cohn et al. 1986, Field et al. 2002, Larsen and O'Hara 2002). Relational difficulties also enhance the likelihood of the development of individual psychopathology, as when negative events in marriage increase the risk of depression in previously nondepressed individuals (Whisman et al. 2006). In some cases relational problems may interact with genetic vulnerabilities in contributing to the development of psychopathology (Wamboldt & Reiss 2006). For example, communication deviance in the adoptive parents of children at genetic risk for schizophrenia puts the child at greater risk for developing schizophrenia, when compared to children whose adoptive parents are low in communication deviance (Tienari and Wynne 1994).

There is also the issue of generalization: Do those who manifest relational problems with a spouse or other family member manifest these same problems with others and in other contexts? Some individuals manifest severe communication difficulties with their spouses or other family members but not with persons outside the family. However, relational problems in the marital dyad are strongly associated with parenting problems and parent–child conflict (Kitzmann 2000). Individuals in discordant intimate relationships display impairment in other social roles (Whisman and Uebelacker 2006). Thus, relational problems may generalize beyond the boundaries of the immediate relationship.

## Definition

Relational problems are placed in the fourth edition of the DSM (DSM-IV-TR) section "Other Conditions That May Be a Focus of Clinical Attention." There is debate on the most appropriate way to capture these clinical processes (First 2006). Five specific relational problems are described:

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**Relational problem related to a mental disorder or general medical condition:** A pattern of impaired family interaction in the presence of a mental disorder or medical condition in a family member.

**Parent–child relational problem:** A pattern of family interaction between parent and child that shows signs of impairment, such as faulty communication, overprotection, or inadequate discipline. The family interaction is associated with clinically significant impairment or symptoms in an individual or in family functioning, or both.

**Partner relational problem:** A pattern of interaction between spouses or partners characterized by negative and distorted communication or noncommunication, which is associated with clinically significant impairment in one or both partners.

**Sibling relational problem:** A pattern of interaction between siblings that is associated with clinically significant impairment in individual or family functioning.

**Relational problem not otherwise specified:** Relational problems not listed here, such as extra-family relational problems or difficulties with others, such as coworkers.

Beach et al. (2006) make a distinction between *relational disorders* which could become the focus of clinical attention in the absence of other disorders (e.g., severe marital conflict) and relational risk factors, which would be unlikely to become the focus of clinical attention but may increase the risk of negative outcomes for an ongoing psychiatric disorder (e.g., high expressed emotion in relatives). We have included both in our review.

## Constructs and Manifestations of Relational Problems

The empirical data substantiate the existence of relational difficulties that can be reliably assessed and have clinical significance (Beach et al. 2006, Clarkin and Miklowitz 1997). The data are sparse in reference to each DSM disorder and coexisting family relational difficulties, with the exceptions of depression, schizophrenia, and youth conduct disorders.

In our examination of the construct of relational problems, we emphasize those constructs that have shown reliable assessment in research and that have been found to (1) distinguish distressed from nondistressed couples or families or (2) identify couples or families in which one or more members manifest significant individual pathologic conditions. Some constructs with theoretical importance were found to lack one or both of these criteria and were not included in this review.

Four major constructs (Table 85–1) have been investigated that describe nodal areas of relational difficulty in the family and marital environment: structure, communication, expression of affect, and problem solving. Relational difficulties in other environments (e.g., work) have not been described in the clinical literature.

It is interesting to compare the constructs investigated in the couples and family contexts. The areas of affective communication and conflict resolution are almost identical in conceptualization, behavioral criteria, and importance in the spouse–spouse and parent–child communication domains. However, three other rather sharply defined constructs in the parent–child literature are not fully represented in the spouse–spouse literature: communication deviance (CD), emotional overinvolvement, and coercive process. In the cognitive realm, the CD construct (unclear, amorphous, or fragmented communication) has been investigated primarily among schizophrenic patients and their parents; comparable work has not been done with couples. The more general construct of communication has been explored with marital couples, with no theoretical link to thought disorder and schizophrenia.

**Table 85–1 Empirically Derived Family Relational Constructs**

| | |
|---|---|
| Structure | Leadership and distribution of functions |
| Overinvolvement | Unclear boundaries; overdependence |
| Communication | Amount and clarity of information exchange |
| Communication deviance | Unclear, amorphous, fragmented, and/or unintelligible communication |
| Coercion | Behavior control by use of aversive communication |
| Expression of affect | Implicit or explicit verbalization of affective tone |
| Problem solving | Definition of problems, consideration of alternative lines of action, agreement to use optimal line of action |
| Conflict and its resolution | Process of resolving differences of opinion |

Coercive processes—the shaping of the behavior of parents by negative behavior on the part of the child—is similar to negative escalation in couples. Although not yet investigated in couples, it is quite conceivable that one spouse could effectively engage in a coercive process with the other spouse. Overinvolvement, which has been explored in the parent–child literature may have a related domain in the marital literature—specifically, structure. The overinvolvement construct specifically has been seen as most relevant with children and parents and has little predictive utility in adult couple samples (Vaughn and Leff 1976a, Butzlaff and Hooley 1998, Hooley et al. 1986). However, it seems that the concept of structure, with the issues of leadership, dominance and submission, and distribution of functions, is an area that needs further exploration in reference to both couples and the entire family.

The Global Assessment of Relational Functioning Scale included in DSM-IV-TR for rating relational units utilizes the constructs that we have found in the empirical literature. The scale anchor points refer to structure ("agreed-on patterns or routines exist that help meet the usual needs of each family/couple member"), affect expression ("a range of feeling is expressed"; "despair and cynicism are pervasive"), communication ("communication is frequently inhibited"), and problem solving and conflict resolution ("decision making is usually competent"; "decision making is tyrannical or quite ineffective"; "unresolved conflicts often interfere with daily routines"). Descriptions and a review of the relevant research on each of these constructs—structure, communication, affect expression, and problem solving—will be reviewed below, both for couples and for families.

### Structure

For a marriage or family to function as a unit requires leadership and distribution of functions. Leadership, dominance, and power distribution can all have a profound effect on the quality of interaction satisfaction and on adequate

functioning of both couples and families, both in ordinary and in stressful circumstances.

### Couples

Power and dominance in relationships have been assessed in a variety of ways and sometimes appear related to relational functioning. For example, using measures of marital partners' influence patterns during discussion tasks, researchers have found that egalitarian couples (those in which couple solutions are equally reflective of each partner's ideas) have higher marital satisfaction than those with unequal power balances (Gray-Little et al. 1996). Power is also reflected in what has been termed the "demand–withdraw" pattern of communication in marriage. In this pattern, one partner makes demands, criticizes, or nags while the other partner withdraws, avoids conflicts, or becomes defensive. In this interaction pattern, the partner who makes demands is in a position of lesser power, as he/she is lobbying for change, while the partner in the "withdraw" position is in a position of greater power, as he/she can grant or deny change. A stable demand–withdraw pattern is frequently associated with relationship dissatisfaction (Eldridge and Christensen 2002). Although the wife-demand/husband-withdraw pattern appears to be more common, a husband-demand/wife-withdraw pattern may be apparent in severely violent couples (Babcock et al. 1993). In these couples, discussions may be characterized by blaming, defensiveness, criticism, and strong/early attempts at persuasion, suggesting intense conflicts over power (Gottman et al. 2003).

Power has been explored in couples with a depressed member. In these couples the power distribution is not always as theoretically hypothesized (i.e., depressed spouse submissive to dominance of the nondepressed partner). Contrary to expectation, Hooper et al. (1977) found that depressed patients produced substantial control-oriented communication with their spouses during an acute depressed episode. In a hospitalized sample, Merikangas et al. (1979) found that during early therapy sessions, the patient was strongly influenced by the behavior of his or her spouse; however, by the last session, there was a more equal balance of power. In contrast, introversion and interpersonal dependency may reflect enduring abnormalities in the functioning of individuals with remitted depression (Barnett and Gotlib 1988).

### Families

Some parent–offspring relationships are marked by unclear boundaries and overdependence, often inhibiting the offspring's ability to separate, individuate, or recover from illness (Minuchin 1974). With respect to psychiatric and sometimes medical disorders, it is not unusual to see a pairing of an overprotective, overinvolved parent with a highly disabled, passive, withdrawn offspring. Because ill offspring in these families often elicit such responses, an overinvolved relationship is best thought of as a dyadic attribute rather than a problem generated by a parent. Overinvolvement is often difficult to define or assess in parents of school-age or adolescent children (Asarnow et al. 1987). However, among studies of youth, those focusing on separation anxiety, and school refusal in particular, describe parental overinvolvement and protectiveness as complicating features (Kearney and Silverman 1995).

A number of inadequately designed studies in the 1950s and 1960s indicated that overprotectiveness characterized the parents of patients with schizophrenia (Tietze 1949, Reichard and Tillman 1950, Clardy1951, Wahl 1954, 1956, Lidz et al. 1964, Gerard and Siegel 1950, Mark 1953, Freeman and Grayson 1955, Kohn and Clausen 1956, Lane and Singer 1957, Horowitz and Lovell 1960, Lu 1961, Garmezy et al. 1961, McGhie 1950, 1961, McKeown 1950, Alanen 1958, 1966). Studies suggest that overinvolvement is a risk factor for later episodes of psychosis among patients diagnosed with schizophrenia, independent of the level of criticism demonstrated by the family (Brown et al. 1972, Vaughn and Leff 1976a, Vaughn et al. 1984, Leff and Vaughn 1985).

The term "expressed emotion" (EE) is used to refer to critical comments, hostility, and/or overinvolvement as expressed by a family member toward another family member with a mental disorder. EE studies and studies of family interaction have delineated other characteristics of overinvolved relationships in families of patients with schizophrenia. In terms of premorbid social adjustment, patients with schizophrenia in emotionally overinvolved families are more likely than those in normally involved families to have had poor premorbid social adjustment and a high level of residual symptoms after acute episodes (Miklowitz et al. 1983). Overinvolvement is reasonably common among families of patients with chronic schizophrenia (Miklowitz et al. 1986) but is infrequently observed among parents of recent-onset patients with schizophrenic disorder (Nuechterlein et al. 1986). Emotionally overinvolved parents of patients with schizophrenia are more likely than normally involved parents to use an excessive number of intrusive, "mind-reading" statements in direct family interaction (Miklowitz et al. 1984). They are also characterized by high levels of communication deviance (CD) (Miklowitz et al. 1986).

Several other studies suggest that parental overinvolvement combined with low levels of caring are retrospectively reported by patients with neurotic depression (Parker 1979, 1983) and borderline personality disorder (Zweig-Frank and Paris 1991). Interestingly, parental overinvolvement was associated with a better course of illness in one sample of individuals with borderline personality disorder (Hooley and Hoffman 1999). A study of adolescents at risk for psychosis found that parental overinvolvement predicted improvements in youths' negative symptoms and social functioning over a 3-month follow-up (O'Brien et al. 2006). Thus, the impact of overinvolvement varies across different forms of psychiatric disorder.

## Communication of Information

Verbal communication between two or more individuals involves the various aspects of information exchange, including the amount and clarity of the information and the reception of the information by another. This broad concept of communication implies the willingness to convey information, the accuracy and clarity of the information, and the accurate decoding of the information by the other.

### Couples

The amount and quality of verbal communication have differentiated distressed and nondistressed couples, and treatment leads to an improvement in communication (Ely et al. 1973). Measures of communication quality taken early in marriage are predictive of marital satisfaction four years later (Rogge and Bradbury 1999). In the area of information

exchange, there are more inaccuracies in the communication of distressed couples than in that of nondistressed couples owing to encoding (sending clear messages) rather than decoding (understanding partner's messages) errors. Distressed husbands were distinguished by more encoding and decoding errors than nondistressed husbands; (Noller 1981, 1984). Although both distressed and nondistressed couples are relatively inaccurate observers of their own interactional behavior, distressed couples are comparatively less reliable (Elwood and Jacobson 1982, 1988).

In addition to the overt verbal communication, various cognitive constructs are thought to be intimately related to the nature and quality of communication. Five areas of cognitive phenomena are hypothesized to play important roles in marital communication and maladjustment: selective attention, attributions, expectancies, assumptions, and standards (Baucom et al. 1989, Robinson and Price 1980). Not all of these areas have been equally investigated. First, distressed spouses focus on negative behavior; positive interactions often are ignored (Fincham and O'Leary 1983). Second, distressed spouses tend to attribute their partner's undesired communication behavior as global and stable (Camper et al. 1988, Holtzworth-Munroe and Jacobson 1985), and the partner is blamed for her or his negative behavior, which is seen as intentional, global, stable, and originating from internal factors. In contrast, nondistressed individuals give each other credit for positive behavior and overlook or exonerate their spouses for negative behavior (Jacobson et al. 1985, Fincham et al. 2000). While the stability or developmental history of these cognitive sets has not been clearly delineated, current evidence suggests that negative attributions for partner behavior may predict marital satisfaction over time (Karney and Bradbury 2000) and in addition to the impact of depression and/or low self-esteem (Fincham and Bradbury 2004). Third, the relationship between these attributions and marital satisfaction may be mediated by spouses' efficacy expectations for the relationship (Markman 1981). In the area of expectations, Pretzer et al. (1991) found that spouses' low efficacy expectations regarding their ability to solve their marital problems were associated with marital distress and depression. Data on premarital communication patterns and later marital conflict also suggest that certain forms of premarital communication (as opposed to specific content areas) predict a growing negative cognitive set held by partners toward each other (Buehlman et al. 1992). Indeed, among both newlywed couples and couples with young children, spouses' cognitions about the relationship were highly predictive of divorce or stability over time (Carrere et al. 2000, Epstein and Eidelson et al. 1981). Fourth, in the area of distorted assumptions that can affect marital behavior, it has been found that distressed spouses make the assumption that their partners cannot change the relationship and that overt disagreement is destructive (Jordan and McCormick 1987). Fifth, and relatedly, unrealistic assumptions and standards about relationships are predictive of general marital distress (Patterson 1982, Patterson et al. 1991).

## Families

Many of the same disordered processes (e.g., expression of hostility or excessive criticism, poor information exchange, lack of conflict resolution) in the spousal communication literature are presumed to disrupt healthy family functioning. Unlike in the marital literature, however, the independent variable in family studies is often the presence or absence of a psychopathologic condition in an offspring or parent rather than high or low levels of marital distress. In this section, we review disordered processes within families that have empirical validity in distinguishing disordered from non-disordered states, including coercive family processes and communication deviance.

### *Coercive Communication Processes*

When two individuals within a family (i.e., a parent and child) are controlling each others' behavior via aversive stimuli or responses that are perceived by these individuals or by others in the family as unpleasant, a "coercive entrapment" has developed (Patterson 1982). The key ingredient to such entrapment is negative reinforcement. In this model, children first learn to perform mild, relatively innocuous aversive behaviors (e.g., whining, teasing, running back and forth, negativism) as a way of terminating aversive behaviors that have been issued from a parent (e.g., scolding, issuing negative commands). The result is that the parent eventually withdraws his/her demands in order to terminate the child's aversive behavior. For the child, her or his aversive behavior has terminated the original aversive parental behavior (e.g., scolding). For the parent, her or his acquiescence has terminated the child's aversive behavior (e.g., whining). In this manner, the parent's attempts to discipline the child often have the effect of reinforcing the child's coercive behaviors and subsequent aggression (Patterson 1982, Patterson et al. 1991).

The coercive behaviors on the part of the child may escalate as this family interactional pattern continues, from minor coercive behaviors (e.g., whining) to more intense (if less frequent) coercive behaviors (e.g., hitting, temper tantrums, stealing). Indeed, coercive exchanges can be thought of as a series of "rounds" that escalate in severity and increase the probability that one or more family members (the child or the parent) will react aggressively (Robinson and Jacobson 1987). Studies of parent–child interactions during early childhood suggest that punitive parenting and a tendency to emotional reactivity in the child may be mutually reinforced, leading to greater parent–child conflict and poor emotion regulation over time (Scaramella and Leve 2004).

A number of studies provide validation for the association between highly coercive family relationships and antisocial/aggressive behavior (Burgess and Conger 1978, Lobitz and Johnson 1975, Patterson 1976, 1980, 1982, Patterson and Cobb 1971, Patterson et al. 1991, Robinson and Jacobson 1987, Snyder 1977, Wahler and Dumas 1987) and substance abuse (Hops et al. 2000) in offspring. For example, members of families containing children who are socially aggressive or who steal engage in higher rates of aversive behavior than do members of families containing normal children (Patterson 1982, Patterson et al. 1991). Mothers of children with conduct problems have been found to be more likely to initiate and continue unpleasant, aversive interchanges with the index child than mothers of normal children (Lobitz and Johnson 1975, Patterson 1982, Patterson and Cobb 1971). In addition, children with behavior problems are more likely to continue coercive interchanges with their mothers than are control children (Patterson 1982). Perhaps as a consequence, coercive relationships are frequently associated with depression in one or more family

members (Patterson 1980). It is not clear, however, whether coercive processes simply reflect the parents' response to the child's aggressive behavior or whether these processes play a direct role in causing aggression in the child.

### *Communication Deviance*

Wynne and Singer (1963a, b) observed that the transactional processes of families of concurrently hospitalized patients with schizophrenia were often unclear, amorphous, fragmented, or unintelligible. In their research, these high levels of CD discriminated parents of children with schizophrenia from parents of children with borderline personality, neurotic, antisocial, or autistic disorders and of normal children (Singer and Wynne 1963, 1965a, b). The authors believed that CD was present before, and was etiologically associated with, the appearance of schizophrenia in genetically prone offspring. Direct evidence for this view derives from one high-risk study demonstrating that high levels of CD among parents of disturbed but nonpsychotic adolescents predicted the onset of disorders within the schizophrenia spectrum (i.e., schizophrenic or schizotypal, schizoid, paranoid, or borderline personality disorders) among these adolescents who had follow-up into adulthood (Goldstein 1987). However, CD may covary with the severity of the offspring's diagnosis rather than the presence of a specific diagnosis. Indeed, high CD is characteristic of the parents of bipolar, as well as schizophrenic, offspring (Miklowitz et al. 1991) and may increase with severity of offspring psychopathology (i.e., from normal to neurotic to borderline to psychotic) (Wynne et al. 1977).

Although CD appears to be correlated with a diagnosis of schizophrenia, a number of mechanisms may explain this association (Miklowitz and Tompson 2003). Two in particular have garnered empirical support. First, CD in parents may be internalized by the child and lead to the development of difficulties in processing information and perceiving reality; thus, CD contributes to the development of vulnerability to schizophrenia. This view receives modest support from the diagnostic discrimination studies and high-risk study cited above. More recently, Wahlberg et al. (1997) demonstrated that individuals with high genetic risk (having a schizophrenic biological parent) who were exposed to high CD adoptive parents were at particularly high risk for developing thought disorder. Second, CD may reflect an indirect expression of the genetic vulnerability to schizophrenia in parents of affected offspring. One study suggested that parents of schizophrenic patients who show high levels of the perceptual-cognitive forms of CD also show dysfunction on information-processing tasks (Wagener et al. 1986). Two other studies demonstrated cross-generational correlations between CD in parents and degree of attentional and information-processing dysfunction in their diagnosed schizophrenic offspring (Nuechterlein et al. 1989, Asarnow et al. 1988). However, levels of CD are not correlated with the presence or absence of DSM-III-R (APA 1987) diagnoses in parents (current or past) (Goldstein et al. 1990).

In summary, studies of CD suggest that high levels of CD correlate with severe psychiatric conditions and may influence the development, and possibly the course, of these conditions. It is premature to refer to CD as an etiological agent in schizophrenia or other disorders.

## Expression of Affect

All messages have cognitive and emotional content and overtones, but it is conceivable that family units could be relatively proficient in one area while deficient and disturbed in the other. Negatively toned communication can consist of intensely personal, "character-assassinating" remarks (e.g., "You are an incompetent person") or, alternatively, an excessive number of specifically delineated criticisms of a person's behavior (e.g., "You never try hard in school"). It is also common to observe "negatively escalating cycles," which become increasingly pejorative and personal as they continue. Often, these cycles are accompanied by negative, defensive, nonverbal behavior that also escalates (Hahlweg et al. 1989, Simoneau et al. 1998).

### Couples

When spousal communication is extremely negative or pejorative, the marriage is likely to be at high risk and symptoms may develop in one or both mates. Because the direct and indirect expressions of affects such as anger, hostility, and resentment seem central to both poor problem-solving behavior and low marital satisfaction, we isolate affect from cognition for conceptual clarity and emphasis.

Depressed and distressed spouses are more likely to express dysphoric affect than are nondepressed and nondistressed spouses (Hautzinger et al. 1982, Kowalik and Gotlib 1987). In addition, distressed spouses exchange more negative affect than do nondistressed spouses (Schaap 1984, Coyne et al. 2002). As the EE literature indicates, a subgroup of spouses of depressed patients demonstrate critical remarks and nonacceptance of the mate, which are associated with a poor prognosis for the depressed partner (Hooley et al. 1986).

Distressed couples, compared with nondistressed couples, are more affectively reactive to ongoing negative and positive stimuli (Jacobson et al. 1980, 1982). There is a greater likelihood that distressed spouses, compared with nondistressed spouses, will react negatively to displeasing behavior by the other spouse (Jacobson et al. 1980). This type of behavior predicted marital dissatisfaction in at least one longitudinal study (Markman 1981). The interactions of spouses headed for divorce are frequently characterized by pervasive negativity, including global criticism, expressions of contempt and defensiveness, and eventual refusal to interact (Driver et al. 2003).

A *circular interactional pattern* has been described in the literature on depression and marriage. This pattern resembles the coercive processes of families of aggressive children described above. In this marital pattern, negative communication and a lack of positive support and responsiveness on the depressed spouse's part elicit hostility and withdrawal from the nondepressed partner, which in turn elicits more depression and more calls for reassurance by the depressed individual (Baucom and Epstein 1990, Birchler et al. 1975, Hinchcliffe et al. 1978, Klerman et al. 1984). Spouses of a depressed mate rated as high in EE showed interactions characterized by negative and critical remarks, frequent disagreement with the depressed spouse, and nonacceptance of what the mate has said to them. In turn, depressed mates showed low frequencies of self-disclosure and high levels of neutral nonverbal behavior (Hooley 1986).

Depressed couples, compared with control subjects, are characterized by negative affect after interactions and

negative appraisals of the other spouse's behavior (Gotlib and Whiffen 1989). Couples with a depressed partner exhibit negative and asymmetrical communication, with frequent expression of dysphoric and uncomfortable feelings (Hautzinger et al. 1982). In general, depressed couples tend to be characterized by negative affect (Kowalik and Gotlib 1987).

### Families

As in couples, families may be able to communicate clearly but may deliver messages that are highly critical, pejorative, hostile, or villifying. Although some degree of this type of communication is to be expected in every family, an excessive number or duration of negatively toned interactions may become associated with disturbance in one or more family members. Although it is not unusual for one family member to be the primary source of hostile emotional communication and another the primary target, it is also common for other family members to "aid and abet" these types of interchanges.

Throughout childhood the emotional quality of parent–child interaction impacts development and adjustment. Negatively toned parental feedback may lead to the internalization of a more negative self-concept and set the stage for future difficulties (Harter 1999), and exposure to intense and on-going parental conflict may lead to the development of poor emotion regulation and increased risk of psychological symptoms (Cummings and Keller 2006). In addition, parental expression of affect in parent–child interactions may be strongly linked to children's social development and acceptance by peers over time (Isley 1996, Parke et al. 2006). Expressions of positive affect among mothers predict greater acceptance by the child's peers, whereas expressions of negative affect among fathers predict poorer acceptance by peers (Isley 1996).

There is now evidence from more than 35 studies to suggest that excessive criticism, hostility, or emotional overinvolvement (high EE), or a combination of these, from parents, as measured by the individually administered Camberwell Family Interview (Vaughn and Leff 1976b), are prospectively associated with the course of numerous psychiatric difficulties (Butzlaff and Hooley 1998), including schizophrenia (Miklowitz and Tompson 2003, Kavanagh 1992, Parker and Hadzi-Pavlovic 1990), bipolar affective disorder (Miklowitz et al. 1988), nonpsychotic depression (Hooley et al. 1986, Vaughn and Leff 1976a), alcoholism (Fichter et al. 1997, O'Farrell et al. 1998) and obesity (Fischmann-Havstad and Marston 1984). High family EE is also predictive of poorer outcome among individuals undergoing behavioral treatments for obsessive–compulsive disorders, agoraphobia (Chambless and Steketee 1999) and posttraumatic stress disorder (Tarrier et al. 1999).

A separate, but related, domain of inquiry has concerned negatively toned family interactions. In a 15-year prospective study of nonpsychotic, disturbed adolescents (Goldstein 1987), affective negativity in parent to adolescent interactions (i.e., criticism, guilt induction, intrusiveness) was independently predictive (along with the family's level of CD) of the severity of outcomes observed in these adolescents at 15-year follow-up. Two other studies (Doane et al. 1985, Miklowitz et al. 1988) using similar procedures and construct definitions, found that the level of affective negativity during interactions between parents and their schizophrenic or bipolar offspring, measured after the patient's hospital discharge, was associated with the risk of the patient's relapse at a 9-month follow-up. Studies are mixed about whether the success of family interventions is mediated by the reduction of negative family attitudes and interactions. In one study, Doane et al. (1986), in a controlled family treatment study, found that family treatment was effective in delaying new episodes of schizophrenia if it was successful in reducing the number of critical comments and intrusive, "mind-reading" statements observed among parents during pretreatment family interaction assessments. However, Leff et al. (2003) found that whereas reducing family EE or reducing patient contact with high EE relatives mediated the efficacy of family treatment for schizophrenia, this was not the case for couples treatment for depression. In sum, there is strong evidence for the prognostic validity of negative affective communication or attitudes within families containing a patient with a severe psychiatric illness, but the mechanisms of action of family based interventions vary with the nature of the condition.

## Problem Solving

Problem solving is a general construct relating to the manner in which two or more people define conflict issues, consider alternative lines of action, and proceed to the most optimal action as demanded by a problem situation (Falloon et al. 1984). The impact of negative life events within a relational unit may be impacted by the strategies they use for approaching and solving problems (Cohan and Bradbury 1997). It is common for families seeking treatment to be unable to solve major family problems—this is often the very reason that they seek treatment. However, when families do not have the skills for solving problems in general, such as the ability to define a problem or generate possible solutions, they may become "stuck" in ways that prevent the growth or individuation of one or more members.

### Couples

Distressed couples manifest more negative communication and fewer positive communication behaviors when solving problems, as rated by observational coding systems (Birchler et al. 1975, Gottman 1979, Gottman et al. 1977, Revenstorf et al. 1984, Schaap 1984). Problem-solving behavior is less frequent (Biglan et al. 1985), more negative (Vincent et al. 1975), and often results in ineffective solutions in distressed couples (Winemiller and Mitchell 1994). Problem escalation (i.e., problem solving by spouse 1, followed by negativity by spouse 2, followed by negativity by spouse 1) is also more characteristic of distressed couples (Revenstorf et al. 1984). Furthermore, negative reciprocity, involving mutual fault finding, cross-complaining (Gottman 1994), and the communication of global and negative attributions, is also greater among distressed than nondistressed couples (Billings 1979, Gottman et al. 1976, Margolin and Wampold 1981, Rausch et al. 1974, Revenstorf et al. 1984). Positive reciprocity is more characteristic of nondistressed couples (Revenstorf et al. 1984), but not in all samples (Margolin and Wampold 1981). Poor problem-solving skills in interactions, combined with lower levels of positive affect, strongly predicts deterioration in marital satisfaction among newlywed couples over time (Johnson et al. 2005). In addition, poor problem-solving ability has been associated with depression among spouses (Basco et al. 1992)

and this association is over and above the effects of marital discord and depression alone (Christian et al. 1994).

Conflict resolution is a specific subset of problem-solving behaviors (i.e., resolving differences of opinion between two or more people). Whereas all couples display conflict, it is especially chains of disagreement that characterize distressed couples (Gottman et al. 1977, Margolin and Wampold 1981, Hahlweg et al. 1984a, 1984b). The reciprocity of negative rather than positive behavior distinguishes distressed from nondistressed couples (Revenstorf et al. 1984, Schaap 1984, Driver et al. 2006).

From a longitudinal perspective, predictors of short-term and long-term marital satisfaction appear to be different (Gottman and Krokoff 1989, Driver et al. 2006). Although disagreement and angry exchanges relate to dissatisfaction in the short run, they may not be harmful across time. In contrast, longitudinal marital deterioration is best predicted by defensiveness, whining, stubbornness, and withdrawal from interaction. Stonewalling, in which one partner adamantly refuses to discuss a problem, is particularly associated with divorce (Gottman 1994). Interestingly, in a large longitudinal study of marriage and economic stress, Conger et al. (1999) found that effective problem solving among couples reduced the impact of marital conflict on perceived marital satisfaction. Thus, when couples are able to generate and implement effective problem solutions, disagreement per se do not lead to unhappiness with the relationship.

### Families

When a family is deficient in solving problems, the tension level in the household is likely to increase and conflict between members tends to escalate. In such a family climate, children do not learn to recognize the steps necessary to solve interpersonal problems and may develop psychiatric problems or their social or academic competence may suffer (Blechman 1990).

In general, a strong relation has been found in the literature between the way parents solve socialization problems of their children and the cognitive abilities of these children (Baumrind 1975, Bee et al. 1982, Bradley and Campbell 1980, Gottfried and Gottfried 1983, Hess and Shipman 1965). For example, in a study of school-age children, Blechman and McEnroe (1985) found that those families that built the tallest towers in a cooperative task were those with the most academically and socially competent children.

Compared to nonclinic families, families seeking help at a mental health clinic demonstrated less problem solving (Krinsley and Bry 1991) and more disagreement (Whittaker and Bry 1991) in problem-solving discussions. Poor family problem solving has been noted in the families of youth with depression (Sheeber and Sorenson 1998). Forehand et al. (1990) found that, during direct interaction between mothers and these adolescents, mothers' problem-solving scores (i.e., ability to define a problem clearly and propose alternative solutions) and positive communication scores (i.e., acknowledgments, openness to others' opinions) were higher when these mothers were from intact rather than divorced families. However, conflict initiation occurred more frequently among divorced than married mothers. Perhaps most significantly, these parenting skills predicted adolescent functioning in the domains of cognitive and social competence. Similarly, Goodman et al. (1999) found that frequent, negative conflict between parents was associated with poorer social problem-solving skills among youth.

Finally, findings from intervention studies indicate that problem-solving skills are amenable to intervention and that improvements in family problem solving are associated with decreases in conflict and enhanced family functioning. Falloon et al. (1984) found that communication- and problem-solving-oriented family treatment (behavioral family management) was far more effective in delaying episodes of psychosis among recently hospitalized schizophrenic patients than was individual treatment for the patient of similar duration. In a reanalysis of Falloon and coworkers' data, Doane et al. (1986) found a marked increase, from baseline to 3-month follow-up, in the number of spontaneously occurring problem-solving statements among families in family treatment. Little or no change in the frequency of these statements occurred among families in which patients received individual treatment. Furthermore, increases in problem-solving ability were most notable when a decrease in emotional negativity among parents as measured by number of critical and intrusive affective style statements was also observed. Thus, an improved ability by the family to address problems in a structured manner may reduce its need to "ventilate."

Barkley et al. (2001) compared problem-solving communication training (PSCT) alone to a combination of PSCT and behavior management training (BMT) among families of youth with attention deficit hyperactivity disorder and oppositional defiant disorder. Both treatments used behavioral techniques to enhance problem-management skills. While the two treatments did not differ in outcomes, they both produced positive change in observed and self-reported measures of parent–child conflict. Thus, teaching problem-solving skills to parents and adolescents may address family conflicts associated with disruptive behavior disorders.

## Diagnosis of Relational Disorders

Although research on structure, expression of affect, communication, and problem solving in couples and families has led to a greater understanding of the difficulties that can afflict these relational units, specific relational problems have only been recently included as a diagnostic entity in the DSM (see DSM-IIIR, DSM-IV-TR) and clear diagnostic criteria have yet to be developed. Current textual descriptions of these conditions refer to impairment in the "pattern of interaction" in these relational units (DSM-IV-TR, p. 736), reflecting the broad range of specific difficulties subsumed under this diagnostic entities.

### Phenomenology

Five specific relational problems are noted in DSM-IV-TR (see the definition section earlier in the chapter). Family relational problems and partner relational problems are delineated below. These difficulties may also afflict relational units in the presence of a mental disorder or medical condition. The phenomenology of sibling relational problems and relational problems with other individuals has not been well explored.

### Partner Relational Problems

Clinical experience and the research descriptions suggest that marital (and couples) relational problems manifest in the following ways:

1. Couple does not clarify mutual requests, provide information, or accurately describe problems.
2. Spouse or spouses verbalize underlying attributions, assumptions, and expectations that are negative (e.g., spouse is globally negatively intentioned) or exaggerated (e.g., couples should never fight).
3. Affective communication is characterized by negative affect (e.g., anger, hostility, jealousy), critical remarks, disagreement with spouse, and nonacceptance of what the mate has communicated.
4. There is a low frequency of self-disclosure of thoughts, feelings, and wishes.
5. Couple demonstrates inadequate problem solving characterized by poor problem definition, lack of task focus, mutual criticism and complaint, and negative escalation.
6. Couple displays sequences of negative communication characterized by criticism, disagreement, negative listening, and refusal to agree.
7. Couple avoids conflict by withdrawal, lack of discussion, and subsequent nonresolution.

### *Associated Features*

Associated features of marital communication difficulties or disorders include poor marital satisfaction, psychiatric disorder in one or both spouses, threatened and contemplated separation and divorce, or concentration and job performance difficulties.

### Family Relational Problems

Family relational problems manifest as the following:

1. Family is unable to communicate clearly, cannot communicate closure, or cannot share a focus of attention (CD).
2. Family communication is characterized by unidirectional hostility or frequent criticism or by bidirectional, negatively escalating cycles of pejorative or critical comments.
3. Parent– offspring relationships are characterized by overprotectiveness, overconcern, unnecessarily self-sacrificing behaviors, intrusiveness, or overdependence (emotional overinvolvement).
4. Parent– offspring interchanges are marked by negatively reinforcing coercive cycles that tend to perpetuate antisocial or aggressive behavior in one or more family members.
5. A broad array of family problems cannot be solved because of the family's inability to agree to try to solve, define, generate, or evaluate solutions to, or implement solutions to, existing problems.

### *Associated Features*

The associated features of parent–child communication difficulties or disorders include adolescent acting out and disruptive behavior, major psychiatric disorders in one or more family members (i.e., schizophrenia, affective disorder), poor parental morale, and parenting dissatisfaction.

## Assessment of Relational Disorders

### Overall Relationship Functioning

The Global Assessment of Relational Functioning Scale (GARF; Group for Advancement of Psychiatry 1996) included in DSM-IV-TR is a 1–100 scale of overall relationship functioning, akin to the Global Assessment Scale for individuals. Recent studies have indicated that the GARF is reliable in clinical settings (Dausch Miklowitz, and Richards 1996, Rosen et al. 1997, Hilsenroth et al. 2000, Mottarella et al. 2001), and that GARF ratings are correlated with self-report measures of relationship functioning (Wilkins and White 2001), and that changes in GARF scores are positively associated with both client and therapist-reported change in treatment and with treatment satisfaction (Ross and Doherty 2001).

### Structure

Family structure can be measured with self-report instruments as a control subscales on both the Family Assessment Measure (Skinner et al. 1983) and the Family Environment Scale (Moos and Moos 1981) and as an organizational subscale on the latter. In interaction research, it has been recommended (Markman and Notarius 1987) that dominance be measured in terms of procedures that assess the consequences of behavior (e.g., influence of dominant one on decisions) rather than on who speaks first and/or for the greatest proportion of the time.

Parental overinvolvement has been defined in various ways in the psychiatric literature (Parker 1982), but the criteria used within the EE coding system (Leff and Vaughn 1985) are the best operationalized: a tendency to be overprotective of, overly concerned about, overly controlling of, or domineering toward an offspring; to engage in numerous self-sacrificing behaviors in the name of good parenting (e.g., the parent denies himself or herself social relationships to satisfy the needs of the offspring); to engage in intrusive, boundary-crossing, or mind-reading interactions with the offspring; and to react to minor events affecting the offspring with exaggerated emotional responses and to overdramatize these incidents. In return, the offspring may react with overt struggles for independence or autonomy or, in contrast, passivity, withdrawal, and overdependency. Parker and coworkers' (Parker et al. 1979) well-validated Parental Bonding Instrument provides a working definition of overprotection: parental overcontrol, intrusion, and excessive contact, and preventing the child from acting independently (Parker 1983).

### Communication

Communication is measured in family and marital questionnaires—for example, with a communication subscale of the Family Assessment Measure (FAM-III; Skinner et al. 1983); the Dyadic Adjustment Scale (Spanier 1976) with a dyadic cohesion subscale; and the Primary Communication Inventory (Navran 1967) with its verbal communication subscale.

Ratings of interpersonal behavior involving self-disclosure, positive solution, negative solution, justification, direct expression, criticism, critique, positive communication, and negative communication can be seen as relating to the general category of communication skills (Markman and Notarius 1987). Numerous coding systems have been devised to examine particular communication processes within families (Kerig and Lindahl 2001). As an example, Kategoriensystem für Partnerschaftliche Interaktion (KPI; Hahlweg et al. 1984a) codes, such as self-disclosure ("I'm too angry to listen

to you at the moment"), positive solutions ("I'll sweep the floor if you play with the kids"), problem description ("We've got a problem with the kids"), and disagreement ("That's not true"), provide evidence of communication skills. The brief Communication Patterns Questionnaire (Heavey et al. 1996) has shown strong associations with both marital satisfaction and the constructiveness of spousal behavior during videotaped problem-solving discussions.

Recently, measures have been developed to evaluate partner's cognitions that have been associated with communication difficulties. The Relationship Attribution Measure (Fincham and Bradbury 1992) assesses the manner in which partners assign responsibility for their spouse's behavior. The Marital Attitudes Survey (Pretzer et al. 1991) assesses spouses' attributions regarding their partners attitudes and behaviors in the relationship and expectancies about the possibility of relationship change.

Communication deviance consists of two primary components: disorders of linguistic-verbal reasoning (i.e., unfinished phrases, unintelligibility, odd word usage) and perceptual-cognitive disturbances (i.e., inability to integrate multiple pieces of information into a coherent message; inability to perceive and describe an object or concept accurately). The majority of studies of CD have relied on transcripts of projective test (i.e., the Rorschach Inkblot Test or Thematic Apperception Test) responses from parents as the primary data source for coding CD. One study (Velligan et al. 1990) found a correspondence between levels of parental CD as measured in a projective and an interactional context, although not all forms of CD were measurable in both contexts.

Measurement of coercive processes usually requires that the observer watch the family interact directly, because these processes often occur on a behavior-exchange rather than a verbal-exchange level. In this way, coercive processes are to be distinguished from affectively negative verbal exchanges.

Perhaps the best-known system for coding coercive processes is the Family Interaction Coding System (Patterson 1982, Patterson et al. 1969). It is a home observation system in which positive, neutral, and negative behaviors on the part of all family members are coded sequentially by live observers, in contiguous 6-second time blocks. Interrater reliabilities for the system have been consistently high across studies (Robinson and Jacobson 1987).

### Expression of Affect

Family and marital questionnaires address affect in terms of expressiveness, a subscale of the Family Environment Scale (Moos and Moos 1981); affective communication, a subscale of the Marital Satisfaction Inventory (Snyder 1979, 1981); affectional expression, a subscale of the Dyadic Adjustment Scale (Spanier 1976); and the affective expression and involvement subscales of the Family Assessment Measure (Skinner et al. 1983). Studies using self-report instruments have also yielded interesting results (Hooley and Teasdale 1989, Kreisman et al. 1979, Haas et al. 1988).

For interaction research, it has been recommended that affect be coded by observing the affective content of both verbalizations and nonverbal behavior (Markman and Notarius 1987). Negatively toned family communication has been measured primarily via structured interviews of individual family members (i.e., the Camberwell Family Interview for rating EE) or observation and coding of family interactions (e.g., the affective style coding system or the KPI).

### Problem Solving

On self-report instruments, the Marital Satisfaction Inventory (Snyder 1979) has a problem-solving communication subscale. In addition, problem-solving behavior is often sampled directly, both as it spontaneously occurs in free-flowing discussion and in the context of solving assigned tasks such as card sorting (Olveri and Reiss 1981) or the revealed differences technique (Strodbeck 1951) and its modifications (Ferreira 1963).

Conflict is measured on the dyadic consensus subscale of the Dyadic Adjustment Scale (Spanier 1976) and on the conflict subscale of the Family Environment Scale (Moos and Moos 1981). It is measured in terms of disagreement about finances, sexual dissatisfaction, and conflict over child-rearing on the Marital Satisfaction Inventory (Snyder 1979), the Conflict Tactics Scales (Straus 1979) obtain self-report on strategies used to resolve conflicts in families, including reasoning, verbal aggression, and violence.

Interactional ratings of conflict are similar in content. Interactional ratings of agreement, disagreement, sequences of positive and negative communication, such as on the KPI, are all under the umbrella of conflict. Conflict has also been operationalized in interactional speech samples as speech interruptions, simultaneous speech, agreement/disagreement ratios (Jacob 1975, Riskin and Faunce 1970) and failure to reach agreement (Farina 1960).

In the family literature, measurement of problem-solving skills has typically involved an unstructured or semi-structured task such as a family problem-solving discussion (Strodbeck 1954) or a tower-building game (Goldberg and Maccoby 1965). Criterion variables generated by these tasks have included tabulations of problem-solving enhancement statements during interaction (Doane et al. 1986), the number of tower blocks the family puts together (Blechman and McEnroe 1985), or the family's self-rated satisfaction with the problem-solving task (Blechman and McEnroe 1985). In other studies (Reiss et al. 1986), problem solving may be measured by such attributes as the level of coordination shown by family members in solving a given problem (e.g., recognizing patterns in an array of symbols) or the family's openness to new information from each other or its ability to change solutions to accommodate new data ("delayed closure").

## Epidemiology of Relational Disorders

The raw frequency of relational disorders (broadly defined) in the general population is unknown. No epidemiological studies have been done, in part because of the absence of accepted diagnostic criteria for these disorders. There are rather vague "proxies" of relational disorders that are useful in making estimations of their prevalence, such as the approximate frequencies of divorce in the general populous (40–50% of all couples; Kreider and Simmons), of marital violence (12–33% of couples; Sagrestano et al. 1999), or of child abuse and neglect (an estimated 3.6 million cases investigated by CPS agencies during 2005). Factors such as divorce or violence, however, are best thought of as relational events rather than relational disorders. A single incident of

marital violence does not necessarily signal the presence of a family relational disorder (in the absence of confirmatory information), nor is a diagnosable relational disorder in a spousal couple necessarily associated with divorce. Thus, the prevalence of specific types of relational disorders, as described in this chapter, is difficult to estimate.

A further difficulty in making these estimations in the normal population is that certain of the constructs conveyed, such as expressed emotion (EE) as based on the Camberwell Family Interview (Vaughn and Leff 1976a, 1976b), assume the presence of a psychiatric disorder in an index family member. Also, the goal of EE and other family psychopathological studies has been to examine family attribute–outcome relationships on a within-group basis in psychiatric disorders rather than to making comparisons between families of psychiatric patients and nonpsychiatric control subjects. Thus, data are lacking on the frequencies of high-EE attitudes or other family attributes in normal control groups.

Estimating the normal prevalence of EE is aided by the availability of the Five-Minute Speech Sample EE coding system (Magana et al. 1986), which simply requires that the parent talk for 5 minutes, uninterrupted, about the relationship with an index offspring (ill or well). This coding system yields an EE rating that has a close but not perfect correspondence (72–89.7%; Magana et al. 1986; Moore and Kuipers 1999) with EE ratings based on the Camberwell Family Interview, the traditional measure of EE (Vaughn and Leff 1976b). Stubbe et al. (1993), in a population-based study of inner-city preadolescents, found that 22% of parents of children with no psychiatric disorders met the Five-Minute Speech Sample coding criteria for high EE, in contrast with 40% of parents of children having one or more psychiatric disorders.

A number of studies of CD have examined rates of speech deviance in the normal population, but most have selected normal comparison groups to match with samples of patients with schizophrenia and, thus, do not reflect a random cross section of the population. Given this limitation, high levels of CD (defined in various ways) appear to occur in about 16% (range 0–39%) of the parents of normal persons, compared with about 63% (range 19–76%) of the parents of patients with schizophrenia (Miklowitz and Tompson 2003, Miklowitz and Stackman 1992). The significant variability in rates across samples probably reflects differences in methods of assessing CD as well as sampling variabilities.

The paucity of studies on the frequency of family relational disorders points to the need to develop strict operational criteria for these disorders and to conduct epidemiological studies using random sampling techniques, much as is done for individual disorders. The availability of epidemiological data would allow us to determine not only the need for treatment of specific relational disorders but also their comorbidity with individual or other relational disorders, their associated features, and the social conditions under which they are most likely to arise.

Specific Axis I and II disorders may have a strong impact on and be strongly impacted by relational problems. For example, much has been written on the association between depression and interpersonal problems (Joiner and Coyne 1999) and between parental depression and youth psychopathology (Goodman and Gotlib 2002). Clinicians should be alert to the probable comorbidity between relational disorders and mood, Axis II, disruptive behavior, and substance use disorders.

## Treatment

### Specific Goals of Treatment

The primary goal of treatment is to bring the relational unit to a more satisfying, organized, and less conflictual level of functioning. The mediating goals of treatment are focused on improvement in the specific areas of functioning of the relational unit (i.e., structure, communication, affect expression, problem solving). In relational units where one member is suffering from a mental disorder or medical condition (e.g., schizophrenia, depression, childhood disruptive behavior disorder), additional goals include the reduction of individual symptoms and improvements in psychosocial functioning.

### Treatment Format

Relational problems are best observed and treated directly in a family format in which the conflicted family members are present with the therapist. However, there may be certain situations in which relational problems are more conducive to change within an individual treatment format. For example, relational problems related to an individual with a mental disorder (e.g., a 25-year-old son with schizophrenia, in conflict with his mother and father) may in some cases best be approached by individual sessions with the affected person. Further, when one adult in a family unit is depressed, individual interpersonal or cognitive psychotherapies may be used and focused on conflict resolution. Parent training is often conducted with parents alone, and skills are then implemented with youth at home.

### Treatment Strategies and Techniques

The specific techniques available to family therapists can be divided into five categories: psychoeducational, cognitive-behavioral, structural, strategic-systemic, and insight-oriented. Psychoeducational approaches are most helpful when there is a family member with a specific medical or psychiatric disorder, and the family can utilize information on how to manage the disorder with the least tension and stress on the patient (Clarkin 1989). Cognitive-behavioral techniques are useful in improving communication and problem-solving skills and the positive interactive behaviors in marital-family units. Structural and strategic-systemic approaches are most useful in rearranging the repetitive interactions in a family that constitute the boundaries and alliances in the social system.

In practice, there are many common elements and much eclectic usage of strategies and techniques across the various schools of family intervention. Family therapy shares many of the common treatment elements with other forms of psychotherapy. All psychosocial treatments require the development and maintenance of a good patient–therapist relationship, or therapeutic alliance. There is an assumption that most patients experience some degree of corrective emotional experience, or reliving of significant life experiences in the presence of an empathic therapist who demonstrates new ways of relating. In this context, the patient (or patients) is able to identify with the therapist and utilize the behaviors

discussed and modeled. In all forms of psychotherapy, there is a certain degree of transmission of new information. The learning can be about methods of behavior, ways of thinking, or increased awareness of complex emotions. Most therapies involve some shaping of people's behavior through implicit and explicit rewards for behavior considered appropriate, and discouragement of behaviors considered harmful. This shaping can occur through advice, suggestion, persuasion, role playing, and practice.

## Standard Approach to Treatment

There is increasing evidence for the efficacy of family and marital interventions in the treatment of a broad range of relational problems and psychopathology, and extensive reviews of this literature can be found elsewhere (Pinsof and Wynne 1995, Glick 1999, Sholevar and Schwoeri 2003). However, several specific questions about treatment efficacy can be asked here in reference to the previous review of relational difficulties:

1. Do the specific relational difficulties (i.e., structure, communication, affect, and problem solving) respond to intervention?
2. Do the individual disorders associated with relational problems (e.g., schizophrenia, affective disorders, adolescent delinquent behavior) show improvements in illness course when the relational problems are at least part of the focus of intervention?

## Empirical Investigations of the Efficacy of Family or Marital Treatment

### Partner Relational Difficulties

Difficulties between romantic partners, including marital distress and relationship conflict, are most often addressed using couples-based interventions. A number of treatment models have been articulated and investigated, including "emotionally focused marital therapy" (Johnson 1999), "insight-oriented marital therapy" (Snyder and Wills 1989) and "integrative behavioral couples therapy" (Christensen et al. 2006). Recent meta-analysis examining findings from 15 couples intervention studies found that, when compared to no treatment, couples therapy resulted in significant positive changes in partners' behavior and evaluations of the relationship (Dunn and Schwebel 1995).

The most well-researched therapy is behavioral marital therapy (BMT; Alexander et al. 1994, Christensen et al. 1995), in which partners are coached on methods for increasing positive interactions and decreasing aversive ones, improving communication and enhancing problem solving. BMT has received extensive empirical support and testing, and recent meta-analytic data suggest only moderate effect sizes (Shadish and Baldwin 2005). However, longitudinal follow-up studies conducted by Jacobson et al. (1984, 1987) indicate that almost half of the couples engaged in these interventions fail to make clinically meaningful improvement and many fail to maintain gains achieved within these interventions.

Modifications of the BMT approach have included a greater emphasis on facilitating "acceptance" of one's partner (Lawrence et al. 1999) and increasing motivation for change (Cordova 2004). This revised model, called the integrated behavioral couple therapy, had a comparable overall outcome to traditional behavioral couple therapy over 2 years. However, couples gained in satisfaction sooner in integrated behavioral couple therapy than couples in traditional behavioral couple therapy, and generally remained more stable over 2 years (Christensen et al. 2006).

Few studies have compared these models directly and thus it is not possible to match them to specific couples. One study found that emotionally focused marital therapy was superior to behavioral marital therapy for the treatment of moderate marital distress (Wood et al. 2005).

### Parent–Child Difficulties

Difficulties between parents and their children or adolescents can take the form of child and adolescent behavioral problems; child abuse and neglect; and difficulties, deficits, or excesses in parenting. Parent Training approaches have been developed to address both the treatment and prevention of parent–child difficulties. Videotaped modeling interventions, such as those developed by Webster-Stratton (2005) provide cost-effective and efficacious methods for training parents in setting limits, using effective discipline, problem solving, and promoting interpersonal and academic skill development. These modeling approaches include specific interventions for early childhood (ages 2–7 years) and school-aged youth (ages 5–12 years) and target parents, teachers, and children for training. Kazdin et al. (1992) have also developed and tested manualized problem-solving skills training and parent management training interventions for youth ages 7–13 years with conduct problems. The problem-solving skills training uses cognitive-behavioral strategies to assist the child in negotiating interpersonal situations. Parents were included in sessions to assist the therapist and to foster problem-solving steps in the home. In parent management training, the parent was seen individually to improve child-rearing practices and to use contingencies to support prosocial behavior by the child. Although in a clinical trial both treatments demonstrated improved child functioning and increased social competence, a combination of the two treatments resulted in more marked changes in child and parent functioning and placed a larger proportion of children within the range of nonclinical levels of functioning. Parent Training has shown moderate effects for the treatment of child abuse, but efficacy is improved by including home visits, training in the home, and individual as well as group sessions (Lundahl, Nimer, and Parsons 2006). Individual sessions may be particularly important when treating economically disadvantaged families (Lundahl, Risser, and Lovejoy 2006). This and other studies (Sayger et al. 1988, Singer et al. 1989) suggest that family therapy has promise in reducing specific problematic child behaviors with behavioral techniques and that the parents have a better personal adjustment after learning parenting skills.

Parent–child interaction therapy (PCIT; Querido and Eyberg 2005) was developed for children ages 2–7 with disruptive behavior problems. Using both didactics and coaching sessions, the therapist helps parents enhance both the parent–child relationship and the implementation of behavior management strategies. During coaching sessions, the therapist provides feedback and direction from behind a one-way mirror directly to the parent (using an "ear bug")

as he/she interacts with the child. PCIT is associated with significant improvements in children's behavior, decreases in parental distress, and increased positive expression in parent–child interactions.

### Nonspecific Parent–Adolescent Conflicts and Adolescent Behavioral Problems and Delinquency

Numerous studies have been completed in this area. The most well-researched intervention for serious behavior problems in youth is the aforementioned parent-management training. This intervention has shown efficacy in the treatment of a wide range of serious behavior problems in youth, including conduct problems and delinquency, oppositionality, and aggressive behavior (Kazdin 1997, Mabe et al. 2001). Henggeler et al. (1992) developed multisystemic therapy and applied it to the treatment of juvenile offenders with records of serious crime. Multisystemic therapy had a duration of 3 months and employed intervention strategies similar to those in family and behavioral therapy (i.e., individualized treatment plans sometimes involving home visits in addition to therapy meetings). Compared with "treatment as usual" (incarceration or probation), multisystemic therapy led to greater reductions in both incarceration and criminal behavior for boys in the treatment condition. Long-term follow-up studies suggest sustained effects of multisystemic therapy (Schaeffer and Borduin 2005).

### Substance Abuse

More research is needed with patients and families suffering from alcohol and substance abuse, a major problem area in our society. The existing family studies show some promise for the use of family therapy (Friedman 1989, Liddle 1999, Stanton and Todd 1979, 1982) but it may be most effective with specific subgroups, possibly with younger abusers still at home and where family assets are substantial. Substance abuse is often comorbid with conduct problems in youth, and the few available studies suggest that both individual cognitive therapy and behaviorally oriented family therapy may be associated with significant improvements for youth with comorbid conduct and substance use problems (Azrin et al. 2001).

### Eating Disorders

The early theoretical and clinical work of Salvador Minuchin, one of the leaders of the family movement, focused on eating disorders. Recent research lends increasing empirical support to the role of family-based treatments in a comprehensive strategy for addressing eating disorders. Russell et al. (1987) randomly assigned patients (57 with anorexia nervosa and 23 with bulimia nervosa) to either family therapy or individual supportive treatment after an inpatient treatment intended to bring the patient to normal weight. The goal of treatment was to help the family support the patient's recovery from eating disorder. After 1 year of treatment, the patients were reassessed for body weight and menstrual functioning. Treatment effects were still apparent at a 5-year follow-up (Eisler et al. 1997). The results are relevant to differential treatment planning, as those patients whose eating disorder was not chronic and had begun before the age of 19 years were more effectively treated with family therapy.

Comparing conjoint family therapy to a separated family therapy (in which parents and the adolescents were seen in separate sessions), Eisler et al. (2000) found separated family treatment to be associated with significant reductions in parental EE and greater symptoms improvements. Robin et al. (1999) compared Behavior Family Systemic Treatment to individual treatment for anorexia nervosa. While improvements were apparent in both treatments, symptom improvement was greater in the family intervention. Group family treatments have also been shown to facilitate recovery from anorexia nervosa (Geist et al. 2000).

### Schizophrenia

Family treatments for patients with schizophrenia and their families have been found to have strong beneficial effects. There are at least eight studies of family interventions of longer term (i.e., 9 months or more) duration (Barrowclough and Tarrier 1990, Falloon et al. 1985, 1987; Falloon and Pederson 1985, Hogarty et al. 1986, 1991, Leff et al. 1982, 1985, 1989, Randolph et al. 1994, Tarrier et al. 1988, 1989, 1994, Xiong et al. 1994). The majority of these treatments focus on providing psychoeducation and enhancing communication problem-solving skills in a family context. Although these multifaceted interventions show strong effects on patient outcomes, more limited provision of psychoeducation to families does not appear to impact patient outcomes (Lam 1991, Pitschel-Walz et al. 2001). Enhancement of coping skills within the family appears to be a necessary component of these interventions.

Illustrative is the treatment approach articulated by Anderson et al. (1986; Hogarty et al. 1986), which is broad based and extensive, including survival skills workshops for the families, reentry of the patient into the family, enhancing work and social adjustment of the patient, problem solving, and maintenance of therapeutic gains. Results of randomized studies (Hogarty et al. 1986, 1991) show the superiority (in terms of relapse rates and social adjustment of patients) of family therapy to individual social skills training or a no-therapy, medication-only control group during a 2-year follow-up.

Both the number and the quality of family therapy studies are impressive. The family treatments have been manualized, and the existing outcome literature suggests that family therapy is a useful and effective part of the overall treatment of these seriously disturbed individuals (Bellack and Mueser 1993, Goldstein and Miklowitz 1995, Penn and Mueser 1996). Recent studies suggest that multiple family group interventions may be more cost-effective than those focused on individual family units (McFarlane 1995). Focus on the individual family units may be appropriate early in the course of illness, whereas later on, a multiple family group format may be optimal (Tompson et al. 1996).

Questions remain as to the most important focus of family intervention (e.g. lowering EE versus increasing family coping) and at what point in the illness of the patient are families most likely to respond positively to family intervention.

### Mood Disorders

Most of the studies of family intervention in families where one member is suffering from a mood disorder have been done in the marital treatment format, reflecting the age

at onset of affective disorders (Beach and O'Leary 1992, Jacobson et al. 1991). There are a few studies involving families. Data from the Cornell Medical Center study of inpatient family intervention with patients with bipolar or major depressive disorders (Clarkin et al. 1990) suggest that inpatient family intervention may be fruitful for some subgroups. These patients and their families were randomly assigned to psychoeducational inpatient treatment with or without family intervention. At both 6- and 18-month follow-up times, patients who received family intervention showed better outcome than those without it. These treatment effects were limited, however, to the female bipolar patients. In contrast, those patients with unipolar depression did better without family intervention. Studies with outpatient samples suggest that, when depression is accompanied by marital distress, couples-based treatments may be superior to cognitive behavioral treatments (Beach and O'Leary 1992). The few studies of family treatment with depressed adolescents suggest that cognitive behavioral interventions may be superior to family-based interventions during this developmental stage (Brent et al. 1997). However, family-based interventions may be optimal for preadolescents (Asarnow et al. 2005).

Clarkin et al. (1998) randomly assigned 33 married bipolar I patients to a psychoeducational marital therapy with medication or to a standard medication treatment. Although the marital treatment did not have differential effects on relapse rates, it was associated with gradually improving Global Assessment Scale scores over 11 months of treatment. Patients in marital treatment also were more consistent with their use of medication than those in standard medical treatment.

Two clinical trials examined a family-focused treatment for adult bipolar I patients (Miklowitz and Goldstein 1997) following hospitalization for mania or depression. Family-focused treatment, delivered along with mood stabilizing medication and consisting of education, communication skills training, and problem-solving skills training, was found to reduce risk of both relapse and hospitalization when compared to treatments consisting of crisis intervention and medication (Miklowitz et al. 2003) or individual therapy and medication (Rea et al. 2003). FFT was also superior to brief psychoeducation in hastening time to recovery among bipolar, depressed patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (Miklowitz et al., in press). More recently, this work has been extended to adolescents with bipolar disorder (Miklowitz et al. 2004, Miklowitz et al. 2006).

## Summary

The research suggests that family treatment is effective with schizophrenia, affective disorders, adolescent and child acting-out difficulties, and eating disorders (Pinsof and Wynne 1995). In terms of strategies and techniques used in the family and marital treatment formats, there is substantial evidence for the effectiveness of cognitive-behavioral and psychoeducational techniques, with few data on the other approaches. Future studies should compare the efficacy of (and estimate the relative treatment effect sizes attributable to) family therapy versus competing therapies (i.e., individual or group therapies). Future research should also determine the optimal format in which to administer family treatment (i.e., home-based versus clinic-based; individual families versus multifamily educational groups).

## Medical Comorbidity

Relational problems can co-occur with virtually any general medical condition. In most cases, it can be convincingly argued that a medical condition in one member (e.g., cancer) can promulgate relational problems between this member and other members or between two other members of the family (e.g., a husband and wife who develop marital problems stemming from disagreements as to how to treat their daughter's juvenile-onset diabetes). In some cases, the relational problems may have prognostic value for the course of the medical condition and thus may become a focus of ancillary treatment.

Numerous attempts have been made to link the family constructs listed earlier (i.e., structure, communication, expression of affect, and problem solving) to the concurrent severity or future outcome of various medical conditions. For example, Koenigsberg et al. (1993) examined levels of spousal EE in relation to glucose control in diabetic patients. The number of critical comments made by the spouse during a modified Camberwell Family Interview significantly predicted glycosylated hemoglobin levels (a measure of glucose control) in the patient, the latter having been measured for the 2- to 3-month period before the interview. Levels of emotional overinvolvement among spouses were not predictive. Among youth with cystic fibrosis, family relationship quality during a family intervention task was positively associated with adherence to medical treatments. However, the problem solving did not add to the prediction of adherence above relationship quality (DeLambo et al. 2004).

Vitaliano et al. (1989) reported that spouses of Alzheimer's disease patients (with early- to middle-stage dementia) infrequently (22%) exhibited high-EE attitudes on the Five-Minute Speech Sample (a measure that may underestimate the prevalence of high-EE attitudes relative to the Camberwell Family Interview). When spouses had high EE, they reported more depression, feelings of being burdened, anger turned inward, and problems in anger control than those who had low EE. However, it was also the case that patients paired with high-EE spouses were rated by interviewers as having higher levels of functional impairment than those paired with low-EE spouses. During a prospective follow-up, the Alzheimer's disease patients with high-EE spouses showed more externalizing behavioral problems (i.e., paranoia, violence, and wandering) than those with low-EE spouses, despite the absence of differences over the follow-up in levels of cognitive decline (Vitaliano et al. 1993).

There is evidence that medical conditions often covary with communication disturbances in marital couples. For example, Hudgens (1979) found that 18 of 24 couples in which one member had chronic pain had communication disturbances. However, extensive communication between spouses where one has chronic pain also carries certain disadvantages. For example, in one study, higher levels of agreement between pain patients and their spouses in their evaluations of the severity and impact of the pain problem predicted poorer outcome for the pain disorder (Swanson and Murata 1980; Roy 1988). Chronic pain in one family member requires changes in the structure or hierarchical organization of the family, such that the well spouse must

become the primary wage earner or take over a considerable proportion of the family's decision-making (Rowat and Knafl 1985). Perhaps in couples where spouses strongly agreed they had made an accommodation to the chronic pain and therefore had reduced motivation to address this condition.

There is evidence that enhanced family problem solving may be a protective factor in the course of certain medical conditions. Using a pattern-recognition procedure, Reiss et al. (1986) examined the problem-solving interactions of families in which one member had end-stage renal disease requiring long-term hemodialysis. The authors found that high family scores on "delayed closure" during the problem-solving task—indicating that the family was "environmentally sensitive," open to new information in choosing solutions, and willing to introduce new solutions when new information was available—predicted fewer medical complications in the affected family member during a 9-month follow-up period.

While family-based interventions for medical conditions have not been sufficiently investigated, there is some evidence of their utility, particularly for the treatment of chronic childhood diseases (Campbell and Patterson 1995) where families are faced with numerous challenges in promoting health and adjusting to often complex medical regimens. Family-based psychoeducational interventions in the treatment of sickle cell disease (Kaslow et al. 2000) have resulted in greater disease knowledge among participating families when compared to treatment as usual. In a clinical trial, behavior family systems therapy with adolescents with insulin-dependent diabetes mellitus resulted in lower diabetes-specific family conflict and improvements in the parent–child relationship when compared to treatment as usual and to an educational support group (Wysocki et al. 2000)

It is clear that chronic and progressive medical illness co-occurs with a host of relational difficulties that may in some cases bode poorly for the outcome of the medical condition. In most instances, these relational disturbances seem to arise in reaction to the medical condition and are not apparently causally related to the disorder itself. Family or marital intervention in medical conditions may, however, reduce the tension in the household and the level of burden and psychosocial stress experienced by the caretaking family member(s), which could in turn provide a more protective environment for the ill family member.

## Case Example

The following case description illustrates one manifestation of relational problem. The case is conceptualized with regard to the relational constructs reviewed above, including structure, communication, expression of affect, and problem solving. A typical treatment strategy is then briefly presented.

### Clinical Vignette

Mr. A, a 26-year-old man employed as an air conditioning mechanic, was referred by a local marital therapist with the recommendation of individual therapy for anxiety and adjustment disorder. He arrived 10 minutes early for his session and entered the therapist's office with an air of anxiety and deference to the therapist's authority. He immediately leaped into his personal story, almost before the therapist could sit down. He and his wife of some 15 months had just had their first child, a son, born 3 weeks ago. In addition, the couple had moved to the suburban area only 6 months ago, and the move had taken them from a city apartment near the wife's parents to a suburban single-family house located near his parents. The problem, according to Mr. A, was his wife's overattachment to her parents and her related dislike of his parents, which spilled over into resentment toward him. This disturbance had led Mr. A to be distracted and less efficient at work. His boss, who had paternal concern toward him, noticed his upset and suggested that he seek counseling. Mr. A had gone to a marital therapist, who told him he could do nothing because the wife refused to attend marital sessions. Mr. A indicated that his wife would not see the present therapist either. The therapist asked Mr. A to talk to his wife about the current therapy and ask her if the therapist, in the effort to help Mr. A, could telephone her. The wife agreed to a telephone call and, subsequent to the call, was willing to come to the therapist's office for an individual session.

She arrived for her appointment, accompanied by Mr. A, who was holding their 4-week-old son, who appeared well-clothed and content. The wife's story was consistent with that of her husband's but quite different in emphasis and focus. She indicated that her husband's loyalty and involvement with his parents, especially his mother, had come to a head with the birth of their son. The mother-in-law had "invaded" her hospital room the day after the son's birth and insisted that Ms. A come directly from the hospital after discharge to her house with the newborn child and stay with her. Although Ms. A had difficulty opposing her mother-in-law, she stated that she was going to their own home and that her own mother would be with them for a couple of days. After receiving that message, the mother-in-law instantly became quiet and abrupt. Indeed, Ms. A felt that from that time on, Mr. A, influenced by the mother, had also become aloof and abrupt with her.

**Diagnostic Evaluation**

Currently, Mr. A exhibits the following diagnoses using the multiaxial system:

| | |
|---|---|
| Axis I | 309.24 Adjustment Disorder with Anxiety |
| | V61.1 Partner Relational Problem |
| Axis II | 799.90 Diagnosis Deferred |
| Axis III | None |
| Axis IV | Recent move to new neighborhood; birth of child |
| Axis V | GAF = 60 |

Mr. A's symptoms of anxiety and agitation in the last few months were clearly related temporally to the difficulties with his wife and their families of origin and possibly exacerbated by the birth of his son. Currently the patterns of interaction within the relationship are impaired and the relational unit has become increasingly distressed and dysfunctional. In addition to Mr. A's distress, Ms. A has been isolated and experienced depressed mood after the birth of her child. Thus, the most efficient approach to the individual difficulties lies in an evaluation of the family situation.

Mr. A clearly has a partner relational problem. In terms of the family relational constructs enunciated in this chapter, the situation can be described as follows. In terms of family structure, there are diffuse and nonfunctional boundaries between the young couple and the families of origin. Mr. A and Ms. A. are both heavily involved with

*(continues)*

Clinical Vignette *continued*

their families of origin, possibly to the neglect of their marital relationship. In particular, Mr. A's pattern of communication with his mother and related lack of intimacy with his wife is quite disturbing to Ms. A. In terms of communication, interactions between husband and wife are characterized by periods of silence and then bursts of verbal exchange characterized by suspicion and accusation, especially about their families of origin. Both parties feel aggrieved and each feels victimized by the other's parents.

In terms of expression of affect, the interactions between the two are characterized by negative emotions of anger, sadness, and mutual withdrawal. Very little positive affect is expressed. In terms of problem solving, few attempts are made to resolve the difficulties, and daily issues become not occasions for normal problem resolution but rather, opportunities for mutual recrimination. For example, Mr. A recently decided that he did not have the time to drop off their annual tax return to the accountant, so he took the returns in an unsealed envelope to his mother to deliver. The wife was enraged at this manner of delivering their private financial accounts and once again accused him of being too close to his parents. This "lack" of problem-solving ability is "situation specific," however, as both husband and wife can effectively problem solve in other settings (e.g., work).

## Treatment

Treatment began with further individual meetings with both spouses. These meetings focused on understanding the history of the relationship, the nature of interactions and expectations within each of their families of origin, and exploration of their individual goals. Conjoint sessions with husband and wife then focused on their relationship. The tasks of therapy can be understood in terms of the previously discussed constructs. First, in terms of structure, the partners needed to develop clearer boundaries within and around the relationship. The therapist repeatedly pointed out how both partners had brought with them, from their families of origin, certain expectations for family relationships. As these expectations became clearer to both partners, the therapy shifted to helping the partners examine their relationship and develop clearer boundaries between the husband/wife subsystem and their respective parents. Second, in terms of communication, listening skills were practiced by each, as the other partner explained his/her expectations and hopes in the relationship. The partners were taught specific communication skills, including giving and receiving positive and negative feedback and making requests for behavior change. Homework assignments between sessions were used to practice and generalize these skills.

In terms of affect expression, improvements in communicating led to decreases in negative exchanges. In addition, partners were encouraged to review the positive aspects in each which had initially brought them into the relationship and, through homework, to practice noticing and commenting on positive aspects of each other's behavior. Finally, problem-solving skills were taught and practiced in and out of sessions. As the couple tried to establish clearer boundaries within and around the relationship, numerous opportunities arose to practice solving problems related to their families of origin.

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# TREATMENTS

## *Organization and Economics of Mental Health Treatment*

## ***Section VII***

## ***Section VIII***

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CHAPTER

# 86 Organization and Economics of Mental Health Treatment

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## Introduction

Psychiatrists and other mental health professionals require an understanding of the organization and financing of care. The structure and funding of mental health care continues to change sometimes predictably but many times unexpectedly. For instance, at the same time that federal, state, and local budgets are strained by health care costs the largest expansion in nearly four decades in the federally funded Medicare program, the MMA (Part D) was approved by Congress in December 2003 (Huskamp 2005). Experiments with expansion of benefits such as the Federal Employees Health Benefit Program's implementation of parity for mental health and substance abuse treatment (Azrin et al. 2007, Goldman et al. 2006) as well as continued attempts at cost containment, and care management through managed care entities in both the public and private sector continue to shape psychiatric care.

New techniques for reforming and improving the care of people with psychiatric disorders require knowledge and skills well beyond basic clinical training. At the same time, as the rate of treatment of mental disorders appears to be increasing from 20.3% between 1990 and 1992 to 32.9% between 2001 and 2003 (Kessler et al. 2005) concerns about access and appropriateness of treatment remain (New Freedom Commission on Mental Health 2003). Psychosocial interventions which provide some of the greatest hope for recovery for people with the most disabling disorders are often the most difficult to access, deliver, and fund within the present structure of the mental health care system.

Astrachan (1980) commented on this issue more than two decades ago, noting that "the future of health care organizations lies primarily in their members' clinical competency and commitment to excellent practice, but is also dependent on their knowledge of such administrative tasks as planning and budgeting, and their management of the physical plant and its employees." Yet the developments in recent years have made these issues even more pivotal than Astrachan anticipated. Economic trends have led to a more significant "corporate presence" in health care, and psychiatry is no exception. Judgments about care of patients and treatment options must consider the cost and efficacy of care, both in the short term and in the course of illness.

The dominant approach to financing health care in the US is private insurance. This is a recent development compared with the long history of mental health care. Since its origins in a single plan at Baylor Hospital in 1929, developed to serve teachers at the University of Texas, private insurance coverage has grown dramatically to become the major financing approach for health care in the US. Fee-for-service reimbursement for physicians and hospitals has been the prevalent payment approach. As this chapter will indicate, these strategies are changing rapidly. Regulation of insurance coverage has increased and will continue to evolve as health care is reformed. Providers are joining together or being organized in groups to compete for contracts based on specialty expertise, price, and efficiency. Hospitals and indeed other services are increasingly owned and influenced by investors. The advent of third-party reviewers and "gatekeepers" of care further complicates the organization and financing of care. Finally, payers and patients search for arrangements to increase quality and decrease costs, leading to continual competition among purchasers and providers. In this environment, the psychiatrist must be aware of financing, payment, and organizational issues to survive and to provide quality care. Current trends also imply that psychiatrists will function less as solo practitioners but more as diagnosticians and care coordinators as well as caregivers.

Historical and political factors have also shaped the evolution of the modern mental health system. To appreciate

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the impact and effect of these factors, some historical review is essential. An understanding of the dynamics and tensions that continue to shape how care is provided is an important complement to clinical skills and an appreciation of organizational and financing factors.

## Historical Trends and Forces in Mental Health

Although theories and practices in mental health care can be traced back to thousands of years, historical trends with clear relevance for today can be found starting in the 18th and 19th centuries. As with many other aspects of culture, European influences are generally thought to have had the most impact on the US practices and have certainly been documented best.

### Important European Influences

Most descriptions of European mental health practices that influenced care in Colonial America focus on the philosophy of moral treatment articulated by Philippe Pinel in France and Samuel Tuke in England. Moral treatment rested on a belief that mental illness resulted in large measure from environmental influences and that it was curable through humane care in an orderly, calm, and supportive milieu. One of the most powerful images of mental health reform is of Pinel removing the chains from the insane in 17th century France. Tuke was a founder of the York Retreat in York, England, and wrote of this experience in his 1813 work, *Description of the Retreat.* The York Retreat, a Quaker charitable institution, was established in the moral treatment philosophy as a facility where the mentally ill could be removed from the stresses and strains that were thought to cause mental illness and receive support and instruction in a complete milieu of supportive treatment.

It is clear that Pinel's treatment philosophy and the concept of the retreat or asylum had a significant effect in America. Such facilities as the Pennsylvania Hospital (1751), McLean Hospital in Boston (1818), and the Hartford Retreat (1844) were established in this tradition. In fact, the American Psychiatric Association had its roots in this tradition, being formed in 1844 as the Association of Medical Superintendents of American Institutions for the Insane.

These highlights of professional leadership in mental health care must be viewed in the context of the political and social influences on mental health care. How did the cruel custodial facilities develop that required the heroic reform of Pinel, and what patterns of community neglect required the creation of asylums? How did these trends influence the course of the US mental health care well into the 20th century? Foucault (1965) has chronicled these developments and shown that the treatment of the mentally ill in Europe was dominated by social trends and public opinion. For example, as leprosy virtually disappeared in Europe the well endowed charitable institutions found themselves without a population to serve. Many leprosariums, with their tradition of serving a feared and alienated population turned to providing asylum for the mentally ill. Thus, at their inception many facilities for people with mental illness were already associated with negative attributions of contagion and the need to isolate the mentally ill from the rest of society not only for the person's benefit but to protect others.

Other less positive European traditions from this era foreshadow troubling current US concerns and problems as well. Another pattern of "care" in Europe was a form of banishment—the ship of fools. Captains of these vessels would accept deranged persons for a fee and ferry them about the waterways of Europe, sometimes to be discharged in an isolated city, sometimes consigned to permanent life on the ship, and usually to be the object of amusement and ridicule when such a ship with its strange cargo came to port. These traditions helped form the fear and misunderstanding about mental illness and its care that still persist as a stigma that may keep sufferers from seeking help.

An important English tradition also formed a foundation element for the US patterns of care. This was the evolution of the "Poor Laws," the common law guarantee of relief for the unfortunate. The notion of relief or general welfare payments, although clearly humanitarian, would come to have several other effects. For one, just as in the unfortunate US experience with deinstitutionalization hundreds of years later, this form of "outside relief" would make other forms of care somewhat less necessary, because after all "the mentally ill were getting some form of help." The concept of relief, when framed as "welfare" in the US political context, would create further image barriers for the mentally ill. From the "fear image" derived from care in the leprosariums to the "fool image" of the ship of fools to the "incompetence image" of welfare, the mentally ill were acquiring a heavy burden that would still have an impact in 21st century America.

This background also puts the work of reformers in perspective. Pinel and Tuke—and later reformers in America—were on the one hand heroic. The conditions they sought to change, whether inside confinement or outside abandonment, were rooted deep in political and social tradition. Making change in mental health programs was then, as now, a difficult proposition. The work of Pinel and Tuke was also the product of new political values being formed in the era of the American and French revolutions. The values of moral treatment were closely linked to, and indeed drew from, the deeper values that led to these broad cultural changes. This is a final lesson in reform from the European tradition—that clinical reform efforts are linked to contemporary social and political reforms. Patterns of care do not exist in isolation. Understanding these linkages, particularly as they have evolved in the US, is essential to understanding how patterns of care have developed and continue to evolve. These influences on mental health care are summarized in Table 86–1.

**Table 86–1 Influences on the Early Evolution of Mental Health Care**

- Unused custodial facilities (serving feared populations)
- Community neglect
- "Ship of fools" approach (stigmatization of treatment population)
- Guarantee of relief of the unfortunate (someone else assumed the caretaker role)
- Linkage of clinical reform to social and political reforms

### Early Developments in Mental Health in the US

The trends and themes of mental health care in the US developed from these European roots. Before the moral treatment

era, there was little organized care. Mentally ill individuals were the responsibility of their family or village. Before the industrial revolution, in a time when manual labor was the order of the day, many individuals survived without any care other than the therapy of hard work. The predominant early "mental health service" that developed in the early 1800s was the almshouse, a kind of reform designed to provide some care, albeit undifferentiated care. As might be expected, the mentally ill did not fare well in such settings, although they constituted a large proportion of those placed in such settings.

The moral treatment era brought the first in a series of largely unsuccessful reform efforts that would characterize the US mental health policy. The early asylums, such as those at Philadelphia, Boston, and Hartford, were philanthropic institutions. During the mid-1800s, the impulse was to establish asylums as a governmental responsibility. Grob (1966) has chronicled this history in depth, focusing on the history of the Worcester (Massachusetts) State Hospital, established in 1830, as the first public asylum in that state. The founding of the hospital was clearly associated with the kind of charitable and humane impulses that derived from the leadership of Tuke and Pinel and recognized the failure of both outside relief and the almshouses to meet the specialized needs of mentally ill individuals. The founding concept was clearly that a kind of social and rehabilitative acute care, in a serene setting, would help people recover. The early records suggest that the hospital was in fact successful. Many patients were discharged, and few in the earliest days stayed for purely custodial care.

## The Growth of Asylums

The early successes of asylums like Worcester, coupled with growing public awareness of the conditions in the almshouses and the social reform impulses of the Jacksonian era, led to a boom in the construction of state hospitals. The catalyst was an extraordinary advocate named Dorothea Dix, a retired Boston schoolteacher who made improving the lot of the mentally ill her second career. During this period, she visited every state legislature east of the Rocky Mountains and succeeded in convincing most to construct a state hospital. Buoyed by this success, she lobbied Congress to enact land grant legislation that would allow the federal government to grant land to each state; the land was to be sold and the proceeds used to establish hospitals. In a foreshadowing of the federal government's role vis-à-vis the mentally ill, the legislation was passed by Congress in 1854 but promptly vetoed by President Pierce, who saw the proposal as an unacceptable responsibility for the federal government to assume.

The moral treatment era probably reached its zenith with the founding of the Association of Medical Superintendents in 1844 and the passage of Dix's legislation 10 years later. This era's decline may also be marked by Pierce's action in vetoing further reform. One can learn much from this period that is relevant today. Just as mental health reforms occurred in the Europe of the French revolution (and as Foucault (1965) has described it, "the age of reason"), there was a connection between general social concern and mental health reform. A new treatment philosophy was articulated that fit with the zeitgeist of the times and was comprehensible to politicians. As Morrissey and Goldman (1984) have shown in a provocative review of mental health reform in America, the new approach was even associated with a particular kind of treatment facility.

However, the seeds of later failure were already embedded in these dynamics, for the tone of political and social concern changed away from humanitarian impulses, and the country was preoccupied with broader concern in the last half of the 19th century. Thus, the social consciousness that had proved a hospitable basis for moral treatment eroded substantially during the industrial revolution. There were at least two major problems embedded within the mental health reforms as well. First, as Morrissey and Goldman (1984) pointed out, moral treatment conceived of mental illness as essentially an acute problem and therefore positioned the hospital as a short-term treatment facility. In the early days, this assumption worked, probably in large measure owing to the enthusiasm and dedication of staff. Then as now, however, a proportion of the mentally ill faced a long-term problem that was not amenable to short-term cure. It was inevitable that longer-term "chronic" problems began to gradually overtake the asylums, creating space, staffing, and resource problems and eroding the mission of the hospitals. This cycle of reform and neglect is outlined in Table 86–2.

**Table 86–2 Cycles of "Reform"**

- Mentally ill populations were neglected
- Neglect was noted, with calls for reform
- "Reform" occurred, but underlying issues ignored (mental illness is chronic, long-term but facilities focused on acute treatment)
- Systems of care were overwhelmed by increasing numbers of very ill patients
- Care becomes custodial rather than recovery focused (neglect)

## The Erosion of Community Responsibility

This problem was exacerbated by another "reform" effort. In almost all the early public asylums, the construction was underwritten by the state legislature, which also provided a small appropriation for operations—a kind of "seed money." These funds were not intended to be adequate for the full operation of the hospitals; because mental health problems occurred in most communities and the almshouses had been a local responsibility, communities were to be billed for the costs of caring for their indigent citizens. At one level, this represented the type of intergovernmental tension that has seemed to plague mental health care ever since. Yet it was a productive tension, because it created a disincentive for the long-term institutionalization of disabled persons; but the arrangement was a problem for the hospitals. Collecting funds from all the towns was inconvenient, and the rates tended to lag behind costs, especially during a period of rapid inflation.

These problems led to the well-meaning State Care Acts, enacted in many states in the second half of the 19th century to solve this problem. Because the institutions were competently run and were essentially a state responsibility, and because the local fees were inconvenient, having the state simply assume financial responsibility was an obvious solution. In Ohio, for example, the operation of asylums is mentioned in the state constitution as a fundamental state responsibility.

This wave of legislation created an obvious problem. Addressing the inconvenience of local responsibility by virtually wiping it out, the State Care Acts eliminated any incentive for local care and created a particular pressure for the institutionalization of long-term disabled individuals. The short-term orientation of the hospitals was subtly erased, and the ability of disabled persons to persist by doing manual labor in an agrarian society was also permanently altered by the onset of the industrial revolution. As a consequence, the history of mental health care in the US in the latter part of the 19th century was disastrous.

This era involved a confluence of negative forces that eroded the moral treatment reforms. The perverse financial incentives created by the State Care Acts led to increased rates of institutionalization. These pressures, combined with the "silting in" effects of disabled patients who could not be discharged, sent the levels of hospitalization soaring. Grob (1966) analyzed the forces that contributed to the decline of moral treatment, using Worcester State Hospital as a case study. Additionally, he noted that the increasing size of the institution created a self-reinforcing dynamic of regimentation and efficiency, which reduced quality of care and increased the custodial nature of the hospital. Grob also found that an evolution in the professional role of psychiatry also contributed to the decline of the hospital. In a perverse way, the profession's focus on psychiatry as a "scientific discipline" estranged the leadership of the hospital from the civic and volunteer leaders who had contributed to its early development. In addition, an emphasis on somatic treatments produced empty results, because they had little to offer at the time and tended to undermine the optimism and egalitarian values that moral treatment had contributed to hospitals.

Cultural and class factors also contributed to a changed and problem role for state hospitals during this period. Not only did the industrial revolution put a premium on skilled labor and begin to hasten the decline of communal, agrarian lifestyles (which were much more suited to sustaining the mentally ill), but the demands of the industrial workplace played off the increased levels of immigration to create new tensions. The role of the hospitals had been subtly refined from "retreat" and recovery to custody and management. In this context, they seemed an appropriate place to detain those immigrants whose behavior was strange and who did not fit into the requirements of the developing modern society. The hospitals inevitably deteriorated into overcrowded custodial institutions, housing the disabled and other misfits and providing only a veneer of treatment.

## The Mental Hygiene Movement

Fortunately, as Morrissey and Goldman (1984) pointed out, the emerging pattern of the US mental health policy shows that cycles of neglect do lead to cycles of reform. Although the professional leadership of the time was crucial in the next wave of reform, especially in the "mental hygiene" approach of Adolph Meyer, it was once again a partnership between citizens and professionals that stimulated change. In this case, the citizen leader was Clifford Beers (1908) whose book *A Mind That Found Itself* focused national attention on the deterioration of the hospitals but also showed the possibilities of recovery. Beers had been hospitalized at both the Hartford Retreat and the Connecticut Asylum for a period of several years and described graphically the degradation and horrors of this experience. He also detailed his positive experiences with recovery, speaking perhaps to the American fascination with the "self-made man" but connecting powerfully to the enthusiasm and new theories of mental hygiene.

As Morrissey and Goldman (1984) noted, this cycle of reform was linked to both a new model or theory and a preference for particular facilities—the psychopathic hospital and the child guidance clinic. Like the moral treatment approach, both facilities and indeed the mental hygiene movement were eventually founded on the same rocks of the intractability of long-term mental illness. The mental hygiene approach—like moral treatment—emphasized brief special treatment with an emphasis on returning to normal functioning. No concept of long-term care had yet developed. The approach was also linked to the dominant cultural values of the time, emphasizing science, order, and classification. Thus, the psychopathic hospital was affiliated with academia and focused on applying diagnostic and treatment expertise to mental illness.

The first prominent facilities included Pavilion F, opened in Albany in 1902, and the Boston Psychopathic Hospital, opened in 1912. The child guidance clinic emphasized similar themes but clearly also stressed the value of early, clinically based intervention as a preventive strategy. Child guidance clinics were developed in a number of cities during the same period. The movement also led to an emphasis on professionalism that extended beyond psychiatry, with the founding of the first school for psychiatric social work at Smith College in 1928.

Like the moral treatment era, the mental hygiene reforms drew on emerging cultural and political developments, included a core treatment philosophy, and emphasized new types of treatment facilities. However, this cycle of reform also emphasized acute care and therefore failed to meet the challenge of the long-term major mental illnesses. In fact, by this emphasis, the approach did not have much impact on the state hospitals, which had essentially become long-term care facilities. Mental hygiene, therefore, did not succeed as comprehensive reform.

## The World Wars and Psychiatry

Mental health issues emerging from both World War I and especially World War II had a dramatic effect on policy. Working with traumatized soldiers in World War I, Thomas Salmon described the "shell shock" syndrome. Drawing from the mental hygiene theory of early intervention, brief treatment that focused largely on separating the soldier from stress—although not removing him too far from the front-lines and maintaining high expectations of early recovery and return to battle—proved successful. Thus, crisis intervention methods were literally developed in the heat of battle.

These same methods were used and further refined during World War II. In addition, however, events in World War II thrust mental health issues into a more prominent national light. A high proportion of those men found unfit to serve in the military were screened out because of mental illness—almost two million individuals. Later, questions were raised about the accuracy and adequacy of screening (Deutsch 1949), but the number of individuals rejected for service was large. In addition, about 40% of the military personnel dismissed from active duty as unfit to serve were

discharged because of mental illness. These extraordinary rates of illness came to public and policymakers' attention at precisely the time when the federal government was poised to affect mental health policy and as the country was poised to enter a period of prosperity and of a relative focus on domestic affairs. As a result, Congress passed the Mental Health Act in 1946, creating the National Institute of Mental Health (NIMH) as a focal point for research, professional training, and policy development.

## Mental Health Policy in Postwar America

The pace and complexity of change in health and mental health care since World War II have been dizzying. Because we are closer to this period, it may be more difficult to see it clearly. Certainly, opinions still vary on the dynamics and nature of many developments, starting with deinstitutionalization (viewed by some as necessary social progress and by others as abandonment). It is wise to recall some of the persistent trends in the US mental health policy that have their roots in European and Colonial traditions, for these trends are still shaping policy and patterns of care in ways that are not immediately evident to the casual observer.

One fundamental and recurring tension is between mental illness and "madness" or between clinical and sociological understandings. Viewed from a clinical perspective, the creation of asylums in the European reformation or in 19th century America was simply the development of an improved treatment system. Yet, as Foucault (1965) and Grob (1966) have shown, these institutions served other purposes. The early asylums filled the niche that had been vacated by leprosy, with certain consequences in terms of stigmatizing the mentally ill. America's asylums were not able to hold their desired quality and acute care orientation for more than a decade or two and quickly became places where the wayward and others unable to play a productive role in the industrial revolution were "stored." Indeed, this trend was accelerated, as (Grob 1983) shown, by the unintended actions of the medical superintendents and their loss of contact with citizen leaders. Thus, an awareness of the balance between clinical requirements and initiatives and their social context and meaning is essential in viewing modern developments.

A second problem trend has been to base reform on an incomplete or unrealistic view of mental illness and therefore its treatment requirements. This is a central point made by Morrissey and Goldman. They emphasized that the first two "cycles of reform" in America (the asylum and the mental hygiene movement) inaccurately conceived of most serious mental illness as acute or temporary, leading to treatment strategies that were ultimately doomed to failure. This limited view would vex another reform era yet to come—the community mental health movement of the 1960s and 1970s.

Finally, the role of the public sector in the US mental health care has been significant; the tensions between states and the federal government, and increasingly between the public and the private sectors, has never been good for patients. This pattern was established with Pierce's veto of the land grant hospital construction legislation in 1854, ceding responsibility to the states, and with the State Care Acts that weakened local responsibility for the mentally ill. Whereas these actions clearly set in place a dynamic of primary state responsibility, the weakened local role encouraged the creation of custodial institutions as a mode of service and did not resolve the federal–state tensions that are so much a part of the US political life. With the establishment of the NIMH in 1946, the federal government reasserted its interests. The Great Society programs that were to follow, in an era of federal activism, would muddy this picture even more.

## The 1950s: New Treatment Technology, Federal Activism, and the Civil Rights Movement

The decade of the 1950s served as an incubator for major changes. The impact of these changes were later felt in a more substantial fashion. Three such developments listed in Table 86–3, were most significant: the introduction of psychoactive medications, an emerging activism on the part of the new federal mental health bureaucracy, and the growth of the civil rights movement and its use of the federal courts.

**Table 86–3 The CMHC Reform Movement**

- Introduction of psychoactive medications
- Emerging federal activism
- Growth of civil rights

### Chlorpromazine and the State Hospitals

Chlorpromazine was first used in the state hospitals in the early 1950s, with several significant effects. The first effect was an immediate clinical impact. The census of the state hospitals peaked at a significant 550,000 individuals in 1954 and has declined every year since then. This decline in the 1950s was clearly related to the impact of chlorpromazine, which provided enough relief to enable the discharge of many patients. The second impact of this new technology was a renewed optimism about mental health treatment—the same sort of optimism that had characterized the moral treatment and mental hygiene eras.

### Civil Rights: Social Change and the Role of the Courts

The emergence of the civil rights movement was marked by the *Brown v. Board of Education* lawsuit filed in Topeka, Kansas, in 1954. Several features of this movement affected mental health reforms in a substantial way. First, the values of human rights served as a foundation for reformers who saw a better life for institutionalized mentally ill individuals. Yet again, emerging community values affected developments in mental health. The second feature of the civil rights movement related to mental health was just as critical—the use of the federal courts to solve a problem that legislatures and the general public were not yet ready to address. Although federal court litigation in mental health did not begin in earnest for another two decades, the seeds of change had been planted.

### An Activist Federal Government

After the veto of Dorothea Dix's legislation by President Pierce a century earlier, the federal government had retreated

from any substantial role in mental health for decades, but the national experience during the two world wars and the establishment of the NIMH marked a change in this pattern. Although the leadership role in service provision clearly rested with the states, there was a mood for change marked by the trends of the 1950s. The passage of the Mental Health Study Act in 1955 marked this new activism. The legislation charged the Joint Commission on Mental Illness and Mental Health with a national study to develop and recommend policy.

## The 1960s: Transformational Change and Unintended Consequences

The National Commission issued its ambitious report, *Action for Mental Health*, in 1961. Formed in the new environment of federal activism and optimism about mental health treatment, the report proposed a broad approach to change. Its recommendations included dramatic increases in funding for mental health care, aggressive approaches to recruitment and training, an increased emphasis on acute and community care, and movement away from the custodial state hospitals. A mental health clinic to serve each population base of 50,000 persons across the country was proposed, as were expanded programs for persons with long-term mental illness.

These recommendations fell on the ears of a receptive president and Congress. President Kennedy was clearly interested in mental retardation and mental health, and these recommendations were less controversial than the changes in other areas of domestic policy that the country confronted. Optimism about treatment and community care, the need to reform the state hospitals, and the ability of the federal government to change things formed the context for reform. The result was the 1963 Community Mental Health Centers Act, with its focus on developing locally managed, and broadly focused mental health centers across the country. The legislation represented the federal government's most ambitious effort in mental health care but was seriously flawed from the outset. In a sense, the most notable success of the legislation was simply its passage, marking public support and recognition of mental health treatment. The legislation eventually led to the establishment of more than 700 centers (although about 2,600 would have been needed to cover the country) and also stimulated passage of parallel legislation and initiatives at the state level.

There were several design flaws in the community mental health center (CMHC) legislation as well. There was a "disconnect" between the growing antipathy for state hospitals and the desire for community care. The centers were to provide a wide variety of community services, but the emphasis was on acute treatment, not the kind of rehabilitation, support, and care needed by the long-term patients in hospitals. Two other aspects of the legislation heightened the separation between the poor, disabled patients of the hospitals and the new centers. First, the federal chauvinism of the time had resulted in the establishment of the CMHC program (like the antipoverty programs of the time) as a federal–local partnership, with the states only tangentially involved. As a result, the state mental health agencies (SMHAs), which ran the hospitals, were cut out of the picture with respect to the CMHC priorities and oversight. Second, the funding mechanism for the CMHC establishment was limited to construction grants and time-limited (7 years) start-up funding.

As during the moral hygiene era, a substantial federal role in funding mental health care was not politically acceptable. (Perhaps it would be more accurate to say that an explicit role in funding mental health was not acceptable, because the soon established Medicaid program eventually became the nation's single largest mental health funder.) As a result of the limited federal financing and the resulting pressure on CMHCs to establish "financial viability," the centers needed to find paying customers. This tension, coupled with the orientation toward broad mental health concerns rather than the care of the seriously mentally ill, led most centers to limit their role as providers for formerly hospitalized patients, focusing instead on other paying customers and efforts. Although probably almost all the centers cared for some formerly hospitalized patients, it was not their central concern. Coupled with the limited population coverage of the new centers, this meant that the program was in no way adequate to support the downsizing of the state hospitals that had probably been intended—and was certainly about to happen.

### Medicaid, Transinstitutionalization, and Privatization

Although the passage of the CMHC legislation is generally viewed as the major federal mental health initiative of the 1960s, it is likely that the enactment of Medicare and Medicaid was more influential, at least in terms of the numbers of patients and practitioners who were affected. Medicare (Title Eighteen of the Social Security Act) was enacted in 1966 to provide insurance to persons older than 65 years eligible for Social Security. It was amended in 1972 to provide for all those older than 65 years, with a premium mechanism to cover costs. At the same time, eligibility was extended to disabled workers and their beneficiaries as well as to patients with chronic renal disease. Medicare rapidly became the dominant insurance mechanism and therefore a major force in health financing policy.

However, Medicaid (Title Nineteen of the Social Security Act), also enacted in 1966, had a dramatic effect on seriously mentally ill individuals almost immediately. Medicaid was designed as a health insurance program for the poor and disabled, primarily covering acute care. However, Medicaid also provided financing for long-term care by coverage of nursing homes. (Both Medicare and Medicaid were thus focused in large measure on the elderly and, together with other measures, had a substantial positive effect on older Americans—a major success of the War on Poverty and Great Society programs, whereas most came to be regarded as failures.)

For the reason that its eligibility included seriously mentally ill individuals, almost all of the patients who were made destitute by their illness, Medicaid was a viable financing vehicle. Since it was largely a federally financed program (the federal share ranged from a minimum of 50% for wealthy states up to 75% for poor states), it was attractive to states. Also, because it covered nursing homes, which substituted for state hospitals for the care of many disabled patients, Medicaid set up an enormous transfer of care. The

state hospitals were increasingly out of favor and expensive, and Congress had ensured that funds from Medicaid would not cover state hospital care by prohibiting payments to "institutions for mental diseases." Indeed, this exclusion of institutions for mental diseases (IMD) prohibited Medicaid reimbursement for treatment in any facility, public or private, greater than 16 beds, serving adults of 21−64 years with a primary diagnosis of mental disease. Psychiatric treatment in general hospitals, even in large specialized psychiatric units, was funded by Medicaid. During the same period, income support–welfare programs were also dramatically expanded by Social Security Disability Income and the introduction of Supplemental Security Income for those individuals who could not qualify for disability income given their absence of a work history.

The results were as predictable as they were unintended. State hospitals proceeded to transfer patients, primarily to nursing homes but also to boarding houses and other settings, at a remarkable rate. Between 1955 and 1965, the rate of decline in the state hospital population had been a percentage point or two per year. The end-of-year census had dropped from more than 550,000 in 1955 to about 475,000 by 1965 (Kiesler and Sibulkin 1987). This decline was attributable to clinical factors (especially the use of chlorpromazine) and to changing opinions. However, the change in the following decade was dramatic, averaging about 6% per year, and led to a census of about 191,000 at the end of 1975. In many states, the state hospital census declined at a double-digit rate between 1966 and 1975. Of the various discharge options, nursing home placements were the most prominent.

This transfer of care, or transinstitutionalization, was the major factor in reducing state hospital capacity, followed by discharges to other settings financed by welfare payments. These transfers were a more potent force in reducing the state hospital population than the CMHCs. These facilities had once been thought of as the vehicle to replace state hospitals but had assumed a broader and less-focused community mental health role. Thus, long-term care and welfare proved more significant than treatment services in changing how care was delivered, repeating a pattern established in the prior century, when broader social policy affected the role of state hospitals more than did changes in clinical practice.

There were several lessons already apparent in the 1960s reform, even before the phenomenon of deinstitutionalization became apparent. Certainly, a major lesson was the extent to which shifts in financing drove policy and practice. The financing dynamics built into the CMHC program implicitly guaranteed that they would need to turn their attention away from individuals with serious and persistent mental illness to survive. The sizable federal participation in Medicaid led inevitably to a transfer of care responsibilities from the states to the federal government, yet neither of these vehicles did much to build the integrated systems of care needed to adequately support disabled individuals with serious mental illness. As Morrissey and Goldman (1984) pointed out, this new cycle of reform, like both the moral treatment and mental hygiene reforms, was implicitly built on an acute care model that was a poor fit for the long-term, multifaceted needs of these patients.

Medicaid also had a dramatic effect at the "front door" of the state hospitals by financing hospital care for psychiatric patients in general hospitals, both in "scatter beds" (medical–surgical beds occupied by patients with psychiatric diagnoses) and in distinct psychiatric units. The availability of Medicaid reimbursement aided a dramatic expansion of general hospitals as a primary locus of acute psychiatric care. Between 1965 and 1980, the volume of psychiatric admissions to these units increased from about 700,000 annually to approximately 1700,000 annually (Kiesler and Sibulkin 1987). Through the 1980s and 1990s the Medicaid reimbursement, available to general hospitals but not to IMDs, continued to fuel expansion of psychiatric care in general hospitals with discharges from these units growing from 1.4 million in 1988 to 1.9 million in 1994 (Mechanic 1989). Conversely, the Medicaid "IMD exclusion" helped further diminish the role of state hospitals in acute care. State hospitals provided 63% of 24-hour hospital and residential treatment episodes in 1955 but only 10% by 1998 (Manderscheid et al. 2000). A recent study shows this trend has continued through 2002 (Watanabe-Galloway and Zhang 2007). From 1995−2002, in the US, the discharge rates from general hospitals for people with severe mental illness increased by 34% from 29.1 discharges per 10,000 adult population in 1995 to 39.2 discharges per 10,000 adults in 2002. Rates increased mainly for blacks, young males, and for the northeast and south regions. Rate increases were also highest for individuals covered by private insurance and in proprietary hospitals. Government payers while still representing the largest funder at 60.6% in 2002 had fallen from 70.3% in 1995.

## The Erosion of State Systems of Care

The advent of Medicare and especially Medicaid thus changed the face of mental health care dramatically. After World War II, mental health care was dominated by the state hospitals and thus by the states. Within the next generation, this change was spectacular. By about 1970, there were more episodes of psychiatric care in general hospitals than in state hospitals, and at about this time, the number of long-term mentally ill individuals in nursing homes became greater than the number of these patients in the state hospitals. Both of these trends were due more to the financing incentives in Medicaid than to the community mental health movement and the CMHCs. Both the CMHC legislation and Medicaid had undercut the SMHAs by providing funding streams that bypassed these agencies. The CMHC grants went directly to local providers with limited SMHA influence, and Medicaid was administered by a designated state agency (usually the welfare department, given its locus as a program for the poor). In addition, both programs provided funds to private for-profit and not-for-profit entities rather than to the public sector. This eventually created powerful; alternative provider forces in mental health to counter whatever political power rested with the SMHAs. The states had also lost potency because their major focus had been to run the discredited state hospitals; they were essentially cut out of the new mental health business in CMHCs and Medicaid-financed services. This change toward community-based care and the accompanying challenges are described in Table 86–4.

**Table 86–4 Challenges Faced by Systems of Care During the CMHC Reform Movement**

- Patients from state hospitals not moved to independent living, but to nursing homes, boarding homes (transinstitutionalization)
- CMHCs not prepared for large numbers of patients with serious and persistent mental illness
- CMHCs had to provide intensive care for acute, less severely ill patients to be profitable
- Expansion of Medicaid led to expanded general psychiatric beds
- State lost authority/responsibility for patients with serious and persistent mental illness

## The 1970s: Increased Complexity, Expanded Services, Federal Indifference

By the mid-1970s, mental health care bore little resemblance to what had existed a generation before. Owing to the impact of Medicare and Medicaid, the new de facto publicly financed system was privately operated and largely outside the control of the states. The state hospitals were no longer the primary focus of either long-term or acute care. Nursing homes probably had more mental health long-term care beds than did state hospitals, although the data are not completely clear, and the number of psychiatric admissions to general hospitals was greater than to state hospitals. Hundreds of CMHCs had been created, serving a broader public and providing increased access to care. Private health insurance coverage had become much more prevalent. Whereas coverage for mental illnesses was generally far more limited than that for physical illnesses (both because of the stigma associated with mental illness and perhaps even more significantly because the state hospitals still existed as a catastrophic care option), private coverage helped expand mental health care dramatically. Access to mental health care had simply exploded, and the expansion took place in new settings. Figure 86–1 illustrates how dramatically the system changed.

The most significant change involved a dramatic expansion of care (from 1.7 million episodes in 1955 to 6.9 million in 1975, just 20 years later). The expansion occurred most significantly in the outpatient arena, in which the number of care episodes exploded from around 400,000 to almost 5,000,000, a more than tenfold increase. However, because of expanded Medicaid, Medicare, and private insurance coverage, the volume of inpatient admissions also rose from around 1,300,000 in 1955 to more than 1,600,000 in 1975, during a period generally thought to be associated with deinstitutionalization. A new mental health "system" was in fact being created, and it looked different from the old system (i.e., the state hospitals). The state hospitals, after dominating the US mental health care for more than a century, were speedily replaced as the primary locus of care. Figure 86–2

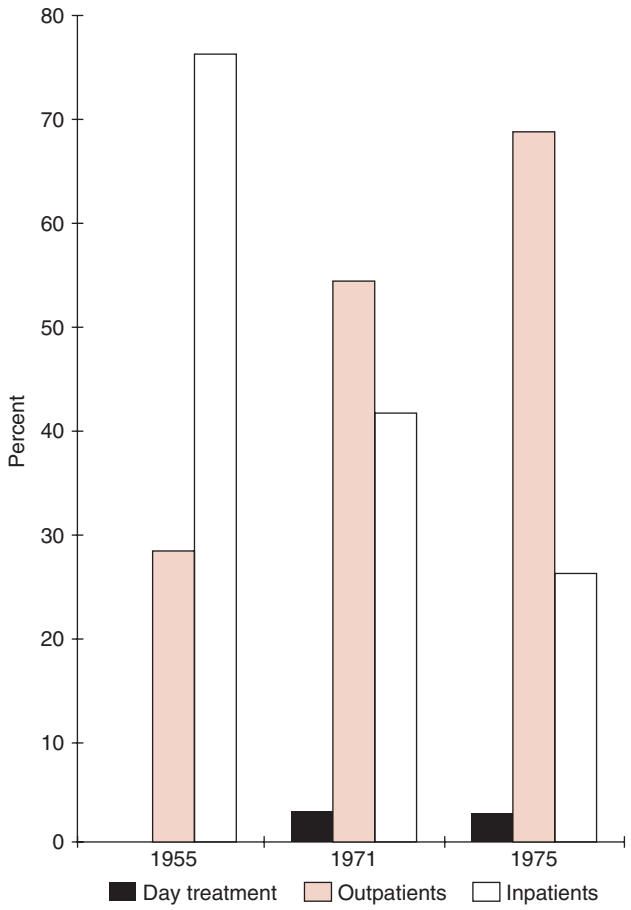



**Figure 86–1** *Episodes of mental health care by modality in the US from 1955 to 1975. (Source: Witkin (1980) Trends in Patient Care Episodes in Mental Health Facilities, 1955–1975. NIMH Statistical note 156. National Institute of Mental Health, Rockville, MD, USA.)*

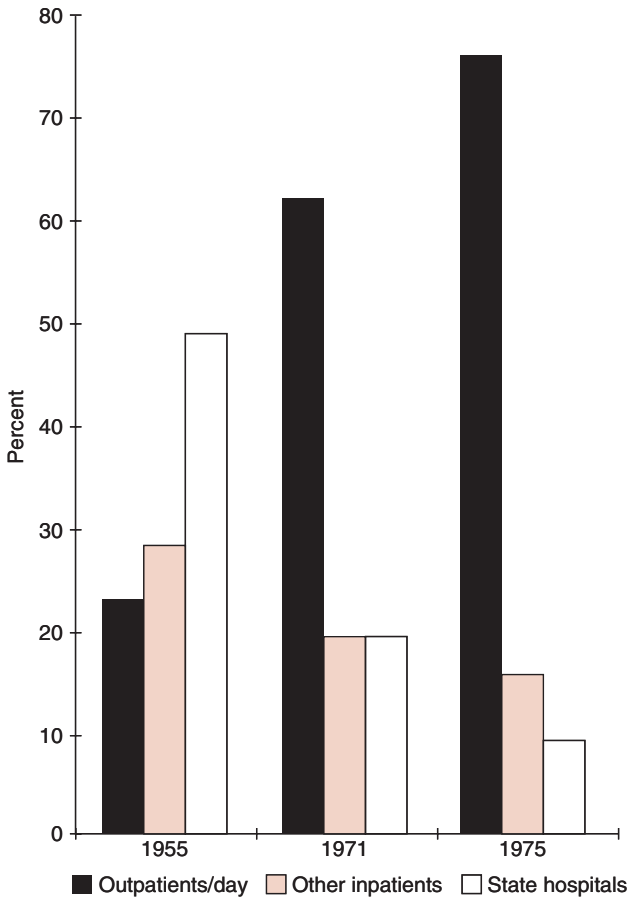



**Figure 86–2** *Episodes of mental health care by modality in the US from 1955 to 1975, showing the diminishing role of state hospitals. (Source: Witkin 1980 Trends in Patient Care Episodes in Mental Health Facilities, 1955–1975. NIMH Statistical note 156. National Institute of Mental Health, Rockville, MD, USA.)*

illustrates this development. In the 20-year period from 1955 to 1975, the proportion of all episodes of mental health care that were provided by state hospitals (whether outpatient or inpatient care) shifted dramatically from half of all episodes to less than 10%.

## State Hospitals Seen as the Problem

The conventional view of mental health policy evolution during this period ignored many of these developments. Because the state hospitals had become such a lightening rod for criticism by policymakers, partly because they had dominated the mental health landscape for so long that new developments were not apparent and partly, perhaps, because data on state hospitals were readily available when data on the new programs were not, the hospitals were still the focus of policy debates. When one examined the budgets of the SMHAs alone, the state hospitals were still a major category of expenditure. Data on the growing private sector system were not available on time, so analysis tended to focus on the state hospitals. Given that the responsibilities of the hospitals for care of patients had been dramatically reduced, their consumption of a significant percentage of all state resources seemed inappropriate. The national mental health leadership at NIMH and a growing number of articles in the professional literature reflected concern about the levels of resources tied up in the state hospitals, at a time when the balance of care had shifted to the community.

The reasons for inflated state hospital costs, noted in Table 86–5, did not seem so critical at the time given the imperative of community care, but they generally reflect developments outside the mental health field that were influencing costs. The unionization of public employees and the resultant wage increases and limited work weeks were a significant factor in increasing costs. In addition, the state hospitals had long relied on the labor of patients. This practice had evolved from a belief in the curative role of work to a managerial "necessity" to operate under-financed, custodial institutions. It was effectively curtailed by a Supreme Court decision (*Souder v. Brennan* 1973), with the result that hired staff were needed to replace the essentially free labor of patients. These external factors increased hospital costs. At the same time, increased governmental regulation designed to redress poor quality of care increased costs of the institutions. These factors, whether legitimate or not, contributed to the reformers' demands to reduce the hospitals and to continue expansion of community mental health services. In a word, the policy preference was for deinstitutionalization. That adequate community supports for the most disabled were not being put in place was not yet apparent.

**Table 86–5 Reasons for Increasing Costs of State Hospitals**

- Unionization of public employees
- Resultant wage increases
- Loss of "free" patient labor (paid staff had to be hired)
- Increased governmental regulation

At the same time, the national mental health "movement" was starting to run into problems. President Nixon was no friend of the NIMH. This may have related to his distaste for the social psychiatry approach of the NIMH leadership. NIMH Director Yolles had opposed Nixon's tough drug sentencing policies, advocating a treatment approach (Rumer 1978). In any event, Nixon fought the community mental health program through the budget process. After proposing lower funding levels in 1971, Nixon actually impounded CMHC funds in 1973 after Congress had appropriated them. As a result, the CMHC program started to slip from its original goal of 1500 centers. From 1965 to 1969, 75% of the $260 million authorized for CMHC construction was actually appropriated. From 1970 to 1973, only 15% of the $340 million authorized was actually budgeted (Bloom 1975).

## Emerging Conflicts in Mental Health Policy

The last half of the 1970s was thus a difficult and transitional period in mental health policy. Dramatic expansions of care had been achieved, with little positive impact on the most seriously mentally ill persons. The state hospitals were discredited, but no viable alternatives were widely available. Nursing homes had become the primary, largely invisible, locus of long-term care—along with other welfare-financed alternatives such as boarding homes. The CMHC and Medicaid programs had dramatically expanded access to care, but not for the most seriously mentally ill and largely outside the influence of the state governments that were responsible for the state hospitals. Given these trends, it is little surprise that a crescendo of criticism began to develop. The 1977 audit report by the General Accounting Office *(Returning the Mentally Disabled to the Community, Government Needs to Do More)* typified the new criticism.

President Carter, assuming office in 1976, was clearly more sympathetic to mental health concerns, and First Lady Rosalynn Carter made mental health her primary concern. The President's Commission on Mental Health was established in 1977 to review the nation's issues in mental health. Its 1978 report was perhaps even broader than the Action for Mental Health report published almost 20 years previously, in part because the system was much more complex and partly because the political tensions associated with new constituencies like CMHC directors made consensus much more difficult. As Mechanic (1989) has pointed out, the report was also produced in a national political environment that had changed dramatically. There was much less certainty about the appropriate role of the federal government and many more competing budget demands. The process of developing legislation based on the report was also correspondingly more difficult.

Two major activities resulted. The first did not have a happy ending. The 1980 Mental Health Systems Act was designed to build on but also redirect the CMHC program by focusing more on seriously mentally ill persons, connecting the program with state government, and emphasizing systems of care rather than facilities. President Reagan, taking office within months after the legislation was signed, proceeded to ignore and dismantle the legislation, in large measure by the conversion of the grant program to a block grant at reduced funding levels. The other major outcome of the President's Commission was less visible but eventually influential. The Department of Health and Human Services had been charged with developing a more integrated federal approach to the problems of the most seriously mentally

ill individuals. Its 1980 report, as described by Mechanic (1989) "recognized the critical importance of Medicaid, Social Security Disability Insurance, and many other federal programs, and presented an incremental approach to modifying them in a constructive way."

Many of the initiatives recommended in this report were also attacked by the Reagan administration. The most notable was the effort, eventually overturned in federal courts after intervention by legal advocates, to drop many seriously mentally ill individuals from disability insurance during the early 1980s. However, many recommendations survived this assault and were actually implemented during the same period that the Mental Health Systems Act was dismantled (Koyanagi and Goldman 1991).

Thus, whereas the momentum for federal leadership in mental health stalled with President Reagan's shelving of the Mental Health Systems Act, federal programs quietly became more relevant and helpful to seriously mentally ill individuals during the 1980s—after the debacle related to disability insurance payments was resolved. The improvements included better disability insurance coverage, targeted attention to the mentally ill homeless, and particularly the development of Medicaid programs focused on community treatment for seriously mentally ill individuals. These programs, including case management and rehabilitation options, were used by many states to expand services during the last half of the decade. However, federal leadership was also significant during the decade, an irony given the budget cuts and retrenchment of the Reagan years. The small Community Support Program (CSP) in the NIMH exercised tremendous influence on the state mental health programs through national working conferences and a focused program of planning grants and demonstration grants directed to the states. During the 1980s, the states began to recover from the federal neglect of the prior decade and take advantage of Medicaid funding and CSP ideas to retool their community care systems. The federal improvements are highlighted in Table 86–6 .

**Table 86–6 Improvements in Federal Involvement in Mental Health**

- Better disability insurance coverage
- Improved targeting of homeless patients with mental illness
- Development of Medicaid programs (case management, rehabilitation options)
- NIMH developed the Community Support Program

## The 1980s: Community Support and the Precursors of Health Care Reform

The state mental health programs had fared poorly during the prior 2 decades. The SMHAs were discredited as the operators of state hospitals, defined by community mental health advocates as the enemies of progress. In addition, the new CMHC and Medicaid initiatives of the 1960s had bypassed the SMHAs. A new mental health "nonsystem" dominated by nursing and boarding homes as well as general hospital psychiatry—all outside the effective control of the SMHAs—was now larger in scope than the programs controlled by the state agencies. Even the CMHCs, once thought of as a treatment alternative to hospitals but serving instead an entirely new group of patients, were under limited SMHA control. As the problems of this chaotic system became apparent—symbolized by the plight of the homeless mentally ill and punctuated by mass media coverage of periodical violent episodes involving mentally ill individuals—the states were the obvious target for criticism. The subtleties of the new "system" were not important in the face of these problems. The states ran the hospitals, let people out of them, and should have been doing a better job.

The changes of the 1980s allowed the states to regroup and recover from the feverish pitch of change. Although the Reagan new federalism approach had resulted in funding cuts, it had restored state control. For example, in the 1980 Reagan budget, the CMHC direct grants to centers were consolidated into a block grant, reduced by about 35%, and placed under state authority. In general, the states used these funds to focus on seriously mentally ill adults and children, using the new CSP model.

The impact of the CSP approach is difficult to overstate. Growing out of the Carter commission, it involved a focused approach to the multifaceted needs of seriously mentally ill individuals in communities. As Morrissey and Goldman (1984) have pointed out, this "fourth era of reform" differed in a fundamental way from the moral treatment, mental hygiene, and community mental health concepts. For the first time, serious mental illness was not conceived of as a fundamentally acute problem but was defined as a long-term and episodic condition requiring multifaceted supports. As a consequence, the service approach was not focused on a particular institution (e.g., the asylum, psychopathic hospital, or mental health center). Rather, consistent with the concepts of President Carter's legislation, a multimodal system of care was necessary, incorporating both treatment services and the practical supports (such as housing, income supports) needed by people with disabilities as well as illness. The CSP approach defined a number of essential elements of such a system which have been included in Table 86–7.

**Table 86–7 Essential Functions of Community Support Systems**

- Identification of the target population and outreach to offer appropriate services to those willing to participate
- Assistance in applying for entitlements
- Crisis stabilization services in the least restrictive possible setting, with hospitalization available when other options are insufficient
- Psychosocial rehabilitation services, including but not limited to:
- Goal-oriented rehabilitation evaluation
- Training in community living skills, in the natural setting where possible
- Opportunities to improve employability
- Appropriate living arrangements in an atmosphere that encourages functional improvement
- Opportunities to develop social skills, interests, and leisure time activities
- Supportive services of indefinite duration, including supportive living and working arrangements, and other such services for as long as they are needed
- Medical and mental health care
- Backup support to families, friends, and community members
- Involvement of concerned community members in planning or offering housing or working activities
- Protection of the person's rights, both in hospitals and in the community
- Case management, to ensure continuous availability of appropriate forms of assistance

*Source:* NIMH (1997) Comprehensive Community Support Systems for SMD Adults: Definitions, Components, and Guiding Principles. NIMH, Rockville, MD, USA.

These concepts were promoted by the small CSP unit within the NIMH in a fervent, focused manner. The combination of small state planning grants (carefully defined to promote change) and demonstration projects was linked to the national CSP meetings in an effective change strategy. There were several remarkable things about the effort. First, the notion of aggressive federal leadership during the Reagan years is something of an anomaly. Probably, the program was too small—and perhaps too effectively protected by Congress—to have been a serious target. Second, the funding levels involved were completely insignificant compared with the hundreds of millions spent on CMHCs or the billions involved in Medicaid. The annual CSP appropriations were in the range of $10 million for the entire program. However, the funds were effectively used to "leverage" other resources, including state budgets, block grant funds, and the new Medicaid programs. The change in SMHA budget portfolios during the 1980s is the clearest example as illustrated in Figure 86–3.

During this decade, the SMHA budgets were essentially level when viewed in constant dollars. In other words, budget increases were essentially equal to inflation. Yet, during the decade, there was a steady shift in investments from state hospitals to community programs. The new community resources were often used to "match" Medicaid dollars and linked with block grant revenues and local funds. As a result, there was a dramatic expansion of CSP-type services that is not apparent from examining SMHA budgets alone. Unfortunately, there are few reliable national data that demonstrate the magnitude of this shift. The best way to get a view of the evolution of services for seriously mentally ill individuals in recent years is to track the development of systems at the state level, for which more complete data are available.

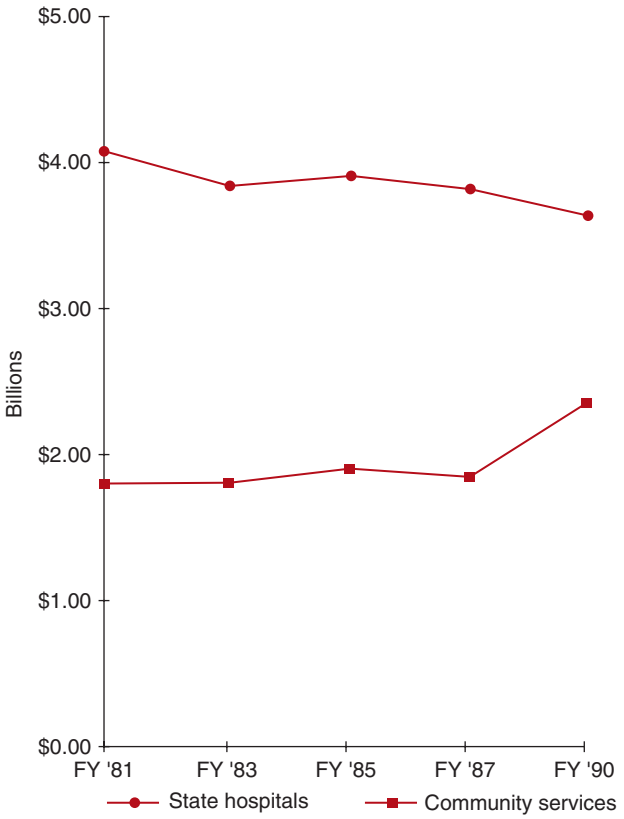



**Figure 86–3** *SMHA expenditures (in constant dollars) for state hospitals and community services between FYs 1981 and 1990. (Source: Lutterman T, Hollen V, and Hogan M (1993) Funding Sources of State Mental Health Agencies: Revenue/Expenditure Study Results FS 1990. National Association of State Mental Health Program Directors Research Institute, Alexandria, VA, USA.)*

## A Case Example of State Mental Health Policy and Funding

Understanding the changes nationwide in the shape of public mental health systems during the 1980s is made difficult because of the limits of available national data. Reliable national data are available on the budgets of the SMHAs, but the Koyanagi and Goldman (1991) analysis makes it clear that federal financing changes during the 1980s (such as the case management benefit in Medicaid) were also significant. However, these changes, unlike the CMHC effort of the prior decades, were not reflected in the categorical budget of NIMH. Rather, a multitude of federal programs were adjusted incrementally during the decade on the basis of recommendations of the 1980 Department of Health and Human Services report and the President's Commission. Because many of these programs (e.g., Medicaid) were not dedicated primarily to mental health, tracking their impact is more difficult, and the changes have not been well recorded or understood. The changes cannot be appreciated by evaluating trends in the cumulative SMHA budgets, because many of the federal revenues flow through other agencies at the state level. Medicaid, for example, is often administered by human service or welfare agencies.

One way to see the impact of the change, and to end this historical review with a picture of the current public mental health system, is to examine the cumulative impact of federal, state, and local changes in a particular state—in this case, Ohio. An argument can be made that Ohio is appropriate for such analysis. Larger in population (seventh among the states in 1994) and smaller in land area (35th) than the average state, Ohio has a mix of urban and rural counties, spanning the range of communities that exist across the country. Its 1990 SMHA budget was $41 per capita, and 59% was spent on state hospital care, compared with the median SMHA expenditure of $38 per capita with an average of 59% spent on hospital care (Lutterman et al. 1993). Therefore, the overall levels and investment patterns of Ohio's SMHA budget are close to national norms. A beginning point to trace the evolution of this system is to evaluate trends in the SMHA budget to determine the pace of movement from hospitals to community services. Figure 86–4 illustrates these trends and Ohio's SMHA budget trends from 1987 to 1993. As illustrated, Ohio made substantial shifts from hospital to community support services during this period. However, the data on state budget expenses alone understate the dynamics of change during this period. Figure 86–5 includes not just the SMHA budget but all revenues used to support community mental health services delivered through the public mental health system in Ohio.

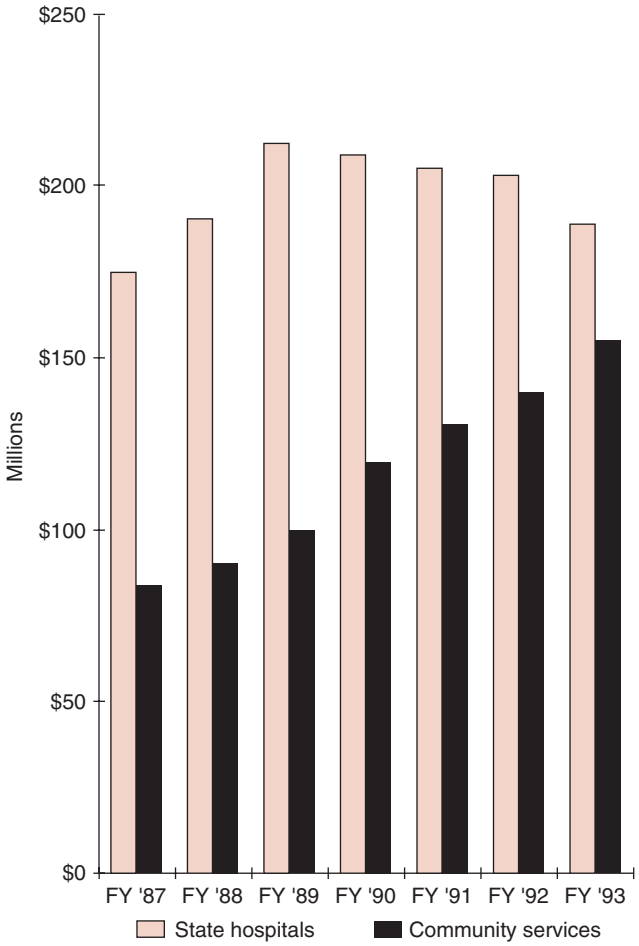



**Figure 86–4** *Ohio state mental health spending: Trends from hospitals to community services between FYs 1987 and 1993. (Source: Ohio Department of Mental Health (1995) Columbus, OH, USA. [Unpublished data])*

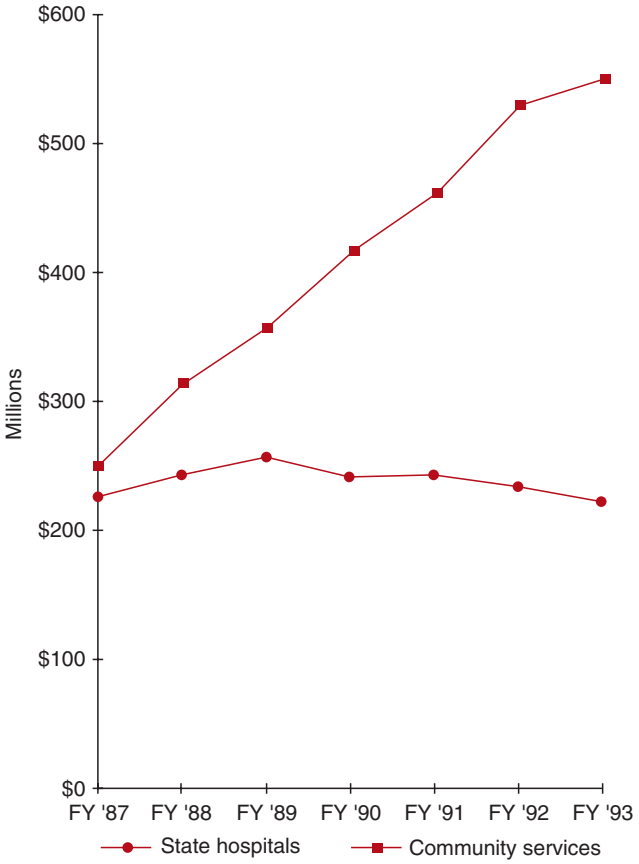



**Figure 86–5** *Funding in Ohio's mental health system: All sources of revenue for community mental health care. (Source: Ohio Department of Mental Health 1995 Columbus, OH, USA. [Unpublished data])*

Figure 86–5 combines all sources of revenue received by the county-based mental health boards that are responsible for community mental health care in Ohio. The shift in investments to community support services is greater when these additional fund sources—principally Medicaid, local taxes, and federal block grants—are added into the picture. It illustrates how examining SMHA funding alone leaves an incomplete picture of mental health investments. Federal changes reflecting the paradoxical combination of budget cuts (e.g., block grants) and the simultaneously more effective financing by Medicaid of community mental health care began to have a significant impact. For example, state hospital costs were 58% of the Ohio general fund mental health budget in 1990, but only 37% when all revenues are considered. Similarly, community mental health services funding increased to 121% from 1987 to 1993 when all funding sources are considered.

The state-level reform in Ohio, although perhaps broader and more aggressive than changes in many other states, does illustrate how the mantle of leadership in the public mental health sector shifted back to the SMHAs during the late 1980s. After the dramatic federal changes of the prior two decades, the states needed to consolidate their efforts. A primary vehicle for this effort in Ohio was the 1988 Mental Health Act. This legislation made services for the most seriously mentally ill the highest priority, required local (county-based or multicounty) systems to develop a community support program, empowered the boards as local mental health authorities, and gradually turned control of state hospital funds over to the local boards.

This step removed the historic and unintended incentive to institutionalize the most needy patients at state expense. The counties were now responsible for the costs of state hospital care on the one hand, but they could also choose to invest in community support services. This state reform legislation therefore followed but extended the themes of the ill-fated 1980 federal Mental Health Systems Act, just as the earlier Ohio legislation establishing the mental health boards in 1968 had followed the 1963 Community Mental Health Centers Act at the federal level. The reforms in Medicaid, which made it more useful as an additional funding source for community support services, added to the value of increased or reallocated state and local funds. There was thus a synergy among federal, state, and local initiatives.

The impact of the 1988 legislation, which followed a period of community program development and capacity building, was extraordinary. The most immediate and obvious impact was the community placement of long-stay disabled patients in a variety of housing arrangements, supported generally by case managers as well as by medication management and day treatment programs. Figure 86–6 shows the reduction in state hospital use in Ohio since this legislation. As illustrated, the reduction in hospital use was

**Table 86–8 Services to SMD and Other Adults: The Impact of Reform***

| | Services to SMD Adults | | | Services to Other Adults | | |
|---|---|---|---|---|---|---|
| | Number of Adults | Units of Service | Units/Adult | Number of Adults | Units of Service | Units/Adult |
| 1989 | 27,712 | 1,551,057 | 56 | 1,33,615 | 2,295,744 | 17 |
| 1992 | 37,183 | 2,645,347 | 71 | 1,21,401 | 1,795,055 | 15 |
| Change | 9,471 | 1,094,290 | 15 | −12,214 | 500,689 | −2 |
| % Change | +34 | +71 | +27 | −9 | −22 | −12 |

*Ohio data for FYs 1989 to 1992. SMD, SMD.

*Source*: Study Committee on Mental Health Services (1993) The Results of Reform: Assessing Implementation of the Mental Health Act of 1988. Study Committee on Mental Health Services, Columbus, OH, USA.

primarily attributable to a reduction in long-stay inpatients. Levels of acute care (less than 30 days) stayed about the same, and levels of forensic care and monitoring increased slightly. (Forensic status refers to patients referred through the criminal justice system, including persons sent by courts to be treated to restore their capacity to assist in their own defense, inmates transferred from local jails for brief treatment, and persons found not guilty of crimes by reason of insanity). These trends were thought to be clinically appropriate in that the majority of long-stay patients were not improving as a result of further hospital care, whereas both short-term admissions and forensic cases were generally appropriate for inpatient treatment.

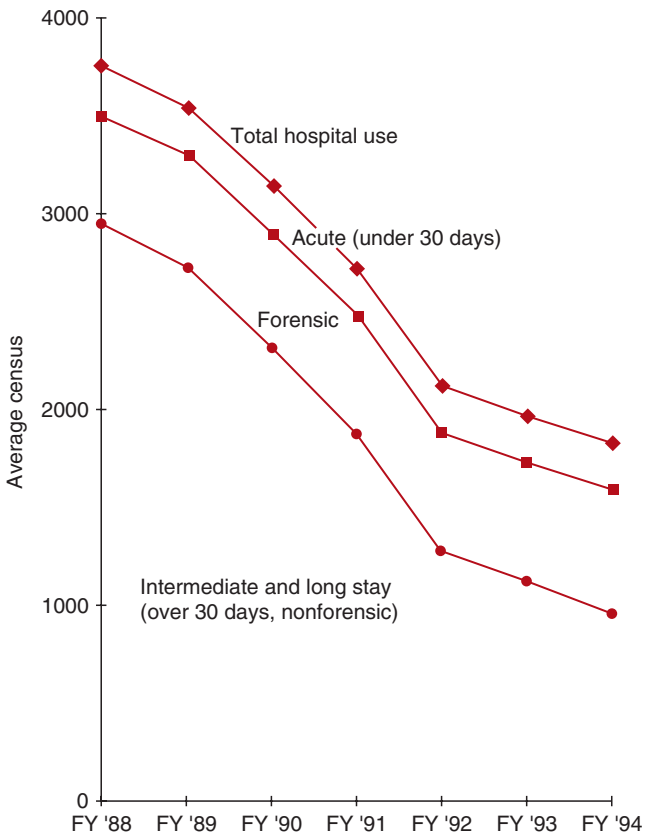



**Figure 86–6** *Ohio state hospital census, by type, for FYs 1988 to 1994. (Source: Ohio Department of Mental Health 1995 Columbus, OH, USA. [Unpublished data])*

Ohio data also reveal substantial changes in patterns of community care during this period. At a gross level, the number of individuals identified as "severely mentally disabled" (SMD) who were served increased, as did the units of service provided to the average SMD individual. However, there was a slight decrease in the number of non-SMD persons served and a decrease in the units of services provided to these individuals. Table 86–8 illustrates these trends.

Changes were also evident in the pattern of services received by SMD persons. Roth et al. (1995) used cluster analysis methods to trace how patterns of care for SMD persons evolved in time and how these related to outcomes. This research revealed that certain patterns of care were relatively stable for a period of time; a consistent 10% of all enrolled SMD persons received substantial levels of various services (labeled custom care by Roth et al. 1995), whereas nearly half of all enrolled SMD persons received low levels of service (about a single formal mental health treatment episode per month). On the other hand, in the 4-year period from 1989 to 1993, there was a significant change in the numbers of SMD persons being served through medication checks without other services. This pattern of care was provided to 23% of individuals in 1989, but this percentage declined to less than 10% by 1993. The apparent shift in this pattern was related to an increase in the use of case management and other services in addition to medical services, reflecting a more comprehensive approach to meeting the treatment needs of these persons. Table 86–9 illustrates these trends.

Roth et al. (1995) also found that outcomes (reduced symptoms and better quality of life) improved overall for SMD consumers during this period. Thus, there is some empirical validation of both the community support

**Table 86–9 Cluster Analysis: Patterns of Care Provided to Percentage of SMD Persons***

| Cluster | 1989 | 1990 | 1991 | 1992 | 1993 |
|---|---|---|---|---|---|
| Few services | 47.70 | 47.80 | 52.80 | 53.10 | 46 |
| Medical | 22.90 | 22.90 | 12.90 | 9.90 | 9.50 |
| Other clusters | 19.80 | 20 | 24.30 | 27.10 | 33.40 |
| Custom care | 9.60 | 9.20 | 10.10 | 9.90 | 11.10 |

*Ohio data for FYs 1989 to 1993.

*Source*: Roth et al. (1995) Final results: Ohio's study of services, systems and outcomes in an era of change. Proceedings: Fifth Annual National Conference on State Mental Health Agency Services Research. National Association of State Mental Health Program Directors Research Institute, Alexandria, VA, USA, pp 85–103.

approach and the reform movement in Ohio during this time. This is not to say that the reform was an unmitigated success. Although community outcomes were positive and the quality of state hospital care improved (as measured by a 72% decline in the frequency of Medicare quality deficiencies from 1991 to 1994), there was conflict in Ohio about funding levels, the pace of change, and the future employment prospects of state hospital staff (Hogan 1992). In addition, the data on reduced levels of non-SMD services reflect a tension between the appropriate goal of increased services for the historically neglected population of seriously mentally ill persons and the unfortunate side effect—given limited public funds—of reduced services to other clients of the public system. However, the Ohio experience does demonstrate that reform in large public mental health systems is possible, and it illustrates the possibilities and dynamics of change in these systems.

## The 1990s: Restoring Focus, Effective Treatments, Defective Funding, Executive Branch Attention

### Restoring Focus: Public Mental Health Systems in the 1990s

The forces converging to change public mental health policy during the 1980s were thus subtler than the "top down" change processes of the mental health establishment during the prior two decades. Whereas the CMHCs are widely thought to have failed the test of serving those with serious mental illness, these organizations formed an essential community infrastructure that survived the dismantling of the federal program in 1980. Thus, many CMHCs became essential elements of the new community support systems that evolved during the 1980s. The new public system is funded through a complex blend of SMHA resources, Medicaid, and local funds. Although consistent national data are not available to document these changes, Ohio data presented in Table 86–8 illustrates how service emphases shifted. From 1989 to 1992, the total volume of services to adults classified as SMD increased to 71% in Ohio; units of services to other adults declined 22%. Similarly, the number of SMD persons served increased to 34% during this period, and the number of service units per SMD person increased to 27%. By comparison, the number of units of service for non-SMD persons decreased by 12%. Through the 1990s these trends continued. CSP services, targeted at adults with SMD and children with severe emotional disturbances (SED), increased as a portion of the Ohio Public Mental Health system spending from 8.17% in fiscal year (FY) 1990 to 16.2% in FY 1997 (Report of Ohio's Mental Health Commission 2001). This data, in graphic form is presented in Figure 86–7. Clearly, the community mental health system was changing its priorities as it was expanding. The locus of care continued its hospital based to community based shift in the 1990s. In 1955, the percentage of patient care episodes occurring in 24-hour hospital care settings was 77%. This dropped to 42% in 1971 and declined further to 24% in 1997 (Manderscheid et al. 2000). On a smaller scale, Ohio Public Mental Health System spending on inpatient care decreased from 46.7% in FY 1990 to 25.4% in FY 1997. (See Figure 86–7) (Report of Ohio's Mental Health Commission 2001). A focus on persons with more serious mental illness and relocation of this care in the community—which had been lacking in the 1960s reforms at both the national and state levels—had been restored.

### Effective Treatments and Defective Funding

Coincident with this refocusing on the care of the severely mentally ill (SMI) in the 1990s, psychiatry reemphasized its expertise in treating biologically based diseases of the brain. Congress declared the 1990s "the Decade of the Brain" (Surgeon General 1999). New antipsychotics beginning with clozapine in 1989, followed by risperidone, olanzapine, quetiapine, and ziprasidone offered promise to individuals with schizophrenia unresponsive to or unable to tolerate earlier medications. Additional medications in the class of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, provided new therapies for people with mood

1. *Implementation of the Mental Health Act has changed funding priorities and redirected state hospital resources to community care, and fundamentally changed the mix of community services.*

For example:

- Savings from Ohio Department of Mental Health hospital downsizing and restructuring have led to increased funding for community services, and the mix of community services now emphasizes community support and other services for SED/SMD persons. (Graphs 1 and 2)

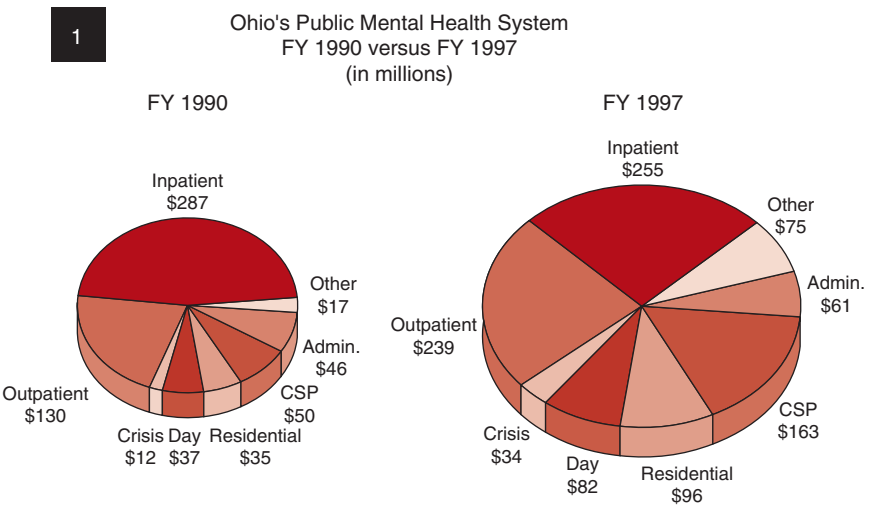



**Figure 86–7** *Trends in funding mental health services in Ohio (2001). Report of Ohio's Mental Health Commission, January 2001. Ohio Department of Mental Health.*

and anxiety disorders. Indeed, depression treatment rates increased substantially from 0.73 per 100 persons in 1987 to 2.33 in 1997 (Olfson et al. 2002). Research supporting the usefulness, including the cost effectiveness of psychotherapies for a broad variety of mental disorders emerged (Gabbard et al. 1997). Studies show the effectiveness of other psychosocial interventions such as assertive community treatment, supported employment, family psychoeducation, integrated substance abuse treatment, and illness self-management techniques (Drake et al. 2001). While psychotherapies, other psychosocial interventions and pharmacologic treatments all offer promise in treating a wide range of mental illness there was a shift for at least some individuals receiving only treatment with medication. These developments helped bolster calls from advocacy and professional groups for parity in mental health coverage; however, public and private mandates to control costs hindered obtaining the full benefits of improved treatments. These efforts at cost control are covered in detail in the later section on Economics in Mental Health.

Results of two recent multicenter studies, one in the US and one in the UK (Jones et al. 2006), comparing the outcomes of people with schizophrenia treated with the newer, more expensive antipsychotic agents to older, less costly medications has dampened some of the early enthusiasm for the newer drugs and called into question the assumption of their greater effectiveness especially compared with the substantially higher cost of these medications. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) antipsychotic studies have highlighted an ongoing area of research and debate in mental health care, that is the cost and effectiveness of mental health treatments and the balancing of these issues. Since it is often difficult to predict and access all the costs of a particular treatment as well do the type of long-term studies comparing various treatments and treatment combinations, the cost effectiveness of a specific treatment approach may take many years to establish. Additionally refinements in the diagnostic subtyping of study subjects may define a population for whom a treatment or treatment combination is more effective than others. For instance, British researchers (Simon et al. 2006) recommended first line combination antidepressant and psychotherapy targeted at individuals with severe depression. Compounding the cost effectiveness question for psychiatric disorders are funding streams which pay from nonclinical but effective interventions such as specialized vocational services. Finally, the issue of cost effectiveness of psychiatric treatment often is related to the potential cost offset for general medical care. However, Strum (2001) asserts that attempts to increase mental health expenditures by policies which promote increased access and utilization of behavioral health care will not be offset by reduction in general medical spending. He does acknowledge that for specific populations (usually those with high rates of general medical care utilization) targeted psychiatric intervention may decrease cost and/or improve clinical outcomes.

### Executive Branch Attention

In the context of the struggle between calls to enhance services and calls to control costs, the executive branch of government drew attention to mental health several times in the 1990s. Although the early efforts at more sweeping health care reform during the Clinton administration failed, a few initiatives limited to mental health merit comment. In September 1997, the Office of the Surgeon General under Surgeon General David Satcher, M.D., Ph.D. authorized the initiation of a *Report on Mental Health.* The report, released in December 1999 drew national attention to mental health problems, noting:

1. "mental health is fundamental to health,"
2. "mental disorders are real health conditions,"
3. the "efficacy of mental health treatments,"
4. the "range of treatments for most mental disorders,"
5. the public are encouraged to seek help for mental health problems,
6. the special needs of specific populations including children and the elderly,
7. the contributions of the advocacy movements,
8. the systems issues of financing complexity, fragmentation of services and access to care.

A supplement highlighted culture, race, and ethnicity (Surgeon General 2001). In July 1999, a Call to Action to Prevent Suicide was issued (Surgeon General 1999).

The Clinton White House held a conference on mental health in 1999 to help decrease stigma and increase awareness of mental health issues (Surgeon General 1999). On June 7, 1999, President Clinton directed the Office of Personnel Management (OPM) to achieve parity for mental health and substance abuse coverage for federal workers by 2001 (OPM News Release 1999). President Clinton believed the federal employees program could serve as a model for other employers and the insurance industry (OPM News Release 1999). Results of this experiment in parity are reported in detail later in the Benefit limits section but in brief there was no significant increase in overall plan spending for either adults or children. (Goldman et al. 2006, Azrin et al. 2007).

## The 2000s: Spotlight Shining, Financing Friction, Public Health, and Prevention

President George Bush kept mental health issues in the spotlight with his announcement on April 29, 2002, of the formation of the New Freedom Commission on Mental Health (White House Press Release 2002). The Commission's report identified recovery as the overarching goal of a transformed system (President's New Freedom Commission on Mental Health 2003). To achieve this goal the following component goals were described:

1. Americans understand that mental health is essential to overall health.
2. Mental health care is consumer and family driven.
3. Disparities in mental health services are eliminated.
4. Early mental health screening, assessment, and referral to services are common practice.
5. Excellent mental health care is delivered and research is accelerated.
6. Technology is used to access mental health care and information.

The report recognizes that to fully realize the potential of treatment and recovery services coordination of clinical care, maximizing the use of multiple funding streams, implementing new technologies in the fiscal, informational, and clinical realms and grappling with inadequate and unequal funding for access to mental health services is necessary. How this recent executive branch attention to and efforts at reforming mental health will be integrated into overall mental health policy remains to be seen. The hurdles to improved mental health care are more challenging as they no longer involve finding the most effective medication or psychotherapeutic treatments to help individuals recover but restructuring systems of care.

### Financing Friction

The complexity of mental health funding has made it difficult to predict all the outcomes of shifts in payment and at times even difficult to collect uniform data regarding finances. While the headlines in the 1980s and 1990s about Medicaid funding were the increase in federal and state dollars spent at the local community level as well as lack of federal dollars available to SMHA's especially at state hospitals, the 1990s and 2000s brought different concerns. Meeting the state portion of the Medicaid match increasingly strained state and local budgets. In addition through a variety of mechanisms an increasing amount of federal Medicaid dollars were being tapped by states. SMHA's facing budget constraints within their own system increasingly looked towards these strategies which included coverage for inpatient services for Medicaid eligible people over 65 in an IMD facility, coverage for nursing facility services for Medicaid eligible people 65 and over in an IMD, coverage for inpatient hospital care for Medicaid eligible people under age 21 in an IMD, paying for IMD services through savings gleaned from Medicaid managed care, programs to incorporate state and county psychiatric hospitals into BHO's which contract with the state's Medicaid program by obtaining IMD expenditure authority through an 1115 Medicaid waiver, use of disproportionate share hospital (DSH) payments to state and county hospitals to offset the costs of caring for large numbers of indigent patients, and obtaining reimbursement for the costs to administer Medicaid programs. The increased use of these strategies did result in some changes designed to limit federal payments back to the states. The extent to which states used these options varied widely and data is somewhat difficult to collect. A state study covering years 2000 and 2003 estimated the Medicaid non-DSH funds as a percentage of total state hospital funding as ranging from 3% in Arkansas and California to a high of 30% in Iowa. Extrapolating these state estimates and other data the total contributions of Medicaid funds toward public hospitals (incorporating DSH funds with non-DSH funds of 29% and 5% respectively) total approximately one-third of public psychiatric hospitals total operating costs in 2001 (Draper et al. 2003).

In Ohio the straining of government budgets at all levels layered on top of the complexity of funding and policy strategies ultimately resulted in the same trends in services and resources noted earlier and captured in Figures 86–4 and 86–5. First SMHA spending on state hospitals care continued to decrease relative to spending on community services with community services spending surpassing hospital spending in 1996 (Figure 86–8). Second, when all revenues received by county-based mental health boards are considered the amplification of the shift in funding from hospitals to community services continued. Community funding more than doubled and state hospital funding remained essentially unchanged which given increases in operating costs actually represented a decline in funding. These changes are summarized in Figure 86–9.

## Public Health and Prevention

Public health in general and public mental health in particular are often neglected in the US health care system with its emphasis on the treatment of individuals and individualized treatment. The US in the 2000s experienced several landmark events which in addition to the Surgeon General and Presidential reports focused additional interest in the area of prevention, detection and treatment of mental disorders. The terrorist attacks in September 2001, the subsequent war in the Middle East with increasing numbers of returning veterans experiencing PTSD and traumatic brain injuries and the Gulf Coast Hurricanes in 2005 with both the effects of the immediate trauma and the longer term issues of displacement and loss drew attention to the impact of mental disorders on both the individual and community.

These mass casualty events captured the attention of the country, especially in the treatment of trauma but also other types of mental illness. During this time there has also been renewed interest in the prevention of mental health problems by attempting to decrease exposure to or intervene early with children and adolescents who are exposed to much more common trauma such as abuse and violence in neighborhoods and schools. Efforts to prevent and increase treatment of drug and alcohol abuse have also been key strategies of federal, state, and local government agencies. Increased effort in the detection and treatment of mental disorders especially in primary care settings has also occurred. Much of this has been fueled by the cost off-set to private insurers or public payors achieved by identifying and treating illness such as depression in high users of general medical services. However, in addition to financial savings overall improvements in clinical outcomes have been demonstrated in multiple studies. Other projects have moved beyond early efforts focused on screening and detection to more sophisticated studies focused on care coordination and improving delivery systems using chronic disease management models (Kates and Mach 2007). A disease management model for depression at the Henry Ford Health System was able to show a decrease in suicide rate of 75% (Perfect Depression Program 2006).

A complementary public health issue emerging on the interface between general medical care and psychiatric care is the excess mortality and morbidity among people with serious mental illness (Miller et al. 2006). Issues raised include the contribution of substance use, including nicotine, rates of obesity, use of atypical antipsychotics, and access to care. Screening for medical illnesses in psychiatric patients and developing models of treatment have been suggested as ways to decrease this problem.

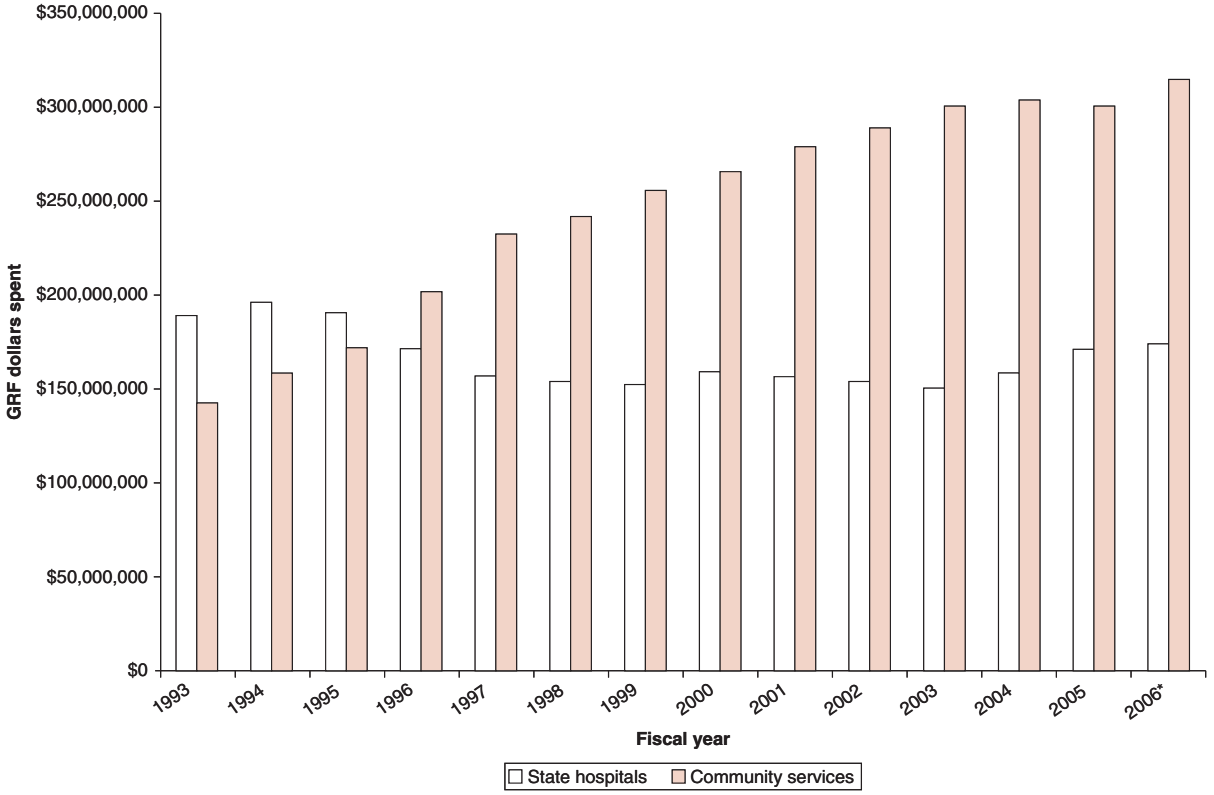



**Figure 86–8** *Ohio state mental health spending from General Revenue Funds therefore continuing trends from state hospitals to community services between FYs 1993–2006. Ohio Department of Mental Health unpublished data 2007. *Beginning in FY 06, the department no longer collected Patient Fee data.*

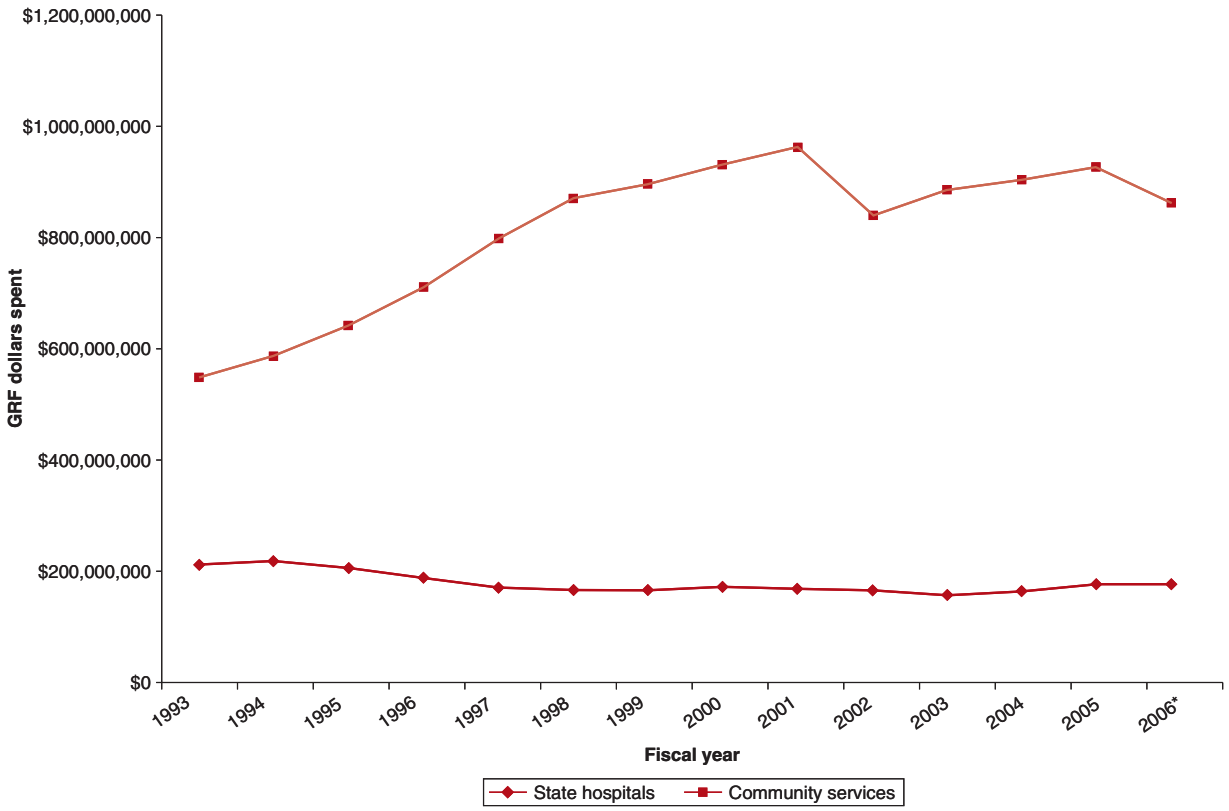



**Figure 86–9** *Funding in Ohio's mental health system. All sources of revenue for community mental health care and state hospital inpatient revenue from GRF and Medicaid. Ohio Department of Mental Health unpublished data 2007*

## Implications for Mental Health Policy

The evolution of mental health policy in the US, outlined in Table 86–10, has thus produced a substantial public sector care system that is also exceedingly complex. Essentially consisting of state hospitals in the 19th century, the system expanded dramatically in the past generation by the community mental health, Supplemental Security Income and Social Security Disability Income, and Medicaid and Medicare initiatives of the 1960s. These efforts contributed to a substantial expansion of public mental health responsibilities but also to great blurring of boundaries and diffusion of these responsibilities. New privately provided but publicly financed alternatives such as nursing homes and general hospital psychiatric services were created outside the boundaries of the specialty "mental health system." Income supports enabled some mentally ill persons to exist mostly on outside relief, such as welfare payments, but also weakened the boundaries of the traditional mental health system. The decade of the 1980s provided an opportunity for some consolidation and organization of this fragmentation. The community support concept provided a conceptual framework for understanding the changes that were needed in the new service system, recognizing its fragmentation on the one hand but focusing on the community survival requirements of people wrestling with the most serious mental illnesses.

**Table 86–10 Evolution of Mental Health Policy**

- State hospitals to complex system of care
- Limited funding to federal and state programs (Medicaid/Medicare), Social Security Income/Social Security Disability Income (SSI/SSDI)
- Focus on acute care for those with less serious illness to focus on chronic care for those with serious and persistent mental illness
- Public systems of care to more local public/private endeavors, nursing homes, general hospitals
- Lack of coordinated services to case management, assertive community treatment

As a result, in most states, the public mental health system is organized around some local entity, whether county government, special purpose boards or commissions, or provider organizations designated by the state to also manage a local system of care. These local systems exercise variable and incomplete control over the array of public supports that exist because the formation of alternatives is so complex and funded and regulated by so many governmental entities. Federal and state mental health grant resources are most likely to be coordinated at this local level. Increasingly, Medicaid-financed mental health care may be coordinated with the local care management system, but Medicaid remains a distinct government reimbursement program that may or may not be coordinated with state or local mental health authorities.

Programs in other human service areas that are relied on by individuals with serious mental illness (e.g., low-income housing, vocational rehabilitation, services for disabled students in higher education, mental health care within the criminal justice system) are probably not controlled by either the state or local mental health authority. However, the empowerment of local authorities has increased their ability to negotiate agreements and improve coordination with other systems. Yet this remains a serious challenge. Marmor and Gill (1989) have noted that meeting the needs of seriously mentally ill individuals is a particularly difficult challenge within the US political and governmental structure. Whereas good treatment and support require a high degree of coordination and "comprehensive" solutions, the US political system is oriented to incremental approaches, and there is a long-standing distrust of government-managed approaches. Therefore, the public mental health approach at the state and local levels remains a complex, open system.

As a remedial strategy for coping with system fragmentation and to aid individuals whose ability to plan and coordinate their own lives and services may be significantly affected by mental illness, most SMHAs and local mental health systems have adopted a case management strategy. Individuals or teams of case managers assume responsibility for guiding persons with serious mental illness through this maze and assisting them with personal planning. Case management programs as distinct entities are usually provided only to persons with more serious disabilities. For example, in the systems approach described by Stein et al. (1990), a well-staffed multidisciplinary community treatment team (analogous to the clinical team and paraprofessionals who work together on an inpatient unit) is the core service for the most needy group of individuals in the Dane County, Wisconsin, system. For other persons receiving care in the publicly funded system, care coordination may be provided by their therapist.

In general, modern public mental health systems still function as a kind of safety net (or, in insurance terms, a "high-risk pool") for the larger health and mental health system, providing care and support for the most needy, seriously mentally ill, and poor individuals in their community. Insurance-financed private care is now available to most Americans, but it is not available for long to those with the most disabling mental illnesses except in the most generous private plans. For these individuals, the public system is the safety net. Mental health is unique in health care with respect to this distinct care and financing system for those with the most serious illnesses. Despite the origins of care in the public sector and the still substantial role of public systems, the private sector—reimbursed by employer-financed insurance—has become dominant in mental health. Understanding the economics of reimbursement systems and their impact on care has thus become essential.

## The Economics of Mental Health

Four interrelated types of financing, listed in Table 86–11, have developed to become critical elements of the economics of health care: out-of-pocket payments by individuals, individually owned or purchased insurance, employer-provided insurance, and government reimbursement. Each has different economic dynamics and affects mental health care in different ways. In general, the development of health care financing patterns in the US has followed this sequence, from individual out-of-pocket payments to government financing. At the same time, each of these patterns persists within the complex US "system" of financing health care. Additionally, in recent decades individually purchased insurance, employer provided insurance, and government funded plans have all been markedly effected by the increased prevalence of the managed care

industry. A review of the evolution and dynamics of these financing approaches provides the best starting point for understanding the complex economic patterns of care.

**Table 86–11 Current Types of Financing of Health Care**

- Out-of-pocket payments by individuals
- Individually owned or purchased insurance
- Employer purchased insurance
- Government reimbursement

## Out-of-Pocket Payment for Care

Before the development of insurance coverage, and indeed well into the 21st century, individual out-of-pocket payment for care was the dominant pattern in health care. This is the simplest and most direct form of financing: people pay for the services they use. There are, however, serious problems with this approach as a financing method for health care and especially for mental health care. The amount of care that any person may need—and thus the amount that must be spent—is unpredictable and may be more than the average citizen can afford when serious health problems arise.

In the case of mental illness, the onset of most serious conditions is often during early adulthood, the prime wage-earning years. By comparison, other health care costs tend to be highest in old age. The most serious mental illnesses also tend to be both long-term and disabling. Many individuals with the most serious mental illness are not able to work and are thus not in a position to pay for the costs of substantial care. Thus, individual out-of-pocket financing is not workable for these individuals. On the other hand, less serious conditions are frequently treatable by psychotherapy or medications. However, psychotherapy in particular and mental health care in general are highly price responsive, meaning that people will use less of it if they have to pay more. In fact, most people will use little mental health care—probably not enough for their good health—if they have to pay the entire cost. Taken together, these factors mean that out-of-pocket financing is a poor primary approach to financing mental health care.

The limit of out-of-pocket reimbursement, the dominant financing approach in the 19th century, provides the economic explanation of the need to create a public care system for people with the most intractable mental illnesses and explains the continuing role of the public sector as a kind of risk pool or safety net for the most needy. An out-of-pocket financing approach fit so poorly with mental health needs that a separate system had to be created. Now that the separate public system exists, its relationship to privately financed care is a problem.

## Individual Private Insurance

In this simplest model of insurance, as Bodenheimer and Grumbach (1994) have described, a third party—the insurer—enters the health care relationship along with the patient and provider. This model was used in 19th century Europe, with guilds and businesses establishing voluntary benefit funds to which members contributed individually, which then provided aid when a member was ill.

The individual insurance approach does introduce the notion of spreading risk across a group of "covered lives," thus shielding individuals from unlikely but extraordinary costs because the risk of incurring these costs is shared by all members. Whereas this essential function of insurance is addressed by the individual insurance approach, this model has a built-in problem: the need to collect contributions and then administer payments for each member individually. This high administrative cost makes individual insurance difficult to sell and expensive to purchase. As a result, only a small percentage of the US population has individual health insurance. The principal sources of health coverage along with population percentage using them are shown in Table 86–12.

**Table 86–12 Principal Sources of Health Coverage**

| Source of Coverage | Population (%) |
|---|---|
| Employment-based private insurance | 52* |
| Government | 25 |
| Uninsured | 14 |
| Individual private insurance | 9 |
| Total | 100 |

*Includes private insurance purchased with public funds.

*Source*: Bodenheimer T and Grumbach K (1994) Paying for health care. JAMA 272, 634–639.

Most of the economic dynamics associated with individual insurance are not different from those of out-of-pocket payment for mental health. Of course, insurance is now involved, and so decisions to purchase coverage as well as to use care are involved. This does have an impact on mental health; people are less likely, on average, to seek coverage for mental illness than for other health problems, perhaps because of the perception that "that could not happen to me." This means that individual policies are less likely to provide adequate mental health coverage. If someone with an established illness were to seek to purchase individual coverage, the cost would be prohibitive because of the high risk the person presents. Therefore, the individual insurance approach also fails to provide adequate answers for mental health financing.

## Employer-Based Private Insurance

Bodenheimer and Grumbach (1994) have also provided a cogent analysis of the growth and dynamics of employer-based coverage, the dominant form of health insurance in the US today. The first such plan was developed at Baylor University Hospital in 1929, under an arrangement whereby the hospital agreed to provide up to 21 days of hospital care per person per year in return for a payment of $6 per person per year. This approach to financing care, with the provider also playing a role as insurer, became a dominant approach in the US. The hospital industry controlled development of Blue Cross plans, providing coverage initially for hospital services; state medical societies stimulated development of Blue Shield plans, which primarily covered physicians' services. Starr (1982) has pointed out how this provider-dominated market acted to protect physicians and hospitals by ensuring a steady income and by keeping reimbursement generous. Cost control, on the other hand, was not a major priority.

Employer-based private health insurance became a dominant factor in the US health care as a side effect

of seemingly unrelated policies: the wage and price controls imposed on companies during World War II. This policy constrained wage and salary increases but did not similarly limit fringe benefits such as insurance. Therefore, insurance coverage was an incentive for employees to join particular companies in a competitive labor market. After the war, unions began to negotiate for benefits, continuing the trend of expanded coverage. In addition, the favorable tax status of employer-paid benefits (because such benefits are by and large not counted as income for tax purposes) contributed to the growth in this type of coverage. As a result, the number of members in group health insurance plans increased from 12 million in 1940 to more than 100 million just 15 years later. Ever since that time, private, employer-financed group health insurance has been the dominant payment and financing mechanism in the US (Bodenheimer and Grumbach 1994).

The fit between employer-financed insurance and mental health care is not inherently a problem, as is the case with individual insurance or out-of-pocket payment. In this case, the adequacy of insurance depends on how the policy is priced and on the type of benefits. Unfortunately, pricing strategies and benefit limits have made the mental health coverage of many employer financed policies inadequate with employees paying a greater share of the cost.

## Community Versus Experience Rating

In the early days of employer-financed coverage, the price of insurance was typically based on the health care use (and thus the cost) of the entire community. Segments of the population were not singled out for differential charges on the basis of their pattern of health care use. This "community rating" approach is consistent with the general purpose of insurance—to spread the costs or risks of costly and unpredictable events across a larger population.

However, as insurers began to compete with each other for business, limiting prices became increasingly important, and the practice of "experience rating" developed: the strategy of pricing insurance on the basis of the actual health care use patterns of the insured population. This approach quickly proved to be a problem for individuals with mental illnesses or other substantial health problems, especially when coupled with other strategies used by employers or payers to limit their costs by controlling "risk" at the point when insurance is purchased. A principal approach to accomplish this is to deny coverage to individuals with expensive "preexisting conditions," which has resulted in denial of coverage to many mentally ill persons.

Experience rating and denial of coverage to potentially expensive consumers (usually those for whom the insurance is most needed) are responses to the competition that has emerged in the private insurance market. By limiting costs through selection of a healthy population, insurers or self-insured employers can partially control their costs, albeit by using strategies that run counter to the basic insurance premise of spreading risk broadly. The other main strategies for controlling insurance costs all target the levels of care that is provided. An obvious first approach is to limit what treatments the policy will cover.

## Benefit Limits

Despite the problems for mental health coverage associated with insurance pricing, benefit limits that discriminate against mental health care have probably been more of a problem. The presence of the public mental health system already created an indirect obstacle to broad mental health benefits, because care for catastrophic conditions was available to those without insurance in this separate system. The competitive pricing strategies of insurers acted to further limit growth in private, employer-financed mental health coverage. A range of coverage limits has been used to control insurance costs: deductibles and copayments (in which the consumer-patient pays a portion of costs before the insurer does) as well as caps on what the insurer will pay (per episode, per year, or in a lifetime). In addition, limits may be placed on what services will be reimbursed, and mental health has not fared well under this approach.

State-of-the-art care for mental illness involves early intervention with medication or psychotherapy. Hospital stays are used sparingly, and a wide variety of rehabilitation and other services are required for many individuals with schizophrenia and other serious disorders. In other words, a wide variety of services may be required and used in a tailored treatment approach over time. In general, benefit limits in mental health preempt almost all of these treatment strategies. Outpatient treatment has been a first target in many mental health plans, for several reasons: the prevailing stereotype that "talk therapy" goes on endlessly without result, and the fact that increases in outpatient therapy use have in fact raised costs substantially in generous plans. As discussed earlier, psychotherapy is in fact highly price responsive: if it is essentially free, people will use a lot of it (in comparison to other visits to physicians, which do not vary as much depending on the cost to the consumer). This high responsivity also makes mental health treatment very sensitive to benefit management.

On the basis of these factors, many insurance plans limited mental health outpatient therapy to a few visits and required a 50% copayment (compared with the typically unlimited visits available to other physicians, with 20% or smaller copayments). Whereas these limits effectively control expenditures in the short term, they create a disincentive for early treatment and thus contribute to higher rates of hospitalization, which costs more.

For the reason that the covering costs of necessary hospital care is a core function of insurance, eliminating psychiatric hospital coverage was generally seen as unacceptable, and most insurance policies provide generally equivalent hospital coverage for psychiatric and physical illness—to a point. Since repeated or long-term hospitalization can lead to extreme costs in serious mental illness during the life span, coverage limits have targeted long or repeated stays by annual or lifetime limits on the amount of care that would be paid.

Using these patterns, in an attempt to reveal the impact of coverage limits on consumers, the *New York Times* concluded in 1989 that a person with schizophrenia could expect lifetime treatment costs of $294,800, with less than 25% covered by insurance. A patient with ischemic heart disease, by comparison, would face lifetime treatment costs of $108,350, with more than 90% covered by insurance. The dramatic expansion of high-technology care for such conditions means that the total medical costs for treating them is dramatically increasing.

A final area in which coverage limits are typically a problem in mental illness also relates to serious conditions

such as schizophrenia, for which flexible care including approaches such as ongoing case management, rehabilitation, partial hospital programs, and crisis care are used to minimize inpatient care. Many of these services are typically not covered in health plans because they appear to be "added expenses." The ironic result is that extended or repeated hospitalization can result from inadequate community treatment, driving up costs to the insurer to the point of coverage limits, and then leaving the patient without coverage. Limits to coverage are thus a problem for patients, and unless the coverage limits are extreme, they tend to fail at cost control, because patients use up whatever coverage is available.

Mental health thus presents a paradox in terms of cost control. Outpatient care is more price responsive than comparable physical health care, and insurance costs will rise unacceptably unless these costs are somehow controlled. During the late 1980s, a period emerged when benefits became more comparable with other health costs, including a 27% increase from 1987 to 1988 (Employee Benefit Research Institute 1990). Yet controlling costs through arbitrary benefit limits does not work well. Too stringent limits on outpatient care and alternatives to hospitalization drive up hospital costs. It is evident that purely economic controls are not adequate to appropriately balance care and costs in mental health.

Recent data suggests that the effect of benefit limits may be overshadowed by the prevalence of managed care techniques which will be more fully explored later in the chapter. As noted earlier President Clinton in 1999 directed the Office of Personnel Management to ensure parity of mental health and substance abuse benefits for the Federal Employees Health Benefits (FEHB) Program. Full parity for these disorders was implemented in January 2001. The impact of parity for both the plans and the beneficiaries has been studied for adults (Goldman et al. 2006) and children (Azrin et al. 2007).

For adults, the study showed no significant increases in spending attributable to the implementation of parity (Goldman et al. 2006). Spending and rates of use did increase in the FEHB plans but also increased for the control plans. In most of the FEHB plans there was a significant reduction in out-of-pocket spending for beneficiaries. Analysis of the effect of parity for children in the FEHB program showed similar results. Although utilization and spending in both, the parity and control plans increased overall there was no additional increase in utilization and spending attributable to parity. Two of the seven parity plans experienced decreased spending the other plans showed no difference. Beneficiary out-of-pocket spending decreased significantly in three out of seven plans, in the other four spending decreased but was not significant. The conclusion in both studies was that parity could be adopted without the outcome of increased costs to the plan and with the benefit of decreased financial liability to plan users. However, they also conclude that parity alone did not improve access.

## Trends and Approaches in Government Financing

Government financing of care (primarily through Medicare and Medicaid) has been a major force in the US since these programs were introduced in the 1960s. The general trends and dynamics of Medicare and Medicaid have already been discussed. However, these programs, especially Medicare, have also served as a laboratory for benefit design and other cost control approaches. As Bodenheimer and Grumbach (1994) pointed out, these programs have greatly expanded coverage and access to care for elderly, poor, and disabled Americans. At the same time, they aggravated the problem of rising costs and contributed to growing federal budget deficits.

Several innovations in paying for care under Medicare have helped to clarify the challenges of appropriate benefit design and payment for mental health care. These innovations were the use of diagnosis-related groups (DRGs) and the Resource-Based Relative Value Scale (RBRVS). Each of these approaches has significantly shaped thinking about reimbursement in the past several decades.

### Diagnosis-Related Groups

The DRG payment methodology was introduced by Medicare in the 1970s as a means to control inpatient costs. The theory was to pay hospitals fairly for an episode of treatment by calculating the appropriate length of stay for treatment of a given illness or condition. Thus, norms for treatment length of stay were established for comparable diagnoses, and payments were made on a per-episode basis rather than by the traditional per diem method. The idea was that hospitals would be rewarded for efficient care by pocketing any savings associated with shorter lengths of stay; inefficient care would cost the hospital more than the DRG payment. Criticism of the approach was loudest from psychiatrists; concern that diagnosis was an inadequate predictor of treatment needs turned out to be correct. Evidence marshaled by the psychiatric community confirmed that diagnosis alone was a poor predictor of the length of stay for psychiatric illness. As a result, Medicare exempted psychiatric units from the DRG payment approach, used nearly universally across other areas of medicine.

The rejection of the DRG approach was initially seen as a victory for mental health treatment, because there was concern that the approach would have led to widespread "creaming" (selection of patients for treatment who in fact had limited needs) and "dumping" (failure to adequately treat needy patients). The rejection of the DRG approach was something of a political victory for the mental health field and particularly for the profession of psychiatry. However, there were also negative effects of the DRG exclusion. First, profit-oriented companies realized that mental health was a less regulated area of health care and rushed in to establish profit-making units, especially in southern states with less general regulation of health care. These units marketed their services heavily and generally paid incentives to staff to maximize the number of admissions. Adolescents with vague "behavior problems" were frequently the major group served in these units, and excessive and often inappropriate treatment stays were typical. These problems led to many investigations and congressional hearings. In some instances, the "milking" of benefits for inappropriate care was so excessive that it consumed patients' insurance coverage up to lifetime limits, meaning that they would be unlikely to ever be able to afford private coverage. The rationale for excluding mental illnesses from DRGs also compounded an image problem for mental health treatment among payers, insurers, and legislators: the perception that psychiatric

diagnosis is subjective and that treatment is both unpredictable and generally ineffective.

Although Medicare-financed inpatient psychiatric care remained excluded from DRGs, a number of states adopted variants of this approach to pay for inpatient psychiatric care under Medicaid. Ironically, these tailored approaches seemed to work reasonably well and to avoid the problems predicted for DRGs in mental health. An approach implemented in New Hampshire is among the best documented of these modified DRG strategies in Medicaid. Described by McGuire et al. (1990) the New Hampshire payment strategy considered the type of admission (scatter bed or psychiatric admission to a medical–surgical unit, admission to a distinct psychiatric unit, or involuntary admission to a specialized unit) and also provided for payment adjustments for "outliers." This adjustment addressed the problem of particular cases for which a longer length of stay seemed justified by providing a reduced payment for extended care, at a level calculated to be low enough to discourage extended inpatient care but high enough to discourage premature discharge. These features, added to diagnostic groupings, seemed to address the problems predicted for mental health care under DRGs. Beginning January 1, 2005, a new Medicare DRG approach to psychiatric inpatient care was implemented.

## RBRVS

Although a significant innovation in payment, DRGs addressed only inpatient care, and medicine in general was moving in the direction already set in mental health—more outpatient care and less hospitalization. (DRGs also failed to address other cost problems in medicine, such as competition to acquire expensive technology, and the problem of high costs associated with treatment during the last few months of life. However, these topics are beyond the scope of this discussion.) The RBRVS was Medicare's effort to set a rational payment approach for outpatient physician care—a kind of DRG approach for funding clinic and office visits. Under this approach, the level of "resources" required for a given visit or treatment was studied and normed. Resources included the amount of time, level of training and expertise, and other factors that interacted with the particular condition under treatment to produce an acceptable level of care. Similar to the DRG approach, the RBRVS then adjusts payment levels to reflect these national norms.

There has been less controversy associated with the practice of psychiatry and the RBRVS approach than occurred with DRGs, partially because psychiatry was treated more like other forms of medicine in the outpatient area. If the approach had any particular significance, it was in the recognition that visits or interventions requiring high levels of "cognitive" training and expertise had traditionally been undervalued in payment schemes, compared with visits to surgeons in particular.

## The Tax Equity and Fiscal Responsibility Act (TEFRA) and the Balanced Budget Act

Exemption from the DRG prospective payment system and inclusion in the RBRVS reimbursement scheme, which recognized cognitive versus procedurally dominant medical services generally enhanced resources for psychiatric services. The 1982 TEFRA reimbursed psychiatric services on a cost-based system per discharge, which included capital costs, bonuses for lower costs, and bad debt, explains Health Policy Alternatives 1998 (Garritson 1999). Under the TEFRA and earlier funding plans, private inpatient psychiatric services boomed in the 1980s. Redick et al. (Mechanic et al. 1998) note that between 1970 and 1992, specialized psychiatric units increased from 664 to 1516, the number of private mental hospitals more than tripled and admissions quadrupled. As noted earlier, some of this expansion resulted in inappropriate utilization of inpatient care but the greater overall effect was the vast expansion of the role that the private (albeit publicly funded) care system played in the provision of acute psychiatric care. Between 1988 and 1994, discharges for a primary psychiatric diagnoses from general hospitals increased approximately 35% from 1.4 to 1.9 million per year with the largest growth (53%) occurring in private nonprofit hospitals (Mechanic et al. 1998). At the same time public general hospitals experienced an approximately one-third reduction in the number of discharges from 132.1 to 83.8 million per year. The number of days of care in mental hospitals, excluded as "IMD" facilities from receiving Medicaid funds, declined overall with the largest decrease occurring in public hospitals (12.5 million days) and far exceeding the increase of 1.2 million in general hospitals (Mechanic et al. 1998). Additionally, the rate of discharges for severe mental illnesses (SMI) in general hospitals increased from 196 to 314 per 100,000 population with the largest increase (almost 90% higher) being found in private nonprofit hospitals. In these institutions 12% more of the total bed days were for patients with SMIs. Mechanic also notes that proprietary hospitals had transfer rates higher than nonprofit hospitals with the differences being more pronounced for patients with SMI in general, and especially for patients with schizophrenia. As a result of an uneven distribution of caring for Medicaid enrollees and uncompensated care, Mechanic argues for identifying those institutions which are assuming the larger share of this burden and targeting them for public support in order for them to provide the public safety net.

In 1997, rather than this targeted support for general hospitals which were providing an ever increasing proportion of acute psychiatric care, including care for individuals with SMI, Congress enacted and President Clinton signed the Balanced Budget Act (BBA) of 1997. The Congressional Budget Office (CBO) estimated that the act would save $112 billion by slowing the growth of Medicare and $7 billion by changes to Medicaid over the 1998 to 2002 period (CBO 1997). A majority of the reduction in Medicare was to come from reduced payments to hospitals, according to Ramsey Wallace (Garritson 1999). Payments to physicians also were targeted for cuts. The Medicaid savings were to be achieved largely by reducing payment to disproportionate share hospitals (facilities that provide a high volume of services to the Medicaid population) (Garritson 1999). The Medicare Balanced Budget Refinement Act of 1999 restored slightly less than 10% of the funding cuts made in the 1997 legislation, increasing federal spending by 10.5 billion for the 2000 to 2004 period (CBO 1999).

These cuts in public funding for private hospital care has raised the concern that the closing of psychiatric units which began in the late 1980s and 1990s in the for-profit

arena as private insurance adopted managed care will spread to the nonprofit institutions that currently provide much of psychiatric care. The National Association of Psychiatric Health Systems (NAPHS) 2001 Annual Survey reported that among its member facilities Medicare and Medicaid accounted for 45.4% of admissions in 2000 (NAPHS). In the US, in 2000, Manderscheid et al. (2000) report the number of psychiatric beds in 1970 was 524,878 (413,066 in state and county psychiatric hospitals), by 1998 the number decreased to 261,903 (63,525 in state and county psychiatric hospitals). The majority of psychiatric beds now are in the private sector and are largely outside of state or federal regulation regarding remaining open. Indeed, while psychiatric beds in the private sector increased from 14,295 in 1970 to 44,871 in 1990, by 1998 these had decreased to 33,635 (Manderscheid et al. 2000). Occupancy rates as reported by the NAPHS had increased from 55.6% in 1996 to 69.2% in 2000. Occupancy rates have continued to rise. By the NAPHS Survey (2005), a quarter of typical hospitals reported occupancy rates exceeding 82%. Anecdotal reports in both professional and lay news described shortages of psychiatric beds across the country. The Ohio Department of Mental Health—Offices of Licensure and Certification and Office of Quality Improvement compiled a report documenting a 9% decrease in private psychiatric hospitals or units in general hospitals and an 18% decrease in psychiatric beds in these units from 1997 to 2002 as shown in Table 86–13 (Ohio Department of Mental Health 2002). The largest decrease was a 28% loss of adolescent beds. The changes occurred across the state with only one region reporting a slight increase of 6% in beds. The other seven regions showed declines with the largest decline being in a rural southeastern region (55%) and a central urban region (51%). The state-wide trend toward decreased number of beds appeared to slow and then reverse in recent years with nearly no difference between the 2003 totals of 2872 licensed beds and 2861 in 2006. (Table 86–13) (Ohio Department of Mental Health 2007) There was a change in distribution with adolescent and child beds increasing from 473 in 2003 to 551 in 2006 while adult beds decreased from 2399 to 2310. Nationally the 2005 NAPHS Annual Survey showed the trend towards decreased number of beds appeared to have reversed with a 3.5% increase in licensed beds and a 5.3% increase in staffed beds being reported by member facilities (NAPHS 2006). Length of stay continued to decline from 9.9 days in 2003 to 9.6 days in 2004 (NAPHS 2006).

The hospital bed and occupancy numbers point to a great shift in acute psychiatric care in the last 20 years. Most patients now receive inpatient care in private hospitals although their care is often publicly funded. Occupancy rates in these hospitals has risen steadily over the last decade. The number of beds and units available in the private facilities is controlled by the hospitals themselves with market forces often being a large factor in these decisions. After the initial tremendous increase in private psychiatric beds from the 1970s to 1990s, the number declined through the late 1990s and early 2000s both nationally and in Ohio. By the mid-2000s, national and Ohio state trends showed stabilization and even small increases in the numbers of beds.

In summary, payment reforms in Medicare, including both DRGs and the RBRVS, have had a significant impact on medicine and psychiatry without fundamentally solving the cost problems in the health care system. Psychiatric care, initially exempt from DRG payment schemes and benefiting to some extent from RBRVS payments has faced increased pressure along with the rest of medical services from implementation of the cost cutting Balancing Budget Act of 1997 which reduced Medicare and Medicaid reimbursements. Current levels of public funding of care within the private sector may not be enough to prevent erosion of this latest safety net for people with mental illnesses.

The impact of the earlier payment reforms (DRG and RBRVS) has extended beyond Medicare, already the largest single payer of health care bills in the US. Surveys of 24 Blue Cross and Blue Shield insurance plans in 1994 found that for physician payment, greater than three-fourth used the Medicare RBRVS approach and for hospital reimbursement, two-third used a DRG approach (Grading Health Care Reform 1994). Thus, systems that attempt to link standards for payment to the type of illness and condition have had a growing impact. Two major problems persist, however. First, these methods do not address other reasons for cost increases in health care. Second, these broad-brush strategies fail to address the normal and appropriate variances in care required by individuals. By using a "lowest common denominator" approach to payment, these methods do not capitalize well on either payer or physician ingenuity in treatment. However, these methods were implemented during a time when there was also active experimentation with these issues and with approaches that blend economics, clinical knowledge, and systems technology to achieve better service quality and cost control. Often labeled managed care, these

**Table 86–13 Trends in Private Psychiatric Hospitals and Beds in Ohio**

| Year | Total | Adult | Adolescent | Child | Number of Hospitals |
|---|---|---|---|---|---|
| 1997 | 3456 | 2792 | 503 | 161 | 96 |
| 1999 | 3390 | 2748 | 477 | 165 | |
| 2001 | 2931 | 2428 | 363 | 140 | |
| 2002 | 2842 | 2341 | 361 | 140 | 87 |
| 2003 | 2872 | 2399 | 339 | 134 | |
| 2004 | 2778 | 2300 | 346 | 132 | |
| 2005 | 2718 | 2247 | 335 | 136 | |
| 2006 | 2861 | 2310 | 380 | 171 | 85 |
| % Change | −17% | −17% | −24% | +6% | −11% |

*Source:* Ohio Department of Mental Health (2002, 2007).

approaches have rapidly shaped health care in general and mental health care in particular.

## The Emergence of Managed Care and Its Impact on Mental Health

It is clear that the evolution of health and mental health policy has involved a dynamic tension among social–political forces, clinical philosophies and practices, economics, and the organization of care systems. In the 19th century, mental health care was shaped more by social forces and related clinical philosophies, as in the connection between Jacksonian reform and the establishment of asylums. In the closing decades of the 20th century, economics has arguably been the dominant force shaping mental health.

There has been a dramatic expansion in the availability of care and the emergence of a substantial private sector of mental health treatment financed by employer-based private insurance. Yet old problems have persisted, and a new problem has become dominant—the costs of health care. By the early 1990s, health care costs in the US were a higher proportion of the gross national product than in any other developed country, and the rate of health care cost inflation was among the world's highest. Despite widespread attention to the costs of healthcare in the US the 2000s brought little change. The US spent $2.0 trillion in health care costs or $6,697 per person in 2005. Although the rate of rise appeared to be moderating in mid-decade, health spending represented 16.0% of the gross domestic product (GDP) in 2005 (CMS 2007). In seeking solutions to this problem, health care has sought new organizational forms involving arrangements such as health maintenance organizations (HMOs), individual practice associations, and preferred provider organizations. These approaches involve variously organized networks or associations of providers and move beyond strictly economic strategies that seek to alter costs by modified payments to providers or charges to consumers.

## The Nature and Growth of Health Maintenance Organizations

HMOs are, fundamentally, group medical practices that are prepaid—the practice organization is paid a set amount by its members in advance to take care of them if they are ill or even, indirectly, to protect their health. The first prepaid group practice was in 1929, when two Los Angeles physicians contracted with employees of the Los Angeles County Department of Water and Power, and their families, to provide comprehensive health care services in return for prepaid fees (Bennett 1992). With the Great Depression, World War II, and the subsequent effort by both employers and health providers to develop insurance-financed care arrangements, fee-for-service arrangements were dominant, and cost control took a back seat. Although some notable HMOs such as Kaiser Permanente developed during this period, the majority of care was paid for by retrospective fee-for-service arrangements. HMOs were viewed as alternative medicine and resisted by most physicians and physicians' groups. HMOs use a wide variety of means to provide care while controlling costs, including controlled staffing levels, salaried staff, "wellness" programs, and use of nurses and other clinical staff who are paid less than physicians.

Ironically, given their image as an alternative social innovation, HMOs received a major boost as a key ingredient in the Nixon administration's health care reform proposals, with Paul Ellwood as the champion of the concept. Credited with coining the term *health maintenance organization*, Ellwood saw HMOs as a way to improve care while containing costs and made the approach a central element of Nixon's proposals. The Health Maintenance Organization Act of 1973 was the result. This legislation subsidized the creation and expansion of HMOs and broadened the approach to allow profit-making corporations to become HMOs and to allow "medical care foundations" to function as HMOs (Bennett 1992). Medical care foundations evolved to be known today as independent practice associations, one of the major variants of prepaid plans. An independent practice association may be described as a "loose HMO," in which a group of practitioners agree to accept fixed fees without formally organizing into a group practice. (In the HMO, by comparison, physicians are employees of the organization and are almost always salaried.)

Certain forms of cost containment are "built into" prepaid plans such as HMOs. The prepaid nature of services itself introduces an incentive to avoid providing unnecessary care. The apparent ability of HMOs and the other prepaid and managed care approaches to control costs is certainly a major factor in their expansion. In 1983, fewer than 14 million Americans were enrolled in HMOs (Goran 1992). By 1991, 47% of Americans with employer-financed health insurance were in managed care arrangements. By 1994, this figure had climbed to 65%, and HMOs claimed more than 50 million members (Eckholm 1994). The increase continued to over 75% of the insured population being in some type of managed care plan by 1998 (Frank and McGuire 2000).

## Preferred Provider Organizations

Preferred provider organizations are another variant on the organization of health care, sharing some similarities with both HMOs and individual practice associations in terms of structure and approach. In the typical preferred provider organization, a group of physicians—who usually do not practice together but maintain their own offices—negotiate discounted rates with insurers in return for "preferred" status as the primary health care providers for the insured group. Thus, the preferred provider organization is not a prepaid arrangement, but payment to the group is based on discounted fee-for-service rates. As in the case of HMOs, members typically pay a penalty for getting care outside of the network. At a minimum, the copayments for care outside the network are higher. In some situations, the insurer will not reimburse at all for care outside the network, except in emergencies.

## HMOs and Mental Health Care

The history and track record of HMOs in providing mental health care is unexceptional. In a way, it parallels the record of mental health care under private insurance in general: limited benefits, an emphasis on a few treatment approaches, and gradual evolution to more satisfactory patterns of care. However, some of the dynamics of HMOs affect mental health care in particular ways. The 1973 Health Maintenance Organization Act required that HMOs provide only a limited mental health benefit (crisis care and up to 20 sessions for evaluation and brief treatment, with no coverage required for inpatient care or for treatment

of ongoing conditions). Whereas many plans found that this low benefit level was unworkable and added coverage for inpatient treatment, the profile of psychiatric care in most HMOs remained low. Martinsons (1988). found that the common level of mental health expenditures in HMOs was 3−5%, contrasted with 8% of all expenditures in fee-for-service plans. Some observers now believe that mental health consumes on average up to 12−14% of expenditures in fee-for-service plans, raising serious questions about the adequacy of mental health service levels in HMOs.

## Emergence of Managed Mental Health Care

Stimulated largely by the substantial increases in mental health expenditures during the 1980s and the failure of strictly economic approaches to control costs, managed care techniques were increasingly applied to mental health care. The primary strategies employed in early managed care efforts might best be described as "managed cost" attempts to intervene in treatment decisions like hospitalization to prevent all unnecessary expenditures. These arrangements typically involved the requirement that third-party reviewers (frequently entry-level clinical staff armed with procedure code-books) authorize any inpatient admissions. This authorization would usually cover a limited time, with the requirement that permission be obtained for any treatment beyond this initial period. The clear target of early managed care efforts was psychiatric inpatient treatment, which had been the area of greatest cost increases during the 1980s as benefits were expanded. These arrangements were successful in limiting costs but angered many psychiatrists.

The early managed care efforts did demonstrate the efficacy of a specialized approach to management of mental illness care, against the typical pattern of high costs in fee-for-service plans and low levels of services in many HMOs. Consequently, a "carve-out" strategy was increasingly used by employers, who would contract with a distinct entity to manage all mental health and substance abuse treatment needs of the covered population. Such arrangements, in addition to limiting treatment costs, started to demonstrate effectiveness in improving outcomes, such as improved access with increased number of people receiving behavioral health services and decreased medical costs (Cuffel et al. 1999).

As expertise in these practices grew, specialized managed care providers, during the late 1980s and early 1990s, moved beyond the crude managed cost efforts of the first-generation programs. The second tier of programs began to use more sophisticated approaches, including selecting their "network" of providers on the basis of reputation and credentials in addition to low cost, offering training in more effective or relevant treatment approaches, and initiating new but lower cost services rather than just denying access to care. For example, partial hospital programs and intensive outpatient services were developed to provide an alternative to inpatient treatment for some patients. Thus, these second-generation efforts focused on managing care as well as cost.

As distinct "behavioral managed care" programs evolved, efforts turned beyond screening—prior authorization methods and the selection of lower cost providers—and put more emphasis on quality assurance protocols that provided feedback to psychiatrists. This evolution has led to the third generation of specialized managed care. The program developed by IBM in the early 1990s provided a benchmark for these more sophisticated efforts.

Like other large employers, IBM had seen its mental health and substance abuse treatment costs rise dramatically under its fee-for-service insurance with generous benefits. The company was committed to cost control but equally insistent that this not be achieved through limiting benefits and crude rationing. In developing specifications for its new program, IBM employed an independent mental health advisory board to both assist in the development of a managed care program and oversee its operation.

The resultant program, operated by one of the new behavioral managed health care firms (American Psych Management), was designed to operate as a complete system responsible for screening needs, establishing a preferred provider network, managing care received through this network, and conducting extensive customer satisfaction and quality assurance monitoring (Bengen 1992). Within this program, more extensive benefits were offered than were available under the prior fee-for-service program (e.g., residential treatment centers and other residential care), but all services were subject to care management and individual treatment planning.

This type of arrangement is relatively typical of third-generation managed care programs, in which the functions of utilization review and care management, as well as responsibility for actually providing care, are assumed by the managed care firm. The firm employs mental health clinicians (supervised by psychiatrists) to conduct the care management function, recruits providers into a closed panel or network, and manages the care network including quality assurance functions. In these arrangements, the firm is essentially a specialized or carved out HMO, responsible only for mental health (and, typically, substance abuse care). The basic concept of this approach is also remarkably similar to the design of the public sector CMHCs developed several decades earlier, although the managed care firm serves a covered population and the CMHC functions as a network of care for a primarily uninsured population.

Behavioral health carve-outs of benefit management alone or combined with the provision of care appear to have improved the quality of mental health care but integration of general medical and psychiatric care especially for people with co-morbid conditions is neither addressed nor improved by this approach.

## Managed Mental Health Care in the Public Sector

By the early 1990s, managed care's presence in employer-sponsored health insurance was well established and new markets were sought. At the same time, state governments concerned about increasing budget deficits and specifically about the ever growing proportion of state budgets spent on Medicaid, looked to managed care as a mechanism to control costs. Together, these factors resulted in a rapid expansion of managed care into both public general medical care and into public mental health care. Mechanic et al. (1998) reviewing HCFA data report that by 1997 nearly half of Medicaid recipients were enrolled in a managed care plan. Croze (2000) citing a Substance Abuse and Mental Health Services Administration (SAMHSA) 1998[report, states that 46 states were implementing managed mental or behavioral

health in some form and 10 states had virtually no fee for service behavioral health care funded by Medicaid. Of these 46 states, 25 handled a significant portion of their Medicaid benefits through risk arrangements in which risk is transferred from the state Medicaid agency to another entity. Seventeen states utilize a managed behavioral health care organization (MBHO) carve-out in some manner. The risk however is transferred to a variety of organizations including a MBHO, a MBHO/provider partnership, the county government itself or an authority appointed by county government, a CMHC or local behavioral health authority. She describes the complexities of these new arrangements, including common emphasis on "medical loss ratio" (maximum dollars directed to care and treatment), use of caps on profit and administration, frequent requirements for reinvestment in service development, financial reserves, and performance bonds and/or lines of credit.

Another common feature is the exclusion of pharmaceutical coverage within the behavioral health contract. This is a strategy recommended by the Department of Health and Human Services—Office of the Inspector General by HHS-0I6 as reported by Ross (2000) due to concern by states that they could not accurately determine the cost for this benefit and were concerned that if not costed correctly managed care organizations would restrict access. However, as pharmaceuticals (psychotropic and other drugs) account for a growing proportion of health care spending this exclusion may need to be reconsidered.

Between 1999 and 2000, spending on drugs in the US increased by 18.8% from $111.2 billion to $132 billion (Charatan 2001). Three factors accounted for most of the increase; a larger number of prescriptions, the use of more expensive drugs, and price increase (Charatan 2001). Aggressive marketing by drug companies also contributed to the spending increase (Charatan 2001). Newer antidepressants and antipsychotics are substantially higher priced than older medications. Together, these families of psychotropics account for a large proportion of the increase in spending on drugs. Antidepressants represented the second highest sales by class of medications in 2000 at $8.3 billion (IMS Health 2001). Antipsychotics ranked sixth in sales at $4 billion (IMS Health 2001). In 2000, the top ten list of the US sales of prescription products included two SSRIs and one new antipsychotic (IMS Health 2001). Antidepressants widely used across both general medical and psychiatric settings have a broader impact in prescription costs. Newer antipsychotics used primarily for the treatment of schizophrenia spectrum disorders disproportionately impact Medicaid spending. Medicaid spending on antipsychotics increased nearly 2.5 times between 1995 and 1998 from $484 million to 1264 million (Mulligan 2002).

Medicaid spending on prescriptions continues on an accelerating course. Between 1994 and 1998, Medicaid spending increased from $8.4 billion to $13.6 billion. The next five year period 1999 to 2003 showed an increase from $16.2 billion to $34.3 billion. Together, these represent a greater than four fold increase in spending over 10 years (Lied et al. 2006). For Medicaid, the increase in spending was due to the increased number of enrollees and an increase in the mean price per prescription (Lied et al. 2006). In 2003, Medicaid spent approximately $7.3 billion on central nervous system drugs (mostly for the treatment of psychiatric disorders), the highest single category of drug spending making up 21% of the total drug reimbursements (Lied et al. 2006). Indeed, in both 1998 and 2003, the antipsychotics Zyprexa and Risperdal held the first and second spots for total reimbursements (Lied et al. 2006). Both drugs experienced over 100% increases in the number of prescriptions during the time period (Lied et al. 2006). The large increase in Medicaid drug costs especially psychotropic costs have led to a variety of strategies by states to control these costs. New Hampshire's attempt in 1981 to control Medicaid spending by limiting prescriptions to 3 per month resulted in savings in drug costs but this was negated by a even higher increase in mental health costs including outpatient visits, emergency services, and partial hospitalization (Soumerai et al. 1994).

Fail-first strategies in which a person must first try a particular drug from a family, such as SSRIs before access to other options are approved, have been adopted by some states either directly or through managed care plans. The pharmaceutical industry, advocacy and physician groups have often opposed these techniques. A more recent tactic meeting with more acceptance and some success has been to focus on physician practices such as prescribing multiple drugs from one family which can increase costs and for which there is little scientific evidence to support the practice. Usually, other quality measures such as recommended dose ranges and multiple prescribers of a drug or drug class are also targeted. Missouri, for instance, implemented the approach in 2003 (Bergman et al. 2006). Anticipated savings for Missourri in 2004 was $7.7 million (Bergman et al. 2006).

Those individuals enrolled in traditional Medicare plans were without any prescription drug benefit to cover these costly medications until the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 went into effect in 2006. This act allows Medicare beneficiaries to enroll if they choose in one of many prescription drug plans. Individuals who were dually eligible for Medicaid and Medicare under this plan, in most circumstances and for most drugs now have their prescriptions paid for under one of the Medicare plans. These plans administered by the private insurance industry utilize managed pharmacy benefit techniques albeit under some government regulations. Solutions to the rising drug cost problem are not easy. Canada controls medication costs via federal regulation. However, while prices are lower than in the US, Canadian prescribing trends toward newer, more expensive psychotropics led to a 216% increase in cost for these drugs between 1992 and 1998 (Dewa and Goering 2001).

Differences in managed mental health care programs abound. Debate continues regarding which programs are successes and the reasons for programs failing. Croze (2000) presents programs in Colorado, Iowa, and Massachusetts as having achieved improvements in some of the following areas: decreased costs, increased penetration, decreased hospital admissions, increased array of services, and decreased waiting times. How much more efficiency and cost saving may be gained by further use of managed care is not clear. Historically, those areas which relied more heavily on inpatient care have produced earlier and more dramatic results using managed care through decreasing the use of inpatient care by decreasing admissions and decreasing length of stay. There may now be more areas,

similar to the Oregon counties, studied by McFarland et al. (2002) in 1995 in which one county switched to a managed Medicaid system while the other remained fee-for-service. Both counties showed decreased length of stay from 1994 to 1996. The county which changed to managed care retained its slightly longer length of stay. As length of stays shorten, in this case to 6 days, it becomes more difficult to discern differences between groups. In some areas there may be little left to squeeze from the inpatient care system.

Finally, greater appreciation by both the managed care industry and by state and local governments about the complexities of providing care for the SMI population may also temper the initial enthusiasm for public managed mental health care. Concerns about the ability of managed care systems, which have traditionally served populations with large numbers of relatively healthy, well functioning individuals, to serve a disabled, severely and persistently ill population remain. Boothroyd et al. (2002) recommend caution in considering risk arrangements for such vulnerable populations on the basis of their finding that Florida Medicaid enrollees in plans in which providers bore financial risk reported less use of both general medical and mental health services and more problems with access than those enrolled in fee-for-service plans. Satisfaction with general medical services but not with mental health services was also adversely effected by the provider bearing risk (Boothroyd et al. 2002).

The structure of risk sharing arrangements varied greatly across the five SAMHSA demonstration sites which targeted adults with severe mental illness; but all five sites showed an inverse relationship between assumption of risk and the application of strict utilization review (Ridgely et al. 2002). Other differences between sites included how substance abuse and pharmacy benefits were provided (Ridgely et al. 2002). Monitoring the effect of managed mental health care on people with severe mental illness will remain a challenge for the upcoming years.

## Emerging Directions in Care Management

It is clear that the more sophisticated managed care approaches have succeeded in controlling mental health care costs while addressing concerns about quality that were serious and legitimate regarding early cost management programs. A 1993 report by the actuarial consulting firm Milliman and Robertson cited experiences with five major US firms that implemented mental health managed care approaches, achieving consistent savings and increasing benefits or use of services among the covered population (Melek 1993). As a result, the growth in use of mental health managed care has been extraordinary. By 1993, specialized behavioral managed care firms were responsible for mental health care for more than 80 million Americans.

Managed care programs in mental health have been more successful at balancing cost control, access to care, and quality than approaches that emphasize benefit limits and payment approaches, such as DRGs. Done well, managed care efforts blend economic incentives with clinical decision-making in the context of a prepaid system of care. Yet, these arrangements cover the gamut from the relatively crude cost management programs that emphasize rationing to sophisticated third-generation efforts that emphasize quality. The trend among larger employers is clearly toward the more sophisticated managed care approaches. However, future directions are uncertain, given the extraordinary cost pressures that still exist in health care.

Kunnes (1994) predicted that future approaches to mental health services will move beyond managed care as it is now known. He forecasted the increased development of "integrated delivery systems" that are "vertically and horizontally integrated, managed, very patient friendly, regional, and inclusive of both behavioral health care and medical/surgical services" (Kunnes 1994). Under this scenario, provider networks will increasingly take on their own insurance functions, capitalizing on their local reputations and relationships while recognizing the need to manage risk. Kunnes also predicted that "distinctions between public and private delivery systems will break down" (Kunnes 1994). Whereas this is only one of many possible future scenarios, it illustrates a direction that builds on emerging developments in the mental health field: increased access, cost control, and strategies to achieve these goals that use economic incentives, clinical decision-making, and organizational approaches.

## The Quality Improvement Movement

Mental health treatment has also been affected by the quality improvement methods and approaches that have evolved from the work of W. Edwards Deming and other industrial quality improvement "gurus." Central themes include the idea of quality improvement as a continuous process, the importance of measurement in aiding in and defining changes in quality, and an orientation to customer requirements and satisfaction. These ideas have been reflected in the accreditation standards of the Joint Commission on Accreditation of Health Care Organizations and signal the evolving direction of quality improvement. Bologna and Feldman predicted that the direction of quality efforts in mental health will evolve toward continuous improvement: "A feedback loop in which clinical outcomes shape patient treatment matching, which in turn changes outcomes, is the core mechanism from which many of the most dramatic changes in behavioral health care will evolve" (Bologna and Feldman 1994, p. 32).

Knowledge of the terms and processes used in quality improvement is essential for mental health professionals. Beaudin and Beaty (2004) describe strategies currently used in behavioral health quality improvement. Quality assurance emphasizes compliance with regulation standards and targets individual performance rather than examining processes. Quality improvement surpasses these minimum standards in order to improve outcomes by enhancing effectiveness and efficiency. Quality improvement targets changes at systems and processes. A basic strategy from Deming's work is Plan-Do-Check-Act (PDCA). Planning involves process investigation, date collection and analysis. In the Do phase, the plan is implemented. The effects of implementation are measured to see if it is having the desired effect in the Check phase. The Action phase leads to the new method being adopted or abandoned, evaluation of corrective plans and communication of results. Examples of application of quality improvement models reviewed are increasing the rate of outpatient follow-up after psychiatric hospitalization, better detection of delirium and other organic disorders in the elderly and better access to specialty behavioral health care.

## Defining and Improving the Quality of Mental Health Care

The issue of the quality of mental health treatment presents several paradoxes. One is the gap between solid knowledge of the general efficacy of treatment and the absence of much specific research that links particular interventions with particular conditions at defined times. A second paradox involves the gap between findings of treatment efficacy (the demonstrated impact of care under research conditions) and broader treatment effectiveness (the results achieved under typical treatment conditions).

The general efficacy of mental health care is well established. In a comprehensive review of research on the epidemiology of mental illness and the effectiveness of care, the National Advisory Mental Health Council concluded that "for persons with serious mental disorders, the chances of obtaining significant benefit through treatment have never been better…a growing body of research knowledge from clinical trials has verified the efficacy of these treatments… this compares very favorably with other areas of medicine" (National Advisory Mental Health Council 1993, p. 1450).

There is also considerable evidence of the efficacy of particular categories of treatment. The volume of research on the efficacy of psychotherapy, for example, is extraordinary. In an analysis of the psychotherapy literature, Lipsey and Wilson (1993) concluded that the evidence of the benefits of psychotherapy is well established. At the same time, the diversity of mental illness and its treatments imposes a humbling reality. Research has not yet established clear findings linking the nature, method, and timing of interventions to particular conditions. Atkinson et al. (1992) concluded that not enough was known about which treatments work, the particular circumstances under which people with serious mental illness benefit, or how services should be sequenced or combined most effectively. Similar issues exist even within the psychotherapy research literature. Lipsey and Wilson (1993) found a relationship between the strength of the therapist–patient alliance and the effectiveness of treatment and the satisfaction with treatment predicted better outcomes, but their analysis did not correlate specific methods with conditions or diagnoses. Thus, there is considerable evidence about the effectiveness of mental health treatment and about which general types of treatment are helpful with which disorders. However, clear data establishing specific parameters for care of particular conditions under defined circumstances remain elusive.

At the same time, fiscal pressures and expectations of patients and payers are leading to an increasing emphasis on defining and improving the quality of treatment. With these pressures, approaches to address quality are evolving from crude, broad approaches like licensure and certification of professionals or programs to increasingly specific and focused strategies such as treatment guidelines for specific conditions.

## The Evolution of Quality of Care Strategies

The most basic approaches to ensuring the quality of care are licensure of practitioners as adequately qualified, certification of providers or agencies for the purpose of reimbursement, and accreditation of provider organizations by independent bodies.

### Licensure

Licensure of practitioners by states is the most basic and universal approach to quality. Licensure is based on training, a review of qualifications, and sometimes passage of an examination. Frequently, professionals must satisfy requirements for continued education to maintain their licensed status. As an approach to ensuring quality, licensure is basic; it focuses on the preparation of the practitioner but does not address the actual conduct, processes, or outcomes of care. Professional licensure is required to be able to practice or, generally, to accept reimbursement. Thus, licensure provides a kind of basic consumer protection, ensuring that patients are not treated by untrained or ill-prepared individuals.

### Certification

In most states, certification of provider organizations by state authorities is the equivalent of professional licensure; in fact, the terms licensure and certification of agencies are sometimes used interchangeably. Certification standards are typically designed to ensure that provider organizations are minimally qualified and usually address such issues as the presence of adequate and safe facilities, acceptable policies and procedures, qualified and licensed staff, appropriate record-keeping and treatment-planning procedures, and the like. Like professional licensure, certification is required as a threshold to provide care, typically being a requirement for public reimbursement or contracts. Certification can ensure that appropriate preconditions for quality care are present but cannot ensure that quality care is actually provided.

### Accreditation

Various independent organizations have developed voluntary standards and review mechanisms that they employ to accredit provider organizations. The most significant accrediting body in health care is the Joint Commission on Accreditation of Health Care Organizations, which predominantly accredits hospitals but also addresses health systems, clinics, and mental health centers. Other accrediting organizations that touch on mental health include the Commission on Accreditation of Rehabilitation Facilities, the Council on Accreditation (which specializes in counseling and family service organizations), and the Utilization Review Accreditation Council. The last organization is the newest and reflects the demand from both payers and treatment professionals that standards be developed to address the growing utilization review and managed care industry.

Accreditation has similarities to state certification and involves review of facilities, staffing, policies and procedures, and so on. However, accreditation is a voluntary process (although increasingly, purchasers insist on accreditation as another assurance of quality). Accreditation is often more demanding than state certification standards, for example, it may address evidence of the actual use of practices such as quality assurance or review of staff members' credentials. However, accreditation, like licensure and certification, indicates only that the conditions for quality care are present—or at least they were present at the time of the most recent survey. Given the increased concern about cost and cost effectiveness that characterizes the current health care environment, more specific methods are increasingly being developed.

## Developing Approaches to the Quality of Care

Beyond licensure, certification, and accreditation a variety of approaches are used to respond to demands for quality of care data. A direct approach that is increasingly in vogue is assessing patients' satisfaction with care received. Whereas "customer satisfaction" is a legitimate issue to assess on its own merits, there is some research justification for assessing patients' satisfaction as an approach to quality. In Lipsey and Wilson (1993) meta-analysis of psychotherapy research, patients' satisfaction was related to outcomes, a finding that also emerged from the study by Roth et al. (1995) of outcomes for SMD patients in community care.

Owing to the increasing understanding of satisfaction as an outcome-related variable and because of its inherent value, managed care firms are increasingly requiring the use of satisfaction measures by practitioners. According to Freeman and Trabin, "The demand for data on quality has led to almost universal implementation of customer (patient) satisfaction measurement through the use of questionnaires as a first step. Measuring self-reported patient satisfaction is often easier than measuring clinical outcomes. Similarly, provider network satisfaction ratings and patient satisfaction measurement queries are finding their way into the audits of managed care plans performed by employee benefits managers" (Freeman and Trabin 1994, p. 30).

Another quality-related practice that is growing in acceptance is the use of standardized assessment scales as an aid to assessment of patients and treatment planning and to assist in checking progress in treatment. Although there is not yet evidence to support the use of standardized measures to dictate treatment regimens, there can be little doubt that these measures provide an element of objectivity and can serve as a reference point. The use of these measures is also generally considered important as documentation that treatment has progressed according to accepted professional standards. The Institute of Medicine's report "Improving the Quality of Health Care for Mental and Substance Use Conditions" emphasized the importance of clinicians and organizations using standardized questionnaires or other assessment tools to measure outcomes of treatment to contribute further to the evidence base of treatments and to monitor and enhance the quality of care (Pincus et al.2007). Clinicians who read outcome reports based on standard measures of patients at baseline and throughout treatment had patients who reported greater improvement (Azocar et al. 2007).

### Practice Guidelines

Research on the effectiveness of different patterns of care is also enabling the development of practice guidelines—recommended approaches to the treatment and management of particular conditions. These guidelines are intended to strike a balance between specificity when it is possible and deference to the psychiatrist's judgment when it is appropriate. Practice guidelines are typically developed by consensus panels of researchers and psychiatrists on the basis of the state of knowledge that exists with respect to a particular condition. Guidelines for the treatment of psychiatric disorders have been published by the American Psychiatric Association (see Table 86–14) (American Psychiatric Association 2006). Other groups are also working on treatment guidelines in mental health. The Agency for Health Care Policy and Research and the NIMH funded a Patient Outcome Research Team (PORT) study to review the literature, study actual practice patterns, and make recommendations for the treatment of schizophrenia. The approach has been used previously to develop treatment recommendations for cataract surgery, hip replacement, and other conditions, but the PORT study of schizophrenia was the first in mental health. The PORT study recommended 30 interventions for the treatment of schizophrenia. The majority of the recommendations focused on adequate use of antipsychotics and other medications but included the use of electroconvulsive therapy, selected forms of psychotherapy (nonpsychodynamic), family support and psychoeducation, vocational rehabilitation, and assertive community treatment (Lehman and Steinwachs 1998). A challenge to implementation of recommended practices is the picture that is emerging of actual practice trends that favor medications over psychotherapy and other psychosocial interventions. West's group assessing conformance to the PORT and APA guidelines for the treatment of schizophrenia noted that conformance for psychopharmacolgic treatment was high (99% received antipsychotic medication with 83% receiving treatment with atypical antipsychotics at target ranges), conformance for a variety of recommended psychosocial treatments was low ranging from 0% for vocational rehabilitation to 43% for illness education or psychotherapy (West et al. 2005).

Similarly, the outpatient treatment of depression has been noted to increasingly favor treatment with antidepressant medication over psychotherapy even for those types of depression for which psychotherapy is as effective (Olfson et al. 2002). This study revealed that while overall rates for treatment of depression increased between 1987 and 1997 from 0.73 per 100 persons to 2.33 per 100 persons the increase was almost entirely due to an increase in antidepressant use. In 1987, 37.3% of people were treated with antidepressants compared to 74.5% in 1997. At the same time the proportion of people receiving psychotherapy for depression declined from 71.1% to 60.2%. A comparison study of the trends in overall use of outpatient psychotherapy showed no significant change with rates between 1987

**Table 86–14 APA Practice Guidelines for Treatment of the Following Psychiatric Disorders Have Been Developed**

- Acute stress disorder and post traumatic stress disorder
- Alzheimer's disease and other dementias
- Bipolar disorder
- Borderline personality disorder
- Delerium
- Eating disorders
- HIV
- Major depression
- Nicotine dependence
- Obsessive compulsive disorder
- Panic disorder
- Psychiatric evaluation of adults
- Schizophrenia
- Substance use (Alcohol, cocaine, opioids)
- Suicidal behaviors

and 1997 (3.2 per 100 persons and 3.6 per 100 persons) (Olfson et al. 2002).

Many efforts to standardize patterns of care whether they be more comprehensive approaches such as the APA guidelines or PORT recommendations or more restrictive medication guidelines or algorithms have heavily favored newer pharmacologic agents. A recent challenge to these guidelines has been the release of two large, longitudinal studies (CATIE and CUtLASS) which has raised some questions about the previously presumed clinical superiority and safety of newer drugs which were given preferred status in some guidelines (Lieberman et al. 2005, Jones et al. 2006). Beyond the challenge to some of the recommended practices, these studies have raised cost effectiveness questions which is further addressed in an earlier section of this chapter "Effective treatments and defective funding." The clinician using practice guidelines should consider the sponsorship and support of the project (including the funding source), by whom the guidelines were developed, the process used and the goals of the guidelines. Some guidelines focus soley on medication algorithms while others review all treatment modalities. Some guidelines or reviews adhere more strictly to using randomized controlled trials (RCT) while other venture recommendations beyond these especially when RCT data is limited. Some guidelines are more user friendly then others. Still, with these caveats in mind, the future will find increased use of practice guidelines in mental health and in health care in general.

## Prospects for the Future

Absent revolutionary changes in the basic landscape of health care—which are certainly possible—the trends described in this chapter are likely to continue. At the same time, the rate and path of change are unpredictable; the complexities of the health care system and of mental health care in particular make this virtually certain. An appreciation of the dynamics and general directions of change is most relevant in this uncertain context.

As the discussion earlier in the chapter illustrates, reform in mental health has been tied to social and political trends in the larger society, and emerging clinical innovations and treatment approaches have often been linked with parallel social changes. This is an important dynamic that is likely to persist. The increasing diversity of society may thus be linked to the reduction in the stigma of mental illness and to seeking help that has been so dramatic in the past generation. On the other hand, there remain strong signals of intolerance, and the income and class differences between rich and poor are not being reduced. The fate of the most seriously and persistently mentally ill, especially the homeless mentally ill, may rest as much on these trends as on advances in treatment.

The relationship between the public and private mental health sectors has been one of the most important and underestimated factors shaping mental health policy. Psychiatry emerged as a profession within the US medicine, by and large, in the public sector of the 19th century. In more recent years, the story has been dominated more by separate and discrete private and public sector systems, for those with means and less serious conditions on the one hand and the seriously mentally ill on the other.

There are numerous signs at this time of the blurring of lines between public and private sectors. The government insurance programs (Medicare and Medicaid) involve publicly financed but increasingly privately provided care. The financial pressures in the private health care sector are increasingly reminiscent of public sector limits. Although the Health Security Act failed to achieve passage in 1994, its proposition that universal, nondiscriminatory mental health coverage should be achieved—requiring the integration of public and private resources—struck a chord among health and mental health practitioners and policymakers.

The gradual fusion of many public and private resources in mental health is also augured by developing trends in the organization and financing of care. It is now abundantly clear that the complexities of treating mental illness cannot be addressed by the same economic approaches that have been used for inpatient and outpatient physical health care. At the same time, the financing and organization of most health care are changing, with much broader reliance on HMOs and the continued development of new provider collaboratives and networks. The implication is that the days of loosely regulated fee-for-service practice are essentially over. Whether the label is managed care, HMO, or practice network, the trends are toward strong controls and expectations by purchasers, collaborative practice, targeted use of expensive interventions, and increased focus on the customer−patient's satisfaction.

Trends in the definition and measurement of quality will buttress these developments. Whereas mental health care will continue to be artful and dependent on professional judgment, research advances and payer–customer demands will lead to the increased use of standardized assessments as an aid to clinical decision-making. Practice guidelines will suggest the optimal approach to and sequencing of care. Increasingly, the care of individual patients will be shaped by data-based feedback on their progress and needs.

Elements of this future may resemble an Orwellian new world in the eyes of some, but there is a positive side as well. The basic characteristic of a profession is the ability to define itself, and psychiatry remains positioned to define its role as mental health care evolves into the 21st century. Similarly, changes in payment systems and approaches to diagnosis and treatment will be used by the best practitioners to their advantage—and most particularly to their patients' advantage. The evolution of more effective and focused treatments, coupled with the reduced stigma of mental illness, may make the new era of psychiatry and mental health care the most productive and exciting era yet.

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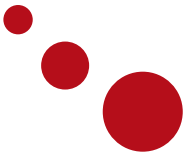
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SECTION VII

William H. Sledge and Bruce J. Rounsaville,
Section Editors

# *Psychotherapeutic and Psychosocial Treatments*

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CHAPTER 87

# Individual Psychoanalytic Psychotherapy

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Psychoanalytic theory provides the modern clinician with a comprehensive system for the understanding of personality development, the meaningfulness of human conflict and emotional pain, and the mutative factors within the doctor–patient relationship. Psychoanalysis is a general psychology, a developmental theory, and a specific treatment. Since its inception, psychoanalytic theory has undergone numerous and substantial revisions. Its history and the movements that contributed to its evolution are described in Chapter 28. With respect to psychoanalysis as a treatment approach, its history has been punctuated by persistent attempts both to simplify the psychoanalytic technique and to shorten its duration of treatment. The synonymous terms psychoanalytic psychotherapy, psychoanalytically oriented psychotherapy, psychodynamic psychotherapy, and expressive psychotherapy have come to represent the most coherent of these attempts.

For many years after World War II, there was an intense controversy among psychoanalysts about the merit of psychoanalytic psychotherapy because it was considered to be a diluted form of psychoanalysis with poorly defined techniques and goals. Today, for a number of reasons, this issue seems to be less important. First, and most recently, managed care, with its emphasis on cost containment and fiscal accountability, has attributed greater importance to episodic care through briefer psychotherapeutic interventions. Second, compared with 20 years ago, psychoanalysis as a treatment option is no longer equitably reimbursed by third-party payers. As a result, many analysts devote more of their professional time to psychoanalytic psychotherapy than psychoanalysis. Third, with only a few notable exceptions, psychoanalysis has all but moved out of psychiatry departments in academic health centers, and most residency training curricula now focus much more on the basic and practical applications of psychoanalytic theory and technique and not on more traditional psychoanalytic metapsychology. Moreover, during the last 35 years, many new, brief, psychoanalytically informed psychotherapies have been developed. These include, but are not limited to, the methods of Malan (1976), Mann (1973), Sifneos (1979), Davanloo (1978), Horowitz et al. (1984), Luborsky (1984), Milrod et al. (1997), and Strupp and Binder (1984). Manual-driven psychotherapies with demonstrated treatment efficacy, such as interpersonal psychotherapy and some forms of cognitive–behavioral psychotherapy, also incorporate many traditional psychoanalytic notions about the physician–patient relationship and the role of interpretation. Last, psychoanalytic theory has remained relatively dynamic and has integrated and consolidated the advances from object relations theory, self psychology, interpersonal theory, and the renewed interest in the study of psychic trauma. This has permitted, in the case of severe personality disorders and serious developmental trauma, the psychodynamic treatment of a broader range of psychological problems than was previously considered possible through classical psychoanalysis.

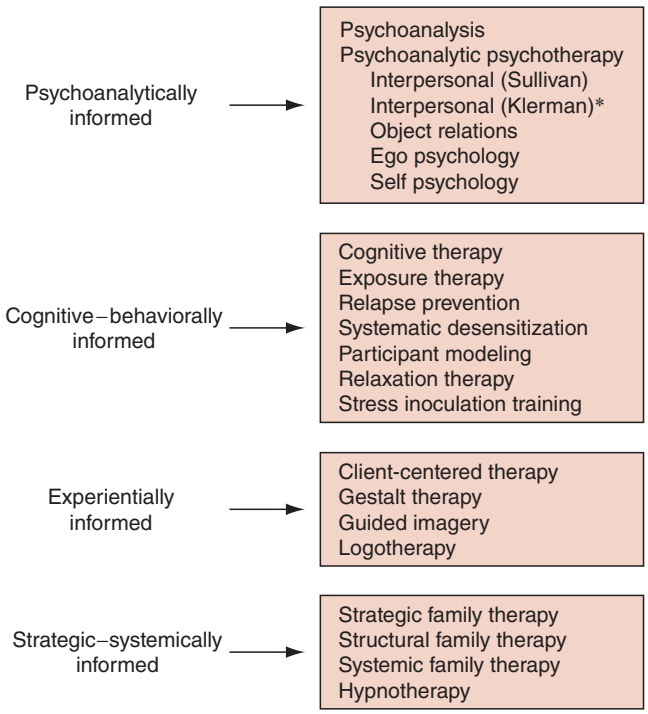
## What Is Psychotherapy?

It is customary to define psychotherapy in a broad fashion as comprising three distinct components: a healing agent, a sufferer, and a healing or therapeutic relationship (Frank and Frank 1991). Strupp (1986) specified that psychotherapy is the systematic use of a human relationship for therapeutic purposes of alleviating emotional distress by effecting enduring changes in a patient's thinking, feelings, and behavior. The mutual engagement of the patient and the psychotherapist, both cognitively and emotionally, is the foundation for effective psychotherapeutic work.

Whereas there are many different types of psychotherapy (Figure 87–1), the core task of the psychoanalytic psychotherapist is to make contact with and comprehend, as thoroughly as possible, the patient's subjective inner world to engage in an analytical (i.e., interpretive)

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conversation about it (Ornstein and Kay 1990). This core task implies that all psychoanalytic psychotherapies may be further defined in terms of three operations: accepting, understanding, and explaining (Ornstein and Ornstein 1985) (Table 87–1). First, and more specifically, the therapist must engage with the patient by accepting the subjective experience of the patient's emotional pain and conflict. This is achieved through the establishment of a therapeutic dialogue based on an empathic, nonjudgmental rapport. Second, within the process of listening to, and feeling with the patient, the therapist will begin to develop an understanding of the intricacies of the patient's plight. Much of what the therapist observes may at first remain outside of the patient's conscious awareness, manifested in the form of reenactments and reliving of earlier experiences within the therapy, rather than in deliberate, conscious, descriptive communication. Last, by the sharing of this beginning understanding with the patient through a simultaneously empathic and interpretive mode, both arrive at a deeper appreciation for the genesis of, and the reasons for, the patient's symptoms. The shared relationship in which understanding is gained is no less instrumental in achieving change than are the insights and modified perceptions that may result from the psychotherapeutic experience.




* Technically this is not a true psychoanalytic psychotherapy, but clinicians often rely on its analytic principles.

**Figure 87–1** *Some types of psychotherapy.*

**Table 87–1 Essential Operations of Psychoanalytic Psychotherapy**

| | |
|---|---|
| Accepting | The therapist affirms the patient's past and present subjective experience |
| Understanding | The therapist appreciates both the conscious and the unconscious contributions to the patient's emotional problems |
| Explaining | The therapist expresses, through interpretations, his or her understanding to the patient |

*Source*: Adapted from Ornstein and Ornstein (1985).

## Expressive–Supportive Continuum

Traditionally, to the degree that psychoanalytic psychotherapy has focused on the recovery of repressed psychological material, it has been called "expressive" and has been distinguished from the supportive psychotherapies, which have concentrated on the shoring up of certain defense mechanisms. Supportive psychotherapy has been the traditional treatment approach for more disturbed patients, for example, those with debilitating thought and personality disorders. Supportive treatment has also been helpful to patients who are not necessarily suffering from serious underlying impairments but whose symptoms are reactive to immediate identifiable precipitants, such as loss, illness, or other major life change. Expressive psychotherapy, on the other hand, has been concerned with the uncovering of unconscious beliefs, wishes, needs, and memories through the analysis of defense mechanisms and has been indicated for the treatment of neuroses and related conditions, as well as traumatic disorders and less dysfunctional personality disorders.

Such a clear-cut distinction is now viewed as arbitrary and scientifically unsound. Indeed, all effective psychoanalytic psychotherapies, including psychoanalysis, use supportive measures. Moreover, effective supportive psychotherapy is frequently psychoanalytically informed, and no systematic studies have demonstrated that the behavioral change and symptom relief from supportive treatment are inferior to, or less enduring than, those gained from expressive therapies (Wallerstein 1986).

It is more appropriate, therefore, to conceptualize psychoanalytic psychotherapy as being on a continuum of expressive to supportive (Luborsky 1984, Gabbard 1994). This implies that any given treatment might employ more or less expressive and supportive interventions, depending on what is transpiring within the psychotherapeutic process. An important skill of the psychoanalytic psychotherapist is then the ability to employ the appropriate balance of both expressive and supportive interventions as dictated by the needs of the patient. Finally, the conceptualization of an expressive–supportive continuum also facilitates the establishment of therapeutic goals, interventional plans, and indications for individual psychoanalytic psychotherapy (Gabbard 1994) (Table 87–2).

**Table 87–2 Comparative Interventions**

| Expressive | ←Continuum→ | Supportive |
|---|---|---|
| Confrontation | | Suggestion |
| Clarification | | Reassurance |
| Interpretation | | Advice giving |
| Interpretation of transference | | Praise |
| | | Environmental intervention and manipulation |

Clinical Vignette 1 illustrates the combination of expressive and supportive measures.

**Clinical Vignette 1**

Ms. S entered twice weekly psychotherapy because of the discouraging lack of career advancement. It became abundantly clear to the therapist that each time the patient was acknowledged by her peers for her outstanding contributions to her law firm, she became profoundly depressed and the quality of her work deteriorated. The therapist shared this observation with Ms. S, who became anxious and frightened. The patient worried that perhaps her reaction to the therapist's words indicated she was "sicker" than she thought. The therapist reassured the patient that she was not "going crazy," and stated that it was important to understand the meaningfulness of the response to the intervention as had been the case with all issues in the psychotherapy.

## Theory of Psychoanalytic Psychotherapy

### Basic Concepts

Because psychoanalytic psychotherapy is derived from psychoanalysis, it is necessary to appreciate the fundamental contributions. Five different but complementary views of mental phenomena constitute the metapsychology or theoretical edifice of psychoanalysis. Whereas none of the five constructs is comprehensive or sufficient to explain all of human behavior, each one has contributed a significant component to the current theory and technique underlying psychoanalytic psychotherapy. Freudian or classical psychoanalysis is, above all, a psychology based on mental conflict in which human beings are constantly defending against strong, unconscious, biologically based, intrapsychic needs and desires. The five metapsychological viewpoints attempt to explain this psychology (Table 87–3).

**Table 87–3 Five Metapsychological Viewpoints of Psychoanalytic and Associated Constructs**

| | |
|---|---|
| Topographical | Conscious, preconscious, unconscious |
| Dynamic | Conflict and resistance |
| Structural | Ego, id, and superego |
| Economic | Psychological investment in ideas and affects |
| Genetic | Past lives in the present, repetition–compulsion |

The topographical point of view states that there are varying levels of mental awareness. Feelings and thoughts may be unconscious, preconscious, or conscious. Repression, about which there is recent neuroscientific support (Anderson and Green 2001, Anderson and Levy 2006, Boag 2006), is the most basic of defense mechanisms that keep conflicted feelings and thoughts inaccessible, thereby preventing emotional discomfort. In addition, there are imaging investigations that demonstrate a specific mechanism in the medial prefrontal cortex for inhibiting memory retrieval and storage.

The dynamic point of view postulates that mental processes are both fluid and the result of opposing forces. This point of view supports the concepts of both conflict and defense. Defense refers to that universal unconscious process whereby patients struggle against the conscious awareness of anxiety-provoking mental content, such as memories, needs, wishes, or fears. There is neurobiological evidence for the existence of signal anxiety, which functions as an alerting or warning system to prompt defense mechanisms (Wong 1999). Resistance refers to defenses as they appear in the therapy when the patient unconsciously protects himself or herself against the anticipated pain of such awareness and therefore, to some degree, against progress in treatment.

The structural point of view is based on a tripartite model of the mind consisting of ego, superego, and id. Each of these theoretical concepts is associated with certain functions. The id, characterized by primary process thinking (does not follow rules of logic, lacks sense of space and time, thoughts and actions are equivalent) is considered the repository of irrational and illogical infantile wishes and impulses; the superego, narrowly defined, represents moral and ethical prohibitions; and the ego is that executive portion of the mind that mediates between the id and superego by allowing a person to establish a stable balance between early powerful feelings and impulses and the demands of socialization. The ego mediates, therefore, between the demands of the unconscious and those of external reality. The ego is conceptualized as containing not only the defense mechanisms but the experiencing and observing functions of the mind as well. Secondary process thinking, characteristic of the ego, provides the capacity for reality testing, logical thought, and appreciation of causality. Ego strength, a significant indicator for patients entering psychoanalysis and psychoanalytic psychotherapy, refers to the overall capacity for both personal and social competency.

The economic point of view attempts to explain the nature of psychic energy as it relates to the expression of feelings and ideas and is helpful in understanding defense mechanisms, those unconscious processes that ward off anxiety and other painful affects. As will be explicated, appreciating the role of defense mechanisms is critical to both understanding why patients behave in specific ways and appreciating the concept of transference.

The genetic point of view, the fifth perspective, addresses the centrality of those childhood experiences, especially traumas, that may account for strong feelings, conflicts, and symptoms later in life. This view is best expressed by the statement that the past lives in the present, meaning that past relationships or the representation of past relationships exist in the mind as if they were present relationships in the here and now. It also provides an explanation as to why certain dysfunctional or self-defeating behaviors are repeated throughout life in an attempt to master earlier psychological problems. It is responsible for the unique transference perceptions and reenactments each patient experiences in relation to persons in her or his present life, including the therapist within the process of psychoanalytic psychotherapy.

The theoretical concepts that derived from these five points of viewing mental activity constitute, more or less, the assumptions behind all psychoanalytic psychotherapy. These include, most importantly, the role of the unconscious, the centrality of transference, the characterological defense mechanisms, and the resistance to self-awareness and thereby to progress in the therapeutic setting. Of secondary importance, but nevertheless closely related to the unconscious, is the concept of psychic determinism, namely,

that people behave in specific ways for specific reasons that are mostly outside of awareness. No experience or memory, according to psychoanalysis, is ever lost but resides in the unconscious, which continues to influence current and future ways of experiencing feelings, thoughts, and behaviors. Advances in cognitive neuroscience have supported the notion that many significant experiences throughout life remain outside of awareness.

## Transference and Resistance, Countertransference, and Counterresistance

Transference and resistance constitute the two most distinctive features of psychoanalytic psychotherapies. Transference is defined as those perceptions of, and responses to, a person in the here and now that more appropriately reflect past feelings about, or responses to, important people earlier in one's life, especially parents and siblings. Whereas transference experiences are ubiquitous in everyday life as well as in psychotherapy, the development of a transference neurosis, or the recreation of a sustained, intensely affective, conflictual relationship to the person of the psychoanalyst, is more likely to occur within the analytical setting. It is promoted by characteristics of that therapeutic interaction (e.g., use of couch, frequent sessions, therapeutic regression, abstinent position of the analyst) and is more likely to be the focus of interpretation in psychoanalysis. However, supportive measures traditionally characteristic of other forms of treatment also have an important role in psychoanalysis. Psychoanalytic psychotherapy stresses the importance of transference within the treatment relationship, but it differs from psychoanalysis in that it does not, to the same degree, promote the depth and intensity of the transference.

Transference is demonstrated by the two patients in a brief clinical vignette (see Clinical Vignette 2).

**Clinical Vignette 2**

A patient comments at the end of the first session that the therapist reminds her of her beloved sister who is bright and generous, and whose style of home decorating is beautiful and warm. The patient was apprehensive about beginning psychotherapy but feels more hopeful and comfortable now that she has met the therapist and seen her office.

Another patient finds the office of this same therapist "sterile, not warm or homey and intentionally unrevealing" of who the therapist is as a person. The patient interprets this "professional decor" as an indication that she should not hope for warmth or emotional involvement from the therapist.

Countertransference is variously defined as (1) the analyst's or psychotherapist's transference reactions to the patient, (2) his or her reactions to the patient's transferences, and (3) any reactions, feelings, and attitudes of the analyst or therapist toward the patient, regardless of their source. Such responses to the patient were once viewed as deviations from the ideal of a consistently bland and comfortable experiencing of the patient by the analyst or therapist. Countertransference reactions were also conceptualized as impediments to progress within the treatment, that is, as interferences in the therapist's ability to understand the patient. They are currently more broadly understood as manifestations of the requisite engagement by the therapist or analyst in the emotional process of treatment. Moreover, these reactions are a rich source of understanding of the patient's experience as it touches the therapist affectively. Although countertransference feelings are at times uncomfortable for the therapist and a challenge to monitor and process, they are understood as a reflection of the glue of the relationship without which no real connection or significant change can occur.

Clinical Vignettes 3A–3C illustrate countertransference reactions in response to intense feelings of helplessness, irritation, and sexual feelings.

**Clinical Vignette 3A**

Dr. J was treating a 30-year-old depressed cardiac transplant patient in brief psychotherapy. The onset of the patient's depression coincided with clinical evidence that his new heart was being rejected. The patient's course deteriorated rapidly, and he was hospitalized. Dr. J continued to see the patient as he awaited the highly unlikely possibility of a new donor. After each of the sessions, Dr. J noted that he was exceptionally tired. On the way to his session with the patient that occurred on Christmas Eve, Dr. J stopped at the nursing station and prepared a plate of Christmas cookies for the patient, something he had never done for a patient regardless of the treatment setting.

**Clinical Vignette 3B**

Dr. C was treating a beginning college student who was having significant difficulty adjusting to her new environment complicated by the breakup of a long-standing relationship prior to the start of school. In the first weeks of treatment, the young woman had two overdoses and the patient's mother called the therapist frequently. Dr. C forgot that she was scheduled to meet with her patient, which precipitated further demanding behavior and a request for hospitalization. With her supervisor's assistance, Dr. C was better able to appreciate her irritation and resentment of both the patient and her mother.

**Clinical Vignette 3C**

A resident was treating an attractive young woman. He soon noticed that he was permitting the sessions to extend beyond his customary 50 minutes. He also became aware of a sense of excitement about his sessions with this patient even to the point of being aware that he paid particular attention to how he dressed on the days of his meetings with this young woman.

Resistance is broadly defined as the conscious or, more often, unconscious force within the patient opposing the emergence of unconscious material. Resistance must be understood not as something the patient does to the therapist, but rather as the patient's attempt to protect herself or himself by avoiding the anticipated emotional discomfort that accompanies the emergence of conflictual, dangerous, or painful experiences, feelings, thoughts, memories, needs, and desires. Resistance occurs through the use of unconscious

mental operations called defense mechanisms, for which there is substantial research support (Vaillant 1992, Horowitz et al. 1995) (Table 87–4). The recognition, clarification, and interpretation of resistance constitute important activities of the psychoanalyst and the psychoanalytic psychotherapist, both of whom must first appreciate how a patient is warding off anxiety before understanding why he or she is so compelled. (The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [DSM-IV-TR] notes the potential helpfulness of a Defensive Function Scale, which requires further study but may elucidate both defense levels and specific defense mechanisms in terms of adaptation, mental inhibitions, image distortion, disavowal, action levels, and defensive dysregulation levels; American Psychiatric Association 1994, pp 752–753.)

**Table 87–4 Some Common Defense Mechanisms***

| | |
|---|---|
| Denial | Refusal to appreciate information about oneself or others |
| Projection | Attribution to others of one's own unacceptable thoughts or feelings |
| Projective identification | Attribution of unacceptable personality characteristics to another followed by an attempt to develop a relationship based on those characteristics |
| Regression | A partial return to earlier levels of adaptation to avoid conflict |
| Splitting | Experiencing of others as being all good or all bad, i.e., idealization or devaluation and acting upon it |
| Conversion | Transformation of unacceptable wishes or thoughts into body sensations |
| Reaction formation | Transformation of an unwanted thought or feeling into its opposite |
| Isolation | Divorcing a feeling from its unpleasant idea |
| Rationalization | Using seemingly logical explanations to make untenable feelings or thoughts more acceptable |
| Displacement | Redirection of unpleasant feelings or thoughts onto another object |
| Dissociation | Splitting off thought or feeling from its original source |
| Sublimation | A mature mechanism whereby unacceptable thoughts and feelings are channeled into socially acceptable ones |

*All defense mechanisms are involuntary and unconscious and are arranged approximately from immature to more mature defenses.

An example of resistance is illustrated in the encounter given in Clinical Vignette 4.

Clinical Vignette 4

Ms. C entered psychotherapy because of anxiety and depression. Later in the treatment, evidence emerged that many of the patient's symptoms were related to her significant sexual conflicts and inhibitions. The therapist noted that each time the subject of her sexual activities was approached, Ms. C became confused and anxious and was unable to remember what had been discussed from one session to the next. This pattern of response was involuntary and left the patient frustrated and pessimistic about the ultimate success of therapy.

Counterresistance refers to those psychological processes within the therapist that impede therapeutic progress. These are reactions to some aspect of the treatment experience that unconsciously create anxiety in the therapist. Such occurrences become accessible first to conscious awareness and then to self-study or self-analytical work, often in the form of a mistake or a symptom experienced in a therapy session. As an example, the therapist might forget the patient's appointment time or feel sleepy or bored during a therapy session. Countertransference feelings may also be manifested in dreams or fantasies about the patient. Analysis of such symptoms of countertransference not only can facilitate progress in a stalled treatment but may lead to significant growth in self-understanding by the therapist, as well as improved understanding of the patient.

## Basic Technique

As noted, the analysis of transference by the repeated interpretation of resistance is the primary activity of the psychoanalyst and an important one for the psychoanalytic psychotherapist. To promote the patient's examination of the phenomena of transference and resistance, both the analyst and the therapist are guided by principles that establish a confidential, safe, and predictable environment geared toward maximizing the patient's introspection and focus on the therapeutic relationship. The patient is encouraged to free-associate, that is, to notice and report as well as she or he can whatever comes into conscious awareness. In the case of psychoanalysis, the depth of the therapeutic process is enhanced by the patient's lying down with the analyst out of the patient's visual range, with a modest level of verbal activity by the analyst, and by meeting frequently, usually four or five times weekly for 45–50 minutes for a number of years (American Psychiatric Association 1985) (Tables 87–5 and 87–6).

**Table 87–5 Characteristics of Psychoanalysis**

| | |
|---|---|
| Goals | Personality reorganization<br>Resolution of childhood conflicts |
| Patient's characteristics | Psychoneuroses and mild to moderate personality disorders<br>Psychological mindedness<br>Introspectiveness<br>Can experience and learn from intense affects or conflicts without acting them out<br>Reasonable object relationships<br>High motivation<br>Can tolerate frustration and therapeutic regression |
| Techniques | Use of couch<br>Four or five sessions weekly<br>Free association<br>Neutrality<br>Abstinence<br>Analysis of defenses<br>Analysis of transference<br>Dream interpretation<br>Genetic reconstruction<br>Less frequent use of medication |
| Length of treatment | 3–6 years or longer |

**Table 87–6 Characteristics of Psychoanalytic Psychotherapy**

| | |
|---|---|
| Goals | Partial personality reorganization<br>Appreciation of conflicts and related defense mechanisms<br>Partial reconstruction of the past<br>Symptom relief<br>Improved interpersonal relationships |
| Patient's characteristics | Includes all criteria for psychoanalysis<br><br>Moderate to severe personality disorders (e.g., borderline)<br>Some affective disorders with and without medication (e.g., major depression, dysthymia) |
| Techniques | Active therapeutic stance<br>Face to face (sitting up)<br>One to three sessions weekly<br>Limited free association<br>Active focus on current life issues<br>Limited transference analysis<br>Some supportive techniques<br>Liberal use of medication<br>Clarification and interpretation |
| Length of treatment | Months to years (may or may not be shorter than psychoanalysis) |

Therapeutic neutrality and abstinence are related concepts. Both foster the unfolding and deepening of the transference, as well as the opportunity for its interpretation. The analyst and psychoanalytic psychotherapist assume a neutral position vis-à-vis the patient's psychological material by neither advocating nor prohibiting the patient's wishes and needs. Essentially, from the structural point of view, the analyst and therapist side with neither the id nor the superego. That is, the patient is encouraged in the therapeutic relationship to develop the capacity for self-observation, a function of the ego, to the best of his or her ability. Neutrality does not mean nonresponsiveness. It is nonjudgmental nondirectiveness, a principle emphasized by psychoanalysts in reaction to the prevalence of suggestion, including posthypnotic suggestions, in the practices of the earliest psychiatrists.

Abstinence refers to the position assumed by the analyst and psychoanalytic psychotherapist of recognizing and accepting the patient's wishes and emotional needs, particularly as they emanate from transference distortions, while abstaining from direct gratification of those needs through action. Abstinence is a principle that guards against the therapist's gratification at the patient's expense. For example, in psychoanalysis, as the treatment experience deepens into a more consolidated transference neurosis, there will be a strong tendency by the patient to experience the analyst as *the* important person in the patient's life around whom the characteristic conflictual issues are manifested. Although it is technically proper to speak of the development of a transference neurosis only in psychoanalysis, many patients in psychoanalytic psychotherapy also develop strong transferences within their treatment experiences. By maintaining a neutral and abstinent position with respect to the patient's needs and wishes, the analyst and psychotherapist create a safe atmosphere for the experiencing and expression of highly charged affects required for the patient's motivation for continued therapeutic work. Although there is a persistent caricature of the psychoanalyst, and to a lesser degree of the psychoanalytic psychotherapist, as working in a withholding and aloof fashion, the concepts of optimal frustration and optimal gratification imply that there is a position held by the psychiatrist that is neither sterile nor overstimulating and that promotes the establishment of a meaningful therapeutic relationship.

The rule of free association, often referred to as the "basic rule," dictates that the patient's primary obligation within the psychoanalytic situation is that of verbalizing, to the best of her or his ability, without editing, whatever comes into awareness, including thoughts, feelings, physical sensations, memories, dreams, fears, wishes, fantasies, and perceptions of the analyst. This rule is relevant to psychoanalytic psychotherapy as well. Whereas at first glance this requirement appears to be unscientific, in fact, the psychiatrist and patient quickly come to appreciate that no thought or feeling is random or irrelevant but rather that all mental content is relevant to the patient's emotional problems. Indeed, much productive therapeutic work is focused on those instances when the patient is not able to speak what is on his or her mind. As an example, a patient suddenly stops talking after enthusiastically reporting the recent achievements of her son. In response to the therapist's asking what is making it difficult to continue, the patient at first states that her mind is blank and then apologizes for "bragging." Further exploration reveals the fear of the therapist's jealousy and resentment of her child's possibly outperforming the therapist's children.

Dream interpretation has been a significant feature of psychoanalysis since the turn of the century. Many psychoanalytic psychotherapists also use this technique, although recently there may be less emphasis on this. Freud placed great emphasis on the interpretation of dreams not only because it was pivotal in his self-analysis but also because he discovered that such a technique provided insights into the working of the unconscious. In a similar fashion, slips of the tongue, jokes, puns, and some types of forgetfulness are attended to carefully by the therapist because they are nonsleep activities that also provide insight into the patient's unconscious mental processes. Good technique does not necessarily include pointing out to the patient these events each time they occur, for they may often be a source of intense embarrassment. Rather, the slips are noted as helpful data in assessing the patient's inner thoughts.

All of these techniques are embedded in a unique manner of listening to the patient's verbalizations within the context of the treatment situation. In particular, two related but specific components initially attributed to the analyst's listening process are worthy of note. First, the concept of the analyst's evenly hovering or evenly suspended attention implies that listening to the patient requires of the analyst that he or she be nonjudgmental and give equal attention to every topic and detail that the patient provides. It also embraces the notion that the effective therapist is one who can remain open to her or his own thoughts and feelings as they are evoked while listening to the patient. Such internal responses often supply important insights into the patient's concerns. Second, empathic listening is of equal importance to both parties. Empathy permits the patient to feel

understood, as well as provides the therapist with a method to achieve vicarious introspection. Indeed, one of the major contributions of self psychology has been the identification of empathic listening and interpretation (the immersion by the therapist into the subjectivity of the patient's experience) as basic to the methodology of psychoanalysis and psychoanalytic psychotherapy (Kohut 1978, 1971). Interferences to successful empathic listening are often the product of countertransference reactions, which should be suspected whenever, for example, the therapist experiences irritation, strong erotic feelings, or inattention during a treatment session.

## How Does Psychoanalytic Psychotherapy Work?

Classical psychoanalysis has held that patients are helped by the acquisition of insight into their intrapsychic conflicts. More specifically, conflict is resolved through precise and accurate transference interpretations, which eventually permit the patient to experience the analyst with fewer distortions from childhood experiences. From a structural point of view, the outcome of this interpretive process is a strengthening of the ego and often a softening of the superego. From a different vantage point, it could be said that psychoanalysis helps by permitting the patient to become increasingly conscious of troublesome feelings, conflicts, and wishes that heretofore had remained out of awareness and that produced unhappiness by promoting repetitive self-defeating behaviors.

Whereas insight has always been valued as a goal of psychoanalysis, insight by itself is insufficient. The process whereby insight is acquired is a lengthy and arduous one that is inextricably linked with the recall of painful affects, memories, and traumatic experiences. For treatment to be effective, there must be then both cognitive and affective experiences for the patient. Neither a purely intellectual nor a purely cathartic experience is likely to result in relief or behavioral change. The support provided by the treatment relationship, which includes commitment, respect, reliability, honesty, and care, is a powerful factor in the mutative or "curative" process. It is this atmosphere that makes bearable the emotional pain that accompanies the healing of the wounds first experienced in isolation, so often inflicted by the first objects of the patient's love, need, and trust. All of these considerations are central to psychoanalytic psychotherapy as well.

The concept of "working through" is helpful in appreciating the lengthy and complex psychoanalytic and psychotherapeutic processes. Working through is that stage or aspect of treatment characterized by repeated identification of reenactment and reliving of earlier experiences through confrontation, clarification, and interpretation of resistance and transference that ultimately promote the patient's self-awareness. In effect, the working through process frees the patient from the position of being at the mercy of unconscious conflicts and fears that have compromised interpersonal relationships and achievement. This is accomplished not only through the analysis of the transference but also of current interpersonal relationships outside of the analysis or psychotherapy. Ultimately, a thorough understanding of the transference and of current relationships permits the patient to appreciate their relationship to important early experiences and to ameliorate the influence of the past on the present.

## Therapeutic Alliance

The "curative" process as first conceptualized in psychoanalysis rested on the analyst's strict interpretation of intrapsychic conflicts as manifested within the transference neurosis. Accurate transference interpretations ultimately permitted the patient to appreciate the limiting or self-defeating distortions in her or his current life that more appropriately resided in early childhood perceptions. Currently, psychoanalysis places greater importance on the role of the *therapeutic* or *working* alliance than was previously emphasized (Zetzel 1956, Greenson 1967). Both of these terms relate to the real component, as distinguished from the transference component, of the therapist–patient relationship. The real component is composed of the patient's conscious, rational, and nonconflictual feelings toward the therapist that permit a collaborative relationship and that provide the motivation for working toward symptom relief.

A great deal of research in the outcome of psychoanalytic psychotherapy has focused on the importance of the therapeutic alliance (Docherty 1985). Increasing appreciation for the role of supportive factors, such as the rapport between the patient and therapist that constitutes the therapeutic relationship, has balanced the earlier and more narrowly defined position that attributed therapeutic success exclusively to insight resulting from the analyst's specific interpretive activity. The clinical consequences of this appreciation of the helpfulness of nonspecific factors have been the psychoanalytic psychotherapist's paying much greater attention to the initial phases of engaging the patient in psychotherapy and a greater respect for those positive and negative factors that the therapist brings to the working relationship. More specifically, earlier psychoanalysis was more likely to understand the patient's responses and attitudes toward the analyst as products exclusively of transference distortions. Currently, psychoanalysis and psychoanalytic psychotherapy hold that the psychiatrist's personality and interventional technique have equal influence on the therapeutic process. In essence, the contemporary view is more dyadic, and places greater importance on the contributions of the therapist (both the conscious and the unconscious), as well as of the patient with respect to progress and impasse in the psychotherapeutic process.

It is important to note, however, that there is strong call for reassessment of the specificity of the role of the therapeutic alliance. Clinicians and researchers alike have argued that the concept of therapeutic alliance must be more clearly defined in terms of the distinct attributes that contribute to positive outcome (Horvath 2006, Meissner 2006, Castonguay et al. 2006, Crits-Christoph et al. 2006, Hatcher and Barends 2006). As examples, Horvath argues for a clearer definition of the alliance in research and how it shifts throughout phases of treatment. Meissner, a psychoanalyst, argues that the confusion in the concept of the therapeutic alliance lies in the blurred boundaries of the three components of the alliance, namely, transference, working alliance, and the real relationship. Both Horvath and Meissner agree on the need for a greater pantheoretical and theory specific appreciation.

## Drives

Freud's psychoanalytic model of the mind continually changed throughout his career. His first conceptualization was based on an id psychology, which directed the analyst to attend to the patient's hidden sexual and aggressive drives in the form of wishes, needs, and impulses as conceptualized within the topographic point of view. His second model, ego psychology, focused more on bringing to the patient's awareness both repressed and disavowed mental content and the role of the unconscious defense mechanisms of the ego as it mediated conflict. Early psychoanalysis then focused on the analysis of drives; later psychoanalysis emphasized drives and their defenses. Analysis based on the later model had limitations as well, especially when the patient did not have a typical symptom neurosis but rather had more characterological problems. It is fair to say that today many psychoanalysts and psychoanalytic psychotherapists attribute less importance to the concept of drives.

## Interpersonal and Object Relationships

One significant clinical and theoretical revision that attempted to transcend the limitations of ego psychology was object relations theory. As with many facets of psychoanalytic theory, object relations theory is not unitary. Some emphasize the quality of interpersonal relations and yet others emphasize how psychic structure is built through the process of internalization. Object relations theory focuses on early organizing experiences with others that not only constitute an important component of the self but also influence the manner in which a person experiences him or herself and others throughout life. Some object relationists retained drive theory (Jacobson 1964, Kernberg 1975, Mahler et al. 1975) whereas others did not (Sullivan 1953, Guntrip 1971). All, however, gave greater credence to the role of internalized object relations both in normal development and in psychiatric illness. Integrating "good and bad objects" was considered the goal of normal development, whereas psychiatric illness resulted when these objects remained separate or "split."

Others (Kohut 1978, Sullivan 1953) thought that object relations theory did not effectively close the gap between theory and practice, especially with respect to the treatment of severe personality disorders. Self psychology deleted the drives as a central organizing principle and raised the development of self-esteem to a supraordinate theoretical and clinical position. Although the contributions of self psychology have been debated for the last 35 years, much of self psychology has now become a part of modern psychoanalysis and psychoanalytic psychotherapy. This is especially true regarding the importance of empathy in treatment, as well as the appreciation of the so-called self-object transference configurations: the idealizing transference, twinship transference, and the mirror transference. (See Chapter 28 for a more in-depth appreciation of both object relations and self psychology.)

In summary, contemporary psychoanalysis and psychoanalytic psychotherapy still emphasize elucidation of the unconscious, especially within the transference, and still use interpretation as the primary clinical intervention but recognize more fully the important role of the mutual emotional engagement of therapist and patient and the curative role of this relationship in addition to other supportive factors. They adhere to a much broader perspective on human development and psychiatric disorders. Psychological problems can result not only from early intrapsychic conflict but also from developmental deficits or failures as well as from psychological trauma (Table 87–7).

**Table 87–7 Indications for Psychoanalysis**

Psychoanalysis is the treatment of choice for repetitive, long-standing, maladaptive problems involving personality or character and chronic, repetitive behavioral, affective, or mental disturbances or symptoms that do not respond to cheaper or quicker forms of treatment. In general, it is used for all the character disorders or personality disorders, except antisocial and schizotypal disorders, as well as numerous symptom disorders.

The chronic symptoms must reflect both of the following:

1. Intrapsychic conflict
2. Developmental arrest or inhibition

In addition, the psychiatrist must expect the following:

3. The patient's symptoms are likely to continue unless analysis is undertaken.
4. Treatments that are less intensive than analysis would likely result in excessive personal or social cost for the patient or just provide temporary relief of acute symptoms related to a current stress, without dealing with underlying issues, hence predisposing the patient to difficulties in future.

Finally, the patient must be able to use psychoanalysis. In general, this rules out the psychotic disorders and a number, but not all, of the borderline disorders.

*Source*: American Psychiatric Association (1985).

Clinical Vignette 5 is a segment of process from the third year of a 4.5-year psychotherapy conducted by a woman therapist illustrating the following:

- Free association.
- Working alliance (threats to and the reestablishment of).
- Transference perceptions and reactions based on experiences both with mother and with father.
- Defense and resistance, including denial, projection, reaction formation, and acting out.
- Failure of defenses, manifested by symptoms of anxiety, depression, and somatization.
- Use of confrontation, clarification, and interpretation of wishes and impulses, defenses , and resistances.
- Dream interpretation.
- Genetic reconstruction.
- Role of neutrality and abstinence in maintaining the safety requisite to the patient's experiencing and expressing highly charged, previously unconscious wishes and fears.
- Development of insight, accompanied by a decrease in symptoms.

Clinical Vignette 5

Ms. J began treatment at age 35 because of anxiety, work inhibitions, and a tendency to "martyr" herself. She also wanted help with her highly ambivalent relationships of 15 years with her husband and of 8 of those years with her married lover. Ms. J had been subjected to chronic verbal, physical, and sexual abuse by her alcoholic father throughout her childhood. Her mother, depressed and overburdened with many children, was hurtful primarily in her collusive blindness to the father's predations.

Two months before the therapist's planned summer vacation, the patient terminated her sexual involvement with her lover. She became increasingly ambivalent about this decision as the interruption approached. She imagined that her therapist (1) valued men more than women and felt that a man's wishes should always be gratified, (2) found her needs burdensome and preferred that she turn to her lover for the attention she wanted, and (3) was going on vacation to punish her for refusing sex. On the other hand, the patient felt that the therapist was possessive of her attention and did not want her to resume the affair with her lover (projection). The patient recognized that her anger about the therapist's attention to her own family and the resulting jealous wish for retaliation (passive into active) had also played a role in her renewed interest in the extramarital love affair. Together, the patient and therapist understood these feelings and ideas (transference) as aspects of the patient's reexperiencing, within the treatment, the relationship with the mother of her childhood who had left her to the father, fostering the incest and who had sometimes given more attention to her siblings.

Moreover, the patient felt that the therapist was possessive of her attention and did *not* want her to resume the affair. The patient experienced the therapist as withholding attention from her during the vacation, preferring to be with others as her father had sometimes preferred to be with the mother or siblings. The patient recognized that her own angry jealousy of the therapist's family and the wish for retaliation against the therapist played a role in her renewed interest in the extramarital involvement.

During the first psychotherapy session after the vacation, Ms. J reported that as soon as the therapist had left town, she had lost interest in understanding her feelings before acting on them and had resumed her sexual affair (acting out). She soon stopped the sexual involvement when she realized having experienced an insight: she had been hoping (unconsciously) that by discontinuing the extramarital affair, she would please her therapist and make her cancel the vacation (insight). She spoke next about having been given a raise at work, which made her depressed and guilty and fearful of the therapist's competitive anger. Ms. J then reported a dream in which she made sure that her lover's wife got more loaves of bread than she. The dream was understood (dream interpretation) as representing both an attempt to compensate for undoing the sexual betrayal and as a protection against the danger of outdoing the therapist with the new "dough" (reaction formation and undoing; denial). The extra income from the raise also ensured funding of the psychotherapy. This fact made the therapist wondered (silently) whether the patient's depression in response to learning about the raise reflected ambivalence implying that she was ambivalent about continuing the therapy, fearful of what might lie ahead (resistance).

The next session began with the patient's reporting that she had felt hurt, inappropriately she thought, when her husband did not want her to touch him. She linked this reaction to her fear of the therapist's rejection because of her sexual behavior during the vacation. She also talked about having "needs that you are unwilling to meet" (neutrality and abstinence). Whereas she had felt last month that the affair was a harmless way of having needs met that were "not being met elsewhere" (displacement), she now stated ambiguously that by "not choosing between the relationships" she was "putting a ceiling on things." The therapist better understood the resistance function of the sexual acting out: it had discharged unconscious sexual impulses in relation to the therapist that were threatening, both because of fears of disapproval and of gratification of those wishes through action. That is, the patient was trying to prevent the therapist from responding sexually as the father had done in her childhood. Putting a ceiling on things seemed to be the patient's attempt to keep things safe, to keep the therapist under control. Testing this hypothesis, the therapist asked, "Might the affair be putting a ceiling on things here with me as well?" The patient stated that it would be dangerous to want or ask more of the therapist because of the risk of rejection and punishment. Also, although getting attention from her lover was "illegitimate, it was less wrong than getting it from you would be. Part of it is sexual," she said, and went on to discuss the role her lover played as mentor and advisor.

Confronting what was being resisted, the therapist asked the patient, "What about the sexual part?" The patient talked about the "infantile part," wanting to be rocked and held by the therapist, and went on to label her physical needs and desires as "excessive, bad, something that should be repressed." In an attempt to interpret the patient's wishes that were as yet unacknowledged (resistance), the therapist addressed both impulse and defense. The therapist used the somewhat ambiguous action word from the patient's statement at the start of the hour, saying, "It's uncomfortable, threatening when you're aware of wanting me to touch you, then." The patient acknowledged that because the psychotherapeutic relationship did not include physical contact, she turned to the sexual affair to have those needs met (displacement). Interpreting the defense, the therapist said, "When you find it threatening to want me to meet that need sexually, you find it safer to return to your lover." "Yes. It protects both of us. I see it as a threat to the relationship. It might ruin things." The therapist interpreted more specifically the patient's fear of her own desires: "I think that you're feeling that the desire might ruin things not only because I might disapprove, but also because you're afraid there will be some actual behavior that would ruin things." The patient agreed. "That's right. I think I'm afraid the desire would lead to behavior. When I was a child, other ways weren't found to deal with things. I think the desire makes me afraid you'll become my father" (transference and genetic reconstruction).

The next day the patient reported that during the latter part of this hour she had been experiencing back pain (an example of somatization as a failure of defenses), a symptom that throughout the psychotherapy accompanied memories of past sexual abuse. The pain, anxiety, and depression she had been feeling the day before had dissipated after the hour (insight accompanied by decrease in symptoms).

## How Does Psychoanalytic Psychotherapy Differ from Psychoanalysis?

The answer to this question has occupied many researchers and psychiatrists throughout the previous and current centuries. Efforts have been made continually not only to elucidate the differences between the two treatments but also, more importantly, to define the underlying principles of psychoanalytic psychotherapy. Whereas some prefer definitions of psychoanalysis and psychotherapy as distinct, separate entities, it is more useful to many psychiatrists to conceptualize psychoanalysis and psychoanalytic psychotherapy as residing on a therapeutic continuum. As discussed, there is much in the conduct of psychoanalytic psychotherapy that has been borrowed from psychoanalysis. Free association, clarification, and interpretation in psychoanalytic psychotherapy are such examples. The centrality of transference is another, although early psychiatrists and researchers advocated that transferences were to be recognized and acknowledged in psychoanalytic psychotherapy and "managed" rather than interpreted so that patients were not subject to the intense therapeutic regressions characteristic of psychoanalysis. Today, such a distinction regarding the approach to transference in psychoanalytic psychotherapy is less rigid.

On the other hand, certain supportive and more directive techniques, such as greater activity of the therapist through focusing the patient on specific current problems and relationships, reassuring and affirming the patient, and the giving of advice, are used much more in psychoanalytic psychotherapy than in psychoanalysis. Therefore, the adherence to the therapist's neutrality is less strict, and as a result, there is often but not always less frustration for the patient in psychoanalytic psychotherapy. The length of treatment may not distinguish the two approaches, but the frequency of sessions (four or five per week) and the use of the couch, however, are characteristic of psychoanalysis (see Table 87–5).

Overall, it is fair to say that psychoanalytic psychotherapy has the following characteristics:

- It places greater emphasis on the here and now in terms of the patient's current interpersonal relationships and experiences outside of the therapy; whereas in psychoanalysis, there is greater emphasis on the experiences within the analysis and the relationship between analyst and analysand.
- It incorporates, more than does psychoanalysis, various other techniques from other dynamic and behavioral psychotherapies.
- It emphasizes the usefulness of focusing on current (dynamic) problems and less on genetic issues.
- It establishes more modest goals of treatment.

The last point is particularly important in that it facilitated the development of brief dynamic psychotherapies that address focal problems generally in up to 20 sessions.

## Tasks of the Psychoanalytic Psychotherapist

What are the challenges of the psychotherapist in performing psychoanalytic psychotherapy? First, the therapist must ensure that the patient feels both emotionally and physically safe within the therapeutic relationship. This is accomplished by acknowledging the goals of the treatment and defining the role of the therapist and through establishing professional boundaries. Boundaries refer to those constant and highly predictable components of the treatment situation that constitute the framework of the working relationship. For example, agreeing to meet with the patient for a specified amount of time, in a professional office, and for an established fee are some of the elements of the professional framework. Boundaries also have ethical dimensions best summarized as the absolute adherence by the therapist to the rule of never taking advantage of the patient: through sexual behavior; for personal, financial, or emotional gain; or by exploiting the patient's need and love for the therapist in any fashion (e.g., by using the therapy sessions to discuss the therapist's own problems). The concepts of neutrality, abstinence, and confidentiality further define the role of the therapist. (See Chapter 5 for more discussion of frame, boundaries.)

A critical task of the psychoanalytic psychotherapist is to detect when a breach in either role or boundary has occurred and to restore the patient's security through clarifying and interpreting the meaningfulness of such a breach. As an example, a patient and a therapist were suddenly interrupted in their session by hospital maintenance personnel who obtained entry into the office through the use of a master key. After dismissing the workers, the therapist observed that the patient became uncharacteristically silent. The therapist acknowledged the unanticipated disruption and its impact on the patient, and requested that the patient share what he was thinking during and after the intrusion. The patient told of the effects of a childhood incident in which his bathroom privacy was violated by a distant family member.

The explication of a boundary violation is but one specific example of the technique of interpretation. Successful interpretation is based on a number of prerequisite skills. These include the capacity to empathize with the patient's plight, the ability to recognize the meaning of one's own fantasies about, and responses to, a patient (countertransference), the ability to maintain the patient's verbal flow through the use of open-ended or focused questions, and the capacity to tolerate a relatively high level of ambiguity within the therapeutic relationship. One important professional characteristic of the skilled psychotherapist is patience. Psychotherapy is often arduous, and the capacity to "stay in the chair" with the patient particularly when patients express strong affects is critical.

The identification of repeated patterns of behavior both within the therapy and in the patient's outside life is a fundamental technique in making sense of the patient's emotional life. This, of course, involves the appreciation of transference and the art of knowing how and when to share this recognition with the patient. Interpretation relies on both appropriate timing and dosage. That is, the psychoanalytic psychotherapist must appreciate when the patient can best integrate the therapist's observations and must respect the patient's defenses, taking care not to overwhelm the patient by insisting that she or he confront more than is tolerable. A poor interpretation is exemplified by Clinical Vignette 6.

Clinical Vignette 6

A patient talks about how unimportant therapy is in his life compared with other things, stating that he never thinks about the treatment or the therapist between appointments. The therapist notes that the patient always arrives early for his sessions and has come even when ill, evidence that he has formed an attachment and does need the therapist despite what he asserts. The patient then cancels all appointments for the next month.

Psychoanalytic psychotherapy requires the successful engagement of the patient and the establishment of a therapeutic or working alliance. The alliance can be threatened by a number of phenomena including, but not limited to, the following:

- The therapist's countertransferences or other limitations in his or her capacity to tolerate the emotions stirred by the patient, resulting in empathic failures and mistakes.
- The emergence of intense feelings and needs within the patient, for example, when an accurate, well-timed intervention evokes feelings in relation to the therapist of appreciation and love accompanied by feelings of vulnerability, erotic desire, or inferiority, which the patient wants to flee.
- The patient's being reminded of the existence of others in the therapist's life, such as other patients or family (e.g., during interruptions due to the therapist's vacations), triggering painful and embarrassing feelings of jealousy and possessiveness.

The therapist's ability to appreciate and respectfully acknowledge to the patient the impact of these temporal events is critical to the progress of treatment.

From another vantage point, the therapist must also be able to "pass the test" (Weiss 1993). That is, in addition to transference reactions, patients may turn the passive into active by replicating within the therapeutic relationship the original conflictual, disappointing, or traumatic parental experience but reversing the roles. Essentially, the patient does to the psychotherapist what was initially done to her or him. For example, a patient whose parents never seemed to have time to listen has the habit of ending the session 2 minutes early to avoid feeling interrupted and rejected. Such behavior is an adaptive, largely unconscious, interpersonal strategy whose objective is to assess the level of safety within the therapeutic dyad and ultimately to master a psychological problem. If the psychotherapist can pass the test, that is, responds differently from the patient's early negative childhood expectations or pathogenic beliefs, the patient feels more secure and can allow deepening of the therapeutic process. Clinical Vignette 7 illustrates this concept of passing the test, a central component of control–mastery theory (Weiss 1995).

All of the psychotherapist's skills and techniques must be embedded in a consistent and coherent theoretical viewpoint that provides the therapist with a framework to understand the etiology and meaning of a patient's symptoms and dysfunctional behaviors both in the past and in the present in each of the phases of psychotherapy (Table 87–8). This includes an organized method for understanding the therapist's unconscious and conscious responses to the patient as well. It requires that the therapist listen to the patient's communications in a manner that is markedly different from other forms of social discourse. So-called "process communication" speaks to the therapist on multiple levels and through displacement, through passing remarks and jokes, through shifts in topics, and through metaphors and symbols. To assist in understanding complicated process communication, psychiatrists often ask themselves: Why is the patient telling me this now? What might the patient be trying to say about his or her uncomfortable feelings? Is something being said about the therapeutic relationship? To illustrate, a patient begins the session by being angry about a bill he received for a medical procedure that had not alleviated his physical symptoms. Its high cost and ineffectiveness seem to reflect the physician's uncaring attitude and willingness to make money at the patient's expense. The therapist asks whether the patient recently received his bill for the psychotherapy and could his concerns about the physician apply to his psychotherapy relationship as well.

Clinical Vignette 7

Dr. S was placed on academic leave by his university because he was unable to get to his classes on time. He grew up in a family dominated by a cold, intimidating, and frequently abusive father. In the second session to which he was 10 minutes late, he shared an early memory of keeping his father waiting in the car each Sunday immediately before church. He acknowledged that only on Sunday mornings would his father not beat him for his tardiness. The patient came late to each of the four successive meetings, after which time the therapist interpreted that by being late, the patient was attempting to determine whether the therapist would treat him in the same fashion as did his abusive father. By not becoming enraged or disappointed with the patient, as was frequently the case with the patient's father, the therapist passed the test. The patient experienced greater security in the therapeutic relationship, and his tardiness to sessions ceased.

**Table 87–8 Phases of Psychoanalytic Psychotherapy**

| | |
|---|---|
| Beginning phase | Patient is educated about roles of both parties<br>Therapeutic alliance is formed leading to symptomatic relief from nonspecific relationship factors |
| Middle phase | Usually the longest phase of therapy<br>Reexperiencing of patient's conflicts within dyad<br>Interpretation of conscious and previously unconscious material leading to new insightfulness about current, past, and sometimes previously forgotten experiences |
| Termination phase | Begins with agreed-on end of treatment<br>Anxiety evoked by impending loss of therapist<br>Initial symptoms may recur<br>Integration and consolidation of therapeutic gains<br>Therapist is viewed with less distortion |

As noted, psychoanalytic psychotherapy differs from psychoanalysis in the weight given to the use of supportive measures and in the establishment of more circumscribed goals. Both the psychoanalytic psychotherapist and the psychoanalyst must be skillful in supporting the patient at times of emotional disequilibrium but they may differ in the degree and manner in which support is provided to the patient. Psychoanalysis has always striven for an extensive transformation of the patient's characterological problems and a thorough analysis of the patient's transference neurosis. The psychoanalytic psychotherapist must be skillful in setting more limited goals with a patient regarding the reconstruction of the patient's past. The objective of this type of treatment is to improve the patient's quality of life largely through enhancing interpersonal relationships by promoting greater insights into perceptual distortion and intrapsychic and interpersonal conflict. Psychoanalytic psychotherapy accomplishes this objective by focusing much more on the patient's current predicaments as manifested in both life activities and relationship with the therapist. Compared with psychoanalysis, it is often, but not always, less concerned with the analysis of transference and the complete discovery of the underlying genetic precursors of the patient's current psychological problems.

## Indications for Psychoanalytic Psychotherapy

Although current psychotherapy research attempts to ascertain what specific disorder in what type of patient is most effectively treated by what specific psychotherapeutic approach, studies have not as yet provided the answers to these questions. At this time, it is possible only to speak in generalities based on case reports and limited studies. Conditions and disorders for which psychoanalytic psychotherapy appears to be indicated include Clusters B&C personality disorders (except antisocial personality disorder), acute and posttraumatic stress disorders, symptom neuroses or neurotic conflicts, adjustment disorders, paraphilias, and *some* mood, anxiety, somatoform, sexual and gender identity, eating, substance abuse, and dissociative disorders (Table 87–9). In addition, psychoanalytic psychotherapy is often employed in treating patients who present with relational problems and those problems that are the result of abuse or neglect. It may also be useful to patients with certain impulse disorders and to patients whose psychological problems are affecting or are the result of their primary medical illnesses. Subthreshold disorders, it must be remembered, may be accompanied by significant psychic pain. In this regard, psychoanalytic psychotherapy is helpful to those who are challenged by intimacy with and commitment to others as well as those suffering from longstanding grief, and those not meeting criteria for Cluster B&C personality disorders but nevertheless are troubled by self-defeating behavior. In short, psychoanalytic psychotherapy, often in combination with medication, is an appropriate intervention in a broad range of disorders, conditions, and psychiatric illnesses (Karasu 1989, Gabbard 1995).

**Table 87–9 Putative Indications for Psychoanalytic Psychotherapy**

| |
|---|
| Neuroses |
| Personality disorders (except cluster A and antisocial personality disorder) |
| Posttraumatic stress disorders |
| Adjustment disorders |
| Paraphilias* |
| Mood disorders* |
| Anxiety disorders* |
| Somatoform disorders* |
| Sexual and gender identity disorders* |
| Eating disorders* |
| Substance abuse disorders* |
| Dissociative disorders* |
| Relational problems |
| Impulse -control disorders* |
| Psychological problems affecting medical illnesses |

*Not indicated for all disorders in these categories.

With increasing frequency, patients who are suitable for psychoanalysis are treated in psychoanalytic psychotherapy because of extrinsic demands such as financial resources, time limitations, and job and family conflicts. The characteristics of the patient assumed to be correlated with positive outcome in psychoanalytic psychotherapy include introspectiveness (psychological mindedness or wish to understand the meaningfulness of behaviors and their relationship with feeling and thoughts), ability to establish and maintain human relationships, even "unhealthy" ones, vocational stability, high degree of motivation, absence of formal thought disorder, and psychological resources sufficient to withstand the frustration of the treatment and its characteristic therapeutic regression and accompanying strong affects.

## Contraindications to Psychoanalytic Psychotherapy

Although it is no longer the case, psychoanalytic psychotherapy had been traditionally reserved for patients who could not tolerate the inherent frustration and therapeutic regression of psychoanalysis. More often than not, the issue of analyzability (roughly comparable to treatability) was framed in terms of the assessment of the patient's ego strengths. If a patient was thought to have insufficient psychological resources to withstand the rigors of a psychoanalysis, especially a patient with severe personality disorders and significant thought disorders, psychoanalytic psychotherapy might be prescribed. Similarly, if the patient was considered to be poorly motivated or had some cognitive deficit that might prevent the integration of interpretations, she or he was urged toward a treatment with more supportive elements. For the most part, contraindications to any psychoanalytic psychotherapy that is heavily weighted toward the expressive end of the therapeutic continuum are as follows (Table 87–10):

**Table 87–10 Contraindications to Expressive Psychoanalytic Psychotherapy**

| |
|---|
| Major ego deficits |
| Poor motivation |
| Significant cognitive deficits |
| Inability to obtain symptom relief through understanding |
| Inability to verbalize affects |
| Lack of psychological mindedness |
| Minimal impulse control |
| No social support network |
| Low frustration tolerance |
| Inability to form therapeutic alliance |

- Poor impulse control
- Significant cognitive deficits
- Severely dysfunctional interpersonal relationships
- Little ability to tolerate frustration, anxiety, and depression
- Significant lack of introspective capacity.

## Supportive Psychoanalytic Psychotherapy

Although only recently systematized, this form of psychotherapy provides psychological stabilization to the patient through the vehicle of a consistent and predictable caring therapist–patient relationship (Werman 1984, Rockland 1989, Novalis et al. 1993, Hellerstein et al. 1994, Misch 2000). The provision of emotional support to patients with psychiatric disorders can be traced to the 18th-century moral treatment movement advocated by Pinel and others. Supportive psychotherapy attempts to shore up the patient's defenses and enhance his or her ability to cope with the trials of illness or psychological deficits and the challenges they impose on the patient's daily activities (Table 87–11). Not unexpectedly, it also strives to prevent decompensation and regression. As such, psychoanalytic supportive psychotherapy employs a psychodynamic understanding of the patient's difficulties but does not emphasize interpretation of the patient's internal world. Rather, supportive psychotherapy focuses on assisting the patient to address interpersonal and environmental challenges in the here and now.

Despite its noninterpretive emphasis, supportive psychotherapy can have substantial impact in the lives of patients with significant ego deficits and those with major mental illness. These patients may include those with high levels of aggressivity, poor impulse control, overreliance on action rather than verbal expression of emotions, compromised reality testing, and limited psychological mindedness. It is also highly effective with higher functioning patients who have experienced recent psychic trauma (e.g., through natural disasters, illness, physical or sexual assault, and unexpected devastating losses).

Supportive psychotherapy techniques consist predominantly of empathically listening to the patient's feelings and experiences, giving advice and reassurance, offering suggestion and helpful coping techniques, and for some patients with severe and chronic maladaptations, gently revealing their misperceptions and how they interfere in daily functioning. Although often unexpressed, the patient's identification with the therapist's values, ideals, and approaches to problems is exceptionally therapeutic. Environmental interventions through helping agencies and the patient's significant others are also effective supportive techniques. Although nonspecific to some degree, these interventions are nevertheless based on a comprehensive understanding of the patient's strengths and weaknesses, and are frequently instrumental in curbing self-destructive and self-defeating behaviors. Transference is appreciated but the therapist rarely interprets it in supportive psychoanalytic psychotherapy, choosing rather to foster a positive working relationship through other means (Pinsker et al. 1992).

Although frequently disparaged, effective supportive psychoanalytic psychotherapy is often more challenging to provide than some forms of expressive psychotherapy. Appreciating the psychological forces that are impinging on a marginally functioning patient whose communicative abilities are suboptimal requires a sophisticated clinical approach. Moreover, in supportive psychotherapy, the therapist must assist the patient to modulate intense affective states that are often frightening to the patient and to those in his or her environment. Needless to say, such affects can be directed at the therapist as well. The establishment of the requisite safe and caring relationship with the patient, which may be frequently disrupted by both internal and external forces, is often a significant clinical challenge.

Supportive psychotherapy can produce significant and lasting behavioral change through the reinforcement of health-promoting behaviors, increased capacity for self-reflection, anxiety reduction, and development of new defenses such as intellectualization that enable the patient to acquire a cognitive, anxiety-reducing conceptualization of her or his difficulties.

**Table 87–11 Characteristics of Supportive Psychoanalytic Psychotherapy**

| | |
|---|---|
| Goals | Maintain current level of psychological functioning<br>Restore premorbid adaptation, if possible<br>Enhance coping mechanisms<br>Strengthen defense mechanisms unless they are maladaptive<br>Support reality testing<br>Relieve symptoms<br>Decrease mental distress |
| Patient's characteristics | Severe character disorders<br>Chronic ego deficits<br>Thought disorders<br>Limited psychological mindedness<br>Limited motivation<br>Poor interpersonal relationships<br>Poor impulse control<br>Low frustration tolerance<br>Regression proneness<br>Some potential for therapeutic alliance<br>Extreme passivity<br>Inability to verbalize affects<br>Those in crisis situations (catastrophic loss, acute psychic trauma, medical illness)<br>Psychologically healthy<br>Effective social network<br>High premorbid adaptation<br>Flexible defenses |
| Techniques | Predictability and consistency of therapist<br>Conversational style<br>Confrontation, clarification, education<br>Problem-solving focus<br>Provide encouragement, advice, praise, reassurance<br>Environmental intervention<br>Strengthen reality testing<br>Shore up defense mechanisms<br>Discourage regression<br>Infrequent genetic reconstruction<br>Infrequent transference analysis<br>Less therapeutic neutrality<br>Frequent use of medication |
| Length of treatment | Usually once weekly or less<br>Duration of sessions flexible<br>Varies from brief therapy for those reactive disorders in individuals who do not need or are not motivated for further help to lifelong treatment of patients with some chronic disorders |

## Gender Issues in Psychotherapy

Does the gender of the psychotherapist have any effect on the psychotherapeutic relationship and treatment outcome? Are certain psychological problems best treated by therapists whose gender is different from that of the patient? Do different phenomena appear in the treatment of those patients whose therapists are of the same gender? Is the duration of treatment affected by the therapist's gender? Does gender have any influence on the choice of therapist by a patient? These are important questions that have been debated in psychotherapy and psychoanalytic literature for more than 50 years.

The influence of the therapist's gender on the treatment relationship was first raised by Freud in 1931 (republished in Freud 1961), who suggested that women analysts might have the ability to promote a greater variety of transferences than their male counterparts. Shortly thereafter, Thompson (1939) articulated what has become of the traditional psychoanalytic psychotherapeutic position regarding the gender of the therapist, namely, that the therapist's personality is much more critical to the treatment outcome than is his or her gender. A classic study of sex role stereotypical beliefs held by psychotherapists (psychiatrists, social workers, and psychologists) demonstrated that psychological health was defined in terms of normative development for men, whereas for women alone, dimensions such as emotional lability, submissiveness, and dependency were denoted as healthy (Broverman et al. 1970). Although the existence of some influence of such attitudes on the therapy is intuitively compelling, studies examining actual behavior of the therapist rather than beliefs and attitudes do not conclusively demonstrate that gender stereotyping of the therapist has direct effects on the treatment process, length of treatment, or outcome (Schwartz and Abromowitz 1975, Abromowitz et al. 1976, Blasé 1979, Orlinsky and Howard 1976). Women psychotherapists, however, do have an advantage over their male counterparts in terms of satisfaction for both female and male patients (Kirshner et al. 1978).

Although the literature regarding the advantages and disadvantages of gender matching of patients and therapists consists largely of anecdotal and negative reports (Zlotnick et al. 1998), it is nevertheless evocative. A number of common themes have emerged, including the following:

- The gender of the therapist may be more critical in supportive treatments that rely on identification with the therapist (Cavenar and Werman 1983).
- The therapist's gender may be less important in psychoanalysis than in face-to-face psychoanalytic psychotherapies, because in the latter the transference can be less intense (Mogul 1982).
- Beginning women therapists have less difficulty with empathy but more difficulty with authority issues than do their male counterparts (Kaplan 1979).

The wish for a woman to be treated by a female psychotherapist, an increasingly common event, may be related to a number of different issues. For example, the woman may wish to rectify an unfulfilling experience with her own mother, seek permission from another woman to be assertive and accomplished, anticipate feelings understood more readily by another woman than by a man, or feel greater physical safety in the therapeutic relationship with another woman, particularly if she has experienced past sexual abuse or has been the victim of sexual misconduct by a previous male therapist.

Similarly, a woman might choose a male therapist if she is fearful of becoming dependent on another woman (Nadelson and Notman 1991). A female psychotherapist could also be valued in the early portion of therapy but then subsequently be devalued as the female patient begins to experience the therapist competitively (Notman et al. 1978) or as other more hostile transferences unfold.

Male patients can have comparable conscious and unconscious reasons for selecting a psychotherapist by gender. For instance, men who are frightened of male competition or intense homosexual concerns might gravitate toward female psychotherapists. Men who have been unsuccessful in establishing meaningful relationships with women might select a female therapist in the hope that she could teach him how to be successful with women. The same might be true for a male patient suffering from sexual dysfunction who yearns for the secret of what sexually pleases women. Conversely, a man fearful of strong women, a man hungry for a strong male figure with whom he can identify, or a man seeking to avoid dependent or strong heterosexual feelings in the treatment relationship might prefer a male therapist. Although therapists are accustomed to operating in an increasingly androgynous world, female therapists may be surprised to encounter stronger resistance in treating "traditional" male patients in settings such as veterans administration hospitals (Deering and Gannon 2005, Good 2005).

In short, although there is only one controlled study and it showed no difference regarding the influence of the therapist's gender on the therapeutic process (Zlotnick et al. 1996), there is much to consider about the influence of actual gender and gender-related beliefs of both patient and therapist on the emergence of transference and countertransference. However, the best psychoanalytic psychotherapies will include ample opportunities for the working through of the patient's issues related to important figures of both genders.

## Ethnocultural Issues in Psychotherapy

Culture refers to meanings, values, and behavioral norms that are learned and transmitted in the dominant society and within its social groups. Culture powerfully influences cognitions, feeling, and "self" concept, as well as the diagnostic process and treatment decisions. Ethnicity, a related concept, refers to social groupings that distinguish themselves from other groups based on ideas of shared descent and aspirations, as well as to behavioral norms and forms of personal identity associated with such groups (Mezzich et al. 1993).

The DSM-IV-TR advocates for the importance of ethnic and cultural considerations through a cultural formulation that augments the multiaxial diagnostic assessment of culturally diverse patients (American Psychiatric Association 1994). The cultural formulation is derived from the traditional biopsychosocial case formulation, and it emphasizes how culture may influence the expression of symptoms, the patient's conceptualization of illness, the treatment, and

the treating relationship (Mezzich et al. 1993). The guidelines for cultural formulation that served as the template for the DSM-IV-TR outline are presented in Table 87–12.

**Table 87–12 Guidelines for Cultural Formulation**

The following guidelines for cultural formulation are meant to supplement the multiaxial diagnostic assessment and to address difficulties that may be encountered in applying DSM-IV-TR criteria in a multicultural environment. The cultural formulation provides a systematic review of the individual's cultural background, the role of the cultural context in the expression and evaluation of symptoms and dysfunction, and the effect cultural differences may have on the relationship between the individual and the clinician.

It is important that the clinician take into account the individual's ethnic and cultural context in the evaluation of each of the DSM-IV-TR axes. In addition, the cultural formulation suggested below provides an opportunity to describe systematically the individual's cultural and social reference group and ways in which cultural context is relevant to clinical care. The clinician should provide a narrative summary of each of the following areas.

| Area | Summary |
|---|---|
| Cultural identity of the individual | The clinician should specify the individual's cultural reference groups. Attend particularly to language abilities, use, and preferences (including multilingualism). For immigrants and ethnic minorities, note separately the degree of involvement with both the culture of origin and the host or majority culture. |
| Cultural explanations of the individual's illness | Identify (1) the predominant idioms of distress through which symptoms are communicated (e.g., "nerves," possessing spirits, somatic complaints, inexplicable misfortune), (2) the meaning and perceived severity of the individual's symptoms in relation to norms of the cultural reference group, (3) any local illness category used by the individual's family and community to identify the condition, (4) the perceived causes or explanatory models that the individual and the reference group employ to explain the illness, and (5) current preferences and past experience with professional and popular sources of care. |
| Cultural factors related to psychosocial environment and functioning | Note culturally relevant interpretations of social stressors, available social supports, and levels of functioning and disability. Special attention should be given to stresses in the local social environment and to the role of religion and kin networks in providing emotional, instrumental, and informational support. |
| Cultural elements of the relationship between the individual and the clinician | Indicate differences in culture and social status between the individual and the clinician and problems that these differences may cause in diagnosis and treatment (e.g., difficulty in communicating in the individual's first language, in eliciting symptoms or understanding their cultural significance, in negotiating an appropriate relationship or level of intimacy, in determining whether a behavior is normative or pathological). |
| Overall cultural assessment for diagnosis and care | The formulation should conclude with a discussion of how these cultural considerations specifically influence comprehensive diagnosis and care. |

*Source*: Mezzich et al. (1993).

In the establishment of a therapeutic alliance, the patient's cultural difference from the therapist may add another level of complexity to the therapeutic process. For example, in engaging a Japanese patient, the psychotherapist must be cognizant of the patient's need for formality because an informal style may lead to embarrassment for the patient (Marsella 1989). In the treatment of some Asian patients, there may be an inherent cultural expectation that the therapist teach the patient how to correct her or his behavior (Blue and Gonzalez 1992). The ability to trust the psychotherapist is a fundamental task of any psychotherapy. Establishing trust with an African-American patient, for example, may be more complicated for a white psychotherapist if the patient's experiences with the dominant culture or white physicians have been disappointing or demeaning. An African-American psychotherapist might have to encounter early in the treatment overt or covert prejudice from a white patient. A Native American patient may have great distrust for a white therapist who represents a dominant culture. In some circumstances, a patient from a different culture might be obsequious in an attempt to please the psychotherapist.

Comas-Diaz and Jacobsen (1991, 2001) have introduced the concept of ethnocultural allodynia to describe an intense sensitivity and response to relatively innocuous or neutral stimuli emanating from previous culturally based painful experiences. They describe how sociocultural and ethnic emotional injuries can have profound impact on self-cohesiveness and object relationships. As is the case in Herman's concept of complex posttraumatic stress disorder (PTSD) (Herman 1992), alterations in self-perception and perception of others, affective lability, interpersonal relationships, world view, and hope can accompany traumatic ethnocultural experiences that, when present, require attention within the treatment relationship (Comas-Diaz and Jacobsen 2001).

Countertransference reactions, too, may be influenced by the patient's culture. For example, novice psychotherapists often become so intrigued by the culturally diverse patient that they behave as if they were clinical anthropologists and neglect the patient's emotional pain by focusing exclusively on the patient's culture (Comas-Diaz and Jacobsen 1991). For other therapists, the struggle with impulses to right historical or sociological wrongs may be expressed in persistent rescue feelings. Under certain circumstances, when culturally diverse therapists treat patients from their own culture, they may distance themselves from their patients or may overidentify with them.

Given the increasing multiculturalism of many cities in the United States, how should the psychoanalytic psychotherapist treat patients from cultures other than his or her own? Whereas therapists are obligated to be culturally informed, Foulks et al. (1995) have argued against the promotion of culturally specific psychotherapies. Although acknowledging that some cross-cultural psychiatrists believe expressive–supportive psychotherapy to be an ethnotherapy appropriate only to the citizens of the Western world, they emphasized the overwhelming problems in establishing separate therapies and clinics devoted to patients from a multitude of specific cultures. Also, they stated that the principles of psychotherapy elucidated in this chapter—accepting, understanding, and explaining—are appropriate for the culturally diverse patient.

## Is Psychoanalytic Psychotherapy Effective?

The short answer to this question is yes. The longer answer would require an extensive chapter on the history of psychotherapy research (Talley et al. 1994, Wallerstein 1995). The effectiveness of psychotherapies was first challenged by the argument that responses to psychotherapeutic treatment were no greater than those achieved through spontaneous remission (Eysenck 1952). Many studies have criticized this finding, the latest of which was based on a reevaluation of Eysenck's (McNeilly and Howard 1991) original data, which demonstrated that approximately 15 sessions of psychotherapy can accomplish the same result as a spontaneous remission that takes 2 years. Meta-analytical studies of psychotherapy have demonstrated unequivocally that psychotherapy is effective (Luborsky et al. 1975, Smith et al. 1980, Lambert et al. 1986). The study by Smith et al. (1980), for example, demonstrated that 80% of those patients treated in psychotherapy fared better on outcome measures than those who received no treatment. Psychological growth achieved through psychotherapy is also enduring (Husby 1985).

The helpfulness of psychotherapy for those patients suffering from significant medical illness has been documented. Spiegel et al. (1989) demonstrated that breast cancer patients enrolled in expressive–supportive group psychotherapy lived an average of 18 months longer than control subjects who were not treated with group therapy. A more recent study of the effect of group psychotherapy on survival of patients with metastatic breast cancer, however, failed to replicate prolonged survival but did note that women receiving supportive–expressive psychotherapy had significant improvement in mood and pain perception particularly in those subjects who were initially more distressed (Goodwin et al. 2001). Similarly, patients with lymphoma, leukemia, and malignant melanoma fared better with their illnesses when treated with supportive individual and group interventions (Richardson et al. 1990, Fawzy et al. 1993). Expressive–supportive psychotherapy is also effective in opioid-dependent patients attending community methadone maintenance programs and is superior to counseling (Woody et al. 1995).

Other cost-offset studies have repeatedly demonstrated the helpfulness of psychotherapy in reducing general health care services by as much as one-third (Mumford et al. 1984, Krupnick and Pincus 1992, Olfson and Pincus 1994). These include reduction in hospital stays for surgical and cardiac patients (Mumford et al. 1982) and decreased treatment costs for those with respiratory illnesses, diabetes, and hypertension (Schlesinger et al. 1983). Brief psychotherapy has also been shown to be effective in general medical clinics, where those patients with significant medical and psychiatric problems improve substantially more than those treated by primary care physicians alone (Meyer et al. 1981).

Whereas earlier meta-analyses addressed psychoanalytic, cognitive, and behavioral therapies as an aggregate, Luborsky et al. (1993) have demonstrated that psychoanalytic psychotherapy is as effective as cognitive, behavioral, experiential, and group therapies and hypnotherapy. For this meta-analysis, rigorous inclusion criteria were established including, but not limited to, adequate sample size with random assignment, suitable length and frequency of sessions, sound outcome measures, adherence by therapists to treatment manuals, and comparable skill levels among therapists.

Milrod et al. (2001) have demonstrated the usefulness of their manualized brief psychodynamic psychotherapy in the treatment of panic disorder. In this open trial, 21 patients on no medication received twice weekly therapy for 24 sessions. Sixteen of the 17 subjects who completed treatment experienced remission of panic and agoraphobic symptoms. Eighty-one percent of patients had a comorbid disorder and those with depression also improved dramatically. In addition, improvements in quality of life were significant and were sustained at 6-month follow-up. More recently, Milrod et al. (2007) reported on their RCT of this treatment of 49 patients. Both the psychodynamic treatment group and the comparison group in this study (applied relaxation training) received twice weekly sessions for 12 weeks. Patients who were treated with psychodynamic psychotherapy had significantly greater reduction in panic symptoms and were significantly more likely to respond at treatment termination (73% vs. 39%). This was true of psychosocial functioning as well.

Transference-focused psychotherapy (TFP) is a manualized twice weekly psychodynamic psychotherapy of 1 year or longer duration for treating those with borderline personality disorder (Clarkin et al. 1999). It attempts to reduce self-defeating and self-destructive behavior and borderline symptomatology through the appreciation and modification of self and others as they are manifested within the treatment relationship. Levy et al. (2006) reported the results from an RCT of 90 patients treated with TFP, dialectical behavior therapy (DBT), and a modified psychodynamic psychotherapy. Because many of the symptoms of borderline personality disorder can best be understood from an attachment theory perspective, this study examined attachment patterns and reflective function (RF) in subjects before and after 12 months of treatment. After 1 year of treatment with TFP, but not with DBT and supportive psychotherapy, participants demonstrated a significant increase in higher order attachment state (secure attachment). Significant changes in narrative coherence (presentation of a balanced and realistic view of attachment relationships) and RF were found in the TFP group. RF is a measurement of mentalization that describes the acquisition of the capacity to make sense of behavior in oneself and in others and thereby appreciating thoughts, feelings, and beliefs of others (Fonagy et al. 2002). This study, however, failed to find any differences between the three treatments regarding resolution of trauma and loss both of which are intimately related to poor attachment styles.

A study of brief psychodynamic psychotherapy in patients with panic disorder combined with medication demonstrated that combined treatment was superior to medication alone (Wilborg and Dahl 1996). In this comparative study, subjects were treated with either clomipramine or 15 sessions of dynamic psychotherapy with clomipramine. After discontinuation of medication at 9 months, the relapse rate for those treated with medication alone was significantly higher. Those treated with combined treatment functioned at higher levels, which was attributed to the gains made in psychotherapy.

A randomized controlled study of psychoanalytic psychotherapy and medication versus standard psychiatric care (which included no psychotherapy) in the treatment of 44 patients with borderline personality disorder demonstrated

the effectiveness of psychoanalytic psychotherapy (Bateman and Fonagy 2001). At 18-month follow-up, those who had received psychotherapy in the context of a partial hospital program of a year and a half not only maintained their improvement in functioning but also demonstrated increased gains in a number of significant domains while receiving ongoing twice weekly psychoanalytic group psychotherapy. These gains included fewer suicide attempts, less self-mutilating behavior, a lower number and shorter duration of inpatient admissions, and less use of other psychiatric services. There was also continued symptomatic improvement in anxiety, depression, and general symptom distress, as well as gains in interpersonal relationships and social adjustment.

Swiss researchers (Burnand et al. 2002) conducted a randomized controlled trial of combined psychodynamic psychotherapy and clomipramine in the outpatient treatment of major depression. Seventy-four patients with major depression received either 10 sessions of psychodynamic psychotherapy with medication or medication and supportive psychotherapy. Those in the former group were treated by nurses who received 6 months of training, followed a manualized protocol, and were supervised weekly by an experienced psychoanalyst. While both treatment groups demonstrated significant improvement, medication plus dynamic psychotherapy was associated with both better work and higher global functioning. Moreover, in the psychodynamic psychotherapy treatment group there were fewer treatment failures and posttreatment hospitalizations, which resulted in cost savings (direct and indirect costs) of $2,311 per patient. For those patients who were employed at the onset of the study, savings amounted to $3,394 in indirect costs.

Svartberg et al. (2004) conducted a randomized controlled study of the effectiveness of short-term dynamic psychotherapy (STDP) of 40 sessions and CBT for 50 Cluster C personality disordered patients. Assessments were performed at the outset, midway of treatment, and follow-up at 2 years. Changes in symptom distress were noted for those patients treated with STDP but not with CBT. Forty percent of both groups improved with respect to interpersonal problems and personality functioning. At 2 years, 54% of the those treated with STDP and 42% of those treated with CBT improved symptomatically. Subjects continued to improve after termination supporting a central concept in brief treatment that the effects of treatment often grow with time.

Leichsenrig and colleagues have published a number of important rigorous meta-analytic studies recently. They compared psychodynamic psychotherapy (14 studies) with CBT (11 studies) in the treatment of personality disorders (Leichsenrig and Leibling 2003). Only those studies were considered that employed standardized measures to assess psychopathology, utilized reliable and valid outcome measures, and yielded data allowing calculation of within-group effect sizes. Analysis of the studies demonstrated a large overall effect size (1.46) for dynamic therapy with effect sizes of 1.08 and 1.79 for self-report measures and observed-rated measures respectively. For CBT, the corresponding values were 1.0, 1.2, and 0.87. For psychotherapy studies, effect sizes are characterized as weak (0.2), moderate (0.5), and robust (0.8). An effect size of 1.0 corresponds to a success rate of 72%. This meta-analysis indicated, moreover, that long-term changes with dynamic treatment were achieved.

A larger second study (Leichsenrig et al. 2004a, 2004b) of the efficacy of short-term psychodynamic psychotherapy (STPP) examined 17 studies (Table 87–13) with the following inclusion criteria:

- Randomized controlled design
- Specific forms of STPP (manualized or manual like with treatment integrity assured)
- Trained and experienced therapists
- Specific disorders treated
- Reliability and outcome measures
- Sufficient data to determine pre- and posttreatment effects.

Results of the study indicated the following gains that were better than treatment as usual or using a waiting list as a control:

- Improvement in target problems (effect size 1.39).
- Improvement in general psychiatric symptoms (effect size 0.090).
- Improvement in social functioning (effect size 0.80).
- At follow-up, effect sizes were stable and corresponded to 1.57, 0.95, and 1.19 respectively.
- Ninety-two percent of patients are better off regarding their target problems with treatment.
- Follow-up at the average of 13 months after treatment showed 95% were better off after termination.
- Seventy-five percent of studies included in the meta-analysis were not included in previous meta-analyses, and interpersonal psychotherapy (IPT) studies were excluded since IPT is not a psychodynamic therapy and its presence in earlier studies have skewed results.

(For a more complete list of psychodynamic psychotherapy studies, many of which were not included in this second study, see Leichsenrig et al. (2006).)

The most recent Cochrane Database of Systematic Reviews of STDPs examined 23 studies of 1,431 randomized patients with common mental disorders for general, somatic, anxiety, and depressive symptom reduction. Psychosocial adjustment was a component of the review as well. This review concluded that outcomes for most categories suggested significantly greater improvement in the treatment groups compared to control groups and that gains were maintained in medium- and long-term follow-up. Limitations were noted regarding the small number and heterogeneity of studies as well as variability in treatment quality (Abbass et al. 2006).

At this time, however, the therapist is left with few data supporting the superiority of one type of psychotherapy over another for a given condition or disorder (Smith et al. 1980). This dilemma must be tempered by the recognition of the enormous complexity of psychotherapy research. The important research questions with respect to brief psychoanalytic psychotherapy have been summarized by Barber (1994) and are relevant to all psychoanalytic psychotherapies (Table 87–14).

**Table 87–13 Studies of Short-Term Psychodynamic Psychotherapy (STPP)**

| | | Number Of Patients | | | |
|---|---|---|---|---|---|
| *Studies* | *Psychiatric Disorder* | *STPP Group* | *Comparison Group* | *Concept of STPP* | *Number of STPP Sessions* |
| Compared With Other Psychotherapy | | | | | |
| Bogels et al. (2003, 2004) | Generalized social phobia | 22 | CBT (*n*=27) | Malan | 36 |
| Brom et al. (1989) | PTSD | 29 | CBT (*n*=31); HT (*n*=29) | Horowitz | Mean, 18.8 |
| Cooper et al. (2003) | Maternal depression | 40 | CBT (*n*=41); NDC (*n*=42) | Cramer et al. | 10 in 10 weeks |
| Crits-Christoph et al. (1999, 2001) | Cocaine dependence | 124 | CBT and group DC (*n*=91); individual DC (*n*=92); group DC (*n*=96)* | Mark and Lubrosky with group DC | 36 individual and 24 group in 4 months |
| Fairburn et al. (1986) | Bulimia nervosa | 11 | CBT (*n*=11) | Rosen, Bruch, and Stunkard | 19 |
| Garner et al. (1993) | Bulimia nervosa | 25 | CBT (*n*=25) | Luborsky | 19 |
| Hamilton et al. (2000) | Chronic functional dyspepsia | 37 | ST (*n*=36) | Shapiro and Firth | 7 |
| Hellerstein et al. (1998) | Personality disorders | 25 | Brief ST (*n*=24) | Davanloo, Laikin and Winston | Mean, 28.5 |
| Munroe-Blum and Marziali (1995) | Borderline personality disorder | 31 | Group IPT (*n*=25) | Kernberg | 17 |
| Shapiro et al. (1994) | Depression | 58 | CBT (*n*=59) | Shapiro and Firth | 8 vs. 16 |
| Svartberg et al. (2004) | Cluster C personality disorder | 25 | CBT (*n*=25) | Malan<br>McCullough-Vaillant | 40 |
| Thompson et al. (1987) | Depression | 24 | CBT (*n*=27); BT (*n*=25) | Horowitz and Kaltreider | 16—20 |
| Winston et al. (1994) | Personality disorders | 25 | Brief APT (*n*=30) | Daavanloo | 40 |
| Woody et al. (1995) | Opiate dependence | 57 | CBT and DC (*n*=34); DC (*n*=27) | Luborsky with DC | 12 |
| Cooper et al. (2003) | Maternal depression | 40 | Routine primary care (*n*=42) | Cramer et al. | 10 in 10 weeks |
| Gowers et al. (1994) | Anorexia nervosa | 20 | TAU (*n*=20) | Crisp | 12 |
| Milrod et al. (2007) | Panic disorder | 26 | PFPP 26; ART 23 | Milrod et al. | 24 in 12 weeks |
| Levy et al. (2006) | Borderline personality disorder | 31 | DBT (*n*=29); SPT (*n*=30) | Kernberg et al. | Twice weekly for 1 year |
| Compared with Waiting-List Control Group | | | | | |
| Monsen and Monsen (2000) | Somatoform pain disorder | 20 | TAU/no therapy (*n*=20) | Monsen and Monsen | 33 |
| Bogels et al. (2003, 2004) | Generalized social phobia | 22 | *n*=27 | Malan | 36 |
| Brom et al. (1989) | PTSD | 29 | *N*=23 | Morowits | Mean, 18.8 |
| Thompson et al. (1987) | Depression | 24 | *N*=19 | Horowitz and Kaltreider | 16–20 |
| Winston et al. (1994) | Personality disorder | 25 | *N*=26 | Davanloo | 40 |

*Source*: Modified from Leichsenrig et al. (2004b).
Abbreviations: APT, adaptive psychotherapy; ART, applied relaxation training; BT, behavioral therapy; CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; DC, drug counseling; HT, hypnotherapy; IPT, interpersonal therapy; NDC, nondirective counseling; PTSD, posttraumatic stress disorder; SPT, supportive psychoanalytic therapy; ST, supportive therapy; STPP, short-term psychodynamic psychotherapy; TAU, treatment as usual; TFP, transference-focused psychotherapy.
*As suggested by one of the anonymous reviewers, manual-guided DC was regarded as a form of psychotherapy rather than TAU.

The majority of studies examining psychoanalysis and psychoanalytic psychotherapy have been outcome studies rather than comparative. Although many early outcome studies of psychoanalysis were methodologically unsound (Wallerstein 1995), a number of these that examined both outcome and therapeutic process were sophisticated (Bachrach et al. 1991). In general, process studies have attempted to examine important variables, such as how interpretation and therapeutic alliance are related to outcome and how transference, central conflict, and internalization

**Table 87–14 Research Challenges for Psychoanalytic Psychotherapy**

| |
|---|
| Determining efficacy for specific disorders |
| Developing treatment guidelines for interpersonal problems and personality disorders |
| Developing reliable and valid self-report measures for core conflicts |
| Measuring potential cost-offset of different therapies |
| Determining efficacy of short-term vs. long-term psychotherapies |
| Matching patients to treatment on the basis of personality, functional level, or developmental stage |
| Examining whether and how experienced therapists can be trained in short-term psychoanalytic treatments |
| Learning the limits of brief therapy and conditions or symptoms for which longer term psychotherapy should be recommended |

*Source*: Barber (1994).

are measured in a reliable and valid manner (Barber 1994). The Menninger Psychotherapy Research Project, for example, attempted to answer not only outcome (what changes accrued from treatment) but also how such changes were brought about in those patients receiving psychoanalysis, psychoanalytic psychotherapy, and supportive psychoanalytic psychotherapy (Wallerstein 1986). The psychotherapy research project's most significant findings centered on the unanticipated effectiveness of supportive psychoanalytic psychotherapy in the treatment of patients with significant psychiatric illness. In short, across all three forms of psychoanalytic psychotherapy, changes emanating from supportive interventions were substantial and in no way inferior to the more expressive interventions of psychoanalysis that were aimed at structural change. Similarly, a recent study by Hoglend et al. (2006) demonstrated that patients with poor object relations profited more from therapy employing transference interpretations than from therapy without transference interpretations.

## Long-Term versus Brief Psychotherapies

Despite the massive economic forces impinging on the current practice of long-term psychoanalytic psychotherapies, both brief and extended expressive and supportive treatments are required in the psychiatrist's therapeutic armamentarium. Whereas the research on brief psychoanalytic psychotherapies has been impressive, patients successfully treated by these techniques have generally met inclusion criteria that place them in the less dysfunctional range of psychiatric illness; that is, they tend to have less severe character disorder. Moreover, more than 80% of patients entering psychoanalysis have previously been unsuccessful in less intensive forms of treatment (Doidge et al. 1994). Up to 25% of all depressed patients do not tolerate medications or they respond poorly to them (American Psychiatric Association 1993), and of course there are always patients who will not agree to take antidepressants. Even the National Institute of Mental Health Collaborative Study of Depression, which assessed cognitive–behavioral therapy and IPT and tricyclic antidepressant medication, demonstrated the exceptional efficacy of psychotherapy. Shea et al. (1992) have argued that 16 weeks of treatment appears to be insufficient for many patients to achieve a full recovery. The need for maintenance psychotherapy in treating unipolar depression has been substantiated (Frank et al. 1990). A significant study of the relationship between the number of sessions and patient improvement in psychotherapy has shown that by 8 sessions and 26 sessions of weekly psychotherapy 50 and 75% of patients, respectively, improve (Howard et al. 1986). When chronic distress and characterological symptoms are examined, however, 74–89% of patients with chronic distress and only 60% of patients with character problems improve after a year of treatment (Kopta et al. 1992). In short, patients with more complex conditions often require longer treatment.

## Disconnection between Psychotherapy Practice and Research

There is a persistent tension in the psychotherapy research literature relating to the perception that therapists do not integrate the findings from psychotherapy research and that psychotherapy researchers fail to study the relevant clinical issues (Stiles 1992). From the therapist's point of view, most psychotherapy research lacks a therapeutic context and fails to answer basic questions such as the following: How is a treatment altered when the patient has unusual characteristics? What intervention should the therapist use if the prescribed treatment is failing? How should therapeutic change be assessed? (See Westen et al. (2004) for a more complete discussion of the limitations of evidence based psychotherapy.) The tension between therapists and researchers has been made all the more strident because of pressures placed on both parties to prove cost effectiveness for all psychotherapeutic interventions. Unfortunately, nationally funded research in psychotherapy has not been a priority, and when such research is funded, more often than not, it must embrace a clinical trials methodology, which may or may not be able to ask the relevant clinical questions.

What can be done about bridging the chasm between psychotherapy practice and research? Talley et al. (1994) have advocated five practices likely to be helpful in creating a rapprochement between researchers and therapists. First, case studies should no longer be disparaged, for they have the ability to be scientifically rigorous by testing specific hypotheses. Second, wherever possible, researchers should endeavor to include clinical vignettes in their published work and emphasize the clinical applicability of specific findings. Third, studies must be conducted that determine what type of psychotherapy research is helpful to therapists. Fourth, the accessibility of psychotherapy research findings to therapists should be studied with respect to knowledge of new findings as well as understandability. Last, training programs must assist students to integrate new research findings, as well as train a new generation of researchers to ask the clinically significant questions.

## Toward a Neurobiology of Psychotherapy

Exciting new research in psychiatry, brain imaging, cognitive neuroscience, genetics, and molecular biology has provided striking insights into how psychotherapy actually changes both brain structure and function (Liggan and Kay 1999, Gabbard 2000, Lehrer and Kay 2002, Etkin et al. 2005). Learning and memory are associated with alterations in central nervous system (CNS) neuronal plasticity including increased synaptic strength and number of synapses. Neurogenesis, or the creation of new brain cells, occurs daily in the human hippocampus (Eriksson et al. 1998), the central

location for the formation of new explicit memories. Not only does memory consolidation lead to persistent modification in synaptic plasticity, but psychotherapy, a form of learning, also produces changes in the permanent storage of information acquired throughout an individual's life and provides new resources to address important psychobiological relationships between affect, attachment, and memory, which is of fundamental importance in psychiatric disorders. Rapidly accruing knowledge about the different types of memory and the role of the amygdala now support the influence of memories that reside outside of the awareness of our patients (LeDoux 1996). Implicit memories formed in infancy and childhood persistently affect the manner in which patients experience themselves and their worlds as manifested, for example, in transference reactions within and outside of the therapeutic relationship.

Research beginning in the last decade has demonstrated that psychotherapy affects cerebral metabolic rates. Two studies have provided preliminary evidence that psychoanalytic psychotherapy alters serotonin metabolism in borderline personality disorder and depression (Viinamaki et al. 1998, Saarinen et al. 2005). Comparative imaging studies testing nonpsychoanalytic psychotherapy versus medication have shown equally normalizing changes in regional cerebral blood flow (rCBF) and neurotransmitter metabolism in patients with obsessive–compulsive disorder (OCD; Baxter et al. 1992) and major depression (Baxter et al. 1992, Brody et al. 2001, Martin et al. 2001, Goldapple et al. 2004) as well as in social phobia (Furmark et al. 2002). Goldapple's study, however, was the first to note similar but also differential changes between psychotherapy and medication. A recent study by Kennedy et al. (2007) also found differential effects between psychotherapy and medication. Other studies have shown restoration of sleep architecture and thyroid hormone levels after psychotherapeutic treatment of patients with major depression (Thase et al. 1998, Joffe et al. 1996) (Table 87–15).

Psychotherapy may have profound impact on neuroimmunology. As noted, providing psychotherapy to patients who have metastatic breast cancer or malignant melanoma can reduce morbidity and perhaps mortality (Spiegel et al. 1989, Fawzy et al. 1993). Elucidating the role of the hypothalamic–pituitary–adrenal system (HPA axis) has also clarified the impact of stress on learning, memory, and lifelong psychological adaptation during important periods of attachment in mammals (Suomi 1991, Rosenblum and Andrews 1994, Kaufman et al. 2000). Many studies have demonstrated enduring elevated levels of cortisol, adrenocorticotrophic hormone, and corticotrophin-releasing factor following episodes of maternal separation. Even with appropriate substitute nurturing, animals respond to stress in a more intense fashion throughout their lives. Early experiences therefore can have profound impact on future psychosocial and neurobiological development as has been demonstrated in reduced hippocampal volumes of children who have experienced abuse and maltreatment (Bremner et al. 1997).

Last, genetic and epidemiological studies have clarified the role of experiences on gene expression and vulnerability to psychiatric illness. Kendler's large study of groups of female twins, both at low and high risk for major depression, eloquently demonstrated that the meaning and valence of a stressor have great influence on illness onset (Kendler et al. 1995). The probability for depression for low-risk twins and high-risk twins who experienced a recent death, assault, or marital problems increased from 0.5 to 6.2% and 1.1 to 14.6% respectively, over a 17-month period. A more recent study by Kendler et al. (2005) addressed the interaction of stressful life events and 5HTT (serotonin transporter) polymorphism in the prediction of major depression. Another study examined the gene–environment interaction by elucidating that children with low monoamine oxidase A (MAOA) and who experienced maltreatment were more likely to have significant antisocial behavior compared to children with abuse but not low MAOA (Caspi et al. 2002).

Similarly, by studying large numbers of teenagers from variously configured families, Reiss demonstrated that the inherited psychological and temperamental characteristics of children can evoke very different types of relatedness from their parents (Reiss et al. 1995). Compared to their siblings, teenagers who had highly conflictual relationships with their parents, for example, a negative way of relating, accounted for nearly two-thirds of variance in antisocial behavior and more than one-third the variance in depressive symptomatology. The experience of a nonshared family environment expressed by the differential treatment of adolescents has significant explanatory power as to why some are at greater risk for mental illness.

The study of psychotherapy from a neurobiological perspective is likely to provide greater understanding of how words in the context of therapeutic relationships can heal. It may be that there are similar mechanisms and anatomical regions that are involved in the successful treatment of psychiatric illness with psychotherapy and pharmacotherapy as monotherapies, as well as in the combined treatment situation (Sacheim 2001). It is also likely to yield a greater understanding of pathogenesis and delineate helpful interventions to decrease genetic vulnerability to emotional disorders. The ability to predict the outcome of treatment with psychotherapy and medication will undoubtedly be available in the near future (Mayberg et al. 1997).

## Conclusion

The practice of psychoanalytic psychotherapy by psychiatrists is currently under scrutiny. Nevertheless, the majority of all encounters with patients in American psychiatry involve some form of psychotherapy, and many of these interventions are based on the principles of psychoanalytic psychotherapy.

At this time, the theory and technique of psychoanalytic psychotherapy provide the most comprehensive orientation to the continuum of expressive–supportive psychotherapy. Psychoanalytic psychotherapy is a potent intervention and, as such, holds great promise when it is used in a sophisticated fashion for appropriate patients with appropriate psychiatric problems. Like medication, psychoanalytic psychotherapy has specific indications, contraindications, and undoubtedly, potentially negative effects. As an effective therapeutic intervention, it requires that the therapist be highly skilled in assessing the inner experience of those who come for help. It also requires extensive training and education in techniques of this treatment modality. In addition, the therapist must acquire significant self-knowledge, sophistication, and dedication in working so intensively with human pain.

**Table 87–15 Neurobiological Studies of Psychotherapy**

| *Investigators* | *Treatment* | *Disorder* | *N* | *Findings* |
|---|---|---|---|---|
| Baxter et al. (1992) (PET) | Fluoxetine vs. exposure/ response prevention therapy | OCD | 9 patients | |
| | | | 9 patients | Decreased activity in the head of the right caudate nucleus in responders with both psychotherapy (6/9) + pharmacotherapy (7/9) |
| Joffe et al. (1996) | CBT | Major depression | 30 patients | Increased $T_4$ in all 17 responders |
| | | | | Decreased $T_4$ in nonresponders |
| Schwartz et al. (1996) (PET) | Exposure/response prevention therapy | OCD | 9 new patients | Decreased caudate activity (R>L) in responders |
| | | | 9 patients from previous study | |
| Thase et al. (1998) (EEG) | CBT | Major depression | 78 patients | Psychotherapy + pharmacotherapy restored normal sleep architecture |
| Viinamaki et al. (1998) (SPECT) | Psychodynamic psychotherapy vs. no treatment | Borderline PD + depression | 2 patients (10 controls) | Increased 5-HT metabolism PFC and thalamus |
| Brody et al. (2001) (PET) | IPT vs. paroxetine | Major depression | 24 patients | Normalization of PFC, AC + temporal lobe with both treatments |
| Martin et al. (2001) (SPECT) | IPT vs. venlafaxine | Major depression | 28 patients | Increased (r)CBF to basal ganglia in both treatments. Increased (r)CBF in limbic system for IPT only |
| Furmark et al. (2002) (PET) | Citalopram vs. CBT | Social phobia | 18 patients | Decreased (r) CBF in public speaking task bilaterally in AMG, hippo, periamygdaloid, rhinal and parahippocampal cortices with degree of attenuation associated with clinical improvement |
| Goldapple et al. (2004) (PET) | CBT vs. paroxetine | Major depression | 31 patients | For CBT, increases in hippo, DC, and decreases in frontal cortex; For paroxetine, increases in PFC, hippo and SC |
| Saarinen et al. (2005) (SPECT) | Dynamic psychotherapy | Major depression | 1 patient | Normalization of midbrain level SERT binding |
| Kennedy et al. (2007) (PET) | CBT vs. venlafaxine | Major depression | 24 patients | For both interventions decreased glucose metabolism bilaterally in OFC and left PFC, increased in right occipital-temporal cortex. Increase in AC and decrease in thalamus with CBT only. Venlafaxine only produced increase in posterior cingulate. |

CBT, cognitive–behavioral therapy; IPT, interpersonal psychotherapy; PFC, prefrontal cortex; AC, anterior cingulate; DC, dorsal cingulate; SC, subgenual cingulate; AMG, amygdala; hippo, hippocampus; SERT, serotonin transporter.

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CHAPTER

# 88 Interpersonal Psychotherapy

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## Introduction

In the 1970s, the late Gerald L. Klerman, M.D., Myrna M. Weissman, Ph.D., Bruce Rounsaville, and Eve Chevron (1984) developed a psychotherapy based on life events and social functioning to use in an antidepressant medication trial. What became known as interpersonal psychotherapy (IPT) is a time-limited, diagnosis-focused therapy has subsequently been tested in numerous randomized controlled clinical trials. Research has established its efficacy as an acute and chronic treatment for patients with major depressive disorder (MDD), and as an acute treatment for bulimia nervosa. Other outcome studies have suggested its promise for other psychiatric diagnoses, such as anxiety disorders, and its lack of efficacy for patients with substance use disorders. The research findings have led to its inclusion in treatment guidelines and increasing dissemination into clinical practice.

IPT is a straightforward, manual-based, focused, pragmatic, and optimistic time-limited psychotherapy. It has been best tested as a treatment of major depressive episodes (MDEs), on which this chapter will focus. IPT has two basic premises. First, depression is a medical illness, which is treatable and not the patient's fault. Second, the disorder does not occur in a vacuum, but rather is influenced by and itself affects the patient's psychosocial environment. Changes in relationships or other life events may precipitate depressive episodes in individuals vulnerable to depression; conversely, depressive episodes strain relationships and provoke negative life events. The goal of treatment is to help the patient solve a crisis in his or her role functioning or social environment. Achieving this helps the patient to gain a sense of mastery over his or her functioning and relieves depressive symptoms. Given its clinical focus on interpersonal functioning, it is unsurprising that IPT has been shown to build social skills. (See Table 88–1.)

IPT was defined in a manual (Klerman et al. 1984, updated by Weissman et al. 2000, 2007). Demonstration of efficacy in research trials for patients with MDEs led to its adaptation and testing for other mood and nonmood disorders. This has included modification for adolescent and geriatric depressed patients, patients with bipolar and dysthymic disorders, depressed HIV-positive and depressed pregnant and postpartum patients, and depressed primary care patients. Most of the modifications have been relatively slight, retaining the general principles and techniques of IPT for major depression. Nonmood targets have included bulimia, substance abuse, borderline personality disorder, and several anxiety disorders. IPT has also been adapted as a maintenance treatment to forestall relapse and recurrence of depressive episodes, for couples and group formats, as a telephone intervention, and in a patient self-help guide (Weissman et al. 2000, 2007).

Begun as a research intervention, IPT has begun to spread among clinicians and in residency training programs. The publication of efficacy data and the promulgation of practice guidelines that embrace IPT among antidepressant treatments have led to increasing demand for IPT training. Managed care and economic pressures have aroused interest in defined, time-limited, empirically supported treatments like IPT. Practice guidelines for mental health professionals (Karasu et al. 1993) and primary care practitioners (Depression Guideline Panel 1993, Vols 1–4) cited IPT as an acute and maintenance treatment for depression, used alone and in combination with medication.

American Psychiatric Association practice guidelines for adults with major depression included IPT among the few recommended psychotherapies. IPT was deemed useful for patients in the "midst of recent conflicts with significant others and for those having difficulty adjusting to an altered career or social role or other life transition" (Karasu et al. 1993, p 6); that is, for depression associated with life events or interpersonal conflicts. Although many patients present with such recent life changes, the empirical support for IPT among depressed patients generally makes these appear minimal, conservative indications.

Both the physician and patient guides in primary care guidelines for depression (Depression Guideline Panel 1993) list IPT, cognitive–behavioral therapy (CBT; Beck et al. 1979), behavioral, brief dynamic, and marital therapy as treatments for depression. The guidelines recommend IPT as an acute treatment for nonpsychotic depression, to remove symptoms, prevent relapse and recurrence, correct

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**Table 88–1 Premises and Goals of IPT**

Principles of IPT
1. Depression is a medical illness, which is treatable and not the patient's fault.
2. Depression influences and is influenced by the patient's psychosocial environment.

Goals
The primary goal is to help the patient solve a difficulty in role functioning or social environment. This
a. relieves symptoms
b. improves the patient's social environment
c. builds interpersonal skills (e.g., self-assertion, effective confrontation)
d. fosters a sense of mastery over the environment

**Table 88–2 Theoretical and Empirical Sources of IPT**

I. Interpersonal theory
  A. Importance of current life events to psychopathology (Meyer, Sullivan, et al.)
  B. Attachment theory (Bowlby)
II. Empirical support: Association of depressive episodes with
  A. complicated bereavement (grief)
  B. marital and other interpersonal disputes (role disputes)
  C. life events (role transitions)
  D. isolation and lack of social support (interpersonal deficits)

provoking psychological problems with secondary symptom resolution, and address secondary consequences of depression. The guidelines note that medication alone may suffice to prevent relapse or recurrence, and to maintain remitted patients with recurrent depression (cf. Frank et al. 1990, 1991). These guidelines consider IPT, CBT, and behavioral treatments "effective in most cases of mild-to-moderate depression" (Depression Guideline Panel 1993, Vol. 2, p 12) but indications "for continuation phase psychotherapy are unclear" (Depression Guideline Panel 1993, p 18) even though "two studies are suggestive that continuation psychotherapy may reduce the relapse rate" (Depression Guideline Panel 1993, p 18). The Patient Guidelines list behavioral, cognitive, and IPT as the "most well-studied [*sic*] for their effectiveness in reducing symptoms of major depressive disorder" (Depression Guideline Panel 1993, Vol. 4, p 23).

IPT is spreading from its initial research base in the United States. The IPT manual has been translated into Italian, German, Japanese, Spanish, and French, and is being used ever more widely around the world. Descriptions of IPT have appeared in Spanish (Puig 1995) and Dutch journals (Blom et al. 1996). An International Society for Interpersonal Psychotherapy (www.interpersonalpsychotherapy.org), established at the American Psychiatric Association Annual meeting in May 2000 in Chicago, has a growing membership and held international scientific meetings in 2004 and 2006.

That IPT has not been included among the psychotherapies required for "competency" in American residency training programs reflects a shortage of trained supervisors rather than lack of evidence of efficacy. Indeed, more evidence supports the utility of IPT than of any of the mandated psychotherapies save CBT.

(For a complete description of IPT technique, see Weissman et al. [2000] or [2007]; for the patient guide, see Weissman [1995]. For the group adaptation, see Wilfley et al. [2000]; for depressed adolescents, see Mufson et al. [2004a]; for dysthymic disorder, see Markowitz [1998]; for bipolar disorder, see Frank [2005].)

## Background

IPT is based on the interpersonal theory of Adolph Meyer, Harry Stack Sullivan (1953), and later John Bowlby (1973) and others. (See Table 88–2.) The principle derived from these theories is that life events occurring after the early childhood years influence psychopathology. Social supports protect against psychopathology, whereas social losses may trigger symptoms in vulnerable individuals. IPT employs this principle for practical, not etiological, purposes. It does not presume to discern the *cause* of a depressive episode—assuming the etiology of depression to be multifactorial—but pragmatically uses the connection between current life events and the onset of depressive symptoms to help the patient understand and combat the episode of illness. IPT is also based on psychosocial and life events research of depression, which demonstrated relationships between depression and complicated bereavement, role disputes (e.g., bad marriages), role transitions (meaningful life changes), and interpersonal deficits (social isolation).

## Conducting IPT

IPT therapists define depression as a *medical illness*, a treatable condition that is not the patient's fault. This definition displaces burdensome guilt from the patient herself to the illness, making the symptoms ego-dystonic and discrete. It also provides hope for a response to treatment. The therapist uses the DSM-IV-TR (American Psychiatric Association 2000) to diagnose the patient, and rating scales such as the Hamilton Depression Rating Scale (HDRS; Hamilton 1960) or Beck Depression Inventory (BDI; Beck 1978) to assess and explain the depressive symptoms. This process begins psychoeducation, helping the patient to recognize that the problem is a common mood disorder with a predictable set of symptoms, not the personal failure, weakness, or character flaw that the depressed patient often believes to be the issue.

Underscoring this approach, IPT therapists give depressed patients the "sick role" (Parsons 1951), temporarily excusing them from what their illness prevents them from doing while obliging them to work as patients in order to recover the healthy role they have lost. The sick role does not encourage disability, as some therapists may fear. Instead, it helps the patient to see how depression interferes with functioning, shifting blame from the guilty patient to the depression itself for this disability, and raising the expectation that functioning will improve as the depression recedes. The resolution of the sick role is to regain the healthy, euthymic role by the end of treatment.

The time-limited structure of IPT also energizes patients and protects against regression during treatment.

By solving an interpersonal crisis—a complicated bereavement, a role dispute or transition, or an interpersonal deficit—the IPT patient has the dual opportunity to improve his or her life situation and simultaneously relieve the symptoms of the depressive episode. This coupled formula, validated by randomized controlled trials in which IPT has been tested, can be offered with confidence and

optimism. Symptomatic relief may correlate with the degree to which the patient solves his or her interpersonal crisis (Markowitz et al. 2006a). This therapeutic optimism, while hardly specific to IPT, very likely provides part of its power in remoralizing the patient. (See Table 88–3.)

**Table 88–3 Phases of IPT**

I. Early phase
  A. Deal with the depression
    1. Review depressive symptoms
    2. Name the syndrome: formal diagnosis
    3. Psychoeducation about depression and its treatment
    4. Give patient the "sick role"
    5. Evaluate need for medication
  B. Relate depression to interpersonal context: **interpersonal inventory**
    1. Nature of interaction with significant persons
    2. Reciprocal expectations of patient and significant others, and whether these were fulfilled
    3. Satisfying and unsatisfying aspects of relationships
    4. Recent changes in key relationships
    5. Changes patient desires in relationships
  C. Identify the major problem area
    1. Determine problem area related to current episode and set treatment goals
    2. Which relationship is related to the episode? What might change in it?
  D. Explain IPT concepts and contract
    1. Outline understanding of the problem: **formulation**
    2. Agree on treatment goals (focal problem area)
      a. *Brief* treatment (time limit)
      b. Target is depression (not character)
    3. Describe IPT procedures: "here and now" focus, need to discuss important concerns; review of current interpersonal relations; discussion of practical aspects of treatment
II. Middle phase
  Specific strategies for treating grief, role dispute, role transition, or interpersonal deficits
III. Termination phase
  A. Consolidate gains
  B. Foster independence
  C. Address guilt (and blame therapy) if nonresponder
  D. Review risk of relapse and recurrence
  E. Recontract for continuation and maintenance treatment if appropriate

It is not its specific techniques but its overall strategies that make IPT a unique and coherent approach. An eclectic therapy, IPT uses techniques seen in other treatment approaches. For example, the medical model of depressive illness IPT employs is consistent with pharmacotherapy (making it highly compatible in combination with medication). IPT shares role playing and a "here and now" focus with CBT, and addresses interpersonal issues in a manner familiar to marital therapists. Although like CBT a time-limited treatment targeting a syndromal constellation (e.g., major depression), IPT is considerably less structured, assigns no explicit homework, and focuses on interpersonal problem areas rather than automatic thoughts. IPT overlaps to some degree with psychodynamic psychotherapies, and many of its early research therapists came from psychodynamic backgrounds. Yet IPT also meaningfully differs from them: in its focus on the present, not the past; its focus on practical, real life change rather than self-understanding; its medical model; and its avoidance of the transference and of genetic and dream interpretations (Markowitz et al. 1998a).

Each of the four IPT interpersonal problem areas has discrete, if partially overlapping, goals for therapist and patient to pursue. The therapist helps the patient relate life events to mood and other symptoms. Techniques include an *opening question*, which elicits an interval history of mood and events, *communication analysis*, the reconstruction and evaluation of recent, affectively charged life circumstances, *exploration of the patient's wishes and options,* in order to pursue these in particular interpersonal situations, *decision analysis*, to help the patient choose which options to employ, and *role playing*, to help patients rehearse tactics for real life.

IPT deals with current rather than past interpersonal relationships, focusing on the patient's immediate social context. The IPT therapist attempts to intervene in depressive symptom formation and social dysfunction rather than addressing enduring aspects of personality. Personality is in fact difficult to accurately assess during an episode of an Axis I disorder such as major depression (Hirschfeld et al. 1983). IPT does build new social skills such as self-assertion and the effective use of anger (Weissman et al. 1981), which may be as valuable as changing personality traits. One study found that maintenance IPT for recurrent depression reduced Axis II Cluster C symptoms over time (Cyranowski et al. 2004).

## Phases of Treatment

As an acute treatment, IPT has three phases. The *first phase*, lasting from one to no more than three sessions, includes diagnostic evaluation, psychiatric anamnesis, and setting the treatment framework. The therapist reviews symptoms, diagnoses the patient as depressed by standard criteria (APA 2000), and gives the patient the sick role (Parsons 1951). The psychiatric history includes the "interpersonal inventory," which is not a structured instrument but a careful review of the patient's past and current social functioning and close relationships, their patterns and mutual expectations. How does this patient relate to other people? This evaluatory interview elucidates changes in relationships surrounding the onset of symptoms; for example, death of a loved one, children leaving home, worsening marital strife, or isolation from a confidant. This review provides a framework for understanding the social and interpersonal context of the onset of depressive symptoms and the basis for a treatment focus.

Having assessed the need for medication based on symptom severity, prior treatment response, and patient preference, the therapist educates the patient about depression by discussing the constellation of emotional, cognitive, and physical symptoms that define major depression, their psychosocial concomitants, and what the patient may expect from treatment. The therapist next links the depressive syndrome to the patient's interpersonal situation in a formulation (Markowitz and Swartz 1997) focusing on one of four interpersonal problem areas: (1) *grief*; (2) interpersonal *role disputes*; (3) *role transitions*; or (4) *interpersonal deficits*. Once the patient explicitly accepts this formulation as the focus for treatment, IPT enters its middle phase.

It is important to keep treatment focused on a simple theme that even a highly distracted depressed patient can grasp. Any formulation necessarily simplifies a patient's life narrative. Although some patients may present with multiple interpersonal problems, the goal of the formulation is to

isolate one or, at most, two salient problems related to the patient's mood disorder (whether as precipitant or consequence). More than two foci would mean no focus at all. The choice of focal problem area depends on clinical acumen, although research has shown that IPT therapists agree in choosing such areas (Markowitz et al. 2000), and patients find the foci credible.

During the opening phase the therapist also sets a time limit for the acute treatment, generally between 12 and 16 sessions. The optimal number of sessions for IPT requires further research; one study suggests that as few as eight sessions may be effective for some patients (Swartz et al. 2004). Sessions are scheduled weekly: this allows sufficient time to pass that things will happen in the patient's outside life, on which the treatment focuses, yet is frequent enough to maintain momentum and thematic continuity.

The *middle phase* involves strategies specific to the chosen interpersonal problem area. For *grief*—complicated bereavement following the death of a loved one—the therapist facilitates the catharsis of mourning and helps the patient find new activities and relationships to compensate for the loss. *Role disputes* are conflicts with significant others: a spouse, other family member, boss, coworker, or close friend. The therapist helps the patient explore the relationship, the nature of the dispute, whether it has reached an impasse, and available options to negotiate its resolution. If these options fail, therapist and patient may conclude that the relationship has reached an impasse and consider ways to change the impasse or to end the relationship. *Role transition* includes change in life status; for example, beginning or ending a relationship or career, moving, promotion, demotion, retirement, graduation, having a baby, or diagnosis of a(nother) medical illness. The patient learns to manage the change by mourning the loss of the old role, recognizing positive and negative aspects of the new role he or she is assuming, and taking steps to master the new role.

*Interpersonal deficits*, the poorly named, residual fourth IPT problem area, is used for patients who lack one of the first three problem areas; that is, patients who report no recent life events. This focus defines the patient as isolated and lacking social skills, including having problems in initiating or sustaining relationships; the goal is to help the patient to develop new relationships and skills. Some patients who fall into this category may in fact suffer from dysthymic disorder, for which separate strategies have been developed (Markowitz 1998).

IPT sessions address present "here and now" problems rather than childhood or developmental issues. They focus on affect and interpersonal behaviors rather than cognitions. Sessions open with the question: "How have things been since we last met?" This focuses the patient on recent interpersonal events and recent mood, which the therapist helps the patient to link. Therapists take an active, nonneutral, supportive, and hopeful stance to counter the depressed patient's pessimism. They elicit and emphasize the options that exist for change in the patient's life, options that the depressive episode may have kept the patient from seeing or exploring fully. Nor does understanding the situation suffice: therapists stress the need for patients to test these options in order to improve their lives and simultaneously treat their depressive episodes. Over the course of therapy, the IPT therapist regularly repeats measurements such as the HDRS so that both therapist and patient can gauge the latter's progress.

The *final phase* of IPT, occupying the last few sessions of acute treatment or last months of maintenance treatment, builds the patient's newly regained sense of independence and competence by recognizing and consolidating therapeutic gains. The therapist underscores the patient's competence to function without further therapy by emphasizing that the depressive episode has improved because of the patient's actions in changing a life situation—and this at a time when the patient had felt weak and impotent. The therapist also helps the patient to anticipate triggers for and responses to depressive symptoms that might arise in the future. Compared to psychodynamic psychotherapy, IPT de-emphasizes termination: it is a bittersweet graduation from successful treatment. The sadness of parting from the therapist is contrasted with depressive feelings. If the patient has not improved, the therapist emphasizes that the *treatment* has failed, not the patient, and that alternative effective treatment options exist. Patients with multiple prior MDEs or significant residual symptoms, who successfully complete acute treatment but remain at high risk for recurrence, may contract for maintenance therapy as acute treatment draws to a close.

Clinical Vignette

Ms. A, a 42-year-old married lawyer, presented with a 6-month history of major depression and a baseline 24-item HDRS score of 27. Her symptoms included a depressed and anxious mood with diurnal variation, early and middle insomnia, fatigue, difficulty concentrating, indecisiveness, and the feeling that life was not worth living. She had no plan and had made no suicide attempts; she denied psychotic symptoms and substance abuse. Although she initially described her symptoms without linking them to a context, her therapist took a careful history and connected the depressive episode to recent life events. Ms. A's symptoms coincided with her worsening relationship with her lawyer husband. She felt he had become increasingly distant, and might be having an affair.

Ms. A had had an episode of depression 12 years before that had resolved with a course of antidepressant medication; she had stopped the medication after about 9 months. Four years before that, she had had 6 months of evidently supportive psychotherapy to address her anxiety about marrying her husband; she had found talking helpful at the time, and had decided to marry. Her family history was notable for maternal depression. Her interpersonal inventory revealed that she had few close friends, in whom she was more likely to confide than her husband. She counted on her mother for support, feeling distanced from a strict and unemotional father and a somewhat sadistic brother.

Ms. A was deferential to her husband, who worked at a smaller and less prestigious law firm and was easily angered. In retrospect, she felt that their marriage had worsened after they had been unable to conceive a child and had gone for infertility treatment in her mid-30s. Her husband had initially blamed her for their difficulties, but since his low sperm count and motility had been identified as the problem, he had sulkily withdrawn from the relationship, and often slept in the living room. He kept ever longer working hours, and Ms. A worried that he might be having an affair. They had rarely discussed their feelings, however, and she felt he would explode with anger if she dared to confront him.

Ms. A declined to take antidepressant medication, as her previous serotonin reuptake inhibitor trial had made her "jumpy" and inhibited her libido—the last thing she now felt her marriage needed. Her therapist diagnosed her as having a recurrent major depressive episode, told her Hamilton score, and suggested that the episode was related to a worsening role dispute with her husband. Ms. A agreed to a 12-week course of IPT and was given the sick role.

Sessions focused on marital communication, but started with the therapist eliciting the patient's feelings about her marriage and her husband. They discussed her own and her husband's disappointment about not having children, and her feelings that her husband found her inadequate in the absence of children. She loved her husband, who also had many good qualities, but was also upset with his withdrawal and apparent blame of her. The therapist normalized Ms. A's feelings, encouraged her to put them into words, and role played with her what she wanted to say, and in what tone of voice. They discussed contingencies: how she might approach him, and what she could do if he got angry.

Ms. A feared her husband's rage, but she agreed with her therapist that it would be helpful to be able to communicate feelings and that their infertility was a major life event (which might alternatively have been characterized as a role transition). After some weeks of rehearsal, she risked confronting him. She noted that they had been going through a hard time, that their marriage had become strained, but that she really wanted to work with Mr. A to make it better. She also confessed her fears that he no longer loved her and was seeing someone else.

Mr. A was initially taken aback and defensive. Ms. A returned to the next therapy session discouraged. Ms. A and her therapist then reviewed the encounter and explored options for how she could broach the topic at a calmer time of the week than previously. They role played this interaction, with Ms. A testing different expressions of her feeling and different tones of voice. On the next try, to the patient's relief, Mr. A opened up rather surprisingly, nearly crying in talking about their inability to have a child and convincingly denying any extramarital affairs—although he admitted having been tempted. Ms. A's symptoms improved markedly in the aftermath of this breakthrough. The couple began to weigh adoption against the benefits of childlessness: the freedom to travel, live a wealthier lifestyle, and so forth. Mr. A began returning home from work earlier, and the couple planned a vacation. By the end of treatment, the marriage was stronger and the couple communicated better than ever previously. They were proceeding with plans for adoption. Ms. A was euthymic, with a Hamilton Depression score of 4.

In the termination phase, the IPT therapist emphasized that Ms. A's improvement was due to her own actions, to her finding more effective ways to communicate with her husband in resolving their role dispute. Although they were terminating acute treatment, the therapist pointed out that Ms. A had now had two episodes of major depression and was at significant risk for a third. Accordingly, they agreed to continuation treatment with monthly sessions of IPT.

## Research Findings: IPT for Mood Disorders

IPT outcome research has been continual, precluding an exhaustive description of studies. What follows is a selection of key research trials of IPT for mood and other disorders. For some of these trials, IPT was adapted in a separate manual, but in all cases the general principles of the treatment remained the same. (See Table 88–4.)

**Table 88–4 Empirically Based Indications for IPT**

- Major depression
  - Acute
  - Recurrent (prophylaxis)
  - Geriatric patients
  - Adolescent patients
  - HIV-positive patients
  - Primary care patients
  - Conjoint therapy for depressed married women
  - Postpartum and antepartum patients
- Bipolar disorder (adjunctive treatment)
- Interpersonal counseling for **subsyndromal depression**
- **Bulimia** (individual or group format)
- **Social phobia***
- **Posttraumatic Stress Disorder***

*Preliminary results encouraging.

### Acute Treatment of Major Depression

In the 1970s, IPT was first tested as an acute antidepressant treatment in a four-cell, 16-week randomized trial. This compared IPT, amitriptyline (AMI), their combination, and a nonscheduled control treatment for 81 outpatients with major depression (DiMascio et al. 1979, Weissman et al. 1979). AMI alleviated symptoms more quickly, but no significant difference appeared between IPT and AMI in symptom reduction at the end of treatment. Each active treatment reduced symptoms more efficaciously than the nonscheduled control, and combined AMI–IPT was more efficacious than either active monotherapy. Patients with psychotic depression fared poorly on IPT alone. At 1-year follow-up, many patients sustained improvement from the brief IPT intervention, and IPT patients had developed significantly better psychosocial functioning whether or not they received medication. This effect on social function was not found for AMI alone and had not been evident for IPT at the end of the 16-week trial (Weissman et al. 1981).

In the landmark, multisite National Institute of Mental Health Treatment of Depression Collaborative Research Program (NIMH TDCRP) (Elkin et al. 1989), investigators randomly assigned 250 outpatients with major depression to 16 weeks of IPT, CBT, or either imipramine (IMI) or placebo with clinical management. Most subjects completed at least 15 weeks or 12 treatment sessions. Patients with milder depression (defined as a 17-item HDRS score >20) improved equally in all four treatments. For more severely depressed patients (HDRS ≥20), IMI worked fastest and most consistently better than placebo. IPT and IMI were comparable on several outcome measures, including HDRS, and superior to placebo for more severely depressed patients. CBT was not superior to placebo among the more depressed patients.

Klein and Ross (1993) reanalyzed the TDCRP data using the Johnson–Neyman technique. They reported an ordering for treatment efficacy with "medication superior to psychotherapy, [and] the psychotherapies somewhat superior to placebo … particularly among the symptomatic and impaired patients" (Klein and Ross 1993, p 241), and found "CBT relatively inferior to IPT for patients with BDI scores greater than approximately 30, generally considered the boundary between moderate and severe depression" (p 247).

The reanalysis does not contradict the earlier report of Elkin et al. (1989), but sharpens differences among treatments.

Following up TDCRP subjects 18 months later, Shea et al. (1992) found no significant difference in recovery among remitters (who had minimal or no symptoms after the end of treatment, sustained during follow-up) among the four treatments. Thirty percent of CBT, 26% of IPT, 19% of IMI, and 20% of placebo subjects who had acutely remitted remained in remission during that time span. Among acute remitters, relapse over the 18-month follow-up was 36% for CBT, 33% for IPT, 50% for IMI (medication having been stopped at 16 weeks), and 33% for placebo. The authors concluded that, for many patients, 16 weeks of specific treatments were insufficient to achieve full and lasting recovery.

## Maintenance Treatment

IPT was first developed for and tested in an 8-month, six-cell trial (Klerman et al. 1974, Paykel et al. 1975). This study today would be considered a "continuation" treatment, as the concept of long-term maintenance antidepressant treatment has lengthened. Acutely depressed outpatient women ($N$ = 150) who had responded (with at least 50% symptom reduction rated by a clinical interviewer) to a 4–6 week acute phase of AMI were randomly assigned to receive 8 months of weekly IPT alone, AMI alone, placebo alone, combined IPT–AMI, IPT–placebo, or no pill. Randomization to IPT or a low contact psychotherapy condition occurred at entry into the continuation phase, whereas randomization to medication, placebo, or no pill occurred at the end of the second month of continuation. Continuation pharmacotherapy prevented relapse and symptom exacerbation, whereas IPT improved social functioning (Weissman et al. 1974). The effects of IPT on social functioning did not appear for 6–8 months. Combined psychotherapy–pharmacotherapy had the best outcome.

Longer antidepressant maintenance trials of IPT have been conducted in Pittsburgh. Frank et al. (Frank et al. 1990, Frank et al. 1991) treated 128 outpatients with multiply and rapidly recurrent depression. Patients initially received combined high dose (>200 mg/day) IMI and weekly sessions of IPT. Responders remained on high dosage medication while IPT was tapered to a monthly frequency during a 4-month continuation phase. Patients who remained remitted were then randomly assigned to 3 years of either (1) ongoing high dose IMI plus clinical management, (2) high dose IMI plus monthly IPT, (3) monthly IPT alone, (4) monthly IPT plus placebo, or (5) placebo plus clinical management. High dose IMI proved the most efficacious treatment, protecting more than 80% of patients over 3 years. In contrast, most patients on placebo relapsed within the first few months. In maintenance IPT, therapists were permitted to switch interpersonal foci in order to deal with patients' current life problems. Once a month IPT, while less efficacious than medication, was statistically and clinically superior to the placebo condition in this high risk patient population. Reynolds et al. (1999) essentially replicated these maintenance findings in a study comparing IPT and nortriptyline for geriatric patients with recurrent major depression.

Women of childbearing age are the modal patients with depression. The study finding of an 82-week survival time without recurrence on IPT would suffice to protect many women with recurrent depression through pregnancy and nursing without medication. Further study is required to determine the efficacy of IPT relative to newer medications (e.g., selective serotonin reuptake inhibitors), and the efficacy of dosages other than once-monthly maintenance IPT. A study of differing doses of maintenance IPT for depressed patients in Pittsburgh, not yet published, has not found differences in outcome based on frequency of sessions. Perhaps optimal dosing of maintenance IPT depends on individual patients' needs.

## Geriatric Depressed Patients

IPT was first used with geriatric depressed patients as augmentation to a 6-week pharmacotherapy trial in order to enhance compliance and to provide some treatment for the placebo control group (Rothblum et al. 1982, Sholomskas et al. 1983). The investigators reported that grief and role transition specific to life changes were the prime focus of treatment. They suggested modifications of IPT including more flexible duration of sessions, greater use of practical advice and support (e.g., arranging transportation, calling the physician), and recognizing that major role changes may be impractical and detrimental (e.g., divorce at age 75). The 6-week trial compared standard IPT to nortriptyline in 30 geriatric depressed patients. Results showed some advantages for IPT, largely because of higher attrition in the medication group due to nortriptyline side effects (Sloane et al. 1985).

Reynolds et al. (1999) conducted a 3-year maintenance study for geriatric patients with recurrent depression in Pittsburgh using IPT and nortriptyline in a design similar to the Frank et al. (1990) study. The IPT manual was modified to allow more flexible length of sessions, under the assumption that some elderly patients might not tolerate 50-minute sessions. The authors found older patients needed to address early-life relationships in their psychotherapy, a distinction from the typical "here and now" focus of IPT. Like Sholomskas et al. (1983), they felt that therapists needed to help patients solve practical problems and to acknowledge that some problems may not be amenable to resolutions, such as existential late life issues or lifelong psychopathology (Rothblum et al. 1982). Elderly depressed patients whose sleep quality normalized by early continuation phase had an 80% chance of remaining euthymic during the first year of maintenance treatment. The response rate was similar for patients who subsequently received either nortriptyline or IPT.

Reynolds et al. (1999) acutely treated 187 geriatric patients (60 years and older) with recurrent major depression using combined IPT and nortriptyline. One hundred seven remitted and then achieved recovery after continuation therapy. They were randomly assigned to one of four 3-year maintenance conditions: (1) medication clinic with nortriptyline alone, with steady-state nortriptyline plasma levels maintained in a therapeutic window of 80–120 ng/ml; (2) medication clinic with placebo; (3) monthly maintenance IPT with placebo; or (4) monthly IPT-M plus nortriptyline. Recurrence rates were 43% for nortriptyline alone, 90% for placebo, 64% for IPT with placebo, and 20% for combined treatment. Each monotherapy was statistically superior to placebo, whereas combined therapy showed superiority to IPT alone and a trend for superiority over medication alone.

Patients in their 70s were more likely to suffer recurrence and to do so more quickly than patients in their 60s.

This study corroborates the maintenance findings of Frank and colleagues, with the difference that combined treatment had advantages over pharmacotherapy alone for the geriatric population. In a follow-up study, Reynolds and colleagues again found that once-monthly maintenance IPT was not efficacious in preventing relapse of depressed patients 70 years or older who had responded to the combination of IPT and paroxetine (Reynolds et al. 2006).

It is easy to misinterpret the comparison of high dose tricyclic antidepressants to low dose IPT-M in both the Frank et al. and the Reynolds et al. (1999) studies. Had the tricyclics been lowered comparably to the psychotherapy dosage, recurrence in the medication groups might well have been greater. Yet this was unprecedented research. Under the circumstances, the choice of monthly dosing for IPT-M, while the lowest ever prescribed in a psychotherapy trial, was reasonable, and indeed showed some benefit.

## Depressed Adolescents (IPT-A)

Mufson et al. (2004a) modified IPT to incorporate adolescent developmental issues. They conducted an open feasibility and follow-up trial, and then a controlled 12-week clinical trial comparing IPT-A and clinical monitoring in 48 clinic-referred adolescents, ages 12–18, who met DSM-III-R criteria for MDD. Patients were seen biweekly by blind independent evaluators to assess symptoms, social functioning, and social problem-solving skills. Thirty-two of the 48 patients completed the protocol (21 IPT-A, 11 control).

Patients receiving IPT-A reported significantly greater improvement in depressive symptoms and overall social functioning, including functioning with friends and problem-solving skills. In the intention-to-treat sample, 75% of IPT-A patients met the criterion for recovery (HDRS score ≤ 6), compared to 46% of control patients. These findings support the feasibility, patient acceptance, and efficacy of 12 weeks of IPT-A with acutely depressed adolescents in reducing depressive symptoms and improving social functioning and interpersonal problem-solving skills (Mufson et al. 1999). Mufson et al. (2004b) subsequently tested IPT-A in an effectiveness study in school-based clinics, where they found it markedly superior to treatment as usual. The same group is now studying IPT-A in a group format for depressed adolescents (Mufson et al. 2004c) and training therapists in IPT-A in larger health care systems.

Rosello, Bernal, and Rivera at the University of Puerto Rico randomly assigned adolescents, ages 13–18, who met DSM-III-R criteria for major depression, dysthymia, or both, to 12 weeks of IPT ($n$ = 22), CBT ($n$ = 25), or a waiting-list control condition ($n$ = 24). The investigators found both IPT (effect size 0.73) and CBT (effect size 0.43) more efficacious than the control condition in reducing adolescents' self-rated depressive symptoms. IPT increased self-esteem and social adaptation more effectively than CBT (Rossello and Bernal 1999).

## Depressed HIV-Positive Patients (IPT-HIV)

Markowitz et al. (1992) modified IPT for depressed HIV patients (IPT-HIV), emphasizing common issues among this population including concerns about illness and death, grief and role transitions. In a pilot open trial, 21 of the 24 depressed patients responded with symptom reduction. A 16-week study randomized 101 subjects to IPT-HIV, CBT, supportive psychotherapy (SP), and IMI plus SP (Markowitz et al. 1998). Echoing the results of the more severely depressed subjects in the TDCRP study (Elkin et al. 1989), all treatments were associated with symptom reduction, but IPT and IMI-SP produced symptomatic and functional improvement significantly greater than CBT or SP. Many patients reported improvement in depressive physical symptoms that they had mistakenly attributed to HIV infection.

## Depressed Primary Care Patients

Schulberg and colleagues compared IPT and nortriptyline for depressed ambulatory medical patients in a primary care setting. (Schulberg and Scott 1991, Schulberg et al. 1993). They did not modify the IPT manual, but integrated IPT into the routine of the primary care center; for example, nurses took vital signs before each session. If patients were medically hospitalized, IPT was continued in the hospital when possible.

Patients with current major depression ($n$ = 276) were randomly assigned to IPT, nortriptyline, or primary care physicians' usual care. They were seen weekly for 16 weeks and monthly thereafter for 4 months in IPT (Schulberg et al. 1996). Depressive symptom severity declined more rapidly with either nortriptyline or IPT than in usual care. Approximately 70% of treatment completers receiving nortriptyline or IPT, but only 20% in usual care, had recovered after 8 months. Brown et al. (1996) found that subjects with a lifetime history of comorbid panic disorder had a poorer response across treatments, compared to those with major depression alone. Frank et al. (2000a) found a similar effect for comorbid panic disorder on depressive outcome.

These studies in depressed medically ill patients suggest that the life event of medical illness may provide a useful focus as a role transition in IPT treatment (cf. Koszycki et al. 2004). On the other hand, a large study recently showed that IPT conferred no advantage to depressed patients with coronary artery disease (Lesperance et al. 2007).

## Conjoint IPT for Depressed Patients with Marital Disputes (IPT-CM)

Marital conflict can precipitate or complicate depressive episodes (Rounsaville et al. 1979). Some clinicians believe that individual psychotherapy for patients in marital disputes may lead to premature rupture of marriages (Gurman and Kniskern 1978). Researchers at Yale University developed a manual for conjoint therapy of depressed patients with marital disputes (IPT-CM) (Klerman and Weissman 1993). IPT-CM includes the spouse in all sessions and focuses on the current marital dispute. Eighteen patients with major depression linked to the onset or exacerbation of marital disputes were randomly assigned to 16 weeks of either individual IPT or IPT-CM. Patients in both treatments showed similar reductions in depressive symptoms, but patients receiving IPT-CM reported significantly better marital adjustment, marital affection, and sexual relations (Foley et al. 1989). These pilot findings require replication with a larger sample and other control groups.

## Peripartum Depression

Pregnancy and its aftermath are times of heightened depressive risk when women may wish to avoid antidepressant medication. Pregnancy and the postpartum also provide natural

role transitions as an IPT focus. Spinelli used IPT to treat women with antepartum depression. Exploring this role transition addresses the depressed pregnant woman's self-evaluation as a parent, physiologic changes of pregnancy, and altered relationships with the spouse or significant other and with other children. Spinelli added "complicated pregnancy" as a fifth interpersonal problem area. Timing and duration of sessions are adjusted in response to bedrest, delivery, obstetrical complications, and child care. Postpartum mothers may bring children to sessions. As with depressed HIV-positive patients, telephone sessions and hospital visits are sometimes necessary (Spinelli 1997). A controlled clinical trial comparing IPT to a didactic parent education group in depressed pregnant women over 16 weeks of acute treatment showed advantages for IPT (Spinelli and Endicott 2003).

O'Hara et al. (2000) randomly assigned 120 women with postpartum depression to IPT or a waiting-list control in a 12-week trial with an 18-month follow-up. The investigators assessed the mothers' symptoms and their interactions with their infants (Stuart and O'Hara 1995). In the IPT group, 38% met HDRS and 44% met BDI remission criteria, compared to 14% on each measure for the waiting-list group. Sixty percent of IPT patients, versus 16% of controls, reported more than a 50% reduction on the BDI. Women receiving IPT also showed significant improvement in social adjustment relative to controls.

Klier et al. (2001) treated 17 women with postpartum depression in 9 weekly 90-minute group sessions plus an hour-long individual termination session. Scores on the 21-item Ham-D fell from 19.7 to 8.0, suggesting the efficacy of this approach. In another trial, Zlotnick et al. (2001) treated 37 women at risk for postpartum depression with either four 60-minute sessions of an IPT-based group or usual treatment. None of 17 in the interpersonal group developed depression 3 months postpartum, whereas 6 of 18 in the control condition did. This preventive application of what sounds like a group form of interpersonal counseling (Klerman et al. 1987) needs replication, but is exciting.

## Dysthymic Disorder (IPT-D)

A modification of IPT for dysthymic disorder encourages patients to reconceptualize what they have considered their lifelong character flaws as ego-dystonic, chronic mood-dependent symptoms: as chronic but treatable "state" rather than immutable "trait." Therapy itself was defined as an "iatrogenic role transition," from believing oneself flawed in personality to recognizing and treating the mood disorder. Markowitz (1994, 1998) openly treated 17 pilot subjects with 16 sessions of IPT-D: none worsened, and 11 remitted. Medication benefits roughly half of dysthymic patients (Kocsis et al. 1988, Thase et al. 1996), but nonresponders may need psychotherapy, and even medication responders may benefit from combined treatment (Markowitz 1994).

Based on these pilot results, a randomized trial at Cornell Medical College compared 16 weeks of IPT-D alone, SP, sertraline plus clinical management, as well as a combined IPT/sertraline. All groups improved, but IPT showed no greater acute benefits than SP, and pharmacotherapy appeared more efficacious than either psychotherapy (Markowitz et al. 2005).

Browne et al. (2002) at McMaster University in Hamilton, Canada, treated more than 700 dysthymic patients in the community with either 12 sessions of standard IPT over 4 months, sertraline for 2 years, or their combination. Patients were followed for 2 years. Using the criterion of a 40% reduction in score of the Montgomery–Asberg Depression Rating Scale (MADRS) at 1-year follow-up, 51% of IPT-alone subjects improved, significantly fewer than the 63% taking sertraline and 62% in combined treatment. On follow-up, however, IPT was associated with significant economic savings in use of health care and social services. Thus combined treatment was as efficacious as, but less expensive than, sertraline alone.

Feijò de Mello et al. (2001) randomly assigned 35 dysthymic outpatients to receive moclobemide with or without 16 weekly sessions of IPT. Both groups improved, but there was a nonsignificant trend for greater improvement on the Ham-D and MADRS in the combined treatment group. Similarly, Hellerstein et al. (2001) found that a group combining interpersonal and cognitive elements improved outcome over fluoxetine alone among dysthymic patients responding to fluoxetine.

Chronic depression is by and large more difficult to treat than acute depression, in part due to the ingrained despair that attends its very chronicity. IPT has not fared particularly well as a monotherapy for chronically depressed patients, but it may yet have benefit as an adjunct to medication, much as it may for bipolar disorder.

## Bipolar Disorder

Frank and colleagues in Pittsburgh assessed the benefits for 175 bipolar patients of adjunctive IPT modified by social Zeitgeber theory—behavioral scheduling of daily and sleep patterns (Ehlers et al. 1988, Malkoff-Schwartz et al. 2000)—as maintenance treatment of medication-treated bipolar patients, comparing IPSRT (interpersonal social rhythms therapy) to medication clinic (Frank et al. 2005). The behavioral component helps to protect sleep patterns and limit the disruptions that may provoke mania; the IPT approach to depression remains largely the same.

Acutely ill bipolar patients were treated with medication and randomly assigned to IPSRT or clinical management (CM). After achieving 4 weeks of stabilization, they were again randomized to either IPSRT or CM for 3 years of maintenance treatment while continuing pharmacotherapy. Overall results of this complicated trial indicated that although there was no difference in time to initial stabilization of symptoms, IPSRT with medication was superior to the comparison condition in delaying recurrence of depressive and manic episodes (Frank et al. 2005).

## Subsyndromally Depressed Hospitalized Elderly

Patients Mossey et al. (1996) noted that even depressive symptoms not reaching the threshold for major depression impeded recovery of hospitalized elderly patients. They conducted a 10-session trial of a simplified modification of IPT called interpersonal counseling (IPC; Klerman et al. 1987), provided by nonpsychiatric nurses, for elderly hospitalized medical patients with minor depressive symptoms. Patients were seen for hour-long sessions on a flexible schedule to accommodate the patient's medical status. Seventy-six hospitalized patients over age 60, who had subsyndromal depressive symptoms on two consecutive assessments, were

randomly assigned to either IPC or usual care (UC). Researchers also followed an untreated, euthymic control group. Patients found IPC feasible and tolerable. Assessment after 3 months showed nonsignificantly greater improvement in depressive symptoms and on all outcome variables for IPC relative to UC, whereas controls showed a slight symptomatic worsening. Rehospitalization in the IPC and euthymic control groups was virtually identical (11–15%), and significantly less than for the subsyndromally depressed group receiving UC (50%). Differences between IPC and UC groups reached statistical significance at 6 months on depressive symptom reduction and self-rated health, but not physical or social functioning. The investigators felt 10 sessions were insufficient for some patients, and that a maintenance phase might have been useful.

## IPT for Nonmood Disorders

The efficacy of IPT as an antidepressant treatment has led to its adaptation as a treatment for other psychiatric disorders. Life events are ubiquitous, but when is it useful to focus treatment on them? Research is beginning to answer such questions.

### Bulimia

Fairburn et al. (1993) altered IPT for bulimic patients, eliminating the use of the sick role and of role playing in order to contrast distinct therapeutic strategies in comparing IPT and CBT. Initial trials showed that although CBT worked faster to relieve bulimic symptoms, IPT had longer term benefits comparable to CBT and superior to a behavioral control condition (Fairburn et al. 1993, 1995). A subsequent multisite trial found CBT superior to IPT (Agras et al. 2000). Nonetheless, IPT is one of the better tested treatments for bulimia, and at least a second line treatment after CBT.

Wilfley et al. (1993, 2000, 2002) modified IPT in a 16-week, 90-minute session group format. The initial IPT phase, in which the therapist identifies problem areas, presents IPT concepts, and offers a treatment contract, is conducted individually; confusion was avoided among IPT problem areas by giving almost all subjects a focus on "interpersonal deficits." They compared IPT-G to group CBT and a waiting-list control for 56 women with nonpurging bulimia. At termination, binge eating decreased in the IPT-G and CBT groups, but not in the control condition. Results persisted at 1-year follow-up. A randomized clinical trial of 162 women, comparing group IPT and CBT for 20 sessions over 20 weeks, yielded similar results (Wilfley et al. 2002).

A research group in Christchurch, New Zealand, studied the application of IPT to anorexia nervosa. In their trial, neither IPT nor CBT showed efficacy as an outpatient treatment, a finding unfortunately consonant with anorexia outcome literature generally (McIntosh et al. 2005).

### Social Phobia

IPT has not yet been tested in controlled studies for anxiety disorders. Two research groups have independently modified IPT for social phobia. Lipsitz et al. (1999) at Columbia University treated 9 IPT pilot cases and found promising results for social phobia. They found that such standard IPT ingredients as the medical model, provision of the sick role, and the supportive therapeutic stance, appear to benefit most patients. A small controlled trial has not yet been published. Weissman and Jacobson at Columbia have adapted IPT in a 10-session group format for shy patients with social phobia in unstructured interpersonal situations: at parties, in intimate discussions with significant others, but not in defined work situations. In Norway, a research group has adapted Lipsitz' model to compare group and individual IPT with CBT in a residential setting for patients with treatment refractory social phobia.

### Panic Disorder

Arzt and colleagues in Maastricht, the Netherlands, are studying IPT as a treatment for panic disorder. Lipsitz et al. (2006) report promise for IPT in a small open trial.

### Posttraumatic Stress Disorder (PTSD)

PTSD is an anxiety disorder defined by a life event, suggesting the utility of IPT in its treatment. Krupnick and colleagues are assessing a group form of IPT for multiply victimized women in public sector gynecology clinics in Virginia. Markowitz and colleagues at Cornell University modified IPT as an alternative to exposure-based psychotherapies for PTSD and found excellent outcomes in a small pilot trial (Bleiberg and Markowitz 2005). A controlled comparison is now planned.

### Substance Abuse

IPT has failed to demonstrate efficacy in three clinical trials for patients with substance dependence. Rounsaville et al. (1983) studied 72 methadone-maintained opiate users and found that adding adjunctive IPT to standard substance abuse care at Yale (which already included a psychotherapy component) had no additional benefit in reducing psychopathology. Both treatment groups improved. The same research group found that 12 weeks of IPT were ineffective and marginally worse than a behavioral control for 42 subjects with cocaine abuse attempting to achieve abstinence (Carroll et al. 1991). Most recently, Carroll et al. (2004) treated 121 cocaine-dependent subjects in a $2 \times 2$ cell, 12-week trial, with either IPT or CBT and disulfiram 250 mg or placebo. CBT and disulfiram were superior to IPT and to placebo. These negative studies suggest limits to the range of utility of IPT, but do not necessarily preclude its use for all substance abuse. IPT might be useful, for example, as a treatment for newly abstinent alcohol-dependent patients, who face psychosocial stressors that have been shown to precipitate relapse.

### Other Applications

Research groups are testing the applicability of IPT to body dysmorphic disorder, chronic somatization in primary care patients, depressed patients post myocardial infarction, depressed cancer patients, borderline personality disorder (Markowitz et al. 2006b), insomnia, and other disorders (Weissman et al. 2000). The IPT focus on life events suggests its potential applicability to patients with medical illness. Swartz et al. (2004) produced preliminary findings suggesting that IPT can be effective in a briefer, eight-session form.

### Interpersonal Counseling (IPC)

Many patients presenting to primary care practices report psychiatric symptoms, but do not meet threshold criteria for a psychiatric disorder. Nonetheless, their symptoms can

be debilitating and may result in high wasted utilization of medical procedures (Wells et al. 1989). IPC, based on IPT, was designed to treat distressed primary care patients who do not meet full syndromal criteria for psychiatric disorders. IPC is administered for a maximum of six sessions by health care professionals who lack formal psychiatric training, usually nurse practitioners. The first session can last up to 30 minutes; subsequent sessions are briefer.

IPC therapists assess the patient's current functioning, recent life events, occupational and familial stressors, and changes in interpersonal relationships. They assume that such events provide the context in which emotional and bodily symptoms occur. Klerman et al. (1987) studied 128 patients in a primary care clinic who scored 6 or higher on the Goldberg General Health Questionnaire (GHQ), randomizing them to IPC or to UC without psychological treatment (Klerman et al. 1987). Over an average of 3 months, often receiving only one or two IPC sessions, IPC subjects showed significantly greater symptom relief on the GHQ than controls, especially mood improvement. IPC subjects were more likely to subsequently make use of mental health services, suggesting a new awareness of the psychological aspect of their symptoms.

A dramatic study demonstrating the transplantability of IPT to a very different culture tested a group variant of IPC in randomly assigned villages in a poverty- and AIDS-stricken region of Uganda where depression rates are high. IPT was selected as an intervention because antidepressant medication was unaffordable and other psychotherapies seemed incompatible with the local outlook. Researchers adjusted for cultural differences but applied the usual IPT paradigm. Local college graduates without mental health experience provided treatment. The group IPC intervention was impressively more effective than treatment as usual (Bolton et al. 2003), and gains persisted at 6-month follow-up (Bass et al. 2006).

## IPT by Telephone

Because many patients avoid or have difficulty reaching an office for face-to-face treatment, IPC is being tested as a telephone treatment. Weissman and Miller at Columbia University conducted a successful pilot feasibility trial comparing IPT by telephone to no treatment in 30 patients with recurrent major depression who had not received regular treatment (Miller and Weissman 2002). Neugebauer et al. (2006) found telephone IPC a helpful intervention for women with minor depression post miscarriage.

## IPT Patient Guide

Weissman (1995) developed an IPT patient guide with worksheets for depressed readers who want information about or are receiving IPT. Worksheets can be used to facilitate sessions or to monitor problem areas after treatment. The utility of the patient book in enhancing treatment has not been studied.

## Summary

IPT has demonstrated efficacy as an acute and maintenance monotherapy and as a component of combined treatment for major depressive disorder. It also appears to have utility for other mood and nonmood syndromes, although the evidence for these is sparser. It has not shown benefit for substance use disorders or as a monotherapy for dysthymic disorder. Since monotherapy with either IPT or pharmacotherapy is likely to suffice for most patients with major depressive disorder, combined treatment is probably best reserved for severely or chronically ill patients (Rush and Thase 1999). How best to combine time-limited psychotherapy with pharmacotherapy—for which patients, in what sequence, etc.— is an exciting area for future research.

When two or more treatments have demonstrated efficacy for a diagnosis such as major depressive disorder, when is one treatment more likely to have a better outcome than another? Comparative trials are beginning to reveal moderating factors or predictors of treatment outcome. Studies such as the NIMH Treatment of Depression Collaborative Research Program, which compared IPT and CBT, have suggested factors that might predict better outcome with either IPT or CBT. (See Table 88–5.)

**Table 88–5 Prescribing IPT and CBT**

I. Points in common
- A. Common factors of psychotherapy
  1. Helping patient feel understood (relationship)
  2. Framework for understanding (rationale)
  3. Providing hope and optimism
  4. Psychoeducation
  5. Technique for getting better (ritual)
  6. Success experiences
- B. Common features of brief antidepressant psychotherapies
  1. Manualized
  2. Active
  3. Time limited (with comparable time courses)
  4. Structured (CBT > IPT)
  5. "Here and now" current focus
  6. Can be combined with antidepressant medication
  7. Goals of self-assertion, mastery
  8. Ultimate goal of new skills for prophylaxis
- C. Technical similarities
  1. Mobilizing patient to greater activity
  2. Linking mood to activities and reactions to events, albeit with different emphases
  3. Problem solving: "exploring options" vs. "empirical hypothesis testing"
  4. Addressing "expectations" vs. "assumptions" about others
  5. Role playing

II. Differences
- A. IPT: medical model
- B. CBT: homework
- C. Focus on affect (IPT) vs. thoughts (→ affect) (CBT); hence more external vs. more intrapsychic approach

III. Differential therapeutics of major depression: Which works better for whom?

| Predictor | IPT | CBT |
|---|---|---|
| Life events | Present | Absent |
| Social dysfunction (baseline) | Low | Very high ("interpersonal deficits") |
| Symptom severity (baseline) | Higher | Lower |
| Personality disorder | Obsessive | Avoidant |

Sotsky et al. (1991) found that depressed patients with a low baseline level of social dysfunction responded well to IPT, whereas those with severe social deficits (probably

equivalent to the "interpersonal deficits" problem area) responded less well. Patients with greater symptom severity and difficulty in concentrating responded poorly to CBT. Initial severity of major depression and of impaired functioning predicted superior response to IPT and to imipramine. Imipramine also worked most efficaciously for patients with difficulty functioning at work, likely reflecting its faster onset of action. Patients with atypical depression responded better to either IPT or CBT than to imipramine or placebo (Shea et al. 1999).

Barber and Muenz (1996), looking only at TDCRP completers, found IPT more efficacious than CBT for patients with obsessive personality disorder, whereas CBT fared better for avoidant personality disorder. Biological factors such as abnormal sleep profiles on EEG predicted significantly poorer response to IPT than for patients with normal sleep parameters (Thase et al. 1997). Frank et al. (1991) found that psychotherapist adherence to a focused IPT approach may enhance outcome. The replication and further elaboration of these predictive factors deserve ongoing study.

## Training

Until recently, IPT therapists were few, and practiced almost exclusively in research studies. Publications supporting its efficacy have led to clinical demand for this empirically supported treatment. IPT training is now increasingly included in professional workshops and conferences, with training courses conducted at university centers in Canada, the United Kingdom, continental Europe, Asia, New Zealand, and Australia. IPT is taught in a small but growing minority of psychiatric residency training programs in the United States (Markowitz 1995, Lichtmacher et al. 2006) as well as some family practice and primary care training programs.

Although the principles and practice of IPT are relatively straightforward, any psychotherapy requires innate therapeutic ability, comfort with the so-called "common factors" of psychotherapy (Frank 1971): tolerating and exploring affect, helping the patient to feel understood, engendering hope, etc. IPT training requires more than reading the manual (Weissman et al. 1982, Rounsaville et al. 1988): psychotherapy is learned by doing. Most IPT training programs are designed to help experienced therapists refocus their treatment by learning new techniques, not to teach novices psychotherapy. Candidates should have a graduate clinical degree (M.D., Ph.D., M.S.W., R.N.), several years of experience conducting psychotherapy, and clinical familiarity with the diagnosis of patients they plan to treat.

The IPT training in the TDCRP (Elkin et al. 1989) became the model for subsequent research studies. It included a brief didactic program, reading the manual, and a practicum in which the therapist treated 2–3 patients under close supervision monitored by videotapes of the sessions (Chevron and Rounsaville 1983). Rounsaville et al. (1986) found that psychotherapists who performed well on an initial supervised IPT case often required no further intensive supervision, and that experienced therapists committed to the approach required less supervision than others (Rounsaville et al. 1988). Some clinicians have taught themselves IPT using as guides the IPT manual (Klerman et al. 1984, Weissman et al. 2000) and peer supervision. For research certification, we continue to recommend at least two or three successfully treated cases with hour for hour supervision of taped sessions (Markowitz 2001).

A loose IPT umbrella organization, the International Society for Interpersonal Psychotherapy (ISIPT; www.interpersonalpsychotherapy.org) has now held biennial international scientific meetings. Although many clinicians would like a formal certificate or diploma in IPT, there is no gold standard of IPT proficiency and no accrediting board. When IPT practice was limited to research settings, this posed no problem: one research group taught another, in the manner described above. As IPT spreads in clinical practice, questions of competence and accreditation gain greater urgency. Training programs in IPT are still not widely available, as a Surgeon General's report noted (Satcher 1999). Many psychiatry residency, psychology, and social work training programs still provide limited exposure to evidence-based treatments like IPT (Weissman et al. 2006).

The educational process for IPT in clinical practice requires further study. We do not know what levels of education and experience are required to learn IPT, nor how much supervision an already experienced psychotherapist is likely to require.

## The Future

The history of IPT has been a succession of outcome trials. These studies have helped to define diagnostic indications for this treatment. Because psychotherapy is underfunded relative to pharmacotherapy, we know far less about the dosage and indications of IPT than about antidepressant medication. Future outcome trials may continue to define the territory of IPT's utility. These should include both tests for different diagnoses, such as the anxiety disorders, testing of dosage—optimal frequency and duration of IPT sessions—and also studies of the sequencing of IPT with other treatments. For example, when, and for whom, is IPT best combined with pharmacotherapy? Is it best to start with pharmacotherapy and then add IPT? If so, at what interval, and with what frequency? When should IPT be used as augmentation for pharmacotherapy, and vice versa? Other research may help to determine the cost-effectiveness and potential cost-offset of IPT as a treatment that improves both symptoms and social functioning.

IPT is also anomalous among psychotherapies in its nearly pure focus to date on outcome studies. Until recent decades, most psychotherapy research was process research, an analysis of what occurred between patient and therapist in sessions. The late Gerald L. Klerman emphasized the primacy of outcome research, emphasizing that if the therapy had no actual clinical benefit, its mechanism would hold little interest. Now that it is clear that IPT helps many patients, process research seems warranted to try to identify its active, mediating factors. Little is known about the specific value of many IPT interventions. It is even unclear, for example, whether focusing on a role transition rather than a role dispute makes a difference for patients, or whether particular sorts of life events are helpful or unhelpful foci. It does appear that solving an interpersonal problem area correlates with treatment outcome, as IPT theory would predict (Markowitz et al. 2006a). Patient and therapist characteristics may also potentially influence treatment outcome.

Clinical training in IPT is growing. How it spreads will be a function of training programs. Training will eventually

require formalized accreditation, both to ensure clinical competence and to satisfy managed care organizations. Research is needed on how best to teach and disseminate IPT.

In summary, IPT is a time-limited, forward-looking, pragmatically focused psychotherapy that defines psychiatric disorders as treatable medical illnesses and links them to the patient's current social situation. This strategy has proved efficacious for patients with major depression and bulimia, and shows promise for other mood and nonmood disorders.

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CHAPTER

# 89 Brief Psychotherapies

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Having evolved from psychoanalytic roots, brief therapy today has a number of distinct models with the common aim of accelerating change through the active, focused interventions of therapists and increased patient involvement in treatment. Brief therapies range from single-session treatments and very brief strategic interventions of several sessions to short-term psychodynamic modalities that frequently exceed 20 sessions. Many schools have developed manuals, making it easier to practice these techniques with fidelity and to conduct research. In fact, most research in psychotherapy is on brief therapy. This rich body of research clearly supports the efficacy of brief therapy in a broad range of patients and is helpful in delineating patients and presenting problems likely to benefit from these approaches. The development of brief therapy models, manuals, and research evidence, combined with financial constraints and the fact that many patients get relief very quickly have led to brief therapy becoming the norm for the majority of patients.

Cognitive and behavioral therapies are the best studied and sometimes considered synonymous with both brief and evidence–based therapy. However, brief psychodynamic, interpersonal and other therapies are also evidence–based and shown to be effective. This chapter will broadly address brief therapy with an emphasis on brief psychodynamic therapy. Cognitive-behavioral and interpersonal therapies are covered in separate chapters.

## A Short History Of Brief Therapy

Many early major figures in psychoanalysis contributed to the development of brief therapy. Freud himself described three cases in which psychoanalytic treatments lasted nine weeks (Lucie R), seven weeks (Emmy Von N) and one week (Katherine) (Breuer and Freud 1955). Brevity and a circumscribed focus are evident in his cure of the impotence of Gustave Mahler in a single, four-hour session (Jones 1957).

In 1920, Ferenczi (1920) first attempted to increase therapist activity in order to decrease the length of psychoanalytic therapy and promoted "active therapy." This key ingredient remains a hallmark of modern brief therapy.

Otto Rank joined Ferenczi (Ferenczi and Rank 1925) in supporting a deliberate change toward brief therapy. He was first to use a fixed time frame: nine months to work on the "trauma of birth" (1924). He replaced the centrality of oedipal problems with the primacy of separation. Rank also suggested that short treatments required "willing" patients.

Alexander and French (1946) were the first to systematically research methods to abbreviate psychoanalysis. They argued that change was not primarily a function of insight, but of experience. Therefore, the therapist's role was to foster "corrective emotional experiences" in which patients are re-exposed to past emotional situations in therapy sessions while the therapist behaves (either naturally or purposefully) in a more accepting, supportive and constructive manner than past significant figures did. For instance, if the patient had grown up in the presence of an ungiving, angry father, the therapist would purposely attempt to be the opposite. The therapists' role changed from "blank screens" to active treatment agents who could utilize their relationships with patients to catalyze needed developmental experiences.

French (1970) contributed another staple of brief therapy–the narrowed focus. He used the term "focal conflict" to describe the instance wherein a patient's wish or impulse comes into conflict with their values and expectations, forcing a defensive compromise. Michael Balint, who founded the British School of brief dynamic psychotherapy at the Tavistock Clinic, further refined this concept into "focal psychotherapy" (Balint et al. 1972), which could be brief by design because it had limited aims and was focused on a narrow sector of the personality. Another important tenet was the direction to the patient to try out in the real world the knowledge and skills gained from treatment and even take periodic breaks from therapy in order to consolidate and integrate gains.

David Malan, Balint's student, brought the British School into prominence by organizing the clinical and research base of focal therapy. Malan made a number of major contributions to the technical aspects of brief therapy. His treatment was truly time-limited and he fixed the termination date (irrespective of the number of sessions, which averaged around eighteen) at the initial meeting. He was the first to detail patient characteristics that made them suitable for brief therapy: absence of severe psychopathology, psychological mindedness, and "some circumscribed aspect

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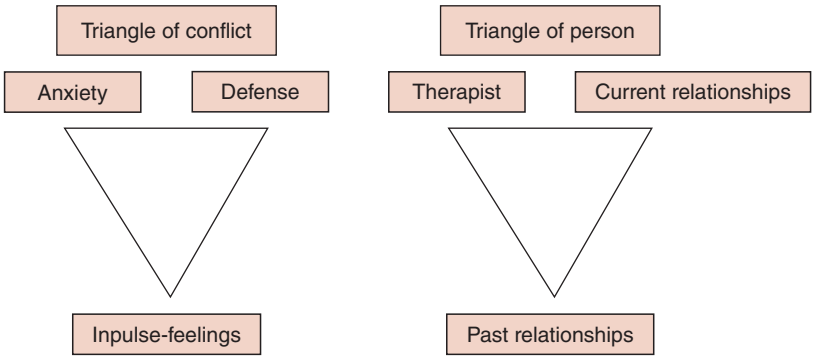



**Figure 89–1** *Triangles of insight, from Malan 1976.*

of pathology that can be made into a focus, and hence . . . . a possible therapeutic plan." (Malan 1976, p 254). His technique was to maintain a narrow, clear focus and to offer transference interpretations of two "triangles of insight" (see Figure 89–1). In the "triangle of conflict," an impulse or wish comes into focal conflict with a person's moral prohibitions or threat of social sanctions, leading to a defensive compromise to reduce anxiety. The therapist was to interpret the defense first, but it was important to uncover the anxiety and underlying impulse. The "triangle of person" consists of recurring maladaptive relationships in the transference, in the present but outside the therapeutic relationship, and in the past with parental or caretaking figures. Interpretations are made to show that the same maladaptive pattern exists in each of the points of this triangle. Repeated transference interpretations linking the impulse from relationships with parental figures in the past and with the therapist currently is hypothesized to be the most beneficial.

Sifneos (1972) also found that patient selection was crucial to the success of his "short-term anxiety-provoking psychotherapy." Patients did best who were intelligent, with good interpersonal skills, a history of at least one meaningful relationship, eagerness to change and presenting with a focused problem. In therapy, the task is to build rapport, construct a psychodynamic formulation of the "core neurotic problem," and engage the patient in a shared focus for treatment. The therapist next addresses the patient's positive transference and the wish to be taken care of in order to prevent regression and urges the patient to take responsibility for working in treatment. The past is explored but resistance is quickly addressed in the transference whenever it arises. Anxiety-provoking questions often also provoke anger and Sifneos models effective problem solving as a therapist-teacher working with a patient-student. When the therapist ascertains that symptomatic and interpersonal improvements have occurred in the area of focus and has generalized beyond the focus, it is time to begin the process of termination and a final date is set. Resistance to termination is addressed briefly and as a matter of fact. The emphasis is on treatment successes and growth. Therapy ends soon thereafter.

Luborsky (1984) built on the work of Sifneos and Malan to create supportive-expressive (SE) psychotherapy, with its characteristic core conflictual relationship theme (CCRT) that consists of three components: a wish, response from others, and a response of the self. SE has been used in some landmark studies of psychotherapy.

Mann's Time Limited Psychotherapy integrates the four psychologies of drive, ego, object, and self. It is based on the "recurring life crisis of separation–individuation" (p 11), which is addressed by "the exact prescription of time" (Mann 1973, p 53). Therapy lasts 12 sessions, and the final session is scheduled during the first. It was critical to accurately ascertain the "central theme." Mann's four central themes relate to the patient's ability to tolerate and manage object loss: independence versus dependence, activity versus passivity, adequate self-esteem versus diminished or loss of self-esteem, and unresolved or delayed grief.

Horowitz (1976) and Horowitz et al. (1984) developed specific dynamic techniques for treating trauma and stress response syndromes. He focused on current stressors but also found it necessary to address personality characteristics and underlying conflicts.

Habib Davanloo (1980) markedly broadened the selection criteria to include severe, long-standing neurotic and character pathology that is generally excluded by all other brief therapists. He emphasizes the importance of psychological resilience and gauges suitability for treatment in a one-to-several-hour-long "trial therapy" during which he works on "unlocking the unconscious". He makes use of psychoanalytic "triangles of insight" but, unlike other theorists, can work with more than one focal conflict, especially when treating severely ill patients. Reminiscent of Wilhelm Reich's classic work on character analysis (Reich 1933), Davanloo has a very active, direct style that insistently confronts the patient's defenses and quickly clarifies and challenges resistance but maintains a therapeutic alliance by carefully allying with patients against their pathology, which is made ego-dystonic.

**The Behaviorists.** *Skinner.* (1974) and Wolpe (1958) established the behavioral therapies in the 1950s. In behavior therapy, patients mastered new coping skills and altered their learned behavioral patterns. Therapy was highly circumscribed, emphasizing directive teaching and structured homework assignments between sessions. By the 1970s, behavior therapy had become part of the therapeutic mainstream (Skinner 1974) and has a wealth of research to support its efficacy in obsessive compulsive disorder, trauma, phobias and panic disorder (Foa and Kozak 1986, Kozak and Foa 1997, Barlow 2002). Also in the 1950s, Albert Ellis applied the learning paradigm to cognition and enunciated rational-emotive therapy, which blended the psychodynamic interest in the patient's inner life with hands-on behavioral methods (Ellis and Harper 1961).

**Cognitive therapists.** Since the 1960s, Aaron Beck (1976) and others have applied cognitive therapy to a remarkably wide range of conditions, including depression, personality disorders and even schizophrenia (Beck et al. 1990, Beck and Rector 2000). In cognitive therapy patients unlearn dysfunctional thought patterns and acquire new, constructive ones. The combination of a tight treatment focus and structured patient involvement between sessions ensures that cognitive therapy, like its behavioral sibling, possesses core ingredients of brevity.

Cognitive-behavioral analysis system of psychotherapy (CBASP) combines cognitive, behavioral and interpersonal therapies. In one study, CBASP combined with nefazodone produced the highest response rate for chronic depression reported with any modality, 85% versus 55 % for nefazodone alone and 52% for CBASP alone (Keller et al. 2000).

**Strategic therapies.** Another mainstream of brief therapy emerged with the writings of Milton Erickson and Jay Haley (Erickson and Haley 1967). Erickson viewed the presenting concerns of patients as failed efforts to solve normal life problems. The role of the therapist is neither as significant other nor cognitive-behavioral teacher, but as a problem solver who interrupts and redirects repeated self-reinforcing failures, often done in just a few sessions through the prescription of directed tasks. With the publication of Watzlawick et al.'s (1974) classic work on change processes, the strategic approach became a therapeutic staple, particularly in the work of family therapists.

The widespread adoption of so many schools of brief therapy raised legitimate concerns regarding the comparative efficacy of these different methods as well as possible limitations of such treatments, especially for severe and persistent emotional disorders and conditions with high relapse rates (Reed and Eisman 2006). Despite these concerns, and bolstered by positive findings, today brief therapies have become the practice rule rather than the exception.

It should be noted that there is a growing body of empirical evidence attesting to the cost-effectiveness of psychotherapy (Creed et al. 2003, Gabbard et al. 1997, Guthrie et al. 1999, Heuzenroeder et al. 2004). Though additional studies comparing psychotherapy to medication treatment cost effectiveness would be welcome (Barrett et al. 2005), a number of comparisons are indicative of why psychotherapy may be more cost-effective. For example, comparative trials of psychotherapy and medication for depression have shown that the beneficial effects of psychotherapy treatments are enduring while those for drug treatments do not continue once the treatments are stopped (Hollon et al. 1992, 2002). Lasting effects for psychotherapy are shown by the significant decrease in relapse rates following treatment (e.g., DeMaat et al. (2006), DeRubeis et al. (2005), Evans et al. (1992), Hollon (2003), Hollon et al. (2005), Shea et al. (1992)). Research indicates that psychotherapy reduces vulnerability to depression once treatment terminates and that this may result from patients becoming more resilient in their ability to handle future stressful situations (Hawley et al. 2007). Therefore, brief therapies are not only clinically effective but also cost-effective.

## Psychodynamic Therapy Issues, Outcomes and Comparisons

Evaluating how effective a particular brand of psychotherapy is has become an important task in recent decades. Relatively newer brands such as cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) have gained widespread acclaim by empirically demonstrating the value of these approaches in a variety of conditions, especially for mood and anxiety disorders (Beck 1995, 2005, Weissman et al. 2000, Stuart and Robertson 2003). Indeed, it has become fashionable to designate treatments as "empirically validated" or "evidence-based" when conventional scientific treatment trials demonstrate their worth. Many volumes and papers (e.g., Chambless 1998, Dewan et al. 2004, Prochaska and Norcross 2007, Smith et al. 1980, Wampold 2001) have documented that treatment conducted from a variety of theoretical schemes produce benefits. In this volume, specific chapters devoted to CBT (Chapter 91) and IPT (Chapter 88) speak to their effectiveness. Therefore, this chapter will focus on the usefulness of brief psychodynamic therapies, a focus that is timely because in the future "there will be no income without outcome" (Greenberg 2004b, p. 145).

After a painstaking review, Fisher and Greenberg (1985, 1996) concluded that therapies labeled "psychoanalysis" did not produce results superior to those from treatments that were often briefer and given other labels. Similar conclusions were reached by others (Bachrach et al. 1991, Luborsky and Spence 1978).

Could it be that orthodox psychoanalysis, with its emphasis on lengthy treatments, is simply an inefficient form of the briefer psychodynamic psychotherapies, which reach comparable levels of improvement in a shorter time? (Fisher and Greenberg 1996). This provocative idea is consistent with meta-analyses that have failed to establish a simple, direct relationship between time in therapy and outcome (e.g., Miller and Berman 1983, Robinson et al. 1990, Shapiro and Shapiro 1982, Smith et al. 1980).

## Efficacy of Brief Psychodynamic Psychotherapy: The Evidence

One problem in assessing how well brief psychodynamic therapy does is that there is no one form of this treatment that has been used in all or even most of the studies. There are several models of brief psychodynamic psychotherapy (Messer and Warren 1995). Prominent proponents of brief dynamic approaches include Davanloo (1978), Luborsky (1984, Luborsky and Crits-Cristoph 1990), Malan (1976), Mann (1973, Mann and Goldman 1982), Sifneos (1972, 1992), Levenson (1995), and Strupp and Binder (1984).Lack of treatment uniformity in the brief therapies is similar to the variability in analyst approach noted in studying long-term psychoanalysis (Fisher and Greenberg 1985, 1996). Nonetheless there are certain therapist interventions that the briefer forms of psychodynamic therapies have in common (Table 89–1).

In addition to the heightened level of therapist activities (Table 89–1), the research literature also reveals seven features, themes, or techniques that characterize brief psychodynamic approaches (Blagys and Hilsenroth 2000). These include: a focus on patients' expression of emotions; exploration of patient resistance or avoiding discussion of

**Table 89–1 Therapist Interventions in Brief Psychodynamic Psychotherapy**

- Designation of time limits (Usually 12 to 40 sessions)
- Attempts to create a prompt, sturdy, working alliance and positive transference
- Identification of core interpersonal problems within the initial sessions
- Increased therapist direction and activity
- More emphasis on predetermined goals
- More rapid use of general and transference interpretations

topics; identification of patterns in relationships, feelings and behaviors; a highlighting of past experiences, interpersonal experiences, wishes, dreams, and fantasies; and an emphasis on the therapeutic relationship.

Though brief psychodynamic therapy approaches have risen to prominence over about the past 40 years, attempts at empirical validation with a wide range of patients in randomized, controlled trials have been most notable for the past 20 years. About 50 studies in the English language have appeared during that period of time (Abbass et al. 2006). The growth in research studies has led to several attempts to analyze and summarize the literature using meta-analysis, a statistical technique that permits the combining of results from many studies to reach an overall conclusion about treatment outcome. Table 89–2 presents a listing of the five meta-analyses of brief psychodynamic psychotherapy conducted with adult outpatients since 1991.

An overview of the five meta-analyses shows that they relied on different groupings of studies depending on which studies were available at the time of the evaluation, the inclusion criteria used, whether studies of Interpersonal Psychotherapy were excluded from the mix, and how studies using different methodologies and measures were evaluated. Yet, even given these differences, they all concluded that brief psychodynamic psychotherapies produced very positive treatment effects compared to those obtained with patients left on waiting lists or given minimal treatments. The results were quite striking indicating that the average person treated with brief psychodynamic psychotherapy was better off than 80% to 90% of the untreated. The first meta-analysis, which included ill-defined therapies and studies with small numbers, yielded the most guarded conclusions (Svartberg and Stiles 1991). These investigators voiced concerns that the evidence—while supporting superiority over no treatment—did not show that the brief psychodynamic treatments were as good or as lasting as alternative treatments.

Prochaska and Norcross (2007) highlighted the consistent indications of treatment benefits from brief psychodynamic psychotherapy and noted the reservations that some researchers had about declaring brief psychodynamic treatment outcomes to be at least as good as those from other types of therapy such as CBT. They cited an "allegiance effect" in which research findings often reflect the biases or preferences of the researchers doing the study. It turns out, as they reasoned, that the small differences in outcome occasionally found between brief psychodynamic therapies and other treatments typically vanish when the researcher's allegiance is statistically factored into the computation. For example, they point to the methodologically rigorous studies that were included in the meta-analysis performed by Leichsenring et al. (2004). This analysis accounted for elements like investigator allegiance and still discovered strong positive outcome effects for psychodynamic approaches and documented equal effectiveness in comparisons with other therapy models.

It can now be added that the most up to date meta-analysis done as a Cochrane review (Abbass et al. 2006) and which included only randomized, controlled studies continues to show the value of brief dynamic psychotherapy across a wide range of common mental disorders. Measures of depression, anxiety, and somatic symptoms all show evidence of treatment gains. Individual studies also reveal benefits as varied as weight gain in anorexia nervosa, improved interpersonal relationships, and reduced self-injury. Further, brief dynamic psychotherapy maintained or improved gains in long-term follow-up, which was up to 4 years. Parallel results have also been published by Leichsenring and colleagues (2006) who, after acknowledging that there are more studies of cognitive-behavioral therapy than psychodynamic therapy, went on to list thirty-two studies of psychodynamic psychotherapy with specific mental disorders that used controlled randomized trials and treatment manuals. These studies provide evidence of efficacy for psychodynamic psychotherapy in treating a broad range of conditions. For example, Milrod and her colleagues (2007) presented a study in which 49 adult patients with panic disorder were randomized to receive either a manualized panic-focused psychodynamic psychotherapy or an applied behavioral relaxation treatment. Therapy for all

**Table 89–2 Meta-analyses of Brief Psychodynamic Psychotherapy**

| Reference | No. of Studies Included | Quality of Studies | Therapies Included in "Dynamic" Group | Benefits Found? |
|---|---|---|---|---|
| Svartberg and Stiles (1991) | 19 | Not randomized, small numbers | Not manual driven, ill-defined therapies | Yes* |
| Crits-Cristoph (1992) | 11 | Controlled, some randomized | Some manual driven, defined dynamic + IPT | Yes |
| Anderson and Lambert (1995) | 26 | Controlled, some randomized | Some manual driven, dynamic + IPT | Yes |
| Leichsenring et al. (2004) | 17 | Controlled, randomized | Only manual driven, dynamic therapies | Yes |
| Abbass et al. (2006) | 23 | Controlled, randomized | Only manual driven, dynamic therapies | Yes |

*Questioned level of benefits from brief psychodynamic therapy compared to other treatments.
**IPT = Interpersonal Therapy.

patients was delivered twice a week for 12 weeks. Outcome was rated by independent blinded evaluators. Subjects in the psychodynamic treatment experienced a significantly greater decline in severity of panic symptoms, lower treatment dropout rates, greater reduction in impairment and a higher response to treatment at termination (73% versus 39%). (See Table 89–3)

**Table 89–3 Disorders That Can Be Treated with Brief Psychodynamic Therapy***

- Depressive disorders
- Anxiety disorders: social phobias, generalized anxiety disorder, panic disorder, post traumatic stress disorder
- Borderline personality disorder
- DSM-IV Cluster C personality disorders
- Eating disorder: bulimia nervosa, anorexia nervosa
- Somatoform disorders
- Moderate alcohol dependence, opiate dependence.

*efficacy shown in randomized, controlled trials with manualized treatment. (Leichsenring et al. 2006)

At this point, the weight of the accumulating evidence indicates that brief psychodynamic approaches demonstrate benefits when applied to a large array of different kinds of problems under rigorous controlled conditions. Moreover, in studies offering direct comparisons with the well-researched cognitive-behavioral approaches, results have shown equivalent benefits (Leichsenring 2001, Leichsenring et al. 2006), though substantial room for improvement remains in the outcomes resulting from all brands of treatment.

Among the questions still to be answered is the degree to which these results hold up under real-world conditions. We do not have enough evidence yet to know if the findings from the well-controlled experimental studies generalize to patients seen in routine clinical practice. Another question revolves around the issue of what accounts for the positive results with seemingly different treatments. Consistent indications of parity in outcomes among different therapy approaches raises the possibility that factors common to the different treatments–such as the establishment of a positive treatment alliance–may be more important than their differences in creating positive change (Greenberg 2004a, 2004b, Smith et al. 1980, Wampold 2001).

Toward the end of his career, when considering the results of his treatment approach, Freud wrote, "I do not think our cures can compete with those of Lourdes. There are so many more people who believe in the miracle of the Blessed Virgin than in the existence of the unconscious" (Freud 1933, p. 152). Today, a look at the data about 75 years after Freud's comment reveals that considerable progress has been made. Freud should be reassured that the scientific evidence shows the treatment he created has been streamlined and found to offer significant relief to many dealing with emotional and somatic discomforts.

## Models of Brief Psychotherapy

Brief therapies cluster within three broad models: relational, learning, and contextual (Steenbarger 2002). These differ in their understanding about the causes of presenting problems and the techniques necessary to alter them (Table 89–4).

### Relational Therapies

Relational therapies include short-term psychodynamic treatments and interpersonal therapy (IPT). Their essential assumption is that presenting problems reflect difficulties in significant relationships.

**Table 89–4 Differential Emphasis Among Traditional (Long-Term) Psychodynamic and Some Brief Treatments**

| Type of Therapy | Goals | Therapist Role | Level of Directiveness | Postulated Change Mechanism | Level of Structure/Brevity | Emphasis (H = Here now; P = Past & Present) |
|---|---|---|---|---|---|---|
| Traditional dynamic | Personality change | Blank screen interpretation | Low | Insight | Low; open-ended | P |
| Short-term dynamic | Intrapsychic and relationship pattern change | Active transference object | Moderate low | Corrective therapy relationship | Moderate, open-ended, time effective | P |
| IPT | Change interpersonal communications and attachments | Problem solver | Moderate | Altered relationship expectations and patterns | Moderate, brief, manualized | H/P |
| CT | Replace cognitive distortions | Collaborative empiricist | Moderate | Altered cognitive schemas | Relatively high, brief, manualized | H |
| BT | Desensitization, skill enhancement, anxiety extinction | Directive teacher | High | Experiences of mastery | High, brief, manualized | H |
| Solution focused | Focus on exceptions to problem patterns and creating solutions | Creating solution patterns | High | Focus on very specific goals and change strategies | Often high, very brief, manualized | H |
| Strategic | Interrupt problem cycles, initiate new action patterns | Facilitator of change through structured tasks and experiences | Very high | Reframe, direct experiences of normal action patterns | Variable, often single session | H |

## Brief psychodynamic therapies

Brief psychodynamic therapies as do all psychodynamic therapies, postulate that presenting problems of patients result from an internalization of conflicts from earlier, significant relationships. Defenses fend off the anxiety from these conflicts and aid short-term coping. However, this prevents the conscious working through and mastery over these core relational issues. These issues re-emerge in future relationships whenever similar anxiety and conflict is experienced, triggering old patterns of defense, which are now no longer appropriate to the current relationship. This creates a secondary conflict and the consequences that typically bring people to therapy. The psychodynamic therapist understands that these presenting problems are the result of outmoded, **currently ma**ladaptive (defensive), efforts in the face of repeated interpersonal conflict.

Traditional (long-term) psychodynamic therapy works backward from presenting complaints to underlying core conflicts, using interpretation as a primary technique to promote insight into outmoded defenses and repeated intrapsychic and interpersonal struggles. The therapeutic relationship becomes the locus for such insight, as those struggles are reenacted in the transference relationship. As patients replay their maladaptive defensive patterns and interpersonal struggles within sessions, the dynamically oriented therapist engages the real relationship—the mature alliance between the self-observing patient and the therapist—to help the patient become aware of what is happening and why. With this insight into repetitive patterns and their consequences, patients can then attempt to rework the ways in which they handle interpersonal threats within the safe confines of the helping relationship.

Since traditional psychodynamic therapy requires the interpretation of unfolding historical patterns within the therapeutic relationship, with insight as the goal, such therapy often spans months, if not years, of analysis. Brief psychodynamic therapy has added several features that enable it to accelerate change:

1. *Circumscribed, here-and-now focus*. Brief dynamic therapy narrows the focus on "core conflictual relationship themes" (Luborsky and Mark 1991) that represent "cyclical maladaptive patterns" (Binder and Strupp 1991), which link current, past, and therapeutic relationships. While the past powerfully informs these conflictual themes, brief dynamic work actively focuses on highly salient, present-day manifestations of the cyclical patterns.
2. *Patient selection criteria*. Brief treatment is not appropriate for all patients and disorders. Patients who are experiencing emotional discomfort, can easily form a trusting relationship, and are willing to view problems in an interpersonal context, are helped the most (Levenson 2004).
3. *Active provision of positive relationship experiences within the therapy*. Brief dynamic therapists may rely primarily on interpretation e.g., Davanloo, but also foster change by becoming involved in the core relationship patterns, and by breaking the cycles of repetition by providing responses different from those anticipated by patients i.e. corrective emotional experiences (Levenson 1995).
4. *Creation of heightened emotional contexts for change*. Change can be accelerated by creating an enhanced state of experiencing among patients (Sifneos 1972, Davanloo 1980). Such anxiety-provoking therapies seek to challenge and break through patterns of defense/resistance. Under these emotionally charged conditions, patients more readily gain access to memories, impulses, and feelings associated with core conflictual patterns, facilitating an accelerated working through of these experiences within therapy.

In short, brief dynamic therapists play an active role, sustain a narrowed treatment focus, initiate interventions to challenge maladaptive defensive patterns and provide new, corrective emotional experiences. (See vignette). This markedly abbreviates the traditional length of psychoanalytically oriented psychotherapy but this brief therapy often extends to 20 or more sessions. Research studies emphasize that relationship factors, persuasion, suggestion, catharsis, and the therapist as a model are important in both brief and long-term psychodynamic therapies (Eisenstein et al. 1994, Fisher and Greenberg 1996, Wallerstein 1986, 1989)

## Interpersonal therapy

Interpersonal therapy (IPT) began in 1984 as a brief, manualized treatment that has been successfully applied to a variety of presenting problems and interpersonal concerns (Stuart and Robinson 2003). As in psychodynamic therapy, IPT also addresses relationship issues and restricts patients, generally to mood and anxiety disorders, but abbreviates treatment even further by not making the therapeutic relationship a primary focus.

Vignette

Gina, a 32-year-old trader, was successful working in the "pits" of the exchange, but had difficulty transitioning to electronic trading, where she felt socially isolated and unsure. For the first time, she failed to make money over the prior two quarters and reported being anxious, worried, with interrupted sleep and a lessened interest in socializing. She said it was "humiliating" to feel like a beginning trader at her age.

Gina's personal and family history was negative for psychiatric disorders. She had strong support from family and friends. She was too "proud" to accept help from others and entered therapy reluctantly.

In initial sessions, Gina described a close relationship with her parents. Her father, protective, conservative, and difficult to please, was disappointed when she pursued trading rather than graduate school. Gina was never good enough for her father. She also did not want to be like her nurturing but submissive mother, without a career and dependent on a husband. During college, Gina briefly consulted with a psychologist when her grades fell precipitously: once she realized she could not maintain all A's, she stopped attending classes and, despite heroic efforts late in the semester, did poorly. She could not face her family and experienced herself as a failure. She only righted herself academically once her parents indicated that her happiness was more important than her grades–a turning point in her relationship with her parents.

Gina was displeased with exploration of her past and insisted she only needed direct advice regarding her trading

style. The therapist indicated that providing advice on trading would not help her regain confidence in her own ability. She expressed frustration with emotionally focused questions, stating she didn't know what the therapist was looking for. Once, Gina insisted she could not recall details of her past when prompted to reflect on the similarities between her current "humiliation" and her feelings as a failing college student. She then missed an appointment for the first time.

During the next meeting, Gina seemed glum. She described taking a break from trading "to get my head together," causing her to miss out on a major opportunity in the market. Feebly, she suggested it wasn't so bad since she had placed her "mental health" ahead of her job. Rather than offer reassurance, the therapist indicated that her glum mood suggested that her "mental health" was not benefiting from missing opportunity. He asked her to re-experience the moment when she learned of the missed market move. Gina chuckled, remarking that she'd rather not think about it.

The therapist pointed out that "not thinking about" her college problems and missing classes had not worked for her. "Not thinking about" her career conflict and missing her session was not going to lead to a successful ***professional career*** as a trader. "You're a professional, Gina," the therapist insisted. "You want to be recognized as a professional. Great. Let's face things like professionals. Did avoidance work for you in college? Did it just work in your trading? It sure won't work between the two of us!"

Reluctantly, Gina admitted that, when she realized she had missed the market movement, her first thought was that the therapist would chide her for her lack of work ethic. The therapist asked her to imagine such an interaction. Gina did so and tearfully acknowledged that it was the same conversation she had feared with her father in college. She didn't want to be a failure, but especially dreaded being blamed for the failure.

The therapist stated he did not view her as a failure, but noted that avoiding difficult situations—in life and in markets—was a strategy that had failed Gina. "Perhaps it's time to face the situation in your career the way you faced your grades in college," the therapist suggested. Gina agreed and met with the manager at her firm. She joined a team of traders to develop trading ideas and a feel for the electronic markets. She reassured her parents that she would seek alternate career paths should this plan not work out. To her surprise and relief, her family was supportive and pleased with her evident maturity. She expressed excitement over working in the team environment and agreed to stay in touch with the therapist. Six months later, she reported her career was going well. When asked what she found most helpful about her eight-session therapy, she said it was the therapist's acknowledgment of her as a professional.

Among the elements of short-term psychodynamic therapy illustrated by this vignette are: the establishment of a circumscribed focus for treatment; the linking of past, present, and therapeutic contexts; the heightening of anxiety through confrontation of defenses and resistances; the active interpretation of core conflictual themes; provision of opportunities for corrective emotional experiences; and how nonspecific factors —most notably the quality of the therapeutic relationship—are central to outcome. It was the therapist's ability to serve as an accepting father–figure that enabled Gina to seek similar acceptance from her trading firm and her own father.

IPT seeks brevity by establishing a narrow treatment focus in the interpersonal life of the patient, generally focusing on role changes or difficulties that the patient is experiencing in relationships: grief, interpersonal disputes, role transitions, and interpersonal sensitivity. IPT emphasizes attachment styles, changing patterns of communication, altering expectations within relationships and using social supports to help patients deal with interpersonal crises (Stuart 2004, Weissman et al. 2000). IPT focuses on current relationships and how these can be better handled. These potential solutions form the basis for between-session efforts by patients, securing their active involvement in treatment. Subsequent sessions review and refine these efforts, casting the therapist in the role of an active, collaborative problem solver. Although IPT is sometimes included under psychodynamic therapy, particularly in some reviews of outcomes research, it is not a dynamic therapy and there are distinct differences (Markowitz et al. 1998). In IPT, resistances to change are dealt with in a straightforward manner by the therapist, not as pattern reenactments to be interpreted and worked through. Lengthy explorations of past relationship conflicts, transference relationships and reenactment of past interpersonal patterns are downplayed. As a result, IPT tends to be briefer than most short-term psychodynamic therapies, with treatment for depression ranging from 12 to 20 sessions (Stuart 2004). The goal of therapy is to promote independent functioning, as well as symptom relief. As Stuart and Robertson (2003) emphasize, IPT, unlike other therapies, does not presume a complete termination of therapy at the end of treatment. Rather, there is an assumption that future sessions may be necessary to maintain gains and prevent relapse.

In sum, the relational model of therapy achieves brevity by carefully selecting willing patients who readily form a therapeutic alliance, have a circumscribed problem, and are able to sustain their focus on this problem. Whereas the role of the therapist is different in short-term dynamic therapy compared with IPT—a significant other, as opposed to a collaborative problem solver—the ultimate goal is similar: altering problem patterns by generating new, constructive relational experiences.

## Learning Therapies

Learning therapies, which include a wide range of cognitive-behavioral therapies, start from a different set of premises from the relational therapies. The presenting concerns of patients are viewed as learned, maladaptive patterns that can be unlearned. Moreover, patients are seen as capable of acquiring new, adaptive patterns of thought and action through skill development. As a result, the learning therapies feature the therapist in an active, directive, teaching mode and the patient as a student. This structuring of the helping relationship lends itself to active skill rehearsal within sessions and directed homework between meetings. The combination of tight learning focus and active practice of techniques ensures that most learning therapies are short term by their very nature.

It is helpful to distinguish between primarily behavioral treatments that emphasize exposure and cognitive approaches that target dysfunctional patterns of information processing for restructuring. While each can be

practiced in the pure form, there is often significant overlap, which affects the conduct and brevity of treatment.

### Behavioral (exposure) therapies

Exposure-based behavior therapies are particularly effective in the treatment of post-traumatic stress disorder, obsessive-compulsive disorder (Hembree et al. 2004) and panic disorder (Barlow 2002). During assessment, patients may keep detailed logs that track the appearance of symptoms and the circumstances that trigger them. Concurrently, therapists educate patients regarding the learning model, explaining how and why symptoms appear. This can be highly reassuring for patients suffering from such disorders as panic, who may be bewildered by their symptoms.

Early in treatment, behavior therapies introduce specific skills designed to help control symptoms. These can include efforts at relaxation, thought stopping, self-reassurance, and seeking social support. Typically, skills are introduced one at a time, explained in detail, modeled by the therapist, and rehearsed in session by patients. Once patients master skills in session, they rehearse them as part of between-session homework.

Triggers for presenting symptoms are then deliberately introduced into therapy sessions via imagery and in vivo exercises. Patients are thus required to actively employ their coping skills while they are exposed to the very stimuli that have provoked symptoms. For example, a patient who has a compulsion to touch the to doorknob three times to magically ward off danger before he can leave a room is prevented from doing so i.e. response prevention. After imagining it in sessions, a patient who was assaulted in a parking garage returns to the scene with the therapist. In both these examples, the escalating anxiety is treated with relaxation exercises. A patient with panic disorder might simulate panic experiences by spinning in a chair, then utilize cognitive and relaxation skills to maintain composure. This real-life exposure provides patients with firsthand, emotionally powerful experiences of mastery, which accelerate the pace of symptom resolution. After one symptom is mastered, these skills are used to challenge and master a variety of symptom-related cues. Patient needs and variations in technique dictate whether exposure is progressively incremental or in a more rapid intensive fashion ("flooding"). This significant immersion into anxiety-arousing situations, often over many hours, can be beneficial (Hembree et al. 2004). Exposure appears to be effective because it allows patients to reprocess cues associated with distress (Shapiro 1995).

### Cognitive therapy

Cognitive reprocessing therapies are now applied to a wide range of disorders, including depression, anxiety, eating disorders, personality, child and adolescent disorders and even schizophrenia (Hollon and Beck 2004). Cognitive therapy postulates that symptoms are due to automatic thought patterns that distort information processing about self, others, and the future ("cognitive triad"). Therefore, therapy attempts to identify these negative thought patterns, challenge them, and replace them with more constructive alternatives (Beck 1995). Time efficiency is obtained by combining in-session rehearsal and out-of-session homework.

Akin to behavior therapy, cognitive restructuring treatments begin with an assessment and psychosocial education. This education teaches patients the relationship between thoughts and feelings as well as ways in which automatic thoughts can sustain unwanted patterns of emotion and action. Cognitive therapists engage patients in a highly collaborative manner, minimizing resistances and sustaining the helping alliance.

Patients maintain a "dysfunctional thought record" in which they track events, reactions to those events, and mediating core beliefs. The main negative beliefs are of being helpless or unlovable (Beck and Bieling 2004), which distorts cognition by forming schemas that filter and darken future perception. The dysfunctional thought record is then used to create cognitive conceptualizations of patients, linking core beliefs to automatic thoughts, emotions and behaviors. The record also helps patients to recognize distortions as they are occurring and to appreciate their role in maintaining presenting symptoms. These specific cognitive distortions become a focus for intervention.

A primary technique in cognitive therapies is a Socratic process of guided discovery between therapist and patient, which raises doubts about the validity of these distortions and encourages a consideration of alternate construals (Beck and Bieling 2004). This process is also encouraged between sessions, as patients are asked to utilize thought records to evaluate their own degree of (dis)belief in the distortions. Each dysfunctional thought pattern is viewed by therapist and patient as a hypothesis to be questioned and tested. Behavioral experiments devised during sessions are carried out between meetings to provide direct, experiential tests of patient assumptions. The goal of this "collaborative empiricism" (Beck 1995) is to create vivid experiences of disconfirmation for patients, which aid the building of new, accurate schemas.

In summary, behavioral exposure therapies seek to extinguish specific conditioned responses in a very narrow focus; the cognitive restructuring therapies seek to establish a collaborative relationship that evaluates and restructures a range of dysfunctional cognitive patterns. Therefore, behavioral treatments tend to be briefer—often lasting less than 10 sessions—than the cognitive therapies, which typically range between ten and twenty visits. Interestingly, Leichsenring et al. (2006) note that in Germany CBT for outpatients averages 40–60 sessions. Despite these differences, these learning therapies have many commonalities. They are highly structured and focused, with active assignments during sessions and "homework" in between. Learning therapies achieve brevity by replacing verbal exploration with experiences of mastery that directly challenge and undercut dysfunctional patterns with a powerful immediacy.

## Contextual Therapies

A third, contextual, model of brief therapy stresses the ways in which presenting problems are situated within—and sustained by—their psychosocial contexts. Whereas the learning and relationship models stress internal sources of symptoms from the individual's history, the contextual approaches to short-term work emphasize here-and-now factors that sustain initial problems. For instance, brief couples therapies view problem patterns as sustained by the reciprocal contributions of each partner (Baucom et al. 2004). Because situational influences are deemed central to the maintenance of problems, targeted problem-solving interventions are

designed to alter these situations. Such a tight focus helps to ensure that the contextual modalities are among the briefest of therapies.

We can identify two major strands of contextual theory in brief therapy: the strategic therapies and solution-focused therapy.

## Strategic therapies

Strategic therapies evolved from the work of Milton Erickson. These include single-session treatments (Hoyt et al. 1992, Talmon 1990), as well as targeted treatments of several sessions. An important premise of the strategic therapies is that patients attempt to solve problems on their own. Many times, these attempts at solution contribute to an exacerbation of the initial concerns, creating self-reinforcing patterns (Rosenbaum 1990). A person who is anxious about being rejected in relationships, for example, might become guarded in a social setting. This could easily cause others to keep their distance, creating a self-fulfilling prophecy of rejection and isolation. In this case, the interpersonal context is a central part of what keeps the problem pattern alive.

Many times, the strategic therapist will attempt to break the vicious cycle by encouraging a reframing of the context (Fisch et al. 1982) and assigning directed tasks (Levy and Shelton 1990) that disconfirm patients' worst fears and expectations. For instance, the therapist might draw upon a conversation with the patient about "procrastination" and frame the avoidant response as procrastinating about making social contacts. This opens the door to new ways of viewing the presenting problem, which, in turn, can help generate new action patterns. Such framings form the basis of directed tasks to break the self-reinforcing cycle, perhaps by challenging procrastination and taking doable initial steps to converse with others. The goal of strategic intervention is to catalyze initial change that patients can sustain independently. The goal is not to effect fundamental personality changes or overhauls in global cognitive or interpersonal processes. For this reason, strategic therapies are highly abbreviated by design.

The initial interview of strategic therapy does not yield a diagnosis or a formulation of personality, but a description of the present contextual factors that help to maintain the patient's presenting concerns. This description includes the people involved in the patient's symptoms and the roles they take; the patient's view of the situation; the sequence of behaviors that result in complaints; and the specific contexts in which these complaints arise (Rosenbaum 1990). From this conceptualization, therapists gain an appreciation for the ways in which patients feel stuck in their attempts at resolution. Very often, the conceptualization will also suggest ways of disrupting problem cycles and encouraging new actions in old situations.

As Rosenbaum (1990) stresses, the goal of the therapy is not to find a solution for a patient's problem, but to create a situation that lends itself to spontaneous goal attainment. The aforementioned patient who is afraid of social interaction, for instance, might access wholly new behaviors to combat "procrastination" rather than "anxiety." When these new behaviors achieve patient goals, they can be accessed repeatedly, creating positive behavior patterns and a virtuous problem/solution cycle. In this sense, strategic therapy is a process for removing barriers to change and not a self-contained change process in itself—a factor that contributes significantly to its brevity.

## Solution-focused brief therapy

An offshoot of strategic therapy, solution-focused therapy (SFBT) provides a somewhat different contextual approach to short-term change. SFBT's essential hypothesis is that people are continuously changing, enacting solution patterns as well as problem ones. Indeed, for the solution-focused therapist, there is an important sense in which problems do not exist at all. When patients cannot reach their goals, they eventually construe that they have a problem. This reification (the notion that the problem is something they "have" as part of them) becomes self-fulfilling. As patients become more focused on their "problem" and ways of solving it, they unwittingly reinforce the distress that comes from feeling beset by problems. Most important, the problem focus blinds patients to their strengths and those occasions in which they do, in fact, attain their goals. It is the immersion of patients in a problem focus and not the independent existence of problems themselves that sustain presenting concerns.

The goal of SFBT is to break this immersion by focusing on solution patterns rather than problems. In a sense, SFBT is as much an epistemological intervention as a psychological one. The initial assessment asks patients to identify positive pre-session changes. The idea is to make these a scaffold upon which further adaptive efforts can be built (Walter and Peller 1992). There is also an initial effort to steer patient consideration toward occasions in which problems either do not occur or occur less often, as these may contain the kernels of adaptive capacities. "What, specifically, were you doing to get your work done without procrastinating on this occasion?" Enacting these exceptions to problem patterns—doing more of what is already working (deShazer 1988, O'Hanlon and Weiner-Davis 1989)—is the focus of therapy. Exploration of problem patterns and even skills-teaching to address problems are minimized, because these would only add to the patient's own immersion in a problem-based mindset. Because SFBT does not seek to initiate new behavior and thought patterns but instead builds upon existing ones, it tends to be a highly abbreviated treatment, lasting several sessions on average (Steenbarger 2004).

Solution-focused therapists stress a high degree of collaboration with patients to avoid resistances to change. This is accomplished through mutual goal setting, highlighting goals that are positively framed, concrete, and behavioral. Only once there is an agreement upon the specific aims of the therapy do the participants engage in an exploration of how the patient may already be achieving the goals in some measure, on some occasions. Homework assignments accomplish much of the "do more of what is already working"; these also are developed collaboratively, avoiding resistances that would unnecessarily extend the change process. The emphasis is upon here-and-now goal attainment and actions that can bring such attainment, further contributing to the brevity of SFBT.

One way in which SFBT differs from strategic therapies is that it lends itself to manualization. SFBT manuals (deShazer 1988, Walter and Peller 1992) view therapy as a series of steps:

- Identification of pre-session change e.g., "many people feel a little better between making the appointment and coming here for the first time. Have you noticed any positive changes?"
- Use of the "miracle question" e.g., "Suppose that one night, while you sleep, there was a miracle and this problem was solved. How would you know? What would be different? How would your husband know without your saying a word to him about it?" (deShazer 1988, p. 5)
- Formulation of solution-based goals e.g., I will put myself into two situations this week in which I have to introduce myself socially.
- Scaling questions to elicit exceptions to patient complaints e.g., "On a scale of 1–10, where 1 is "constant bickering" and 10 is "perfect harmony," how would you rate your relationship over the past week?"
- Provision of feedback to support change
- Assignment of tasks to facilitate the generalization of solution patterns e.g., "Standing up for yourself worked well for you. You let your father know exactly what you were thinking and feeling in a polite, constructive way. Perhaps that is something you can try with your brother as well and see what happens."

Like the strategic modalities, SFBT relies less upon verbal exploration and more upon direct experience to break circular patterns. The goal of both is not so much to resolve a problem as to help patients see that what they took for a problem was in fact a function of their punctuation of experience and the way they understand themselves and their world.

## Factors Common to the Brief Therapies

The various brief psychotherapies–including behavioral, cognitive, interpersonal, short-term psychodynamic, strategic, and solution-focused—make different assumptions about the nature of presenting problems and their treatment (see Dewan et al. 2004 for an overview). Nevertheless, a host of common ingredients make these approaches to change more similar (Greenberg 2004a, 2004b) than differences in their underlying theories might suggest. In fact, factors common to all long- and short-term models account for a significant proportion of the variance in patient change. (Lambert and Ogles 2004, Wampold 2001) See Table 89–5 .

**Table 89–5 Common Therapeutic Factors**

- A strong therapist–patient alliance
- Opportunity to confront and face problems
- The development of patient mastery experiences
- Facilitation of patient hope, positive expectations of the future.

Some of the common ingredients found across the brief treatments and their role in accelerating change include the following:

### Time-Effectiveness

All brief therapies make time an explicit part of treatment planning. Some, such as IPT, are time-limited, allotting a fixed number of sessions at the start of treatment. Others allocate sessions as cases progress, balancing twin concerns for effectiveness and efficiency. The actual duration can vary considerably. Strategic and solution-focused therapies of several sessions—and even a single session (Talmon 1990)—are not uncommon. Behavioral treatments often are completed within 10 sessions, but cognitive therapy may take 10–15 visits. Brief dynamic therapies of 20 sessions—or more—are common. Given such variation, it is difficult to say that time itself is a common ingredient of the brief modalities.

Linking these approaches, however, is the value of efficiency in the change efforts. Budman and Gurman (1988) have used the term "time effective" to capture the brief therapist's concern with maximizing the use of time during and between treatment sessions. This time-effective mindset entails several values, including an emphasis upon circumscribed change efforts over global, personality change and encouragement of short, intermittent helping through the lifespan (Cummings and Sayama 1995). For these reasons, applications as diverse as dialectical behavior therapy for borderline patients (Linehan et al. 2001); short-term dynamic therapy for relational concerns (Levenson 2004); and solution-focused therapy for the problems of families and couples (Walter and Peller 1992) are considered to be time-effective, although these will not be equally brief.

The absolute brevity of a therapy is a function of outcome measures utilized, presenting problems, goals sought in treatment, and the patient's readiness for change (Steenbarger 1994). Enhanced well-being and symptom relief typically occur earlier than functional change at work and in relationships, suggesting that therapies seeking the latter (which typically include cognitive, interpersonal, and short-term dynamic modalities) will tend to be lengthier than their behavioral, strategic, and solution-focused counterparts.

The time-effective therapist is thus less bound by absolute session durations, focusing instead on the process of change and ways in which it can be accelerated. Most of the remaining common factors discussed below help to achieve this end by targeting changes and encouraging concentrated, intensive work on these.

## Patient Inclusion Criteria

Brief treatment—certainly that of less than 20 sessions—is not equally effective for all patients and presenting problems. Anderson and Lambert (2001) reported that patients with more severe presenting issues took longer to achieve clinically meaningful gains than those with more benign presentations. Overall, it took 13 sessions for half of all patients in their study, and over 50 sessions for 75% of them, to reach a level of clinically significant change. Interestingly, Lambert and Ogles (2004) found that it takes 21 sessions for highly dysfunctional patients to achieve meaningful clinical change; those with characterological difficulties required about a year of treatment, suggesting a dose-response relationship based on differences in severity.

When patients are in the action phase, i.e. ready for change, aware of problem patterns and motivated to take action to deal with these—therapy is generally briefer than when patients are unclear about their problems and ambivalent about change (Steenbarger 1994). The latter, precontemplative or contemplative patients (Prochaska and Norcross 2002),

need time to explore their patterns and their consequences, necessarily adding to the duration of treatment.

What this means in practice is that abbreviated treatments are appropriate for some patients and problems and inappropriate for others. Accordingly, all brief therapies attempt to implement inclusion/exclusion criteria during the initial phase of treatment using their own specific criteria. Summarizing the clinical literature in brief therapy, Steenbarger et al. (2004) identify six common inclusion criteria that form the acronym DISCUS.

- Duration of the presenting problem is relatively recent, not chronic.
- Interpersonal history of the patient reveals the ability to sustain meaningful relationships.
- Severity of presenting problems is mild to moderate, not impairing the ability to sustain between-session and within-session work toward change.
- Complexity of presenting problems—the variety of symptomatic manifestations—is low, enabling patient and clinician to focus on a specific pattern for change.
- Understanding of problems and the need for change is high, enabling patients to begin work quickly and sustain motivation for change.
- Social supports outside of therapy are present, so that treatment does not have to serve a patient's ongoing support needs.

Situations in which one or more of the DISCUS criteria are not present may still be addressed by time-effective treatments, although not ones that are highly abbreviated. The dialectical behavior therapy (DBT) of Marsha Linehan and colleagues (2001) is a good example of how short-term modalities, employed in sequence, can address the longer term treatment needs of populations with more chronic, severe impairments.

## Focal Aims

Personality reconstruction is a common goal of time-unlimited psychoanalytic therapies. Brief treatments typically seek more circumscribed aims. Indeed a common ingredient of the short-term therapies is an initial assessment in which presenting complaints are formulated as focal patterns that can be addressed in a concerted manner.

Examples in the short-term dynamic therapies are re-ferred to as cyclical maladaptive patterns (Binder and Strupp 1991, Levenson 2004), or core conflictual relationship themes (Luborsky and Mark 1991). Malan (1976) and Davanloo (2001) conceptualize these as "triangles of insight," linking past, present, and helping relationships and characterized by warded-off impulse-feelings that are defended against in the face of anxiety (Figure 89–1).

In interpersonal therapy, the focus is on problem areas such as grief and loss, interpersonal disputes, role transitions, and interpersonal sensitivity (Stuart 2004). Cognitive therapies (Beck 1995, Beck and Bieling 2004) frame presenting concerns as dysfunctional schemas: patterns of automatic thought that distort perceptions of self, others, and the future, the "cognitive triad." Behavioral treatments (Hembree et al. 2004) stress sequences of situations and responses, focusing on the unlearning of maladaptive conditioned patterns and the learning of new, adaptive ones.

Strategic therapies focus on patterns of problems and attempted solutions in which the latter unwittingly reinforce the former (Rosenbaum 1990). This emphasizes here-and-now patterns, rather than ones that link past and present. Solution-focused therapies (Steenbarger 2004) minimize a problem focus altogether, instead channeling therapeutic efforts toward exceptions to problem patterns that capture patient strengths. Indeed, it might be said that the solution-focused treatments find their aims in client goals, rather than problems.

Perhaps the most important function of the treatment focus in brief therapy is its ability to help patients make sense of their problems and see themselves in a novel light (Steenbarger 2006). This opens the door to new, positive patterns of thought and behavior that, with repetition, can be internalized. Such novelty helps to create the "corrective emotional experiences" (Alexander and French 1946) that appear to be central to the short-term therapies (Budman et al. 1992).

## Therapist and Patient Activity

Whereas such time-unlimited therapies as client-centered treatment and psychoanalysis tend to be nondirective, encouraging patterns to unfold on their own, brief therapies tend to be more active and directive. Working with a limited number of sessions and emphasizing efficiency as well as effectiveness of change, both brief therapists and their patients are expected to become actively involved and maximize the use of time both within and between sessions.

The work of Sifneos (2004) and Davanloo (2001) illustrate therapist activity within sessions. Both provoke patient anxiety by directly confronting resistances to change and defenses against impulses and feelings. Such active confrontation heightens patient experiencing, which triggers access to fresh memories and perspectives that yield the aforementioned corrective emotional experiences. Levenson (2004) stresses the role of the therapist in providing new relationship experiences for patients, so that cyclical maladaptive patterns can be disrupted and revised. Many times, this requires responding to patients in unexpected ways. For instance, a therapist may respond to a patient's attempts to push the therapist away with empathy and understanding, rather than defensiveness, encouraging a different way of handling fears of rejection.

Behavioral (Hembree et al. 2004) and cognitive therapies (Beck and Bieling 2004) require patients to be actively involved in change efforts between sessions as well as within. Both rely heavily upon assigned tasks to face and challenge existing problem patterns. Behavioral treatment, for example, may stress in-session exposure to stimuli that provoke presenting symptoms, creating direct experiences of mastery. This exposure work continues between sessions to make maximal use of time and to cement initial changes. Similarly, cognitive therapies stress the collaborative exploration of problem patterns (Beck 1995), with the therapist providing Socratic challenges to dysfunctional thought patterns. These challenges serve as a model for clients to interrupt and alter their own automatic thoughts, particularly during between-session exercises. With repetition, individuals internalize new ways of processing information about themselves and the world, generating fresh schemas.

A similar structuring of between-session experiences can be found in interpersonal therapy. Stuart (2004) notes

that maintenance of a high level of emotional experiencing is crucial to sustaining the motivation to change, requiring therapists to focus on emotions associated with both the process of treatment and the content of what is being discussed. Within sessions, the therapist helps patients explore their patterns of communication and relatedness and how these might be interfering with the meeting of interpersonal needs. Between sessions, the patient is encouraged to try alternate modes of communicating and relating, actively using current relationship contexts as opportunities for change.

A somewhat similar emphasis on the completion of therapeutic tasks underlies strategic and solution-focused brief therapies as well. In the strategic modalities, the therapist may prescribe tasks that interrupt self-perpetuating cycles of problems and attempted solutions (Rosenbaum 1990). Drawing upon the work of Milton Erickson, for example, Haley (1984) describes how clients can be prescribed "ordeals" that require them to deal with their life situations in novel ways. In solution-focused work (Steenbarger 2004), once clients discover exceptions to problem patterns—ways in which they are already meeting personal goals—they are encouraged to do more of it through assigned exercises (Walter and Peller 1992).

In sum, the brief therapies represent *doing* approaches to change. Relatively less emphasis is placed upon the exploration, insight, and catharsis emphasized in many time-unlimited treatments. Instead, priority is accorded to the provision of in–and between–session activities that disrupt, challenge, and replace existing patterns of thought, feeling, and action. This places both therapists and patients in the role of change agents, actively generating novel, positive experiences that can become part of an ongoing repertoire.

## Sequencing of Change

The brief therapies are similar, not only in their aims, but in their structuring of the change process. Steenbarger et al. (2004), reviewing the brief psychotherapies, note that they follow a common three-phase course:

- *Engagement*. An introductory period of collaborative exploration, rapid alliance formation, and establishment of focal aims. During the engagement period, the brief therapist helps patients view their presenting concerns through new lenses, clearing the way for both optimism regarding change and for new action patterns. The various schools of short-term therapy serve as different lenses that enable patients to make sense of their concerns and gain a sense of mastery over these.
- *Discrepancy*. During the second phase, the therapist creates novel experiences that undercut presenting patterns and encourage the generation of new ones. This typically involves a heightening of affect within the therapy and the provision of new insights and tasks. Indeed, the chief aim of the brief therapies is the provision of new, positive experiences under altered emotional states that facilitate learning and internalization.
- *Consolidation*. In the final phase of brief therapy, the role of the therapist is to sustain initial changes by creating a series of experiences that reinforce new patterns. Without consolidation, initial changes are apt to be followed by relapse (Steenbarger 1994), an important limitation on the absolute brevity of treatment. Therefore, many of the brief therapies extend their limited sessions by spacing them over a lengthy period once initial changes have been achieved. This permits therapy to remain brief in terms of the number of sessions, but also retain much of the advantage of longer term work, in which changes become internalized.

In their change methods and structuring of change, the brief therapies are not so much different from their longer term siblings as intensifications of these. By stressing the factors that are crucial to the success of all the major therapies and becoming more intentional in their incorporation into treatment, therapists are able to accelerate change for selected populations. They accomplish this by focusing on limited aims and actively creating in-session and between-session environments that are conducive to experiential learning.

## Conclusion

As early as 1995, a review by Messer and Warren found that 84–89% of patients were treated in less than 20 sessions, 63–70% in under 10 sessions, and 34% in 1–2 sessions. "The conclusion is clear," they wrote. "Most people receive brief treatment, whether in public or private settings" (p 7). Consistent with this, they found that "the research literature indicates that most clinicians conduct brief therapy and that it makes up a substantial percentage of their practice" (p 9). Since then—pushed by continuing financial pressures and aided by manuals for many of the brief therapies and applicability to an increasing range of disorders—the practice of brief therapy has grown and there is an increased emphasis on making therapy brief by design rather than by default.

For many nonpsychotic disorders, there is data supportive of robust efficacy of brief therapies when compared to placebo or to medications alone in terms of symptom relief and prevention of relapse. Brief therapies have also been studied in combination with medications, either simultaneously or sequentially, and found to be useful (Dewan and Pies 2001). The majority of carefully controlled studies involve CBT or IPT and are reviewed elsewhere in this volume (Chapters 88 and 91).

*Therapist training and competence.* Some of these studies also highlight a point that needs repeated emphasis: therapist training, competence, and experience matter. It has been shown that higher levels of training are correlated with greater improvement in patients' symptoms and decreased rates of attrition and recidivism (Burlingame et al. 1989). Even this may not be enough. Several studies which used trained and certified therapists found that therapists who were independently rated as above average and therapists with greater experience had more positive outcomes. In one study, patients of the above average therapists did as well as the medication group, whereas patients of the below average therapists did only as well as the group on placebo (Elkin et al. 1995, DeRubeis et al. 2005). Clearly, even though the therapy is brief, optimal training is not. Therefore, self-study, week-end or short courses are not adequate (Burlingame et al. 1989). Messer and Warren (1995) and

Strupp et al. (1988) emphasize that training courses must be extensive and carefully designed. They must not focus merely on the technical manual but must also pay attention to the common factors and interpersonal aspects crucial to all therapies. Ongoing training and supervised clinical experiences are critically important and are becoming increasingly offered by training institutes and professional organizations.

This is an exciting time for the field of brief therapy, with the clinical application of established treatments to new disorders (Milrod et al. 2007) and to increasing levels of severity as well as the introduction of creative new ways to be more time-effective. The next challenge is to distill this data for the benefit of a single patient, in order to best establish a base of common factors on which a specific therapeutic technique could be added to maximize real-world effectiveness for each patient.

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CHAPTER

# 90 Group Psychotherapy

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Human beings live in a social world where their ability to gain self-esteem and self-definition significantly follows from their success in personal relationships. A psychotherapy group is a social arena where members can learn about their assets and deficits through interactions with peers (fellow members) and authority (the therapist). Members also have opportunities to experiment with new behaviors in the protected atmosphere of the group in preparation for using them in their external world.

A broad spectrum of theoretical approaches help therapists focus on varying aspects of group behaviors and interactions. Some focus on individuals as seen through the psychoanalytic lens of transference and resistance; others stress interpersonal transactions arising from childhood constrictions or distortions; still others focus on properties of the group as a whole, emphasizing group dynamics and systems theories as the central organizing concepts. Social learning principles are present in almost all orientations and are central to cognitive-behavioral approaches. Integration of these approaches has yet to be accomplished. Therapists may maintain a central theoretical orientation and pragmatically adapt elements from other orientations to address particular problems as they emerge during treatment.

This chapter primarily addresses outpatient work with adults in the psychodynamic tradition. Groups for specialized populations (e.g., persons with persistent and serious mental illness, trauma, and eating disorders) and behavioral group treatment formats are then discussed in separate segments of the chapter A fuller explication of many of the topics in this chapter is contained in Rutan et al. (2007).

## History

Joseph Pratt, an internist, who treated tuberculosis patients in organized classes, is generally credited with founding modern group psychotherapy. Most early contributors to group psychotherapy were schooled in psychoanalysis, which they modified for the group setting. Jacob Moreno emphasized action and spontaneity in founding a psychodramatic approach to treatment. S.R. Slavson, a self-taught psychotherapist, expanded his initial interest in children's groups to adults and was a central figure in the founding of the American Group Psychotherapy Association in 1942.

Group therapy received a stimulus during World War II when many therapists were exposed to group work during their military experience. Theoreticians in England (Bion, Bridger, Ezriel, Foulkes, Rickman, and Sutherland) and in the USA (Horwitz, Glatzer, Lieberman, Scheidlinger, Schwartz, Whitaker, Wolf, and Yalom) applied psychoanalytic or interpersonal (Sullivanian) concepts to a rapidly expanding interest in group treatment.

Interest in group processes, stimulated by the work of Kurt Lewin, led to the educational experiments in group dynamics at Bethel, Maine. The social upheavals of the 1960s resulted in a burgeoning of sensitivity training experiences (T-groups) and a variety of personal growth groups. The emergence of transactional analysis, gestalt therapy, bioenergetics, existential models for group therapy, and many additional innovative variations have enriched the group therapy field.

Activity groups for children began in 1930 and later developed into verbal groups for children and adolescents. Groups for special populations have gained popularity and are used in schools to address issues such as parental divorce, substance abuse, and acquired immunodeficiency syndrome (AIDS) prevention. Short-term models are also widely applied to special adult issues, including psychological trauma, bereavement, and a host of medical and social situations. Such groups may be used with dynamic or behaviorally oriented formats. Time-limited psychoeducational groups, with an emphasis on imparting information and sharing experiences, provide additional therapeutic opportunities.

The self-help (SH) movement, which traces its origins to the efforts of Alexander Low and Recovery Inc. in the 1930s, and the emergence of Alcoholics Anonymous and the 12-step model, which is also applied to other addictions, have increased the awareness of the therapeutic potential of collective interaction in the recovery and maintenance of individual emotional well-being.

The future will continue to see the use of a broad spectrum of group modalities and a variety of different models as the entire psychotherapeutic field endeavors to find a balance between efficiency and effectiveness. For an excellent review of nine decades of group psychotherapy, see Scheidlinger (1994).

## Group Therapy Theory

The theoretical spectrum informing the practice of group therapy is broad. Within psychodynamics, group clinicians

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embrace, either singly or in combination, drive, object relations, interpersonal, self-psychology, attachment, or systems theory (Freud 1955, Kibel 1992, Harwood and Pines 1998, Billow 2003a, Yalom and Leszcz, 2005, Rutan et al. 2007). Other therapists favor behavioral or cognitive-behavioral approaches. Transactional analysis, originating from the work of Berne (1966), and Gestalt therapy (Perls et al. 1951) emphasize interpersonal transactions arising from more traditional psychodynamic theory. In addition, group theoreticians are generally categorized along a continuum of group as a whole, interpersonal, and intrapsychic. There are few purists, and varying degrees of integration is the norm (Table 90–1).

**Table 90–1 Group Theories**

| Theory | Authors | Key Phrases |
|---|---|---|
| Group as a whole | Bion | Basic assumption, work group |
| | Whitaker and Lieberman | Group focal conflict |
| | Ezriel | Required, avoided, calamitous relationship |
| | Foulkes | Group analysis, group matrix, figure/ground |
| | Horwitz | Integrative, inductive |
| Interpersonal | Yalom | Cohesion, therapeutic factors, feedback |
| Intrapsychic | Slavson | Limited regression, transference |
| | Wolff and Schwartz | Standard analytic, alternate sessions |
| | Durkin and Glatzer | Group-as-preoedipal mother, transference neurosis |
| | Gustafson and Cooper | Unconscious planning |
| General system | Durkin | Exchange across boundaries |
| | Agazarian | Subgrouping |
| | Ettin | Social and cultural values and attitudes |
| | Hopper | Social unconscious |

A common thread in many of these theories is that individuals in their interaction and discourse within the group will exhibit their difficulties in relationships, which in turn provides a window into their internal world. In short, the group becomes a microcosm in which their inner world is displayed (Slater 1966).

## Group-as-a-Whole Approaches

These theories emphasize whole-group processes as the primary therapeutic vehicle. They subscribe to notions that members are influenced by the group dynamics and that one or more persons may "speak" (verbally or behaviorally) for the entire group.

Bion (1960), working within a Kleinian object relations model, conceptualized groups as having two levels: work and basic assumptions. Work groups operate on a reality principle and are goal directed. Basic assumptions groups function as if the group were meeting to satisfy members' emotional needs. Bion identified three basic assumptions that suffuse the work group: dependency, fight or flight, and pairing. Bion suggested that individuals have a basic tendency toward one of the basic assumptions with which they will enter group life. Therapists working in this model focus on members' relationship to the leader, particularly as expressed through basic assumptions. Billow (2003b) has elaborated on Bionian theory in combination with relational theory, with greater emphasis on the contributions of the clinician to the therapeutic process.

Tripartite conflict models, in which an impulse, a wish, or an object need was met with a counterreaction or a fear leading to a compromise, were applied to group therapy by Whitaker and Lieberman (1964) (group focal conflict with the three elements: disturbing motive, reactive motive, and solution) and Ezriel (1973) (psychoanalytic group therapy with the three elements: required, calamitous, and avoided relationships). Therapeutic efforts are directed to elucidating the conflicts, thereby freeing up constricted solutions or avoided relationships.

Foulkes (1961) formulated group analysis, applying a figure-ground gestalt framework that emphasized analysis of communication and relationships network (matrix) among the members and with the conductor. The conductor's (therapist's) attention shifts between group and individual, with one representing the figure and the other the ground in the gestalt of the group interaction. This is the primary group therapy model in Europe and Israel.

## Interpersonal Approaches

Elaborating on Sullivanian interpersonal principles of psychotherapy, Yalom and Leszcz (2005) have evolved a group therapeutic approach that focuses on the relational nature of emotional problems. In this model, the group setting provides patients opportunities to learn about their recurrent difficulties in developing and sustaining relationships. Members reenact and have opportunities to learn about and modify their previously acquired dysfunctional interpersonal and relational behaviors in the group microcosm where dysfunctional relationships are demonstrated as well as described.

The interpersonal group therapist works to create an environment where members' creation of their outside world can be examined in a therapeutic atmosphere. The therapist steers the members to the-here-and-now focus, which is conceptualized as a two-tier integrated experience: the first element is the person's experience in the immediacy of the therapy session—this takes precedence over members' outside current life and distant past; the second is illuminating the process, by which is meant "[i]t must examine itself; it must study its own transactions; it must transcend pure experience and apply itself to the integration of that experience" (Yalom and Leszcz 2005, p. 142). The process is formulated as helping members recognize their intentions and their impact on others, which illuminates how they are viewed by others and open opportunities to view their own self-regard. In the group, members explore their satisfaction with their habitual relational style and their motivation to change.

Group cohesion, a concept that speaks to the relationships among the members, with the leader, and with the group, is seen as essential for the therapeutic process.

Cohesiveness is not an easily delineated concept; it includes a sense of belonging to and valuing the group, a sense of feeling supported and accepted, an esprit de corps. Cohesiveness is not static. It may be enhanced as members feel that they are learning about themselves or they can be helpful to others, or it may be disrupted by interruptions in scheduled meetings or advent of new members. One of the key elements enhancing cohesion is members learning to give and receive feedback, a process linked to helping members learn about how they impact others and their own emotions in the process. In this respect, the group then comes to represent a healthy family in which conflict can be resolved and healing relationships exist.

In concert with other dynamic therapies, interpersonal group therapy (IGP) values norm building, including focusing on the here and now, taking responsibility for looking at one's own behavior and its impact on the self and other, and examination of transferences (often described as parataxic distortions). Dynamic processes such as scapegoating, emotional contagion, and the impact of norms are carefully monitored. Whole group interventions are seen as useful when the group processes appear to interfere with learning. Linkages to the outside world and to the past help consolidate learning. Group dynamics are appreciated as impacting upon the individuals (additional interpersonal group therapeutic factors are discussed in the section below).

### Intrapsychic Approaches

Intrapsychic theories are primarily application of dyadic theory into the group setting. The emphasis is on unconscious processes, with the group providing opportunities for patients to regress to a level of internal conflict or developmental arrest. These theories explore individual transferences, resistances, and developmental arrests as the primary therapeutic focus. Peers may be experienced as siblings or as displacement objects from parental figures (Slavson 1950, Wolf and Schwartz 1962). Groups may either dilute or intensify transferences to the leader (Horwitz 1994), which enables "stuck" patients to resolve impasses occurring in dyadic treatment. Regression is limited, and the presence of others creates a balance between the external and the internal worlds (Durkin 1964). Integration of an intrapsychic framework with that of the group as a whole is contained in descriptions of members' transferences to the group as a preoedipal maternal experience (Scheidlinger 1974).

Gustafson and Cooper (1979) posited that individuals enter groups with unconscious and conscious plans to determine if they will be traumatized in the group as they had been in the (developmental) past. They present "tests" to determine if they will be attacked or to learn new ways of problem solving. Passing the tests enables patients to disconfirm old beliefs and to restart development.

### General Systems Approaches

General systems theory is based on open systems theory (von Bertalanffy 1966). Emphasis is placed on the boundaries separating the group from the external world and members or subgroups from one another (Durkin 1981). Agazarian (1997) elaborated systems concepts into a model of group treatment that focused on subgroups as the primary site of therapeutic attention. She asserted that by focusing on subgroups, which contain individual differences and similarities, members are more prepared to address intrapsychic defenses and resistances.

A systems perspective highlights participants' cultural background and the impact of such forces on conscious and unconscious values and attitudes (Ettin 1994). Similarly, events in the culture and "politically correct attitudes" may constrain or stimulate members and are transported into the consultation room often outside of awareness as a social unconscious (Hopper 2003).

## Group Dynamics and Group Development

The basic science informing group treatment is group dynamics and development, an understanding of which allows the therapist to select and integrate interventions directed to individual, interpersonal, and intrapsychic levels of group process (Table 90–2).

**Table 90–2 Stages of Group Development**

| Stage | Theme | Dynamics |
|---|---|---|
| Formative (joining) | Engagement | Dependency<br>Safety<br>Norms |
| Reactive (storming) | Power | Testing<br>Competition<br>Autonomy |
| Mature (performing) | Work | Affect tolerance<br>Leadership<br>Self-reflection |
| Termination (departing) | Separation | Loss<br>Hope |

### Group Dynamics

Group dynamics is a study of the forces that shape a group as an "organism." The group is examined from a different perspective than merely as a sum of individual dynamics. Dynamic processes are present in every group as it pursues its goals, with overt and hidden behavioral (verbal and nonverbal) rules (norms) and ideals (values), which constitute the group culture. For example, group norms are reflected in the "proper way" for latecomers to enter a meeting. In one group latecomers apologize for their tardiness, in another they provide an explanation, and in a third they quietly sit down. Many norms highlight positive "behaviors," such as thinking about process, reflecting on one's impact on others or on one's experience in the moment. Other examples are sanctions on eating, drinking, or physical contact during the session. Less overt norms may limit emotional expression. Respect for others' opinions and helping others would represent group values.

Each group develops its own culture. Individuals are influenced by their race, gender, age, religion, education, and the broader culture, including values of the family of origin, subculture, and the local and national identity. Group structures influencing the dynamics include size, frequency, and duration of the meetings. Illustrative of a broad cultural dynamic is the impact of the changing view of what is politically correct. Individuals must be aware of when and where

certain expressions may be spoken, because inadvertent gaffs may result in severe sanctions. In sum, group dynamics comprise study of how the whole group functions.

Groups evolve specialized functions (roles), which serve to modulate the emotional climate and the work. Roles may be filled by a single person or by a number of individuals—from a whole group perspective, it is the function that matters. Four roles describe these functions: structural, sociable, divergent, and cautionary (MacKenzie 1997). The structural (leadership) role addresses group work. The therapist is the primary occupant of this role, but members also function in keeping the group on task. A structural leadership role might be a member's comment that the group starts and stops on time or that the members are not addressing a member's absence. The social (emotional) role helps contain or express feelings and assists in managing social relationships within the group. The role might be expressed by individuals who relieve group tensions by changing the topic, making a joke, smoothing ruffled feelings, or encouraging expression of less acceptable and/or painful feelings. A member might identify emotions, saying "perhaps we all might wish to avoid talking about the absence because we are so angry with the person." The cautionary role is often filled by a silent member, or who speaks in generalities. These individuals represent the need for safety, but secretiveness may be felt as threatening. The divergent role is filled by persons who seem oppositional, who "don't go along with the crowd," or who seem to fight authority. They are likely to become a container for others' unacceptable thoughts or emotions (projective identification). Such individuals are vulnerable to becoming scapegoated, a process in which inadmissible feelings are seen (or placed) in one person and thereby kept out of awareness in the others. Roles may also be seen in Bionian basic assumptions, where one person may represent a dependency or a fight–flight group. The concept of role helps clinicians maintain awareness of individuals and the group as a whole. As a way of thinking about roles, therapists may silently consider if the person is acting as an individual or fulfilling a group function.

## Group Development

The seminal work of Bennis and Shepard (1956) produced a spate of studies demonstrating that groups have a natural developmental sequence. Groups must accomplish certain tasks as they move from a collection of individuals to a functioning and working organization. Group development is nonlinear, being subject to perturbations and reorganizations with regressive and progressive movement.

The concept of group development is an abstraction, roadmap, or guideline. Development is contingent on leadership function and on membership composition. Group developmental achievements are not always equivalent to individual's therapeutic success. For some patient populations, treatment might be considered a success at earlier development stages (with only brief forays into more advanced stages), whereas optimal therapeutic benefit would not accrue for other populations until the group more consistently functioned at the later developmental stages.

## Formative (Engagement, Orientation) Phase

In a typical psychodynamic therapy group in which expectations are to expose hidden shameful or guilty secrets, members in efforts to feel protected and to gain information may turn to the therapist for guidance, similar to looking to a parent or teacher. They may become dependent or idealize the therapist as all-knowing, hoping for simple procedural formulas. Alternatively, they may alleviate isolation by searching for similarities with other members by asking seemingly superficial questions: Where were you born? Do you work? Are you married? They may self-stabilize by remaining silent or testing the limits of behavior. These latter attempts include various oppositional or "difficult" behaviors, including persistent demands for topics to discuss, dominating the conversation, suggesting facile solutions to problems, and being impervious to observations about one's own behavior or to the impact of behavior on others.

In the formative phase, the therapist orients members on how the group will function by trying to understand the meaning of various behaviors, primarily within the here-and-now of the meeting. Interventions may be addressed to individuals, subgroup, or the group as a whole. Cohesion is fostered by highlighting common themes or concerns, wishes for protection or guidance, and fears of criticism or humiliation.

Gradually members verbally and behaviorally reveal themselves, all the while monitoring "safety." In this process norms emerge, which contain anxiety and set standards for acceptable behavior. As the process continues, members learn that the leader is not omniscient or omnipotent. They discover that they can contribute to the process and understanding of one another. In this formative phase, members may learn a good deal about how they meet strangers and what promotes or undermines feelings of safety. They have experiences helping them understand how they manage anxieties with newcomers and look to or reject authority.

## Reactive (Power, Differentiation) Phase

The reactive phase is characterized by periods of conflict and intense emotions. Threats to quit are common and at times acted on. Two elements contribute to this phenomenon. First, group membership means abiding by rules (initial norms may feel restrictive), which activates protest. These behaviors serve to modify restrictive norms, providing for greater flexibility. Second, members compete for leadership, which can become quite intense.

The therapist is subjected to considerable stress during this phase. As "author" of group treatment, he may feel bombarded and ineffective. The clinician's ability to understand the criticisms as members' antidote to frustration, powerlessness, or diminished control helps maintain his/her inner balance.

The reactive phase may provide members powerful therapeutic benefits. For many, the phase provides an important space where they may more freely express aggression and anger and learn that such expressions are not inevitably met with retaliation but, instead, are examined for their emotional basis. Individuals emerge from this phase with a greater sense of their own authority. They experience that conflict does not lead to disaster, leaders can be challenged, and productive change may occur.

This picture of the reactive phase is incomplete because, as with adolescence, not everyone or every group rebels. Some groups progress more smoothly along the continuum of marked conflictual or quiet change.

### Mature (Working) Phase

Mature phase groups can be seen as moving effectively toward their goals. Personal safety is addressed at deeper levels. Members share leadership roles; they reflect on their interactions and inner "unspoken" dialogues, thereby exposing hidden intentions and emotions. They are more collaborative with one another and with the therapist. The therapist is more readily accepted as an individual with helpful skills and abilities, but also as someone who may misunderstand or be mistaken. Tolerance for differences increases, and conflict is allowed to emerge more fully. Conflict is examined for sources rather than seen only as a disruption. Violations of norms are not automatically sanctioned but are seen as learning opportunities. Group transactions are more focused on the here and now, and exchanges are appreciated as containing reactions to the present and vestiges from prior relationships (transferences). Members attempt to understand one another at both surface and in-depth levels.

The therapist increases efforts to understand and interpret behaviors in the here and now, linking them with prior in-group experiences and with extra-group, developmental, or family of origin experiences. The therapist may take pleasure in seeing growth and sharing leadership.

In this phase, members can more flexibly assume multiple roles. They see others as separate individuals with their own wishes, desires, strengths, and difficulties.

### Termination Phase

When groups prepare to terminate, members respond to the impending loss in a fashion similar to stages of grief: denial, anger, bargaining, depression, and acceptance (Kubler-Ross 1967). At first, there is disbelief that the group will end, and discussion of the ending date is quickly squashed. Some members, in the service of denial, will talk about all the things they can do when they are relieved of regular attendance. Anger is voiced at not having achieved idealized treatment goals and is fueled as protest against the loss of real relationships with peers and the therapist. Commonly, patients try to bargain for extensions, or they discuss the possibility of finding another therapist or meet another therapist on their own. As the reality of the ending comes closer, evidence of depression appears. Finally, acceptance appears mixed with appreciation for the gains that have been made and the recognition of the undone work. The future is explored with a mixture of apprehension and anticipation of trying out one's new experiences as a more integrated and flexible person.

Members revisit previously examined behaviors and inner conflicts—these regressive features are not identical to what had been exhibited earlier, because of learning during the treatment. Dependency strivings, idealizations, or anger in response to powerlessness (to alter the ending) reappear. These regressive experiences provide the members additional opportunities to examine problems and reenforce gains. Characteristic of the termination phase, these periods are of briefer duration and lessened intensity.

### Summary

Groups do not uniformly traverse developmental phases. They will shift to earlier stages in response to various stresses, such as vacations or change in membership. Considerable therapeutic work takes place at each developmental level. A group of individuals experiencing problems with basic trust may require considerable time in an initial stage, for the members to become familiar with and to gain mastery over their basic sense of distrust. The group work could be considered a success with that achievement. Patients who need to address competitive feelings need to work at more advanced stages. Understanding group development provides a framework for therapists to appreciate the forces that impact on members' feelings and behavior.

## Therapeutic Factors

In dynamic therapies, specific and nonspecific elements contribute to therapeutic change. In groups, the presence of others adds to factors present in all dyadic healing relationships (Yalom and Leszcz 2005). Nonspecific factors are embedded in the relationships established through a consistent, accepting, nonjudgmental, and supportive environment. These are all elements of a cohesive group. Groups provide a corrective emotional experience in which patients experience others (including the therapist) responding to them differently than those in their past. Members share their stories (catharsis) and feel less isolated when others have shared similar stories (universalization); they have opportunities to be helpful to others through both cognitive understanding and emotional linking (imparting information, providing feedback, and altruism). They also see others improve, which conveys hope. These elements contribute to the sense of collaboration and a willingness to adopt norms (i.e., discuss feelings about the interactions in the meeting) that further members' sense of efficacy and belonging. Taken together, these nonspecific elements add to group cohesion, which has been likened to the therapeutic alliance in dyadic treatment. They contribute to an experience of support and acceptance, which may be sufficient therapeutic gain for a number of patients.

Additional nonspecific elements that contribute to change are opportunities for imitative learning. Patients observe and imitate others' successful interactions. Members may model and practice new ways of interacting in the protected setting of the group and thereby disaffirm prior beliefs that their behaviors will elicit noxious responses.

Each theoretical school emphasizes its own specific contributions to therapeutic change. The interpersonal tradition privileges giving and receiving feedback about behaviors in the here and now as central therapeutic factors. Other psychodynamic theorists emphasize resolution of transferences, resistances, or unblocking developmental arrests. The group is conceptualized as re-creating the family of origin or as a microcosm where enactments of previous experiences with parents or siblings or other important relationships will emerge. These then become available for modification through the relational experiences and interpretation.

Within the psychodynamic tradition, change mechanisms of confrontation, clarification, and interpretation promote imitation and identification, optimally leading to internalization and change in psychic organization (Rutan et al. 2007). Members and therapist contribute to these processes, albeit in an unequal manner. Indeed, an asset of group treatment is that participants learn to appreciate less than conscious motivations in themselves and in others and develop a capacity to empathize with others in the immediacy of the group setting. Moreover, they can experiment with novel ways of behaving. Individuals successfully completing group treatment cite the help of member-to-member

interactions; those who fail are more likely to focus on therapists' shortcomings.

## The Practice of Group Therapy

### Organization a Group

Forming a psychodynamic therapy group is complex, and attention to organizational details will anticipate hazards and smooth the path to success. Composition, size, fees, place, duration, and time of meetings are elements that require decisions in advance of recruiting and preparing potential members.

The size of dynamically oriented groups ranges from six to 10 members. Groups at the upper size range generally meet for lengthier periods to provide sufficient time to participate for each person. Smaller groups (four members or less) may be threatened by fears of dissolution. The duration of meetings generally ranges from 75 to 120 minutes, the norm being 90 minutes. Groups meet once or twice weekly. Physical arrangements require attention, including place for members to gather before the meeting begins: an unobstructed treatment room allowing members comfortable, but not necessarily identical, seats.

The therapist should make advance decisions regarding the day and time of the meeting. Most outpatient adult groups meet in the evening, maximizing opportunities to recruit members. Initially, the group time can be used to interview candidates, thereby clarifying the patient's ability to attend. Attempts to adjust time or day to accommodate one or two prospects are generally inadvisable.

Most therapists prefer to establish a uniform group fee. Nevertheless, managed care stipulates charges and does not permit "balance billing," thereby limiting this policy. Policies about charges for missed appointments should be decided in advance. Whatever the ultimate arrangements, as set in the agreement (discussed later), therapists have the task of helping patients be responsible for their fees.

Careful thought must be given to optimal group composition (Table 90–3).

**Table 90–3 Selection of Patients**

| Type of Group | Positive Attributes | Negative Attributes |
|---|---|---|
| Dynamic | Ego strength | Crisis situation |
| | Motivation for change | Active substance abuse-related disorder |
| | Capacity for insight | Sociopathy |
| | History of satisfying relationship | Cognitive disorder or mental retardation |
| Supportive | Diminished ego strength | Acute psychosis |
| | Limited reflective capacity | Disabling cognitive disorders |
| | Motivation for support | Substance abuse |
| | Most relationships problematical | |
| Specialized focus | Common characteristic | Psychosis |
| | Focus on single problem | Motivation for personality change |

Patients chosen for groups that will explore intrapsychic and relational difficulties should have a capacity for self-reflection and empathy. If possible, members with different personality styles should be selected to provide a spectrum of interactive patterns. Other long-term groups may be established with supportive goals and include patients with significant ego deficits. Groups designed with a specialized format (e.g., survivors of sexual abuse or other traumas, male perpetrators, or individuals with eating disorders) generally are more focused on a symptom, a specific experience, or behavior, and in such cases balanced membership is of lesser importance.

The task of composition is not to exclude differences but to create a group where the differences are not so great that emotional links cannot be achieved. Groups can be started with unequal numbers of men or women, but open places should be used to equalize membership. If possible, at least two members of each gender should be included to reduce stereotyping and isolation and to promote identifications. Age ranges might be limited in groups composed of late teenagers, young adults, or elderly persons; however, in groups whose members have attained their late 20s, the range may be quite broad.

### Recruiting, Selecting, and Preparing Patients

Few applicants requesting psychotherapy consider group treatment. Thus, gathering 6–10 individuals together may not be a simple task. The optimal place to recruit patients is from the therapist's own individual practice. These individuals have a relationship with the therapist and can more readily collaborate in a decision to join a group. Colleagues are helpful referral sources, but the therapist must provide the necessary information regarding the group's goal and patient characteristics to facilitate referrals. In clinic settings, admission staff are in a particularly helpful position to assist recruiting members.

Patients are more likely to agree to enter a group if they are provided a detailed rationale for the treatment format. The therapist needs clarity about the relationship between group goals and patient goals (to be discussed below). In interviewing prospective members, the therapist should become familiar with the patient's history, coping style, symptoms, and personality configurations. In obtaining a patient's developmental history, the therapist can specifically search for the person's interaction in group settings, such as school, church, recreation, and family. Discussion of the person's typical reactions to group situations helps engage the patient in examining his/her response to interpersonal situations. An important element in informing patients about group treatment is the clear boundary between what is introduced in the group and dyadic settings (either the preparatory interviews or the individual treatment sessions). The patients are responsible for bringing information from those interviews to the group. The therapist will respect the patient's privacy and autonomy. The screening and preparatory interviews have five major tasks (Rutan et al. 2007):

1. Establish a preliminary alliance between patient and therapist.
2. Define the patients' therapeutic goals.
3. Provide information about the nature of group treatment.

4. Explore the patients' anticipatory anxiety.
5. Discuss the group agreement and gain the patient's acceptance.

Several individual interviews may be necessary to determine applicants' suitability for the group. Before joining a group, some individuals then benefit from or choose to work on understanding their feelings more thoroughly in dyadic treatment.

For those who seem suitable, preparatory interviews help them anticipate their emotions about joining and form a beginning alliance with the therapist. Careful preparation will decrease but not eliminate premature termination.

Patients may be informed that a group goal is establishing free-flowing interaction and discussion where members may experience and learn about problematic aspects of their inner and relational worlds. Individual goals may be formulated in both interpersonal and intrapsychic terms. For example, a patient who wishes to address his/her difficulty in sustaining intimate relationships may use the group to examine his/her feelings, in order to determine which interactions stimulate or diminish his/her desires for intimacy. The goal would be to learn about both the current (in-group) stimuli and the past experiences that evoke these emotions and responses. Inquiry into a patient's recent dreams, either in anticipation of preparatory sessions or between screening interviews, will expose less conscious aspects of anticipatory anxieties. The patient can also be told that he/she might discover previously unrecognized problems that he/she wishes to pursue in his/her group treatment.

Therapists often are discouraged or frustrated by the difficulties they encounter in gathering sufficient members to begin group treatment. Clinicians unable to recruit prospects from their own practice may have hidden resistance to group treatment. Consultation is useful in providing support and may expose countertransference responses to prospects or uncover resistance to assuming the leadership tasks (Billow 2001).

## The Group Agreement

The group agreement represents the framework in which treatment will proceed. It promotes a structure that defines boundaries between the group and the environment, among the members and with the therapist. Although members accept the agreement, they also disregard it. Such behaviors provide valuable opportunities for understanding a person's inner world. The therapist must distinguish between acts that are disruptive to the group and those that carry more benign communications (Nitsun 1996).

Rutan et al. (2007) list the elements of the agreement as shown in Table 90–4.

The initial element in the agreement addresses patients' ability to attend all sessions. Those who have responsibilities that regularly interfere with attendance should not be admitted into the group (e.g., executives whose conflicts make them unavailable on a regular basis). Similarly, persons who have time conflicts and would consistently come late or leave early should delay entry until their schedule can be adapted to that of the group.

In establishing goals, the patient and therapist enter into a conscious agreement to work toward specified change. However, unconscious elements contributing to a patient's behaviors are likely to emerge in the therapeutic process that may point to additional goals worthy of pursuit. Instructions regarding termination are an additional part of this agreement element. Patients generally have little idea how to end treatment, and leaders can indicate that allowing sufficient time to terminate is an important part of the therapy. Plans to leave should be discussed and a departure date established, which will allow sufficient time to say meaningful goodbyes.

**Table 90–4 The Group Agreement**

| |
|---|
| Attend all meetings, be on time, and remain throughout the session |
| Actively work toward treatment goals, remain until they have been achieved, and discuss plans to stop treatment |
| Observe one's inner reactions to interactions in the group and comment on them |
| Use the group for therapeutic and not social purposes |
| Put feelings into words and not action |
| Be responsible for fees |
| Understand the therapist's role |
| Protect the confidentiality of the meetings and the anonymity of members |

The succeeding three elements in the agreement address patient behaviors within the group. Patients slowly learn that addressing feelings and reactions to one another and to the therapist in the here and now is very helpful. Consistent attainment of this goal suggests that the group has reached a mature level. Physical contact and verbal abuse are prohibited. Although physical touching or hugging may seem soothing and reassuring to some individuals, for others it is a threat to their personal boundaries. Patients unable to contain these behaviors may be asked to leave the session temporarily, or rarely, permanently.

Inevitably, members will have contact with one another outside the sessions. Contact may be limited to brief encounters immediately before or after the meeting, or eating together after a session. On occasion, patients develop substantial relationships with one another. The therapeutic aim is to create an environment in which these contacts can be discussed and their meaning addressed. Rarely do these extra-group meetings lead to sexual liaisons, which may be destructive to treatment. With patients understanding that continuing such liaisons will interfere with their remaining in the group, most will discontinue their sexual relationships. The greatest danger to the group exists in silence surrounding outside contacts.

Members may be asked to file insurance forms and to be responsible for their fees and copayments. If payments are not made within the agreed time frame, the failure should be openly raised within the group. Money often assumes major importance in patients' lives, with linkages to self-esteem, shame, competition, and power. The therapist "swims upstream" when he/she introduces problems with fees in the group, but failure to do so excludes from therapeutic scrutiny important aspects of patients' inner experiences.

As part of the agreement, therapists include a description of their role. They may merely indicate that they will try to help members understand themselves and others. They should describe how they will inform the members in advance

when they are to be absent or will make arrangements in case of emergency. When insurance requires disclosures in order to continue providing benefits, the therapist needs to inform the patient of what information (including diagnoses) will be disclosed.

Discussion of confidentiality is left to last in order to emphasize its importance. No guarantee can be made about member confidentiality, but stressing the significance of maintaining others' anonymity if material from the group is discussed is easily understood and does not interfere with members' freedom to process their treatment experience with persons outside the group.

The agreement creates a structure within which the therapeutic work can proceed. However, it leaves room for considerable ambiguity, which can be used for therapeutic discussion. The agreement is presented to prospective members before joining and should be repeated at the time of the initial group session when new members are added and subsequently woven through the treatment process.

## Therapist's Role

The group leader assumes a major, but not the sole, responsibility for the treatment. The therapist's special role is established in part by the agreement. Within that framework, clinicians begin to shape the group to provide participants a way of using their experience to learn about themselves. Assuming that patients' optimal learning emerges from a focus on within-group transactions, psychodynamically oriented therapists try to find ways of helping members examine resistances and defenses against such engagement. In contrast, clinicians using a more strictly interpersonal (Yalom and Leszcz 2005) or a system-centered orientation (Agazarian 1997) may actively instruct members to address one another directly in the here and now. The therapist's interventions contribute to bonding to himself/herself and with one another, thereby furthering cohesion (Billow 2003b). The goals of the different approaches are similar—to use the intragroup processes to promote personal change. Whatever perspective therapists take, they should attend to their own contributions to the group dialogue.

The therapist's focus, however, is not exclusively on in-group processes. Rutan et al. (2007) list six foci for the therapist's attention (Table 90–5):

**Table 90–5 Therapist's Focus**

| | | | | |
|---|---|---|---|---|
| Past | | (here and now) | | future |
| In group | | | | out of group |
| Group as a whole | (subgroup) | (interpersonal) | | individual |
| Affect | | | | cognition |
| Process | | | | content |
| Understanding | | corrective emotional experience | | |

The major but not exclusive focus promoting change is members learning from the here and now of treatment. Groups develop a rhythm in which members might address outside events as a warm-up to exploring in-group interactions, or they might focus on current feelings and then expand on those experiences in respect to their outside lives, in the present, past, or future. Integration of a person's experiences across an extended period enhances feelings of continuity and stability of the self.

In a similar fashion, to-and-fro movement takes place in the therapist's focus from group as a whole, to subgroups to interpersonal to individual. Whole-group processes seldom completely disappear. Group-as-a-whole interventions tend to address individuals earlier developmental levels than do more interpersonal or intrapsychic interventions (Kernberg 1975). Premature group-as-whole interventions may be experienced as insensitive and injurious. Horwitz (1977) proposed that therapists identify a group theme and explore individual experiences linked to the theme before making a whole-group interpretation. (Recent contributions to group as a whole perspective are provided by Kibel 2005, Agazarian and Gantt 2005, and Stone 2005). No matter the level therapists choose to intervene, all levels of the group will be affected by the therapist's activities.

The therapist monitors the ebb and flow of affects. Members' capacity to tolerate intense feelings is enhanced as trust and cohesion increase. A dialectical tension between affect and cognition is seen in members' roles, as they attempt to contain dysphoric states and sustain emotional contacts with one another. Some individuals require cognitive understanding before risking immersion into feelings, whereas others search for affective connections before integrating their experience cognitively.

The therapeutic process is partly fueled by members' repeating of old conflicts and defenses and partly by searching for new solutions to their developmental arrests and conflicts (Stone 2003). Members may unconsciously communicate feelings about their in-group experience through associations to events in their outside world. As such, the associations can be understood as metaphoric communication that informs the treatment process. After a successful interpretation or clarification, associations to external or historical events may represent integration of those experiences into members' psychic structure.

Considerable individual change takes place via the group relationship without overt cognitive integration. The sense of sharing, of being understood, of having needs met, and of being responded to in an empathic manner may stabilize a shaky psychic structure, and, some patients, to their therapist's surprise, may successfully terminate treatment without having achieved understanding (Rutan et al. 2007). These are the powerful forces for change, labeled "corrective emotional experiences." Patients also strive for cognitive integration of their thoughts and feelings, and, through experiencing and then understanding the here-and-now, external, and developmental incidents, they consolidate their learning. Patients are then more prepared to transfer their learning from therapy to situations in their outside world.

## Initiating Treatment

Beginning a group is suffused with anxiety for all involved. Therapists worry, "Will anyone come? Will the members get along? Will they learn to work together? Will affects get out of control?" Patients have similar concerns, and they face the additional tasks of figuring out how to meet strangers and how to use the group to achieve their therapeutic goals.

The therapist provides the initial structure, which can be accomplished by reviewing the agreement and asking individuals to introduce themselves. Following these

introductions, the therapist may continue the process by simply stating that members can continue in any way they wish. Patients are likely to question the therapist about aspects of the treatment. Whether the therapist chooses to answer some questions directly or to explore anxieties underlying questions is a matter of style. However, extended silence is often counterproductive, particularly in initial meetings.

As patients orient themselves to the relatively unstructured situation, they utilize previously learned ways of coping (regression). They search for answers from the therapist as an authority and as the person with whom they have had prior contact (dependency themes), or they cautiously test to determine what they can reveal about themselves to strangers (safety themes). Stories may be told about other novel experiences or of travels that symbolically represent the therapeutic journey. Personal roles will emerge, which fulfill collective needs and modulate anxiety.

A fictive example will illustrate beginning group processes and possible member roles. Following introductions, a member tells the (edited) history of his or her "illness," which may be a harbinger of an emotional leader role. A second person recalls of recent dangerous encounter, a potential cautionary role. A third person inquires how this discussion fits with what the members are trying to do, a potential task role. Finally, someone protests that this is all a waste of time, a divergent, potential scapegoat role. Although each person may be speaking as an individual, each comment might well represent internal aspects of each member that is expressed through another's voice.

In the opening phase, people attempt to orient themselves and determine what can be safely discussed. They are often uncertain about what they have to offer others and commonly share a (false) belief that only the leader has the skills to be helpful. Providing suggestions or antidotes to others' problems is typical early behavior. Making suggestions may be understood as members' efforts to be helpful or as a demonstration of their ineffectiveness, thereby covertly pleading for the therapist's help. Some groups begin with members taking turns telling their story as a way of structuring the treatment and avoiding competitive conflicts. Sometimes a single individual's problems become the primary group focus, suggesting that others may not feel safe in exposing their own difficulties until they determine the fate of the person who has been the center of attention.

Therapists help members bond so that no individual feels isolated. They draw themes from the discussion that helps members appreciate commonalities. Processes of universalization, linking, acceptance, altruism, and feeling that one can be helpful to another (i.e., by observing a behavior or identifying a feeling) are emphasized. A beginning effort is made to focus members' attention on their in-group experiences. However, premature exploration of anger or rage can disrupt a sense of safety and cohesion in early formative phases. Feelings, which may emerge among members, can be displaced reactions to disappointments with the clinician. For example, a member who arrives late may be the recipient of anger in his/her own right, but patients may also be angry that the therapist was unable to control the member's behavior.

In early sessions, the group may seem unstable. Some members may become dissatisfied and terminate treatment, sometimes without notice. Early terminations vary from 20% to 50% of the membership, and therapists must examine the impact of these events on the remaining group, as well as find replacements (Roback and Smith 1987). Repeated dropouts may lead to demoralization among the members.

Despite the stress, the majority of members derive benefit from this treatment phase by sharing problems and experiencing diminished isolation and shame about psychological problems. Not surprisingly, many individuals report feeling better, and, as a consequence of their membership, they may experience a disappearance of somatic or emotional symptoms.

## Treatment Course

Members' level of self and ego development influence the course of the group as a therapeutic agent. Persons suffering from archaic conflicts of trust or psychic safety, as expressed in a variety of personality disorders (the difficult patient), may require an extended period of therapy exploring these issues. Transferences to the group, leader, or peers emerge, which reflect these developmental levels. The group may be experienced as an archaic maternal image: warm and protective or hostile and destructive (Scheidlinger 1974). The therapist may be cast in a similar light or splits may occur in which the therapist is experienced as the bad parent and the group as the good parent. Interactions may be conceptualized in the paradigm of self-psychology, with the therapist being experienced as an idealized self-object.

For some individuals, achieving a treatment alliance in which others are experienced as separate and unique may be a sufficient treatment goal. Stabilizing the self, as a result of feeling understood or accepted, may be sufficient for some patients who may terminate treatment, often to the surprise of the therapist (Stone 1985).

Patients gradually learn to address their in-group transactions. Use of tension-deflecting mechanisms diminishes or is more quickly recognized (e.g., scapegoating, invoking humor, or externalizing), and members assume leadership in redirecting derailed conversations. Members develop a useful group memory and make linkages between current interactions and past meetings as part of the working-through process. Triangular themes emerge, and patients examine competitive strivings and their envy, jealousy, guilt, and shame (Alonso and Rutan 1988). Their sense of efficacy is enhanced as they experience themselves capable of becoming truly empathic and contributing to group work.

Individual termination represents an important emotional phase in treatment. Until a person successfully terminates therapy, groups do not reach their full potential. The therapist may be aware of patients' readiness to terminate treatment before a member will directly address leaving. Some therapists ask members to remain for a specified number of sessions after announcing a decision to leave. Members generally resist fully facing the feelings associated with saying goodbye. Some persons abruptly announce that they are leaving in the following one or two sessions, an all too brief goodbye. Optimally, members will discuss their thoughts about terminating over the course of a number of sessions before making a final decision. Then a future date should be set.

Terminations often stimulate regression that enables the departing person to gain additional self-knowledge. Other members become embroiled in feelings of saying goodbye, becoming critical of the decision or searching for

defects in the departing member that would contraindicate termination. Envious or shameful emotions fuel these interchanges. The therapist must carefully assess the situation and may need to "protect" the person's decision to leave. Affect contagion from members' anxieties over loss may spread to the leader and interfere with his/her judgment. Moreover, therapists may experience countertransferences over losing a member who significantly contributed to the process (Karterud and Stone 2003). Patients may wish to celebrate departures with a party or exchange of gifts. Careful discussion may help determine the value or the defensiveness of such rituals (Shapiro and Ginzberg 2002). In most instances, the patient's final session is filled with considerable sadness as well as pleasure.

## Special Treatment Considerations

### Dreams

Many therapists encourage members to present dreams by including in the agreement that dreams may be helpful in understanding not only the individual but also aspects of the group itself. Some dreams directly portray members and/or the therapist, whereas others may dramatize emotionally laden collective situations, seemingly unrelated to the group experience (Stone and Karterud 2006).

The dreamer should be provided an initial opportunity to examine the dream. The therapist may inquire if others have responses and, after their associations are made, may ask about feelings or unexplored dream elements. An important clue to the meaning of the dream may be in the interactions that immediately precede the dreamer's report or in the associations following inquiry of the dreamer and other members. Complete analysis of dreams is infrequent. Dream work may help surface many unexpressed conscious feelings, expose unconscious conflicts, and facilitate more direct interaction.

### Scapegoating

Group psychotherapy has been called a hall of mirrors (Foulkes 1961), where aspects of oneself are seen reflected in others. Scapegoating is the process in which individuals, by "observing" characteristics in another that are unacceptable in themselves, try to deny their feelings and place them solely in the "offending" person. This process, involving projective identification, is frequently activated during treatment and is by no means entirely conscious (Cohen and Schermer 2002).

Many affects, such as anger, envy, or romantic feelings, may serve as stimuli evoking scapegoating. If the affective intensity is magnified, through emotional contagion or personal vulnerability, and the scapegoat is isolated or extruded, the group is depleted because these affects become walled off and unavailable for examination.

The therapist protects the scapegoat and helps members expand their emotions through assisting them in "taking back" feelings attributed solely to the scapegoat. A simple illustration is members' anger with an individual who habitually arrives late. That person might be accused of wanting to avoid the group. Analysis of the members' vitriol may reveal that they are avoiding their own wishes to distance from the group. Such an analysis links the scapegoat to others and decreases an isolating experience.

### Nonverbal Communication

Patients communicate powerful feelings nonverbally. Discrepancy between verbal and nonverbal messages is confusing, but frequently the latter element is perceived as the "truth." Patients may tell sad stories and laugh, or they may relate a success in a dreary manner. Seating arrangements may reflect important emotions. Members may pull their chairs outside the group circle, sit close to or opposite the therapist, shift position in their chair, or not look at one another during emotionally laden interchanges. White knuckles, crimson blushing, or a black dress are additional colorful communications.

Patients learn to address these behaviors as meaningful communications. However, many times the person may be unaware of sending nonverbal messages, and confrontations can be experienced as intrusive and threatening. Stereotyping certain behaviors as carrying predetermined meanings is a common error, and patients learn, sometimes through painful experience, that the sender may have highly personal meanings attached to the behavior. Exploration of nonverbal behaviors often is a powerful entry into the recipient's and the sender's current and past emotions.

### Difficult Groups and Patients

All clinicians, regardless of experience, find their groups difficult some of the time. Therapists may feel incompetent when they are destabilized by the group process, content, or emotions. Inexperienced clinicians have greater difficulty regaining their equilibrium and may feel unable to do so (Rutan et al. 2007). Such difficulties may arise from the selection and mix of patients, which interfere with the group making progress in accord with the clinician's therapeutic ambitions.

A number of individuals who appear to be good group candidates subsequently prove to benefit little from participation or obstruct the treatment process. These individuals, generically labeled "difficult patients," can be conceptualized as having significant relational problems that interact with a particular group culture (Roth et al. 1990). Although such individuals are often diagnosed as having borderline or narcissistic personality disorder, not all difficult patients can readily be given those specific diagnoses. Nitsun's (1996) felicitous expression, "the antigroup," characterizes these individuals as having the potential to disrupt the entire therapeutic endeavor.

The difficult patient should be seen in context. Some groups can accept individuals who seldom speak, whereas others see such a person as seriously harming cohesion and, therefore, as "difficult." Difficult patients fill roles and are frequently labeled "monopolizer," "help-rejecting complainer," or "the silent one." The role embodies both the individual personality and the group function. Evidence for this assertion is found when the difficult individual is removed and another rises to fill his or her place, which suggests that, in part, the role was necessary to deal with members' anxieties.

A careful examination of the processes involved in the emergence of a difficult patient may expose that such individuals are covertly coconstructed by others in the group (Gans and Alonso 1998). Interactions among members and the therapist tend to evoke and/or exaggerate particular character tendencies of members who often have underlying

issues of forming intimate relationships. The therapeutic challenge is to deconstruct the processes so that all can see their contributions to the difficult individual.

Nevertheless, some patients persist in behaviors that do not change or become destructive to the treatment process. They evoke responses in others, including the therapist, that interfere with a sense of safety, limiting members' willingness to expose their inner thoughts and feelings (Stone 2001). Many difficult patients seem unable to process their interactions cognitively but remain enmeshed in emotional exchange. Others may interrupt emotional exchange with intellectual dissertations.

Not infrequently, these individuals prematurely terminate treatment, leaving those remaining with feelings of relief, frustration, and anger. Other difficult patients remain in the group, and at times the therapist is faced with making a decision that favors the group over an individual. The patient is informed that she or he is not benefiting from the treatment modality and is asked to leave. Such a decision should be reached only after the therapist has completed a thorough self-scrutiny and has sought consultation to explore countertransference contributions to the impasse.

## Alternative Treatment Formats

### Cotherapy

A cotherapy format provides opportunities for clinicians to learn from one another, share leadership responsibilities, increase member recruitment, and provide continuity in the absence of one leader. Therapists can directly observe another clinician's work and learn about countertransferences. In the treatment process, when one therapist is engaged in a particularly stressful interaction, the second clinician can have sufficient distance to help understand the situation. The model is most often utilized for training neophyte therapists who can be paired with a more experienced therapist. For patients, this model is thought to offer a recreation of the family, as therapists are cast in parental roles, whether or not the therapists are of the same or different gender.

The conduct of cotherapy is not without difficulties (Lang and Halperin 1989). Cotherapists are susceptible to a variety of transference responses to one another, most commonly competitive and narcissistic strivings. These emotions may be artfully stimulated by the members. Therapists should routinely schedule time to review their emotional responses to one another and to the members, in order to keep their relationship on course and enhance their therapeutic efficacy.

For patients, cotherapy offers opportunities to observe two individuals working together and observe how their relational problems are addressed. In their transference or realistic responses, they may assign roles or split cotherapists into good and bad. These responses may either derail treatment or provide new opportunities for therapeutic growth. Consultation is advisable when therapists seem to reach an impasse in resolving conflicts or the group seems stuck.

Determining fees for cotherapy sessions is complex. Some therapists set a fee for the session that remains the same with one or both therapists present. This is compatible with insurance policies of paying for a service. Some cotherapists charge individually and only when they are present. Therapists should be prepared to explain their policy but also to examine responses to whichever policy they choose. Money is a difficult topic in our culture and often evokes countertransferences.

### Concurrent Therapy

The practice of combining individual and group psychotherapy has gained considerable acceptance. Patients may be seen either by the same (combined) or by a second (conjoint) therapist. Each modality potentially complements the other. In dyadic settings, therapists can focus in greater detail and more readily explore developmental (transference) contributors to group transactions. Similarly, material brought into focus in the dyadic setting can be explored as it is displayed in the group.

In the combined model, therapists have opportunities to observe individuals in both settings. Most therapists draw a clear boundary between the two modalities—that is, they will not introduce information into the group that was learned elsewhere; the patient is encouraged to assume that responsibility (Lipsius 1991).

In the concurrent model, the majority of therapists obtain the patient's consent to communicate about the treatments. For some, absence of consent rules out this treatment arrangement. Therapists, by exchanging information, inform one another to the emerging transferences. The format may stimulate splitting, in which a patient may denigrate one treatment and idealize the other. Through consultation with one another, therapists can sort out precipitants for those behaviors and diminish the potential for countertransference responses and unproductive treatment experiences.

Not uncommonly, some group members may be treated in concurrent formats, whereas others are not. These arrangements stimulate direct questions or allusions to specialness, favoritism, and degree of illness that require exploration, e.g., persons in concurrent treatment may be viewed as sicker, or getting special attention. Generally, the patient may be the one to initially reveal his/her individual sessions to the group. The timing of such references often carries considerable meaning that can be examined therapeutically.

### Pharmacotherapy and Group Therapy

Combing pharmacotherapy with dynamic group psychotherapy is widely practiced. Inclusion of medicated individuals broadens the population available for treatment. Medications are often seen as helping patients focus effectively and thereby make greater therapeutic gains. Arguments against combining psychotropic medication with group therapy include therapists' belief that medication interferes with patients feeling ownership over themselves. Nonmedical therapists may be adverse to introducing medicated patients to their group because of problems in collaboration with physicians.

A common dynamic process is exposure of attitudes derogating medicated members and a "we–they" split, which may result in medicated patients becoming scapegoated as "too ill". Focusing on medication may become a group resistance. Discussion of treatments of other medical illnesses that involve medications (diabetes, hypertension, and arthritis) may also contain displaced emotions regarding psychotropic drugs.

## Time-Limited Groups

As pressure mounts to conduct therapy more rapidly, interest in time-limited groups has increased (MacKenzie 1997). The number of sessions may range from 12 to 30. Many insurance companies limit coverage to 20 sessions, and thus a 16-session model allows for preparatory interviews and, if necessary, one or two sessions after termination of the group.

Groups may be organized along specific symptom constellations, such as bereavement, sexual abuse, bulimia, or anorexia nervosa, or they may explore a personality trait (assertiveness and anger control) with the expectation that the individual will continue to utilize the learning after termination. Therapists may opt to organize groups to provide support (e.g., during a crises) or with patients able to work in an interpretative mode. Applicants should be assessed for capacity to reflect on themselves and their interactions, and on their ability to find a focus for their work. Difficulties should be formulated in interpersonal terms to facilitate the exploration of the problems in the group setting (e.g., a delayed grief reaction, Piper et al. 2001).

In most models, once treatment begins, additional members are not accepted to the group. The agreement is similar to that of longer-term groups, with the exception that the number of sessions is limited. Using this format, the therapist needs to be more active in defining the focus for the members and attending to the therapeutic alliance. Interventions are most effective that focus on interpersonal exchange, which also reflects the stage of group development. Time-limited groups can be particularly useful in addressing issues of engagement, trust, unfulfilled hopes, separation, and loss. The combination of time pressure, maintaining focus on interpersonal processes, and providing encouragement to apply learning in the external world has produced a treatment format that may be as effective as individual treatment (Budman et al. 1988).

## Cognitive-Behavioral Group Therapy

Cognitive-behavioral group therapy (CBGT) is an adaptation of the dyadic treatment format to the group setting. One of the cornerstones of the cognitive-behavioral therapy (CBT) approach is the concept that one's thoughts, beliefs, and assumptions (i.e., interpretations) of events can lead to overly negative (or unrealistic) thoughts. The purpose of cognitive restructuring is to identify less negative (or more realistic) thoughts, which will then expand options available to the individual and alter depressive and anxious feelings. This evidence-based treatment has been applied to a broad spectrum of disorders and patient populations (White and Freeman 2000, Bieling et al. 2006). Suls et al. (2000) list 10 common CBT methods that are utilized both in individual and in group settings:

1. recording of automatic thoughts;
2. challenging the thoughts—what is the evidence, what are alternative interpretations;
3. mood monitoring—use of checklists;
4. developing hierarchy of arousal—stimuli cause anxiety;
5. active monitoring—keep records during the day;
6. problem solving—no single answer, multiple solutions;
7. relaxation strategies;
8. risk assessment—counters "catastrophizing";
9. treatment protocols—embedded within a therapeutic relationship;
10. relapse prevention—learn to identify and deal with triggers.

Patients are offered a description of the therapeutic value of group participation. Groups are generally time limited (10–sessions), and the therapeutic value of group treatment is outlined, which would include vicarious learning, universalization, altruism, hope, and a public commitment to change (Heimberg and Becker 2002).

Individual interviews are employed to assess and prepare applicants for group treatment. During these interviews, patients are introduced to the principles of CBT. Included in the general criteria for participation in a group are patients' abilities to help others and a commitment to change. Exclusion criteria are similar to those of psychodynamic groups, including persons whose fear of groups was too great, active use of illegal substances, or acute situational disorders. Patients using anxiolytic or antidepressant medications may be included, often with the goal of discontinuing these medications as symptoms improve. Group size is from four to six. Sessions typically range from 120 to 150 minutes. Groups are led singly or with cotherapists.

The group sessions are semistructured; usually the first session orients patients to the procedures, the middle sessions are used to work on the problems, and the final session focuses on change during the treatment, consolidation of learning, and anticipation of the future, with attention to relapse prevention. In the orientation session, therapists provide an overview of the therapeutic procedures, generally including a member's check-in and report of homework, developing an agenda or topic, working on members' experiences or thoughts related to the topic, determining homework for the next sessions, and completing weekly outcome measures. In the middle phase, sessions are devoted to exploring members' hierarchy of automatic thoughts and core beliefs. For anxiety disorders (social anxiety, phobias, or panic disorder), the hierarchy consists of the feared situations, and they are addressed in the group and in the members' lives as part of the homework. In some approaches, the therapist lists members' suggestions for topics or issues on a chalkboard, and members vote on which topic will be addressed. In other models, the members take turns in introducing the topic for discussion. In the final phase, members are asked to review their progress, consolidate their learning, and attend to triggers that may lead to recrudescence of symptoms.

During the middle phase, considerable emphasis is placed on cognitive restructuring. At the beginning of each session, homework is reviewed. Failures to complete homework are viewed as opportunities to explore automatic thoughts that have interfered with completion of the task. The topic of the session is established. Fearful situations may be role played or may be imagined, and automatic thoughts challenged, looking for evidence for or against the feared outcomes. The therapist monitors members' level of arousal, or tension, and assesses progress in the direction of mastery and pleasure. The therapist may ask Socratic-type questions eliciting alternative adaptive responses. Members are taught not to give advice and that no single solution is "correct." Members are engaged in considering adaptive alternatives to their habitually feared outcomes. In some groups,

relaxation exercises and meditation are included as additional adaptive strategies.

Group dynamics are activated by empowering the participants, diminishing dependency, and promoting cohesion. Members have opportunities to see how they are faring by reviewing the status/outcome measures, thereby providing evidence for their state of progress. These models emphasize problem solving (adaptive responses) and minimize exploration of intragroup conflict. Norms develop that help members assist one another in facing feared situations or conflicts, which then enhance self-efficacy.

Some models limit treatment to a single series of sessions. Others have follow-up sessions, which serve to reinforce learning or then move to individual treatment to explore difficulties in further depth. Outcome is measurable, and patients can see for themselves what they have achieved.

## Persons with Persistent and Severe Mental Illness

This special population of patients requires modification of traditional dynamic approaches (Kanas 1996, Stone 1996, Schermer and Pines 1999). The population is broader than individuals with major psychiatric disorders (schizophrenia or bipolar disorders) and includes some disabling anxiety or personality disorders. Indeed, chronicity is determined primarily by duration and disability rather than by diagnosis. In some instances, groups are organized homogeneously for patients with schizophrenia or bipolar disorder. These groups often emphasize the importance of continuing with medication and include significant educational components. They may have greater structure and focus on particular topics, such as managing hallucinations, paranoid thinking, or social relations (Stone 1996).

More typically, groups are structured to include a spectrum of patients within a relatively small range of impairment. Patients are prone to attend erratically, and a flexible format that accepts this propensity may serve these individuals well (Stone 1996). The sessions last 45–75 minutes, and the group census may range from 12 to 16 persons. In the flexible format, core and peripheral subgroups develop, and, over extended periods, groups develop a sense of continuity and cohesion.

Treatment goals should be concordant with patients' strengths and are generally formulated to help adapting to everyday problems, improving social relations, and managing feelings. The agreement is modified, and patients may be encouraged to socialize outside of the meetings. Therapists attempt to help patients manage their isolation and sense of shame over their illness.

Countertransferences require particular attention in part due to the difficulty patients have in linking to their therapists, which may leave the clinician expecting more than the patients can deliver. Moreover, in the current climate, particularly for major mental illness, medications are valorized, and therapy is depreciated, a state of affairs that affects the therapist.

## SH Groups

The SH group movement, emerging from Alcoholics Anonymous, is a massive, varied, and not fully delimited social phenomenon. It has been estimated that upward of 12–14 million people participate. SH groups are widely available for almost every illness, experience, or social problem. Groups are advertised in local newspapers for widely varied conditions, including bereaved parents, siblings of children with special needs, and multiple sclerosis patients. SH groups can be conceptualized with an overarching perspective that "all are collections of fellow sufferers in high states of personal need and that all require some aspect of the personal and often painful affliction to be shared in public" (Lieberman 1993, p. 293). Groups are held face to face and more recently through the Internet. Common characteristics of the SH group include: (1) a similar presenting problem, an illness, status, or problem. (2) expectation of reciprocal help among the members. (3) indigenous leadership. (4) no fees, minimal charges, or voluntary contributions (Goodman and Jacobs 1994). Common goals include mutual support, normalization of condition or social situation, sharing of information, developing coping skills, and reality testing.

SH groups are not defined as therapy; participants do not define themselves as patients or clients. They have emerged for many as an alternative or a supplement to medical care or social or emotional needs.

SH groups develop their own structures and norms, with considerable variation in frequency, duration, and membership. Leadership is generally provided by indigenous members. Members, thereby, are both providers and consumers (Yalom and Leszcz 2005). Professional leadership is uncommon, but professionals may be involved through referrals, as consultants to the process or for information, or members.

Mutual sharing is the bedrock of the SH group. Therapeutic factors include catharsis, universalization, altruism, cohesion, gaining information, imitative behavior, and hope. The group process is characterized by greater emphasis on listening and acceptance, with less questioning, with acceptance of others illness or emotional state. Responses often reflect similarity of the difficulties, which increases cohesion and potentiates further self-revelation of members' shameful or guilty secrets. Conflict and working with relationships within the group are generally eschewed. Conflict may be addressed through generalizations and suggestions for alternatives to anger. Relief or change of the participants does not follow a planned, structured, or initiated intervention according to any theoretical approach.

SH groups have emerged in the Internet and expanded opportunities for participation to individuals who are unable to physically belong, either through distance or through infirmity. The PEW survey estimated that 15,000,000 visited an online group during 2003 (Pew Internet & American Life Project 2003). They may be professionally led and held at specified times or, similar to chat rooms, may be available 24/7. Internet groups have the potential for greater anonymity, which may provide safety and more selective participation. Drawbacks include lack of personal information, the potential for dissembling, uncontrolled exchange of angry feelings, crude aggression, or only selective reading of postings. The effectiveness of Internet groups may be equal to face to face groups (Lieberman and Russo 2001–2002).

SH groups fulfill an important social need. After an initial period of caution, they are generally embraced by the medical and psychological communities as a resource that can provide additional assistance that may not be available in the mainstream of care.

Individuals have been shown to benefit by combining participation in an SH group concurrently with another traditional medical treatment (Owen et al. 2004).

## Treatment Failures

Treatment failures may be examined from an individual or group perspective. Failures may be further classified by individuals who fail to benefit and those who are harmed by the treatment.

Among those who do not benefit or may be harmed are many individuals who terminate therapy prematurely and/or abruptly. The early treatment dropout rate is substantial (Roback and Smith 1987) and can probably never be reduced to zero. Patients terminate treatment prematurely because they have been poorly prepared, have wished for supportive rather than dynamic treatment, or find themselves in a confrontational atmosphere. Occasionally, patients may be placed in a group that functions at a level substantially different from that of their own development. Patients in a sustained divergent role (monopolizer, scapegoat, help-rejecting complainer, or isolate) often invite rejection and, in that respect, repeat previously learned patterns. Some patients initially reveal themselves extensively, feel overexposed, and abruptly terminate treatment.

Other forms of treatment failure include individuals who may remain for extended periods, participating in their stereotypical patterns, without any evidence of change. Certain patients continually violate group boundaries, and their behavior seems impossible to change after examination of collective and individual factors. Extragroup socializing (which might include sexual liaisons), inability to refrain from attacking others, and schedules that preclude regular attendance are examples of situations that suggest that continued treatment might be harmful. For individuals who do not seem to change or cannot adjust to therapeutic norms, an open discussion might lead to a mutual decision to discontinue the treatment format.

Countertransference feelings may be a signal of treatment failures. Overestimation of patients' abilities to benefit from dynamic treatment evokes frustration in the therapist, which may be communicated to a patient who then terminates treatment. Therapists who find themselves experiencing extended periods of boredom, frustration, or anger may be reflecting group-wide affects (via projective identification). The members may be attempting to communicate through this channel their experiences of being stuck or that the therapy is ineffective. Therapist's affect can be very useful in identifying. Such co-constructed therapeutic impasses (Gans and Alonso 1998). In groups where there have been multiple treatment failures or dropouts the therapist may benefit from consultation.

## Research

Research in treatment outcome in group therapy is considerably more complicated than dyadic treatment. Group treatment adds a large number of elements that must be taken into account. Some of these elements are the type of group (psychoeducation, cognitive, cognitive behavioral, interpersonal, supportive, or psychodynamic), duration of treatment, length and frequency of sessions, experience of the therapist (trainee or seasoned), age (children, adolescents, and adults), functional level (chronically mentally ill or "typical" outpatient), personality factors such as self-reflective capacity, and the more complex question of patient–therapist fit.

Several large meta-analyses of the effectiveness of treatment have been conducted. Toseland and Siporin (1986) reviewed 32 well-controlled experimental studies and reported that in 24 (75%) no significant differences were found in effectiveness between individual and group treatments; in the other eight (25%), group treatment was more effective. Tillitski (1990) conducted a meta-analysis of nine studies that compared group, individual, and control conditions within the same experiment. Group and individual therapies yielded similar outcomes, and the average effect size indicated that 80% of the treated patients were improved in comparison with the control group.

Lorentzen (2006), reviewing group outcome literature, concludes:

1. Group psychotherapy is better than placebo or wait-list control conditions.
2. Group psychotherapy has an equivalent effect on individual psychotherapy or other psychological treatments.
3. Therapies of different theoretical persuasions give equal results (p. 323).

He notes that these are aggregate level results and suggests that nonspecific relational factors are present in all psychotherapies. No outcome studies of long-term dynamic group treatment have been reported in over a decade.

A study of patients randomized either to time-limited individual therapy or to group therapy was reported by Budman and colleagues (1988). On multiple measures, patients in both treatments showed similar improvement and maintained these changes at a 1-year follow-up. The authors carefully reported that almost nine times (26 vs. three) the number of patients withdrew from the study after they were informed that they had been assigned to group treatment (i.e., they had time conflicts, job changes). Moreover, patients' subjective responses indicated a strong preference for individual treatment.

Reviews of research in group psychotherapy proposed that greater attention needs to be paid to the characteristics and preparation of patients and group composition (Dies 1993, Piper 1993). The fit of patients in a particular group may well be instrumental to outcome. Patients' coping styles may differentially interact with the type of therapy (cognitive, focused expressive, and supportive) and affect outcome. A valuable addition to the group research literature focuses on the variety of measurement systems used to assess change (Beck and Lewis 2000). Piper and colleagues (2001) investigated two patients' personal characteristics (quality of object relations [QOR] and psychological mindedness [PM]) with either interpretive or supportive forms of time-limited short-term group therapy for patients with "complicated grief." Patients in both therapies improved, although those with high PM did better. For grief symptoms, an interaction was found with high QOR doing better in interpretive therapy and low QOR doing better in supportive treatment.

The complexity of conducting research has limited continuing efforts to define more precisely many of the elements contributing to that success. A somewhat worrisome

tendency is for clinics under pressure from funding agencies to substitute consumer satisfaction in place of other evaluative measures. As the study of Budman and coworkers (1988) illustrated, there may be dissociation between improvement and satisfaction, particularly in short-term group.

## Training

Therapists with a background in dyadic treatment do not find the shift to conducting groups simple. Adequate training is necessary to ensure that the therapist and patients alike have a satisfactory experience (Alonso 1993).

The components of training include: (1) didactic presentations. (2) opportunities to observe groups conducted by experienced therapists. (3) participation as a member in an experiential group or as a patient in a therapy group. (4) coleadership of a group with an experienced clinician. (5) solo leadership of a group (Alonso 1993). Supervision is essential to assist therapists in achieving increasingly sophisticated understanding of group dynamics and process, intervention options, transferences, and countertransferences. An important additional element of training in groups is exploration of ethical issues, including confidentiality, dealing with sexual contacts (between patients and those involving the therapist), dangerousness, and informed consent (Lakin 1991).

Therapists are subjected to many powerful emotional forces evoked by the group setting, and they often try to translate individual approaches to the multiperson setting, where dynamic forces have a different impact. Increased awareness of these forces is gained through participating in a group. The American Group Psychotherapy Association offers brief group experiences at their annual conference and regional societies, or independent psychotherapy training centers may provide additional opportunities to participate as a member.

The most important element in training is supervision. Beginning supervision is most often provided individually. However, many therapists continue supervision well beyond learning the basics, and they often participate in small-group supervision of their therapy endeavors. This format provides support and an opportunity for the therapist again to reexperience group dynamics in action. Often unconscious aspects of the therapist's behavior (countertransferences) emerge in the supervisory group in a manner that can be utilized to gain greater understanding of the therapeutic process.

Many graduate-level training programs (psychiatry, psychology, social work, and nursing) provide only a modicum of training in group dynamics and therapy, and clinicians turn to other training settings, which may include a 2-year program combining the elements described earlier.

## The Future

While, historically, group psychotherapy was sometimes misrepresented as a less expensive, watered-down treatment, the overall research findings and clinical impressions have helped establish it as an effective, cost-efficient, and rigorous therapeutic modality applicable to a wide variety of patient problems. It provides a more direct experience for patients working with peers, as well as with those in "authority." The individual's difficulties with people are not limited to the experience of a particular individual therapist but emerge in the relational context of a number of individuals, thereby broadening the entire treatment context. In this era of emphasis on cost containment and efforts to provide rapid, brief therapies, groups can provide for some a positive time-limited treatment and for others an extended opportunity to address and alter significant intrapsychic and interpersonal difficulties.

Effective group treatment, like any other therapeutic modality, depends on opportunities for training and ongoing exchange among colleagues to enhance skills and provide the best possible treatment experience for group members.

### Clinical Vignette 1

In the opening minutes of a new group's first session, a member asked the therapist how he would like to be addressed—as "doctor" or by his first name. He did not reply. Subsequent associations included several references to rudeness, followed by emergence of angry and destructive themes, quite uncharacteristic of a new group. The members appeared to have reacted to the therapist's nonresponse as a narcissistic injury that led to displaced rage.

### Clinical Vignette 2

In a session in which members had been discussing feelings of attraction to one another and consequent jealousies, Ms. K reported the following dream: Ms. L (a member) was in the corner of the room watching some little children. The therapist was having a heart attack, and she (Ms. K) ran out into the hall trying to find someone to help.

Ms. K said that she had been angry with the therapist, and that is why she dreamed about the therapist having a heart attack. A member wondered what kind of help Ms. K was seeking in the dream, leading to a discussion of cardiac resuscitation, which became elaborated into ideas of mouth-to-mouth resuscitation, and then exposed sexual feelings. Ms. L's position in the dream, her interest in playing with the children, isolated her from the competition. Prior and present competitive and romantic feelings among the members and toward the therapist emerged and were more sharply focused in the ensuing discussion. The concrete expression "heart attack" had a clear double meaning of both wishing ill on the therapist for not reciprocating Ms. K's romantic feelings and simultaneously exposing those feelings more directly.

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CHAPTER

# 91 Cognitive and Behavioral Therapies

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The cognitive and behavioral therapies have evolved as an alternative to more traditional nondirective and insight-oriented modes of psychotherapy (Beck 1991, Wolpe 1982, Kazdin 1982, Robins and Hayes 1993). The family of cognitive and behavioral therapies includes a diverse group of interventions. Nevertheless, the treatments share several pragmatic and theoretical assumptions. First, these therapies emphasize psychoeducation: patients learn about the nature of their difficulties and are provided reasons for use of particular treatment strategies. Second, the cognitive and behavioral therapies typically employ homework and self-help assignments to provide patients the opportunity to practice therapeutic methods that enhance the generalization of newly acquired skills outside of the therapy hour. Third, objective assessment of psychiatric illness is an integral part of treatment, and the selection of therapeutic strategies derives logically from such assessments. Fourth, the therapeutic methods used are structured and directive, and as such require a high level of therapist activity (often they are described in treatment manuals). Fifth, for most disorders, the cognitive and behavioral therapies are time-limited interventions. Sixth, and perhaps most important, these therapies are built on empirical evidence that validates their theoretical orientation and guides the choice of therapeutic techniques. Specifically, learning theories (i.e., classical, operant, and observational models of learning) and the principles of cognitive psychology are relied on heavily in constructing cognitive–behavioral treatment models.

## Cognitive Model

The basic theories of the cognitive model are rooted in a long tradition of viewing cognitions as primary determinants of emotion and behavior. Cognitive therapy concepts have been traced as far as the writings of the Greek Stoic philosophers (Beck 1976, Ellis 1989, Dobson and Block 1988) and have been linked to a number of other influences, including the phenomenological school of philosophy, Albert Ellis' rational emotive therapy, and the contributions of Adler and other neofreudians (Wright et al. 2003, Wright et al. 2006). However, the greatest impetus for the development of cognitively oriented therapy has been the work of Aaron T. Beck (Beck 1991, Beck 1976, Beck 1963, Beck 1964, Beck 1967, Beck 1993). For reviews of the historical bases of cognitive therapy, see Dobson and Block (1988), Clark et al. (1999), and Wright et al. (2006). Clark et al. (1999) also provide an excellent review of the philosophical and theoretical assumptions of the cognitive theory of depression.

At the time Beck began to formulate his theories, the predominant treatment approach was psychoanalytically oriented psychotherapy. Freud conceived of depression as the result of anger turned inward (Freud 1950). However, when Beck attempted to study depression from this perspective, he noted that stereotypical patterns of pessimistic and self-critical thinking and distorted information processing were essential characteristics of depression (Beck 1963). This early work led to development of a cognitive model of depression (Beck 1964), the description of specific treatment interventions, and a substantial research effort to study cognitive functioning and treatment outcome in a variety of disorders (Beck 1976, Beck et al. 1979, Beck and Rush 2000, Wright et al. 2003).

Along the way, contributions from cognitive psychologists, behavioral therapists, and other clinical practitioners have been incorporated into the cognitive model (Meichenbaum 1977, Nelson and Craighead 1977, Hollan and Kendall 1980, Lewinsohn et al. 1982, Clark 1986, Dobson and Shaw 1986, Barlow and Cerny 1988, Wright and Thase 1992). The description of cognitive

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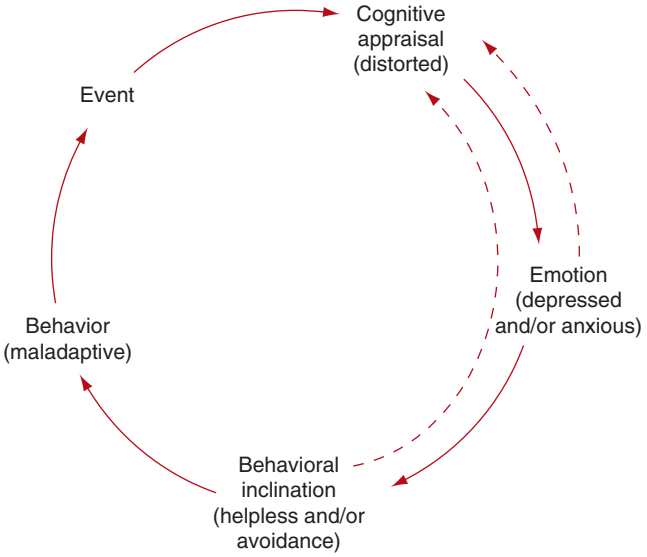



**Figure 91–1** *Reprinted with permission from the American Psychiatric Association.*

theories given here is based largely on Beck's concepts. This model of therapy tends to give somewhat more emphasis to cognitive than behavioral factors in treatment interventions, but both are considered to be integral parts of the model (Figure 91–1).

Depending on the case formulation and the phase of therapy, attention may be directed primarily at cognitive or behavioral aspects of the disorder. In most cases, a combination of cognitive and behavioral techniques is used. For this reason, we use the term cognitive–behavioral therapy (CBT) throughout the chapter unless referring to a specific form of behavioral treatment.

Figure 91–2 displays a simplified model for understanding the relationships between environmental events, cognitions, emotion, and behavior (Wright et al. 2003, Wright 1988, Friedman and Thase 2006). This model is based on the theoretical assumption that environmental stimuli trigger cognitions associated with personal meaning that elicit subsequent physiological and affective arousal (emotions). These emotions, in turn, have a potent reciprocal effect on cognitive content and information processing, stimulating dysfunctional thoughts and worsening negative affect. Thus, the individual's behavioral responses to stimuli and thoughts are viewed as both a product and a cause of maladaptive cognitions. In doing CBT, treatment interventions may be targeted at any or all components of the model.

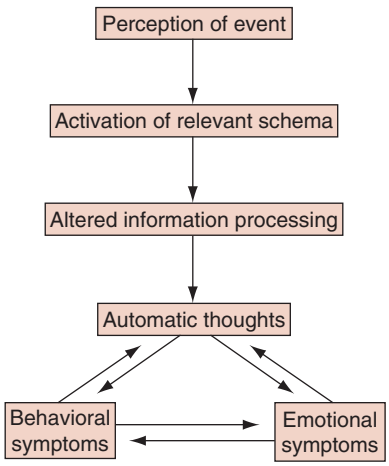



**Figure 91–2** *Cognitive model of information processing.*

Of course, many other factors are involved in psychiatric disorders, including genetic predisposition, state-dependent neurobiological changes, and various interpersonal variables. These influences are also included in the case conceptualization in CBT. Wright and Thase (1992) have outlined an expanded cognitive-biological model that can be used for synthesizing cognitive and neurobiological factors in a combined therapy approach. Contemporary psychiatric research is striving to understand how best to combine and/or sequence CBT and pharmacotherapy, and relate CBT technique to new understandings in cognitive neuroscience. Nevertheless, the working model in Figure 91–2 can be used as a practical template to guide the therapist's case formulation and interventions.

## Automatic Thoughts and Schemas

Dysfunctional information processing is apparent in many psychiatric disorders at two major levels of cognition-automatic thoughts and schemas (Beck 1976, Dobson and Shaw 1986, Teasdale 1983, Segal 1988, Alfrod and Correia 1994). Automatic thoughts are cognitions that stream rapidly through an individual's mind, either spontaneously or in response to some prompt or stimulus. Automatic thoughts may be triggered by affective arousal (i.e., anger, anxiety, or sadness), or conversely, affective shifts are generally accompanied by automatic negative thoughts (Teasdale 1983). Their automatic nature refers to their speed of entry into awareness and their implicit truthfulness. In this way, automatic thoughts have emotional validity (Friedman and Thase 2006). For most people, before therapy, automatic thoughts are usually not examined carefully for validity. In fact, many people susceptible to anxiety or depression often use an affectively biased manner of thinking referred to as emotional reasoning (i.e., "I *feel* that this is correct, therefore it is correct"). Although we all experience automatic thoughts, in depression, anxiety, and other psychiatric disorders the thoughts are distinguished by their greater intensity and frequency (LeFebvre 1981).

Beck (1967) coined the term *negative cognitive triad* to describe the content of automatic negative thoughts. Typically, automatic negative thoughts may be grouped by themes pertaining to (1) self, (2) world (i.e., significant others or people in general), and (3) future. As described subsequently, the themes revealed in one's characteristic automatic negative thoughts can be used to infer deeper levels of cognition: beliefs, rules, and schemas. Once they are comfortable recognizing their automatic negative thoughts, patients can be taught to examine their beliefs and the operational rules that underlie beliefs. Although patients are not fully aware of their schemas (relatively stable cognitive patterns that are the product of ones beliefs, attitudes, and behavioral responses), these cognitions are usually accessible through the questioning techniques used in CBT (Wright et al. 2003).

Beck and coworkers (Beck et al. 1979, Beck and Emery 1985, Wright and Beck 1983) have noted that stereotypic errors in logic (termed cognitive errors or cognitive distortions) also shape the content of automatic thoughts. Examples of these processes include personalization, magnification and minimization, all-or-nothing thinking, jumping to conclusions and ignoring the evidence (e.g., disregarding the positive, or selective abstraction). Definitions of a number of common cognitive errors are included in Table 91–1. Cognitive errors help to translate between the "surface" level of cognition (revealed in automatic negative thoughts) and deeper cognitive structures such as basic assumptions, rules and schemas (Friedman and Thase 2006, Segal 1988, Young and Lindermann 1992). It has been proposed that such apparently illogical thinking during times of heightened emotion may have had evolutionary value (Friedman and Thase 2006). Specifically, cognitive distortions during periods of affective arousal tend to narrow one's focus of attention, simplify information processing, and intensify behavioral responses. Thus, the individual may be primed to respond decisively to the crisis at hand. This is consistent with recent findings that elucidate the neurocircuitry of brain fear pathways (distinct affective and cognitive pathways). LeDoux has shown that activation of the fear pathway causes a sequential activation of affective (limbic-amygdala branch) and cognitive (hippocampal-cortical branch) pathways. However, the affective pathway is shorter allowing activation milliseconds before the cognitive pathway. This primes the system with a sequenced affective/cognitive response to fearful environmental stimuli (LeDoux 1988).

**Table 91–1 Common Patterns of Irrational Thinking in Anxiety and Depression**

| Cognitive Error | Definition |
|---|---|
| Overgeneralization | Evidence is drawn from one experience or a small set of experiences that reach an unwarranted conclusion with far-reaching implications. |
| Catastrophic thinking | An extreme example of overgeneralization, in which the impact of a clearly negative event or experience is amplified to extreme proportions, e.g., "If I have a panic attack, I will lose *all* control and go crazy (or die)." |
| Maximizing and minimizing | The tendency to exaggerate negative experiences and minimize positive experiences in one's activities and interpersonal relationships. |
| All-or-none (black or white, absolutistic) thinking | An unnecessary division of complex or continuous outcomes into polarized extremes, e.g., "Either I am a success at this, or I'm a total failure." |
| Jumping to conclusions | Use of pessimism or earlier experiences of failure to prematurely or inappropriately predict failure in a new situation; also known as fortune telling. |
| Personalization | Interpretation of an event, situation, or behavior as salient or personally indicative of a negative aspect of self. |
| Selective negative focus – "ignoring the evidence" "mental filter" | Undesirable or negative events, memories, or implications are focused on at the expense of recalling or identifying other, more neutral or positive information; in fact, positive information may be ignored *or* disqualified as irrelevant, atypical, or trivial. |

Adapted from Beck et al. (1979).

Schemas represent the sum of one's beliefs and attitudes. They are the basic assumptions or unspoken rules that act as templates for screening and decoding information from the environment (Segal 1988, Wright and Beck 1983, Young and Lindermann 1992). Psychological wellbeing may be understood to represent the development of a set of schemas that yield realistic appraisals of self in relation to world (e.g., "I'm reasonably attractive, but looks aren't everything," "I can be loved under the right circumstances," or "I must work harder to compensate for an average intellect"). Although unspoken, schemas may be inferred from one's beliefs and attitudes. In the cognitive model, dysfunctional attitudes are the structural "bridge" between pathological schemas and automatic negative thoughts. Schemas pertaining to safety, vulnerability to threat, self-evaluation, one's lovability, and one's competence or self-efficacy contain the ground rules for personal behavior that are particularly relevant to the understanding of disorders such as anxiety, depression, or personality disorders (Segal 1988. Young and Lindermann 1992, Blackburn et al. 1986a, Beck et al. 1990). A number of schemas relevant to psychiatric illness are listed in Table 91–2. Bowlby has noted that most psychopathologically relevant schemas are developed early in life, when the individual is relatively powerless and dependent on caregivers (Bowlby 1985).

The cognitive model of psychiatric illness emphasizes the concept of stress-diathesis (Friedman and Thase 2006, Metalsky et al. 1987). From this perspective, a schema such as "I must be loved to have worth," might remain latent until activated by a relevant life stressor (i.e., a romantic breakup). Thus, being "dumped" by a romantic partner may trigger marked emotional response in a person with a "matching" schematic vulnerability but only a normal amount of sadness in someone with a healthier schema (e.g., "The fact that she dumped me means I'm worthless" versus "I am still a worthwhile person that someone else can love") (Hammen et al. 1989). Some schemas may be influenced by neurobiological factors. In panic disorder, exquisite sensitivity to neurobiological signals, such as the evolutionarily ancient "suffocation alarm," may simultaneously trigger noradrenergic arousal and fearful cognitions (Klein 1993). This combination may underpin the schema "I am weak and unable to cope with distress." In recurrent depression, neurobiological changes may exaggerate stress responsivity, undermine the individual's hardiness in the face of adversity, and dampen hedonic capacity (Wright and Thase 1992). As a result, the individual may develop the dysfunctional attitude "I am powerless to change my destiny."

Underlying schemas may be buttressed by either maladaptive or adaptive attitudes (e.g., "No matter how hard I try, I'm bound to fail" versus "I'm a survivor; if I just hang in there things will be okay"), but many of these cognitive structures have mixed features (Wright et al. 2003). Schemas such as "If I'm not perfect, I will fail" may lead to driven obsessional behavior, rigid attitudes and beliefs,

**Table 91–2 Proposed Maladaptive Schemas**

| | |
|---|---|
| | Autonomy |
| Dependence | The belief that one is unable to function with the constant support of others |
| Subjugation-lack of individuation | The voluntary or involuntary sacrifice of one's own needs to satisfy others' needs |
| Vulnerability to harm or illness | The fear that disaster (i.e., natural, criminal, medical, or financial) is about to strike at any time |
| Fear of losing self-control | The fear that one will involuntarily lose control of one's own impulses, behavior, emotions, mind, and so on |
| | Connectedness |
| Emotional Deprivation | The expectation that one's needs for nurturance, empathy, or affect will never be adequately met by others |
| Abandonment-loss | The fear that one will imminently lose significant others or be emotionally isolated forever |
| Mistrust | The expectation that others will hurt, abuse, cheat, lie, or manipulate you |
| Social isolation/ alienation | The belief that one is isolated from the rest of the world, is different from other people, or does not belong to any group or community |
| | Worthiness |
| Defectiveness-unlovability | The assumption that one is inwardly defective or that, if the flaw is exposed, one is fundamentally unlovable |
| Social undesirability | The belief that one is outwardly undesirable to others (e.g., ugly, sexually undesirable, low in status, dull, or boring) |
| Incompetence-failure | The assumption that one cannot perform competently in areas of achievement, daily responsibilities, or decision-making |
| Guilt-punishment | The conclusion that one is morally bad or irresponsible and deserving of criticism or punishment |
| Shame-embarrassment | Recurrent feelings of shame or self-consciousness experienced because one believes that one's inadequacies (as reflected in the preceding maladaption schemas of worthiness) are totally unacceptable to others |
| | Limits and standards |
| Unrelenting standards | The relentless striving to meet extremely high expectation of oneself at all costs (i.e., at the expense of happiness, pleasure, health, or satisfactory relationships) |
| Entitlement | Insistence that one should be able to do, say, or have whatever one wants immediately |

From Thase ME, Beck AT: An overview of cognitive therapy. In Wright JH, Thase ME, Beck AT, Ludgate JW (eds): Cognitive Therapy with Inpatients: Developing a Cognitive Milieu. New York: Guilford Press, 1992:9. Adapted from Young J: Schema-focused cognitive therapy for personality disorders. Unpublished manuscript, Cognitive Therapy Center of New York, 1987.

and frequent bouts of dysphoric or irritable moods. On the other hand, perfectionistic beliefs tempered by realistic expectations and actual achievement can also result in high levels of performance and success.

The concept of attributional style (Hammen et al. 1989) describes an alternative view of cognitive vulnerability. Derived from human studies of the learned helplessness paradigm, (Seligman 1975) attributional style refers to the characteristic way that people explain the causality, controllability, and impact of events. People susceptible to depression are more likely to have an attributional style in which negative events are perceived to be personally controllable (i.e., internality), far-reaching (i.e., globality), and enduring (i.e., stability) (Peterson et al. 1985, Abramson et al. 1989, Sweeney et al. 1986). There is an obvious parallel between the depressogenic attributional style of Abramson and colleagues (1978) and Beck's negative cognitive triad.

In general, studies of people suffering from depression and anxiety have confirmed that pathological information processing is an important part of these disorders. Negative automatic thoughts and cognitive errors have been found to be more common in depressed patients than in control subjects (Dobson and Shaw 1986, Blackburn et al. 1986b, LeFebvre 1981, Watkins and Rush 1983). Similarly, automatic thoughts concerning uncontrollability, threat, or danger have been documented in patients with high levels of anxiety (Kendall and Hollon 1989, Ingram and Kendall 1987). In clinical studies, depressed subjects also demonstrated elevated levels of dysfunctional attitudes (Blackburn et al. 1986b, Simons et al. 1984, DeRubeis et al. 1990), distorted attributions to life events (Abramson et al. 1978, Peterson et al. 1985, Sweeney et al. 1986, Zautra et al. 1985, Deutscher and Cimbolic 1990), and negatively biased responses to feedback (DeMonbreun and Craighead 1977, Rizley 1978, Wenzloff and Grozier 1988). Anxious individuals have been found to have an unrealistic view of the danger or threat in situations (Mathews and MacLeod 1987, Fitzgerald and Phillips 1991), an attentional bias toward threatening stimuli (Mathews and MacLeod 1987), and an enhanced memory for anxiety-provoking situations (Ingram and Kendall 1987, Cloitre and Liebowitz 1991.

Taken together, the results of these studies suggest that disturbances in information processing are essential features of depression and anxiety. Theoretical assumptions and treatment strategies for CBT of many other conditions, including the eating disorders, substance abuse, personality disturbances, and psychoses, have been articulated. The reader is referred to publications on these topics for descriptions of how the cognitive model can be adapted for treatment of a wide variety of psychiatric disorders (Beck et al. 1990, Linehan et al. 1993, Freeman et al. 1989, Beck et al. 1993, Wright et al. 1993, Kingdon and Turkington 1995, Wilkes et al. 1994, Beck and Emery 1985, Wright 2004). Specific applications of cognitive and behavioral treatment strategies are described later in the chapter.

## Behavioral Model

The learning theories underpinning the behavioral therapies date to the work of Pavlov (Pavlov and Gantt 1928) and Skinner (1938). Voluminous laboratory research on learning in animals subsequently established certain lawful relationships in the acquisition and maintenance of behavior (Hull 1943, Mowrer 1947, Spence 1956). Moreover, demonstrations that abnormal or "neurotic" behaviors in animals could be either induced by repeated pairings of a noxious stimulus with a neutral one (i.e., classical conditioning) or shaped by controlling reinforcement schedules (i.e., operant conditioning) suggested that these

approaches were relevant to psychiatric illness as well (Watson and Rayner 1920, Masserman 1943, Skinner 1948, Wolpe 1952, Lindsley 1956).

By the late 1950s, there was considerable dissatisfaction with the medical and psychoanalytic models of psychopathological processes and treatment, particularly from within academic clinical psychology (Kazdin 1982). Such ferment was underpinned by the low levels of diagnostic reliability, even for well-established illnesses such as schizophrenia, (Kanfer and Saslow 1965, Mischel 1968) as well as by the lack of evidence supporting the effectiveness of psychodynamic psychotherapy (Eysenck 1952, Zubin 1953). Moreover, the revolution that has become modern psychopharmacology was still in its infancy and no alternative paradigm at the time had adequate scientific currency. The behavioral therapy movement was thus born, emphasizing the use of scientific principles of investigation with a focus on learned and measurable behaviors (Kazdin 1982, Beck et al. 1990). Further demonstrations of the utility of operant conditioning (i.e., behavior modification experiments in institutionalized, chronically mentally ill patients by use of contingent reinforcement or extinction (Ayllon and Azrin 1968, Ullmann and Krasner 1965) and counter-conditioning treatment of anxiety disorders (such as systematic desensitization (Marks and Gelder 1965, Paul 1966) triggered a surge of enthusiasm for these more objective treatment methods. By the late 1970s, behavioral therapy had become the most academically influential model of treatment outside of the medical setting (Kazdin 1982, Beck and Emery 1985).

The behavioral model is based on the relatively straightforward "chain" of events and responses illustrated in Figure 91–3. Through the years, considerable effort and debate have concerned whether stimulus-response and response-reinforcement relationships could be invoked to account for the complexity of human behavior (Kazdin 1982, Staats 1964). In its maturity, behavioral therapy has broadened beyond an exclusive focus on observable behaviors (i.e., radical behaviorism) and now incorporates cognitive processes and other individual variables that affect learning (Bandura 1977a, Goldfried and Davison 1994). For example, in observational learning, the stimulus-response contingency relationship is established vicariously, by watching, reading about, or imagining the event in question. Reinforcement does not have to take place explicitly; it may occur vicariously, or it may simply be imagined. Other factors, such as the individual's past history, inherent talents, or skillfulness of his or her pertinent response repertoire, help account for the wealth of inter-individual variability in stimulus-response relationships. Bandura's cognitive–behavioral formulation of self-efficacy is one example of a "mental" construct that has abiding behavioral implications. This modifiable attitude or belief (roughly akin to self-confidence) influences persistence, willingness to try new things, optimism, and capacity to endure setbacks (Bandura 1977b).

One of the most important enduring experimental models of depression (learned helplessness) is the direct descendant of studies of animal learning (Seligman 1975, Maier and Seligman 1976, Miller and Seligman 1975). Learned helplessness is a state of behavioral passivity and apparent apathy induced by repeated exposure to noxious, yet inescapable, stimuli. The learned helplessness paradigm is based on a modification of escape or avoidance conditioning. A wide variety of species, ranging from goldfish to humans, can readily learn to avoid or escape from a setting when given advance notice (i.e., a light or tone) of an impending noxious event (i.e., a painful shock) (Maier and Seligman 1976). However, when escape is impossible (e.g., a dog is harnessed, or the walls of the experimental box are too high to be scaled), the animal is observed to be passive and inactive. During such "helplessness training," the animal's affect and behavior shift progressively from a state of apprehensive arousal (perhaps similar to human anxiety?) to one that may be analogous to depression. After repeated pairings, the animal will become unable or unwilling to escape from the stimulus when unharnessed. The parallels to human experiences are obvious, although it is not known if the animal cognates helpless thoughts ("It won't work… why bother to try…I'm better off just to be still") (Oakes and Curtis 1982). Nevertheless, neurochemical and pharmacological studies underscore the phenomenological similarities between learned helplessness and depression (Weiss and Simson 1985, Willner 1991). Further, "helpless" dogs can be retrained to escape with techniques much like those used in behavioral therapy (Klein and Seligman 1976).

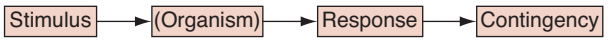



**Figure 91–3** *Chain of events.*

Over the past decade, several researchers have attempted to distinguish the extent to which the behavioral components of CBT are responsible for its therapeutic effect. The BA approach derives from the work of Ferster (1973), Lewinsohn (1974) and Rehm (1977). They hypothesized a link between avoidant (and withdrawal) behavior and the maintenance of depression. They recommended activation strategies that undermine avoidance, reduce antidepressant reinforcers, and increase positive reinforcement from the environment (Dimidjian et al. 2006). Recently, Dimidjian and colleagues (2006) described an "expanded BA model" that included increased focus on assessment and treatment of avoidance behaviors, the establishment/maintenance of regular routines, and behavioral strategies for targeting rumination. This latter strategy emphasizes the functional impact of ruminative thinking and moves away from the analysis of content toward a focus on direct, immediate experience (Dimidjian et al. 2006).

## Cognitive and Behavioral Treatment Strategies

The cognitive and behavioral therapies are well known for their use of specific treatment techniques. Commonly used CBT procedures are directly linked to the theoretical constructs and empirical research of this school of therapy. Although techniques are given somewhat more emphasis in CBT than in some other forms of psychotherapy, there is still considerable room for therapists to be creative and flexible in developing a treatment plan. In fact, novice therapists sometimes focus too much on applying techniques at the expense of nurturing the therapeutic alliance and case formulation (Rush and Beck 1995). Development of a productive therapeutic relationship and an individualized case conceptualization should always take precedence over the implementation of specific cognitive or behavioral

techniques. A number of the more important CBT strategies are described briefly here. More detailed accounts of CBT interventions can be found elsewhere (Beck et al. 1979, Beck 1995, Barlow and Cerny 1988, Freeman et al. 1989, Persons 1989).

## Collaborative Empiricism

As in all effective psychotherapies, the therapeutic relationship is important in CBT. However, interchanges between therapist and patient often differ from those observed in supportive or dynamically oriented treatment. One difference is that the therapist is responsible for managing the pace of the session. Using and adhering to an agenda makes each session as efficient as possible. Another difference is that CBT therapists adopt a therapeutic relationship that emphasizes: 1) a high degree of collaboration and 2) a scientific attitude toward testing the validity or usefulness of particular cognitions and behavior. This therapeutic stance is referred to as collaborative empiricism. The empirical nature of the relationship reflects that therapist and patient work together as an investigative team to develop hypotheses about cognitive or behavioral patterns, examine data, and explore alternative ways of thinking or behaving. At first, therapists usually spend more time teaching and explaining in CBT than in other forms of therapy, yet in the course of therapy, patients are actively engaged to become increasingly involved in the direction and the work of treatment.

Critics of CBT sometimes suggest that the patient-therapist relationship is compromised by the therapist's attempt to "replace" negative thoughts with positive ones. One jaded senior colleague referred to CBT as a "feel good therapy," and another stated that CBT's unspoken strategy was to teach people to lie to themselves. CBT *is* a cautiously optimistic therapy, but effective therapists do not use a "Pollyanna" approach to treatment. The data demonstrating CBT's efficacy, discussed below, is the basis for our prognostic optimism. The collaborative empirical stance requires that the therapist and patient work together to honestly appraise the validity of cognitions as well as of the adaptive or maladaptive aspects of beliefs and behaviors. If a negative assessment proves to be accurate (e.g., the patient actually has made serious mistakes, the individual's spouse is highly likely to leave, or the patient has engaged in a repetitive self-defeating behavior pattern), then the therapist and patient need to work together in a problem-solving mode to develop a plan to cope with the problems at hand or practice more adaptive strategies for use in the future.

Wright and Beck, and others, have recommended several strategies for enhancing collaborative empiricism (Wright et al. 2003, Clark et al. 1999). These include: 1) adjusting the therapist's level of activity to match the patients' symptom severity or the phase of treatment; 2) encouraging the use of self-help procedures; 3) attending to the "nonspecific" variables important in all therapeutic relationships (e.g., empathy, respect, equanimity, kindness, and good listening skills); 4) promoting frequent two-way feedback; 5) devising coping strategies to help deal with real losses or implementing a plan of action to address maladaptive behavior; 6) recognizing transference phenomena; 7) customizing therapeutic interventions; and 8) using humor judiciously. It is also important to recognize and account for the wide variety of individual differences in cultural backgrounds, social attitudes, and expectations that each patient brings to the therapy encounter (Wright and Davis 1994).

## Psychoeducation

Most forms of CBT integrate explicit psychoeducational procedures as a core element of the treatment process. Psychoeducational procedures are typically blended into treatment sessions in a manner that de-emphasizes formal teaching. There is a concerted effort to teach the patient *why* it is important to challenge automatic thoughts, identify cognitive errors, and practice implementing a more rational thinking style. Behavioral interventions are also preceded by psychoeducation to convey the background for principles such as extinction, reinforcement, self-monitoring, exposure, and response prevention.

There are a number of ways in which therapists employ psychoeducation in CBT. Perhaps the most important is the demonstration of basic concepts, which usually begins in the first therapy session (Beck et al. 1979, Thase and Wright 1991). Patients are more likely to grasp and implement therapy concepts when cognitive–behavioral principles are applied to situations that are personally significant. On occasion, therapists may give "mini-lectures," (Epstein et al. 1988) but an interactive and guided method of instruction, called Socratic questioning usually predominates (Beck et al. 1979, Overholser 1993a, 1993b, 1993c).

In the early phases of treatment, special attention is paid to socializing the patient to CBT. The basic cognitive-behavioral model is demonstrated, and expectations for both patient and therapist are conveyed. Some of the frequently used psychoeducational procedures in CBT include brief, impromptu explanations (often written on a chalkboard or a pad of paper to increase the chances of comprehension and retention) and reading assignments (bibliotherapy), such as *Coping with Depression* (Beck and Greenberg 1974), *Feeling Good* (Burns 1980), or *Mind Over Mood* (Greenberger and Padesky 1995), or *Getting Your Life Back* (Wright and Basco 2001). Psychoeducational initiatives typically become more complex as therapy proceeds. For example, detailed explanations and repeated exercises may be needed before the patient fully grasps abstract concepts such as attributional style or schemas. As therapy progresses, homework assignments continue to explicitly reinforce and expand upon material covered during therapy sessions.

As in other forms of learning, individual differences in homework compliance may influence the progress of therapy. For example, some evidence suggests that homework compliance is correlated with treatment outcome (Whisman 1993, Burns and Spangler 2000). We have found that homework compliance is influenced partly by the therapist's consistency, enthusiasm, and ability to integrate the assignments into the treatment plan.

Because psychoeducation can be time consuming and is a routine part of therapy, several investigators have developed computer programs that provide education on cognitive therapy, encourage homework completion, and actively involve patients in self-help exercises. One of the earliest programs, developed by Selmi and coworkers (1990, 1991), was found to be efficacious in the treatment of depression. Although this software relies completely on

written text for conveying information and is not available for clinical use, it demonstrated the potential benefits of computer tools for CBT. More recently, Wright and coworkers (1995, 2002, 2005) have introduced a multimedia form of computer-assisted CBT ("Good Days Ahead") that uses full screen video and vivid graphics to engage users in the learning process. Research with this program has demonstrated strong effects on learning, high levels of acceptance by patients, and evidence for efficacy in the treatment of depression (Wright et al. 2002, 2005). Marks and coworkers (Shaw et al. 1999, Kenwright et al. 2001) have been using a text-based computer program (Fear Fighter) in Great Britain for treating anxiety disorders with exposure therapy. This group has reported significant increases in treatment efficiency when the computer program is used to provide psychoeducation and involve patients in exposure protocols (Kenwright et al. 2001). The use of computers as treatment adjuncts has been reviewed in several publications (Locke and Rezza 1996, Wright and Wright 1997, Wright 2004). Computer-assisted treatment is still in the early stages of development, but there appears to be considerable potential for using these new technologies to augment the process of psychotherapy.

## Modifying Automatic Thoughts

The first step in changing automatic thoughts is to help the patient recognize when she or he is having them. The therapist is often able to illustrate the presence of automatic negative thoughts during the initial session by gently calling attention to a change in the patient's mood. Such "mood shifts" can be excellent learning experiences that give personally relevant illustrations of the linkage between cognitions and feelings. Use of a mood shift to identify automatic thoughts is illustrated in the following interchange.

> ***Therapist:*** *I noticed a moment ago that your mood appeared to change. All of a sudden, you looked very sad. Do you mind if we talk about what was going through your mind?*
> **Patient:** No…but I'm not really sure what you mean…I guess I just felt that this therapy might be too hard to handle.
> **Therapist:** *I'd like to make a distinction between what you thought and what you felt. It looked like you were sad. Am I right? (patient nods) And, at about that time, you had the thought that this therapy might be too difficult? (patient nods) This could be an example of what we call a negative automatic thought. Let's spend a few minutes to see if it is one, and if so, what it might mean.*

One common misconception of CBT is that its practitioners disregard the role of affect or feelings in the etiology and treatment of psychiatric disorders. Actually, one of the principal components of CBT is the stimulation and modulation of emotion (see, for example, Figure 91–1). In fact, Beck referred to emotion as "the royal road to cognition" (Beck 1991). In contrast to experiential therapies, variations in emotion are used in CBT to establish links with cognition and identify errors in information processing. Getting in touch with feelings is thus not a goal in CBT but only a means by which therapy helps patients to gain greater control over the processes that influence their moods and behaviors.

### Socratic Questioning

The most frequently used technique to uncover and modify automatic negative thoughts is Socratic questioning (or guided discovery) (Beck et al. 1979, Overholser 1993a, 1993b, 1993c). Socratic questioning teaches the use of rationality and inductive reasoning to ascertain whether what is thought or felt is actually true. The therapist models the use of Socratic questioning and encourages the patient to start raising questions about the accuracy and validity of his or her thinking. There are few formal guidelines for Socratic questioning (Overholser 1993a). Rather, therapists learn to use their experience and ingenuity to frame good questions that engage the patient in a process aimed at recognizing and modifying a biased or distorted cognitive style. Typical questions include: What ran through you mind at that time? What is the evidence that your impression is accurate? Could there be any alternative explanations? If this were true, what would be the worst thing that would happen? When guided discovery methods are not sufficient to draw out automatic thoughts, the therapist may turn to several alternative ways of eliciting dysfunctional cognitions, as described in the following.

### Imagery Techniques and Role-Playing

Imagery techniques and role-playing are used when direct questioning does not fully reveal important underlying cognitions. When imagery is used, the therapist sets the scene by asking the patient to visualize the situation that caused distress. Although some patients can readily imagine themselves in a previous scene, many need prompts or imagery induction to encourage their active participation in the exercise. Several types of questions can be used to help frame the scene. These include inquiries about (1) the physical details of the setting, (2) occurrences immediately before the interaction, and (3) descriptions of the other people in the scene (Wright et al. 2003). In role-playing exercises, the therapist and patient act out an interpersonal vignette to uncover automatic thoughts or to try out a revised pattern of thinking. This technique is used less frequently than imagery by most cognitive–behavioral therapists and may be reserved for situations in which transference distortions are unlikely (Wright et al. 2003).

### Thought Recording

Thought recording is one of the most useful procedures for identifying and changing automatic thoughts. This technique is first presented in relatively simple two- or three-column versions in the early stages of therapy. When the two-column procedure is used, patients are instructed to write down events in one column and thoughts in the other. Alternatively, they can record events, thoughts, and emotions in the three columns. The purpose of this exercise is to encourage patients to begin to use self-monitoring to increase awareness of their thought patterns. Next, the strength of the emotion and the believability of the automatic negative thoughts are rated on a scale of 0 to 100. In subsequent sessions, a more complex five-column thought record, the thought change record (TCR) is introduced (Figure 91–4). The fourth column of the TCR

| Date | Event | Automatic thoughts | Emotions | Rational thoughts | Outcome |
|---|---|---|---|---|---|
| | a. Describe actual event preceding unpleasant emotion or<br>b. Stream of thoughts, daydream, or memories preceding unpleasant emotion. | a. Write automatic thought(s) that led to emotion(s).<br>b. Rate of belief in automatic thought(s), 0–100%. | a. Specify sad, anxious, angry, tense, and so on.<br>b. Rate degree of emotion, 0–100. | a. Identify cognitive errors.<br>b. Write rational response to automatic thought(s).<br>c. Rate belief in rational response, 0–100%. | a. Specify and rate subsequent emotion(s), 0–100. |
| 1/30/95 | My boss asks for a progress report. | I'm in big trouble. (85)<br>I can't handle this job. (90)<br>I've messed everything up. (95) | Anxious (95)<br>Sad (80) | Magnification, ignoring the evidence, overgeneralization.<br><br>I'm slightly behind schedule, but I can catch up. (95)<br>I've had a good track record with this job. (100)<br>I'm doing O.K. in some other areas of my life. (95) | Anxious (40)<br>Sad (20) |
| | My son comes home late from a party. | Nobody listens to me. (90)<br>He doesn't care. (75)<br>What's the use of trying? (80) | Angry (75)<br>Sad (85) | All or none thinking, ignoring the evidence, personalizing.<br><br>My son pays attention a fair amount of the time, but he doesn't always do what I want. (90)<br>There's plenty of evidence that he cares about me. (100)<br>We need to improve how we communicate. (95)<br>I need to tell him that I'm angry. (100) | Angry (30)<br>Sad (25) |

**Figure 91–4** *Daily record of dysfunctional thoughts.*

encourages the patient to develop rational alternatives that rebut the automatic negative thoughts; the fifth column used for a reevaluation of the mood and cognitive ratings. Work on identifying cognitive errors can also be included in this form of thought recording.

## Examining the Evidence

The examining the evidence procedure is a collaborative exercise used to test the validity of automatic negative thoughts. Cognitions are set forth as hypotheses rather than established facts. The patient is encouraged to write down evidence that either supports or refutes the automatic thought using a two-column form (i.e., pros and cons). For example, examining the evidence for the automatic thought "everyone always looks down on me" might reveal data in support of both sides of the question. It is likely that the patient will recall many times when he or she felt looked down on, treated disrespectfully, or criticized unfairly. On the other hand, it would be virtually impossible that others *always* perceive the individual in this way. Specific evidence of good job performance, positive relationships with relatives and friends, and successes in school or recreational activities may then be used to help counterbalance the patient's negatively biased and overgeneralized automatic thought. More ambiguous examples may also be revealed in which the evidence does not clearly point in one direction or the evidence is not clear. In these situations, the therapist may suggest homework to collect additional information. Cognitive errors such as overgeneralization, catastrophic thinking, maximizing or minimizing, personalization, and all-or-nothing thinking are frequently revealed in these situations (see Table 91–1).

Next, the therapist helps the patient to revise the automatic negative thought in light of the evidence (e.g., "I *often* feel inferior to others, even when there's no good evidence that I should feel that way" or "I have had a number of difficulties with my teachers and employers, but not all relationships have been bad and some have been very good"). The process thus moves from the patient's general and globally negative interpretations to more specific, factually based statements.

When an honest appraisal uncovers evidence in support of negative cognitions, the therapist may choose to focus on the patient's attributions of causality or internality. The patient who posits a negative attribution for poor work evaluation (e.g., "My performance was poor because I don't have what it takes") can usually be aided to consider a more neutral attribution (e.g., "My performance was poor because I was not prepared . . . my depression and lack of motivation contributed to this too"). The treatment plan may also be revised to develop better methods of coping in similar situations or to work on ways of remediating skill deficits. Sometimes, particular difficulties cannot be changed (e.g., physical handicaps,

markedly unattractive physical looks, or severe financial limitations). A trainee once remarked to one of us, "I'm not sure that CBT is the right treatment for my patient. He really is ugly and dumb, and as far as I can tell, no one has ever loved him!" Before turning supervisory attention to the patient's problems, the therapist-in-training was engaged in a guided discovery exercise to clarify his assumptions and beliefs about the essential importance of physical beauty, intelligence, and romantic love. Subsequently, the patient was able to address these issues successfully in therapy as well.

### Generating Alternatives

If automatic thoughts prove to be largely dysfunctional, the patient is encouraged to generate alternatives that are more accurate or factual. Many of the techniques discussed earlier can be used to help generate alternatives to automatic thoughts. Socratic questioning is used in therapy sessions to help the patient start to think more creatively. Also, psychoeducational procedures may be employed to teach brainstorming techniques. For example, the patient may be taught to use "expert testimony" or the opinions of someone who knows her or him well (i.e., a sibling, spouse, or best friend) to help develop less emotional and more rational alternatives. Thought records are often used to record alternatives to automatic thoughts. We often encourage patients to collect their thought records in notebook form for ongoing use. Figure 91–4 illustrates the use of rational alternatives during CBT for a depressed patient.

Many patients with depression, anxiety, and related conditions have relatively rigid cognitive styles that perpetuate dysfunctional thought and behavior patterns. For example, an individual who was given the homework assignment of challenging the automatic negative thought "I am a loser" presented the "realistic alternative" that "whenever I start thinking about how I'm a loser, I will force myself to stop thinking about it". These thoughts about thoughts tend to undermine the credibility of the rational responses and may dampen the patient's enthusiasm for using the procedure. The therapist may notice a particular facial expression or a change in the patient's posture that suggests the existence of second-order thoughts. In such cases, more active therapeutic assistance may be needed. For example, the therapist may need to act as a teacher or coach in the area of adaptive cognitive functioning, rapidly rebutting automatic thoughts as they arise. Coping cards, which are index cards with helpful reminders on the use of CBT methods (in this case, rational responses to repetitive automatic negative thoughts), may be written during sessions and carried by the patient in his or her pocket, wallet, or purse for later use.

### Cognitive–Behavioral Rehearsal

Cognitive–behavioral rehearsal is a treatment strategy that is particularly useful for preparing patients to put their experiences in CBT to work in real-life circumstances. After automatic thoughts have been elicited and modified through procedures described before, the therapist guides the patient in a series of rehearsal exercises to try out alternative cognitions in a variety of situations. By using imagery and role-playing scenarios to practice generating more adaptive cognitions, the patient may become aware of problems that could interfere with implementation of the new style of thinking. Further practice and targeted homework assignments may then be needed before alternative cognitions can be fully used. For example, the effects of cognitive–behavioral rehearsal may be extended to real situations by assigning homework to test use of the modified automatic thoughts.

## Modifying Schemas

The emphasis in the early phases of therapy is usually on behavioral activation, identifying and changing automatic thoughts, and the reduction of symptoms. However, as the patient gains knowledge of cognitive–behavioral principles and acute symptoms begin to subside, the focus of the treatment sessions usually shifts toward work on the schema level. Schemas are relatively stable cognitive patterns that are the product of one's beliefs, attitudes, and behavioral responses. Because schemas serve as underlying templates for the processing of new information, they play a major role in the modulation of more superficial cognitions (automatic thoughts), regulation of affect, self-esteem, and control of behaviors. Thus, schema modification is an important component of cognitively oriented therapies.

With Axis I disorders such as major depressive disorder and panic disorder, schema revision efforts are directed at correcting dysfunctional attitudes that may predispose the patient to symptomatic recurrences. After several months of productive therapy, schema modification may be placed in the context of reducing future vulnerability. CBT of personality disorders typically requires that a major portion of therapy be devoted to modifying schemas and related patterns of behavioral dysfunction (Beck et al. 1990). When schematic work cannot be fully addressed in time-limited therapy, the model of ongoing change may be introduced. Thus, the patient may begin to change her or his "life course" by development of a long-term self-help plan. Jarrett has proposed continuation and maintenance phases of CBT treatment of depression, and she argues for focusing on schema change in these phases of treatment if it is not accomplished in the acute phase of treatment (Jarrett et al. 2001).

Many of the techniques used to test and modify automatic thoughts are also used to identify and revise schemas. Psychoeducational interventions are usually required as a first step. Most patients are not aware of their "guiding principles," so the therapist may need to begin by introducing and illustrating this concept. It is often useful to review the connection between automatic negative thoughts, basic assumptions, core beliefs, personal rules, and behavior patterns using material from the patient's own experience (Wright et al. 2003). Socratic questioning is the core procedure used for schema modification (Beck et al. 1979, Overholser 1993c).

The downward arrow technique (Figure 91–5) is a particularly powerful way to move from surface cognitions to deeper cognitive structures (Friedman and Thase 2006). This technique describes asking the patient a question such as: "If this automatic thought were true, what would it mean about you as a person?" Another useful approach is to examine patterns of automatic thoughts from thought records to sort out common themes. The therapist may suggest themes based on her or his knowledge of the patient's

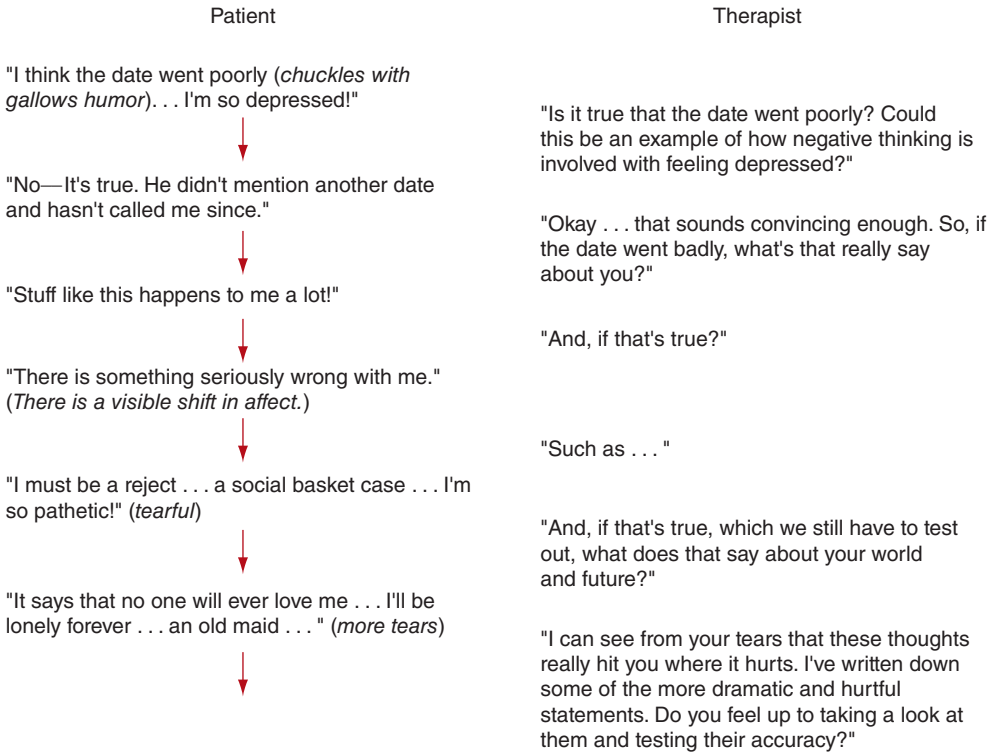



**Figure 91–5** *The downward arrow technique.*

automatic negative thoughts. In some situations, it may be helpful to have patients review a description of common pathological schemas to recognize some of their core beliefs (see Table 91–2). On occasion, it may be useful to have the patient write a brief autobiography to help elucidate the historical antecedents of the schema. Computerized learning programs can also be employed to help patients uncover their schemas and may be particularly useful in teaching patients how to change core beliefs (Wright et al. 2002, 2005). A study comparing computer-assisted cognitive behavior therapy (CCBT) with standard CBT found that depressed persons treated with CCBT had statistically greater change in dysfunctional attitudes than those treated with standard CBT (Wright et al. 2005).

Because schemas are so strongly held (in essence, they have helped define reality and mold behavior for years), they may require intensive work in a number of therapy sessions to undergo significant change. Sometimes long-term continuation and maintenance CBT is required to accomplish schematic restructuring. Therapists can select from a number of CBT techniques, including examining the evidence, listing advantages and disadvantages, generating alternatives, cognitive response prevention, and cognitive–behavioral rehearsal, as they attempt to modify schemas (Wright et al. 2003). Examining the evidence, generating alternatives, and cognitive–behavioral rehearsal were described earlier as methods of changing automatic thoughts.

## Cognitive Response Prevention

In cognitive response prevention, the patient agrees to complete a homework assignment in which she or he must behave in a way that is inconsistent with the pathological schema. For example, a person with perfectionist attitudes may be assigned a task in which she or he must perform in a "so-so" manner. This is intended to activate the schema that is triggering automatic negative thoughts (e.g., "They'll think I'm a sloth" or "I'll never be trusted with an important assignment again"). By not responding to the perfectionist demands dictated by the schema, the individual, thus, has the opportunity to cope with the automatic negative thoughts consequent to this "rule violation."

## Listing Advantages and Disadvantages

The listing advantages and disadvantages procedure is particularly useful when a schema appears to have both adaptive and maladaptive features. Schemas that have damaging effects are often maintained because they also have a positive side. For example, the schema "I must be perfect to be accepted" can have significant benefits (e.g., hard work and attention to detail often lead to success in work or school). Nevertheless, because perfection is seldom possible, the individual may remain vulnerable to setbacks. Other schemas, such as "I'm a complete loser," may not seem to have any advantages at first glance. However, even such a markedly negative basic assumption can reinforce other behaviors associated with it. For example, a person who believes that he or she is a loser may avoid making commitments, withdraw from challenging assignments, or refuse to exert a sustained effort to solve a difficult problem. This strategy may thus protect the person from painful setbacks at the expense of achieving successes. The advantages and disadvantages analysis provides the patient and therapist with essential information for planning modifications. Schemas are most likely to be revised when they take into account both the maladaptive and the adaptive features of the old basic assumption.

In general, it is recommended that patients keep a list of the schemas as they have been identified. The schema

list helps to focus the patient's attention on the overarching nature of these maladaptive principles. Because schemas often become manifest only during periods of increased stress or symptom expression, they may appear to fade in significance as the patient begins to improve. For example, behavioral treatment programs that neither endorse nor aim to modify schemas are generally as effective as CBT in the short run. However, there may be a false security engendered by symptom relief. The cognitive model posits that the individual will remain vulnerable to the depressogenic impact of "matching" life events unless schema revision is accomplished (Friedman and Thase 2006).

## Behavioral Techniques

In CBT, behavioral methods are usually integrated with cognitive restructuring in a comprehensive treatment plan. Behavioral strategies may be given a greater emphasis earlier in therapy with more severely symptomatic patients such as those with intense depression, bipolar symptoms, or schizophrenia (Beck et al. 1979, Thase and Wright 1991, Kingdon and Turkington 1995, Basco and Rush 1996, Scott and Wright 1997). Some cognitive-behavior therapists may rely primarily on behavioral interventions for conditions such as obsessive-compulsive disorder (OCD) or simple phobias. Commonly used behavioral strategies are described here in alphabetical order.

### Activity Scheduling, Graded Tasks, and Mastery-Pleasure Exercises

Depressed people may spend excessive amounts of time alone or have tangible reductions of pleasurable activity. One of the earliest behavioral formulations of depression viewed the disorder as an "extinction state" resulting from the loss of reinforcers (Ferster 1973). Neurobiological changes accompanying prolonged stress may also dampen hedonic capacity, which in turn reduces the salience of reinforcers (Weiss and Simson 1985, Willner 1991). Thus, the learned helplessness paradigm brings together behavioral and neurobiological domains. Depressed operant (i.e., goal-directed) behavior may elicit negative cognitions as well (Teasdale 1983). For example, depressed people often procrastinate against performing potentially "overwhelming" chores or tasks. Procrastination, in turn, elicits guilty thoughts and self-criticisms. Moreover, the depressive cognitive state increases the likelihood that individuals will minimize the positive value of the activities they are able to complete. As a result, it may also be said that depressed people suffer from a deficit of self-reinforcement (Rehm 1977).

One key to the behavioral approach for treatment of depression is the interruption of the downward spiral linking mood, inactivity, and negative cognition (Beck et al. 1979, Lewinsohn et al. 1982) (Figure 91–6). Completing an activity schedule is often the first behavioral homework assignment used in CBT (Beck and Greenberg 1974). Depressed patients are asked to begin to keep a daily log that is used to chart the relationship between their moods and their activities (Figure 91–7).

The nature of the activities is examined, and deficits in activities that might elicit pleasure or feelings of competence are identified. Next, assignments are made to engage in discrete pleasurable activities (or, in the case of an anhedonic individual, activities that were rewarding before becoming depressed). If needed, a Pleasant Events Schedule can be used to identify a "menu" of reinforcers (Lewinsohn et al. 1982). Following operant principles, activities that have been "high-grade" reinforcers in the past are scheduled during times of low moods or decreased activity. Next, subjective ratings of mastery or competence and pleasure are added to the activity schedule by use of a simple scale (i.e., 0 to 5), to avoid the tendency of dichotomous thinking. In this way, achieving a small degree of pleasure or mastery during a scheduled activity may be framed as an accomplishment, particularly early in the course of therapy.

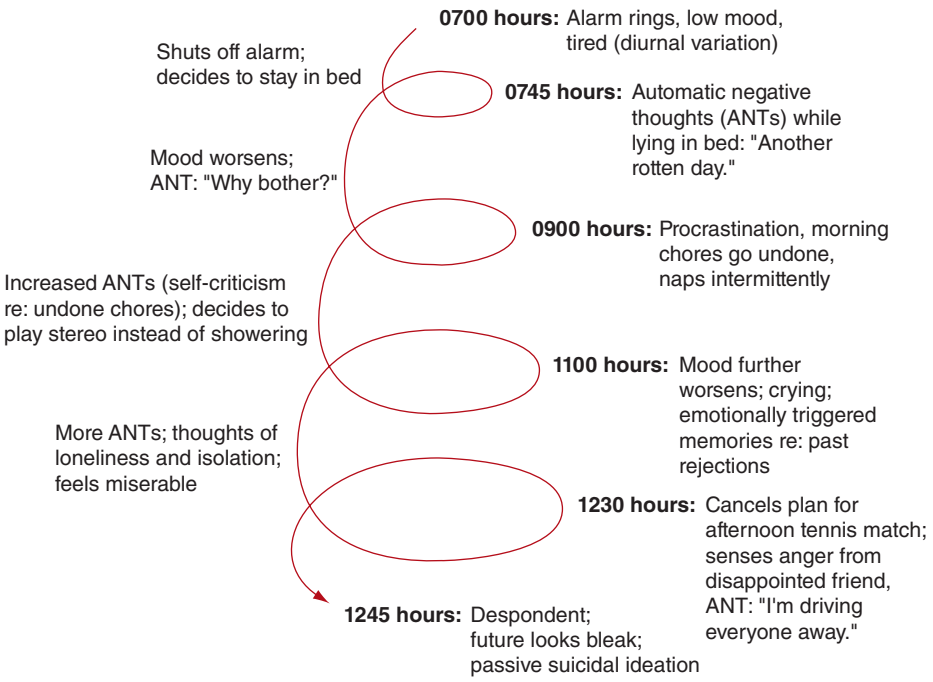



**Figure 91–6** *The downward spiral: interaction of affect, behavior, and cognition in severe depression. ANTs, Automatic negative thoughts.*

**Note**: Grade activities **M** for mastery and **P** for pleasure

| | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday |
|---|---|---|---|---|---|---|---|
| AM 6:00 6:30 | | | | | | | |
| 7:00 7:30 | | | | | | | |
| 8:00 8:30 | | | | | | | |
| 9:00 9:30 | | | | | | | |
| 10:00 10:30 | | | | | | | |
| 11:00 11:30 | | | | | | | |
| PM 12:00 12:30 | | | | | | | |
| 1:00 1:30 | | | | | | | |
| 2:00 2:30 | | | | | | | |
| 3:00 3:30 | | | | | | | |
| 4:00 4:30 | | | | | | | |
| 5:00 5:30 | | | | | | | |

Mastery, accomplished, achieved something
Pleasure, fun, amusement, enjoyment

Scale: 0–5; 0, none, 5, most

**Figure 91–7** *Weekly activity schedule.*

The activity schedule may also be used, prospectively, to begin to tackle overdue chores or other dreaded activities. The graded task approach is based on the premise that in a depressed state, many normal activities are indeed too demanding for depressed patients to complete according to their usual standards or with their characteristic efficiency. Thus, the task is broken down into units or components. The first homework assignment is typically to identify and complete a minimally acceptable initial step. For example, a depressed businessman had concealed from his family that he was 6 months behind in paying their income taxes. When he tried to tackle the project, he thought, "I'm too tired to do it now…I can't concentrate on this stuff…I'll get more depressed if I try and fail." These cognitions were so discouraging that he invariably postponed working on the taxes. As a result, he felt some relief immediately (a reinforcer for procrastination). However, within minutes he was plagued by automatic negative thoughts about the implications of putting off such an important task yet again. He also had shameful thoughts about what his family or friends would think about him when his secret was discovered. In this case, the man estimated that the task would require at least 10 hours *if he were well*. He also estimated that he had only about 50% of his normal energy and ability to concentrate. Therefore, 20 hours of work was planned in small blocks spaced out for the next 20 days. The first assignment was for the man to spend only 15 minutes organizing the forms necessary to do the overdue income taxes. The use of self-instruction and visual imagery can help patients to initiate action, and self-reinforcement after completion of each step furthers therapeutic momentum.

## Breathing Control

An important component of CBT for anxiety disorders involves teaching the patient breathing exercises that may be used to counteract hyperventilation and/or reduce tension (Clark et al. 1985). Slow, deep breathing can have a calming effect not unlike progressive muscle relaxation (Bernstein and Borkovec 1973). These exercises also help to distract the patient from autonomic cues. After initial instruction and practice, the breathing skills are then applied anxiety-provoking situations of increasing intensity.

A note of caution is in order when teaching patients breathing control exercises. We have seen many patients who have misunderstood instructions and who have developed a pattern of overly deep breathing in response to stress. Instead of reducing anxiety, their breathing changes may increase the likelihood of hyperventilation. Thus, we typically recommend teaching patients about the pace and form of normal breathing patterns. Next clinicians can model normal, calm breathing as compared to rapid breathing typical of an anxiety attack. A second hand of a watch can be used to time breaths to slow them to a normal rate. Positive, calming images can also be used to reduce anxiety during the breathing exercises. Finally, we suggest that

patients regularly practice breathing exercises to reinforce their mastery of this anxiety management technique.

## Contingency Contracting and Behavior Exchange

These strategies use the principles of operant conditioning (Skinner 1938) to modify the probability of occurrence of either undesired or desired behaviors. Malott and colleagues (1993) have written an excellent introduction to these methods. One key to applied behavioral analysis is understanding the control over the contingencies or reinforcers. Another important factor is that the terms of the contract are negotiated and should be specific and relatively straightforward. The positive contingency or reinforcer should be desirable and available shortly after the terms of the contract have been met. A paycheck is a good example of a contingency contract. Another common strategy is to chain, or pair, a high-frequency behavior (e.g., reading, watching television, or listening to music) to a low-frequency one (e.g., doing paperwork, doing housework, spending time with the children). Contingencies should generally start out relatively "rich" (e.g., 1 hour of video game time after 15 minutes of paperwork) and may be progressively "thinned" in time (Malott et al. 1993). Punishments or "response cost" contingencies are less widely used because of their negative affective responses (Azrin and Holz 1966).

Behavior exchange contracts are used with couples or families. For example, a distressed couple may voice dissatisfaction about two distinctly different behavioral tendencies, as illustrated.

> ***Partner 1:*** *You never help me out around the house.*
> **Partner 2:** That's not true, I'm always pitching in. My problem is that on the weekends you never want to go out and have fun.
> ***Partner 1:*** *That's partly true…but if I wasn't so sick and tired of being stuck with all the housework, maybe I'd feel more like going out.*

Rather than join the debate to ascertain which partner is right about what, the therapist suggests a contract to objectify the communication and increase the likelihood of mutually rewarding experiences. The contingencies used in the contract represent an exchange of desired behaviors. In the example, partner 1 desires assistance with specific household tasks (e.g., wash the dishes, fold the laundry). A desired frequency is also determined (e.g., nightly). For partner 2, a weekend outing is specified, and a mutually acceptable activity is chosen. The contract is written and signed by both parties and the therapist. Consequences for nonadherence may also need to be formulated.

Behavioral contracts may be particularly useful for assisting patients with medication adherence. For example, the therapist may help the patient identify barriers to taking medication as prescribed and then work out behavioral solutions that are written in contract form. Behavioral methods may include pairing medication taking with routine activities such as brushing teeth or meals, reminder systems, and reinforcement from significant others. We recommend explicit discussion of adherence problems and mutual agreement on a plan for taking medications when patients have difficulty in following the pharmacotherapy plan.

## Desensitization and Relaxation Training

Systematic desensitization (Wolpe 1958) was one of the first behavioral strategies to gain wide acceptance. Systematic desensitization relies on exposure through a progressive hierarchy of fear-inducing situations. This procedure may use pairing of progressive deep muscle relaxation and visualization of the target behavior to decondition fearful responses. Systematic desensitization is useful for treatment of simple phobias, social phobia, panic attacks, and generalized anxiety (Wolpe 1982). Some evidence suggests that the active ingredient of systematic desensitization is exposure to the feared situation, first in imagination and later in reality, rather than an actual counterconditioning through the relaxation response (Kazdin and Wilcoxin 1976). Progressive deep muscle relaxation is also useful as a self-directed coping strategy and for treatment of sleep-onset insomnia (Goldfried and Davison 1994, Bernstein and Borkovec 1973).

## Exposure and Flooding

The purpose of these strategies is to speed extinction of conditioned fear or anxiety responses. Behavioral theory dictates that fearfulness is reinforced by avoidance and escape behaviors (Rachman et al. 1986). Because the basis of the fear or phobia is irrational, the optimal strategy is to increase exposure to the feared activity without aversive consequences. In obsessive-compulsive disorder, the ritualistic behavior (e.g., hand washing or checking) is hypothesized to be reinforced by the relief of the anxiety associated with the compulsion (e.g., hand washing temporarily relieves the fear of contamination) (Rachman et al. 1986). In exposure, there are at least three means of fear reduction: autonomic habituation, recognition that the fear is irrational, and explicit enhancement of morale or self-efficacy that accompanies mastering the previously dreaded activity.

In graded or progressive exposure, a hierarchy is established, ranging from least-to-most anxiety-provoking situations. The individual is taught one or more ways to cope with anxiety (e.g., relaxation or self-instruction), and with the help of the therapist, the items on the hierarchy are worked through, one item at a time. Mastery is predicated on maintaining a sufficient duration of exposure for the fear to extinguish or dissipate. In some cases, imagery (exposure "in vitro") is used before moving to exposure to the actual feared stimulus. Exposure may also be enhanced by guided support (i.e., the therapist's presence during the session) or by use of coping cognitions for the duration of the exposure exercise.

Flooding, which relies on the same principles, dispatches with the hierarchical approach. The individual is exposed to the maximal level of anxiety as quickly as possible. The rationale for this accelerated approach is that it may hasten autonomic habituation. To be effective, flooding needs to be accompanied by response prevention. In response prevention treatment of obsessive-compulsive disorder, the individual agrees not to perform the compulsion despite strong urges to do so. Because obsessions are more private than compulsions, there can be less certainty that

the individual has fully participated in response prevention exercises (Stern 1978).

Participant modeling or contact desensitization is an accelerated form of exposure that produces rapid response in the treatment of simple phobias. The therapist serves as a supportive coach or guide and assists the patient through a progressively more demanding level of exposure to the feared situation. In most cases, lifelong fears of air travel, tunnels, heights, matches, dogs, water, or insects can be fully treated in a few hours of guided exposure.

### Social Skills Training

Satisfactory interpersonal relationships require a complex set of skills, including reciprocity, respect for another's opinion, appropriate modulation of self-disclosure, the tempered ability to yield on some occasions and to set limits at other times, the natural use of social reinforcers, and the capacity to express anger and resolve conflicts in a constructive manner (Lewinsohn et al. 1982, Hersen et al. 1984). Many people with psychiatric disorders suffer from either a state-dependent deterioration of these social skills or lifelong deficits of such skills. Once established, social skills deficits can increase the likelihood of experiencing stressful life events as well as "turn off" family members and other sources of social support that may help to buffer people against stressors (Coyne et al. 1987).

Problems as diverse as lack of assertiveness, temper "attacks," excessive self-disclosure, monopolistic conversational style, under-reinforcement of significant others, and splitting (i.e., playing one against another) are amenable to social skills training. The methods employed include modeling (i.e., the therapist demonstrates a more effective alternative approach), role playing and role reversal, behavior rehearsal, and specific practice assignments. Often, the interpersonal anxiety and lack of self-confidence that go hand in hand with social skills deficits lessen in response to successful mastery of targeted assignments.

### Thought Stopping and Distraction

Automatic negative thoughts and repetitive, intrusive ruminations are sometimes too intense to address with purely cognitive interventions. The technique of thought stopping capitalizes on the individual's ability to use a selectively narrowed attentional focus to suppress the intrusive cognitions. For example, a ruminative individual may be asked to visualize a large red stop sign, including its octagonal shape and white lettering. The command Stop! is paired with the image. The image and command are then used to interrupt a "run" of ruminations. At first, the technique is practiced in sessions at times when automatic thoughts or ruminations are mild. After initial success, the technique is next applied to more intensely disturbing cognitions. For individuals who find visualization difficult or ineffective, a rubber band may be worn on the wrist as a distractor. In a manner similar to that described before, the command Stop! is paired with a brisk snap of the rubber band.

Anxious patients may benefit from use of other distraction techniques to cope with panicky thoughts or increased sensitivity to interoceptive cues. Specifically, patients susceptible to panic often have a heightened awareness of otherwise normal physiological cues (e.g., alterations in heart rate, dryness in the throat, muscular tightness in the chest, or increased peristalsis). In turn, such sensitivity triggers automatic negative thoughts about an imagined impending calamity. Distractions such as counting backward, praying, or imagining a calming scene may be applied to direct attention away from the internal stimuli. Distraction techniques thus help the individual exert some control over the symptoms, permitting greater exposure and a growing sense of self-efficacy.

## Formulation of Treatment

### Indications for Treatment

The cognitive and behavioral therapies are indicated as primary treatments for adults suffering from several nonpsychotic, nonorganic Axis I disorders in the *Diagnostic and Satistical Manual of Mental Disorders*, fourth Edition (DSM-IV). These include major depressive disorder, dysthymic disorder, panic disorder, social phobia, OCD, PTSD, generalized anxiety disorder and bulimia nervosa (Wright et al. 2002). Cognitive and behavioral therapies are also useful as adjunctive treatments for patients with bipolar disorder (Basco and Rush 1996, Basco and Thase 1998, Lam et al. 2000, 2005b, Scott et al. 2003, and Zaretsky et al. 1999) and schizophrenia (Mueser 1998, Kingdon and Turkington 1995, Sensky et al. 2000). Although not extensively studied, cognitive and behavioral therapies incorporating coping skills training and relapse prevention strategies may also improve the outcome of individuals with substance abuse disorders (Wright et al. 2002).

Cognitive and behavioral therapies, like most other types of treatment, have not been studied widely in patients with Axis II disorders. However, the CBT approach to problem specification and explicit training in coping skills may be well suited for treatment of individuals willing to work on changing these habitual, ingrained patterns of thinking and behavior (Beck et al. 1990). Specific cognitive-behavioral formulations have been developed for each of the personality disorders, and modifications of CBT methods have been described for working with patients with Axis II problems (Beck et al. 1990). Linehan's model of CBT (dialectical behavior therapy) has been shown to be efficacious in reducing parasuicidal behavior in patients with borderline personality disorder (Linehan et al. 1991, Linehan et al. 1993, 2006).

### Selection of CBT Treatment

Perhaps the greatest "rate-limiting step" in selection of CBT is having access to a well-trained therapist. However, there are a growing number of training programs in CBT, and centers for CBT are available in many cities throughout the world. Cognitive-behavior therapy is now a required element in the education of psychiatry residents and is the major orientation of many psychology graduate programs. The Academy of Cognitive Therapy (academyofct.org) is a nationally recognized body that certifies therapists in this approach.

Selection of CBT for an individual patient should be based on the appropriateness of cognitive-behavior therapy for the treatment situation. Relevant questions include: Is the patient psychotic? If so, are there specific target behaviors and has psychopharmacological treatment been optimized? Does the patient suffer from a disorder for which there is evidence for the efficacy of CBT? Within groups of

patients with potentially treatable disorders, other indicators of responsivity include chronicity, severity, and comorbidity (Whisman 1993, Thase et al. 1993). A good general rule is that patients with acute, mild to moderately severe, mood and anxiety disorders are the best candidates for treatment with traditional CBT alone (Thase 1995). Patients with more chronic, severe, or complicated illnesses may be better candidates for combined treatment strategies than for CBT alone (Wright and Thase 1992, Thase and Howland 1994, Friedman 1997, Friedman et al. 2006). McCullough (2000) has developed a variant of CBT for chronic depression that has shown much promise alone and combined with antidepressant medication.

An outpatient trial of acute phase CBT typically ranges from 10 to 20 weekly treatment sessions (Wright and Beck 1983, Beck et al. 1979, Barlow and Cerny 1988, Persons 1989). However, shorter courses of treatment have been shown to be efficacious in some situations (Wright et al. 2005). Deterioration or noncompliance of the patient may warrant early termination of a treatment trial, and for certain chronic conditions such as borderline personality disorder and bipolar disorder, longer courses of therapy may be indicated (Beck et al. 1990, Linehan et al. 1993, 2006, Basco and Rush 1996). Jarrett and Kraft (Jarrett and Kraft 1997, Jarrett et al. 2001) have conceptualized treatment across the acute, continuation, and maintenance phases of the depressive disorder. We will discuss these phases of treatment in greater detail below. During treatment of major depressive disorder and panic disorder, a majority of patients who will benefit from CBT will show a significant reduction in symptoms within 6–8 weeks of starting therapy (Ilardi and Craighead 1994). Moreover, those who show a late response to CBT (i.e., between weeks 12 and 16) may be at high risk for subsequent relapse (Thase et al. 1992).

## Issues of Gender, Race, and Ethnicity

The cognitive and behavioral therapies appear equally effective for men and women and people of various races (Dobson 1989, Thase et al. 1994a). As with other forms of psychotherapy, a productive CBT working alliance is based on mutual respect for individual differences (Wright and Davis 1994). For some persons with gender, racial, or ethnically related issues, it may be useful to select therapists with special skills or experiences (e.g., therapists specializing in gay and lesbian issues or posttraumatic stress syndromes due to rape or incest). It has been recommended that cognitive–behavioral therapists receive special training and supervision in methods of responding to gender, race, and ethnicity variations (Wright and Davis 1994).

## Case Formulation

An individualized case conceptualization is used for directing the course of CBT. An analysis of cognitive–behavioral elements is combined with assessment of biological, social, interpersonal, and other possible influences on symptoms in order to produce a comprehensive formulation and treatment plan (Wright et al. 2006). Both cross-sectional (typical cognitive–behavioral responses to current environmental stressors) and longitudinal (developmental and life history contributions to develop schemas and core behavioral strategies) perspectives are considered. Details of how to perform cognitive–behavioral case formulations are provided in a basic CBT text with video illustrations (Wright et al. 2006). Also, the Academy of Cognitive Therapy Website (academyofct.org) has examples of written case conceptualizations.

## Preparation of the Patient

The cognitive and behavioral therapies explicitly incorporate strategies to increase involvement and preparedness of the patient for therapy. Patients are typically encouraged to read relevant written materials describing the theory and strategies of the therapy; for common disorders, such as major depressive disorder and panic disorder, self-help manuals for patients are now available (Burns 1990, Greenberger and Padesky 1995, Wright and Basco 2002). It is likely that multimedia programs will have an increasing role in therapy preparation (Locke and Rezza 1996, Wright and Wright 1995, Wright et al. 2002). Regardless of the mode of application, patients beginning CBT need to become acculturated to the following: 1) they will be active participants in trying out new strategies; 2) they will be expected to do homework; 3) the outcome of therapy will be measured and strategies will be altered if they are not helping; 4) therapy will be focused on symptoms and social functioning and generally will be time limited in nature; and 5) the chances of success after treatment termination can be gauged by the patients' incorporation of the therapy into their day-to-day life.

## Phases of Treatment

Most cognitive and behavioral therapies may be viewed as using a three-stage process. The initial phase includes the processes of clinical assessment, case formulation, establishment of a therapeutic relationship, socialization of the patient to therapy, psychoeducation, and introduction to treatment procedures. The middle stage involves the sequential application and mastery of cognitive and behavioral treatment strategies. The second stage ends when the patient has obtained the desired symptomatic outcome. The final phase of therapy is characterized by preparation for termination. The frequency of sessions is reduced, and there is a steady transfer of the responsibility for the continued use of therapeutic strategies from the therapist to the patient. The third stage of treatment also focuses on relapse prevention. Strategies used at this point include anticipation of reaction to future stressors or high-risk situations, identification of prodromal symptoms, rehearsal of self-help procedures, and establishment of guidelines for return to treatment (Otto et al. 1993, Thase 1993). The failure to achieve a remission of depressive symptoms after 16–20 weeks of treatment may indicate a need for continuation phase treatment to achieve these goals and maintenance phase treatment for relapse prevention. Incomplete symptomatic remission after 20 weeks of CBT may also indicate the need for adding pharmacotherapy to the treatment plan as we discuss in greater detail below.

## Intensity of Treatment

Outpatient CBT is normally conducted once or twice a week. In selected cases, three times weekly or even daily sessions may be useful, but the cost-effectiveness of such a labor-intensive approach is uncertain. One of the authors (J.H.W.), who often uses CBT in combination with pharmacotherapy

and computer-assisted treatment, has found that he can reduce sessions for ambulatory patients to every other week or to a shortened time frame (i.e., 20-25-minute sessions) when a good therapeutic relationship has been established and the patient has started to make significant progress.

When patients are seen in a day treatment hospital or inpatient setting, sessions are typically provided on a daily or every-other-day basis. Many programs blend individual and group therapies (Wright et al. 1993). In our experience, holding sessions more frequently helps to offset symptom severity and demoralization in severely ill patients (Thase and Wright 1991). The cost-effectiveness of more or less intensive cognitive–behavioral strategies has not been systematically studied. Nevertheless, we believe that therapists should adjust the frequency and intensity of treatment according to the needs of patients as well as the therapy resources that are available.

## Duration of Treatment

In most cases, treatment is conducted in a period of 3–6 months. For those who begin therapy as inpatients, a similar period of aftercare is strongly recommended (Thase 1993). Unsuccessful therapy (e.g., failure to effect significant symptomatic improvement) should generally not continue past 12–16 weeks for outpatients. Therapy should not be terminated until patients have achieved symptomatic remission. Ideally, at least two or three sessions are planned on an every-other-week basis in preparation for termination.

## Outcome Assessment

Cognitive and behavioral therapies are, in part, distinguished by their integrated use of objective assessment methods. For depression and the anxiety disorders, a number of well-established rating scales are available. Therapist-administered scales include the Hamilton Anxiety Rating Scale (Hamilton 1959) and the Hamilton Depression Rating Scale (Hamilton 1960) as well as the Yale-Brown Obsessive-Compulsive Scale (Goodman et al. 1989). Self-report assessments of symptoms include the Beck Depression Inventory (Beck et al. 1961), the Beck Anxiety Inventory (Beck et al. 1988), the Fear Survey Schedule (Wolpe and Lang 1964), the Fear Questionnaire (Marks and Matthews 1979), and the Hopkins Symptom Checklist (Derogatis et al. 1974). These scales are typically administered before treatment and repeated periodically (e.g., weekly or monthly) to monitor progress. The Dysfunctional Attitudes Scale, the Attributional Style Questionnaire, and the Automatic Thoughts Questionnaire may be used to evaluate distorted cognitions (Dobson and Shaw 1986). As suggested earlier, high residual levels of cognitive symptoms most likely convey an increased risk for relapse after termination of treatment (Thase et al. 1992, Simons et al. 1986, Fava et al. 1998a). Similarly, high scores on the Hopelessness Scale (Beck et al. 1974) have been associated with a high risk for subsequent suicidal behavior (Beck et al. 1985).

## Augmentation of Therapy

One of the major methods of augmenting a cognitive and behavioral therapy is to add an appropriate form of pharmacotherapy. For example, a depressed or agoraphobic person who has not benefited much from eight weeks or more of CBT alone should probably be considered for pharmacotherapy. In such cases, the neurobiological substrate of the illness may be too severely disturbed to be responsive to the CBT without concomitant pharmacotherapy (Wright and Thase 1992, Jindal et al. 2002). In clinical practice, psychiatrists who are trained in CBT often combine cognitive therapy and pharmacotherapy from the beginning of treatment unless the patient expresses a strong desire to receive only a single form of therapy.

There are no contraindications to combining CBT and pharmacotherapy (Wright and Thase 1992). In fact, these modalities are highly compatible in theory and practice. As noted earlier, pharmacological stabilization is a prerequisite for CBT for some Axis I disorders (e.g., psychotic depressions, schizophrenia, and bipolar disorder). When these treatments are used in combination, the treatment team should have a well-defined division of labor, open lines of communication, and an explicit sense of collaboration. Treatment of patients with severe, refractory, or incapacitating mood and anxiety disorders may represent the best use of combined therapies (Thase and Howland 1994, Bowers 1990, Otto et al. 1994, Scott 1992, Whisman et al. 1991). Other strategies used to enhance CBT include increasing the frequency of visits, switching emphasis (i.e., from cognitive to behavioral or vice versa), or involving the spouse or significant others in the therapy (Beach et al. 1994, Emmelkamp and Gerlsma 1994). The last strategy has been shown to be particularly useful in cases of depression associated with marital discord (Jacobson et al. 1991, Beach and O'Leary 1992). Computer augmentation is a new addition to the tools available for CBT (Selmi et al. 1991, Wright and Wright 1997, Kenwright et al. 2001, Wright et al. 2002, Wright et al. 2005). Greater availability of personal computers with multimedia capability and increased pressure to reduce the cost of treatment may make this form of therapy augmentation a more common practice in clinical settings.

## Continuation and Maintenance Phase CBT

When Beck and associates (Beck et al. 1979) described CBT in the late 1970's depression researchers were primarily concerned with the issue of response to treatment—is psychotherapy or pharmacotherapy effective in reducing the symptoms of the disorder over a given time period (generally 1 month to 10 weeks for efficacy studies of the tricyclic antidepressants, 6–12 weeks for efficacy studies of SSRI'S and 12–20 weeks for studies of psychotherapies)? This phase of treatment has come to be called the "acute phase." Because some patients do not completely achieve a remission of symptoms (their return to premorbid well state) and because many patients experience depression as a recurring illness, there is a need for longer-term treatment methods for major depression (Kupfer et al. 1986). Furthermore, incomplete remission of depression leads to recurrence, and this conveys many adverse economic, interpersonal and medical consequences (Thase 1992).

Over the past 18 years, studies conducted by Thase and coworkers at the University of Pittsburgh have identified and replicated correlates of relapse (return of symptoms during continuation phase treatment) and recurrence (return of symptoms after one year of remission of the illness) following the termination of acute phase CT (A-CT). Failure to achieve a complete remission of the index episode by the sixth week of A-CT is associated with a 3–5-fold increase in the subsequent risk of relapse or recurrence. Thase and

coworkers have found that between 50 and 60% of A-CT responders meet this criteria for risk and Jarrett's group has demonstrated that an 8-month course of continuation-CBT essentially neutralizes this higher risk of relapse. C-CT focuses on the vulnerabilities for recurrent depression in three domains: biologic (genetics, biology, familial, and developmental), psychosocial (personality, interpersonal, and social), and cognitive (Jarrett et al. 2001). By identifying and modifying risks and vulnerabilities and learning more effective ways of managing mood symptoms, C-CT helps prevent relapse and recurrence.

Fava (Fava et al. 1994) has developed another interesting approach to reduce the risk of relapse, the sequencing of treatment depending upon the degree of response following acute therapy. He found that a 12-session course of CBT focusing on healthy lifestyle changes significantly reduced depressive symptoms (Fava et al. 1994), increased the likelihood of successfully withdrawing from antidepressants (Fava et al. 1996, Fava et al. 1998b), and decreased the risk of subsequent relapse after withdrawing anti-depressant medications (Fava et al. 1998a). Other studies (Blackburn and Moore 1997, Paykel et al. 1999) support the strategy of using a short course of focused CBT to offset the risks of relapse and recurrence of major depression.

## Efficacy of CBT

The cognitive and behavioral therapies are, as a class, the best studied type of psychotherapy. Numerous research studies have demonstrated the efficacy for a variety of Axis I disorders.

### Mood Disorders

Most of the evidence for the effectiveness of Beck's model of CBT for mood disorders is derived from studies of outpatients with major depressive disorder (nonbipolar, nonpsychotic subtype). There is no doubt that CBT is an effective treatment of major depression compared with a waiting list control condition (Thase 1995, Dobson 1989, Depression Guideline Panel 1993). Dating to an initial study by Rush and associates (Rush et al. 1977), one major research focus has been to establish the efficacy of CBT vis-á-vis antidepressant pharmacotherapy. At this time, eight controlled trials contrasting CBT and tricyclic antidepressants have been completed (McCullough 2000), as have a legion of studies using other designs and other comparison groups (Thase 1995, Jarrett and Rush 1994). Several meta-analytical reviews have been published (Dobson 1989, Depression Guideline Panel 1993, Gloaguen et al. 1998, Butler et al. 2006). Dobson found CBT to be superior to untreated controls, wait-list participants, pharmacotherapy with tricyclic antidepressants, and other therapies (Dobson 1989). Gloaguen et al. (1998) reported CBT was superior when compared with wait-list and placebo control conditions; modestly superior to other therapies. Recently Butler and colleagues (2006) reviewed meta-analyses of CBT and report that CBT was somewhat superior to antidepressants in the treatment of adult depression, OCD and several other disorders.

Thase and coworkers (2000) have reported on a retrospective comparison of consecutive cohorts treated with CBT or supportive counseling and pill-placebo. The findings of this analysis suggest that CBT has greater therapeutic effects than this competently administered control condition, the ideal comparator for pharmacology efficacy studies.

The results of the National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP) (Elkin et al. 1989), a large, controlled three-site clinical trial, initially appeared to be inconsistent with these findings. The study reported that CBT was as effective as the tricyclic antidepressant imipramine in the full sample, but neither CBT nor imipramine was significantly more effective than the control condition, supportive clinical management and pill-placebo. Furthermore, in the more severely ill patients or in patients with greater functional impairment, CBT appeared to be less effective than imipramine. Moreover, the study results suggested that CBT was slightly, although not statistically, less effective than interpersonal psychotherapy (IPT), especially when recovery (stable symptomatic remission lasting greater than 8 consecutive weeks) was the outcome measure examined. However, when this same cohort was observed over the course of 18 months of follow-up (Shea et al. 1992), it was determined that there was no significant difference among any of the treatments with respect to the number of patients that recovered and remained well. When the follow-up outcome of the CBT patients was reviewed, the authors found that CBT patients had the lowest rates of receiving some kind of treatment during the follow-up period and CBT patients had the lowest rates of relapse after 18 months. This led the authors to be encouraged about the prophylactic value of CBT.

Ablon and Jones (2002) also question the validity of the results of the psychotherapy findings of the Treatment of Depression Collaborative Research Program. The authors used actual transcripts of the IPT and CBT sessions and rated CBT and IPT sessions with respect to therapy process, therapy technique, and intervention styles. They report that both the IPT and CBT sessions adhered most strongly to the ideal prototype of CBT. In addition, adherence to the CBT prototype yielded more positive correlations with outcome measures across both types of treatment.

The acute-phase treatment findings of the Treatment of Depression Collaborative Research Program have raised questions about the suitability of CBT as a treatment of severe depression (American Psychiatric Association 1993). Alternatively, the adequacy of CBT provided in the Treatment of Depression Collaborative Research Program trial has been challenged by some who believe CBT therapists may need a longer period of training than that required to become proficient at interpersonal psychotherapy (Thase 1994). Nevertheless, in other groups' hands, CBT is fully the equal of pharmacotherapy (Blackburn et al. 1981, Murphy et al. 1984, Hollon et al. 1992). A recent three-site study by DeRubeis and colleagues randomized 240 moderately to severely depressed patients to CBT, antidepressant medication therapy (paroxetine), or placebo. Overall, CBT was shown to be as effective as antidepressant medication in the treatment of moderate to severe depression when provided by highly experienced cognitive therapists (there was a significant difference in site treatment interaction at one site) (DeRubeis et al. 2005). Furthermore, CBT has also been demonstrated to be effective for inpatients with severe and chronic depression (DeJong et al. 1986). An intensive CBT protocol has been demonstrated to be an effective treatment of 60% to 70% of unmedicated depressed

inpatients suffering from nonpsychotic major depression (Thase et al. 1993, Thase et al. 1991).

There is additional evidence for the effectiveness of CBT in the treatment of severely ill depressed patients. In a large multisite randomized clinical trial of a difficult cohort of severe and chronically depressed patients, McCullough's CBT-based treatment, The Cognitive–behavioral Analysis System for Psychotherapy, (Keller et al. 2000, McCullough 2000) has shown equal efficacy to the serotonin-norepinephrine reuptake inhibitor, nefazodone, each being effective in 55% of cases, but the combination of the two treatments produced an impressive response rate of 85% at the end of 12 weeks of treatment. Thus, a version of CBT modified to specifically address the problems of severe and chronic depression has shown efficacy. Further evidence supporting the use of CBT in severe depression is found in a study that suggests a benefit for CBT in preventing suicide attempts. These investigators compared CBT to enhanced treatment as usual in patients who recently attempted suicide. The CBT subjects had a significantly lower reattempt rate, were 50% less likely to reattempt suicide than the control group, and reported less severe depression and hopelessness in follow-up (Brown et al. 2005).

More recently, results of the multi-site, NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial compared CBT as a second-step treatment in patients with unipolar major depression who did not receive benefit from an adequate trial of the SSRI medication citalopram (Thase et al. In press). In one comparison, participants were randomized to augmentation of citalopram with either CBT or medication (either bupropion SR or buspirone). CBT augmentation was as effective as medication augmentation, but the latter was associated with a more rapid response. In the second comparison patients were switched to CBT or medication (sertraline, bupropion SR, or venlafaxine XR). There were also no differences in the effectiveness of switch to CBT or medications, although pharmacotherapy was associated with significantly more adverse side effects. The authors conclude that for patients without adequate benefit from citalopram, CBT was an effective pharmacotherapy whether used as a switch or augmentation strategy (Thase et al. 2007).

Regarding the efficacy of combining CBT and medications, a meta-analysis of studies that examined treatment with medication alone (including tricyclics amitriptyline, chlomipramine, nortriptyline, desipramine, and nefazodone) versus medication combined with CBT, Friedman and colleagues (2006) found the benefit favoring combination treatment over pharmacotherapy alone to be almost twice as great.

Interestingly, group CBT strategies for treatment of depression have been found to be nearly as effective as individual treatment in both direct comparisons (Ross and Scott 1985) and composite meta-analytical comparisons (Depression Guideline Panel 1993, DeRubeis and Crits-Christoph 1998). These studies, which have not yet dramatically affected practice habits, suggest that a significant savings in cost-effectiveness might be gained by more regular use of group treatments. One study (Ravindran et al. 1999) in dysthymic patients compared the efficacy of sertraline and group cognitive behavioral therapy, alone or in combination. These authors found the group CBT to be less effective than sertraline in alleviating clinical symptoms. However, CBT augmented the effects of sertraline with respect to some functional changes, and in a subgroup of patients it attenuated the functional impairments characteristic of dysthymia.

Marital CBT also appears to be as effective as individual CBT in treatment of depression associated with marital discord (Jacobson et al. 1991, Beach and O'Leary 1992). When effective, this marital therapy also typically produces concomitant improvement in dyadic adjustment, whereas effects of individual CBT are primarily limited to symptom variables (Jacobson et al. 1991, Beach and O'Leary 1992). Because marital discord plays a major role in the pathogenesis of many depressive episodes, greater use of couples treatment strategies may be indicated (Beach et al. 1994, Baucom et al. 1990) and such strategies have been described (Baucom and Epstein 1990).

Some evidence suggests that CBT reduces the risk for relapse after termination of treatment (vis-á-vis patients withdrawn from antidepressants) (Simons et al. 1986, Evans et al. 1992, Blackburn et al. 1986a). In the study of Evans and colleagues, (Evans et al. 1992) CBT responders had the same degree of prophylaxis against relapse at more than 1 year of follow-up as did antidepressant responders treated with continuation phase pharmacotherapy (Figure 91–8). The risk for relapse after CBT may be particularly low for patients who achieve a complete remission before ending treatment (Thase et al. 1992). The use of CBT for relapse prevention by Fava's group has been discussed (Fava et al. 1994). In a 12-month naturalistic follow-up study of patients who responded to acute phase treatment (see DeRubeis et al. 2005, discussed above), it was found that compared to successfully treated pharmacotherapy patients, CBT patients were significantly less likely to relapse, suggesting a possible enduring prophylactic effect for CBT (Hollon et al. 1992). These findings are supported by a study comparing patients with recurrent major depression who achieved remission and were assigned to continued treatment as usual with pharmacotherapy compared to such treatment augmented with a brief course of CBT over 2 years duration. These investigators found the addition of CBT resulted

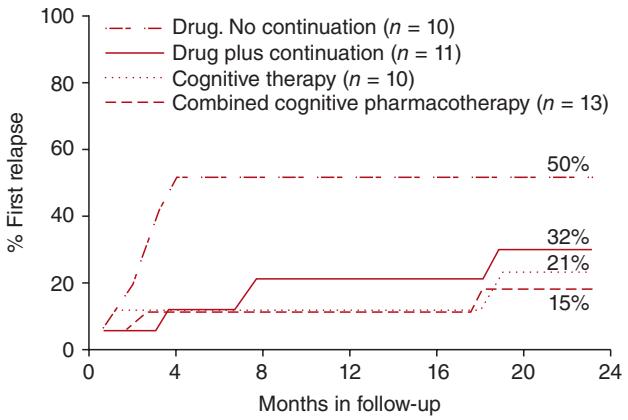



**Figure 91–8** *Risk of relapse after cognitive therapy and pharmacotherapy, singly or in combination. (From Evans MN, Hollon SD, DeRubeis RJ, et al: Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 1992; 49:802-808. Copyright 1992. American Medical Association.)*

in a significant protective effect, which intensified with the number of previous depressive episodes experienced (Bockting et al. 2005).

Other models of cognitive and behavioral therapy have also been studied in randomized clinical trials of major depressive disorder, and they have generally matched or exceeded the results of the antidepressant condition (McLean and Hakstian 1979, Wilson 1982, Hersen et al. 1984). In two studies, the combination of behavioral therapy and antidepressants resulted in significantly more rapid improvement (Wilson 1982, Roth et al. 1982). Behavioral strategies emphasizing self-control skills, problem-solving skills, and increased pleasant activities have also been consistently found to be superior to waiting list control conditions (Thase 1995, Depression Guideline Panel 1993). Jacobson and colleagues (1996) performed a randomized trial comparing standard CBT with behavioral activation (BA), a condition in which cognitive interventions were proscribed. They found that BA produced as much symptomatic improvement as did the full CBT treatment. When the relapse rate in these groups was examined after 2 years, there was also no difference between the treatments (Gortner et al. 1998). More recently, Dimidjian and colleagues (2006) compared an "expanded BA model" to standard CBT and antidepressant medication (ADM) in a randomized placebo controlled design in adults with nonpsychotic major depression. In the less severe patients there was no difference between the treatments but among the more severely depressed patients, BA was comparable to ADM and both significantly outperformed CBT (in this condition behavioral techniques were proscribed). These results support the contention that more severely depressed patients require BA techniques to achieve symptomatic improvement and that BA is the preferred focus initially in such cases. As a result of these studies, Dimidjian and colleagues (2006) question the necessity of targeting negative thinking to achieve therapeutic response.

## Anxiety Disorders

Controlled studies have established the efficacy of cognitive and behavioral therapies for generalized anxiety disorder, obsessive-compulsive disorder, simple phobia, social phobia, panic disorder, and agoraphobia (Wolpe 1982, Clum et al. 1993, Beck and Zebb 1994, Chambless and Gillis 1993, Durham and Allan 1993, Butler et al. 1991, Barlow et al. 2000, Clark et al. 2006, Haby et al. 2006, Schuurmans et al. 2006). CBT has also been shown in a randomized clinical trial to be an effective treatment for anxiety disorders in older adults at the end of therapy and over 12 months of follow-up. These authors included patients with a wide range of anxiety disorders to allow generalization of their findings to a greater "real-world" population (Barrowclough et al. 2001).

CBT is very effective for *simple phobias*. The cognitive and behavioral treatments emphasizing progressive (graded) exposure, systematic desensitization, relaxation training, and the use of homework assignments are well established and are considered the psychotherapeutic treatment of first choice for the simple phobias (Wolpe 1982, Rachman and Wilson 1980, Chambless and Gillis 1993).

CBT interventions are effective and frequently used interventions for the treatment of Obsessive-compulsive *disorder* (OCD). Whereas OCD is often refractory to traditional psychosocial treatments, response rates of 50% to 70% are typically reported in CBT trials (Emmelkamp and Beens 1991, Foa et al. 1992, Stekette 1994, Rufer et al. 2005). Behavioral strategies generally take precedence over cognitive interventions, with the paired strategies of exposure and response prevention proving particularly useful (Emmelkamp and Beens 1991, Foa et al. 1992, Salkovskis and Westbrook 1989). In a recent study, Whittal and colleagues (2005), found exposure and relapse prevention (ERP) to be equally effective as CBT in 59 completers at 3-months of follow-up. Although comparative studies are fewer, therapies emphasizing exposure and response prevention have been found to be comparable to antiobsessional pharmacological agents (such as clomipramine) in patients with behavioral compulsions (Foa et al. 1992, Marks et al. 1988). Interestingly, in a small study by Baxter and colleagues (1992), behavioral treatment of obsessive-compulsive disorder produced a change in glucose metabolism in the caudate nucleus (a putative neurobiological marker of obsessive-compulsive disorder) comparable to that observed in patients treated with pharmacotherapy. Several studies have examined whether pharmacological and cognitive–behavioral strategies can be used fruitfully in combination or in sequence (Kampman et al. 2002, Marks et al. 1980, Turner et al. 1980, van Oppen et al. 2005). Van Oppen et al. (2005) studied the long-term effectiveness of CBT alone, exposure in vivo and response prevention (ERP) alone, and CBT or ERP plus fluvoxamine. They concluded that (1) the prevalence of OCD declined in all three treatment conditions, (2) that these benefits were maintained for 5 years, (3) OCD complaints were more severe for treatment drop-outs than for completers, and 4) about half of the fluvoxamine patients continued antidepressant use. Regarding the question of treatment sequencing, Kampman and colleagues (2002) found the addition of CBT was effective in fluoxetine nonresponders.

*Generalized anxiety disorder* and *social phobia* are common and protean conditions, often presenting with much depressive and Axis II comorbidity. CBT emphasizing relaxation training, cognitive coping skills, social skills training, and graded exposure to feared situations has generally been shown to be superior to waiting list or nonspecific therapy control conditions (Blowers et al. 1987, Borkovec et al. 1987, Borkovec and Mathews 1988, Borkovec and Costello 1993, Butler et al. 1991, Durham et al. 1994, Heimberg 1990, Linden et al. 2005). An average of 60% to 80% of patients treated in clinical trials have responded to cognitive and behavioral methods (Gelernter et al. 1991, Power et al. 1990). In a controlled trial of patients with generalized anxiety disorder comparing CBT to behavioral therapy (BT) and a wait-list control group, results show a clear advantage for CBT over BT. There was a consistent pattern of change favoring CBT in measures of anxiety, depression, and cognition. A randomized, controlled trial in older adults with GAD of CBT versus a nondirective supportive psychotherapy found no significant differences between the treatments although both reduced worry anxiety and depression (Stanley et al. 1997). Linden and colleagues (2005) randomized 72 outpatients with GAD to either CBT or a contact control group and after the control period these patients were treated with CBT as well. They reported that CBT significantly reduced anxiety and that

the clinical effect remained stable over 8 months of follow-up. Their conclusion was that CBT is an effective treatment for GAD with an effect size comparable or larger than those reported for antidepressant medications. These results are supported by an 8-14 year follow-up study of CBT treatment which concluded that CBT and the complexity and severity of presenting problems appear to influence the long-term outcome of GAD (Durham et al. 2003). Another interesting study randomized 61 patients to either CBT or a nonspecific therapy control group to facilitate benzodiazepine discontinuation. They reported that 75% of patients in the CBT group ceased benzodiazepine use versus 37% in the control group and that a greater number of patients in the CBT group no longer met GAD criteria. However, discontinuation rates were twice as high in the CBT condition (Gosselin et al. 2006).

The comparative efficacy of cognitive and behavioral treatments and pharmacotherapy for *panic disorder* and *agoraphobia* is currently a topic of intensive investigation (Clark et al. 1994, Clum et al. 1993, Beck and Zebb 1994, Margraf et al. 1993, National Institutes of Health 1991, Ost et al. 2004, Otto and Deveney 2005). These treatments teach patients to disregard or deemphasize internal cues linked to sensitivity to anxiety while mastering behavioral self-control strategies such as breathing exercises and deep muscle relaxation. Cognitive strategies are also used in these models to decrease exaggerated thinking patterns (e.g., catastrophization) and reduce worrying.

In general, between 70% and 90% of patients treated with CBT become panic free within 2 to 4 months of beginning therapy (Clum et al. 1993, Chambless and Gillis 1993, National Institutes of Health 1991, Otto and Deveney 2005). The specific models of CBT introduced by Beck and Emery (1985), Clark (1986), and Barlow and Cerny (1988) have been shown to be superior to waiting list or nonspecific control conditions (Margraf et al. 1993, Barlow et al. 1989, Beck et al. 1992). In a study using an across-subjects design, CBT is significantly superior to information-based therapy in reducing panic attacks in patients with panic disorder and secondary depression (Laberge et al. 1993). Meta-analyses (Beck et al. 1985, Chambless and Gillis 1993) suggest comparability of CBT and pharmacotherapy (i.e., tricyclic antidepressants or potent benzodiazepines) during acute phase therapy. In one trial, the selective serotonin reuptake inhibitor fluvoxamine was superior to CBT (Black et al. 1993). However, in other studies, similar advantages favored CBT (Margraf et al. 1993, Klosko et al. 1990, Marks et al. 1993). In this regard, Heldt and colleagues (2006) found sustained significant benefit after one year in 63 patients who completed group CBT for panic disorder after failing to respond adequately to previous pharmacotherapy.

Even if it is comparably effective, the cost efficiency of pharmacologic treatment may be reduced (relative to CBT) by high rates of relapse after discontinuation of pharmacotherapy (DuPont et al. 1992, Noyes et al. 1991, Pollack et al. 1993). Evidence collected to date suggests that there may be fewer relapses after cessation of CBT compared with relapse rates after medication discontinuation (Otto and Deveney 2005). This prophylactic effect may be related to significant changes in neurophysiological sensitivity (Beck and Zebb 1994). For example, Shear and colleagues (1991) found that successful CBT resulted in a significant reduction in patients' sensitivity to sodium lactate, a biological probe that reliably induces panic attacks in a significant number of patients susceptible to panic.

As with treatment of depression, CBT has shown value when it is used sequentially to reduce the risk of relapse after withdrawal of pharmacotherapy (Otto et al. 1993, Spiegel et al. 1994). To date, evidence does not indicate that the combination of CBT and pharmacotherapy yields a strongly synergistic effect (Clum et al. 1993, Marks et al. 1993, Hegel et al. 1994, Mavissakalian and Michelson 1986, Gelder 1998).

There is also interest in the application of CBT to posttraumatic stress disorder. A recent review of controlled outcome studies indicated that CBT is the psychological treatment of choice and that is more effective than eye movement desensitivization and reprocessing (Bryant and Friedman 2001).

## Eating Disorders

Many research studies have demonstrated the efficacy of CBT for bulimia nervosa (Agras et al. 1992, 1994, 2000, Fairburn et al. 1991, 1992, 1993, 1995, Garner 1992, Goldbloom et al. 1997, Walsh et al. 1997). Reviews of controlled studies of CT have found strong evidence for the efficacy (Wilson 1999, Ricca et al. 2000) and theoretical utility (Reas and Grilo 2004) of CBT. Combined cognitive and behavioral therapy has been shown to be superior to a behavior therapy alone approach to bulimia (Thackwray et al. 1993). At the six-month follow-up assessment after treatment, 69% of the subjects who received CBT reported no binge eating and purging as compared to 38% abstinence in the behavior therapy group and 15% abstinence in the attention placebo group. In a comparison of CBT and a guided self-help condition, subjects in both treatment conditions showed a significant decrease over time in binge eating and vomiting frequencies (Bailer et al. 2004). Reviews of research on combined CBT and pharmacotherapy for bulimia have found that CBT has an additive effect to antidepressant therapy (Wilson 1999, Ricca et al. 2000). But, there appears to be no advantage to adding medication to CBT for anorexia nervosa. In addition, CBT has also been advocated for binge eating disorder (Vaidya 2006).

## Bipolar Disorders

There are several randomized control trials of CBT in patients with bipolar disorder. Cochran (1984) studied whether CBT improved lithium compliance at 6 and 12 months after treatment as compared to a control group. The results indicated no difference in lithium compliance on the self-reports, informant-reports, or serum lithium levels, but the physician (who was not blind to which group the patient belonged) reported more compliance. Scott et al. (2001) reported the results of a pilot study of cognitive therapy in patients with bipolar I ($n = 34$) and bipolar II ($n = 8$) disorders. Half the patients were assigned to immediate CBT or 6-month wait-list control, which was then followed by a course of CBT. At six-month follow-up, subjects who had CBT showed statistically significantly greater improvement in symptoms and functioning than those in the waiting-list control group. In the 29 patients who eventually received CBT, relapse rates in the 18 months after commencing CBT showed a 60% reduction in comparison with the 18 months

prior to commencing CBT. Seventy percent of the subjects who commenced CBT found it to be a highly acceptable form of treatment. Immediately after receiving CBT changes in symptoms and functioning were significant but these changes were not maintained at 6 months after CBT was finished. Interestingly, in the CBT group, reductions in depressive symptoms were more robust than reductions in manic symptoms. Interestingly, this same group (Scott et al. 2006) recently reported on a subsequent study of 253 bipolar subjects, which found no overall benefit of CBT, compared to treatment as usual, in reducing relapse rates. However, CBT was effective in preventing relapse in persons who had fewer than 12 previous bipolar episodes.

Another line of research into the benefit of CBT for bipolar patients examines using CBT to prevent relapse in patients with bipolar disorder who are taking mood stabilizer medications. The authors modified CBT by (1) a psychoeducational component that modeled bipolar illness as a stress-diathesis illness; (2) adaptive CBT shills to cope with producers (identifying the onset of symptoms of bipolar disorder characteristic of the patient's illness pattern); (3) promoting the importance of circadian regularity by emphasizing the importance of routine and sleep; and (4) dealing with the long-term vulnerabilities and difficulties of the illness. Therapy consisted of 12–20 sessions and lasted 6 months and outcomes were measured at 6- and 12-month points. The CBT group had significantly fewer bipolar episodes, higher social functioning, better coping strategies for bipolar problems, evidence of less fluctuation in symptoms of mania and depression, less hopelessness, better medication compliance, and they used significantly less neurologic medication (Lam et al. 2000). Recently, Lam and colleagues (2005a) reported on the 30-month follow-up of this cohort. They report that over 30 months the CBT group had significantly better outcome in terms of time to relapse. Patients in the CBT group also had significantly fewer days in bipolar episodes. However, there was no significant additional CBT effect in relapse reduction over the last 18 months of the study period, suggesting the need for booster or maintenance CBT treatment sessions. Additionally, this group found that CBT plus mood stabilizers was superior to mood stabilizers alone in terms of cost-effectiveness for those with frequent relapses of bipolar disorder (Lam et al. 2005b).

Another recent study by Ball et al. (2006) observed that 6 months of CBT for bipolar disorder had clinical benefit in reducing depression, dysfunctional attitudes, and global ratings of symptom severity. There was a trend for lower relapse rates in patients treated with CBT. These authors note that the short-term effects of CBT treatment were greater than the long-term effects, which may suggest that maintenance phase therapy may be needed to sustain the therapeutic effects of CBT in bipolar patients. In the recent, multisite, NIMH-sponsored study of the effectiveness of treatments in bipolar disorder, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, several intensive psychotherapies were compared to a minimal psychosocial intervention (called collaborative care) (Miklowitz et al. 2007). The intensive psychotherapies included CBT, family-focused treatment (FFT) and the Interpersonal and Social Rhythm Therapy (IPSRT). These investigators found that despite equal rates of attrition across groups, patients receiving intensive psychotherapy had significantly higher year-end recovery rates and shorter times to recovery than patients in the collaborative care group. These patients were also 1.58 times more likely to be clinically well during any study month than those in collaborative care. No statistically significant differences were observed in the outcomes of the three intensive therapies.

### Other Disorders

Although CBT is not as well established as a primary treatment for other disorders, promising preliminary data are available in studies of borderline personality disorder (Linehan et al. 1991, Linehan et al. 1993, Salkovskis et al. 1990). Cognitive and behavioral therapies have also been studied in substance abuse disorders and tend to be more effective than standard counseling approaches only with patients with concomitant psychiatric illness (Woody et al. 1984, Carroll et al. 1994, Higgins et al. 1994). The directive methods employed by cognitive–behavioral therapists may help to lessen the resistance characteristic of more sociopathic substance-abusing patients, who may have limited ability to make use of reflective and insight-oriented strategies (Kadden et al. 1989).

For the psychotic Axis I disorders, including schizophrenia and bipolar disorder, the cognitive and behavioral therapies have been shown to be useful adjunctive treatments for patients stabilized with appropriate psychotropic agents. The first trials of CBT for psychosis were uncontrolled but suggested that this treatment approach could be used effectively for hallucinations, delusions, and other symptoms of schizophrenia (Fowler and Morley 1989, Chadwick and Birchwood 1994, Kingdon and Turkington 1991). Subsequently, several randomized controlled trials have found that CBT can add to the effect of medication (Drury et al. 1996a, 1996b, Kuipers et al. 1997, Tarrier et al. 1993, Sensky et al. 2000).

For example, Drury and coworkers (1996a, 1996b) observed that positive symptoms improved more in hospitalized patients who received CBT than those patients receiving nonspecific and supportive treatment. This research group also observed reduced time required for recovery in those treated with CBT. Sensky and coworkers (2000) studied 90 patients with schizophrenia who had persistent, drug resistant symptoms. In this study both forms of psychotherapy (CBT and an equal amount of time in "befriending") were effective at the end of active treatment. However, 9 months after treatment subjects who received CBT had significantly lower ratings on measures of positive and negative symptoms.

## Conclusion

The cognitive and behavior therapies are based on well-articulated theories that have a strong empirical basis. These therapies emphasize objective assessments and use of directive interventions aimed at reducing symptomatic distress, enhancing interpersonal skills, and improving social and vocational functioning. Cognitive interventions are focused primarily on identifying and modifying distorted thoughts and pathological schemas. Behavioral techniques to increase exposure, increase activity, enhance social skills, and improve anxiety management are useful modalities, and can complement or amplify the effects of cognitive

strategies. Similarly, the cognitive perspective can add depth to behavioral models for therapy by teaching patients how to recognize and modify their attitudinal vulnerabilities.

The cognitive and behavioral therapies are the best-studied psychological treatments of major depressive, panic, generalized anxiety, and obsessive-compulsive disorders. Overall, there is good evidence for the effectiveness of these interventions within these indications. Cognitive and behavioral therapies are being adapted for adjunctive use with pharmacotherapy for treatment of bipolar disorder and schizophrenia. There are no contraindications for use in combination with pharmacotherapy. The cognitive and behavioral therapies have become one of the standard psychosocial treatment approaches for mental disorders.

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CHAPTER

# 92 Family Therapy

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## Introduction

Family therapy is psychotherapy that directly involves family members in addition to the identified patient, and/or explicitly attends to the interactions among family members (Hoffman 1985, Pinsof and Wynne 1995). Family therapy thus engages relational and communicational processes of families and social networks as a primary context for solving clinical problems or treating psychiatric disorders, even though one family member may be the sole bearer of distress or symptoms. By educating family members or altering family patterns of relating or communicating, such clinical problems as depression, anxiety, marital conflict, or disruptive childhood behavior can be resolved or attenuated.

Although social workers met therapeutically with families as early as the late 1880s, family therapy as known today emerged in the 1940s (Broderick and Schrader 1981). The sudden reuniting of families at the conclusion of World War II precipitated marital discord, divorce, delinquency, and emotional breakdowns, leading to requests for professional help (Goldenberg and Goldenberg 1980). The subsequent failure of psychoanalysis to find therapeutic breakthroughs for such problems as schizophrenia and juvenile delinquency shifted attention away from the interior emotional life of individuals to their family relationships as a potential point of intervention. During the late 1940s and 1950s isolated pockets of family therapy practitioners proliferated across the US. Each group brought its unique perspective to the observation of families, and from each a distinct "school" of family therapy developed (Slovik and Griffith 1992).

Over the ensuing decades, these different clinical approaches to family therapy began coalescing into clinical traditions defined by their core theoretical assumptions and methods, supported to varying extents by research. Each of the major family therapy traditions has contributed to the repertoire of mental health professionals its unique framework for understanding clinical problems, and an associated set of interventions. Some approaches have insisted that whole families be involved in most sessions, while others have worked focally with individuals or subunits of families. The different family therapy traditions can be usefully contrasted by comparing how each structures perceptual, cognitive, and executive processes when clinicians work with families—from each of these perspectives.

- What does a therapist look for?
- What does a therapist think about?
- What does a therapist do?

When multiple traditions or schools of psychotherapy are considered, the question naturally arises: which works best? There has been ample clinical evidence that each tradition "works," somewhat better than others for particular problems, or with particular families, or in the hands of particular therapists, or at different phases of recovery from illness (Pinsof and Wynne 1995). The evolution of mental health services, however, has led not to a dominance of any one of the family therapy traditions, but to comprehensive family-centered programs that now draw broadly from multiple traditions. These family-centered programs for preventing or treating psychiatric disorders have been validated to a substantial extent in empirical research studies, as discussed below. Different family therapy traditions are themselves best regarded as different sets of ideas and interventions to be valued as potential tools within comprehensive, multimodality treatment programs.

It should also be noted that the different family therapy traditions bear features in common. Each views a symptomatic patient not only as an individual, but as a family member in a family system organized by (1) affiliative bonds among its members, (2) a power hierarchy in terms of decision-making and who has what access to information, and

**Clinical Vignette 1**

Bill and Roberta requested therapy due to the fights they were having over parenting their two stepchildren. Roberta's 11-year-old son, David, with significant problems from attention-deficit disorder with hyperactivity, lived with them. Bill's 10-year-old son, whom he coparented with his former wife, lived with them every other weekend and one night each week. The arguments were so severe that they threatened the marriage.

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(3) shared values that constitute a sense of family identity. Each family therapy tradition addresses in its own ways a family's emotional relationships among its members, its organization as a system, and the meaning of its values in order to effect therapeutic change in the symptomatic member.

In the following paragraph we will illustrate the range of perspectives and interventions available in the different traditions by examining, in turn, how psychodynamic, structural, strategic, cognitive–behavioral, and postmodern family therapy traditions each might approach an identical clinical problem. The problem is explained in Clinical Vignette 1.

## Psychodynamic Family Therapy

Psychodynamic psychotherapy helps family members solve relational problems by understanding better how emotional processes influence the perceptions, feelings, and actions of those involved. The early psychoanalysts noted that intrapsychic processes of an individual powerfully shape his or her interactions with other people, and most so in emotionally intimate relationships of couples and families. Extending the concepts and language of psychoanalysis to family behavior was a logical next step for those who began meeting with parents and children, couples, and whole families. In particular, object relations theory provided a bridge from the individual intrapsychic processes to the interpersonal processes of families (Scharff and Scharff 1987, Framo 1991, Slipp 1991).

The era of ascendancy for psychoanalytic thinking coincided with development of general systems theory and cybernetics as conceptual models for understanding, controlling, and predicting the behavior of complex physical and biological systems. Psychodynamic family therapists adopted such systems concepts as boundaries and levels of hierarchy, and such cybernetics concepts as negative feedback and homeostasis. Such systems described complex family interactions, while preserving the psychological language of psychoanalysis in describing such motivational processes as projective identification.

**What to Think About.** In order to understand how one family member acts in relation to other family members, psychodynamic family therapy concentrates upon motivations, conflicts, defenses, and relationships from the past that currently influence the present. Family interactions are explained in terms of internal processes within individual family member. Therapeutic change is sought through family members gaining conscious insight into previously unconscious processes that have been generating problems in family relationships.

**What to Look For.** Psychodynamic family therapy grounds its work in historical information. Extensive individual and family histories are elicited in order to understand family members' experiential models of the world. These experiential models govern how meanings are attributed to such family patterns as rules for how people should respond and models for being a man or a woman, husband or wife, or mother or father. These models have developed out of each family member's personal history, the family's history and mythology, and their cultural history. Some of the diagnostic patterns upon which psychodynamic family therapists focus when assessing families include the following.

- *Projective identification*. Projective identification is an ego defense to which psychodynamic family therapists have attributed a crucial role in conflictual family relationships. In projective identification, one family member (a parent or couple partner) relates to another family member (a particular child or the other couple partner) as if he or she embodied a projected part of self. The projecting family member then interacts with, or relates to, the projected part of self as if that part were an internalized part of himself or herself. The projecting family member unconsciously prompts the other to conform to the way in which he or she is being perceived, evoking in the other the associated feelings and behaviors as if they were authentic. When viewed from the outside by the therapist, it appears as if the two are in collusion with one another in order to sustain these mutual, projected perceptions. Projection of disavowed elements of the self, whether positive or negative, has the effect of charging the relationship with emotion that has been transposed from an intrapsychic sphere into an interpersonal one. Acted out interpersonally, it serves to decrease psychic anxiety at the expense of an increase in tension and impasse in the relationship.
- *Unresolved grief*. When a family member, or the family as a whole, has not fully grieved losses, the family can become developmentally frozen. While so preoccupied with the past, it can be difficult to focus enough time and energy on current problems.
- *Clarity of ego boundaries and capacity for intimacy/separateness*. Conflicted family relationships can represent an alternative method for stabilizing emotional distance when the involved family members lack the emotional maturity to regulate closeness and distance in more differentiated ways. This has been a common model for understanding couples who chronically fight yet never separate.

**What to Do.** Psychodynamic family therapists employ the fundamental tools of psychodynamic psychotherapy (opening emotional expression, clarifying communications, encouraging family members to speak from the "I" position, and interpretation of unconscious conflicts) to resolve projective processes, cutoff relationships, and difficulties in modulating closeness and distance in family relationships. Psychodramatic techniques, such as doubling and role reversal, can play useful roles in implementing these interventions (Blatner 1994). Therapeutic rituals are particularly useful in facilitating grief over losses and in facilitating developmental transitions, such as a young adult leaving home or a couple moving into retirement years (Imber-Black and Roberts 1992). For example, a therapist can suggest to family members that they gather over dinner with their recent college graduate, both to review family photographs with fond remembrances from her childhood and to hear her speak as an adult about her future plans for a career. Such occasions marking existential time provide an opportunity to grieve losses, to embrace a new future, an to express openly the sadness and joy of each.

Psychodynamic family therapists commonly utilize family genograms when taking a family history. A genogram can provide a map of family life over time in a visual form

that can help family members grasp interactional patterns, particularly when the patterns extend across the generations (McGoldrick and Gerson 1985). A psychodynamic family therapy with Roberta and Bill might begin as given in Clinical Vignette 2.

Clinical Vignette 2

The therapist asked to meet with Roberta and Bill as parents before meeting with 11-year-old David. Utilizing a genogram she elicited a history, not only of their current nuclear family but also for Roberta's and Bill's parents' and grandparents' generations. She learned that Roberta had been ashamed of her family of origin. She characterized her mother as "a slut who stayed out all night." Eventually, Roberta's mother was diagnosed with bipolar disorder, but it was poorly controlled with multiple hospitalizations. Roberta was the oldest of six children, all from different fathers. Roberta stated, "Nobody raised me, but I raised my brothers and sisters." At age 12 years, a new stepfather entered the family but was verbally and emotionally abusive towards her. Consequently, "stepfathers" have had a negative connotation in Roberta's mind. Out of her childhood experiences, Roberta came to believe that "I'm okay so long as I can be on my own, because I can't trust or depend on anybody."

Bill, on the other hand, was the second oldest child in a strict, rigid family. Both parents were emotionally and physically abusive, his father more than his mother. At one point Bill tried to stop his father from beating his older brother and was himself badly beaten. Although angry and afraid of his father's violence, Bill also blamed his brother's out-of-control behavior for provoking his father. At 16, Bill pinned his father to the wall and said, "If you hit me, I'll kill you." His father never hit him again. Bill's mother was also abusive. Once she kept hitting him across the face, and he responded by telling her, "I hope you like it" and let her hit him until she finally stopped.

The therapist used the genogram session as an opportunity for Roberta and Bill to hear the stories from each others' childhoods that so charged with emotion their discussions about disciplining David, that arguing always had ensued. The therapist actively interpreted to them how Roberta's aversive experiences with a stepfather put her on guard with Bill and made her more protective of David whenever Bill tried to discipline him. In contrast, Bill's experiences with his brother and parents, people he described as "having out-of-control behavior," led him to overreact to David's attention-deficit/hyperactivity disorder (ADHD). Each of them, operating out of their own well-meaning logic, was making the problem worse. The therapist then used psychodramatic techniques and had them create and then practice ways in which they could work as a team in disciplining David.

## Structural Family Therapy

Structural family therapy considers problems involving a particular family member to be inextricably linked to the organizational context of the entire family. It solves problems by changing the family's organizational context. Structural family therapy thus emphasizes an understanding of a family in terms of the family rules and roles that shape its members' actions.

Family structure is the internal organization of the family that dictates how, when, and to whom family members relate while carrying out the various functions of the family (Aponte and VanDeusen 1981, Colapinto 1991). Some important elements of family structure for clinical work are boundaries, hierarchy, alliances, and coalitions.

- *Boundaries*. Rules defining who participates and how, in particular moments of family life. For example, a boundary around the parental couple means that the children are included in discussions of certain topics but not in others.
- *Hierarchy*. Relative influence of each family member upon the outcome of an activity. For example, all family members may have opinions about spending money, but the parents as a couple typically have the final say.
- *Alliances*. Family members joining together to support another family member. For example, older children may join the well-parent in organizing to parent younger children if the other parent were to become seriously ill.
- *Coalitions*. Family members joining together in opposition to another family member. For example, a grandchild and grandmother might quietly ally together for the child to stay up late at night against the mother's wishes when the child is at grandmother's house.

The family structure should provide cohesive and flexible responses to life stresses so that important family functions—parenting, providing income, marital intimacy, recreation, and other activities—can be carried out successfully, and family members can grow and mature in their individual lives.

**What to Look For.** A structural family therapist observes closely the flow of family structures as family members talk about and interact together around the presenting problem of the therapy. The therapist wishes to witness how sequences of family behaviors are enacted during interactions in the sessions, particularly the occurrence of a symptom as it is embedded within different configurations of organized family interactions. The therapist observes how boundaries, hierarchy, alliances, and coalitions are associated with the presenting symptom, as well as any repetitive behavioral sequences (verbal or nonverbal) that involve symptomatic behavior.

**What to Think About.** The structural family therapist considers the problem to be sustained by the current family structure and its community ecosystem. Important questions to answer in assessing these relationships include the following.

- To what elements of family structure—boundaries, hierarchy, alliances, coalitions—do occurrences of the presenting problem appear linked?
- What family functions are blocked by the problem? If not for the problem, what would be happening that is not happening now?
- For whom is the problem a concern? Who is most affected? Who would need to change for the symptom to disappear?

**What to Do.** Structural family therapists ameliorate symptoms by shifting family structure. Boundaries can be strengthened or weakened by behavioral assignments that

exclude a particular family member from certain moments of family life (e.g., an assignment for parents to leave children with a baby sitter to go on a date alone) or include a particular family member where that person had been absent (e.g., involving both parents in collaborative disciplining of a misbehaving child when the father had been only peripherally involved). Alliances are encouraged when they support the individual development of family members and strengthen the family as a whole. Secret coalitions, particularly when they cross generational boundaries, are targeted for therapeutic disruption as when one parent covertly supports a child's oppositional behavior with the other parent. A structural family therapy with Roberta and Bill might include the following as given in Clinical Vignette 3.

Clinical Vignette 3

Before Roberta's marriage to Bill, Roberta and David had lived together as a unit for years, which had fostered an intense bond between them. In order to shift successfully to the structure of a stepfamily, Roberta needed to let a relationship build between David and Bill, and that between her and David to loosen. She also needed to build a relationship with Bill's son.

In their spousal relationship, both Bill and Roberta needed to enhance their sexual intimacy. They needed to develop a style of working together as a parental team. Bill, in addition, needed to limit appropriately his involvement with his ex-wife. Both boys needed to have time to create a relationship with each other.

In planning a strategy to counter fights around disciplining the two boys, the therapist began by viewing Roberta and David as an enmeshed-couple. That is, Roberta would "know" what David felt when Bill attempted to discipline him, so she stood up for David "to protect him." Although she saw herself as a protective parent, she was not allowing Bill and David to work things out for themselves. Moreover, David learned how to provoke Bill in order to prompt his mother to side with him.

The therapist gave Bill and Roberta an assignment to go out to dinner in a quiet, comfortable restaurant and to make a list of David's positive qualities and actions that they felt good about. They were then told to make a list of those behaviors, which they felt were destructive, and what they thought should be done about them. The therapist then met with Bill and Roberta alone and discussed their lists. As the therapist had anticipated, a fight ensued about David's behavior in the subsequent family meeting with David present. Through this spontaneous enactment, the therapist helped the family rechoreograph the sequence of interactions. In a new pattern, the couple would first establish decisions together, then would support each other in avoiding David's moves to side his mother against Bill.

## Strategic Family Therapy

Strategic therapy is built upon the premise that a therapist is responsible for planning a strategy that solves successfully the family's presenting problem. The therapist sets clear goals that intervene by changing relational and communicational processes in the family (Madanes 1981, Stanton 1981). Strategic therapy was designed as a counterpoint to psychodynamic psychotherapy by emphasizing "how" people can behave differently in order to solve problems, rather than "why" they behave as they do. Its development was heavily informed by Ericksonian hypnotherapy and application of cybernetics principles to human systems (Madanes 1981). Its impetus also came from the discovery of the one-way mirror, permitting detailed tracking of repetitive family processes that triggered symptoms. Strategic therapy planned interventions that would disrupt such behavioral sequences, whether by direct behavioral prescriptions or by indirect paradoxical interventions.

**What to Think About.** The focus of strategic therapy is upon problem solving. Problems are viewed as persistent efforts by one or more family members to apply a solution that makes sense but is inadequate for the problem at hand, such that "the solution becomes the problem." Common-sense understandings often lead people to pursue unsuccessful strategies even though it ought to be apparent that the problem is not resolving. For example, people intuitively attempt to cheer up a person who is depressed, even though cheering up (a solution) usually makes the depression (the problem) worse.

Strategic therapists commonly view clinical problems as emerging out of difficult life-cycle transitions, both predictable ones (e.g., marriage, birth of a child, separating/individuating of an adolescent) and unpredictable ones (e.g., loss of job, sudden illness, a death in the family) that necessitate shifting to new patterns of perceiving and acting. At such times when innovative problem solving is needed, people nevertheless persist with once successful strategies that are now outdated.

**What to Look For.** Strategic therapists are most interested in the here-and-now context of the problem, rather than in its history. They seek to learn what each involved person believes about the problem, and how these beliefs are acted upon in efforts to generate a solution. Questions are asked about who, what, when, where, and how people are involved, in order to ascertain how moves are sequenced in the family game.

**What to Do.** The central aim of a strategic therapist is to motivate family members to try novel solutions, rather than repeating what has been tried in the past. Psychoeducation, direct behavioral assignments, and paradoxical or defiance-based directives are the cornerstones of strategic therapy. In-session interventions and out-of-session homework are used. Strategic therapists have become best known for their paradoxical directives. Paradoxical directives include the following.

- *Reframing or relabeling the symptom*. By changing the context of actions constituting the symptom, the meaning of the event is reframed. For example, a husband's emotional distancing could be reframed as "his way of getting his wife to notice him."
- *Prescribing the symptom or behavioral sequence*. By using a rationale that is plausible in its logic, a therapist can encourage family members to engage in the very behavior that needs to be eliminated. For example, a wife whose husband is emotionally distancing might be told to continue to pursue her husband because "this lets him know that he is the center of her life and that there is nothing else about her life that she finds valuable or interesting." She might be instructed to continue in her behavior for

his sake, even though it may give her friends a distorted idea about her. When the reframe "fits," yet the new meaning feels distasteful, the rebound against the directive can paradoxically propel therapeutic change.

- *Restraining the system*. The therapist can attempt to discourage or even deny the possibility of change. For example, a therapist may tell couple partners to "go slow" or may emphasize dangers of improvement. Family members may then react against the therapist's conservative outlook by pressing forward to change.
- *Positioning*. The therapist attempts to shift a problematic "position" (usually an assertion that the patient is making about self, the problem, or a partner) by accepting but exaggerating that position. This intervention is used when the partner's position is thought to be maintained by its complementary, reciprocal response from the other partner. For example, when one partner takes an optimistic stance and the other a pessimistic one, a therapist may suggest the pessimistic spouse to worry even more so that the optimistic spouse can feel more secure and even more happily optimistic. Here, too, if a new explanation has a plausible logic, but frames the behavior in a manner that renders it aversive, the behavior will change. A strategic therapist might have tracked the characteristic pattern of arguments between Bill and Roberta as given in Clinical Vignette 4.

Clinical Vignette 4

When Roberta felt unheard, she yelled louder. As her voice became louder, Bill became more emotionally distant and coldly rational. As the fight escalated, Roberta first threw an object at Bill, then asked him to leave, then threatened divorce. The strategic therapist considered each of these behaviors to be efforts at a solution that likely had worked successfully in past conflicts, but now, was amplifying the problem.

The therapist noted that each time the couple "made up" each reported having "the greatest sex." She referred to their pattern as an "accordion dance" and told them that should they persist in it, they would in time reach a point of no-return. She then modified its rules by suggesting that Bill ask Roberta to leave the room to cool off when she appeared to be losing control. If Roberta refused to leave, then Bill would say that he needed to take a walk to clear his head.

Alternatively, the therapist might have suggested to Roberta that "if you don't want to be heard, then you should continue to scream louder … but if you do want Bill to hear you, then you should do an 'EF Hutton,' that is, to whisper instead of yell."

## Cognitive–Behavioral Family Therapy

Cognitive–behavioral family therapy applies principles of learning theory to help family members solve problems by modifying cognitive distortions and repetitive problem-inducing interactions, and by learning new knowledge and skills. Cognitive–behavioral family therapy relies heavily upon family psychoeducation and a teaching/coaching stance of the therapist.

Behavioral family therapy emerged from behavioral modification programs for young children with such problems as bedtime tantrums, nocturnal enuresis, and aggressive behavior (Arias 1992, Falloon 1991). It is based upon the influence family members hold by offering positive and negative reinforcements to other family members. Parents and spouses are trained to eliminate reinforcement contingencies for undesirable behaviors.

Cognitive interventions engage family members as coinvestigators who study the ecology of family problems and symptoms and discern how thoughts, feelings, and behaviors interplay. A therapist assists family members in identifying when such cognitive distortions as catastrophic thinking, overgeneralization, or misattributions lead to conflicts in relationships (Epstein et al. 1988, Freeman et al. 1989) (see Clinical Vignette 5).

Clinical Vignette 5

Addressing David's attention-deficit disorder was an important aspect of the therapy, and Bill and Roberta began reading materials about the disorder. In sessions, they were taught to make distinctions in David's behavior according to Green's (2000) concept of three baskets. In Basket A steps relevant to safety that must be taken regardless whether the child becomes agitated in response; in Basket B are new skills to be taught and practiced, pacing the teaching according to the child's capacity to respond; in Basket C are the child's behaviors that should be ignored. During the family sessions the therapist worked on problem-solving techniques and empathic listening, helping family members to notice and comment on positive feelings and to speak negative feelings respectfully.

**What to Look For.** Families presenting problems for therapy often have

- difficulties in recognizing deviant behavior
- lack of clearly-defined family rules
- problems in emotional communication among family members, usually a paucity of expression of positive feelings coupled with an excess of negative expressions
- relational conflict associated with either a paucity of relational skills or interpretive errors based on faulty assumptions or cognitive distortions.

**What to Think About.** A cognitive–behavioral family therapist considers each member of the family to be doing his or her best to cope with the behavioral contingencies perceived at that point in time, given the practical and emotional restraints experienced. Family members need to acquire knowledge about cognitive and behavioral principles, to gain skills needed to reinforce desired behaviors, to eliminate reinforcement of undesired behaviors, to modify faulty assumptions and interpretations of others' actions, and to learn skills for communicating clearly and effectively.

**What to Do**

- *Psychoeducation*. Educational modules about the presenting problem are taught when family members appear to lack a significant understanding of issues, ranging from such general topics as developmental milestones of children and principles of learning theory, to specific

information about a particular psychiatric disorder (Falloon 1991)
- *Communication training*. Empathic listening, expressing positive feelings, and speaking negative communications more respectfully are taught as skills (Falloon 1991)
- *Problem-solving training*. Family members practice consistent, structured approaches for resolving conflicts (Falloon 1991)
- *Operant-conditioning strategies*. Behavior shaping and time-out procedures are taught to increase desirable behaviors among children (Falloon 1991)
- *Contingency contracting*. Coercive, blaming patterns of family behavior are replaced by contracts that specify what behaviors involved family members each to agree to perform (Falloon 1991)
- *Thought diaries*. Out-of-session, assignments are made to track habitual patterns of thoughts, feelings, and behaviors in generating symptoms (Freeman et al. 1989).

## The Postmodern Family Therapies

The postmodern family therapies include narrative, solution-focused, collaborative language systems, and feminist family therapies (Anderson 1987, 1997, de Shazer 1985, Epston 1989, Epston and White 1992, Freedman and Combs 1995, Griffith and Griffith 1994, Madsen 1999, O'Hanlon and Weiner-Davis 1989, Penn 2001, Tomm 1987, Weiner-Davis 1992, Weingarten 1995, White 1989, 1995, 2000). Postmodern family therapies emerged in the 1990s as an effort to render family therapy more relevant to cultural and political challenges that families were facing. Psychodynamic, structural, strategic, and cognitive–behavioral therapies each originated as psychological theories to explain how family relationships and communications could generate symptoms in individual members. By the late 20th century, however, the impact of the wider culture on family life began overtaking the internal processes of families in their importance for explaining symptoms. Increasing numbers of single-parent and other nontraditional types of families were seeking mental health services. Racism, healthcare disparities, economic hardship, and other external stressors seemed to account most for many families' distress. The growing cultural diversity of American families further diverged from the stereotypic middle-class families that had inspired the first generation of family therapies. From different vantage points, each postmodern family therapy has sought dual objectives—first, to liberate family members from constraining language and ways of being imposed by a larger culture; second, to empower families by organizing therapy around their strengths and competencies. Postmodern therapies have focused less on how families operate as closed behavioral systems and more upon how family life is shaped by its cultural container of language and social practices.

Each postmodern therapy has sought to empower families in its own unique way. Feminist therapists explicitly challenged implicit gendered assumptions about power, decision-making, and roles in families. Solution-focused and narrative therapists, rather than focus upon family pathology, have made family strengths and competencies their centerpiece of therapy. They have helped family members become more creative problem solvers by "thinking outside the box" of prevailing culture and by utilizing learning drawn from their own lived experiences. Collaborative systems therapists organized family dialogues that were tailored to be protective, inclusive, and responsive to each family member. The therapist would then step back from an authoritative stance as expert so that this empowered dialogue itself could originate solutions.

The postmodern therapies have made contributions that have broadly influenced family therapy through the following methods.

- Methods for crafting questions that maximize reflection and creative problem solving.
- A persistent focus upon family strengths, skills, competencies, resources, and other sources of resilience.
- Clinical methods that counter adverse cultural influences that help generate and maintain family problems.

Narrative and feminist therapists encourage family members to become mindful how narratives from the broader culture constrain their lives. Solution-focused therapists examine how people construct solutions to problems in daily life. They help family members learn from those occasions when the problem is *not* occurring and to learn from those "exceptions" when the problem might have been expected to occur but did not. By studying occasions when the problem did not happen, family members can practice tasks that amplify the frequency and intensity of these "solution sequences."

While postmodern family therapies have reoriented family therapy toward family resilience, empowerment, and strategies to counter cultural oppression, they also have continued to utilize techniques and methods from other therapeutic traditions as needed to solve particular problems. For example, a feminist family therapist might well work with a couple on gendered marital roles that have contributing to the wife's depression. At the same time, she might work in the manner of a structural family therapist in facilitating an alliance between parents to communicate clearly to their child and to provide consistent behavioral consequences for their child's temper tantrums.

**What to Think About.** Each person makes sense out of his or her life experiences by attributing meaning to them. This meaning is shaped by a canon of personal narratives that are told and retold to self and others. Among the most important are those of identity about who one is as a person and to whom one belongs as a family. Certain dominant narratives play a larger role than other narratives in organizing perceptions, thoughts, and actions. How a family member views oneself and other family members is shaped by the limits of available language for articulating experience—the metaphors, stories, and beliefs that he or she employs. Relational impasses occur and problems emerge when

- one or more family members lack either the emotional vocabulary or narrative skills necessary for making one's personal experiences understandable to others;
- available narratives preclude any ways of relating other than conflictual ones;
- specific words hold very different meanings for different family members due to unique personal stories connected to that language (e.g., "loyalty," "trust," "safety");

- family members have become positioned relationally such that they cannot hear, tell, and/or expand their stories in conversation. They have become so confused by or habituated to the conflict that they have stopped listening.

Therapy can provide a context in which family narratives that limit relationships can be identified. Effects of constraining narratives can be attenuated when specific historical, cultural, or political contexts out of which they emerged are discussed, and the interpretive assumptions upon which they rest are made explicit. Alternatively, more useful narratives can be identified that have gone unnoticed within forgotten experiences family members have had with each another.

**What to Look For**

- Listen for the specific words and precise manner in which people use language. A focus of therapy is the language itself and the limited possibilities it entails.
- Metaphors, oft repeated phrases, and other evocative uses of language are noted as "doors to be knocked upon" by asking specific questions about family members' stories of lived experiences that gave them meaning.
- "Unique outcomes" or "exceptions" when problems might have been expected to occur, but did not.

**What to Do.** Narrative approach to therapy consists of two phases—first, eliciting family narratives that have been important in their influence upon family life; second, authoring new narratives and reauthoring old ones that have been too limiting in their possibilities.

- *Eliciting important narratives*. First priority is creation of a therapeutic relationship within which important first-person narratives can be safely told, acknowledged, and understood. In particular, the therapist carefully watches for nonverbal signs that the dialogue is opening up or shutting down as indicated by family members' breathing, posture, and flow and tone of speech.
- *Authoring new narratives and reauthoring constraining ones*. As narratives relevant to the problem are told, the therapist crafts questions that facilitate:

(a) Retrieval of other forgotten, or unnoticed, narratives that might enhance solving the problem of the therapy, in contrast to a narrative that has been dominant. For example, an elderly husband might be asked: "In what year of your life were at the top of your game? What was happening then in your life?" Such a question conceivably might bring forth stories of vitality about this elderly man's preferred identity that had been forgotten in the present era of his life, with its frail health, depressed mood, and conflicted marriage.
(b) Asking questions about details of a constraining narrative that shift its meaning through expanding awareness of its historical contexts; punctuating differently its time-line; adding forgotten characters whose actions had also contributed to the story; heightening awareness of complexities in characters' states of mind.

- The therapist employs such questions as circular, reflexive, unique outcome, or relative influence questions (Tomm 1987, White 1989) to gather fresh descriptions of family life that might constitute an alternative, preferred narrative. For example, a unique outcome question such as "Have there been occasions when you had every reason to expect your son to disobey the rules, but to your surprise he did not?"can elicit new accounts of a son who at times can exercise judgment and self-control, rather than a pervasive narrative of "conduct disorder." Likewise, such a relative influence question as [to the son] "When you and your mother spend the day together, how many times out of 10 does 'disobedience' take charge of you? How many times out of 10 do you take charge of 'disobedience'?" can open a path to a treatment plan in which the son joins an effort to increase from 3 to 4 the number of times out of 10 then he takes charge of disobedience.
- A solution-focused therapist may assign family members the task of studying segments of time when the problem is not occurring, looking for exceptions. Examples of solution-focused questions include

(a) Between now and the next time we meet, I want you to observe what happens between both of you that you do value, would NOT want to change, and would like to see happen more often in the future."
(b) The miracle question (de Shazer 1985)—"Suppose that one night, while you were asleep, there was a miracle and this problem was solved. How would you know? What would be different? How would other family members know without you even saying a word about it?" [The therapist then negotiates with family members what part of this new reality that they would be willing to implement the next day, as if the miracle had occurred.]
(c) (Weiner-Davis 1992) "If the problems between you and your partner got resolved all of a sudden, what would you do with the time and energy you have been spending on fixing or worrying about the marriage? Describe what you would do instead."
(d) (Weiner-Davis 1992) "What might be one or two small things that you can do this week that will take you one step closer to your goal?"
(e) (Weiner-Davis 1992) "What, if anything, might present a challenge to your taking these steps this week, and how will you meet the challenge?"

Some interviewing methods associated with the postmodern therapies are illustrated in Clinical Vignette 6:

Clinical Vignette 6

Roberta repeatedly referred to her anger as a "flash flood." Noting her selection of this metaphor, the therapist asks what important stories of her life experience gave special meaning to "flash flood." She described growing up in the Southwest where in the middle of an arid summer, a thunderstorm could trigger a flash flood that suddenly and without warning swept away everything in its path. Later during a couple's session with Bill present, the therapist asked Roberta: "Were there times when, to your surprise, you felt the thunder and lightening of your emotion, but instead of overflowing the river ran smoothly?" Roberta

responded with an account of a time when she suddenly felt angry with Bill, but had "used words instead of action" and said, "I am mad." The therapist then asked more detailed questions about what each of them noticed, thought, felt, and enacted on this occasion that had been different. She then said to Roberta, "Between now and the next time that we meet, I would like you to observe those times when your emotions begin to churn but you are able to ride the rough waters to a successful conclusion." She then instructed Bill to notice those times when he would have expected Roberta to "blow up," but she didn't … and to notice what happened and how each of them felt at the time. In subsequent sessions a new plan for engaging in conflict was constructed out of their observations and reflections on this "unique outcome."

## From Family Therapy to Family Psychiatry

Family therapy through its early years treated families while often minimizing any need for psychiatric treatment of patients as individuals. The earliest approaches to family therapy built upon psychodynamic theory and extended to the family similar ideas about "family pathology" instead of psychopathology. Early versions of psychodynamic, structural, strategic, and cognitive–behavioral family therapies each sought to treat family pathology as the primary source of mental illnesses. By the late 1990s, however, family therapies were becoming more measured in their curative claims. They shifted to more collaborative stance in which families were regarded as allies in treatment, rather than sources of pathology. A new focus was placed on educating families about mental illnesses and their treatments, including pharmacological treatment for severe symptoms (Berman and Heru 2005).

Meanwhile psychiatry as a discipline was showing a renewed interest in roles of families in psychiatric treatment. Clinical research produced vulnerability/stress models for psychiatric illnesses that pointed consistently to both biological factors and family factors in the genesis and maintenances of mental illnesses. American Psychiatric Association Practices Guidelines for most psychiatric illnesses mandated attention to families (Berman and Heru 2005). Although seldom conducting formal family therapies, psychiatrists utilized family therapy skills when treating individual patients and in clinical work involving larger systems (Guttman et al. 1999, Slovik et al. 1997).

Family psychiatry that has emerged since 2000 has emphasized family skills for assessment, education, and intervention as essential components of biopsychosocial treatment for individual patients. These family skills have focused on involvement of family members as collaborators in treatment, education of family members about medical, psychosocial and behavioral issues, interventions to reduce the burden of illness upon families, and mobilization of family strengths as resilience factors for preventing illness progression or relapse (Berman et al. 2006, Berman and Heru 2005, Heru 2006).

## Family Psychoeducation

Family psychoeducation is a program of cognitive, behavioral, educational, and supportive interventions implemented in close consultation and partnership with family members. Family psychoeducation for schizophrenia best illustrates the evolution from pathology-focused family therapy to family-centered treatment that engages family members as collaborators. Early family therapists had hoped that a family approach would open new venues for treating schizophrenia where both psychoanalysis and the then available psychopharmacology had faltered. The Bateson project in Palo Alto made famous the double-bind theory of schizophrenia, concluding from analyses of audiotaped family conversations that psychosis was a coherent response to communications with conflicting directives between the explicit verbal message and the implicit nonverbal one (Sluzki and Vernon 1971). Subsequently, Jay Haley, a Bateson research team member, tailored family interventions around a Hamlet-like assumption that psychotic behavior represented a move by the psychotic family member to wield power through force of illness (Haley 1976, 1980).

These family therapy models that located the genesis of schizophrenia in family relationships and communications never gained strong support from empirical research. Moreover, family advocates were alienated by the implicit pathologizing of families with psychotic members. By the 1980s, some family therapists working with these disorders were proposing that family therapy could be more effectively applied by engaging families as partners in treatment, instead as sources of psychopathology. These efforts were characterized by a fresh set of assumptions (Dixon and Lehman 1995).

- Severe psychiatric disorders, such as schizophrenia and bipolar disorder, are regarded as illnesses.
- The family environment does not cause the disorder but can influence its course and severity.
- Support is provided to families who are enlisted as partners and collaborators in treatment.
- Family interventions are only one component in a treatment program that includes routine drug treatment and outpatient clinical management.

These new clinical approaches integrated psychoeducation, behavioral problem-solving training, family support, and crisis management in interventions with either individual families or groups of families.

The construct of expressed emotion (EE) played a significant role in the evolution of family psychoeducation (Anderson et al. 1986, Leff and Vaughn 1985). During a structured interview, families were given an EE rating based on observations of critical comments, hostility, and overinvolvement among family members. Over two decades an enormous body of research suggested that patients living with families characterized by high levels of EE were more vulnerable to relapse (Bebbington and Kuipers 1994). Interventions were then designed that relied heavily upon family psychoeducation in order to help high EE families to change to a low EE status.

Development of family psychoeducation was also propelled by the self-help family education movement that emerged after the Reagan assassination attempt by a man with schizophrenia. Families mobilized by the National Alliance Against Mental Illnesses and related advocacy organizations demanded information that would help families

cope with severe mental illnesses. Family psychoeducation approaches emerged that sought to "put the illness in its place" (Gonzalez et al. 1989) by helping families acquire the knowledge, skills, and resources needed to minimize the loss of time, money, and energy from a chronic medical or psychiatric disorder. These approaches avoided promising a cure. Rather, treatment was considered successful when family members accepted the presence of the illness but refused for it to organize the life of the family. Unlike earlier family therapies that avoided psychopharmacology, family psychoeducation approaches made maximal use of psychotropic medications to control disruptive symptoms and openly embraced interventions drawn from other individual, family, or social network therapies.

Family psychoeducation for schizophrenia was honed into a systematic therapeutic approach by well-conducted empirical research programs during the 1970s and 1980s and validated by empirical research studies (Goldstein et al. 1978, Leff et al. 1982, Hogarty et al. 1986). For example, the University of Pittsburgh Schizophrenia Research Project, by using intramuscular depot antipsychotic medications, determined that the benchmark relapse rate for psychosis in schizophrenia was 40–50% over a 2-year period, even with optimal adherence to medication treatment, and that rates were still higher among patients with multiple past relapses (Hogarty et al. 1986). They designed a family psychoeducation program in which family alliance-building and education about the illness began before hospital discharge. Groups of families were gathered for a "survival skills workshop" consisting of discussions about schizophrenia diagnosis, etiology, use of antipsychotic medication, and the needs of patients and family members when there is a psychotic member. They made practical suggestions for adjusting performance expectations, diminishing high expressed emotion, simplifying family communications, normalizing family routines, and making best use of professionals. Subsequent family meetings after discharge then addressed both adherence to antipsychotic medications and family psychosocial processes in a phased plan covering the first-year "reentry phase," social and occupational rehabilitation, and latter stages of treatment. Family meetings focused particularly upon elements of schizophrenia for which therapeutic responses by family members would be often counterintuitive—the need to soften criticism and lessen expectations for high performance because of vulnerability to emotional overstimulation and confusion from negative symptoms of schizophrenia (apathy, isolation, amotivation) are considered to be symptoms of the illness rather than laziness or a flawed character.

The subsequent treatment outcomes were impressive. The first-year relapse rate dropped from the expected 50%, with antipsychotic medications alone, to 19% when family psychoeducation was added, and to 0% when medications, family psychoeducation, and social skills training for the patient were combined.

The effectiveness of family psychoeducation was shown to be further amplified when applied to family groups, rather than to individual families in isolation. Single-family therapies often involve only 2 or 3 people, while a multifamily group commonly involves 10 or more people. Multifamily groups thus expand the patient's and family's social network (McFarlane 2002). Their usefulness has been demonstrated not only for psychiatric, but also for nonpsychiatric disabling medical conditions (Gonzalez et al. 1989, Steinglass 1998).

For schizophrenia, William McFarlane and colleagues designed a multifamily group therapy that has shown particularly robust therapeutic effects in empirical studies (McFarlane 2002, McFarlane et al. 1995, 1996). A group of families meets regularly to work toward creating home and social environments in which affects would be relatively warm, communications clear and simple, change kept to a minimum, the impact of life events cushioned, and graduated expectations set at a level consistent with the patient's state of symptoms. In an initial workshop, patients do not join other family members during the initial orientation and educational sessions, but do join them for later illness management sessions. Each multifamily group meets biweekly, led by two cotherapists and including patients. An individual patient's or family's problem is addressed by the entire multifamily group in a structured, problem-solving process guided by the clinician. These family meetings focus upon management issues for different symptoms and families' uncertainties about how best to promote recovery and rehabilitation. After the second year, the ongoing groups typically evolve into natural social networks for mutual support in enhancing rehabilitation and quality of life. McFarlane's multifamily group treatment, which included family psychoeducation and maintenance antipsychotic medications, reduced risk of relapse for an extended period of time and did so more effectively than family psychoeducation with individual families. Elements that appeared to be tied to its outcome effectiveness included

- creation of social contacts and support;
- problem solving with others bearing the burden of the same disorder;
- countering stigma;
- cross-parenting of adolescents;
- normalizing family communications;
- intervening effectively during crises.

In a cost-saving estimate, the multifamily psychoeducational groups achieved a 1:16.50 ratio, saving $16.50 for every dollar spent on mental health services.

Family-focused psychoeducational interventions have been developed for other psychiatric disorders. Family-focused treatment for bipolar disorder, for example, integrates family psychoeducation, communication training, and problem solving into a 20-session therapy extending over most of a year. This intervention in a controlled study has been shown to delay relapse of bipolar disorder (Miklowitz and Goldstein 1997, Miklowitz et al. 2000).

## Family Resilience

While family psychoeducation approaches have focused on roles that families can play in reducing frequency of illness relapse or buffering its severity, family resilience interventions extend this strategy to identify salutary family processes that not only buffer severity of illness, but prevent its onset for those at risk. Key processes can be identified that enable couples and families facing disruptive crises or persistent stresses to strengthen relationships, regain functioning, and further the growth of its individual members (Walsh 1998, Wolin and Wolin 1993). For example, twin studies of schizophrenia have identified some families who

seemed capable of reducing the risk of illness onset for genetically at-risk adopted children. In addition, some children exposed to horrific childhood experiences with alcoholism, mentally ill parents, physical abuse, sexual abuse, or emotional deprivation, nevertheless have grown up to be psychologically healthy and hardy adults. Michael Rutter's (1985, 1987) research found that even combinations of severe risk factors were predictive of mental illness for no more than half the affected children.

Family resilience refers to coping and adaptational processes in the family as a functional unit (Walsh 1998, Wolin and Wolin 1993). From this perspective, a stressor affects at-risk children only to the extent that they disrupt crucial family processes that otherwise would neutralize or buffer the stressor (Patterson 1983). Family resilience rests upon several systemic principles (Walsh 1998, p. 24).

- The hardiness of individuals is best understood and fostered in the context of the family and larger social world, as a mutual interaction of individual, family, and environmental processes.
- Crisis events and persistent stresses affect the entire family, posing risks not only for individual dysfunction but also for relational conflict and family breakdown.
- Family processes mediate the impact of stress on all members and their relationships, with protective processes fostering resilience by buffering stress and promoting recovery, and maladaptive responses heightening vulnerability and risks for individual and relationship distress.
- All families have the potential for resilience, which can be maximized by encouraging their best efforts and strengthening key processes.

Innovative research programs during the 1980s and 1990s sought to identify family factors contributing to the resilience of at-risk children and to design interventions that could help families better protect vulnerable children. These family resilience programs regarded resilience not to be embedded within the character of the person, but immanent within the communicational and relational systems of the person's family and social networks.

The family resilience program best validated by empirical research has been the family-based program of William Beardslee and colleagues at Boston Children's Hospital to reduce risk of onset of depression for children reared by a parent with a major depressive disorder. Epidemiological studies have established that children growing up in a home with a depressed parent have a 50% likelihood of developing a depressive disorder during adolescence and a four- to sixfold greater likelihood of receiving a psychiatric diagnosis in adulthood, particularly a depression diagnosis, than children growing up in a home with neither parent depressed (Beardslee 1998, Beardslee et al. 1998, 1999). Beardslee's group studied children who ultimately showed no signs of adult life depression, despite growing up with a depressed parent, in order to identify individual and family processes that could attenuate this risk. Factors conferring protection upon children at risk for depression were identified as

- becoming activists and doers;
- becoming heavily involved in school and extra-curricular activities;
- developing deep commitments to and involvement in interpersonal relationships;
- seeking self-understanding as a way to deal with a parent's depression;
- expressing articulate understanding of the parent's illness and problems ensuing from it;
- refusing to feel blame or guilt for the parent's illness.

Beardslee and colleagues designed a family-based cognitive–behavioral intervention that attempted to educate families about depression, using either a clinician's visit or group lecture as format. The intervention sought to enhance the understanding of depression in all family members and to promote resilience in children at risk. Its steps consisted of an initial assessment of all family members. A program of psychoeducational material about affective disorders not only taught facts but linked the educational material to that family's life experiences. Family members were counseled to counter children's feelings of guilt and blame. Children were encouraged to develop relationships both within and outside the family. Parents were encouraged to facilitate their children's independent functioning in school and outside home (Beardslee 1998). This clinician-facilitated format was conducted over four to eight sessions, initially alone with parents then individually with the children, ending with a whole family session and a wrap-up session. Follow-up studies have validated sustained reduction in family risk factors for depression three years after intervention including an improved understanding of the parent's illness by the child; better communication between parents and children about the illness; and enhanced attunement of parents to their child's experience; and higher adaptive functioning by the child. Children who began showing symptoms of depression were identified early in the course and treated (Beardslee et al. 1999). Two notable processes that appeared correlated with effectiveness of the intervention were

1. active linking of life experiences of the family to information presented, rather than simply delivering factual information;
2. giving the child an active voice in family discussions about the illness.

With programs such as Beardslee's, family resilience programs have moved past treatment of acute illness and relapse prevention, to primary prevention of the disorder itself. Such programs identify risk factors and protective factors for onset of illness, relate these factors to family organization, communications, and knowledge of the disorder; and design family interventions that enhance family understanding, attenuate risk factors, and amplify protective factors (see Table 92–1).

## Reducing Caregiver Burden in Chronic Disorders

Family interventions have helped relieve suffering of family members who care for patients with chronic illnesses. Family members of patients with chronic disorders, both medical and psychiatric, suffer financial difficulties, limited social lives, loss of recreation, and constant worry and vigilance. Family members in turn impact both the psychological well-being and capacity for disease management by the

**Table 92–1 Resilience Factors That Protect Children at Risk for Depression Due to Living with a Depressed Parent**

- Becoming activists and doers
- Becoming heavily involved in school and extracurricular activities
- Developing deep commitments to and involvement in interpersonal relationships
- Seeking self-understanding as a way to deal with a parent's depression
- Expressing articulate understandings of the parent's illness and problems ensuing from it
- Refusing to feel blame or guilt for the parent's illness
- Learning to link life experiences in the family to factual information about depressive disorders
- Acquiring an active voice in family discussions about the illness

*Source*: Beardslee WR (1998) Prevention and the clinical encounter. Am J Orthopsychiatr 69(4), 521–533; Beardslee W, Versage EM, Salt P, et al. (1999) The development and evaluation of two preventive intervention strategies for children of depressed parents. In Rochester Symposium on Developmental Psychopathology, Vol. 9, Development Approaches to Prevention and Intervention, Cicchetti D and Toth SL (eds). University of Rochester Press, Rochester, New York.

ill family member. Objective burden describes the effects of caregiving on health, activities, and finances of caregivers, while subjective burden consists of anxiety, depression, and psychosomatic symptoms associated with the caregiving role (Heru et al. 2005).

Caregiver burden reduction strategies have most commonly targeted dementias and such commonly occurring diseases as cancer and heart diseases. A metaanalysis of 70 research studies found that family interventions including only spouses successfully reduced patient's depressive symptoms. Further, interventions including other family member reduced depressive symptoms among the care givers (Martire et al. 2004). The Resources for Enhancing Alzheimer's Caregiver Health (REACH) has served as a research program for developing multimodality strategies to reduce family burden in Alzheimer's Disease, emphasizing family psychoeducation and behavioral problem-solving skills (Gitlin et al. 2003, Teri et al. 2005). Caregiver burden reduction programs have similarly been developed for chronic pain, heart disease, cancer, end-stage renal disease, and other chronic physical disorders.

Schizophrenia has been found to produce as great an objective family burden as does severe physical disease. However, its subjective burden is even greater due to the impact of the psychosis upon family members, including the perceived lack of patient contributions to family well-being, rejection of the patient by relatives, more limited social networks, and family worry over suicidal ideation (McDonell et al. 2003, Mueser et al. 2001, Perlick et al. 2006). Significant improvement in family burden in families with schizophrenia has been demonstrated in a controlled study utilizing a psychoeducation family intervention. This family intervention educated family members about symptoms, treatment, and early signs of relapse; provided communication skills training; and provided problem-solving skills training (Magliano et al. 2006). Childhood autism produces a high level of family burden, similar to that of schizophrenia (Hastings et al. 2005). Family psychoeducation has been found to reduce family burden for caregivers of patients with chronic mood disorders (Heru et al. 2005).

## Family-Centered Treatment in International Mental Health

The extent to which North America values differentiation by individuals has arguably made it a less favorable climate for family-focused approaches than other cultures of the world. High divorce rates, fluid urban lifestyles, and frequent geographic relocations, all served to weaken the bonds of both nuclear and extended families during the latter half of the 20th century. Although couples therapy is firmly established in the American mental health system, family therapy has remained marginal.

People worldwide, however, both in their local cultures and in American immigrant groups are far more based within their families. In many world cultures, a person is more a family member than an individual, psychologically as well as in commitments of time and personal resources. Consequently, family-centered therapies are often more fitting for non-Western cultures than the individual psychotherapies developed in North America and Western Europe (Weine et al. 2004). Moreover, family-centered approaches hold an advantage in resource utilization in many countries where there are few mental health professionals and little funding of mental health programs for large, poor populations (Baron 2002, Baron et al. 2002). Treating non-Western patients as individuals outside their family and community contexts has been described as the most common cross-cultural error among psychotherapists (Elsass 1997, p. 118).

Family-centered treatment can serve as a point at which Western psychological methods and local culture can meet on more equal footing than in individual psychotherapies. Rebuilding family and social networks after migration is vital to successful adaptation in a new land (Sluzki 1992, 1998). Culturally sensitive family therapy focuses upon the problems of a family in transition between old and new cultures. It rests upon negotiation and collaboration and the capacity of a therapist to hold multiple perspectives simultaneously, moving back and forth between the family culture "insider" view and the "outsider" Western psychiatric view of a clinical problem. Such family therapy utilizes family meetings to create a context in which family predicaments can be presented through the narratives of everyday family life, while interweaving clinical methods for working with and making sense of these stories in their cultural contexts (DiNicola 1997).

Family-centered community mental health services has emerged as an organizing principle for mental health recovery programs in refugee communities and post-war settings following the campaigns of genocide, ethnic violence, and civil warfare of last quarter of the 20th century (Baron 2002, Baron et al. 2002, Weine et al. 2003). The Kosovar Family Professional Educational Collaborative (KFPEC) is an example of a successful family-centered approach toward community mental health services in Kosovo, a country with many mental health needs but few available funds or trained mental health professionals (Griffith 2002, Griffith et al. 2001, Weine et al. 2003). The KFPEC incorporated the strengths of family psychoeducation and family resilience-building programs discussed above, in a collaboration with Kosovar mental health professionals to train Kosovar clinicians in family therapy skills and to organize mental health services around the strengths and needs of Kosovar families.

Kosovo, a Kentucky-size country of two million, was left after the 1999 war with only five psychiatrists, two psychologists, no psychiatric social workers or nurses, and no hospital for the chronically mentally ill. In recognition of the extended family as the core unit of Kosovar society, the KFPEC was established to link the University of Prishtina School of Medicine with American university and professional organizations (Griffith et al. 2001, Griffith 2002). The KFPEC has supported development of a family-focused community mental health system by training clinicians and developing services fitted to the strengths, skills, and traditions of Kosovar families. The following vignette illustrates the application of this family resilience approach with a traditional Kosovar family who were coping with the loss of five family members from the violence of the war:

The T family was engaged as the primary unit of therapy by the University of Prishtina clinicians. They met with T family members in their family home, drawing upon family and cultural traditions, and helping them adapt where flexibility and innovation were needed. Kosovar families particularly in villages and rural areas, are distinguished by a well-defined hierarchy of authority and clearly specified roles for each family member, determined largely by age and gender. Loyalty among family members is intense. Decisions about work, marriage, and the handling of money are all made in the context of what is best for the family as a whole. Amplifying these family strengths in recovery from trauma was an approach that can be contrasted with one more commonly employed in North America, in which individuals are screened for posttraumatic symptoms and then treated in professional offices.

Clinical Vignette 7

The T family suffered the murder of five family members during an attack upon their rural village during the war and ethnic violence of 1999. Soldiers ordered the women into the street and the men into the barnyard. As the women listened to the gunshots, the grandfather, two adult sons, and two grandsons, 8 and 10 year old, were each executed. A surviving son who had been working in Germany returned to the village to care for his mother, his sister with schizophrenia, two widowed daughters-in-law, and nine fatherless nephews and nieces.

A University of Prishtina team of psychiatrist, psychologist, and psychiatry resident conducted eight home visits to the T family, spread over several months. They supported the grandmother in her new position as head of the family, an unprecedented female role within traditional Albanian culture. They administered acute, in-home treatment for the daughter with schizophrenia whose psychosis had been exacerbated by the violence. Family sessions with adults and children provided a context for the shared expression of sorrow, grieving, and open communication. They encouraged reorganization of the family around the needs of the nine children. Team members visited the graves together with the family members and met with the family during Ramadan, when it was expected that their grief would be most intense.

Follow-up interviews conducted periodically for 2 years after the in-home family therapy found that the family had successfully reorganized with the grandmother heading the household, and the other adults sharing roles as needed to parent the children and provide support for the family. The children were excelling academically and socially in school. The daughter's psychosis was in remission, and the other family members appeared free of clinical symptoms.

## Summary

Family therapy has evolved from a treatment modality that searched family relationships for the causes of mental illness to a framework for engaging the strengths and competencies of families in solving clinical problems and treating psychiatric disorders. The various clinical traditions of family that matured during the 1960s and 1970s remain rich sources of ideas and interventions that can be integrated into multimodality programs alongside family psychoeducation, individual psychotherapy, and psychopharmacology. Such family-centered approaches as multifamily psychoeducation groups are sufficiently supported by empirical research to be regarded as evidenced-based practices. Family-centered models for primary prevention of major psychiatric disorders and family-centered community mental health programs for immigrant, refugee, and international populations represent the developing frontiers of family therapy.

## Appendix I: Psychodynamic Family Therapy

### What to Look For

- Projective identification.
- Unresolved grief.
- Clarity of ego boundaries and capacity for intimacy/separateness.

### What to Think About

- Internal processes within individual family members shape family interactions.
- Family members' motivations, conflicts, defenses, and relationships from the past, currently influence present relationships.
- Therapeutic change occurs through family members gaining conscious insight into previously unconscious processes generating problems in family relationships.

### What to Do

- Opening emotional expression in family relationships.
- Clarifying communications.
- Encouraging family members to speak from the "I" position.
- Interpretation of unconscious conflicts to resolve projective processes, cutoff relationships, and difficulties in modulating closeness and distance in family relationships.
- Psychodramatic techniques, such as doubling and role reversal.
- Therapeutic rituals to facilitate developmental transitions and grief over losses.
- Family genograms.

## Structural Family Therapy

### What to Look For

Contrasting the particular family structure with that "normal" to the culture and developmental stage in terms of the following.

- Organization (structure)
- Rules (sequences of action)
- Roles that shape family members' actions
- Boundaries
- Hierarchy of power
- Alliances
- Coalitions
- Verbal and nonverbal behavioral sequences.

**What to Think About**

Presenting problem results from a family structure out of alignment with the culture and the developmental stage of the family.

**What to Do**

- Actively shift the family structure
- In-session enactments
- Out-of-session homework assignments

## Strategic Family Therapy

**What to Look For**

- Here-and-now context of the problem.
- Who, what, when, where, and how people are involved in trying to solve the problem.

**What to Think About**

- "The solution to the problem is the problem."
- Difficult life-cycle transitions give birth to clinical problems when people persist in old coping strategies but relational and communication processes need to change to meet new life contexts.

**What to Do**

- Psychoeducation.
- Direct behavioral assignments to adopt new problem-solving strategies.
- Defiance-based, paradoxical interventions.

## Cognitive–Behavioral Family Therapy

**What to Look For**

- Family member difficulties in recognizing deviant behavior.
- Lack of clearly defined family rules.
- Problems in emotional communication among family members, usually a paucity of expression of positive. feelings coupled with an excess of negative expressions.
- Relational conflict due to a paucity of relational skills.
- Relational conflict due to interpretive errors based on faulty assumptions or cognitive distortions.

**What to Think About**

- Each member of the family is assumed to be doing his or her best to cope with the behavioral contingencies perceived at that point in time, given the practical and emotional restraints experienced.
- Family members need to learn cognitive and behavioral principles of learning.
- Family members need to gain skills needed:

1. To reinforce desired behaviors;
2. To eliminate reinforcement of undesired behaviors;
3. To modify faulty assumptions and interpretations about other family member's actions;
4. To learn skills for communicating clearly and effectively.

**What to Do**

- Conduct psychoeducation about the presenting problem.
- Conduct skill training in empathic listening expressing positive feelings, and speaking negative communications respectfully.
- Conduct training in problem-solving and conflict-resolution skills.
- Teach operant conditioning strategies for behavior shaping with children.
- Teach principles for contingency contracting to replace coercive and blaming behaviors with contracts specifying what each family members agrees to perform.
- Teach family members to utilize behavioral observation and thought diaries in out-of-session assignments to track patterns of thoughts, feelings, and behaviors that generate symptoms.

## Postmodern Family Therapies

**What to Look For**

- Listen for exact usage of language expressed as metaphors, stories, and beliefs.
- Listen for first-person narratives from family members' lived-experiences that imbue with meaning such abstractions as "love," "trust," and other important language of relationships.
- Note exceptions, or unique outcomes, when problems might have occurred but surprisingly did not.
- Note what is happening at times when problems are absent.

**What to Think About**

- The limits of a person's language constitutes the limits of his or her experiential world.
- Narratives, or stories, are the basic units of human experience.
- A canon of personal narratives shapes the meaning each family attributes to his or her experience.
- Narratives of identity, about who one is as a family member, and who we are as a family, strongly influence family interactions.
- Family conflicts emerge:

1. when lack of narrative skills makes their experiences unintelligible to others;
2. when the available narratives preclude ways of relating other than conflictual ones;
3. when specific words or expressions hold very different meanings for different family members due to the personal narratives with which they are associated;
4. when family members become positioned relationally such that they cannot hear, tell, and/or expand their stories in conversation.

**What to Do**

- Focus on creating a dialogue in which important personal narratives can be safely expressed, heard, and reflected upon by family members.

- Ask questions that elicit forgotten, or unnoticed, narratives of family life that open better possibilities for solving problems than the current narratives that have dominated the family dialogue.
- Engage family members in an inquiry of

1. what is happening in family interactions when problems are being solved successfully and symptoms are not occurring;
2. skills, practical knowledge, competencies, and resources of the family that can be brought to bear upon the problem.

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CHAPTER

# 93 Couples Therapy

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## Introduction

Humans as a species are hardwired to form romantic attachments for the purposes of emotional connection and security and raising the next generation. Culture dictates the ways in which these biologically based needs are structured. For example, in some cultures primary attachments remain within the family of origin and marriage is more of a business institution; in cultures with arranged marriages love is assumed to develop after the wedding, not to be its cause. In Western industrialized society in the last decades, several notable trends have emerged:

- Decreasing rates of marriage and increasing rates of alternative forms of couples and families, including long term cohabiting unmarried couples, gay and lesbian partnerships, long term monogamous couples not living together, and serial monogamy with complex stepfamily forms.
- An ongoing and consistent, if not universal, move toward more gender equality in marriage. In the majority of these marriages, both partners work and share child care. (Less than 10% of marriages in America consist of a working father, stay at home mother and children under 18 and most of those women will eventually enter the workforce at some point in their lives.) This pattern is complicated by the needs of children, which still fall disproportionately, on women, and by men's greater earning power.
- An increasing assumption that a marriage should fill deep emotional needs for intimacy and friendship and if it does not, it should probably end. In previous years, it was assumed that the needs of the family and community should outweigh, to some extent, one's personal needs.
- Greatly increased life expectancy and increased health in the later years. This has lead to longer post-childrearing stages of life, and also to somewhat increased later life divorces and remarriages as people contemplate more years to explore and develop themselves.
- What has stayed the same is the wish for a sense of trust and emotional security; the possibility of romantic love, which can develop at any age, and the need to have a few consistent adults present to take care of children's attachment needs during the childrearing years.

The couples therapist of this decade must have a sense that there are many ways to do "family," but that attachment needs, in and of themselves, are very powerful. Social neuroscience research demonstrates the biological basis of attachment, its power and the dysregulation and grief consequent to its loss. Couple relationships are a true example of biopsychosocial structures.

## Definition: What Is "Couples Therapy?"

Marital or couples therapy can be defined as a format of intervention involving both members of a dyad in which the focus of intervention is the problematic interactional patterns of the couple. In this chapter, we will use marital and couples therapy interchangeably as the majority of the issues are the same. The focus of couples therapy is on the dyad and its intimate emotional and sexual aspects.

Currently, there are various models and strategies for treating couples, as described in the chapter on Family Therapy. Each may emphasize different assumptions and types of interventions. Some therapists prefer to operate with one strategy in most cases, whereas others combine these strategies, depending on the presenting problem and the phase of treatment. Whether a therapist specializes in one or another approach, or is eclectic, some hypotheses will be formed about the nature of the couple's difficulty and the preferable approach to adopt.

Some therapists emphasize reconstruction of past events, whereas others choose to deal only with current behavior as manifested during the therapy session. Some therapists favor verbal exploration and interpretation, whereas others are more in favor of utilizing an action or experiential mode of treatment, either in the session itself

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or by requiring new behavior outside the interview. Some therapists think in terms of problems and symptoms and attempt to decode or understand possible symbolic meanings of symptomatology, whereas other therapists focus on the potentials for growth and differentiation that are not being fulfilled. One new method, not mentioned in the chapter of the previous edition, is Emotionally Focused Therapy, (Johnson and Whiffen 2003), which explicitly uses the new research on attachment as its base and is a well researched model. Some therapists utilize one or a very limited number of methods in dealing with a whole range of "problems," but others are more eclectic and attempt to tailor the treatment techniques to what they consider the specific requirements of the situation.

In our experience in training and working with various therapists, it seems they choose one school or another based on their training and or their personality style. For example, a therapist who has had psychoanalytic training would frequently choose to employ psychodynamic techniques when working with couples. For example, a very directive person would probably prefer cognitive–behavioral methods, while a person who prefers long-term emotional intensity over problem solving might gravitate to experiential models. Individuals and families as well may prefer some ways of working over others. This chapter encourages the integration of a variety of techniques depending on the particular problem and personalities of the couple as well as the skill-set of the therapist. It also encourages the therapist to look beyond the problem at hand, that is, the presenting complaint, to issues of power, intimacy, and personal growth. Our approach is to emphasize models that have (at least some) empirical data.

With the therapeutic focus on one person, the emphasis is often on the individual's perceptions, reactions, and conflicts, and also on the alliance and transference-countertranference that develops within the therapy. When two people are the operative system, attention is directed to the relationship itself—projections, communications, emotional regulation and attachment, and repetitive interactional cycles. Therapists who think in terms of a unit of three people look at coalitions, structures, and hierarchies of status and power. It is possible to do individual work in couples therapy, (looking at how the person's past affects the present) and to do some couples work within an individual therapy model by examining the patient's part in the cyclic transactions. The number of people in the room at a particular time may not be as important as how many people are involved in the therapist's way of thinking about the problem. These concepts will be elaborated on below.

## Coupling and the life cycle

### Marriage in its Historical Context

Marriage is typically structured along two important factors: generation (parents are peers); and gender. America, in the mid-20th century, experimented with a highly gendered based version of marriage. Interestingly and not often acknowledged, the function of marriage put forward by Parsons was not only to produce new citizens in the form of creating and raising children, but it was also to bind together in an intimate relationship two people in an effort to try to correct the defects of their personality development. Love-based marriage is a product of late Victorian Europe with a particular American twist of increasing egalitarianism. Increasingly, marriage has been seen as an institution by which people realize their most personal ambitions and fulfillment with their sexual relationship as the cornerstone of this fulfillment. Whether marriage can carry these heavy burdens remains to be seen, as the evolution of feminism and the increasing liberalization of women's role in Western culture plays out. While women's opportunity has continued to evolve through the institutions of law, religion, politics, commerce, and education, a corresponding and reciprocal modification of men's privileges and responsibilities in the domestic sphere of child rearing has not evolved in a complementary fashion. Consequently, the last quarter of the 20th century has been marked by an ebb and flow of conflict and dissatisfaction, primarily on the part of women and manifested through the high divorce rate of roughly 50% (Whitehead 1997).

Westernized, current marriage practices are characterized by freedom to choose a spouse, equality in terms of marriage vows (though not necessarily in terms of marital roles), emancipation from relatives, and an increased emphasis on intimacy. Marriage, of all family relationships, is most distinguished by the peculiar set of power differentials dictated by gender. In an emotional sense, at the level of intimacy and connection, the couple are equal partners. The issue of power inequality in relationships bound by love is complex (Goldner et al. 1990), skewed by who has the greater earning power men's greater physical strength, and the tendency of many women to marry men who are older and more successful than they are. In addition, the strong belief that women are in charge of children and the household makes it more difficult for women to have power in the world during the childbearing years (Gordon 2002). Women are more likely to diminish their investment in their careers or drop out of the labor force temporarily while their children are young, and during this time may experience a loss of earning power, career track mobility, and an internal sense of independence. It remains a great challenge for our society to establish a culture that truly recognizes and accommodates women's growing independence and autonomy while allowing them the freedom to have time to raise their children. Couplehood consists of various forms throughout the life cycle as one can see below.

### Serial Relationships

Between 1900 and 1960, the typical American life cycle included shorter courtships and long-term marriage with couples typically marrying in their early twenties. As people are living longer and divorce has become more acceptable, some individuals have sequential relationships that may include several marriages with the creation of two or three family units. It is often difficult to tell whether this model indicates emotional problems and fear of commitment, or whether it represents personal growth for the persons involved. A person who selects the same type of partner several times, or who goes directly from one partner to another without an effort to understand himself or herself or what happened to the earlier relationship, is more likely to perpetuate a dysfunctional pattern.

## Cohabiting

In the US, living together as unmarried lovers has gone from being scandalous to normative in less than a generation. In other parts of the world, such consensual unions have been common for centuries. Couples cohabit for many reasons, ranging from convenience to a trial marriage to a permanently committed relationship for emotional or economic reasons that avoid a legal marriage contract. Cohabiting couples have both the advantages and the disadvantages of a looser relational contract, including a sense of freedom, aliveness, and uncertainty. Although the basic tasks of couple coalition, dealing with intimacy, power, boundaries, and sexuality are present, by definition cohabitation implies less agreement on beliefs about permanence, for example, what the couple's status means, and also implies more permeable boundaries with the outside world than are found among married people.

Early research on cohabitors suggested that those who married after cohabiting were more likely to divorce (Messinger 1976). The reasons for the finding were never quite clear, although in the 1960s and 1970s one common explanation was that people who were unconventional enough to cohabit were more willing to behave in other unconventional ways, for example, by seeking divorce. In more recent cohorts in which cohabitation is more frequent, the differential in dissolution rates has been declining and has even reversed slightly (Schoen 1992). Approximately 40% of cohabiting couples live with children from one or both partners. Research (e.g., Isaacs and Leon 1988) suggests that living with a biological parent and the parent's lover is an extremely difficult situation for children, who are asked to relate to a person who may leave them and has no real rights to discipline or parent them yet who cannot be ignored. Evidence suggests that both physical and sexual abuse is more likely with a biologically unrelated adult in the house. While children from former relationships are in the house, cohabitation should be limited to permanent or soon-to-be-married couples, whenever possible, to avoid children becoming attached to other adult figures that may leave them as their primary parent did. These multiple attachments and losses can be traumatic for children although many children handle these transitions without significant problems.

## Marital Separation

Separation is a relatively common crisis of marital life. Although it is emotionally traumatic for the individuals involved, it can serve as an opportunity to reassess the marital contract and individual goals and sometimes can lead to a renewed and more functional marriage. Different precipitants may have brought about the separation; therefore, different issues may need to be addressed. For some couples, differences in adult development lead to a situation in which partners no longer have much in common. Spouses whose children are grown and have left home may not easily become accustomed to living alone together as a marital couple. With the parental role diminished or absent, there may be little emotional or functional viability left in the marriage.

Although it is natural to think of marital separation as an unfortunate event, it can also be viewed as symptomatic of the marital-system problems that need attention. In this sense, separation and its subsequent resolution may offer the potential for growth and change for the better. Trial separations can be useful to provide a cooling-off period for couples whose difficulties seem insurmountable. It offers the partners the opportunity to examine their relationship more objectively. At the same time the individuals can test their ability to adapt to living alone. This separation, together with new life experiences of various sorts (which may not have taken place had the couple stayed together), will often enable the husband and wife to change their behavior and feelings toward each other by the time they attempt reconciliation. Sometimes one of the spouses may use separation to manipulate the other spouse, or the separating person may move immediately into a new relationship. If the partners are unable to communicate with each other or learn about themselves, the separation will not be much help, regardless of whether the couple reconciles. Clinical experience suggests that about half of those couples that separate get back together; of those couples, about half divorce later on.

## Divorce

The divorce rate in most developing countries has been rising, although since the mid-1980s it has shown signs of leveling off. If the relationship has been long enough for true attachment to take place (about 2 years is considered long enough), divorce is one of the most painful experiences in anyone's life.

Divorce is a process, not an event, with its own developmental path. It usually represents one in a series of transitions that began with marital dissatisfaction and may or may not end with remarriage. A number of authors (Kessler 1975, Salts 1979) have delineated stages of the divorce process. In summary, these stages include the following:

1. A pre-divorce phase involving growing disillusionment and dissatisfaction with the marriage and arrival at some consideration of divorce.
2. The separation itself, including moving out of the house and dealing with immediate grief. For many people, this is a period of great emotional distress, confusion, and grief—the so-called crazy time.
3. A period of 1−2 years during which the couple deals with reorganizing their life structure, parenting issues within the new family structure, financial and family reorganization, community status, and legal ramifications of divorce. Negative life stresses are most marked during the first 2 years following divorce. Children are most likely to experience diminished parenting during the period because of the parents' preoccupation with divorce-generated problems. Children are likely to respond with noncompliant, angry, demanding, or depressed behavior.
4. For each spouse, reforming of an identity from being a part of a couple to being a single person occurs next. This phase occurs during the latter part of the process and concerns regarding children tend to decrease unless partners continue to use children as weapons in the divorce proceedings. The legal aspects of the divorce itself may take from 3 months in some states with an uncontested divorce to several years, depending on the laws and the amount of anger. The psychological

sequelae have their own time table. If the couple have children, they must find ways to remain connected as parents while separating as partners. Marriage is also distinguished among family relationships by its voluntary nature; while you can never truly be an "ex-parent" or an "ex-child," it is possible to be an ex-spouse, to choose to truly sever the relationship. This lends the relationship a particular complexity which is central to treatment.

## Couples Function and Dysfunction

### The Biology of Couples

Recent work on the neurobiology of attachment and love has greatly enhanced our understanding of couple processes and their relationship to health and illness (Lewis et al. 2000). The biology of couplehood involves three somewhat separate neurochemical processes: lust, romantic love (the "high" that accompanies the formation of an attachment bond), and attachment itself. Many neurochemical processes occur in bonding and bonded partners are very similar to those occurring between mothers and babies. During the falling in love period, dopamine and endorphins increase in the brain, producing a euphoric mood, restlessness, obsessive thinking about and desiring to be with the loved one, which keeps the lovers fantasizing about and wishing to be close to each other. This chemically altered state of consciousness often keeps new lovers from noticing, or taking seriously, the potential flaws in the relationship. Falling in love involves a complicated mix of cognition, feeling and behavior, as well as poorly understood biological connectors such as pheromones. Lust, which is a wish to connect with another person sexually, is more driven by testosterone and a different set of processes in the brain. The desire for sexuality may occur within a loving relationship, but sexual desire does not have to be "person focused," as the frequency of "one night stands" indicates. Sexuality and attachment are usually interconnected; having a sexual experience frequently stimulates a desire for more closeness, and "falling in love," with its increased dopamine, can stimulate the production of testosterone, so that once in a state of romantic love there is usually a desire for sexuality. As the relationship progresses (assuming it does) these processes subside and the couple moves into the more "companionate" phase of love, in which oxytocin most likely plays a crucial role (Insel 1997). This generally happens somewhere between 6 months and 2 years. At this point, there is a true attachment bond, with comfort, rather than euphoria, in closeness, and anxiety if the partner cannot be located or is not available during periods of stress. Generally during this phase, the intense sexual focus of the earlier relationship decreases, although sex itself can become more meaningful and emotionally connected. Some people find the loss of intensity, particularly sexual intensity, troubling; the high frequency of affairs indicates the conflict between wishes for high levels of lust and for security.

Bonded partners regulate each other's physiology, and in good relationships decrease stress responses and increase immune response. (Because humans are highly social animals, the presence of familiar, supportive friends, and in some cases, pets, can also affect stress and immune responses, but the degree of coregulation is much higher in romantically bonded couples. This occurs regardless of whether the couples are the same or opposite sex.) In highly conflicted relationships these protective mechanisms do not occur and there is a higher incidence of both physical and psychiatric disorders. (Graham, et al. 2006). With the death or desertion of one partner, the incidence of anxiety, depression and serious illness or death in the other increases dramatically (Duffy 2005, Prigerson 1997).

### Couples Development

Dym (1993) has described how couples relationships evolve over time. Members of couples are influenced by past and present relationships and tend to form ties that have a distinct character that emerges through regular cycles of conflict and resolution. Dym draws attention to broad, normative changes in couples, characterizing these developmental shifts as periods of expansion, contraction, and resolution. For example, in the early expansive years of a committed romantic relationship, the lives of two are in a sense woven into one. Some refer to this period of optimism, promise, and fusion as moving from "I" to "We."

In the next years of the relationship, Dym describes a predictable stage of contraction and a feeling of betrayal, in which members of the couple reconnect with a need for an "I." This desire can be marked by experiences of doubts, fears, and insecurities, and many couples retreat from their established routines. Partners may find themselves feeling "out of synch" with their own personal ambitions, describe themselves as feeling trapped or lonely, and may believe they are progressing at different tempos from each other. Stormy times may ensue with bitter conflict and blame. During the resolution stage couples may resort to compromise, negotiation, or even a more radical restructuring of their relationship in an effort to make room for both the individual and the relationship. In considering this dialectical movement from expansion to contraction to resolution, this cycle repeats several times over the course of the relationship. Dym notes that many couples have what he calls a "home base" where they tend to reside, in terms of the sense of "We," "I," or "working on it." A home base is the point of the cycle of expansion and contraction where the couples find themselves most often.

The couple's development is also strongly affected by the age of their children, if they have children, as the demands on the couple change dramatically as their children progress through different developmental stages. Couple development is also affected by the spouses' place in the individual life cycle. For example, a man who marries at 26 may be far more work focused than family focused, while the same man at 50, in the same or a different marriage, may be far more willing to put time and energy into his intimate and family life if he has achieved sufficient personal and financial success already in the workplace. Periods of major questioning, developmental change, or stalled transition during the individual life cycle (especially at decade markers and the beginning of midlife) may destabilize marriages.

### The Family of Origin and Couple's Dynamics

The family of origin is not only of historical interest, but also serves as the crucible of the beliefs and behavior patterns that the partners bring with them into couplehood. In most couples, multiple family members, including parents,

stepparent, and sibs, are deeply involved in the couples' present life, especially during the early years of marriage and child rearing. The family's approval and acceptance of a partner, or conversely their disapproval or excessive intrusion, can have a major impact on the couple's life.

One of the first tasks of a new couple is to create a couple boundary while still connecting with the larger family (Carter and McGoldrick 1999). If the families approve of and support the new couple while allowing for appropriate boundaries, the couple develops a sense of being part of a loving system of people toward whom they can turn to for help if needed. However, if either partner privileges their sibs or parents over the new spouse consistently, the sense of safety and security of the marriage is seriously compromised. If a parent disapproves of the new family member and their adult child sides with the parent, problems are inevitable. If the adult child acts helpless or declares themselves "caught in the middle" and unable to privilege the new relationship, the partner will not be able to develop a sense of trust. Sometimes the new spouse will take up arms in the secret battle that their partner has had with a parent, thus becoming the "bad guy" while the adult child looks like the "good guy" (resulting in conversations such as "oh, we can't come to visit because my wife doesn't want to"). To preserve the couple, the child of the disapproving parent must be willing to deal with their parents directly, by at the least, refusing to listen to critiques of their spouse either in public or in private, by insisting on civility during family gatherings, and by making it clear that "new couple house rules" (for example, no candy for the children) be followed.

Frequently couples develop a "family of heritage"—that is, they tend to lean more toward the traditions, rituals, and holidays, of one of the families more than the other. Often the family of the wife becomes the family of heritage, since in this culture it is more usual for a woman to remain close to her mother than for a son to remain close to his (and since women still tend to do a larger share of the work of the family ritual building). If one family lives nearer than the other, or if one family is noticeably more psychologically functional or more powerful in the community, these factors will also affect family ties. Partners in marriages which cross religious, cultural, or class boundaries have to work harder and more deliberately to develop their own traditions and find ways to include both families.

Contact between different generations varies over the life cycle, tending to increase when help is needed, particularly with the presence of young children or illness in either generation, and to decrease if the children of the younger couple are grown and the grandparents are still vital (Combrinck Graham 1985). Family businesses, which force family members into constant touch, have their own strengths and difficulties (Gersick et al. 1997).

## The Culture and the Couple's Dynamics

No couple functions in a vacuum; they are constantly impacted by the larger system issues of race, class, ethnicity and gender which to some extent define possibilities and constraints for couplehood. It is important to consider both the larger American cultural norms, and those of the multiple subcultures in which the couple might be embedded. For example, nonmonogamous marital relationships may be generally thought unacceptable for either partner in the wider American culture, acceptable for males only in some subcultures, and acceptable for both partners in gay male culture. The lack of job opportunities and increased risks of physical danger for African American males may make marriage and gender roles different, and in some ways more difficult, for African American couples than for European-American privileged couples. Living in an Orthodox Jewish community in which large families are common, an Orthodox couple may have multiple children, while the same partners, living in a less religious framework, might have felt the need to have only one or two. Gender, race, and class are inextricably mixed in the development of power and marital roles that affect how the couple structures their lives. Couples in therapy should be specifically asked about the norms of their immediate social systems and subculture (and whether they follow or disregard them). Unless the therapist lives in the same social system, one cannot assume that they understand the norms of the couple's community.

## Secrets and Confidentiality in the Relationship

Unless a therapist sees both parties together at all times, he/she will eventually face a situation in which family secrets are disclosed in individual sessions. Since secrets are a common source of dysfunction, discovering and dealing with them is a frequent occurrence. As Imber-Black (1993) says, "secrets, decisions about secrecy and openness, and the management of information are woven into the fabric of our society. The paradoxes of what is to be kept secret and what is to be shared and with whom are all around us and are embedded in each encounter between family and therapist."

The therapist needs to make a distinction between *secrecy* and *privacy*. Privacy is usually considered to mean information held by one person that they would prefer not to share but that does not directly affect their relationship with others. It usually implies a zone of comfort free from intrusion. Secrets are usually considered to be feelings or information that would directly affect a relationship. They are most often connected to fear, anxiety, and shame, and are often shared—that is, some people in the system know, whereas some do not. There is also a gray area in which different people have different ideas about whether the information is important or not. (Does a spouse consider an extramarital affair that ended 10 years ago private or secret?)

Secrets define hierarchy and relationships, leaving the unaware mystified and out of alliance. Some are about the past such as an affair many years ago, and some about the present such as an ongoing affair, or an impending bankruptcy. The majority of toxic secrets are in some way related to sex (including abortions and illegitimate birth), money, or betrayal.

> In general, the best rule of thumb is that a secret should be disclosed if it is seriously affecting connections between people, posing danger to a family member (sexual abuse), or shaping family coalitions and alliances. In general, keeping secrets is such a serious barrier that it is better to disclose them, even if painful—because otherwise the sense of mystification and isolation in the unaware is

very strong. (This seems to be true in many areas affecting children that were formerly always kept secret, such as adoption, out-of-wedlock birth, and artificial insemination.) Such issues are, however, very dependent on situation. For example, if a husband is bisexual or homosexual and does not tell his wife but engages in unprotected (or even protected) intercourse with men, the wife is in serious danger and needs to know. Since the husband's sexuality is definitely the wife's concern, not telling her this secret is a serious threat to the relationship. However, some secrets (such as an affair of several years before) when disclosed to an insecure partner, may lead to such permanent anxiety that intimacy is compromised rather than increased. The therapist should be careful to leave this type of decision to the spouse, without urging one choice or another, but carefully reviewing the plusses and minuses of each approach.

The therapist must carefully consider the timing and type of disclosure. Premature disclosure, before the therapist has an alliance with the family or couple, can cause those involved to leave therapy with no place to deal with potentially explosive material. This is particularly true when there has been a history of violence or abuse. It is generally believed that if a patient refuses to disclose a secret so serious that therapy will be derailed, the therapist may terminate therapy but should not disclose the secret himself or herself. An exception is in cases of potential violence to another, especially in child abuse or threats to murder, where the therapist is required to report to the authorities and the potential victim, so the secret will have to be disclosed. The confusion many therapists feel—faced with the requirement for reporting and knowing this may end their relationship with the couple—is difficult to manage, and these cases must be discussed with a supervisor or mentor. Issues around disclosure also arise in cases where one partner is HIV positive and has not disclosed. Legally, the therapist is not obliged to do so—ethically, it is extraordinarily hard not to. The patient should be strongly urged to share this important information.

In the following section, guidelines for assessing and treating couples are offered. Although these guidelines do not sufficiently cover all couples' problems and situations, they do represent a generic set of ideas that therapists may apply to the specifics of many marital issues.

## Evaluation of the Couple

The evaluation of a couple involves obtaining data on the current point in the marital and/or family life cycle, why the couple approaches for assistance at a particular time, and each partner's view of the marital or relationship problem (Table 93–1). Often the couple's therapist will hold one individual session with each partner after the first or second conjoint session. This gives each partner an opportunity to divulge information that might otherwise not be obtainable. Issues of confidentiality need to be carefully addressed.

In formulating the marital difficulties, the evaluator will want to consider the couple's communication, problem solving, roles, affective expression and involvement, and behavioral expression, especially in sexual and aggressive areas. The clinician will also want to evaluate gender roles, cultural and racial issues, and power inequities resulting from gender, class, age, or financial status. It is critical to ask about alcohol and substance abuse, health and reproduction, Attention Deficit Disorder, and violence (Table 93–2).

**Table 93–1 Outline for Couples' Evaluation**

I. Current phase of Couple's life cycle and identifying data
II. Explicit interview data:
  A. What is the current couple problem?
  B. Why does the couple come for treatment at the present time?
  C. What is the background of the couple problem?
  D. What is the history of past treatment attempts or other attempts at problem solving in the couple?
  E. What are the couple's goals and expectations of the treatment? What are their motivations and resistances?
III. Formulating the couples' problem areas:
  A. Rating important dimensions of family functioning:
    1. Communication
    2. Problem solving
    3. Roles and coalitions
    4. Affective responsiveness and involvement
    5. Behavior control
    6. Operative couples' beliefs
  B. Family classification and "diagnosis"
IV. Planning the therapeutic approach and establishing the treatment contract

Even if the partners do not mention their children as a problem, it is wise to spend some time developing a sense of how the children are doing, whether or not there is a favored child or a difficult child, and whether the children are being pulled into marital conflicts. At times children can be the source of a couple's conflict and at other times they may function as the glue that keeps the relationship together. If a large part of the couple's difficulty centers around concerns regarding their children, family therapy may be the preferred treatment modality (see Chapter "Family Therapy").

The therapist must also assess current relationships with parents, siblings, and friendship circles. Work–family balance issues are also critical to assess; one spouse's preoccupation with work, or alternatively joblessness, may be a primary issue in the marriage. The clinician must always ascertain whether there is a concomitant psychiatric condition, especially on Axis I Disorders (see subsection "Treatment of Axis I Disorders"). If one exists, the impact of the condition on each member of the couple must be explored. In addition to major mental illness, substance abuse, paraphilias, and ADD are particularly likely to alter marital dynamics.

Other areas deserving special attention include each spouse's commitment to the marital union and the couple's sexual life. Assessment is complicated when one spouse is keeping commitment doubts or extramarital sex a secret. Conjoint and individual sessions with each partner may be needed. When infidelity or serious commitment questions arise, the therapist and couple must address whether or not the couple should stay together.

### Genograms for Evaluation

A helpful device when evaluating a couple is the use of a genogram. The therapist can collect and organize historical

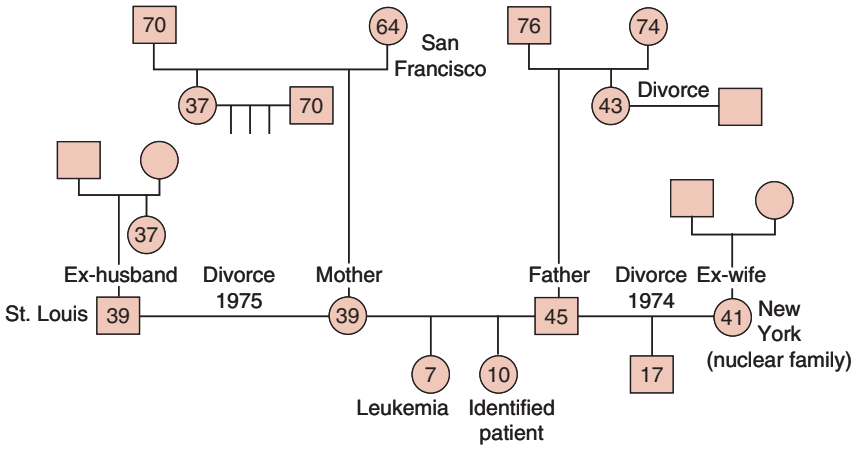



**Figure 93–1** *Example of a genogram.*

**Table 93–2 Guidelines for Interviewing Couples—The Process**

- Can you tell me about yourself? As individuals? As a couple? (Joining, forming an alliance with each member and the couple, creating a safe place)
- What brings you here? How do you understand the problem? What feelings does it elicit for each of you? (Developing an interactional problem focus)
- How does the problematic pattern actually work? Can you show me how it works? (Observing by staging an "enactment")
- How did this pattern originate? How did you create it? (Placing the problem in context of their relationship, family of origin, and their own individual development)
- How have you maintained this pattern? What have you done to keep it going? (Placing the pattern or problem under their joint control)
- Tell me about what you believe should be happening. (Myths, stories, ideas, expectations about love, sexuality, marriage, and closeness)
- In what other ways is the pattern currently reinforced? What do your family and friends believe is the problem? (How do jobs, extended family members, and friends contribute to the pattern's resilience?)
- Is this pattern always occurring or are there exceptions? (How pervasive is it, is it chronic, or related to a life transition?)
- What have you done to try to change the pattern? (Trying to avoid redundancy by inquiring about solution behavior)
- Have your efforts to change the pattern made things better or worse? (Looking at the problem as "attempted solutions")
- What has been the influence of this problem in your lives? (Again looking for the "influence" of the problem over their lives)
- How motivated are you to change the pattern now? (Assessing individual and couples motivation)
- What would happen if you succeeded in changing the pattern? (Anticipating possible consequences of change, both positive and negative)
- What patterns of relating have you created that you want to keep? (Identifying and honoring assets and resources)
- Are you ready to make a change? How about trying something different? (Preparing the couple for exploring new patterns of interaction)

The therapist is then free to track themes (always keeping an interactional focus), invent tasks and experiments designed to provide new experiences for the couple, and to evaluate the changes that occur or do not occur as a result of the couple's efforts to change their patterns of interaction.

data through the use of a genogram, the three-generational family tree depicting the family's patterns regarding either specific problems or general family functioning. The genogram technique suggests possible connections between present family events and the prior experiences that family members have shared (e.g., regarding the management of serious illnesses, losses, and other critical transitions), thereby placing the presenting problem in a historical context (Shorter 1977, McGoldrick and Gerson 1985). Constructing a genogram early on in treatment can provide a wealth of data that frequently offers clues about pressures, expectations, and hopes regarding the marriage. This pictorial way of gathering a history allows each member of the couple to learn about beliefs or themes that characterize his/her family background. An example of a genogram can be seen in Figure 93–1.

## Assessment of Concomitant Psychiatric Illness

Having a spouse with a serious Axis I disorder, such as anxiety disorder, mood disorder, or substance abuse puts realistic strain on the marital relationship. The marital interaction prior to, during, and following the onset of the symptoms in the spouse is influenced by numerous factors and is quite variant across dyads. It is incorrect to assume that in all cases the interaction between the spouses brought on, or caused, or even helped trigger the mental disorder and symptoms in the other. Indeed, a supportive spouse can allow a quite dysfunctional partner to continue to manage reasonably well. Whatever the symptoms in one spouse, the relationship of symptoms to the marital interaction is on a continuum and can take any one of the following forms:

1. The marital interaction neither causes the symptoms nor stresses the psychologically vulnerable spouse. The spouse may be a source of support, balance, and growth.
2. The marital interaction does not stress the vulnerable individual but following onset of symptoms the marital interaction declines and becomes dysfunctional, thus causing more distress.
3. The marital interaction acts as a stressor that contributes to the onset of symptoms in a vulnerable spouse.

4. The symptoms can be explained totally as under the control and function of the interactional patterns between the spouses.

The therapist meeting a new couple therefore can entertain a range of different ideas that may help illuminate and explain their distressing circumstances. The Axis I condition can be a useful focus and often is what brings the couple in for help.

## Indications and Contraindications for Couples Therapy

The process of choosing a type of therapy is complex and research is just beginning to develop guidelines for such decisions. The therapist must most often base his or her judgment on clinical intuition, general clinical opinion, and the wishes and judgments of the people involved.

One of the most common questions for clinicians who are proficient in both individual and couples therapy, is to determine the timing and type of each therapy. The basic theoretical premise of couple/family therapy is that many problems are purely relational, that individual symptoms in one person can be viewed as interpersonal in terms of etiology or problem maintenance, and that they can be changed by altering the system. The basic principle of individual therapy is that problems or symptoms develop because of the biochemistry or dynamics of the individual, and that change occurs in the individual (either behaviorally or because of cognitive understanding of the problems) in the presence of an intense and exclusive relationship with the therapist. In truth, for many people, both forms of therapy may be useful or necessary. Self-knowledge does not always help the person understand the complex family system and how one's behavior affects and is affected by family members. Family therapy often does not allow for intense exploration of psychodynamic issues. Individual therapy also does not allow the clinician to see how the problems of other family members may also be affecting the system. For example, a woman who requested individual treatment for depression was found on family evaluation to have a husband who had undiagnosed and untreated bipolar I disorder. Much of her depression was due to his behavior in manic or hypomanic states, and one of the key factors in treating her depression was treating his symptoms and having him acknowledge the truth of her concerns about him. On the other hand, for many people symptoms occur regardless of the different systems around them over time.

Since people tend to pick partners at similar stages of psychological development or maturity, it is not unusual for people with psychological difficulties to have spouses with similar or complementary degrees of psychological difficulties. In addition to the need to evaluate the partner, it must be recognized that such couples may create problem-maintaining systems that need to be addressed directly. Children in such families often suffer. The complex relationship between parent characteristics and child characteristics which determines which children are most at risk for developing symptoms, has been studied by, among others, Reiss et al. (2000) and Kendler (1996) either from genetically based similar illnesses (such as depression) or symptoms as a result of dealing with parental problems. These are often best treated with family therapy, but this does not rule out special time just for the child. For many people, both types of therapy are helpful, allowing for increased pleasure with the partner and also a context for personal and private growth.

The choice of timing of therapy is always of interest. If the person is highly symptomatic and has a problem which is usually amenable to medications, it is often helpful to begin medication and family psychoeducation/therapy first, in order to reduce the symptoms and educate the family, as well as to eliminate family sources of stress.

In general, one tries to deal with the most acute problems first. If it is possible in terms of timing and finances, it is easily possible to do individual and couples therapy at the same time. It is often recommended that the therapies be done by different therapists; however, in this strategy, it is imperative that the therapists remain in contact to avoid splitting or conflicting treatment. Some therapists have treated both the couple and one member of the couple individually, although this presents additional challenges to the therapist to remain neutral and unbiased. The therapist's criteria depend more on the characteristics of the couple and how they function than on the particular diagnosis or problem area. The bias of the couple or individual must also be taken into account.

### Contraindications for Couples Therapy

Couples therapy is not indicated for every couple in distress. In fact, at times, it may even be contraindicated. If one member is keeping an important secret, an attempt to work with them as a pair may fail and the therapist often has to take a strong stand and refuse to treat the couple, as in the case of an HIV positive male who refused to share this information with his wife. At times, one member of a couple may be too ill to benefit from couples therapy. This may be the case when one partner has a bipolar disorder or schizophrenia and is acutely psychotic.

Other couples feel more comfortable when each partner has his or her own therapist. At times it can be more effective to have each member in individual therapy with good coordination between the two therapists. Finally, cases may arise where seeing a couple together may put one member of the couple in physical danger. Some couples with a history of unilateral or mutual violence can work in couple's therapy with a no-abuse contract. There is little data assessing the effectiveness of no-abuse contracts and the clinician would be naïve to assume that such a contract would protect their patient against future abuse. If there is a serious question about safety, the male (it is most often the man in these cases) may need to be referred to an appropriate anger management or abuse group.

Sex therapy may be contraindicated in the same situations as above. In addition, many couples do not feel comfortable in a therapy exclusively focusing on sex. These couples may make more progress if the sex therapy is carefully included in the overall treatment of the couple. When referring to a sex therapist, it is particularly important to be familiar with the skill and credentials of the therapist.

## Treatment

We believe that for most people the strongest predictor of overall life satisfaction is the quality of the person's central

relationship. In addition, it seems that a good and stable relationship buffers against the genetic vulnerability to both medical and psychiatric disorder. Thus, helping a couple achieve a more satisfying relationship can have widespread and profound influence on their life and lives of those with whom they interact.

The treatment of each couple is unique and may require a combination of couples therapy, individual therapy, group therapy (particularly self-help groups such as Alcoholics Anonymous) family therapy, and medication management. By using an integrative approach with each couple, the therapist maximizes the chances for success. Identifying goals of treatment will help determine which modalities will be most effective and in what order they need to be applied.

Goals most likely attained by employing couples therapy include the following:

- specification of the interactional problem
- recognition of mutual contributions to the problems
- clarification of marital boundaries
- clarification and specification of each spouse's needs and desires in the relationship
- increased communication skills
- decreased coercion and blame increased differentiation and resolution of marital transference distortions.

Final goals of the marital intervention may involve the following:

- resolution of presenting problems
- reduction of symptoms
- increased intimacy
- increased role flexibility
- balance of power
- clear communication
- resolution of conflictual interaction
- improved relations with children and families of origin

The treatment of couples is often conceived of as a relatively brief therapy, 6−12 sessions, (though it need not be), usually meeting once weekly, with a focus on the marital interaction. The major indication for marital intervention is the presence of marital conflict but other indications include symptomatic behaviors that impact both parties such as depression, anxiety disorders, substance abuse, and illness in a child, marital partner, or other family member.

## Strategies and Techniques of Intervention

Couples therapy utilizes strategies for imparting new information, opening up new and expanded individual and marital experiences, psychodynamic strategies for individual and interactional insight, communication and problem-solving strategies, and strategies for restructuring the repetitive interactions between the spouses or partners.

As the divisive spirit of the era of the earlier schools of psychotherapy recedes and pluralism and clinical pragmatism grows, clinicians attempt to integrate the various strategies into a coherent treatment approach that can be adapted to the individual case. The authors advocate an integrative marital therapy model that utilizes psychodynamic, behavioral, and structural−strategic strategies of intervention (see subsection "Treatment of Axis I Disorders").

Evidence suggests that the diagnosis and symptom picture of one spouse and characteristics of the other spouse stand in complex relationship to the issues in the marital interaction and should, therefore, influence the planning of intervention, that is, the goals. For example, if one spouse has a nonendogenous unipolar depression with no clear precipitating stressful life events, the marital interaction could be a chronic stressor and contributor to the condition. Marital therapy in this situation could well be a preferred mode of intervention. On the other hand, if the spouse is suffering from a bipolar illness, manic episode, and the marital interaction has been good prior to the episode, psychoeducational intervention with the couple may be in order with little or no attention to the ongoing marital interaction.

Sometimes, couples present with chronic histories of unresolved and unrelenting conflict. Other couples are in a state of transition, perhaps moving from the initial expansion stage of their marriage to the inevitable crisis related to the reevaluation of the contraction stage. In either case, clarifying the couples' process and their reoccurring patterns of behavior represents the starting place for couples therapy.

The focus should be primarily on the interpersonal distortions between husband and wife, and not on the couple–therapist transference. However, negative transference distortions toward the therapist must be addressed quickly and overtly.

There are three strategies in this focused, active treatment of marital discord:

1. The therapist interrupts collusive processes between the spouses. The interaction may involve either spouse failing to perceive positive or negative aspects of the other that are clear to an outsider (e.g., cruelty or alternately generosity) or when either spouse behaves in a way aimed at protecting the other from experiences that are inconsistent with the spouse's self-perception, (e.g., husband working part time views himself as breadwinner, whereas wife works full time and manages checkbook to shield husband from reality of their income and finances).
2. The therapist links individual experience, including past experience and inner thoughts, to the marital relationships.
3. The therapist creates and allocates tasks that are constructed to (a) encourage the spouses to differentiate between the impact of the other's behavior versus (the other's) intent, (b) to bring into awareness the concrete behavior of the partner that contradicts (anachronistic) past perceptions of that partner, and (c) to encourage each spouse to acknowledge his/her own behavior changes that are incompatible with the maladaptive ways each sees himself/herself and is seen by the marital partner. These tasks also help reconstruct the couple's narrative to make it more positive.

Among the above-mentioned tasks, (c) is most important. In fact, in the initial stage of marital treatment the authors ask that each partner focus on what they want to change in themselves, not how they want the other spouse to be different.

In this integrative model, the focus is on three related domains:

- the functional relationships between the antecedents and consequences of discrete interactional sequences
- the recurrent patterns of interaction including their implicit rules
- each spouse's individual schemata for intimate relationships

In the initial stage, alliances must be developed between the therapist and each marital partner, with the therapist offering empathy, warmth, and understanding. The therapist must also ally with the couple as a whole and learn their shared language as well as their different problem-solving styles and attitudes.

Behavioral techniques, including giving between-session homework, in-session tasks, communication skills, and problem-solving training, can facilitate the process of helping marital partners reintegrate denied aspects of themselves and of each other. However, the focus is not on behavioral change alone, as overt behavior is seen as reflecting the interlocking feelings and perceptions of each spouse. Ideally, the process of treatment should be one where each partner can consider what they want to change in themselves as opposed to how they want the other spouse to be different; safely explores new beliefs, feelings, and behaviors; and experiments with new patterns of interaction that are unfamiliar and even anxiety-provoking.

## Treatment of Axis I Disorders

With increasing evidence of the multiple causes (including genetic, neurochemical, familial, and environmental) of many psychiatric syndromes, attention must be paid to both individual diagnoses and family interactions. In the last 20 years as diagnostic categories have become clearer, our treatment approaches have also become clearer. Many DSM IV-TR diagnoses are now treated with pharmacotherapy at some point in the course of the illness. For example, antipsychotic medications are used to treat the positive and negative symptoms of schizophrenia while antidepressants are usually indicated when an individual is diagnosed with a major depression. In most instances, treatment is also indicated for the problems of a couple and interactions accompanying these conditions. Couples therapy has been shown to be effective in providing psychoeducation and enhancing compliance with medication and psychosocial interventions when one member is suffering from any DSM IV-TR diagnosed conditions including, but not limited to, schizophrenia (American Psychiatric Association Work Group on Schizophrenia 2004), depression (American Psychiatric Association Work Group on Depression 2000), bipolar disorder (American Psychiatric Association Work Group on Bipolar Disorder 2002), anxiety disorders, dementia, substance abuse, adult ADD and some Axis II conditions. Attention to and evaluation of the couple and family systems is specifically mentioned as part of the treatment plan in many of the recent practice guidelines of the APA. Disorders diagnosed in infancy, childhood, and adolescence such as pervasive developmental disorders, attention deficit disorder, conduct disorders, mood and anxiety disorders, and eating disorders most often require family therapy as part of the overall treatment program. We look forward to more data emerging to support the use of combination therapies which in our combined clinical experience has been the most effective way of aiding our patients suffering from major mental disorders.

Some of the problems may be related to the etiology of the individual illness, some may be secondary to it, others may adversely affect the course of the illness, and still others may not be connected at all. For example, if panic disorder with agoraphobia has developed in a spouse early in the marriage, the therapist's attention must be directed not only to treating the illness but also to the nature of the marital interaction, including its possible role in exacerbating or ameliorating the illness. In addition, if a major psychiatric diagnosis occurs in one spouse, attention must be paid to the partner's ability to cope with the illness. In fact, a recent study found that for some mother's with borderline personality disorder, being a parent can lead to positive self-esteem, while other's can be paralyzed by the difficulties of child rearing (Gunderson et al. 2006). A child may respond to his or her mother's severe depressive illness by becoming a caretaker for a younger sibling, risking his or her own development, or the child may begin acting out. Moreover, the treatment of a child with a DSM IV-TR diagnosis will be greatly assisted by the couple's recognition of the problem and adherence to the treatment program.

By way of example, let us look at the review of Prince and Jacobson (1995) which suggests that medication plus marital therapy is better than individual therapy alone. In these cases, individual therapy does little to moderate the "toxic" marital problems that increase the depression. Drugs alone are also ineffective for this type of problem. Most therapy for depression has been done on depressed women so we have little information on working with depressed married men. However, some men are deeply troubled by the experience of talking about problems, preferring to work on them in private. Many depressed men have wives who are very angry, which might increase their depression if discussed in therapy. Parenthetically, there is some evidence that women with other Axis I conditions such as substance abuse respond better to couples therapy than men with other Axis I conditions (Haas et al. 1990).

## Effectiveness and Efficacy of Couples Therapy

There are two major sources for reviews of efficacy of couples therapy. Shadish et al. (1995) summarized 163 randomized studies, 62 marital, and 101 family therapy. Pinsof and Wynne (1995) in a commentary have summarized the data. These studies point to the following general conclusions:

1. Family treatment is more effective than no treatment. This conclusion is manifest in studies that contrast family and marital treatment to no-treatment control groups. Roughly 67% of marital cases and 70% of family cases improve. The outcome may be slightly better if the identified patient is a child or an adolescent than if he or she is an adult. These findings were statistically significant. No one therapy method was demonstrated clearly to be better than another.

2. The deterioration rate (i.e., the percentage of patients who become worse or experience negative effects of therapy) is estimated at about 10%—lower than for individual therapy. Pinsof and Wynne (1995) believe the rate is lower than 5−10% and describe family therapy as not harmful.
3. In several areas evidence indicates that family treatment is the preferred intervention strategy. In other areas family therapy and individual therapy were tied—often in situations in which the identified patient had a significant Axis I problem (Shadish et al. 1995). These treatments of choice are of great importance for practitioners and students.

Importantly, a recent study of effectiveness of treatment with long-term follow-up reported that, "of 300 couples enrolled, just under half completed the end-of-treatment assessment and just over 40%, a 2 year follow-up. Outcomes of treatment showed significant improvements in relationship matters, individual mental health, and enhanced coping abilities. At long-term follow-up, all results remained the same and some aspects improved for both sexes." (Lundblad and Hansson 2006). Although it is diffcult to draw definitive conclusions from these studies, it seems that the preponderane of data suggests the effectivenss of couples therapy.

### Couple Distress or Problems

The data over three decades suggest that couples therapy is superior to individual therapy for marital conflict situations (Pinsof and Wynne 1995). The strongest effects are for increasing marital satisfaction and reducing conflict. (It should be pointed out that these are not synonymous—some people who have high marital conflict still report high marital satisfaction, and some couples have low conflict because the marriages are "dead.") Not surprisingly, couples who are less distressed show more improvement. Some of these effects wash out over time, as is common in chronic conditions.

What happens if the outcome of marital treatment is separation or divorce? One might automatically assume that such an outcome is deleterious and that marital and family therapy should be designed to hold the families together. On reflection, experience seems to indicate otherwise. Marital therapy allows the partners to examine whether or not it is to their advantage to stay together, and it gives them permission to separate if that is what they need to do. Clinical Vignette 1 illustrates a couple that had difficulties from early on in their marriage. In the course of treatment the couple decided to separate. It is important that the outcome of treatment be determined by the couple's desires not by the therapist's bias about whether a couple should remain together or separate.

### Dropouts

The dropout rate in the early stage of couple or family therapy is relatively high. In one study, about 30% of all the families or couples referred for family treatment failed to appear for the first session (defected) and another 30% terminated in the first three sessions, leaving about 40% who continued (Shapiro and Budman 1973). The main reason families gave for termination was a lack of activity on the part of the therapist, whereas defectors in general had a "change of heart," and denied that a problem existed. The issue usually is that no matter how bad a situation was, it was preferable to what might happen if a couple changed their behaviors. The motivation of the husband appeared to play a crucial role—the more motivated he was, the more likely the family was to continue treatment. The idea that a dropout is "denying a problem" may or may not be true. Because the process of entering therapy is frightening for many people and because the therapist must meet the needs of several people, it is unsurprising that the process of engagement is rocky.It is important to try to establish a strong therapeutic alliance early on with both members of the coulple to minimize the chance of dropouts.

Clinical Vignette 1

The couple presented for treatment in their thirties. He was a dentist, and she was a housewife who had previously been a teacher. She came from a family in which her father had been a chronic "run-around," and she married her husband because he appeared to be reliable and stable. He came from a family in which the mother was dull and masochistic, and he married his wife because she seemed exciting and interesting.

The couple came to therapy after five years of marriage when it was "discovered that the husband was having extramarital affairs." (He had left several notes from girl friends around.) Exploration of the situation revealed that soon after marriage Mrs. A. had become slowly and imperceptibly disillusioned with her husband when she found that he was very insecure about himself, was very unreliable, and characteristically "lied and cheated." Dr. A. perceived after several years that his wife was not as exciting as he had thought and would not fulfill the role he had envisioned for her—that is, being the "slave" to a professional husband.

The therapy allowed the couple to examine some of the original premises on which they had gotten together and they found them faulty. The process of therapy, and not the therapist's values, gave them the necessary permission to separate.

## Special Considerations for Couples Therapy

### Ethical Issues in Couples Therapy

The fundamental ethical dilemmas inherent in psychotherapy: confidentiality, limits of control, duty to warn/reporting of abuse, and therapist–patient boundaries become more complex when the treatment involves more than one person. The couple's therapist has an ethical responsibility to everyone in the family. In some cases, individual needs and system needs may be in conflict. For example, a husband may wish to conceal a brief episode of unprotected sex with another woman, while his wife is better protected, for health reasons as well as psychological reasons, if she knows about it. A wife's wish to be divorced from a psychiatrically ill and demanding husband may conflict with his need for her care. Such clinical situations provide a set of ethical dilemmas for the therapist. The therapist must be clear that his/her job in most cases (such as impending divorce) is to help the partners sort out their values, obligations, and options rather than making a decision for them. In some cases, however (such as the reporting of child abuse), reporting abuse is not just an ethical issue but also becomes a legal one. And in

some cases the therapist faces difficult gray areas which must be decided on a case-by-case basis. The therapist also has certain unalterable ethical obligations such as not engaging in "dual relationships" (see later) with patients or exploiting them for their own benefit.

While the operative concept is "first do no harm," the issues of how one defines harm, and who will or will not be harmed by a certain action, are complex and difficult questions, especially when treating a couple or family.

## The Conflicting Interests of Family Members

It is not unusual for the interests of each member of the couple to conflict at some point. Borzormenyi-Nagy and Spark (1973) years ago emphasized the contractual obligations and accountability between persons in the multigenerations of a family. Relational ethics are concerned with the balance of equitable fairness between people. To gauge the balance of fairness in the here-and-now, and across time and generations, each member must consider both his/her own interests and the interests of each of their partner. The basic issue is one of equitability, that is, everyone is entitled to have his or her welfare and interests considered in a way that is fair to the related interests of other family members.

There may be times when it is difficult to decide whether a therapeutic action or suggestion may be helpful for one individual, but not helpful or even temporarily harmful to the other individual. In their concern for the healthy functioning of the system as a whole, therapists may inadvertently ignore what is best for one individual. An ethical issue is how the decision is made. Should it be the therapist's concern alone or should it be shared with the couple? How much information should they be given on the pros and cons of modalities? The authors' bias is to negotiate and give the couple all the relevant information so that they can make the most informed decision possible (for further discussion, see also Hare-Mustin et al. 1979, Hare-Mustin 1980).

## Boundaries

The issue of boundaries and dual relationships is a critical one in all forms of psychotherapy. Because couples therapy involves more than one patient in the consulting room, there is less likelihood of inappropriate sexual contact between therapist and patient. However, there have been cases in which a therapist, working with a couple, began an affair with one of the spouses, either during couple's therapy or after the couple separated. The American Psychiatric Association (APA) and The American Association of Marital and Family Therapy (AAMFT) (1998) have a very sensible code of ethics making clear the inappropriateness of this kind of behavior. The American Psycological Association's position is consistent with these other organizations.

Oftentimes the therapist may find that the couple faces the same issues that the therapists face in his or her own life. It is vitally important for the therapist to recognize his or her countertransference reactions to avoid taking sides in the therapy session. For example, seeing a couple going through a separation at the same time one is going through the early stages of one's own divorce is an extremely difficult thing to do, and it may be very difficult to remain neutral during therapy sessions. While it is obviously impossible for a therapist to stop treating patients while going through a divorce, he or she could certainly choose not to accept a new patient whose situation is very similar to their own or who reminds them of their departing spouse.

"Confidentiality" and "boundaries" issues are mentioned in the Code of Ethics of AAMFT (1998) Three of these have special relevance to couples therapists:

1. Marriage and family therapists are aware of their influential position with respect to patients, and they avoid exploiting the trust and dependency of such persons. Therapists, therefore, make every effort to avoid dual relationships with patients that could impair professional judgment or increase the risk of exploitation. When a dual relationship cannot be avoided, therapists take appropriate professional precautions to ensure judgment is not impaired and no exploitation occurs. Examples of such dual relationships include, but are not limited to business or close personal relationships with patients. Sexual intimacy with patients is prohibited. Sexual intimacy with former patients for 2 years following the termination of therapy is prohibited.
2. Marriage and family therapists respect the right of patients to make decisions and help them understand the consequences of these decisions. Therapists clearly advise a patient that a decision on marital status is the responsibility of the patient.
3. Marriage and family therapists have unique confidentiality concerns because the patient in a therapeutic relationship may be more than one person. Therapists must respect and guard confidences of each individual patient.

## Financial Concerns

Who pays the bill is relatively simple in individual treatment with adult patients, but is not necessarily so in couples therapy. Determining who pays the bill can become especially tense in marital treatment of spouses in conflict. For example, if both spouses have insurance coverage from their respective employers, the question arises as to whose insurance should be used? This becomes most delicate when the spouses have conflicting views of the matter for any number of reasons, for example, "I don't want my secretary seeing the insurance forms," "using my insurance makes me the patient," and so on. As with many concrete issues of conflict, the family therapist should approach the matter with a sense of fairness. The symbolic meanings of who pays should be thoroughly explored. When both partners have separate income and separate financial arrangements, they should each pay half the bill. Other financial questions involve sudden changes of fortune. If a woman married to a well-to-do man divorces her and her income drops severely and suddenly, should the therapist be willing to continue treatment even if the husband refuses to pay? For many therapists and many patients, money is the most taboo subject, even more than sex. It is the therapist's job to clarify their own understanding and feelings about money so they can support discussions with patients.

# Sexuality and the Treatment of Sexual Dysfunction

It is important to emphasize that there are substantial differences in frequency, type of preferred sexual activities,

and meanings implied by sexual behavior by gender, gender orientation, and in different cultures, different regions of the world. For example, premarital sexual activity is common in our current society buts remains unacceptable for women in many countries. Contrary to popular belief, there is no universal trend to earlier sexual intercourse, but the shift to latter marriage in most countries has led to an increase in pre-marital sex (higher in developed than in nondeveloped countries) and higher in men then women (Wellings et al. 2006). Studies consistently show that married people have the more sex than single people (Laumann 1995). Twenty-five years of experience in treating sexual difficulties with some combination of sex and couples therapy has shown the combination to be consistently superior to individual therapy in the treatment of sexual dysfunction. Although the original success rates of Masters and Johnson (1970) have not been repeated in later studies, 60−95% of sexual dysfunctions can be treated, depending on the type of sexual problem. Recent advances in sex therapy have seen a movement from mostly behavioral to more integrative treatment models with more attention to cognitive and systemic factors, and increasing focus on organic causes and medical treatment for male dysfunction, especially erectile dysfunction (Rosen and Lieblum 1995).

## Sexual Functioning of Couples

Schnarch (1997) contends that for many married people the magnetic force that drew them together eventually weakens to the point where sexuality and eroticism play a minor role in their lives. Sometimes, specific problems in sexual functioning affect the couple's relationship. Although the DSM-IV-TR (American Psychiatric Association 2000) and most of the early sex therapists make a dichotomous distinction between sexual function and dysfunction, sexuality is probably best thought of as a set of experiences on a continuum of satisfaction. It is possible, for example, to have a sexual life in which there is, physiologically, sexual arousal and orgasm, but the experience feels passionless and boring, while the same "functioning" couple could have more passionate and exciting sex after therapy. It is possible to have an erotic sexual experience even if there is technical "dysfunction" as in the case of the male partner being unable to achieve erection because of physical illness, but the couple uses other methods of sexual expression. It is possible to have have a satisfying sexual experience even if there are serious arguments between the couple around issues of frequency or type of sexual practice. There is an old wives tale that men use sexual intimacy in relationship in place of verbal intimacy. In our experience, this pattern may exist and be used by women as well.

It has been estimated that 50% of American marriages have some sexual problems. These can be divided into "difficulties" (such as inability to agree on frequency) which are clearly dyadic issues; and dysfunction which are specific problems with desire, arousal, and orgasm, as listed in the DSM-IV-TR (American Psychiatric Association 2000). Dysfunctions may be organic or psychological at base, and may be lifelong or acquired, generalized or situational. They may be deeply embedded in relational power or intimacy struggles, or may be the only problem in an otherwise well-functioning relationship. While most family therapists believe that there is no uninvolved partner when one member of a couple presents with sexual dysfunction, that is different from saying that the relationship itself is the cause of the dysfunction. The job of the therapist is to ascertain as best as possible the etiology of the problem and to choose the most effective therapy, whether medical, individual, or relational. It is also within the therapist's purview to inquire about whether the couple would like to improve a technically functional but not very satisfying sexual relationship, in the same way that the therapist can offer methods or B to increase intimacy in a couple that wishes personal growth.

## Diagnosis/Systems Issues

Sexual dysfunction or dissatisfaction is seldom caused by a psychiatric disorder (although depression and anxiety may often decrease sexual desire). It is commonly caused by ignorance of sexual anatomy and physiology, negative attitudes and self-defeating behavior, anger, power, or intimacy issues with the partners, or medical/physiological problems. Medication side effects are a particularly common cause of sexual dysfunction in patients who are receiving selective serotonin reuptake inhibitors (SSRIs). Male erection problems are proving increasingly amenable to medical forms of treatment such as prescription use of Sildenafil Citrate. It is also important to remember that people vary enormously in the importance they place on sex or eroticism in their lives. For example, in *The Social Organization of Sexuality: Sexual Practices in the US* (Laumann and Michael 1994), about one-third of the people surveyed have sex at least twice a week, about one-third a few times a month, and the rest, have sex with a partner a few times a year or not at all. In general, when sex is not part of a marriage over a long period of time, the relationship has less vitality and life. However, even well-functioning marriages may have periods in which sexuality is much less part of their lives (such as after the birth of a first child, or during a family or health crisis). Different people have vastly different tolerance for such periods.

## Some Parameters of Sexual Function

Healthy sexual functioning can be thought of as resulting from relatively nonconflicted and self-confident attitudes about sex and the belief that the partner is pleased by one's performance. In this type of situation, a reinforcing positive cycle can be activated.

However, when either partner has doubts about his or her sexual abilities or the ability to please the other, his or her sexual performance may suffer. This self-absorption and anxiety will characteristically produce a decrease in sexual performance and enjoyment and can lead to impotency and orgasmic difficulties. Couple and individual difficulties of various sorts might then follow. A vicious cycle may be activated, with worries being increased, leading to increasingly poor sexual performance.

Because sex is a way of each person being vulnerable to the other, it is difficult to have sex when one is angry or not in a mood to be close (although some people can block out other feelings and keep the sexual area more separate). In addition, people who feel abused, mistreated, or ignored in a relationship are less likely to want to please the other. For some who feel that they have no voice in the relationship, lack of desire is sometimes the only way they feel able to manifest displeasure.

Couples who continue in marital or individual treatment for long periods of time can resolve some of their marital problems but can still suffer from specific sexual difficulties in their marriage. It is also true that specific sexual problems may be dramatically reversed after relatively brief periods of sex therapy, even though such problems may have proven intractable following long periods of more customary psychotherapy. However, sexual functioning which is suffering because the partners do not want to be close is not likely to respond to sex therapy unless other issues are also addressed.

Usually, when a marital couple has a generally satisfactory relationship, minor sexual problems may be only temporary. Resolution of sexual problems, however, will not inevitably produce positive effects in other facets of a relationship as well.

Marital and sexual problems interact in various ways:

1. The sexual dysfunction produces or contributes to secondary marital discord. Specific strategies focused on the sexual dysfunctions would usually be considered the treatment of choice in these situations, especially if the same sexual dysfunction occurred in the person's other relationships.
2. The sexual dysfunction is secondary to marital discord. In such situations, general strategies of marital treatment might be considered the treatment of choice. If the marital relationship is not too severely disrupted, a trial of sex therapy might be attempted because a relatively rapid relief of symptoms could produce beneficial effects on the couple's interest in pursuing other marital issues.
3. Marital discord cooccurs with sexual problems. This situation would probably not be amenable to sex therapy because of the partners' hostility to each other. Marital therapy would usually be attempted first, with later attention given to sexual dysfunction.
4. Sexual dysfunction occurs without marital discord. This case might be found in instances where one partner's medical illness has affected his or her sexual functioning, forcing the couple to learn new ways to manage the change. Another example might be when one partner has a history of sexual abuse or a sexual assault that creates anxiety related to the sexual experience. While individual therapy can be helpful in both of these cases, couples therapy can be especially useful in creating a safe place to address painful feelings and anxious expectations, and to provide education and guidance for couples undergoing these transitions.

## Evaluation of Sexual Disorders

A careful evaluation of the couple's total interactions needs to be done by the therapist as well as a physical assessment when dysfunction is present. When it appears that the basic marriage is a sound one, but that the couple suffers from specific sexual difficulties (which may also lead to various secondary marital consequences), the primary focus might be sex therapy per se. In many cases, however, specific sex therapy cannot be carried out until the relationship between the two partners has been improved in other respects; indeed, the sexual problems may clearly be an outgrowth of the marital difficulties. When marital problems are taken care of, the sexual problems may readily be resolved. It may be difficult to disentangle marital from sexual problems or to decide which came first. The priorities for therapy may not always be clear.

The DSM-IV-TR (American Psychiatric Association 2000) recognizes the following as dysfunctions:

- Sexual desire disorders: hypoactive sexual desire disorder (HSDD), sexual aversion disorder
- Sexual arousal disorders: female sexual arousal disorder, male erectile disorder
- Orgasmic disorders: female orgasmic disorder, male orgasmic disorder, premature ejaculation
- Sexual pain disorders: dyspareunia (not due to a general medical condition), vaginismus (not due to a general medical condition), vaginismus (due to a general medical condition). They are coded separately if they are due to a general medical condition or are substance induced.

Many people have more than one dysfunction (e.g., HSDD plus orgasmic disorder) and frequently each member of a couple will have a dysfunction, for example, premature ejaculation in the man with hypoactive desire in the woman. It is important to understand the sequencing of the onset of the dysfunctions to understand how they influence each other. As we have said, many sexual problems are not dysfunctions but are relationally based dissatisfactions.

Specific techniques are available which have been devised for eliciting a sexual history and for evaluating sexual functioning. The marital therapist should become familiar with these ideas and obtain experience in their utilization. A systemic assessment of sexual difficulties includes, at the minimum, the following details as listed in Table 93–3.

**Table 93–3 Assessment of Sexual Problems**

1. Definition of the problem
   (a) How does the couple describe the problem? What are their theories about its etiology? How do they generally relate to their sexuality, as reflected in their language, attitudes toward sexuality, comfort level, and their permission system?
   (b) How is the problem a problem for them? What is the function of the problem in their relationship system? Is the relationship problem the central problem? Why now?
2. Relationship history
   (a) Current partner
   (b) Previous relationship history
   (c) Psychosexual history, including information about early childhood experiences, nature of sexual encounters prior to the relationship, sexual orientation and feelings about masculinity and femininity.
   (d) Description of current sexual functioning, focusing on conditions for satisfactory sex, positive behaviors, specific technique, etc. Who initiates sex, who leads, or do both? How does their sexual pattern of intimacy and control reflect on or compensate for other aspects of their relationship?
3. Developmental life-cycle issues (births, deaths, transitions)
4. Medical history, focusing on current physical status, medications, and present medical care, especially endocrine, vascular, metabolic.
5. Goals (patients' and therapist's viewpoints): The task is to examine whether goals are realistic and what previous attempted solutions have yielded.

In addition, in couples where there is any possibility that the problems may have an organic component, it is crucial to insist on a medical workup. This is particularly important for men, for whom small physiological changes in potency may produce anxiety that exacerbates the problem.

The taking of an intimate sexual history of husband and wife should, of course, be conducted with the couple without children present. The process of taking a sexual history should be handled with care and regard for each person's level of comfort.

What type of language should be used when discussing sexual topics? Obviously, one should not use terms that would be offensive or uncomfortable for either the therapist or the couple. At the same time, care must be taken to avoid using bland generalities which fail to elicit specific sexual information. Frankness is encouraged, and when there is vagueness, the therapist needs to follow up with more specific questions.

The therapist should use simple language or use the simplest technical sexual term that the patient is comfortable with. Some patients will misunderstand technical terms. For others, the use of the vernacular by the therapist may be inappropriate. The problem faced in the choice of language is itself an indication of our general cultural discomfort with sexuality. The therapist's own use of a particular sexual vocabulary can be a model to help the marital partners feel comfortable in communicating with each other more openly.

Taking a sexual history of lesbian and gay couples may be particularly difficult for a heterosexual therapist, either because of discomfort with homosexuality or lack of knowledge of homosexual norms and mores. In addition, the couple may have a wider or different set of sexual practices than the therapist is used to (of course, this may be true with heterosexual couples as well). Therapists have the options of educating themselves about homosexual sexuality, either by reading books available in mainstream bookstores about gay and lesbian life, and/or asking the couple about their own and other common practices. If the therapist is very anxious in this situation, he/she must decide when the therapy is not proving effective and if he/she should refer to another therapist. Gay and lesbian couples may present with any of the dysfunctions or dissatisfactions of heterosexual couples.

## Individual, Couple, or Sex Therapy for Sexual Problems

This distinction was clearer 10 years ago when sex therapy was primarily focused on a specific and highly detailed behavioral protocol. Sex therapy in the last few years has moved in the direction of further understanding of the physiologic causes of sex dysfunction on one hand, and cognitive–behavioral issues on the other. It is clear at this point that, in general, sexual problems do not disappear with couple therapy unless specific attention is paid to the nature and quality of the sexual problems. Usually, it is most effective to deal with severe couple conflict before beginning to deal with sexual issues directly (Table 93–4). Sex therapy includes education, a focus on the intimacy and power aspects of sex, and often homework assignments that in some way deal with sexual anxiety and expansion of sexual options. Individual therapy is indicated if the problems are clearly related to the partner's history (sexual abuse, hatred of women), have occurred in multiple relationships, and are not amenable to being worked on in the couple. Individual therapy is the most inefficient way of dealing with most couple-centered sexual problems. It is also important to consider the possible role of organic problems in any dysfunction.

**Table 93–4 Criteria for Sex and Couples Therapy**

| Sex Therapy | Couples Therapy |
|---|---|
| The marital problem is clearly focused on sexual dysfunction | Sexuality not an issue, or it is one of many issues in marital dysfunction. |
| **Enabling Factors** | **Disabling Factors** |
| Willingness and ability to carry out the sexual functioning tasks that would be assigned by therapist. | Anger and resistance too intense to carry out extra-session tasks around sexual functioning. |
| Strong attachment to marital partner; both partners interested in reversing the sexual dysfunction. | Couple not committed to each other; there are covert and/or overt behaviors to dissolve the marriage. |

Recent research has demonstrated that no single school of therapy is definitively superior to another (Shadish et al. 1995). In general, the trend in the last few years has been toward a more integrative approach, drawing from a variety of models and allowing for a more fluid type of work (Lebow 1997). Integrative models are likely to combine some form of here and now work (cognitive or behavioral) with some type of historical understanding of the patterns that led to the current problem.

## Treatment of Sexual Dysfunction

Treatment of psychosexual disorders, in the form developed by Masters and Johnson (1966), consisted of a thorough assessment of the partners and their relationship, education about sexual functioning, and a series of behavioral exercises. These sensate focus exercises were designed predominantly for behavioral desensitization, but also functioned to teach the partners about their own and the other's sexual desires, and also served to elicit relationship problems. In these exercises, the couple pleasures each other, alternating in the role of giver and receiver, first in nongenital areas, then genitally, and then with intercourse. In the traditional form, intercourse is prohibited during the early stages to remove performance anxiety. There are also specific exercises for each of the sexual dysfunctions (Table 93–5). Different authors developed different exercises and ways of approaching

**Table 93–5 Marital and Sexual Problems Interact in Various Ways**

| |
|---|
| Sexual dysfunction produces or contributes to secondary marital discord. Sex therapy is preferred. |
| Sexual dysfunction is secondary to marital discord. Marital therapy is preferred. |
| Marital discord cooccurs with sexual problems. Marital therapy first, with later attention given to sexual dysfunction. |
| Sexual dysfunction occurs without marital discord. Sex therapy is preferred. |

them. For a complete description of these exercises, we recommend Kaplan (1995), LoPiccolo and Stock (1996), and Zilbergeld (1992). This method works best when there is ignorance, shame, or specific dysfunction such as premature ejaculation. These exercises are difficult to complete if the couple feels angry or unloving toward each other.

Many of the patients who saw Masters and Johnson in the 1970s had sexual difficulties related to sexual ignorance and inexperience. Two decades later, the increase in premarital sex and the proliferation of easily available articles and books on sexuality and information on the Internet have decreased the number of these couples, and allowed some couples with sexual dysfunction to work on their problems at home. Recent studies of couples requesting sex therapy have shown a higher proportion having concomitant, complicated marital problems. Recent writers in the field, notably Schnarch (1997), have focused on cognitive/emotional issues in sexuality, and especially on the meanings attached to a particular act, and the level of intimacy involved. Having learned a great deal about the more mechanical and organic components related to arousal and orgasm, it is important to rethink other aspects of sex, such as eroticism, passion, mystery, and dominance/submission which make the act itself meaningful. This is particularly true in areas of sexual boredom or situational lack of desire. These therapists do not use rigidly staged exercises, but focus on the couple's relatedness during sex; they may, however, suggest specific homework to help a couple focus on a particular aspect of their sexuality.

Although not mentioned in the DSM-IV-TR, sexual compulsions or addictions may be seen in couples. In these cases, one partner's unceasing compulsion to think about, view (print or on-line), talk about, and/or have sex may be very wearing to the other partner or to oneself. A key component of this problem is that such persons may become extremely anxious if sex is denied. They may present with multiple affairs or with constant demands on the partners. However, most people who have affairs do not have a sexual compulsion.

Treatment for these disorders is still controversial. Some therapists use a 12-step addiction model along with group therapy; some treat it as a compulsion with individual therapy and medication (particularly with SSRIs such as fluoxetine). Couples therapy is still a critical component part of treatment—to educate the couple, and if multiple affairs have taken place, to discuss the viability of the marriage.

In recent years, emphasis has shifted to the role of biomedical and organic factors in the etiology of sexual dysfunction, along with the growing use of medical and surgical treatment interventions. Particular focus has been given to their role on vascular disorders and neuroendocrine problems, as well as the tendency for many medications to effect sexual functioning. It is critical for the patient to have a thorough physical workup. For a good review on the interaction of medication and sexuality, see Abramowicz (1992).

A variety of medical approaches to the treatment of erectile disorders in men have been developed in recent years. These include, but are not limited to, surgical prostheses or penile implants (seldom used in the last few years), intracorporal injection of vasoactive drugs such as papavarine, constriction rings and vacuum pump devices, and urethral suppositories. In 1998, oral medications for the treatment of impotence were introduced (sildenafil, Viagra). Because our understanding and treatment of impotence is developing so rapidly, it is important to stay current on new research in the field. Surgical treatments are available for the correction of arterial insufficiency or venous leakage problems. These methods may be more or less acceptable both to the man and his partner. The partner's response to the changes is often a key element in their success. There has been some success in treating premature ejaculation with SSRIs and clomipramine; however, since these may also decrease sexual desire, caution and careful monitoring are indicated (Abramowicz 1992). Buproprion is sometimes helpful in preventing loss of sexual desire in patients treated with SSRIs.

In women, most medical interventions have been for dyspareunia. Female dyspareunia due to the decreased lubrication of aging can be treated with topical estrogen cream or lubricant jelly. Even when an organic cause is found and treated, the conditioned anxiety and lack of arousal associated with sex usually require an additional course of couples therapy with a sexual focus (Clinical Vignette 2). Hormone treatment for lack of desire has not proven effective (Rosen and Lieblum 1995).

Clinical Vignette 2

Mrs. L. had problems with anger during adolescence, generally due to feeling neglected by her busy parents. She had a period of intense sexual activity during adolescence, which was related to looking for affection through sexuality; she reported that she had no sexual problems during this time. Through twice a week individual psychotherapy in her twenties she worked through these problems, married Mr. L., and had a child. Mr. L was a kind but rather distant man who soon after the marriage made a series of career moves that made him extremely busy. For the first two years, there were no sexual problems. Two years after the marriage, marital problems developed, and Mrs. L.'s desire decreased. Mr. L. then became more sexually demanding. Frequency and enjoyment of sex for both partners was markedly decreased. Mrs. L. refused to have sex, saying that she was too upset. When they had sex, occasionally however, both were orgasmic.

Mr. and Mrs. L. had both been raised in traditional backgrounds, and had been taught that sex should not be discussed. Although both had previous sexual experiences, they were unable to talk about their sexual problems. Mrs. L also began fantasizing about other men. Although fantasies of other partners are not unusual, Mrs. L.'s fantasies only occurred when she was particularly angry with her husband. Whereas at one time individual psychotherapy for Mrs. L. might have been the treatment of choice, the therapist decided to use both marital therapy and sex therapy. Marital therapy helped to open communication between the couple. It was discovered that Mrs. L. was feeling very abandoned by her extremely hard working husband and feeling that she was being ignored-as she had been in her childhood. In addition, she was angry at her husband for not helping with child-rearing responsibilities. Her fantasies about other men, which seemed to be a way of wishing for the original affection she craved, were upsetting her and making her wonder if she loved her husband. Mr. L's inability to challenge her

and insist on her connecting with him emotionally before demanding sex was experienced as further withdrawal.

The couple was encouraged to deal more directly with their differences and with the disappointments underlying their anger. Issues related to each partner's family of origin were brought up. Roles were restructured—Mr. L. took over more of the child-rearing responsibilities. As the marital relationship improved, their sexual problems decreased. The couples were also given a series of sensate focus exercises in which they were asked to focus on giving and receiving pleasure. They were encouraged to talk with each other about their sexual wishes and to pay attention to the connection between themselves while being sexual. They also discussed deepening their nonsexual physical connection, that is "constructing" a new reality for themselves as a couple.

This case demonstrates the use of combining different models and strategies to change behaviors which are complex in origin.

## Homosexuality or Bisexuality

The authors believe that couples therapists should be adequately educated in the area of human sexual orientation and sexual identity. These terms in themselves are confusing. *Sexual orientation* is another way of indicating an individual's tendency to be attracted to one or both sexes. Sexual orientation, like most psychological phenomena, is not an absolute or mutually exclusive trait. One may be sexually attracted to the opposite sex, the same sex, or both. Sexual orientation falls along a continuum, with completely homosexual and completely heterosexual preferences falling at the extreme ends, and many gradations in between. Sexual orientation may also change over time. Some persons change from heterosexual to homosexual or the reverse in their thirties, forties, or fifties. Some remain bisexual during their adult lives. Some persons may move along a continuum of homosexual to transgender. *Sexual identity* describes how a person identifies related to their sexual orientation. Hence a man who exclusively prefers women will usually have a *straight* or *heterosexual* sexual identity, and a woman who exclusively prefers women usually a *lesbian* or *homosexual* sexual identity.

Observations of human sexual behavior, affectional attachments, erotic fantasies, arousal, and erotic preference have suggested that sexual orientation and identity are not static. In fact, both may fluctuate over a person's lifetime. Sometimes changes in sexuality are "just phases"; sometimes they become the predominant disposition of sexual relation. Regardless, deviation from heterosexuality in Western society is frequently accompanied by rejection, not only by one's immediate family, but also by one's peers and, in some cases, society in general. Accusations of discrimination and violence, "gay bashing," have been a constant news story in metropolitan headlines. Bisexuals have the added nonacceptance by gay and lesbian friends or associates who may accuse them of "fence-sitting," of "sleeping with the enemy," or of being deviant because they are unable to choose whether to be hetero- or homosexual. For the therapist, the issue should be centered on understanding and listening to other's experiences, even if they are quite different than our own.

Infidelity, communication, and substance abuse are all issues that are common to all couples including homosexual or bisexual couples. However, what differentiates homosexual and bisexual couples from heterosexual couples is the effects of internalized homophobia, societal oppression, and "coming out," as well as greater fluidity in gender roles. (Connolly 2004).

Internalized homophobia is when homosexual or bisexual individuals experience negative feelings and emotions toward themselves when recognizing their own sexuality (Herek 1997). This can bring about feelings of guilt, self-hatred, and negativity regarding the durability of long-term relationships (Ossana 2000). Difficulties in identity formation, identity management, and the "coming out" process can all precipitate from internalized homophobia (Connolly 2004).

Societal oppression comes in two forms: homophobia and heterosexism. Homophobia is defined by any negative belief, reaction, attitude, or action toward homosexuals (Bernat 2001). Homophobia can be hostile due to its inherent discriminatory and prejudicial nature (Connolly 2004). Heterosexism is the belief that heterosexual relationships are preferable and superior to homosexual or bisexual relationships. This belief in and of itself is oppressive (Connolly 2004).

Many persons who are bisexual or whose homosexuality is admitted consciously later in life may spend some years in heterosexual marriages. Many such people are able to function well heterosexually, changing their sexual focus when they realize that "something is missing" or that their level of desire and love is greater for their own sex. Some have low levels of sexual desire in the marriage and develop affairs. Because there may be a great deal of love and affection between the marital partners, the discovery that one member is homosexual is very painful. The desire to remain in the marriage may be strong on one or both sides. Although sex therapy can improve sexual functioning, there is no treatment which has proven effective in decreasing homosexual desires and fantasies. The couple must decide how to handle the situation—that is, whether to divorce, remain in the relationship and allow for alternative sexual behaviors, or whether the homosexual person can remain monogamous in the marriage and give up expressing the other parts of themselves. Therapy can help the couple clarify these alternatives and make decisions. Experience shows that even with the most loving spouses the most common final event is divorce.

## Homosexual Civil Unions or Marriages

Homosexual long-term committed relationships have always existed; legalized civil unions or marriages are increasingly common as state laws change. Homosexual and lesbian couples have many of the same issues as heterosexual couples such as struggles over intimacy, power, boundaries and commitment. Some issues particular to such couples need to be noted by the therapist. There is the presence of both external and internalized homophobia, including the ever-present possibilities of legal discrimination, job discrimination and violence. Members of one or both families of origin may not accept the couple as legitimate, so that the couple needs to develop a family of choice. Adding children to the family

becomes complex, requiring adoption or surrogacy for men and the question of sperm donation (and who will carry the child) for women, unless there are already children from previous relationships. Sexual difficulties, in addition to the usual individual and couple issues, may arise from disagreements over monogamy, HIV-related issues, or the tendency of female couples to reduce their sexual frequency. Normal sexual practices of gay and lesbian couples may include a wider variety of activities than those of most heterosexual couples; heterosexual therapists need to be knowledgeable about this. In most ways, however, the same techniques used for heterosexual couples are applicable here.

### Sexual Problems after Medical Illness

Adults treated for cancer, diabetes, heart disease, prostatitis, HIV, and chemical dependency may face extraordinary sexual challenges due to the underlying disorder, their treatment, or the illness' effect on the couple's relationship. Two separate kinds of problems can occur. In one, the illness specifically affects sexual functioning. For example, surgery for prostate cancer may produce erectile dysfunction. This is now generally treated medically with alprostadil or similar medication in various forms; in few cases penile prosthesis may be necessary. Close communication with the urologist is necessary. The therapist should also help partners expand their repertoire of nonintercourse sexual behaviors. In the second type of situation, sex is still possible but the couple is anxious that having sex will injure one person. The classic example here is sex following myocardial infarction (Cobb and Schaffer 1975). There is no evidence that sex with a known partner in familiar surroundings is problematic for the heart. The very few heart attacks related to sex are most likely to involve affair partners and heavy intake of food or alcohol. The couple should be advised to resume sex as soon as any reasonable exercise is permissible.

Erectile dysfunction may be the predictable side effect of certain antihypertensive medications. Narcotics such as heroin, barbiturates, and alcohol have a similar effect. Obviously, addictive drugs should be stopped or efforts made to change necessary medications. Serious illness of any kind, plus treatment for certain illnesses like cancer, may leave the person with no sexual interest. In this case, the couple may have to live with it, and the therapist's task is to help the couple decide the best way to handle it within the marital relationship. It is important that the lack of sexual intimacy not end other forms of "comfort touch." Similarly, surgery, chemotherapy, or radiation for cervical, ovarian, and prostate cancer can reduce desire and performance. HIV and AIDS should alter a couple's approach to sex, and safe sexual practices must be recommended.

## Conclusion

Couples and sex therapy are important forms of psychotherapy. There is little question that developing the skills needed to successfully work with couples presenting with a wide range of difficulties requires an understanding of how normal couples' relationships change over time, how problems emerge and are maintained, and how focused marital treatment can alleviate distress and dysfunction. The rewards, however, are great when therapists can assist couples in recognizing and shifting the patterns that inhibit their abilities to live rich, intimate lives together.

This chapter provides the basics of evaluation and treatment of the most common types of couples. It also succinctly details the kinds of results a therapist might expect and discusses not only when to prescribe couples therapy, but also the practical issues in carrying it out to successful completion.

As mentioned in the introduction to this chapter, long-term relationships that are mutually supportive with a high level of intimacy are rare. As societies around the world (including our own) continue to evolve, unexpected events create havoc even for very stable families. What couples ask of their psychiatrists is the basic knowledge and skills, artfully applied to their joint relationships, to improve the quality of their lives.

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CHAPTER

# 94 Hypnosis

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Hypnosis is a natural state of attentive, focused concentration. As such, most individuals are able to experience trancelike states at different times in their daily lives. An example is the alteration of awareness experienced by some persons as they concentrate intently on a movie or a play while disconnecting from awareness of the surrounding environment. Depending on the degree of natural ability to enter a trance state (hypnotic capacity or hypnotizability), a given subject will require more or less help to enter and use his or her hypnotic capacity. That is, highly hypnotizable individuals enter trance states with ease, on many occasions even without being fully aware of it. Individuals with low hypnotizability require more direction or help from the therapist who facilitates the trance experience. High hypnotic capacity may actually become a liability to patients who are unaware of their hypnotic capacity or of their unconscious use of this mechanism, as is the case of individuals suffering from a dissociative disorder. Even when we do not intend to use hypnosis formally, we must remember that the ability to enter a trance state is widely and naturally distributed throughout the normal population. Thus, some of our patients may be experiencing trance states even without our planning.

## Historical Background

The phenomenon of "trance experiences" has been described throughout history. In ancient Greece, trancelike states were used as a vehicle for treatment of mental or physical illness by allowing or facilitating contact with gods or spirits deemed causative of human malaise. Official reports of the use of hypnosis in the modern world date to the 18th century (Table 94–1). Friedrich (Franz) Anton Mesmer (1734–1815) is considered the father of hypnosis. He described the use of "mesmeric passes" (manipulations) by which he believed he was able to influence the "magnetic fluid" throughout his patients' bodies. Franz Anton Mesmer employed hypnotic interventions as an alternative treatment for many ills that we would now label as stress related or psychosomatic (Lopez 1993). Despite the fact that his work was discredited by a panel of French experts appointed by King Louis XVI (1784), it represented the first Western formal method of psychological treatment, or psychotherapy (Ellenberger 1970). The Royal Commission, headed by Benjamin Franklin (then American ambassador to France), did acknowledge that the phenomenon of suggestion, the influence of one individual on another, was at the root of social order as well as personal change. Now we know that suggestibility not only is one of the main components of the hypnotic experience but also is ever present in any form of therapeutic interaction between physicians of any specialty and their patients.

In the late 18th century, José Custodi Di Faria (1756–1819) proposed the theory of expectancy and receptivity as the clue for hypnotic success. He also moved away from the mesmeric passes to the use of verbal suggestions. During the 19th century, interest in hypnosis persisted in America through the writings of William James (1902), Boris Sidis (Sidis and Goodhart 1905), and Morton Prince (1906), who founded the *Journal of Abnormal Psychology*. They were fascinated by the extreme symptoms observed in patients with such dissociative symptoms as conversion reactions and multiple personality disorder.

Yet, the use of hypnosis has not been limited to the field of psychiatry. In fact, we owe the name hypnosis to the British surgeon James Braid (1785–1860), who initially coined the name *neurohypnology* or nervous sleep (Braid 1843), which was later shortened to the current term, hypnosis. The earliest reported use of hypnoanesthesia is attributed to the French surgeon Jules Cloquet, who in 1829 used it while performing a mastectomy (Fourmestraux 1934). In 1836, the first use of hypnosis as an anesthetic in the US was reported in Boston (West 1836). John Elliotson (1843) is credited with the introduction of hypnosis as a form of anesthesia in Great Britain. The British surgeon James Esdaile (1957) reported excellent surgical success rates (up to 85%) using hypnosis as the only form of anesthesia while practicing in India. Throughout the years, the routine use of hypnosis as a form of anesthesia has declined, probably because of the uniformity of results obtained by chemical agents. Nevertheless, the use of hypnosis in medicine has been extended to the treatment of other medical symptoms, including chronic pain and procedural anxiety.

In France, the noted neurologist Jean Martin Charcot (1825–1893) reported cases of patients suffering from pseudoneurological disorders that responded to the use of

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**Table 94–1 History of Hypnosis**

| | |
|---|---|
| 1734–1815 | Friedrich (Franz) Anton Mesmer, the father of modern hypnosis; "magnetic fluid theory" |
| 1751–1825 | Marquis Armand De Puygseur described the forerunner steps of the "cathartic cure" or spontaneous talk in a somnambulistic state |
| 1756–1819 | José Custodio Di Faria proposed the theory of expectancy and receptivity as the clue for hypnotic success; moved from "mesmeric passes" to verbal inductions |
| 1785–1860 | James Braid initially called it neurohypnology or nervous sleep, later shortened to hypnosis; introduced the principle of monoideism as hypnotic induction |
| 1791–1860 | John Elliotson, professor of surgery at the University College in London, is attributed with the introduction of hypnosis as anesthetic in England |
| 1808–1859 | James Esdaile performed surgery using hypnosis as the only form of anesthesia |
| 1823–1904 | Auguste-Ambroise Liebault stressed the role of "suggestibility" in hypnosis; combined Braid's eye fixation procedure with Di Faria's verbal suggestions |
| 1825–1893 | Jean Marie Charcot discovered that many hysterical symptoms could be both induced and removed by hypnosis; erroneously identified hypnosis as a disease of the central nervous system and stated that only sick (hysterical) people could be hypnotized |
| 1829–1838 | Hypnosis as anesthesia in the Western Hemisphere<br>1829, France: Jules Cloquet—mastectomy<br>1836, Boston: Hypnosis used as anesthetic for dental surgery<br>1838, England: John Elliotson—orthopedic surgery |
| 1837–1919 | Hippolyte Bernheim hypothesized that the causes of hypnotic induction were psychological and not organic; described suggestion as the main factor underlying hypnosis |
| 1842–1925 | Josef Breuer suggested that hysteria was the result of repressed memories and emotions. Along with his colleague, Freud, he discovered that these symptoms could be removed by asking the patient to talk about these memories and emotions. This made Breuer move from attempting to remove the symptoms by direct hypnotic removal to uncovering of the original traumatic memories under hypnotic trance, by either age regression or hypnotic reenactment. This became the precursor to the cathartic method |
| 1854–1919 | Morton Prince used hypnosis on the treatment of multiple personality disorders and conversion disorder; founded the *Journal of Abnormal Psychology* |
| 1856–1939 | Sigmund Freud became interested in hypnosis after watching Breuer at work. In 1885, he went to study with Charcot (Paris) and later with Bernheim and Liebault (Nancy). He believed, at first, that hypnosis gave access to the unconscious and therefore could be used in the treatment of neurotic symptoms. It was not until 1889 that Freud used the cathartic method with his patients. He described the treatment of his patients with this method and detailed their progress in *Studies in Hysteria* (1895). As he developed his psychoanalytic theories, he used hypnosis less frequently. Soon after the publication of the hypnosis-based *Studies in Hysteria*, he abandoned its use as a treatment modality in favor of his psychoanalytic method |
| 1859–1947 | Pierre Janet proposed that "while under hypnosis the conscious mind is gradually suppressed, which allows the unconscious mind to take over" |
| 1947 | Kardiner and Spiegel described the usefulness of hypnosis in the treatment of traumatic neurosis or shell shock syndrome during World War II |
| 1949 | The Society for Clinical and Experimental Hypnosis was founded |
| 1957 | Milton Erickson founded the American Society of Clinical Hypnosis |
| 1959 | Weitzenhoffer and Hilgard published the Stanford Hypnotic Susceptibility Scale for research purposes |
| 1960 | Hypnosis is officially recognized as a legitimate therapeutic tool in both medicine and psychiatry by the American Medical Association and the American Psychiatric Association |
| 1975 | Hilgard and Hilgard published the first hypnotizability scale designed for clinical settings, the Stanford Hypnotic Clinical Scale |
| 1978 | Spiegel and Spiegel introduced the Hypnotic Induction Profile specifically designed to assess hypnotic capacity and clinical applications |

suggestion (Charcot 1890). Later, he found that these "hysterical symptoms" could be both induced and removed by hypnosis. Following the steps of his predecessor, Pierre Janet (1859–1947) built a theory of the unconscious involving compartmentalization of memory (Janet 1907). This differed from Freud's model in being horizontal rather than vertical and archeological (Hilgard 1977). According to Janet's dissociative model, information kept out of awareness was relatively untransformed, but it could be accessed directly by use of techniques such as hypnosis. Janet used the ability of highly hypnotizable individuals as evidence of experimentally induced psychiatric illness. Hippolyte Bernheim (1964) took a contrary (and ultimately correct) view that hypnotic phenomena were essentially normal rather than evidence of disease, a viewpoint further developed by Freud's early collaborator Joseph Breuer. Breuer suggested that hysteria was the result of an uncontrolled hypnotic-like state driven by repressed memories and emotions. Later, Breuer and Freud (1955) discovered that these symptoms could be alleviated by asking the patient to talk about these memories and emotions. Thus they began the use of hypnotic age regression or hypnotic reenactment (the "cathartic method") to treat hysterical symptoms. This led to the development of their theory linking unconscious

determinants to conscious symptoms. They believed that "hypnoidlike" states constituted the building blocks of hysterical symptoms. This became one of the first recognitions that hypnotic processes are indeed normal and yet could often be mobilized in the service of resolving an unconscious conflict. Later, as he developed his psychoanalytic theories, Freud (1958) abandoned hypnosis in favor of free association, viewing it as a manipulation of transference phenomena.

During the early part of the 20th century hypnosis was little scientific activity related to the use of hypnosis in clinical settings. Nevertheless, during World War II there was a revival of the technique, as manifestations of the traumas of war required a new treatment approach. Army psychiatrists described the usefulness of hypnotic interventions in treating so-called shell shock syndrome or traumatic neurosis (Kardiner and Spiegel 1947). In the second part of the 20th century investigations in the area of hypnosis ranged from studies of the relationships among hypnotizability, placebo response, and acupuncture, to studies of the differential hypnotizability of patients with psychosis and other psychiatric disorders, to investigations used in determining neurophysiological correlates of the hypnotic state and hypnotic capacity, all with varying success (Alden and Heap 1998, Barabasz and Lonsdale 1983, De Pascalis 1999, Engstrom et al. 1970, Graffin et al. 1995b, Jasiukaitis et al. 1980a, Jensen et al. 2001, Maldonado 1997, Maldonado and Jasiukaitis 2003, Morgan et al. 1974b, Sabourin et al. 1990, Spiegel 1991a, Spiegel and Barabasz 1988, Spiegel et al. 1982, 1985). Novel treatment techniques involving hypnotic manipulations became popular in the 1960s (Erickson 1967a). An era of serious laboratory investigation of the phenomenon began with the development of several hypnotizability scales, such as the Stanford Hypnotic Susceptibility Scales (Hilgard 1965, Hilgard et al. 1958, Weitzenhoffer 1962a, 1962b, Weitzenhoffer and Hilgard 1959). This was followed by the development of several shorter hypnotizability scales specifically designed for use in clinical settings (i.e., Stanford Hypnotic Clinical Scale [Hilgard 1975b] and the Hypnotic Induction Profile [Eliseo 1974, Spiegel and Spiegel 1978, 1987]).

In 1960, the American Medical Association (AMA) and the American Psychiatric Association (APA) officially recognized hypnosis as a legitimate therapeutic tool. Two professional hypnosis societies emerged at the national level, each publishing a journal. The Society for Clinical and Experimental Hypnosis emphasizes research in the field of experimental hypnosis, and the American Society for Clinical Hypnosis focuses more on the clinical applications of hypnosis. Hypnosis is currently part of the curriculum in many medical schools and psychiatric residency programs. The American Psychological Association has devoted a division (Division 30) to its study. At present, the uses of hypnosis in clinical and investigational areas continue to grow, as does research on the neuropsychological mechanisms involved in the hypnotic process.

## Definition

Hypnosis is a natural psychophysiological state of attentive, receptive concentration, during which individuals experience a relative suspension of peripheral awareness. Hypnotic phenomena occur spontaneously, but it can be elicited at will. During the context of a therapeutic relationship the alteration of consciousness that hypnotized individuals experience may have a variety of therapeutic applications. The hypnotic experience may be understood as involving three main factors: absorption, dissociation, and suggestibility (Cardena and Spiegel 1991) (Table 94–2).

**Table 94–2 Components of the Hypnotic Process**

| Component | Explanation |
|---|---|
| Absorption | Refers to the tendency to engage in self-altering and highly focused attention with complete immersion in a central experience at the expense of contextual orientation and more peripheral perceptions, thoughts, memories, or motor activities |
| Dissociation | Permits keeping out of conscious awareness many routine experiences that ordinarily would be conscious. Dissociated material may be temporarily and reversibly unavailable to consciousness, but it continues to influence conscious and unconscious experiences and behavior |
| Suggestibility | Involves heightened responsiveness to social cues. It allows subjects to suspend the usual conscious curiosity that makes us question the reason for our actions, making subjects more prone to accept suggestions given no matter how irrational |

## Absorption

By absorption we refer to the tendency or ability of individuals to engage in self-altering and highly focused attention with complete immersion in a central experience at the expense of contextual orientation (Hilgard 1970, Tellegen 1981, Tellegen and Atkinson 1974). As one becomes deeply involved in a central focus of consciousness, one tends to ignore more peripheral perceptions, thoughts, memories, or motor activities. Hypnotized individuals can become so intensely absorbed in their trance experience that they often seem to ignore the environmental context and other peripheral events. This intense exclusion of information that is considered by the subject to be peripheral to the trance state allows the phenomenon known as *trance logic*.

Trance logic implies a thinking pattern that does not obey the rules of "normal" logical processes. For example, it may be suggested that the individual sustain a conversation with a person who is not present in the room. A highly hypnotizable subject may hallucinate the necessary elements of experience without "thinking twice" about the absurdity of talking to an empty chair. An extreme form of pathological absorption is seen in cases of traumatic flashbacks. In these instances, patients become so absorbed in the experience triggered by an environmental cue that they act as though they were reliving the whole experience, despite the impossibility of it.

There is abundant scientific evidence that demonstrates a correlation between hypnotizability and a spontaneous tendency for people to undergo absorbing or self-altering experiences (Tellegen and Atkinson 1974). Therefore, we can assume that individuals who tend to get deeply caught up in external or internal experiences, such as watching a movie or imagining something, that they seem to loose awareness of

where they are or the context of what they are experiencing may be entering spontaneous trance states and thus may fall in the higher range of hypnotizability. This is because individuals with hypnotic ability may use it spontaneously, not simply when formally instructed to do so. This tendency of highly hypnotizable individuals to enter spontaneous hypnotic states may be a liability to them and may have important interpersonal and clinical implications, as spontaneous trance states may be unwittingly elicited during highly stressful or emotional situations, potentially leading to pathological symptoms (i.e., conversion symptoms and dissociated states) (Barber 1956, Bentler 1963, Duke 1969, Eysenck 1943, Maldonado 2006, Maldonado and Spiegel 2005, 2007).

## Dissociation

By dissociation we imply the ability to separate mental processes so that they seem to occur independently from each other. The process of dissociation is complementary to absorption. Thus, there is nonpathological and pathological dissociation. During hypnosis, the intense absorption characteristic of the hypnotic state permits keeping out of conscious awareness many routine experiences that would ordinarily be conscious by the process of nonpathological dissociation. When working properly in our daily lives it allows us to carry out several complex tasks simultaneously (e.g., knitting while conversing or watching television).

On the other hand, pathological dissociation may arise as a result of severe trauma or abuse (Maldonado and Spiegel 1994). Even complex emotional states, motor functions, or sensory experiences may be dissociated. Dissociated perception of the internal or external world results in depersonalization or derealization. Restricted access to memory results in cases of dissociative amnesia or dissociative fugue. Motor dysfunction elicited by dissociated phenomena may include cases of conversion disorder, such as conversion paralysis or psychogenic paresthesias. As described by Charcot (1890), most of these phenomena can be both induced and reversed with the structured use of hypnosis.

Dissociated memories may be temporarily and reversibly unavailable to consciousness, but they continue to influence conscious (or other unconscious) experiences and behavior (Hilgard 1977, Kilhstrom 1984). Out of sight does not mean out of mind. Many of the symptoms experienced by patients suffering from posttraumatic stress disorder (PTSD; DSM-IV-TR) (APA 1994) can be explained by the influence exerted by memories unavailable to consciousness. This is the case when a sensory stimulus triggers a flashback in a trauma survivor. The process of absorption complements that of dissociation; the state of intense focal attention (absorption) facilitates putting information outside of conscious awareness (dissociation).

## Suggestibility

Suggestibility implies the ability to influence someone's beliefs or behaviors by suggestion. Owing to the intense absorption experienced during trance, hypnotized individuals have a heightened responsiveness to social cues, including suggestions given by the therapist. This enhanced suggestibility allows hypnotized subjects to accept instructions relatively easily. Hypnotized individuals are not deprived of their will, but they do have a tendency to accept instructions in an uncritical way when under trance. This quality of the hypnotic process allows subjects to suspend the usual conscious curiosity that makes us question the reason for our actions. Because of this, hypnotized individuals are more likely to accept suggestions or directions, no matter how irrational they might be. Subjects under hypnosis are less likely to distinguish an instruction coming from an outside source (i.e., from the therapist) from those coming themselves, a phenomenon known as *hypnotic source amnesia*. This allows highly suggestible individuals to act on another person's ideas as though they were their own. This aspect of hypnosis may be used by conscientious therapists to bypass the patient's defenses and mobilize the patient's strengths. On the other hand, a hypnotized patient is less likely to correct a therapist's mistakes and may be confused by hypnotic instructions that are vague or misguided.

## Myth Dispelled: What Hypnosis Is and What It Is Not

Several principles provide guidance for the use of hypnosis in medicine and psychiatry. We attempt to clarify some of the myths and misconceptions about hypnosis by establishing what hypnosis is and what it is not (Table 94–3).

**Hypnotizability is a stable and measurable trait.** Not everyone is hypnotizable. Hypnotizability or hypnotic capacity varies throughout the population. Just as some people have more or less ability to play a musical instrument or no ability at all, there is considerable variation in individuals' ability to undergo and use hypnosis, and these differences are stable over time (Hilgard 1965, Hilgard and Hilgard 1975, Spiegel and Spiegel 1978, 1987). Hypnotizability is as consistent as intelligence for a 30-year interval in adulthood (Piccione et al. 1989). Hypnotizability is highest in late childhood and declines gradually throughout adulthood. Recognizing this fact is helpful in demystifying hypnosis and reducing anxiety on the part of both the physician inducing hypnosis and the patient. About 75% of the population has some usable hypnotic capacity; of these, about 10% are highly hypnotizable. This means that about one in four adults has no usable hypnotic capacity (Spiegel and Spiegel 2004). It is advantageous to determine this early and encourage those with the ability to use it; other treatment modalities are offered to those who are not hypnotizable.

**Table 94–3 What Is Hypnosis?**

| What It Is |
|---|
| Hypnosis is a form of focused concentration |
| Hypnotizability is a stable and measurable trait |
| Hypnosis is something you do with, rather than to, a subject or patient |
| All hypnosis is self-hypnosis |
| **What It Is Not** |
| Hypnosis is not sleep |
| There are no apparent sex differences in hypnotizability |
| Hypnotizability is not a sign of weak-mindedness |
| Hypnosis is not intrinsically dangerous |
| Hypnosis is not therapy |
| There is nothing you can do with hypnosis that you cannot do without it |

**Hypnosis is something you do *with*, not something you do *to*, a subject or patient.** A therapist inducing hypnosis is in the position of the Socratic teacher, helping students discover what they already know (Spiegel and Spiegel 1978). A useful metaphor to share with subjects is that of a coach. A correctly performed hypnotic induction allows the patient and physician to assess and explore the patient's hypnotic capacity or lack of it, just as a trainer assesses the athlete's natural capacities and then attempts to maximize them. This approach tends to minimize power struggles between the physician and the patient. For example, there is less chance of misinterpreting a patient's inability to experience a hypnotic trance as resistance.

**All hypnosis is self-hypnosis.** The therapist helps the patient use his or her own hypnotic capacity to undergo a trance state. Helping patients to understand the degree of control they have over their mental processes is a good way to foster mastery and control. By doing this, patients may be able to comprehend the extent to which the unconscious use of their hypnotic abilities may create or contribute to their psychiatric symptoms, as in the case of dissociative disorders (Bliss 1980, 1984a, Spiegel 1974, Spiegel and Fink 1979). Similarly, hypnosis may help patients understand how certain physical symptoms may have unconscious etiological factors, as in the case of conversion phenomena (i.e., psychogenic blindness and pseudoseizures) (Maldonado and Spiegel 2000a) or psychosomatic conditions (i.e., asthma and headache) (Maldonado and Spiegel 2000b).

**There are no apparent sex differences in hypnotizability.** Men and women are equally hypnotizable (Hilgard 1965, Stern et al. 1978).

**Hypnosis is not sleep.** The most prevalent misunderstanding derives from the name itself. Unfortunately, in the late 1800s, James Braid coined the word neurohypnology to describe what he considered to be a special kind of sleep (Braid 1843). Later, this was shortened to its current name, derived from the Greek root *hypnos*, which means "sleep." The hypnotized individual is not asleep but rather awake and alert. To an outside observer, hypnotized individuals may appear asleep owing to their apparent lack of responsiveness to the environment. This is due to their intense absorption and concentration on their internal experience, rather than due to their lack of will. Similar to a sleeping person, a hypnotized individual has suspended peripheral awareness. Yet, in contrast with what occurs in sleep, the subject's focal attention is intensely and carefully controlled. Studies show that the power spectral electroencephalogram (EEG) of hypnotized individuals is closer to that of a resting, but alert individual rather than a sleeping subject (Chertok and Kramarz 1959, Evans 1977, Fujisawa 1971, LaRiccia et al. 1985, Shpil'Berg 1955).

**Hypnotizability is not a sign of weak-mindedness.** Charcot described the ability to undergo a hypnotic trance as a sign of a defective central nervous system. Today, we know that on the contrary, a hypnotic trance requires an intact capacity for focused concentration. If anything, high hypnotizability is associated with the absence of serious psychotic and neurological disorders (Lavoie and Sabourin 1980, Pettinati 1982, Spiegel et al. 1982).

**Hypnosis is not intrinsically dangerous.** For the most part, it is a benign process. The same cognitive flexibility that allows patients to enter the trance facilitates their exit from it with clear structure and support from the therapist. The dangers of hypnosis lay not in the process itself but in how it is used. There are few contraindications for the use of hypnosis. An occasional paranoid schizophrenic patient may incorporate an attempt at inducing hypnosis into a delusional system. A severely depressed individual may interpret a failure to benefit from hypnosis as further evidence of little self-worth. These problems can be avoided in part by use of hypnotizability testing at the beginning of the intervention. The most serious problem involves possible effects of hypnosis on memory. This is discussed at length under the section "Forensic Applications of Hypnosis," later in the chapter.

**Hypnosis is not therapy.** Entry into a hypnotic state does not have any therapeutic effects of its own, although many find it pleasant and relaxing. Instead, hypnosis is another tool a skilled, trained mental health professional can use to achieve change within the therapy process. Therapeutic change comes not from the state itself but from what happens during it. In this regard, hypnosis is not a treatment itself but rather a facilitator of a variety of treatment strategies. The state of intense concentration elicited in hypnosis can facilitate attention to a variety of strategies that enhance control over somatic function, reduce pain, allow the recovery and restructuring of memories, elicit the reproduction and control of conversion symptoms or fugue episodes, and provide control of dissociated states.

**There is nothing you can do with hypnosis that you cannot do without it.** As an adjuvant to therapy, hypnosis may help speed the process by which information can be accessed and processed because of its ability to heighten concentration and focus attention; however, it is not a treatment in and of itself.

## Hypnotizability Scales

Hypnosis is a stable and measurable trait. Given not everyone is hypnotizable to the same degree, it is helpful to perform a clinical assessment of a patient's hypnotizability before embarking on the use of hypnosis as a therapeutic technique (Spiegel and Spiegel 1987). Most of the hypnotizability scales developed in the early part of the 20th century were designed for use in research settings, most notably the Stanford Hypnotic Susceptibility Scale (Hilgard 1965, Hilgard et al. 1958, Weitzenhoffer 1962a, 1962b, Weitzenhoffer and Hilgard 1959) and the Harvard Group Scale of Hypnotic Susceptibility (Shor and Orne 1962). These scales involve a structured hypnotic induction and an assessment of the subject's response to a variety of instructions, including alterations in control over movement, sensation, temporal orientation, and perception, such as hallucinatory experiences. Some of the forms have been translated and validated to other languages. The Stanford Hypnotic Susceptibility Scale, From C, had been translated to Italian (De Pascalis et al. 2000) and Spanish (Sanchez-Armass and Barabasz 2005). Meanwhile, the Harvard Group Scale of Hypnotic Susceptibility has been translated to and validated in Australian (Sheehan and McConkey 1979), Czechoslovakian (Svoboda 1989), Danish (Zachariae et al. 1996), Finnish (Kallio and Ihamuotila 1999), German (Bongartz 1985), Romanian (David et al. 2003), Spanish (Lamas et al. 1989), and Swedish (Bergman et al. 2003) populations. Research scales are very accurate and useful in research settings (Angelini et al. 1999, Kumar

et al. 1996, Younger et al. 2005); on the other hand, they are lengthy, making their frequent use impractical in the clinical setting. Because of these, newer and shorter versions of the same scales have been developed (Bowers 1993, Pekala 1995, Robin et al. 2005).

Over the years, shorter and more practical hypnotizability scales were developed for clinical use, such as the Hypnotic Induction Profile (Spiegel and Spiegel 1978, 1987) and the Stanford Hypnotic Clinical Scale (Hilgard and Hilgard 1975). These scales are briefer (about 5–10 minutes for the Hypnotic Induction Profile and 20 minutes for the Stanford Hypnotic Clinical Scale, compared with 1 hour for the research scales) and are designed for comfortable use even with patients who have severe psychiatric disturbances (Spiegel et al. 1982, 1988, Spiegel and Spiegel 1978, 1987). Clinical scales are well accepted by patients and their use help bypass performance anxiety by shifting the focus of the interaction from one in which the therapist tries to make the patient have a hypnotic experience (i.e., patient's performance) to one in which the therapist assesses the patient's response to a set of instructions (i.e., therapeutic intervention) (Spiegel and Spiegel 1987). The therapist focuses on evaluating the patient's ability to enter the state rather than on getting the person into the state. They all involve a structured hypnotic induction and an assessment of the subject's response to a variety of instructions, such as alterations in the sense of control over body movements, physical sensations, orientation to time and space, and perception. Furthermore, such a standardized testing induction permits an important deduction regarding the hypnotic capacity of the subject. The restricted range of input from the therapist maximizes the information provided by variations in subjects' responses. After the results of the testing are discussed with the subject, both can proceed knowledgeably, choosing to use hypnosis or other techniques in the service of an agreed on treatment goal.

The use of this kind of objective measurement has several clinical advantages and therapeutic implications (Table 94–4):

(a) It takes the pressure off both the therapist and the patient. Hypnotizability testing helps to clarify the hypnotic interaction. The therapist objectively assesses the patient's natural ability to use her or his hypnotic capacity, if any, rather than pushing the patient to respond in a certain manner. By objectively determining the patient's ability, there is no pressure on the therapist to see whether he or she can hypnotize the patient. Likewise, it reduces the sense of pressure on the patient to either comply or resist. The test setting creates an atmosphere of scientific exploration that encourages rather than coerces involvement.

(b) Hypnotizability testing provides objective data about the patient's ability to respond to treatment via hypnosis. If the patient is a highly hypnotizable individual, she or he can be rationally encouraged to proceed with the use of hypnosis. Nonhypnotizable individuals can be offered an alternative approach that is likely to be more efficacious, such as relaxation techniques, biofeedback, or medication.

(c) Objective standardized tests of hypnotic capacity used across a large population provide the therapist with scientific data to make rational inferences about the patient's expected response. Patients' relative ability, or inability, to restructure their inner experience by hypnosis will provide helpful information to the therapist about the subject's interpersonal style and/or level of psychiatric disturbance.

(d) The intense concentration and increased receptivity characteristic of the trance phenomenon will make us predict that the capacity to experience hypnosis correlates with responsiveness to psychological treatment. Indeed, research has found a high correlation between high hypnotizability scores and responsivity to a number of selected clinical problems, such as pain (Hilgard and Hilgard 1975), cigarette smoking (Spiegel and Spiegel 2004), and a variety of medical and psychosomatic conditions (Maldonado and Spiegel 2000b).

**Table 94–4 Benefits of the Use of Hypnotizability Measures**

| |
|---|
| It objectively assesses the patient's natural ability to use his or her hypnotic capacity |
| It relieves performance pressure on both therapist and patient |
| It provides objective data about the patient's ability to respond to treatment employing hypnosis |
| It provides the therapist with scientific data to make rational treatment choices |
| It provides helpful information about the subject's interpersonal style and possible psychiatric illness |
| It helps predict the patient's likely response to psychotherapeutic treatment |

## The Hypnotic Induction Profile

The Hypnotic Induction Profile (Figure 94–1) (Eliseo 1974, Otani 1993, Spiegel 1977, Spiegel et al. 1976, Spiegel and Spiegel 1978, 1987, Stern et al. 1978) is a useful clinical screening test for hypnotic capacity. It consists of a number of the simple instructions that allow the measurement of patients' natural ability to tap into and use their hypnotic capacity. It begins with a simple and quick induction, counting from 1 to 3, accompanied by the eye roll. This involves instructed upward gaze and lowering of the eyelids (Figure 94–2). The dissociation between upward gaze and lowering of the eyelid can be scored (Figure 94–3), providing the therapist with an initial, but crude, prediction of the subject's hypnotic capacity (Hilgard 1981, Sheehan et al. 1979, Spiegel and Spiegel 1978). The eye roll is then followed by a series of instructions to briefly influence the subject's behavior during and shortly after the test (posthypnotic suggestions). The Hypnotic Induction Profile allows the therapist to rate the subject on five items (Table 94–5) assessing cognitive and

**Table 94–5 Items Tested by the Hypnotic Induction Profile**

| |
|---|
| Body dissociation |
| Hand levitation |
| Level of unconscious compliance |
| Response to posthypnotic suggestion |
| Sensory alteration |

Name _____ Date _____

Sequence ☐ Initial _____ Previous _____ When _____

Position of subject ☐ Standing _____ Supine _____ Chair _____ Chair–stool _____

| Item | | |
|---|---|---|
| A | *Up–gaze* | *0 – 1 – 2 – 3 – 4* |
| B | Roll: | 0 – 1 – 2 – 3 – 4 |
| C | Squint: | 0 – 1 – 2 – 3 – 4 |
| D | Eye-roll sign (roll and squint) | 0 – 1 – 2 – 3 – 4 |
| E | *Arm (R–L) levitation instruction* | *0 – 1 – 2 – 3 – 4* |
| F | *Tingle* | *0 – – 1 – 2* |
| G_____ | Dissociation | 0 – – 1 – 2 |
| H_____ | Levitation (postinduction) { No reinforcement; 1st "; 2nd "; 3rd "; 4th " } | 3 – 4; 2 – 3; 1 – 2; 1 –; 0 – ; Smile _____; Surprise _____ |
| I _____ | Control differential | 0 – – 1 – 2 |
| J _____ | Cutoff | 0 – – 1 – 2 |
| K_____ | *Amnesia to cutoff or no–test* _____ | *0 – – 1 – 2* |
| L _____ | Floating sensation | 0 – – 1 – 2 |

Summary scores

_____ Induction score  Profile score 0 – 1 – 2 – 3 – 4 – 5

_____ Soft  _____ Zero  _____ Intact

_____ Minutes  _____ Decrement  _____ Special zero  _____ Special intact

**Figure 94–1** *Hypnotic Induction Profile score sheet. [Spiegel and Spiegel 1978. Reprinted 1987 American Psychiatric Press, Washington DC.]*

behavioral aspects of the single continuous but brief hypnotic experience elicited during the test. These are (1) ability to experience a sense of dissociation of the left hand from the rest of the body; (2) hand levitation, or floating of the hand back up in the air after being pulled down; (3) sense of involuntariness or unconscious compliance while elevating the hand; (4) response to the cutoff signal ending the hypnotic experience; and (5) sensory alteration in the hand or elsewhere in the body.

Scores on the Hypnotic Induction Profile are significantly but moderately correlated with those on the Stanford scales (Frischholz et al. 1980, Frishholz et al. 1981, Hilgard 1981, Orne et al. 1979, Otani 1993) and provide useful discrimination among different psychiatric disorders, as described in the following section.

## Hypnotizability and Psychiatric Disorders

As we have discussed above, absorption and dissociation are key elements of the hypnotic experience. As it would be expected, research data and clinical experience suggest that certain psychiatric disorders, especially those in which high levels of absorption or dissociative features are present, may be associated with high hypnotizability scores (Table 94–6).

Examples include patients with acute stress disorder (ASD; DSM-IV-TR) (Bryant et al. 2001, 2005, 2006) and posttraumatic stress disorder (PTSD; DSM-IV-TR) (Iglesias and Iglesias 2005b, Kluft 1982, 1993, Putnam 1992, Spiegel 1992, Spiegel et al. 1988, Stutman and Bliss 1985, Watkins 2000). Several studies have shown significantly higher hypnotizability among individuals with PTSD than among

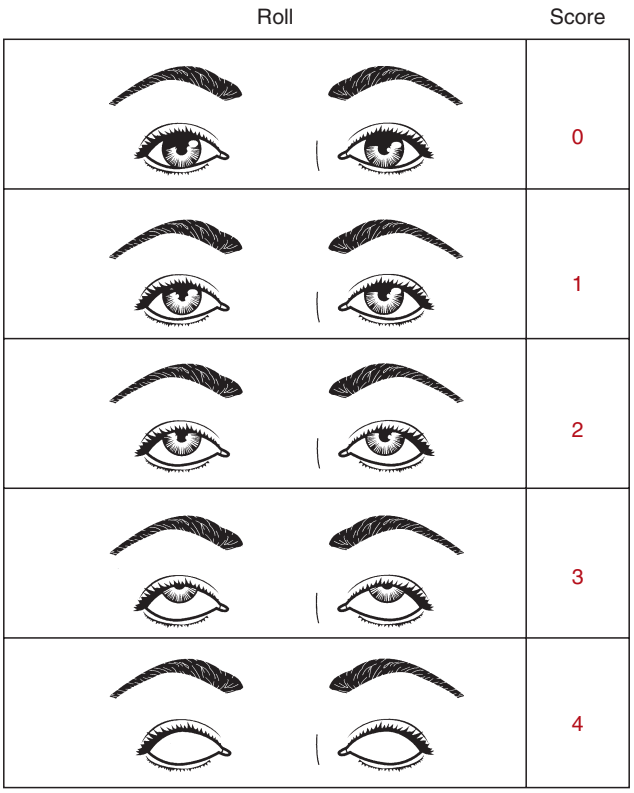



**Figure 94–2** *Eye-roll sign for hypnotizability. (Source: Spiegel and Spiegel 1978. Reprinted 1987 American Psychiatric Press, Washington DC.)*

similar individuals without PTSD (Stutman and Bliss 1985) or in comparison to psychiatric patients with other disorders (Spiegel et al. 1988). Patients with dissociative disorders (DSM-IV-TR) such as fugue, amnesia, or dissociative identity disorder (DID) (multiple personality disorder) also tend to be highly hypnotizable (Allen and Smith 1993, Bliss 1986, Braun and Sachs 1985, Carlson and Putnam 1989, Coons and Milstein 1986, Frischholz 1985, Frischholz et al. 1992, Kluft 1985a, 1985c, 1985d, 1992, 1993, Maldonado and Spiegel 2002a, Putnam et al. 1995, 1996, Spiegel 1984, 1989). Most patients with DID report histories of severe physical and sexual abuse in childhood (Braun and Sachs 1985, Kluft 1985b, Maldonado and Spiegel 1995, 2000a, Spiegel 1984). It is thought that these patients enhanced their natural ability to dissociate by separating themselves from painful physical experiences over time. Later, the same defenses are unconsciously mobilized during periods of extreme anxiety or stress. The same temporary dissociation that allowed the victim to tolerate overwhelming fear and pain earlier in life becomes an ongoing part of the personality structure. This tendency to compartmentalize memories and experiences by

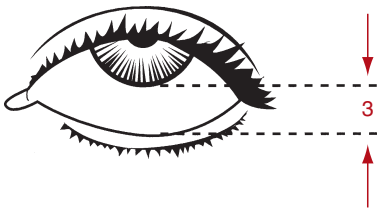



**Figure 94–3** *Eye-roll measurement. (Source: Spiegel and Spiegel 1978. Reprinted 1987 American Psychiatric Press, Washington DC.)*

**Table 94–6 Psychiatric Disorders Associated with High Hypnotizability**

| |
|---|
| Victims of overwhelming trauma |
| Adjustment disorders |
| Acute stress disorder |
| Posttraumatic stress disorder |
| Dissociative disorders |
| Fugue states |
| Dissociative amnesia |
| Dissociative identity disorder |
| Anxiety disorders |
| Phobias |
| Performance anxiety |
| Bulimia nervosa |
| Borderline personality disorder |
| Conversion disorder |

the processes of repression and dissociation allows the victim of PTSD to split into multiple dissociated selves. Some of them suffered the pain and humiliation, while others took on themselves the function of protecting the patient from the experience of further injury. The literature on posttraumatic and dissociative disorders reveals a close relationship between trauma, dissociation, and hypnotizability. The data on DID (DSM-IV-TR) highlights that most patients with DID are highly hypnotizable (Bliss 1984b, Frischholz 1985, Kluft 1985a, Maldonado and Spiegel 2002a).

Years ago, a syndrome resembling histrionic personality disorder was described (DSM-IV-TR) but in this particular group, the capacity for hypnotic dissociation was deemed to be central. It was labeled the "Grade 5" syndrome (Spiegel 1974). These patients are described to be highly hypnotizable, to repeatedly establish naive and dependent relationships, and to express their distress in dramatic ways. They are slow in becoming aware of their internal cues, requiring much external reassurance. They tend to develop superficial but intense affiliations with new ideas and people that tend not to last over time. Because of their tendency to become overly dependent, they require a therapeutic environment that is highly structured. The goal of therapy with these patients is to help them recognize their tendency to repeatedly seek relationships in which they make themselves vulnerable owing to their tendency to relinquish control.

As in the case of dissociative disorders, several studies described an increased hypnotic capacity in patients suffering from anxiety disorders, especially phobias (Benson et al. 1978, Bodden 1991, Daniels 1975, Davidson et al. 1978, Frankel and Orne 1976, Gilbertson and Kemp 1992, Granone 1980, Hurley 1980, Marks et al. 1968, McCarthy 1967, McGuinness 1984, Meares 1966, Menzies and Clarke 1993, Morcas 1984, Mott 1986, Smith 1990). Some explain this increased hypnotizability as being secondary to a heightened dissociative response triggered by phobic symptoms. The symptoms of phobia or anxiety may represent a state of absorption in the fearful situation, with subsequent suspension of critical judgment. This is not true for all anxiety disorders. Other researchers failed to replicate this finding (Frischholz et al. 1982b). At least one other study showed that patients suffering from generalized anxiety disorder (GAD; DSM-IV-TR) obtained markedly lower hypnotizability scores than normal subjects (Spiegel et al. 1982).

Impulse–control behaviors characteristic of *eating disorders* (Covino et al. 1994, Evans and Staats 1989, Kranhold et al. 1992) and *personality disorders* (Baker 1983, Copeland 1986, Murry-Jobsis 1991, Pettinati et al. 1990), especially borderline personality disorder (BPD), may represent a state of dissociation associated with higher hypnotizability scores (Maldonado and Spiegel 2005). Some of the common symptoms of patients suffering from eating disorders are strikingly similar to those of patients suffering from some forms of dissociative disorders and include trancelike states during episodes of pathological eating behavior (Pettinati et al. 1985), reliving of the trauma, dissociation, personality disorders (particularly cluster B symptoms), pathological relationship with food, distortion of body image, suicide attempts, and self-inflicted punishment (Molinari 2001, Pettinati et al. 1985). Indeed, Pettinati et al. (1990) administered both the Stanford Hypnotic Susceptibility Scale (Form C) and the Hypnotic Induction Profile to patients with eating disorders. They observed higher hypnotizability in bulimic patients compared with restrictors (e.g., anorexia nervosa). These findings and clinical experience suggest a possible opportunity for intervention employing hypnosis in controlling some forms of disordered eating (Anbar and Savedoff 2005, Gross 1984, 1986, Mantle 2003, Spiegel and Debetz 1978a, 1978b, Torem 1992).

Likewise, many patients suffering from self-destructive behavior described dissociative or trancelike states surrounding periods of self-mutilation (Scagnelli 1980). This is not uncommon among individuals with dissociative and borderline personality disorder (DSM-IV-TR). There is high comorbidity between borderline personality disorder and dissociative disorders (Anderson et al. 1993, Brodsky et al. 1995, Horevitz and Braun 1984, Shearer 1994, Yargic et al. 1998). Studies (Shearer 1994) have demonstrated that high dissociative experiences in patients with BPD were characterized by more self-reported traumatic experiences, posttraumatic symptoms, behavioral dyscontrol, self-injurious behavior, and alcohol abuse. Zanarini et al. (2000) found that compared to control groups, BPD patients have much higher levels of dissociation (26% in BPD group vs. 3% in controls). Low et al. (2000) found that the frequency of patients engaging in deliberate self-injurious behavior was primarily related to increased dissociation. Wildgoose et al. (2000) studied personality disordered subjects and found that subjects with BPD (compared with non-BPD, personality disorders) had higher levels of a number of aspects of psychiatric symptomatology, particularly personality fragmentation, most of which were mediated by aspects of dissociation.

Charcot (1890) described a relationship between conversion phenomena and high hypnotizability. He first became fascinated by how the process of mesmerism could reproduce conversion symptoms. Unfortunately, he incorrectly attributed both phenomena (i.e., conversion and hypnotic ability) to a pathological process afflicting the central nervous system. Charcot erroneously concluded that only sick or "hysterical" people could be hypnotized. Later on, others, including Bernheim, Janet, and Breuer, refuted that idea, although all recognized that patients suffering from conversion symptoms were highly hypnotizable (Bernheim 1964, Breuer and Freud 1955, Janet 1907). They attributed the symptoms of conversion to unconscious mechanisms and viewed hypnosis as a tool useful in both the elicitation and the removal of such states. Recent research in hypnosis has been directed at understanding the relationship between hypnotizability and psychiatric illness. More recently, Bliss (1984a) reported that patients with conversion disorder tend to be very hypnotizable, and other studies have corroborated that such patients are more highly hypnotizable than the population at large. These findings have been corroborated by others. For example, Peterson et al. (1950) found that even though only about 20–30% of the general population is highly hypnotizable, nearly 70% of patients with psychogenic seizures exhibit high levels of hypnotizability. Kuyk et al. (1999) also found increased levels of hypnotic susceptibility in patients with pseudoepileptic seizures (PESs) compared with patients experiencing true epileptic seizures (ESs). Finally, Roelofs et al. (2002) found that conversion patients scored significantly higher on hypnotic susceptibility and were more responsive to hypnotic suggestions than were control subjects. He also found a significant correlation between hypnotic susceptibility and the number of conversion complaints presented by patients.

Patients with psychosis, suffering from delusions, loosening of associations, and hallucinations, might be expected to do poorly in tests requiring attention and concentration. Hypnosis represents a state of heightened concentration and focused attention. If these two premises are true, we could predict that severely psychotic patients would not be hypnotizable. Indeed, Copeland and Kitching (1937) made the observation that some previously diagnosed psychotic patients who proved to be hypnotizable had been, in fact, misdiagnosed. Somewhat lower scores have been obtained on the Hypnotic Induction Profile (Pettinati 1982, Pettinati et al. 1990, Spiegel et al. 1982), and a restricted range of scores and the absence of high hypnotizability scores have been found in studies employing the Stanford Hypnotic Susceptibility Scale among schizophrenic subjects (Lavoie and Elie 1973, Lavoie and Sabourin 1973, 1980, Pettinati 1982, Pettinati et al. 1990, Weitzenhoffer 1962b, Weitzenhoffer and Hilgard 1959). The reason for these findings may be that hypnotic responsiveness requires complex cognitive tasks. Actively psychotic subjects (i.e., experiencing delusions, loose associations, and hallucinations) might not be able to adequately focus, thus performing poorly on hypnotizability tests, as they do on many other psychological tests. These findings were independent of psychoactive medication use (Spiegel 1980a). Even though hallucinatory activity can be artificially produced in hypnotic states, psychotic patients, especially those with schizophrenia, have shown impairment in their ability to sustain a high level of attention, which interferes with hypnotic concentration. Patients suffering from a major affective disorder have been found to score between normal subjects and schizophrenic patients in hypnotizability (Spiegel et al. 1982). These findings were independent of psychoactive medication use (Spiegel 1980a).

Thus, several psychiatric syndromes (i.e., schizophrenia, GAD, and to a lesser extent major affective disorder) (DSM-IV-TR) have been associated with generally lower hypnotic responsiveness (Lavoie and Elie 1973, Lavoie and Sabourin 1980, Murry-Jobsis 1991, Pettinati 1982, Scagnelli 1980, Spiegel et al. 1982). It may be that the primary illness process impairs the use of a patient's natural capacity for hypnotic concentration. Because of this, hypnotizability testing can

sometimes be used to clarify diagnoses. As always, the presence or absence of hypnotic capacity should be interpreted within the context of the presentation, medical and psychiatric histories, and genetic background. In the case of an acute psychosis in which there is no familial background, the presentation is later in life than normal, there is a past history of physical or sexual abuse, and the patient has a high hypnotizability score, a diagnosis of hysterical psychosis or a dissociative disorder should be strongly considered when the possibility of schizophrenia is evaluated (Spiegel and Fink 1979, Steingard and Frankel 1985).

## Applications of Hypnosis

### General Considerations

Because of the intrinsic qualities of the hypnotic state, it can be an effective adjunct to the treatment of a variety of symptoms and problems, both in psychiatry and in medicine in general. The first criterion to consider is the patient's level of hypnotizability. Once it has been determined that the patient has usable hypnotic capacity (defined by moderate to high scores in hypnotizability scales), a discussion about the nature of the hypnotic process follows. It is important at this point to dispel any myths and correct misconceptions the patient may have about the process. This includes the cooperative nature of the hypnotic process, rather than the "tell me what to do" most patients expect. Finally, the therapist must decide whether the problem presented by the patient is amenable to hypnotic intervention or whether other steps should be taken instead.

We have divided the discussion of the applications of hypnosis into five areas: general psychiatry, general medicine, psychosomatic disorders, habit control, and forensic psychiatry (Table 94–7).

**Table 94–7 Applications of Hypnosis**

| |
|---|
| **General Psychiatry** |
| Anxiety disorders |
| Phobias |
| Posttraumatic stress disorder |
| Dissociative disorders |
| Dissociative amnesia |
| Dissociative identity disorder |
| Conversion disorder |
| Eating disorders |
| **General Medicine** |
| Anxiety associated with medical, surgical, and dental procedures |
| Pain control |
| Insomnia |
| Dermatological conditions |
| Gastrointestinal disturbances |
| Respiratory conditions |
| Emesis (chemotherapy, hyperemesis gravidarum) |
| **Habit Control** |
| Smoking cessation |
| Weight control |
| **Forensic Psychiatry** |
| Memory enhancement |

### Application in Psychiatric Disorders

The use of hypnosis in the context of conventional psychotherapy can facilitate the therapeutic process in a number of ways. For example, hypnotherapeutic techniques may be used to enhance the patient's sense of self, restructure traumatic and phobic experiences, or access to repressed memories that have not emerged with use of other techniques. This is true not only of painfully repressed memories but also of situations in which both the patient and the therapist have worked on resistance issues and feel that some additional leverage is necessary. In conventional psychotherapy, the transference is observed and analyzed; in hypnosis, the transference is used as part of the therapeutic process.

Conventional psychoanalytic psychotherapy involves observation and analysis of the meaning of the transference reaction that arises during therapeutic interactions. On the other hand, when hypnosis is used, transference is not avoided or bypassed but may be amplified. All the usual therapeutic rules and processes of psychotherapy apply when hypnosis is used in the psychotherapy context, which may intensify or accelerate the therapeutic process (see Clinical Vignette 1).

Clinical Vignette 1

A young woman sought consultation with me (JRM) because of a phobia about crossing bridges that had begun 5 years earlier. The patient, a psychiatric nurse, was psychologically minded and despite having seen several therapists for her problem had not been able to resolve it using psychotherapy. The problem was now a major issue in her life because she had just bought a car and was angry that her problem impeded her "new freedom."

She reported that her phobia initially occurred when she was driving in her sister's car down a long bridge in one of the coastal eastern states. As she was midway across the bridge, she looked around, noticing that her sister, her sister's boyfriend, and a cousin were all asleep. She reported becoming slowly anxious. Then, all of a sudden, she became extremely frightened. She slammed on the car brakes and stopped the car in the middle of the bridge. Since then, she has not been able to drive across a bridge again. She proceeded to describe her multiple attempts to do so in the preceding few months.

She agreed to try hypnosis and proved to be an excellent candidate. Her Hypnotic Induction Profile score was 9 out of a possible maximum of 10. After induction of a hypnotic state, age regression was used to return her to the first known episode of panic. It was suggested that she would become both physically and mentally relaxed and then allow her unconscious mind to take her to the first time she ever felt this way. The patient spontaneously curled up in the chair; she began to sob and then scream, "Please, mommy, don't leave me."

After the abreaction was over, she spontaneously exited her hypnotic state, and we proceeded to examine and reframe the experience. She reported that under trance, she was able to remember how when she was 7 years of age her mother came home with a box full of plastic bags and began to pack the belongings of each of her children. The mother then put the children and the bags in her car and drove out of town, over the bridge, and into a neighboring state where many of her relatives lived. The patient ended up staying with her grandmother, while her siblings lived

*(continues)*

with two different aunts. She had completely forgotten these facts even though she had always been fully aware that she had been raised by her grandmother.

Still, the question of timing remained. Why did it begin 5 years ago and not before? She closed her eyes and easily entered a hypnotic state. This time she was able to review the events surrounding the initial episode of phobia. She remembered how before initiating her trip down the East Coast, she had arrived home one day and found a message from her long disappeared mother. In it, her mother said that she was going to visit the East Coast and that she intended to visit her and her sisters. The patient contacted her sisters, but their conversation was limited. "Did she also call you?" "Yes," replied her sister; that was all. She had completely avoided talking or thinking about what was going to happen shortly after her trip. As she was driving over the bridge, noticing that everyone was asleep, her mind began to wander. Fear about what was to happen came to mind. She wished that there was a way by which she could avoid the encounter. Suddenly, she froze. The car stopped and she was unable to continue. She just could not cross the bridge. Once again, she spontaneously exited the trance state and began to provide her own appropriate explanation about what might have happened. She saw this long bridge as a kind of umbilical cord that would reunite her with her mother. Then conflict arose accompanied by feelings of ambivalence and then fear. The only way to avoid the situation was not getting there, and because she was in control of the car, her only way out was to panic, to freeze, and to stop.

After a debriefing session and reframing of her past and how to reinterpret the original trauma as well as the phobia, she expressed feeling confident about her skills as a survivor. She was able to move from being in the position of the indefensible victim (the 7-year-old child) or the handicapped adult and talked about the new challenge that lay ahead. She politely agreed to a plan to test her ability to drive across a bridge. For the third and final time in this session, she entered (now on her own) a hypnotic state and saw herself being able to drive through the bridge. She agreed to return in 2 weeks, after stating that she planned to test herself the following weekend.

Two weeks after the initial contact, the patient returned. She proceeded to recount the events of the three trips she had made by the second session, each of increasing difficulty. To this day, 11 years later, the patient has not had any further episodes of phobia associated with bridges and has an amicable but distant relationship with her mother.

Because of the intense emotions that are characteristic of the hypnotic retrieval (which facilitates expression of inner fantasies), intense feelings and deep personal experiences may be elicited. Some patients may find that the hypnotic state facilitates a sense of infantile dependency in which the therapist becomes the transferential object. The quality of this transference reaction will be based on the patient's early object relations, just as in any other therapeutic relationship. Indeed, the transference reaction may develop so fast that the inexperienced therapist may not have the opportunity to recognize it or may do so too late. The difference here is the intensity of the feelings developed as a result of the strong emotions that arise during trance. As in the case of victims of abuse, the therapist may use the transference relationship under hypnosis to foster the patient's ability to help her- or himself.

An example of this is the use of self-mothering techniques (Scagnelli 1975, Spiegel 1989, 1992, Spiegel and Cardeña 1990), in which patients are able to go beyond the anger toward a parent or perpetrator and become able to provide for themselves the nurturing and protection that they needed but never had. The therapist may also use the influence he or she has over the patient to suggest alternative ways to deal with problems. Sometimes a patient recovers a memory under hypnosis but then forgets it once the trance state has ended. The therapist who is aware of this may lead the patient to the goal, always respecting the principle that the patient will remember when she or he is ready to remember.

Another technique is the so-called ego-strengthening technique, in which hypnosis is used to provide positive reinforcement for behavior change (Crasilneck and Hall 1985). Some therapists would provide direct instructions for a symptom to disappear. This authoritarian approach often puts both therapist and patient in an awkward situation; it is unwise to tell a patient something one is not certain to be true, whether or not the patient is in a trance. No one can be certain that a symptom will disappear, even in the case of a highly hypnotizable patient. Alternatively, Milton Erickson (1967) promoted the use of a "therapeutic bind," mobilizing the patient's resistance to treatment by intensifying, or "prescribing," the same symptoms the patient was complaining of. The patient would then construe eliminating the symptom as a victory over the therapist. This approach has the virtue of demonstrating to patients their ability to modulate symptoms, bypassing defensiveness by worsening rather than lessening them (Erickson 1967b).

We recommend a hypnotic approach that emphasizes the educational aspects of the therapeutic experience. It is better to structure the intervention as a lesson in self-hypnosis, which the patient can later employ in the service of symptom reduction, thus recruiting the patient as a partner, rather than a dependent, while at the same time empowering the patient to have a more active approach in health management. This is the main focus of an approach known as *hypnotic restructuring* (Spiegel and Spiegel 2004). Restructuring in hypnosis involves using the intense state of concentration characteristic of the hypnotic trance to help patients develop a strategy for change that amounts to an affirmation experience rather than a struggle, focusing on "what they are for rather than what they are against." For example, instead of suggesting that "cigarettes taste bad" or "you will become nauseated when you smoke," patients use the self-hypnosis exercise to focus on a broader commitment to protect their body in the same way that they would protect a child from poison, viewing their bodies as trusting, innocent creatures that depend on them for their protection. In this approach, mind and body are viewed as distinct but interdependent, and the goal is to change the relationship to the body rather than to prevent smoking. Thus, these patients' perspective on the problem is enlarged, which makes the resolution of the problem itself an example of a broader pattern of relating to one's body.

This kind of restructuring strategy can be applied to other problems as well, such as mild-to-moderate overeating (Barabasz and Spiegel 1989), and to the treatment of pain (Brose et al. 1992, Hilgard and Hilgard 1975, Spiegel 1985). In the latter case, patients are taught to transform the pain

signal by making the affected body area colder or warmer, or numb, or to focus on a sensation in some other part of the body. The management of anxiety or panic attacks is not taught by an instruction to relax or not be anxious; rather, patients learn to affiliate with a physical metaphor that connotes relaxation, such as floating in water. In this way, patients can overcome urges or symptoms not by struggling against them but by subsuming them under a commitment to a new way of relating to the body, or through a hypnotically developed capacity to transform sensation (Spiegel and Spiegel 2004).

Finally, we do not use the term hypnotherapist, because there are no hypnotherapists. Instead, there are therapists who use hypnosis within the context of the therapeutic practice to achieve a specific therapeutic result. The difficult aspect of doing hypnosis is not the induction of the hypnosis trance, but what happens once the patient is under trance. Remember that all hypnosis is self-hypnosis. Thus, there are two factors that will predict the success of the hypnosis intervention: the patients' hypnotizability and the therapeutic skills of the therapist.

## Anxiety Disorders

Anxiety disorders are among the most widely prevalent psychiatric disturbances. They afflict as much as 15% of the population (Myers et al. 1984). Anxiety can be seen as a state of hyperarousal experienced by both emotional and somatic discomfort. Patients describe their experience in physical terms, such as palpitations, gastrointestinal discomfort, chest pain, sweating, and motor restlessness. Among anxiety disorders most responsive to hypnotic intervention are panic disorder, phobias, and posttraumatic anxiety disorders. (These will be discussed in the section that follows.)

GAD can be seen as a chronic state of anxiety that usually inhibits psychological comfort and social functioning. GAD involves excessive anxiety, occurring more days than not and lasting over a 6-month period. The anxiety is more like a "free-floating" worry or fear about a number of events or activities and is commonly associated with multiple symptoms, including restlessness, muscle tension, fatigue, insomnia, difficulty in concentrating, and irritability. In contrast, panic attacks are sudden and intense states associated with extreme anxiety and physical and emotional distress, and usually occur in a very discrete period of time. The disorder is usually associated with irrational avoidance behavior and anticipatory anxiety. Studies have shown that patients with GAD have markedly lower scores than do subjects without the disorder (Spiegel et al. 1982).

Whereas, as noted earlier, the hypnotizability of patients with GAD is low, studies show that phobic patients are at least normally and perhaps highly hypnotizable (Frankel and Orne 1976). Phobic reactions involve marked, excessive fear cued by the presence or anticipation of an object or specific situation. Invariably, the exposure to the stimulus provokes an immediate and extreme anxiety response. Hypnosis can be helpful as an adjunctive tool for treating some anxiety disorders because of its ability to help patients control their somatic response to anxiety-provoking stimuli (Brough et al. 1965, Clarke and Jackson 1983, Daniels 1976, Domangue 1985, Erickson 1967b, Forgione 1988, Frutiger 1981, Maldonado and Spiegel 2000b, McGuinness 1984, Morse and Cohen 1983, Scott 1970, Scrignar 1981, Somer 1995, Spiegel et al. 1981b, Stanton 1989, 1993). This enables patients to attend to the stimuli long enough to alter their point of view about them and achieve a sense of mastery over them.

Many case reports and several studies suggest that hypnosis may be an effective adjunct in the treatment of panic attacks and panic disorder (Der and Lewington 1990, Iglesias and Iglesias 2005a, Somer 1995, Stetter et al. 1994, Swartz 1981, Van Dyck and Spinhoven 1997a, 1997b). Similarly, a 7-year follow-up of 178 patients treated with a single session of self-hypnosis for flying phobia indicated that 52% were either improved or cured (Spiegel et al. 1981b).

Most of the strategies in the treatment of anxiety disorders employing hypnosis combine instructed physical relaxation with a restructuring of cognition, using imagery coupled with physical relaxation (Benson et al. 1978, Butler et al. 2005, Daniels 1975, Davidson et al. 1978, Erickson 1967b, Gilbertson and Kemp 1992, Hurley 1980, McCarthy 1967, Meares 1966, Morcas 1984, Smith 1990). As in the treatment of anxiety disorders by systematic desensitization or progressive relaxation, patients are instructed to maintain a physical sense of relaxation (e.g., floating) while picturing the feared situation or stimulus (Marks et al. 1968). It is important that the relaxation instruction uses an image that connotes reduced somatic tension, such as floating or lightness, rather than being a direct instruction to relax. The more cognitive term "relax" may actually induce more anxiety, whereas affiliation with a somatic metaphor usually produces some reduction in tension. Unlike systematic desensitization, hypnosis produces a physically relaxed state that can be rapidly achieved with a quick induction. Also different from systematic desensitization, the coupling of relaxation to a fearful stimulus does not require the development or working through of a hierarchy. A typical self-hypnosis induction can be rapid. For example, a patient can be told,

> Now just get as comfortable as you can. There are many ways to enter a state of self-hypnosis. One simple but useful method is to count to yourself from 1 to 3. On 1, do one thing: look up. On 2, do two things: slowly close your eyes and take a deep breath. On 3, do three things: let your eyes relax but keep them closed, let your breath out, and let your body float. Then let one hand or the other float up into the air like a buoyant balloon. This is your signal to yourself and to me that you are ready to concentrate.

Initially, the use of hypnosis in the session can help in demonstrating to patients that they have a greater degree of control over somatic responsiveness than they had imagined. It is often useful to begin by teaching patients to create a place in their mind's eye where they feel safe and secure. On occasion, it helps the subjects to learn how to project their image onto an imaginary screen. Later, they can learn to manipulate the screen by making it either bigger or smaller, having the screen nearer or farther away, as needed:

> Just allow your body to float, as if you were floating in a bath, a lake, or a hot tub. Enjoy this sense

> of floating lightness. Now, picture in your mind's eye an imaginary screen. It might be a movie screen, a television screen, or a piece of clear blue sky. First picture a pleasant scene, somewhere you enjoy being.

Allow the patient to experience this state for a minute or two and then inquire about the experience:

> With your eyes closed and remaining in this state of concentration, describe how your body is feeling right now. What image are you picturing?

After receiving the answers, add

> Notice how you can use your store of memories and fantasies to help yourself and your body feel better.

After they have learned to manipulate the screen and their physical sensations, patients may be ready to do therapy work. They may, for example, learn to re-create the physical state of relaxation while projecting the fearful situation onto the screen. This, then, becomes a useful procedure by which to control and obtain mastery over anxiety-producing situations by dissociating the somatic reaction from the psychological response to the feared stimulus. Initially, the patient is asked to re-create the physical feeling of relaxation. Then, the patient projects onto the screen images associated with the feared situation; only this time the somatic reactions associated with anxiety do not develop. On occasion, it helps for patients to foresee likely physical sensations or situations associated with a fearful experience to master them. For example, in the case of plane phobia, the patient can learn to couple the real sensation of floating in the air with the hypnotic experience: "Learn to float with the plane."

Patients may also use the trance state as a means of facing their concerns more directly. As in the preceding cases, they may make use of the screen technique (Spiegel and Spiegel 2004). They can achieve this by placing an image of an upcoming performance or fearful situation on one side of the screen, testing out various strategies for mastering the situation on the other side.

Other approaches using hypnosis have included instructing patients in a trance to imagine that they are literally somewhere else, away from the fearful stimulus, thus separating themselves from the anxiety-producing experience (Erickson 1967b, Marks et al. 1968). Positive reinforcement or "ego-strengthening" techniques have also been used; for example, hypnotic instructions are given to patients suggesting that their capacity to master the situation and their response to it will improve (Crasilneck and Hall 1985). There is little reason to use uncovering techniques seeking to link anxiety to some early traumatic experience in cases of phobia or generalized anxiety disorders. This is different in cases of PTSD (DSM-IV-TR), however, in which more work may be needed to confront and place into context the traumatic experience.

Certainly, in some cases, understanding the cause of the feared situation may help resolve the conflict. One of the techniques used to facilitate the recovery of traumatic memories associated with fearful situations is the affect bridge technique (Watkins 1987).

## Acute and Posttraumatic Stress Disorder

The use of hypnosis for treatment of traumatic experiences was initially described by Breuer and Freud (1955). At the time, they observed that an abreaction was accompanied by the release of psychic tension and, on occasion, relief of physical symptoms. That was the premise behind the use of the cathartic method. The idea was that some intense affect associated with the traumatic event needed to be released, and that simply repeating the event with its associated emotion in the trance state would suffice to resolve the symptoms. It did not take long for Freud to realize that conscious, cognitive work must be done on the recovered material for it to be successfully worked through (Freud 1946, 1958). Hypnotic techniques for the treatment of posttraumatic conditions were often used by the clinical pioneers of the end of the 19th century and by military therapists treating soldiers during the 20th century's conflagrations. More recently, hypnosis has also been used with survivors of sexual assault, accidents, and other traumas.

For the psychotherapeutic treatment of trauma victims to be effective, the patient must cognitively recollect the traumatic events with an enhanced sense of control over the memories of the experience; abreaction alone is not enough. The idea is not to reexperience the trauma; patients do that on their own every time they experience a traumatic flashback. In fact, there is actually a risk of further retraumatization in the continuous reliving of traumatic experience without adequate restructuring (Maldonado and Spiegel 1994, Spiegel 1992, Spiegel and Cardeña 1990, Spiegel and Spiegel 1987). The cognitive restructuring technique takes the form of a symbolic restructuring of the traumatic experiences under hypnosis and the use of a grief work model (Spiegel 1981). As adapted for the treatment of PTSD (DSM-IV-TR), hypnosis can be used to provide controlled access to the dissociated or repressed memories of the traumatic experience and then to help patients restructure their memories of the events (Maldonado and Spiegel 1994, 1995, Spiegel 1981, 1988, 1989, 1998, Spiegel and Spiegel 1987).

Trauma constitutes a sudden discontinuity in both physical and mental experiences. The effect of the traumatic experience forces the victim to reorganize mental and psychophysiological processes to buffer the immediate impact of the trauma. This process is meant to be an adaptive mechanism to maintain psychological control during a time of enormous stress. Unfortunately, a number of trauma victims go on to suffer acute or chronic symptoms, such as dissociation, intrusive thoughts, anxiety, withdrawal, and hyperarousal, leading to a diagnosis of ASD or PTSD.

Multiple authors have described how victims use dissociation to cope with a traumatic event as it is occurring (Spiegel 1986, 1988, 1990, Spiegel et al. 1988, van der Kolk and van der Hart 1989). Others have suggested that major stress and trauma are common antecedents of dissociative phenomena, including some of the symptoms observed in PTSD victims (Bremner and Brett 1997, Cardeña and Spiegel 1993, Classen et al. 1993, Coons et al. 1989, Keane and Wolfe 1990, Maldonado et al. 2000, Maldonado and Spiegel 2002a, McFarlane 1986, 1988, 1992, McFarlane et al. 1993,

Solomon et al. 1989, Spiegel 1986, 1990, van der Kolk 1989, van der Kolk and van der Hart 1989, Wilkinson 1983).

There may be a relationship during childhood between stress, such as early trauma, and high hypnotizability. In support of this idea are reports of high hypnotizability in children who were victims of severe punishment during childhood (Nash et al. 1984, Spiegel and Cardeña 1991). It is possible that the impact of the stress suffered encouraged them to use their self-hypnotic abilities more effectively (Kluft 1984, 1992, Spiegel et al. 1982).

The major categories of symptoms in PTSD are similar to the components of the hypnotic process (APA 1994, Maldonado and Spiegel 2002a). Hypnotic absorption is similar to the intrusive reliving of traumatic events experienced by these patients. When in a flashback, trauma victims become so absorbed in the memories of the traumatic event, they lose touch with their present surroundings and even forget that the events took place in the past. Likewise, highly hypnotizable individuals may become so intensely absorbed in the trance experience that they can reenact a previous life event (during hypnotic age regression) as if they were reliving it. A hypnotized patient may dissociate a body part to the extent of not recognizing it as part of his or her body. Similarly, PTSD patients may dissociate feelings to the extent of experiencing the so-called psychic numbing. This allows them to disconnect current affects from their everyday experience in an attempt to avoid emotions triggering memories associated with the trauma. Finally, suggestibility is comparable to hyperarousal. The heightened sensitivity to environmental cues observed in those patients suffering from PTSD is similar to that experienced by a hypnotized individual who responds to suggestions of coldness by shivering.

Because many patients suffering from PTSD are highly hypnotizable (Spiegel et al. 1988, Stutman and Bliss 1985), and because of the resemblance between the symptoms of PTSD and the hypnotic phenomena, it makes sense to use hypnosis in its treatment. Similarly, available reports suggest high hypnotizability in children who were victims of severe punishment during childhood (Nash et al. 1986, Spiegel and Cardeña 1991). Some trauma researchers (Kluft 1984, 1992, Spiegel et al. 1982) have proposed that the impact of the stress suffered during trauma encouraged a more effective use of self-hypnotic abilities, which in turn may enhance or mediate some of the observed symptomatology. If patients suffering from PTSD are unknowingly using their own hypnotic capacities (Kluft 1991, 1992, Maldonado and Spiegel 1994, 2000a, Spiegel 1986, 1988, 1989, Spiegel et al. 1988), it is therapeutically useful to teach them how to enter, access, and control their trance potential. Hypnosis may be invaluable as a tool to access previously dissociated traumatic material.

We do not refer here to uncontrolled abreaction. The purpose is not simply to help the patient remember the trauma, because in a way, every time a patient goes through a flashback, an uncontrolled abreaction is experienced. An abreaction that is not conducted within the context of cognitive restructuring and before new defenses are in place can lead to the further retraumatization of the patient (Kluft 1992, Spiegel 1981).

For therapy of intense trauma to be effective, cognitive restructuring of the traumatic memories must be facilitated along with adequate emotional expression and relationship management. The therapy process must provide an enhanced sense of control over the traumatic memories. This can be facilitated by the process of symbolic restructuring of the traumatic experiences during the hypnotic process (Cardeña et al. 2000, Spiegel and Spiegel 2004), based on the grief work model (Spiegel 1981). Hypnosis then can be used to provide controlled access to the dissociated or repressed memories of the traumatic experience and then to help patients restructure their memories of the events.

Research data support the notion that many victims enter a dissociated state during physical trauma (Bremner, Southwick, and Brett 1992, Butler et al. 1996, Cardeña and Spiegel 1993, Putnam 1985, Spiegel and Cardeña 1991, van der Kolk et al. 1994, van der Kolk and Fisler 1995). If this is the case, it makes sense that enabling trauma victims to enter a structured dissociative state in therapy would facilitate their access to memories of the traumatic experience. The therapy process can help patients work through traumatic memories in order to resolve the posttraumatic symptomatology. The memories can be experienced for a time with the assurance that they can be put aside afterward. In a trance, patients can be quickly taught how to produce a state of physical relaxation despite whatever psychological stress they experience, thereby dissociating the somatic reaction from the psychological preoccupation, allowing for modulation of the traumatic memory and an enhanced sense of control over the experience. Patient and therapist can then find a condensation image that symbolizes some aspect of the trauma.

The most distressing aspect of a traumatic event is the sense of absolute helplessness that it engenders on its victim. This helplessness is reenacted in PTSD through loss of control over state of mind during spontaneous dissociative states, startle reactions, or intrusive recollections of the event. Thus, it is crucial that the therapy of traumatic experiences, especially when such a powerful technique as hypnosis is used, be structured so that the process enhances patients' sense of control. This approach can allow patients to integrate the image of themselves as victims with the ongoing, more global image of themselves as persons coping effectively with severe stress, making the repressed material conscious and therefore less powerful and enabling them to establish a new, more congruent self-image and absorb the loss into the ongoing flow of their lives. At the end of the following section (Dissociative Disorders), we summarize a comprehensive approach to the use of hypnosis in the treatment of psychiatric syndromes associated with severe trauma.

## Dissociative Disorders

Hypnosis is one of the most helpful tools in the treatment of patients suffering from dissociative disorders (Kluft 1992, Maldonado et al. 2000, Maldonado and Spiegel 1995, 2007, Putnam 1992, Spiegel 1986). As a rule, these patients experience their symptoms (i.e., fugue states, dissociated identities, and blackouts) as occurring unexpectedly and beyond their control. Because these patients are unknowingly using their hypnotic capacities, it makes sense to teach them how to turn their weakness into a strength (Maldonado and Spiegel 1995). Hypnosis can be used formally both as a diagnostic tool and for therapeutic purposes. The hypnotic state can be seen as a controlled form of dissociation (Nemiah 1985). Hypnosis is useful in the treatment of these patients, first in

determining whether they have a dissociative disorder and second in providing rapid access to these dissociated states. When used by the therapist in the context of treatment, it can demonstrate to patients the amount of control they have over these states, which they normally experience as "automatic and unpredictable."

Thus learning and mastering the hypnotic process not only serves to teach patients how to control dissociation, but it also allows them to establish a process of communication that will eventually lead to a reduction in spontaneous dissociative symptoms. These patients have already suffered physical, emotional, or sexual abuse. Therefore, it is imperative that we recognize and take account of the impact of whatever trauma occurred and help patients work through their reactions to it. Recognizing and teaching patients with dissociative disorders how to master their capacity to dissociate is among the most important psychotherapeutic tasks in the course of their treatment (Maldonado et al. 2000, Maldonado and Spiegel 2002a).

Studies have demonstrated a high frequency of dissociativelike defenses in victims of early childhood abuse, and it is possible that exposure to traumatic events may be one of the natural paths toward developing high hypnotizability. Indeed, studies have shown a positive correlation between severity of punishment during childhood and hypnotizability (Hilgard 1974, Nash et al. 1984, Putnam 1991, 1995). It is possible that the impact of the stress suffered by the victims of childhood abuse allows a more effective use of hypnotic traits naturally found in children. Whether these children do so consciously or not, the frequent use of their hypnotic capacity in an attempt to "avoid" repeated exposure to abuse may prevent its extinction later in life (Morgan et al. 1974a, Putnam 1991, 1995). The unconscious "practicing" of this trancelike trait may account in part for the high level of hypnotizability seen in adults who were once victims of abuse (Kluft 1985a, 1990, Maldonado and Spiegel 1994, 1995, Spiegel et al. 1982).

We can make use of hypnotic techniques as a way to help patients access repressed and dissociated memories. Teaching patients self-hypnosis allows them to obtain a sense of control over their symptoms and eventually their lives. The repression or dissociation of traumatic events and the realities that surround them may serve a defensive purpose of avoiding painful affect associated with the memories. The memories are still there, either transformed or interspersed with fantasy. Our approach to the treatment of these victims is directed at helping them acknowledge the extent of the emotional pain caused by the trauma. Then, through therapy, we can assist in the development of more mature and adaptive coping mechanisms that will allow the patient to place the traumatic experience into proper perspective. The goal is to allow patients to come to terms with the trauma and to redefine themselves in view of the past, but with a firm hold on the realities of the present.

Dissociation as a defense serves a dual purpose. It represents an effort to preserve some form of control, safety, and identity when faced with overwhelming stress. At the same time, victims use it in an attempt to separate themselves from the full impact of the trauma. Unfortunately, these individuals may ward off memories of the trauma so well that they may act as if it is not happening and later as if it never happened. Some individuals can so effectively repress traumatic memories that they become unable to consciously work through them. As a consequence, they are unable to put the facts surrounding the events associated with the trauma into perspective, but slowly, the dissociated feelings and memories leak into consciousness. This creates some of the classic symptoms associated with PTSD and DID, such as flashbacks or intrusive thoughts.

The advantage of using hypnosis comes from the facilitation of the recovery of affect or memories, the ability to dissociate memories from cognition, and the speed with which the process is achieved. Finally, because of the relationship between a history of childhood abuse and trance, these patients are usually highly hypnotizable (Chu and Dill 1990, Hilgard 1984, Nash et al. 1984, Putnam 1993, Spiegel 1988, 1990, Spiegel et al. 1988).

Many former victims of childhood abuse may unknowingly use their hypnotic capacities to keep out of awareness the content of traumatic memories, and in effect create different degrees of psychiatric illness (Sanders and Giolas 1991, Spiegel 1984, 1986, 1989, Spiegel et al. 1988, Terr 1991). Teaching these patients self-hypnosis is a way of turning a weakness into a strong tool for self-mastery and control. The controlled use of hypnosis, then, becomes a way to systematically access previously dissociated material.

A hypnotic-like state may be spontaneously elicited during traumatic experiences. The principle of state-dependent memory teaches us that we store memories along with their associated affect (Bower 1981). If this is indeed true, the experience of a situation with similar affective charge may facilitate the retrieval of the initial memory. While working with hypnosis in the context of psychotherapy, we may elicit memories of a traumatic experience, resulting in the reactivation of the formerly repressed painful affect. The transition into the hypnotic trance can facilitate access to memories related to a dissociated state, as might have happened at the time of the trauma.

### *The Condensed Hypnotic Approach*

The use of hypnosis in the treatment of PTSD and dissociative disorders can be conceptualized as having two major goals, which can be achieved by the use of six different techniques (Maldonado and Spiegel 1994, 1995, 2007, Spiegel 1981, 1988, 1989, 1992) (Table 94–8). The goals are to bring into *consciousness* previously repressed memories and to develop a sense of *congruence* between memories associated

**Table 94–8 Condensed Hypnotic Approach**

| Goals |
|---|
| To bring into consciousness previously repressed memories |
| To develop a sense of congruence between the traumatic memories and the self |
| **Treatment Stages** |
| Confrontation |
| Condensation |
| Confession |
| Consolation |
| Concentration |
| Control |

with the traumatic experience and current self-images. By making conscious previously repressed memories, the patient has the opportunity to understand, accept, and restructure them. These goals are achieved by working through six treatment stages: confrontation, condensation, confession, consolation, concentration, and control.

First the patient must *confront* the trauma. The therapist helps the patient recognize and understand the factors involved in the development of the symptoms for which help is now being sought. Hypnosis is then used to help the patient *condense* the traumatic memories. The hypnotic experience can be used to define a particularly frightening memory during the revision of the patient's history, which summarizes or condenses the main conflicts. The focused concentration achieved during the hypnotic state not only can facilitate recall of traumatic material but also helps place boundaries around it. After memories are recovered, we can help patients restructure them and even "become aware of things you did at the moment of trauma to survive." Once memories are recovered, patients usually need to *confess* feelings and experiences of which they are profoundly ashamed. These are usually things that they may have told no one else before; in fact, they have been running from them all their lives. At this time, the therapist must convey a sense of "being present" for the patient while remaining as neutral as possible. This is followed by the stage of *consolation*. Here, the therapist needs to be emotionally available to the patient. This stage must be carried on with caution and in a most professional manner. Therapists should be aware that the body and emotional boundaries of these patients may have been violated in the past. Then comes the stage of *concentration*. This component of the trance experience allows patients to have access or "turn on" the traumatic memories during the psychotherapeutic session and then "shut them off" once the work has been done. During the final stage, the patient comes to define her- or himself as being in *control* again.

The underlying principle to remember is that the most damaging effect of overwhelming trauma is that it renders its victims defenseless. Because of the lack of physical and emotional control, patients activate dissociative defenses in an attempt to master their experiences. By using self-hypnosis, the therapist can model and teach the patient to regain control over her or his memories. Patients must be encouraged to remember as much as they feel is safe to remember at a given time. The goal is that patients learn how to think about traumatic experiences, rather than negating their existence. The use of self-hypnosis teaches patients that they are in control of their experiences. Patients must dispel the magical beliefs that therapists "can take away the memories." Rather, by modeling this sense of trust in their therapists, patients learn to trust themselves. They relearn trust in their own feelings and perceptions.

The challenge in treating victims of abuse is to achieve a new sense of unity within the patient after the initial fragmentation caused by the traumatic experience. Overwhelming trauma tends to cause sudden and radical discontinuities in consciousness, which leaves the victims with a polarized view of themselves, involving, on one hand, the old self (before the trauma) and, on the other, the helpless, defenseless, and traumatized victim. Our goal is to find ways to integrate these two aspects of the self. Here, the patient's task is to acknowledge and place into perspective painful life events, thereby making them acceptable to conscious awareness.

One of the advantages of the use of hypnosis is that the affect elicited can be so powerful that most patients do not need to remember every single event of abuse or trauma. In fact, through the use of hypnosis, the therapist may help the patient consolidate the memories in a constructive way, thus facilitating recovery. After a condensation of the traumatic experiences, patients become ready to accept the victimized self. Instead of continuing the self-blame and shame because of what happened to them, they can learn to acknowledge and even thank themselves for what they did to survive. This restructuring allows them to shift their perception of self, changing their self-image from that of a victim to that of a survivor.

**Therapeutic precautions.** Therapeutic precautions are shown in Table 94–9. The strength of transference during the psychotherapy of trauma victims is enormous. The use of hypnosis does not prevent development of a transference reaction; it may actually facilitate its emergence earlier than in regular therapy owing to the intensity with which the material is expressed and memories are recovered (Maldonado and Spiegel 1994, 1995, 2007, Spiegel 1992).

Reliving the traumatic experience along with the patient may allow a special feeling of "being there with them" at the moment of trauma. This allows the therapist to provide guidance, support, protection, and comfort as the patient goes through the difficult path of reprocessing traumatic memories. On the other hand, this kind of *traumatic transference* between the therapist and the victim of sexual assault is different in the sense that the feelings transferred are related not so much to early object relationships but to the abuser or circumstances that are associated with the trauma (Maldonado and Spiegel 1994, 1995, 2007, Spiegel 1992). Instead of seeing this expressed anger at the therapist as a form of negative transference reaction, we should explore the possibility that this may be a healthy attempt for the patient to experience anger toward the perpetrator. As therapists, we should not minimize or shut off these feelings. This will only confirm the patient's former perception that there was something wrong with him or her for having these feelings, which will probably activate further use of primitive defenses, including dissociation or acting out.

A more serious complication of the use of hypnosis with trauma victims is the possible creation of *false memories*. Hypnosis, with its heightened sense of concentration, allows the patient to focus intensely on a given time or place, enhancing memory recall. The principle of state-dependent memory also makes it plausible that the mere entrance into this trance state can facilitate retrieval of

**Table 94–9 Therapeutic Precautions**

| |
|---|
| Traumatic transference |
| Confabulation |
| Concreting |
| Contamination of memories |
| False memories |
| Possible compromise of patient's ability to testify in court |
| Electronic recording of all contacts with patient |

memories associated with a similar state of mind that may have occurred during the trauma and subsequent flashbacks. However, not every memory recovered with the use of hypnosis is necessarily true. Hypnosis can facilitate improved recall of true as well as confabulated material (Dywan and Bowers 1983). Suggestibility is increased in hypnosis, and information can be implanted or imagined and reported as verdict (Laurence and Perry 1983, McConkey 1992). Because of this, therapists are warned about "believing" everything a patient is able to recall. Just as we use therapeutic judgment to analyze and interpret our patients' (nontraumatic) childhood memories, fantasies, and dreams, so should we treat hypnotically recovered material with caution.

To this date, no evidence proves that the patient's confrontation with alleged perpetrators of childhood abuse or pursuit of legal retribution toward the perpetrator provides any therapeutic benefit. As therapists, we cannot be certain of which memories are real, which are completely confabulated, and which are a combination of both. Because of this, we should not encourage our patients to take legal actions. If, on the other hand, our patients insist in pursuing this avenue, it is our duty to warn them of our concerns but to be supportive of whatever final decision they make. Certainly, we will do a service to our patients if we inform them of all the legal ramifications that the use of hypnosis, or any other form of memory enhancement, may have for their defense, including their ability to testify in court or to use the material recovered by such techniques.

## Conversion Disorder

Several studies have suggested that patients suffering from conversion disorders are highly hypnotizable (Bliss 1984a, Peterson et al. 1950). Janet described that the symptoms of conversion disorder can be understood in part as reflecting the presence of uncontrolled hypnotic states (Janet 1907). Maldonado et al. have hypothesized that patients suffering from a conversion disorder may indeed be using their own capacity to dissociate in order to displace the uncomfortable feelings or affects into a chosen part of the body, which then becomes dysfunctional (Maldonado 1996a, 1996b, 1997, Maldonado and Jasiukaitis 2003).

Highly hypnotizable individuals have demonstrated an unusual capacity for psychological control over somatic function. Therefore, it makes sense that hypnotic phenomena may be involved both in the etiology of some somatoform symptoms and in their control (Spiegel and Vermetten 1994). Certain classic conversion disorders such as hysterical paralysis and pseudoseizures may well represent dissociative phenomena, because profound alterations in sensation and experience of control over motor function are standard hypnotic phenomena (Spiegel and Vermetten 1994). Indeed, hypnosis may be useful in both the diagnosis and the treatment of many psychosomatic illnesses and conversion symptoms (Barry and Sanborn 2001, Bowman 1993, Maldonado 1997, Maldonado and Jasiukaitis 2003). Of interest, Goldstein et al. (2000) found that pseudoseizure patients demonstrated higher levels of dissociation and escape-avoidance coping strategies.

In the case of conversion disorders, hypnosis can be used not to remove the process or restore function, but to allow patients to control the effects of their emotional stress and mind states over their body. It is not advised to force a cure in a patient, as this may lead to other complications (e.g., symptom substitution). Instead, patients are trained in the use of self-hypnotic techniques directed at gaining control over physiological and somatic processes and then are allowed to improve at a pace that feels comfortable, while the clinician provides suggestions for improved control and mastery and explores the unconscious psychological reasons behind the presence of symptoms.

Thus, in the case of conversion disorders, hypnosis may have two uses. First, hypnosis may be used to facilitate the accurate diagnosis (Kuyk et al. 1995, 1999, Maldonado 2006, Maldonado et al. 2000, Peterson et al. 1950, Sumner et al. 1952). In fact, during a hypnotic induction the clinician may bring on symptoms, worsen, or ameliorate them demonstrating the psychological responsivity of the symptoms. As already reported by others (Krumholz and Niedermeyer 1983, Ramchandani and Schindler 1993), between 37 and 42% of patients with "true epilepsy" have coexistent pseudoseizures. We must also consider the fact that even though studies have suggested that only 20–30% of the general population is hypnotizable to a somnambulistic level (i.e., highest level of hypnotizability), nearly 70% of patients with psychogenic seizures are capable of reaching the same hypnotic level (Peterson et al. 1950). Given this context, it may be dangerous to assume that hypnotically induced non-epileptogenic events (NEEs) is equivalent to a diagnosis of pseudoseizures (i.e., conversion disorder), as some have suggested (Barry and Sanborn 2001).

Because of the high coexistence of seizures and pseudoseizures and the risks inherent in the misdiagnosis, a quite different use for hypnosis in the diagnosis of pseudoseizures was suggested by Sumner et al. (1952). Instead of eliciting an ictal episode under hypnosis, they proposed the use of hypnosis to elicit memories associated to the time of the seizure itself. In their study, none of the subjects suffering from true epilepsy had any recollection of the events associated with the ictal episode. In contrast, 100% of the patients suffering from pseudoseizure recalled the events. This test had a very high correlation with the EEG data obtained at the time of the ictal activity. Ninety-three percent of those diagnosed as epileptic had abnormal EEG recordings, whereas only 7% of those diagnosed as psychogenic had an abnormal EEG. Nearly half a decade later, Kuyk et al. (1995, 1999) achieved similar results. They studied ESs and patients with PESs, and under hypnosis, which was performed by an investigator who was blind to other data, attempted to recover memories of events, which transpired during the ictal episode. If recall was obtained, the experimental diagnosis of PES was given; if not, ES was diagnosed. These results were then compared with the clinically, EEG-confirmed diagnoses. Hypnotizability was measured in all subjects. They found that recall for the ictus was obtained in 85% of the patients diagnosed with PES. None of the patients with the clinical diagnosis of ES recovered any memories. Fifteen of the patients with PESs reported no memories of the ictal event. This result yields a specificity of 100% and a sensitivity of 85% for the recall technique. They also found that hypnotizability was significantly higher in patients with PESs than in patients with ESs. The authors suggest that a positive recall test indicates PES. As in the case of an EEG, a positive test is positive, but a negative test is inconclusive.

Second, hypnosis may be therapeutic. Such changes in the symptom during or after a trial of hypnosis can be used constructively to teach the patient to utilize self-hypnosis as a means of enhancing control over the severity of the symptom. This hypnotic modulation makes the symptom seem less alien and threatening. Hypnosis can be appropriately used as part of a rehabilitation strategy, particularly insofar as it can help patients master the reactive anxiety that is associated with real physical dysfunction as well as conversion symptoms. A patient can be taught to use a state of self-hypnosis to develop the sense of floating relaxation while picturing bothersome problems on an imaginary screen. The patient can then work on, for example, improving use of a dysfunctional hand by developing tremors that gradually build up strength and circulation.

The clinical use of hypnosis in the context of conversion disorder encompasses three phases (Maldonado 2006, Maldonado et al. 2000, Maldonado and Spiegel 2000b). The *first phase* involves the exploration of the meaning that the symptoms have to the patient. By engaging in this process, the therapist will gain a better understanding of the underlying purpose(s) served by the symptom(s). Two golden rules apply to hypnotic exploration of unconscious symptoms: (1) never eliminate a symptom without understanding first its value and purpose, and (2) never take away a symptom without giving the patient a better (i.e., more mature and adaptive) defense and obtaining the patient's agreement. The *second phase* involves symptom alteration. The best form of symptom alteration is one that takes the patients mind away from the presenting symptoms while simultaneously allowing the patient to discover more appropriate ways to cope with their anxiety. This may be accomplished by any one of two symptom-alteration techniques: symptom substitution, in which a given symptom is exchanged for another symptom that is less impairing or pathological until the patient is ready to do away with the symptom (i.e., exchanging the perception of intense pain for a numbing, tingling sensation in the same area); or symptom extinction, in which the patient agrees to "give up" the symptom after working through the problem in psychotherapy. The *third phase* in the hypnotic treatment of conversion symptoms involves maximizing the patient's level of functioning. Posthypnotic suggestions may be quite useful when the patient is very concrete (i.e., not psychologically sophisticated) and in need of constant support or reassurance. Hypnotic techniques can be used as a transitional object while the patient gets on the road of total physical and psychological health (i.e., free of impairing physical symptoms and psychological conflicts). Similarly, the use of projective techniques can become quite valuable in helping the patient to envision him- or herself doing better and living without the illness. At this phase, hypnosis may be used in order to increase the level of motivation, enhance patients' sense of mastery, and strengthen his or her (ego) defenses.

Maldonado (2001, 2006, Maldonado et al. 2000) described a "reverse symptom identification technique" whereby the therapist, using the positive transference/countertransference in the therapeutic relationship, may mobilize the patient's healthy defense mechanisms and accelerate the rate of recovery while facilitating a more meaningful exploration of the patients' symptoms, their significance, and the true etiological reason beneath the symptoms (i.e., the psychological conflict that has been covered or displaced/converted by the presenting symptoms). Patients are taught how to achieve a state of self-hypnosis and are then hypnotized by the therapist. Following trance induction, the therapist proceeds to produce—in a nonaffected body part, preferably a nonaffected contralateral part—a symptom similar in nature and magnitude to the patient's presenting symptom. The therapist discusses with the patient the mechanisms involved in the production of that phenomenon. By stressing the fact that all hypnosis is self-hypnosis, the therapist teaches patients that if they can cause the deficit, they will also be able to effect the cure "whenever they are ready to do so, and not before." Toward the end of the session the therapist models for the patient what is expected of him or her by providing suggestions for normalization in sensation and function of the "hypnotized" extremity being used as an example. Patients are then encouraged to use the newly learned skills to restore sensation and/or function—as they did in the office, either in the office with the therapist or "at any time in the future when they felt safe and ready."

The above-described phases and techniques are designed to help the patient understand that all hypnosis is self-hypnosis; thus, at the end, patients are taught that their hypnotic ability—which they perceived as a sign of weakness, as they caused their symptoms—can be harnessed and used constructively (i.e., turned into a strength) not only to resolve the current problem (i.e., conversion symptom) but as a tool for mastery and self-control to prevent future deficits and symptoms. This treatment method involves a collaborative approach, rather than the old suggestive methods used by Bernheim, Janet, and Freud. The therapist adopts the role of a coach guiding the patient through the process rather than doing things for the patient. The patient is helped through the process of understanding the nature, meaning, and usefulness of the conversion symptoms and then given all the necessary tools to cope with the deficits and to "give up the symptoms when ready."

## Eating Disorders

Despite some discordant opinions, there is general consensus establishing that the experience of abuse in early childhood may be important for understanding the complex genesis of the eating disorders of some women (Berger et al. 1994, Molinari 2001, Valdiserri and Kihlstrom 1995a, 1995b). A close analysis of the symptoms demonstrated by eating disorder patients reveal that they are strikingly similar to those of patients suffering from some forms of dissociative disorders. These symptoms include reactualization of the trauma, dissociation, significant personality traits, a pathological relationship with food, distortion of body image, suicide attempts, and self-inflicted punishment (Maldonado and Spiegel 2005).

Studies assessing the hypnotizability of patients with bulimia and anorexia nervosa have demonstrated higher hypnotizability in the bulimic patients than in the restricting patients (Pettinati et al. 1985). These researchers noted that many of the bulimic patients reported that they were in a trancelike state when they engaged in their compulsive bingeing and purging behavior. Researchers (Covino et al. 1994) examined the levels of hypnotizability and dissociation in an outpatient sample of bulimic women of normal weight and compared these levels with

those of healthy controls. They found that bulimic patients were significantly more hypnotizable than healthy controls and that they scored higher on self-report scales of dissociative experiences. Corroborating these findings, others (Vanderlinden et al. 1995) have found that compared with control subjects, eating disorder patients scored significantly higher on the Dissociation Questionnaire (DIS-Q) and the Stanford Hypnotic Clinical Scale (SHCS). Using semistructured interviews and self-report measures to evaluate the association between childhood physical and sexual abuse researchers compared bulimic women and normal control subjects (Leonard et al. 2003). The study measures assessed eating symptoms, comorbid psychiatric disturbances, personality pathology, and histories of childhood and adulthood abuse. The study found that compared with the normal eaters, bulimic women reported higher levels of childhood abuse.

All these findings suggest a possible opportunity for intervention employing hypnosis in controlling this form of eating disorder (Gross 1986).

## Applications in General Medicine

### Medical, Surgical, and Dental Procedures

Because hypnosis can be used to produce a state of relaxation and to reduce anxiety, it has proved to be valuable as an adjuvant to medical procedures (Flory et al. 2007). Once patients have been trained in the use of self-hypnosis, they can use it both in preparation for a hospital visit and while in the clinic or hospital. Once in that state, they can imagine themselves being somewhere they enjoy and feel safe, thereby dissociating their mental experience from the physical (and possibly painful or unpleasant) aspects of the procedure (see Clinical Vignette 2). It can also be used as a way of mastering the anxiety associated with potentially threatening procedures (Rape and Bush 1994), either diagnostic, such as endoscopies (Cavallo et al. 1985, Sutherland and Knox 1976), colonoscopies (Cadranel et al. 1994, Elkins et al. 2006), imaging techniques (i.e., computed tomography and magnetic resonance imaging) (Chandler 1996, Covino and Frankel 1993, Friday and Kubal 1990, Mize 1996, Schulz-Stubner et al. 2004, Simon 1999b, 1999c), bone marrow aspirations (Ellis and Spanos 1994, Hageman-Wenselaar 1988, Liossi and Hatira 1999), needle phobia (Bell et al. 1983, Cyna et al. 2007, Dash 1981, Morse and Cohen 1983, Nugent et al. 1984, Robertson 2007, Simon and Canonico 2001, Usberti et al. 1984), breast biopsy (Montgomery et al. 2002, Montgomery et al. 2007), liver biopsy (Adams and Stenn 1992), and lumbar punctures (Hageman-Wenselaar 1988, Kellerman et al. 1983, Simon and Canonico 2001), or therapeutic interventions, such as chemotherapy (Axelrod et al. 1988, Cotanch et al. 1985, Covino and Frankel 1993, Faymonville et al. 1995, Genuis 1995, Hilgard and LeBaron 1982, Jacknow et al. 1994, Katz et al. 1987, Marchioro et al. 2000, Renouf 1998, Richardson et al. 2006, Syrjala et al. 1992, Zeltzer et al. 1983, 1984, Zeltzer and LeBaron 1982), external beam radiation therapy (Bertoni et al. 1999, Steggles 1999), surgery and its recovery (Kessler and Dane 1996, Lambert 1996), labor, delivery, and post-partum states (Brown and Hammond 2007, Marc et al. 2007, Yexley 2007) and interventional radiology (Lang et al. 1996b, 2000b, Spiegel 2006).

Clinical Vignette 2

A 43-year-old woman who suffered several episodes of convulsions refused to undergo magnetic resonance imaging (MRI) testing because of feelings of claustrophobia. On two previous occasions she agreed to try, but even after several milligrams of diazepam, she was unable to relax sufficiently to lie comfortably during the procedure. Finally, she accepted a referral to psychiatric consultation. In my office (JRM), she proved to be highly hypnotizable (a score of 9 of 10 on the Hypnotic Induction Profile). During hypnosis, we explored the associations between the scanner and her anxiety. Images of a coffin came to mind. These were then followed by memories of her father lying in the funeral home—he had died of a massive stroke. We then proceeded to explore her anxiety as it related to fears of what the test might show, including the possibility of a malformed blood vessel or other pathological change affecting her brain, as had happened to her father. Once this was discussed, she felt that it "was better to know than to avoid." She was trained in self-hypnosis. After inducing a relaxed state, she was instructed, "Create in your mind's eye a place where you can feel safe and comfortable, knowing that sounds and people in the room will not disturb you." We also "practiced" going to the scanner room by having her imagine that she was both the patient in the room and the technician operating the machine. In this fashion, she felt more "in control" of the situation.

The next day, I met her at the scanner room. Once she was on the imaging table, the patient followed the procedure we practiced. When the test began, I left the room with the agreement that the technician would let her know when the test was over. She imagined herself walking through a forest and crossing a river. As she walked to the riverbank, instead of floating, she sank slowly as she followed the contours of the river. Once on the bottom, she held on to some algae. When she exhaled her breath, it formed a gigantic bubble or cocoon that allowed her to breathe underwater and be safe. As the magnets in the magnetic resonance imager shifted in position, she imagined that this was the clanking sound of motorboat engines on the surface. She remained in this state for approximately 2 hours while tests were performed with and without contrast material. She tolerated the procedure well and easily came out of the trance state when the signal was given.

A number of articles have been published concerning the use of hypnosis as adjunct to dental procedures and in the treatment of dental phobia (Hypnosis—against dental phobias 1974, Study finds hypnosis is more effective 1978, Benson 1974, 1975, Fassbind 1983, Forgione 1988, Gall 1969, Gaspar et al. 2003, Hammarstrand et al. 1995, Katcher et al. 1984, Kevesater 1977, Kisby 1977, Kroll 1962, Lu 1994, Lucas 1975, McAmmond et al. 1971, Moore et al. 1996, 2002, Newman 1973, Peretz 1996, Reis e Almeida 1983, Robb and Crothers 1996, Romanson and Clark 1981, Rustvold 1994, Schey 1976, Schmierer and Schmierer 1990, Seidner 1967, Shaw and Niven 1996, Shaw and Welbury 1996, Smith 1986, 1969a, 1969b, Weyandt 1976, Wilks 1994) and other dental problems including periodontal disease (Wood and Zadeh 1999), promotion of routine flossing (Kelly et al. 1988), excessive gagging (Morse et al. 1984), placement of dental implants (Gheorghiu and Orleanu 1982), dental extractions (Lucas 1965, McCay 1963), psychogenic oral

pain (Golan 1997), idiopathic orofacial pain (Abrahamsen, Baad- Hansen, and Svensson 2007) and temporomandibular joint disease (Simon and Lewis 2000). The success of use of hypnotic techniques in dental work has created a new interest in teaching these techniques in American dental schools (Badra 1976, Benson 1975, Clarke 1996, Herod 1995, Kline 1957, Kuhner 1979, Richardson 1980, Simpson et al. 1982, Tobey 1970, Wegner 1979, Winter 1989).

## Pain Control

Pain is always a psychosomatic phenomenon, combining somatic with subjective distress. It never exists in a vacuum and always represents a combination of tissue injury and the emotional reaction to it. James Esdaile (1957), a Scottish surgeon working in India, described 80% surgical anesthesia for amputations with the use of hypnosis. He also reported a lower mortality rate (5%) when using hypnosis for anesthesia in his procedures, compared with the surgical mortality rates in Great Britain (40%), probably because of the high risks of anesthesia or the difficulty of performing surgery without anesthesia at that time. Unfortunately, he later withdrew his findings after being severely censured by his colleagues.

Despite the organic factors causing pain, it is clear that psychological factors are major variables in the intensity of the pain experience. More than 100 years after Esdaile, at the Massachusetts General Hospital, Beecher (1956) demonstrated that the intensity of pain was directly associated with its meaning. For example, to the extent that pain represented threat and the possibility of future disability, it was more intense than it was among a group of combat soldiers to whom the pain of injury meant that they were likely to get out of combat alive.

Hypnosis can facilitate an alteration in the subjective experience of pain (Brose and Spiegel 1992). Several techniques can be used to achieve this goal. Most techniques involve the production of physical relaxation coupled with visual or somatic imagery that provides a substitute focus of attention for the painful sensation.

The use of hypnosis as an adjunct to anesthesia has been described in patients undergoing angioplasty (Kostka 1992, Weinstein and Au 1991), plastic surgery (Faymonville et al. 1994, 1995, Scott 1975, Tucker and Virnelli 1985), thyroidectomies (Faymonville et al. 1998, Meurisse 1999, Meurisse et al. 1996, 1999a), orthopedic surgery (Mauer et al. 1999, Sacerdote 1963), surgical neck dissection and exploration (Defechereux et al. 1999, Meurisse et al. 1999a, 1999b, Rapkin et al. 1991), management of burn injuries (Ben-Hur and Izak 1975, Everett et al. 1993, Ewin 1992b, May and DeClement 1983, Merz 1983, Ohrbach et al. 1998, Patterson et al. 1992, 1997, 2006, Schafer 1975, Van der Does and Van Dyck 1989), limb fracture reduction (Iserson 1999), and chronic tension-type and migraine headaches (Andreychuk and Skriver 1975, Berlin et al. 1985, Carasso et al. 1985, Daniels 1977, Drummond 1981, Gysin 1999, Gysin and Ziegler 1994, Matthews and Flatt 1999, Spinhoven et al. 1992, Spinhoven and ter Kuile 2000, ter Kuile et al. 1995, Vietor and Zwart 1968, Weiss 1962). It has also been described as effective in the management of pain in general (Reducing pain by hypnosis 1985, Hypnosis: Deep relaxation can relieve pain and more 2002, Hypnosis: A safe and potent pain reliever 2005, Ament 1982, Brown and McInnes 1986, Bryant 1956, Chaves 1994, Coppolino 1963, Cotanch et al. 1987, Covino and Warfield 1985, Croft et al. 2002, Cuellar 2005, Dane 1996, Deltito 1984, Dinges et al. 1997, Elliott 1979, Ewin 1978, Feldman 2004, Gay et al. 2002, Hauser et al. 2002, Hilgard 1973, 1975a, Hilgard and Hilgard 1975, Holden 1977, Holroyd 1996, Isele 1982, James et al. 1989, Kaplan 1960, Kupers et al. 2005, Lambert 1999, Loitman 2000, Lu 1994, Mason 1956, Mauer et al. 1999, Mohide 2002, Mutter and Karnilow 1983, Nickelson et al. 1999, Ouellette 2000, Palsson and Whitehead 2006, Patterson et al. 1992, 2006, Patterson and Jensen 2003, Rosatti 1989, Sacerdote 1978, Sala Paya 2003, Savitz 1983, Sharma and Kaur 2006, Snow 1985, Spanos et al. 1989, Spira and Spiegel 1992, Tan and Leucht 1997, Thompson 1981, Valente 2006, Van der Does et al. 1988, Van der Does and Van Dyck 1989, Velden and Wolk 1987, Veldesi 1960, Vignier 1990, Wain 1980, Walker 1980, Wallace 1987, Woods 1989), as well as cancer pain (Ament 1982, Barber 1978, Barber and Gitelson 1980, Clawson and Swade 1975, Genuis 1995, Katz et al. 1987, Kellerman et al. 1983, Lynch 1999, Mohide 2002, Spiegel 1985, Syrjala et al. 1992, Zeltzer and LeBaron 1982), labor pain (Cyna et al. 2004, Marc et al. 2007, Vadurro and Butts 1982), and the painful experiences of phantom limb syndrome (Barker 1984, Cedercreutz 1955, Rosen et al. 2001, Siegel 1979, Simon and Dahl 1999), fibromyalgia (Castel et al. 2007), HIV (Langenfeld et al. 2002), and fibromyalgia (Castel et al. 2007). Only a few of these studies have been randomized clinical trials, but those that demonstrate significant advantages for hypnosis over control conditions, for example, Zeltzer and LeBaron (1982) (Lang et al. 1996a, 2000a, 2006, Spiegel and Bloom 1983). The Lang studies are noteworthy for being large-scale randomized trials in interventional radiology with two control conditions, one involving standard care including an indwelling catheter providing patient-controlled pharmacological analgesia and another involving supportive attention that did not specifically involve hypnosis (Spiegel 2006). In these trials, the use of hypnosis was associated with half the medication use, half the pain, significantly reduced anxiety over time, fewer procedural complications, and an average reduction of 17 minutes per procedure. Even taking into account adding additional personnel for support and hypnosis, the intervention wound up saving $238 per procedure with shorter time in the procedure suite and recovery room and fewer complications (Lang and Rosen 2002).

The specific technique employed may depend on the degree of hypnotic ability of the subject. For example, patients can be taught to develop a comfortable floating sensation on the affected body part. Highly hypnotizable individuals may simply imagine an injection of procaine hydrochloride (Novocain) in the affected area, producing a sense of tingling numbness similar to that experienced in previous dental work. Other patients may prefer to move the pain to another part of their body or to dissociate the affected part from the rest of the body. As an extreme form of hypnotically induced, controlled dissociation, some patients may imagine themselves floating above their body, creating distance between themselves and the painful sensation or experience.

For some more moderately hypnotizable patients, it may be easier to focus on a change in temperature, either warmth or coolness. A sensation of warmth could be elicited while patients imagine they are floating in a warm bath or applying

a heating pad to a given area of the body. A cooling sensation can be elicited by imagining that the afflicted extremity is immersed in an ice-cold mountain stream or in a bucket of ice chips. Temperature metaphors are especially effective. This may be related to the fact that pain and temperature fibers run together in the lateral spinothalamic tract.

The images or metaphors used for pain control employ certain general principles. First, the hypnotically controlled image may serve to "filter the hurt out of the pain." Patients also learn to transform the pain experience. They acknowledge that it exists (the pain), but there is a distinction between the signal itself and the discomfort the signal causes.

The hypnotic experience that patients create and control helps them transform the signal into one that is less uncomfortable. Patients expand their perception from an experience in which the pain either is there or is not to a third option—the pain is there but transformed by the presence of such competing sensations as tingling, numbness, warmth, or coolness.

Finally, patients are taught not to fight the pain. Fighting pain only enhances it by focusing attention on the pain, enhancing related anxiety and depression, and increasing physical tension that can literally put traction on painful parts of the body and increase the pain signals generated peripherally.

For patients undergoing painful procedures, such as bone marrow aspirations, the main focus is on the hypnotic imagery rather than on relaxation. This works especially well with children because they are so highly hypnotizable and easily absorbed in images (Hilgard and Hilgard 1975, Zeltzer and LeBaron 1982). Patients may be guided through the experience while the procedure is performed, or a given scenario may be suggested, and the patient later undergoes the experience hypnotically while the procedure is under way. This enables patients to restructure their experience of what is going on and dissociate themselves psychologically from pain and fear of the procedure.

Even though the precise mechanism for hypnotic analgesia is not known, it is suspected to have components of two complementary mechanisms: physical relaxation and attention control. Patients in pain tend to splint the painful area instinctively, which in turn increases muscle tension around the painful area, often resulting in increased pain. Therefore, creating a state of hypnotically induced relaxation may easily decrease their experience or perception of pain.

This can be more easily achieved by creating images that facilitate a relaxing response, such as a warm bath, floating on an air mattress in a pool, or just floating out in space. Second, and probably more important, because hypnosis involves intensification and narrowing of the focus of attention, it allows patients to pay selective attention to the action or ideas contained in the metaphor or images, therefore placing pain at the periphery of their awareness. It thus diminishes the amount of attention they pay to painful stimuli. A third possible mechanism affecting the pain experience may be related to the psychological meaning of the pain itself (see Clinical Vignette 3). Some patients have been in pain so long that pain has become an intrinsic part of their existence.

Hypnotic analgesia cannot be explained by simple social compliance alone—merely enacting a role and telling the therapist what he or she wants to hear. Rather, there is evidence that it involves neurophysiological changes in information processing. Studies of the effects of hypnosis on cortical event-related potentials (ERPs) indicate that highly hypnotizable individuals diminish the P100 and P300 components of their event-related response to a somatosensory stimulus by focusing on a hallucinated image that blocks their perception of the stimulus (De Pascalis et al. 2001, Spiegel et al. 1989).

A number of studies have tested the idea that endogenous opiates are involved in hypnotic analgesia. With one partial exception (Frid and Singer 1979), studies with both volunteers (Goldstein and Hilgard 1975) and patients in chronic pain (Spiegel and Albert 1983) have shown that hypnotic analgesia is not blocked and reversed by a substantial dose of naloxone given in double-blind, crossover fashion. Therefore, the cortical attention deployment mechanism is at the moment the most plausible explanation for hypnotic reduction of pain.

Regardless of the underlying mechanism, there is no doubt about the efficacy of hypnotic analgesia. Hypnosis has been shown to be superior to an attentional control condition for analgesia among children undergoing painful procedures (Zeltzer and LeBaron 1982). Furthermore, in a randomized prospective study, a combination of hypnosis and group psychotherapy was shown to result in a 50% reduction in pain among patients with metastatic breast cancer (Spiegel and Bloom 1983). This was accompanied by a significant reduction in mood disturbance (Spiegel et al. 1981a).

Studies have also shown the superiority of hypnotic analgesia to the level of analgesia provided by either placebo (McGlashan et al. 1969) or acupuncture (Knox and Shum 1977). Studies (Study finds hypnosis is more effective 1978, Belshe 2007, Frost 1978, Katz et al. 1974, Kuhn et al. 1981, Li et al. 1975, Loitman 2000, Lu et al. 2001, Moret et al. 1991, Samuels 2005, Stern et al. 1977) have demonstrated a correlation between hypnotizability and responsiveness to acupuncture, proving that hypnotic mechanisms of pain

Clinical Vignette 3

A 62-year-old woman was referred to me (JRM) with hopes that hypnosis would help alleviate her experience of chronic pain associated with cancer. A formal test of hypnotizability demonstrated that she was in the highly hypnotizable range. Under hypnosis, she was instructed that all the pain would "go away," or at least she would be able to block it, but as soon as she exited the trance state, the pain returned. Because of the curious dynamics of this phenomenon, I decided to explore the meaning pain had for her. She told me how her oncologist had warned her that she would be in pain as long as she is alive. It became clear that she associated pain with being alive and that she would be "pain free" only on the day she died.

After I explored this and discussed it with the patient, she decided that it was "not fair that after suffering so much, I still have to deal with the pain." She gave herself permission to live without pain and to enjoy as many of her remaining days as she could. She ended her trance experience and discussed it. Shortly afterward, she left the office, inadvertently leaving her cane behind. A few hours later, I called her home to let her know she had forgotten her cane in my office. To which she replied, "You can keep it as a souvenir."

control may be mobilized by other treatment techniques. Nevertheless, the explicit use of hypnosis with hypnotizable patients has proved to be the most powerful means of controlling pain. Hilgard and Hilgard (1975) estimated a 0.5 correlation between hypnotizability and treatment responsiveness for pain control. However, even older subjects who are somewhat less hypnotizable can benefit significantly (Lutgendorf et al. 2007). It is believed that the ability of highly hypnotizable patients to focus their attention on and alter their response to perception while at the same time producing a physical state of relaxation gives them an unusual ability to restructure their experience of pain, which in turn allows them to develop a sense of mastery over it.

## Insomnia

As we discussed earlier, hypnosis is a state of increased concentration and awareness. From this point of view, the hypnotic state is far from sleep, although both are restful altered mental states with reduced awareness of the peripheral environment. So, it might seem paradoxical to use hypnosis to help people fall asleep. Nevertheless, hypnosis can be helpful for inducing a state of physical relaxation that is at least compatible with sleep. As in the treatment of anxiety, a relaxing trance state may diminish the sympathetic arousal usually associated with anxious preoccupation and could facilitate entering into a restful sleep. Patients can be instructed to enter a state of self-hypnosis and then to induce a sense of floating and physical relaxation. Once this is achieved, they may use one of many different mechanisms to put worries or thoughts on hold "for tonight," knowing that they can always deal with them tomorrow. For example, the patients can project these thoughts onto an imaginary screen. Then they can become a kind of "traffic director" for their thoughts, dealing with them on the screen, thereby dissociating them from the physical response to them while remaining in a quiet and relaxed state (Spiegel and Spiegel 2004).

Another useful method is to have patients imagine themselves lying restfully in a comfortable and safe place while they see themselves placing the disturbing thoughts "onto the clouds, watching the breeze slowly carry them away," or they can even imagine their worries to be like "leaves floating on the surface of a river, flowing with the current," rather than holding on to any particular thought. Such approaches can be helpful in conjunction with standard sleep hygiene practices, which include keeping the bedroom as a place to sleep, avoiding working and other anxiety-arousing activities in bed, and avoiding looking at the clock when awakened. It is also important to distinguish routine insomnia due to situational reactions and anxiety from the more severe forms that are associated with major depression, an anxiety disorder, or a sleep disorder, such as sleep apnea syndrome (DSM-IV-TR). Few results of formal studies demonstrating the effectiveness of hypnosis in the treatment of insomnia have been reported, but most case reports suggest that hypnosis is useful in the treatment of not only primary insomnia but other sleep disturbances as well (Bauer and McCanne 1980, Becker 1993, Schenck and Mahowald 1995).

## Dermatological Conditions

Psychogenic factors have been implicated in essentially all skin diseases (Arone di Bertolino 1983, Bellini 1998, Cheek 1961, Elitzur and Brenner 1986, Gherardi et al. 1993, Johnson 1980, Manferto 1975, Shenefelt 2000, 2002, 2003a, 2003b, Tobia 1982, Tsushima 1988). Studies suggest that a wide spectrum of dermatological disorders may be improved or cured using hypnosis, including acne excoriee, alopecia areata, atopic dermatitis, congenital ichthyosiform erythroderma, dyshidrotic dermatitis, erythromelalgia, furuncles, glossodynia, herpes simplex, hyperhidrosis, ichthyosis vulgaris, lichen planus, neurodermatitis, nummular dermatitis, postherpetic neuralgia, pruritus, psoriasis, rosacea, trichotillomania, urticaria, verruca vulgaris, and vitiligo (Bellini 1998, Shenefelt 2000, 2003a). More specifically, hypnosis has been shown to be helpful in the treatment of multiple dermatological conditions, in particular atopic dermatitis (Stewart and Thomas 1995, West et al. 1961), chronic urticaria (Shertzer and Lookingbill 1987), eczema (Goodman 1962, Hajek et al. 1989, 1990, Mantle 1999, Zheltakov et al. 1963), pruritus (Arone di Bertolino 1983, Rucklidge and Saunders 2002), psoriasis (Frankel and Misch 1973, Kantor 1990, Tausk and Whitmore 1999, Winchell and Watts 1988), scleroderma (Seikowski et al. 1995), and warts (Arone di Bertolino 1983, Clawson and Swade 1975, Dreaper 1978, Ewin 1992a, French 1973, Johnson and Barber 1978, Phoenix 2007, Sinclair-Gieben and Chalmers 1959, Spanos et al. 1988, 1990, Steele and Irwin 1988, Surman et al. 1973, Tasini and Hackett 1977, Tenzel and Taylor 1969).

Specifically, warts have been treated with hypnosis (Ewin 1992a), and one carefully controlled study demonstrated that simple hypnotic instructions to the effect that the warts would tingle and disappear resulted in a rate of improvement that was substantially better than the spontaneous remission rate for warts (Surman et al. 1973). Studies employing hypnosis in the treatment of warts have reported success rates ranging from 27% (Johnson and Barber 1978) to 80% (Ewin 1992a). Other studies have shown specific benefits of hypnosis over simple task-motivating instructions in the elimination of warts (Spanos et al. 1988, 1990). Even more remarkable is Ewin's (1992a) observation regarding the use of hypnosis in the treatment of warts: "I use the term *cure* because there is not a single case report in the literature of recurrence after healing with hypnosis." Ewin reported an 80% cure rate in his study (Ewin 1992a).

Fox et al. (1999) were able to demonstrate the effects of hypnosis in treating patients suffering from frequently recurrent genital herpes simplex virus (rgHSV). Following hypnosis intervention, they recorded a significant overall reduction in the number of reported episodes of rgHSV, accompanied by a corresponding increase in the numbers of CD3 and CD8 lymphocytes, significant rises in natural killer cell counts, HSV-specific lymphokine-activated killer activity, and reduced levels of anxiety when compared to nonimprovers.

## Gastrointestinal Disorders

Hypnosis has been reported as useful in the treatment of many gastrointestinal conditions, including dysphagia (Black 1980, Gurian 1981, Kopel and Quinn 1996, Magonet 1961), irritable bowel syndrome (Hypnosis helps irritable bowel syndrome 2004, Agrawal and Whorwell 2005, Byrne 1973, Forbes et al. 2000, Francis and Houghton 1996, Gonsalkorale et al. 2002, 2003, Gonsalkorale and

Whorwell 2005, Houghton et al. 1996, Lea and Whorwell 2004, Palsson 2006, Palsson et al. 2002, 2006, Simren 2006, Snape 1994, Tan et al. 2005, Vidakovic-Vukic 1999, Whitehead 2006, Whorwell 1989, 2005, Whorwell et al. 1984, 1987), peptic ulcer disease (Bick 1958, Chiarioni et al. 2006, Colgan et al., 1988, Eichhorn and Tracktir 1955, Francis and Houghton 1996, Hall et al. 1967, Klein and Spiegel 1989, Montera 1968, Stacher et al. 1973), ulcerative colitis and related conditions (Schafer 1997, Susmano et al. 1960), and uncontrolled belching (Spiegel 1996). Even hyperemesis gravidarum and morning sickness have been reported to respond to hypnotic intervention (Baram 1995, Fuchs et al. 1980, Iancu et al. 1994, Piscicelli 1968, Poliakov 1989, Savel'ev 1974, Simon 1999a, Simon and Schwartz 1999, Spiegel 1963, Torem 1994). The studies by Whorwell et al. are notable for being randomized prospective trials with well-defined control comparisons. They show hypnotic effects on objective (bloating and abnormal bower habits) as well as subjective symptoms of gastrointestinal disease.

Similarly, hypnosis has been reportedly used with great success in the treatment of emesis of all causes, in both children (Keller 1995) and adults (Covino and Frankel 1993, Faymonville et al. 1995, Renouf 1998, Spiegel 1991b). Specifically, hypnosis has been reported with significant reduction in chemotherapy-induced nausea and vomiting (Spiegel and Moore 1997, Zeltzer et al. 1983, 1984). In fact, hypnosis has been proven to be effective in both, the treatment of acute emesis associated with chemotherapy treatment (Cotanch et al. 1985, Genuis 1995, Hilgard and LeBaron 1982, Jacknow et al. 1994, Syrjala et al. 1992, Zeltzer et al. 1983, 1984) and the prevention of anticipatory anxiety and emesis associated with cancer therapy (Marchioro et al. 2000, Redd et al. 1982).

For example, a recent study compared the effectiveness of "gut-directed hypnotherapy" (six sessions) and a specially devised audiotape intervention in a randomized controlled trial of irritable bowel syndrome patients during a 12-week study (Forbes et al. 2000). All patients had previously failed to respond to dietary and pharmacological therapy, and their median symptom duration was of 60 months. Successful trance was induced in all hypnotherapy patients. The authors found that symptom scores improved in 76% of the hypnotherapy patients and in 59% of the tape patients. In addition, a reduction in median symptom score, from 14.0 to 8.5, was seen in hypnotherapy patients, compared with an unchanged score of 13 in audiotape patients ($P < 0.05$).

Klein and Spiegel (1989) observed significant hypnotic control of gastric acid secretion among highly hypnotizable subjects. When these subjects were hypnotized and instructed to eat an imaginary meal, basal acid output increased by 89%. In another trial designed to test reduction in acid output, subjects were instructed to use hypnosis to experience deep relaxation. This exercise was accompanied by a 39% decrease in basal acid output. This study highlights the fact that high hypnotizability is a two-edged sword, in that it may increase or decrease a given physiological parameter, depending on the mental content during the hypnotic state.

These observations may have clinical relevance is illustrated by the findings of a controlled trial of hypnosis in relapse prevention of duodenal ulcers (Colgan et al. 1988). In this study patients with rapidly relapsing ulcer disease were randomly assigned, after administration of ranitidine, to hypnosis treatment or no treatment. All of the control subjects but only 53% of the hypnosis patients relapsed. Over the years, several studies have reported the benefits of hypnosis in the treatment of ulcer disease (Bick 1958, Colgan et al. 1988, Francis and Houghton 1996, Montera 1968).

## Respiratory Conditions

A number of studies have addressed the negative effects of stress in pulmonary function, as well as the efficacy of hypnosis in helping various pulmonary conditions, primarily asthma (Hypnosis for asthma 1968, Anbar 2003, Aronoff et al. 1975, Ben-Zvi et al. 1982, Clarke 1970, Collison 1975, Davis et al. 1998, Ewer and Stewart 1986, Fry et al. 1964, Gilder 1968, Hackman et al. 1996, 2000, Herraiz Ballestero et al. 1952, Kelly and Zeller 1969, Kohen 1986, 1987, Kohen and Wynne 1997, Luparello et al. 1968, Magonet 1952, Maher-Loughnan 1970, Maher-Loughnan et al. 1962, McFadden et al. 1969, Moorefield 1971, Morrison 1988, Neinstein and Dash 1982, Smith et al. 1970, White 1961). In most cases, patients can learn to use self-hypnotic techniques rather than medication when they begin to feel an anxiety-precipitated asthmatic attack coming on. This may help interrupt the vicious cycle of anxiety and bronchoconstriction. A common technique is to have asthmatic patients enter a state of self-hypnosis and imagine that they are somewhere where they naturally breathe easily, such as in a beach breathing cool ocean spray (Spiegel and Spiegel 1987).

The results of these studies suggest that there is a significantly positive correlation between hypnotizability and treatment responsivity in asthmatic patients. In one such study, Collison (1975) described that one fifth of his asthma patients experienced "complete symptom resolution" and that one third had "considerable improvement in symptoms" after hypnotic treatment and training. In another randomized, controlled trial, after brief treatment with hypnosis, patients with a high hypnotizability score showed marked improvement (74.9%) in the degree of bronchial hyperresponsiveness to a standardized methacholine challenge test and experienced a 26% decrease in the use of inhaled bronchodilators (Ewer and Stewart 1986). In yet another study after brief hypnotic treatment and training, patients reported a two-thirds decline in the number of hospital admissions due to complications of asthma (Morrison 1988). In addition, subjects reported a decreased need for steroid medications, reduced lengths of hospital stay, and overall perceived themselves as healthier. Similar responses have been described in pediatric asthmatic samples (Aronoff et al. 1975, Gluzman and Zisel'son 1987, Kohen 1986, 1987).

These dramatic therapeutic responses to hypnosis are not limited to asthmatic patients. Anbar (2000, 2001) demonstrated that patients suffering from cystic fibrosis may also substantially benefit from the use of hypnosis. These studies demonstrated that patients successfully used self-hypnosis for symptom control 86% of the time. No patient reported worsening of symptoms due to the use of hypnosis. More than 30% of the patients continued to practice hypnosis on their own for 6 months or longer. Many of the patients used hypnosis for more than one purpose, including relaxation (61% of patients), relief of pain

associated with medical procedures (31%), headache relief (16%), changing the taste of medications to make the flavor more palatable (10%), and control of other symptoms associated with cystic fibrosis (18%), thus demonstrating that patients can learn to use hypnosis to enhance their control over discomforts associated with cystic fibrosis and its therapy. Similar results have been obtained in the management of chronic dyspnea (Anbar 2001). That is, after 1 month of hypnosis training, 82% of the subjects reported that their dyspnea and associated symptoms had resolved. The remaining patients reported that their symptoms had improved. At a follow-up 9 months after hypnosis training the authors found that there was no recurrence of dyspnea or onset of new symptoms in patients in whom the dyspnea resolved.

Finally, several papers have reported on the use of hypnosis, guided imagery, and biofeedback to help "difficult-to-wean" patients discontinue use of ventilators in the critical care setting (Bowen 1989, Jacavone and Young 1998).

## Applications of Hypnosis in Habit Control

### Smoking Cessation

A number of studies demonstrate the efficacy of hypnosis as a tool to facilitate control of smoking. These studies, generally limited to nonrandomized outcome evaluations, show success rates in cigarette abstinence after treatment with hypnosis ranging from 13 to 64%. In some studies, abstinence is strictly defined as no smoking during a follow-up time of at least 6 months (Schwartz 1983, 1987, Schwartz and Dubitzky 1968, 1969). Spiegel (1970) developed a single-session approach for smoking cessation that is widely used. Since Spiegel's original study, many others have replicated his findings and yielding long-term abstinence rates in the 20–35% range (Berkowitz et al. 1979, Spiegel D et al. 1993, Williams and Hall 1988). Some have developed variations to the single-session method increasing the number of sessions to three (Elkins and Rajab 2004) or five (Watkins 1976). Other case studies have reported abstinence rates as high as 64% at 6 months (Crasilneck and Hall 1985, Holroyd 1980, 1991, Hyman et al. 1986, Schwartz 1987, Williams and Hall 1988), but presumably in highly selected and motivated samples, since these numbers are far better than the rates of unassisted quitting, which are around 10% (Gritz and Bloom 1987). As one would expect, studies have also shown that higher hypnotizability predicts better outcome (Barabasz et al. 1986, Spiegel and Spiegel 1987). Other factors that may affect the outcome in addition to hypnotizability include the presence of external incentives and gender (Agee 1983, Baer et al. 1986, Barkley et al. 1977, Berlin 1980, Cohen 1969, Covino and Bottari 2001, Crasilneck and Hall 1968, Ewin 1977, Frank et al. 1986, Gravitz 1988, Green et al. 2006, Green and Lynn 2000, Holroyd 1980, Hyman et al. 1986, Johnston and Donoghue 1971, Kinnunen 2001, Moses 1964, Pederson et al. 1975, Prokop 1980, Rabkin et al. 1984, Tonnesen and Wennike 1999, West 1977, Wollman 1972).

There are several mechanisms by which hypnosis may contribute to success in smoking cessation. The ritualistic process of the hypnotic exercise may provide a kind of substitute physical relaxation for the "breathing exercise" that accompanies the act of smoking; the positive affirmations in self-hypnosis provide positive reinforcement for behavior change and promote positive self-image; its use enhances self-observation and self-monitoring; and finally it can facilitate cognitive restructuring of the smoking habit.

The single-session method (Spiegel 1970) emphasizes teaching patients self-hypnosis rather than having multiple sessions with a therapist. It uses a strategy that is intrinsically self-reinforcing and meaningful to the patient. It can be practiced whenever the urge to smoke comes on the patient. This method of cognitive restructuring involves emphasizing that the act of smoking is destructive specifically to the patient's body and thereby limits what the patient can do with his or her life by shortening the life span and deteriorating the quality of life. Hypnosis is used to emphasize the patient's commitment to protect the body from the poison in cigarettes. This approach gives the patient the ability to examine priorities and to balance the urge to smoke against the urge to protect his or her body from damage. Smokers are instructed to focus on what they are *for*—protecting their bodies—rather than what they are *against*—smoking. This reduces the amount of attention they pay to smoking or its absence and provides immediate internal reinforcement for attending to care of the body (Spiegel and Spiegel 2004).

In summary, while the proportion of smokers who become abstinent using hypnosis in some trials is higher than that found with other types of interventions for smoking, there have been no head-to-head comparisons that could determine whether this is due to sample bias or differences in motivation. At the least the limited research literature suggests that techniques facilitated with hypnosis are comparable in effectiveness to other approaches, perhaps because they enable patients to employ a self-administered treatment strategy (self-hypnosis) to reinforce a more adaptive cognitive restructuring while providing patients with an exercise in physical relaxation.

### Weight Control

The usefulness of hypnosis in the treatment of eating disorders has already been discussed above in the section dealing with psychiatric disorders. Here we cover only the use of hypnosis as a method for loosing weight. Seldom will the use of hypnosis alone be sufficient for the treatment of weight problems. It is usually employed as an adjunct to a comprehensive dietary and exercise control program for weight reduction and management. Similar to the use of self-hypnosis in the control of smoking, the purpose in dietary control is to restructure the patient's experience with overeating. Patients are asked to examine their excess food intake and to pay attention to the damaging effects to their body. This then translates into an exercise about learning to eat with respect for one's body. Once again, the emphasis is on what the patient is *for*, rather than being *against* food.

An important component of such an approach consists of teaching the patient to use self-hypnosis training to control the urge to overeat. This is better accomplished by preparing a list of food items that constitute eating with respect and then comparing an urge for a particular food item with the list. If the desired food is on the list, the patient is encouraged to eat it like a gourmet, focusing intently on all aspects of the eating experience and enjoying it. If the food is not on the list, the patient is asked to recognize the desire rather than fight the urge. Then the patient is encouraged to

use self-hypnosis to compare this urge with her or his overall commitment to protect and treat her or his body with respect and therefore to eat with respect. This involves dissociating the urge to eat from the need to act on that urge. By using this method, patients can see their desire to eat not as an occasion to feel deprived but rather as one in which they are enhancing their mastery over the urge by choosing to protect their body. Patients are also instructed to pay more attention to their somatic signals of hunger and satiety and to eat when they are hungry, but stop eating as soon as they are full.

Some of the early clinical reports on the use of hypnosis for weight control seemed promising (Bolocofsky et al. 1985, Stanton 1975, Wadden and Flaxman 1981, Winkelstein 1959). Unfortunately, long-term outcome studies on the usefulness of hypnosis for weight control are lacking. In fact, the few systematic reviews of the limited available literature are not very optimistic (Pittler and Ernst 2005) and most have yielded equivocal results (Johnson and Karkut 1996). Clinical experience suggests that those within 20% of their ideal body weight may obtain some benefit from such restructuring techniques with self-hypnosis, combined with a regimen of a balanced diet and exercise. Some have postulated that high hypnotizability is correlated with enhanced weight reduction (Andersen 1985, Deyoub 1979). Barabasz and Spiegel (1989) performed a randomized controlled study comparing the usefulness of hypnosis with a self-management group for weight reduction. All members in the study were highly motivated. The control group was exposed to an active self-management treatment program resulting in adequate weight reduction. On the other hand, the hypnosis subjects were given suggestions emphasizing their desire to protect and care for their bodies rather than to fight the desire for certain foods, along with a behavioral intervention. The results showed significantly greater weight loss among the hypnosis plus behavioral intervention group (mean weight loss, 6.4 kilograms), as contrasted with the group using behavioral intervention only (mean weight loss, 1.3 kilograms). One of the most important aspects of the study was the significant relationship between weight loss and hypnotizability. The study demonstrated a significant correlation between hypnotizability scores and weight loss.

Other studies employing hypnosis for weight loss have proven to be modestly effective (Stradling et al. 1998). On the other hand, some studies have found that adding hypnosis to cognitive–behavioral approaches for weight reduction may yield significant better results (Andersen 1985, Kirsch 1996, Kirsch et al. 1995).

## Applications of Hypnosis in the Forensic Setting

In the forensic setting, hypnosis could have a number of practical applications, but the one that is more common and potentially problematic is the use of hypnosis for the purpose of refreshing the recollection of both victims and witnesses (Gravitz 1995). Several widely popularized cases, like the Chowchilla school bus hijack and the use of hypnosis to enhance the recollections of the driver that led to the recovery of the children kidnapped and the capture of the perpetrators, have increased its popularity as a method for memory enhancement (*People v Schoenfeld* 1980). Unfortunately, it has helped cement a long-standing misconception regarding the use of hypnosis as a truth serum.

Any memory-enhancing technique has potential problems regarding the veracity of the recovered memories. That also applies to hypnosis. The most serious problem involves possible effects of hypnosis on memory. There is evidence that hypnosis can distort memory in two ways: through *confabulation*, the creation of pseudomemories that are reported as real, or through *concreting*, an unwarranted increase in the confidence with which hypnotized individuals report their memories, either true or false (McConkey 1992, Orne et al. 1985, Spiegel 1994, Spiegel and Spiegel 1986, Spiegel and Vermutten 1994). Hypnosis can facilitate the recall of dissociated memories, especially when recall is hampered by the strong affect associated with trauma (Kardiner and Spiegel 1947, Spiegel 1992, Spiegel and Spiegel 1984). However, the research literature indicates that the most clearly reproducible problem is the production of confident errors, exaggerating the true value of memories unearthed in hypnosis.

This is especially a problem when the memories involve witnessing a crime and civil or criminal action in court is a possibility. Most states prohibit the use of hypnotically induced testimony, but some prescribe witnesses who have been hypnotized regarding the content of their potential testimony (Spiegel and Scheflin 1994). If the possibility exists that a patient may be required to testify, it is wise to discuss the use of hypnosis with the patient and (with the patient's permission) the patient's attorney or the district attorney and obtain written agreement regarding its use. If the patient is likely to be called to testify, the therapist should obtain electronic recording of all contact with the patient (preferably on videotape) so that the court can examine for possible suggestive influences. Full guidelines for use of hypnosis in the forensic setting include careful debriefing of the subject before hypnosis is employed, the use of nonleading questions, complete videotaping of all contact with the patient, and careful debriefing afterward (Maldonado et al. 2000, Scheflin and Spiegel 1998, Spiegel and Spiegel 1986).

The controversies surrounding the so-called false memory syndrome have reignited questions regarding the validity of the material recovered by the use of hypnosis. One of the most common applications of hypnosis in the court and legal settings had been refreshing recollection of witnesses and victims of crimes. Even though the current controversy focuses on the dangers of hypnotically induced confabulation or excessive confidence in memories (Diamond 1980), there have been some positive results. A well-known example is the case involving the driver of a hijacked school bus in Chowchilla, California (1980). Under hypnosis, the bus driver was able to recall the license plate number of the car driven by the kidnappers. This information, not consciously available to him before hypnotic intervention, led to the arrest and conviction of the criminals.

Because hypnosis involves a suspension of critical judgment, and therefore a state of heightened suggestibility or responsivity to social cues, it is important that the interview be conducted with a minimum of inserted information. To minimize the risk of contaminating subjects' memories, it is important to use open-ended questions, such as "What happens next?" rather than "How did he sexually abuse you?"

Information retrieved with the aid of hypnosis may simply be the result of an additional recall trial (Erdelyi and

Stein 1981), it may be new and true (Dywan and Bowers 1983), or it may be a confabulation (Laurence and Perry 1983). It may indeed be a combination of all three (Orne et al. 1985). As a result, courts have long been unwilling to admit the testimony of a person hypnotized while testifying and have also begun to exclude testimony of witnesses who have previously been hypnotized about the event in question. Even when a subject is acting in good faith, hypnosis can amplify both truth and falsehood. A good guideline is that hypnosis increases the recovery of memories, both true and confabulated. Spiegel (1980b) described what he called the "honest liar," a hypnotized witness who in his or her desire to please the hypnotist or simply as a result of being in the suggestible state of hypnosis makes up material and believes the newly created story to be real. This poses obvious dangers for the legal system. A witness who produces "confident errors" (McConkey 1992) may mislead a jury looking for signs of discomfort or insecurity in their evaluation of the veracity of testimony. This has been termed *concreting* (Diamond 1980, Orne et al. 1979).

On the other hand, people do dissociate during trauma, often failing to recall events despite being conscious at the time (Cardeña and Spiegel 1993, Spiegel and Cardeña 1991). There is evidence that such memory gaps may persist for years or even decades after such traumatic events as physical or sexual abuse (Williams 1994).

Therapists treating victims of sexual abuse must be aware that the use of hypnosis may compromise the ability of a witness to testify in court. Indeed, several states, including Arizona (*State ex rel Collins v Superior Court* 1982), California (*People v Guerra* 1984, *People v Shirley* 1982), New Jersey (*People v Hurd* 1982) (Cox and Mackay 1982), and New York (*People v Hughes* 1983) restrict the testimony of victims or witnesses who have used hypnosis to refresh their recollection. The reason for the courts' objection to the use of hypnosis is a combination of real and exaggerated dangers of hypnosis.

Researchers conducted a meta-analytic review of 24 research studies dealing with the recall accuracy for hypnotized vs. nonhypnotized eyewitnesses in forensically relevant settings (Steblay and Bothwell 1994). They found that the recall accuracy for nonleading questions after a 1- to 2-day delay favored the hypnotized subjects ($d = 0.46$); however, less accurate recall was evidenced for hypnotized subjects following a delay of less than 24 hours ($d = –0.29$) or a 1-week delay ($d = –0.24$). As expected and theorized by many memory and hypnosis experts, the recall of hypnotized subjects also displayed more intrusion of uncued errors and higher levels of pseudomemory. Also expected was the finding that hypnotized subjects also expressed higher levels of confidence in recall accuracy compared to nonhypnotized subjects. These findings have urged caution to be used when dealing with hypnotically refreshed memory.

Some legal commentators have argued that testimony derived from hypnosis should not be allowed as evidence in a court room because of its inherent unreliability and the unduly powerful impact it may have on a jury. Nevertheless, research using a jury simulation technique designed to study the impact that a hypnotically refreshed witness has upon jurors' decision making found that jurors view hypnotic testimony with a certain amount of skepticism (Greene et al. 1989). The researchers concluded that the impact of witnesses who have undergone hypnosis is comparable to that of testimony based on delayed recall, and rarely does it have the impact of testimony from an immediate report. Of interest, they found that jurors' judgments about hypnotically refreshed testimony affected the way they evaluated other evidence at trial. For example, jurors who learned that a prosecution witness had been hypnotized were less believing of other prosecution witnesses than were jurors not exposed to hypnotic testimony.

After much legal battling, some courts now allow witnesses to testify after the use of hypnosis provided that certain guidelines are followed (California Legislature 1985). These primarily relate to the training and independence of the professional doing the hypnotic interrogation and the electronic recording of the entire process (Spiegel and Spiegel 1986).

To address this controversial issue, the Council on Scientific Affairs of the American Medical Association convened a panel of experts to examine the research evidence relevant to this problem. The report issued by the panel concluded that the existing evidence indicates that the use of hypnosis tends to increase the productivity of witnesses, resulting in new memories, some of which are true and some of which are incorrect (Orne et al. 1985). Furthermore, some studies showed an increase in the confidence assigned by hypnotized subjects to their memories despite the fact that their percentage of correct responses had not improved. The panel noted that the analogy between the laboratory setting in which most of the studies were done and the real-life situation in the courtroom must be drawn with great caution and that situations in which extreme emotional and physical trauma had occurred differ markedly. The panel recommended that careful guidelines similar to the ones adopted by the state of California be followed when hypnosis is used in the forensic setting (Table 94–10).

As a rule, it is advisable to caution attorneys and witnesses that the use of hypnosis might open the possibility of challenge to the credibility or even the admissibility of a witness. The kind of situation in which hypnosis is most likely to be worth the risk is one in which there is a traumatic amnesia for the events of a crime or in which all other avenues of exploration have been exhausted. Hypnosis is by no means a truth serum, and the courts must weigh the effects of any hypnotic procedure on a witness.

**Table 94–10 Hypnosis and Forensic Psychiatry**

If you consider the use of hypnosis in a trial case, certain guidelines need to be observed:

- Caution attorneys and witnesses that the use of hypnosis might open the possibility of challenge to the credibility or even the admissibility of a witness
- Carefully document memory before hypnosis of the witness
- Use an expert psychiatrist or psychologist as a hypnosis consultant
- Electronically record all interaction preceding, during, and after hypnosis sessions. Document and record all contact with the victim
- Conduct the interview in a neutral tone. Guide the victim through the experience but avoid using leading or suggestive questions. Avoid introducing information during the interrogation

Because it is almost impossible not to add some degree of contamination to the procedure, we recommend that at least the following steps be undertaken. First (with the patient's permission), consult with the victim's attorney. If an investigation is in progress or court proceedings are likely, you may also want to contact the district attorney's office or the police. Second, make a video (preferably) or audio recording of all contact with the victim. Make certain that you can clearly hear the voice of the victim and your own voice or that of anyone else participating in the process. Third, conduct the interview in a neutral tone. Guide the victim through the experience but avoid using leading or suggestive questions. It is imperative to avoid introducing information during the interrogation. This is best achieved by asking open-ended, neutral questions based on the information already provided by the victim. For example, ask questions such as "Now what is happening?" rather than "Did he knock you down?" or "Who raped you? Was it your father?"

The medico–legal aspects of the use of hypnosis in psychiatric practice have already been discussed at length elsewhere (Maldonado and Spiegel 2002b, 2007, Spiegel and Spiegel 1986).

## Neurophysiological Correlates of Hypnosis

Since the earliest days of hypnosis, scientists have been trying to understand its neurophysiological underpinnings. Mesmer initially explained the mechanism of action of his technique as the manipulation of the body's energies, or magnetic fluid. In the late ninetieth century, Rudolf Heidenhain explained hypnosis physiologically in terms of cortical inhibition (Windholz 1996). By the beginning of the twentieth century, Pavlov provided a new model, suggesting that hypnotic states could be understood in terms of partial inhibition of the cortex (Windholz 1996). Subsequently, the debate regarding the mechanisms mediating the hypnotic phenomenon continued between Charcot (1890), who described hypnosis as a disease of the nervous system and argued that normal people could not be hypnotized, and Bernheim (1964), who challenged Charcot's ideas of hypnotizability as a disease and rather described it as a trait exhibited to different degrees by normal individuals (Widlocher and Dantchev 1994).

Since those early times, many research efforts have attempted to correlate the hypnotic experience with actual physiological changes. To date, a "seat of hypnosis" has not been found in the brain, although recent research points toward involvement of the frontal and anterior cingulated cortex (Kropotov et al. 1997, Rainville et al. 2002, Spiegel 2003). There is ample clinical and research experience indicating that the hypnotic process affects both electrical and metabolic processes in the brain. Similarly, as we have observed in clinical experience, hypnotic activity is capable of causing various physiological changes. Some of these have been simulated under laboratory conditions.

The ability of highly hypnotizable individuals to control peripheral skin temperature and blood flow has been replicated in several well-controlled experiments (Grabowska 1971, Kistler et al. 1999, Zimbardo et al. 1970). Conn and Mott (1984) demonstrated plethysmographic measure changes caused by hypnotically mediated rapid vasodilatation after direct suggestion in cases of Raynaud's disease treated with hypnosis.

Gemignani et al. (2000) studied the physiological and electroencephalographic responses of highly hypnotizable volunteers suffering from simple phobia. Under hypnotic suggestion, subjects exposed to aversive stimuli experienced significant increases in heart rate (HR) and respiratory rate (RR) with a shift of the sympatho–vagal indexes toward a sympathetic predominance. These subjects also experienced a significant increase in the EEG gamma band with left frontocentral prevalence.

Finally, Williamson et al. (2001) using healthy, highly hypnotizable volunteers demonstrated dramatic changes in ratings of perceived exertion (RPE) when asked to imagine themselves in an uphill bicycle grade. They found significant increases in RPE, HR, mean blood pressure (BP), regional cerebral blood flow (rCBF) in the right insular cortex, and right thalamic activation. Conversely, when subjects were asked to imagine themselves on a perceived downhill grade, they observed decrements in the ratings of both RPE and rCBF in the left insular cortex and anterior cingulate cortex, but it did not alter exercise HR or BP responses.

### Neurotransmitters

Hypnotizability has been found to be significantly correlated with cerebrospinal fluid levels of homovanillic acid, a metabolite of dopamine (Spiegel and King 1992) (Table 94–11). This provides evidence for the involvement of the frontal cortex in the hypnotic process because levels of homovanillic acid in the cerebrospinal fluid primarily reflect activity in the frontal cortex and basal ganglia, which are rich in dopaminergic synapses. Some have suggested that the administration of dopaminergic agents such as amphetamine may enhance hypnotizability (Sjoberg and Hollister 1965). It has been postulated that the automaticity observed in hypnotic motor behavior could represent an activation of the basal ganglia, which is involved in both implicit memory (Graf and Schacter 1985, Mishkin and Murray 1994, Schacter 1987, 1992) and routine motor activity.

**Table 94–11 Neurophysiology of Hypnosis**

| |
|---|
| **Neurotransmitters** |
| High correlation between cerebrospinal fluid levels of homovanillic acid and hypnotizability |
| **Brain Electrical Activity** |
| Alpha laterality difference favoring the left hemisphere among highly hypnotizable individuals |
| Theta power, especially in the right frontal region, best differentiates highly hypnotizable individuals from subjects with low hypnotizability |
| Highly hypnotizable subjects experiencing a hypnotic hallucination revealed significant reductions in P300 amplitude of event-related potentials |

### Brain Electrical Activity

Even though it was initially described as a form of nervous sleep, today we know that hypnosis and sleep share no common characteristics. The brain electrical pattern of a hypnotized subject actually resembles that of a fully awake and attentive individual more than the pattern of a person

who is asleep (see Table 94–11). Power spectral analysis of brain electrical activity has provided some limited understanding into the physiological mechanism of the hypnotic state. More recently, Fingelkurts et al. (2007) hypothesized that alteration in functional connectivity of the brain may be regarded as a neuronal correlate of hypnosis (at least in very highly hypnotizable subjects) in which separate cognitive modules and subsystems may be temporarily incapable of communicating with each other normally during the hypnotic state.

Various researchers (Edmonston and Grotevant 1975, Morgan et al. 1974b) have reported an increased alpha activity among highly hypnotizable individuals. This difference is present whether or not the subjects were in trance. They also found an alpha laterality difference favoring the left hemisphere among highly hypnotizable individuals. This difference suggested that hypnosis might preferentially involve the right cerebral hemisphere, because alpha is the noise the brain makes when resting but alert, so relatively less alpha on the right suggests more activity. These findings are supported by observations that highly hypnotizable individuals tend to be left-lookers, preferring to activate their right hemisphere (Bakan 1969, Gur and Reyher 1973). Finally, Meszaros and Szabo (1999) demonstrated that in highly susceptible subjects the right parietotemporal region shows more electric power than the left one, while the low susceptible subjects have left-side predominance or equilibrated power in all derivations.

Other studies have questioned the right hemispheric dominance theory of the hypnotic process. Edmonston and Moscovitz (1990) obtained bilateral EEG measures on highly hypnotizable subjects while performing hemisphere-specific tasks during hypnosis and no-hypnosis control conditions. These studies suggest a lack of task-appropriate activity during hypnosis, indicating that data analysis techniques were the source of potential misinterpretations of previously obtained data.

Jasiukaitis et al. (1997b) raised new questions regarding the old theory of right-cerebral-hemisphere dominance of brain activity during hypnosis. They conducted a review of the literature and included in their analysis data from electrodermal responding, visual event-related potentials (VERPs), and Stroop interference. Their analysis suggests, instead, that although hemispheric activation on hypnotic challenge may depend in large part on the kind of task the challenge might involve, several general aspects of hypnosis might be more appropriately seen as left-hemisphere rather than right-hemisphere brain functions, including concentrated attentional focus and the role of language in the establishment of hypnotic reality.

There may also be frontal vs. posterior topographical differences among high and low hypnotizable individuals. In fact, more recent studies of power spectral analysis suggest that theta power, especially in the frontal region, best differentiates highly hypnotizable from poorly hypnotizable individuals (Sabourin et al. 1990). Similarly, Graffin et al. (1995a) found greater theta power in the more frontal areas of the cortex for highly hypnotizable subjects. During the actual hypnotic induction, theta power increased markedly for both groups in the more posterior areas of the cortex, whereas alpha activity increased across all sites. In the period just preceding and following the hypnotic induction, poorly hypnotizable subjects displayed an increase in theta activity, whereas highly hypnotizable subjects displayed a decrease. Taken together, these findings suggest that anterior/posterior cortical differences may be more important than hemispheric laterality for understanding the hypnotic processes.

ERPs have been used to study the effects of hypnotic hallucination on brain electrical activity. These studies are based on the premise that hypnotically induced changes in perception should be reflected in alterations in ERP amplitude. The results of early studies showed varying and contradictory effects. Halliday and Mason (1964) and Amadeo and Yanovski (1975) found no effect of hypnotic hallucinations on the EEG, but studies by others (Clynes et al. 1964, Wilson 1968) did. These studies were limited because of small sample sizes, nonquantitative analysis of EEGs, limited use of hypnotizability testing, and use of subjects with comorbid neurological or psychiatric disorders.

On the other hand, evidence suggests that highly hypnotizable subjects experiencing a hypnotic hallucination may alter their perception of an external stimulus with corresponding amplitude changes in the response evoked to an external stimulus (Clynes et al. 1964, Wilson 1968). Some have found that highly hypnotizable subjects who experience a visual hallucination obstructing their view of a monitor showed significant reductions in P300 amplitude throughout the scalp and of N200 in the occipital region (Spiegel et al. 1985). This alteration occurred only in highly hypnotizable subjects in which a hallucination was suggested. It was not seen in any other hypnotic condition, and it was not evident among a group of subjects with low hypnotizability attempting to experience the same perceptual alteration.

Jasiukaitis et al. replicated these results (Spiegel et al. 1985) with visual hypnotic obstruction but included an additional condition in which highly hypnotizable subjects were instructed to simply ignore half of their visual field (selective inattention) outside of the hypnotic trance. Both hypnotic obstruction and selective inattention reduced P100 and P300 peaks of visual evoked potential (Figure 94–4). However, the P200 peak differentiated hypnotic from nonhypnotic conditions. Hypnotic obstruction decreased P200, whereas selective inattention actually increased it. These results suggest that subjects performing positive hypnotic hallucination employ, to a degree, elements of inattention along with processes unique to hypnosis. Later, new visual ERP research implicated the left cerebral hemisphere in hypnotic perceptual alteration (Jasiukaitis et al. 1996). This study found a greater reduction of occipital P200 amplitude during hypnotic obstructive hallucination when visual stimuli were presented to the right visual field than when they were presented to the left visual field, which demonstrates a stronger hypnotic effect of imagery in the left than the right occipital cortex.

The effect of auditory hallucination has been studied with similar results. Sigalowitz et al. (1991) found P300 differences among highly hypnotizable individuals hallucinating a reduction or increase in tones; subjects with low hypnotizability did not show such a change. The amplitude reduction did not reach statistical significance, but the increase during positive hallucination did. Crawford et al. (1996) studied the effect of hypnotic susceptibility levels on auditory event-related potentials (AERPs) and found that high hypnotizable

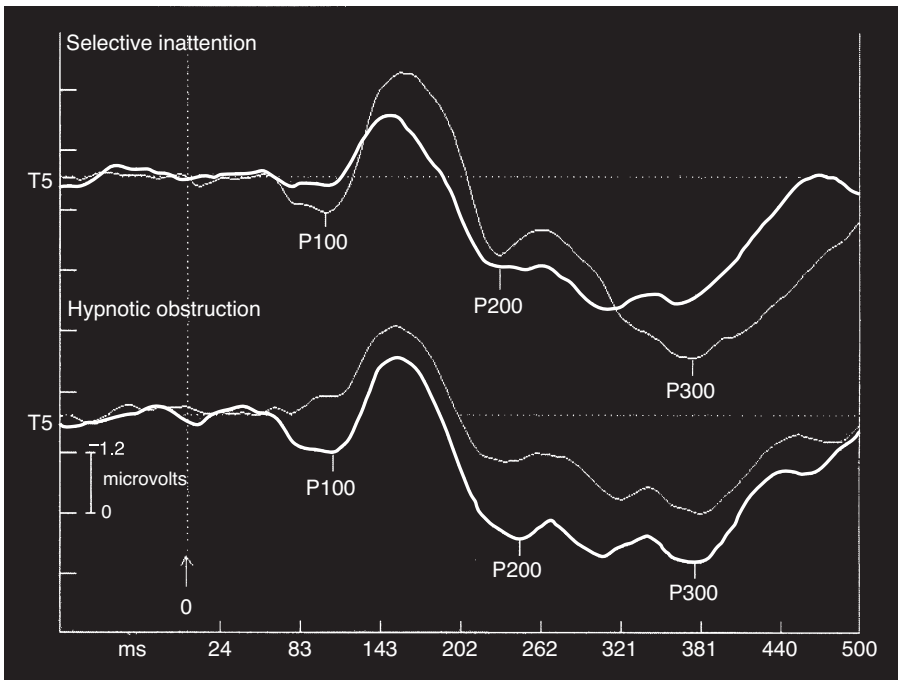



**Figure 94–4** *Grand mean (N = 22) visual evoked potentials to right visual field stimuli at electrode T5. (Top) Dark waveform is the visual evoked potential while the visual field is attended. Light waveform is the visual evoked potential while the right visual field is ignored. (Bottom) Dark waveform is the visual evoked potential while the right visual field is not obstructed during hypnosis. Light waveform is the visual evoked potential while the right visual field is obstructed by positive hypnotic hallucination. Note that from 140 to 320 milliseconds after the stimulus, hypnotic obstruction and selective inattention appear to exert opposite effects on the visual evoked potential.*

individuals appeared to divert greater attentional processing to the tasks at hand and were also slower to respond to not-to-be-attended stimuli. These findings confirmed the hypothesis that hypnotic susceptibility is associated with efficient attentional processing such that high hypnotizable individuals can more effectively partition attention toward relevant stimuli and away from irrelevant stimuli than can low hypnotizable individuals. Lamas and Valle-Inclan (1998) found that there were increases in reaction times and P300 latencies as a function of noise and spatial stimulus–response incompatibility (Simon effect), and that hypnotic suggestions decreased the response times for all types of trials nonsignificantly indicating a specific effect of hypnotic suggestions in the processing of hallucinated stimuli, which is consistent with the hallucinatory experience reported by the subjects.

A study by Barabasz et al. (1999) examined the effects of positive obstructive and negative obliterating instructions on simultaneous VERPs and AERPs—P300 signals. Subjects were selected on the basis of high and low hypnotizability and were requested to perform identical tasks during waking and alert hypnotic conditions. The study found that highly hypnotizable subjects showed greater ERP amplitudes while experiencing negative hallucinations and lower ERP amplitudes while experiencing positive obstructive hallucinations, in contrast with low hypnotizable subjects and their own waking imagination-only conditions. These results constitute a rather robust physiological marker of hypnosis, an alteration in consciousness that corresponds to participants' subjective experiences of perceptual alteration.

Hypnotically induced hallucinated experiences in other sensory modalities have yielded similar results. Similar to the use of hypnosis for pain control, hypnotic suggestions given to filter somatosensory (electrical) stimulation applied to peripheral nerves affect ERP amplitude. Suggestions of a tingling, cool, numbing sensation were given with the idea that it would filter out any other sensations in the area. This approach produced a significant reduction in P300 amplitude and also in P100 amplitude, suggesting earlier filtering of the somatosensory signal in the hypnotic hallucination condition. The interpretation of these data suggests that these subjects responded cortically as though the stimulus were less intense. When suggestions to increase attention to the stimuli were given, a significant increase in P100 but not in P300 amplitude was observed. This is further evidence that highly hypnotizable subjects were capable of producing bidirectional changes in ERP amplitude to sensory stimuli, depending on the cognitive task employed during hypnosis (Spiegel et al. 1989). Subjects with low hypnotizability or volunteers trying to simulate these conditions were not able to reproduce these findings. De Pascalis and Carboni (1997) studied somatosensory target selection in women and found that highly hypnotizable subjects demonstrated significant suppression of P3 peak amplitude to target stimuli in the left frontal and posterior scalp sites during hypnotic obstructive hallucination as compared to a normal attention condition. The researchers concluded that hypnotically induced obstructive hallucination to somatosensory stimuli involve alterations in neural and autonomic responses that are consistent with a trait conception of hypnotizability. Crawford et al. (1998) studied the somatosensory responses under hypnotic analgesia of moderate to highly hypnotizable adults with chronic low back pain. They found that hypnotic analgesia led to highly significant mean reductions in perceived sensory pain and distress, suggesting that this was an active process that required inhibitory effort, dissociated from conscious awareness, where the anterior frontal cortex participates in a topographically specific inhibitory feedback circuit that cooperates in the allocation of thalamocortical activities.

In a related topic, the somatosensory event-related potential (SERP) literature (Naatanen and Michie 1979) demonstrated the presence of a clearly defined response to SERP's selective attention, evidenced by a negative deflection 140 milliseconds after the stimulus was administered, known

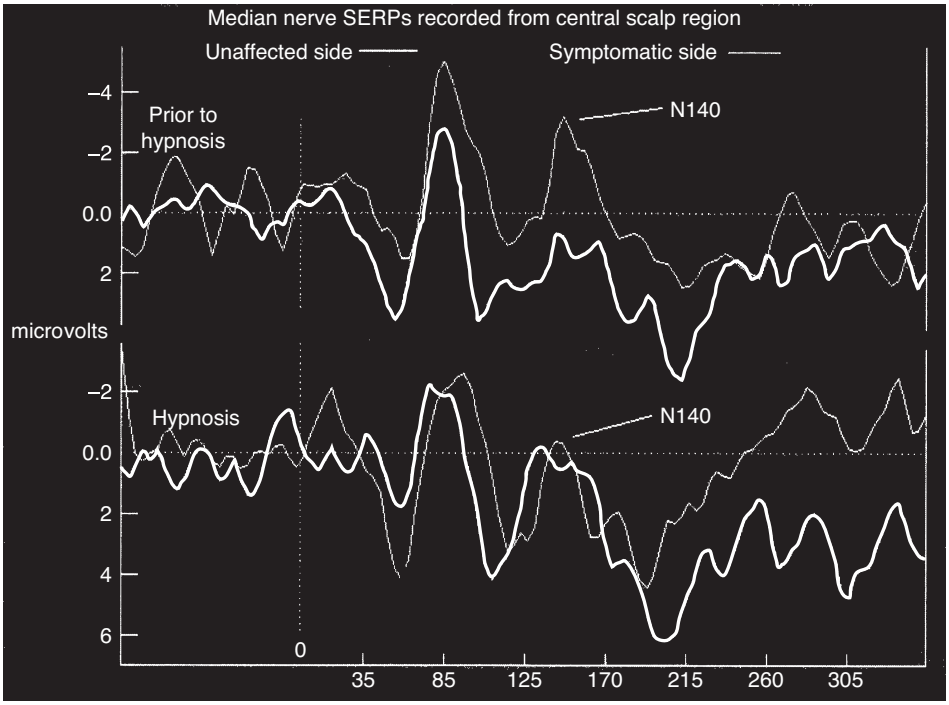



**Figure 94–5** *Somatosensory evoked potentials (SERPs) of a patient diagnosed with a lateralized conversion paralysis affecting the right side of the body. (Top) Baseline recording. The dark waveform represents the patient's response to electrical stimulation of the nonaffected side; the light waveform represents response to stimulation of the affected side. The affected side exhibits a larger N140 peak than the nonaffected side. (Bottom) Recording obtained during hypnosis. Suggestions were given for symptom resolution. The patient appeared clinically to have no neurological deficits. As above, dark and light waveforms represent nonaffected and affected sides, respectively. Under hypnosis, along with a resolution of symptoms observed, the N140 peaks for both sides are now equal.*

as the N140. This negative deflection is consistently seen as a response to selective attention to somatic stimulation (Allison 1982, Michie 1984, Naatanen and Michie 1979). Postulating that somatic conversion disorders may represent a form of selective attention, Maldonado (1997, 2001) studied a group of patients presenting with lateralized (i.e., unilateral) deficits using SERPs. If indeed these patients are constantly monitoring the affected body part or side, they should show an enhanced N140 on the affected side. This proved to be the case. Maldonado found that subjects exhibited a "normal N140" on the unaffected side (as expected in all "normal controls"), but an *enhanced* N140 on the affected side (Maldonado 2006). Even more remarkably, when the researchers provided suggestions for time regression (e.g., 2 weeks prior to the onset of symptoms), subjects experienced complete normalization of the SERP's response, showing only the "classic N140" bilaterally (Figure 94–5). At the end of the trial, the SERP's tracing returned to the previous pattern, that is, a classic N140 on the unaffected side and an enhanced N140 on the affected side. These findings suggest the possibility of an unconscious, autohypnotic model used by patients suffering from conversion disorder in order to create their symptoms.

## Brain Imaging

Despite the relatively limited research on hypnosis using newer brain-imaging techniques, such as positron-emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), new data are slowly emerging. PET scan studies have demonstrated a global increase in cerebral perfusion during hypnosis (Ulrich et al. 1987), while they demonstrated no change during the use of autogenic training in normal subjects. Work using PET imaging of the brain has led to the discovery that attentional processes can be subdivided into a series of components with different neuroanatomical localizations (Posner and Petersen 1990). The posterior attentional system involves orienting, with activation of the posterior or prestriate cortex. Focusing of attention is associated with activity in the anterior cingulate gyrus. Arousal involves activity in the right frontal cortex, consistent with the definition of hypnosis as a state of focal attention and heightened concentration. This suggests that during hypnosis, there is specific activation of the anterior attentional systems involving focusing (anterior cingulate) and arousal (frontal, especially on the right). Therefore, these imaging techniques may prove useful in identifying subsystems within the brain devoted to specific types of perceptual and cognitive processing in hypnosis.

In the last few years new studies shed further light into the neurophysiology of hypnotic phenomena. Rainville et al. (1997) demonstrated that hypnotic reduction of the perceived unpleasantness of a stimulus was associated with significant changes in pain-evoked activity within anterior cingulate but not somatosensory cortex in PET studies. PET scans were also used by Szechtman et al. (1998) to measure rCBF of highly hypnotizable subjects asked to produce vivid auditory hallucinations. They found that subjects capable of producing the hallucinations had increased rCBF in the right anterior cingulate gyrus. Of interest, the "externality" and "clarity" of the hallucinations were highly correlated with blood flow in this region.

Later, they investigated the effects of hypnosis and suggestions to alter pain perception on the PET-measured rCBF and the EEG measures of brain electrical activity, in highly hypnotizable subjects under different experimental conditions (Rainville et al. 1999). Pain was induced by immersion of a hand in either water at room temperature or painfully hot water. The findings suggest that hypnosis was accompanied by significant increases in both occipital rCBF and delta EEG activity, which were highly correlated with each other ($r = 0.70$, $P < 0.0001$). Peak increases in rCBF

were also observed in the caudal part of the right anterior cingulate sulcus and bilaterally in the inferior frontal gyri. Hypnosis-related decreases in rCBF were found in the right inferior parietal lobule, the left precuneus, and the posterior cingulate gyrus. Hypnosis with suggestions produced additional widespread increases in rCBF in the frontal cortices predominantly on the left side. Moreover, the medial and lateral posterior parietal cortices showed suggestion-related increases, overlapping partly with regions of hypnosis-related decreases. Results support a state theory of hypnosis in which occipital increases in rCBF and delta activity reflect the alteration of consciousness associated with decreased arousal and possible facilitation of visual imagery. Frontal increases in rCBF associated with suggestions for altered perception might reflect the verbal mediation of the suggestions, working memory, and top–down processes involved in the reinterpretation of the perceptual experience.

Several years later, the same group of researchers replicated and extended their original findings using PET in normal volunteers (Rainville et al. 2002). Immediately after each of eight PET scans performed before (four scans) and after (four scans) the induction of hypnosis, subjects rated their perceived level of "mental relaxation" and "mental absorption." Regression analyses between rCBF and self-ratings confirm the hypothesized involvement of the anterior cingulate cortex (ACC), the thalamus, and the pontomesencephalic brainstem in the production of hypnotic states. Hypnotic relaxation further involved an increase in occipital rCBF that is consistent with our previous interpretation that hypnotic states are characterized by a decrease in cortical arousal and a reduction in cross-modality suppression (disinhibition). In contrast, increases in mental absorption during hypnosis were associated with rCBF increases in a distributed network of cortical and subcortical structures previously described as the brain's attentional system. These findings support the state theory of hypnosis in which the basic changes in phenomenal experience produced by hypnotic induction reflect, at least in part, the modulation of activity within brain areas critically involved in the regulation of consciousness.

Wik et al. (1999), using PET scans, studied the effect of hypnoanalgesia in patients with pain associated to fibromyalgia. When comparing the results during hypnotically induced analgesia and resting wakefulness they found that patients experienced less pain during hypnosis than at rest. At the same time the cerebral blood flow was bilaterally increased in the orbitofrontal and subcallosial cingulate cortices, the right thalamus, and the left inferior parietal cortex, and was decreased bilaterally in the cingulate cortex. They concluded that the observed blood-flow pattern supported the notion of a multifactorial nature of hypnotic analgesia, with contributions from cortical and subcortical brain regions. Hypnotic alteration of perception involves changes in primary sensory association cortex as demonstrated by Kosslyn et al. (2000). The authors performed PET scans using $^{15}O$-$CO_2$ of highly hypnotizable subjects asked to see a colored pattern in color in a number of visual stimuli, included gray and white stimulus. Under hypnosis, both the left and right hemisphere color areas were activated when they were asked to perceive color, whether they were actually shown the color or the grayscale stimulus; moreover, these brain regions had decreased activation when subjects were told to see the grayscale, whether they were actually shown the color or grayscale stimulus.

Similarly, Faymonville et al. (2000) used PET scans to identify the brain areas in which hypnosis modulates cerebral responses to noxious stimuli. They compared brain images of subjects in a hypnotic resting state with mental imagery and a hypnotic state with stimulation (warm nonnoxious vs. hot noxious stimuli applied to right thenar eminence). Statistical parametric mapping demonstrated that noxious stimulation caused an increase in rCBF in the thalamic nuclei, anterior cingulate, and insular cortices. The hypnotic state induced a significant activation of a right-sided extrastriate area and the anterior cingulate cortex. The interaction analysis showed that the activity in the anterior (mid-) cingulate cortex was related to pain perception and unpleasantness differently in the hypnotic state than in control situations. Results also showed that hypnosis decreased both pain sensation and the unpleasantness of noxious stimuli and suggest that hypnotic analgesia with an instruction that the pain will not be bothersome (rather than literally reduced in intensity) is mediated by reduced activity in the ACC.

Later in 2003, his team assessed changes in cerebral functional connectivity related to the hypnotic state, compared to simple distraction and the resting state among highly hypnotizable right-handed volunteers using H2(15)O-PET (Faymonville et al. 2003). The experimental conditions were hot noxious or warm non-noxious stimulation of the right hand during resting state, mental imagery, and hypnotic state. They found that hypnosis, compared to the resting state, reduced pain perception by 50%, while the pain perception during rest and mental imagery was not significantly different. Analysis of PET data showed that the hypnotic state, compared to normal alertness (i.e., rest and mental imagery), significantly enhanced the functional modulation between midcingulate cortex and a large neural network encompassing bilateral insula, pregenual ACC, presupplementary motor area, right prefrontal cortex and striatum, thalamus, and brainstem. These findings point to a critical role for the midcingulate cortex in the modulation of a large cortical and subcortical network underlying its influence on sensory, affective, cognitive, and behavioral aspects of nociception, in the specific context of hypnosis.

More recently, PET imaging studies have confirmed that hypnosis, when used to produce hypnotic analgesia, can modulate the cerebral network involved in noxious perception (Faymonville et al. 2006). Compared to the resting state, hypnosis reduced pain perception in somatosensory cortex by approximately 50%. The hypnosis-induced reduction of affective and sensory responses to noxious thermal stimulation were modulated by the activity in the midcingulate cortex (area 24a'). Also, compared to normal alertness (i.e., rest and mental imagery), the hypnotic state significantly enhanced the functional modulation between midcingulate cortex and a large neural network involved in sensory, affective, cognitive, and behavioral aspects of nociception.

Thus, the observed changes in subjective experience achieved while in a hypnotic state are reflected by changes in brain function similar to those that occur in perception. These findings suggest that hypnotic alteration of perception is more than mere compliance with suggestion, but rather it involves alteration in sensory experience.

## Enhancing Hypnotizability

A number of articles have addressed the issue of enhancement of hypnotic capacity. To date, all the published papers in this topic consist of case reports, small samples, or anecdotal cases, making it difficult to generalize the results. Efforts to enhance measured hypnotizability through behavioral training sometimes result in an increase in scores, but trait hypnotizability still accounts for three times the variance in performance (Frischholz et al. 1982a). Nevertheless, the limited data available suggest that sensory deprivation (Sanders and Giolas 1991) and certain stimulant psychotomimetic drugs (Sjoberg and Hollister 1965) may enhance hypnotic responsiveness. In summary, there are no well-conducted studies proving that any particular technique, device, or substance may enhance hypnotic capacity. In fact, every study conducted so far seems to suggest that hypnotizability may not be enhanced (Page et al. 2002).

Whether high hypnotic ability enhances other forms of alternative healing or just predicts it is not clear. Nevertheless, Lu and Lu (1999) studied the combined effect of acupuncture and hypnosis. Their findings suggest that there is synergy between the two treatment modalities. In their study, hypnosis augmented the effect of acupuncture, resulting in better treatment outcomes. Similarly, hypnosis can be used to enhance the effect of other therapeutic techniques such as cognitive–behavioral therapy (Allison and Faith 1996, Bryant et al. 2005, 2006, Frischholz et al. 1982aa, Kirsch et al. 1995), biofeedback (Frischholz and Tryon 1980, LaRiccia et al. 1985, Tellegen 1981), acupuncture (Katz et al. 1974, Knox and Shum 1977, Loitman 2000, Lu et al. 2001, Lu and Lu 1999), relaxation techniques (Covino and Frankel 1993, Garvin et al. 2001, Isham 1962, Morrison 1988, Spira and Spiegel 1992), meditation-based techniques (Biswas et al. 2000, Brown et al. 1982, Delmonte 1990), and other behavioral techniques (Brown and Fromm 1987).

## Conclusion

Hypnosis is a natural state of mind. As a trait, it can be measured and mastered. Even though it occurs naturally, not every body has the same hypnotic capacity. It involves the ability to concentrate intensely, the capacity to receive new information, and the flexibility to change behavior. The capacity to experience hypnosis constitutes a therapeutic resource in the patient that can be mobilized by formal hypnosis during the therapy session and self-hypnosis exercises afterward. Strategies such as cognitive restructuring under hypnosis can help patients alter their perspective on their symptoms by experiencing symptom resolution as an occasion to enhance their sense of mastery. Many therapeutic approaches using hypnosis involve changing the patient's perspective on the relationship between the psychological and the physical state, dissociating mental from physical stress and suffering (i.e., pain), adopting a stance of protectiveness toward the body rather than fighting destructive urges (i.e., quality of life vs. smoking), or learning to see sudden discontinuities in consciousness (i.e., flashbacks and episodes of dissociation) as understandable and controllable hypnotic phenomena.

Training patients in the use of self-hypnosis can facilitate the therapeutic process. This use of hypnosis can communicate the therapist's desire to enhance the patient's mastery and independence. Thus, patients can learn to use their hypnotic capacity rather than be used by it. This newly developed ability can be understood as an exercise in self-control rather than submission to the will of the therapist. It can be used to enhance control of somatic processes, reactions to anxiety-provoking stimuli, and impulsive behavior.

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CHAPTER

# 95 Behavioral Medicine

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As illustrated in the case example, a patient's emotional and behavioral responses to illness may be as important to address as the concurrent medical condition. Challenging patient presentations are common across a wide range of medical settings—from inpatient wards to outpatient clinics, from primary care clinics and various medical specialty practices. Some patients are relentless in their presentations of unexplained symptoms. Many of these patients often demonstrate a corresponding high level of emotional and physical disability and distress that further complicate medical efforts and cloud effective treatment planning. Other patients fail to engage in their medical care appropriately despite ongoing efforts from their healthcare providers. Examples include the patient with consistently uncontrolled diabetes, the patient who continues to smoke despite rapid progression of chronic obstructive pulmonary disease, and the patient who goes through much effort to avoid necessary medical care as illustrated in Case Example 1. Healthcare providers can become perplexed by these types of patients. They often ask, "Is there a medical explanation for their patient's reactions or is it psychogenic?" While this seems like a simple and obvious question to ask, the answer is often neither simple nor obvious. Nonetheless, the benefits of psychological interventions have been demonstrated to offset costs associated with various medical conditions. In a classic meta-analysis of 58 controlled studies and the Blue Cross/Blue Shield Federal Employee Plan, Mumford and colleagues demonstrated an 85% reduction of total healthcare utilization, primarily through a reduced inpatient stays (Mumford et al. 1984). Thus, the need to provide holistic healthcare that attends to the emotional and physical well-being of the patient is evident.

Behavioral medicine is one approach to address the overlap between health and human behavior. In this chapter, we provide a general introduction to behavioral medicine for the healthcare provider who may have a limited or extensive understanding of traditional mental health concepts and techniques. A brief summary of key historical movements and the events leading to the formal emergence of the field of behavioral medicine are reviewed to provide the reader with a solid understanding of the foundation and principles upon which behavioral medicine rests. Next, we seek to provide the reader with a sense of how the behavioral medicine specialist approaches clinical situations. We provide a brief overview of selected content areas of historical significance or novel interest within the field of behavioral

**Case Example 1**

A 55-year-old married real estate salesman was brought to the emergency room with a symptom similar to what he experienced 6 months earlier when he had a myocardial infarction. His symptoms began at about 10:00 in the morning when, alone at his desk, he began to experience general unease and discomfort; and then during the next few minutes growing "pressure" of his mid-anterior chest and an aching sensation down the left arm to the elbow. While he initially thought that he was having a second heart attack, he dismissed this possibility in favor of "fatigue," "gas," "muscle strain," and finally "emotional tension." He alternated between sitting quietly to "let it pass," pacing about the office to "work it off," and taking Alka Seltzer. When he could no longer deny the probability, if not the certainty, of another heart attack, a different set of values emerged as his fear of losing control over his own destiny gained ascendancy. He was finally persuaded by a coworker to seek care. By the time he was admitted to the emergency department, he was no longer having any discomfort. Thirty minutes later, however, in the midst of a continuing and stressful workup, he abruptly lost consciousness. The monitor documented ventricular fibrillation, which was successfully corrected by defibrillation and he made an uneventful recovery.

*Source:* Adapted from Engel 1980.

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medicine, albeit with the following caveat: While highlighting the impressive and pioneering efforts within the field, we readily acknowledge the dynamic and rapidly advancing status of behavioral medicine research. Thus, our review of behavioral medicine should be understood as being *representative* rather than *comprehensive*. Similarly, we provide a review of selected methods of assessment, case formulation, and treatment planning as a representative overview of techniques commonly employed by behavioral medicine specialists. Finally, we include a demonstration of how behavioral medicine techniques might be applied in a clinical setting.

## Historical Foundations of Behavioral Medicine

Even before the emergence of behavioral medicine, there have been efforts to understand the interactions between human behavior and physiology. While a comprehensive review of previous philosophical and scientific attempts toward explaining mind–body interactions is beyond the scope of this chapter, brief reviews of the historical context and key concepts preceding the establishment of the field of behavioral medicine are important to mention.

During ancient times, Hippocrates and Galen are credited for proposing the notion of *temperaments* to explain the relationship between the body and mind by categorizing patterns of human behavior according to the relative distribution of four principal bodily fluids: blood, yellow bile, black bile, and phlegm (Maher and Maher 1994, Irwin 1947). For example, an excess of phlegm was associated with a phlegmatic disposition characterized by a tendency to be slow or lazy while an excess of black bile was believed to contribute to a melancholic or depressive disposition. The concept of *dualism* emerged during the Renaissance period, primarily through the philosophical works of Rene Descartes. In his original conceptualization of dualism, Descartes posited not only the separation between the mind and body, but also suggested that the pineal gland was the site of mind–body interactions. Dualism further suggested a division of labor among healers: Physicians and other traditional healthcare specialists were expected to practice within the domain of the body, which was metaphorically presumed to be a "machine." In contrast, philosophers and theologians would address concerns of the "soul," which was presumed to continue beyond the death of the body and was readily incorporated into existing Judeo-Christian notions of spirituality. In the 19th century, Franz Gall proposed the "science" of *phrenology* based on the following beliefs: (1) the mind is located in the brain; (2) there is localization of intelligence and personality factors within the brain; and (3) well-developed intellectual and personality factors would correlate with an increase in size of the corresponding part of the brain and interpreted by impressions of the skull (Hilgard 1987).

These three earlier approaches—Hippocrates' temperaments, Descartes' dualism, and Gall's phrenology—are a few examples of prior efforts to understand the mind–body connection before the emergence of behavioral medicine. All three approaches live on in many of our theories and formulations that we consider "modern." For example, Switankowsky (2000) posits that dualism has contributed to the pervasive mechanistic and reductionistic models commonly seen in medical practices by which the locus of intervention focuses on the body to the exclusion of the "lived experience" of the whole person.

Subsequently, psychoanalytic theory has also addressed the mind–body issue. In fact, psychoanalysis came to its beginnings through a consideration of physical or somatic symptoms. Sigmund Freud and Joseph Breuer, in their *Studies of Hysteria* (Breuer and Freud 1895/1955), formulated a specific theory of mental functioning to explain the inexplicable symptoms of patients diagnosed as hysteric. The idea that symptoms of bodily dysfunction could be related to the mental phenomenon of suppressed and conflicted wishes may have grown out of the work of Mesmer and other 19th century French and German physicians, but when it was put forward by Freud and Breuer it was instantly controversial. Nonetheless, Freud's theories quickly gained popularity. His notion was that somatic involvement occurs in hysteria when psychic energy is repressed and therefore dammed up and becomes discharged by excitations through somatic realms. Freud also pointed out that the symptoms have symbolic meaning. This work was taken to extremes by some of his followers who applied it to various medical conditions—including Ferenczi, Dunbar, Borsch, Greenacre—all of whom developed various aspects of the relationship between psychoanalytic ideas and physical diseases.

Franz Alexander's work was influential in his time. He put forward the concept of *specificity*, alleging that the route of influence of the emotions, especially those based on mental conflict (and defense against the conscious realization of these conflicts) between unconscious wishes and the conflicting imperatives that opposed them, was through the autonomic nervous system. He had a specific psychodynamic formulation for particular illnesses. Other psychoanalytic thinkers followed. Alexander Wolff in the 1940s attempted to relate illness to life stress. Karen Horney and others emphasized the role of culture in the development of psychosomatic illness. However, these theories slowly lost ground to increasing knowledge of specific biological mechanisms of illness. The concepts such as unconscious conflict, repression, and temperament were no match for the specificity and experimental rigor of later biologically based knowledge in understanding and treating medical illnesses. For instance, the specific formulation of the role of oral fixation in duodenal ulcer disease ultimately fell to the explication of the role of the *helicobacter pylori* bacteria. Likewise, other illnesses yielded to biological mechanisms, though the role of emotions in the form of nonspecific influences of stress through corticosteroids and the pituitary–adrenal axis as well as the link between the psychological and immune systems are still present. As these theories of causality based on intrapsychic organization waned in influence, new directions emerged.

In the early part of the century, the need for behavioral approaches to health and disease resurfaced. One variation of this movement contributed to the parallel development of the related fields of *consultation and liaison (CL) psychiatry* and *psychosomatic medicine*. CL psychiatry began when certain hospitals explored the usefulness of psychiatrist consultants for their medical and surgical patients. The Massachusetts General Hospital, Henry Ford Hospital, Detroit, the University of Rochester, the University of Colorado, Mount Sinai Hospital in New York, and other institutions served particular roles as pioneers (Gitlin et al. 2004). In

the 1930s, the Rockefeller Foundation under the leadership of Alan Gregg funded the start of psychiatric divisions in medical hospitals, and continued to fund the development of CL psychiatry services into the 1950s. By the 1960s most academic medical centers had CL programs. Support from the National Institutes of Health under the leadership of James Eaton was also a key impetus in the 1970s and 1980s. The Academy of Psychosomatic Medicine became the chief professional group for the field. In 1987 training requirements in CL were instituted for psychiatry residency programs in the United States. Today, all residency programs must include at least 2 months of training in CL psychiatry. In 2002, CL psychiatry was recognized by the American Board of Medical Specialties as a subspecialty of psychiatry albeit under the controversial term *psychosomatic medicine* (Gitlin et al. 2004).

Even though CL and psychosomatic medicine are closely related to behavioral medicine, the three disciplines are *not* identical and have evolved from different yet converging movements. All three disciplines recognize the critical interplay of psychological, social, and physiological factors and often share similar clinical approaches. However, CL also includes areas of medical and physiological function less related to behavior *per se*-–including medical effects of psychiatric conditions and medications. Compared to behavioral medicine practitioners, CL psychiatrists and psychosomatic medicine specialists work in acute situations with patients who are already ill and often admitted to the hospital. Consequently, most medically ill patients do not receive continuing care from specialists in CL. In contrast, outpatient services and ongoing follow up are more characteristic of behavioral medicine specialists. The following section will provide further details on the origins of the field of behavioral medicine.

## The Beginning of Behavioral Medicine

The term "behavioral medicine" was likely first coined to describe biofeedback and its use for the treatment of medical conditions such as asthma and headaches (Birk 1973). However, this narrow definition was quickly supplanted by definitions of a field characterized by explicit emphasis on the integration of science of behavior with a focus on behavioral interventions in the context of health and illness. An important distinction with the existing field of psychosomatic medicine was also made that emphasized the behavioral science, as opposed to the biomedical science, roots of behavioral medicine, and this distinction almost certainly served a key role in defining and advancing this new enterprise (Gentry 1984).

Given our affiliations with Yale University, we have been particularly sensitive to the legacy that our predecessors have had in the field of behavioral medicine. For example, the efforts from two pioneering researchers—Gary E. Schwartz and Stephen M. Weiss—spearheaded the genesis of the field of behavioral medicine through their efforts to bring together a collaborative group of researchers at what would later be known as the *Yale Conference on Behavioral Medicine*. The impetus for their efforts drew from two distinct, yet interrelated, trends. First, scientists as well as the public at large were developing an interest in the interactions between behavior and health. However, there was no formal mechanism to evaluate and ultimately fund research that addressed these mind–body interactions. Second, the emerging interest in health and behavior interactions had not yet crystallized into a cohesive area of specialization with a foundation in theory and research as well as the development of clinical applications. It was their hope that by providing structure and definition to the evolving interest in health and behavior, a formal interdisciplinary field could be established and recognized by the public, researchers, and funding agencies (Schwartz and Weiss 1978a).

**The Amended Definition of Behavioral Medicine**

Behavioral medicine is the *interdisciplinary* field concerned with the development and integration of behavioral *and* biomedical science knowledge and techniques relevant to health and illness and the application of this knowledge and these techniques to prevention, diagnosis, treatment and rehabilitation (Schwartz and Weiss 1978).

*Source:* Schwartz and Weiss (1978b), p 250.

During the Yale Conference on Behavioral Medicine (Schwartz and Weiss 1978a) held in early February of 1977, the diverse group of behavioral and biomedical scientists met with the intentions of defining "behavioral medicine" and identifying goals and recommendations that would guide the development of this new field. This group initially defined "behavioral medicine" with the explicit emphasis on the importance of addressing health and illness within an integrated interdisciplinary and scientific framework as well as the recognition that contributions to specific "subareas"—such as behavioral interventions to improve health—would likely develop and should be included within the larger field of behavioral medicine. Topics related exclusively to areas of traditional behavioral research and thereby lacking any clear link with physical health—such as mental illness, substance abuse, mental retardation, and social welfare problems—were explicitly excluded from the original definition of behavioral medicine. Attendees also actively sought to distinguish behavioral medicine from psychosomatic medicine. Psychosomatic medicine was seen as a field dedicated to identifying behavioral factors that indirectly mediate biomedical endpoints. In contrast, behavioral medicine established behavioral factors as also being able to *directly* interact with physiology to contribute to health and illness. The emphasis on the integration and synthesis of the mind and body were clearly evident in the discussions of the forefathers of the newly evolving interdisciplinary field. To further highlight the unique aspirations of the field of behavioral medicine, the attendees also proposed to create a new peer-reviewed journal and new professional society to meet its objectives.

In a second meeting of many of the original Yale conference attendees and others at the Institute of Medicine, National Academy of Sciences, the following year, the interdisciplinary nature of the field was further emphasized and an amended definition for the field of behavioral medicine was adopted. The ramifications of increased emphasis on integration of behavioral and biomedical factors had profound influences. In essence, the field of behavioral medicine

sought to extend *beyond* the issue of mind–body dualism and instead view all phenomena as cohesive integrations of biomedical and behavioral elements that could not be separated. In essence, efforts to describe health or illness as resulting exclusively from biological (or conversely, psychosocial) factors would be rejected. Moreover, this same conceptualization stood in sharp contrast to earlier efforts to exclude traditional psychiatric illnesses from the domain of behavioral medicine. With the advent of preliminary data suggesting possible underlying neurobiological contributors to mental illness, it was recognized that psychiatric disorders also likely arose from an inherent synthesis of contributing biological and psychosocial factors. Hence, the increased focus on integration of traditional mind–body issues precluded the need to limit the field of behavioral medicine to the study of diseases traditionally conceptualized as physical (vs. psychiatric) disorders (Schwartz and Weiss 1978).

In quick succession following this second meeting, significant developments secured the future of the field. In 1978, the *Journal of Behavioral Medicine* was first published, a permanent National Institutes of Health Study Section on Behavioral Medicine was created, and behavioral medicine branches of the National Heart Lung and Blood Institute and the National Cancer Institute were quickly established (Schwartz and Weiss 1978). In that same year, the *Society of Behavioral Medicine* was organized as a "multidisciplinary organization of clinicians, educators, and scientists dedicated to promoting the study of interactions of behavior with biology and the environment to improve the health and well-being of individuals, families, communities, and populations" (The Society of Behavioral Medicine; www.sbm.org). By 1984, numerous edited and single authored volumes were published that further served to define the field's scientific and scholarly roots, its scope, and an agenda for future research, education, clinical application, and policy (Gentry 1984, Ferguson and Taylor 1980a, 1980b, Ferguson and Taylor 1981, Turk et al. 1983).

Thirty years following the Yale Conference on Behavioral Medicine, the field of behavioral medicine is clearly alive and well. The strength of the field can be judged through a consideration of its impact on life in the Western societies. For instance, it is now almost universally accepted that behavior plays key roles in the development and perpetuation of disease and illness, and that changes in behavior can promote health and well-being, reduce risk for the development of disease, promote recovery from acute illness, and enhance adjustment and adaptation to persistent health problems. Significant advances in several health-relevant domains across the entire lifespan have been informed by explicit attention to behavioral factors. There is strong evidence that behavioral interventions can improve health outcomes across several domains including, but not limited to, preventing disease onset (Kalichman 1998), decreasing pregnancy complications (Walker et al. 2002), and enhancing the immune responses (Kiecolt-Glaser et al. 2002).

Finally, a few additional developments serve to highlight more recent advances of the field. On July 1, 1995, the Office of Behavioral and Social Sciences Research (OBSSR) was established within the NIH to further institutionalize an emphasis on research at the interface of behavioral and social sciences and health-relevant concerns and to provide oversight for this focus. Additional premiere scientific journals that publish behavioral medicine research have appeared over the past three decades, including the *Annals of Behavioral Medicine*, the official journal of the Society of Behavioral Medicine. Not surprisingly, the field now has a strong international scope as manifest by the International Society of Behavioral Medicine and the *International Journal of Behavioral Medicine.* In the last several years, the American Psychological Association has recognized clinical health psychology, a discipline-specific enterprise closely linked to the field of behavioral medicine, as a specialty within the professional practice of psychology. Finally, the recent adoption by the American Medical Association of new Health and Behavior Assessment and Intervention Current Procedural Terminology (CPT) codes has been identified as an important advance that permits billing for behavioral medicine services that are linked with medical, rather than psychiatric, diagnoses, in a manner that is entirely consistent with some of the key principles and definitions of the field.

## Theoretical Foundations within Behavioral Medicine

Behavioral medicine emerged from empirical evidence linking behavior and health that began to expand rapidly in the 1970s. Several overlapping theoretical perspectives served primary roles in informing the bulk of the research as well as the practice of behavioral medicine. Many of these theories—either in their original version or a revised re-formulation—continue to guide research and practice within behavioral medicine.

Proponents of *behaviorism* (Brady 1981) and *cognitive social learning theory* (Bandura 1977) cited the experimental analysis of behavior and a growing body of research on the efficacy of behavior therapy and behavior modification targeting the evaluation, prevention, management, and treatment of disease and physiological dysfunction. As the field continued to emerge, proponents of a *cognitive–behavioral* perspective articulated and emphasized a primary role of cognition, particularly appraisals, as determinants of the ways that individuals—primarily patients and/or their significant others—define health, illness, and disease. For example, cognition has an influential role in determining if a person decides to engage in health-promoting behaviors, how a person might respond to symptoms and incapacities associated with illness and subsequently engage the assistance of the healthcare system and/or community, as well as directly influencing illness and disease (Turk et al. 1983). Ultimately, the utility of these models continues to inform scientific inquiry, including the articulation of testable, meaningful hypotheses about causal and explanatory links between behavior and health and/or illness. These models have also contributed to the rapid and continued growth of the field.

*Systems perspectives*, particularly the *biopsychosocial model*, also had an influential role (Engel 1980, Engel 1977). The biopsychosocial perspective, advocated persistently and eloquently by George Engle, drew attention to the inextricable and reciprocal links between health and illness, behavior, and social context. This perspective highlighted the importance of inquiry at multiple levels of the organism (e.g., molecular, organ, person, family). Additional key principles of the model include the ideas that components

of the system are hierarchically arranged, that each component has multiple subcomponents and that each component is part of a larger whole, and that change or intervention at one level of the system necessarily results in changes in other levels. Systems theory stands in direct contrast to traditional medical models of disease that are largely viewed as reductionistic and stuck in mind–body dualism. And many of the implications of systems theory are difficult to implement in the present healthcare system of research, education, and patient care. The model encourages a comprehensive consideration of multiple levels of analysis when conducting a clinical assessment and when designing a treatment plan. The relationship between healthcare providers, patients, and families is also emphasized by the model. In fact, Engel suggested that the failure to appreciate the importance of the interaction between providers and patients is a critical flaw of the medical model and the practice of medicine. Similarly, the field of shared medical decision making has emerged as another area of specialization that explicitly examines the nature of patient–provider interactions (Charles et al. 2003). The complexity of the biopsychosocial model, however, also represented a challenge to scientists and clinicians who appreciated the limits of control and establishment of causation in the laboratory and healthcare setting. As Schwartz (1979, p 552) noted,

> One frustrating aspect of general systems theory is that it not only teaches us how much we do not know but also points out how many things we should know in order to do justice to the specific problems under investigation.

Struggles to balance a commitment to a scientific basis of behavioral (OR behavior in clinical) medicine and the complexities represented in systems perspectives such as the biopsychosocial model continue to be a source of consternation for many in the field.

Schwartz (1977) articulation of a *psychobiological model of self-regulation* (and disregulation), with its roots firmly in systems theory, served influential roles in advancing both the science and practice of behavioral medicine. Schwartz's model highlighted five core components of self-regulation: (1) environmental demands; (2) central nervous system information processing; (3) peripheral organs; (4) (internal) negative feedback; and (5) (external) biofeedback (See Table 95–1). Schwartz emphasized the central role of the brain as a "healthcare system" designed to promote automatic self-regulation in the face of environmental challenges. Consistent with other systems perspectives, Schwartz further suggested that disregulation could occur at any level of the system, and that the design of interventions to promote self-regulation necessarily affect all stages or components of the regulatory system. This model of self-regulation and disregulation has served an important heuristic purpose of contributing to advances in research on biofeedback and its application in clinical settings. However, the broader influence of such thinking on investigations of self-regulatory processes and the interface between behavioral and biological systems cannot be overstated. The emergence of the field of psychoneuroimmunology is a further important outgrowth of self-regulation theory. The pioneering work of Janice Kiecolt-Glaser and others provides answers to questions such as how the experience of social stress can alter neuroimmunologic systems regulation and contribute to the common cold, influence wound healing, and influence recovery from acute illness (Kiecolt-Glaser et al. 2002).

**Table 95–1 The Cognitive–Behavioral Treatment of Illness**

Five Key Assumptions

1. People are active processors of information rather than passive reactors to environmental contingencies
2. Thoughts (e.g., appraisals, attributions, expectancies) can elicit or modulate affect and physiological arousal, both of which serve as impetuses for behavior. Conversely, affect, physiology, and behavior can instigate or influence one's thinking processes
3. Behavior is reciprocally determined by both the environment and the individual
4. If people have learned maladaptive ways of thinking, feeling, and responding, then successful interventions designed to alter behavior should focus on maladaptive thoughts, feelings, physiology, and behaviors and not one to exclusion of the others
5. In the same way that people are instrumental in developing and maintaining maladaptive thoughts, feelings, and behaviors, they can, are, and should be considered active agents of change of their maladaptive modes of responding.

*Source:* Turk (2002), p140.

The "cognitive revolution" in American Psychology in the 1970s and 1980s also had an impressive influence on the emerging field of behavioral medicine, and this influence persists. In 1983, Turk and his colleagues published a seminal volume articulating a *cognitive–behavioral perspective* on behavioral medicine and health and illness issues. The example of pain management was employed to emphasize the central role of cognition in determining adjustment, adaptation, and recovery from acute and chronic illness. Turk (2002) articulated five key assumptions that characterize the cognitive–behavioral perspective on treatment of illness and other health-related problems, although these assertions have certainly had much broader influences on behavioral medicine research and practice.

The concept of stress looms large in both the biological and social sciences. Although the concept has been around for several centuries, only in the past 60 years or so has it been operationalized to the extent that it has served heuristic ends in terms of systematic investigation, particularly in the health arena. In the behavioral medicine field, no theoretical discussion of stress has a greater impact than the *stress, appraisal, and coping model* of Lazarus and his colleagues (Lazarus and Folkman 1984). In contrast to the historical roots of the concept of stress that have characterized it as either an environmental stimulus *or* an organism's response, Lazarus emphasizes the *relationship between the person and the environment*. This interactional model takes into account individual differences in persons' biological, emotional, and behavioral responses to similar environmental events. The model proposes that *psychological stress* is a function of a person's *cognitive appraisal* of an interaction with the environment that taxes or exceeds the person's resources and endangering his or her well-being. Also central to the model is the concept of *coping* that Lazarus and Folkman define as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are

**Table 95–2 The 10 Processes of Change**

| Examples | |
|---|---|
| 1. Consciousness raising: provide information | 6. Stimulus control: remove triggers from environment |
| 2. Dramatic relief: examine and express feelings | 7. Helping relationships: elicit social support |
| 3. Environmental reevaluation: consider impact on others | 8. Counter conditioning: substitute with an alternative behavior |
| 4. Social liberation: pass laws to facilitate change | 9. Reinforcement management: reward progress |
| 5. Self-reevaluation: consider impact on self | 10. Self-liberation: commit to new behavior |

*Source:* Velicer et al. 1988.

appraised as taxing or exceeding the resources of the system" (p 141). This comprehensive model has its historical roots in a broad array of theoretical perspectives and empirical evidence. It continues to be refined and asserts influence on the field of behavioral medicine from basic studies of mechanisms underlying the development of disease to public health campaigns informed by population-based studies of health risk behavior modification and health promotion.

The *transtheoretical model (TTM) of behavior change* (Prochaska and DiClemente 1984) has been offered as an integrative theoretical model that may help to explain differences in persons' success during treatment for a range of psychological and physical health problems. The model was developed as a result of a comparative analysis of influential theories of behavior change that culminated in a "systematic integration" of theories. This comparative research identified 10 distinct processes of change that individuals used at different times (stages) in their behavior change (e.g., developing conscious awareness of unconscious dynamics from Freudian theory, contingency management from Skinnerian theory, and helping relationships from Rogerian theory). The TTM was based on cognitive concepts such as emotions, feelings, beliefs, and attitudes and provided an alternative to a number of established theoretical frameworks including those articulated above. The core constructs of the TTM are the processes of change, decisional balance, self-efficacy, and temptation. Each construct represents an important dimension in terms of explaining how and why individuals make health-related behavioral changes. This model posits that individuals go through specific "stages of change" when attempting to modify a certain behavior and that they vary in terms of their "readiness" or how prepared they are to make a behavioral change. The stages are typically described as *precontemplation* (no intention of behavioral change in the near future), *contemplation* (thinking about the possibility of behavioral change at some point in the future but have yet to commit to taking action), *preparation* (actively considering making changes in their behavior within the next month), *action* (active work toward desired behavioral change including modification of environment, experiences, or behavior), and *maintenance* (ongoing, active work to maintain changes made and relapse prevention). Research has suggested that persons who successfully change their behavior may use different behavior change strategies or processes of change to progress from one stage to the next (e.g., increasing insight into unconscious intrapsychic dynamics, catharsis, and counterconditioning)—an observation that has implications for tailoring interventions to specifically target persons in a specific stage to promote or motivate "forward stage movement." Not surprisingly, this model has been influential in encouraging the investigation of its validity and utility in promoting health-relevant behavior change such as tobacco use cessation, promotion of exercise, weight management, improved lipid control, cancer screening, and self-management of pain, and other health concerns.

> When we speak of psychological processes and physiological processes, we are speaking of different ways of approaching one phenomenon. The phenomenon itself is not so divided. In this sense, there is neither psychogenic or somatogenic disease, but only disease.

*Source:* WHO (1964), p 6. This particular report was submitted by the WHO Expert Committee on Mental Health following their 13th meeting.

Upon review of key theories within the field of behavioral medicine, several patterns emerge. First, these theories are empirically based. Experimentation in both clinical and laboratory settings have contributed to subsequent development of clinical applications within behavioral medicine. Second, the endorsement of a biopsychosocial perspective within behavioral medicine remains a prominent, central focus. Behavioral medicine clearly favors integration and synthesis over reductionism; hence, it stands in sharp contrast to the concepts and implications of dualism, as well as other monocausal theories of health and illness. Third and less evident than the themes noted before in the second set of patterns is the broad developmental context through which behavioral medicine seeks to understand health behaviors. Indeed, a firm understanding of proximal as well as distal causes of health and health-related behaviors is required to formulate the prototypical biopsychosocial conceptualization that defines behavioral medicine. Hence, behavior medicine focuses on health-related concerns across the lifespan with theories and applications to address health promotion and disease prevention as well as adjustment and coping to acute and chronic illness.

## Selected Health Issues within Behavioral Medicine

This section will provide a representative rather than an exhaustive review of selected topics within behavioral medicine. We have organized these topics into preventive measures and treatment of specific diseases and symptom complexes, multidisciplinary approaches to delivery of services, and special topics. In many respects, the field of behavioral medicine can be conceptualized as a large interdisciplinary umbrella that attempts to integrate biological, behavioral, and psychosocial factors in an effort to understand health and illness. Within this large umbrella, there are multiple lines of inquiry that have advanced the comprehension of the etiology, maintenance, and/or treatment of a variety of health-related problems. Examples include nicotine

use, chronic pain, insomnia, and palliative care as well as a wide array of specific disease states. There are also areas of study that explore broader issues faced within the healthcare environment that range from interpersonal factors (e.g., the doctor–patient relationship) to population-based concerns (e.g., health disparities). In this section, we present a brief overview of the various research and clinical applications within the field of behavioral medicine.

## Prevention and Approaches to Lifestyle Modification

### Smoking and Tobacco Use

An expansive body of research has established a strong link between nicotine use (including cigarette smoking) and multiple physical disorders including heart diseases, lung diseases, and several forms of cancer (Brantley and Garrett 1993, Russell and Eptein 1988), not to mention the deleterious effects on the unborn fetuses of pregnant smokers (Kleinman et al. 1988). Furthermore, recently emerging literature highlights the harmful effects of second-hand smoke (Stayner et al. 2007). According to epidemiological research, 20.8% of Americans are current smokers (Health, United States 2006) with the highest risk for nicotine dependence occurring in the first 16 years after daily smoking began (Breslau et al. 2001). The Centers for Disease Control (CDC) currently ranks nicotine use as the leading cause of preventable death in the United States, with approximately 440,000 deaths per year attributed to nicotine use ((CDC) CfDCaP 2000). The annual financial burden due to cigarette purchases *alone* for the average smoker is estimated to be $1,000 per year (Group VPSH 2005). Despite the landmark Surgeon General's Report of 1964 (US Department of Health, Education, and Welfare 1964) that conclusively documented the pervasive health risks associated with tobacco use, it remains a formidable public health concern associated with staggering financial costs across the globe—especially in areas where there is little advocacy for antismoking efforts.

Consequently, efforts to reduce nicotine use have the extraordinary possibility of not only being salubrious, but also cost-effective. Mass media campaigns including community and school-based interventions have demonstrated modest success (Flynn et al. 1994, Geller and Costanza 1992), although the efficacy of these programs at educating minority and undereducated populations has been questioned (Pierce et al. 1989). Within the United States, legislative action warning label mandates on tobacco products (Federal Cigarette Labeling and Advertising Act. Vol 15 U.S.C. 1965) and bans on radio and television cigarette advertising have been credited with the gradual decline in the prevalence of US cigarette smokers since the 1950s (Myers et al. 1981).

With medical settings, there are three broad approaches for promoting tobacco cessation: (1) the use of a nicotine replacement therapy (NRT), such as the nicotine patch, gum, or lozenge; (2) the use of prescription medications specifically for smoking cessation (such as buproprion SR); and (3) behavioral interventions (Law and Tang 1995). While all three of these broad modalities of treatment as well as provider-delivered behavioral interventions as brief as 3 minutes have been found to be effective, higher smoking cessation quit rates are associated with the more intensive treatments that include continued counseling either delivered alone or in combination with a nicotine replacement aid (Fiore et al. 2000, Fiore and Schroeder 2003). As a result, a team approach—including primary care providers as well as multiple modes of intervention including written materials, videos, telephone calls, and brief telephone and face-to-face contact with other allied healthcare professionals, in addition to standard nicotine replacement and/or prescription medications—has been advocated to address nicotine dependence (Lichtenstein et al. 1996).

### Obesity and Sedentary Behavior

Obesity is an obvious public health concern. There has been a noteworthy increase in the prevalence of obesity since the 1980s with approximately 67% of Americans between the ages of 20 and 74 being classified as overweight or obese by 2003–2004 national surveys (Gibson et al. 2006). Obesity is also associated with the increased mortality and morbidity of a variety of conditions such as hypertension, hypercholesterolemia, diabetes, coronary artery disease, congestive heart failure, stroke, gallbladder disease, osteoarthritis, sleep apnea, back pain, and certain types of cancer (Mokdad et al. 2001, Must et al. 1999). Children and adolescents who are overweight or obese are also at increased risk for hypercholesterolemia, liver problems, diabetes, as well as continued obesity throughout adulthood (Dietz 1998).

The cost of obesity due to increased healthcare utilization, and loss of productivity and/or wages earned, is estimated to be over 110 billion annually in the United States alone (Thomas 1995). Moreover, there is an emerging body of research that highlights the pervasive negative effects of social stigma and discrimination that is commonly experienced by individuals who are obese and that also contributes to reduced employment and inferior medical care (Puhl et al. 2005, Puhl and Brownell 2003, Crandall 1994, Kutcher and Bragger 2004, Pingitore et al. 1994).

Scholars and policy makers are engaged in an ongoing debate on how to address most effectively the current global obesity epidemic. An ever-growing variety of medical and commercial diet programs for weight reduction clamor for adherents with current trends focusing on overall calorie restriction, regulation of glycemic load, and targeted reduction of fats, carbohydrates, and/or sugars—either as a sole approach toward weight loss or in combination. Though each diet boasts positive results, a recent randomized clinical trial demonstrated overall modest weight reduction and decreases in health risks and little difference among highly popularized dieting approaches (Dansinger et al. 2005). Other approaches include behavioral interventions (Brownell 2004), surgical approaches including the recently popularized gastric bypass approach and the lapband procedure (Shinogle et al. 2005), as well as public policy and legislation changes aimed at restricting public access to high caloric products (Brownell and Horgen 2003).

## Specific Disease and Symptom Complexes

In this section, we discuss representative approaches to specific diseases and symptom complexes. Many of the illnesses and symptom complexes that we have chosen are chronic illnesses, and before discussing them specifically, it may be well to review briefly some of the ideas that have been put forward

about managing and caring for chronically ill patients. Wagner et al. (1996) have been substantial leaders in proposing an organized approach to those with chronic illness. Their view of the optimal approach to healthcare improvement entails six elements: (1) patient self-management support; (2) decision support to use the highest standards of evidence-based medicine; (3) clinical information systems to provide clinicians with useful data at each encounter; (4) delivery system design of a multidisciplinary team that is well disciplined in the conduct of the different roles and which communicates well; (5) use of community resources; and (6) positive interactions with the healthcare system.

In addition, the managed care industry has created an approach to chronic disease management, disease management, which is estimated to be a $1.1 billion segment of American healthcare (Web site MCM; http://www.managedcaremag.com/archives/0509/0509.qna_lewis.html). Disease management is a coordinated system of healthcare interventions and communications with both practitioners and patients, designed to educate and urge/require that prevention and evidence-based practice guidelines be followed. It is used heavily in illness in which patient discretionary behavior is believed to be important such as diabetes, chronic obstructive pulmonary disease, ischemic heart disease and heart failure, as well as asthma. The Disease Management Association of America (DMAA) has defined six essential elements of disease management: (1) population identification and orientation; (2) evidence-based practice guidelines; (3) collaborative practice models; (4) patient self-management education; (5) process and outcome evaluation and management; and (6) routine feedback reporting (Web site D; http://www.dmaa.org/dm_definition.asp). Generally, these approaches are carried out by industry and the claimed results of return on investment are not always available to be evaluated by disinterested third parties.

## Somatoform Disorders and other Unexplained Medical Symptoms

Somatoform (i.e., having the form of physical illness) disorders are marked by persistent symptoms or concerns that cannot be accounted for by diagnosable medical conditions. They are grouped together by their presentation, rather than by etiology or pathophysiology. Somatoform disorders should be distinguished from factitious disorder, which is the conscious feigning or induction of illness for the secondary gain of the sick role, or malingering, which is the conscious production of illness for objective gain. As defined by the DSM-IV-TR (Association 2000), the somatoform disorders include hypochondriasis, the continuing presence of anxiety regarding the presence of medical illness beyond any reasonable medical basis. Somatization disorder is distinguished by multiple unexplained medical symptoms in a range of organ systems, beginning before age 30 and persisting over years. Conversion disorder is the presence of sensory or motor symptoms not related to a medical condition and thought related to psychological factors, while pain disorder is similarly defined with regard to pain not due to or disproportionate to illness. Body dysmorphic disorder is unreasonable preoccupation with a defect in appearance, either imagined or beyond that objectively present. Undifferentiated somatoform disorder is the diagnosis applied to patients with unexplained symptoms persisting over more than 6 months, and all other patients with "somatoform" symptoms are lumped together as somatoform disorder NOS. The largest fraction of patients with a somatoform disorder certainly are those who fall into the undifferentiated or NOS groups (Janca et al. 2006, Barsky et al. 2005): for example, in a recent study in a general practice population 13% of patients were found to have undifferentiated somatoform disorder and 3% were found to have other somatoform disorders (de Waal et al. 2004).

Unexplained medical symptoms represent a substantial clinical problem. About 25–50% of primary care medical visits concern symptoms that lack medical explanation (Barsky et al. 2005). About 13% of patients in primary care clinics present with recurrent or persisting unexplained symptoms, meeting criteria for undifferentiated somatoform disorder (de Waal et al. 2004). Somatizing patients use approximately twice the outpatient and inpatient care that nonsomatizing patients do, even controlling for psychiatric and medical conditions (Barsky et al. 2005). Somatizing patients often generate considerable frustration in their physicians, who lack the expertise or the time to deal with the patient's unrelenting complaints.

From the behavioral medicine viewpoint, the most exciting development of the last 15 years has been the demonstration that cognitive–behavioral therapy (CBT), in individual therapy with a trained practitioner, is effective in somatoform disorders. With hypochondriasis, two randomized controlled trials of CBT, addressing illness beliefs and illness-related behaviors, have demonstrated therapeutic effects (Clark et al. 1998, Warwick et al. 1996). A recent NIMH-funded trial in 187 subjects also found modest but significant improvement (treatment effect size 0.31 at 6-month follow up), with a 6-visit intervention that was scripted in detail (Barsky et al. 2005). Therapeutic studies in conversion disorder in general are numerous but have been limited to case reports and case series, and with few true randomized controlled studies (Ruddy and House 2005). With regard to nonepileptic seizures ("pseudoseizures"), there is one open label trial of CBT that demonstrated notable effect on seizure frequency, with mean seizure frequency decreased approximately sixfold and with 13 of 16 completing subjects having at least a 50% decrease in seizure frequency (Goldstein et al. 2004). Somatization disorder was found to have some response to CBT group interventions in controlled trials (Lidbeck 1997, Kasner et al. 1995). A recent government-funded, well-manualized randomized controlled trial in 84 subjects found a 10-visit CBT intervention more effective than a control intervention, with 40% of subjects with the CBT intervention rated as at "much improved" or better, compared to 5% with the control intervention at 15-month follow up (Allen et al. 2006). With regard to the patient with multiple medically unexplained symptoms or undifferentiated somatoform disorder, several randomized controlled trials have demonstrated the benefit of CBT (Sumathipala et al. 2000, Smith et al. 2005) as well as in several disorders that are at least in part functional, such as irritable bowel syndrome or fibromyalgia (Kroenke and Swindle 2000). It should be noted that many studies have examined methods for improving the ability of primary care providers to interact with and treat somaticizing patients, but such research has also highlighted the difficulty

of teaching CBT approaches to practitioners and the usefulness of consultants with expertise in behavioral approaches in medicine (King et al. 2002).

In this chapter, we have emphasized the need for an integrated, biopsychosocial approach in behavioral medicine. Nowhere is this better illustrated than in the somatoform disorders. Somaticizing patients often have difficult personal, social, and familial circumstances, and may have other disorders, both psychiatric and medical, complicating their care. The behavioral medicine consultant may apply therapies directed toward a somaticizing illness specifically, but likely will need to take a broader view of the patient and his environment as well. In somatoform illness, a guiding principle should be to treat the whole patient first. The somatoform disorders are an exciting area of rapid development in behavioral medicine.

## HIV and AIDS

AIDS is a devastating medical event and the co-occurrence of psychiatric illness can predominate throughout the course of the illness and have a major impact on the patient's ability to adhere to the regimented, highly active antiretroviral therapy (HAART) and other aspects of medical care (Starace et al. 2002, Wagner et al. 2003). Furthermore, the course of illness can be complicated by not only the vicissitudes of the biological illness but also by the extremely stressful, co-occurring life events, thereby further complicating efforts to distinguish between AIDS/HIV symptoms that may mimic psychiatric conditions, psychosocial factors contributing to emotional stress, and combinations thereof. These include unusual infections, such as toxoplasmosis, cryptococcal meningitis, syphilis, as well as medication effects of interferon, antibiotics, antihypertensive agents, steroids, and other symptoms such as abdominal distress, chronic pain, and signs of central nervous system activation.

Nonetheless, psychiatric conditions are common among individuals suffering from HIV/AIDS and are often underdiagnosed (Asch et al. 2003). Prevalence rates of depression within the patient population range between 4 and 45%, with most estimates hovering around 36% (Basu et al. 2005). Similarly, rates of anxiety disorders can be as high as 38% among individuals with HIV/AIDS (Bing et al. 2001, Elliott 1998). Cognitive disorders including AIDS dementia complex (ADC) (Price 2002) and substance abuse can also be present. Mental illness among individuals with HIV/AIDS can be especially problematic. In order to provide the highest quality of care, the practitioners must not only address exacerbation of depression and dementia but also high risk behaviors including unsafe sex practices as well as suicidal and homicidal risks among individuals with co-occurring HIV/AIDS and psychiatric conditions (Haller and Miles 2003, Douaihy et al. 2003).

A major challenge among individuals with HIV/AIDS is the "pill burden" phenomenon associated with having a complex oral medication regime (Basu et al. 2005). Thus, special effort should be made to simplify treatment regimes and avoid unnecessary polypharmacy. Recommended psychopharmacological approaches are available for managing symptoms of depression and anxiety among individuals with AIDS/HIV that take into account not only the potential for substance use but also medication interactions with HAART (Fernandez and Levy 1991, Tonks 2003). In addition, CBT, interpersonal psychotherapy (IPT), and physical exercise have been found to be effective for managing psychiatric symptoms that often co-occur with HIV/AIDS (Fulk et al. 2004, Ciccolo et al. 2004).

## Chronic Pain

Perhaps no other area of behavioral medicine has had a greater influence on practice and policy than the field of pain management. Accepted definitions of pain highlight the multidimensional nature of pain and emphasize interactions between biological and psychological systems (Flor et al. 1990, Melzack and Wall 1982, Turk and Okifuji 2002). According to the International Association for the Study of Pain, pain is "[a]n unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merskey 1979). It is accepted as a complex perceptual experience involving all domains of persons' lives, and multidimensional and multidisciplinary approaches to pain assessment and management that attend to concomitant changes in physical and emotional functioning and overall quality of life, in addition to pain, per se, are essential components of optimal pain care (Smith et al. 2005, Dworkin and Brietbart 2004, Gatchel and Turk 2002, Turk and Gatchel 2002).

A large, broad, and growing empirical literature continues to inform sophisticated understanding of key psychological and behavioral factors that reliably influence the perpetuation, if not the development, of pain and pain-related disability. Early work focused on personality factors—such as having a predisposition toward denying emotional and/or interpersonal distress, being overly preoccupied with somatic symptoms, or displaying features associated with a "depression-prone" personality such as pessimism—that were hypothesized to be associated with pain severity and the persistence of pain over time (Smith et al. 2005, Blumer and Heilbronn 1982, Gentry et al. 1974). Laboratory and clinical studies on relationships between pain and affect continues to be a primary focus of investigation (Fernandez and Kerns, in press). Operant behavioral theory (Fordyce 1976) has been influential in emphasizing the role of social learning in the experience of pain. Specifically, the model has played an important heuristic role in informing research that has identified the role of social contingencies (e.g., expressions of sympathy from family members and friends, disability payments, prescription medications) for overt expressions of pain, termed "pain behaviors" including verbal complaints of pain and nonverbal expressions of pain (e.g., sighing, moaning), visits to doctors, avoidance of work-related activities and social responsibilities (Leonard et al. 2006, Romano et al. 1995, Weiss and Kerns 1995). Turk's cognitive–behavioral perspective (Turk et al. 1983) played an important role in encouraging research that led to the identification of cognitive factors strongly and reliably positively associated with pain severity and disability. Among factors that have the strongest empirical support are such constructs as pain catastrophizing (Turner and Aaron 2001), fear avoidance (Vlaeyen and Linton 2000), low self-efficacy and lack of perceived control (Arnstein et al. 1999, Litt 1988), and passive pain coping (McCracken and Eccleston 2003).

Significant advances have continued on the clinical assessment and management front as well, including the

proliferation of an extensive array of psychometrically sound assessment strategies including semistructured interviews, questionnaires and inventories, diaries, behavioral observation methods, psychophysiological methods, and strategies for assessing the family context (Turk and Melzack 2001). As early as the late 1960s, data began to emerge that supported the effectiveness of psychological interventions for persistent pain, either in the context of multidisciplinary pain programs or in isolation of other interventions. A range of specific psychological interventions have considerable support for their efficacy including cognitive–behavioral interventions, as well as self-regulatory interventions such as relaxation training, hypnosis, and biofeedback. Research has documented the benefits of various psychological interventions for such pain conditions as headache (Holroyd et al. 2001), low back (Hoffman et al. 2007), and arthritis (Keefe et al. 2002), among many others. One particularly influential meta-analysis of the cost-effectiveness of multidisciplinary pain care, published by Flor and her colleagues, documented the benefits of such programs on pain and functioning, including return to work (Flor and Fydrich 1992). A recent line of investigation has begun to focus on identification of predictors of change during pain treatment, the process of change, and the potential to improve outcomes through a process of matching individual characteristics with different treatments (Turk and Okifuji 2002, Kerns and Habib 2004). Although not specifically attributable to the contributions of a behavioral medicine perspective, research has informed an approach to practice and policy that encourages identification of psychiatric comorbidities and concurrent pharmacological and psychological management of common mood and anxiety disorders.

## Cancer

Psychooncology is a rich area for behavioral health practitioners as cancer is typically a frightening prospect. No matter how benign the course may appear, the general cultural imagery of cancer—with the implications of death and disability, combined with the shame and stigma—places cancer among the most dreaded human illnesses. The uncertainty of outcome and treatment combined with a potentially disfiguring or fatal illness is alarming. Distress and defensiveness of threatened mortality becomes a part of the medical situation with a diagnosis of cancer. These reactions are based on the patient's personality style, characteristic coping mechanisms, and/or cultural beliefs—all of which can be exacerbated by misinformation and fear. There is much work for the skilled and interested mental health professional in this setting.

One of the great debates has been the relationship between the onset and course of cancer and associated psychopathological states and/or characteristics. Currently, there is little evidence that particular psychopathological states precede cancer in a predictable fashion (Hahn and Petitti 1988, Dattore et al. 1980). Furthermore, there is little evidence that stress or stressful life events have any relationship to the onset of various cancers (Fox 1983).

The value placed on psychosocial care has recently shifted: The current clinical research is *less* focused on internal qualities of the patients that may contribute to the course of cancer treatment and *more* focused on identified behavioral risk factors such as smoking cessation and sunscreen use. As a result, research findings have been more promising. Holland (2004) notes that the influx of behavioral medicine in the 1970s brought a new group of researchers to psychosocial care with a desire to examine lifestyle changes and the impact of nursing care on palliative care. Clearly, certain behaviors increase the risk of developing cancer, tobacco use being among the most notable. Psychological treatments aimed toward lifestyle modification have been effective. Supportive group therapy has also demonstrated success in positively influencing important dimensions of the cancer experience, especially with respect to improvements in the quality of life and treatment response for cancer patients as well as decreased pain and distress (Spiegel and Bloom 1989, Groth-Marnat and Schumaker 1995, Fawzy and Cousins 1990).

Cancer impinges on the mental state of patients in several different ways including experiences of shock, worry, and demoralization that can evolve into subsequent depression and/or anxiety (Derogatis et al. 1985). Some people respond to the impending knowledge that something is wrong by denying illness and delaying seeking medical help (Facione 1992). In some, the risk of suicide is increased in the early stages (Harris and Barraclough 1995). Major depression can occur throughout the course of the illness, effecting 10–68% of patients (Harris and Barraclough 1995, Noyes and Kathol 1986). Such variation is a function of the heterogeneity of cancer and higher rates associated with specific cancers. However, the overall prevalence for depression in cancer patients is around 30%. Among patients who develop depression, antidepressant medications are extremely helpful. However, medication metabolism in the cancer patient should be given special consideration as medically ill patients with multiple treatments are particularly prone to alterations of enzyme inhibitory systems due to concurrent use of other agents (Kalash 1998).

A big part of the cancer care also involves providing appropriate communication, understanding, reassurance, consolation, practical assistance, emotional support, information, direction, and psychological treatment. This care is given by all members of the treatment team according to his/her role with the patient and the practitioner's skill level, according to established guidelines (Turner et al. 2005). Interventions such as CBT and IPT have also been used effectively for the treatment of depression and anxiety among patients with cancer (Noyes and Kathol 1986, Holland and Reznik 2005, Sellick and Crooks 1999). Sometimes the complications of treatment can include mental status changes associated with the toxic agents of treatment, and sedating and tranquilizing medications can be an extremely helpful intervention as the patient and family members negotiate the disorientation of delirium (Eakin and Strycker 2001).

Unfortunately, some patients with cancer may have difficulty using available services. Eakin and Strycker note that while difficulties can be related to having adequate support, it is more often the case that the patient's educational status, the nature of the existing referral and current social supports, the degree of discrepancies between patient and provider perspectives on support services, and patient's level of spirituality influence how successfully the patient is able to access care (Eakin and Strycker 2001). For instance, the providers reported referring approximately 70% of their patients to cancer support services, while only 24% of the

patients reported that their physicians mentioned any such support services. Providers also estimated that 40% of the patients actually used support services; however, less than 10% of patients actually used these services.

Folkman and Greer have proposed a theoretical orientation of promoting psychological well-being in the face of serious illness in which all practitioners treating individuals who are coping with a serious illness are encouraged to address not only psychiatric symptoms and/or emotional distress, but also psychological well-being (Folkman and Greer 2000). They provide several practical guidelines, such as creating conditions for challenge by finding out what is meaningful and matters to the patient, and then identifying relevant and obtainable goals by emphasizing opportunities for personal control. Encouragement of goal-directed behavior is also highlighted in their recommendations. Finally, it is important to maintain an environment that supports a positive mood: In a review of 44 empirical studies of cancer support groups, the high levels of patient satisfaction, high morale and other quality of life benefits short of prolonging life have been demonstrated (Gottlieb and Wachala 2006).

The two major barriers to the treatment of depression and cancer are cost and uncertainty; however, structural strategies to improve depression care in cancer patients include nursing interventions and telephone monitoring, depression screening and education, targeted prevention, development of guidelines and policy. Curiously, the importance of co-location of behavioral health services in a cancer setting has not been emphasized (Greenberg 2004).

The experience of the treatment of cancer can also have associated behavioral and psychological symptoms, sometimes leading to specific diagnoses. At times, the treatments themselves physically cause these symptoms. Radiotherapy and various forms of infusion chemotherapy certainly cause nausea, vomiting, fatigue, anhedonia, and malaise. The disfiguration—such as the mutilating aspects of surgical solutions such as mastectomy and head and neck surgery—can clearly contribute to emotional distress. In addition, interferon associated with dramatic responses has been associated with delirium (Rosenstein et al. 1999).

Sometimes the illness itself causes changes in mental state. This can be from direct impingement of the tumor in the case of central nervous system lesions or the effect of metastases, either directly into the central nervous system, or secondarily, into organs that influence CNS function, such as endocrine functions. Obviously, providers must pay attention to the needs of the family members of a person who has cancer; particularly if the identified patient is a child living with parents (Mitchel et al. 2006).

### *Genetic Counseling and Cancer*

Meiser (2005) reviews the literature on the psychological impact of counseling of patients for hereditary breast and ovarian cancer as well as hereditary forms of colorectal cancer and adenomatous polyposis and concludes that noncarriers obtain considerable benefit from the knowledge derived from the testing and that for carriers they also obtain benefit but their response is filtered through their former experience with cancer. Overall, among people attending family cancer clinics, about 50% opt for genetic testing but the number goes closer to 80% in some settings.

### *Organization of Services and Cancer*

Behavioral health services are provided by many members of the clinical team depending on expertise and role (Holland 2004, Spiegel and Bloom 1989, Holland and Reznik 2005, Folkman and Greer 2000, Mitchel et al. 2006, Thomas et al. 2004, Grossarth-Maticek and Schmidt 1984). Specialty services are best organized in such a way so that patients experience the mental health treatment as an integral part of the treatment rather than a separate aspect of treatment. Holland makes the point that patients are much more likely to feel a double stigma of cancer and mental illness if they have to go somewhere else for the treatment of the depression or anxiety associated with their circumstance of cancer.

## Some Other Multidisciplinary Approaches

### Palliative Care

Palliative care grew out of the hospice movement most likely initiated by Dame Cicely Saunders, the founder of St. Christopher's Hospice near London in the 1940s. In America, the hospice movement began in Branford, Connecticut, in 1974. Since then, the notion of palliative care gradually entered into mainstream hospital care, propelled along by a variety of patient autonomy issues, such as DNR directives, the physician assisted suicide movement, and the specialization of medicine that requires expertise in providing the *care of comfort* as well as the *care of cure*. According to the American Board of Psychiatrists and Neurologists, palliative care is a recognized subspecialty that requires additional training and qualifications. Nonetheless, the establishment of palliative care units has faced ongoing challenges largely due to anticipated costs and budgetary limitations. The well-publicized report in the *Wall Street Journal* that cited reduced total costs associated with palliative care in an academic medical center has sparked heightened interest (Naik 2004). Currently, there are several professional organizations affiliated with palliative care, including the International Association of Hospice and Palliative Care (http://www.hospicecare.com), the National Hospice and Palliative Care Organization (http://nhpco.org), and the Center to Advance Palliative Care (http://www.capc.org).

Palliative care is defined as the provision of comfort and the improvement of quality of life in the context of an illness in which cure is no longer possible or sought. The emphasis of care is on the relief of symptoms and the resolution of existential crises through reassurance, spiritual counseling, and the provision of sound medical care. Patients receiving palliative care often exhibit a wide range of physical symptoms related to their terminal illnesses—such as pain, delirium, fatigue, dysthenia, incontinence—that have profound psychological consequences for themselves, their families, and their caregivers. Moreover, it is estimated that 20–50% of patients receiving palliative care have a comorbid psychiatric condition, with increased rates of emotional distress noted especially among individuals who are experiencing significant pain and among individuals in the more advanced stages of their progressive terminal illnesses. Common psychiatric concerns include adjustment disorders, depression, anxiety, delirium, and other cognitive disorders (Gibson et al. 2006).

**Surgeon General's Report on Mental Illness**
This report recognizes the inextricable, intertwined relationship between our mental health and our physical health and wellbeing. The report emphasizes that mental health and mental illnesses are important concerns at all ages. Accordingly, we will continue to attend to needs that occur across the lifespan, from the youngest child to the oldest among us (US Department of Health and Human Services 1999).

*Source:* US Department of Health and Human Services (1999), p 5.

**Table 95–3 Selected Core Principles from the 1999 Surgeon General's Report on Mental Illness**

| Selected Core Principles |
|---|
| 1. Patient and family centered |
| 2. Address health disparities |
| 3. Provide financial incentives for collaborative care |
| 4. Provide co-located primary care and mental health services |
| 5. Foster continuity of care |
| 6. Assess quality and outcomes |
| 7. Building on existing, evidence-based models |
| 8. Invest in training and information technology |

*Source:* US Department of Health and Human Services (1999).

Palliative care is a multidisciplinary approach that involves various types of healthcare specialists who share a solid commitment to clear, genuine communication during the final stages of life (Fins 2000). In addition to addressing physical discomfort and psychological distress, spiritual support is oftentimes a key component of preparing for end-of-life transitions and often provided by religious ministries who serve on the palliative care team (Ferrell 2005, Chochinov and Cann 2005). In these instances, the intense feelings that patients and their loved ones experience are not necessarily signs of psychopathology, but rather normal emotions and feelings such as fear, grief, and loss. As the patient and the patient's family deal with death, the consideration of "a good death"—meaning dying with dignity, with appropriate palliative measures, and being supported by loved ones—becomes more prominent (Chochinov 2000, Lyness 2004, Chochinov 2006). Within this context, existential issues related to the limitations of one's life frequently need to be addressed. Patients must be assisted to come to terms with the meaning of their lives and to try to reconcile any differences or problems with their family and friends.

## Integration of Mental Health into Primary Care Settings

One of the more recent initiatives within the field of behavioral medicine, integrating mental health services into primary care settings is the result of efforts of the Surgeon General who published *The first Surgeon General's Report on Mental Illness* in 1999, Dr. David Satcher (US Department of Health and Human Services 1999).

This landmark report includes several key features. First, it takes the somewhat provocative stance that mental and physical health concerns are interrelated. Moreover, efforts to separate the mind from the body are not only oversimplistic, but misguided. Second, this report emphasizes that mental illnesses are genuine health concerns with significant negative effects both for the individual and for society at large. Nonetheless, it explicitly recognizes the wide range of effective treatments for most mental health concerns and the unfortunate fact that many Americans do not obtain such treatment. The report ends with a call to action to resolve the myriad barriers that prohibit individuals from obtaining needed mental health services (US Department of Health and Human Services 1999).

One response to this call to action was the 2000 Surgeon General's Working Meeting on the integration of mental health services and primary healthcare (DHHS 2001). Prevalence estimates suggest that at least 25% of patients who seek primary care services also meet criteria for a psychiatric illness (Barrett et al. 1998, Olfson et al. 1997) and approximately 70–80% of all primary care visits address mental health concerns as a primary or secondary complaint (Von Korff et al. 1998, Von Korff and Simon 1996). It is clear that primary care providers are "a critical link" (US Department of Health and Human Services 1999) in pioneering efforts to identify and treat a broad spectrum of mental disorders.

Clearly, the integration of mental health resources within primary care settings represents a revolutionary, cutting-edge opportunity for behavioral medicine to address the recurrent mental health needs often seen in primary care settings. Most recently, the White River Junction model has been commended not only for its progressive integration of a full range of behavioral health interventions within a VA primary care setting, but also for its ability to demonstrate increased overall access to mental health services through integration (US Department of Health and Human Services 1999). The basic premise of this model includes embedding mental health providers within primary care clinics who could provide immediate access to psychiatric services for patients with a wide range of mental health concerns. Similar approaches have demonstrated improved outcomes for addressing depression and alcohol use issues treated through integrated, collaborative approaches as well as a sense of overall decreased stigmatization of their mental health concerns and increased success with mental health screenings (Bartels et al. 2004). Such increased efforts to address depression are taking hold within primary care settings and with just cause: Depression is often present among 6 out of every 10 patients seen within a primary care setting yet often unrecognized by primary care practitioners (Katon and Schulberg 1997). In fact, the majority of individuals with depression receive treatment outside the traditional mental health environment and within primary care clinics (Coyne et al. 1994, Reiger et al. 1993). This finding alone suggests that increased efforts to identify depression within the primary care setting will likely lead to improvements in treatment (Pignone et al. 2002).

## Technology in the Future of Behavioral Medicine

The proliferation of technology in the home, workplace, and a wide range of public settings is evident, especially within highly industrialized nations. Undoubtedly, such technology is becoming ever-present within the healthcare system and can influence—directly and indirectly—health

and wellness. A comprehensive overview of the impact of technology on behavioral medicine is beyond the scope of this chapter; however, we present a brief introduction to a particular example of the use of technology within the field of behavioral medicine to illustrate some of the promise of the new technology.

One particularly timely and relevant example is the use of Geographic Information Systems (GIS) within behavioral medicine. GIS is a technological tool for linking environmental, social, behavioral, and health-related data for more meaningful interpretation. As a result, findings can be displayed not only by traditional numerical and statistical methods (e.g., frequency tables, means, standard deviations, etc.) but also within a graphical representation of their physical surroundings. For example, intersections that are prone to automobile accidents can be displayed on a map that also accounts for the frequency of such accidents per site. The impact of this type of graphical data representation for health promotion is highly promising due to the inherent parsimony. Extending the same automobile accident example, GIS data can be used to monitor driving behavior, educate the general public, inform legislation and public policy, as well as guide community-based health promotion interventions (Thomas 2007).

Similarly, ecological momentary assessment (EMA) is another example of the use of technology in behavioral medicine. EMA is an in vivo technique for obtaining self-report data that employs specialized software specifically designed to interface with existing technological devices—such as personal digital assistants, cellular phones, or similar electronic devices. Compared to existing mechanisms for obtaining self-report data, data obtained through EMA is believed to be more timely, more accurate, and less susceptible to recall bias and faked compliance (Cooney 2006). Although EMA has only recently been incorporated into behavioral medicine research, the promise for further development of technology to promote health and behavior in research and clinical settings remains strong.

## The Practice of Behavioral Medicine

### Clinical Evaluation and Interviewing

The evaluation in behavioral medicine will include examination and history as in other healthcare areas, but a broad view of the history of the patient in context will be taken (Blumenfield and Strain 2006, Levenson 2004). The patients' spontaneous accounts frequently are complex and may not initially reveal a full history. The behavioral medicine specialist will be interested not only in symptoms but also in the circumstances in which they occur and the psychological, behavioral, and social responses they elicit. Understanding the patient's view of his diagnosis and treatment may be important in securing full adherence with treatment. Collateral information from family will help to reconstruct the context of the patient's illness and to understand the patient's function in the real world. The evaluation will include behaviors with delayed but important long-term health consequences, such as smoking or exercise. The evaluation in behavioral medicine will examine aspects of medical history that receive inadequate attention from our crisis-oriented healthcare system. A full evaluation is a basis for correct diagnosis and treatment, but also reassures the patient that he has been heard. This may be a critical first step in treating the difficult or somaticizing patient.

The evaluation will likely require the review of medical records and contact with other healthcare providers. Past medical records may be needed to complete a complicated history or verify diagnostic results and treatment. Patients may report a positive diagnosis that in fact was negative or ambivalent, or conversely a positive diagnosis may have been missed. A history of repeated unexplained symptoms or repeated doctor visits may reveal a somaticizing or factitious diagnosis. Contacting other healthcare providers may be essential in clarifying the history, and also in understanding the interaction of the patient and the healthcare system, which is a key domain in behavioral medicine. The consultant will need to obtain consent required by local or national laws. The provisions of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 have eased restrictions on the exchange of information among current providers (Hodge 2003). It is advisable to clarify with the patient at the outset that effective care can be provided only with free communication among all providers of care and to seek the patient's consent to freely share clinical information.

A broad view of the patient and his context is also essential because the behavioral medicine specialist is often called upon to diagnose and treat not only the patient but also his interaction with the healthcare system. The behavioral medicine specialist may need to be sure that all healthcare providers are aware of each other, the full medical history, and the treatments they are pursuing. He may need to detect and repair problems in communication among the patient and providers. The behavioral medicine specialist may be the healthcare provider best able to assess the patient as a part of a larger system and should play an assertive role in working with other providers to coordinate his patient's care.

In addition to assessment of the patient, the attitude and approach of the clinician is important. Recently, the concept of mindfulness has been brought forward by Epstein. Mindfulness skills can help the behavioral medicine specialist listen attentively to the patient's pain and suffering, make evidence-based decisions, and clarify values and assumptions. Epstein (1999) conceptualizes mindfulness as being willing to examine and set aside categories and prejudices and instead to approach situations with a "beginner's mind." The characteristics of mindful practice include active observation of oneself and the patient within the social context; an ability to draw on "peripheral vision" and feelings, thoughts, and memories just below consciousness and just outside of attention; and critical curiosity and courage to see the world in its reality rather than what one hopes or wishes it to be. The mindful practitioner is able to attend to his or her own mental processes in a neutral fashion during the everyday job of caretaking. While mindful practice is fundamentally invisible, it nonetheless allows the practitioner to react to the patient's condition with a robust and empathically accurate understanding and provides additional rich information about the patient's experience. In this context, the mindful practitioner is able to make evidence-based decisions consistent with the values of the patient as well as the practitioner; values that entail compassion, insight, and adherence in a flexible fashion, to the role of the physician healer.

## Clinical Assessment and Use of Self-Report Devices

It is not surprising that reliable assessment of key constructs looms large in the field of behavioral medicine given its historical and contemporary roots in behaviorism and cognitive-social learning theory and the emphasis of these perspectives on quantification and measurement. The enormous array of assessment strategies that have been developed for use in clinical and research settings reflect the interdisciplinary nature of the field, its emphasis on the biopsychosocial model and interacting systems, the multiple theoretical and clinical perspectives that inform the field, and its broad scope. A comprehensive review of even the most commonly employed strategies is well beyond the reaches of this chapter.

Central to assessment in behavioral medicine is a keen awareness that health, disease, and illness are ambiguous concepts that vary in meaning and experience that often have little to do with "objective" physical evidence (Mechanic 1968). Given this assumption, it may seem obvious that efforts to improve the reliable measurement of constructs that are critical to the field of medicine, such as symptoms, stress, and adherence, among enumerable others, are critically important. Crucial to investigation and clinical assessment is the ability to develop sensitive strategies that will (1) delineate individual and group differences and (2) assess factors that potentially mediate or moderate these differences (Turk and Kerns 1985). Much of the development of assessment strategies in the field of behavioral medicine has been specifically informed by these goals.

Consistent with an interdisciplinary field, assessment in behavioral medicine encompasses strategies that are most consistent with specific disciplines and research and clinical methodologies commonly employed within these disciplines. The fields of epidemiology and public health, for example, have contributed to the development of a broad array of specific tools and general strategies for the assessment of psychosocial epidemiology and health-related quality of life. The field of psychophysiology continues to contribute increasingly sophisticated and precise strategies for the detection, amplification, and quantification of physiological systems including, most importantly, the functioning of the central and peripheral nervous system. Sociology, social ecology, social psychology, and family medicine have played critically important roles in drawing attention to the measurement of context, including the structure and function of family, community, and other social networks.

Dominating the field are assessment strategies informed by clinical (health) psychology's roots in development of reliable tests and measures. Although few would argue that the primary and "gold standard" assessment strategy in behavioral medicine settings remains the clinical interview, the use of self-report strategies such as questionnaires, inventories, and diaries and other self-monitoring procedures are commonly used to supplement the interview in many clinical settings, and these strategies are often the preferred methods in research settings due to their emphasis on quantification, brevity, face validity, and ease of use. Methods for the direct observation of health-relevant behaviors have also been developed primarily for use in research settings, although some of these strategies, such as those used by nursing staff for the assessment of pain among persons with severe dementia or others who are unable to orally communicate about their experiences of pain, are increasingly utilized.

Commonly employed self-report strategies continue to include measures originally developed outside the field of behavioral medicine for use with general populations such as the Minnesota Multiphasic Personality Inventory and the Beck Depression Inventory. However, the past 30 years have seen the proliferation and increasing use of health-specific measurement strategies that were developed for addressing behavioral medicine questions and problems and were validated using specific populations experiencing the problem. This large group of health-relevant measures can be further classified as either standardized measures for use in clinical settings versus those that were developed solely for research purposes, and those that are enduring personality (trait-like) measures and those that are situation-specific (state-like) measures. For example, in the area of pain management, a large array of measurement strategies has been developed specifically for use in measuring factors important in characterizing individual differences in persons with persistent pain (e.g., measures of pain severity or pain-related disability) as well as hypothesized mediators of these experiences (e.g., pain coping, pain-related self-efficacy). In this context, several well-validated self-report questionnaires and inventories are available for the assessment of the multidimensional nature of pain (e.g., the West Haven, Yale Multidimensional Pain Inventory (Kerns et al. 1985)).

## Biofeedback

In the late 1960s and early 1970s, Neil E. Miller (1978) made what was at the time quite a controversial and provocative claim: A person could learn to control behaviors—such as breathing, heart rate, and other automatic physiological responses—that were under the control of the autonomic nervous system. Such a claim drew expected criticism until research on what would later be called *biofeedback* provided the necessary supporting empirical evidence.

Biofeedback is based on operant-reinforcement principles applied to automatic musculoskeletal responses. A feedback signal—such as a light or sound—alerts the participant if the physiological parameter under investigation is within expected parameters. Over a series of successive trails, individuals gradually gain control over the selected physiological responses and can eventually elicit the desired physiological response upon demand. Early studies on biofeedback demonstrated its clinical utility in promoting deep muscle relaxation and other autonomic responses (Budzinski and Stoyva 1969, Thornton and Van Toller 1973, Taub and Emurian 1976). Biofeedback remains a viable modality of treatment for a wide range of health issues including asthma (Lehrer 1998), arthritis (Astin et al. 2002), chronic pain (Teunissen et al. 2004), and headaches (Rains et al. 2005). While a comprehensive review of the efficacy of biofeedback across various health concerns is beyond the scope of this chapter, it is important to note that empirical studies and reviews continue to provide evidence in support of biofeedback. For example, biofeedback has been demonstrated to reduce incontinence among the elderly by over 80% and achieved significantly better outcomes than medications (oxybutynin, which lead to a 68% reduction in incontinence) or placebo (Teunissen et al. 2004). Similarly, a comprehensive review of treatments for pediatric migraines

reveals that biofeedback—used alone or in conjunction with other behavioral strategies, such as progressive muscle relaxation—is superior to all other treatment modalities including calcium channel blockers, serotonergic medications, and other pharmacological interventions (Hermann et al. 1995).

## Psychotherapeutic Interventions

As mentioned briefly throughout the previous section of this chapter, there is a wide variety of behavioral and psychotherapeutic interventions that can be beneficial in promoting health behavior change. These include approaches such as motivational interviewing (Miller and Rollnick 2002), traditional psychotherapeutic approaches such as cognitive, behavioral, and CBTs (Wolpe 1997), which have been beneficial across a wide range of health conditions such as somataform disorders (Kroenke and Swindle 2000), chronic pain (Heapy et al. 2005, Reid et al. 2003), insomnia (Zhdanova 2004), as well as improving adherence of medical treatment (Dyer et al. 2005) as well as overall health and wellness (Grossman et al. 2004). This is in addition to the use of these modalities in the treatment of depression and anxiety co-occurring with cancer and HIV/AIDS as noted above.

## Psychiatric Training in Behavioral Medicine

In 1987 training requirements in consultation–liaison (CL) were instituted for all psychiatry residency programs in the United States. At this time, all such programs must include at least 2 months of full time training in CL psychiatry, and certainly in all programs residents will receive additional training in the interplay of medical and psychiatric conditions throughout. In 2002 CL psychiatry was recognized by the American Board of Medical Specialties as a subspecialty of psychiatry. Trainees must complete one year of postresidency fellowship training meeting specific standards established by the American Council on Graduate Medical Education, and pass a written examination in the field. The name chosen for the subspecialty, Psychosomatic Medicine, has been controversial. However controversial the new term may be, it does acknowledge the inextricable link of psyche and soma in human health.

## The Application of Behavioral Medicine: A Case of Chronic Pain

The case of FL is taken from the seminal paper by Blumer and Heilbronn (1982) in which they offered a compelling articulation of a prevailing model of the time of chronic pain of uncertain origin as a variant of depressive disease, sometimes referred to as "masked depression." According to this framework, and informed by prior descriptions in the clinical and theoretical literature, these authors suggest that once efforts to identify a neurological basis for complaints of pain have failed, and instead of invoking a stigmatizing label of "psychogenic disorder," Blumer and Heilbronn proposed the diagnosis of a depressive disorder with well-specified clinical, psychodynamic, and genetic/familial features (e.g., hypochondriacal preoccupation; alexithymia and denial of conflicts; history of relentless activity; current anergia, anhedonia, insomnia, and depressed mood; family history of depression and alcoholism). The authors relied on naturalistic, observational data, and uncontrolled data to support their conceptualization. Consistent with the diagnosis of a depressive variant, the authors encouraged treatment with antidepressants and behavioral modification designed to promote increased functional activity.

The case of FL provides an opportunity to consider how the various theoretical approaches described earlier might be applied clinically to assess and treat this patient from a contemporary behavioral medicine perspective as briefly described in previous sections of this chapter. From

**Case Example 2**

At 18 years of age, FL began working in an automobile factory. He regularly worked 10–16 hours a day, often 6 days a week. At 20 years of age he was married and the couple had a son. At 22 years of age, FL began to experience pain in his back, legs, and neck. The patient was no longer able to work. . . . He was referred at 24 years of age, after being in continuous pain for 2 years and expressed considerable hostile feelings about his job, stating that for nearly a year he "wanted to kill when it was not necessary," explaining that he wanted to do away with the foreman who supervised his work. FL felt that his employers and their physician did not take his illness seriously. FL stated that he had no difficulties getting along with other people . . . [However], he and his wife were feeling financially stressed. He was using no medication, but reported that he was afforded some relief from his pain when his consciousness occupied his "astral body." He was prescribed amitriptyline and after 1 month reported feeling better but continued to focus on his inability to work. With encouragement, he was able to return to his job for nearly 2 months. He soon began having "heart pain" and was concerned regarding the effect the vapors in his work environment had upon his health. He independently increased his daily dosage of amitriptyline from 300 to 500 mg daily. He began having abdominal pain as well which ended up in his having gallbladder surgery. About 6 weeks following his surgery, he returned to work for a couple of weeks but stopped reporting for work when he found his persistent abdominal pain intolerable. He stayed in treatment for the next 2 1/2 years but was never able to return to work. . . . At 26 years of age, FL became a father for the second time. Shortly thereafter, he and his wife had frequent, heated arguments over their mounting financial problems; the fights later became laden with threats and physical abuse. Thioridazine was added to his antidepressant regime; however FL failed to use the drugs properly or regularly. He began drinking a pint of scotch daily in addition to using marijuana and cocaine. . . . He continued to be volatile and abusive toward his wife. . . . In the interim, his wife had obtained employment at a restaurant and left FL the following month, taking the children with her.

*Source:* Adapted from Blumer and Heilbronn (1982) (pp 402–403).

the onset, the biopsychosocial perspective on pain and pain management would have been used to inform a comprehensive pain assessment of FL designed to develop an integrative multidisciplinary plan of care. Certainly, prior to engaging in psychological or psychiatric treatment of a "pain disorder," appropriate medical/neurological evaluation of his pain complaints is indicated and should include a detailed history, including attention to the psychosocial and cultural context, and a targeted physical and neurological examination. In the absence of any medical "red flags" indicating the potential presence of infection, fracture, or malignancy, no further medical diagnostic procedures would probably be indicated.

Given the presence of significant emotional distress and apparent functional decline, a comprehensive psychological assessment appeared to be appropriate. This assessment would almost certainly rely heavily on an extensive interview designed to identify the range of negative functional and emotional impacts of his experience of pain and to begin to engage FL in an open consideration of the possible role of similar variables as contributors to his experience of pain, disability, and distress. In addition to an elicitation of detailed description of FL's experience of pain, the interview would attempt to capture a behaviorally specific understanding of his current level of physical functioning including activities of daily living and the broader array of social and recreational functioning. Specific attention to his negative emotional experiences would almost certainly be an important focus of the interview including efforts to identify the presence of Axis I and II disorders common among persons with persistent pain such as depression, anxiety, and substance use disorders. Candidate contributing variables include the range of psychological factors described in the earlier review including negative cognition (e.g., pain catastrophizing), fear avoidance, low self-efficacy and perceptions of a lack of self-control, and passive coping, among other factors. Responses of significant others, particularly his wife and friends, to his complaints of pain would specifically be assessed, and ideally, the involvement of his wife in this discussion would be secured.

In many settings, extensive interviewing would be supplemented by the administration of a range of standardized psychological questionnaires and inventories that have been validated for use in the assessment of persons with chronic pain. Often included in this battery are measures of pain intensity and quality, pain-related interference, emotional functioning, health-related quality of life, as well as measures of the range of potentially relevant psychosocial factors described above. These measures are important for efficient and reliable assessment of numerous psychological factors that are potentially relevant for informing the treatment plan, for deriving quantitative indices of potential targets for intervention, and in developing a baseline for future evaluation of treatment efficacy. Less frequently, diaries for self-monitoring of pain intensity, mood, activity, and other variables are used to further supplement the interview and questionnaires.

Ultimately, the goal of the psychosocial assessment is the development of an integrative conceptualization of FL's experience of pain, disability, and distress and the potential relevance of a range of psychological and interpersonal factors that may be serving to perpetuate this experience. In the case of FL, a more "here and now" focus on his current reports of severe pain, his withdrawal from many previously enjoyable and productive activities, his pervasive anger, and growing tensions in his marriage would serve as primary targets for intervention. Although the description by Blumer and Heilbronn leaves unclear the most salient psychological and interpersonal contributors to these negative outcomes, the presence of pervasive feelings of helplessness and hopelessness, low self-efficacy and lack of self-control, passive and avoidant coping, and an unsupportive spouse are likely contributing factors.

State-of-the-art treatment for someone with FL's history and presenting problems would incorporate aspects of virtually each of the models in the specification of an integrated, multidisciplinary, and multidimensional plan for rehabilitation (Turk and Gatchel 2002). The specific design of the intervention would be informed by a comprehensive pain assessment based on theory-driven research that has led to the identification of common psychosocial contributors to the experience of pain, disability, emotional distress, and poor health-related quality of life (Turk and Melzack 2001). Empirical support for multidisciplinary treatment for chronic pain—especially the inclusion of psychological interventions as a key component—is strong and compelling (Hoffman et al. 2007, Flor and Fydrich 1992).

Fordyce's (Fordyce 1973, Fordyce et al. 1973) operant behavioral model is instrumental in promoting a consideration of behavioral factors and the role of social learning in the perpetuation and development of chronic pain. Fordyce hypothesized an important reinforcing role of environmental responses (e.g., expressions of sympathy from family members, attention from healthcare providers, release from work and household responsibilities, financial compensation) contingent on displays of pain and infirmity termed "pain behaviors" (e.g., complaints of pain, facial grimacing, distorted ambulation, withdrawal from activities, use of pain medications) in maintaining pain and pain-related disability in the absence of continued nociception. His model informs research investigating the role of social learning in fostering pain and interventions to shift the delivery of reinforcement to "well behaviors" such as exercise, return to work, and reduction of reliance on pain medications, and increased social, recreational, and other productive activities. A treatment approach for FL informed by the operant behavioral perspective would emphasize the use of contingency management techniques to promote similar behavioral goals (Sanders 2002). For example, the clinician might offer praise whenever FL discusses examples of increased functioning and consciously avoid efforts that might inadvertently reinforce pain-related behaviors such as encouraging increased reliance on others for tasks that FL could reasonable perform independently. In fact, it is interesting to note that this component of a comprehensive plan is evidently similar to that described by Blumer and Heilbronn in their characterization of treatment for persons with a "pain-prone disorder." For example, prior to engaging in outpatient treatment and after completion of a comprehensive pain assessment, FL and therapist would collaborate in the articulation of specific behavioral goals for treatment, including those just noted such as regular exercise and reduction of pain medications. Weekly intersession goals linked to these overarching treatment goals would be specified as "homework," and plans for accomplishing the goals would be specified. Strategies for self-reinforcement

for goal accomplishment, and certainly praise from the therapist, would be important in efforts to promote future action. Almost certainly, given the focus of the treatment on the responses from the social environment, this treatment would have encouraged explicit involvement of FL's wife in an effort to promote more positive communication overall, decreased attention to pain behaviors, and increased cuing and praise for health-promoting goals of treatment.

CBT that specifically targeted idiosyncratic, negative beliefs about pain, particularly thoughts characterized as catastrophizing and consistent with a lack of personal control and low self-efficacy related to pain management would be prescribed for FL. CBT treatment would incorporate education and encouragement to adopt adaptive pain coping skills such as activity pacing, effective use of distraction, exercise, and stress management skills in either an individual or group format. Development of anger management skills would also be indicated. Biofeedback targeting muscle tension in the paraspinal muscles of the lower back and/or more electromyographic or thermal feedback assisted mental relaxation training might also be prescribed. Pharmacological interventions, physical therapy designed to promote proper body mechanics, muscle strengthening, and overall fitness, and vocational counseling would also be prescribed. Finally, given the extent of FL's apparent problems with alcohol and other illicit substances, substance use treatment would be integrated into the overall treatment plan.

## Summary and Conclusions

Behavioral medicine formally emerged as a distinct, multidisciplinary approach toward understanding health and illness following the 1977 Yale Conference. Building upon the biopsychosocial model, the field of behavioral medicine stands in contrast to previous historical efforts to understand health and human behavior—most notably mind–body dualism. Key experimental and theoretical advancements in the study of human behavior from the classical studies on behaviorism to more recent developments such as the TTM have been readily incorporated into the dynamic and expanding field of behavioral medicine. The theoretical, empirical, and clinical implications of behavioral medicine have proliferated at a rapid and impressive rate. It is clear that the field of behavioral medicine holds much promise for continued efforts to understand health, illness, and behavior.

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CHAPTER

# 96 Psychosocial Rehabilitation

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## Psychosocial Rehabilitation

Evidence accumulated over the last several decades has led to a general consensus that schizophrenia is a brain disease or set of related diseases caused by genetic and/or prenatal and perinatal insult (Roberts 1991, Weinberger 1987). Replicated data point to problems in neural structure (e.g., enlarged cerebral ventricles, hippocampus), neurotransmitter systems (including dopamine, serotonin, acetylcholine, and glutamate, among others), neural circuitry (e.g., especially including circuits mediated by frontal cortex), and cerebral blood flow and metabolism (especially in dorsolateral prefrontal cortex, cingulate gyrus) (Selemon 2001, Thaker and Carpenter 2001).

While the definitive neurobiological substrate of the illness remains to be determined, it is clear that treatment for schizophrenia must be based at least in part on effective psychopharmacological interventions. Conversely, no extant pharmacological treatment is sufficient. Twenty percent or more of people with the illness are not responsive to antipsychotic medication, and the majority although responsive, have residual symptoms. In addition, many are substantially nonadherent. Even among those who are judged to be responsive and compliant, only a small proportion achieve adequate outcomes, including a return to premorbid levels of function. Schizophrenia is a multiply handicapping disorder marked by poor social role performance, chronic unemployment (or under-employment), excess medical morbidity and mortality, shortened life expectancy (including a markedly elevated risk for suicide), high levels of substance abuse, and increased risk for criminal victimization. Antipsychotic medications are demonstrably effective in reducing positive symptoms and have a modest effect on negative symptoms (especially on secondary negative symptoms), but they have limited impact on cognitive impairment and psychosocial functioning (Sharma and Harvey 2000). Even the new generation drugs are insufficient to restore premorbid levels of functioning, produce normative role performance, or substantially improve quality of life for most patients (Bellack et al. 2007).

Moreover, it seems highly unlikely that medication alone can be sufficient until and unless discoveries emanating from genetics and genomics lead to different and more effective compounds for pharmacotherapy. Accumulating evidence indicates that schizophrenia is a neurodevelopmental disorder in which many patients demonstrate subtle attentional, cognitive, and neuromotor abnormalities in early childhood, long before the onset of overt psychotic illness, in keeping with "neurodevelopmental" models of the illness (Cornblatt and Keilp 1994, Walker et al. 1994, Weinberger 1995). Perhaps the most remarkable investigation demonstrating this was performed by Jones and colleagues (1994) who followed up subjects originally studied as part of the Medical Research Council National Survey of Health and Development, a study of all births in England, Scotland, and Wales during 1 week in 1946. These children were assessed at multiple time points with measures of developmental milestones, educational achievement, and social-behavioral assessments. Of the 4746 English subjects, 30 developed schizophrenia by the age of 43, with cases identified and diagnosed on the basis of multiple medical record sources and direct interview data when subjects were aged 36. These subjects demonstrated delayed achievement of motor and speech milestones in infancy, lower estimated IQ scores by middle childhood, and increased social anxiety by early adolescence in comparison to the 4716 controls. These data suggest that adult schizophrenia is preceded by multiple manifestations of subtle developmental compromise across neurological, intellectual, and social domains.

The developmental consequences of the illness are magnified with the first psychotic episode in late adolescence or young adulthood. People with schizophrenia become progressively more removed from their peer group, fail to achieve (or sustain) adult milestones such as marriage, higher education, and employment, and often become socially isolated. These functional, psychosocial consequences become more severe and entrenched as illness duration increases, and result in multiple treatment needs that are superimposed on the neurobiological aspects of illness.

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While innovative new medications could potentially ameliorate (or compensate for) some of the consequences of anomalous neural development, it is unlikely that any pharmacological approach could restore normal brain function. Furthermore, no medication could undo the lifelong consequences of impaired learning, failure to master adult developmental tasks, and social withdrawal. These impairments mandate a multifaceted approach to treatment that includes an array of psychosocial strategies, of which rehabilitation plays a key role (Bellack 2004). This conclusion is supported by a series of consensus treatment guidelines, including the Schizophrenia PORT (Lehman et al. 2004a), and guidelines from the American Psychiatric Association (Lehman et al. 2004b), and the Canadian Psychiatric Association (1998), among others.

In the following sections, critical issues involved in effective use of rehabilitation and other psychosocial interventions are discussed and brief reviews of the most promising approaches are provided. The term *rehabilitation* is not precisely defined in our field. It is generally used to imply a subcategory of psychosocial treatment in which there is an emphasis on teaching/training, rather than discussion, and the focus is primarily on behaviors and functioning, rather than on intrapsychic processes (thinking and feeling). Reference is made to *psychosocial intervention* when the issues have generality to the broader domain of psychological treatment.

## Issues in the Design of Psychosocial Interventions

The potential benefits of psychosocial treatment are often not achieved in the community due to poor understanding of the special needs and liabilities of people with schizophrenia. Five factors need to be taken into account when implementing psychosocial interventions and evaluating the results: (1) timing and duration of treatment; (2) individual differences in treatment needs; (3) the role of the person in treatment; (4) the limitations imposed by impairments in information processing; and (5) the need to base interventions on a compensatory model.

## Timing and Duration of Treatment

Schizophrenia is a chronic condition that frequently has devastating effects on many aspects of the person's life and carries a high risk of suicide and other life-threatening conditions. The care of most people with the illness involves multiple efforts to reduce the frequency and severity of episodes and to reduce the overall morbidity and mortality of the disorder. Many individuals require comprehensive and continuous care over the course of their lives with no limits as to duration of treatment. Despite common agreement about the extent of chronicity and disability most research on psychosocial interventions has focused on time-limited strategies, typically in the range of 3 to 6 months. This treatment duration is generally guided more by the pragmatics of grant design than by an analysis of patient needs. Nevertheless, such brief treatments have been found to be helpful for achieving specific goals, such as teaching people how to discuss medication side effects with a physician, how to engage in safe sex, and how to communicate more effectively with family members. Research indicates that gains from such brief, focused treatments can be maintained over time (Bellack et al. 1984, Eckman et al. 1992). However, given the pervasive neurodevelopmental and psychosocial effects of the illness, these brief interventions are unlikely to produce broad-based improvement in overall functioning, or enduring changes in vulnerability to symptom exacerbations and relapse. Brief and highly focused rehabilitation programs designed to accomplish specific goals (e.g., to teach people how to negotiate with health care providers or to go grocery shopping) can be quite effective. However, most people with the illness will require intermittent booster treatment even for such circumscribed skills training programs, while others will need continuing support (e.g., prompting to perform activities of daily living) throughout their lives.

Unfortunately, the literature does not give much guidance in how to predict individual patient needs or systematically plan how long the course of rehabilitation treatment should be. Many community agencies have responded to this uncertainty by permanently enrolling people in day treatment. However, few individuals can, or do, actively participate in such endless treatment programs. They may come to the treatment center, especially if directed to do so by family members or residential managers, but that does not mean that they are actively participating or learning new skills. Our own experience, while not supported by data, strongly supports the use of time limited training curricula that address current needs and goals. The person may repeat a curriculum (e.g., begin a new 3–6-month period in social skills training) if she/he desires but this should be a mutual choice between the person and program that reflects continuing motivation and need, not a reflection of diagnosis or economics (e.g., agencies cannot bill unless the patient receives some intervention). This latter point relates to another issue addressed in the APA guidelines (Lehman et al. 2004b): timing of treatment. The guidelines contend that the illness transpires in three phases: (1) *acute*, during which the primary aim is to reduce acute symptoms; (2) *stabilization*, during which aims are to minimize likelihood of relapse, further reduce symptoms, and enhance adaptation in the community; and (3) *stable*, during which aims are to maintain or improve level of functioning and quality of life, while continuing to monitor. Rehabilitation is generally not applicable during acute stages of illness. With hospital stays often limited to a few days to one week there is little opportunity to conduct a systematic rehabilitation program, and acutely ill patients generally are unable to effectively participate in cognitive–behavioral interventions during this period.

The role for psychosocial treatment increases as the person becomes more stable and shifts from support and stress reduction to specific rehabilitation strategies such as social skills training and cognitive rehabilitation. This three stage model and associated treatment emphasis has good face validity. However, both the model and assumptions about shifting goals of psychosocial treatment are based more on anecdotal evidence and clinical assumptions than on empirical data. More research is needed on how to determine which treatments are best provided to which individuals at which times in their lives.

## Individual Differences in Treatment Needs

Schizophrenia is a heterogeneous disorder, with wide variability in symptom presentation, severity, course, and

treatment response. Indeed, the term *schizophrenias* may be more applicable. This heterogeneity has been interpreted as reflecting either multiple etiologies or multiple disease entities (Carpenter et al. 1993, Tsuang et al. 1990). It also undoubtedly reflects the idiosyncratic impact of each person's environment and experiences throughout life, which influence both how the illness manifests itself and individual differences unrelated to the core illness (e.g., comorbid vulnerability to depression or substance abuse). For example, Mueser and colleagues (1991a) found that 50% of people with schizophrenia had persistent deficits in social skill over a 1-year period, while 11% did not differ from nonpatient controls, and the remainder showed variable performance. Thus, the common assumption that everyone with schizophrenia has significant social skill deficits is true for many but not all individuals.

Similar evidence of heterogeneity exists in regard to neuropsychological deficits. People with schizophrenia, as a group, perform very poorly on the Wisconsin Card Sorting Test (WCST) (Heaton 1981), a measure of prefrontal cortical functioning, and performance deficits are associated with hypoactivation of the dorsolateral prefrontal cortex (Berman et al. 1986, Weinberger et al. 1986). Yet, as many as 20% of individuals may perform within normal levels on the WCST, and those exhibiting poor performance appear to have a broader pattern of neuropsychological deficits than those who can perform at normative levels (Braff et al. 1991, Goldstein et al. 1996). Stratta and colleagues (1997) suggest that there are important differences in how different individuals perform the task, as well as in how well they do. They subdivided subjects into good- and poor-performing groups on the basis of categories correct at baseline, and then requested them to enunciate their selection strategy on readministration. The good-baseline performers improved significantly with this technique, while the poor performers got worse. The additional task demand apparently further disrupted their already impaired ability to solve the task. There is also considerable variability in the extent to which people can be taught to improve their performance (Bellack et al. 1990a, 1990b, Wiedl 1999) and in the extent to which performance improvements generalize to other tasks (Bellack et al. 2001, Tenhula et al. in press).

In a study of patient heterogeneity that has considerable implications for rehabilitation, Bellack et al. (1999) compared groups of schizophrenia subjects with good and poor vocational outcomes on a battery of neuropsychological tests and MRI. Robust differences between the two groups in both domains were found. Individuals with poor vocational outcome performed more poorly on measures of processing speed and social judgment, and they showed evidence of reduced cortical asymmetries. These results have two implications for a consideration of rehabilitation in schizophrenia. First, the data suggest that good outcome individuals have certain strengths and basic competencies that may compensate for liabilities. It is important to be able to identify those who appear to have these competencies but who are not currently functioning well in order to provide special clinical attention, as their treatment needs should be different than the needs of those who lack these strengths. Second, the fact that poor outcome is associated with greater abnormality of brain morphology is not surprising; previous reports have documented relationships between poor outcome and ventricular size (Pearlson et al. 1984, Vita et al. 1991, van Os et al. 1995). It is also not a cause for therapeutic nihilism. It appears likely that such individuals may require very different services to achieve maximal independence than those who have much more intact cognitive performance. However, it will not be possible to develop such services in an effective manner until we have achieved a clearer understanding of the determinants of disability in schizophrenia.

In addition to the variability between individuals, significant changes occur within people over time that have a bearing on treatment needs. Younger individuals need special help in dealing with the fact that they have a serious illness which may interfere with their personal goals and their ability to achieve independence, a problem that may contribute to their high vulnerability to suicide and substance abuse (Caldwell and Gottesman 1990, Test et al. 1989). Older people may adjust to the difficulties of the illness through withdrawal or positive coping strategies (Strauss 1989, Wing 1987), but they face unique problems of their own. For example, as parents grow older they are generally less able to continue caring for an offspring with schizophrenia, necessitating a shift in care taking responsibility to either siblings (Horwitz et al. 1992) or the mental health system. A survey of the needs of individuals with schizophrenia in regular contact with their families indicated that concern over what happens when a parent dies was ranked fourth highest out of 45 topics (parents ranked this concern fifth) (Mueser et al. 1992).

Taken together, these data underscore that treatment planning must be individualized. While this might seem like a given, many outpatient treatment systems are designed with a *one-size-fits-all* model, in which most individuals are assigned to a standard set of group treatments paired with case management. This is a strategy that maximizes dropouts and minimizes effectiveness. This is a population that is difficult to treat effectively under the best of circumstances. Positive outcomes are likely only if both the content of treatment and the format of treatment are tailored to the individual's needs and learning capacities.

## The Role of the Person

The combination of psychosis, thought disorganization, and negative symptoms (especially anergia, apathy, and anhedonia) often lead to the false assumption that people with schizophrenia are not capable of being active participants in their own treatment. Indeed, many individuals seem unmotivated and are noncompliant, but such seeming disinterest and passivity should not be interpreted as accurate reflections of the person's goals and desires or as immutable traits. Negative symptoms are not always stable, and they may be secondary to demoralization, psychotic symptoms, medication side effects, and other factors that vary over time (Carpenter et al. 1988, McGlashan and Fenton 1992). A large of number of trials and have clearly demonstrated that even extremely withdrawn, chronic persons can be motivated by systematic incentive (social learning) programs (Dickerson et al. 2005). Similarly, desire to change and inclination to do the work required for treatment also vary over time in the same way that motivation to lose weight or quit smoking varies in nonpatient populations.

The importance of developing a respectful, optimistic partnership between provider and consumer is clearly reflected in the consumer model of recovery and the

associated recovery movement (Bellack 2006). Over the past few decades a growing group of consumers, family members, and professionals have expressed increasing dissatisfaction with what has been seen as a paternalistic and unresponsive mental health system. At its most extreme, advocates of this consumer movement have seen traditional mental health services as iatrogenic, generating feelings of hopelessness and helplessness, promoting dependence, and fostering stigma. The more moderated view is that mental health professionals often fail to promote a sense of hope and optimism, to give consumers real choices, or to include consumers and family members as partners in the treatment process.

Two important reports from the US government provided considerable momentum to the recovery movement. First, the Surgeon General's Report on Mental Health (1999) concluded that all mental health care should be consumer and family oriented and have the promotion of recovery as its primary aim. While this report did not have the force of law to produce changes, it served as a focal point for change among many state and municipal mental health systems, and stimulated discussion among advocacy organizations and the professional community.

The Surgeon General's report was echoed more forcefully in the report of the President's New Freedom Commission report: Achieving the promise: Transforming Mental Health Care in America (2003). Consistent with the recovery model, the New Freedom Commission report stated, *First, services and treatments must be consumer and family centered, geared to give consumers real and meaningful choices about treatment options and providers* (p 5). The report goes on to say, *Consumers, along with service providers, will actively participate in designing and developing the systems of care in which they are involved. . . . In partnership with their health care providers, consumers and their families will play a larger role in managing the funding for their services* (p 8).

The general recommendations about the structure of treatment and treatment systems in the Surgeon General's and President's New Freedom Commission reports were concretized in a recent consensus statement from the Substance Abuse and Mental Health Services Administration (SAMHSA) (2005. The statement identified 10 characteristics of effective recovery-oriented services.

*Self-direction:* consumers lead, control, exercise choice over, and determine their own path of recovery.

*Individualized and person-centered*: there are multiple pathways to recovery based on the individual person's unique needs, preferences, and experiences.

*Empowerment*: consumers have the authority to exercise choices and make decisions that impact their lives and are educated and supported in so doi*ng*.

*Holistic:* recovery encompasses the varied aspects of an individual's life including mind, body, spirit, and community.

*Nonlinear:* recovery is not a step-by-step process but one based on continual growth with occasional setbacks.

*Strengths-based*: recovery focuses on valuing and building on the multiple strengths, resiliency, coping abilities, inherent worth, and capabilities of individual.

*Peer support:* the invaluable role of mutual support in which consumers encourage one another in recovery is recognized and promoted.

*Respect:* community, systems, and societal acceptance and appreciation of consumers—including the protection of consumer rights and the elimination of discrimination and stigma—are crucial in achieving recovery.

*Responsibility:* consumers have personal responsibility for their own self-care and journeys of recovery.

*Hope:* recovery provides the essential and motivating message that people can and do overcome the barriers and obstacles that confront them.

The scientific literature on the prevalence of recovery as defined by consumers and on the factors that contribute to it is in its infancy. Consequently, it is not yet clear if recovery oriented care is simply good clinical care from the perspective of client satisfaction, or if it actually leads to better care vis-à-vis cooperation and outcomes. Nevertheless, combining the public and consumer mandate with the preliminary data that are available provides a strong argument for providing recovery oriented care and approaching treatment as a partnership in which each participant brings unique and valued elements to the process.

## Impairments in Information Processing

It is now well established that impaired information processing represents one of the most significant areas of dysfunction in schizophrenia. The illness is marked by neuropsychological deficits in multiple domains, including verbal memory, working memory, attention, speed of processing, abstract reasoning, and sensorimotor integration (Braff 1991, Green and Nuechterlein 1999). These deficits are highly related to social functioning and role performance in the community, as well as to performance in skills training programs (Green et al. 2000, Koren et al. 2006). For example, Mueser and colleagues (1991b) found that poor memory had a deleterious effect on learning in social skills training, while pretreatment symptomatology was unrelated to social skill acquisition. Kern and colleagues (1992) also found that memory impairment as well as poor sustained attention (on the Continuous Performance Test) was associated with decreased learning in social skills training.

A related issue concerns the impact of neurocognitive deficits on the generalization of treatment effects. A basic assumption of all psychotherapies is that skills acquired in treatment sessions must be transferred or generalized to the person's natural environment. Yet, such generalization is contingent upon cognitive processes that are often disrupted in schizophrenia, especially "executive functions" mediated by the dorsolateral prefrontal cortex (Weinberger 1987). Several analog studies suggest that generalization is limited at best, even when explicitly programmed (Bellack et al. 2000, Tenhula et al. in press).

Unfortunately, clinical rehabilitation programs have lagged behind the experimental literature in this arena and neurocognitive deficits have not been addressed in a systematic manner. To be sure, most sophisticated rehabilitation programs do adjust the rate at which information is presented and the amount of detail or nuance provided. Allowance is also generally made for the need for repetition and regular review. However, these adjustments do not necessarily compensate for deficits in working memory and higher level executive processes. For example, there are impairments in the ability to perceive the continuity of experience

over time and to plan behavior accordingly: that is, to see how past experiences relate to current circumstances, or how what is currently being discussed can be applied in the future (Hemsley 1996). This problem would interfere with the ability to utilize newly acquired skills at appropriate times, to pursue goals in a systematic manner, or to use past experience to solve the problem. Similarly, there are deficits in self-monitoring and error detection that limit the ability to self-correct behavior after errors (Koren et al. 2006). While there are strong data to document that rehabilitation programs are effective in teaching new behavior (Smith et al. 1996), the literature does not document that newly acquired skills are applied in the community. Even in cases where interventions result in better clinical outcomes, the data do not support the face valid assumption that changes are due to what has been taught. This point was amply illustrated in the Treatment Strategies in Schizophrenia Project, in which family treatment was associated with reduced relapse rates despite an absence of any change in communication patterns, the purported mechanism of change (Bellack et al. 2000). Determination of the mechanisms that mediate behavior change in the community is perhaps the greatest challenge facing the field over the next decade if we are to develop more effective treatments.

## Adoption of a Compensatory Model

As indicated above, schizophrenia is a multiply handicapping disorder. It impacts on the ability to perform activities of daily living (ADLs) and the ability to fulfill social roles, including worker, homemaker, student, parent, and spouse; it increases the risk of substance abuse and disease, including HIV; and it interferes with performance of appropriate health care behaviors, including compliance with both medical and psychiatric treatment. A large proportion of individuals with schizophrenia also have residual psychotic symptoms and periodic exacerbations and they experience high levels of depression and anxiety. Overall, they suffer from poor quality of life. In light of this panoply of impairments, no single treatment is likely to have a sufficiently broad-based impact. This circumstance stands in marked contrast to less severe disorders such as unipolar depression and anxiety disorders in which a single intervention may be expected to produce substantial amelioration of the condition. Nevertheless, psychosocial treatments for schizophrenia have often been held to this same standard leading to the faulty conclusion that they are not effective.

A rehabilitation model, the primary focus of this chapter, is more appropriate than the standard treatment model as (1) it implies a narrower focus on specific skills and behaviors, and (2) it aims to improve functioning in specific areas, rather than eliminating or curing an entire condition. As indicated above, cognitive impairment is a central feature of the disorder, evident in childhood and progressing sharply with the onset of psychotic illness. It is reasonable to speculate that the impairments observed in ill adults are at least of two types: (1) those present from early in development; and (2) those that are related to chronic psychotic illness. The existence of such early, developmentally based impairments suggests that the concept of "premorbid" functioning in schizophrenia may no longer be tenable; rather, there is a prepsychotic period during which there is subtle evidence of the "morbid" process. Thus, the challenge confronting attempts at cognitive enhancement may not be restoration of function, but instead may be the development of critical competencies and strategies for coping with deficits.

Consistent with this hypothesis, a compensatory approach to treatment may be more appropriate than the restorative or reparative approach characteristic of most treatment programs. For example, rehabilitation for people with visual impairments involves teaching them to rely more on other senses, to use special appliances such as Braille keyboards, to use aides such as canes and guide dogs, and to systematically arrange their environment to minimize the need for sight. Success is achieved by improving independence, role functioning, and quality of life, not by restoring vision. Comparable rehabilitation programming is provided for stroke patients, individuals with paralysis, and amputees. Of note, these activist, goal oriented approaches are inconsistent with either the short-term up-and-out philosophy or the lifelong day care approach often seen in public mental health centers. Individuals receive ongoing support, but the support is oriented to skill development and solving problems in daily living, not restoration of premorbid functioning. Conversely, effective rehabilitation is neither infantilizing nor paternalistic; it is supportive, but it is also task and goal oriented.

Cognitive adaptation training (CAT) is a creative compensatory approach developed by Velligan and colleagues (2000, 2002). Case managers provide patients with home-based, compensatory environmental strategies to help structure the person's living environment which maximizes the likelihood that she/he can complete requisite activities of daily living. Examples include posting reminders about appointments on the exit door from the apartment, listing items of clothing to be worn on the closet door, and placing medications in a location that makes it maximally likely that the patient will see it and be reminded to take it. Prompts and other environmental aides are individually tailored to the person's level of apathy, disinhibition, and executive dysfunction. CAT can be administered in a time limited fashion, but may be a lifelong service for severely impaired patients. Velligan and colleagues found 9-months of CAT to be superior to an attention placebo and standard outpatient care on positive symptoms, negative symptoms, motivation, community functioning, global functioning, and incidence of rehospitalization. This is an excellent model for compensatory interventions, and warrants further study.

## Rehabilitation Strategies

The following sections will briefly describe and evaluate the three types of rehabilitation programs that have had considerable clinical and heuristic impact on the field, and are generally regarded as evidence-based practices: social skills training, cognitive rehabilitation, and supported employment.

## Social Skills Training

Social dysfunction is a defining characteristic of schizophrenia that is semi-independent of other domains of the illness (Lenzenwerger et al. 1991, Strauss et al. 1974). Social functioning is also predictive of the course and outcome of the illness (Johnstone et al. 1990, McGlashan 1986). The most useful perspective for understanding social functioning and social dysfunction in the illness has been the "social skills model" (Bellack et al. 2004, Meier and Hope 1998).

Social skills are specific response capabilities necessary for effective performance. They include verbal response skills (e.g., the ability to start a conversation or to say "No" when needed), paralinguistic skills (e.g., use of appropriate voice volume and intonation), and nonverbal skills (e.g., appropriate use of gaze, hand gestures, and facial expressions). These skills tend to be stable over time and make a unique contribution to the performance of social roles and quality of life (Bellack et al. 1990a, 1990b, Mueser et al. 1991a). Increasing social competence and improving social role functioning has been a major focus of rehabilitation efforts for the past 25 years, and a well-developed technology for teaching social skills has been developed and empirically tested: social skills training (SST) (Bellack et al. 2004, Liberman 1995).

The basic technology for training social skills was developed in the 1970s and has not changed substantially in the intervening years. It is a highly structured educational procedure that is generally conducted in small groups. Complex social repertoires such as making friends and dating are broken down into steps or component elements such as maintaining eye contact and asking questions. People are first taught to perform the elements and then gradually learn to smoothly combine them. Each session has a specific focus such as how to initiate conversations with strangers and how to refuse an unreasonable request. Trainers are more like teachers than traditional therapists. They first give participants simple instructions about how the behavior is to be performed, then they model appropriate behavior in a simulated conversation, and then they engage participants in role playing of simulated social encounters as a vehicle for practicing new skills. The therapists provide social reinforcement after each role played response and shape improved performance.

The content of training programs is organized into teaching units or curricula, such as job interview skills, dating skills, and safe sex skills. Training can last from 4–8 sessions for a very circumscribed skill, to as long as 1–2 years for a comprehensive skills training program. Sessions are typically held 2–3 times per week. Training is structured to minimize demands on neurocognitive capacity, and extensive use is made of audiovisual aides such as hand outs, flip charts or white boards. There is frequent repetition and review in an attempt to produce *overlearning*, so responses can be elicited relatively automatically in the environment.

Bellack et al. (2004) have published a user-friendly SST manual that provides a detailed *how-to* for clinicians wishing to develop social skills programs in their facilities. Another variant that has been widely disseminated skills is the UCLA Social and Independent Living Skills Program (Liberman 1995). This program includes carefully crafted videotapes and instruction manuals for both trainers and participants. Training employees standard skills training techniques (e.g., role play, modeling) and includes modules (curricula) covering seven areas: Medication Management, Symptom Management, Recreation for Leisure, basic Conversation Skills, Substance Abuse Management, Workplace Fundamentals, and Community Reentry (skills for the transition from inpatient to outpatient environments).

In addition to its role as a stand-alone treatment, SST has also been combined with other interventions to address clinical problems in which social skills deficits are only one component. For example, several studies have combined SST with supported employment to improve workplace interactions and enhance vocational outcomes (Liberman et al. 2006, Wallace and Tauber 2004). Bellack et al. (2006) employed social skills training to teach drug abusing clients how to refuse drugs as part of a comprehensive substance abuse program. The specific contribution of skills training in these approaches has generally not been experimentally teased out, but it is widely assumed to be effective when the treatment package has proved to be successful. However, the one critical question that has not been clearly answered either in specific social skills training programs or when it is bundled into other treatments is the extent to which learning in the clinic translates into either specific behavioral changes or generally improved role functioning in the community.

There is scant evidence that there is spontaneous generalization from office based training to the community, which is not surprising given the well established behavioral aphorism that generalization must be programmed, not expected. That is, treatment must bridge the gap between office based training and the community by systematically prompting and reinforcing desired behavior and/or by engaging significant others in the community to do so. Liberman et al. (2001) have addressed this problem with a creative strategy referred to as in vivo Amplified Skills Training (IVAST). It combines standard skills training with intensive case management, based on the Assertive Community Treatment (ACT) model (Stein and Test 1985). The case manager helps support completion of homework assignments, identifies and reinforces opportunities to use trained skills, and establishes links with support systems (e.g., significant others) in the community to reinforce use of newly learned skills. Glynn et al. (2002) reported that IVAST was more effective than an office-based version of SST.

## Empirical Support

The basic social skills training strategy was refined and validated in a number of single case studies and small group designs conducted in the 1970s and 1980s. These early reports were followed by a series of randomized clinical trials that has provided a clearer picture of areas in which SST is and is not effective. There have been at least 10 narrative reviews and four meta-analyses published in peer reviewed (English language) journals since 1990, including six published since the year 2000. Pilling et al. (2002) review of nine randomized trials was the most negative, and concluded that SST was not substantially effective. In contrast, the other reviews were all positive, and support the following conclusions (e.g., Bellack 2004, Kopelowicz et al. 2006).

1. SST is not highly effective for reducing symptoms or preventing relapse. This finding is not surprising. The only reason why SST might be expected to affect these domains is indirectly, by teaching skills that help to reduce social failure that could cause sufficient stress to precipitate exacerbations. This stress diathesis model depends on several mediating factors which are themselves unproven (e.g., that social failure produces sufficient stress to precipitate relapse).
2. SST has a reliable and significant effect on behavioral skills.
3. SST has a positive impact on social role functioning, although the findings here are not entirely consistent.

The results are better for defined skills, such as medication management or HIV prevention skills, than for general measures of social functioning.

4. SST appears to have a positive effect on satisfaction and self-efficacy: participants report feeling more self-confident in (targeted) social situations after training. SST is clearly an effective teaching technology that is well-received by both participants and clinicians.

These general findings are reflected in the following recommendation from the 2003 update of the Schizophrenia PORT (Lehman et al. 2004a)

*Persons with schizophrenia who have skill deficits such as problems with social skills or activities of daily living should be offered skills training. The key elements of this intervention include behaviorally based instructions, modeling, corrective feedback, and contingent social reinforcement. Clinic-based skills training should be supplemented with practice and training in the individual's day-to-day environment (p 203).*

## Cognitive Rehabilitation

Recognition of the importance of neurocognitive deficits has stimulated increasing interest in the prospects for cognitive remediation. It is difficult to trace the history of interest in this approach, but it certainly goes back at least as far as the early 1970s (Meichenbaum and Cameron 1973, Platt and Spivack 1972). However, these somewhat anomalous studies were not replicated and interest in cognitive training languished. Two reports in the late 1980s rekindled interest in the possibility of cognitive rehabilitation. Hans Brenner and colleagues (1990)AQ developed a multistage approach, integrated psychological therapy (IPT), that attempted to marry cognitive training with higher level social skills training. Results have not been particularly robust but the work has had tremendous heuristic value.

The second study that had a significant impact was influential for very different reasons. Goldberg and colleagues (1987) reported that people with schizophrenia were unable to benefit from explicit instructions and practice on the WCST. Coupled with data demonstrating diminished blood flow while responding to the WCST, these data implied that schizophrenia was marked by an unmodifiable abnormality of the dorsolateral prefrontal cortex. The NIH (National Institutes of Health) work stimulated a series of mostly successful demonstrations that WCST performance deficits, albeit widespread, are neither endemic to the illness nor immutable (Bellack et al. 1990a, 1990b, Nisbet et al. 1996, Vollema et al. 1995). Other studies employed cognitive remediation strategies to improve performance on other measures of information processing as well. For example, Wexler and colleagues (1997) provided subjects with extensive practice on a motor dexterity task and either a visual reading task or a dot spatial memory task. Improved performance was gradually shaped over 10 weeks. A majority of subjects reached normative levels on the reading and dot tasks, and most showed improvement on the dexterity task as well. These results are consistent with other studies demonstrating that modest improvements can be observed on a variety of tasks using practice, shaping, and errorless learning (Silverstein et al. 2001). Stimulated by this early laboratory work, the last decade has seen a spate of clinical trials built around a series of innovative, clinically sophisticated strategies.

Several clinical programs are illustrative of the directions the field is pursuing. Wykes and colleagues (1999) developed an intervention called *cognitive remediation therapy (CRT)*, that focuses on executive functioning (e.g., cognitive flexibility, working memory, and planning). The approach employs a sophisticated training model that is based on principles of errorless learning, targeted reinforcement, and guided practice on cognitive tasks. Training media consist of a variety of paper and pencil games and neurocognitive tests. This group has conducted a series of trials that have yielded positive results for CRT, including some evidence of stability of effects over time (Reeder et al. 2006, Wykes et al. 2003)., including some evidence of stability of effects over time (Reeder et al. 2006, Wykes et al. 2003). A limitation of this program is that it employs a highly tailored individual treatment model and demands high levels of therapist skill to slowly shape behavior. However, the focus on executive functioning seems much more likely to lead to transferable effects than narrowly focused programs designed to strengthen working memory or attention.

An alternative approach capitalizes on the ease of standardization and flexibility provided by computer software. Wexler and colleagues (1997) and Bell and colleagues (2001, 2004) reported positive results for similar programs that provide self-directed practice on basic attention, memory, and reasoning tasks (e.g., visual tracking, pyramids). Notably, the intervention had a positive impact on work outcomes, and the effects were maintained over time (Bell et al. 2004). These programs are limited in that the tasks are repetitive and boring for many participants, and they do not receive training per se. Participants may become more skilled on the specific tasks, but they do not necessarily learn effective strategies that normalize dysfunctional neural circuitry or foster generalization to other situations.

Medalia (Medalia and Revheim 1999, Medalia et al. 2000) developed an innovative program called *Neuropsychological Educational Approach to Remediation* (NEAR) that employs commercially available educational software. These tasks are intrinsically interesting to subjects and have built-in feedback mechanisms to guide performance. The intervention is administered in an open classroom format in which people attend on an *ad lib* basis, select tasks they are interested in working on each day, and move at their own pace. Medalia emphasizes self-guided practice, rather than structured training, in order to foster "intrinsic motivation" for learning and to allow people to enhance their preferred problem-solving styles. This is an appealing approach, but reliance on self-guided practice seems unlikely to lead to learning. Neuroimaging data suggest that individuals use inefficient neurocognitive operations and are unable to utilize appropriate (i.e., normal) neural circuits to perform cognitive tasks (Frith 1995, Weinberger et al. 1992). Consequently, practice without training may improve performance on the specific task practiced but it is not likely to normalize functioning or lead to transferable gains.

Bellack and colleagues (2005) have developed a remediation strategy that is built around educational software developed for children: *Computer Assisted Cognitive Remediation* (*CACR*). CACR was guided by four premises about cognitive impairment and the rehabilitation needs of people with schizophrenia.

1. Remediation should target *controlled and coordinated cognitive activity*, rather than individual neurocognitive domains. Thinking problems in schizophrenia arise out of abnormalities in the coordinated activity of many brain regions that subserve a wide range of integrated neurocognitive abilities; thus, a focus on any specific neurocognitive domain is premature and remediation must target this coordinated activity.
2. Remediation should thoughtfully integrate *training* and *independent practice*. Prior investigations have shown that strategy training, on the one hand, and repetitive, independent practice, on the other, can improve neurocognitive performance. Strategy training likely addresses deficits in the strategic, "top–down" cognitive control and coordination of mental activity. Independent, repetitive practice may better target the more discrete "bottom-up" processes and may build up speed and capacity for mental effort. These appear to be separate and complementary pathways to beneficial cognitive change and remediation must coordinate and integrate their use.
3. Bearing in mind the goal of standardization, remediation should be *individualized*, to the extent possible. Given the variability in the severity and distribution of cognitive deficits, in compensatory adaptations, and in learning styles and preferences, remediation must also provide enough flexibility to accommodate substantial individual differences.
4. Remediation must take account of *motivational/emotional* deficits. Motivational and emotional processes are part of the foundation for cognitive performance. Given that negative symptoms and motivational impairment are core features of schizophrenia, it is essential that a remediation program build in strategies to secure engagement and sustained, active participation in remediation procedures.

CACR employs six commercially developed educational software tasks. Three specifically target planning, reasoning and problem solving skills, while also tapping attention, memory, and other capacities. Two place a premium on the use of attention, working memory and learning. The last is a speeded task that emphasizes rapid perceptual integration, decision making and response.

The graduated nature of the CACR exercises ensures that most clients will face impasses at multiple points, giving rise to numerous discrete opportunities for active intervention by trainers. The structure trainers provide in these instances comes under the rubric of *scaffolding* in the learning literature and also draws on principles of *errorless learning*. A scaffolding approach implies a division of current task responsibilities between the client and trainer. The client manages those parts of the task within his or her ability (e.g., the individual actions within a sequence). The trainer provides the complementary skills to enable successful performance (e.g., the larger strategy and goal orientation). Trainers shape and monitor individual strategies and actions, model more global problem solving processes, and provide gentle pressure to try more difficult task levels as client performance improves. The flexible support provided by trainers prevents preservative use of unproductive strategies, allows clients to progress while keeping errors to a minimum, and counteracts client frustration with positive reinforcement. The trainer gradually relinquishes strategic control as the client increases in competence.

Preliminary data from two randomized clinical trials of CACR are quite promising. Subjects clearly improve in performance on each of the training tasks and report very positive subjective experience of the intervention. Further work is required to determine whether the effects translate into improved community functioning.

Judging the potential for cognitive rehabilitation based on existing trials (analog or clinical) is difficult due to the risk of Type II error (e.g., incorrectly concluding that it is ineffective). It may be safe to conclude that a particular strategy is not effective, but one cannot extrapolate from any single trial or group of trials to the broader domain. For example, a particular technique that fails to produce an effect in 10 training sessions might be effective after 50. Ten sessions of practice on computerized memory tasks may not be sufficient to produce a generalizable increase in processing capacity, but meaningful changes may become apparent after 100 sessions. Alternatively, an innovative program based on a different conceptual model could produce results that the simpler practice/rehearsal strategies currently in vogue do not. The literature is also difficult to evaluate given the broad diversity of training procedures, subject samples, and outcome measures employed in trials.

Several reviews have concluded that cognitive remediation can be effective and merits the designation as an evidence-based practice (e.g., Twamley et al. 2003a, Velligan et al. 2006). Conversely, Pilling et al. (2002) were quite critical, based on data collected at the time of their review. At the least, the evidence suggest that cognitive remediation is a promising avenue to pursue, having demonstrated the ability to produce statistically significant changes in neurocognition that are sustained over time in several studies. There is also evidence that remediation programs can produce meaningful changes in community behavior, including social functioning and work (Bell et al. 2004, Reeder et al. 2006). However, there is not yet strong evidence to support the widespread dissemination of any particular approach as a cost-efficient, evidence-based practice, and cognitive remediation was not identified as an evidence-based practice in the most recent Schizophrenia PORT update (Lehman et al. 2004a). Further, it remains unclear which aspects of neurocognition are critical targets for training, or which are most likely to be malleable (Bellack et al. 2005, Reeder et al. 2006). This is a significant problem for the field and is retarding progress in developing truly effective intervention strategies.

## Vocational Rehabilitation

The ability to perform productive work, earn money, and achieve a degree of independence is generally regarded as a major factor in self-esteem, quality of life, and relationships with significant others. Yet it is a domain that is particularly difficult for people with schizophrenia. Rates of competitive employment for persons with the illness are generally less than 25%, and participation in sheltered employment is not much better (Lehman 1995). Nonetheless, many, if not most people with schizophrenia express the desire to work, especially in competitive jobs (Cook et al. 2005a).

There are many forms of vocational programs available in the community, including sheltered workshops, job clubs,

transitional employment, the Boston University model, and programs of job support. With the exception of programs involving job support, there is little evidence that these types of vocational interventions often result in sustained competitive employment among patients with severe mental illness (Lehman 1995). Rather, such programs appear to provide many individuals with structured opportunities for socialization and individuals, it is clear that traditional approaches to psychiatric rehabilitation have proven to be disappointingly ineffective for those interested in competitive employment. In part, this lack of efficacy may be attributed to residual symptoms and the severe disability that is common among people with schizophrenia. Further, the negative financial incentives that have traditionally been built into the Supplemental Security Income (SSI) and Social Security Disability Income (SSDI) systems may have played an important role in people choosing long-term involvement with rehabilitation programs rather than actual competitive employment. Thus, there are both illness and systems factors that may contribute to the limited efficacy of traditional rehabilitation approaches. Even allowing for these factors, it is clear that improvement of vocational functioning among people with severe mental illness remains a critical goal for psychosocial intervention.

Optimism about the potential to increase rates of employment has increased since the mid 1990s with the development of *supported employment*, an innovative strategy that provides support in the community to help people find and keep competitive jobs, rather than assigning them to an extended period of vocational training. The most widely studied and disseminated model of supported employment, *Individual Placement and Support* (IPS) was developed and standardized by Robert Drake and Deborah Becker (Becker and Drake, 1993, 2003). It is based on six principles (Bond 2004): (1) services are focused on competitive employment; (2) eligibility is based on consumer choice, not screening criteria or counselor determined readiness; (3) the focus is on rapid job search, rather than a preliminary period of training or rehabilitation; (4) the program involves active integration of mental health and vocational services, rather than a balkanized or brokered model; (5) services are based on consumer preferences and choices rather than professional judgments of what the person can/should do; (6) The program is not time-limited: vocational staff provide follow-along support for as long as needed to help the person succeed on the job and/or find successive jobs if the person does not like or cannot retain the first (or second, etc.) position.

There is a growing body of literature documenting the efficacy of supported employment (Bond 2004, Twamley et al. 2003b). Studies have been conducted in diverse geographic regions in the US and Europe, with heterogeneous client groups. Summarizing the results of nine randomized trials completed at the time of his review, Bond (2004) reported that competitive employment rates for subjects in supported employment averages 56%, compared to 19% for those in traditional vocational rehabilitation programs. Cook and colleagues (2005a,b) conducted a multi-site trial in which 1273 outpatients recruited from seven (US) states were randomly assigned to supported employment or control conditions for 24 months. Fifty-five percent of those in supported employment had achieved competitive employment for at least part of the time, versus 34% of those in the control condition. Those in supported employment also had significantly higher earnings and were significantly more likely to be working for 40 hours or more per month.

While the results for supported employment are, thus, quite promising, it should be noted that it is not a cure for unemployment among people with severe mental illness. The majority of clients are employed at minimum or close to minimum wages, albeit in competitive employment. Few are able to work full time (i.e., 35—40 hours per week), and many are unable to retain jobs for long periods of time. Conversely, many who lose jobs are able to find subsequent employment and there is some suggestion that stability of employment increases over time (Bond 2004). Much attention in the literature is now being placed on strategies to increase employment success through the use of adjunctive treatments, such as cognitive remediation (McGurk et al. 2005) or social skills training (Wallace and Tauber 2004).

Overall, despite the limitations in its effects, the evidence base for supported employment is very strong and it is widely regarded as an evidence-based practice. It is one of the 6 psychosocial strategies recommended by the Schizophrenia PORT (Lehman et al. 2004a): *Persons with schizophrenia should be offered supported employment, the key elements of which include individualized job development, rapid placement emphasizing competitive employment, ongoing job support, and integration of vocational and mental health services* (*p 202*).

## Summary and Conclusions

This chapter has provided an overview of issues involved in providing effective rehabilitation programming for people with schizophrenia. Interest in psychosocial treatment, including rehabilitation has waxed and waned over the last several decades, but there is now widespread agreement that it plays a critical role in comprehensive care for people with the illness. Schizophrenia is the result of a failure in normal neurodevelopment, with subtle manifestations evident long before the first exacerbation. There appears to be a lifelong disruption of normal socialization coupled with enduring neurocognitive impairments that make it unlikely that medication alone can be sufficient to produce adequate quality of life. That being said, several factors were discussed that must be addressed if psychosocial treatments are to be effective, including: (1) timing and duration of treatment; (2) individual differences in treatment needs; (3) the role of the person in treatment; (4) the limitations imposed by impairments in information processing; and (5) the need to base interventions on a compensatory model.

Three rehabilitation strategies that have received considerable attention were then reviewed: social skills training (SST), cognitive rehabilitation, and vocational rehabilitation. SST is an effective teaching/training strategy but it is not clear that the intervention can produce meaningful changes in community performance unless it is embedded in a comprehensive, community oriented intervention program. The potential for cognitive rehabilitation is less clear. Several approaches seem to be based on an overly simplistic model of neurocognitive functioning and place too much reliance on an *exercise* model that attempts to alter brain function by repeated practice. Newer strategies that focus on improving higher level integrative processes may prove

to be more effective, especially those that employ computerized educational software that clients find inherently engaging. Traditional vocational training that emphasizes sheltered workshops and job training have not been highly effective. The integrated placement and support model is an innovative new approach that helps place clients in competitive employment and provides ongoing support in the real workplace. Initial results are very promising, although job retention and total hours clients are able to work remain problematic.

As evidenced by these three approaches, the scientific literature is moving away from long-term, unfocused day treatment approaches to targeted intervention strategies designed to deal with specific problems. This approach, which is much more likely to produce useful outcomes has not yet had adequate penetration of community services. Further research is required to match interventions with individuals to determine when specific interventions should be provided, and to build in sufficient booster or follow-up procedures to maximize the chances for enduring change in the community. It is by now very apparent that neither a *one-size-fits-all* nor a time-limited, up-and-out approach works with this population.

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CHAPTER

97

# Psychiatric Rehabilitation for Achieving Successful Community Living for Adults with Psychiatric Disabilities

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Psychiatry now recognizes the critical need to integrate psychopharmacological treatments with psychotherapeutic supports and services for adults with a severe psychiatric disorder to achieve an optimal level of social and role function, a reduction in relapses, and a satisfactory quality of life. Since psychiatric medications only target the positive symptoms of these disorders, they do not address the functional disabilities that often result from the illness (Keefe et al. 1999). Psychiatric treatments are focused on controlling symptoms of severe mental illness, while the intended purpose of the psychosocial interventions described in this chapter are to ameliorate the associated functional loss of these illnesses or the consequent disability. Hence, without this combination of interventions, many adults with a severe psychiatric illness would not improve in the realm of the psychosocial sequelae of these disorders, and consequently, not be able to achieve successful community living.

Currently, there is a diversity of effective psychotherapeutic programs and services specifically designed to meet the needs of adults with psychiatric disabilities. This chapter will focus on the psychotherapeutic half of the equation, with specific emphasis on those interventions that are considered to be evidence-based practices (EBPs). The chapter will begin by defining the population of those with psychiatric disabilities, followed by a discussion of psychiatric rehabilitation, including what it is, the history of its emergence and development, its principles, and specific practice approaches. Next, a presentation of the recovery orientation will be provided with an examination of its relevance to the provision of these service interventions. Finally, an in-depth discussion of each of the five accepted psychotherapeutic EBPs will be presented, placing each within the context of related services and providing a summary of the empirical evidence.

## Defining Adults with Psychiatric Disabilities

Adults with psychiatric disabilities are individuals who, as a result of their mental disorder, are unable to achieve commonly accepted age-appropriate milestones in major life domains, such as participating in educational programs, employment, or engaging in social commitments, including intimate relationships and marriage. An important aspect of this definition is that psychiatric disability is based on a diagnosable mental illness. The diagnoses that frequently result in psychiatric disability are those considered to be the severe mental illnesses, which include the schizophrenia spectrum disorders and the major affective disorders, major depression, and bipolar disorders. In some cases, individuals with anxiety and personality disorders are also included, but the former diagnoses are characteristic of the

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majority of the population. It is important to note that not everyone with these disorders has a psychiatric disability. Only those in which the symptoms of the disorder interfere with the individual's ability to pursue their life goals, which are socially and culturally appropriate for their given physical developmental state, are considered disabled. However, the US National Health Interview Survey found that 79% of over 3 million adults with severe mental illness have at least one functional limitation (Barker et al. 1992 as cited in Bassett et al. 1998). Sanderson and Andrews (2002) caution that assessing disability just for those with severe psychiatric disorders underestimates the prevalence of disability, as those with affective, panic, posttraumatic stress, and generalized anxiety disorders were the most prominent diagnostic categories with the highest levels of disability in their Australian National Survey of Mental Health and Wellbeing. Overall, this household survey determined that 68% of adults with any mental disorder had anywhere from a mild to a severe disability, but only 23% of those without a mental disorder were assessed to have a disability, with most being mild.

There is a wide diversity of definitions of disability for both research and services purposes. For example, definitions of disability vary by benefit programs, such as the Social Security Administration, Rehabilitation Services Administration, and Substance Abuse and Mental Health Services Administration (SAMHSA), as these definitions determine eligibility for the provision of services and resources, including financial support in the case of Supplemental Security Income or Social Security Disability Income. Despite this diversity, all definitions appear to share some basic principles. Those with disabilities are considered to suffer from an illness, i.e., a disease or disorder; experience signs and symptoms of the disorder that are significant enough to cause impairments, i.e., loss of physical or mental functions; and also experience a loss of ability or competence in social role functions (see Table 97–1 for examples of definitions of disability by federal agencies).

**Table 97–1 Definitions of Disability by Federal Agencies**

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| The Rehabilitation Act of 1973 Sections 501 and 505 which concerns employment: |
| A disability means . . . any person who (i) has a physical or mental impairment which substantially limits one or more of such person's major life activities, (ii) has a record of such an impairment, or (iii) is regarded as having such an impairment. The Act has been revised to comply with the Americans with Disabilities Act and other legislations to exclude those currently engaging in the illegal use of drugs. |
| Social Security Administration: |
| Disability is based on the inability to work. An individual is considered disabled under Social Security rules if the individual cannot do work that he/she did before, and it is decided that the individual cannot adjust to other work because of medical condition(s). The disability must also last or be expected to last for at least one year or to result in death. |

An investigation by the World Health Organization (WHO) determined that mental illnesses are the leading cause of disability worldwide. The WHO study determined that the severe mental illnesses, schizophrenia, depression, and bipolar disorders, accounted for almost one quarter of all disability in the industrialized countries (WHO 2001). The Global Burden of Disease Study by WHO, which calculated disease burden by disability adjusted life years (DALYs), enabled a comparison across a diversity of diseases. DALYs estimate the lost years of healthy life, regardless of whether the years are lost to premature death or years lived with a disability. The disability component of the DALY measure is weighted for disability severity. Based on this calculation, major depression was ranked in the top 10 priority diseases and was second only to ischemic heart disease with regard to the burden of disease (Utsun 1999). Furthermore, mental disorders accounted for almost 10% of the burden of disease in established market economies (Utsun 1999). Consistent with these findings, Marcote and Wilcox-Gok (2001) estimated that in the US alone, 5–6 million people between the ages of 16 and 54 lose, do not seek, or are unable to secure employment due to the consequences of mental illness. They further estimated that those with mental illness who do work have their annual incomes reduced anywhere from $3,500 to $6,000. Based on an examination of the US National Comorbidity Survey data, Kessler and Frank (1997) determined that work impairment was a primary adverse consequence of psychiatric disorders. They found that the average days of work lost due to psychiatric disorders was 6 per month per 100 workers, and an average of 31 days per 100 workers reduced their performance or productivity at work, and moreover, work disability was more highly concentrated among those with comorbid psychiatric disorders.

## Prevalance Estimates Of Psychiatric Disability

US Public Law (PL) 102-321, the Alcohol, Drug Abuse, and Mental Health (ADAMHA) Reorganization Act of 1992 required the states to estimate the incidence and prevalence of adults with serious mental illness (SMI) in order to determine the allocation of block grant funds for community mental health services. This law defined serious mental illness as any diagnosis in the *Diagnostic and Statistical Manual (DSM)* other than a substance use disorder accompanied by a "serious impairment," operationally defined as a Global Assessment of Functioning (GAF) score below 60.

SAMHSA, an agency created by the 1992 legislation, established a task force to develop a methodology for determining the estimates of those with SMI, based on two national surveys of DSM disorders in the United States: the Epidemiolgic Catchment Area (ECA) study (Robins and Regier 1991) and the National Comorbidity Survey (NCS) (Kessler et al. 1994). Given that these studies were not designed to assess impairment, imprecise indicators were used. The task force "estimated that 5.4 percent of the US noninstitutionalized civilian population met [sic] criteria for SMI at some time each year" (Kessler et al. 2002, p 156). More specifically, these authors noted that "[p]reliminary prevalence estimates based either on post hoc secondary analysis of previously collected psychiatric epidemiological surveys or on indirect estimates from screening scales suggest that 2.4 to 3.3 percent of the US adult population meet criteria for SMI in any given month and that 5.4 to 7.2 percent do so at some time during the year" (p 163).

Bassett and colleagues (1998) estimated the prevalence of disability by utilizing various measures of disability that were applied to data from Eastern Baltimore Mental Health Survey, an ECA site. The proportion of adults with a disability (functional limitation) varied between 2.5 and 19.5% contingent on which measure was employed. The low rate was produced with a score of 5 or greater on Axis V of social and occupational functioning of the DSM, while the highest was produced when the presence of two or more chronic medical conditions was used. Overall estimation of the prevalence of being disabled by at least one of the indicators employed was 39.5%. Of adults classified as being disabled by any of the measures examined, 56–92% had a psychiatric disorder.

## Defining Psychiatric Rehabilitation

Characteristically, adults with severe psychiatric disabilities are generally unemployed, unmarried, and have difficulty with interpersonal relationships. Given their lack of employment, they are often financially supported through federal disability programs or have intermittent employment or limited family financial support. Consequently, this population tends to be economically disadvantaged and to be vulnerable to a diversity of societal ills, including relatively high rates of substance abuse, psychological trauma, homelessness, criminal justice involvement, and loss of custody of their children. They also have a number of cognitive deficits and medical comorbidities as well as high rates of suicide.

Given the functional limitations of the population, a diversity of psychotherapeutic practices, programs, and services within the domain of psychiatric rehabilitation have been developed to meet the population's multiplicity of needs. A commonly accepted definition of psychiatric rehabilitation is assistance to adults with psychiatric disabilities in increasing their ability to function effectively with life satisfaction in the environments of their own choosing with the least amount of continuing intervention by professionals (Anthony et al. 2002). The emphasis of psychiatric rehabilitation is on consumers acquiring the necessary skills and resources for living in the community as independently as they desire and are capable. The primary practice goal is "to enable individuals to compensate for or eliminate the functional deficits, interpersonal barriers and environmental barriers created by the disability, and to restore ability for independent living, socialization, and effective life management" (Hughes 1994, p 11). The primary practice domains of psychiatric rehabilitation include independent living, education and employment, personal relationships, health, criminal justice, and spiritual life and recreation, thereby encompassing all aspects of social functioning and community living. Psychiatric rehabilitation employs systematic practice efforts that assist adults with psychiatric disabilities to progress in their own course of recovery (Corrigan et al., in press). Psychiatric rehabilitation practice differs from psychiatric treatment, which is comprised of psychiatric medication administration and management and psychotherapy. It is important to note that intensive insight-oriented psychotherapy is not commonly utilized for adults with psychiatric disabilities as it has been empirically determined that these interventions tend to have negative consequences for those with schizophrenia disorders (Drake and Sederer 1986). However, supportive psychotherapies have been shown to be effective with this population, as have some cognitive behavioral treatments.

Although the identification of the practice of psychiatric rehabilitation began in the 1940s, psychiatric rehabilitation has become designated as a field of practice much more recently. Psychiatric rehabilitation is the integration of a multiplicity of program approaches and models that were all designed to treat the psychosocial conditions and functional limitations of adults with psychiatric disabilities. This is the single professional practice field that is limited to working with only one very specific population. Psychiatric rehabilitation is more than specific practices. It is also comprised of principles and values that guide rehabilitation practices.

## Development of Psychiatric Rehabilitation

The roots of the field go back to the 18th century with the introduction of moral treatment, where patients were to be treated with respect and kindness, and relocated to the rural pastoral areas where it was believed that the setting would restore prior functioning (Corrigan et al. in press, Morrissey and Goldman 1984). The emergence of the principles of psychiatric rehabilitation goes back even further, to the provision of normalized housing for those who made pilgrimages to the village of Geel Belgium in the 13th century in search of a cure for their mental illness. Town folks took in pilgrims with mental illness to live in their homes on a permanent basis. In the US, Dorothea Dix crusaded for the establishment of mental hospitals in order to offer more humane treatment, rather than having adults with mental illness living in almhouses, jails, or on the streets. The US mental hygiene movement of the 19th century was a reaction to the poor quality of care for those served in public psychiatric institutions. In the 20th century, the deinstitutionalization movement was a major precipitant to the further development of psychiatric rehabilitation practices by treating those with SMI in their community rather than warehousing them in large institutions. With the recognition of the inadequacies of the community mental health movement of the 1960s in meeting the psychosocial needs of adults with SMI, the National Institute of Mental Health (NIMH) developed the Community Support Program (CSP). CSP promoted an approach of an entire system of care that was ongoing, rather than episodic or crisis oriented. The principles of CSP were very much influenced by psychiatric rehabilitation movement leaders. Consequently, the values and beliefs of the field were evident in the articulation of these CSP principles (Corrigan et al. in press). The philosophy of CSP was embodied in a set of principles, which included services being consumer centered, empowering, culturally and racially appropriate, flexible to meeting consumer needs, focused on consumer strengths, normalized with inclusion of natural supports, accountable to consumers, families, and administrators, and coordinated with a system of care (Stroul 1993). CSP promoted the dissemination of programs and approaches of psychiatric rehabilitation, which helped to promulgate and further the development of the field.

Psychiatric rehabilitation has now achieved legitimacy as a field of practice. For a number of years, the Commission on Accreditation of Rehabilitation Facilities (CARF) has accredited vocational rehabilitation services in behavioral health care, and they now also accredit programs such as

Assertive Community Treatment (ACT). Psychiatric rehabilitation practitioners have recently obtained certification. Many of the practices have a research base, with some of them considered to be EBP. A number of books that define the field and explicate the principles, practices, approaches, as well as service models have been and are being published (e.g., Corrigan et al. in press, Pratt et al. 2006). Furthermore, there is at least one academic department that is totally dedicated to the teaching of psychiatric rehabilitation and that grants all levels of postsecondary degrees, the Psychiatric Rehabilitation Department at the University of Medicine and Dentistry of New Jersey, while other departments or schools like psychology programs and schools of rehabilitation have a specialization in psychiatric rehabilitation.

## Principles and Service Elements of Psychiatric Rehabilitation

The emphasis in psychiatric rehabilitation is on the strengths of the individual, rather than on their deficits. Implicit in the strengths perspective is the empowerment of the person. Furthermore, there is a belief in the self-determination of the individual with attention given to personal goals and preferences. Consequently, a key element of psychiatric rehabilitation is the active involvement of the consumer in the development, implementation, and ongoing evaluation of service plans and recovery process. Consistent with the orientation of psychiatric rehabilitation is the centrality of hope, optimistic activist philosophy, and a belief in consumers' own recovery to gain control and acceptance of their life and their illness, despite their disability.

Given the nature of mental illness and its resulting disability in many functional areas, psychiatric rehabilitation takes a comprehensive approach focusing on practical concerns with daily living and integration with psychiatric treatment, specifically pharmacotherapy. A key principle is that services need to be normalizing, offering experiences that are not different from those without disabilities. Rehabilitation emphasizes the teaching of skills, as well as the modification of environments and the provision of environmental supports with the goal of maximizing the likelihood that the individual will succeed in the environment of choice. Rehabilitation is not a one-time intervention, but rather an ongoing process. Rehabilitation is best performed when it is situationally based in the consumer's own environment. Services are most beneficial when integrated in the community, the locus of the training. This approach is based on experiences that the more the services are delivered in the consumer's own environment, the more likely that the acquired skills will be used in that setting. The rehabilitation process is more effective with the inclusion of family members and other natural supports of the consumer's own choosing (Kopelowicz et al. 2006).

## Examples of Psychiatric Rehabilitation Practices

Psychiatric rehabilitation is an amalgamation of a diversity of practice approaches. Four primary practice approaches, with each promoting the rehabilitation of adults with SMI and each developing rather independently of the other, have merged together to form the foundation of what is now considered the field of psychiatric rehabilitation: psychosocial rehabilitation centers, specifically the clubhouse model (Rutman 1987); social skill training (Bellak 2004); Boston University approach, particularly the choose, get, keep model (Anthony et al. 1987); and peer support approaches developed and delivered by consumers (Solomon 2004, Solomon and Draine 2001).

### Psychosocial Rehabilitation Center Movement and the Clubhouse Model

One of the primary impetuses in the development of the field was the psychosocial rehabilitation center movement, which started with the establishment of Fountain House in New York City in 1948. A group of discharged psychiatric patients formed a self-help organization, We Are Not Alone Society. This self-help group, with assistance from volunteers and funded by a charitable foundation, eventually evolved into a community-based program known as Fountain House. This organization was frequently referred to as a psychosocial "center"; hence, with the development of other similar programs across the country, these agencies became the psychosocial center movement. The particular program model came to be identified as the Clubhouse model, as this was a central meeting place for members to socialize. There are now over 300 clubhouses in 24 countries worldwide. Individuals who participate in these programs are called "members," rather than patients or clients, so as to communicate an atmosphere of support, acceptance, and respectfulness. The services are offered in a nonstigmatizing environment and in an atmosphere that maximizes the members "feeling of responsibility and self-worth and encourages ownership in the rehabilitation process" (Rutman 1987, p 204). These centers provide opportunities for work, socialization, and, in some cases, housing (Rutman 1993). These programs have a number of groups that meet on an ongoing basis to offer skills and support to other members. Members participate in the operation of the organization by holding functional jobs in the program. A central feature is the work ordered day; thus, members work as receptionists, perform janitorial or housekeeping services, prepare the noon day meal, and maintain fiscal and clinical records. The service programs are aimed at improving educational, vocational, and independent living and socialization skills of the members. Today, a number of comprehensive community mental health agencies have added clubhouse programs as a component of their array of services.

The clubhouse model of psychiatric rehabilitation is a place where individuals with a mental illness "come to rebuild their lives." Members are free to choose the frequency and intensity of contact with the clubhouse, including its staff, other members, and program elements. The focus is on members' strengths. Fellow members reaching out to other members is the core healing process, and members work with staff in partnership, sharing roles and responsibilities. Staff do not function as therapists. One of the program features of clubhouses is transitional employment (TE). TE is the placement of a member in a time-limited, usually 6 months, job in the community where the employee receives the prevailing wage. The clubhouse guarantees that the job will be performed, with staff filling in should the member be unable to attend. However, these are not permanent jobs, but rather the agency "owns" the position, and every 6 months places another member in the same position. These job placements are a step toward increased independence.

In 1994, the International Center for Clubhouse Development (ICCD) was formed to help and to represent this growing movement worldwide. ICCD was established to provide training in the model, offer consultation to developing programs, and to certify that operating clubhouses meet the standards of a clubhouse to ensure that the integrity of the model is maintained (Macias et al. 1999) (www.iccd.org). Unfortunately, there has been limited research to determine the effectiveness of this model.

## Social Skills Training

A more highly structured approach to the practice of rehabilitation of adults with psychiatric disabilities is social skills training. Social skills training is systematic strategies and techniques to teach interpersonal skills that are based in social learning theory. The general approach of highly structured curriculums that employ systematic behavioral techniques has virtually remained unchanged since its inception in the 1970s (Bellack 2004). An underlying principle of skills training is that essentially all social behaviors are learnable (Bellack 2004). The settings in which these trainings occur is wide ranging, from hospitals and community-based service settings to the actual locations in which the skills that are being taught will be used. A number of social skill programs started in hospitals. For example, some were token economies, where patients were given tokens that could be exchanged for goods, e.g., candy and cigarettes, for engaging in positive behaviors. Given the cognitive limitations of the population, evidence indicates that teaching skills *in vivo* is more effective than in service arenas that require subsequent generalization of the acquired knowledge to other settings and situations (Corrigan et al. in press).

Skill trainers are essentially teachers as opposed to therapists (Bellack 2001). These trainers employ principles and techniques of behavior therapy for teaching social skills (Kopelowicz et al. 2006). Social skills training entails consumers learning specific interpersonal skills and personal competencies through methods that promote the maintenance and generalization of new or rehabilitated skills to increase social competencies, social role functioning, and quality of social relationships (Bellack 2001, Mueser et al. 1997). Initially, much of the training focused solely on behavioral skills, but now includes social, perceptual, and cognitive skills as well (Mueser et al. 1997). Given the grounding of the approach in social learning theories, social skills training is conducted with highly structured educational procedures, in contrast to less-specific resocialization experiences. Group social experiences, such as attending an organized social activity at a psychosocial center, provide opportunities to practice interpersonal skills, receive consensual validation for acceptable behaviors, and obtain positive as well as negative feedback. However, these responses depend on the chance occurrence of the nature of attendees and events, rather than on prepackaged or systematically prescribed training experiences.

The resocialization experiences offered in psychosocial clubhouses are different from social skills training. In contrast to informal socialization experiences, the highly systematized programs of social skills training employ specific behavioral techniques such as role playing, social modeling, positive and corrective feedback regarding appropriate behaviors, coaching, didactic instructions, attention-focusing procedures, problem-solving techniques, and homework assignments. Once deciding on the targeted behavior to be taught, complex behaviors are broken down into discrete behavioral elements, and the individual is trained for each element employing various techniques. Once the individual can perform the elements, then gradually the elements are taught to be combined. Skills are frequently taught in groups with two trainers, one directs sessions and the other role plays. Teaching a circumscribed skill usually takes 4–8 sessions, while a more comprehensive skill may take anywhere from 6 months to 2 years. Training sessions frequently occur 2–3 times per week (Bellack 2004). Sessions can also be conducted on an individual basis or with family members or other social network members, as these individuals can help to encourage and reinforce the use of the skill (Kopelowicz et al. 2006).

Robert Liberman, and his colleagues at the Center for Research on Treatment and Rehabilitation of Psychosis have developed a number of skill training modules that have been widely disseminated and are available for purchase (http://www.mentalhealth.ucla.edu/). These modules include medication management, symptom management, recreation for leisure, community reentry, job seeking, and workplace fundamentals training. The modules contain a videotape of a role play demonstration, a trainer's manual, and a patient workbook. The center also has a number of clinical manuals available, such as management of aggressive behavior, and involving families in mental health services for adults with SMI.

The patient outcomes research team (PORT) on schizophrenia has recommended social skills training (Lehman et al. 2004). Research has demonstrated the efficacy of the approach for teaching a range of behaviors, including conversational skills, assertiveness, heterosocial skills, and medication management. However, many of the studies have been conducted with those with schizophrenia and in inpatient settings (Dilk and Bond 1996). Bellack (2004) reviewed 12 meta-analytic and narrative reviews of social skills training and concluded that social skills training does not reduce or prevent relapse; but this psychotherapeutic approach does improve targeted behavioral skills; seems to have a positive impact on social role functioning, although results are inconsistent in this regard; and improves consumer's sense of self-efficacy with targeted social situations after training. Furthermore, consumers and providers are highly satisfied with the technology. The approach is most effective when it is in embedded in a broad, comprehensive rehabilitation program (Kopelowicz et al. 2006). Recently, social skills training has been incorporated into community-based case management services in order to help to increase the transfer of skills to community settings. For example, enlisting family members, coworkers, and peers to provide feedback and cues in "real" situations has been demonstrated to be useful. Combining psychoeducation and skills training is effective in improving communication among family members and, consequently, reducing environmental stress. Skills training has been found to enhance cognitive functioning. However, to date, no studies of cognitive rehabilitation have demonstrated a clinically significant effect on community outcomes. Cognitive rehabilitation seems to have potential, but data demonstrating its effectiveness are not yet available (Bellack 2004). Wexler and Bell's (2005) research on cognitive remediation

treatment with work therapy and supported employment demonstrates clinically significant improvements in cognition as well as work functioning.

Although some attempts have been made to enhance social skills into the consumers' own environment, questions remain as to the efficacy of this approach in terms of the transfer of learned behavioral skills by consumers to every day life settings and in terms of improved social functioning in daily routines by the use of such skills (Kopelowicz et al. 2006). Efforts to facilitate the transfer of skills from the training environment to the natural environment is essential, otherwise generalization may not occur. There has been a variety of recent attempts that "offer opportunities, encouragement, and reinforcement for using in the community those skills learned in training" (Kopelowicz et al. 2006, p S16). For example, In Vivo Amplified Skills Training (IVAST) involves specialized case managers who assist with the application of newly learned skills to the community setting. Research has found that those with this supplementary support have higher levels of interpersonal problem-solving skills, significantly improved social adjustment, and a better quality of life over a 2-year time frame than those who received only the skills training (Glynn et al. 2002). Kopelowicz et al. (2006) studied the use of indigenous or natural supports serving some of the functions of the case manager. In this approach, the consumer selects supporters based on criteria of cooperativeness, accessibility, and familiarity with the environmental setting. The selected supporters were provided brief training and weekly supervision by the case manager for their efforts on behalf of the consumer. Evaluation of this approach revealed that participants who received this support in addition to the skill training increased their interpersonal and community functioning during the 18-month follow-up period post-training; while those who only received the skill training lost some of their improvements during the course of the study (Tauber et al. 2000). A similar approach employed Latino family members to teach skills and enhance the application of these skills for their relatives with schizophrenia. Again, this approach demonstrated improvements, i.e., fewer hospitalizations compared to those receiving usual care (Kopelowicz et al. 2003). Thus, there is some promise in approaches that promote supplemental skills training to offer opportunities for application to daily life activities in the community.

## Boston University Rehabilitation Approach and the Choose-Get-Keep Model

The Center for Psychiatric Rehabilitation at Boston University engages in research, training, and service provision to improve the lives of those with psychiatric disabilities. The Director of the center, William Anthony, who was educated in physical rehabilitation, has been very influential in the promotion of the practice and values of psychiatric rehabilitation. He was one of the first professionals to define, articulate, and promote the relevance of the concept of recovery for this population. This center has developed a specific rehabilitation approach.

The Boston University or BU approach consists of three phases: the diagnostic, planning, and intervention phases (Pratt et al. 1999, Anthony et al. 1987). This approach is based on the premise that successful rehabilitation processes begin with an assessment of the client's readiness to engage in rehabilitation activities, the client's current skills, and the environments in which the client operates. Based on this information, a plan which prioritizes goals and objectives is formulated in partnership with the client. Finally, strategies and interventions for accomplishing the goals and objectives are delineated (Pratt et al. 1999).

The client with the aid of a rehabilitation practitioner defines the rehabilitation goal(s) in a selected domain, such as socialization, housing, self-care, employment, or education that the client wishes to achieve in a reasonable period of time, often in 6–18 months. The diagnosis then involves a crucial step, i.e., a functional assessment, during which the client and the rehabilitation practitioner develop a list of the client's assets or abilities, as well as handicaps or disabilities relevant to the achievement of the goal(s). The assessment proceeds to explore questions such as which skills does the client have and which additional skills does the client require to achieve the goal successfully, for example, in acquiring a job or date, living independently in an apartment, or succeeding in school (Anthony et al. 1987).

A third dimension of the assessment or diagnosis is an evaluation of the client's environment and support system. The client's environment is assessed as to whether it is conducive to the achievement of the client's goals and the extent to which there are environmental barriers that may hinder their accomplishment. Thus, an assessment of both the client's personal needs and environmental requirements is essential to a realistic psychiatric rehabilitation diagnosis (Anthony et al. 1987). For example, questions such as the following are posed with regard to obtaining and maintaining employment: Can the person handle a full-time job or is a part-time position a better fit? Can the person share a job? Is she or he best able to function with written rather than oral instructions?

Upon completion of the diagnostic assessment, the client and practitioner jointly determine priorities for skills development and environmental or resource modifications that are the basis for initial interventions. Each skill to be mastered and/or each resource to be obtained is commonly assigned one or more strategies or interventions. These are the basis for the written plans to be signed by the client and the practitioner (Anthony et al. 1987).

The primary rehabilitation intervention strategies employed in this approach are skill acquisition and resource development. Skill acquisition involves direct skill teaching, and is employed when the functional assessment indicates that the client does not have the required skills to achieve the desired goals. This technique leads the client through a series of instructional activities to the point where the client can use the newly acquired skill. The resource development approach is a step-by-step process to overcome the barriers to using the new skill in the particular environment of choice. Resource development strategies involve resource coordination or modification. In resource coordination, a preferred resource is selected, arrangements for its use are made, and supports are obtained and provided in the employment of the needed resource. Resource modification involves adapting existing resources so that they meet the needs of the client (Anthony et al. 1987). This may entail negotiating with a program to make resource adjustments to fit the client's functional objectives.

In the late 1980s, Danley and Anthony developed the choose-get-keep model of supported employment. They recognized the importance of consumers being involved in the process of achieving employment, rather than being placed in a job. This process involves consumers in choosing, getting, and keeping a job that is consistent with their interests, preferences, skills, and aspirations. This approach includes assisting the client in the job choice, helping the client to develop job-seeking skills, and teaching appropriate job behaviors, such as dressing appropriately and being on time for work. Clients are helped to obtain a job and then provided with the necessary supports for performing the job once employed (placed). The choose-get-keep model involves consumers much more in the decision-making about securing employment. In the get phase, specific employers are identified, contacted, and interviewed with obtaining employment being the ultimate goal. In the keep phase, the client applies appropriate work behavior skills as well as technical abilities to do the job. This model replaced the practice of training clients, and then, placing them in jobs or what was called the train-then-place approach, which was the traditional approach to vocational rehabilitation of getting clients ready for competitive employment.

The research of the BU model, specifically, the choose-get-keep model of supported employment has been limited. However, the technological orientation and beliefs have been the foundation for a number of programs and other models, which have reached the level of EBP, specifically supported employment.

### Peer Support Approaches

Peer support approaches encompass services and supports that are provided by individuals who have a severe mental illness to other individuals with similar disorders. This psychotherapeutic approach is recovery oriented as it engenders empowerment and is based on a belief of consumer self-determination. The underlying assumption of peer support approaches is that those who have shared common experiences are in a better position to offer supports to each other in a safer environment than those who have not had a history of psychiatric treatment (Corrigan et al. in press). Peer support is defined as the provision of emotional support frequently accompanied with instrumental support that is mutually offered by individuals who have both a mental illness and partner together with the specific intention of bringing about social and personal change (Gartner and Reissman 1984). Within the domain of peer support services, there are two approaches: mutual support or self-help groups and peer provided services.

Mutual aid or self-help groups are usually initiated by peers who voluntarily join with others like themselves to mutually assist each other to satisfy a common need or problem (Katz and Bender 1976). These groups instill hope, and offer information and opportunities to mutually help the members. Typically, these are face-to-face groups, but recently there has been a development of internet peer support groups. The most well-known of peer support groups for individuals with psychiatric disabilities are GROW, Schizophrenia Anonymous, and Depression and Bipolar Support Alliance. The research that has been conducted on self-help has not been able to determine its effectiveness, as the use of randomized designs is antithetical to the notion of voluntary participation in self-help groups. However, less rigorous studies, i.e., those employing pre-post test designs or correlational studies, have found benefits derived from participation in these groups (Solomon and Draine 2001).

Peer provided services are provided by individuals who self-identify as a person who is receiving or has received services for their mental illness, and who then delivers his services to others with a similar psychiatric disorder. There are three types of services that fall within this categorization: peer run or operated services, peer partnership services, and peer employees. One of the primary differences among these three approaches is the amount of control and decision-making over the operation and nature of the service provision. In peer operated services, peers have total control over the administrative operation and functioning of the service, whereas with partnerships these functions are shared with nonpeers. Frequently, the types of peer provided services have been drop-in centers, case management services, and crisis programs. With peer employees, the amount of control and power that they have in an organization vary with the position held, as is the situation with nonpeer employees. There has been limited research on peer provided services, but the few randomized clinical trials (RCTs) that have been conducted have found positive outcomes, with no detrimental effects (Corrigan et al. in press). These services are being promoted by SAMHSA and were identified by the New Freedom Commission as an emerging best practice, as there are not enough RCTs to achieve the level of EBP.

## Recovery and Rehabilitation

With the publication of the first Surgeon General's Report on Mental Health (U.S. Department of Health and Human Services 1999) and the final report of the US President's New Freedom Commission on Mental Health (2003), the idea of recovery among those with SMI has gained prominence and achieved legitimacy, although consumers have been writing about this since the 1980s. These reports, with their authority of government documents, have stimulated the transformation of mental health service delivery to that of a recovery orientation. Thus, the idea of recovery is having a major impact on both mental health policy and practice in the US SAMHSA has issued a consensus statement on the definition of recovery and the fundamental components of recovery. This statement emerged from an expert panel of consumers, family members, providers, advocates, researchers, academicians, managed care representatives, accreditation organization representatives, state and local public officials (see Table 97–2 for SAMHSA's consensus statement of mental health recovery).

Unlike the medical approach, recovery does not require individuals with SMI to achieve a total elimination of symptoms and related deficits resulting from the disorder, and consequently, may not necessitate a reduction in the need for medical care. Recovery is different from rehabilitation. Rehabilitation refers to services and technologies that are delivered by mental health providers to help consumers and their families improve their functional capabilities and ultimately the quality of their lives (Barton 1998, U.S. Department of Health and Human Services 1999). Recovery is a "lived experience of persons as they accept and overcome the challenge of disability" (Deegan 1988). Recovery has been

**Table 97–2 SAMHSA's Consensus Statement of Mental Health**

Recovery

Mental health recovery is a journey of healing and transformation enabling a person with a mental health problem to live a meaningful life in a community of his or her choice while striving to achieve his or her full potential.

Fundamental Components of Recovery

- *Self-direction:* consumer leads and chooses direction of recovery.
- *Individualized and person-centered:* recovery varies by an individual's strengths, needs, preferences and experiences.
- *Empowerment:* consumers have the authority to participate in all decisions that affect their lives.
- *Holistic:* recovery encompasses all aspects of one's life, including mind, body, spirit, and community.
- *Nonlinear:* recovery is one of growth, setbacks, and learning from experience.
- *Strengths-based:* recovery builds on personal strengths, capacities, resiliencies, talents, coping abilities and personal worth.
- *Peer support:* mutual support from other consumers is essential to recovery process.
- *Respect:* community, systems, and societal acceptance and protecting rights, along with self-acceptance.
- *Responsibility:* consumers have a personal responsibility for their own self-care and journeys of recovery.
- *Hope:* hope is the catalyst for recovery and can be fostered by others.

referred to as a process, a vision, an attitude, an experience, a way of life, and a guiding principle. There is no one definition that is agreed upon by everyone (See Table 97–3 for definitions of recovery). The recovery message is one of hope, as well as a belief that those with SMI can have a meaningful life, despite their illness (Anthony 1993, Deegan 1988). "[T]he recovery process is governed by internal factors (their psychological perceptions and expectations), external factors (social supports), and the ability to self-manage care, all of which interact to give them mastery over their lives" (U.S. Department of Health and Human Services 1999, p 99). Thus, the process of recovery is a unique journey for each individual.

There is still much confusion about the concept of recovery. In the mental health context, it does not mean an outcome or cure or remission to premorbid functioning, but an ability to function in the community and live a satisfying life. It also differs from other medical and psychiatric concepts of recovery. Davidson et al. (2005) delineated three other concepts of recovery: physical, trauma, and addiction recovery. Physical recovery is used predominately with acute illnesses to mean returning to a prior state, usually referring to a normal condition. If physical recovery is employed in reference to chronic conditions, one is considering a "partial return to normal functioning." Trauma recovery is conceived of as a process "of making sense of the trauma [i.e., in this context, referring to having SMI] and incorporating it into one's life in such a way that its' destructive impact decreases over time" (p 482). Addiction recovery is not viewed as a cure, but rather that individuals are no longer using substances; however, due to the nature of addiction, they remain vulnerable to relapse, and consequently must continue to be vigilant to maintain their sobriety. Thus, recovery in the current mental health context is somewhat related to each of these, but in other aspects it is defined differently from each.

A recovery orientation does not "pathologize" consumers, their aspirations, or interpret goals in terms of their illness, but believes in the capability of consumers and supports them to accomplish their goals and aspirations (see case example of recovery orientation). The impact of recovery on service delivery results in the active participation of consumers in the process, rather than passive recipients of services. Recovery-oriented services are conceived of as believing in and supporting consumers in the process of recovery. A recovery orientation requires a different type of relationship between the provider and service recipient to one in which the providers share power, communicate hope, have recipients set their own goals for service planning, and strengthen recipients autonomy as opposed to increasing their dependence on the service system (Felton et al. 2006).

**Table 97–3 Examples of Recovery Definitions**

"Recovery from mental illness is the process of healing the effects of (a) one's illness and its consequences, (b) the social stigma attached to the illness, and (c) the iatrogenic effects of treatment interventions…Recovery implies a process of retrieval (regaining what was lost because of one's illness and its treatment) and a process of discovery (moving beyond the illness and its limitations)" (White et al. 2005).

"Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of psychiatric disability (Anthony 1993).

"A personal process of overcoming the negative impact of a behavioral disability despite its continued presence…recovery is a process by which an individual with a disability recovers self esteem, dreams, self worth, pride, choice, dignity, and meaning…not tied to symptom relief…relapse may be part of the process" (Wilma Townsend, MSW, mental health consumer, consultant, and trainer).

"Recovery is a process, a way of life, an attitude, and a way of approaching the day's challenges. It is not a perfectly linear process. At times our course is erratic and we falter, slide back, regroup and start again…The need is to meet the challenge of the disability; the aspiration is to live, work and love in a community in which one makes a significant contribution" (Deegan 1988, p 15).

**Case example: Recovery Orientation**

A young man, diagnosed with schizophrenia, who had numerous hospitalizations over the past ten years and periodic homeless episodes, was assigned to a case manager. He had not been employed, except for intermittent work as a day laborer. When asked by his case manager about the goals that he wanted to work on, he indicated that he wanted to be an astronaut, a goal he had dreamed of for many years. However, the case manager did not take this goal seriously. When with further questioning he refused to identify another goal, the case manager wrote in her progress notes "client is delusional and uncooperative." Needless to say, the young man did not progress in his recovery, and he was assigned to another case manager.

**Case example: Recovery orientation *continued***

Again, he was asked the same question, with the same response. This case manager perceived his interest as a pipe dream. Again, no progress was made. The young man was assigned to another case manager. This time, this case manager was more supportive of the client's recovery and rather than dismissing his goal, she suggested finding out what it would take to achieve this goal. He did just this and learned that it was more work than he was interested in doing. However, his interest in space persisted. The case manager worked with him to try to obtain a job in the space industry. He was able to get a job in a company that was affiliated with NASA, and he continued to remain employed there. This example is derived from an article demonstrating that a recovery orientation is the "heart and soul of treatment" (Townsend and Glasser 2003).

The practice of recovery varies from traditional approaches in two ways. One, as previously mentioned, is an orientation that is in contrast to the elimination of symptoms and maintenance of community living. Second is the necessity for a simultaneous focus on intervening at both the individual and environmental level. When the goal is to maximize community inclusion, the importance of enhancing supports for community life becomes essential (Davidson et al. 2005). Recovery in its approach and orientation is relatively consistent with psychiatric rehabilitation.

Recovery is also about providers communicating hope. This is in contrast to what is too frequently still communicated to individuals with severe psychotic disorders that they are on a downward course with limited hope for the future, despite the fact that research in the last 20 years has demonstrated that these individuals do recover in a variety of realms (Harding et al. 1987). Hope is essential for motivating individuals to move toward the process of recovery. Recovery-oriented psychopharmacology is the integration of medication with rehabilitative services. In prescribing medication for their patients with SMI, psychiatrists can engage in a recovery-orientation by providing education about the illness and the treatment, teaching self-management skills, and engaging in shared decision-making about treatment (Noordsy et al. 2002).

## Psychotherapeutic Evidence-Based Practices

Five psychotherapeutic service interventions are now recognized as EBPs for individuals with SMI along with medication algorithms. These are Assertive Community Treatment (ACT), Family Psychoeducation, Personal Illness Management, Integrated Care of Co-Occurring Mental and Substance Use Disorders, and Supported Employment (SE). These have been endorsed and promoted by the President's New Freedom Commission, the PORT study of schizophrenia (Lehman et al. 2004), a series in *Psychiatric Services*, books devoted to these interventions (Drake et al. 2005), and by SAMHSA, which has developed toolkits to assist in their implementation. Although dissemination of these practices has been extensive, for the most part, these EBPs have not been extensively implemented in mental health service delivery systems nationwide.

## Assertive Community Treatment And Other Case Management Models

ACT is considered to be a model of case management services for adults with severe psychiatric disorders. Although ACT serves the functions of case management, it goes well beyond traditional models of case management. In order to comprehend ACT, it is best to have an understanding of what case management is as well as some of the more widely implemented models that are more likely to be encountered in the community mental service delivery system.

### Background of Case Management

With the advent of deinstitutionalization, the need for case management services emerged. As discharged psychiatric patients entered the community, it became apparent that they needed assistance in navigating a complex and fragmented service delivery system. Given the multiplicity of needs of those with SMI, the services, supports, and resources that they need are provided by a diversity of services and systems. CSP saw the need for a centralized coordinating mechanism to ensure that those with psychiatric disabilities received the services and supports that they required, and that there was a clearly designated central point of responsibility and accountability. With the passage of such legislation as the State Comprehensive Mental Health Services Plan Act of 1986 (PL 99-660), case management continued to be the central service element of a comprehensive system of care for those with SMI and has grown in prominence ever since. Case management is essentially the process of identifying, accessing, coordinating, and ensuring that individuals with SMI effectively and efficiently receive the services, support, and resources that they need to live in the community with the greatest degree of independence of which they are currently capable. The core functions of case management are outlined in Table 97–4. The primary goals of case management are to maintain contact with services to avoid decompensation, to increase psychosocial functioning, and to improve the quality of life of persons with SMI and their family caregivers (Corrigan et al., in press). In some cases, case managers may function as enforcers of legal mandates, such as monitoring outpatient commitment or probation and parole stipulations, being a representative payee, or withholding housing, particularly with clients who are substance abusers and/or heavy users of crises services (Solomon 1996a, Monahan et al. 2001). Case management may be delivered by an individual, a pair of case managers, or a team.

**Table 97–4 Core Functions of Case Management**

- Assessing
- Planning
- Linking
- Monitoring
- Advocacy

### Other Models of Case Management

There is a diversity of models of case management (see Table 97–5 for characteristics of case management

models). The most basic of the models is the broker or traditional approach. Broker case managers engage in all the basic functions, but are usually delivered in workers' offices. Therapists may provide these functions in the course of doing supportive counseling. If all the provider does is case management services, then the caseloads are extremely high. This service is one that generally consists of information sharing and making referrals, and then, the client is expected to proceed with limited support or assistance to access these resources on his own behalf. This service provides the bare minimum of case management, and is not very effective with persons with SMI who require additional help in achieving these case management goals. However, given limited financial resources, this model is still widely offered, especially with individuals who are assessed as relatively high functioning.

**Table 97–5 Major Characteristics of Case Management Models**

Broker Case Management
- Linking and brokering services and resources
- Information sharing
- High client/staff ratio
- Office-based service

Clinical Case Management
- Provision of support, skills training, and accessing environmental resources
- Provision of psychotherapy, mostly supportive counseling
- Qualifications of case managers include formal clinical education and supervised therapeutic experiences

Personal Strengths Case Management
- Identification of client's strengths
- Utilization of community resources to enhance client's strengths
- Teaching resource acquisition skills
- Group supervision of case managers

Rehabilitation Case Management
- Functional assessment
- Involvement of client in establishing a rehabilitation plan
- Assessment and goals related to specific environment of client's choosing
- Provides skill teaching to overcome environmental barriers

Intensive Case Management
- Reserved for high users of service
- Assertive outreach
- Services delivered *in situ*
- Moderate staff/client ratio

Assertive Community Treatment
- Self-contained comprehensive program
- Interdisciplinary team, requires psychiatrist and nurse
- Services delivered on continuous basis
- High staff/client ratio
- Assertive outreach
- Available 24/7
- Teaches social and behavioral skills
- Reserved for most difficult to manage clients
- EBP, manualized program

Clinical case management is designed whereby a therapist serves as a case manager, thus, engaging in both clinical and administrative functions. While this approach makes good conceptual and clinical sense, given the integration of these primary functions, it does not, however, work very well in reality (Sullivan and Rapp 2002). This model requires a skilled therapist who usually does not have either the time or the interest in engaging in broker case management activities. Furthermore, reimbursement of these functions by managed care companies for this service by a therapist is problematic. Commonly, the term clinical case management is employed for essentially broker case management with supportive counseling, as opposed to the provision of psychotherapy.

Strengths case management is based on the belief that individuals who are successful in living in the community have the ability to develop their own potential and to access the needed resources that enable them to reach their own goals. This model focuses on a person's strengths rather than deficits, and makes use of an individual's own natural support system to assist in community integration. In this model, case managers do more than broker services; they deliver services to clients in the community. They help individuals with SMI to identify, obtain, and maintain the environmental and personal resources that they need to live, work, and participate in the community. The approach is for case managers to teach clients to access the resources that they need to live in the community of their choice. The philosophy of this model is that persons with SMI can learn, grow, and change, and that the community is viewed as a resource, not a barrier (Sullivan and Rapp 2002).

The rehabilitation case management model was developed by the Psychiatric Rehabilitation Center at BU. The rehabilitation case manager assists clients by negotiating for services, teaching personal skills, and developing environmental supports to overcome personal and environmental barriers to achieve their own goals (Farkas and Anthony 1993). This model serves the functions of brokering, as well as engaging in rehabilitation.

Intensive case management (ICM) arose as a result of the recognition that the broker model was ineffective with many individuals with SMI. ICM is delivered in the community where clients live and work. In contrast to a broker model, this service model has lower caseloads, engages in assertive outreach, and assists clients in meeting their needs so that they can live as independently as possible in the community. The service elements of this model are not particularly well specified (Schaedle and Epstein 2000). This model is widely implemented, and has borrowed some elements from ACT, specifically delivering services in the community and assertively reaching out to clients.

## Description of ACT

Although ACT was developed in the early 1970s as an alternative to hospitalization for individuals with SMI, it was not until the 1990s that this model was widely implemented. This model, developed in Madison, Wisconsin, was originally called Training in Community Living, and today goes by such names as continuous care teams, full service support, assertive outreach, and mobile treatment teams (Bond et al. 2001b). The intention of this model was to transfer all functions served by a long-term psychiatric hospital to the community. Consequently, ACT is often described as a hospital without walls.

The goals of the model are to reduce hospitalization, increase psychosocial functioning, decrease psychiatric symptoms, and improve life satisfaction and quality of life. The specific tenets of this model are that the locus of care is the community with treatments and supports being comprehensive; and that treatments must be designed to be flexible and individualized to meet the diversity and the ever-changing needs of those with SMI (Test 1998). The notion is that teaching skills *in vivo* reduces the need to generalize skills learnt in one environment to another in which they will be used. In contrast to other models of case management, this is a full service extremely comprehensive program model, with case management being a component of the service. The case managers function as "assertive resource coordinators" (Test 1992). This program is reserved for the most difficult to manage clients, for example, those who have had extensive stays in hospitals and/or living on the streets, and who have problems with substance abuse or encounters with the criminal justice system. Estimates are that ACT is most appropriate for 10–20% of those served in the public mental health service delivery system.

One of the central features of the model is that the service is provided by a multidisciplinary team, comprised of a psychiatrist, nurse, other specialists, and case managers. Frequently, social workers and rehabilitation counselors are also members. The type of specialists included on the team are contingent on the characteristics of the clients being served and the targeted service goals, such as substance abuse counselors, employment or benefit counselors. Caseloads are relatively low, one staff serves 10–12 clients, with teams serving about 120 persons.

The team is the primary provider and responsible entity for all services, rehabilitation, and treatment. The program is self-contained and offers all services that their clients need on an integrated basis. The team meets daily to ensure that all team members are up-to-date regarding each client's clinical and psychosocial status. The team members provide medication, clinical care, supportive counseling, skills training, crisis intervention, assistance with benefits, housing acquisition and maintenance, employment assistance, and specialized services such as substance abuse treatment. Anything that clients need to live successfully in the community is provided by the team. The team is available 24 hours a day 7 days a week. This service is also considered a time-unlimited service, although research has indicated that this policy can be modified. However, it is necessary to have a modulated transfer process that ensures a smooth transition with the possibility that clients can return if necessary (Salyers et al. 1998).

By virtue of being a full service model, ACT is not contingent on the availability of resources in its service environment. This is in contrast to other case management models that are dependent on services and resources in the community. ACT programs generally need to rely on local communities for housing, but for little else.

There have been a number of modifications to ACT programs that have been designed to serve specialized populations or to target a specific objective, such as increasing employment. For example, ACT teams have been developed for forensic clients to assist either in community reentry or in diversion from the criminal justice system (Solomon 2003, Solomon and Draine 1995). ACT teams have also been enhanced with the inclusion of family members or family interventions in order to provide support and education for families of clients served by the team. In addition, ACT teams have been comprised of consumers, thus, using the model as a consumer provided service. Others have reconfigured the staff complement of the teams and, thus, employ fewer staff and serve fewer clients. Even when a change in staffing has been made, psychiatrists are always included on the teams. ACT has served as a basis on which to build other specialized programs for adults with SMI, as for example, the addition of social skill training and SE.

ACT has been widely disseminated. The National Alliance for Mental Illness (NAMI) has distributed manuals to assist in the implementation of this program model. NAMI's objective is that all states will establish a policy to develop ACT programs in all communities across the country.

**Case Example: ACT**

Teresa is a 43-year-old woman who has major depressive disorder with psychotic features, co-occurring alcohol dependence, and a history of numerous psychiatric hospitalizations. For over a year, Teresa lived between a homeless shelter and the streets. She had a broker case manager at a local community mental health agency, but had not attended a psychiatric evaluation with the psychiatrist because she missed three scheduled appointments. Teresa hoped to move out of the shelter, and her case manager informed her that in order to proceed with an application for housing, she needed a copy of her birth certificate, social security card, proof of income, and photo identification. However, Teresa's purse containing these items was stolen at the end of the summer when she spent several months sleeping in a local park. Teresa's attempts to get a new photo id failed as the Department of Motor Vehicles required copies of a birth certificate and social security card. Discouraged about remaining on the streets indefinitely, Teresa's drinking escalated and her psychotic features became more prominent, landing her in the hospital. At the hospital, she was referred to an ACT team, who met her at the shelter. The psychiatrist on the team worked with her to determine an effective regime of medication, while the substance abuse counselor assessed her readiness to quit drinking, and the case manager facilitated Teresa's scheduling and getting to requisite appointments as well as obtaining her photo identification, birth certificate, and social security card. Within a year of receiving ACT services, Teresa's psychiatric symptoms have stabilized, her drinking has decreased, and she has moved out of the shelter into an apartment. The ACT team negotiated with a local landlord by ensuring that they would remain involved in Teresa's treatment, and then, used Teresa's motivation to obtain housing as leverage to encourage her abstinence from alcohol. The ACT team meets with Teresa at her apartment on at least a weekly basis to ensure that she maintains her sobriety and her recovery.

## Evidence of ACT and Other Case Management Models

It is important to note that there have been specific criticisms leveled at the models of case management other than ACT, with others leveled at ACT (Gomory 2004). Stein (1992) noted that there are structural problems with case management models, other than ACT. These models do not have a multidisciplinary team approach, which Stein believes to be essential to treat and care for the complex needs of persons with SMI. Most case management models are dependent on resources that are either unavailable or in insufficient supply in the community system of care. Some critics assert that too much responsibility has been placed on case managers for fixing an uncoordinated, underfunded, and fragmented mental health service delivery system. A latent assumption of case management programs is that they will be able to compensate for the lack of needed community services and resources. However, case managers frequently do not possess the diversity of skills required to correct for these system deficiencies nor do they have the power to change the established system of care (Stein 1992).

A number of studies have evaluated the different models of case management with regard to both system, e.g., rehospitalizations and reincarcerations, and clinical and psychosocial outcomes, e.g., symptoms and social functioning. However, most studies, particularly employing RCTs, have been conducted on ACT or ICM (Mueser et al. 1998). Furthermore, ACT is easier to research as it is a more specified model, and currently, there are a few measures for assessing the fidelity of the implemented model to ensure that new and existing programs achieve the standards of ACT.

There have been numerous reviews, both narrative and meta-analytic, of research on various case management models. Based on these reviews, the conclusions have been quite consistent. ACT, as compared to other models of case management, results in increased likelihood of maintaining individuals with psychiatric disabilities engaged in service, higher degrees of stability in housing, reductions in hospitalizations, and when hospitalized, decreased lengths of stay, and high degrees of both client and family satisfaction. A few reviews did conclude that there were improvements in symptomatology and quality of life. However, most reviews concluded that ACT programs had little effect on social functioning outcomes (Corrigan et al. in press). In order to obtain benefits on specific outcomes, such as vocational or substance abuse outcomes, services need to be directed toward that specific objective by specialized service elements and by the inclusion of specialists on the team. Research has also determined that ACT programs are more effective if they have greater fidelity to the original model (Bond et al. 2001). Reviewers have questioned whether the positive outcome of reduction in hospitalizations is due to the intervention being more coercive than other forms of case management and, therefore, resulting in an increase in medication adherence. However, there has been limited research on adherence to medication in these models.

For those reviewers who assessed the cost effectiveness of ACT, they determined that the program was effective. However, this was primarily attributed to the reduction in hospitalizations or in length of stays when hospitalized. There are those that caution that as systems come to rely less on hospitals for the care of SMI, ACT will result in less of a cost differential with other case management models, such as ICM (Latimer 1999). With the costliness of ACT and with fewer cost benefits, there may be less incentive for mental health authorities to implement this intervention, even though it is considered an EBP.

Reviews that have assessed other forms of case management, excluding ACT, have come to very different conclusions. These other models, usually broker or intensive case management, increase the likelihood that clients remain in treatment, but frequently result in increased hospitalizations and longer lengths of stay when hospitalized, and in some cases result in an increase in the use of mental health services (Corrigan et al. in press). These outcomes are not surprising since these models are not full service models and have a heavy reliance on other services and resources in the community. Thus, outcomes of case management are very much affected by the service environmental context in which they are embedded.

## Family Psychoeducation

Family Psychoeducation is considered an EBP for working with the families of persons with SMI. In order to understand Family Psychoeducation and other family treatment models, it is important to first comprehend the need for family interventions in general.

### *Need for Family Interventions*

Ever since deinstitutionalization, family members have become caregivers and *de facto* case managers. Estimates are that 30–60% of adults with SMI live with their families (Carperntier et al. 1992). This shift in the locus of care has resulted in emotional and financial burden to family members, regardless of whether their relative lives with them or not. Consequently, professionals have increasingly recognized the importance of families in the care of their clients and the necessity of supporting families in caring for their relatives with SMI. However, families frequently do not have the knowledge or skills to undertake these responsibilities. As a result, there has been a growth in family educational interventions. These interventions fall within three domains: family psychoeducational interventions, family education, and family consultation.

### *Description of Family Psychoeducational Interventions*

Family psychoeducational interventions emerged in response to family environmental stress research, which found that patients recently discharged to families' with high expressed emotion (EE), i.e., highly critical, hostile, and emotionally overinvolved, had a high likelihood of psychotic relapse and subsequent rehospitalization (Brown et al. 1958, Brown et al. 1962). Regardless of the intellectual controversies around EE findings continuing to blame the family for the exacerbation of their relative's illness, the findings were an impetus to the development of psychoeducational interventions designed to assist families in coping with disturbing, distressing, and difficult behaviors of their relatives with SMI. The promotion of these interventions has been based on the assumption that behavioral competencies, adaptive coping, problem solving, and communication skills, along with emotional support can assist families to reduce their stress

and, hence, environmental stress. As a consequence, patients, specifically those with schizophrenia, who have biological vulnerability to environmental stress will protect them from exacerbation of their illness, with this protection ultimately preventing relapse and rehospitalization. Although the initial research was on patients with schizophrenia, a recent review by Butzlaff and Hooley (1998) concluded that although EE is a robust and significant predictor of relapse in schizophrenia, it is an even stronger predictor for those with affective disorders.

Family psychoeducational interventions were developed by mental health professionals, frequently by psychiatrists. These interventions are a combination of educational and therapeutic service elements. Given that these interventions were based on the EE construct, these programs have the common goals of reducing relapse and improving the quality of life for both the family members as well as the relative by enhancing the family member's capability of managing their relative's illness. Initially, these interventions were designed for high EE families, but were relatively quickly available to low EE families as well. Although they vary in program content and structure, all provide information about diagnosis, symptoms, signs, etiology, course and treatment, including medication and their side effects. These programs are generally designed to teach problem-solving and coping strategies, management and communication skills to family members. These educational interventions are provided as part of an overall clinical treatment package; therefore, the relative with SMI is required to be in treatment. These interventions usually last at least 9 months, but may go as long as 5 years. These psychoeducational programs are delivered by a team of professionals from a variety of disciplines, including psychiatry, social work, psychology, and family therapy. The major focus for these interventions is on outcomes for the individual with SMI, and secondarily, for family members.

These interventions vary in their theoretical orientation; program elements including the location of the service, i.e., family's home, clinic, hospital or elsewhere; length of service and credentials and qualifications of the provider(s); the content emphasized and the information provided; the degree of emotional support; the focus on problem-solving skills, communication skills, and behavioral management; the use of multiple-family *versus* single-family approach; and approach to delivery of information, such as degree of didactic information, skill teaching, and role playing. Lam (1991) identified the common elements in the various models of psychoeducation (see Table 97–6).

**Table 97–6 Elements Common to Psychoeducational Models**

- Positive approach believing in the capability of families
- Highly structured intervention
- Teaching coping skills and strategies
- Supporting the development of clear interpersonal boundaries within the family
- Education about the illness and its course
- Employment of a behavioral approach
- Teaching family communication techniques

Lam (1991).

Research on the various models of family psychoeducation has not resulted in determining that any particular one is superior to another. It is suspected that since the models have so much in common, such a distinction is not possible. However, McFarlane (2002) multiple-family group approach has been widely promoted. SAMHSA's draft EBP toolkit uses McFarlane's model.

**Case Example: Family Psychoeducation**

Jane is a 25-year-old woman who was diagnosed with schizophrenia at the age of 23. Due to her illness, she was unable to maintain her corporate job and apartment in the city and ended up moving into her parents' house. While they were initially supportive of Jane, her parents soon grew tired of what they perceived to be her lack of motivation and laziness. Within a year of living together, her parents began to criticize, nag, and threaten Jane with eviction in an attempt to motivate her to return to work. Every few months, these disagreements would escalate into open and hostile conflicts that would result in shouting matches between Jane and her mother, lasting several hours long. Following these conflicts, Jane would lock herself in her room, stop eating or taking her medication, and within a few days, Jane would experience psychotic symptoms and suicidal ideation, prompting rehospitalization. After her fourth hospitalization in 2 years, Jane's therapist recommended that she and her parents participate in a family psychoeducation program in conjunction with her existing treatment. Despite Jane's initial reluctance, she and her parents, feeling at their wit's end, eventually agreed to participate in the program. For the first time, Jane's parents were provided with information about the signs, symptoms, and behaviors associated with schizophrenia, and began to understand that what they had perceived to be Jane's lack of motivation was actually symptomatic of her illness and the side effects of her medications. Her parents were also provided with the opportunity to grieve the loss of the hopes and dreams they had had for their daughter and, subsequently, to accept and support her new goal of obtaining part-time employment. Jane and her parents worked together to improve communication, reduce conflict, and start problem-solving as a family. Jane continues to live at home, reports a significantly improved relationship and enhanced communication with her parents, and has not been hospitalized for over a year.

### *Effectiveness of Family Psychoeducation*

There have been at least 14 narrative and meta-analytic reviews of family psychoeducation, and almost all have consistently concluded that these interventions are effective in either delaying or preventing relapse (Corrigan et al. in press). As a result, they have proved to be cost effective due to a reduction in days of hospitalization. In order to achieve these positive outcomes, these interventions need to last for at least 9 months, as brief interventions have not

been found to be effective. Most of these reviews have not drawn conclusions regarding family outcomes, as the intention of these interventions is to improve the family environment so that their relative with the psychiatric disability does better. Given the large number of studies with consistent positive findings, these interventions have achieved the level of EBP. The majority of the studies have been conducted on samples of families with a relative with schizophrenia, and only a few with depression. Some reviews have noted that these interventions have increased adherence to medication by the relative with a psychiatric disability and, consequently, decreased the potential for exacerbation of the symptoms of the illness (Corrigan et al. in press).

### *Family Education*

In contrast to psychoeducation interventions, family education interventions are nonclinical, and their primary objective is to meet the educational and practical needs of the family and to consequently improve outcomes for their relative with SMI (Solomon 1996b, 2000). Many of these programs were developed as grassroot efforts by family members themselves in response to their needs for advice and information to overcome their feelings of inadequacy promoted by encounters with professionals. Families frequently feel that they do not need family therapy, but rather very practical information about their relative's illness and strategies for coping with it. Family therapy generally takes a pathological or deficit perspective as opposed to a competency perspective. The goals of these educational interventions are focused on the family to decrease their stress and burden, increase their coping skills, and improve their quality of life.

The theoretical basis for many of these programs is a coping adaptation framework as well as a social support approach of a supportive network that helps to buffer stress. NAMI's Family-to-Family is based on a trauma model of recovery, which views having a relative with SMI as a traumatic event from which one needs to recover (Burland 1998). These programs are usually freestanding community-based and are delivered in nonstigmatizing environments, such as churches, libraries,, and other convenient and accessible locations rather than as part of a mental health clinic. In contrast to psychoeducation, they are led by families, although professionals are frequently invited to present on specific topics, such as psychiatrists discussing medications. In some cases, these interventions may be co-led by a mental health professional. These are group interventions that are open to anyone with a relative or significant other who has a mental illness, regardless of whether their relative is in treatment or not. When relatives deny their illness or are resistant to treatment [estimates are that up to 50% do so (Kessler et al. 2001)], families often are in need of assistance. Generally, these groups do not include the ill relative, so that family members can feel comfortable to speak freely. Some groups are focused on specific diagnoses and relationships, such as parents, spouses, and children. These educational programs have a didactic component, sometimes using videos and other informational material, and also a sharing component. In some regards, the didactic components are not very different from those of the psychoeducational interventions. Frequently, these groups have a specified curriculum, as does NAMI's Family-to-Family. Some have homework assignments that participants are to do between sessions. Given that these are group interventions, participants experientially learn from other group members and also receive support and empathy. Some of these programs have a skill training component, where participants can practice skills in handling situations that they are likely to encounter during the course of their relative's illness. These are very brief interventions that last anywhere from one session of a few hours or a day to 10–12 sessions, such as meeting weekly for an hour or two. Usually, these groups are offered free of charge or for a nominal fee, as state departments of mental health or local mental health authorities may financially assist in defraying some of the cost.

There have been a few randomized studies, all with some positive outcomes. However, the studies have employed a diversity of outcome measures. Consequently, there is limited consistency in positive outcomes (Solomon 2000). Furthermore, since prevention of relapse is not a target of these interventions, none have demonstrated a reduction in hospitalizations which would accrue cost savings, as psychoeducation does (Solomon 1996b). One study did find improved attitudes toward medication compliance by the relative diagnosed with mental illness (Solomon et al. 1996). But, the number of randomized studies on family education is increasing, and these too are showing positive outcomes (Pickett-Schenk et al. 2006). Therefore, it is likely that these educational interventions may well achieve the status of EBP (Corrigan et al. in press).

### *Family Consultation*

Family consultation or supportive family counseling is an individual approach to providing information, advice, support, and counseling, either to a single family member or a family unit (Bernheim and Lehman 1985). This is an attractive intervention for families who have a relative who resists treatment. This is a collaborative approach between the family and the provider. The provider is usually a mental health professional, but may also be a trained family member (Solomon et al. 1997). The provider and family collaboratively decide on the goals to be addressed and develop a plan for achieving the objectives. The consultant is just that, a consultant, not a therapist. The consultant works with the family in a consultative manner to achieve the agreed upon goals. During the course of consultation, the family member(s) is provided with education and information relevant to their current situation and problem-solving skills, and may be accompanied by the needed resources and/or services by the consultant. Families find that having the consultant available on an ongoing basis is extremely helpful (Budd and Hughes 1997). Just knowing that as issues arise, there is someone available to answer their questions is often stress reducing for families. This service may also be provided via the telephone, but is usually provided in person. This is a short-term approach, with only a few sessions that are highly focused on one or two very specific objectives. Termination is mutually agreed upon. When new issues arise, the consultation may resume (Solomon 2000). There has been limited research on this particular intervention, but the empirical evidence does indicate that this intervention has promise (Solomon et al. 1997). Table 97–7 compares

**Table 97–7 Comparison of Psychoeducation, Family Education, and Family Consultation**

| | Psychoeducation | Family Education | Family Consultation |
|---|---|---|---|
| Theoretical Basis | Historically, EE; currently, coping adaptation, social support | Coping adaptation, social support, sometimes trauma-recovery | Coping adaptation |
| Developers | Professionals, frequently psychiatrists | Mainly families, sometimes collaboration of professional and family member | Professionals |
| Goals | Primary—reduce relapse and rehospitalization; secondary—reduce family environmental stress, improve communication, coping, and problem-solving skills | Meet educational and practical needs of family; reduce their stress and burden | Resolve family concerns around agreed upon objectives of family and consultant |
| Duration | 9 months—5 years | Couple hours, 1 day, weekly sessions for 10–12 weeks | Brief hourly sessions, usually for 1–3 months, contingent on need; may resume at future time |
| Deliverer | Team of professionals, psychiatrist, psychologist, or social worker | Primarily, family members; professional lecture by invitation; some models cofacilitated by professional and family member | Professional, sometimes trained family member |
| Location | Clinic, MH agency, family home | Community setting, e.g., church, school, library | Professional's office, via the telephone |
| Structure | Group process; sharing information about concerns | Educational curriculum | Advising, facilitate problem solving; share information as needed and relevant |
| Format | Individual family unit or group of families, dependent on model | Group of family members | Individual family member or family unit |
| Relationship of Professional and Family Member | Collaborative | Primarily none; some models partner | Partnership |
| Inclusion of Ill Relative | Include ill relative | Usually exclude | Usually exclude, periodically may include |
| Relationship to Ill Relative's Treatment | Adjunctive to relative's treatment | Independent, freestanding of mental health system | Independent, frequently independent of mental health system, currently incorporated in mental health system |

family consultation with family psychoeducation and family education.

### *Family Support and Advocacy Groups*

Family support groups involve families voluntarily coming together to provide and receive support, empathy, information, and advice from others who share the common experience of having a relative or significant other with a psychiatric disorder. Families facilitate these groups. The groups are open-ended in terms of intensity or duration of participation and meet in a nonstigmatizing environment. The goals of these groups are to increase knowledge, decrease burden and stress, and increase skills to deal with the illness. These groups also afford an opportunity to engage in advocacy efforts to make changes in policy, services, and practices regarding mental health issues. Most local communities have some family groups available, and mental health professionals have been known to refer family members of their clients to these groups.

There has been almost no research on the effectiveness of these groups, as the use of randomized designs is antithetical to these voluntary groups. Less rigorously designed studies have indicated positive outcomes, such as increased knowledge, improved social support, and decreased burden and stress (Corrigan et al. in press).

## Personal Recovery Management

Illness Management and Recovery (IMR), an EBP, consists of weekly sessions in which specifically trained providers assist individuals with psychiatric disabilities develop personal strategies to manage their symptoms, cope with their illness, prevent relapse, and subsequently move forward on their own personal recovery. This program was developed as part of the National Implementing Evidence-Based Practices Project funded by Robert Wood Johnson and SAMHSA (Mueser et al. 2006).

The impetus for the development of IMR came from increased enthusiasm for recovery, which led to the "recognition that practitioners are most effective when they empower consumers to learn how to manage the symptoms of mental illnesses and increase control over their own lives" rather than doing for their clients (Gingerich and Mueser 2005, p 397). Based on a review of the research, five service components of the IMR program were identified (Mueser et al. 2006) (see Table 97–8).

**Table 97–8 Service Components of IMR**

1. Psychoeducation about mental illnesses and treatments
2. Cognitive–behavioral approaches for adherence to medication
3. Social skills training to increase social supports
4. Coping skills training to manage symptoms
5. Developing relapse prevention plan

Mueser et al. (2006).

The theoretical basis for IMR comes from two models: the stress-vulnerability model and the transtheoretical model. The stress-vulnerability model poses that course and outcomes of schizophrenia are the result of the interaction of biological vulnerabilities, environmental stress, and ability to cope with stressors. The cycle of stress and vulnerabilities can be broken through teaching illness self-management. Ultimately, the distal goal of recovery can be achieved through the pursuit of one's own personal goals and managing one's illness. The transtheoretical model asserts that an individual's motivation to change occurs over a series of stages from precontemplation, to contemplation, followed by preparation, then action, and finally, maintenance. To facilitate the process of change, intervention strategies need to be directed to the client's particular stage of change. Motivational interviewing is used initially and throughout the IMR program to assist clients in the development of their personal goals, their recovery vision, and exploring how illness self-management helps to achieve their own goals (Mueser et al. 2006).

### *Description of IMR*

IMR can be provided on an individual or group basis, and was originally designed to take 9 months to complete. More recently, it was indicated that it can be completed in 3–6 months. The curriculum was designed to be weekly, with each session lasting from 45–60 min. The program has a highly structured curriculum that is comprised of nine topic areas: recovery strategies, practical facts about schizophrenia, stress-vulnerability model and treatment strategies, building social supports, using medications effectively, reducing relapse, coping with stress, coping with problems and persistent symptoms, and getting needs met in the mental health system. The topics are covered using educational, motivational, and cognitive–behavioral teaching strategies. For each topic, there are corresponding handouts. Homework assignments are developed collaboratively with clients at the end of each session. The homework assignments include practicing the skills they have learned, reviewing the information provided, and/or sharing the information with others. A specific homework assignment might be to start a conversation with a coworker or share information with a sibling. Based on client choice, members of clients' support system, such as family members and friends, are encouraged to participate in assisting the consumer to learn self-management strategies and to pursue their own goals (Gingerich and Mueser 2005, Mueser et al. 2006).

### *Effectiveness of IMR*

Mueser et al. (2002) reviewed RCTs of the individual service components of IMR and determined that the evidence supports the intervention components as EBP. This review found that psychoeducation is effective in increasing knowledge about mental illness; behavioral tailoring was effective in increasing medication adherence; relapse prevention programs reduced relapses and rehospitalizations; and coping skills training and cognitive–behavioral treatment reduced the severity of psychotic symptoms. Each of these intervention techniques is the primary component of IMR. Research on comprehensive illness management programs provides promising evidence for a program like IMR. Since this review, IMR has been pilot tested in two sites in the US and one in Australia, either on a group or individual basis. The pilot data from these sites support both the feasibility and acceptability of IMR, with generally good rates of participant retention. Clients were quite satisfied with the intervention and found it to be helpful in managing their symptoms and making progress toward their own personal goals. With regard to posttreatment outcomes, IMR improved clients' coping with their illness,

**Case Example: IMR**

Robert is a 34-year-old man with a diagnosis of schizophrenia and a history of recurrent hospitalizations. After his most recent hospitalization, he was referred to an Intensive Outpatient Program at a community mental health center (CHMC), which allowed him to attend anywhere from 1–8 group sessions per week on a range of topics from "social skills" to "current events" to "trauma recovery." Despite attending 2–3 groups per week, Robert continued to have difficulty remembering to take his medications daily and had several relapses related to stress caused by family conflicts. On the suggestion of his case manager, he attended a new IMR group offered at the CMHC. Although the group only met once a week, it offered a structured curriculum that provided information about mental illness, covered specific treatment strategies, and assigned "homework" based on what had been learned. For the first time, Robert felt that he understood and could control or manage his illness. One group session focused exclusively on the importance of psychotropic medications in recovery, and each group member developed his/her own individualized strategy to enhance their medication compliance. Since Robert could never remember to take his medications, he developed a plan to put the pills next to his toothbrush every night in order to ensure that he would not forget to take them. Robert also learnt to identify his relapse triggers (family conflicts) and how to avoid them or minimize his reaction to them (go out for a walk or go up to his room). The group provided an opportunity for members to practice social relationship skills, which led to the development of peer friendships between Robert and several other group members. Since attending the IMR group, Robert has continued to take his medication on a daily basis, has maintained his peer friendships, and has not had any relapses.

and specifically with their symptoms. Furthermore, the research also demonstrated an improvement in functioning for participants. Recognizing that these data are limited in that this research did not employ a randomized design, and data are from early treatment experience, they provide evidence supporting the promise of this intervention (Mueser et al. 2006).

## Integrated Dual Disorder Treatment

Integrated Dual Disorder Treatment (IDDT) is considered to be an EBP intervention model for adults with SMI and co-occurring substance use disorders. In order to understand IDDT, it is important to have an understanding of the prevalence of these disorders and the treatment models that were used prior to IDDT.

### *Prevalence of Dual Diagnosis*

Dual diagnosis refers to the co-occurrence of SMI and substance use disorders (abuse or dependence on alcohol or other drugs). Among persons with SMI, a co-occurring substance use disorder is the most common and clinically relevant comorbidity. Studies have estimated that approximately half of persons with SMI report symptoms of substance use disorders (Kessler et al. 1996). This is likely an underestimate, as people tend to underreport substance abuse and dependence. Co-occurring substance use disorders can significantly impede the accurate assessment and consequent appropriate recommendations for treatment unless explicitly assessed when working with persons with SMI.

Co-occurring disorders often complicate the clinical trajectory and long-term outcomes of persons dually diagnosed with substance use and psychiatric disorders. For example, among persons with SMI, a co-occurring substance use disorder is associated with a number of negative outcomes, such as hospitalization and relapse (of both disorders), violence and criminal justice involvement, and homelessness. Individuals with co-occurring disorders are more likely to experience a chronic course of their illness and to utilize more services than individuals with either a psychiatric disorder or a substance use disorder alone (U.S. Department of Health and Human Services 1999). Despite, or perhaps contributing to, these worse outcomes, only 12% of dually diagnosed persons received treatment for both mental health and substance abuse, and more than half of the adults with these co-occurring disorders received no treatment for mental health or substance abuse, resulting in 2 million adults with co-occurring disorders in 2002 not receiving any form of treatment (Office of Applied Statistics 2004).

### *Background of Treatment for Dually-Diagnosed Individuals*

Co-occurring disorders came to light in the 1980s, and interventions were developed in an attempt to address the problems associated with them. Early treatment models included adding auxiliary traditional substance abuse treatment to standard mental health services. For example, a psychiatrist or therapist would recommend that a client with SMI, such as schizophrenia, supplement their mental health treatment with Alcoholics Anonymous meetings in order to address their co-occurring problem with alcohol. Early attempts at treatment for dually diagnosed individuals almost always involved parallel or sequential services for substance abuse treatment and mental health treatment, requiring clients to contend with the difficult process of navigating two different provider systems in an attempt to piecemeal together what was often a fragmented recovery program. In addition, often the two systems of care promote significantly divergent messages, which enhance the existing disconnect between them. For example, some 12-step programs eschew taking any form of drug, including psychotropic medications. Substance abuse providers frequently believe that mental health issues are actually a consequence of substance abuse and, therefore, will be resolved or alleviated once the substance use disorder has been effectively treated, so that there is no need for psychotropic medications. However, psychopharmacological treatment is often an integral component of mental health treatment, which forces the client to make sense of and incorporate these mixed messages into his or her own program of recovery. As a result, many clients end up dropping out of one program in order to assuage the other, or else may become so discouraged that they drop out of treatment altogether.

Other traditional approaches provide treatment in steps or stages; often a client is only eligible to receive treatment for one disorder after completing the treatment for the other disorder. For instance, receiving mental health treatment may be contingent upon completing a substance abuse treatment program (generally a staged program of inpatient, intensive outpatient, and outpatient services), which is often provided by an altogether different agency. In segregated systems such as these, the staff of substance abuse programs are often unaware of or untrained in how to address co-occurring disorders, which results in the psychiatric disorder being viewed as secondary or remaining neglected or untreated. As such, traditional services are typically fragmented and disjointed. In addition, since relapse is a fairly common occurrence among substance abusers, many clients who are unable to fully abstain from drugs or alcohol end up becoming alienated from both the systems. These uncoordinated attempts have been largely unsuccessful because they fail to provide relevant services that effectively address the needs of dually diagnosed individuals, which can jeopardize clients' attempts at recovery and increase their risk for subsequent relapse, hospitalization, criminal justice involvement, and other adverse outcomes. Despite this, many of these parallel service systems still exist and continue to provide fractured psychiatric and substance abuse treatment.

Resulting from this disconnect between treatment services and between systems of care, NIMH funded demonstration projects in the late 1980s to develop comprehensive and effective treatment services for dually diagnosed individuals. As a result, many interventions developed since the combination and/or integration of mental health and substance abuse treatment. These integrated services and the philosophy behind them have come to be known as IDDT.

### *Description of Integrated Dual Disorder Treatment*

In an attempt to address some of the shortcomings of traditional services to persons with co-occurring disorders,

interventions have moved toward integrating these services and providing them in a common setting and in a coordinated fashion. Interventions focus on the treatment of both disorders concurrently by the same team of clinicians providing services in one location. While these interventions may take different shapes or forms, SAMHSA's Co-Occurring Center for Excellence has developed 12 overarching principles that are integral to addressing the needs of persons with co-occurring disorders [(Center for Substance Abuse Treatment 2006) see Table 97–9 for these principles]. Essential to the provision of services to dually diagnosed individuals is the need for integrated screening, assessment, intervention, and systems of care that address both disorders. Drake et al. (2005) identified the main characteristics of IDDT as: services provided by a multidisciplinary team, which should include a mental health treatment team and an integrated substance abuse specialist; stagewise interventions consistent with each client's stage of recovery; time-unlimited services; and access to comprehensive services (i.e., residential services, SE, etc.).

**Table 97–9 Principles for Addressing Needs of Individuals with Co-occurring Disorders**

- Co-occurring disorders should be expected in all behavioral health settings.
- Integrated system of care emphasizing continuity and quality.
- Access via multiple points of entry.
- System of care based on individual needs and preferences.
- System of care supporting the application of evidence- and consensus-based practices.
- Behavioral health systems collaborate with primary care, human services, housing, criminal justice, education, and related fields.
- Co-occurring disorders should be expected when evaluating, assessing, and treating any client.
- Both co-occurring disorders should be considered primary within the treatment context.
- Provider attitudes of empathy, respect, and belief in the capacity for recovery.
- Treatment should be individualized to incorporate the specific needs, goals, and cultural perspectives.
- All phases of assessment, treatment planning, and service delivery recognize and address special needs of children and adolescents.
- Program policy, treatment planning, and consumer advocacy recognize reciprocal role between community and client.

There are a number of models of integrated treatment, including individual therapy, group therapy, family therapy, structural interventions (e.g., case management, day programs), procedural interventions (e.g., contingency management), residential or housing interventions, and vocational rehabilitation interventions. Individual therapy interventions generally address mental health, substance abuse, and/or posttraumatic stress, and are usually provided in conjunction with other services. Most of the group interventions that are used in treating dually diagnosed individuals employ a self-help approach and provide information, discussion, feedback, (peer) support, and an expanded social network to participants. Family interventions involve education, support, and skills in order to support family members who are caring for or are otherwise impacted by their relatives' psychiatric illness and substance abuse. Structural interventions encompass changes in the organization of the health care delivery system, and most commonly include enhancing the intensity and integration of services. Procedural interventions, such as contingency management, involve the provision of incentives or disincentives for specific behaviors and outcomes to reduce substance use. Housing interventions include integrated residential treatment programs to prevent or address homelessness. Vocational rehabilitation services that address social and vocational functioning are often integrated into IDDT programs. In addition, integrated services also encompass pharmacologic interventions that address both the substance use disorder and the psychiatric disorder (Corrigan et al. in press). Regardless of the form of integrated treatment, the overall goal of IDDT is to help clients learn how to manage both illnesses in a complimentary and concurrent manner. Best practices in integrated treatment have emerged from the research on these various forms of IDDT interventions and inform the guiding principles of all IDDT services, which are delineated in Table 97–10.

**Table 97–10 Guiding Principles of IDDT Services**

- *Integrated treatment:* coherent package of mental health and substance abuse services by same clinician or same clinical team.
- *Stagewise treatments:* interventions tailored to client's stage of treatment or recovery.
- *Engagement interventions:* outreach, motivational counseling, flexibility, practical and culturally competent services.
- *Motivational counseling:* clients identify own goals, which enhances readiness for change.
- *Active treatment interventions:* clients acquire skills and supports to manage illness.
- *Relapse prevention:* minimize risk of relapse.
- *Focus on long-term retention:* flexibility managing relapses.
- *Comprehensive services:* individualized to address a wide range of clients' needs.
- *Interventions for treatment of nonresponders:* engage unresponsive clients.

Drake et al. (2004).

## *Effectiveness of IDDT*

The research shows that there is sufficient evidence supporting IDDT in general, as well as several of its components

**Case example: IDDT**

Andy is a 28-year-old male who was referred to his local CMHC after he began exhibiting symptoms of mania. At his intake appointment, Andy also disclosed that he had been using cocaine on a daily basis for the last 3 months. He was given a provisional diagnosis of Bipolar Disorder and Co-occurring Cocaine Dependence and referred to an unaffiliated residential substance abuse treatment facility, with instructions to return upon completion of the program in order to receive mental health treatment. Despite remaining abstinent from cocaine for several weeks into the program, Andy still found himself with racing thoughts, unable to sleep, extremely talkative, and acting out by engaging in sexual relationships with female residents

*(continues)*

**Case example: IDDT *continued***

despite several warnings and threats of being discharged from the program. When Andy met with his substance abuse counselor to express his worries over the trouble his actions had been causing him, stating "my mind just doesn't feel right—I just can't seem to control myself or stop my mind from racing," his counselor dismissed these concerns by telling him that once he had more clean time, everything would begin to fall into place. One week later, Andy grew frustrated that his symptoms had not abated and checked himself out of the program, relapsing back to his prior levels of cocaine use almost immediately. Two months later, after a brief psychiatric hospitalization, he was referred to a residential facility that provided integrated and concurrent mental health and substance abuse treatment. There, Andy received psychotropic medication to control his symptoms of mania, individual therapy to identify the signs and symptoms of his psychiatric disorder and how it contributed to his substance use, and participated in a 12-step recovery program that helped him identify his triggers and provided him with peer-support on how to remain clean and sober. Upon completing the residential program, Andy continues to receive medication management and individual therapy on an outpatient basis while also attending Double Trouble meetings twice weekly. He has been clean and sober, and had no manic episodes in over 6 months.

specifically as EBPs. A review of controlled studies of integrated psychosocial interventions between the years 1994–2003 found substantial evidence supporting IDDT as an effective practice for persons with co-occurring psychiatric disorders and substance use disorders (Drake et al. 2004). With regard to the specific principles of IDDT, there is strong evidence supporting integrated treatment, stagewise treatment, outreach engagement interventions, and motivational counseling. For example, research has found that adding assertive outreach to an intensive integrated outpatient program improved engagement, retention, hospitalization outcomes, and abstinence from substances; and that motivational counseling, even as a brief intervention, reduced substance use and dependence, psychopathology, and hospitalizations when compared with standard treatment or educational sessions or advice (Drake et al. 2004). A review of pharmacological treatments found that the atypical antipsychotic clozapine can be helpful in treating substance use disorders in people with schizophrenia; valproic acid and lithium is associated with improvements in alcohol-related disorders in people with bipolar disorders; and that disulfiram and/or naltrexone have positive effects on alcohol abuse for dually diagnosed individuals (Corrigan et al. in press).

In terms of specific interventions, all forms of IDDT appear to have advantages over nonintegrated treatment. For instance, short-term integrated residential treatment interventions had higher rates of completion, less relapse, and less reincarceration and criminal activity (among persons released from prison) over treatment-as-usual (e.g., substance abuse residential treatment). Long-term residential integrated treatment also had better engagement and more successful discharges over long-term residential mental health or substance abuse treatment alone (Drake et al. 2004). The existing research has found that there is enough evidence to qualify IDDT, both as an intervention comprised of specific components and as an overarching philosophy, as an EBP that provides effective services to persons with psychiatric and co-occurring substance use disorders.

## Supported Employment

Employment is often an essential component of the recovery process because of its ability to imbue a sense of hope and meaning into the lives of persons with SMI and contribute to their enhanced integration into the community at large. In order to address the desire of many individuals with psychiatric disorders to obtain employment, a number of interventions have been tried with varying success over the years. SE evolved out of the psychiatric and vocational rehabilitation movements, and has been researched extensively and is now considered an EBP.

### *Rates of Unemployment of Persons with Psychiatric Disorders*

Persons with psychiatric disorders have extremely high rates of unemployment and limited participation in the labor force. In 2005, the employment rates of persons with a mental disability (defined as a mental or emotional condition, lasting 6 months or longer that results in difficulty learning, remembering, or concentrating) were 29.0%; however, these rates were only 14.2% when examining rates of full-time, full-year employment of 35 or more hours per week for 50 or more weeks per year. As a result, in 2005, among individuals with all types of disabilities, persons with mental disabilities had the lowest annual labor earnings, the lowest median household income, and the highest poverty rate (Rehabilitation Research and Training Center on Disability Demographics and Statistics 2005). Among adults with SMI, the unemployment rate hovers around 90% (National Institute on Disability and Rehabilitation Research 1992).

Persons with psychiatric disabilities face numerous obstacles in obtaining and maintaining employment, which include, but are not limited to: an inconsistent or interrupted work history; lack of access to information, social capital, and social networks; lack of skills and training; interpersonal difficulties; difficulty balancing psychiatric symptoms and work; side effects from psychotropic medications (sedation, difficulty concentrating, etc.); stigma or bias toward persons with mental illness; and fear of losing disability (SSI or SSDI) and medical benefits (Medicaid). Despite these numerous obstacles, employment still remains an important life goal for many persons with SMI. In addition to providing meaningful daily activity and social networks and connections, work can provide structure and routine into an otherwise unstructured and often isolated existence.

### *Background of Vocational Rehabilitation*

Vocational rehabilitation is comprised of interventions that target work-related skills with the goal of placing

participants in competitive employment. While these programs were initially targeted to persons with physical disabilities, the Rehabilitation Act of 1973 mandated access to services in the state–federal vocational rehabilitation system for individuals with severe disabilities, which included persons with severe psychiatric disabilities. However, the literature shows that the rehabilitation rates of these programs have been much higher for persons with physical disabilities than for persons with psychiatric disabilities and that persons with severe psychiatric disabilities generally have the lowest rehabilitation rate (Andrews et al. 1992). These results may reflect the mismatch between traditional vocational rehabilitation services and the needs of persons with severe psychiatric disabilities, many of whom suffer from cognitive impairments which can impact their ability to obtain and maintain competitive employment (McGurk and Mueser 2004) within a relatively short timeframe and without ongoing assistance and supports, as is generally expected of traditional vocational rehabilitation participants.

Despite this mismatch, a number of employment interventions for persons with psychiatric disorders have been influenced by traditional vocational rehabilitation programs, most notably in their train and place orientation, emphasizing extensive training before placing individuals in jobs. In practice, this translates into the bulk of services addressing the "front-end" of the job search process, such as job readiness skills, social and interpersonal skills training, and basic technical or vocational skills training, rather than targeting job obtainment and retention phase, which is when persons with psychiatric disabilities may need additional supports. While this type of strategy may be successful for persons with physical disabilities, it may not be appropriate for persons with psychiatric disabilities, as they often need ongoing assistance navigating the processes of interacting with coworkers and supervisors, as well as balancing psychiatric symptoms, treatment, and medication side effects with their jobs, all of which are integral components of ensuring long-term job tenure.

Traditional vocational rehabilitation programs for persons with psychiatric disabilities included hospital-based work, sheltered work settings, job clubs, prevocational training, and transitional employment. While many of these programs still exist (see Table 97–11 for a summary of settings and approaches to vocational rehabilitation), in general, newer models have been developed to address the fact that traditional vocational programs do not place much of an emphasis on obtaining competitive employment, consumer job preferences, or the integration of persons with SMI with persons without such disabilities. Further limitations of these traditional programs are that many of these programs are time-limited and do not tailor their interventions to specific or individual needs. Many of these approaches are waning and being replaced with newer approaches, specifically SE.

Vocational rehabilitation interventions, which have developed more recently, have incorporated the recovery orientation into their services by focusing on empowerment, consumer choice, and the full integration of persons with psychiatric disabilities into society. SE, which grew out of the psychiatric rehabilitation movement, incorporates all of these tenets. It has become the most accepted model of vocational rehabilitation, and over the past 15 years, it has been one of the most thoroughly researched interventions (Corrigan et al. in press).

**Table 97–11 Summary of Settings and Approaches to Vocational Rehabilitation**

- *Sheltered work:* segregated setting, unskilled jobs, paid less than minimum wage, focus on therapeutic outcomes, and teaching job readiness skills.
- *Job clubs:* group approach to assist patients in finding work, focus on providing resources for effective job search.
- *Transitional employment*: placement in time-limited jobs to learn job-related skills (e.g., punctuality and social behaviors), focus on providing successful but temporary work experiences.
- *Supported employment*: competitive work with ongoing supports in integrated work settings.
- *Job coaches*: one-to-one support and contact at the work site, focus on specific job skills.
- *Job enclaves*: employment in a business as a segregated group and paid prevailing wage.
- *Mobile work crew*: travel as a group with a supervisor to fulfill contracted work (i.e., janitorial or landscaping work).
- *Consumer-run businesses and programs*: developed and operated by consumers.
- *Small businesses*: developed and operated by mental health agencies providing transitional or permanent employment.
- *ACT with vocational component*: teams include employment or vocational specialist(s).

### *Description of Supported Employment*

SE is defined by Public Law 99–506 as "competitive work in integrated settings (a) for individuals with severe handicaps for whom competitive employment has not traditionally occurred, or (b) for individuals for whom competitive employment has been interrupted or intermittent as a result of a severe disability and who, because of their handicap, need ongoing support services to perform work" (Federal Register Title 1988). The major components of SE are: competitive employment, integrated work setting, and provisions for ongoing support. Competitive employment is defined as work that is performed on a full-time or part-time basis, averaging at least 20 hours per week and compensating the employee in accordance with the Fair Labor Standards Act. An integrated work setting is one in which an individual with a disability works in a conventional work setting with other workers who are not disabled and has the opportunity to have ongoing contact with workers without disabilities. Ongoing support refers to the provision of continuous or periodic services that are provided either onsite or offsite in order to promote job tenure and can include transportation, counseling, and mediation between employee and employer.

As a vocational strategy, SE shifts the orientation from train and place to place and train. As a result, programs emphasize on helping clients to identify and obtain a job as quickly as possible in order to engage them and then provide the training and/or supports necessary to maintain employment successfully by problem-solving along the way. This approach reduces the amount of time spent at the "front end" of the job search process, which is often a time when clients become frustrated with the time spent on prevocational training and drop out of the program altogether. Instead, SE assists persons with SMI to obtain and maintain competitive employment opportunities that are consistent with

their individual preparedness, goals, strengths, and abilities. In addition, services are provided in a collaborative and integrated manner.

In general, an SE team consists of at least two employment specialists who work collaboratively with a mental health treatment team or ACT team to provide integrated care, which is considered a key element of this service. Integrated care means that staff associated with all core services work together to develop an appropriate treatment plan with the client. A typical team consists of employment specialists, case managers, a psychiatrist, a nurse, and a substance abuse specialist (if applicable). Together, the team and client identify the client's treatment goals and then plan collaboratively on how to best achieve them. To this end, the employment specialist works with clients at all stages of employment, including skills assessment, job search and identification, and finally obtaining and maintaining employment. Clients are also provided with benefits counseling to assist with navigating between public benefits systems and wages/benefits received from employment.

Drake and Becker (Becker and Bond 2002) developed the Individual Placement and Support (IPS) model to standardize SE principles for persons with SMI in order to operationalize, research, and implement SE as an intervention. Many existing SE programs around the country follow the principles of the IPS model (Bond et al. 2001), which also serves as the foundation of SAMHSA EBP Implementation Resource Kit on Supported Employment. The core principles of this model are delineated in Table 97–12. There is relatively strong evidence supporting the effectiveness of the principles of eligibility based on consumer choice, rapid job search, and integration of vocation and mental health (Bond 2004).

**Table 97–12 Core Principles of Supported Employment**

- Eligibility based on consumer choice
- Integrated treatment with coordinated services
- Competitive employment
- Rapid job search
- Time-unlimited and individualized support
- Consumer preferences inform job placements

### *Effectiveness of Supported Employment*

Research has found that the intensive range of services encompassed in SE produce higher rates of competitive employment, longer job tenure, and higher earnings for persons with SMI over traditional approaches to vocational rehabilitation across a broad range of client characteristics and community settings (Bond et al. 2001a). A review of quasi-experimental and RCTs identified the critical elements of SE that are predictive of better employment outcomes: agency commitment and resources devoted to competitive employment; rapid job search approach; individualized job placement based on client preference, strengths and work experience; follow-up supports maintained indefinitely; and close integration of SE with the mental health treatment team (Bond et al. 2001a). These components are in keeping with a psychiatric rehabilitation orientation and its focus on hope and belief in consumer's recovery.

In order to systematically evaluate the effectiveness of SE, SAMHSA designed the Employment Intervention Demonstration Project (EIDP), which was a multisite RCT of SE in eight locations across the country (Cook et al. 2005). Experimental study groups received SE models of treatment while control groups received treatment as usual (standard vocational services), with a 24-month follow-up for both the groups. The major findings from this large-scale study confirmed SE as an effective EBP for persons with SMI. Participants in the experimental groups were more likely to achieve competitive employment, work more than 40 h in a given month, and earn more money than

**Case example: SE**

Joe is a 48-year-old man living with schizophrenia. Due to his psychiatric disability, Joe has not worked for over 10 years, but finds himself at a point in his life where he would like to seek employment. His symptoms have been stable for the last 6 months and, with the help of his ACT team, he recently moved into his own apartment located in the center of a suburban area. His sporadic work history includes manual labor, construction work, and stock clerk positions at supermarkets and warehouses. His personal hygiene is minimal, and as a result, his appearance is somewhat disheveled and often gets mistaken for being homeless when walking through the center of the town. He also has difficulty rising in the morning due to his combination of psychotropic medications and often sleeps until noon. Despite his desire to return to work, he feels ambivalent about possibly losing his SSI checks and Medicaid benefits. He occasionally looks for help wanted signs on the windows of the three local convenient stores he frequently passes by, but is afraid to ask about employment directly as he feels that people perceive him as "different." When he does mention his interest in employment to his ACT case manager, she suggests that he meet with the employment specialist (ES) on the team. Joe and the ES discuss his goals, preferences, and strengths, and then focus on finding a part-time job within walking distance that allows Joe to retain his Medicaid benefits and only requires him to work in the afternoons. The ES stresses the importance of appearance at the workplace and, consequently, brings Joe to get a haircut and purchase a dress shirt and slacks for interviews. Within a month and a half, Joe secures part-time employment at a local supermarket stocking shelves. When an issue arises within the first several weeks regarding Joe's difficulty communicating with his supervisor, the ES intervenes by helping the supervisor understand Joe's illness and facilitating a conversation between the two men. Joe has maintained this job for more than 6 months.

participants in control groups even when controlling for demographic, clinical, work history, disability benefit status, and potential study site confounders; in addition, the advantages attributed to the experimental groups over the control groups continued to increase during the 24 month follow-up period (Cook et al. 2005). The results from this study also confirmed some of the basic principles of SE. For example, participants who received well-integrated vocational and mental health services had significantly better employment outcomes than those who did not receive integrated services; integrated employment services produced positive employment outcomes regardless of client characteristics, diagnoses, work histories, and level of functioning; and better employment outcomes were associated with more vocational services received (Cook et al. 2005). There is similarly a strong evidence confirming the effectiveness of SE for use with individuals who have schizophrenia and other psychotic disorders (Twamley et al. 2003). Finally, research has also identified that the benefits of SE are lasting, with the average job tenure being 32 months (Salyers et al. 2004).

### *Brief Overview of Supported Education*

Supported education is a psychiatric rehabilitation approach for those persons with psychiatric disabilities who would like to return to school, generally for postsecondary education. It involves the provision of services that increase access and retention in postsecondary educational institutions for individuals who have had difficulty attending or completing their education due to a mental illness (Unger 1993). Supported education evolved out of SE and employs many of the same principles, such as integrated services, consumer preferences, provision of services in the community, and individualized and time-unlimited services. The focus of supported education is to assist those clients who desire to pursue education rather than work, which is often the case for younger clients whose educational careers have been disrupted as a result of their illness. Since the typical or modal age at the onset of many psychiatric disorders is in the late teenage years or early to middle 20s, educational careers are often interrupted and/or terminated at that point. The goal of supported education is to provide individuals with psychiatric disabilities with the skills and credentials necessary to eventually obtain competitive employment, without which many of these young adults would end up underemployed or unemployed and impoverished.

The mission of supported education programs is to empower adults with psychiatric disabilities to choose their own educational goals and attain their highest potential by providing opportunities for skill development and collaborative support (Mowbray et al. 2005). While supported education models vary (see Table 97–13), core services include: career planning, academic survival skills, and outreach to services and resources. The principles of supported education include hope, normalization, self-determination, support and relationships, and systems change (i.e., reducing barriers to recovery). In a review of supported education interventions, Mowbray et al. (2005) found evidence that for persons with psychiatric disabilities, these programs increased access to and completion of postsecondary education; increased educational enrollment as well as employment participation; improved self-esteem; and resulted in a decrease in hospitalizations. While supported education has a significant amount of research supporting it as a psychosocial intervention for persons with psychiatric disorders, additional studies need to be conducted in order for it to reach EBP.

**Table 97–13 Summary of Supported Education Interventions**

- *Self-contained classroom model*: segregated classes on college or university campuses; specialized curriculum; focus on career planning before entering mainstream academic or vocational setting.
- *On-site model*: students attend regular academic classes with support provided on-site, usually by educational staff; students integrated into campus life with additional advising and support to assist them.
- *Mobile SE model*: students attend regular academic classes in any educational setting (i.e., not just one with supports for students with psychiatric disabilities), support provided by independent mental health staff, least restrictive and most individualized model.

Mowbray et al. (2002).

## Conclusion

This chapter has provided an overview of psychiatric rehabilitation principles, practices, and program interventions that are geared at the major life domains: independent living (housing supports will be provided in another chapter), education and employment, personal relationships, health, criminal justice, and spiritual life and recreation. The major goal of these service interventions and supports is to assist adults with psychiatric disabilities to live successfully in the community with as little professional assistance as possible. The strategies employed by the multiplicity of approaches are to develop and/or modify the individual's skills and environmental supports. The principles and practices of psychiatric rehabilitation ensure that the individual with a psychiatric disability is an integral and central decision-maker in the process of service planning and provision and, consequently, in his/her own recovery process. Client self-determination is valued and emphasized.

Psychiatric rehabilitation providers work in concert with treatment providers, most specifically, the psychiatrist who is responsible for prescribing the medication and clinically monitoring the client. Many of these rehabilitative interventions are designed to enhance the work of the psychiatrist treating this population. The role of the psychiatrist in the rehabilitative process includes being a member of the team, as well as promoting the values of self-determination and taking recovery orientation to serving those with psychiatric disabilities. Furthermore, it is also essential for psychiatrists to provide education, information, and support to those with psychiatric disabilities, as well as their families and support systems. It is important for psychiatrists to be knowledgeable about these community mental health resources in order to make appropriate recommendations and referrals.

Although a number of these program interventions have achieved the status of EBP, while others are considered emerging best practices, these rehabilitative approaches are still available on a limited basis. The support of psychiatrists in the dissemination and implementation of these programs is crucial.

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CHAPTER 98

# Advocacy, Self-Help, and Consumer-Operated Services

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## Introduction

A mentally ill woman involved with a self-help group writes to thank a peer who has helped her recover from an episode of hopelessness and despair.

> We've all known so much pain and so many years of struggling, that I feel we share a bond the likes of which the so-called "normal" world will never know. I consider it a privilege to be associated with people who have survived, and survived, and survived again, but still have the courage, the compassion, and the humanity to keep on striving and caring about themselves and reaching out to touch others in trouble. Although the rest of the world perceives us as different and pretty much useless, I think we're about as special as you can get. (Deegan 1994)

The letter captures some of the therapeutic aspects of the self-help experience. These include the feeling of not being alone, of bonding with peers who have shared the experience of mental illness. The woman is grateful for role models who have been able to reach out and help others. Viewing these examples of strength in persons with psychiatric disabilities, the writer rejects the world's stigmatization of the mentally ill and reevaluates with pride her own identity. There is a new appreciation of herself as someone able to transcend the pain and emerge as a survivor.

What is the relation of the self-help enterprise to the practice of psychiatry? Within the field of mental health, concepts such as advocacy, volunteerism, self-help, and consumerism represent interrelated activities that may share common objectives and yet differ substantially in process and impact. Each of these concepts has had some influence on psychiatric knowledge and practice. They designate extraprofessional efforts that, first of all, appear to be helpful to many patients. However, some of these concepts also describe social movements that have far-reaching effects on the funding of basic etiological research as well as services, the shape of mental health law, clinical training and patient–physician relationships, and the parameters and structures of treatment systems. Continuing research on self-help and consumerism may also add considerably to our knowledge of the mechanisms of therapeutic growth.

Advocacy and self-help cover a wide range of mental health-related issues. In this chapter, these concepts are defined in terms of how they relate to a variety of conditions. However, the primary focus is on their application to the population of persons with major mental illnesses, that is, persons who have been psychiatrically hospitalized, have received crisis services, or have manifested functional impairment and a need for prolonged outpatient care. Much of the discussion relates to people who rely on psychiatric services for extended periods of their lives. The involvement of such persons with self-help movements is of considerable interest to the psychiatrists from whom they receive their professional care.

## Conceptual Distinctions

### Advocacy

Advocacy groups focus on social and legal remedies to improve the lives of the particular constituency they represent. A primary focus of groups operating with a mental health agenda is legislative advocacy. This typically involves active lobbying for funding for research and services. Advocates may also work to promote legislation to protect the rights of mentally ill persons; extend entitlements; mandate insurance parity in order to ensure equal access to benefits of mentally, developmentally, and physically disabled persons; and improve standards and quality of care. Advocacy efforts may involve public education and antistigma campaigns and promoting and publicizing programs with innovative models of treatment and rehabilitation. Advocates may attempt to

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influence the agendas of federal agencies to focus on persons with serious mental illness, accompanied by budgetary advocacy to increase the funding for these agencies. Although tax-exempt groups cannot engage in political sponsorship of candidates, individual members are likely to offer active support for legislators with a favorable voting record on mental health issues.

Currently, there are strong initiatives to ensure that the needs of persons with chronic mental illness will not be lost in the acute care models of most managed care systems. In most cases, lay advocacy organizations will collaborate with professional associations to promote mutual agendas for standards, credentialing, clinical services, and research. This adds the considerable weight of a citizen constituency to what may be perceived as the vested interests of a practitioner group.

## Volunteerism

Volunteerism, or work without remuneration, involves the participation of concerned individuals in a variety of unpaid activities that improve the lives of persons with mental illness. These are typically offered by nonprofessionals contributing their time and energy to augment professional services. However, as may be seen in some of the descriptions of citizen and consumer organizations, professionals may also act as volunteers. They may contribute their time to educate the public, lead support groups, serve on boards, or otherwise act in an unpaid advisory capacity.

Volunteerism may involve efforts devoted to the development of ancillary resources for persons with mental illness or the provision of personal services to supplement the professional system of care. A notable example is COMPEER, a nationwide program that trains volunteers to provide social companionship and role models for persons with severe and persistent mental illnesses.

Volunteerism has been considered a uniquely U.S. product, but there is increasing evidence of its application in other countries. In northern Italy, numerous volunteers contribute to a network of cooperative enterprises employing deinstitutionalized patients. In Japan, *Zenkaren*, the oldest family organization (organized in 1965), administers more than 800 sheltered workshops for persons with mental illness and in many other ways supplements the official mental health system (Mizuno and Murakami 2001). Newly organized family advocacy groups in Europe and Asia are also beginning to augment services with a volunteer capability. The World Federation for Schizophrenia and Allied Disorders, with headquarters in Toronto, Canada, is an international umbrella organization for family groups with volunteer components. The scope of volunteer activities in the United States is suggested in some of the organizational descriptions in the following section.

## Self-Help

Self-help refers to the organization of groups of individuals sharing a common problem who meet for purposes of mutual aid and support, education, and personal growth. Although advocacy may also be included in the agenda, self-help groups primarily focus on relief of personal problems through unburdening, sharing experiences and solutions to mutual problems, role modeling, positive reinforcement from peers, and information exchange. Through these activities, self-help groups improve coping skills and also provide social support. Self-help groups aim toward therapeutic growth and skill development through mutual efforts rather than through professional interventions.

In 1990, it was estimated that between 9 and 12 million U.S. adults used self-help groups (Lieberman 1990). Given the explosion of self-help groups in successive editions of *The Self-Help Group Source Book* (White and Madara 2002), there may be double that number today. Almost all of these groups deal with mental health-related problems. Included are the primary substance abuse organizations, Alcoholics Anonymous (AA) and Narcotics Anonymous (NA), with almost 100,000 chapters. Their famous 12-step paradigm has been extended to other addictions (Overeaters Anonymous, Gamblers Anonymous, and the like). Parents Anonymous uses the self-help model for treatment and prevention of family violence. Other groups deal with bereavement; victimhood; physical and developmental disabilities; parenting; and social discrimination issues relating to gender, sexual orientation, or ethnicity. There are also specialized groups for adoptees, adult children of alcoholic persons, victims of sexual abuse, and persons who have suffered a range of other human problems. After the World Trade Center (WTC) disaster of September 11, 2001, a surge of local face-to-face WTC groups were organized by survivors and families and friends of victims to deal with the traumatic effects.

Included among the self-help groups outside of the professional system are those for people coping with serious psychiatric disorders. Long-term general organizations such as Recovery Inc., and GROW (not an acronym), and those that are diagnosis-specific, tend to be oriented toward mutual support and aid rather than political advocacy. However, there is some overlapping membership in the growing movements of psychiatric consumer advocates.

## Consumerism

Consumerism as applied to mental illness is the doctrine that service recipients have essential contributions to make to mental health planning, service delivery, and research. In this context, psychiatric service recipients generally refer to themselves as consumers, the most widely accepted term. However, they are also self-defined as clients, patients, ex-patients, persons who are psychiatrically disabled, persons who are psychiatrically labeled, inmates, and survivors, depending on the orientation of the speaker.

The Center for Mental Health Services (CMHS) of the Substance Abuse and Mental Health Services Administration (SAMHSA) (2001) defines a consumer simply as "an individual, 18 years of age and older, with severe mental illness."

**Table 98–1** Strategies to Establish Collaborative Partnerships Between Professionals and Self-Help Group

| |
|---|
| Welcome support groups |
| Endorse these groups as adjunctive to treatment |
| Avoid viewing groups as competing systems of care |
| Utilize two-way referrals for treatment and social support |
| Understand that peer leadership enhances the therapeutic process |
| Recognize issues related to disempowerment, control, and self-determination |

Most persons identified as consumers typically have been psychiatrically hospitalized or have received outpatient care for a serious psychiatric condition. As persons who have experienced mental illness and who have been exposed to various treatment and rehabilitative modalities, consumers have long been considered to be valuable judges of whatever will best serve the needs of their peers, both by SAMHSA (Substance Abuse and Mental Health Services Administration 2001) and the National Association of State Mental Health Program Directors (NASMHPD) (1989). Consumers who serve in this capacity may have various levels of functioning. Although some may have a diagnosis of schizophrenia, these are individuals who are articulate and rarely cognitively disabled (Frese 1998). Indeed, many consumers have superior talents in writing, organizing capability, or in various areas of technical skill.

**Table 98–2** Self-Help Groups and Peer Services—Positive Research Findings

| | |
|---|---|
| Larger social networks | Increased sense of control |
| More goal-orientation | Greater self-efficacy |
| Lower levels of symptoms | Increased capacity for empathy |
| Fewer rehospitalizations | Improved education |
| Fewer inpatient days | Increased independence |
| Improved consumer employment | Enhanced quality of life |
| Greater self-confidence | Greater hope for the future |

For more than a decade, consumer input has been solicited by government agencies at all levels of knowledge development and service building. This may range from formulating basic research questions to consumer roles in design, interviewing, and data analysis; from program monitoring and evaluation to state and local systems planning (Trochim et al. 1993).

Targeted requests for grant applications from federal and state authorities solicit consumers in remission for service delivery roles both as staff members in professionally run services and as operators of alternative services for persons with mental illness. Evaluations of some of these enterprises are discussed in the section on Research. In the following section, commonalities and differences of citizen, family, and consumer, and strictly consumer organizations are described. A sample of major organizations with their differentiating characteristics and Websites is indicated in Table 98–3.

## Citizen and Family Advocacy Movements

In the United States, many serious diseases and disabilities have long had organized constituencies of patients, families, and interested others who advocate for expanded research and services. The American Cancer Society, American Heart Organization, National Multiple Sclerosis Society, and the Alzheimer's Disease and Related Disorders Association are a few examples. Organizations devoted to developmental disabilities, such as the National Association for Retarded Citizens or the National Society for Autistic Children have advocated for state-of-the-art diagnostic and treatment procedures as well as appropriate education for children, enhanced rehabilitative resources, public information resources, and the like.

**Table 98–3** Selected Sample of National/International Mental Health Organizations

**Primarily Citizen Organizations**
Mental Health America (MHA) formerly National Mental Health Association
http://www.mentalhealthamerica.net

**Protection and Advocacy Organizations for Rights of Persons with Mental Disabilities**
Bazelon Center for Mental Health Law
http://www.bazelon.org
Protection and Advocacy for Individuals with Mental Illness (PAIMI) Program
http://mentalhealth.samhsa.gov/cmhs/p&a/about.asp
List of State Protection and Advocacy Centers
http://ojjdp.ncjrs.org/pubs/walls/appen-g.html
http://www.protectionandadvocacy.com/
National Association for Rights Protection and Advocacy
http://www.narpa.org

**Primarily Stakeholder Organizations (Families and Consumers)**
Federation of Families for Children's Mental Health
http://www.ffcmh.org
National Alliance on Mental Illness (formerly National Alliance for the Mentally Ill)
http://www.nami.org
World Fellowship for Schizophrenia and Allied Disorders (WFSAD) (International)
http://www.world-schizophrenia.org

**Primarily Consumer Organizations**
**Coalition of Self-Help Groups (Political Advocacy Model)**
National Coalition of Mental Health Consumer/Survivor Organizations
http://www.ncmhcso.org

**General Mental Health (Therapeutic Support Group Model)**
GROW Inc. (International)
Email: growil @sbcglobal.net
Emotions Anonymous (International)
http://www.emotionsanonymous.org
Recovery Inc. (International)
http://www.recovery-inc.com

**Diagnosis Specific (Therapeutic Support Group Model)**
AIM (Agoraphobics in Motion)
http://aim-hq.org
Anxiety Disorders Association of America
http://www.adaa.org
BPD Central (Borderline Personality Disorder)
http:www.bpdcentral.com
Depression and Bipolar Support Alliance (DBSA) Formerly Depressive and Manic Depressive Association
http://www.dbsalliance.org
Obsessive–Compulsive Anonymous
http://members.aol.com/west24th/index/htmil
Schizophrenics Anonymous
http://sanonymous.org

**Consumer Resource Centers**
CONTAC (Consumer Organization and Networking Technical Assistance Center)
http://www.contac.org.
National Empowerment Center
http://www.power2u.org
National Mental Health Consumers Self-Help Clearinghouse
http://www.mhselfhelp.org

**Directories of Mental Health Groups in the United States**
American Self-Help Group Clearinghouse
http://mentalhelp.net/selfhelp
College Campus Mental Health Groups
http://www.activemindsoncampus.org

Until recent years, mental illness has been different from these other conditions in the composition of its advocacy groups. Encompassed within the framework of safeguarding

human rights and the global promotion of mental health, advocacy for persons with severe psychiatric disorders was largely the province of concerned citizens rather than that of acknowledged stakeholders whose own lives are invested in treatment and cure. For many years, former patients and relatives who participated in these movements maintained a relatively low profile. Internalizing societal (and often professional) stigma, they rarely acknowledged their own experiences in public advocacy efforts or in leadership roles. The history of mental health advocacy in the United States has, therefore, had two major developmental stages: citizen organizations, and since the late 1970s, family and consumer organizations.With respect to the latter, we also discuss the radical antipsychiatry movement that arose in the 1960s among some former patients, which analysts note has evolved into a patient-based consumerist movement today (Rismiller and Rismiller 2006).

## Citizen Advocacy Organizations

### Mental Health America (Formerly the National Mental Health Association)

Mental Health America (MHA) changed its name from the National Mental Health Association in 2006. MHA has been the major advocacy group for persons with serious mental illness until the organization of the National Alliance on Mental Illness (NAMI, formerly the National Alliance for the Mentally Ill) in 1979. Founded by a former mental hospital patient, Clifford Beers, MHA in previous years was a strong advocate for people with serious mental illness, but its main mission was aimed at improving mental health in the population at large, with a strong emphasis on primary prevention. Examples of activities by local branches included conferences on sexuality, police training to deal with interethnic conflict, support groups for newly widowed persons, and training volunteers to befriend troubled schoolchildren or to work with victims of natural disasters.

In most areas, the local MHA branch was the major umbrella organization linking professionals with interested citizens, facilitating joint advocacy efforts and providing mental health education for the public. Mental health professionals have been actively involved in governance boards of the lay organization, and there are friendly affiliative relationships with professional societies. In contrast to self-help groups, MHA support groups traditionally were led by volunteer professionals, and persons needing further help were urged to use psychotherapists in the mental health system. Today, many more MHA affiliates are offering space and resources for peer-led groups that function independently of the host organization. MHA has taken increasing interest in consumer groups, has a CMHS-funded Consumer Supporter Technical Assistance Center, and provides affiliative support to the oldest and strongest resource center for consumers, the National Mental Health Consumer Self-Help Clearinghouse (NMHCSHC) in Philadelphia. Despite their broad-based interests, MHA groups have always lobbied for legislation for persons with serious mental illness and developmental disabilities at both state and national levels. For many years, they were the major citizen voice, working in tandem with professional societies and persons interested in mental health law and patients' rights.

### Bazelon Center for Mental Health Law

The Judge David L. Bazelon Center for Mental Health Law, formerly the Mental Health Law Project, was organized in 1972 to halt abuse and neglect in state mental hospitals and training schools for persons with mental and developmental disabilities, and to prevent exclusion of disabled children from publicly funded education. Its current agenda is much more comprehensive. In addition to its basic focus on protecting patients' civil liberties, the center provides legal resources to combat exclusionary zoning and rental policies; promotes patients' access to health care, social services, and income support; reforms state systems of care; and helps generate a continuum of community services for persons with psychiatric and developmental disabilities. Working in the courts and in legislative and policy arenas, the Bazelon Center offers legal assistance to consumers, other advocacy groups, and policymakers.

### State Protection and Advocacy Centers

State Protection and Advocacy Centers (P&As) are federally mandated to protect disabled persons from neglect and abuse and to protect their rights in institutional and community settings. Initially passed by the Congress in 1986 and reauthorized in 1991 (PL102-173), the legislation is now known as the Protection and Advocacy for Individuals with Mental Illness Act, extending rights already afforded to persons with developmental disabilities. The law provides grants to existing P&As for the developmentally disabled. Much of their work involves grievance casework for individuals, although they also initiate lawsuits to upgrade institutional conditions. Many P&As also view their mission as reforming the service delivery system, which may include shifting resources from institutional to community vendors. All 50 states, the District of Columbia, and five territories have federally funded programs under the Protection and Advocacy for Individuals with Mental Illness Act. State P&As are members of the National Association of Protection and Advocacy Systems.

## Stakeholder (Family and Consumer) Organizatons

A scientific national survey in 2002 found 7467 groups and organizations run by and for mental health consumers and/or family members in the United States. Included were 3315 mutual support groups, 3019 self-help organizations, and 1133 consumer-operated services (Goldstrom et al. 2006). Some of these are described later, primarily in terms of membership and national influence.

### The National Alliance on Mental Illness (NAMI), Formerly The National Alliance for the Mentally Ill

The organization of NAMI has been termed one of the most important events in the history of U.S. psychiatry (Kaplan and Sadock 1991). Indeed, former NIMH director Herbert Pardes has hailed the political influence of NAMI as "the single most positive event in the history of mental illness." (Flynn 1993, p 8). For the first time, the major psychiatric disorders had their own important national presence, a grassroots constituency of families with a profound commitment to improving services, research, and public awareness and to reducing the stigma of mental illness.

Although local family support groups had been organized in the 1960s, and at least one state family federation existed in 1971 (Shetler 1986), it was not until 1979 that 284 family members convened at the University of Wisconsin, Madison, to form the national organization. Since that time, NAMI has grown exponentially into a powerful movement. Currently, there are NAMI organizations in every state and 1100 local communities around the country. A well-functioning NAMI office in Arlington, Virginia disseminates information and lobbies for research and services at the national level, and 50 state NAMI organizations work for improved services in their individual states.

Like most organizations that are formed by stakeholders rather than interested outsiders, NAMI merges self-help and advocacy. Thus, the basic armature in all localities is mutual support groups and membership education about all aspects of major mental illnesses. Most groups have also engaged in public education; resource development; antistigma campaigns; and service on mental health planning, policy, and governance boards at local and national levels. Consumers and family members are trained to become effective lobbyists and advocates for patients. Professional educators within NAMI have developed models for training family education specialists. NAMI has also had an impact on clinical training. The NAMI Curriculum and Training Network focused on influencing mental health professionals to work with persons with severe mental illness and on ensuring state-of-the-art education in clinical training programs from preservice to continuing education levels. Several national conferences cosponsored by NAMI and the National Institute of Mental Health (NIMH) brought together leading clinical educators, researchers, and practitioners with family member–mental health professionals for concept development and curriculum planning in the core professions (Lefley and Johnson 1990, National Institute of Mental Health 1990).

A major phenomenon is the NAMI Family-to-Family program, developed by a psychologist–family member as a 12-week educational program on major psychiatric disorders (Burland 1998). This manualized program is carefully structured to train family members as educators. They provide some of the content of evidence-based psychoeducational intervention, such as problem-solving and communication skills, as well as understanding the patient's experience. The program also teaches families how to cope with family burden, avoid overinvolvement, set limits, and see to their own needs and those of other family members. Family-to-Family is available in numerous states with state mental health authority sponsorship, and has been administered to more than 100,000 families.

NAMI also has a program for consumers, Peer-to-Peer. This 9-week course focuses on education, self-help, and recovery principles for people with a major mental illness. It is taught by two consumer-mentors who have received intensive training. Additionally, an antistigma public education program, In Our Own Voice: Living with Mental Illness has received considerable community acclaim. Trained consumer speakers use a nationally produced video to inform the public about the human face of mental illness and the potential for recovery. Consumer feedback from these courses highlight self-determination and empowerment skills. Both of the consumer programs provide the presenters with a salary. For persons attempting to reenter the traditional workforce, this provides employment experience following a period of disability.

Additionally, NAMI has targeted educational activities for providers with the NAMI Provider Education Course. This 12-week course uses a team of two family members, one consumer, and one professional to educate providers about the actual experience of mental illness. These educational programs, which offer a wealth of materials to participants, are usually funded through state mental health program offices.

On the national level, the family constituency has been powerfully influential in raising research dollars for mental illness. NAMI has successfully lobbied for substantial increases in congressional appropriations for NIMH research on the major psychiatric disorders and helped launch the National Schizophrenia and Brain Research campaign. NAMI cofounded the National Alliance for Research on Schizophrenia and Depression (NARSAD) in 1985 and has generated millions of dollars in research awards through the Ted and Vida Stanley Foundation.

NAMI-sponsored research and publications have had a substantial influence on mental health services. Early survey findings included *Care of the Seriously Mentally Ill: A Rating of State Programs* (Torrey et al. 1990) and *Criminalizing the Seriously Mentally Ill: The Abuse of Jails as Mental Hospitals* (Torrey et al. 1992). Most recently, the organization published a comprehensive report that again graded the states on their mental health systems, in terms of infrastructure, information access, services, and recovery supports (NAMI 2006). Although the states received an overall "D" rating, they found examples of innovative programs in virtually every state. Some state administrations used their poor rating to receive additional funds for needed services. In addition, NAMI publishes numerous educational booklets on mental illness, in English and Spanish. Their contents are supervized by members of NAMI's Scientific Council, composed of psychiatry's leading researchers and educators.

With a major stake in legislative advocacy at the federal level, NAMI was active in promoting passage of Public Law 99-660, which required all 50 states to develop a comprehensive mental health plan including provision of community care to persons with serious mental illness. The legislation, for the first time, required family and consumer participation on a state advisory council. Reauthorization language linked the approved state plans to the federal block grant, and local NAMI groups became active in monitoring their state's compliance with the plan's objectives. NAMI fought for the Protection and Advocacy legislation previously discussed, and the organization was a vocal advocate for the Americans with Disabilities Act. NAMI has been actively working for mental health parity legislation, and for implementation of the Wisconsin Program for Assertive Community Treatment (PACT) as evidence-based practice in all states. The organization was actively involved in the dissemination of the findings of the Schizophrenia Patient Outcomes Research Team (PORT), which recommended specific parameters for prescribed antipsychotic medications (Lehman and Steinwachs 1998). NAMI also helped develop and disseminate the "Guide for Patients and Families" appended to the 1999 Expert Consensus Treatment Guidelines for Schizophrenia (Weiden et al. 1999).

Current advocacy efforts focus on preventing changes to Medicaid that would limit needed services for mental illness, guidance about Medicare part D drug benefits, and funding for the "Mentally Ill Offender Treatment and Crime Reduction Act," among numerous other efforts. NAMI's CIT Technical Assistance Resource Center provides help to many communities that are developing programs to train police officers about serious mental illness and the appropriate treatment of potential offenders who appear to be mentally ill. Funding for jail diversion programs and mental health courts are high on the NAMI lobbying agenda. The NAMI Consumer Council is a group of primary consumers who function as a separate interest group within NAMI with a very substantial role in policymaking. Frese et al. (2001) report that during the past several years at least one-quarter of the members of NAMI's board of directors have been consumers. Its current president (2006), Suzanne Vogel-Scibilia, M.D., is consumer, family member, and working psychiatrist. Thirty percent of NAMI members are consumers. Members of the NAMI Consumer Council generally support the NAMI agenda, but many have overlapping affiliations and common interests with other consumer organizations.

### The Federation of Families for Children's Mental Health

Although this chapter focuses primarily on self-help and advocacy for adults with serious mental illness, mention should be made of the Federation of Families for Children's Mental Health (FFCMH), a national parent-run federation organized in 1988. Like NAMI, this family movement was organized with joint academic–government support; in this case, the Portland State University Research and Training Center on Family Support and the National Institute on Disabilty and Rehabilitation Research.

In contrast to NAMI, which generally has focused on severe mental illness and Axis 1 diagnoses, FFCMH is a broad-based organization that addresses the needs of children and youth with a wide range of emotional and behavioral disorders. In functions similar to those of NAMI, however, the FFCMH is engaged in information dissemination, mutual support, and advocacy for research, prevention, early intervention, family support, education, transition services, and all other services needed by children and youth with emotional, behavioral, or mental disorders and their families. Their focus, like NAMI's is on systems transformation. In addition to knowledge dissemination and legislative advocacy, major initiatives are to ensure parents' involvement in their children's treatment and the availability of a flexible, affordable, and individualized array of supports to maintain family integrity.

The Federation has been active in legislative advocacy for children, including supporting Public Law 102-321, the Child Mental Health Service Program, and the Family Preservation and Support Services Act (PL103-66). They are currently addressing children's needs for mental health services in managed care systems.

The FFCMH has collaborated with other organizations to facilitate studies and publish materials on children's mental health. In conjunction with the MHA, the organization published *All Systems Failure*, a report providing school-related data on a state-to-state basis, detailing the progress of educational and mental health systems to work together to deal with serious emotional disturbance in children and adolescents. In collaboration with the Bazelon Center for Mental Health Law, the Federation has issued publications on managed care for children, *Your Family and Managed Care* and *A Family Advocate's Guide.* Like NAMI, FFCMH publishes materials in Spanish as well as English, has manualized training curricula, and a corps of Federation-Certified Trainers. Although FFCMH and NAMI share many functional characteristics as an adult organization, NAMI has been progressively driven by consumer roles in policy and decision making. We turn now to the various types of organizations that have been generated and maintained by patients and former patients themselves.

## Consumer Self-Help and Advocacy Organizations

Consumer self-help organizations generally merge mutual support with a focus on one of two basic objectives: political advocacy or personal problem resolution and growth. A study of 104 self-help groups of present and former psychiatric patients identified two major service models, which the author differentiated as social movement versus individual therapy. The social movement groups were oriented toward social change and offered public education, legal advocacy, information referral networking, and technical assistance to other consumers. The individual therapy groups offered more "inner-focused" individual change through mutual support meetings with a focus on coping with their illness (Emerick 1990). This distinction is still valid today,

### The Depression and Bipolar Support Alliance (DBSA)

A major consumer organization that combines both social movement and therapeutic functions is the DBSA, formerly the National Depressive and Manic-Depressive Association. Like NAMI, the DBSA views mood disorders as primarily biogenic and disseminates public education on unipolar depression and bipolar disorder. The organization has a large network of local support groups and holds annual conferences with professional presentations. There is an emphasis on fighting stigma and promoting basic research with a variety of advocacy efforts, including providing expert testimony for the Congress. National DBSA publishes brochures, books, and videotapes about the treatment of mood disorders. Publications are reviewed by members of the DBSA Scientific Advisory Board, which includes prominent psychiatrists and researchers.

The DBSA has a strong alliance with professionals and an influential role in developing practice guidelines and consensus statements on the treatment of patients with bipolar disorder. Consultants from the DBSA were involved in the *Practice Guidelines for the Treatment of Bipolar Disorder* (American Psychiatric Association Practice Guidelines 2002). In a major undertaking, the organization convened mental health professionals, policymakers, researchers, clinicians, patients, and families for a national conference to seek solutions for the undertreatment of depression. A consensus statement was published in *JAMA* (Hirschfeld et al. 1997). This made it available not only to the mental health community but to all physicians who might encounter the symptoms of affective disorders. The organization convened

a large group of mood disorder researchers on the use of placebos in clinical trials. The conference consisted of expert presentations on bioethics, biostatistics, unipolar depression, and bipolar disorder (see Rosack 2002). The consensus statement, published in the *Archives of General Psychiatry,* underscored that patients' safety and well-being must come first, but stressed the importance of placebo in developing new treatment options (Charney et al. 2002). The DBSA's emphasis on informed consent, appropriate placebo usage, and responsibility of pharmaceutical companies suggests that consumer groups may assume an active role to insure informed participation in clinical trials and optimal availability of useful medications.

## The Therapeutic Support Group Model

At this writing, the American Self-Help Group Clearinghouse lists approximately 1100 national self-help organizations with thousands of local support groups for specific psychiatric conditions, general mental health, addictions, bereavement, disabilities, abuse, parenting, caregiver concerns, and stressful life situations (retrieved December 20, 2006 from http://mentalhelp.net/self-help). Just a few of the major national organizations for psychiatric patients can be mentioned, excluding groups that specifically focus on addictions. Almost all these groups offer a caring and sharing community, with a focus on attaining emotional maturity, personal responsibility, and recovery from mental illness.

Among the general groups are GROW, an international organization founded in Australia in 1957. GROW in America has a 12-step program to provide skills for emotional growth and for avoiding and recovering from a breakdown. Recovery Inc., founded in 1937, offers a self-help method of will training for people suffering from emotional and mental conditions. They claim that their principles parallel those found in cognitive-behavioral therapy. Emotions Anonymous is another general national organization with a 12-step program to gain better emotional health.

Diagnosis-specific national self-help organizations with local chapters include Schizophrenics Anonymous, which focuses on recovery and uses a 6-step program, along with medication and professional help. Anxiety Disorders Association of America supports groups that deal with phobias, posttraumatic stress disorder (PTSD), and all anxiety-related disorders. The organization lists local professionals providing relevant treatment and also provides a national listing of clinical trials. The Obsessive–Compulsive Foundation offers support groups plus a newsletter, books, audio and videotapes, and an annual conference. Agoraphobics in Motion (AIM) claims to use specific behavioral and cognitive techniques in its support groups. Dual Recovery Anonymous and Double Trouble in Recovery Inc. are self-help fellowships for individuals in recovery from mental illness and addiction.

Panic Survivor and the Panic Center are online support groups for panic disorder. Social Phobics Anonymous is a 12-step telephone group. BPD Central and BPDWORLD provide on-line links and message boards for persons with Borderline Personality Disorder. An interesting type of organization is the National Education Alliance for Borderline Personality Disorder (NEA-BPD). Composed of family members and professionals, NEA-BPD hosts national conferences with leading BPD researchers, and participates in an ongoing funded research project, Family Connections, which offers dialectical behavior training for families.

## The Political Advocacy Model

Among some former psychiatric patients, self-help in itself is viewed as a political statement. They increasingly advocate for and receive federal and state funding to develop programs that they believe will speed recovery more effectively than services offered by the professional mental health system alone. A few believe that psychiatric interventions are countertherapeutic rather than helpful. Zinman et al. (1987) gave the essential characteristics of self-help groups as self-definition of needs, equal power of members, mutual respect, voluntary participation, autonomy, and responsiveness to other special populations. The self-help mission is for optimal personal independence with the option of choosing interdependence with other consumers.

For many years, self-help was incorporated in organizations of former psychiatric patients with names such as the Insane Liberation Front (Portland, Oregon) or the Mental Patients Liberation Project (New York) and publications such as *The Madness Network News* (California). These groups of former psychiatric patients were angry at a system that they thought had abused and dehumanized them rather than helped them. They tended to have strong antipsychiatry views; they were vehemently opposed to electroconvulsive therapy and often to psychotropic medications as well. Many thought that the only valid help for persons who were "psychiatrically labeled" would come from peers who had experienced a similar history of psychiatric hospitalization. Many of the pioneers of the consumer movements developed and provided models for today's consumer-operated services. An analysis of the evolution of the movement states that today's antipsychiatry adherents no longer focus on dismantling organized psychiatry but try to promote radical reform in the mental health system (Rismiller and Rismiller 2006).

Although contemporary consumer groups have a common agenda of self-determination, a sociological analysis indicates that former psychiatric patients are still divided in their views regarding the etiology and the validity of the concept of mental illness (Kaufmann 1999). A few still view mental illness as psychogenic or as a social construct, rejecting biogenesis, but most seem to accept a diathesis-stress model and many describe themselves as having a brain disease or "a chemical imbalance" (Kersker 1994). Some consumers are totally opposed to any kind of forced treatment while others have stated that without it, they might not be alive today (Rogers 1994). Some members of the consumer movement think that hospitalization is harmful and would like to eliminate all hospital beds. However, their views are not supported empirically. In the California Well-Being Project (Campbell 1989), a survey of psychiatric clients designed and conducted by consumers and directed by a professional researcher-consumer, more than 50% of the respondents believed that their hospitalization had been helpful, 22% reported both positive and negative aspects, and only 20% found hospitalization harmful.

Former national consumer organizations were disbanded and were largely supplanted by state and local groups networking at annual conferences. They were engaged in coalition building and developing local consumer-run

initiatives, with support from federal and state governments. Today, members meet at annual national Alternatives Conferences that bring together consumers from all over the country for organizational skill building and knowledge sharing. However, a national presence was needed, and in October, 2006, The National Coalition of Mental Health Consumer/Survivor Organizations was organized, with representatives from 28 states and the District of Columbia. The Coalition, whose office is in Washington, DC, received start-up funding from the Public Welfare Foundation.

Thirty states have an Office of Consumer Affairs staffed by consumers, and most have local consumer groups and drop-in centers. The state directors' organization, NASMHPD, has a division composed of departmental managers who self-identify as consumers. This is The National Association of Consumer/Survivor Mental Health Administrators (NAC/SMHA). According to their Website, members meet "to develop strategies for balancing the often disparate demands and expectations of the two constituencies they serve: consumers/survivors and mental health bureaucracies" (www.nasmhpd.org/nac_smha.cfm.).

In research centers studying self-help and psychiatric rehabilitation at Boston University, University of Illinois at Chicago, University of California, Berkeley, and University of Michigan, Ann Arbor, consumers have been involved in all phases of research including design, instrument development, interviewing, and analysis. At the Missouri Institute of Mental Health, under the direction of Dr. Jean Campbell, a consumer-researcher, a 5-year, multisite, $20-million project is currently investigating the efficacy of consumer-operated services. Data already collected are presented in the section on research findings.

## Government Roles in Consumer Empowerment

A major element in helping the organization of both family and consumer movements is the Community Support Program (CSP) of the federal government. Initially under the NIMH and now part of CMHS, the CSP was organized in 1978 to deal with problems of deinstitutionalization. The federal program focused on developing in each locality a comprehensive continuum of care for deinstitutionalized patients that would include all needed resources for survival, treatment, rehabilitation, and hopefully, a satisfactory quality of life (Stroul 1989). Through targeted grants to state administrations, the CSP fostered public–academic linkages and funded research and demonstration grants for model programs, including case management, crisis services, programs for homeless persons with mental illness, and other innovative community rehabilitative projects.

The CSP also had a heavy emphasis on aiding the development of state and local self-help and advocacy groups and facilitating dissemination of their ideas on a national basis. Through the years, the program promoted Learning Community Conferences to bring together researchers, service providers, family advocates, and primary consumers. CSP helps fund the annual Alternatives Conferences that bring together members of consumer organizations from all over the United States to pursue a national agenda. The CSP has probably been the major catalyst in helping develop services in which former psychiatric patients are staff employees or primary providers.

The CMHS funds three Consumer Technical Assistance Centers and two Consumer Supporter Technical Assistance Centers whose purpose is "to develop and implement activities that assist in the improvement of mental health service systems at the state and local levels (Substance Abuse and Mental Health Services Administration 2001). The National Mental Health Consumer Self-help Clearinghouse (NMHCSHC) in Philadelphia, under the direction of Joseph Rogers, encourages the development of consumer self-help groups and provides information, materials, and referrals on fundraising and program development. Organized in 1986, the NMHCSHC has worked to develop the infrastructure of consumer movements nationwide. They have helped build new local and state self-help groups by providing technical assistance (TA) and disseminating information, developing consumer networks and coalitions, and generally building the capacity of consumer groups. The National Empowerment Center (NEC) in Lawrence, Massachusetts, directed by psychiatrist-consumer Daniel Fisher, similarly supplies TA to self-help groups. NEC has specific departments that focus on resource development and training conferences, consumer-run organizations, managed care and coalition building, information and referral, media relations, and training professionals on the consumer viewpoint.

Consumer Organization and Networking Technical Assistance Center (CONTAC), located in West Virginia, is the third consumer TA center funded by the CMHS. In collaboration with the other centers, CONTAC works nationwide to provide informational materials, on-site training and skill-building curricula, electronic and other communication capabilities, networking, and customized TA to build leadership and teach business management skills to local consumer groups.

In addition to the Consumer TA Centers, federal funding is received for two Consumer Supporter TA Centers. MHA has a grant to provide TA to consumer and consumer supporter organizations in areas such as education, advocacy, systems change, and coalition building, with a current focus on working with women who have experienced trauma. TA is provided in the form of research, training, information, and financial support. NAMI has the other Consumer Supporter grant. Their prior TA grant focused on implementing the evidence-based Wisconsin PACT program in service systems throughout the nation. The current STAR Center targets the promotion of cultural competence through knowledge dissemination, training, and on-site TA.

The Consumer/Survivor Mental Health Research and Policy Work Group was established in 1992 with support from the Mental Health Statistics Improvement Program and the Survey and Analysis Branch of the CMHS. The purpose was "to modify the relationships and dialogue between mental health professionals/service providers/policy administrators and consumers/survivors including fostering significant roles for consumers/survivors in all phases of mental health research, data standards development, planning, policy, and implementation of mental health services (Consumer/Survivor 1993, p 11).

A major focus of this work group was on outcome measures used in the CMHS-funded services research. A concept-mapping project resulted in a publication by NASMHPD titled *Mapping Mental Health Outcomes from*

*the Perspective of Mental Health Consumers* (Trochim et al. 1993). This project generated recommendations to the mental health research community on outcome measures of greatest interest to consumers.

## Service Development by Family and Consumer Groups

The 1999 Report of the Surgeon General (U.S. Department of Health and Human Services 1999) strongly recommended consumer participation in mental health services. For many years now, the CMHS has been funding demonstration projects that required public mental health agencies to hire and train former patients to deliver services. They have also funded self-help agencies that are managed and staffed by former patients. According to Segal et al. (2002), these free-standing self-help agencies often serve as adjunct or referral sources for community mental centers, and, sometimes, represent alternative service sites.

For many years, NAMI groups in various localities developed resources to fill in gaps in their service delivery systems. Multiple housing facilities, employment opportunities ranging from thrift shops to furniture workshops, psychosocial rehabilitation programs, and even a psychiatric hospital are examples of resources developed throughout the United States. However, many NAMI members thought that families should be investing their energies in legislative advocacy rather than in service development. NAMI's major mission is to augment and strengthen the service delivery system, such as encouraging the implementation of evidence-based practices, ensuring cultural competence and a focus on recovery, and offering an array of adequate services, including those required for jail diversion programs.

The consumer movements have had a different view of their role in services. Their focus is on using the experiences and skills of former psychiatric patients both within the system and as operators of consumer-run alternatives. Numerous CSP initiatives have been devoted to helping consumers achieve that end through funded model projects and inducements to the states. We have noted that as of 2002 there were reportedly at least 1133 consumer-run programs and enterprises. These have included housing and residential placement services, case management, peer companion programs, social centers, employment services including job training and consumer businesses, crisis respite houses, and special programs for homeless people. CSP-funded demonstration projects include a variety of consumer enterprises. Almost all states have networks of drop-in centers that provide socialization outlets outside of the traditional mental health system and, sometimes, fulfill an advocacy function as well. In many states, the sponsorship of consumer drop-in centers by state hospitals and community agencies is a common practice, typically with maximal independence offered to the consumer group.

## Research Findings on Consumer Self-Help

Most of the early evaluations of therapeutic self-help groups tended to be qualitative or process research. Some studies of efficacy were inferred from the members' satisfaction by use of normative data as a control condition. For example, a study of Recovery Inc. members, half of whom had been hospitalized for mental illness, focused on the benefits of membership to volunteer leaders of the organization. As a result of their participation, volunteer leaders gave high ratings to their overall satisfaction with life, health, work, leisure, and community. Their quality of life ratings were equivalent to the levels of satisfaction of a sample of the general public (Raiff 1982). A collaborative study of GROW by University of Illinois researchers compared members for 9 months or more with those who had been members 3 months or less. GROW members for the longer period were significantly better off in terms of larger social networks, a higher rate of employment, and lower levels of psychosis and depression (Rappaport et al. 1984). Another quantitative study looked at patients discharged from a state psychiatric hospital who participated in a Community Network Development self-help program. The research found that 10 months after discharge, participants required 50% less rehospitalization and two-thirds fewer inpatient days than a comparable group of nonparticipating patients (Gordon et al. 1982).

A study of four self-help groups for families of persons with mental illness showed in a time series analysis that the perceived helpfulness of the program for families was significantly related to the patients' functioning in terms of fewer number of hospitalizations and fewer total days in hospital (Biegel and Yamatani 1986). The efficacy of the self-help sharing experience for family members has also received tangential empirical support from the work of McFarlane (2002) on psychoeducational interventions. His research found that interventions with multiple family groups were significantly superior to individual family interventions in deterring patients' relapse, a finding attributed to the mutual support and information exchange of the group experience.

Family members and consumers have been increasingly involved in grand rounds, as lecturers in clinical training programs, and in training service providers. A randomized evaluation of consumer versus nonconsumer training of state mental health service providers found positive reactions to the use of consumers as trainers (Cook et al. 1993).

A process evaluation of six consumer-run drop-in centers in Michigan found that the centers were meeting their programmatic goals to provide acceptance, social support, and problem-solving help. The study found high levels of consumer satisfaction together with the participants' reported feeling that they actually ran their centers (Mowbray et al. 1998), A 6-month survey of nine consumer-operated drop-in centers in Pennsylvania indicated a high level of client satisfaction (Kaufmann et al. 1993).

In California, the use of former patients as peer counselors on locked inpatient wards received enthusiastic evaluations from clinical staff, with most staff asking that the program be extended. The peer counselors reported personal benefits in terms of greater self-confidence, increased empathy, and feelings of being needed and responsible (McGill and Patterson 1990). A study of a Rehabilitation Services Administration training program for consumer case manager and human service worker aides, comparing team and individual approaches with intensive case management for frequent users of psychiatric hospitals, found significant advantages in consumer employment (Bond et al. 1991) Family members participating in a randomized trial of consumer versus nonconsumer case management teams reported equal satisfaction with the capabilities of consumer case managers (Mowbray et al. 1997).

A major question relates to job stress and the stability of former psychiatric patients as mental health service providers. A project in Denver, Colorado, trained consumers as case management aides in a psychiatric rehabilitation program. Of 25 trainees, 18 completed the program and 17 were employed as case management aides. At 2-year follow-up, the 15 trainees who were still employed had required a total of only 2 bed-days of psychiatric hospitalization (Sherman and Porter 1991).

Positive results were found in recent overviews of consumer-run services and CSP research demonstration projects based on consumer services. A comprehensive retrospective review of federally funded consumer/survivor-operated service programs in 13 states concluded that "Consumer/survivor-operated services are successful in increasing the overall quality of life, independence, employment, social supports, and education of consumer/survivors." (Van Tosh and del Vecchio 2000, p. 79). This study found, moreover, that 70% of the federally funded initiatives were continued with other funding sources. The consumer recipients were objectively successful in capturing ongoing financial support, and, subjectively, they reported increased self-efficacy and self-esteem on standardized scales.

A multisite study by the CMHS found reduced symptoms, larger social networks, and enhanced quality of life when peer support was offered within traditional mental health services (Campbell et al. 2004). Prior research had indicated that peer support resulted in reduced hospitalization (Solomon and Draine 1995) and more effective case management (Felton et al. 1995). An overview of consumer programs by the International Association of Psychosocial Rehabilitation Services reported similar findings and stated that "Consumer service provision may be an essential feature of a support system devoted to recovery." (Mowbray et al. 1997). A study of 255 long-term users of four self-help agencies found that "the significant ingredient promoting positive outcomes for clients of self-help agencies appears to be the provision of opportunities for clients to meaningfully participate in decisions about their care and the care of others in their organization (Segal and Silverman 2002).

Although consumers seem to be doing well on many of the evaluated programs, there are some negative or problematic findings as well. According to an evaluator for the CSP, consumer alternatives were never envisioned to serve as substitutes for mental health services; they were meant to empower consumers to gain some control over their lives. A qualitative analysis based on systematic observations of consumer-run services found that many consumer alternatives fell short of these empowering principles. Power conflicts and hierarchies developed in many programs. Consumers often tried unsuccessfully to replicate services provided by the local mental health clinic rather than to offer self-help alternatives (McLean 1994). The National Council for Community Behavioral Healthcare addressed some of these issues in a recently published handbook for providers on employing consumers in the mental health workforce (Townsend and Griffin 2006).

## Relations of Professionals and Self-Help Groups

Many health and mental health professionals have welcomed the advent of the self-help movement. In a Workshop on Self-help and Public Health held by the Surgeon General's Office of the Department of Health and Human Services, the major focus was on collaborative partnerships of professionals and self-help groups and a key recommendation that "exposure to the concepts and benefits of self-help should be included in the training curriculums of all helping professions." (Surgeon General's Workshop 1988, p. 32) The American Psychiatric Association's Task Force on Treatments of Psychiatric Disorders views self-help groups as part of the therapeutic armamentarium. In their four-volume publication on treatment, Borman (1989) noted that self-help groups redefine pathological states, provide a shift in human service paradigms, promote and maintain competence, and reinforce positive mental health.

An increasing number of community mental health centers and rehabilitation facilities are welcoming support groups of patients and families, offering organizational help and free staff facilitators. Most professionally-run substance abuse programs include participation in AA or NA as a component of treatment. Newsletters for professionals and administrators often give information on self-help resources.

Under certain conditions, self-help groups may compose a parallel and sometimes competing system of care. Although most members simultaneously use clinical services, some may join self-help groups because of dissatisfaction with professional mental health treatment. A few self-help groups reduce the demand for clinical services because they offer alternatives and are hostile to the mental health system. Other groups, however, may raise awareness of deeper problems and provide referrals to preferred psychiatrists. Referrals work both ways and typically are mutually beneficial. Self-help group members learn about recommended professionals from their peers. Psychiatrists treating persons with a chronic mental illness are usually happy to learn about a local drop-in center to which they can refer their socially isolated patients.

Consumers who participate in self-help groups seem to be comfortable using dual systems of care. A Boston University study of six consumer-run self-help programs in various parts of the United States found that 50% of the self-help members were currently taking antipsychotic medication. Most also utilized professional mental health services such as counseling, day treatment, and inpatient care (Chamberlin et al. 1996). Drop-in centers whose funding comes from the state mental health system generally require that participants be under psychiatric care. Most self-help groups with seriously disabled members agree that they cannot deal with decompensation or other issues requiring clinical expertise.

Although concurrent psychiatric oversight is recommended, research suggests that self-help groups function best on their own without professional help in running the group. Emerick's (1990) study of 104 self-help groups of psychiatric patients found that more than 70% reported little to no interaction with professionals. As previously indicated, only a third of these groups were considered to have a therapeutic orientation, and as might be expected, these were more amenable to professional alliances. A study of professional involvement with members of GROW, one of the therapeutic orientation models, compared social climate data and behavioral data among members of groups led by either a mental health professional ($n = 36$) or an indigenous

group member ($n$ = 70). The study found no difference in members' outcomes but significant differences in perceptions and behaviors. Members of groups led by professionals showed fewer agreements and self-disclosures, had less small talk and information giving, and rated their groups lower in cohesion and higher in leader control than did members of groups with indigenous leaders. The authors surmised that the professionals' more formal approach may have discouraged behaviors that they thought were less psychologically relevant and cautioned against professionalizing mutual help groups (Toro et al. 1998).

The picture is different on an individual basis, however. First-person accounts of consumers indicate numerous favorable recollections of their interactions with professionals (Hatfield and Lefley 1993). Many attribute the turning point of their recovery to a specific psychotherapist or to a rehabilitation specialist who helped them. Nevertheless, a number of former patients still tend to view negatively their overall experiences with the mental health system itself (Campbell 1989). In these cases, their negativity is typically related to feelings of disempowerment, external control, and loss of options for self-determination.

## Consumerism and a New Recovery Orientation in Mental Health Care

Currently, there is strong emphasis on a recovery orientation in mental health services, strengthened by the recommendations in the President's New Freedom Commission on Mental Health Report (2003). These confirmed the vision of the director of Boston University's Center for Psychiatric Rehabilitation, who wrote almost a decade ago that recovery from mental illness was "the guiding vision of the mental health service system in the l990s (Anthony 1993, p 7). In this vision, recovery is viewed as a subjective attitude change that enables one to live a life of meaning and purpose, even with the limitations imposed by mental illness. A consumer leader, director of a state network of drop-in centers, credited his psychiatrist with enabling him to fulfill the advocacy role that has shaped his recovery. He defined recovery as follows: "Recovery is not remission, nor is it a return to a pre-existing state . . . Recovery is the development of new ego and identity structures to replace those damaged by our illnesses . . . Recovery takes place through creation of new patterns of behavior that make our lives more satisfying and productive. People in recovery like themselves as they are, accept their disability, and enjoy the life they have. Acceptance of one's disability can lead to greater appreciation of one's own strengths and new levels of self-esteem." (Kersker 1994, p 337). In a qualitative analysis of personal accounts of the recovery process, Davidson (2003) lists a number of cogent elements. The first and, perhaps, the primary area is one of *redefining self.* The person eschews an encompassing label of "mental patient" and views the illness as only one aspect of a multidimensional self. Additional areas are: *accepting illness; overcoming stigma; renewing hope and commitment; resuming control and responsibility; exercising citizenship; managing symptoms; being supported by others;* and *being involved in meaningful activities and expanded social roles*.

Do peer-run services reinforce positive aspects of recovery, with a measurable therapeutic effect? A study of 1824 patients indicated that participation in a peer support program within the past 4 months showed a modest but significant association with recovery and empowerment factors such as confidence and hope, willingness to ask others for help, goal-orientation, self-esteem, self-efficacy, autonomy, optimism, and control over the future (Corrigan 2006).

## Conclusions

The growth of the family and consumer movements has had a revolutionary impact not only on service delivery systems and funding resources but also on knowledge and practice. Like the National Society for Autistic Children before it, NAMI has helped change professionals' attitudes toward families in numerous ways. By eliciting public statements and support from world-class researchers and authorities, and disseminating their information on the neurobiological substrates of major psychiatric disorders, NAMI has reinforced the changing ideas about familial roles in etiology among psychiatrists and other mental health professionals as well as the general public. The family movement has influenced clinical training curricula to provide state-of-the-art education, helped attain increased funding for basic research; and through advertising, television, and other media events, aided in accelerating the slow historical process of destigmatizing mental illness.

The advent of a powerful grassroots constituency has generated pronounced respect on the part of professional leaders and policymakers and an eagerness for political alliances. There has been consistent personal participation of American Psychiatric Association presidents and NIMH directors at all annual NAMI conferences. Many state psychiatric associations have urged their members to join NAMI as associate members. Clinical training programs have, sometimes, required their students to attend local NAMI meetings as part of their training, and some psychiatric residents have regularly attended as resource persons for NAMI family support groups (Lefley 1988).

Family members and consumers are increasingly involved on governance and advisory boards of service providers and on state mental health planning councils. In various departments of psychiatry, family members and consumers have lectured, given grand rounds, or made presentations at professional association meetings. They have also been encouraged to enter professional training programs through various governmental training initiatives.

The growth of the consumer movement has dramatically highlighted the heterogeneity of psychiatric patients. An unexpectedly high level of organizational skill and leadership is evident among many people with histories of psychiatric hospitalizations and diagnoses of major disorders. In mental health service delivery, some former psychiatric patients are apparently able to fulfill staff functions ranging from crisis intervention to case management, with the added therapeutic advantage of offering role models and experiential empathy to the patients receiving their services. Qualified consumers function as administrators in state mental health offices, directors of agencies, and principal investigators of grants.

The consumer movement itself has helped develop a wide range of skills and knowledge that are invaluable for psychiatric rehabilitation. These include writing, technical assistance, education in communications media, information dissemination, and decision-making skills. The political

advocacy process has brought empowerment, respect, and influence on important leadership figures to individuals who believe that their residual psychological deficits were related to powerlessness, marginality, and internalized stigmas (Campbell 1989). The job of helping one's peers brings rewards of competence, altruism, and efficacy (Van Tosh and del Vecchio 2000). All of these would appear to be important factors in therapeutic growth.

Involvement in self-help and advocacy efforts seems to have additive therapeutic benefits, particularly for individuals adhering to a careful treatment regimen. These new developments are heuristic and warrant continuing research on the mechanisms of growth and paradigms of successful outcome in mental illness.

On a policy level, the primary consumer movement has had an impact both on state services and on rehabilitation ideology. Consumers have been particularly effective in promoting a recovery orientation in mental health services systems. Research shows that although there are concerns about the promises implicit in the recovery concept, the emphasis seems to be on persons living more positively with mental illness rather than presumptions of cure (Davidson et al. 2006). Cautions have been raised, however, about unrealistic expectations of persons with severe long-term mental illnesses. A group of consumer-professionals, writing in *Psychiatric Services* (Frese et al. 2001), have distinguished between categories of consumers with respect to the recovery vision. These authors note that advocacy for evidence-based practices, such as that offered by NAMI, is essential for the most seriously disabled consumers. Advocates who focus on consumer empowerment are those who are further along the road to recovery. These consumers merit increasing autonomy and input into the types of treatment and services they receive. The authors propose an integrative theory that maxmizes the virtues and minimizes the weaknesses of each model. They also suggest that graduate and professional schools should be encouraged to recruit consumers in recovery for their training programs, both as teachers and as students. This way the programs will benefit from consumers' experiential input and provide a scientific background for consumers to become knowledgeable mental health providers.

Consumerism is attractive to state and federal mental health authorities. This is demonstrated in the documents of NASMHPD, the allocations of funds by state program directors to support consumer-operated services, and the funding investments of the federal CMHS in developing the consumer movement. The influence of service-recipients was apparent in the Bush administration's New Freedom Commission on Mental Health Report (2003), which called for a mental health system that is consumer and family driven. Nevertheless, there is a relatively small pool of qualified former patients who are capable of assuming meaningful roles in mental health agencies or in the development of alternative services. Consumer-operated programs for long-term patients are still a minor variable in the mental health service delivery systems of most states. These systems will clearly continue to require professionalism and, particularly, a psychiatric capability for all the foreseeable future. This need is acknowledged by the majority of patients and families. A consumer member of the NAMI board of directors described receiving almost 500 letters from consumers sharing their positive experiences with new medications and basing their hopes on continuing biological research (Beall 1994).

In an era of health care reform, an alliance of NAMI, MHA, interested consumer groups, and mental health professionals is essential for adequate coverage of mental health services. At the 1994 annual meeting of the National Association of Psychiatric Health Systems, the *Psychiatric News* reported the following message from former American Psychiatric Association president Paul Fink:

> Not too many years ago, patient advocacy was an unknown for most therapists or one they chose to ignore. … Now nobody "in their right mind" would make major policy decisions or testify before governmental bodies without including patients or their advocates in the process (Alliances 1994).

This alliance has been reconfirmed in successive meetings of psychiatrists and advocates. The Association of Community Psychiatrists has been involved for many years in open discussions with consumer groups. NAMI president Dr. Suzanne Vogel-Scibilia gave an invited address at the APA 58th Institute on Psychiatric Services in 2006, and APA President Pedro Ruiz has stated that one of his decisions is "to build additional bridges and cement the relationship between APA and NAMI. . . . Partnering with NAMI strengthens our advocacy efforts" (Ruiz 2006, p 3). Professionals' alliances with advocates, as well as peer support in service delivery where its benefits are shown to be evidence-based, appear to be the wave of the future in mental health systems.

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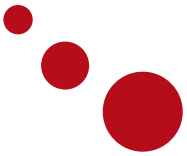
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SECTION

# VIII

Steven P. Roose, Section Editor

# *Pharmacological and Brain Stimulation Treatments*

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CHAPTER 99

# General Principles of Pharmacologic Therapy

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## Introduction

Psychotropic medications are extensively used, with a recent survey indicating 7.2% of the general population taking at least one such medication (Beck et al. 2005). Nearly one in five community dwelling elderly (Aparasu et al. 2003) and 47% of nursing home residents (Snowdon et al. 2006) were found to be taking regular psychotropic medications, and 10% of adolescent office visits may result in the prescription of a psychotropic (Thomas et al. 2006). Prescribing physicians believe that they are equipped with knowledge of the primary actions of the drugs and the doses that need to be administered in order to treat psychiatric patients. Nonetheless, it is important to note the lack of diagnostic precision and pathophysiologic understanding of what in fact is being treated with medication. Psychotropic treatment is based on treating symptoms, which have a heterogeneous etiology. The strategy for drug discovery in psychiatry has relied on the serendipitous observation of the symptomatic benefit of a known drug, study of the putative mechanisms of that compound, and efforts to develop similar compounds with similar apparent mechanisms of action (Insel and Scolnick 2006). Moreover, it is important to appreciate the extensive variability in drug concentrations that occur in individual patients, given the same dose of a medication. As discussed below, there are a host of factors that will confound the individual patient's actual exposure to a medication and thus contribute to variable therapeutic and adverse effects.

Newer approaches to drug development include development predicated on understanding the pathophysiological properties of illness (Lewis and Gonzalez-Burgos 2006) and based on population pharmacokinetics (PK) to model dosing (Bigos et al. 2006) as well as innovations in clinical trial design (Roose and Schatzberg 2005). Regardless of when these innovations will impact the pharmacopeia and evidence base, clinicians need to incorporate general clinical pharmacological principles when treating the patients who are suffering now.

This chapter will address many of the components of clinical pharmacology. Included are pharmacokinetics, pharmacodynamics (PD), pharmacogenomics, as well as the role of herbal supplements, drugs of abuse, aging, and comorbid medical illness. These factors will ultimately help address the issues of efficacy and safety. Only by investigating each of these variable components can one measurably affect the end result and decrease variability in drug response (Urquhart 2004).

## Pharmacokinetics

Pharmacokinetics is a description of how drug concentrations change with time and ultimately describes the relationship between a given dose and plasma concentration. More simply, PK describes what the body does to the drug. A pharmacokinetic study describes these concentration changes and is classically performed using a small number of subjects given a single dose of medication followed by multiple blood samples. These studies provide information on absorption, bioavailability, distribution, metabolism, steady state, and elimination—factors that will be addressed here. This section will also address the growing field of population PK and the effects of aging on the above. See Figure 99–1 and Table 99–1.

### Absorption/Formulation

The formulation of a drug and its route of administration are significant factors involved in the dose–concentration relationship. These factors contribute to variabilities in the system and can determine the onset of actions of administered medications.

Intravenous (IV) administration is the fastest and easiest route of administration to control medication exposure, given the absence of the first-pass effect (see below). However, it is almost never encountered in psychiatry. More common is the intramuscular (IM) formulation, especially in the treatment of agitated behavior and in the face of nonadherence. Benzodiazepines (such as lorazepam)

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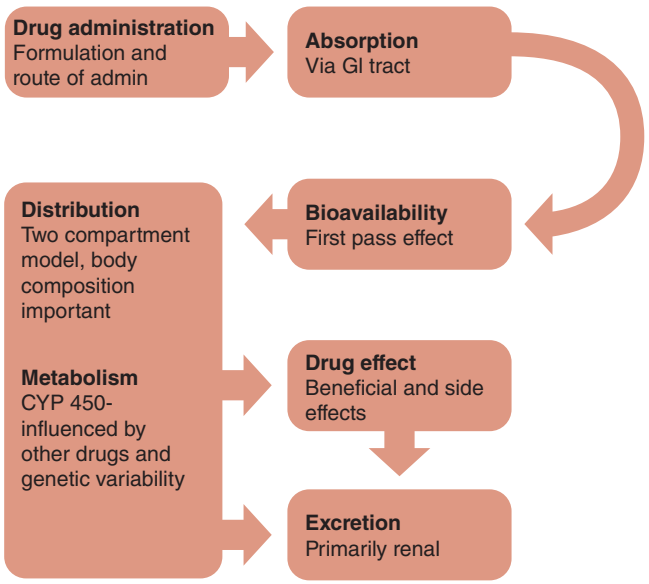



**Figure 99–1** *Aspects of pharmacokinetics.*

and antipsychotics (both in short-acting and in depot formulations) are often given this way. IM antipsychotics can be typical (e.g., haloperidol and loxapine) or atypical (e.g., risperidone and ziprasidone). At present, the only long-acting IM atypical antipsychotic is risperidone.

Most commonly used is oral (p.o.) administration, the utility of which is conferred by the highly lipophilic nature of central nervous system (CNS) medications. Formulation is a major factor involved in the rate of p.o. absorption. Whereas rapidly dissolving oral wafers (e.g., olanzapine wafer and risperidone M-tab), as well as solutions, suspensions, and sublingual formulations can be absorbed quickly, coatings and capsules with differential release technologies (e.g., buproprion XL and methylphenidate OROS formulation) as well as transdermal patches (nicotine) can delay absorption of medications. These changes in absorption can confer single daily dosing onto a medication or provide variation on classic PK profiles. The rate of absorption can affect peak plasma levels with slow absorption having lower peak levels than those with fast absorption. By minimizing the effects of peaks far above the minimum effective concentration (MEC) and troughs far below the MEC from immediate release formulations, slow release formulations can minimize peak-associated side effects and trough-related lack of efficacy. They may allow therapeutic action overnight and potentially improve adherence as well.

Oral drugs are absorbed via passive diffusion across the intestine, although some are absorbed via facilitated diffusion or active transport across gastrointestinal (GI) membranes via P-glycoprotein. Passive transport occurs as the drug diffuses down a concentration gradient and is driven by the magnitude of the concentration gradient. Most psychotropics are well absorbed from the GI tract with an onset of 30–45 minutes and full absorption within 2–3 hours. Anticholinergic medications can decrease intestinal motility and delay the rate of absorption. Antacids can delay the absorption of medications by altering their ionization and delaying gastric emptying time, and high-fiber supplements or cholestyramine can do this as well.

**Table 99–1 Pharmacokinetic Changes with Aging**

| |
|---|
| **Absorption** |
| • No change in passive diffusion |
| • Decreased GI blood flow can decrease rate of absorption |
| • Antacids can delay gastric emptying or alter ionization |
| • Delayed gastric emptying can delay absorption |
| **Bioavailability** |
| • Decreased blood flow may also decrease first-pass metabolism, thus increasing bioavailability |
| **Distribution** |
| • For water-soluble drugs, volume of distribution decreases and plasma concentration increases |
| • For lipid-soluble drugs, volume of distribution increases and half-life increases |
| • Increased blood–brain barrier permeability |
| • Protein composition changes: decreased albumin, increased alpha 1 acid glycoprotein |
| **Metabolism** |
| • Possible decreased phase I metabolic reactions 2C19 3A4 |
| **Excretion** |
| • Decreased renal clearance |

## First Pass/Bioavailability

In transition from the GI tract to the systemic circulation, many drugs are metabolized as they pass through the GI membranes and hepatic circulation. This is known as the first-pass effect (Burton et al. 2002). Cytochrome P 450 3A4 (CYP3A4) is predominantly responsible for first-pass metabolism both in the small intestinal lumen and in the liver (Kolars et al. 1992). P-glycoprotein is involved in first-pass effect as well. P-glycoprotein causes an ATP-dependent active transport efflux of various drugs from cells and is present in small intestine and kidney, as well as the blood–brain barrier (BBB) and is subject to genetic variation in functioning (Benet et al. 1999, Doherty and Charman 2002).

The term bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation. Bioavailability depends on the amount of drug absorbed through the GI mucosa, the proportion of drug that passes unmetabolized into hepatic portal blood and remains unaltered by the first-pass mechanisms of the liver, irrespective of the rate or amount of absorption. Thus, some active drug is metabolized and rendered unavailable to act at the effect site. If the first-pass hepatic clearance for a drug is extensive, biovailability will be low. Although unmetabolized drug generally provides the desired effect, some drugs such as codeine are prodrugs, which are transformed into active metabolites to produce the therapeutic effect.

With aging, gastric acid secretion decreases and drugs that require an acidic environment to be ionized can be affected (e.g., ketoconazole and iron) (Iber et al. 1994). Decreased blood flow may also decrease first-pass metabolism, thus increasing bioavailability (McLean and Le Couteur 2004).

## Distribution

As drugs are administered and absorbed they are distributed to tissues, and this is dependent on circulation

and membrane permeability. Well-perfused tissues such as liver, kidney, and brain receive most of the drug initially, while distribution to muscle fat and skin is slower, delaying equilibrium between peripheral tissue concentration and that of the blood. A two-compartment mathematical model describes the distribution of drugs into tissue—a central compartment of circulation and rapidly distributed tissues, followed by equilibration in the peripheral compartment of less accessible tissues (Gibaldi and Perrier 1975). Plasma drug concentration decreases with distribution to tissues, and it is only unbound drug that is able to cross into tissue. The volume of distribution ($V_D$) is a measure of the apparent space in the body into which a drug distributes, that is, the volume in which the amount of drug would need to be uniformly distributed in to produce the observed blood concentration. $V_D$ is not a real volume but rather a reflection of how a drug will distribute throughout the body. For lipophilic drugs, the $V_D$ describes the size of the reservoir of fatty tissues, and, for water-soluble drugs, it describes the total body water. It is expressed by the following formula:

$$V_D = \text{total amount of drug in the body/drug blood concentration}$$

Factors affecting distribution include lipid solubility of the drug, the permeability of the BBB, and plasma protein binding. Highly lipophilic drugs can be distributed more widely than those that are not. As the BBB is a lipid membrane, increasing lipid solubility confers a faster onset of action due to increased permeability through the membrane. Also, P-glycoprotein is present in the BBB and may affect distribution of drug (Benet et al. 1999). Plasma protein binding affects distribution as only unbound drug can be redistributed to tissues. Drugs bind to plasma albumin and α1 acid glycoprotein. Protein binding may decrease drug distribution, as bound drug stays in the blood stream and only free drug equilibrates outside the bloodstream. Only the free fraction of drug exerts a pharmacologic effect and undergoes hepatic metabolism or renal filtration. Although changes in protein levels can theoretically affect distribution, these are now thought to be less clinically relevant than before except in rare cases of drugs with a high extraction ratio and narrow therapeutic index that is given parenterally (Benet and Hoener 2002). However, changes in protein binding may affect interpretation of drug levels, which typically measure total drug, as opposed to bound or unbound portions.

With aging, body water decreases by 10–15% and body fat increases by 20–40% (Beaufrere and Morio 2000). Water-soluble drugs will have a decreased volume of distribution, increased plasma concentration, and, thus, an increased potential for toxicity. Examples of this include lithium and digoxin. For lipid-soluble drugs (as most psychotropics are), this will result in an increased volume of distribution and therefore a longer half-life, leading to drug accumulation. Protein composition changes with age as albumin decreases and α1 acid glycoprotein increases, but as mentioned, this is not likely clinically significant. The BBB also changes with age such that permeability increases with increasing age (Pakulski et al. 2000).

## Metabolism

Drug metabolism occurs via two phases, I and II. Phase I involves primarily oxidation reactions including dealkylation, hydroxylation, oxidation, deamination, desulfuration, and sulfoxide formation and is mediated by the cytochrome P 450 (CYP450) system. Phase II metabolism involves conjugation or synthetic reactions that render the molecule more water soluble and hence available for renal excretion.

The CYP450 system is a generic name describing a superfamily of oxidative enzymes important in plant, animal, and human physiology. They metabolize not only endogenous compounds but also xenobiotics including environmental compounds and drugs (Nemeroff et al. 1996). This superfamily contains over 30 related enzymes, and five human CYP450 proteins metabolize more than 90% of drugs used today. These include CYP 1A2, 2D6, 2C9, 2C19, and 3A4. CYP450 enzymes are found primarily in the liver but also in the GI tract, kidney, and lung. Tables 99–2 through 99–6 list the common substrates for these enzymes. An up-to-date website highlighting the CYP450 system can be found at http://medicine.iupui.edu/flockhart/table.htm (Flockhart).

Pharmacokinetic drug interactions are well described and result from one drug affecting the metabolism of another. Substrate drugs or xenobiotics for CYP450 can be inducers (increasing enzyme activity) or inhibitors (decreasing enzyme activity) of various CYP450 isoenzymes. Competitive or noncompetitive inhibition by one drug on the relevant hepatic enzyme can result in slowed or decreased metabolism of another drug metabolized by the same enzyme. The increase in plasma concentration of the affected drug is immediate, and this second drug reaches a new steady state. For example, giving fluvoxamine to a patient already taking clomipramine will result in increased clomipramine levels. This occurs because of inhibition of clomipramine demethylation via CYP2C19 by the added agent. If the new

**Table 99–2 CYP1A2 Isoenzyme Substrates, Inducers, and Inhibitors**

| CYP1A2 | | |
|---|---|---|
| **Substrate** | **Inducers** | **Inhibitors** |
| Antidepressants: | Broccoli | Cimetidine |
| Amitriptiline | Brussel sprouts | Ciprofloxacin |
| Clomipramine | Char-grilled meat | Fluvoxamine |
| Fluvoxamine | Insulin | Interferon |
| Imipramine | Modafinil | |
| | Omeprazole | |
| Antipsychotics: | Tobacco | |
| Clozapine | | |
| Haloperidol | | |
| Olanzapine | | |
| Other: | | |
| Acetaminophen | | |
| Caffeine | | |
| Estradiol | | |
| Naproxen | | |
| Propanolol | | |
| Tacrine | | |
| Theophylline | | |
| Verapamil | | |
| R-warfarin | | |
| Zolmitriptan | | |

**Table 99–3 CYP2C19 Isoenzyme Substrates, Inducers, and Inhibitors**

| CYP2C19 | | |
|---|---|---|
| **Substrate** | **Inducers** | **Inhibitors** |
| Antidepressants: | Carbamazepine | Antidepressants: |
| Amitriptiline | Prednisone | Fluoxetine |
| Citalopram | Rifampin | Fluvoxamine |
| Clomipramine | | |
| Imipramine | | Mood stabilizers: |
| Moclobemide | | Oxcarbazepine |
| | | Topiramate |
| Anticonvulsants: | | |
| Diazepam | | Other: |
| Phenytoin | | Cimetidine |
| Phenobarbitone | | Indomethacin |
| | | Ketoconazole |
| Other: | | Lansoprazole |
| Proton pump inhibitors | | Modafinil |
| Indomethacin | | Omeprazole |
| Progesterone | | |
| Propanolol | | |
| R-warfarin | | |

steady state for the affected drug is too high, toxicity can ensue (see Clinical Vignettes 1 and 2 for further discussion). Conversely, induction requires synthesis of CYP isoenzymes, and this effect may not be immediately apparent. Once the CYP450 isoenzyme is produced, plasma levels of the affected drug will decrease accordingly. Examples include the induction of CYP3A4 by carbamazepine, which then increases metabolism of oral contraceptives, decreasing their steady-state concentration and rendering them less effective. A high index of suspicion is recommended for identifying pharmacokinetic drug interactions. This is especially true if a drug is highly toxic or has a narrow therapeutic window, two or more inhibitors of the same system are used, a substrate or inhibitor is suddenly discontinued, or if there is a sudden change in clinical picture.

Variability in the CYP450 system exists due to genetic polymorphisms in coding genes. Differences in copy number, activity, or substrate affinity of the isoenzymes can result in enzymes with inactive, decreased, normal, or increased activity (Ingelman-Sundberg et al. 1999). These interindividual and interethnic differences can result in variable response to drugs.

**Table 99–4 CYP2C9 Isoenzyme Substrates, Inducers, and Inhibitors**

| CYP2C9 | | |
|---|---|---|
| **Substrate** | **Inducers** | **Inhibitors** |
| Antidepressants: | Rifampin | Antidepressants: |
| Amitriptiline | Secobarbital | Fluoxetine |
| Fluoxetine | | Fluvoxamine |
| | | Sertraline |
| Other: | | Other: |
| ACE inhibitors | | Amiodarone |
| NSAIDS | | Fluconazole |
| Oral hypoglycemics | | Isoniazid |
| Celecoxib | | Lovastatin |
| Phenytoin | | Sulfamethoxazole |
| Rosiglitazone | | |
| S-warfarin | | |

Clinical Vignette 1

A 28-year-old man with schizophrenia was admitted with a relapse of his psychosis. He was last well approximately 6 weeks ago when he started hearing voices and feeling like people were watching him. This was similar to his first episode of illness. He deteriorated to the point that he was agitated and started walking around with a knife. He became acutely paranoid and pulled the knife on a bystander. The police were called and he was brought to the hospital. He was stabilized on the inpatient unit with a combination of olanzapine 15 mg p.o. qhs and over the next 2 weeks his auditory hallucinations resolved and his paranoia diminished. He was discharged home at that time with follow-up in clinic. Four weeks later, there was an urgent phone call from his parents stating that he was once again psychotic. They insist that he had been taking his medications. Of note is the fact that he had been smoking many cigarettes since his discharge.

**Discussion**:

The patient was stabilized in hospital in a nonsmoking unit, although he did smoke a little toward the end of his hospitalization when he went on passes. Upon discharge, he resumed his previous smoking regime, which induced CYP1A2 metabolism. With increased activity of this isoenzyme, there was increased metabolism of olanzapine, which then decreased to subtherapeutic concentrations resulting in relapse. This is an example of a pharmacokinetic drug interaction often seen in clinical practice.

Clinical Vignette 2

A 76-year-old woman with dementia is stable in long-term care on a regime of quetiapine 50 mg bid, aplprazolam 1 mg bid, and donepezil 10 mg qd. She vis moved to a different floor in the nursing home and after a few days is noted to be listless, less interested in socializing, and more sedated. She was noticed to be drinking quite a bit of grapefruit juice, which was freely available on this unit. After several days, she is diagnosed with depression and treated with fluoxetine 10 mg p.o. qd. Two days later, she becomes excessively sedated such that her drive to breathe is decreased and she is difficult to rouse. She is sent to hospital.

**Discussion:**

In this case, the addition of grapefruit juice results in inhibition of CYP3A4, which metabolizes both alprazolam and quetiapine. Increasing blood levels of those drugs results in sedation and listlessness, which is diagnosed as depression. The addition of fluoxetine complicates matters as it further inhibits CYP3A4 through its active metabolite norfluoxetine, resulting in a complex pharmacokinetic drug interaction and hospitalization of this patient.

**Table 99–5 CYP2D6 Isoenzyme Substrates and Inhibitors**

| CYP2D6 | | | |
|---|---|---|---|
| **Substrate** | | | **Inhibitors** |
| Antidepressants: | Other: | Dexamethasone | Antidepressants: |
| Amitriptiline | Beta blockers | Rifampin | Buproprion |
| Clomipramine | Atomoxetine | | Citalopram |
| Duloxetine | Codeine | | Clomipramine |
| Desipramine | Debrisoquine | | Doxepin |
| Fluoxetine | Dextromethorphan | | Duloxetine |
| Fluvoxamine | Metoclopramide | | Escitalopram |
| Imipramine | Methoxyamphetamine | | Fluoxetine |
| Nortriptiline | Oxycodone | | Moclobemide |
| Paroxetine | Tamoxifen | | Paroxetine |
| Venlafaxine | | | Sertraline |
| Antipsychotics: | | | Antipsychotics: |
| Aripiprazole | | | Chlorpromazine |
| Chlorpromazine | | | Haloperidol |
| Haloperidol | | | |
| Perphenazine | | | Other: |
| Promethazine | | | Celecoxib |
| Risperidone | | | Cimetidine |
| Thioridazine | | | Cocaine |
| Zuclopenthixol | | | Ritonavir |
| | | | H1 antagonists |

**Table 99–6 CYP3A4,5,7 Isoenzyme Substrates, Inducers, and Inhibitors**

| CYP3A4,5,7 | | | |
|---|---|---|---|
| **Substrate** | | **Inducers** | **Inhibitors** |
| Antidepressants: | Other: | CNS meds: | Antidepressants: |
| Nefazodone | Buspirone | Barbiturates | Fluvoxamine |
| Sertraline | Macrolide | Carbamazepine | Nefazodone |
| Trazodone | antibiotics | Modafinil | Norfluoxetine |
| | Quinidine | Phenobarbital | |
| Antipsychotics: | HIV antivirals | Phenytoin | Other: |
| Aripiprazole | Cisapride | Oxcarbazepine | HIV antivirals |
| Haloperidol | Antihistamines | | Cimetidine |
| Pimozide | Calcium channel | Other: | Clarithromycin |
| Quetiapine | blockers | Glucocorticoids | Erythromycin |
| Risperidone | HMG CoA | HIV antivirals | Fluconazole |
| Ziprasidone | reductase inhibitors | Rifampin | Grapefruit juice |
| | Caffeine | St. John's wort | Ketoconazole |
| Benzodiazepines: | Cocaine | | Star fruit |
| Alprazolam | Codeine | | Verapamil |
| Diazepam | Dexamethasone | | |
| Midazolam | Dextromethorphan | | |
| Triazolam | Fentanly | | |
| | Methadone | | |
| | Oral Contraceptives | | |
| | Propanolol | | |
| | Sildenafil | | |
| | Tamoxifen | | |
| | Terfenadine | | |
| | Zaleplon | | |
| | Zolpidem | | |

The most studied genetic polymorphism affecting drug metabolism is that of CYP2D6, where the poor-metabolizer status is an autosomal-recessive trait. Null mutations on this gene result in impaired CYP2D6 activity. Clinically, this can manifest in drug toxicity. For example, when perphenazine was given to poorly metabolizing elders, extrapyramidal symptoms were exaggerated (Pollock et al. 1995). Conversely, 4% of Caucasians are ultrarapid metabolizers due to increased CYP2D6 activity. Ultrarapid metabolizers are often misdiagnosed as treatment resistant due to poor response. They frequently require higher than expected doses of CYP2D6 drugs and therapeutic blood monitoring (especially for tricyclic antidepressants) may be helpful in treating these patients. Thus far, over 100 allelic variants have been identified in the CYP2D6 system, contributing to the broad variability in metabolism via this isoenzyme (Ingelman-Sundberg et al. 2007) some of which are shown in Table 99–7.

With aging, there appears to be no uniform decline in liver metabolism by the CYP450 system (Pollock et al. 1992b, Schmucker 2001). However, it is possible that functioning of CYP2C19 may decline with age (Bebia et al. 2004). For example, citalopram's clearance is reduced in older patients (Bies et al. 2004), and this may be in part due to decreased CYP2C19 function. Reductions in both hepatic blood flow and hepatic mass place greater emphasis on interindividual differences in the metabolic capacity of the elderly (Wynne et al. 1990). Drugs metabolized by CYP3A4, such as alprazolam, triazolam, sertraline, and nefazodone, appear to be cleared less well in elderly patients (Greenblatt et al. 1991, Ronfeld et al. 1997, Timmer et al. 1997). However, this may also be because metabolism of some CYP3A4 drugs is perfusion limited and thus decreased in the elderly. Liver disease can also modulate CYP450-mediated metabolism (Frye et al. 2006) but not equally across isoenzymes, suggesting sequential progressive model of hepatic dysfunction.

**Table 99–7 Select CYP 2D6 Alleles**

Select CYP2D6 mutations

| CYP 2D6 Allele | Effect |
|---|---|
| Wild type | Normal enzyme activity |
| *1, *1A, *1B | Normal enzyme activity |
| *2X2, 2X3, 2X4, 2X5, 2X13 | Increased enzyme activity |
| *3 (CYP 2D6A)† | Decreased enzyme activity |
| *4A (CYP 2D6B)§,*4B§, 4C§, 4D§, *6A†, *6B†, *7‡, *8□, *11§, *12‡, *13†, *14‡, *15¶, *16†, *17‡ | Decreased enzyme activity |
| *5# (CYP 2D6D) | CYP 2D6 gene deleted |
| *9††, *10A‡, | Decreased enzyme activity |
| *10B‡, *10C‡ | Decreased enzyme activity |

†Frameshift.
‡Amino acid change.
§Splicing defect.
□ Stop codon.
¶Insertion.
#Gene deletion.
††Amino acid is deleted.

Reproduced from Ingelman-Sundberg M et al. (2007).

## Elimination/Excretion

After conversion to hydrophilic metabolites, drugs are eliminated from the body by renal excretion via the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. Clearance (Cl) is defined as the volume of blood from which drug is removed per unit time. Clearance is described by the following equation, which is analogous to the Michaelis–Menten equation for enzyme kinetics (Gibaldi and Perrier 1975):

$$\mathrm{Cl} = v_m/(K_m + C)$$

where $K_m$, the Michaelis–Menten constant, represents the concentration at which half the maximal rate of elimination is reached, $C$ is plasma concentration of drug, and $v_m$ is equal to the maximal rate of elimination. Clearance does not indicate how much drug is being removed but rather the volume of blood or plasma from which drug would have to be removed completely to account for the clearance. From a clinical perspective, creatinine clearance (CrCl) is used to estimate the clearance of drugs and can be calculated by the Cockroft–Gault equation (Cockroft and Gault 1976):

$$\mathrm{CrCl\ (ml/min)} = (140 - \mathrm{age}) \times (\mathrm{body\ wt\ (kg)} \times 0.85 \text{ if female}))/(72 \times \mathrm{sCr\ (mg/dl)})$$

where sCr is serum creatinine.

Half-life ($T_{1/2}$) of a drug is the time required to decrease concentration by 50%, and this determines the rate of drug accumulation in the body. Half-life can be expressed by the following formula:

$$T_{1/2} = (V_D/\mathrm{Cl}) \times 0.693$$

Increased $V_D$ (volume of distribution) and decreased Cl (clearance) can increase $T_{1/2}$, leading to drug accumulation. Different drugs have different types of elimination kinetics. First-order or linear kinetics occur when the amount of drug eliminated over time varies with the amount available for elimination, that is, it is proportional to dose. Most psychotropics are eliminated this way. Zero-order kinetics occurs when fixed amount of drug removed per unit time. Due to rapid saturation of elimination mechanisms, drug metabolism is constant. Alcohol is the classic example of zero-order elimination. Intermediate kinetics occurs between the zero and first order. At low doses drug metabolism is first order and then saturates at high doses becoming zero order.

With aging, there is a well-established decline in glomerular filtration rate (GFR). This change in clearance varies and can be exacerbated by concomitant illness (diabetes and hypertension) and concurrent medications (nonsteroidal anti-inflammatories) (Pollock et al. 1992b). Accumulation of active metabolites can be a significant clinical concern, as is the case with tricyclic antidepressants (Pollock et al. 1992a). Diminished renal clearance will result in accumulation of water-soluble drugs (lithium and digoxin) and active metabolites of some medications (e.g., risperidone and venlafaxine).

## Steady State

After a single dose of a drug there is an initial rise to a peak plasma level, after which concentration falls until the drug is

completely eliminated from the plasma. The concentration below which no drug effect is seen is termed the minimal effective concentration (MEC). The MEC defines the lower limit of the therapeutic window, the upper limit of which is defined by the concentration at which the drug produces toxicity. Drugs that have a wider therapeutic window are safer and less prone to serious pharmacokinetic interactions. As drugs are given in multiple dosing, concentration rises to reach steady state. Steady state is when the amount of drug entering the body equals the amount of drug leaving the body. This level occurs after approximately 4–5 half-lives of the drug and is described by the following equation (Gibaldi and Perrier 1975):

$$C_{SS} = (1.44 \times D \times T_{1/2}) / V_D \times Di$$

where $C_{SS}$ is the average steady-state plasma level,
$D$ is the absorbed dose,
$T_{1/2}$ is the elimination half-life,
$V_D$ is the volume of distribution, and $Di$ is the dosing interval

Steady states achieved with multiple dosing result in peaks and troughs in the plasma concentration. Dose, interval, and formulation determine these peaks and troughs. In general, decreased frequency of administration results in increased peak-to-trough differences. The ratio of the peak-to-trough plasma concentration is known as the fluctuation index, and extended release formulations can result in a decreased fluctuation index.

### Population PK

Classical PK studies involve multiple samples from carefully selected volunteer subjects and generate PK models that are then generalized to other populations such as the elderly. Although helpful, they do not capture the subtlety of PK changes, nor can they identify unexpected factors influencing PK. For example the unexpected interaction between ketoconazole and terfenadine resulted in fatal toxicity and removal of terfenadine from the market (Dresser et al. 2000).

Population PK developed as a way to identify unexpected influences of drug PK (Ette and Williams 2004) and to characterize and model sources of variability in drug concentration. Population PK involves studying large numbers of people in minimally invasive ways. It models drug concentration by looking at the central tendency of a PK parameter across an entire population and assesses inter- (between subject) and intraindividual (within subject) differences in drug concentration. Population PK thus identifies factors that contribute to pharmacokinetic and pharmacodynamic variability using the concept of mixed effects models (i.e., fixed + random). Fixed effects include parameters such as clearance and volume of distribution, as well as covariates such as age, weight, sex, and ethnicity. Random effects include variability, both intra- and interindividual. Every data point from all individuals contributes to the identification of sources of variability (Bigos et al. 2006). A recent population pharmacokinetic study with paroxetine in elderly subjects with major depression involved 171 subjects and a total of 1970 paroxetine concentrations. A nonlinear mixed-effects model was developed for these subjects and demonstrated that a two-compartment nonlinear PK model best described the data. Weight and CYP2D6 polymorphisms influenced maximum velocity of metabolism, and gender had an effect on volume of distribution of the central compartment. The results showed that weight, gender, and genotype contributed to variability in PK parameters and suggested that dosing should vary according to these parameters (Feng et al. 2006).

## Pharmacodynamics

PD addresses the time course and intensity of drug effects on the body or what the drug does to the body. Variability in PD can exceed that of PK such that similar plasma concentrations can produce different pharmacological effects in different patients. This section will discuss the drug–receptor concept, dose–effect relationships, metabolism and its variability, and pharmacodynamic drug interactions. The role of kinetic–dynamic (KD) modeling in clinical pharmacology will also be reviewed.

### Drug–Receptor Concept

The pharmacological effects of most drugs derive from their interaction with a receptor, which then modulates the intrinsic physiology of the organism. If the drug emulates or enhances the function of the endogenous ligand, it is called an agonist. Conversely, if by binding the receptor a drug blocks function at that receptor, it is called an antagonist. Partial agonists are active at the receptor, but to a lesser extent than the endogenous ligand. Beneficial effects of medications often come from activity at target receptors, and side effects often arise from activity at other receptors. For example, the atypical antipsychotics may gain their efficacy from antagonism at both the serotonin 2A (5HT2A) and the dopamine 2 receptors (DRD2). Antagonism at histaminergic 1 (H1) and muscarinic receptors results in sedation, weight gain, constipation, urinary retention, dry mouth, and cognitive impairment. Antagonism at the α1 adrenergic receptor may cause orthostatic hypotension. Benzodiazepines are examples of GABA agonists, and memantine has partial antagonist activity at NMDA-operated cation channels. Aripiprazole is a partial agonist on the dopamine system where antagonistic effects occur in areas of high dopamine activation and agonism at sites of low dopamine activation, resulting in fewer adverse hormonal or motor events (Ohlsen and Pilowsky 2005).

Drug–receptor interactions may be saturable, selective, and reversible. Saturability implies that increasing the dose or concentration of the drug will no longer increase the effect due to maximum binding and rate of receptor activity. Selectivity of a receptor describes its high affinity for the drug over other compounds, but increasing concentration can result in decreased selectivity. Binding at the receptor can be reversible or irreversible depending on the nature of the bonds (i.e., covalent or ionic). Most psychotropics bind reversibly with receptors.

### Dose or Concentration–Effect Relationships

If a drug has physiological activity, there has to be a relationship between its concentration at its effector site and its actions. The nature of this relationship may be hard to assess. Nonetheless, understanding the concept of

concentration–response as it relates to a specific drug can help with treatment. For example, the sigmoid concentration–response curve is the most common description of how concentration and response are related. On the flat, initial part of the curve, concentration increases result in minimal therapeutic effects. The most direct relationship between increasing concentration and increasing effect is on the linear part of the curve. Maximal efficacy is reflected in the flat, terminal part of the curve. The shape of the curve is specific to an individual and is a source of pharmacodynamic variability. Even within individuals, the shape of the curve can change, depending on comorbid medical illness. If there exists drug toxicity, a parallel sigmoid curve exists delineating the toxic effects. The therapeutic window in this case is defined as the difference in concentration between effective and toxic doses. For example, tricyclic antidepressants have a therapeutic window, above which cardiotoxicity can occur. With aging, the therapeutic window can be narrower, as the elderly are more sensitive to the adverse effects of psychotropics at lower concentrations (Pollock 1999). The concentration–response curve can shift to the left, resulting in toxicity at lower doses. Physiological factors such as orthostatic control of blood pressure, water balance, postural control, and thermoregulation can be less robust in the aged, resulting in greater difficulty-tolerating medications. For example, SSRIs are more likely to result in syndrome of inappropriate antidiuretic hormone secretion and fragility fractures in the elderly (Kirby and Ames 2001, Richards et al. 2007). The existence of a therapeutic window for older medications gave rise to the practice of therapeutic drug monitoring (TDM), but a lack of information on concentration–effect relationships of newer psychoactive medications has resulted in less frequent use of this technique. Also, newer medications with wider therapeutic windows are dosed on the flat part of the curve. Currently, in light of better understanding of the large interindividual pharmacokinetic variability for virtually all psychoactive drugs, and worse clinical efficacy in inadequate and excessively high concentrations, an argument can be made for resuming this practice. A TDM "nouveu" model advocates for modeling both inter- and intraindividual PK variation over time in order to optimize dose. The therapeutic "window" should be used as a guiding principle rather than an absolute reference value (Bengtsson 2004).

## Pharmacodynamic Drug Interactions

More difficult to elucidate than pharmacokinetic drug interactions, pharmacodynamic drug interactions occur due to alteration of the clinical effects of a drug by another drug at the same receptor site. For example, concurrent use of alcohol and benzodiazepines can result in exacerbation of psychomotor impairment due to additive effects at the same GABA receptor. Similarly, addition of SSRIs and MAOIs can result in serotonin syndrome. Anticholinergic toxicity is a common example of pharmacodynamic drug interactions in the elderly. Many common drugs may have modest anticholinergic effects, and these are cumulative (Tune 2000). An assay may quantify serum anticholinergic activity in order to assess and minimize this serious pharmacodynamic interaction but currently is only available in research settings (Carnahan et al. 2002, 2006) (Clinical Vignettes 3 and 4 highlight this area further).

Clinical Vignette 3

A 70-year-old woman is living at home. She is taking ranitidine for esophageal reflux and oxybutynin for urinary incontinence. She develops mild depression with sleep disturbance and starts taking OTC antihistaminergic sleep agents to help her with initial insomnia. She becomes more anxious and her sleep worsens. She starts getting confused, presents to her primary care provider who queries dementia as she is starting to get lost. She is prescribed alprazolam as a hypnotic and she gets more confused as her cognition worsens. She goes again to the primary care provider who diagnoses dementia and starts her on donepezil. Her reflux worsens, and she stops eating. Her mood worsens, and she becomes dehydrated, resulting in delirium with symptoms of disorientation and hallucinations. She is brought by emergency medical services (EMS) to the emergency room and is admitted to hospital.

**Discussion**:

This is an example of the cumulative anticholinergic effect of multiple medications. OTC sleep aids that are potently anticholinergic, as well as other medications that are not always recognized as being anticholinergic, result in a pharmacodynamic drug interaction. The potent benzodiazepine alprazolam will also contribute to further confusion, and, being short acting, it may not be effective as a hypnotic. The prescription of donepezil, which is procholinergic, may counter some of the anticholinergicity of the other medications but has its own side-effect burden including procholinergic effects on the GI system. The GI disturbance is iatrogenic and contributes to her overall morbidity.

Clinical Vignette 4

A 55-year-old man with a previous vascular history is taking warfarin for anticoagulation. He has a family history of depression and has had two previous episodes at the ages of 24 and 38 years, successfully treated with fluoxetine. Due to the previous response he is started on fluoxetine again. Within 2 days his prothrombin time international normalized ratio (PT INR) is elevated and he has a cerebral bleed.

**Discussion**:

This is an example of a complex drug interaction involving both pharmacokinetic and pharmacodynamic mechanisms. Warfarin's two enantiomers are metabolized differently: more biologically active S-warfarin is metabolized by CYP2C9 while R-warfarin is mainly metabolized by CYP1A2. Inhibition of CYP2C9 by fluoxetine results in increased warfarin activity and increased PT INR. Further, platelet activity is depressed by SSRIs due to serotonergic activity on platelets (Pollock et al. 2000), and this is reflected in prolonged bleeding times. Thus, by two mechanisms, this patient is at risk of a bleed with the addition of fluoxetine to warfarin.

## Genetic Components of Variability

Studying the genetic contribution to the variability in drug response is the cornerstone of pharmacogenetics (Kalow et al. 1986) and historically this has involved single gene variations in metabolism of medications. The study of single nucleotide polymorphisms (SNPs) has led us to the

understanding that 20% of Chinese and 7% of Caucasians are deficient in functional activity of the CYPs 2C19 and 2D6, respectively (Preskorn 2006). Pharmacogenomics addresses multigenic controls of drug variability (Grant 1999) and aspires toward treatment individualization. Genetic differences may affect every aspect of pharmacokinetic and pharmacodynamic processes.

The clinical significance of genetic variability depends on the drug and the type of variability. In terms of metabolism, poor metabolizers are at risk of toxicity for drugs that are inactivated by the CYP isoenzyme in question and that have a narrow therapeutic index (Pollock et al. 1992a). Conversely, drugs with a wider therapeutic window may be of less clinical concern. In a study of 46 elderly patients receiving venlafaxine-XR, CYP2D6 genotype and steady-state plasma levels of venlafaxine (VEN) and *o*-desmethylvenlafaxine (ODV—the active metabolite) were determined. Although VEN concentration per unit dose was significantly higher and ODV concentration per unit dose was significantly lower in participants who carried intermediate or poor 2D6 metabolizer status, CYP2D6 genotype was not associated with medication-associated side effects (Whyte et al. 2006). Conversely, poor metabolizers would have a low conversion rate of a prodrug, like codeine, to an active metabolite, thus resulting in an inadequate therapeutic response.

Receptors and drug transporters are also targets for pharmacodynamic variability. Dopamine 3 receptor (DRD3) polymorphisms have been shown to play a role in medication-induced movement disorders. An Ser9Gly polymorphism in the N-terminal extracellular domain of this receptor is associated with an increased rate of tardive dyskinesia in patients treated with typical antipsychotics (Basile et al. 1999). Presence of the Taq1A A1 allele of the DRD2 and the nine repeat allele of the dopamine transporter (DAT1) variable number of tandem repeats polymorphism might be risk factors for EPS caused by antipsychotic drugs in schizophrenia (Guzey et al. 2007), as may polymorphisms of the 5HT 2A and 2C receptors (Gunes et al. 2007). Another recent example found butyrylcholinesterase (BuChE) genotype may influence the response to rivastigmine (Blesa et al. 2006).

### KD Modeling

Whereas PK addresses the relationship between time course of a drug and its attendant body concentration, PD addresses the relationship between time course and drug effects on the body. Pharmacodynamic differences are difficult to interpret without concentration data, and thus combining PK and PD to address the relationship between concentration and effect is the charge of KD modeling. A KD study involves assessing both drug concentration and drug effect at multiple times after dosing in laboratory conditions. The effect measurement can be subjective, semiobjective, or objective and can depend on the drug under study. Subjective measurements can involve assessment of mood or anxiety, semiobjective measurements can involve speed or motor performance, and objective measurements can involve evoked response potentials or neuroimaging. Various models can describe the concentration–effect relationship including linear, exponential, and sigmoid, in increasing complexity. The model can generate effect measures such as $EC_{50}$ (the concentration that produces 50% effect) and $E_{max}$ (concentration that produces maximal effect) having implications for dosing regimes. Difficulties arise when the wrong model is applied or when peripheral drug concentrations are not representative of effect site concentrations (Greenblatt and Harmatz 1993). By assessing concentration and accounting for variability in exposure to medication, the power and interpretation of pharmacogenetic, neuroimaging, and clinical studies should improve, with fewer subjects needed to improve this power (Lotrich et al. 2006). Poor correlations between peripheral and central concentration measurements can be a source of error in the model. For example, differences in P-glycoprotein transport activity can account for differential entry of medications into the brain, and this has been demonstrated via positron emission tomography (PET) (Sasongko et al. 2005).

## Safety and Efficacy

A prescribing physician must balance the two fundamental areas of safety and efficacy when it comes to choosing a medication. Although some safety issues are evident in initial clinical trials, others become apparent after marketing and extensive prescriber experience with the medication. Of new molecular entities approved by the FDA from 1980 to 1999, 21% underwent a dosing label change for the original indication and patient population. Of those medications, 80% of the changes represented a dosing reduction (Peck 2003). In special populations, dosing is an even greater issue. Package inserts (PIs) for oral medications often do not contain dosing information for older patients, with only 28% of PIs for the most commonly prescribed drugs in the elderly having specific dosing recommendations (Steinmetz et al. 2005). Further, 66% of admissions to an acute geriatric medical unit were preceded by at least one inappropriate medication, and of those patients taking appropriate medications, adverse drug reactions (ADRs) had a prevalence of 16.4% (Laroche et al. 2007). We have discussed many of the factors that contribute to variability in a patient's exposure to a medication, and awareness of these factors may assist in prescribing. Knowledge of these factors is important since greater variability may result in greater risk of toxicity.

### Compliance/Adherence

An often overlooked component of variability in the dose–effect relationship is compliance. Whether by commission, ommission, or confusion, patients often miss medications or take them inappropriately. In psychiatry, many illness states can result in nonadherence; paranoia from psychosis, denial in mania, or confusion in dementia can all result in missed medications or medication errors. Providers may attribute lack of treatment response to treatment resistance when adherence may be the issue. It is important to consider this when reassessing the efficacy and safety of a medication and to try to verify adherence when considering dosing changes. Caregivers can be asked to provide information, and drug levels may at least help to determine the presence or absence of prescribed medications. Nonadherence has significant clinical consequences. A California Medicaid study estimated adherence by prescription refills in a population of patients with schizophrenia. Rehospitalization rates correlated with increasing medication gaps, highlighting the clinical significance of both nonadherence and partial adherence (Weiden et al. 2004).

**Table 99–8 How to Prescribe Appropriately**

- Obtain a complete drug history
- Review medications regularly and before prescribing a new medication
- Know the actions, adverse events, and toxicity profiles of prescribed medications
- Start drug therapy at a low dose and titrate on the basis of tolerability and response,
- Attempt to reach a therapeutic dose before switching to or adding another drug
- Educate patient and/or caregiver about each medication
- Avoid using one drug to treat the adverse events caused by another
- Use combination products cautiously
- Communicate with other prescribers
- Avoid using drugs from the same class or with similar actions

## Adverse Drug Events/Reactions

ADRs are unintentional, unexpected, or undesired medication responses that result in clinically significant outcomes such as admission to hospital, a change in medication regime, morbidity, or mortality. As more psychotropics are prescribed, ADRs increase in their incidence. A recent study quantified adverse events in a high-risk multimorbid population of nursing home residents with Alzheimer's disease and psychosis (Oliveria et al. 2006). Of 7728 residents studied over 2 years, at least 90% had psychiatric comorbidity, and the most common adverse event was accidental injury occuring at a rate of 97.7 per 100 person years. This study of high-risk patients highlights how pharmacokinetic and/or pharmacodynamic interactions can result in ADRs. Another potential cause of ADRs is medication error. A review of 5366 medication errors from 1993 to 1998 found 469 to be fatal. Of those, 48.6% occurred in patients over 60 years. The most common types of errors resulting in patient death involved administering an improper dose (40.9%), administering the wrong drug (16%), and using the wrong route of administration (9.5%) (Phillips et al. 2001). The Institute of Medicine (IOM) issued a report "To Err Is Human: Building a Safer Health System" in 1999 and a follow-up report in 2005, addressing systemic ways to decrease medical errors. By recommending a specific reporting system, the IOM has highlighted the importance of awareness on medical errors and the systematic evaluation of these errors (Leape and Berwick 2005). In light of these systemic issues, Table 99–8 highlights ways that physicians can prescribe with greater safety.

## Drug of Abuse, Herbal Remedies, and Social Drugs

In addition to taking drugs that are prescribed by caregivers, patients take over-the-counter (OTC) remedies, herbal supplements, street drugs, and drugs of abuse as well as social drugs. These other compounds are subject to the same rules of pharmacology as are prescription medications and can result in pharmacokinetic and/or pharmacodynamic drug interactions with prescribed medications. The results can have great significance. It is important to be aware as fully as possible about all the products that the patients use and try to minimize drug interactions. Table 99–9 describes common OTC and herbal remedies and their role in drug interactions (Reuben et al. 2006).

## Interpretation of Evidence

The movement toward evidence based medicine is grounded in the assumption that the evidence is valid, reliable, and clinically meaningful. In contrast to other areas of medicine, psychiatric evidence is more difficult to interpret, and

**Table 99–9 Common Herbal Medications and Potential Interactions**

**Commonly Used Herbal and Alternative Medications**

| Product | Common Uses | Adverse Events | Drug Interactions |
|---|---|---|---|
| Chondroitin | Osteoarthritis | Nausea, dyspepsia, and changes in intraocular pressure | Anticholinergics |
| Echinacea | Immune stimulant | Hepatotoxicity | Immunosuppressants |
| Garlic | Hypertension, hypercholesterolemia, and platelet inhibitor | Bleeding, GI upset, and hypoglycemia | NSAIDs, antiplatelet agents, and anticoagulants |
| Ginger | Antiemetic, anti-inflammatory, and dyspepsia | Bleeding | NSAIDs, antiplatelet agents, and anticoagulants |
| Ginkgo | Alzheimer's disease, memory, intermittent claudication, and macular degeneration | Bleeding, nausea, headache, GI upset, diarrhea, and anxiety | MAOIs |
| Ginseng | Physical and mental performance | Tachycardia | Antiplatelet agents, anticoagulants, NSAIDs, and MAOIs |
| SAMe (S-adenosyl-methionine) | Depression, fibromyalgia, insomnia, osteoarthritis, and rheumatoid arthritis | GI distress, insomnia, dizziness, dry mouth, headache, and restlessness | Antidepressants, St. John's wort, NSAIDs, antiplatelet agents, and anticoagulants |
| Saw palmetto | BPH | Headache, nausea, GI distress, and erectile dysfunction | Finasteride, α1-adrenergic agonist properties in vitro may decrease efficacy |
| St. John's wort | Depression and anxiety | Photosensitivity and hypomania | Potent CYP3A4 inducer |
| Valerian | Anxiety and insomnia | Sedation and benzodiazepine-like withdrawal | |

Reproduced from Reuben et al. (2006).

there are numerous components of clinical trial design and psychiatric diagnostics that obfuscate the results (Roose and Schatzberg 2005). First, the gold standard trial design for efficacy includes a placebo comparison group. However, placebo treatment involves a host of pychosocial and supportive measures that are not systematically measured. Placebo is not an inactive agent but rather has demonstrable neurobiological effects. For example, the placebo analgesia effect can be localized to the anterior cingulate cortex and is mediated by μ-opioid receptors, and the placebo antidepresant effect may be related to functional connectivity between the ventral striatum, lateral prefrontal, and subgenual cingulate cortices (Benedetti et al. 2005). A placebo response can decrease the sensitivity and power of a trial to detect meaningful effect of a medication and may involve other mechanisms to confuse the results. There exists a correlation between placebo response rate in clinical trials for major depression and year of publication such that the placebo response is becoming more robust with time, relative to active medication (Walsh et al. 2002). Clinical trials in which an active comparator is used are often powered to be noninferiority trials. This leads to the interpretation that medications are equally effective when they may not be. Second, dosing in clinical trials must be at least adequate and ideally optimal. Adequate doses achieve a clinical response, and optimal doses are the lowest doses needed to achieve this full therapeutic response. Dosing becomes even more critical when medications are of different mechanisms or their mechanism changes with drug concentration. For example, venlafaxine is serotonergic at lower doses with an additional noradrenergic component in the middle dosing range of 150 mg, while mirtazapine has this dual mechanism from the initial dose. Trials involving these medications should take these dose effects into account. A third critical component of trial design is the duration of the trial. Treatment must be given at an adequate dose for an adequate duration but must also minimize patient exposure to ineffective treatments. Although clinical trials in depression have been historically of 12 weeks duration, recent evidence has demonstrated that in late-life depression, 4 weeks of treatment may be enough to identify full responders at 12 weeks (Mulsant et al. 2006). Fourth, a diagnostic system based on symptomatology rather than pathophysiology and outcome measures based on small reductions in scores on rating scales rather than remission of illness throw clinical trial data into question (Levine and Fink 2006). Comorbidity in psychiatric diagnoses further diminishes their discriminative value. Rating scales try to approximate improvement in illness burden and can quantify response or remission of symtoms. However, the psychometric properties rating scales can vary and can over- or underrepresent various symptom clusters and components of illness. For example, in the Hamilton Rating Scale for Depression (HAM-D), neurovegetative symptoms are more represented than they are in the Geriatric Depression Scale (GDS). In the Calgary Depression Scale for Schizophrenia (CDSS), negative symptoms of psychosis are discriminated from psychological symtoms of depression (Addington). Whether improving scores on rating scales actually represents clinical improvement is another area of concern. Sedation from a medication can result in improved sleep and thus improvement in HAM-D scores, irrespective of improvement in mood or overall illness severity. Similarly, sedation can improve positive and negative symptoms of schizophrenia (PANSS) scores, in the face of continued psychosis. The fifth concern regarding interpretation of evidence is that of subject inclusion. In the same manner that variabilities in pharmacokinetic or pharmacodynamic parameters can result in differences in the dose–effect relationship, heterogeneity in the in the study population can result in variability in outcomes of clinical trials. Results from a clinical trial sample, which is highly selected, may not be generalizable to the population in clinical settings, and it may be that open-label trials are a better approximation of typical clinical practice. Completion rates in clinical trials affect dosing and labeling as well as safety and efficacy evaluations of psychotropics; these completion rates differ based on psychiatric diagnosis and treatment with medication versus placebo (Khan et al. 2007) again affecting generalizability of results.

In light of the above concerns over design in efficacy trials, recent large effectiveness trials, including the Sequenced Treatment Enhancement Alternatives to Relieve Depression (STAR*D) (Rush et al. 2004), Systematic Treatment Enhancing Program for Bipolar Disorder (STEP-BD) (Sachs et al. 2003), and Clinical Antipsychotic Trials of Intervention Effectivness (CATIE) (Lieberman et al. 2005), have tried to address these concerns. Elders are frequently excluded from clinical trials, and extrapolating adult data to this population may be inappropriate (Lotrich and Pollock 2005). Future trials will try to systematically address clinical questions in real-world practice using representative populations and common treatment algorithms, giving physicians better information on how to prescribe appropriately.

## Summary

There is an ongoing question about the validity of current clinical trial design in psychiatry. Concerns include high placebo response, clinical trial completion rates, lack of rigorous methodology and data analysis, generalizability of highly selected clinical trial subjects group to the general population, and treatment effectiveness (Roose and Schatzberg 2005). In addition, there is a critical need to enlarge the evidence base across the lifespan, including comparative trials. With respect to safety, the IOM has issued a report highlighting the importance of a "lifecycle" approach to monitoring drugs (Baciu et al. 2006) such that safety issues are addressed not only in early phases of clinical testing, but also long after medications have been released. Historically, drug approval for brand name medications has been expedited, and follow-up safety studies have not always been done by industry. In response to the IOM report, the FDA has initiated changes in the way it does such monitoring (FDA 2007). Given the extensive variability in the dose–response relationship, and the evolving nature of drug safety and efficacy issues, it is imperative that prescribing physicians are aware of the many factors involved in producing both the therapeutic benefits and the adverse events related to drugs. The role of the prescriber is to incorporate often new and uncertain information with his or her best clinical judgment. This chapter has highlighted the potential contributors to the response to psychotropics and the importance of critically addressing the evidence for benefits and risks in the prescription of medications for psychiatric illness.

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CHAPTER 100

# Psychopharmacology: Ethnic and Cultural Perspectives

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The advent of the modern era of psychopharmacology in the last half century represents one of the most significant milestones in the history of psychiatry. This relatively young field has not only provided a myriad of interventions that are increasingly safe and efficacious but has also invigorated research to enrich our understanding of the function of the brain, both in normal and in abnormal states. As more effective medications enable a greater number of severely disturbed patients to move from confined settings to community living, the field of psychopharmacology has, furthermore, contributed toward the development of psychosocial rehabilitation programs and the reshaping of the mental health-care delivery system.

The power of these modern-day drugs is demonstrated by the fact that, within a few years of their discovery, they were introduced into practically all geographic areas in the world and quickly became the mainstay for treatment of the mentally ill in all societies (Lin et al. 1993). Similarly, along with the rapid diversification of populations in the USA and other industrialized countries, it has now become clear that the effectiveness and specificity of different classes of psychotropics seem to transcend cultural and ethnic boundaries (Lin et al. 1993). It appears that, in general, psychiatric medications are widely accepted and are regarded as useful and helpful by patients and their families, irrespective of their cultural backgrounds.

Without disputing the universally important role that psychopharmacotherapy plays across different cultures, accumulated practice experiences in divergent cultural and ethnic settings have also revealed numerous reports of cross-cultural/cross-ethnic variations in psychotropic responses (Lin and Poland 1995). Until most recently, practically all psychiatric medications have been developed and tested in North America and Western Europe, involving predominantly Caucasian population. Consequently, scientifically based information regarding the extent of cultural and ethnic influences has been incomplete and scattered. However, both theoretical considerations and data derived from divergent fields have made it increasingly clear that cultural and ethnic factors, similar to age and gender, deserve much more careful consideration than previously thought necessary.

## Dispelling the "Color-Blind" Approach

Substantial individual variation in drug responses, at times huge differences in terms of optimal dosing, is the rule rather than the exception. Although the current understanding of such remarkable variability remains incomplete, it is clear that the interplay between genetics and environmental factors plays a pivotal role in pharmacotherapeutic responses, particularly in the context of an individual's ethnic origin, lifestyle, and other sociodemographic variables. Clinicians and researchers have tended to ignore such variables for several reasons: (1) there has been a profound tendency in our field to equate biology with universality and to regard response variations to biomedical interventions as "noise." (2) when taken out of the context of the often equally substantial, or greater, individual variability that exists in any population groups, findings of ethnic differences run the risk of being interpreted simplistically and stereotypically. Because of these and other reasons, ethnic variations in pharmacological responses have often been regarded with suspicion and are not taken seriously.

However, as shown in Figure 100–1, virtually all factors affecting pharmacological responses are significantly influenced by culture and ethnicity. Furthermore, patterns of genetic polymorphism, often with substantial ethnic

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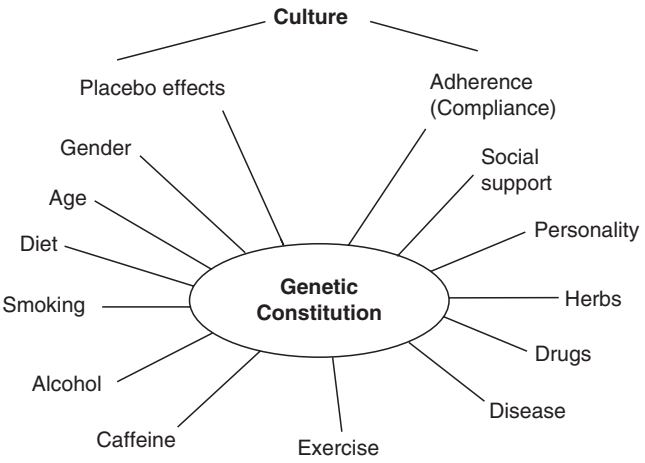



**Figure 100–1** *Factors affecting drug response.*

variation, exist in a large number of genes encoding drug-metabolizing enzymes as well as receptors and transporters believed to be targets of pharmaceutical agents. The expression of these genes is often significantly modified by a large number of environmental factors, including diet and exposure to various substances (e.g., tobacco). Of even greater importance, the success of any therapy, including pharmacotherapy, depends on the participation of the patient and those in his/her social network and, as such, depends significantly on the quality of interaction between the clinician and the patient. The importance of culture in this regard is paramount.

## The Cultural Context of Psychopharmacotherapy

Perhaps one of the biggest problems in contemporary medical healing practice is its tendency to focus, often exclusively, on technological biomedical interventions. This tendency frequently obscures the fact that treatment almost always takes place in the context of interactions among individuals. In these interactions, all participants bring their own knowledge, predispositions, values, priorities, modes of thinking, and belief systems into play. Further, these interactions are traditionally discussed in terms of the dyadic relationship between the clinician and the patient. However, both members of the dyad act in concert. No matter how isolated a patient may be, she or he almost always makes decisions within the context of real or imagined input from other people. Similarly, as members of professional groups, clinicians are profoundly influenced by the opinions of their peers and the prevailing ideologies of the field. Moreover, as medical care in most societies becomes increasingly organized, institutional control and influences over the practice of physicians become progressively more prominent. The pharmaceutical industry represents a powerful source of influence on clinicians' prescription behaviors as well as researchers' focus and priorities. Thus, while most pharmacotherapeutic decisions may be technical and straightforward in appearance, on closer look they are always imbedded in the rich sociocultural milieus that both the patient and the clinician bring into the transaction (Lin et al. 1993).

Despite their apparent significance, these contextual issues have rarely received adequate attention from both clinicians and researchers. Often they are regarded as "noise" or even "nuisance." Consequently, there has been a dearth of information regarding the nature and determinants of related issues, such as adherence and the "expectation effect" (including the placebo effect). Even less is known on how sociocultural factors impact these processes. While much awaits further clarification, the extant literature in aggregate does support the suggestion that social and cultural forces play a major role in determining the expectations and behaviors of both clinicians and patients. These in turn affect the process and outcome of the treatment.

## Clinicians' Attitudes

A large body of literature indicates that patients' cultural/ethnic backgrounds significantly determine the way clinicians conceptualize and label their problems, which in turn dictate the choices for therapeutic intervention (Mezzich et al. 1995). Using case vignettes that are identical except for ethnic group identification, a number of studies demonstrated that cases identical in every other aspect were nevertheless given significantly more severe diagnoses if the patients were identified as being of ethnic minority origin. For example, African-American psychiatric patients are more likely to have been given a diagnosis of schizophrenia as compared to their Caucasian counterparts (Lopez 1989). Interestingly, in studies where patients were reassessed with the use of structured interviews, such differences largely disappeared, suggesting that such a differential diagnostic pattern is largely determined by variables related to clinicians' biases rather than to the patients' clinical conditions (Adebimpe 1981). It is likely that similar biases led to the pervasive use of higher doses of neuroleptics in treating African-American patients, irrespective of diagnosis. Similarly, studies have shown that African-American patients were more likely than their Caucasian counterparts to be treated with depot neuroleptics, presumably due to a general prejudice of their problem with nonadherence (Price et al. 1985).

The potential consequence of these diagnostic and treatment biases may be far from innocuous. Several large-scaled studies have documented that the rate of tardive dyskinesia is significantly higher in African Americans (Sramek et al. 1991). Although other reasons for this heightened risk for tardive dyskinesia among African Americans have not been ruled out, it is very likely that their increased exposure to neuroleptics accounts for at least part of such a risk.

## Adherence

The magnitude of the problem with nonadherence to psychotropic medications has commonly been estimated in the range of 20–90% (Becker 1985). Although factors such as insight and motivation may render treatment adherence particularly challenging for psychiatric patients, the problem is far from unique for the field of mental health. In fact, similar high rates of nonadherence have been reported with the treatment of a large number of chronic medical conditions requiring long-term pharmacotherapy. Most studies exploring correlates of nonadherence have focused on patient and treatment variables and have shown that a large number of factors significantly predict problems with adherence. These include the sociodemographics of the patient, the financial burden of the treatment, and the side-effect profile of the medications. The health belief model has served as the theoretical framework for a large number

of seminal research endeavors, which in aggregate demonstrate that the beliefs held by patients and those significant in their lives to a large extent determine their participation in and response to treatment decisions. The model has also been proven useful in guiding the development of intervention strategies that effectively enhance treatment adherence (Becker 1985). In comparison, little empirical data are available on the influence of factors related to clinician(s) involved in the treatment transaction, the institution(s) where such transactions take place, as well as the nature and quality of the interactions between the clinician(s) and the patient (and those close to him or her).

Following the logic of the health belief model, one would expect adherence to be an even larger problem in cross-cultural clinical situations. This has been substantiated by a number of clinical observations and reports of the service utilization of particular ethnic minority groups. Compared to Caucasians, ethnic minority patients are often found to enter treatment at a significantly delayed stage, and they also are more likely to drop out of psychiatric treatment prematurely. Programs aiming at bridging cultural gaps have been shown to significantly improve treatment retention and outcome (Acosta et al. 1982).

Findings from two studies underscore the importance of cultural factors in determining medication adherence: Kinzie and colleagues (1987) reported that 61% of their depressed medicated refugee patients showed no tricyclic antidepressants (TCAs) in their blood and that another 24% of them revealed only very low TCA serum levels, even though all of them were treated with adequate TCA dosage. When questioned, these patients admitted to nonadherence for a variety of reasons. Education emphasizing the importance of long-term medication and the maintenance of appropriate blood levels resulted in significant improvement in adherence in some, but not all, refugee groups. Similarly, a study in South Africa (Gillis et al. 1987) followed 406 patients belonging to three ethnic groups (whites, blacks, and Asian Indians) for a 2-year period after discharge from a psychiatric hospital. They found that the nonadherence rate for oral phenothiazines was approximately two-thirds for black patients, one-half for Asian-Indian patients, and one-quarter for white patients. The authors noted that the understanding of the treatment protocols by the relatives of the black and Asian-Indian families was particularly poor, with the possibility of culture and communication being significant factors contributing to the results; but one must also consider the impact of structural barriers such as cost and availability of transportation, as well as discrimination. Perhaps for analogous reasons, blacks in the USA are reportedly less compliant and consequently more likely to be placed on injectable antipsychotics (Price et al. 1985).

Adverse effects of psychotropics are often substantial. Various drug-induced symptoms, including not only the classical extrapyramidal and anticholinergic side effects but also the problems such as paradoxical agitation and weight gain, have been found to significantly contribute toward nonadherence and treatment termination. Some of the most dramatic and disabling untoward effects of these therapeutic agents undoubtedly would be regarded with alarm by patients irrespective of their ethnic/cultural backgrounds. However, depending on their beliefs and expectations, many other drug effects could be interpreted as either negative or positive. For example, in a study of Hong Kong Chinese bipolar patients treated with lithium, Lee and colleagues (1992) found that, unlike Western patients, the Chinese rarely complained of "missing the highs" and "loss of creativity" and actually regarded polydipsia, polyuria, and weight gain as part of the therapeutic effect of the medicine. In contrast, lethargy, drowsiness, and poor memory represented serious concerns for many of these patients and were prominent in their complaints, even though objectively they were not likely to be due to the medications they were taking, since they occurred at similar rates among matched controls. Such findings highlight the importance of culturally based beliefs and expectations in determining how physical and psychological experiences associated with drug treatment and recovery are attributed.

The explanatory model (EM) approach, as originally proposed by Kleinman et al. (1978), may be a particularly effective way for the systematic assessment of such beliefs and expectations. By methodically eliciting the patient's perspectives on the symptoms that are most salient and worrisome to them (patterns of distress), their attributions (perceived causes), their help-seeking experiences and preference, as well as their perception on stigma, discrepancy between the patients' and the professionals' EMs could be systematically identified and bridged (Weiss 1997). Elements of the EM are included in Appendix I of the DSM-IV-TR manual as part of the outline for cultural formulation. It is likely that the routine use of such tools will enable clinicians to more effectively enhance adherence, without which no therapeutic interventions can exert their effects.

## Expectation ("Placebo") Effects

Although placebo control is an essential ingredient of modern clinical trials, the nature and determinants of the so-called "placebo" effect remain largely elusive and unexplored. Researchers generally recognize that such effects are typically substantial and, in fact, often account for a larger proportion of the improvement than that attributable to the "specific" effect of the therapeutic agent being tested (Swartzman and Burkell 1998). Despite the potency of the "placebo," it has rarely been the focus of attention to researchers. Consequently, much ambiguity currently exists in regard to this important phenomenon, and there is no consensus regarding which term to use when referring to such effects. The most commonly used term, "placebo," carries a negative connotation and is easily misunderstood as implying deception as well as ineffectiveness. The term "nonspecific effect" could be similarly misleading, since much of the therapeutic effects elicited by "inert" agents might well be mediated through specific biological mechanisms.

The concept of "expectations effect," commonly used in the field of psychotherapy research, may represent a broader and, at the same time, less controversial notion for such a phenomenon. This term reflects the importance and power of expectation and beliefs on treatment effects in determining patients' response to any therapy, whether psychosocial or pharmacological. Expectations regarding the safety and effectiveness of any therapeutic interventions, in turn, are shaped by patients' sociocultural backgrounds as well as individual "idiosyncratic" experiences (e.g., past experiences of side effects). Since patients' beliefs regarding medical treatments are often shaped by their cultural backgrounds,

it stands to reason that patients' expectation regarding the therapeutic effect of the offered treatment would be largely affected by their cultural construct of the illness.

Despite rapid modernization, traditional medical theories and practices remain deeply rooted and influential in determining individuals' health beliefs and behaviors in many societies. For example, most traditional medical systems emphasize the importance of maintaining a dynamic balance between "coldness" and "hotness" (Castro et al. 1994) or between "Yin" and "Yang" in the case of the Chinese system (Lin 1981). These principles provide guidance for assessment as well as for formulating treatment approaches. For patients who subscribe to such beliefs, a perceived mismatch between the therapeutic agents and the afflictions may significantly lower the expectation effect. For example, red-colored pills might be regarded as capable of enhancing the "hot" element and less effective in the treatment of conditions perceived as a result of excessive "hotness" (e.g., fever, anxiety state, or mania). Interestingly, Buckalew and Coffield (1982) reported findings from a well-controlled study showing significant ethnic differences in response to placebo pills with different colors. In this study, white capsules were seen as analgesics by Caucasian subjects but as stimulants by their African-American counterparts. In contrast, black capsules were seen as stimulants by Caucasians and as analgesics by African Americans.

## The Concomitant Use of Alternative/ Indigenous Treatment and Healing Methods

As mentioned above, the worldwide ascendancy of modern "cosmopolitan" ("Western") medicine has not replaced the traditional or "indigenous" medical and healing systems (Lin et al. 1990). Instead, "alternative" traditions (e.g., Chinese and Ayurvedic medicines) have evolved and continue to be widely used. Multiple medical and healing traditions and treatment modalities coexist in all societies, and patients often utilize these services simultaneously or sequentially, frequently without informing their physicians. This phenomenon has long been observed in "non-Western" countries as well as ethnic minority populations in the USA, although its significance in Western societies has not been adequately appreciated until recent years. When Eisenberg and colleagues (1998) first reported that middle-class Americans (predominantly Caucasians) utilized more "alternative" than "orthodox" medical services, their findings came as a surprise to most health professionals. In the ensuing years, it appears that, both in North America and Western Europe, the popularity of "alternative" medical and healing methods, including many imported from non-Western traditions, has increased exponentially (Eisenberg et al. 1998). Thus, problems with drug–drug interactions that could potentially arise from such practices are no longer limited to particular ethnic groups and constitute an important consideration for clinicians prescribing medications.

Contrary to general perceptions, alternative treatments are not always mild or "benign" and are capable of inducing severe toxic effects. Indeed, various herbs utilized by traditional practitioners and healers are biologically active (it has been estimated that approximately 40% of our "modern" pharmacotherapeutic agents originated from natural sources). Although much remains unclear, herbal preparations do exert significant impact on various biological systems, including those crucial for the functioning of the central nervous system. For example, many herbal preparations possess potent anticholinergic properties and may cause atropine psychosis, particularly when used concomitantly with psychotropics with similar side-effect profiles. Numerous herbs have distinctive stimulant or sedative properties and may either potentiate or attenuate the intended effects of medications prescribed by mental health clinicians. Since most patients do not regard herbs as medicines and typically fail to inform their physicians of such uses unless specifically inquired, toxicities or treatment failures due to "herb–drug interactions" are likely widespread and unsuspected.

As will be further elaborated later, a limited number of enzymes are involved in the biotransformation of all drugs, including psychotropics. Although the activity of these enzymes are crucial for determining the pharmacokinetics and hence the fate and disposition of modern drugs, their primary substrates are not the medications prescribed by physicians but are xenobiotics (natural substances) existing in the environment. Many herbs are thus natural substrates for these "drug-metabolizing enzymes." Further, through inhibition and/or induction, xenobiotics, including a large number of herbs, exert powerful influences on the expression of these enzymes, which then determine the rate of metabolism of the prescription medications.

Herbal preparations may modulate the effect of modern therapeutic agents, including psychotropics, not only at the pharmacodynamic level (the effect of the drugs on the organism) but also at the pharmacokinetic level. Pharmacokinetic herb–drug interactions occur when the coadministration of an herbal remedy results in the alteration of the absorption, distribution, metabolism, or excretion of the prescribed drug. For example, tetracycline's antibiotic efficacy is diminished when taken concurrently with the herb, cassia cinnamon (D'Arcy 1991). In this example, tetracycline is absorbed by the cassia bark in the herbal remedy, thereby decreasing its bioavailability. Additionally, tannins contained in tea have been shown to bind psychotropic medications, preventing their gastrointestinal absorption and subsequent entrance into the blood stream and central nervous system (D'Arcy 1991). Herbal medications can also impact the metabolism of a number of different medications, including psychotropics. For example, a number of case studies have cited a decrease in effectiveness of medications such as oral contraceptives (Fugh-Berman 2000) and warfarin (Yue et al. 2000) when taken in combination with St. John's Wort. The proposed mechanism for these herb–drug interactions is induction of CYP enzymes and/or the p-glycoprotein drug transport system involved in their metabolism by St. John's Wort (Fugh-Berman 2000). In contrast to the inductive effects of St. John's Wort, significant inhibition of CYP3A4 and resultant toxicity of medications that are substrates of this enzyme have been noted with grape fruit juice. The results of these studies suggest that grapefruit juice–drug interactions may be due to compounds such as flavonoids, which are also found in fruits, vegetables, and many commonly used herbals (Oesterheld and Kallepalli 1997).

## Biological Diversity and Its Consequence in Psychotropic Responses

The central importance of biodiversity in maintaining and ensuring the survival of any species and promoting its

adaptation to the local environment is a fundamental principle that unfortunately has not been adequately appreciated. Possibly because of this underappreciation of the extent and significance of biological diversity in the past, recent findings of the widespread existence of genetic polymorphisms have appeared surprising to many researchers. Emerging data now convincingly demonstrate that for the majority of the genes, polymorphism is the rule rather than the exception. Furthermore, the frequency and distribution of alleles responsible for such polymorphisms often vary substantially across ethnic groups, effectively requiring that ethnicity always be considered in genetic studies (National Institute of Mental Health 1997). These phenomena have long been known in blood and human lymphocyte antigen typing. In recent years, it has become increasingly clear that equally extensive polymorphisms exist in genes governing key aspects of how drugs are metabolized (see Table 100–1) as well as how they affect the target organs. These processes, commonly called pharmacokinetics and pharmacodynamics, are depicted in Figure 100–2 (Greenblatt 1993). Together, these genetic factors may explain to a large extent the often extensive interindividual cross-ethnic variations in drug responses (Lin et al. 1993). Some of the relevant findings in these regards will be highlighted in the following section.

## Genetic Polymorphism of Genes Encoding "Drug-Metabolizing Enzymes"

As shown in Figure 100–2, of the four factors (absorption, distribution, metabolism, and excretion) that together determine the fate and disposition of most drugs, variability in the process of metabolism is most substantial and usually is the reason for interindividual and cross-ethnic variation in drug responses (Lin and Poland 1995). Most drugs are metabolized via two phases: Phase I, commonly mediated by one or more of the cytochrome P-450 enzymes (CYPs), leads to the oxidation of the substrate; Phase II involves conjugation and is usually mediated by one of the transferases. There is clear evidence of interindividual and cross-ethnic variations in the activity of enzymes in both phases, the genetic basis of which has been increasingly elucidated in recent years. Since far more information is currently available in regard to the CYPs than the Phase II enzymes, and since the CYPs appear to control the rate-limiting steps in the metabolism of most psychotropics, the following discussion will focus mainly on these enzymes.

Table 100–2 includes a list of major CYPs that are responsible for the Phase I metabolism of commonly used psychotropics as well as selected substances that are psychoactive and are commonly used by psychiatric patients. With very few exceptions (e.g., lithium does not require biotransformation; lorazepam and oxazepam are directly conjugated without first going through oxidation), the pharmacokinetics of practically all psychotropics are dependent on one or more of the CYPs, whose activity significantly influences the tissue concentrations, dose requirement, and side-effect profiles of their substrates.

Functionally significant genetic polymorphisms exist in most of the CYPs (Lin and Poland 1995), leading to extremely large variations in the activity of these enzymes in any given population (Table 100–2 ). CYP2D6 represents the most dramatic example, with more than 50 mutations that inactivate, impair, or accelerate its function (Ingelman-Sundberg 2005). Significantly, most of these mutant alleles are to a large extent ethnically specific. For example, CYP2D6*4, which leads to the production of defective proteins, is found in approximately 25% of Caucasians but is rarely identified in other ethnic groups. This mutation is mainly responsible for the poor metabolizers (PMs) in Caucasians (5–9%), who are extremely sensitive to drugs metabolized by CYP2D6. Instead of CYP2D6*4, extremely high frequencies of CYP2D6*17 and CYP2D6*10 were

**Table 100–1 Some Examples for Genetically Variable Enzymes of Drug Metabolism**

| Enzymes | Clinical Significance |
|---|---|
| Alcohol dehydrogenase (ADH) (Eriksson et al. 2001) | Example of substrate: ethanol<br><br>ADH2*2: It exhibits 100 times more catalytic activity and are highly prevalent in Asians (79%) but rare in other populations. It has been regarded as a protective allele from alcohol drinking. |
| Aldehyde dehydrogenase (ALDH) (Chen et al. 1999) | Example of substrate: acetaldehyde<br><br>ALDH2*2: It is the dominant allele that inactivates the enzyme, resulting in a significant increase of acetaldehyde, and is highly prevalent in Asians (50%) but rare in other populations. Evidences of researches revealed that it has been clearly demonstrated to be associated with a decreased risk for alcoholism. |
| Catechol-*O*-methyltransferase (COMT) (Rivera-Calimlim and Reilly 1984) | Example of substrate: catecholamines (dopamine, etc.)<br><br>Higher COMT activity predicts the occurrence of side effects of levodopa in treating Parkinsonism. (see the text in this Chapter for more information on polymorphism of COMT) |
| CYP2E1 (Stephens et al. 1994) | Example of substrate: ethanol and acetaldehyde<br><br>Rsa I c2: The highest frequency was observed in the Taiwanese (28%) and Japanese (19–27%), whereas in African Americans, European Americans, and Scandinavians the frequency is much lower, ranging between 1% and 5%. CYP2E1 generates free radicals that may be responsible for alcohol-induced organ injuries. |

This table just presents several examples of different polymorphism frequencies across ethnic groups and how the variations influence the drug metabolisms.
More detailed information can be obtained from Kalow W (1992) Pharmacogenetics of Drug Metabolism. Pergamon Press, New York, USA; and Lin and Poland (1995).

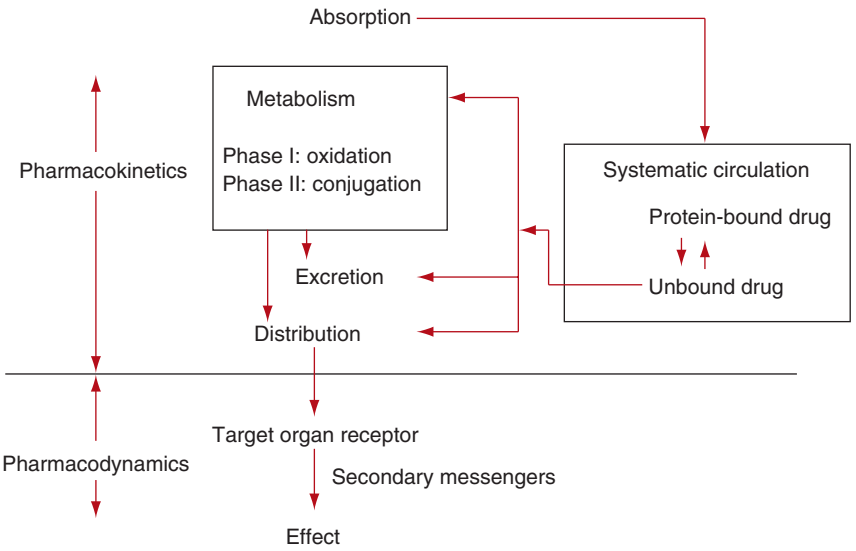



**Figure 100–2** *Pharmacokinetics and pharmacodynamics.*

found among those of African and Asian origins, respectively. Both of these alleles are associated with lower enzyme activities and slower metabolism of CYP2D6 substrates (Figure 100–3) and may in part be responsible for previous findings of slower pharmacokinetic profiles and lower therapeutic dose ranges observed in Asians in regard to both classes of psychotropics, and in African Americans in regard to TCAs (Lin and Poland 1995). Interestingly, our recent study showed that Mexican Americans had very low rates of any of these "impairing" mutations. Correspondingly, they also showed significantly faster overall CYP2D6 activity (Mendoza et al. 2001).

CYP2D6 also is unique in that the gene often is duplicated or multiplied (up to 13 copies). Those possessing these duplicated or multiple genes have proportionally more enzymes and faster enzyme activity and are termed "ultrarapid" metabolizers (UMs). This is found in 1% of Swedish, 5% of Spaniards (white Americans are in between these two figures), 19% of Arabs, and 29% of Ethiopians. UM patients are likely to fail to respond to usual doses of medications biotransformed by CYP2D6, since they typically will fail to achieve therapeutic levels unless treated with extremely high doses of the same drugs. There have been reports of UM patients being regarded as nonadherent because they did not show any evidence of drug effect while given seemingly adequate doses of medications (Akullu et al. 1996).

CYP2C19 represents another dramatic example for the existence of both cross-ethnic and interindividual variations in drug metabolism. This enzyme is involved in the metabolism of commonly used psychotropics such as diazepam and tertiary TCAs, as well as one of the new antidepressants, citalopram. Using S-mephenytoin as the probe, earlier studies demonstrated that up to 20% of East Asians (Chinese, Japanese, and Koreans) are PM, which is true only in 3–5% of Caucasians (Xie et al. 1999). After the gene for the enzyme had been identified and sequenced, it became clear that such enzyme deficiency is caused by two unique mutations (CYP2C19*2 and CYP2C19*3). While *2 can be found in all ethnic groups, *3 appears to be specific to those with Eastern Asian origins. The presence of *3, together with a higher rate of *2, is responsible for the higher rate of PM among Asians, as well as their often increased sensitivity in the clinical setting to drugs such as diazepam (Goldstein et al. 1997).

Genetic polymorphism also exists in CYP2C9, CYP2E1, CYP3A4, as well as the majority of other drug-metabolizing enzymes (see Tables 100–1 and 100–2). It is interesting to note that, almost without exception, wherever genetic polymorphism is identified, the allele frequency of the mutations typically show substantial ethnic variations.

## Factors Affecting the Expression of Drug-Metabolizing Enzymes

In addition to genetic endowment, a large number of nongenetic factors also significantly influence the expression of the genes. These factors are both external and internal. External factors include nutrients, various plant products, pharmaceutical agents, and other chemicals. Internal factors include steroid hormones and other endogenous substances. These substances either inhibit or induce the activity of the enzyme and thus affect the metabolism of drugs that are dependent on a particular enzyme. Such shifts in the enzyme status could at times lead to serious clinical consequence. The following are selected examples that have caught the field's attention in recent years: (1) A number of the newer antidepressants, including fluoxetine and paroxetine, two of the most widely used selective serotonin reuptake inhibitors (SSRIs), are potent inhibitors of CYP2D6, capable of converting an extensive metabolizer into a PM. Thus, when these drugs are prescribed for a patient who has already been taking a CYP2D6 substrate (e.g., TCAs or neuroleptics), the concentration of the latter could be pushed unexpected into the toxic range (Brosen 1995). (2) Smoking has long been known to significantly reduce the serum concentration of psychotropics, and it is likely that many patients suffer from relapse soon after discharge from the hospital because they resume smoking (Guengerich et al. 1994). This effect is now known to be due to the induction of CYP1A2 by constituents of tobacco. (3) Many drugs and natural substances significantly inhibit the activity of CYP3A4, altering its ability to metabolize drugs that are

**Table 100–2 Major Human Cytochrome P-450 Enzymes and Their Psychotropic Substrates**

| | Substrates | Genetic Polymorphisms |
|---|---|---|
| CYP1A2 | Antidepressants: amitriptyline, clomipramine, imipramine, and fluvoxamine | No report of polymorphism until 1999; the significance of the following findings remain unclear (Nakajima et al.1999) |
| | Neuroleptics: haloperidol, phenothiazines, thiothixine, clozapine, and olanzapine | *1C: reduced activity; 23% in Japanese |
| | Others: tacrine, caffeine, theophylline, acetominophen, and phenacetin | *1F: higher inducibility; 32% in Caucasians |
| CYP2C19 | Benzodiazepines: diazepam | *2: no activity; 23–39% in Asians, 13% in Caucasians, and 25% in African Americans |
| | Antidepressants: imipramine, amitriptyline, clomipramine, and citalopram | *3: no activity; 6–10% in Asians and 0% in others |
| | Others: propranolol, hexobarbital, mephobarbital, proguanil, omeprazole, and *S*-mephenytoin | *6 *7 and *8 contain mutations that result in the poor metabolizer phenotype in Caucasians (Ibeanu et al. 1998, 1999) |
| CYP2D6 | Antidepressants: amitriptyline, clomipramine, imipramine, desipramine, nortriptyline, trimipramine, *N*-desmethyl-clomipramine, fluoxetine, norfluoxetine, paroxetine, venlafaxine, and seltraline | *2: accounts for 60% of intermediate metabolizers in Caucasians (Raimundo et al. 2000). |
| | Neuroleptics: chlorpromazine, thioridazine, perphenazine, haloperidol, reduced haloperidol, risperidone, clozapine, and sertindole | *3: no activity; 1% in Caucasians (Shimada el al. 2001)<br>*4: no activity; 25% in Caucasians; 0–10% in others |
| | Others: codeine, opiate, propranolol, and dextromethorphan | *5: no activity; 2–10% in all groups<br>*10: reduced activity; 47–70% in Asians and ≤ 5% in others (Mendoza et al. 2001)<br>*17: reduced activity; 25–40% in blacks and 0% in others (Wan et al. 2001)<br>*2XN: increased activity; 19–29% in Arabs and Ethiopians and ≤5% in others |
| CYP3A4 | Antidepressants: mirtazepine, nefazadone, and sertraline | Several single nucleotide polymorphisms have been identified with racial variability in their frequency. However, functional significance of these polymorphisms have not been clearly elucidated (Dai et al. 2001) |
| | Neuroleptics: thioridazine, haloperidol, clozapine, quetiapine, risperidone, sertindole, and ziprasidone | |
| | Mood stabilizers: carbamazepine, gabapentin, and lamotrigine | Recent reports of the functional significance of a variant with mutation in the regulatory region (*1B) has been suggested. The prevalence of *1B is 10% in Caucasians and unknown in other ethnic groups. |
| | Benzodiazepines: alprazolam, clonazepam, diazepam, midazolam, triazolam, and zolpidem | |
| | Calcium channel blockers: diltiazem, nifedipine, nimodipine, and verapamil | |
| | Steroids: androgens, estrogens, and cortisol | |
| | Others: erythromycin, terfenadine, cyclosporine, dapsone, ketaconazole, lovastatin, lidocaine, alfentanil, amiodarone, astemiazole, codeine, and sildenafil | There are preliminary reports of two other promising alleles (*2 and *3), but details of these mutations are not yet available.<br>*4, *5, *6 have been suggested to possibly decrease 3A4 activity in Chinese subjects, but the incidences of these mutations are rare and their prevalence in other ethnic groups is unknown (Hsieh et al. 2001) |

Other important human CYPs include CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP2E1. CYP2A6 is involved in the metabolism of nicotine and cotinine, CYP2C9 is responsible for the biotransformation of drugs including phenytoin and warfarin, CYP2E1 metabolizes acetaminophen, theophylline, as well as alcohol and is associated with the production of free radicals.

dependent on this enzyme for their biotransformation. A widely known example is the grape fruit juice (Oesterheld and Kallepalli 1997), which is capable of increasing the blood level of antiviral drugs as well as psychotropics such as nefazodone and alprazolam by several folds, if taken concurrently. In addition, reports of lethality caused by the combination of ketoconazole and terfenadine have led to the withdrawal of the latter from the market (Jurima-Romet et al. 1994). (4) A large body of literature indicates that macronutrients (i.e., high protein versus high carbohydrate diet) also significantly influence the activity of CYPs. High protein diet accelerates the metabolism of drugs such as antipyrine and theophylline, and high carbohydrate diet appears to have the opposite effect (Anderson and Kappas 1991).

These examples demonstrate the importance of environmental factors in substantially modifying the activity of drug-metabolizing enzymes. Patients from different ethnic/cultural backgrounds live divergent lifestyles and are likely to be exposed to unique substances that may have strong

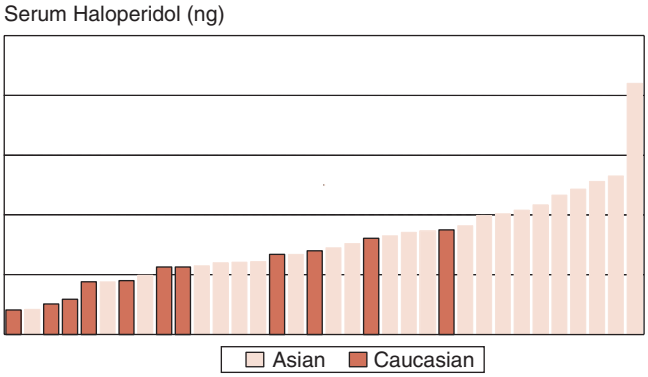



**Figure 100–3** *Variability of haloperidol concentrations in normal volunteers after the administration of haloperidol (0.5 mg, IM). The graph shows: (1) substantial interindividual variability within each of the ethnic groups. (2) dramatic differences in the pharmacokinetics of haloperidol between the two ethnic groups. (3) overlap of the pharmacokinetics between the two groups. [Reproduced from Lin et al. (1988).]*

effects on the expression and activity of drug-metabolizing enzymes. Thus, what we currently know about environmental influences on drug metabolism may represent only the tip of the iceberg. This may be especially true in regard to ethnic minority and other non-Western populations. For example, studies have shown that Asian Indians and Africans were significantly slower in metabolizing substrates of CYP1A2, such as theophylline, antipyrine, and clomipramine. However, after they immigrated to Europe and adapted to the new dietary habits, their metabolic profiles for these drugs became indistinguishable from the "native" Westerners (Allen et al. 1977).

As discussed earlier, herbal medicines are routinely and extensively used by people worldwide. Since patients typically are not aware of the potential of herb–drug interactions, they often combine the use of herbs and "Western medicines." When severe toxic effects subsequently emerge, they usually blame them on drugs prescribed by clinicians, rather than on herbal preparations obtained over the counter, or from traditional/alternative practitioners. Since thousands of herbs are widely in use, and the indication and popularity of these herbs vary greatly across cultural traditions, the potential for interactions between herbs and modern pharmaceutical agents is endless and largely unexplored.

## Genetic Polymorphism of Genes Encoding Receptors, Transporters, or Other Therapeutic Targets

Monoamines, including dopamine (DA), serotonin (5-HT), and norepinephrine (NE), have been the focus of intensive research attention in the past several decades. In addition to being implicated in the pathogenesis of psychiatric disorders including schizophrenia and major depression, they have also been regarded as the putative targets of psychotropics. Confirming the importance of the 5-HT system in affective and other psychiatric disorders, a number of SSRIs have been developed and are now widely in use for a wide range of clinical conditions. At the same time, although the far more diffuse receptor-binding profiles of the "atypical neuroleptics" call into question the primacy of the "DA hypothesis" in schizophrenia research, the function of the dopaminergic system remains important in understanding the schizophrenic process and its pharmacological management.

Along with the cloning and sequencing of the genes encoding the receptors and transporters that mediate and regulate the function of these important neurotransmitters, it has become apparent that, contrary to earlier predictions, these genes are almost without exception highly polymorphic, and the pattern of these polymorphisms vary significantly across ethnicity. For example, the frequency of the TaqI A restriction fragment length polymorphism (RFLP) polymorphism of the dopamine $D_2$ receptor (DRD2), one of the most extensively investigated brain receptors, ranges from 5% to 18% in Caucasians to approximately 36% in African Americans and 37% to 42% in Asians (Blum et al. 1995). Earlier studies suggesting the existence of an association between this allele and alcoholism have been criticized because ethnicity as a potential confounding variable was not taken into consideration. Similarly, dramatic ethnic variations exist in the pattern of genetic polymorphism of many other receptor and transporter genes. These include other DRD2 mutations (Taq1 B, 311Ser/Cys, and exon 8 A/G substitution), other DA receptors such as DRD4 and DRD3 (Sander et al. 1995), the dopamine transporter gene (DAT1; locus symbol SLC6A3) (Vandenbergh et al. 1992), the serotonin transporter gene (5-HTT), and a number of serotonin receptors (5-$HT_{2A}$-1438 A/G and 5-$HT_{2A}$-102 T/C) (Greenberg et al. 1998).

These polymorphisms are likely to have functional significance and hence might be associated with the risk for psychopathology as well as the response to treatment regimens. For example, recent studies show that the basal transcriptional activity of the serotonin transporter gene (5-HTT) is significantly higher in those possessing a long variant in the promoter region of this gene, which results in differential 5-HTT expression and 5-HT cellular uptake (Greenberg et al. 1998). The clinical significance of these findings was demonstrated in a number of studies of the effect of SSRIs in treating various types of psychotic depression (Kirchheiner and Suringer 2006). In the majority of these studies, patients who were either homozygote or heterozygote long variant (*5-HTTLPR l/l* and *l/s*) responded significantly better than those who were homozygote short variant (*s/s*). However, the frequency of the *l* allele varies significantly across ethnicity, and it remains unclear if such association exits in groups possessing predominantly the *s* allele, such as East Asians (Kim et al. 2006). Similarly, DRD2 TaqI A RFLP, located in the *l* flanking region of the DRD2 gene, has been shown in brain imaging (Hietala et al. 1994) and postmortem (Noble et al. 1991) studies to affect $D_2$ receptor density in different parts of the brain and thus might affect the receptor's response to neuroleptics, in addition to its possible association with the risk for alcoholism. It is, however, at present unclear if such associations might be true across ethnic groups, and if ethnic differences in the polymorphisms might result in ethnic variations in the pharmacodynamics of drugs whose effects are mediated by these receptors/transporters.

## Genetic Polymorphism of Other Genes Affecting Pharmacological Responses

The synthesis and catabolism of the catecholamines are controlled by a number of enzymes including tryptophan

hydroxylase, tyrosine hydroxylase, catechol-*O*-methyltransferase (COMT), and the monoamine oxidases (MAO). Tryptophan hydroxylase controls the rate-limiting step for the production of 5-HT from tryptophan, and tyrosine hydroxylase plays a central role in the production of DA and NE. On the catabolic side, MAO mediates the oxidation and deamination of 5-HT into 5-hydroxyindole-3-acetic acid (5-HIAA) and other metabolites, and both MAO and COMT are responsible for the metabolism of the catecholamines (DA and NE). Interestingly, all of these enzymes are highly polymorphic. For example, COMT activity has long been known to have a trimodal distribution (McLeod et al. 1994). Recent studies demonstrate that the reduction of its activity is caused by a single nucleotide mutation whose allele frequency is approximately 26% in African Americans, 18% in Asians, and 50% in Caucasians. Higher COMT activity is correlated with the ratio between 3-*O*-methyldopa and levodopa, which in turn predicts the occurrence of side effects of levodopa in treating Parkinsonism. Reflecting this, a higher percentage of Asians have been found to be poor responders to levodopa (Rivera-Calimlim and Reilly 1984). It is at present unclear whether, and to what extent, such interindividual and cross-ethnic variations in the polymorphism of these enzymes might influence the pharmacodynamics of psychotropics used in the clinical settings.

Although much less understood, it is commonly agreed that the signal transduction cascade is also of tremendous importance in mediating the effect of psychotropics. Components of this cascade include G-proteins, ion channels, "secondary messengers," and protein kinases. Interindividual and cross-ethnic variations in the genes coding these proteins are likely to exist and may also be responsible for the individual variability in drug response as observed clinically.

## Summary and Future Research Directions

This brief survey serves to highlight the significance as well as the complexity of issues surrounding the influence of cultural and ethnic forces on psychotropic responses. Taken together, the literature reviewed above clearly demonstrates the importance of these factors in psychopharmacotherapy. At the same time, it is equally important that any findings regarding ethnic variations in pharmacological responses not be interpreted stereotypically. In this regard, it is useful to keep in mind that almost all ethnic and cultural contrasts are superimposed on usually very substantial interindividual variations in all human groups. This is true not only in regard to biological traits such as the ones reviewed above, but equally so (or even more so) with regard to "cultural" and psychosocial variables. Stereotypic interpretations of cultural and ethnic differences in either psychological or biological characteristics are not only misleading but also potentially divisive and dangerous.

Further, in interpreting biological diversity, both within and across populations, it is important to keep in mind that biological systems are dynamic rather than static, and the expression of genetic predisposition is constantly modified by environmental exposure. This is most clearly demonstrated in the case of the induction and inhibition of the drug-metabolizing enzymes, which could radically alter an individual's metabolic profile, such that a genetically "extensive metabolizer" might appear to possess nonfunctioning gene(s). Although it is reasonable to believe that social and psychological events would similarly exert powerful influences on the functioning of relevant genes, such influences are likely to be far more subtle and complex and have remained largely unexplored.

In addition to culture and ethnicity, other key sociodemographic variables, such as age and gender, have also been known to significantly influence the pharmacokinetics and pharmacodynamics of psychotropics and other pharmaceutical agents. For example, the activity of most P-450 enzymes shows significant decline in older individuals (Kinirons and Crome 1997), who are also likely to suffer from progressive loss of neuron cells as well as receptors targeted by psychotropics. Both of these changes render the elderly more sensitive to the effects of medications in general. Similarly, steroid hormones including sex hormones have been demonstrated to be substrates of some of the P-450 enzymes and have the capacity to alter the activity of these enzymes through competitive inhibition and/or other mechanisms. They have also been known to exert powerful influences on some of the brain receptors that might directly or indirectly affect the pharmacodynamics of psychotropics. It is at present unclear to what extent such age and gender effects interact with the effect of ethnicity, and whether such interactions are "synergistic" or "additive." Studies examining such interactions might be of utmost clinical importance, since they might help identify groups with heightened possibility of "unusual" dose response and side-effect profiles.

Progress in the research on P-450 enzymes and other drug-metabolizing enzymes in the past three decades has led to the development of a number of laboratory procedures that could be used for determining the activity of these enzymes as well as polymorphisms of the genes encoding these enzymes. These procedures have been found to be predictive of the pharmacokinetics and side-effect profiles of a number of psychotropics. In addition, emergent data suggest that some of the polymorphisms of genes encoding neurotransmitter transporters and/or receptors might also predict treatment outcome. Thus, it appears that technology may be in place for researchers to systematically test the utility of these procedures in the clinical settings. It is likely that progress in this direction will eventually lead to the development of a panel of genotyping and/or phenotyping procedures that could be used by clinicians to guide their decisions in terms of the choice of antidepressants, the starting dosage, strategies for titration, as well as the prediction of likely side effects. Such a panel will not only enhance the treatment response rate, but also reduce the duration for dose titration, minimize the development of untoward effects, and thus ensure better treatment compliance. Thus, it should also result in treatment strategies that are not only more effective but also more cost effective than "traditional" titration methods. With the development of high throughput of gene array technologies, such as the matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (TOLFI MS) (Ross et al. 1998), thousands of samples could be processed on a daily basis, so that the turnaround time for test results could be short enough to be useful for clinicians ordering such tests. Together, these exciting new developments should help make psychopharmacotherapy increasingly more rational, evidence based, and effective.

The progress in pharmacogenetics might also stimulate research on "nonbiological" issues such as cultural influences on adherence and other factors that determine patients' perception and help-seeking behavior, which in turn contribute toward their sense of satisfaction and their being able to maximally benefit from psychotropic treatment. With such an integrative approach, we would be best able to define elements for optimal pharmacotherapeutic practices that would take both cultural and biological diversity into consideration and tailor treatment to individual characteristics rather than relying on global guidelines.

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CHAPTER

# 101 Antidepressants

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This chapter reviews current knowledge about antidepressant medications. Theoretical and clinical data will be considered, particularly those representing recent developments in this field. The use of antidepressants in the treatment of depression remains the best-understood use of these medications, and this is the focus of the chapter.

## Theoretical Basis for Treatment

The discovery of antidepressants did more than provide a revolutionary therapy for depression; it has slowly helped to change the concept of mood disorders and, by analogy, the mind itself. Although other somatic antidepressant treatments preceded antidepressants (most notably electroconvulsive therapy), the widespread use of antidepressants for all types of depression (i.e., those thought to be "exogenous" as well as "endogenous") forced psychiatrists to reappraise their ability to influence areas of existence previously thought unreachable through physical manipulation.

## The Development of Antidepressants

There are a number of good reviews of the history of antidepressants. A paper by Pletscher (1991) provided many of the data for this discussion.

The first antidepressant was the monoamine oxidase inhibitor (MAOI), iproniazid. It was soon followed by the tricyclic antidepressant (TCA), imipramine. Although both were developed in the early 1950s, they represented different paths of discovery: iproniazid was the result of clinical and laboratory collaboration, whereas imipramine's introduction was largely based on clinical observation. Imipramine's mechanism of action was clarified only later.

Iproniazid was synthesized from isoniazid in an attempt to improve the chemotherapy of tuberculosis. Three unexpected actions of the drug—monoamine oxidase inhibition, reversal of reserpine-induced sedation, and psychostimulation—resulted in its introduction as the first modern antidepressant. Serious side effects, particularly hypertensive crises and hepatic necrosis, prevented general acceptance of the drug.

Imipramine was synthesized from chlorpromazine. Unlike its parent, imipramine proved ineffective as an antipsychotic, and research on it was almost abandoned. Clinical investigators, however, observed that imipramine had a beneficial effect on depression. Equally important, it did not show the serious side effects associated with iproniazid. Imipramine eventually became widely accepted as a safe and effective antidepressant.

## Mechanisms of Actions

Investigations into the biochemistry of depression have taken their lead from antidepressants. All known antidepressants affect monoamine neurotransmission, and this is believed to be their mechanism of action. Research into these monoamines evolved into the monoamine hypothesis of depression.

### The Monoamine Hypothesis of Depression

The monoamine theory of depression suggests, in its simplest form, that depression relates to abnormal levels of monoamines: neurotransmitters thought important in the regulation of mood. Antidepressants themselves provide the strongest evidence supporting the role of monoamines in mood, as all known antidepressants affect the levels of monoamines in the brain. Other evidence for the monoamine hypothesis included the observation that reserpine (which depletes norepinephrine and serotonin) frequently causes depression.

Originally, norepinephrine was the monoamine thought to be most involved with mood, as most of the early antidepressants primarily affected this transmitter. Newer drugs had more of an effect on serotonin; as a result, this too became a focus of theories on depression. Serotonin may have a direct effect on mood, and may interact in a regulatory way on norepinephrine. It has been shown repeatedly that tryptophan depletion (the precursor for serotonin) can render antidepressants ineffective. This is true regardless of whether the antidepressant is thought primarily to affect noradrenergic systems, thus supporting the regulatory function of serotonin (Reilly et al. 1997). TCAs also block reuptake of dopamine, and several antidepressants seem to act primarily on the dopamine system, including bupropion and nomifensine. Dopamine may interact with norepinephrine, perhaps through augmentation of alpha-1-receptors.

Several observations argue against the adequacy of the monoamine theory of depression. For example, investigators have been unable to demonstrate consistently

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decreased monoamine levels in depressed patients. Furthermore, there is a time lag between reuptake inhibition, and clinical response, approximately several weeks. This effect is independent of the half-life or other pharmacokinetics of the particular drug. This latency is difficult to reconcile with simple monoamine theories, as central nervous system (CNS) monoamine levels can be altered within hours of the introduction of a drug.

### Receptors

Looking for a more complex correlate of antidepressant action, investigators focused on transmitter–receptor interactions. Vetulani and Sulser (1975) described beta-adrenoreceptor down regulation in response to antidepressant administration. This receptor effect was demonstrated in animal experiments, and observed with all antidepressants. Down regulation of the beta-receptor not only involves the noradrenergic system, but also requires an intact serotonin system as well. Down regulation also shows a time lag, making it a better model of antidepressant action. When investigators administer antidepressants to animals for a significant time, they consistently find both reductions in the number of beta-adrenoreceptor recognition sites and a down regulation of beta-adrenoreceptor functioning. Increased monoamine availability affects not only beta-receptor down regulation, but also up regulation of the alpha-receptor, an autoreceptor that regulates neurotransmission (Ackenheil 1990). Of the serotonin receptors, 5-hydroxytryptamine type 1A (5-HT1A) appears most related to the therapeutic effects of antidepressants. This receptor influences norepinephrine, dopamine, acetylcholine, neuropeptides, other serotonin receptors, and probably beta-receptor down regulation.

The most compelling argument for depression-associated receptor changes would be a direct demonstration of such an association in humans. The availability of selective ligands for specific receptors has begun to lend support to such hypothetical associations. A number of serotonin receptor subtypes have been shown to have a reduction in sensitivity in response to selective serotonin reuptake inhibitor (SSRI) administration, including 5-HT1A (Cowen et al. 1994) and 5-HT1D (Whale et al. 2001). In both cases, these receptor changes were seen most markedly in patients with melancholic depression.

### Intracellular Systems

Second-messenger systems offer a final common pathway for the variety of transmitter and receptor effects. That is, despite the myriad of ways in which receptor and transmitters can be affected, the result is the overall effect on intracellular mechanisms. Most of the monamine receptors are linked to G-protein. The activation of the receptor by a neurotransmitter brings about a functional change in the G-protein. G-protein is then able to bind to GTP, which then affects intracellular concentrations of such second messengers as adenyl cyclase. Though the details are complicated, the relevance to antidepressants is simple: a variety of extracellular effects are transduced to a limited number of intracellular responses. This may explain how many different chemicals, with different potential actions, can have the same antidepressant effect.

The role of G-protein may also explain some of the inherent limitations in antidepressant response. Alteration in G-protein synthesis and activity takes several weeks, which is consistent with the latency in effect of antidepressants.

Though G-protein may be crucial in understanding the overall antidepressant effect of drugs, it probably is not directly related to an antidepressant's mechanism of action. The action of most antidepressants seems to be extracellular, and there is no evidence to suggest that any antidepressant has a direct effect on the G-protein. Other medications, such as the lithium ion, may directly influence GTP binding, and this may explain lithium's efficacy as an adjunctive medication.

The relationship between neurotransmitter activity and the mechanism of antidepressant action is depicted in Figure 101–1.

### Beyond the Monoamines

Newer theories attempt to include new information from neurophysiologic and genetic studies. For example, brain-imaging studies suggest that there is subtle atrophy in hippocampal and other limbic structures in depressed individuals. These findings may relate to hypothetical abnormalities in the genetic transcription of brain-derived neurotrophic factor (BDNF). BDNF is involved in neurogenesis and stability; however, when exposed to environmental stress, the gene for BDNF is inhibited, which leads to atrophy of vulnerable neurons (Duman and Monteggia 2006). A full discussion of this exciting research is not possible here; however, it is of great interest as it points to treatments that are not solely based on monoamine theories. Some implications of this and related research are discussed at the end of this chapter.

## Antidepressants: Taxonomy and Relation to Mechanism of Action

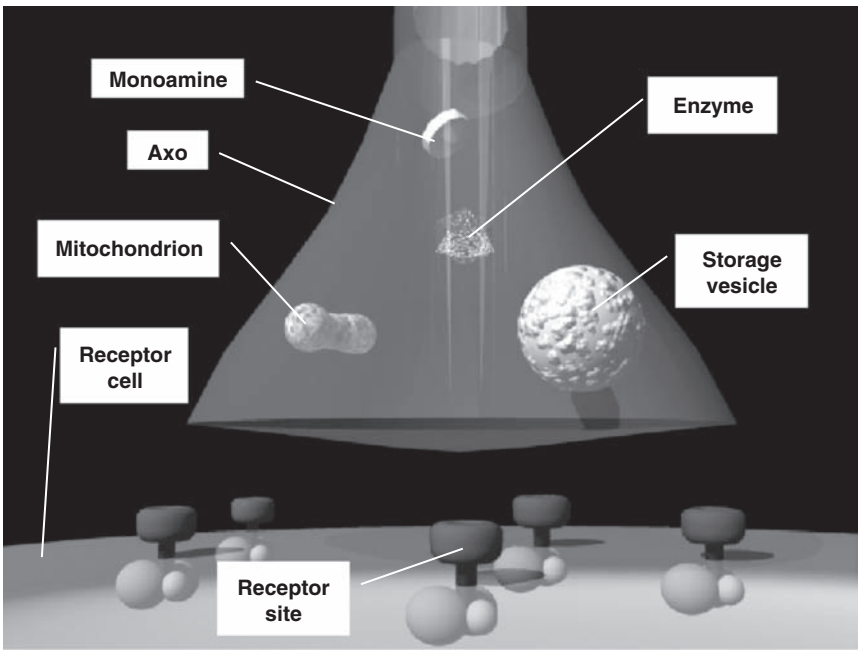
Antidepressants are grouped in several ways. One is historical, in which antidepressants are roughly divided by the period in which they were introduced (e.g., such terms as "first-generation" antidepressants). Another is by chemical structure (e.g., "tricyclic" antidepressants). Alternatively, they are classified by their presumed mechanism of action ("selective serotonin reuptake inhibitors"). In practice, a combination of these is used; thus, some TCAs, which primarily act through serotonin reuptake inhibition (e.g., clomipramine), are usually included with other TCAs rather than as an SSRI, even though they could rightly claim membership in either category.

### First-Generation Antidepressants

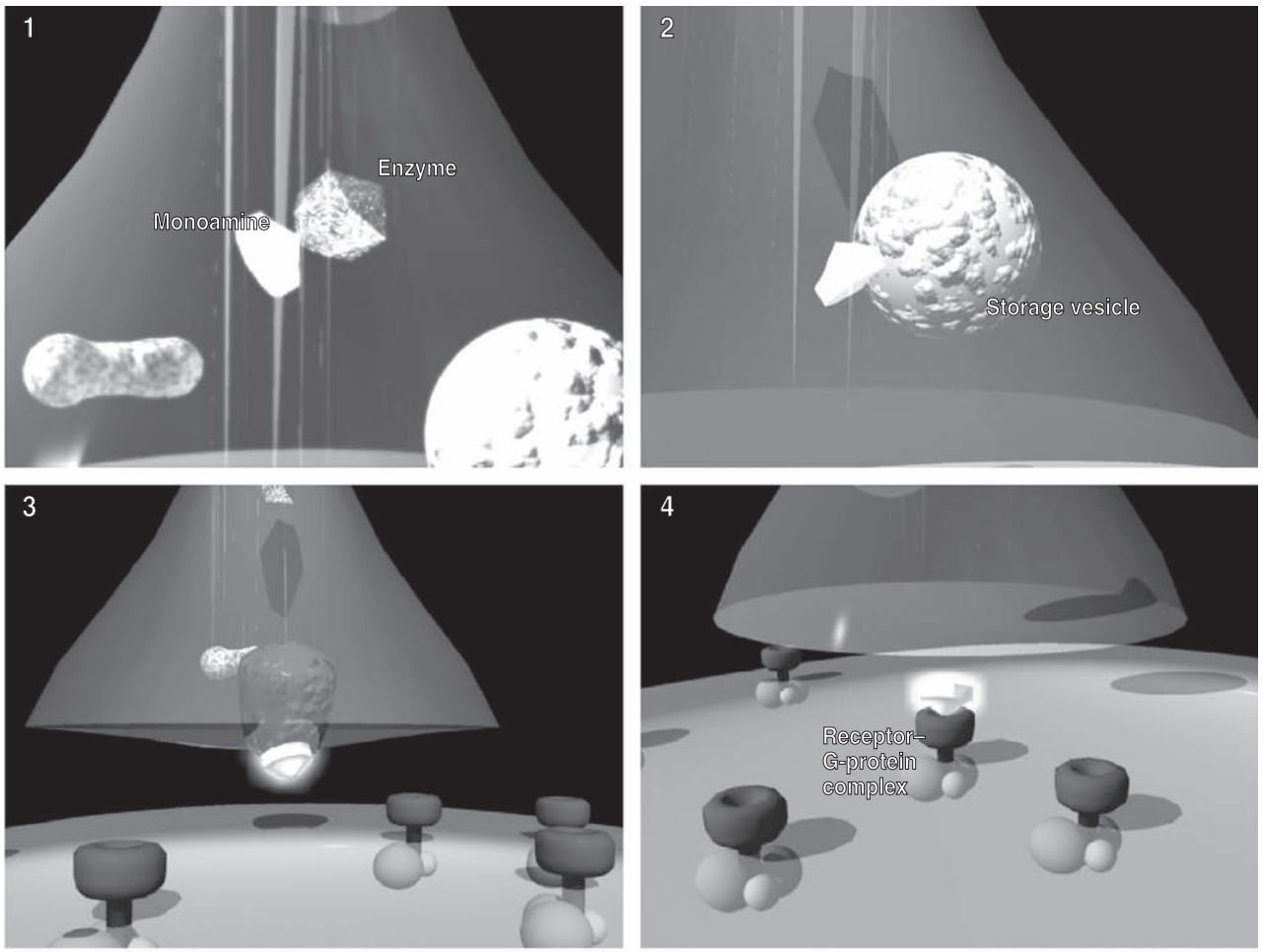
These were the first antidepressants developed. Most were discovered through serendipity. They include the monoamine antidepressants and the TCAs.

#### *Monoamine Antidepressants (MAOIs)*

Historically, these are the first antidepressants discovered. They are all characterized by their unique mechanism: they inhibit the action of monoamine oxidase (MAO), the primary catabolic enzyme for the monoamines. The result is an overall increase in available monoamines. However, owing largely to their side effects, and dietary restrictions, they have rarely enjoyed popular use. Recently, however, a transdermal formulation of selegiline has been introduced, reducing the concentration of MAOI in the gastrointestinal tract, and diminishing the likelihood of diet-related side effects.




A




B

*(continues)*

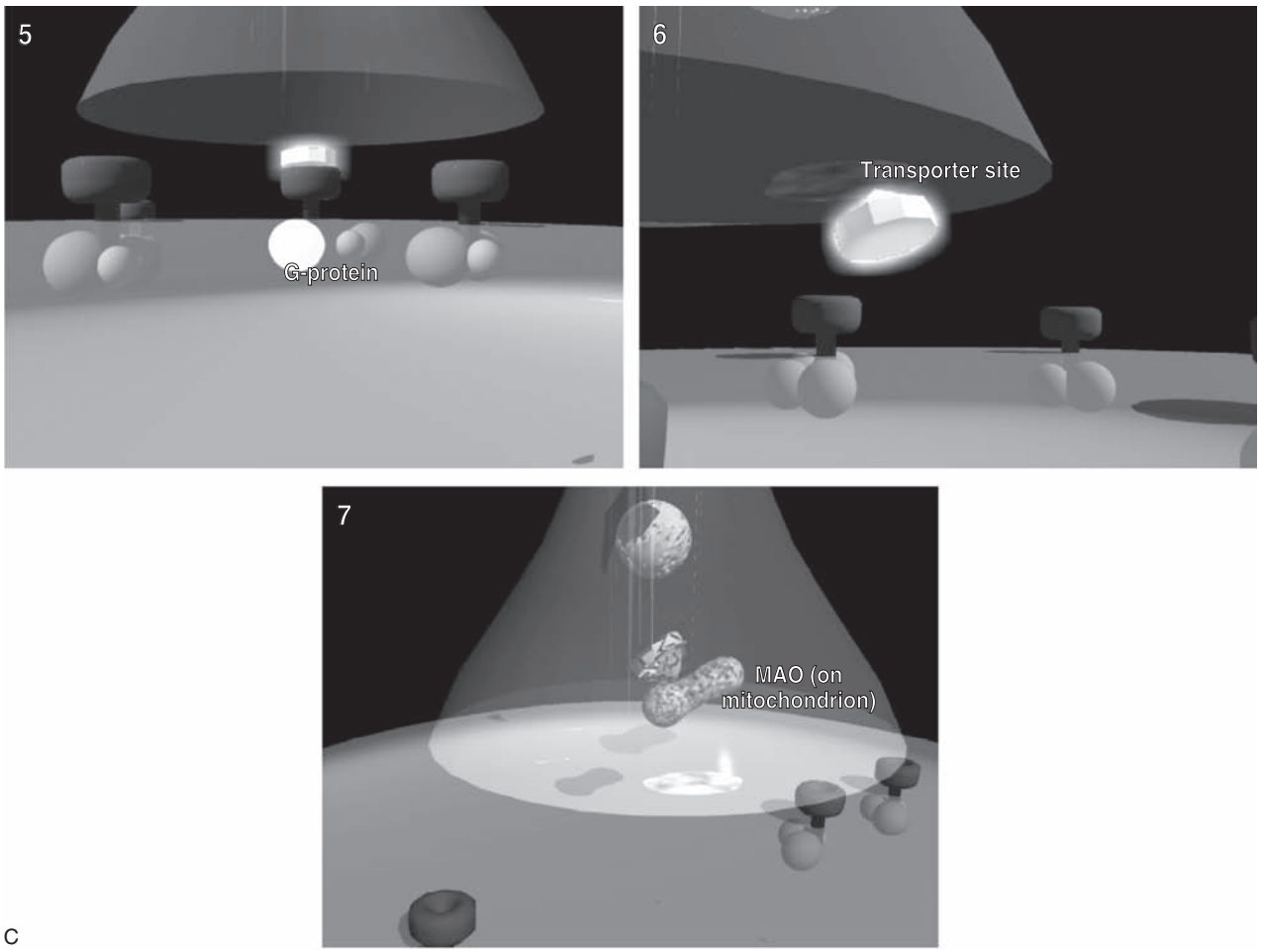



**Figure 101–1** *(A and B) The "life cycle" of a monoamine neurotransmitter, and potential sites for pharmacological intervention.*

*This presents a schematic of monoamine activity. An overview of the neuronal axon–receptor relationship is shown in the overview (A), with several key structures pointed out, including the axon, and receptor cell, whose membranes are rendered here as transparent to illustrate key intracellular components.*

*The monoamines norepinephrine, serotonin, and dopamine are synthesized within the neuron (1) from dietary amino acids, and then stored within vesicles (2). This vesicle can then bind with the axonal membrane, releasing its contents into the synapse (3).*

*Upon binding to a receptor complex (4), a resultant cascade of reactions is possible. In general, the binding process causes a destabilization of the subunits comprising the receptor-G-protein complex (5). G-protein, now activated, can then regulate a number of second-messenger systems, such as adenylate cyclase and phospholipase C. The potential results can involve alterations at various levels of neuronal function: from physical structure and membrane permeability to direct regulation of genetic transcription. In this way, it is possible for the many brief and simultaneous inputs to be transduced into coherent and lasting influences on neuronal function. Neurotransmitters can even regulate their own production through binding to presynaptic autoreceptors.*

*Once the reaction is complete, the receptor-G-protein complex restabilizes, and the monoamine is released from the receptor site. The neurotransmitter can then be metabolized in the extracellular space or, more commonly, taken back in the axon through a transporter site (6). Monoamines undergoing such reuptake can be again stored within vesicles, or be deaminated by intracellular monoamine oxidase (residing on the wall of mitochondria) (7).*

*Virtually all of these steps can be influenced pharmacologically. For example, enzymatic synthesis can be inhibited by such agents as alpha-methyltyrosine (which inhibits tyrosine hydroxylase) (1). Reserpine and tetrabenazine can inhibit uptake into the storage vesicles (2), and amphetamines increase the release of norepinephrine from synaptic vesicles (3). A number of drugs can inhibit receptors sites, such as phentolamine and phenoxybenzamine, which act at alpha-receptors (4), and most antipsychotics medication, which block dopamine. The lithium ion may act directly on G-protein and second-messenger systems (5).*

*Most antidepressants appear to act either by inhibiting monoamine oxidase (e.g., the monoamine oxidase inhibitors that can inhibit step 7), or by preventing the reuptake on one or more monoamines (the TCAs and SSRIs, venlafaxine and bupropion) (9). Several of the newer generation antidepressants may have a direct effect on the receptor site (4).*

### *Tricyclic Antidepressants (TCAs)*

These medications all have a structural similarity in common. They are subdivided by the number of amine groups they possess, hence their designation as "tertiary" or "secondary" TCAs. Several are related by metabolism; thus the tertiary amines—amitriptyline and imipramine—are metabolized to the secondary amines—nortriptyline and desipramine—respectively. They all act through reuptake inhibition, and are generally selective for the norepinephrine transporter; several, however, have equal or greater affinity for the serotonin transporter. Normally, excess monoamine is taken up through monoamine transporters into the neuron, where it can be stored, or, more often, catabolized by intracellular MAO. Reuptake inhibitors prevent this through inhibition of the transporter; the excess neurotransmitter remains in the synaptic space where it can bind with receptors. That this

is the mechanism of action of these and many other antidepressants is reinforced by the fact that correlations have been demonstrated between transporter inhibition and clinical improvement in depressive symptoms (Hrdina et al. 1997). The TCAs were the drugs of choice for depression throughout the 1980s. Though very effective, their somewhat nonselective actions, acting on cholinergic, presynaptic adrenergic receptors, for example, resulted in a number of side effects.

## Second-Generation Antidepressants

These medications were developed using knowledge gained from the first-generation antidepressants. An effort was made to produce medications with more selective actions. The primary benefit of such selectivity was a decrease in unintended side effects.

### *Selective Serotonin Receptor Inhibitors (SSRIs)*

The SSRIs were first introduced in the late 1980s. Within a few years, they eclipsed the TCAs as the drugs of choice for depression. As the name suggests, they all act through inhibition of the serotonin transporter. Though very similar, they have some subtle differences, mainly in terms of their half-life, their potency for reuptake inhibition, and their affinity for some other receptors.

Fluoxetine was the first SSRI available in the US. It was introduced in 1986 and has been used in over 54 million patients worldwide. Sertraline has been available in the US since 1992 and by the late 1990s it became one of the most popular medications ever prescribed: by the time the US patent expired in 2006, it was estimated to have grossed over $3 billion dollars in sales. Paroxetine was first introduced in 1993 and it gradually overtook sertraline in sales; by 2005, it was the most prescribed drug of any type. Citalopram and fluvoxamine, both introduced later, have similar data attesting to their efficacy in depression. Escitalopram is the S-enantiomer of the SSRI citalopram. Pharmacologic studies indicate that this form is predominantly responsible for the 5-HT reuptake by racemic citalopram. This drug became the second most prescribed medication in the US in 2005.

### *Selective Norepinephrine Reuptake Inhibitors (NRIs)*

Like the SSRIs, medications in this class share a similar mechanism with the SSRIs, but act on the norepinephrine transporter and have little affinity for the serotonin transporter. Atomoxetine is an example of an NRI; currently it is approved for use in attention-deficit/hyperactivity disorder; however, there is evidence to suggest that it is useful for depression as well (Kratochvil et al. 2005). Reboxetine (not currently available in the US) is another example of such a medication.

### *Tetracyclic Antidepressants*

This class includes trazodone, which was structurally related to the TCAs but has a primary serotonergic mechanism.

### *Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs)*

Bupropion, an aminoketone, is an unusual antidepressant in that it is structurally more similar to several stimulants (cathinone, diethylpropion and the phenethylamines) than to previous antidepressants. It appears to have a clinically significant effect on both dopamine and norepinephrine reuptake. Currently, it is approved both as an antidepressant and as a smoking cessation aid. In addition, radafaxine, a potent metabolite of bupropion, is currently in clinical trials.

### *Dopamine Reuptake Inhibitors (DRIs)*

Several antidepressants have been introduced, both in the US and internationally, which appear to act primarily through inhibition of dopamine reuptake. Most are no longer available, because of either side effects or abuse potential. Nomifensine, initially studied in the 1970s, is no longer commercially available after international reports of severe hemolytic anemias were reported. Amineptine, a potent dopamine reuptake inhibitor (which, to a lesser degree, also inhibited norepinephrine reuptake), is now banned in most countries because of its abuse potential.

## Third-Generation Antidepressants

The next generation of antidepressants involved various attempts to expand the potential of second-generation compounds. One important feature of this group is that many of them have multiple actions. In some cases, this involves actions on multiple neurotransmitters. In other cases, it involves multiple mechanisms of action.

Even though this may seem a return to the broader acting first-generation compounds, the attempt with these drugs is to maximize the presumed "clinically relevant" effects of the drugs, while minimizing the less important (and potentially adverse) actions.

### *Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)*

These antidepressants share a common mechanism with the SSRIs, but differ in that they have equal affinity for the norepinephrine and serotonin transporter. Medications in this class include venlafaxine and duloxetine. Other medications (available in other countries), such as milnacipran, have similar mechanisms of action. Although, like several of the TCAs, venlafaxine and duloxetine have multiple receptor effects, and are relatively free of the anticholinergic and antihistaminic side effects that are common with the TCAs.

### *Mixed Serotonin Antagonist/Reuptake Inhibitors*

These agents have multiple mechanisms of action, all of which appear to be of clinical importance. Nefazodone is an example of such an agent, with both serotonin (as well as norepinephrine) transporter inhibition as well as antagonism of 5-HT2A and alpha-1-receptors. Trazodone may be similar; however, its effects are somewhat less specific, and as a result, it resembles the TCAs in most respects.

### *Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)*

Currently, the only agent in this class is mirtazapine. This agent is unique in that it appears to work primarily through receptor blockade, specifically through blockade of the alpha-2-autoreceptors on presynaptic noradrenergic neurons, which enhances noradrenergic output. They may exert a similar effect toward autoreceptors on serotonin neurons. Antagonism of 5-HT2 and 5-HT3 receptors may also concentrate the effect of serotonin on 5-HT1A receptors.

The antidepressants available in the US (as of the second quarter of 2007), their class, and relative costs are listed in Table 101–1.

**Table 101–1 Antidepressants Available in the US**

| | Class | Name | Brand Name(s) | Generic | How Supplied | Price Index: * |
|---|---|---|---|---|---|---|
| First generation | TCAs | Amitriptyline | Elavil | Y | Tablets (mg): 10, 25, 50, 75, 100, 125,150 | 0.12 |
| | | Imipramine | Tofranil | Y | Tablets (mg): 10, 25, 50 | 1.76 |
| | | Nortriptyline | Pamelor, Aventyl | Y | Tablets (mg): 10, 25, 50, 75 | |
| | | Desipramine | Norpramin | Y | Oral solution: 10 mg/5 mL<br>Tablets (mg): 10, 25, 50, 75, 100, 150 | 0.33<br>0.63 |
| | | Amoxapine | Asendin | Y | Tablets (mg): 25, 50, 100, 150 | 2.40 |
| | | Doxepin | Sinequan | Y | Tablets (mg): 10, 25, 50, 75, 100, 150 | |
| | | Protriptyline | Vivactil | N | Oral solution: 10 mg/mL<br>Tablets (mg): 5, 10 | 0.33<br>0.87 |
| | | Trimipramine | Surmontil | N | Tablets (mg): 25, 50, 100 | 1.97 |
| | | Clomipramine | Anafranil | Y | Tablets (mg): 25, 50, 75 | 1.30 |
| | | Maprotiline | Ludiomil | Y | Tablets (mg): 25, 50, 75 | 1.03 |
| | MAOIs | Isocarboxazid | Marplan | N | Tablets: 10 mg | 1.76 |
| | | Phenelzine | Nardil | N | Tablets: 15 mg | 1.86 |
| | | Tranylcypromine | Parnate | N | Tablets: 10 mg | 2.78 |
| | | Selegeline transdermal | Emsam | N | Transdermal patch (mg/day): 6, 9, 12 | 15.12 |
| Second generation | SSRIs | Fluoxetine | Prozac, Sarafem | Y | Tablets (mg): 10, 20, 40<br>Extended release: 90 mg ("Prozac Weekly") | 0.83 |
| | | Sertraline | Zoloft | Y | Oral solution: 20 mg/5mL<br>Tablets (mg): 25, 50, 100 | 2.30 |
| | | Paroxetine | Paxil | Y | Oral solution: 20 mg/mL<br>Tablets (mg): 10, 20, 30, 40 | 1.10 |
| | | Fluvoxamine | Luvox | Y | Oral solution: 10 mg/5 mL<br>Tablets (mg): 25, 50, 100 | 1.80 |
| | | Citalopram | Celexa | Y | Tablets (mg): 10, 20, 40 | 1.33 |
| | | Escitalopram | Lexapro | N | Oral solution: 10 mg/5 mL<br>Tablets (mg): 5, 10, 20 | 2.53 |
| | Atypical | Bupropion | Wellbutrin, Wellbutrin SR, Wellbutrin XL Zyban | Y | Oral solution: 5 mg/5 ml<br>Tablets (mg): 75, 100<br>SR (mg): 100, 150, 200<br>XL (mg): 150, 300 | 2.33 |
| | | Trazodone | Desyrel | Y | Tablets (mg): 50, 100, 150, 300 | 0.53 |
| Third generation | SNRI | Venlafaxine | Effexor<br>Effexor XR | N | Tablets (mg): 25, 37.5, 50, 75, 100<br>Extended release (mg): 37.5, 75, 150 | 3.20 |
| | | Duloxetine | Cymbalta | N | Tablets (mg): 20, 30, 60 | 6.74 |
| | Mixed serotonin antagonist/ reuptake inhibitors | Nefazodone[a] | Serzone | Y | Tablets (mg): 50, 100, 150, 200, 250 | 0.70 |
| | Mixed serotonin/ norepinephrine antagonists | Mirtazapine | Remeron | Y | Tablets (mg): 7.5, 15, 30, 45<br>Dissolvable tablets (mg): 15, 30, 45 | 2.35 |

*Price Index = cost/pill × recommended pills/day. This is a rough calculation, assuming an average recommended dose for the treatment of major depression, and assuming that the most efficient dosing regimen, and least expensive tablet choice is prescribed. When available, generic prices are used. Source of prices: www.drugstore.com (accessed 3/1/07).

[a]Brand has discontinued by manufacturer; available only in generic.

## The Basis for Determining Efficacy

### Clinical Trials

As with any drug, the gold standard for proving efficacy is a double-blind placebo-controlled trial. There have been many such studies for antidepressants. As a whole, these studies lend strong support for the efficacy of antidepressants.

There have been some limitations in these data. Some have questioned the effectiveness of the blinding techniques, and it has been demonstrated that subjects in some

supposedly blinded studies can accurately guess whether they are on a drug or a placebo. Such potential bias could inflate the perceived efficacy of these drugs (Moncrieff et al. 1998). A somewhat opposing dilemma is the high placebo response in many intervention studies on depression, requiring large samples before a significant effect can be found. These biases, though important, have occasionally been exploited with the purpose of discrediting data proving the efficacy of antidepressants. However, there are very many carefully performed studies investigating antidepressants, and the sheer enormity of these add considerable weight to the contention that these drugs are very effective in the treatment of major depressive disorders.

### First-Generation Antidepressants

Since the first reports of the efficacy of amitriptyline (Kuhn 1958) and iproniazid (Kline 1958), numerous controlled trials have demonstrated the efficacy of first-generation antidepressants. A potential antidepressant is compared to either a placebo or a gold standard antidepressant, usually imipramine. All TCAs have been shown to be either superior to placebo or equal to imipramine in the treatment of depression. Overall, the first-generation agents have been found to be comparable with each other, although there has been some suggestion, admittedly controversial, that the MAOIs are not as effective as the TCAs in severe "typical" depression (Thase et al. 1995), but that they may have a preferential action in patients with "atypical" depression (Quitkin et al. 1990).

### Second-Generation Antidepressants

All of the second-generation antidepressants have shown efficacy in randomized controlled trials when compared to placebo or to older antidepressants (Williams et al. 2000). The majority of drug trials involving second-generation antidepressants have been in outpatient populations. However, there are increasing studies that examine these drugs in more complicated patients, including the severely depressed (Hirschfeld 1999). Similarly, the majority of the studies investigate the treatment of acute depression.

### Third-Generation Antidepressants

All of the third-generation antidepressants have shown efficacy in randomized controlled studies when compared to placebo or other antidepressants (Williams et al. 2000). There is modest evidence to suggest that some of these agents may have improved efficacy or time to effect; this evidence is discussed in the next section.

## Comparative Trials

Is one antidepressant any more efficacious than another? In studies employing various comparisons, antidepressants of different classes are generally found to be equal in efficacy. There are some caveats to this statement. As already noted, placebo-response rates in many studies of depression are quite high, and it is difficult to show a statistically significant effect. Large sample sizes are needed: assuming that any difference between two antidepressants is likely to be small; a study would require thousands of subjects before it could detect this difference in efficacy. Some of these limitations can be addressed by meta-analyses, which pool the results from different studies to increase the sample size. However, the use of meta-analysis has inherent limitations and a potential for bias, and cannot replace well-done controlled studies.

### SSRIs Compared with Other SSRIs

In a 2005 review, Hansen et al. (2005) identified 22 studies comparing one SSRI with another SSRI. They rated 21 of the studies as "fair" and 1 as "good." Three of the studies were classified as "effectiveness studies" (in that they replicated "real world" treatment conditions); the remainder was classified as efficacy trials. The majority of studies found no difference in efficacy or effectiveness between individual SSRIs. Occasionally, studies did find differences on a single outcome measure. For example, one comparative study found greater efficacy for escitalopram when compared with citalopram (Lepola et al. 2003). Another study found that paroxetine had greater efficacy when compared with fluoxetine (Shone and Ludwig 1993). In both cases, other similarly designed trials did not find differences. On other clinically important measures, such as speed of response, the different agents were generally found to be equivalent. Again, individual studies occasionally found small differences in the speed of response, but similar studies did not confirm this difference. Hansen and colleagues concluded that the reported differences were the result of chance in relatively small studies. They also noted that the majority of published studies were funded by pharmaceutical companies and that when differences were found they inevitably favored the company's product.

### SSRIs Compared with Other Antidepressants

Hansen et al. (2005) also investigated studies comparing SSRIs with other second- and third-generation antidepressants. They found 24 efficacy trials: 21 were rated as "fair" and 3 were "good." Most trials found similar efficacy. However, a number of studies found better rates of response with venlafaxine when compared with other agents. Only a few reached statistical significance: 1 compared venlafaxine with sertraline (Mehtonen et al. 2000), and 2 compared it with fluoxetine (Dierick et al. 1996, DeNayer et al. 2002). However, the majority of studies comparing venlafaxine with another agent did not find a statistical difference and efficacy. Hansen and colleagues could not find a reason to explain these conflicting data, and differences in study design did not seem to explain the disparities. Study size may again play a role; it is notable that in one pooled analysis of eight double-blind studies comparing venlafaxine with SSRIs (all of which individually showed no difference between the drugs), Thase and colleagues (2001) did report a significant difference in remission rates between venlafaxine, which began at 2 weeks. One must conclude from these data that if a difference does exist, it must be small.

Some differences have been found on other measures. Mirtazapine has consistently been shown to have a faster onset of action than comparable SSRIs, although the SSRIs catch up by the end of each study. This was shown in comparison with fluoxetine (Hong et al. 2003), sertraline (Behnke et al. 2003), and paroxetine (Benkert et al. 2000, Schatzberg et al. 2002). Venlafaxine has occasionally been shown to have a faster response time; however, the data are mixed and conflicting.

## Summary

Numerous controlled studies support the efficacy of the antidepressants for the treatment of depression. The bulk of data suggests that all antidepressants have equal efficacy. As new drugs are introduced to the market, one sees a variation on the two primary themes: selectivity versus multiplicity. Agents that are more selective potentially offer cleaner profiles with fewer side effects. However, there are some data to suggest that multiply acting agents can offer advantages, including improved efficacy or faster action. These pharmacological strategies seem more likely to be successful in improving side effects rather than dramatically improving efficacy. Modest improvements in efficacy may be possible; ones that are more dramatic will likely have to wait for truly unique agents to be developed. Finally, effectiveness studies in real world settings suggest that remission rates may be more modest than that reported in efficacy trials.

## The Development of New Antidepressants

### Animal Trials

The development of a new drug is generally divided into three phases: phase I is an initial screening for a desired activity; phase II is a more elaborate determination of desired activity and pharmacokinetics; and phase III is a definitive judgment of the drug's pharmacology. Of particular interest is the phase I, or initial screening of a drug. In the past, such a screening was largely a matter of serendipity. Methods that are more analytic have largely supplanted this. Such methods can take two approaches: a behavioral approach, or a mechanistic approach. In a behavioral approach, investigators attempt to develop an animal model of a particular pathological condition. In a mechanistic approach, the investigator targets particular actions of a potential drug—actions that are presumed to be the basis of a therapeutic effect.

### Behavioral Models

Traditionally, investigators rely on animal models that attempt to reproduce psychiatric pathology. Three examples of such tests are the separation syndrome in rhesus monkeys (McKinney 1988), learned helplessness models (Seligman and Maier 1967), and the behavioral despair or "forced swimming" test (Porsolt et al. 1979). Most behavioral tests are complicated and expensive to perform. The behavioral despair test is probably the most practical of these tests. In this test, an investigator places a mouse or rat in a confined space filled with water. Usually, the immersed animal will first attempt to escape, and then become immobile: "behavioral despair" refers to the assumption that the animal has given up hope of escaping. On subsequent immersions, the animal becomes immobile more quickly. Most antidepressants, regardless of class, delay this effect, and the ability of a new agent to delay immobility in animals is a good predictor of antidepressant action in humans. There is even a correlation between the potency of an agent in this test and its clinical potency as an antidepressant: this feature is not demonstrable in any other animal model of depression (Willner 1990). The mechanism of this response has been shown to be mediated by both pre- and postsynaptic serotonergic 5-HT1 receptors (Redrobe et al. 1996); however, the behavioral despair is not necessarily limited to these receptors alone.

### Mechanistic Models

The most common mechanistic tests evaluate antagonism of reserpine—a feature of all TCAs and many newer agents. Several experiments evaluate different examples of reserpine antagonism. The ability to block reserpine-induced hypothermia depends on an agent's proficiency at increasing postsynaptic norepinephrine or potentiating beta-adrenergic receptors. Antagonism of reserpine-induced ptosis is dependent on alpha-noradrenergic or serotonergic activity, and antagonism of reserpine-induced akinesia appears to be dopamine dependent. In combination, these three tests can differentiate between several monoamine-dependent effects. Other methods include antagonism of oxotremorine (related to anticholinergic activity), the high-dose apomorphine test (specific for norepinephrine reuptake), and the yohimbine test. The ability to potentiate yohimbine lethality, an alpha-2-agonist, appears to be highly specific for antidepressants.

Thus, a variety of psychopharmacological tools may be of use in screening potential antidepressants. They are generally simple to perform and relatively inexpensive, particularly when compared with clinical trials. They may also be more reliable than standard neurochemical screening in predicting the antidepressant action of an agent (Bourin 1990).

### Limitations of Behavioral and Mechanistic Models

An ideal model of depression should be able to meet the same criteria as any model of human disease. It should reproduce the symptoms and the etiology of the disease, show common biological mechanisms, and show reversal of symptoms by proven therapeutic agents (Delina-Stula 1989). Neither the behavioral model nor the mechanistic model of depression meets all these criteria. The behavioral model suffers from inherent limitations in attempting to simulate a complex human behavior in an animal. Usually, one compromises by simulating certain aspects of depressive behavior in an animal. Such a "target symptom" may not be a true extrapolation of human depression. Though recent attempts to breed for "depressed" mice (Vaugeois and Costentin 1998) (using a predilection toward helplessness behaviors as a target symptoms) might improve the situation, the behavioral models continue to suffer from significant limitations. Behavioral models can also be cumbersome and expensive.

Mechanistic models are simple and inexpensive, but suffer from limited specificity (e.g., aspirin, with no antidepressant action, can antagonize reserpine-induced hypothermia) and a reliance on available theories about the critical ingredient of antidepressants. For this reason, the mechanistic model is less likely than the behavioral model to reveal truly novel antidepressants. Used together, the two models can complement each other.

A potentially greater inherent limitation is that these models, to date, have only been successful in identifying drugs that work through actions on monoamine neurotransmitters. This may simply reflect the fact that these types of drugs are the most frequently tested; however, the fear is that this reflects a more fundamental problem that the models are only testing for disturbances in monoamine activity. If this is true, then these models will be limited in their ability to identify novel treatments for depression,

and new models may be required. Models based on neurophysiologic and genetic data are being developed; the implications of these newer paradigms are discussed at the end of this chapter.

## The Formulation of Treatment

### Indications

#### Acute Major Depression

All antidepressants are indicated for the treatment of acute major depressive episodes. The major depressive disorder is, most likely, a variety of neuropsychological disorders that have in common their negative effects on mood, thought and vegetative symptoms. There is much room for variation, with phenomenology ranging from anxiety and irritability to anergy and melancholia. The heterogeneity of the diagnosis is recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM), of which the DSM-IV-Text Revision (DSM-IV-TR) (American Psychiatric Association 2000a) is the most recent edition. DSM-IV-TR lists nine possible symptoms. Of these, either depressed mood or loss of interest is required for the diagnosis, with at least four other symptoms present during a 2-week period.

Though there have been some attempts to match different types of depression with different medications, there is no convincing evidence to suggest that there is a preferential efficacy between specific presentations of depression and certain medications. Some investigators have suggested that certainly personality types may differentially respond to different agents (Tranter et al. 2002); however, it is not clear whether these data reflect actual differences in efficacy or personality differences that then affect adherence.

#### Prevention of Relapse and Recurrence

Beyond the acute period, there is also evidence for the use of antidepressants in the prevention of relapse and recurrence. However, the further one gets from the initial episode, the sparser the data. Most of the commonly used antidepressants have at least one placebo-controlled study justifying their use in relapse prevention. However, few studies go beyond a year of treatment (these are discussed later in this chapter).

#### Other Depressive Disorders

There are a number of more minor forms of depression, many of which may also respond to antidepressant medication. Best studied of these is dysthymic disorder, which appears to be responsive to most antidepressants. There are four published placebo-controlled studies investigating the treatment of dysthymia with second-generation antidepressants. Of these, one study using fluoxetine (Devanand et al. 2005) showed no difference from the placebo group. Two studies using sertraline (Thase et al. 1996, Ravindran et al. 2000), and one with paroxetine (Barrett et al. 2001) showed positive results. To date, no studies comparing different agents in dysthymia have been published.

Other minor depressive disorders include minor depression and recurrent brief depression. Though rigorous data are largely lacking in the treatment of these disorders, they seem to show an at least modest response to antidepressant medications.

#### Other Disorders

Antidepressants are used in an ever-increasing number of nondepressive disorders: such uses are discussed under the appropriate sections of the textbook, and are listed in Table 101–2.

**Table 101–2 Various Uses of Antidepressants**

| Major Depression* |
|---|
| Acute depression* |
| Prevention of relapse* |
| Other depressive syndromes |
| Bipolar depression |
| Atypical depression |
| Dysthymia |
| **Other Uses** |
| **Tricyclic Antidepressants** |
| Strong evidence |
| Panic disorder (most) |
| Obsessive–compulsive disorder (clomipramine) |
| Bulimia (imipramine, desipramine) |
| Enuresis (imipramine) |
| Moderate evidence |
| Separation anxiety |
| Attention-deficit/hyperactivity disorder |
| Phobias |
| Generalized anxiety disorder |
| Anorexia nervosa |
| Body dysmorphic disorder |
| Migraine (amitriptyline) |
| Other headaches |
| Diabetic neuropathy, other pain syndromes (amitriptyline, doxepin). |
| Sleep apnea (protriptyline) |
| Cocaine abuse (desipramine) |
| Tinnitus |
| Evidence for but rarely used for these disorders |
| Peptic ulcer disease |
| Arrhythmias |
| **Monoamine Oxidase Inhibitors** |
| Strong evidence |
| Panic disorder |
| Bulimia |
| Parkinson's Disease (selegeline) |
| Moderate evidence |
| Other anxiety disorders |
| Anorexia nervosa |
| Body dysmorphic disorder |
| **Second Generation Drugs** |
| Trazodone |
| Insomnia |
| Dementia with agitation |
| Minor sedative/hypnotic withdrawal |
| Bupropion |
| Attention-deficit/hyperactivity disorder |
| Smoking cessation* |
| **Serotonin Reuptake Inhibitors** |
| Strong evidence |
| Obsessive Compulsive Disorder* |

(continues)

**Table 101–2 Various Uses of Antidepressants** *continued*

**Serotonin Reuptake Inhibitors** *continued*

Strong evidence *Continued*
- Bulimia*
- Premenstrual Dysphoric Disorder (PMS)*
- Post Traumatic Stress Disorder (PTSD)*
- Panic Disorder*
- Social phobia*
- Generalized anxiety disorder*

Moderate evidence
- Pathological gambling
- Tension headaches
- Obesity
- Substance abuse
- Impulsivity, anger associated with personality disorders
- Pain syndromes

Preliminary evidence
- Obsessive jealousy
- Body dysmorphic disorder
- Hypochondriasis
- Behavioral abnormalities associated with autism and mental retardation
- Anger attacks associated with depression
- Depersonalization disorder
- Raynaud's syndrome

Fibromyalgia
- Attention-deficit/hyperactivity disorder (as an adjunct)
- Chronic enuresis
- Paraphilic sexual disorders
- Nonparaphilic sexual disorders

**Third Generation Drugs**

Sleep Disorders (mirtazapine, nefazodone)
Generalized anxiety disorder (venlafaxine)*
Social phobia (venlafaxine)*
Other Anxiety Disorders
Pain disorders (duloxetine)*
Premenstrual Dysphoric Disorder

* FDA approval for at least some agents in the class.

## Selection of an Antidepressant

The decision whether to treat depressive symptoms with pharmacotherapy requires an assessment of both the need for intervention and the likelihood that treatment will be successful. Assessing the need for intervention involves longitudinal and cross-sectional factors. Assessing the likelihood that treatment will be successful is somewhat more difficult, but may rely on clinical, demographical, and biological factors.

### Assessing the Need for Intervention

This involves assessing the likely result if pharmacological treatment is not given. It is essential in making a useful risk–benefit assessment.

#### *Longitudinal Factors*

The physician should consider the course and duration of previous episodes of depression. Such episodes can predict the potential severity of the current episode, the likely time to recovery, and the probability of a subsequent recurrence. The physician should also consider the likely complications of depression for the individual patient, which may include substance abuse and suicide.

#### *Cross-Sectional Factors*

The physician should consider the severity of symptoms and the degree of functional impairment. Suicidal ideation is of particular concern and needs rapid and intensive treatment. Such treatment often includes hospitalization. Even with less pressing symptoms, but significant occupational or social impairment, the risk–benefit ratio generally still favors a trial of antidepressants, particularly now that safer and more easily tolerated agents are available.

### Assessing the Likelihood of Success

The ability to predict the likely response to pharmacotherapy would be invaluable for planning a treatment strategy. Such an assessment is difficult.

A number of symptoms have been suggested as predictors of good and poor response. In the past, depressive illness was distinguished by whether it was "endogenous" or "exogenous." Endogenous depression was thought to have a primary biological etiology, whereas exogenous depression implied a reactive response to environmental stressors. It was assumed that endogenous depression would respond better to somatic therapy and exogenous to psychosocial interventions. This distinction proved excessively simplistic. The categories did not have adequate construct validity. Usually, the attribution of cause was assigned retrospectively, and it was subject to various interpretations. As a result, these subgroups did not adequately predict treatment response.

A refinement of such categories has been the concept of "melancholic depression." This subtype contains many of the criteria thought to describe the endogenous type of depression, but it does not imply any specific etiology. Melancholic depression is, by definition, highly responsive to somatic therapy. Individuals in this subgroup tend to have a positive family history for depression and a 2:1 female–male ratio.

Another subtype, "atypical depression," describes a group of patients who differ from the melancholic type, primarily with neurovegetative symptoms: they have hypersomnia, hyperphagia, and psychomotor agitation and are more likely to be anxious or irritable. Earlier studies suggested a preferential response to certain classes of antidepressants, with MAOIs often suggested as the drug of choice. However, studies that are more recent have not supported a differential effect on depression among different classes of antidepressants (McGrath et al. 2000).

Additional possible predictors of poor response include personality features (such as neurotic, hypochondriacal, and hysterical traits), multiple prior episodes, delusions, and psychomotor agitation.

## Selection of a Particular Agent

Although, as noted earlier, the various antidepressants seem to have equal efficacy in the treatment of depression, a given patient may respond preferentially to one, or a class of agents. Again, cross-sectional and longitudinal factors should be taken into account.

## Longitudinal Factors

Longitudinal factors include a history of response to a particular agent, a family history of good response, a history of prior side effects (particularly if they resulted in drug discontinuation), and a history of symptoms that could suggest mania (or more minor variants of manic episodes). TCAs are less desirable for patients with prior manic episodes, as they may precipitate manic episodes. Although less well understood, MAOIs may produce the same effect (Keller et al. 1986).

## Cross-Sectional Factors

Cross-sectional factors would include data from the physical examination and laboratory work-up, which might suggest susceptibilities to certain antidepressant agents or contraindications based on physical illness. For instance, an examination that revealed prostatic hypertrophy or an electrocardiogram that showed a conduction abnormality should influence the physician against a TCA. A seizure disorder would be a relative contraindication against using bupropion. Aspects of the psychiatric examination are useful as well. For example, the presence of manic symptoms, indicative of a mixed bipolar illness, argues for treatment with lithium or anticonvulsants over standard antidepressants.

Anxiety has been often used as a predictive symptom. Specifically, there is often a belief that patients with anxiety symptoms do better with more sedating antidepressants. Even though an early sedating effect may increase adherence in patients with prominent anxiety, there is no evidence that more sedating agents are more effective in patients with comorbid depression and anxiety.

The presence of psychotic symptoms requires combined treatment with antidepressants and antipsychotics, as either agent alone is less effective for these symptoms. An alternative is to use electroconvulsive therapy.

An issue often neglected is that of cost. Older agents that are available in generic form are 10–100 times less expensive than newer agents are. Although older agents tend to have more side effects, cost can also influence compliance. In 2001, fluoxetine became the first SSRI to be available in the US in generic form. By the year 2010, all but one of the currently available antidepressants will be off patent and eligible to be produced generically. Table 101–1 lists the relative costs of antidepressants, as of the first quarter of 2007.

## Pharmacokinetic Concerns

### *First-Generation Antidepressants*

The pharmacokinetics of TCAs is complex. This complexity is reflected in the diversity of half-lives reported, which vary roughly from 10 to 40 hours. TCAs are primarily absorbed in the small intestine. They are usually well absorbed, and reach peak plasma levels 2–6 hours after oral administration. Absorption can be affected by changes in gut motility. The drugs are extensively metabolized in the liver on first pass through the portal system. They are lipophilic, have a large volume of distribution, and are highly protein bound (85–95%). TCAs are metabolized in the liver by hepatic microsomal enzymes, via demethylation, oxidation, or hydroxylation. They are generally metabolized to active metabolites, and are excreted by the kidneys. There is a large range of elimination half-lives among the antidepressants.

MAOIs are also well absorbed from the gastrointestinal tract. Their metabolism, although quite efficient (they have a half-life of 1–2 hours), is not well understood. The short half-life of these compounds is not entirely relevant however, as they bind irreversibly with MAO. Thus, the activity of these drugs depends less on pharmacokinetics, and more on the synthesis of new MAO to restore normal enzyme activity. This synthesis requires approximately 2 weeks.

### *Second-Generation Antidepressants*

All of the available SSRIs are well absorbed, and not generally affected by food administration. Sertraline is an exception to this rule, and its blood level may be increased by food. All SSRIs have large volumes of distribution and they are extensively protein bound. They are metabolized by hepatic microsomal enzymes and are potent inhibitors of these enzymes (a fact that will be discussed later in detail).

The only SSRI with an active metabolite is fluoxetine, whose metabolite norfluoxetine has a half-life of 7–15 days. Thus, it may take several months to achieve steady state with fluoxetine. This is considerably longer than citalopram, which has a half-life of about 1.5 days, or sertraline and paroxetine, which have half-lives of about a day.

As previously discussed, there is no correlation between half-life and time to onset. Drugs with shorter half-lives have an advantage in cases where rapid elimination is desired (e.g., in the case of an allergic reaction). Drugs with a longer half-life may also have advantages: fluoxetine, for example, is available in a once-weekly formulation. All SSRIs are eliminated in the urine as inactive metabolites. Both fluoxetine and paroxetine are capable of inhibiting their own clearance at clinically relevant doses. As such, they have nonlinear pharmacokinetics: changes in dose can produce proportionately large plasma levels.

As with most of the other antidepressants, bupropion undergoes extensive first pass metabolism in the liver. Although the parent compound has a half-life of 10–12 hours, it has three metabolites that appear to be active. One, threohydrobupropion, has a half-life of 35 hours and is relatively free in plasma (it is only 50% protein bound). There is considerable individual variability in the levels of bupropion and its metabolites. In addition, the drug is available in an immediate release, intermediate release, and extended release formulation. Trazodone has a half-life that is relatively short, having a range of 3–9 hours. Given this, and its apparent lack of active metabolites, the plasma levels of trazodone can be quite variable during a day. For this reason, the medication requires divided dosing.

### *Third-Generation Antidepressants*

Venlafaxine has a short half-life (4 hours); however, it is available in an extended release formulation that allows once-daily dosing. It appears to have a dual effect, in which at lower doses it primarily acts on the serotonin transporter, and clinically significant norepinephrine reuptake inhibition is not seen until higher doses are used (150 mg/day and above).

Nefazodone has relatively low bioavailability, and a short half-life (2–8 hours), and thus it is usually given in twice-daily doses. Mirtazapine has a half-life of 13 to 34 hours.

Duloxetine is absorbed over a 2-hour period, although this absorption is delayed if the medication is taken in the evening. It is highly protein bound (>90%), and undergoes

rapid metabolism after being absorbed. It has a half-life of approximately 12 hours.

The relative half-lives of available antidepressants are depicted in Figure 101–2.

## Gender, Ethnic, and Racial Issues

### Gender

Women may have slower gastrointestinal absorption than men, as they have less gastric acid and slower gastric emptying. A woman's volume of distribution differs as well, given her increased ratio of adipose tissue to lean body mass. Water retention associated with the menstrual cycle may also affect the volume of distribution.

Few clinical studies specifically look at the pharmacokinetics of antidepressants in women. Existing studies show conflicting results: some studies suggest that at similar doses women will have increased plasma levels, while other studies do not show such a difference. In some of the studies, the patients used oral contraceptives, which can alter the hepatic metabolism of TCAs, and this may explain the discrepancy between studies.

There may be pharmacodynamic differences as well. Possible gender differences in responses to antidepressants have been suggested for decades, but rarely examined in detail. Kornstein et al. (2000) reanalyzed data from a study comparing imipramine and sertraline for chronic depression. They found that women responded better to sertraline than to imipramine whereas men had the opposite pattern of response. Women also had a longer time to response. Of interest was the fact that this effect was only seen in premenopausal women; postmenopausal women had similar rates of response to both medications.

### Race and Ethnicity

As with gender, there are insufficient studies available on the effects of race and ethnicity on differential dosing, pharmacology, and treatment response. Some studies have suggested that Hispanic patients may have an increased sensitivity to antidepressants; however, there are conflicting data on this subject (Bond 1991).

Some pharmacokinetic differences are found in Asian populations; for example, Asians tend to carry the poor metabolizer trait for cytochrome P450 2C19 (Roden et al. 2006). There may be pharmacodynamic differences in Asian populations, as a number of pharmacogenetic studies have found that the associations between monoamine transporter polymorphisms and antidepressant response are not found in Asian populations (Nnadi et al. 2005).

African-Americans may differ from Caucasian Americans in their ability to metabolize certain antidepressants. Generally, it has been reported that they can be slow metabolizers of some antidepressants, particularly the TCAs (Strickland et al. 1997). One genetic study of African-Americans from the Southeastern US had a lower prevalence of the P450 2D6 poor metabolizer mutation (Evans

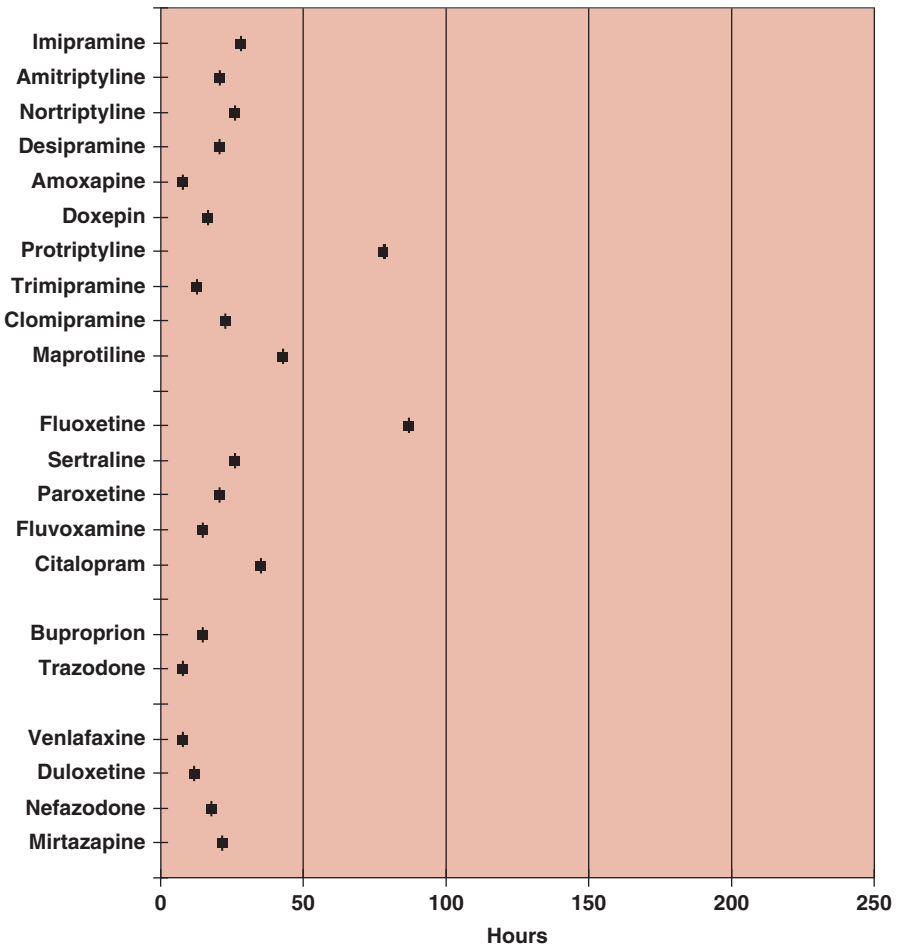



**Figure 101–2** *Approximate mean (black square) and range (blue line) of various antidepressant half-lives.*

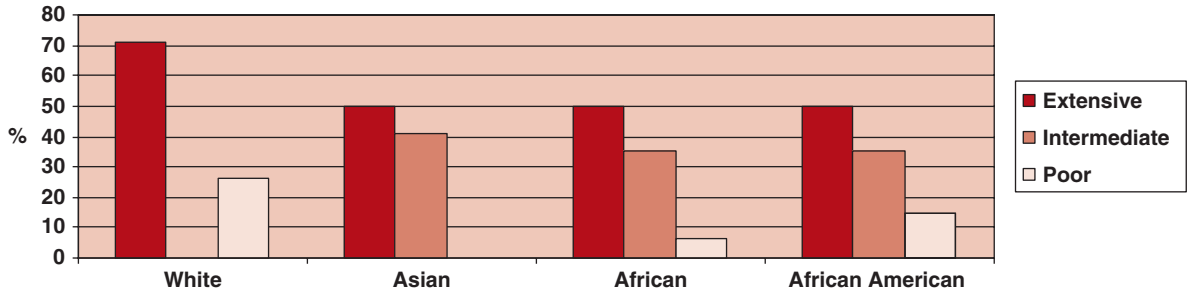



**Figure 101–3** *Distribution of Cytochrome P4502D6-related metabolic variations by race. (Source: Bradford 2002.)*

et al. 1993). Some differences in metabolism by racial group are illustrated in Figure 101–3.

Clearly, these issues need to be explored further. However, the greatest concern regarding race and ethnicity remains the disparities in access to treatment for African-Americans and other minority groups (Sleath et al. 2006).

## Preparation of the Patient

### Side Effects of Antidepressants

Good preparation and reassurance are essential. Side effects—even relatively benign ones—are a major cause of treatment nonadherence. Dropout rates ranging from 7 to 44% have been reported in various studies of TCAs, and from 7 to 23% in studies of SSRIs. Proper education and reassurance about side effects can help reduce this rate. It should reassure the patient to know that many of the side effects diminish with time, or with an adjustment of dose. It may also help frame side effects in a positive light, as they represent concrete evidence that the medication is exerting its effect on the body.

The best approach may be to consider both frequency and clinical importance. That is, one should discuss those side effects that are likely to occur, as well as considering rare but potential dangerous or irreversible side effects. A number of common, uncommon, and hypothetical side effects are discussed here.

The importance of discussing side effects as soon as possible is made particularly crucial given the wide variety of other sources of information at patients' disposal. Many pharmacies now include printed information to accompany medications, which include comprehensive lists of side effects. Various books on medications are available and a popular offering in many bookstores and libraries. On the Internet, mental health sites have become an extremely popular source of information for patients. The information on Internet sites may range from very reputable and informative, to anecdotal, to clearly hostile and misrepresentative. It should be the role of the physician to give such information context, and, if indicated, to correct misinformation.

It is useful to divide side effects into "predictable" and idiosyncratic effects. Predictable side effects result from known pharmacological actions of the drug. Idiosyncratic side effects are not well understood. What follows is a brief summary of antidepressant side effects; for a fuller discussion, the reader is referred to more comprehensive works (e.g., Schatzberg and Nemeroff 2004).

### Predictable Side Effects

These side effects are the result of the action of the agent at various neurotransmitters and enzyme sites. The major neurotransmitters affected by antidepressants are as follows.

#### *Muscarinic Acetylcholine Receptors*

Blockade of this receptor produces a variety of peripheral and central effects. Gastrointestinal effects include decreased salivation and decreased peristalsis. Decreased salivation is the most common of these effects and can cause drying of the mucous membranes. Such drying can exacerbate gum disease and dental caries. Decreased peristalsis can cause constipation and, in the extreme, paralytic ileus. Contraction of the bladder wall is inhibited, causing urinary hesitancy and even urinary retention. In the case of TCAs, concomitant sympathomimetic effects that cause constriction of the bladder neck and urethra worsen this effect on urination. Inhibition of the parasympathetically mediated accommodation reflex, in which the ciliary body muscles normally contract to thicken the lens and focus near objects on the retina, results in blurry vision and mydriasis. Such accommodation paresis can occur without other anticholinergic side effects. A more serious ocular effect is the precipitation of acute narrow-angle glaucoma, through pupillary dilatation. Antidepressant-induced narrow-angle glaucoma is quite rare. Anticholinergic cardiac effects include decreased vagal tone that can cause tachycardia. Central nervous effects include impaired memory and cognition. In severe cases, such cognitive impairment can reach the point of a delirium. Central anticholinergic effects can also worsen existing tardive dyskinesia.

These effects are usually dose related, and are worse in people with preexisting defects. For example, the cardiac effects are of most concern in patients with preexisting cardiac defects, and urinary blockade generally occurs only in the presence of prostatic hypertrophy. These side effects are also more common in patients taking other anticholinergic medications, which is a common feature of many over-the-counter preparations.

The relative affinities of antidepressants for blocking muscarinic receptors are compared in Figure 101–4. As MAOIs have little direct effect on receptors, and their side effects relate to enzymatic inhibition, they are discussed separately.

#### *Histamine*

Blockade of the histamine H1 receptor is typically associated with sedation. Histamine blockade may also cause

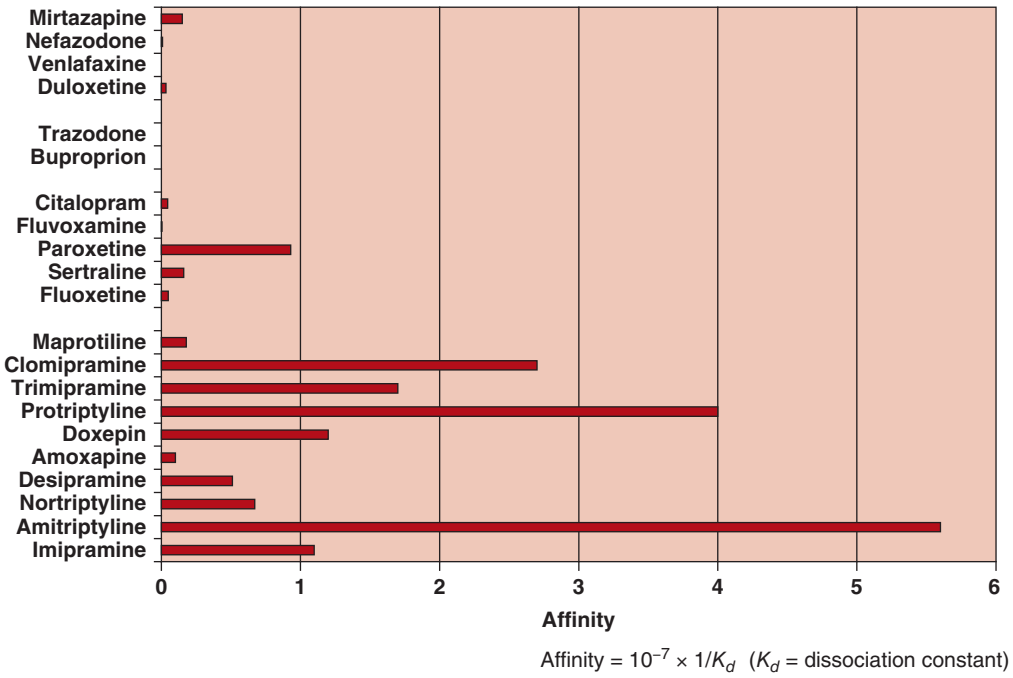



**Figure 101–4** *Relative affinities of antidepressants for blocking muscarinic receptors. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

orthostatic hypotension and weight gain. It can impair psychomotor coordination and cause falls in the elderly. Cognitive impairment can occur as well. H2-receptor blockade causes decreased gastric acid production. This is the mechanism of many antiulcer medications. The relative affinities of antidepressants for blocking histaminic receptors are compared in Figure 101–5.

### *Norepinephrine*

Synaptic increases in norepinephrine, through either inhibition of norepinephrine reuptake or decrease in MAO degradation, cause sympathomimetic effects. Increases in norepinephrine can cause anxiety, tremors, diaphoresis, and tachycardia. This tachycardia can potentiate anticholinergic cardiac effects. As noted, sympathomimetic effects on the bladder neck and urethra can potentiate the anticholinergic inhibition of normal urinary function. The relative potencies of antidepressants for blocking the reuptake of norepinephrine are compared in Figure 101–6.

### *Receptor Blockade*

Blockade of alpha-1-receptors occurs as a chronic effect through both down regulation and desensitization of the beta- and alpha-2-receptors. Blockade of the noradrenergic

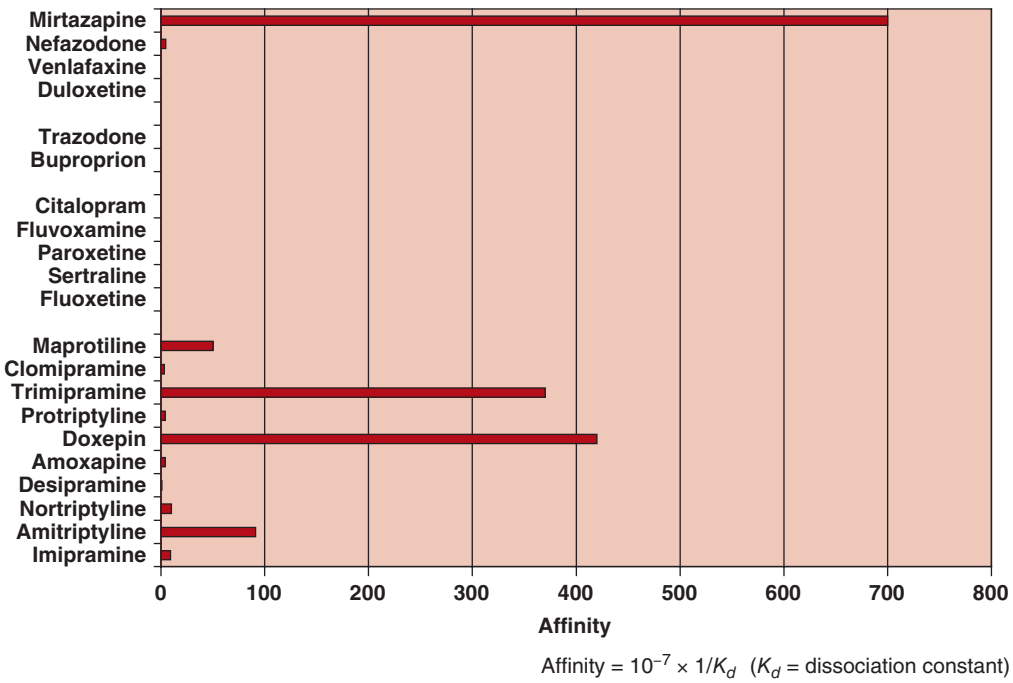



**Figure 101–5** *Relative affinities of antidepressants for blocking histaminic receptors. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

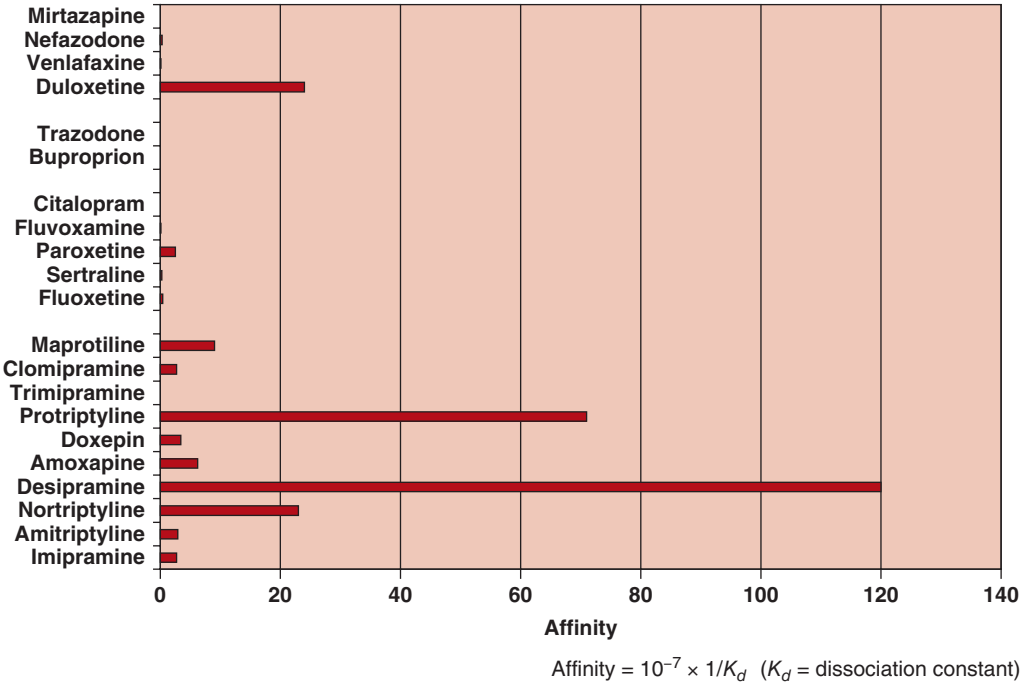



**Figure 101–6** *Relative potencies of antidepressants for blocking the reuptake of norepinephrine. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

alpha-1-receptor is responsible for postural hypotension. In the elderly or medically ill, this postural hypotension can be significant, and lead to dizziness or falls. It may also be responsible for ejaculatory delay or impotence. Other potential effects include reflex tachycardia and memory dysfunction. The relative affinities of antidepressants for blocking alpha-1-adrenoceptors are compared in Figure 101–7.

### *Serotonin*

Potentiation of serotonin can cause anorexia, nausea, vomiting, diarrhea, "jitteriness," and anxiety. Conversely, potentiation of serotonin has also been associated with weight gain; the mechanism of this action is poorly understood. Akathisia, a syndrome of motor restlessness usually associated with antipsychotics, may also be reported: this may be due to either the general effect of serotonin potentiation or direct effects on the basal ganglia, which may also manifest as an exacerbation of Parkinsonism. Sedation, which has been reported with all SSRIs, appears to be a primary serotonin effect. Insomnia, however, is more common at higher doses, particularly with fluoxetine. Weight gain has also been associated with potentiation of serotonin. A

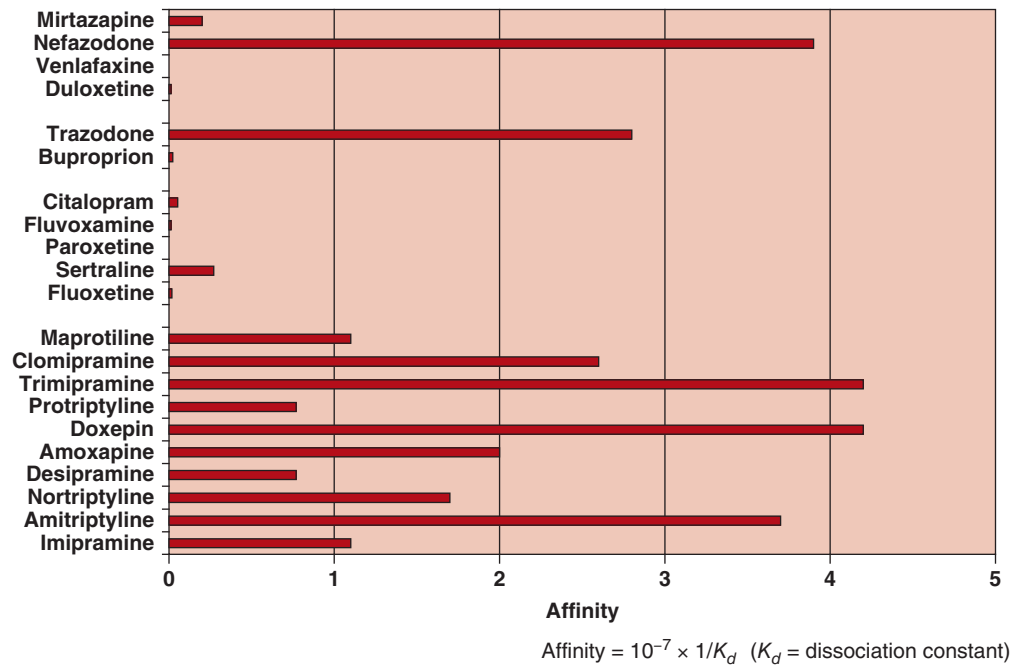



**Figure 101–7** *Relative affinities of antidepressants for blocking alpha-1-adrenoceptors. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

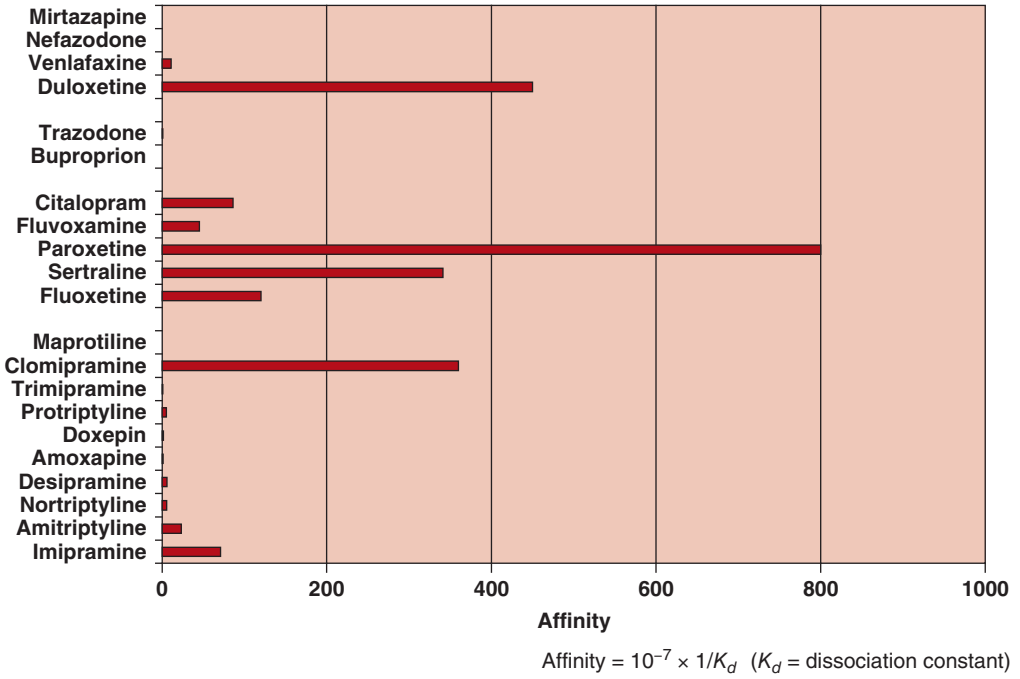



**Figure 101–8** *Relative potencies of antidepressants for blocking the reuptake of serotonin. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

number of sexual side effects have been attributed to serotonin reuptake blockade, including anorgasmia, ejaculatory difficulties, and even spontaneous orgasms (Yanik 2004). The relative potencies of antidepressants for blocking the reuptake of serotonin are compared in Figure 101–8.

### *Receptor Antagonism*

Blockade of the 5-HT2 receptors may result in hypotension and ejaculatory disturbances. Antagonism of serotonin receptors may also be responsible for weight gain and carbohydrate craving. Potency for blockade of this receptor (specifically of the 5-HT2A receptor) is compared in Figure 101–9.

### *Dopamine*

Increases in dopamine resulting from reuptake blockade can have an anti-Parkinsonian effect. It can also cause psychomotor activation and aggravation of psychosis. The relative potencies of antidepressants for blocking the reuptake of dopamine are compared in Figure 101–10.

### *Receptor Antagonism*

The blockade of dopamine receptors can result in extrapyramidal symptoms. These symptoms include cogwheel-type rigidity, tremor, dyskinesia, masked facies, and acute dystonia. Prolonged dopamine blockade appears to be responsible

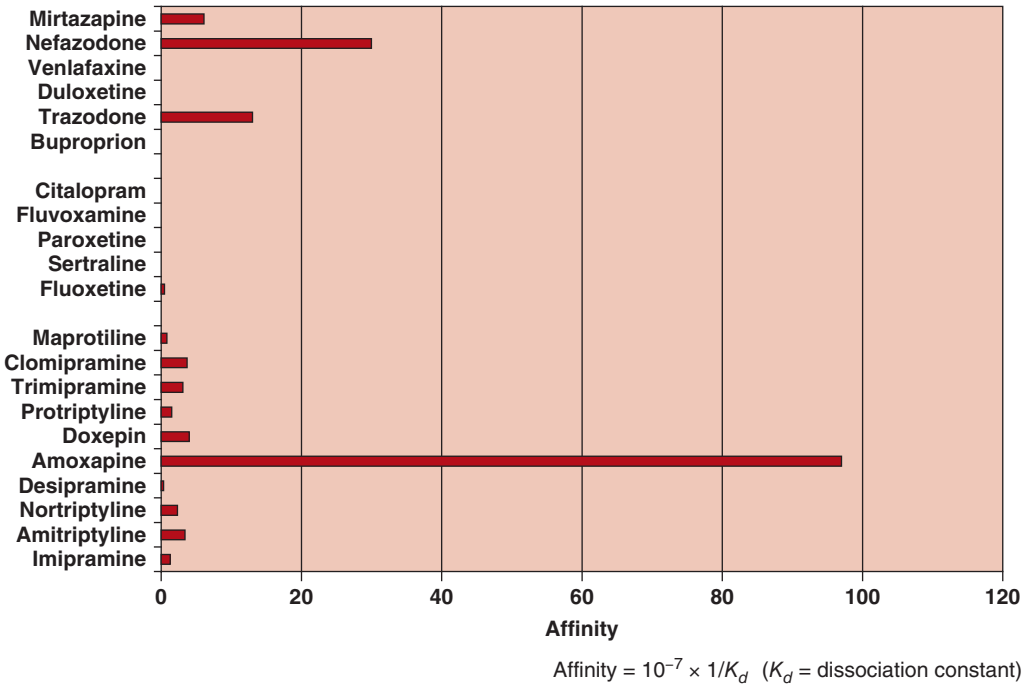



**Figure 101–9** *Relative affinities of antidepressants for blocking 5-$HT_{2A}$ receptors. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

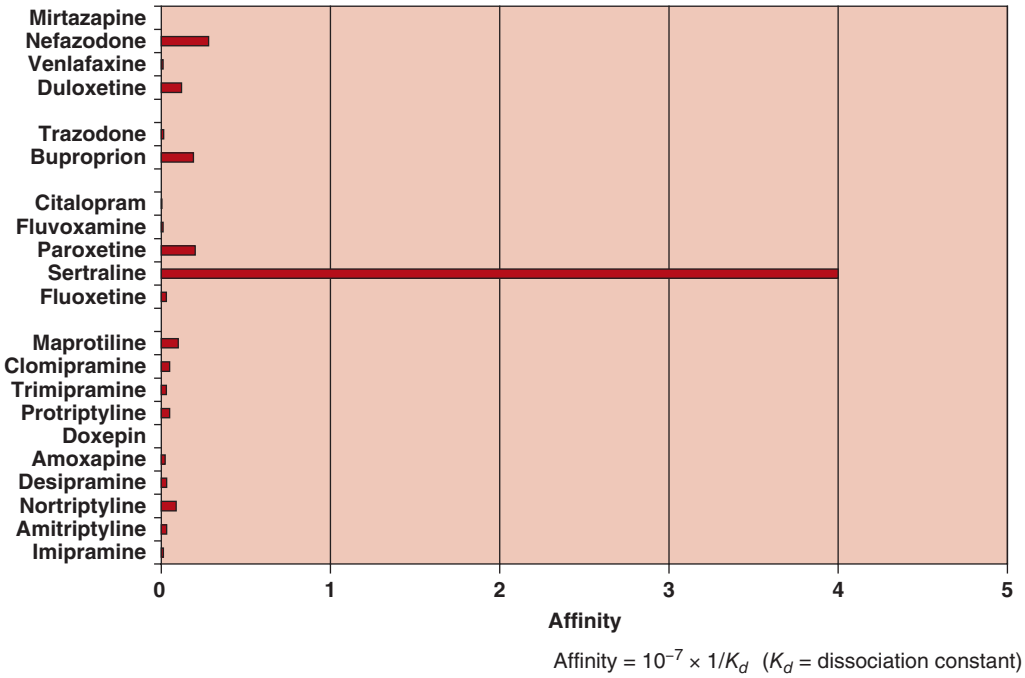



**Figure 101–10** *Relative potencies of antidepressants for blocking the reuptake of dopamine. (Source: Richelson 2001, Wong et al. 1993, Bymaster et al. 2001.)*

for tardive dyskinesia. Dopamine receptor blockade has also been associated with endocrine changes and sexual dysfunction. The relative affinities of antidepressants for blocking dopamine receptors are compared in Figure 101–11.

### *Monoamine Oxidase*

MAO is the main enzyme responsible for the metabolism of monoamines. There are two main types of MAOIs, identified as types A and B. Type A is selective for serotonin and norepinephrine, and accounts for 80% of the MAO in the brain. Type B selectively deaminates phenylethylamine. Both forms oxidize dopamine and tyramine.

### *Dietary Restrictions*

The dietary restrictions required when using MAOIs represent the major limitation to widespread use of these effective antidepressants. Nonselective inhibition of MAO prevents the normal hepatic metabolism of tyramine-containing foods or sympathomimetic agents. The increased level of tyramine in the circulation stimulates the release of norepinephrine from sympathetic terminals. This sudden increase in norepinephrine is the basis for the "tyramine–cheese" reaction,

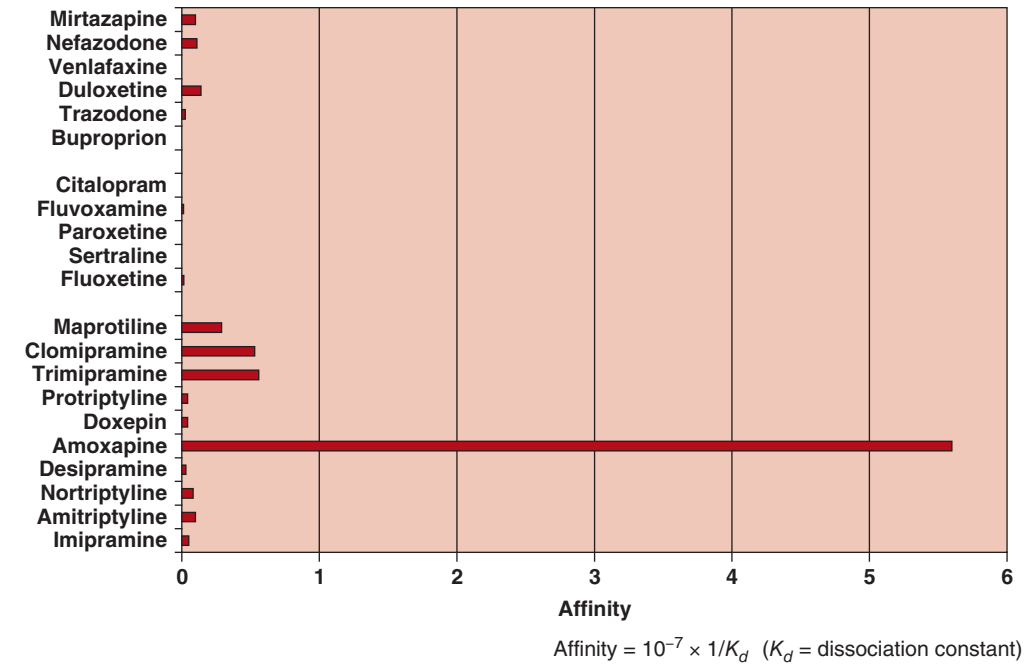



**Figure 101–11** *Relative affinities of antidepressants for blocking dopamine receptors.*

so named because cheese is the most common source of the tyramine that causes this reaction. In fact, other pressor amines, such as levodopa, can also cause the reaction, but tyramine—a natural product of food fermentation and bacterial decarboxylation—is the most common in foods. The result of a tyramine–cheese reaction can be a hypertensive crisis. Thus, patients should be well educated as to the foods that must be avoided while using MAOIs. In the past, there has been a tendency toward conservative dietary restrictions, often based on single case reports or indirect analogies. More research and experience have suggested that not all the foods commonly restricted are equally likely to precipitate a reaction. Better compliance is likely if a more reasonable diet is prescribed.

Despite the best of preparation, some patients may err and suffer a hypertensive crisis. This is often experienced as a severe, pulsating, occipital headache that then generalizes. It may be alleviated with 10 mg of nifedipine, either oral or sublingual.

MAOIs can cause an increase in standing systolic blood pressure, absent of tyramine-containing foods, or sympathomimetics. Generally, this effect is not clinically significant; however, serious unprovoked hypertensive episodes have been reported (Lavin et al. 1993), and blood pressure should be monitored for 1–2 hours after beginning or increasing an MAOI. Hypotension is also a reported effect of MAO, but the mechanism is not known. MAO inhibition can also cause sedation or overstimulation. Once again, the mechanism of this is not well understood.

### *Membrane Stabilizing Activity*

TCAs have effects on cardiac conduction that are independent of anticholinergic or noradrenergic effects. Destabilization of the cardiac membrane can cause dysrhythmia and asystole, particularly in overdose.

## Idiopathic Effects

### *Allergic Reactions*

Allergic reactions can occur with any of these agents. Effects include dermatological (rashes, urticaria, photosensitivity, pigmentation changes, and Stevens–Johnson syndrome) and hematological (agranulocytosis) sensitivities. Fluoxetine has been associated with bleeding, inflammation, and, most seriously, a fatal systemic vasculitis. It should be stopped if a rash develops.

In most cases of allergic reactions, the primary treatment is to stop the agent. On occasion, granulocyte colony stimulating factor has been used to treat allergic agranulocytosis (Rajagopal et al. 2007).

### *Liver Effects*

Abnormal liver function tests have been associated with a number of antidepressants, which can be independent of dose. The risk for such effects may be worsened by chronic alcohol or anticonvulsant use.

Even though sudden liver effects are possible for most antidepressants, the greatest concern is with nefazodone, which is reported to cause liver failure resulting in death or transplant in 1 in 250,000 to 300,000 patient-years of nefazodone treatment (Schwetz 2002). This rate is approximately 3–4 times the background rate of liver failure. This can occur suddenly, and in individuals with previously normal liver functioning. In response to this information, the FDA required the manufacturer of nefazodone to add a "black box" warning to nefazodone's prescription information. The brand version of nefazodone was subsequently discontinued. It remains available in generic formulations.

### *Seizures*

A preexisting seizure disorder increases an antidepressant's likelihood of precipitating a seizure. Other predisposing factors include a family history of a seizure, an abnormal pretreatment electroencephalogram, brain damage, previous electroconvulsive treatment, abuse or withdrawal from sedatives, alcohol or cocaine, and concurrent use of CNS-activating medications. Seizures may be more likely to occur early in treatment, or after a large escalation in dose.

The risk of seizure with TCAs is usually reported as 0.1%. This incidence applies to outpatients, without predisposing factors for seizures, receiving low to moderate doses of medications.

SSRIs appear to have a lower incidence of seizures; however, the evidence for or against an increased risk of seizures in this group is inadequate for any definitive conclusion. In one chart review of 538 patients with deliberate self-poisoning with antidepressants, seizures were more common in patients with venlafaxine overdose than in patients with TCA or SSRI overdose (Whyte et al. 2003).

Bupropion is thought to have a higher rate of seizures, approximately 2–4 times that of other antidepressants. Again, however, the data are limited. Two open-label studies of bupropion treatment for 8 weeks found rates that were similar to that reported for other antidepressants (Johnston et al. 1991, Dunner et al. 1998). Bupropion's effect on the seizure threshold has never been directly compared with other antidepressants.

### *Precipitation of Mania*

Antidepressants have been associated with the precipitation of mania and rapid cycling bipolar disorder. This appears to be most common in patients with a preexisting history of mania. For those with unipolar depression, it is thought likely that many had undiagnosed bipolar disorder (Chun and Dunner 2004). Compared with TCAs, the risk appears lower with second- and third-generation agents; however, the precipitation of mania has been reported with all antidepressants. It seems to occur coincident with the time of antidepressant effect (Wada et al. 2006). In one prospective randomized trial of second- and third-generation antidepressant use for bipolar depression, venlafaxine had the highest rate of mania switch, and bupropion had the lowest (Leverich et al. 2006). Some research points to a particular polymorphism of the serotonin transporter as predisposing to this side effect (Mundo et al. 2001).

### *Sexual Dysfunction*

A variety of sexual side effects can be caused by antidepressants, and they can affect all aspects of sexual response. Thus, antidepressants can decrease libido, increase impotence and anorgasmia, and cause delayed or retrograde ejaculation.

All antidepressant have the potential to cause sexual side effects.

In a large natural study of patients in primary care, Clayton et al. (2002) found that SSRIs, mirtazapine and venlafaxine, had the highest rates of sexual dysfunction (36–43%), and bupropion had the lowest (22% for the immediate release formulation, and 25% for the sustained release). However, other studies with similar methodology have found surprisingly different rates of sexual dysfunction. It must be acknowledged that investigating the prevalence of sexual dysfunction in antidepressants is complicated by the baseline rate of sexual dysfunction in the general population and the higher prevalence in patients suffering from depression (Balon 2006). The most common antidepressant-related side effects are delayed orgasm or anorgasmia.

Though these side effects may in part be receptor mediated, at least some degree seems to be iatrogenic and not dose related. As such, sexual side effects can occur at even low therapeutic doses, and dose reduction may not be possible. A change of agent may be the only alternative.

Trazodone has been associated with penile priapism; the risk is around 1 in 6,000 to 8,000 men. Although rare, it is notable that a third of these cases required surgical intervention, and some resulted in permanent impairment. Clitoral priapism has been reported as well (Pescatori et al. 1993). The actual cause of these sexual dysfunctions is not clear, although some of these effects may result from anticholinergic, presynaptic alpha-2-adrenergic, or serotonergic effects.

### *Miscellaneous*

Fine tremors have been noticed with both TCAs and SSRIs. Although the mechanism is not clear, serotonin reuptake inhibition may be involved. Excessive sweating has been associated with both fluoxetine and paroxetine. The syndrome of inappropriate secretion of antidiuretic hormone has been seen with fluoxetine, as well as with a number of other antidepressants. SSRIs have been reported to cause alopecia, usually at higher doses of the medication. Although antidepressants are often used to treat headaches, they have on occasion been reported as causing both migraine and nonmigraine headaches. These reports should be tempered by the fact that headaches are a frequent nonspecific complaint both in depressed and normal individuals, and the relationship may not always be causal.

One should always be alert to the possibility of rare, undiscovered allergic reactions. For example, the subsequent discovery of serious hepatic and hematological effects caused the withdrawal of nomifensine well after the drug's approval.

## Drug–Drug Interactions

Drugs can affect other drugs in a variety of ways. These can be divided into pharmacodynamic and pharmacokinetic interactions. Pharmacodynamic reactions involve the propensity of one drug to affect the ability of another drug to bind to its target receptor. An example of this may be found with the TCAs, which may compete with other drugs for binding sites.

Pharmacokinetic interactions involve the ability of one drug to influence the pharmacokinetics (absorption, distribution, rate of metabolism, and elimination half-life) of another drug. One way in which this can happen is through binding. Many of the antidepressants are protein bound. If another drug is introduced that has an affinity for the same binding site, the result may be the displacement of a drug and a subsequent increase in the free drug concentration. This effect may be counteracted by a compensatory increased elimination of the now freed drug, thus the overall effect of protein binding may be hard to predict.

The most common drug–drug interaction with antidepressants is their influence on the metabolism of other drugs. Antidepressants are metabolized through catabolic enzymes located in a variety of places, but primarily in the smooth endoplasmic reticulum of hepatocytes: the cytochrome P450 (CYP) enzymes. Many other drugs are also metabolized through similar pathways: it is estimated that about half of all drugs prescribed depend on CYP for their metabolism. Indeed, CYP is a ubiquitous enzyme, present not only in humans, but also in all animals, plants, bacteria, and fungi. There are a number of CYP enzymes, and multiple alleles for each. These are catalogued and updated by the Human Cytochrome Committee, whose Web page can be found at www.cypalleles.ki.se.

In humans, most drugs are metabolized by the enzymes CYP3A4 (50%) and CYP2D6 (20%). Other clinically important CYP enzymes include CYP2C9, CYP2C19, and CYP1A2; the latter is found in the brain and it may affect CNS distribution of antidepressants.

CYP2D6 is probably the best studied of these enzymes. It can have multiple mutations, due to an autosomal recessive trait known as "debrisoquine polymorphism" (debrisoquine is an antihypertensive, in the same chemical class as guanethidine, and its metabolism by this pathway is well understood). Thus, a person can be phenotypically an "extensive," "intermediate," or "poor metabolizer" (Bradford 2002). These phenotypes account for much of the pharmacokinetic variability among individuals taking the numerous drugs oxidized by this pathway. Poor metabolizers can have unusually long half-lives for these drugs and a higher risk of toxicity. Extensive metabolizers, on the other hand, can have great difficulty in achieving therapeutic levels with standard doses. The different phenotypes are found in different ratios across various racial and ethnic groups and these differences are summarized in Figure 101–3.

## First-Generation Antidepressants

### *Tricyclic Antidepressants*

As with any combination therapy, the side effects described previously can be additive with other similar drugs. Most problematical are the anticholinergic effects of the TCAs. Such cholinergic—particularly muscarinic—blockade is a property shared by many other medications, including numerous over-the-counter preparations. The general sedative properties of these medications can also augment any soporific. The slowing of cardiac conduction can also potentiate other medications that produce similar effects, such as type IA antiarrhythmics and anticholinergic medications. Adrenergic receptor blockade can worsen the orthostatic hypotension caused by other medications, including vasodilators and low-potency antipsychotic medications.

### *Pharmacokinetic Effects*

Absorption of TCAs can be inhibited by cholestyramine, which therefore must be given at different time intervals than the antidepressants. TCA levels can be raised by

substances that inhibit enzyme activity, and lowered by substances that induce it. Specific substances reported to increase TCA levels include fluoxetine, antipsychotic medications, methylphenidate, and cimetidine. Enzyme "inducers" that can lower TCA levels include phenobarbital and carbamazepine. The nicotine from cigarettes can also induce enzyme activity.

Guanethidine is contraindicated with TCAs, as it relies on neuronal reuptake for its antihypertensive effect. Clonidine, a presynaptic alpha-2-receptor noradrenergic agonist, is also contraindicated, as it works in an antithetical fashion to TCAs.

### *Monoamine Oxidase Inhibitors*

As with the dietary proscriptions, any medication that increases tyramine can precipitate a hypertensive crisis. Such medications include numerous over-the-counter preparations for coughs, colds, and allergies. The same rule applies to sympathomimetic drugs (such as epinephrine and amphetamines) and dopaminergic drugs (such as anti-Parkinsonian medications).

The combination of MAOIs and narcotics—particularly meperidine—can cause a reaction that varies from symptoms of agitation and hyperpyrexia to cardiovascular collapse, coma, and death. Originally, this was thought to be the result of inhibition of meperidine metabolism; however, it now appears more likely that the reaction is a type of serotonin syndrome (described in the next section), as meperidine inhibits serotonin reuptake (Latta et al. 2002). A similar reaction can occur with any potentiator of serotonin (such as an SSRI).

Similar to the dietary restrictions, some of the drug restrictions associated with MAOIs are based on little actual data. Best established are the restrictions against the combination of MAOIs with amines, meperidine, dextromethorphan, hypoglycemic agents, L-Dopa, reserpine, tetrabenazine, and tryptophan. TCAs are frequently included on this list as causing a "central excitory syndrome" in combination with MAOIs, although the two have been combined safely.

## Second-Generation Antidepressants

### *Selective Serotonin Reuptake Inhibitors*

SSRIs are potent inhibitors of the CYP2D6 pathway, and the drug–drug interactions that can result from this have been the subject of a number of books and articles. As such, an in-depth discussion is not possible in this chapter, and some concerns will be briefly discussed. The reader is also referred to our earlier discussion of CYP-related drug interactions.

SSRIs can slow the metabolism of any drug that is also metabolized by that pathway. Such drugs include TCAs, carbamazepine, phenothiazines, butyrophenones, opiates, diazepam, alprazolam, verapamil, diltiazem, cimetidine, and bupropion. Paroxetine appears to be the most potent inhibitor of this metabolic pathway, with fluoxetine also showing high potency. Sertraline is a somewhat less potent inhibitor. These pharmacokinetic interactions are best managed with dosage adjustment.

Particular caution should be used when a patient using multiple medications starts an SSRI, as the interactions with other drugs can cause dangerous increases in levels. For example, in the cardiac patient, levels of warfarin should be monitored as fluoxetine can raise the levels of these and other medications.

A single case report suggested that fluoxetine could raise lithium levels; however, this was not replicated in controlled studies combining lithium with various SSRIs (Lane et al. 1997). A more practical concern is the risk of serotonin syndrome, as lithium can potentiate serotonergic function.

### *The Serotonin Syndrome*

This syndrome occurs when an SSRI is combined with another drug that can potentiate serotonin. In theory, any drug or combination of drugs that have the effect of increasing serotonin levels to the point of overwhelming normal mechanisms of metabolism or reuptake can precipitate the syndrome (Lane et al. 1997). The result is serotonin toxicity, which can include cognitive–behavioral changes (delirium, agitation), autonomic dysfunction (abdominal pain, nausea, vomiting, diarrhea, hyperpyrexia, diaphoresis, tachycardia, hypertension), and neuromuscular abnormalities (see Table 101–3). Some of the most severe reactions have been the result of combining MAOIs with SSRIs, and such a combination can result in coma, cardiovascular shock, and death. For this reason, a clearance period is required before switching between an SSRI and an MAOI. Switching from fluoxetine to an MAOI is particularly difficult, given fluoxetine's long clearance time—about 6 weeks. Clearance is considerably more rapid for most of the other SSRIs, and a 2-week "wash-out" period is advised when changing from one of these agents to an MAOI.

### *Other Second-Generation Antidepressants*

Few reports exist of interactions with other drugs and trazodone, although trazodone may increase levels of digoxin, phenytoin, and possibly warfarin. Trazodone can theoretically contribute to a serotonin syndrome, and some reports of serotonin syndromes due to the combination of trazodone and an SSRI have been reported (Lane and Baldwin 1997). Bupropion causes few drug–drug interactions. The

**Table 101–3 Criteria for the Serotonin Syndrome**

A. Following the initiation or increase of a serotonergic agent, at least three of the following symptoms are found:

- Agitation
- Mental Status Changes (Confusion or hypomania)
- Myoclonus
- Hyperreflexia
- Diaphoresis
- Shivering
- Tremor
- Diarrhea
- Incoordination
- Fever

B. Other potential causes of these symptoms (infection, withdrawal, substance abuse) have been ruled out.

C. These symptoms are not associated with the initiation or increase of an antipsychotic medication (i.e., it is not neuroleptic malignant syndrome).

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main interactions reported have occurred when bupropion is combined with another dopaminergic agent, the combination of which can cause restlessness and agitation.

### Third-Generation Antidepressants

Venlafaxine does not substantially inhibit the CYP enzymes, and is not highly protein bound; thus it tends to have few clinically significant drug–drug interactions. Duloxetine is both a substrate and a moderate inhibitor of CYP2D6, and is metabolized by CYP1A2. Both venlafaxine and duloxetine can potentially contribute to a serotonin syndrome. Nefazodone is highly protein bound, and has several active metabolites. It is also a strong inhibitor of CYP3A4, and affects other drugs also metabolized by that pathway; however, it has little affinity for the CYP2D6 enzyme. Mirtazapine is highly protein bound as well, but only weakly affects the cytochrome enzymes.

## Initiation of Treatment

### Choosing a Drug

On average, all antidepressants are equally effective. Although an individual patient may preferentially respond to a certain antidepressant, it is difficult to predict this in advance. Without a personal or family history of such a response, side effects are the most influential factors in choosing an agent. Side effects may be particularly relevant in the following groups of patients.

### Elderly Patients

#### *Pharmacokinetic Concerns*

Two pharmacokinetic changes are of great importance in aging patients: decreased efficiency of the hepatic microoxidase system and a decreased muscle–fat ratio. Decreased efficiency of hepatic microoxidases results in the slower metabolism of antidepressants and other drugs. Normal increases in body fat and a loss of muscle mass result in an alteration of the volume of distribution for a substance. Thus, lipophilic drugs—including all antidepressants—are more widely distributed in the elderly body.

Both the resulting slower metabolism and the increased volume of distribution increase the half-lives of the various antidepressants. The elderly, therefore, are likely to have a greater incidence of side effects. This concern is underscored by several studies that have found an increased risk of fractures in patients taking antidepressants. A meta-analysis of 16 studies estimated the relative risk to be 1.6 (Takkouche 2007), which was higher than the risk for benzodiazepines and antipsychotics.

The half-lives and steady state concentrations of the SSRIs are only minimally affected by age. Paroxetine may be an exception to this, and it may have an increased half-life in the elderly.

#### *Pharmacodynamic Concerns*

Numerous changes in the densities and sensitivities of various receptors have been reported; the clinical significance of most of these changes is not well understood. The assumption that elderly patients require lower blood levels of antidepressant medication is not correct. Although pharmacokinetic concerns may require lowering of the medication dose, plasma levels are comparable to those in young adults.

#### *Efficacy*

A number of antidepressants have been studied in the elderly. The consensus is that antidepressants are just as useful in the elderly as in younger adults. Most studies have been done in elderly patients who would be considered "young-old," and the patients studied are generally in good health. In some cases, the definition of "elderly" in the studies is extended to as young as 55 years of age. As such, the elderly patients used in efficacy studies may not be representative of elderly population.

Of the studies in the medically healthy elderly, there is some support—albeit limited—for the efficacy of virtually all antidepressant agents. Most TCAs (Salzman et al. 1993) and all SSRIs (Altamura et al. 1989, Guillibert et al. 1989, Cohn et al. 1990, Dunner et al. 1992) have been studied in this population. Few studies have looked at longer term results, although some studies have documented the usefulness of TCAs for the continuation (Reynolds 1992) and maintenance phases (Old Age Depression Interest Group 1993) of treatment. The SSRI paroxetine was also shown to be useful in a continuation study of depressed patients over the age of 70 (Reynolds et al. 2006). Several studies compare the use of different second- and third-generation agents in the elderly, including various combinations of fluoxetine, sertraline, paroxetine, mirtazapine, bupropion, and venlafaxine. In general, most comparative studies show equal efficacy for different agents when used in the elderly.

Few studies have looked at antidepressants in the frail elderly. One controlled trial demonstrated the superiority of nortriptyline to placebo in very old and frail elderly patients (Katz et al. 1990); however, a significant percentage of the patients studied could not tolerate nortriptyline's side effects. Another study compared venlafaxine with sertraline in frail elderly nursing home patients, and found that patients on venlafaxine had significantly more side effect and discontinuation rates (Oslin et al. 2003). The large number of patients lost to follow up limited the validity of this study.

Although these studies are promising, a number of elderly depression studies have not found antidepressant effects. One comprehensive review of antidepressant treatment in the elderly identified only 17 studies of sufficient methodological strength with a combined total of fewer than 2,000 patients. Of this group, 54% received SSRIs or placebo, 36% TCAs or placebo, and 8% received MAOIs or placebo. Pooled analysis found that each drug was superior to placebo; however, the effect sizes were often disappointingly low (Wilson et al. 2006).

In summary, it appears that antidepressants are effective in the elderly; however, there is a good deal less evidence in the elderly than in younger adult populations. An additional concern is that the elderly may have more difficulty tolerating these medications.

### Medically Ill Patients

Few studies are available on the pharmacological treatment of depression in medically ill patients, and even less on medically ill elderly patients. At least one attempt at studying

this population was discontinued because of the difficulty in recruiting such unstable patients. Although it has been suggested that depression in the setting of medical disease (or "secondary" depression) is less responsive to antidepressants than "primary" depression, few studies exist to inform this suggestion. One systematic review published in 2003 found only 18 randomized controlled studies investigating antidepressant efficacy in depressed patients with comorbid medical illnesses (Gill and Hatcher, 2003). Until this is better understood, it seems ill advised to withhold treatment for depression because of comorbid medical illness. In initiating such treatment, the physician should understand the effects of various illnesses on pharmacokinetics and the potential side effects that may result.

### *Cardiovascular Patients*

There is a high rate of depression in patients who have had a myocardial infarction, and the presence of depression adversely affects the prognosis of cardiac disease. It is important to appreciate this point, as a premorbid cardiac condition can cause concern about potential antidepressant side effects, which may delay the treatment of the depressed cardiac patient. Though some concerns may be justified, they must also be weighed against the potential morbidity from under treatment of depression in the cardiac patient.

**Tricyclic Antidepressants.** The major cardiovascular side effect of TCAs is orthostatic hypotension. This can be clinically significant in both the hypertensive patient and the elderly patient. TCAs can more than double the risk of hip fractures in these patients (Ray et al. 1987). Some of the TCAs have a lower risk of orthostatic hypotension, notably nortriptyline and doxepin.

TCAs do not show a negative inotropic effect and do not seem to worsen congestive heart failure. Patients with congestive heart failure may, however, be at a higher risk for orthostatic hypotension. Again, nortriptyline is the safest TCA in this case.

TCAs slow conduction at the bundle of His. Their effect is analogous to type 1A antiarrhythmic agents such as quinidine and procainamide. In therapeutic doses, they can slow cardiac conduction and in overdose they can cause atrioventricular blockade. These effects are of most concern in patients with preexisting cardiac conduction defects. The majority of research in this area has been done by Roose and Glassman (1989). They believe that the group at greatest risk for conduction defects from TCAs has either a bundle branch block (right or left), or a significant intraventricular conduction defect (QRS interval > 0.11 seconds). There is no evidence that any one TCA is safer than another.

Certain findings may further limit the role of TCAs in heart disease. A large multicenter study found that type 1A antiarrhythmics can increase the risk of mortality among patients with ventricular arrhythmias. Data also suggest that antiarrhythmic drugs cause increased mortality in atrial fibrillation as well (Glassman et al. 1993). As a result, Glassman et al. (1993) recommend caution when using TCAs in all patients with ischemic heart disease.

**Selective Serotonin Reuptake Inhibitors.** The SSRIs differ from the TCAs in that they do not prolong the PR or heart wave (QRS) interval. Thus, they probably lack any of the proarrhythmic and antiarrhythmic activities associated with TCAs. They do not cause orthostatic hypotension.

Several large-scale studies have investigated the safety and efficacy of SSRIs in cardiac patients. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) tested the use of sertraline in 369 patients with acute myocardial infarctions or unstable angina (Glassman et al. 2002). They found that the antidepressant improved depressive symptoms in patients with severe depression, and found no adverse cardiac effects. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial looked at a use of citalopram and interpersonal therapy in 284 patients with coronary heart disease, and found citalopram to be efficacious and safe in that population (Lesperance et al. 2007).

Such data are reassuring and suggest that SSRIs are likely safe in cardiac patients. What is needed next are large studies to determine whether treatment of depression improves the course of cardiac disease, as has often been suggested.

**Other Agents.** Trazodone has less proarrhythmic effect than the TCAs. However, there have been reports of trazodone-related ventricular ectopy and complete heart block (Martyn et al. 1993). In patients with preexisting heart disease, bupropion does not appear to affect conduction, contractility, or orthostatic hypotension. It has rarely been reported to cause palpitations. Of most concern is that, when it is used as an antismoking agent in combination with a nicotine transdermal system, it can increase blood pressure as high as 6% (Khawaja and Feinstein 2003). Venlafaxine can rarely increase the QT interval and cause conduction defects. Its most common cardiac effect is an increase in blood pressure, which can be significant at higher doses (> 300 mg/day). In one study, the mean diastolic increase was 7 mm of Hg after 6 weeks of treatment (Khawaja 2003). Duloxetine appears to have a similar effect as venlafaxine on blood pressure (Westanmo et al. 2005). Mirtazapine can rarely cause bradycardia and orthostatic hypotension, owing to its alpha-blocking activity.

### *Poststroke Depression*

Three placebo-controlled studies of antidepressant treatment in patients who have had a cerebral vascular accident (CVA) have been published; all suggest that antidepressants are superior to placebo. Of interest is Robinson et al.'s (2000) study, which suggested that patients with CVAs preferentially responded to the TCA nortriptyline over the SSRI fluoxetine. Not all studies have confirmed this finding, and the results may in part reflect the original group assignments.

The question has also been raised whether antidepressants should be used to prevent poststroke depression. A review of 10 studies examining this question (Anderson et al. 2004) concluded that there were inadequate data to justify the preventive use of antidepressants.

### *Cancer*

Although there is a good deal written about the need to treat depression in patients with cancer, there are surprisingly few studies of the pharmacotherapy of depressed patients with cancer. Of the randomized controlled studies that are available, two investigate mianserin (Van Heeringen

and Zivkov 1996, Costa et al. 1985), one investigates the TCA imipramine (Evans et al. 1988), and one compares desipramine with fluoxetine (Holland et al. 1998). Among the SSRIs, paroxetine has been investigated in a randomized controlled study (Raison and Nemeroff, 2000), although many of the newer drugs have efficacy data from open trials and case studies. In general, all of the studies above conclude that antidepressants are safe and effective in cancer patients.

### *Renal Impairment*

The interaction between renal impairment and TCAs is variable, with some studies reporting increased levels of TCAs in renally impaired patients and others reporting little change. Fluoxetine's, fluvoxamine's, and sertraline's blood levels are relatively unaffected by renal impairment. However, paroxetine's maximum plasma concentration was increased by 100–150% in subjects with renal disease (Rasmussen and Brosen 2000). Conclusions from these data are limited as they were all single dose studies, and all of these drugs have nonlinear pharmacokinetics. Hence, they may represent an underestimation of the effect of renal disease on drug levels.

### *Hepatic Impairment*

Most antidepressants can cause liver abnormalities. For the TCAs, these abnormalities can range from benign aberrations in biochemical tests to potentially fatal complications, such as hepatitis and cholestasis. Most of the more severe effects are unpredictable and dose independent. As always, the potential morbidity of a depressive relapse—a likely event if effective antidepressant therapy is prematurely discontinued—must be weighed against the risk of precipitating such effects.

Also to be considered is the effect of hepatic disease on the medication. Liver disease can increase the levels of TCAs, and blood levels should be monitored. The literature suggests that the SSRIs are safe in patients with hepatic impairment, but, given their extensive liver metabolism, lower doses are required. In single dose studies, the elimination half-lives of all SSRIs were doubled in patients with cirrhosis (Rasmussen 2000). Though these higher levels may be safe in themselves, they, along with the hepatic impairment, can seriously affect drug–drug interactions in cirrhotic patients who are taking multiple medications. In practice, a one-half dose reduction in patients with cirrhosis is generally recommended by the manufacturers of each drug.

The pharmacokinetics of bupropion appears only minimally affected by alcoholic liver disease (Devane et al. 1990). There have been several reports of hepatic injury associated with trazodone, and one of trazodone-induced chronic active hepatitis in a patient with remote exposure to hepatitis B (Beck et al. 1993).

Given its association with hepatic injury, nefazodone is not recommended for patients with hepatic disease.

### *Endocrine Disorders*

Patients who have an endocrine disorder predisposing them to depression (e.g., hypothyroidism or diabetic hypoglycemia) should first undergo medical stabilization of the disorder before attempting antidepressant treatment. To date, no large-scale trials of antidepressant treatment for depressed diabetic patients exist. Among controlled trials, there exist only two medication studies, one with nortriptyline (Lustman et al. 1997a) and one with fluoxetine (Lustman et al. 2000). Both studies show good effect in treating depression. There is also evidence that treatment of depression in patients with diabetes can improve their diabetic control (Lustman et al. 1997b). Though there has been some concern that antidepressants can cause hyperglycemia (particularly the TCAs), it has generally been shown that glycemic control improves with the use of antidepressants.

### *Iatrogenic Depression*

The list of drugs purported to cause depression is large; however, one systematic review (Patten and Barbuib 2004) concluded that such drugs do not generally cause the symptoms of classic major depression. Several drugs can cause atypical depressive symptoms, these include corticosteroids, interferon-alpha, interleukin-2, gonadotropin-releasing hormone agonists, mefloquine, progestin-releasing implanted contraceptives, and propranolol. In such cases, the most obvious first step is to try to remove the offending agent. However, at times a crucial drug has no practical substitute. An example of this is the concern over interferon-related drugs: the most common reason for discontinuation of interferon is the sudden onset of severe depression, often with suicidal ideation. In a randomized placebo-controlled study with 40 patients, Musselman et al. (2001) found that pretreatment with paroxetine reduced the emergence of interferon-alpha-induced depression in patients with malignant melanoma.

## Suicidal Patients

Much concern was generated by a report of six cases documenting the emergence of sudden, violent suicidal ideation with the administration of fluoxetine (Teicher et al. 1990) and sertraline (Balon 1993). Previous reports of a theoretical relationship between serotonin and violence combined with this single uncontrolled series resulted in a wild speculation—particularly among the popular media and "antipsychiatry" groups—that fluoxetine was a "suicide pill."

Though definitive data are lacking, more recent studies continue to raise concern about the relationship between antidepressants and suicide. Although actual mortality rates from suicide appear to be declining, meta-analyses of randomized controlled trials (Khan et al. 2003, Fergusson 2005) show small but significant associations between antidepressant use and suicidal behavior. One possible explanation of this apparent discrepancy is suggested in a study by Tiihonen et al. (2006) in Finland, who followed over 15,000 patients hospitalized in Finland through a national computerized database. They found that for those subjects who had ever used any antidepressant, the current use of an antidepressant was associated with an increased risk of suicide attempts, and yet a decreased risk of completed suicides.

Because of such studies, along with the previously noted concern over suicidal behaviors in child and adolescent patients, the FDA issued a public health advisory in June of 2005 warning of a possible risk of suicide in adults treated with antidepressants (Food and Drug Administration 2005). In December of 2006, after a further review of available data, an FDA advisory panel voted in favor

of updating "black box" warnings on antidepressants to state that there is an increased suicide risk for young adults up to age 25.

These concerns must be balanced over the well-proven and much greater risk of suicidal ideation and attempts when depression is not treated. Given this, and the propensity of suicidal patients to choose medication overdose as the method of suicide, the wide safety margin of the second- and third-generation antidepressants makes them preferable to first-generation agents when suicide is a concern. Bupropion has generally not been fatal in overdose, although about a third of such cases experience a seizure.

## Starting Doses

### First-Generation Antidepressants

#### *Tricyclic Antidepressants*

TCAs are usually begun at a relatively low dose. For the majority of TCAs, including imipramine, amitriptyline, desipramine, maprotiline, and doxepin, the initial starting dose is in the range of 50–75 mg/day. Notable exceptions include nortriptyline and protriptyline, which are more potent agents. In the case of nortriptyline, the usual starting dose is 25–50 mg/day, and for protriptyline, 10–15 mg/day. The lower doses are preferred in patients who are elderly. In the frail elderly, further dose reductions may be needed (about one-half or less of the usual starting dose).

Once a medication is initiated, it is gradually increased to a therapeutic level. A number of strategies have been suggested for this increase. Most TCAs can be increased to 150 mg/day by the second week, and then to a range of 300 mg/day by the third or fourth week. This can be achieved through small daily increase of 25 mg or weekly increase of 75 mg. Younger patients will tolerate larger and more rapid increases, whereas the elderly benefit from smaller (25 mg/day) and less frequent (every other day) increases with a lower target dose (150 mg/day).

Protriptyline is increased by 5–10 mg/week to a target dose of 60 mg/day. For nortriptyline, increases of 50 mg/week are usually tolerated in the young, with the elderly requiring smaller increases (25 mg/week). Of particular interest is nortriptyline's therapeutic window: doses above and below a certain range appear to be less effective. The effective range is approximately 50–150 mg/day. Plasma blood monitoring (described later in this chapter) can aid determining the proper level.

#### *Monoamine Oxidase Inhibitors*

Phenelzine is usually begun at a dose of 30 mg/day. It is increased by 15 mg after 3 days, then weekly to a target range of 45–90 mg/day. Tranylcypromine is started at 20 mg/day. It is increased by 10 mg after 3 days, with additional daily increases of 10 mg after 1 week, to a target range of 30–60 mg/day. Isocarboxazid is usually begun at 20 mg/day. It is titrated in a manner similar to tranylcypromine to a target of 30 mg/day. Selegiline is administered as a transdermal patch: initial dose is 6 mg/day, and then increased to 9 mg/day after 2 weeks. The maximum dose is 12 mg/day (the patch is available in all three doses, and should not be cut).

### Second-Generation Antidepressants

#### *Selective Serotonin Reuptake Inhibitors*

These agents are usually started at the lowest effective dose and increased as indicated by clinical response. Reasonable doses are 20 mg/day for fluoxetine, 50 mg/day for sertraline, 20 mg/day for paroxetine and citalopram, and 10 mg/day for escitalopram. For children, adolescents, the elderly, and patients who find medications generally difficult to tolerate, 50% reductions in these doses are reasonable starting doses.

For fluoxetine, paroxetine, and citalopram, the initial doses should be maintained for 1–2 weeks, after which they can be increased in 10 or 20 mg increments to a dose of 40 mg/day if there is no response. A maximum dose of 60 mg/day of fluoxetine is recommended for the treatment of depression. A similar strategy can be used for sertraline, which can be begun at 25–50 mg, and increased in 25–50 mg increments to a target dose of 50–150 mg. Escitalopram can be increased by 5 mg increments to a maximum of 20 mg/day. Other disorders, particularly OCD and bulimia nervosa, may require higher doses: for example, as high as 80 mg/day for fluoxetine.

As with TCAs, there is a significant delay between initiation of medication and response, and there is no reason to believe that increasing the dose prematurely hastens response.

#### *Other Second-Generation Antidepressants*

Trazodone is generally dosed in a manner similar to TCAs, with starting doses of 50–75 mg/day, and target ranges of 150–300 mg/day, with doses not exceeding 400 mg/day in outpatients and 600 mg/day in inpatients. Unlike many of the TCAs, trazodone's short half-life requires divided doses, usually twice daily.

Bupropion, like trazodone, requires divided doses. It is available in a short acting form that requires three times a day dosing, an intermediate form that allows twice-daily dosing, and a long acting form that allows once-daily dosing. The starting dose is 100–150 mg/day, and increased to a recommended dose of 300 mg/day; however, in patients not responding to that dose, it can be increased to 450 mg/day. If taking the immediate release preparation, patients should avoid taking more than 150 mg in a single dose. In the elderly, doses are usually begun at half that for adults, although full adult doses may be needed for effect.

### Third-Generation Antidepressants

#### *Venlafaxine*

Originally available in a short acting form that required twice-daily dosing, it is currently available in a slow release preparation that enables once-daily dosing. Venlafaxine is usually begun at a dose of 37.5 mg and is increased within 1/2 to 1 week to a dose of 75 mg. If further increases are needed, it can be titrated at a rate of 75 mg every 4 days or more. Although a maximum dose of 225 mg per day is recommended by the manufacturer, doses as much as 300–450 mg/day have been employed to good effect in some patients.

### *Mirtazapine*

Adults should be started on a dose of 15 mg/day. It is usually given as a before bedtime dose. The dosage generally needs to be increased in 15-mg intervals every 1/2 to 1 week to a target dose. The effective dose is usually between 15 and 45 mg/day; however, higher doses such as 60 mg have been useful in some patients.

### *Nefazodone*

Nefazodone is given in twice-daily doses. Patients can be started at a dose of 100 mg twice daily and increased at a rate of 100–200 mg a week. The recommended effective dose is 300–600 mg/day.

### *Duloxetine*

The recommended dose of duloxetine for major depressive disorder is 40–60 mg/day, given either once a day or in divided doses twice daily. Higher doses are used for diabetic neuropathy: from 60 mg/day to 60 mg twice a day.

## Therapeutic Drug Monitoring

Although blood levels are available for many antidepressants, those for imipramine, desipramine, and nortriptyline have been best established. Imipramine and desipramine appear to have a curvilinear dose–response curve with an optimal range of 150–300 ng/mL. Nortriptyline appears to have a therapeutic window in the range of 50–150 ng/mL. These blood levels are nominal, as some patients do respond above or below these ranges, and blood level monitoring should not be a substitute for clinical observation.

Drug levels have not been well established for the MAOIs.

A review of therapeutic monitoring for SSRIs (Rasmussen et al. 2000) concluded that such monitoring is not clinically useful, as most studies have not found a correlation between plasma levels and clinical response. In addition, the studies have not shown a threshold level for toxic effects.

# Phases of Treatment

Treatment can be divided into several phases. At each phase, the goals of treatment and the potential pitfalls differ. These phases are illustrated in Figure 101–12 and described below.

## Early, or Preresponse, Period

Patients should initially be followed weekly to judge their response to treatment. The goal at this point is to manage the side effects of the various medications. Given realistic time and economic constraints, such contacts may at times be by telephone. However, it remains crucial that patients feels that they can communicate freely with their doctors regarding any side effects or other concerns about the medications. This is of great importance as such side effects are a primary reason for treatment nonadherence, and patients may be more inclined at this early phase to simply discontinue medications rather than to first discuss it with their physicians.

It can be difficult to persuade a depressed patient to remain on medication. Perhaps the greatest intervention at the disposal of the physician is reassurance. It is inevitable that patients will experience some side effects from their medications. Patients are able to tolerate this better when properly prepared. The patients may tolerate these side effects better when they are framed in a positive light—as a sign that the drug is present in their system.

The side effects can become intolerable, and reassurance may be inadequate. Several strategies for mitigating side effects can be considered. Many side effects are decreased or eliminated through dose reductions or changes in the dosing regimen. SSRIs, through scored capsules or liquid preparations, can be begun at one-half or one-fourth their normal starting dose in patients who are particularly sensitive to side effects. The TCAs, although often given in a single-daily dose, could be divided across the day to minimize dose-related side effects. Taking medications with food may decrease nausea. Although most physicians are aware that sedating medications should be taken in the evening, and activating ones in the morning, the patient may need these strategies reinforced. Flexibility is required as well; for example, a significant percentage of patients taking SSRIs experience sedation rather than insomnia, and this would warrant a change to evening dosing. However, the practice of starting the "less activating" SSRIs (such as paroxetine and citalopram) in the evening a priori seems unjustified as they still cause significant insomnia.

Failing these approaches, adjunctive agents may be employed to minimize the side effects. Anxiolytics can be added to treat the arousal and insomniac effects of the SSRIs. Although these adjunctive agents can be continued for the duration of treatment, discontinuation should be attempted after several weeks of treatment because many of the side effects may be limited to the early phase of treatment. The dry mouth caused by TCAs (and some newer agents) can be treated with saliva substitutes, although more mundane salivary stimulants such as sugar-free hard candy may be just as effective. Over-the-counter bulk-forming

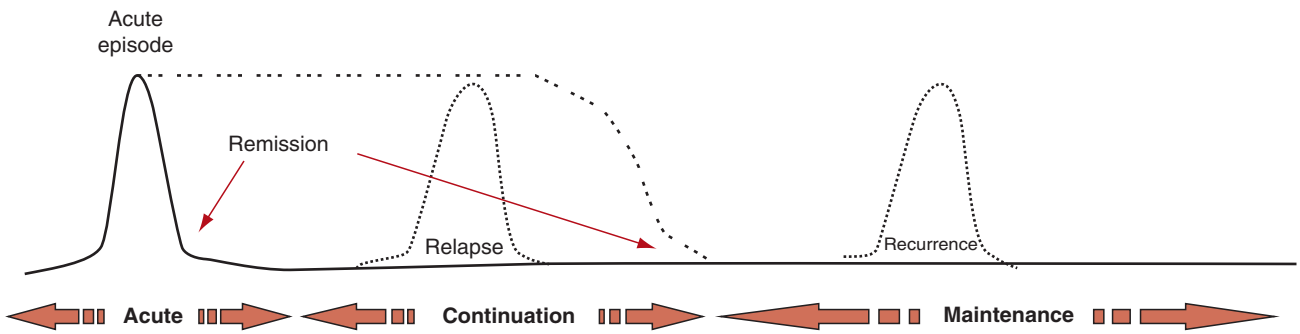



**Figure 101–12** *Phases of treatment.*

laxatives can treat the constipation caused by some agents (particularly TCAs but also seen with some newer agents). The cholinergic agonist bethanechol has been used to treat anticholinergic side effects, particularly urinary hesitancy and blurred vision. The usual adult dosage is 10–50 mg three to four times a day. Pilocarpine eye drops have been used to treat the blurred vision as well.

Intolerable side effects may warrant a change in medication. If side effects are the only reason for medication change, it is reasonable to choose a medication in the same class as the first, but with a different side effect profile. Anecdotal evidence suggests that patients can have variable reactions to different SSRIs despite their apparent similarity. For example, a patient who experiences significant anorgasmia with one SSRI may find little or no side effects with an equipotent dose of an alternative SSRI. The reasons for such an idiosyncratic response are not clear, but do encourage the physician to try to stay within a single class of drug if the initial response has been favorable. When switching from one SSRI to another, cross tapering is generally not necessary, as the substances are usually similar enough to prevent discontinuation syndromes, although occasionally patients will report discontinuation symptoms when switching; in such cases, a brief taper may be indicated.

## Response, or Acute Treatment, Period

This period overlaps with the initial phase of treatment and continues until response is achieved, and usually lasts from 2 to 4 months. The goal during this phase is to control the acute symptoms of depression.

It is important to differentiate between partial and complete response. Complete response implies total recovery from all symptoms of depression, whereas a partial response is usually defined as a reduction in symptoms.

The time to response varies with the patient. Classically, it has been reported that patients will not show a significant response to antidepressants before 2 weeks, and often have to wait 3–6 weeks for a response. However, some recent data, based on meta-analyses of placebo-controlled trials have challenged this rule, finding that most patients show significant improvement within the first week, and then gradually continue to improve over 6 weeks (Taylor et al. 2006). This meta-analysis has been supported by other similar analyses and some prospective studies (Katz et al. 2006). If this is true, it will have enormous implications both for clinical practice, and for basic research into mood disorders (which has generally concentrated on the delayed effects of antidepressants as being the fundamental ones).

For patients who complete a satisfactory treatment regimen, the response rate for antidepressants is about 60–70% (American Psychiatric Association 2000b), although some of these responses will be partial. Response rates may be as high as 80% with antidepressants when an adequate dose is given for an adequate time.

Changes in treatment strategy should be considered after the physician is satisfied that the patient has been treated with an adequate dosage of the antidepressant for an adequate time. The American Psychiatric Association (2000b) recommends waiting at least 4 and as much as 8 weeks before changing a treatment strategy. For the patient showing inadequate response, these medications are increased to the limit of side effect tolerance before attempting a new strategy.

In patients showing an inadequate response after a reasonable time, the physician must decide whether to continue with the same medication and augment with an additional agent, or to switch medications altogether. This decision depends on an assessment of whether the patient has shown any response to the current strategy. Partial responders may be more likely to benefit from treatment augmentations, whereas patients who show no response or worsen during treatment warrant a new agent.

### Strategies for No or Inadequate Response

There are several approaches to an incomplete or nonresponse. These include maximizing current treatment, augmenting the treatment, or switching to an alternative agent. These strategies are discussed in more detail in the Section "Treatment Failure."

## Continuation Period

This period usually lasts 5–8 months after the end of the acute treatment period. The goal at this phase is the prevention of relapse. There is a high risk of relapse if treatment is discontinued after the acute treatment phase. Keller et al. (1982) found that the two best predictors of relapse were a high number of previous depressive episodes (greater than 3 predicted relapses) and underlying dysthymic disorder.

Once a patient has responded to a medication, the medication should be continued for a minimum of 4–6 months, beginning from the point of initial response. The World Health Organization (1989) recommended 6 months as a minimum period for continuation of treatment after the acute phase, and the American Psychiatric Association (2000b) recommended a minimum of 16–20 weeks of treatment following the full remission of symptoms. This period should be lengthened for the patient with a history of longer depressive episodes.

Few studies exist that look at the efficacy of antidepressants for continuation therapy. However, there exists at least one placebo-controlled study for each of the SSRIs (Montgomery et al. 1988, 1993, Montgomery and Dunbar 1993, Doogan and Caillard 1992), nefazodone (Feiger et al. 1999), mirtazapine (Montgomery et al. 1998) venlafaxine (Nemeroff et al. 2002), and duloxetine (Perahia et al. 2006). These studies are summarized in Table 101–4.

In the past, it was suggested that, on achievement of euthymia, doses could be reduced. However, it is more likely that levels similar to those needed at the acute stage of treatment will be required throughout the continuation period.

## Discontinuance of Treatment

After the continuation period, somatic therapy is usually discontinued in the patient with a single episode of major depression. Before discontinuing, however, it is important to remember that depression is often a lifelong disease with a chronic course. One should always weigh the benefits of discontinuance against the risks of recurrent depression.

In the past, a distinction between exogenous and endogenous depression was used to predict the risk of recurrence. Inferences about etiology, however, are not an accurate predictor of recurrence. More useful information is the age of onset during the initial episode and the number of episodes. Patients with a single episode of acute depression,

**Table 101–4 Continuation Studies of Antidepressant Medications.***

| Drug | Weeks of Treatment | Relapse (Drug) (%) | Relapse (Placebo) (%) | *P* Value |
|---|---|---|---|---|
| Fluoxetine | 52 | 26 | 57 | < 0.01 |
| Paroxetine | 52 | 16 | 43 | < 0.001 |
| Sertraline | 44 | 13 | 46 | < 0.001 |
| Citalopram | 24 | 11 | 31 | < 0.05 |
| Escitalopram | 36 | 26 | 40 | < 0.01 |
| Mirtazapine | ~30 | 4 | 28 | < 0.05 |
| Nefazodone | 36 | 17 | 33 | < 0.05 |
| Bupropion | 52 | 37 | 52 | < 0.004 |
| Venlafaxine | 52 | 33 | 54 | < 0.01 |
| Duloxetine | 38 | 23 | 39 | < 0.05 |

*See text for references.

who have an onset before age 50 years, are the best candidates for discontinuance (Greden 1993).

### Tapering and Withdrawal

For the TCAs, the usual strategy is to taper the medications at a rate of 25–50 mg/day every 2–3 days. Too rapid a discontinuation may produce symptoms of cholinergic "rebound" or supersensitivity. Such a rebound includes severe gastrointestinal symptoms (nausea, vomiting, and cramping), other signs of autonomic hyperactivity (diaphoresis, anxiety, agitation, headaches), and insomnia (often with vivid nightmares). In severe cases, a full delirium may result. Cholinergic rebound may occur as early as 48 hours or as late as 2 weeks after discontinuation. These symptoms may account for some cases of presumed early relapse from antidepressant discontinuation.

MAOIs may also have a withdrawal syndrome, including symptoms of psychosis, on abrupt withdrawal; however, this syndrome is rarer than that seen with TCAs.

Fluoxetine has a long half-life, and abrupt discontinuation should be permissible. Sertraline, citalopram, paroxetine, and escitalopram, with shorter half-lives of around a day, may require several weeks to taper. With the shorter acting agents, a withdrawal syndrome including symptoms of fatigue, insomnia, abdominal distress, and influenza-like symptoms has been reported when they are too abruptly discontinued.

Venlafaxine and duloxetine have both been reported to have discontinuation symptoms; venlafaxine with its shorter half-life appears to have the most severe version. The symptoms are similar to SSRI discontinuation, but may include symptoms of an anticholinergic rebound as well, particularly if the patient was receiving high doses of the medication.

On discontinuance, the goal is to enable early intervention should symptoms recur. A first episode of depression has a high risk of recurrence, and the risk of recurrence is even higher in patients who show only partial response to medication. The patient should be educated to recognize symptoms of depression. The patient's own history suggests which symptoms were prodromal to the patient's full depressive episode.

## Maintenance Period

The goal of the maintenance period is to prevent the recurrence of depression. There are a number of reasons to consider long-term prophylactic therapy for depression rather than medication withdrawal. Depression is a lifelong disease, with recurrence being the norm rather than the exception (Keller and Boland, 1998). As the number of acute episodes increases, the risk of future episodes increases as well, and the interval between episodes shortens. Each subsequent episode carries a higher morbidity and disability.

A number of factors can influence the decision of when it is appropriate to maintain long-term prophylaxis for depression. The seriousness of previous episodes, the severity of impairment caused by such episodes, the degree of response to previous treatments, and the ability of the patient to tolerate the drug all play a role. Central in the decision process is the concept of recurrent depression that some patients are more likely than others to have a recurrence of the disease. Three previous episodes of depression make recurrent depression likely. The best predictors of the likelihood of recurrence appear to be older age of onset and number of episodes. Greden (1993) proposed that long-term maintenance is the treatment of choice for the following groups of patients: (1) those who were at least 50 years old at the time of the first depressive episode, (2) those who were at least 40 years old at first episode and had at least one subsequent recurrence, and (3) anyone who had more than three episodes.

The recommended length of maintenance treatment needs further clarification as well. Recommended lengths of time vary from 5 years of treatment to indefinite continuation. There are only a handful of studies on maintenance antidepressant treatment. One study (Prien et al. 1984) compared patients successfully treated for acute major depression, who were then randomized to a medication or placebo group for 2 years. The imipramine groups (with and without lithium) had the longest time until a recurrence, with the lithium group having an intermediate time until recovery. A second study (Kupfer et al. 1992), the longest of any such study, compared medication (imipramine) with and without psychotherapy to placebo, for 3 years, with a continuation of 2 years for a subset of the group for a total of up to 5 years. This study provided strong evidence for the efficacy of antidepressant medication: by the end of 3 years, most of the placebo group had relapsed, whereas a substantial portion of those patients on imipramine (about 80%) remained well. In the 2-year extension of the study, those patients

who had remained well were randomized to imipramine or placebo, and, again, most of the patients on placebo had a recurrence of depression, whereas the majority of those on medication did not.

A more recent study looked at the use of venlafaxine in patients with recurrent depression. Subjects who continued to be treatment responders after 10 weeks of acute treatment and 6 months of continuation treatment were randomly assigned to receive either venlafaxine extended release or a placebo. After 1 year of maintenance treatment, it was found that the placebo group was twice as likely to have a recurrence of major depression as the venlafaxine-treated group (Kocsis et al. 2007).

These studies were in patients with recurrent depression. Another indication for maintenance treatment is for patients with chronic depression. Again, few studies have looked at this population for a sufficient time, but what studies exist do support the efficacy of antidepressants in this population. One such study compared sertraline with placebo for maintenance treatment of depression (Keller et al. 1998), and found that the placebo group was four times more likely to have a recurrence than the medication group.

Regarding choice of an agent, there are no rigorous studies comparing different antidepressants during the maintenance period. It is usually assumed that the same agent used in the acute and continuation period will be the preferred one in the maintenance period.

### Summary

Despite limitations in data, it is reasonable to believe that most agents used for the acute treatment of depression are also effective for long-term treatment of depression.

Equally important in preventing recurrence of depression is the problem of maintaining adherence to medication long after the acute episode has resolved. Proper education and support will help with compliance. Toleration of side effects is important and evidence suggests that patients are more likely to comply with the agents that have more favorable side effect profiles. The SSRIs are generally the best tolerated antidepressants.

Although lower doses for prophylaxis have been recommended, there are few data to support this contention. Even though lower doses may increase compliance, full doses should be used until new information indicates otherwise.

## Outcome Assessment

The results of a treatment are simplest to judge when the treatment focuses on clear goals. At the time of initiating pharmacotherapy for depression, the physician should document what particular symptoms justify a diagnosis of depression. The outcome of treatment can then be judged against these symptoms. Often a patient will report still feeling "depressed" and yet show observable symptom improvement.

Although clinical judgment remains the mainstay of treatment assessment, this judgment can be reinforced with a number of well-validated scales. These scales can be either interviewer-rated or self-rated scales. Some scales are more (or less) reliable in certain groups, such as the aged, or the medically ill.

### Clinician-Rated Scales

Perhaps the most widely used scale is the Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960); a clinician-rated scale that requires some training to be performed properly. The Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) has good inter-rater reliability and high validity for severity. It shows high sensitivity to change, which would be useful in monitoring the progress of treatment, and it appears useful in patients with comorbid somatic illnesses.

### Self-Rated Scales

Self-rated scales can be easier to use and less time intensive—a patient can be filling them out while waiting for an appointment; however, they are generally less reliable than clinician-rated scales. Self-rated scales include the Beck Depression Inventory (BDI) (Beck 1978) and the Zung Depression Scale (Zung 1965). These scales, which test for a number of somatic symptoms of depression, may be less reliable in medically ill or elderly populations. The Geriatric Depression Scale (GDS) (Yesavage et al. 1983), a self-report questionnaire, is specifically intended for initial screening in the elderly. Such scales have largely been avoided in clinical practice because of added time and relative impracticality of such scales. However, the wider acceptance of computer-assisted devices, particularly palm held personal assistant devices could make such scales practical.

## Treatment Failure

Failure to respond to treatment is most often due to inadequate treatment rather than "true" nonresponse. Inadequate treatment can be due to an inadequate length of treatment or an inadequate dose. These can result from the physician's error (either improper dosing strategies or impatience in waiting an appropriate amount of time) or the patient's error (through misunderstanding or nonadherence).

Patients may not report these errors as they fear rejection from treatment, and they certainly are unlikely to admit to it if their physician does not ask them. The best remedy for nonadherence is prevention, through proper education of the patient about likely side effects that might otherwise unnerve the patient. A flexible approach is also necessary. Gentle reassurance and encouragement can be helpful; however, dogmatic insistence on adherence to a prescription leaves the patient with no choice except to hide nonadherence, or look elsewhere for treatment.

Thus, "true" nonresponse can be defined as the lack of response to an adequate dose for an adequate time. In the case of such failure, a number of issues should be examined.

### Diagnostic Issues

The physician should reconsider the patient's diagnosis. A number of medical conditions can cause some depressive symptoms without actually causing depression. In such cases, the symptoms are unlikely to abate with treatment of the primary disorder. Similarly, a number of other psychiatric disorders have symptoms that overlap with depression, including the anxiety disorders and personality disorders. Fortunately, many of these other diagnoses may respond to antidepressants; however, this is not always the case, and therapy targeted at the alternative disorder may be preferable.

### Psychotic Depression

The physician should also consider whether the patient has a type of depression that would predict a poor response. Psychotic depression is an example of a condition less likely to respond to antidepressants alone. Psychotic depression is usually treated with either combination pharmacotherapy (an antidepressant and an antipsychotic) or electroconvulsive therapy.

### Strategies for Treatment-Resistant Patients

In most cases, there should be some response by 3–4 weeks. When patients report a partial response, the treatment may simply be to wait and follow the response; as long as there remains evidence of gradual improvement, no further intervention is necessary.

In cases in which little or no response is seen, a new trial of an alternative agent should be considered. It is generally believed that the best strategy is to change to an alternative class of agent. However, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the particular type of switch did not seem to effect the remission rates: changing from one SSRI to another had the same rate as a change to venlafaxine or bupropion (Rush et al. 2006). The study also suggested that a switch after a first treatment failure makes sense; however, the remission rates for single agent strategies decline significantly after two treatment failures—at that point augmentation or combination strategies should be considered.

## Treatment Augmentation

For a partial response, with no sign of continued improvement, treatment augmentation can be of benefit. Possible augmentation strategies include lithium augmentation, thyroid hormone augmentation, stimulant augmentation, and the use of a second antidepressant.

### Lithium Augmentation

Lithium augmentation has the best evidence as an augmentation strategy. It is generally begun in low doses (300 mg twice a day) and increased to a therapeutic blood level (0.6–1.3 mEq/L). It can take about 3–6 weeks for a response.

### Thyroid Hormone

Thyroid hormone supplementation can be helpful, even in cases in which the patient is clearly euthyroid. It is usually begun at 25 μg/day of triiodothyronine, and increased to 50 μg/day if needed, and can take at least 3 weeks to show an effect. In the STAR*D trial, T3 augmentation appeared to be as helpful as lithium, and it was better tolerated (Nierenberg et al. 2006).

### Stimulants

Among the stimulants, methylphenidate and dextroamphetamine have been used successfully, and there are some preliminary data supporting the use of newer agents such as modafinil to potentiate antidepressant response.

### Atypical Antipsychotics

Atypical antipsychotics have also been shown useful for augmentation: one study demonstrated that olanzapine combined with fluoxetine had greater efficacy than either agent did alone in treatment-resistant patients (Shelton et al. 2001).

### Combining Antidepressants

A common clinical practice is to combine antidepressants in different classes in the hope of augmenting response by combining effects. The support for this practice is limited, and mostly limited to case studies, case series, and open studies (Rojo et al. 2005). However, the data are promising. As noted earlier, the STAR*D study included an arm using combined venlafaxine and mirtazapine for patients who had failed three previous single antidepressant trials (McGrath et al. 2006). Remission rates were modest (~14%) but encouraging for this group as this was a highly treatment-resistant group of patients.

### Psychotherapy

The use of nonpharmacological augmentation should be considered as well, and any patient showing an inadequate response to medication alone should be considered for psychotherapy. A large number of studies have supported the use of combination psychotherapy and medication for depression, and in some cases the combined effect is dramatically better than medication or therapy alone (Keller et al. 2000).

### Electroconvulsive therapy (ECT)

ECT remains a safe and effective nonpharmacological treatment. Indications for ECT include a history of poor response to medication, a prior good response to ECT, a need for rapid response (as with life-threatening depressive symptoms, e.g., food refusal or suicide attempts), psychotic depression or a medical contraindication to antidepressants.

### Other Somatic Therapies

A number of other nonpharmacological somatic therapies show promising preliminary results, including transcranial magnetic stimulation, vagal nerve stimulation, and deep brain stimulation, and these may offer additional alternatives for the treatment-resistant patient.

Strategies for treatment-refractory patients are summarized in Table 101–5.

## Conclusions

There remain a number of important limitations regarding the pharmacotherapy of depression. Some of these limitations can be addressed by continued progress on current research. Other limitations await truly novel research into the mechanism of depression.

## Recommendations for the Use of Antidepressants

Allowing for the many limitations, one can generalize from available data to make the following recommendations:

1. All patients with acute major depression should be considered reasonable candidates for pharmacotherapy.
2. There is adequate evidence to make the same recommendation for other forms of depression. This is particularly true for dysthymia, and may be true for other minor forms of depression as well.

**Table 101–5 Therapeutic Options for Treatment-Refractory Depressed Patients.**

| Treatment | Efficacy | Replicability |
|---|---|---|
| Lithium augmentation of antidepressants | +++ | +++ |
| Electroconvulsive therapy | +++ | +++ |
| Thyroid ($T_3$) augmentation of antidepressants | ++ to +++ | ++ |
| Stimulant augmentation of antidepressants | + to ++ | ++ |
| TCA and MAOI combination | + | ++ |
| TCA and SSRI combination | + | + |
| Venlafaxine + Mirtazapine | ++ | ++ |
| SSRI and atypical antipsychotic combination | +++ | ++ |
| High-dose MAOI | ++ | + |
| Transcranial magnetic stimulation | ++ | + |
| Antiglucocorticoid therapy | + to ++ | + |
| Estrogen | 0 to + | ++ |
| Vagus nerve stimulation | ++ | + |
| Psychosurgery (Deep Brain Stimulation) | ++ | + |

Efficacy ratings: 0, ineffective; +, slightly effective; ++, moderately effective; +++, very effective;

Replicability ratings: +, primarily based on open studies or pilot studies; ++, several controlled studies support, but further investigation needed; +++, multiple controlled studies with consistent results.

3. There is good evidence for the use of antidepressants for nonmood disorders as well, particularly the anxiety disorders.
4. There remains no strong evidence from choosing one medication over another, and treatment recommendations should be made based on tolerability and, if appropriate, cost.
5. Extended treatment should be recommended both for patients with chronic depression and recurrent depression.
6. Maintenance treatment should consist of the same dose of antidepressant as used to achieve acute phase remission.
7. The exact length of maintenance treatment is not known. The decision for indefinite treatment should be a risk–benefit decision, made with the informed consent of the patient, who is entitled to be informed of the limitations in our knowledge.

## Future Pharmacotherapies

A number of potential antidepressants are in various stages of development. Any listing of such compounds is likely to change rapidly and likely to be obsolete by the time this chapter is published: as little as 5 in 5,000 compounds that enter preclinical testing ever make it to human testing, and only 1 of these 5 is approved for sale. This list, however, does provide some insight into what types of drugs one can expect to see in the next decade.

### Variations on Current Themes

Many of the new drugs will be similar to current drugs. Some will be directly based on currently available drugs (e.g., desvenlafaxine). Others will be novel chemicals that potentiate norepinephrine or serotonin. As an example, the drug Lu AA21004, is a novel compound (a bis-aryl-sulphanyl amine). Although it is the first of a new class of drug, it appears to be another approach to serotonin agonism, having action both on serotonin receptors and on the transporter molecule. Some drugs of these types that are currently in development are listed in Table 101–6.

### Drugs Targeting Substance P

Substance P, a neuropeptide, is an agonist of neurokin-1 (NK-1) receptors in the CNS. Substance P is released in response to fear, and the NK-1 receptor is found in high concentrations along the brain's anxiety circuitry. In animal models, administration of substance P agonists can produce fearful and defensive behaviors. In humans, the administration of NK-1 receptor antagonists shows anxiolytic and antidepressants effects. The substance P antagonist MK-869 showed comparable efficacy to paroxetine in a trial of patients with major depressive disorder and moderate anxiety (Kramer et al. 1998). Most significantly, the drug did not appear to interact with monoamine systems in a way typical of standard antidepressants, suggesting a novel mechanism of action. This is supported by basic research that shows increased levels of substance P in cerebrospinal fluid, and changes in those levels in response to acute stress (Geracioti et al. 2006). Though the initial enthusiasm was dampened by some disappointing results in subsequent pharmaceutical trials, a number of NK antagonists remain in development and are listed in Table 101–6.

### Drugs Targeting the HPA Axis

Investigators have looked at the role of endocrine hormones in affecting depression. This is a reasonable inquiry given the long appreciated finding of hypothalamic–pituitary–adrenal axis dysfunction in depressed patients. The HPA axis is intimately involved in the stress response. The majority of patients with depression demonstrate hyperactivity of the HPA axis, leading to increased production of corticotrophin-releasing factor (CRF) by the paraventricular nucleus of the hypothalamus. This results in reduced feedback inhibition by CRF and glucocorticoids (which is the basis of the dexamethasone suppression test). Normalization of the normal functioning of the HPA axis appears to be necessary for successful treatment of depression. Strategies at decreasing the hypercortisolemia in such cases have led to investigations with a variety of cortisol-lowering agents, including ketoconazole, metyrapone, and aminoglutethimide (Zoumakis et al. 2006), which have all had preliminary success in depressed patients, but have been limited by side effects. A preliminary open study of the CRF r-1 antagonist r-121919 showed promise as well, but the drug has been withdrawn because of potential liver toxicity (Zobel et al. 2000). Glucocorticoid antagonists can mitigate the effects of hypercortisolemia, and the agent RU486 (Murphy et al. 1993) has shown promising preliminary results. Vasopressin (VP) can also regulate the HPA axis in that stress can release VP, which then potentiates CRF. A number of CRF and glucocorticoid antagonists and at least one VP receptor antagonists are currently under development and are listed in Table 101–6.

**Table 101–6 Drugs under Development (compiled 12/06)***

| Drug Name | Pharmacologic Action | Developer | Indication | Developmental Phase (US) |
|---|---|---|---|---|
| | | **Drugs Targeting Monoamine Transmitters and Receptors** | | |
| Pristiq® (DVS-233 SR, desvenlafaxine) | Metabolite of venlafaxine | Wyeth | Depression, anxiety | Received "Approvable" letter from FDA on 1/07 |
| Gepirone ER | 5-HT1A partial agonist | Fabre-Kramer | Depression, anxiety | Supplemental New Drug Use form submitted 4/07 |
| Amibegron, SR 58611 | beta-3-adrenoceptor agonist | Sanofi-Aventis | Depression, anxiety | Phase III |
| Valdoxan (agomelatine, S-20098) | 5-HT2C antagonist, 5-HT2B antagonist, melatonin M1/M2 receptor agonist | Servier, Novartis | Depression, anxiety, sleep disorders | Phase III |
| Vilazodone | 5-HT1A partial agonist, serotonin reuptake inhibitor | Clinical Data Online, Inc. | Depression | Phase III |
| PRX-00023 | 5-HT1A agonist, sigma receptor antagonist | Epix | Depression | Phase II |
| DOV 216,303 | DA/NE/5-HT reuptake inhibitor | DOV | Depression, anxiety | Phase II |
| DOV 21, 947 | Dopamine, serotonin, and norepinephrine, reuptake inhibitor | DOV/Merck | Depression, ADHD, restless leg syndrome | Phase II |
| NERI IV | Norepinephrine reuptake inhibitor | Lilly | Depression, ADHD | Phase II |
| TGBA01AD | Serotonin reuptake inhibitor, 5-HT2 agonist, 5-HT1A agonist, and 5-HT1D agonist | Fabre-Kramer | Depression | Phase II |
| GW372475, NS2359 | Dopamine, serotonin, and norepinephrine, reuptake inhibitor | GSK, NeuroSearch | Depression | Phase II |
| Elzasonan CP-448,187 | 5-HT1B and 5-HT1D receptor antagonist | Pfizer | Depression, anxiety | Phase II |
| Lu AA21004 | bis-aryl-sulphanyl modulator (serotonin modulator). | Lundbeck | Depression, anxiety | Phase II |
| TRIDMAC Mecamylamine | Nicotinic receptor antagonist Combined w/ citalopram | Targacept | Depression | Phase II |
| SEP-225289 | DA/NE/5-HT reuptake inhibitor | Sepracor | Depression, anxiety | Phase I |
| 163090 | Mixed serotonin receptor agonist | GSK | Depression, anxiety | Phase I |
| TC-2216 | Nicotinic alpha-4-beta-2 antagonist | Targacept | Depression | Phase I |
| Tyrima | Reversible MAOI | CeNeRx | Depression, anxiety | Phase I |
| | | **Drugs targeting Substance P** | | |
| Saredutant SR 48968 | NK2 antagonist | Sanofi-Aventis | Depression, anxiety | Phase III |
| Casopitant, GW679769 | NK1 antagonist | GSK | Depression, anxiety, emesis | Phase III |
| Vestipitant, GW597599 | NK1 antagonist + paroxetine | GSK | Depression, anxiety | Phase II |
| LY686017 | NK1 antagonist | Eli Lilly | Anxiety | Phase II |
| GW823296 | NK1 antagonist | GSK | Depression, anxiety | Phase I |
| SSR 241586 | NK2 and NK3 receptor antagonist | Sanofi-Aventis | Depression, anxiety, irritable bowel syndrome (IBS), COPD | Preclinical |
| SAR 102279 | NK2 receptor antagonist | Sanofi-Aventis | Depression, anxiety | Preclinical |
| | | **Drugs targeting the HPA axis** | | |
| ORG 34517/34850 | GR antagonist | Organon | Depression | Phase II |
| CP-316,311 | CRF1 antagonist | Pfizer | Depression, anxiety | Phase II |
| BMS-562086 | CRF1 antagonist | Bristol-Myers Squibb | Depression, anxiety | Phase II |
| GW876008 | CRF1 antagonist | Neurocrine/ GSK | Depression, anxiety, IBS | Phase II |
| SSR149415 | V1B(vasopressine) antagonist | Sanofi-Aventis | Depression, anxiety, hyperphagia | Phase II |
| ONO-2333Ms | CRF1 antagonist | Ono Pharmaceuticals | Depression, anxiety | Phase I |
| JNJ-19567470 or TS-041 | CRF1 antagonist | Janssen (Johnson & Johnson), Taisho | Depression, anxiety | Phase I |

*(continues)*

**Table 101–6 Drugs under Development (compiled 12/06)*** *continued*

| | | | | |
|---|---|---|---|---|
| **Drugs targeting the HPA axis** | | | | |
| SSR 125543 | CRF1 antagonist | Sanofi-Aventis | Depression, anxiety, | Phase I |
| – | CRF1 antagonist | Neurogen | Depression, anxiety | Preclinical |
| SSR 126374 | CRF1 antagonist | Sanofi-Aventis | Depression, anxiety, hyperphagia | Preclinical |
| CRF1 antagonist (backup) | CRF1 antagonist | GSK/ Neurocrine | Depression, anxiety | Preclinical |
| **Drugs targeting Glutamate** | | | | |
| PRE703 | MgluR agonist | Prescient | Anxiety | Phase I |
| Delucemine, NPS 1506 | NMDA antagonist | NPS | Depression, stroke | Phase I |
| **Drugs Which May Target Hypothalamic Feeding Peptides** | | | | |
| Lu AA44608 | Neuropeptide Y receptor antagonist | Lundbeck | Depression, anxiety | Phase I |
| Nemifitide INN 00835 | Pentapeptide analog of melanocyte-inhibiting factor (MIF-1) administered intravenously | Tetragenex | Depression | Phase II |
| **Drugs With Miscellaneous, Unknown and Undisclosed Actions** | | | | |
| Miraxion, LAX-101 | "Purified" Omega-3 (EPA) | Amarin | Huntington's disease, depression | Phase II |
| YKP-10A, R228060 | Phenylalanine derivative? | Janssen (Johnson & Johnson)/SK Pharmaceuticals | Depression | Phase II |
| Lu AA24530 | Undisclosed mechanism of action | Lundbeck | Depression, anxiety | Phase I |
| Lu AA34893 | Undisclosed mechanism of action | Lundbeck | Depression, anxiety | Phase I |
| SSR 411298 | FAAH (fatty acid amide hydrolase) inhibitor | Sanofi-Aventis | Depression, anxiety, hyperphagia | Preclinical |
| YKP581 | Undisclosed mechanism of action | SK Pharmaceuticals (Johnson & Johnson) | Depression | Preclinical |

*Source:* James R Becker, http://www.neurotransmitter.net/newdrugs.html.(Used with permission.)

## Drugs Targeting Glutamate

Glutamate serves a general excitatory role in the brain, and both glutamate and glutamate receptors (e.g., NMDA) are assumed to play a central role in the expression of psychiatric illness. That NMDA antagonists may be useful in depression is supported by the observation that ketamine can rapidly improve mood in depressed individuals undergoing surgery (Goforth and Holsinger 2007). In addition, basic research suggests that treatment with antidepressants down regulate NMDA receptors. Direct NMDA antagonists are limited by their psychiatric side effects; however, weaker antagonists are being investigated. Clinical trials with such agents as memantine have had only modest effect to date (Zarate et al. 2006). Agents with a direct effect on glutamate receptors are under development. Examples of drugs targeting glutamate are listed in Table 101–6.

## Drugs Targeting Brain-Derived Neurotrophic Factor (BDNF)

Interest in BDNF initially stemmed from observations that the decrease in hippocampal volume found in stressed rodents seemed to be mediated by BDNF. Depressed patients appear to have decreased levels of BDNF, infusion of BDNF (in rodents) appears to cause depression, and blockade decreases depressive behaviors (Kalueff et al. 2006). However, a variety of practical and theoretical obstacles (the size of the molecule, its multiple roles in various pathways) make direct antagonism of BDNF both difficult and potentially dangerous. Some indirect approaches may be more practical, for example, phosphodiesterases (PDEs) induce BDNF expression in the hippocampus. Agents targeting PDE have been limited by nausea (due to PDE inhibition in the brainstem); however, an attempt continues to find agents that may act preferentially in the hippocampus. Currently, to the best of our knowledge, no drugs using this mechanism have reached the stage of clinical trials.

## Drugs Targeting Hypothalamic Feeding Peptides

A number of the hypothalamic peptides that have a role in feeding behavior also appear to have a role in depression. For example, melanin-concentrating hormone (MCH) stimulates feeding behavior; blockade of the MCH receptor

can produce an antidepressant-like effect in rodents (evidenced by the forced swimming test) (Georgescu et al. 2005). Several other peptides involved in feeding behavior may have a role in depression, including the appetite-stimulating peptides orexin (hypocretin), neuropeptide Y (NPY), and agouti-related peptide (ARP), as well as appetite suppressant peptides, such as melanocortin, cocaine- and amphetamine-regulated transcript (CART), and CRF. The fact that peptides that both stimulate and suppress appetite can be helpful offers a potential clue to the different natures of classical and atypical depression. Examples of drugs targeting these peptides are listed in Table 101–6.

## Other Lines of Development

YKP-10A, a phenylalanine derivative, is presumably being tested because of phenylalanine's inhibitory relationship with tryptophan. Miraxion (LAX-101), a purified form of omega-3 found in fish, seems to act as a neuroprotectant. Although current data refute early hope that it may have a role in cancer prevention, some preliminary work suggests that it is useful in a number of psychiatry disorders, including major depression (Su et al. 2003).

Whether any of these particular approaches will become part of psychiatry's clinical armamentarium is too early to say. Clearly, there is a great motivation for pharmaceutical companies to develop novel products, as it is predicted that by 2010 the many patent expirations will decrease pharmaceutical profits from antidepressants by at least 50%. Such financial predictions should not be the direct concern of the psychiatrist. It is acknowledged, however, that the considerable economic benefits reaped from contemporary antidepressants should provide a strong practical incentive for drug developers to be on the forefront of the next generations of antidepressants.

For the psychiatrist, the promise of new and different approaches to treating depression is exciting. Until recently, research into antidepressants has informed research in depression. In the future, the reverse will have to be true: in order to develop better antidepressants, researchers will have to understand the pathophysiology of depression. With the new investigatory tools available, such discoveries seem right around the corner.

### Clinical Vignette

Ms. W was a 34-year-old married woman who began having depressive symptoms approximately 8 months before presented to a psychiatrist. Initially, she began to notice intense fatigue, weakness, and dizziness, to the point where she was spending a good deal of time in bed. Her primary care doctor tested her for a variety of possible medical disorders, with no abnormalities found. When he suggested an emotional disorder, she initially was reluctant; feeling convinced that her symptoms had to be medical in nature. As further months saw only worsening symptoms, she eventually agreed to psychiatric consultation.

At the time of her first psychiatric evaluation, her main complaint was of insomnia. She described herself as being constantly "on edge" during the day, often exhausted by the end of it, falling asleep briefly in the early evening, but then waking up around 3 a.m., and being unable to fall back asleep. On further discussion, she admitted feeling "miserable" all the time, frequently broke into tears "for no reason." She had no interest in activities, and took no pleasure in anything. She also felt extremely guilty, particularly in her inability to be a mother to her 2-year-old child or a wife to her husband. In the latter case, she reported that her husband was perplexed by her emotions, but was very kind toward her, despite the fact that she frequently took out the bulk of her angry outbursts on him. In the context of her guilt, she had fleeting thoughts that her family would be better off without her, and her fantasies ranged from leaving her husband to suicide.

The diagnosis of depression was again suggested to the patient. She again had difficulty believing this diagnosis, as she saw her physical symptoms as primary. She felt that if she could only "get a decent night's sleep" she would not be so tired, and perhaps would feel better. Antidepressant medication was discussed at that time, but she declined a trial. The agreement was made to continue meeting and discussing this further. In the interim, she approached her family doctor, and received medication for sleep (temazepam).

After 2 weeks of continued misery (despite relatively good sleep) she again met with her psychiatrist. Now desperate, she reluctantly agreed to an antidepressant trial. Various options were discussed with her, and she was clearly very fearful of any medication for which anxiety might be a potential side effect. Eventually, she and her psychiatrist agreed on paroxetine (the patient had seen a television commercial that had convinced her that this medication would be preferable for anxiety). She was prescribed 20 mg/day, taking in the morning.
After 2 days, she called her psychiatrist, saying that the drug was making her mouth dry, and was making her feel tired during most of the day. She worried that this drug was going to turn her "into a zombie" and wondered whether she should stop it. She was encouraged to continue the medication, and her psychiatrist suggested that she should switch to evening dosing to decrease the apparent daytime sedation. She did so, but called again several days later, saying that she felt that the drug was making it hard for her to wake up in the morning. Again she suggested giving up, but was encouraged instead to halve the dose.

When she next met with her psychiatrist, she had been on the drug for 2 weeks. At that time, the side effects seemed to have partially abated. She was discouraged all the same, as her symptoms were largely unchanged. She questioned whether this was the proper drug, and indeed whether she had been diagnosed properly. Various approaches were employed over the next few weeks. Continued education regarding the likely course of treatment was provided. The psychiatrist empathized with her frustration over what seemed a painstakingly slow trial, and gave a somewhat paternal reassurance that he had treated many patients like her. He also reassured her that her impressions were not unusual or a cause for further worry. Frequent reinforcement of these approaches was sufficient to convince the patient to continue the medication trial.

Over the next 2 weeks, the patient felt that there might have been some small improvement. She was somewhat less anxious during the days, and when asked, she admitted that she was crying less. She remained disappointed; however, her most troubling symptoms (the fatigue, weakness, and insomnia) remained, and she still reported her mood as being depressed (a word she was now more comfortably using). Her psychiatrist continued attempting to supply her with the enthusiasm she lacked, explaining that this

*(continues)*

Clinical Vignette *continued*

response at 4 weeks of treatment was a very positive sign. She agreed to a dose increase of 20 mg/day.

The patient then gradually improved over the next few weeks, and within 12 weeks of beginning treatment she could declare herself to be at her baseline. In some ways, she felt that she might even be "improved" from her baseline, saying that she was more assertive with friends and relatives than she was used to being, and would seem euphoric at times. She had more energy than she was used to, and she wondered at times if she was becoming "manic," having heard that this could happen with antidepressants. On further questioning, however, her symptoms suggested nothing more than euthymia.

Soon after she improved, she began to suggest discontinuing medication. She admitted that she felt ashamed that she was taking psychiatric medication, and feared that her friends or relatives might discover what she was doing. The high risk of relapse at this early period was explained to her, and reasons for continuing medication during the asymptomatic period were reviewed with her. Though she agreed to continue, several weeks later she guiltily admitted that she instead discontinued her medication for 3 days, only to restart after feeling what she interpreted to be a relapse. The psychiatrist admitted that time course of her "relapse" combined with her description of the symptoms as "flu-like" made a withdrawal syndrome more likely than a relapse; however, this event was enough to convince her to remain on the medications for the full course.

Some symptoms remained during this period. Although she was largely euthymic, she admitted to continuing dissatisfaction with areas of her life, and she often reported a general sense of a lack of purpose or direction in her life. Similar dissatisfaction was reported when she discussed her marriage, though she now had great satisfaction in her role as a mother. Though psychotherapy had been suggested since the beginning of treatment, she had been even more opposed to it than she was toward medication. Now, she tentatively agreed to meet with a therapist to discuss some of these issues.

As the months passed, the patient's initial dislike for medication changed into more of an ambivalence. Though the patient still voiced wishes to be off medication, she also admitted that she was becoming apprehensive about discontinuing it. After 9 months of medication treatment, she met with her psychiatrist to discuss future options. Though she continued to feel that her episode of depression was her first, she was not as sure whether she had been entirely well before her acute episode. She noted some longstanding, though less dramatic, feelings of pessimism and sadness before taking antidepressants. She had never considered these feelings abnormal until encountering their absence. Despite these concerns, she chose to discontinue her antidepressants, a decision that seemed reasonable to her psychiatrist as well. She again felt some symptoms of withdrawal as the medication was lowered and discontinued; however, these improved over the course of a week.

Four weeks after her discontinuation, she remained well and hopeful that she would not need medication. However, by 2 months she was beginning to notice some returning symptoms. Though she did not experience the dramatic anxiety, dysphoria, and neurovegetative symptoms that first brought her into treatment, she began to feel increasingly "moody," irritable, and apathetic. Her husband noticed this as well, and though he originally had been skeptical of her need for antidepressants, he now began questioning her decision to discontinue them. After one particularly angry incident, in which she began inappropriately yelling at her child, she called her psychiatrist, asking to be put back on her medication. This was done, and she again responded after about 4 weeks of treatment.

In discussions with her psychiatrist now, she became despondent, wondering whether this meant that she would have to remain on medication for the rest of her life. It was admitted that this might be a possibility, particularly as many of her symptoms during the current episode seemed similar to her reported "usual state" before treatment. However, there remained the possibility that the patient had been discontinued too early from medication, and that the current symptoms represented a late relapse of the original episode. It was agreed to continue medication for a minimum of 6 months before again entertaining the idea of a discontinuation.

Though somewhat more resigned to this second period of pharmacotherapy, Ms. W became more critical of the particular medication she was taking. Initially fearful that people would discover she was on medication, she eventually was surprised to find that several of her family and friends were also taking antidepressants. The subsequent exchange of anecdotes left her curious as to whether she was on the best agent. She began to wonder whether some of the weight gain she had experienced (perhaps 5 pounds over the last year) was due to the paroxetine. An even greater complaint became apparent after a discussion between the psychiatrist and the patient's therapist, in which the therapist felt that Ms. W was minimizing her sexual problems, and that this might be an important influence on her frequent requests for the discontinuation of medication. Previously, Ms. W had rarely voiced any sexual side effects to her psychiatrist, and when asked would relate any such problems to her ongoing marital tensions. At this time, a more detailed sexual discussion led to the admission that Ms. W had been largely anorgasmic for the entire time that she had been on the paroxetine. Though she said that she preferred this side effect to a return of her depression, it was clear that the effect was troubling both her and her husband.

Various approaches were taken to improving this side effect. Lowering the dose from 20 to 10 mg/day gave only minor improvement, and she felt that she had some increase in irritability at this lower dose. Adjunctive medications had little effect and were contrary to the patient's reluctance to take medication. Eventually, the decision was made to switch the patient to an alternative medication. As the patient had had a good response to paroxetine, it was agreed that an alternative medication with serotonin reuptake properties would be chosen. However, trials of sertraline and venlafaxine were not successful in decreasing these side effects, and the patient felt that her response to these other medications was less robust than it has been to paroxetine. Paroxetine was eventually restarted. The psychiatrist discussed the possibility of using alternative classes of medication. After these two unsatisfactory trials, however, the patient feared any further changes.

After approximately 2 years of treatment, a second discontinuation was discussed. At this point, the patient was even more reluctant to discontinue, having enjoyed mood stability over most of this period; however, the continuing side effects of anorgasmia and, perhaps, continued weight gain convinced her to try again. This was done, and within 2 weeks after discontinuation she reported normal sexual functioning. She continued to complain of difficulty losing weight, but as her weight seemed to be normal throughout

the 2 years of treatment, the validity of her concerns was difficult to assess. Within 2 months of her discontinuation trial, she again relapsed. Again, her symptoms were minor, consisting of irritability and dysphoria. However, there was a clear change from her state on medication. At this time, the possibility of long-term maintenance was discussed with the patient. Frustrated with yet another relapse, she readily agreed; however, she remained concerned by side effects. Bupropion was suggested as an alternative that has relatively few sexual side effects. Within a month she was taking 150 mg twice daily of the slow release capsule. As was hoped, she did not report any sexual side effect. She did report an antidepressant response to the drug; however, she felt that the response was not as complete as that she had had on paroxetine. Although she was less dysphoric, she had somewhat greater anxiety and irritability with the bupropion.

After a trial of over several months, her psychiatrist suggested combination therapy. It was suggested that the bupropion be continued, but that a small dose of an SSRI be added in the hope that it would address some of these remaining symptoms. Experiences with medication were reviewed, and the patient felt that, of the SSRIs tried, citalopram had had the least sexual side effects, and the closest efficacy to paroxetine. With that in mind, citalopram was begun at a dose of 10 mg/day, and with this combination the patient reported complete response with no return of her previous side effects.

## Case Discussion

Many lessons can be drawn from the above case. Perhaps the most important is that medication management is not a mechanical discipline that can be diagrammed with simple algorithms. All of the skills learned in psychiatric training, both psychopharmacological and psychotherapeutic, are crucial for successful treatment of the patient. In the initial phases of this treatment, the emphasis was on fostering a trusting relationship in a skeptical and fearful patient. This effort translates into a great deal of time spent, both in person and on the telephone. Although, superficially, one might argue against the justification for so much contact during a period when the medication is unlikely to show any benefit, the effort applied was probably the most important intervention during the treatment. Not only was such an effort helpful in fostering adherence during this period, but also it made the negotiation of later challenges much simpler. In the beginning, the psychiatrist had to assume a paternal role, taking on most of the responsibility for the treatment. As the patient improved, this gradually gave way to a much more collaborative effort.

The importance of ongoing education should also be emphasized. Many, if not most, patients who present to a psychiatrist have seen another doctor before this. Education, however, is an ongoing process. Often the bulk of the information is given at the initial phases of treatment—a time when the patients' illness makes them least able to integrate this knowledge. Throughout the treatment, the psychiatrist often had to review and reinforce the treatment strategies discussed originally. Though written material can aid this process, and the patient clearly sought external sources of information, there remains no substitute for educational power in the human interaction.

The inappropriate minimization of sexual side effects during treatment is a problem that has been improving, through education of both patients and physicians. Patients are often reluctant to bring up sexual issues, and quick or vague inquiries regarding sexual functioning may be insufficient to elicit such symptoms. Inattention to this is unfortunate, as sexual side effects are a major reason for discontinuing medication that has otherwise been very effective. In this case, the patient's therapist first understood the importance of this side effect. This underscores another point: in cases where the medication treatment and psychotherapy are split, it is crucial that there be frequent and regular contact between the treatment team.

Finally, cases like this emphasize the art as well as the science of pharmacotherapy. Though some treatment-related decisions have a clear scientific basis, others are more rooted in judgment and experience. Certainly, the switch to bupropion to minimize sexual side effects has a clear pharmacodynamic rationale. However, the subsequent adjunctive use of an SSRI likely relied less on science, and more on the psychiatrist's experience in interpreting the irritability as a symptom that might be more amenable to a serotonergic agent. Though the practice of clinical medicine should be informed by research, the greatest clinicians are still those unique individuals who can integrate research into their own observations and wisdom.

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CHAPTER

# 102 Antipsychotic Drugs

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## Introduction

The therapeutic armamentarium for the treatment of schizophrenia and related psychotic disorders has grown and diversified in the half century since the advent of chlorpromazine, the prototypical first-generation antipsychotic (FGA). A primary aim of antipsychotic drug development has been to obtain compounds with a broader efficacy profile, targeting positive, negative, cognitive, and affective symptoms while inducing fewer extrapyramidal symptoms (EPS). The introduction of clozapine and other second-generation antipsychotics (SGAs) partially achieved this aim and, at present, many clinicians prescribe SGAs (excluding clozapine) as first-choice agents for acute and maintenance therapy for psychotic disorders. A number of randomized, controlled trials (RCTs) suggest that SGAs may offer some advantages over FGAs, such as fewer acute EPS; less tardive dyskinesia (TD); and possibly improvement in negative, affective, and cognitive symptoms. The aggressive marketing of SGAs has contributed to their increased use and has expanded clinical expectations. Accordingly, SGAs are being increasingly prescribed for nonpsychotic conditions, with or without empirical support, as happened with FGAs (Miyamoto et al. 2003a). However, recent meta-analyses and government-funded, large-scale, practical clinical trials have provided conflicting information about the relative advantages of FGAs and SGAs (Davis et al. 2003, Geddes et al. 2000, Jones et al. 2006, Leucht et al. 2002, Lewis et al. 2006b, Lieberman et al. 2005a, McEvoy et al. 2006, Rosenheck et al. 2006, Stroup et al. 2006). Of particular concern, the extrapyramidal side effects of FGAs appear not to have been eradicated with SGAs so much as replaced by such distressing adverse effects as weight gain, diabetes mellitus, and dyslipidemia. Investigators are still in the process of elucidating the impact of SGAs on a variety of domains (Miyamoto et al. 2005), including subjective well-being, quality of life (QOL), and cost-effectiveness. Meanwhile, our understanding of the neurobiology of antipsychotic treatment is rapidly expanding, and more agents with antipsychotic and/or cognitive-enhancing effects are in development. This chapter presents an updated review of the history, pharmacology, uses, efficacy, and side effects of antipsychotic drugs on the basis of currently available evidence, and discusses the benefits and limitations of individual SGAs in the management of psychosis and other disorders.

## History of Antipsychotic Drug Development

The era of antipsychotic pharmacotherapy began with the serendipitous discovery of the antipsychotic properties of chlorpromazine in the early 1950s by Delay and Deniker. A "first generation" of neuroleptics was subsequently developed based on the hypothesis that schizophrenia reflects a disorder of excess dopaminergic activity and that antagonism of the dopamine $D_2$ receptor is most strongly associated with antipsychotic response (Seeman 1992). For many patients with schizophrenia, the widely used FGAs (phenothiazines, butyrophenones, and others), which are also referred to as "conventional," "standard," "classical," "traditional," or "typical" antipsychotic drugs, are effective in the treatment of positive symptoms of the illness, and also in preventing psychotic relapse. Accordingly, these agents have permitted many patients to live independently in the community. Almost a half century of experience, however, has revealed substantial limitations with the use of these drugs. Twenty-five to sixty percent of patients treated with FGAs remain symptomatic and are considered either treatment refractory or only partially responsive (Miyamoto et al. 2003a). In particular, these drugs at best only modestly improve negative and cognitive symptoms. FGAs also cause a variety of objective and subjective side effects, both acutely and with long-term exposure. These side effects, in many instances, reduce compliance, which leads to relapse and rehospitalization.

For many years after the discovery of chlorpromazine's therapeutic effects, drug developers held the view that any compound with antipsychotic properties must induce considerable EPS. Clozapine and other SGAs disproved this hypothesis. These newer drugs are sometimes termed "atypical" because, in contrast to most FGAs, they demonstrate substantial separation between the doses at which

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they display antipsychotic action and the doses at which they are likely to induce EPS (Lieberman 1996).

Clozapine, the prototypical SGA, underwent extensive clinical testing in the 1970s, until its development was halted in the U.S. and limited in other countries because of a relatively high incidence of a potentially fatal side effect, agranulocytosis. Nonetheless, the drug's superior efficacy ultimately led to its reintroduction in the U.S. in 1990 (Lieberman et al. 1989). The renaissance of clozapine was based on several advantages: it is superior to FGAs for treatment-refractory schizophrenia (Kane et al. 1988); it may ameliorate some of the negative, cognitive, and mood symptoms of schizophrenia (Lieberman 1993); it may reduce the likelihood of suicidal behavior (Meltzer et al. 2003); it has very low liability for acute and chronic EPS; and it does not induce sustained hyperprolactinemia (Lieberman et al. 1989).

In the years that followed the reintroduction of clozapine, concerted research and development efforts were made to replicate the drug's therapeutic profile while avoiding the associated risk of agranulocytosis. Although this goal was never fully realized, the initiative spawned a second generation of atypical antipsychotic medications (Table 102–1), including risperidone, olanzapine, quetiapine, ziprasidone, remoxipride, sertindole, amisulpride, perospirone, zotepine, aripiprazole, paliperidone, iloperidone, and bifeprunox. Remoxipride was withdrawn after approval because of rare but serious hematological adverse effects. Sertindole was voluntarily withdrawn in 1998 due to concerns about its cardiac safety, but it was relaunched in 2002 in some European countries, solely for use in clinical trials. Amisulpride and zotepine are widely used in European and other countries, but sertindole, amisulpride, and zotepine are not marketed in the U.S. Perospirone is available only in Japan. Aripiprazole is sometimes called the first of the "third-generation antipsychotics" because its mechanism of action, partial dopamine receptor agonism, distinguishes it from previously developed FGAs and SGAs (Keltner and Johnson 2002). Paliperidone, the active metabolite of risperidone, was approved by the U.S. Food and Drug Administration (FDA) in December 2006. A phase III trial of iloperidone has recently been completed in the U.S., and the results appear to be encouraging. Asenapine is yet another antipsychotic under development for the treatment of schizophrenia. Bifeprunox, like aripiprazole, is a partial dopamine agonist. Its manufacturer filed for FDA registration in 2006; however its expected market launch is still pending. Although none of these second- and third-generation agents have matched the singular effectiveness of clozapine, they have broadened the therapeutic repertoire available for the treatment of schizophrenia and other psychotic illnesses.

**Table 102–1 Names and Manufacturers of Second-Generation Antipsychotics**

| Generic Name | Pharmaceutical Company | Trade Name |
|---|---|---|
| Clozapine | Sandoz, Novartis | Clozaril (Leponex) |
| Risperidone | Janssen | Risperdal |
| Olanzapine | Eli Lilly | Zyprexa |
| Quetiapine | ICI, Zeneca, AstraZeneca | Seroquel |
| Ziprasidone | Pfizer | Geodon (Zeldox) |
| Sertindole | Lundbeck | Serdolect |
| Amisulpride | Lorex, Sanofi | Solian |
| Perospirone | Dainippon Sumitomo Pharma | Lullan |
| Zotepine | Orion, Astellas | Zoleptil (Lodopin) |
| Aripiprazole | Otsuka, Bristol-Myers Squibb | Abilify |
| Paliperidone | Johnson & Johnson | Invega |
| Iloperidone | Hoechst, Novartis | Zomaril |
| Asenapine | Organon | |
| Bifeprunox | Solvay, Lundbeck, Wyeth | |

## Mechanism of Action of Antipsychotic Agents

### Dopamine Receptor Modulation

The role of dopamine systems in the pathophysiology and treatment of psychotic disorders has been a subject of intense investigative scrutiny for the past 50 years. Although other systems have since been implicated, the dopamine $D_2$ receptor is still regarded as the primary target associated with antipsychotic effect, as well as with the induction of EPS and prolactin elevation. All clinically approved, currently used antipsychotic drugs share $D_2$ receptor antagonism properties to some extent.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies support the importance of in vivo $D_2$ receptor occupancy as a predictor of antipsychotic response and adverse effects (for review, see Remington and Kapur 1999). Prospective studies demonstrate that, for at least some FGAs, antipsychotic effect requires a striatal $D_2$ receptor occupancy of 65–70%, and $D_2$ occupancy greater than 80% significantly increases the risk of EPS (Remington and Kapur 1999). Similarly, PET studies showing that therapeutic doses of risperidone and olanzapine produce greater than 70% occupancy of $D_2$ receptors suggest that $D_2$ receptor antagonism could be a mechanism of action of at least some SGAs (Kapur et al. 1998). However, the observations that therapeutic response occurs below this threshold for some agents and some patients, and that nonresponders can be seen in spite of adequate $D_2$ receptor blockade, reflect the limitations of the $D_2$ receptor occupancy model (Miyamoto et al. 2005). Clozapine and quetiapine, for example, exhibit less than 70% striatal $D_2$ receptor occupancy at therapeutically effective doses (Farde et al. 1992, Kapur et al. 2000b), indicating that $D_2$ receptor antagonism alone cannot explain the superior therapeutic efficacy of clozapine. The low occupancy of striatal $D_2$ receptors by clozapine and quetiapine could, on the other hand, account for their low EPS liability.

Differences among antipsychotics in dopamine receptor activity have been proposed to account for the "atypicality" of SGAs, that is, their tendency to produce antipsychotic effects at considerably lower doses than those that induce EPS. For example, Kapur and colleagues proposed that low affinity for, and fast dissociation from, $D_2$ receptors may be the key to atypicality (Kapur and Seeman 2001). FGAs such as haloperidol and chlorpromazine bind more tightly than dopamine itself to the $D_2$ receptor and dissociate from it slowly in vitro and in vivo (Seeman 2002). In contrast, SGAs such as quetiapine and clozapine bind more loosely than dopamine to the $D_2$ receptor, with dissociation constants (expressed as "$k_{off}$") that are higher than those for dopamine.

As a group, SGAs have higher $k_{off}$ values (i.e., faster dissociation rates) than do FGAs, though they vary considerably on this dimension. Kapur and Seeman hypothesized that the greater the $k_{off}$, the more quickly the drug responds to dopamine surges, allowing for a more physiological dopamine transmission (Kapur and Seeman 2001). However, this theory does not explain the apparently greater therapeutic efficacy of clozapine, compared with agents with still higher $k_{off}$ values (e.g., quetiapine). At present, the exact relationships among the $D_2$ receptor dissociation rate, therapeutic effects, and adverse effects remain obscure.

Another hypothesized mechanism of SGA atypicality involves regionally selective dopamine receptor binding. It has been suggested that dopamine receptors in mesolimbic and mesocortical pathways are more relevant than striatal dopamine receptor populations for the pathophysiology of schizophrenia and that they mediate the therapeutic effects of antipsychotic drugs. A regionally selective binding of SGAs to dopamine tracts projecting to corticolimbic areas has been proposed as a contributor to atypicality. A number of animal studies have found preferential effects of SGAs on ventral tegmental area (A10) as compared to substantia nigra pars compacta (A9) dopamine neurons. In humans, several PET studies using [$^{76}$Br]FLB457 and SPECT studies using [$^{123}$I]epidepride have demonstrated this corticolimbic $D_2$ receptor specificity for clozapine, risperidone, olanzapine, amisulpride, quetiapine, and sertindole. However, PET studies using [$^{11}$C]raclopride and [$^{11}$C]FLB 457 have not supported the hypothesis of regional selectivity for clozapine, risperidone, or olanzapine. More recent PET studies with [$^{18}$F]fallypride found that clozapine and quetiapine, but not olanzapine, preferentially occupy temporal cortical, as compared to putamenal, $D_2$ receptors (Kessler et al. 2005, 2006). Further research in humans is needed to clarify the neurochemical basis of "corticolimbic selective" $D_2$ receptor occupancy by SGAs, as it raises the possibility of spatial targeting of antipsychotics in the future.

The concept of mesolimbic and mesocortical pathway dysfunction has also been used to update the original dopamine hypothesis of schizophrenia. Imaging studies point to a dopaminergic "imbalance" involving a primary mesocortical hypodopaminergic state associated with hypofunctioning glutamatergic signaling that results in hypostimulation of prefrontal $D_1$ receptors (Abi-Dargham and Moore 2003). Reduced $D_1$ function may lead to negative and cognitive symptoms, and later developed episodic hyperactivity of the mesolimbic $D_2$ receptor-mediated dopamine system may account for the emergence of psychotic symptoms (Laruelle et al. 2003).

Partial dopamine agonists, such as aripiprazole, represent a new strategy of attempting to normalize dopaminergic imbalance in psychotic disorders, without the adverse effects associated with full $D_2$ antagonists. These agents have lower intrinsic activity at $D_2$ receptors than full agonists, allowing them to act either as functional agonists or as antagonists, depending on synaptic dopamine levels (Lieberman 2004). In schizophrenia, an effective partial $D_2$ agonist is thought to act as a functional antagonist in the mesolimbic dopamine pathway to control positive symptoms and as a functional agonist in the mesocortical pathway to improve negative and cognitive symptoms. In addition, such an agent should ideally maintain dopaminergic tone in the nigrostriatal and tuberoinfundibular pathways, avoiding EPS and hyperprolactinemia associated with $D_2$ antagonism. Thus, partial $D_2$ agonist activity could "stabilize" the dopamine system in multiple areas of the schizophrenic brain.

## Serotonin Receptor Modulation

Meltzer and colleagues proposed that a high ratio of serotonin 5-$HT_{2A}$ receptor to $D_2$ receptor blockade might predict antipsychotic atypicality (Meltzer et al. 1989). 5-$HT_{2A}$ antagonism can increase dopaminergic transmission in the nigrostriatal pathway, thus reducing the risk of EPS, and could theoretically improve negative symptoms and cognitive impairment in schizophrenia by increasing dopamine release in the prefrontal cortex. This "dopamine-serotonin antagonism theory" appears to apply, to some degree, for most of the SGAs, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, sertindole, perospirone, zotepine, paliperidone, and iloperidone (Table 102–2). There are, however, critical limitations to this concept (Sharif et al. 2007). First, some FGAs (e.g., chlorpromazine and loxapine) have high 5-$HT_{2A}$ affinity (Seeman 2002) but do not have an atypical profile. Second, amisulpride has no substantial affinity for the 5-$HT_{2A}$ receptor, and aripiprazole has higher $D_2$ than 5-$HT_{2A}$ affinity, and yet both agents have atypical profiles. Third, risperidone and olanzapine exhibit high 5-$HT_{2A}$ receptor occupancy at doses that are not antipsychotic, and as the doses of these drugs are increased beyond their usual therapeutic ranges, the risk of EPS increases despite maximal 5-$HT_{2A}$ receptor antagonism. Fourth, the relative ratios of 5-$HT_{2A}$/$D_2$ receptor affinities of the atypicals do not always predict their clinical EPS liability. (For example, risperidone has the highest and quetiapine the lowest 5-$HT_{2A}$/$D_2$ ratio, but the EPS liability of risperidone is greater than that of quetiapine.) Finally, at equivalent $D_2$ receptor occupancies, risperidone and haloperidol demonstrate comparable EPS liability, despite different 5-$HT_{2A}$ receptor affinities (Knable et al. 1997). Thus, high 5-$HT_{2A}$ affinity may contribute to the modulation of dopamine in the striatum and prefrontal cortex, but high 5-$HT_{2A}$ occupancy does not protect against the risk of EPS if $D_2$ receptor occupancy is greater than the EPS threshold (Sharif et al. 2007). The 5-$HT_{2A}$/$D_2$ hypothesis, therefore, does not satisfactorily explain atypicality (Kapur and Remington 2001). In addition, the apparent lack of efficacy of monotherapy with the selective 5-$HT_{2A}$ receptor antagonist M-100907 indicates that 5-$HT_{2A}$ antagonism alone does not account for the efficacy of SGAs. Further studies examining combination therapy with $D_2$ antagonists and M-100907 may help to elucidate the potential role of 5-$HT_{2A}$ antagonism in the mechanism of action of SGAs.

It has been suggested that partial agonism of 5-$HT_{1A}$ receptors, resulting in activation and blockade of pre- and postsynaptic receptors, respectively, is a possible mechanism of action of some SGAs, including clozapine, ziprasidone, perospirone, quetiapine, and aripiprazole (Millan 2000). 5-$HT_{1A}$ receptors are located presynaptically in the raphe nuclei, where they act as cell body autoreceptors to inhibit the firing rate of 5-HT neurons, and are located postsynaptically in limbic and cortical regions, where they also attenuate firing activity. 5-$HT_{1A}$ partial agonistic properties are thought to improve negative symptoms and cognitive impairment by enhancing the release of dopamine in the prefrontal cortex. In addition, 5-$HT_{1A}$ receptor agonists

**Table 102–2 Relative Neurotransmitter Receptor Affinities of Antipsychotics at Therapeutic Doses**

| Receptor | Halo-peridol | Perphe-nazine | Sulpiride | Clozapine | Risperidone | Olanzapine | Quetiapine | Ziprasidone | Sertindole | Amisulpride | Perospirone | Zotepine | Aripiprazole | Paliperidone | Iloperidone | Bifeprunox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $D_1$ | + | | − | + | + | ++ | − | + | ++ | − | ++ | + | − | + | + | |
| $D_2$ | ++++ | ++++ | ++++ | ++ | ++++ | +++ | + | +++ | ++++ | ++++ | ++++ | ++ | ++++ | ++++ | +++ | ++++ |
| $D_3$ | +++ | | ++ | + | ++ | + | − | ++ | ++ | ++ | | ++ | ++++ | ++ | ++ | ++++ |
| $D_4$ | +++ | + | − | ++ | +++ | ++ | − | ++ | + | − | | + | ++ | +++ | ++ | ++++ |
| 5-$HT_{1A}$ | − | | | + | − | − | + | +++ | | | +++ | ++ | +++ | − | ++ | +++ |
| 5-$HT_{1D}$ | − | | | − | + | − | − | +++ | | | | | | + | | |
| 5-$HT_{2A}$ | + | +++ | − | +++ | ++++ | ++++ | ++ | ++++ | ++++ | − | ++++ | +++ | +++ | ++++ | +++ | − |
| 5-$HT_{2C}$ | − | | − | ++ | ++ | ++ | − | ++++ | ++ | − | | ++ | ++ | ++ | ++ | − |
| 5-$HT_6$ | − | | | ++ | − | ++ | − | + | | | | ++ | + | | + | |
| 5-$HT_7$ | − | | | ++ | +++ | − | − | +++ | | | | ++ | ++ | +++ | + | |
| $\alpha_1$ | +++ | ++ | − | +++ | +++ | ++ | +++ | ++ | ++ | − | ++ | ++ | + | +++ | +++ | − |
| $\alpha_2$ | − | − | − | + | ++ | + | − | − | + | − | + | ++ | − | ++ | + | − |
| $H_1$ | − | | − | +++ | + | +++ | ++ | + | + | − | ++ | ++ | + | + | + | − |
| $M_1$ | − | − | − | ++++ | − | +++ | + | − | − | − | − | + | − | − | | − |
| $D_A$ Transporter | | | | ++ | | ++ | | | | | | | | | − | |
| NA Transporter | | | | + | | ++ | | ++ | | | | ++ | | | − | |
| 5-HT Transporter | | | | | | | | ++ | | | | | | | | |

−, minimal to none; +, low; ++, moderate; +++, high; ++++, marked.

*Source:* Adapted and modified from Miyamoto et al. (2003a) and Jarskog et al. (2007).

have been reported to possess antidepressant and anxiolytic properties and to attenuate the EPS liability of $D_2$ antagonists (Miyamoto et al. 2005).

## NMDA Receptor Modulation

The ability of noncompetitive *N*-methyl-*D*-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) and ketamine, to induce a spectrum of positive, negative, and cognitive schizophrenia-like symptoms has led to the hypothesis that hypofunction of NMDA receptors is involved in the pathophysiology of the disease (Coyle 1996, Javitt and Zukin 1991, Krystal et al. 1994).

A wide range of preclinical studies have demonstrated that acute treatment with some SGAs, but not FGAs, selectively antagonizes the consequences of experimentally induced NMDA receptor hypofunction at the cellular and behavioral levels (for review, see Duncan et al. 1999). For example, clozapine and olanzapine, but not haloperidol or raclopride, inhibit the electrophysiological effects of PCP in sectioned brain tissue and attenuate NMDA-antagonist-induced deficits in prepulse inhibition (PPI) and social behavior. In addition, ketamine-induced brain metabolic activation in rats is blocked by acute administration of clozapine and olanzapine, but not haloperidol (Duncan et al. 2000). In contrast to acute treatment with haloperidol, chronic administration of the drug blocks PCP-induced deficits in PPI and ketamine-induced brain metabolic activation. Thus, adaptive changes elicited by both FGAs and SGAs appear to attenuate the effects of NMDA antagonists (Miyamoto et al. 2005).

The well-documented effects of SGAs on responses to NMDA antagonists raise the possibility that the therapeutic action of these agents may involve a correcting of NMDA receptor hypofunction. However, since none of the SGAs has direct affinity for any of the glutamate receptors, including the NMDA receptor, the mechanism by which these effects might be mediated is poorly understood. Numerous animal studies have reported increases, decreases, or no changes in the binding site of glutamate receptors in various brain regions after chronic administration of antipsychotics (for review, see Miyamoto et al. 2005). Inconsistent and often conflicting findings have been reported regarding the gene expression of sub-units composing different glutamate receptors following long-term treatment with FGAs or SGAs. These discrepancies appear to be due to differences in treatment regimens, brain regions examined, and method of assessment. Recently, Javitt and colleagues found that clozapine inhibits synaptosomal glycine transport through system A transporters (Javitt et al. 2005). Such regulation of synaptic glycine levels may indirectly play a role in the potentiation of NMDA receptor function. Further studies are needed to determine whether the inhibition of the effects of NMDA antagonists by SGAs involves molecular modifications in glutamate receptors and/or other neurotransmitter–glutamate interactions.

## Depolarization Inactivation

Although antipsychotic drugs can produce a high level of $D_2$ receptor occupancy in humans within hours of oral administration, it has traditionally been believed that antipsychotics must be taken for several weeks before their clinical effects can be fully realized in patients with schizophrenia. One possible explanation for this lag in efficacy is the hypothesis of dopaminergic neuron "depolarization inactivation."

Acute administration of at least some FGAs (e.g., haloperidol and chlorpromazine) induces an increase in dopaminergic neuron firing in both the substantia nigra pars compacta (A9) and the ventral tegmental area (A10) in rats. Repeated treatment with FGAs for 3 weeks or more, however, results in a decrease in the number of spontaneously active dopaminergic neurons in the A9 and A10 regions. After chronic treatment, dopaminergic neurons are not in a hyperpolarized, inactive state, but are instead tonically depolarized to such an extent that their spike-generating mechanism is inactive. This neuroleptic-induced inhibition of spontaneous cell firing has been termed "depolarization inactivation" or "depolarization block" (for review, see Grace 1992). The depolarization inactivation hypothesis is supported in part by studies demonstrating that systematic administration of the dopamine agonist apomorphine, which hyperpolarizes dopaminergic cells in anesthetized animals, can reverse the effects of chronic treatment with antipsychotics by causing previously nonfiring dopaminergic cells to become active (Grace 1992).

In contrast to FGAs, chronic treatment with SGAs, including clozapine, olanzapine, quetiapine, and iloperidone, results in depolarization inactivation of A10 neurons, but not A9 dopaminergic cells. It has been suggested that the inability of these drugs to decrease A9 dopaminergic neuronal activity may contribute to their lower incidence of EPS and that inactivation of mesolimbic (A10) dopamine areas may be involved in the delayed onset of therapeutic effects (White and Wang 1983).

Of note, the hypothesis that slow onset of antipsychotic effect is associated with depolarization inactivation has recently been thrown into question by work suggesting that antipsychotics may act more quickly than originally believed (Kapur et al. 2005). For example, a meta-analysis of 42 double-blind, comparator-controlled studies found that antipsychotic effect was evident within the first week of treatment and that improvement in the first 2 weeks was greater than during any subsequent 2-week period (Agid et al. 2003). Kapur and colleagues reported in a double-blind, placebo-controlled study comparing intramuscular (IM) olanzapine to IM haloperidol that onset of specific antipsychotic effect was evident within 24 hours of drug initiation and that improvement in psychosis was independent of change in agitation (Kapur et al. 2005). These observations warrant further investigation.

## Effects on Intracellular Signal Transduction and Gene Expression

Studies suggest that antipsychotic action is associated with long-lasting adaptive modifications in neural functioning that involve changes in intracellular signal transduction and, ultimately, changes in gene expression in target neurons (for review, see Miyamoto et al. 2003a). These changes appear to be initiated by the binding of antipsychotic drugs to dopaminergic, serotonergic, muscarinic, cholinergic, adrenergic, histaminergic, or other receptors (Table 102–2). Most of these receptors belong to the G-protein-coupled receptor superfamily. Agonism of G-protein-coupled receptors stimulates specific heterotrimeric G-proteins, the subunits of which then regulate multiple downstream effectors, such as adenylate cyclase, phospholipases, and various ion channels. Some components of signal transduction, such as cyclic

adenosine monophosphate (cAMP) and cAMP-dependent kinase (PKA), have been implicated in antipsychotic drug action. The regulation of phosphorylation by specific protein kinase C and phospholipase C isoenzymes, which play important roles in mediating receptor-induced cellular responsiveness, may also represent an intracellular target of both FGAs and SGAs (Dwivedi and Pandey 1999).

DNA microarray expression profiling has been used to identify candidate target genes that may be involved in the mechanism of action of antipsychotic drugs. Employing this technique, Kontkanen and colleagues found that treatment of rats with clozapine or haloperidol regulated the expression of genes involved in synaptic function and intracellular $Ca^{2+}$ metabolism (Kontkanen et al. 2002). Gene expression profiles of rat cortices exposed to haloperidol or risperidone indicate that these agents modulate cell survival, neural plasticity, signal transduction, ionic homeostasis, oxidative changes, and metabolism (Feher et al. 2005). Altered expression of genes involved in presynaptic function has also been observed, postmortem, in the prefrontal cortices of patients with schizophrenia (Mirnics et al. 2000). Bauer and colleagues did not, however, detect significant changes in cortical synaptic protein levels or their encoding mRNAs in rats after chronic haloperidol administration (Bauer et al. 2000). Similarly, several genes involved in presynaptic function were not altered in the prefrontal cortices of monkeys after chronic haloperidol treatment (Mirnics et al. 2000). Further research is needed to clarify the nature and extent of influence exerted by antipsychotics on neuronal gene expression and cellular function.

### Neuroplasticity

Structural neuroimaging studies have demonstrated that pathomorphological brain changes, such as ventricular enlargement and reduction in gray and white matter volumes, may be present by the time of the first psychotic episode of schizophrenia (Lieberman et al. 2001a). Longitudinal studies have shown that schizophrenic patients manifest progressive cortical gray matter loss, which may be associated with functional decline (Cahn et al. 2002, Ho et al. 2003). These findings raise the question of whether antipsychotic drugs might mitigate such pathomorphological progression in the early stages of the illness. A number of investigators have found that antipsychotics produce neuroplastic changes at structural and molecular levels in the brain (for review, see Dean 2006, Harrison 1999, Konradi and Heckers 2001). Lieberman and colleagues, for example, reported that long-term treatment with olanzapine, but not haloperidol, prevented progressive gray matter volume reductions in patients with psychosis (Lieberman et al. 2005b). Although the precise mechanisms by which antipsychotics may arrest or delay the pathomorphological process remain unknown, there is growing evidence that some SGAs, both in vitro and in vivo, may have neuroprotective effects, including the production of neurotrophic factors; the mitigation of glutamate excitotoxicity, oxidative stress, or apoptosis; and the enhancement of neurogenesis and connectivity (Table 102–3), all of which could provide a rationale for pharmacological intervention with SGAs during the initial stages of schizophrenia (Lieberman et al. 2005b).

In contrast, striatal enlargement after chronic treatment with FGAs, but not SGAs, has been reported in schizophrenic patients and rats. This augmented striatal volume is accompanied by increases in the size of axon terminals, postsynaptic density, and the number of vesicles per synapse (for review, see Konradi and Heckers 2001). It should be noted that neurotoxic effects may occur concurrently with the neurotrophic effects of FGAs, with the balance depending in part on factors such as dose, length of treatment, and individual sensitivity (Dean 2006). At present, it is unclear whether FGA-induced neuroplastic changes relate to the therapeutic action of these drugs and/or to their propensity to cause EPS.

## Pharmacology of Antipsychotic Agents

### First-Generation Antipsychotic Agents

FGAs, as a class, are equally effective in the treatment of psychotic symptoms of schizophrenia, though they vary in potency, side effect risks, and other pharmacological properties (Lehman et al. 2004). Attributes common to all FGAs are a high affinity for, and full antagonist activity at, dopamine $D_2$ receptors (Marder and Van Putten 1995). In addition, all FGAs are capable of producing EPS and increasing serum prolactin concentration, to varying degrees, when used in the usual clinical dose range (Meltzer 1985).

Based on their chemical structure (Figure 102–1), FGAs may be divided into three groups: butyrophenones, phenothiazines, and others. The butyrophenones, represented by haloperidol, tend to be potent $D_2$ antagonists and to have minimal anticholinergic and autonomic effects (Marder and Van Putten 1995) (Table 102–2). The phenothiazines block $D_2$, acetylcholine, serotonin, histamine, and norepinephrine receptors, each of which is associated with certain adverse effects. The phenothiazines are often subdivided into three classes, according to substitutions at position 10 (for review, see Marder and Van Putten 1995), and these classes vary in their receptor affinities. The aliphatic class (e.g., chlorpromazine) consists of medications that have relatively low potency at $D_2$ receptors. Compared with other FGAs, aliphatic agents have greater antimuscarinic, sympathetic, and parasympathetic activity, and more potential for sedation. The piperidine class (e.g., thioridazine) possesses a similar receptor activity profile to the aliphatic class, with somewhat reduced affinity for $D_2$ sites. The piperazine class (e.g., perphenazine and fluphenazine) is characterized by fewer antimuscarinic and autonomic effects, but greater potency at $D_2$ sites and, thus, higher EPS liability.

### Second-Generation Antipsychotic Agents

In this chapter, SGAs refer to clozapine, risperidone, olanzapine, quetiapine, ziprasidone, sertindole, amisulpride, perospirone, zotepine, aripiprazole, paliperidone, iloperidone, and bifeprunox (Figure 102–2). These drugs bind with varying affinities to a broad range of receptors (Table 102–2). Intensive research efforts by the pharmaceutical industry and the academic psychopharmacology research community continue to clarify the pharmacological properties of SGAs, especially as they compare and contrast with those of FGAs. Since clozapine is the prototypical and most efficacious SGA, investigators are particularly eager to elucidate and replicate the complex actions of this drug (Miyamoto et al. 2002).

#### Clozapine

Clozapine is a tricyclic dibenzodiazepine derivative. Distinguishing features of clozapine, as compared to FGAs, are its

**Table 102–3 Neuroprotective Effects of Antipsychotics**

| | Clozapine | Olanzapine | Risperidone | Quetiapine | Ziprasidone | Aripiprazole | Haloperidol | References |
|---|---|---|---|---|---|---|---|---|
| Blockade of NMDA-R antagonist-induced neurotoxicity | + | + | − | | | | − | Farber et al. (1996), Fujimura et al. (2000), Johnson et al. (1998) |
| Blockade of NMDA-R antagonist-induced reduction in BDNF | | + | | | | | − | Fumagalli et al. (2003) |
| Blockade of kainic acid-induced striatal injury | + | | | | + | + | − | Cosi et al. (2005) |
| Gene expression of SOD1 | ↑→ | ↑→ | ↑→ | ↑ | | | ↓ | Bai et al. (2002), Li et al. (1999) |
| Enzyme activity or protein levels of MnSOD | → | → | → | | | | ↓ | Parikh et al. (2003) |
| Enzyme activity or protein levels of catalase | → | → | → | | | | ↓ | Parikh et al. (2003) |
| Decrease in p75NTR gene expression | + | + | + | + | | | | Bai et al. (2002), Li et al. (1999) |
| Prevention of MPP+-induced apoptosis | + | + | + | + | | | − | Qing et al. (2003) |
| Prevention of beta-amyloid peptide25-35-induced oxidative stress and apoptosis | | + | | + | | | | Wang et al. (2005 |
| Gene expression of BDNF | ↑→↓ | ↑ | →↓ | | | | ↓ | Bai et al. (2003), Chlan-Fourney et al. (2002), Linden et al. (2000), Lipska et al. (2001) |
| Protein levels of NGF | ↑ | ↑ | → | | | | ↓ | Parikh et al. (2004) |
| Stimulation of neurogenesis | + | + | + | + | | | +, − | Dawirs et al. (1998), Kodama et al. (2004), Luo et al. (2005), Wakade et al. (2002), Wang et al. (2004) |

SOD1, Cu/Zn superoxide dismutase; MnSOD, manganese superoxide dismutase; p75NTR, p75 neurotrophin receptor;

$MPP^+$, *N*-methyl-4-phenylpyridinium ion; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; +, studies support effect; −, studies do not support effect; ↑, increase in activity; ↓, decrease in activity; →, no change in activity.

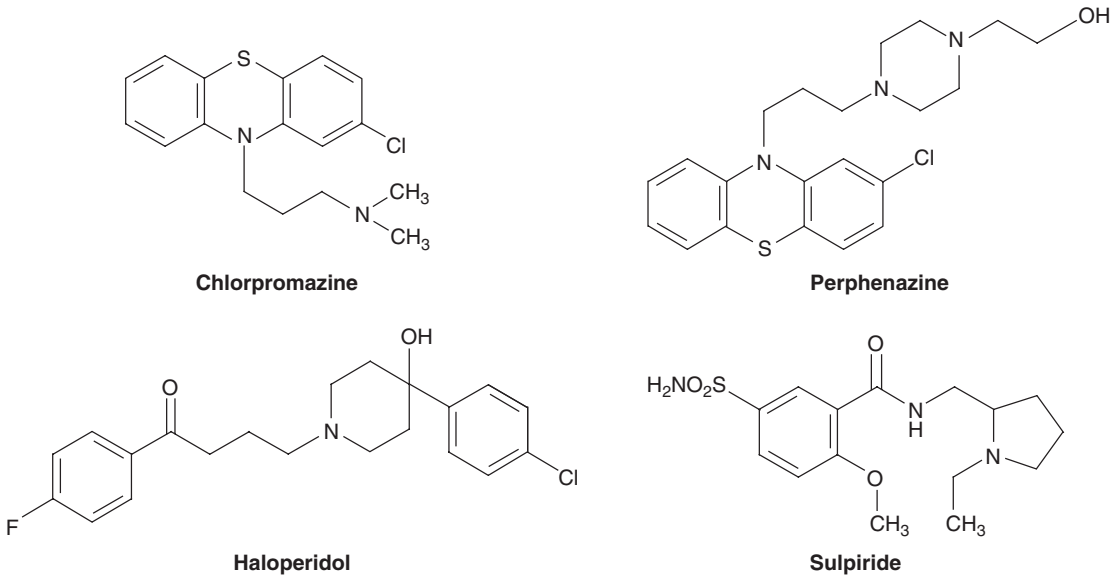



**Figure 102–1** *Chemical structures of selected first-generation antipsychotics.*

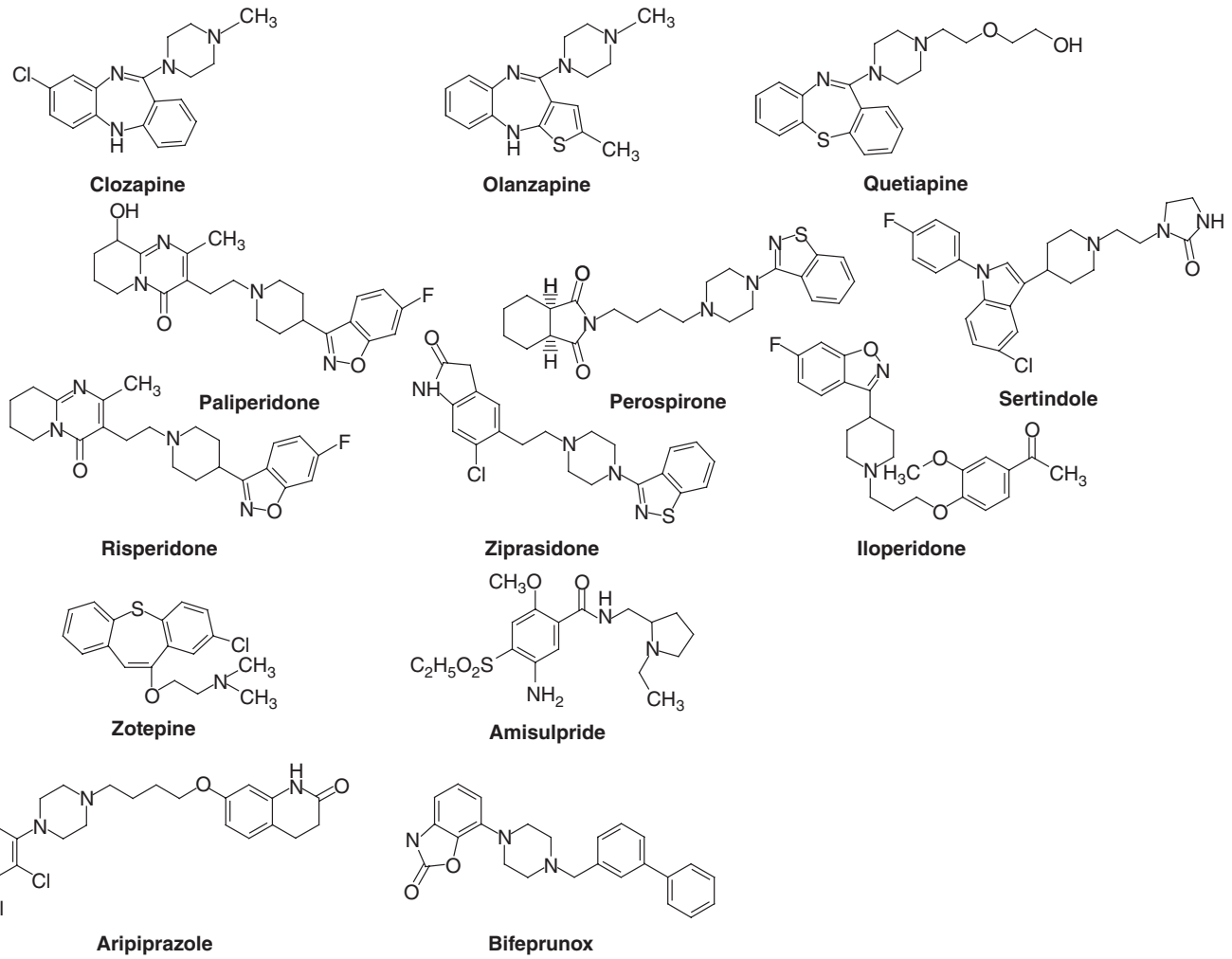



**Figure 102–2** *Chemical structures of second-generation antipsychotics.*

relatively high affinity for 5-$HT_{2A}$ receptors and lower affinity for $D_2$ receptors (for review, see Duncan et al. 1999, Lieberman 1993). Clozapine has high antagonist affinity for $H_1$ histaminergic, muscarinic, and $\alpha_1$- and $\alpha_2$-adrenergic receptors (Bymaster et al. 1996). The drug exhibits weak partial agonist effects at 5-$HT_{1A}$ receptors and at muscarinic $M_1$, $M_2$, and $M_4$ receptors, and the latter pharmacological properties have been hypothesized to contribute to antipsychotic activity and cognitive enhancement in animal models (Bymaster et al. 2002). *N*-desmethylclozapine, the major metabolite of clozapine, has potent partial agonist activity at the $M_1$ receptor and can potentiate NMDA currents in the hippocampus (Sur et al. 2003). It is possible that clozapine's unique therapeutic profile may be due, at least in part, to such $M_1$ receptor-mediated potentiation of NMDA receptor function.

## Risperidone

Risperidone has substantially higher affinity for 5-$HT_{2A}$ and $D_2$ receptors than does clozapine. A PET study found that risperidone occupies 75–80% of striatal $D_2$ receptors and 78–88% of cortical 5-$HT_2$ receptors when administered to schizophrenic patients at a dose of 6 mg/day (Farde et al. 1995). Despite high levels of $D_2$ receptor occupancy, moderate-dose risperidone treatment (4–6 mg/day) poses a somewhat lower EPS risk than treatment with some FGAs. This may be due to the 5-$HT_{2A}$ antagonistic properties of the drug (Meltzer et al. 1989). However, at higher doses, risperidone produces EPS consistently (Marder and Meibach 1994), indicating that 5-$HT_{2A}$ receptor antagonism alone cannot eliminate EPS associated with substantial $D_2$ receptor blockade. Risperidone, like clozapine, has relatively high affinity for $\alpha_1$- and $\alpha_2$-adrenergic receptors, but whether adrenergic receptor antagonism contributes to the therapeutic action of these drugs is unknown.

## Olanzapine

Olanzapine is closely related to clozapine in chemical structure, and the two drugs share many receptor-binding characteristics (for review, see Miyamoto et al. 2001). Primary considerations in the selection of olanzapine for development were the drug's relatively potent antagonistic effects at $D_2$ and 5-$HT_{2A}$ receptors (Bymaster et al. 1997). Olanzapine is more potent at 5-$HT_{2A}$ than at $D_2$ receptors, similar to clozapine. Other receptor-binding characteristics of olanzapine are similar to those of clozapine, but there are some notable differences between the two drugs. For example, olanzapine has substantially lower affinity for 5-$HT_{1A}$ and 5-$HT_7$ receptors, in comparison with clozapine. A PET study found a striatal $D_2$ receptor occupancy of 71–80% in olanzapine's usual clinical dose range of 10–20 mg/day, while doses of 30 mg/day and higher were associated with more than 80% $D_2$ occupancy in schizophrenic patients (Kapur et al. 1998). Although olanzapine displays little physiological evidence of anticholinergic activity, it produces a substantial blockade of muscarinic sites in vivo, as demonstrated by PET imaging (Raedler et al. 2000).

## Quetiapine

Quetiapine is another drug with greater affinity for 5-$HT_{2A}$ than for $D_2$ receptors. It also has some affinity for $\alpha_1$-adrenergic and $H_1$ receptors and weak partial agonist effects at 5-$HT_{1A}$ receptors. PET studies have shown that quetiapine occupies 22–68% of striatal $D_2$ receptors and 48–70% of cortical 5-$HT_2$ receptors at therapeutic doses in schizophrenic patients (Gefvert et al. 1998). Interestingly, quetiapine produces transiently high striatal $D_2$ occupancy in schizophrenic patients, but the effect lasts for only a few hours (Kapur et al. 2000b).

## Ziprasidone

Ziprasidone has potent 5-$HT_{2A}$ and $D_2$ affinities and, like clozapine, exhibits partial 5-$HT_{1A}$ agonist properties that may protect against the development of EPS (Ferris 2000). Ziprasidone also has significant affinity for 5-$HT_{1D}$, 5-$HT_{2C}$, $H_1$, and $\alpha_1$-adrenergic receptors (Arnt and Skarsfeldt 1998), and it inhibits the reuptake of norepinephrine and 5-HT (Waddington and Casey 2000). Although initially ziprasidone was found to produce substantial $D_2$ receptor occupancy at low doses (20- and 40-mg single doses) in healthy volunteers (Bench et al. 1996), a subsequent study (Mamo et al. 2004) found that 60% $D_2$ occupancy was not achieved until plasma levels corresponding to a 120 mg/day dose were reached, suggesting that the optimal dose of the drug is 120 mg/day or higher. This latter finding is consistent with clinical trial data (Daniel et al. 1999, Keck et al. 1998). The surprising absence of weight gain with ziprasidone, which has relatively high 5-$HT_{2C}$ and $H_1$ affinities, may be related to its partial agonism at the 5-$HT_{1A}$ receptor.

## Sertindole

Sertindole is a phenylindole derivative with high-affinity antagonism at 5-$HT_{2A}$, 5-$HT_{2C}$, $\alpha_1$-adrenergic, and $D_2$-like receptors (Schotte et al. 1996). In conventional preclinical models, the receptor-binding profile of sertindole accurately predicted antipsychotic efficacy with low EPS liability (for review, see Arnt and Skarsfeldt 1998). In schizophrenic patients, SPECT studies found that sertindole is similar to risperidone in occupying a high percentage of striatal $D_2$-like receptors and cortical 5-$HT_{2A}$ receptors (Bigliani et al. 2000). Electrophysiologically, sertindole exhibits dose-dependent, marked limbic selectivity (for review, see Daniel and Copeland 2001).

## Amisulpride

Amisulpride, a substituted benzamide analog of sulpiride, is a selective antagonist at $D_2$ and $D_3$ receptors, with little affinity for $D_1$-like or nondopaminergic receptors (Waddington and Casey 2000). At low doses, the drug preferentially blocks presynaptic dopamine autoreceptors, and postsynaptic dopamine receptor antagonism arises at higher doses. The effect of low doses on negative symptoms may be attributable to the presynaptic dopamine-releasing effect, which may have a psychomotor stimulatory action. Low doses also appear to selectively block temporal cortical $D_2$ and $D_3$ receptors, whereas higher doses result in considerable striatal $D_2$ and $D_3$ receptor occupancy, with associated EPS (Xiberas et al. 2001). Amisulpride has a propensity to elevate prolactin secretion even in the absence of EPS, suggesting that the drug antagonizes tuberoinfundibular $D_2$ receptors more potently than striatal $D_2$ receptors.

## Perospirone

Perospirone is a benzisothiazole derivative with high-affinity antagonism at 5-$HT_{2A}$ and $D_2$ receptors (Onrust and

McClellan 2001). It displays partial 5-$HT_{1A}$ agonist properties and some affinity for $D_1$, $\alpha_1$-adrenergic, and $H_1$ receptors. The drug has no appreciable affinity for muscarinic receptors. Perospirone has at least four active metabolites, but all of them have lower affinity for $D_2$ and 5-$HT_{2A}$ receptors than the parent drug. A preliminary PET study showed that it possesses the in vivo properties of a serotonin-dopamine antagonist in healthy volunteers (Sekine et al. 2006).

### Zotepine

Zotepine is a dibenzothiepine analog of clozapine with high affinity for 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_6$, 5-$HT_7$, $\alpha_1$-adrenergic, and $H_1$ receptors (Needham et al. 1996). It has modest affinity for $D_1$, $D_2$, $D_3$, and $D_4$ receptors. It is also a potent norepinephrine reuptake inhibitor (Blin 1999). Preclinical studies suggest that low-dose zotepine increases dopaminergic neurotransmission, while, at higher doses, the drug acts as a dopaminergic antagonist. In schizophrenic patients, SPECT studies indicate that zotepine occupies 68–78% of striatal $D_2$-like receptors at usual clinical doses (Barnas et al. 2001).

### Aripiprazole

Aripiprazole is a partial dopamine agonist with high affinity for $D_2$ and $D_3$ receptors, and acts on both postsynaptic $D_2$ receptors and presynaptic autoreceptors. The drug demonstrates properties of a functional agonist and antagonist in animal models of dopaminergic hypoactivity and hyperactivity, respectively (Kikuchi et al. 1995, Lawler et al. 1999). Partial agonist activity at dopamine receptors could theoretically stabilize the aberrant dopamine system of schizophrenia by restoring dopamine function in the mesocortical pathway, reducing hyperdopaminergia in the mesolimbic pathway, and maintaining dopaminergic tone in the nigrostriatal and tuberoinfundibular pathways. It has been proposed that aripiprazole's activity at $D_2$ receptors is "functionally selective," meaning the drug may activate a specific set of $D_2$ receptors, which are in turn coupled to particular G proteins that mediate aripiprazole's clinical effects (Lawler et al. 1999, Shapiro et al. 2003). In addition, aripiprazole displays partial 5-$HT_{1A}$ agonism and 5-$HT_{2A}$ antagonism. It also has modest affinity for $\alpha_1$-adrenergic, $H_1$-histaminergic, 5-$HT_6$, and 5-$HT_7$ receptors, and no appreciable affinity for $D_1$ or muscarinic receptors (Lawler et al. 1999). The clinical significance of these in vitro receptor-binding affinities has not been determined, apart from their association with side effects.

Aripiprazole does not conform to the usual 5-$HT_{2A}$/$D_2$ model of atypicality. Its affinity for $D_2$ receptors exceeds that for serotonin receptors by an order of magnitude (Shapiro et al. 2003), and PET studies in normal humans indicate that aripiprazole occupies up to 90% of striatal $D_2$-like dopamine receptors at clinical doses (Yokoi et al. 2002). In spite of this, aripiprazole causes few EPS, suggesting that its inherent partial agonism properties may protect against excessive blockade of the $D_2$ system.

### Paliperidone

Paliperidone is 9-hydroxy-risperidone, the active metabolite of risperidone. The pharmacological properties of paliperidone are similar to those of risperidone with respect to receptor activity, potency, and onset and duration of action (van Beijsterveldt et al. 1994). However, paliperidone displays slightly less potent in vitro affinity for $D_1$, $D_2$, 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2C}$, $\alpha_1$, $\alpha_2$, and $H_1$ receptors than does risperidone (Schotte et al. 1996). A paliperidone extended-release tablet (paliperidone ER), which is associated with small 24-hour peak-to-trough fluctuations in plasma concentration, has recently been approved by the U.S. FDA for the treatment of schizophrenia. Paliperidone ER undergoes limited hepatic metabolism and, consequently, may avoid significant hepatic-related drug–drug and drug–disease interactions (Kane et al. 2006).

### Iloperidone

Iloperidone is a piperidinyl-benzisoxazole derivative with relatively high affinity for 5-$HT_{2A}$ and $\alpha_1$-adrenergic receptors, and moderate affinity for $D_2$, $D_3$, and 5-$HT_6$ receptors. Similar to clozapine and olanzapine, it induces a depolarization blockade of A10 mesolimbic dopaminergic neurons, but not of A9 nigrostriatal neurons (Hesselink 2000). Iloperidone has also been shown to increase dopamine and acetylcholine levels in the prefrontal cortex. In conventional preclinical models, the profile of iloperidone predicted antipsychotic efficacy with reduced EPS liability (Hesselink 2000).

### Bifeprunox

In in vitro and in vivo studies, bifeprunox (DU-127090) displayed partial agonist activity at $D_2$ and 5-$HT_{1A}$ receptors, with high affinity for both. It also demonstrates high affinity for $D_3$ and $D_4$ receptors, but has virtually no activity at 5-$HT_{2A}$, 5-$HT_{2C}$, $\alpha_1$, $\alpha_2$, muscarinic, and histaminergic receptors (Lieberman 2004). In animal models, bifeprunox demonstrated activity consistent with antipsychotic, antidepressant, and anxiolytic effects. A preliminary PET study involving six healthy subjects found that a single 10-mg dose of bifeprunox occupied 90% of striatal $D_2$-like dopamine receptors after 2 hours and 79% after 24 hours (De Vries et al. 2000).

## Conditions Treated with Antipsychotic Medications

At present, SGAs are prescribed primarily for schizophrenia; however, they are being used increasingly for other psychiatric disorders, as happened with FGAs (Glick et al. 2001, Marder 1997). A proportion of these uses are empirically well supported, but only preliminary or moderate evidence exists for others. In particular, the prescription of SGAs for nonpsychotic disorders in children and adolescents has become progressively more common, despite limited data regarding the efficacy and safety of this practice (Olfson et al. 2006).

### Schizophrenia and Schizoaffective Disorder

Nearly all acute psychotic episodes in schizophrenia and schizoaffective disorder, including first-episode psychosis and recurrence in chronic schizophrenia, should be treated with antipsychotic medication. In these instances, the patient's mental status and physical condition should be evaluated promptly, and then pharmacotherapy should be prescribed as early in the episode as possible (American Psychiatric Association 2004).

#### First-Episode Schizophrenia

The past decade has witnessed a rise in clinical research focused on treatment response during first-episode

schizophrenia, in large part because of the widely held belief that early intervention with antipsychotic medication may favorably alter the subsequent course of the illness (for review, see Lieberman 1996, Wyatt 1991, 1995). Investigators have proposed a "toxic psychosis" hypothesis, asserting that a limited neurodegenerative process may be involved in the pathophysiology of schizophrenia, that this pathologic process occurs principally in the early stages of the illness, and that it is reflected in the patient's psychotic symptoms (Lieberman 1999a, Lieberman et al. 1996, Loebel et al. 1992, Wyatt et al. 1997). Such a link between psychotic symptoms and a toxic process is supported by the finding that the duration and number of periods of psychosis prior to receiving antipsychotics appear to be significant predictors of the time to treatment response, the time to relapse, and long-term outcome (Lieberman et al. 1990, Loebel et al. 1992, Wyatt 1991). Further evidence is provided by two meta-analyses of studies involving patients with first-episode psychosis, which concluded that there is a significant association between duration of untreated psychosis and outcomes such as positive symptoms, negative symptoms, and functionality (Marshall et al. 2005, Perkins et al. 2005). These findings have stimulated enthusiasm for the idea that early detection and intervention at, or even prior to, the onset of the first episode might improve response to antipsychotic treatment and long-term outcome. Large-scale clinical trials investigating this possibility are currently under way.

The preferential use of SGAs over FGAs is now common in the treatment of first-episode patients because of their generally lower EPS burden and possible superiority in relapse prevention. It has also been hypothesized that the glutamatergic effects of some SGAs may provide a neuroprotective function, potentially resulting in better long-term outcomes (Lieberman et al. 2001b). To date, four large-scale, double-blind studies comparing an FGA and an SGA in first-episode patients have been published: clozapine vs. chlorpromazine (Lieberman et al. 2003a), risperidone vs. haloperidol (Emsley and Risperidone Working Group 1999), risperidone vs. haloperidol (Schooler et al. 2005) and olanzapine vs. haloperidol (Lieberman et al. 2003b). None has found statistically significant differences in response rates between the FGA and the SGA, but some found that more patients were retained in the SGA arm, without relapse, than in the FGA arm (e.g., Lieberman et al. 2003b, Schooler et al. 2005). Thus, SGAs may be preferable to FGAs in first-episode schizophrenia, not because of superior acute treatment efficacy but because of modestly better relapse rates.

### The Prodromal Stage of Schizophrenia

The average time from onset of psychotic symptoms to first effective treatment is often 1 year or more, but when the prodromal period is taken into account, the average delay is 3 years (McGlashan 1996). In an effort to reduce this delay and to improve long-term outcomes, early intervention research has been extended to include the prodromal stage of schizophrenia. Investigators use clinically defined prodromal diagnostic criteria to identify "at-risk" subjects with a 35–40% likelihood of developing a psychotic disorder within 1 year (Keefe et al. 2006a). In all, about 85% of individuals experience prodromal symptoms prior to developing psychosis (Yung and McGorry 1996).

There have been at least two randomized, controlled studies in people with prodromal symptoms assessing the efficacy of SGAs in reducing these symptoms and delaying or preventing conversion to psychosis. The first was a nonblinded trial involving "ultra-high-risk" individuals in late prodromal stages, which compared treatment with low-dose risperidone plus cognitive–behavioral therapy to routine clinical care over a 6-month period, followed by 6 months of need-based intervention (McGorry et al. 2002). Significantly fewer subjects in the risperidone group transitioned into psychosis after 6 months, and in those subjects who were compliant with risperidone treatment, the benefits extended through the ensuing 6-month extension period, even though risperidone was discontinued. In the second study, a randomized, double-blind trial, olanzapine was superior to placebo in reducing prodromal positive symptoms and conversion to psychosis (McGlashan et al. 2006). Over the follow-up year, the conversion rate did not differ significantly between the two groups. Further prodromal recognition and intervention programs are currently being developed in several countries, and data from associated studies are needed to clarify the utility and safety of antipsychotic treatment during the prodromal stage.

### Intermittent Maintenance Medication

It has been suggested that patients with schizophrenia might be better treated by administering antipsychotic medication during periods of acute symptomatology and offering medication discontinuation when symptoms remit. Such "targeted" or "intermittent" treatment was once considered a potential means of reducing the short- and long-term risks associated with antipsychotic agents. This strategy has been tested in a number of controlled studies (for review, see Gaebel 1995), all of which yielded relapse rates that were approximately twice as high as those with continuous treatment, with the possible exception of first-episode patients (Gaebel et al. 2002). Therefore, continuous antipsychotic treatment is likely to be preferable for most patients with schizophrenia, even if they are symptom free (Marder 1997).

## Major Depression with Psychotic Features

Psychotic symptoms, such as delusions or hallucinations, have been observed in up to 25% of patients with major depressive disorder. Major depression with psychotic features is seen in patients of all ages, and carries a high risk of short-term morbidity and suicide. Psychosis in the context of major depression often responds poorly to antidepressant monotherapy and usually requires the use of adjuvant antipsychotic medication (Marder 1997). Some data support the use of SGAs as monotherapy in the treatment of this disorder (for review, see Buckley 2001). However, several double-blind trials have found the combination of an antidepressant and an antipsychotic to be superior to an antipsychotic alone (Muller-Siecheneder et al. 1998). In the absence of convincing evidence for the efficacy and safety of antipsychotic monotherapy in the treatment of psychotic depression, most patients with this disorder should be treated with a combination of an antidepressant and an antipsychotic agent.

## Bipolar Disorder

Antipsychotic medications can effectively treat both the mood and the psychotic symptoms of mania, often demonstrating improvement more rapidly than traditional mood stabilizers (for review, see Buckley 2001, Marder 1997). During the past decade, SGAs have gained increasing favor over FGAs for the treatment of mania because of their lower risk of EPS. A large number of double-blind studies support the efficacy of olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone for the treatment of acute manic or mixed episodes, either alone or as adjuvant treatment. A meta-analysis of randomized, placebo-controlled trials of SGAs for acute bipolar mania concluded that all five of these agents are efficacious as monotherapy (Perlis et al. 2006). Pairwise comparisons identified no significant differences in efficacy among individual medications, and the magnitude of improvement was similar whether the antipsychotic was utilized as monotherapy or as adjuvant treatment. To date, there have been no double-blind, controlled, monotherapy studies of clozapine in the treatment of acute bipolar mania, but reports suggest the drug may be beneficial in the management of treatment-refractory bipolar disorder.

Antipsychotic agents have also shown efficacy in the treatment of bipolar depression, which carries a greater overall burden of suicide risk, functional impairment, and duration of active symptomatology than does bipolar mania. The findings of a large-scale, placebo-controlled, double-blind RCT of olanzapine alone and in combination with fluoxetine suggest that the drug may be efficacious in treating depressive symptoms in patients with bipolar I disorder, though the combination of olanzapine and fluoxetine was superior to monotherapy (Tohen et al. 2003). It should be noted, however, that the relatively longer half-life of fluoxetine, as compared to olanzapine, represents at least a theoretical concern with this combination, because drug discontinuation will result in a period of unopposed antidepressant exposure, which could potentially increase the risk of mania in a patient with bipolar disorder. Quetiapine monotherapy has similarly been shown to be efficacious and well tolerated in the treatment of depressive episodes in bipolar I and II disorders. Large, controlled trials are necessary to determine whether other SGAs are effective for bipolar depression.

## Tourette's Disorder

Tourette's disorder is a neurobehavioral illness characterized by motor and vocal tics that usually begin in childhood and may persist indefinitely. The pathophysiology of the disorder is not well understood.

When motor or vocal tics interfere with functioning, an antipsychotic medication can be effective in reducing their severity. Historically, haloperidol and pimozide have been the most commonly used agents for the treatment of moderate to severe tics. SGAs also show promise in this respect. Most of these data come from placebo-controlled and active comparator trials involving risperidone. The drug appears to be comparable to pimozide in efficacy, with a lower incidence of EPS but a greater potential for weight gain. Given the risk of side effects with both agents, risperidone and pimozide should be reserved for patients with significant tic-related functional impairment or pain, which is refractory to safer treatments. One small RCT found ziprasidone to be effective and well tolerated in the treatment of Tourette's disorder, suggesting the drug may be a viable alternative to agents with less favorable side effect profiles.

## Borderline Personality Disorder

Antipsychotic agents are occasionally used in the treatment of borderline personality disorder (BPD). Although psychotherapy is the mainstay of BPD treatment, antipsychotics may be useful as adjunctive therapy in some cases. A number of studies indicate that aspects of BPD may improve with low doses of an FGA, such as thiothixene or haloperidol (Marder 1997). Case reports, open-label studies, and controlled trials have shown that some SGAs, including risperidone, olanzapine, aripiprazole, and clozapine, may also be beneficial for at least some symptoms of BPD. The largest body of evidence exists for olanzapine, which in several controlled trials has shown superiority over placebo in patients with BPD for such symptoms as anxiety, depression, paranoia, anger/hostility, impulsive aggression, and interpersonal sensitivity. There are not, however, convincing data that suggest any antipsychotic agent changes the underlying character structure of patients with BPD or alters the long-term course of the disease. Given the circumscribed utility of antipsychotics for BPD, and their potential for causing adverse effects, most patients with this condition should not routinely be treated with antipsychotic medication.

## Substance-Related Disorders

A variety of substances, including amphetamines, cocaine, alcohol, cannabis, and phencyclidine, can cause psychotic symptoms during intoxication or drug withdrawal (Marder 1997). In addition, substance-use disorders are common in patients with schizophrenia, and the presence of these disorders may negatively influence response to antipsychotic medication.

FGAs are not generally helpful for patients with schizophrenia and concurrent substance-use disorders, and may even worsen the abuse of substances in this population (Green et al. 2007). In contrast, several case reports, open-label studies, and a few randomized trials suggest SGAs may have a role in reducing substance abuse when it is comorbid with a psychotic disorder. Clozapine appears to be particularly effective for reducing psychosis and substance abuse in patients with comorbid schizophrenia and substance-use disorder, though randomized studies are lacking (Green et al. 2007). When a psychotic disorder is not present, antipsychotic agents are not generally efficacious in the treatment of substance-use disorders.

## Behavioral Disturbances in Patients with Dementia

Dementia, whether due to Alzheimer's disease (AD) or other causes, is frequently associated with behavioral disturbances and psychosis. SGAs are often used to manage these symptoms, in part because of perceived safety advantages relative to FGAs. However, concerns have recently emerged regarding an increased risk of cerebrovascular adverse events (e.g., stroke and transient ischemic episodes), the metabolic syndrome (MS), cognitive decline, and mortality with at least some SGAs (Schneider et al. 2005). Because of these concerns, Health Canada issued an advisory in late 2002, and the U.S. FDA issued its own public health advisory in

April 2005, warning of an increased risk of mortality with SGAs, but not FGAs, in elderly patients with dementia. Consistent with the FDA's assessment, a meta-analysis by Schneider and colleagues found an increased risk of death with SGA use, relative to placebo treatment, in patients with dementia (Schneider et al. 2005). In a retrospective cohort study of 22,890 elderly patients treated with FGAs or SGAs, Wang and colleagues concluded that FGAs were at least as likely as SGAs to increase the risk of death (Wang et al. 2005). The greatest increases in risk of death occurred soon after therapy was initiated and with higher dosages of FGAs. Schneider and colleagues recently reported a meta-analysis of 15 randomized, placebo-controlled trials of aripiprazole, olanzapine, quetiapine, and risperidone in 3,353 patients with AD or other dementia (Schneider et al. 2006a). Small therapeutic effect sizes supported the efficacy of aripiprazole and risperidone. Worsening of cognitive test scores was observed with SGA use, and there was a significant risk of cerebrovascular events, especially with risperidone. The authors concluded that SGA use in this population should be considered within the context of medical need and the efficacy and safety of alternatives.

Schneider and colleagues conducted a federally funded, multisite, randomized, double-blind, 36-week, placebo-controlled trial to determine the effectiveness of olanzapine, quetiapine, and risperidone, as compared with placebo, in 421 outpatients with AD and psychosis, aggression, or agitation (Schneider et al. 2006b). The primary outcome of median time to discontinuation of treatment for any reason ranged from 5 to 8 weeks, with no significant differences among the four groups.

Together, these studies suggest a modest therapeutic efficacy, if any, with the use of SGAs for psychosis and behavioral disturbances in patients with dementia, with probable small increases in the risk of cerebrovascular-related morbidity and mortality. The use of antipsychotics in this patient population should be assessed on a case-by-case basis, giving judicious consideration to the risks and benefits of neuroleptic and alternative treatment strategies. When antipsychotics are used in elderly patients, a lower dosage is indicated because of an age-related decline in drug metabolism, vulnerability to drug–drug interactions, a high incidence of comorbid physical illness, and a heightened sensitivity to EPS (Miyamoto et al. 2003a).

## Parkinson's Disease and Huntington's Disease

Patients with Parkinson's disease (PD) may experience psychotic symptoms, which are often induced by treatment with dopaminergic agents. These symptoms may improve with reduction in the dopaminergic medication dose, but this usually worsens Parkinsonism and is often not tolerated. In years past, FGAs were effectively used to alleviate psychotic symptoms in PD, but at the cost of considerable worsening of motor dysfunction (Buckley 2001). Although literature in this area is relatively sparse, a handful of open-label and double-blind, placebo-controlled studies have found that clozapine and quetiapine may offer a substantial benefit to this patient population by decreasing psychotic symptoms without significantly worsening Parkinsonism. In contrast, olanzapine and risperidone have produced mixed results regarding efficacy for PD-related psychosis, and more potential for EPS than clozapine or quetiapine.

Patients with psychiatric manifestations of Huntington's disease (HD) may also benefit from antipsychotic medication (Marder 1997). As with PD, the use of FGAs in HD frequently worsens motor dysfunction (Buckley 2001). Several case reports and open-label studies suggest that risperidone, olanzapine, quetiapine, and ziprasidone may be efficacious and tolerable in the management of psychiatric symptoms of HD.

## Childhood Schizophrenia

Childhood-onset schizophrenia is a rare and severe form of the disorder, characterized by the onset of psychotic symptoms before 13 years of age. Children with schizophrenia experience predominantly negative symptoms, but positive symptoms, most commonly auditory hallucinations, also occur (for review, see Masi et al. 2006). Functional decline may be marked.

Pharmacotherapy is usually necessary for the control of psychotic symptoms, and children with schizophrenia may require chronic antipsychotic treatment. One double-blind, placebo-controlled, crossover study found haloperidol to be superior to placebo for reduction of target symptoms in children with schizophrenia (Spencer et al. 1992). Unfortunately, the value of FGAs in children and adolescents is limited by this population's sensitivity to certain adverse effects, including dysphoria, cognitive impairment, Parkinsonism and akathisia.

SGAs have also shown efficacy in children and adolescents with schizophrenia and are felt by some to have a preferable side effect profile (for review, see Fleischhacker 2002). One double-blind, controlled trial compared clozapine and haloperidol in treatment-refractory, childhood-onset schizophrenia and found that clozapine had a striking superiority in reducing positive and negative symptoms, although observed neutropenia and seizures were major concerns with this drug (Kumra et al. 1996). Another double-blind RCT, comparing the efficacy and tolerability of treatment with risperidone, olanzapine, or haloperidol in children and adolescents with schizophrenia and/or affective psychoses and prominent positive symptoms, showed that all of the treatments were effective with similar magnitudes of improvement (Sikich et al. 2004). The majority of participants experienced at least mild-to-moderate weight gain, sedation, and/or EPS, but the two SGAs had a lower risk of acute, severe EPS than haloperidol. A double-blind RCT comparing clozapine with olanzapine in treatment-refractory childhood-onset schizophrenia demonstrated a superior clinical response with clozapine, particularly with respect to negative symptoms, though clozapine was also associated with a greater side effect burden (Shaw et al. 2006). A number of open trials and case reports indicate possible effectiveness for quetiapine, ziprasidone, and aripiprazole.

Unfortunately, as with FGAs, pediatric patients appear to have a greater susceptibility than adults to SGA-induced side effects, particularly EPS, weight gain, and dysphoria, but also hyperprolactinemia and leukocyte dyscrasias (for review, see Masi et al. 2006). SGA-associated weight gain is especially of concern in this population, given the worsening epidemic of childhood obesity and type II diabetes mellitus

(T2DM). Metformin has shown some potential for mitigating weight gain in children treated with SGAs (Klein et al. 2006), but further research will be required to clarify the utility of this agent.

### Other Conditions in Children and Adolescents

Patients with pervasive developmental disorders may demonstrate periods of hyperactivity, screaming, and agitation with combativeness. SGAs have shown some efficacy in treating these conditions. For example, in a randomized, double-blind trial involving children with autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior, risperidone was superior to placebo in reducing irritability and affecting meaningful clinical improvement (69% vs. 12%), but also caused substantially more weight gain (McCracken et al. 2002). A number of case reports and open clinical trials with clozapine or olanzapine found an improvement in behavioral symptoms of pervasive developmental disorders with the use of these drugs. Some evidence suggests that SGAs may also be helpful in the management of conduct disorder and behavioral disturbances in children with borderline or impaired intellectual functioning.

Nonetheless, the increasingly widespread use of SGAs for the treatment of nonpsychotic disorders in children and adolescents (Olfson et al. 2006) is largely unsupported by empirical data. In particular, studies addressing the safety of this practice are limited. Further controlled studies are required to determine the role, if any, of antipsychotic agents in the treatment of nonpsychotic disorders among pediatric patients.

## Effects of Antipsychotic Agents on Symptoms of Schizophrenia

### Positive Symptoms

All antipsychotic agents are capable of ameliorating the "positive" symptoms of schizophrenia, including hallucinations, delusions, and disordered thought process. Control of these symptoms and associated behaviors is often critical to allowing patients to return to mainstream activities (Miyamoto et al. 2002).

In many patients with schizophrenia, FGAs are effective in alleviating positive symptoms and in preventing their recurrence (for review, see Miyamoto et al. 2002, 2003b). Approximately 30% of patients with acutely exacerbated symptoms, however, have little or no response to FGAs, and up to 50% have only a partial response (Fleischhacker 1995, Kane 1989). Because of this inconsistency in response, and because of the risk of EPS, some have argued that the only patients for whom FGAs are clearly preferable are those with a history of good response and tolerable side effects during treatment with an FGA (Schulz and McGorry 2000).

A number of double-blind, placebo- and active comparator-controlled studies have compared the efficacy and tolerability of SGAs with FGAs, or with other SGAs, in chronically schizophrenic patients with acute psychotic exacerbations (for review, see Markowitz et al. 1999, Miyamoto et al. 2003a, Remington and Kapur 2000). Despite great variation among individual trials in the proportion of patients who improve and the magnitude of therapeutic effects, these studies, and the carefully performed meta-analyses (Leucht et al. 1999) in which they were later included, suggest that SGAs as a group are at least as effective for psychotic symptoms as FGAs (for review, see Markowitz et al. 1999, Remington and Kapur 2000). The data are more equivocal, however, with regard to the hoped-for superiority of SGAs over FGAs.

Leucht and colleagues found modest to moderate efficacy advantages for SGAs over placebo, haloperidol, and low-potency FGAs, and greater tolerability for SGAs relative to haloperidol, but not relative to low-potency FGAs (Leucht et al. 1999, 2003b). Similarly, a large meta-analysis by Davis and collaborators concluded that the efficacy effect sizes for certain SGAs (clozapine, amisulpride, risperidone, and olanzapine) were significantly greater than the effect sizes for FGAs, and even those for other SGAs (Davis et al. 2003). In contrast, a meta-regression analysis by Geddes and colleagues showed no difference in efficacy between FGAs and SGAs when only trials that used 12 mg or less of haloperidol were included in the analysis, suggesting that the superior efficacy of SGAs observed in some trials may be due to a negative effect on efficacy of an excessively high dose of FGA comparator (Geddes et al. 2000).

It should be noted that, as with all meta-analyses, the studies described above were constrained by the biases and methodological limitations of the individual trials on which they were based. Most of these individual trials were sponsored and designed by the pharmaceutical industry, with narrow inclusion and exclusion criteria, moderate sample sizes, variable drug dosages, relatively short durations, and potentially bias-generating statistical methods (e.g., last-observation-carried-forward analyses), all of which could limit the generalizability of the results (Stroup et al. 2003). Furthermore, publication bias may have limited the data available for meta-analysis and potentially biased the findings in favor of SGAs.

Recently, two major, government-sponsored, multicenter RCTs succeeded in avoiding or minimizing many of these biases, and thereby provided some of the soundest evidence available for comparing FGAs and SGAs in the treatment of patients with schizophrenia. One of these, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, was the largest, longest, and most comprehensive independent trial ever conducted to examine existing pharmacotherapies for schizophrenia. The trial was intended to be "pragmatic," involving a representative sample of 1,493 schizophrenic patients from numerous "real-world" outpatient settings and using a primary outcome measure—time to drug discontinuation — that captured both efficacy and tolerability. Subjects in the CATIE trial were randomized in a double-blind fashion to treatment with olanzapine (7.5–30.0 mg/day, mean dose of 20.1 mg/day), quetiapine (200–800 mg/day, mean dose of 534.4 mg/day), risperidone (1.5–6.0 mg/day, mean dose of 3.9 mg/day), ziprasidone (40–160 mg/day, mean dose of 112.8 mg/day), or the midpotency FGA perphenazine (8–32 mg/day, mean dose of 20.8 mg/day) for up to 18 months of treatment (Lieberman et al. 2005a).

In phase I of the study, a humbling 74% of patients discontinued their randomly assigned antipsychotic in less than 18 months, with olanzapine showing the lowest discontinuation rate and, thus, possibly the greatest effectiveness. All five medications displayed comparable changes in Positive

and Negative Syndrome Scale (PANSS) scores. Surprisingly, perphenazine was similar in efficacy and tolerability to the SGAs, suggesting that certain FGAs remain viable treatment options in chronic schizophrenia.

In phase II of CATIE, patients were treated in one of two pathways. Those who had discontinued their phase I drug because of insufficient therapeutic efficacy could be randomly allocated to open-label treatment with clozapine ($n$ = 49), or blinded treatment with olanzapine ($n$ = 19), quetiapine ($n$ = 15), or risperidone ($n$ = 16) (McEvoy et al. 2006). There were no significant differences in PANSS positive symptom subscores either between or within groups at baseline, 3 months, and 6 months, although the relatively small number of subjects could have affected power. Clozapine-treated patients were significantly less likely to discontinue for any reason compared to patients receiving risperidone or quetiapine, and significantly less likely to discontinue for inadequate therapeutic response compared to any other SGA.

In the other phase II pathway, 444 patients who had discontinued their phase I SGA due to intolerability or lack of efficacy were rerandomized to a different SGA (Stroup et al. 2006). Time to discontinuation for any reason was significantly longer for patients treated with olanzapine or risperidone than for those receiving quetiapine or ziprasidone. PANSS positive symptom subscale scores were significantly lower in the olanzapine group than in the other three, and in the risperidone group as compared to the ziprasidone group.

Jones and colleagues conducted the other recent, government-sponsored, multicenter RCT comparing FGAs and SGAs (Jones et al. 2006). The open Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) assessed outcomes of QOL, symptoms, adverse effects, participant satisfaction, and costs of care over 1 year. CUtLASS 1 was funded by the National Health Service in the U.K. and was similar in design to CATIE (Lewis et al. 2006b). As in the CATIE trial, CUtLASS 1 found no advantage for SGAs in terms of PANSS total and positive subscale scores. In fact, patients treated with FGAs demonstrated a trend toward greater improvements in symptom scores, and neither inadequate power nor patterns of drug discontinuation accounted for the result. Like all studies, CUtLASS 1 had certain methodological idiosyncrasies that limit the generalizability of the results. For example, the protocol permitted clinicians to choose which antipsychotic agent, within the assigned class, they wished to prescribe for each patient; this resulted in the majority of patients in the FGA group receiving sulpiride, a substituted benzamide that is different from other FGAs in some respects (Lieberman 2006).

## Negative Symptoms

Negative symptoms of schizophrenia include affective blunting, emotional withdrawal, poverty of speech, anhedonia, and apathy. They may be divided into three subtypes that are often difficult to distinguish clinically: (1) primary enduring (or deficit), (2) primary nonenduring, and (3) negative symptoms that are secondary to other causes, such as depression, positive symptoms, EPS or other iatrogenic effects, and substance misuse (Buchanan and Gold 1996, Murphy et al. 2006). Approximately 70% of schizophrenic patients develop primary negative symptoms before the onset of positive symptoms (Hafner et al. 1992). These represent a core feature of the illness and may be associated with long-term disability and prolonged hospitalization (Buchanan and Gold 1996).

FGAs are, in general, substantially less effective for negative than for positive symptoms of schizophrenia (for review, see Miyamoto et al. 2002). Therefore, the comparative efficacy of SGAs for negative symptoms has received much attention. Double-blind studies of individual SGAs have found evidence of efficacy for clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, sertindole, zotepine, and amisulpride in the treatment of negative symptoms of schizophrenia. However, few of these studies have specifically examined the effect of SGA treatment on primary negative symptoms, and those that have reported little or no evidence of efficacy against this symptom domain. A notable exception is amisulpride, which does appear to demonstrate superiority over placebo and perhaps FGAs with regard to efficacy against primary or predominantly negative symptoms of schizophrenia.

In addition to these individual trials, several reviews and meta-analyses suggest that SGAs, as a group, may be more effective than FGAs against negative symptoms (Leucht et al. 1999, Tandon and Jibson 2003, Wahlbeck et al. 1999), though the effect sizes are moderate at best (Goff and Evins 1998, Leucht et al. 1999, Murphy et al. 2006). Ongoing debate exists as to whether these effects are related to a reduction in primary negative symptoms, secondary negative symptoms, or both. Path analyses have suggested that risperidone and olanzapine exert direct effects on primary negative symptoms, independent of changes in positive, depressive, or extrapyramidal symptoms (Moller 1993, Tollefson and Sanger 1997). However, these statistical approaches were performed post hoc, and only the most efficacious doses of the SGAs were used. Complicating matters further, one double-blind, placebo-controlled trial found that, in healthy individuals, single doses of haloperidol (5 mg) or risperidone (2.5 mg) produced observer-rated and self-rated negative symptoms without EPS, which may have been due to drowsiness (Artaloytia et al. 2006). This suggests that multiple properties of antipsychotic drugs may confound assessment of negative symptoms. Large, prospective studies comparing SGAs, FGAs, and placebo in patients with primary negative symptoms are needed to settle the issue.

The CATIE trial provides a notable opportunity to compare the effectiveness of multiple SGAs in the treatment of negative symptoms. In phase II of the study, there were no significant differences in PANSS negative symptom subscores either between or within treatment groups at baseline, 3 months, and 6 months (McEvoy et al. 2006). At 6 months, however, clozapine showed a trend toward greater reduction in negative symptom scores (−5.3), as compared to quetiapine (−1.1), olanzapine (−0.7), and risperidone (0.0). For patients randomized to receive olanzapine, quetiapine, risperidone, or ziprasidone in phase II, there were similarly no significant differences in PANSS negative symptom subscores among treatment groups at 12 months (Stroup et al. 2006). Thus, the results of CATIE phase II suggest only modest efficacy for SGAs in the treatment of general negative symptoms of chronic schizophrenia, with a probable small advantage for clozapine.

Encouragingly, there is growing evidence that adding certain augmentation agents to FGAs or SGAs may improve negative symptoms. Some glycine site agonists of NMDA receptors (e.g., glycine, d-cycloserine, and d-serine) and glycine transporter-1 inhibitors (e.g., sarcosine) appear to be effective in reducing negative symptoms when they are added to non-clozapine antipsychotic treatment (for review, see Miyamoto et al. 2005). Several selective serotonin reuptake inhibitors (SSRIs), including fluvoxamine, fluoxetine, and paroxetine, have shown efficacy for primary or undifferentiated negative symptoms, as adjuvants to FGAs or SGAs in placebo-controlled trials. Another antidepressant, mirtazapine, may also improve negative symptoms when used to augment haloperidol or clozapine. Double-blind, controlled trials using the neurosteroid dehydroepiandrosterone (DHEA), selegiline, Ginkgo biloba, naltrexone, or pergolide as augmenters of antipsychotic medication have suggested efficacy in the treatment of general negative symptoms of schizophrenia (for review, see Murphy et al. 2006). Many of these studies await replication.

## Cognitive Symptoms

Cognitive impairment is now widely recognized as a core feature of schizophrenia, and almost all schizophrenic patients have some degree of such deficit, as compared to the level of cognitive function that would be expected of them based on premorbid factors (Keefe et al. 2005). Schizophrenics typically perform one to two standard deviations below normal on a variety of neuropsychological measures, particularly those that assess attention, verbal skills, processing speed, and executive function (for review, see Woodward et al. 2005). Progressive decline in cognitive function occurs before the onset of any other clinical manifestations of the illness, and a wide range of cognitive deficits is usually present by the time of the first psychotic episode. After the initial psychotic episode, cognitive deficits tend to remain relatively stable, or to worsen slowly (Harvey et al. 1999). Cognitive impairments are consistently and robustly associated with negative symptoms (Galderisi et al. 2002). They are also more closely related to social and vocational functioning than are positive symptoms, and may substantially impair activities of daily living and QOL (Green 1996, Harvey et al. 1998). Because cognitive deficits are among the strongest predictors of functional outcome in schizophrenia (Green et al. 2000), the targeting of these symptoms has become a major focus of treatment.

Prior to the 1990s, many believed that the cognitive deficits observed in schizophrenia are largely a side effect of FGAs (Heinrichs 2007). Cognitive performance may, in fact, be impaired by antipsychotic-induced EPS, anticholinergic effects, or sedation (Green and Braff 2001), as well as by anticholinergic or other anti-Parkinsonian agents used to treat EPS. More recent research, however, supports the century-old observation of Kraeplin and Bleuler that cognitive dysfunction is an intrinsic feature of the disease. Consequently, the view that antipsychotics are primarily unhelpful or even detrimental to cognitive performance has been replaced with optimism regarding the potential for medications to have a salubrious effect on cognition in schizophrenia (Heinrichs 2007).

A number of investigators have tested this hypothesis with FGAs and SGAs. Two quantitative reviews reported a significant advantage for SGAs over FGAs in several domains, including verbal fluency, vigilance, selective attention, secondary memory, and visuomotor skills (Harvey and Keefe 2001, Keefe et al. 1999), although these reviews have been criticized for the small number of studies they included (Woodward et al. 2005). More recently, Woodward and colleagues conducted two comprehensive meta-analyses (Woodward et al. 2005). The first of these analyzed 14 controlled studies in which patients were randomized to treatment with an SGA (clozapine, olanzapine, risperidone, or quetiapine) or an FGA. This analysis found SGAs to be superior to FGAs, haloperidol in particular, for ameliorating overall cognitive function, and specific improvements were noted in learning and processing speed. The second analysis, which included 41 uncontrolled, prospective trials of SGAs, further supported the benefits of SGAs for a wide array of cognitive functions.

It is unclear, however, whether the improvements observed with SGAs in these studies represent true cognitive enhancement or only a relative reduction in EPS- and anticholinergic-related cognitive effects, as compared with FGAs (Carpenter and Gold 2002, Harvey and Keefe 2001). This has led to debate as to whether lower doses of FGAs might show comparable efficacy to SGAs for cognitive symptoms of schizophrenia (Mishara and Goldberg 2004). Recent studies with improved methodology suggest that low doses of haloperidol may, in fact, have a less deleterious impact on cognitive function (Green et al. 2002, Keefe et al. 2004, 2006b, 2006c).

Furthermore, some studies have found mild benefits in cognitive performance with certain FGAs (Heinrichs 2007). The most compelling of these is the CATIE trial, in which the sole FGA included, perphenazine, yielded more improvement in cognition after 18 months than any phase I SGA (Keefe et al. 2007). Notably, the magnitude of cognitive improvement was small and probably not clinically significant for all agents assessed in this analysis.

Together, the variable results of the studies reviewed here suggest that FGAs and SGAs, when dosed properly, may yield at most modest improvements in the cognitive deficits of schizophrenia. Neither class appears to be clearly superior to the other.

Recognizing the need for new drugs to treat the cognitive symptoms of schizophrenia, the U.S. NIMH has introduced the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Buchanan et al. 2005). One of the primary goals of MATRICS is to develop and facilitate the regulatory approval of novel procognitive agents. Studies in rodents, nonhuman primates, and patient populations have already revealed a number of potential molecular targets for improving cognition (Miyamoto et al. 2005).

## Affective Symptoms

Depressive symptoms are common in all phases of schizophrenia, and are associated with poorer outcomes, impaired social and vocational functioning, lower QOL, and an increased risk of relapse and suicide (Burton 2006). The modal rate of comorbid depression in schizophrenia has been reported to be 25% (Siris 2000). When schizophrenic patients experience depressive features, differential diagnostic considerations should include major depression,

antipsychotic-induced side effects, demoralization, concurrent abuse of or sudden withdrawal from substances, schizoaffective disorder, and primary negative symptoms (Lehman et al. 2004).

FGAs have been found to have at least some degree of antidepressant activity in patients with schizophrenia (Siris 2000). SGAs also appear to improve affective symptoms in schizophrenia. Specifically, olanzapine, risperidone, quetiapine, amisulpride, and aripiprazole all have demonstrated greater efficacy than placebo and/or haloperidol in reducing depressive symptoms in this patient population. Clozapine has shown a significant effect on depressive symptoms in partially responsive and treatment-refractory schizophrenia. Whether there are differences among SGAs in their capacity for ameliorating depressive symptoms comorbid with schizophrenia has yet to be determined.

Antidepressants are often used in combination with antipsychotic drugs when schizophrenic patients experience depressive symptoms that meet the criteria for major depressive disorder, are causing significant distress, or are interfering with function. Several trials of tricyclic antidepressants added to FGAs support their use for acute and maintenance treatment of depressive symptoms in patients with stable schizophrenia (Hogarty et al. 1995, Siris et al. 1994). However, in one placebo-controlled trial, the addition of desipramine or amitriptyline to haloperidol in actively psychotic schizophrenic inpatients was associated with worsening of psychosis and no significant therapeutic advantage for depressive symptoms (Kramer et al. 1989). This and other studies suggest that tricyclic antidepressants may be successful for the treatment of depression in schizophrenia only once the acute psychotic episode has stabilized. As of yet, neither the use of SSRIs nor the addition of antidepressants to SGAs has been adequately studied in patients with schizophrenia and comorbid depression.

### Suicidal Behavior

Suicidal behavior is common in schizophrenia. Approximately 50% of patients with schizophrenia or schizoaffective disorder attempt suicide, and about 10% "succeed" in taking their own lives. Although there is some evidence to suggest that FGAs probably reduce suicide risk to some extent, other studies suggest that side effects, especially akathisia, may be significant risk factors for suicide.

Among the SGAs, clozapine appears to possess particular antisuicidal properties. The International Suicide Prevention Trial (InterSePT), a double-blind RCT, compared suicidal behavior in 980 patients at relatively high risk for suicide, who were randomized to clozapine or olanzapine treatment and followed for up to 2 years (Meltzer et al. 2003). Approximately 25% of these patients had treatment-resistant schizophrenia. Suicidal behavior was significantly less common in patients treated with clozapine, as reflected by fewer patients attempting suicide, requiring hospitalizations or rescue interventions to prevent suicide, or requiring concomitant treatment with antidepressants, anxiolytics, or soporifics. Although the InterSePT study has been criticized for certain methodological limitations, such as lack of blinding among patients and clinicians, the results were compelling enough to garner the U.S. FDA's approval of an indication unique to clozapine: reduction of the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

### Quality of Life

Marking a conceptual shift in therapeutic outcome criteria, QOL is now considered by many to be a key measure of response to antipsychotic treatment in schizophrenia (Karow and Naber 2002). Schizophrenic patients generally score very poorly on subjective and objective measures of QOL. Research suggests that several factors can affect QOL, including severity of symptoms, presence of anxiety or depression, age, antipsychotic-induced side effects, sociodemographic variables, and patients' subjective responses to medication (Hofer et al. 2004).

The majority of recent QOL studies involve SGAs, and many use haloperidol as a comparator. Although most of these studies suffer from methodological and design limitations, a preponderance of evidence suggests a favorable impact on subjective QOL with at least some SGAs (Awad and Voruganti 1999, 2004). For example, in large double-blind trials, both clozapine and amisulpride produced greater improvements in Quality of Life Scale (QLS) scores than did haloperidol in patients with schizophrenia or schizophreniform disorder. Olanzapine, in contrast, has shown mixed QOL results relative to haloperidol.

As with other measures of antipsychotic drug response addressed above, CATIE and CUtLASS found no clear differences between SGAs and FGAs with respect to QOL. During phase I of the CATIE trial, there were no significant differences between perphenazine and any SGA, as measured by quality-adjusted life year ratings that combined measures of symptoms and side effects (Rosenheck et al. 2006). Similarly, CUtLASS 1 found no statistical advantage for SGAs in terms of QOL, symptoms, or associated costs of care across 1 year (Jones et al. 2006). In fact, patients treated with FGAs in CUtLASS 1 demonstrated a trend toward greater improvements in QLS and symptom scores, and neither inadequate power nor patterns of drug discontinuation accounted for these results.

CUtLASS 2, an extension of the National Health Service-funded, pragmatic, open, multicenter RCT, compared clozapine against other SGAs and found no statistically significant differences in QLS scores, but did detect a trend ($p = 0.08$) toward higher scores with clozapine (Lewis et al. 2006a).

## Treatment of Different Phases of Schizophrenia

### Treatment during the Acute Phase

#### Route of Administration

Antipsychotic medications may be available as tablets, liquid concentrates, orally-dissolving formulations, short-acting parenteral preparations, or long-acting preparations. In most cases, patients who are cooperative prefer oral to parenteral administration (Marder 1997). Even agitated patients will often accept oral medication. In a survey of 51 psychiatric emergency services, only an estimated 10% of patients required injectable formulations (Currier 2000). In general, oral medication should be offered whenever it is possible to communicate with the patient. Once given,

oral formulations tend to be rapidly and well absorbed from the gastrointestinal tract and reach a peak plasma concentration in 1–10 hours (Burns 2001). The long half-life and active metabolites of most oral antipsychotic drugs allow for once- to twice-daily dosing (Burns 2001, Marder 1997). Among SGAs, quetiapine and ziprasidone have relatively shorter half-lives (Table 102–4) and consequently are usually administered in divided doses. Once- or twice-daily dosing of an oral preparation will typically result in steady-state blood levels in 2–5 days, depending on half-life. One disadvantage to oral administration is that it may be less dependable than parenteral administration (Marder 1997). For example, sometimes patients will appear to accept oral medication but will actually "cheek" or spit the drug, rather than swallow it. Liquid concentrates or orally disintegrating tablets are available for some antipsychotics and may be used to circumvent this problem. A further disadvantage of oral antipsychotic administration is that pharmacokinetic factors such as hepatic disease or slow gastrointestinal absorption may increase the half-life of the drug and the time required to attain steady-state concentration (Marder 1997).

Short-acting IM formulations are particularly useful in the management of acute pathological agitation. Such formulations are commonly used to treat severely disturbed patients who cannot be verbally redirected, who may be violent, and who may require medication over objection. In these situations, many clinicians favor a combination of an antipsychotic and a benzodiazepine, often including an anticholinergic agent if a high-potency neuroleptic is being used (for review, see Miyamoto et al. 2003b). Most short-acting IM antipsychotic preparations reach a peak serum concentration approximately 30–60 minutes after administration. Parenteral administration bypasses first-pass metabolism in the liver and gut, resulting in greater bioavailability of the drug. A single IM injection of a high-potency FGA such as haloperidol or fluphenazine can result in rapid calming. This calming effect is thought to be the result of sedation and the patient's perception of having his or her needs addressed. True antipsychotic effect was formerly believed to develop only after several days or weeks (American Psychiatric Association 2004). Kapur and colleagues, however, have presented evidence that the onset of antipsychotic action of IM haloperidol may occur within 24 hours of first injection (Kapur et al. 2005). A disadvantage of IM administration is the risk of injury to the patient and to the caregiver, usually by needle stick or accompanying physical

**Table 102–4 Dosing Parameters of Second-Generation Antipsychotics**

| | Half-life (h) (mean) | Starting Dose (total mg/day) | Average Dose Range (mg/day) | | Average Maintenance Dose (mg/day) | Routes of Administration |
|---|---|---|---|---|---|---|
| | | | First episode | Recurrent episode | | |
| Clozapine | 10–105 (16) | 25–50 | 150–300 | 400–600 | 400 | Oral |
| Risperidone | 3–24 (15) | 1–2 | 2–4 | 4–6 | 4–6 | Oral, extended release injectable |
| Olanzapine | 20–70 (30) | 5–10 | 10–20 | 15–30 | 10–20 | Oral, IM |
| Quetiapine | 4–10 (7) | 50–100 | 300–400 | 500–800 | 400–800 | Oral |
| Ziprasidone | 4–10 (7) | 40–80 | 80–120 | 120–200 | 120–160 | Oral, IM |
| Amisulpride | (12) | 50–100 | 50–300 | 400–800 | 400–800 | Oral |
| Zotepine | 12–30 (15) | 50–100 | 75–150 | 150–450 | 75–300 | Oral |
| Aripiprazole | (75) | 10–15 | 10–30 | 15–30 | 15–30 | Oral |
| Paliperidone | (23) | 3–6 | 3–12 | 6–12 | 3–12 | Oral |

*Source:* Adapted and modified from McEvoy et al. (1999), Burns (2001), and Worrel et al. (2000).

restraint. In addition, high doses of high-potency drugs can lead to dystonia or akathisia, which may increase the patient's agitation. Coadministration of an anticholinergic medication may reduce this risk.

Among SGAs, short-acting IM formulations of olanzapine and ziprasidone are available in some countries. These appear to be well tolerated and to substantially reduce symptoms of acute agitation in patients with psychotic disorders.

In the past, FGAs were sometimes administered intravenously in the acute setting. This practice is generally associated with a more rapid onset of therapeutic action than occurs with IM preparations. Intravenous antipsychotic use, however, may increase the risk of cardiac arrhythmias and autonomic complications, and consequently is now usually avoided (Allen et al. 2001).

Several FGAs (e.g., haloperidol and fluphenazine) are available in long-acting depot formulations, and risperidone is available in an analogous preparation of extended release (ER) microspheres. These long-acting formulations are seldom prescribed for acute psychotic episodes because they take months to reach steady-state levels and are eliminated very slowly (Miyamoto et al. 2003a). They are, however, especially advantageous in patients with compliance problems, and those with a history of severe relapse upon medication discontinuation. Long-acting formulations also simplify compliance monitoring, as they are generally administered at scheduled intervals by a health care provider. This type of medication may therefore be particularly helpful in the maintenance phase of treatment.

A short-acting depot preparation of clopenthixol, a neuroleptic of the thioxanthene group, is available in some areas. Recommendations regarding the use of zuclopenthixol acetate, the *cis*-(Z)-isomer of clopenthixol, in emergency psychiatric settings should be viewed with caution due to a lack of well-conducted RCTs (Miyamoto et al. 2003a).

## Selection of an Antipsychotic Agent

In addition to route of administration, clinicians selecting an agent for the acute management of agitation associated with psychosis should also consider the patient's clinical symptoms and history of response to individual agents, as well as differences in side effects and half-life of candidate drugs. An ideal medication would be available in parenteral and oral preparations, be well tolerated, and be effective in both acute and long-term settings (Miyamoto et al. 2003b).

### *First-Generation Antipsychotics*

Many clinicians favor oral or IM preparations of high-potency FGAs (e.g., haloperidol) in the acute setting. These agents are felt to be reliable, and possibly safer than older alternatives such as low-potency FGAs and barbiturates (Allen 2000). Droperidol, a butyrophenone antipsychotic closely related to haloperidol, was formerly a popular agent for the control of acute agitation, but the drug received a "black-box" warning from the U.S. FDA in 2001 because of a risk of QTc prolongation, cardiac dysrhythmia, and death. Some authors still consider droperidol to be safe and effective when prescribed in appropriate doses with close monitoring (Marco and Vaughan 2005), but it is no longer routinely recommended for acutely agitated patients (Rund et al. 2006). As mentioned above, an anticholinergic agent is often coadministered when a high-potency antipsychotic is prescribed in the acute setting, in order to reduce the risk of EPS.

### *Second-Generation Antipsychotics*

Many experts now recommend SGAs (except clozapine) as first-line treatment for schizophrenia, including in an acute episode (Kane et al. 2003b). One advantage of SGAs is their lower risk, compared with many FGAs, of akathisia and dystonia, which may worsen agitation. In general, sequential trials of individual SGAs are preferable to combining multiple antipsychotics at once. It is usually possible to safely and rapidly escalate the dose of SGAs in the psychiatric emergency setting. A strategy often used is to combine an oral SGA and a benzodiazepine (Allen et al. 2001). Some experts recommend reducing or discontinuing benzodiazepines once behavioral control is achieved.

A number of studies suggest that certain SGAs may possess antiaggressive properties. Clozapine, for example, appears to reduce aggression in chronically psychotic patients (Volavka et al. 2004), and this effect may be independent of the drug's antipsychotic and sedative actions (Krakowski et al. 2006). However, rapid dose titration of clozapine for the treatment of aggression is contraindicated because of the potential for serious side effects, including seizure and agranulocytosis. Risperidone and quetiapine have also been found in some studies to specifically reduce hostility during acute psychotic episodes, but other studies have shown no such effect.

The above-mentioned studies notwithstanding, relatively little research has been conducted on the utility of SGAs in the management of acute aggression, and there has been less clinical experience with them than with FGAs. A major challenge in carrying out this research is the difficulty of obtaining informed consent from patients who are, by definition, hostile.

More attention is now being paid to the important clinical issue of SGA efficacy in first-episode schizophrenia. Two studies examined clozapine as an initial treatment (Lieberman et al. 2003a, Woerner et al. 2003), and neither found advantages that would warrant its use as a first-line agent. The European Foundation for Research in Schizophrenia is currently conducting the European First Episode Schizophrenia Treatment Trial (EUFEST), in which patients with first-episode schizophrenia are treated with ziprasidone, olanzapine, quetiapine, amisulpride, or low-dose haloperidol (Fleischhacker et al. 2005). It is hoped that this effort will inform the clinician's difficult decision of which antipsychotic agent to initiate early in the course of the illness.

## Antipsychotic Dose

The goal of pharmacotherapy is to maximize efficacy and minimize adverse effects with the lowest effective dose (Janicak and Davis 1996). Most current dosing guidelines rely on clinical impressions to achieve this goal. Not surprisingly, doses recommended in these guidelines often differ considerably, sometimes threefold or more (Davis and Chen 2004).

Determination of optimum antipsychotic dose is complicated by the fact that responses may differ from patient to patient and may differ across phases of the illness. For example, first-episode patients generally respond to lower

antipsychotic doses than do patients with recurrent episodes (Robinson et al. 2005). Poor or partial responders may benefit from somewhat higher doses than robust responders (Davis and Chen 2005), and those in the maintenance phase may be treatable with lower doses than when they were acutely psychotic (Kane et al. 1983). The physiology of this variability is not well understood, but it seems likely that individual variation in pharmacokinetic factors and in brain receptor density and/or sensitivity plays a role.

### *Rapid Neuroleptization*

Rapid neuroleptization was proposed decades ago as a strategy for managing agitation in acutely psychotic patients (for review, see Donlon et al. 1979). This practice involved the use of high doses of IM high-potency FGAs, usually haloperidol, administered repeatedly over a 24-hour period, until the patient demonstrated obvious sedation or other side effects (Donlon et al. 1979). In the years after the introduction of rapid neuroleptization, a number of well-controlled, double-blind studies comparing high-dose strategies with standard-dosage regimens revealed no significant superiority for high dosage in either degree or rapidity of response in acutely psychotic patients (for review, see Miyamoto et al. 2003a). Moreover, very high doses of FGAs produced a significantly greater incidence of EPS, particularly akathisia and akinesia, which can cause significant discomfort and worsen outcome. Thus, rapid neuroleptization has been largely abandoned as a therapeutic strategy.

A modified approach to rapid neuroleptization, called rapid initial dose escalation, was investigated in a randomized, double-blind study (Baker et al. 2003). One hundred forty-eight acutely agitated patients received treatment over 4 days with either 10 mg/day or up to 40 mg/day of olanzapine. Higher doses produced a more rapid and more robust reduction in the PANSS Excited Component, despite the fact that the 10-mg group received almost 20-fold more supplemental lorazepam.

### *Effective Doses of FGAs*

Even after several decades of use, the optimum dose of FGAs, particularly haloperidol, is still debated. The "neuroleptic threshold hypothesis" contends that fine motor phenomena, as opposed to classic EPS, signal the minimum effective dose for many acutely psychotic patients (for review, see Janicak and Davis 1996, McEvoy et al. 1991). The "therapeutic window hypothesis" posits that therapeutic effects are not achieved until a certain dose or serum drug level is reached, and that these effects are lost beyond another, higher dose or drug level (Davis and Chen 2004). Most experts would agree that therapeutic effects do not continue to increase with very high FGA doses, but considerable controversy persists as to whether the efficacy of FGAs actually diminishes at higher doses. Geddes and colleagues argued that doses equivalent to more than 12 mg/day of haloperidol are less efficacious than lower doses because of the negative effects of EPS and perhaps other side effects such as sedation (Geddes et al. 2000). In contrast, a meta-analysis of 42 double-blind, random-assignment studies comparing various doses of FGAs found that doses under 3.3 mg/day, expressed in haloperidol equivalents, were clearly less effective than higher doses, but that all doses above this threshold were fully efficacious (Davis and Chen 2005). Data from imaging studies further support the use of low-to-moderate doses of FGAs in acute schizophrenia. For example, PET research has found that a dose of 2–5 mg of haloperidol induces 53–74% striatal $D_2$ receptor occupancy, with substantial clinical improvement (Kapur et al. 1996, 2000a). These studies do not preclude the requirement of some patients for a higher than normal antipsychotic dose, but they do suggest that when groups of patients are assigned to very high doses, such as more than 2000 mg/day of chlorpromazine or 40 mg/day of haloperidol, the average rate and amount of improvement are likely to be no greater than for those assigned to more moderate doses, and may in fact be lower (Marder 1996).

### *Effective Doses of SGAs*

The dosage recommendations for SGAs are summarized in Table 102–4. As with FGAs, optimal dosing of SGAs is a controversial issue. Many clinical trials of SGAs use placebo controls and active comparators, but the active comparator is usually given in one fixed dose or fixed dosage range, whereas the SGA may have more dosing options. This practice has led to much disagreement around the interpretation of such studies.

When risperidone was first released, a dose of 6 mg/day was recommended on the basis of data from large, fixed-dose trials (Marder and Meibach 1994), which found that 6 mg/day was associated with the greatest improvement and with rates of EPS comparable to placebo. A review of clinical trials and market research later concluded that the most effective dose with minimal side effects is 4–6 mg/day (Kasper 1998). Brain imaging studies support the use of lower doses of risperidone. For example, a PET study demonstrated that the mean $D_2$ occupancy in eight first-episode or drug-free schizophrenic patients who received 6 mg/day of risperidone was 82%, which is probably higher than necessary for achieving optimal clinical effects without EPS (Nyberg et al. 1999). After dose reduction to 3 mg/day, mean $D_2$ occupancy was 72%, suggesting that 3–4 mg/day may be an optimal dose. On the basis of naturalistic trials, clinical audit, phase IV trials, PET data, and 5 years of practical experience, Williams concurred that the optimal dose of risperidone with respect to efficacy and tolerability is 4 mg/day for most schizophrenic patients (Williams 2001). A randomized study of risperidone ER microspheres found the near-maximal effective dose to be approximately 50 mg/month, with 25 and 75 mg/month producing less improvement (Kane et al. 2003a).

The recommended starting dose of olanzapine is 5–10 mg/day. Ten to 20 mg/day has been shown in clinical trials to be an effective dose for most schizophrenic patients (for review, see Bhana et al. 2001). These findings are consistent with PET studies that demonstrated 71–80% striatal $D_2$ occupancy in schizophrenic patients treated with 10–20 mg/day of olanzapine (Kapur et al. 1998). Doses above 20 mg/day resulted in greater than 80% $D_2$ occupancy, EPS, and prolactin elevation. Nonetheless, in some cases, greater efficacy may be achieved at doses above 20 mg/day (Lieberman et al. 2005a, Volavka et al. 2002).

Dosing recommendations for clozapine vary two- to threefold between the U.S. and the Europe (Fleischhacker et al. 1994). This may be due to the fact that in the U.S. clozapine use is restricted to patients with severe treatment resistance, while in Europe the drug is used somewhat more flexibly.

Quetiapine has demonstrated superiority over placebo for the treatment of positive symptoms at dosages of more than 150 mg/day, and for negative symptoms at a dosage of 300 mg/day (Arvanitis et al. 1997). Clinical experience has shown that considerably higher doses of quetiapine may yield further benefit, and some practitioners will prescribe up to 1200 mg/day.

Several trials have found 150–300 mg/day of zotepine to be as effective as some FGAs in improving positive and negative symptoms of schizophrenia (Barnas et al. 1992, Cooper et al. 2000, Petit et al. 1996).

Sertindole in the dose range of 12–24 mg/day may reduce positive symptoms, whereas 20 mg/day may be required to improve negative symptoms (Zimbroff et al. 1997).

Conversely, lower doses of amisulpride (50–300 mg/day) have been found to improve negative symptoms (Boyer et al. 1995, Danion et al. 1999, Paillere-Martinot et al. 1995, Speller et al. 1997), while higher doses (400–800 mg/day) are sometimes necessary to control positive symptoms (Moller et al. 1997, Puech et al. 1998).

A number of short- and long-term double-blind trials have shown aripiprazole to be efficacious against psychotic symptoms in the dose range of 10–30 mg/day (for review, see Lieberman 2004). In these studies, increasing the dose above 15 mg/day did not appear to augment efficacy. Interestingly, in schizophrenic patients with an acute psychotic exacerbation, treatment with 5 mg/day of aripiprazole produced improvements in some outcome measures, including negative symptoms, but not in the PANSS total score (Cutler et al. 2006).

## Maintenance Treatment

### Therapeutic Goals

The principal goals of treatment during the stable or maintenance phase are to preserve symptom remission, prevent psychotic relapse, implement a plan for rehabilitation, optimize functioning, and improve QOL (American Psychiatric Association 2004, Marder 1999). Antipsychotic medication is central to the achievement of these goals. A review of 24 double-blind studies of maintenance treatment with FGAs found that approximately 70% of patients who were switched to a placebo relapsed during the subsequent year, whereas only about 30% of patients receiving an antipsychotic agent suffered a relapse (Davis 1975, Gilbert et al. 1995).

Due to a paucity of long-term studies, the optimum duration of maintenance antipsychotic pharmacotherapy for schizophrenia has not been rigorously determined. Some guidelines recommend that first-episode patients be treated for 1–2 years; however, 75% of patients will relapse after this treatment is discontinued (Davis et al. 1994, Kissling 1991, Lehman and Steinwachs 1998). Schizophrenic patients who have suffered multiple psychotic episodes should receive at least 5 years of maintenance therapy (Kissling 1991), and in clinical practice many of these patients are treated indefinitely (Davis et al. 1994). Those with severe or dangerous episodes should likewise receive chronic antipsychotic pharmacotherapy.

### Oral First-Generation Antipsychotics

The risk of FGA-induced long-term side effects, especially TD, inspired a search for strategies to reduce patients' exposure to these agents while still providing adequate protection against psychotic relapse (Marder 1999). Studies of the dose–response relationship found that lowering the acute treatment dose by approximately 80% may be relatively safe during the maintenance phase, but that relapse rates are excessively high when the dose is reduced further (Marder et al. 1987, Hogarty et al. 1988, Kane et al. 1983). An international consensus conference recommended a gradual reduction in antipsychotic dose of approximately 20% every 6 months until a minimal maintenance dose is reached (Kissling 1991). A minimal maintenance dose was considered to be as low as, for example, 2.5 mg of oral fluphenazine or haloperidol daily, 50 mg of haloperidol decanoate every 4 weeks, or 5 mg of fluphenazine decanoate every 2 weeks (Kissling 1991). If this strategy is employed, patients should be followed closely, as a significant proportion will relapse during dose reduction. As noted previously, targeted or intermittent pharmacotherapy is associated with increased risks of symptom exacerbation, relapse and rehospitalization, and consequently should be avoided (Gaebel 1995).

### Oral Second-Generation Antipsychotics

The potential of SGAs to delay psychotic relapse in patients with schizophrenia or schizoaffective disorder has been evaluated in a number of studies. Risperidone, olanzapine, and clozapine have each shown superior efficacy, relative to haloperidol or chlorpromazine, in reducing the rate of psychotic relapse. Fewer studies have investigated the effectiveness of other SGAs during the maintenance phase of treatment; however, a limited amount of evidence suggests that aripiprazole, zotepine, ziprasidone, and sertindole are capable of delaying relapse.

Phase I of the CATIE study provided a rare opportunity to compare the long-term effectiveness of multiple SGAs with that of an FGA. In this phase, treatment with olanzapine resulted in the lowest rate of discontinuation, the longest time to discontinuation, and the fewest hospitalizations, as compared with quetiapine, risperidone, ziprasidone, and perphenazine (Lieberman et al. 2005a). Another informative study prospectively followed a cohort of 2,230 patients hospitalized for the first time due to schizophrenia or schizoaffective disorder. Patients treated with perphenazine depot, clozapine, or olanzapine had a lower risk of rehospitalization and of all-cause discontinuation of their first treatment than did those treated with haloperidol (Tiihonen et al. 2006). Finally, in a meta-analysis of relapse prevention studies comparing SGAs and FGAs, the rates of relapse and overall treatment failure were found to be modestly but significantly lower with SGAs (Leucht et al. 2003a). Important methodological limitations acknowledged by the authors included the choice of comparator FGAs, doses, relapse criteria, and adherence-monitoring protocols employed in the original studies.

Collectively, the studies described here suggest that some SGAs, such as clozapine and olanzapine, may be associated with a slightly greater reduction in relapse risk, relative to FGAs and other SGAs, during the maintenance phase of treatment.

### Adherence

Reported rates of antipsychotic nonadherence (i.e., noncompliance) range from 20 to 89% (Dolder et al. 2002).

Consistent with this, a dispiriting 74% of patients in phase I of the CATIE study discontinued their medication before 18 months had elapsed, although these patients knew they were then allowed to be rerandomized to another agent in phase II (Lieberman et al. 2005a).

It is unclear whether FGAs and SGAs differ with respect to adherence rates. Some investigators have found no significant difference in adherence between the two classes of medication (Cabeza et al. 2000). Others have identified differences that approached significance (Olfson et al. 2000), and still others have reported a significant difference favoring SGAs in some measures of adherence (Rosenheck et al. 2000). The variability of these findings may be due to differences in methodology, specific medications evaluated, frequency of assessments, and/or treatment settings (Dolder et al. 2002).

In a first-episode algorithm study involving treatment with FGAs, Parkinsonian side effects increased the likelihood of medication nonadherence, and relatively better executive functioning decreased it (Robinson et al. 2002). This suggests that efforts to minimize side effects and improve cognitive deficits may enhance adherence (Robinson et al. 2005).

### Long-Acting Formulations

Long-acting antipsychotics provide continuous medication delivery and reduce plasma drug level fluctuations. Long-acting depot formulations of FGAs, which were introduced in the 1960s, lowered relapse rates by an average of 15% compared to oral neuroleptics in six double-blind, randomized trials (Glazer and Kane 1992). A preparation of risperidone ER microspheres, the first long-acting SGA, demonstrated superior efficacy relative to placebo in a 12-week study (Kane et al. 2003a). The efficacy of long-acting risperidone is further supported by several open-label, flexible-dose studies involving stable patients. Studies comparing the efficacy of long-acting SGAs and long-acting FGAs are needed.

## Treatment Resistance

One fifth to one third of all patients with schizophrenia experience significant psychotic symptoms despite adequate trials of pharmacological treatment, and are considered "treatment resistant" (Lieberman 1999b). Additional subsets of patients may be treatment intolerant, treatment noncompliant, or slow to respond (Conley and Kelly 2001). The exact definition of treatment resistance is controversial (for review, see Peuskens 1999). The most widely accepted criteria derive from the work of Kane and collaborators (1988). These criteria are strict and focus particularly on positive symptoms. Some of the more recent definitions of treatment resistance give greater weight to persistent negative symptoms and cognitive impairments, which have an important impact on level of functioning, psychosocial integration, and QOL (Conley and Kelly 2001, Peuskens 1999).

### Clozapine

Clozapine is the only medication to consistently display efficacy for psychotic symptoms in well-defined, treatment-refractory patients, and it is the only antipsychotic approved by the U.S. FDA for this indication (Conley and Kelly 2001, Kane et al. 1988). The drug's singular efficacy in treatment resistance was first conclusively demonstrated in a pivotal study involving 268 patients who were prospectively established to be treatment resistant using narrow criteria (Kane et al. 1988). Thirty percent of patients receiving clozapine responded at 6 weeks, compared to 7% treated with chlorpromazine. A subsequent review and meta-analysis of seven controlled trials comparing clozapine to an FGA in treatment-resistant schizophrenia found clozapine to be superior to FGAs in terms of overall psychopathology reduction, EPS, and compliance, although the magnitude of the drug's therapeutic effect was not consistently robust (Chakos et al. 2001).

### Other Second-Generation Antipsychotics

Investigators have explored the use of other SGAs in treatment-resistant schizophrenia, with largely uninspiring results. A few controlled trials did not detect a difference in efficacy between risperidone and clozapine (Bondolfi et al. 1998), but overall the literature does not provide convincing evidence of equivalence between the two drugs in treatment-resistant schizophrenia (Gilbody et al. 2000). Early clinical reports also suggested a possible role for high-dose olanzapine in the management of treatment-refractory schizophrenia (Dursun et al. 1999); however, a preponderance of evidence from controlled trials has not shown this strategy to be as effective as treatment with clozapine (Conley et al. 1998, Kelly et al. 2003). The CUtLASS 2 trial compared the effectiveness of clozapine with that of other SGAs (amisulpride, olanzapine, quetiapine, and risperidone) in 136 schizophrenic patients with clinician-defined poor response to two or more antipsychotics (Lewis et al. 2006a, 2006b). Clozapine showed a statistically significant advantage with respect to total PANSS score, but not QOL or associated costs of care over 1 year.

Because of clozapine's superior efficacy relative to FGAs and other SGAs, monotherapy with this agent represents the "gold standard" for treatment of patients with refractory schizophrenia. Unfortunately, side effects and the need for regular blood monitoring render it unsuitable as a first-line medication. Most experts recommend trials of other SGAs before proceeding to clozapine in almost all patients (Conley and Kelly 2001, Miyamoto et al. 2002). Certain patients may respond preferentially to a single agent of this class and potentially avoid the burden of treatment with clozapine. Clinicians should not, however, routinely withhold clozapine from patients who have failed treatment with multiple other agents.

### Adjuvant Treatment

Even with clozapine treatment, a considerable number of patients do not respond or are only partially responsive. One strategy commonly employed in the management of such patients is to augment clozapine with other psychotropic medications. The evidence supporting this practice, however, is very limited. One group investigated the efficacy of clozapine as monotherapy and with sulpiride adjuvant pharmacotherapy, using a double-blind, placebo-controlled design (Shiloh et al. 1997). The clozapine-sulpiride group exhibited significantly greater improvement in positive and negative symptoms. RCTs assessing the augmentation of clozapine with risperidone in treatment-refractory schizophrenia have yielded inconsistent and largely negative findings. Lamotrigine has likewise produced mixed results in

this patient population. Adjuvant treatment with another anticonvulsant agent, topiramate, effectively reduced general psychopathological symptoms in one double-blind RCT involving patients with schizophrenia resistant to treatment with SGAs (Tiihonen et al. 2005).

In sum, no drug has consistently and repeatedly demonstrated efficacy as an adjuvant to clozapine in treatment-resistant schizophrenia. Consequently, antipsychotic polypharmacy should not routinely be employed in this population, as it may worsen side effects without conferring therapeutic advantage. Further controlled studies are needed to clarify the potential of other psychotropic agents to serve as adjuvants in treatment-resistant schizophrenia.

## Use of Plasma Levels of Antipsychotic Drugs

The clinical use of plasma antipsychotic levels to guide dose titration remains controversial. Enormous inter-individual variation in plasma drug levels exists among patients treated with the same antipsychotic dose, and for most drugs there is at best a moderate correlation between these levels and clinical effects (Kane and Marder 1993, Van Putten et al. 1991). It is likely that advances in pharmacogenetics (the study of genetic variation that gives rise to differing responses to medication) will be required to elucidate the complex and idiosyncratic relationships among drug dosage, plasma level, therapeutic efficacy, and adverse effects in individual patients.

Nonetheless, it may be useful to monitor the plasma level of antipsychotic medication in certain circumstances. For example, before deciding that an agent is ineffective despite an adequate trial duration at a sufficient dose, it is important to determine whether lack of efficacy may be due to such factors as pharmacokinetic variables (e.g., cytochrome P450 oxidase polymorphisms) or medication nonadherence (Van Putten et al. 1991). A low plasma level (e.g., less than 5 ng/ml of haloperidol) at a normally therapeutic drug dose may prompt the clinician to raise the dose, investigate etiologies of poor absorption or accelerated metabolism, or address medication compliance. A high plasma level (e.g., greater than 15 ng/ml of haloperidol), on the other hand, may suggest lowering the dose, because adverse effects may be overshadowing therapeutic ones. This approach is practicable for the many FGAs for which therapeutic ranges have been established.

With clozapine, the case for routine plasma drug level monitoring is somewhat stronger. Miller and colleagues (1994) reported that plasma clozapine concentrations higher than 350 ng/ml were associated with greater likelihood of response in a small group of patients with treatment-refractory schizophrenia. Similarly, VanderZwaag and colleagues (1996) found that patients randomly assigned to receive treatment with clozapine at a serum level range of 200–450 ng/ml responded better than did patients receiving clozapine at a serum level range of 50–150 ng/ml. Given these and related findings, it is reasonable to monitor plasma drug levels during clozapine treatment, with the goal of titrating the dose to achieve levels between 200 and 400 ng/ml. This typically requires a clozapine dose of 300–400 mg/day (Lehman et al. 2004).

## Drug Interactions and Antipsychotic Agents

Most antipsychotics are metabolized by the hepatic cytochrome P450 (CYP) system. The major CYP isoenzymes responsible for the metabolism of SGAs are CYP1A2, CYP2C19, CYP2D6, and CYP3A4. A notable exception is amisulpride, which is excreted relatively unmetabolized in the urine (Spina and de Leon 2007). SGAs have little effect on the elimination of other medications, and this represents an advantage over some FGAs, such as phenothiazines, which can potently inhibit CYP2D6 and other CYP isoenzymes, thereby increasing the levels of medications metabolized by this system (Spina and de Leon 2007). Plasma levels of SGAs are affected by drugs that induce or inhibit CYP isoenzymes, sometimes with consequences for antipsychotic efficacy and adverse effects. These interactions usually involve antidepressant and antiepileptic drugs, with the classic example being an up-to-10-fold increase in clozapine levels following addition of fluvoxamine. Table 102–5 summarizes clinically significant pharmacokinetic drug interactions affecting SGAs. With some FGAs, clearance can be decreased by co-administering certain heterocyclic antidepressants, beta-blockers, antibacterials, antifungals, or cimetidine; cigarette smoking, in contrast, increases clearance of high-potency FGAs (Ereshefsky 1996).

There are other common interactions that will concern clinicians. Via an unclear mechanism, valproic acid increases quetiapine levels by 70–80% (Spina and de Leon 2007). Antipsychotic medications can antagonize the effects of dopamine agonists and levodopa, agents used in the treatment of PD. Antipsychotics may also enhance the effects of central nervous system depressants, such as analgesics, anxiolytics, and hypnotics. Rarely, co-administration of clozapine and benzodiazepines can cause respiratory arrest.

In general, avoidance of unnecessary polypharmacy and readiness to adjust antipsychotic dosage based on clinical response, and possibly plasma drug concentration, will help to minimize adverse drug interactions (Spina and de Leon 2007).

## Antipsychotic Medications and Pregnancy

A substantial number of women of childbearing age suffer from schizophrenia and other psychiatric disorders that require treatment with antipsychotic medication, and approximately one third of pregnant women with psychotic symptoms use antipsychotics at least once during pregnancy (Iqbal et al. 2005). Treatment with antipsychotic medication during pregnancy is likely to serve a protective function for women with schizophrenia, as antipsychotic discontinuation often leads to rapid relapse (Baldessarini and Viguera 1995, Gilbert et al. 1995). Such relapse may pose risks to the fetus and mother, including stillbirth, prematurity, small size for gestational age, difficulties with parenting, and, in the majority of cases, loss of custody (Nilsson et al. 2002, Yaeger et al. 2006).

Complicating matters, antipsychotic treatment itself incurs risks for the developing fetus. Most antipsychotics readily cross the placenta and are secreted into breast milk to some degree (Trixler and Tenyi 1997). Metabolite concentrations may be higher in the fetal than in the maternal circulation (Gentile 2004). Animal studies have shown evidence of teratogenic effects with most FGAs and SGAs (Iqbal et al. 2005). In human pregnancies, however, FGAs, particularly high-potency agents, appear to be relatively safe for the fetus (Lehman et al. 2004). For example, a multicenter, prospective, controlled cohort study evaluated the outcomes of 188 haloperidol-, 27 penfluridol-, and 631 non-teratogen-exposed

**Table 102–5 Cytochrome P450-Mediated Drug Interactions Affecting Metabolism of Second-Generation Antipsychotic Agents***

| Drug and Relevant Cytochrome P450 Isoenzyme(s) | CYP Inhibitors | CYP Inducers |
|---|---|---|
| Clozapine | | |
| 1A2† | Caffeine, fluvoxamine | Carbamazepine, phenobarbital, smoking |
| 2D6 | Fluoxetine, paroxetine | |
| 2C19 | Fluoxetine, fluvoxamine | |
| 3A4 | Fluoxetine, fluvoxamine | Carbamazepine, phenobarbital |
| Risperidone | | |
| 2D6† | Fluoxetine, fluvoxamine, paroxetine | |
| 3A4† | Fluoxetine, fluvoxamine | Carbamazepine |
| Olanzapine | | |
| 1A2† | Fluvoxamine | Carbamazepine, smoking |
| 2D6 | | |
| Quetiapine | | |
| 3A4† | Ketoconazole | Carbamazepine, phenytoin |
| Sertindole | | |
| 2D6† | | |
| 3A4† | | |
| Ziprasidone | | |
| 3A4 | Ketoconazole | Carbamazepine |
| Aripiprazole | | |
| 3A4† | | |
| 2D6† | | |

*Only findings of controlled trials are represented.

†Isoenzymes most likely to be clinically relevant.

*Source:* Adapted and modified with permission from Worrel et al. (2000).

pregnancies and found that the rate of congenital anomalies did not differ between the antipsychotic-exposed group (3.4%) and the control group (3.8%) (Diav-Citrin et al. 2005).

There are fewer data regarding the safety of SGAs in human pregnancy. All SGAs have been assigned by the U.S. FDA to pregnancy category C (except clozapine, which is a category B agent), but the category C designation is more a reflection of the paucity of studies examining SGAs in pregnancy than of known risk. Most existing information concerning the outcomes of pregnancies during which the mother was treated with an SGA derives from case reports and two manufacturers' data collections (Gentile 2004), and thus is subject to reporting bias. McKenna and colleagues conducted the first prospective, controlled study examining pregnancy outcomes in 151 women exposed to SGAs, including olanzapine, risperidone, quetiapine, and clozapine, during the first trimester (McKenna et al. 2005). In comparison to healthy control subjects, the exposed group showed no statistical differences in the rates of miscarriage, stillbirth, prematurity, delivery complications, congenital malformations, or perinatal syndromes. Exposed mothers did, however, have a higher body mass index (BMI), and their infants had lower birth weights than in the control group. Although this study did not find higher rates of caesarean section delivery, gestational diabetes, or pregnancy-induced hypertension in antipsychotic-exposed women, these remain concerns, given the association of some SGAs with obesity and diabetes.

Thus, the safety of antipsychotics in pregnancy remains an unresolved issue. More encouraging data exist for FGAs than for SGAs. The risk of antipsychotic treatment during breastfeeding is similarly unknown, and there are not sufficient data to ensure that the benefits of breastfeeding outweigh the risks of drug exposure to the infant. Whenever possible, patients should obtain a prepregnancy consultation to discuss with their clinician(s), partner, and family the known and potential risks and benefits of antipsychotic treatment during pregnancy. In negotiating this difficult decision, emphasis should be placed on optimizing the mother's health and ability to parent (Yaeger et al. 2006). Social supports should be maximized during pregnancy and in the postpartum. If an antipsychotic agent is used, monotherapy at the lowest effective dose may help to minimize risks to the fetus.

## Adverse Effects

### Acute Extrapyramidal Symptoms (Dystonia, Parkinsonism, and Akathisia)

Antipsychotic-induced EPS can occur acutely or after chronic treatment, and all antipsychotic medications are capable of producing EPS. In general, this liability is more pronounced with FGAs than with SGAs (see Table 102–6). Among FGAs, agents that possess a high potency with respect to the $D_2$ receptor, such as haloperidol and fluphenazine, carry the highest risk of EPS. Mid- and low-potency FGAs pose less risk. Two recent, large-scale, prospective studies and one meta-analysis suggest that moderately dosed, mid- and low-potency FGAs may, in fact, cause no more EPS than most

**Table 102–6 Side Effect Profiles of Antipsychotic Drugs**

| Drug Side effect | FGAs | Clozapine | Risperidone | Olanzapine | Quetiapine | Ziprasidone | Sertindole | Amisulpride | Aripiprazole | Iloperidone |
|---|---|---|---|---|---|---|---|---|---|---|
| EPS* | + to +++ | 0 | ++ | + | 0 | + | 0 | ++ | + | + |
| TD | + to +++ | 0 | ++ | + | 0 | + | 0 to + | + | + | + |
| NMS | + to ++ | + | + | + | + | + | + | + | + | ? |
| Prolactin elevation* | ++ to +++ | 0 | +++ | + | 0 | + | 0 to + | ++ | 0 | 0 to + |
| Weight gain | + to ++ | +++ | ++ | +++ | ++ | 0 | + | + | 0 | ? |
| Type II DM | 0 to + | ++ | 0 to + | ++ | 0 to + | 0 | ? | 0 | 0 | ? |
| Dyslipidemia | 0 | ++ | + | ++ | + | 0 | ? | 0 | 0 | ? |
| Prolonged QT* | + to +++ | + | + | 0 to + | + | ++ | +++ | + | 0 | 0 |
| Hypotension* | + to +++ | +++ | + | ++ | ++ | + | + | 0 | + | + |
| Sinus tachycardia* | + to +++ | +++ | + | ++ | ++ | + | + | 0 | 0 | + |
| Myocarditis and DCM | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anticholinergic effects* | + to +++ | +++ | 0 | ++ | + | 0 | 0 | 0 | 0 | 0 |
| Hepatic transaminitis | + to ++ | ++ | + | ++ | + | + | + | + | 0 | + |
| Agranulocytosis | 0 to + | ++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sedation | + to +++ | +++ | + | ++ | ++ | + | 0 to + | + | + | + |
| Seizures* | 0 to + | ++ | 0 | 0 to + | 0 to + | 0 to + | 0 to + | 0 to + | 0 to + | 0 to + |

FGAs, first-generation antipsychotics; EPS, extrapyramidal symptoms; TD, tardive dyskinesia; NMS, neuroleptic malignant syndrome; Type II DM, type II diabetes mellitus; DCM, dilated cardiomyopathy; 0, minimal to no risk; +, low risk; ++, moderate risk; +++, high risk; ?, unknown risk.
*Known to be dose dependent.

*Source:* Adapted and updated with permission from Dawkins et al. (1999) and Burns (2001).

SGAs (Jones et al. 2006, Leucht et al. 2003b, Lieberman et al. 2005a). Among SGAs, clozapine and quetiapine are exceptional for carrying almost no risk of EPS (Dev and Raniwalla 2000, Kane et al. 1988, Small et al. 1997). In contrast, risperidone may produce dose-dependent EPS as often as some FGAs (American Psychiatric Association 2004, Gasquet et al. 2005). EPS with olanzapine, ziprasidone, and aripiprazole appear to be less common than with risperidone, but more common than with quetiapine or clozapine (American Psychiatric Association 2004).

Commonly occurring acute EPS include Parkinsonism, dystonia, and akathisia. Acute EPS typically develop within hours to weeks of antipsychotic initiation. These movement disorders are dose dependent and almost always reversible, remitting after the offending agent is discontinued (American Psychiatric Association 2004, Casey 1995). It has been estimated that more than 60% of patients who receive acute treatment with FGAs develop some form of clinically significant EPS (American Psychiatric Association 2004), though the evidence for this comes primarily from studies of high-potency agents administered at very high doses. The increasing use of SGAs is believed to have substantially reduced the burden of acute EPS.

Medication-induced Parkinsonism is the most common form of EPS caused by FGAs (American Psychiatric Association 2004). The disorder usually occurs within days to weeks of antipsychotic treatment initiation, and is characterized by rigidity, tremor, and bradykinesia. Care should be taken to distinguish these patients from those with depression, catatonia, or the negative symptoms of schizophrenia (American Psychiatric Association 2004). Medication-induced Parkinsonism occurs most commonly with high-potency antipsychotics, especially when anticholinergic medication is not administered concurrently. Other risk factors include older age, higher dose, a history of Parkinsonism, and underlying basal ganglia damage (Marder 1997).

Dystonia presents as sustained muscular contraction, with contorting, twisting, or abnormal posturing affecting mainly the muscles of the head and neck, but sometimes the trunk or extremities. It tends to be sudden in onset, with 90% of cases occurring in the first 3 days of antipsychotic treatment (American Psychiatric Association 2004). Dystonia is often dramatic in presentation and may be extremely disturbing for patients. Laryngeal dystonia is potentially fatal, as it may compromise the airway. Risk factors for acute dystonias include a history of prior dystonia, young age, male gender, use of high-potency antipsychotic agents, higher dose, and IM administration (American Psychiatric Association 2004).

Akathisia is characterized by both subjective and objective somatic restlessness. Patients with akathisia typically experience an inner sensation of restlessness or an irresistible urge to move various parts of their bodies (American Psychiatric Association 2004). The disorder appears objectively as psychomotor agitation, such as continuous pacing, rocking from foot to foot, or the inability to sit still. Akathisia usually begins within hours to days of antipsychotic administration (Casey 1993) and can occur in as much as 25% of patients treated with FGAs (Braude et al. 1983). It can be extremely distressing for patients and may contribute to medication nonadherence or self-injurious behavior (American Psychiatric Association 2004).

Patients should be monitored for EPS at weekly intervals during antipsychotic initiation and until their medication dose has been stable for at least 2 weeks (Marder et al. 2004). The treatment of acute EPS depends on the specific side effect (see Table 102–7).

The initial treatment of Parkinsonism is to lower the antipsychotic dose, since doses above the EPS threshold are unlikely to yield additional clinical benefit (American Psychiatric Association 2004). If symptoms persist, switching to an antipsychotic associated with fewer EPS should be considered. Alternatively, adding an anticholinergic agent or dopaminergic medication (e.g., amantadine) may be efficacious, though these drugs carry their own risk of adverse effects and so should be used sparingly (American Psychiatric Association 2004).

Acute dystonia responds rapidly to treatment with an anticholinergic (e.g., benztropine) or an antihistaminergic (e.g., diphenhydramine) agent, especially when administered parenterally. Oral anticholinergic medication should then be continued for a few days to prevent dystonia recurrence.

Initial treatment options for akathisia include lowering the antipsychotic dose, or switching to an antipsychotic agent with a lower risk of akathisia. If symptoms persist, or if psychotic symptoms necessitate a higher antipsychotic dose, individual trials of β-adrenergic antagonists (e.g., 30–90 mg/day of propranolol) or benzodiazepines may be attempted; anticholinergic agents, in contrast, are generally less effective for akathisia (American Psychiatric Association 2004, Casey 1993, Miller and Fleischhacker 2000).

Because of the frequency with which acute EPS occur, especially with high-potency agents, clinicians may wish to consider the prophylactic use of anticholinergic agents. In a large, double-blind, randomized trial conducted at the U.S. Department of Veterans Affairs, patients taking olanzapine did not experience significantly fewer EPS overall than those taking haloperidol plus benztropine, though less akathisia

**Table 102–7** Medications Used to Treat Extrapyramidal Side Effects

| Generic Name | Dose (mg/day) | Elimination Half-life (h) | Target Extrapyramidal Side Effects |
|---|---|---|---|
| Benztropine mesylate | 0.5–6.0 | 24 | Akathisia, dystonia, Parkinsonism |
| Trihexyphenidyl hydrochloride | 1–15 | 4 | Akathisia, dystonia, Parkinsonism |
| Amantadine | 100–300 | 10–14 | Akathisia, Parkinsonism |
| Propranolol | 30–90 | 3–4 | Akathisia |
| Lorazepam | 1–6 | 12 | Akathisia |
| Diphenhydramine | 25–50 | 4–8 | Akathisia, dystonia, Parkinsonism |

*Source:* Adapted and modified with permission from American Psychiatric Association (2004).

occurred in the olanzapine group (Rosenheck et al. 2003). Pretreatment with an anticholinergic agent has been used elsewhere to prevent acute dystonia (Lavin and Rifkin 1991, Winslow et al. 1986). A disadvantage to anticholinergic drugs is that they may themselves cause side effects, including dry mouth, constipation, urinary retention, blurry vision, and cognitive impairment. The risk–benefit ratio of prophylactic anticholinergic medication is optimized when the anticholinergic drug is used at the lowest effective dose, and with those patients at highest risk for EPS, such as those with a history of EPS and those taking a high-potency antipsychotic.

## Chronic Extrapyramidal Symptoms (Tardive Dyskinesia and Related Syndromes)

TD is a repetitive, involuntary, hyperkinetic movement disorder caused by months to years of exposure to antipsychotic medication. It has been associated with reduced QOL and with increased morbidity and mortality (Correll et al. 2004). TD is characterized most commonly by orofacial movements, such as lip-smacking, chewing, and tongue protrusion, and also by choreoathetoid movements of the neck, limbs, trunk, and occasionally the diaphragm (American Psychiatric Association 2004, Casey 1999, Glazer 2000). Younger patients with TD tend to exhibit slower, athetoid movements of the trunk, extremities, and neck (Marder 1997). The abnormal movements of TD usually increase with emotional arousal and are absent during sleep (Marder 1997). According to the diagnostic criteria proposed by Schooler and Kane (1982), the movements should be present for at least 4 weeks, and exposure to antipsychotic drugs should total at least 3 months. Dyskinetic movements should begin either while the patient is receiving an antipsychotic agent or within a few weeks of discontinuing an antipsychotic.

Less common than the choreoathetoid movements described above are variants of TD known as tardive dystonia and tardive akathisia. These syndromes resemble their acute counterparts, but by definition emerge after longer term antipsychotic treatment. Tardive dystonia and tardive akathisia can be particularly disabling, and often persist despite antipsychotic discontinuation. More than one variant of TD may be present simultaneously.

Determination of the risk of antipsychotic-induced TD is complicated by the observation that spontaneous dyskinesias occur in some never-medicated schizophrenic patients, and thus are part of the natural history of the disease (American Psychiatric Association 2004). Prevalence surveys indicate that mild forms of TD occur in approximately 20% of patients who receive chronic treatment with FGAs (Casey 1995, Kane and Lieberman 1992), and 10% of patients with TD experience moderate or severe symptoms (American Psychiatric Association 2004). A large, prospective study found the cumulative incidence of TD in patients receiving an FGA to be 5% after 1 year, 10% after 2 years, 15% after 3 years, and 19% after 4 years (Kane et al. 1986). Among the predictors of TD are older age, a history of EPS, substance abuse, duration of antipsychotic exposure, and possibly antipsychotic dose (Casey 1999, Miller et al. 2005). Prevalence rates of TD may exceed 50% in high-risk groups, such as the elderly (Casey 1995). The prevalence of tardive dystonia has been estimated to be between 1.5 and 4% (Barnes and McPhillips 1998).

TD has been observed with all antipsychotic drugs (American Psychiatric Association 2004). Given that EPS represent a risk factor for later development of TD, and in light of the relatively lower liability of SGAs to cause EPS, it is reasonable to expect that SGAs should cause less TD than FGAs, at least as compared with high-potency FGAs. The strongest evidence for this hypothesis exists for clozapine (Casey 1999). In addition, a recent review found that SGAs as a class pose less risk of TD than the high-potency FGA haloperidol, but acknowledged that supporting trial data are limited (Correll et al. 2004). The CATIE investigators concluded that patients being treated with an FGA at baseline were more likely to have TD than those not taking an FGA (Miller et al. 2005), but also found that, among patients without a history of TD, treatment with the midpotency FGA perphenazine during the study did not pose more of a risk of abnormal involuntary movements than treatment with an SGA (Lieberman et al. 2005a). Carefully designed, long-term, prospective comparison studies are needed to clarify the relative risks of TD among the available antipsychotic agents.

Management of TD begins with monitoring. Patients should be evaluated for signs of dyskinesia before beginning treatment with an antipsychotic agent, and every 3 months during treatment (American Psychiatric Association 2004). If dyskinetic movements emerge, a neurological evaluation should be considered to rule out other etiologies.

If TD develops in the context of FGA treatment, the clinician may consider reducing the antipsychotic dose, or switching to an SGA. Either of these approaches may paradoxically cause an initial worsening of TD, but in many cases TD will eventually improve or resolve. Switching to an SGA soon after TD develops may be advisable, as the likelihood of TD reversibility declines with sustained exposure to the offending FGA (American Psychiatric Association 2004). While most SGAs have been observed to reverse FGA-induced TD, clozapine is the best supported of these, with reported efficacy against TD and tardive dystonia (Casey 1999).

Although a large number of other agents have been examined for their potential therapeutic effects on TD, there is no known definitive pharmacological treatment. Numerous studies have investigated the potential benefits of benzodiazepines, anticholinergic agents, calcium channel blockers, γ-aminobutyric acid agonists, essential fatty acids, estrogen, insulin, and other drugs, without encouraging results (American Psychiatric Association 2004, Casey 1999). Several small trials support a protective function of vitamin E against TD deterioration, but there is no evidence that vitamin E improves TD symptoms (Soares and McGrath 2001). Given the very low incidence of side effects with vitamin E, patients may be prescribed 400–800 IU daily for possible prophylaxis against development or worsening of TD (American Psychiatric Association 2004).

## Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is characterized by the triad of rigidity, hyperthermia (>38°C), and autonomic instability (especially tachycardia and blood pressure lability), occurring in association with the use of antipsychotic medication. NMS is often associated with an elevated serum creatine kinase level, leukocytosis, and

alteration in level of consciousness. The disorder usually develops during the initial weeks of antipsychotic treatment, and can be sudden in onset. NMS is a psychiatric emergency that should be distinguished from such differential diagnostic considerations as serotonin syndrome, sepsis, endocrinopathy, and heat stroke. If not diagnosed and treated promptly, death can occur in 5–20% of cases (American Psychiatric Association 2004).

NMS is relatively rare, occurring in less than 1% of patients treated with FGAs (Caroff et al. 1998). The relative risk of NMS among SGAs is likely to be even lower, but conclusive data are not yet available. Proposed risk factors include a prior episode of NMS, younger age, male gender, acute agitation, physical illness, dehydration, use of high-potency antipsychotics, rapid dose titration, use of IM preparations, and preexisting neurological disability (American Psychiatric Association 2004).

If NMS is suspected, the offending antipsychotic agent should be discontinued immediately, and the patient should be transferred to a medical setting where supportive treatment can be initiated. Small studies suggest that dantrolene and dopaminergic drugs such as bromocriptine and amantadine may decrease NMS-associated mortality, compared with supportive treatment alone (Caroff et al. 1998). Electroconvulsive therapy has also been reported to be effective in treatment-refractory NMS; however, it should be used with caution given the occurrence of several cases of cardiac arrhythmia (Caroff et al. 1998).

After several weeks of recovery, an antipsychotic agent may be gradually reintroduced. Generally, an SGA or lower potency FGA is selected, and the dose is titrated slowly while observing for signs of NMS recurrence (American Psychiatric Association 2004).

## Endocrine and Sexual Effects

All FGAs can elevate serum prolactin levels by antagonizing the tonic inhibitory actions of dopamine on lactotrophic cells in the pituitary (American Psychiatric Association 2004). Among SGAs, risperidone and amisulpride can increase serum prolactin levels to an extent comparable to FGAs (Grunder et al. 1999, Haddad and Wieck 2004, Yasui-Furukori et al. 2002). In contrast, quetiapine, clozapine, and aripiprazole do not elevate serum prolactin levels, and olanzapine causes hyperprolactinemia only at high doses (Haddad and Wieck 2004, Turrone et al. 2002, Worrel et al. 2000). Ziprasidone is uncommonly associated with prolactin elevation. Although some patients develop partial tolerance to the pituitary effect of antipsychotics after several weeks, most have chronic serum prolactin elevation so long as antipsychotic treatment is continued (Haddad and Wieck 2004).

Women experience, on average, significantly greater elevation in prolactin than do men during long-term treatment with the same antipsychotic dose (Haddad and Wieck 2004). Hyperprolactinemia may manifest differently in men and women, and there is great individual variation in the prolactin level at which symptoms appear (Haddad and Wieck 2004). In women, prolactin elevation often leads to menstrual disturbances, including anovulatory cycles and infertility, menses with abnormal luteal phases, or frank amenorrhea and hypoestrogenemia. Women may also experience decreased libido, impaired arousal, anorgasmia, and, at least theoretically, increased long-term risk of osteoporosis. Approximately 20% of women develop galactorrhea during treatment with an FGA (Windgassen et al. 1996), and one large, retrospective study found dopamine antagonist use to be associated with a 16% increase in the risk of breast cancer (Wang et al. 2002). The major effects of hyperprolactinemia in men are loss of libido, hypospermatogenesis, erectile or ejaculatory deficits, and occasionally galactorrhea or priapism. Antipsychotic-induced sexual side effects can be particularly bothersome for some patients, while for others sexual dysfunction associated with schizophrenia itself may improve with antipsychotic treatment (Haddad and Wieck 2004). A large, manufacturer-funded, observational study found that patients treated with olanzapine or quetiapine experienced significantly less sexual dysfunction than those treated with risperidone or haloperidol (Dossenbach et al. 2006).

Clinicians should screen for signs and symptoms of hyperprolactinemia prior to and during treatment with prolactin-elevating antipsychotics (Marder et al. 2004). If symptomatic hyperprolactinemia is present, consideration should be given to lowering the antipsychotic dose or to switching to a "prolactin-sparing" agent. If this is impractical or ineffective, a dopaminergic drug, such as bromocriptine, amantadine, or cabergoline, can be considered, though these medications carry a small risk of psychotic relapse (Haddad and Wieck 2004).

## Weight Gain and Obesity

Obesity can negatively affect self-image, impair social adjustment, and reduce medication compliance (Marder et al. 2004). Furthermore, it can have serious deleterious effects on health and life expectancy via a number of disease processes, including hypertension, coronary artery disease, osteoarthritis, T2DM, stroke, sleep apnea, and certain cancers. Approximately half of all people with schizophrenia meet criteria for obesity, representing a relative risk of nearly two when compared with the general population (Newcomer 2007). Genetic and lifestyle factors may contribute to this phenomenon, but in large measure antipsychotic-induced weight gain is responsible. Up to 40% of patients treated with FGAs gain weight, with low-potency agents posing the greatest risk and high-potency FGAs causing minimal mean weight increases (American Psychiatric Association 2004). Differences have also been discovered among SGAs with respect to weight gain (Table 102–6). One meta-analysis estimated weight change after 10 weeks of treatment at standard antipsychotic doses and found mean increases of 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.10 kg with risperidone, and 0.04 kg with ziprasidone (Allison et al. 1999). Quetiapine appears comparable to risperidone with respect to short-term weight gain, and aripiprazole resembles ziprasidone in being weight neutral (Newcomer and Haupt 2006). Longer term antipsychotic-induced weight gain follows a similar, hierarchical pattern. Pooled analyses, for example, suggest that aripiprazole and ziprasidone are associated with a gain of about 1 kg over 1 year, amisulpride with a gain of 1.5 kg over the same period, quetiapine and risperidone with a gain of 2–3 kg, and olanzapine with a gain of greater than 6 kg (Newcomer and Haupt 2006). Clozapine appears to cause at least as much long-term weight gain as olanzapine.

The mechanism of action underlying antipsychotic-induced weight gain has been hypothesized to involve changes in appetite and satiety mediated by $H_1$ receptor antagonism (Newcomer 2007). Consistent with this hypothesis, antipsychotics possessing high affinity for $H_1$ receptors, such as clozapine, olanzapine, thioridazine, and chlorpromazine, are associated with considerable weight gain potential. Agents with little $H_1$ affinity, such as aripiprazole, ziprasidone, and haloperidol, tend to be more weight neutral. Antagonism of 5-$HT_{2C}$ receptors may also contribute to antipsychotic-induced weight gain.

Recognizing the considerable potential for obesity to impact negatively on morbidity and mortality, expert consensus guidelines recommend frequent monitoring of BMI, computed by using the formula $kg/m^2$, for every patient with schizophrenia (American Diabetes Association et al. 2004, Marder et al. 2004). As defined by the World Health Organization, a BMI between 18.5 and 25 is "normal," while 25–30 is "overweight" and ≥30 is "obese" (Newcomer 2007). Waist circumference monitoring is also recommended, as central obesity is a risk factor for diabetes, hypertension, and dyslipidemia, independent of BMI. A waist circumference of >102 cm (>40 in.) in men or >88 cm (>35 in.) in women is indicative of abdominal obesity (Newcomer 2007). Most experts agree that, for patients with a baseline BMI ≥ 25, the relative weight gain potential of the various antipsychotics should be a consideration in medication selection (Marder et al. 2004), and some have advocated avoiding SGAs with the greatest weight gain propensity as first-line treatment (Sernyak 2007). Clinicians should encourage exercise and a healthy diet in all schizophrenic patients to prevent initial weight gain and obesity, since subsequent weight loss is often very difficult. Unless a patient is underweight (BMI < 18.5), an increase of one BMI unit should prompt an intervention, such as engagement in a weight management program, use of an adjunctive agent to reduce weight, or consideration of an antipsychotic with less weight gain potential (Marder et al. 2004). Similarly, a waist circumference ≥35 in. in a woman or ≥40 in. in a man should prompt an intervention. Behavioral therapy programs involving self-monitoring, stimulus control, diet, and exercise have shown efficacy for short-term weight loss and prevention of weight gain in antipsychotic-treated patients, but few long-term studies of behavioral therapy have been undertaken in this population (Ganguli 2007). Although no pharmacological interventions for antipsychotic-induced weight gain have demonstrated proven efficacy, small controlled trials suggest possible benefit with amantadine, topiramate, reboxetine, and sibutramine (Faulkner and Cohn 2006). Metformin was not effective in preventing weight gain in olanzapine-treated adults, but did stabilize weight in a small group of SGA-treated children and adolescents (Klein et al. 2006).

## Diabetes

The prevalence of T2DM is twice as high among patients with schizophrenia as in the general population (Dixon et al. 2000), placing these patients at increased risk of coronary artery disease, stroke, peripheral vascular disease, retinopathy, nephropathy, neuropathy, and ketoacidosis. Data are rapidly accumulating that indicate that some SGAs increase this burden. Clozapine and olanzapine, for example, are more often associated with T2DM than are FGAs or other SGAs (American Diabetes Association et al. 2004, Newcomer and Haupt 2006). One study found that during 5 years of treatment with clozapine, 37% of patients received a diagnosis of T2DM (Marder et al. 2004). It is unclear whether the risk of T2DM with clozapine and olanzapine is entirely accounted for by the relatively greater increase in adiposity associated with these agents, or whether an additional mechanism is partially responsible, such as a direct effect of the drugs on insulin-sensitive target tissues. Studies investigating the risk of T2DM with quetiapine and risperidone have produced discrepant results, whereas the limited data available for ziprasidone and aripiprazole suggest that these agents do not predispose to T2DM (American Diabetes Association et al. 2004, Newcomer and Haupt 2006).

Expert consensus guidelines recommend measurement of baseline plasma glucose level before starting a new antipsychotic agent; a fasting glucose level is preferred, but a hemoglobin $A_{1c}$ level is acceptable (Marder et al. 2004). Elevation of either of these levels (>100 mg/dl and >6.1%, respectively) should prompt a referral to a primary care provider for management. Fasting plasma glucose or hemoglobin $A_{1c}$ measurement should be repeated 3–4 months after antipsychotic initiation, at least annually thereafter, and whenever a patient endorses symptoms of new-onset diabetes (American Diabetes Association et al. 2004, Marder et al. 2004). Clinicians should inquire and educate patients about the symptoms of new-onset diabetes, which include weight loss, polyuria, polydipsia, and blurry vision. Laboratory or symptomatic evidence of diabetes should lead to a primary care referral.

## Dyslipidemia

Elevated lipid levels, particularly low-density lipoprotein (LDL) and triglyceride (TG) levels are associated with coronary artery disease and myocardial infarction. Clozapine and olanzapine increase total cholesterol, LDL, and TG levels significantly, as compared with FGAs and other SGAs (American Diabetes Association et al. 2004, Lieberman et al. 2005a, Marder et al. 2004, McEvoy et al. 2006, Newcomer and Haupt 2006). Quetiapine and risperidone appear to raise cholesterol levels modestly, whereas ziprasidone and aripiprazole are cholesterol neutral (American Diabetes Association et al. 2004).

Because patients with schizophrenia are, as a group, at increased risk of coronary artery disease, lipid levels should be monitored more frequently than in the general population. Consensus guidelines recommend that a complete lipid panel be obtained once every 2 years so long as the LDL level is normal (≤130 mg/dl), and every 6 months when the level is greater than 130 mg/dl (Marder et al. 2004). If lipid abnormalities are present, the clinician should refer the patient to a primary care provider. If this is not possible, the clinician should advise the patient to reduce dietary fat intake, and should be prepared to prescribe a lipid-lowering drug in the event that cholesterol levels do not normalize with this intervention (Marder et al. 2004).

## Metabolic Syndrome

MS is defined by three or more of the following criteria: abdominal obesity (waist circumference ≥35 in. for women or ≥40 in. for men), elevated fasting TGs (≥150 mg/dl), decreased high-density lipoprotein (<40 mg/dl for men or

<50 mg/dl for women), hypertension (≥130/85 mm Hg or on antihypertensive medication), and elevated fasting glucose (≥100 mg/dl or on diabetes medication). Patients with this constellation of conditions may be at even greater risk of cardiovascular disease than those with isolated obesity, T2DM, or dyslipidemia. One study found that a diagnosis of MS was associated with a three-fold increase in risk of both coronary artery disease and stroke over a 7-year period (McEvoy et al. 2005).

As with individual components of MS, the complete syndrome is distressingly common among patients with schizophrenia, especially those that have been treated with antipsychotics. For example, among patients entering the CATIE trial, 53% of women and 36% of men met criteria for MS (McEvoy et al. 2005). Compared to matched controls, women and men were, respectively, 251 and 138% more likely to have MS. Even when controlling for differences in BMI, CATIE subjects were still substantially more likely to have MS than controls. The CATIE investigators concluded that MS is "highly prevalent in U.S. schizophrenia patients and represents an enormous source of cardiovascular risk, especially for women" (McEvoy et al. 2005). Further implicating antipsychotics as contributors to MS risk, a 26-week, randomized, double-blind study found an MS worsening incidence of 19% with olanzapine treatment, 13% with placebo, and 8% with aripiprazole (Newcomer and Haupt 2006).

Unfortunately, metabolic and cardiovascular disorders are often not adequately treated in this population. In CATIE trial subjects at baseline, nontreatment ranged from 30% for diabetes, to 62% for hypertension, to 88% for dyslipidemia (Nasrallah et al. 2006). Given the high prevalence of MS among patients with schizophrenia, and the morbidity and mortality risks conferred by the syndrome, clinicians should vigilantly screen for and promptly treat component disorders of MS in the manner outlined in the preceding sections. When the complete syndrome is present, collaboration with a primary care physician is particularly important.

## Cardiovascular Effects

In addition to coronary artery disease, common cardiovascular effects of antipsychotic agents include orthostatic hypotension, sinus tachycardia, and electrocardiogram (ECG) changes.

Orthostatic hypotension occurs most frequently with low-potency FGAs and clozapine, as a result of their high $\alpha_1$-adrenergic affinities, but may be seen with other agents as well. Orthostatic hypotension is most likely to occur early in treatment and with dose titration. Patients should be assessed regularly during these times for vital sign changes consistent with orthostatic hypotension and for symptoms such as dizziness, light-headedness, presyncope, and syncope. Those with pronounced symptoms should be cautioned against rising quickly. Elderly patients are particularly vulnerable to this side effect, which may predispose to falls and related injuries (American Psychiatric Association 2004). Most patients develop tolerance to the orthostatic effects of antipsychotics over a period of weeks. Gradual dose titration often reduces the risk of orthostatic hypotension. Management strategies include reducing or dividing the medication dose, or switching to an antipsychotic with a lower $\alpha_1$-adrenergic affinity. Supportive measures include the use of support stockings, an increase in dietary salt intake, and, in severe cases, administration of the corticosteroid fludrocortisone to augment intravascular volume (American Psychiatric Association 2004).

Sinus tachycardia may result from the anticholinergic effects of antipsychotic medications, or be secondary to orthostatic hypotension. Tachycardia can occur with any antipsychotic agent, but is especially common with clozapine, affecting approximately 25% of patients treated with the drug (Lieberman 1998). While an increase in resting heart rate may be well tolerated in most patients, caution should be exercised when treating elderly patients and those with preexisting heart disease (American Psychiatric Association 2004). If tachycardia is sustained or accompanied by symptoms of cardiac ischemia, an ECG should be obtained and a serum marker of myocardial damage (e.g., troponin or creatine kinase MB) should be considered. In the absence of hypotension, tachycardia due to antipsychotic-associated anticholinergic effects can be managed with low doses of a peripherally acting beta-blocker, such as atenolol (Lieberman 1998).

Abnormalities in cardiac electrophysiology, as reflected in ECG changes, have been observed with most antipsychotic agents (Glassman and Bigger 2001). Prolongation of the QTc interval, especially beyond 500 ms, is of particular concern because it increases the risk of *torsades de pointes* (TdP), a ventricular tachyarrhythmia that can lead to sudden death. While modest, dose-dependent QTc prolongation has been reported with many antipsychotics, pimozide, sertindole, mesoridazine, haloperidol, and especially thioridazine can increase the QTc interval considerably, and all of these have been associated with fatal or potentially fatal arrhythmias (Glassman and Bigger 2001, Yap and Camm 2000). This association prompted restricted marketing of sertindole in Europe, and a U.S. FDA advisory against using thioridazine in patients responsive to other antipsychotics. Among SGAs available in the U.S., ziprasidone appears to cause the greatest QTc prolongation (20 ms, on average), but TdP has only once been reported in a ziprasidone-treated patient (Heinrich et al. 2006), and this patient had multiple other risks factors for TdP. Expert consensus guidelines recommend that pimozide, mesoridazine, and thioridazine not be prescribed to patients with known heart disease, a personal history of syncope, a family history of sudden death before age 40 years, or congenital long QT syndrome (Marder et al. 2004). A baseline ECG is appropriate prior to treatment with other QTc-prolonging antipsychotics (e.g., ziprasidone) in patients with any of the aforementioned risk factors, in elderly patients, and in those who are taking other drugs known to prolong the QTc interval (Glassman and Bigger 2001, Marder et al. 2004). An ECG is also indicated if the patient presents with syncope or other symptoms associated with a prolonged QTc interval (Marder et al. 2004). The risk of QTc prolongation may be decreased by correcting hypokalemia and hypomagnesemia, and by minimizing concomitant exposure to other QTc-prolonging drugs.

In recent years, evidence has accumulated that clozapine is uncommonly associated with myocarditis and cardiomyopathy. Case series and data-mining studies have estimated the risk of clozapine-induced myocarditis at 0.015–0.188%, though the true risk is likely somewhat higher (Merrill et al. 2005, 2006). Myocarditis typically occurs during the first 2

months of clozapine treatment and manifests with nonspecific signs and symptoms, including fever, tachycardia, chest pain, dyspnea, flu-like symptoms, eosinophilia, elevated cardiac enzyme levels, and ECG changes. No single finding is pathognomonic, and diagnosis is usually guided by a preponderance of clinical evidence. If untreated, progression to fulminant myocarditis may be rapid, with an attendant mortality rate as high as 50%. If the condition is diagnosed early, however, drug discontinuation and supportive treatment frequently lead to spontaneous recovery. At present, it is unknown whether routine screening for clozapine-induced myocarditis, such as with serial measurements of serum levels of cardiac enzymes during the first months of treatment, would result in earlier detection of the disorder. Clinicians should also be vigilant for the development of clozapine-associated dilated cardiomyopathy, which may develop after months to years of clozapine treatment and may itself be associated with significant morbidity and mortality. Although these adverse cardiac effects may have grave consequences, they should be considered in the context of clozapine's many salubrious properties, including its distinction as the most efficacious of currently available antipsychotics.

## Gastrointestinal Effects

The anticholinergic effects of antipsychotic medications include xerostomia (i. e., dry mouth) and constipation. These are relatively commonly encountered with clozapine and low-potency FGAs, and less often with olanzapine and quetiapine (American Psychiatric Association 2004). Because they are frequently dose-related, constipation and xerostomia may improve with antipsychotic dose reduction. Elderly patients are particularly susceptible to anticholinergic effects, owing to reduced cholinergic function.

Patients with xerostomia should be advised to maintain hydration, use sugarless gum or hard candy, and obtain regular dental care. Constipation can usually be treated with stool softeners and laxatives. In rare instances, paralytic ileus occurs in association with clozapine or haloperidol, in which case antipsychotic medication should be discontinued and medical or surgical consultation sought promptly. Paradoxically, clozapine may also cause sialorrhea (excess salivation). This may be treated with a few drops of 1% atropine solution, mixed in a glass of water and administered as a mouthwash on an as-needed basis.

## Hepatic Effects

Asymptomatic elevations of liver enzyme levels occur with both FGAs and SGAs, usually during the first 3 months of treatment (Barnes and McPhillips 1999, Burns 2001, Casey 1997). These abnormalities may be present in more than 20% of patients treated with some antipsychotics (Selim and Kaplowitz 1999), though the relative liabilities of individual agents to cause liver enzyme elevations have yet to be elucidated.

More severe antipsychotic-induced hepatic effects are rare. Approximately 0.1–0.5% of patients treated with chlorpromazine develop cholestatic jaundice, usually within the first month of treatment, and a proportion of these cases progress to cirrhosis (American Psychiatric Association 2004, Selim and Kaplowitz 1999). Occasionally, symptomatic hepatotoxicity (cholestatic or hepatitic) may be associated with SGAs (Burns 2001). In these cases, the offending medication should be promptly discontinued. Patients taking an antipsychotic medication who develop nausea, abdominal pain, and jaundice should have their liver function evaluated to exclude hepatotoxicity. Since antipsychotic-induced jaundice is infrequent, other etiologies should be ruled out before the cause is judged to be antipsychotic treatment (American Psychiatric Association 2004).

## Hematological Effects

Antipsychotic medications may cause blood dyscrasias, including leukopenia, neutropenia, agranulocytosis, and eosinophilia. Benign leukopenia, for example, occurs in up to 10% of patients treated with chlorpromazine (American Psychiatric Association 2004). Clozapine-induced agranulocytosis (defined as an absolute neutrophil count less than 500/mm$^3$) is a much less common, but potentially fatal, adverse effect. Early agranulocytosis-related fatalities led to the withdrawal of clozapine in some European countries and severe restrictions on its use in others. With the advent of mandatory, systematic blood count monitoring, the reported rate of clozapine-induced agranulocytosis has fallen below 0.4% in the U.S. (American Psychiatric Association 2004). Less than 2% of these cases now result in mortality, in part because clozapine-induced agranulocytosis is usually reversible if the drug is withdrawn immediately (American Psychiatric Association 2004, Lieberman et al. 1988). If agranulocytosis does occur, the clinician should discontinue clozapine treatment, monitor for signs of infection, and consider bone marrow aspiration; if granulopoiesis is deficient, protective isolation is advisable (American Psychiatric Association 2004). In addition, treatment with granulocyte colony stimulating factor may be considered, as this agent may restore granulopoietic function and reduce recovery time (American Psychiatric Association 2004). Clozapine rechallenge should not be attempted in patients who have experienced agranulocytosis because of the high likelihood of recurrence. FGAs and non-clozapine SGAs pose a lower risk of agranulocytosis, though a number of cases have been reported, some involving patients with a history of this adverse event during previous clozapine exposure (Ruhe et al. 2001).

## Ocular Effects

Cataracts are ocular lens opacities that can impair vision. The low-potency FGAs chlorpromazine and thioridazine increase the risk of this condition, especially when used at high doses (American Psychiatric Association 2004, Marder et al. 2004). Cataracts have also been found in beagles treated with supratherapeutic doses of quetiapine, but not in other nonhuman animal species, including monkeys. Some case reports exist of lens opacities developing in quetiapine-treated humans; however, most of these patients had known risk factors for cataracts (Marder et al. 2004). Until the risk of cataracts with quetiapine is clarified, clinicians may wish to follow current recommendations of obtaining a slit-lamp eye examination or equivalent shortly after initiation of quetiapine treatment, and every 6 months thereafter while quetiapine is continued. Because patients with schizophrenia often have known risk factors for cataracts (e.g., diabetes, hypertension, and poor nutrition), regular ocular evaluations are advisable even for those not treated with quetiapine. A reasonable frequency for visual monitoring

in schizophrenic patients not taking quetiapine is yearly for patients over 40 years of age, and every 2 years for younger patients (Marder et al. 2004). Clinicians should also inquire about visual changes and should ask specifically about the quality of distance vision and blurry vision (Marder et al. 2004). If changes are present, referral for ophthalmologic evaluation is warranted.

### Other Side Effects

Sedation can occur with virtually any antipsychotic, but is particularly common with low-potency FGAs and the SGAs clozapine, olanzapine, quetiapine, and zotepine. This side effect is typically most pronounced during dose titration, as the majority of patients develop some tolerance with continued antipsychotic administration. Significant sedation may persist in some individuals, however, especially in those treated with clozapine. While the sedation that accompanies antipsychotic initiation may be beneficial in agitated patients, persistent sedation can be socially and vocationally disabling. This effect can sometimes be mitigated by lowering the antipsychotic dose, by consolidating divided doses into a single evening dose, or by switching to a less sedating agent. In spite of the high prevalence of antipsychotic-induced sedation, pharmacological treatments have not been well studied. Caffeine is considered a relatively safe option, and the psychostimulant modafinil is sometimes used (American Psychiatric Association 2004). It should be noted, however, that stimulants may aggravate psychosis, and some have been associated with clozapine toxicity (American Psychiatric Association 2004). Caution, therefore, should be exercised when administering stimulants for the treatment of antipsychotic-induced sedation.

Antipsychotic medications, in particular clozapine and low-potency FGAs, can lower the seizure threshold in a dose-dependent fashion (American Psychiatric Association 2004). When used at therapeutic doses, the risk of seizure with FGAs is usually less than 1%. The seizure rate with clozapine is 1% at doses below 300 mg/day, 2.7% at doses between 300 and 600 mg/day, and 4.4% at doses above 600 mg/day (American Psychiatric Association 2004). Because the seizure rate rises with rapid dose increases, clozapine should be titrated gradually.

Finally, medication cost may be regarded as a kind of adverse effect, present in varying degrees with all antipsychotic treatment, and frequently burdening the health care system more than individual patients. Antipsychotic costs can be substantial, especially for SGAs, which may be up to 100-fold more expensive than generic forms of some FGAs (Rosenheck 2006). The preferential use of SGAs since their introduction in the 1990s comes at a cost of over $10 billion annually in the U.S., 75% of which is paid through Medicaid (Rosenheck et al. 2006). Despite the high price of SGAs, several studies have found favorable results for the overall cost-effectiveness of these drugs, though the studies suffered from a variety of threats to validity (Polsky et al. 2006). An analysis of the CATIE study data concluded that treatment with the FGA perphenazine was less expensive than treatment with non-clozapine SGAs, with no significant difference in effectiveness (Rosenheck et al. 2006), but this analysis also had several methodological limitations. A similarly constrained analysis of the CUtLASS trial data showed a trend toward lower costs in those patients receiving FGAs, as compared with those receiving SGAs (Jones et al. 2006). Given the limitations of these studies, clinicians should not select an antipsychotic agent based on cost alone, though consideration of intermediate potency drugs like perphenazine is warranted when a medication change is indicated. Clinicians should also be aware that the cost-effectiveness calculus is likely to evolve over the coming years as a greater number of less expensive, generic versions of SGAs become available.

### Adverse Effects and Antipsychotic Agent Selection

Readers of this chapter will understand that—despite earlier hopes to the contrary—two recent, large, federally funded effectiveness trials provided strong evidence that SGAs, with the exception of clozapine, are not substantially more effective than FGAs (Jones et al. 2006, Lieberman et al. 2005a, McEvoy et al. 2006). Consequently, when selecting an antipsychotic agent, clinicians should not regard their decision as a choice between FGAs and SGAs. They should instead endeavor to individualize treatment, choosing an agent that is likely to be effective and tolerable for the particular patient in question. Primary considerations include the patient's past response to antipsychotic medications, available formulations (e.g., oral or IM depot), adverse effect profiles, potential for drug interactions, and the patient's stated preference. In general, the patient should be included in a discussion of these considerations, and informed consent should precede medication administration. Exceptions to the requirement of informed consent include emergencies, instances in which the patient has waived the right to informed consent or lacks decision-making capacity, and cases in which the process of informing the patient about the treatment might be directly damaging to them (Appelbaum and Gutheil 2006). When considering antipsychotic treatment, the risk of adverse effects, both immediate and delayed, should be weighed against the profound disability that can accompany severe mental illness, and the potential for antipsychotic medication to greatly ameliorate the lives of patients and their families. It is prudent for clinicians to document their reasoning when selecting an antipsychotic medication.

## Future Directions in Antipsychotic Drug Research and Treatment

Antipsychotic drug research has two primary aims: to increase our understanding of existing medications, and to develop novel agents with greater effectiveness. To date, most antipsychotic drug trials have been funded, conducted, and/or reported by representatives of the pharmaceutical industry. Many of these studies met high methodological standards and improved our knowledge of antipsychotic treatment. However, an exploratory analysis of published head-to-head comparison studies of SGAs found that reported outcomes favored the sponsor's drug in 90% of cases (Heres et al. 2006). This suggests that a number of sponsored studies with negative findings never reach publication. Those that are published are often of short duration and involve only a selected subset of the larger population of patients with schizophrenia (Lieberman 2006). Several government-funded, long-term, large-scale trials, conducted under "real-world" conditions and involving representative patient samples, have sought to redress the limitations of

industry sponsorship (Jones et al. 2006, Lieberman et al. 2005a, McEvoy et al. 2006, Rosenheck et al. 2006, Stroup et al. 2006). These studies, including CATIE and CUtLASS, have advanced our understanding of antipsychotic treatment considerably. Their findings are reliable, generalizable, and have the power to transform contemporary clinical practice. Further studies of this nature are eagerly awaited.

Future research on existing antipsychotic drugs is likely to evaluate outcomes that have received relatively less attention, historically, than has short-term reduction in positive symptoms of schizophrenia. These outcomes include impact on negative and cognitive symptoms, relapse prevention, improvement in social and vocational functioning, suicide prevention, and reduction in family and caregiver burden. Early intervention strategies, targeting first-episode, prodromal and high-risk patients, are also likely to be an area of intensive investigation. While most non-clozapine agents demonstrate approximately equal efficacy for positive symptoms, it is possible that certain agents may have specific utility in other symptom domains, or in particular stages of the illness.

Potential between-drug differences in symptom- and stage-specific efficacy, as well as known differences in side effect profiles, suggest that a priority for future research should be the individualization of antipsychotic treatment. At present, one cannot reliably predict which antipsychotic medication is best suited for any given patient (Crismon et al. 2003). However, it is likely that individual genetic differences are important determining factors in the efficacy and side effect profiles of antipsychotic medication (Basile et al. 2001), and identification of these differences may in the future help to tailor pharmacotherapy to the particular needs of individual patients (Arranz et al. 2000, Shastry 2002). Recent developments in simultaneous profiling of gene transcripts (e.g., gene chips) and proteomics are already helping to clarify the genes and proteins that are affected by antipsychotic medication. In addition, neuroimaging (e.g., structural magnetic resonance imaging, functional magnetic resonance imaging, and magnetic resonance spectroscopy) and electrophysiological (e.g., event-related potentials) studies are becoming increasingly sophisticated, providing more detailed information about brain morphologic changes, pathways, and circuits involved in the pathophysiology of schizophrenia (Rowley et al. 2001). It is hoped that individual differences in these variables may ultimately serve as predictors of treatment response.

The second aim of antipsychotic drug research, to develop agents with greater effectiveness, is being pursued in the NIMH-MATRICS initiative and elsewhere. Several novel antipsychotic compounds, including asenapine, ocaperidone, and lurasidone, which have 5-$HT_{2A}$ and $D_2$ antagonist properties, are currently in phase II or III U.S. FDA clinical trials. As yet, only agents with activity at dopamine $D_2$ receptors have proven to have antipsychotic efficacy. Other systems, however, are being actively investigated. For example, emerging evidence of glutamatergic dysregulation in schizophrenia has led to research on a number of agents with direct or indirect effects on the glutamate system. Glutamate-based drugs in various stages of development include agonists at the glycine site of the NMDA receptor, glycine reuptake inhibitors, glutamate release inhibitors, AMPA agonists and antagonists, and ampakines (for review, see Miyamoto et al. 2005). Some of these agents have already shown promise for the treatment of negative and cognitive symptoms of schizophrenia. Similarly, the central cholinergic system is being investigated for its potential role in the cognitive deficits observed in schizophrenia. Compounds that enhance cholinergic activity have been hypothesized to improve these deficits. Currently available treatments that are potentially suitable for this purpose include acetylcholinesterase inhibitors (e.g., galantamine), muscarinic partial agonists (e.g., xanomeline), nicotinic agonists, and allosteric potentiators of nicotinic receptor function (for review, see Friedman 2004). Other potential cognitive enhancers include modafinil (a wake-promoting agent currently used to treat narcolepsy), talnetant (a neurokinin-3 antagonist), and tolcapone (a catechol-O-methyltransferase inhibitor), all of which are currently in phase II FDA clinical trials. These and other agents merit further investigation and will likely engender a wealth of research in the near future.

## Conclusions

CATIE, CUtLASS, and other studies have taught us that SGAs are not the therapeutic breakthrough they were once hoped—and briefly believed—to be. Rather, SGAs represent an incremental advance in antipsychotic pharmacotherapy, with pharmacological properties and side effect profiles that are somewhat different than those of FGAs (Lieberman 2006). The one possible exception is clozapine, which has been found to be the most effective antipsychotic drug in virtually every study in which it has been used. However, more than 30 years after its discovery, we still do not know the pharmacological basis of clozapine's superiority, or even whether it is qualitatively or quantitatively different than other antipsychotic drugs. In the absence of a clearly superior class of medication, clinicians should rely on risk–benefit analysis, clinical judgment, and shared decision making in an effort to pair patients with antipsychotic agents that are likely to be safe and effective for them. Novel compounds with potential efficacy against a variety of symptoms and sequelae of schizophrenia are in development and are eagerly awaited.

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CHAPTER

# 103 Mood Stabilizers

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## Introduction

A highly recurrent and often chronic affective illness such as bipolar disorder produces significant distress and dysfunction, even when correctly diagnosed and treated. The unique clinical challenges posed by this chronic illness include various acute phases of mood instability: depressive, hypomanic, manic, and mixed episodes. In addition, these acute phases can present in a range of patterns and at varying intervals both in the individual patient and across patients carrying the identical diagnosis. Bipolar disorder mandates prescription of lifelong maintenance treatment in an effort to minimize relapse, recurrence, and functional impairment. This wide spectrum of affective pathology requires thoughtful psychopharmacologic strategies that often must be adjusted over time, individually tailoring specific drug therapy in an attempt to meet every unique patient's changing needs.

In many regards, the pharmacologic treatment of bipolar disorder is still in its infancy. Less than four decades have passed since lithium was first approved by the U.S. Food and Drug Administration (US-FDA). The first approval for treatment of acute bipolar depression did not come until late 2003 with a second following in 2006. The core principles of medication management for bipolar disorder revolve around the use of "mood stabilizers." However, true to the developing maturity of this field, even this key term—"mood stabilizer"—is not recognized by the US-FDA and a single widely agreed upon definition does not exist.

This chapter reviews the concept of mood stabilizer therapy in the management of bipolar disorder and offers new suggested hierarchical criteria to define "mood stabilizer." The bulk of this chapter will cover treatments for the acute phases of mania and depression, as well as long-term maintenance. It should be noted that the mood stabilizers effective for mania are generally thought to also be effective for mixed mania and hypomanic states although there is admittedly little data to make definitive conclusions about the veracity of this assumption.

## Defining Mood Stabilizers

Varying definitions for a "mood stabilizer" have been increasingly debated over the past decade. Although many believe that the term was first used in relation to lithium, its first appearances in the literature were with regard to the antipsychotic chlorpromazine and the tranquilizer aminophenylpyridone (Laborit et al. 1952, Litchfield 1960).

The ideal mood stabilizer would work in all phases of the illness and in all stages of treatment—from treating acute depression, mania, hypomania, and mixed states to preventing all abnormal elevations or depressions of mood. This ideal mood stabilizer would not aggravate or worsen any feature of the illness, that is, precipitate depression or mania, or lead to rapid cycling or cycle acceleration. In other words, the best "mood stabilizer" would work in all four-treatment roles in bipolar disorder, treating the highs and lows as well as preventing the highs and lows. The picture becomes more complex if we consider the need to treat mixed states and rapid cycling. To date no such ideal mood stabilizer exists, although many would argue that lithium comes closest (Bauer and Mitchner 2004).

A more relaxed definition of mood stabilizer was offered by Sachs (1996). The term mood stabilizer could be applied to any medication that was able to "decrease vulnerability to subsequent episodes of mania or depression" and not exacerbate the current episode or maintenance phase of treatment. Such a definition does not require absolute antidepressant or antimanic efficacy.

The therapeutic benefits of lithium have inspired definitions of a mood stabilizer as any agent that possesses "triple threat" properties (antimanic, antidepressant, prophylactic) in the management of bipolar disorder (Keck and McElroy 2003). The lack of such triple-threat mood stabilizers, as well as criticisms of lithium's antidepressant powers, led to definitions of mood stabilizers of a uniphasic nature—efficacy in at least one pole of bipolar disorder without exacerbating another phase (Keck and McElroy 2003).

Ketter and Calabrese (2002) suggested a reconceptualization of bipolar disorder that emphasized implications for

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treatment that "highlight unmet needs and the importance of differential spectra of efficacy" given the lack of any current medication meeting the most stringent and ideal definition of mood stabilizer. For treatment of aberrant states of mood, behavior, and cognition that deviate above the euthymic baseline, the term "Class A" mood stabilizers was suggested to define agents that (1) stabilize mood from *above* baseline and (2) possess marked antimanic properties without causing a worsening of depression. For those abnormal conditions where mood deviates below the euthymic baseline, the term "Class B" mood stabilizers has been suggested to define agents that (1) stabilize mood from *below* baseline and (2) possess marked antidepressant properties without destabilizing the course of illness by inducing switches into mania or episode acceleration.

Bauer and Mitchner (2004) proposed a "two-by-two" definition by which an agent is considered a mood stabilizer if it has efficacy in treating acute manic and depressive symptoms and in prophylaxis of manic and depressive symptoms in bipolar disorder. In an analysis of peer-reviewed; high quality controlled trials, the authors identified lithium as the only agent that can be able to meet the above a priori definition of a mood stabilizer.

Others have sought to define mood stabilizers more pragmatically as agents that demonstrate efficacy more in prophylaxis than in acute episode management (Malhi et al. 2005). In any case, experts in the field continue to discuss the issue of precisely defining mood stabilizers while cautioning against the indiscriminate use of the term. Most importantly, these experts acknowledge that we are still unable to define mood stabilization at a molecular or even physiological level (Goodwin and Malhi 2006). With this caution in mind, we will review medical management of acute and maintenance phases of bipolar disorder with mood stabilizers, acknowledging the imperfections in the use of the term as well as the agents so putatively defined.

## Mood Stabilizers for Acute Mania

### General Considerations

The management of mood states that they are pathologically above the healthy euthymic baseline typically focuses on mania although similar treatments could be considered for hypomania, psychotic mania, mixed states and subsyndromal mood elevations. For further details on accurate diagnosis of mania and these related states please refer to other chapters in this book.

Classical manic, hypomanic, and mixed bipolar episodes share distinctive traits of hyperactive behavior and/or thoughts, a mixture of mood elevations and irritabilities, affinity for impulsivity and lability, and degrees of functional impairment or distress. Hospitalization is most often necessary when attempting to control acute bipolar mania. The first step in choosing initial mood stabilizer therapy for mania should involve assessment of the severity of symptoms, which may guide need for monotherapy versus combination therapy. Patients with hypomanic to mild manic presentations may be candidates for monotherapy, whereas patients with more severe manic or mixed episodes should almost always be treated urgently with combinations of antimanic agents. Other considerations, such as first episode versus break-through episode, rapid cycling or refractory illness, and patient preference and tolerability issues also impact decisions for initial management choices. In addition, some thought should be given to maintenance therapy planning even in acutely manic patients given the recurrent nature of bipolar disorder.

The available evidence suggests that lithium, certain anticonvulsant or antiepileptic drugs (AEDs), and all of the atypical antipsychotic drugs are effective for acute mania and may possess other therapeutic properties that could support calling them "mood stabilizers."

Table 103–1 lists approved drugs for treatment of bipolar disorder in the US, including the 10 drugs approved for acute mania and 6 for mixed states.

**Table 103–1 Approved Medications in the US for Bipolar Disorder**

| Drug | Mania | Mixed | Maintenance | Depression |
|---|---|---|---|---|
| Aripiprazole | X | X | X | |
| Carbamazepine ER | X | X | | |
| Chlorpromazine | X | | | |
| Divalproex DR | X | | | |
| Divalproex ER | X | X | | |
| Lamotrigine | | | X | |
| Lithium | X | | X | |
| Olanzapine | X | X | X | |
| Olanzapine–fluoxetine | | | | X |
| Quetiapine | X | | | X |
| Risperidone | X | X | | |
| Ziprasidone | X | X | | |

### Lithium

Since the introduction of lithium for the treatment of "psychotic excitement" (Cade 1949) and later confirmation of antimanic effect by a team led by Mogens Schou (Schou et al. 1954), this mood stabilizer has been the keystone of bipolar disorder therapy. It received the approval for use in mania by the US FDA in 1970. The short-term efficacy of lithium in the treatment of acute mania is supported by at least five placebo-controlled trials, with more recent studies indicating that about half of acutely manic patients respond well to lithium (Kukopulos et al. 1980, Small et al. 1988, Small et al. 1991). These studies, as well as decades of collective experience, clearly support the use of lithium for acute mania. Cotherapy with other antimanic mood stabilizers or benzodiazepines is frequently necessary for most manic patients.

#### Pharmacokinetics

Lithium is absorbed completely within 8 hr of oral intake with peak plasma levels reached between 1 and 3 hr after ingestion. Absorption is not affected by the presence of food, making it preferable for some patients experiencing gastric

irritation to take lithium right after meals. Distribution of lithium after absorption into the bloodstream is rapid with the majority entering the intracellular space. Its final concentration in blood and tissue is determined by complicated transport mechanisms. On an average, the brain concentration of lithium is lower than the plasma concentration while the half-life of lithium in the brain is longer than in blood (Plenge et al. 1994). Renal clearance is the primary route of lithium elimination. Age-related changes necessitate more careful use of lithium in the elderly as elimination may be significantly decreased, lending to greater risk of elevated or toxic levels. It is reabsorbed from the glomerular filtrate in the proximal tubule so clinicians must know that lithium elimination may be substantially increased by certain medications, while certain diuretics that act at the distal tubule may lead to unwanted lithium retention (Table 103–2).

**Table 103–2 Potential Interactions with Lithium**

| Increase Lithium Levels | Decrease Lithium Levels | Adverse Reactions |
|---|---|---|
| Angiotensin-converting enzyme inhibitors | Acetazolamide | Iodides (hypothyroidism) |
| Indomethacin | Alkalinizing agents | Calcium channel blockers |
| NSAIDs, including ibuprofen | Caffeine | Carbamazepine |
| COX-2 inhibitors | Carbonic anhydrase inhibitors | ECT |
| Fluoxetine | Laxatives | Succinylcholine |
| Thiazide diuretics | Osmotic diuretics | Methyldopa |
| Metronidazole | Theobromine diuretic | Fluvoxamine |
| | Theophylline | Antipsychotics (neurotoxicity) |
| | Urea | |
| | Xanthine preparations | |

## Mechanism of Action

Lithium's mechanism of action as an antimanic mood stabilizer may be related to its interaction with various neurotransmitter systems. Little is known about the effects of lithium on noradrenergic neurotransmission in manic individuals although lithium administration has been reported to be associated with the decreased excretion of norepinephrine and its metabolites in manic patients while increasing this excretion in depressed patients (Beckmann et al. 1975, Bowers and Heninger 1977, Greenspan et al. 1970). Lithium may exert antimanic effects via its ability to prevent dopamine receptor supersensitivity. However, just as with its reported effects of increasing acetylcholine synthesis and uptake, these changes in receptor sensitivity have been found to be associated with chronic, but not acute, lithium administration (Jope 1979).

A growing body of research has begun to elucidate the complex effects of lithium on various cellular signal transduction pathways, beginning with initial direct targets of lithium, its second messenger roles, and ultimate effects on gene expression and cellular resilience. An established mechanism of lithium's antimanic properties has yet to be determined although compound effects at different levels and pathways seem most likely. Again, most studies on the effects of lithium on signal transduction mechanisms have explored chronic lithium administration and resultant changes.

Lithium has significant inhibitory effects on the cyclic adenosine monophosphate (cAMP)-generating system, induced by various neurotransmitters and hormones (Forn and Valdecasas 1971, Marmol et al. 1992) while increasing basal cAMP in several regions of the brain with chronic administration (Mork et al. 1992). Signal transduction may thus be stabilized by lithium via a balancing effect of increasing basal activity while inhibiting stimulated activity.

Studies have suggested that the untreated manic patients may have raised myo-inositol and phosphomonoester (PME) concentrations and that lithium may be clinically effective due to its normalizing actions on the phosphoinositol second messenger system (Silverstone et al. 2002). Lithium has demonstrated effects on the arachidonic acid cascade, glycogen synthase-kinase-3, protein kinase activities and protein phosphorylation, and G-proteins (van Calker 2006). These varied effects ultimately are believed to alter gene expression and cellular resilience in patients with bipolar disorder treated with lithium.

## Clinical Application

While lithium is effective for mania, clinical improvement is relatively slow, with an initial onset of therapeutic response generally occurring no sooner than 7–14 days after it is started. Additionally, lithium has a significant adverse effect profile that complicates long-term management (Table 103–3). These effects may be less apparent during acute treatment with lithium than during maintenance treatment.

Pretreatment procedures and testing are recommended before beginning therapy with lithium: general medical history, physical exam and weight, BUN and creatinine determination, thyroid function studies, and pregnancy testing for women of child-bearing age. Lithium carries a teratogenicity category D warning. Electrocardiography and complete blood count measurement should be obtained for patients over the age of 40. Some experts recommend more detailed screening to include fasting glucose determination and dehydration test with vasopressin to determine renal concentrating capacity. Calculation of an estimated creatinine clearance may be more practical and serves to provide a baseline reference value for monitoring of potential renal problems on lithium (Table 103–4) (Cockcroft and Gault 1976).

For treatment of acute mania, lithium should be dosed to achieve therapeutic plasma concentrations (sampled 12 hr after the last dose) between 0.8 and 1.2 mEq/L, avoiding toxic effects more commonly seen with levels at or above 1.5 mEq/L. A routine initial dosing regimen is the administration of lithium carbonate 300 mg four times daily with trough plasma level determination on Day 4 or Day 5 of the treatment, targeting the therapeutic range and watching for any signs of toxicity. A lower starting dose and slower titration are recommended in older patients and those with impaired renal function. When used to treat milder mania or hypomania, lower starting doses (300 mg bid) and lower

**Table 103–3 Adverse Effects of Lithium**

| System Affected | Adverse Effect(s) | Treatment/Comments |
|---|---|---|
| Cardiovascular | Bradycardia, syncope, AV block, EKG changes, sick-sinus syndromes | Infrequent or rare events; EKG monitoring; do not use lithium with sick sinus; discontinuation of lithium may be needed |
| Central Nervous System | Mental dullness, headache, memory troubles, muscle weakness | Commonly seen, especially at start of therapy. Dose reduction may help |
| Dermatologic | Acne, hair loss, psoriasis, skin reactions | Standard dermatologic treatments, avoid or discontinue lithium if severe |
| Endocrine | Goiter, elevated TSH, hypothyroidism, hyperparathyroidism with hypocalcemia | Thyroid problems common with long term therapy. Can be treated with exogenous L-thyroxine |
| Gastrointestinal | Nausea, GI pain/distress, vomiting, diarrhea, frequent loose stools | More common at start of therapy but may indicate toxicity, check lithium levels, take lithium with food or change preparation, lower/slower dosing |
| Hematological | Leukocytosis | Common, reversible |
| Metabolic | Weight gain | Avoid caloric beverages, healthy diet, increase physical activity |
| Neurologic | Postural tremor, confusion, ataxia | Fine tremor is frequent side effect, dosage reduction and/or Beta-blockers may help. Other effects should prompt lithium level check |
| Ophthalmic | Blurry vision, nystagmus, eye pain | Rare. Reduce dose or discontinue lithium |
| Renal | Polydipsia, polyuria, reduced concentration capacity | Diuretics with caution, lower dosage, take dose once daily at bedtime, decrease dietary protein |

**Table 103–4 Cockcroft-Gault Formula to Estimate Creatinine Clearance***

Clearance of creatinine (mL/min) = [(140 – age) × (body weight (kg)] ÷ [72 × serum creatinine (mg/dl)]

*In women, this equation is multiplied by 0.85 to correct for gender difference and normal range is less than 90 mL/min.

blood levels (0.6–0.8 mEq/L) may sufficiently stabilize mood over a period of several weeks to months. Lower doses and levels of lithium may be sufficient when combination pharmacotherapy strategies, such as lithium plus an anticonvulsant or antipsychotic, are used. These lower doses may greatly reduce the frequency of troublesome side effects during early treatment and thus enhance adherence.

The most common side effects of lithium are nausea, vomiting, tremor, diarrhea or more frequent stools, polydipsia, and polyuria. During acute treatment, gastrointestinal disturbances and tremor can be mitigated by slower dosing strategies. These adverse effects typically subside within 1–2 weeks, although on occasion they can persist. Worsening of any of these adverse effects, as well as the development of bradycardia, syncope, confusion, or ataxic gait should prompt the clinician to immediately measure lithium blood levels and consider changes in dosing or treatment alternatives. Psoriasis, acne, and other skin/hair reactions have also been described in association with lithium therapy.

Lithium toxicity may be heralded by emergence or aggravation of any of the above adverse effects, progressing to include one or more other symptoms such as coarsening tremor, sluggishness, slurred speech, parkinsonism, hyperreflexia, myoclonic twitches, and mental status changes. Early recognition of toxicity is critical as is investigation of cause (Table 103–5). The possibility of drug interactions with lithium must always be considered, particularly with thiazide (and possibly loop) diuretics, angiotensin converting enzyme (ACE) inhibitors, nonsteroidal antiinflammatory drugs, and other psychotropics.

**Table 103–5 Potential Causes of High Lithium Levels and/or Toxicity**

- Excess dosing
- Overdose
- Lab error, or less than 10–12 hr between last drug dose and blood sampling
- Increase in lithium absorption
  - Diarrhea
  - Vomiting
- Drug-interactions reducing renal clearance (NSAIDS, thiazides)
- Dehydration
  - Fever/illness
  - Hot weather/heat exhaustion
  - Intense physical activity/profuse sweating
  - Sauna/steam room
- Renal insufficiency or intercurrent renal disease
- Sodium deficiency (low caloric or low-sodium diet)

## Antipsychotics

Antipsychotic drugs are presented in greater detail elsewhere in this book, including distinctions between "typical" or conventional, older antipsychotics and the newer "atypical" or second generation antipsychotics. The chemistry, pharmacology, adverse effects, and precautions associated with the use of these drugs for schizophrenia apply as well to bipolar disorder. Particular attention should be paid to the metabolic risks associated with the atypical antipsychotics described in Chapter 97 of this book, along with monitoring and safety requirements.

Although typical antipsychotics can be used effectively to treat mania, there is very little evidence to suggest that they meet any definition of a mood stabilizer. Here we will focus only on the use of newer atypical antipsychotics to treat acutely manic patients with bipolar disorder, as growing evidence suggests that one or more of these medications may be considered mood stabilizers by some definitions.

## Atypical Antipsychotics

Randomized, placebo-controlled trials have demonstrated the efficacy of all five second-generation atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole) and led to their US FDA approval for the management of acute bipolar mania with or without psychotic features. With the exception of quetiapine, they are all approved for mixed states in bipolar disorder. A recent meta-analysis of randomized controlled trials of these five atypical antipsychotics in the treatment of acute mania, as monotherapy or adjunctively, concluded that differences in efficacy between these agents are likely to be small (Perlis et al. 2006).

### *Olanzapine for Bipolar Mania*

Olanzapine became the first atypical antipsychotic, and the first antipsychotic since chlorpromazine, indicated for the treatment of mania associated with bipolar disorder when it received approval by the US FDA in 2000 based on data from two large placebo-controlled trials (Tohen et al. 2000, Tohen et al. 1999). Response rates to olanzapine monotherapy in these trials ranged from 49–65%. Olanzapine has been reported to bring about symptomatic remission from mania significantly earlier than divalproex (Tohen et al. 2003a). A recent Cochrane Database System Review substantiates some superior efficacy for olanzapine over divalproex for acute mania, but notes the increased risk of weight gain for olanzapine compared to divalproex (Rendell et al. 2003).

In manic patients only partially responsive to either lithium or divalproex, the use of adjunctive olanzapine led to significantly faster antimanic response and a greater reduction in symptom severity than placebo augmentation (Tohen et al. 2002). Coexisting depressive or mixed symptoms also improved substantially. Olanzapine has been reported to be efficacious for treatment of the acute manic and depressive symptoms associated with dysphoric mania and a rapid cycling course (Gonzalez-Pinto et al. 2002, Sanger et al. 2003).

The antimanic dose of olanzapine is between 15–20 mg/day, although lower doses may be effective when used adjunctively with other mood stabilizers. During initial treatment of a severe manic episode in clinical practice, off-label doses of 30–40 mg/day may be required, which can be safely reduced once the acute episode has resolved.

Olanzapine is also available in an intramuscular (IM) formulation approved for use in the treatment of agitation associated with schizophrenia or bipolar I mania. The IM use of olanzapine is of particular utility in the hospitalized manic patient with severe agitation and can be administered as an initial 10 mg dose and repeated if needed in 2 hr and again 4 hr later up to a maximum daily IM dose of 30 mg. This maximal dosing may lead to substantial orthostasis and so must be employed with much caution. Concomitant administration of IM lorazepam should be avoided as this combination may lead to a pronounced sedation and a respiratory depression.

Olanzapine has structural and pharmacologic similarities to clozapine. Olanzapine binds with high affinity to dopaminergic, serotonergic, adrenergic, and muscarinic and histaminergic receptors. Like clozapine it has a low risk for causing extrapyramidal side effects or raising prolactin. Although its exact mechanism of action as an antimanic agent remains unknown, the broad and unique binding properties of this drug provide multiple potential therapeutic means which may account for its efficacy in bipolar disorder (Bymaster et al. 1996).

### *Risperidone for Bipolar Mania*

Substantial evidence supports the efficacy of risperidone in acute mania. An initial 1998 study compared risperidone with haloperidol and lithium and demonstrated that all three agents significantly reduced manic symptoms by study endpoint of 4 weeks (Segal et al. 1998). Two subsequent multicenter, double-blind, placebo-controlled monotherapy studies of risperidone for acute mania found response rates at 3 weeks of 43–73% compared with only 24–36% in placebo-treated subjects (Hirschfeld et al. 2004, Khanna et al. 2005). A third international trial conducted by Smulevich et al. (2005) included extension to 12 weeks and demonstrated ongoing reductions in mania with risperidone; this study allowed a slightly slower initial dosing schedule for risperidone, reaching a maximum of 6 mg/day by Day 5.

Two trials of risperidone added to mood stabilizers (lithium, valproate, or carbamazepine) for 3 weeks have shown an advantage of risperidone over placebo in acutely manic bipolar patients, with or without psychotic features (Sachs et al. 2002, Yatham et al. 2003). In the Yatham et al. (2003) study, risperidone was able to separate from placebo add-on despite allowing carbamazepine as one of the mood stabilizers (which was associated with a 40% reduction in serum risperidone levels). The risperidone data is consistent with observations made from the olanzapine studies—combined atypical antipsychotic and traditional mood stabilizer therapy leads to greater improvement in mania than monotherapy.

The mean modal antimanic doses for risperidone as monotherapy or add-on therapy ranged from 4–6 mg/day, with the lower end of the range used when combined with another mood stabilizer. Again, clinical practice and individual patient needs may demand doses that are above or below this dose range.

Risperidone is presently the only atypical antipsychotic with a long acting intramuscular injection form that employs encapsulation of the active drug in microspheres of a biodegradable polymer (glycolic acid-lactate, also used for sutures). Slow release of risperidone occurs with gradual hydrolysis of the polymer beginning about 3 weeks after initial injection. It is estimated that the 50 mg injectable dose given every two weeks is roughly equivalent to up to 4 mg of oral risperidone given daily. For individual patients with mania prone to frequent relapse or recurrence due to poor oral medication adherence, the long acting injection of risperidone holds much promise.

Risperidone is a potent 5HT-2A and $D_2$ antagonist similar to clozapine but has less affinity for $D_3$ and $D_4$ receptors. It also blocks H1, alpha-1, and alpha-2, but not acetylcholine receptors. Doses of risperidone above 6 mg/day are known to produce greater than 80% blockade of $D_2$ receptors in the basal ganglia, resulting in an increased likelihood of extrapyramidal side effects. As with olanzapine, its exact mechanism of therapeutic action in bipolar disorder is not known although antipsychotics in general may exert antimanic actions, at least in part, via $D_2$ receptor

antagonism. Central dopaminergic hyperactivity has been postulated as the pathophysiology of mania (Gerner et al. 1976).

### Quetiapine for Bipolar Mania

Unlike other acute mania trials, quetiapine mania studies excluded mixed states. Accordingly, quetiapine is FDA approved only for the treatment of acute manic episodes associated with bipolar disorder. McIntyre et al. (2005) reported a 12-week randomized trial with quetiapine monotherapy in which quetiapine treatment produced a response rate of 43.6% as compared with a 35.0% placebo response rate at Day 21. By Day 84, the response rate with quetiapine treatment grew to 61.4% as compared with 39.0% in the placebo group. In a second 12-week study of identical design, the response rate in quetiapine-treated subjects was 53.3% versus 27.4% with placebo; at Day 84, quetiapine response rate was 72.0% versus 41.1% for placebo (Bowden et al. 2005). In a combined analysis of these two studies, the quetiapine monotherapy response rate for mania was 48% with only 31% placebo response at Day 21 (Vieta et al. 2005).

Quetiapine combined with lithium or divalproex in a 3 week, multicenter, randomized controlled trial resulted in a 54% response rate compared with a 33% response rate in those receiving mood stabilizer plus placebo (Sachs et al. 2004). In both monotherapy and adjunctive therapy indications for bipolar I mania, the recommended dose for quetiapine is 600 mg/day, following a bid titration schedule over 5 days after starting with 50 mg bid.

There are more than 20 metabolites of quetiapine, and almost all of them are inactive. Quetiapine is metabolized by 4 routes, including hydroxylation, sulfoxidation, oxidation, and dealkylation. The latter generates the primary active metabolite of the parent compound, norquetiapine, and is hypothesized to act by inhibiting the norepinephrine transporter. Therefore, quetiapine is now believed to interact with three principal neurotransmitter systems, including dopamine, serotonin, and norepinephrine.

Quetiapine is an antagonist at multiple neurotransmitter receptor sites in the brain, including $5HT_{1A}$, $5HT_2$, $D_1$, $D_2$, histamine H1, alpha-1 and alpha-2. It has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors. Its dopamine antagonism may be responsible for its antimanic effects. Rapid disassociation from the $D_2$ receptor is thought to contribute to quetiapine's minimal propensity for inducing extrapyramidal side effects or prolactin elevation. Antagonism of H1 receptors may explain somnolence observed with quetiapine use.

### Ziprasidone for Bipolar Mania

Ziprasidone monotherapy has also demonstrated rapid onset of antimanic activity leading to significantly greater symptomatic reduction and response rates compared to placebo in two double-blind; randomized controlled trials (response rates for ziprasidone 46–50%, for placebo 29–35%) (Keck et al. 2003a).US FDA regulatory approval was given in 2004 for acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

Similar to the other atypicals, ziprasidone has high affinity for dopamine, serotonin, and alpha-adrenergic receptors with only a moderate affinity for histaminic receptors. Although its clinical significance can be debated, ziprasidone is unique among the atypicals in that it does display some inhibition of synaptic reuptake of serotonin and norepinephrine.

Ziprasidone may be started at 40 mg twice a day (given with meals to enhance absorption) and increased up to 160 mg/day within the first week, with an average dose of around 120 mg/day in study responders. Ziprasidone is available in an IM form that can help to rapidly control associated agitation with 10 mg IM every 2 hr (or 20 mg every 4 hr) as needed up to 40 mg/day.

### Aripiprazole for Bipolar Mania

This newest atypical antipsychotic has been investigated in two randomized placebo controlled trials of acute bipolar mania, which led to US FDA approval in 2004 for monotherapy treatment of acute manic or mixed episodes associated with bipolar disorder. In the first 3-week placebo-controlled monotherapy trial, aripiprazole produced significant reduction in manic symptoms compared to placebo-treated patients by day 4 of the study and this statistically-significant difference was maintained throughout the trial (Keck et al. 2003b). These results were confirmed by a second placebo-controlled study by Sachs et al. (2006).

Compared to the other approved atypical antipsychotics aripiprazole possess a novel mechanism of action, appearing to mediate its primary therapeutic effects through partial agonism at the $D_2$ receptor. Partial agonism is also seen at the $5HT_{1A}$ receptor, while like other atypicals aripiprazole displays antagonism at the $5HT_{2A}$ receptor. Aripiprazole has moderate affinity for histamine and alpha-adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors.

Treatment of manic or mixed episodes in bipolar disorder with aripiprazole may commence with 15–30 mg/day, with responders requiring an average daily dose near 30 mg/day. An IM formulation of aripiprazole has recently received approval to treat agitation associated with schizophrenia or bipolar mania. The recommended dose is 9.75 mg IM and can be repeated every 2 hr up to a maximum of 30 mg/day.

Table 103–6 provides dosing information for the use of atypical antipsychotics for the management of acute bipolar mania.

**Table 103–6 Dosing of Atypical Antipsychotics for Acute Mania**

| Atypical | Starting Daily Dose (mg) | Target Daily Dose (mg) |
|---|---|---|
| Olanzapine | 5–10 | 15–20 |
| Risperidone | 2–4 | 4–6 |
| Quetiapine | 100 | 400–800 |
| Ziprasidone | 80 | 120–160 |
| Aripiprazole | 15–20 | 25–30 |

### Tolerability and Safety Issues with Atypicals

Atypical antipsychotics generally have superior tolerability when compared with typical antipsychotics in the management of bipolar disorder. Side-effect profiles vary among the different atypical agents, while monitoring needs

remain the same. Of principal concern with longer-term use is the risk for metabolic derangements, notably weight gain, type-2 diabetes, and lipid elevations. Prior to initiating therapy for mania with any atypical antipsychotic, baseline determination of fasting glucose, weight, waist circumference, and lipid profile is recommended (refer to Chapter 97 in this book.).

## Anticonvulsants/AEDs

Reports of the beneficial behavioral effects associated with the use of AEDs in patients with bipolar disorder, particularly for mania, date back to the 1960s. Discussions regarding the potential for some shared etiologic process between epilepsy and bipolar disorder, such as kindling, were common in the literature of the time. Theoretically, as in epilepsy where repeated subthreshold neuronal stimulation can generate an action potential that triggers a seizure, kindling in a patient with bipolar disorder could produce activation of or switching to disordered mood states—mania, depression, mixed states. The proposed reduction of kindling by AEDs such as carbamazepine along with observations of positive "mood stabilizing" effects led to widespread investigation of virtually every developed AED in bipolar disorder (Post et al. 1982).

It does not appear that a distinct class effect for AEDs in the management of bipolar disorder exists since not all anticonvulsants have been able to demonstrate efficacy for this mood disorder. The likely explanation for this variability for AEDs in bipolar disorder relates to the complex differences in the mechanisms of action for these drugs (Muzina et al. 2005). Multiple mechanisms of action have been proposed for AEDs as anticonvulsants, including glutamate receptor blockade, enhanced effects of gamma-amino-butyric-acid (GABA), sodium and/or calcium channel blockade, activation of potassium conductance, carbonic anhydrase inhibition, and synaptic vesicle protein modulation. Despite assumed primary modes of anticonvulsant action for any individual AED, each has a dissimilar profile in terms of possessing multiple distinct mechanisms that may confer anticonvulsant properties. These mixed effects may also potentially explain the differential effects among AEDs in terms of treating disordered mood states and why not all AEDs can effectively treat mania.

Future exploration of pathophysiologic causes beyond simple catecholamine "imbalances" will better inform our understanding of how AEDs affect mood and direct focused AED drug development that may impact other proposed causes for mood disorders, such as defective G-proteins, altered second-messenger systems, mitochondrial disorders, and excessive methylation of DNA-histone proteins (Muzina et al. 2006).

Here, we will consider AEDs that may provide antimanic mood stabilization based on randomized, double-blind, placebo-controlled studies with adequate sample size. Other than divalproex and carbamazepine, other AEDs have not demonstrated strong enough evidence to qualify for inclusion here.

### Divalproex Sodium/Valproate

Divalproex sodium became the first anticonvulsant approved as a treatment for bipolar mania by the US FDA in 1995, after a large-scale, randomized, double-blind parallel-group study found divalproex equivalent to lithium in superiority over placebo for the management of acute mania (Bowden et al. 1994). In this study, efficacy of divalproex appeared independent of prior responsiveness to lithium. Both active treatments demonstrated a nearly 50% response rate with monotherapy, while placebo response was only 25%. A new extended release (ER) preparation of divalproex recently received approval for acute manic or mixed episodes of bipolar disorder, with or without psychotic features, demonstrating a similar response rate of nearly 50% although placebo response was numerically higher in this study, 34% (Bowden et al. 2006).

Divalproex is recommended as a first-line acute treatment option for mania in most evidence-based practice-guidelines, either as monotherapy or in combination with antipsychotics for more severe manic episodes. Table 103–7 lists factors associated with an acute response to divalproex compared to lithium and/or carbamazepine.

**Table 103–7 Factors Associated with Acute Response to Divalproex/Valproate**

- History of prior poor response to lithium
- Higher number of lifetime episodes of mania or depression
  - 8 or more total lifetime episodes
  - More than 2 prior major depressive episodes
- Mania with depressive features
- Presence of irritability
- Atypical manic states
  - Later age of illness onset
  - Comorbid substance abuse
  - Mania associated with neurological or medical illness

#### *Pharmacokinetics*

Following oral administration of divalproex, its absolute bioavailability quickly approaches 100%; the ER preparation bioavailability is closer to 90%. This suggests that a slightly higher dose of the ER form is needed in order to reach bioequivalence with the immediate release preparation (8–20% higher dose for ER). Peak plasma concentrations are achieved within 3–5 hr although up to 17 hr may be needed to reach peak concentration for the ER form. Mean terminal half-life is about 12–16 hr for either preparation, with steady state conditions usually being achieved within 3–4 days.

This AED is metabolized almost entirely by liver via the cytochrome P450 2D6 system. Mitochondrial beta-oxidation is the other major metabolic pathway. It does not induce its own metabolism. It inhibits drug oxidation and may increase serum levels of other oxidatively metabolized drugs, such as phenytoin, phenobarbital, and tricyclic antidepressants. Coadministration with other microsomal enzyme-inducing drugs, such as carbamazepine, will decrease plasma valproic acid levels. Inhibitors of the P450 system, such as selective serotonin reuptake inhibitors, can increase levels of valproic acid in the plasma. Toxicity can also be induced when divalproex is given along with other drugs that may be highly protein bound.

#### *Mechanism of Action*

As discussed above regarding AEDs in general, the exact mechanism of antimanic or "mood stabilizing" action for

divalproex is not known. Presumably this AED is able to treat mania via increasing levels or activity of the primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Alternatively, divalproex may mimic or enhance GABA's effects at postsynaptic receptor sites.

### *Clinical Application*

Before initiating acute treatment of mania with divalproex, a general medical history with special attention to any past problems of hepatic or hematological nature should be obtained, as well as baseline liver profile, and complete blood cell count. Pregnancy screening should be conducted before starting divalproex, particularly given its FDA black-box warning of teratogenicity category D.

Divalproex can be dosed with either an oral-loading or standard-titration strategy. For acute management of severely ill manic patients, divalproex oral-loading with a therapeutic starting dose of 20–30 mg/kg per day is suggested over standard, gradual titration schedules. Oral-loading typically achieves serum concentrations of valproic acid greater than 50 mg/L by Day 2, which represents the low end of the therapeutic range of serum concentrations for this agent of 50–125 mg/L. Similar results can be obtained by using the ER preparation. This oral-loading strategy for divalproex has been demonstrated to lead to a more rapid antimanic effect when compared with standard-titration divalproex, lithium, or placebo; it is also better tolerated than olanzapine and as well tolerated as lithium or standard-titration divalproex (Hirschfeld et al. 2003). Lower, divided doses are initially recommended (250 mg tid or 500 mg bid) for patients with less severe mania or in elderly patients.

Adverse effects seen during initial therapy with divalproex are usually mild, transient, and easily managed. Gastrointestinal distress and sedation are the most commonly seen side effects during acute treatment, although other dose-related effects including tremor and benign hepatic transaminase elevations are occasionally encountered. Reduced dosage or slower upwards titration can be helpful, in addition to use of divalproex sodium formulation or ER divalproex instead of valproic acid may also lessen these side effects. Tremor may be minimized through dose reduction or concomitant beta-blocker medication. During acute treatment with divalproex, clinicians should consider the possibility of rare but potentially serious adverse effects such as irreversible hepatic failure, hemorrhagic pancreatitis, or hyperammonemic encephalopathy when patients experience severe abdominal distress, confusion or delirium.

Divalproex commonly displaces otherwise highly protein-bound drugs from their protein binding sites, requiring greater awareness of clinically significant drug interactions. Divalproex can also inhibit the metabolism of other drugs cleared by the liver. Most notably, it inhibits lamotrigine metabolism by 50% resulting in the critical need to initiate lamotrigine at 50% lower doses when coadministered with divalproex.

## Carbamazepine

There were approximately 20 double-blind studies examining the efficacy of carbamazepine and its 10-keto analog oxcarbazepine in the treatment of mania prior to the completion of the first large, randomized, double-blind, placebo-controlled parallel trial of carbamazepine monotherapy using a beaded, extended-release formulation (Muzina et al. 2002, Weisler et al. 2004). Prior to this (Weisler et al. 2004) study, earlier double-blind studies of carbamazepine in the treatment of acute mania were confounded by effects of other allowed psychotropic medication such as lithium or antipsychotics. The response rate using this formulation of carbamazepine to treat acute mania over three weeks was 41.5%, significantly greater than response of 22.7% with placebo treatment although separation from placebo was not noted until Week 2. A post-hoc analysis found benefit for patients with mixed states as well.

### *Pharmacokinetics*

Carbamazepine is 80% bioavailable after oral administration, with immediate and beaded release formulations bioequivalent. Nearly 80% is protein bound with the primary route of hepatic metabolism via the cytochrome 3A4 system to its active epoxide form. With initial administration of the ER form, half-life averages between 35–40 hr, but with repeated administration this falls to 12–17 hr due to auto-induction. Inhibitors of the P450 system will increase carbamazepine levels while inducers can decrease levels.

### *Clinical Application*

Before treatment with carbamazepine, a general history and physical exam should be performed, including screening for any history of liver disease or blood dyscrasias. Routine laboratories including complete blood count, liver profile, and electrolytes with creatinine should be obtained. More frequent monitoring is indicated in the elderly or in any individual on carbamazepine who develops fever, easy bruising or bleeding, weakness, or infection.

There is no clear target serum level of carbamazepine for acute mania. Immediate release carbamazepine therapy may be started at a total divided daily dose of 200–600 mg, with incremental increases of 200−1000 mg/day followed by careful monitoring of blood levels, side effects, and clinical efficacy. The beaded, ER form may be started at 400 mg/day and increased as tolerated up to 1600 mg/day. Many factors can affect carbamazepine blood levels beyond direct dosing, including auto-induction of metabolism and significant drug interactions.

During acute treatment with carbamazepine, the most commonly observed side effects are nausea, fatigue, blurred vision, and ataxia. More gradual initial titration of the dose may minimize these effects. Infrequently, liver transaminase elevations, rash, hyponatremia, and blood dyscrasias may complicate acute treatment.

## Summary: Mood Stabilizers for Acute Mania

There has been a surge in the number of medications effective to treat mania acutely in the past decade, mostly due to the emergence of atypical antipsychotics and their demonstration of efficacy for bipolar mania and mixed states. All of the atypicals, lithium, carbamazepine, and divalproex have had large positive studies supporting their role as antimanic agents. Table 103–8 summarizes the positive monotherapy studies that have produced evidence from large randomized, double-blind, placebo-controlled studies (Sachs 2007). Analyses of these studies find that these agents produce fairly robust clinical effects, with the numbers-needed-to-treat (NNT) ranging from 2.7−6.7 and

**Table 103–8 Positive Studies* of Monotherapy Treatment for Acute Mania**

| Investigators and Sample Size | Placebo Response (%) | Active Treatment Response (%) | NNT† |
|---|---|---|---|
| Bowden et al. 1994 *N* = 179 | 25 | Lithium: 49 | 4.2 |
| | | Divalproex: 48 | 4.3 |
| Weisler et al. 2004 *N* = 204 | 22 | Carbamazepine: 42 | 5.0 |
| Tohen et al. 1999 *N* = 139 | 24 | Olanzapine: 49 | 4.0 |
| Tohen et al. 2000 *N* = 115 | 43 | Olanzapine: 65 | 4.5 |
| Khanna et al. 2005 *N* = 290 | 36 | Risperidone: 73 | 2.7 |
| Hirschfeld et al. 2004 *N* = 259 | 24 | Risperidone: 43 | 5.3 |
| Vieta et al. 2005 *N* = 403 | 31 | Quetiapine: 48 | 5.9 |
| Keck et al. 2003a *N* = 210 | 35 | Ziprasidone: 50 | 6.7 |
| Keck et al. 2003b *N* = 262 | 19 | Aripiprazole: 40 | 4.8 |
| Sachs et al. 2006 *N* = 272 | 32 | Aripiprazole: 53 | 4.8 |

*Category A evidence derived from randomized, double-blind, placebo-controlled studies with adequate sample size.

†NNT = 1 ÷ (Active response rate - Placebo response rate) and NNT provides an estimate of the number of additional patients needed to treat in order to produce one additional positive response beyond what would be produced by placebo.

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no remarkable differences between the drugs in terms of acute antimanic effect.

## Mood Stabilizers for Acute Bipolar Depression

### General Considerations

Acute bipolar depression presents diagnostic and treatment challenges for most clinicians more commonly than other major mental disorders. A detailed exploration regarding diagnosis of bipolar depression can be found elsewhere in this book. The clinical approach to managing bipolar depression, once recognized, has been guided for many years by extrapolations and assumptions based on evidence from unipolar major depression studies. The use of agents deemed "antidepressants" based on efficacy in treatment trials for unipolar major depression has not been well studied for bipolar depression. From 1968 to 2001, there were only 12 randomized, placebo-controlled trials of traditional antidepressants in the treatment of bipolar depression (Ghaemi and Thase 2002). Only five of these studies reported the antidepressant studied to be more effective than placebo.

In addition, there remains much uncertainty and debate about the potential danger of cycle acceleration or "switching" associated with the use of antidepressants for patients with bipolar depression. While the phenomenon has not been thoroughly investigated, there is a growing consensus among US psychiatrists that traditional antidepressants should be avoided in the treatment of acute bipolar depression, particularly if their use is not counter-acted or "protected" by coadministration of known antimanic mood stabilizers. Although some may posit that a traditional antidepressant medication that is able to acutely treat bipolar depression and is also effective in terms of prophylaxis against depressive recurrence may represent a "mood stabilizer," the use of this term has not included antidepressants. Indeed, a recent effectiveness trial of adjunctive antidepressant treatment for bipolar depression found no efficacy for the use of the agents even when the common clinical practice of adding the antidepressant to a mood stabilizer was employed (Sachs et al. 2007).

**Effectiveness of Adjunctive Antidepressants**

Both common clinical practice and various treatment guidelines have recommended the addition of an antidepressant medication to a mood stabilizer in the treatment of acute bipolar depression. Many have believed that doing so would provide efficacy for the treatment of depression while protecting against manic switches or cycling. The recent publication of an effectiveness trial designed to investigate this issue raises significant doubts about the utility of this common practice (Sachs et al. 2007).

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a collaboration sponsored by the National Institute of Mental Health created to assess the effectiveness of treatments for bipolar disorder. The design of this large, naturalistic treatment study seeks to provide results that are generalizable to routine clinical practice. In this multicenter, double-blind, placebo-controlled, parallel-group study of standard antidepressants prescribed adjunctively with mood stabilizers for acute bipolar depression, 366 depressed patients with bipolar disorder were randomized to active adjunctive treatment (bupropion or paroxetine in addition to mood stabilizer) or to placebo (mood stabilizer alone) and followed for 26 weeks. The population studied included bipolar I or II disorder, with or without rapid cycling, and were allowed treatment for ongoing co-existing substance use disorders, anxiety disorders, or psychotic symptoms. Baseline depression was in the moderate range (mean Montgomery Asberg Depression Scale score ~ 24) in both groups.

The a priori primary outcome for this study was durable recovery, defined as euthymia for at least 8 consecutive weeks. Results demonstrated no significant differences between the use of adjunctive antidepressant or adjunctive placebo in

the percentage of patients meeting the criteria for durable recovery or any effectiveness outcome. In fact, nonsignificant trends consistently favored the mood stabilizer plus placebo over the adjunctive antidepressant. Overall rate of durable recovery with adjunctive placebo was 27.3% and with adjunctive antidepressant only 23.5%. Treatment-emergent affective switches occurred at about the same rate of 10% in both groups.
These results do not support the use of antidepressants (bupropion or paroxetine) for the treatment of acute bipolar depression, even in combination with a mood stabilizer. Monotherapy with a mood stabilizer alone was just as effective, although overall durable recovery was low in both groups (Sachs et al. 2007).

Discussion here will focus on the very limited evidence from large, randomized controlled trials of agents studied for use in acute bipolar depression which has led to regulatory approval in the US of only two medications: olanzapine–fluoxetine combination, and quetiapine. We will also briefly review evidence related to lithium and the AEDs for bipolar depression.

## Atypical Antipsychotics for Acute Bipolar Depression

It is interesting to note that the first antipsychotic drug, chlorpromazine, came to attention due to its positive effects on mood. Its calming effects led to study in psychotic states launching the birth of psychopharmacology. Attempts to develop better antipsychotics after chlorpromazine's discovery by creating similar structural analogues paved the way for the discovery of imipramine. Over the years, the use of antipsychotics to treat affective states such as depression gradually grew out of favor due mostly to concerns about neurological side effects. The emergence of atypical antipsychotics has placed these drugs on the frontline in treating bipolar depression.

### Mechanism of Action

Although research has focused on serotonin and norepinephrine in depression there are lines of evidence suggesting that dopamine may play a major role in the pathophysiology of depression. This is important to explore if we hope to better understand how atypical antipsychotics may effectively treat bipolar depression.

Innervation of the nucleus accumbens, amygdala, ventral hippocampus and prefrontal cortex by mesocorticolimbic circuits is believed to support behavioral functions related to reward and motivation. Alterations in this circuitry may be responsible for many of the core features of depression, with a deficiency in dopamine as a leading candidate cause (Willner 1983). Several studies have found reduced levels of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid of patients with bipolar depression, while CSF HVA is increased in manic patients. Chronic treatment with antidepressant medications is known to potentiate dopamine transmission and dopaminergic agonists, such as L-dopa and amphetamine, have long been known to elevate mood. Recent reports of efficacy in bipolar depression using the $D_2/D_3$ receptor agonist pramipexole adjunctive to mood stabilizer therapy further add to the speculation that enhancing dopamine can treat depression (Goldberg et al. 2004).

Atypical antipsychotics may address depression through blockade of both $D_2$ and $5HT_{2A}$ receptors. Blockade of the $5HT_{2A}$ receptors by atypical antipsychotic drugs on presynaptic dopamine neurons leads to an increase in the release of dopamine. Rapid dissociation from the $D_2$ receptor, as with quetiapine, may explain why less dysphoria is observed with this agent compared with other more potent $D_2$ blockers. It has been postulated that the $D_2$ antagonism of atypicals such as quetiapine and olanzapine in combination with $5HT_{2A}$ antagonism accounts for the mood stabilizing properties of these agents (Brugue and Vieta 2007). Since an excess of dopamine may lead to mania, the simultaneous blockade of $D_2$ receptors in the mesolimbic system may help to prevent manic switches by producing a regionally selective balance between dopamine and serotonin circuits thereby stabilizing mood from below baseline as well as from above (Yatham et al. 2005). Other mechanisms of potential antidepressant action by atypicals may include positive induction of neurotrophic changes, including those involving brain derived neurotrophic factor (BDNF) and glial fibrillary acidic protein (Qing et al. 2003, Xu et al. 2002). These and other findings suggest complex mechanisms beyond simple alterations in levels of serotonin, dopamine, and norepinephrine, in explaining the antidepressant activity of atypical antipsychotics.

### Olanzapine–Fluoxetine Combination (OFC) and Olanzapine for Bipolar Depression

The first controlled study of an atypical antipsychotic for the treatment of bipolar depression was completed by Tohen et al. (2003b). This 8-week, placebo-controlled, parallel-group trial randomized patients with bipolar I disorder to olanzapine, OFC, or placebo. Bipolar II patients were not included. Subjects were required to be at least moderately depressed and could not meet criteria for mania to be enrolled. Treatment with olanzapine was initiated at 5mg/day and could be increased to 20 mg/day in 5 mg increments. OFC was initiated at 6 and 25 mg/day (olanzapine 6 mg with fluoxetine 25 mg) but could be increased to 6 and 50 or 12 and 50 mg/day after at least 1 day at each dose.

Both olanzapine and OFC demonstrated significantly greater and sustained mean symptomatic improvements over placebo. The response rate was significantly higher in the OFC-treated group (56.1%) compared to the olanzapine-treated group (39%), both of which were higher than the 30.4% rate of response for patients taking placebo. When examining rates of remission, OFC was found to result in a remission rate of 48.8%, significantly higher than either olanzapine monotherapy (32.8%) or placebo (24.5%).

Further analysis of individual depression symptoms showed that olanzapine and OFC significantly improved inner tension, sleep, and appetite compared with placebo. However, only OFC significantly improved core mood items such as apparent sadness, reported sadness, lassitude, inability to feel, and pessimistic thoughts. Olanzapine monotherapy and OFC did not separate from placebo in reducing suicidal thoughts.

## Quetiapine for Bipolar Depression

Completion of two large, multicenter double-blind, placebo-controlled, parallel-group 8 week studies of quetiapine monotherapy has led to its approval as the second pharmacologic agent for acute bipolar depression (Calabrese et al. 2005a, Thase et al. 2006). These studies included subjects experiencing either bipolar I or II depression and did not exclude rapid cycling. After meeting enrollment criteria similar to the aforementioned OFC trial, subjects were randomized to quetiapine 300 mg/day, quetiapine 600 mg/day, or placebo. Quetiapine was initiated at 50 mg/day and titrated to achieve a target dose of 300 mg/day by Day 4 or 600 mg/day by Week 1.

Both studies confirmed significant antidepressant benefits associated with quetiapine over placebo, regardless of bipolar I or II status or the presence of rapid cycling.

Overall, the response rate with quetiapine treatment was 60% and the placebo response rate was 40%. There was no added benefit with the higher 600 mg dose of quetiapine. More than half of all quetiapine-treated patients experienced remission by 8 weeks compared to 33% remission rate with placebo. Significant improvements in anxiety, sleep, and quality of life were also observed in quetiapine-treated subjects.

Furthermore, at the final assessment, quetiapine was associated with significant reductions in suicidal thoughts as compared with placebo.

## Other Atypical Antipsychotics

Limited data is available regarding the use of the other atypical antipsychotics other than olanzapine and quetiapine in the treatment of bipolar depression. One small open-label study of risperidone augmentation assessed its efficacy for improving depressive symptoms in patients with bipolar or schizoaffective disorder and reported response in nearly 70% of risperidone-treated subjects(Vieta et al. 2001). However, risperidone has also been compared to quetiapine in a small, 4-month, open-label study of psychotic patients with depressive symptoms. Quetiapine produced a greater improvement in depression scores than did risperidone in patients with a primary mood disorder including bipolar disorder (Sajatovic et al. 2002).

A double-blind adjunctive trial of risperidone given singly or in combination with paroxetine in a small sample of BD (I or II) patients ($n$ = 30) who were receiving a stable dose of mood stabilizer demonstrated that risperidone, risperidone plus paroxetine, and paroxetine were all modestly effective when added to a mood stabilizer (Shelton and Stahl 2004).

In a randomized open-label trial for treatment-resistant bipolar depression, no statistically significant differences in response rates were found for lamotrigine (24%), inositol (17%), or risperidone (5%). Despite the lack of significance in the primary efficacy measure, post hoc analysis of data revealed greater improvements in depressive symptoms, overall severity, and functioning in the lamotrigine-treated patients at study conclusion (Nierenberg et al. 2006). These results suggest that only a limited number of patients with treatment-resistant bipolar depression would completely recover with the addition of risperidone.

In a retrospective chart review of 12 patients receiving aripiprazole for treatment-refractory bipolar depression only three of 12 patients were found to be much improved or very much improved on Clinical Global Impression of Improvement (CGI-I) scores (Kemp et al. 2007). Another small open-label study reported benefit in 7 of 10 subjects with bipolar I depression prescribed adjunctive aripiprazole (Sokolski 2007). Larger, placebo-controlled trials are needed to further investigate aripiprazole's role in the management of bipolar depression.

## Anticonvulsants/AEDs for Acute Bipolar Depression

As noted earlier, the AEDs are a heterogeneous group of medications that have demonstrated variable effects in the treatment of bipolar mania. The antidepressant effects of AED's in bipolar disorder are less well-studied and there is very limited supportive evidence for their use in acute bipolar depression although clinical practice often includes these agents in utilitarian fashion (Muzina et al. 2005, Muzina et al. 2006). Most of the attention to date has centered on divalproex/valproate and lamotrigine with very little controlled data regarding the use of other AEDs in acute bipolar depression.

### *Divalproex/Valproate*

Large-scale, consistent efficacy in the treatment of acute bipolar depression has not been demonstrated to date by this AED despite initial open-label data that suggested that divalproex may have benefit in the treatment of nonrefractory bipolar I or II depression (Sachs 1996). A later unpublished report, presented in poster format only, examined antidepressant effects in 45 subjects with bipolar I or II depression randomized to receive either divalproex (mean dose ~ 1.4 g/day) or placebo (Sachs et al. 2001). The results of this 8-week trial were negative, with changes in depression scores not reaching a statistically significant difference between the two groups. On the other hand, a twelve-week open trial of single daily dosing of divalproex by Winsberg et al. (2001) in medication-naïve and mood-stabilizer-naïve bipolar II depression found that divalproex was well tolerated and that 63% of subjects responded to treatment favorably. There was a trend towards a higher rate of antidepressant response to divalproex in medication-naïve patients (82%) compared to mood stabilizer naïve patients (38%). The authors speculated that the medication-naïve group responded at a higher rate due to a milder form or earlier phase of illness, lack of prior medication failures, or that they were less likely to have the course of their illness worsened by exposure to previous antidepressants.

In an 8-week, double-blind, placebo-controlled, randomized clinical trial of 25 mostly male outpatients with acute bipolar I depression, divalproex was significantly more likely to reduce symptoms of both depression and anxiety (Davis et al. 2005). The mean serum divalproex level was 81 mcg/ml at week 8. The extended-release preparation of divalproex has also been evaluated in a small sample ($N$ = 18) of patients with bipolar I, II, or Not Otherwise Specified (NOS) depression. After 6 weeks of double-blind treatment, divalproex significantly improved depressive symptoms with associated reductions in apparent sadness and pessimistic thoughts (Dunn et al. 2006).

### *Lamotrigine*

The results from the first double-blinded, placebo-controlled study of lamotrigine in the acute treatment of bipolar

depression contributed to its common off-label use while awaiting confirmation from subsequent trials (Calabrese et al. 1999). However, to date, replication of these findings has not occurred as seen in recently published reports of 4 additional separate failed trials in acute bipolar depression (Calabrese et al. in Press).

In the first study, Calabrese et al. (1999) randomly assigned 195 subjects with acute bipolar I depression to receive lamotrigine 50 mg/day, 200 mg/day or placebo in the first study of 7 weeks' duration. Patients in the lamotrigine 200-mg/day group had significant improvement in their depressive symptomatology as compared to placebo. Improvement was seen as early as Week 3 in both the active treatment groups compared to placebo and more than half of the patients treated with lamotrigine 200 mg/day experienced an antidepressant response by study end. The efficacy of the 50 mg/day dose of lamotrigine was similar to placebo on several measures, supporting the higher 200-mg/day dose.

Subsequent lamotrigine monotherapy trials for acute bipolar depression did not confirm this first study (Calabrese et al. in Press). No significant differences were found between groups treated with lamotrigine or placebo over an 8–10-week study period on primary endpoints. Table 103–9 briefly summarizes the results from the five lamotrigine monotherapy trials for acute bipolar depression. A high placebo response rate in these four studies may explain the failure of lamotrigine to separate from placebo, although it would appear that given the large numbers of subjects studied, robust antidepressant effects with lamotrigine as a monotherapy for acute bipolar depression should not be expected for the majority of patients. Other reports point towards a more adjunctive antidepressant role for lamotrigine in acute depressive disorders, including treatment refractory cases (Nierenberg et al. 2006).

**Table 103–9 Results from Five Placebo-Controlled Lamotrigine Monotherapy Trials for Acute Bipolar Depression**

| | Sample Size/ Study Duration in Weeks | Response Rate* with Lamotrigine (%) | Placebo Response Rate* (%) |
|---|---|---|---|
| Study 1 (Calabrese et al. 1999) | *N* = 195/7 | 54.0 | 29.0 |
| Study 2 | *N* = 206/10 | 50.0 | 49.0 |
| Study 3 | *N* = 257/8 | 46.0 | 39.3 |
| Study 4 | *N* = 221/8 | 45.5 | 40.0 |
| Study 5 | *N* = 259/8 | 54.1 | 45.7 |

*Based on 50% reduction in Montgomery Asberg Depression Rating Scale scores.

## Lithium for Acute Bipolar Depression

Lithium continues to hold position as a first-line treatment for acute bipolar depression, either as monotherapy or in combination with an antidepressant, in many practice guidelines despite very limited evidence to support it in this phase of bipolar disorder. There have only been eight small placebo controlled trials comprising a total of 116 bipolar patients and none have been completed since 1978. All employed crossover designs with seven of eight trials reporting lithium superior to placebo with moderate to marked antidepressant response in 79% of bipolar patients. A 1991 meta-analysis by Souza and Goodwin confirmed efficacy of lithium in the acute treatment of depression of unipolar variety (Souza and Goodwin 1991).

Although not well studied, most recommendations for the use of lithium to acutely manage depression associated with bipolar disorder are to dose to a minimum serum lithium level of 0.8 mEq/L. There is scant evidence available by which to compare the efficacy of lithium relative to standard antidepressants. In a double-blind, placebo-controlled study of bipolar depressed patients on lithium, the addition of either paroxetine or imipramine was not effective in alleviating depressive symptoms in patients with serum lithium levels greater than 0.8 mEq/L (Nemeroff et al. 2001). However, this post hoc analysis result likely minimizes the antidepressant efficacy of lithium since this study enrolled subjects who had already demonstrated nonresponse to lithium prior to intake and subsequent addition of an antidepressant.

## Summary: Mood Stabilizers for Acute Bipolar Depression

Bipolar depression remains an area of unmet need in terms of therapeutics. As we have reviewed here, compared to acute mania there is relatively limited data to provide a strong evidence base to treat bipolar depression with the exception of OFC and quetiapine. Table 103–10 summarizes the positive studies of acute treatment for bipolar depression based on evidence from large randomized, double-blind, placebo-controlled studies (Sachs 2007). This table includes the one positive trial for lamotrigine. OFC and quetiapine have demonstrated efficacy with NNT's ranging from 3.9–7.4, comparable to effective treatments for mania. As noted already here, although lamotrigine was able to demonstrate efficacy for acute bipolar depression in one trial (NNT 4.5–8.3), these results have not been replicated.

**Table 103–10 Positive Studies* of Treatment for Acute Bipolar Depression**

| Investigators and Sample Size | Placebo Response (%) | Active Treatment Response (mg) | NNT† |
|---|---|---|---|
| Calabrese et al. 1999 | 29 | Lamotrigine:50<br>Lamotrigine: 200 | 8.3<br>4.5 |
| *N* = 195 | | | |
| Tohen et al. 2003 | 30.4 | Olanzapine<br>Olanzapine–fluoxetine | 11.6<br>3.9 |
| *N* = 833 | | | |
| Calabrese et al. 1999 | 36.1 | Quetiapine: 300<br>Quetiapine: 600 | 4.5<br>4.7 |
| *N* = 542 | | | |
| Thase et al. 2006 | 44.7 | Quetiapine: 300<br>Quetiapine: 600 | 6.5<br>7.4 |
| *N* = 509 | | | |

*Category A evidence derived from randomized, double-blind, placebo-controlled studies with adequate sample size.

†NNT = 1 ÷ (Active response rate - Placebo response rate) and NNT provides an estimate of the number of additional patients needed to treat in order to produce one additional positive response beyond what would be produced by placebo.

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Reports of other pharmacological agents not known to be mood stabilizers but able to treat bipolar depression are

emerging, most recently the eugeroic stimulant modafinil (see sidebar or shaded paragraphs below) (Frye 2005). These and other novel compounds will require further investigation in all phases of bipolar disorder management to explore their potential inclusion as mood stabilizers.

**The Use of Modafinil for Bipolar Depression**

Modafinil, a stimulant medication in the eugeroic class, is most commonly used to treat narcolepsy. This wakefulness-promoting agent has less abuse potential than other psychostimulants and has been studied in a placebo-controlled trial for acute bipolar depression (Frye 2005).

Patients with bipolar I or II disorder were eligible for inclusion into this study if experiencing an active depression of at least mild severity based on Clinical Global Impression score or an Inventory of Depressive Symptomatology – Clinician Rating 30-item (IDS-C30, score >16) and having an inadequate response to therapeutic dose or blood level of a mood stabilizer, with or without an antidepressant. A total of 85 patients were enrolled and randomized in double-blind fashion to receive either adjunctive modafinil or adjunctive placebo. Modafinil was dosed at 100 mg/day for the first week of the study and then increased to 200 mg/day for the remaining 5 weeks.

Significantly greater improvement in depressive symptoms on the IDS-C30 was observed in the group receiving adjunctive modafinil compared with placebo ($P < 0.05$). Response rates were also significantly better with modafinil than with placebo (44% versus 22%, respectively). The results suggest that modafinil may help address acute depressive symptomatology in patients with bipolar disorder who have not adequately responded to traditional mood stabilizer alone or in combination with standard antidepressant medication.

## Mood Stabilizers for Maintenance Treatment of Bipolar Disorder

### General Considerations

Prevention of acute bipolar episodes through effective maintenance treatment is critical in order to improve the poor long-term outcomes that exist for individuals with bipolar disorder. Mood stabilizers have emerged as the cornerstone of prophylactic treatment in bipolar disorder, with lithium being the first known effective agent, supported by first-generation maintenance studies conducted and published during the 1960s and 1970s.

The need for alternatives to lithium for maintenance treatment of bipolar disorder is clear since not all patients respond to and/or tolerate it. AEDs and atypical antipsychotics have been studied and offer alternatives to lithium for long-term treatment of bipolar disorder.

Prevention of acute bipolar manic episodes through maintenance treatment is critical in order to minimize the deleterious and far-reaching consequences associated with mania. There remains significant debate as to the most appropriate treatments for prevention of future manic episodes. The most common practice in the Unites States is the continuation of the medication(s) that resolved an acute manic episode. More commonly in Europe, acute manic episodes are treated with typical or atypical antipsychotic medication that is later discontinued and replaced with lithium or another mood stabilizer choice for maintenance. Despite these differences, most experts agree that some form of maintenance pharmacotherapy should be prescribed following acute manic episodes or other frequently recurrent and disruptive states such as hypomania.

Given its highly recurrent nature and propensity for illness relapses and recurrences to be depressive, the ability to prevent depression could have a profound impact on ameliorating the burden of bipolar disorder. The 2003 FDA approval of lamotrigine for the prevention of mood episodes associated with bipolar disorder, with specific mention of preferential prophylaxis of depressive episodes, was a milestone event in the therapeutics of bipolar disorder. The approved availability of a treatment option other than lithium for this phase of preventative therapy is critical given the large unmet need in the treatment of bipolar depression and the relatively high rate of depressive relapse despite lithium maintenance.

Of concern in the management of this depressive risk is the potential for any medication prescribed to precipitate a manic switch or to destabilize the course of bipolar disorder. Significant debate exists over the long-term use of antidepressants in bipolar disorder, where controlled data is lacking to support efficacy but there are data to suggest an unacceptably high rate of manic relapse during long-term follow-up of patients treated with antidepressants for maintenance (Prien et al. 1984).

Pertinent to our earlier discussion of mood stabilizer definitions and limitations is the recognition that the available medications appear to have some differential spectra of efficacy in their prevention of mania versus depression. It should be noted that the studies that established efficacy for the medications discussed below all included randomly assigned subjects who had experienced remission from an acute episode during treatment with the study medication before randomization. This methodological issue means that the evidence supports the use of these maintenance medications only when they are initiated as part of a successful acute treatment regimen. Switching to or starting maintenance therapy after an acute episode is resolved is not supported by these data.

### Lithium

In a review of maintenance therapies it was noted that early studies consistently reported lithium to be more effective than placebo for bipolar prophylaxis (Muzina and Calabrese 2005). Examination of eight early controlled bipolar I prophylaxis studies that allowed for cumulative analyses of relapse rates supports the superiority of lithium over placebo for maintenance treatment as 31% of lithium-treated patients experienced a relapse during a 5–24 month period of maintenance compared to 76% of placebo-treated patients. Placebo-treated patients had an almost threefold increased rate of manic relapses compared to lithium maintained patients (59% placebo vs. 22% lithium). The

combined data from these early controlled studies demonstrate a twofold reduction in depressive relapses in lithium treated patients compared to those on placebo (16% lithium vs. 33% placebo).

A larger and more heterogeneous analysis of 28 studies of various designs demonstrated similar positive results for lithium prophylaxis (Baldessarini et al. 2002). Yielding 2,985 different subjects, their analyses posited an overall crude ratio of 3.2-fold lower recurrence risk with lithium. Lithium-treated patients were less likely to be hospitalized, experienced fewer days ill per year, and when recurrences occurred their average duration was decreased. Long-term lithium treatment was found to reduce morbidity in patients with bipolar I or II disorder. Frequency of episodes decreased by 47% in bipolar I disorder and by 65% in bipolar II disorder. Depression was also prevented by lithium, more successfully for bipolar II patients who experienced 54% fewer episodes of depression per year than the 35% reduction seen in bipolar I disorder.

However, many of these early studies pre-1975 used discontinuation study designs that involved patients with a known positive response to lithium being abruptly discontinued from lithium if randomly assigned to the nontreatment or placebo group of the maintenance phase of the study. This design may have inflated the preventative effect of lithium due to the known effect of rapid lithium discontinuation, which can increase early relapse into depression or mania. Additionally, early lithium studies may have lacked specification of diagnostic criteria, not differentiated unipolar from bipolar depressed patients, and reported response rates as a percentage of only those patients completing the study while failing to report reasons for premature discontinuations. In 1999, Davis et al. (1999) analyzed data from 19 blinded, randomized, controlled trials of prophylaxis in 865 patients and controlled for the possible effects of abrupt lithium withdrawal inflating efficacy as mentioned above. They reported lithium significantly reduced relapse by 50% in bipolar disorder.

A study conducted by Bowden et al. (2000) provided randomized, blinded and placebo-controlled data that supported both divalproex and lithium as effective maintenance therapies in patients with bipolar I disorder. This study was the original maintenance study to employ modern methods, including enrollment of patients during an index manic phase and tapering lithium over two weeks instead of rapid discontinuation. Although the primary outcome measures in this study did not discriminate between the two "active" compounds and placebo and neither active treatment separated from placebo in terms of the primary outcome measure there were secondary measures of note. Lithium extended the time until relapse by 55% compared to placebo. However, divalproex was more successful than lithium in extending the duration of prophylaxis as well as preventing depressive symptoms.

The efficacy of lithium as maintenance therapy in bipolar I patients over an 18-month period has also been investigated using modern methods as an active arm in the lamotrigine maintenance trials (Bowden et al. 2003, Calabrese et al. 2003). In a pooled analysis of the data from these two lamotrigine bipolar trials, lithium was more effective than placebo in preventing relapse in patients with bipolar disorder, with significant efficacy against manic relapse but with a less substantial effect against depressive relapse (Goodwin et al. 2004).

Standard dosing to achieve blood levels of lithium between 0.8 and 1.0 mmol/L or higher is generally recommended over "low" dosing to levels between 0.4 and 0.6 mmol per liter. Maintenance at lithium levels in this low range has been associated with a 2.6 greater risk of relapse compared to standard dosing into the higher range (Keller et al. 1992). Furthermore, patients maintained in the higher range are less likely to experience subsyndromal episodes. Lithium side effects are more frequent when standard dosing is employed. However, these results may have been affected by study design that called for an abrupt reduction of lithium by 50% for those patients randomized into the "low" dosing group who had lithium on board in the standard range. These patients accounted for nearly all of the relapses in the "low" dose group.

## AEDs for Maintenance Therapy

### Lamotrigine

The Bowden and Calabrese 18-month maintenance trials noted above provide further support for the use of lamotrigine as a mood stabilizer, perhaps complementary to the effects of lithium (Bowden et al. 2003, Calabrese et al. 2003). Their results led to approval by the US FDA in June 2003 as a maintenance treatment for bipolar I disorder.

In recently manic or hypomanic patients with bipolar I disorder, both lithium and lamotrigine were superior to placebo at delaying the time until additional pharmacotherapy was required for treatment of a mood episode. Lamotrigine demonstrated significantly greater efficacy for prolonging time to a depressive episode compared with lithium. In recently depressed patients with bipolar I disorder, both lamotrigine and lithium were significantly superior to placebo at delaying time to intervention for any mood episode. Lamotrigine and lithium were superior to placebo on the analysis of overall survival in the study, while lamotrigine, but not lithium, was superior to placebo in terms of delaying time to intervention for depressive episodes. These studies established that lamotrigine was significantly more effective than placebo in preventing relapse in patients with bipolar disorder while demonstrating primary effectiveness against depression.

These complementary studies enrolled patients in a double-blind phase of maintenance therapy after a recent depressed, hypomanic, or manic episode remitted with open-label stabilization during which lamotrigine was initiated as adjunctive or monotherapy and other psychotropics were discontinued. In both studies, 50% of patients achieved stabilization criteria allowing for progression into double-blinded maintenance therapy with lamotrigine (50−400 mg/day), lithium (0.8−1.1 mEq/L), or placebo. The primary efficacy endpoint used was time to intervention for any mood episode.

In both of these studies, lamotrigine and lithium demonstrated effective prophylaxis against any emerging mood episode compared with placebo. There were statistically fewer relapsing mood episodes and longer median survival in lamotrigine and lithium treated patients compared with placebo. Median survival before intervention for any mood episode for lamotrigine-treated patients ranged from

118−256 days, significantly better than placebo (only 85−93 days). Lithium also beat placebo with a median survival of 170−292 days. However, there were important differences in the spectra of maintenance efficacy.

In both studies, lithium, but not lamotrigine was superior to placebo at delaying the time to intervention for a manic or hypomanic episode. In total for both studies 123 hypomanic/manic events emerged during maintenance, with 25% of placebo treated patients experiencing a hypomanic, manic, or mixed episode (47 of 188); 21% of the lamotrigine group relapsed (58 of 273), but only 11% of patients in the lithium-treatment arm had breakthrough mania or hypomania (18 of 164). Lithium was clearly more effective than placebo and lamotrigine in preventing manic and hypomanic relapse in recently symptomatic bipolar I patients.

In contrast, lamotrigine appears to be more effective than lithium in the prevention of depressive relapse in bipolar I patients. Lamotrigine but not lithium, was significantly better than placebo at prolonging time to intervention for a depressive mood episode in both studies. There were 209 depressive relapses in the patients observed in the two studies, with a higher rate of relapse in the placebo (68 of 188, or 36%) and lithium treatment groups (56 of 164, or 34%); lamotrigine was better at preventing recurrence of depression with a 31% rate of depressive relapse and a longer median survival before treatment of depression was necessary. The difference was particularly evident in the treatment of recently manic or hypomanic patients in whom only 14% of those receiving lamotrigine (8 of 58) needed intervention for emergent depression compared with 23% of patients receiving lithium (10 of 44) and 30% receiving placebo (21 of 69).

### *Clinical Application of Lamotrigine*

No pretreatment laboratories are required before initiating lamotrigine, although routine physical examination, basic baseline chemistries, and pregnancy testing are advisable.

A history of hypersensitivity to lamotrigine is the only contraindication to use. The risk of rash must be discussed before initiating therapy with lamotrigine and may be better informed by data from multicenter trials of lamotrigine in mood disorders. Calabrese et al. (2002) reviewed data on 3,153 patients treated with lamotrigine in mood disorder trials and compared rash rates to the 1,056 placebo-treated patients and found rates of benign rash were 8.3% and 6.4% in lamotrigine- and placebo-treated patients, respectively. Rates of serious rash were 0% with lamotrigine and 0.1% with placebo. In the open-label setting, the overall rate of rash for lamotrigine was 13.1% and of serious rash, 0.1%. One mild case of Stevens-Johnson syndrome was reported in a patient treated with lamotrigine and there were no cases of toxic epidermal necrolysis. Any lamotrigine-treated patient developing any rash that cannot readily be explained by a known other cause, i.e. contact dermatitis, should immediately discontinue lamotrigine and notify their treating physician prior to resuming therapy. In unclear or difficult cases, dermatologic consultation should be obtained before restarting or rechallenging with lamotrigine.

Following a careful and gradual dosage titration schedule reduces the risk of rash. Lamotrigine should be initiated at 25 mg/day with the first dosage increase to 50 mg/day 2 weeks later. Lamotrigine may be increased to 100 mg/day in Week 5 and to 200 mg/day in Week 6. The presence of enzyme-inducing drugs, such as carbamazepine, requires doubling of the lamotrigine dose while concomitant administration with divalproex dictates a 50% reduction in lamotrigine dosing. Concomitant prescription of estrogen-containing oral contraceptives may lead to enzyme-induction and increased metabolism of lamotrigine, which may necessitate an increase in lamotrigine dose during the maintenance phase in some patients based on clinical circumstances.

The most common side effects observed with lamotrigine are dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, and vomiting. These side effects are typically mild and rarely lead to treatment discontinuation. Decreasing the dose or slowing the rate of dose escalation may alleviate these bothersome side effects.

## Divalproex/Valproate for Maintenance

This AED is commonly used as both antimanic and maintenance therapy for bipolar disorder although it does not carry labeled indication for maintenance in the US. Early studies suggested comparable efficacy with lithium for maintenance with better tolerability.

Bowden et al. (2000) conducted the first double-blind, randomized controlled maintenance study in bipolar I disorder which followed patients from an index manic episode through a subsequent 52-week maintenance phase. Subjects who met recovery criteria after initial open-label antimanic treatments were randomized into the placebo-controlled, double-blind, parallel-group maintenance study and placed into divalproex, lithium, or placebo groups. Patients that were randomized off of their divalproex or lithium and onto the other agent or placebo had the drug gradually tapered off during the first 2 weeks of maintenance treatment. Study drugs were administered three times per day and dosed to serum trough concentrations of between 71 and 126 μ/g/mL for valproate and 0.8 to 1.2 mmol/L for lithium.

No significant difference was found in time to recurrence of any mood episode during maintenance therapy between these 3 groups. Specifically examining the time to either a manic episode or a depressive relapse for the three treatment groups favored divalproex compared to lithium on several secondary outcome measures, including less deterioration in depressive symptoms. Early termination for intolerance or noncompliance during the study also favored divalproex over lithium.

The Cochrane Database of Systematic Reviews reviewed the available evidence to clarify the justification of the increasing use of valproate, especially in the United States, for bipolar disorder prophylaxis (Macritchie et al. 2001). Of 19 trials detected by their search criteria, the above Bowden et al. 2000 study was the only one that met their inclusion criteria for a randomized, controlled trial comparing valproate with placebo or other mood stabilizers for specific use in maintenance therapy. This review concluded that there was little data available to robustly support valproate in the maintenance treatment of bipolar disorder.

In a comparator study of olanzapine versus divalproex over a 47-week period of initial acute treatment of mania or mixed state followed by maintenance treatment of 251 patients with bipolar disorder, the mean improvement in mania rating scale scores was significantly greater in the olanzapine-treated group (Tohen et al. 2003a). However,

there were no significant overall differences between the two treatments in the rates of symptomatic remission or subsequent relapse over the entire 47-week period, suggesting comparable maintenance efficacy for the two agents.

### Carbamazepine for Maintenance

A meta-analysis on mood stabilizers in the prevention of recurrent affective disorders that included 10 double-blind, randomized studies comparing carbamazepine to lithium found no significant difference in relapse rates over a 1–3 year maintenance period (55% versus 60%, respectively) (Davis et al. 1999). However, studies regarding maintenance with carbamazepine monotherapy have produced variable results and consensus based on available data and expert opinion is that carbamazepine is inferior to lithium in the maintenance treatment of bipolar disorder (Muzina et al. 2002). There is stronger evidence supporting its use in combination with other mood stabilizers for maintenance, particularly with lithium.

## Atypical Antipsychotics for Maintenance Therapy

At the time of this chapter's creation, only two atypical antipsychotics have published long-term maintenance studies of monotherapy that were of sufficient rigor to warrant regulatory approval for maintenance in the US—olanzapine and aripiprazole. Data regarding the use of the other atypical antipsychotics for maintenance therapy in bipolar disorder is pending.

It should be noted that no published long-term maintenance study of atypical antipsychotic agents has enrolled patients presenting recently depressed. The olanzapine and aripiprazole maintenance trials began by enrolling recently manic or mixed bipolar I patients into an initial stabilization phase followed by the randomized and blinded phase of the study with active monotherapy or placebo. This study design has important implications related to attempts to investigate full mood stabilizing efficacies of these and other medications since it has been demonstrated that the polarity of the index episode tends to predict the polarity of relapse into a subsequent episode in a ratio of about 2:1 to 3:1 (Calabrese et al. 2004). The impact of this "like breeds like" phenomenon on maintenance studies is that in order to fully assess prophylactic efficacy for any agent these trials must include and stratify for both recently depressed and recently manic episodes. Interpreting the results of the atypical antipsychotic maintenance studies described below should take this issue into consideration when attempting to best understand the maintenance mood stabilizing effects of these agents.

### Olanzapine

An 18-month placebo-controlled study evaluating the preventive efficacy of olanzapine added to either lithium or valproate found that among patients who experienced syndromic remission from an acute manic episode following the addition of olanzapine to lithium or valproate, those remaining on the combination therapy sustained symptomatic remission longer than those on lithium or valproate monotherapy (Tohen et al. 2004). There was no reported difference in duration of syndromic remission. In a head-to-head comparison olanzapine monotherapy was significantly more effective than lithium in preventing manic and mixed episode relapse/recurrence in patients acutely stabilized with olanzapine and lithium cotreatment (Tohen et al. 2005). Olanzapine and lithium were comparable in preventing relapse or recurrence of depression.

In the first placebo-controlled, double-blind study to examine the efficacy of olanzapine monotherapy in relapse prevention in bipolar I disorder the median time to symptomatic relapse into any mood episode after open-label stabilization of acute mania with olanzapine was significantly longer among patients continuing to receive olanzapine than in placebo-treated patients (174 days versus 22 days, respectively). This study suggests that olanzapine prevents bipolar I relapse into any mood state for significantly longer periods of time than placebo. Olanzapine monotherapy is FDA approved as a maintenance therapy in bipolar I disorder.

### Aripiprazole

An international randomized, double-blind, parallel-group, placebo-controlled study of aripiprazole monotherapy in patients with recent bipolar I mania or mixed episode provided 26 weeks' of maintenance data supporting the mood stabilizing effect of this atypical antipsychotic (Keck et al. 2006a). Recently manic or mixed bipolar patients who had been stabilized during an open-label phase with aripiprazole 15 or 30 mg/day over 6–18 weeks were randomized to receive either aripiprazole monotherapy or placebo for the 26-week, double-blind maintenance phase. Aripiprazole was superior to placebo in delaying the time to relapse, although this effect was found for manic prophylaxis and not for depression. Aripiprazole-treated patients had significantly fewer relapses (25%) than placebo patients during this 26-week study (25% versus 43%, respectively).

This 26-week aripiprazole relapse prevention study was designed *a priori* with a prospective, 74-week, double-blind, placebo-controlled extension phase (Keck et al. 2006b). Patients who completed the initial 26-week stabilization continued on into the 74-week extension phase on double-blinded aripiprazole or placebo. The results of this extended maintenance study of aripiprazole monotherapy demonstrated that time to relapse into any mood episode was significantly longer for patients who received active treatment than placebo. Only 33% of aripiprazole-treated patients experienced any relapse by Week 100 of the study, whereas 51% of patients in the placebo group relapsed by then. Notably, when looking at phase-specific relapse aripiprazole was able to demonstrate prophylactic efficacy against mania but not depression. Aripiprazole was well-tolerated over this extended period with on average less than 1 lb (0.4 kg) of weight gain.

### Other Atypical Antipsychotics

Limited evidence from case reports or small open-label studies exists to support the use of risperidone, quetiapine, or ziprasidone as maintenance therapy in bipolar disorder. Based on the known acute antimanic effects of these atypical antipsychotics and the results from the olanzapine and aripiprazole maintenance studies, it might be assumed that these agents will have similar prophylactic profiles with a tendency for better efficacy against manic relapse than depressive relapse. The antidepressant efficacy of quetiapine acutely plus its antimanic properties raises the possibility

**Table 103–11 Maintenance Treatments for Bipolar Disorder**

| | Maintenance Dose (mg/day) | Advantages | Disadvantages | Monitoring Needs |
|---|---|---|---|---|
| Aripiprazole | 15–30 | Less sedating for many patients, ease of dosing; little/no weight gain; potentially less risk for metabolic side effects | Too activating for some patients, insomnia; restlessness/akathisia; metabolic risks associated with atypical antipsychotics; less effective against depression | Weight<br>Fasting glucose<br>Fasting lipids<br>Baseline and routinely during course of treatment |
| Lamotrigine | 200 | Generally well tolerated; little/no weight gain; more robust against depressive than manic relapses/recurrences | Slow titration required to minimize rash risk; 1:6,000 risk of Stevens–Johnson Syndrome; drug interactions; less effective against mania | Cautions regarding rash, observe for skin changes during initiation and dose escalation phases |
| Lithium | 900–1200 | Established history; over 20 randomized controlled trials of prophylaxis; potential anti-suicide effects | Gastrointestinal irritation, tremor, cognitive dulling; negative effects on thyroid and kidney function; less effective against depression | Lithium blood levels, thyroid function tests, serum creatinine |
| Olanzapine | 5–20 | Potent antimanic agent, ease of dosing, improved sleep | Propensity for weight gain, sedation; metabolic risks associated with atypical antipsychotics; less effective against depression than mania | Weight<br>Fasting glucose<br>Fasting lipids<br>Baseline and routinely during course of treatment |
| Divalproex/ Valproate* | Not established (est 20–25 mg/kg/day) | Established antimanic history, duration of clinical experience | Lack of data in maintenance phase; drug interactions; weight gain; hematological effects; rash | Weight<br>Blood levels<br>Blood counts |

*Not US-FDA approved for maintenance treatment of bipolar disorder.

that it or one of these atypical antipsychotics may eventually demonstrate mood stabilization that is closer to the elusive "ideal" definition of a mood stabilizer.

## Summary: Mood Stabilizers for Maintenance

Clinical management of maintenance needs in bipolar disorder is benefited by a growing number of treatment options, each with its own particular profile of advantages and disadvantages (see Table 103–11). Five agents (lithium, divalproex, lamotrigine, olanzapine, and aripiprazole) have been able to demonstrate efficacy in maintenance treatment of bipolar disorder based on evidence from large randomized, double-blind, placebo-controlled studies, although divalproex did so only on secondary outcome measures and lithium was able to effectively prophylax against manic recurrence only. Table 103–12 provides a summary of these results, where the NNT for the effective maintenance mood stabilizers ranged from 3.0−6.7.

**Table 103–12 Positive Studies* of Maintenance Treatment for Bipolar Disorder**

| Investigators and Sample Size | Recurrence Rates | | NNT† |
|---|---|---|---|
| | Placebo (%) | Active Treatment (%) | |
| Bowden et al. 2000†† | 39 | Valproate: 24<br>Lithium: 33 | 6.7<br>16.7 |
| N = 372 | | | |
| Goodwin et al. 2004 | 78 | Lamotrigine 63 | 6.7 |
| N = 638 | | | |
| Tohen et al. 2006 | 80 | Olanzapine: 47 | 3.0 |
| N = 361 | | | |
| Keck et al. 2006 | 43 | Aripiprazole: 25 | 5.6 |
| N = 161 | | | |

*Category A evidence derived from randomized, double-blind, placebo-controlled studies with adequate sample size.

†NNT = 1 ÷ (Active response rate − Placebo response rate) and NNT provides an estimate of the number of additional patients needed to treat in order to produce one additional positive response beyond what would be produced by placebo.

††Valproate positive on secondary outcomes only.

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## Mood Stabilizers for Rapid Cycling Bipolar Disorder (RCBD)

The demanding treatment issues posed by RCBD have been identified for decades now, dating to early reports that patients did not respond adequately when treated with lithium (Dunner and Fieve 1974, Kukopulos et al. 1980). Frequently recurring and refractory depressive episodes appear to be a "hallmark" of RCBD and may be exacerbated (cycle induction or acceleration) by antidepressant use (Calabrese et al. 2001a).

It was initially suggested that divalproex was more effective in this patient population, particularly for the prophylaxis of hypomanic or manic phases of the illness (Calabrese and Delucchi 1990). However, a more recent double-blind comparator study did not find divalproex superior to lithium in the long-term management of RCBD (Calabrese et al. 2005b). In this 20-month study, recently hypomanic/manic patients who had experienced a persistent bimodal response to combined treatment with lithium and divalproex were randomly assigned to either lithium or divalproex monotherapy. It should be noted that of the 254 patients enrolled in the open-label acute stabilization phase, only 60 experienced a sufficient persistent bimodal response and subsequent randomization into the double-blind

maintenance phase. The preponderance of nonresponse to combined lithium and divalproex was refractory depression versus mania (3:1). Of those randomly assigned to double-blind maintenance monotherapy, more than half relapsed with no significant differences in time to relapse between lithium and divalproex treatment. Depressive relapse was more common than hypomanic/manic relapse. Lithium-treated patients were more likely to experience side effects leading to premature discontinuation than those receiving divalproex (4:1). This study confirms earlier observations suggesting highly recurrent refractory depression as the hallmark of RCBD.

Lamotrigine monotherapy has been reported to be effective for some patients with RCBD based on data from a study using open-label lamotrigine added to ongoing pharmacotherapy followed by double-blind, placebo controlled maintenance monotherapy in responders after concomitant psychotropics were tapered off (Calabrese et al. 2000). Forty-one percent of lamotrigine patients versus 26% of placebo patients were stable without relapse over the 6 months of study.

Atypical antipsychotics may provide additional utility in the treatment of RCBD although limitations such as study design and sample size may hamper generalizability of the available data. Clozapine has demonstrated prophylactic efficacy in RCBD (Calabrese et al. 1991) and risperidone also has some data to suggest efficacy for rapid cyclers (Vieta et al. 1998, Coconcea et al. 2002). Similarly, there have been reports of efficacy using olanzapine for RCBD when acutely manic as either adjunctive therapy (Demopulos et al. 2000) or as monotherapy (Sanger et al. 2003) or for dysphoric mania (Gonzalez-Pinto et al. 2002). More recently, the atypical antipsychotics quetiapine and aripiprazole have also been studied in patients with RCBD with favorable results.

Quetiapine monotherapy has also been associated with benefits for patients with RCBD. In a recent post-hoc analysis of the acute bipolar depression quetiapine monotherapy trials, quetiapine was found to be clinically effective and well tolerated in the short-term treatment of depressive episodes in patients with bipolar I or II disorder that have a rapid cycling course (Vieta et al. 2007). This sub-analysis included 108 subjects with RCBD in the acutely depressed phase randomized to double-blinded, placebo-controlled treatment over 8 weeks. Effect sizes for quetiapine treatment were > 1.0 and were similar in bipolar I and II disorder.

Although small in sample size, data regarding aripiprazole use in patients with RCBD from the aripiprazole maintenance study (totalling 100 weeks) has been analyzed (Muzina et al. 2007). Subjects with bipolar I disorder received aripiprazole or placebo as part of this double-blinded maintenance study, with 28 of the 161 patients who met stabilization criteria for 6 consecutive weeks diagnosed with rapid cycling. The time to relapse was significantly longer with aripiprazole treatment compared with placebo at 26 weeks and 100 weeks, with an overall 81% reduction of relapse risk associated with aripiprazole maintenance in RCBD.

Management of RCBD requires careful investigation and elimination of any potential mood-destabilizing forces as well as consideration of the best regimen mood stabilizer(s) pharmacotherapy. Traditional antidepressants, often avoided or used with caution in bipolar disorder, should be viewed even more suspiciously in RCBD given the lack of supportive evidence for their use and concerns for cycle acceleration. Lithium, divalproex, lamotrigine, and the atypical antipsychotics are the current mainstays of treatment although given the tendency of RCBD to be refractory to treatment, combination strategies are most often necessary. Thyroid hormone augmentation may also be of great benefit for some patients with RCBD and should be considered particularly when refractoriness to mood stabilizers is observed (Post et al. 1997, Kilzieh and Akiskal 1999, Calabrese et al. 2001b).

## Redefining Mood Stabilizers

In their provocative paper entitled "What is a mood stabilizer?" Goodwin and Malhi (2006) effectively dissect the limitations of various definitions and the inherent weakness of "terminologic exactitude" in pharmacology. Despite the intrinsic flaws of the term 'mood stabilizer' the discussions surrounding it have prompted clinicians to attend to both poles of the illness and in all phases of treatment. They conclude that by using the strictest definition proposed by Bauer and Mitchner (2004)—a mood stabilizer should treat both poles of bipolar disorder acutely and prevent recurrence—that only lithium just barely qualifies. They go on to suggest that the term should be reserved only for agents that have been compared to lithium and have performed adequately in such a comparison. This suggestion has much merit, although as we have covered here, lithium itself does not clearly rise to these high criteria given the limited evidence for its efficacy in treating bipolar depression acutely and preventing depressive recurrence.

We propose reserving the term mood stabilizer for use in general discussions about the search for an ideal agent that is effective in all poles of illness and as such recognize that no complete mood stabilizer has been discovered. Perhaps such an agent may become reality once we uncover the underlying pathophysiology of bipolar disorder and begin to develop drugs with targeted molecular actions that restore normal mood stabilizing controls.

In clinical practice we must acknowledge that current psychotropic agents are partial mood stabilizers at best. A very minimal requirement should be the lack of evidence for causing switches to mania or depression or cycle acceleration. Lack of mood *destabilizing* effects plus efficacy in at least one area of bipolar disorder management should allow for use of the term "partial mood stabilizer." Partial mood stabilizers may be further categorized based on level of evidence for specific directional efficacy, either unidirectional, bidirectional, intermediate, or mixed. Table 103–13 seeks to define these proposed terms and to include the reviewed putative mood stabilizers into these new categories.

## Conclusion

The evidence base for and theoretical concepts of pharmacological treatments of bipolar disorder have undergone remarkable growth and evolution over the past decade. Increasing study of medications in all poles of the disorder and in maintenance has challenged the common usage of the term "mood stabilizer." Simply defining this type of medication has not been easy and continues to spark debate. The search for a perfect and complete mood stabilizer continues, while in clinical practice we must employ evidence-based

**Table 103–13 Redefining Mood Stabilizers: Partial Mood Stabilizers***

| Unidirectional PMS† | Bidirectional PMS†† | Intermediate PMS§ | Mixed PMS¶ |
|---|---|---|---|
| Ziprasidone | Quetiapine | Lamotrigine | Lithium |
| Risperidone | | | Olanzapine |
| Carbamazepine | | | Aripiprazole |
| Olanzapine–fluoxetine combination | | | Divalproex /valproate |

*Any pharmacologic agent with evidence of efficacy in at least one area of bipolar disorder management (acute depression, acute hypomania, acute mania/mixed, or maintenance) and no evidence suggesting that it is associated with increased risk of mood switching or cycle acceleration.

†Any drug that meets the definition of PMS, with its primary therapeutic activity being one-directional—either effectively treating depression or hypomania/mania/mixed episodes.

††Any drug that meets the definition of PMS, with its primary therapeutic activity being two-directional—both effectively treating depression and hypomania, mania, or mixed episodes. A bidirectional PMS has not demonstrated full maintenance efficacy.

§Any drug that meets the definition of PMS, with its primary therapeutic activity being maintenance efficacy. An intermediate PMS has no established acute efficacy.

¶Any drug that meets the definition of PMS and has unidirectional or bidirectional mood stabilizing properties and only partial maintenance efficacy. Alternatively, maintenance efficacy plus unidirectional efficacy.

strategies using partial mood stabilizers as well as other off-label, less well-studied drug therapies.

The management of mania has become simpler, if only due to having a wider variety of medication options—either in monotherapy or in combination—to employ in stabilizing mood from above the normal baseline. Bipolar depression remains a therapeutic challenge, although the emergence of better-studied and approved medications to stabilize mood from the depressive pole is encouraging. Maintenance therapy is a lifelong necessity in bipolar disorder and should be considered and reviewed at every encounter with the patient, during acute episodes as well as during periods of euthymia that might be threatened by recurrence or tolerability issues.

Beyond the scope of this chapter, nonpharmacological treatments should also be considered for their potential "mood stabilizing" properties. These treatments range from electroconvulsive therapy through cognitive-behavioral therapy and into family-based and other supportive psychotherapies. Individually tailoring a "mood stabilizer" treatment plan for each and every patient with bipolar disorder is a dynamic process and must include all of these considerations.

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CHAPTER

# 104 Anxiolytic Drugs

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## Introduction

There has been an exponential increase in the number of medications demonstrated to be effective for the treatment of anxiety and anxiety disorders (Table 104–1). This chapter will provide a brief review of the history and evolution of these treatment strategies, followed by descriptions of each class of medication. Then the efficacy and adverse effects data from clinical trials with different disorders will be presented so that the reader can compare and contrast the advantages and disadvantages of different classes of medications for the treatment of each anxiety disorder described in the *Diagnostics and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).

Beginning in the late 19th century, there was a progression from alcohol, bromides, and opiates to barbiturates developed in the early 20th century. Barbiturates were effective in decreasing anxiety, but they were addictive and lethal in overdose. There was continued advancement in the development of anxiolytics like meprobamate (effective but again addictive and lethal in overdose) and the antihistamine hydroxyzine, which was less effective than meprobamate and barbiturates and very sedating. The next major advance in anxiolytic therapy was the work pioneered by Klein and Fink (1962) demonstrating that some tricyclic antidepressants (TCAs) were useful in the treatment of panic disorder. This was rapidly followed by studies reporting that monoamine oxidase inhibitors (MAOIs) could be used to treat certain patients with anxiety disorders. However, the major advancement in the field of anxiolytics in the 1960s was the development and approval of benzodiazepines. These agents were much safer than the barbiturates and meprobamate, had a rapid onset of action (so patients felt better quickly), and had a broad spectrum of efficacy extending from situational anxiety to pathological anxiety disorders. Many different benzodiazepines, with different absorption times and half-lives, were developed and have been valuable not only for treating anxiety and anxiety disorders but for treating seizure disorders and alcohol withdrawal. Unfortunately, with wide scale usage some individuals did develop craving and dependence on benzodiazepines as well as significant problems with withdrawal when abruptly discontinued. The next major class of agents approved was the azopyrones, of which buspriorone is the most well known. This agent was found to be effective in generalized anxiety disorder but was not effective for the treatment of most other anxiety disorders or situational anxiety.

There was a cascade of anxiolytic research in the 1990s. The selective serotonin reuptake inhibitors (SSRIs) as a class were demonstrated to be efficacious treatments for most of the anxiety disorders described in the DSM-IV-TR. Although these agents have a delayed onset when contrasted with the benzodiazepines, they have a broader spectrum of action, no problems with dependence, and much less of a problem with withdrawal symptoms. The 1990s also saw the approval of venlafaxine as a treatment for generalized anxiety disorder. One of the most intriguing transitions in anxiolytic development has been the ongoing research investigating the use of anticonvulsant medications for the treatment of anxiety disorders.

## A General Approach to Using Medication with Anxious Patients

Patients may present physicians with many different concerns related to anxiety. However, one need that all patients who seek help for symptoms of anxiety have is the need for reassurance that they are not alone, that their physicians truly hear their concerns, and that their physicians will attempt to help them. One important step in building rapport and reassuring a patient is taking a complete history. This is not only essential for making an appropriate diagnostic formulation, but also demonstrates an interest in the patient's situation.

Formulating an appropriate differential diagnosis is critical to the success of any psychopharmacological

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**Table 104–1** The Efficacy of Psychotropic Medications for the Treatment of Anxiety Disorders

| | Generalized Anxiety Disorder | Social Anxiety Disorder | Panic Disorder | Posttraumatic Stress Disorder | Obsessive–Compulsive Disorder |
|---|---|---|---|---|---|
| Proven efficacy | SSRIs<br><br>Venlafaxine<br>TCAs<br>Trazodone<br>Benzodiazepines<br>Buspirone | SSRIs<br><br>MAOIs/ RIMAs<br>Benzodiazepines<br>Venlafaxine | SSRIs<br><br>Venlafaxine<br>Mirtazapine<br>MAOIs<br>TCAs<br>Benzodiazepines | SSRIs | SSRIs<br><br>Clomipramine |
| Some evidence | Nefazodone<br>Mirtazapine<br>Pregabalin<br>Risperidone<br>Olanzapine<br>Tiagabine<br>Topiramate<br>Lesopitron<br>Riluzole<br>Opipramol<br>Hydroxyzine | Mirtazapine<br>Bupropion<br>Clonazepam*<br>Nefazodone<br>Gabapentin<br>Pregabalin<br>Topiramate<br>Levetiracetam<br>Olanzapine | Nefazodone<br>Reboxetine<br>Pagoclone<br>Gabapentin Tiagabine<br>Valproic acid<br>Olanzapine*<br>Levetiracetam | Mirtazapine<br>Venlafaxine<br>Reboxetine<br>MAOIs<br>TCAs<br>Nefazodone<br>Trazadone<br>Tiagabine<br>Topiramate<br>Fluphenazine<br>Olanzapine<br>Risperidone<br>Quentiapine<br>Propanolol<br>Lamotrigine | MAOIs<br>Venlafaxine<br>Topiramate<br>Pindolol*<br>Amisulpiride<br>Olanzapine*<br>Quetiapine<br>Risperidone* |
| Not effective | | TCAs<br>Buspirone<br>Pindolol<br>Valproic acid | Bupropion<br>Trazodone | | Bupropion<br>Mirtazapine TCAs<br>Trazodone<br>Buspirone<br>Haloperidol<br>Nefazodone |
| No data | MAOIs<br>Bupropion | Trazodone | | | |

*Listed medication augmented with SSRI.

intervention. The diagnosis dictates the class of medication to be used and the length of pharmacotherapy. Potential differential diagnoses for patients with anxiety disorders include the following: adjustment disorders secondary to life stressors, anxiety disorders secondary to a medical condition, symptoms of anxiety secondary to a medical condition, anxiety secondary to alcohol or substance abuse or dependence, generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobia, posttraumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD). Since patients with either symptoms of anxiety or an anxiety disorder are in distress and usually feel vulnerable, sharing the diagnostic formulation with the patient is an important intervention that facilitates the patient's commitment to the treatment plan. Formulating this therapeutic alliance is crucial since anxious patients may be reticent to take medication. When they do take medications, they commonly ruminate about medication side effects. As discussed in other chapters in this text, patients with anxiety disorders or anxiety as a symptom are more likely to have somatic preoccupations and heightened somatic sensitivity. A collaborative approach where physicians and patients form a "team" to monitor both the potential benefits and the liabilities of any medication intervention frequently enfranchises the patient and enhances adherence. An important rule in general is "to start low and go slow" when initiating pharmacological treatment for patients with anxiety disorders. Interestingly, although treating patients with anxiety disorders frequently requires a more gradual initial titration schedule, patients usually attain maintenance dosages of antidepressant medications that are greater than the dosage commonly used to treat major depressive disorder.

## Antidepressant Medication

Since the reports by Klein and Fink in the early 1960s, medications initially identified because of their antidepressant properties have been succ essful at treating anxiety disorders. The basic action of the majority of the antidepressants is to increase the availability of neurotransmitters in the synaptic cleft. As is demonstrated in Table 104–2, antidepressants work by a variety of mechanisms of action. The most widely used antidepressants that also have anxiolytic properties are the SSRIs. These agents have the broadest spectrum of activity that spans the entire spectrum of anxiety disorders detailed in the DSM-IV-TR. Although all of the SSRIs have a slightly different site of action, their basic mechanism of action is the inhibition of the serotonin reuptake pump. This facilitates an increase in levels of serotonin throughout the body. Table 104–3 presents the inhibition constants for the SSRIs, some TCAs, and several other antidepressant agents.

**Table 104–2** The Mechanisms of Action of Common Antidepressant Medication

| |
|---|
| Blockade of 5-HT uptake |
| Fluoxetine |
| Sertraline |
| Paroxetine |
| Citalopram |
| Escitalopram |
| Blockade of NE uptake |
| Desipramine |
| Nortriptyline |
| Bupropion (and modest dopamine effects) |
| Reboxetine |
| Blockade of 5-HT and NE uptake |
| Clomipramine |
| Venlafaxine (at high doses) |
| 5-$HT_2$ antagonism (and modest transient 5-HT uptake blockade) |
| Nefazodone |
| $\alpha_2$ antagonism (releases 5-HT and NE; and 5-$HT_2$ and 5-$HT_3$ antagonism) |
| Mirtazapine |

As illustrated in Table 104–4, a variety of serotonin receptor subtypes have been implicated in the modulation of anxiety disorders, depressive disorders, migraine, pain, and neuropsychiatric disorders. The stimulation of those receptors also accounts for the commonly observed side effects of SSRIs (Table 104–5). The pharmacokinetic properties of the SSRIs are presented in Table 104–6.

The mechanism of action of the TCAs also involves the inhibition of reuptake sites thereby increasing the amount of the neurotransmitter present throughout the body and in the synaptic cleft. The disadvantage of the TCAs includes their side effect profile and their potential lethality in overdose (Table 104–5). Other antidepressants have a variety of different mechanisms of action. The MAOIs inhibit the enzyme monoamine oxidase, a crucial intracellular enzyme for the catabolism of serotonin, norepinephrine, dopamine, and phenethylamine. The first-generation MAOIs irreversibly bind to monoamine oxidase. After cessation of MAOI treatment, it takes approximately 2 weeks for restoration of monoamine oxidase functioning through the generation of new enzyme. The other major mechanisms of action for antidepressants that also have anxiolytic effects include the inhibition of both serotonin and norepinephrine transporter sites, as is seen with venlafaxine and clomipramine. However, venlafaxine does not begin to exhibit this effect until one gets to a minimum of 150 mg per day. Mirtazapine works primarily through antagonism of the presynaptic alpha-2-adrenergic receptors. This increases serotonin, norepinephrine, and possibly dopamine levels in the synapse. The primary mechanism of action of nefazodone is the antagonism of postsynaptic serotonin type-2 receptors. While the precise mechanism of action of bupropion is not fully appreciated, it is thought to increase norepinephrine levels. The pharmacokinetic properties of the antidepressants are illustrated in Table 104–6. The relative differences in terms of major pharmacokinetic and pharmacodynamic properties are outlined in Table 104–7.

## Benzodiazepine Medication

The benzodiazepines as a class work by increasing the relative efficiency of the gamma-aminobutyric acid (GABA) receptor when stimulated by GABA. The benzodiazepines bind to a site located adjacent to the GABA receptor and cause an allosteric change to the receptor that facilitates the increased passage of the chloride ions intracellularly when GABA interacts with the receptor complex. This leads to a relative hyperpolarization of the neuronal membrane and inhibition of activity in the brain. The benzadiazepines as a group have different affinities for GABA receptors; in fact some agents bind to only one of the two types of GABA receptors. For example, both clonazepam and alprazolam work only on the central $GABA_A$ receptor, while diazepam binds to both $GABA_A$ and $GABA_B$ receptors. The pharmacokinetic properties of the benzadiazepines are outlined in Table 104–6. The relative pharmacodynamic and pharmacokinetic properties of the benzadiazepines are further outlined in comparison to the other medications in Table 104–7. As a class, benzadiazepines are efficacious for the treatment of PD, SAD, GAD, alcohol withdrawal, and situational anxiety. Although OCD falls within the taxonomy of anxiety disorders, benzodiazepines do not seem to be particularly effective in treating these patients.

## Buspirone

Buspirone is a member of the group of agents called azaspirodecanediones. It is believed to exert its anxiolytic effect by acting as a partial agonist at the 5-$HT_{1A}$ autoreceptor. Stimulation of the 5-$HT_{1A}$ autoreceptor causes a decreased release of serotonin into the synaptic cleft. However, buspirone also exerts another effect through its active metabolite 1-phenyl-piperazine (1-PP) that acts on

**Table 104–3** The Inhibition Constants ($K_i$) for Norepinephrine, Serotonin, and Dopamine Reuptake Blockade for Selected Antidepressant Medications

| | NE | 5-HT | DA |
|---|---|---|---|
| Amitriptyline | 13.90 | 84 | 8,600 |
| Desipramine | 0.61 | 180 | 11,000 |
| Fluoxetine | 143 | 14 | 3,050 |
| Sertraline | 220 | 3.4 | 260 |
| Paroxetine | 33 | 0.73 | 1,700 |
| Citalopram | 6,000 | 1.8 | >10,000 |
| Escitalopram | 6,514 | 2.5 | >100,000 |
| Nefazodone | 570 | 137 | 2,380 |
| Venlafaxine | 210 | 39 | 5,300 |

*Source*: Bolden-Watson and Richelson (1993); Hytell (1993).

**Table 104–4** The Proposed Function of Different 5-HT Receptors

| | |
|---|---|
| 1A | Anxiety<br>Depression<br>Sexual behavior<br>Appetite<br>Aggression<br>Pain<br>Emesis<br>? obsessions<br>Vasoconstriction |
| 1D | Migraine<br>Appetite<br>Depression |
| 2A | Vasoconstriction<br>Migraine<br>Anxiety |
| 2B | Depression<br>Sleep<br>Hallucination<br>Suicide |
| 2C | Appetite<br>Anxiety<br>Depression<br>Learning<br>Psychosis |
| 3 | Emesis<br>Anxiety<br>Psychosis<br>Migraine<br>Reward |
| 4 | Muscle contraction, gut, and heart<br>Learning<br>Cognition<br>Anxiety<br>Sleep<br>Emesis |
| 5 | Unknown |
| 6 | OCD? |
| 7 | Circadian rhythms |

*Source*: Dubovsky and Thomas (1995).

alpha-2-adrenergic receptors to increase the firing rate of the locus coeruleus. Some not yet well-characterized combination of these effects may be responsible for anxiolytic effect of buspirone. It usually takes approximately 4 weeks for the benefit of buspirone therapy to be noticed in patients with GAD. One major advantage of buspirone is that it does not cross-react with benzodiazepines. The most common side effects associated with buspirone include dizziness, gastrointestinal distress, headache, numbness, and tingling. The pharmacokinetics and average daily dosage are described in Table 104–6. The most common pharmacokinetic and pharmacodynamic actions of buspirone are described in Table 104–7.

## Beta-Blocker Medication

Beta-adrenergic blockers competitively antagonize norepinephrine and epinephrine at the beta-adrenergic receptor (Table 104–7). It is thought that the majority of positive effects of beta-blockers are due to their peripheral actions. Beta-blockers can decrease many of the peripheral manifestations of anxiety such as tachycardia, diaphoresis, trembling, and blushing. The advent of more selective beta-blockers that only block the $beta_2$-adrenergic receptor has been beneficial since blockade of $beta_1$-adrenergic receptors can be associated with bronchospasm. Beta-blockers may be useful for individuals who have situational anxiety or performance anxiety. They generally have not been effective in treating anxiety disorders such as generalized SAD, PD, or OCD.

## Anticonvulsant Medication

One of the areas of greatest investigation has been the use of anticonvulsant medication to treat anxiety disorders. Monotherapy and augmentation trials with anticonvulsants have been performed in GAD, SAD, PD, and OCD. Despite a rather sizable investment on the part of the pharmaceutical industry and investigators, at this time there are no FDA-approved convulsant agents for the treatment of anxiety disorders. Please see Tables 104–6 and 104–7 for a review of some of the more salient pharmacological properties of anticonvulsants.

## Antipsychotic Medication

The conventional or typical antipsychotic medication, whose mechanism of action is primarily to block dopamine type- 2

**Table 104–5** Common Reported Side Effects of Antidepressant Medications

| SSRI | SNRI | Mirtazapine | Nefazodone | Venlafaxine | Bupropion | MAOI | TCA | Reboxetine |
|---|---|---|---|---|---|---|---|---|
| Headache | SSRI side effects | Increased appetite | Sedation | Nausea | Numbness | Hypertension | Dry mouth | Dry mouth |
| Nausea<br>Decreased motivation<br>Insomnia<br>Fatigue<br>Ejaculatory dysfunction<br>Anorgasmia<br>Decreased libido<br>Weight gain? | Dry mouth<br>Constipation<br>Agitation<br>Diaphoresis<br>Increased blood pressure<br>Weight gain? | Weight gain<br>Sedation<br>Fatigue | Liver failure<br>Fatigue<br>Ataxia<br>Dry mouth<br>Constipation | Dizziness<br>Fatigue<br>Insomnia<br>Vertigo<br>Dry mouth<br>Sexual dysfunction<br>Sweating<br>Vivid dreams<br>"Brain shiver"<br>Akathisia | Dizziness<br>Spaciness<br>Seizures (in high doses)<br>Ataxia | Initial anxiety<br>Weight gain<br>Insomnia<br>Dry mouth<br>Blurred vision<br>Ejaculatory dysfunction<br>Anorgasmia<br>Constipation<br>Dizziness | Blurred vision<br>Constipation<br>Weight gain<br>Fatigue<br>Sedation<br>Insomnia<br>Hypersomnia<br>Ejaculatory dysfunction<br>Initial jitteriness/ anxiety | Constipation<br>Headache<br>Drowsiness<br>Dizziness<br>Excessive sweating<br>Insomnia |

**Table 104–6** Pharmacokinetic Properties of Psychotropic Medication Used for the Treatment of Anxiety Disorders

| | SSRIs | | | | | |
|---|---|---|---|---|---|---|
| | **Citalopram** | **Fluoxetine** | **Fluvoxamine** | **Paroxetine** | **Sertraline** | **Escitalopram** |
| $T_{max}$ h | 2–4 | 6–8 | 3–8 | 5.2 | 4.5–8.4 | 3–5 |
| Dose-proportional plasma level | Yes | No | No | No | Yes | Yes |
| $T_{1/2}$ (h) | 33 | 24–72 | 15.6 | 21 | 26 | 30 |
| Metabolite activity | <10% | Norfluoxetine (equal) | <10% | <2% | Desmethyl-sertraline 6–15% | None |
| Metabolite $T_{1/2}$ | – | 4–16 d | – | – | 62–104 h | 50—60 |
| Steady state plasma level | ~1 wk | 4–5 wk | ~1 wk | 10 d | ~1 wk | 10d |
| Usual daily dosage range | 10–60 mg | 10–80 mg | 100–300 mg Other Antidepressants | 10–60 mg | 50–200 mg | 10–20 mg |
| | **Mirtazapine** | **Nefazodone** | **Venlafaxine** | **Venlafaxine XR** | **Reboxetine** | **Buproprion** |
| $T_{max}$ h | 2 | 1 | 2 | 5.5 | 2 | 2 |
| Dose-proportional plasma level? | Yes | No | Yes | Yes | Yes | |
| $T_{1/2}$ (h) | 37 (females), 26 (males) | 2–4 | 5±2 | | 12 | 3–4 |
| Metabolite activity | Negligible | Hydroxynefazodone | O-desmethyl-venlafaxine | C-desmethyl-venlafaxine | O-desmethyl-reboxetine | Hydroxybupropion |
| Metabolite $T_{1/2}$ (h) | – | 1.5–4 | 11±2 | 11±2 | 13 | 14 |
| Steady state plasma level | 5 d | 4–5 d | 3 d | 3 d | 5 d | 8 d |
| Usual oral dosage | 15–60 mg | 100–800 mg | 45–75 mg Antianxiety | 75–225 mg | 8 mg | 300 mg t.i.d. |
| | **Buspirone** | **Alprazolam** | **Clonazepam** | **Moclobemide** | | |
| $T_{max}$ h | 0.6–1.5 | 1–2 | 1–4 | 1–2 | | |
| Dose-proportional plasma level | No | Yes | Yes | No | | |
| $T_{1/2}$ (h) | 21 | 6.3–26.9 | 30–40 | 2 | | |
| Metabolite activity | Unimportant | α-hydroxyl-alprazolam 50% | No | Yes | | |
| Steady state plasma level | – | 3–4 d | 1 wk | ~ 1 wk | | |
| Usual oral dosage | 15–90 mg | 1–10 mg | 1–6 mg Antipsychotics | 300–600 mg | | |
| | **Aripiprazole** | **Fluphenazine** | **Haloperidol** | **Olanzapine** | **Quetiapine** | **Risperidone** |
| $T_{max}$ h | 3–5 | 2.8 | 2–6 | 6 | 1.5 | 1 |
| Dose-proportional plasma level | | | Yes | Yes | Yes | Yes |
| $T_{1/2}$ (h) | 75–146 | 33 | 10–38 | 21–54 | 6 | 21–30 |
| Metabolite activity | Yes | Yes | Yes | No | No | 9-hyroxyrisperidone |
| Steady state plasma level | 14 d | | varies widely | 4–6 d | 2 d | 5–6 d |
| Usual oral dosage | 5.25–30 mg | 2.5–10 mg | 2–5 mg Anticonvulsants | 2.5–10 mg | 300–400 b.i.d. | 0.5–8 mg |
| | **Gabapentin** | **Levetiracetam** | **Pregabalin** | **Tiagabine** | **Topiramate** | **Valproic Acid** |
| $T_{max}$ h | | 1 | 1.5 | 0.75–3 | 1.5–4 | 4–5 |

*(continues)*

**Table 104–6** Pharmacokinetic Properties of Psychotropic Medication Used for the Treatment of Anxiety Disorders *continued*

| | Gabapentin | Levetiracetam | Pregabalin | Tiagabine | Topiramate | Valproic Acid |
|---|---|---|---|---|---|---|
| Dose-proportional plasma level | No | No | No | | No | No |
| $T_{1/2}$ (h) | 5–7 | 6–8 | 6 | 7–9 | 18–24 | 9–16 |
| Metabolite activity | No | No | No | No | Yes | No |
| Steady state plasma level | 1 d | 2 d | 1–2 d | 2 d | 4 d | 7 d |
| Usual oral dosage | 2,400 mg | 500–3000 mg b.i.d. | 100–200 mg t.i.d. | 4–56 mg | 200–40 mg | 10–250 mg |

$T_{1/2}$, terminal half-life; $T_{max}$, time of maximum plasma concentration.

receptors, has been used as adjuvant medication for the treatment of anxiety disorders for years. However, because of problems with extrapyramidal side effects and the risk of developing tardive dyskinesia, these agents had fallen out of favor. The newer class of atypical antipsychotic medications have a markedly decreased risk of both extrapyramidal side effects and tardive dyskinesia, and so those antipsychotic medications are beginning to be used again as adjuvants in patients with treatment-resistant anxiety disorders. This simultaneous blockade of both neurotransmitter systems seems to decrease extrapyramidal side effects and the risk of developing tardive dyskinesia. Although the different atypical antipsychotic medications have different affinities for dopamine type-2 and serotonin type-2 receptors, this is the common mechanism of action of these agents. The atypical antipsychotic medications also differ dramatically in terms of their pharmacodynamic properties. As described below, there are very few published studies investigating atypical antipsychotic medication augmentation for the treatment of anxiety disorders. Please review the pharmacokinetic and side effect data for the antipsychotic medications that have been used to treat anxiety disorders in Tables 104–6 and 104–7.

## Generalized Anxiety Disorder

### Selective Serotonin Reuptake Inhibitors

Pollack et al. (2001) published an 8-week randomized, double-blind, placebo-controlled, flexible-dosage trial investigating the efficacy of paroxetine in 326 adult outpatients with GAD. Inclusion criteria both at screen and baseline were a Hamilton Anxiety Rating Scale (HAM-A) total score ≥ 20 and a score ≥ 2 on HAM-A items 1 (anxious mood) and 2 (tension). Eligible patients underwent a 1-week, single-blind placebo run-in, and then were randomized to paroxetine or placebo. Patients assigned to paroxetine started treatment at 10 mg/day for the first week and were titrated to 20 mg/day by week 2. After the second week, patients tolerating the medication could have their medication increased every 7 days by 10 mg/day to a maximum 50 mg/day. The primary efficacy measure in this study was the mean change in total HAM-A score from baseline to week 8. Response to treatment was defined by a score of (1) "very much improved" or (2) "much improved" on the CGI-Global Improvement Scale. Remission was defined by a HAM-A total score of 7 or less. The trial was completed by 78.9% of paroxetine patients and 81.6% of placebo patients. Seventy-four percent of paroxetine patients met response criteria versus 55.6% of placebo-treated patients. Forty-three percent of paroxetine-treated patients met remission criteria compared to 26.3% of placebo-treated patients. The mean daily dose of paroxetine was 26.8 ± 7.5 mg/day. Rickels et al. (2003) published an 8-week randomized, double-blind, placebo-controlled trial using two fixed doses of paroxetine to treat GAD. Five hundred sixty-six outpatients with DSM-IV-TR diagnosis of GAD and a score of ≥ 20 on the HAM-A were randomized to receive either 20 or 40 mg/day of paroxetine or placebo. The primary outcome measure was the change from baseline in total score on the HAM-A. Response was defined as a rating of "very much improved" or "much improved" on the CGI. Remission was defined as a HAM-A total score of ≤ 7. Both the 20 mg and 40 mg paroxetine-treated groups demonstrated statistically significant reductions in HAM-A total scores when compared with the placebo group. Response rates were 62% and 68%, respectively, for the 20 and 40 mg/day paroxetine-treated groups, compared with 46% response rate for the placebo group. Remission rates were 30% and 36% of patients in the 20 and 40 mg paroxetine groups, respectively, compared with 20% given placebo. Stocchi et al. (2003) published a 24-week double-blind GAD study contrasting paroxetine and placebo. Six hundred fifty-two adult outpatients with DSM-IV-TR GAD and a CGI-S score of ≥ 4 received paroxetine (20–50 mg/day) or placebo for 8 weeks. Patients whose CGI-S scores decreased by at least 2 points to ≤ 3 at week 8 were randomly assigned to double-blind treatment with paroxetine ($n$ = 278) or placebo ($n$ = 288) for an additional 24 weeks. The primary efficacy measure was the proportion of the patients relapsing (an increase in CGI-S score of at least 2 points to a score of ≥ 4 or withdrawal due to lack of efficacy) during double-blind treatment. Significantly fewer paroxetine relapsed during the 24-week double-blind phase (10.9% vs. 39.9%; $p$ > 0.001). Subjects randomized to placebo discontinuation were almost five times more likely to relapse than those continuously on double-blind paroxetine (estimated hazard ratio = 0.213 [95% CI = 0.1 to 0.3]; $p$ < 0.001). Therefore, studies demonstrate that paroxetine is an effective short-term and continuous treatment for patients with GAD.

Escitalopram also has been extensively studied as a treatment for GAD. Davidson et al. (2004) conducted an 8-week randomized, double-blind, placebo-controlled, multicenter, flexible-dose study of escitalopram (10 mg/day for the first 4 weeks and then flexibly dosed from 10–20 mg/day) of 315 US outpatients that met DSM-IV-TR

**Table 104–7** A Summary of Pharmacologic Properties of Medications Commonly Used to Treat Anxiety

| | Mechanism of Action | Onset of Action | Titration | Abuse Liability | Need for Discontinuation Titration | Potential for Withdrawal Syndrome | Probability of Lethality in Overdose |
|---|---|---|---|---|---|---|---|
| Sertraline | SSRI | Delayed (In 2 wk) | Yes | Very low | Yes, but not mandatory | Very low | Low |
| Paroxetine | SSRI | Delayed (In 2 wk) | Yes | Very low | Yes | Moderate | Low |
| Fluvoxamine | SSRI | Delayed (In 2 wk) | Yes | Very low | Yes, but not mandatory | Very low | Low |
| Fluoxetine | SSRI | Delayed (In 2 wk) | Yes | Very low | No | Lowest | Low |
| Citalopram | SSRI | Delayed (In 2 wk) | Yes | Very low | Yes, but not mandatory | Very low | Low |
| Escitalopram | SSRI | Delayed (In 2 wk) | Sometimes | Very low | Yes, probably not mandatory | Very low | Low |
| Venlafaxine | SNRI | Delayed (In 2 wk) | Yes | Very low | Yes | Moderate | Low |
| Reboxetine | NARI | Delayed (In 2 wk) | Yes | Very low | Yes | Low | Low |
| Mirtazapine | $\alpha_2$-antagonist | Delayed | Yes | Very low | Yes | Moderate | Low |
| Nefazodone | $5HT_2$ blockade | Delayed | Yes | Very low | Yes | Moderate | Low |
| Bupropion | Norepinephrine? | Delayed | Yes | Very low | Yes | Low | Low |
| TCAS | Reuptake blockade | Delayed (2 wk) | Yes | Very low | Yes | Moderate | Moderate–high |
| MAOIs | Monoamine inhibition | Delayed (2 wk) | Yes | Very low | Yes | Moderate | Moderate–high |
| Buspirone | $5HT_{1A}$ partial agonist | Delayed (2 wk) | Yes | Very low | Yes | Low–moderate | Low |
| Clonazepam | Modulates $GABA_A$ receptor | Rapid | Yes | Moderate | Yes | Moderate–high | Low |
| Alprazolam | Modulates $GABA_A$ receptor | Very rapid | Yes | Moderate | Yes | High | Low |
| Alprazolam XR | Modulates $GABA_A$ receptor | Rapid | Yes | Moderate | Yes | Moderate–high | Low |
| Lorazepam | Modulates $GABA_A$ receptor | Very rapid | Yes | Moderate | Yes | Moderate–high | Low |
| Diazepam | Modulates $GABA_A$ receptor | Rapid | Yes | Moderate | Yes | Moderate | Low |
| Beta-blockers | Blocks beta-adrenergic receptors | Rapid | Sometimes | Low | No (acute use) | No (acute use) | Low–moderate |
| Gabapentin | Not fully known but GABAergic | Moderate (d) | Yes | Low | Yes | Low–moderate | Low |
| Pregabalin | Not fully known but GABAergic | Rapid | Yes | Low | Yes | Low–moderate | Low |

*(continues)*

**Table 104–7 A Summary of Pharmacologic Properties of Medications Commonly Used to Treat Anxiety *continued***

| | Mechanism of Action | Onset of Action | Titration | Abuse Liability | Need for Discontinuation Titration | Potential for Withdrawal Syndrome | Probability of Lethality in Overdose |
|---|---|---|---|---|---|---|---|
| Aripiprazole | $D_2$, $D_3$, 5-$HT_{1A}$ and 5-$HT_{2A}$ | Delayed (2 wk) | Yes | unknown | Yes | Unknown | Low–moderate |
| Risperidone | 5-$HT_2$ and $D_2$ blockade | Rapid | Probably | Low | Yes | Low | Low |
| Haloperidol | $D_2$ blockade | Rapid | Yes | Low | Yes | Low | Low |
| Olanzapine | 5-$HT_2$ and $D_2$ blockade | Rapid | Probably | Low | Yes | Low | Low |

criteria for GAD. Mean change from baseline to week 8 in the HAM-A was used as the primary efficacy variable. The escitalopram group ($n$ = 158) demonstrated statistically significant and clinically relevant, greater improvement ($n$ = 157) on all efficacy parameters in this study. Mean changes from baseline to week 8 on the HAM-A total score using a last-observation-carried-forward approach were −11.3 for escitalopram and −7.4 for placebo. Response rates at week 8 were 68% for escitalopram and 41% for placebo among completers, and 58% for escitalopram and 38% for placebo looking at the last-observation-carried-forward values. There was no statistical difference in reported adverse events in the escitalopram-treated group (8.9%) compared to the placebo-treated group (5.1%). Davidson et al. (2005) also examined the safety and efficacy of long-term, open-label treatment of GAD with escitalopram. Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted with escitalopram in GAD (DSM-IV-TR criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10–20 mg/day). Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The HAM-A score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continued improvement in anxiety and quality-of-life measures. Of those completing 24 weeks of treatment, 92.0% were responders (CGI ≤ 2). The mean HAM-A score in the completer analysis was 6.9, and the mean HAM-A score in LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. Although uncontrolled, these data mirror the type of improvement observed in double-blind continuation studies with other SSRIs.

Allgulander et al. (2004) performed the first large, global multicenter, placebo-controlled, flexible-dose study of sertraline (50–150 mg/day) compared to placebo in GAD outpatients. After a 1-week single-blind placebo lead-in, patients were randomly assigned to 12 weeks of double-blind treatment with placebo ($n$ = 188) or flexible doses of sertraline ($n$ = 182). The primary outcome measure was the change from baseline to endpoint in the HAM-A total scores. Sertraline-treated subjects had significantly greater improvement (mean = 11.7) over placebo patients (mean = 8.0) on the HAM-A at week 4. Brawman-Mintzer et al. (2006) performed a similar study comparing sertraline (50–200 mg/day) to placebo in outpatients with GAD for 10 weeks. The primary efficacy measure was change from baseline in HAM-A total score. Response was defined as ≥ 50% decrease in HAM-A total score at endpoint. Sertraline produced statistically significant reduction in anxiety symptoms, as measured by the HAM-A total changes scores ($p$ = 0.032). Response rates were 59.2% for the sertraline group compared to 48.2% for the placebo group. Ball et al. (2005) conducted an 8-week, randomized, double-blind, flexible-dose study investigating paroxetine (10–40 mg/day) versus sertraline (25–100 mg/day) in 53 outpatients meeting DSM-IV-TR criteria for GAD. Both paroxetine and sertraline were associated with significant decreases in mean HAM-A scores (paroxetine = 57% ± 28%; sertraline = 56%, ± 28%). There were no significant differences between the two groups in either remission rates, as defined by a CGI-S score of 1, (paroxetine = 40%, 10/25; sertraline = 46%, 13/28) or response rates, defined as at least a 50% reduction in score from baseline to posttreatment (paroxetine = 68%, 17/25; sertraline = 61%, 17/28). Thus in this small study the two SSRIs were comparable to one another on all efficacy assessments.

## Special Populations

The efficacy and safety of sertraline treatment for children with GAD was investigated in a 9-week, double-blind, placebo-controlled study by Rynn et al. (2001). Twenty-two children and adolescents, ages 5–17 years, who met DSM-IV-TR criteria for GAD and had a HAM-A rating ≥ 16 participated in this study. All patients underwent a 2- to 3-week preevaluation period, followed by a 9-week double-blind treatment phase. Sertraline was initiated at 25 mg/day for the first week then titrated to 50 mg/day for weeks 2–9. Primary outcome measures were the HAM-A total score, HAM-A psychic and somatic scores as well as the CGI-Severity and Improvement Scale scores. Mean HAM-A scores for the sertraline group reduced from 20.6 ± 3.6 at baseline to 7.8 + 5.7 at week 9, while those receiving placebo decreased from 23.3 ± 4.0 at baseline to 21.0 ± 7.8 at week 9. Mean CGI-Severity scores significantly improved for the sertraline-treated group (4.0 baseline to 2.4 weeks) while the placebo-treated group remained unchanged (4.0 baseline to 3.9 weeks). Importantly, no statistically significant differences were found in adverse events between the two groups. Only two patients in the placebo-treated group and one patient in the sertraline group dropped out prior to study completion.

These data suggest that low doses of sertraline may be effective and well tolerated for children with GAD.

Lense et al. (2005) examined efficacy and tolerability of citalopram in 30 subjects with anxiety disorders aged 60 or older (30 subjects meeting DSM-IV-TR criteria for GAD). Subjects were randomly assigned to treatment with citalopram or placebo for 8 weeks. Response was defined as a score of 1 (very much improved) or a 2 (much improved) on the CGI-I scale or a 50% reduction in the HAM-A scale score. Ten (67%) of the 15 citalopram-treated subjects diagnosed with GAD met response criteria versus 4 (27%) of the 15 placebo-treated subjects with GAD.

In summary, data from randomized, placebo-controlled treatment trials suggest that SSRIs may be useful in the treatment of adults, children, and elderly patients with GAD. The medication dosages used to treat individuals with GAD are similar to the dosages used to treat major depressive disorder.

## Serotonin–Norepinephrine Reuptake Inhibitors—Venlafaxine and Reboxetine

There have been several placebo-controlled multicentered studies demonstrating that venlafaxine XR is an effective treatment of GAD. Davidson et al. (1999) performed an 8-week placebo-controlled trial of 75 and 150 mg/day of venlafaxine XR contrasted with 30 mg/day of buspirone. Venlafaxine XR reduced HAM-A scores significantly more than either placebo or 30 mg/day of buspirone. In an additional study by Rickels et al. (2000b), patients with GAD were randomized to three doses of venlafaxine XR, namely 75, 150, or 225 mg/day; all three doses were more effective in decreasing HAM-A scores than placebo. Results from a 6-month, fixed-dose study of venlafaxine XR (37.5, 75, or 150 mg/day) versus placebo suggests that patients treated with venlafaxine did significantly better than patients treated with placebo. Secondary analysis from this study suggests that the two higher doses of venlafaxine were also associated with significant improvement in social functioning (Haskins et al. 1999). Gelenberg et al. (2000) compared the 6-month efficacy and safety of flexible doses of venlafaxine XR in adult outpatients with GAD. Two hundred and fifty-one adults who met DSM-IV-TR criteria for GAD without comorbid major depressive disorder met the following criteria: (1) a screen and baseline score of at least an 18 on the HAM-A, (2) at least 2 on items 1 and 2 of the HAM-A, (3) a total score of at least 9 on the Raskin Depression Scale at screen and baseline, and (4) a Covi Anxiety Scale score greater than the total score on the Raskin. Patients were started on venlafaxine XR at 75 mg/day or placebo during week 1. After day 8, the dose could be increased to 150 mg/day of venlafaxine XR or placebo. At day 15, increases were again allowed to the maximum 225 mg/day or placebo. Primary efficacy measures included the HAM-A total score, the HAM-A psychic anxiety factor score, and the CGI-Severity and Global Improvement Scale scores. Response to treatment in this study was defined as a 40% decrease from baseline on HAM-A total score or a CGI-Global Improvement Scale score of (1) "very much improved" or (2) "much improved." By week 2, 42% of patients in the venlafaxine XR group were categorized as responders compared to 21% of placebo patients. During weeks 6–28, response rates were 69% for venlafaxine XR and 42–46% for placebo. Adverse events led to treatment discontinuation for 17% of the placebo-treated subjects and 26% venlafaxine-treated subjects.

Doses as low as 37.5 mg/day and as high as 225 mg/day are effective in decreasing symptoms of anxiety for patients with GAD. Studies indicate that venlafaxine XR is an effective short-term and long-term treatment for GAD. Side effects appeared to be mild and tended to decrease in number and intensity over the course of the studies. Nausea, dry mouth, and somnolence were the most commonly reported side effects.

## Tricyclic Antidepressant Medication and Monoamine Oxidase Inhibitors

A variety of TCAs have been demonstrated to be effective treatments for GAD (Hoehn-Saric et al. 1993, Liebowitz et al. 1988). However, the side effects and difficulty to titrate the dosage of these medications have made their use uncommon. Many patients discontinued the imipramine-treatment group because of side effects.

## Other Antidepressant Medication (Bupropion, Mirtazapine, Nefazodone, Trazodone)

There are some older studies that suggest that trazodone is an effective treatment for GAD (Rickels et al. 1993). There has been one open-label study suggesting that nefazodone may be efficacious for patients with GAD (Hedges et al. 1996).

## Benzodiazepine Medication

There have been hundreds of studies demonstrating that benzodiazepines as a class are more effective than a placebo in the treatment of both symptoms of anxiety and GAD (Greenblatt et al. 1983). In general, the response rate from these benzodiazepine studies is between the 60 and 80% range (Rickels et al. 1983, Uhlenhuth et al. 1998). Unfortunately, benzodiazepine treatment of GAD is controversial. Despite evidence that the anxiolytic effect does not tend to diminish over time and that the majority of patients do not abuse benzodiazepines, most physicians are reticent to initiate long-term treatment for GAD (Bowden and Fisher 1980, Ciraulo et al. 1988).

There have been a variety of studies with abecarnil. In general abecarnil has not been demonstrated to be more effective than either buspirone or a traditional benzodiazepine (Pollack et al. 1997, Rickels et al. 2000a).

Rapaport et al. (2006) investigated combination therapy with alprazolam ODT and SSRI/SNRI compared with SSRI/SNRI monotherapy. One hundred twenty-nine subjects with a primary diagnosis of GAD were randomized 1:1 to 8 weeks of open-label treatment with alprazolam or no augmentation. The primary efficacy measure was time to response, defined as a ≥ 50% decrease from baseline in HAM-A total score. There was no statistically significant difference between treatment groups in time to response. Results did reveal that at weeks 2 and 4 CGI-I scores demonstrated that combination therapy (SSRI/SNRI + alprazolam) was associated with earlier improvement in response than SSRI/SNRI monotherapy (week 2, 42.9% vs. 21.1%, $p < 0.01$; week 4, 63.3% vs. 41.3%, $p < 0.05$). Similarly, subject-rated measures of global improvement (PGI) suggested combination therapy ameliorated symptoms earlier than monotherapy (week 2, 41.9% vs. 20.4%, $p < 0.05$; week 3, 50.8% vs. 30.2%, $p < 0.05$; week 6, 70.0% vs. 42.8%, $p < 0.01$). Of concern,

approximately one third of patients in this trial could not be tapered off alprazolam ODT during the specified taper phase. This requires more investigation.

In summary, the short-acting benzodiazepines, longer acting benzodiazepines, and even the low potency benzodiazepines have all been demonstrated to be effective monotherapies or adjunctive treatments for GAD. The choice of an agent should take into account the age, medical health, and comorbid diagnosis of the patient.

## Buspirone

Buspirone has been shown to be more effective than placebo in decreasing HAM-A scores in a large number of placebo-controlled trials (Laakmann et al. 1998, Rickels et al. 1982, 1988). It is thought that buspirone may be particularly effective against psychological symptoms such as worry, tension, irritability, and apprehension, but less effective in ameliorating somatic symptoms because of its activation of locus coeruleus (Riblet et al. 1982, Rickels et al. 1982).

Data from placebo-controlled and comparative studies against benzodiazepines suggest that the onset of action of buspirone usually takes at least 2 weeks (Connor and Davidson 1998, Laakmann et al. 1998). However, clinical experience suggests that buspirone treatment may take 3–4 weeks before one sees a truly beneficial effect in patients with GAD. Buspirone also requires multiple daily administration to be effective. Although a recent meta-analysis suggests that buspirone may be given twice a day for the treatment of anxiety and GAD, the majority of studies and the current labeling for buspirone suggests that it should be administered three times a day (Sramek et al. 1999). Discontinuation of buspirone has not been associated with development of withdrawal symptoms; however, over time patients discontinued from pharmacotherapy tend to relapse (Rickels et al. 1988).

In a placebo-controlled comparative study of hydroxyzine versus buspirone, both agents were found to be more effective than placebo treatment (Lader and Scotto 1998).

In summary, although there are considerable data suggesting that buspirone is an effective treatment for GAD, most of these data are from acute trials. It is clear that buspirone's time to onset is delayed in contrast to the benzodiazepines and that it may not be as useful as benzodiazepines for the treatment of GAD patients with primarily somatic symptoms.

## Anticonvulsant Medication

Two different anticonvulsants have been studied for the treatment of GAD: pregabalin and tiagabine. There are four large multicenter placebo-controlled studies investigating the efficacy of pregabalin in patients with GAD. Pande et al. (2003) published a 6-week, double-blind, four-armed placebo-controlled comparison of pregabalin (150 mg/day and 600 mg/day) and lorazepam (6 mg/day). This study, as was the case with most other pregabalin studies, had three phases: a 1-week placebo lead-in phase, a 4-week double-blind treatment phase, and a 1-week taper phase. The primary efficacy measure in this study was the change in HAM-A tools scores over 4 weeks. In this study, both pregabalin groups and the lorazepam groups significantly differentiated from placebo in terms of decreases in HAM-A total scores. However, pregabalin was well tolerated and had a lower drop-out rate than lorazepam in this study. Feltner et al. (2003) performed an identical study in a 600 mg/day pregabalin group and a 6 mg/day lorazepam group separated from placebo on the HAM-A, but the 150 mg/day pregabalin group did not. Rickels et al. (2005) published a five-arm, double-blind, placebo-controlled study in outpatients with GAD. In this 6-week study, three doses of pregabalin (300 mg/day, 450 mg/day, and 600 mg/day) were contrasted with alprazolam 1.5 mg/day and placebo. All three pregabalin groups and the alprazolam group caused statistically significantly greater change in HAM-A total scores than placebo. In this study, all three pregabalin groups as well as alprazolam caused statistically significant decreases in the HAM-A psychic anxiety subscale when compared to placebo. Two of the three pregabalin groups also statistically separated from placebo on the HAM-A somatic anxiety subscale. However, it was the middle 450 mg/day group that did not separate from placebo on this measure, making it difficult to interpret these results. Montgomery et al. (2006) published a 421-patient study investigating the efficacy of two doses of pregabalin versus venlafaxine and placebo for the treatment of moderate to severe GAD (HAM-A ≥ 20). Primary outcome measure was the change in HAM-A mean total score. In three active treatment groups, pregabalin (400 mg/day and 600 mg/day) and venlafaxine (75 mg/day) caused significantly greater decreases in HAM-A total scores than placebo. The active groups did not differentiate in other measures. The discontinuation rates were slightly higher for the venlafaxine group; 20.4% versus 6.2% for 400 mg/day pregabalin, 13.6% for pregabalin 600 mg/day, and 9.9% for placebo. In summary, there are four positive studies demonstrating that pregabalin, in a dose range from 150 mg/day through 600 mg/day, was effective in the treatment of GAD. Despite this rather impressive array of data, pregabalin is not approved by the FDA for this indication at this time.

There has been one large double-blind, placebo-controlled trial of tiagabine as a treatment for patients with GAD. Pollack et al. (2005) published a large 8-week randomized, double-blind, flexible-dose, placebo-controlled study investigating tiagabine (4–16 mg/day) versus placebo. Tiagabine did not differentiate from placebo in the last-observation-carried-forward analyses of the HAM-A, but it did differentiate from placebo when a mixed models' repeated measures analysis was performed. It was well tolerated and was not associated with problems with sexual functioning, weight or sleep-related side effects.

## Antipsychotic Medication

At this time, there are two published augmentation trials evaluating the efficacy of atypical antipsychotic medication for patients with treatment-resistant GAD. Pollack et al. (2006) openly treated individuals with fluoxetine. Those who did not respond to fluoxetine entered into a double-blind phase where they were randomized to receive either olanzapine (20 mg/day) or placebo. In this small study, olanzapine augmentation significantly improved CGI-I scores and caused a significant reduction in HAM-A total scores. The rates of both response and remission were much greater in the olanzapine-treated group than in the placebo-treated group. However, olanzapine was associated with significant increase in weight. Brawman-Mintzer et al. (2005) investigated the efficacy of risperidone augmentation for treatment-resistant GAD. In this trial, individuals who

continued to have a HAM-A score of ≥ 18 or a CGI-S score of moderate or greater after 4 weeks of anxiolytic treatment were randomized to receive flexible-dose risperidone (0.5–1.5 mg/day). Risperidone augmentation caused a statistically significant decrease in HAM-A total scores.

### Treatment Conclusions

People with GAD suffer from a combination of both physical symptoms as well as psychic anxiety. There has been a wealth of clinical trials that demonstrate that a myriad of classes of agents are effective in the short-term treatment of GAD. These include the TCAs, trazodone, buspirone, benzodiazepines, SSRIs, and SNRIs like venlafaxine XR. Several of the SSRIs and venlafaxine XR have received FDA approval as a short-term treatment for GAD. The longer term maintenance studies clearly suggest that patients continue to improve and are more likely to achieve remission from their symptoms of GAD if they are continued at full dose of their treatment over a period of at least one year. There also are data suggesting that discontinuation of pharmacotherapy is associated with the recurrence of illness. At this time, a clinician could choose any of the existing SSRIs or SNRIs as a first-line treatment and anticipate that the majority of patients would realize significant relief of symptoms over 8–12 weeks.

On many occasions, individuals have difficulty with the initial upward taper of traditional antidepressant medications, so it is not unreasonable to consider adding, for a short period of time, a benzodiazepine. Unfortunately, it is also apparent that there is a subgroup of individuals with GAD who have a more refractory course. There are limited data available to suggest the most appropriate augmentation or switch therapies for patients with GAD. However, there is an emerging body of literature suggesting that acute augmentation with low doses of atypical antipsychotic medications may be beneficial in relieving residual symptoms of GAD. Such patients' medications should be selected based on the types of persistent target symptoms that are present.

## Social Anxiety Disorder

### Selective Serotonin Reuptake Inhibitors

SSRIs have emerged as first-line treatment for SAD. Most of the efficacy data are derived from multicenter, double-blind trials of paroxetine, sertraline, and fluvoxamine. The first study to demonstrate that an SSRI was efficacious in treating SAD was a 12-week trial of 183 patients randomized to either paroxetine (20–50 mg/day) or placebo. Fifty-five percent of patients randomized to paroxetine improved significantly, versus 24% of those randomized to placebo (Stein et al. 1998). These results have been replicated in a second, large multicenter study for SAD (Baldwin et al. 1999).

Multiple large-scale studies of escitalopram for acute treatment and relapse prevention of SAD have been published (Kasper et al. 2005, Montgomery et al. 2005, Lader et al. 2004). Kasper et al. (2005) recruited 358 adult outpatients for their 12-week, multisite, randomized, placebo-controlled, flexible-dosage study. Two hundred and ninety (81%) participants completed the study, with 145 patients enrolled in each treatment group at the study's endpoint. Although escitalopram was significantly better than placebo on all primary and secondary efficacy measures, it also had a higher incidence of headache, nausea, and sexual side effects than placebo, which should be taken into consideration. Among completers, escitalopram was significantly better than placebo on all efficacy measures, even with an extremely high placebo response rate of 39%. Lader et al. (2004) enrolled 837 participants in a 24-week, multisite, randomized study where patients received placebo ($n$ =166), 5 mg escitalopram ($n$ =167), 10 mg escitalopram ($n$ =167), 20 mg escitalopram ($n$ =170), or 20 mg paroxetine ($n$ =169). Twenty milligrams escitalopram was significantly more effective than placebo or 20 mg paroxetine on 5 of 6 symptom dimensions of the Liebowitz Social Anxiety Scale (LSAS).

Liebowitz et al. (2003) conducted a study enrolling 415 outpatients with severe generalized social anxiety in a 12-week, double-blind study of flexible-dose sertraline (50–200 mg/day) versus placebo. Among completers, sertraline was significantly more effective than placebo in causing improvement on a wide array of measures including the LSAS, CGI-I, Q-LES-Q, and the SDS. In a subgroup analysis, 87 subjects were identified as having Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores more than two standard deviations below mean normative community values. Thirty-seven percent of these subjects randomized to sertraline treatment had restoration of Q-LES-Q scores back to the normal range versus 11% of placebo-treated subjects. These data further support the findings of previous studies, strengthening the use of sertraline as treatment for patients with SAD.

In a study of fluvoxamine treatment for 82 patients with SAD, 42% of patients randomized to fluvoxamine responded to treatment (mean dose 202 mg/day), as compared to 24% of patients who received placebo (Stein et al. 1999). There are also smaller trials demonstrating that other SSRIs, including fluoxetine and citalopram, also seem to be effective in the treatment of SAD (Bouwer and Stein 1998, Van Ameringen et al. 1993). (For more on social anxiety, please see Chapter 70.) In another large double-blind study, Westenberg et al. (2004) enrolled 300 patients in a 12-week, multicenter study comparing 100–300 mg/day fluvoxamine controlled release (CR) with placebo. Fluvoxamine CR caused greater improvement on the primary outcome measures when compared with placebo. Ratings of sexual functioning were performed and were not statistically significant between the groups.

In a longer maintenance study, Montgomery et al. (2005) examined the effects of 12 weeks of open-label treatment with flexible doses of 10–20 mg escitalopram, where all responders were then randomly assigned to 24 weeks of fixed-dose, double-blind treatment with escitalopram or placebo. Four hundred and thirty six patients completed the open-label phase and 198 completed the double-blind extension phase.

The use of sertraline for the longer term treatment of SAD was investigated in a two-part study where subjects entered a 20-week, double-blind, placebo-controlled study that was followed by a 24-week double-blind extension for first phase treatment responders (Van Ameringen et al. 2001). This study was conducted at 10 outpatient clinics in Canada. Two hundred and four adult outpatients with SAD were randomly assigned 2:1 to sertraline or placebo. Following a 1-week placebo run-in period, patients received an initial dose of 50 mg/day of sertraline or placebo. After 4 weeks,

the dose could be increased 50 mg/day every 3 weeks up to a maximum of 200 mg/day. In the event of intolerable side effects, doses could be reduced to a minimum of 50 mg/day. Primary efficacy measures included the CGI-Improvement Scale, the patient-rated Marks Fear Questionnaire (FQ), and the physician-rated Brief Social Anxiety Disorder Scale. At study endpoint, 53% of sertraline patients compared to 29% of placebo patients were (2) "much improved" or (1) "very much improved" as measured by the CGI-Improvement Scale. The mean score on the FQ decreased from 23.07 at baseline to 15.54 at endpoint for the sertraline-treated group, while the placebo-treated group decreased from 21.72 at baseline to 19.38 at endpoint. The mean score on the Brief Social Anxiety Disorder Scale for the sertraline-treated group decreased from 47.48 at baseline to 31.18 at endpoint, versus 45.72 to 37.23 at endpoint for the placebo-treated group. The mean dose of sertraline was 146.7 mg/day. Fifty sertraline responders and 15 placebo responders entered the double-blind, placebo-controlled relapse-prevention phase of the study. Patients who were randomly assigned to continue sertraline treatment received a mean daily dose of 148.0 mg/day. Eighty-eight percent of sertraline-treated patients, 40% of placebo-switched patients, and 40% of the initial placebo-responder patients completed the study. Four percent of the subjects who received sertraline maintenance relapsed as compared to 36% of the placebo-switch group. These findings agree with work by Katzenick et al. (1995) and a general practice trial by Blomhoff et al. (2001).

In summary, SSRIs are a useful first-line medication for patients seeking treatment for SAD, especially those patients presenting with comorbid depression. Maintenance therapy trials with escitalopram and sertraline confirm the continued benefit shown by maintenance pharmacotherapy.

## Serotonin–Norepinephrine Reuptake Inhibitors—Venlafaxine and Reboxetine

The first case reports and open-label studies investigating the efficacy of venlafaxine in SAD were published in the mid-1990s (Kelsey 1995). Recently, multiple double-blind studies examining the efficacy of venlafaxine ER in SAD have been published (Allgulander et al. 2004, Rickels et al. 2004, Liebowitz 2005). Rickels et al. (2004) conducted a 12-week, double-blind, placebo-controlled study of venlafaxine extended release (ER) in 272 outpatients with generalized SAD. Among 172 completers, venlafaxine ER was significantly more effective than placebo, as demonstrated by LSAS, CGI-I, and CGI-S scores. These results were supported by the double-blind, placebo-controlled, flexible-dose trial by Liebowitz et al. (2005), which examined the effects of venlafaxine ER (75–225 mg/day) in 440 patients with SAD. The study's primary efficacy measure was the LSAS total score, with CGI-I, CGI-S, Social Phobia Inventory (SPIN), and LSAS subscales serving as secondary measures. Venlafaxine ER treatment caused significant improvement over placebo on the LSAS, with response rates being 44% in venlafaxine-treated patients versus 30% in placebo-treated patients, where response was defined as a CGI-I score of 1 or 2. In addition, remission rates were significantly greater in the venlafaxine ER group than in the placebo group (20% vs. 7%, where remission was an LSAS score ≤ 30). Allgulander et al. (2004) conducted a similarly designed study, examining the efficacy of 75–255 mg/day venlafaxine ER, 20–50 mg/day paroxetine, or placebo for 12 weeks. Treatment with venlafaxine ER demonstrated a significant improvement over placebo on all efficacy variables, although no significant differences were observed between the venlafaxine ER and paroxetine groups. Even so, both active treatments led to remission in less than half of patients, suggesting that short-term, 12-week studies may not be long enough to attain the medications' full therapeutic effects with a chronic illness like SAD. The aforementioned placebo-controlled trials confirm the benefit of venlafaxine in the acute treatment of social phobia patients, thus calling for the examination of the medication's long-term effects.

## Tricyclic Antidepressant Medication and Monoamine Oxidase Inhibitors

In general, TCAs have not been found to be effective for the treatment of SAD. A recent open-label study of nine patients diagnosed with SAD found no difference between imipramine and placebo. However, six patients dropped out early because of side effects (Simpson et al. 1998a).

MAOIs have been shown to be superior to placebo treatment for SAD (Gelernter et al. 1991, Versiani et al. 1992). The mean daily dose of the drug in these trials ranged between 60 and 90 mg/day. Although surpassed by the SSRIs as first-line agents, there is no doubt that first-generation MAOIs are effective. Unfortunately, the risk of hypertensive crisis and the need for patients to follow a tyramine-free diet makes this class of drugs unappealing for the majority of patients. Selegiline (L-Deprenyl) is of clinical interest because at low doses it is selective for MAO-B and has fewer side effects. Simpson et al. (1998b) conducted a 6-week open trial of selegiline in 16 patients with SAD. The dose of selegiline was fixed at 5 mg twice a day, and patients were instructed to follow a standard MAOI diet. Responders were defined by a score of 1 or 2 on the CGI at the last observation. Nine subjects completed the trial; three were considered responders. Of completers, mean LSAS scores decreased from 85.9 ± 25.4 at baseline to 58.0 ± 25.4 at endpoint, and mean Liebowitz Social Phobic Disorders Scale—Overall Severity (LSPD) scores decreased from 5.0 ± 0.9 at baseline to 4.4 ± 1.2 at endpoint. These data suggest that low dose selegiline may have a modest effect in SAD.

The promising results derived from efficacy studies of first-generation MAOIs spawned the study of reversible monoamine oxidase inhibitors (RIMAs) for this indication. RIMAs have significantly less risk of hypertensive crisis and subsequently no need for a tyramine restricted diet. They also have a more tolerable side effect profile. Brofaromine and moclobemide are the two most studied RIMAs. However, there is conflicting evidence about their efficacy for the treatment of SAD. Of four published placebo-controlled multicenter moclobemide studies, three have been positive (Stein et al. 2002b, International Multicenter Clinical Trial Group 1997, Blanco and Liebowitz 1998, Noyes et al. 1997, Schneier et al. 1998). Two controlled studies of brofaromine in SAD showed superior efficacy to placebo (Fahlen et al. 1995, Van Vliet et al. 1993). However, brofaromine is no longer under development in the US, and moclobemide is not available in the US.

## Other Antidepressant Medication (Bupropion, Mirtazapine, Nefazodone, Trazodone)

Emmanuel et al. (1991, 2000) have published two papers investigating bupropion treatment for SAD. In the most recent work, a small 12-week open-label flexible-dose study, the efficacy of bupropion SR in the treatment of SAD was evaluated (Emmanuel et al. 2000). Eighteen subjects with DSM-IV-TR diagnosed SAD were seen weekly for the first 4 weeks, then biweekly for the next 8 weeks. Bupropion SR was initiated at 100 mg/day and titrated to a maximum of 200 mg twice a day, depending on response to treatment. Ten subjects completed the 12-week treatment period; 5 of the 10 were responders. The mean dose of bupropion SR was 366 ± 68 mg/day. The mean CGI-I scores changed from 4.3 ± 0.7 at baseline to 2.5 ± 0.9 at week 12, and the mean Brief Social Phobia Scale (BSPS) scores decreased from 42.2 ± 13 at baseline to 21.0 ± 11 at week 12.

Muehlbacher et al. (2005) conducted a double-blind, placebo-controlled trial of mirtazapine treatment for SAD patients. Sixty-six women enrolled in the 10-week, fixed-dose study of 30 mg/day mirtazapine or placebo. After 10 weeks of treatment, significant differences were noted between mirtazapine and placebo on the SPIN and the LSAS. Large-scale studies examining the efficacy of mirtazapine in SAD are warranted.

## Benzodiazepine Medication

The benzodiazepines, clonazepam and alprazolam, have been shown to be efficacious in treating SAD (Dubuff et al. 1995, Gelernter et al. 1991, Nardi and Perna 2006). The limitations of these drugs are the same as when used in any indication. Due to the potential for abuse and drug withdrawal, their use must be monitored carefully. This is a particularly problematic issue in SAD because of the high rate of comorbid substance abuse. Benzodiazepines may be best suited for patients with situational and performance anxiety on an as-needed basis.

## Buspirone

Buspirone showed promise during open-label studies of SAD but did not differentiate from placebo in controlled trials (Van Vliet et al. 1997). Data from open-label trials also suggest that buspirone may be used as an adjuvant with SSRIs when patients exhibit only partial response to monotherapy (Van Ameringen et al. 1996).

## Beta-Blocker Medication

Stein et al. (2001) conducted a double-blind, placebo-controlled crossover study of pindolol potentiation of paroxetine for the treatment of SAD. Pindolol was selected as an adjunct to SSRIs because it is a 5-$HT_{1A}$ autoreceptor antagonist besides being a beta-adrenergic receptor blocker. It is postulated that antagonism of the 5-$HT_{1A}$ autoreceptor would stimulate presynaptic release of serotonin. In fact, pindolol has been shown to accelerate the antidepressant response of SSRIs in some studies (Perez et al. 1997, Zanardi et al. 1997). Fourteen patients who were less than "very much improved" on CGI-I ratings after 10 weeks of maximally tolerated dose of paroxetine were randomized to receive 5 mg of pindolol t.i.d. or placebo for 4 weeks. After 4 weeks, subjects were tapered and crossed over to receive the other agent (pindolol or placebo) for another 4-week period. Pindolol augmentation was not more effective than placebo augmentation in this study.

## Anticonvulsant Medication

There are three double-blind, placebo-controlled studies evaluating the efficacy of anticonvulsant therapy for patients with SAD. Two of these studies were performed with either gabapentin or pregabalin. A third study was performed using levetiracetam. Pande et al. (1999) published a study where 69 patients with SAD were randomized for 14 weeks to receive either gabapentin (900–3600 mg/day) or placebo. In this study, 32% of patients randomized to flexible-dose gabapentin were considered responders versus 14% of patients receiving placebo. Pande et al. (2004) published a 10-week, double-blind, placebo-controlled trial of two fixed doses of pregabalin (150 mg/day or 600 mg/day). The 600 mg/day dose of pregabalin significantly reduced total scores on the LSAS when contrasted with placebo. The 600 mg/day dose was associated with a significant reduction in total fear, total avoidance, social fear, and social avoidance as measured on the brief social phobia scores. Zhang et al. (2005) published the results of a small, double-blind, placebo-controlled trial of levetiracetam for the treatment of SAD. Eighteen patients were randomized to receive a flexible dose of levetiracetam (500–3000 mg/day) or placebo for seven weeks. In this small study, the two groups did not significantly differ on response rates, BSPS scores or CGI-I scores. The authors did indicate that there were significant reductions in both the BSPS and CGI-I scores, but they felt the study was underpowered to demonstrate statistical significance. Further studies, especially maintenance studies, are still called for in order to determine the potential benefits of anticonvulsant therapy for patients with SAD.

## Treatment Conclusions

SSRIs, MAOIs, benzodiazepines, and venlafaxine XR have all been demonstrated to be effective pharmacotherapies for patients with SAD. Since all of the antidepressants can cause activation, it is important to start the initial titration at a very low dose and to taper the patient up over a period of weeks to months. There is some evidence to suggest that starting a benzodiazepine with a stimulating antidepressant may allow patients to tolerate the antidepressant more easily and may facilitate a more rapid titration of the antidepressant. Although these data are limited, this approach is widely practiced in many clinical settings.

SAD frequently requires not only pharmacotherapy, but also some form of adjunctive cognitive behavioral therapy in order to facilitate decreasing anxious behaviors. For individuals who cannot tolerate traditional antidepressants and who are fearful of benzodiazepines, there are some data supporting the use of anticonvulsants. Although none of the anticonvulsants are currently approved for treatment of SAD, gabapentin, pregabalin, and levetiracetam have all been reported to be efficacious for patients with SAD. As we had previously discussed with GAD, some individuals are not fully responsive to a first or second treatment intervention. There is a paucity of evidence-based data to guide further intervention, although many patients do seem to respond best to either combination therapy.

## Panic Disorder

### Selective Serotonin Reuptake Inhibitors

SSRIs are generally accepted as a first-line treatment for PD. The major advantage of these agents is their tolerability and thus longer term acceptance by patients. As of now there is evidence that fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram are effective in the acute treatment of PD.

There are two published large multicenter double-blind, placebo-controlled studies investigating the efficacy of fluoxetine versus placebo. Michelson et al. (1998) conducted a large multicenter double-blind, placebo-controlled trial investigating the efficacy of 10 or 20 mg/day fluoxetine versus placebo. Results suggested that fluoxetine reduced panic attack frequency, global distress, and agoraphobic distress. Patients with a CGI-Improvement score of (1) "very much improved" or (2) "much improved" at the end of the randomized, placebo-controlled trial were entered into a 24-week continuation study (Michelson et al. 1998). During this study patients either continued on active treatment or received placebo. Patients randomized to fluoxetine continued to improve during the course of 24 weeks while patients who were randomized to placebo demonstrated a marked exacerbation in symptoms and were more likely to meet criteria for a recurrence of PD (Michelson et al. 1999). A more recent study by Michelson et al. (2001) was a 12-week, randomized, placebo-controlled trial of fluoxetine (10–60 mg/day) conducted at nine sites in Europe. One hundred and eighty adult patients who met DSM-IV-TR criteria for PD and had a minimum of four full panic attacks in the month preceding entry into the study, and two full panic attacks during the 2-week baseline evaluation period, were randomized to treatment. Patients also had to have at least moderate symptom severity, as measured with the Panic Disorder Severity Scale (PDSS), and a CGI-Severity rating of 4 or greater. Fluoxetine was initiated at 10 mg/day for week 1 and increased to 20 mg/day until week 6. Patients who had not achieved a CGI-Severity score of 2 or less were, at week 6, increased to 40 mg/day. Fluoxetine could be further increased to 60 mg/day. Fluoxetine was statistically superior to placebo at both the 6-week point and at study endpoint. Fluoxetine-treated patients also had statistically significant improvement on the Sheehan Disability Scale (SDS). The final mean daily dose of fluoxetine was only 29.6 mg/day. Reports of adverse events among the placebo and fluoxetine groups were similar and low.

Four large multicenter trials investigating the efficacy of sertraline in the treatment of PD have been published. Two studies were placebo-controlled, fixed-dose trials and two studies were placebo-controlled, flexible-dose studies. In the flexible-dose sertraline trials, patients were started on 25 mg/day for the first week and then the dose was escalated to 50 mg/day of sertraline. Sertraline-treated patients experienced significant reductions in panic attack frequency, CGI-Improvement and Severity Scales, the PDSS, the Patient Global Evaluation (PGE) Rating Scale, and the Q-LES-Q (Londborg et al. 1998, Pollack et al. 1998, Rapaport et al. 1998). Sertraline was also found to be efficacious in fixed dose with the 150 mg/day dose seeming to be the most effective dose in these studies (Dubuff et al. 1995). There is one large multicenter long-term trial by Rapaport et al. (2001) where individuals who initially entered 10-week treatment trials were then offered 1 year of open-label treatment of sertraline and responders were then entered into a double-blind, 26-week placebo discontinuation trial. Frequency of panic attacks was recorded by patients in panic attack diaries. Clinically significant deterioration was examined over the course of the double-blind phase; deterioration was specified as (1) relapse, (2) discontinuation due to insufficient clinical response, and (3) exacerbation of panic symptomology. At the end of 26 weeks of double-blind treatment, patients randomized to placebo were twice as likely to discontinue due to lack of efficacy than patients treated with sertraline. Similarly, 13% of sertraline patients experienced acute exacerbation of panic symptoms versus 30% of placebo patients. These data demonstrated that maintenance treatment with sertraline was associated with continued improvement and protected patients from recurrence (Rapaport et al. 2001). The mean daily dose of sertraline was 112.1 mg/day. A head-to-head comparison trial was conducted by Bandelow et al. (2004), comparing paroxetine to sertraline. Two hundred twenty-five patients with PD were randomly assigned in a double-blind study to paroxetine 40–60 mg/day or sertraline 50–150 mg/day. Patients were assessed with the Panic and Agoraphobia Scale (PAS) scores, CGI-I (responders defined as those with a score ≤ 2), and panic attack frequency. At endpoint, paroxetine and sertraline were associated with equivalent levels of improvement on the PAS total score, as well as all secondary measures. Seventy-eight percent of patients taking paroxetine and 82% of patients taking sertraline were CGI-I responders. Paroxetine and sertraline had equivalent efficacy in the acute treatment of PD, but sertraline treatment had less weight gain and less clinical worsening during taper phase.

There have been a number of double-blind, placebo-controlled multicenter studies demonstrating the efficacy of paroxetine for the treatment of PD. Ballenger et al. (1998) reported that 40 mg/day of paroxetine was more effective than placebo in reducing panic attacks and the symptoms of PD. In one large multicenter European trial, paroxetine (20–60 mg/day) was contrasted with clomipramine (50–150 mg/day) and placebo. Both active treatments were more effective than placebo in reducing the number of panic attacks. The paroxetine group also seemed to have a more rapid onset of action and reported fewer side effects (Lecrubier et al. 1997). Patients who completed the study were entered into a 9-month extension study; subjects treated with paroxetine and clomipramine demonstrated continued improvement over time (Lecrubier and Judge 1997). A head-to-head comparison trial of paroxetine and citalopram was conducted by Perna et al. (2001). Fifty-eight patients with PD were randomly assigned to one of the two active treatments (both 10–50 mg/day) in a single-blind design. Patients were assessed by the PASS, the SDS, and the FQ at baseline, day 7, and day 60. Responders were defined by a reduction of at least 50% from baseline on both PASS and SDS global scores at day 60. At endpoint, 84% of patients receiving paroxetine and 86% of patients receiving citalopram responded. PASS total scores decreased from 9.3 ± 4.9 at baseline to 3.5 ± 4.6 at day 60 for the paroxetine-treated group, and from 8.7 ± 3.7 at baseline to 3.1 ± 3.0 at day 60 for the citalopram group. Only one patient from each group dropped out because of side effects. Sheehan et al. (2005) published a pooled analysis that combined three identical trials investigating the efficacy

and tolerability of controlled-release paroxetine (paroxetine CR) treatment of adults with PD. Subjects were randomly assigned to paroxetine CR (25–75 mg/day; $n = 444$) or placebo ($n = 445$) in these double-blind, 10-week clinical trials. The primary outcome measure used was the percentage of patients who were free of panic attacks in the 2 weeks prior to endpoint. Sixty-three percent of paroxetine CR treated subjects were panic free as compared to 53% of placebo-treated subjects ($p < 0.005$). Adverse events leading to study withdrawal were minimal and occurred in 11% of the paroxetine CR group and 6% of the placebo group.

Several smaller placebo-controlled trials and one large multicenter placebo-controlled acute trial have been published demonstrating that citalopram is an effective treatment of PD. In the large multicenter study of citalopram, placebo, and clomipramine, 475 patients were randomized to 8 weeks of treatment. The patients received three flexible doses of citalopram and one of clomipramine. All three doses of citalopram (10–60 mg/day) and clomipramine (60–90 mg/day) were more effective than placebo in decreasing panic attacks to zero and decreasing phobic symptoms. The 20–30 mg/day dose of citalopram seems to be the most effective of the doses (Wade et al. 1997). Patients, who in the physician's judgment were responders in the acute trial, were offered continued double-blind treatment for 10 months. In this double-blind continuation study, citalopram was demonstrated to be more effective than placebo in decreasing phobic avoidance and interpersonal sensitivity (Leinonen et al. 1999). A number of studies report that fluvoxamine is more effective than placebo for the treatment of PD (Boshuisen et al. 2001, Hoehn-Saric et al. 1993). Asnis et al. (2001) performed an 8-week, double-blind, parallel-group study comparing fluvoxamine with placebo in 188 patients with DSM-III-R defined PD (with or without agoraphobia). Patients in this study were required to have at least one panic attack per week for at least 4 weeks. Patients were randomized to double-blind treatment if they had an average weekly panic attack severity score of 25 (of attacks × severity 0–10) and had at least one full panic attack in the final week of placebo washout. Treatment was initiated at 50 mg/day of fluvoxamine or placebo. It was titrated upward to 150 mg/day during the first 2 weeks. Thereafter, it was titrated to 300 mg/day as needed, based on side effects and efficacy. Fluvoxamine was significantly superior to placebo at endpoint on three of four primary outcome measures: proportion of patients free from full panic attacks, percentage reduction in frequency of full panic attacks per week, and PD severity. Fluvoxamine was superior to placebo with respect to a global improvement in CGI-Severity Scale scores, 64% versus 42%. Pollack et al. (2003) extended Goddard and colleagues' work by investigating the acute and continuation efficacy of combination treatment with benzodiazepines and SSRIs. In a double-blind, three-arm study, 60 patients with PD were randomized to paroxetine and placebo (PP), paroxetine coadministered with clonazepam followed by a tapered benzodiazepine discontinuation phase (PC-D), or paroxetine plus clonazepam with ongoing combination treatment (PC-M). All treatment groups demonstrated significant improvement by endpoint (PP 68.2%; PC-M 60.0%, PC-D 77.8%). However, the results of this should be interpreted cautiously since this is a moderate size study and there was a high rate of early termination (60 subjects at baseline with only 34 study completers). Combined treatment with paroxetine and clonazepam resulted in more rapid response than with the SSRI alone, but there was no differential benefit beyond the initial few weeks of therapy. This suggests that combined treatment followed by benzodiazepine taper may provide early benefit while avoiding the potential adverse consequences of long-term combination therapy.

In summary, the majority of data suggests that SSRIs as a class are effective in the treatment of PD. One of the advantages of SSRIs is that they tend to be fairly well tolerated in contrast to some of the other treatments available for PD. Although a few individuals may have some initial problems with restlessness and increased anxiety, data suggest that starting at lower doses such as 25 mg/day of sertraline or 10 mg/day of paroxetine may decrease the risk of antidepressant "jitteriness." Patients will certainly experience other types of side effects such as headaches, nausea, and diarrhea. However, most of these side effects diminish with time and are well tolerated, particularly if the patients are informed of the possibility of these transient side effects. As is the case with our pharmacotherapies for other types of medical disorders, there will certainly be a need to fine-tune a treatment of PD as one sees patients over time.

## Serotonin–Norepinephrine Reuptake Inhibitors—Venlafaxine and Reboxetine

There are several double-blind, placebo-controlled studies (Pollack et al. 1996, Bradwejn et al. 2005) suggesting that venlafaxine may be an effective treatment for patients with PD. Bradwejn et al. (2005) studied 361 adult outpatients with PDs. Subjects were randomly assigned to receive venlafaxine ER (75–225 mg/day) or placebo for up to 10 weeks in a double-blind study. Venlafaxine was associated with lower mean number of panic attacks (venlafaxine −5, placebo −3.7), higher response (venlafaxine 68.1% and placebo 55.4%) and remission rates (venlafaxine 35.6%, placebo 24.4%) in CGI-I. Pollack et al. (2007) were first to report a large-scale, controlled trial of venlafaxine XR, paroxetine, and placebo. Six hundred sixty-four nondepressed adult outpatients who met DSM-IV-TR criteria for PD (with or without agoraphobia) were randomly assigned to 12 weeks of treatment with placebo, or fixed doses of venlafaxine XR (75 or 150 mg/day), or paroxetine 40 mg/day. The primary efficacy measure was the percentage of patients free from full-symptom panic attacks, assessed with the PAAS. Response was defined as a CGI-I rating of very much improved or much improved; remission was defined as a CGI-S rating of not at all ill or borderline ill and no PAAS full-symptom panic attacks. Measures of depression, anxiety, phobic fear and avoidance, anticipatory anxiety, functioning, and quality of life were also assessed. Intent-to-treat, last-observation-carried-forward analysis showed that mean improvement on most measures was greater with venlafaxine XR and paroxetine than with placebo. No significant differences were observed between active treatment groups. Panic-free rates at endpoint ranged from 54% of those treated with venlafaxine XR and 61% of those treated with paroxetine, compared with 35% for placebo. Approximately 75% of patients given active treatment were responders, and nearly 45% achieved remission. The placebo response rate was approximately 55%, and the remission rate approximately twenty-five percent.

There have been a few studies suggesting that reboxetine is effective in the treatment of PD. Versiani et al. (2002) conducted a multicenter, randomized, placebo-controlled, parallel-group, double-blind clinical trial conducted in Brazil and Italy. Eighty-two patients with DSM-III-R diagnosis of PD with or without agoraphobia and who had experienced at least four panic attacks in the month preceding their admission to the study were included in the study. Participants had an initial 7-day washout period and then were randomly assigned to receive 6–8 mg/day of reboxetine or placebo for 8 weeks. Primary parameters of efficacy were the mean number of total panic attacks symptoms (spontaneous and situational) per week (as measured by the Sheehan Panic Attack and Anxiety Scale [SPAAS]), the global scores of severity and phobic symptomatology (Phobia Scale), and the score on the CGI. Efficacy measurements were determined by comparing baseline and last assessment scores. The study revealed that there was a significant reduction in the mean number of panic attacks and phobic symptoms in the reboxetine group compared with the placebo group. Consistent with the reduction of both major panic attacks and improvement in phobic symptomatology, significantly greater improvement in mean CGI scores for severity of illness was observed for patients in the reboxetine group (5.2 at baseline vs. 2.5 at last assessment) compared with those in the placebo group (5.0 at baseline vs. 3.8 at last assessment; $p = 0.0002$).

## Tricyclic Antidepressant Medication and Monoamine Oxidase Inhibitors

Imipramine was the first TCA noted to effectively treat panic attacks and PD and is one of the best studied TCAs (Boyer 1995, Klein 1964, Klein and Fink 1962). Double-blind, placebo-controlled trials of desipramine and nortryptiline have also been performed (Kalus et al. 1991, Lydiard et al. 1993, Munjack et al. 1988); however, clomipramine has been the TCA most widely studied. There are a large number of double-blind, placebo-controlled trials demonstrating clomipramine's efficacy as a treatment for PD (Calliard et al. 1999, den Boer 1998). Interestingly, there are a number of both placebo-controlled and crossover design studies suggesting that clomipramine may be more efficacious than imipramine in the treatment of PD (Cassano et al. 1988, Modigh et al. 1992, Sasson et al. 1999). In contrast to these data demonstrating clomipramine's efficacy, studies with maprotiline, a noradrenergic reuptake inhibitor, failed to differentiate from placebo (den Boer and Westenberg 1988). Longitudinal data suggest that patients who achieve complete remission with imipramine treatment will maintain their remission with continuous treatment (Mavissakalian and Perel 1992b). Mavissakalian and Perel (1992a) demonstrated that patients who met stringent remission criteria for at least 6 months could sustain their panic-free status even after their imipramine dosage was decreased by 50%. This finding is particularly important because such a dosage reduction might increase tolerability and thus the adherence of patients to therapy. Longer term adherence is important because Mavissakalian and Perel (2001) found that the longer periods of panic-free maintenance therapy were associated with a greater likelihood of remaining in remission after discontinuation of imipramine therapy. Eighteen patients participated in the second year of a double-blind extension study, 7 patients in the placebo group continued on placebo, 7 of the imipramine group were switched to placebo, and 4 continued with imipramine. Two patients from the imipramine–placebo switch group relapsed and two patients in the placebo continuation group relapsed. None of the imipramine continuation group subjects relapsed. This suggests that there may actually be an advantage of continued prophylaxis beyond the first year of maintenance imipramine therapy.

TCAs, unfortunately, are associated with a significant side effect burden. There is a problem with jitteriness associated with the initiation of TCAs. This jitteriness is frequently frightening and may be intolerable for some patients with PD. It requires that TCAs be started at very low doses and titrated up very slowly. Other problems with TCAs that decrease adherence include anticholinergic side effects, orthostatic hypotension, sexual dysfunction, and weight gain. In a naturalistic follow-up study by Noyes et al. (1989), the majority of patients discontinued TCA treatment because of side effects (Noyes et al. 1996). Although TCAs have been widely used for the treatment of PD, their side effect profile and slow time to onset of action makes them a difficult class of medication for many patients to tolerate.

The first-generation MAOIs such as phenelzine and tranylcypromine have been demonstrated to be effective in placebo-controlled trials (Sheehan et al. 1980). There are also a variety of smaller studies demonstrating that RIMAs, moclobemide, and brofaromine are effective in the treatment of PD (Bakish 1992, Kruger and Dahl 1999, Tiller et al. 1999, Van Vliet et al. 1993). Unfortunately, it is unlikely that either of the newer reversible and selective MAOIs will be available in the US. Therefore our pharmacotherapy is limited to the older irreversible and nonselective agents.

The irreversible and nonselective agents have problems with dietary restrictions, weight gain, insomnia, sexual dysfunction, medication interactions, and orthostasis. They can be lethal in overdose and hypertensive crises can be precipitated by tyramine-rich food and by some commonly sold over-the-counter cold medicines. Despite these concerns, many expert clinicians feel that MAOIs may be a useful treatment for severely ill patients with PD, particularly those with comorbid PD and depressive disorder.

## Other Antidepressant Medication (Bupropion, Mirtazapine, Nefazodone, Trazodone)

There have been a few double-blind trials of bupropion and trazodone for the treatment of PD, but neither was found to be more effective than placebo (Charney et al. 1986, Sheehan et al. 1983). Case series and some small studies suggest, however, that mirtazapine and nefazodone may be effective treatments for patients with PD (Carpenter et al. 1999, DeMartinis et al. 1996, Falkai 1999, Papp et al. 2000). Ribeiro et al. (2001) compared mirtazapine and fluoxetine in a randomized double-blind, flexible-dose trial of 27 patients with DSM-IV-TR PD. Participants were required to have a minimum of three panic attacks during the 2 weeks before enrollment into the study. Patients had to have a score greater than 18 on the HAM-A, and could not have been previously treated with mirtazapine. Following a 1-week, single-blind, placebo run-in, patients were randomly assigned to mirtazapine 15 mg/day or fluoxetine 10 mg/day. At week 3, doses could be raised to 30 mg/day of mirtazapine or 20 mg/day of fluoxetine according to clinical response. Each patient maintained

a self-report diary of panic attacks. Clinician-rated assessments included the CGI-Severity and CGI-Improvement Scales, and the HAM-A. The Sheehan Phobic Scale provided patient global evaluation of phobic anxiety. Fourteen were treated with mirtazapine and 13 were treated with fluoxetine. Three patients treated with mirtazapine and two patients treated with fluoxetine dropped out because of side effects. Among completers, the mean daily dose of mirtazapine was 18.3 ± 1.3 mg/day and was 14.0 ± 1.0 mg/day for fluoxetine. HAM-A scores decreased from 15.7 ± 10.0 at baseline to 10.7 ± 11.2 at endpoint for the mirtazapine, and from 28.8 ± 6.5 at baseline to 11.8 ± 7.5 at endpoint for fluoxetine-treated subjects. In both groups, the number of panic attacks decreased from three at baseline to zero at endpoint, suggesting that both medications eliminated spontaneous panic attacks.

## Benzodiazepine Medication

There are two high potency benzodiazepines that have been approved by the FDA and are widely used in the treatment of PD. The first high potency benzodiazepine to be approved was alprazolam. Alprazolam has a relatively short half-life, requires frequent dosing (up to four times a day), and may cause significant discontinuation problems in some patients. In the Cross-National Collaborative Panic Disorder Study, alprazolam at a mean dose of 5.7 mg/day was found to be more effective than placebo in decreasing the number of panic attacks and allowing patients to become free from panic attacks (Ballenger et al. 1988). In phase 2 of the Cross-National Collaborative Panic Study (1992), 1,168 PD patients were randomized to receive either alprazolam, imipramine, or placebo. Both imipramine and alprazolam were more effective in treating PD than placebo. Rickels and Schweizer (1998) have published a number of papers comparing alprazolam to imipramine and placebo. In a recent report of an acute 8-week study, they found that alprazolam and imipramine were equally effective in treating PD but there were a large number of dropouts in the imipramine-treatment group. During a 6-month maintenance phase, 62% of alprazolam-treated patients completed the study and were panic free in contrast to only 26% imipramine-treated and placebo-treated patients. The 15-month follow-up of the same cohort found that 85% of patients who completed the maintenance phase study remained panic free in contrast to 55% of patients who were not able to complete the maintenance study. In general, alprazolam has been demonstrated in both short-term and long-term studies to be effective. There has been considerable concern about the risk of dependency and also the difficulties discontinuing alprazolam for a significant minority of patients.

Although clonazepam has been used for the treatment of PD for a long time, it was not until the 1990s that two large definitive multicenter double-blind, placebo-controlled studies demonstrated clonazepam's efficacy for patients with PD. In a large fixed-dose study, 413 patients were randomized to receive one of five doses of clonazepam (0.5 mg/day, 1.0 mg/day, 2.0 mg/day, 3.0 mg/day, 4.0 mg/day) or placebo. There was a 3-week dosage escalation period followed by 6 weeks of fixed-dose therapy and then a 7-week discontinuation phase. Doses of clonazepam greater than 1 mg were effective in decreasing the number of panic attacks and were well tolerated. There was some exacerbation of symptoms experienced by patients during the double-blind discontinuation phase, but patients with these symptoms did not approach the initial baseline level of dysfunction (Rosenbaum et al. 1997). In a flexible-dose study, 222 patients were randomized to clonazepam treatment and 216 patients received placebo. Patients randomized to clonazepam had a decrease in the number of panic attacks and an improvement in CGI-Severity scores. Clonazepam was well tolerated but there was some worsening of symptoms during the discontinuation phase (Moroz and Rosenbaum 1999). There were no significant adverse effects associated with longer term clonazepam treatment (Pollack et al. 1997). Goddard et al. (2001) looked at early coadministration of clonazepam with sertraline for PD in a double-blind trial of 50 patients. Patients received open-label sertraline for 12 weeks (target dose of 100 mg/day) and were randomized to receive either 0.5 mg/day of clonazepam three times a day or placebo for the first 4 weeks of the trial. Response rates were markedly different at the end of week 1 with 41% of sertraline/clonazepam patients responding to treatment versus 4% of sertraline/placebo patients. At week 3, 63% of sertraline/clonazepam patients responded versus 32% of sertraline/placebo patients. Katzenick et al. (2006) investigated combination therapy with alprazolam ODT and SSRI/SNRI compared with SSRI/SNRI monotherapy. Two hundred forty-five subjects diagnosed with PD, with or without agoraphobia, were randomized to 8 weeks of open-label treatment with alprazolam. The primary efficacy measure was time to response, a ≥50% decrease from baseline in HAM-A total score. Secondary measures included change from baseline in HAM-A total scores, CGI-I, and PGI scales. Statistically significant difference between treatment groups in time to response was not found. Analyses did reveal that combination treatment was statistically significantly more likely to show an earlier response than monotherapy ($p < 0.05$). Combination treatment also demonstrated that a significantly higher proportion of subjects met response criteria than those receiving monotherapy (35% vs. 22%, $p < 0.05$). Additionally, combination treatment demonstrated statistically significant earlier improvement than monotherapy on the mean change from baseline in total HAM-A, CGI-I, and PGI scores. Both treatment regimens were generally well tolerated.

Other benzodiazepines have also been demonstrated to be effective in the treatment of PD. In an 8-week, double-blind, placebo-controlled trial, alprazolam (4.9 mg/day) and diazepam (40 mg/day) were equally effective and superior to placebo for the treatment of PD (Noyes et al. 1996). In a smaller comparative study, lorazepam was as effective as alprazolam in the treatment of PD (Schweizer et al. 1988). In summary, it is clear that two high potency benzodiazepines, alprazolam and clonazepam, are effective in the treatment of PD. There also are data suggesting that a number of the other benzodiazepines may be useful in the treatment of PD. Unfortunately, there are concerns about dependency and stigma associated with the use of benzodiazepine medication.

## Buspirone

There is a case report suggesting that buspirone may be a useful adjuvant in some patients with treatment-resistant PD (Gastfriend and Rosenbaum 1989). In general, buspirone is not thought to be an effective monotherapy for PD.

### Anticonvulsant Medication

There are published case reports, case series, and small studies investigating at least five different anticonvulsant medications. Sandford et al. (2001) conducted a small randomized, double-blind, placebo-controlled crossover trial of pagoclone versus placebo in 16 patients with PD. Pagoclone is believed to act as a partial agonist at the $GABA_A$ benzodiazepine receptor. Patients were randomized to receive either pagoclone 0.1 mg t.i.d. during weeks 1 and 2 or pagoclone 0.1 mg t.i.d. during weeks 4 and 5. There was a decrease in the number of full panic attacks from baseline among pagoclone-treated patients but not among placebo patients. This decrease was observed for patients receiving pagoclone regardless of whether they received it in the first or second crossover arm; however, this difference did not reach statistical significance.

Zwanzger et al. (2001) investigated the putative anxiolytic properties of tiagabine in a clinical case series. Tiagabine has been shown to reduce neuronal excitability by increasing brain GABA levels, by inhibiting GABA reuptake. Four patients meeting DSM-IV-TR criteria for PD were treated. All patients reported a reduction of panic attacks and improvement in anxiety levels within 4 weeks, although one patient discontinued treatment because of side effects.

There are some scattered reports suggesting that the valproic acid and gabapentin maybe useful, particularly in either atypical or treatment-resistant patients with PD (Keck et al. 1993, Woodman and Noyes 1994).

Papp (2006) reported the results of an open-label, flexible-dose study of levetiracetam treatment for 18 subjects meeting criteria for PD with or without agoraphobia. Eighteen patients completed this 3-month, open-label study and 85% of them were rated very much or much improved on the CGI-I. Panic attack frequency, total HAM-A scores, and CGI-S scores decreased significantly during these 12 weeks of open-label treatment. Median dose of levetiracetam used in the study was 1138 mg/day. The most common side effects were sedation, headaches, and some irritability.

### Antipsychotic Medication

The largest study to date investigating the efficacy of atypical antipsychotic medication augmentation of SSR-resistant PD was published by Sepede et al. (2006). In this study of 31 adult outpatients with PD who were unresponsive to standard SSRI treatment, subjects were given 5 mg/day of olanzapine. Twenty-six patients completed this 12-week, open-label study. By week 12, 82% of patients were defined as responders and demonstrated significant improvement on all the rating scales. Fifteen patients achieved remission status (no panic attacks and a HAM-A total score of less than 7). Common side effects in this 12-week study were weight gain and drowsiness. Further double-blind, placebo-controlled trials of atypical antipsychotic medication augmentation of SSRIs in resistant PD are needed.

### Treatment Conclusions

Although panic attacks are a cardinal feature of PD, there are many patients who suffer from PD but rarely have spontaneous panic attacks. These individuals are plagued by problems with anxiety sensitivity and anticipatory anxiety. In general, patients with PD, with or without agoraphobia, tend to be exquisitely sensitive to their body's somatic cues, and therefore they are remarkably sensitive to all of the potential somatic effects of pharmacotherapy. Clinicians treating patients with PD must help their patients have a sense of control and mastery as pharmacotherapy is initiated. One approach to ensuring that this occurs is to enlist the patient as an active participant in monitoring both the potential positive and negative effects of pharmacotherapy. At this time, there are a host of effective short-term treatments for PD including the SSRIs as a class, venlafaxine XR, MAOIs, TCAs, and benzodiazepines. SSRIs and SSNIs are generally accepted as first-line treatments for PD. However, if one does not daily, gradually titrate a patient with PD up on these medications, one can assure noncompliance due to their side effect burden. A second pharmacological technique that has been effective for patients who suffer from PD is to coadminister a small dose of a long-acting benzodiazepine such as clonazepam or alprazolam XR with an antidepressant, and then withdraw the benzodiazepine over a period of several weeks, after the patient has reached a therapeutic dosage of the antidepressant.

Panic attacks may be effectively controlled relatively early in the course of treatment; however, anticipatory anxiety and somatic sensitivity take significantly longer to resolve. Some form of behavioral intervention, even a brief one in a medication management session, can facilitate more rapid improvement in anticipatory anxiety and phobic behavior. Aside from the widely used augmentation of antidepressants with benzodiazepines, there are very few data guiding our choice of second- and third-line approaches to the treatment of patients with PD.

## Posttraumatic Stress Disorder

### Selective Serotonin Reuptake Inhibitors

There have been several open-label and double-blind, placebo-controlled studies demonstrating that SSRIs are effective for the treatment of PTSD. Open-label trials with the SSRIs currently available suggest that each may be effective in decreasing the core symptoms of PTSD. Three of the SSRIs have been studied in a double-blind, placebo-controlled fashion. Fluoxetine was the first of the SSRIs to be studied in randomized, controlled trials. In two small studies, civilian patients treated with fluoxetine demonstrated significant improvement as compared with placebo treatment. In one of these trials, Van der Kolk et al. (1994) included a veteran cohort as well; fluoxetine did decrease symptoms of PTSD in the veteran subgroup. Martenyi et al. (2002) conducted a double-blind, randomized study comparing fluoxetine and placebo's effects on relapse prevention in 131 subjects meeting DSM-IV-TR criteria for PTSD. Subjects underwent 12 weeks of acute treatment; subjects who responded were rerandomized and continued in a 24-week relapse-prevention phase with fluoxetine or placebo. Subjects in the fluoxetine/fluoxetine group were found less likely to relapse than those in the fluoxetine/placebo group ($p = 0.027$).

Two SSRIs have been approved by the FDA for the treatment of PTSD. The first agent approved for the treatment of PTSD is sertraline. There have been two published large placebo-controlled acute treatment trials of sertraline for noncombat-related PTSD. In these studies, Davidson et al. (2001) and Brady et al. (2000) found that sertraline

was more effective than placebo treatment in decreasing the Clinician Administered Posttraumatic Stress Disorder Scale 2 (CAPS-2), the patient-rated Impacts of Events Scale, and the CGI-Severity and Improvement Rating Scales. Both of the studies were flexible-dose studies where 50–200 mg/day of sertraline was administered. Londborg et al. (2001) published open-label continuation data for individuals who had participated in these acute trials (Davidson et al. 2001). They demonstrated that patients who responded during the acute phase not only maintained their response but continued to improve after 6 months of continuation treatment. Fifty-four percent of individuals who did not acutely respond to SSRI treatment during the initial 12-week trial had a significant decrease in their CAPS-2 scale scores by the end of 6 months of open-label treatment. Davidson et al. (2001) reported the results of the placebo discontinuation phase of this study. Individuals who responded to 6 months of open-label therapy were rerandomized to receive double-blind treatment with sertraline or placebo. Placebo discontinuation was associated with a significant risk of relapse (26% vs. 5%) and reemergence of the core symptoms of PTSD. Rapaport et al. (2002) investigated the effects of sertraline treatment on quality of life in the samples described in the Londborg et al. (2001) and Davidson et al. (2001) studies. By the end of the 12-week acute phase, 58% of sertraline responders had achieved Q-LES-Q total scores within 10% of community norms and had shown significant improvement on the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) subscale scores. Continuation of treatment resulted in a further 20% improvement in quality-of-life and psychosocial measures. During the double-blind maintenance phase, randomization to placebo was associated with significant worsening of Q-LES-Q scores and quality of life. These findings from Davidson et al. (2001), Londborg et al. (2001), and Rapaport et al. (2002) suggest that some patients with PTSD will require sustained SSRI treatment, possibly for years, in order to protect them from exacerbation of PTSD. Zohar et al. (2002) conducted a double-blind, placebo-controlled pilot study of sertraline (50–200 mg/day) in military veterans with PTSD. Forty-two patients were randomized to 10 weeks of sertraline or placebo. Primary efficacy measures included the CAPS-2 and CGI-I. Although the sertraline treatment group demonstrated improved scores on the CAPS-2, no statistically significant difference was observed. At study endpoint, mean CGI-I scores were lower in the sertraline-treated group compared to placebo (2.4 ± 0.3 for sertraline and 3.4 ± 0.3 for placebo ($p = 0.016$). CGI-I responders rates were 53% for sertraline and 20% for placebo ($p = 0.057$) and combing CGI-I and CAPS-2 responders rates (≥ 30% reduction in baseline CAPS-2 score) were 41% for sertraline and 20% for placebo ($p = 0.238$). Sertraline was well tolerated and may be an effective treatment for patients with combat-related PTSD, although larger studies are needed to confirm these results.

Paroxetine is also approved as an acute treatment for PTSD by the FDA. There has been one fixed-dose study demonstrating that both 20 and 40 mg/day of paroxetine were more effective than placebo for the treatment of PTSD (Marshall et al. 2001). In this study, patients treated with paroxetine had significantly greater improvement in the CAPS-2 and were more likely to have CGI-Improvement Scale scores of (2) "much improved" or (1) "very much improved." In the 12-week flexible-dose study, 20–50 mg of paroxetine treatment was more effective than placebo treatment in decreasing the CAPS-2 scale, the Davidson Trauma Scale, and the SDS (Tucker et al. 2001).

In conclusion, data from open-label studies and double-blind, placebo-controlled studies suggest that SSRIs, as a class, are effective in the treatment of PTSD. In addition, longer term research with fluoxetine and sertraline confirms the continued benefit with extended treatment.

## Serotonin–Norepinephrine Reuptake Inhibitors—Venlafaxine and Reboxetine

Davidson et al. (2006b) compared and contrasted venlafaxine ER, sertraline, and placebo in a 12-week, double-blind, randomized, flexible-dose, multicenter trial of adult outpatients. Patients met DSM-IV-TR PTSD criteria of at least 6 months duration and had a score >60 on the Clinician Administered PTSD Scale (CAPS-SX-17). Subjects were randomly assigned to receive placebo, venlafaxine ER (37.5–300 mg/day, mean maximum dose 225 mg/day), or sertraline (25–200 mg/day, mean maximum dose 151 mg/day). Mean changes in CAPS-SX-17 scores were −41.8, −39.4, and −33.9 for venlafaxine ER ($p < 0.05$ vs. placebo), sertraline, and placebo, respectively. Week 12 remission rates were 30.2% for the venlafaxine XR group ($p < 0.05$ vs. placebo), sertraline 24.3%, and placebo 19.6%. Davidson et al. (2006a) also conducted a 6-month, double-blind, placebo-controlled trial, multisite study of venlafaxine ER with 329 adult outpatients. Patients were randomly assigned to placebo or venlafaxine ER (37.5–300 mg/day, mean maximum dose 221.5 mg/day) for 24 weeks. Mean changes from baseline to CAPS-SX-17 total scores at endpoint were −51.7 for venlafaxine ER and −42.9 for placebo ($p = 0.006$). Results from these studies suggest that venlafaxine ER is an effective short- and long-term (6-month) treatment for PTSD.

Spivak et al. (2006) compared reboxetine (8 mg/day) and fluvoxamine (150 mg/day) in the double-blind treatment of 40 patients presenting with motor vehicle accident-related PTSD. Both medications led to significant improvement in CAPS-2 scores during the 8-week study, with no significant differences between the treatment groups. In this fixed-dose study, fluvoxamine treatment was associated with lower withdrawal rates than reboxetine.

## Tricyclic Antidepressant Medication and Monoamine Oxidase Inhibitors

There are several small double-blind, placebo-controlled trials suggesting that both amitriptyline and imipramine are more effective than placebo in decreasing signs and symptoms of PTSD. However, after the advent of SSRIs that have significant safety and tolerability advantages, additional studies with TCAs were not pursued (Davidson et al. 1990, Kosten et al. 1991).

There is little literature suggesting that MAOIs are more effective than placebo in the treatment of PTSD. The two best studied MAOIs are the irreversible nonselective MAOI phenelzine and the reversible selective MAOI, brofaromine. Placebo-controlled studies by Kosten et al. (1991) and Davidson et al. (1987) suggest that phenelzine is more effective than placebo in decreasing symptoms of PTSD. Their findings have been supported by work of Lerer et al. (1987), who demonstrated that phenelzine was a beneficial treatment for veterans with PTSD. As summarized by

Stein et al. (2000), there have been several studies investigating the efficacy of brofaromine in the treatment of PTSD. International studies with brofaromine have demonstrated that it was more effective than placebo, while the initial work performed in the US differentiated brofaromine from placebo treatment. Although failed studies are not uncommon, this has unfortunately led to a discontinuation of the research program with brofaromine in the US. A third reversible selective MAOI is moclobemide. Moclobemide, fluoxetine, and tianeptine were compared and contrasted in a 12-week, open-label, randomized, flexible-dose study of 103 subjects who met DSM-IV-TR criteria for PTSD (Onder et al. 2006). The primary measure of efficacy was the CAPS. All three treatments led to a significant improvement in PTSD severity (CAPS; $p < 0.001$). CAPS subscales, reexperiencing, avoidance, and hyperarousal were significantly reduced by all three treatments (all $p < 0.001$). There was no significant difference observed in treatment effect between the three treatment groups.

## Other Antidepressant Medication (Bupropion, Mirtazapine, Nefazodone, Trazodone)

Davis et al. (2004) conducted a 12-week, double-blind, placebo-controlled study of nefazodone's effects on chronic PTSD. Forty-one individuals enrolled in this study, where all but one patient suffered from combat-related PTSD. Patients were given either placebo or 100–600 mg nefazodone twice daily. After 12 weeks, subjects showed significant improvement on CAPS total score, as well as the CAPS hyperarousal criterion and HAM-D scores. No significant between-group differences were found on the other study efficacy measures. Future placebo-controlled studies should be conducted, for this study had a high attrition rate that may have affected its results.

Two studies have compared the efficacy of nefazodone versus sertraline (McRae et al. 2004, Saygin et al. 2002), with mixed results. Saygin et al. (2002) recruited 60 outpatients suffering from PTSD relating to an earthquake trauma and randomized them to flexible doses of nefazodone (200–400 mg/day) or sertraline (50–100 mg/day) for 5 months. Both medications produced similar improvement in symptoms, as measured by CGI scores, but sertraline scores on the 8-item Treatment-Outcome Posttraumatic Stress Disorder Scale (TOP-8) reached significance over TOP-8 scores for nefazodone-treated patients. In a shorter, 12-week study, McRae et al. (2004) randomized 37 patients to either 25–100 mg sertraline given twice daily or 50–300 mg nefazodone given twice daily. Both medications significantly reduced PTSD symptoms, with no statistical difference between treatment groups on outcome measures, which included the 17-item CAPS-2 severity score, CGI-I, Davidson Trauma Scale (DTS), TOP-8, SDS, MADRS, HAM-A, and Pittsburgh Sleep Quality Index (PSQI). These trials suggest that nefazodone and sertraline may be equally effective for short-term treatment of PTSD symptoms, with sertraline separating from nefazodone in longer continuation treatment.

There have also been six open-label studies investigating the efficacy of nefazodone in PTSD. The overall results of these six trials are summarized in a paper by Hidalogo et al. (1999), where they suggest that nefazodone treatment has decreased the core symptoms of PTSD, improved sleep, and decreased symptoms of anger. Among these six open-label studies, three of them focused on patients who were veterans with chronic PTSD. Both Davis et al. (2000) and Hertzberg et al. (1998) found that open-label nefazodone treatment decreased core symptoms of PTSD. Zisook et al. (2000) demonstrated that open-label nefazodone treatment was helpful for patients who were refractory to SSRI treatment for PTSD. In all of the open-label studies, nefazodone was titrated to what was considered to be a clinically effective dose, in the 400–600 mg/day ranges. Recently, the FDA revised nefazodone's labeling to include a warning of rare cases of liver failure in patients receiving this medication, but none of the aforementioned studies found any adverse hepatic events during the course of the studies.

Kim et al. (2005) investigated the effectiveness of mirtazapine during an open-label, 24-week continuation treatment study ($n$=12). The results from this study suggest that mirtazapine may be effective in short- and long-term treatment of PTSD. Mirtazapine also was studied in an 8-week, placebo-controlled, double-blind trial of 29 subjects who met DSM-IV-TR criteria for PTSD. The primary measures of efficacy were the Short Posttraumatic Stress Disorder Rating Interview (SPRINT) Global Improvement item and the measure's total score, with response defined as a score of very much or much improved. Approximately 65% of mirtazapine-treated subjects met response criteria versus 20% for the placebo-treatment group. Chung et al. (2004) conducted a 6-week, flexible-dose study comparing and contrasting mirtazapine and sertraline in 95 outpatient and 18 inpatient Korean veterans who met DSM-IV-TR criteria for PTSD. Efficacy measures included the CAPS-2, HAM-D-17, and CGI-I. Response was defined as a ≥30% decrease in CAPS-2 total severity, a ≥50% decrease in total HAM-D-17 score, and a CGI-I score <3. The mean daily dose of mirtazapine was 34.1 mg/day and 101.5 mg/day for sertraline. The mirtazapine-treated group showed a statistically significantly higher response rate than the sertraline-treated group on the CAPS-2 total score (88% vs. 69%, $p = 0.039$). The HAM-D-17 total score and the CGI-I score decreased in both treatment groups with no significant difference between the groups. There are also case reports suggesting that mirtazapine augmentation may be helpful (Good and Petersen 2001).

## Beta-Blocker Medication

Results from two pilot studies that investigated a course of propanolol among individuals who had recently experienced an acute traumatic event indicated that propanolol was effective in decreasing PTSD symptoms and severity. Pittman et al. (2002) gave 40 mg propanolol four times a day for 10 days (with initial dosing beginning within 6 hours following the acute traumatic event) and found the dosing regiment to be effective in reducing PTSD symptoms 1 month later. Similarly, Vaiva et al. (2003) studied the efficacy of propanolol prescribed shortly after trauma exposure in the prevention of PTSD symptoms and diagnosis. Eleven patients were given 40 mg of propanolol 3 times a day for 7 days and the results were compared to those of 8 patients who refused the propranolol but agreed to participate in the study. PTSD rates measured 2 months after the trauma were higher in the refusal group (3/8) compared with the propranolol-treated group (1/11), as were the levels of PTSD symptoms.

## Anticonvulsant Medication

Anticonvulsant medications may also prove useful for the treatment of PTSD. A series of small case studies using carbamazepine as a treatment for PTSD have been reported. In these open-label case series, patients seemed to have a decrease in intrusive thoughts and improvement in sleep associated with carbamazepine treatment. Two small studies have investigated the efficacy of tiagabine with PTSD patients (Taylor 2003, Connor et al. 2006). Taylor (2003) conducted a case series of 7 patients where 8 mg/day tiagabine was added to patients existing medication regiments. During the 16-week trial, 6 of the 7 patients markedly improved after 2 weeks of augmentation therapy. Tiagabine alleviated the severity of nightmares, avoidance, and arousal characteristics of PTSD. Complementing these results, Connor et al. (2006) enrolled 26 PTSD patients in 12 weeks of open-label treatment with 2–16 mg tiagabine daily. The 18 subjects who showed minimal response on the CGI-I scale were then randomized to 12 weeks of double-blind treatment with tiagabine or placebo, either being tapered off their medication or remaining at the same dose as they had taken at the end of the open-label phase. Among the 8 completers, symptoms decreased 68% in tiagabine-treated patients and 54% in placebo-treated patients, with relapse rates equal in placebo and tiagabine groups. These studies offer mixed results, which may be resolved through larger double-blind clinical trials of tiagabine better characterizing its value as a treatment for PTSD.

Berlant has pioneered the use of topiramate as a monotherapy or an adjuvant treatment for PTSD. In his published case series (Berlant 2001), topiramate seems to be particularly useful in improving sleep, decreasing nightmares, and decreasing intrusive thoughts. More recently, two open-label studies have been published on the same topic, examining topiramate's effects on PTSD patients with and without hallucinations (Berlant and van Kammen 2002, Berlant 2004). Berlant and van Kammen (2002) found higher response rates in nonhallucinatory patients, who experienced a definite reduction in nightmares or intrusions. In the second study noted, only nonhallucinatory PTSD patients were recruited. Among the 33 patients enrolled in this 12-week, open-label study, 70% were responders, as reflected by a 30% reduction in PTSD Checklist-Civilian Version (PCL-C) scores. Although these results are promising, both studies were open-label and had high attrition rates. Further research is called for on topiramate's effects on PTSD, especially double-blind studies.

To date there has been one double-blind, placebo-controlled study of lamotrigine for the treatment of PTSD (Hertzberg et al. 1999). In this study, 15 patients were randomized in a 2:1 ratio to either lamotrigine or placebo. Five of the 10 patients who received lamotrigine had a significant decrease in their global PTSD Scale score as compared to one of four patients who received placebo. Lamotrigine-treated patients showed improvement in avoidance, numbing, and reexperiencing symptoms. Further studies will be necessary to determine whether anticonvulsant treatment, either as a monotherapy or as an adjuvant with antidepressants, will be beneficial for patients with PTSD.

## Antipsychotic Medication

With the development the atypical antipsychotics, there has been a reemergence of interest in the possible use of antipsychotic medication as both a primary treatment for PTSD or as an adjuvant treatment for PTSD. However, in a large secondary analysis of veteran inpatients and outpatients with PTSD, only 9% of inpatients and 10% of outpatients had been treated with antipsychotic medications (Sernyak et al. 2001). These patients tended to have more severe PTSD, more intrusive thoughts, and be more dysfunctional, although their incidence of traumatic experiences did not differ significantly from those patients who were not treated with antipsychotic medications. In this study, the antipsychotic augmentation did not have any additional benefit.

More recently, risperidone has been examined as an adjunctive agent in the treatment of PTSD. Reich et al. (2004) studied 21 adult female outpatients who had a history of childhood abuse. In this 8-week, double-blind, placebo-controlled comparison of flexible-dosage risperidone (0.5–8 mg/day), risperidone-treated patients experienced a significant reduction in the total CAPS-2 and all subscales except for the avoidant subscale (nine patients took concomitant medications during this study). Two studies have explicitly examined risperidone as an augmenting agent in PTSD patients' medication regiments (Hamner et al. 2003, Bartzokis et al. 2004). Hamner et al. (2003) randomized 37 combat veterans with PTSD to a 5-week, flexible-dose, double-blind, placebo-controlled trial of 1–6 mg/day risperidone augmentation to preexisting antidepressant/psychotic medication regimen. Outcome measures included the Positive and Negative Syndrome Scale (PANSS) and the CAPS. Among the 22 patients who completed the study, risperidone-treated patients showed a significantly greater decrease in psychotic symptoms, as measured by PANSS. Both groups showed a substantial decline in CAPS scores, with no significant difference between treatment groups. Bartzokis et al. (2004) recruited 65 patients with severe combat-related PTSD for a double-blind, placebo-controlled trial. These patients participated in a 5-week residential program followed by 3 months of outpatient follow-up. The mean CAPS score was 100. Both treatment groups showed significant improvement during the initial inpatient phase, but by week 16, risperidone treatment separated from placebo on the CAPS-Total, CAPS-D, HAM-A, and PANSS. Risperidone augmentation helps decrease intrusive thoughts and markedly improves symptoms of PTSD.

Four studies have examined olanzapine's efficacy in PTSD. Stein et al. (2002a) studied 19 male war veterans with military-related PTSD in a 12-week, double-blind, placebo-controlled study of 10–20 mg/day olanzapine versus placebo. Outcome measures included CAPS, PSQI, and the Center for Epidemiologic Studies Depression Scale (CES-D). Olanzapine-treated patients experienced a significantly greater reduction in PTSD symptoms, depressive symptoms, and sleep disturbance. Response rates as measured by the CGI-I were fairly low (30%) among olanzapine patients, and they were not statistically superior to scores for placebo patients. In another small double-blind, placebo-controlled, flexible-dose study of olanzapine, 11 patients completed the study and there was no difference in the response rates between the two groups (Butterfield et al. 2001). Pivac et al. (2004) conducted an open-label trial of olanzapine versus fluphenazine. In this study, 55 male war veterans with combat-related PTSD received 5–10 mg/day olanzapine or fluphenazine for 6 weeks. Both medications helped alleviate symptoms of

PTSD, but olanzapine was more efficacious than fluphenazine at reducing negative symptoms, avoidance and arousal. As expected, fluphenazine caused more extrapyramidal symptoms and olanzapine caused greater weight gain. Petty et al. (2001) published an open-label study of 48 individuals who were started on open-label olanzapine treatment. Thirty patients completed the 8-week trial and tolerated olanzapine well. These patients had clinically significant improvement in their CAPS-2 scores, HAM-D scores, and Brief Psychiatric Rating Scale (BPRS) scores. Large-scale studies are needed to examine the potential benefit of atypical antipsychotic medications as a monotherapy or an augmentation therapy for PTSD patients, especially those with psychotic symptoms.

### Novel Treatments

Several alternative treatments for PTSD are being investigated. Raskind et al. (2003) compared and contrasted prazosin and placebo in a 20-week, double-blind, crossover study of 10 Vietnam combat veterans diagnosed with chronic PTSD and severe trauma-related nightmares. Prazosin is a centrally active adrenergic antagonist commonly used in treating hypertension. Primary efficacy measures included two items from the CAPS (recurrent distressing dreams item and difficulty falling/staying asleep item), and the change in overall PTSD severity and functional status according to the CGI. Prazosin was shown to be more effective than placebo at study endpoint in decreasing symptoms of recurrent distressing dreams (3.6 vs. 6.7, respectively, $p < 0.001$) and with difficulty falling/staying asleep (4.0 vs. 7.1, respectively, $p < 0.01$). At study endpoint, prazosin displayed an average of 57.3 on the CAPS compared to 86.5 for the placebo group ($p < 0.01$). Prazosin was also associated with improved global functioning compared to placebo (prazosin mean CGI score 2.0, compared to placebo mean CGI score 4.5, $p < 0.01$). Prazosin was well tolerated.

A small study by Heresco-Levy et al. (2002) investigated D-cycloserine (DCS) as a treatment for PTSD. D-cycloserine, a NMDA receptor partial agonist, is being investigated as a treatment for schizophrenia, chronic low back pain, SAD, and Alzheimer's disease. In a double-blind, placebo-controlled crossover trial, eleven subjects who met DSM-IV-TR criteria for PTSD were treated with 50 mg/day D-cycloserine or placebo for 12 weeks. The CAPS was the primary efficacy measure. D-cycloserine therapy significantly decreased scores on the numbing and avoidance clusters of the CAPS but not total scores or other subscales.

### Treatment Conclusions

Patients with PTSD typically fall into one of two broad categories: those who have recently experienced a trauma and are bothered by persistent symptoms of PTSD but do not have co-occurring other disorders, and those patients with more long-standing PTSD who frequently have one or more secondary co-occurring psychiatric condition(s). The former group is much more responsive in the short term to pharmacotherapy. At this time, SSRIs are the FDA-approved treatment of choice for patients with PTSD. In contradistinction to patients with PD and SAD, these patients do not seem to have as much antidepressant-induced anxiety. Patients who have had PTSD for a long time and present with comorbid psychiatric syndromes are far more difficult to treat. They generally respond very slowly to treatment and their care is frequently confounded by their overall complex psychiatric presentation. The key to successfully treating such individuals is to be clear about the target symptoms and to give the patient sustained treatment because improvement many times will require months of therapy. There are some promising smaller studies suggesting that such patients may do well with an augmentation approach. Some of the most exciting data have used atypical antipsychotic agents to augment SSRIs. Another very intriguing approach is to add Prazosin, an alpha-adrenergic antagonist, to patients with PTSD suffering from problems with disrupted sleep. Recent studies suggest that this is very effective even in treatment-resistant PTSD. As previously stated, there are few data to guide clinical treatment beyond first-line treatment intervention.

## Obsessive–Compulsive Disorder

### Selective Serotonin Reuptake Inhibitors

Large, well-designed, double-blind, placebo-controlled trials demonstrate that fluoxetine, paroxetine, fluvoxamine, citalopram, and sertraline are effective acute treatments for OCDs (Carpenter et al. 1996, Cartwright and Hollander 1998, Greist and Jefferson 1998, Koponen et al. 1997, Mundo et al. 1997, Thomsen 1997, Todorov et al. 2000).

There have been two large 12-week, parallel-group, double-blind, placebo-controlled multicenter trials of fluoxetine in fixed doses of 20, 40, and 60 mg/day versus placebo (Tollefson et al. 1994a, 1994b). Response was defined as a decrease of 35% or greater on the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS). The three fluoxetine doses each had response rates of 33%. There was some suggestion that the 40 and 60 mg/day doses acted more rapidly and facilitated greater improvement in Y-BOCS scores. Montgomery et al. (1993) previously reported that 40 and 60 mg/day of fluoxetine, but not 20 mg/day, was more effective than placebo.

Although there are data available from a number of placebo-controlled multicenter trials contrasting paroxetine with placebo, only one 12-week fixed-dose trial (20, 40, and 60 mg/day) has been published (Ballenger et al. 1998). In this study, all patients were initially started at 20 mg/day, and the 40 and 60 mg/day groups were titrated to these doses by the end of week 2. The 40 and 60 mg/day groups demonstrated statistically significant decreases on the Y-BOCS and the CGI-Severity Scale. The greatest improvement seemed to be present in the 60 mg/day group. Paroxetine has also been studied as a treatment of OCD in children. Geller et al. (2004) performed a multisite, double-blind, placebo-controlled, flexible-dose study randomizing 203 patients to receive either 10–50 mg/day paroxetine or placebo for 10 weeks. One hundred and forty-five patients completed the study, with 33/98 (33.7%) treatment responders among patients receiving paroxetine in contrast to 25/105 (23.8%) responders among those patients receiving placebo. The Children's Yale-Brown Obsessive–Compulsive Scale (CY-BOCS) scores demonstrated a significant decrease for the paroxetine-treated group when compared with the placebo-treated group. However, the two treatment groups did not differ in terms of CGI-S, CGI-I, and Global Assessment of Functioning (GAF) ratings.

There have been several smaller trials and one large 10-week, double-blind, placebo-controlled multicenter trial of fluvoxamine (100–300 mg/day) versus placebo in the treatment of OCD (Goodman et al. 1989, Greist et al. 1995c, Jenike et al. 1990, Perse et al. 1987). In the large study, Greist et al. (1995c) reported that 40% of fluvoxamine-treated patients were responders on the CGI-Improvement Scale as compared to 15% of placebo-treated patients. The fluvoxamine-treated patients also had a significantly greater decrease in the mean Y-BOCS scores (Greist et al. 1995c). Riddle et al. (2001) conducted a 10-week, double-blind, placebo-controlled, multisite study investigating the efficacy of fluvoxamine in childhood OCD. Out of 120 individuals who were randomized, 24/57 (42.1%) treated with fluvoxamine and 17/63 (26%) treated with placebo were responders (defined as ≥ 25% decrease in CY-BOCS scores). These studies suggest that fluvoxamine is effective in treating both adults and children with OCD.

In addition, Pallanti et al. (2002) conducted an open-label study of intravenous citalopram infusion in 39 treatment-resistant OCD adult patients. Thirty-eight patients completed the 21-day study of 20–80 mg intravenous citalopram. Twenty-three patients (59%) had a ≥ 25% decrease in their Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) scores. These patients were then given oral citalopram and they continued to improve daily during this 63-day phase. Although intravenous citalopram was rapidly effective in this study, an increased incidence of cardiovascular adverse events was noted. Furthermore, placebo-controlled, double-blind studies should be performed to extend these results. Montgomery et al. (2001) performed a 401-patient, multisite, double-blind, placebo-controlled study of 20, 40, and 60 mg/day doses of citalopram. In contrast to previous SSRI studies for OCD, during the 12-week study, 20 mg was found to be an effective dose, as measured by the change in Y-BOCS from baseline to study endpoint. All three doses were significantly superior to placebo in treating both obsessions and compulsion, although the study was not large enough to discriminate any difference between dose regiments. There are data from single-blind comparator trials of citalopram versus paroxetine and fluvoxamine that suggest that there is no significant difference in Y-BOCS scores between these medications (Mundo et al. 1997). These data are consistent with other open-label studies with adults and children suggesting that citalopram may decrease symptoms of OCD (Koponen et al. 1997, Thomsen 1997).

In one large 12-week, double-blind, placebo-controlled multicenter fixed-dose study of sertraline (50, 100, and 200 mg/day), all three doses of sertraline caused a significant reduction in Y-BOCS scores (Greist et al. 1995a). The higher doses did show selectively greater improvement on all measures but this did not reach statistical significance. There are two other double-blind, placebo-controlled multicenter flexible-dose trials of sertraline versus placebo in the treatment of OCD (Chouinard et al. 1990, Kronig et al. 1999). In both of these trials, sertraline was more efficacious than placebo on standard outcome measures. Greist et al. (1995a) also demonstrated the ability of sertraline to maintain improvement after 12 weeks of double-blind, placebo-controlled treatment during an additional 40-week double-blind fixed-dose trial of sertraline (50, 100, and 200 mg/day) (Greist et al. 1995b). At the 52-week endpoint, mean scores for all four outcome measures, Y-BOCS, the NIMH Global Obsessive–Compulsive Scale, and CGI-Severity and Improvement Scales, revealed significantly greater improvement for the sertraline group versus the placebo group (Noyes et al. 1997). Fifty-one of the patients who participated in the double-blind, placebo-controlled trial of sertraline entered into a 2-year sertraline open-label study. Outcome data suggested that efficacy was not only maintained, but improvement continued; first year mean Y-BOCS scores were 11.4 compared to second year mean Y-BOCS scores, 3.2.

Koran et al. (2002) performed a relapse-prevention study where patients who had achieved a sustained response during a 52-week single-blind treatment phase were randomized to an additional 28 weeks of double-blind treatment with either sertraline or placebo. This 80-week study was conducted at 21 sites in the US. Following a 1-week washout, 649 patients entered 16 weeks of single-blind treatment with flexible doses of sertraline. Patients were titrated up on a 50 mg incremental schedule to a maximum 200 mg/day depending on response and tolerability. Patients who failed to meet response criteria by the end of week 16 were withdrawn from the study. Response was defined as a decrease of 25% from baseline on the Y-BOCS, and a CGI-Improvement Scale score ≤ 3. Those who met responder criteria continued to receive single-blind sertraline treatment for an additional 36 weeks. Data from the single-blind trial revealed consistent improvement throughout the 52 weeks of treatment. Mean Y-BOCS scores decreased from 26.1 at baseline to 15.9 at the end of week 16 to 10.3 at the end of week 52. Symptomatic improvement was associated with improvement in quality of life as measured by Q-LES-Q scores from 60% at baseline to 73.7% at the end of week 16 to 78.2% at the end of week 52. (The mean Q-LES-Q score for a population of normal subjects is 80%.) At the end of week 52, patients who continued to meet responder criteria were randomized to the 28-week double-blind discontinuation trial. Those patients randomly assigned to sertraline treatment were continued on the same daily dose as at week 52. Patients assigned to placebo had their dose decreased by 50 mg/day every 3 days until they were taking only placebo tablets. Continued sertraline treatment was associated with sustained improvement during the 28-week relapse-prevention phase. Sertraline treatment was also significantly more effective than placebo in decreasing study discontinuation due to relapse or insufficient clinical response, and acute exacerbation of obsessive–compulsive symptoms. One third of patients experienced acute relapse, which is striking when compared to earlier discontinuation studies that show relapse rates of 90% or greater as measured by the Y-BOCS.

Another recent study evaluated the efficacy of long-term sertraline treatment of children and adolescents, ages 6–18 years with OCD (Cook et al. 2001). One hundred and thirty-seven patients were assigned to 12 weeks of double-blind, placebo-controlled treatment with subsequent open-label sertraline treatment (50–200 mg/day) for 52 weeks. At study endpoint, the mean daily sertraline dose was 108 mg/ day for children (6–12 years), and 132 mg/day for adolescents (13–18 years). Outcome measures included the Children's Yale-Brown Obsessive–Compulsive Scale (CY-BOCS), the NIMH Obsessive–Compulsive Scale, and the CGI-Severity and Improvement Scales. Mean CY-BOCS scores changed from 22.8 at study entry to 17.0 at the

completion of the double-blind phase to 10.8 at the 52-week endpoint. The mean CGI-Severity scores declined from 4.6 to 3.7 to 2.7, respectively. Only 12% of patients discontinued because of side effects.

These data suggest that SSRIs are a first-line pharmacotherapy for both acute and maintenance treatment of OCD in children and adults (Greist and Jefferson 1998, March and Frances 1997). Discontinuing SSRI treatment is associated with an exacerbation of symptoms and worsening in quality of life. (For more on OCD, please see the Chapter 71.)

## Serotonin–Norepinephrine Reuptake Inhibitors—Venlafaxine and Reboxetine

Hollander et al. (2003) conducted an open-label trial of venlafaxine and venlafaxine XR treatment of OCD. There were 39 patients in this trial, where 74% of these patients had not responded to at least one previous SSRI trial. The CGI-I was used to assess global improvement. Sixty-nine percent of patients were classified as responders (CGI-I of 1 or 2) by the end of the 18 months of treatment. Future placebo-controlled studies with venlafaxine XR seem warranted at this time.

## Tricyclic Antidepressant Medication and Monoamine Oxidase Inhibitors

There have been seven meta-analyses comparing and contrasting clomipramine and SSRIs (Abramowitz 1997, Cox et al. 1993, Greist 1998, Kobak et al. 1998, Piccinelli et al. 1995, Stein et al. 1995). In each case, clomipramine has been found to be significantly more effective than the SSRIs. There has been some concern that this conclusion may be biased because many of the clomipramine studies were performed in patients who had not been previously treated with an effective pharmacotherapy, while patients in the later studies of the SSRIs had failed treatment with clomipramine or other agents. There also is concern that differences in study design might bias these results in favor of clomipramine (Greist 1998). There have been double-blind comparison studies of clomipramine against fluoxetine, fluvoxamine, sertraline, and paroxetine (Bisserbe et al. 1997, Freeman et al. 1994, Koran et al. 1996, Lopez-Ibor et al. 1996, Milanfranchi et al. 1997, Zohar and Judge 1996). None of these studies had the power to differentiate clomipramine from the SSRI in question. Therefore, findings of no difference between the two groups is not surprising. However, if one takes the entire body of evidence as a whole into account, analyses suggest that clomipramine is at least as effective as the SSRIs and may, in some instances, be more effective (Greist 1998, Todorov et al. 2000).

Although there have been several studies with MAOIs, the results of these studies have been equivocal at best (Jenike et al. 1990, Vallejo et al. 1992). The two other strategies for enhancing serotonergic neurotransmission have involved manipulating the ratio of clomipramine to its metabolite desmethylclomipramine. One strategy has involved the use of intravenous clomipramine in order to decrease first-pass hepatic metabolism and thus increase the ratio of clomipramine metabolite desmethylclomipramine. These studies found that intravenous clomipramine reduces symptoms of OCD more rapidly than oral clomipramine (Koran et al. 1994, 1997, Warneke 1984, 1985, 1989). Yet, over time, patients treated with intravenous clomipramine did not have a greater response than patients treated with oral clomipramine. The second strategy combines giving clomipramine with an SSRI (fluvoxamine) that inhibits its hepatic metabolism. This, again, shifts the ratio of clomipramine to desmethylclomipramine in favor of clomipramine.

## Other Antidepressant Medication (Bupropion, Mirtazapine, Nefazodone, Trazodone)

Mirtazapine treatment was studied in a 10-week open trial of 10 adult outpatients who met DSM-IV-TR criteria for OCD for at least 1 year and had a Y-BOCS score greater than 18 (Koran et al. 2002). Mirtazapine was started at a dose of 15 mg/day then increased after 4 days to 30 mg/day, and to 45 mg/day at the end of the second week. OCD severity was measured with the Y-BOCS and the CGI-Severity Scale. In this study, mean Y-BOCS scores decreased from 28.7 at baseline to 23.7 at week 10. Only 2 of the 10 subjects met responder criteria. These results suggest that mirtazapine may not be a useful treatment for subjects with OCD. Bupropion has also been studied in patients with OCD. Vulink et al. (2005) found that bupropion was an ineffective treatment for 12 patients with OCD in an open-label, fixed-dose study. Two patients responded (≥ 25% reduction in YBOCS score) while eight patients deteriorated during the 8-week study.

## Benzodiazepine Medication

Pigott et al. (1992) conducted a controlled trial of clonazepam augmentation in OCD patients treated with clomipramine or fluoxetine. Augmentation with clonazepam was found to be more effective than placebo in decreasing global measures of anxiety but not Y-BOCS scores.

## Buspirone

Harvey and Balon (1995) reviewed the double-blind augmentation studies of buspirone used for patients with treatment-resistant OCDs, noting that none have demonstrated any advantage over placebo treatment.

## Beta-Blocker Medication

Pindolol augmentation has been evaluated in one small double-blind study for patients with treatment-resistant OCD. In this two-phase study performed by Dannon et al. (2000) 23 treatment-resistant patients were perspectively treated openly with 60 mg of paroxetine a day. Nonresponse was defined as a 25% improvement on the Y-BOCS during this open-label treatment phase. Sixteen patients were randomized to receive double-blind augmentation therapy with either pindolol 2.5 mg t.i.d. or matching placebo for 6 weeks. The primary outcome measure was a change in Y-BOCS score or secondary measures included changes in HAM-A scales total scores and MADRS total scores. A significant decrease in Y-BOCS score was noted, but there were no changes compared to placebo in the MADRS or the HAM-A rating scores. This suggests that pindolol might have a unique role in decreasing symptoms in OCD, but is consistent otherwise with findings in both major depressive disorder and in SAD where pindolol augmentation did not cause a significant change in ratings.

## Anticonvulsant Medication

Anticonvulsant medications have begun preliminary testing as an adjunctive agent in OCD treatment. Rubio et al.

(2006) examined topiramate augmentation to current antidepressant medications in 12 treatment-resistant patients during a 12-week study. Topiramate was titrated from 25 mg/day to 400 mg/day as tolerated, and 10 of the 12 subjects were treatment responders with a ≥30% reduction in their Y-BOCS scores.

## Antipsychotic Medication

Patients with OCD frequently do not respond to monotherapy with SSRIs or clomipramine. One possible augmentation strategy has been to block the dopamine type-2 receptor. Preliminary studies suggest that blockade with typical neuroleptics for patients with tics may be beneficial (McDougle 1997). Open case series suggest that the newer atypical neuroleptics, risperidone and olanzapine, may be useful in augmenting clinical response in treatment refractory OCD (McDougle 1997, Weiss et al. 1999). Pfanner et al. (2000) investigated the use of risperidone as an adjunct to SSRI therapy in an 8-week open-label trial of 20 patients with refractory OCD. Patients in this study had a DSM-IV-TR diagnosis of OCD with duration of illness of at least 2 years, had demonstrated less than a 25% improvement with an SSRI after 6 months of treatment, and had a baseline Y-BOCS score of 30. Risperidone was added at 1 mg/day and titrated up to 3 mg/day over 2 weeks. The mean Y-BOCS score decreased 26% over the course of the trial from 36.1 at baseline to 24.8 at week 8. At endpoint, 8 patients had a CGI-Improvement score of 1 (very much improved), 9 patients had a 2 (much improved), while only 3 patients had a 3 (minimally improved). Li et al. (2005) published the results of a 16-patient, 9-week, crossover design study investigating the efficacy of risperidone and haloperidol augmentation of SSRI-resistant OCD. Individuals were randomized to different sequences of the 3 augmentation strategies (placebo–risperidone–haloperidol). Each active treatment sequence was followed by a 1-week washout phase in order to minimize carryover effects between augmentation strategies. Twelve individuals completed all three arms of this study. In this study, risperidone was better tolerated than haloperidol. Neither risperidone nor haloperidol differentiated placebo augmentation on Y-BOCS scale scores or other outcome variables.

Marazziti et al. (2005) added olanzapine to patients' previous medication regimen at a dose of 2.5 mg/day, titrating the medication up to 10 mg daily within 2 weeks. In this study, a significant number of patients had at least a 35% reduction in total Y-BOCS score, which was maintained during one year of follow-up. Due to the variability of SSRIs, future studies may benefit from conducting double-blind procedures involving olanzapine and a specific SSRI.

There have been at least three double-blind, placebo-controlled augmentation trials of quetiapine augmentation in SSRI-resistant patients with OCD. Denys et al. (2004) randomized 40 SSRI nonresponding subjects with OCD to either quetiapine up to 300 mg/day or placebo for 8 weeks. Forty percent of the quetiapine-treated cohort were classified as responders as compared to 10% of placebo augmented subjects. Fineberg et al. (2006) recently performed a combined analysis of the three double-blind, placebo-controlled quetiapine augmentation studies and published in literature. They suggested that there seemed to be a clinically significant signal associated with quetiapine augmentation. However, large-scale placebo-controlled studies are clearly indicated in order to confirm and extend these findings.

A preliminary study conducted by Metin et al. (2003) investigated the efficacy of amisulpride augmentation (200–600 mg) in 20 OCD patients who did not respond to SSRI treatment. In this open-label trial, 35% of patients reported significant improvement with combination therapy and 60% of patients reported moderate improvement.

In summary, preliminary studies suggest that augmentation with a variety of atypical antipsychotic agents may result in a substantial benefit for a subset of patients with treatment refractory OCD. However, at this time, it is difficult to identify who these patients are.

## Treatment Conclusions

The SSRIs and clomipramine are the only FDA-approved treatments for OCD. These agents require individualized titration and there are many instances where patients end up on much higher doses than those used in the treatment of mood disorders. Although this clinical observation is not unambiguously supported by existing clinical trial data, there seems to be merit to this approach. Patients who have comorbid tic disorders with OCD may be more responsive to the combination of an antipsychotic with a serotonergic agent. Although a myriad of augmentation strategies are used in clinical practice, there are few data to support this

### Clinical Vignette

Ms. K is a 46-year-old Hispanic female who presents with a chief complaint of recurrent major depressive disorder. Ms. K has had multiple brief treatments for depressive disorder but always discontinues her treatment. Ms. K reports that she was physically abused by her older brother while in adolescence and 2 years ago was involved in a car jacking. Although Ms. K was not harmed during the car jacking, she developed a depressive disorder immediately following the incident. When questioned further, it is clear that Ms. K has recurrent nightmares about this event, has flashbacks, startles easily, avoids driving on all streets except main arteries and the freeway, and has complained of feeling distant from her husband and children. During the interview Ms. K breaks down and is tearful. She discusses how ashamed she feels for being "weak" and having these pervasive symptoms. When the concept of posttraumatic stress disorder is introduced to Ms. K, she is relieved to know that she is not the odd person out.

Ms. K was started on sertraline 25 mg/day and this dose was gradually tapered up by 25 mg/week until 100 mg. Ms. K had a gradual reduction in her intrusive thoughts and nightmares that began during the second week of treatment. Ms. K's depressive symptoms began to resolve as well by week 4. Since Ms. K was not having side effects and still was symptomatic at 6 weeks, the dosage of sertraline was increased to a 150 mg/day. Over the next 8 weeks, Ms. K had continued improvement on both her depressive symptoms and many of her symptoms of posttraumatic stress disorder. She became more active with her family and affectionate with her husband. She began to expand the areas where she felt comfortable driving. Over time Ms. K continued to demonstrate improvement in symptoms. She is currently maintained on 150 mg/day of sertraline and has been able to return to work and most of her normal activities over a period of 2 years.

approach. Recent studies suggest that the combination of pharmacotherapies with behavioral modification may be the optimal approach for the care of these patients.

## Future Directions

The development of future pharmacological treatments for anxiety disorders may take new and exciting avenues. There is a growing body of preclinical evidence suggesting that basic fear involves the interaction between 3 of the 13 nuclei of the amygdala with decreased activation of the medio-prefrontal cortex and concomitant increased activation of the hypothalamus, the noradrenergic system, and specific areas related to fear such as the peri-aqueductal gray region of the brain. This has led investigators to begin to explore the use of both NMDA antagonists in an attempt to inhibit the development of fear responses as well as other compounds such as NMDA receptor agonists, which might be used to facilitate new learning and thereby decrease fear. In particular, there is ongoing research investigating whether one might be able to potentiate the effects of psychotherapy by using compounds like D-cycloserine. This research may be the harbinger of a variety of new pharmacological approaches targeted at specific aspects of anxiety, instead of merely using strategies that massively perturb neurotransmitter systems such as SSRIs or SNRIs; future treatments may target more specific receptors and secondary messenger systems. Pilot studies employing medication augmentation strategies are currently on their way for SAD and PTSD.

## Conclusion

In closing, clinicians have a wide array of medications available for the treatment of anxiety and anxiety disorders. The breadth of accessible treatment options greatly facilitates our ability to help patients. We have safe and effective treatments for everything from short-term treatment of pathological anxiety to previously intractable anxiety disorders like OCD. Yet, the most important therapeutic agent we possess is still sound clinical skills and judgment. Appropriate diagnosis and rapport are the foundations of any pharmacological intervention we make with our patients.

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CHAPTER

# 105 Pharmacologic Treatment of Insomnia

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## Introduction

Insomnia is a common complaint in the general adult population, and the prevalence is significantly greater in patients with psychiatric disorders. Approximately 30% of adults experience occasional insomnia and about 10% suffer with chronic symptoms. (National Institutes of Health 2005) Insomnia may occur idiopathically or may arise with distressing circumstances, psychological conditioning, environmental factors, jet lag and shift work schedules, medication effects, and medical, psychiatric, and sleep disorders. Insomnia among psychiatric patients may be influenced by particular disorders, the severity of the illness, and the treatment approaches. Individuals with mood and anxiety disorders are especially likely to experience insomnia; however, most psychiatric disorders increase the risk of sleep disturbances. Often insomnia is the earliest symptom heralding a depressive episode, and it may remain a residual symptom following effective treatment of the mood disturbance (Nierenberg et al. 1999, Perlis et al. 1997).

The relationship of sleep and psychiatric illness has many different dimensions. In addition to psychiatric illness increasing the likelihood of insomnia, the presence of persistent insomnia increases the future risk of relapses or the new onset of mood, anxiety, and substance abuse disorders. Several psychotropic medications include insomnia as common side effects. Certain psychiatric disorders, particularly major depression, may be associated with changes in the distribution and amount of sleep stages. There are commonalities among neurotransmitters known to regulate sleep, mood, and anxiety. Strategic manipulations of sleep may have antidepressant effects, while sleep deprivation can precipitate mania in bipolar disorder patients.

Although insomnia simply may describe the inadequate quantity or quality of sleep when one has the opportunity to be sleeping, insomnia nosologies typically require the presence of difficulty falling asleep, staying asleep, excessively early awakening, or unrefreshing sleep in conjunction with daytime consequences (American Psychiatric Association 1994). These daytime effects may include fatigue, poor concentration, irritability, and excessive worry about sleep. Insomnia episodes may be acute or chronic and may be primary or associated with comorbid medical, psychiatric, or other sleep disorders. Chronic insomnia has been associated with increased absenteeism, decreased quality of life, higher health-care costs, and a significant societal economic burden.

Insomnia treatment generally addresses the context of the sleep disturbance, with the goal of optimizing the management of comorbid disorders and creating an environment conducive for sleep to improve. Typically this requires a comprehensive evaluation to identify associated conditions and specific factors that may undermine the experience of good-quality sleep. Treatment approaches may involve a variety of general sleep hygiene recommendations, as well as specific behavioral recommendations. Psychotherapeutic interventions may be valuable for selected patients. Cognitive behavioral therapy for insomnia has been shown to be an effective modality for chronic insomnia subjects. Pharmacologic approaches to the treatment of insomnia often are recommended in combination with these educational, psychotherapeutic, and behavioral modalities (Smith et al. 2002).

## Sleep–Wake Cycle Regulation

Under normal conditions, sleep and wakefulness are strongly influenced by a network of central nervous system processes that promote sleepiness or arousal according to time-dependent mechanisms. Key brainstem arousal pathways include acetylcholine-producing cell groups activating the cortex through thalamic relay neurons and monoaminergic cell groups with projections to hypothalamic and basal forebrain regions. These latter arousal mechanisms include noradrenergic and serotonergic, as well as hypothalamic histaminergic pathways. The hypothalamic ventrolateral preoptic nucleus (VLPO) has been identified as a critical sleep-active cell group that inhibits the stimulation

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from the monoaminergic arousal pathways. Inhibitory gamma-aminobutyric acid (GABA) and galanin-related VLPO activity serve as a switch that stabilizes the states of sleep and wakefulness, which are further modulated and reinforced by the neuropeptide orexin. The hypothalamic suprachiasmatic nucleus (SCN) maintains 24-hour periodicity through a complex transcription–translation feedback loop involving multiple genes. The primary input to the SCN is retinal photoperiod information, which entrains the circadian rhythm to the environmental day–night cycle (Saper et al. 2001).

Homeostatic and circadian process interactions have been postulated to explain the normal human pattern of daytime and evening wakefulness for approximately 16 hours alternating with about 8 hours of nighttime sleep. The homeostatic process represents the overall balance of sleep and waking whereby a sleep drive increases with continued wakefulness. The homeostatic sleep drive is low in the morning following nighttime sleep but then increases steadily until nighttime sleep again occurs to reverse the process and reduce the sleep drive. In spite of the increased homeostatic evening sleep drive, people generally are the most awake and alert during the evening hours. This is due to the circadian arousal that peaks in the evening and opposes the homeostatic sleepiness. As bedtime approaches, the circadian arousal declines and allows sleep onset to occur due to the unopposed homeostatic sleep drive. The SCN directs the pineal gland activity in producing and releasing the hormone melatonin. The SCN contains a high concentration of melatonin receptors. Agonist activity at these SCN melatonin receptors reduces their firing rate, which contributes to the arousal decline and subsequent sleep onset. Essentially, the homeostatic process determines the sleep need, while the circadian process optimizes sleep to occur at nighttime (Richardson 2005).

## Historical Overview

A wide assortment of substances and medications with sedating characteristics has been employed in the attempt to promote sleep. Fermented beverages and opium have been available for millennia. Sedating concoctions, such as opium-containing laudanum, were very commonly used for ailments including insomnia from the seventeenth through the nineteenth centuries. Numerous patent medicine compounds were promoted as sleep aids. Chloral hydrate and paraldehyde became available in the mid-nineteenth century. Barbiturates and related compounds frequently were recommended for insomnia from the early twentieth century until recent decades. Meprobamate, methyprylon, ethchlorvynol, glutethimide, and methaqualone commonly were prescribed for insomnia in the mid-1900s. Benzodiazepine receptor agonist hypnotics, including the structural benzodiazepines and the newer nonbenzodiazepine agonists, have been the predominant selection for pharmacologic insomnia management since the 1970s. Compounds currently taken with the intention of treating insomnia include bedtime alcohol, unregulated complementary and alternative substances, over-the-counter (OTC) antihistamines, sedating prescription medications (e.g., antidepressants and antipsychotics) used on an off-label basis, and Food and Drug Administration (FDA)-approved insomnia treatment medications. A useful historical generalization is that efficacy has always been present with many older substances being capable of inducing sleep. However, earlier remedies often were associated with serious safety problems, including lethality and dependence. The predominant evolutionary theme of insomnia pharmacotherapy has been the trend of improved safety. Current treatment options represent significant progress regarding tolerability, adverse events, and abuse liability.

## FDA-Approved Insomnia Treatment Medications

Currently, the insomnia treatment medications approved by the US FDA include a variety of benzodiazepine receptor agonists and a single selective melatonin receptor agonist. Table 105–1 shows the available doses, approximate elimination half-lives, and US Drug Enforcement Administration (DEA) schedule for each of these medications. All have demonstrated efficacy in treating one or more insomnia symptoms and have been shown to have satisfactory safety characteristics in clinical trials with populations of normal subjects and individuals suffering with chronic insomnia. Generally, insomnia treatment medications have been evaluated with objective sleep laboratory and outpatient

**Table 105–1 United States FDA-Approved Insomnia Treatment Medications**

| Medications | Available Doses (mg) | Elimination Half-Life (hour) | DEA Schedule | Active Metabolite |
|---|---|---|---|---|
| **Benzodiazepine Receptor Agonists** | | | | |
| *Immediate-release benzodiazepine* | | | | |
| Estazolam | 1, 2 | 8–24 | IV | Yes |
| Flurazepam | 15, 30 | 48–120 | IV | Yes |
| Quazepam | 7.5, 15 | 48–120 | IV | Yes |
| Temazepam | 7.5, 15, 22.5, 30 | 8–20 | IV | No |
| Triazolam | 0.125, 0.25 | 2–4 | IV | No |
| *Immediate-release nonbenzodiazepine* | | | | |
| Eszopiclone | 1, 2, 3 | 5–7 | IV | No |
| Zaleplon | 5, 10 | 1 | IV | No |
| Zolpidem | 5, 10 | 1.5–2.4 | IV | No |
| *Modified-release nonbenzodiazepine* | | | | |
| Zolpidem ER | 6.25, 12.5 | 2.8–2.9 | IV | No |
| **Selective Melatonin Receptor Agonist** | | | | |
| Ramelteon | 8 | 1–2.6 | None | Yes |

subjective assessments. These two types of evaluations provide complementary efficacy information. In recent years, there has been a trend toward longer-term efficacy and safety trials and primary outcome measures reflecting sleep-onset latency and sleep maintenance. These directions have paralleled the approved prescribing guidelines.

Previously, all of the insomnia treatment medications were approved with indications for short-term use; however, the three new medications approved by the US FDA since 2005 (eszopiclone, ramelteon, and zolpidem extended release) have had no implied limitation on their duration of use. Accordingly, these may be prescribed as long as medically appropriate. Recent approvals have also included language specifying sleep onset and/or sleep maintenance indications. This information can help direct appropriate medication selection for individual patient insomnia patterns. Abuse liability is reflected in the DEA scheduling. All of the benzodiazepine receptor agonist hypnotics are categorized as Schedule IV controlled substances due to a relatively low risk of abuse; however, the melatonin receptor agonist has no abuse liability and is classed as a nonscheduled medication.

## Benzodiazepine Receptor Agonist Hypnotics

The benzodiazepine receptor agonist hypnotics have been the primary medications prescribed for the treatment of insomnia for over 35 years. This class includes agents with the benzodiazepine structure and newer compounds that do not have the benzodiazepine structure but that are agonists for the benzodiazepine recognition site. The typical benzodiazepine structure is a seven-member diazepine ring fused with a benzene ring.

The benzodiazepine hypnotics were approved by the FDA in the 1970s and 1980s. All of the benzodiazepine receptor agonist hypnotics approved since the 1990s have had unique nonbenzodiazepine structures. There has been a trend toward short to intermediate half-life hypnotics, in contrast to earlier long-acting medications. Until recently, all of these hypnotic medications have depended on standard pharmacokinetics; however, at least one controlled-release formulation hypnotic has now become available. Some investigational benzodiazepine receptor agonist hypnotics employ rapid-acting alternate delivery formulations, such as oral dissolvable tablets and a liquid spray.

### Mechanism of Action

The medications in this class function as positive allosteric modulators of GABA responses at the $GABA_A$ receptor complex, which is a five-subunit, ligand-gated, transmembrane structure with a central chloride ion channel (see Figure 105–1). GABA is the primary inhibitory neurotransmitter in the central nervous system, and it influences the intracellular–extracellular negative chloride ion balance. In humans, the $GABA_A$ receptor complex most typically comprises two α, two β, and one γ glycoprotein subunits. A benzodiazepine recognition site exists at the interface of α and γ subunits. When a benzodiazepine agonist is present at this site and GABA activates the receptor, a greater number of chloride ions are able to enter the cell due to an increase in the frequency of ion channel opening. The result is greater hyperpolarization and enhanced inhibitory activity. The action of all of the benzodiazepine receptor agonists can be reversed by the benzodiazepine receptor antagonist, flumazenil. Although the wide distribution of $GABA_A$ receptors may lead to global sedating effects, targeted action at VLPO GABAergic neurons likely plays a key role in the hypnotic effect of the medications in this class. Various benzodiazepine receptor agonist medications may also be employed as sedatives, anxiolytics, muscle relaxants, and anticonvulsants. Other medications and substances influencing the function of the $GABA_A$ receptor include barbiturates, propofol, ethanol, and picrotoxin.

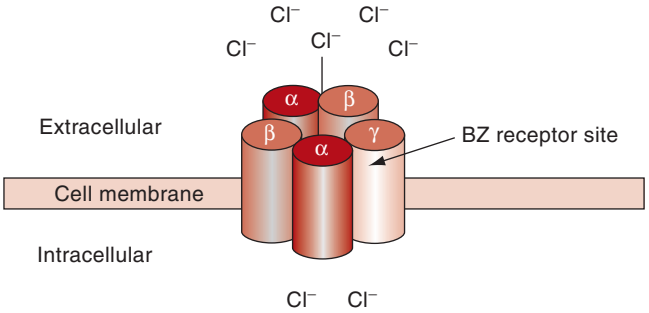



**Figure 105–1** *$GABA_A$ receptor complex with benzodiazepine recognition site.*

Multiple subtypes have been identified for the glycoprotein subunits constituting the $GABA_A$ receptor complex (Bateson 2006). The α subunit, which has at least six subtypes, serves a key role in the pharmacodynamic effects of this receptor. The most common configuration in the central nervous system is α1β2γ2. Benzodiazepines are relatively nonselective among the α subunits, with affinity for the 1, 2, 3, and 5 α subunit subtypes. The nonbenzodiazepine hypnotics have greater selectivity for the α1 subtype, which is associated with sedation, but also amnesia and ataxia (Mohler et al. 2002). This subtype selectivity may contribute to improved tolerability and decreased discontinuation effects among the nonbenzodiazepine agents.

Pharmacokinetic properties vary widely among the benzodiazepine receptor agonist hypnotics. All of these medications approved for the treatment of insomnia are absorbed relatively rapidly and may enhance sleep onset. The elimination half-life predicts the relative duration of sedating effects during the desired sleep period, but also potential undesired sedation or impairment during waking hours. Generally, tolerance to the sleep-enhancing effects of the benzodiazepine receptor agonist hypnotics has not been demonstrated in controlled clinical trials.

The benzodiazepine receptor agonist hypnotics generally are well tolerated. Adverse effects may include somnolence, headache, dizziness, nausea, diarrhea, and anterograde amnesia. Rarely patients may exhibit sleep walking or confused behaviors within a few hours after taking a hypnotic dose. Longer elimination half-lives and dosages increase the risk for next-day residual daytime effects and associated impairment. Rebound insomnia, characterized by worsened sleep for several nights relative to the pretreatment baseline insomnia, may occur upon sudden discontinuation of the medications in this class. Tapering the dose may reduce the magnitude of this effect. Recrudescence of the original insomnia symptoms also may occur with hypnotic discontinuation. New withdrawal symptoms rarely will occur with

rapid discontinuation of shorter-acting benzodiazepines (Roehrs and Roth 2006).

### Benzodiazepine Hypnotics

Generally, benzodiazepines have sedative, antianxiety, muscle-relaxant, anticonvulsant, and amnestic properties. The five benzodiazepine hypnotics currently available in the USA are estazolam, flurazepam, temazepam, triazolam, and quazepam. Their elimination half-lives range from a few hours (triazolam) to a few days (flurazepam and quazepam). Estazolam, flurazepam, and quazepam have active metabolites. Benzodiazepine hypnotics not available in the USA include flunitrazepam, loprazolam, lormetazepam, and nitrazepam. Flunitrazepam is considered an abused substance in the USA.

### Nonbenzodiazepine Hypnotics

There are four nonbenzodiazepine hypnotic formulations available in the USA: eszopiclone, zaleplon, zolpidem, and zolpidem extended release. The elimination half-lives range from the ultrashort zaleplon at 1 hour to eszopiclone at approximately 6 hours in adults. Zopiclone is available in selected countries outside of the USA. Eszopiclone and zolpidem extended release are approved by the FDA, with indications for treating insomnia associated with difficulty with sleep onset and sleep maintenance, and both have no implied limitation on their duration of use.

While the clinical trials for benzodiazepine hypnotics have been relatively short term, nightly and non-nightly dosing studies with the nonbenzodiazepine hypnotics have been conducted for extended periods. These have included placebo-controlled, double-blind subjective efficacy assessments for 6 months of treatment and open-label safety and tolerability studies for 1 year of use. It has been demonstrated that efficacy is maintained without the development of tolerance and that adverse events remain relatively infrequent with extended use (Ancoli-Israel et al. 2005, Erman et al. 2006a, Krystal et al. 2003, Perlis et al. 2004, Roth et al. 2005).

### Prescribing Guidelines

The benzodiazepine receptor agonist hypnotics should generally be taken when one is going to bed. Doses prior to bedtime may risk psychomotor impairment, confusion, and amnesia. Patients should avoid hazardous activities after taking the hypnotic and should be prepared to spend at least 7–8 hours in bed following ingestion of the medication. The exception is the very short-acting zaleplon, which no longer should be active 4 hours following ingestion. Although none of these hypnotics specifically is indicated for middle-of-the-night dosing, the short half-life of zaleplon does allow greater flexibility in the timing of the dose.

Lower doses generally are recommended for older adults and patients with hepatic impairment. The concomitant use of other CNS depressants, including alcohol and various psychotropic medications, may lead to excessive sedation, as well as cognitive and psychomotor impairment. There is a relatively low risk of pharmacokinetic interaction with these approved hypnotics, as none are significant inducers or inhibitors of hepatic metabolic isozymes. Concomitant medications will rarely inhibit the metabolism of the hypnotics and increase their pharmacokinetic area under the curve and the peak serum concentration (Hesse et al. 2003). All of the benzodiazepine receptor agonist hypnotics are pregnancy category C, with the exception of immediate-release zolpidem, which is category B.

### Clinical Considerations

The benzodiazepine receptor agonist hypnotics have durations of action ranging from very short to very long. Accordingly, medication selections can be made to optimize insomnia efficacy for individual patients while minimizing the risk of undesired daytime effects. The newer nonbenzodiazepine hypnotics have been popular choices due to the short to moderately short half-lives and the generally positive tolerability and safety profiles. Although primarily intended for bedtime dosing and nighttime sleep, they may be employed later during the night or when schedules require daytime sleep. Caution regarding the hypnotic duration of action is necessary when less than 8 hours is available for sleep. Patients taking longer-acting hypnotics should avoid hazardous daytime activities until they can assess potential impairment from the medications. The long half-life benzodiazepine hypnotics can accumulate with nightly dosing so that daytime blood levels increase and reach a steady state only after 1 week or longer (Vermeeren 2004).

Hypnotic medications may be taken nightly or on an as-needed basis, which may be episodic, frequent, or rare. Patients may begin with nightly use and transition to intermittent dosing. Placebo-controlled clinical trials with both zolpidem formulations have demonstrated continued efficacy for several months of non-nightly use (Erman et al. 2006a, Perlis et al. 2004, Walsh et al. 2000). Rebound insomnia was not evident on discontinuation from intermittent use. Insomnia is a chronic disorder, and some patients clearly benefit from chronic treatment. The formal indications for the two most recently approved hypnotics, eszopiclone and zolpidem extended release, do not include any implied restriction on the duration of use.

The potential for abuse or dependence of benzodiazepine receptor agonist medications has been a long-standing concern. Although these hypnotics do share some degree of abuse liability, the risk is very low with insomnia patients who do not have substance abuse comorbidity. Most patients taking hypnotics use them for up to a few weeks. Longer-term bedtime use at therapeutic doses generally reflects therapy-seeking behavior, rather than abuse. Dose escalation of hypnotics is rare (Roehrs and Roth 2006, Walsh et al. 2005).

## Selective Melatonin Receptor Agonist

Several investigational agents have targeted the sleep-promoting and circadian rhythm-entraining activity associated with the SCN and the effects of endogenous melatonin. One selective melatonin receptor agonist is currently available; however, others are in developmental phase.

Ramelteon is the single (S)-enantiomer of a tricyclic indan derivative. It was developed to target the sleep-enhancing role performed by the melatonin receptors in the SCN. Ramelteon is unique in being a nonsedating, sleep-promoting medication with a novel mechanism of action. It does not interact to a significant degree with other neurotransmitter systems, including GABA and the monoamines. The FDA approval is for the treatment of insomnia characterized by difficulty with sleep onset. There is no implied limitation for

the duration that it may be used. Clinical trials have demonstrated efficacy in improving sleep onset in both objective and subjective assessments in adult and older adult subjects (Seiden et al. 2005, Zammit et al. 2005).

### Mechanism of Action

Ramelteon attenuates the circadian arousal signal that normally is present in the evening (see Figure 105–2). Over time it may improve sleep onset through stabilization of the circadian system. It is a selective agonist for the $MT_1$ and $MT_2$ melatonin receptor subtypes, which are present in high concentrations in the SCN. Agonists at the $MT_1$ subtype promote sleep onset by decreasing the firing rate of selected SCN neurons, while the $MT_2$ subtype appears to have a central role in the reinforcement and entrainment of the circadian rhythm that strongly influences the timing of the sleep–wake cycle (Kato et al. 2005). Animal studies have shown greater potency in comparison with exogenous melatonin (Miyamoto et al. 2004, Yukuhiro et al. 2004). Human studies have shown a relatively flat dose–response relationship (Erman et al. 2006b).

### Pharmacokinetics

Ramelteon is rapidly absorbed and reaches a peak concentration within 1 hour. A high fat meal will decrease absorption and may decrease efficacy. The elimination half-life is under 3 hours. Ramelteon is metabolized primarily through the CYP1A2 isozyme and secondarily through the CYP2C subfamily and CYP3A4 isozymes. There is one active metabolite (M-II), which has an elimination half-life of 2–5 hours and the same pharmacodynamic characteristics as the parent compound, but at markedly reduced potency (Karim et al. 2006, Takeda Pharmaceuticals North America 2005).

### Prescribing Guidelines

Ramelteon is available in a single 8-mg strength, which is the dose recommended for adults and older adults, and in patients with mild-to-moderate COPD, sleep apnea, and hepatic impairment. It should not be coadministered with fluvoxamine, which may inhibit the metabolism of ramelteon. It may be taken approximately 30 minutes prior to bedtime, as there are no psychomotor or cognitive impairments associated with the medication. However, patients should avoid hazardous activities after taking the medication due to the anticipated sleepiness. It may be used on a chronic basis and is classed as nonscheduled by the DEA (Takeda Pharmaceuticals North America 2005).

### Clinical Considerations

Ramelteon may be beneficial for patients with difficulty falling asleep and remaining asleep during the early part of the night. It may not help with symptoms of sleep maintenance or early morning awakening. Patients taking ramelteon may not experience the medication's maximum benefit in reducing the sleep-onset latency until they have taken it for several nights or, perhaps, a few weeks. They should be informed that their experience with ramelteon will not cause the presleep sedation that they may have noted with other sedating OTC or prescription medications.

Ramelteon generally is well tolerated. The adverse events reported by at least 2% more of the ramelteon subjects compared to placebo subjects during the clinical trials included somnolence, dizziness, and fatigue (Takeda Pharmaceuticals North America 2005). It is not associated with any discontinuation effects, such as withdrawal symptoms or rebound insomnia. Ramelteon has been assessed for up to 1 year of nightly use in an open-label study (DeMicco et al. 2006).

Ramelteon has been shown to have a complete absence of abuse liability in studies with animals and humans. In a double-blind, crossover study, sedative abusing subjects were given ramelteon (16, 80, and 160 mg), placebo, and an active control (triazolam). Measures of drug likeability, behavioral and cognitive performance, and ataxia all showed no differentiation between ramelteon and placebo, whereas high-dose triazolam was associated with impairment and elevated likeability (Johnson et al. 2006).

## Prescription Medication Off-Label Use

A wide assortment of sedating medications without formal indications for the treatment of insomnia is prescribed

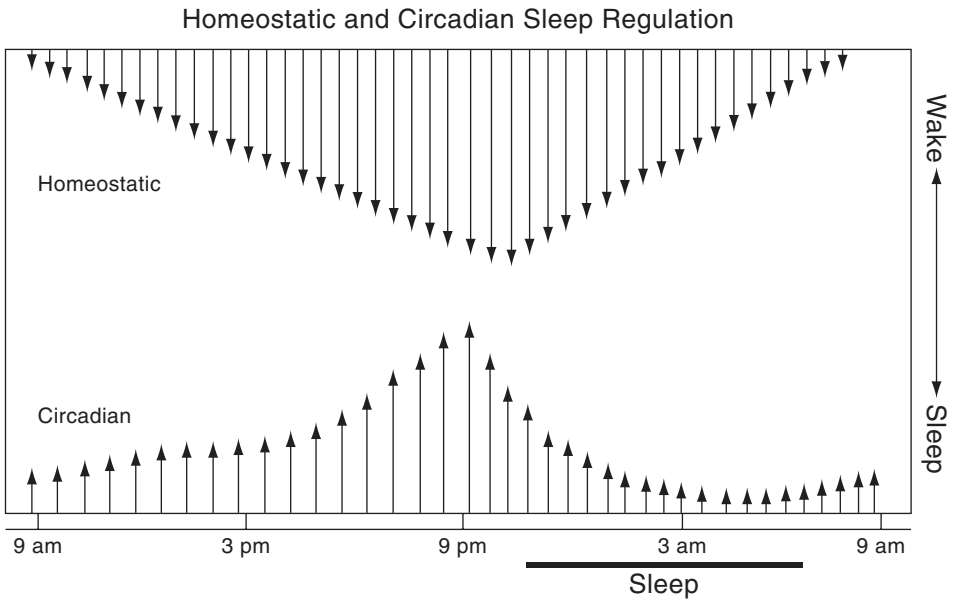



**Figure 105–2** *Normal homeostatic and circadian sleep-wake cycle influences during a 24-hour period.*

with the primary intention of improving sleep onset, maintenance, and quality (Roehrs and Roth 2004). These are mostly antidepressants but also include antipsychotics and other psychotropic agents. A survey of prescribing practices during the year 2002 showed that three of the top four medications prescribed in association with insomnia were sedating antidepressants (Walsh 2004). Historically, a decline in benzodiazepine prescriptions for insomnia during the 1980s and 1990s coincided with a significant rise in the use of trazodone (Walsh and Schweitzer 1999).

Several factors likely have contributed to the widespread off-label use of these medications. Although these sedating agents may be selected for psychiatric patients with prominent insomnia symptoms, often they are prescribed for individuals with no psychiatric comorbidity. Since insomnia frequently is associated with depressive disorders, it may seem that an antidepressant always would be beneficial. The appeal of these medications may be enhanced by the lack of abuse liability and an absence of restrictions on their duration of use. Until recently, all FDA-approved insomnia treatment medications were DEA Schedule IV controlled substances and were indicated for short-term use. In some cases, cost may also have been an issue due to the availability of generic formulations of older antidepressants.

Generally, there is limited insomnia efficacy evidence in nonpsychiatric populations, and there are significant safety concerns with all of these medications. Many clinical studies are short term, have few subjects, are not placebo controlled, have only subjective outcome measures, and do not incorporate dose–response analyses. Moreover, risk–benefit considerations have not been well delineated for insomnia populations without psychiatric comorbidity. Common to all of these medications is the risk of undesired daytime sedation and related impairment due to the relatively long elimination half-lives, generally in the range of 15–30 hours. Although prominent withdrawal effects are unlikely, rebound insomnia may occur with sudden discontinuation.

## Sedating Antidepressants

Antidepressant medications with sedating properties are among the most widely prescribed drugs for insomnia patients with and without psychiatric comorbidity (Walsh 2004). In mood and anxiety disorder patients, they may be employed as a single agent to promote both improved sleep and other psychiatric symptomatology. Often this is associated with residual daytime sedation. More commonly, these agents are prescribed at a relatively low dose, sometimes in combination with other psychiatric medications. The antidepressants most commonly recommended for the treatment of insomnia have been the tricyclic antidepressants amitriptyline and doxepin, trazodone, and mirtazapine. Nefazodone previously had been used to enhance sleep but currently is prescribed infrequently due to an increased risk of liver failure. The majority of sleep-related studies with sedating antidepressants have been with populations of depressed patients, although some have been done with insomnia subjects and healthy individuals with no sleep complaints.

Most available antidepressants have varying degrees of serotonin (5-HT) and norepinephrine (NE) presynaptic reuptake inhibition and assorted postsynaptic receptor interactions. While these are thought to be fundamental to the antidepressant effects, sedation likely results from the postsynaptic antagonist activity of medications on 5-HT, NE, and histamine receptors.

### Tricyclic Antidepressants

Tricyclic antidepressants include both tertiary and secondary amines. The tertiary amine tricyclics, which tend to be more sedating, include amitriptyline, doxepin, imipramine, and trimipramine. Doxepin has been shown to decrease sleep-onset latency, increase total sleep time, decrease the amount of REM sleep, and delay the onset of the first REM episode (Hajak et al. 2001, Roth et al. 1982). The tricyclic antidepressants may exacerbate periodic limb movements in vulnerable individuals and are associated with a wide range of adverse effects. Potential toxicity includes cardiac arrhythmias and seizures. Anticholinergic effects may include blurred vision, dry mouth, constipation, urinary hesitancy and retention, confusion, and delirium. Antihistaminic effects may include sedation, increased appetite, and weight gain. Hypotension may result from postsynaptic alpha$_1$ adrenergic receptor antagonist activity. Amitriptyline is strongly anticholinergic, and doxepin is strongly antihistaminic. Recent studies have examined the sleep-enhancing effects of ultra-low-dose doxepin in strengths less than 10 mg.

### Trazodone

Although trazodone is widely prescribed to treat insomnia, there is minimal clinical trial evidence to support its efficacy (Mendelson 2005, Montgomery et al. 1983, Saletu-Zyhlarz et al. 2002). Antidepressant doses often range from 300 to 600 mg; however, it generally is prescribed for insomnia in the range from 25 to 150 mg. Studies have reported improved sleep latency, total sleep time, and sleep efficiency. Trazodone has postsynaptic antagonist activity at 5-HT$_{1A}$, 5-HT$_{1C}$, 5-HT$_2$, histamine H$_1$, and alpha$_1$ adrenergic receptors, as well as weak presynaptic serotonin reuptake inhibition. It has an elimination half-life of approximately 5–9 hours and is metabolized to a serotonergic metabolite, meta-chlorophenylpiperazine (mCPP). Residual sedation is a common complaint. Orthostatic hypotension may occur due to the alpha$_1$ antagonism. Priapism is a rare adverse event. Case reports suggest that trazodone may contribute to ventricular arrhythmias and the development of serotonin syndrome (Janowsky et al. 1983, Rao 1997).

### Mirtazapine

Mirtazapine is commonly associated with sedation that may be beneficial for nighttime sleep, but undesired during waking hours. The elimination half-life is approximately 20–40 hours. It has presynaptic antagonist activity at alpha$_2$ autoreceptors and postsynaptic antagonistic effects at 5-HT$_1$, 5-HT$_2$, histamine H$_1$, and alpha$_1$ adrenergic receptors. The sedating property likely results from a combination of these actions. Clinical studies have demonstrated improvements in sleep-onset and maintenance parameters in normal subjects and patients with major depression (Aslan et al. 2002, Winokur et al. 2003). Mirtazapine also has been shown to increase slow-wave sleep (Schmid et al. 2006). It has been suggested that mirtazapine may be more sedating at lower doses due to the balance of serotonergic and histaminic effects relative to noradrenergic activity. Adverse effects may include increased appetite and weight gain.

## Sedating Antipsychotics

Patients with psychiatric disorders often report improved nighttime sleep when taking antipsychotic medications. Among the atypical antipsychotics, clozapine, olanzapine, and quetiapine are especially sedating. Although the clinical studies are limited in size and number, they have examined the subjective and polysomnographic sleep effects of sedating antipsychotics in populations of psychiatric patients, insomnia subjects, and healthy subjects without sleep complaints. Studies have reported improvements in sleep latency, total sleep time, and sleep efficiency (Cohrs et al. 2004, Salin-Pascual et al. 1999). There have been variable effects on specific sleep stages. Beneficial sleep effects may result from combinations of antagonist activity at histaminic and multiple subtypes of 5-HT receptors. Both typical and atypical antipsychotics are associated with a wide spectrum of potential adverse effects. The atypical antipsychotics increase the risk of weight gain and impaired glucose utilization. Undesired sleep effects may include excessive sedation, sleep fragmentation, and increased periodic limb movements during sleep. The antipsychotics are employed optimally as sleep-promoting agents within the confines of the approved psychiatric indications.

## Miscellaneous Prescription Medications

Aside from approved insomnia treatment medications, antidepressants, antipsychotics, and antihistamines, various other psychotropic agents occasionally are prescribed for the treatment of insomnia. Among these are barbiturates, chloral hydrate, cyclobenzaprine, gamma-hydroxybutyrate (GHB), and assorted anticonvulsants. All may have sedating effects but are associated with significant safety concerns, including toxicity and potential lethality.

### Chloral Hydrate

Currently chloral hydrate most commonly is used for its acute sedating effects in preparation for medical tests and procedures. It rarely is recommended for the treatment of insomnia due to toxicity and the development of tolerance and dependence. Chloral hydrate is available in oral capsule, syrup, and suppository formulations. It is very rapidly metabolized to trichloroethanol, which modulates the $GABA_A$ receptor complex. The elimination half-life is approximately 5–10 hours. Chloral hydrate has been shown to improve sleep onset and continuity, but tolerance to the beneficial effects evolves with repeated doses. Discontinuation may result in withdrawal symptoms. Adverse effects may include unpleasant taste, GI distress, respiratory depression, hypotension, and ataxia. It can be lethal in overdose.

### Gamma Hydroxybutyrate

GHB is a sedating abused substance, which simultaneously is classed by the DEA as Schedule I and III. As sodium oxybate (Xyrem), GHB is approved by the FDA for the treatment of the cataplexy and excessive daytime sleepiness in narcolepsy patients and is distributed through a single centralized pharmacy. Clinical trials have shown that it enhances nighttime slow-wave sleep. Typically it is given in a liquid form in two nighttime doses. The approximate elimination half-life is less than 1 hour. The pharmacodynamic actions are not fully elucidated; however, there are effects on dopamine activity and the $GABA_B$ receptor. The improvements to nighttime sleep have led some practitioners to prescribe GHB on an off-label basis for insomnia patients who have not benefited from standard treatments. Potential adverse effects include nocturnal enuresis, confusion, mental depression, respiratory depression, coma, and death. GHB should not be combined with alcohol or other CNS depressants.

### Anticonvulsants

Several anticonvulsant medications have been observed to have sedating properties that may be beneficial for nighttime sleep but represent an undesired effect during the daytime. Clinical trials assessing insomnia treatment efficacy have been performed with selected anticonvulsants, and some are occasionally prescribed with the primary intention of improving sleep. Two examples are gabapentin (Neurontin) and tiagabine (Gabitril).

Gabapentin is indicated for the treatment of epilepsy and postherpetic neuralgia. The mechanism of action is unknown. The observed sedating effects have led to clinical use with insomnia patients and controlled clinical trials (Bateson 2006). It has been reported to increase slow-wave sleep in normal subjects (Foldvary-Schaefer et al. 2002). Adverse effects include dizziness, somnolence, fatigue, and ataxia.

Tiagabine presynaptically inhibits GABA reuptake through binding at the GAT-1 transporter. The result is increased GABA availability at the synapse. It is indicated as adjunct therapy in the treatment of partial seizures. Clinical studies have demonstrated increases in slow-wave sleep (Walsh et al. 2006). Adverse effects include dizziness, somnolence, nervousness, and tremor. An FDA warning has noted that tiagabine has been associated with new-onset seizures and status epilepticus in individuals without epilepsy

## OTC Medications

OTC antihistamine sleep aids are regulated substances that are available without a prescription. Most of these first-generation, centrally acting antihistamine products contain diphenhydramine hydrochloride; however, some have diphenhydramine citrate or doxylamine succinate as the active ingredients. They are marketed as single agents or in combination with acetaminophen or aspirin and are approved for occasional sleeplessness for people having difficulty falling asleep. None are specifically indicated for the treatment of insomnia. There are very limited efficacy data in the treatment of sleep disturbances (Kudo and Kurihara 1990). In the USA, OTC diphenhydramine is available in doses up to 50 mg and doxylamine up to 25 mg.

Sleep may be promoted by a sedating action resulting from postsynaptic $H_1$ receptor blockade that inhibits the stimulating effect of histamine in the mammillary nucleus of the posterior hypothalamus. Normally, these histaminergic neurons promote wakefulness through extensive projections to the cerebral cortex and brainstem (Tashiro and Yanai 2007). The OTC sleep aids are rapidly absorbed and typically reach a peak blood level within 1 hour. The relatively long half-lives of these compounds (approximately 8 hours) may lead to residual next-morning sedation and a complaint of grogginess. Tolerance to the sedating effects may develop (Richardson et al. 2002). Adverse effects may include paradoxical stimulation and restlessness, and thickening of bronchial secretions. Postsynaptic muscarinic

receptor blockade may produce anticholinergic effects, such as blurred vision, urinary hesitance and retention, and confusion and delirium. Elderly patients and those concomitantly on medications with anticholinergic effects are especially vulnerable for these adverse reactions. Additionally, there may be additive effects with other CNS depressants.

## Complementary and Alternative Substances

Numerous unregulated compounds are marketed as sleep aids. Limited efficacy evidence supports the claims, and safety data generally are lacking. Common ingredients in these homeopathic and herbal preparation sleep aids are valerian, hops, kava, passion flower, skullcap, and lavender. Generally these compounds include large numbers of individual chemicals. Therefore, specific active ingredients and mechanisms of action are difficult to determine. Valerian preparations have been the best studied one in this category. Improved sleep parameters have been reported in some studies; however, the overall findings remain inconclusive (Bent et al. 2006).

Melatonin preparations have been used extensively in the attempt to improve sleep. Endogenous melatonin has a central role in the regulation of the sleep–wake cycle. Since endogenous melatonin normally is elevated during the nighttime when humans sleep, theoretically supplementing the body's melatonin could enhance sleep onset, duration, and quality. Melatonin is synthesized primarily in the pineal gland. Exogenous melatonin is rapidly absorbed and has an elimination half-life of less than 1 hour. Melatonin has been studied across a wide dose range. Meta-analyses of clinical trials examining the efficacy of melatonin for various insomnia populations have failed to provide consistent positive findings. However, it appears to be safe for short-term use. Potential long-term risks are unknown. While bedtime use to enhance sleep onset may have limited value, melatonin may be beneficial in the treatment of circadian rhythm disorders, particularly the delayed sleep phase syndrome.

## Insomnia in Psychiatric Patients

In recent years, the relationship between psychiatric disorders and insomnia has come to be appreciated as circular and synergistic. Psychiatric illnesses, particularly anxiety and mood disorders, have long been recognized as frequent causes of insomnia. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnostic criteria formalize this association in some cases (American Psychiatric Association 1994). Clinical experience suggests that almost all patients with mood and anxiety disorders have sleep disturbances either chronically or surrounding exacerbations of their psychiatric illnesses. However, it has become evident that insomnia also increases the risk of future relapse or the development of new onset mood, anxiety, and substance abuse disorders. This association can promote a downward spiral of symptom severity and quality of life for patients that may further complicate treatment efforts. On the other hand, the close relationship of insomnia, depression, and anxiety symptoms can be viewed as an opportunity for targeted approaches that may provide significant benefits for patients.

In addition to major depression and dysthymic disorder, insomnia often occurs with bipolar disorder during depressive and manic episodes. Although manic patients may report a decreased need for sleep, many others feel distressed due to an inability to sleep. Sleep loss from any cause, including jet lag and work schedules, may lead to the onset or progression of mania in patients with bipolar disorder. Early sleep-targeted interventions may prevent or limit exacerbations for these patients (Leibenluft et al. 1996, Young 1995).

Insomnia is especially problematic for anxiety disorder patients with panic disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia. Patients with panic disorder often will experience distressing panic episodes that awaken them from sleep. They may evolve considerable anticipatory anxiety about going to sleep, which ultimately may lead to sleep insufficiency and increased anxiety. Posttraumatic stress disorder patients often experience poor sleep quality and vivid nightmares (Green 2003). Patients with generalized anxiety disorder often experience chronic anxiety that affects them throughout the night, with resulting difficulty falling asleep and repeated awakenings. Social phobia patients report significantly worse sleep quality and difficulty falling asleep in comparison with healthy control subjects (Stein et al. 1993).

Treating the insomnia symptoms of patients with concurrent psychiatric disorders is a two-pronged approach. Specific therapeutic interventions addressing the primary psychiatric condition may include psychotherapeutic, behavioral, and pharmacologic strategies. Optimizing the treatment of the underlying disorder should ultimately improve sleep. However, many commonly prescribed antidepressants, such as the SSRIs, rarely improve the sleep symptoms rapidly, and some patients develop insomnia as a side effect from the medication. The use of a sedating antidepressant to treat depression and insomnia is limited by daytime sedation and other adverse effects.

General approaches to insomnia are those applicable to a broad range of patients and include sleep hygiene and behavioral interventions, cognitive behavioral therapy, and insomnia treatment medications. These therapies may be employed concurrently, with specific treatment strategies targeting the psychiatric disorders. There are several advantages to this two-pronged approach. First, there is greater choice among medications for the psychiatric symptoms, rather than restricting the options to sedating agents. There also is greater opportunity for flexibility in the dosage, timing, and duration of use of medications targeting different symptoms. Second, hypnotic medications may provide immediate relief and, subsequently, decreased distress and improved quality of life. A hypnotic can offset the stimulating effect of some antidepressants. Finally, these general insomnia treatment approaches can directly address the perpetuating factors that reinforce chronic insomnia.

In clinical practice, hypnotics often are prescribed concomitantly with antidepressants for patients with mood and anxiety disorders. Pharmacokinetic and pharmacodynamic studies of fluoxetine and sertraline combined with zolpidem have been performed in healthy, nondepressed women (Allard et al. 1998, 1999). No clinically significant interactions were identified. In another clinical study, patients prescribed an SSRI concurrently with zolpidem or a placebo were assessed. The study population included individuals successfully treated for depression with an SSRI, but who were complaining of persistent insomnia. The hypnotic-treated

patients reported significantly improved sleep and daytime functioning (Asnis et al. 1999). Eszopiclone was studied in a placebo-controlled trial in depressed patients treated with fluoxetine. The patients in the eszopiclone–fluoxetine group demonstrated rapid improvement in sleep parameters as well as a greater magnitude of the antidepressant effect (Fava et al. 2006).

While it is important to recognize and manage the insomnia symptoms that may result from psychiatric illnesses, it also is critical to evaluate psychiatric patients for other potential causes of their sleep disturbances. These may include the stimulating effects of psychotropic and other medications, medical disorders, underlying primary sleep disorders, circadian rhythm disorders, irregular schedules, and maladaptive habits and routines. Sleep apnea patients can present solely with insomnia complaints. Restless legs syndrome and periodic limb movements, which can be exacerbated by most antidepressants, can result in difficulty falling asleep and repeated awakenings. Agoraphobic or socially withdrawn patients may spend excessive time at home, sleep at irregular times, and avoid the photoperiod that normally reinforces the sleep–wake cycle.

## Summary or Conclusions

A wide assortment of substances and medications has been recommended for individuals suffering with insomnia. Compared with older insomnia treatment medications, the current-generation medications maintain efficacy but have significantly improved safety profiles. The diversity of approved agents allows for the medication selection to be customized for individual patients, depending on their clinical histories. Recently, there have been significant advances in both pharmacodynamic and pharmacokinetic approaches in promoting improved sleep. The most recently approved insomnia treatment mediations no longer have an implied limitation of their duration of use, and the indications specifically note efficacy for sleep onset and sleep maintenance. New pharmacologic approaches continue to be developed.

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CHAPTER

# 106 Stimulants

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## Treatment of Children with Disruptive Behavior Disorders

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This chapter concentrates on the use of psychostimulants in the long-term treatment of children with disruptive behavior disorders—in particular, attention-deficit/hyperactivity disorder (ADHD). The indications for stimulants use, the methods for initiating treatment, as well as the interactions of their effects with comorbid psychiatric problems and developmental disorders are discussed. Especially important will be evidence for the efficacy of the sustained-release preparations.

### Medications

Amphetamines and methylphenidates (MPHs), and magnesium pemoline are two groups of stimulants that received U.S. Food and Drug Administration (FDA) approval for the ADHD treatment in pediatric population. They are available in both brand and generic formulations, as well as in long- and short-duration (immediate-release) preparations. In the past decade, there has been a flurry of new stimulant drug approvals by the FDA for the pediatric ADHD treatment. Previously, only dextroamphetamine (DEX), MPH, and pemoline (PEM) were sanctioned for use in children. More recently, osmotic-release methylphenidate (OROS-MPH), beaded methylphenidate (B-MPH), dexmethylphenidate, long-duration mixed salts of amphetamine (MAS), and several other formulations have been approved. Characteristics of these medications can be found in Tables 106–1 and 106–2. Both DEX and MPH form the active ingredients of these new preparations. Structurally, they are related to the catecholamines, dopamine (DA), and norepinephrine (NE). The term *psychostimulant* used for these compounds refers to their ability to increase CNS activity in some, but not all, brain regions.

As demonstrated by more than 200 placebo-controlled investigations, psychostimulants are highly effective in reducing core symptoms of childhood ADHD. Approximately 70% of patients respond to stimulants compared with 13% responding to placebo. Short-term efficacy is more pronounced for behavioral rather than cognitive and learning abnormalities. The stimulant treatment evidence has been supplemented by two large multisite randomized controlled trials (RCTs)—the Multimodal Treatment Study of ADHD (MTA Study; MTA Cooperative Group 1999) and the Preschool ADHD Treatment Study (PATS)—that further support the short-term efficacy in young children. These studies, plus the 1998 NIH Consensus Development Conference on ADHD and the publication of the McMaster Evidence Based Review of ADHD Treatments (Jahad et al. 1999), have emphasized a strong evidence base for the ADHD treatment with stimulants.

RCTs conducted prior to 1998 reported a few key adverse events associated with stimulants—insomnia,

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**Table 106–1 Stimulant Drugs, Doses, and Pharmacodynamics**

| Medication | Forms | Pediatric Dose Start/Typical | Peak Effect (hr) | Duration of Action (hr) |
|---|---|---|---|---|
| Dexmethylphenidate | | | | |
| Dextromethylphenidate | 2.5, 5, 10 mg tabs | 2.5 mg AM/10 mg b.i.d. | 1–4 | 5–6 |
| Beaded dextromethylphenidate sustained release* | 5, 10, 15, 20 mg caps | 5 mg AM/10 mg AM | 1; 4 | 12 |
| DEX | | | | |
| Short-acting | | | | |
| Generic* | 5, 10 mg tabs | 5 mg b.i.d./10 mg b.i.d. | 1–3 | 4–6 |
| Dextroamphetamine generic* | 5, 10 mg tabs | 5 mg b.i.d./10 mg b.i.d. | 1–3 | 4–6 |
| Dextroamphetamine brand* | 5 mg tabs | 5 mg b.i.d./10 mg b.i.d. | 1–3 | 4–6 |
| Long-acting | | | | |
| Generic* | 5, 10, 15 mg caps | 5 mg AM/15 mg AM | 1–4 | 6–8 |
| Dextroamphetamine brand* | 5, 10, 15 mg caps | 5 mg AM/15 mg AM | 1–4 | 6–8 |
| Lisamfetamine mesylate | 30, 50, 70 mg caps | 30 mg AM/70 mg AM | 2–3 | Up to 12 |
| MPH | | | | |
| Short-acting | | | | |
| Methylphenidate generic | 5, 10, 20 mg tabs | 5 mg b.i.d./10 mg t.i.d. | 1–3 | 3–5 |
| Methylphenidate brand | 5, 10, 20 mg tabs | 5 mg b.i.d./10 mg t.i.d. | 1–3 | 3–5 |
| Methylphenidate generic | 5, 10, 20 mg tabs | 5 mg b.i.d./10 mg t.i.d. | 1–3 | 3–5 |
| Methylphenidate generic chewable tablets | 2.5, 5, 10 mg tabs | 5 mg b.i.d./10 mg t.i.d. | 1–2 | 3–5 |
| Methylphenidate oral solution | 5 mg/5 mL, 10 mg/5mL† | 5 mg b.i.d./10 mg t.i.d. | 1–3 | 3–5 |
| Immediate-acting | | | | |
| Methylphenidate immediate release generic | 20 mg tabs‡ | 20 mg AM/40 mg AM | 3 | 3–8 |
| Methylphenidate immediate release brand | 20 mg tabs‡ | 20 mg AM/40 mg AM | 3 | 3–8 |
| Methylphenidate immediate release generic | 10, 20 mg tabs‡ | 10 mg b.i.d./30 mg AM | 3 | 3–8 |
| Methylphenidate immediate release generic | 10, 20 mg tabs‡ | 10 mg b.i.d./30 mg AM | 1–3 | 3–8 |
| Long-acting | | | | |
| Methylphenidate beaded long-acting generic | 10, 20, 30, 40, 50, 60 mg tabs | 10 mg AM/30 mg AM | 5 | 8–12 |
| Methylphenidate beaded long-acting brand* | 10, 20, 30, 40 mg caps | 10 mg AM/30 mg AM | 5 | 8–12 |
| OROS methylphenidate | 18, 27, 36, 54 mg tabs‡ | 18 mg AM/36 mg AM | 8 | 10–12 |
| Transdermal methylphenidate patch | 12.5 cm† (10 mg), 18.75 cm† (16 mg), 25 cm† (20 mg), 37.5 cm† (27 mg) | 10 mg patch on 9 hrs, off 15 hrs | 7–9 | 10–12 |
| | transdermal patch§ | 30 mg patch on 9 hrs, off 15 hrs | | |
| MAS | | | | |
| Short-acting | | | | |
| Mixed salts of amphetamine generic* | 5, 7.5, 10, 12.5, 15, 20, 30 mg tabs | 5 mg b.i.d./10 mg b.i.d. | 1–3 | 4–6 |
| Dextroamphetamine brand* | 5, 7.5, 10, 12.5, 15, 20, 30 mg tabs | 5 mg b.i.d./10 mg b.i.d. | 1–3 | 4–6 |
| Long-acting | | | | |
| Mixed salts of amphetamine long acting* | 5, 10, 15, 20, 25, 30 mg caps | 5 mg AM/30 mg AM | 1–4 | 8–10 |
| PEM | | | | |
| Pemoline | 18.75, 37.5, 75 mg tabs | 37.5 mg AM/112.5 mg AM | 2–4 | 4–6 |
| | 37.5 mg chewable tabs | | | |

*Should not be taken with antacids or other drugs that decrease gastric acidity.

†Available in bottles containing 500 mL.

‡Must be swallowed whole, not crushed or chewed.

§The four patch sizes deliver 10, 15, 20, 30 mg over 9 hrs, respectively. It is supplied in sealed trays containing 10−30 patches in individual pouches.

**Table 106–2 Commercial Forms of Stimulants Available**

| Drug | Mechanism of Drug Release | Duration of Action (hr) | Sprinkle Form Available? | Total Pediatric Daily Dose (mg) | Dose Strengths Available |
|---|---|---|---|---|---|
| Mixed salts of amphetamine | 1 pulse | 4–6 | No | 20 | 5, 7.5, 10, 12.5, 15, 20, 30 mg |
| Mixed salts of amphetamine long acting | 2 pulse | 8–10 | Yes | 30 | 5, 10, 15, 20, 25, 30 mg |
| OROS methylphenidate | 3 pulse | 10–12 | Yes | 36 | 18, 27, 36, 54 mg |
| Transdermal methylphenidate patch | Transdermal | 10–12 | No | 30 | 12.5, 18.75, 25, 37.5 $cm^2$ |
| Dextroamphetamine sustained release | 1 pulse | 6–8 | No | 15 | 5, 10, 15 mg |
| Dextromethylphenidate | Chiral | 5–6 | No | 10 | 2.5, 5, 10 mg |
| Beaded dextromethylphenidate | Chiral | 12 | Yes | 10 | 5, 10, 15, 20 mg |
| Beaded methylphenidate Celltech | 2 pulse | 8–12 | Yes | 30 | 10, 20, 30, 40, 50, 60 mg |
| Methylphenidate sustained release Celltech | Wax matrix | 3–8 | Yes | 30 | 10, 20 mg |
| Methylphenidate sustained release methylin | Wax matrix | 3–8 | Yes | 30 | 10, 20 mg |
| Methylphenidate brand | 1 pulse | 3–5 | No | 30 | 5, 10, 20 mg |
| Methylphenidate beaded brand | 2 pulse | 8–10 | Yes | 30 | 10, 20, 30, 40 mg |
| Methylphenidate sustained release brand | Wax matrix | 3–8 | Yes | 40 | 20 mg |
| Lisamfetamine mesylate | 1 pulse (delayed) | Up to 12 | No | 70 | 30, 50, 70 mg |

decreased appetite, stomachache, and headache—but did not support rarer and unexpected problems, such as visual hallucinations, cardiovascular accidents, or sudden unexpected death (SUD), which were reported in 2006 in the FDA's Adverse Event Report System (AERS). Although psychostimulants have been shown to retain their efficacy for as long as 14 months, concern remains that the long-term academic and social benefits of these medications have not yet been adequately demonstrated.

Stimulants demonstrate substantial efficacy in ameliorating the target ADHD symptoms by reducing gross motor overactivity, decreasing off-task behavior, increasing compliance with adult requests, and decreasing aggressivity (Greenhill et al. 1999). Not only are they effective, but they are also well tolerated and have a low rate of adverse events, with only 4% of children having to change to another medication in a controlled study of adverse events (Barkley et al. 1990). Their rapid action, relatively low-priced generic forms, the frequency with which the ADHD diagnosis is made, and wide range of tolerated doses are other reasons for popularity among practitioners.

Stimulants reduce disruptive behaviors cross-situationally (classroom, lunchroom, playground, and home) when repeatedly administered throughout the day. Compared to placebo, they have a significantly greater ability to decrease ADHD symptoms that interfere with classroom environment and have negative impacts on social relationships (Jacobvitz et al. 1990). Children interrupt and fidget less (Abikoff and Gittelman 1985b). In social situations, stimulants improve problem-solving activities with peers and ameliorate peer nomination rankings (Whalen et al. 1989). Stimulant treatment also reduces signs of conduct disorder (Klein et al. 1997), as well as overt and covert aggression (Gadow et al. 1990, Hinshaw et al. 1992). For these children, the maternal rates of disapproval, commands, and control diminish to the extent seen in interactions between non-ADHD children and their mothers (Barkley and Cunningham 1979, Barkley et al. 1984, Humphries et al. 1978).

On cognitive tasks, stimulants produce significant decreases in variability and impulsive responses. Research suggests that these medications can increase the accuracy of performance while improving short-term memory, reaction time, seatwork computation, problem-solving games with peers, and sustained attention (Hinshaw et al. 1989, Tannock et al. 1995b). Studies of time-action stimulant effects demonstrate different patterns of improvement for behavioral and attentional symptoms, with behavior affected more than attention. For example, a controlled, analog-classroom, MAS trial ($N = 30$) found rapid improvements on teacher ratings of behavior and math performance. These improvements occurred 1.5 hrs following the medication intake, with the duration of effects on behavior being specifically dependent on individual doses (Swanson et al. 1998). While stimulants show a large 0.8–1.0 effect size for behavioral measures, smaller 0.6–0.8 effect sizes are reported on cognitive measures (Spencer et al. 1996a). However, cognitive effects are still significant with major improvements observed during experimenter-paced continuous performance tests (Halperin et al. 1992, Pelham and Bender 1982, Spencer et al. 1996a). Some studies show correlations between plasma levels of MPH and performance on laboratory tasks (Greenhill et al. 2001a). Notably, these levels correlate with performance effects only if the plasma sampling timing is exact.

Similar beneficial effects of stimulants on behavior and attention have been shown in children without psychiatric disorders (Rapoport et al. 1980); thus, stimulant response is not diagnostically specific to ADHD. Stimulants continue to play a therapeutic role in other medical conditions such as narcolepsy and depression (Goldman et al. 1998). In addition, they can reduce manifestations of covert antisocial behaviors, such as stealing and property destruction (Hinshaw et al. 1992). Hyperactive conduct-disordered children treated with stimulants show reductions in aggressive behavior (Hinshaw 1991).

## Pharmacology

The exact CNS mechanism by which stimulants ameliorate ADHD symptoms is unknown. The drug's effect based on a single neurotransmitter has been discounted (Zametkin and Rapoport 1987), as well as its ability to correct the under- or overaroused CNS (Solanto 1984). According to the two-part theory of stimulant action (McCracken 1991), stimulants increase DA release, thus producing enhanced autoreceptor-mediated inhibition of ascending DA neurons. Simultaneously, stimulants increase adrenergic-mediated

inhibition of the noradrenergic-locus coeruleus via epinephrine activity. This theory awaits confirmation from basic research in animals and imaging studies in humans.

According to the positron emission tomography (PET) research, adults with a past history of ADHD have 8.1% lower levels of cerebral glucose metabolism compared to control subjects (Zametkin et al. 1990). The greatest differences were found in the superior prefrontal cortex and premotor areas. These areas are involved with functions deficient in children with ADHD, such as the modulation of attention and the ability to inhibit inappropriate responses. While several PET and $^{18}$F-fluorodeoxyglucose studies showed that stimulants increase brain glucose metabolism in the striatal and frontal regions (Ernst and Zametkin 1995), other studies (Matochik et al. 1993, 1994) did not find any changes in glucose metabolism during acute and chronic stimulant treatment. Also, no changes in cerebral glucose metabolism were found with PET scans for 19 MPH-treated and 18 DEX-treated adults with ADHD, even though significant changes in behavior were observed.

In related studies, single-photon emission computed tomography (SPECT) showed reduced frontal cerebral blood flow in five children with ADHD when given MPH compared to normal subjects (Vyborova et al. 1984). This agrees with another SPECT finding of greater overall uptake asymmetry present in ADHD children compared to normal subjects. Investigations of neuroanatomical relationships further support these findings. The midsagittal cross-sectional area of the corpus callosum, a structure that has multiple connections to frontal cortical areas, was measured using magnetic resonance images (MRIs) of 15 boys with ADHD and 15 matched boys without psychiatric disorders. Two out of seven anatomical areas were found to be significantly smaller in boys with ADHD.

Dopamine transporter (DAT) blockade is regarded as the putative mechanism for psychostimulants in the human CNS. For instance, MPH has high affinity for the DAT. PET scan data in adult substance abusers show that [11C] MPH concentration is maximal in striatrum, an area rich in DA terminals where DAT resides (Volkow et al. 1995). These scans reveal a significant difference in the pharmacokinetics of [11C] MPH and [11C] cocaine. Although both drugs display rapid uptake into striatum, MPH is more slowly cleared from brain. The authors interpret the slow reversal of binding to DAT to mean that MPH is not as reinforcing as cocaine, and why it is less likely to lead to self-administration. More recently, the same authors (Volkow et al. 2001) showed that therapeutic oral MPH doses significantly increase extracellular DA in the human brain: "Because DA decreases background firing rates and increases signal-to-noise in target neurons, we postulate that the amplification of weak DA signals in subjects with ADHD by MPH would enhance task-specific signaling, improving attention and decreasing distractibility."

Other hypotheses regarding the neurochemical basis of ADHD have focused on roles for both NE and DA, because all stimulant medications have their primary effects on these two neurotransmitter systems. Since DA has been associated with the maintenance of the activity levels and NE is important for the central regulation of attention, arousal, and vigilance, ADHD may be the result of a dysregulation in the NE and/or DA neurotransmitter systems. Drugs that selectively block the NE reuptake, including atomoxetine and the tricyclics, such as desipramine, imipramine, and clonidine, have been found to reduce ADHD symptoms in children.

One of the non-catecholamine neurotransmitters not affected by stimulants is serotonin (5-HT). However, data from several animal studies raise the possibility of the involvement of central 5-HT mechanisms in the ADHD pathophysiology. For instance, in rats, lesions and pharmacological manipulations that result in diminished 5-HT activity have been consistently reported to induce an increase in impulsive and aggressive behavior, and lead to a persistent pattern of overactivity. Furthermore, developmentally early DA-depleting lesions, which can result in hyperactivity, cause sprouting of 5-HT terminals. It is conceivable that this early interaction between the DA and the 5-HT neurotransmitter systems could have a substantial impact on the clinical presentation of ADHD in children.

Human biological data also raise the possibility of central 5-HT mechanisms involved in those children with ADHD who are comorbid for aggressive behavior. In a group of boys with disruptive disorders, approximately two-thirds of whom had ADHD, reduced cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid were associated with high aggression ratings at the 2-year follow-up (Castellanos et al. 1994). A reduced number of (3H)-imipramine binding sites, a putative index of presynaptic 5-HT activity, was reported in another study (Stoff et al. 1987). Halperin et al. (1994) found enhanced prolactin responses to a challenge dose of the 5-HT release reuptake inhibitor fenfluramine in a subgroup of children with ADHD characterized by aggressive behavior.

Neuroendocrine studies have indicated that psychostimulants produce central effects in children, suggesting that psychoneuroendocrine responses may be mediated by monoamine neurotransmitters. DEX releases DA, which exerts a tonic inhibitory control over prolactin release. DEX was reported to produce a suppression of mean sleep-related prolactin levels in 13 boys treated with 0.8 mg/kg per day for 6 months. Reports of the MPH effect on human growth hormone secretion have been divergent. This may be due to the 2.5-hr half-life of MPH, which is shorter than the 6–8-hr half-life of DEX. However when given acutely, MPH does not suppress prolactin release during the sleep period the way DEX does. However when given chronically, MPH has been shown to suppress prolactin levels and release human growth hormone, while increasing beta-endorphin levels. Psychostimulants also suppress somatomedin in vitro, which would limit long bone growth if it occurred in vivo. This could explain the decrease in height velocity that has been reported during treatment. For example, the prolonged use of DEX (0.8 mg/kg) during a 12-month period in 13 boys with ADHD produced a trend ($P < 0.07$) toward decreased somatomedin. These same patients had shown medication-related decreases in height and weight velocity (Greenhill and Schwartz 1989, unpublished manuscript).

Psychostimulants are rapidly absorbed from the gut and thus act quickly, often within the first 30 min after ingestion. The metabolism of MPH is fast and complete, because it is not highly bound to plasma protein and does not disappear into fat stores. MPH peaks in plasma in 2–2.5 hrs and falls to half the peak (half-life) after 3 hrs. The parent compound

is metabolized by hydrolysis of the ester group to yield ritalinic acid. Approximately 20% is oxidized to p-hydroxy and -oxomethylphenidate by the liver. Although early pharmacokinetic data reported bioavailabilities of MPH in the 80% range, more recent studies have placed the actual figure close to 30%. Plasma concentrations of DEX in children with ADHD range between 40 and 120 ng/mL. Compared to DEX, clinically effective MPH oral doses produce much lower plasma concentrations—as low as 7–10 ng/mL—suggesting a large first-pass effect. However, relatively low MPH concentrations are surprisingly effective. It is due, in part, to the low plasma-binding rate (15%) of MPH, which makes it highly available to cross the blood–brain barrier. This situation creates a favorable brain–plasma partition, with a higher MPH concentration in the CNS than in plasma (Patrick et al. 1987). The concentration-enhancing and activity-reducing MPH effects can disappear well before the medication leaves the plasma, a phenomenon termed clockwise hysteresis.

Animal studies have shown a wide therapeutic/toxic ratio for MPH; a 100:1 margin of safety exists between a single dosage, approximating a human clinical dose, and one that produces lethality in two other animal species. As a result, MPH is considered as one of the safest medications used in pediatric treatment when given in the standard 0.3–1.2 mg/kg per day oral dose range. The median lethal MPH dose in dogs is 48.3 mg/kg, via intravenous route, and 367 mg/kg, by oral route. On the other hand, the median lethal amphetamine dose in rats is 55 mg/kg.

The stereochemical structure of the psychostimulants is related to their CNS activity. MPH is thought to block reuptake of DA into presynaptic neurons in the CNS, increasing its concentrations in the interneuronal space. The MPH molecule has two asymmetrical carbon atoms, resulting in four optical isomers: both d- and l-forms of the threo- and erythro-racemates. The threo-isomer appears to have more potency than the erythro, perhaps owing to the 60º skew relationship between the tertiary amine and the carbomethoxy groups, which may increase their ability to block DA reuptake. In the erythro form, these groups are transstaggered, and therefore no bond is formed between the nitrogen and carbonyl atoms (Patrick et al. 1987). The commercial manufacturing process produces equal parts of d- and l-isomers of threo-methylphenidate (d,l-MPH). A double-blind crossover study was carried out to compare the two isomers. The d-isomer was found to act more quickly and to produce greater improvements on measures of attention than the l-isomer. It appears that the d-isomer also has a greater effect on locomotor activity and reuptake inhibition of labeled DA (Patrick et al. 1987). This has been incorporated into a new MPH preparation, dexmethylphenidate (d-MPH), that has shown efficacy in controlled trials (Wigal et al. 2004). Two brand formulations of d-MPH (*Focalin, Focalin XR*) are currently marketed in the US.

OROS-MPH is a racemic mixture of d- and l-threo-methylphenidate. The d-enantiomer appears to be not only the more effective of the two, but also better absorbed; plasma concentrations of d-methylphenidate taken orally are 10−40 times higher than those of the l-enantiomer (Ding et al. 1997, Modi et al. 2000b). MPH is primarily metabolized extra-hepatically by de-esterification to an inactive metabolite. About 90% of radiolabeled MPH can be recovered from urine (Drugs for Treatment of ADHD 2006a).

Differences between the short- and long-acting preparations relate primarily to pharmacokinetic considerations, not necessarily to clinical ones. Standard short-acting MPH 10 mg b.i.d. tablets produce higher peak plasma concentrations and yield a steeper absorption phase slope than does the longer acting MPH-SR20 (*Dexedrine Spansules*) preparation. Greenhill (1992) studied a sample of 42 ADHD children in a parallel-group 8-week design comparing MPH 10 mg b.i.d. and MPH-SR20. Despite the differences in lower peak concentration ($C_{max}$) between MPH-SR20 and MPH 10 mg b.i.d., no differences were seen in Continuous Performance Task (CPT) performance, motor activity levels, or teacher reports for the two groups. One speculation concerning MPH-SR20 is that its longer duration of action may alter pharmacokinetics or receptor pharmacodynamics (Table 106–3), therefore inducing tolerance.

Pharmacokinetic studies show that the sustained-release stimulant preparations have properties different from those of the standard tablets. For example, the pharmacokinetic curves of MPH-SR20 are flattened, with no sharp peaks. Lower peak concentration ($C_{max}$) and longer time from ingestion to peak ($T_{max}$) are also observed. In a pharmacokinetic study of nine ADHD males by Birmaher et al. (1989), the $C_{max}$ was 20 ng/mL for standard MPH (10 mg t.i.d. or b.i.d.), but only 7 ng/mL for MPH-SR20. The $T_{max}$ for MPH at 10 mg b.i.d. was 90 min but was much longer (3.4 hrs) for MPH-SR20. This may explain why behavioral and cognitive studies show that the peak MPH-SR20 benefit occurs at 3 hrs, an hour later compared to the standard preparation. A mean plasma elimination half-life value (using a single-compartment model with a monoexponential decline in plasma levels from $C_{max}$) was calculated to be 2.5–3.3 hrs for standard MPH and 4.1 hrs for MPH-SR20. As with the standard preparation, the MPH-SR20 concentrations of the d-enantiomer were 8 to 10 times higher than those of the l-enantiomer.

**Table 106–3 Short-Acting Stimulant Pharmacokinetics and Pharmacodynamics**

| Parameter | DEX | MPH | MAS |
|---|---|---|---|
| Metabolism | Hepatic to inactive metabolites | Hepatic to inactive metabolites | Hepatic to inactive or weakly active metabolites |
| Excretion | Renal, of metabolites; rate accelerated by acidification | Renal, of metabolites | Renal; rate accelerated by acidification |
| $T_{max}$ | 2–4 hrs | 1–3 hrs | 2–4 hrs |
| Half-life | 6–8 hrs | 2–4 hrs | 5–7 hrs |
| Effect onset | 30–60 min | 30–60 min | 30 min |
| Effect peak | 1–3 hrs | 1–3 hrs | 1–3 hrs |
| Effect duration | 4–6 hrs | 3–5 hrs | 4–6 hrs |

Lisdexamfetamine dimesylate (*Vyvanse*) is a new once-a-day formulation of amphetamine manufactured by Shire. It is an inactive pro-drug in which d-amphetamine is covalently bonded to l-lysine, an essential amino acid. After ingestion, the pharmacologically active d-amphetamine is released when the covalent bond is cleaved by proteolytic enzymes in the digestive tract. Lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and is converted to d-amphetamine and l-lysine by non-cytochrome P450 hepatic enzymes or intestinal metabolism. Lisdexamfetamine dimesylate was designed to have much less potential for abuse, diversion, or overdose toxicity compared to amphetamine (Janinsky and Krishnan 2007). Only minimal amounts of d-amphetamine are released when the drug is administered parenterally.

Pharmacokinetic study in 18 children, 6–12 years old, exposed to single doses of 30, 50, or 70 mg has shown the $T_{max}$ of 1 hr, but the $T_{max}$ of free d-amphetamine occurred at 3.5 hrs after dosing. High-fat meals delay the d-amphetamine $T_{max}$ from 3.8 to 4.7 hrs (Arora and Krishnan 2007). Most of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate was recovered in the urine. Plasma elimination half-life of the intact pro-drug averaged less than 1 hr, and by 8 hrs it was not detectable.

## Indications and a Review of Efficacy Data in Children

Bradley (1937) was the first physician to treat behaviorally disturbed children and adolescents with stimulants. He administered benzedrine, a racemic form of amphetamine, which produced a dramatic calming effect while increasing compliance and academic performance. Subsequently, Bradley published several case reports showing that children's behavioral problems were ameliorated by the amphetamine treatment. Interest in psychostimulants increased after the first controlled investigations of these drugs were carried out between 1960 and 1970 (Conners 2000). During this period, psychostimulants were reported to increase the seizure threshold, decrease oppositional behavior of boys with conduct disorder, and improve the target ADHD symptoms.

In subsequent years, many controlled treatment studies have shown psychostimulants to be effective in reducing symptoms of gross motor overactivity, inattention, impulsivity, and noncompliance. A meta-analysis (Kavale 1982) of stimulant treatment studies reported effect sizes of 0.5–0.9. This suggests that response to stimulants is in the range found with antibiotic treatments of infection, making the stimulant medications the most effective single therapeutic modality for the ADHD treatment in child psychiatry. These findings have been confirmed by a major review of 111 studies (4,777 children; Spencer et al. 1996a). Other reviews of psychostimulants efficacy have indicated their efficacy on measures of academic performance, mechanisms of action, diagnostic specificity, and the ability of these medications to enhance other therapies (Barkley 1977, DuPaul and Barkley 1990). However, controversy remains. Another critical review found no evidence for diagnostically specific medication response, specific biochemical mechanism of action, or maintenance of the short-term effects lasting longer than a few months (Jacobvitz et al. 1990).

In the past 10 years, psychostimulant research has progressed from single to multisite RCTs. The primary objective of these trials is to gather controlled data for new FDA approvals, as shown in Table 106–4. These modern-day controlled trials have matured with the field and now employ multiple-dose conditions with various stimulant medications (Elia et al. 1991), parallel designs (Spencer et al. 1995), and optimization of each child's dose response (Abikoff and Gittelman 1985a, Rapport et al. 1994). These studies also assess psychostimulant treatment in special ADHD populations, including adolescents (Klorman et al. 1990), adults (Spencer et al. 1995), mentally-retarded children (Horn et al. 1991), ADHD subjects with anxiety and internalizing disorders, and ADHD subjects with tic disorders (Gadow et al. 1995). A review by Wilens and Biederman (1992) reported that a Medline search generated more than 990 citations about psychostimulants published between 1982 and 1991. Later reviews documented a much greater increase in citations (Greenhill et al. 1999) demonstrating beneficial short-duration psychostimulant effects on children with ADHD. A major meta-analysis (Swanson 1993) revealed that over 200 reviews and thousands of specific studies were published.

Even though short-duration stimulant studies have shown robust efficacy, their effects last only as long as the patient continues taking medication. Research using the double- or single-blind placebo discontinuation model to determine whether the stimulant response continues after one or more years of treatment found that 80% of children with ADHD relapsed when switched single-blind from MPH to a placebo after 8 months of treatment (H. Abikoff, personal communication 1994). Other long-duration trials have shown that stimulant effects can be maintained over periods ranging from 12 (Gillberg et al. 1997) to 24 months (Abikoff et al. 2004b). Unfortunately, most stimulant RCTs end in less than 3 months, with only 22 published studies lasting longer (Schachar and Tannock 1993). Most long-duration studies before the 1990s were constrained by their retrospective methods, lack of nonstandard outcome measures, irregular medication prescribing patterns, restrictive inclusion criteria of rejecting patients with comorbid disorders, and irregular prescribing patterns (Richters et al. 1995, Sherman 1991).

Although 70% of ADHD subjects respond to stimulants and less than 13% respond to placebo (Greenhill et al. 2001b), investigators have studied stimulant nonresponders. Some drug trials (Douglas et al. 1988) report a 100% response rate in small samples in which multiple MPH doses were used. Elia et al. (1991) reduced the 32% nonresponse rate to a single psychostimulant to less than 4% when a second stimulant was titrated sequentially in the same subject. However, only noncomorbid children with ADHD were included in these studies. The rate of medication nonresponse might have been higher if children with comorbidities had been included. Although current RCTs have parallel designs, which can determine if the placebo response emerges at some point over the entire clinical trial, these data have not been reported. Since treatment studies rarely prescreen out placebo responders, the numbers of actual medication responders in any sample of children with ADHD might be closer to 55%, not the 75–96% often quoted. These estimates apply to group effects, and thus cannot inform clinicians about the individual patient.

The NIMH MTA Study was conducted to assess the relative effectiveness of different treatment modalities on

**Table 106–4 Controlled Studies Showing Stimulant Efficacy in ADHD Drug Treatments (*N* = 2,234)**

| Study (Year) | *N* | Age Range (Years) | Design | Drug (Dose) | Duration | Response | Comment |
|---|---|---|---|---|---|---|---|
| Abikoff and Gittelman (1985a) | 28 | 6–12 | ADHD* Controls | MPH (PB, 41 mg) | 8 weeks | 80.9% | ADHD children normalized |
| Abikoff and Hechtman (2004a) | 103 | 6–12 | ADHD | MPH t.i.d. (33.7 mg) | 2 years | 100%; 2.7 SD | Multisite, multimodal study; all children on MPH |
| Barkley et al. (1989) | 74 | 6–13 | X-over 37 agg 37 non-agg | MPH (PB, 0.3, 0.5) | 4 weeks | 80% | Aggression responsive to MPH |
| Barkley et al. (1991) | 40 | 6–12 | X-over 23 ADHD 17 ADHD-W | MPH b.i.d (5, 10, 15 b.i.d.); PB b.i.d. | 6 weeks | ADHD 95%; ADHD-W 76% | Few children with ADHD-W respond, need low dose |
| Castellanos et al. (1997) | 20 | 6–13 | X-over | MPH 45 mg b.i.d.; DEX 22.5 mg b.i.d. | 9 weeks | ADHD + TS | Dose-related tics at high doses |
| Douglas et al. (1988) | 19 | 7–13 | X-over | MPH (PB, 0.15, 0.3, 0.6) | 2 weeks | 100%* | Linear D/R relationships |
| Douglas et al. (1995) | 17 | 6–11 | X-over | MPH (0.3, 0.6, 0.9); PB | 4 weeks | beh 70% | No cognitive toxicity at high doses; linear D/R curves |
| DuPaul and Rapport (1993) | 31 | 6–12 | X-over 31 ADHD 25 controls | MPH (20 mg); PB b.i.d. | 6 weeks | beh 78%; att 61% | MPH can normalize classroom behavior; 25% of ADHD subjects did not normalize in academics |
| DuPaul et al. (1994) | 40 | 6–12 | X-over 12 high ANX 17 mid ANX 11 low ANX | MPH (5, 10, 15 mg); PB single dose | 6 weeks | high 68% nortriptyline; mid 70% nortriptyline; low 82% nortriptyline | 25% in internalizing group deteriorated on medications ADHD subjects with comorbid internalizing disorders less to be normalized or to respond to MPH |
| Elia et al. (1991) | 48 | 6–12 | X-over | MPH (0.5, 0.8, 1.5); PB b.i.d.; DEX (0.25, 0.5, 0.75) | 6 weeks | MPH 79%; DEX 86% | Response rate for two stimulants = 96% |
| Gadow et al. (1995) | 34 | 6–12 | X-over ADHD+tic | MPH (0.1, 0.3, 0.5); PB b.i.d. | 8 weeks | 100% MPH | No nonresponders to behavior; MD = s motor tic ratings show 2 min increases on drug; only shows effects of 8 wk treatment |
| Gillberg et al. (1997) | 62 | 6–12 | Parallel | MAS (17 mg); PB b.i.d. | 60 weeks | 70%; 27–40% impr | No dropouts but only 25% placebo group at 15 mo assessment |
| Greenhill et al. (2001b) | 277 | 6–12 | Parallel | Long-acting MPH; PB | 3 weeks | 70% | Mean total dose 40 mg/day. FDA registration |
| Greenhill et al. (2006) | 97 | 6–17 | Parallel | d-MPH-ER (*Focalin LA*) (5–30 mg) q.d; PB | 7 weeks | d-MPH-ER 67.3%; PB 13.3% | Mean d-MPH-ER daily dose = 24.0 mg |
| Greenhill et al. (2002a) | 321 | 6–16 | Parallel | MPH-MR (*Metadate-ER*) (20, 60 mg) q.d; PB t.i.d. | 3 weeks | MPH-MR 64%; PB 27% | Mean MPH-MR *ER* daily dose =40.7 mg (1.28 mg/kg per day) |
| Greenhill et al. (2006) | 165 | 3–5.5 | X-over | IR-MPH (1.25, 2.5, 5, 7.5 mg) t.i.d.; PB t.i.d. | 70 weeks | 88% | Optimal IR-MPH dose =14.22 ± 8.1 mg/day (0.7 + 0.4 mg/kg per day); treatment effect sizes < than in school-age children |
| Klorman et al. (1990) | 48 | 12–18 | X-over | MPH t.i.d.; (0.26); PB b.i.d. | 6 weeks | MPH 60% | Less medical benefits for adolescents |
| Klein et al. (1997) | 84 | 6–15 | Parallel | MPH b.i.d. (1.0) | 5 weeks | MPH 59–78%; PB 9–29% | MPH reduced ratings of antisocial behaviors |

**Table 106–4 Controlled Studies Showing Stimulant Efficacy in ADHD Drug Treatments (*N* = 2,234) *continued***

| Study (Year) | *N* | Age Range (Years) | Design | Drug (Dose) | Duration | Response | Comment |
|---|---|---|---|---|---|---|---|
| McGough et al. (2006) | 97 | 6–17 | X-over | MPH transdermal system on 9 hrs/day (12.5, 18.75, 25, 37.5 $cm^2$); PB | 2 weeks | 79.8% | MPH transdermal system is well tolerated and significantly more efficacious than PB |
| MTA Cooperative group (1999) | 579 | 7–9 | Parallel | MPH t.i.d. (<0.8) | 4 weeks (14 mo) | MPH 77%; DEX 10%; None 13% | Titration trial for multisite multimodal study; full study data for 288 on 38.7 mg MPH |
| Musten et al. (1997) | 31 | 4–6 | X-over | MPH b.i.d. (0.3, 0.5) | 3 weeks | MPH > NA | MPH improves attention in preschoolers |
| Pelham et al. (1990) | 22 | 8–13 | X-over | MPH 10 b.i.d.; PB b.i.d.; DEX spansule 10 mg; PEM 56.25 q.d. | 24 days | Stim 68% | DEX span, PEM best for behavior 27% did best on DEX; 18% on SR; 18% on PEM; 5% on MPH b.i.d. |
| Pelham et al. (1995) | 28 | 5–12 | X-over | PEM (18.75, 37.5, 75, 112.5 mg); PB o.d. | 7 weeks | PEM 89%; PB 0% | PEM dose ≥ 37.5 mg/d lasts 2–7 hrs; efficacy and time course = MPH |
| Rapport et al. (1988) | 22 | 6–10 | X-over | MPH (PB, 5, 10, 15 mg) | 5 weeks | 72% | MPH response same in home and school |
| Rapport et al. (1994) | 76 | 6–12 | X-over | MPH (5, 10, 15, 20 mg); PB b.i.d. | 5 week | 94% beh; 53% att | MPH normalizes behavior > academics; higher doses better, linear D/R curve; |
| Schachar et al. (1997) | 91 | 6–12 | Parallel | MPH (33.5 mg); PB b.i.d. | 52 weeks | 0.7 SD effect size | 15% side effects: affective, over-focusing led to dropouts |
| Spencer et al. (1995) | 23 | 18–60 | X-over | MPH (1 mg/kg per day) | 7 weeks | 78%; PB 4% | MPH at 1 mg/ kg per day produces improvement in adults equivalent to that seen in children |
| Swanson et al. (1998) | 29 | 7–14 | X-over | MAS (5, 10, 15, 20, PB, MPH) | 7 weeks | 100%* | Adderall peaks at 3 hrs; MPH at 1.5 hrs |
| Tannock et al. (1995a) | 40 | 6–12 | X-over | MPH 22 (0.3, 0.6); 17 ADHD–Anx | 2 weeks | 70% | Activity level better in both groups; working memory not improved in anxious kids |
| Tannock et al. (1995b) | 28 | 6–12 | X-over | MPH (0.3, 0.6, 0.9); PB | 2 weeks | 70% | Effects on behavior D/R curve linear, but effects on response inhibition U-shaped suggest adjustment dose on objective measures |
| Taylor et al. (1987) | 38 | 6–10 | X-over | MPH (PB, 0.2–1.4) | 6 weeks | 58% | Severe ADHD symptoms, better response |
| Whalen et al. (1989) | 25 | 6.3–12 | X-over | MPH (PB, 0.3, 0.5) | 5 weeks | 48–72% | MPH helps, not normalizes, peer status |
| Wigal et al. (2004) | 132 | 6–17 | Parallel | d-MPH; d,l-MPH; PB b.i.d. | 4 weeks | d-MPH 67%; d,l-MPH 49% | Average d-MPH dose (18.25 mg) is as safe and effective as half of the average d,l-MPH dose (32.14 mg) |
| Wilens et al. (2006) | 177 | 13–18 | Parallel | OROS-MPH (18, 36, 54, 72 mg) q.d.; PB | 2 weeks | OROS-MPH 52%; PB 31% | OROS-MPH is well tolerated and effective in adolescents at up to 72 mg daily dose |
| Wolraich et al. (2001) | 277 | 6–12 | Parallel | OROS-MPH 36 mg; PB MPH t.i.d. | 4 weeks | 62% | Concerta rated effective by teachers and parents |

Doses listed as mg/kg per dose, and medication is given twice daily unless otherwise stated.

PB, placebo; X-over, crossover design; ANX, anxiety; MPH, methylphenidate; DEX, dextroamphetamine; PEM, pemoline; AMP, d-, l-amphetamine (*Adderall)*; mg/kg per day, dosage in mg/kg per day; Agg, aggression; ADHD-W, ADD without hyperactivity; beh, behavior; att, attention; FDA, Food and Drug Administration; D/R curve, dose–response curve.

long-term outcomes of ADHD in school-age children. Four randomly-assigned 14-month treatment modalities consisted of medication management (MedMgt), behavioral treatment (Beh), combination (Comb), or community comparison group (CC) that received treatment as usual (Arnold et al. 1997). The null hypotheses were postulated as follows: (1) Beh and MedMgt treatments would result in comparable levels of improvement over time; (2) participants assigned to Comb would show similar improvement over time compared to those assigned to either MedMgt or to Beh; (3) participants assigned to any of the three MTA-intensive treatments would show similar improvement over time compared to those assigned to treatment as usual in the CC.

To have sufficient power to address these questions, 579 children with ADHD, combined subtype, ages 7–9 were recruited at seven sites nationwide. They were assessed across six domains at four different points in time (Hinshaw et al. 1997). At the study entry, they were randomized to 14 months of treatment in one of four groups: (a) MedMgt, (b) Beh (parent, school, and child components, with therapist involvement gradually fading over time), (c) Comb, or (d) CC. Treatment outcomes were assessed in multiple domains before, during, and at treatment endpoints (with Comb and MedMgt subjects taking medication at the time of assessments). Children randomized to MedMgt ($N = 144$) or to Comb ($N = 145$) also participated in a 28-day double-blind, placebo-controlled titration study designed to identify optimal individual MPH dose. Three doses of MPH and placebo were used three times daily (Greenhill et al. 2001b), with medication conditions switched daily to reduce error variance. Parents and teachers rated ADHD symptoms and impairment on a daily basis.

During medication titration, the repeated-measure analysis of variance (ANOVA) revealed a main effect of MPH/placebo dose with greater effects on teacher ratings ($F[3] = 100.6$, $N = 223$, $P = 0.0001$; effect sizes 0.8–1.3) compared to parent ratings ($F[3] = 55.61$, $N = 253$, $P = 0.00001$; effect sizes 0.4–0.6) (Greenhill et al. 2001b). Dose did not interact with between-subjects factors (period, dose order, comorbid diagnosis, site, or treatment group). Parents reported more medication-related adverse events than teachers. Contrary to parents' reports, teachers' ratings for irritability were highest when the children were on placebo, not the active drug. The distribution of the best MPH starting doses ranged between 10 and 50 mg/day and the response rate was 77%. The effect sizes and adverse event rates found in the MTA study replicated those previously reported in single-site MPH trials (Spencer et al. 1996a). These findings suggest that MPH titration in office practice should explore the full dosage range of stimulants.

The intent-to-treat random-effects regression demonstrated that all four treatment groups had sizeable reductions in symptoms over time, with significant differences in degrees of change (MTA cooperative group 1999). For most ADHD symptoms, children in the Comb and MedMgt groups showed significantly greater improvement compared to those enrolled in the Beh or CC. The outcomes of the Comb and MedMgt treatments did not differ significantly on any measure of ADHD symptoms. However for internalizing symptoms, teacher-rated social skills, parent–child relations, and reading achievement, the Comb treatment proved significantly more effective in reducing symptom scores compared to the intensive Beh and/or CC treatments. Overall, the MTA treatment modalities were superior to the CC, even though two-thirds of CC subjects were taking ADHD medications prescribed by their personal doctors while participating in the study.

Being the largest pediatric ADHD randomized controlled treatment study; the MTA addressed key treatment questions. It showed that stimulant medication efficacy is feasible across diverse settings and patient groups, and can be maintained during chronic therapy lasting longer than a year. The study findings replicated those from smaller long-duration stimulant trials—the 102-child New York/Montreal Study (Abikoff et al. 2004b), the 91-child Toronto Study (Schachar et al. 1997), and the 62-child Gillberg Study (Gillberg et al. 1997). Following 12–24 months of MPH treatment, collectively, these multisite studies indicate a persistence of medication effects over time as long as the drug was taken. Within-subject effect sizes resembled those previously reported in short-duration studies (Elia et al. 1991, Thurber and Walker 1983). The domain of showing greatest improvement differs among studies, with some having greater effects at home (Gillberg et al. 1997), and others demonstrating greater effects at school (Schachar et al. 1997). The total mean MPH daily doses reported by these long-duration studies ranged between 33 and 37.5 mg. One DEX study reported a mean dose half of this level, agreeing with the general DEX to MPH dose ratio.

Stimulant treatment in preschoolers was described in a comprehensive review (Connor 2002) of nine controlled studies ($N = 206$) in children under the age of 6 (Barkley 1988b; Barkley et al. 1984, Conners 1975, Mayes et al. 1994, Musten et al. 1997, Schleifer et al. 1975, Handen et al. 1999). In these studies, the MPH doses were weight-adjusted (0.15–1.0 mg/kg per day) and ranged from 2.5 to 30 mg/day. The treatment efficacy was comparable to that found for older children, producing improvements in structured situations but not in free play (Schleifer et al. 1975). However, the findings also indicated that preschoolers, especially those with developmental delays, may be prone to higher rates of side effects, including tearfulness and irritability, compared to school-age children (Handen et al. 1999). Therefore, it was concluded that preschoolers should be started on low MPH doses. Interpretations of these early data are difficult due to the methodological differences among the nine studies, which varied in their inclusion/exclusion criteria, diagnostic definition, ratings forms, and study designs, thus making a meta-analysis impossible. Without conclusive data, the FDA package insert instructions warn against using MPH in children younger than age 6. In spite of these warnings, there has been a 180% increase in the MPH prescriptions for preschoolers since 1996.

To address the lack of methodologically sound safety and efficacy data in preschoolers, the NIMH launched a randomized, placebo-controlled, multisite MPH trial entitled Preschool ADHD Treatment Study (PATS). This trial randomized 303 children. Two hundred seventy-nine families enrolled in a 10-week course of parent training. After completing the parent training, only 183 of these families agreed to participate in the PATS medication protocol. Of these, 165 families were randomized into a double-blind, placebo-controlled, crossover, dose-optimization study.

Prior to entry into the double-blind phase of the protocol, all children received medication treatment as part of the 1-week, open, stepwise, safety phase. In the following double-blind phase, they were administered placebo or active medication (1.25, 2.5, 5, or 7.5 mg) three times daily, with their dose switched weekly. Blind raters selected the MPH dose for each child that produced the best compromise between lowering ADHD symptoms and not creating significant adverse events (Kollins et al. 2006). The mean "best" MPH daily dose was determined as 14 mg or 0.75 mg/kg per day. This dose was lower than the mean 1.0 mg/kg per day MPH daily dose reported in the MTA Study (Greenhill et al. 2006). On their optimal MPH doses, all preschoolers had a significantly higher decrease in ADHD symptoms compared to that on placebo.

A subset of the 114 children in PATS remained in the study to be randomized into a later double-blind, parallel design phase, with half of the sample randomly assigned to their optimal MPH doses and the other half to placebo. The teacher reports showed significant continued improvements for children assigned to MPH.

However, 11% of subjects discontinued the trial due to the MPH-associated adverse events, which is far more than 2% of subjects who terminated from the MTA Study for MPH-associated adverse events. The preschool group showed a significantly higher rate of irritability, decreased appetite, delay in sleep onset, and proneness to crying in the MPH condition compared to placebo (Wigal et al. 2006). An open, pharmacokinetic, pilot study conducted in a small subset of the PATS sample indicated that preschoolers show significantly lower MPH clearance than do school-age children, even when corrected for weight (Wigal et al. 2006).

One of the most important findings in the stimulant treatment literature is the high degree of short-term efficacy for behavioral targets, with weaker effects for cognition and learning. Conners (personal communication) notes that 0.8, 1.0, and 0.9 effect sizes are reported for behavioral improvements in type 4 meta-analytic reviews of stimulant drug actions (Kavale 1982, Ottenbacher and Cooper 1983, Thurber and Walker 1983). Less powerful effects are found for laboratory measures of cognitive changes, in particular on the CPT, for which medication effect sizes range between 0.6 and 0.5 for omissions and commissions, respectively, in a within-subject design (Milich et al. 1989); and 0.6 and 1.8 in a between-subject study (Schechter and Keuezer 1985).

Behavioral changes in children treated with psychostimulants are often identified as decreases in the intensity of target ADHD symptom scores based on teacher and parent global ratings. Commonly used forms include the 93-item Conners Parent Rating Scale (CPRS), the 39-item Conners Teacher Rating Scale (CTRS), the 28-item Conners Teacher Rating Scale–Revised (CTRS–R), the Iowa Conners Teacher Rating Scale (ICTRS), and the ADD–H Comprehensive Teacher Rating Scale (ACTeRS). These scales and their psychometric properties have been summarized in detail by Barkley (1988a). Subjecting the results of these scales to factor analysis, Conners et al. (1994) produced threshold scores useful for screening children in treatment studies. Approximately 75% of children treated with psychostimulants show moderate to marked improvement when assessed using teacher rating scales. Changes can be picked up as early as 30 min after the first MPH dose is administered.

Neurocognitive ADHD theories have played a crucial role in our understanding of the functional deficits underlying symptomatic behavior. These theories explain the disorder etiology by connecting behavioral sequences with neuronal mechanisms (Barkley 1997). Neuropsychological research, particularly as it relates to concepts of executive functioning, has addressed the validity of ADHD subtypes. Nigg defines executive functions as mental processes governing the regulation of response to context and maintenance of behavior on goal (Nigg et al. 2002). Research has shown that, relative to placebo, psychostimulants improve the performance of children with ADHD on various laboratory measures of cognitive functioning.

The CPT is an experimenter-paced task, in which the subject is seated in front of a display and told to press a button whenever certain letters or numbers (the targets) appear on the display. The task generally lasts between 8 and 15 min and tests the subject's ability to sustain attention. Typical CPT outcome measures indicate a reaction time to the target, a correct identification of a target signal ("a hit"), a mistaken identification of a nontarget ("a false alarm") stimulus, or a complete response lack when a target appears ("a miss"). Virtually all studies report that children with ADHD have a significant reduction in the number of CPT omission errors and/or in the reaction time after taking stimulants (Matier et al. 1992, Rapoport et al. 1980). The reduction in omission errors and response latency is generally interpreted as improved attention and impulse control. However, data suggest that the commission errors are less sensitive to stimulant effects than the omission errors. Studies, which found significant stimulant medication-induced reductions in the omission errors, have either failed to identify reductions in the number of the commission errors or only detected some reductions at high doses.

Findings regarding the shape of the dose–response curve have been less consistent. Whereas large medication effects relative to placebo have been reported, some investigators have failed to find significant between-dose effects, while others have reported linear dose–response effects, and yet others have found quadratic effects indicating that performance somewhat decreases at the highest dose (Rapport et al. 1989a). The causes of these differences are not fully apparent, but it is likely that they can be at least partially attributed to task differences. A review of various CPTs (Epstein et al. 2003) suggested that task difficulty, as indicated by the overall number of errors, is related to the ability of individual CPTs to distinguish among different diagnostic groups. Furthermore, data from these authors show that the decline in performance at peak doses may be apparent only on the most difficult CPT versions.

Although it has been shown that the CPT performance is enhanced with stimulants, the clinical utility of this measure for either predicting or monitoring medication response is less clear. To evaluate its utility, two questions must be addressed: Is the CPT performance prior to stimulant intake predictive of clinical or behavioral response to medication? Do changes in the CPT performance post medication administration parallel clinically observed changes in the natural environment? To date, research studies have been unable to answer these questions positively for individual patients. Relatively few studies have directly

addressed these issues, yet the majority of data suggest that the answer to both questions is negative.

The utility of one CPT version, known as the Test of Variables of Attention, was assessed by comparing performance before and after stimulant treatment in children classified as medication responders and nonresponders. Following the 6 weeks of MPH treatment, medication response was assessed via parent and child reports, clinical observations, and teacher rating scales. Medication responders and nonresponders did not differ significantly on any premedication CPT measure, suggesting that baseline performance could not be used to predict treatment response. However, the responders, compared with the nonresponders, showed greater improvement on several CPT measures after psychostimulant treatment, indicating that the CPT may be useful for assessing medication response. In a separate experiment, the same group of investigators assessed performance changes on the Test of Variables of Attention in a different sample of children with ADHD after a single 10 mg challenge MPH dose. They reported that the responders had a significantly greater enhancement in performance after the initial medication dose and suggested using the CPT changes for predicting medication response.

However, other investigators have generated only limited evidence to support the clinical CPT utility for predicting and/or monitoring response to stimulants. The fact that normal and ADHD children appear to respond similarly to stimulants with regard to improved attention and reduced activity level, even though normal children make relatively few CPT errors at baseline, suggests that laboratory performance does not predict medication efficacy (Rapoport et al. 1980). One study (Aman and Turbott 1991) assessed the ability of several measures for predicting MPH response in children. The investigators found no significant relationship between the CPT performance and clinical improvement, even though both measures were altered by the medication. Alternatively, Taylor et al. (1987) reported that before medication, poor performance on a battery of attentional tests, which included CPT, was among the strongest predictors of pediatric clinical response to MPH.

In two separate studies using different CPTs, Rapport and DuPaul (1986) and Rapport et al. (1987) found large clinical and CPT changes following MPH treatment. In their first study (1986), the dose–response curve for the number of omission errors for the entire sample closely paralleled the curve generated for on-task behavior in classroom environments. However, there was considerable intersubject variability. In the subsequent study with a larger sample, the same authors (1987) noted similar medication-induced CPT and behavioral changes. However, the CPT performance was highly variable and not predictive of behavioral response to medication on an individual level. Consistent with this, Nigg et al. (unpublished manuscript) reported similar dose–response curves for several CPT performance variables and direct behavioral observations in 22 boys enrolled in a summer treatment program for children with ADHD. Nevertheless, despite similarities across the group, individual medication response could not be predicted by the CPT performance. Even though substantial evidence indicates that the CPT performance changes as a function of stimulants, limited data suggest any clinical utility for these instruments with regard to predicting medication response. Further research is warranted to prove their usefulness to the physician planning to medicate an ADHD child. In the meantime, CPTs should be considered only in the context of a thorough clinical assessment.

In addition to the neurocognitive testing in the laboratory environment, stimulant effects on cognition have been measured in school settings. Classroom arithmetic tasks (Carlson and Thomeer 1991) and concentration during sports (Pelham et al. 1990) show medication–placebo effects. Sprague and Sleator (1977) demonstrated that higher psychostimulant dosages may interfere with complex memory tasks involving effortful cognitive processing. In their study, 10 hyperkinetic school-age children were given a short-term memory paired associates task. The best percent correct score was reported on the lowest, 0.3 mg/kg, dose whereas increasing the dose to 1 mg/kg elevated the error rate. In contrast, these same children obtained the best teacher global ratings of improved behavior on the higher, 1 mg/kg, dose. One might conclude, as did many clinicians, that the use of behavioral ratings for dosage adjustment may select doses that impair cognitive processes. This "window of response" can be modeled best as an inverted-U curvilinear dose–response curve.

Although Sprague's findings have not been replicated in other studies, a question of stimulant-induced cognitive overfocusing remains a concern to physicians, parents, and teachers. They report that children on high stimulant doses can become perseverative, repetitive, and less spontaneous. A review of 11 studies, evaluating the stimulant dose–response relationship on cognitive tasks in 180 children, reported linear dose–response curves, with only two studies showing the decrease of cognitive abilities at higher doses (Rapport et al. 1989b). One ADHD study (Solanto and Wender 1989) found no cognitive problems on the Wallach-Kogan battery when 19 boys were treated with three different MPH doses (0.3, 0.6, and 1.0 mg/kg). Another study (Tannock et al. 1989) replicated these findings, showing that attention was enhanced, with no overfocusing, at higher MPH dosages. Short-term pediatric ADHD studies reveal that stimulants enhance arithmetical productivity, efficiency, and accuracy with children spending less time between problems. These studies were characterized by optimal experimental procedures, including standardized medication dosages and relevant dependent measures.

Even with this lack of replication of Sprague's finding, the impact on practice of this one study has been profound. Prior to its publication, investigators used higher MPH dosages in their research, for example, 51 mg/day (Gittelman-Klein et al. 1976), and individual doses were titrated to maximum effect or toxicity. From 1977 to 1990, clinicians adopted an increasingly conservative approach to MPH dose adjustments. Rather than increasing the drug through its full range to 60 mg when starting treatment, dosing was often weight adjusted on a mg/kg basis according to Sprague's published optimal MPH dose for fewest errors (0.3 mg/kg). This resulted in total daily MPH doses between 15 and 25 mg, which are lower than the mean total dose used in the large multisite trials, such as the MTA Study. There is a great diversity among children in their dose–response curves, both between individuals and across domains of behavior and learning (Murphy et al. 1986, Solanto 1991). Pelham recommends that optimal dosing of the individual ADHD

child should not be done a priori, but must be carried out carefully on an empirical basis, adjusting the dose level to correct the child's most serious area of difficulty (Pelham and Milich 1991).

Rapport et al. (1989a) suggested that a subset of children have divergent dose–response curves for behavior and academic output. This might explain why earlier reports indicated that psychostimulants could not maintain the improvements seen during the first week of treatment on academic tasks in hyperactive children. The idea was further strengthened by the results of reading remediation study in 61 children, half assigned to MPH (mean dose of 44 mg/day) and half to placebo. No differences in reading skills between groups were found 6 months following the 18-week treatment. A 2-year MPH follow-up study of 72 reading-disabled children also did not show any significant differences between children taking MPH and those treated with other therapies. These long-term studies suggest that stimulants do not affect the clinical course or outcome of the ADHD treatment in children.

Prospective longitudinal studies (Klein and Mannuzza 1991) that reviewed high school histories found more failing marks on report cards, failure to advance, and higher dropout rates in adults with childhood ADHD than those present among control subjects. Swanson (1993, personal communication) has suggested that certain factors obscure the "expected long-term benefits of psychostimulants," including the diagnostic heterogeneity of the ADHD syndrome, the task specificity needed to measure stimulant response, and the possible cognitive toxicity associated with clinical dose titrations.

A number of double-blind, placebo-controlled crossover studies have reported variable reductions in aggressivity in stimulant-treated children with ADHD. This is a critical area of concern, because childhood aggressivity predicts future morbidity. Klorman et al. (1988, 1990) carried out two studies of MPH treatment (0.6 mg/kg) in 63 school-age patients and noted that children with and without aggressive features showed improvement. On the other hand, Hinshaw et al. (1989) found only slight reductions in aggressivity in 24 school-age ADHD children treated with the same MPH dose. Another ADHD study (Gadow et al. 1990) reported dose-related reductions in verbal aggressivity in 11 boys treated with MPH (0.3 and 0.6 mg/kg). Aggression in 9 severely aggressive adolescent inpatients with ADHD was reduced by MPH treatment, as measured by ratings on a standardized nursing form, the Adolescent Antisocial Behavior Checklist. Klein et al. (1997) also found that MPH treatment reduced aggression in children with ADHD comorbid for conduct disorder.

Matier et al. (1992) found that aggressive and nonaggressive subgroups of children with ADHD responded differentially to a low MPH dose (5 mg) and demonstrated various subtypes of CPT errors. The error subtypes used in this study distinguished among inattention, impulsivity, and dyscontrol errors. Whereas the inattention score was primarily (although not exclusively) based on the number of the omission errors, the impulsivity and dyscontrol scores were derived from distinct subsets of the commission errors, which are believed to assess different underlying cognitive processes. Both aggressive and nonaggressive children demonstrated reductions in the inattention score after taking the medication. However, neither group showed a significant change in the impulsivity score, which was elevated only in the aggressive ADHD subgroup relative to normal subjects. Finally, the nonaggressive ADHD subgroup had a greater reduction in dyscontrol errors (as well as objectively assessed motor activity) than did the aggressive ADHD subgroup, even though, prior to taking medication, both subgroups scored equally high on this measure compared to control subjects.

These data were interpreted as reflecting differential neurochemical mechanisms in aggressive and nonaggressive ADHD children, as well as distinct neurochemical mechanisms underlying the various types of CPT errors. Specifically, impulsivity and aggressive behavior were hypothesized to be associated, at least in part, with the central serotoninergic function, whereas inattention was thought to be more closely related to the catecholaminergic mechanisms. Since stimulants act primarily on the central catecholaminergic mechanisms, they had a greater impact on the CPT measure of attention (omission errors) compared to the measure of impulse control (commission errors).

Several studies have found significant reductions of excessive motor behavior in children with ADHD. Early studies were limited to brief laboratory observations using stabilimetric chairs and mechanical (modified automatically winding wristwatches) wrist or ankle actometers. Other approaches, such as counting grid crossings, did not measure restlessness and fidgetiness but frequently reported problems among these children. Some postulated that the levels of motor activity did not differentiate children with ADHD from normal subjects, but rather the purposelessness of their activity did. Advances in miniaturization and solid-state memory devices were needed to obtain activity level data outside the laboratory in the very settings reporting the motor overactivity (i.e., home and school). Colburn, at the NIMH, developed an actometer that consisted of an acceleration-sensitive device with a solid-state memory, which stored data on the number of movements per unit time during a 10-day period (Porrino et al. 1983). This technology measured acceleration, thus capturing impulsivity in addition to activity within many brief periods, so it was possible to determine the child's ability to modulate his or her activity level to the levels appropriate for the situation on hand.

Using the Colburn device, activity level readings taken on 12 boys with undulated hyperactivity were consistently higher than those of control subjects at all times, including during sleep and weekends. Thus, an elevated motor activity is not a response to situational set demands, but rather a trait of these children. The same research team treated ADHD boys with DEX (15 mg/day) in a 4-week double-blind study. Motor activity was significantly decreased for 8 hrs after dosing, followed by a slight increase in activity, which served as the first objective demonstration of "rebound." These readings confirmed improvements reported during both global ratings and direct observations. Borcherding et al. (1989), working in the same laboratory and using the Colburn NIMH actigraph, replicated this work with 18 ADHD boys in a day hospital setting in an 11-week, double-blind, crossover trial comparing DEX (0.2–0.6 mg/kg b.i.d.) and MPH (0.45–1.25 mg/kg b.i.d.). Although plasma drug concentrations failed to directly correlate with activity level

changes, the parent compounds were substantially higher than those reported elsewhere. This may have produced a ceiling effect, restricting the range of response and reducing the correlation. Both MPH and DEX decreased motor activity, with MPH producing lower activity readings compared to DEX. Borcherding et al. (1989) were among the first to differentiate the effects of these two stimulants on gross motor activity, which is a cardinal sign of ADHD.

The problem of validating hyperactive behaviors and their treatments has been greatly ameliorated by direct classroom observations with raters blind to the student's psychiatric and medication status. One such study (Whalen and Henker 1976) evaluated 23 hyperactive and 39 comparison boys. The study design had a number of systematically varied conditions, including difficulty of work materials, self- versus other-paced activities, and a single morning MPH dose (mean 12.3 mg). Hyperactive boys on placebo were more often off task and displayed higher rates of gross motor movement, verbalizations, noise, and disruption than control subjects. These findings were replicated in another crossover design study with a higher mean MPH dose (41.5 mg/day; Abikoff and Gittelman 1985a), whereby placebo-treated hyperactive children had much higher rates of off-task, out-of-seat, or verbalization behaviors compared to children treated with MPH, whose ADHD symptoms were normalized.

## Side Effects

Stimulant side effects are dose dependent and range from mild to moderate in most children. These have been described by Barkley in a placebo-controlled study comparing the baseline and on-medication double-blind parent ratings (Barkley et al. 1990). Common side effects include insomnia, decreased appetite, weight loss, headache, heart rate elevation at rest, stomach pain, and minor increases in systolic blood pressure. Many of these side effects can be managed with temporary dose reduction. Severe insomnia can be alleviated by changing time of dosing, with most of the medication given early in the day. Complaints of upset stomach, nausea, or pain may benefit from a change to transdermal MPH, or give the oral medication in the middle of the meal. Otherwise, the problem can be treated symptomatically with antacid tablets or by switching to sustained-release MPH, which is absorbed more slowly.

Infrequent side effects include motor tics and reductions in weight velocity. The appearance of minor facial tics is a frequent reason for stopping stimulants in clinical practice. Despite a lack of studies demonstrating a causal link between stimulant treatment and tic disorders, the Physicians' Desk Reference (PDR) warns against the use of stimulants in children with preexisting tic disorders. A history of chronic or episodic involuntary muscle movements (tics) or a family history of Tourette's disorder has become a contraindication to the MPH use, as it may unmask or exacerbate Tourette's disorder. Switching to another stimulant, such as d-amphetamine, may worsen the adventitious movement disorder, so it is best to discontinue all psychostimulants and consider a clonidine trial.

However, both ADHD and tic disorders are quite prevalent and may coexist in the same individual, so the question of the risk of stimulant treatment can frequently arise. This worry was expressed in an editorial that accompanied a retrospective chart review (Cohen and Leckman 1989). The report included 17 patients with both ADHD and Tourette's syndrome, who had been previously treated with stimulants, and whose tics were exacerbated by stimulant therapy (Lowe et al. 1982). Another study (Erenberg et al. 1985) examined 48 patients with Tourette's disorder who had prior stimulant treatment. Of the 39 patients who had both ADHD and Tourette's disorder, 11 showed a worsening of the tics when stimulants were restarted.

The two controlled prospective stimulants studies in ADHD children comorbid for Tourette's syndrome have included long-term longitudinal follow-ups extending 2–4 years (Castellanos et al. 1997, Gadow et al. 1995). Conclusions derived from these studies are tentative, because they are based on a sample of only 56 subjects. However, in both studies, stimulants produced improvements in ADHD symptoms and no long-term worsening in tics, even after the tics worsened on high MPH or DEX doses. Despite the variable adverse event rates of across the entire sample in the Castellanos study (1997), up to one-third of subjects did not continue long-term treatment with stimulants because of tics worsening. Thus, both sides of the argument have been validated: tics are unacceptably, although reversibly, worsened for a minority of comorbid children, but the majority can be treated cautiously with low-to-moderate doses of stimulants, particularly MPH (Comings and Comings 1987).

Some argue that since a child with ADHD and Tourette's disorder already has both conditions, Tourette's disorder could no longer be triggered by the stimulants. Treatment of these cases with stimulants sometimes improves both the ADHD and the tics, whereas others find that the tics worsen. Overall, caution is still indicated when treating children with tic disorders. To date, there has been no prospective published study showing that stimulants have any affect whatsoever on the tic severity. Nevertheless, the most conservative and safe approach would be a trial of clonidine or desipramine.

Many stimulant treatment studies in school-age ADHD children exclude patients who are considered to have mental retardation (MR) as indicated by the full-scale IQ score below 70. This is unfortunate, for the ADHD signs are far more prevalent in children whose IQs are in the MR range (Aman et al. 1991). Pharmacotherapy reviews have reported that institutionalized patients with severe or profound MR respond poorly to stimulants. However, studies with community samples of MR children have shown that they do respond to MPH. Thirty children with MR treated in a double-blind crossover study using MPH (0.4 mg/kg per day), thioridazine (1.75 mg/kg per day), and placebo showed consistent MPH-related improvement on teacher global ratings of behavior. This same report found that three "cognitive maturity parameters" (breadth of attention, mental age greater than 4.5 years, and full-scale IQ above 45) predicted a good MPH response on 21 outcome variables. In contrast, children with IQs below 45 or mental age of less than 4.5 years had more adverse side effects or a poor response to MPH. Another controlled study reported responses to MPH doses of 0.3 and 0.6 mg/kg given to 27 ADHD children with IQs ranging between 48 and 74. Although 67% of this group was deemed stimulant responders, 6 of the 27 children had side effects of such severity that medication had to be discontinued. These included motor tics in three children and symptoms of social withdrawal in two children. Therefore,

it appears that children with ADHD and mild or moderate MR may be more vulnerable to certain stimulant-related adverse side effects.

Children comorbid for fragile X syndrome and MR often have avoidance of eye contact, perseverative behaviors, and severe ADHD symptoms. These children can be misdiagnosed with ADHD, even though their behavior disorder is only a phenocopy of the ADHD seen in children without an inborn genetic disorder. This misdiagnosis is possible due to the lack of clear differentiation among disorder etiologies in the DSM-IV-TR. However, stimulant treatment is effective in this population, as shown by a double-blind crossover study of 15 patients with fragile X syndrome who were treated with MPH, DEX, and placebo.

The DSM-IV-TR guidelines state that a diagnosis of pervasive developmental disorder (PDD) or early infantile autism rules out the ADHD diagnosis, even if the patient meets all criteria for the disorder. Symptomatically, children with PDD may exhibit severe overactivity, inattentiveness, and impulsivity that require treatment. Early studies cautioned that children with PDD may be sensitive to stimulant side effects and may show increased irritability, motor activity, and stereotypies. On the other hand, Birmaher et al. (1988) reported improvements in global parent and teacher rating scales for hyperactivity and inattentiveness in nine PDD children treated with open-label MPH at doses of 10–50 mg/day. Although these findings are based on an open study, they are encouraging, particularly because many of these children have been treatment failures on other medications. It was shown that MPH reduced overactivity in subjects with autism (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network 2005).

Children with ADHD taking psychostimulants routinely show appetite suppression when starting treatment. For this reason, dosing should optimally occur after breakfast and lunch. Even though the daytime appetite is reduced, hunger rebounds in the evening. These effects on appetite often weaken within the first 6 weeks of treatment. Safer and Allen (Safer et al. 1972, 1975, Safer and Allen 1973) were first to report that treatment for two or more years with MPH and DEX can produce decrements in weight velocity on age-adjusted growth rate chars. Stopping the medication can produce a quick return to baseline growth velocities. DEX, with a half-life two to three times that of MPH, produces more sustained effects on weight velocity and on mean sleep-related prolactin concentrations suppression compared to MPH (Greenhill 1981). In MPH-treated children with ADHD, followed for 2–4 years, dose-related decreases in weight velocity were seen (Gittelman-Klein et al. 1988, Satterfield et al. 1979), with some tolerance of the suppressive effect developing in the second year. Hechtman et al. (1984) reported growth slowdown in untreated children, suggesting that there may be differential growth associated with the ADHD disorder itself. Spencer et al. (1996b) detected similar differential growth rates for children with ADHD, and also suggested an association with the disorder itself, rather than with the stimulant treatment alone.

In addition to changes in weight trajectory, it has been reported that the MPH-related growth effects appear to be minimal. Satterfield et al. (1979) followed 110 children and found decreases in height velocity during the first year of psychostimulant treatment, but this reversed during the second year of treatment. An initial growth loss during MPH treatment was seen in 65 children followed to age 18, but these children "caught up" during adolescence and reached heights predicted from their parents' heights (Gittelman and Mannuzza, 1988). These results confirm the observations by Roche et al. (1979) that psychostimulants have mild and transitory effects on weight and only rarely interfere with height acquisition.

Most recently, growth slowing for height and weight was reported for children, ages 7–10, treated with MPH at mean doses of 30 mg/kg per day in the MTA Study (Swanson et al. 2002). School-age children grew 1.0 cm less per year and gained 2.5 kg less than the predicted norms from the Centers for Disease Control growth charts. Similar effects were observed for preschool children in the NIMH PATS Study (Swanson et al. 2006), who grew 1.5 cm less height and gained 2.5 kg less than predicted by the Centers for Disease Control growth norms while treated with mean MPH doses of 14 mg/kg per day. Two major reviews (Faraone et al. 2005, Poulton 2005) have concluded that stimulant treatment most likely slows height acquisition in children, at least during the first 1–3 years of treatment. Patients who were randomized to the stimulant treatment arms in the MTA Study showed significantly less height acquisition over the first 2 years of treatment compared to patients in the nonstimulant arms (MTA Cooperative Group 2004). Interestingly, compared to average children, ADHD participants in both MTA and PATS studies were heavier and taller than average at the start of treatment. Thus, clinicians may not observe growth slowdown as often as predicted, because the ADHD-treated children do not slow down in height acquisition to become shorter than average.

The actual psychostimulant mechanism for any growth slowdown is unknown. Early theories attributed the drug's supposed growth-suppressant action to its effects on growth hormone or prolactin. Although research studies on 13 children treated for 18 months with DEX at 0.8 mg/day (Greenhill et al. 1981), and on 9 children treated for 12 months with MPH at 1.2 mg/kg per day (Greenhill et al. 1984) failed to demonstrate a consistent change in growth hormone release. The most parsimonious explanation for this drug effect is the appetite suppression that leads to a reduced caloric intake. No study, however, has collected the standardized diet diaries necessary to track calories consumed by children on psychostimulants (Greenhill et al. 1981).

Even if height acquisition is reduced during the first year of stimulant treatment, this effect has been shown to attenuate afterwards (Faraone et al. 2005). Pliszka et al. (2006) found that amphetamine more than MPH affected the rate of weight acquisition, but neither had significant effects on the rate of height acquisition. The American Academy of Child and Adolescent Psychiatry (AACAP) Work Group on Quality Issues (2007) for ADHD recommend that no adjustment in treatment should occur until the patient has a change in height or weight percentile that crosses two percentile lines on the Centers for Disease Control chart. If this happens, the clinician can reduce the dose, switch to another ADHD medication, or temporarily discontinue stimulant treatment.

MPH has an excellent safety record, probably because the duration of action is so brief. When side effect reports have been gathered on children with ADHD

taking placebo, anxiety, staring, disinterest, and sadness were observed. Only parent reports of decreased appetite, stomachaches, and insomnia differentiated children with ADHD on stimulants from those taking placebo. In that study, less than 4% of children had to discontinue their medication due to these side effects.

One adverse effect, commonly known as behavioral rebound, appears when children experience psychostimulant withdrawal at the end of the school day. These children present with afternoon irritability, over talkativeness, noncompliance, excitability, motor hyperactivity, and insomnia that occur 5–15 hrs following the last dose. In one study involving 14 hyperkinetic boys treated with DEX, rebound was reported by three quarters of the group on stimulants and no placebo subjects. In a later study, the same authors reported significant increases in afternoon activity for 21 boys treated with DEX. This finding was the first quantitative evidence for the rebound phenomenon. Although no evidence for an afternoon symptom worsening was found in a third study, which used a controlled crossover design of 21 boys with ADHD taking MPH at doses of 0.6 and 1.2 mg/kg per day or placebo. At this time, it is not clear if these contradictory reports represent differences between DEX and MPH. Furthermore, it is not known whether longer acting stimulant preparations produce fewer rebound effects. The controlled drug treatment literature does not report rebound effects, which may be due to the use of global parent rating forms that are not specific for time of day. If rebound occurs, many physicians add a small dose of afternoon MPH or a tricyclic antidepressant.

It has been shown that higher than therapeutic doses of amphetamines reliably induce brief paranoid psychoses in adult volunteers. Stimulant-related toxic psychosis, including MPH-induced visual hallucinations, is a rare phenomenon in children, with fewer than 30 cases having been reported. Even though the psychotomimetic effects are short lived, this side effect can be serious and requires immediate cessation of stimulant treatment. Since psychosis is a contraindication for psychostimulant use (Greenhill et al. 2002b), the physician should consider dispensing neuroleptics instead of psychostimulants to agitated children with psychotic symptoms. The neuroleptics addition to the treatment regimen of a severely disturbed ADHD child raises the possibility that the hyperactivity and poor attention span were secondary to an underlying psychotic condition. Although neuroleptics and psychostimulants do not interact in a negative fashion, the *Psychotherapeutic Drug Manual for Use in New York State Mental Health Facilities* warns against prescribing a stimulant along with an antipsychotic.

The PDR lists a number of other adverse reactions, without stating frequency, which are not found in standard clinical practice or published reports from treatment studies. Rare side effects of stimulants include alopecia and leukocytosis. This suggests an inclusion of a yearly routine complete blood count in the therapeutic drug monitoring plan. Other rare adverse affects are hypersensitivity (i.e., rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis and hrombocytopenic purpura), angina, and cardiac arrhythmia.

Clinical benefits associated with stimulant use have to be weighed against reports of serious unexpected adverse events. Concerns arose from a series of reviews conducted by the FDA of cardiovascular and psychiatric adverse events associated with use of approved stimulant medications. On June 30, 2005, the agency began this review by examining the passive surveillance reports concerning treatment with OROS-MPH (*Concerta*) (http://www.fda.gov/ohrms/dockets)/ac/05/slides/2005–4152s2.html). The review uncovered 135 adverse events, including 36 psychiatric and 20 cardiovascular adverse events. In particular, the reports documented 12 instances of tactile and visual hallucinations (classified under "psychosis"). These OROS-MPH adverse event reports represent 135 per 1.3 million cases, and thus seem to be rare unexpected adverse events.

More worrisome were reports of 20 cases of SUD in 14 children and 6 adults, as well as 12 cases of stroke in patients taking MAS. These reports led to Health Canada suspending the sales of MAS extended release formulation (*Adderall XR*) (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_01_e.html). The deaths occurred in five patients with preexisting structural heart defects, and the rest of the victims had "family history of ventricular tachycardia, association of death with heat exhaustion, dehydration and near-drowning, very rigorous exercise, fatty liver, heart attack, and type 1 diabetes mellitus" (http://www.fda.gov/cder/drug/advisory/adderall.htm). Pliszka (AACAP Work Group on Quality Issues 2007) notes that the SUD rate on MAS is estimated at 0.5 per 100,000 patient-years, the rate on MPH is estimated at 0.19, whereas the rate of SUD in the general population has been estimated at 1.3–8.5 (Liberthson 1996). Nevertheless, patients with preexisting heart disease should be referred to a cardiologist prior to initiating stimulant treatment.

In summary, serious unexpected cardiac or psychiatric adverse events associated with stimulants have been known for years and are extremely rare. The rates of cardiac adverse effects are too low to prove a causal association with stimulants in patients with no history of previous heart disease. Routine EKGs and echocardiograms are not indicated before initiating stimulant treatment for a patient with unremarkable medical history and physical examination. It is advised that the physician prescribing stimulants first asks patients and their families about a history of structural heart disease, and if they have previously consulted a cardiologist. Known cardiac problems that raise a caution include postoperative tetralogy of Fallot, cardiac artery abnormalities, and obstructive subaortic stenosis. If the patient has a history of hypertension and/or complains of syncope, arrhythmias, or chest pain, then the clinician should be concerned because these symptoms may indicate hypertrophic cardiomyopathy, which has been associated with SUD.

An important serious and unexpected adverse reaction associated with PEM use is liver failure (Safer et al. 2001). Changes in liver function tests suggesting hepatotoxicity can also occur, thus necessitating routine liver function tests every 2 weeks for patients taking PEM.

Mixing psychostimulants with other psychotropic medications is generally not advisable. Most serious is the addition of a psychostimulant to a monoamine oxidase inhibitor antidepressant regimen, a potentially lethal combination that can elevate blood pressure to dangerous levels. Zametkin et al. (1987) do not recommend using the monoamine oxidase inhibitor medication tranylcypromine

for ADHD children, despite its efficacy, because of a possibility that a parent might mistakenly substitute MPH for tranylcypromine causing a potentially lethal blood pressure surge. Additive effects between psychostimulants and the systemic agents used to treat asthma can produce feelings of dizziness, tachycardia, palpitation, weakness, and agitation. Theophylline, for example, when taken orally, can have this undesirable agitating effect. It is best to ask the pediatrician or allergist to switch from the orally ingested preparation to an inhalant to avoid such additive sympathomimetic effects.

The psychostimulants can also interfere with the action of other medications. MPH can block the antihypertensive action of guanethidine. DEX blocks the action of some beta-adrenergic antagonists (e.g., propranolol) and slows down the intestinal absorption of phenytoin and phenobarbital. The renal clearance of DEX is enhanced by urine acidifying agents, so that grapefruit juice will shorten the elimination half-life of the medication. Conversely, urine alkalinizing agents decrease clearance. This is also true for ritalinic acid, although this metabolite is not active in the CNS.

Published case reports do not show an additive increase in side effects when combinations of other drug classes are used. However, MPH may elevate plasma levels of antidepressants, anticonvulsants, coumarin anticoagulants, and phenylbutazone. One group of researchers (Pataki et al. 1993) treated 12 boys with ADHD in a double-blind crossover study of combined MPH and imipramine. They reported an increase in nausea and dry mouth but no incidences of blood pressure elevation were recorded. Theoretically, MPH may increase the concentration of the serotonin reuptake inhibitor, fluoxetine, potentially enhancing agitation. Although no such side effect was described in a single case report concerning the treatment of an 11-year-old boy comorbid for ADHD and obsessive–compulsive disorder. Clonidine has been added to reduce sleep disturbances associated with stimulant medications. Other medications have been successfully combined with MPH, such as clonazepam to reduce tics. The combination of fenfluramine and MPH proved effective when tested in a double-blind crossover study of 28 children with both ADHD and MR. However, when bupropion was added to MPH, the tics in ADHD children were exacerbated.

Although psychostimulants have been abused by adults, the risk for addiction in children with ADHD is low. Klein (1980) found that the psychostimulants differ in their ability to induce euphoria, with "DEX the most euphorigenic, MPH, less so, and magnesium PEM, hardly at all." Adolescents and young adults with ADHD do not list the psychostimulants among medications used recreationally, regardless of whether they had stimulant treatment. Adolescents previously diagnosed with ADHD during school-age years are at greater risk for substance abuse than control subjects, but those who do abuse medications tend not to pick stimulants. Reports of MPH abuse include adolescents who snort ground up MPH tablets. A review assessing the MPH abuse potential noted that there is evidence, from non-scientific sources, that MPH use and abuse may be widespread among adolescents (Kollins et al. 2001). One should also be aware that there is a distinction between MPH clinical abuse and its misuse or diversion. There are only a few case reports of MPH abuse that have lead to role impairment. Kollins et al. (2001) believe that these issues are important for consideration when MPH is prescribed in clinical practice.

Even though the evidence from the literature suggests that the abuse potential of psychostimulants by children with ADHD is low, DEX and MPH have been classified by the US FDA as potentially drugs of abuse (schedule II) and have warnings concerning abuse in the PDR. MPH was reclassified as a schedule II medication in 1971, due to a concern that the order issued by the Bureau of Narcotics and Dangerous Drugs to schedule methamphetamine and DEX would direct potential drug abusers to MPH. American physicians prescribing these psychostimulants for childhood psychiatric disorders first are required to obtain a US Drug Enforcement Administration (DEA) registration number. As a schedule II medication, the annual amount of manufactured stimulants must be approved or allocated. This requirement led to widely publicized MPH shortages in the fall of 1993. As a result, a parent special-interest group, Children and Adults with Attention Deficit Disorder (CHAAD), petitioned the US DEA of the Department of Justice in May 1994 to reclassify MPH from schedule II to III, as to "eliminate all likely future MPH shortages." After a thorough review of the substance abuse literature, this scholarly petition could find "no substantial dependence liability and a very limited potential for significant MPH abuse or diversion into illegal drug channels." However, MPH classification was not changed, and it has remained a schedule II drug of abuse.

In the US, nine states (California, Hawaii, Illinois, Idaho, Indiana, Michigan, New York, Rhode Island, and Washington) adopted multiple-copy prescription programs between 1967 and 1982 to monitor schedule II drugs, including DEX and MPH (PEM, on the other hand, is classified as a schedule IV medication and does not require such forms). Physicians practicing in these states are required to use multiple prescription copy pads (triplicates) to order DEX and MPH. The resulting data have been instrumental for exposing illicit distribution of psychostimulants, as well as for conducting research on local trends in office practice. With such data, it is possible to compare the MPH treatment prevalence of children in primary school in Suffolk County in 1988 (0.04%) to the percentage of 3rd graders treated in 1987 in Baltimore County (7%; Safer and Krager 1988).

The New York State Department of Public Health (Eadie J, personal communication) reported that four times as many prescriptions were written for MPH as for DEX in the second quarter of 1990 (20,271 for MPH, and only 4,514 for DEX). This was partly due to public and professional concern about amphetamine. On the other hand, many physicians view MPH as a nonamphetamine. Amphetamine's notoriety as a highly euphorigenic and addictive substance has greatly reduced its use, as shown by a 95% drop in triplicate prescriptions for DEX in New York State in the decade following introduction of triplicate prescriptions (Eadie, personal communication). In addition, pharmacists may refuse to carry DEX once they stock MPH.

## Clinical Use

The PDR has two main indications for the MPH use, which are narcolepsy and ADHD. Other stimulants differ somewhat, with the indications for methamphetamine including

ADHD and obesity, and for PEM including only ADHD. The decision to use medication for any pediatric psychiatric condition should be based on a balance of risks and benefits. Risks must be examined not only in terms of when medication is used, but also when medication is *not* used and the child continues to be impaired in social and academic functioning. Before stimulants can be prescribed for treatment of behavioral problems, the child must meet the DSM-IV-TR ADHD diagnostic criteria.

Other health conditions might prevent one from using a stimulant. If the child has Tourette's disorder, stimulants would not be used because of the likelihood of exacerbating the motor or vocal tics. Malignant hypertension might also prevent one from using a psychostimulant because of the risk of raising the blood pressure. Otherwise, the risks from these compounds are few.

The short-term benefits of stimulants are unequivocal, whereas the long-term outcomes are less well documented. Similarly, evidence supporting efficacy is strongest for preadolescents, weaker for adolescents, and equivocal for adults (Shaffer 1994).

Medication treatment begins with a choice of medication. Although the MPH or DEX psychostimulant types have equal efficacy, MPH is often used first. Elia and Rapoport (1991) strongly suggested for the physician to try both MPH and DEX, "because the overlap of who is a nonresponder is not great." These researchers defined nonresponders as those patients given medication, but whose behavior remained unimproved, or those who suffered severe adverse effects from the drug. Because of PEM's hepatotoxicity, it is used infrequently. If it is used, liver function studies should be done and repeated at 6-month intervals.

Standard MPH package instructions warn against its use in patients with tics or in patients with a family history of tics. One study showed that stimulant treatment of ADHD children maintained on effective anticonvulsant doses did not produce any increases in seizure frequency, changes in the electroencephalogram waveforms, or difficulties in regulating anticonvulsant blood levels. Current practice is to give children with both ADHD and epilepsy a combination of anticonvulsant and MPH. Plasma levels of the anticonvulsant should be monitored to avoid toxicity resulting from MPH competitive inhibition of metabolic pathways. At the doses used to treat ADHD in children, the psychostimulants have variable but minimal effects on the seizure threshold.

Table 106–1 is an inventory of stimulant drugs and doses. Immediate-release DEX (IR-DEX) is usually started at 2.5–5 mg/day and gradually increased in 2.5–5 mg increments. Immediate-release MPH (IR-MPH) is usually initiated at 5 mg b.i.d. and then titrated in increments of 5 mg/dose every 4−7 days. Peak behavioral effects are noted 1−3 hrs after ingestion and dissipate in 3−6 hrs for both IR-MPH and IR-DEX. Although stepped-dose open-label IR-MPH and IR-DEX trials are the rule in clinical practice, double-blind, placebo-controlled, titration trials—using parent and teacher ratings plus an "objective" measure of attention, such as the CPT—can be helpful in distinguishing a true drug effect from a placebo response and in establishing the optimal individual dose.

Medication titration serves two purposes: acclimatization of the child to the drug and determination of his or her best dose. School-age children should be started with low doses to minimize adverse effects. Psychostimulant medication should be taken at or just after mealtime to lessen the anorectic effects. Studies have also shown that food may enhance drug absorption. IR-MPH treatment can be initiated with a single 5 mg dose at 8:00 a.m. for 3 days; then a 5 mg dose at 8:00 a.m. and at noon for the next 3 days; then 10 mg at 8:00 a.m. and 5 mg at noon for 3 days; and finally 10 mg at 8:00 a.m. and 10 mg at noon for at least 2 weeks. Preschoolers may start as low as 2.5 mg at 8:00 a.m. but build to the same total 20 mg/day IR-MPH total daily dose. The dosing instructions should be written down for the parent, with dates and times specified in detail.

Because MPH's short half-life prevents it from reaching a steady state in the plasma, the standard tablet must be given several times a day to maintain behavioral improvement throughout the school day. Although the PDR suggests giving MPH before meals, standard administration times are after breakfast (8:00 a.m.), after lunch (noon), and before homework (about 3:30 p.m.). Three-times-daily stimulant administration has been utilized in treatment studies (Greenhill et al. 1996) with doses given before school, at lunch, and at home prior to homework. The dose can be increased in 5 mg increments every 5–7 days, up to a maximum of 20 mg t.i.d. Preschool children generally needs a total daily dose of about 15 mg, and school-aged children need about 30 mg daily (Greenhill et al. 2006). Although not FDA-approved, some older children may require more than 60 mg/day.

A brand formulation (*Methylin*) of a single-pulse MPH is available in chewable tablets. It is designed as an oral solution for young children who have difficulty swallowing tablets or capsules. Peak plasma concentrations are achieved within 1−2 hrs; high-fat meals delay the peak by 1 hr. No large CRTs using this formulations have been published (Drugs for Treatment of ADHD 2006a).

Dexmethylphenidate (*Focalin*), the d-threo-enantiomer of MPH, can be given in half the dose of racemic MPH. Patients switching from another immediate-release MPH should start with half as much dexmethylphenidate. Stimulant-naïve subjects should begin with 2.5 mg doses twice daily, 4 hrs apart. Dosage can be increased in weekly increments to a maximum of 20 mg daily (Drugs for Treatment of ADHD 2002).

Current practice recommends switching as soon as possible to a long-duration preparation, such as OROS-MPH or modified-release MPH (MPH MR; Greenhill et al. 2002a, Wolraich et al. 2001). There are three reasons for the implementation of longer acting stimulant preparations. First, children who take medications in school can be subjected to peer ridicule when they leave activities to go to the nurse. Second, some school officials refuse to allow school personnel involvement in the administration of medication. Third, the time–action course of standard stimulant medications allows only a brief 1–3-hr effect window, therefore, some medicated children may experience periods of little or no drug action during important parts of the school day.

Long-acting MPH formulations include single-pulse and beaded double-pulse preparations (Drugs for Treatment of ADHD 2006a). Both generic and brand formulations are available. Single-pulse, sustained-release formulations use a wax matrix to prolong release. Compared to the IR-MPH, they have a slower onset of action with duration for up to

8 hrs. Some clinicians have found the duration of action to be highly variable and consider these medications as less effective in practice than immediate-release, beaded double-pulse, or osmotic-release MPH preparations. Often, the single-pulse formulations are prescribed twice daily, and sometimes an immediate-release tablet is added in the morning.

Beaded MPH (*Ritalin LA*) products use an extended-release formulation with a bimodal release mechanism. The long-acting MPH capsules are designed with half the dose being contained in the immediate-release beads and the other half in the enteric-coated, delayed-release beads. The beaded products can be opened allowing the medication to be sprinkled into small amounts of apple sauce or ice cream to disguise its bitter taste.

The OROS-MPH (*Concerta*) tablet uses an osmotic delivery system to extend the duration of MPH action to up to 12 hrs (Wolraich and Doffing 2004, Swanson et al. 2004). The tablet is coated with IR-MPH for immediate action. The rest of the dose is delivered by an osmotic pump that gradually releases the drug over a 10-hr period, producing slightly ascending MPH serum concentrations. Taken once daily, serum concentrations are similar to those produced by IR-MPH taken three times daily, but with less variation (Modi et al. 2000a). The tablets themselves are excreted in the stool.

Three double-blind RCTs have compared OROS-MPH to IR-MPH in children with ADHD. The results showed that the reductions in ADHD symptoms that occur with once-daily doses of OROS-MPH match those achieved with multiple doses of IR-MPH (Pelham et al. 2000, Swanson et al. 2003, Wolraich et al. 2001). Studies in adolescents have also demonstrated the effectiveness of OROS-MPH (Wilens et al. 2006).

Transdermal MPH patch appears to be as effective as other long-duration MPH preparations. Adverse effects such as anorexia, insomnia, and tics have occurred more frequently with this formulation. Especially common are mild skin reactions (Drugs for Treatment of ADHD 2006b). After application of the transdermal patch, MPH is steadily absorbed and reaches peak concentrations in serum after 7−9 hrs. Chronic dosing with the patch leads to higher MPH levels than with equivalent OROS-MPH doses. The MPH duration of action for a 9-hr wear period is about 12 hrs. A double-blind, placebo-controlled crossover study conducted in a laboratory classroom showed significantly lower ADHD symptom scores and higher math test scores with the MPH patch compared to a placebo patch during post-dose hr 2 through 12 (McGough et al. 2006). An advantage of the transdermal formulation is that it can be removed early in patients who have insomnia problems.

Similar to MPH formulations, amphetamine preparations are available as either the d-isomer, DEX, or in racemic forms, which are mixtures of d- and l-amphetamine. DEX has been equally effective to MPH in ameliorating pediatric ADHD symptoms. Some children unresponsive to MPH may respond to DEX, and vice versa. DEX absorption is rapid; the onset of action occurs within 1 hr of ingestion; plasma concentrations reach a peak 3 hrs after oral administration; and the duration of action is up to 6 hrs, which is somewhat longer than that of MPH. Twice-daily DEX administration is needed to extend the treatment through out the school day. Taking the medication with ascorbic acid or fruit juice tends to decrease amphetamine absorption, while taking alkalinizing agents such as sodium bicarbonate tend to increase its absorption. Acidification of the urine increases amphetamine excretion.

Short- and long-acting mixtures of amphetamine salts are available in both generic and brand formulations. Long-acting preparations are manufactured in double-pulse capsule formulations containing immediate- and extended-release beads. There is no evidence that these medications offer any advantage over MPH or DEX, although clinically some patients respond to one and not to another.

Lisdexamfetamine dimesylate (*Vyvanse*) was recently approved by the FDA for the ADHD treatment in children aged 6–12 years. It has not yet been investigated in children younger than 6 or older than 12 years of age. Lisdexamfetamine dimesylate is available in 30-, 50-, and 70-mg capsules, which are equivalent to 10, 20, and 30 mg of mixed amphetamine salts, respectively. The starting dose should be 30 mg once daily in the morning. The dose can be raised in 20 mg/day increments no more often than once per week. The maximum dose for school-aged children is 70 mg (Drugs for Treatment of ADHD 2007).

Two double-blind, placebo-controlled, randomized clinical studies in 342 children with ADHD demonstrated that subjects taking lisdexamfetamine dimesylate in doses between 30 and 50 mg for 3–4 weeks showed more improvement on the ADHD ratings scales compared to children on placebo. The first study, a phase 2, double-blind, placebo-controlled, randomized, crossover trial in 52 children with ADHD found significant reductions for lisdexamfetamine dimesylate and MAS compared to placebo. The ratings were completed by trained and blind observers across 8-hr sessions in a 12-hr day (Biederman et al. 2006). The second study, a multisite, phase 3, parallel-design, randomized controlled clinical trial of 290 children demonstrated significant decreases in ADHD behaviors reported by parents for mornings, afternoon, and early evening on the CPRS. (Biederman et al. 2007). Adverse effects occurred in at least 5% of children assigned to active medication at a rate twice that of placebo group. Common adverse effects included upper abdominal pain, decreased appetite, nausea, vomiting, decreased weight, dry mouth, irritability, rash, and insomnia. Children taking lisdexamfetamine dimesylate have also had minor but statistically significant increases in blood pressure and pulse. Rash had occurred in 3% of patients taking the active medication versus none in the placebo group. A total of 21 out of 297 children terminated the trial due to adverse events.

Lisdexamfetamine dimesylate should not be used in patients with symptomatic cardiovascular disease, moderate to severe hypertension, advanced arteriosclerosis, hyperthyroidism, glaucoma, during or within 14 days following treatment with monoamine oxidase inhibitors (hypertensive crises may result), or known hypersensitivity to sympathomimetic amines. It should not be taken by patients with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or coronary artery disease without a prior consultation with a cardiologist. Monoamine oxidase and lisdexamfetamine dimesylate should not be used together or within 2 weeks of each other.

There is no evidence that lisdexamfetamine dimesylate offers an advantage over other amphetamine formulations.

Although, it may prove useful for the ADHD treatment in adults and adolescents with current or past history of stimulant abuse, in general, older medications with better established dosages and safety records are preferred.

PEM has been removed from many formularies and is no longer used in Canada because of the rare hepatic failure noted. When used, it is usually started at 37.5 mg once in the morning and titrated in 18.75 mg increments to maximal clinical effectiveness. Most children respond at a total daily dose of 56.5 mg/day or about 2 mg/kg per day in a single dosing. For patient safety, consent forms should be presented to the parents for their signature, and hepatic function tests should be gathered biweekly.

Drug response may be altered by comorbid ADHD. In anxious ADHD children, it has long been speculated that comorbid anxiety may influence the outcome of ADHD treatment. For example, Pliszka compared children with nonanxious ADHD to children comorbid for ADHD and anxiety disorder and found that the latter combination reduced the risk of comorbid conduct disorder, decreased impulsive responding on a CPT, and produced sluggish reaction times on a Memory Scanning Test (Pliszka 1989). These children also showed a poorer response to MPH and more side effects than subjects with ADHD alone. Although failing to replicate the results of Pliszka (1989) with respect to behavioral outcomes, Tannock and others later demonstrated that children comorbid for anxiety and ADHD have an enhanced risk for tics and dysphoria associated with MPH treatment. These children also had less improvement in memory when given a single MPH dose.

Conversely, using a flexible clinically appropriate titration trial, Diamond et al. (1999) found no difference in short-term outcome or side effects in children with ADHD alone and those comorbid for ADHD and anxiety, implying that a method variance may in part account for conflicting results in these studies. Analyses of the MTA Study, which addresses a priori questions about the individual and combined effects of pharmacological and psychosocial (behavioral) treatment for ADHD children ages 7–9 (Arnold et al. 1997), suggested that parent-reported child anxiety differentially moderated the treatment outcome. In particular, it generally favored the addition of psychosocial treatment for anxious ADHD children irrespective of the presence or absence of comorbid conduct problems. Contradicting earlier studies, no adverse effect of parent-reported child anxiety on medication for core ADHD symptoms or other outcomes were found. For some outcome domains, anxious ADHD children showed significantly greater gains than nonanxious children even when treated with medication only. On the other hand, exploratory analyses documented that child self-reported anxiety on the Multidimensional Anxiety Scale for Children (MASC) was only weakly correlated with parent- or teacher-reported anxiety at baseline, and changed little with treatment, raising questions whether the parent Diagnostic Interview Schedule for Children (DISC) accurately detects anxiety in ADHD children.

Response to a stimulant may not be related to child's attitude. Concerns that medications may create negative attributions or dysphoric effects in ADHD children have not, as a rule, been confirmed in direct tests. Excellent studies show that there is considerable variability in children's attributions, as well as their mood response to pills. Pelham et al. (1992) identified a subgroup of "depressogenic" children who gave external credit for positive events and felt internal blame for negative events. This group was above the median on success attributions to their medications. Comorbidity and family history for anxiety and/or depression seemingly are relevant variables in prediction of such attributional effects. During treatment, a small percentage of stimulant-treated children become dysphoric, weepy, and mournful. Since depressed children can present with symptoms of irritability, children who respond with depressogenic attributions or dysphoria may be the ones whose depressive diathesis is indistinguishable from ADHD. They are mistakenly diagnosed with ADHD and treated with stimulants. Given the overlap of depression and ADHD, as well as the findings that depressogenic cognitive styles predict later depression, it is important to identify children prone to attribute their success to medication rather than to their own effort, even though the majority of patients do not do so.

Children often have negative attitudes about treatment, thinking of it as a punishment. Taking medication can be socially stigmatizing to the child if the daily trips to the nurse generate peer ridicule. Discussing the problems of in-school medication administration may be of great help to the child. He or she should be included in all discussions about dosing and changing of doses. Optimally, these discussions may enhance treatment compliance.

Since ADHD is a chronic disorder, an effective treatment plan for follow-up and monitoring is imperative. Techniques encompass regular follow-up visits, the use of parent and teacher rating scales, and the monitoring of academic progress in school. Seeing the patient and a family member regularly is essential, often on a once-monthly basis when the medication prescription must be renewed. Medication therapy can be divided into baseline, titration, and maintenance phases. Before the first pill is given, baseline data on height, weight, blood pressure, heart rate, and complete blood count should be collected. Progress assessment is handled by a timetable of *regularly scheduled visits to the physician's office.* Based on the success of the MedMgt strategy of the MTA Study (MTA cooperative group 1999), children on stimulants should be monitored with monthly or bimonthly visits. These visits work well if scheduled for 30 min in duration and involve both parent and child. They allow the physician to observe the child's activity level and attentiveness, to collect information on beneficial effects and adverse reactions, and to review the teacher reports on the academic and social progress. Clinical progress is reviewed so that the physician can track ADHD symptoms, academic progress, and success with peers. Any counseling, therapy, or educational guidance can be provided at that time. With the parental permission, report cards can be copied and placed in the medical chart. The physician can keep anecdotal records about social events, including invited play dates and sleepovers, teams joined, and Boy or Girl Scout activities.

*Maintenance* plans should incorporate schedules for the regular collection of information that constitutes the therapeutic drug monitoring. Each child's response to psychostimulants is different. Likewise, each family's needs are different. Plans for medication vacations, weekend and after-school dosing must be individualized. Many parents,

concerned about long-term side effects, feel most comfortable with their child not taking medication every weekend and through the summer, despite the costs to family harmony. A summer off medication, although it may seem idyllic, may become much less desirable if the child's summer camp has difficulty with the ADHD symptoms. On the other hand, a child with MPH-induced anorexia and some weight loss can benefit from a summer without medication.

Medication *compliance* should be monitored at each visit. The parent is to be instructed to bring the medication bottle along, so that pill counts can be done monthly and compared with the prescription dates. Height and weight should be taken every 6 months, and the child's pediatrician can be requested yearly to perform a complete physical examination and blood work (complete blood count and liver function studies). The visit frequency depends on the other therapies recommended. These may include once-monthly parental counseling, twice-monthly individual therapy, and weekly meetings for individual psychotherapy or behavioral modification management. A minimal frequency should be once monthly, particularly in the nine states requiring multiple-copy prescription forms, which limit the amount of psychostimulant ordered to a 30-day supply.

The next component of monitoring is the use of *structured rating scales.* These have been the backbone of psychostimulant treatment research but also have utility in clinical practice. Each physician should choose a scale that she or he finds easy to interpret and convenient to use. It should be available in both parent and teacher versions. The rating scales, however, should not be used as substitutes for an open discussion with the teacher. They should be collected every 4 months, and whenever the physician needs to make decisions about dosage adjustment, time of dosing, or continuation of medication treatment.

Although the original 39-item CTRS is ubiquitous in the field of child psychopharmacology, Satin et al. (1985) have shown the validity of the shorter, 10-item Abbreviated Rating Scale both as a repeated measure and as a screening tool for identifying school-age ADHD children. This short form is effective for tracking children in maintenance treatment. Like most scales, the Abbreviated Rating Scale assigns weights to each scale point. In the 10-item scale, each point is weighted between 0 ("not at all") and 3 ("very much"). Ten checks by a parent in the "very much column" yield a total score of 30. The physician should use these forms prior to the initiation of treatment. Two copies of each form are to be collected from both parents and the teacher 1 week apart. Each pair of forms is averaged to determine the child's baseline pretreatment score. The average score counteracts any tendency for the rating scores to drift downward. Current thinking indicates that a 25% drop (with a lower total score indicating improvement) from baseline is required after medication is started to establish that the child has had a positive clinical response. Once the maintenance stimulant dose is set, the teacher and parent rating scales can be repeated at 4-month intervals.

Unlike the findings with anticonvulsants, it has not proved effective to monitor psychostimulants by maintaining plasma concentrations within a therapeutic range. Once absorbed, levels of the parent compound, MPH, can be obtained in bodily fluids. However, they do not prove to be a practical aid in the treatment of ADHD children according to the studies of saliva and plasma samples. Because MPH concentration is not independent of saliva flow, saliva MPH concentrations cannot be used to predict its concentrations in plasma or brain. In addition, plasma levels do not correlate with behavioral or cognitive measures. Nevertheless, MPH saliva levels provide a good check of pill-taking compliance.

As stated above, MPH plasma levels do not correlate with clinical response and provide no more predictive power than teacher and parent rating scales, because therapeutic drug monitoring efforts are hampered by MPH short half-life, as well as its tendency to degrade unless strict collection and storage methods are used. Its short half-life means that no true steady-state level is reached. This hampers the usual standard peak or trough collection time strategies used with the other psychotropic medications, such as lithium and carbamazepine, monitored with blood tests. There is no exact agreement in the literature concerning a standard time after oral dosing to draw blood for MPH levels. A variation of ½ hr can make an enormous difference in the resulting blood level of MPH if the physician is restricted to only one sample. Furthermore, there is considerable intraindividual variability, with poor intertest reliability for peak MPH plasma levels. Alternative medications such as desipramine, however, do lend themselves to regular plasma level monitoring every 3 months.

Treatment duration is an important step in generating a therapeutic plan for an ADHD child. Although there is no clear-cut recommendation for the length of psychostimulant treatment, many parents have a reasonable expectation that it will not be open ended. The onset of puberty is one possible stopping point for psychostimulant medication. School-age children were thought to respond "paradoxically," calming down on stimulant medication, an effect that was supposedly lost at puberty. Adolescents with ADHD, who may be at risk for substance abuse, have been regarded as vulnerable to psychostimulant euphoria and to abuse of their medications. In addition, more recent prospective follow-up studies suggest that the motor hyperactivity of ADHD diminishes between ages 16 and 23. Although, hyperactivity does not necessarily go away. Prospective follow-up studies have shown that approximately 25% of children with the full ADHD syndrome at age 10 will continue to show all signs of the disorder at age 18, including motor hyperactivity. These adolescents demonstrate the same beneficial response to MPH, in magnitude and direction, as do school-age ADHD children. Furthermore, MPH produces no more signs of euphoria in adolescents than it does in school-age children. With clear evidence that some individuals continue to suffer from ADHD in adult life, one could advocate psychostimulant treatment indefinitely. As such, what is the physician to tell the parents?

Dulcan et al. (1997) and Greenhill et al. (2002b) recommended that treatment duration should be planned on an individual basis. One method is to plan in single school year units, starting at the present time, and projecting treatment to last through the current school year plus at least one additional month into the following academic year. Once the child has responded to an initial level of medication, maintenance doses can be set at slightly lower levels. Treatment can be continued, if need be, and the next decision point can be set for the following fall.

This provides a framework for the second concept, a trial-off medication, which can be used to determine whether the treatment should be continued for another year. Medication can be discontinued during the school year at some stable period. This should not be the beginning of the school year or during crucial placement examinations. Since placebo tablets are no longer available from the companies manufacturing MPH, the psychostimulants are to be simply stopped. Most children do not need to taper their dose off medication at discontinuation, unless they show signs of marked afternoon rebound.

A therapeutic plan may include other treatment components in addition to medication. New standards have been promulgated recommending multimodal therapy for the ADHD treatment. This was first reported by Satterfield et al. (1980) as successful in maintaining the short-term stimulant gains for periods of two or more years. Some combination treatments, such as behavior modification plus medication, have been shown to be somewhat more effective than medication treatment alone. However, the combination of medication and cognitive–behavioral therapy was not more effective than medication alone. More recent studies (Abikoff et al. 2004b, MTA cooperative group 1999) have evaluated a multimodal package variously including MTA given in multiple doses, parent training, educational supplementation, and social skills training for the child. This type of therapy is more costly, in time and money, than MedMgt accompanied by regular but infrequent counseling. Testing the relative efficacy of combination therapies is more challenging than assessing the stimulant efficacy, since more control groups are required to tease out the effects of each component and their combinations. Controlled studies of multimodal therapy have been confounded by the need to use a fixed package rather than tailoring the therapy to the child's needs, thus generating high refusal rates and reluctance by families to accept the entire treatment package.

Treatment plans that center only on psychostimulant medication have flourished for a number of reasons. The effects of psychostimulants are rapid, dramatic, and normalizing. The risk of long-term side effects remains low, and no substantial impairments have emerged to lessen the remarkable therapeutic benefit–risk ratio of these medications. More expensive and demanding treatments, including behavior modification and cognitive–behavioral therapies, have, at best, merely equaled the treatment with psychostimulants. In a number of instances, the combination of behavioral and medication therapies have at best moderately surpassed treatment with psychostimulants alone (MTA cooperative group 1999). Current and future studies of multimodal therapies will test whether combined treatment results in better overall functioning in the long run and decreases appearance of comorbid conditions as compared to monomodal treatment with psychostimulants alone. It is essential to demonstrate that the continuation of stimulant medication during long-term maintenance benefits the patient with ADHD.

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# Treatment of Adult Depression

J. Craig Nelson

The use of stimulants for depression has a long history. Myerson (1936) first reported the use of amphetamine sulfate. Wilbur et al. (1937) also noted marked improvement of mood following administration of amphetamine, sometimes within 24 hrs, in depressed subjects. Wilbur also provided the first description of apparent habituation with time so that responding patients lost the initial effect. This remains one of the best descriptions of the principal limitations of this drug.

## Acute Effects

The acute effects of stimulant drugs are well documented. Fawcett and Siomopoulos (1971) described the "stimulant challenge test" as a predictor of response to tricyclic antidepressants (TCAs). The usual test dose was dextroamphetamine 5 mg given orally three times a day. About 50% of severely depressed patients showed clinically meaningful change. Although the predictive value of this test for TCA response has been debated (Little 1988, Gwirtsman and Guze 1989), for a time many clinicians attempted this strategy. In contrast to the gradual effects of traditional antidepressants, the effects of dextroamphetamine were evident within 48 hrs.

Subsequent to the observation of Fawcett and Siomopoulos, several placebo-controlled studies or dextroamphetamine or methylphenidate confirmed the observation of acute response (Van Kammen and Murphy 1978, Brown et al. 1978, Van Kammen et al. 1981, Silberman et al. 1981, Ettigi et al. 1983, Sabelli et al. 1983). Changes in mood were commonly observed within 24–48 hrs although effects could be observed within 20 min after intravenous administration. The onset of effects was dependent on dose and route of administration. Clearly, amphetamine had rapid antidepressant effects.

## Chronic Effects

Unfortunately, the dramatic acute effects of stimulants were not confirmed with chronic administration (3–12 week trials). In a previous review (Satel and Nelson 1989) we found 10 double-blind, random assignment, placebo-controlled trials of stimulant drugs in depressed subjects. Nine of the 10 studies were published between 1958 and 1972 with the 10th study published in 1985. Samples ranged in size from 20 to 204 and six samples were outpatients and four were primarily inpatients. Some studies excluded agitated or highly anxious patients. Half of the studies administered dextroamphetamine and half methylphenidate. Doses of amphetamine ranged from 10 to 40 mg/day. Methylphenidate doses were quite variable and ranged from 15 to 90 mg/day. In one 4-week comparison, methylphenidate was superior to placebo (Rickels et al. 1970). A second study found

methylphenidate superior to placebo by patient report but not clinician rating. The other eight studies failed to find an advantage for the stimulant. Patients were responsive, but in some studies placebo response was as high as 72% (Wheatley 1969).

These studies are easy to criticize. Several were short 3–4 weeks trials but that might favor a drug with rapid effects. Several were crossover studies, which have limitations in depression. Most of these studies were conducted prior to the use of diagnostic criteria. Rating scales in the early studies were idiosyncratic. Nevertheless, during the same time period, 14 of 23 studies of imipramine using relatively similar methods demonstrated clear efficacy (Klerman and Cole 1965). It seems fair to conclude that the stimulants are not as effective as a standard TCA, imipramine in patients with depression.

## Studies in Medically Ill and Geriatric Patients

Stimulants have been commonly used in medical settings. Murray and colleagues at Massachusetts General Hospital have been advocates of the use of stimulants on their consultation service. As Murray (Murray and Cassem 1998) noted, "We were looking for a faster acting antidepressant since most of the medical and surgical patients seen were not hospitalized for 2 or more weeks." The MGH group published two large series of patients treated with stimulants on their consultation service. The first was a series of 66 patients treated between 1979 and 1983 (Woods et al. 1986). The second nonoverlapping series included 198 patients treated between 1983 and 1988 (Masand et al. 1991). In both series, almost all patients met Washington University criteria for "secondary depression," meaning that medical illness preceded the depression (Feighner et al. 1972). Most of the patients were older; mean ages in the two series were 72 years and 65 years. In the first series, about half of the patients received dextroamphetamine and half methylphenidate. In the second series three-quarters were treated with dextroamphetamine. Mean doses of dextroamphetamine were 12 and 8 mg/day. Mean doses of methylphenidate were 13.5 and 11 mg/day. On the Clinical Global Improvement scale 48% of patients in the first series and 70% in the second series had marked or moderate improvement. Peak response was seen within 2 days. Although all of these patients were hospitalized because of medical illness and some were seriously ill, side effects were relatively infrequent and transient. In the two series 7 and 10% discontinued treatment because of adverse effects. Most common side effects were central nervous system effects such as confusion, agitation, nervousness, hypomania, or delusions. In the larger series, six patients had cardiovascular symptoms—sinus tachycardia (3), elevated systolic blood pressure (2), and atrial fibrillation; however, in a medically ill, older population, these changes are not uncommon and it is not possible to attribute these changes to drug treatment without a placebo control group.

These two open series are presented in some detail because they are relatively large, they included "real-life" patients, and the findings are compelling. They are, however, uncontrolled. Two placebo-controlled studies in medically ill patients have been reported. Wallace et al. (1995) reported a double-blind crossover study of methylphenidate in 16 older medically ill patients (mean age 72). Patients were randomized to methylphenidate up to 10 mg twice a day or placebo for 4 days then crossed over to the other agent. During the first 4 days, patients in both groups improved. After the crossover only the patients on methylphenidate continued to improve. Few side effects were noted and no changes in vital signs were observed. The small numbers, further reduced by dropouts in the placebo group, limit conclusions.

Wagner and Rabkin (2000) reported a second placebo-controlled study. This was a 2-week randomized trial in 23 patients (age range 18–65) who had various DSM-IV-TR depression diagnoses, fatigue, and advanced HIV illness. The mean baseline Hamilton score was 14.9. Patients were randomized to dextroamphetamine or placebo. Dextroamphetamine was started at 2.5 mg twice a day and increased 2.5 mg every 2 days up to 40 mg/day (mean 22.9 mg/day). All but one patient (a patient on placebo who became anxious) completed the 2-week trial. Eight of the 11 patients randomized to drug responded while 3 of 12 patients on placebo responded (Fisher exact test, $p < 0.05$). Of 15 patients who had either responded during the trial or were switched to drug after the trial, 10 maintained their response after 6 months. The authors noted that the value of stimulants appeared to be greater in less severely depressed patients. Side effects were infrequent and transient, and no serious side effects occurred.

## Stimulants in Late Life Depression

Numerous case reports or small series have described the use of stimulants in older depressed patients and have been reviewed previously (Satel and Nelson 1989, Chiarello and Cole 1987, Nelson 2004). In many cases the older patients also had medical illness. There are no placebo-controlled studies of stimulants in late life patients with clear Major Depression. There are five placebo-controlled studies, previously reviewed (Satel and Nelson 1989), in institutionalized older patients and four of these studies noted some advantage for the stimulants. These studies, however, are difficult to interpret. Diagnoses were not clearly defined. Patients included had depressed mood, fatigue, and apathy and some were described as "senile." While stimulants appeared to be useful, it was unclear what disorder was being treated.

## Stimulant Augmentation in Depression

There are two types of stimulant augmentation studies. The early studies of stimulant augmentation added stimulants to patients who had not responded to an antidepressant. Subsequently stimulants were used to accelerate response. Five open label trials in 67 patients used stimulants to augment a TCA or monoamine oxidase inhibitor (MAOI) and have been previously reviewed (Ayd and Zohar 1987). In the largest of these, Fawcett et al. (1991) reported that 25 of 32 refractory patients responded to the addition of a stimulant and that response was maintained for several months. When used for augmentation the usual dose of dextroamphetamine was 10–15 mg/day and for methylphenidate about 30 mg/day.

Stimulants have also been used to augment second-generation agents. Favorable results were reports in a single case (Gupta et al. 1992) and two small series of five and seven cases (Stoll et al. 1996, Masand et al. 1998). Recently,

a placebo-controlled study of 60 subjects was published (Patkar et al. 2006). An extended release formulation of methylphenidate was administered in patients who had failed or were partial responders to antidepressants. Subjects were randomized to a 4-week double-blind trail of methylphenidate (dose 18–54 mg/day, mean dose 34 mg/day) or placebo. The reduction on the HAMD was not significantly greater in the methylphenidate group and response rates in the drug and placebo groups, 40.0 and 23.3%, did not differ significantly, although the study may have been underpowered to detect a difference. Common side effects were loss of appetite, nausea, headache, and anxiety. There were no significant differences in weight, heart rate, or blood pressure.

## Acceleration of Response with Stimulants

A particularly interesting question is whether the documented acute effects of a stimulant might be used to "jump start" treatment. This was first suggested by Gwirtsman et al. (1994), who added methylphenidate to TCAs. This idea was later taken up by Postolache et al. (1999), who began a randomized trial adding methylphenidate or placebo to sertraline at the beginning of treatment. The authors abandoned the trial, however, when no early effects were observed in any of the first nine patients. Alternatively, Lavretsky and Kumar (2001) reported that methylphenidate added to citalopram at the beginning of treatment appeared to hasten response during open label treatment of 10 elderly patients. Subsequently, Lavretsky et al. (2006) performed a randomized placebo-controlled trial in 16 elderly patients. Three of five subjects in the citalopram plus methylphenidate group met their criterion for rapid response while none of the patients in the citalopram plus placebo group met this criterion. Because of the age of the subjects, the dosing schedule for methylphenidate was rather cautious. To my knowledge, no one has attempted to combine the dextroamphetamine test dose of 5 mg three times a day while starting a second-generation antidepressant.

## Dextroamphetamine vs. Methylphenidate

An obvious question is whether one stimulant is more effective or potent than the other. In large series, such as those reported by the MGH group (Woods et al. 1986, Masand et al. 1991), there were no significant differences between agents. Individual patients, however, may respond to one class but not the other. Little (1993) described a 1-day test dose strategy in 18 depressed inpatients (mean HAMD score = 22.8). Patients received dextroamphetamine 20 mg or methylphenidate 40 mg and were then crossed over to the other agent. Drugs were administered in a double-blind balanced order. Acute response was noted with both drugs in 5 of the 18 patients while 7 responded to dextroamphetamine only and 5 to methylphenidate only. One responded to neither. The authors noted that while both agents enhance catecholamine release, specific mechanisms differ and patient response can only be determined empirically.

Murray and Cassem (1998) state that the experience of the MGH group suggests that dextroamphetamine is somewhat more effective than methylphenidate, although the drugs did not show a significant difference in either of their case series. They also note that the apparent perception of greater safety of methylphenidate was not supported by their data. (Both were safe.) Alternatively in their review, Chiarelli and Cole (1987) suggested that dextroamphetamine might be associated with more side effects. A major problem in making these comparisons is determination of equivalent doses. On a mg-per-mg basis, dextroamphetamine appears to be more potent. Usual doses of methylphenidate were approximately double that of dextroamphetamine in the controlled depression trials cited above. Dosing of methylphenidate is complicated by its very short half-life, and absorption of methylphenidate may be dependent on the dosing schedule (Teicher et al. 2006). It is possible that the greater apparent efficacy of dextroamphetamine and the perception of greater safety of methylphenidate are the result of underdosing of methylphenidate.

## Side Effects and Safety

In the MGH studies of medically ill patients, both dextroamphetamine and methylphenidate appeared safe with relativity low rates of discontinuation for adverse effects, 7 and 10% (Woods et al. 1986, Masand et al. 1991). In our previous review of depression studies (Satel and Nelson 1989), we also found little evidence of serious adverse effects. When stimulants are used at the usual oral doses, cardiovascular effects are uncommon. Two early reports examined the safety of stimulants in patients with cardiac disease and found little evidence of serious adverse effects (Dube et al. 1956, Ferguson and Funkerbunk 1956). In one of the recent controlled studies that systematically measured vital signs, no changes were noted (Wallace et al. 1995).

While these data suggest that stimulants can be used safely, it should be remembered that the database from systematic prospective controlled studies in depressed patients is quite limited. Nine of the 12 controlled studies in depression were performed prior to 1973. Electrocardiograms were not routinely performed. The three controlled studies after 1984 (Mattes 1985, Wallace et al. 1995, Wagner and Rabkin 2000) had small samples of 20, 15, and 23 patients. Several studies were of brief duration. Sample size and trial duration are very important for detection of serious adverse events with low incidence rates. Stimulants have not been systematically studied in older patients who may be especially vulnerable to serious adverse events or in patients with heart disease. Thus while small controlled studies and anecdotal reports suggest that these drugs can be used safely, this suggestion cannot be confirmed.

The most common side effects are behavioral and include confusion, irritability, nervousness, or anxiety. Stimulants can induce hypomania and psychosis. "Amphetamine psychosis" was described early in the history of these agents (Young and Scoville 1938, Connell 1958).

The interaction of the stimulants with preexisting anxiety is interesting and not well understood. Early observations (Davidoff et al. (1957) of increased anxiety during open treatment led to the clinical impression that these agents should be avoided in anxious patients. Alternatively, some controlled studies (Overall et al. 1966, Rickels et al. 1972) found similar rates of emergent agitation in the drug and placebo groups. All of these data were collected prior to more recent observation of increased anxiety or restlessness during initial treatment with an SSRI. It is not clear that the stimulants are more likely to provoke anxiety and restlessness than current second-generation antidepressants.

Because the stimulant drugs have sometimes been used for weight reduction, clinicians may be concerned about the use of stimulants in older patients with weight loss. In fact, severe weight loss or cessation of eating is one of the acute problems encountered in older depressed patients that can require hospitalization or electroconvulsive therapy. In these patients stimulants can have a "paradoxical effect." The acute beneficial effects of stimulants on mood can be associated with increased appetite and resumption of eating. Use of stimulants in this acute clinical situation can be dramatically effective. Alternatively during chronic treatment, loss of appetite has been observed with dextroamphetamine in patients with HIV illness (Wagner and Rabkin 2000).

## Abuse Potential

Although the potential abuse of amphetamines is well recognized, increased abuse of these agents in depressed patients or patients with attention deficit hyperactivity disorder has not been established or observed (Nelson 1995). Recent evidence in ADHD suggests that successful treatment of the disorder may reduce the risk of substance abuse that is otherwise associated with ADHD (Wilens 2004, Wilens et al. 2003). Clinicians should remember, however, that diversion of prescribed stimulants might still be a problem.

## Modafinil for Depression

Modafinil is a new agent approved by the FDA for promoting wakefulness. It is unclear if it should be classified as a stimulant. It does not have meaningful effects on dopamine release or reuptake as do amphetamine and methylphenidate and its mechanism of action is unclear. Nevertheless, modafinil has some stimulant-like properties.

Modafinil has been explored as a treatment for depression either as monotherapy or augmentation. Case series (Price and Taylor 2005) and case reports (Kaufman et al. 2002) have described the use of modafinil monotherapy in depression. Use of modafinil for atypical Major Depression was examined in a 12-week open trial in 66 subjects (Vaishnavi et al. 2006). Subjects significantly improved. Then 50 of the subjects who had at least minimal improvement were randomly assigned to modafinil or placebo for another 12 weeks. During this period there was no difference in relapse between the drug and placebo groups. This could suggest that the early effects of modafinil were maintained; however, the advantage of antidepressant treatment during relapse prevention is one of the best validated attributes of effective antidepressants (Geddes et al. 2003). It seems quite likely that the initial benefits were placebo-like effects and that is why no difference with placebo was observed during the controlled phase.

There are several reports of the use of modafinil for augmentation. Most of these reports are open label studies (Konuk et al. 2006, Rasmussen et al. 2005, Price and Taylor 2005, Nasr 2004, Schwartz et al. 2004, Markovitz and Wagner 2003, Menza et al. 2000). One of these open label studies added modafinil at the beginning of treatment to accelerate response (Ninan et al. 2004).

Fava et al. (2005) described the only placebo-controlled, double-blind, acute phase trial. In this study, 311 subjects with Major Depression, who had fatigue or excessive sleepiness, and were SSRI partial responders, were randomized to an 8-week trial of modafinil 200 mg or placebo. At the final visit modafinil was significantly superior to placebo on the CGI scale but trend findings were noted on the Hamilton and MADRS scales. An open label 12-week extension of this study suggested that subjects continued to improve including those who failed the initial trial (Thase et al. 2006). In these reports the most common side effects were nausea, jitteriness, headache, and dizziness. Modafinil was also associated in some studies with weight loss, which was seen as an advantage.

## Conclusions

Stimulants have been used to treat depression for over seven decades, yet their current use appears to be quite limited. Given the long history and the variable quality of research over this period, determination of the best available evidence for the stimulants is a challenge. The following conclusions seem warranted. The acute (24–48 hrs) effects of the stimulants on depressed mood are established in controlled studies and are consistent with clinical reports of 24–48 hrs response observed during the dextroamphetamine test and the MGH case series. Two small controlled trials indicate that stimulants accelerate response to TCAs and citalopram. Ten placebo-controlled studies of stimulants in primary or Major Depression indicate lack of efficacy of stimulants during sustained (4–6 week) treatment. Use of stimulants for augmentation of antidepressants is supported by open trials but controlled data are lacking. During oral administration and at usual doses, dextroamphetamine and methylphenidate appear to be safe, well tolerated, and without predictable effects on pulse and blood pressure; however, the data for stimulants in depression are not comparable to new antidepressants coming to market in terms of systematic collection of adverse events or vital sign data for 2,000–3,000 patients. Preliminary data for modafinil suggest that it may have a role for augmentation of antidepressants. One controlled trial supports its use in partial responders with residual symptoms of fatigue and excessive sleepiness.

The clinical utility of stimulants for geriatric depression or depression secondary to medical illness is supported primarily by case series and two small controlled trials. Yet the case series from MGH are compelling. It could be argued that the short-term benefits in medically ill patients are mainly placebo effects and that the period of observation in the MGH series was too short to systematically document sustained improvement. Alternatively, Wittenborn (1982) has suggested that geriatric depression might be different from depression in younger individuals. Two emerging conceptual models support this view. One model suggests that some older patients with late onset depression have early degenerative disease, particularly vascular disease (Alexopoulos et al. 1997). These patients also tend to have cognitive disturbance in the form of executive dysfunction and appear to be less responsive to conventional treatments (Alexopoulos et al. 2005). Perhaps the stimulants are especially useful for both the mood disturbance and the cognitive disturbance these patients experience. The other model is based on the observation that some medically ill patients present with a depression-like syndrome described by Engel (1967) as a "giving up–given up complex" or more recently by Kissane et al. (2001) as a demoralization syndrome. Conventional antidepressants appear to be less useful for these patients. Perhaps the short-term effects of stimulants are

especially helpful in reducing the hopelessness of demoralized patients, and if prevention of relapse is less an issue for this syndrome (as opposed to recurrent depression), perhaps short-term effects of stimulants along with supportive care are sufficient. Both of the above hypotheses are untested.

Finally, the field of psychopharmacology has been interested in the bridge between the observed antidepressant effects of a compound, its known pharmacologic actions, and what this might suggest about the neurophysiology of depression and antidepressant mechanisms. Agents that have acute antidepressant effects are of particular interest. For example, a recent report of acute effects of ketamine on mood (Zarate et al. 2006) has received considerable attention. As we consider the neuropharmacologic implications of these clinical data, the acute effects of the stimulants ought to be kept in mind.

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CHAPTER

# 107 Cognitive Enhancers and Treatments for Alzheimer's Disease

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## History and Background

Prior to the 1970's, various medications were proposed for the treatment of dementia based on clinical experience or prevailing theories of dementia and aging. These included psychostimulants, vasodilators, ergoloids, and medication "cocktails." In the US, the only one medication, ergoloid mesylates (dihydroergotoxin mesylate) was approved for an ill-defined condition, senile mental decline. By the late 1980's, the advent and acceptance of research-based diagnostic criteria for the dementia of Alzheimer's disease (AD), (McKhann et al. 1984) an initial understanding of its underlying pathology, and the development of mechanism-based pharmacological therapeutics provided the framework for clinical trials to exploit new treatment strategies that might positively impact the illness.

Since AD is defined by the presence of dementia, attempts have been made to identify a predementia state of cognitive impairment, likely to lead to AD. Criteria for "age-associated memory impairment" (AAMI), a construct for functionally significant, although mild and probably nonprogressive cognitive impairment has not been generally acceptd as a diagnosis, although the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) includes a code for "age-related cognitive decline," equivalent to AAMI. "Mild cognitive impairment" (MCI) has been the target of several clinical trials of medications previously used for AD. The evolving validity of MCI will rest mainly on its ability to predict the onset of the dementia of AD. In research clinics a diagnosis of MCI implies a conversion rate to AD of about 12−15% per year (Petersen et al. 2001). However, MCI is not necessarily a predementia stage of AD, since many people who fulfill criteria do not progress to dementia and some improve to not being cognitively impaired.

During the 1990's, research- and consensus-based criteria emerged to address vascular dementia (Chui et al. 1992, Roman et al. 1993), dementia with Lewy bodies (McKeith et al. 1996), frontotemporal dementia syndrome, and Parkinson's disease dementia. These latter criteria are still evolving and thus clinical trials including these populations have been limited.

## Regulatory and Methodological Issues

The Food and Drug Administration (FDA) utilizes *de facto* guidelines for establishing that a drug has "antidementia efficacy" (Leber 2002). These require that: (1) clinical trials are double-blind and placebo-controlled, (2) patients fulfill criteria for a primary dementia such as AD (e.g., DSM-IV-TR or National Institute of Neurological and communicative Disorders and Stroke−Alzheimer's Disease and Related Disorders Association (NINCDS-ADRD) Work Group Criteria) (McKhann et al. 1984), and (3) appropriate efficacy instruments are used. Further, a putative antidementia drug must show efficacy at improving memory or retarding its deterioration since memory impairment is one of the primary features of dementia. The drug also must have an effect, determined independently from neuropsychological assessment, using a global clinical measure or a measure of functional incapacity in order to address the concern that drug-related memory improvement may be observed with psychometric testing but not be clinically meaningful. Changes in behavior are considered to be of secondary importance for regulatory purposes.

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Most clinical trials of antidementia drugs undertaken in the US to seek regulatory approval for mild-moderate AD have used the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADASc) (Mohs et al. 1997) as the index of cognitive change and a version of a clinical global impression of change (CGIC) as the "global" clinical measure (Schneider et al. 1997). The ADASc includes the following measures: word recall, naming, commands, constructional and ideational praxis, orientation, word recognition, spoken language, comprehension of spoken language, word-finding, and recall of test instructions. The CGIC is usually rendered as a seven-point, ordinal scale upon which a clinician indicates his or her impression of clinical change from "no change" to "minimal," "moderate," or "marked" improvement or worsening. Trials conducted in people with moderate and severe dementia have used other cognitive measures, such as the Severe Impairment Battery (SIB) (Saxton et al. 1990), and/or the Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) Scale to assess aspects of daily functioning (Galasko et al. 1997).

Limitations to the current guidelines include the lack of recognition of improvement in behavior as a legitimate therapeutic goal or indications in the prescribing information, despite the fact that behavioral symptoms occur in the majority of dementia patients. The FDA draft guidelines that patients fulfill established criteria for a primary dementia is an attempt to avoid the inclusion of ill-defined dementia syndromes in clinical trials, to obtain sample homogeneity, and to achieve consensus that the medication is effective in a specific group of patients with an illness such as AD accepted by a substantial number of experts.

This chapter focuses on the dementia of AD, because most work has been done in this area in recent years. Many of the issues raised will become relevant to other dementias or cognitive impairment syndromes as clinical investigators continue to study these syndromes.

## Typical Inclusion Criteria for AD Clinical Trials

These include the presence of probable AD (NINCDS-ADRDA workshop criteria) (McKhann et al. 1984), a specified Mini Mental State Examination (MMSE) (Folstein et al. 1975) score (e.g., typically between 10 and 26 for "mild-moderate AD"); a score of less than 4 on the Modified Hachinski Scale (Rosen et al. 1980); a CT scan or MRI consistent with AD and showing no evidence of significant focal lesions; generally good physical health other than the dementia (confirmed by medical history, physical exam, neurological exam, ECG, and laboratory tests); normal blood pressure; English speaking; and having a reliable caregiver to participate in clinical evaluations.

Exclusion criteria typically consist of a history of other psychiatric or neurological disorders, of a stroke or CT/MRI evidence of a stroke, significant concurrent physical illness, or abnormal laboratory findings. Therefore, dementia populations studied in clinical trials consist mainly of mildly-to-moderately impaired outpatients living at home with their families, who are otherwise medically healthy and lack significant behavioral symptoms. Recently, some trials of disease modifying drugs have expanded inclusion criteria to allow the concurrent use of approved antidementia therapies.

# Etiopathology and Implications for Treatment

This chapter offers a survey of treatments for AD ranging from approved therapies to those that have been or are in clinical trials. The survey is organized according to the etiopathologic basis of the therapy. This approach has merit because the field is changing rapidly, and a host of new approaches are being put to the test. Certain approaches of theoretical interest will be mentioned as well, since the field is changing so quickly. The review begins with a schematic summary of the pathobiology of AD, in order to provide a theoretical framework within which to present the surprisingly wide array of emerging therapies.

## Neuropathology of AD

The definitive diagnosis of AD is based on the clinical dementia syndrome together with certain neuropathologic features first described by Alois Alzheimer in 1907. These include neuritic *plaques* and neurofibrillary *tangles* spread diffusely through the cerebral cortex and hippocampus (Khachaturian 1985, Mirra et al. 1991) (Figure 107–1). Plaques, found outside the neuron, are spherical structures possessing a central core of amyloid protein surrounded by distended abnormal neuronal dendrites and small axons. Tangles consist of bundles of filaments in cell bodies, axons, and dendrites. These histologic abnormalities are associated with loss of synaptic density and neuronal death. Much has been learned in recent years about the chain of events leading to these defining features of Alzheimer's, knowledge that has lead to rational drug development and therapeutic candidates far different from the agents of the 1970s.

## Dominant theories of AD Pathobiology

How do these pathological features come to pass? The "amyloid cascade" hypothesis posits that dysregulation in amyloid precursor protein (APP) occurs early in the illness and leads to increased production of Amyloid Beta Protein (Aβ 1-42) and other Aβ peptide fragments. This in

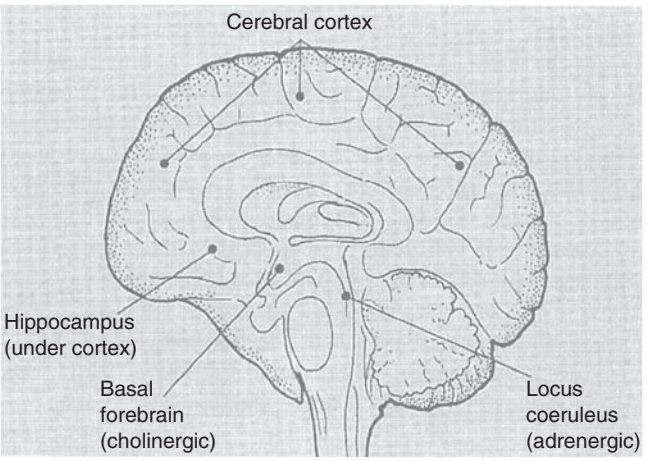



**Figure 107–1** *The right half of a human brain (facing left) showing some of the areas affected by AD. The hippocampus is affected early in the course of the disease, which accounts for short-term memory losses. As the disease progresses, the cerebral cortex is increasingly involved, causing the cognitive and personality defects. Regions that are the sources of transmitters to wide areas of the brain also form neurofibrillary tangles, including the cholinergic basal forebrain, the noradrenergic locus coeruleus, and the serotoninergic dorsal raphe (not shown).* Source: *Tariot et al. (1993a).*

turn leads to a number of downstream events including the development of neurofibrillar pathology (tangles), extracellular amyloid plaques, and cell death. This hypothesis is supported the fact that a macromolecular form of Aβ is toxic by itself. The exact reasons that Aβ leads to synaptic dysfunction and cell death are not fully elucidated, but important insights have been gleaned. Proteolytic cleavage of APP can occur via 3 different secretases, α, β, and γ. When α secretase cleaves APP, generation of pathogenic Aβ species is precluded. When α secretase activity is diminished, or that of β secretase is increased, the generation of pathogenic Aβ species is enhanced, a process also involving subsequent cleavage by γ secretrase. The discovery of presenilin 1 and 2 mutations in familial AD kindreds and the discovery of their role in aberrant APP processing further strengthen the amyloid hypothesis.

Another theory is the so-called tau and tangle hypothesis, which addresses some observations about the evolution of AD not accounted for by the amyloid hypothesis. For instance, plaques and tangles in AD can be separated in time and space, and it is actually the extent of tangle, not plaque, burden that correlates with the overall severity of dementia. Further, in mice genetically modified to overexpress familial APP mutations, which alter APP processing, there is relatively little neuronal death, abnormal phosphorylation of tau, or tangle burden, meaning that aberrant APP processing may not be sufficient to account for the molecular and pathological phenotype of AD. Finally, there are certain mutations in the gene coding for tau that have been identified; these people will develop the clinical phenotype of dementia with a tangle-only pathological phenotype. There are, therefore, nonamyloidogenic pathways for the development of dementia supported by evolving cellular and molecular studies of the evolution of tangles. Much of this work focuses on aberrant kinase phosphorylation of tau, with results that would be expected to include synaptic dysfunction, impaired cellular signaling, and vulnerability to a variety of stressors including Aβ accumulation.

It is likely that these pathways, historically regarded as distinct, are actually connected. For instance, glycogen synthase kinase-3 (GSK-3) has been shown to phosphorylate tau *in vitro*. Inhibiting GSK-3 in transgenic mice overexpressing human AD mutations in the APP and PS1 genes results in reduced expression of Aβ peptides. Findings such as these strongly indicate that the pathways share molecular links at certain nodal points (Mudher and Lovestone 2002).

## A Pathogenic Cascade Hypothesis

For purposes of organizing emerging treatment strategies, we offer an even broader schematic view of the evolution of Alzheimer's Disease (AD) (Figure 107–2). We posit that the disease begins relatively early in life, and the times of onset of cognitive impairment and dementia are influenced by a variety of interacting factors such as aging; genetic susceptibility or resistance; environmental susceptibility factors such as toxin exposure, head injury, or smoking; possible exogenous protective factors such as exposure to certain medications; and endogenous susceptibility or protective factors such as menopause, diet, exercise, degree of educational attainment, depression and major depression, chronic psychological stress, or even social connectedness. The balance between stress and resilience tips at some point that varies tremendously from person to person, initiating a series of molecular events such as oxidative stress, excitotoxicity, altered APP processing, or early apoptosis. Compensatory mechanisms may protect against cell injury for some period of time, such as alterations in DNA repair, and enzyme upregulation. These stress reponses eventually break down, leading to neuronal injury in common cellular signaling pathways and eventual loss of synapses, neurotransmitter failure, and cell death. The molecular phenotype may precede both the neuropathology and clinical phenotype by many years, perhaps decades; and the clinical manifestations may not emerge until there is significant cellular damage.

The neurodegenerative process is asynchronous, meaning that viable neurons coexist with damaged or dead cells, and highly variable both within an individual and among individuals over time. The fact that both inherited and sporadic forms of AD share many clinical and pathological features supports the hypothesis that there is a convergence of biochemical abnormalities downstream from the various initiating factors.

Each aspect of this cascade offers a potential therapeutic target. For instance, neurotransmitter-based therapies might afford symptomatic relief without altering the pathological outcome. Impaired signaling has been identified in cholinergic and glutamatergic pathways, and restorative therapies targeting cholinergic and glutamatergic neurotransmission have been approved. Interventions that decrease pathogenic Aβ production, fibrillization of Aβ, or decrease tau protein phosphorylation may prevent neuronal degeneration; and treatments with neuroprotective properties might result in enhanced cellular resistance and slower decline in clinical deterioration. This hope has yet to be realized.

# Treatment Paradigms

Approaches to the treatment of AD can be grouped into several conceptual categories (Table 107–1). One approach attempts to treat the associated features of the illness such as sleep–wake cycle or appetitive disruption, or behavioral disorders such as aggression, psychosis, agitation, depression, anxiety, or apathy. This approach, while valid, will not be the focus of our chapter. A second approach addresses the cognitive signs of the illness such as memory, language, praxis, attention, and orientation. Most neurotransmitter based therapies have this goal in mind. A third approach aims to slow the rate of progression of the illness, preserving patients' quality of life or autonomy. A fourth conceptual treatment approach is primary prevention, delaying the time to onset of illness. Success at this approach could have considerable impact. For example, delaying the onset of AD by 5 years would halve its incidence (Brookmeyer et al. 1998, Jorm et al. 1987). We will not emphasize preventive therapies here, but bear in mind that interventions that can slow the progression of the disease once present might well have prevention potential, while it is also possible that treatments may be effective for prevention but not slowing disease progession.

## Neurotransmitter-Based Approaches

Activity of cerebral cortical choline acetyltransferase (ChAT), the key enzyme in acetylcholine synthesis (Bowen et al. 1976, Davies and Maloney 1976, Perry et al. 1977), is

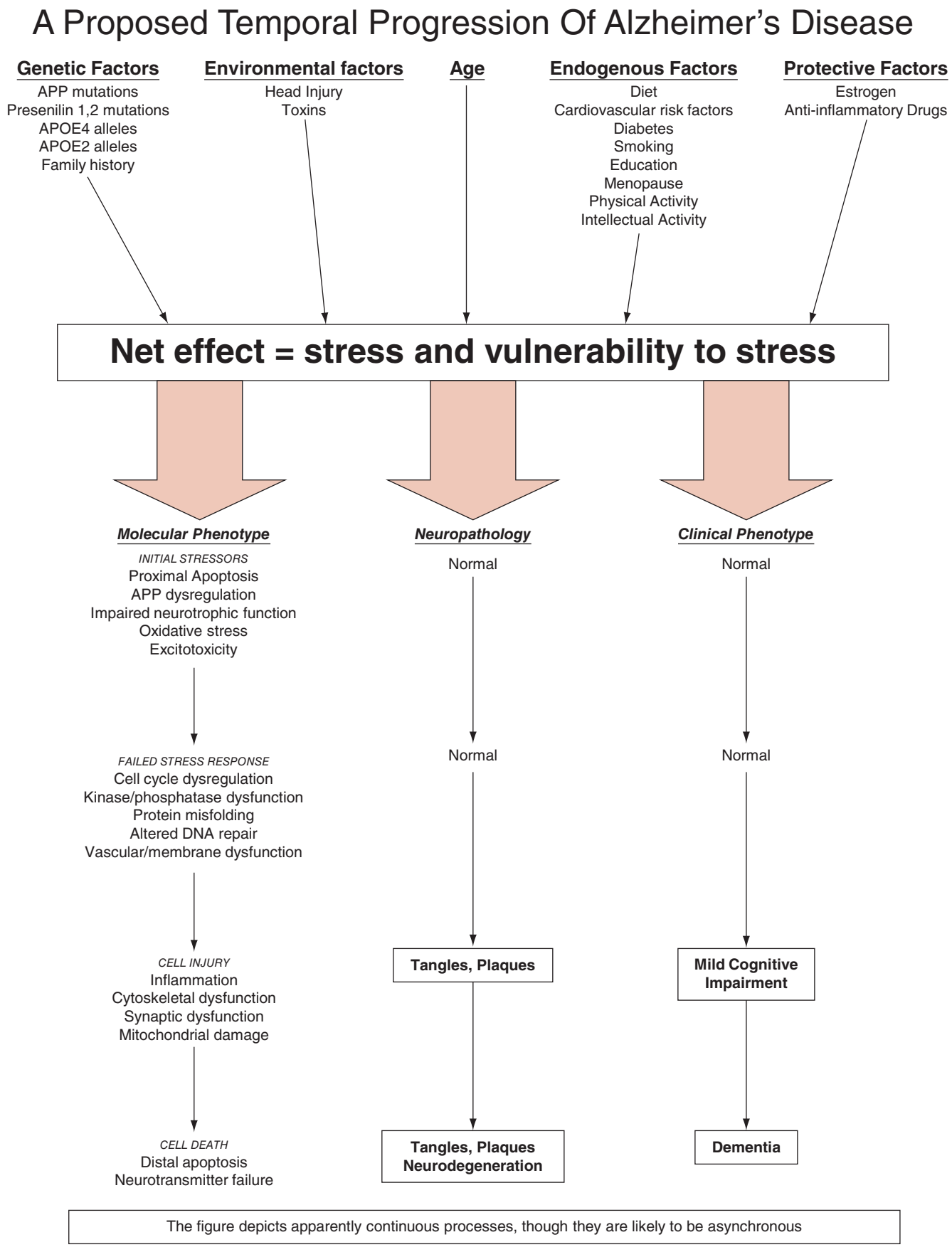



**Figure 107–2** *The evolution of AD. (Source: Modified from Tariot and Federoff [2003].)*

**Table 107–1 Conceptualized Treatment Strategies for Patients with Cognitive Impairment**

| |
|---|
| Symptomatic and/or Restorative |
| Targets: Impaired cognition, depression, psychosis, agitation, aggression, anxiety, insomnia |
| Examples: ChIs, various cholinergic agonists, antidepressants, antipsychotics, mood stabilizers, antianxiety agents, hypnotics, NMDA and AMPA receptor modulators, angiotensin converting enzyme inhibitors |
| Neurotrophic factors: NGF, brain-derived neurotrophic factors, estrogens |
| *Note*: Some substances may have symptomatic or restorative effects but are unproven. These may include Hydergine and neotropics such as piracetam. |
| Pathophysiologically Directed |
| Targets: Underlying pathophysiology of neurodegeneration, including inflammation, production of oxidizing free radicals, excitatory amino acids. |
| Examples: Anti-inflammatory agents, calcium channel blockers, NMDA and AMPA receptor modulators. Transplantation of hormonally active tissues, or NGF gene therapy using viral vectors have been undertaken experimentally. |
| Etiologically Directed |
| Targets: β-Amyloid formation or hyperphosphorylated tau protein. |
| Examples: Modulators of APP expression, β- and γ-secretase inhibitors, inhibitors of beta-amyloid protein aggregation or deposition, active or passive immunization with antibodies to beta-amyloid. |
| Note: The interventions listed above include some that are available and marketed, as well as some that have not been demonstrated effective or safe, and some conceptual treatments not yet developed. |

reduced, along with the loss of cholinergic cell bodies in the nucleus basalis (Arendt et al. 1983, Whitehouse et al. 1982). There are correlations between cortical ChAT reduction or nucleus basalis cell reduction and plaque densities in cortical areas (Arendt et al. 1985, Etienne et al. 1986) (Figure 107–3). The cholinergic deficit correlates with the decline in scores on the Blessed-Roth Dementia Rating Scale (Perry et al. 1978). After initial enthusiasm for the cholinergic hypothesis of AD, it became clear that many other neuronal systems also are affected in this disorder.

Variable involvement of noradrenergic systems, including the nucleus locus coeruleus (nLC) occurs in AD (see Figure 107–3) (Bondareff et al. 1982, Mann et al. 1984). Significantly greater neuronal loss in the nLC occurred in AD patients who showed clinical manifestations of depression before death than in those who did not (Zubenko and Moossy 1988, Zweig et al. 1988). Similarly, demented patients with major depression had a tenfold reduction in norepinephrine than nondepressed demented patients (Zubenko et al. 1990). These findings suggest that many symptoms in AD may be modulated through nLC function as they are in primary depression and anxiety.

Neurotransmitter perturbations in AD provide the most accessible targets for therapeutic interventions. Since cholinergic deficits represent the most consistent transmitter depletion and appear early in the disease process (Francis et al. 1985, 1999), cholinergic manipulation has been major focus of applied clinical pharmacological research.

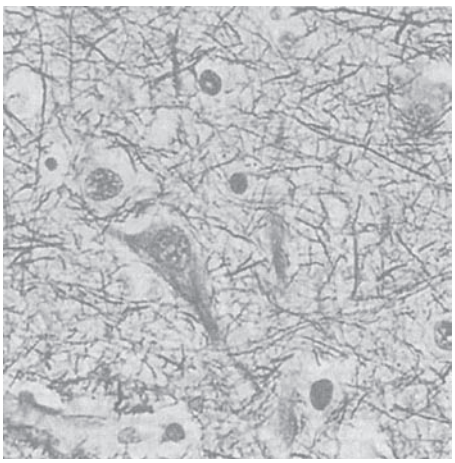


**Figure 107–3** *Human brain tissue in AD, showing neurofibrillary tangles.* Courtesy: *U.S. Department of Energy/Science Photo Library.*

## Cholinergic Treatment Approaches

The primary implication of the cholinergic hypothesis is that potentiation of central cholinergic function should improve the cognitive and behavioral impairment associated with AD. This simple "neurotransmitter replacement" rationale has been validated by the consistent effects of cholinesterase inhibitors (ChIs) across trials (see Figure 107–4). Other cholinergic treatment approaches, including precursor loading, direct cholinergic receptor stimulation, and indirect cholinergic stimulation, have proven ineffective, effective but too toxic, or have not been completely developed.

Cholinergic therapies may have effects beyond the short-term symptomatic improvement of cognition and may modify the pathogenetic processes of the illness (Radebaugh et al. 1996, Thal et al. 1997). For example, activation of $M_1$ muscarinic receptors can stimulate secretion of APPs via the α-secretase pathway such that there is a decrease in the production of toxic and insoluble β-amyloid peptides, thus theoretically decreasing the formation of amyloid plaques and promoting the normal processing of APP (Inestrosa et al. 1996, Muller et al. 1997, Nitsch et al. 1992). These effects have been reported with some cholinergic agonists and ChIs (Buxbaum et al. 1992, Haroutunian et al. 1997, Lahiri et al. 1992, Nitsch et al. 1992), but remain to be proven in clinical trials (Buxbaum et al. 1992, Haroutunian et al. 1997, Lahiri et al. 2000).

### *Precursor Loading*

Early investigations focused on acetylcholine precursors, including choline and phosphatidyl choline (lecithin), in attempts to augment acetylcholine synthesis. Numerous trials of cholinergic precursors, most with small sample sizes, have generally failed to improve cognitive performance in patients with AD; only 10 of 43 such trials report any positive effect (Jorm 1986).

### *Muscarinic Agonists and Antagonists*

The rationale for the use of direct cholinergic agonists rests on the fact that postsynaptic, $M_1$, cholinergic receptors are relatively intact in AD and that presynaptic, $M_2$, cholinergic receptors, which are decreased in AD, regulate

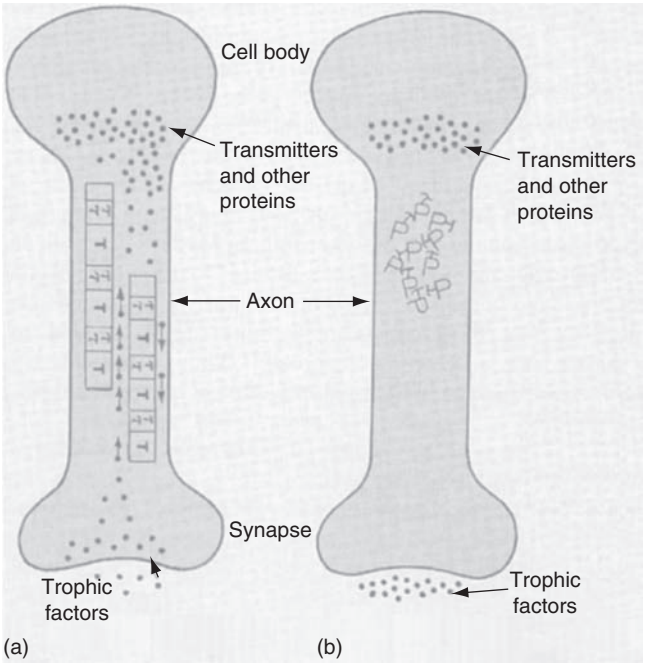



**Figure 107–4** *(A) A normal neuron. The microtubule-associated protein tau (τ) promotes the assembly of tubulin (T) into tubular microtubules. The microtubules serve as the highways for transporting transmitters and other proteins from the cell body to the synapse, and also of trophic factors (necessary for survival of the neuron) from the synapse back to the cell body. In AD (B), tau is abnormally phosphorylated (represented by Ps attached to τ). This destroys tau's ability to promote the polymerization of tubulin into microtubles, robbing the cell of the major highways for transporting many proteins from the cell body to the synapse and from the synapse back to the cell body. Proteins pile up in the cell body, unable to be moved. It is presumed that trophic substances pile up outside the synapse, also unable to be transported. The abnormal phosphorylation of tau is associated with its self-aggregation into the neurofibrillary tangles.* Source: *Tariot et al. (1993a).*

acetylcholine release. Cholinergic agonists studied in the past included bethanechol, oxotremorine, pilocarpine, RS-86, and arecoline. These agents have generally had little or no efficacy and significant cholinergic side effects.

Clinical trials results of numerous cholinergic agonists have been disappointing due to doubtful efficacy and high incidences of muscarinic-related adverse effects. The muscarinic agonists included alvameline (LU 25-109), arecoline, cevimeline (AF-102B), milameline, sabcomeline (SB 202026), SR 46559, talsaclidine, and xanomeline. The failure of these muscarinic agonists with predominant $M_1$ activity, albeit each with a somewhat different receptor profile, suggests that direct stimulation of muscarinic receptors may not be sufficient to treat AD. Also, nonselective, direct receptor agonists may be relatively ineffective because they provide a prolonged and tonic cholinergic stimulation of postsynaptic cells; or perhaps they actually inhibit acetylcholine release through their action on presynaptic $M_2$ receptors. By comparison the relative efficacy of ChIs may reflect their additional actions, such as nicotinic stimulation or nonenzymatic actions.

A newer selective M1 agonist, NGX267, based on cevimeline, is in phase I studies for AD and cognitive impairment associated with schizophrenia. In a transgenic mouse AD model, NGX267 improved cognitive deficits in a spatial task but not in contextual fear conditioning, and decreased Aβ and tau pathology. The decrease in Aβ was caused by selective activation of ADAM17, a protein with α-secretase properties and the reduction in tau pathology was due to a decrease in GSK3β activity decreasing tau protein kinase activity (Caccamo et al. 2006).

### *Other Indirect Cholinergic Enhancing Strategies*

Various methods of indirect cholinergic enhancement included DuP 996 (linopirdine) that enhances the presynaptic, potassium-mediated release of acetylcholine, ondansetron, a 5-$HT_3$ antagonist, may act as a cholinergic facilitator, enhancing acetylcholine release, and various partial nicotine agonists. Despite interesting preclinical rationales these drugs have not shown clinical effectiveness (Rockwood et al. 1997, Dysken et al. 2002).

### *Nicotinic Agonists*

Nicotinic acetylcholine receptors (nAChRs) are reduced in the hippocampus and the temporal and frontal cortex as an early phenomenon of patients with AD compared to age-matched controls (Nordberg 2001). Nicotine can improve memory, cognition, and attention in AD patients; and a nicotinic antagonist produces the opposite effect (Newhouse et al. 2001). Because nAChRs are found in both the CNS and PNS, nicotine usefulness is limited by the extent of its peripheral and parasympathetic effects. Therefore efforts have focused on development of a selective CNS nicotinic agonist, active at the α4β2 subtype of nAChRs, because of high densities of these receptors in brain regions involved in memory processes and AD (Nordberg 2001).

Ispronicline (TC-1734, AZ 3480) is a partial nAChR agonist with a high affinity and selectivity for the α4β2 subtype. A phase I study showed it to be tolerable, with dizziness and headache being reported as the most frequent adverse events (Dunbar et al. 2006). A Phase II study was completed in 2006, the results are currently unpublished. According to the manufacturer's Web site, this study enrolled 193 subjects with age-associated memory impairment for 16 weeks in which there was significance in cognitive measures. The drug was reportedly well tolerated (www.targacept.com).

The α -7 nAChR subtype has also received particular attention (Mazurov et al. 2006). There are a number of α -7 nicotinic agonists in development including MEM 3454, SSR 180711C, PH-399733 and GTS-21 currently in phase II trials.

### *ChIs*

Table 107–2 presents the aspects of ChIs. Modest, significant, and reliable improvement in memory was produced in early trials of the acetylcholinesterase (AChE) inhibitor, physostigmine (Christie et al. 1981, Davis and Mohs 1982, Mohs et al. 1985, Stern et al. 1987), but it caused adverse reactions and required frequent dosing. Early success with dosage-individualization (Jorm 1986) led to multicenter trials of the ChIs tacrine, velnacrine, and sustained-release physostigmine (Antuono 1995, Davis et al. 1992, Thal et al. 1996), and subsequently provided the rationale and justification for larger clinical trials, and eventual approval and marketing of several ChIs.

Tacrine was the first ChI approved for treatment of AD, but it is no longer actively marketed. The newer ChIs

**Table 107–2 FDA-Approved Drugs to Improve Cognitive Function in Alzheimer's Disease: Dosages* of Marketed ChIs**

| Drug | How Supplied | Initial Dosage | Maintenance Dosage | Comments |
|---|---|---|---|---|
| Tacrine | 10, 20, 30, and 40 mg capsules | 10 mg q.i.d. | 30 or 40 mg q.i.d. | 120−160 mg/day are efficacious doses. Reversible direct hepatotoxicity in about 1−3 patients, requiring initial biweekly transaminase monitoring and dose titration. Not commonly used. |
| Donepezil | 5 and 10 mg tablets and orally dispersible tablets | 5 mg q.d. | 5–10 mg q.d. | 5 and 10 mg are both effective doses; 10 mg may be somewhat more efficacious in some trials; higher doses not tested. |
| Rivastigmine | 1.5, 3, 4.5, and 6 mg capsules, transdermal patch | 1.5 mg b.i.d. | 3, 4.5, or 6 mg b.i.d. | Effective dosage range 3–6 mg b.i.d. Doses of 4.5 mg b.i.d. may be most optimal. May be taken with food. |
| Galantamine | 4, 8, and 12 mg tablets Solution 4 mg/mL, 8, 12, and 24 mg extended release capsules | 4 mg b.i.d.<br>8 mg q.d. | 8 or 12 mg b.i.d.<br>16 or 24 mg q.d. | Effective dosage range is 16−24 mg/day, 16 mg/day is the modal optimal dose. |

*Initial dosages should be maintained for at least 2 and preferably 4–6 weeks before increasing. Adverse events may occur with dosage titration.

*Note:* The FDA approved indication for these drugs is: "indicated for the treatment of mild to moderate dementia of the Alzheimer's type," except for donepezil which is approved for mild, moderate, and severe AD. Websites for prescribing information on ChIs: tacrine, http://www.horizonpharm.com/downloads/Cognex2.pdf, donepezil, www.aricept.com/productinfo.htm http://www.pfizer.com, rivastigmine http://www.novartis.com, http://www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf, galantamine, http://razadyneer.com/razadyneer/pages/pdf/razadyne_er.pdf

donepezil, rivastigmine, and galantamine are currently used in clinical practice. Other ChIs are under development including phenserine, huperzine A, ZT-1 (a pro-drug of huperzine A), ladostigil, bisnorcymserine. Phenserine is a long-acting ChI that additionally is thought to have properties that reduce Aβ levels (Haroutunian et al. 1997). In an unpublished, small sample size, 6-month trial (unpublished), this drug did not achieve statistical significance over placebo in cognitive measures. The positive isomer of phenserine has little ChI activity but may decrease the formation of Aβ. Huperzine A is an extract from club moss commonly used as a herbal remedy in Asia and available in the US as a dietary supplement. The optimal dose is unknown, and there have been no definitive trials of safety and efficacy. An NIH-funded trial involving over 200 participants will be completed by early 2008. Ladostigil is a combination ChIs and monoamine oxidase type-B (MAO-B) selective inhibitor, and bisnorcymserine is a selective butyrylcholinesterase inhibitor.

### *Mechanisms of Cholinesterase Inhibition*

Acetylcholine is inactivated when it is hydrolyzed to choline and acetate by AChE. By inhibiting the actions of AChE, ChIs effectively increase the amount of ACh available for intrasynaptic cholinergic receptor stimulation. Butyrylcholinesterase (BuChE), another central enzyme that hydrolyzes ACh, is being targeted for AD therapy. AChE-positive neurons diffusely project to the cortex and are thought to modulate cortical processing and responses to new stimuli; BuCHE-positive neurons project principally to the frontal cortex and might have a role in influencing attention, executive function, emotional memory, and behavior (Lane et al. 2006).

An AChE inhibitor can work at either of two sites on AChE, an ionic subsite or a catalytic esteratic subsite to prevent the interaction between ACh and AChE. Tacrine and donepezil act at the ionic subsite. Rivastigmine acts at the catalytic esteratic subsite (Enz and Floersheim 1997). Galantamine acts at both the ionic site and catalytic binding site (Lane et al. 2006)

Donepezil and galantamine are relatively selective for AChE (Brufani and Filocamo 1997) whereas tacrine and rivastigmine inhibit both AChE and BuChE. Binding to the AChE sites may be either reversible or irreversible, and may be competitive or noncompetitive with acetylcholine. Galantamine is an example of a competitive ChI, competing with acetylcholine for AChE.

In addition, AChE is present in a few molecular forms containing one (monomeric G1), two (dimeric G2), or four (tetrameric G4) catalytic subunits. The G1 and G4 forms are present in the human brain, varying in proportion in different brain regions (Atack et al. 1986). The tetrameric G4 is located on the presynaptic membranes within the cholinergic synaptic cleft; the monomer G1 is found on postsynaptic membranes. While G4 is decreased along with the neuronal loss of presynaptic cholinergic neurons, postsynaptic cholinergic receptor neurons and G1 ACh are not decreased significantly with AD or aging (Enz and Floersheim 1997). Similar to AChE, BuChE exists in G1, G2, and G4 molecular forms, with a preponderance of the G4 isoform in the brain (Arendt et al. 1992). The BuChE monomeric G1 increases by 30−60% in the AD brain whereas the BuChE tetrameric G4 isoform decreases or remains the same. Thus, investigations of ChI should consider the molecular form-specific characteristics of AChE and BuChE inhibition. Rivastigmine is a ChEI that is highly selective for the postsynaptic G1 monomer form of AChE, while galantamine is less so, and donepezil is not.

A summary of pharmacokinetics and pharmacodynamics is in Table 107–3.

## Individual ChIs—Clinical Studies, Dosing, and Adverse Effects

Despite the slight variations in the mode of action of the three clinically available ChIs (Table 107–4) for treatment

**Table 107–3 Pharmacodynamic and Pharmacokinetics of Marketed ChIs**

| Drug | Pharmacodynamics | Absorption | Bioavail ability (%) | Peak Plasma (hr) | Elimination Half-life (hr) | Protein Binding (%) | Metabolism/ Comments |
|---|---|---|---|---|---|---|---|
| Tacrine | Noncompetitive, reversible ChI, both butryrl and acetyl ChI, also multiple other actions | Delayed by food | 17 | 1–2 | 2–4 | 55 | Via 1A2, nonlinear pharmacokinetics; hepatoxicity requires regular monitoring of serum alamine aminotransferases |
| Donepezil | Noncompetitive, reversible acetyl-ChI | Not affected by food | 100 | 3–4 | 70 | 96 | Via 2D6, 3A4. Nonlinear pharmacokinetics at 10 mg/day |
| Rivastigmine | Noncompetitive ChI, both butryrl and acetyl ChI, may differentially effect different acetyl ChEs | Delayed by food | 40 | 1.4–2.6 | <5 | 40 | Hydrolysis by esterases and excreted in urine (nonhepatic). Duration of cholinesterase inhibition longer than plasma half-life. Nonlinear pharmacokinetics |
| Galantamine | Competitive, reversible ChI, modulates nicotine receptors | Delayed by food | 90 | 1 | 7 | 18 | Via 2D6, 3A4 |

*Note*: Pharmacodynamic effects of some ChIs are longer than their elimination half-lives. Drugs that inhibit or induce the cytochrome enzymes above might be expected to increase or decrease blood levels. For the most part, clinically however, drug interactions with donepezil, rivastigmine, and galantamine have not been clinical problems.

of AD, there is no evidence of meaningful difference among them with respect to efficacy (Birks, 2006).

### *Tacrine*

Tacrine is a noncompetitive reversible inhibitor of ChE. It binds near the catalytically active site of the AChE molecule to inhibit enzyme activity, and has other actions as well (Adem et al. 1990). Two clinical trials resulted in FDA approval of tacrine in 1993 (Farlow et al. 1992, Knapp et al. 1994), demonstrating, tacrine's significant effect on the ADAS (Alzheimer's Disease Assessment Scale) cognitive subscale assessment and on measures of daily function. Tacrine is no longer actively marketed due to a high incidence of hepatotoxicity and frequent dosing schedule.

**Dosing**. The recommended starting dose is 10 mg q.i.d. to be maintained for 6 weeks, while serum transaminase levels are monitored every other week. If the drug is tolerated and transaminase levels do not increase above three times the upper limit of normal, the dose is then increased to 20 mg q.i.d. After 6 weeks, dosage should be increased to 30 mg q.i.d., again with biweekly monitoring and then, if tolerated, to 40 mg q.i.d. for the next 6 weeks.

### *Donepezil*

Donepezil is a long-acting piperidine-based highly selective and reversible AChE inhibitor. Two phase III clinical trials (Rogers et al. 1998a, 1998b) resulted in FDA approval for early to moderate stages of AD in late 1996. Subsequent randomized clinical trials have included a trial of 6 months duration (Burns et al. 1999), a Scandinavian study of 12 months (Winblad et al. 2001), a study of nursing home patients (Tariot et al. 2001), a trial assessing functional decline (Mohs et al. 2001) and a 6-month trial in which a large proportion were more severely impaired than in previous trials (Feldman et al. 2001).

Two 24-week clinical trials conducted in nursing home patients in Sweden (Winblad et al. 2006) and outpatients in Japan (Homma et al. 2000) with severe AD (MMSE 1-10) provided sufficient cognitive and global efficacy for the FDA to approve donepezil for this indication in 2006. Donepezil is the only ChI indicated for severe AD.

A trial sponsored by the UK's Medical Research Council confirmed the modest benefits in cognition and activities of daily life over a 2-year period with a modal donepezil dose of 5 mg/day. However, it did not demonstrate that donepezil delayed time to nursing home placement or progression of disability (Courtney et al. 2004). Despite methodological limitations, the trial results undermined assumptions that such improvements in cognition and daily activities translated to cost-effectiveness of treatment or a meaningful delay in institutionalization.

Donepezil may decrease the rate of hippocampal atrophy in AD suggesting a neuroprotective mechanism (Hashimoto et al. 2005).

**Dosing/Formulation.** Donepezil is initiated at 5 mg/day and then increased to 10 mg/day after 4−6 weeks. Raising the dose earlier increases the risk for cholinergic adverse events. Five or 10 mg/day are effective doses; 10 mg tends to be somewhat more effective and to have more adverse effects than 5 mg when the various trials as a group are evaluated.

**Table 107–4 Key Published Placebo-Controlled, Randomized ChI Clinical Trials***

| Citation | Duration (Weeks) | Number | Age | Dose (mg/day) | Completers (%) |
|---|---|---|---|---|---|
| **Tacrine** | | | | | |
| Knapp et al. (1994) | 26 | 663 | 73 | 120 | 32 |
| | | | | 160 | 28 |
| | | | | *P* | 68 |
| **Donepezil** | | | | | |
| Rogers et al. (1998b) | 24 | 473 | 73 | 5 | 85 |
| | | | | 10 | 68 |
| | | | | *P* | 80 |
| Burns et al. (1999) | 24 | 818 | 72 | 5 | 78 |
| | | | | 10 | 74 |
| | | | | *P* | 80 |
| Tariot et al. (2001) | 24 | 208 | 86 | 10 | 74 |
| | | | | *P* | 82 |
| Feldman et al. (2001) | 24 | 290 | 74 | 10 | 67 |
| Winblad et al. (2001) | 52 | 286 | 73 | *P* | 67 |
| **Rivastigmine** | | | | | |
| Corey-Bloom et al. (1998) | 26 | 699 | 75 | 1–4 | 85 |
| | | | | 6–12 | 65 |
| | | | | *P* | 84 |
| Rosler et al. (1999) | 26 | 725 | 72 | 1–4 | 86 |
| | | | | 6–12 | 67 |
| | | | | *P* | 87 |
| **Galantamine** | | | | | |
| Tariot et al. (2000) | 20 | 978 | 77 | 8 | 76 |
| | | | | 16 | 78 |
| | | | | 24 | 78 |
| | | | | *P* | 84 |
| Raskind et al. (2000) | 24 | 636 | 75 | 24 | 68 |
| | | | | 32 | 58 |
| | | | | *P* | 81 |
| Wilcock et al. (2000) | 24 | 653 | 72 | | |

*All trials included only patients with probable AD (NINCDS-ADRDA criteria) or dementia of Alzheimer's type (DSM-IV-TR criteria), and generally with baseline MMSE scores between 10 and 26 inclusive, except for the galantamine trials that used narrower ranges of 10–22 and 11–24.

*Note:* Rounded to two figures. All trials had 58–64% female subjects except for tacrine (Knapp et al. 1994, 53%), and donepezil nursing home trial (Tariot et al. 2001, 82%). Drop-outs are for all reasons to avoid bias; not just those attributed to side effects.

Donepezil is also available as an oral disintegrating tablet avoiding the need to swallow tablets.

### *Rivastigmine*

Rivastigmine is a pseudo-irreversible, selective AChE subtype inhibitor. Although it inhibits butyrylcholinesterase as well, it is relatively selective for the postsynaptic G1 monomer form of AChE in areas of the cortex and hippocampus. After binding to AChE, the carbamate portion of rivastigmine is slowly hydrolyzed, cleaved, conjugated to a sulphate and excreted. Thus, its metabolism is essentially extra-hepatic and is unlikely to have significant pharmacokinetic interactions.

Four phase III randomized, placebo-controlled, 26-week-long clinical trials were completed of similar design, but differing mainly in dosing methods. Two have been published (Corey-Bloom et al. 1998, Rosler et al. 1999). Some results of the third have been included in secondary reports (Birks et al. 2000, Schneider 2002, Schneider et al. 1998, Spencer and Noble 1998).

In the two published trials, doses were titrated weekly during the first 7 weeks to one of two dosage ranges, 1–4 mg/day or 6–12 mg/day, and dose decreases were not permitted, possibly contributing to lesser tolerability and seemingly more side effects during these stages of treatment.

A 6-month, multicenter trial of transdermal rivastigmine showed that the patch provided similar benefits to oral rivastigmine at lower doses but with fewer side effects, with similar side effect burden at higher doses (Winblad et al. 2007).

**Dosing/Formulation.** The recommended starting dose of rivastigmine is 1.5 mg b.i.d., taken with meals, increasing to 3 mg b.i.d. after a minimum of 2 weeks of treatment if the initial dose is well tolerated Subsequent increases to 4.5 mg and then 6 mg b.i.d. should be based on good tolerability with the previous, dose and may be considered after a minimum 2-week treatment interval. Higher daily doses, averaging about 9–10 mg were associated with better efficacy than lower doses. It is available as an oral solution. Transdermal rivastigmine is started with an initial 4.6 mg patch per day for at least 4 weeks before the dose is raised to a 9.5 mg patch per day maintenance dose, based on good tolerability with the previous dose.

### *Galantamine*

Galantamine, an alkaloid originally extracted from Amaryllidaceae (*Galanthus woronowi*, the Caucasian snowdrop), but now synthesized, is a reversible, competitive inhibitor of AChE with relatively little butyrylcholinesterase activity

(Harvey 1995). Competitive inhibitors compete with ACh at AChE binding sites, so their inhibition is, theoretically, dependent on intrasynaptic ACh. Another characteristic is its allosteric modulation of nicotinic receptor sites, thus possibly enhancing cholinergic transmission by presynaptic nicotinic stimulation (Maelicke et al. 2001).

Four multicenter trials, involving over 2,400 subjects (Raskind et al. 2000, Tariot et al. 2000, Wilcock et al. 2000, Rockwood et al. 2001), and a systematic review (Loy and Schneider 2006) have been published. The results of two trials indicated that treatment with either 24 or 32 mg/day galantamine improved cognition, clinician's global assessment of change, and ADL scores, with lesser adverse effects at the lower dose. The results of the third showed that daily doses of 16 mg or 24 mg were effective, and 8 mg was not.

**Dosing/Formulation.** Initial dosing of the original formulation of galantamine is 4 mg b.i.d., and should be raised to 8 mg b.i.d. after 2−4 weeks. For patients who are tolerating medication but not responding the dose can be raised to 12 mg b.i.d. after another 4 weeks. The FDA approved galantamine in April 2001 under the trade name Reminyl™. Due to confusion with the diabetes medication glimepiride (Amaryl™), in 2005, the trade name Reminyl™ was changed to Razadyne™. An extended release formulation of galantamine (Razadyne ER™) was subsequently FDA approved for once daily use (Brodaty et al. 2005). The extended release formation of galantamine is started at 8 mg/day and increased to 16 mg/day after 4 weeks. After 4 weeks, the dose can be further increased to 24 mg/day based upon clinical benefit and tolerability. The Cochrane Database of Systematic Reviews indicate that 16 mg/day showed statistically indistinguishable efficacy from higher doses (Loy and Schneider, 2006).

## Adverse Effects of ChIs

Adverse events of the marketed ChIs are summarized in Table 107–5. Significant cholinergic side effects can occur in up to about 25% of patients receiving higher doses. Often they are related to the initial titration of medication. Patients tend to rapidly become tolerant to the adverse events when they occur. Nausea, diarrhea, vomiting, and weight loss are the most common side effects of the ChIs. Few trials have directly compared ChIs. One comparing donepezil and rivastigmine showed more frequent adverse events associated with rivastigmine during the titration phase but similar frequencies as donepezil in the maintenance phase (Bullock et al. 2005). Two clinical trials testing galantamine in MCI showed an increased mortality rate in the galantamine group (1.5%) compared to placebo (0.4%) leading to an FDA alert (http://www.fda.gov/cder/drug/InfoSheets/HCP/galantamineHCP.htm). However, two clinical trials testing donepezil and one with rivastigmine in MCI did not show an increase in mortality compared to placebo (Salloway et al. 2004, Petersen et al. 2005, Feldman et al. 2007). A donepezil trial in vascular dementia also showed an increased incidence of deaths in one trial (10 vsl 0) but not in two others (Kavirajan and Schneider, 2007).

Because of the actions of ChIs, these drugs require caution when used in patients with significant asthma, significant chronic obstructive pulmonary disease, cardiac conduction defects, active peptic ulcers, or clinically significant bradycardia. Appropriate considerations are involved in general anesthesia as well since they may prolong the effects of succinylcholine-type drugs.

**Table 107–5 Adverse Effects of ChIs**

Summary of adverse event data in placebo-controlled, randomized clinical trials. The method of obtaining adverse events and their reporting vary among trials

| Drug | Adverse Events |
|---|---|
| **Tacrine** | Nausea, vomiting, diarrhea, dyspepsia, myalgia, anorexia, dizziness, confusion, insomnia, rare agranulocytosis<br>Approximately 50% of patients will develop direct, reversible hepatotoxicity manifested by elevated transaminases<br>Drug interactions may include increased cholinergic effects with bethanacol; increased plasma tacrine levels with cimetidine or fluvoxamine. This may occur by inhibition of P450 1A2. The association of tacrine with haloperidol may increase parkinsonism and tacrine increases theophylline concentration. |
| **Donepezil** | Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, dizziness, abdominal pain, myasthenia, rhinitis, weight loss, anxiety, syncope (2 vs. 1%) |
| **Rivastigmine** | Nausea, vomiting, anorexia, dizziness, abdominal pain, diarrhea, malaise, fatigue, asthenia, headache, sweating, weight loss, somnolence, syncope (3 vs. 2%). Rarely, severe vomiting with esophageal rupture |
| **Galantamine** | Nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, dizziness, tremor, syncope (2 vs. 1%) |

Adverse event estimates vary widely among the ChIs from study to study and thus relative adverse event rates among drugs are difficult to estimate. Cholinergic side effects generally occur early and are related to initiating or increasing medication. They tend to be mild and self-limited. Medications should be restarted at the lowest doses after temporarily stopping. See prescribing information referenced in Table 107–2.

**General precautions with ChIs** (as indicated in the prescribing information)

By increasing the central and peripheral cholinergic stimulation, ChIs may:

1. increase gastric acid secretion, increasing the risk for GI bleeding especially in patients with ulcer disease or those taking anti-inflammatories
2. produce bradycardia, especially in patients with sick sinus or other supraventricular conduction delay, leading to syncope, falls, and possible injury
3. exacerbate obstructive pulmonary disease
4. cause urinary outflow obstruction
5. increase risk for seizures
6. prolong the effects of succinylcholine-type muscle relaxants

### Tacrine

Elevated transaminases due to direct, reversible hepatotoxicity were the main reason for treatment withdrawals in the two larger pivotal studies. Transaminases were elevated above three times the upper limit of normal in the approximately 30% of patients. Nearly 90% of patients, who had elevated

transaminases and then were rechallenged, were able to tolerate and continue medication (Watkins et al. 1994).

Common adverse effects related to cholinergic mechanisms are dose-related and include: nausea and/or vomiting in 28% of patients versus 8% in the placebo group, diarrhea in 16% versus 5%, anorexia in 9% versus 3%, myalgia in 9% versus 5%. Tacrine is not tolerated in about 10−20% of patients because of such peripheral cholinergic effects (Prescribing Information, October 2000) Due to the high side effect profile including hepatotoxicity, with the advent of newer ChIs for AD treatment, tacrine fell out of favor and is generally no longer used.

### Donepezil

The most common gastrointestinal side effects of donepezil include nausea, vomiting, diarrhea, and anorexia. Some patients develop muscle cramps, headache, dizziness, syncope, flushing, insomnia, weakness, drowsiness, fatigue, and agitation. Weight loss of >7% of baseline occurred at twice the rate of placebo in the nursing home study, but not in outpatient trials. Adverse effects occur at higher rates when the titration from 5−10 mg was made in 1 week compared to 6 weeks.

### Rivastigmine

Adverse effects are primarily gastrointestinal and occurred in the high-dose (6–12 mg/day) group. They occurred mainly during dose escalation and led to withdrawal in one study in 23% of the high-dose group, 7% of the low-dose group and 7% of the placebo group. Inclusion criteria for these clinical trials allowed for patients with a broad range of medical comorbidities to be entered into the studies, perhaps partially explaining the relatively high adverse event rate. Also, the protocols did not allow for the medication dose to be decreased in patients who developed adverse effects during the titration period.

Adverse effects in the higher dose group were sweating, fatigue, asthenia, weight loss, malaise, dizziness, somnolence, nausea, vomiting, anorexia, and flatulence. In the maintenance phase, dizziness, nausea, vomiting, dyspepsia, and sinusitis occurred more in the 6−12 mg/day group than in the placebo group. The FDA approval letter requested that the manufacturer do further analyses to better characterize these effects, especially weight loss and anorexia.

### Galantamine

Principal adverse effects are nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, dizziness, and tremor. Again, adverse events were more frequent earlier in the course of treatment and during the dosage titration from 16−24 mg/day and higher. In one trial the effective dosage of 16 mg/day was not associated with overall greater adverse events than the placebo-treated group. According to the Cochrane Database of Systemic Reviews, doses of 16 mg/day when titrated over a 4-week period were best tolerated. (Loy and Schneider, 2006)

## Particular Adverse Events with ChIs

An increased but modest incidence of anorexia appears to be a consistent finding across clinical trials and appears to be dose related. The absolute reported incidence varies across trials from approximately 8−25% at the highest dose of ChI compared to 3−10% in comparable placebo patients. Similarly, there is an increased rate of significant weight loss with higher doses of ChIs compared to placebo patients. The proportion of patients losing greater than 7% of their baseline weight varies from approximately 10−24% in the higher doses and from 2−10% of the placebo-treated patients in those trials reporting the statistic. Anorexia and weight loss are significant clinical problems for many elderly patients independent of medication effects, and whether or not demented.

Cholinergic side effects such as diarrhea, nausea, and vomiting, tend to occur at initiation of treatment and when titrating to higher doses. They may be transient or self-limited and can often be managed with encouragement and maintenance of the present dose level, by omitting one or more doses, or by temporarily decreasing dosage. However, anorexia and weight loss may be clinically significant problems over the longer term, especially in older, more medically ill, and nursing home patients, so these parameters should be monitored.

Uncommonly, the vagotonic effects of ChIs may cause significant bradycardia, and this can be a particular concern to patients with supraventricular conduction impairments or sick sinus syndrome.

Because gastric acid secretion may be increased with ChIs, there may be an increased risk for developing ulcers or gastrointestinal bleeding. Uncommonly, ChIs may cause bladder outflow obstruction, seizures, and exacerbate asthma or obstructive pulmonary disease, and interfere with succinylcholine-like anesthetics.

## Glutamatergic Therapies

The *N*-methyl-d-aspartate (NMDA) receptor, a glutamate receptor subtype, has important effects in learning and memory. Stimulation by the excitatory amino acid glutamate results in long-term potentiation of neuronal activity basic to memory formation (Cotman et al. 1988). There appears to be a decrease in cerebral cortical and hippocampal NMDA receptors in AD. Glycine, acting at an adjoining glycine-B receptor, modulates the effects of glutamate. Milacemide, a prodrug that readily crosses the blood–brain barrier where it is converted to glycinamide and glycine, although effective at facilitating various aspects of memory in animal models, did not significantly improve any efficacy parameter in a multicenter trial in 228 AD patients (Dysken et al. 1992).

### Memantine

Memantine is an uncompetitive NMDA antagonist that binds to the NMDA receptor-operated cation channels and may act by inhibiting calcium ion influx thus modulating the excitotoxicity. Memantine also acts as an uncompetitive antagonist at the $5HT_3$ receptor but the clinical significance of this is unknown (Rammes et al. 2001). The FDA approved memantine for moderate to severe AD in 2003. Three randomized placebo controlled trials have shown benefits over placebo in moderate or severe AD on several measures. Two studies, one of which evaluated participants who were being treated with donepezil, showed significant improvements on the SIB, the modified ADCS-ADL Scale, and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global score (Reisberg et al. 2003 and Tariot et al. 2004). A fourth 6-month trial

in moderate to severe AD did not show significant effects in favor of memantine. (The SIB assesses attention, orientation, language, memory, and social interactions)

The third study, conducted in nursing homes in Latvia showed a significant advantage of memantine over placebo in the Behavioral Rating Scale for Geriatric patients (BGP), which assessed day-to-day functioning and a global impression of change (Winblad and Poritis, 1999). Another 6-month-long placebo-controlled trial in moderate to severe AD outpatients did not show advantages for memantine (Van Dyck et al. 2007)

Three trials evaluated memantine in mild to moderate AD. Two of the three failed to show advantages for memantine on cognitive, global, functional or behavioral outcomes (www.forestclinicaltrials.com; unpublished data, 99679, data on file, H. Lundbeck A/S, 2004; unpublished data, Peskind et al. 2006). According to the Cochrane Database of Systemic Reviews, pooled data on memantine in mild to moderate AD show a marginal beneficial effect at 6 months that was clinically insignificant with no effect on behavior or ADLs (McShane et al. 2006) and the drug is not FDA approved for mild AD.

There is no evidence that memantine prevents or slows neurodegeneration in AD, although preclinical evidence suggest that this may be a possibility. Second generation NMDA receptor antagonists are currently in development including delucemine, which is currently in a phase I study, and neramexane which is in phase II clinical trials.

### *Dosing*

Memantine is available in tablet and oral solution form. Treatment is initiated with 5 mg/daily for one week and increased by 5 mg/daily in divided doses to a maintenance dose of 10 mg twice a day. The nursing home trial in Latvia showed efficacy with 10 mg/day doses.

### *Adverse Effects*

Significant side effects can include dizziness, constipation, headache, and confusion. Generally, memantine is well tolerated, and is thought to have low potential for drug interactions.

## AMPA Receptor Modulators

The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor is a non-NMDA-type ionotropic transmembrane receptor for glutamate found in many parts of the brain. These receptors are thought to be integral to encoding memory. A class of drugs called ampakines has been developed which augments the AMPA receptor ionic current flow, enhancing fast, excitatory synaptic responses. Several animal studies have shown improved encoding of memory in rats in many paradigms including spatial cues, odor discrimination, and cue matching (Ingvar et al. 1997). The ampkine CX516 appears to have a possible positive affect on delayed recall of nonsense syllables (Lynch et al. 1996). In another study in normal healthy adults, this drug showed some improvement in some aspects of memory including visual associations, recognition of odors, and acquisition of a visuospatial maze (Ingvar et al. 1997). CX516 is currently under investigation for AD and is also being tested for treatment of schizophrenia, fragile X syndrome and autism.

LY450108 and LY451395 are biarylsulfonamides, a new class of centrally acting AMPA receptor potentiators. Doses of 1 mg and 5 mg have crossed the blood brain barrier and appeared well tolerated in healthy subjects (Jhee et al. 2006). The biarylsulfonamides are currently in early phase clinical trials.

## Treatment Approach with Approved Compounds

Optimal duration of treatment with approved compounds is unknown but overall efficacy extends at least 9−12 months based on the clinical trials and open-label extension phases. Maintenance treatment can be continued as long as a therapeutic benefit for the patient seems apparent. The potential clinical benefit should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. It is difficult to assess individual patient response because of the variability of the deteriorating course of AD, and because most of the effect of medication is due to a stabilization or lack of worsening of symptoms or cognitive function while placebo-treated patients continue to decline. Therefore, the clinical observations of minimal or no clinical worsening may be sufficient reasons to continue medication treatment if patients are tolerating therapy.

## Effect on Behavior

The evidence that ChIs may improve behavior is based on case series and secondary analyses of efficacy trials (Kaufer et al. 1996, Raskind et al. 1997). Patients enrolled into ChI trials were selected largely on the basis of their ability to cooperate; they are not generally agitated, psychotic, or depressed. There is little consistency in the subscales of the behavioral rating instruments that might improve from study to study. For example, in two trials each there was a significant effect on the hallucination or aberrant motor behavior items and in one trial each on agitation or apathy. One prospective clinical trial with donepezil in patients with AD and significant psychpathology was designed as a withdrawal trial (Holmes et al. 2004) in which patients received open label donepezil for 3 months and were then randomized to either placebo or donepezil. The placebo group showed relative worsening of behavior.

Clinical experience suggests that they may be effective at least for mildly disturbed behavior, and in delaying the onset of troublesome behaviors, perhaps by maintaining cognitive function or perhaps through enhancing attentional processes and activation. However, there was no effect on behavior in any of the three donepezil trials in severe AD; and a trial targeting patients with severe AD and significant behavioral disorder also found no significant effect with donepezil on behavioral symptoms (Howard et al. 2007).

Memantine showed beneficial effects on behavior in one (Tariot et al. 2004) of three trials in moderate-severe AD (Reisberg et al. 2003), and inconsistent and nonrobust effects in patients with mild-moderate AD (McShane et al. 2006).

## Other Neurotransmitter Based Approaches

Structural and functional disturbances of central catecholaminergic systems in AD and their important role in brain-related functions provide the rationale for

pharmacological enhancement of these systems. The general strategies employed are analogous to those used with cholinergic agents: precursor loading, inhibition of degradative enzymes, and use of agonists. Studies of dopamine precursors (e.g., with tyrosine, l-dopa) and agonists (e.g., clonidine, guanefacine, amantadine, bromocriptine) have largely been negative (Schneider and Tariot 1997).

At a dose of up to 10 mg/day, selegiline relatively selectively inhibits MAO-B. The overall effect of selegiline at this dose may be to increase CNS levels of dopamine and some trace neurotransmitters such as phenylethylamine without affecting norepinephrine levels. Selegiline is currently marketed for the treatment of Parkinson's disease for which it has demonstrated effects in maintaining motor function (Parkinson Study Group 1993). Selegiline also may have potential to preserve surviving neurons (Tatton 1993). Elevated levels of MAO-B, found in the brains of patients with AD, might lead to elevated levels of neurotoxins such as 6-hydroxydopamine, quinones, and free radicals, or even environmental toxins. In either case, inhibition of monoamine oxidase (MAO) on a chronic basis could theoretically retard progression of the illness based on antitoxic mechanisms. Finally, selegiline may have neuronal "rescue" effects, based on neurotrophic-like properties not involving MAO inhibition. It is notable that rodents and dogs treated with selegiline have increased survival (Knoll 1988, Milgram et al. 1990, Ruehl et al. 1997).

Numerous clinical trials with selegiline have been performed, with variable results and insufficient evidence to justify routine clinical use in AD (Birks and Flicker, 2003). One multicenter trial found that selegiline, 5 mg b.i.d., both alone and combined with vitamin E, 1,000 IU b.i.d., was associated with maintenance of ADLs and survival in the community compared to placebo in moderately to severely impaired AD patients but with no improvement in cognition (Sano et al. 1997).

Othe MAO-B inhibitors under development include rasagiline and safinamide. Ladostigil combines MAO-B inhibition with cholinesterase inhibition in a single molecule, is in phase II trials, and is neuroprotective in neuronal cell cultures, possibly due to the S-isomer (Youdim et al. 2006).

### Histamine

The H3 histamine receptor is thought to play a role in control of arousal and cognition. Cortical histamine levels are significantly reduced in brains of patients with AD (Panula et al. 1998). Mounting evidence suggests that H3 receptor antagonists may improve cognition in AD. Preclinical tests have shown increased performance in attention and memory tasks whereas H3 receptor agonists have produced a decline in cognitive function (Witkin and Nelson 2004). At least two drugs that affect CNS histamine are currently in clinical trials.

One of these is dimebon, which had been approved in Russia as an antihistamine since the early 1980s but is not currently available. It is under investigation as a therapy for AD and Huntington's disease. Dimebon was thought to block the histamine binding site of the NMDA receptor, thus modulating activity of the NMDA receptors (Grigorev et al. 2003), and also inhibits AChE, but these effects occur at concentrations outside the human therapeutic range. Animal studies (Lermontova et al. 2000), and an *in vitro* study suggested improved survival of cerebellar granule cells during long-term incubation with Aβ (Lermontova et al. 2001). Thus, its mechanism of action must be considered unknown at present. According to the manufacturer's website, a 6-month, randomized, double-blind, placebo-controlled trial, conducted in Russia, that included 183 patients with mild to moderate AD, showed significant improvement on cognition, global assessment, ADL, and behavior compared to placebo.

### Somatostatin

Somatostatin is a neuropeptide that is believed to play a role in learning and memory (Schettini, 1991 and Matsuoka et al. 1995). Some studies have shown a correlation between an impairment in somatostatin-mediated neurotransmission in the brain and AD (Davies et al. 1980 and Bissette and Myers, 1992). FK960 is a synthetic compound that enhances somatostatin release and has been shown to improve memory in animal models of amnesia (Yamazaki et al. 1996 and Matsuoka and Aigner, 1997). FK962 was developed to further optimize the pharmacological action and pharmacokinetic properties of FK960, and was shown to be beneficial in animals (Tokita et al. 2005). This compound completed phase I and II testing, but showed no efficacy in AD.

## Neurotrophic Factors

### Nerve Growth Factor (NGF)

NGF, a trophic factor for cholinergic neurons, may target forebrain cholinergic neurons that release the majority of acetylcholine in the cortex and hippocampus. Profound degeneration of these cells is thought to contribute to cognitive decline in AD. Because NGF does not cross the blood-brain barrier, it was directly infused into brain ventricles in a study that was terminated prematurely due to significant adverse events including weight loss and pain. Additionally, animal studies of intraventricular NGF showed abnormal axonal sprouting of sympathetic nerves and migration of Schwann cells into the subpial space surrounding the brainstem and spinal cord forming a dense sheath (Tuszynski 2002).

Subsequently, a trial introducing the actual NGF gene was performed (Tuszynski et al. 2005) by engineering patient's own fibroblasts to produce human NGF, and then to stereotactically inject the cells into the nucleus basalis. The first two patients had serious brain hemorrhages resulting in death in one patient due to movement during the injection procedure. These patients were alert but sedated for the procedure. There were no surgical complications in the following 6 patients, as the surgery was performed under general anesthesia. Patients were followed for 18−24 months. One patient developed two syncopal events, possible related to the procedure. Two of six subjects showed improved MMSE scores, one showed no decline, two showed minor decline, and one had a large decline. Compared to historical controls, rates of decline in the ADAS-Cog also showed improvement. PET scans in four patients showed significant increases in FDG uptake rather that the usual decline observed in AD. Increases were observed in most cortical regions receiving cholinergic input from the nucleus basalis. Brain autopsy in one patient who died showed

survival of the implanted autologous fibroblasts with little evidence of inflammation. *In situ* hybridization for messenger RNA encoded NGF showed robust NGF expression by the transplanted fibroblasts. Immunocytochemistry showed sprouting of cholinergic axons in and around the transplant site. The absence of controls and the small number of patients preclude conclusive evidence; however, this trial serves as an impetus for future studies in gene therapy. A new gene delivery method using adeno-associated virus (AAV) is currently completing a phase I trial, and a phase II trial is in the planning stages.

## Other Trophic Factors

### *Cerebrolysin*

Cerebrolysin is a synthetic compound comprised of neurotrophic peptides from the porcine brain that has been found to reduce amyloid burden and improve synaptic plasticity in transgenic mice (Rockenstein et al. 2003). It is thought to regulate APP maturations and transport to sites where Aβ protein is generated (Rockenstein et al. 2006). In an initial placebo-controlled trial, small improvements in ADAS-cog scores and global assessments of severity were seen (Reuther et al. 2001). A second randomized trial of 192 patients did not find significant effects on the ADAS-Cog but did on global assessment (Panisset et al. 2002); a third observed improvements on ADLs (Muresanu et al. 2002).

### *Leteprinim*

Leteprinim (AIT-082) is a derivative of the purine hypoxanthine that is thought to stimulate the production of several neurotrophic factors (Glasky et al. 1994, 2001). A one-week phase I randomized, double-blind, placebo-controlled, dose escalation trial randomized 36 patients to one of three different dose groups. It was safe and well tolerated, but there were no improvements in cognitive testing (Grundman et al. 2003). A phase II trial was completed but no results were reported.

### *Xaliproden*

The compound xaliproden (SR57746A) mimics the neurotrophic effect of NGF in cell cultures (Fournier et al. 1992). In rats with a vincristine-induced septohippocampal lesion, which is thought to serve as a model forebrain cholinergic neuron and memory deficits, xaliproden reversed the reduction in hippocampal ChAT. There was a significant improvement in the behavioral impairments observed (Fournier et al. 1993). Two phase III clinical trials of 18 months duration were recently completed but results have not been reported.

### *Paliroden*

Paliroden (SR57667B) has been found to be neuroprotective and neurotrphic in both *in vitro* and *in vivo* models. In the intra-septal vincristine lesion model in rats, this compound was found to activate migration of neural stem cells from the lateral ventricle with increased numbers of these cells reaching the lesioned site and differentiating into neurons (Labie et al. 2006). This compound is currently in a phase II clinical trial, and is also being tested for Parkinson's disease.

### *MK-0677*

MK-0677 is a compound that induces secretion of insulin-like growth factor-1 (IGF-1). In a 1-year study (unpublished), 563 AD patients were randomized to MK-0677 or placebo daily. Although MK-0677 increased IGF-1 serum levels by 60%, the primary endpoints of the CIBIC-plus and ADAS-Cog scales showed little change. Secondary endpoints were also did not show significance.

### *Estrogens*

Estrogens may have cholinergic neurotrophic and neuroprotective effects and may enhance cognitive function (Simpkins et al. 1994). In ovariectomized rats, estradiol replacement enhanced learning; reversed the decrease in neuronal choline uptake and ChAT caused by ovariectomy; prevented the ovariectomy-associated decline in NGF and in brain-derived neurotrophic factor mRNA.

A beneficial role for estrogen in AD, cognitive function, mood, and aging is suggested by observations of an inverse relationship of estrogen replacement therapy dose and duration with dementia diagnoses on death certificates (Paganini-Hill and Henderson 1994); by preliminary trials suggesting a cognitive enhancing effect of estradiol, estrone, and conjugated estrogens in AD (Asthana et al. 2001, Fillit et al. 1986, Honjo et al. 1989, Ohkura et al. 1994).

Clinical trials of conjugated equine estrogens (CEE) to improve cognition in both hysterectomized and nonhysterectomized women with AD have not led to success, and indeed women treated with CEE somewhat worse both in cognition and safety including 5% developing deep vein thrombosis (Henderson et al. 2000, Mulnard et al. 2000).

The Women's Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial, examined whether postmenopausal CEE supplementation (both CEE alone and estrogen plus progestin) reduces the risk of all-cause dementia (primary outcome) and subclinical (mild) cognitive impairment (secondary outcome) in healthy women aged 65 years or older (Shumaker et al. 2003). (CEE plus progestin was associated with increased risk for heart disease, stroke, pulmonary embolism, and breast cancer). CEE alone and CEE plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older and did not prevent MCI. These outcomes do not preclude the possibility for a beneficial effect of estrogens for younger women.

### *Glucocorticoid Antagonists*

Mifepristone, a glucocorticoid II receptor antagonist also known as RU-486, has received wide media attention because it is used to terminate intrauterine pregnancies and as an emergency contraceptive. Abnormalities in the hypothalamic pituitary adrenal axis have been implicated in the pathophysiology of AD, and a correlation has been shown between increased plasma cortisol with cognitive decline and hippocampal atrophy (Lupien et al. 1998). It was thus hypothesized that mifepristone, a long-acting antagonist of progetserone and glucorticoid receptors, may be useful for treatment of AD by countering any effects of exposure to glucorticoids.

One pilot study randomized nine mild-to-moderate AD patients for a 6-week trial to mifepristone 200 mg or placebo

but was too small to show effects (Pomara et al. 2002). A larger trial was reported by Corcept, the manufacturers of mifepristone, to not have shown significance but details were not provided.

Prospective neurotrophic proteins thought to promote neurite outgrowth under study include activity-dependent neuroprotective protein (ADNP) and activity-dependent neurotrophic factor (ADNF) as well as short peptide derivatives of these proteins such as ADNF-9 and NAP (Gozes and Spivak-Pohis 2006). AL-108 is an eight amino acid peptide based on NAP tested in a Phase Ia study for AD, and will be tested in Parkinson's disease as well.

## Metabolic Enhancement

In view of regional decreases in glucose utilization and abnormal oxidative metabolism, drugs have been employed with the aim of correcting these abnormalities, including ergot alkaloids and nootropics. A discussion of the ergot alkaloids can be found in the previous edition of this book and in a Cochrane systematic review (Olin et al. 2001). Although it was, once, one of the most frequently prescribed medications in the world, it is rarely prescribed now. Numerous clinical trials in various elderly patient groups have not clarified its efficacy or clinical role. Another ergoloid derivative available in Europe, nicergoline, was associated with significant improvement on some areas such as orientation and attention and has been undergoing clinical testing (Fioravanti and Flicker 2001). Nicergoline, dihydroergotamine, and other ergolines can induce chronic pleural thickening, fibrosis and effusion, however.

### Nootropics

Piracetam, oxiracetam, pramiracetam, aniracetam, CI 933, and BMY 21502 are pyrrolidone derivatives of γ-aminobutyric acid (GABA). Although they do not appear to have GABA-like effects, they are postulated to have neuroprotective properties. These drugs may also enhance the CNS microcirculation by reducing platelet activity, by reducing adherence of red blood cells to vessel walls, and may stimulate central cholinergic activity. These diverse effects are termed nootropic to indicate the class of drugs that are structurally related to piracetam and may improve learning and memory (Nicholson 1990). Double-blind, multicenter, controlled studies have shown mixed results with piracetam in the treatment of dementia in the elderly (Flicker and Evans 2001, Vernon and Sorkin 1991). Pramiracetam and oxiracetam have been evaluated in large scale multicenter studies with no sufficiently significant clinical effects in dementia. Piracetam is undergoing a clinical trial for MCI.

## Amyloid-Based Interventions

Significant progress has been made toward developing disease-modifying anti-amyloid therapies producing several promising agets that are now in clinical trials.

### Immunotherapy

#### *Active Immunotherapy*

Active immunotherapy introduces an antigen that triggers an immune response. Investigations with AN 1792 in transgenic mice exhibiting CNS pathology similar to AD showed reduced development of amyloid plaques and decreased cognitive decline (Janus et al. 2000). The phase II trial of AN 1792 in humans was terminated early due to the development of a T-cell immune mediated aseptic meningoencephalitis in 18 of 300 (6%) subjects who were randomized to the study drug. A total of 59 subjects (19.7%) developed an antibody response. No significant differences were found between antibody responder and placebo groups for ADAS–Cog, Disability Assessment for Dementia, Clinical Dementia Rating, MMSE, or CGIC.

A subset ($n$ = 11) of antibody responders had CSF analysis showing no change in Aβ levels, but a decrease in tau (Gilman et al. 2005), suggesting the possibility of a reduced rate of cellular degeneration in antibody responders. A series of autopsies of antibody responders showed a markedly reduced number of amyloid plaques compared to patients treated with placebo or active vaccine who did not show high antibody titers (Nicoll et al. 2003; Orgogozo 2006), thus suggesting the possibility that Aβ immunotherapy may reduce plaque burden. Paired MRI scans of antibody responders showed a greater decrease in brain volume and greater ventricular enlargement as compared to placebo with no correlation to cognitive decline. The reasons for these findings are unclear but the authors postulate the role of amyloid removal and fluid shifts.

A second active vaccine, ACC-001, has been developed to induce a highly specific antibody response to Aβ that will hopefully avoid the adverse effects associated with AN 1792, and is in phase II testing. CAD106 is another active vaccine that has recently entered clinical testing. This vaccine is based on the first six N-terminal amino acids of Aβ which is believed to stimulate human B cells without a T-cell response thereby possibly avoiding the adverse effects seen with AN 1792.

#### *Passive Immunotherapy*

Antibodies are delivered directly, averting the need to mount an immune response; however antibodies have to be given frequently and have a relatively short life span (less than 1 month) as compared to active immunization.

Several different formulations are being studied. The anti-Aβ antibody m266 has been found to restore hippocampal cholinergic dysfunction and impaired learning in APP transgenic mice (Bales et al. 2006). LY206430 is a humanized version of the m266 monoclonal antibody that binds to the Aβ16-23 amino acid region. Data from early human studies are not published yet. Although no significant improvement was measured on the ADAS-Cog, a 150−600-fold increase in plasma $A\beta_{40}$ levels was demonstrated this antibody will be further tested.

AAB-001 (bapineuzumab) is a monoclonal antibody to Aβ currently entering an 18-month-long phase III trials while a phase II trial assessing safety and tolerability with approximately 200 AD patients is ongoing.

Human intravenous immunoglobulin (IVIg), polyclonal antibodies which contain antibodies against Aβ, is currently being studied for therapeutic benefit in AD. In a small pilot study, IVIg was administered monthly for 6 months to 5 patients with AD. The total Aβ levels in the CSF decreased by 30.1%, serum Aβ increased by 233%, and ADAS-cog and MMSE scores essentially stabilized (Dodel et al. 2004). A second open-label pilot study reported similar findings (Relkin et al. 2005) and a placebo-controlled trial is underway.

## Secretase Inhibitors

Both β-secretase (β-site APP cleavage enzyme; BACE) and γ-secretase abnormally cleave APP, an early action in the cascade of pathological events. Both enzymes have been targeted for therapeutics as anti-amyloid disease modifying-treatments, however, development of this class of compounds has been challenging. BACE inhibitors have yet to be studied clinically as they are large molecules that have difficulty penetrating the blood-brain barrier and the receptor site is difficult to bind (Walker et al. 2005).

The current γ-secretase inhibitors also block the Notch signaling protein, a physiologically essential substrate that acts as an important intermediate in many cellular functions, most notably, the regulation and differentiation of cells in the gastrointestinal tract and immune system. Interference with Notch can result in untoward biological consequences, gastrointestinal adverse events, and is of concern in the development of some γ-secretase inhibitors.

The first γ-secretase to be studied in clinical trials is LY450139. In a phase I trial, 37 healthy adults were randomized to LY450139 at doses ranging from 5−50 mg. Plasma Aβ concentrations decreased in a dose-dependent manner over a 6-hr interval following drug administration, but transiently increased thereafter. CSF Aβ levels were unchanged (Siemers et al. 2005). A phase II trial randomized 70 patients with mild-to-moderate AD who were on stable doses of ChIs. Subjects were given 30 mg of LY450139 for 1 week followed by 40 mg for 5 weeks. There were no changes in CSF concentrations of Aβ during treatment, but a similar pattern of a decrease in plasma Aβ with rebound were found in the serum. No changes in cognitive function were found. Modest gastrointestinal side effects were reported (Siemers et al. 2006). A follow-up Phase II study has been completed.

Another γ-secretase inhibitor, MK-0752 showed a dose-dependent Aβ40 reduction and was adequately tolerated which has led the way towards an ongoing phase I trial.

## Selective Aβ42-Lowering Agents

A subset of nonsteroidal anti-inflammatory drugs (NSAIDs) may have direct $A\beta_{42}$ lowering properties. In contrast to γ-secretase inhibitors, selective $A\beta_{42}$-lowering agents (SALAs) do not interfere with physiologically essential substrates such as Notch because they do not bind to the active site. The SALAs allosterically modulate γ-secretase that alter the enzymatic site of action on APP to produce shorter, less toxic Aβ fragments (Beher et al. 2004).

The R-enantiomer of flurbiprofen (R-flurbiprofen, tarenflurbil) has no significant cyclo-oxygenase inhibitory, which is a target of S-flurbiprofien and other NSAIDs. Preclinical animal studies showing improved spatial memory led to a phase I trial in normal volunteers (Galasko et al. 2004). A 12-month phase II trial of 207 participants with mild-to-moderate AD evaluated two different doses, 400 mg b.i.d. and 800 mg b.i.d. Although there was no overall treatment effect, a post hoc analysis of the patients with mild AD (MMSE 20-26) taking the higher dose showed a statistically significant improvement in cognition and function, and the few patients taking the higher dose and continuing throughout a 1-year open-label extension seemed to have worsened cognitively a little less than expected (Wilcock et al. 2006). Two phase III 18-month placebo-controlled trials of R-fluribuprofen 800 mg b.i.d. in patients with mild AD are underway with the first to be completed in March, 2008.

Two nitric oxide (NO) releasing derivatives of flurbiprofen, HCT 1026 and NCX 2216, possess anti-amyloidogenic activity in AD models (Gasparini et al. 2005). These drugs consist of a NO-donating moiety coupled to flurbiprofen. When in the presence of cells or tissues, NO is slowly released, mimicking the physiological levels of NO. This NO release is thought to improve the tolerability of the parent drug flurbiprofen (Wallace et al. 2004). In AD transgenic mice models, HCT 1026 and NCX 2216 both reduced cerebral amyloid, and the latter drug was associated with persistent activation of microglia in the peri-plaque areas (Van Groen and Kadish, 2005).

## Anti-Aggregation Agents

After APP is cleaved into Aβ fragments, glycosaminoglycans (GAG) bind to the Aβ protein which enables polymerization into amyloid plaques. Agents that interfere with this aggregation process may be therapeutic.

Tramiprosate is a GAG mimetic that binds to Aβ at GAG binding sites, thus reducing Aβ aggregation by thwarting GAG binding (Gervais et al. 2001). A transgenic mouse model of AD showed a dose-dependent reduction of both soluble and insoluble $A\beta_{40}$ and $A\beta_{42}$ levels in the brain and plasma. A phase II study of 58 patients with mild-to-moderate AD demonstrated tolerability over a 3-month period at 3 different doses, and 42 subjects entered an open-label phase for 17 months. The most frequent adverse events were nausea, vomiting, and diarrhea. A dose-dependent reduction in CSF $A\beta_{42}$ levels, but not $A\beta_{40}$ was observed after 3 months; suggesting that the drug is affecting brain amyloid. There were no significant differences in cognition after 3 months (Aisen et al. 2006). A multicenter phase III trial involving two doses and over 1050 patients failed to show efficacy. A second phase III trial is ongoing in Europe.

A second anti-aggregation agent, scyllo-cyclohexanehexol (AZD-103) also shows salutary effects in preclinical studies (McLaurin et al. 2006). Fibril formation due to aggregated Aβ is strongly facilitated by phosphatidylinositolipds. Scyllo-cyclohexanehexol is a phosphatidylinositolipd derivative that competes with the phosphatidylinositolipds for binding to Aβ and interferes with Aβ fibril assembly. An initial phase I study in 12 healthy volunteers suggested the drug was well tolerated, and a second phase I study with higher doses is currently underway.

## Metal Chelators

The fibrillization of Aβ is influenced by heavy metal ions, leading to the hypothesis that heavy metal chelators can reduce polymerization. Clioquinol was used for parasitic gastrointestinal disease but reoved from the market because it was linked to a rare form of optic nerve damage called subacute myelo-optico-neuropathy (SMON) (Tateishi 2000). It has copper and zinc chelation properties, and reduced brain amyloid in transgenic mice (Cherny et al. 2001). A small phase II study in 36 patients with moderately severe AD did not show evidence of cognitive benefit but did show a decline in plasma Aβ levels (Ritchie et al. 2003). Further development of this drug for AD has been halted due to

concerns regarding toxicity and impurities in the clinical formulation. PBT-2 is another chelator with similar properties as clioquinol is under development.

### Colostrinin

Colostrinin, a proline-rich polypeptide found in sheep colostrum inhibits Aβ aggregation in cellular assays through an unknown mechanism (Bilikiewicz and Gaus 2004). A randomized placebo controlled study followed 105 patients for 30 weeks. The first 15 weeks patients were randomized into a double-blind place phase followed by 15 weeks of an open-labeled phase where all patients received colostrinin. There were significant improvements on cognition and daily function measures. It is currently under investigation.

### Statins

Epidemiological studies have suggested an association between cholesterol-lowering therapy with the HMG-CoA reductase inhibitors and a lower risk of AD (Jick et al. 2000 and Wolozin et al. 2000). The mechanism underlying this possible relationship is uncertain, but could be related to cholesterol reduction and mediation of inflammatory effects. Another proposed method of action suggests that statins may activate the α-secretase pathway, shifting Aβ processing away from the β-secretase and γ-secretase. The result of increased α-secretase activity translates to increased levels of a less toxic form of Aβ and lower levels of Aβ42.

Simvastatin did not significantly alter CSF levels of Aβ overall although Aβ40 levels were decreased in a post hoc subgroup with mild AD, in a randomized, placebo-controlled, double-blind trial of 44 pateints over 26 weeks (Simons et al. 2002). Also a randomized, placebo-controlled trial of atorvastatin in mild-to-moderate AD in 67 patients over 12 months was not statistically significant (Sparks et al. 2005). There are two ongoing placebo-controlled studies of statins that are currently underway, one sponsored by NIA with simvastatin and one by Pfizer with atorvastatin.

### Curcumin

This curry spice is a potent antioxidant and has been investigated for possible protective roles in AD inflammatory processes. Curcumin inhibits Aβ40 aggregation in a dose-dependent manner in vitro (Ono et al. 2004); and reduces plaque burden in mice by disaggregating Aβ and preventing fibril and oligomer formation (Yang et al. 2005). Curcumin is currently in clinical trials.

### Docosahexaenoic Acid (DHA)

Epidemiological studies suggest a reduced risk of AD associated with fish consumption (Kalmijn et al. 1997 and Barberger-Gateau et al. 2002). DHA is one of the major omega-3 fatty acids found in fish oil, an integral component of neural membrane phospholipids, and the major polyunsaturated fatty acid in the brain (Lauritzen et al. 2001). Data from several animal studies support the use of DHA by means of anti-amyloid, antioxidant, and neuroprotective mechanisms. Safety and tolerability studies (Arterburn et al. 2006) have led the way to a multicenter phase III randomized placebo-controlled study being conducted by the ADCS.

### Peroxisome Proliferator-Activated Receptor-γ Agonists

Attention has been placed on insulin modifying therapy in view of the association between AD with elevated plasma insulin levels and reduced insulin sensitivity. Several theories of how insulin may influence AD pathophysiology have been proposed. In animals, insulin was found to facilitate Aβ release from intraneuronal compartments and interfere with degradation of Aβ (Leissring et al. 2003). Insulin may also contribute to cerebral inflammation as increased plasma insulin levels in response to a glucose challenge are associated with elevated inflammatory markers (Hak et al. 2001). Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists improve insulin sensitivity, and thus is it has been hypothesized that PPAR-γ agonists may protect neurons from the presumed harmful effects of insulin resistance.

Rosiglitazone is a PPAR-γ agonist currently being tested in clinical trials. A pilot study suggested improvement in delayed recall (Watson et al. 2005). A trial of 511 nondiabetic AD patients over 6 months did not show significant effects. A post hoc analysis of APOE status, however, found that subjects lacking an APOE ε4 allele showed improvements (Risner et al. 2006) compared to placebo, and led to three ongoing large-scale placebo-controlled multicenter trials assessing rosiglitazone in AD patients stratified by APOE status.

## Tangle–Based Therapies

Some studies suggest that lithium and valproic acid have anti-amyloid and neuroprotective properties (Tariot et al. 2002). Valproic acid protects cultured rat hippocampal neurons against Aβ and glutamate induced injury, possibly due to stabilization of intracellular calcium levels (Mark et al. 1995). Endoplasmic reticulum (ER) stress-induced intracellular lipid accumulation and cell death may play a role in the pathogenesis of AD. Glycogen synthase kinases (GSK)-3alpha/beta also play an important role in signaling downstream effects of ER stress including the phosphorylation of tau. Valproic acid also inhibits GSK-3, and may protect against cell damage due to ER stress (Kim et al. 2005). A multicenter phase III clinical trial is currently underway assessing the potential neuroprotective effects of valproate in AD patients (Tariot et al. 2002). Lithium also inhibits GSK-3, but in one small placebo-controlled trial showed a nonsignificant effect on cognitive scores. A phase III trial will soon be implemented.

## Inflammatory Processes

Emerging evidence indicates overactivity of aspects of immune function in AD (Aisen and Davis 1994). Immune/inflammatory reactions may be established by reactive microglia surrounding senile plaques and astrocyte proliferation; and inflammatory cytokines are produced such as tumor necrosis factor alpha, interleukin-1 (IL-1), α-2-macroglobulin, and α-1-antichymotrypsin. IL-1 and IL-6 promote the synthesis of β–APP.

### Anti-inflammatory Medications

Epidemiological evidence supports the use of nonsteroidal anti-inflammatories as preventative of AD. However, clinical trials data are discouraging. The potential role for

anti-inflammatory agents is supported by a small 44-patient placebo-controlled trial of indomethacin (Rogers et al. 1993). Low-dose prednisone (10 mg) did not prove effective in a 1-year-long, placebo-controlled trial by the ADCS (Aisen et al. 2000). There have been clinical trials failures with cyclo-oxygenase-2 inhibitors, celecoxib and rofecoxib, as well as with the nonspecific cyclo-oxygenase inhibitor naproxen (Aisen et al. 2002). Thus, overall efficacy of anti-inflammatories agents in AD has yet to be demonstrated.

## Antioxidants

Many studies report evidence of increased level of oxidative or free radical damage to neurons in Alzheimer's disease as well as normal aging, and there are some empirical findings supporting this.

### Vitamin E and Selegiline

In a trial comparing vitamin E, 1,000 IU b.i.d. and selegiline, 5 mg b.i.d. in outpatients with moderate-to-severe dementia (Sano et al. 1997), overall, both drugs were effective in maintaining patients' ADLs and prolonging survival in the community by about 5−7 months. There was no effect on cognition, however. A subsequent trial in MCI comparing vitamin E with donepezil and placebo did not find efficacy with vitamin E (Petersen et al. 2005).

### Ginkgo Biloba

*Ginkgo biloba* extract (GbE) may exert neuroprotective effects under conditions of hypoxia, ischemia preventing neuronal cell death (Spinnewyn 1992), inhibit the toxic effects of β-amyloid (Bastianetto et al. 2000), and act as a free radical scavenger (Dorman et al. 1992, Dumont et al. 1992, Pietschmann et al. 1992). In aged animals, oral GbE treatment leads to increases in the densities of hippocampal muscarinic acetylcholine receptors and cortical 5-$HT_{1A}$ receptors (Huguet et al. 1994, Taylor 1985) and enhances high affinity choline uptake into hippocampal synaptosomes (Kristofikova et al. 1992).

A GbE preparation (EGb761) is approved in Germany and other countries for the treatment of disturbances of cerebral function related to dementia syndromes. Several clinical trials have been conducted in patients with dementia, including AD (Le Bars et al. 1997, Maurer et al. 1997, Weitbrecht and Jansen 1986, Hofferberth 1994) and mixed populations with patients suffering from either vascular dementia or dementia of the Alzheimer type (Haase et al. 1996, Kanowski et al. 1996). Doses used in these trials are either 120 or 240 mg/day. Results have varied with some earlier trials showing outcomes in favor of EGb 761. However, a recent, 6-month-long placebo controlled trial involving over 500 patients with mild to moderate AD showed no differences between 240 mg/day, 120 mg/day and placebo in cognitive or global outcomes (Schneider et al. 2005). A long-term prevention trial involving over 2,500 patients followed over 3 years for the development of dementia is ongoing.

## Anti-Excitotoxic Therapies

### Calcium Channel Blockers

The process of neuronal death in aging and in AD may be mediated by an increase in intracellular free calcium, which activates various destructive enzymes (such as proteases, endonucleases, and phospholipases) and disrupts intracellular processes. Neuronal calcium levels are regulated by specific proteins known as L-type calcium channels. Abnormal regulation of these channels is believed to be an early step in the AD process. In principle, blocking the increase in intracellular free calcium may retard these mechanisms and thus slow progression of disease.

Three calcium channel blockers that have been tested in AD patients are nimodipine, a Bristol-Myers Squibb investigational compound, and MEM 1003. In one trial, the low-dose nimodipine group (30 mg t.i.d.) showed less deterioration on several memory tests over a 10−12-week treatment period than the placebo or high-dose nimodipine (60 mg t.i.d.) group (Tollefson 1990). Another trial showed significant cognitive effects for nimodipine compared with dihydroergotoxin mesylates ("Hydergine") and placebo (Kanowski et al. 1988). It is not clear, however, whether study subjects fulfilled criteria for possible AD.

Although nimodipine has shown some benefits in AD clinical trials (Fritze and Walden, 1995), a meta-analysis of dementia trials concluded that although there may be evidence for short-term benefits, there was no justification for its use as a long-term anti-dementia agent (López-Arrieta and Birks 2002). Nimodipine is used for cognitive impairment and dementia in several continental European countries, but has not been approved by the FDA for dementia.

MEM 1003 has a longer elimination half-life than nimodipine may have little or no effect on blood pressure at highest dose tested (180 mg b.i.d.), and also may have cerebral selectivity in that it may improve cerebral blood flow (Lowe et al. 2006). In late 2005, a phase II study in patients with mild to moderate AD was initiated.

### Idebenone

Idebenone is a benzoquinone derivative that is hypothesized to improve brain metabolism and protect cell membranes against lipid peroxidation. A placebo-controlled trial that randomized 300 patients for a period of 6 months, found a mild improvement in cognitive function (Weyer et al. 1997). A second trial that randomized 450 patients for a 2-year period, showed an improvement during the first year of treatment with some decline in effect in the second year (Gutzmann and Hadler 1998). However, a third large trial which randomized 536 subjects over one year showed no improvements in cognition, global assessments, or ADL (Thal et al. 2003). It was concluded that this drug failed to slow cognitive decline in AD.

### Propentofylline

Propentofylline blocks the uptake of adenosine and inhibits phosphodiesterase which appears to inhibit the production of free radicals and reduce the activation of microglial cells. A Cochrane review analyzing results from several clinical trials concluded that there is limited evidence that propentofylline might benefit cognition, global function and ADL of people in AD.

## Combined Therapies

The combination of drugs with different mechanisms of action may be more effective than individual medications

alone. As a past example, choline precursors were combined with ChIs but with no evident augmenting effect. One clinical trial addressed the effect of adding memantine or placebo to ongoing donepezil therapy in people with moderate-severe AD, showing significant benefit of memantine vs placebo but cannot be interpreted as an additive effect (Tariot et al. 2004). There has not been a direct comparison of memantine with a AChI and the combination. Most practicing clinicians would take a dim view of combining two ChIs since their actions are additive. Physicians should be skeptical also of combining available anti-inflammatories or hormones with ChIs: first because of the lack of demonstrated efficacy of these drugs, and second because of the additive adverse events, especially gastrointestinal events. Clinical experience suggests that the combination of ChIs with vitamin E or *ginkgo biloba* does not appear to worsen adverse effects, but there is no efficacy evidence for this practice either, nor of the clear efficacy of the latter drugs. Selegiline has been combined with ChIs in small pilot studies suggesting an additive effect but this remains to be unequivocally demonstrated. Additional strategies employing combination therapies in AD are likely to emerge.

## Summary

There is an explosion of clinical trials for treatment and prevention of AD, many addressing new mechanisms of action based on recent research. It is too soon to predict which, if any, of these approaches will bear fruit. The prospects for cognitive enhancement in elderly patients are encouraging. As we await results from these trials, currently approved therapies remain part of the therapeutic portfolio for the foreseeable future. ChIs are the best proven efficacious symptomatic treatments for AD. They provide consistent effects in many patients with mild-to-moderate dementia, and have become the current pharmacological standard of treatment. Memantine is effective in moderate to severe AD and is associated with very mild adverse events. Vitamin E, selegiline, and ginkgo biloba are all available for use, but there is little evidence for efficacy.

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CHAPTER

# 108 Complementary and Alternative Treatments in Psychiatry

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Consumer interest in complementary and alternative medicine (CAM) has been driven by concerns about medication side effects, nonresponse to standard medications, and the high cost of prescription medications. The scientific community is beginning to realize that CAM approaches can influence many of the regulatory systems involved in the pathogenesis of psychiatric disorders, providing new avenues for treatment. The Sequential Treatment Alternatives to Relieve Depression (STAR*D) trial highlighted the benefits and limitations of combining or switching antidepressants (Rush et al. 2006). Treatment resistance is an indication of our incomplete understanding of the neurobiological basis of mood disorders. Paradigms for treating affective disorders are expanding beyond monoamine neurotransmission models to incorporate other regulatory systems. The explosion of information about the effects of immune function, autonomic nervous system balance, neuroendocrine systems, antioxidants (cellular defense and repair), the arachindonic acid cascade, second messengers, and gene activation opens the way for new therapeutic approaches including CAM treatments.

Many of the medicines used today derive from botanicals known to herbalists for centuries. In addition to herbal medicines, nutrients, and nootropics, CAM encompasses prevention, optimal nutrition, exercise, mind–body practices, and balancing of work and play (Muskin 2000). CAM treatments are particularly useful for patients who have incomplete responses or undesirable side effects with prescription medications. Misunderstanding leading to misuse of natural medicines and the potential for contaminants in unregulated herbal preparations can cause serious health hazards and herb/drug interactions (Ko 1998, Schaumburg and Berger 1992, De Smet 2002). To optimize the benefits and minimize the risks of CAM physicians need a working knowledge of herbs and other nutritional supplements (Brown and Gerbarg 2000).

This chapter focuses on CAM treatments supported by scientific evidence for mechanisms of action, clinical trials demonstrating safety and efficacy, and observations of benefit from the authors' clinical experience. In some cases, the data are limited but this should not deter physicians interested in exploring the widest range of therapeutic possibilities from considering these substances for appropriate patients. Rigorous controlled studies have been completed for many agents. Potentially worthwhile compounds have not attracted the large research investments necessary to obtain FDA approval. As more clinicians discover the benefits of CAM, interest in supporting larger controlled studies will develop. Although CAM may include any treatment that is not used by the majority of allopathic physicians, this discussion will selectively cover treatments that have practical uses in psychiatry: herbs, nutrients, vitamins, nootropics, neurotherapy, and mind–body practices such as yoga and meditation. The first section of this chapter explores mood disorders, depression and bipolar. The second section covers anxiety and stress-related disorders: generalized anxiety disorder (GAD), panic disorder, insomnia, post-traumatic stress disorder (PTSD), and obsessive–compulsive disorder (OCD). The third section reviews disorders of attention, memory, and cognition: age associated memory impairment

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(AAMI), Alzheimer's Disease (AD) and other dementias, ischemia, stroke, traumatic brain injury (TBI), attention deficit disorders (ADD) and attention-deficit hyperactivity disorder (ADHD) and learning disabilities. The fourth section covers, side effects, drug interactions, legal–ethical issues, product variability and quality. Guidelines for safely using reliable products (Tables 108–1–108–3), physician education, and resources for updating information are provided.

## Mood Disorders

### St. John's Wort (SJW) (*Hypericum perforatum*)

In the US, SJW became popular after publication of a 1996 meta-analysis of 23 randomized depression trials (Linde et al. 1996) in which 13 studies showed that 55% of patients on SJW improved compared to 22% on placebo, with a side effect rate similar to placebo. This meta-analysis noted that the studies were limited by vague definitions of depression, less rigorous methodology, unclear outcome measures, low doses of the comparison antidepressants, and short length of trials. A 1999 meta-analysis using more stringent criteria concluded that SJW was similar in efficacy to low dose TCAs in treatment of mild to moderate major depression (Kim et al. 1999). Another review found evidence that SJW yielded higher rates of improvement than placebo but lower rates than TCAs, even at suboptimal starting doses (Gaster and Holroyd 2000).

SJW 500 mg/day was comparable to fluoxetine 20 mg/day in mild/moderate depression ($N = 240$) in a double-blind randomized control trial (DBRCT) (Schrader 2000). In a 6-week double-blind, randomized, multicenter (DBRMC) trial, 209 hospitalized patients with severe major depression given either hypericum LI 160 (Kira) (a standardized preparation of SJW) 600 mg thrice a day (*ter in die* (t.i.d.)) or imipramine 150 mg/day. Hamilton Rating Scale for Depression (Ham-D) scores at the end of the trial were similar for both groups. There were fewer side effects with SJW. The study indicated that treatment with SJW requires higher doses (1800 mg/day) and takes longer to achieve response (6–12 weeks) than with imipramine (3–6 weeks) (Vorbach et al. 1997). *The journal of the American Medical Association* (JAMA) published a double-blind randomized multi-center

**Table 108–1 Treatment Guidelines for Disorders of Mood, Anxiety, and Sleep**

| CAM | Clinical Uses | Dose | Side Effects and Drug Interactions |
|---|---|---|---|
| SJW (*Hypericum perforatum*) | Depression mild–mod | 300–600 mg t.i.d. | Nausea, heartburn, loose bowels, jitteriness, insomnia, fatigue, bruxism, phototoxic rash, mania in bipolar. Affects CYP 450 and Pgp: ↓ digoxin, warfarin, indivir, cyclosporine, theophyline, birth control pills. D/C: surgery, pregnancy |
| S-adenosyl-L-methionine (SAMe) | Depression<br>Arthritis<br>Fibromyalgia<br>Parkinson's<br>Liver diseases | 400–1,600 mg/day, 800–1,200 mg/day, 1,600–4,800 mg/day, 1,200–1,600 mg/day | Mild nausea, loose bowels, activation, anxiety, mania in bipolar, headache, occasional palpitations |
| *Rhodiola rosea* | Depression | 150–900 mg/day | Agitation, insomnia, anxiety, headache, palpitations, chest pain |
| B-vitamins and Bio-Strath | Depression | $B_{12}$ 1,000 µg/day<br>B-complex | Rare: activation |
| Inositol | Depression | 12–20 g/day | Gas, loose bowels, mania |
| Omega-3-fatty acids | Bipolar | 6–10 g/day | Belching, loose stools |
| Choline | Mania | 2,000–7,200 mg/d | Excess doses: depression |
| Kava (*Piper methysticum*) | Anxiety, insomnia | 100 mg standardized extract (70 mg kavalactones) t.i.d. | GI, allergic skin, headache, photosensitivity. Occasional: ↓ energy, drowsiness, tremor, restlessness, ↓ effects of levodopa, hepatitis, liver failure. D/C: pregnancy Toxic dose > 240 mg kavalactones/day |
| Passionflower (*Passiflora incarnata*) | Anxiety | | |
| Chamomile (*Matricareia recutita*) | Minimal sedative | | Ragweed family—allergic reactions. D/C: pregnancy |
| Lemon balm (*Melissa officianalis*) | Anxiety | | No serious side effects |
| Garum Amoricum | Anxiety | 2–3 pills/day | None |
| Valerian (*Valerian officianalis*) | Sleep | 450–900 mg h.s. | Occasional GI, headaches, minimal hangover on high doses > 600 mg. D/C: pregnancy, hepatic disease |
| Melatonin | Sleep | 1–12 mg h.s. | Occasional agitation, abdominal cramps, fatigue, dizziness, headache, vivid dreams. D/C: pregnancy |

**Table 108–2 Treatment Guidelines for Hormonal Conditions and Sexual Disorders**

| CAM | Clinical Uses | Dose | Side Effects and Drug Interactions |
|---|---|---|---|
| Evening primrose oil (*Oneothera Biennes*) | PMS No evidence of efficacy | | GI, headaches. ↑ risk seizures with phenothiazines |
| Magnesium | PMS | 360 mg/day | |
| Calcium | PMS | 600 mg b.i.d. | Mild GI. Take with meals to avoid stone formation |
| B-vitamins, Minerals | PMS | | Limited information. No side effects |
| Carbohydrate | PMS | PMS Escape | Study needs replication |
| L-tryptophan | PMDD | 2,000 mg t.i.d. | Pharmaceutical grade by prescription only is safe |
| Chaste tree, chasteberry (*Vitex agnus-castus*) | PMS, menopause, female infertility, hyperprolactinemia | 40 mg/day standardized extract | No significant side effects. Rarely: allergic reaction, dry mouth, headache, nausea. D/C: pregnancy |
| Soy | Hot flashes | 20–60 g/day | Best results with whole soy or whole food |
| Red clover (*Trifolium pratense*) | Menopausal sxs, estrogenic effects | 500 mg/day, 40 mg isoflavones | D/C: pregnancy, bleeding disorders, estrogen-sensitive tumors |
| Black cohosh (*Cimifuga racemosa*) | Menopausal sxs, hot flushes, PMS, dysmenorrhea | 8 mg/day standardized extract | High level of safety. Minimal side effects: GI, ↓ BP, headache, dizziness. D/C: pregnancy, estrogen sensitive tumors, antihypertensive meds |
| Licorice (*Glycyrrhiza glabra*) | Adrenocortical steroid type effect | | Headache, lethargy, sodium and water retention, potassium depletion, hypertension. D/C: diuretics |
| Dong Quai (*Angelica sinensis*) | Menopausal sxs | | Rigorous studies needed. Used in combination with other herbs. Photosensitivity. D/C: anticoagulants |
| Hops (*Humulus lupulus*) | Estrogenic effects | | Inadequate evidence of efficacy. Allergic reactions. May affect CYP450. Fatigue. D/C: pregnancy |
| Blue cohosh (*Caulophyllum thalictroides*) | Menopausal sxs | | No adequate scientific studies. May interact with antihypertensive meds. Neonatal stroke. |
| Dihydroepiandosterone (DHEA) | Menopause, osteoporosis | 25–100 mg/day | More studies are needed |
| Skullcap (*Scutellaria lateriflora*) | | | No adequate studies. Possible adverse effects on liver function. Avoid with hepatic insufficiency |
| *Rhodiola rosea* | Menopause, amenorrhea | 450–600 mg/day | Activation, anxiety, insomnia, vivid dreams, headache, palpitations, chest pain |
| Saw palmetto (*Serenoa repens*) | BPH | 320 mg/day | Mild occasional GI, constipation, loose stools |
| Pygeum (*Pygeum africanum*) | BPH | 75–150 mg/day | None reported |
| Stinging nettle (*Urtica dioica*) | BPH | 300 mg/day | Mild GI, allergic reactions. May ↑ effects of diuretic and antihypertensive meds |
| Yohimbine (*Pausinystalia yohimbe*) | Erectile dysfunction | 18–42 mg/day | Anxiety, dizziness, chills, headache, ↑ BP, ↑ heart rate, insomnia, nausea bronchospasm, vomiting. D/C: HT, cardiac, renal, liver, psychotropic meds |
| Asian ginseng (*Panax Ginseng*) | Erectile dysfunction | 100 mg t.i.d. | Insomnia, GI, mania, abuse potential. D/C: MAOIs, hypoglycemic meds, pregnancy |
| *Ginkgo biloba* | Erectile dysfunction | 120 mg b.i.d. | GI. D/C: anticoagulants, pregnancy |
| Arginine | Erectile dysfunction | | May predispose to herpes |
| Muira Puama (*Ptychopetalium guyanna*) | ↑ libido, erections, arousal, orgasm in men and women | 1,000–1,500 mg/day | Promising. Needs further study. Works best with ginkgo and other sexual enhancers. |
| Maca (*Lepidium myenii*) | ↑ erections, menopause, fertility | 6 pills/day | No toxicity. D/C: estrogen sensitive tumors, prostate cancer, endometriosis |

PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder; BPH, benign prostatic hypertrophy; GI, gastrointestinal side effects; BP, blood pressure; HT, hyper-tension; sxs, symptoms.

**Table 108–3 Treatment Guidelines for Cognitive Enhancers**

| CAM | Clinical Uses | Dose | Side Effects and Drug Interactions |
|---|---|---|---|
| Galantamine | AD | 16–32 mg/day | Mild nausea, GI |
| Huperzine | AD, TBI, CVD | 100–400 µg/day | Rare: mild nausea |
| Centrophenoxine | AD, TBI | 500–2,000 mg/day | Minimal. When combined with other cholinergic agents: headache, muscle tension, insomnia, irritability, agitation, facial tics |
| Acetyl-L-carnitine | AD—slowed progression, TBI and CVA | 1,500 mg b.i.d. | Mild gastric upset. Take with food. |
| CDP-choline | TBI | 1,000–2,000 mg/day | None significant |
| S-adenosyl-L-methionine (SAMe) | AD, dementia, TBI Parkinson's | 800–1,600 mg/day 400–4,000 mg/day | Mild occasional GI, agitation, anxiety, insomnia; rare palpitations. Mania in bipolars. Take 30 min before breakfast and lunch |
| Picamilon | TBI, CVA, toxic brain lesions | 50 mg b.i.d.–up to 100 mg t.i.d. | High dose: hypotension. Not allergenic, carcinogenic or teratogenic in 6-month test. |
| Idebenone | CVD, AD, TBI | 270–900 mg/day | |
| Vinpocetine | CVD, TBI | 10 mg t.i.d. | Rare: nausea, low BP |
| *Rhodiola rosea* | Cognitive enhancement, memory TBI | 150–600 mg/d | Activation, agitation, insomnia, jitteriness, mania. Rare: ↑BP, angina, bruising. Avoid in bipolar I. Take 20 min before breakfast and lunch. |
| *Ginkgo biloba* | AAMI, MCI, AD, CVD | 120–240 mg/day | Minimal, headache, ↓ platelet aggregation. D/C prior to surgery |
| Ginseng | Dementia, neurasthenia | 400–800 mg/day | Activation GI, anxiety, insomnia, headache, tachycardia, ↓ platelet aggregation |
| Kava (*Piper methysticum*) | Anxiety | 70–140 mg/day kava lactones | Sedation, dependency, hepatitis, liver failure. Can be toxic at doses > 240 mg/day |
| Racetams | Post-stroke aphasia, dyslexia | aniracetam 750 mg b.i.d. | Minimal. Rarely: anxiety, insomnia, agitation, irritability, headache |
| L-deprenyl | TBI | 10–15 mg/week | Take 2.5 mg 5 days a week. Higher doses > 10 mg/day may cause MAOI effects |
| B-vitamins, Bio-Strath | TBI | $B_{12}$ 1,000 µg/day B-complex | None |

AD, Alzheimer's disease; TBI, traumatic brain injury; CVA, cerebrovascular accident; CVD, cerebrovascular disease; AAMI, Age Associated Memory Impairment; MCI, Mild Cognitive Impairment; BP, blood pressure; GI, gastrointestinal side effects.

placebo-control trial (DBRMCPC) study of 20 patients with major depression using 900 mg/day Kira (low dose). At 4 weeks nonresponders got 4 weeks of Kira at 1,200 mg. The study concluded that Kira was no better than placebo (Shelton et al. 2001). However, placebo response rate of 19% raises the question that the patients were more severely depressed or treatment resistant. This study showed no separation from placebo for SJW (900–1,500 mg/day) or sertraline (50–100 mg/day) possibly due to subtherapeutic dosing in severely depressed patients (Davidson and the Hypericum Depression Trial Study Group 2002). In a 6-week DBRCT, 300 mg t.i.d. hypericum extract WS®5570 was as effective as paroxetine 20 mg/day in a study of 251 adult outpatiens with severe depression (17-item HAM-D ≥ 22 at baseline). Those who did not show at least 20% improvement after 2 weeks were increased to 600 mg t.i.d. WS®5570 or 40 mg paroxetine with improved response. Hypericum extract was better tolerated than paroxetine (Szegedi et al. 2005). A randomized clinical trials (RCT) of 135 patients with major depression (mean HAM-D = 19.7± 3.2) compared SJW 900 mg/day with fluoxetine 20 mg/day and placebo. A greater numerical reduction occurred in mean HAM-D scores in the SJW group than in the fluoxetine and placebo groups, however, these were not statistically significant differences (Fava et al. 2005). A 6-week DBRMCPC trial of 332 outpatients with HAM-D ≥ 18 compared hypericum extract WS®5570 600 mg/day ($p < 0.0001$), WS®5570 600 mg twice in a day (*bis in die* (b.i.d.)) ($p < 0.0001$), and placebo. Response rates (> 50% reduction in HAM-D) were 69.8% for 600 mg/day, 61.3% for 600 mg b.i.d., and 31.1% for placebo. Remission rates (HAM-D ≤ 7) were 32.8% for 600 mg/day ($p < 0.004$), 40.3% for 600 mg b.i.d. ($p < 0.001$), and 14.8% for placebo (Kasper et al. 2006).

The "side-effect profile" of SJW at higher doses is similar to selective serotonin reuptake inhibitors (SSRIs). Common side effects with SJW are nausea, heartburn, loose bowels, jitteriness, insomnia, and fatigue. High doses may cause sexual dysfunction and bruxism. Phototoxic rash occurs in less that 1% of people taking the usual dose (900 mg/day) but may be more frequent at higher doses. Nierenberg et al. (1999) reported four possible cases of SJW-induced mania in bipolars. SJW causes slight reuptake inhibition of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (Muller et al. 1998), and a change in monocyte cytokine production of interleukin 6 (leading to decreased corticotrophin-releasing hormone) (Thiele et al. 1994). There have been six cases of serotonin syndrome reported with SJW in combination with both SSRIs and nefazodone (Anonymous 2000, Gelenberg 2000). Whether this is due to the weak serotonin effect of SJW or other factors is not yet clear (DeMott 1998). Some authors have suggested that SJW is effective in 50−70% of patients with mild depression, particularly if wintertime seasonal affective disorder (SAD) is present (Cott and Fugh-Berman 1998, Hansgen et al. 1994, Wheatley 1999).

SJW has serious potential medication interactions. Digoxin levels decreased by 28% in healthy volunteers given SJW versus a 9% drop in the placebo group (Jonte et al. 1999). Researchers hypothesize that SJW induces cytochrome P450 3A4 and 1A2 intestinal wall P-glycoprotein (resulting in gut loss of digoxin). SJW can lower levels of warfarin, HIV protease inhibitors, and reverse transcriptase inhibitors (Piscitelli et al. 2000, Ruschitzka et al. 2000). SJW's ability to induce hepatic enzymes can result in lower levels of cyclosporine (which has caused transplant rejection), theophylline, and other drugs. Breakthrough bleeding has been reported in women on birth control pills who take SJW. Anesthesiologists anecdotally report changes in heart rate and blood pressure, particularly in patients taking SJW, ginkgo, and ginseng. These herbs should be discontinued 2−3 weeks before surgery (Voelker 1999). A review of adverse effects of SJW from 35 DBRCTs found that the reported rates of side SJW effects were similar to placebo and lower than those of comparison antidepressants (Knüppel and Linde 2004). Evidence suggests that Hypericum extracts are well tolerated and safe if taken under the guidance of a physician who is aware of the potential risks, clearly informs the patient, and monitors the patient for changes in medications.

Most independent analyses of SJW brands report the amount of hypericin and/or hyperforin, but do not test for quality or activity. Although a concentration of hypericin 0.3% of the extract is the usual standard, the measurement of hyperforin 0.3−0.5% may be more relevant. Two double-blind randomized placebo-control trial (DBRPC) studies suggest that clinical response rates and changes in brain waves are related to the concentration of "hyperforin", not "hypericin" (Muller et al. 1998, Schellenberg et al. 1998). Independent testing of SJW brands by ConsumerLab.com found that 14 out of 21 met their requirements for having the amount of active compound claimed on product labels and a minimal amount of cadmium (a carcinogenic contaminant) (ConsumerLab.com 2001). Another independent study by www.vitacost.com found that only two out of eight brands contained adequate hyperforin (Schardt 2000)]. Double-Blind Placebo-Controlled (DBPC) clinical trials and studies showing activity *in vitro* for particular products provide more compelling evidence of efficacy. In 2000, the Boston Globe sent brands of SJW to two labs for testing. Two of the brands, Quanterra and Nature Made, showed significant ability to block serotonin re-uptake in animal cells *in vitro*. Research trials have shown Kira (LI 160), Remotiv (ZE 117), STW3, and WS®5570 to be effective. In the authors' clinical experience Natures Way Standardized Extract (Perika), Kira, Quanterra, and Nature Made are reliable brands.

## S-Adenosyl-L-Methionine, (SAMe), Adometionine, AdoMet

SAMe has been widely used in Europe for over 20 years, primarily for treatment of depression, arthritis, and liver disease. Tested in more than 80 clinical trials involving over 24,000 people, it was approved as a nutraceutical by the FDA in 1998. SAMe is a prescription medication in some countries and is sold over-the-counter in others. Knowledge of the biochemistry of SAMe is necessary to understand its multiple therapeutic effects. The US Department of Health and Human Services Agency for Healthcare Research and Quality (2002) based on a search of 25 biomedical databases, concluded that treatment with SAMe was equivalent to standard pharmacotherapy for depression and osteoarthritis. It was not possible to pool the data on liver disease because the studies were too diverse. However, SAMe was found to be more effective than placebo in reducing bilirubin and pruritis in intraheptic cholestasis and cholestasis of pregnancy.

SAMe is a physiologically essential molecule in all living cells. The human diet supplies only part of the body's needs for SAMe, generated by *de novo* synthesis from methionine and adenosine triphosphate (ATP); the liver is the largest producer (3 g/day). Oral SAMe supplementation is the easiest way to boost SAMe levels. Though most concentrated in brain and liver, SAMe is an active metabolite in all tissues of the body and is crucial for three central metabolic pathways involving more than 200 different biochemical reactions (Figure 108–1): *transmethylation* (donation of methyl groups, $CH_3$), *transsulfuration* (donation of sulfur), and *transaminopropylation* (donation of aminopropyl moieties). Transmethylation increases 5-HT, DA, and NE levels (Otero-Losada and Rubio 1989a, 1989b), probably contributing to antidepressant activity (Czyrak et al. 1992, Fava et al. 1990). Donation of methyl groups protects catecholamine neurons. SAMe improves nerve cell membrane uptake of phospholipids for a more fluid lipid bilayer, enabling the coupling of protein receptors to second messengers and enhancing transmission of impulses by neurons (Bottiglieri 1997). Methyl groups protect DNA from attack by carcinogens and reduce homocysteine (Finkelstein 1998), a major risk factor for heart attack and stroke. SAMe is necessary for synthesis of the most important antioxidant, glutathione, as well as secondary antioxidants, cysteine and taurine (Colell et al. 1997, Evans et al. 1997)]. Through the transsulfuration pathway, SAMe stimulates proteoglycan synthesis for cartilage regeneration in arthritis (Barcelo et al. 1987). Transsulfuration and aminopropylation (generation of polyamines) contribute to analgesic properties, antiinflammatory action, and protection of gastrointestinal mucosa. SAMe methylation pathways require $B_{12}$ and folate as cofactors (see Figure 108–1) (Crellin et al. 1993). $B_{12}$ (1,000 µg/day), folate (800–1,000 µg/day), and $B_6$ (50–100 mg/day) may enhance the antidepressant effect of SAMe. Low levels of SAMe in cerebral spinal fluid, red cell folate deficiency, high homocysteine, and low monoamine metabolites (5-HT, NE, DA) were found in 24 out of 46 patients hospitalized for severe depression (Bottiglieri et al. 2000).

When SAMe was discovered in 1952 (Cantoni 1952), there was no stable oral preparation (Stramentinoli 1987). Early studies, therefore, used intravenous (i.v.) and intramuscular (i.m.) formulations. Agnoli et al. (1976) published the first clinical study demonstrating antidepressant effects. Over the past 40 years more stable preparations, resistant to oxidation and gastric enzyme degradation (enteric coated, with demonstrated bioavailability and clinical efficacy) have been developed. Lower than normal levels of SAMe are found in cerebral spinal fluid in some patients with depression, AD, dementia, Parkinson's disease treated with levodopa, disorders of folate metabolism, and other illnesses (Bottiglieri et al. 1990, Bottiglieri and Hyland 1994). SAMe was found to be a safe and effective treatment

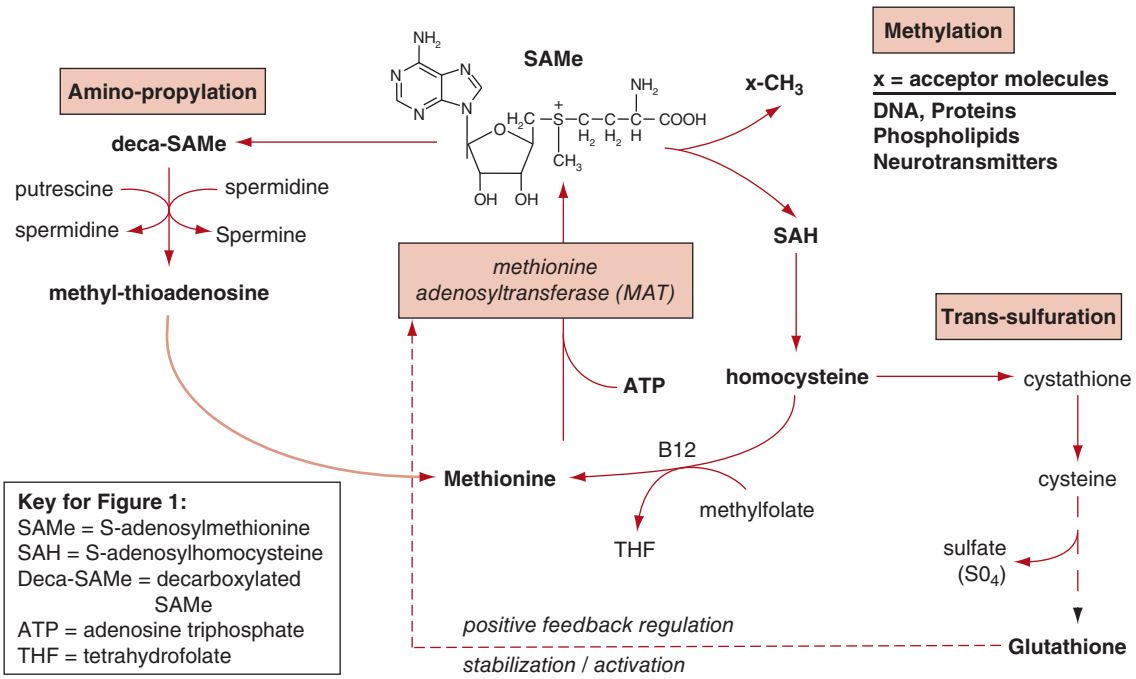



**Figure 108–1** *SAMe: Central metabolic pathways.*

for depression in 16 uncontrolled trials (660 patients), 13 DBRPC trials (535 patients), and 19 controlled DB trials, comparing it to other antidepressants including imipramine, amitriptyline, clorimipramine, nomifensine, minaprine, and desipramine (1,134 patients) (Bressa 1994, Delle Chiale and Boissard 1997, Brown et al. 2000), and three trials using SAMe to augment response to imipramine (Berlanga et al. 1992, Friedel et al. 1989). All but one study showed that SAMe was more effective than placebo and equivalent to the comparison antidepressant for major depression. The study that did not find SAMe superior to placebo used an unstable form of SAMe and had a high placebo response rate (Fava et al. 1992). Two recent DBRMC controlled efficacy and safety trials (MC3 and MC4) compared SAMe with imipramine for major depression. Depression was evaluated by several measures including HAM-D (21 item) ≥ 18. In MC3 281 patients were given oral mediciation, randomized to either SAMe 1,600 mg/day or imipramine 150 mg/day for 42 days. The MC4 study compared 295 patients on SAMe 400 mg/day i.m. to imipramine 150 mg/day through the mouth (*per os* (p.o.)) for 28 days. In MC3 and MC4 the antidepressant effect of SAMe was equal to imipramine, but the SAMe treated group had fewer side effects (Delle Chiale et al. 2000a, 2000b, Di Padova et al. 2000).

SAMe was successfully combined with psychoactive medications in a 6-month study that included 350 patients on tricyclic antidepressants (TCAs), 500 on benzodiazepines, 60 on monoamine oxidase inhibitors (MAOIs), 445 on anticonvulsants, and 18 alcoholic patients on antidepressants or anticonvulsants. No adverse effects were reported. Patients on SAMe/TCA combination responded in 7−10 days as compared to the 10−15-day period for TCA-only group. Forty-eight of the SAMe/imipramine patients improved on 30% lower doses of imipramine. In all cases, SAMe reversed or prevented the elevation of gamma-glutamyl-transpeptidase (GGT), an indicator of liver toxicity, that occurred in the patients taking MAOIs or anticonvulsants and in the alcoholic group (Torta et al. 1988). In a DBRPC study of 63 outpatients with moderate to severe major depression, the imipramine/SAMe group improved more rapidly and reduced their benzodiazepine use in comparison to the imipramine/placebo group. By Day 14, the groups were comparable (Berlanga et al. 1992). In two well-designed, DBRPC studies, SAMe was rapidly effective in "postpartum depression" (Cerutti et al. 1993) and "postmenopausal depression" (Salmaggi et al. 1993). In a 4-week open study, 48 patients with depression secondary to physical illnesses (40 were medically hospitalized) showed a 50% decrease in depression ratings and tolerated SAMe well (Criconia et al. 1994). Some reports describe dramatic responses to SAMe even after patients have failed or been unable to tolerate prescription antidepressants (Bell et al. 1994, Criconia et al. 1994, Kagan et al. 1990, Rosenbaum et al. 1990).

Studies show that SAMe improves liver function, reverses physical symptoms and biochemical markers (abnormal liver function tests) of alcoholic and infectious hepatitis and cirrhosis. It has also been used to dissolve gallstones (Frezza et al. 1990, Friedel et al. 1989, Lieber 1999, Milkiewicz et al. 1999, Osman et al. 1993). Mato et al. (1999) reported a 2-year, DBRPC study of 123 patients with alcohol-induced liver cirrhosis. In Child's Class A and B cases, SAMe 1,200 mg/day p.o. increased the rate of survival and delayed liver transplantation. Preliminary studies support the use of SAMe for depression complicating alcohol and opiate withdrawal (Agricola et al. 1994). Methamphetamine depletes SAMe and DA levels in rat brain (Cooney et al. 1998). SAMe may be useful to relieve post methamphetamine depression and drug craving.

In general, SAMe side effects are mild and usually transient: headaches, anxiety, agitation, insomnia, loose bowels, upset stomach and, occasionally, palpitations. SAMe does not cause weight gain or sexual dysfunction. SAMe is

contraindicated in patients with a personal or family history of bipolar disorder because SAMe can induce mania (Carney et al. 1987, 1989, Kagan et al. 1990). There is no evidence that SAMe interacts with other drugs, affects cytochrome P450 metabolism, or displaces other drugs from protein binding. There are no clear cases of serotonin syndrome even when SAMe is combined with prescription antidepressants, including SSRIs and MAOIs. Nevertheless, until more information is available, SAMe and MAOIs should only be combined under close medical supervision. No teratogenic (Cozens et al. 1988) or mutagenic activity has been found *in vitro* or in animals (Pezzoli et al. 1987). The amount of SAMe passed to infants through breastfeeding is unknown. Infants normally have SAMe levels three to seven times higher than adult levels (Surtees and Hyland 1989). Therefore, an infant would probably not be harmed by the amount of SAMe in breast milk. Nevertheless (as with prescription antidepressants), no definitive prospective studies are available to rule out the possibility of adverse effects in infants.

The usual dosage of SAMe is 400 mg/day for minor depression and 800−1,600 mg/day for major depression. Higher doses may be needed for severe treatment-resistant depression and in neurological disorders such as Parkinson's disease. SAMe is best absorbed on an empty stomach. Starting with 200 mg 30 min before breakfast and 30 min before lunch minimizes the stimulation, which some patients report in the first few weeks of treatment. This can be switched to 400 mg before breakfast after a few days. The dose can be raised by 200−400 mg every 3−7 days. Patients notice an improvement in their energy level within 2 weeks. Starting with low doses and increasing more gradually in geriatric, medically ill, and anxious patients minimizes the risk of side effects. It is sometimes possible to treat a bipolar II patient whose mania is under good control with a mood stabilizer such as lithium or valproate by using lower starting doses (e.g., 100 mg four times a day (*quater in die* (q.d.)) or b.i.d.), smaller increases, and careful monitoring.

SAMe tends to oxidize rapidly when exposed to air. The manufacturing and packaging of SAMe tablets is critical to assure full potency. Unfortunately, few companies test their products for self life. Bargain brands may lose 50−100% potency before use. Tablets are best preserved in individual blister packs and should not be refrigerated. The table at the end of this chapter lists several brands of good quality. It is useful to consult ConsumerLab.com periodically for updated information on SAMe brands. Nonresponse to an appropriate dose of SAMe or the occurrence of excessive side effects are usually due to the use of a poor quality brand. Changing to a better brand and adding folate and B-vitamins may improve response. Physicians should become knowledgeable about SAMe in order to advise patients on its use to augment antidepressant treatment or as an alternative to traditional pharmacotherapy. Further research is needed to clarify SAMe's role as a first-line treatment in affective disorders (Brown et al. 2000).

## Rhodiola Rosea

The Section "Cognitive Enhancement" contains a complete discussion of the adaptogenic herb, *Rhodiola rosea. R. rosea* increases 5-HT, increases transport of tryptophan and 5-HT into the brain (Saratikov and Krasnov 1987b), and may reduce the breakdown of 5-HT by carboxy-O-methyl transferase (COMT) inhibition. One hundred and twenty-eight depressed patients were given 150 mg t.i.d. *R. rosea* or placebo. Two-thirds of those on *R. rosea* improved significantly (Brichenko and Skorokhova 1987, Saratikov and Krasnov 1987a, 1987b).

A DBRPC study of *R. rosea* as a mono-therapy for 89 adults who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Revised (DSM-IV-TR) criteria for mild to moderate depression (baseline HAM-D ranging from 12−31) found that those given a standardized extract of R. rosea produced by the Swedish Herbal Institute named SHR-5® 340 mg/day or SHR-5® 680 mg/day for 6 weeks showed significantly greater improvements in mean HAM-D compared to a group given placebo (Darbinyan et al. 2007). *R. rosea* is a useful activating agent to augment the treatment of depression, particularly for target symptoms of fatigue, apathy, psychomotor retardation, anhedonia, memory impairment, poor concentration, and loss of libido. Its use as a mono-therapy for mild to moderate depression warrants further study.

## Other Herbs for Mood Disorders

Lavendar (*Lavandula angusifolia*) significantly enhanced/accelerated antidepressant effect of 100 mg/day imipramine ($p < 0.0001$) in a 4-week DBRPB study of 45 outpatients with major depression (DSM IV-TR) mean baseline HAM-D ≤ 18 (Akhondzadeh et al. 2003).

Saffron (*Crocus sativa*) has been used for depression in traditional Persian medicine. An extract of the petal 15 mg b.i.d. was compared to fluoxetine in an 8-week pilot DBRCT of 40 outpatients with major depression (DSM-IV-TR) baseline HAM-D ≥ 18. *C. sativa* was equally as effective as fluoxetine in treating mild-to-moderate depression. Remission rate was 25% for both treatments (Akhondzadeh et al. 2006). Comparison of petal of *Crocus sativus* and fluoxetine in the treatment of depressed outpatients; a pilot double-blind randomized trial). Previous studies had shown that the stamen of *C. sativa* had antidepressant effects in mild-to-moderate depression greater than placebo and comparable to imipramine and fluoxetine (Akhondzadeh et al. 2004, 2005, Noorbala et al. 2005). This study focused on the petal as a more practical source of material because the stamen is used as one of the most expensive spices in the world. More long-term RCTs, are needed to validate the benefits of *C. sativa* petal as a treatment for depression.

A Chinese herbal compound, Jai-Wei-Xiao-Yao-San or Jia-Wey Shiau-Yai San (Free and Easy Wanderer Plus (FEWP)) or Kami-Shoyo-San in Japanese has been used in traditional medicine to relieve mood swings, PMS, and menopausal symptoms. It contains extracts of 11 medicinal herbs: *Bupleurum chinense, Scutellaria baicalensis, Zingiber officianale, Angelica sinensis, Gardenia jasminoides, Paeonia sufruticosa, Paeonia lactiflora, Atractylodes macrocephala, Poriae Cocos, Mentha haplocalyx, and Glycerrhiza uralensis*. FEWP has been studied as an adjunctive treatment with carbamazepine in bipolar disorder and as a monotherapy. In a 12-week DBRPC study of 87 unipolar and 62 bipolar depressed patients, those given FEWP showed significantly greater improvements on HAM-D, Montgomery−Åsberg Depression Rating Scale (MADRS), and Clinical Global Impression of Severity (CGI-S) compared to those on placebo (Zhang et al. 2006).

## Effects of Vitamins and Nutrients on Mood

Low levels of $B_{12}$ (cyanocobalamin) and folate have been associated with disorders of mood, memory, and cognition, particularly in depressed patients and the elderly (Bottiglieri 1996, 1997, Crellin et al. 1993). Studies have demonstrated that B-vitamins can improve mood and cognitive functions (Benton et al. 1995, 1997, Riggs et al. 1996). In a DBRPC study of 14 depressed geriatric inpatients on TCAs, 10 mg each of vitamins $B_1$, $B_2$, and $B_6$ improved depression and cognitive function (Bell et al. 1992). A study of 129 healthy adults given Vitamin C, Vitamin E, and seven B-vitamins at 10 times the US FDA recommended daily allowance for 1 year, resulted in significantly greater improvement in mood than in a placebo group. Higher serum levels of riboflavin ($B_2$) and pyridoxine ($B_6$) correlated with improved mood in men, while higher levels of thiamine ($B_1$) correlated with better mood in women. Improved mood correlated with levels of Vitamin E and biotin (B-vitamin associated with skin, nail and hair growth) regardless of gender (Benton et al. 1995). $B_{12}$ deficiency (associated with high methylmalonic acid) more than doubled the risk of severe depression in 700 disabled women over the age of 65 (Penninx et al. 2000). In a study of dietary folate and B vitamins, 121 out of 865 Japanese women developed postpartum depression. Consumption of riboflavin ($B_2$) in the third quartile decreased risk of postpartum depression (Miyake et al. 2006).

Low levels of folate have been associated with nonresponse to antidepressants (Fava et al. 1997, Lerner et al. 2006). In a DBRPC study, 127 women on fluoxetine 20 mg/day were given either folate 500 μg/day or placebo. In the fluoxetine/folate group, 94% of the women had a good response versus 61% in the fluoxetine/placebo group. In women treated with fluoxetine/folate, plasma folate increased and homocysteine decreased (Coppen and Bailey 2000). Low folate levels were associated with delayed response to fluoxetine in a study of 110 patients with major depressive disorder (MDD) (Papakostas 2006). Although further studies of antidepressant supplementation with folic acid would be useful, at this time it is reasonable to give folate 2 mg/day during acute treatment (Abou-Saleh and Coppen 2006) and 1 mg/day for maintenance.

Inositol (a vitamin in the $B_2$ complex) boosts cyclic adenosine monophosphate (AMP), a second messenger in neurons. Inositol 12−20 g/day has been superior to placebo in a series of randomized trials for depression (Benjamin et al. 1995a), panic (Benjamin et al. 1995b), and OCD (Fux et al. 1996) (see for review: Bender 2000). A study from the National Institute of Mental Health (NIMH) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP) compared the effects of antidepressant augmentation with lamotrigine, inositol, and risperidone for refractory depression in 66 bipolar patients. Differences in recovery rates with lamotrigine (24%), inositol (17%), and risperdidone (5%) did not reach statistical significance (Nierenberg et al. 2006). This suggests a possible role for inositol augmentation in bipolar depressed patients who do not respond to lamotrigine, who develop side effects (allergic rash or photosensitivity), or who cannot afford the high cost of lamotrigine. Gastrointestinal side effects include gas and loose bowels. Because a therapeutic dose requires at least six large inositol 650 mg pills t.i.d., compliance is a problem. In one case, mania was induced by 3 g/day.

Choline (a B-complex vitamin) reduced mania in a number of case reports and case series. A small case study of treatment-refractory, rapid-cycling bipolars who were taking lithium found that four out of six responded to the addition of 2,000−7,200 mg/day of free choline. The two nonresponders were also taking hypermetabolic doses of thyroid medication. Clinical improvement correlated with increased intensity of the basal ganglia choline signal as measured on proton magnetic resonance imaging (MRI). The effect of choline on depressive symptoms was variable (Stoll et al. 1996).

Acetyl-l-Carnitine ALCAR 500 mg b.i.d. was compared to amisulpride 50 mg t.i.d in a 12-week DBRPC study of 204 patients with pure dysthymia (DSM-IV-TR). Both groups showed improvement on HAM-D21 with no significant difference between groups. Improvements on Clinical Dementia Rating (CDRS), MADRS, and CGI were also similar between groups. ALCAR cause fewer side effects (Zanardi and Smeraldi 2006).

Essential polyunsaturated fatty acids (PUFAs) interact with biochemical pathways involved in mood regulation (Sublette et al. 2004). Some functions of PUFAs include: (1) membrane fluidity essential for neuronal responsiveness, (2) functioning of ion channels, receptors (including monoamine pathways), and enzyme systems, (3) gene expression, (4) second messengers, and (5) precursors to eicosanoids and prostaglandins. Arachadonic acid (AA) and docosohexanoic acid (DHA) account for 90% of PUFAs in brain tissue. Dietary supplementation with fish or soy oil increased heart rate variability (HRV) (indicator of increase vagal activity) in elderly patients. The effect was greater and more rapid with 2 g/day fish oil (Holguin et al. 2005). Eicosopentanoic acid, an omega-3 fatty acid, was added to ongoing antidepressant treatment in a DBPC 4-week study. Twenty patients with "breakthrough depression" given 2,000 mg/day eicosopentanoic acid showed significant improvement on HAM-D compared to placebo (Nemets et al. 2002). A DBRPC pilot study by Stoll et al. (1999) explored the possibility that omega-3 fatty acids (omega-3FAs) could improve bipolar disorder by inhibiting neuronal transduction pathways in a mechanism similar to that of lithium carbonate and valproate. Thirty bipolar patients, most of whom were on mood stabilizers, were randomized to placebo or omega-3FAs (6.2 g eicosopentanoic acid plus 3.4 mg DHA per day). Those given omega-3FAs showed significant reduction in symptoms and relapse rates. In another study, eight out of ten bipolar patients showed 50% or more decrease in depression scores when given 1.5−2.0 g eicosapentaenoic acid (EPA) (Osher et al. 2005). The addition of 1−3 g/day ethyl-EPA to standard treatment in a DBRCT of 75 bipolar patients significantly reduced depression (Frangou et al. 2006).

Studies of omega-3FAs for depression have been reviewed (Parker et al. 2006, Sontrop and Campbell 2006). Treatment with ≥ 1 g/day eicosopentanoic acid significantly improved depression in four out of seven DBRCTs. Variable findings may be due to the use of difference doses, proportions and preparations of EPA and DHA. To what extent clinical improvement depends upon co-administration of antidepressants or pretreatment levels of omega-3FAs remains to be determined. Although larger studies are needed to confirm the findings, overall evidence is adequate for the use of omega-3FAs to augment treatment

of depression and bipolar disorder. Omega-3FAs are one of the few interventions known to be safe and potentially beneficial to neural development during pregnancy and breast-feeding (Bourre 2006). Although doses of 1−2 g/day omega-3FAs have been shown to reduce depression ratings in bipolar patients, the authors (R.B. and P.G.) find that higher doses of 8−10 g day are more effective for mixed symptoms of mania and depression and for rapid cyclers. High doses may cause gastrointestinal distress.

### Yoga for Depression and Bipolar Disorder

Stress and sympathetic activation are associated with an increase in proinflammatory cytokines. Evidence suggests that vagal activity (parasympathetic activation) inhibits inflammation via cholinergic signaling (Pavlov and Tracey 2005, Saeed et al. 2005). The cholinergic antiinflammatory pathway inhibits local cytokine release by the release of acetylcholine from vagus nerve endings that binds to α7 receptors on macrophages and other cells in the reticuloendothelial system, preventing damage from excess cytokine production (Tracey 2005). The role of inflammatory response in the pathophysiology of depression has been reviewed (Raison et al. 2006). Central acting cytokines alter monoamine metabolism in emotion regulatory circuits, reward systems, and the hypothalamic-pituitary-adrenal axis (HPA) axis. Interventions that reduce stress, decrease sympathetic nervous system (SNS) activity, and increase parasympathetic nervous system (PNS) activity may be beneficial in treating depression. The proposed neurophysiological model for rapid activation of the PNS by yoga breathing leading to widespread effects on peripheral and central nervous system (CNS) is presented in the section on anxiety disorders below. Literature on yoga for depression is of mixed quality and often difficult to interpret. In part of this is due to the reluctance of some schools of yoga to divulge details of their practices outside of their training settings. Reluctance may stem from a sense of sacredness attached to the practices, the tradition that the yoga teacher must impart wisdom, and concern that without proper training some practices may cause harm. While this protectiveness toward sacred practices is understandable, it can impede research that would provide evidence of efficacy (see for reviews of yoga and depression: Brown and Gerbarg 2005a, 2005b). Yoga is a comprehensive program that integrates yoga knowledge with physical and mental practices in the context of an individual relating to a teacher and a group. Studies of isolated componenets may not capture the combined effect. "Yoga for Depression" by Weintraub (2004) is an instructive example of the clinical integration of yoga practices for depressed clients.

### Sudarshan Kriya Yoga (SKY) Breathing

An open study of 46 patients with dysthymia (mean illness duration 3.15 years) showed significant improvement on Beck Depression Inventory (BDI) and Clinical Global Impression scales 1 and 3 months after SKY breath training. Among the 37 patients who completed the program, 67.5% achieved remission (Janakiramaiah et al. 1998). In a randomized, controlled study, 45 hospitalized patients with severe melancholic depression received either SKY, imipramine 150 mg/day, or electroconvulsive therapy (ECT) three times a week. SKY was as effective as imipramine and almost as effective as ECT in significantly reducing scores on BDI and HAM-D. Significant prolactin elevations were noted after Sudarshan Kriya (SK) cyclical breathing (Janakiramaiah et al. 2000).

### Iyengar Yoga

Twenty-eight healthy volunteers (not being treated for depression), ages 18−29, with mild depression (BDI = 10−15) were randomly assigned to two 1-hr Iyengar yoga classes for 5 weeks or wait-list control. Postures believed to alleviate depression (back bends, standing poses and inversions) were emphasized with breath practices. The yoga group showed significantly greater decreases in scores for depression and anxiety on BDI, State-Trait Anxiety Inventory, and Profile of Moods States compared to the control group (Woolery et al. 2004). Another wait-list RCT of 24 women with perceived stress found that those assigned to a 3-month Iyengar yoga class experienced significant improvement in depression (Michalsen et al. 2005). While these small studies did not select patients with a diagnosis of depression, they suggest a positive impact on depressed mood that warrants further study.

### Kundalini Yoga

Kundalini Yoga breathing meditation techniques recommended for depression that include establishing a meditative state of mind, imagery, chanting, and several yoga breath techniques and postures (Shannahoff-Khalsa 2004). However, these have yet to be studied in controlled trials for depression.

## Anxiety Disorders

### GAD, Panic Disorder, Social Phobia, Posttraumatic Stress Disorder (PTSD), OCD, Insomnia, and Stress-related disorders

Estimates of the use of CAM by people with anxiety disorders range from 40−50% (Eisenberg et al. 1998) and is highest among those with panic attacks (Unutzer et al. 2000). Individuals with anxiety disorders are vulnerable to substances abuse and dependence on prescription anxiolytics. Mind−body practices provide significant relief without the risk of drug dependence and are used more frequently than herbs for anxiety (Bandelow et al. 1995). This section begins with mind−body practices that address the pathophysiological mechanisms that underly anxiety.

### Mind–Body Approaches for Anxiety Disorders and Insomnia

Meditative and yogic practices are being integrated into Mindfulness Based Stress Reduction (MBSR) and Cognitive Behavioral Therapy (CBT) Stratyner (2006). As these programs become more sophisticated in their approaches to affect regulation and awareness of internal experience, they are embracing Eastern psychology, Zen and Buddhist philosophy, and Hindu yoga. Mindfulness Based Cognitive Behavioral Therapy (MBCBT) researchers have expanded their scope of behavioral practices to include yoga.

Rresearch on mind−body practices faces the challenges of any emerging field. Early studies were mainly either descriptive or open pilots. Recent work has greater methodological rigor. Nevertheless, there is much to learn from

the evidence, clinical observations, and the long history of traditional healing practices. Criteria for evaluating research on mind–body practices must take into account the impossibility providing double blinding (done easily with placebo tablets in medication studies). Studies using blinded raters and control groups such as psychoeducation, other stress reduction interventions or wait-list controls are preferable to uncontrolled trials. While it has been argued that just the provision of attention may account for clinical improvement, this is unlikely in serious anxiety disorders, which are often resistant to standard psychotherapy and medication. Another problem is the difficulty of funding large-scale studies. For the present, studies should not be disregarded because of small sample size, particularly when a large effect size may indicate statistical significance. Literature reviews may not represent the available data because tight exclusion criteria may eliminate studies of medical illnesses in which anxiety may have improved if it was not the primary focus.

## Autonomic Balance, Brain waves, Neuroplasticity

Anxiety and PTSD are associated with over activity or erratic activity of the SNS and underactivity of the PNS (Berntson et al. 1998, Thayer and Brosschat 2005). Low respiratory sinus arrhythmia (RSA) and low HRV, reflecting decreased vagal tone, are associated with negative states of mind in adults, fear and depression in infants, aggression and antisocial behavior in adolescent boys, anxiety disorder and panic disorder (Beauchaine 2001, Carney and Ellis 1988, Carney et al. 1995, Mezzacappa et al. 1996, 1997). Certain mind–body practices shift autonomic balance in favor of PNS dominance.

Meditation has been shown to reduce SNS activity and to increase PNS activity. However, the process of meditation requires mental focus and the ability to quiet the mind. Many people with anxiety disorders cannot focus or quiet their mind enough to achieve a meditative state. Most meditation practices include breath-centered work such as slow breathing, focused attention on the breath, or deep abdominal breathing. Yoga breathing normalizes SNS activity and increases PNS tone. For treating anxiety disorders, it is important to enhance PNS activity and to increase the flexibility of the stress response system. Voluntarily changing the pattern of breath influences emotional states (Philipot 2002). Even simple slow breathing can stimulate the PNS and that effect is enhanced by more advanced breath techniques (Brown and Gerbarg 2005a).

Afferent autonomic and somatosensory feedbacks from the body are central to peripheral models of emotion and their extension into self-awareness (Bechara et al. 1997, Damasio 1999). Interoception, the perception of "feelings" (e.g., visceral sensations and pain) that reflect the physiological state of the body may have primary representation in the dorsal posterior insula and meta-representation in the right anterior insula, a possible substrate for emotional awareness (Craig 2003). This converges with Damasio's "somatic marker" hypothesis that brain regions involved in mapping and regulation of internal states contribute to representational images of body states, a basis for awareness of feelings states (Critchley 2005).

The PNS calms the stress response system through cholinergic pathways and neuroendocrine activity. It not only slows the heart and respiratory rates, but also quiets the mind and restores energy supplies. A few tracts of the PNS run through the spinal cord, but its main pathways are the right and left vagus nerves that innervate the organs and tissues of the throat, chest, abdomen and periphery. Approximately 20% of the vagal fibers (efferents) carry messages from the brain to the body, whereas 80% (afferents) carry information from the body up to brainstem nuclei and from there to the limbic system, hypothalamus, thalamus, and broad areas of the cerebral cortex. This influences how we experience our bodies, our emotions, and our state of consciousness. Thayer and Brosschat (2005) propose that the medial prefrontal cortex (mPFC) inhibits lower centers such as the amygdala. Disturbances in the dynamics between prefrontal cortex (PFC), amygdala and thalamus may contribute to depression and fear-related symptoms as in PTSD (Das et al. 2005, LeDoux 2000). Low PNS activity and hypoactivity of the PFC are associated with poor affective processing. Therapeutic implications of these concepts have been demonstrated in the use of Vagal Nerve Stimulation (VNS) (Figure 108–2) of the right vagus nerve for epilepsy and treatment-resistant depression (Sackeim et al. 2001). However, the use of electrical devices to stimulate part of the vagus nerve is a crude method compared to the intricate network of afferent sensory vagal fibers that constantly dialogue with the brain. The lungs and airways contain pressure receptors and mechanoreceptors, stretch sensors (Yu 2005) that fire in response to lung inflation and deflation, sending signals to vagal afferents. The authors propose that voluntarily changing the pattern of breath alters the firing of lung sensors and the visceral somatosensory (including pharynx, larynx, chest wall, diaphragm, baroreceptors, and chemoreceptors) information carried by vagal afferents leading to changes in emotional and cognitive processing by shifting the balance of input to the prefrontal cortex, insula and related areas involved in emotion regulation and the representation of bodily feeling states.

Enhancement of alpha and theta activity and phase synchrony (Hebert et al. 2005, Lehmann et al. 2001, Satyanarayana et al. 1992), interhemispheric asymmetry in alpha and beta activity, and high voltage gamma synchrony (Benson et al. 1990, Davidson et al. 2003, Lutz et al. 2004) occur with meditation and yoga breathing. Data from electroencephalogram (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) studies are being used to study the effects of mind–body practices on emotional and cognitive processing, neuroplasticity, and brain aging (Lazar et al. 2000, Lazar et al. 2005). The long-term practice of meditation and yoga breathing has been associated with sustained changes in resting EEG, which may reflect changes in brain structures in areas being exercised during those practices. Repeated experience may lead to neuroplastic development in specific cortical regions. The right insula has been associated with interoception and breath awareness. Lazar et al. (2005) found that this area showed the largest changes between meditators and controls. Awareness of breathing is fundamental to the practice of meditation and yoga. Most practitioners learn to focus on the breath as the first interoception. Attending to the breath leads to slowing of the respiratory rate. In the Lazar study respiratory rate correlated with cortical thickness in the inferior occipitotemporal visual cortex and the right anterior insula.

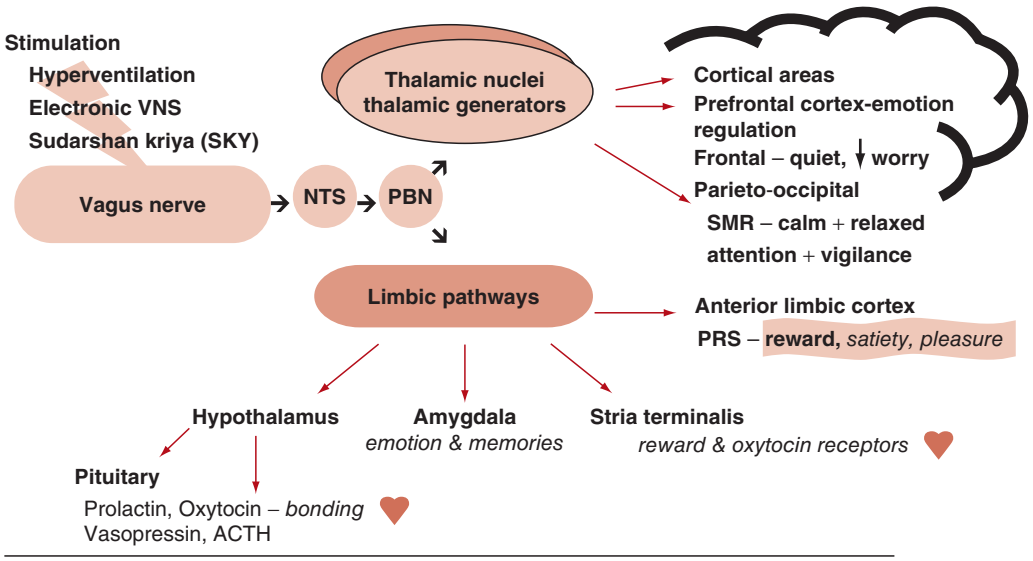



**Figure 108–2** *Neurophysiological model of vagus nerve stimulation pathways.*

## Review of Research

### Mindfulness Meditation

In Kabat-Zinn's et al. (1992) open pilot study of mindfulness meditation for GAD and panic disorder 24 participants were carefully screened using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (SCID), Beck Anxiety Inventory (BAI), BDI, Hamilton Rating Scale for Anxiety (HAM-A), HAM-D, and ratings of panic attacks. The intervention included an 8-week course in meditation, followed by a weekly 2-hr class of daily meditation up to 45 min, and a 7.5 hr silent retreat two weeks before the program ended. Meditation included body scan, sitting meditation, and mindful hatha yoga (postures with breath control). Significant declines were found in scores on HAM-D, HAM-A, BAI, and frequency of panic attacks over the course of the intervention and 3-month follow-up. A follow-up study of 18 of the original subjects showed that most subjects continued mindfulness practices and maintained improvements on HAM-A and BAI (Miller et al. 1995). This study supports the short- and long-term benefits of the intervention, but requires validation by larger RCTs.

A review of meditation for anxiety disorders identified 50 relevant studies of which 48 failed to meet inclusion criteria (Krisanaprakornkit et al. 2006). Studies in which anxiety was not the primary focus were excluded. The review defined two types of mind training based on the attentional strategies: concentrative meditation and mindfulness meditation. Meditation therapies may include one or both approaches. Two well-known forms of concentrative meditation, Transcendental Meditation ™ (TM) and the relaxation response (Benson 1975), focus attention on an object until the mind becomes still. Meditations intended to open up awareness rather than focus on one-pointed attention include Mindfulness meditation, pranayama (Hindu breathing), Sahaj Samadhi Meditation, Anapasati (Buddhist breathing meditation), Qigong, and "Open Focus" (Fehmi and McKnight 2001). With open awareness, the practitioner cultivates detached observation of any conscious mental contents with a nonreactive, accepting attitude. In the first of the two RCTs considered of "moderate quality" by the Cochrane review, TM was compared to muscle biofeedback and relaxation training in an 18-week program for 31 subjects with Anxiety Neurosis (*Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (DSM-II)) who were symptomatic for one year or more (Raskin et al. 1980). All three interventions were equally effective in reducing anxiety as measured on the Taylor Manifest Anxiety Scale, Current Mood Checklist, and Social Rating Scale. Sleep disturbance did not improve. The total dropout rate was 44%. The second RCT was a 12-month randomized comparison of Kundalini Yoga (eight practices including slow (1 cpm) left-nostril breathing with breath holds, mantra meditation, and postures) versus relaxation and mindfulness meditation in OCD. The Yoga group showed significant mean reduction (−38.4%) on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) versus the control group (–13.9%). No adverse events were reported. Improved ratings of OCD were noted in a previous12-month pilot study (Shannahoff-Khalsa et al. 1999). Both groups merged for an additional year of the Kundalini program. The 11 completers had a mean improvement of 70.1% on Y-BOCS compared to baseline (Shannahoff-Khalsa 2003). In a 4-month RCT of 35 Swedish employees comparing a stress management program based on CBT with a Kundalini Yoga program, both groups attained significant improvement on self-rated measures of stress, behavior, anger, exhaustion, and quality of life. Most variables showed medium-to-high effect sizes. There were no significant differences between the groups suggesting that both are promising stress management interventions. Physiological measures approached but did not reach statistical significance except for a significant decline in mean noradrenaline levels: $t(14) = 3.15$, $p < 0.007$ in the yoga groups (Granath et al. 2006). Hatha Yoga and Iyengar Yoga: Hatha Yoga, in its secular adaptation to Western

culture, involves physical postures and breath practices. It can include meditation, chanting, and Eastern philosophy. Weak evidence supports benefits of Hatha yoga for well-being. Iyengar Yoga, a form of Hatha Yoga, stresses structural alignment of the body through postures aided by props such as blocks, straps, and sand bags. In a nonrandomized wait-list control study of self-referred women who perceived themselves as "emotionally distressed," those who participated in 90-min; bi-weekly; 3-month Iyengar Hatha Yoga classes demonstrated significant improvements in Cohen Perceived Stress Scale, State-Trait Anxiety Inventory, Profile of mood States, CESD-Depression Scale, and ratings of physical well-being compared to controls. Salivary cortisol decreased significantly in the yoga group (Michalsen et al. 2005). A 6-month RCT compared Hatha yoga (90-min weekly class, 18 postures, relaxation, visualization, meditation, and daily practice) with aerobic exercise (1-hr weekly class of walking and daily exercise), and wait-list control. 135 relatively healthy seniors (aged 65–85 years) showed no improvements in attention, alertness or mood (Profiles of Mood States (POMS)). However, the Hatha yoga group had significantly greater improvement in quality of life, particularly vitality, energy, and fatigue (SF-36, $p = 0.006$), bodily pain ($p = 0.006$), social functioning ($p = 0.0150$) and physical composite scale ($p = 0.005$) compared to the other groups. The authors cautioned that improvement in social function could be due to greater opportunities for social interaction in the Hatha yoga class (Oken et al. 2006).

Qigong is an ancient Taoist and Chinese system of yoga used for health and longevity. Internal Qigong uses primarily concentrated attention with inhalation, exhalation and breath holds to stimulate the circulation of blood and the vital life energy, Qi. External Qigong focuses on physical movements with internal quiescence. Most studies of Qigong are of limited value because of methodological limitations and small sample sizes. The effects of Qigong on HRV were assessed in several studies comparing healthy sedentary adults with healthy Qi-trainees. During controlled respiration Qi training increased high frequency (HF) power and decreased low frequency/high frequency (LF/HF) power ratio of HRV, indicating increased cardiac parasympathetic tone. Moreover, experienced Qi-trainees had higher HRV than age-matched sedentary controls (Lee et al. 2002, Lee et al. 2005a, 2005b). Tai Chi Chuan (a system of meditation in smooth movements) was found to reduce psychological and physical indicators of stress and anxiety in a nonrandomized comparison study of 33 experienced and 33 beginning practitioners before, during and after the practice (Jin 1989). Compared to baseline POMS, ratings of tension, depression, anger, fatigue, and confusion were significantly lower during and after Tai Chi. State anxiety was significantly lower before than during Tai Chi ($f(1.60)$, $0 < 0.001$). Larger RCTs are needed to confirm these observations.

A 3-month study of medical students compared a program of yoga postures and breathing, prayer, visualization and meditation with a control reading group. The yoga group had significant mean reduction on state-trait anxiety inventory the day of examinations (−34%) vs. control (+3.4%) ($p < 0.001$) (Malathi and Damodaran 1999). Kirkwood et al. (2005) reviewed eight studies of yoga for anxiety disorders reporting positive findings, but only the Shannahoff-Khalsa et al. (1999) OCD study documented adequate randomization procedures. Methodological flaws precluded general conclusions other than that results are promising and further research is needed.

A systematic review of studies of the effects of yoga on indices of cardiovascular disease (CVD) risk and insulin resistance syndrome (IRS) included 26 uncontrolled trials, 21 nonrandomized controlled trials, and 22 RCTs. These studies suggest that yoga may decrease many IRS-related risk factors for CVD. However, methodological limitations in most studies point to the need for better quality studies to confirm these positive findings (Innes et al. 2005). A 16-week RCT compared the effects of TM on metabolic syndrome to a control intervention of health education. The study included 103 people with stable coronary artery disease. At the end of 16 weeks, the TM group showed modest improvements in measures of mean blood pressure ($-3.4 \pm 2.0$), insulin resistance, and HRV (high frequency) compared with the control group (Paul-Labrador et al. 2006). Additional studies are needed to validate the benefits of TM in modulating stress response and risk factors for coronary heart disease (CHD). Twenty-five adolescents with irritable bowel syndrome in a RCT were assigned to either 1 hr of yoga instruction followed by four weeks of daily home practice or a wait list control. Those in the yoga group showed significantly lower scores on gastrointestinal symptoms and emotion-focused avoidance (Kuttner et al. 2006). Musicians were offered a yoga and meditation program in a nonrandomized, self-selected study. Those who did not choose yoga served as controls. Musicians in the yoga program ($N = 10$) reported improvement in performance anxiety compared with control ($N = 8$) (Khalsa and Cope 2006).

## Yoga Breathing

Hundreds of yoga breath practices have been used to maintain health, treat illness, and promote self-development. Identifying common elements among diverse practices, Brown and Gerbarg developed a neurophysiological theory for the effects of yoga breathing, providing a framework for further study (Brown and Gerbarg 2005a, 2005b).

Slow yoga breathing usually begins with focusing attention on the breath and increasing awareness of the breath. Most forms of slow deep breathing will produce some calming effects. Slow yoga breathing (including Ujjayi) increases RSA, HRV, and PNS activity (Cappo and Holmes 1984, Lehrer et al. 1999), arterial baroreflex sensitivity, and oxygenation. Reducing respiratory rate to 5−6 bpm enhances synchronization between the respiratory and cardiovascular (CV) systems and optimizes oxygen exchange (Bernardi et al. 2005, Vaschillo et al. 2004). Using CDs or DVDs enhances compliance (see for a CD with paced breathing at 5−6 bpm: www.coherence.com). The mental and physical calming of slow yoga breathing is substantially enhanced by resistance breathing, prolonged expiration, breath holds, alternate nostril breathing and left nostril breathing. Ujjayi (Victorious Breath or Ocean Breath) is an effective form of resistance breathing. Contraction of laryngeal muscles with partial closure of the glottis (creating a sound like the ocean) increases airway resistance, intrathoracic pressure, baroreceptor stimulation, HRV, RSA (Calabrese et al. 2000), and stimulation of somatosensory. Airway resistance

enhances breath control. Ujjayi can first be done slowly with inspiration equal to expiration. Lengthening the expiratory phase and adding breath holds further increases PSN activation and effectiveness (Telles and Desiraju 1992). The "Ha" breath used by ancient priests (Kahunas) of Hawaii for storing energy and healing has similarities to Ujjayi in that the whispered sounds of "Ha" on exhalation and "Ho" on inhalation create airway resistance. Although there have been no formal studies of these practices, they are used during meditative contemplation and to overcome physical and emotional stress (Kahn 2004). During slow chanting, such as "AUM" or "Om," the contraction of the vocal cords creating the sound also creates airway resistance. Chanting may increase PNS and decrease SNS activity, contriburting to calmness and well-being that many people experience singing hymns. Alternate nostril breathing, slow paced expiration and inspiration through one nostril alternating with expiration and inspiration through the other nostril for 10−20 min, is easy to master and calming in most clinical disorders, with no adverse side effects. Bhastrika (Bellows Breath), a forceful rapid breathing (30 cpm) activates the SNS inducing CNS excitation followed by emotional calmness with alertness. Cyclical breathing at different rates produces a variety of effects. For example, breathing at 8−12 bpm decreases PNS withdrawal in response to threat and reduces anxiety (Sakakibara and Hayano 1996). High frequency breathing stimulates the SNS. While the possibility that this could benefit anxiety disorders may seem counterintuitive, when done in short bursts for short periods of time and balanced by slow breath forms, these techniques can increase the range and flexibility of the stress response system. In many traditions the sounds So Ham or Ham So (So'Hum, Su-Hum) are used to pace cyclical breathing. Some teachers chant in monotone at a fixed rate (http://www.swamij.com/cd-soham.htm), while others deliver So Hum as a melodic chant with varying rates as in SK. Ham So translates from Sanskrit as "I Am That I Am," the name God gave for himself to Moses in the Bible (Exodus 3:14). It is considered to be the natural mantra of the true self.

SKY is a unique system of four breath techniques that require 20−30 min daily practice and that have the potential to relieve symptoms of stress, anxiety, panic, OCD, and PTSD. It is hypothesized that SKY affects emotional and cognitive processing via shifts in autonomic activity, CNS electrical patterns, and neuroplasticity. SKY begins with a technique combining arm postures with Ujjayi breathing (2−6 cpm) using expiration longer than inspiration and breath holds, intensifying PNS activation such that even highly anxious individuals often experience complete mental and physical relaxation within minutes. This is followed by the "om" chant, Bhastrika (rapid forceful breathing) for about 90 s, and SK, a highly advanced technique using So Ham to pace rounds of cyclical breathing at varying rates. High frequency breathing activates the SNS and may prepare the brain for more rapid information processing. SK cyclical breathing may disrupt fixed patterns within neural networks, the the legacy of stress and trauma-related emotional schemas (Gerbarg 2007, Bucci 2003). We postulate that the physiological challenge of SKY temporarily disrupts established brain wave patterns and neuronal connections in areas containing stress- and trauma-related schemas, creating opportunities for new input (perceptions, experiences, cognitions, emotions, etc.) with positive affective valence to access previously closed areas (containing trauma schemas) and form new linkages leading to structural change and recovery (Gerbarg 2007).

A study comparing EEGs of 19 regular SKY practitioners at rest with 15 healthy age-matched controls found significant increase in $\beta$-1 and $\beta$-2 activity in left frontal, midline and occipital regions of the SKY group (Bhatia et al. 2003). Another EEG study of 12 volunteers during SKY and meditation showed increased spectral power of $\alpha$-rhythm in the middle band (10−10.5 cps) in $O_1$ and $O_2$ montages ($p < 0.005$), interpreted as heightened alertness. Significant inter-hemispherical asymmetry disappeared. The highest $\alpha$-activity appeared at the end of SK in centrencephalic mediobasal structures and occipital cortex ($p < 0.05$), suggesting enhancement of inter-hemispheric communication and integrative function ($p < 0.05$) (Snayder et al. 2006). Electrophysiological studies of SKY practitioners show that daily practice of SKY over time is associated with increased coherence and high amplitude synchrony (Larsen et al. 2006). Increased high amplitude gamma synchrony was found in long-term meditating Tibetan Buddhist monks (Lutz et al. 2004). Coherence and synchrony are associated with improved perception, cognition (Mizuhara et al. 2005), memory (Guderian and Duzel 2005), and neuroplasticity.

## PTSD

In severe anxiety disorders and PTSD, slow, deep, or abdominal breathing is insufficient, as the following study illustrates. An RCT comparing relaxation (simple instructions to relax in a reclining chair), relaxation with deep breathing (gradual filling of the lungs and slow complete exhalation), and relaxation with deep breathing and thermal biofeedback in 90 Vietnam veterans with PTSD found all interventions to be mildly therapeutic. Addition of deep breathing and thermal biofeedback did not produce further improvements on PTSD scales (Watson et al. 1997).

In an open trial, 139 war-traumatized high school students in Kosovo were given an 8-week mind−body skills program including meditation, biofeedback, movement, guided imagery, breathing techniques, autogenic training, drawing, family genograms, psychoeducation about stress, and group discussions of their experiences (Gordon et al. 2004). Scores on an Albanian version of the PTSD Reaction Index (16 dichotomous questions derived from DSM-III-R) were significantly reduced after the mind−body skill program and remained reduced at 9- and 15-month follow-up. This study lacked a control and had other methodological limitations. It is difficult to evaluate which of the many components were essential for the therapeutic effect. Nevertheless, it suggests that a multimodal program of mind−body practices may reduce symptoms of PTSD.

SKY breath practices have been used to relieve psychological suffering among masses of civilians and military personnel in the wake of natural and man-made disasters such as floods, earthquakes, industrial accidents, wars, and terrorist attacks (Gerbarg and Brown 2005). In a wait-list comparison controlled study, 180 village survivors of the 2004 Asian Tsunami who had been living for nine months in refugee camps in Nagapattinam and who scored above 50 on the Post Traumatic Stress Disorder

Checklist-Civilian (PCL-C), were assigned to one of three groups. The first was given Breath Water Sound (BWS), a short (8-hr) group program of SKY breath techniques. The second group was received the same 8-hr BWS program followed one week later by Trauma Incident Reduction (TIR) in which a trained listener encourages the subject to repeatedly describe the trauma over one to four sessions until the subject achieves emotional relief. The third group served as a wait-list control for five weeks and then received BWS. In four days BWS dramatically reduced symptoms of PTSD and depression on standardized measures (PCL-C and BDI) and the benefits were sustained at 6-week, 3-month, and 6-month follow-ups. Scores on PCL-C fell below 50 for all subjects. The addition of TIR showed no further impact on PCL-C scores, possibly due to a floor effect, the scores having dropped too low after BWS (Descilo et al. 2006).

A 6-week Iyengar Yoga program was given to disabled Australian veterans of the Vietnam War with PTSD in four small open studies. Although the Iyengar Yoga postures (Iyengar 2001) improved symptoms of depression, the addition of yoga breathing (particularly Ujjayi) and Ham Su meditation significantly reduced symptoms of PTSD, including anxiety, insomnia, flashbacks, and anger outbursts (Carter and Byrne 2004). In a wait-list controlled study of 30 disabled Australian Vietnam veterans with PTSD, those given SKY showed significantly greater reductions on the Clinician Administered PTSD Scale (CAPS) and the self-administered PTSD Checklist-Military (PCL-M) than those in the wait-list group (Carter and Byrne 2006, Brown et al., in press). Veterans using yoga breathing to calm themselves when they awoke at night or when they felt "road rage." Yoga techniques could be developed as adjunctive treatment for the full range of PTSD symptoms in veterans, providing an alternative for those who do not accept psychiatric treatment.

Patients with PTSD due to sexual abuse benefit when SKY breathing is combined with traditional psychiatric and psychological therapies (Sageman 2002, 2004, Sageman and Brown 2006a). Yoga breathing reduces arousal, anxiety, and overreactivity, enabling the patient to recall and discuss traumatic material without feeling overwhelmed. Other beneficial components of SKY course includes cognitive–behavioral teaching and psychoeducation in human values of acceptance, social responsibility, and community service (Sageman 2002). In a 4-day RCT, 40 women who had been abused by an intimate partner were randomly assigned to tell about the abuse (two 45-min sessions of testimony with a trained listener over two consecutive days), participate in yoga breathing (two 45-min sessions of yoga breathing including slow deep breathing with some breath holds, sound, and yoga postures), a combined testimony/yoga breathing intervention (45-min testimony immediately followed by 45 min of yoga breathing), or serve as wait-list controls (Franzblau et al. 2006). Those who received both testimony and yoga breathing showed the greatest improvement on scores for self-efficacy on the Franzblau Self Efficacy Scale (FSES) 20, particularly in feelings of control, security, and confidence. This study is limited by small sample size, brief duration, and the use of only one measure, the FSES 20. Nevertheless, it highlights the potential for developing integrative treatments for psychological trauma.

## Insomnia: Evidence for Mind–Body Techniques

Pharmacotherapy for insomnia in geriatric populations is associated with problematic side effects including confusion, motor incoordination, intellectual and memory impairment, syncope, daytime sleepiness, and dysphoria. In an RCT, 69 residents in a home for the elderly (over the age of 60) were randomly assigned to three groups: a 6-week yoga program (postures, relaxation, breath practice, and lectures on yoga philosophy; an herbal Ayurveda preparation, Rasayana Kalpa, composed of *Withania somnifera* root 2 g, *Emblica officianalis* 1 g, *Sida cordifolia* 0.25 g, and *Piper longum* 0.5 g); or a wait-list control (no intervention) (Manjunath and Telles 2005). On a self-rating sleep questionnaire, the yoga group showed significant decrease in the time to fall asleep (average decrease of 10 min, $p < 0.05$), increase in the number of hours slept (average increase 60 min, $p < 0.05$), and improved feelings of being rested ($p < 0.05$) compared to no change in the Ayurveda or wait-list control groups. Findings from subjective self-assessments suggest that yoga programs may be a safe and effective for sleep disorders in the elderly. However, they should be confirmed using more objective measures such as polysomnography.

## Clinical Issues: Referrals and Precautions

In recommending yoga practices to patients, one must look for programs that can achieve significant results with a relatively small amount of practice. It is difficult to motivate most patients to do more than 20 min of any daily practice. Some techniques must be learned in courses with certified instructors. However, there are beginning techniques that therapists can learn to teach patients. Most people are able to experience yoga breathing and meditation courses without difficulty. However, clinicians should be aware of the following precautions: Pregnant women and patients with uncontrolled hypertension, migraine headaches, severe COPD, acute asthma symptoms, recent injuries of the neck, shoulders, or chest, or recent myocardial infarction should not do breath holds, Bhastrika or any rapid or forceful yoga breathing. Gentle basic Ujjayi (without breath-holds), alternate nostril breathing, and meditation are safe and soothing. Yoga breathing is generally contraindicated in seizure disorders. Bipolar patients may be triggered to become manic, particularly from Bhastrika and rapid cycle breathing. Bipolar II patients whose mood swings are under good control on medication may do yoga breathing under supervision if they avoid Bhastrika and rapid cycle breath forms. However, if they become agitated or anxious, the yoga breathing should be discontinued. Yoga breathing can increase excretion of lithium causing a drop in serum lithium levels. Bipolar patients being treated on lithium alone should not undertake yoga breath training. Patients on lithium in combination with other mood stabilizers who begin yoga practices should have lithium levels monitored. A review of Qigong-induced mental disorders (Ng 1999) concluded that incorrect or excessive practice of Qigong could induce abnormal psychosomatic responses and mental disorders. Most cases occurred in individuals with underlying bipolar or psychotic disorders in whom Qigong may have served as a trigger. Individuals with PTSD primarily due to recent trauma or trauma during adulthood usually do well with SKY. Patients with chronic PTSD from childhood abuse can benefit from SKY if they

do not have significant dissociative symptoms. In such cases, the therapist could contact the teacher, prepare the patient, and help process trauma-related material that may emerge. Severe character disordered patients may not be suitable for the group setting. Psychosis is a contraindication for yoga breathing. However, schizophrenic patients have been shown to benefit from gentle basic Ujjayi, alternate nostril breathing, and gentle yoga postures (Descilo et al. 2006).

### How and When to introduce Yoga as a Complementary Treatment

Factors to consider in suggesting yoga during psychotherapy include the patient's readiness to engage in mind−body practice, availability of yoga programs, and the quality of yoga instructors. Clinicians who learn about mind−body practices by taking classes themselves, are better equipped to make appropriate referrals, prepare patients, and help overcome obstacles to daily practice. Although there are immediate gains, long-term benefits may not appear for 6−12 months (a time course similar to VNS and biofeedback). Practitioners who become proficient in yoga breathing can learn how to teach the simpler practices to their patients providing a nonaddicting, inexpensive method to control anxiety, insomnia, and other symptoms of hyperarousal. Slow gentle Ujjayi and alternate nostril breathing are the two techniques that have the broadest clinical applications with virtually no side effects when practiced properly.

Many psychiatric patients are unable or unwilling to undertake yoga classes because of social anxiety, disbelief in the benefits, bias against Eastern practices, time constraints, or financial limitations. In such cases, it can be very helpful to teach the patient one or two basic yoga breath techniques in the office. For example, alternate nostril breathing or simple Ujjayi will usually give the patient an immediate experience of calmness, relaxation, quieting of the mind, and relief from distress. This becomes a potent motivator for daily practice with encouragement by the therapist. After one to three months of such practice, many patients are ready to learn more by taking classes. CDs that guide the breath practices can be useful, but the quality is variable. It is advisable for the therapist to evaluate CDs before recommending them to patients.

## Hormones for Anxiety Disorders and Insomnia

Melatonin, the primary hormone secreted by the pineal gland, affects sleep circadian rhythms by interacting with melatonin receptors. Unlike most hypnotics, melatonin does not disturb sleep architecture. In patients with insomnia, DBRPC trials show that melatonin improves sleep, reduces sleep onset latency (Kayumov et al. 2001), and restores sleep efficiency (Zhdanova et al. 2001). Melatonin has a direct action on sleep and on circadian effects on sleep; this dual activity makes it particularly useful in treating delayed sleep phase syndrome (DSPS), insomnia in dementia and jet lag (Pandi-Perumal et al. 2005). A DBRPC study in elderly melatonin-deficient insomniacs found that 1 week of 2 mg sustained-release melatonin effectively maintained sleep, while 1 week of 2 mg fast-release melatonin improved sleep initiation. 1 mg/day sustained-release melatonin for 2 months improved sleep initiation and maintenance with no adverse effects (Haimov et al. 1995). In a 4-week, open pilot study, melatonin 3 mg at the hour of sleep (*hora somni* (h.s.)) reduced sun downing (agitated behaviors) and daytime drowsiness in 11 elderly nursing home residents with dementia (Cohen-Mansfield et al. 2000). Numerous other short- and long-term studies of melatonin for insomnia in Alzheimer patients show improvements in sleep, mood, memory, reduced sundowning, and delay in cognitive deterioration (see for review: Pandi-Perumal et al. 2005, 2006). A recent DBRPC crossover trial of 40 patients with Parkinson's disease revealed significant improvements in sleep using melatonin 50 mg and 5 mg versus placebo (Dowling et al. 2005). Melatonin is a powerful antioxidant for the DA system. This promising treatment for insomnia in Parkinson's patients warrants further study. In a DBRPC trial, 24 patients being treated with fluoxetine 20 mg for major depression and insomnia, sleep quality and continuity improved in the group given up to 10 mg h.s. melatonin. Melatonin caused no more side effects than placebo (Dolberg et al. 1998). Melatonin significantly improved sleep in a DBRPC cross-over trial in schizophrenics (Shamir et al. 2000) and in a pilot study of 11 patients with bipolar disorder, manic type (Bersani and Garavini 2000).

Rapid eye movement (REM) sleep behavior disorder (RBD), a chronic progressive parasomnia, is characterized by loss of paralysis during REM sleep. Patients physically act out their dreams causing injury to themselves or their partner. Many cases occur in neurodegenerative disorders and in Parkinson's patients treated with DA agonists and levodopa. In neurologically vulnerable patients, stimulants, TCAs, and SSRIs may trigger RBD (Schenck et al. 1986). Traditional treatments for RBD, clonazepam (0.5–2 mg h.s.) or carbamazepine (100 mg t.i.d.) may worsen cognitive function or cause ataxia (increasing the risk of falling). Carbamazepine can cause hepatitis, blood cell dyscrasias, and hyponatremia. Melatonin rarely has side effects even at 9−12 mg h.s., the doses necessary to treat RBD (Kunz and Bes 1997, Paparrigopoulos 2005).

A DBRPC trial in 15 children with pervasive developmental disorders or autism with severe insomnia found that all children given melatonin had significant improvement in insomnia, irritability, alertness, and social ability (Jan et al. 1994). Eight out of 10 epileptic children with severe sleep waking rhythm pathology ages 6 months to 10 years responded to melatonin 5−10 mg h.s. with improved sleep and daytime alertness. Six of the responders gained better seizure control (Fauteck et al. 1999). A study of 20 developmentally disabled children with sleep problems showed benefit from melatonin (Dodge and Wilson 2001). Two DPRPC trials in 40 and 62 children with chronic sleep onset insomnia found that melatonin 5 mg was better than placebo (Smits et al. 2001, 2003).

The heterogeneity of melatonin studies has been attributed to variability in product quality and onset of action (slow vs. fast release), diagnostic differences, comorbid conditions, and timing of administration. A review of 14 RCTs found that melatonin reduced sleep onset latency more in people with DSPS than in those diagnosed with insomnia (Buscemi et al. 2005). Distinguishing between DSPS and insomnia accounted for much of the heterogeneity in study results. Ten of the studies reviewed for safety indicated a low incidence of adverse events (headaches, drowsiness, dizziness, and nausea) with no difference between melatonin

and placebo in any study. No study ran more than 3 months, limiting conclusions about long-term safety.

Jet Lag: In a DBRPC study of 320 people followed for four days after a long plane trip, the group given 5 mg fast-release melatonin slept better, fell asleep faster, and were more awake and energetic during the day than groups given 5 mg slow-release, 0.5 mg fast release, or placebo (Suhner et al. 1998). Another small DB study found that airline crews were more rested using 10 mg fast-release melatonin compared to placebo. The benefits of melatonin were equivalent to ropiclone, without next day impairment in cognition (Paul et al. 2001). People who travel across five or more time zones benefit most from melatonin (Arendt et al. 1997). The brain can more easily delay than advance the sleep cycle. It is difficult to advance more than 1 hr at a time. Melatonin given in the evening helps the biological clock advance more by enhancing homeostatic sleep mechanisms. For example, flying from the East coast of the US to Europe requires a sleep phase advance of six or more hours. Taking 5 mg fast-release melatonin to sleep on an evening flight accelerates adaptation to European time and reduces Jet Lag. If this dose causes excess sedation, a smaller dose may be sufficient. Prescription sedative/hypnotics may impair the ability to function in an emergency or the next day. By reducing the tendency to move and walk during long flights, sedating medications increase the risk of deep vein thrombosis (Herxheimer and Petrie 2001).

Benzodiazepine Withdrawal: Many patients start benzodiazepines for sleep during a period of stress, but are unable to discontinue it due to recurrence of insomnia. Melatonin may be useful in helping patients discontinue the benzodiazepine while maintaining sleep quality. For those unable to completely discontinue BZD, it was possible to significantly reduce the dose of BZD by using melatonin concurrently (Pandi-Perumal et al. 2005).

Clinical Guidelines, Safety and Side Effects. One report indicated that four out of six brands of melatonin had ill-defined impurities (Anonymous 1995). Consumers should choose supplements from mainstream companies with pharmaceutical grade melatonin. Side effects, cramps, fatigue, dizziness, headache, and irritability, are infrequent and usually mild. Melatonin is a safe short-term alternative to prescription hypnotics for insomnia. In therapeutic doses, 1.0−3.0 mg h.s. (with increases up to maximum 9 mg h.s. prn), it has few side effects. Elderly patients who are susceptible to cognitive/memory impairment and daytime drowsiness from benzodiazepines, may benefit from melatonin without risk of these adverse effects. Melatonin is best given about 30 min before bedtime. Patients should be instructed to turn lights out for at least 30 min before bedtime to achieve the best effect. Taking melatonin during the daytime bright light may sensitize the eyes to light damage. The safety of high-dose melatonin has not been established. The possibility exists that very high doses (above 50 mg/day) might have long-term effects on testosterone or prolactin levels. Clinicians who prescribe chronic melatonin or damelteon should monitor patients for adverse effects (Bellon 2006).

## 7-Keto Dehydroepiandrosterone (DHEA) for Post Traumatic Stress Disorder and Bipolar Disorder

There is a limited literature on the treatment of patients with comorbid PTSD and Bipolar Disorder. Retrospective studies show that in adults with Bipolar disorder, about half have a history of severe trauma and about 35% have comorbid PTSD. These patients tend to have more frequent and severe mood swings, a high incidence of comorbid substance abuse, more frequent hospitalizations, and poorer response to standard treatments (Goldberg and Garno 2005, Leverich and Post 2006). A small case series (5 women) with severe chronic PTSD due to severe early abuse, reported rapid and substantial improvement in dissociative symptoms, emotional numbing, avoidance, irritability, energy, mood, memory, concentration, cognitive function, libido, anxiety, and insomnia when treated with 3-acetyl-7-oxo-dehydroepi-androsterone (7-keto DHEA), a metabolite of DHEA (Sageman and Brown 2006b). These patients were symptomatic despite years of psychotherapy and pharmacotherapy. Levels of DHEAS prior to treatment were below normal or in the lower quartile of normal. Doses of 7-keto DHEA ranged from 50−75 mg/day. None of the 5 patients reported any adverse side effects. A previous study of 13 women with chronic PTSD had found that those with a higher level of DHEA in response to adrenal activation by adrenocorticotrophic hormone had less severe PTSD symptomatology (Rasmusson et al. 2004). Cortisol-lowering treatments have been found to reduce the kinds of symptoms associated with PTSD. DHEA has been shown to counteract effects of circulating glucocorticoids and to improve memory, mood, and cognition. Unlike DHEA, 7-keto DHEA is not aromatized to testosterone or estrogen and therefore is unlikely to increase the risks of acne, baldness, hirsuitism, prostatic changes, or increased estrogenicity (risk of uterine or breast cancer). Further trials are needed to explore the benefits of 7-keto DHEA in treating PTSD. For patients with chronic PTSD who show poor or limited response to standard treatments, 7-keto DHEA should be considered. Serum DHEA and DHEAS levels should be obtained on patients with refractory PTSD or depression. Those with levels below normal or in the lower 50% of normal may benefit from a trial of 7-keto DHEA. The range of normal on laboratory tests of DHEA/DHEAS may not reflect the values seen in healthy age- and gender-matched controls (see for guidelines, the values listed under, Treatment and Disease Prevention Protocols: www.lef.org)

## Herbs and Nutrients for Anxiety Disorders and Insomnia

### Kava

Kava (extracted from *Piper methysticum*), a social and ceremonial drink in the Pacific Islands, has intoxicant, sedative, anxiolytic, anticonvulsant, and analgesic properties. These effects are mediated by alpha-pyrones (kavalactones) which have sodium and calcium channel blocking activity as well as some serotonin blocking action. In reviewing seven DBRPC studies of kava for anxiety, Pittler and Ernst (2000) concluded that it was relatively safe and superior to placebo. In the three studies that met criteria for meta-analysis (Lehmann et al. 1996, Warnecke 1991, Volz and Kieser 1997), patients had mild anxiety symptoms and short treatment periods. A meta-analysis of 3 DBRPC trials of kava for GAD found no beneficial effect from kava (Connor et al. 2006). Ships' logs of vessels visiting Polynesia in the

1800s describe kava intoxication in natives and seamen left behind by Captain Cook (see for review: Singh and Blumenthal 1996). After kava was introduced to the Maori in northern Australia, long-term users suffered facial swelling, scaly rash, increased patellar reflexes, and dyspnea. Low levels of albumin, increased GGTPase, abnormal CBCs with decreased white cell and platelet counts, and hematuria were found. Tall P waves on ECGs were consistent with pulmonary hypertension (Mathews et al. 1988). A report on 62 indigenous Kava users showed increased liver enzymes which reversed after several weeks abstinence. (Clough et al. 2003). Two postmarketing studies of over 3,000 patients found a 1.5% and 2.3% incidence of side effects, mostly gastrointestinal, allergic reactions, headache, and light sensitivity. Less commonly, restlessness, drowsiness, lack of energy, and tremor were reported. In four cases, kava induced dystonic reactions, oral/lingual dyskinesias, and worsening parkinsonian symptoms in a woman on levodopa. These effects are consistent with DA blocking. In one case, a 45 year-old woman developed severe parkinsonism after kava treatment (Meseguer et al. 2002). No studies of long-term safety, teratogenicity, or mutagenicity beyond 6 months have been reported. Combining kava with alcohol or other sedatives such as alprazolam or muscle relaxants has resulted in coma (Almeida and Grimsley 1996).

Since 1998, serious liver toxicities including liver failure requiring transplantation have been associate with kava extracted with acetone or alcohol. Aqueous kava extracts did not affect liver function in a rat study (Singh and Devkota 2003). The U.S. Food and Drug Administration (FDA) issued a Letter to Health Care Professionals and a Consumer Advisory about the potential risk of liver injury (FDA 2002, Kraft et al. 2001). Kava extract and kava lactones inhibit P450 enzymes involved in the metabolism of most pharmaceuticals (CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11) (Mathews et al. 2002). Considering the minor benefits of kava versus the potential for rare serious side effects, intoxication, abuse, and dependency, there seems little reason to recommend kava unless more compelling data on safety and efficacy become available.

## Valerian

Valerian (*Valeriana officianalis*) is thought to bind to GABA-A receptors. One review of DBRPC trials of valerian for sleep found the evidence to be encouraging but not compelling (Stevinson and Ernst 2000). Another review found subjective improvement in sleep in six out of seven DBRPC trials with no side effects other than minimal hangover in doses of 600−900 mg (Krystal and Ressler 2002). One DBRPC cross-over study of 16 mild insomniacs using polysomnography reported a significant decrease in slow wave sleep (SWS) onset latency and an increase in the percent of SWS time (Donath et al. 2000). The effect of valerian improves over time and maximal benefit may take 2 weeks.

A small study of 36 patients compared valerian (mean daily dose 81.3 mg valepotriates), diazepam (mean daily dose 6.5 mg), and placebo (Andreatini et al. 2002). There were no significant differences in this 4-week RCT among the three groups on either baseline or the change from baseline scores on HAM-A. All three groups had significant reduction in HAM-D scores. However, only the diazepam and valepotriates groups showed significant reductions on the HAM-A psychic factor. In a MCRPC parallel-group study of 184 adults with mild insomnia (Morin et al. 2005), the groups given valerian-hops or diphenhydramine showed modest improvements in subjective sleep parameters, most of which did not reach statistical significance. The valerian-hops produced greater, but not statistically significant, reductions in sleep latency than diphenhydramine and placebo. Quality of life improved significantly in the valerian-hops group compared to placebo, suggesting that valerian-hops may be a useful adjunct for mild insomnia. No serious adverse events occurred and there were no residual symptoms.

Reports of dystonia and hepatitis from preparations containing a mixture of ingredients (including valerian) are difficult to interpret. Valerian tea and tablets have an unpleasant taste and odor. One advantage of valerian over other sedative/hypnotics is that there have been no cases of habituation or abuse and only one case of possible withdrawal symptoms. Valerian should be avoided in pregnancy. A review and meta-analysis of 16 Valerian studies concluded that it might improve sleep without causing side effects and that further studies wer needed (Bent et al. 2006).

## Lemon Balm

Lemon Balm (*Melissa officianalis*): In a DBRPC cross-over study of *Melissa officianalis* using a 20-min laboratory-induced psychological stressor, the Defined Intensity Stressor Simulation (DISS) battery in 20 healthy volunteers, subjects were given single doses of 600 mg, 1000 mg, and 1600 mg, or placebo (Kennedy et al. 2003). The 600 mg dose significantly improved self-ratings of "calmness" Bond-Lader scales. A combination of *Melissa officinalis* and *Valerian officinialis* in three doses (600 mg 1200 mg, and 1800 mg) was given to 24 healthy volunteers in a DBRPC cross-over trial using a 20-min laboratory-induced psychological stressor, the DISS battery (Kennedy et al. 2004). Mood and anxiety were evaluated at baseline and 1, 3, and 6 hr. The 600 mg dose significantly reduced anxiety ratings, while the 1800 mg dose somewhat increased anxiety ratings. Within a therapeutic window, the combination of *M. officinalis* and *V. officinalis* may reduce anxiety under stress. A DBRPC internet-based study of kava and valerian reported no significant differences between kava and placebo for anxiety or between valerian and placebo for sleep disturbance (Jacobs et al. 2005). Subject selection was based on State-Trait Anxiety Inventory subtest (Stai-State) and on self report of "a problem going to sleep or staying asleep over the past 2 weeks" rather than on standard diagnostic criteria. The negative results may have been due to selection of a heterogeneous population, comorbid conditions, inadequate doses of herbs, or other limitations of internet surveys. A large uncontrolled MC study of a combination valerian/lemon balm product was tested in 918 children under the age of 12 years with restlessness and dyssomnia (Muller and Klement 2006). Substantial improvement occurred in 80.9% of the children with dyssomnia and 70.4% of those with restlessness. Controlled trials would be useful in assessing safety efficacy of herbs for children.

## Passionflower

Passionflower (*Passiflora incarnata*) has been approved by the Komission E for treatment of nervous restlessness.

Passionflower contains a dihydroflavone, chrysin, which binds to benzodiazepine receptors. In a DBRPC comparison trial, 36 patients with a DSM-IV-TR GAD (HAM-A ≥ 14) were given Passiflora extract 45 drops/day plus a placebo tablet, or oxazepam 30 mg/day plus placebo drops for 4 weeks. Although the oxazepam effect was more rapid, Passiflora was as effective in reducing anxiety and caused less impairment in job performance (Akhondzadeh et al. 2001). Larger studies are needed tovalidate these findings.

### Chamomile

Chamomile (*Matricaria recutita*). There is little scientific evidence to support the use of, chamomile for sleep or a82ety. Apigenin, a component of chamomile, has high affinity for benzodiazepine receptors, but minimal sedative or muscle-relaxant effects (Brown 1996). People who have ragweed allergy should not use chamomile.

## Clinical Considerations in Using Herbs for Anxiety and Insomnia

Herbs are most useful in patients with mild-to-moderate anxiety/insomnia who:

1. are at risk for addiction or abuse; may be sensitive to prescription medication side effects (e.g., children and geriatric patients);
2. require maximal alertness the next day; show adverse effects from medications (e.g., night eating syndrome with Ambien or amnesia from BZDs); and
3. have not responded to or complied with mind−body practices or who need more time to learn them.

Patients with recurrent major depression and anxiety/insomnia usually need more sedating medications (e.g., BZDs, TCAs, mirtazepine, or atypical neuroleptics). Psychotherapy or CBT, lifestyle changes, mind−body practices, and daily exercise over a period of months or years are usually needed to gradually discontinue such medications.

# Cognitive Enhancement

## Cognitive Enhancement in AAMI, AD, Dementia, Poststroke, TBI, ADHD, and Dyslexia

Cognitive enhancement should begin *in utero* and continue throughout the life cycle by providing (1) nutrients for the developing brain, (2) neuroprotective supplements for the aging brain, and (3) treatments for organic brain diseases. After age 20 years, memory decreases by 1−2% per year and usually memory loss becomes significant by age 45 (Crook et al. 1991). Age-associated memory impairment (AAMI) and age-related cognitive decline (ARCD) can be ameliorated by cognitive enhancers. Many neuropsychiatric conditions such as dyslexia, ADHD, AAMI, AD, dementias, ischemia, stroke, and TBI are affected by similar or overlapping pathophysiological processes. For example, TBI is often complicated by secondary ischemia. This section explores the emerging role of alternative treatments based upon the probable mechanisms by which they affect neurophysiological processes, cellular metabolism and repair, and neuronal electrical activity. Recent reviews of herbal medicines in AD found evidence for good therapeutic effectiveness with *Melissa officianalis, Salvia officianalis*, Yin-Gan-San, Ba Wei Di Huang Wan and *Ginkgo biloba*. However, limitations in the studies, such as small size and variations in preparatinos leave us with a need for larger studies using protocols such as the Consolidated Standards of Reporting Trials (CONSORT) to improve the standardization and reporting of the contents of the herbal preparations (Dos Santos-Neto et al. 2006).

For more detailed discussions of these processes, refer to the following:

1. Neurotransmitter theories: the cholinergic hypothesis (acethylcholine) (Arciniegas 2003, Arciniegas and Silver 2006); catecholamines (DA, NE, and 5-HT); and N-methyl-D-aspartate (NMDA)-glutamate receptor systems (Bell et al. 1998).
2. Biochemical and metabolic derangements: decreases in cellular energy (mitochondrial) production; free radicals (Long et al. 1996); hypoxia; secondary ischemia; nerve membrane alterations and the membrane hypothesis of aging (Zs-Nagy 1994); decreased calcium channel conductance; nitric oxide (McCann et al. 2005); blood–brain barrier damage (Hayes and Dixon 1994).
3. Anatomic areas sensitive to injury and age-related deterioration include the hippocampus, ventro–medial cortex, ventro–basal forebrain, cingulate gyrus, and reticular system (Murdoch et al. 1998, Schmidt and Grady 1995). The decline of hippocampal cells in the CA3 region during aging has been associated with decreased neuronal firing, increased lipid peroxidation, and increased lipofuscin (membrane fragments that accumulate). Stimulation of hippocampal CA3 fibers induces long-term potentiation (LTP) of synaptic transmission, a critical process for memory and learning. Information transfer across the corpus callosum is also important in learning and memory.
4. Computerized EEG maps show excess slow wave activity and decreased beta and/or alpha activity in patients with TBI, stroke, dementia, and ADD (Rozelle and Budzynski 1995). Cognitive activating agents decrease slow wave activity and increase alpha and beta activity (Itil et al. 1998).

## Vitamins

The Cache County study of 4,740 elderly subjects followed over 3 years showed that combined use of Vitamin C plus E supplements (neither alone nor B-complex) reduced prevalence and incidence of AD (Zandi et al. 2004). Other data support this finding (see for a review of earlier data: Sano 2003).

### B-Vitamins, Folate, Bio-Strath, and Homocysteine

The methylation pathways that maintain cellular proteins, membranes, and antioxidants depend on B-vitamins and folate as cofactors. B-vitamin and folate deficiencies are associated with abnormalities of mood, memory, and cognitive function (Bottiglieri 1996, Hassing et al. 1999). Higher folate, $B_6$, and $B_{12}$ concentrations have been associated with better cognitive performance. The fasting concentration of Homocysteine (tHcy) and its cofactors, folate, $B_6$ and $B_{12}$ were analyzed in $8_{12}$ adults (mean age 61) from the

Maine-Syracuse study who had no evidence of dementia or stroke. tHcy levels were inversely related to cognitive performance, with adjustment for age, gender and CVD. Folate, $B_6$ and $B_{12}$ levels were positively related to cognitive performance, but after adjustment for CVD, and CV risk factors, the relationship persisted for $B_6$ only (Elias et al. 2006). Supplementation with B-vitamins improves mood and cognitive function in healthy subjects (Benton et al. 1997). Bio-Strath, a B-vitamin supplement was given at double the usual adult dose to 75 patients, 55−85 years of age, with mild dementia in a 3-month DBRPC trial. The placebo group deteriorated. In contrast, the Bio-Strath group showed improvement in short-term memory as well as physical and emotional benefits. It took 3 months for the differences to appear (Pelka and Leuchtgens 1995). Given the relationship between B-vitamins and cognitive function and the probable role of antioxidants, it is important to treat geriatric and brain-injured patients with B-vitamins.

## Nutrients

### Omega-3FAs

Omega-3FAs, especially docosahexanoic acid (DHA), are important in neuronal development (Bourre 2005, Bourre 2006, Crawford et al. 1993) and in infant formula supplementation. Research on the benefits of essential fatty acid (EFA) supplementation of formula for normal infants has yielded mixed results. DBPC studies have shown that infants given omega-3 enriched formula have improved brain and eye development (Jensen et al. 1996), better problem solving at 10 months (Willatts et al. 1998), and an increase in scores on the mental development index (Birch et al. 2000). Long-term, large-scale studies with measures of development are needed. EFAs play a role in the synthesis of the PUFAs (necessary to maintain membrane fluidity), membrane enzyme activities, and production of prostaglandins, leukotrienes, and thromboxanes. Increasing free radical damage with loss of membrane PUFAs (lipid peroxidation) occurs with age and is associated with neurodegenerative disorders such as Parkinson's disease and AD. Abnormally low levels of omega-3FAs have been found in patients with depression and aggression (Hibbeln et al. 1997, Maes 1998, Peet et al. 1998), a subset of ADHD (Stevens et al. 1995), dementia, and AD (Conquer et al. 2000). A prospective study of 1,200 elderly subjects found that after 8 years, those with low DHA serum levels had a 67% greater chance of developing AD than those with high DHA levels (Kyle et al. 1998). Neurological symptoms improved in AD patients given DHA (Nidecker 1997, Soderberg et al. 1991). In a recent DBRPC study, 174 AD patients, 600 mg EPA slowed cognitive decline in very mildly impaired patients over a 6-month period (Freund-Levi et al. 2006). Although much work needs to be done in this area, supplementation with antioxidants and omega-3FAs may protect against neurodegenerative processes (Youdim et al. 2000). In many countries the average diet is deficient in omega-3FAs. Cold water fish, nuts, flax, and dark green vegetables are good sources. Fish or flax oil capsules are convenient for patients unwilling to change their diets. Although there is evidence that omega-3FAs may enhance cognitive development and protect against neurological decline, additional research is needed. High intake of unsaturated, nonhydrogenated fats may lower risk of AD, whereas high consumption of saturated or trans fats may increase risk (Morris et al. 2003). A recent epidemiologic study found reduced AD risk with increasing adherence to a Mediterranean style diet (Scarmeas et al. 2006).

### SAMe

SAMe is formed by the condensation of the amino acid methionine and ATP (see Figure 108–1). As a methyl donor, SAMe helps maintain neuronal membrane integrity and fluidity, neurotransmitter synthesis, and energy metabolism. The authors have reviewed the data on SAMe (Brown et al. 2000). In primate studies, SAMe reduced impairments and facilitated recovery from ischemic lesions in the motor cortex and dorsolateral prefrontal cortex and from reserpine. Microscopic data suggested that SAMe enhanced migration of macrophages engaged in tissue repair (Takahashi et al. 1986, 1987). SAMe improved cholinergic function and reduced learning deficits in aged rats (Pavia et al. 1997). Rats given 10 mg/kg per day SC SAMe had nearly 50% decreased free radical production, 50% increased glutathione, and nearly 100% increased glutathione peroxidase and transferase in brain tissue (De La Cruz et al. 2000).

Forty-one patients enrolled in a DBRPC pilot study received (within 24 hr of ischemia or hemorrhagic stroke) either SAMe 2,400 mg/day IV, SAMe 3,200 mg/day IV, or placebo for 14 days. SAMe improved survival and was well tolerated (Monaco et al. 1996). In a less rigorous single-blind (SB) study, 40 elderly patients with mild to moderate organic brain syndromes treated with SAMe for 2 months showed improvement in 13 out of 19 items on the Sandoz clinical assessment geriatric scale with a 25−45% improvement on scales of energy, drive, confusion, and self-care (Fontanari et al. 1994). In a DBRPC 1-month study of postconcussion syndrome, 30 patients were given either placebo or SAMe 150 mg/day IV. Mean clinical scores of postconcussion symptoms decreased 77% in patients taking SAMe compared to 49% in the placebo group. SAMe also shortened hospital stays (Bacci Ballerini et al. 1983).

### Picamilon

Picamilon, a combination of gamma-aminobutyric acid (GABA) and the B-vitamin niacin, decreases cerebral blood vessel tone and increases intracranial circulation rate. A double-blind (DB) controlled study showed that picamilon was more effective than vinpocetine in improving cerebral blood flow (Mirzoian et al. 1989). Picamilon has a mild tranquilizing action and decreases aggression. Paradoxically, it also has mild stimulative properties, improving alertness and cognition. In animal models it counteracts stress and reduces the CNS depressive effect of ethanol. Picamilon rapidly crosses the blood–brain barrier (Dorofeev and Kholodov 1991) and has low toxicity in animal experiments (median lethal oral dose is more than 10 g/kg of body weight). Russian researchers in 16 medical centers conducted large clinical trials using picamilon 20−50 mg, two to three times a day in therapies ranging from 2 weeks to 3 months. Patients with organic brain syndromes due to head trauma, cerebral atherosclerosis, and toxic brain lesions showed the best effects (Kruglikova 1997). Picamilon is useful in patients with cerebral vascular impairment,

particularly with decreased alertness, anxiety, and depression (see Section on ADHD for other uses).

## Cholinergic Enhancing Agents

The cholinergic hypothesis is based on observations that hippocampal cholinergic dysfunction underlies cognitive impairments in many animal models of TBI (Arciniegas 2001). Cholinergic deficits are also the most consistent pathophysiological findings in AD. The ability of cholinergic agents to improve cognitive function and delay deterioration in AD adds weight to this hypothesis.

### Citicholine

Citicholine (Cytidinediphosphocholine (CDP-choline), Cch) has been used to treat stroke, dementia, and brain injury in Europe and Japan (Alvarez et al. 1999). After crossing the blood–brain barrier, Cch breaks down into choline (a precursor of Ach) and cytidine (a ribonucleoside). Phospholipid incorporation of the choline restores membrane structural integrity. Cch improves mitochondrial metabolism and synthesis of phospholipids. In animal models, Cch alleviates cerebral hypoxia and protects against ischemia, edema, and neuronal death in the cerebral cortex, forebrain, and hippocampus, in part by decreasing brain glutamate release, boosting ATP levels (Hurtado et al. 2005) and increasing levels of NE, DA, and 5-HT (Petkov et al. 1990). Cch improved memory and cognitive performance in a rat brain injury study (Dixon et al. 1997). In a 6-week study of middle cerebral artery ischemic stroke, 62 patients were given CDP-choline 2,000 mg/day, 41 were given 500 mg/day, and 111 were given placebo. MRIs taken within the first 24 hr and at 12 weeks showed an increase in lesion volume of 1.8% in the 2,000 mg/day group, 34% in the 500 mg/day group, and 84.7% in the placebo group (Mitka 2002). Meta-analysis of controlled trials by the Cochrane Stroke Review Group concluded that patients with acute and subacute stroke benefit substantially from choline precursors such as CDP-choline (Mitka 2002). A more recent review of studies of CDP-choline for stroke was not as enthusiastic. It may be that CDP-choline must be started within 24 hr of stroke onset for benefits (Conant and Schauss 2004). In a study of 30 AD patients randomized to either 1,000 mg/day CDP-choline or placebo for 12 weeks. The patients given CDP-choline showed improved cognitive function without side effects. The effects were more evident in those with early, mild AD (Alvarez et al. 1999). Studies in head-injured patients, including case reports, five open series, three DBRPC, and two comparative studies, indicate that Cch treatment is associated with earlier recovery of consciousness, clinical and EEG improvements, accelerated motor rehabilitation, and shortened hospital stays (Calatayud Maldonado et al. 1991, Levin 1991, Lozano 1991, Spiers and Hochanadel 1999). Cch causes virtually no side effects and toxicity studies confirm its safety. Data suggest that CDP-choline may have a role in age-related memory decline (McDAniel et al. 2003).

### Huperzine-A

Huperzine-A (*Huperzia serrata*), derived from club moss used in Chinese medicine for inflammation and senility, is a strong acetylcholinesterase blocker with neuroprotective properties. Animal and primate studies show enhancement of learning and memory (Tang 1996, Xu et al. 1996). Three DB trials (more than 450 people) showed significant benefits in AD. Four trials in vascular dementia and AD using Huperzine-A combined with other nicergoline, estrogen compounds, or mental training, showed favorable outcomes. Other trials found benefits in vascular dementia, TBI, age-related memory decline, and schizophrenia (Akhondzadeh and Abbasi 2006, Wang et al. 2006). RCTs are needed to confirm benefits. In our experience, Huperzine-A is well tolerated with fewer side effects than other cholinergic enhancing agents.

## Herbal Cognitive Enhancers

### Rhodiola Rosea

Rhodiola Rosea (Golden Root, Arctic Root, or Roseroot) flourishes in the mountains of Eastern Europe, Siberia, and the Far East. It has been used for centuries in Russian and Scandinavian folk medicine. Gerbarg discovered evidence of its use in epic poems dating back to the Greek Bronze Age (Brown and Gerbarg. 2004). Since the 1960s, the former Soviet Union conducted extensive animal and human studies of *R. rosea*. The Soviet government sequestered *R. rosea* research in classified documents because its abilities to enhance physical and mental performance under stress were of strategic interest. It has been used to enhance performance in the military, in cosmonauts, and in Olympic athletes. Declassification of these documents has freed scientists to release their research, but many documents are still difficult to obtain. A comprehensive review, *R. rosea*—"a valuable medicinal plant" (Saratikov and Krasnov 1987c), has been translated by Zakir Ramazanov (2001, personal communication). More accessible reviews are also available (Furmanowa et al. 1995, Germano et al. 1999, Kelly 2001, Petkov et al. 1986). Brown et al. (2002) presented a phytomedical overview in Herbalgram. The Soviets exhaustively analyzed the diets of the people of the Province of Georgia searching for the secret of their longevity. Extensive epidemiologic studies have documented that the high percentage of centenarians and the high percentage of mentally and physically well elderly is based on environmental and dietary (rather than genetic) factors (Agakishiev 1962, Ferrell et al. 1985). *R. rosea* is believed to be an important dietary factor contributing to the longevity of Georgians who live at the highest altitudes. They prepare an extract of *R. rosea* root to make tea. All members of the families, from toddlers to great grandparents, drink *R. rosea* tea regularly.

*R. rosea* extracts contain bioactive alkaloids, polyphenols, and phenylpropanoids including tyrosol and salidroside (found in other plants). High pressure liquid chromatography (HPLC) identified the cinnamyl alcohol betavicianidines, rosavin, rosin, and rosarin as being specific to *R. rosea* (Bikov et al. 1999, Dubichev et al. 1991, Kurkin and Zapesochnaya 1986). The whole root extract has greater physiological activity than individual compounds. *R. rosea* extracts should be standardized to a minimum of 1% salidroside and 3% rosavin and should be free of drying agents such as maltodexrin or other carriers. Soviet scientists identified complex effects of *R. rosea* extracts on brain function: cognitive stimulation with emotional calming; enhanced learning and memory; increased accuracy in mental performance for prolonged periods of time. This powerful plant "adaptogen" protected every organism tested, from snails to humans,

against physical and mental stresses, exercise, toxins, and mental fatigue. Brekhman and Dardymov defined an adaptogen as a substance that would increase resistance against multiple stressors including biological, chemical, or physical insults; normalize physiology (whether a body parameter was too high or too low, the adaptogen would bring it towards normal); and not perturb normal body functions more than necessary to improve resistance (Breckhman and Dardymov 1969, Panossian and Wagner 2005). *R. rosea* increases the efficiency of energy metabolism and maintains energy rich compounds in brain (including the brain stem reticular formation and cerebral hemispheres), muscle, liver, and blood (Furmanowa et al. 1998, Kurkin and Zapesochnaya 1986). Mechanisms of action include effects on monoamines in cerebral cortex and brain stem (increasing NE, DA, and 5-HT) and in the hypothalamus (increasing NE and DA) (Petkov et al. 1986, 1990, Stancheva and Mosharrof 1987). *R. rosea* has "antiarrhythmic" and positive "inotropic" effects on the heart. In the myocardium, it prevents catecholamine release (and cAMP elevation) and stress related depletion of adrenal catecholamines (Maslova et al. 1994).

DBRPC studies have shown that *R. rosea* enhanced intellectual work capacity, abstract thinking, and reaction time in healthy subjects while reducing mental and physical fatigue (Saratikov and Krasnov 1987a, Shevstov et al. 2003, Spasov et al. 2000). *R. rosea* has been beneficial in patients with organic brain syndrome, most dramatically in posttraumatic and vascular brain lesions, especially in early postinjury stages. Piracetam augmented *R. rosea's* improvement of cognitive function. Based on findings that *R. rosea* exacerbated patients described as "volatile or euphoric" (Saratikov and Krasnov 1987b, Ramazanov (2001, personal communication)), there may be some risk of inducing mania in bipolar patients. *R. rosea* can be even more effective when combined with ginseng or ginkgo. In patients with brain injury, *R. rosea* has a mild stimulant effect while emotionally calming. It has not shown any drug interactions. In clinical practice, the authors have found *R. rosea* to be beneficial in a wide range of disorders of memory, cognition, and fatigue. Increased clinical use and research would be highly beneficial

## Ginkgo biloba

*Ginkgo biloba* extract has been used to treat AD and cerebral vascular diseases in Europe. An excellent review, including DBRPC studies was done by Wong (Wong et al. 1998). Memory improvements with ginkgo are slight at best and are dose related. Side effects are rare and can be minimized by starting at 60 mg/day and increasing gradually to 120 mg b.i.d. in Alzheimer patients. Occasionally nausea, headaches, and skin rashes occur. Although ginkgo somewhat decreases platelet aggregation, it does not appear to affect coagulation or bleeding time (Cott 2002), fibrinogen, prothrombin time or partial thromboplastin time (Kudolo 2000). Nevertheless, caution should be exercised when using ginkgo in patients on anticoagulants, and gingko should be discontinued 2 weeks prior to surgery. *G. biloba's* effects on cognitive performance in healthy adults are slight: long term memory on associational learning improved in a large well-done DBRPC study of 55−57 year olds (Burns et al. 2006), However, similar improvement has not been documented in healthy young adults. *G. biloba* extract has neuroprotective effects and benefits for memory, AAMI, vascular dementia, and AD. In a DBRPC MC 52-week study of 236 patients with AD, *G. biloba* extract (EGb 761) 120 mg/day improved cognitive performance in patients with mild to moderate cognitive impairment and also slowed the deterioration in patients with severe impairment (Le Bars et al. 2002). A DBRPC comparison study of 109 schizophrenic patients found that patients given Haldol plus EGb 360 mg/day had significant reductions in Scales for Assessment of Negative Symptoms (SANS) and of Positive Symptoms (SAPA) compared to patients treated with Haloperidol only. In addition, the EGb-treated group had fewer "extrapyramidal side effects." These benefits were hypothetically attributed to EGb scavenging of free radicals (Zhang et al. 2001). Ginkgo potentiates CPH and piracetam (Diamond et al. 2000). The author's clinical experience is that in TBI it is best used as an augmenting agent. Ginkgo is now the subject of the GuidAge 5-year DBRPC study of 2854 elderly subjects with memory complaints enrolled between 3/02 and 9/04 to determine if 450 mg/day ginkgo reduces the conversion to AD (Vellas et al. 2006). In the US, the GEM study has a similar goal and design. Ginkgo may have a stronger role in prevention than treatment of AD. Other sources of polyphenols similar to ginkgo that may help AD prevention include green or black tea, blueberries, resveratrol and curcumin (Ramassamy 2006).

## Ginseng

Ginseng (Panax, Korean) contains compounds with complex effects. It increased production of nitric oxide by endothelial cells (crucial for blood flow and oxygen delivery) in rabbits (Kang et al. 1995). In a DBPC 8-week study of 36 patients with secondary diabetes, ginseng improved psychomotor performance but not memory (Sotaniemi et al. 1995). A DBPC 8-week study of 24 geriatric patients given 80 mg/day of ginseng versus 25 given placebo found no benefits in cognitive performance. This is not surprising because that 80 mg of ginseng is quite a low dose (Thommessen and Laake 1996). Healthy volunteers over 40 years of age were randomized to either ginseng 400 mg/day or placebo for 8 weeks. The ginseng group showed significantly better abstract thinking and reaction time, but no significant differences in memory or concentration (Sorensen and Sonne 1996). One study that merits replication showed cognitive enhancement with a gingko/ginseng combination (Wesnes et al. 1997).

## Vinpocetine

Vinpocetine-periwinkle (*Vinca minor*), a semisynthetic alkaloid derived from periwinkle (*Vinca minor*), has been used in Eastern Europe as a vasodilator for cerebral vascular disorders. Neuroprotective effects include: inhibition of calcium/calmodulin-dependent cyclic GMP-phosphodiesterase 1; increased intracellular cyclic GMP in vascular smooth muscle; reduced resistance of cerebral blood vessels; and increased blood flow. Vinpocetine inhibits the molecular cascade precipitated by increases in intracellular calcium. A review of DBRPC trials in 731 patients with chronic cerebral vascular disease, including PET scan studies of 12 patients with middle cerebral artery infarcts, concluded that vinpocetine improves cerebral glucose kinetics and blood flow in the peristroke area (Bonoczk et al. 2000). The authors find

it helps patients with ischemia secondary to TBI and/or a single photon emission computed tomography (SPECT) scan evidence of blood flow abnormalities.

### Lemon balm (*Melissa officianalis*), Dalmation Sage (*Salvia officianalis*), and Spanish Sage (*Salvia lavandulaefolia*)

A 4-week DBRPC trial of *M. officianalis* aromatherapy in 71 severely demented patients showed decreased agitation and withdrawal with improvements in activities of daily living. In a DBRPC trial of two different doses of lemon balm in 18 healthy volunteers, the 600 mg/day dose reduced the effects of stress with better ratings of calmness but less alertness, wilst the 300 mg/day dose improved math processing speed without reducing accuracy (Kennedy et al. 2004). In a DBRPC 4-month trial in patients with mild-to-moderate AD, those given lemon balm showed cognitive benefit and reduced agitation compared to placebo (Akhondzadeh and Abbasi 2006). Another 4-month DBRPC study showed that sage (Salvia officianalis) had similar benefits in AD (Akhondzadeh et al. 2006). In a DBRPC crossover study of *Salvia lavandulaefolia*, 24 healthy undergraduates (ages 18−37) took either placebo or 25 μL or 50 μL *S. lavandulaefolia*. On Cognitive Drug Research Battery (CDB) and mood ratings at 1, 2, 4, and 6 hr, those given the herb, particularly at higher dose showed significant improvements in Speed of Memory and Secondary Memory factors, alertness, calmness, and contentedness compared placebo. Memory enhancement was attributed to increased efficiency of information retrieval. *S. lavandulaefolia* was chosen rather than *S. officianalis* because it contains the same bioactive compounds as *S. officianalis*, but has a lower concentration of thujone, a terpenoid ketone that can be toxic in high doses (Tildesley et al. 2005).

Two Chinese herbal preparations have shown promise in AD treatment. A 4-week SBRPC study in 52 AD patients given Yi-Gan-San showed cognitive improvement and gentle sedation. Ba Wei Di Huang Wan (BDW), a traditional tonic containing 8 herbs, is known is the US as Rehmannia 8. In a 2-month DBRPC study of 50 AD patients BDW improved cognition and reduced agitation. In addition to cholinergic enhancement, other actions are probable (Dos Santos-Neto et al. 2006).

## Ayurvedic Herbal Preparations

### Ashwaganda

Ashwaganda (*Withania somnifera)* has antistress (calming and mildly sedating) effects and may protect against AD (Anonymous 2004). This adaptogen, used in traditional medicines for centuries, has been studied extensively in animals. Data suggest that Ashwagandha is a cholinesterase inhibitor (Hawkins 2000).

Another Ayurvedic preparation occasionally used by the authors, particularly because for those Indian patients who are more receptive to traditional preparations, is Maharishi Ayurvedaa Student Rasayana (MA-SR). In a 5-month DBRPC study, 34 third-grade students were given either MA-SR or placebo. The MA-SR group showed a 10 point increase in IQ compared to five points in the placebo group with 78% of the MA-SR group showing improvement in IQ compared with 50% of the placebo group (more than would be expected from test–retest practice effects) (Nidich et al. 1993). *In vitro* models show that MA-SR decreases lipid peroxidation and enhances LTP in the hippocampus. Additional clinical studies are needed.

## Nootropics

### Pyrrolidones

Pyrrolidones (Racetams) are nootropics; neural metabolic enhancers. Although piracetam has been most frequently studied, aniracetam, oxiracetam, and pramiracetam are more potent. While results in animal studies are intriguing, human studies in mild dementia and AAMI have shown weak support (Itil et al. 1986, Flicker and Grimley 2001). Piracetam increases nerve cell membrane fluidity, activates EEGs, improves red cell deformability, and normalizes hyperactive platelet aggregation. In animal-learning models and aged rodents, effects on memory deficits are potentiated by CDP-choline, idebenone, vinpocetine, and deprenyl (Gouliaev and Senning 1994, Vernon and Sorkin 1991). Human studies combining racetams with CDP-choline and cholinesterase inhibitors would be worthwhile. Although positive studies of piracetam in postconcussion syndrome have had methodological problems (Cicerchia et al. 1985, Russello et al. 1990), in a DBRPC study of 60 patients with postconcussion syndrome of 2−12 months duration, piracetam 4,800 mg/day for 8 weeks reduced the severity of symptoms, especially vertigo and headache (Hakkarainen and Hakamies 1978). In large DBPC studies, piracetam (given within 7 hr of stroke) enhanced language recovery in combination with speech therapy (De Deyn et al. 1997) and improved task-related blood flow in left hemisphere speech areas on PET scan (Kessler et al. 2000). Studies of a combination of piracetam and ginkgo in dyslexia and aphasia showed significant enhancement of cognitive retraining: gingko improved attention and perception while piracetam improved learning (Enderby et al. 1994) (see the Subsection "Dyslexia and Learning Disabilities" further on). The authors (R.B. and P.G.) find in practice that aniracetam 750 mg b.i.d. is effective in improving cognitive function in bipolar patients with anticonvulsant-induced cognitive impairment, in unipolar depressives on antidepressants, for Chronic Fatigue Syndrome (CSF) and in patients with dyslexia.

### L-Deprenyl

L-Deprenyl is known as a prescription MAOI antidepressant in the US. It is considered to be an alternative agent in this discussion because most physicians are not familiar with its neuroprotective properties in organic brain disorders. Recent data suggest a mechanism of action different from its MAOI effect, when used in very low doses. Animal studies suggest that L-deprenyl protects catecholaminergic and cholinergic neurons by increasing antioxidants (Kitani et al. 2000, Maruyama and Naoi 1999). In a model of rat TBI, L-deprenyl improved cognitive function and neuroplasticity, particularly in the hippocampus (Zhu et al. 2000). Joseph Knoll, the discoverer of L-deprenyl, described a novel mechanism of action at a receptor site for an endogenous enhancer, which selectively improves impulse propagation mediated release of catecholamines and serotonin in the brain. The enhancer effects on catecholamine and serotonin systems are most marked in the hippocampus.

In response to stimulation of this receptor, glial cells and astrocytes secrete significantly higher amounts of numerous nerve growth factors (NGFs). Higher activity levels in enhancer-sensitive neurons appear to delay the age-related degenerative changes in the brain and to significantly increase longevity in animal experiments. In several studies, L-deprenyl slowed the progression of Parkinson's and ADs (Knoll 2000). Several human studies show slight improvements in cognitive function in early AD (Mangoni et al. 1991). Our clinical experience is that l-deprenyl given in ultra low doses (that do not cause MAO inhibition) giving half of a 5 mg pill 5 days of the week) may help prevent or slow neurodegenerative changes of aging, neurological diseases, and TBI. The authors use it to enhance neuronal repair and response to other treatments. Liquid L-deprenyl citrate may be more effective, convenient, and tolerable but no comparative studies have been done. The neuroprotective potential of L-deprenyl deserves further study.

### Phosphatidyl Serine

Bovine-derived phosphatidyl serine (Ptd Ser or PS) has been studied for AAMI (Caffarra and Santamaria 1987, Cenacchi et al. 1987), AD (Amaducci 1988), and related conditions. DBPC studies have shown modest memory improvement in these conditions (Crook et al. 1991, 1992). Crook found that in AAMI 300 mg/day for 1 month followed by 100 mg/day improved memory. (see for a review: Pepeu et al. 1996). Ptd Ser, a small component of the inner phospholipid layer, may make the nerve cell membrane more fluid (as discussed in the Subsection "SAMe"). Bovine brain-derived Ptd Ser, rich in DHA (22:6n3) increased brain DA, NE, and epinephrine levels in animals (Salem 1989, Salem et al. 1986). In contrast, Ptd Ser from soy, which is low in DHA, did not alter catecholamine levels. The apparent benefits of bovine Ptd Ser may be due to cognitive enhancing effects of omega-3FAs (Hibbeln and Salem 1995). Although no cases of Mad Cow Disease have been reported with bovine Ptd Ser, further research is needed to determine if this is a possibility. Considering the risk of acquiring prions from bovine tissue, at this time we would advise only using products derived from soy beans or from animals kept New Zealand or Australia where the surveillance for prion-related diseases is highly regulated. Although studies of Ptds Ser have used bovine derived products, in clinical practice, the soy-derived compound appears to be effective. Ptd Ser is often combined with other nutrients such as ginkgo despite the fact that the Ptd Ser effect on memory is more robust than that of ginkgo in normal elderly people. Some patients notice improvement in cognition on Ptd Ser, although the research data is limited (McDaniel et al. 2003).

## Other Cognitive Enhancing Agents

### DHEA

DHEA is produced primarily in the adrenal glands and secondarily in the ovaries and testes. Among its neurological effects, DHEA has been reported to improve memory, brain activation on EEG, and mood (Wolkowitz et al. 1999). A 3-month study of normal older men found no change in cognition or well-being with DHEA (van Niekerk et al. 2001). Patients whose DHEA is low for age (e.g., menopausal women who have had ovaries and adrenal glands removed) (Gurnell and Chatterjee 2001, Yen 2001) and debilitated geriatric patients with medical or neurological diseases are more likely to show improved memory and mood when given DHEA. Side effects include insomnia, irritability, slight increases in estrogen or testosterone, and potential interactions with steroids. Effects on prostate can be monitored by serial testing of prostate specific antigen (PSAs). Physicians should only administer pharmaceutical grade DHEA in doses sufficient to restore physiologic levels (25–50 mg/day).

### Melatonin

Melatonin has numerous neuroprotective properties. Its secretion is abnormal in AD and Parkinson's Disease. Melatonin can improve cognitive function to some extent in long-term use (see sections above and for a review: Srinivasan et al. 2006).

### Melatonin

Progesterone reduced by more than half the death rate and improved outcomes in a DBRPC study of 100 patients with TBI (Wright et al. 2006).

### ADD

ADD with or without hyperactivity is a constellation of symptoms that appears by age 7 years and often persists into adult life. Symptoms derive from inability to inhibit impulsiveness and/or to focus attention. Although the etiology and pathophysiology are not understood, theories involving DA, NE, and Ach neurotransmitter systems and under-arousal of the brain have heuristic value for research and treatment. It is particularly important to develop more effective treatments for ADHD because of the high incidence in children; frequent comorbidity with learning disabilities, oppositional behavior, depression, anxiety, bipolar, tics, obsessive–compulsive behavior; and high risk of later substance abuse and antisocial behavior. Stimulants such as methylphenidate are the mainstay of conventional ADD treatments. However, many parents would prefer CAM for their children. Their legitimate concerns about potential abuse and long-term side effects are fueled by reports that methylphenidate affects the brain like slow-acting cocaine (Vastag 2001); that stimulants (e.g., amphetamine) deplete the brain of high-energy compounds (Volkow et al. 2001a), SAMe (Cooney et al. 1998), and DA (Volkow et al. 2001b, 2001c); and that liver cancer increases in mice treated with methylphenidate (Dunnick and Hailey 1995, Ernst and Pittler 2000) (see for a review of CAM for ADHD: Arnold 2001, Kidd 2000 and for a discussion of biofeedback for ADD, Subsection "Neurotherapy" in this chapter). Misuse of prescription stimulants is increasingly prevalent. A survey of middle school and high school students treated with stimulants found that 23.3% reported being approached to sell, give, or trade their medication (McCabe et al. 2004). In a Web survey of more than 9,000 undergraduate college students, 8.1% reported lifetime illicit use of prescription stimulants (Teter et al. 2005).

### Dietary Elimination Strategies

Dietary elimination strategies have been supported by acceptable scientific evidence since the 1970s. The typical responder (a sizable minority of ADD children) is a preschooler with

insomnia, irritability, atopy, physical symptoms, behavioral problems, and sometimes high copper levels. Most families have difficulty maintaining the "few foods" diet. Eliminating the more suspicious food items may help in about 50% of children. Methodological problems and investigator bias in sugar elimination studies have left this issue unresolved (Kidd 2000). The role of toxicity from heavy metals (lead, aluminum) and organic chemical pollutants (pesticides, dioxin, polychlorinated biphenols, hydrocarbons, etc.) in the developing brain needs more research.

### Vitamin and Mineral Supplementation

Vitamin and mineral supplementation (not megavitamins) is promising in studies in normal children, retarded children, and teen delinquents. In a DBRPC 3-month trial ($n$ = 245), children whose pretesting showed low serum levels of B-vitamins or C-vitamins, those treated with vitamin supplements showed decreased aggression and antisocial behavior as well as improved cognitive performance (IQ increased 2.5 points) in those treated with vitamin supplements. A subset (20% of subjects) showed a mean IQ increase of 16 points (Schoenthaler and Bier 1999). The authors use Bio-Strath, a Swiss tonic of Brewer's yeast grown on antioxidant herbs and high in minerals, vitamins, and nutrients. In a 6-week DBRPC trial of 44 ADHD children, zinc (15 mg elemental) augmented methylphenidate better than placebo (Akhondzadeh et al. 2004). Zinc was found to be helpful in a 12-week DPRPC study of 328 boys and 72 girls with ADHD. Zinc sulfate 40 mg/day was significantly more effective in reducing symptoms of ADHD than placebo (Bilici et al. 2004). These studies were done in Turkey and Iran where zinc deficiency may be more prevalent. Nevertheless, in a study of middle-class American children low serum zinc levels correlated with inattention but not hyperactivity−impulsivity (Arnold and DiSilvestro 2005). Mineral supplementation for deficiencies of magnesium, iron, and zinc needs further study (Kidd 2000, Arnold 2001).

### Cognitive activators, antioxidants, nutrients, and nootropics

Cognitive activators, antioxidants, nutrients, and nootropics that have been shown to ameliorate symptoms in patients with TBI, dementia, and learning disorders may also be beneficial in ADD. Conventional and alternative treatments probably improve ADD symptoms by cognitive activation, but CAM treatments may also ameliorate underlying cell membrane dysfunction. Deficiencies of omega-3FAs have been found in a subgroup of ADHD boys (Antalis et al. 2006). Until further study, no treatment recommendations can be offered. Omega-3FAs improved behavior and cognitive function children with Developmental Coordination Disorder (ADHD is often part of this syndrome) (Richardson 2006). Although there have been no studies of Picamilon for adult ADHD, Richard Brown has found it to be extremely beneficial in several adult patients. RCTs in ADD treatment using the these compounds are needed. Acetyl-L-carnitine affects cell membranes, energy reserves, cholinergic function, and EFA utilization (Pettegrew et al. 2000). In a DBRPC study, 20 fragile-X boys with hyperactivity benefited from acetyl-L-carnitine (Torrioli et al. 1999). Dimethylaminoethanol (DMAE) is a common component of OTC supplements used in ADHD. Most of the DBPC trials were done so long ago that their methodology is considered inadequate. However, a more recent rigorous trial suggested a modest effect size, though less than methylphenidate (Arnold 2001). The authors prefer meclofenoxate, a combination of DMAE and PCPA, an excellent antioxidant in nerve cell membranes. It is well studied, inexpensive, and low in side effects. It is potentiated by ginkgo and caffeine. The author has found meclofenoxate with pyrrolidones to be particularly effective in a small number of children and adults with ADD and learning disabilities.

### Herbal treatment for ADHD

Herbal treatment for ADHD may be used for cognitive activation and/or calming. Controlled trials of ginkgo and ginseng are indicated because these herbs improve learning in animals and humans, they affect the appropriate neurotransmitter systems, and they are cognitive activators (Itil 2001, Petkov et al. 1990). An open trial in 36 children with ADHD given American ginseng (*Panax quinquefolius*) 400 mg/day plus *G. biloba* 100 mg/day for 4 weeks found that 74% improved significantly on the Conner's ADHD scale and 44% improved on a social problems measure. Only two children experienced mild side effects (Lyon et al. 2001). *R. rosea* has a similar profile and may be used in ADHD. However, it can be very stimulating in younger children. Although Passionflower is a frequent ingredient in OTC preparations for ADD no studies have been done in ADD. Side effects and toxicity have not been investigated. Huperzine (see the Subsection "Cholinergic Enhancing Agents") is of interest because it has minimal side effects (unlike prescription cholinesterase inhibitors). Pycnogenol® (extract from French maritime pine bark) was superior to placebo in a DBRPC study of 61 children with ADHD. On standardized measures and teacher and parent ratings after one month, students on pcynogenol had significantly greater improvements in hyperactivity, attention, concentration, and visual-motor coordination (Trebatická et al. 2006). Larger RCTs are needed to explore these findings. In a DBRPC trial in 36 children with ADHD for 12 weeks followed by 4-week wash-out, those given Bacopa showed better sentence repetition, logical memory, and paired associate learning. These improvements persisted 4 weeks after Bacopa was discontinued (Negi et al. 2000). A study of 40 normal children found that maze learning, perceptual organization and reasoning improved in those given Bacopa compared to controls. However, this was a nonblinded RPC 12-week trial (Sharma et al. 1987).

ADHD children (like adults with AD, TBI and seizure disorders) have excess theta and reduced beta and/or alpha rhythms. Animal data show a reduction of physical activity with appearance of beta frequencies in the sensorimotor areas when an animal is vigilant and still (e.g., a cat waiting to pounce on a mouse). Promising results have been associated with enhancement of alpha and/or beta rhythms, but further controlled studies are needed (Lubar and Lubar 1984, Ramirez et al. 2001, Nash 2000). The authors have found "disentrainment neurotherapy," a modification of this approach, to be helpful in ADD (Larsen 2006) (see Subsection "Neurotherapy" in this chapter).

### Mind–Body Practices for ADHD

Meditation, which effects EEG rhythms similarly to theta/beta biofeedback training, improved attention, particularly

in the classroom, in two controlled studies in ADHD children (Arnold 2001). In a pilot study of 19 boys with ADHD ages 8−13, a program of yoga postures, yoga breathing, and relaxation led to significant improvements on standardized ADHD tests such as the Conners. (Jensen and Kenny 2004). Nineteen children with ADHD were randomized to a yoga program or conventional motor exercises. For all outcome measures, including scores of attention and parent ratings, yoga training was superior with a medium-to-high effect size (0.60−0.97) (Haffner et al. 2006). More studies are warranted. The authors refer children to a program of yogic postures, breathing and meditation combined with games to improve life skills and self-esteem called ART-Excel taught by the Art of Living Foundation (AOLF) that seems to calm the children and improve their attention and behavior.

## Dyslexia and Learning Disabilities

Early studies of racetams in dyslexic children showed mixed results, probably due to heterogeneity of subjects and inadequate duration. A DBRPC MC study of 225 dyslexic children (ages 7–12 years) using piracetam 3,600 mg/day demonstrated significant improvements in reading and comprehension evident at 12 weeks and sustained for the 36 weeks of the trial (Wilsher et al. 1987). Piracetam was well tolerated with no adverse effects. In dyslexics piracetam preferentially activates the left hemisphere (Ackerman et al. 1991, Tallal et al. 1986, Helfgott et al. 1986). In clinical practice, the authors find aniracetam is somewhat preferable.

## Neurotherapy

Traditional Neurotherapy (neurofeedback or EEG biofeedback) trains patients to notice and influence their state of alertness based on EEG measures. This form of operant conditioning requires many treatments and patient cooperation. (see for a review of neurotherapy in ADD: Nash 2000, Butnik 2005, Holtmann and Stadler 2006). A modern innovation of neurotherapy uses the International 10−20 system of brain mapping and therapeutic procedures based on changing the frequency or amplitude of "brain waves" at specific sites on that system (Robbins 2000). It requires no effort on the part of the patient. Protocols have been developed for seizures using the sensori–motor rhythm (SMR, 12–15 Hz) (formerly called "lo-Beta") (Lubar and Bahler 1976, Sterman and Macdonald 1978), ADHD (Lubar and Lubar 1984, Sovik 2000), TBI (Ayers 1987), and PTSD combined with alpha training (alpha–theta protocol) to reduce the risks of re-traumatization during recall (Ochs 1994), and in depressed alcoholics (Peniston and Kulkosky 1989). quantitative EEGs (QEEGs), measuring frequencies and amplitudes over the entire brain, have improved the quality of diagnosis and treatment protocols. Inhibition of theta and reinforcement of SMR (immobile attention, still, but alert) have been postulated to explain the therapeutic effects of biofeedback. "EEG-driven stimulation" uses the patients brain waves to provide "fed back" to the brain via light emitting diodes (LEDs). Ochs included all brain wave ranges in protocols emphasizing the brain's flexibility in moving between them. Commercial light and sound machines entrain brain waves to a fixed frequency. Light flashing at exactly the brain's own frequency can amplify and drive existing instabilities, producing adverse reactions (e.g., seizures) in people with CNS damage. Ochs developed "offsets" to decrease rather than increase amplitudes producing "disentrainment" rather than "entrainment" (Glieck 1988) using radio waves at a level of intensity far below those of cell phone are used. Called the Low Frequency Neurotherapy System (LENS), this method has been beneficial in ADD, PTSD, affective disorders, pain syndromes, chronic fatigue, and fibromyalgia (Larsen 2006). Some of the best responses were in TBI (including patients with seizures). A preliminary, randomized study of 12 mild-to-moderately severe TBI patients with substantial cognitive impairment given 25 LENS (previously called Flexyx) treatments found significant improvements in BDI, mental fatigue, digit span backwards, delayed recall on the auditory verbal learning test (AVLT), ability to function at work and at school, and other measures when compared to a wait-list control group (Schoenberger et al. 2001).

LENS neurotherapy is a promising treatment with few adverse effects when administered by an experienced clinician. Side effects include temporary re-experiencing of symptoms related to trauma. Excess treatment can cause fatigue and restlessness. Biofeedback practitioners use other systems to reduce theta and enhance alpha and/or beta frequencies for ADD/LD children (Fox et al. 2005, Monastra et al. 2002, Becerra et al. 2006, Beauregard and Levesque 2006). Larger RCTs are needed to follow-up on positive clinical experience and preliminary trials.

## Clinical Guidelines in Using Cognitive Enhancing Agents

The main considerations in choosing alternative treatments are the specific target symptoms, mechanism of action, side effects, cost, and availability. For example, memory deficits respond well to cholinergic agents. Patients who have neural fatigue or problems with drive and energy, in addition to memory and abstract thinking may do best with *R. rosea*, SAMe, idebenone, or dopaminergic agents. Those who need treatment for depression and/or to improve stress resilience may benefit most from *R. rosea*, SAMe, L-deprenyl, and mind−body practices. Impaired alertness and vigilance may be helped by any of the cholinergic agents, *R. rosea*, picamilon, vinpocetine, or SAMe. Patients with a prominent vascular component in their lesion (by history, SPECT scan, or other blood flow studies) may benefit most from picamilon, vinpocetine (with or without) idebenone, or SAMe. Another example of combining agents would be to choose one that works primarily on the cholinergic system and another that works primarily on the catecholamine and/or serotonin system. Patients who, under psychological testing or on EEG, show over-activation of one cerebral hemisphere compared to the other, and who seem to have impaired transfer of information across the corpus callosum (on neurological testing), may do best with one of the racetam agents in combination with a cholinergic agent. The cholinergic compounds for which there is most evidence of efficacy in cognitively impaired populations or in animal models are galantamine, centrophenoxine, acetyl-L-carnitine, and particularly CDP-choline. Centrophenoxine may work best in combination with the racetam agents. Although piracetam has been the most widely used and studied, aniracetam may be more effective.

## How to Use CAM Treatments Safely and Effectively

### Herb–Drug Interactions

Our discussion of significant interactions between drugs and herbs must be brief and selective. See Tables 108–1–108–3 for a summary of the major side effects and drug interactions. Because alternative compounds tend to have low side effect profiles, few difficulties are encountered combining them with most conventional treatments. However, herbs (such as SJW) that affect the cytochrome P450 (CYP) drug metabolizing enzyme systems or the P-glycoprotein (Pgp) transmembrane pump can reduce serum levels of numerous medications (see Subseection "St. John's Wort (SJW) (*Hypericum perforatum*)") (Cott 2002). John Neeld, Jr., President of the American Society of Anesthesiologists, warned that a number of anesthesiologists have anecdotally reported significant changes in heart rate and blood pressure particularly in patients taking SJW, ginkgo, and ginseng. He recommends that patients be advised to stop herbal medications 2−3 weeks before surgery (Voelker 1999). Herbs which can affect bleeding time (feverfew, garlic, ginkgo, ginger, and ginseng) should not be used with warfarin and should also be stopped prior to surgery. The use of SJW with medications that have significant action on the serotonin system (SSRIs or MAOIs) should be avoided at the current time because of limited testing for safety. Valerian and kava should not be used with other sedating medications, such as benzodiazepines, because of the potential for additive sedative effects. Evening primrose oil and borage oil (a source of omega-3FAs) should not be used with anticonvulsants because they may lower seizure thresholds. Licorice may counteract the pharmacological effects of spironolactone. Chromium picolinate, and ginseng may affect blood glucose levels and should be stopped prior to surgery. Herbal laxatives and licorice, by depleting potassium, may affect the therapeutic action of digoxin, beta-blockers, and diuretics (see for more extensive information on interactions between natural products and prescription medications: Miller 1998, Ernst et al. 2001, Scott and Elmer 2002, Fugh-Berman 2000, Hu et al. 2005). When patients taking standard antidepressant medications are given activating compounds such as *R. rosea* or SAMe, they may experience over-stimulation and/or induction of hypomania in rare cases. Nevertheless, overall these agents are extremely well tolerated (see for an approach to risk management of herb−drug interactions: De Smet 2006).

### The Importance of the Doctor–Patient Relationship

Communication between a patient and his or her physician is the cornerstone of all therapeutic interactions. Thus it comes as no surprise that a patient's use of CAM becomes part of the therapy. This is particularly important in light of the expanding information regarding interactions between alternative and traditional treatments, which can be both advantageous and adverse. Surveys indicate that only 25−70% of patients inform their physicians about CAM use. Patients often use alternative therapies without consulting a qualified CAM practitioner. Asking a cashier at the health-food store may be the extent of their "consultation." Obviously, some patients are well informed about CAM from their own research, or from having consulted with an experienced herbalist or other CAM expert. We are practicing in a time of rapidly growing CAM use when few physicians have been trained in CAM therapies. While many physicians are scrambling to meet this challenge, others are ignoring the need to gain competence in this emerging field of medicine. Ignorance and/or insecurity about CAM treatments may contribute to a potential countertransference enactment in which the physician discounts *all* CAM approaches as unfounded and misinterprets the patient's interest in CAM as merely a form of resistance (Kenny et al. 2001). This can create a situation in which the patient cannot tell the doctor about their interest and/ or use of a CAM. Patients are more likely to share information with a physician who is open-minded and nonjudgmental. We suggest the discussion start with a comment such as, "I am interested in the ways you maintain wellness such as diet, exercise, herbs, and other activities." This is preferable to, "Do you use any of *those* things?" Many CAM treatments enhance and maintain well-being, however, an alternative treatment may render a traditional one less effective, creating confusion in the therapy. Open dialogue between patient and physician helps prevent adverse outcomes.

As with all human endeavors, a patient's desire to pursue a CAM therapy may reflect a spectrum of psychological meanings. No discussion could cover them all, but a few general themes are worth considering. First, to what extent does the desire for CAM indicate a resistance to conventional treatment that should be clarified and interpreted? Could there be negative transference feelings towards the therapist as an inadequate caretaker or as a controlling conservative authoritarian, mistrust or disappointment stemming from unrealistic expectations of cure, or a need to control the therapy by pursuing treatments outside the therapist's control? Second, to what extent is the patient's interest in CAM a legitimate expression of dissatisfaction with traditional treatments and a genuine desire to explore other avenues to seek symptom relief? Three additional points should be considered when patients discuss CAM therapies: What is the patient's knowledge about the particular CAM treatment and with whom has the patient consulted; What is the physician or therapist's knowledge about the treatment and with whom should she/he consult; How can the therapist support and assist the patient's pursuit of safe and effective CAM treatments? (see Subsection "Physician Education" below).

### Quality of Alternative Compounds

Doctors and consumers are concerned about the quality of alternative products, particularly herbs and nutrients. Advances in biochemistry have enhanced the purity and stability of many compounds (Wagner 1999). Although the publication of specific brands is not the norm in a text of this kind, in the field of alternative medicine it is particularly important to choose products that have proven to be of good quality. To help the clinician find a way through the morass of unreliable, ineffective look-a-likes and bargain brands, Table 108–1 lists particular brands that we have investigated. Invariably some products and companies will change over time. Physicians need to stay current using unbiased sources of product information. Independent evaluation of many brands with updates can be found at www.consumerlab.com

or www.supplementwatch.com Recalls and warnings to stop use of certain brands, which is available at: http://www.fda.gov/medwatch or http://www.cfsan.fda.gov/~dms/supplmnt.html.

## Medical Liability Issues

Using alternative treatments and compounds from other countries raises the issue of medical liability. The fundamental principles are the same as with mainstream treatments. A good relationship with the patient and family is key. For informed consent, the physician should clearly explain why the alternative treatment is being recommended, what is known about the compound and how it works, the potential risks and benefits, and the risks and benefits of standard treatment options. The entire explanation should be documented in the chart, including the symptoms that have not responded to standard treatment attempts and the particular indications and considerations involved in the decision. This may include the patients' philosophy, cultural background, or the fact that they have had difficulty tolerating conventional agents. Physicians, wishing to learn more about the background of data supporting the use of CAM treatments, may examine the references cited in this chapter (see for an excellent review of these issues: Cohen and Schouten 2007).

## Physician Education

Patients need help to understand how to choose products of quality whose efficacy has adequate clinical and research support. Physicians can educate themselves by starting with a recent review article on the most common herbal remedies used in North American populations (Wong et al. 1998). The Herb Research Foundation, started by Andrew Weil, in coordination with the American Botanical Council, publishes the Herbalgram, a journal that reviews herbs and features abstracts of recent studies in scientific journals. *The ABC Clinical Guide to Herbs* (Blumenthal et al. 2003) contains a collection of monographs, user-friendly descriptions of herbs, lists of research studies, and patient information sheets. The American Botanical Council individual Monographs may be obtained from the Herb Research Foundation for a small fee (Tel: 303-449-2265). When faced with a patient taking an unfamiliar herb or nutrient, a good source of information is the Natural Medicines Comprehensive Database (Tel: 209-472-2244 or www.naturalmedicine.com). However, the clinical recommendations on the Natural Medicines Database website are quite conservative. Detailed information is also available from The Natural Product Research Consultants (Tel: 973-762-0840) or the American Botanical Council (Tel: 512-926-4900). The National Center for CAM (http://nccam.nih.gov) provides information on research trials. *The Desktop Guide to Complementary and Alternative Medicine*: *An Evidence-Based Approach* (Ernst et al. 2001) is an extremely well-organized and well-documented resource for any clinician. The *Complementary and Alternative Treatments in Mental Health Care* (Lake and Spiegel 2007) offers evidence-based discussions by experts on different aspects of CAM. Another reference is *How to Use Herbs, Nutrients, and Yoga in Mental Health Care* (Brown et al. in press). Drawing upon research and years of clinical supervisory experience, the authors have written this biblio–supervision to help clinicians understand ways to integrate CAM into standard psychiatric practice. Updated CAM information and resources are available on the Brown and Gerbarg website: www.haveahealthymind.com

## Summary

This review focused on treatments supported by evidence from clinical trials, mechanisms of action, animal models and *in vitro* studies with relevance to human conditions, and the authors' experience. All of the substances discussed have relatively low side-effect profiles and high margins of safety. There is reason to believe that alternative agents have neuroprotective effects as well as abilities to help repair the injured nervous system and enhance its plasticity. Although many CAM treatments have not been generally used by physicians in the US, nor approved by the FDA, based on scientific evidence and the above criteria, they can offer significant benefits for many individuals. Clinically, it often requires several attempts to design an effective combination of treatments. A well-informed clinician is best qualified to help patients and their families understand and develop their alternative treatment regimens.

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CHAPTER

# 109 Brain Stimulation in Psychiatry

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## Introduction

Brain stimulation in psychiatry encompasses a growing list of tools for therapeutic neuromodulation (Lisanby 2004a). These tools include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), transcranial direct current polarization (tDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) (Figure 109–1 and Table 109–1).

With the introduction of ECT in 1938, brain stimulation has been in continuous use in psychiatry for the past nearly 70 years (Figure 109–2). As with other medical procedures, ECT technique has evolved over this time, becoming progressively safer and better tolerated with innovations in anesthesia and ECT treatment parameters. After the introduction of ECT, there was a 50-year gap before the next brain stimulation intervention appeared in the field of psychiatry. Breaking the five-decade hiatus was the first published use of pulsed magnetic fields to stimulate the brain (a procedure called TMS) in 1985 (Barker et al. 1985). Initially used in neurology for nerve conduction studies, TMS rapidly caught the attention of psychiatrists who were eager to explore whether TMS could represent a less invasive, nonconvulsive alternative to ECT. The therapeutic potential of TMS in the treatment of a number of disorders in psychiatry (including depression, schizophrenia, anxiety disorders) and neurology is under active study with some promising results (Stanford et al. 2007, Lisanby et al. 2002). A parallel line of development has been to use TMS as a more focal means of inducing seizures (a procedure called MST, in an attempt to retain the excellent efficacy of ECT, but with fewer cognitive side effects (Lisanby et al. 2003, Lisanby et al. 2001, Lisanby 2004b, Moscrip et al. 2006).

The next two developments in the field of brain stimulation came just a short decade after the introduction of TMS, and they were the approval of DBS for the tremor of Parkinson's disease, and the approval of VNS in the treatment of epilepsy in 1997 (Figure 109–2). As was the case for TMS, these new developments originated in the field of neurology. However, psychiatrists rapidly appreciated the therapeutic potential of these novel modalities. VNS subsequently received FDA approval for the treatment of chronic, medication refractory depression in 2005 (Rush et al. 2000). Likewise, DBS is under active study in the treatment of obsessive compulsive disorder and depression (Mayberg et al. 2005, Greenberg et al. 2006). In the past decade, several new technologies have emerged in the field of neurology. These include responsive stimulation paradigms and epidural cortical stimulation. Again, psychiatric interest in these modalities is high, and at a very early stage.

As this timeline suggests, the evolution of brain stimulation techniques in psychiatry appears to be gaining momentum. Often developments in neurology have been co-opted for psychiatric indications. However, it is not clear whether the technologies and dosages that are designed for neurological indications will be ideal for psychiatric indications. Indeed, we are at an early stage of testing the clinical value of recent developments in the brain stimulation armamentarium, and weighing what the new modalities have to offer relative to the original brain stimulation technique in psychiatry—ECT. This chapter reviews the current state of the evidence for each of the brain stimulation modalities.

## Brain Stimulation: A Unique Family of Neuromodulation Interventions

### Mechanisms of Action

#### Electrical Stimulation of the Brain

The various brain stimulation modalities share a common characteristic in that they stimulate the brain electrically. This electrical stimulation may be directly applied or indirectly induced via magnetic fields. The direct application of electrical stimulation can be performed transcranially as in the case of ECT, transcranial electrical stimulation (TES) and tDCS. However, electricity can also be applied epidurally (e.g., epidural electrical stimulation), or intracerebrally (as in the case of DBS). The epidural and intracerbral modalities

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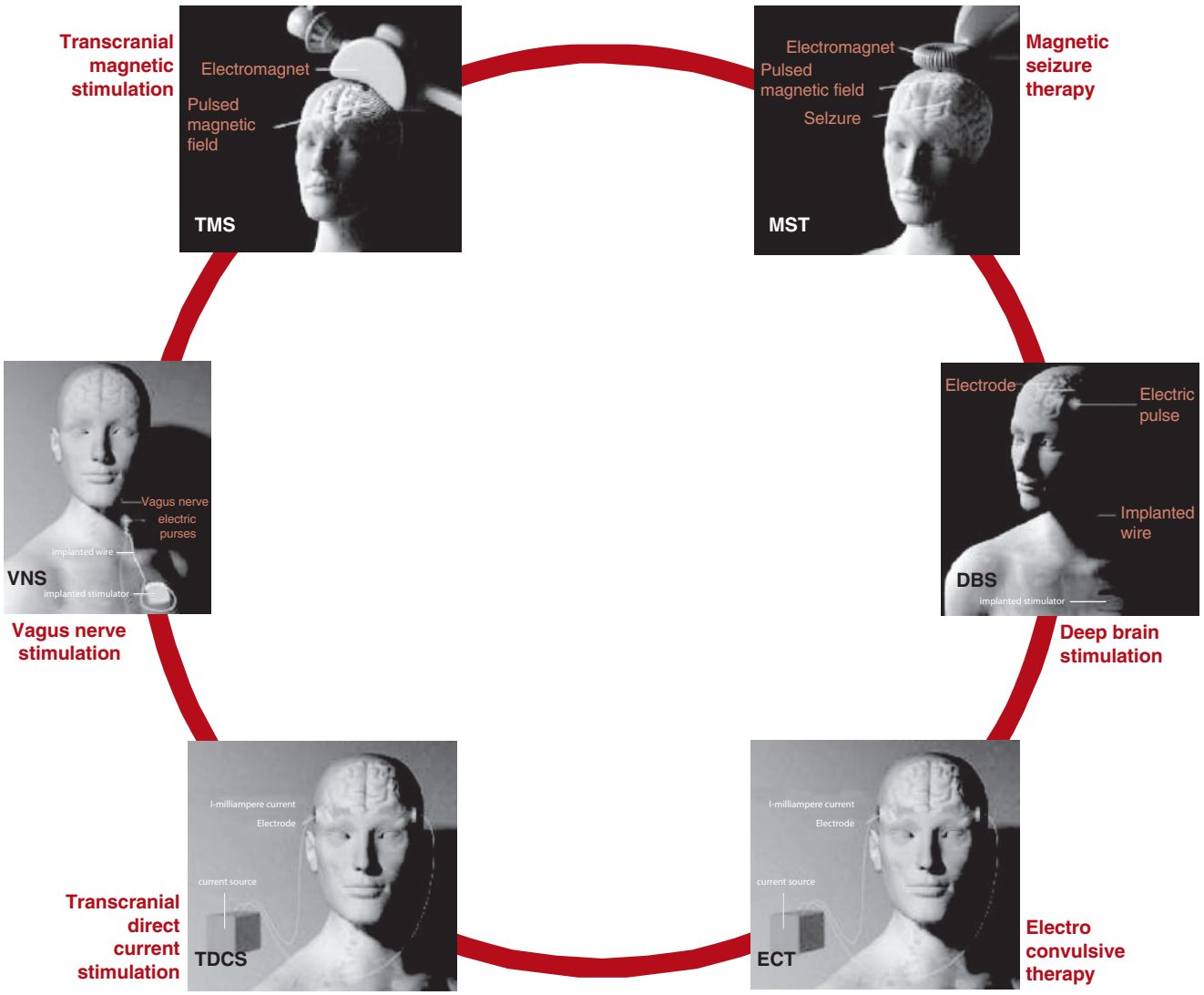



**Figure 109–1** *Brain stimulation tools.*

**Table 109–1 Brain Stimulation Modalities: Definitions**

| |
|---|
| **DBS:** A wire electrode with multiple stimulating sites is surgically implanted into the brain and chronically administers electrical stimulation |
| **ECT:** Electricity is applied transcranially via electrodes placed on the scalp to induce a seizure under anesthesia |
| **MST:** High intensities of TMS are applied to induce focal seizures under anesthesia, as a less invasive form of ECT |
| **tDCS:** Weak direct electrical currents are applied to the scalp via sponge electrodes to polarize underlying brain tissue |
| **TMS:** Rapidly alternating magnetic fields are applied to the scalp to induce small, focused electrical currents in superficial cortex. |
| **VNS:** An implanted pacemaker administers electrical pulses to the vagus nerve in the neck, activating the vagal afferents |

are more focal than transcranial application of electricity because they bypass the impedance of the scalp and skull.

The magnetic modalities (TMS and MST) induce electricity in the brain indirectly via the principle of electromagnetic induction. Rapidly alternating magnetic fields will induce an electrical current in a conducting medium, like the brain. The magnetic modalities bypass the impedance of the scalp and skull, but they achieve this enhanced focality noninvasively without needing to implant an electrode within the skull as is required for the direct application of electricity. Therefore, the magnetic modalities offer an unparalleled degree of focality without the need for surgery.

## Comparison with Psychopharmacology

Psychopharmacology and brain stimulation differ as therapeutic modalities in several clinically relevant respects (Table 109–2). For example, while psychopharmacology relies on molecular action at presynaptic or postsynaptic receptors or intracellular targets, brain stimulation can induce action potentials via electrical depolarization of axons in a manner that is independent of receptor binding. In this sense, brain stimulation has the potential to work when medications have failed, and also the potential to act synergistically with medications, because their sites of action are distinct. Because stimulation is applied directly to the brain, it avoids the systemic side effects seen with medications that are systemically distributed and may be metabolized to biologically active compounds. Brain stimulation has no metabolites,

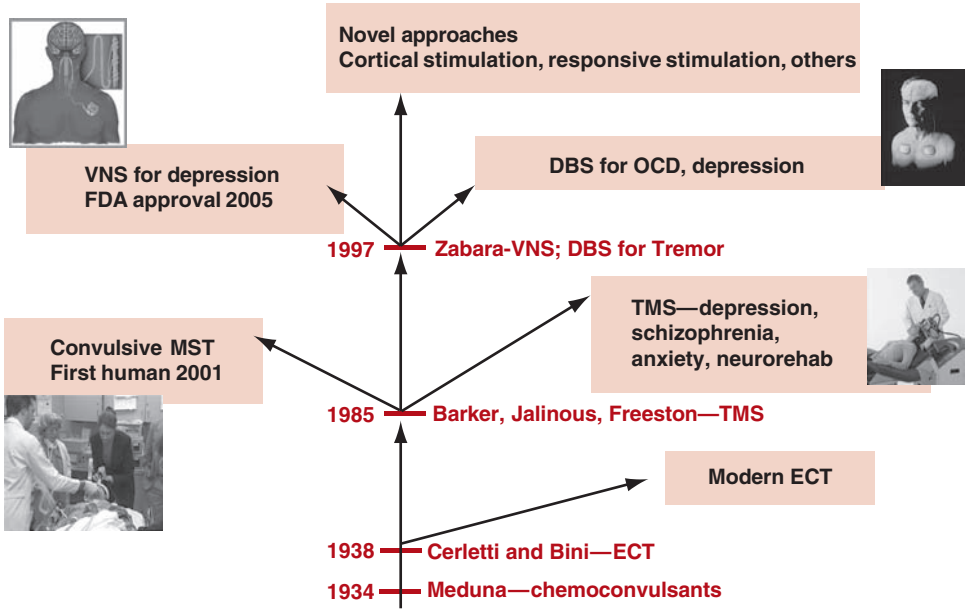



**Figure 109–2** *Evolution of brain stimulation in psychiatry.*

does not undergo clearance, is not protein bound, and has no known interactions with the metabolism or clearance of psychopharmacological agents.

While medications continue to be biologically available for hours to weeks, depending upon half-life, brain stimulation is applied in a phasic fashion, and because it is electrical, it is not subject to metabolism or clearance. Brain stimulation modalities that administer alternating currents (AC) (e.g., ECT, DBS, VNS) deliver pulses that typically last a millisecond or less. Direct current stimulation (tDCS) is typically applied for up to 30 min. The phasic nature of brain stimulation provides immediate washout in a manner that is not possible for pharmacological agents that must be metabolized and cleared. However, the transient nature of brain stimulation poses a challenge to the induction of lasting effects that will persist beyond the period of stimulation.

## Acute Versus Chronic Effects

The actions of brain stimulation can be separated into acute and chronic effects (Figure 109–3). Single electrical pulses, delivered at sufficient intensity, can induce neuronal depolarization and trigger transsynaptic action, resulting in the activation of a function circuit. For example, a single TMS pulse applied to the hand area of the primary motor cortex, can activate the cortical spinal track and induce a visible twitch in the contralateral hand muscle. These acute effects of brain stimulation can induce positive effects, as in the case of a muscle twitch or phosphenes (sensation of seeing light), or the acute effects can be disruptive, as in the case of visual masking.

Repeating pulses at regular intervals can exert even more powerful acute effects on brain function. For example, repetitive TMS (rTMS) to the language dominant hemisphere can induce speech arrest (Epstein et al. 1999). In these studies, speech returns to normal after the stimulation is terminated.

Some brain stimulation modalities, like DBS, deliver repetitive pulses continuously, in which case the therapeutic action may rely on acute effects of the stimulation. However, the less invasive and nonsurgical modalities typically involve intermittent stimulation, which presumably requires the induction of some form of neuroplasticity, or other process yet to be determined, that persists beyond the period of stimulation.

## Neuroplasticity

Repeated stimulation of a circuit can induce lasting changes in the subsequent activity of that circuit. Neuroplasticity is

**Table 109–2 Comparisons Between Psychopharmacology and Brain Stimulation as Therapeutic Modalities**

| Therapeutic agent<br>Temporal characteristics | Psychopharmacology | Brain Stimulation |
|---|---|---|
| | Neurochemical | Electromagnetic |
| | Tonic | Phasic |
| Delivery | Dependent upon patient compliance | Automated or clinician administered |
| Site of action | Molecular target | Neuronal depolarization |
| Distribution | Systemic | Focally applied to the brain |
| Duration of availability | Typical half life hours to weeks | Millliseconds to seconds |
| Dosage parameters | Milligrams, blood level | Intensity, frequency, intertrain interval, number of pulses, site of stimulation |
| Metabolism | Hepatic | None |
| Clearance | Renal | None |
| Interactions with metabolism of other agents | Possible | None known |

- **Acute effects**
  - **Direct activation of neural circuits**
  - **Elicits observable responses (motor twitch) or disrupts (e.g., speech arrest) or facilitates (e.g., speeds reaction time) ongoing processing**
- **Lasting effects**
  - **Neuroplasticity**
    - **Synaptic efficacy, LTP/LTD**
    - **Neurotropic factors**
    - **Modulation of cortical excitability**
    - **Modulation of functional connectivity**

**Figure 109–3** *Brain stimulation mechanisms of action.*

thought to occur through dynamic alterations in synaptic efficacy. For example, repeatedly electrically stimulating the perforant pathway at high frequency induces a lasting increase in the efficacy of that circuit, while low frequencies depress it. These phenomena are termed long-term potentiation (LTP) and long-term depression (LTD), respectively. There is evidence that TMS may act in ways that resemble these aspects of neuroplasticity. Specifically, low frequency rTMS (≤1 Hz) induces a sustained depression in measures of the excitability of the motor cortex, while high frequency rTMS (≥5 Hz) increases motor excitability (Chen et al. 1997, Wang et al. 1996). Recent work coupling TMS with topographical electroencephalogram (EEG) measurements of TMS-evoked potentials provides the first evidence suggesting that these changes in excitability may come about through an enhancement of a brain potential (Esser et al. 2006). While not definitive proof that TMS causes LTP, this in vivo evidence is consistent with that hypothesis.

### Impact of Development and Illness on the Brain's Response to Stimulation

Because brain stimulation acts via neuronal depolarization, and possibly via alterations in synaptic efficacy, it is not surprising that factors that influence neural transmission and plasticity may influence the brain's response to exogenous stimulation. For example, before the process of myelination is complete, infants and children have higher thresholds for activation of circuits via single pulses of TMS (Mall et al. 2004). Likewise, it has been reported that patients with schizophrenia fail to show inhibitory effects of low frequency rTMS over the motor cortex, which may reflect abnormalities in glutamatergic functioning in that illness (Fitzgerald et al. 2004).

Aging probably also impacts the brain's response to stimulation. While less relevant for the electrical modalities, cortical atrophy seen with aging or other processes, can reduce the delivered dosage of magnetic stimulation (Kozel et al. 2000). Independent of issues of distance, animal models suggest that aging can also blunt the ability of TMS to induce LTP (Levkovitz and Segal 2001).

## Relative Focality and Invasiveness of Brain Stimulation Modalities

The various brain stimulation modalities differ in their relative degrees of focality and invasiveness (Figure 109–4). Noninvasive technologies clearly have the advantage that they may be used with fewer concerns regarding adverse effects, making them more acceptable earlier in the course of illness. Focality is an advantage for brain mapping studies that seek to identify brain regions involved in selected functions. Focality is also a therapeutic advantage if the specific therapeutic target is known, and if stimulation of adjacent regions might be counter-therapeutic. However, if the therapeutic target is broad, or not precisely known, then focality could have drawbacks with respect to efficacy.

DBS is the most focal, since the electrode is implanted directly into the target brain region, but is also the most invasive. On the opposite end of the spectrum, tDCS is the least invasive, but also the least focal modality as it involves the transcranial application of electricity. Also nonfocal is ECT, for the same reasons of scalp and skull impedance faced by tDCS. ECT is more invasive, however, by virtue of

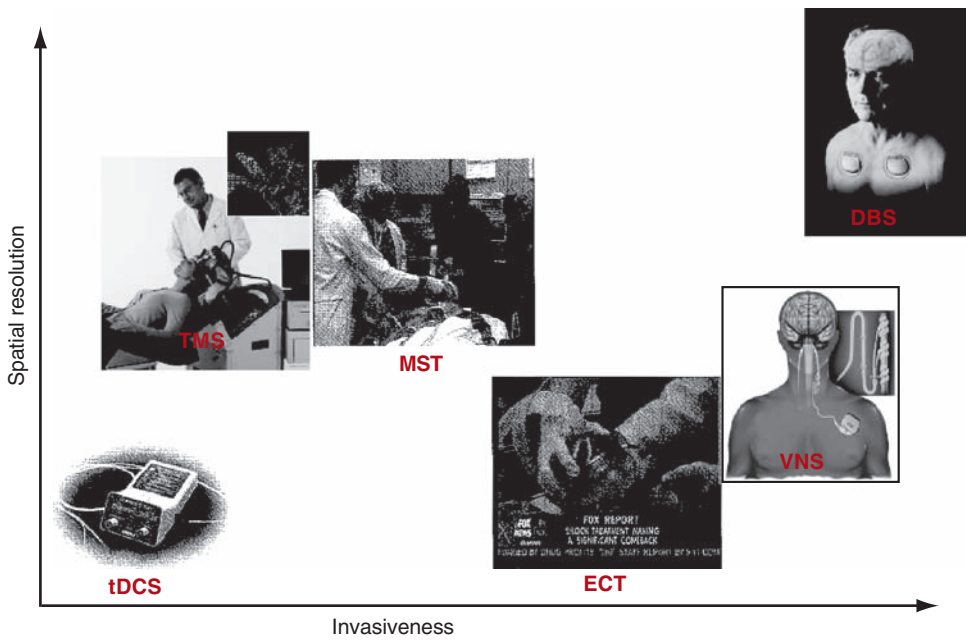



**Figure 109–4** *Brain stimulation landscape.*

the necessity for seizure induction. TMS and MST are more focal than their electrical counterparts because magnetic field passes through the scalp and skull without impedance, allowing more control over site and extent of stimulation. VNS is less invasive than DBS, but also less focal because it stimulates the vagal afferents which are widely distributed.

## Applications of Brain Stimulation in Psychiatry

### Parallel Approaches: Probing Brain Function in Health and Disease, and Treating Psychiatric Disorders

Brain stimulation modalities have contributed to our field in multiple parallel ways: (1) as tools of discovery to examine normal brain function, (2) as tools to examine the pathophysiology of psychiatric disorders, and (3) as novel therapeutic agents (Figure 109–5).

Unlike neuroimaging that passively acquires information regarding brain function in various conditions, brain stimulation actively changes brain function and induces measurable effects on brain activity. Because neuroimaging is a passive modality, the information yielded in this manner represents correlates of behavior, but cannot test causal relationships. Brain stimulation, on the other hand, is an intervention that can test causal relationships between brain and behavior. As such, brain stimulation can test hypotheses generated via functional neuroimaging. Independent of its ultimate clinical role, noninvasive brain stimulation modalities like TMS have already offered unprecedented means of examining brain-behavior relationships.

Because brain stimulation actively modulates neuronal activity in ways that may be lasting, it additionally carries the potential for therapeutic effects. This potential has been actively explored in a range of psychiatric disorders, as reviewed below.

### Integration of Brain Stimulation with Neuroimaging and Neurophysiology

Coupling brain stimulation with functional imaging and/or neurophysiology represents a powerful paradigm for studying neurocircuitry in health and disease, and provides intermediate outcome measures that may be useful in the development of novel treatments. For example, TMS has been successfully combined with positron emission tomography (PET) (Paus et al. 1997), functional magnetic resonance imaging (fMRI) (Bohning et al. 1999), and EEG (Ilmoniemi et al. 1999). A common strategy is to perform the imaging or physiological measures before and after the TMS intervention. However, it is now also possible to perform simultaneous stimulation and imaging.

Simultaneous imaging is useful for examining acute effects of brain stimulation. For example, Strafella and colleagues used dopamine receptor PET to demonstrate that prefrontal TMS releases dopamine in the caudate, providing a functional probe of the activity of frontostriatal dopaminergic regulation (Strafella et al. 2001). On the other hand, the pre/post paradigm may be useful for identifying lasting and chronic effects of stimulation. For example, Speer et al. (2000) found that a course of daily rTMS given to depressed patients induced lasting increases in regional cerebral blood flow in bilateral frontal, limbic, and paralimbic regions implicated in depression. Such results could inform the mechanisms of action of brain stimulation modalities, and could be used to screen for stimulation paradigms predicted to have therapeutic effects based upon their ability to modulate activity in the circuitry implicated in the illness.

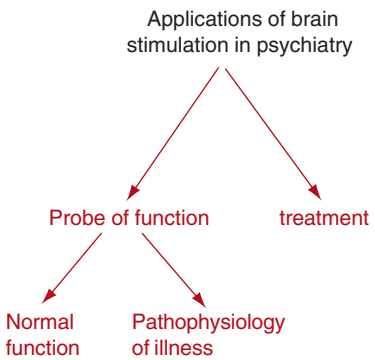



**Figure 109–5** *Applications of brain stimulation in psychiatry.*

## Brain Stimulation Tools in Psychiatry

### ECT

#### Definitions

During ECT, an electric current is passed through the brain via electrodes placed against the head to produce a seizure. A series of treatments constitute an acute course of the ECT therapy, which is used to treat several psychiatric conditions when other treatment modalities have either failed, cannot be tolerated, or are not expected to produce satisfactory results quickly enough. The procedure is performed under anesthesia to block the motor convulsion that would otherwise occur in the absence of a muscle relaxant, and to insure adequate oxygenation throughout the procedure. Typically, ECT will relieve the most profound symptoms of depression, the most commonly treated illness, within 2–3 weeks, with treatments usually given 2–3 times per week during the acute course of ECT. Continuation ECT refers to the continued application of ECT in the weeks immediately following the end of the acute course, at a tapered schedule, to stabilize remission. Maintenance ECT refers to the continued use of ECT over the months following a successful ECT course to prevent relapse.

#### History

Initially, convulsive therapy was performed via chemoconvulsant agents, a procedure introduced by Meduna in 1934 (see for a review of the history of ECT: Dukakis and Tye 2006). The first electroconvulsive treatment was performed on a human patient by the Italian team of Ugo Cerletti and Lucino Bini in 1938. From its inception, the procedure remained almost the exclusive way of treating serious mental illness and steadily gained in popularity until approximately the early 1960s. At that time, it's popularity started to wane, both as a result of introduction of novel medications and as concerns regarding the side effects of the treatment. In the pre-anesthesia era, besides memory impairment, ECT side effects infrequently included bone fractures secondary to the effects of the motor convulsion. Fractures are now mitigated by the use of a muscle relaxant. The introduction

**Table 109–3 Innovations in ECT Practice**

| Advance | Impact on the Field |
|---|---|
| Anesthesia | Improved medical safety of ECT |
| Brief pulse | Replaced sine wave ECT and significantly reduced cognitive side effects |
| Unilateral electrode placement | Provided an alternative to BL electrode placement, with fewer cognitive side effects |
| Seizure threshold titration | Provided another means to individualize dosage, in addition to age-based dosing to optimize safety and efficacy |
| Ultra-brief pulse | Shorter pulse widths appear to carry even lower risk of side effects |

of the use of anesthesia in combination with a muscle relaxant in the 1970s in many ways revolutionized the safety profile of ECT therapy. Further innovations that progressively improved its risk to benefit ratio in the subsequent decades included the change from sine wave to brief pulse ECT in the 1980s, and the introduction of right unilateral (RUL) ECT (Table 109–3). Today, ECT plays a prominent role in the treatment of medication resistant disorders. ECT has been in continuous use in psychiatry since its inception due to its unparalleled efficacy in helping with the most treatment-resistant forms of depression, bipolar mania, catatonia or affective episodes in schizophrenia.

## Mechanisms of Action

Given the unparalleled efficacy of ECT and its broad spectrum of action, elucidating its mechanisms of action could significantly advance understanding of the pathophysiology of psychiatric disorders and facilitate the development of more targeted and effective treatments. Previous psychological theories based on fear, regression and selective memory loss, have been now discounted in favor of neurobiological theories. Much is known about the neurobiological effects of ECT. For example, ECT exerts a range of neurobiological effects on functional brain activation, neurotransmitter systems, hypothalamic–pituitary–adrenal axis (HPA-axis) (normalizing the dexamethasone suppression test), and neuroplasticity. ECT is also a powerful anticonvulsant. The field presently lacks a single unifying explanation for why ECT should work so well when other modes of treatment have previously failed, and this is the focus of active research.

The ECT procedure involves the administration of anesthesia, the application of electricity, and the induction of a seizure. There is general agreement that it is the seizure itself, rather than the anesthesia or electrical stimulation in the absence of seizure expression, which is responsible for the beneficial clinical effects of ECT. ECT-induced seizures result in a collection of neurochemical, neuroendocrine, and neurophysiological effects (Lisanby and Belmaker 2000). Seizures release neurotransmitters, alter neurotransmitter receptor expression, alter gene expression, exert neurotrophic effects, affect cerebral blood flow and metabolism, and trigger anticonvulsant effects that terminate the seizure. Which constellation of these neurobiological effects is necessary and sufficient for the beneficial effects of ECT, and which contribute to side effects, is a topic under active study.

A clue to the mechanisms of action of ECT comes from the clinical observation that different forms of ECT (e.g., RUL versus bilateral (BL), low dosage versus high dosage relative to seizure threshold) result in differential clinical effects. For example, high dosage RUL provides better antidepressant efficacy than low dosage RUL, but without proportional increases in memory loss (Lisanby et al. 2000). This dissociation demonstrates that efficacy and amnesia can be uncoupled, supporting the view that memory loss is not essential to the mechanisms of action of ECT. Differences in electrode placement and dosage result in seizures that have different patterns of expression. These studies suggest that the efficacy and side effects of ECT are heavily dependent upon the topography of the seizure itself. For example, distinct patterns of effects involving anterior frontal regions have been associated with antidepressant response, while others involving temporal regions have been more strongly linked to the cognitive side effects of ECT (Nobler et al. 1994, Luber et al. 2000). These observations have been used in the development of more focal forms of convulsive therapy that might in future retain the superior efficacy of ECT, but with fewer side effects (Lisanby et al. 2003).

Antidepressants have been reported to increase cell proliferation, neuronal viability, and neurogensis in rodents and primates. Likewise, ECT exerts neuroplastic effects, increases neurotropic factors, upregulates genes related to neuroplasticity (Erraji-Benchekroun et al. 2007), and increases cell proliferation (Scalia et al. 2004, Perera et al. 2007) in the hippocampus of rodents and nonhuman primates. Unlike antidepressant medications, ECT induces mossy fiber sprouting. The functional significance of these changes, and their potential relationship to antidepressant response, is a topic under active study.

The anticonvulsant actions of ECT are so powerful that they have been successfully harnessed to treat medication refractory epilepsy and status epilepticus (Lisanby et al. 2001). The massive anticonvulsant action of ECT has been hypothesized to be related to effects on GABA neurotransmission.

Depression is reported to be associated with deficient intracortical inhibition and cortical GABA levels, while ECT increases intracortical inhibition (Bajbouj et al. 2006) and cortical GABA (Sanacora et al. 2003), providing another clue to possible mechanisms of action.

## Side Effects

ECT involves a number of risks that need to be evaluated prior to starting the treatment. The risk of death with ECT is relatively low (about 1 per 10,000 patients), comparable to the rate expected from a series of brief anesthetic procedures alone. The most common cause of death with ECT is cardiovascular. Other causes include prolonged apnea, status epilepticus, and cerebral herniation (e.g., in unrecognized cases of brain tumor).

The cognitive side effects of ECT are especially important to consider in the informed consent process and in the selection of ECT treatment parameters. Acutely, ECT causes anterograde amnesia from which patients typically recover soon after stopping ECT. Retrograde amnesia is the most persistent adverse effect of ECT. Shortly after ECT, most patients have gaps in memory for events that occurred close

in time to ECT, but retrograde amnesia may extend back months to years, in some cases. Memory for autobiographical material is relatively less affected by ECT than memory for events of an impersonal nature (Lisanby et al. 2000). While retrograde amnesia often improves during the first few months following ECT, for many patients recovery is incomplete, with persisting amnesia for events that occurred close to the time of treatment (Donahue 2000). Pre-existing cognitive impairment is one of the few predictors of ECT's adverse effects (Mulsant et al. 1991).

Much research has been dedicated to this and it has been shown that the placement of the electrodes (RUL versus BL) as well as technical characteristics of the electrical current applied (pulse shape and width) will affect the degree of risk of memory impairment (Sackeim et al. 2000, Sackeim et al. 1993, Sackeim et al. 1986) with the least risk demonstrated while using unilateral electrode placement in conjunction with ultra-brief pulse delivery. Sine wave ECT is no longer considered standard of care, due to the higher risk of causing long-lasting memory problems.

Other side effects of ECT include headache, muscle aches, nausea, and fatigue. ECT produces a transient increase in pulse and blood pressure; occasionally it may affect the cardiac rhythm. Thus, a detailed cardiac history is important to identify individuals at increased risk such as in the immediate post-myocardial infarction setting, unstable angina, or intractable arrhythmias. ECT can be given in the presence of cardiac pacemakers and implanted defibrillators, but cardiology consultation is important in those cases.

The pre-ECT workup should include complete medical and neurological screening to detect such as history of acute myocardial infarction, space occupying brain lesion or other cause of increased intracranial pressure, unstable aneurysm or vascular malformation, poorly controlled diabetes mellitus, carcinoma, renal failure, or hepatic failure. Although ECT is not contraindicated during pregnancy, careful consideration of risks and benefits is important, as is consultation with Obstetrics and the use of fetal monitoring.

ECT has an excellent safety profile, even among the elderly. We recently reported the case of a 92 year old woman who had received 91 ECTs in her lifetime and showed no pathological effects at postmortem examination of her brain when she died of other causes (Scalia et al. 2007). Careful neuropathological examination of nonhuman primates receiving electroconvulsive shock has also failed to reveal evidence of neuropathological lesions (Dwork et al. 2004).

## Clinical Studies

There have been numerous studies that describe ECT as a safe and an effective treatment for severe or treatment-resistant depression, bipolar disorder (both manic and depressive phases) and schizophrenia. Depression is the most frequently treated diagnosis.

The Consortium for Research in ECT (CORE) reported a 75% remission rate among 217 patients who completed an acute course of ECT (Husain et al. 2004). A systematic review conducted by the UK ECT Review Group (2003) found ECT significantly more effective than sham (6 trials, $n$ = 256 patients, effect size = 0.91) and than pharmacotherapy (18 trials, $n$ = 1144, effect size = 0.80). Patients with psychotic subtype of depression respond to ECT at higher rates than those without psychosis (Petrides et al. 2001). The efficacy of ECT is quite technique dependent with remission rates ranging from 20% to over 80% depending upon how the treatment is performed. Double-masked, randomized controlled trials demonstrate powerful interactions between electrode placement and dosage relative to seizure threshold in the efficacy and side effects of ECT (Sackeim et al. 2000). The UK ECT Review Group (2003) found BL to be moderately more effective than RUL ECT (22 trials, $n$ = 1408, effect size = 0.32) though it should be noted that the efficacy of RUL ECT is dosage sensitive. Several studies have found that high dose RUL ECT is as effective as BL ECT, with the advantages of lower cognitive side effects, especially at long-term follow-up (Sackeim et al. 2000, McCall et al. 2000).

While with optimal technique ECT can be highly effective, success rates in the community hospital setting have been less robust (30–47%, roughly half that seen in clinical trials) (Prudic et al. 2004). Some of these discrepancies may be related to diagnostic comorbidity, but some may also be related to the tendency to halt ECT prior to complete remission (often to mitigate side effects). Only 23.4% of ECT nonremitters immediately following the acute treatment course, were found to have sustained remission at 6 months (Prudic et al. 2004), underscoring the need to "treat to wellness" and not prematurely terminate the acute course of ECT.

Following an effective course of ECT, it is important to initiate maintenance therapy with an antidepressant and mood stabilizer, or in some cases maintenance ECT. Without any form of maintenance treatment, patients relapse at a rate of 84% six months post ECT (Sackeim et al. 2001). Monotherapy with nortriptyline reduced the relapse rate to 60%, but combination therapy with nortriptyline and lithium reduced relapse to 39% (Sackeim et al. 2001).

## Current Status in Treatment Algorithms

ECT is usually considered in medication-resistant cases, where several adequate prior drug trials have failed to sufficiently relieve the symptoms. Usually a trial of two or more single action antidepressants (e.g., selective serotonin reuptake inhibitors (SSRIs)) is followed by a dual action antidepressant (serotonin norepinephrine reuptake inhibitors (SNRIs)) trial and possibly a trial of a tricyclic antidepressant (TCA), or monoamine oxidase inhibitor (MAOI) pharmacotherapy, with or without augmentation strategies. However, in cases of severe depression with psychotic features or severe melancholic depression where patient's safety is a pressing clinical issue, ECT should be considered much earlier.

Most practice guidelines for depression recommend ECT for difficult-to-treat cases, often as a 5th, 6th, or 7th step. In routine clinical practice, however, ECT is often used even later in the course of treatment, due both to its stigma and cognitive side effects. The National Institute for Clinical Evidence (NICE) issued guidance on the use of ECT in the UK which recommended the restriction of ECT to patients with severe depression, catatonia, or prolonged or severe mania, and stated that ECT is not recommended as a maintenance therapy (National Institute for Clinical Evidence 2003). Those guidelines have been critiqued (McDonald 2006, Cole and Tobiansky 2003) for being at odds with the substantial clinical literature on the efficacy of ECT in other conditions (such as schizophrenia) (Tharyan and Adams 2005), and with the clinical utility of maintenance ECT (Kellner et al. 2006). The APA guidelines continue to

support the use of ECT in other conditions and for relapse prevention.

### Patient Selection

There are several criteria used in selecting ECT as a treatment modality. The first and most obvious one is the diagnosis. ECT has been demonstrated as a very effective treatment for depression, where response rates for depression with psychotic features can approach 90%. It appears the more severe the depression the better the treatment response. For example, Dysthymic Disorder or depressive symptoms in the setting of a personality disorder, have not been particularly responsive to ECT. Persistent catatonia, both phases of Bipolar Disorder, as well as positive and particularly affective symptoms of schizophrenia have all responded well to ECT. A second criterion in selecting ECT is the severity of the symptoms; ECT may and should be considered as an early treatment modality in psychiatric emergencies, particularly where there is little expectation that medications will change the course of the illness. Prior response to treatment is another criterion to be taken into account and may be life saving in cases of recurrent severe depression that has previously responded only to ECT in the past. Another important criterion is the medical safety of the treatment. The risks and benefits need to be carefully weighed for each case, especially if the patient has health conditions that may necessitate modifications to the procedure, such as morbid obesity (with respiratory effects complicating anesthesia and airway protection), central nervous system lesions increasing intracranial pressure, or severe cardiovascular disease.

### Dosing

ECT dosage planning involves selection of electrode placement, electrical dosage, and methods for individualizing the dosage. Commonly used electrode placements include BL, RUL, and bifrontal (BF). Selection among the electrode placements involves weighing their relative efficacy and risks. For example, RUL or BF may be selected to lower side effect burden, while BL may be selected if RUL or BF are unlikely to be effective (as in the case of a prior failure). Studies suggest that higher relative dosage within the RUL condition enhances its efficacy, while higher dosage within the BL condition enhances its side effects.

Dosage may be individualized by titrating seizure threshold or by using an age-based method. Age is a predictor of seizure threshold, but it only accounts for a small percentage of the variance in seizure threshold, which is highly variable across individuals (Lisanby et al. 1996). An advantage of empirical seizure threshold titration is that it provides a sensitive means of adjusting dosage relative to seizure threshold that has been useful in maximizing the efficacy of RUL electrode placement, which is highly dosage-sensitive in its efficacy.

### Future Directions

Future directions in the field of ECT include identifying more effective ways of preventing relapse following an effective course of ECT, and reducing the cognitive side effects of the treatment. The CORE group found that only 46% of patients who remit following ECT remain well at 6 months when receiving maintenance treatment with combination pharmacotherapy or with maintenance ECT (the two groups did not differ) (Kellner et al. 2006). In the community setting, the percentage remaining well drops to 36%, perhaps due to less aggressive maintenance treatment or premature termination of the ECT course in the presence of residual symptoms (Prudic et al. 2004). More effective strategies for relapse prevention might involve the combined use of maintenance ECT with combination pharmacotherapy, and a more structured format for adapting the maintenance ECT schedule to fluctuations in patient status.

Regarding the cognitive side effect burden of ECT, beyond electrode placement, shorter pulse width has been reported to reduce amnesia from ECT (Sackeim et al. 2001). Other approaches have included improving the focality of seizure induction using magnetic fields which can be targeted more precisely than electrical stimulation due to the lack of impedance (see MST section below) (Lisanby et al. 2003). Other work has examined the efficacy of subconvulsive dosages of TMS (see section below)) in the treatment of depression with encouraging results and excellent safety profile (Avery et al. 2006), but with a lower effect size than that seen with ECT. VNS is an FDA approved alternative for the adjunctive management of treatment resistant depression, which lacks known cognitive side effects and has shown some benefit in long-term management (Marangell et al. 2002), but does not possess the speed of action or effect size of ECT. While these novel treatments offer promise for the future, ECT continues to have a unique role in the acute treatment of severe depression.

## TMS

### Definitions

TMS refers to the induction of small electrical currents in the superficial layers of the cerebral cortex by applying rapidly alternating magnetic fields to the head. TMS is administered using an electromagnetic coil that is held on the scalp. The coil emits strong, pulsed magnetic fields. Magnetic fields pass through the scalp and skull freely and enter the brain without the impedance encountered by the direct application of electricity. This makes it easier to focus TMS to smaller regions of the brain than is possible with ECT or tDCS. The rapid change in the strength of the magnetic field induces electrical current in the brain through the principles of electromagnetic induction. TMS has been referred to as "electrode-less" electrical stimulation because it uses magnetic fields to indirectly induce electrical pulses. Because magnetic fields are noninvasive, TMS can be given to awake subjects without the need for anesthesia. As such, it represents a noninvasive means of stimulating focal regions of the brain.

"Single pulse TMS" refers to TMS when it is given one pulse at a time, at an irregular rhythm and at low rates (>0.3 Hz). rTMS refers to stimulation that is repeated at regular intervals. The frequency of this repetition generally ranges from 1–25 Hz. "Low frequency rTMS" refers to repetition rates of ≤1 Hz, while "high frequency rTMS" refers to stimulation at higher frequencies (usually 5–20 Hz).

### History

The first human use of pulsed magnetic fields to stimulate the human brain was reported by Barker, Jalinous, and Freeston from University of Sheffield in 1985 (Barker et al.

1985). The first generation TMS stimulators were capable of low repetition rates (typically < 0.3 Hz). Single TMS pulses proved useful in the study of motor conduction and other basic brain processes. In early work, these very low frequencies of TMS were applied in exploratory studies on the treatment of depression and schizophrenia (Geller et al. 1997, Belmaker and Fleischmann 1995). These early studies typically used large round coils that were nonfocal, but nevertheless, there were early suggestions of benefit that encouraged further work with TMS in psychiatry.

In the mid-1990s, repetitive stimulators capable of higher repetition rates (up to 20 Hz) became available. Higher frequency stimulation was able to influence higher brain functions like language, mood, and memory. Early studies with high frequency rTMS suggested that it might have antidepressant properties when applied to the dorsolateral prefrontal cortex (DLPFC) (Pascual-Leone et al. 1996, George et al. 1995). Subsequently, the potential therapeutic value of focally applied rTMS, targeted to the neural circuitry underlying depression and other disorders, has attained heightened attention.

## Mechanisms of Action

Alternating magnetic fields induce electrical currents in the superficial cortex underlying the TMS coil. These electrical currents are called "eddy currents" because they are circular in shape, and are oriented in the plane perpendicular to the plane of the TMS coil. At sufficient intensity, electrical currents will stimulate neuronal depolarization, which can result in an action potential. For example, when the TMS coil is positioned over the hand area of the motor strip, it induces local currents at the site of stimulation that cause the neurons in Primary motor area (M1) to fire. This stimulation activates the polysynaptic corticospinal tract, and results in a twitch in the contralateral hand muscle. Thus, TMS uses magnetic fields to indirectly induce focal electrical currents in the brain, which in turn trigger the firing of functional neuronal circuits and can lead to observable behavioral effects. By moving the TMS coil to the cortical representation of neighboring muscle groups, single TMS pulses can be used to map the homunculus and study the excitability of the corticospinal system.

When moved to other cortical areas, single TMS pulses can exert other effects, such as transient scotoma, or "blind spots" when positioned over the primary visual cortex (V1). This paradigm is called "visual masking" (Luber et al. 2007). Thus, TMS can transiently disrupt functions. This mode of action has been termed the "virtual lesion" technique.

These various actions of single pulse TMS represent the acute effects of the activation of neural circuits triggered by TMS-induced neuronal depolarization (Figure 109–3). Generally speaking, the effects of single TMS pulses are immediate or short-lived. The motor twitch induced by TMS to area M1 is nearly instantaneous, with the hand movement occurring approximately 20 ms after the TMS pulse is applied. Likewise, visual masking operates on a millisecond timescale. However, TMS can exert longer lasting effects when the pulses are repeated at regular intervals (rTMS), or when they are paired with other forms of stimulation (such as in the paired-associative stimulation paradigm (Quartarone et al. 2006) where TMS pulses are paired with electrical stimulation of a peripheral nerve, or when TMS is paired with audiovisual stimuli as in the example of classical conditioning of the brain response to TMS (Luber et al. 2007) The mechanisms underlying these lasting effects of TMS are thought to be related to neuroplasticity and alterations in synaptic efficacy, as reviewed above.

Because rTMS has the ability to induce lasting changes in cortical excitability at the site of stimulation and in connected regions within neural circuits, its application in the treatment of psychiatric disorders has been driven by the attempt to focally alter abnormalities in cortical excitability linked to illness. For example, studies point to reduced activity of the DLPFC (especially on the left), as well as other regions that form a distributed network, during clinical depression. Therefore, studies have applied high frequencies of rTMS, which have been reported to increase excitability, to the left DLPFC in an attempt to normalize activity in this region. Furthermore, some theories implicate abnormal interhemispheric balance in activation between the right and left DLPFC. Building upon these theories, some studies have applied low frequency rTMS, which has been reported to be inhibitory, to the right DLPFC, in an attempt to normalize that interhemispheric balance.

Further supporting the potential therapeutic role of focally modulating cortical excitability, animal studies suggest that rTMS can exert effects on neurotransmitter release, receptor expression, and gene expression that are similar to some of the effects of antidepressant medications and ECT (Lisanby and Belmaker 2000). It should be noted, however, that animal models of the effects of rTMS do not perfectly replicate the effects of rTMS on the human brain, due to size differences and how they impact the strength and distribution of the induced electric fields.

## Side Effects

While TMS is clearly less invasive than ECT, it is not entirely without risk. The most serious known risk of TMS is seizure. The relative risk of seizure with TMS depends upon the form of TMS (single pulse versus rTMS), the dosage (intensity, frequency, train duration, inter-train interval), and subject factors that may place the individual at increased risk (such as the presence of a neurological disorder or seizure lowering medications).

Single pulse TMS is generally considered minimal risk when administered to adults lacking risk factors for seizure. rTMS can induce seizures in individuals without predisposing conditions when given at sufficiently high dosages. Safety guidelines (Figure 109–6) were developed to mitigate the risk of seizure (Wassermann 1998). When given within the safety guidelines, rTMS has not induced seizures in appropriately screened individuals. However, since seizure is a possibility, subjects should always be advised of this potential. It is also recommended that rTMS be administered under medical supervision, and that procedures be in place to medically screen and monitor patients for changes in clinical status that could affect seizure risk. The treating clinician should have the proper training and equipment to manage a seizure should one occur (Belmaker et al. 2003).

The most common side effects of TMS are scalp discomfort and headache. These effects are attributable to scalp muscle stimulation, and stimulation of the facial nerve. Earplugs are worn by the patient and administrator to protect hearing. The risks of TMS during pregnancy have not been

| | % Motor threshold | | | | |
|---|---|---|---|---|---|
| Hz | 100% | 110% | 120% | 130% | 140% |
| 1 | >1800 | >1800 | 360 | >50 | >50 |
| 5 | >10 | >10 | >10 | <10 | 7.6 |
| 10 | >5 | >5 | 4.2 | 2.9 | 1.3 |
| 20 | 2.05 | 1.6 | 1.0 | 0.55 | 0.35 |
| 25 | 1.28 | 0.84 | 0.4 | 0.24 | 0.2 |

Table shows the duration in seconds that could be administered at each combination of frequency and intensity prior to the emergency of spread of excitation, a warning sign of seizure. Values preceded by > indicate that this is the longest duration that was tested.

**Figure 109–6** *Safety guidelines.*

thoroughly studied. Since TMS is experimental, it may carry as yet unknown risks.

## Basic Studies

Apart from its clinical potential, TMS has already demonstrated a number of advantages in the study of normal brain function and of the pathophysiology of psychiatric disorders (Luber et al. 2007). Advantages of TMS as a functional probe include the fact that it is noninvasive, has good spatial resolution and excellent temporal resolution, exerts frequency-dependent effects, and can serve as a companion to neuroimaging by testing the functional role of areas of activation seen with PET or fMRI (Figure 109–7). As an example, we used fMRI to identify a network of brain regions implicated in working memory, then used stereotaxically applied TMS to test the functional role of those regions. We found that TMS applied to one region, the precuneus, facilitated working memory performance (Luber et al. 2007). This result informs our understanding of the brain networks involved in a normal brain function, and also suggests that future studies might explore clinical applications for TMS-enhancements of cognitive performance.

## Clinical Studies

Major Depression is the disorder that has been most thoroughly studied with TMS to date. A growing number of randomized controlled trials, (O'Reardon et al. in press) supported by several meta-analyses (Burt et al. 2002), reveal evidence of significant antidepressant effects of rTMS when given to the DLPFC. However, not all studies have been positive. The average effect size in depression is moderate—less than that seen with ECT but close to that seen with antidepressant medications.

- Scalp position, target localization method
- Coil shape and orientation
- Single pulse vs. repetitive vs. convulsive
- Train: frequency, duration, intensity, total pulses
- Intertrain interval
- # Trains/session
- # sessions/day
- # days/course
- Taper/Maintenance/reintroduction

**Figure 109–7** *Advantages of TMS as a functional probe.*

Schizophrenia has also been studied, with some promising results using low frequency rTMS to inhibit temporal–parietal regions of the cortex reported to be hyperactive during hallucinations (Hoffman et al. 2005). Though less studied, TMS has shown some promising early results in anxiety disorders (Mantovani et al. 2006, Mantovani et al. 2007).

## Current Status in Treatment Algorithms

At the time of this writing, TMS is not currently FDA approved, and therefore is not included in treatment algorithms. Should it ultimately be found safe and effective for depression, it would likely be most useful positioned between medications and ECT.

## Patient Selection

Given the lower effect size of TMS, ECT would remain the primary treatment for the most severely depressed and highly medication resistant cases. TMS might be considered in less severe and less refractory cases after a failed trial of one or more antidepressant medications, or medication intolerance.

## Dosing

There are many aspects to TMS dosing (Figure 109–8). Certain dosage-related factors that have begun to emerge as possibly related to antidepressant response with rTMS include stimulation intensity, frequency, number of pulses administered and duration of the treatment course (Gershon et al. 2003, Padberg et al. 2002, Sachdev et al. 2002). The delivered intensity of rTMS is related to the distance of the coil from the target cortex. Increasing the distance decreases the intensity of the stimulation reaching the brain, which has been found to be negatively correlated with antidepressant response and with the degree of stimulation-induced brain activation as evidenced by functional imaging (Mosimann et al. 2002, Nahas et al. 2001). Other treatment-related factors that have been shown to be related to neurophysiological responses to TMS include variation in coil and stimulator type, waveform shape and polarity, and coil position and orientation relative to target cortex (Thielscher and Kammer 2004, Maccabee et al. 1998, Davey and Epstein 2000, Kammer et al. 2001, Kammer et al. 2001). Even when these factors are held constant, considerable within-subject variability in physiological response to TMS has been reported in the motor system (Wassermann 2002).

## Future Directions

Emerging evidence will shed light on the ultimate clinical role of TMS in psychiatric treatment. It will be important to replicate key findings, identify optimal dosing parameters

- Noninvasive, can study normal subjects
- Effects reversible
- Focal stimulation
- Excellent temporal resolution
- Selective frequency dependent neurophysiological effects—effects akin to LTP and LTD
- Complement to functional imaging

**Figure 109–8** *TMS dosage parameters.*

to maximize efficacy, examine dose-response relationships, determine patient characteristics that predict response, and explore the impact of concomitant medications on TMS effects. As with ECT, post TMS relapse prevention is an area yet to be definitively addressed. Future work may develop coils optimized for deeper penetration, and pulse shapes that are more physiologically optimized to human neurophysiology. One such example is controllable pulse shape TMS (cTMS) which can induce pulses that are rectangular in shape (like ECT pulses) (Peterchev et al. 2007). Traditional TMS devices induce pulses that are sinusoidal, a waveform that was abandoned with ECT due it its inefficiency and excessive side effects.

## MST

### Definition

MST is a new convulsive treatment under development that uses alternating magnetic field to cross the scalp and the calvarium and induce a more localized electric current in targeted regions of the cerebral cortex than is possible with ECT. The aim is to produce a seizure whose focus and patterns of spread may be controlled. MST attempts to marry the focality provided by magnetic fields with the powerful antidepressant efficacy of ECT (Lisanby and Peterchev 2007).

Like ECT, MST is performed under general anesthesia. MST is given using a modified TMS device that can administer higher output than conventional TMS devices. The MST procedure is also performed with a muscle relaxant and requires very similar staffing and infrastructure resources to those of ECT. MST is at the stage of clinical trials, and is not presently FDA approved. Current studies concentrate on optimizing the efficacy through discovery and convulsive treatment applied to the putative depressive centers of the brain, while avoiding those brain areas involved in memory formation and consolidation.

### History

The first MST-induced seizures, induced in rhesus monkeys, were performed in 1998 using a custom modified TMS device (Lisanby et al. 2001). Following safety testing in nonhuman primates (Dwork et al. 2004), the first human case of a 20 year-old inpatient with a medication-resistant major depressive episode treated in Berne, Switzerland, was published in 2001 (Lisanby et al. 2001). The treatments were well tolerated, resulted in a 50% drop in the depression scores and had no effect on Mini Mental State Exam scores, which stayed at 30 throughout the treatment course. The first trial of MST in the US, performed at Columbia University in NY and published in 2003, reported fewer acute cognitive side effects with MST than with ECT in a within-subject cross-over blinded trial (Lisanby et al. 2003). The second center to perform MST in the US was University of Texas Southwestern Medical Center. Now there are also MST centers in Wales (Cardiff University), Scotland (Royal Edinburgh Hospital), and Germany.

### Mechanisms of Action

Like ECT, MST induces a seizure which is hypothesized to be central to its mechanism of action. As a focal means of seizure induction, MST represents a tool that can be used to study the mechanisms of action of ECT. By inducing seizures from differing regions of the brain, MST could systematically address questions regarding the linkages between seizure topography and outcome.

Seizures induced by MST are distinct from those induced by ECT (Lisanby et al. 2003). MST induced seizures show less impact on parasympathetic outflow, less generalization to hippocampus and deeper brain structures, and result in less serum prolactin surge. Lack of physiological and structural changes in the hippocampus with MST may relate to its differential cognitive profile (Moscrip et al. 2006).

### Side Effects

The risks of MST are similar to those of ECT and are largely connected to the risks associated with anesthesia and generalized seizure. In addition, MST coil produces a clicking noise that may potentially affect hearing and to prevent any cumulative damage, earplugs should be worn by both the patient and members of the treating team. With respect to memory, studies suggest MST results in less retrograde amnesia than ECT (Moscrip et al. 2006, Lisanby et al. 2003), though this result should be replicated in a larger trial. MST seizures are less well generalized and tend to produce less robust motor convulsions. For this reason, it has been noted that the dosage requirement for the muscle paralytic agent (succinylcholine) is lower than with conventional ECT (White et al. 2006). Shortening the period of paralysis could reduce the risks of the procedure by reducing the period of respiratory suppression.

### Clinical Studies

The first human patient received a course of four MST sessions in Switzerland during 2000, using 40 Hz at 100% intensity of the MST equipment available at that time (Lisanby et al. 2001). The same centre went on to report a second case that received a full course of MST with similar parameters.(Kosel et al. 2003) Both patients tolerated the treatments well and their depressions responded. This was followed by a trial on 10 depressed patients who received two MST sessions during a course of ECT, in a blinded, randomized within-subject cross-over trial which found the acute side effects of MST to be superior to ECT (Lisanby et al. 2003). This time a custom-modified Magstim device (Magstim, Whitland, Wales, UK) was used, which consisted of 16 booster modules and was capable of producing 50 Hz stimulation at a peak magnetic field of 1.2 Tesla for 8 s, with a pulse width of 500 μs. Although seizures were induced in all patients, it was noted that in three cases the seizure threshold was at the maximum output of the device, highlighting the need for technological improvements in the equipment. Subsequently, 20 depressed patients were treated with a full course of MST using the same 50 Hz MST device in a 2-center trial conducted at Columbia University and University of Texas Southwestern Medical Center in 2003 (Lisanby et al. 2003). MST improved depression scores and patients demonstrated remarkably rapid reorientation with few side effects (White et al. 2006).

These early trials demonstrated the feasibility of MST in a clinical setting. However, the maximum stimulation of 400 pulses per session was estimated to be on average only 1.3 times the magnetic seizure threshold, perhaps

contributing to the suboptimal antidepressant efficacy since some modes of ECT are known to be highly sensitive to dosage relative to seizure threshold. Subsequently, available MST technology has significantly advanced. A new prototype MST device capable of stimulation at 100 Hz, 100% of stimulator output, for up to 10 s trains became available for animal use in 2004 (Magstim Company Limited). MST at 100 Hz was performed with this device for the first time in 2004 in an ongoing study of rhesus monkeys. Results to date continue to demonstrate a superior safety profile with high dose MST compared to ECT in the nonhuman primate model (Peterchev et al. 2007). Human trials with 100 Hz MST have commenced and demonstrate the feasibility of implementing the new 100 Hz device in the clinical setting, with encouraging early results (Peterchev et al. 2007).

Randomized trials contrasting the efficacy and safety of 100 Hz MST with ECT are underway. In the US, there is currently a two-center (Columbia University Medical Center and University of Texas Southwestern Medical Center) ongoing clinical trial which intends to randomize 75 medication treatment-resistant patients to either ECT or MST. Similar collaborations exist with two UK clinical research centers (Cardiff University in Wales and the Royal Edinburgh Hospital in Scotland) exploring alternate sites of seizure induction, and contrasting MST with gold-standard ECT.

### Current Status in Treatment Algorithms

MST is not FDA approved, and as such does not have a defined place in current treatment altorighms. If the hypothesis that MST can approach the efficacy of ECT but with fewer side effects, then it might in future play a role prior to referral to ECT. However, more research will be needed to establish its safety and efficacy before it can be recommended clinically. As general anesthesia is part of the MST procedure, it will still likely be reserved for medication treatment resistant patients after medications have been tried.

### Patient Selection

MST is being tested in the population of patients referred for ECT, the primary indication for which is depression.

### Future Directions

MST is at the early phases of clinical testing. Unanswered questions about dosimetry, optimal coil placement, patient selection, and mechanisms of action are the topics of future studies.

## TDCS

### Definition

tDCS uses very weak (1–3 mA) electrical fields applied to the scalp to polarize the brain. The fields are applied using direct current (DC), rather than the AC used in ECT, VNS, and DBS. Since the technique does not actually result in an action potential firing in cortical neurons, the term "tDCS" is favored by some modern investigators, and both terms appear in the literature today. The device is battery operated and easily portable.

### History

tDCS is an old technology that has experienced a modern resurgence of interest. Reports from Briain in the 1960s detailing dramatic recovery from even ECT resistant depression, from catatonic and manic states and recovery, in one case, of a schizophrenic man with mutism, have not been replicated. However, new controlled work examining the effects of tDCS in cognitive and motor function have been encouraging.

### Side Effects

tDCS appears well tolerated with no known serious adverse effects. Common side effects include a slight tingling at the site of stimulation, and some cases of skin irritation.

### Mechanisms of Action

Little is known about the mechanisms of action of tDCS. DC polarizes tissue. Polarization can change the firing rate of neurons. tDCS appears to act via an NMDA mediated alteration of neuronal membrane polarization which might lower the threshold for activation, facilitating neurotransmission. Depending on the direction of current flow, this polarization can either inhibit (cathodal) or facilitate (anodal) function.

### Clinical Studies

Work with this technology is at the very early stages. Research suggests that tDCS may enhance certain brain functions. Current research is focusing on its potential effectiveness in facilitating recovery from stroke and from certain forms of dementia. A recent double blind, randomized, sham controlled trial of tDCS in depression found significant antidepressant effect after anodal stimulation over the DLPFC given for 20 min a day over five alternate days (Fregni et al. 2005).

A randomized, double-blind clinical trial of 40 patients diagnosed with major depression compared three groups (anodal tDCS of DLPFC, anodal tDCS of the occipital cortex (active control group) with sham tDCS (Boggio et al. 2007). tDCS was applied for 10 sessions during a two week period. In the group receiving anodal tDCS, HDRS reduction of 40.4% was seen compared to occipital (HDRS reduction of 21.2%) and sham tDCS (HDRS reduction of 10.4%). There was a significantly greater number of responders after DLPFC tDCS (8 responders, compared with sham and occipital tDCS (2 and 0 responders, respectively)). There were five remissions in the DLPFC group and no remissions in the other two control groups. Beneficial effects for the active DLPFC group persisted for one month after the end of treatment. This intriguing finding awaits replication.

### Current Status in Treatment Algorithms

tDCS is not FDA approved for brain stimulation, and is therefore considered experimental. Much work is needed to demonstrate its efficacy in psychiatry. If ultimately found to be successful, tDCS could represent a safe and cheap alternative that could reach communities with less access to technological advancements. Given its noninvasiveness and lack of known serious side effects, it would be considered prior to the relatively more invasive technologies.

### Future Directions

Basic issues of efficacy, indications, patient selection, dose-response relationships, and predictors of response remain to

be worked out. Current tDCS technology uses large, nonfocal electrodes. Future developments might examine optimal electrode configurations and shape to optimize desired clinical effects.

## VNS

### Definition

VNS entails the direct, intermittent electrical stimulation of the left cervical vagus nerve via a pulse generator implanted in the left chest wall. The electrode is wrapped around the left vagus nerve in the neck and is connected to the generator subcutaneously. Intermittent left vagal nerve stimulation sends afferent signals to the nucleus tractus solitarius and connected limbic and cortical areas (George et al. 2000). Implantation surgery involves two incisions—one for the generator in the chest and another in the neck for the electrode. Surgery is usually performed under brief general anesthesia, as day surgery or with an overnight stay. Stimulation parameters are adjusted with a programming wand that communicates with the generator. Patients may turn off the stimulation when needed by holding a magnet over the generator.

### History

VNS was originally FDA approved for the treatment of resistant epilepsy, and in 2005 was approved for the adjunctive treatment of chronic, treatment-resistant depression.

### Mechanisms of Action

The left vagus nerve contains 80% afferent fibers, therefore stimulating it activates predominantly vagal afferents. Chronic stimulation of the vagal afferents changes activity in brainstem nuclei (such as the nucleus of the solitary tract), and from there, neighboring nuclei (e.g., Raphe) that alter serotonergic activity in cortical and limbic structures. Chronic stimulation of the vagal afferents is anticonvulsant, and this effect appears to be dependent upon the locus ceruleus.

### Side Effects

VNS is generally well tolerated. Voice alteration, dyspnea, and neck pain are the most frequently reported adverse events (George et al. 2005). The surgical implantation does carry the risks of infection, vocal cord paralysis, and bradycardia or asystole (all < 0.5% in the US pivotal (D02) study). In the long-term naturalistic study of VNS for major depression, only 3 out of 235 patients (1%) terminated VNS because of adverse events (Rush et al. 2005). VNS does not cause apparent cognitive side effects (Sackeim et al. 2001). In fact, neurocognitive performance was significantly improved with VNS—apparently due to the improvement in depression (Sackeim et al. 2001).

Contraindications to VNS include a history of bilateral or left cervical vagotomy and use of short-wave diathermy, microwave diathermy, or therapeutic US diathermy. Patients with VNS implanted cannot receive routine magnetic resonance imaging (MRI) scans, but can receive MRI with a special "send/receive" coil.

### Clinical Studies

In the first study of 30 treatment-resistant depressed patients (Rush et al. 2000), response rates were 40% after ten weeks of open-label, adjunctive VNS treatment. The response rate was sustained (46%) and the remission rate significantly increased from 17–29% after an additional 9 months of VNS, and significant improvements in function were reported with long-term VNS treatment. In a subsequent report of an extended sample ($n$ = 59) (Sackeim et al. 2001), the short (3 months) and longer-term (24 months) effects of adjunctive VNS treatment (Nahas et al. 2005) revealed 10-week response rates of 31% (after 3 months), 44% (after 1 year), and 42% (after 2 years). Remission rates were 15%, 27%, and 22%, respectively, demonstrating continuous and stable improvement. By 2 years 81% were still receiving VNS.

However, a 10-week randomized, controlled, and masked multi-center trial comparing adjunctive VNS with sham treatment in 235 outpatients with treatment resistant unipolar or bipolar depression failed to show a significant difference on the primary outcomes between active and sham treatment (Rush et al. 2005).

A naturalistic follow-up study of long-term (1 year) VNS treatment of the same cohort ($n$ = 202) revealed progressively increasing improvement with a 12-month response rate of 27.2% and a remission rate of 15.8%. These results, when compared to a comparably matched but nonrandomized control group that received treatment as usual, indicated VNS was associated with greater improvement than pharmacological treatment alone (27% vs. 13%) (George et al. 2005). The significant longer-term benefit of adjunctive VNS to active treatment excluding VNS were open label and treatment was not controlled. On the other hand, the improvement in VNS patients was not attributable to medication changes in the VNS patients, nor is a delayed placebo effect likely in such chronically ill treatment resistant patients.

### Current Status in Treatment Algorithms

The FDA label states that VNS is indicated for the adjunctive long-term treatment of chronic or recurrent depression in patients 18 years or older who are experiencing a major depressive episode (unipolar or bipolar) and have not had an adequate response to four or more adequate antidepressant treatments. Consultation with another clinician experienced with treatment resistant depression and VNS is recommended.

Success rates with VNS are considerably lower than with ECT and onset of action is comparatively slow (e.g., approximately 30% response rate after 1 year). Therefore, VNS may be worth considering when patients have failed to respond to less invasive treatments, ECT was ineffective, or post ECT relapse cannot be prevented with less invasive means. There is hope that VNS might be helpful with longer-term relapse prevention, but results of controlled trials would be useful to guide practice.

### Patient Selection

Steps in the evaluation of a patient for VNS are outlined in Figure 109–9. VNS is approved as an adjunctive long-term treatment for chronic or recurrent depressive episodes in adults with a major depressive episode who have not had an adequate response to 4 or more adequate antidepressant trials. The efficacy of VNS in other disorders is unknown.

- Does this patient meet FDA labeling criteria?
  - – unipolar or bipolar disorder in an MDE
  - – long-term MDE (≥2 years)
  - – recurrent depression
  - – Inadequate response to 4 or more adequate treatments
- Have other causes of med resistance been ruled out?
  - – Medical, substance, Axis II
  - – Compliance with adequate dosages and durations
- Can the patient tolerate a slow-acting therapy?
- Does the patient need acute response now?
  - –ECT may be a better option for the acutely suicidal
- Get a second opinion

**Figure 109–9** *Evaluation for VNS.*

| VNS or ECT? | |
|---|---|
| • Acutely suicidal, in need of rapid response | ECT |
| • Psychotic depression | ECT |
| • Acutely depressed, medication resistant, never had ECT | ECT |
| • Chronically depressed, able to tolerate slow onset of action | VNS |
| • Had ECT before but always relapses quickly despite adequate medication | VNS |
| • Cannot be tapered off maintenance ECT, and it isn't even working that well | VNS |

**Figure 109–10** *VNS or ECT?*

Determination of what constitutes an "adequate" trial requires careful assessment of whether adequate dosages were prescribed (and taken) for an adequate period of time. Optimally this should be substantiated by careful review of treatment records, pharmacy reports, and blood levels where appropriate. Failed trials should include different medication classes (i.e., not just SSRIs or SNRIs, but also TCAs, MAOIs), or various augmentation strategies with or without ECT. A second opinion from a clinician specializing in treatment resistant depression and knowledgeable regarding VNS is advisable.

Sample clinical scenarios when ECT might be favored over VNS, and vice versa, are outlined in Figure 109–10. For example, VNS does not exert rapid antidepressant action, thus acutely suicidal patients and others in need of rapid response would be more appropriately treated with other strategies. VNS is indicated as a long-term treatment option only for those with chronic or recurrent course of illness.

ECT can be safely used in patients with an implant if the VNS generator is turned off during delivery of ECT, to avoid anticonvulsant effects of VNS. Whether VNS would be useful in relapse prevention post ECT deserves study.

### Dosing

The optimal dose of VNS is unknown. The published studies were not designed to identify optimal dosing parameters (time on, time off, frequency, current, pulse width). The epilepsy literature suggests that there is a threshold current for efficacy. However, given our current knowledge of VNS dosing, current is typically increased up to >1 mA clinical benefit assessed over several months. The side effects of VNS are known to be dose dependent (e.g., lowering pulse width reduces neck pain, allowing patients to tolerate higher currents).

### Future Directions

More research is needed to define the dose-response relationships for VNS, investigate optimal medication strategies to augment responses, test the potential role of VNS for long-term relapse prevention, and study its mechanisms of action.

## DBS

With DBS, intracranial electrodes are implanted and chronically stimulate targeted brain areas. Unlike

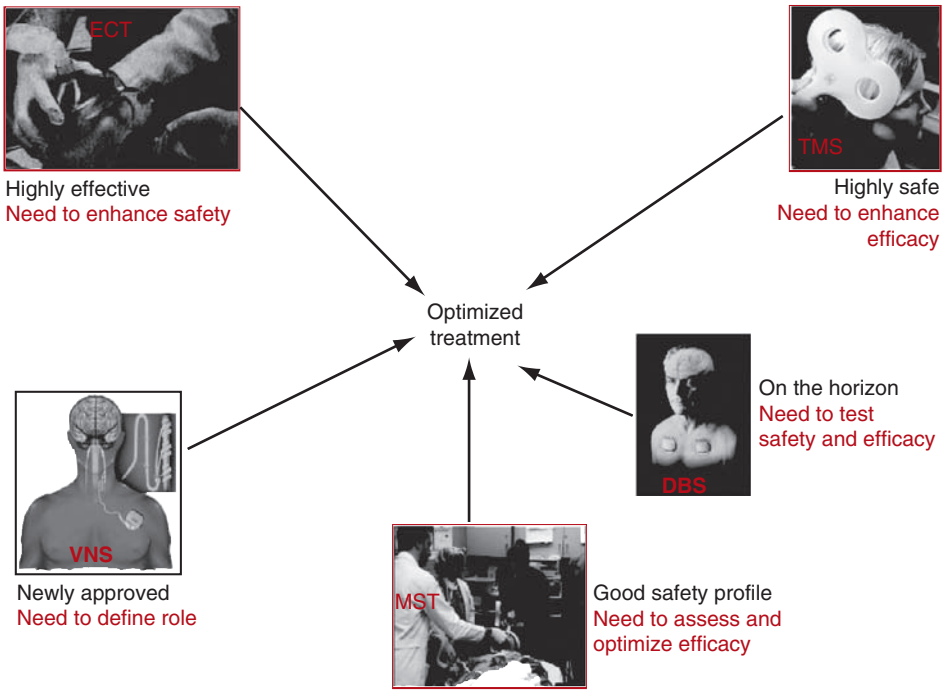



**Figure 109–11** *State of the evidence.*

lesioning procedures, DBS is believed to be reversible, and the intensity of stimulation can be adjusted according to the acute effect on symptoms.

DBS is FDA-approved for the treatment of Parkinson's disease and is under study for the treatment of severe and treatment-resistant OCD and major depression (Kopell et al. 2004). At this time about 20 patients worldwide have received DBS for depressive disorder, with varying stimulation sites: white matter underlying cingulate area 25 (Mayberg et al. 2005), internal capsule/nucleus accumbens (Bonn/Cologne group), and the inferior thalamic peduncle (Jimenez et al. 2005).

An open label series of six patients with treatment refractory depression treated with DBS and demonstrated very encouraging results (Mayberg et al. 2005). Upon activation of DBS, all six patients spontaneously reported immediate improvement in mood, feeling of calm, increased interests etc. In four out of six patients, antidepressant response was maintained at 6 months, and three of these four subjects achieved full remission. Subsequent controlled studies are needed to establish the safety and efficacy of this most focal, though most invasive, treatment for refractory depression.

## Conclusions and Future Directions

Brain Stimulation in psychiatry today represents an emerging family of technologies to modulate brain function using electrical and magnetic stimulation. The technologies differ in their evidence basis, focality, mechanisms, and clinical spectrum. Figure 109–11 summarizes the state of the evidence for each. ECT has unmatched efficacy, but the challenges for the future are improving its safety and preventing relapse. TMS is highly safe, and future challenges involve enhancing its efficacy. MST likewise has a good safety profile, and current needs are to optimize and test its efficacy against the gold-standard ECT. VNS is newly approved for chronic illness management, and its role as an adjunctive therapy for treatment resistant depression awaits verification with real-world clinical experience in the post-approval era. DBS offers the promise of placing the electrode precisely in the target circuitry, but this also poses the challenge to the field to identify just what that circuitry is to ensure efficacy.

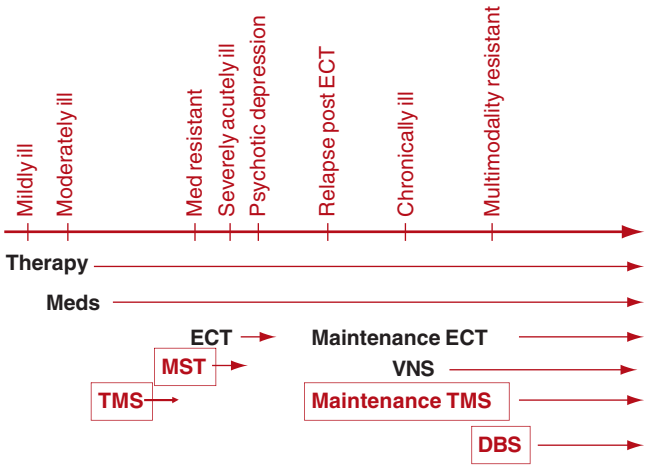



**Figure 109–12** *Putting it all together: What to use and when.*

The potential for brain stimulation in psychiatry has never been more exciting. There are now a collection of technologies that may address different phases of depression (Figure 109–12). Along with this exciting promise, there is also a great need for research in this field to create the science of how intermittent stimulation affects brain function. A better understanding of that science could guide developments in this field. Rather than taking off-the-shelf technology designed for neurological applications, a basic science of brain stimulation optimized for psychiatric disorders offers the promise of creating purpose-built devices tailored to the specific needs of our patients. The stages of drug development (target identification, pharmacokinetics, pharmacodynamics, safety and toxicology) are well known. Less well developed are the device analogues to these stages (Figure 109–13). As we approach rational device development in psychiatry, the device analogues of these stages will need to be addressed through basic and preclinical research.

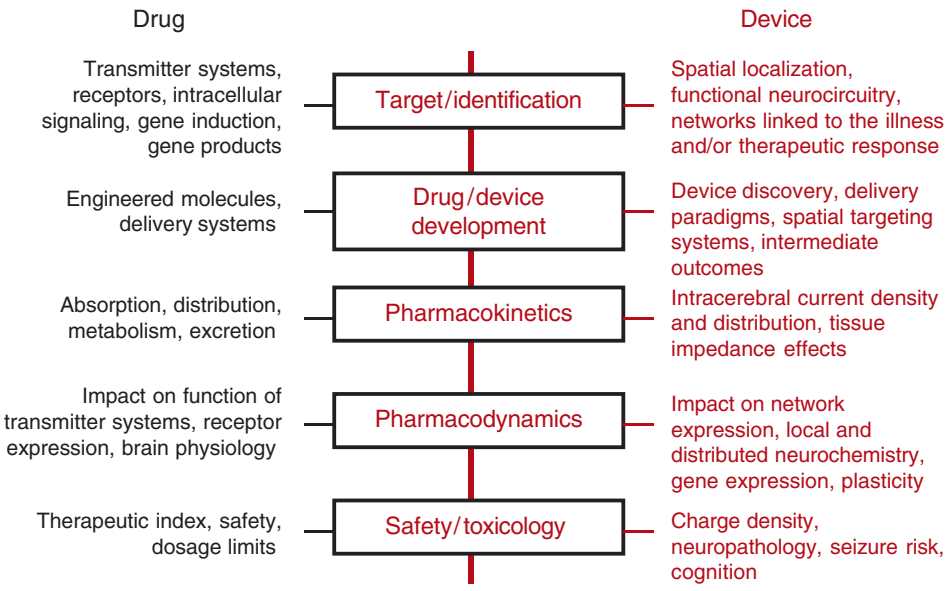



**Figure 109–13** *Intervention development stages.*

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CHAPTER

# 110 Pharmacologic Management of Treatment-Resistant Unipolar Depression

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## Introduction

### Definition and Staging

Treatment-resistant depression (TRD) is a common and challenging problem facing the practicing psychiatrist. Patients with TRD are at higher risk for suicide, relapse of depressive illness, and increased health-care utilization (Souery et al. 1999). There is no universally accepted operational definition of TRD, which has limited comparisons between studies across the existing literature on the subject (Souery et al. 1999). TRD has been defined as "an inadequate response to an adequate trial of an antidepressant" (Petersen et al. 2005), with response defined as at least a 50% reduction in symptom severity. However, this definition is based on the convention for testing efficacy of a new compound compared to placebo, which shows that a compound is active in depressive illness. In practice, no patient's goal is to have their depressive symptoms reduced by half, but rather to be restored to their normal, essentially depression-free state. Remission, an essentially complete resolution of depressive symptoms, has increasingly become recognized as the goal of antidepressant treatment both for this reason and because response without remission has been convincingly shown to lead to increased risk of relapse and poorer functional outcomes (Fava 2003).

Lack of response or remission from a single antidepressant trial is so common as to be insufficient to qualify as true treatment-resistance, which is better defined as a minimum of two treatments not fully effective when given at adequate dosage and for sufficient duration (Souery et al. 2006). While some proportion of patients with TRD will actually have an unrecognized bipolar disorder, often Bipolar II Disorder or Bipolar Disorder Not Otherwise Specified (BPNOS) by DSM-IV-TR criteria, this chapter will focus primarily on unipolar TRD. Also, some patients with ostensibly treatment-resistant depression have actually previously responded to treatment and then have relapsed. While it is not clear how patients who have relapsed are different from those who have not responded, it may be worth making that distinction. Some data suggest that those who have relapsed respond well simply to dosage increase of the agent they had relapsed on, but more study is needed to clarify how best to treat such patients (Fava et al. 2006a, Fava et al. 1994).

One way of quantifying the degree of resistance to treatment is to employ a staging system. The two best-known systems are the Thase and Rush 5-stage model and the Massachusetts General Hospital (MGH) staging method (Petersen et al. 2005). In the Thase and Rush method, resistance stage is determined by nonresponse to sequential trials of antidepressant monotherapy with medications with varying mechanisms of action, or with electroconvulsive therapy (ECT). Specifically, Stage I resistance is defined as lack of response to an adequate trial of a first antidepressant medication; Stage II resistance is defined as Stage I plus a lack of response to a subsequent trial of an antidepressant with a different mechanism of action; Stage III as Stage II followed by nonresponse to a tricyclic antidepressant (TCA); Stage IV as Stage III followed by nonresponse to a monoamine oxidase inhibitor (MAOI); and Stage V as Stage IV followed by nonresponse to ECT. Fava (2003) has described some limitations to this method: it assumes a hierarchy of different levels of effectiveness of medications according to mechanism of action; it does not allow for differentiation of medication trials on the basis of dose or duration; and it does not incorporate augmentation and combination treatments.

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The MGH Staging method, in contrast, assigns one point per antidepressant monotherapy trial of adequate dose (explicitly defined) of at least 6 weeks duration, and adds 0.5 points for each of the following: optimizing the dose or duration of a medication trial, augmenting, or combining medication trials, with an additional three points added for a trial of ECT (Petersen et al. 2005). One retrospective chart review assessed both staging methods as predictors of remission from the index major depressive episode, and found that the MGH staging score, but not the Thase and Rush staging score, was predictive of remission status in a logistic regression model, although the two staging scores were significantly correlated with one another (Petersen et al. 2005). This study provides some evidence in favor of the MGH staging method, although the Thase and Rush method may be more familiar to practicing clinicians.

The major importance of each of these staging systems is that they emphasize that neither doctor nor patient should be discouraged if a single trial of an antidepressant is ineffective. Good treatment demands persistence on both the doctor's and patient's part with trying multiple medications at adequate dosage and over a sufficiently long time to explore the many treatment options now available for TRD, including of course, multiple pharmacologic strategies as well as brain stimulation treatments like ECT. To familiarize oneself with these staging methods, one may wish to read Clinical Vignette 1 and categorize the patient's stage of resistance according to the two methods.

## Prevalence and Predictors

### Prevalence

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a recent prospective, multi-center, practical clinical trial funded by the National Institutes of Health and not by the pharmaceutical industry, provides some of the best available data on the prevalence and predictors of TRD (Trivedi et al. 2006c). Unlike traditional efficacy trials, STAR*D is highly applicable to real world settings, in that recruitment methods, inclusion and exclusion criteria were designed to obtain a study sample representative of patients seeking treatment for MDD in the community. In the first treatment phase of the study, 2,876 patients in a major depressive episode (MDE) underwent a 12-week trial with open treatment with citalopram titrated to 60 mg daily according to a treatment protocol. The primary outcome measure of the study was remission, an essentially complete resolution of depressive symptoms. Remission rates were 28% using the Hamilton Depression Rating Scale (HAM-D) and 33% using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR), consistent with previous estimates from efficacy trials. These highly reliable estimates indicate that despite vigorous treatment with a single effective antidepressant, more than half of patients with major depression do not experience significant improvement, and only about one-third attain full remission. Lack of remission to a first antidepressant trial is common rather than exceptional, even with careful and vigorous treatment.

The STAR*D study also provides some of the best available data on remission rates after multiple sequential treatment trials in MDD. Subjects who did not achieve remission following the initial trial of citalopram were eligible to enroll in sequential, open-lebel, randomized treatment trials that employed varying therapeutic strategies for TRD, including medication switches, medication augmentation, and switch to or augmentation with cognitive behavioral therapy (CBT) (Figure 110–1) (Rush et al. 2006a). The details of these trials are discussed in Sections "Switching Antidepressants," "Augmentation," and "Combination Antidepressant Strategies" of this chapter. The cumulative percentage of subjects initially enrolled who actually achieved remission after one treatment trial was 37%; after two sequential treatment trials, cumulative remission increased to 49%; after three trials, it increased only to 50%, and after four treatment trials, only to 51%. Some of these diminishing returns can be accounted for by patient drop-out from the study, and by patients who were satisfied by response without remission, who therefore chose not to advance to the next treatment offered. Nonetheless, the small gains in total remission rates with the third and fourth treatments in STAR*D demonstrate how depressive episodes that are increasingly treatment-resistant become increasingly difficult to treat effectively. For those patients who do ultimately achieve remission with a third or fourth treatment trial, these gains are of course very clinically significant. This finding is consistent with a previous related study, a chart review of naturalistic treatment for depression in two academic centers, where the cumulative remission rate after a mean of 17 months of treatment reached only 50% (Petersen et al. 2005). In a prospective multicenter study of treatment-resistant depression, Dunner et al. (2006) found remission rates of only 3.6% at 12 months and 7.8% at 24 months. However, other data suggest higher remission rates can be achieved in some specialized treatment settings (Quitkin et al. 2005).

Another important consequence of lack of remission is that such patients have a higher rate of relapse, even if they continue the treatment which was associated with remission. In STAR*D, patients who required more treatment steps to achieve remission subsequently relapsed at a much higher rate than those who attained remission with fewer treatments (Rush et al. 2006a). Taken together, these studies clearly indicate that even after multiple treatment trials, only about half of patients with major depression experience remission, the relapse rate is unacceptably high, and there is a great need for more effective antidepressant treatments.

### Predictors of TRD

The most commonly identified predictor of nonresponse to antidepressants is chronicity of depression, which clearly lowers response rates. Chronicity of depression is associated with lower response rates not only to active treatments but to placebo as well (Stewart et al. 1989, Stewart et al. 1993). This implies that chronicity of depression may affect response by altering nonspecific factors such as patients' expectation of response, rather than by altering specific pharmacologic effects per se. In a recent study, chronicity, as measured by the duration of the index episode, was found to predict a decreased rate of remission in the STAR*D Level 1 treatment sample treated with citalopram monotherapy, as it has in many previous studies (Trivedi et al. 2006c).

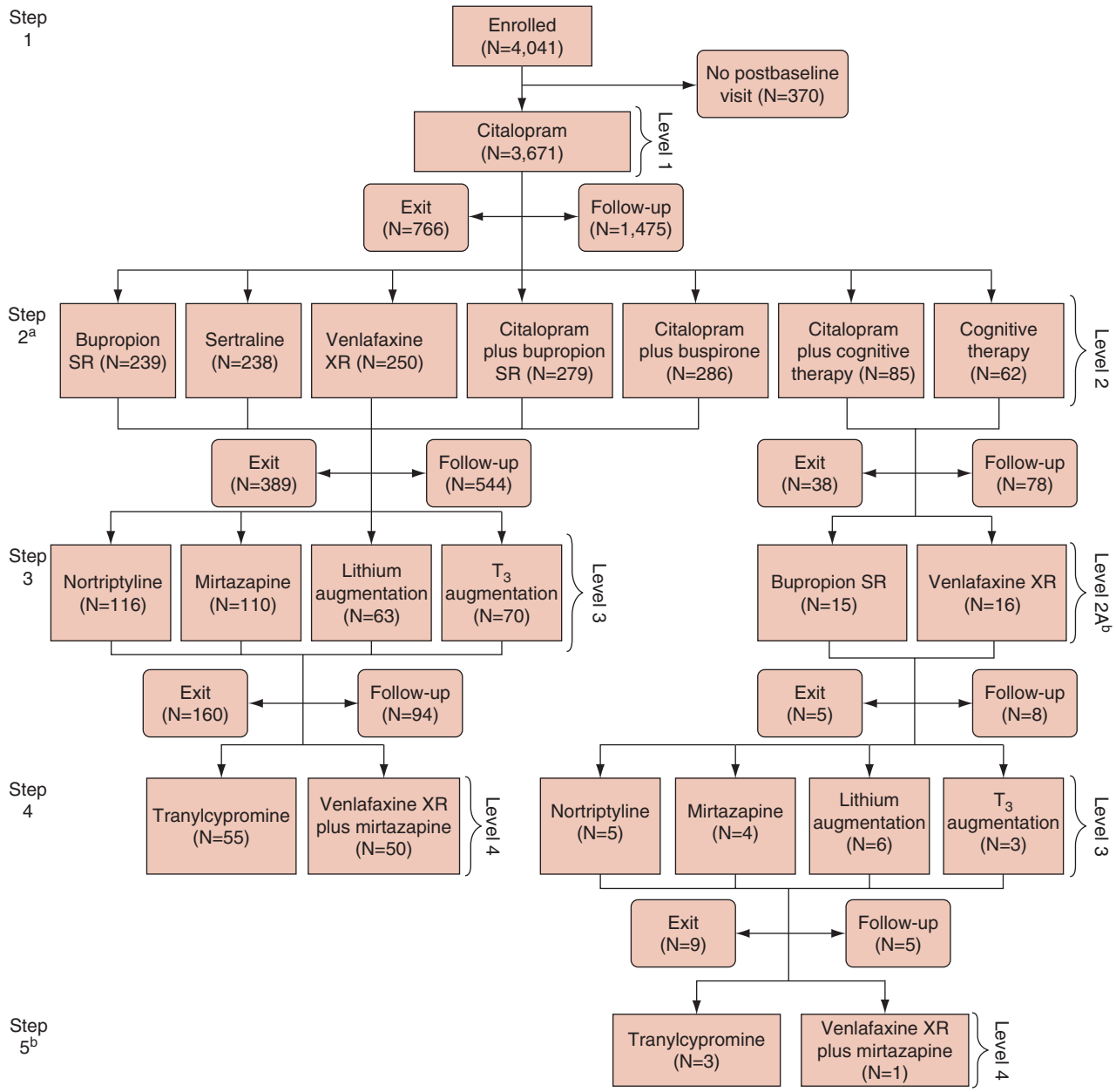



**Figure 110–1** *STAR*D study design (Rush et al. 2006). Reproduced with permission from the American Journal of Psychiatry, Copyright 2006. American Psychiatric Association.*

Other clinical variables have been less consistently associated with nonresponse but several baseline demographic and clinical variables were identified as predictive of nonremission following citalopram treatment in STAR*D. These included male gender (relative risk [RR] = 1.22, 95% confidence interval [CI] = 1.07–1.39), unemployment (RR = 1.51, 95% CI = 1.32–1.73), lower income, lower educational status, poorer baseline function and quality of life, and comorbid anxiety disorders (Trivedi et al. 2006c). Other studies have not been able to confirm a differential response by gender (Quitkin et al. 2001), which in any case seems small. This also appears true of the remaining predictors, so that as of this point, treatment response cannot be reliably predicted by any clinical variables except chronicity, which seems invariably to decrease response rates.

Clinical Vignette 1

Denise is a 36 year-old divorced woman employed part-time as a customer sales representative. She describes a turbulent and unhappy childhood which she relates to her angry and explosive mother, who is described as often verbally abusive. The patient's mother appeared to have marked mood-swings by the patient's description, but never received any psychiatric attention. The patient had many brief periods of depressed mood as a child and adolescent, never clearly meeting criteria for Major Depression until age 16, when she was a junior in high school. At that time, she developed symptoms consistent with a MDE which remained unrecognized and for which she received no treatment.

Over the ensuing years, she has had at least five MDEs, treated with a combination of insight-oriented

Clinical Vignette 1 *continued*

psychotherapy and a series of antidepressant medications. The first two episodes appeared to resolve fully, but she had residual depressive symptoms between subsequent episodes. She denies ever having euphoric mood, but has had brief periods, lasting a day or two, when she was energetic, productive, and happy. She denies that anyone ever complained of her behavior during these times and denies reckless and impulsive behavior, although she sometimes slept only 6 or 7 hours instead of her usual 8 or 9. The patient reports having been treated with fluoxetine very successfully in a previous episode, but she discontinued the medication after about one year due to sexual dysfunction and weight gain, which she attributed to the medication.

In the current episode, which has lasted over two years, she was treated with citalopram for about 6 weeks at a maximum dose of 40 mg with no improvement and was then switched to venlafaxine extended release, which she has taken at a maximum dose of 225 mg for the last eight weeks. She also reports trials of bupropion, escitalopram, and paroxetine with minimal or no improvement. She now reports a slight improvement in her mood, but she is still depressed most of the day every day, is anhedonic, sleeps excessively and has no energy. Since she became unable to work 18 months ago, she has been supported by savings and help from her family. The patient's family has suggested that she consider ECT but the patient wishes to try further medication trials before considering ECT.

## Evaluation of the Patient

### Adequacy of Previous Treatment

A critical piece of clinical history to obtain is how vigorous each previous ineffective treatment trial to which the patient has been exposed has been, in terms of both dose and duration. There are few systematic data dealing with what constitutes an adequate dose for second-generation antidepressants, that is, antidepressants other than TCAs and MAOIs. For working purposes, a dose of at least two-thirds the maximum recommended dosage, administered for a total of eight weeks, can be considered an adequate clinical trial. Because notes from previous clinicians are often inadequately detailed, a summary printout of computerized pharmacy records can be invaluable for the purpose of reconstructing the adequacy of previous treatment trials.

While treating a patient, it is essential to their further care to keep a record of approximate start and stop dates, maximum dosage achieved, duration of the maximum dosage, side effects, estimated compliance, and therapeutic response. If at least the medication names and current dosages are consistently written in the margin of each clinical note, the psychiatrist will find it dramatically easier to quickly peruse the chart to look for a particular trial than if all the information is buried in undemarcated text. A simple form such as that reproduced in Table 110–1 can be highly useful when reviewing a patient's pharmacologic treatment to plan the next step, either by the primary psychiatrist or by a psychopharmacologic consultant. Ideally this information would be collected prospectively, but the table can also be a useful tool to fully summarize a patient's pharmacologic treatment history for further consideration of options or for use by a consultant.

At least 50% of patients with TRD referred to specialists in several recent studies were found to be on inadequate medication doses, and subsequently responded when doses were raised (Fava et al. 2003b). It is clear for some medications like the TCAs that inadequate dosage is responsible for poor response since response to higher dosages has been shown to be superior to low dosages (Watt et al. 1972). There are essentially no systematic data for second generation antidepressants to support the idea that there is a dose response relationship within usually administered dose ranges. However, it is reasonable to assume that dose response, like most biologic characteristics, has a distribution and that this distribution is such that some patients respond well to very small doses and some require dosages higher than the usual range. This likelihood has been recognized in treatment guidelines which strongly suggest increasing dosage in patients inadequately responsive to treatment with virtually all antidepressant medications, contemplating the possibility that not all response is obtained within the usually administered dosage range (Depression Guideline Panel 1993, American Psychiatric Association 2000).

Duration of treatment with previous agents is likewise critical. It has become clear that a substantial minority of patients attain their first significant clinical response only late in treatment. For example, in level 1 treatment with citalopram in the STAR*D trial, fully one-third of ultimate responders to treatment were first considered nonresponders after their sixth week of treatment (Trivedi et al. 2006c). While it is beyond the scope of this text to review the evidence for late response, it appears clear that both dosage and duration of exposure to antidepressant treatment are critical variables in gauging adequacy of treatment exposure.

### Differential Diagnosis

As in all areas of medicine, differential diagnosis is critical to success in treatment, especially in cases with poor response to initial treatment. Because depression can be associated with non-psychiatric disorders and induced by medication, these must be considered in the evaluation of TRD. A detailed discussion of these issues is presented elsewhere in this book. In this section, we will discuss psychiatric differential diagnosis and the contributions to TRD by psychiatric disorders.

#### Bipolar Disorder

One source of treatment resistance appears to be the unsuspected presence of bipolar disorder, usually BP II or BP NOS.

**Table 110–1 Sample Medication Flow-Chart for Monitoring Medication Trials**

| Medication | Start | End | Dose Maximum | Response | Side Effects | QIDS Rating |
|---|---|---|---|---|---|---|
| Fluoxetine | ~10/1/06 | ~11/10/06 | 40 | NR | Sexual dysfunction | 22 |
| Fluoxetine + bupropion | ~11/10/06 | ~1/20/07 | Fluox 40 +bup 300 | Partial response | Libido improved, anorgasmia continued | 12 |

Bipolar depression has been shown to be relatively resistant to treatment with usual antidepressants, and the depressed phase of the illness predominates, often with only transient hypomanias, which may not be appreciated by the patient to be pathologic (Angst et al. 2003, Post et al. 2003a). The patient will often experience and describe these as periods of normal mood relieving him from depression. The single most important tool in establishing this diagnosis is gathering information from a reliable collateral informant who has known the patient well over a long period of time (see Clinical Vignette: Follow-Up). Such an informant should be carefully interviewed to determine the occurrence of sudden mood changes, periods of euphoria, irritability, or increased energy and productiveness, associated with the other symptoms of hypomania, including impulsiveness, grandiosity, decreased need for sleep, and increased rate or amount of speech. Epidemiologic data suggest that classically euphoric hypomania accounts for only some hypomanic episodes (Angst et al. 2003), and that it is common for irritability or increased activity rather than euphoria to be the cardinal symptom manifested.

Another useful tool is the use of a bipolar mood chart, enabling the prospective collection of data on mood-swings, mixed states, rapid cycling, sleep length, and the relation of these symptoms to menses and psychological stress. One such chart, publicly available for download at http://www.manicdepressive.org/tools_all.html is reproduced below with an illustrative case of bipolar mood-swings documented (Figure 110–2). Establishing a diagnosis of bipolar disorder is often critical in attaining remission of otherwise intractable depression by the use of mood stabilizing medications, especially lamotrigine and lithium carbonate, which have demonstrable antidepressant actions in bipolar depression and do not precipitate mood cycling, as antidepressants can do (Post et al. 2003b).

## Substance Abuse

It is widely believed that ongoing alcohol or drug abuse may render antidepressant treatment ineffective. Retrospective studies indicate that recovery from depression in patients with comorbid alcohol abuse or dependence is impaired (Mueller et al. 1994). It appears that some alcohol abusing or dependent patients who are depressed are "self-medicating" their depression with alcohol or drugs of abuse, and that antidepressant treatment can be effective for depression in these cases (McGrath et al. 2000a). Some, but not all controlled trials indicate that depression is treatable despite ongoing alcohol abuse or dependence. Recent data is available from a study conducted ancillary to STAR*D which examined the rate of response and remission to an SSRI in a sample of patients prospectively diagnosed with major depression and a concomitant alcohol use disorder (McGrath PJ, unpublished data). In that study, concurrent alcohol abuse or dependence, which did not require inpatient detoxification, did not impair either response or remission, when usual clinical treatment of modest intensity was given to patients treated in either primary or in specialty care settings. It must be noted that the degree of substance dependence in that study was relatively mild and these data are applicable only to patients with similarly mild substance use disorders.

Likewise with drug abuse and dependence, there are studies, albeit fewer, which indicate that depression can be treated in drug abusing or dependent patients. A recent comprehensive review of available literature indicates that there is evidence that antidepressants can be effective in the face of substance abuse and dependence, especially if concurrent treatment for the substance use disorder is provided (Nunes and Levin 2004). The practical clinical conclusion of these data is that evidence of alcohol abuse or dependence should be sought in a patient with TRD and a period of abstinence should be strongly encouraged to help eliminate the possibility that it is a contributory factor to treatment-resistant depression. Nevertheless, treatment of depression can be effective in substance abusers, especially if concomitant treatment of substance abuse is provided.

## Personality disorder

It is very common and tempting to conclude that a patient's inadequate response to antidepressant treatment is the result of personality disorder, either known or, more often, suspected, based on mood reactivity to environmental or interpersonal stresses, excessive anger, or unstable interpersonal relationships. Most often, it is borderline personality disorder or a mixed personality disorder with borderline features which is thought to limit the effectiveness of antidepressant medication. While the literature reviewing this issue is complex and sometimes contradictory, it appears useful to consider that it is possible for ongoing mood dysregulation to be central to personality disorders such as borderline personality disorder. It might be considered that such dysregulation, which is sometimes incompletely responsive to antidepressant medication, may render depression treatment-resistant. Many clinicians believe that what appears to be personality disorder may be especially likely to be an undiagnosed bipolar mood disorder, with its accompanying irritability, grandiosity, anger, and impulsivity (Katzow et al. 2003). This makes the careful evaluation of patients presenting with treatment-resistant depressive syndromes and concurrent personality disorders, especially DSM-IV-TR cluster B disorders (antisocial, borderline, histrionic, and narcissistic), essential, as bipolar disorders respond to different treatments and can sometimes be worsened by antidepressant pharmacotherapy without accompanying mood stabilization.

Recent reviews of the pharmacotherapy of personality disorder make clear that while most of the evidence is based on case series or open-label clinical trials, there are beginning to be controlled trials to guide this treatment (Raj 2004). These studies provide support for commonly used treatments of low doses of either typical or atypical antipsychotics (Soloff 2000) as well as for MAOIs, SSRIs, and omega-3 fatty acids in the treatment of borderline personality disorder (Raj 2004). Several reviews have emphasized that pharmacotherapy for personality disorder may best be tailored to specific psychopathological states such as impulsive aggression or overwhelming anxiety, with better results than if a treatment is simply selected on the basis of a broadly defined personality category (Gunderson and Phillips 1991, Kapfhammer and Hippius 1998, Soloff 2000).

## Other Psychiatric Comorbid Disorders

Among seriously ill patients, especially those with bipolar disorders or severe personality disorders, the presence of psychosis should be carefully evaluated by both empathic interviewing of the patient and interviewing others who

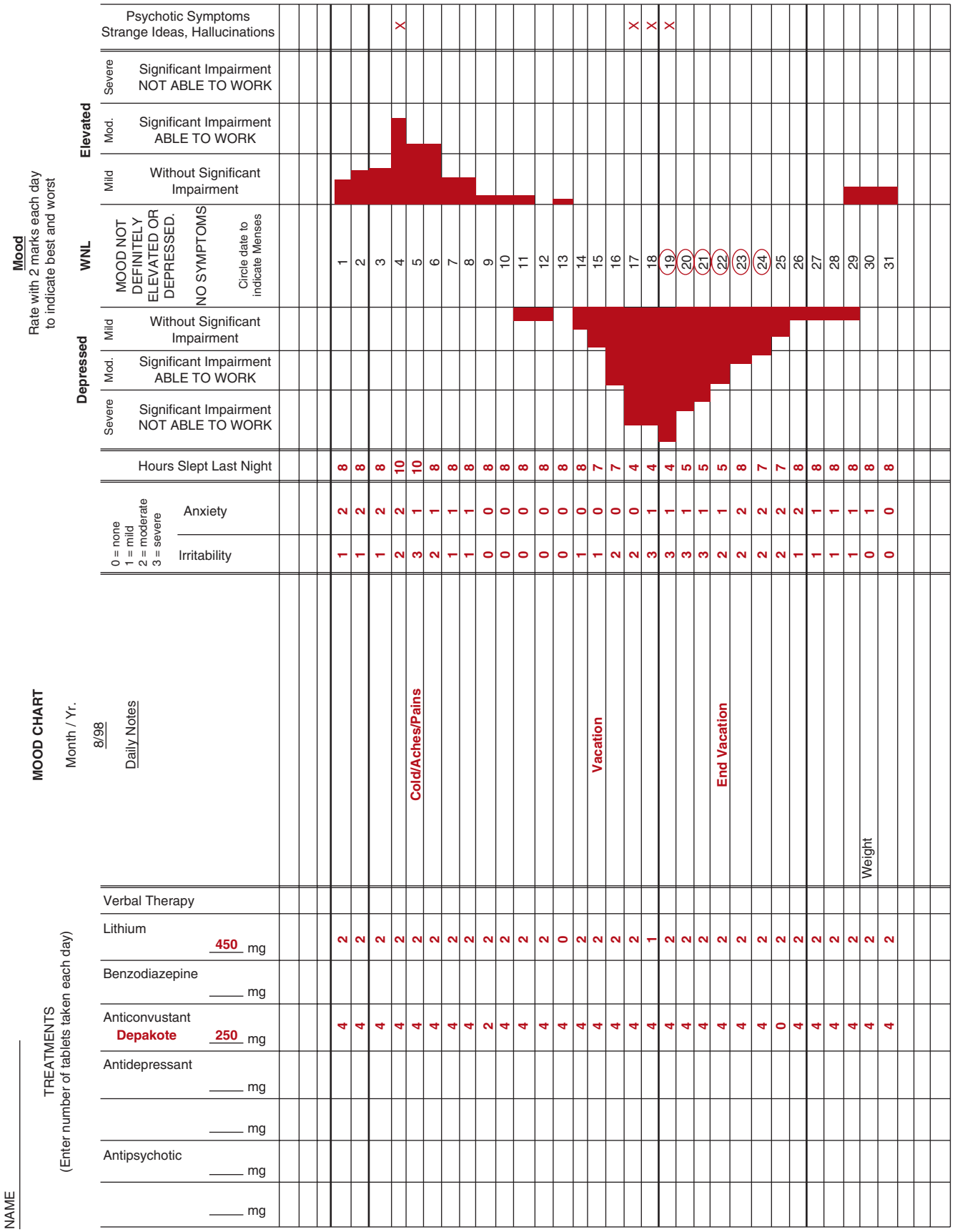



**Figure 110–2** *Sample mood chart for monitoring mood and relationship as well as relationship to medications and environmental events. Available at http://www.manicdepressive.org/images/samplechart.gif (blank forms available at http://www.manicdepressive.org/images/moodchart.pdf). Reproduced by permission of Gary Sachs M.D., Massachussetts General Hospital Bipolar Clinic and Research Program.*

know him well. An empathic interview will use open-ended questioning which does not challenge the patient's view prematurely, to elicit fears about being harmed, delusions of worthlessness or guilt, and delusional beliefs regarding somatic illness. Evidence of guardedness and frank paranoia as well as overvalued ideas and frank delusions should be sought. Delusions of worthlessness and guilt are the most common, although delusions of somatic illness and other delusions also occur. Substantial evidence has shown that such patients benefit more from either an antipsychotic combined with an antidepressant or from ECT rather than from antidepressant monotherapy.

### Subtyping of Major Depression

There is some literature suggesting that the subtypes of major depression such as melancholic, atypical, and seasonal may be predictive of outcome with specific treatments. While melancholia does not appear to predict treatment outcome with second generation antidepressants, there are data suggesting that tricyclics may be particularly effective for patients with the melancholic subtype of depression.

For atypical depression, MAOIs have been shown in multiple studies clearly to be more effective than tricyclics. Further, one controlled study has shown that tricyclics and SSRIs are equivalent in atypical depression (McGrath et al. 2000b). Though not definitive, this is presumptive evidence which suggests that MAOIs may be superior to SSRIs for the treatment of atypical depression.

Seasonal depression does not ordinarily present as TRD, but seasonal exacerbation of nonseasonal depression does occur and is responsive to augmentation of the pharmacotherapy with phototherapy, especially if optimized to the sleep phase of the depressed patient (Terman and Terman 2005).

Anxiety disorders are highly comorbid with major depression and some, but not all studies, have shown either delayed response or a poorer rate of response when they are present (Fava et al. 2004). Recent data from the STAR*D study have shown that prospectively identified anxious depression was associated with a significantly poorer response rate to treatment with an SSRI antidepressant (Fava et al. in press). What has not been adequately investigated is whether there are any treatments which are more effective for patients with anxious depression, whether anxious depression forms a subtype based on criteria other than treatment response, and whether concomitant treatment with anxiolytic medication may help achieve remission for these patients.

## Medication Management

### General Principles

Once the alternative causes of TRD described above have been excluded, there are several important principles in the management of subsequent medication treatment. First, the attitude of the clinician is critical to success. To optimize patient outcomes, the clinician should remain firmly committed to optimizing pharmacotherapy despite the presence of any psychological factors or environmental stressors, which might be thought contributory to the disorder. Given the current state of knowledge of depressive disorders, it is essentially impossible to determine the extent to which antidepressant medication will be effective in any given depression. Therefore, the most rational principle should be to optimize *both* pharmacotherapy and psychotherapy (we will not discuss optimization of psychotherapy for depression here as it is covered elsewhere in this book). Optimum pharmacotherapy involves characteristics of the clinician which include the ability to tolerate uncertainty regarding the etiology of depression without being paralyzed into inaction, the ability to sustain realistic optimism on both her own part and that of the patient, and a thorough understanding of the medication options available for this condition. For those not specializing in the treatment of depression, this will often require consultation with a specialist, as many of the options, such as the use of MAOIs or the use of brain stimulation techniques such as ECT or vagal nerve stimulation (VNS), require specialized expertise.

Finally, conduct of the treatment must include careful monitoring and documentation of dosage, duration, and result of any medication trial, so that adequate exposure to any treatment can be determined, leaving the result unambiguous. Although rating scales are seldom used outside of research settings, the clinician will often find that these are very helpful in objectifying the judgment of whether and to what degree a treatment is working, and their use should be seriously considered in all such cases. The standard rating scale for depression severity in research settings the Hamilton Rating Scale for Depression (HAM-D), which is available in multiple versions, and rates depressive symptoms reliably. Its advantages include its demonstrated sensitivity to change with treatment and its being a "gold standard" for treatment response in depression research. Its major disadvantage is that it requires clinical time to rate, and the structured inquiry it requires is not comfortable for many clinicians.

Many clinicians will find that a brief self-rated scale is easier to incorporate into their practice. Fortunately, a newly developed rating scale for depression which addresses the difficulties of the HAM-D is publicly available without cost. The QIDS-SR is a 16-item self-rated scale which correlates well with the HAM-D, takes only a few minutes of a patient's time, and has been shown to be sensitive to change with treatment. It is available for download at the STAR*D website: www.star-d.org. Excellent alternative scales are either the Beck Depression Inventory (BDI) or the revised BDI-II, which has had items substituted to bring it more in line with DSM-IV-TR criteria for Major Depression. These are each 21-item copyrighted self-report scales which are readily available for clinical use at modest cost and have the same advantages as the QIDS-SR over clinician-rated scales.

If a patient with TRD does not improve sufficiently, one possible reason is that an adequate trial was not attained due to intolerable side effect which could not be ameliorated by adjunctive treatment or other strategies. For the reason that it is common for patients with TRD not to have tolerated various medication trials, the option of ultra-slow dose escalation should be familiar to all clinicians. A patient who experiences intolerable activation by an initial dosage of 20 mg daily of fluoxetine, for example, might tolerate 1 mg daily of fluoxetine concentrate more easily and ultimately respond to this treatment if it is increased by only a milligram or two per week. Practical experience shows that patients will develop tolerance to many adverse effects

of antidepressant medications, especially to activation and gastrointestinal distress, and this procedure will often help a patient seemingly unable to tolerate any medication to have a full therapeutic trial of most agents.

The vigorous treatment of treatable side effects is also helpful in this regard. Hypnotics for insomnia, anxiolytics for anxiety, salt or 9-alpha flurorohydrocortisone supplementation for hypotension, sildenafil for erectile dysfunction, and modafinil augmentation for sedation are examples of adjunctive medications which can be used successfully to enhance tolerability of various agents.

## Dosage and Duration of an Adequate Trial

The dosage and duration of an adequate trial for most antidepressants have not been fully established, as there are not clear data showing at what point no further benefits are gained. A general principle here is that any treatment which has not produced the desired effect but is not causing significant adverse effects might be effective if the dosage were raised to a higher level. The recommended dosage range in the package insert is determined by many factors which include the manufacturer's strong motivation to determine a dosage which allows separation from placebo in a pivotal clinical trial for submission to the Food and Drug Administration (FDA) for approval, yet produces the most acceptable side effect profile. This is both understandable and rational in that the lowest effective dosage of any medication should minimize adverse effects, and if it is fully effective, maximize the risk-benefit ratio of the treatment. These dosage ranges, however, do not adequately account for the obvious fact that there will be a distribution of effective dosages for a population of patients, with some patients requiring much higher than usual dosage for maximum or even minimal benefit. Unfortunately, since higher than the recommended dosages have not been tested for safety, raising the dosage beyond the maximum recommended dosage is intimidating for many psychiatrists. Such prescribing, termed "off label," is sometimes erroneously thought to be prohibited by the FDA. In fact, under federal regulations, any approved medication can be prescribed by a physician for any indication and in any dosage deemed reasonable by prevailing community standards of practice. So in a patient with TRD not responding adequately to a therapeutic trial but experiencing no significant side effects, cautious dosage increase beyond the recommended maximum is a rational and sometimes essential maneuver. Pertinent examples include the recommended maximum dosage of 225 mg daily for extended release venlafaxine, while immediate release venlafaxine has a recommended dosage limit of 375 mg daily. Clearly, a patient experiencing inadequate benefit from 225 mg of extended-release venlafaxine and tolerating it well should be tried on a higher dosage, with appropriate notification to the patient of the rationale for, and potential risks of, "off label" treatment and documentation of this in the medical record. Experienced psychopharmacologists often resort to higher than recommended dosages for patients who are inadequately responsive even in cases where less support for higher dosage levels exists, with careful weighing of the risk-benefit ratio at each decision point and ongoing reaffirmation of informed consent by the patient to this procedure (see Clinical Vignette: Follow-Up). Other examples of frequently-used "off label" prescribing are the use of antidepressant augmentation strategies and combinations of several antidepressants. Some of these augmentation and combination strategies now have efficacy and safety data collected through the conduct of the STAR*D study.

Regarding duration, many efficacy trials of antidepressants have durations of eight or even six weeks. As described previously, there was a high incidence of late response in the STAR*D level 1 study. Late remission rates in that study are perhaps even more striking: approximately one-third of patients who eventually achieved remission with citalopram did so in treatment week 10 or later, sharply underscoring the potential benefit of extending medication trials beyond six or eight weeks in patients who have shown some initial benefit (Trivedi et al. 2006c). An important counterpoint to this finding of late response and remission comes from a recent meta-analysis which found *initial* improvement from SSRI treatment occurring by the end of the first week of use when compared with placebo (Taylor et al. 2006). Thus, in patients with *no* evidence of clinical improvement after a six or eight week antidepressant trial of adequate dose, increasing the duration of the trial seems ill-advised for most patients.

## Emergencies

The major emergencies in treating TRD are the emergence of significant suicidal risk, and the development of psychosis, mania, or a mixed bipolar state where depressive and manic symptoms occur together. As in treating all depressive illness, ongoing assessment of suicidal risk is an essential part of good clinical care. Recent studies suggesting an increased risk of suicidal ideation in both adolescents and adults taking selective serotonin reuptake inhibitors (SSRIs) have resulted in a strong warning by the FDA that treatment with SSRIs could possibly increase suicidal risk. While it is presently highly controversial whether antidepressants do carry some small risk of increasing suicidal thoughts or even behavior, the admonition that depressed patients be monitored for suicidal risk is unexceptionable.

The consistent data showing that untreated anxiety and agitation are associated with an increased risk of suicide should encourage the clinician to address these symptoms early and vigorously with adjunctive medication as a potential preventative technique for the development or worsening of suicidal ideation. Unfortunately, to our knowledge no clinical study has addressed such intervention, probably because of the difficulty of conducting a properly controlled trial in this situation. However, it is reasonable to hypothesize that vigorous treatment of anxiety or agitation with appropriate adjunctive medication may decrease suicidal risk, even among those hospitalized, and should be considered in cases of anxious or agitated patients with significant suicidal impulses. Hospitalization, either voluntary or involuntary, obviously also is an important tool to prevent suicide, although the number of patients who commit suicide while in psychiatric hospitals makes it clear that hospitalization alone is not sufficient.

The development of psychosis or a mixed state should prompt immediate consideration of hospitalization, as both psychotic depression and mixed states have been shown to increase the risk of suicide. A patient's beginning to

call repeatedly between sessions in sometimes ill-defined heightened distress should prompt immediate evaluation for the development of psychotic or mixed state symptoms rather than be ascribed simply to personality disorder. In such cases, the relief brought by the early and vigorous use of antipsychotic or anxiolytic medication can potentially be literally life-saving, and should be considered along with the possible need for hospitalization, which is often either unacceptable or not readily available to the patient.

## Switching Antidepressants

Table 110–2 (Anderson 2003) provides a hierarchy of study design quality that will be referred to in describing the strength of evidence for various treatment approaches discussed in this section. In addition to study design, effect size, sample size, and source of funding (industry-sponsored vs. government or other independent sponsorship) inform this discussion of the evidence for specific treatments.

**Table 110–2 General Principles for Assessing Quality of Intervention Studies**

High quality: systematic reviews of good-quality RCTs or a large definitive RCT

Intermediate quality: small RCTs, nonrandomised or open studies

Low quality: case reports, opinion

*RCT caveats*

Designs may be biased or selected to achieve specific aims

There may be 'spin' in reporting results or a bias in publication

Heterogeneity within groups may be concealed

There may be a lack of generalisability or clinical practice relevance

Reproduced by permission of The Royal College of Psychiatrists from Anderson (2003) Drug treatment of depression: Reflections on the evidence. Advances in Psychiatric Treatment, 9, 11–20.

### Within Class

Clinical wisdom among psychopharmacologists held until recently that if a patient did not achieve remission following a first medication trial, they would be more likely to remit on a subsequent trial with a medication with a different mechanism of action, rather than with a switch to a medication with the same mechanism of action as the first. Indeed, a survey of 423 psychiatrists by Fredman et al. revealed that the most popular treatment choice following an unsuccessful trial of an SSRI was to switch to a non-SSRI antidepressant (44% of respondents), most frequently dual-acting agents or bupropion (Fredman et al. 2000). Data from clinical trials, however, provides some support for switching to a second SSRI following initial unsuccessful SSRI treatment. A recent review described seven open studies of switching to a second SSRI following nonresponse or intolerance to a first (Ruhe et al. 2006). They reported response rates varying from 42–58% in the studies of patients who had not responded to a first SSRI, and response rates from 56–72% in the studies of patients who had not tolerated a first SSRI. They also describe three randomized controlled trials with SSRI arms as a second step of treatment following first SSRI nonresponse (including the STAR*D trial, to be described next), with reported remission rates varying from 17.6–52.1%. It should be noted that the majority of these trials, with a notable exception of the STAR*D study, were industry-sponsored, and as such were subject to potential bias in study design.

STAR*D was the largest study to date to assess prospectively the efficacy of different switching strategies. Seven hundred and twenty-seven patients who did not achieve remission after a 12-week trial of citalopram or who could not tolerate its side effects were randomized into one of the three possible medication switch strategies: switching to a second SSRI, sertraline; to a dual serotonin and norepinephrine reuptake inhibitor, extended-release venlafaxine; or to sustained-release bupropion, whose mechanism of action may involve norepinephrine and dopamine reuptake inhibition (Rush et al. 2006b). Remission rates did not differ significantly among these three groups (sertraline = 17%, extended-release venlafaxine = 26% and sustained-release bupropion = 21%), a finding that was surprising to study investigators. For the reason that there was no placebo control in this study, these remission rates cannot be solely ascribed to the active effects of the antidepressants to which subjects were switched, but may be due to nonspecific effects, including placebo effects and spontaneous remission. Remission rates between 17–26% in a second stage of treatment following nonremission to a SSRI are clinically significant, however. These data taken cumulatively provide strong evidence that a clinically significant group of SSRI nonresponders may respond when treated with a second SSRI.

There are several possible mechanistic explanations for the effectiveness of a second SSRI in some patients after nonresponse to a first SSRI. The first SSRI trial may have been too short to yield maximal benefit from this class of medication, and by switching to a second SSRI, the cumulative duration of SSRI treatment is extended, yielding a benefit. An interesting alternative explanation is that remission with a second SSRI may be related to unique pharmacological properties of different SSRIs. For example, paroxetine has been shown to exhibit greater reuptake inhibition for norepinephrine than other SSRIs, and sertraline has been shown to inhibit reuptake of dopamine more than other SSRIs (Nemeroff and Owens 2004). As STAR*D level 2 did not find different remission rates between medications with far more disparate mechanisms of action, this must be considered an exploratory hypothesis at best.

A recent meta-analysis of randomized-controlled trials that compare switching to a second SSRI or to a medication with a different mechanism of action following a first unsuccessful SSRI trial included four double-blind controlled trials including this STAR*D study (Papakostas et al. 2007). They reported 4.5% lower remission rates with a second SSRI compared to a different class of medication, which was statistically significant in the pooled analysis ($p = 0.007$). They argued that STAR*D was underpowered to detect differences between groups of less than 15% in rates of remission, but that such differences were clinically meaningful.

### Between Classes

#### Dual Mechanism

The recent Ruhe et al. (2006) review of switching strategies included a meta-analysis of the three randomized controlled

trials that have compared switching to a second SSRI with switching to venlafaxine: the STAR*D trial just described, a trial by Poirier and Boyer (1999), and a trial by Baldomero et al. (2005) (Ruhe et al. 2006). The Poirier (1999) study was a double-blind, randomized controlled trial comparing extended-release venlafaxine to paroxetine in a moderate sized sample ($n$ = 122) of patients with TRD who had previously not responded to at least two prior antidepressant treatments. That individual study found a statistically and clinically significant advantage of venlafaxine over paroxetine, with response rates of 52% vs. 42% ($p$ = 0.044). The Baldomero (2005) study, sponsored by the manufacturer of venlafaxine, was an unblinded randomized trial of venlafaxine extended-release versus "conventional antidepressants" (CAs) following nonresponse or intolerance to a first CA; 92% of CAs were SSRIs. It found 24-week remission rates of 59% in the venlafaxine-treated group vs. 52% in the CA-treated group ($p$<0.0001). While this represents a small difference clinically, this study achieved a high level of statistical significance due to its large sample size of 3,097 patients. From the meta-analysis of these three studies, Ruhe et al. (2006) reported a number needed to treat (NNT) of 13 for benefit of venlafaxine over SSRI, and concluded that there was "a modest and clinically equivocal benefit" of venlafaxine over a second SSRI following SSRI nonresponse. From this review of the data, there is good evidence supporting the efficacy of switching to venlafaxine following an unsuccessful SSRI trial, and equivocal evidence for a small advantage of venlafaxine over a second SSRI after nonremission from a first SSRI.

## Bupropion

As described above, the STAR*D level 2 trial did not find significant differences in response or remission rates to sustained-release bupropion, extended-release venlafaxine, or sertraline in a large sample of patients who did not remit with or who could not tolerate a first trial of citalopram. In addition to this high-quality randomized controlled trial (RCT), two earlier open studies explored switching to bupropion. Fava et al switched 26 fluoxetine nonresponders to an eight-week trial of sustained-release bupropion, starting at 150 mg with the possibility of dose escalation based on clinical status (Fava et al. 2003a). They noted a remission rate of 23.1% and a response rate of 34.6% using a modified intent-to-treat analysis, which is highly comparable to the findings in STAR*D. Another open study examined 31 patients with MDD who experienced sexual side effects on fluoxetine, switching them to bupropion to determine whether there was an effect on reported sexual side effects (Walker et al. 1993). After a two-week washout followed by eight weeks of treatment with bupropion, 81% of patients described feeling "much" or "very much" more satisfied with their sexual functioning, although some improvement began during the washout, and prior to bupropion treatment. This study did not report response or remission rates during the bupropion trial. Taken together, there is reasonable evidence supporting switching to bupropion following an unsuccessful trial of an SSRI, although no data for its superiority over other switching strategies. Clinicians may consider switching to bupropion in particular for patients who have significant sexual side effects from a trial of an SSRI or dual reuptake inhibitor.

## Mirtazapine

Mirtazapine is an antidepressant that acts via central $\alpha_2$ antagonism as well as serotonin 2 and 3 receptor antagonism (Fava et al. 2001). It was previously studied in an open-label trial as a switch option for 103 patients who had not responded to or did not tolerate an adequate SSRI trial (Fava et al. 2001). This study found response rates of 48%, with the most commonly reported side effects being sedation, increased appetite, and weight gain.

Mirtazapine was evaluated in a study with more rigorous methodological design in the STAR*D study, as a third step of medication treatment for patients who did not achieve remission with or could not tolerate two prior medication trials (a trial of citalopram monotherapy followed by either a switch or an augmentation) (Fava et al. 2006b). It was compared to the TCA nortriptyline in a randomized-controlled trial ($n$ = 235), of patients who were, by definition, more treatment-refractory than those in the second step of the STAR*D trial described above. Patients were treated with flexible dosing using a protocol, and received mirtazapine at an initial dose of 15 mg, which could be titrated up to 60mg daily. Nortriptyline was started at 25 mg, and was titrated up to a maximum of 200 mg daily. Remission rates were low for patients treated with either mirtazapine (12.3%) or nortriptyline (19.8%), as were response rates (13.4% vs. 16.5%), and did not differ significantly between the two groups. The authors concluded that antidepressant monotherapy with either of these agents in patients with this degree of treatment-refractoriness is effective for only a minority of patients. Discrepancies between these two studies of mirtazapine may be partially accounted for by the different primary outcomes of response vs. remission, the nonrandomized nature of the first study, and the more treatment-refractory population in this phase of STAR*D. The evidence provides some support for the use of mirtazapine as a switching agent, with a higher expected likelihood of response or remission in less treatment-resistant patients. The side-effect profile of mirtazapine, which includes sedation and weight gain, may make it most appropriate for patients whose depressive symptoms include insomnia and weight loss as some clinicians find tolerance problematic in those without these symptoms.

## TCAs

TCAs are used less frequently than SSRIs in current psychiatric practice, due to their side-effect profiles, toxicity in overdose (Nierenberg et al. 2003), and requirements for therapeutic drug level monitoring. Less experience with this class of medication among clinicians likely contributes to lower prescribing rates, as well. While these real disadvantages should not be underestimated, the TCAs remain a useful class of medication for clinicians treating patients with TRD. There is some evidence of benefit of TCAs over SSRIs in melancholic depression (Perry 1996), and TCAs can be obtained at significantly reduced cost compared to antidepressants that are not yet available generically. In addition to the STAR*D study just described, nortriptyline was studied as a treatment for TRD in an open study that enrolled subjects with between one and five prior unsuccessful antidepressant trials in their current MDE (Nierenberg et al. 2003). Patients were treated with nortriptyline at a starting dose of 25mg, which was titrated to a final mean

dose of 121.2mg. They reported response rates of 42% and remission rates of 12% at 6 weeks, in a group with an average of 2.3 prior unsuccessful medication trials. A large, double-blind RCT switched 117 chronically depressed subjects who did not respond to a trial of sertraline to a 12-week trial of imipramine following a 2-week washout (Thase et al. 2002). This study found remission rates of 23% and response rates of 44%, which are impressive given the degree of chronicity and treatment resistance of their sample. Higher response and remission rates might be expected for TCAs if used in less chronic or treatment-resistant patients, although this has not been studied.

It is important to note that nortriptypline, one of the best tolerated of the TCAs, is believed to have a dose-response curve with a specific therapeutic window that has been associated with optimal response (Perry et al. 1994), with reduced efficacy both below and above the therapeutic window.

### MAOIs

MAOIs inhibit enzymes involved in the breakdown of monoamines including serotonin, epinephrine, norepinephrine, and dopamine (Krishnan 1998). MAOIs have been used since the 1950s as antidepressant medications. Concerns about the potential for hypertensive crisis that can result following consumption of foods containing tyramine have limited the use of this class of medication in recent years, although it remains a highly effective treatment option for some individuals, which can be prescribed safely with proper patient education. A relatively conservative MAOI diet can be found at http://patienteducation.upmc.com/Pdf/MaoiDiet.pdf although less restrictive diets may be safe and may contribute to greater adherence (Gardner et al. 1996).

In the STAR*D study, 109 depressed subjects who had not remitted with or could not tolerate three prior medication trails were randomized to treatment with the MAOI tranylcypromine or with the combination of extended-release venlafaxine and mirtazapine (McGrath et al. 2006). Tranylcypromine was initiated at 10mg daily and increased weekly to a maximum of 60 mg, the maximum dose according to the United States FDA guidelines. The venlafaxine/mirtazapine combination was initiated at 75 mg/15 mg daily, and titrated to a maximum of 300 mg/45 mg daily. They found relatively low remission rates of 6.9% for tranylcypromine and 13.7% for venlafaxine/mirtazapine, which did not differ significantly from one another. There was higher exit from the study due to side effects in the tranylcypromine group (41.4%) than in the venlafaxine/mirtazapine group (21.6%).

There are at least six earlier studies of tranylcypromine in treatment-resistant depression, four of which were RCTs, with response rates ranging from 29−75% (McGrath et al. 2006). The two open studies found improved treatment efficacy using high-dose tranylcypromine treatment above the FDA maximum, using 70–120 mg daily (Amsterdam and Berwish 1989, Nolen et al. 1988). Explanations for the low remission rates reported in the STAR*D study include the relatively treatment-refractory nature of the sample studied, the short treatment duration achieved, and the lower target doses of tranylcypromine that were achieved compared with previous studies. That said, dropout in the tranylcypromine arm was quite high in the STAR*D study, so achieving a higher maximum dose might be challenging in this population, at least in the hands of physicians not experienced with using these medications. MAOIs remain an effective treatment for some patients with TRD, and may be considered especially in patients whose depression manifests atypical features, given their demonstrated high efficacy in this condition (Liebowitz et al. 1988). When switching from an SSRI to an MAOI, the SSRI should be stopped at least two weeks prior to initiating MAOI treatment (5 weeks in the case of fluoxetine) to reduce the likelihood of serotonin syndrome (Krishnan 1998).

## Augmentation

There may be some advantages to treatment approaches that utilize augmentation, rather than switching, particularly for patients who have derived a partial benefit from the initial medication trial. There is some evidence of shorter onset of action with augmentation as opposed to switching, as it obviates the possible need for a medication washout, and allows for possible late-effects of the first medication to occur (Joffe 1997). Some potential disadvantages of augmentation approaches include the greater complexity for patients of regimens with more than one medication, which may reduce treatment adherence, as well as the pharmacodynamic and pharmacokinetic drug-drug interactions that can accumulate with increasing polypharmacy (Joffe 1997).

Level 2 of STAR*D included both switch and augmentation options; the switch trial was described previously. Patients were *not* randomized across all of these options in equal measure; they were given the choice of whether they would accept randomization to a switch strategy only, to an augmentation strategy only, or to either strategy. Subjects who entered the augmentation trial had lower HAM-D scores at study entry than those who entered the switch trial, indicating that patients with greater improvement on citalopram were more likely to choose augmentation over switch. This makes outcome measures between the STAR*D level 2 switch and augmentation studies not directly comparable.

A distinction has been traditionally made in the literature between *augmentation*, which involves adding a medication not traditionally used as an antidepressant to a previously prescribed antidepressant, and *combination*, which involves administering two known antidepressants simultaneously. Augmentation strategies, which have a longer-standing base of evidence, will be discussed first, followed by combination strategies.

### Lithium

#### Evidence

At least 10 double-blind, placebo-controlled trials of lithium augmentation in the acute treatment of MDD nonresponsive to antidepressant monotherapy have been conducted. A meta-analysis of nine of these studies found response rates of 45% in subjects randomized to lithium ($n$ = 113) versus 18% in those randomized to placebo ($n$ = 121), yielding a relative benefit of 2.5 compared to placebo (confidence interval = 1.6−3.8) (Bauer and Dopfmer 1999). While this benefit of lithium over placebo is both clinically and statistically significant, most of these studies were of augmentation of TCAs, and not of SSRIs or other antidepressants used most commonly today, which limits the conclusions that can be drawn from them. One of the nine studies found a

benefit of lithium over placebo when augmenting the SSRI fluoxetine, but this effect was only significant when subjects with lithium levels <0.4 were excluded from the analysis. In a recent review, Fava and Rush (2006) noted that more recent studies have found lower response rates with lithium augmentation than those reported in the earlier literature. In addition to possible differences in efficacy when augmenting SSRIs as opposed to tricyclics, they noted that greater attention has been paid in recent years to excluding bipolar-spectrum depression from studies of unipolar depression, with earlier studies possibly showing greater benefit of lithium due to inclusion of such patients. While intriguing as a hypothesis, there are no data to support this theory to date.

The STAR*D study examined lithium augmentation of citalopram, sertraline, sustained-release bupropion, and extended-release venlafaxine. Lithium augmentation was used as a third step of medication treatment after unsuccessful trials of both citalopram and then either a medication switch or augmentation (see Figure 110–1) (Nierenberg et al. 2006). These subjects were therefore more treatment-resistant than subjects enrolled in prior studies of lithium augmentation in MDD. This is more likely to be representative of real-world clinical practice, as lithium augmentation is often not initiated until multiple other strategies have proved ineffective, due to its side-effect profile, requirement for monitoring of therapeutic levels, and relatively poor acceptability to patients. Subjects in STAR*D were randomized to augmentation with either lithium at doses of up to 900 mg/day or triiodothyronine (T3) at doses of up to 50 μg/day, and were treated for up to 14 weeks. 15.9% of subjects achieved remission on T3, and 24.7% achieved remission on lithium, but this difference was not statistically significant. The incidence of side effects and of dropout due to side effects were higher in the lithium group than in the $T_3$ group. The authors concluded that there may be a slight advantage for T3 over lithium in this patient population given its greater tolerability.

### Prescribing Principles

Lithium can be initiated at a dose of 300mg daily when used for augmentation of antidepressant monotherapy, or at even lower doses for patients who have historically been medication-sensitive. As with the use of lithium for mood stabilization in bipolar disorder, it is important to monitor therapeutic levels of lithium when used as augmentation, as they are correlated with the incidence of side effects. While an earlier study found reduced rates of relapse in bipolar disorder when serum lithium levels were maintained at higher levels (0.8−1.0 mmol/L) as compared to a group of patients maintained at lower levels (0.4 to 0.6 mmol/L) (Gelenberg et al. 1989), a subsequent study called these findings into question (Perlis et al. 2002). In the case of lithium augmentation for unipolar depression, it is most prudent to initiate treatment in the lower range of the therapeutic window, and to increase levels gradually according to clinical judgment. Screening for side effects of hypothyroidism, diabetes insipidus, and other renal complications should include monitoring of electrolytes, blood urea nitrogen, creatinine, and thyroid-stimulating hormone at a frequency indicated by clinical judgment. For example, if a patient who previously had a good response to lithium augmentation subsequently experiences worsening depression, causes including a reduction in lithium levels or lithium-induced hypothyroidism should be considered. The very rare case reports of serotonin syndrome developing when lithium is combined with serotonergic agents, including venlafaxine, SSRIs, and TCAs should not deter the clinician from lithium augmentation, but should remind her of the need for awareness about this rare but serious complication. In considering various treatment strategies for TRD, lithium augmentation may be considered preferentially for subjects who have a positive family history of bipolar disorder or soft signs/symptoms themselves of bipolarity.

## Thyroid Hormone

Thyroid hormone has been used in various formulations in the treatment of depressive illness since the 1950s. As with lithium, T3 has been most extensively studied as an augmentation to TCAs, limiting the generalizability of this literature. There are at least four controlled or partially controlled trials of T3 augmenting TCAs, and another eight studies with open-label treatment. A meta-analysis of studies conducted prior to 1996 found a benefit of T3 over placebo when all open studies and RCTs were included, but found no difference when only RCTs were considered (Aronson et al. 1996). The STAR*D data described above are perhaps more applicable to current practice, however, in that T3 was used to augment antidepressants that are more frequently prescribed today. The STAR*D data argue for T3 augmentation of modern antidepressants being at least as effective as lithium augmentation, and better tolerated, providing good evidence supporting its use in TRD.

## Buspirone

Buspirone is a partial agonist of the serotonin 1A ($5\text{-}HT_{1A}$) receptor, and may act via affecting pre-synaptic autoreceptors on serotonergic neurons. In the STAR*D trial, augmentation of citalopram with buspirone was compared to combination of citalopram with sustained-release bupropion as the second step of pharmacologic treatment following an unsuccessful trial of citalopram in a randomized trial (Trivedi et al. 2006b). While bupropion has been described as a norepinephrine and dopamine reuptake inhibitor, the mechanism that mediates its antidepressant effects remains unclear. In this study, buspirone was started at a dose of 15 mg daily, and increased weekly by 15 mg to a final daily dose of 60 mg, administered in divided doses. Sustained-release bupropion was started at 200 mg daily and increased by 100 mg every two weeks to a final dose of 400 mg daily, also given in divided doses.

This study did not find significant differences in remission rates between the group receiving sustained-release bupropion (29.7%) and the one receiving buspirone (30.1%). However, they did note greater tolerability of bupropion than buspirone. Whether buspirone might be more effective for the subgroup of patients with significant anxiety as part of their depressive syndrome has not yet been addressed by analysis of the STAR*D database.

## Pindolol

Pindolol is a beta-blocker that also acts as a $5\text{-}HT_{1A}$ receptor antagonist. Inhibition of pre-synaptic $5\text{-}HT_{1A}$ receptors on serotonergic neurons has been hypothesized as a possible means of potentiating the effect of SSRIs. While

two placebo-controlled trials from the same research group showed some benefit of augmenting fluoxetine or low-dose trazodone with pindolol, three placebo-controlled trials have failed to show benefit of pindolol over placebo when used for augmentation, including a recent trial of 42 SSRI nonresponders treated with pindolol 2.5 mg three times a day vs. placebo (Perry et al. 2004). Despite lack of clear antidepressant efficacy in that study, pindolol did exhibit active beta-blocking effects at this dose, with reductions in heart rate observed at one week. A positron emission tomography (PET) imaging study found limited occupancy of 5-$HT_{1A}$ receptors by pindolol at this dose, indicating that higher doses may be required to achieve physiologic effects on the 5-$HT_{1A}$ receptor (Mertinez et al. 2000). The current evidence provides little support for pindolol augmentation in TRD.

## Combination Antidepressant Strategies

### Citalopram and Bupropion

Please see Section "Buspirone."

### Venlafaxine and Mirtazapine

The combination of venlafaxine and mirtazapine used in the fourth stage of medication treatment in STAR*D was previously described (Section "MAOIs"). The mechanistic rationale for this combination stems from the idea that mirtazapine would reduce inhibition of serotonin and norepinephrine neurons via its presynaptic alpha-2 inhibitory activity while venlafaxine would inhibit reuptake of both of these neurotransmitters, thereby enhancing serotonin and norepinephrine neurotransmission (Stahl 2000).

## Novel Agents

### Glutamatergic agents

Because the glutamatergic system is the main inhibitory neurotransmitter system in the brain, agents active in this system have been proposed as augmenting agents for TRD with the rationale that treatment resistance in depressive disorders may arise from excess inhibitory function. Lamotrigine, which inhibits the release of glutamate, did not separate from placebo in a small controlled augmentation trial (Barbosa et al. 2003). An open label trial of riluzole given as monotherapy suggested some efficacy (Sanacora et al. 2007) although there is as yet no controlled clinical trial data to support this interesting finding.

### Atypical Antipsychotics

Interest in the use of atypical antipsychotics for depression began in 2001 with the first publication of an augmentation study in which 28 patients with major depression unresponsive to fluoxetine monotherapy experienced significantly greater improvement when randomized to receive olanzapine augmentation compared to those continuing fluoxetine monotherapy (Shelton et al. 2001). Two subsequent and larger studies, however, one by the same author, failed to confirm these findings with fluoxetine (Corya et al. 2006, Shelton et al. 2005). Subsequently, seven new double-blind controlled clinical trials have been presented or published since 2006, with five of the seven showing greater efficacy for augmentation with an atypical antipsychotic compared to placebo addition to the antidepressant (Papakostas and Zarate 2007). Because none of the studies tested ziprasidone or quetiapine, there is uncertainty whether the efficacy extends to all of the atypicals or is limited to only some. Nonetheless, this augmentation strategy has become popular with clinicians faced with TRD cases, especially in those where bipolar disorder is known or suspected, since the data for the use of atypical antipsychotics in bipolar disorder is much more robust. The recent approval of quetiapine as monotherapy for the treatment of bipolar depression based on two well controlled clinical trials has reinforced this trend and encouraged the use of atypical antipsychotics in unipolar as well as bipolar depression. The metabolic and neurological side effects of this class of medication should not be underestimated. They should be discussed clearly with patients prior to initiating treatment, and monitored once treatment has begun.

## Proposed Algorithm for Treatment

There are no comprehensive treatment algorithms for TRD that incorporate the evidence base accumulated in the STAR*D trial. Prior treatment algorithms must therefore be viewed as models for subsequent algorithm development, and not as definitive tools to guide treatment. With these caveats in mind, the best-known treatment algorithm for major depressive disorder, which notably has an established evidence base, comes from the Texas Medication Algorithm Project (TMAP) (Figure 110–3) (Trivedi et al. 2004). This algorithm was tested prospectively in a nonrandomized design against treatment as usual over a period of 12 months. Symptom reduction was significantly greater in the group receiving algorithm-based treatment. These differences were significant at three months, and persisted through 12-month follow-up. A criticism that has been made of this algorithm is that it relies too heavily on monotherapy trials and does not advocate for augmentation or combination strategies early enough in the decision-tree (Trivedi et al. 2006a). This algorithm is nonetheless a good starting point that in the least includes many of the possible strategies that are available to the clinician confronting a challenging case of TRD.

## General Principles of Management

It is important to educate patients about several aspects of medication-based treatments for depression. It is not uncommon for patients to believe that antidepressants can be effective even if taken only on days when they feel particularly depressed, and not on days when they are feeling better. Such beliefs and practices will only be elicited if patients are asked about how they are taking their medications, and if this is done in an open, nonjudgmental manner. Educating patients in a straightforward manner about the believed mechanism of antidepressants, and the need for these medications to be taken daily in order to achieve their therapeutic effect, can be helpful in these situations.

It is similarly important to ask detailed questions about patients' sleep. Irregular sleep patterns, reduced sleep, or disturbed sleep architecture can all have deleterious effects on patients' moods, and can be addressed both behaviorally and pharmacologically. Educating patients about basic sleep hygiene can be extremely helpful to patients whose sleep habits are not conducive to good sleep (see Table 110–3).

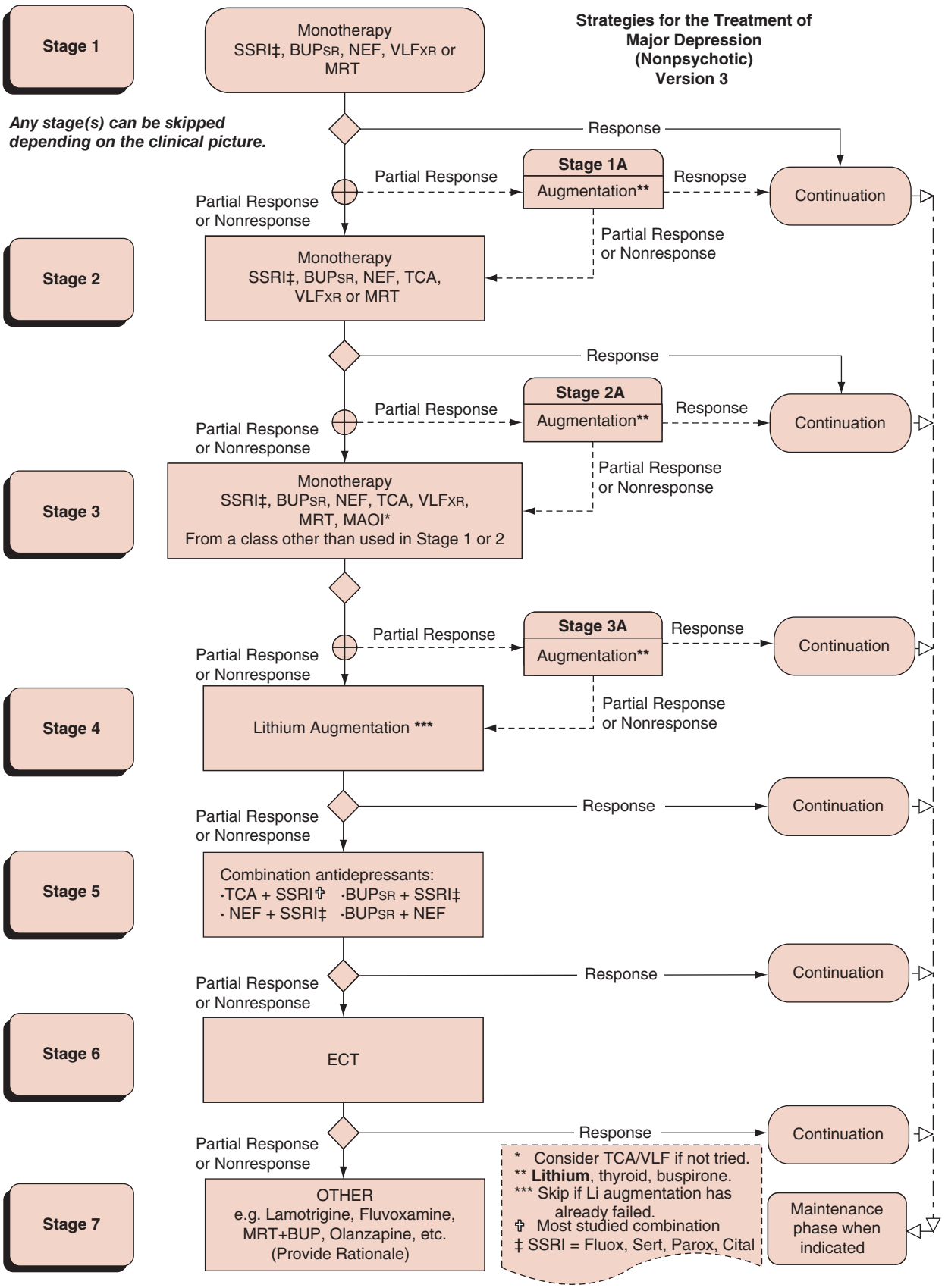



**Figure 110–3** *TMAP algorithm for treatment of major depressive disorder. In the public domain and available at http://www.dshs.state.tx.us/mhprograms/timamdd1algo.pdf.*

**Table 110–3 Sleep Hygiene**

1. Try to go to bed and get up in the morning at approximately the same time each day.
2. Avoid caffeine and exercise late in the day.
3. Avoid alcohol at night. While alcohol may seem like it helps you fall asleep, it interferes with sleep architecture, making you less rested the following day.
4. Warm baths or showers prior to bed can be sleep-inducing.
5. Maintain a very dark, quiet room to sleep in. Light-blocking shades are very helpful in this regard. If you cannot make your room extremely dark or quiet, try using a sleep mask, a white noise machine, or earplugs. Animals in bed can be disruptive in some cases.
6. Beds should be used for sleep and sex *only*. Do not watch television, eat, or do other activities in bed. This will help to create an internal association between being in bed and sleeping.
7. If you go to bed and cannot fall asleep after 30 or 45 minutes, get out of bed and go to another room. Do something calming like reading for a period of time, and then try again.

Patients' personality styles can significantly affect their approach to taking medications. Some patients with narcissistic features may wish to have greater control over certain aspects of their treatment, including adjustments in dosing. It is often the case that some degree of flexibility on the part of the clinician, within clinically safe limits, can be very helpful in establishing a therapeutic alliance in such situations. Patients with obsessional or dependent features, in contrast, may go to great lengths to follow psychiatrists' instructions extremely precisely. Dependent patients, in their eagerness to please their psychiatrist, may minimize side effects or overemphasize benefits from medications, and it is important to find ways of allowing such patients to feel comfortable disclosing their disappointments regarding treatment effectiveness or tolerability. For patients with significant anxiety related to taking medications, it can sometimes be reassuring to start at extremely low doses of medication, and titrate the dose gradually, an approach which also serves to increase tolerability/reduce side effects.

It can be extremely helpful to engage patients' family members and significant others in treatment planning, which occurs too infrequently in the outpatient setting. Family members can be educated about the natural history of depressive illness, the importance of medication adherence, the triggers that seem to worsen an individual patient's symptoms, and nonpharmacologic approaches that are being employed as well. In addition, parallel history obtained from family members with a patient's consent can often elucidate previously unconsidered environmental or biological factors that may be contributing to the refractoriness of a patient's illness. With the preceding section of this chapter in mind, you may wish to read the Clinical Vignette: Follow-Up for an example of how TRD may be managed in a hypothetical case.

## Indications for Brain Stimulation Treatment

Most patients who initiate a trial of ECT have had at least two prior unsuccessful antidepressant medication trials (Eitan and Lerer 2006). ECT is the sixth step in the Texas treatment algorithm described previously. Factors which may lead to consideration of ECT earlier in the course of treatment of depression include the presence of psychotic features, catatonia, suicidality, and melancholia to the point of food refusal that leads to malnourishment (Eitan and Lerer 2006). The use of ECT and other forms of brain stimulation in the treatment of depression are described in greater detail elsewhere in this book.

## Limitations of Current and Likely Research

There are major obstacles to the development of techniques to increase remission rates in TRD. Despite decades of research, our understanding of the pathophysiology of depression remains rather incomplete. Significant progress in diagnostic techniques, novel medication development, and rational application of the therapeutic armamentarium are unlikely to occur until relevant pathophysiology is further elucidated. New developments in neuroscience will teach us a great deal about how to intervene in TRD. These include functional imaging, the discovery of genes causative of, or predisposing to, depression or related to the likelihood of medication responsivity, the creation of genetic knock-out animal models of relevant neurochemical systems, and the development of neurochemical ligands allowing the probing of the biochemistry of the depressed state.

Of these developments, one likely to find a role in clinical care of TRD is functional brain imaging including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A major limitation of this technology will be that imaging is complex, expensive, and sometimes involves radiation exposure. It may play a role in the evaluation and treatment of TRD as more is learned about prediction of treatment response by studying activation of discrete areas of the brain using imaging technology. Already, the confluence of studies suggesting increased activity in the subgenual area of the anterior cingulate cortex (Brodmann's area 25) has been used to direct the implantation of an electrode for brain stimulation in patients with extremely TRD (Mayberg et al. 2005). Early results with deep brain stimulation targeted to decrease anterior cingulate hyperactivity have been very promising, but not uniformly effective. The fact that some studies have shown decreased rather than increased metabolic activity in this area, while possibly due to differences in imaging techniques between studies, may additionally point to between-patient variability that may be of use in the future to optimize individual treatment outcomes by targeting brain stimulation based on knowledge of an individual's level of regional activation.

More likely to be widely applicable in the near future is pharmacogenetics, which is molecular genetic profiling to predict drug response. This may be available in only a few years to give a profile from which probability of response to therapeutic agents can be determined and treatment resistance can be categorized by genotype, which will be associated with strategies to relieve it. Even now, some companies are marketing clinical genotyping of polymorphic alleles in the cytochrome system, which are associated with variable expression of drug metabolizing enzymes. The idea behind this is to determine an individual's genotype to predict whether that individual is a slow, normal- or extensive metabolizer of a particular compound. This would allow selection of an optimal dosage, avoiding the toxicity associated with too high a dose for a slow metabolizer or the lack of efficacy with too low a dose for an extensive metabolizer.

Clinical Vignette: Follow-Up

Denise and her psychiatrist discuss the risks and benefits of various treatment options. As she has experienced some benefit from venlafaxine extended release at a dose of 225 mg without significant side effects, they decide to gradually increase the dose to 375 mg, well beyond the maximal FDA-approved dose for the extended release formulation, but equal to the maximal FDA-approved dose for the immediate release formulation. Her psychiatrist carefully documents the rationale for this approach, including her discussion with Denise about the risks and benefits. Denise's blood pressure does not increase with the dose increase. Over the ensuing eight weeks, she experiences a gradual improvement in her energy level to the point that she is able to go on her first job interview in over a year. She no longer feels the need to nap during the day. Despite these clear improvements, her mood is only mildly improved compared to how she felt when taking 225 mg of venlafaxine. She remains largely anhedonic, and relatively socially isolated.

With Denise's agreement, her psychiatrist arranges a family meeting with Denise and her parents. Denise's mother describes a history of several first-degree family members with a history of bipolar disorder about which the psychiatrist was not previously aware. They discuss ways in which Denise's parents can help her engage in activities that will be likely to improve her mood. Given the emerging family history of bipolar disorder and Denise's history of hyperthymic symptoms, Denise and her psychiatrist agree to augment the venlafaxine she is taking with lithium, which they begin at 300 mg and increase a few weeks later to 900 mg with a plasma lithium level of 0.8 meg/L. After eight weeks, Denise reports significant improvement in her mood. With encouragement from her parents, she has reached out to a few friends she had been avoiding, and has been surprised at how easy it felt to reconnect with them. Denise and her psychiatrist decide to stay on this medication regimen for twelve weeks to observe whether further improvements in her depressive symptoms will occur over time.

Such a paradigm presumes that advance knowledge of likely plasma levels from given dosages would be more effective than the gradual dose titration now generally employed. At present, this has not been demonstrated to be beneficial and some studies have shown that the genotype of metabolic enzyme pathway genes is not predictive either of outcome or of side effects, at least with citalopram (Peters et al. 2007).

Finally, the development of more effective treatments will depend on the results of controlled clinical trials to take advantage of the pre-clinical science generated from the new paradigms in neuroscience and molecular genetics. Unfortunately, there are major obstacles to doing such clinical trials. An ideal clinical trial for TRD requires a very large number of subjects, because the first step in treatment is effective for many of the entering subjects, dramatically reducing the relevant subject pool for the next step of the study. The second step, if it is to be controlled, requires the use of a placebo, which is unacceptable to many subjects and IRBs, because it means that an ineffective treatment must be continued to compare the effect of time and the placebo effect of a double-blind change in treatment to the putative new agent. There has been no mandate for this kind of study from regulatory authorities and the expense of conducting it has meant that few such studies have been performed.

One promising alternative is to conduct studies where treatments are compared without the use of a placebo, a so-called effectiveness study, as compared to an efficacy study, which uses placebo to establish that a treatment has benefit beyond nonspecific factors and is usually conducted in highly selected populations of depressed patients. The STAR*D clinical trial is an example of such an effectiveness study. Such studies have numerous advantages over standard clinical efficacy studies. Because placebo is not necessary, these can be conducted in usual clinical settings with much easier recruitment because they are acceptable to patients and to clinicians. When conducted in usual settings, they can include a wide range of patients who would normally be excluded from efficacy trials, but who are representative of the patients really seen in clinical practice, such as those with extensive psychiatric and medical comorbidity and subjects with concurrent drug or alcohol abuse or dependence. The ability to include large samples means that sample sizes relevant for pharmacogenetic studies can be collected and that subgroups of particular diagnostic subtypes can be examined.

## Acknowledgments

We wish to thank the many patients whose clinical treatment has helped to fill the gaps in knowledge always left by sole reliance on the results from clinical research studies.

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CHAPTER

# 111 Pharmacological Treatment of Substance Abuse Disorders

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Addiction to legal drugs like alcohol, or to illegal ones like cocaine, is the end result of changes in the brain caused by repeated use of a drug or combination of drugs. The so-called reward system in the brain is especially susceptible to drug use. This phylogenetically ancient system, built around meso-limbic and meso-cortical dopamine fibers, is an essential brain substrate of learning through reinforcement. The system is activated in the presence of normal physical or social reinforcers (food, sex, shelter, company), and this is accompanied by a subjective sense of well-being or pleasure. This orients an organism's behavior toward procurement of such reinforcers, and thus is essential to survival. What all drugs of abuse, including alcohol, have in common, and what distinguishes them from all other drugs, is their ability to powerfully activate this system, over and beyond usual stimuli like hunger for example. Under the influence of drugs, changes in the activity of the reward system lead to physiological and behavioral manifestations that are the hallmark of addiction, such as craving for more drug, drug-seeking behavior, or withdrawal symptoms in the absence of the drug. The drug becomes an important, if not the most important reinforcer, supplanting other normal healthy reinforcers so much so that an individual's behavior becomes oriented toward procuring and consuming the drug. As drug abuse becomes more entrenched, drug-induced changes in the brain become more pronounced, as susceptible nerve cells adjust to the frequent presence of a drug in the blood stream. These changes occur according to patterns predetermined in the genes regulating each nerve cell, and can involve alterations in nerve cell functioning, alterations in neurotransmitter levels and neurotransmitter receptors, changes in morphology, even nerve cell death in some instances.

Clinicians attempting to help individuals struggling with addiction have long sought medications to help them in this task. In 1884, in a pamphlet entitled *Über Coca*, Freud recommended cocaine for seven conditions, including the treatment of opiate and alcohol dependence, although he later relented on this recommendation. Nonetheless, his search for medications spoke for a whole medical community in need of pharmacological agents to counteract the effect of drug addictions. Cocaine turned out to be every bit as addictive and destructive as alcohol or opioids, although in one sense Freud was anticipating one of the principal mechanisms of medication treatment for addiction, namely substitution with an agonist medication. Fortunately, clinicians now have access to effective medications, especially for alcohol, nicotine, or opiate addiction, while medications for cannabis and for cocaine and other stimulants are under development. This chapter seeks to instruct clinicians on the use of available agents approved by the Food and Drug Administration (FDA) to treat drug dependence. It will also highlight significant findings in medication developments for marijuana and stimulants like cocaine. The next section gives an overview of general pharmacological mechanisms or strategies for treatment of substance use disorders. This is followed by sections detailing medication treatments for each of the major addictive substances, including alcohol, opioids, nicotine, stimulants, and cannabis.

## Pharmacological Mechanisms of Treatment for Substance Use Disorders

**Agonist Replacement.** Among the several basic pharmacological mechanisms of effective medication treatments for addiction, perhaps the most successful approach has been agonist

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replacement, in which an agonist or analog of the addictive drug is administered in a slowly absorbed and slowly eliminated form. Examples include nicotine patch treatment for nicotine dependence, and methadone or buprenorphine treatment for opioid dependence. Dronabinol (oral THC) is under investigation as a treatment for cannabis dependence. The reinforcing effects of drugs of abuse relate in part to rapid absorption and rapid onset of effect, experienced subjectively as the "rush," while the ups and downs in blood levels contribute to withdrawal symptoms and drug craving. A slowly absorbed and slowly eliminated agonist replaces the addictive drug, producing little or no euphoria or impairment, while also preventing withdrawal symptoms. This approach seems to be most applicable to drugs of abuse that mimic a neurotransmitter that itself is a direct agonist at a clearly defined receptor (e.g., the nicotinic receptor, and opioid receptors). Addictive drugs, such as alcohol, cocaine, or other stimulants, that may be characterized as indirect-acting agonists, seem to have been less amenable to the agonist replacement approach. For example, a range of dopamine agonist and stimulant-like medications have been tested for cocaine dependence with some hints of efficacy but no clear signals to date.

**Antagonist Treatment.** Treatment with an antagonist that blocks the pharmacological and reinforcing effects of a drug of abuse is another classic strategy. The prototype here is the opioid receptor antagonist naltrexone, which is a powerful blocker of opioid effects including euphoria and reinforcement, as well as analgesia. This is an efficacious treatment of opioid dependence as long as the patient takes the medication; when a patient on naltrexone tries to use opioids there are no effects, and drug using and drug-seeking behavior tend to cease. However, adherence to naltrexone has typically been poor, as patients tend to stop taking the medication and resume opioids. Adjunctive behavioral therapy and long-acting injectable formulations of naltrexone have shown promise in improving adherence and effectiveness of this approach. Interestingly, naltrexone also displays some indirect antagonism of alcohol effects, and is a modestly effective treatment for alcohol dependence. Blockade of essential neuropharmacological systems in the brain may produce unpleasant effects, and this also seems to have been a limitation of antagonist treatment approaches. Mecamylamine, a nicotinic antagonist, developed originally for treatment of hypertension, has shown some promise in clinical trials as a treatment for nicotine dependence, although it was associated with unpleasant side effects. Neuroleptic medications have been tried as treatments for cocaine dependence based on their blockade of dopamine receptors, but have not been well tolerated, and animal models suggest that, if anything, blockade of dopamine may increase drug-seeking behavior. Disulfiram represents an antagonist strategy of sorts in that it impairs liver metabolism of alcohol, which makes a patient violently ill if alcohol is consumed due to a buildup of acetaldehyde; like naltrexone for opioid dependence, disulfiram is effective for alcohol dependence if the patient remains adherent to the medication, and behavioral strategies have been useful in improving adherence.

**High Affinity Partial Agonists.** The high affinity partial agonist is a relatively new strategy for pharmacotherapy of substance use disorders, with the currently available examples being buprenorphine for opioid dependence and varenicline for nicotine dependence. These agents can be thought of as residing in the middle of a continuum between full agonists and antagonists, binding their respective receptors, but only partially activating them. Thus they suppress withdrawal and replace agonist effects, but in theory have less abuse potential and a better safety profile. Because of high receptor affinity, these agents are not easily pushed off the receptors by other agonists, resulting in blockade of effects of other agonists.

**Indirect Modulatory Strategies.** The neuropharmacological mechanisms of addictive disorders are complex. While it remains clear that meso-limbic and meso-cortical dopamine fibers are essential to the positive reinforcing effects of substances of abuse, animal and human laboratory models have begun to elucidate distinct circuits and neurotransmitter systems underlying withdrawal, cue-induced craving, stress-induced craving, drug-seeking behavior, and relapse after a period of abstinence. GABA (ϑ-aminobutyric acid) and excitatory amino acids (EAA) such as glutamate have been implicated in these phenomena, and a number of medications with effects on these systems have been tried, particularly for alcohol and cocaine dependence where classic agonist and antagonist strategies have not been available. Examples include acamprosate, FDA approved for alcohol dependence and thought to act through EAA mechanisms, and topiramate, an anticonvulsant with GABAergic properties that has shown promise for alcohol dependence in recent clinical trials. The modest effectiveness of naltrexone for alcohol dependence suggests that the opioid system modulates response to alcohol, exerting a relapse preventive effect. Antidepressant medications with a noradrenergic mechanism, including bupropion and nortriptyline, are effective for treatment of nicotine dependence, independent of a history of depressive disorder, perhaps by attenuating dysphoric symptoms that emerge during nicotine withdrawal (Hall et al. 2004). Medications that may dampen the stress response represent another investigative strategy.

**Treatment of Co-Occurring Psychiatric Disorders.** An increased prevalence of other psychiatric disorders among individuals with substance use disorders has been a consistent finding from studies of both clinical samples and community-based surveys of the general population (Hasin et al. 2006). Disorders for which this relationship is best documented, listed in decreasing order of strength of association, include antisocial personality, schizophrenia, bipolar disorder, anxiety disorders, and depressive disorders. There are several possible reasons for such associations, including that substance use may cause psychiatric symptoms, such as mood or anxiety symptoms, as a toxic effect. The possibility that patients may be drawn to substances of abuse as "self-medication" for psychiatric disorders, or that psychiatric disorders may otherwise worsen the prognosis of substance use disorders, has led to the hypothesis that effective treatment of the psychiatric disorder may improve substance use outcome. Depression is the most prevalent disorder observed among substance-dependent patients, and its treatment has received the most study. A series of clinical trials, summarized in two meta-analyses (Nunes and Levin 2004, Torrens et al. 2005), suggest that antidepressant medication is effective in treating depression among alcohol-dependent patients, and that such treatment is associated with improvements in self-reported

drinking behavior. Similar findings exist in some studies among drug-dependent patients, although the data here are less consistent. Findings were strongest for studies that diagnosed depression during periods of enforced abstinence, or otherwise took pains in the history to distinguish independent depressive disorders from depressive symptoms that are toxic effects of substances. Thus, a good general principle for treatment of substance-dependent patients is to gather a thorough history to determine the presence of other psychiatric disorders, and to determine whether these disorders are being appropriately treated.

## Alcohol

The presentation of a patient with alcohol-related problems can vary widely, from the visibly intoxicated adolescent who occasionally drinks excessively to the clear-eyed professional who is dependent on a blood alcohol level of 250–300 mg/dL to maintain composure. For this reason, a good set of questions to quickly assess a history of drinking is helpful. A particularly sensitive and specific set of questions is the CAGE questionnaire (Ewing 1984) (Table 111-1):

**Table 111–1 History of Alcohol Consumption, CAGE Questionnaire**

- Have you ever felt you ought to **Cut down** on your drinking?
- Have people **Annoyed** you by criticizing your drinking?
- Have you ever felt bad or **Guilty** about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**Eye-opener**)?

Other Pertinent Questions:

- When was your last drink?
- How much did you drink then?
- How many days in the past week have you had a drink?
- How many drinks each day?
- Do you have any medical illness?

Simply asking about the number of standard drinks consumed per day can also be a useful screen. A standard drink contains roughly an ounce of alcohol, and would include one 12–16 ounce beer, one glass of wine, one mixed drink, or one shot of hard liquor. Evidence suggests that 5 or more standard drinks per day for a man, and 4 or more for a woman, represents heavy or problem drinking and signals the likely presence of DSM-IV-TR alcohol abuse or dependence (Saha et al. 2007, Li et al. 2007, in press).

By knowing the history and current drinking pattern, whether there is medical comorbidity, as well as by observing the patient for agitation, jitteriness, or sweating, the clinician can reasonably determine if the patient is at risk of withdrawal, or worse, of developing *delirium tremens* (DTs). Insomnia, agitation, tremor, tachycardia may begin within a few hours and last 24–48 hours. If withdrawal is allowed to continue, increasing autonomic instability, disorientation, visual or auditory hallucinations, and seizures can occur after 12–48 hours after drinking ends. DTs, the most severe of alcohol withdrawal states, presents most frequently in the first week after cessation of drinking, and encompasses symptoms of altered consciousness, perceptual disturbances, disorientation, autonomic instability, sweating, and confusion (Pelic and Myrick 2003). It is lethal in approximately 10% of cases (Devenyi and Saunders 1986). For this reason, clinicians have sought to predict who is at highest risk for DTs. A previous history of DTs and tachycardia appear to be sensitive indicators: Lee et al. (2005) found that if neither are present, DTs would occur in 20% of cases; if one indicator was present, DTs occurred in 46% of cases; and if both were present, 100% of cases developed DTs. Other risk factors also reported in the literature include older age, hyponatremia, hypokalemia, blood alcohol > 300 mg/dL on presentation, and abnormal liver enzymes (Wetterling et al. 1994).

### Detoxification

The goal of detoxification is to safely allow metabolism of serum alcohol while protecting the patient against the consequences of central nervous system (CNS) excitability, now unchecked by the inhibitory effect of alcohol. A second goal is to emphasize that detoxification is only the beginning phase of treatment, and that longer term treatment for alcohol dependence will be necessary (see below).

#### Mild Withdrawal Syndrome

During the detoxification, the presence and severity of withdrawal signs and symptoms need to be assessed. A quantitative and reliable method to do this is with the revised Clinical Institute Assessment for Alcohol (CIWA-Ar). This practical scale evaluates sweating, nausea and vomiting, tremor, agitation, tactile, visual, or auditory disturbances, headache, and orientation, all of which are assessed on a scale of 0–7, except orientation (0–4). This scale has been extensively validated in clinical settings (Sullivan et al. 1989), with a score of 10 being a good cut-off to separate those who will and will not require medications. Hence, patients who score less than 10 and do not have a history of withdrawal seizures or DTs, and do not have medical illnesses, usually can detoxify safely with supportive treatment not necessarily aided by pharmacological intervention (Nuss et al. 2004).

If the patient can stop drinking, then a CIWA-Ar score of less than 10, sufficient psychosocial support (family, friend, housing, adequate nutrition), and daily contact with the patient by a clinician most often indicate that outpatient detoxification can be attempted. In outpatient situations, the clinician may opt to provide the patient with a benzodiazepine at low to moderate dosage to alleviate withdrawal anxiety and insomnia. Benzodiazepines that are slowly absorbed and more slowly eliminated are preferred as they may have less abuse potential (e.g., lorazepam 1 mg three to four times per day; clonazepam, 1 mg three times per day; chlordiazepoxide 25 mg twice per day). If nutrition has been wanting, 100 mg of thiamine (Vit B1) daily will protect the patient from developing Wernicke's encephalopathy, characterized by the acute onset of ataxia, nystagmus, and ophthalmoplegia, or from developing a sixth cranial nerve palsy. When in doubt, an intramuscular dose of thiamine followed by regularly multivitamins is prudent, given the potentially serious sequelae of Wernicke's encephalopathy.

When abstinence is not attained, it may be necessary to hospitalize the patient to avoid repeated cycles of drinking and abstinence that may worsen the intensity and dangerousness of alcohol withdrawal reactions (Ballenger and Post 1978).

## Moderate to Severe Alcohol Withdrawal Syndrome

When the CIWA-Ar score is above 10 (moderate), or greater than 20 (severe), then medications are required to protect patients from withdrawal symptoms. Blood alcohol levels tend to be elevated in withdrawal-prone patients, although cannot always be relied upon as a predictor of withdrawal. Benzodiazepines (Ntais et al. 2005), anticonvulsants (Polycarpou et al. 2005), and adrenergic agonists to reduce sympathetic activation (Hawley et al. 1985) form the essential armamentarium available to the clinician.

With the CIWA-Ar, monitoring of vital signs, electrolytes, and nutritional status, the effect of administered medications can be readily assessed. Benzodiazepines remain first-rank medications to treat alcohol withdrawal, since they both effectively treat withdrawal symptoms, and protect against the advent of withdrawal seizures. Several protocols exist; these either involve fixed-dose or symptom-induced dosing (Saitz et al. 1994). The choice of benzodiazepine can be guided by the serum liver enzyme levels (ALT, AST). When normal, diazepam can be used, whereas when liver function tests (LFTs) are elevated, oxazepam or lorazepam are preferred as they are not metabolized by the liver. Table 111–2 illustrates fixed-dose and symptom-induced dosing for at-risk patients (Romach and Sellers 1991, Mayo-Smith 1997, Daeppen et al. 2002).

Two randomized trials comparing symptom-triggered dosing versus fixed dose (Saitz et al. 1994, Daeppen et al. 2002) concluded that administering benzodiazepines when symptomatic shortened the duration of treatment, and decreased the amount of medication used, without compromising on the safety and comfort of patients.

**Table 111–2 Approaches to Moderate or Severe Alcohol Withdrawal Syndrome**

CIWA-Ar ≥ 10 (moderate) or ≥ 20 (severe) Fixed Dose Method

| Normal Liver Enzyme Levels Diazepam | Elevated Liver Enzyme Levels Oxazepam |
|---|---|
| 1. 20 mg po q 1 hr for three consecutive doses. | 1. 30 mg po q 6 hr for 4 consecutive doses, then 15 mg for 8 doses. |
| 2. CIWA-Ar assessment after third dose. | 2. CIWA-Ar assessment 30 min after each dose. |
| 3. If CIWA-Ar < 10, then monitor VS, CIWA q 2 hr. | 3. If CIWA-Ar between 10 and 15, give 15 mg oxazepam po prn; if CIWA-Ar > 15, give 30 mg oxazepam po prn. |
| 4. If CIWA-Ar 3 10, diazepam 20 mg po, repeat CIWA-Ar q 1 hr. | |
| 5. Administer diazepam 20 mg po q 1 hr until CIWA-Ar < 10. | |
| 6. Continue diazepam 20 mg q 6 hr for 48 hr; CIWA-Ar, VS, q 6 hr. | |

Symptom-Triggered Dosing

Depending on liver enzyme status, diazepam 10 mg doses can be substituted for oxazepam 15 mg doses.

1. Vital signs, CIWA-Ar assessment every 6 hr.
2. If CIWA-Ar score between 10 and 15, give oxazepam 15 mg po. If CIWA-Ar score > 15, give oxazepam 30 mg.
3. Monitor CIWA-Ar every 30 min, continue to give oxazepam until CIWA-Ar < 10.
4. Patients are monitored for 72 hr.

## Anticonvulsants and Other Adjunct Medications

Despite ongoing research for better medications to treat alcohol withdrawal, benzodiazepines continue to hold gold-standard status. Nonetheless, among the anticonvulsants, phenytoin, carbamazepine, and those with action on the γ-aminobutyric acid (GABA) system (tiagabine, baclofen, pregabalin), appear beneficial; especially if the patient has a history of withdrawal seizures (Romach and Sellers 1991, Polycarpou et al. 2005, Mariani et al. 2006).

Phenytoin loading has long been used if the patient has a substantial risk of withdrawal seizures because of its ease of administration (iv and po) and tolerability. Practices vary, but a loading dose of 10 mg/kg is generally used, given completely or partially by the intravenous route, followed by 300 mg po every day for 5 days. If no other cause of seizures is found besides alcohol, phenytoin can then be discontinued (Devenyi and Saunders 1986).

Carbamazepine has become increasingly popular, especially for alcohol-dependent patients who have attempted detoxification repeatedly, and have developed neurological and psychiatric morbidity. It is thought that repeated cycles of drinking, withdrawal, and abstinence induce *kindling* in vulnerable areas of the brain. Kindling refers to a cellular process whereby neurons become sensitized by increasing their response to certain stimuli; leading to epileptogenic activity in instances such as alcohol withdrawal (Ballenger and Post 1978). At an approximate dose of 800 mg a day in divided doses, carbamazepine was found to be equally effective as oxazepam in reducing withdrawal symptoms. Moreover, patients expressed less psychological distress on the SCL-90 when treated with carbamazepine as opposed to patients assigned to oxazepam (Malcolm et al. 1989). Carbamazepine holds therapeutic potential for longer term treatment of alcohol dependence: compared to placebo, patients randomly assigned to carbamazepine drank for fewer days, and drank fewer drinks on the days when they did drink (Mueller et al. 1997).

GABAergic anticonvulsants like baclofen, tiagabine, and pregabalin appear promising for the treatment of alcohol withdrawal. In mice, pregabalin reduced seizure activity caused by abrupt ethanol withdrawal (Becker et al. 2006). In a retrospective chart study, tiagabine is reported to have equal effectiveness against withdrawal symptoms than either lorazepam or oxazepam, and appeared to have a relapse-preventing effect after detoxification (Myrick et al. 2005). Long used as a muscle relaxant, baclofen is reported by an Italian group (Addolorato et al. 2006) to be as effective as diazepam, and recommend that it be considered as a new drug for uncomplicated withdrawal. However, the potential of these medications needs to be further evaluated in larger randomized trials.

Considerable benefit to the patient can be gained by decreasing the sympathetic activation that occurs during withdrawal. By using clonidine, a centrally active alpha-2 receptor agonist, clinicians can reduce heart rate, blood pressure and respiratory rate, as well as the anxiety, restlessness, insomnia and diaphoresis commonly encountered, to the greater comfort of the patient. An analog of clonidine,

lofexidine, with a lesser propensity to cause orthostatic hypotension, has also been used with benefit (Cushman and Sowers 1989). An important caveat is that these medications are probably not effective at preventing withdrawal seizures. Thus, although adrenergic medications are not central to the treatment of alcohol withdrawal, they can add considerable ease for the patient to the experience of detoxification.

Complications such as delirium or hallucinosis can occur during detoxification. DTs is a medication emergency requiring hospitalization and close monitoring of both physiological and mental status. Treatment with a benzodiazepine should be continued, but may not impact the delirium per se. In the absence of medical or psychiatric comorbidity, 0.5–5.0 mg of haloperidol daily, administered po, iv, or im, can be used to control the agitation, disorientation, and perceptual disturbances (Sellers and Kalant 1982). Alcoholic hallucinosis in the presence of an otherwise clear sensorium (auditory hallucinations) can be distinguished from alcohol withdrawal delirium, which involves disorientation and often vivid visual hallucinations. Its treatment implications are less clear, although it is thought to represent chronic toxicity of alcohol to the nervous system, and as such should trigger greater concern and vigilance for emergence of serious withdrawal symptoms.

### Benzodiazepine Withdrawal

A mention should be made of benzodiazepine withdrawal, a condition frequently encountered by psychiatrists. While the presentation of benzodiazepine withdrawal may resemble alcohol withdrawal (anxiety, hyperreflexia, insomnia, restlessness, anorexia, emesis, leading to tonic–clonic seizures and life-threatening delirium), there is often more psychomotor and autonomic dysregulation. The onset may occur from 2 to 14 days following discontinuation. For this reason, the duration of treatment should be extended to at least 2 weeks, as manifestations such as delirium can occur into the second or even third week.

Long-acting benzodiazepines such as diazepam or chlordiazepoxide constitute the mainstay of treatment. Diazepam is more lipophilic than chlordiazepoxide and thus has a more rapid onset of action. This is deemed a favorable feature given the serious risks associated with benzodiazepine withdrawal. The clinician can be helped in this task by familiarity with a given benzodiazepine equivalent potency compared to lorazepam (Devenyi and Saunders 1986) (see Table 111–3).

**Table 111–3 Equivalent Dose for Benzodiazepines**

| Benzodiazepine | Common Trade Name | Overall Elimination Rate | Equivalent Dose (mg) |
|---|---|---|---|
| Alprazolam | Xanax | Intermediate | 0.25 |
| Chlorazepate | Tranxene | Slow | 3 |
| Chlordiazepoxide | Librium | Slow | 10 |
| Diazepam | Valium | Slow | 5 |
| Flurazepam | Dalmane | Slow | 15 |
| Clonazepam | Klonopin | Intermediate | 0.5 |
| Lorazepam | Ativan | Intermediate | 1 |
| Oxazepam | Serax | Rapid | 15 |
| Temazepam | Restoril | Intermediate | 10 |
| Triazolam | Halcion | Rapid | 0.25 |

A common practice is to convert the estimated daily dose of benzodiazepine into diazepam equivalents, and reduce the dose by approximately 10 mg every 2–3 days, or as the patient tolerates. As the dose reaches approximately 20 mg of diazepam, the dose should be tapered by 5 mg every few days. Carbamazepine has also been shown to be effective in benzodiazepine withdrawal (Reis et al. 1989, Schweizer et al. 1991), and there is some evidence from animal studies that levetiracetam may be particularly well suited to treat benzodiazepine withdrawal (Lamberty et al. 2002).

Withdrawal from benzodiazepines or other sedative hypnotics can also, like alcohol withdrawal, develop into delirium in its most severe forms. Again, this is a medical emergency indicating hospitalization for close physiological and mental status monitoring.

## Treating Alcohol Dependence

While some individuals remit from alcohol dependence without specific treatment and do not relapse, alcohol dependence is often a chronic-relapsing illness, calling for long-term treatment. Part of the difficulty in treating individuals struggling with alcoholism is that the diagnosis of alcohol dependence paints with same color individuals who are in fact very different types of "alcoholics." Age alone, for example, is a significant discriminator. Alcoholics who started to drink before age 20 have more severe alcohol-related problems, have a family history of alcoholism, more cravings, more overt aggression and a poorer social functioning than those whose drinking started after age 20 (Johnson et al. 2000a). The importance of this distinction between early onset and late onset alcohol dependence extends also to treatment response, as alcoholics with onset before age 20 had worse drinking outcomes when treated with fluoxetine (then evaluated as a treatment for alcohol dependence) than later onset alcoholics (Kranzler et al. 1996, Pettinati et al. 2000). Nonetheless, medications can assist patients seeking treatment for excessive drinking. More specifically, available medications target drinking by different mechanisms, allowing the clinician to match treatment and patient. For example, disulfiram creates a sense of psychological threat that deters from active drinking, acamprosate appears to maintain established abstinence by reducing cravings to drink, and naltrexone reduces the reinforcing effect of alcohol. Hence, clinicians can reasonably make a best-fit recommendation for treatment.

### Disulfiram

Disulfiram blocks the enzyme acetaldehyde dehydrogenase, a key enzyme that transforms acetaldehyde derived from alcohol into acetate. When alcohol is consumed—even in small quantity—the inhibition of the enzyme causes the accumulation of acetaldehyde, which leads to an increasingly unpleasant sensation as the blood concentration of acetaldehyde increases. This reaction, known as the disulfiram–alcohol reaction, involves a general sensation of malaise, nausea, perhaps vomiting, restlessness, tachycardia, hypotension, sweating, and dyspnea. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death. It usually begins 20–30 minutes after drinking, and will continue as long as alcohol is being metabolized. The strength of the reaction

varies according to the amount of alcohol ingested. Severe reactions are generally restricted to patients with underlying medical vulnerabilities, and thus patients with cardiovascular or renal or other serious systemic illnesses should not be treated with disulfiram in most cases. Detailed informed consent regarding the risks of disulfiram is important at the outset of treatment. In the case of a severe disulfiram reaction, supportive measures to restore blood pressure and treat shock should be instituted in hospital. Medical management of severe reactions involves oxygen, carbogen (95% oxygen and 5% carbon dioxide), vitamin C intravenously in massive doses (1 g) and ephedrine sulfate. Antihistamines have also been used intravenously. Potassium levels should be monitored, particularly in patients on digitalis, since hypokalemia has been reported.

Disulfiram renders the enzyme inactive within 12 hours of ingestion by irreversibly binding to it. In clinical terms, no tolerance to disulfiram develops with ongoing use: the longer a patient takes disulfiram, the greater the proportion of enzymes blocked, and the more sensitive to alcohol the patient becomes. Hence, even discontinuing disulfiram for 1–2 days will not change the strength of the reaction; normal alcohol metabolism returns approximately 2 weeks after stopping disulfiram (Devenyi and Saunders 1986), although this may vary. Similarly, there are some patients who appear less sensitive to the disulfiram reaction; this may simply represent poor medication adherence, although higher disulfiram doses may be required for some patients.

Patient selection and the environment in which the medication is given are most important. Patients with a strong motivation to stop drinking, but who feel they lack the self-determination to carry it through can benefit the most from disulfiram, especially if it can be given in a supervised setting (Sereny et al. 1986). Supervised daily intake can be made an integral part of a network therapy as it testifies concretely to motivation to be in treatment (Galanter 1993, Jung and Namkoong 2006). It is especially important for a successful outcome to involve a significant other in monitoring daily intake of disulfiram. This can be a family member, close friend, or it could be a clinician or clinic where the patient attends regularly. Disulfiram is a powerful treatment if the patient takes the medication. Conversely, the most common reason for treatment failure is nonadherence. Patient, physician, and the designated medication monitor need to agree to a plan. The designated monitor should witness and confirm that the patient has taken the medication each day, verbally reinforce and encourage adherence, and report to the treating clinician if the medication is not taken. Nonadherence should trigger a clinic or office visit to review the plan and seek to bolster the patient's motivation.

Disulfiram, at a dose of 250–500 mg per day, should be administered at bedtime. While disulfiram is usually well tolerated, one must monitor liver enzymes as cases of hepatotoxicity have been reported (Berlin 1989). Contraindications to its use include digitalis intake for heart disease, liver disease, neuropathy, and chronic hypotension. Patients can be given a card provided by the manufacturer to alert emergency personnel of its use. This card also carries a description of the reaction in case they are called during its occurrence (Available from Odyssey Pharmaceuticals upon request).

In randomized trials (Fuller and Williford 1980, Gerrein et al. 1973, Sereny et al. 1986) disulfiram was effective in producing more abstinent days for periods of up to a year. It is a medication that can also be integrated into various psychosocial treatments with ease, especially with the designation of a medication monitor as noted above (Gallant 1991). Disulfiram may be especially useful for the patient with alcohol abuse in combination with cocaine or other drug dependence, a frequent occurrence. To the extent that alcohol functions as a disinhibitor, or as a conditioned cue triggering other drug use, elimination of alcohol from the picture with disulfiram may improve other drug problems as well. Interestingly, Carroll et al. (2004) have reported that disulfiram is effective for treatment of cocaine dependence, independent of whether the patient is drinking alcohol. The authors hypothesize that disulfiram may produce this effect through its inhibition of the enzyme dopamine-β-hydroxylase, the first enzyme in the biosynthetic chain of dopamine, for which cocaine is a blocker of the synaptic reuptake system.

## Naltrexone

When alcohol is ingested, the rewarding, calming, and euphoric effect that is experienced in some individuals appears linked to the activation of the opiate system. This is supported by reports that alcohol increases plasma levels of β-endorphins, especially in individuals with a strong family history of alcoholism (Gianoulakis et al. 1996). Congruent with this observation, naltrexone, an opiate receptor blocker, has been shown to decrease drinking (Volpicelli et al. 1994, Stromberg et al. 2001, Gonzales and Weiss 1998, O'Malley et al. 1992) and the number of relapses during a course of treatment (Garbutt et al. 1999). Three meta-analyses have corroborated the efficacy of naltrexone to treat alcohol dependence (Kranzler and Van Kirk 2001, Streeton and Whelan 2001, Srisurapanont and Jarusuraisin 2002).

Naltrexone also appears to reduce cravings for alcohol (Williams 2005), and its abstinence-promoting effect has been positively correlated to the degree of craving, as assessed with the Obsessive Compulsive Drinking Scale (Anton et al. 1995). Whether severity of craving identifies a trait that segregates among alcoholics is a tantalizing prospect, on which genotyping studies may bring further clarity. An increased risk of alcohol dependence has been associated with a variant of the μ-opiate receptor named A118G (Bart et al. 2005). The presence of this variant in individuals has been correlated with greater stimulation from alcohol in laboratory investigations of nonalcohol-dependent volunteers (Ray and Hutchison 2004). Moreover, patients with this variant displayed a better treatment response to naltrexone than those without this variant (Oslin et al. 2006). If replicated, this could be a useful clinical marker to assist clinicians in selecting treatment. This also points to the future promise of pharmacogenetics to better match patients with pharmacological treatments from which they are most likely to benefit.

The usual dose of oral naltrexone is 50 mg per day. Doses as high as 150 mg per day may be indicated, although higher doses have been associated with reversible liver toxicity. Prior to administration, liver enzyme status should be verified with a blood test, and patients should be informed to watch for signs of possible liver toxicity (Physician's Desk Reference 2006). In addition, clinicians should ascertain that the patient is not using opiate medications or drugs, as administration of naltrexone would precipitate withdrawal. Common side effects encountered with naltrexone

include nausea, gastric upset, and diarrhea. As with any oral medication, compliance is key to successful treatment, and it is worth inquiring candidly from patients concerning their routine about medication intake. Lack of a specified routine likely points to irregular medication intake (Orwig et al. 2006, Rosen et al. 2007). As with disulfiram, involvement of a significant other to monitor medication adherence can be useful. Naltrexone can also be dosed on a three times per week schedule (e.g., 100 mg on Monday, 100 mg on Wednesday, 150 mg on Friday), which may make monitoring more convenient, for example in conjunction with three times per week clinic attendance. Shortcomings with oral naltrexone adherence have stimulated interest in long-acting formulations, one of which has just become available.

Long-acting naltrexone (380 mg per injection unit) is a microsphere formulation for intramuscular gluteal injection that can be administered monthly by a health care professional, as part of a comprehensive care program involving regular contact with a clinician (Vivitrol 2007). In addition to the safeguards mentioned for oral naltrexone, one must also monitor injection site, as local reactions such as hyperemia and induration can occur, especially if the medication is injected repeatedly at the same site. Clinical trials have shown it to be well tolerated and effective at reducing drinking days, extending time to a first drinking day, and better abstinence rate (Dunbar et al. 2006, Garbutt et al. 2005, Kranzler et al. 2004). In the pivotal clinical trial (Dunbar et al. 2006) naltrexone was most effective in patients who had achieved at least brief abstinence prior to beginning medication. This could indicate that the medication is most useful in the more highly motivated patients, or it could indicate that the mechanism of action depends in some physiological sense on a period of abstinence. Injectable naltrexone should be particularly considered for patients with a history of relapse, or with uneven adherence to prior treatments, and could for example be administered to patients immediately after completion of a detoxification (inpatient or outpatient) in an effort to reduce relapse in the postdetoxification period.

Two clinical notes of interest concerning naltrexone. A report by Hernandez-Avila et al. (2006) looked at the effectiveness of targeted naltrexone use versus daily use. During counseling, high-risk situations were identified, and the patients were then instructed to take naltrexone prior to these high-risk situations. This approach produced a greater reduction in daily drinking than did daily naltrexone or targeted placebo use. These results suggest that clinicians can discuss with patients ways to take oral naltrexone that may be most suited for their drinking pattern. Another report by Pettinati et al. (2006) reviewed 29 published trials of opioid antagonists, most with naltrexone, and found that it may have greatest effectiveness in reducing heavy or excessive drinking, as opposed to inducing complete abstinence. This concurs nicely with the observation that naltrexone may be of most benefit for those who derived a greater sense of reward from drinking alcohol excessively.

## Acamprosate

Acamprosate is an analog of the amino acid taurine, and was approved for the treatment of alcohol dependence in December 2004 (Boothby and Doering 2005). With chronic or excessive alcohol consumption, the brain glutamatergic system becomes sensitized and disinhibited; once a patient is abstinent from alcohol, an hyperactive glutamatergic system may elicit agitated cravings for alcohol (abstinence craving) that may lead to relapse (Mariani and Levin 2004). Acamprosate appears to confer a relapse prevention effect by antagonizing the glutamate system, which in turn is thought to reduce cravings to drink (Jung and Namkoong 2006). Worldwide clinical experience with acamprosate is considerable, with over 1.5 million alcohol-dependent patients treated, at the time of approval in the United States (Berglund et al. 2003, Mason 2003, Mann et al. 2004).

Two meta-analyses have found that acamprosate improved drinking outcome, with a relatively small effect size overall, and both concurred that the strongest effect was on prolonging abstinence (Kranzler and Van Kirk 2001, Mann et al. 2004). It does not seem to be as effective if patients are actively drinking at the time of treatment. This is reminiscent of findings from naltrexone trials, where there is some evidence that the medication effect is larger for patients who achieve abstinence prior to beginning medication.

Acamprosate is well tolerated, and can be started at the treatment dose of 660 mg three times a day, although doses up to approximately 3 g per day have been used (Anton et al. 2006), preferably once the patient has undergone detoxification and has stopped drinking. Diarrhea, headache, and abdominal pain are the most frequently experienced side effects.

Because of their different mode of action, and different impact on drinking behavior, treatment combining naltrexone and acamprosate has had conceptual appeal. In one randomized, double-blind, placebo-controlled trial including 160 patients, naltrexone outperformed acamprosate in terms of abstinence maintenance. When combined, the medications were better than placebo or acamprosate monotherapy, but not naltrexone monotherapy (Kiefer et al. 2003). In a recent published trial, naltrexone also was found superior to acamprosate in terms of abstinence maintenance (Morley et al. 2006). Although acamprosate has not fared well in these trials compared to naltrexone, these results should be interpreted with caution because of the great differences encountered among alcohol-dependent individuals seeking treatment. However, the COMBINE study, described in more detail below, found no evidence for an added benefit of combining acamprosate with naltrexone. COMBINE also found no evidence for benefit of acamprosate alone.

## Combined Pharmacotherapies and Behavioral Intervention for Alcohol Dependence: The COMBINE Study

Given the public health importance of treating alcohol dependence, there is great interest in making treatment accessible to as many individuals with alcohol dependence as possible. One concern about the institutions where treatments for alcohol dependence were first developed and tested is that these tended to be tertiary care, specialty settings. There, specially trained clinicians administered the treatments being evaluated, raising the question of whether this extensive training of the clinicians was a pivotal factor for treatment effectiveness. The COMBINE study was devised to test whether these treatments can be effectively delivered using models adaptable to primary care, nonspecialty settings (Anton et al. 2006).

The COMBINE study examined the treatment effects and interactions of naltrexone (oral), acamprosate, and two behavioral interventions: medical management (aimed at reproducing primary care settings) and combined behavioral therapy (a more intensive individual therapy designed specifically for alcohol dependence). Each behavioral therapy was matched to four possible medication therapies: placebo, acamprosate, naltrexone, or naltrexone–acamprosate combination. In addition, a no-pill option was paired with the combined behavioral therapy, for a total of nine possible medication–behavioral therapy combinations. Carried out at 11 academic centers in the United States between 2001 and 2004, the COMBINE study examined the effect of these therapies on 1,383 recently abstinent alcohol-dependent patients. All treatment groups improved substantially after treatment entry, suggesting a large favorable effect attributable to entering treatment itself, be it motivation, or nonspecific therapeutic effects of the clinic milieu. Beyond this large early nonspecific benefit, a small further advantage was found for naltrexone, compared to placebo. There was no evidence of efficacy for acamprosate. The results of this study demonstrate the feasibility of treatment for alcohol dependence with medications in conditions approximating primary care settings, and a modest effect of naltrexone. More work is clearly needed to understand clinical predictors of benefit from naltrexone or acamprosate, in terms of patient characteristics or the accompanying treatment conditions.

An interesting aspect of the COMBINE study highlighted the impact that an intervention by a trusted clinician can have. Administration of a placebo pill with medical management led to better outcomes than the more intensive combined behavioral therapy intervention. Clinical attention to the problem of alcoholism can have a significant impact. It also speaks of the power of the placebo effect, which should always be considered by physicians prescribing medications for psychiatric disorders. Overall, naltrexone as well as acamprosate and disulfiram are effective tools that can bring treatment of alcohol dependence in the mainstream of primary care medicine.

### Treatment of Co-Occurring Psychiatric Disorders and Alcohol Dependence

Major depression is common among alcohol-dependent patients and is associated with worse clinical outcome (Nunes and Raby 2005). Although there have also been negative studies, two meta-analyses (Nunes and Levin 2004, Torrens et al. 2005) support the conclusion that treatment of major depression in alcohol-dependent patients is an effective strategy associated with improvement in depression and modest improvement in self-reported drinking. A favorable medication effect was more likely in studies that required patients to be abstinent before depression was diagnosed and treatment initiated. This suggests that a careful history is needed to separate independent mood disorders from transient depressive symptoms that may result from chronic alcohol use, and that ideally the diagnosis should be made during at least a brief period of abstinence to minimize confusion of alcohol effects with independent depression. Behavioral therapy may be effective for treatment of depression for some alcohol-dependent patients who show interest in therapy.

In terms of choice of antidepressant medication for an alcohol-dependent patient, the findings are complex. Serotonin reuptake inhibitors (SRIs) probably have a greater margin of safety among alcoholics because they are less sedating and arguably less prone to adverse interactions with alcohol. However, most of the positive evidence for efficacy comes from trials of tricyclic antidepressants. Most of the trials of SRIs were negative, although two such trials that diagnosed depression while patients were abstinent on an inpatient unit were positive (Nunes and Levin 2004). Furthermore, several trials of SRIs in alcohol-dependent patients not selected for depression have now shown that SRIs may actually worsen drinking outcome for drinkers with early age of onset, many of whom have depressive symptoms (Kranzler et al. 1996, Pettinati et al. 2000). A prudent approach would be to begin with an SRI, exercising particular caution in early onset alcoholics, and if the response is not adequate to switch to an antidepressant with a noradrenergic mechanism.

Anxiety and anxiety disorders are also common among alcohol-dependent patients. One clinical trial supports the efficacy of buspirone for alcoholics with elevated scores on a scale of general anxiety after completion of detoxification (Kranzler et al. 1994). Buspirone is a well-tolerated, nonsedating medication and should be considered among alcohol-dependent patients whose anxiety can be shown to persist in abstinence. The SRI antidepressant sertraline has been studied among alcohol-dependent patients with posttraumatic stress disorder (PTSD). In a finding reminiscent of the SRI trials with early versus late onset alcoholics, sertraline was found to be more effective than placebo in reducing drinking among patients with early onset PTSD and mild alcohol dependence, but less effective than placebo for the patients with early onset alcohol dependence and late onset PTSD, (Brady et al. 2005).

### Future Research

Other promising developments include a report on topiramate, an anticonvulsant with a broad spectrum of action, including effects on GABAergic and glutamatergic systems. With medical management, topiramate reduced self-reported drinking, and cravings for alcohol in a double-blind, randomized, placebo-controlled clinical trial (Johnson et al. 2003). A large-scale clinical trial seeking to replicate this effect is now completed and under analysis.

The advent of a long-acting injectable naltrexone also promises to extend abstinence from alcohol, especially when compliance with taking oral naltrexone daily is a major difficulty. Coupled to the enhanced response to naltrexone that appears associated with the A118G allele of the μ-opiate receptor gene, it may become possible to identify those individuals most likely to benefit from this form of treatment and reduce the burden of alcoholism.

## Opiates

"Opiate addiction is a curse wrapped-up in a gift." This statement from a patient accurately describes how opiates can ensnare people into a painful state of physical and psychological dependency. As clinicians well know, the benefit of effective pain control can become dulled by the development of tolerance unless opiates are carefully used. Even then, patients who have used opiates for pain control can

develop such a state of physical dependence that withdrawal symptoms ensue if opiate intake is not continued. Hence, for addicted as well as tolerant patients, the problem posed by opiates is often how to overcome withdrawal. Fortunately, even though opiate withdrawal can be painful and stormy, it is not life threatening as alcohol or sedative withdrawal can be. Opioid withdrawal may begin anywhere from 4 to 24 hours after the last dose of opiate drug or medication, depending on the half-life. Typically, it will begin with yawning, rhinorrhea, tearing, tachycardia, back and limb pain, abdominal cramps, leading to restlessness, irritability, muscle cramps, and shaking chills. As withdrawal appears to closely follow the clearance rate of opiates from receptors, first symptoms emerge sooner with a short-acting opiate like heroin, and later with methadone. In any case, treatment must begin with detoxification to ease the transition to a nondependent state, followed by ongoing maintenance treatment.

## Detoxification

Detoxification is only the beginning of treatment for opioid-dependent patients, as the need or desire for opiates can persist long after the detoxification is complete. It follows that long-term treatment is usually necessary to assist with abstinence from illegally procured opiates, and to develop alternate coping strategies to deal with the individual daily enticements (persons, places, and things) associated with opioid use that can lead to relapse.

Patients with opiate dependence can present with a variety of medical conditions that relate to the drug using lifestyle, and that may require intervention. Daily intravenous injections can produce local and disseminated infections such as phlebitis, cellulitis, endocarditis, cardiac valvular disease, and pulmonitis. Rates of hepatitis C have sky-rocketed in the last decade and warrant performing a hepatitis screen on admission if LFTs are abnormal (Liao et al. 2006). Hepatitis B can also transmitted by unclean needle use, although its impact may have been somewhat reduced by widespread availability of the Hepatitis B vaccine in recent years. Certainly, any drug-dependent patient not already vaccinated or carrying Hepatitis B antibodies should be encouraged to undergo Hepatitis B vaccination. Intravenous drug use is also a major mode of transmission of HIV. The more widespread availability of needle exchange programs and other modes of access to clean needles (e.g., pharmacies) have had a beneficial public health effect in reducing blood-borne disease transmission among drug-dependent patients. There is also evidence that chronic heroin use affects physiological mechanisms of aging, accelerating the process of premature aging (Missenden and Reese 2006). These and other medical concerns make heroin and drug use in general a major public health problem.

Detoxification methods are usually based on the premise that an intense short-lived withdrawal (measured in terms of days) precedes a milder but more protracted one (lasting weeks to months). Most methods aim at aiding patients withstand the rigors of the initial phase. This is achieved by using the medication on which the patient is dependent (detoxification of low potency opiate like propoxyphene), by using medications that exert a cross-tolerance effect (methadone substitution in heroin dependence), by using medications that provide relief of withdrawal symptoms (benzodiazepines for restlessness and insomnia), or finally, by using medications that target withdrawal-induced sympathetic activity (alpha-2 adrenergic agonists) (Kleber 1981).

The methods currently in use include the following: (1) alpha-2 adrenergic agonists clonidine and lofexidine; (2) long-acting μ-receptor agonist methadone; (3) μ-receptor partial agonist buprenorphine; (4) rapid detoxification with general anesthesia. Methadone and buprenorphine are also used following detoxification for opioid agonist maintenance treatment.

### Alpha-2 Adrenergic Agonist Based Treatment

The use of this class of medication is predicated on its inhibition or reduction of the opiate withdrawal symptoms caused by sympathetic nervous system hyperactivity (insomnia, tachycardia, sweating, nausea, malaise). Other symptoms such as craving for opiates, muscle aches, and pain are not significantly suppressed however (Jasinsky et al. 1985). Thus, clonidine is not usually used by itself but is rather often combined with a benzodiazepine (for anxiety), NSAID (for muscle pains), and medications for GI distress. In general, clonidine-based detoxification is not as effective as detoxification methods based on agonists (methadone or buprenorphine), but it remains a useful component of the armamentarium.

Clonidine and lofexidine belong to this class of medications, and although not FDA approved for this purpose, clonidine is well known in the medical community as a useful medication to treat opiate withdrawal symptoms and to attempt detoxification with. Lofexidine could not obtain FDA approval as an antihypertensive medication in the 1980s, rendering it unavailable for use as medication to treat opiate withdrawal. However, its lack of hypotensive effect gives it an advantage over clonidine, in that sufficient dosages can be given to bar withdrawal symptoms with less concern of producing iatrogenic hypotension. This appears to be due to the high affinity of lofexidine to only one of the three subtypes of alpha-2 adrenergic receptors, as opposed to the high affinity of clonidine to all receptor subtypes (Herman and O'Brien 1997). Since opioid withdrawal may involve nausea, vomiting and diarrhea, and consequent volume depletion, attention to hydration (oral or parenteral if necessary) is always important during opioid withdrawal. Lofexidine has been used in Europe for opiate withdrawal treatment, where it has proved to be as effective as clonidine with less hypotension and sedation when used at doses up to 2 mg/day (Bearn et al. 1996). Lofexidine is currently being reevaluated as a medication for opiate withdrawal in the USA.

Most detoxification methods using clonidine involve an abrupt cessation of opiate intake, with a transfer onto clonidine that same day, preferably performed as an inpatient. Typical methods for short and long-acting opioids are outlined in Table 111–4.

Symptoms of withdrawal begin to diminish usually within 30 minutes, with a peak effect reached after 2–3 hours. The blood pressure should be checked before each dose, and when lower than approximately 85/55 mm Hg the dose should be held, and the patient encouraged to remain supine and to drink a lot of fluids. Clonidine detoxification should not be attempted in pregnant patients, or patients with cardiac disease, or in patients who have been on antidepressants, as these tend to produce desensitization of alpha-2 adrenergic receptors.

**Table 111–4 Guidelines for Clonidine Detoxification for Opiate Dependence**

**Clonidine Detoxification for Short-Acting Opiates**

Day 1: 0.1–0.2 mg po every 4–6 hr, up to 1 mg/d.

Day 2 to 4: 0.2–0.4 mg po every 4–6 hr, up to 1.2 mg/d.

Day 5 to completion: reduce daily dosage by 0.2 mg/d, eliminating the nighttime dose last.

**Clonidine Detoxification for Long-Acting Opiates (Methadone)**

Patient daily methadone dose should be lowered to 20–30 mg/d prior to detoxification.

Day 1: 0.3 mg po per day, in divided doses every 4–6 hr.

Day 2: 0.4–0.6 mg/d, in divided doses every 4–6 hr.

Day 3: 0.5–0.8 mg/d, in divided doses every 4–6 hr.

Day 4: 0.5–1.2 mg/d, in divided doses every 4–6 hr.

Days 5 to 10: dosage of day 4 continued.

Day 11 to completion: reduce dosage by 0.2 mg/d, removing the nighttime dose last.

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Clinicians have attempted to address two shortcomings of this method by devising ways to shorten the duration of the detoxification, and by attempting to expand the effect of clonidine to more fully cover all the symptoms of opiate withdrawal.

Vining et al. (1988) described a method of "ultra rapid detoxification" in which the opiate antagonist naltrexone is used to precipitate withdrawal, and clonidine preceding and following naltrexone is used to treat the withdrawal symptoms. For those symptoms not responsive to clonidine, adjuvant medications such as oxazepam for muscle cramps and insomnia or antiemetics are used. Table 111–5 illustrates the typical inpatient (or outpatient) course of treatment with this method.

This method requires trained and experienced medical personnel to assess vital signs and the severity of withdrawal symptoms to adjust medications, including monitoring for hypovolemia and intervening as needed, as well as the appropriate medical setting. There is some evidence that this method shortens the time required for detoxification. However, it does not appear to result in longer periods of abstinence (O'Connor and Kosten 1998).

Some clinicians have combined clonidine with buprenorphine, a partial μ-receptor agonist to offer a more complete control of withdrawal symptoms, and offer a more comfortable detoxification.

The usual methods involve a 3-day detoxification procedure, or a longer procedure up to 14 days, either method involving clonidine administration (0.1–0.4 mg po q 4–6 hours prn, not exceeding 1.2 mg per day) with buprenorphine induction and detoxification (see below) (O'Connor et al. 1997).

While a good adjunct medication to support opiate detoxification using other agents, clonidine-assisted detoxification itself is not popular among dependent individuals. A recent comparison of detoxification methods revealed that clonidine-assisted methods produced the lowest retention in opiate dependence treatment (Collins et al. 2005)

## Methadone for Detoxification

Most hospital-based opiate detoxification programs use methadone, a long-acting μ-receptor agonist. Its half-life is approximately 72 hours, it can be taken orally, and it reduces or eliminates all the components of the withdrawal syndromes. The extensive experience acquired in the medical community with its use has also rendered it quite safe.

The first hurdle for the clinician is to determine the initial dose. When dealing with someone who is tolerant to medically prescribed opiate, the initial dose can be arrived at by the use of an analgesic potency conversion table (see Table 111–6), once the daily dosage of the prescribed opiate is known.

These figures are approximate as they are based on dosages that provide nearly equivalent analgesic effect

**Table 111–5 Guidelines for Rapid Detoxification for Opiate Dependence Using Clonidine and Naltrexone**

| Day | Time | Medication |
|---|---|---|
| 0 | | Heroin, methadone, or other opiate use as usual |
| 1 | 9 a.m. | Clonidine 0.2–0.4 mg po<br>Oxazepam 30–60 mg po |
| | 10–11 a.m. | Naltrexone 12.5 mg po<br>Clonidine 0.1–0.4 mg q 4–6 hr, up to 1.2 mg<br>Oxazepam 30–60 mg q 4–6 hr prn. |
| | Patient remains in clinic until 5 p.m. if outpatient<br>Vital signs monitored hourly, with liberal fluid intake | |
| 2 | 9 a.m. | Clonidine 0.1–0.2 mg po; repeat q 4–6 hr prn up to 1.2 mg<br>Oxazepam 30–60 mg; repeat q 4–6 hr prn up to 120 mg<br>Naltrexone 25 mg po |
| | 10 a.m.<br>If vital signs are stable, patient can leave 2 hr after naltrexone if outpatient; encourage liberal fluid intake | |
| 3 | 9 a.m. | Clonidine 0.1–0.2 mg; repeat q 4–6 hr prn, begin tapering the dose by 0.2–0.4 mg/d<br>Oxazepam 15–30 mg; repeat q 4–6 hr prn<br>Naltrexone 50 mg po |
| | 10 a.m.<br>If vital signs are stable, patient may leave after 1 hr after naltrexone; encourage liberal fluid intake | |
| After day 3 | Treatment continues according to clinician judgment | Clonidine: continue 0.1–0.2 mg q 4–6 hr prn over next 2–3 days<br>Oxazepam: continue 15–30 mg q 4–6 hr prn over next 2–3 days<br>Naltrexone 50 mg po q day |

**Suggested prn medications.** Muscle cramps: NSAIDS, oxazepam 30–60 mg prn; nausea/vomiting: ondansetron; insomnia, anxiety: oxazepam 30–60 mg prn.

| Table 111–6 Equipotent Analgesic Doses for Opiate Medications | |
|---|---|
| Methadone | 1 mg |
| Codeine | 7 mg |
| Heroin | 1–2 mg |
| Hydromorphone (Dilaudid) | 0.5 mg |
| Meperidine (Demerol) | 15 mg |
| Morphine | 1.5 mg |
| Hydrocodone | 1.5 mg |
| Oxycodone | 1.5 mg |

(Hardman et al. 2001). Hence, the initial response to methadone must be monitored, even though one is converting between known entities. In the case of someone using illegal opiate, the amount of narcotic actually used varies according to the quality of the opiate procured, hence the clinician must make an educated guess. The dose must be sufficient to treat withdrawal symptoms, but not excessive so as to be life threatening. The most common cause of morbidity and mortality in this setting is the overestimation by the patient or the clinician of the patient's tolerance to opiates. For this reason, most protocols dispense 10–20 mg of methadone initially, followed by a gradual taper at a rate of around 5 mg per day (Devenyi and Saunders 1986). With this dose, withdrawal symptoms should be suppressed in 30–60 minutes, if not, an additional 5–10 mg can be given, up to about 40 mg usually, keeping the patient under observation for excessive drowsiness and depressed breathing. Most commonly, these symptoms and motor impairment are evidence of excessive dosing. Symptom scales, such as the Clinical Opioid Withdrawal Scale (COWS; Wesson and Ling 2003), can be used to monitor the level of withdrawal symptoms during the detoxification procedure.

Following reports of deaths, cardiac arrests and other serious adverse events, the FDA issued an advisory (FDA 2006) concerning the prescription information for methadone hydrochloride, just as methadone is finding an expanded use as an analgesic for chronic pain. The advisory encourages clinicians and patients to be watchful of interactions with medications and dietary supplements, and alerts clinicians to be especially attentive to the emergence of side effects (trouble breathing, shallow breathing, blurred vision, sleepiness, inability to think, walk, or talk normally) during the conversion of patients from one form of opiate analgesic to methadone. The advisory also reminds physicians of a consequence of long-term opiate use: individual tolerance can vary according to the opiate medication used, and awareness of this issue is paramount when initiating or converting a patient to treatment with methadone to avoid life-threatening side effects.

If the history, drug screen, and clinical observation are not sufficient to determine physical dependence, a *naloxone challenge test* can be used. By administering 0.2–0.4 mg subcutaneously of naloxone, a short-acting μ-receptor antagonist, the clinician can determine if the patient is still under the influence of an opiate drug. The withdrawal induced by naloxone usually peaks 5–10 minutes after administration, and rarely exceeds 30 minutes. Should it become excessive, 4–8 mg of morphine by mouth can be used to reverse the reaction.

Once the initial dosage of methadone is set, based on the absence of withdrawal and on vital signs, it should be continued at least for another day. The dosage can then be decreased over a period of 5–10 days. Two practices are most commonly used for this: the dose is either decreased by a fixed amount, either 10% or 5 mg every day or two until zero dosage is reached (linear withdrawal method), or it can be decreased by 10 mg/day until a dose of 10 mg is reached. Following this, it is decreased at a slower rate of 2 mg/day by the inverse exponential withdrawal method (Strang and Gossop 1990).

Even though the acute withdrawal can be managed by these methods, the clinician must be aware that fatigue, insomnia, irritability, and anxiety may persist for several weeks to even months. These must be addressed even though there may no longer be any signs of acute withdrawal. This subacute withdrawal syndrome may respond nicely to low dose clonidine (0.1–0.2 mg, three to four times per day). Insomnia can be treated with medications like zaleplon or trazodone, as improved sleep tends to reduce anxiety and irritability (Sullivan et al. 2006). Benzodiazepines are very useful during acute withdrawal, but are best avoided or else used with particular caution because opioid-dependent patients are at increased risk to develop benzodiazepine dependence. If used, recommendations such as a low dose of a long-acting benzodiazepine, a taper schedule, and close monitoring for signs of abuse of the benzodiazepine should be implemented. Nonsteroidal anti-inflammatory medications like ibuprofen, ketorolac, or tramadol can be used for pain if present. Sufficient fluid intake and proper nutrition, with vitamin supplementation if necessary, should also be encouraged.

## Buprenorphine for Detoxification

Methadone is a safe, well-known treatment to help with opiate withdrawal, and it has the virtue of being inexpensive. However, methadone also has drawbacks for detoxification. Withdrawal symptoms often emerge after a taper is completed, increasing risk of relapse; it has a certain stigma attached to it because of diversion and misuse; and it can only be administered for treatment of opioid dependence either on an inpatient unit or in specially licensed clinics. The high affinity partial agonist buprenorphine is an alternative, which is a superior agent for detoxification in most respects, and can be prescribed by any physician who has taken a brief certification course. As a partial agonist, buprenorphine relieves withdrawal symptoms, while having a ceiling on its agonist effects, resulting in greater safety (low risk of overdose) and low abuse potential, and the starting dose for buprenorphine is less dependent on the amount of opioids the patient has been taking. Because it has very high affinity for opioid receptors, it dissociates from the receptors very slowly, thus having an inherent self-tapering effect. Several multisite clinical trials in community-based treatment settings have demonstrated its effectiveness and high acceptability for opioid detoxification (Amass et al. 2004, Ling et al. 2005). One drawback is its expense (it is substantially more expensive than methadone). Another drawback is that if buprenorphine is given too close in time to the last doses of other opioids, particularly with slowly eliminated agents such as methadone, withdrawal can be precipitated because a partial agonist is displacing full agonists from receptors. For this reason, when initiating buprenorphine,

it is important to wait until a patient is clearly developing withdrawal symptoms before starting buprenorphine, and greater delay is prudent when the patient has been taking a long-acting opioid such as methadone. After withdrawal signs and symptoms begin to emerge a test dose of 2 mg sublingual can be administered. If withdrawal symptoms should begin to improve, or at least do not worsen, then another 2 mg can be given 1 hour later, followed by 4 mg, for a total of 8 mg to 16 SL on the first day. The most accepted method involves a 3-day protocol, which provides good control of withdrawal symptoms with few side effects. After initiation of buprenorphine, the first day dose is repeated on the second day, and decreased to 4–8 mg on the third day. Abrupt withdrawal of buprenorphine leads to a comparatively mild withdrawal syndrome (Cheskin et al. 1994). Early reports on this form of detoxification suggest that it may lead to better retention in longer term treatment (Renzelli and Capretto 2006). Longer detoxification protocols also exist; involving a more gradual 10–14 day taper schedule was also shown to be effective in several multisite clinical trials (Amass et al. 2004, Ling et al. 2005).

It is important to bear in mind that withdrawal precipitated by buprenorphine can be atypical in its presentation, with impaired sensorium, and less of the typical symptoms of autonomic overdrive. Precipitated withdrawal can be treated with waiting and adjunctive medications (e.g., clonidine).

### Summary of Opioid Detoxification Techniques

As outlined above, clinicians and patients have several effective pharmacological treatment regimens to choose from for treatment of opioid withdrawal. The most serious drawback with detoxification is that the risk of relapse to opioid dependence after completion of detoxification is very high. Thus, it is important to have a strong aftercare plan in place, consisting of either residential treatment, a solid outpatient program, or pharmacological treatment with either agonist maintenance (methadone or buprenorphine) or antagonist treatment with naltrexone. For patients with a history of relapses, long-term pharmacological treatment is indicated in most cases. The following sections describe maintenance treatment with methadone, buprenorphine, and naltrexone.

## Maintenance Treatments

### Methadone

Methadone maintenance was introduced over 30 years ago by Dole and Nyswander (1965) and represented a major advance in the treatment of opioid dependence. It allowed many chronic opioid-dependent patients who had previously been refractory to psychosocial treatments to become abstinent and lead productive lives. Methadone maintenance treatment is tightly regulated by Federal regulations, and can only be administered at specially licensed clinics, according to criteria summarized below. In principle, methadone maintenance is indicated for any patient who has failed to maintain abstinence and relapsed after one or more attempts at "drug-free" psychosocial treatment. According to the regulations, to be eligible for methadone maintenance, an individual must show evidence of at least 1 year of physiological dependence, demonstrated by at least a positive urine toxicology, and signs and symptoms of opiate withdrawal. Having met this criteria, the following individuals can be eligible:

- Individuals from penal institutions who met the criteria prior to incarceration (risk of relapse is high in such individuals despite the fact that they may have been abstinent for some time in prison).
- Pregnant women (methadone maintenance is the treatment of choice in pregnant opioid-dependent patients; since it is most likely to eliminate or minimize drug use, it appears to be relatively safe in pregnancy, and it prevents withdrawal symptoms, which can be harmful to the fetus).
- Patients previously on methadone maintenance for up to 2 years after treatment is terminated.
- An individual younger than 18, after two documented attempts at opiate detoxification or drug-free treatment at least 1 week apart. A parent or legal guardian must sign *Form FDA-325 Consent to Methadone Maintenance*.

Individual states are permitted to make these criteria more stringent, but not less so. Federal regulation prohibits daily doses greater than 120 mg without first obtaining permission from state authorities. Some patients, particularly those who are rapid metabolizers of methadone, may require higher doses; for patients who continue to use opioids despite methadone doses in the 100–120 mg range, drawing of peak and trough methadone blood levels should be considered to assess rate of metabolism, and permission sought to attempt higher doses if appropriate.

The reason for methadone's effectiveness in maintenance treatment lies is its pharmacokinetics and in the phenomenon of tolerance blockade. Methadone displays the prototypical pharmacokinetic profile of an effective agonist substitution agent, with relatively slow absorption, and long half-life. It is absorbed from the stomach and reaches peak plasma levels in about 4 hours, which contrasts with the rapid spikes in blood level associated with injection, inhalation, or insufflation of heroin. It becomes tightly bound to proteins in all tissues, including the brain. After 3–4 weeks of daily intake, methadone concentration reaches a steady state level. Further, with chronic administration at adequate doses (in the 60–100 mg per day range) methadone induces marked tolerance in brain opioid system, such that other agonists are effectively blocked. Thus, after 1–2 weeks on methadone, as the dose is titrated upward, patients will begin to report that they no longer get high when they take heroin, and heroin use often ceases completely at that point. Because of tolerance, intoxication or sedation are also avoided, so that methadone maintenance should not impair functioning, allowing patients to work and otherwise function normally in society. If sedation persists as a side effect, this suggests that the dose is too high, or that the patient does not tolerate methadone well. Estimating the initial dose for maintenance is similar to that for withdrawal (see above), and the practice of observing the patient for 1–2 hours is worth repeating here. The maintenance dose should aim at eliminating any sign of withdrawal, not produce any euphoria or sedation, and prevent the use of any illegal opiates (as evidenced by urine toxicology and report from the patient). What this dose will be varies considerably from patient to patient, but a national survey reported that better retention was obtained with doses in excess of

60 mg per day (Hargreaves 1983), and that the target dose range is usually 60–100 mg. Generally the dose is started lower, at 20–30 mg per day, for safety reasons, and gradually increased over 1–2 weeks into the target range. The concern here is that since methadone is a full agonist, and a patient's level of tolerance may vary, too high an initial dose of methadone could lead to overdose, particularly if the patient continues to use illicit opioids on top of the methadone at the outset. However, it cannot be stressed enough that, as in many other instances in psychopharmacology, the most common reason for treatment failure with methadone maintenance is inadequate dosage, and every effort should be made to advance the dose to the target range, or beyond as tolerated, until abstinence is achieved.

The public health benefits of methadone maintenance have been documented thoroughly: to name three, methadone has reduced the spread of HIV among intravenous users of heroin (Barthwell et al. 1989, Novick et al. 1990), and methadone use has decreased needle sharing with all the health ramifications that ensue from it (Ball et al. 1988), and methadone reduces the risk of opioid overdose, an otherwise common cause of death among opioid abusers. Also, there are the considerable benefits of the reduction in personal suffering from achievement of abstinence and the social benefits of getting patients back to normal social functioning.

### *Special Management Issues During Methadone Maintenance*

Three situations that may be encountered while on methadone maintenance warrant special mention: (a) the patient who continues to use drugs despite apparently adequate methadone doses; (b) the patient who needs surgery; and (c) the pregnant patient.

**Continued Drug Use During Methadone Maintenance.** The optimal response to methadone maintenance is full remission of opioid dependence (i.e., abstinence confirmed by regular urine toxicologies) and of any other substance use problems. Anything short of that should warrant clinical attention and ongoing efforts to achieve full remission. Full coverage of this topic is beyond the scope of this overview chapter, but several main points should be highlighted. Firstly, methadone maintenance treatment almost always reduces the quantity of illicit opioids used, usually substantially, even if complete abstinence is not achieved. Although this does not represent remission, it is often a clinically significant improvement, suggesting that methadone treatment should be continued and augmented, and not abandoned. Secondly, ongoing opioid use should prompt efforts at increased counseling and behavioral treatment, increased methadone dosage, and/or blood level studies to determine if the patient is a rapid metabolizer. The effectiveness of methadone maintenance has been shown to depend upon concurrent counseling (McLellan et al. 1993). Specific behavioral methods, such as voucher incentives, exchangeable for goods and services, contingent on drug-free urines, have been shown to increase abstinence among methadone maintained patients (Pierce et al. 2006). Nonopioid substance use is also common since methadone does not have a specific pharmacologic effect on nonopioid drug use. Alcohol, cannabis, cocaine, and benzodiazepines is frequently seen. Again, the presence of these other substance problems should not prompt discontinuation of a methadone treatment that is otherwise succeeding in reducing opioid use. Instead, specific treatment efforts for each of these substances should be mounted, including both counseling and behavioral therapies, as well as the pharmacological approaches described elsewhere in this chapter.

**Surgery or Pain Control During Methadone Maintenance.** In the case of surgery requiring general anesthesia, the opiate-dependent patient may require larger than expected doses of anesthetic because of preexisting tolerance. Tolerance also means that methadone is not an effective analgesic in patients maintained on methadone (Kreek 1979). If the patient requires analgesia, the maintenance dose of methadone does not contribute analgesia. Efforts should be made to control such pain with nonopioid medications or nerve blocks. Additional opioids can be carefully added to control pain, but need to be administered at the usual frequency and dosages, at least initially, to avoid an overdose. The patient on methadone maintenance therapy should not receive any partial agonist medications like buprenorphine, or full antagonists, like naltrexone that would induce a sudden withdrawal. For the whole perioperative period, the patient should receive his/her usual methadone opiate dose.

**Pregnancy and Methadone Maintenance.** The pregnant patient with opiate dependence presents with special challenges. Opioid withdrawal, which is unpleasant but benign for an adult, can cause seizures, organ damage, premature labor, and even death to a fetus (Fisher et al. 2006). Thus, opioid withdrawal is to be avoided during pregnancy. Methadone maintenance is currently the treatment of choice since it will prevent withdrawal, reduce or eliminate illicit opioid use, and has a good safety record in pregnancy. The clinician should seek the lowest dose that will keep the patient comfortable, as this reduces the risk of withdrawal for the fetus or neonate. As the pregnancy advances, this dose may need to be adjusted because of the increased fluid volume and metabolic rate (Finnegan and Kaltenbach 1992). The safety of buprenorphine in pregnancy is not yet fully established, although a large multisite trial is currently underway.

At birth, the newborn will be physiologically dependent on opioids and will require close monitoring in a neonatal intensive care unit preferably. The neonate, contrary to the mother, lacks a fully functional enzyme system to metabolize opiates, delaying thus the onset of withdrawal, and often attenuating its severity. With methadone, 45–68% of neonates need treatment for neonatal abstinence syndrome, the presentation of which ranges from failure to thrive to hyperreflexia, tremor, diarrhea, and dehydration (Senay 1999). Treatment with oral phenobarbital or morphine is usually effective (Ebner et al. 2007). If it is medically necessary to withdraw a mother from methadone because of the emergence of a severe comorbid medical condition (such as cardiovascular or pulmonary illness), withdrawal should be performed gradually to avoid worsening of the physiological stress due to the illness. Preferably, withdrawal should occur during the second trimester. During the first trimester, fetal organ development may be affected, while the risk of premature labor and other adverse fetal outcomes is excessive during the third trimester (Kleber 1999).

Methadone is an effective treatment, especially for the patient using illegal opiates like heroin with a strong psychological dependence, a situation where the cross tolerance

with heroin provides a stabilizing effect. In the era of HIV, the public health benefits are undeniable. Given this impact, methadone will continue to remain in the armamentarium available to the clinician for the foreseeable future.

## Buprenorphine

A major advance in the treatment of opiate dependence was the 2002 approval by the FDA of buprenorphine for office-based treatment of illegal and medical opiate dependence. From a doctor who is qualified to prescribe buprenorphine, patients can receive treatment in total confidentiality in a range of clinic or office-based settings. The need is large: according to latest estimates, there are between 810,000 to 1 million chronic users of heroin, and only 200,000 patients receiving methadone maintenance treatment (McCance-Katz 2004). With buprenorphine, the goal is to expand the availability of opiate dependence treatment to primary care settings, beyond the capability of the methadone clinic system. There, one hopes, the clear benefits rendered by methadone programs can be expanded, while the strong stigmatization lorded onto opiate-dependent patients can be avoided.

To dispense buprenorphine for treatment of opiate dependence, physicians who already hold a DEA license to prescribe controlled substances must meet certain requirements as specified in the Drug Abuse Treatment Act of 2000 (see Table 111–7), mainly completion of a brief training course. Courses are offered online or by seminars sponsored by professional organizations such as American Academy of Addiction Psychiatry (AAAP) and American Society of Addiction Medicine (ASAM). Physicians who are Board Certified in Addiction Psychiatry or have passed the ASAM certifying examination automatically qualify. Afterward, the physician submits a notification request to the Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration (CSAT/SAMHSA). After verification with the DEA for an established number, a unique DEA number solely for the purpose of prescribing buprenorphine will be assigned. The physician may opt to be listed on a physician locator on the Substance Abuse Mental Health Administration SAMHSA's Web site as a provider of buprenorphine treatment.

**Table 111–7 Required Physician Qualification to Prescribe Buprenorphine for Opiate Dependence**

Drug Abuse Treatment Act of 2000, (as amended in H.R. 6344, 2006)

**Physician Qualification for Office-Based Treatment of Opioid Dependence**

Qualified Physicians must complete a Waiver Notification form certifying the following:

- Possession of valid state license to practice medicine
- Valid DEA registration
- Commitment of physician or group practice to treat no more than 30 patients *if the physician has submitted the waiver notification less than one year ago, or is a new physician submitting notification.* Physicians who have submitted their notification at least one year ago *can treat up to 100 patients.*
- Capacity for physician to refer for ancillary services
- Satisfaction of training and experience criteria, such as added qualification in addiction medicine (American Board of Medical Specialties). Complete list of criteria can be viewed at http://www.buprenorphine.samhsa.gov.

As previously described in the section on detoxification above, Buprenorphine is a high affinity partial agonist at the μ-opiate receptor, binding the receptor but only partially activating it, while blocking access to the receptor by other opioids. Advantages include greater safety, including, importantly, low risk of respiratory depression, and lower abuse liability due to the ceiling on agonist effects, and muted withdrawal effects due to slow dissociation from the receptor. When compared to ascending oral doses of methadone, SL buprenorphine displayed a ceiling—that is, did not produce any further effect beyond a certain dose—for inducing respiratory depression (Walsh et al. 1994). Buprenorphine is available as 2 mg and 8 mg tablets for sublingual administration, as either buprenorphine alone or buprenorphine–naloxone combinations. Buprenorphine has been available for a number of years by injection for analgesic purposes, but this parenteral formulation has been diverted and abused (Auriacombe et al. 2004). To counteract any potential for parenteral abuse, a 4:1 combination of buprenorphine–naloxone (2/0.5 and 8/2.0 mg tablets) for sublingual administration has also been produced. As naloxone is a poorly absorbed SL, when buprenorphine–naloxone is placed under the tongue, the predominant effect emanates from buprenorphine, an effect that can last as long as 96 hours (Walsh et al. 1994); if an opioid-dependent individual attempts to dissolve the buprenorphine–naloxone combination for illicit injection purposes, naloxone will cause precipitated withdrawal, which is a strong deterrent, as well as blocking most of the effect of buprenorphine, thus diminishing its reinforcing effect (Stoller et al. 2001, Comer and Collins 2002).

The previous section on buprenorphine for detoxification, provides a brief overview of methods for inducting patients onto buprenorphine, and a more detailed coverage is provided below. Readers may wish to read recent reviews on establishing a buprenorphine practice where many details beyond the scope of this chapter can be gleaned (McCance-Katz 2004, Boothby and Doering 2007).

### *Induction Procedure for Buprenorphine*

The goal of induction is to establish the dose of buprenorphine that will eliminate all withdrawal symptoms, decrease or abolish the use of other opiates, minimize cravings, with few side effects. Buprenorphine can be used for opiate dependence due to prescription as well as from illicit opiates. Dependence on prescription opiates like Oxycontin is growing problem in the United States, especially among recreational and street drug users (Cicero et al. 2005).

Like all of medicine, selecting the patients most suited for this treatment is key. The Center for Substance Abuse Treatment (2004) has published guidelines to help clinicians in this regard (see Table 111–8).

Induction onto buprenorphine first requires a medical and psychiatric evaluation. Many psychiatrists will want to establish a relationship with a medical clinic to obtain a report from a recent medical examination that includes blood chemistry with LFTs and hematology results. A room dedicated to induction, with vital sign monitoring equipment and comfortable chairs, is also useful. Buprenorphine has been known to increase LFTs, especially in individuals

**Table 111–8 Prognostic Factors for Buprenorphine Treatment of Opiate Dependence**

Patient Factors Favorable to Treatment

- Interest in office-based treatment
- Understand the risks and benefits of buprenorphine
- Can anticipate good compliance
- Can anticipate that patient will follow safety procedures
- Patient is psychiatrically stable
- Stable and supportive psychosocial circumstances
- Patient is not taking medications that can interact with buprenorphine, such as benzodiazepines, or medications that can interfere with buprenorphine (metabolized by cytochrome 3A4)
- The dispensing clinician has sufficient resources to meet the need of the patient (such as treatment or referral for psychotherapy)

Patient Factors Less Favorable to Treatment

- Dependence on benzodiazepines or other CNS depressants
- History of violence, suicidality or homicidality
- Documented unsuccessful treatment with buprenorphine

previously infected with the hepatitis virus (Petry et al. 2000), although short of sensitivity to buprenorphine itself, there are no absolute medical contraindications to buprenorphine treatment. However, the individual seeking treatment must meet criteria for opioid dependence, as evidence by the history of increasing use, tachyphylaxis requiring ever increasing dosage, and evidence of withdrawal, or of intravenous injections such as drug marks, or else, evidence of past opioid dependence in the face of imminent risk of relapse. Documentation and evaluation of withdrawal is paramount for verifying dependence, as well as for a proper induction.

Prior to receiving the first sublingual dose of either buprenorphine or buprenorphine/naloxone, individual seeking treatment must display signs of mild to moderate withdrawal. This is important because in the absence of withdrawal signs, the partial agonist action of buprenorphine will precipitate withdrawal, causing profound discomfort to the patient. An objective scale like the Objective Opioid Withdrawal Scale (OOWS) can assist the physician in estimating the extent of withdrawal (Handlesman et al. 1987), or the Clinical Opiate Withdrawal Scale (Wesson and Ling 2003). Using these scales, a minimal score of 3 on the OOWS, or 13 on the COWS is required to proceed with the induction. This can be usually achieved by instructing the patient to abstain from all opioids from around 9 pm on the evening prior to the induction until the scheduled time to present at the office, optimally in the morning, best if not on a Friday. If at the scheduled time, the minimal withdrawal scores are not obtained, the patient should wait or return home until the next day, with the admonition to avoid taking any opiates, which would only delay the induction further.

### *Day 1 of Buprenorphine Induction*

Either buprenorphine alone or the combination of buprenorphine/naloxone can be used for short-acting opioids. A first dose of 2/0.5 mg or 4/1 mg of buprenorphine/naloxone can be used. It is important to tell the patient to keep the tablet under the tongue until the tablet is completely dissolved, and only then swallow. The patient should then be monitored for the next 2 hours, during which some relief from withdrawal is experienced, usually within 30–45 minutes. If so, another dose similar to the first dose can be given, up to 8 mg for the first day, although clinicians can prescribe up to 16 mg if clinically indicated. If, however, the patient reports worsening of withdrawal symptoms shortly after receiving buprenorphine, this suggests a precipitated withdrawal. In this case, the clinician may consider giving another dose of buprenorphine to favor the agonist effect and relieve withdrawal, or else may opt to delay continuing the induction until the next day, or treat specific withdrawal symptoms, as outlined in Table 111–9.

**Table 111–9 Ancillary Medications for Buprenorphine Treatment of Opiate Dependence**

| | |
|---|---|
| Clonidine/lofexidine | Hypertension, tachycardia, anxiety |
| Acetaminophen/ibuprofen | Muscular aches and pain |
| Dicyclomine | Abdominal cramps |
| Loperamide | Diarrhea |
| Diphenhydramine/ trazodone | Insomnia |

This eventuality can be avoided by ensuring that objective withdrawal signs and symptoms are documented prior to induction.

For patients dependent on long-acting opiates like methadone, the induction process may be more arduous. According to the Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioids Dependence, patients on methadone should decrease their dosage to 30 mg a day or less a week before buprenorphine induction is scheduled (McNicholas 2004). At least 24 hours should precede the beginning of the induction process, allowing for withdrawal signs and symptoms to emerge and be tabulated with the OOWS or the COWS. In this instance, buprenorphine alone is preferred, starting at 2 mg, adding 2 mg every 1–2 hours, usually not exceeding 8–16 mg in the first day.

For patients with past history of opiate dependence who are now abstinent but seeking relapse-prevention treatment, withdrawal symptoms are usually not present. They should be given 2/0.5 mg dose, with a very gradual, slower rate of dosage increase aimed at decreasing cravings and psychological dependence.

Before departing at the end of the first day, patients should be advised that they may experience some withdrawal, for which some of the medications mentioned above may be used.

### *Day 2 of Buprenorphine Induction*

When patients return, clinicians should inquire about withdrawal problems since leaving the office, and about any use of opiates, preferably verified by urine toxicology. If withdrawal signs are noted, the buprenorphine dose should be increased to reach 12–16 mg per day, in 2–4 mg increments. Sedation would suggest excessive dosing, for which the dose should be lowered. Should the patient continue to present with withdrawal symptoms or cravings, the dose may be increased further on a third day of induction. The maximal approved daily dose is 32 mg, in divided doses.

Once the patient has reached a stable and optimal dose, it may be continued as a daily dose, or taken only twice or

thrice weekly. Evaluation of different dosing frequencies did not reveal differences in treatment retention, opiate abstinence, or reduction in HIV risk between these dosage frequencies. The dose is thus adjusted to reflect the number of days when buprenorphine is not taken. For example, if taken three times a week, the dosage on Monday would be double the daily dose to account for Tuesday, similarly on Wednesday, and on Friday, the dose is tripled to account for Friday, Saturday, and Sunday (Marsch et al. 2005).

### *Buprenorphine Maintenance*

Buprenorphine treatment is currently best conceived as a maintenance treatment. Several reports from clinical trials have confirmed the efficacy of buprenorphine for the treatment of opiate dependence (Strain et al. 1996, Johnson et al. 2000b, Fudala et al. 2003). Johnson and colleagues compared high methadone (60–100 mg) and low methadone (20 mg) doses to 8 mg of buprenorphine as maintenance treatment. After 18 weeks, treatment retention for patients on low methadone and buprenorphine was similar, and only bested by high methadone treatment, suggesting that for some patients with severe opiate dependence, high dose methadone treatment may prove more effective (Johnson et al. 2000b).

Given the unique pharmacological properties of buprenorphine could its use alter the chronicity of opiate dependence, and serve as a transition to abstinence? A study by Kakko et al. (2003) looked at the 1-year treatment retention and abstinence between two groups: one maintained on 16 mg of SL buprenorphine and another who underwent a 6-day detoxification with buprenorphine, followed by placebo capsules. The results differed dramatically between the groups: at the end of 1 year, no one from the detoxification group remained in treatment, and all had left treatment after a return to opiate use. Seventy-five percent of patient in buprenorphine maintenance remained at 1 year, and 75% of all urine samples were negative for any drug. Even though both arms of the trial were provided with an intense psychosocial treatment, the dismal outcome of those receiving placebo highlights the persistent and grave nature of opiate dependence. Moreover, there was a 20% mortality rate in the detox/placebo group as opposed to 0% in the buprenorphine group. Published mortality rate during methadone or buprenorphine treatment is about 1% (Soyka et al. 2006). Hence, it appears that maintenance treatment with buprenorphine leads to better outcomes. If abstinence can be achieved, it seems that it should occur after a longer period of time on maintenance treatment, long enough to shore up psychosocial skills damaged by drug use. How this transition should be made with buprenorphine remains to be fully worked out presently.

Buprenorphine is also having a social impact; by bringing the treatment of opiate dependence into ordinary medical practice, it reduces and shields the patient from the stigmatization that methadone treatment centers often draw. Its dual indication for analgesia as well as for opiate dependence makes buprenorphine an attractive choice for those with a chronic pain syndrome who are seeking an agent with a favorable side effect profile.

## Anesthesia-Assisted Heroin Detoxification

This highly publicized method of detoxification promises a fast and painless way to withdraw from opiates. In light of the high cost of these procedures (up to $15,000) and the lack of insurance coverage, it was important to investigate whether this procedure offered a distinct advantage over more traditional methods. Only recently has the practice of anesthesia-assisted opiate detoxification been systematically evaluated. Collins et al. (2005) compared anesthesia-assisted opioid detoxification to buprenorphine-assisted and clonidine-assisted opioid detoxification, each followed by transition to naltrexone antagonist treatment lasting 12 weeks (see below). Thirty-five patients were assigned to receive anesthesia, 37 to receive buprenorphine, and 34 to receive clonidine. All patients met criteria for opiate dependence for at least 6 months and were seeking treatment. Treatment outcomes were opioid withdrawal scores (measured by the Subjective and Objective Opiate Withdrawal Scales; Handlesman et al. 1987), induction onto naltrexone treatment, and treatment retention. For those assigned to anesthesia-induced detoxification, withdrawal scores peaked before detoxification; after the procedure, withdrawal scores did not differ significantly from the other two detoxification methods. Ninety-four percent of those receiving anesthesia and 97% with buprenorphine received at least one 50 mg dose of naltrexone, in contrast to 21% with clonidine detoxification. Beginning naltrexone treatment lowered the risk of dropping out during the outpatient treatment phase. Overall, retention in treatment during the outpatient phase was similar for all treatments, nonetheless, 20% of anesthesia and 24% of buprenorphine assigned patients completed all 12 weeks of outpatient treatment, compared with 9% in the clonidine group. No group differences were found in urine toxicology for opiates or any drug. Another study by Favrat et al. (2006) compared clonidine- to anesthesia-assisted detoxification. Better opiate abstinence rates at 3 months were seen with anesthesia, but that difference disappeared at 6 months.

As previously mentioned, withdrawal from opiates can be painful and protracted, but rarely dangerous. This fact makes the report of two severe adverse events for the anesthesia group in the study by Collins et al. (2005) especially noteworthy. One patient developed pulmonary edema and aspiration pneumonia 14 hours after extubation, necessitating intensive care unit monitoring and treatment. With reevaluation of the medical history, prior episodes of complicated pneumonias were found. Another patient with diabetes mellitus and a prior episode of diabetic ketoacidosis developed ketoacidosis within 48 hours of anesthesia detoxification. The possibility of detoxification without pain has made anesthesia-assisted detoxification alluring to patients. However, the findings of Collins and colleagues suggest that anesthesia provides no added benefit over cheaper, safer buprenorphine-assisted detoxification as a bridge to naltrexone treatment. Unless the clinician faces exceptional circumstances, this appealing form of treatment cannot be recommended.

## Opiate Antagonist Treatment: Naltrexone

Naltrexone is an antagonist at the μ-opioid receptor, and blocks the action of endogenous and exogenous opiates at this receptor. This effect on endogenous opiates is thought to account for naltrexone's effect to reduce drinking (see section on alcohol dependence). In the context of opiate dependence, its action on exogenous opiates prevents

readdiction to opiates, and allows patients to continue treatment despite lapses or relapses without having to undergo repeated detoxification. While on naltrexone, all objective and subjective effects are blocked, rendering heroin no longer rewarding. In this context, at least when studied in a human laboratory, heroin-addicted individuals taking naltrexone gradually diminish and stop their use of heroin (Mello et al. 1981). When ingested by someone without opiate dependence, naltrexone produces few or no side effects. In recently detoxified individuals, complaints of worsening abdominal pain, nausea, diarrhea are frequent as withdrawal symptoms are worsened by the introduction of naltrexone. Aside from instances in which patients already have elevated liver enzymes or liver failure and who should not receive naltrexone, a review of several studies has failed to demonstrate that naltrexone causes elevation of liver enzymes (O'Brien and Cornish 1999).

Contrary to methadone or buprenorphine, no dependence develops with naltrexone: it provides no reward, and does not cause withdrawal. To not feel any effect may be a disadvantage to someone who is used to feeling some drug effect. Overconfidence in having overcome one's dependence is one pitfall that lulls many individuals with opiate addiction and leads to relapse.

For those who must approach the treatment of opiate dependence without resorting to some form of substitute opiate (like methadone or buprenorphine), naltrexone represents a very good option. Physicians, other health care professionals, individuals in critical administrative, technical, and social occupations would be particularly well served by this treatment approach. Judiciously, O'Brien and Cornish (1999) wrote: "For someone recovering from addiction who works in a field such as nursing, pharmacy or medicine, there is an added benefit to naltrexone maintenance: it reduces the concern about relapse felt by colleagues who are aware of the person's history." In this way, professionals in health services and other fields can find solace against the stigmatization that comes with addiction; especially if there is a policy of witnessed naltrexone intake.

For those addicted to heroin, the results of naltrexone treatment are mixed. In most trials, the drop out rates are high, as high as 70%, with a further surge associated with methadone use and a high number of heroin bags per day used (Tucker et al. 2004, Sullivan et al. 2006). Other concerns also arise. One is related to whether naltrexone might lead to greater incidence of depression in opiate dependent, although rates of depression are high among heroin users. Research to date does not support a link between naltrexone and accrued depression (Ritter 2002). Another is a higher rate of overdose during naltrexone treatment due to reduced tolerance. Existing data suggest that the mortality rate during and subsequent to naltrexone treatment is comparable to that seen in nontreated heroin users, but is higher than that seen in methadone or buprenorphine treatment (Ritter 2002). Time in treatment is the most important factor leading to naltrexone's effectiveness, as with time in abstinence, patients feel gradually more secure against their impulse to seek heroin to overcome physical and psychological adversity (Johansson et al. 2006). For all these reasons, naltrexone is only effective if integrated in a structured rehabilitation program.

Naltrexone treatment begins with detoxification as outlined above. There are no preferred methods beyond what is dictated by the opiate being abused, and time available. However, buprenorphine has been reported to be an excellent bridge between an agonist like heroin to an antagonist like naltrexone (Collins et al. 2005, Nunes et al. 2006). Ideally, one should allow as much time as possible between the end of the detoxification and starting naltrexone to avoid precipitating withdrawal. Medications like clonidine can ease residual withdrawal symptoms and remove a strong incentive to resume heroin use. When to begin naltrexone after detoxification is a question of clinical judgment, as the clinician must weigh the risk of relapse without opiate antagonist protection and the risk of precipitating some withdrawal when introducing naltrexone. Performing a naloxone challenge to test for residual opiate dependence can help the clinician to arrive at this decision (see above). When the naloxone challenge test is positive, naltrexone induction should be delayed by at least another day. While the usual dose of naltrexone for the treatment of opiate dependence is 50 mg, treatment may be begun with 12.5 or 25 mg on the first day, then increased to 50 mg thereafter. Naltrexone can also be dosed three times per week (e.g., Monday 100 mg; Wednesday 100 mg; Friday 150 mg).

As already mentioned, the psychotherapeutic structure surrounding naltrexone treatment is of paramount importance, and there have been efforts to define which type of intervention work is the best. Two strategies have yielded encouraging results: contingency management and involvement of significant others in the treatment. Contingency management provides some form of voucher that is acquired when abstinence from opiates and intake of naltrexone is verified. For example, voucher points (amounting to $1) can be earned for each day of abstinence and each day of naltrexone intake, and the earnings become a topic in the psychotherapy to decide how they will be used to sustain a drug-free lifestyle. The presence of a significant other during the treatment sessions and to witness naltrexone ingestion also improves the chances of reaching and maintaining abstinence. It appears that when spoken in the presence of a significant other, verbal commitments made by the patient to achieve abstinence predict better treatment adherence takes on greater commitment value (Brooks et al. 2006). Behavioral therapy can be used to improve adherence to naltrexone and improve its clinical outcome (Preston et al. 1999, Carroll et al. 2001, Fals-Stewart and O'Farrell 2003, Nunes et al. 2006). An approach that has sought to combine several behavioral approaches is behavioral naltrexone therapy (BNT). BNT seeks to embed naltrexone treatment in a strong psychotherapeutic structure constructed around three elements: (1) the presence of a significant other to monitor medication intake and participate in some therapy session; (2) the use of contingency management with vouchers to encourage abstinence and medication intake; and (3) a rapid, medication-aided transition to naltrexone in the hospital to decrease withdrawal symptoms and reduce the risk of relapse immediately after the detoxification (Rothenberg et al. 2002). Nunes et al. (2006) reported on a 6-month trial comparing BNT with a standard treatment control mimicking a physician visit (compliance enhancement or CE). While BNT produced better retention overall, retention at 6 months was only 22%, compared to 9% for CE. Although some patients achieved long-term stability with naltrexone maintenance, the authors noted that the 6-month retention

rate was far below the 50% rate usually seen in methadone or buprenorphine treatment (Johnson et al. 2000b, Mattick et al. 2004), without the added risk of lethality due to decreased opiate tolerance (Ritter 2002).

Although in theory, naltrexone, like buprenorphine, could be dispensed in primary care settings, in practice, naltrexone therapy for opiate dependence requires a level of ancillary care that would necessitate specialty level training in most instances. Another difficulty arises from noncompliance with naltrexone, in that if the patient relapses while not taking naltrexone, dependence rapidly returns, and resumption of naltrexone intake can be complicated. This may be addressed by long-acting naltrexone (see in alcohol dependence section) or by naltrexone implants that would allow for constant medication levels with less of an emphasis on compliance. This new approach notwithstanding, for the moment, treating opiate dependence with naltrexone will likely be carried out in specialty settings for selected patients.

### Treatment of Co-Occurring Depression and Opioid Dependence

Major depression is common among opioid dependence and has been associated with poor outcome. Several studies suggest that tricyclic antidepressants are effective for treatment of depression in opioid-dependent patients who are on methadone maintenance, and that such treatment is associated with improvement in drug use (Woody et al. 1975, Nunes et al. 1998). However, other trials, particularly trials of serotonin reuptake inhibitors, have been negative (for a review, see Nunes and Levin 2004). A reasonable recommendation would be that major depression should be identified and treated among opioid-dependent patients, once the opioid dependence has been stabilized with methadone, buprenorphine, or naltrexone. It is important to take a careful history in an effort to identify a clear-cut major depressive syndrome, as opposed to depressive symptoms that may reflect toxic effects of drugs.

## Summary

The recent approval of buprenorphine for the treatment of opiate dependence has brought forth an excellent medication that can be used in a primary care setting. It can be used for detoxification, to help transition to naltrexone treatment, or can be used as a maintenance tool if abstinence-based treatment is not successful. Clonidine or Lofexidine are good ancillary medications to help control withdrawal symptoms, although their popularity as tools for detoxification is waning. Methadone continues to be a well-used medication for both detoxification and maintenance treatment, although the regulations surrounding its use do not make it amenable to primary care. Anesthesia-based detoxification does not appear to provide any added benefit when compared to detoxification with buprenorphine, and involves a significant risk of medical complications and adverse events. Naltrexone remains an excellent option for those patients who must receive an abstinence-based treatment.

# Nicotine Dependence

Ever since European colonizers discovered tobacco in the new world, written reports have crossed the centuries to attest to its addictive properties. Bishop Barthalamus de las Casas wrote in his memoirs dated from 1532, at the inception of tobacco cultivation in Hispanola (now the Dominican Republic) by Spanish colonists: "The fashion of smoking is widespread among colonists and when they are asked why they do it, their only answer is they cannot do without it anymore" (Brongers 1964). But it is only recently that tobacco has been linked to life-threatening disease; in the USA, approximately 430,000 die each year of illnesses related to tobacco smoking (Giovino 2002). For both primary care and addiction medicine objective, helping patients quit smoking deserves the most dogged persistence from clinicians, something Mark Twain knew very well: "To quit smoking is one of the easiest things in the world, I must have done it over a dozen times." While many individuals succeed in quitting on their own, others find it a most difficult and vexing task, and may turn to clinicians for guidance and assistance. This section will discuss briefly nicotine's effects in the brain, and will describe FDA-approved medications to treat nicotine dependence.

## Features of Nicotine Dependence

Nicotine can induce all the features of a psychoactive substance, in that it induces repeated use (usually daily smoking of cigarettes for 98% of smokers), tachyphylaxis of effects causing to smoke more and more often, tolerance to the aversive effects of nicotine such as nausea, and clear symptoms of withdrawal upon cessation of smoking (dysphoria, anxiety, irritability, and cravings for tobacco). Smoking is the preferred method of consuming tobacco, likely because inhaled nicotine reaches the brain within 15 seconds, and because it allows the smoker to exactly titrate the nicotine dose to achieve the desired effect (Malaiyandi et al. 2005). Rapidly repeated inhalations tend to deliver a stimulating effect, while slower inhalation favors a calming, soothing effect. Although nicotine is emphasized as the main psychoactive substance in tobacco, there are over 4,000 substances in unadulterated tobacco (George and O'Malley 2004). Some are known to inhibit brain monoamine oxidases and perhaps add to the reinforcing properties of tobacco (Fowler et al. 2003). Most of the approved treatments for nicotine dependence resort to nicotine replacement therapy as the main pharmacological intervention. Bupropion and varenicline therapy for nicotine dependence will be discussed separately.

## Nicotine Replacement Therapy

All forms of nicotine replacement therapy (NRT) have demonstrated good efficacy in clinical trials of smokers seeking to quit smoked tobacco over placebo. These are summarized in Table 111–10 (George and O'Malley 2004, Silagy et al. 2004).

All forms of NRT deliver good efficacy to support efforts at quitting smoking. Approximately 2 weeks after starting NRT, the patient should be encouraged to set a quit date. In preparation for this date, patients are instructed to rid themselves and their home and office of all cigarettes and smoking paraphernalia. Quit date notwithstanding, all patients should be instructed to reduce their smoking when starting NRT. Heavy smokers tend to prefer a high NRT beginning dose. From there, patients are encouraged to gradually decrease their NRT dose over a period of weeks to months. Side effects are usually few, but common ones include nausea (especially if smoking is continued while on

**Table 111–10 Dose, Pharmacological Mechanisms, and Efficacy of Nicotine Replacement Therapies**

| Medication | Route and Dose Range | Pharmacological Mechanisms | Odds of Abstinence with NRT over Placebo (Odds Ratio, OR) |
|---|---|---|---|
| Nicotine patch | Transdermal (7–21 mg/d) | ↓ Nicotine cravings and withdrawal | 1.81 (95% CI = 1.63–2.02) |
| Nicotine gum | Buccal (20–40 mg/d; 2–4 mg pieces up to 10×/d) | ↓ Nicotine cravings and withdrawal | 1.66 (95% CI = 1.52–1.81) |
| Nicotine lozenges | As for the gum | ↓ Nicotine cravings and withdrawal | 2.05 (95% CI = 1.62–2.59) |
| Nicotine nasal spray | Intranasal (1–2 mg spray in each nostril, up to 16×/d) | ↓ Nicotine cravings and withdrawal | 2.35 (95% CI = 1.63–3.38) |
| Nicotine vapor inhaler | Inhalation and buccal (6–16 mg/d, puffing up to 120×/d | ↓ Nicotine cravings and withdrawal | 2.14 (95% CI = 1.44–3.18) |

NRT) and gastric irritation from increased stomach acidity. Caution is warranted in patients with histories of gastric or duodenal ulcers, gastritis or reflux; as well as patients with cardiovascular disease.

The NRTs that deliver constant nicotine like the patch provide a more uniform effect most suited to those who experience predominantly nicotine withdrawal symptoms (agitation, nervousness, restlessness, insomnia). On the other hand, rapidly acting NRTs provide a comprehensive contextual (reproducing the ritual of smoking with the inhaler for example) and physiological relief of craving for nicotine. This is in part related to the fast rate of desensitization of nicotinic receptors after exposure to nicotine, and rapid resensitization after nicotine is catabolized. An overnight abstinence is thought to be sufficient for full reactivation of nicotinic receptors (Gotti et al. 2006), lending support to the oft-reported finding that the first cigarette of the day is the most satisfying. The issue of contextual use is fertile ground for supportive therapy aimed at preventing continued smoking in tobacco-prone circumstances and settings.

On the issue of supportive therapy, a meta-analysis looking at the effectiveness of NRT (Silagy et al. 2004) found that it was beneficial in facilitating the likelihood of quitting, but that it was not essential to the success or NRT. This makes NRT a particularly useful method to help patients quit smoking in primary care settings.

## Antidepressant Medications: Nortriptyline and Sustained Release Bupropion

Two antidepressant medications have demonstrated effects on smoking independent of their effects on depression: nortriptyline and sustained release bupropion. To date, six clinical trials (see Hughes et al. [2005] for review) have shown that doses of 75–100 mg of nortriptyline doubled the quite rate (OR = 2.1), but that between 4 and 12% of participants interrupted treatment because of side effects such as dry mouth and constipation. This high rate of side effects occurrence has placed nortriptyline on a second-tier level compared to sustained release bupropion or NRT.

In 1997, the FDA approved sustained release bupropion for nicotine dependence. This derived from a serendipitous observation that there was an antismoking effect among US veterans receiving bupropion to treat depression, regardless of an antidepressant response. Its efficacy at inhibiting smoking was demonstrated in a pivotal clinical trial against placebo, during which the 150 and 300 mg doses demonstrated better efficacy than placebo, with better smoking cessation rates achieved with the highest dose (44.2% for 300 mg; 38.6% for 150 mg; 19.9% for placebo) (Hurt et al. 1997). The mechanism by which it exerts this effect is linked to its blockade of dopamine and norepinephrine reuptake, and to some antagonism of nicotinic acetylcholine receptor (Ascher et al. 1995, Slemmer et al. 2000). The simplicity of its use and the good tolerability have made bupropion a first line agent against nicotine dependence.

Treatment with bupropion does not require that patients quit smoking at the inception of treatment. Rather, clinicians are advised to set a quit date approximately 1 week after bupropion is begun, although many smokers prefer to gradually reduce their smoking as their cravings decrease. While there continues to be a contraindication to the use of bupropion patients have a preexisting history of seizures, the rate of new onset seizures with bupropion is about 0.3%, and is mostly associated with the use of the immediate release formulation at a dose exceeding 450 mg. The most common side effects reported are headaches, agitation, and insomnia. An emerging consensus supports the use of bupropion for at least 6 months after smoking cessation (Steinberg et al. 2006), and success at 6 months appears related to increased age, continued use of medication, longer time to the first morning cigarette. Certain variants of the catechol-o-methyltransferase gene (COMT) may also predict a positive smoking cessation outcome with bupropion (Berrettini et al. 2007). However, as the results of the double-blind trial suggest (Hurt et al. 1997), a good number of smokers do not quite smoking with bupropion. As in treatment of other forms of addiction, failure of an initial quit attempt should prompt adjustment of the treatment regimen followed by renewed quit attempts. The more quit attempts a patient makes, the more likely he/she is to ultimately succeed in achieving sustained abstinence from nicotine. Nonetheless, results with bupropion prompted the investigation of combined medications, either combined NRTs or NRT with bupropion.

## Combined Treatments for Smoking Cessation

On the assumption that combining slow- and fast-acting NRTs might provide more comprehensive effects in inducing smoking cessation, Bohadana et al. (2000) found combined transdermal nicotine with a nicotine inhaler superior to transdermal nicotine with a placebo inhaler. Sustained release bupropion combined with transdermal nicotine had a better effect than placebo with transdermal nicotine (Jorenby et al. 1999). A similar effect was also demonstrated with the nicotine inhaler and bupropion (Croghan et al. 2007). It appears that combining medications with different mechanisms of action is a worthwhile strategy should the single agent alone not deliver the expected results.

### Varenicline

The newest FDA-approved medication for nicotine dependence is the nicotine receptor antagonist varenicline. Nicotine receptors come in complex pentameric arrangements of alpha (2–10) and beta (2–4) subunits with extensive brain distribution, and the one targeted by varenicline is the alpha-4/beta-2 subtype. Animal studies indicate that beta-2 receptor subtypes are involved in nicotine reinforcement, but not in withdrawal (Besson et al. 2006). A major reason why varenicline can deliver a therapeutic effect is due to the fact that it is a partial agonist. This means that while varenicline binds potently to the alpha-4/beta-2 nicotinic receptor, it stimulates less receptor-mediated activity than nicotine itself. This is important because of the rapid desensitization characteristic of nicotinic cholinergic receptors. It also binds the receptor with greater affinity than nicotine, so that it blocks the effects of nicotine, if, for example, a patient smokes while on the medication. The end result of these pharmacological properties is the blockage of nicotine-induced dopamine release in the meso-limbic system, where neuronal systems related to reinforcement are located. This blockade is the proposed mechanism for the effect of varenicline in tobacco smokers.

In industry-sponsored trials, abstinence from tobacco is evaluated by measuring carbon monoxide in the exhaled breath of participants. High CO reflects recent tobacco use. During the clinical trials reviewed by the FDA, continuous abstinence rates were greater with varenicline than with placebo, and comparatively better than abstinence rates with bupropion in the last 3 weeks of 12-week trials (Gonzales et al. 2006, Jorenby et al. 2006, Tonstad et al. 2006). The differences in abstinence rates were all statistically significant. Of particular clinical interest were the poststudy evaluations of abstinence rates, up to 40 weeks after conclusion of the acute phase. In these instances varenicline was better than placebo, but not statistically superior to bupropion. Nonetheless, varenicline represents a significant advance in the treatment of nicotine dependence.

When starting varenicline treatment, the manufacturer recommends that a quit date be set, and to begin varenicline a week before the set date. It is recommended to take varenicline with food to reduce the incidence of nausea, the most common side effect. The recommended titration is 0.5 mg per day with food for the first 3 days, then 0.5 mg twice a day for the next 4 days, followed by 1 mg twice a day. The treatment is then continued for a first period of 12 weeks. If the patient achieves abstinence, clinicians may consider continuing treatment for an additional 12 weeks to encourage long-term abstinence.

Besides nausea, insomnia, headaches, and gastric disturbances are the other commonly encountered side effects. Although the necessity of supportive therapy during varenicline treatment is not as of yet fully ascertained, good clinical care would suggest that its provision would favor a positive outcome.

## Co-Occurring Psychiatric Disorders and Nicotine Dependence

Major depression is common among cigarette smokers and predicts failure to successfully quit. Furthermore, smoking cessation has been associated with worsening of depression (Covey et al. 1997), suggesting that nicotine might actually exert antidepressant effects for some patients. As noted above, noradrenergic antidepressants, including bupropion and nortriptyline, are effective for treatment of smoking cessation, regardless of whether the patients suffer from major depression at the time of treatment. Some evidence suggests that nortriptyline works by reducing dysphoria that follows a quit attempt. One limitation of this literature is that smokers with current major depression have generally been excluded from medication trials. Clinical experience would suggest that smokers who are being treated with medication for major depression can be encouraged to quit smoking and will sometimes succeed.

The majority of patients with schizophrenia smoke cigarettes and are nicotine dependent. Here nicotine, which can enhance cognitive performance, may function to self-medicate of cognitive deficits that are part of the schizophrenia syndrome, or it may relieve side effects of neuroleptics. Recent evidence suggests that an allele of the nicotine receptor may be associated with schizophrenia (Olincy et al. 2006) In any case, smoking is responsible for substantial health problems among schizophrenic patients. More research is needed on the treatment of smoking in schizophrenia, but a reasonable clinical recommendation would be to attempt to treat smoking in schizophrenia, while carefully monitoring the effects of abstinence from nicotine on mental status.

## Future Directions

Tobacco dependence continues to be the object of intensive research efforts. Several lines of investigations deserve to be brought to the attention of the clinician: (1) the potential impact of manipulating the hepatic cytochrome system as a therapeutic tool; (2) research into treating the use of smokeless, oral tobacco.

Cytochrome CYP2A6 is the main enzyme that catalyzes nicotine into cotinine. There are 26 documented variants of the gene for CYP2A6, leading to some CYP2A6 allele combination that results in a greater or lower turnover rate of nicotine. A slow nicotine metabolizer may be more prone to experience the aversive effects of nicotine, such as nausea, dizziness, and malaise; as a result, inheriting such an allelic pair of genes may confer some protection against nicotine dependence. Messina et al. (1997) were the first to hypothesize that the metabolic rate set by the allelic pair of CYP2A6 gene variant might increase or decrease the risk of nicotine dependence. This has been substantiated in multiple cohorts of patients of different ethnicities, with the Japanese population displaying the highest frequency of low activity alleles (Malaiyandi et al. 2005). In Japanese cohorts, individuals possessing high activity CYP2A6 alleles smoked their first cigarette of the day earlier after awakening than individuals with low activity alleles. Moreover, nicotine withdrawal symptoms were more prominent in high activity CYP2A6 group (Kubota et al. 2006).

Based on these population genetic studies, the thought occurred that mimicking gene defects by pharmacological blockade of CYP2A6 could provide a treatment for nicotine dependence. Familiar to psychiatrists, the antidepressant tranylcypromine offers such an intriguing possibility, and some evidence exists to support this use (Sellers and Tyndale 2000). Other similar agents are in development.

### Oral Smokeless Tobacco

Although great attention is focused on tobacco smoking, oral smokeless tobacco use is quite widespread, and is increasing in the USA especially among young male adults (NIH Consensus Statement 2006). There is some evidence that NRT may be effective for this type of tobacco use (Ebbert et al. 2007), although a recent trial with sustained release bupropion did not induce significant abstinence rates in smokeless tobacco users (Dale et al. 2007). More research attention needs to be directed at this important public health issue.

## Stimulants: Cocaine and Amphetamines

With this section on stimulants, we will begin to discuss addiction disorders for which no FDA-approved treatment exists. The devastation brought upon by the crack epidemic of the 1980s gave great impetus to develop effective treatments for stimulant addiction. Unfortunately, despite many studies on many different compounds, pharmacological agents of sufficient effectiveness to warrant FDA approval for the treatment of cocaine dependence have not emerged. At the same time, behavioral therapies, including cognitive–behavioral relapse prevention and voucher incentives made contingent on abstinence, have been shown to be effective for treatment of cocaine dependence. Thus counseling and behavioral treatment should be considered the treatment of choice for cocaine dependence at this point.

We now briefly review medications that have shown some promise in clinical trials. These medications may be considered if counseling and behavioral treatments have failed. An overall pattern in the field of cocaine medication development is that after small, single site open or placebo-controlled trials look promising, large placebo-controlled trials fail to replicate the positive effects. This may represent placebo effects that bias the initial tests of new agents, or effect sizes that are quite small. The effect size may simply be small across the board, or a favorable effect could reside in a subgroup. Another formulation is that a given medication might impact only one phase of the recovery process, for example abstinence induction versus relapse prevention (Bisaga et al. 2006), suggesting that combinations of medications might be needed.

### Antidepressant Medications

The tricyclic antidepressant desipramine was the first medication to show promise for treatment of cocaine dependence. An initial placebo-controlled trial showed that desipramine increased the likelihood that patients would initiate at least 3 consecutive weeks of abstinence, confirmed by a negative urine toxicology (Gawin et al. 1989). Two subsequent studies showed similar trends for desipramine (Weddington et al. 1991) and the related tricyclic antidepressant imipramine (Nunes et al. 1995). However, a number of other trials of desipramine failed to replicate any beneficial effects. One possible explanation is that desipramine may have been effective in more mildly ill, or more motivated patients who presented to treatment early in the cocaine epidemic; a conclusion supported by a subsequent clinical trial in which desipramine showed no advantage over placebo overall in terms of cocaine use outcome, but was superior among patients with less severe cocaine dependence at treatment entry (Carroll et al. 1994). Another trial showed some promise for desipramine among cocaine-dependent patients with major depression, although the findings were not definitive (McDowell et al. 2005). Other recent trials suggest that desipramine was ineffective for opioid-dependent cocaine users with a history of depression (Kosten et al. 2004), and that the behavioral treatment regimen of voucher incentives contingent on abstinence may be effective among cocaine abusing opioid addicts with a history of depression (Gonzalez et al. 2003). Interestingly, a recent trial has shown that another noradrenergic antidepressant, bupropion, may be effective for cocaine dependence when combined with a behavioral regimen of voucher incentives contingent on abstinence (Poling et al. 2006). Studies of SRI antidepressants for cocaine dependence have been negative (Schmitz et al. 2001). At the least, the findings suggest that independent major depression should be identified and treated among cocaine-dependent patients with either medication or behavioral therapy, and that more research is needed to pursue a potential synergy between antidepressant medications such as bupropion and behavioral treatment with voucher incentives.

### Disulfiram

As alcohol and cocaine are frequently abused simultaneously, clinical trials with disulfiram (see section on alcohol dependence) were conducted with cocaine and alcohol-dependent patients (Carroll et al. 1993, McCance-Katz et al. 1993). Patients on disulfiram displayed better cocaine and alcohol outcomes, but it was not clear whether the effect on cocaine depended on a reduction in alcohol use. Another trial was conducted in strictly cocaine-dependent patients (Carroll et al. 2004), which showed that patients on disulfiram significantly reduced their use and displayed greater abstinence than those receiving placebo. The authors noted that greater benefits were accrued to patients on disulfiram who were not alcohol dependent when they began treatment, or abstained from drinking during the study, implying a direct effect of disulfiram on cocaine use. Disulfiram is an inhibitor of dopamine-β-hydroxylase, which catalyzes the conversion of dopamine into norepinephrine; inhibition of the enzyme leads to an increase in brain dopamine levels, which could counteract depletion of dopamine resulting from chronic cocaine use. It has also been hypothesized that disulfiram treatment may make cocaine use less pleasurable and more aversive. In summary, disulfiram may be considered for treatment of cocaine-dependent patients, with or without concurrent alcohol use. Guidelines for treatment of alcohol-dependent patients with disulfiram (see above section on alcohol dependence) should be consulted. Patients should be warned to remain abstinent from alcohol, because any alcohol intake will trigger an unpleasant disulfiram reaction.

### Baclofen, Topiramate, and Other GABA Active Medications

In recent years, the GABA system has received increasing attention as a potential target for pharmacotherapy of cocaine dependence, especially since it has been observed that potentiating GABA neurotransmission decreases cocaine self-administration. For example, baclofen, a GABA-B receptor agonist (frequently used as a muscle relaxant) decreased cocaine seeking in baboons (Weerts et al. 2007), cocaine self-administration in humans (Haney et al. 2006), and cocaine use in a randomized, placebo-controlled trial (Shoptaw

et al. 2003). Other GABA-B receptor modulators are also being investigated (Weerts et al. 2007, Lhuillier et al. 2007). Topiramate (Kampman et al. 2004) and tiagabine (Gonzalez et al. 2007) have shown some promise in small clinical trials. Gabapentin showed a nonsignificant trend toward prevention of relapse among patients who were abstinent from cocaine at the outset of the trial (Bisaga et al. 2006).

### Stimulant-Like Medications

There has been considerable interest in the idea of treating cocaine dependence with other stimulant-like medications in what amounts to an agonist replacement approach. Medications that have shown some promise include d-amphetamine (Grabowski et al. 2004), bupropion (Poling et al. 2006), and modafinil (Dackis et al. 2005). Findings have been mixed and more research would be needed before these can be recommended as routine treatments. However, for patients who have been refractory to other forms of treatment and present with persistent cocaine abuse, medications in this class may be worth considering. With amphetamine, the risk of the abuse liability of the medication needs to be considered, and long-acting formulations should be considered. The effect of bupropion seems to depend upon combining it with behavioral therapy, specifically contingency management. With any of these medications, stimulant-like side effects of cocaine or abused stimulants and the medications may be additive and should be monitored.

### Treating Co-Occurring Psychiatric Disorders and Cocaine Dependence

Depression is a common complaint mentioned by individuals with cocaine dependence. Depression and cocaine dependence display similar neurochemical features in terms of monoamine and other transmitter systems (see Markou et al. [1998] for review). The difficulty for clinicians is to ascertain whether a patient presents with a depressed state arising from cocaine withdrawal or intoxication, or whether there is a preexisting or independent depressive disorder. Clinicians can inquire about previous periods of abstinence lasting at least 2–3 months. The persistence of depression during an extended period of abstinence, or prior to the onset of drug or alcohol problems, is more likely to represent an independent depressive disorder.

Treatment for depression in cocaine-dependent individuals can be approached as outlined in the previous section on antidepressant medications.

Attention deficit hyperactivity disorder (ADHD) is an increasingly recognized psychiatric disorder conveying an increased risk of substance use, especially stimulants. The link between ADHD and stimulants could represent an attempt to self-medicate ADHD symptoms, or could reflect impulsive behavior (Wilens et al. 1995). In either case, it is plausible to hypothesize that treatment of ADHD symptoms could lead to improvement in substance use. A recently published double-blind trial of sustained release methylphenidate (up to 60 mg/day) for cocaine-dependent individuals with ADHD revealed a small favorable effect of the medication on one of the several cocaine use outcome measures (Levin et al. 2007). Both these trials found sustained release methylphenidate relatively safe with little abuse potential. As with depression, symptoms of ADHD may be difficult to distinguish from toxic effects of chronic cocaine use. It seems fair to conclude that cocaine-dependent patients with clear-cut childhood onset ADHD should have their ADHD treated, although again the equivocal findings of the clinical trials suggest caution in terms of how much improvement in cocaine use symptoms may be expected.

### Methamphetamines and Other Stimulants

Presently, as the use of methamphetamine is expanding across the USA, there are no known effective pharmacological methods to treat methamphetamine addiction. Animal studies are investigating specific antagonists to methamphetamines (Ginawi et al. 2005), manipulating the endocannabinoid system to prevent relapse to methamphetamines (Anggadiredja et al. 2004), or GABA(B) agonists like baclofen to decrease self-administration (Ranaldi and Poeggels 2002). Research in this area continues to be a high priority (Vocci et al. 2005).

## Marijuana and Cannabinoids

Like cocaine, cannabis found in the marijuana plant is mentioned in historical texts going back 6,000 years, although many of these records revolve around the cultivation of hemp for textile production. Smoking, eating of marijuana leaves, and use of hashish make cannabis the most widely used illegal drug worldwide, with nearly 150 million people using cannabis annually (UNODCCP 2002). However, the number of individuals seeking treatment for cannabis dependence has been low, although increasing in the past few years (SAMHSA 2003). This trend seems to be driven by several factors. (1) Marijuana is perceived as an innocuous drug in many circles, but with the increasing potency of the available cannabis, regular daily users may experience an abstinence syndrome if they decrease or stop smoking. This abstinence syndrome, which was only clearly identified in the past decade, is characterized by irritability, restlessness, insomnia, anorexia, even aggressive behavior, lasting up to several weeks after stopping cannabis, and of sufficient severity to force a return to daily smoking (Budney et al. 2003). The realization of an inability to control the use of cannabis often brings people to treatment. (2) Unlike heroin, alcohol, or cocaine, cannabis rarely brings individuals to the edge of destitution. However, some individuals realize that regular cannabis use dulls their attention and concentration, renders them inattentive to details, decreases their motivation, thus diminishing their professional acumen, or bothers their significant others. Events like being passed over for a promotion, increasingly negative performance evaluation, or repeated firings may drive home the deleterious effects of regular cannabis use. Some patients have referred to this as "their life reaching a plateau and going no further." (3) Cannabis smoking, like tobacco smoking, can lead to pulmonary disease (Joy et al. 1999), and can precipitate psychosis in individuals with increased risk of psychosis by virtue of a family history of mental illness, or smoking cannabis before the age of 15 (Arseneault et al. 2004). Hence there is an increasingly pressing need for effective treatment modalities for cannabis dependence.

Presently, there are no FDA-approved medications to treat cannabis dependence, although three leads appear promising.

Some addiction medicine physicians have been using synthetic $\Delta^9$ tetrahydrocannabinol (THC) found in the

medication dronabinol, currently approved and marketed for treatment of HIV-related wasting and chemotherapy-induced nausea, to help patients overcome the cannabis abstinence syndrome and dependence. This represents an agonist substitution strategy, similar to nicotine replacement products such as nicotine patch for cigarette smoking. Haney et al. (2004) have found that at a dose of 50 mg (10 mg, 5×/day) dronabinol reduced cannabis withdrawal symptoms, and restored psychomotor performance impaired by withdrawal. Clinical experience suggests that a model can be followed that is similar to that for nicotine replacement. Namely, the patient sets a quit date and uses dronabinol as a pharmacologically equivalent, but longer acting oral $\Delta^9$ THC substitute to stabilize and minimize withdrawal symptoms, and to abolish any urge to use cannabis. Once this is achieved, dronabinol is gradually reduced and discontinued. With this procedure in mind, clinicians report using from 20 to 80 mg/day of dronabinol to stabilize patients, with a gradual decline in the daily dosage over a period of 8–12 weeks. In the hands of one of the authors (WNR), this approach has provided satisfactory results for both the physician and the patient. A formal clinical trial of this approach using up to 40 mg/day of dronabinol is being conducted by one of the authors (FRL).

Alpha-2 receptor agonists such as clonidine or lofexidine may be helpful to treat the cannabis abstinence syndrome. Cone et al. (1988) have shown that pretreatment with clonidine reduces the increase in heart rate caused by acute cannabis use. Conversely, abstinence syndromes, be they from alcohol, opiates, or cannabinoids all involve some degree of sympathetic activation (Sell et al. 2005). Clonidine or lofexidine could be useful medications to help patients traverse the cannabis abstinence syndrome phase if it proves problematic for them.

Lastly, the FDA is currently investigating the cannabinoid antagonist rimonabant as a possible antiobesity medication. An indication for the treatment of cannabis dependence is not being sought presently. However, some human clinical investigations indicate that pretreatment with rimonabant attenuated the increased heart rate and the intoxicating effect of smoked marijuana (Huestis et al. 2007). More independent investigations are being conducted to further evaluate rimonabant as a potential therapeutic tool for cannabis dependence.

## Summary

Like the pharmacology of psychiatric disorders in general, the pharmacological treatment of substance abuse disorders is rapidly advancing, driven by active research. A number of FDA-approved medications for addictive disorders are available, including methadone, buprenorphine, and naltrexone for opioid dependence, disulfiram, naltrexone and acamprosate for alcohol dependence, nicotine replacement (patch, gum, etc.), bupropion, and varenicline for smoking cessation. Other potentially promising medications are emerging, including disulfiram and baclofen for alcohol and cocaine dependence, tiagabine for cocaine dependence, topiramate for alcohol and cocaine dependence; for which of these, data are accumulating to support their use in addiction disorders. Clinicians can expect that in the coming years, more medications will be at their disposal to assist patients in overcoming addictions to legal and illegal drugs.

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CHAPTER

# 112 Pharmacologic Issues During Pregnancy

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## Introduction

Mood disorders including major depressive disorder (MDD), minor depressive disorder, dysthymic disorder, and seasonal affective disorder are common conditions in women. A number of studies find that women are twice as likely as men to develop these illnesses (Hasin et al. 2005, Kessler et al. 1997), with the highest risk occurring during their childbearing years (Kessler et al. 1993, Kessler 2003). Given these statistics, it is not surprising that many women who are pregnant will develop a depressive disorder. It is estimated that between 14% and 23% of pregnant women will suffer from significant depressive symptoms or a depressive disorder while pregnant (Bennett et al. 2004, Gaynes et al. 2005). Although some reports find that the highest absolute risk of depression is during the third trimester (Evans et al. 2001, Hobfoll et al. 1995) recent meta-analyses do not show differences in the relative risk according to stage of pregnancy. (Bennett et al. 2004, Gaynes et al. 2005).

Some suggest that the regular prenatal care received by most pregnant women affords an opportunity to screen and treat those who are depressed. Advantages are that for some women, the only time that they will have health insurance is when they are pregnant or immediately postpartum; for other women pregnancy may be the time a young women is most likely to see a medical provider. Since depression can occur anytime in pregnancy, the relatively frequent visits to an obstetrical provider constitute multiple opportunities to screen for depressive symptoms or follow the severity of the condition. Finally, women who are pregnant are more likely to adopt positive health habits, and they may consider treatments that decrease stress and promote mental health.

On the other hand, primary-care physicians and obstetrical providers may be reluctant to identify a unipolar mood disorder during pregnancy because they may have difficulty linking the patient with mental health service and may not be comfortable treating MDD on their own. If an obstetrical provider does wish to initiate treatment, antidepressant medication is easiest to administrate in an obstetrical setting, but such treatment necessitates exposing the fetus to medication. In such instances consultation and collaboration with psychiatric providers is optimal, since together they can offer patients a treatment plan and information about the relative risks of various treatments as well as the lack of treatment. In this chapter, we review information on the risks to a fetus that is exposed to maternal depression and we provide an overview on the risks and benefits of treating depression during pregnancy, which may be helpful to providers with pregnant patients.

Some maintain that the safest strategy to protect a fetus is for the depressed mother to avoid medication. However, depression can be a devastating illness, and for some women, it is not possible to stay healthy while medication free. Moreover, there may be risks to the fetus associated with the underlying illness or associated behaviors. As an example, compared to pregnant patients who are not depressed, those with a mood disorder are more likely to smoke, use hazardous substances (alcohol or illicit drugs), have concurrent general medical and other psychiatric conditions, and are less likely to have adequate prenatal care (Kitamura et al. 1993, Misra et al. 2001, Pritchard 1994). The underlying biology of the depressive illness may also contribute to perinatal risk. Stress has been associated with adverse birth outcomes including low birth weight (LBW) and preterm deliveries (Hobel et al. 1998), and depression is a stressful illness. There is also information suggesting associations between depression and specific perinatal events including miscarriage, delivering early, delivering an LBW infant, structural anomalies, and perinatal adaptation. These topics are reviewed below.

## Stress, Mood, and Adverse Birth Outcomes

### Spontaneous Abortion

Preclinical data suggest that high levels of stress may lead to spontaneous abortion (Nepomnaschy et al. 2006). Establishing an association between stress and miscarriage in

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humans has been more difficult possibly because the majority of miscarriages occur prior to the fifth week after the last menstrual period, but studies have focused on miscarriage after 6 weeks of pregnancy. Some studies support the animal literature and suggest, specifically, that psychological stress contributes to rates of early pregnancy loss that are not attributable to malformations (Schenker et al. 1997, Neugebauer et al. 1996), but not all studies agree (Klebanoff et al. 1990). Interestingly, one study found that urinary cortisol levels were elevated in women who went on to miscarry, compared to women who did not experience early miscarriage (Nepomnaschy et al. 2006).

There have been fewer investigations into a possible association between a depressive disorder and miscarriage. Among women with recurrent spontaneous abortion, depressive symptoms conferred a higher risk of subsequent miscarriage, although the group of women who conceived ($n$ = 41) was small. A cohort study ($n$ = 972) of women identified as pregnant in an emergency room setting did not find differences in risk of spontaneous abortion according to level of depressive symptoms (Nelson et al. 2003).

## Preterm Delivery and LBW

There is substantial evidence that maternal stress (Copper et al. 1996, Hedegaard et al. 1993, Misra et al. 2001, Paarlberg et al. 1995, Reeb et al. 1987, Zimmer-Gembeck and Helfand 1996, Wadhwa et al. 1993) and depression (Hoffman and Hatch 2000, Oberlander et al. 2006, Orr et al. 2002, Steer and Scholl 1992) are associated with preterm delivery (PTD) and delivery of an LBW baby or a small for gestational age (SGA) infant, although not all studies agree (Andersson et al. 2004, Brooke et al. 1989, Chung et al. 2001, McCormick et al. 1990, Suri et al. 2004).

Using the Beck Depression Inventory (BDI) (range 0–63) administered at 28 gestational weeks to determine depressive symptoms, researchers found that scores of ≥21 significantly predicted an increase in PTD and LBW in the offspring of adult women, but not adolescents (Steer and Scholl 1992). Negative findings in adolescents may be due to the fact that the BDI detects adjustment problems rather than depression in this age group (Steer and Scholl 1992), or it may be a result of the small cohort size and limited power to detect differences in birth weight or length of gestation in a group already at high risk of these outcomes. Nonetheless, the adjusted odds ratio for PTD among adult women was 3.4 (95% CI 3.3–3.6), whereas the odds ratio for LBW delivery was 3.9 (95% CI 3.8–4.2). There was an increment in the risk of lighter birth weight or shorter gestation: a one point increase on the BDI elevated the risk of PTD by 7% and LBW baby by 6%.

Investigators in a pregnancy study that used the Center for Epidemiological Studies Scale for Depression (CES-D) (range 0–60) found that women in the most symptomatic group were at high risk of PTD (Orr et al. 2002). The median CES-D score among the 1399 pregnant African-American women was 16, a threshold used to identify individuals at high risk of depression (Radloff 1977). Researchers compared the top decile of symptomatic women to the remaining group of gravidas. Women in the top decile had scores ranging from 33 through 57. Spontaneous PTD occurred in 12.7% of this symptomatic group but only in 8.0% in the remaining cohort. After adjusting for drug use, low prepregnancy weight, smoking, and previous poor perinatal outcome, the risk of PTD among high CES-D scorers was 1.96 (95% CI = 1.04–3.7).

In an investigation (Andersson et al. 2004) that assessed perinatal risk for women who had a depressive disorder diagnosis generated by administration of the Patient Health Questionnaire (PHQ) (Spitzer et al. 2000), investigators did not find an association between diagnosis of a mood or anxiety disorder and deliveries that were preterm, LBW, or SGA. However, the number of women with these illnesses was small, hence limiting power.

Among all of these studies is the profound problem of adequately controlling for negative health habits that are not equally distributed among depressed and nondepressed pregnant women. One investigation attempted to account for possible confounding factors through the use of propensity scores and found that the risk of LBW delivery was still higher among women suffering from a depressive illness (Oberlander et al. 2006).

## Congenital Anomalies

Some of the most problematic adverse perinatal outcomes are development of congenital malformations. We are unaware of studies that controlled for medication use and specifically investigated whether there is an association between depression during pregnancy and the development of congenital malformations in the child. On the other hand, there is a single study that assessed associations between severe life stress during the first trimester of pregnancy, such as having a spouse or a child develop and/or succumb to a life-threatening illness, and risk of neural-crest defects (Hansen et al. 2000). The type of anomalies that were investigated in this national linkage study included craniofacial and conotruncal heart defects (e.g., double-outlet ventricle, tetralogy of Fallot, and ventricular septal defects). To the extent possible in a linkage study, investigators controlled for medical conditions and health habits that could have confounded an association including seizure disorders, diabetes, alcohol abuse, and smoking, although residual confounding from these or other poor health behaviors may be responsible for the presumed association.

In summary, the literature does not support an association between depression and subsequent miscarriage. High levels of stress may increase the risk of early miscarriage, although more work is needed to definitely establish this association. Similarly, stress has been associated with PTD, early delivery, and congenital malformations. Depression may also be associated with PTD or delivery of an LBW baby, although definitive studies are needed.

## In Utero Exposure to Antidepressants and Birth Outcomes

Over 80% of women will take a medication at some point in their pregnancy (Headley et al. 2004). The rate of antidepressant use during pregnancy is about 13% (Cooper et al. 2007) and tends to be higher during the early first trimester, before women confirm a pregnancy (Yonkers, unpublished data). Thus, many fetuses are exposed to antidepressants in utero, but given the likelihood that a woman may also take other medication, the possible effects of antidepressants need to be differentiated from those of other compounds.

While many antidepressants agents are currently available, in current practice the selective serotonin reuptake inhibitors (SSRIs) are most commonly used. Pregnant women are also more likely to be undergoing treatment with SSRIs than with other antidepressants (Cooper et al. 2007).

## Spontaneous Abortion

Several investigations have found that women taking antidepressants are at higher risk of spontaneous abortion (Chambers et al. 1996, Chun-Fai-Chan et al. 2005, Einarson 2001, Einarson et al. 2003, Kulin et al. 1998, Pastuszak et al. 1993, McElhatton et al. 1996). A meta-analysis of studies completed prior to 2005 ($n$ = 3567) showed that 8.7% of controls and 12.4% of pregnant women exposed to antidepressants had a spontaneous abortion (RR = 1.45; 95% CI = 1.19–1.77) (Hemels et al. 2005). While risk was significantly higher in women who were taking SSRIs compared to controls (12.4% vs. 8.4%; RR = 1.52%; 95% CI = 1.17–1.98), differences were not significant between the various classes of antidepressant agents. The possible effects of an underlying illness and confounding health habits were variably controlled among the studies included in this meta-analysis.

## Preterm Delivery

PTD has been associated with tricyclic and SSRI use (Chambers et al. 1996, Costei et al. 2002, Djulus et al. 2006, Ericson et al. 1999, Kallen 2004b, Simon et al. 2002) and may be greatest for exposures occurring during the third trimester (Chambers et al. 1996, Costei et al. 2002, Kallen 2004b). Fortunately, these deliveries tend to be shortened by 1 week or less in those exposed compared to those not exposed (Simon et al. 2002, Sivojelezova et al. 2005, Einarson et al. 2003), although very premature deliveries are far less common and may not be detected unless sample sizes are large. While this literature shows differences in outcomes for women who took antidepressants compared to those who did not take antidepressants, there are little differences between classes of antidepressant medication associated with these outcomes (Djulus et al. 2006, Sivojelezova et al. 2005). Thus, it remains possible that this effect is the result of some unmeasured factor not related to the specific drug, including the underlying illness, health habits, or other characteristics of the exposed cohort. In the few studies that have attempted to analytically control for the underlying illness, one found that SSRIs no longer increased risk of PTD (Oberlander et al. 2006), while the other showed continued risk of PTD among SSRI users (Simon et al. 2002).

## Low Birth Weight

Reductions in overall birth weight, or an increased likelihood of either delivering an LBW or an SGA infant, have been found after in utero exposure to SSRIs (Kallen 2004a, Oberlander et al. 2006, Simon et al. 2002) and TCAs (Kallen 2004a). However, large linkage studies have been required to show these events since the increase in risk was typically small. In one study, the risk of SGA went from 7.4% among those exposed to an SSRI to 8.5% among controls (Oberlander et al. 2006). Attempts to control for maternal depressive illness do not appear to remove the risk of delivering smaller babies (Simon et al. 2002, Oberlander et al. 2006). In the later report, the difference in risk of delivering an SGA infant for mothers who had a history of depression and took SSRIs compared to moms with a similar history and personal characteristics but no antidepressant exposure was 3.3% (95% CI = 0.7%–5.9%) (Oberlander et al. 2006).

## Congenital Malformations

### Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been marketed for many years. Therefore, they have the longest history of use during pregnancy. They are used less frequently now because of side effects including dry mouth, constipation, sedation, and orthostatic hypotension. In general, nortriptyline and desipramine are preferred tricylics for use during pregnancy because they are least likely to cause anticholinergic effects and exacerbate the orthostatic hypotension that may occur during pregnancy (Eberhard-Gran et al. 2005).

To date, studies do not support an association between major malformations in neonates born to mothers who used TCAs during pregnancy (Altshuler et al. 1996, McElhatton et al. 1996). The European Network Teratology Service collected and evaluated prospective data on 689 pregnancies of which 330 were exposed to TCAs (McElhatton et al. 1996). Exposure in the first and second trimester occurred in 74% of the pregnancies, and 23% of women took TCAs throughout pregnancy. There was no overall increase in the rate of major malformations in the live-born infants. Similar results were found by Simon and colleagues (2002), who conducted a historical cohort study of 209 infants exposed to TCAs during the first trimester.

### Serotonin Reuptake Inhibitors

There are conflicting reports as to the teratogenic risk associated with in utero SSRI use. A recent meta-analytic study (Einarson and Einarson 2005) compared outcomes in 830 infants exposed to SSRIs or bupropion and 934 infants not exposed to these agents. There was no increase risk of major malformations among those who were exposed. Similarly, results from a large Finnish cohort showed no increase in major malformations attendant to in utero SSRI exposure (Malm et al. 2005). Conversely, a Danish linkage study found that fetuses exposed to SSRIs during the second or third month or pregnancy were at higher risk of malformations when compared to children who were not exposed to an SSRI (6.8% vs. 3%; RR = 1.84; 95% CI = 1.25–2.71) (Wogelius et al. 2006). Offspring who were exposed during peak embryogenesis had the highest risk. Twenty-nine percent of malformations identified were cardiovascular, although the specific type was not reported.

A Swedish Medical Birth Registry (Kallen and Otterblad Olausson 2006), a study of three European Teratogen Information Services (Diav-Citrin et al. 2005b), and a historical cohort study using a large HMO database (GSK 2006) have also recently reported 1.8–2.0 higher rates of congenital heart disease among infants whose mothers received paroxetine, but not other antidepressants. Recent work finds that malformations were predominantly atrial and ventricular septal defects and were associated with use of 25 mg or more of paroxetine during the first trimester (Bérard et al. 2007). However, two case cohort studies with large sample sizes specifically tested for associations between septal defects and paroxetine and did not replicate

the previously noted relationship (Alwan et al. 2007, Louik et al. 2007).

### Bupropion

Bupropion is an antidepressant that inhibits norepinephrine and dopamine. Results from the first prospective study of pregnancy outcomes among children exposed to bupropion for depression or smoking cessation used "another antidepressant" control group and a "no antidepressant" control group (Chun-Fai-Chan et al. 2005). Results did not show major malformations above the baseline of 1–3% among antidepressant-exposed women. Subsequent to that study, a report emerged from the GlaxoSmithKline Bupropion Pregnancy Registry, suggesting a higher-than-expected frequency of neonatal cardiac malformations. To further investigate a possible association, several large databases were analyzed although findings have not yet been published in peer-reviewed literature (GSK 2006). In one of these analyses, Cole and colleagues (2006) presented a study in which the population was drawn from the Ingenix Research Data Mart (RDM), which contains medical and pharmacy claims data from United Healthcare-affiliated health plans. They identified all women who dispensed bupropion ($n = 1213$) or other antidepressants who had live-born deliveries between 1995 and 2004. Two comparison cohorts were created consisting of: (1) women dispensed bupropion within 18 months before delivery or after the estimated first trimester of pregnancy and before delivery ($n = 1049$). (2) women dispensed antidepressants other than bupropion during the estimated first trimester or before the first trimester with days extending into the first trimester ($n = 4743$). There were no significant differences between groups in the rate of major malformations. All women in this analysis took an antidepressant agent, and so there were no "unexposed" infants that could be assessed. However, the general population rate for cardiac malformations is about 1%, which is slightly lower than the rate of 1.5% seen for babies that were exposed to paroxetine in utero.

### Monoamine Oxidase Inhibitors

In a study of 21 prenatal exposures to monoamine oxidase inhibitors (MAOIs) in pregnancy, there was a relative risk of 3.4 for congenital malformations (Heinonen et al. 1999). Although this study was small, other risks associated with MAOI use, including the risk of a hypertensive crisis, contribute to recommendations that these medications should not be used in pregnancy.

### Other Antidepressants

Other antidepressants that do not fall into either the TCA or the SSRI class, including venlafaxine (Einarson 2001), trazodone (Einarson et al. 2003), and mirtazapine (Djulus et al. 2006), have been the focus of small studies. None of these investigations reported higher rates of malformations with the various antidepressants under study.

There are limited data regarding the risks associated with atypical antipsychotics but the increasing time that these agents have been available has led to an increase in information about possible effects in pregnancy. An uncontrolled, administrative database that included outcomes to women exposed to risperidone during pregnancy showed that rates of malformations and spontaneous abortion were no higher than expected population rates (3.8% and 16.9%, respectively) (Coppola et al. 2007). However, this was based on prospective outcomes to only 68 women. Notably, the retrospectively reported cases had much higher rates of malformations, but it is difficult to interpret these findings given the risk of reporting bias.

The newer atypical antipsychotic olanzapine is used to control psychosis and mania. The pharmaceutical company registry of prospectively ascertained cases found that 13% of women experienced for spontaneous abortion, 5% had a still birth, 5% delivered preterm, and no infants exposed in utero were born with malformations (Goldstein 2000). Although these are also uncontrolled data, the rates are within the range expected for nonexposed populations. Other complications sporadically noted among pregnant women undergoing treatment with olanzapine were gestational diabetes and preeclampsia (Kirchheiner et al. 2000). Diabetes has been associated with the use of olanzapine in nonpregnant populations and may be a consequence of insulin resistance and/or weight gain (Dickson 1998, Guo et al. 2007).

## Perinatal Complications

Other perinatal complications concurrent with late pregnancy use have been reported in association with antidepressant use. A six-fold increased risk of persistent pulmonary hypertension (PPHN) was found among newborns whose mothers were treated with SSRIs after 20 weeks of gestation compared to controls (Chambers et al. 2006). The absolute risk with exposure is 6–12 per 1000 in comparison to 1–2 per thousand and was only found for SSRI, not TCA exposure. There was no increase in risk of PPHN for babies born to women who took SSRIs prior to 20 weeks or to children born to women who took a non-SSRI medication. While this study has not been replicated, it follows up on a nonsignificantly higher rate of PPHN found by the same group in an earlier cohort study (Chambers et al. 1996). This study suggests that considerations other than malformation rates attendant upon first trimester exposure may need to be considered by patients and their clinicians. However, it should be emphasized that the absolute risk was very small and this should be weighed against the possible risk of maternal relapse into depression during pregnancy.

Respiratory distress has also been found documented by other workers who investigated the consequences of in utero exposure to SSRIs (Kallen 2004b, Costei et al. 2002) and TCAs (Kallen 2004b). Rates of respiratory distress remain higher in neonates exposed to SSRIs even after controlling for maternal depressive illness (Oberlander et al. 2006).

Other complications to neonates exposed to SSRI antidepressants include outcomes such as low APGAR scores, and convulsions (Sanz et al. 2005) have been reported as higher in some studies evaluating the effects on neonates for women who took SSRIs (Kallen 2004b, Costei et al. 2002) or TCAs (Kallen 2004b) during the third trimester compared to controls (cf. Moses-Kolko et al. (2005) for a review). It is not clear whether these effects are due to "withdrawal" or are a type of fetal toxicity. While some have suggested that these possible complications can be obviated by tapering the medication prior to delivery, this strategy could hypothetically lead to fetal distress in utero (Moses-Kolko et al. 2005).

At this point, there is a paucity of data regarding the long-term consequences to children who are exposed to

antidepressants in utero. For infants exposed to antidepressants, neither neurocognitive effects at 6–9 months after delivery (Nulman and Koren 1996, Nulman et al. 2002) nor attention-deficit and externalizing behaviors are associated with antidepressant use (Oberlander et al. 2007).

### Electroconvulsive Therapy

Women who are severely and acutely ill, not eating, or psychotic may require inpatient hospitalization to save the mothers' life and the life of her baby. In such instances, electroconvulsive therapy (ECT) may provide life-saving treatment. Additionally, in a number of countries outside the United States, many psychiatrists prefer ECT, given the uncertain effects of antidepressant drugs on the health of a fetus. While there are no prospective controlled trials of ECT in pregnancy, a comprehensive review of 300 case reports is was published in 1994 (Miller 1994). Of those 300 cases, 28 cases (9%) reported complications including mild cardiac arrhythmia with no sequela in nine, three with vaginal bleeding that resolved, two with uterine contractions that resolved, four with preterm labor and five with miscarriage well after the ECT treatments, three with still births not related to ECT, and five with congenital malformations. In the later set, too little detail was available to determine the likelihood of causality in most reports although one mother received treatment with phenobarbital. The results of this qualitative review do not support a high level or risk for ECT treatment in pregnancy, a view also reflected in a second review (Stewart and Robinson 2001). Nonetheless, careful monitoring and several precautions should be used when performing ECT with pregnant women (Miller 1994, Yonkers et al. 2004). Delayed gastric emptying that often occurs in pregnancy may prompt intubation with a pediatric cuff or administration of an antacid to decrease gastric pH. Anticholinergic medication prior to ECT can lower esophageal sphincter tone and should be avoided if possible in pregnant women.

## Psychotherapy

A 16-week controlled clinical treatment trial compared Interpersonal Psychotherapy for Antepartum Depression (IPT-P) to a Parenting Education Program (PEP) control group (Spinelli 2001). Fifty outpatient antepartum women who met DSM-IV-TR criteria for MDD were recruited to receive either the IPT-P treatment ($n$ = 25) or the PEP control ($n$ = 25). Thirty-eight women were included in the data analysis. Depressed mood was measured by the Edinburgh Postnatal Depression Scale (EPDS), the BDI, and the Hamilton Depression Rating Scale (HAM-D). The IPT-P treatment group showed significant improvement compared to the PEP control group on all three measures of mood at termination. The mood of the IPT-P treatment group improved significantly more than PEP control on all scores of EPDS ($p$ = 0.005) and HAM-D ($p$ = 0.02) and BDI (0.02). Recovery criteria was met in 60% of the IPT-P treated women according to the CGI < 2 ($p$ = 0.011). In addition, there was a significant correlation ($p$ = <0.05) between maternal mood and mother–infant interaction.

### Antipsychotics

Some women with a unipolar mood disorder may express psychotic symptoms and require treatment with an antipsychotic agent. While most of the available data are derived from women who suffer from schizophrenia and bipolar disorder, a brief review is included that may be useful to managing women with a psychotic depression. A general rule to follow when using a medication to treat a pregnant woman is to use medications that have been on the market for a longer period of time and have better-known fetal safety profile (Diav-Citrin et al. 2005a). Overall, high-potency antipsychotics may be a first choice for use during pregnancy because of anticholinergic effects associated with low-potency agents. Additionally, one meta-analysis (Altshuler et al. 1996) found a small but statistically significant increase in the relative risk of congenital malformations in fetuses exposed to low-potency antipsychotics in the first trimester of pregnancy.

### Haldol

Haloperidol is a high-potency butyrophenone with a long history of use during pregnancy. In a multicenter prospective controlled study conducted within the European Network of Teratology Information Services (ENTIS), 215 offspring were exposed to haloperidol ($n$ = 188) and penfluridol ($n$ = 27), including 78% in the first trimester (Diav-Citrin et al. 2005a). Children from these pregnancies were compared to 631 ENTIS controls. The rate of congenital anomalies did not differ between the exposed group and the control group. There were two cases of limb defects in the butyrophenone group (one with haloperidol and one with penfluridol), which was no higher than the expected base rate. However, babies exposed to antipsychotic agents had twice the rate of PTD (13.9% vs. 6.9%; $p$ = 0.006) and significantly lower median birth weights compared to controls.

### Atypical Antipsychotics

The use of atypical antipsychotics in the treatment schizophrenia has resulted in an increased number of pregnancies for these women. Unlike the older antipsychotic medications, the newer drugs do not impair fertility with the exception of risperidone, which may increase prolactin levels. Women with schizophrenia are more likely to have unplanned pregnancies, which results in delayed prenatal care and risky behaviors that may place the mother and fetus at risk. Schizophrenia itself has been known to be associated with adverse outcomes such as pregnancy and delivery complications and poor neonatal health (Yaeger et al. 2006).

The atypical antipspychotics have also gained popularity in the use of other psychiatric disorders. In the first prospective comparative study documenting pregnancy outcomes of women taking atypical antipsychotics, McKenna et al (2005) followed patients with varying diagnoses including schizophrenia, bipolar disorder, schizoaffective disorder, psychoses, psychotic depression, obsessive compulsive disorder, posttraumatic stress disorder, and schizophreniform disorder. They combined outcomes for women who were undergoing treatment with olanzapine ($n$ = 60), risperidone ($n$ = 49), quetiapine ($n$ = 36), and clozapine ($n$ = 6). While there was no significant difference between the rates of major malformations, prematurity, or neonatal complications, there was a nonsignificant increased rate of spontaneous abortions and elective abortions and a significant increase in the likelihood of delivering an LBW baby.

### Risperidone

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### Olanzapine

The newer atypical antipsychotic olanzapine is used to control psychosis and mania. The pharmaceutical company registry of prospectively ascertained cases found that 13% of women experienced for spontaneous abortion, 5% had a still birth, 5% delivered preterm, and no infants exposed in utero were born with malformations (Goldstein 2000). Although these are also uncontrolled data, the rates are within the range expected for nonexposed populations. Other complications sporadically noted among pregnant women undergoing treatment with olanzapine were gestational diabetes and preeclampsia (Kirchheiner et al. 2000). Diabetes has been associated with the use of olanzapine in nonpregnant populations and may be a consequence of insulin resistance and/or weight gain (Dickson 1998, Guo et al. 2007).

### Mood Stabilizers

#### *Lithium*

Lithium use in pregnancy has been comprehensively reviewed by the Institute for Evaluating Health Risks (Moore 1995). There are multiple sources of lithium exposure, including drinking water. Medicinal lithium requires much higher doses of the ion. Alarm was raised by earlier reports from the International Registry of Lithium Babies (Schou et al. 1973), a voluntary physician-reporting database, which noted a 400-fold increased rate for cardiovascular malformations. The malformation that raised the greatest concern was Ebstein's anomaly, which is a downward displacement of the tricuspid valve along with right ventricular hypoplasia. Subsequent investigations found that 1/1000 (0.1%) to 2/1000 (0.05%) babies exposed to in utero lithium treatment will have Ebstein's anomaly; this is 20–40 times higher than rates in the general population (Edmonds and Oakley 1990, Jacobson et al. 1992, Cohen et al. 1994). In a population-based study from a large administrative database (Kallen and Tandberg 1983) the odds ratio for any cardiac malformation was 7.7 (5% CI = 1.9–7.7), although none of these anomalies were Ebstein's type. There was still an elevation in the odds ratio for any malformation (OR = 3.3; 95% CI = 1.2–9.2) in this study.

Other complications that have been reported among offspring exposed to medicinal lithium in utero include fetal growth restriction (Jacobson et al. 1992, Moore 1995), acute lithium toxicity in neonates (Ananth 1976, Moore 1995), and possibly neonatal mortality (Moore 1995, Stewart 1988). Long-term data are limited but available information does not support neurodevelopmental complications from medicinal in utero exposure to lithium (Jacobson et al. 1992, Schou 1976).

#### *Valproic Acid*

Valproic acid is a teratogen and its use during pregnancy is associated with neural tube defects in about 5–9% of exposed offspring (Omtzigt 1992b, Kennedy and Koren 1998). Neural tube-related teratogenicity occurs early, at 17–30 days postconception, and is worrisome because by the time women typically realize that they are pregnant their offspring may have already been exposed. The risk of neural defects is dose related (Omtzigt 1992a, Jager-Roman 1986).

As with lithium and carbamazepine (see below), fetal growth restriction (Jager-Roman 1986) has been found among babies exposed to valproic acid in utero. Additional possible complications include decelerations (Jager-Roman 1986), withdrawal symptoms of irritability, jitteriness, feeding difficulties, abnormal tone (Kennedy and Koren 1998, Felding and Rane 1984), and hypoglycemia (Thisted and Ebbesen 1993). Case reports include possible difficulties with reductions in neonatal fibrinogen levels (Majer and Green 1987) and mental retardation (DiLiberti et al. 1984).

#### *Cabamazepine*

Carbamazepine is also considered a human teratogen. As with valproic acid, neural tube defects are prominent, occurring in 0.5% and 1% of fetuses exposed in utero (Jones et al. 1989, Rosa 1991). Other anomalies that have been noted include craniofacial defects (11%), fingernail hypoplasia (26%), and developmental delay (20%) among live-born offspring (Jones et al. 1989).

The teratogenic potential of carbamazepine may be caused by the toxic epoxide metabolites (Lindhout 1992). Oxcarbazepine does not produce the epoxide metabolite, but lower teratogenic potential has not been confirmed by empirical data.

Carbamazepine exposure in pregnancy has also led to babies that are lighter (about 250 g) (Diav-Citrin et al. 2001) and have smaller head circumference (standardized for gestational age and sex) (Hillesmaa et al. 1981).

#### *Lamotrigine*

Lamotrigine is approved for treatment of bipolar depression and relapse prevention. Workers who maintain the Lamotrigine Pregnancy Registry maintained by GlaxoSmithKine presented possible consequences of lamotrigine exposure among 785 exposures with prospective follow-up data (Cunnington et al. 2005). In this data set, defects among infants exposed were similar to the base rate estimated for nonexposed populations. However, unpublished results from the North American Antiepileptic Drug Pregnancy Registry suggest a possible association in utero exposure to lamotrigine and cleft palate (Communication with GSK, July 2007). A small follow-up study of 23 infants exposed demonstrated no alterations in development at 12 months of age (Mackay et al. 1997).

## Perinatal Complications

Exposure to lithium in utero increases the risk of neuromuscular complications, respiratory difficulties, cardiac arrhythmias, and renal and hepatic dysfunction among neonates (Moore 1995, Newport et al. 2005). The likelihood of complications increases as levels of exposure increase, so decreasing the dose to the lowest effective dose during pregnancy is optimal (Newport et al. 2005). Complications among

neonates exposed in utero exposure to antipsychotic agents have also been reported and include hypertonicity, motor restlessness, tremor, and difficulty with feeding (Trixler et al. 2005). Symptoms are rare and generally resolve within days.

## Benzodiazepines

Benzodiazepines fall into three categories: long acting (diazepam and chlordiazepoxide), intermediate acting (clonazepam and lorazepam), and short acting (alprazolam). These are the most commonly used medications in the United States. All are assumed to be excreted into the breast milk and diffuse readily across the placenta to the fetus. The data on the use of these drugs in pregnancy are conflicting, often because of the differences in methodology. However, if administered near term they may induce sedation, fetal dependence, or withdrawal symptoms (Iqbal et al. 2002).

A meta-analysis pooled data from case–control studies (Dolovich et al. 1998). The seven cohort studies demonstrated no association between first trimester fetal exposure to benzodiazepines and major malformations (OR = 0.90; 95% CI 0.61–1.35), while four case–control studies showed that major malformations were associated with the use of benzodiazepines during pregnancy (OR = 3.01; 95% CI 1.32–6.84). Specifically, the latter association showed a relationship between oral clefts and benzodiazepine use only among case–control studies (OR 1.79 95%:1.13–2.82) (Dolovich 1998). The results from case–control studies of the relationship between benzodiazepine exposure and cleft lip or palate have suggested a risk rate of about 11:10,000, which translated into an increase of about 80% over the base risk of 6:10,000 in the general population.

### Diazepam and Chlordiazepoxide

Investigations of single agents such as diazepam or chlordiazepoxide yield conflicting data for major malformations (Iqbal et al. 2002, Aarskog 1975, Saxén 1975, Rosenberg et al. 1983, Milkovich and van den Berg 1974), although an increased rate of congenital cardiac malformations with chlordiazepoxide cannot be ruled out (Czeizel et al. 2004). A case-time-control study reported (Kjaer et al. 2007) an increased risk of neural tube defects and facial clefts and limb deficiencies in mothers exposed to diazepam in the first trimester compared to later in gestation. Furthermore, the authors recommend that benzodiazepine doses should be tapered in weeks before delivery if possible to avoid potential "floppy baby," neonatal withdrawal, or other toxic defects.

### Clonazepam

While there have been various case reports of congenital malformations and other adverse effects with clonazepam (Iqbal et al. 2002), no adequate studies have determined the risk of congenital anomalies in the fetus of mothers exposed to the drug. Clonazepam is metabolized by hydroxylation, a metabolic pathway that is generally impaired in newborns, so respiratory depression must be monitored in the neonate and the nursing infant (Iqbal et al. 2002).

### Lorazepam

Lorazepam is a high-potency benzodiazepine with a half-life of 12 hours in adults. Newborn elimination is slow (up to 8 days in a newborn and shorter for premature infants). Lorazepam and its pharmacologically inactive glucuronide metabolite do not cross the placenta as easily as other benzodiazepines. The metabolite does not accumulate in the tissues. Cord blood concentrations have been reported to be lower than maternal concentrations. No epidemiological studies have reported congenital anomalies in infants of mothers who were treated with lorazepm during pregnancy (Iqbal et al. 2002); however, Bonnot et al. (2001) reported data from a French registry of congenital malformations using a case–control approach. A significant association was found between lorazepam and anal atresia.

### Alprazolam

Alprazolam has a shorter half-life than other benzodiazepines (10–24 hours) and readily crosses the placenta. One prospective study found no association with alprazolam and congenital anomalies (St Clair and Schirmer 1992), while other work did demonstrate congenital defects (Iqbal et al. 2002). Alprazolam is assumed to be capable of increasing the risk of various congenital abnormalities when administered during the first trimester.

## Perinatal Effects

Overall, benzodiazepine use in the last month of pregnancy has been associated with CNS and respiratory depression in the newborn, particularly in long-acting benzodiazepines. Other neonatal consequences of short-acting benzodiazepines include case reports of withdrawal symptoms (Iqbal et al. 2002) including hypertonia, hyperreflexia, crying, tremors, apnea, and diarrhea and vomiting. This is particularly true for premature infants. Symptoms of higher doses during labor may induce "floppy baby syndrome" and respiratory problems (Iqbal et al. 2002).

As a general rule, exposure to benzodiazepines in the first trimester should be avoided but is not absolutely contraindicated. To avoid risk, benzodiazepines with long safety records should be prescribed as monotherapy at the lowest effective dosage for the shortest possible duration. Daily dosages should be divided into at least two doses, and tapering prior to delivery may help.

# Pharmacotherapy During Lactation

Psychotropic medications are typically alkaline and, because of the need to access the central nervous system, are lipid soluble. These characteristics promote diffusion into breast milk. There may be different consequences to a baby's exposure to a specific blood level compare to an adult because babies have immature renal and hepatic systems. Moreover, a baby's blood–brain barrier is more permeable, and this may render the baby more vulnerable to side effects. Several excellent reviews of the use of psychotropic medications in lactating women are available (Bar-Oz et al. 2000, Burt et al. 2001, Eberhard-Gran et al. 2006, Gentile 2006, 2007). A number of factors should be considered when discussing the possibility of psychotropic treatment for a mother who plans to nurse. Among these issues are the benefits of breastfeeding to the infant, the severity of the mother's symptoms if left untreated, mother's and her partner's preference, and the potential risk to the infant should psychotropic drugs be ingested via breast milk.

There are a number of reasons that serum levels of a drug will differ from one neonate to another. If the baby was exposed to a psychotropic agent during pregnancy, he or she

will have higher neonatal levels if also given the medication only through breast milk (Wisner and Perel 1996). Genetic differences will lead to metabolic differences between mothers, and genetic differences can also influence metabolism in babies. Mothers may or may not exclusively breastfeed, and the less the total exposure to breast milk with a psychotropic, the lower the exposure in the infant. Assays of breast milk concentration may differ, depending on how soon after taking a daily dose the milk was collected, what section of the breast milk was collected (foremilk or hindmilk) (Stowe et al. 1997, 2000), and the number of days postpartum.

If a mother elects to breastfeed, the infant should be monitored for problems with sucking, fussiness, tremulousness, muscle rigidity, difficulties with arousal, failure to gain weight, and sleep and state disturbances, as well as the onset of other difficulties.

## Benzodiazepines

All benzodiazepines are secreted into breast milk. For diazepam these findings have correlated with sedation and weight loss in the neonate. For drugs with a long half-life, caution should be exercised during breastfeeding and the infant monitored for sedation and respiratory depression. For short-acting benzodiazepines, caution should always be advised and the neonate monitored for drowsiness in addition to withdrawal symptoms (Iqbal et al. 2002).

## Antidepressants

Elevated infant plasma levels for each drug are defined as those above 10% of the average maternal level (Weissman et al. 2004). While nortriptyline, paroxetine, and sertraline produce undetectable infant plasma levels, fluoxetine produces the highest proportion (22%) of infant levels that are elevated above 10% and citalopram produces elevated levels at 17%.

### Tricyclic Antidepressants

TCAs are excreted into human breast milk in low concentrations with a wide range of reported infant serum concentrations (Whitby and Smith 2005). In one study, the authors determined that the average daily dose of the nursing infants was about 1% of the maternal dose/kg (Yoshida et al. 1997). According to a review by Misri and Kostaras (2002), no adverse events have been reported for desipramine, amitriptyline, imipramine, nortriptyline, and clomipramine. However, in two cases doxepin was found to have an active metabolite with long half-life. Exposure was associated with hypotonia, respiratory depression, and jaundice, and doxepin is generally not recommended for use in breastfeeding infants (Misri and Kostaras 2002).

Four clomipramine-treated breastfeeding mother–infant pairs were assessed for serum concentrations of clomipramine, N-desmethylclomipramine, and corresponding 8-hydroxymetabolites. Parent drug and metabolites were nondetectable or below the quantifiable limit in the sera of all infants. No adverse clinical effects were observed (Wisner et al. 1995).

### Serotonin Reuptake Inhibitors

#### *Paroxetine*

The amount of paroxetine appears to be minimal with respect to the maternal drug concentrations (Gentile 2007). The relative infant dose for the suckling infant is lower than that reported for fluoxetine and citalopram, but higher than that reported for sertraline and fluvoxamine. In more than 120 case reports, three infants had adverse effects, which included one case of acute pain response; one case of lethargy, poor weight gain, and hypotonia; and one case of irritability.

#### *Sertraline*

Breastfed infants have undetectable serum concentrations of sertraline and its metabolite, and only one out of >120 cases showed a higher drug concentration. There was one case of altered acute pain response, one case of benign neonatal sleep myoclonus, and one infant with agitation, crying, insomnia, and startle (Gentile 2007).

#### *Citalopram*

In 75 mother–infant pairs who were exposed to citalopram (Gentile 2007), only one infant reported adverse effects. One case was a child who was a late walker, one case was of uneasy sleep, and one case was of colic, poor feeding, and restlessness. Franssen et al. (2006) presented a recent case of intensified therapeutic drug monitoring of citalopram in mother and newborn infant after clinically observing SSRI-associated symptoms from 2 weeks until 2 months after delivery. The SSRI-associated symptoms observed in the infant (up to 3 weeks after delivery) were irregular breathing, sleep disorders, hypotonia, and hypertonia. We conclude that the SSRI-associated symptoms in the infant represent citalopram withdrawal effects rather than side effects caused by breastfeeding.

#### *Escitalopram*

Escitalopram is excreted into breast milk. The total relative infant dose for escitalopram plus its desmethyl metabolite was 5.3% (Rampono et al. 2006). Of nine reported cases, all met developmental milestones and no adverse effects were seen. The absolute infant dose seemed to be lower than that for the equivalent antidepressant citalopram. Hence, escitalopram should be preferred over citalopram for breastfeeding women (Gentile 2007).

#### *Fluoxetine*

The concentration of fluoxetine in breast milk represents a significant predictor of the total infant serum concentration of the drug. The amount of drug transferred to an infant depends largely on the maternal drug concentration. Fluoxetine has an active metabolite norfluoxetine with a long half-life that predicts high concentrations in the neonate, and a significant number of adverse events have been reported in neonates. In over 200 case reports compiled by Gentile (2007), several adverse events have been described including elevated platelet serotonin levels, high rate of admissions to infant care units, colic, irritability, fever, and hyperactivity.

#### *Fluvoxamine*

More than 10 cases of fluvoxamine in the literature provide overall reassuring results with only one case of spontaneously resolved neonatal jaundice (Gentile 2007).

### Serotonin Norepinephrine Reuptake Inhibitors

Gentile's (2007) analysis of venlafaxine describes 15 reported cases free of adverse events. Ilett et al. (2002) evaluated six

women and seven infants to determine plasma concentrations and effects of the drugs on the infants. Venlafaxine was detected in the plasma of one infant, while O-desmethyl venlafaxine (ODV) was detected in four infants. All infants were healthy, and mean total drug exposure was 6.4%, which was below the 10% national level for concern. Breastfed infants should be monitored carefully since ODV was detected in four infants.

## Other Antidepressants

### *Buproprion*

Buproprion accumulates in human breast milk in concentrations much higher than that in maternal plasma. Two metabolites are also excreted into the milk. Neither buproprion nor its metabolites are detected in the infant's plasma, indicating that accumulation did not occur in the infant (Briggs et al. 2002). Results from four studies indicate that the daily dose of buproprion and its metabolites delivered to an infant of a mother taking a therapeutic dose of the medication is relatively small. Thirteen of 14 infants had no adverse events, while one infant experienced a seizure (Gentile 2007).

### *Mirtazapine*

Two cases of mother–infant breastfeeding pairs (Klier et al. 2007, Aichhorn et al. 2004) showed undetectable infant levels of mirtazapine. Infants had no adverse effects.

### *Nefazodone*

Only four cases of reboxetine were reported with no adverse events, and three cases of nefazodone were reported with limited and conflicting data (Gentile 2007).

In summary, sertraline and paroxetine are considered as first-line medications in women who need to start medications in the postpartum period. Since citalopram and fluoxetine are associated with a relatively higher risk of adverse events, the risk and benefit of continuing these medications must be considered. The question of whether chronic exposure to low doses of antidepressant medication poses long-term nuerodevelopmental risks to the infant remains unanswered. Despite the low dosage transferred to the infant through breast milk, premature infants and those with neonatal diseases may be vulnerable to such exposure (Eberhard-Gran et al. 2006). For treatment of postpartum women with a history of successfully treated depression, the most practical approach may be to continue therapy with the previously effective agent.

## Mood Stabilizers

### *Lithium*

Lithium equilibrates well in breast milk (Schou 1990), which can lead to equivalent concentrations in maternal serum and breast milk. Lithium has a narrow therapeutic, and because of this and a baby's immature renal status, some experts recommend avoiding this agent during lactation (Eberhard-Gran et al. 2006), although the American Academy of Pediatrics does not absolutely contraindicate breastfeeding for women undergoing lithium treatment (Drugs 2001). As noted above, neonates should be monitored for complications during breastfeeding.

### *Valproic Acid*

Valproic acid is secreted into breast milk but in low amounts (Bar-Oz et al. 2000). In general, the percentage baby will receive is well below 10% of the maternal level. A single case report noted difficulties with thrombocytopenia (Stahl et al. 1997). The American Academy of Pediatrics suggests that maternal treatment with valproic acid is consistent with breastfeeding (Drugs 2001).

### *Carbamazepine*

The percentage of maternal carbamazepine dose that a neonate would receive from breast milk averages between 1% and 8% (Bar-Oz et al. 2000). There are generally few concerns with use of carbamazepine during pregnancy.

### *Lamotrigine*

The milk:plasma ratio of lamotrigine is about 0.6, and although this is slightly higher than what is seen for valproic acid and carbamazepine (Bar-Oz et al. 2000), the plasma level of lamotrigine infants is much higher. This appears to occur because the drug's elimination is dependent on glucuronidation, and this reaction is slowed in neonates (Liporace et al. 2004). Some neonates have achieved "therapeutic levels" of this compound but adverse effects among neonates have not been a problem.

### *Atypical Antipsychotics*

It may be best to avoid breastfeeding while undergoing treatment with the atypical antipsychotic, clozapine, because of the possible side effect of agranulocytosis. There is little information on the use of other newer antipsychotic agents during lactation. Case reports of risperidone, olanzapine, and quetiapine have not raised concerns (Gentile 2006).

### *Typical Antipsychotics*

There is surprisingly little information on the use of typical antipsychotics in breastfeeding mothers, and information is based on case reports (Burt et al. 2001). The majority of reports have not shown adverse effects among neonates, although sedation was noted in a report of infant exposure to chlorpromazine during lactation.

## Management Recommendations

A number of factors need to be considered when determining a treatment plan for a woman who requests consultation regarding the management of a depressive disorder during pregnancy. These factors include: (1) Is the woman contemplating pregnancy or currently pregnant? (2) If the woman is pregnant, what stage of pregnancy is she in? (3) What are the patient's and her partner's preferences with regard to pharmacological and nonpharmacological approaches to treatment? (4) Has she had a history of treatment and, if so, what has she received? (5) If she has discontinued treatment before, has she remained well for a period of months or longer? (6) Does the patient have evidence of psychotic or suicidal symptoms?

The ideal time to conduct a consultation is prior to conception. This affords the clinician the time to have a thoughtful discussion of the risks and benefits with the patient and her partner. It also gives the patient and her physician time to assess whether she can stay well for a period of time off medication or, if ongoing medication is required,

time to select a medication with the most reassuring safety profile. Should the patient be in the process of recovering from an episode of illness, a preconceptual assessment will allow her a period of psychiatric stability prior to conceiving. Finally, planning for pregnancy may allow the patient an opportunity for a trial of empiric-based psychotherapy such as cognitive-behavioral therapy or interpersonal therapy if she has not previously received such treatment. For some, a behavioral therapy may help them keep stable off medication during pregnancy or may decrease symptoms.

The severity, prior clinical course, and duration of time since the most recent episode of illness should be considered when determining whether a patient can discontinue medication for her depressive disorder. Women with severe recurrent illness, suicidal ideation and attempts, as well as psychosis may not be able to safely stop pharmacotherapy (Cohen et al. 2006). Similarly, women who have just remitted from a depressive episode may relapse if they stop pharmacotherapy too soon. Many patients with these characteristics may elect to continue psychotropic medication during pregnancy. Nonetheless, a trial of a behavioral therapy, as an option, should be discussed. Documentation of discussions regarding treatment options with the patient and her partner, risks and benefits related to the various treatment options, as well as patient's consent should be included in the medical chart. For patients who require and elect to continue pharmacotherapy, the lowest effective dose should be used. It is best to select from medications that have been on the market for a number of years, since this allows for observing outcomes from offspring intentionally or unintentionally exposed. Some recent data suggest that paroxetine should not be a first-line medication unless this is the only treatment to which a person has responded (see above). However, more recent data have failed to show an association between paroxetine and septal defects (Alwan et al. 2007, Louik et al. 2007). If a woman must continue paroxetine, keeping the dose at 25 mg daily or less may decrease the risk of cardiac malformations if such a risk exists (Bérard et al. 2007).

A similar clinical assessment is required for a woman who is pregnant and symptomatic. The severity of illness, prior clinical course, and patient and partner preference are important components of the decision to treat or not to treat with medication. Again, discussions regarding treatment with the patient and her partner should be documented along with the patient's consent. Medications that have previously been helpful should be considered with the possible exception of paroxetine. Again, if this is the only antidepressant to which a patient has responded, this medication may be necessary.

If a patient has been undergoing pharmacological treatment for depression, current clinical status, including severity, suicidal ideation, and psychosis, are important to assess when determining if medication should be continued. Prior treatment history as well as information regarding clinical course after medication discontinuation, patient preference, and response to empiric-based psychotherapy should be elicited to determine if medication is appropriate.

Given the information about possible PPHN after later in utero exposure to SSRIs (Chambers et al. 2006), it is important for clinicians to discuss this possible adverse effect with their patient and the patients' partners. While we await further information regarding this possible adverse effect to offspring, some patients and clinicians may prefer to switch treatment to a TCA or to a behavioral therapy. However, there is a risk of relapse with a change in treatment, and this should also be discussed with the patient and documented in her medical chart.

## Summary

An increasingly large database is becoming available to assess the safety of antidepressant treatment in pregnancy. It may be that clinicians are more likely to hear about problems associated with antidepressant use than about adverse effects of discontinuing treatment. We outline information about a number of perinatal effects that have been associated with stress, depression, as well as antidepressant treatment, but a number of questions remain. Perhaps chief among these are what are the consequences of the illness and what are the results of pharmacological treatment. Thoughtful planning and a thorough discussion of risks and benefits for all approaches are important in the clinical management of pregnant or preconceptual patients, with depression and will contributing to the most optimal outcomes.

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CHAPTER

# 113 Combined Treatment with Medications and Psychotherapy

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## History of Combined Treatments

Whether at the beginning of a treatment or months after its initiation, psychiatrists today widely believe that more than one treatment modality—often psychotherapy and medication—is needed to optimize patient outcome. This has not always been true. When the psychoanalytic model of the mind was the major theoretical influence in the 1950s and 1960s, most American psychiatrists believed that the use of medications "reduces the motivation of the patient to pursue the psychotherapeutic work and deeper personality changes that are sought for in the psychoanalytic process" (Marmor 1981). Gradually, many psychodynamically oriented psychotherapists and psychoanalysts began to realize that the use of medication and psychotherapy could be a therapeutically powerful combination (Kubie and Margon 1945, Goldhamer 1983, Norman and Bluestone 1986, Kantor 1990) and, in fact, make patients more amenable to psychotherapeutic interventions (Cooper 1990).

As evidence for the effectiveness of medications for schizophrenia and mood disorders accumulated after 1950, some psychiatrists rejected the combination of medication and psychotherapy for the opposite reason, i.e., there was little reason to consider nonpharmacologic treatments, whose likely mechanisms were persuasion and contact with a caring doctor rather than a specific treatment.

Fortunately, most psychiatrists have shifted from dogmatic positions for or against certain treatment modalities to more inclusive views. As the literature on combined treatment has expanded, many have concluded that treatment with medication and psychotherapy may be advantageous in a number of respects. First, combining treatments may increase the magnitude of response for individual patients, resulting in fewer residual symptoms. Second, combining treatments may enhance the acceptability and effectiveness of each individual treatment—psychotherapy may help increase compliance rates and help patients tolerate side effects, while adding medication may make the problems of psychotherapy patients more tractable (Hollon et al. 2005).

It appears that combining medication and psychotherapy may enhance the strengths of each individual treatment while minimizing their respective weaknesses. For instance, the neurobiological substrate of an individual's depression may be too severely disturbed for psychotherapy alone to be effective, and adding antidepressant medications may be more effective in reversing abnormalities such as sleep or neuroendocrine dysfunction. Patients with chronic depressive symptoms, severe psychosocial stressors, or depression in patients with personality disorders may benefit from psychotherapy in addition to medication alone (Frank et al. 2005).

### Clinical Vignette

A clinical vignette helps to illustrate the possible benefits of combined treatment and potential costs of monotherapy.

A, a 32-year-old woman with no history of major depression is in her third year of psychodynamic psychotherapy with Dr. B, a male psychiatrist. Her chief complaint was difficulty engaging in a committed relationship with a man. Raised primarily by her mother after a contentious divorce, A had great difficulty believing that men cared about her. Despite early mistrust of her therapist, she had gradually learned to trust him and to acknowledge that he was interested in her and invested in her improvement. One weekend, while shopping at the mall, A ran into Dr. B and his pregnant wife. Although she denied the importance of this event and wished the therapist well with his new baby, she became increasingly depressed in the ensuing weeks. The therapist believed that A's depression was the result of her seeing him with his wife, confirming for her that he cared more about

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another woman than about her. He repeatedly made this interpretation. A gradually came to agree with this idea but continued to have early morning awakening, decreased appetite, anhedonia, and difficulty concentrating at work. Dr. B did not prescribe medication, believing that this was a problem "in the transference," which needed to be worked through in order for the patient to understand her problem in relationships. Fearing that her decreased concentration might lead her to lose her job, she consulted another psychiatrist, who prescribed antidepressants. She soon quit her treatment with Dr. B.

In this case, the psychiatrist allowed his belief in a particular theory of etiology to guide his treatment planning, preventing him from initiating combined treatment with medication and psychotherapy. Ultimately, this led to a rupture in the treatment. Sometimes personal biases or emotional reactions can interfere with a psychiatrist's ability to consider and initiate combination treatment when it may be the optimal treatment for the patient. For instance, patient and practitioner may hope psychotherapy alone is sufficient treatment for the patient's symptoms and problems. The need to use medications in combination with psychotherapy may be seen as a failure of the psychotherapy, the method, the theory, or the practitioner. When this belief is held by the patient, the practitioner's suggestion to add medication may be met with devaluation, anger, disappointment, or hopelessness. If so, it may influence the practitioner to delay the use of medication or to avoid their use at all.

## Evidence for Combined Treatments

### Overview

Combined treatment with medications and psychotherapy is frequently utilized in the clinical care of patients with depression, anxiety, and other conditions (Beitman and Klerman 1991, Riba and Balon 2005). In approaching such patients, what evidence informs the clinician's decision regarding when and how to utilize combined treatment? To address this question, this section will review the available data on the relative efficacy of medications and psychotherapy for different disorders, when medications or psychotherapy are specifically indicated for certain patient populations, and when combined treatment should be considered as opposed to monotherapy.

Randomized controlled trials (RCTs) are now the standard means for demonstrating treatment efficacy, whether of psychotherapy or of medications. Numerous studies comparing psychotherapy and medications have been conducted, and many provide significant insights. However, reviewing the literature also highlights the very limited evidence in favor of combining medications and psychotherapy and the need for more research.

### Medication vs. Psychotherapy: Is One Treatment Better Than the Other?

During the 1970s and 1980s, more pharmacologic treatment options became available, and researchers systematically began to investigate the efficacy of these treatments in clinical trials. Likewise, psychotherapy researchers began to develop treatment manuals and therapist training programs so that psychotherapies could be standardized and studied systematically. These developments appeared to make possible the direct comparison of treatment with medications and psychotherapy, to determine their relative efficacy for depression, anxiety disorders, and other conditions. Therefore, the first generation of trials involving medications and psychotherapy was competitive in that they compared two treatment modalities to determine if one was superior. These trials did not usually have a combined psychotherapy and medication treatment cell, so the question of whether combined treatment offered a benefit over monotherapy was left unanswered. In addition, a serious problem facing these types of trials was the difficulty of demonstrating significant differences between two active treatments, which is much harder than demonstrating significant differences between active treatment and placebo or between posttreatment measurements and baseline.

#### Depressive Disorders

One of the first studies of psychotherapy and medication was carried out by Rush et al. (1977). This trial randomized 41 depressed outpatients to cognitive behavior therapy (CBT) (maximum of 20 sessions over 12 weeks) or imipramine (up to 250 mg per day for 12 weeks). Both treatment groups showed significant improvement compared to baseline, but CBT was significantly superior to imipramine in reducing depressive symptoms, as measured by the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HRSD). Of the patients receiving CBT, 79% had a final BDI < 10, compared to 23% of the patients treated with imipramine.

Perhaps the most famous trial comparing psychotherapy and medication was the National Institute of Mental Health's (NIMH) Treatment of Depression Collaborative Research Program (TDCRP) (Elkin et al. 1985), whose results began to be published in 1989. The TDCRP was a multicenter clinical trial that randomized 250 outpatients with current major depressive disorder to 16 weeks of treatment with (1) CBT, (2) interpersonal therapy (IPT), (3) imipramine plus clinical management, or (4) pill placebo plus clinical management. The study goal was to determine the relative efficacy of two psychotherapies for depression as well as their efficacy compared to imipramine, which served as the standard reference treatment. Since it is considered to be a proven effective treatment, including an imipramine treatment condition allowed the investigators to interpret the CBT and IPT results. In case no significant differences were found between CBT and IPT, comparing each to the imipramine group would help adjudicate whether the treatments were similarly ineffective or effective. A placebo group was necessary to demonstrate that imipramine was effective in the study population.

Patients were assessed every four weeks during their treatment course, at study termination and at 6, 12, and 18 month follow-up. The primary observer-rated outcome measures were the 17-item HRSD (Hamilton 1960) and the Global Assessment of Functioning (GAS) (Endicott et al. 1976), while the primary self-report outcome measures were the BDI (Beck et al. 1961) and the Symptom Checklist-90 (SCL-90) (Derogatis 1992).

Patients enrolling in the study were 70% female, aged 35 ± 8 years, and most had recurrent depression (Elkin et al.

1989). Dropout rate was 32% in the CBT group, 23% in the IPT group, 33% in the imipramine group, and 40% in the placebo group. In the intent to treat analyses, patients in all four treatment conditions (including placebo) showed significant reduction in depressive symptoms over the course of the study, as measured by all four of the primary outcome measures. Few significant differences were found between the treatments: imipramine was superior to placebo on the GAS measure, and IPT as well as imipramine showed a trend for superiority to placebo on the HRSD. Significantly more patients experienced remission of their depression (as measured by HRSD < 7) in the imipramine and IPT groups compared to placebo, but CBT was not significantly different from either of the other active treatment groups or placebo. Despite the few statistically significant differences, the order of the treatments was consistent, with imipramine usually doing best, followed by IPT, CBT, and placebo.

The TDCRP was the first comparative clinical treatment trial involving psychotherapy and medication sponsored by the NIMH, and it was also the first study to compare CBT and IPT. The study benefited from a number of important methodological advances, including standardization of the treatments (by means of treatment manuals, clinician training, and monitoring of adherence), use of standard outcome measures for depression, and a multisite design permitting a larger sample to be recruited. However, questions were immediately raised about the authors' statistical methods (Klein 1990). Reanalyses of the data showed that imipramine was significantly superior to placebo on the HRSD and the GAS, superior to IPT on the GAS, and nearly superior to CBT on the GAS (Klein and Ross 1993). CBT and IPT were not superior to placebo among patients entering the study or among completers, but CBT was inferior to IPT on the BDI among more severely depressed patients.

Continuing debate following publication of the TDRCP results made clear how dissatisfied many researchers were with the study. Pharmacologists were not satisfied with the medication treatment; e.g., imipramine at doses of 150 mg per day will not achieve a therapeutic blood level in most patients, and no blood levels were measured to guide dose adjustment. However, most did feel the inclusion of a pill placebo treatment condition was a welcome advance, since such "internal calibration" of the study was necessary to demonstrate that it took place in a drug-responsive population (Klein 1996). Psychotherapists were unhappy with potential therapist allegiance effects and lack of documentation of treatment fidelity, as recent studies have raised the possibility that the treatment administered in the IPT cell was not significantly different from CBT (Ablon and Jones 1999).

While many psychotherapy and pharmacotherapy researchers have moved on to ask whether combined treatment with medications and psychotherapy is better than monotherapy, the legacy of this first generation of competitive studies can still be seen today. First, and most directly linked to the TDCRP debate, psychotherapy researchers have continued to address the question of whether psychotherapy is as effective as antidepressant medications for severe depression. For example, DeRubeis et al. (1999) conducted a "mega analysis" of original data from four studies of combined therapy and CBT in patients with severe major depression (defined as HRSD > 20 or BDI > 30). These studies included the TDCRP, as well as an early study of imipramine vs. CBT by Rush et al. (1977), nortriptyline vs. CBT by Murphy et al. (1984), and a study of imipramine vs. CBT by Hollon et al. (1992). Adjusting for pretreatment differences in depression severity among the studies, they found no significant differences in pooled posttreatment HRSD or BDI scores of patients treated with CBT and antidepressant medication.

It should be noted that some researchers consider the definition of "severe" depression in analyses such as the above to be arbitrary. These definitions are often determined by dividing the patient sample into two groups—those having depression scores above and below the mean—and the group above the mean depression score is considered to represent severe depression. Many researchers and clinicians would object to the DeRubeis et al.'s (1999) definition of severe depression as HRSD > 20, since they would not consider patients to have severe depressions unless the HRSD is 26 or more.

More recently, Jarrett and colleagues (1999) randomized 108 patients with major depressive disorder and atypical features to treatment with CBT, phenelzine, or pill placebo. They found significantly greater response rates for CBT and phenelzine compared to placebo, but CBT and phenelzine did not significantly differ from each other. In another study, DeRubeis et al. (2005) compared CBT to antidepressant medications in 240 patients with severe major depression and found that the two treatments did not significantly differ over 16 weeks. "Severe" major depression was defined as scores of 20 or greater on the 17-item HRSD at the screening and baseline visits for the study. Response rates were 58% for both CBT and medications, while remission rates were 46% for medication and 40% for CBT. Similarly, Dimidjian et al. (2006) compared behavioral activation therapy, CBT, and antidepressant medication in 241 adults with major depressive disorder. Medications were significantly more effective than placebo in this study, and behavioral activation, as well as medications, was significantly better than CBT without being different from one another. In all of these rigorously conducted studies, therapist qualifications and training were described, treatments were manualized, and adherence and competence were assessed by blinded raters using validated rating scales.

Competitive studies continue to be performed to determine if medication or psychotherapy is more effective at achieving complete remission of depression. There has been an increasing acceptance of remission rather than response as a goal of treatment, since even depression "responders" may have a significant degree of residual illness that places them at higher risk of depression relapse, physical and functional morbidity, and suicide (Paykel 1995). Remission is defined as a state in which patients are asymptomatic or have no more than minimal symptoms and no longer meet diagnostic criteria for depression (Frank et al. 1991). Remission is often operationalized in terms of preset minimum HRSD scores, such as a measured final HRSD < 7, while response is defined as a 50% reduction in baseline depression rating score or else an "improved" or "much improved" score on the CGI.

For example, Casacalenda et al. (2002) performed a meta-analysis of six randomized, double-blind clinical trials including psychotherapy (primarily CBT and IPT) and

pharmacotherapy (mainly TCAs and phenelzine) treatment cells to determine their effects on depression remission. Remission was defined separately by each study included in the meta-analysis: three studies defined remission as HRSD < 6, two as HRSD < 7, and one as Raskin Depression Scale < 5. This meta-analysis included 883 patients having nonpsychotic major depression in both outpatient settings and psychiatric hospitals. Analyses indicated that pharmacotherapy and psychotherapy were significantly more effective than control conditions (e.g., pill placebo or treatment as usual) but not significantly different from one another (46.4% and 46.3%, respectively).

Meta-analyses have also compared psychotherapy and pharmacotherapy for the treatment of depression in older adults. Pinquart and colleagues (2006) performed a meta-analysis of 89 controlled clinical trials for depressive disorders in older adults. These trials included 57 studies of antidepressants alone, 27 studies of psychotherapy alone, and five studies of combined treatment. The 5328 patients in studies included in the analysis were 64% female, mean age 70.9 years, and represented a mix of in- and outpatients as well as patients with and without medical comorbidities. The authors found significantly larger effect sizes in psychotherapy treatment cells compared to pharmacotherapy treatment cells on clinician-rated depression scores, whereas self-rated depression scores were not significantly different between pharmacotherapy and psychotherapy treatment cells.

Results from this first phase of research studies comparing treatment for depression with psychotherapy and medications are mixed (Table 113–1). Some trials demonstrate a significant difference in favor of psychotherapy compared to medications, while others report the opposite finding. However, the result found by most of the studies cited is that no significant difference was observed between the two treatment modalities. This finding reiterates the difficulty of demonstrating significant differences between two active treatments rather than between an active treatment and baseline or a control condition. Clinically, this result also led to the consensus that either medications or psychotherapy with CBT or IPT can be a reasonable first choice for the treatment of many unipolar, nonpsychotic depressions (AHCPR 1993, APA 1993).

## Anxiety Disorders

Similar types of research studies have compared medications and psychotherapy for anxiety disorders such as panic disorder and obsessive compulsive disorder (OCD). For instance, Klosko et al. (1990) compared behavior therapy (BT), alprazolam, pill placebo, and a wait-list control in 69 patients with panic disorder. They found significantly lower clinical ratings of severity of panic disorder, lower Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959) scores, and decreased subjective ratings of panic frequency and intensity in the alprazolam and BT groups compared to the placebo and wait-list control groups. No differences were observed between alprazolam and BT.

Black et al. (1993) randomized 75 outpatients with panic disorder to 8 weeks of treatment with fluvoxamine, CBT, or pill placebo. In this study, patients treated with fluvoxamine had significantly greater improvement at the study endpoint on the Clinical Anxiety Scale and the Clinical Global Impressions (CGI) Scale than patients receiving CBT or placebo. Patients receiving CBT showed significantly more

**Table 113–1 Clinical Trials Comparing Medication to Psychotherapy**

| Author | Patient Population | Treatments Studied | Total Sample Size | Length of Treatment (Weeks) | Results |
|---|---|---|---|---|---|
| Rush et al. (1977) | Adults with depressive disorders | CBT Imipramine | 41 | 12 | CBT > imipramine |
| Elkin et al. (1989) | Adults with MDD | CBT IPT Imipramine Placebo | 250 | 16 | Imipramine > IPT > CBT > placebo |
| Jarrett et al. (1999) | Adults with atypical MDD | CBT Phenelzine Placebo | 108 | 10 | CBT = phenelzine > placebo |
| DeRubeis et al. (2005) | Adults with severe MDD | CBT ADs | 240 | 16 | CBT = ADs |
| Dimidjian et al. (2006) | Adults with MDD | BAT CBT Ads Placebo | 241 | 16 | BAT = ADs > CBT > placebo |
| Black et al. (1993) | Adults with PD | CBT Fluvoxamine Placebo | 75 | 8 | Fluvoxamine > CBT > placebo |
| Clark et al. (1994) | Adults with PD | CBT ART Imipramine | 64 | 12 | CBT > ART = imipramine |
| Klosko et al. (1990) | Adults with PD | BT Alprazolam Placebo Wait-list control | 69 | 15 | Alprazolam = BT > placebo = wait-list control |
| Haan et al. (1998) | Children and adolescents with OCD | BT Clomipramine | 22 | 12 | BT > clomipramine |
| Clark et al. (2004) | Adults with SP | CBT Fluoxetine + self-exposure Placebo + self-exposure | 60 | 16 | CBT > fluoxetine + self exposure > placebo plus + self-exposure |

'>' denotes statistically significant different favoring one treatment. '=' denotes no statistically significant difference between treatments. MDD = major depressive disorder. PD = panic disorder; OCD = obsessive compulsive disorder; SP = social phobia; CBT = cognitive behavior therapy; BAT = behavioral activation therapy; ART = applied relaxation therapy; ADs = antidepressants.

improvement on the CGI and calculation of mean weekly number of panic attacks than patients receiving placebo. Lastly, Clark et al. (1994) compared 12 weekly sessions each of CBT, applied relaxation therapy, and imipramine for patients with panic disorder. They found significantly lower scores on a panic/anxiety composite measure and higher percentages of panic-free patients in the CBT relative to the applied relaxation or imipramine groups. This difference between imipramine and CBT disappeared at 3 months follow-up, but both treatments remained superior to applied relaxation therapy.

Similar competitive studies have been performed in patients with OCD. Haan et al. (1998) compared the effectiveness of BT and clomipramine in 22 children, aged 8–18 years, with OCD. Patients were randomized to 12 weeks of BT or treatment with clomipramine at doses of 2.5 mg/kg. The authors found significant improvement of symptoms as measured by the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS) for both treatment conditions, but BT was significantly superior to clomipramine.

Finally, Clark et al. (2004) randomized 60 patients with generalized social phobia to cognitive therapy (CT), fluoxetine plus self-exposure (SE), or pill placebo plus SE. Patients were treated for 16 weeks, at which point the blind was broken and patients entered a 3-month booster phase. Statistically significant improvement in social phobia symptoms occurred in all three treatments, but CT was superior to fluoxetine plus SE and pill placebo plus SE at the end of acute treatment, the 3-month booster period, and a 12-month follow-up period.

Similar to the results observed in comparative trials of psychotherapy and medication for depression, those found by the above trials for anxiety disorder are mixed (Table 113–1). Some studies found psychotherapy significantly superior to medication, whereas others found medication superior to psychotherapy, but most determined both medication and psychotherapy to be effective without differing significantly. Many consensus treatment guidelines reflect these findings in recommending either an evidence-based psychotherapy or a proven effective medication for the treatment of anxiety associated with OCD, social phobia, or panic disorder (APA 2006a, 2006b).

## Combined Treatment with Medications and Psychotherapy vs. Monotherapy: Are Two Treatments Better Than One?

The next generation of combined treatment studies was aimed less at determining which treatment was more effective, medications or psychotherapy, and more at addressing the question of whether combined treatments are superior to monotherapy.

### Depressive Disorders

Blackburn et al. (1981) conducted one of the first studies of CBT and medication in Scotland. Sixty-four hospital outpatients and general practice patients diagnosed with recurrent depression were assigned to CBT alone, tricyclic antidepressant medication alone, or CBT plus medication. Patients received a maximum of 20 weeks' treatment and were then followed for 2 years. There were no between-group differences among the hospital outpatients, but combined treatment and CBT both resulted in significantly higher response rates than the medication-only group. Overall in the acute study, 82% of patients receiving CBT plus medication responded, compared to 73% of patients receiving CBT and 55% of patients receiving tricyclic medication. Strikingly, after 2 years of naturalistic follow-up, significantly fewer patients in the combination treatment and CBT groups relapsed (0% and 6%, respectively), compared to 30% in the tricyclic-only group (Blackburn et al. 1986).

Other investigators found similar results. Murphy et al. (1984) randomized 87 patients with unipolar depressive disorders to CBT, nortriptyline, CBT plus nortriptyline, and CBT plus active placebo. No outcome differences were observed between groups at 12 weeks. After 1 year of follow-up, 36% of patients who responded by 12 weeks subsequently relapsed, with no differences in relapse rates between the four treatment groups. In addition, Hollon et al. (1992) randomized 107 patients with unipolar, nonpsychotic depression to pharmacotherapy with or without continuation, CBT, and combined CBT/pharmacotherapy. These authors found all three treatments effective but not significantly different from each other.

In terms of maintenance treatment, the University of Pittsburgh conducted an important study of patients with recurrent depression (Frank et al. 1990, Kupfer et al. 1992). In this study, all patients were initially treated with a combination of IPT and imipramine until their HRSD was 7 or less, which was then required to be maintained for 17 weeks. After this stabilization, the 127 eligible patients were randomized to receive combination imipramine and IPT, imipramine plus clinical management, IPT plus placebo, IPT alone, or placebo plus clinical management. Relapse was defined as an elevation in HRSD to 15 or more and the diagnosis of a new depressive episode. Followed over 3 years, patients receiving imipramine had the lowest relapse rates, with no difference between imipramine plus clinical management and imipramine plus IPT. IPT alone showed a trend toward better outcomes compared to placebo but was significantly less effective than imipramine (3-year recurrence rate of 61.5% compared to 20%).

Paykel and colleagues (1999) and Scott et al. (2000) randomized 158 patients with recent major depression that had partially remitted to antidepressant treatment after at least 8 weeks of treatment. At the beginning of the study, 60% of patients were receiving selective serotonin reuptake inhibitors (SSRIs) and 40% were receiving tricyclic antidepressants. During the treatment phase, patients received continuation antidepressants at the same dose and were randomized to receive 16 sessions of CBT and clinical management over 20 weeks or clinical management alone for 20 weeks. Patients then entered a follow-up period, during which ratings, antidepressants, and clinical management were continued, for an additional 48 weeks. The investigators found that patients receiving CBT had significantly higher remission rates at the end of 20 weeks compared to the clinical management group (25% vs. 13%, respectively). During follow-up, patients in the CBT group relapsed at significantly lower rates (29%) than did patients in the clinical management group (45%).

The results of these studies illustrate that little evidence supports the superiority of combined treatment with medications and psychotherapy over monotherapy with either medication or psychotherapy. Few studies have found

a significant benefit of combined treatment, and many more have found either no significant difference with monotherapy or else that monotherapy was significantly superior.

In response to this, some researchers have argued that the lack of evidence for superiority of combined treatment with medications and psychotherapy results from studies that were inadequately powered to detect more modest effect sizes. More recent, larger studies of combination treatment with psychotherapy and medications have found combined treatment superior to monotherapy with either treatment. In a large trial published in the *New England Journal of Medicine*, Keller and colleagues (2000) randomized nearly 700 adults with chronic major depressive disorder to 12 weeks of nefazodone, 16–20 sessions of the cognitive behavioral analysis system of psychotherapy (CBASP), or both. Combined treatment had a 73% response rate, which was significantly better than treatment with psychotherapy (48%) or medication (48%) alone. Rates of discontinuation were low and not significantly different between the treatment cells in the acute phase of the study.

Combined treatment studies of children/adolescents and the elderly are sparse. The Treatment for Adolescents with Depression Study (TADS), a multicenter RCT, enrolled 439 outpatients aged 12–17 years with major depressive disorder (TADS Team 2004). Subjects were randomized to receive 12 weeks of CBT alone, fluoxetine alone, combined CBT and fluoxetine, or pill placebo. Primary outcome measures were change in Children's Depression Rating Scale-Revised (CDRS-R) score and a dichotomized CGI score (responder or nonresponder). Combined treatment was superior to all other cells on the CDRS-R, while it was superior to CBT alone and placebo and not significantly different from fluoxetine alone on the CGI. Fluoxetine alone and CBT alone failed to separate from placebo on CDRS-R scores, but each was superior to placebo on dichotomized CGI score. Fluoxetine alone was significantly superior to CBT alone on both primary outcome measures. The authors concluded that "the combination of fluoxetine with CBT produced the greatest improvement in symptoms of MDD (p. 816)."

In a study enrolling 102 patients with late life depression, Thompson and colleagues (2001) compared desipramine to CBT and combined CBT/desipramine. Patients received 16–20 CBT sessions if they were assigned to one of the psychotherapy conditions, and they received a mean dose of desipramine of 90 mg, which produced therapeutic mean blood levels of 123 ng/ml. Significant improvements in HRSD scores were observed across the three treatment conditions, while improvements in BDI scores were only significant for the CBT and combined treatment conditions. Breaking down the treatment sample based on depression severity, the authors concluded that combined treatment was most effective for severely depressed patients, while CBT alone could be an effective treatment for older patients with mild-to-moderate depressions.

Additionally, Reynolds et al. (1999) compared a combination of nortriptyline and IPT, nortriptyline alone, IPT plus placebo, and placebo alone in 84 elderly outpatients with bereavement-related depression. They found a significant drug effect, with 69% of patients in the combined treatment group and 56% of nortriptyline-only patients remitting over the 16-week study. Patients treated with IPT plus placebo did not differ from patients in the placebo-only group. The rate of relapse into major depression over the 16-week follow-up period was low and not significantly different across the four treatment groups.

Another relatively understudied area regards combinations of medication and psychotherapy other than IPT or CBT. Burnand et al. (2002) randomized 74 adults with major depression to 10 weeks of clomipramine or clomipramine combined with psychodynamic psychotherapy. Both groups of patients experienced significant improvement in their depression as measured by the HRSD, with no significant differences found between the two treatment conditions. However, patients in the combined clomipramine and psychodynamic psychotherapy treatment cell had significantly higher posttreatment GAS scores, lower rates of hospitalization, and fewer lost days of work due to illness than patients treated with clomipramine alone.

Psychotherapy, medication, and their combination have been relatively less studied in dysthymia. In one notable study, Ravindran et al. (1999) compared treatment with sertraline, pill placebo, group cognitive behavior therapy (GCBT) plus placebo, and sertraline plus GCBT in adults with dysthymia. They found sertraline and combined treatment superior to GCBT plus placebo and placebo alone, but sertraline and combined treatment were not different from one another. Browne et al. (2002) compared sertraline, brief IPT, and their combination in almost 700 patients in primary care, finding that sertraline alone and combination treatment were superior to IPT alone and not significantly different from one another.

In sum, while some larger studies have succeeded in showing significant differences in favor of combined treatment compared to monotherapy, the data remain mixed (Table 113–2). Given how frequently combined treatments are advocated for the treatment of depression and the relatively greater investment of resources they require, these results compel further research in studies with sample sizes large enough to detect small-to-medium effect sizes in favor of combined treatment (APA 2006a, 2006b).

## Anxiety Disorders

Many combination studies have been performed in panic disorder. For instance, Marks et al. (1993) compared treatment with alprazolam and exposure therapy, each alone and combined, in patients with panic disorder and agoraphobia. Relaxation treatment served as a psychological placebo, so patients were randomized to one of four groups: alprazolam plus exposure therapy, alprazolam plus relaxation, pill placebo plus exposure therapy, and pill placebo plus relaxation. Over the 8 weeks of acute treatment, patients in each treatment condition experienced significant improvement of their panic symptoms as measured by 10 separate rating scales, and there were no between-group differences observed.

In another study, Barlow et al. (2000) randomly assigned 312 patients with panic disorder to receive imipramine up to 300 mg per day, pill placebo, CBT alone, CBT plus imipramine, or CBT plus pill placebo. Patients were treated weekly for 12 weeks in the study's acute phase, then were seen monthly in the study's maintenance phase, and were seen 6 months after follow-up. The investigators found both imipramine alone and CBT alone were superior to placebo on the Panic Disorder Severity Scale (PDSS),

**Table 113–2 Clinical Trials Comparing Combined Treatment with Medication and Psychotherapy to Monotherapy**

| Author | Patient Population | Treatments Studied | Total Sample Size | Length of Treatment | Results |
|---|---|---|---|---|---|
| Blackburn et al. (1981) | Outpatients with recurrent depression | CBT TCAs CBT + TCAs | 64 | 20 weeks | CBT + TCAs = CBT > TCAs |
| Murphy et al. (1984) | Unipolar depressive disorders | CBT Nortriptyline CBT + nortriptyline CBT+ active placebo | 87 | 12 weeks | No differences between groups |
| Hollon et al. (1992) | Outpatients with MDD | CBT ADs CBT + ADs | 107 | 12 weeks | No differences between groups |
| Reynolds et al. (1999) | Elderly with bereavement-related MDD | IPT + placebo IPT + nortriptyline Nortriptyline Placebo | 84 | 16 weeks | IPT + Nortriptyline = nortriptyline > IPT + placebo = Placebo |
| Ravindran et al. (1999) | Adults with DD | GCBT + placebo GCBT + sertraline Sertraline Placebo | 97 | 12 weeks | GCBT + sertraline = sertraline > GCBT + placebo = placebo |
| Keller et al. (2000) | Adults with chronic MDD | CBASP Nefazodone CBASP + nefazodone | 681 | 12 weeks | CBASP + nefazodone > CBASP = nefazodone |
| Thompson et al. (2001) | Elderly with MDD | CBT CBT + desipramine Desipramine | 102 | 16–20 weeks | No differences between groups |
| Burnand et al. (2002) | Adults with MDD | Psychodynamic PT + clomipramine Clomipramine | 74 | 10 weeks | No differences between groups |
| Browne et al. (2002) | Adults with DD | Brief IPT Brief IPT + sertraline Sertraline | 707 | 24 weeks | Brief IPT + sertraline=Sertraline > Brief IPT |
| TADS Team. (2004) | Children and adolescents with MDD | CBT CBT + fluoxetine Fluoxetine Placebo | 439 | 12 weeks | CBT + fluoxetine = fluoxetine > CBT > placebo (on CGI outcome measure) |
| Paykel et al. (1999) | Adults with recurrent MDD | CBT + ADs ADs | 158 | 48 week continuation study | CBT + ADs > ADs |
| Frank et al. (1990) | Adults with recurrent depression | IPT IPT + placebo Imipramine + IPT Imipramine Placebo | 127 | 3 year continuation study | Imipramine = Imipramine + IPT > IPT = IPT + placebo = placebo |
| Marks et al. (1993) | Adults with PD | ExT + alprazolam ART + alprazolam ExT + placebo ART + placebo | 154 | 8 weeks | No differences between groups |
| Barlow et al. (2000) | Adults with PD | CBT + imipramine CBT + placebo CBT Imipramine Placebo | 312 | 12 weeks | All groups superior to placebo, no differences between groups |
| POTS Team 2004 | Children and adolescents with OCD | CBT CBT + sertraline Sertraline Placebo | 112 | 12 weeks | CBT + sertraline > CBT = sertraline > placebo |
| Foa et al. (2005) | Adults with OCD | ERP ERP + clomipramine Clomipramine Placebo | 122 | 12 weeks | ERP = ERP + clomipramine > Clomipramine = Placebo |
| Davidson et al. (2004) | Adults with SP | CBGT CBGT + fluxoetine Fluoxetine Placebo | 295 | 14 weeks | All groups superior to placebo, no differences between groups |

'>' denotes statistically significant different favoring one treatment. '=' denotes no statistically significant difference between treatments. MDD = major depressive disorder; DD = dysthymic disorder; PD = panic disorder; OCD = obsessive compulsive disorder; SP = social phobia; CBT = cognitive behavior therapy; CBGT = cognitive behavioral group therapy; BAT = behavioral activation therapy; ART = applied relaxation therapy. ExT = exposure therapy. ERP = exposure and response prevention therapy.

with no significant differences found between CBT alone and imipramine alone. Combined treatment with CBT and imipramine did not result in higher response rates on the PDSS compared to CBT plus placebo, CBT alone, or imipramine alone. Furthermore, combined treatment did not result in significantly lower relapse rates compared to the other treatments.

The Pediatric OCD Treatment Study (POTS) is a multicenter RCT of 112 adolescent outpatients with OCD and a CY-BOCS score of 16 or higher (POTS Team 2004). Subjects were randomized to CBT alone, sertraline alone, combined CBT and sertraline, and pill placebo, while blinded raters assessed subjects' CY-BOCS score and remission status at 4, 8, and 12 weeks. The study investigators found combined CBT and sertraline superior to CBT alone, sertraline alone, and placebo, while CBT alone and sertraline alone were each superior to placebo but not different from one another. They concluded that "children and adolescents with OCD

should begin treatment with CBT alone or with CBT plus an SSRI (p. 1974)."

A second influential study for patients with OCD was carried out by Foa et al. (2005). This double-blind, randomized trial compared exposure and response prevention (ERP), clomipramine, combination ERP and clomipramine, or pill placebo for 122 outpatients with OCD. Patients received 4 weeks of intensive ERP, followed by 8 weekly maintenance sessions and/or 12 weeks of clomipramine at doses up to 250 mg per day. At 12 weeks, all three active treatments were significantly superior to pill placebo on the primary outcome measure, which was the Yale–Brown Obsessive Compulsive Scale (Y-BOCS). Both ERP and combined ERP/clomipramine were significantly superior to clomipramine alone. Response rates were 62% for ERP, 70% for ERP and clomipramine, 42% for clomipramine, and 8% for placebo.

Results for combined treatment with medications and psychotherapy have been less impressive in social phobia. Davidson et al. (2004) compared fluoxetine, cognitive behavioral group therapy (CBGT), pill placebo, CBGT plus fluoxetine, and CBGT plus pill placebo in 295 patients with generalized social phobia. Treatment entailed 14 weekly sessions of CGBT, fluoxetine at doses of 10–60 mg, or both, and the primary outcome measures were the Brief Social Phobia Scale (BSPS) and the CGI. The authors found response rates on the CGI to be 51% for fluoxetine, 52% for CBGT, 54% for CBGT/fluoxetine, 51% for CBGT/placebo, and 32% for pill placebo. All treatments were significantly superior to pill placebo but were not different from one another on the primary outcome measures.

Similar to the studies cited for the treatment of depression, most studies of combined treatment compared to monotherapy for anxiety disorders fail to demonstrate significant superiority of combined treatment (Table 113–2). Some larger studies, such as the POTS trial for OCD in adolescents, do demonstrate superiority of combined treatment, which raises the possibility that the smaller studies are underpowered to detect the relatively small effect sizes in favor of combined treatment. More research is needed before combined treatment can be recommended as the treatment of choice over monotherapy with either medications or psychotherapy.

### Meta Analyses

A number of meta-analyses have combined data from individual trials to investigate combined psychotherapy and medication for depression. In one of the first such quantitative reviews, Conte et al. (1986) analyzed 17 reports of 11 studies containing a combined psychotherapy and medication treatment cell and at least one comparison group for nonpsychotic unipolar depression. They designed a rating scale for determining the quality of study design and combined disparate psychotherapies and medications for the purposes of analysis. They found that combined treatment was slightly but consistently superior to monotherapy with either psychotherapy or antidepressant medication. However, an unusual statistical method of weighting studies was employed that leads to questionable interpretation of results.

Thase et al. (1997) reanalyzed data from 595 patients with major depressive disorder enrolled in six standardized protocols between 1982 and 1992. Each individual study provided 16 weeks of treatment with CBT, IPT, or combined IPT and antidepressant treatment, and the primary outcome measure examined was remission of depression as determined by HRSD < 7 at study endpoint. They found a remission rate of 37% for psychotherapy alone compared to 48% with combined therapy, which was not a significant difference. However, in a subanalysis of severely depressed patients, combined treatment was found to be significantly more effective than psychotherapy alone (43% vs. 25%). Furthermore, combined therapy was associated with significantly shorter times to remission of depression.

Pampalona et al. (2004) reviewed the literature to find RCTs comparing antidepressant treatment alone to the combinations of antidepressants and psychotherapy for the treatment of depressive disorders. They included 16 RCTs, in which a total of 932 patients were randomized to antidepressants alone and 910 to combined treatment. Psychotherapy interventions included CBT, IPT, psychodynamic psychotherapy, marital therapy, social skills training, and problem-solving training. The authors found that combined treatment with psychotherapy and medication had a significant advantage over treatment with antidepressants alone. Patients receiving combined treatment were nearly twice as likely to experience depression response compared to antidepressants alone (odds ratio 1.86, 95% CI, 1.38–2.52).

Meta-analysts have also evaluated combined treatments for anxiety disorders, such as panic disorder. Furukawa et al. (2006) examined 23 RCTs comparing combination treatment to monotherapy with antidepressants or psychotherapy for panic disorder. For acute-phase treatment, combination therapy was more likely to produce panic response than antidepressants (relative risk of response 1.24, 95% CI, 1.02–1.52) or psychotherapy alone (relative risk of response 1.16, 95% CI, 1.03–1.30).

Van Balkom et al. (1994) examined pharmacotherapy and psychotherapy treatments for OCD and reported that serotonergic antidepressants, BT, and combination treatment were each more effective than placebo. BT and combination BT/medication were significantly more effective than medication alone, while not being different from one another. Abramowitz (1997) evaluated published reports of psychological treatments (ERP, BT, and CBT) and pharmacotherapy for OCD. ERP and CBT were found to be similarly effective and more effective than relaxation therapy in relieving the symptoms of OCD, while serotonergic medication (clomipramine most robustly) was more effective than placebo.

## Augmentation Strategies for Nonresponders: Is Adding Another Treatment Modality Helpful When Patients Do Not Respond to Treatment with the First?

### Depressive Disorders

In one of the earliest augmentation treatment studies, Klerman et al. (1974) randomized 150 depressed women who improved after 4–6 weeks of open treatment with 100–200 mg daily amitriptyline to weekly IPT alone, continued amitriptyline alone, combined IPT and amitriptyline, and placebo with no psychotherapy. They found similar relapse

rates of depression in all of the active treatment conditions (12% amitriptyline, 12.5% combination treatment, and 16.7% IPT alone), with placebo having the highest relapse rate (36%). The general absence of large effect sizes in favor of combined treatment observed in this study would continue in later studies of acute treatment.

A unique perspective on the use of medications and psychotherapy to treat depression has been provided by the NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which is the largest prospective trial for depression ever conducted. Patients presented to one of 41 sites seeking treatment, and inclusion/exclusion criteria were structured so as to promote maximum generalizability. All 3271 patients received monotherapy with citalopram in Level 1, and those whose depressions did not remit were encouraged to proceed with additional trials until remission was achieved. At Level 2, patients were allowed to express preferences for medication vs. psychotherapy and switching treatments vs. augmenting. Switch options comprised buproprion, sertraline, venlafaxine, and CBT, while augmentation options comprised adding buproprion, buspirone, or CBT to citalopram. Patients whose depressions still did not remit could be randomized at Level 3 between two switch options (nortriptyline or mirtazipine) or two augmentation options (adding lithium or T3 to whatever antidepressant they were taking). The final step, Level 4, involved randomizing patients to tranylcypromine or the combination of venlafaxine and mirtazipine.

After initial treatment with citalopram, 37% of patients were in remission from their depression (Trivedi et al. 2006b). Level 2 results for the switch (Rush et al. 2006) and augmentation (Trivedi et al. 2006a) options followed. Patients who switched medications received buproprion SR up to 400 mg daily, sertraline up to 200 mg daily, or venlafaxine XR up to 375 mg daily. Remission rates as measured by HRSD < 7 on these medications were 21.3%, 17.6%, and 24.8%, respectively, which were not significantly different from one another. Augmentation of citalopram was with buproprion SR up to 400 mg daily or buspirone up to 60 mg daily, and remission rates as measured by the HRSD were not significantly different (29.7% and 30.1%, respectively). In the Level 3 augmentation trial, 15.9% of patients achieved remission with lithium compared to 24.7% of patients receiving T3, which was not a significant difference (Nierenberg et al. 2006). However, there was a suggestion that T3 was better tolerated than lithium. Likewise, in the Level 4 trial, 6.9% of patients receiving tranylcypromine and 13.7% of patients receiving combined venlafaxine and mirtazipine remitted, which were not significantly different McGrath et al. 2006).

Interestingly, only 26% of participants entering Level 2 found assignment to the augmentation or switch options including CBT acceptable (Thase et al. 2007). As a result, only 147 patients were assigned to CBT in Level 2. The authors found that augmentation of citalopram with CBT resulted in a depression remission rate of 23.1%, which was not significantly different from the rate observed with augmentation with buproprion or buspirone (33.3%). Switching to CBT after unsuccessful treatment with citalopram resulted in a 25.0% remission rate, compared to 27.9% after switching to sertraline, buproprion, or venlafaxine (no significant difference). However, the authors did note that pharmacologic augmentation resulted in faster speed of depression response, and patients appeared to tolerate treatment with medication or CBT equally well.

## Methodological Issues in Combined Treatment Studies

In pharmacotherapy trials, randomization, a pill placebo comparison group, and double blinding ensure that potential confounders and nonspecific factors (such as health-care provider attention, patient expectations, and spontaneous remission) associated with every experimental treatment are equivalent between groups. These methods allow researchers to demonstrate that the effects observed are due to the specific effects of the treatment being studied rather than due to incidental factors associated with the treatment. Moreover, the inclusion of a placebo condition allows one to interpret differences observed between treatment cells, since in the absence of placebo control, one would not know whether two treatments showing similar results were equally effective or equally ineffective (Klein 1997).

A major difficulty in comparing psychotherapy, medication, and combined treatment is introduced by the absence of a psychotherapy placebo condition. Without such a placebo, it is impossible to conduct the optimal study of combined treatment, which would be a four-cell study comparing psychotherapy plus medication, psychotherapy plus pill placebo, psychotherapy placebo plus medication, and psychotherapy placebo plus pill placebo. Such a study would answer many questions, including the efficacy of medication or psychotherapy alone, the relative efficacy of the two treatments, and the value of adding one treatment to the other. Since no adequate psychotherapy placebo condition has been established, investigators have resorted to comparing placebo-controlled medication treatment to the open administration of psychotherapy.

In the TADS discussed above, adolescents with major depression were randomized to CBT alone, fluoxetine alone, combined CBT and fluoxetine, and pill placebo (TADS Team 2004). The benefit of this design is that the study can be "internally calibrated," meaning differences between the psychotherapy and medication conditions can be more easily interpreted when it is known whether or not the medication treatment condition was effective compared to placebo. However, the study compares blinded treatments (fluoxetine or pill placebo) to unblinded treatments (CBT and combined CBT and fluoxetine). In other words, patients in the CBT-alone condition knew that they were receiving psychotherapy (active treatment), while patients taking pills did not know whether they were fluoxetine (active) or placebo (inactive). Similarly, patients in the combined cell knew that they were receiving two active treatments rather than one (CBT alone) or possibly none (fluoxetine and pill placebo).

Recent studies suggest that comparisons between unblinded and blinded treatments may be flawed. Sneed et al. (2007) recently examined how antidepressant response rates differ between placebo-controlled (i.e., active vs. inactive treatment) and comparator (i.e., active vs. active treatment) trials for late-life depression. Patients in comparator trials know that they are receiving a medication without knowing the exact agent, while patients in placebo-controlled trials do not know whether they are receiving an active

medication. Sneed et al. found that the odds of being classified a responder in comparator trials were nearly two times the odds of responding in the placebo-controlled trials. The estimated probability of response in placebo-controlled trials was 0.46 compared to 0.63 in comparator trials.

Rutherford et al. (2007) followed up on these results in a systematic analysis of clinical trials of antidepressants for major depression in adults aged 18–65 years. Response and remission rates to antidepressant medications were compared across placebo-controlled and comparator trials. In the 48 placebo-controlled and 42 comparator trials examined, the odds of being classified as a responder to medication in comparator trials were 1.8 times the odds of being classified as a responder in placebo-controlled trials (95% CI = 1.45–2.17, $p < 0.001$), and the odds of being classified as a remitter to medication in comparator trials were 1.5 times the odds of being classified a remitter in placebo-controlled trials (95% CI = 1.11–2.11, $p < 0.001$). The estimated probability of response to medication in placebo-controlled trials was 0.52, as compared to 0.65 in comparator trials.

These results demonstrate that antidepressant response and remission rates are lower when patients do not know that they are receiving active treatment (i.e., placebo-controlled trials) vs. when they know that they are receiving medication without knowing the exact agent (i.e., comparator trials). This situation is relevant to the open and blinded administration of treatments given to patients in many combined medication and psychotherapy studies. It appears that clinical trials comparing open to blinded treatments are significantly biased against the blinded treatment (i.e., placebo-controlled medication). Since most studies comparing medication and psychotherapy have included a placebo treatment condition (e.g., the TADS study), the possibility exists that the current literature may underestimate the effect of medications compared to psychotherapy and combined treatment. These studies need an open medication treatment cell in order to correct this bias.

## Future Combined Treatment Studies

Some important questions cannot be answered from the results of studies using current clinical trials methodology. First, the efficacy of psychotherapy cannot be definitively determined, since the absence of a psychotherapy placebo rules out performing a double-blind, randomized clinical trial comparing psychotherapy to psychotherapy placebo. Rather, the effectiveness of psychotherapy and combined medication/psychotherapy can only be judged relative to comparison groups. As discussed above, one must avoid confounding such a study by comparing openly administered psychotherapy to placebo-controlled treatment with medication. Placebo-controlled treatments can only be validly compared to other placebo-controlled treatments, as occurs in a three-cell study of two medications and pill placebo with treatment allocation concealed. Known active treatments can only be compared to other active treatments, such as a study of one medication vs. another (without a placebo cell), one psychotherapy vs. another, or psychotherapy vs. medication (without a placebo cell).

For studies including medication and psychotherapy treatment cells, all treatments must be administered openly, which allows one to answer the question of whether combined treatment is superior to monotherapy with either psychotherapy or medication. There is a recent example of such a study design, namely the three-cell design of Keller et al.'s (2000) study of combined psychotherapy/nefazodone vs. nefazodone and psychotherapy alone. Interestingly, this study has provided some of the most compelling data to date showing the value of combined treatment for depression over monotherapy, but it also took place in a special population of chronically depressed patients.

However, it is possible to determine whether adding medication to treatment with psychotherapy is beneficial. In a study comparing psychotherapy plus pill placebo, psychotherapy plus medication, medication, and pill placebo, the medication vs. pill placebo comparison allows one to determine whether the sample studied was medication responsive and supports the validity of the study's methods. If medication is found to be superior to placebo, then the comparison of psychotherapy plus medication to psychotherapy plus pill placebo allows one to determine the value added by combined treatment relative to psychotherapy alone. An example of this study design is the Reynolds et al. (1999) study discussed above, which compared a combination of nortriptyline and IPT, nortriptyline alone, IPT plus pill placebo, and pill placebo alone in 84 elderly outpatients with bereavement-related depression. It should be apparent that the lack of a psychotherapy placebo condition makes it the case that one cannot determine whether it is helpful to add psychotherapy to treatment with medication. Additionally, fair comparisons cannot be made between the psychotherapy and medication/placebo cells due to the problems of comparing open and placebo-controlled treatments.

Future clinical trials of medication, psychotherapy, and combined treatment must heed the limitations discussed above, in order to avoid confounding their results. Experimental treatments include factors that may affect patient outcome beyond the specific effect of the treatments under study. In order to validly compare specific treatment effects, all variables beyond these specific treatment effects must be controlled and standardized across the treatments being compared. In particular, since the open vs. placebo-controlled administration of the same treatment may affect patient outcomes, blinding (i.e., what patients, doctors, and outcome raters know about the treatment received by the patient) must be the same for all treatments in a research study.

## Technical Considerations in Doing Combined Treatment

Evaluating a patient with depressive or anxiety disorders, reviewing the empirical evidence for different medication classes and psychotherapeutic modalities, and deciding to recommend combined treatment are only the beginning of the clinician's task when treating such a patient. Clinicians must then execute the treatments recommended, which can present unique challenges due to the use of multiple treatment modalities for a single patient. How does one actually do combined treatment with medications and psychotherapy? To begin a discussion of the techniques and strategies for doing combined treatment, it is helpful to be aware of three issues arising in nearly all combined treatments. What follows is meant to be generally applicable to all psychotherapeutic modalities and patient disorders.

## Deciding Whether to Initiate Combined Treatment—the Mind of the Therapist

When conducting a diagnostic evaluation of a psychiatric patient, psychiatrists learn about the extent and development of the presenting symptoms, as well as the patient's personal and developmental history. As yet, we do not definitively know the etiology of the symptoms—we can only know what symptoms are present and make inferences about potential etiologies. In constructing a treatment plan, we can offer the patient our expertise regarding which treatments are known to best treat the symptoms, character traits and/or interpersonal difficulties that have brought the patient to treatment.

Nevertheless, we are influenced in our treatment recommendations by our hypotheses about the etiologies of our patients' symptoms, and these hypotheses are in turn influenced by many factors; our training, clinical and personal experiences, and exposure to research studies are all powerful influences. Being aware of these potential influences on our thinking about differential therapeutics broadens the range of potential treatment options and helps avoid clinician bias.

## Deciding Whether to Initiate Combined Treatment—One or Two Disorders?

There are two different types of clinical situations for which combined treatment may be recommended:

- Combined treatment may be prescribed for a single disorder. For example, combined treatment with medication and CBT is a common treatment plan for major depressive disorder. An analogy to internal medicine might be the use of diet and blood pressure medication to control hypertension in a person at risk of myocardial infarction.
- In the second situation, two types of treatment may be used for a single individual because two *different* disorders are being treated. For example, a patient who is being treated with psychodynamic psychotherapy for chronic maladaptive character patterns may have generalized anxiety disorder for which medication is prescribed. In this case, two treatment modalities are being used simultaneously without being combined treatment for the same disorder, even though the disorders may be related. This is analogous to the combined use of an antihypertensive and a cholesterol-lowering agent in the treatment of two cardiac risk factors.

It is important for both the practitioner and the patient to understand whether the combined treatment is for one or two (or more) disorders, not only to best inform the patient about his/her treatment, but also because it may direct the way in which the treatment is optimally conducted. A combined treatment that has been shown to be effective for a single entity may be optimal only when the medication and psychotherapy are conducted simultaneously; on the other hand, if two disorders are being treated, sequential treatment might be optimal (see below for further discussion of simultaneous vs. sequential treatment). It is also important for the clinician to at least consider the idea that the two different disorders may ultimately be shown to be part of the same syndrome. For example, a patient who is being treated with medication for anxiety and psychotherapy for borderline personality disorder may exhibit fewer borderline traits once his/her anxiety is properly medicated.

## Deciding Whether to Initiate Combined Treatment—Simultaneous or Sequential Treatment?

As discussed above, different clinical situations may call for different ways of conducting a combined treatment. One choice involves whether to administer both forms of treatment simultaneously or whether to sequence them. Again, this will depend in large part on whether it is the simultaneous administration of the psychotherapy and medication that has been shown to make the combination an effective treatment. When the two modalities are treating different disorders, sequential treatment may often be preferable. This is often true when symptoms of a severe affective or anxiety disorder may make engagement in psychotherapy difficult.

For example, a patient who presents with symptoms of major depression in the setting of a string of poor relationship choices may be best treated by sequencing the treatment. Here, pharmacologic treatment for the major depression needs to begin immediately, but the patient may be better able to engage in psychotherapy after his/her depressive symptoms have at least partially resolved. Sequencing treatments may also be helpful diagnostically. The patient who seems to have chronic self-esteem issues, who is having symptoms of a depression, may have fewer issues with esteem once out of the throes of the affective disorder, since feelings of low self-esteem can be a symptom of depression.

It should be noted that sequential treatment is often used in other areas of medicine, whether in a planned fashion (i.e., chemotherapy regimens) or due to the failure of one medication to provide the desired outcome (i.e., antibiotics). Fava (1999) has outlined four psychiatric applications of sequential treatments: (1) changing the orientation of psychotherapy when the first orientation has not achieved treatment goals. (2) switching antidepressants or augmenting treatment when the first medication has not resulted in adequate symptom relief. (3) introducing psychotherapy when medication alone has not been completely effective. (4) starting medication when psychotherapy alone has not been completely effective (Fava 1999).

## Technical Considerations

Once the clinician and the patient decide together that the optimal treatment for the patient is combination treatment with psychotherapy and medication, the next question is which treatment model to use to best effect the treatment plan. There are three basic models for the use of combined treatment in clinical practice:

- The one practitioner model—one psychiatrist administers both medication and psychotherapy to the patient.
- The split treatment model—two practitioners treat the patient—one administers psychotherapy and one is the psychopharmacologist.
- The consultant model—one psychiatrist is the primary practitioner, administering both psychotherapy and medication, but a consultant is involved to add expert advice and to potentially see the patient on an as-needed basis.

Each of these models may be more or less appropriate for different clinical situations, and each has a unique profile of benefits and drawbacks. These models are applicable to any type of psychotherapy—CBT, IPT, DBT, supportive psychotherapy, behavioral therapy, and psychodynamic psychotherapy. It is important for the clinician to be well versed in the characteristics and logistics of each of these models and to have a clear sense of how to choose among them.

## Choosing a Treatment Model for Combined Treatment with Medication and Psychotherapy

If the practitioner decides that combined treatment is the optimal approach, then determining which treatment model to use is an essential part of designing the treatment plan and should be an active choice on the part of the clinician and the patient. Too often, psychiatrists assume that a single clinician will administer both medication and psychotherapy, or, conversely, that the treatment will be split. While the decision is based on multiple factors, it can be carefully thought through; the following algorithm is a guide to best effect the optimal treatment plan.

### What Are the Clinician's Clinical Strengths?

In choosing the appropriate treatment model for combined treatment with medication and psychotherapy, the clinician must first assess his/her clinical strengths. Some psychiatrists feel that they are well trained in psychopharmacology but not in psychotherapy. Others may be more confident of their psychotherapy skills. Some practitioners who frequently practice combined treatment may feel that they are not knowledgeable about the particular type of psychotherapy appropriate for a specific patient. A psychiatrist who routinely prescribes medication may still recommend a medication with which he/she is relatively unfamiliar. In constructing the treatment plan that best serves the patient, the clinician will do well to be honest about his/her capacity to administer the treatment that is optimal for the patient.

### Will Either Treatment Modality be Compromised if Administered by the Same Clinician?

Even if the clinician feels capable of delivering each type of treatment that is appropriate in a given clinical situation, the clinician may not feel able to administer them concomitantly to the same patient. For example, a clinician may decide that techniques that are important for good pharmacologic management, such as giving opinions, talking to family, and monitoring vital signs, would interfere with his/her ability to maintain an appropriate therapeutic stance in a psychodynamic treatment. Similarly, clinicians conducting certain manual-driven treatments, such as CBT, might decide that ongoing pharmacologic management would be to intrude unproductively on the work of the sessions. In weighing this consideration, the clinician needs to clearly delineate the optimal working conditions for helping the patient to receive the best possible psychotherapy and psychopharmacologic care.

*Possibilities:*

- The clinician may elect the split treatment model if the technique required for one treatment modality would render the technique for another modality suboptimal.
- The clinician may elect the consultant model if these difficulties are periodic in the treatment.

### Are There Reasons Why the Treatment Should Not Be Split?

In some circumstances, the practitioner may feel that a split treatment would jeopardize the quality of the treatment. For example, patients who tend to idealize and devalue different members of the treatment team (e.g., some patients with borderline personality disorder) might be better served by having one clinician administer both the psychotherapy and the medication, since this can jeopardize the essential communicative link between clinicians and sabotage the treatment. Patients behaving in such a way are often best treated by a single clinician in order to minimize the potential for manipulation and to keep all of the information in one treatment setting. A clinician who needs assistance in this situation may seek consultation rather than splitting the treatment. Another situation might be one in which the medication has to be monitored closely, such as on a weekly basis. This might be true for any unstable patient, such as a rapidly cycling bipolar patient or a patient with affective instability and borderline personality disorder.

### Does the Patient or Clinician Have Preconceptions about Combined Treatment that Should Be Addressed to Optimize Clinical Decision Making?

The clinician who is considering combination treatment with psychotherapy and psychopharmacology needs to be well versed in the myriad preconceptions that this situation engenders in both doctor and patient. These may include (but are not limited to) the following:

*Patient:*

- Since I am going to a psychiatrist, he/she should be able to administer all of the treatment.
- Psychiatrists do not know how to conduct psychotherapy.
- If my psychiatrist refers me to another clinician for part of the treatment, it is because he/she is not particularly interested in my case.

*Clinician:*

- As a psychiatrist, I should be able to administer all types of treatments to my patients without having to split the treatment.
- Administering medication to a patient in psychotherapy is no different than administering medication to a patient who is not in psychotherapy.
- My patient will think that I am not competent if I bring another clinician into the treatment plan to split the treatment or to act as a consultant.

If unaddressed, thoughts and feelings such as these can erroneously guide treatment decisions, often leading the clinician to choose a treatment model for inappropriate reasons.

### What Is the Patient's Preference?

When patient and clinician begin a treatment, both participants have opinions about how the treatment should be conducted. Aside from preconceptions about the treatment, patients may have realistic preferences about

whether the treatment should be conducted with a single practitioner or as a split treatment. If the practitioner feels that he/she does not have the skills to offer both the psychotherapy and the medication, the patient may prefer to be referred to a practitioner who is able to offer both treatments. If the practitioner thinks that the one practitioner model would be either optimal for this patient or at least equal to a split treatment, the option of referring to another practitioner should be offered as an option to the patient.

### Are There Logistical and/or Financial Considerations That Need to Be Taken into Account?

Although choosing a treatment model for administering combined treatment should be based primarily on clinical considerations, there are often logistical and financial considerations that need to be taken into account. These occur in the following types of situations:

- The clinician may be the only practitioner who is geographically near the patient.
- The clinician may be working in a managed care situation.
- The patient may not be able to afford to see more than one clinician at a time.
- The patient may be more able to afford psychotherapy with a non-MD practitioner.
- The pharmacologic treatment must be affordable enough for the clinician to be able to see the patient as often as necessary.

In these situations, the clinician and the patient need to choose options for the clinical situation that optimize the treatment plan within the context of the logistical and/or financial constraints.

### Summary

The clinician can use these six basic points as a simple algorithm for making decisions about which treatment model to choose for administering combined treatment with medication and psychotherapy.

## Treatment Models for Combined Treatment with Medication and Psychotherapy

Each model for combined treatment with medication and psychotherapy is uniquely suited to particular clinical situations. Each has advantages and disadvantages, as well as characteristic transferences and countertransferences that are commonly encountered. In what follows, three models for combined treatment are discussed.

### The One Practitioner Model

The psychiatrist/clinician has a unique position among mental health professionals in that he/she may elect to administer combined treatment without splitting the treatment. This allows the clinician to not only construct an integrated, multimodal treatment plan, but also to conduct an ongoing treatment that includes many treatment modalities simultaneously. This can be an advantage when the clinician is trying to parse out whether a given symptom is best treated pharmacologically or psychotherapeutically. If one clinician is administering both treatments, he/she can decide on an ongoing basis about therapeutic options. Additionally, the patient in psychotherapy is generally seen on a weekly or multiple-time per week basis, which can allow the clinician to notice changes in symptomatology and medication side effects and rapidly make adjustments.

These advantages are balanced, however, by the potential pitfalls inherent in trying to "wear two hats" while treating the patient. Each treatment modality—psychotherapy and psychopharmacology—is challenging to administer and takes time. A psychopharmacologist is trained to carefully monitor both symptoms and side effects on a regular basis (often using structured interviews or scales), check vital signs, and suggest changes in the medication regimen when needed. If the visits are also devoted to psychotherapy,

Vignette

Ms. T is a 27-year-old single woman who presented to Dr. B with symptoms of anxiety and depression 3 weeks after being fired from her job. Her symptoms included insomnia, low self-esteem, difficulty concentrating, tearfulness, and occasional panic attacks triggered by things that reminded her of her boyfriend. Although she had never seen a psychiatrist before, she had been persuaded to seek a consultation by her mother, who was being successfully treated with a combination of psychotherapy and medication for an unclear affective disorder. In the initial visit, Ms. T told Dr. B about her current symptoms, as well as her lifelong history of anxiety, including childhood separation anxiety and chronic social phobia. In addition, Ms. T explained that she was in the middle of her parents' very contentious divorce. She no longer knew which parent was right or whether either of them had her best interests at heart. In response to Dr. B's questions about her usual patterns of adaptation, Ms. T described a life-long pattern of losing self-esteem during interpersonal crises. There was also some suggestion of chronic difficulties with anxiety and affect regulation. Dr. B both diagnosed a major depressive disorder and suspected that an anxiety disorder was present prior to the current illness. He prescribed escitalopram 10 mg per day and also suggested to Ms. T that she begin once-weekly supportive psychotherapy to address symptoms of depression as well as her chronic issues related to self-esteem management.

In the third week of treatment, when Ms. T was still on 10 mg of escitalopram, she called Dr. B saying that she was having a strange reaction to the medication. She felt that her thoughts were racing and that she could not concentrate. She also described odd sensations running through her arms. Dr. B felt that this was most likely increased anxiety after starting the SSRI; however, he was also concerned about possible hypomania. He was relieved to see her the next day, when she displayed no evidence of hypomania—her speech was normal in rate and rhythm, and she was interruptible. She did seem anxious, and on further questioning, akathisia seemed likely. Dr. B recommended low-dose clonazepam and suggested that Ms. T decrease the escitalopram and titrate up more slowly. The symptoms resolved, but Ms. T continued to have tremendous sensitivity to medication changes, which Dr. B was able to address swiftly since he was seeing her on a weekly basis. This prevented breaches in the pharmacologic treatment and helped Dr. B to diagnose the symptoms.

when does or should the pharmacologic management take place? Often, it is discussed "on the fly," either before or after the "real" content of the session occurs. Once a satisfactory medication regimen is established, the clinician and patient may "forget" about the medication and not discuss the pharmacologic treatment, despite the fact that the clinician is still prescribing medication for the patient. This can lead to many things being overlooked, such as changes in symptoms, side effects, and opportunities to discontinue medication after an appropriate amount of time.

The clinician who elects with the patient to use the one practitioner model must be aware of these potential pitfalls and must construct ways of working with the patient that do not slight either treatment modality. It is important to remember that even though the clinician and patient may elect one model as part of the initial treatment plan, this can change during the course of the treatment. For example, if a patient's medication management becomes very complicated, the clinician and patient may elect to switch to a split treatment so that each modality has adequate time devoted to it, or to temporarily involve a consultant until stability is once again achieved. Avoidance of one or the other treatment modality in a combined treatment should signal to the clinician that something is amiss in the balance of the treatment.

As illustrated in the above vignette, use of the one practitioner model for combined treatment may also present challenges for the delivery of psychotherapy. Time spent in medication management may detract from valuable session time that could be spent in psychotherapy. In addition, techniques used by the pharmacologist may present a challenge to the psychotherapist who is attempting to maintain technical neutrality as part of the psychotherapy, or who is trying to listen with evenly hovering attention. Good pharmacologic treatment is often quite goal directed—the pharmacologist has specific questions that he/she needs to address at each visit and cannot simply wait to see if certain topics are brought up by the patient.

This may present a challenge for psychotherapists who also prescribe medication. Each practitioner needs to decide for him/herself how to work in both modalities if choosing the one practitioner model. Rather than practicing substandard psychopharmacologic management, clinicians may modify their psychotherapeutic approach while discussing medication management. This is essential regardless of the psychotherapy type—it is as true for CBT or IPT as it is for psychodynamic or supportive psychotherapy. This type of discussion may also enhance the clinician's understanding of the patient's mind rather than detracting from the treatment.

Vignette

Mr. R is a 55-year-old man who entered psychotherapy after the death of his mother prompted him to think about his goals for the rest of his life. Having chronically denied himself pleasure, he had worked hard to support his family and now felt "cheated" out of many things that he had wanted to accomplish. His work in psychodynamic psychotherapy with Dr. F helped to clarify many masochistic patterns that had led him to chronically make choices with which he was no longer happy. Approximately 1 year into the treatment, Mr. R began to experience low energy, early morning awakening, poor appetite, and passive suicidality. After a few weeks, Dr. F diagnosed major depressive disorder and suggested treatment with sertraline, which Mr. R accepted.

After 5 weeks of treatment produced no improvement, Dr. F decided to switch to venlafaxine. Again, 5 weeks later, after appropriate increases in the medication, there was only moderate improvement. In addition, the patient had severe gastrointestinal symptoms. At this point, Mr. R began to come late to psychotherapy sessions for the first time in the course of the treatment. When Dr. F discussed this with the patient, it became clear that Mr. R felt that he was being cheated in his psychotherapy because his sessions were being exclusively taken up with questions about dosages and side effects. At this point, Dr. F suggested to Mr. R that he consult a psychopharmacologist to continue the pharmacologic treatment so that the psychotherapy could proceed.

## The Split Treatment Model

Perhaps due to reimbursement mechanisms, much of the combined treatment that is currently practiced today occurs in the split treatment model. Treatments may be split for many reasons including the following:

- The patient's therapist is not an MD.
- The practitioner may not feel competent in both treatment modalities.
- The practitioner may feel that one or the other treatment would be compromised if they were administered by a single practitioner.
- Logistical and/or financial considerations (such as payment by a managed care company) may dictate that the psychiatrist can only be paid for part of the treatment.

Splitting the treatment can often free up each practitioner to concentrate solely on one treatment modality. Unlike the practitioner in the one practitioner model, the therapist or pharmacologist need only focus on that treatment modality when meeting with the patient. However, effective split treatment necessitates that both practitioners consider the ways in which things that the patient reports might be related to the other treatment modality. For example, a patient's worsening symptoms reported to a psychopharmacologist might be related to something that is happening in the patient's psychotherapy, while increased irritability or anxiety reported to a therapist might be best treated with a medication.

Communication between the clinician prescribing medication and undertaking a patient's psychotherapy is essential, especially since these clinicians may have different professional backgrounds. Most frequently, psychiatrists serve the pharmacologic role, while psychologists, social workers, or licensed therapists serve as the patient's psychotherapist, but many more arrangements are possible. For instance, psychiatrists treating patients with psychotherapy or psychoanalysis may also elect to have their patients' pharmacologic treatment managed by another psychiatrist. Additionally, primary-care physicians are now prescribing psychotropic medications with increasing frequency. In such a situation, it is important for the mental health professional undertaking psychotherapy to communicate with the internal medicine

physician about psychiatric illness and the medical ramifications of treatment.

When a patient comes for an evaluation with a psychiatrist, he/she may hope that the psychiatrist can administer all aspects of the treatment. Referral to a second practitioner for either psychotherapy or psychopharmacology may prompt the patient to feel rejected or think less of the evaluating psychiatrist. These reactions are best handled via straightforward discussions of the reasons for referral and the patients' thoughts and feelings. Once the split treatment is underway, the patient may feel more comfortable with one practitioner or another and is likely to discuss each treatment with the other practitioner. A patient may value the psychopharmacologist more because of the "rapid help" that comes from medication or may value the psychotherapist more, complaining that the psychopharmacologist "never asks about my life." Sometimes, a session in which both practitioners are present can be helpful to ensure that all three people involved in the treatment are "on the same page."

Psychiatrists who are trained in both psychotherapy and psychopharmacology may feel like failures if they are unable to offer both treatments to the patient. This may lead them to underestimate themselves or to join with their patients in the devaluation of nonmedical therapists. As above, communication between the two practitioners involved in a case is critical to avoid problems like those mentioned above. In addition, developing ongoing relationships with practitioners with whom one frequently splits treatment helps to develop trust between practitioners. Mutual respect between the practitioners in a split treatment is essential for the development of a good working relationship in which undermining can be minimized. This type of ongoing communication can also result in mutual learning, as the two practitioners share their perspectives about patients over time.

### The Consultation Model

Usually, combination treatment with medication and psychotherapy takes the form of the one practitioner model or the split treatment model. However, a third model, the consultation model, is also important. In this model, the patient's primary clinician enlists the help of a consultant, who is usually an expert in one or the other treatment modality. This may be helpful during diagnostic situations, such as when a patient in an ongoing psychotherapy has worsening symptoms of depression that might require the addition of a medication. In this situation, the primary practitioner may feel hampered in his/her ability to objectively evaluate the diagnostic situation, given the close work in which he/she is engaged with the patient.

Here a consultant may be called upon to join the treatment for some period of time. For example, he/she could see the patient and the patient's family for a diagnostic consultation. In another situation, a psychotherapist may call a consultation when the psychopharmacologic management of a patient becomes so complex that session time is exclusively devoted to medication management questions. Also, clinicians may find themselves needing help with a pharmacologic situation with which they are unfamiliar—such as the need to use a medication that they have never used or in the case of a particularly refractory mood disorder. In these situations, the consultant can either interact with the therapist only or serve to temporarily split the treatment. If the treatment is temporarily split, open lines of communication are as important to this success of this model as they are to the split treatment model.

## Conclusions

The empirical study of medications and psychotherapy for depression and anxiety started with competitive trials of medication vs. psychotherapy, progressed to studies comparing combined treatment and monotherapy, and has most recently focused on augmentation studies of medication and psychotherapy. Most early studies comparing antidepressant medications and psychotherapy for depression did not show clear superiority of one treatment modality over the other. Therefore, as an initial treatment strategy for mild-to-moderate, unipolar, nonpsychotic depression, it appears that either antidepressant medication or an evidence-based psychotherapy such as IPT or CBT would be reasonable choices.

In light of the frequency with which combined treatment with psychotherapy and antidepressant medication appears to be prescribed, the dearth of evidence demonstrating superiority of combined treatment vs. monotherapy as an acute treatment for depression and anxiety disorders is surprising. Many early studies comparing combined treatment to psychotherapy or medication alone did not find improved outcomes, although meta-analyses of these treatments have generally found small but consistent results in favor of combined treatment. These early studies may not have been adequately powered to detect these small differences, and as discussed, comparisons of combined treatment to monotherapy can be flawed when they are made between open and blinded treatments. Nonetheless, while combined treatment may not be appropriate as an initial treatment for all patients, there are some data to support its use in cases of more severe or chronic depression, or where noncompliance, comorbidities, and treatment refractoriness have complicated the initial presentation.

The most important clinical question may relate to the sequencing of treatment with psychotherapy and medications, as well as the augmenting of one treatment modality with the other. As results from the STAR*D study indicate, less than 40% of patients are likely to experience remission with the first treatment prescribed. This makes it critical to study augmentation and switching strategies for those patients not experiencing remission, and combining treatment modalities is one strategy that should be considered.

The decision to recommend combined treatment with psychotherapy and medications is only the first step. Executing this recommendation requires serious consideration of the preconceptions doctor and patient bring to the treatment, logistical realities of the clinician's credentials and the patient's resources, and the nature of the illness or illnesses under treatment. There are few empirical data to guide clinicians deciding between the various models of combined treatment. The most that can be recommended at present is candid discussion with the patient of the benefits and disadvantages of various treatment strategies and awareness of the difficulties of combined treatment in the mind of the clinician.

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CHAPTER

# 114 Patient Compliance

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## Introduction

Epidemiological research suggests that one-half to two-thirds of persons with psychiatric disabilities that may benefit from treatment either fail to seek help; or, when they do, are noncompliant with treatment (Kessler et al. 2001, Regier et al. 1993).

In the past 15 years the number of psychiatric medications has increased to well over 200 actively used medications; yet, in order to be effective, these medications must be taken by the patient. Medication should be prescribed according to a rational regimen that is based on integration of general pharmacokinetic and pharmacodynamic principles with "real-life" variables. Medication regimens should be both efficacious and feasible (Katzung 2007, Haynes et al. 1979).

Poor compliance can adversely affect medical decisions. Physicians, unaware of compliance problems, may incorrectly assume that poor therapeutic outcomes are due to failure of the prescribed treatment and increase the dose, add medication, or prescribe medication with potentially more serious adverse reactions (Katzung 2007).

Although thousands of studies have been published regarding medication noncompliance, interventions developed to date have had only limited impact on the problem (Sackett and Snow 1979, Haynes et al. 2005). Compliance to psychiatric medication poses special challenges, due to many factors—some related to medications in general and some specific to psychiatric medications. Psychiatric illness has a direct impact on the ability and motivation of patients to take the very medications that have been prescribed to treat their symptoms. In addition, a growing body of literature suggests that mental illness stigma and ubiquitous fears about psychiatric medications may be of particular significance in determining compliance to psychiatric medications (Sirey et al. 2001, Corrigan and Watson 2006).

This chapter details the complexity of medication compliance and the impact of noncompliance on treatment of psychiatric disorders. Methods for quantifying medication compliance are reviewed. Risk factors for medication noncompliance are discussed, including lack of perceived necessity for medication, cognitive deficits, medication side effects, financial burden (e.g., poverty, lack of insurance, insurance nonparity), mental illness stigma, poor doctor–patient relationship, and negative patient/family beliefs about medication. This chapter also reviews emerging strategies that providers can use to maximize patient compliance to psychiatric medication. Practical and specific suggestions are given with clinical examples.

## Definition: "Compliance" versus "Adherence"

Haynes (1979) defined compliance as the "extent to which a person's behavior coincides with medical advice," e.g., taking medication or engaging in other prescribed treatments. Patients who are noncompliant to prescribed treatment are often seen as derelict. Because of the pejorative connotation of the term compliance, many researchers have adopted the use of adherence. In his thoughtful and comprehensive analysis of current medical paradigms for medication treatment, Trostle (2000) argues from an anthropological perspective, that discussing patients' "compliance" or "adherence" to treatment is tantamount to discussing "the authority of medical professionals."

When viewed through the eyes of physicians, patient noncompliance to prescribed medication may seem irrational. In reality, patient compliance to any treatment recommendation is a complex behavior related to many factors that are patient, provider, and disease based. In addition, there are contextual factors that influence patients' compliance to prescribed medication, such as the increasing influence of managed care, pharmaceutical direct-marketing strategies, and societal stigma of psychiatric medication. Adequate medication compliance is achieved by agreement between the doctor and patient, rather than a unilateral decision by either.

Understanding treatment compliance is more problematic in pediatric and adolescent patients, and can present psychodynamic and ethical challenges. Assumptions about patient responsibility, rationality, and control do not apply with pediatric patients who generally have neither the cognitive nor legal ability to consent or refuse to take psychiatric medication. There is considerable state-to-state and national variation regarding consent for, right to, and confidentiality regarding psychiatric treatment in minors. Readers are encouraged to refer to their local mental health codes to familiarize themselves with local legislation.

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## Treatment Refusal

Grossly categorized, patients may be classified into:

- Those who overtly refuse medication treatment(s)
- Those who ostensibly accept medication treatment but never fill their prescription(s)
- Those who are poorly compliant with the prescribed medication regimen(s)
- Those who adequately comply with the prescribed medication regimen(s)

Patients who are adamantly opposed to psychiatric medication may not (voluntarily) present to a psychiatrist. A substantial percentage of those patients who *are* evaluated by psychiatrists still refuse treatment with psychiatric medication.

Refusal of psychiatric medication can be viewed from a legal perspective. The legal right to refuse treatment varies by jurisdiction. Most psychiatrists recognize clinical situations in which it is reasonable to pursue involuntary treatment (e.g., patients who are a danger to themselves or others). However, short of life-threatening situations and/or cases of patient incompetence, it is advisable to consider that forced treatment may severely compromise future therapeutic efforts with the patient. Rather than immediately attempting to override a patient's refusal, it behooves the physician to examine the factors underlying the refusal, with the aim of resolving the issue within the framework of the therapeutic alliance. Relevant factors may include reality-based concerns (e.g., potential side effects), idiosyncratic meanings of treatment (e.g., if I take medication I am crazy), primary and secondary gains, transference effects, and familial and cultural factors (Appelbaum and Gutheil 1982).

## Overview of Theoretical Models

Various conceptual models have been developed to describe patients' health behavior during treatment of chronic conditions (Leventhal and Cameron 1987, Conrad 1985). Major models of health behavior that have been developed from social cognitive theory include: (1) Health Belief Model; (2) Theory of Reasoned Action and Theory of Planned Behavior; (3) Stages of Change Theory; and (4) Protection Motivation Theory. Although these models differ in important ways, they all assume that medication compliance can be predicted by patients' perceptions of threat from the medical condition and their expectancy regarding the consequences of medication compliance.

The Health Belief Model (HBM) assumes that medication-taking is a rational decision made by the patient based on a cost–benefit analysis (Janz and Becker 1984, Rosenstock 1988). Regardless of the "objective" view of the prescribing physician, it is the patient's perception of the benefits and risks of medication that determines their compliance behavior.

The HBM has been demonstrated to have predictive value with regard to medication compliance in a variety of chronic medical conditions, including tuberculosis, diabetes, and hypertension (Becker and Maiman 1975, Becker 1985). More recently, the HBM has been used in studies of medication compliance in psychiatric disorders (Budd et al. 1996). Lingam and Scott (2002) conducted a review of research (1976–2001) on treatment noncompliance in adults with affective disorders. They concluded that patients' attitudes and beliefs are at least as important as side effects in predicting compliance with medication for affective disorders and that the HBM is a promising tool for identification of individuals at risk for noncompliance.

Bush and Iannotti (1988, 1990) adapted the Health Belief Model for use in children and adolescents. They added key developmental and contextual components to the model, including caretaker attitudes (perceived threat to child from illness, perceived benefit of medication), parent–child interactions, level of child/adolescent autonomy, and child readiness factors (illness concern, expectancy for efficacy of medication treatment). Their model, called the Children's Health Belief Model, was based on data from 420 elementary age children and tested the model with a sample of 270 adolescents. The model accounted for 64% of the variance in adolescents' behavioral response to illness. Based on these findings, the best predictors of adolescent compliance to treatment were their perception of the severity of the illness and the predicted/perceived benefit of the medication. They found that primary caretaker's attitudes influenced their adolescents' readiness and expectancies regarding medications, but that the adolescents' own cognitions and attitudes were most important in determining compliance to medication. Bush and Iannotti (1988, 1990) concluded that while parents do influence their children's health beliefs and health behavior, these influences are small when compared to other developmental influences on children's attitudes and behaviors.

The Theory of Reasoned Action (TRA) by Ajzen and Fishbein (1980) and its more recent extension the Theory of Planned Behavior (TPB) by Ajzen (1988) resemble the HBM in the assumption that people make rational decisions (i.e., cost–benefit analyses) about their behavior based on information and beliefs about the behavior, and that health behaviors are under volitional control. The TRA and TPB differ from the HBM in two major ways. TRA and TPB assert that patient intentions are the most important determinant of their behavior. Furthermore, they state that intentions are a function of a person's attitude toward the behavior and the person's perceptions of social norms regarding the behavior. When applied to patient compliance to psychiatric medication, a patient's attitude toward medication compliance is based on their predicted consequences of taking medication and the value (costs and benefits) they attribute to these consequences. For example, if a person believes that a medication is effective in the treatment of a particular symptom/illness, then they may believe that the consequence of *not* taking the medication will be persistence or return of the symptom/illness. If so, depending on the degree of distress from the symptom/illness, they may see a benefit in taking the medication; however, the "cost" of taking the medication may outweigh this benefit. According to TRA/TPB theory, however, an important factor influencing their decision is a person's expectation of whether significant others in their life (i.e., family and friends) will support their taking psychiatric medication. Of course, the person's motivation to comply with the preferences of their significant others, will determine the impact of perceived social norms on predicting their medication compliance.

Stages of change theory is based on the premise that behavior change occurs in stages or phases and the

factors that influence behavior may change from one stage to another. Implicit in stage models is the assumption that, initially, behavior change is largely under the control of deliberate cognitive processes. As the new behavior is repeated over time, situational cues to decisions begin to elicit the cognitive processes that result in decisions and intentions. Over time actions may come to be performed automatically in response to situational cues such that they are no longer under volitional control (Prochaska et al. 1994).

Protection Motivation Theory (PMT) was originally proposed to provide conceptual clarity to the understanding of fear appeals. It was later extended to a theory of persuasive communication, with an emphasis on the cognitive processes mediating behavioral change. According to the theory, appraisal of a health threat and appraisal of possible coping responses result in the intention to perform adaptive responses (protection motivation). The intention to protect oneself depends upon four factors: (1) perceived severity of the threat; (2) perceived vulnerability; (3) perceived response efficacy—expectancy that carrying out recommendations can remove the threat; and (4) perceived self-efficacy—the belief in one's ability to execute the recommended courses of action successfully (Rogers 1983).

## Prevalence of Medication Noncompliance

Rates of medication compliance/noncompliance depend on many factors, e.g., whether the prescribed regimen is short term or long term, whether the medication is for prophylaxis or for treatment of disease. Based on their comprehensive literature review, Sackett and Snow (1979) approximated that the average compliance for short-term regimens is 62% versus a range of 33–94% (mean 57%) for long-term preventive regimens and 41–69% (mean 54%) for long-term treatment regimens. Patients prescribed medications for long periods of time, for prophylaxis, or for chronic diseases appear to be less compliant.

The large variation in reported rates speaks to the complexity of the behavior. Rates vary substantially depending on the method of measurement. Medication-taking varies according to many other factors, even when considering the behavior of only one patient. A patient may be more or less compliant to a prescribed medication depending on the complexity of the regimen, the severity and type of illness, side effects, past experience with medication, and trust in their physician.

The specific type of medication prescribed may also be important. Psychiatrists have observed that some patients appear to be more apprehensive about taking psychiatric than nonpsychiatric medications. The explanation undoubtedly varies from patient to patient. Available research suggests that both societal stigma of mental illness and psychiatric medication, and fears specific to psychiatric medications, contribute to this phenomenon. An individual's fear of psychiatric medication may be influenced by current and past experience with mental illness and psychiatric medication. This frequently includes input from family and friends regarding psychiatric medication. Individuals' attitudes about mental illness and psychiatric medication are highly influenced by societal lore based on actual history of treatment of the mentally ill, cinematic portrayals of psychiatry, media reports, and information on the Internet.

## Patterns of Medication Noncompliance

There are many patterns of medication noncompliance. Despite its apparent simplicity, taking medication as prescribed is a complex and dynamic behavior. Empirical evidence demonstrates that noncompliance is best understood as a variable behavior, rather than a trait characteristic. Rudd et al. (1989) reported marked inter- and intra-subject variability in medication compliance on a week-to-week basis. Patients may continue to keep appointments, while not taking prescribed medications, so attendance at appointments should not be overly reassuring. Patients prescribed more than one medication may take one medication but not others. Patients also may initially adhere to medication recommendations, but later may discontinue their medication without informing their physician. Based on a comprehensive review of reported rates, patterns, and correlates of medication noncompliance, the following have been observed:

1. Medication compliance tends to decline over time
2. Baseline compliance is the strongest predictor of long-term compliance to medication
3. Patients who have been poorly compliant in the past are more likely to be noncompliant in the future

Many studies treat compliance as dichotomous and univariate, rather than as a continuous phenomenon with multiple dimensions. A patient may adhere to one part of treatment recommendations but not to others (Fotheringham and Sawyer 1995, Orme and Binik 1989). Failure to comply with medication-taking may include omissions of doses, taking more than the prescribed dose, errors in dosage or prescribed frequency of doses, taking medication for the wrong reason, taking medication as needed rather than on a regular schedule, and discontinuing medication early.

Both the pattern and rate of missed medication doses are important. Converging evidence suggests that we view medication compliance on a continuum with many different patterns of partial compliance, but 100% compliance is abnormal. Bachmann et al. (1999) studied methods to achieve high therapeutic success despite less than perfect compliance. They suggest this may be achieved by selection of an agent that, based on its pharmacological properties, is "more forgiving" of delayed or omitted doses, such as fluoxetine. Forgiveness is defined as the drug's post-dose duration of action minus the prescribed interval between doses.

Delays and omissions in dose administration are the predominant medication errors. Electronic monitoring shows a skew toward dose omission, with widely variable intervals between doses, though dosing in the day or two prior to scheduled visits is usually correct (Feinstein 1990). Appropriate administration of the medication for the few days preceding an appointment, the so-called "white coat" compliance, does not reflect long-term compliance. One in six patients is very punctual in the timing of prescribed doses. Three in six make minor errors in timing that are too small to reduce the full-dose action of any but the least forgiving medications (Urquhart 1995, 1997).

Medication errors can be further classified according to whether the error was unintentional (forgetting or misunderstanding the dose or frequency) versus intentional (conscious decision to modify medication dose/frequency for any reason). There is a substantial difference between

forgetting to take a pill despite knowing the proper regimen, and believing, incorrectly, that only two rather than three pills are needed daily and adjusting the regimen without consulting the doctor (Rudd 1993). Patients may alter their dose of medication(s) without consulting their physician, or may take medication only "as needed." Lapses between prescribed doses of three or more days are called "drug holidays." Drug holidays occur monthly to quarterly in two-thirds of patients (Urquhart 1995, 1997). If patients have prolonged or more frequent drug holidays, not only will the medication likely be ineffective, but patients may experience side effects due to the recurrent rebound and/or first-dose effects. These side effects may, in turn, contribute to persistent or worsened compliance to the medication regimen.

## Measurement of Medication Compliance

Measurement of medication compliance is difficult. Physician estimate is a poor measure of compliance and more experienced clinicians do no better than trainees. Faithfully attending appointments does not ensure compliance with prescribed treatment, although compliance is much worse in those who fail to keep appointments. Rudd (1993) demonstrated that physicians' estimated rate of compliance is only weakly correlated to rates obtained by objective measurement or electronic monitoring. Mushlin and Appel (1978) reported that physicians correctly identify less than one half of noncompliant patients.

Although there are hundreds of studies debating the merits of different measurement methods, no existing measure is entirely fool proof. In general, measures of compliance to medication treatment can be classified as direct or indirect:

### Direct Measures

#### Supervised Doses

This is impractical and often unreliable. Even under direct observation by trained staff on an inpatient psychiatric unit, patients can feign medication ingestion. For adolescent patients, direct observation, particularly by parents, may provoke negative emotions in the adolescent struggling for autonomy.

#### Blood Levels

Blood levels of drugs and/or their metabolites are only useful when accurate measurements of all significant active metabolites of the drug are available and there is a known relationship between the clinical effects of the drug and blood/serum concentration (Morselli and Bianchetti 1983, Gualtieri and Golden 1984). In general, blood levels are clinically useful for lithium carbonate, tricyclic antidepressants, and certain mood stabilizer medications. None of the SSRI medications have serum levels that are sufficiently reliable to warrant the cost, inconvenience, and pain of blood draws. When obtained, typically the only useful information derived from an SSRI level is the gross presence or absence of the medication at the time of the blood draw (Dulcan 1998, Green 1995). Even for medications with reliable pharmacokinetic information, many drugs achieve target levels after a few doses so that appropriate administration for a few days before a blood draw ("white coat" compliance) could result in normal levels. Although a concentration of zero shows no recent medication ingestion, "spot concentrations" are of limited use.

### Indirect Measures

#### Patient/Other Self-Report

Patient self-report is the most widely used method of measuring compliance to prescribed treatment. In usual practice, clinicians do not use standardized methods; instead questions regarding compliance, if asked, are often closed and relatively leading; e.g., "are you taking your medication?" One difficulty of self-report data is the risk of misreporting. Cramer (1995) concluded that direct questioning during a patient interview has been proven inadequate to evaluate medication compliance because patients tend to tell doctors what they think the doctor wants to hear. A second limitation is lack of reliability of patient recall. Daily diaries have been used to circumvent this problem; however, few data are available on their utility or acceptability to patients. Parents or other caregivers can be asked whether the adolescent is taking his/her medication as prescribed; however, unless these individuals are present for administration of the medication, their report is presumptive. To increase the reliability and validity of self-report data, a number of researchers have attempted to develop and use structured tools for gathering patient self-report information (Morisky et al. 1986, Svarstad et al. 1999).

#### Pill Count

This refers to counting tablets returned in bottles at scheduled appointments. This method has been shown by many studies to be inadequate in measuring actual medication compliance (Pullar and Feely 1990, Cramer 1989, Rudd et al. 1989, Kruse et al. 1993, Urquhart 1995). Patients often forget or are reluctant to bring bottles to appointments. Some patients put their medication in other containers. Patients, perhaps in an attempt to please their doctor, may discard or hoard remaining tablets and bring the empty bottle.

#### Pharmacy Records

Prescription renewals can be used to monitor the frequency of refills. This method has been demonstrated by numerous studies to be inadequate in measuring actual usage of medication. Patients sometimes obtain medications from more than one pharmacy, more than one doctor, or from friends or family. HMOs and insurance plans may require patients to refill their medication quarterly. Patients may accept unneeded prescriptions because they are embarrassed to admit that they are not taking the medication as prescribed (Rudd et al. 1989).

#### Electronic Monitoring (EM)

Available since 1986, EM is now considered to be nearly a "gold standard" for measuring compliance to prescribed medication (Cramer 1989, Riekert and Rand 2002). Medication is dispensed from a container that has a microprocessor (usually in the cap) that records the date, time, and duration of each container opening. Connecting to a computer using commercially available software retrieves data. Using EM, the variability of dosing in ambulatory trials practice has been shown to be far greater than previously indicated by other methods (Feinstein 1990b, Pullar and Feely 1990,

Stichele 1990, Bond and Hussar 1991). EM provides more complete longitudinal information than any other currently available method and it does not rely on the memory of patients or doctors. EM has also been demonstrated to be superior to other methods in demonstrating important findings. For example, in their study comparing SSRIs to TCA antidepressants, Thompson (2000) found that only electronic monitoring allowed collection of data sufficiently complete to measure prolonged periods of noncompliance. Using pill count and patient questionnaires, they found no significant differences in compliance to SSRI versus TCA medication, despite marked differences in side effect profile and dose regimen. However, using survival analysis of data from electronic monitoring, they found an association between compliance and efficacy and showed superior compliance and efficacy of SSRIs versus tricyclics.

There are also potential disadvantages of electronic monitoring. EM is not completely accurate—opening the EM cap does not correlate one-to-one medication ingestion. EM is expensive—the substantial minimum investment needed to purchase sufficient devices for simultaneous patients is compounded because patients may lose or damage the devices (Riekert and Rand 2002).

## Risk Factors for Noncompliance

Commonly reported reasons for medication discontinuation include side effects, low perceived need for medication, feeling better, and perceived medication ineffectiveness. Refer to Table 114–1 for more factors commonly associated with poor medication compliance.

**Table 114–1** Factors Associated with Poor Medication Compliance

| |
|---|
| Level of distress/Low perceived necessity for medication; e.g., "Only really sick people take medication," "I feel better so I don't need medication" |
| Medication is not perceived as beneficial |
| Negative influence of family and friends |
| Learned helplessness |
| Poor treatment alliance |
| Complex medication regimen |
| Side effects; e.g., "I don't feel like myself," weight gain, sexual dysfunction |
| Fear of side effects; e.g., "I won't be able to feel my emotions," "Medication will make me a zombie," "The medication will change my personality" |
| Avoidance of dependency |
| Concern about stigma/discrimination; e.g., "Only crazy people take psychiatric medications" |

Just as individual patients' medication compliance pattern may vary over the course of treatment, the relative significance of specific barriers to compliance vary greatly between patients. Based on their review of pediatric literature, Logan et al. (2003) identified the most important correlates of noncompliance: (1) disease and regimen factors (duration and course of illness, symptom severity, type and complexity of regimen, efficacy, and side effects); (2) patient factors (developmental characteristics such as cognitive developmental level, level of autonomy); (3) interpersonal or attributional tendencies(depression,psychologicalcopingstrategies,self efficacy); (4) peer/family influences (stigma of disease/regimen, perceived need for secrecy, family cohesion/conflict, parental support, shared responsibility for regimen); (5) relationship with medical team. Using these a priori factors, they developed the Illness Management Survey, which is a self-report measure designed to identify the relative importance of common compliance barriers for individuals patients. Their results were striking; they discovered that four of the five most important barriers to compliance cited by adolescents could be classified as due to internal processes (cognitive ability, perceived support from their family and doctor, and perceived stigma of disease/treatment). Adolescents' perceived burden of the disease/treatment (complexity of regimen, interference with normal life, unpleasantness of side effects) was also an important factor. Refer to Figure 114–1 for an integrated model of factors that influence patients' compliance to medication.

## Demographic Factors

Converging data suggests that no single demographic variable (with the exception of age) predisposes an individual to noncompliance (Haynes et al. 1979, Jay et al. 1984). Studies have failed to identify differences in patient compliance to treatment based on race, gender, religion, educational level, or socioeconomic status (Horne and Weinman 1999).

Medication compliance does appear to be influenced by age/developmental level. Past research has shown that compliance to medication in children is related to the mother's perception of the severity of her child's illness, but not to the physician's estimate of severity of the child's illness. Data also suggests that adolescents are less compliant to medical recommendations than younger children or adults, which may be due to developmental factors (Cromer and Tarnowski 1989, Riekert 2002). Developmental factors that may influence compliance (see Table 114–2) in adolescents (and developmentally delayed adults) include: (1) Brain Maturation & Development of Cognitive Processes; (2) Psychological Development (see Table 114–2).

Adolescence is characterized by experimentation and risk-taking, limited insight, a sense of invulnerability, increased influence of peers, and lack of future orientation. Although a sense of autonomy is a positive developmental milestone, a child who feels autonomous may view health-promoting influences as a restriction to autonomy.

Only a small percent of mental health treatment in adolescents is self-initiated. Compliance to medication among children and adolescents requires the consent and cooperation of a parent as well as the assent and cooperation of the youth. The involvement of adults may create conflict for teens because help-seeking and utilization of adult-provided services is inconsistent with their desire for autonomy, privacy, and independence.

## Patient-Related Factors

### Pragmatics

Some examples of pragmatic barriers to improved medication compliance include income, stability/stress in home life, homelessness, transportation, phone service, medical and prescription coverage, travel time to doctor's office, waiting times to see physicians, access to prescription

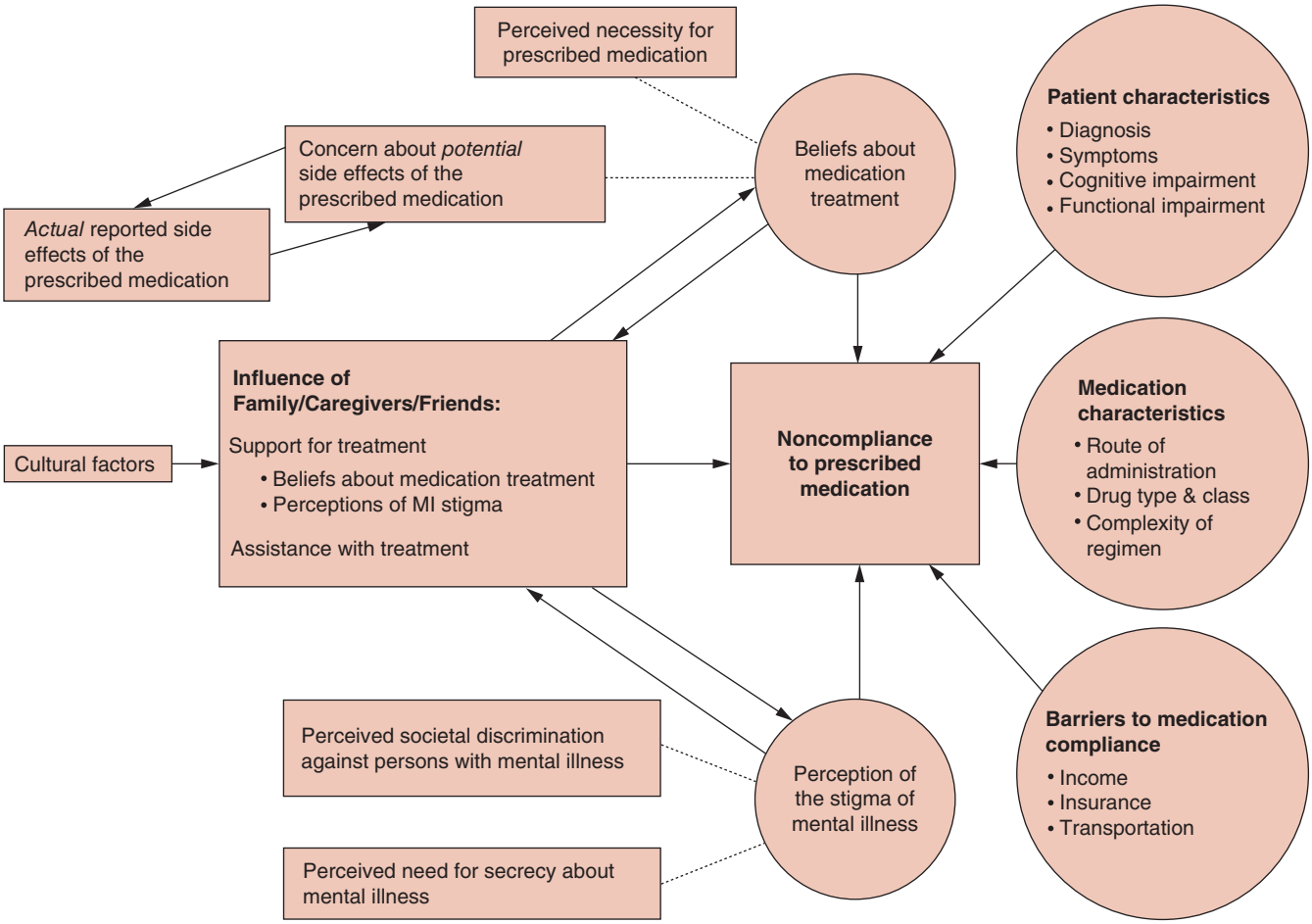



**Figure 114–1** *Hypothetical model of factors related to patients' medication compliance.*

refills, access to nurse/physician to answer questions, practices of third-party payers, and national health care policies.

## Ability

A patient's ability to take medications as prescribed is influenced by the patient's cognitive functioning, motor functioning, and knowledge about the medication. Their cognitive functioning is determined by level of alertness, orientation to person/place/time, sustained attention, memory, ability to use a calendar/reminders/organizers, thought processes, processing speed, problem-solving skills, capacity for logical operations (understanding of cause and effect), intelligence, literacy, math skills, executive functioning, and impulse control. A patient's motor functioning consists of fine motor control, physical mobility, ability to drive or obtain transportation, ability to swallow medication and can affect physical ability to obtain and take medication. Finally, a patient's knowledge about medication influences their compliance to medication. A number of studies have examined the impact of patient knowledge about their illness and treatment on medication compliance. Most studies have concluded that while patient instruction is an important component of treatment and may improve compliance to short-term medication treatment, patient education alone does not assure compliance to long-term medication treatment (Morris and Halperin 1979). Sackett and Snow (1979) showed that even "mastery learning" about medication treatment does not necessarily improve medication-taking behavior.

**Table 114–2** Developmental Issues in Medication Compliance

(1) Brain Maturation & Development of Cognitive Processes
   a. Age-related; e.g., Piagetian stage, Eriksonian stage, psychological autonomy, legal competency, executive functioning
   b. Biologically related; e.g., Head injury, IQ, mental illness, substance abuse, encephalopathy, attention deficit hyperactivity disorder, impulse control disorders
(2) Psychological Development
   a. Age-related; e.g., Development of ego strength and psychological defense mechanisms
   b. Biologically related; e.g., innate temperament, family history of psychiatric illness, genetic variation of drug metabolism, organ maturity, physical growth and development, disorders of kidney and/or liver functioning, drug–drug interaction

## Motivation

A patient's motivation to take prescribed medication is influenced by many complex and interrelated factors:

- Severity of psychiatric symptoms—which, in turn, impacts the patient's cognitive functioning, insight, future orientation, and confidence
- Past experience with prescribed medication, especially psychiatric
- Personal history of mental illness
- Personal beliefs—health/illness beliefs, acceptance of illness, understanding of illness, concerns about medication, perceived necessity for medication, perceived medication efficacy, concerns about mental illness stigma
- Treatment goals
- Temperament/personality

## Patient Beliefs/Attitudes about Medication

In a landmark publication, Frank (1973) described the close association between beliefs and attitudes toward treatment-seeking, expectancies of change, and actual illness outcome. Subsequent research supports the importance of medication beliefs in determining patient compliance to medication recommendations. For example, Lingam and Scott (2002) conducted a review of research from 1976 to 2001 on treatment noncompliance in affective disorders and reported that attitudes and beliefs are at least as important as side effects in predicting noncompliance to antidepressant treatment. Research in patients with chronic medical illness suggests that how patients understand their illness has a significant impact on treatment compliance (Leventhal et al. 1992). Horne and Weinman (1999) proposed a theoretical model for the relationship between patient beliefs about medication and compliance to medication treatment in adults with chronic illness. In their study of 324 patients with chronic illness (asthma, renal, cardiac, and cancer), they found that patient beliefs about medication were more powerful predictors of compliance than clinical or demographic factors. Based on their findings, the authors concluded that patients' general beliefs about medication influenced their initial orientation toward prescribed medication, but it was patients' specific beliefs about their prescribed medication that is most strongly related to their medication compliance.

Studies have documented the resistance of adolescents to psychiatric medication. Scott et al. (1992) found that 58% of mentally ill adolescents (with diagnosed schizophrenia, unipolar depression, and bipolar depression) disagreed with the need to take prescribed medication. Williams and Hollis (1998) report that 61% of adolescents with various psychiatric diagnoses had a bias against taking medication and a lack of positive expectancy for effect of medication.

Noncompliant patients can be classified into subgroups based on their particular risk factors or barriers to compliance (Conrad 1985):

- Testing—The patient stops medication in order to "test" whether it is needed and/or effective
- Control of dependency—The fear that medication is a crutch; fear of dependency on medication; medication becomes a symbol of the dependence created by a chronic illness and is a constant reminder of the illness
- Destigmatization—The fear of societal stigma of illness and "flight to health"; avoiding medication is a way to avoid the stigma of the illness
- Practical considerations—e.g., expense and/or burden of the regimen; wish to avoid problems that might occur by mixing alcohol or illicit drugs with the medication

## Patient Concerns about Medication

Many patients have substantial suspicions about prescribed medication and these beliefs may influence how information about medication is interpreted and acted upon. Certain beliefs about medication are highly prevalent across diverse populations, e.g., medications are addictive and accumulate in the body to produce adverse long-term effects.

Williams et al. (1998) studied attitudes about psychiatric medications among incarcerated female adolescents. The most common concerns reported by this sample were: (1) "Medicine might be hard to swallow or taste bad," 44.4%; (2) "I feel strongly that people should solve problems on their own—medicines are a crutch," 33.2%; and (3) "Medicine might change my personality or not let me be myself," 30.8%. Other concerns included: "I wouldn't want others to know I was taking medication to help with my feelings or behavior—I might get teased by my peers" and "Medicine might cost too much for my family to afford."

## Patient Concerns about Mental Illness Stigma

The word stigma literally means "mark of shame." Link and Phelan (2001) defined stigma as any trait of an individual or group that evokes a negative or punitive social response. In common parlance, people refer to the stigma associated with individual traits (e.g., skin color, obesity), events (e.g., personal history of psychiatric hospitalization, incarceration, or substance abuse), or groups (e.g., persons with mental illness, persons who are HIV+). Mental illness stigma specifically refers to status loss and discrimination due to negative stereotypes about people labeled with mental illness.

The mentally ill are one of the most stigmatized social groups (Sayre 2000, Link et al. 2004). Derogatory messages about mental illness are ubiquitous in society, seen in colloquial expressions, cartoon characters, and mass advertisement (Philo 1996, Wahl 1995, Wilson et al. 2000). Link (1987) found that people learn negative stereotypes long before they themselves become patients and that the experience of illness triggers internalized negative beliefs.

The 1999 Surgeon General's Report on Mental Health cited stigma as a powerful obstacle to seeking care (Satcher 1999). Jorm and Korten (1997) found that the public more often perceives psychiatric medication as more harmful than helpful. Studies of stigma and compliance to depression treatment have found that perceived stigma predicts treatment discontinuation (Lai et al. 1997, Sirey et al. 2001). If a person believes that the mentally ill are less competent than other people, it is not surprising that they may wish to distance themselves from such a label. Taking psychiatric medication implies mental illness; noncompliance with prescribed medication can reflect denial or ambivalence.

## Perceived Necessity for Medication Treatment

Studies across medical conditions show that people prescribed the same medication for the same condition differ in their perceptions of personal need for medication (Horne and Weinman 1999). The factors determining perceived necessity for medication in depression are not fully

understood. According to the common sense model of self-regulation patients do not blindly follow medical advice, but assess the threat posed by their illness to determine whether treatment is needed, and if so, what treatment is appropriate (Leventhal et al. 1992). A number of factors may contribute to perceived need for medication, including perceived severity of illness, level of distress/impact of illness, understanding of illness (e.g., beliefs about causation, expected duration, beliefs about amenability to treatment), perceived efficacy of medication, and perceptions of personal resilience (Horne 2006).

Adams and Scott (2000) found that perceived benefit of treatment and perceived severity of illness, together, accounted for 43% of variance in compliance. Using the Health Belief Model, Budd et al. (1996) found that perceived severity of symptoms was associated with greater medication compliance.

### Perceived Efficacy of Medication Treatment

Patients' perceptions of the efficacy of medication may not be the same as those of their doctors. An individual's perception of the effectiveness of a treatment depends on whether the outcome of treatment matches their expectations. For example, a patient who believes that effective treatment of depression means that they will be "happy" after taking medication for one week is likely to be disappointed.

Perceived efficacy of prescribed medication has a complex relationship to perceived necessity for medication and compliance to prescribed medication. In their study of depressed adults in primary care, Brown et al. (2001) found that, although most patients acknowledged the negative impact of depression on their lives, less than 40% viewed antidepressants as effective in treating their symptoms. Moreover, clinical experience and published data suggest that regardless of their clinical response to medication treatment, patients commonly have attitudes and beliefs about psychiatric medication that are inconsistent with medication compliance (Williams et al. 1998).

Physicians often assume that if a medication produces significant reduction in a patient's symptoms, then the medication is "necessary"; however, it is not uncommon for patients who have experienced some benefit from medication to discontinue medication prematurely, stating "I feel better so I don't need to take the medication anymore."

## Provider-Related Factors

### Pragmatics

Some examples of pragmatic barriers to improved medication compliance include the quality/quantity of office staff, location of practice, practices of third-party payers, national health care policies, continuity of care, and communication between various medication providers. Goldfinger et al. (1984) examine the role of service systems breakdown in patients whose treatment fails.

### Ability

A physician's ability to facilitate patient compliance with medication is influenced by innate talents, interpersonal skills, empathy, psychological mindedness, confidence, openness, quality of training, and clinical experience.

### Motivation

A physician's motivation to improve their patients' medication compliance is influenced by personal history of mental illness, personal beliefs (especially about the stigma of mental illness and beliefs about medication efficacy and safety), family and/or friends with mental illness, ethical principles, perceived professional mission—and; on the darker side, perhaps avoidance of legal liability and high malpractice rates.

### Therapeutic Alliance

Patients' medication compliance is substantially influenced by perceived support from their physician. Doctors and patients develop a relationship that is based on communication that includes information, affect, and social learning. Therapeutic alliance is as important for success in psychopharmacology as it is for psychotherapy. With increasing pressure from all sides for doctors to perform "medication checks," the interpersonal aspects of the doctor–patient relationship are dismissed. Optimal therapeutic alliance depends on mutual trust, respect, honesty, openness, and comfort between doctor and patient, all of which take time.

Based on their study of compliance with medication treatment for tuberculosis, Sumartijo (1993) concluded that poor performance by the health team often was responsible for poor compliance to medication (Sumartijo 1993). Medication compliance is affected by continuity of care. Charney et al. (1967) demonstrated that compliance was worse when patients saw the partner of their regular physician than when they saw their regular physician (Charney et al. 1967). Other factors that contribute to the quality of the doctor–patient relationship include: (1) availability of the physician (or appropriate medical staff) between appointments; (2) length, frequency, and quality of appointments; (3) waiting times to see the doctor. Finally, the quality of office support staff can have a significant impact on patient care.

Patients who are poorly compliant with treatment frequently elicit strong countertransference responses in their providers. Doctors may experience feelings of disappointment, anger, and/or defensiveness. They may blame the patient, as exemplified by the statement; the patient is "resistant" or "doesn't want to get better." These responses are counterproductive and serve only to further erode the therapeutic alliance. In this light, medication noncompliance can be seen as a failure of the relationship, rather than as a failure of the patient (Weiden and Rao 2005).

## Contextual Factors

### Family Factors

Chesla (1989) and Rose (1983) reported an association between relatives' beliefs about illness and their beliefs about treatment and found evidence that family beliefs influence patient compliance. They observed that family members who consider mental illness caused by a chemical imbalance strongly reinforced the use of medication in the patient. In a cross-cultural study sponsored by the World Health Organization, Bush and Hardon (1990) found that medication use, family beliefs, and health-related practices are instilled in children by school age and influence their readiness to take prescribed medication.

Stine (1994) reported several reasons for noncompliance to psychiatric medication in children and adolescents

despite clinical improvement and absence of side effects, including parental discomfort with the idea of psychiatric medication, patient fear of stigma, and child refusal and resistance. Public awareness of the controversy regarding efficacy and safety of SSRI medications in children and adolescents may impact parent/family concerns about medications. Prescribing providers need to be sensitive to concerns about medication safety.

### Financial Factors

For patients without health insurance and/or prescription coverage, the cost of medication and medical care may be a significant barrier to medication compliance. Patients with health insurance may still sustain significant medical costs that effect medication compliance. Many health insurance plans do not include prescription coverage or have restricted formularies. Managed care formularies increasingly restrict medication choices. These restrictions are especially severe for psychiatric medications due to nonparity of coverage for mental health problems. More patients are required to pay deductibles and co-pays, which vary in amount, but can be as high as 20–80% of the actual cost of the prescription or service. Some patients are required to obtain prescriptions for a 3-month quantity of medication and receive their medications by mail. Patients with Medicaid and Medicare insurance are now required to enroll in a managed care plan that regulates prescription benefits. These plans have restricted formularies and require prior authorization for all nonformulary medications (Kihlstrom 1998). Although co-pays for patients on Medicaid are much lower than those with private insurance plans, they can still pose a substantial financial burden for patients living on severely restricted incomes, particularly if they are on multiple medications (as is frequently the case).

## Clinical Factors

### Medication Regimen

Studies of the number, type, dose, frequency, and time of medication prescribed in relationship to medication adherence have revealed variable results. In a review of studies using electronic monitoring to measure adherence, Claxton et al. (2001) found an inverse relationship between number of daily doses and adherence. Kruse et al. (1993) report higher patient compliance with twice daily (85%) versus four times daily regimens (65%), and that evening doses are omitted twice as often as morning doses. Horne and Weinman (1998) found no relationship between the total number of prescribed medications and compliance.

### Severity of Illness/Level of Distress

Multiple studies of patient medication compliance, across a range of chronic illnesses, have shown that physicians' assessments of medication necessity or illness severity often have little correlation with patients' level of medication compliance (Kiley et al. 1993, Phipps and Decuir-Whalley 1990, Lemanek 1990). Even when the patient's reported symptoms underlie the physician's assessment (e.g., using the Beck's Depression Inventory (Beck et al. 1961) to assess severity of depression), this may not predict patient compliance to prescribed medication.

One predictor of medication noncompliance is the absence of patient distress (Ellison 2000). Without the motivation provided by distress, taking medication may seem pointless and not worth the side effects. Even patients who are sufficiently motivated by distress to schedule an evaluation with a psychiatrist may, in a "flight to health," experience relief prior to starting medication. Many patients, after taking medications and experiencing relief from symptoms, may discontinue medication prematurely—with or without the physician's knowledge. Other patients, perhaps pressured into seeing a psychiatrist, may not acknowledge the distress observed by others for a number of reasons (e.g., denial of illness, lack of insight).

Finally, depending on the type of disorder and severity of symptoms, psychiatric illness itself may interfere with patients' willingness and/or ability to comply with medication (Chen 1991). These factors will be discussed at length below under "Specific Populations," e.g., schizophrenia, bipolar disorder, attention deficit disorder.

### Side Effects

It is a mistake to ignore the possibility that a patient's noncompliance to medication is based on concerns about current or potential side effects of treatment. Side effects to prescribed medication, even if considered "mild" by the medical provider, may have a significant impact on medication compliance. Patients may discontinue medication that has been effective if the side effect is sufficiently noxious, e.g., nausea, sexual dysfunction. Patients' concerns about the possibility of side effects or adverse events (even in the absence of past or current problems) may also be a significant factor in compliance to prescribed medication. For example, fear of severe adverse events (potentially fatal or causing disability, e.g., hepatotoxicity, cardiac arthymia, tardive dyskinesia), even if rare, may be a significant deterrent to patient compliance.

Even when a patient offers no reason for not taking the medication, or points to some other cause; the physician should make specific inquiries about embarrassing (e.g., sexual dysfunction) or difficult to describe side effects (e.g., akathesia). If no current side effects can be elicited, past experiences with medications should be reviewed, as well as whether patients have witnessed or heard reports of bad experiences with psychiatric medications from family, friends, the media, or internet reports (Appelbaum and Gutheil 1982).

Side effects are associated with noncompliance to medication, but to a lesser extent than initially believed. Prevalence of antidepressant noncompliance has not substantially changed with the advent of new medications (Lingam and Scott 2002). In their study of medication noncompliance in severe affective disorders, Adams and Scott (2000) reported that side effect fears were more predictive of noncompliance than actual side effects. It is important to remember that it is subjective distress about the side effect, rather than the side effect itself, that is most linked to medication noncompliance.

## Specific Patient Populations

Psychiatric diagnoses are associated with poorer medication compliance than are nonpsychiatric illnesses (Litt and Cuskey 1980, Haynes et al. 1979). Psychiatric illness, by

virtue of impact on patient ability and motivation, presents particular challenges for compliance with medication treatment. While it is beyond the scope of this chapter to address compliance issues related to every psychiatric disorder, factors unique to a few specific diagnostic groups are outlined below.

## Depression

Approximately 8–10% of patients never fill their antidepressant prescription (Rashid 1982). Subsequent antidepressant compliance decays over time and medication discontinuation is greatest within the first month of treatment. Johnson (1981) reported antidepressant discontinuation rates of 16% within the first week, 41% within two weeks, 59% within three weeks, and 68% within four weeks. In their meta-analysis of discontinuation of SSRIs and tricyclic antidepressants, Hotopf et al. (1997) found 30% of patients stopped taking their antidepressant within one month and 45–60% stop by 3 months.

Rapid cessation of selective serotonin reuptake inhibitors (SSRIs) can produce a discontinuation syndrome consisting of somatic and psychological symptoms. In some situations, symptoms related to medication discontinuation may re-enforce the need for compliance to medication; however, if these symptoms are attributed to the medication itself, they may serve as a barrier to future compliance.

Depression has been shown to independently predict noncompliance. Depression-specific factors in noncompliance include reduced motivation, reduced task initiation, and cognitive impairment (slowed processing speed, poor concentration, and impaired executive functioning). The severely depressed patient may lack the energy and motivation to participate in treatment of any kind. Feelings of hopelessness or frank suicidal ideation related to depression may prevent patients from complying with medication or other treatments prescribed for co-morbid medical illnesses. This phenomenon can be particularly devastating to the treatment of patients with chronic or potentially fatal illness (diabetes, end-stage renal disease, cancer, transplant patients).

## Bipolar Disorder

The problem of medication noncompliance in treatment of bipolar disorder has likely been experienced by many readers. Barriers to compliance in bipolar disorder can be classified as: (1) Pragmatic/ability to take medication—In both the manic and depressed phases of the illness, there are a number of core symptoms that can decrease the patient's ability to take the medication as prescribed: impaired concentration/memory, disorganization, anergia, and altered sleep cycle; (2) Willingness—Patients with bipolar disorder may be hesitant to take medication that reduces hypomanic periods that they associate with exuberance, peaks of creativity, periods of increased goal-directed behavior, and decreased need for sleep. The manic phase of bipolar disorder is characterized by grandiosity, and occasionally frank psychosis, both of which impact the patient's insight and willingness to comply with treatment; (3) Aversive nature of treatment—Medications typically used to treat bipolar disorder (i.e., mood stabilizers, antipsychotics) commonly have odious side effects (e.g., weight gain, sedation, movement disorders) or require frequent blood levels which can be a roadblock for some.

Rates of medication noncompliance among patients with bipolar disorder range from 18 to 52% (Scott and Pope 2002, Rosa et al. 2007, Keck et al. 1998). In a study of patients prescribed mood stabilizers, 50% of subjects admitted to some degree of medication noncompliance (Scott and Pope 2002). Scott and Pope (2002) report 32% of patients admitted to only partial compliance to medication which was defined as missing 30% or more of their medication. Factors associated with noncompliance were greater length of time on mood stabilizers, past history of noncompliance, denial of the severity of the illness, fear of side effects (not actual side effects), and negative attitudes toward medication (Rosa et al. 2007, Scott and Pope 2002). Gitlin et al. (1989) reported increased medication noncompliance in patients reporting coordination problems and/or cognitive side effects in response to lithium. In their study of medication compliance in patients with bipolar disorder, Keck et al. (1989) reported increased medication noncompliance in patients with comorbid substance abuse disorders.

## Schizophrenia

Results from the CATIE study (the largest clinical trial of schizophrenia) indicate that 74% of patients with schizophrenia discontinued their medication treatment within 18 months (Lieberman et al. 2005). A number of other studies report noncompliance rates in excess of 50% (Valenstein et al. 2006, Rettenbacher et al. 2004, Novak-Grubic and Tavcar 2002). Valenstein et al. (2006) found that poor compliance was associated with young age, nonwhite race, substance abuse diagnosis, psychiatric hospitalization, and predominant treatment with first generation antipsychotics. Rettenbacher et al. (2004) found compliance positively associated with patients' feelings of a positive effect of the drug on the illness, and greater negative symptoms.

In addition to deficits in judgment and insight present during active psychosis, persons suffering from schizophrenia have a number of cognitive deficits which are present not only in acute phases of illness, but also during periods of remission (Gold and Harvey 1993). Specific areas of impairment include attention, memory, and executive function. Similar to patients with other mental disorders (e.g., major depression, bipolar disorder), patients with schizophrenia often have irregular sleep and meal patterns and/or chaotic lives, making taking medications on a regular schedule very challenging.

Olfson et al. (2000) found that schizophrenic patients with substance use, difficulty recognizing their own symptoms, a weak alliance with inpatient staff, or poor family support were at increased risk for noncompliance following discharge from inpatient treatment.

## Attention Deficit Hyperactivity Disorder (ADHD)

The characteristic features of ADHD, such as inattention, disorganization, and distractibility, can all contribute to noncompliance to medication. Since ADHD is a chronic illness with significant morbidity, it requires compliance to a medication regimen for many years. Due to the strong genetic etiology, parents of children with ADHD frequently have ADHD themselves and suffer from cognitive and temperamental characteristics similar to their children which can contribute to noncompliance (Stine 1994).

One study examined the length of time children with ADHD were compliant to stimulant treatment over a 3-year period. The authors reported 81% compliance rate at 1 year, but only 52% at 3 years (Thiruchelvam et al. 2001). Children who were compliant were younger, tended to have more severe symptoms of ADHD, but no oppositional/defiant symptoms. Children who were compliant to medication had more improvement in teacher-rated symptoms at 5-year follow-up (Charach et al. 2004). In an older study of compliance to ADHD medications, Firestone (1982) found that 26% of participants refused medication at the start of the study. Of those who accepted medication, 20% stopped their medication after 4 months, and 55% stopped after 10 months (Firestone 1982). Even more striking, less than 10% of families talked to their physician prior to discontinuing medication.

The reasons for noncompliance among patients with ADHD are multiple. Thiruchelvam et al. (2001) reported greater rates of noncompliance in older children and children with ODD symptoms. This suggests that older and more defiant children may resist and ultimately stop taking medication. Reported side effects were not related to compliance in this study.

Stine (1994) published an eloquent discussion of psychodynamic and psychosocial factors related to psychiatric medication compliance in the treatment of ADHD. The most commonly reported reasons for medication discontinuation were: (1) the child's impression that the medication makes them feel strange or uneasy; (2) belief that the medication makes the child less popular or entertaining when they take it; (3) the difficulty of having to take the medication at school; (4) the belief that taking medication makes the child different from friends or that friends will treat them differently because of their medication; (5) desire to disavow symptoms or the need for treatment; and (6) beliefs about the dangers of drugs (these fears are sometimes extreme; e.g., "medications are poisonous").

### Substance Abuse Disorders

It is not in the scope of this chapter to discuss specific treatment regimens for the various substance abuse disorders. The key point is that co-morbid substance abuse (in addition to any other medical or psychiatric disorder) increases the risk of medication noncompliance with prescribed medications, either psychiatric or nonpsychiatric. A number of factors likely contribute. Patients who are actively using alcohol and/or illicit drugs are often fearful that the prescribed medication(s), particularly psychiatric medications, will interact dangerously with alcohol or other substances. Unfortunately, physicians, family, and friends, frequently reinforce many of these beliefs, regardless of scientific evidence—perhaps hoping to "be careful" or that the patient will be "forced into quitting." In long-term medication regimens, one must consider whether such advice is *necessary* or *realistic*. Many patients, especially when feeling a bit better, will simply stop their prescribed medication(s), or take them irregularly or as needed, in order to "safely" use alcohol or other substances. Data support an increased risk of secondary depression/anxiety/insomnia in patients with significant alcohol or cannabis abuse; however, alcohol does not directly interact with many of the newer generation antidepressants. While, as physicians, we need to assess the degree of the substance abuse openly with the patient, monitor for abuse of prescription medications as well as signs of CNS toxicity/oversedation, and collaborate with the patient—initially to provide nonjudgmental guidance and education, and later, to explore the patient's motivation to engage in treatment for substance abuse, generally while *continuing* medication for the patient's psychiatric disorder.

### Developmentally Disabled/Cognitively Impaired

Cognitive developmental level affects the capacity and motivation for treatment compliance in a number of ways, including through memory, perception of time, and understanding of causality and consequences. Patients may not comply with physician's recommendations because of physicians' use of abstract rather than concrete reasoning in education about the illness and treatment required. Complex cognitive processes are required to understand the varied presentation of psychiatric symptoms, the multiple causes of mental illness, and the factors that contribute to severity of symptoms. Patients must have an adequate understanding of causality to understand how compliance (or noncompliance) affects the course of illness. They must have adequate perception of time to understand the short- and long-term consequences of depression and to understand the need to take medication regularly despite the delayed time to effect of medications. They must possess the ability for formal operations to fully understand the multiple abstract causes and consequences involved in illness and treatment of depression. Pediatric patients differ considerably in these cognitive skills.

In early adolescence, youth are able to think about illness in increasingly complex ways. By later adolescents, most youth have the capacity for somewhat scientific understanding of illness and treatment. Even adult patients may not have the health knowledge or logical operations necessary to understand the necessity to fully understand various components of treatment. Bush and Iannotti (1990), using their Children's Health Belief Model, found that adolescents' perceptions of the severity of illness and benefit of medication were the most important factors contributing to their compliance to medication. Both these factors require the understanding of causality and consequences. It is clear that efforts to enhance treatment compliance should match the intervention with the cognitive level of the patient.

## Intervention Strategies

In an early publication, Haynes et al. (1976) identified six major strategies to improve medication compliance:

1. Informational and instructional
2. Reduction of barriers to compliance
3. Behavior modification approaches—problem solving, skills training
4. Increased patient supervision
5. Medication reminders and cues
6. Pharmacy interventions
7. Increasing resources/supports
8. Collaborative treatment teams

Much later, in a systematic review of interventions for enhancing medication compliance, Haynes et al. (2005) concluded that improving short-term compliance is relatively successful with a variety of simple interventions; however, interventions for enhancing long-term compliance in chronic health problems have been more complex and not very effective. Unfortunately, many medication regimens in psychiatry are long term.

Given the number of past intervention trials which have failed or produced results of marginal clinical utility for chronic medication regimens, it seems probable that past paradigms must be examined. The limited success of past interventions may be due to attempts to address unintentional but not intentional noncompliance. The simple strategies listed above fail to consider the power of psychosocial factors, such as patient beliefs, therapeutic alliance, and the influence of family, friends, and the community.

## Selected Promising Intervention Strategies

### Patient Self-Regulation of Medication

For some patients, self-regulation of dosage can be beneficial (Epstein and Cluss 1982). Nessman et al. (1980) utilized a self-control package that included self-monitoring of blood pressure and self-selection of dose regimen. Patients with insulin-dependent diabetes mellitus have long used the "sliding scale" method for fine tuning blood sugar control to avoid dangerous highs and lows (Epstein and Al. 1981). In pediatrics and child psychiatry, parents are commonly trained to administer "as needed" doses of medication (e.g., use of nebulized medication treatments as needed in asthma, use of anxiolytic or antipsychotic medication as needed for acute agitation in severely behaviorally disturbed patients).

### Motivational Interviewing

Motivational interviewing uses a collaborative style of interaction between patient and provider to assess patient motivation to change. Over 70 clinical trials have established motivational interviewing as an effective method to promote behavioral change, including increasing treatment compliance. Miller and Rollnick (2002) demonstrated that adding even one motivational interviewing session in early treatment can improve patient retention, increase compliance, and improve outcome. The three principles of motivational interviewing are the use of collaboration between the physician and the patient, evocation of patient responses, and autonomy for the patient.

### Tailoring Medication Regimens: Using Pharmacokinetics to Optimize Medication Compliance

What is good enough compliance? Unfortunately, the overwhelming majority of published studies set an arbitrary cutoff point for what constitutes compliance. Many studies even treat compliance as a dichotomous construct (e.g., compliant versus noncompliant). Even those studies that begin with a continuous measure of compliance (e.g., percent of doses taken as prescribed) generally set an arbitrary cutoff point for satisfactory compliance (e.g., 80%). In reality, the minimal level of compliance necessary to achieve the desired clinical outcome (e.g., remission of depression symptoms) depends on many factors, including the pharmacokinetic properties of the medication, individual differences in drug absorption and metabolism, individual variation in response to medication, with respect to efficacy and side effects (Epstein and Cluss 1982). For some conditions/medications, 50% compliance may be sufficient; whereas, for others, 80% or more may be necessary.

The pharmacokinetic (absorption, distribution, elimination) and pharmacodynamic (pharmacological effect, clinical response, toxicity, efficacy) profile of any medication varies across patients and can vary within the same patient due to many factors, e.g., age, race, gender, organ functioning due to maturation/disease, disease severity and comorbidity, and pregnancy (Katzung 2007).

Individual patterns of drug taking ("medication compliance") influence the pharmacokinetics and pharmacodynamics of a medication; known pharmacokinetic properties of medications can be used to select more feasible, "forgiving," medication regimens that can be tailored to individual patients (Rudd and Lenert 1995, Urquhart 1992, Levy 1993).

Weiden and Rao (2005) propose using a mnemonic of the "four Fs" to guide psychopharmacological treatment to increase medication compliance: (1) effectiveness, (2) flexibility, (3) forgiveness, and (4) user-friendly (Weiden and Rao 2005).

1. Effectiveness: Not only can noncompliance lead to relapse, but relapse can lead to noncompliance. One of the most commonly given explanations for medication discontinuation is that "the medication wasn't working." Systematically reviewing symptoms periodically during treatment can be helpful for both the doctor and patient in determining whether the medication is effective. Efficacy of psychiatric medication is especially important, as psychiatric symptoms themselves may interfere with compliance behavior (e.g., by preventing patients from learning from experience, interfering with ability to understand psychoeducation, and decreasing ability to remember the medication schedule).
2. Flexibility: Flexibility refers to considering as many pharmacological options as possible and actively collaborating with the patient to select medication. This approach allows the physician to tailor the medication regimen to target symptoms based on the patient's priorities, while minimizing side effects that are most distressing to the patient.
3. Forgiveness: Because less than perfect compliance is the norm rather than the exception, medications that are forgiving of dosage irregularities should be selected.
4. User-friendly: Consideration should be given to ease of administration (number and time of daily doses; route of administration), number of medications, cost of medication, difficulty of obtaining the medication, and burden of side effects.

### Treatment Concordance/Shared Decision Making

Many researchers now argue that only through increased collaboration with patients, can physicians determine the optimal medication regimen for any given patient (e.g., a regimen that is both feasible and effective for that patient). Using the paradigm of treatment concordance, physicians actively collaborate with patients to identify patients'

**Table 114–3 The Model of Shared Decision Making**

| | "Traditional Medical Model" (Paternalistic) (Paternalistic Model) | Shared Decision Making | Informed Choice |
|---|---|---|---|
| Role of the doctor | Active: Gives selected information to patient and chooses treatment *for* the patient | Active: Gives all information to patient and chooses treatment *with* the patient | Passive: Gives all information to patient. Patient chooses treatment |
| Role of the patient | Passive: Expected to accept & comply with prescribed treatment | Active: Receives all information. Discusses concerns & preferences. Chooses treatment *with* the doctor | Active: Receives all information. Chooses treatment alone |
| Information flow | One-way patient → physician | Bi-directional patient ↔ physician | One-way patient ← physician |
| Responsibility | Lies with the physician alone; high risk of litigation | Lies with physician and patient together | Lies with patient alone; low risk of litigation |

Reproduced with permission from Hamann et al. (2003).

priorities and select medication regimens that target as many of the *patient's* goals as possible. The model of shared decision making is illustrated in Table 114–3.

This method of prescribing medication utilizes evidence-based practices for selecting a range of medication regimens, all of which have sufficient empirical and/or clinical data support and then integrates known pharmacokinetic properties of medications, awareness of risk factors for noncompliance, and substantive understanding of the individual patient's goals and priorities to compare the ability of the selected medication regimens to minimize barriers to medication compliance and compensate for imperfect patient behaviors. This process is tailored to individual patients and must be dynamic and interactive, just as medication compliance is a dynamic process, influenced by many factors.

Examples: If a depressed patient is bothered by insomnia and weight loss, mirtazepine or paroxetine might be reasonable choices. For patients who are obese and/or at risk for diabetes or elevated cholesterol, the physician should avoid medications that are apt to increase weight, glucose, cholesterol, and/or glucose (e.g., second generation antipsychotic agents). Optimally, through the use of patient education regarding symptom targets and potential side effects, several potential medication regimens can be identified and the physician can collaborate with the patient to select the regimen that best suits that individual.

## Conclusions

Given the preponderance of data supporting the high prevalence of medication noncompliance across all age, racial, and disease groups, physicians must accept the reality that perfect medication compliance is unattainable.

In addition, given the number of past intervention trials which have failed or which have produced results of marginal clinical utility, it seems probable that past paradigms must be re-examined. Some of the more recent efforts appear promising, e.g., training providers to take more responsibility, and to take a more proactive role in tailoring medication regimens to better fit the needs of patients. Physicians must allow patients to speak freely about real-life barriers to medication compliance as well as their feelings, beliefs, and attitudes regarding medication, all of which can contribute to both unintentional and intentional noncompliance.

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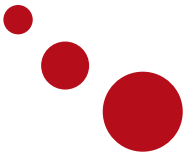
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SECTION

# IX

Michelle B. Riba, Section Editor

# *Special Populations and Clinical Settings*

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CHAPTER

# 115 Managing Psychological Consequences in Disaster Populations

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## Disaster Psychiatry

Disaster is defined in the Oxford English Dictionary as "[a]nything . . . of ruinous or distressing nature; [a] sudden, great misfortune" (Oxford English Dictionary Online 2006). This definition captures both the catastrophe and the human tragedy that characterizes all disaster events. Disasters occur abruptly, and often with little predictability. Their destructive force can destroy communities, or even nations. Physical destruction (e.g., bodily integrity or health, homes or other cherished possessions, loved ones, and pets) and equally important emotional disruption and impairment (e.g., sense of safety, trust in government, questioning of spirituality, and connection to community) are expected with disasters. Although individuals and communities may grow from such experiences, disasters, by their *ruinous and distressing nature*, are costly, and always reason for anxiety, fear, and at times horror. Disasters vary in type, duration, and intensity (see below). Most if not all members of communities exposed to disaster will experience some degree of emotional distress. Depending on degree of personal exposure and loss, a disaster may precipitate mental disorders in some individuals and can lead to health-risk behaviors, such as increased smoking and alcohol consumption. Large-scale disasters create challenges for recovery amongst individuals and their communities (e.g., evacuation, loss of workplaces, disruption of the physical and interpersonal community, and social infrastructures).

Disasters differ from other types of traumatic events, as they strike across all strata of society (North 2003). Those who are most poor and disadvantaged, however, often bear the largest burden (Lima et al. 1989) because of where they build homes, the vulnerability of their home structures, and the lack of resources for recovery. An estimated 162 million people were affected by disasters in 2005. Nearly 105,000 people died and damages totaled over 176 billion dollars (World Health Organization, Collaborating Center for Research on the Epidemiology of Disasters 2006). Weather-related disasters (such as hurricanes and tsunamis) have received increased interest over the past decade. Historically, pandemic influenza has resulted in tremendous worldwide morbidity and mortality. The 1918 flu is said to have killed from 20 to 50 million people worldwide. The potential for the emergence of another pandemic influenza looms once again with the concerns of mass casualties around the globe. Current planning for a pandemic suggests that efforts to implement health-protective behaviors (e.g., adherence to medical recommendations, social distancing, quarantine, and travel restrictions) will present a significant challenge in a free and mobile society.

Disasters involving intentional mass violence, such as terrorism and war, have gained increased recognition in recent years. The Oklahoma City bombing, the World Trade Center attacks in 1993 and 2001, the anthrax attacks in the U.S., train bombings in Madrid, London tube attacks, sarin attacks in Tokyo, and ongoing terrorist attacks in the Middle East demonstrate the breadth and scope of intentionally caused disasters. Terrorist acts, by definition, target the very sense of safety and cohesion of society.

Demands produced by disasters overload community resources (e.g., health, law enforcement, and public works). The supply–demand mismatch hits directly at community weaknesses and vulnerabilities. Basic needs, such as water, food, and shelter, may be in short supply. Conflicts in responsibilities (e.g., family care vs. professional duties) can also contribute to further stress and emotional and behavioral changes in community members, including emergency first responders and community leaders.

As the immediate impact of a disaster subsides, survivors are confronted with the challenge of rebuilding their lives and sustaining their families. As they strive to return to

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a sense of "normalcy," energy, money, and time are devoted to rebuilding lives, routines, jobs, and structures. This often overlooked (and often prolonged) period of rebuilding exacts an emotional toll on disaster-affected communities. From a disaster mental health management perspective, mitigating the psychological and behavioral effects of disaster requires an appreciation of both the types of disasters and the range of distress-related pathology in individuals and communities.

This chapter describes the types of disasters and their potential effects. Mental health response must be based on an action plan that effectively utilizes available resources (e.g., material, monetary, and personnel) and balances individual and community-based (or public health) approaches to treatment and the identification of at-risk groups. A public health approach addresses both individual and population care needs. This perspective targets those most severely affected, provides guidance and assistance for all who experience distress, and facilitates effective community leadership. Public health focus on mental and behavioral responses to disaster can provide for the public's health and foster the resilience of disaster-exposed individuals and communities.

## Types of Disasters

Disasters can be broadly divided into two types: human-made and natural disasters (Figure 115–1). Natural disasters (e.g., hurricanes, floods, tsunamis, and earthquakes) are considered by some to be "acts of God," or result from the destructive forces of nature. Present science provides little an individual and community can do to prevent the most destructive natural disasters. Advances in science and technology have afforded increasing degrees of warning for some natural disasters. However, there is little that can be done to alter its occurrence or course.

Human-made disasters (e.g., transportation accidents, building collapses, nuclear and industrial accidents, and acts of mass violence, such as terrorism) make up the other category of disaster. Human actions contribute to the creation of this type of disaster and, to a certain extent, develop from human technology and engineering advancement. These types of disasters include structural failure, the failure of safety mechanisms, or intentionally caused destruction.

There is evidence that human-made disasters precipitate a more prolonged and difficult recovery for affected populations (Norris et al. 2002a). In human-made disasters, the belief (real or otherwise) that the event was preventable may contribute to the emotional sequela. In some cases, a source of human error or oversight contributing to the event is readily identifiable.

The distinction between human-made and natural disasters is less clear in some cases. For example, an earthquake may cause initial damage and loss. However, the losses and damages may be more pronounced if preventable structural flaws in buildings lead to the collapse of additional structures. In the case of floods, if dams or other structures meant to divert water are not effectively located or structurally intact, their failure will make a natural disaster more widespread.

Terrorism is a special category of human-made disasters. Unlike other human-made disasters, terrorist acts are conducted with the purposes of causing fear (terror). Terrorist acts are implemented by those who wish to coerce societies and who believe that inducing fear, shock, horror, and revulsion will prompt societal change. These acts are often motivated by ideological, religious, and political agendas. Terrorist acts can lead to death, injury, property damage, and evacuation of communities. However, the main aim of these acts is to challenge a society's sense of well-being, cohesion, and security.

The effects of terrorism can be magnified with the use of CBRNE (chemical, biological, nuclear, radiological, and high-yield explosive) agents. These mechanisms are well suited to causing terror (Holloway et al. 1997, Ursano et al. 2003b). The infectiousness and insidiousness of biological agents, the persistence and disfiguring effects of chemical weapons, and the delayed and uncertain effects of radiological agents, in particular, perpetuate fear and induce terror. Use of such agents on a large scale may not only result in injury and death upon immediate deployment but may complicate an otherwise already-prolonged recovery process.

## Types of Responses

Disasters evoke a variety of immediate reactions at the individual and community level; grief, dismay, shock, dissociation, and other manifestations of distress may occur among the vast majority of community members. Some persons will experience exacerbations of preexistent mental

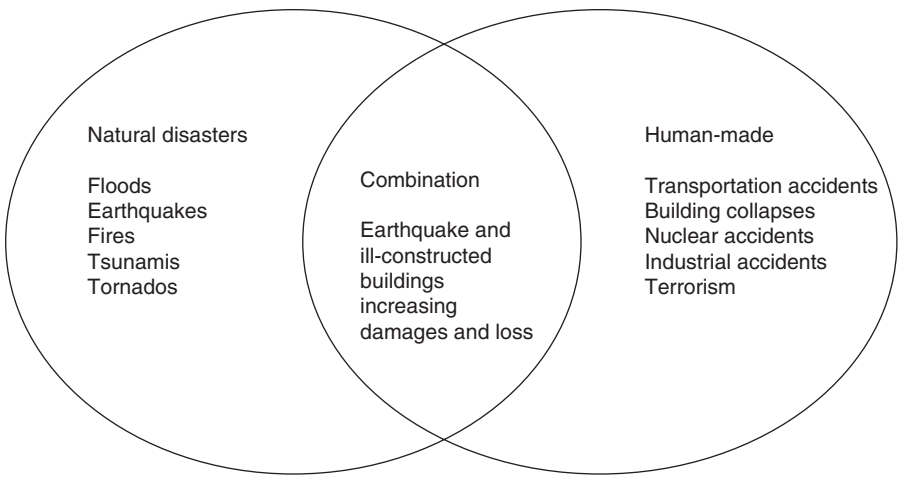



**Figure 115–1** *Types of disasters.*

disorders and still others may develop new mental disorders. At the individual level, response depends on a number of variables. The severity of response is greatest in those with high perceived threat to life, low controllability (e.g., those who feel powerless to alter the course of their own problems), high loss, injury, threat of disaster recurring, and exposure to death and the dead (Boudreaux et al. 1998, Epstein et al. 1997, Green et al. 1985, North et al. 1999, Schuster et al. 2001, Ursano et al. 2007, Wain et al. 2006, Zatzick et al. 2001). It is noteworthy that despite the universality of distress-related experiences, resilience and recovery after disaster are the rule. Most victims will not develop chronic problems. This tendency toward recovery is often termed resilience, a dynamic process of health recovery and coping in the face of adversity (Bonanno 2004). Optimism, intelligence, humor, creativity, and active coping are related to resilience and positive outcomes after crises (Charney 2004). Through active coping individuals accept the impact of a traumatic event (such as a disaster) and implement attainable, concrete measures to improve things.

Even in resilient populations, acute behavioral and emotional manifestations of distress (e.g., problems with sleep, transient worry, and anxiety) are common. Most of these psychological reactions to disasters may be considered ordinary or adaptive responses to stress (IOM 2003). For most, these symptoms will abate and do not require formal treatment. However, their resolution may be sped by educational outreach and community-wide supportive interventions (IOM 2003). A smaller subset of affected individuals may experience more persistent psychological sequelae, such as anxiety, insomnia, increased smoking, increased alcohol consumption, or grief and bereavement. This group may also benefit from supportive psychological interventions, and in some cases transient pharmacological intervention targeting specific symptoms (e.g., insomnia). A smaller subgroup may develop psychiatric illness, including anxiety disorders (generalized anxiety disorder and posttraumatic stress disorder, PTSD), depressive disorders, or substance-use disorders. Such individuals may require formal and more prolonged intervention including psychiatric treatment. A major challenge in disaster mental health response is identifying those that require more intensive treatment approaches and delivering such care in a timely fashion. A related challenge is the delivery of appropriate psychosocial, educational, and supportive interventions to the much larger population of potential beneficiaries in the resource-deprived environment created by disaster.

A useful model of psychological and behavioral response to disaster is one which organizes responses into interrelated domains (Figure 115–2).

First, there are *distress responses* (Table 115–1) that can be thought of as significant emotional states or behaviors related to the stress of the disaster. These include problems sleeping or feelings of anxiety, worry, anger, fear, or vulnerability. These can manifest as work absenteeism or presenteeism (e.g., being physically present but unable to function adequately), family conflict, increased irritability, and accidents or work injury due to being preoccupied or distracted. These are often the initial responses to a disaster. For some, these can be the prologues to the other domains of response.

Distress may also present as somatic symptoms represented by a myriad of physical complaints, including headaches, stomachaches, unexplained pain, and fatigue (Engel 2001). Somatic symptoms are frequently associated with anxiety or depression, and patients with these symptoms often seek care in a primary care clinic. Collaborative care between psychiatry and primary care is of particular importance after disaster for health surveillance, early detection, and treatment of stress-related physical symptoms.

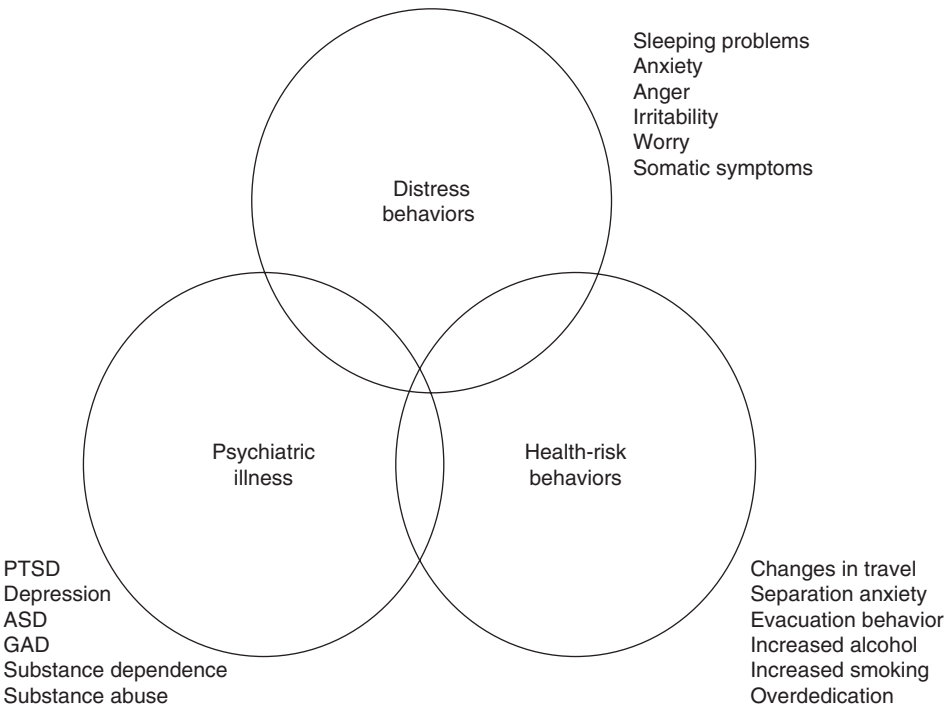



**Figure 115–2** *Types of responses to traumatic events.*

**Table 115–1 Distress Reactions after a Disaster**

| |
|---|
| Grief reactions and other normal responses to an abnormal event |
| Changes in safety and travel |
| Sleep disturbance |
| Altered interpersonal interactions (withdrawal, aggression, violence, and family conflict) |
| Decreased work functioning (ability to do work, ineffectiveness at job, problems with concentration, and absenteeism) |
| Somatic symptoms |

*Health-risk behaviors* (Table 115–2) are those actions made in response to experiencing a disaster. In some cases these behaviors aim to reduce perceived risk of harm (e.g., changing travel route or mode of travel). They may reflect efforts to reduce or "self-medicate" distress (e.g., increase in smoking or alcohol consumption). Increased smoking and drinking has been reported after disaster (Norris et al. 2002a, Shalev et al. 1990). Increased substance use does not necessarily lead to substance-use disorders (Katz et al. 2002). Other health-risk behaviors may result from a necessary or excessive focus on meeting basic needs (e.g., failure to maintain sleep pattern or exercise regimen).

Increases in domestic violence and family relationship problems after a disaster (Adams and Adams 1984) represent another form of health-risk behavior after disaster. Effects of disaster on parenting have not been well studied; however, some data suggest increases in child abuse following disasters (Keenan et al. 2004).

For community leaders and disaster responders, overdedication is a disaster behavior that may initially extend, but ultimately diminish one's capacity to contribute to disaster recovery. Voluntary and altruistic assumption of long work hours, limited sleep, and decreased intake of food and water may be undertaken to benefit others, but the resultant cognitive and performance errors may put others at risk (Norwood et al. 2000). Evacuation behavior is a disaster behavior with implications for morbidity and mortality. After the First World Trade bombing in 1993 many persons either did not evacuate or took significantly longer to do so than necessary, as they sought to quell their anxiety by leaving the building with familiar peers (Aguirre et al. 1998). After the 9/11 attacks, those who evacuated from buildings in New York City tended to congregate near the site of the disaster (Gershon et al. 2004). These seemingly innocuous behaviors may result in increased casualties in cases of secondary building collapse.

The third interrelated psychological consequence of disasters is *psychiatric illness*. This category includes posttraumatic stress disorder, acute stress disorder, depression, and other anxiety disorders (Table 115–3).

**Table 115–2 Health-Risk Behaviors**

| |
|---|
| Changes in smoking |
| Changes in alcohol use |
| Balancing home and work |
| Disaster behaviors |
| • evacuation |
| • overdedication |
| • adherence to medical recommendations |

**Table 115–3 Possible Psychiatric Diagnoses in Those Exposed to Trauma**

| |
|---|
| Posttraumatic stress disorder |
| Acute stress disorder |
| Major depressive disorder |
| Substance-use disorders |
| Generalized anxiety disorder |
| Adjustment disorder |
| Somatoform disorders |
| Organic mental disorders secondary to head injury, toxic exposure, illness, and dehydration |
| Psychological factors affecting physical disease (in the injured) |

PTSD is a frequent subject of study following disasters (for review, see Breslau et al. 2005, Saigh and Bremmer 1999). This disorder is relatively common in the aftermath of large-scale disasters, with prevalence ranging from 10 to 40% in various studies (David et al. 1996, Galea et al. 2002, Green et al. 1991, Ironson et al. 1997, North et al. 1999, Schlenger et al. 2002). Individuals with PTSD experience symptomatology in a number of domains that lead to functional impairment. These domains include hyperarousal symptoms (e.g., problems with sleep, easy startle, and irritability), avoidance (e.g., numbing, not recalling important aspects of the trauma, and sense of foreshortened future), and recollections (e.g., nightmares, reliving the event, and having physiological response to reminders of the event).

The National Comorbidity Study found rates of PTSD to be 7.8% (Kessler et al. 1995), while the National Women's Study found rates to be 12.3% (Resnick et al. 1993). Following the Katrina hurricane, the disaster region had approximately 30% incidence of PTSD (Ursano 2006). In its acute and milder forms, PTSD may be more analogous to the common cold and experienced by nearly everyone at some point in their lives. Like a common cold that becomes pneumonia, it is when it persists that it can be debilitating and require more formalized (and possibly) prolonged intervention.

Acute stress disorder (ASD) is a disorder similar to PTSD but persists for a minimum of 2 days to a maximum duration of 4 weeks. (If it persists longer, then PTSD is the appropriate diagnosis.) The diagnostic criteria for ASD include the symptoms of PTSD with the additional requirement for peritraumatic dissociative symptoms. Dissociative experiences are quite common in the immediate aftermath of trauma (Fullerton et al. 2004).

PTSD and ASD are by no means the only trauma-related psychiatric disorders and may not even be the most common (Fullerton and Ursano 1997, Norris et al. 2002b, North et al. 1999). Exposure to disaster has been associated with increased risk for depression (Miguel-Tobal et al. 2006), generalized anxiety disorder, panic disorder, and increased substance-use disorders (Breslau et al. 1991, Kessler et al. 1995, North et al. 2002, Vlahov et al. 2002). There is suggestion that these disorders occur at higher than average rates (Galea et al. 2002, Kessler et al. 1999, Miguel-Tobal et al. 2006) and may be relatively common in the 6- to 12-month period after a disaster.

Bereavement and grief associated with traumatic loss pose special challenges to survivors of disasters and other traumatic events. Even when not directly witnessing death, family members may develop intrusive images based on information from authorities or the media. A syndrome related to PTSD, with excessive yearning for, and intrusive recollections surrounding the death of a significant other is termed complicated grief. Complicated grief has been proposed for addition to the DSM. Whether or not it is formally recognized complicated grief represents a distinct subset of disaster-related psychopathology for which prevention, recognition, and treatment approaches are being developed. At the community level, effective leadership after disaster includes "grief leadership," an important aspect of giving permission for, and teaching and showing communities how to grieve (Ursano and Fullerton 1990).

### Community Response

Just as individuals are affected by disaster, so are the communities to which they belong. The community response to disaster often runs a predictable and, at times, paradoxical course. Communities temporarily coalesce immediately after a traumatic event, in a phase referred to as the "honeymoon period." Groups and individuals work together under a common, altruistic cause. Accounts of heroism are reported and a sense of "we will survive" pervades the community (Zunin and Myers 2000).

As time evolves, the sense of optimism turns to disillusionment and anger. Scapegoating often occurs and the search for accountability often ensues. Mayors, police chiefs, politicians, and community leaders are often targets. The search for blame often exposes the social fault lines of conflict and suspicion that present along racial, ethnic, economic, and religious divides. Communities encompass not only geographical areas in which disaster victims reside but also the less tangible groups with which individuals share a "sense of belonging." Communities may include workplaces, neighborhoods, churches, schools, ethnic groups, families, and other circumscribed populations with which individuals may choose to associate or find membership.

Communities serve as important physical and emotional support systems that individuals can look to after a disaster. Disasters, however, may impair a given community's ability to function, self-sustain, and provide safety for its members. In disasters that cause widespread destruction and evacuation, jobs, friends, schools, and areas of worship may be destroyed or displaced. The recovery environment may not be intact or be able to support its members (Hobfoll and Jackson 1991, Noji 1997).

There is ample evidence that available social support after disaster can affect outcome and that the perception of available resources can increase feelings of safety (Norris et al. 2002a). Replacing lost resources as quickly as possible is one of the most useful interventions in the immediate aftermath of disaster (Hobfoll and Lilly 1993). Organizations within the community including churches, schools, and employers may be well positioned to provide support and information to individuals with specific concerns and/or needs. Individuals naturally look to these community resources as providers of such support. Recent studies suggest that businesses vary significantly in their human capital continuity resources and preparedness to offer assistance to employees and their families after disaster (Ursano et al. 2007).

One aspect of community response to disaster is community-related grief or bereavement. Gestures of sympathy for the injured, dead, and missing as well as their families are common. Observed rituals, such as burials and funerals, are observed. As times passes, the creation of memorials—both formal (such as structures and monuments) and informal ones (wreaths, candles, and pictures)—often occurs. Memorials may assist some in recovery and remembrance, while others may see these as constant and intrusive reminders. Anniversaries of the disaster additionally stir memories and renew the grieving process (Ursano et al. 2003a).

## At-Risk Groups

Protecting those who are at risk from disasters is critical. Studies are now only beginning to explore why some people exposed to disasters develop posttraumatic pathology and others do not. This research has generally demonstrated particular at-risk groups. Persons most directly exposed to trauma, physically injured persons, women, those with preexisting psychiatric conditions, children, refugees, other displaced persons, and those with ongoing negative life events may be at increased risk for psychological problems following a disaster (Table 115–4).

In general, women appear to be at greater risk for PTSD and major depression, while men are at greater risk for substance abuse after disasters (Kasl et al. 1981a, 1981b, Lopez-Ibor et al. 1985, Maes et al. 1998, North et al. 1999, Weisaeth 1985). These gender-related distinctions diminish in military populations engaged in combat (Hoge et al. 2004) perhaps as a result of selection, specific training or the nature of war-related trauma. Other demographic factors from disaster literature, such as age, race, and socioeconomic status, present either mixed finding or insufficient evidence to conclude consistent association as they apply to postdisaster outcome.

Those *directly exposed* are at greatest risk for psychiatric disorders after the disaster. The directly exposed group usually includes individuals most proximal to the disaster (Galea et al. 2002, North et al. 2002), those who were in physical danger, and those who directly witnessed traumatic events. In addition, individuals who have attachments with primary victims, first responders, and support providers are at greater risk (Wright and Bartone 1994) than "detached" bystanders.

*Injured persons* are a particularly vulnerable population. The Epidemiologic Catchment Area Study of Vietnam

**Table 115–4 High-Risk Groups**

| |
|---|
| Directly exposed to life threat |
| Injured |
| First responders |
| Children |
| Women |
| Refugees/displaced individuals with |
| • on-negative life events after disaster |
| • prior posttraumatic stress disorder |
| • prior exposure to trauma |
| • prior or current psychiatric or medical illness |
| • lack of supportive relationships |

veterans demonstrated a higher rate of PTSD in the wounded solider cohort (Helzer et al. 1987). Also, high levels of physical problems early after injury were predictive of the subsequent development of PTSD and depression in injured U.S. soldiers (Grieger et al. 2006). In addition, psychiatric symptoms are frequently seen in injured survivors dealing with the stress and extent of injury (Brandt et al. 1997, North et al. 1999, Shore et al. 1989, Zatzick et al. 2001).

*First responders* (e.g., fireman, police, and emergency medical technicians) are an at-risk population by virtue of their job and degree of exposure (Duckworth 1986, Fullerton et al. 2004, Jones 1985, Weiss et al. 1995). Well-trained individuals can develop persistent problems as a consequence of frequency and degree of exposure, particularly to the disfigurement and grotesquery of the immediate post-disaster scene. First responders must also contend with their own safety as well as that of others at the disaster scene. First responders may "identify" with victims and think "it could have been me," or be reminded of their own (and their family's) vulnerability. This phenomenon has been particularly associated with increased rates of psychopathology in handlers of human remains (McCarroll et al. 2001, 2002, Ursano et al. 1999).

First responders may also include bystanders in the vicinity when a disaster occurs. It is estimated that 50% of those who initially report to assist after a disaster are these types of bystanders. These individuals may be at particular risk, as they are exposed to tasks and scenes for which they have little training or previous experience in handling.

Preexistent psychiatric conditions are not necessary for psychiatric morbidity after a disaster and they are not sufficient to account for it (Goldberg et al. 1990, McFarlane 1989, Ursano et al. 1981). Those with *preexisting psychiatric conditions* are at increased risk of psychiatric illness after a disaster (Bromet et al. 1982, McFarlane 1989, North et al. 1989, 1994, 1999, Ramsay 1990, Smith et al. 1990, Weisaeth 1985). In addition to psychiatric illness, personality features have shown to be associated with development of psychopathology (including PTSD) after a disaster (Chen et al. 2001).

*Children* are a population of concern after all disasters (Cohen et al. 2006, Pfefferbaum 2005, Pynoos et al. 1997). Limited cognitive level and maturity to understand, displacement, experiences of altered parenting and observation of parental distress (Michael and Julia 2006), loss of parental figure, and injury are all thought to contribute to their risk. Overt manifestations of distress may include lability, problems falling asleep, frequent crying, fear, and anniversary grief. Alternatively, presentations may also be more subtle, such as manifesting in multiple, medically unexplained somatic complaints (Michael and Julia 2006).

Depression, anxiety, and PTSD in children of disaster have been well characterized. The prevalence of PTSD symptoms 2 months after the Asian tsunami in children aged 7–14 was 13% (children in camps), 11% (children affected in villages), and 6% (children in unaffected villages) (Thienkrua et al. 2006). In New York public schools after the 9/11 attacks, 28.6% of children in grades 4 through 12 had one or more of six probable anxiety/depressive disorders (Hoven et al. 2005) and were largely represented by probable diagnoses of agoraphobia, separation anxiety, and PTSD. Comorbidity is not uncommon in adolescents after disasters. One recent study (Kar and Bastia 2006) noted comorbidity in 39% of adolescents with psychiatric diagnoses. Distress without psychiatric disorder has also been demonstrated. A significant proportion of children also worry about the future and the potential to be victims of terrorism (Schuster et al. 2001).

*Refugees/displacement*. Being displaced (e.g., evacuated to a refugee camp) is associated with elevated rates of depression and anxiety (Thapa and Hauff 2005), PTSD (Bland et al. 2005), and—for children—insecure attachment style in their adult years (Foster et al. 2003). The refugee population encounters many problems (such as loss of job, loss of home, and loss of community) that are associated with issues of attachment, familiarity, and identity (Fullilove 1996).

*Ongoing negative life events*. Research has also focused on those who experience further negative life events *after* a disaster. These negative life events are usually brought upon by the disaster and its subsequent effects, such as loss of community employer that in turn produces loss of job, financial constraints, relationship difficulties, etc. These contribute to increased likelihood of PTSD (Adams and Boscarino 2006), PTSD severity (Maes et al. 2001), and depression (Person et al. 2006). Negative life events have also been linked to an increase in workdays lost (Boscarino et al. 2006) as well as poorer mental health outcome (Adams et al. 2006). Longstanding psychosocial and personality issues that predate the disaster may confound the risk for experiencing negative life events after a disaster (North 2003).

## Mitigating Disaster-Related Distress and Dysfunction

During a disaster, mental health providers must anticipate and respond to a range of emotional and behavioral demands from those affected. In the case of disasters involving epidemics or bioterrorism, stressors include quarantine, shelter in place, and travel restrictions. The public health system must address mental health care across the dimensions of distress, disorder, and behavior.

Mental health professionals are an essential part of planning for and responding to disasters. Mental health disaster response includes the identification and treatment of those who need immediate psychiatric care as well as interventions for those populations that will benefit from support, guidance, and the provision psychological health-related information. Public education, consultation to leadership, and schools are important tools for mitigating community-wide distress and facilitating early identification of those in need of treatment.

The range of responses for which mental health disaster planners must account requires that new models of monitoring community health care needs in real time (i.e., mental health surveillance) as well as innovative models for delivering care are developed (Bryant 2006). The mental health care system, as part of the medical care system, must join with the public health and emergency response system to address the needs for triage, surge capacity, and health surveillance in order to best provide care for communities exposed to disaster (Raphael 2006). The knowledge base from a variety of disciplines including sociology, risk communication, education, and disaster mental health can contribute to the development of effective response plans (Litz et al. 2002). This knowledge can provide guidance for

community leaders, local emergency planners, health and mental health planners, and health care providers in order to create an informed and well-prepared plan for psychological and behavioral consequences of disasters (Litz et al. 2002). Therefore accurate assessment, and appreciation and proper use of community resources can help mitigate the effects of disaster and its responses (Table 115–5).

## Planning and Preparation

Planning is the first and most important step in forming an effective and coordinated response. It is often difficult to obtain resources for planning, as these needs must be balanced against resources utilized for more immediate needs. Disasters are often unexpected and, although there is very little that can be done to control the timing and occurrence of such events, the effects can be mitigated with a considerate and well-formed plan. In preparation for disasters, *leaders of the community response need to be identified*. Elected officials, religious leaders, educators, and military leaders provide a pool of appropriate candidates. This cross section should include those who provide expertise in essential human needs during a disaster, such as communications, security, and aid assistance. Leaders are in the best position to know of the resources in the community and its present need. Knowing the most efficient way of reaching those who require assistance is also a function of leadership identification.

Leaders are often looked upon as the "voice" and the communicators of the community. In times of crises, this is an expectation. Clear, concise, and accurate updates from community leaders can help inform and calm a populace looking for answers. Thus, for leaders, training in the principles of good risk communication and public education may prove invaluable. Risk communication is a scientifically informed approach to communicating in stressful situations. Principles of good risk communication enable leaders to inform and direct diverse populations (Table 115–6).

**Table 115–5 Mental Health Intervention Planning and Response**

Planning

Leadership should be identified in order to

- perform accurate assessment of resources in community
- identify at-risk populations within the community
- determine the best way to assist community in culturally acceptable ways
- be trained in the principle of good risk communication
- prepare populace (i.e., having emergency provisions and plans)

During Event

After a disaster

- Most important initial need is to address the medical and emergent needs of those affected
- Psychological first aid may be of benefit
- Those least injured will present for evaluation first
- Medical assets will be overwhelmed
- Large numbers of presenters will be distressed and will seek reassurance
- A side area by the emergency room should be established for those who are not reassured and need time to reconstitute
- A volunteer registry for subsequent contact can be established for subsequent follow-up (health surveillance)

**Table 115–6 Principles of Good Risk Communication**

Delivers information from credible, consistent source
Avoids speculation
Never mixes facts with reassurance
Outlines specific steps on how to protect themselves and their families

Individuals in the community look to their leaders for information, inspiration, a sense of control, optimism, and help during a period of grief (Barbera et al. 2001). Effective risk communication helps to provide these by delivering frequent information from credible and consistent sources. This information should avoid speculation, outline specific steps people can do to protect themselves, and inform when the next messages will be delivered; this can assist in reducing negative psychological responses, encourage safe and responsible behaviors, build trust, and minimize misinformation (Aakko 2004, Covello et al. 2001, Glik 2007). Leaders must also understand what is culturally and socially appropriate in terms of aid, timing, and assistance measures.

Being aware of the presence and needs of at-risk groups is an important function of leaders. This is especially true in the diverse and multicultural communities. Different cultures may have markedly different responses as a result of past experiences with disasters, with government's aid and assistance, and with security forces, police, or other first responders. Many immigrant groups and individuals have limited proficiency in the language of their current homelands and have previous experience with torture or abuse by authorities, multiple losses, minimal resources, and limited access to care. Any of these may place them at greater risk. In the planning phase for disaster response, awareness and information must be culturally sensitive and accessible.

Leaders must be aware of their community's inherent strengths. Fostering resilience is a primary goal of preparedness. Resilience represents both decreased adverse responses and more rapid recovery. Town meetings that occur prior to crises may foster community efficacy by enabling community networks to work together in order to anticipate "cracks" in the support network. For example, these meetings can set forth plans, such as who will watch children on the block if a mother or father is not home. Such cohesion efforts can develop community efficacy (Sampson 2003, Sampson et al. 1997) and channel fear into a flow of constructive action instead of community chaos.

Efforts to promote individual and family pre-event preparation are vitally important to minimizing the psychological consequences of disaster. In surveys conducted after hurricanes Katrina and Rita, less than half of respondents reported having a family emergency plan familiar to all members. In addition, less than a third had emergency provisions (e.g., 2 days of food and water, flashlight, radio, spare batteries, emergency phone numbers, and a preplanned emergency meeting place) (Redlener and Berman 2006). Forming a communication plan with loved ones (in the case of separation), establishing and mapping out of evacuation routes, having extra medication supplies, developing care plans for

pets, and having extra necessities on hand (e.g., such at least half tank of gas in car at all times, extra batteries, extra bottled water, and nonperishable food items) (CSTS 2006) are not elements of traditional mental health treatment. However, effective public education efforts to encourage these behaviors may again minimize the psychological and behavioral consequences of traumatic events. And in the same manner that one might ask one's patient about smoking as a health-risk behavior that warrants concern and focus, clinicians can inquire of their patients about what they have done to "prepare" in preevent of a disaster. Caring for oneself and one's loved ones is a part of health, which includes preparedness for expectable disasters.

## Immediate Response

When a disaster strikes, the most important initial response is to address the medical emergency and basic care needs of those affected. The medical assets and capabilities in disasters are often overwhelmed in the event of a disaster. Those who are least injured present for care and evaluation first; those more seriously injured require stabilization and transport (which may be further complicated by closure of routes and availability of transportation assets). In cases of nuclear, biological, or chemical terrorist attack, demand surge at medical treatment facilities is complicated by a population presenting for evaluation and treatment under the belief that they were exposed (Karsenty et al. 1991, Ohbu et al. 1997). Other individuals will be distressed and seek reassurance. Screening procedures may allow for the rapid diagnosis of those with psychiatric disorders requiring immediate attention (e.g., delirium and psychosis) or near-term follow-up. Reassurance and educational/supportive interventions may be sufficient for some persons seeking care. Others who do not respond to initial reassurance and evaluation can be moved to an area close to the emergency room, so monitoring may continue allowing further time to reconstitute (Benedek et al. 2002). Establishing a voluntary registry (in order to facilitate follow-up) for those who present will establish a mechanism for health surveillance.

Early symptoms usually respond to a number of educational and supportive approaches, such as helping patients and their families to limit further exposure (e.g., by avoiding excessive news footage of the traumatic event). Reminders to take care of basics, such as getting enough rest and food, as well as maintaining biological rhythms (e.g., sleep at the same time every evening and eating at the same time each day), can prove valuable.

Talking with others about the disaster, sharing available resources, learning new coping strategies, and seeking help are involved in the normal process of recovery. Treatments for PTSD, ASD, depression, and other disaster-related disorders are available (Ursano et al. 2004) and include both psychological and pharmacological interventions (Foa 2006, Foa et al. 2000, Ritchie et al. 2006, Yehuda 2002).

## Early Intervention at the Community Level

Identifying vulnerable populations, providing psychoeducational support, assessing population needs, and providing access to care are areas of emphasis when managing disaster mental health. Referred to as Critical Incident Needs Assessment Teams (CINAT), these multidisciplinary teams are formed from the community and workplaces from which they live and serve (Hamaoka et al. 2007). Team membership may include not only mental health authorities, but also others such as leaders, information specialists, and security specialists. These teams provide a vehicle for the delivery of psychological first aid (PFA), leadership consultation on grief leadership and other behavioral issues, and health surveillance.

PFA may be helpful and appropriate in the immediate aftermath (hours to days) of disaster (CSTS 2005, Parker et al. 2006, Watson and Shalev 2005, Weisaeth 2004). This evidenced-informed interventional structure aims to reduce distress by using several principles (Table 115–7) and is best thought of as a flexible, supportive, population-based approach to distressed persons. Since outcome studies are lacking, intervention should be considered as "likely to be helpful." Its main objectives are to limit distress, emphasize healthy behaviors, and minimize negative health behaviors. PFA is an intervention that can be accomplished by anyone who had been trained. (That is, it does not have to be accomplished by a mental health provider.) In addition, this training does not require formal mental health training. Principles of PFA include promoting *safety*, *calm*, *connectedness*, *hopefulness*, and *self-efficacy.*

*Promoting safety* focuses on the physical needs and emotional needs of those affected. This primarily refers to supplying items such as food, water, and shelter as well as minimizing from further trauma. Another component to this principle for individuals to *feel safe*. Sometimes difficult to discern, *feeling safe* differs from *being safe* in that the former takes on a qualitative component. Feeling safe not only can be addressed by meeting the needs of those affected, but may also be enhanced by seeing others in need

**Table 115–7 Components of Psychological First Aid**

1. Safety
   - Help people meet basic needs for food and shelter and obtain emergency medical attention
   - Provide repeated, simple, and accurate information on how to obtain these items
2. Connectedness
   - Help people contact friends and loved ones
   - Keep families together; keep children with parents or other close family members whenever possible
3. Self-efficacy
   - Give practical suggestions to help steer people to help themselves
   - Engage people in meeting their own needs
4. Calm
   - Listen to people who wish to share their stories and emotions. Remember there is no right or wrong way to feel
   - Be friendly and compassionate even if people are being difficult
   - Offer accurate information about the disaster or trauma
5. Hope
   - Find out about the types and locations of services and direct people to them
   - Remind people (if you know) that more help and services are on the way when they express fear or worry

receiving assistance. In the same way, promoting calm is another tenant of PFA. *Promoting calm* may seem to be a challenge in the chaotic environment after a disaster, but providing accurate information about the disaster and relief efforts so that they are apprised of the situation can assist in producing calm. Another example would allow for victims to share their stories and emotions if they choose. Providing and maintaining a friendly and compassionate stance even if others are being difficult is another way to promote calm.

By remembering to *promote connectedness*, PFA helps providers remember that family and loved ones are important and that helping them connect with them is important. Even if the disaster makes it physically prohibitive for family members to meet, promoting connectedness can even include telephonic communication or information from separated family members about their location and status. In promoting connectedness, it is also important to remember that, if at all possible, family members should remain together. Connectedness both increases emotional support and provides opportunities to obtain practical help and information.

Finding and sharing the types and locations of available services can assist in instilling *hopefulness*. If one knows that more help and services are on the way, reminding people of this can be helpful when they express fear or worry. In addition, recognizing and reminding people that "things will get better" is an important clinical task in most settings where the clinician may be able to see further ahead than the patient in distress. *Promoting self-efficacy* enables victims to help themselves in the aftermath of a disaster and to believe that they have the skills to survive and move forward. Ways to help promote this tenant are providing suggestions that steer people toward helping themselves, thereby helping them meet their own needs. This helps victims take control in their environment and empowers them.

Brief simple conversations and informal on-site talks with survivors can be of great assistance. This early "walk-around" intervention offers support and education, avoids mental health labeling, and makes possible early assessment of those in most need. Mental disorders that occur in response to disasters appear to respond to the same therapeutic approaches as disorders observed in traditional treatment environments. Psychotherapy (e.g., cognitive therapy, cognitive–behavioral therapy, and interpersonal therapy) and medication (e.g., selective serotonin reuptake inhibitors, selective norepinephrine-serotonin reuptake inhibitors, and dopamine-norephinephrine reuptake inhibitors) are evidenced-based treatments for depression (APA 2000). Treatment guidelines for ASD and PTSD have also been established (Ursano et al. 2004). Evidence-based treatments for PTSD include medications (e.g., selective serotonin reuptake inhibitors, such as paroxetine and sertraline) as well as therapies (e.g., cognitive–behavioral therapy) (Bryant et al. 1998, 2003). Other medications may improve sleep or reduce posttraumatic nightmares. Combinations of psychotherapy and medication may promote maximal response. One well-publicized disaster intervention known as "psychological debriefing" has not been shown to prevent PTSD and may be harmful in certain circumstances (Rose et al. 2002).

## Sustaining Recovery

The longer term morbidity associated with disasters has not been well studied. However, the prevalence of psychiatric disorder in refugee populations, war veterans, and holocaust survivors and the chronic and recurrent nature of depression, anxiety disorders, and substance-related pathology suggests that the long-term emotional and behavioral consequences of disaster are substantial. The institution of new health programs and resources and public health awareness campaigns in rebuilding communities may result in persons with illness that predated the disaster seeking adding to the burden of those affected "purely" by the disaster. Traditional psychopharmacological and psychotherapeutic approaches may serve these populations (if resources are sufficient) but vulnerable populations (the elderly, the chronically mentally ill, and the poor) may continue to require targeted interventions for years after a large-scale disaster.

### Pandemic Flu: A Case Example

Pandemic flu is a present-day concern that highlights the need for planning and attention. It is estimated that the next influenza pandemic may result in millions of casualties and substantial morbidity associated. A response plan for a disaster of such magnitude will require leaders and communities to work together. Obstacles to such a coordinated international response include cultural differences, geographical and political boundaries, and the willingness of those affected to respond and adhere to recommendations from various sources of authority.

There have not recently been large enough infectious outbreaks to fully inform a consensus response to a potential pandemic flu. Recent data and observations on infectious disease outbreak and mental health responses provided by SARS (Des Jarlais et al. 2006, Hawryluck et al. 2005, Ko et al. 2006, Ursano 2005) and contained outbreaks of influenza in the far east suggest that planning must include the notion that care providers will be reduced in number and effectiveness by the outbreak itself (Chong et al. 2004, Lin et al. 2007).

Although much of the initial attention will focus on the contagion and casualties, planners need to remain cognizant of distress behaviors, health-risk behaviors, and psychiatric illness. The attention to such issues can influence the adherence to recommendations to help control the outbreak. The scope of this potential disaster has widespread implications and special considerations. This pertinent example reinforces the content of this chapter and discusses some special considerations of this disaster.

General responses (and special considerations for each stage) can be divided into three parts: preparedness, early response, and later response and recovery (Table 115–8).

*continues*

**Pandemic Flu: A Case Example *continued***

**Preparedness**

Public education must begin immediately and embed into existing disaster public education campaigns and initiatives. Such education should focus on facts, to include what is known, what is not known, and how individuals, communities, and organizations can prepare. This public education should be inclusive of the varying degrees of threats, to include those of reasonably low threat potential to those with the highest potential. This can provide usable information on which to base choices (Morse et al. 2006).

Leadership serves a critical function in the preparation phase. Leaders are valuable in identifying those groups who may be at the greatest risk for problems related to the contagion, such as those with psychiatric illness, children, elderly, homeless, and those with losses. They also serve to affect communities and influence individual behaviors; these can be especially helpful in the endorsing and modeling of proper protective health behaviors. Special attention to the workplace is imperative (as this venue can potentially reach large audiences), as well as enlisting the media as partners.

**Early Pandemic Response**

There will likely be widespread morbidity and mortality. In the midst of such event and ongoing loss, there will also be the challenge of sustaining community and function in the midst of a restrictive environment (e.g., shelter in place, contact precautions, and treatment adherence).

In the early pandemic response, the role of communication will be of utmost importance. Dissemination of uncomplicated and empathically informed information on normal stress reactions can help to normalize reactions and emphasize hope, resilience, and natural recovery. This will be essential as recommendations to prevent exposure, infection, and halting of the disease process will be met in a variety of ways: hope, skepticism, and fear. Compliance with vaccinations and medication regimen will vary greatly and will not be complete. The public must be clearly and repeatedly informed about the rationale and mechanism for distribution of limited supplies of medication and resources. Likewise, leadership must adhere to policies regarding such distribution, as abuses of policy will undercut the public safety and adherence to other recommendations.

Certain events, known as "tipping points," will occur that can dramatically increase or decrease fear and health-risk behaviors. Events that present tipping points are the death of important figures, deaths of the particularly vulnerable (e.g., children), new unexpected or unknown risk factors, and treatment shortages. Such events can present widespread distress in individuals and communities already weathering a great deal of stress and fear. Anticipation of the effect of these events may help inform a response to address these.

Those who believe they have been exposed (but have actually not been) will outnumber those exposed and may quickly overwhelm a community's medical response capacity. Planning for the psychological and behavioral responses of the health demand surge and responses to shortages should be anticipated.

**Later Response and Recovery**

Maintenance of community and its social supports will be important. These may be diminished because of movement restrictions due to concerns of contagion. Virtual contacts, via Internet, telephone, television, and radio, will be increasingly important at these times. At other times, local gathering places—religious places, schools, post office, and grocery stores—are points of access for education, training, and distribution.

Instilling a sense of normalcy, in as much as is allowed, may be effective in fostering resilience. Observing rituals and engaging in regular activities (such as school and work) can help manage the community and organizational distress into constructive behaviors. Providing tasks for community action can supplement needed functions, decrease helplessness, and instill optimism.

Under conditions of continuing threat, the management of ongoing racial and social conflicts in the immediate period and during recovery takes on added significance. Stigma and discrimination may marginalize and isolate groups, thereby impeding recovery.

In the later phases, the management of bodies and the community response to losses will be significant. Containment measures related to bodies and contagion may conflict with religious ritual of burial and therefore have the potential to complicate bereavement. In a pandemic, funeral resources will be overwhelmed. In addition, careful identification of bodies must be ensured and appropriate, accurate records maintained.

## Conclusion

Disasters are ubiquitous; they affect individuals, families, workplaces, and communities. Whether from natural or human-made causes, disasters will continue to be a primary cause of mental health need. Proper preparation, effective leadership, attention to community and individual needs, and well-placed interventions can help mitigate the distress produced by disasters and help maximize community restoration.

**Table 115–8 Issues for Pandemic Flu**

| |
|---|
| Preparation Phase |
| Immediate public education (on influenza, personal preparation) |
| Assessment of resources (personnel, monetary, capital) |
| Identification of natural emergent leaders for communication and modeling of protective behaviors |
| Identification of most vulnerable populations |
| Early Pandemic Response |
| Dissemination of uncomplicated and empathically informed information on normal stress reactions |
| The public must be clearly and repeatedly informed about<br>• rationale and mechanism for distribution of limited supplies of medication and resources<br>• recommendations to prevent exposure, infection, and halting of the disease process |
| "Tipping points" can dramatically increase or decrease fear and health-risk behaviors |
| Medical system may be overwhelmed with those who believed they have been exposed (but who have not) |
| Later Response/Recovery |
| Maintenance of community and social supports by virtual contact (e.g., phone, Internet) |
| Instilling a sense of normalcy, in as much as is allowed, through school and work |
| Ongoing racial and social conflicts in the immediate period and during recovery takes on added significance |
| Containment measures related to bodies and contagion may conflict with religious ritual of burial and therefore have the potential to complicate bereavement |

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CHAPTER

# 116 Management of the Suicidal Patient

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## Introduction

Management of the suicidal patient is one of the most challenging clinical tasks faced by the clinician. A clear and thorough approach to risk assessment and a comprehensive, yet focused management plan is required. Accurately predicting which patients will eventually commit suicide is not currently possible. However, factors that raise and protect against risk have been identified. This chapter provides a guide for the clinician managing the suicidal patient. The risk and protective factors for suicide are presented, as well as suggested assessment and treatment approaches for suicidality.

## What is Suicidal Ideation and Behavior?

While the field is troubled by the use of inconsistent terminology for suicidal ideation and behavior (O'Carroll et al. 1996, Andriessen 2006), the following definitions, previously used in recent research (e.g., Posner et al. 2004, Hammad et al. 2006) will be used for suicidal ideation, suicide attempt, completed suicide, and nonsuicidal self-injurious behavior in this chapter.

Suicidal ideation is the occurrence of passive thoughts about wanting to be dead or active thoughts about killing oneself (Posner et al. 2007). Suicidal thoughts may range from the occasional and fleeting to the ruminative and omnipresent. Typically, they fluctuate and are ambivalent, countered by the will to live.

A suicide attempt is defined as a potentially self-injurious behavior with at least some intent to die as a consequence of the act (O'Carroll et al. 1996, Oquendo et al. 2003). The intention of suicidal behavior is to end one's own life. Suicidal intent is necessary for a potentially self-injurious behavior to be labeled an attempt; however other motivations may also be present, for example, to influence another. Attempting suicide may or may not cause actual injury. Self-injurious behavior without suicidal intent is engaged in for purposes other than death, such as communicating distress and stimulating or coping with strong emotions. Self-harming behavior that is undertaken without at least some intent to die is not classified as suicidal. Populations with suicidal behavior and self-injurious behavior without suicidal intent can be meaningfully distinguished by these behaviors (Nock and Kessler 2006), although the overlap between these populations is not small. Completed suicide is a self-injurious behavior that has the consequence of death which must be accompanied by at least some intent to die as result of the behavior (O'Carroll et al. 1996, Oquendo et al. 2003).

## Scope of The Problem of Suicidal Behavior: Mortality and Morbidity

In 2000, suicide accounted for up to 1 million deaths worldwide including approximately 30,000 in the US (World Health Organization 2007, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2007). Globally, suicide is among the top three leading causes of death for ages 15−44 years (World Health Organization 2007). Suicide rates vary by country with high rates recently reported in the Baltic States, Russia and some Eastern and Northern European countries (World Health Organization 2007). Rates also vary over time, for example, rates of youth suicide rose in many countries between the 1960s and 1990s (Gunnell 2000, Cantor et al. 1996) and have declined or stabilized in some countries since the 1990s and early 2000s (Gunnell 2000, Lester and Yang 2005, Bridge et al. 2005). National rates may be influenced by factors including, religion, socioeconomic factors, access to means, and mental illness (Levi et al. 2003). In addition, the quality and type of data collection and classification varies between countries and limits the utility of this data.

The burden of suicide has come to governmental attention with the development of strategy and policy to combat

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the problem (e.g., the US Surgeon General's Call to Action to Prevent Suicide; U.S. Public Health Service 1999). The UK aims to cut suicide by 25% by 2010 (Robinson et al. 2006), given both its enormous human cost for surviving family (Mitchell et al. 2005) plus economic cost (Clayton and Barceló 1999). But the burden is not limited to the costs of completed suicide alone. In a large US national survey, 4.6% of respondents admitted to attempting suicide, 13.5% reported lifetime suicidal ideation, and 3.9% admitted to ideation with a plan during their lifetime (Kessler et al. 1999). In the US, suicidal and nonsuicidal self-injury requiring hospitalization numbered more than 154,000 in 2005 (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2007) and account for 0.4% of all emergency department visits (Doshi et al. 2005). Moreover, a sizeable proportion of suicide attempters do not attend emergency departments or receive medical or psychiatric care (Suominen et al. 1998). Thus, the problem of suicidal behaviors is significant.

## Risk and Protective Factors

While suicide is responsible for a substantial number of preventable deaths, it accounts for only a small percentage of all deaths. The relatively infrequent nature of suicide and the complex etiology of suicide contribute to the difficulty in identifying predictors of attempted and completed suicide that possess reasonable levels of sensitivity and specificity. Typically, risk factors have a low level of specificity, in that they produce a high proportion of false positives. For example, psychiatric diagnosis is highly associated with suicide but the majority of people with a psychiatric diagnosis do not attempt suicide (Mann and Currier 2006). Factors that protect against suicidal behavior have also been identified. Like risk factors, knowledge of protective factors, such as employment and social support, in some cases, can provide targets for treatment. Knowledge of risk and protective factors for suicidality are therefore important for the clinician managing a suicidal patient. The following is a summary of those factors.

## Demographic Risk and Protective Factors

### Gender

Males are almost four times as likely to die by suicide as females (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2007). Females are twice to three times more likely to think about suicide (Kessler et al. 1999, De Leo et al. 2005) and almost twice as likely to attempt (Kessler et al. 1999). These differences may be explained in terms of an unequal distribution of risk factors. For example, while females experience greater levels of depression (Kessler et al. 2005) which raises risk, they typically use less lethal means when attempting (Hawton 2000), and are less likely to experience substance abuse or impulse control disorders (Kessler et al. 2005) than males, which reduce risk.

### Age

In the US, completed suicide increases markedly from childhood, where it is a very rare event (6–11 years, 0.13/100,000), to early adolescence (1.34/100,000) and mid-late adolescence (8.2/100,000), before stabilizing in early adulthood (20–24 years 12.47/100,000) to adult levels (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2007). While frequency of completed suicide is generally stable throughout adult life, there is a sharp, dramatic increase in completed suicide in elderly populations (Conwell 2001). In contrast, suicidal ideation and attempts have been noted to decline with age (De Leo et al. 2005, Kuo et al. 2001, Kessler et al. 2005). Apart from the possibility that risk of suicidal ideation indeed decreases with age, this could imply that attempts become more lethal and/or better planned resulting in fewer remaining ideators or that as the population ages, more of the at-risk individuals have died by suicide or other causes.

### Religiosity

Religious belief or affiliation is associated with a reduced risk of suicide (Anglin et al. 2004, Dervic et al. 2004, Eagles et al. 2003, Hilton et al. 2002). The protective effect of religion may be due to the deterrent effect of religious beliefs, such as suicide is a sin or is morally wrong or social support from family (Dervic et al. 2004) or a religious group (Neeleman et al. 1997). The protective effect of religion may not be universal, however, with some religions having beliefs that are congruent with suicide, for example, condoning suicide as an honorable way of dealing with problems or that death may be a way of being reunited with loved ones (American Psychiatric Association 2003). Considering this variability, clinicians ought to query patients about their religiosity and the likely impact of religious beliefs on suicidality.

### Family and Social Factors

Separated, divorced, and widowed individuals have been found to be at twice the risk of attempted suicide (Kessler et al. 1999, 2005). Another study has shown that risk varies with gender and is only elevated in divorced males (Kposowa 2000). The relative protective effects of marriage may be gained from companionship, social support and a sense of responsibility (American Psychiatric Association 2003). Having children appears to attenuate risk (Clark and Fawcett 1994) and number of children has been negatively associated with suicide risk in women (Høyer and Lund 1993). Heikkinen et al. (1994) found social support to be lacking prior to suicide, while others found adequate self-reported social support in European suicide attempters, however, lower support predicted future attempts (Bille-Brahe et al. 1999, Bille-Brahe and Jensen 2004). Suicidal patients may require encouragement and assistance in establishing or connecting with their social network, particularly given the impact of psychiatric disorders on social functioning.

### Familial Association

A family history of suicide raises the risk of suicidal behavior (Jeglic et al. 2005, Mann et al. 2005). Brent et al. (2002) found suicide attempt to be six times more likely in the offspring of depressed suicide attempters compared with depressed nonattempters. Further, suicide attempters with a family history of suicide were more likely to have made multiple attempts than those without a family history (Jeglic et al. 2005). Evidence suggests that risk is transmitted via an impulsive–aggressive trait (Roy 2006, Brent et al. 2002,

Mann et al. 2005), experience of child sexual abuse in parents and offspring (Brent et al. 2002, Mann et al. 2005) and early onset of depression in offspring (Mann et al. 2005). Jeglic et al. (2005) proposed that learning of negative problem solving after exposure to a suicidal parent could contribute to the transmission of risk. Collectively, these findings suggest that a family history of suicidality should be taken during the assessment of an individual for suicide risk.

## Employment

Suicide attempts (Beautrais et al. 1998, Kessler et al. 1999) and completed suicide (Kposowa 2001, Brown et al. 2000) are more prevalent in unemployed compared with employed populations. Unemployment has been found to place women at greater risk of suicide relative to males (Kposowa 2001). Unemployment may not have a direct causal effect on suicidality. When Beautrais et al. (1998) adjusted for confounding factors (psychiatric diagnosis and childhood, family, and educational factors) the relationship between unemployment and suicide was no longer significantly related to serious suicide attempt confirming previous hypotheses about its role. (Jones et al. 1991). In particular, unemployment may be a consequence of psychiatric morbidity, as psychiatric disorders are known to have an impact on workplace performance, productivity, and absenteeism (e.g., Olfson et al. 1997, Kessler et al. 2006, Lim et al. 2000). Employed patients may need support to protect their position such as, additional sick leave, reduced duties, and time for attending treatment appointments. Referral of unemployed patients appropriate for employment to rehabilitation services is worth consideration. In particular, supported employment programs have been found to be efficacious (e.g., Crowther et al. 2001).

## Clinical Risk and Protective Factors

### Past Suicidality

A history of suicidal ideation and behavior are consistently identified as predicting further suicidality and completed suicide. Suicidal ideation prospectively predicts completed suicide (Brown et al. 2000, Beck et al. 1999) and suicide attempt (Kuo et al. 2001) while ideation with a plan was found to be a stronger predictor of suicide attempt than ideation without (Kessler et al. 1999). Suicide attempts have been found to be a marker of future suicidal acts (Mann et al. 1999b, Oquendo et al. 2004) and completed suicide (Beck and Steer 1989, Brown et al. 2000, Nordström et al. 1995). Thus a thorough assessment of the patient's past history of suicidal behavior or ideation is critical.

### Psychiatric Disorder

Prevalence of psychiatric diagnosis in completed suicide populations is as high as 90% in both child and adolescent (Shaffer et al. 1996) and adult samples (Conwell et al. 1996), as determined by psychological autopsy. This rate is similar to that found in attempters who make medically serious attempts (Beautrais et al. 1996). Increasing comorbidity has been associated with increasing risk of suicide attempt in clinical (Beautrais et al. 1996) and general population samples (Kessler et al. 1999). Kessler et al. (1999) found that those with more disorders, regardless of type of disorder, were more likely to attempt suicide. For all age groups, the presence and number of psychiatric disorders should be considered when estimating risk.

### Mood Disorders

Suicidal ideation is a symptom of a major depressive episode; hence it is predictable that a substantial and widely replicated increased risk of suicide will be evident in those with a mood disorder (Beautrais et al. 1996, Baxter and Appleby 1999, Conwell et al. 1996, Harris and Barraclough 1997, Kessler et al. 1999). A 20-fold increased risk of completed suicide has been estimated for major depressive disorder and a 12-fold increased risk for dysthymic disorder (Harris and Barraclough 1997). The odds of lifetime attempt are 12 times higher in those with major depressive disorder and eight times higher with dysthymic disorder (Kessler et al. 1999). Similarly, bipolar disorder has been consistently found to be a risk factor for suicide (Brown et al. 2000, Harris and Barraclough 1997) with an estimated 15-fold increased risk of completed suicide (Harris and Barraclough 1997). The depressive phase of the illness has been shown to be the time of greatest risk, but suicide may also occur in a mixed state and very rarely in a purely manic state (Isometsä et al. 1994, Simpson and Jamison 1999). Given the risk afforded by mood disorders and the lifetime community prevalence of about 20% (Kessler et al. 2005), management of suicidality becomes a common task for the clinician working with this population.

### Schizophrenia

Individuals with schizophrenia are at high risk of suicide attempt and completion. A recent estimate suggests that the lifetime suicide rate for individuals with schizophrenia is 5% (Palmer et al. 2005). Younger age and the initial years after onset of illness have been identified as the times of greatest risk (Nordentoft et al. 2004, Hunt et al. 2006, Harkavy-Friedman et al. 1999). Others have identified depressive disorder, drug misuse and poor treatment compliance (Hawton et al. 2005, Hunt et al. 2006) as risk factors for completed suicide in populations with schizophrenia. In those with chronic schizophrenia, hopelessness, insight into illness and higher cognitive function show an association with greater suicidality, with hopelessness affording the greatest risk (Kim et al. 2003). Others have found that self-insight into schizophrenia may precipitate depression and hopelessness but might also have a beneficial effect on treatment adherence (Bourgeois et al. 2004). While most of these identified risk factors are evident in other suicidal populations, a number provide targets for treatment strategies (e.g., management of depression, strategies to improve treatment adherence, and increasing risk surveillance).

### Anxiety Disorders

Anxiety disorders have been suggested to increase risk of suicidal ideation and attempt (Simon et al. 2007, Kessler et al. 1999, Sareen et al. 2005). Sareen et al. (2005) suggested that most anxiety disorders (social phobia, simple phobia, generalized anxiety disorder, panic disorder, agoraphobia, and obsessive compulsive disorder) independently and significantly elevated risk of future suicidal ideation and attempt. While some have found panic disorder to independently increase risk of suicide attempts (Weissman et al. 1989), others have found that increased risk is only

evident when comorbid disorders, including depression and substance abuse are present (Friedman et al. 1999, Vickers and McNally 2004, Warshaw et al. 2000). Further, Placidi et al. (2000) found that a lifetime history of suicide attempts was unrelated to panic disorder comorbid with major depressive episode and that higher anxiety was evident in those without a suicide attempt. These findings were interpreted as suggesting that another factor(s) may explain the elevations in suicide attempts associated with panic disorder or that anxiety in some cases might even be protective. Post-traumatic stress disorder has been associated with increased risk of suicide attempt of up to eight times greater than non-PTSD populations (Davidson et al. 1991, Tarrier and Gregg 2004) while even subthreshold PTSD raised risk of suicidal ideation while controlling for depression (Marshall et al. 2001). However, there is at least some data that suggests that the association between PTSD and suicidal behavior is mediated by the presence of comorbid borderline personality disorder (Oquendo et al. 2005). Thus, although some evidence suggests that an anxiety disorder in combination with a mood disorder is associated with greater risk of suicidality than that of a mood disorder alone (Simon et al. 2007, Sareen et al. 2005), the mediating role of other comorbidities has not yet been adequately addressed. Nonetheless, while suicidality is not a symptom of any anxiety disorder, attention must be paid to assessment of anxiety disorders when completing a risk assessment given the evidence that supports their contribution to risk.

## Alcohol and Substance Use Disorders

Alcohol and substance use disorders raise risk of suicide attempts (Landheim et al. 2006, Kessler et al. 1999) and completed suicide (Wilcox et al. 2004, Borges et al. 2000, Beck and Steer 1989). Psychological autopsy studies have detected alcohol use disorder in approximately 50% of completed suicides (Conwell et al. 1996, Kolves et al. 2006) while toxicological testing has found one third of completed suicides tested positive for alcohol at time of death (Centers for Disease Control and Prevention 2006). Alcohol use disorders are less common in females (Grant et al. 2004) but have been shown to be more highly associated with suicide attempts in females compared with males (Wilcox et al. 2004). Comorbidity between alcohol use disorders and other psychiatric disorders, depression in particular, raises risk of suicide (Wilcox et al. 2004, Preuss et al. 2003). Further, Borges et al. (2000) has found that substance abusing suicide ideators are at significant risk of an unplanned attempt. Risk of suicide associated with opiate and mixed substance abuse has been associated with even greater risk of suicide than alcohol (Wilcox et al. 2004). Others have found that the *number* rather than *type* of substances is more important for predicting suicide attempts (Borges et al. 2000). Given the common comorbidity and increased risk, it is essential that patients are screened for the presence of alcohol and substance use disorders (Sher 2006).

## Borderline Personality Disorder

The diagnostic criteria for borderline personality disorder include multiple risk factors for suicide including recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior as well as impulsivity (American Psychiatric Association 2005). In clinical populations, it is estimated that up to 10% of those with borderline personality disorder complete suicide (Black et al. 2004) and approximately 75% attempt suicide (Black et al. 2004, Soloff et al. 1994). Presence of comorbid depressive and drug and alcohol disorders, hopelessness, and childhood sexual and physical abuse also independently contribute to the risk of suicide in those with borderline personality disorder (Brodsky et al. 1997, Isometsä et al. 1996a, Soloff et al. 2000, 2002). In assessing the borderline patient for suicide risk, it is important to distinguish between self-injury with suicidal intent from self-injury without suicidal intent. While both behaviors elevate risk of suicide, self-injury with intent to die suggests a greater risk; however self-harm with low lethality remains an important risk factor not to be ignored. In addition, the borderline patient may underestimate the lethality of self-injury made without suicidal intent (Stanley et al. 2001).

## Hopelessness

A sense of hopelessness within the context of a psychiatric illness can make current problems seem untenable and make suicide seem like a reasonable solution (Beck et al. 1990). Hopelessness is considered a risk factor for suicidal ideation (Kuo et al. 2004, Beck et al. 1993), attempt (Beautrais et al. 1999, Kuo et al. 2004), and completed suicide (Kuo et al. 2004, Beck et al. 1985, Beck et al. 1990, Brown et al. 2000). This association has been replicated in both clinical (Beck et al. 1990, Beautrais et al. 1999) and normal populations (Kuo et al. 2004). Moreover, a recent study demonstrated that improvement in hopelessness and depression preceded reduction in suicidal ideation (Sokero et al. 2006). In sum, hopelessness elevates risk of suicidality independent of psychiatric illness and is often stable over time (Haatainen et al. 2003) making it an important factor to assess.

## Impulsivity and Aggression

Impulsivity has been linked with suicide attempts in a variety of psychiatric populations (Corruble et al. 1999, Brodsky et al. 1997, Swann et al. 2005). Impulsivity may relate to behavioral disinhibition and therefore increase risk of suicidal behavior. However, impulsive suicide attempts might be less lethal (Baca-Garcia et al. 2001, 2005) than those that are carefully and deliberately planned. Aggressive behavior comorbid with a mood disorders has been found to be associated with greater risk of suicide attempt (Malone et al. 1995, Oquendo et al. 2000) and completion (Dumais et al. 2005). A trait impulsivity/aggression factor was found to be more predictive of a lifetime attempt (Odds Ratio: 3.3) than depression or psychosis in a psychiatric sample (Mann et al. 1999b) highlighting the importance of this troubling trait. A patient's history of impulsivity and aggression should be assessed and might be elucidated by enquiring about previous trouble with the police for assault or violence, fighting, hostile behavior, agitation, conflict in relationships, domestic violence, actions lacking forethought and disinhibited behavior.

## Abuse

Physically abused children were found to be more likely to exhibit suicidality and depressive symptoms than children who had experienced neglect or those who experienced neither abuse nor neglect (Finzi et al. 2001). Molnar et al.

(2001) demonstrated that while being mediated by psychopathology, childhood sexual abuse significantly elevates risk of suicide attempt in females and even more so in males. Sexually abused children were likely to experience an earlier suicide attempt, most likely during their teenage years or early adulthood. While the specific mechanism(s) explaining the increased risk are unknown, Joiner et al. (2007) provided evidence linking greater severity of abuse (physical and violent sexual abuse) with more lifetime suicide attempts and Brent et al. (2002) reported that offspring with depressed parents with a sexual abuse history had increased risk of both suicide attempt and sexual abuse. Moreover, offspring with sexual abuse were more likely to attempt suicide. Put together, these findings suggest that intergenerational transmission of sexual abuse is related to transmission of suicide attempts. Given the suicidal sequelae of childhood abuse, risk assessment needs to include specific questioning about such experience of such events, and their type and magnitude.

### Medical Illness

Chronic medical illness is associated with elevated risk of suicide attempt and completion. Illnesses identified as having suicide rates greater than the normal population include epilepsy (Pompili et al. 2005), human immunodeficiency virus and acquired immune deficiency syndrome (Bellini and Bruschi 1996, Marzuk et al. 1988), multiple sclerosis (Stenager et al. 1992, Brønnum-Hansen et al. 2005), and Huntington Disease (Schoenfeld et al. 1984). Elevated levels of comorbidity are often present between chronic medical illness and mental illness, for example, lifetime prevalence of major depression is approximately 50% for those with multiple sclerosis (Siegert and Abernethy 2005). However, this relationship may only partially explain the association between chronic medical illness and suicide, as some medical illnesses have been found to independently contribute to suicide risk above and beyond the effect of mental illness. For example, after controlling for comorbid psychiatric disorders, increased risk of attempt was associated with lung disease, ulcer, and AIDS (Goodwin et al. 2003), and wish to die has been associated with myocardial infarction (Kim et al. 2006). Given patients with medical illnesses are routinely treated in primary care provider, and evidence suggests that suicide attempters often consult physicians prior to attempt (Ikeda et al. 2001) an ideal opportunity for screening and assessment of suicidal risk is available.

### Neurobiological

The functioning of the serotonergic and the hypothalamic-pituitary-adrenal axis has been implicated in the search for biological risk factors for suicide (Arango et al. 1995, Mann et al. 2000). Serotonin (5-HT) dysregulation in suicide victims and attempters is the most robust neurobiological finding. Autopsy studies have found that suicide victims have fewer presynaptic serotonin transporter sites in the hypothalamus, occipital cortex and brainstem (Mann 2003). Greater blunting in response to the fenfluramine challenge (a test that causes the release of serotonin and while preventing its reuptake) is associated with a history of more lethal suicidal behavior (Mann et al. 1999a). Cerebrospinal fluid (CSF) concentrations of hydroxyindole acetic acid (5-HIAA), a metabolite of serotonin have been found to predict suicide risk in the one–two year period following an index attempt (Nordström et al. 1994, Samuelsson et al. 2006). Some evidence suggests that suicidal behavior may be associated with an abnormal physiological stress response given findings from studies of the HPA axis, the neuroendocrine system that regulates stress responses (Carballo et al., in press). While biological markers of suicidal risk show promise, at present they do not have any clinical application in the management of the suicidal patient. A comprehensive review of prospective studies of biologic predictors of suicidal behavior in mood disorders can be found in Mann and Currier (2007).

## Management of the Suicidal Patient

### Engaging the Suicidal Patient

Establishing a therapeutic relationship is the first task for the clinician managing the suicidal patient and comes before assessing risk (Meichenbaum 2005). Engaging the suicidal patient may be a challenging task given ambivalence about life, possible previous negative experiences in therapy, severity of illness, and the clinician's competing need to establish an assessment of risk. The therapeutic relationship, however, is particularly important given the high proportion of suicidal patients who discontinue treatment early (Dahlsgaard et al. 1998) and that risk of suicide remains high after a suicide attempt (Nordström et al. 1995). A variety of techniques can be used to establish a therapeutic relationship for example, empathic listening of the patient's concerns, validation of their feelings to ensure that the patient feels heard and understood and taking a collaborative approach to the sessions with the patient.

### Assessment

The aim of the assessment of a suicidal patient is to evaluate the patient's current suicidal risk by determining diagnosis as well as demographic and clinical suicide risk and protective factors. Although there are no definitive empirically based approaches to predicting suicide risk, in this section, we suggest clinical approaches that may be of utility in delineating risk for suicidal behaviors in general. Ideally, assessment provides a diagnostic profile and an estimate about current level of suicidal risk which informs the type and intensity of intervention required. Suicide risk is known to fluctuate; therefore risk assessment should be updated regularly. Unfortunately, there is no empirically derived information regarding the frequency of these assessments. Of note, the limits of confidentiality and the circumstances in which the clinician is ethically required to breech the confidence are best discussed at the first interview.

Interviewing a patient about current suicidality requires the asking of direct questions about thoughts and behaviors in a sensitive manner. Clinicians may opt to begin with querying passive thoughts of suicide (e.g., Have you had any thoughts of wanting to be dead or of ending your life?) followed by enquiring about active thoughts of killing oneself (Has it gotten more serious, where you had thought about killing yourself?). While lowest on the suicidality spectrum, passive thoughts are an important risk factor for completed suicide (Brown et al. 2000). Determine whether the patient has a plan for how they would kill themselves (Have you thought about how you would kill yourself? Do you have a plan?) and whether they intend to act upon the

plan (When having these thoughts, have you had an intention to act upon them?). Suicidal ideators with a plan were found to be at greater risk than ideators without a plan (Kessler et al. 1999). A profile of suicidal ideation should be determined including the following information: duration and frequency of thoughts, ability to cope with the thoughts, adaptive and maladaptive coping strategies, and deterrents to completed suicide.

Beyond ideation, the clinician next asks about suicidal behavior including preparation for a suicidal attempt, for example, stockpiling of pills, acquisition of a firearm, poison or rope. Questioning about previous self-injurious behavior and its intent then follows (Have you ever hurt yourself in any way on purpose? What did you intend to happen? Did you intend to kill yourself?). The intention of self-harming behavior may be suicidal or for other purposes or a combination of both.

Valuable details about suicidality include time of onset, course (e.g., episodic, escalating), levels of suicidal intent associated with attempts, precipitants (e.g., conflict with spouse, isolation, unemployment, command hallucinations), probability of rescue from attempt (i.e., remote location with low chance of rescue versus in a populated or public area), medical seriousness, need for medical attention, actual lethality of the attempt, and the patient's understanding of lethality. These details may provide insight into the risk of future attempts and provide information about targets for intervention. A brief tool to assess and track both suicidal ideation and behavior during management of a patient, such as the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al. 2007) may enhance clinical practice. The C-SSRS is the prospective counterpart to the suicide classification system developed for the Food and Drug Administration (FDA) safety analyses of antidepressants (Posner et al., 2007).

If permission is granted by the patient, consulting other informants (e.g., family, general practitioner) might provide important information about the patient's behavior. This contact may provide an opportunity to discuss and clarify the various roles of those involved in the patient's care, for example, psychotherapy from the psychologist, transport to appointments from a relative.

Interviewing the patient or involved family members about family history of mental illness (particularly depression, bipolar disorder, schizophrenia, alcohol, and substance abuse) is indicated. While knowledge of relatives' illnesses may be nonspecific (e.g., grandparent with "nervous breakdown") further clues might be gained by asking about use of psychopharmacological treatment, impact on functioning and hospitalization.

Upon the completion of a risk assessment a clinician is not expected to be able to predict the future, but will develop a judgment about a patient's current level of risk and respond accordingly in the interest of the patient's safety. This may include referral for inpatient treatment, increased monitoring as an outpatient, engagement of the support group or family to provide more intensive supervision of the patient, development of a plan regarding procedures to institute if the patient becomes more suicidal (e.g., go to the local emergency department, contact the clinician, etc.) (see description of safety plan in Section "Treatment").

## Treatment

There are two common approaches to treating the suicidal patient. The primary approach is to address the disorder underlying the suicidality. The second approach is to directly treat the suicidality, as is the focus of some psychotherapeutic approaches. Treatment might also be useful to stabilize additional risk factors for suicide while enhancing any protective factors (American Psychiatric Association 2003). Treatment planning should be informed by results of risk assessment, while also considering the patient's capacity to self-care particularly in a crisis and understanding of treatment options (American Psychiatric Association 2003). If consent is granted by the patient, useful information about the management may come from their previous treatment and interactions with clinicians, for example, previous hospitalization for suicide attempt is a risk factor for future attempt. Evaluation of the patient's expectations of treatment may reveal a sense of hopelessness and futility in commencing or continuing treatment that may require addressing. Provision of psychoeducation about mental illness being a disease rather than a personal flaw or inadequacy and suicidal behavior as being related to mental illness may reduce self-blame and misperceptions within the family. Treatment options and setting should be discussed with the patient and family, where appropriate, and written consent gained.

When risk of suicide attempt is highly elevated or considered imminent, and/or confidence in a patient's ability to refrain from acting on suicidal thoughts is low, inpatient hospitalization may be required on a voluntary or involuntary basis. The decision to hospitalize can be complex. Hospitalization offers the opportunity to closely monitor a patient's behavior, restrict access to suicidal means and stabilize medication. However, hospitalization may interrupt employment, disrupt the family, reduce contact with supports and may foster dependency (American Psychiatric Association 2003).

Suicide risk is highest during the first week of an inpatient stay and in the week after discharge (Qin and Nordentoft 2005) suggesting the need for close monitoring on the ward and follow-up after discharge during these periods. Long-term inpatient treatment may not be indicated for those with borderline personality disorder (Paris 2004). However, a short-term admission may be required when risk is elevated, and particularly in the presence of a comorbid axis I disorder (Oldham 2006).

Risk of self-harm may be reduced during treatment by the development of a 'safety plan' for the patient. Safety plans are typically multifaceted and may include detecting triggers to suicidality and methods of avoiding or addressing them, removal of materials used for self-harm, scheduling regular appointments and arranging plans for transport, organization of a support team that the patient can contact for support in case of a suicidal crisis whatever the time (e.g., clinician, family, friends, emergency department, mobile crisis team). A safety plan differs from a "no-harm contract" which is an agreement to contact someone before self-harming (discussed in Subsection "No-harm Contracts").

Treating suicidal patients for modifiable risk factors, such as depression, anxiety, and unemployment can present challenges for the clinician. Suicide attempters frequently do not follow through with referral for treatment (Jauregui

et al. 1999) and discontinue treatment early (Dahlsgaard et al. 1998). This indicates a need for strategies to increase treatment engagement and compliance. Programs designed to extend the length of treatment have had limited success. Van Heeringen et al. (1995) found that home visits improved attendance but did not reduce suicidality. A related problem is the generally inadequate levels of treatment received by individuals with mental illness (Oquendo et al. 2002, Wang et al. 2005, Fernández et al. 2007).

## Treatment Modality

Both psychopharmacological and psychosocial treatments have a role in the management of the suicidal patient. The few treatments that have empirical support specifically for suicidality are reviewed below. In the absence of comprehensive efficacy evidence for the treatment of suicidality, clinicians are advised to aggressively treat the underlying psychopathology following current treatment guidelines (e.g., American Psychiatric Association Practice Guidelines; American Psychiatric Association 2006).

### Pharmacological Treatment

#### *Lithium*

The prophylactic property of lithium in protecting against suicidality in major affective disorders (bipolar I and II disorder, recurrent major depressive disorder) has often been reported (American Psychiatric Association 2003, Baldessarini et al. 2001, Cipriani et al. 2005, Jamison 2000, Kallner et al. 2000, Bowden 2000). Baldessarini et al. (2001, 2003) reviews concluded that the rate of completed and attempted suicide during long-term lithium treatment reduced by 13–15-fold in comparison with no lithium or discontinuation. The protective effect is possibly strongest in those with recurrent major depression followed, by bipolar II disorder and bipolar I disorder (Baldessarini et al. 2003). In a recent 10-year follow-up of bipolar I disorder adults, those noncompliant with lithium maintenance were not only at greater risk of suicidal behavior but also were more severely ill (greater substance abuse and more hospitalizations) (Gonzalez-Pinto et al. 2006). These findings are made all the more noteworthy given the potential lethality of lithium in overdose (Zetin 2004). Prospective randomized controlled clinical studies investigating lithium as a treatment to protect against suicidality are currently underway in adults but lacking for youth.

#### *Antidepressants*

Antidepressant medications have established efficacy in the treatment of depressive disorders (Rush et al. 2006)—the most common diagnosis experienced by those who complete suicide. In the last few years, debate has re-emerged about the impact of antidepressants on suicidality. While the efficacy of antidepressants in reducing risk of suicide has not been demonstrated in clinical trials or meta-analyses of these data, these trials were not typically designed to address this question. Other studies of large databases have shown a reduction of risk associated with antidepressant treatment.

Recently, the FDA has conducted analyses with both pediatric ($N$=4582) and adult ($N$=99 839) samples from randomized clinical trials to examine links between suicidality and antidepressant use compared to placebo (Hammad et al. 2006, Stone and Jones 2006). Put together, the results suggest an age effect in which risk of suicidality is increased for children, adolescents, and young adults up to 25 years who were treated with antidepressants, no different for adults aged over 25 years and less than 65 years treated with either placebo or antidepressants and reduced for those over 65 years treated with antidepressants, suggesting a protective effect (Stone and Jones 2006). These findings initially led to the implementation of a black box warning on all antidepressants warning of a 4% vs. 2% risk of suicidality in children and adolescents taking antidepressant medication versus placebo, which is soon to be extended to include young adults. While the FDA analyses were conducted with the best data available, that is, spontaneously generated adverse events from clinical trials, concerns have been raised about the validity of using randomized controlled trial (RCT) data that lacked prospective, standardized assessment of suicidality. Alternative explanations for the association include the ascertainment bias, in that those who were treated with an active drug might be more likely to discuss suicidal thoughts or those treated with the active drug and experienced some improvement might be more prone to discussing their suicidality for the first time (Posner et al. 2007).

Meanwhile, analyses using alternate data sources have failed to demonstrate the risk of antidepressants, in fact, evidence suggesting a protective effect has been found. Lower youth suicide rates were found in the US counties with higher selective serotonin reuptake inhibitor (SSRI) prescription rates (Gibbons et al. 2006). Greater risk of suicide has been found in the month prior to commencement of antidepressant treatment compared with during treatment (Simon et al. 2006). Further, autopsy studies have found that SSRI use is very rarely evident at time of death in youth who commit suicide (Gray et al. 2003, Leon et al. 2004).

Recent studies have examined the impact of antidepressant safety warnings on physician behavior. The US pediatric antidepressant prescriptions have declined since the introduction of the warnings in 2003 (Nemeroff et al. 2007), meaning that fewer youths are likely to be receiving treatment for depression. Meanwhile, suicide in 10–19-year olds increased by 13.3% (between 2003 and 2004) following a decline in rates over the previous four years (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2007). This pattern was also found in the Netherlands where a 22% decrease in youth SSRI prescriptions occurred between 2003 and 2005 at the same time as a 49% increase in youth suicide (Gibbons 2006). The increase in suicide may represent a fluctuation in rates or be explained by other causes. However, further investigation of this potential relationship is warranted, as it is feared that declining prescription of antidepressants may be responsible for rising suicide rates amongst youth.

Antidepressants may have a role to play in the prevention of suicide in youth and young adults as well as adults due to their ability to successfully treat depressive disorders—a major risk factor for suicide. It is considered that untreated depression portends a far greater risk of suicidality than that of antidepressant medication. Commencement of antidepressant treatment should include regular and careful monitoring to assist with achieving optimal dose and the management of possible side effects. For youth, parents

should be recruited to assist with monitoring for side effects and therapeutic response. A baseline of suicidal ideation and behavior should be taken to assist with the detection of treatment emergent suicidality versus that which is a part of the illness (American Psychiatric Association 2003). Patients should be clearly informed about the likelihood of side effects and their types, and the likely latency before onset of therapeutic effect. While the SSRIs are relatively safe in overdose (Whyte et al. 2003) care should be taken in amount prescribed to avoid stockpiling.

### *Antipsychotics*

The current first line treatment for schizophrenia and schizoaffective disorder are the second-generation antipsychotics. However, most lack empirical evidence supporting their efficacy reducing suicide risk and rate with the exception of clozapine (Meltzer and Okayli 1995, Walker et al. 1997, Reid et al. 1998, Modestin et al. 2005). As clozapine patients are required to have weekly to biweekly hematological monitoring for early detection of the very rare but potentially fatal side effect agranulocytosis (Lieberman 1998), it was originally thought that the additional clinical monitoring might be responsible for the decline in suicidality (Kerwin and Bolonna 2004). The clinical attention may result in a more rapid detection and treatment of suicidality. However, the most compelling evidence of the benefits of clozapine on suicidality came from a two-year study of 980 patients with schizophrenia or schizoaffective disorder randomized to either clozapine or olanzapine which controlled for clinical attention (Glick et al. 2004). The clozapine group was found to have fewer suicide attempts and hospitalizations to prevent suicide. The olanzapine group also used significantly more concomitant psychotropic medications. However, this did not improve the group's performance (Glick et al. 2004). The strength of this evidence led to the FDA's approval of clozapine for suicidality in schizophrenia in the late 2002. While persuasive evidence exists supporting its use, it is not widely used probably given the chance of agranulocytosis which occurs in less than .5% (Honigfeld et al. 1998) other adverse events (Lieberman and Safferman 1992) and cost (Sernyak et al. 2001).

## Psychosocial Treatments

### *Cognitive Behavioral Therapy*

Cognitive behavioral therapy (CBT) is an established treatment for a number of psychiatric disorders that are suicide risk factors including unipolar depressive disorders and anxiety disorders (Butler et al. 2006) and is used as an adjunctive treatment in the treatment of schizophrenia (Bechdolf et al. 2005, Sensky et al. 2000, Turkington et al. 2006) and bipolar disorder (Lam et al. 2005, Ball et al. 2006). However, the following two treatments differ in that they aim to directly treat suicidality rather than a diagnosis underlying the behavior.

Building on the efficacy of cognitive therapy for depression, Brown et al. (2005) modified cognitive therapy for the treatment of suicidal patients regardless of diagnosis. The manualized cognitive therapy focused on proximal thoughts, images, and core beliefs that were activated prior to the suicide attempt. Cognitive and behavioral strategies were used to modify suicidal thoughts and beliefs and to develop adaptive ways of coping with stressors that might precipitate an attempt. Hopelessness, poor problem solving, impaired impulse control, treatment noncompliance and social isolation, notable risk factors for suicide were also targeted in the treatment. After 18 months, significantly fewer suicide attempts were made by the cognitive therapy group (24%) compared with treatment as usual (42%) (Brown et al. 2005). This program has been modified for use with adolescent and young adult suicide attempters (Henriques et al. 2003) but not yet evaluated.

### *Dialectical Behavior Therapy*

Dialectical behavior therapy (DBT) is a combination of change focused cognitive−behavioral type strategies and acceptance and validation techniques (Stanley and Brodsky 2005). This manualized treatment was developed to address suicidality and self-harming behavior in borderline personality disorder. The key goal of DBT is to reduce life-threatening behaviors, followed by therapy interfering-behaviors and quality-of-life-threatening behaviors. DBT consists of two treatment components. Treatment includes one or two weekly individual sessions, supplemented by group skills training (Linehan 1993). Group treatment modules include mindfulness, distress tolerance, emotion regulation and interpersonal effectiveness. DBT has been demonstrated to be superior to nonbehavioral expert therapy (Linehan et al. 2006) and treatment as usual (Linehan et al. 1991, Verheul et al. 2003) in reducing self-harming and suicidal behavior and increasing treatment retention in the treatment of borderline personality disorder.

### *Family Treatments*

A number of findings point to the importance of involving family in the treatment of suicidality. Suicidal individuals often come from poorly functioning family environments (McDermut et al. 2001). Family members are regularly called upon to help maintain safety of a suicidal individual, involvement in treatment could provide them with skills to aid problem solving and other crisis strategies. To date, few studies have evaluated the anti-suicidal effects of family intervention. Family intervention targeting problem solving and communication skills for young people who had deliberately self-poisoned has been found to be no better than treatment as usual in reducing suicidality (Harrington et al. 1998). The association between poor family environment and the course of bipolar disorder led to the development of family-focused treatment (Miklowitz et al. 2000). The approach is comprised of 21 outpatient sessions that address psychoeducation, communication skills training and problem solving components conducted over 9 months. The approach has been found to be a useful adjunctive treatment to pharmacotherapy for bipolar disorder, with studies demonstrating its advantages over crisis management (Miklowitz et al. 2000) and individual treatment (Rea et al. 2003). The treatment has been adapted for suicidal bipolar disorder (Miklowitz and Taylor 2006), but has not yet been evaluated.

## No-harm Contracts

A "no-harm" contract is a written or verbal agreement by a patient to contact a health care provider, friend or relative for assistance before engaging in any self-injurious behavior. The contract will typically have a specified time frame, for

example, until next treatment session. While the no-harm or no-suicide contracts were first introduced more than 30 years ago, empirical investigation of the benefits of this technique is still lacking (Rudd et al. 2006, Buelow and Range 2001). A common criticism of these contracts includes their medico-legal emphasis, however, such a contract does not protect the clinician from malpractice liability if a client completes suicide (Lee and Bartlett 2005). Concern also exists that fake agreement to a contract by a frankly suicidal patient might distract a clinician from the appropriate precautions to minimize risk of harm. It is considered that such contracts can be a rough indicator of difficulties in the therapeutic alliance when not agreed to by the patient (American Psychiatric Association 2003).

### Electroconvulsive Therapy (ECT)

ECT is a validated treatment for major depressive disorder given evidence from randomized controlled trials (Carney et al. 2003). Modest support exists for its use to treat suicidality (Kellner et al. 2005, Prudic and Sackeim 1999, Isometsä et al. 1996b) in the absence of evidence from controlled trials. Advantages of ECT in treating acute suicidality include its rapid onset of therapeutic action and good response rates, however the treatment is known to be unpopular with patients before all other alternatives have been tried (Kellner et al. 2005). The short-term therapeutic impact of ECT needs to be considered in treatment planning and the use of concurrent or subsequent pharmacological and/or psychosocial treatment might be required. While usually seen as the final treatment option, there have been recent calls for ECT to be promoted in the treatment hierarchy for suicidality given evidence of efficacy (Kellner et al. 2005, Patel et al. 2006). ECT is administered to approximately 5% of psychiatric inpatients (Munk-Olsen et al. 2006) and was found to be a rare treatment in the three months prior to completed suicide (Isometsä et al. 1996b).

## Legal and Ethical Issues

Clinicians are required to be aware of their relevant state, professional and workplace guidelines and procedures with regards to working with suicidal patients. The limits of confidentiality need to be explained to suicidal patients as well as the clinician's ethical duty to warn if an opinion is formed that a patient or others are in imminent danger as a result of the patient's behavior. Documentation of risk assessments, treatment planning and progress, secondary consultations, and supervision ought to be kept to demonstrate quality of clinical care.

## Conclusions

Suicide risk assessment is a central competency in the management of psychiatric patients. Risk and protective factors for suicidality have been identified and inform suicide risk assessment and ultimately also treatment. Few treatments have demonstrated efficacy in reducing suicidality, limiting evidence-based practice with this population. Of the pharmacological treatments, both lithium for mood disorders and clozapine for psychosis may have efficacy in reducing risk of suicide. Evidence suggests that dialectical behavior therapy reduces suicidality in borderline populations. Treatments that show promise include Brown et al. (2005) modified CBT and ECT. In the absence of empirical evidence to guide management, treatment of the underlying psychopathology may reduce risk.

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CHAPTER

# 117 Restraints and Seclusion

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This chapter reviews the use of restraint and seclusion (R/S) in psychiatry and efforts in the mental health community at reduction and prevention. Use of seclusion and physical restraint has a long history in psychiatric facilities (Fisher 1994). Often learned "on the job" they have been an assumed part of the therapeutic armamentaria available to clinical staff. R/S are implemented typically, by nursing staff, in response to behaviors deemed aggressive, violent, disruptive, out-of-control, or dangerous to self, others, or property.

R/S definitions vary across agencies and organizations; use varies widely among hospitals, states, and in the research literature (Busch and Shore 2000). Even the United States federal regulatory agencies cannot agree on definitions, with agencies defining physical restraint in accordance with their culture and statutory authorities.

The definitions referred to in this chapter are those developed by the U.S. Centers for Medicare and Medicaid Services (CMS), Department of Health and Human Services (2001):

A *physical restraint* is any manual method or physical or mechanical device, material, or equipment attached to a person's body that restricts freedom of movement or normal access to one's body. *Seclusion* is the involuntary confinement of a person in a hazard-free room or area that is often locked and where the person can be directly observed.

## Controversies Regarding Restraint and Seclusion

Over the years, the use of R/S has been questioned by professionals as to efficacy and usefulness (Garrison 1984, Natta et al. 1990), and promoted for their "therapeutic" value (Cotton 1989, Troutman et al., 1998). Proponents view such procedures as unfortunate last resorts in situations where patients pose a danger to themselves or others. Agitated, angry, and hostile patients have been secluded or physically restrained until they became demonstrably calmer. Although previously seen as an acceptable way to manage crises and keep patients and staff safe, R/S are no longer considered "therapeutic" and their use has been under intense scrutiny and the subject of lawsuits.

## State of Research

Attempts have been made to study R/S. Most of these studies have questionable methodological rigor or problematic theoretical assumptions (Day 2002a, Child Welfare League of America, [CWLA] 2002). Most significant has been lack of support for the "therapeutic use" hypothesis, as most studies indicate that R/S are traumatizing to staff and patients (Richter and Berger 2006). Most R/S research conducted in clinical settings has focused on patient characteristics associated with their use. This literature had an a priori bias, wherein salient variables were to be found in personal pathologies. Emerging evidence supports a *situational stance* involving the role of the environment, including staff knowledge, behaviors, and attitudes that are equally, if not more, implicated in the willingness to use these measures (Gadon et al. 2006).

Research into R/S fails to demonstrate their therapeutic efficacy. Indeed, studies show that R/S do not lead to positive behavior change and are ineffective unit management tools (Garrison et al. 1990). They lead to superficial compliance and to staff–patient power struggles. A number of studies discovered that R/S paradoxically increased misbehavior or unwanted behaviors (Magee and Ellis 2001, Natta et al. 1990).

Several comprehensive reviews agree that research on R/S lacks cohesion and their use has no sound theoretical basis or research foundation. Day (2002a) concluded that theoretical paradigms supporting restraint use are outdated

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and there is limited research to support their therapeutic utility. These same observations have been noted by many others (CWLA 2002, National Executive Training Institute [NETI] 2005).

There is little in published standard practices to guide clinical decisions to employ R/S, no overall benchmarks for their use, and no data about the appropriate mix of R/S and medication for what kinds of patients. Although there are numerous vendors who have developed aggressive management programming and training for staff, there are no data comparing training programs to determine a best practices model. The use of R/S has been based on convention and vendor marketing efforts in lieu of empirical evidence. The literature validates that R/S procedures have often been used inappropriately, as punishment or consequence for "bad behavior," and, sometimes, for staff convenience (NETI 2005).

What is clear is that the use of R/S is not benign. Their use can cause serious patient and staff injury and have resulted in many deaths (NETI 2005). A discussion of restraint lethality first appeared in the forensic literature when pathologists, Donald Rea and Ronald O'Halloran, documented restraint death (O'Halloran and Lewman 1993, Reay et al. 1992). Previous pathologists had labeled these deaths as "death by natural causes," "sudden in-custody death syndrome," or "death due to cardiac arrest," when physically healthy psychiatric patients or prisoners were autopsied. The forensic studies focused on death by asphyxiation, and this cause subsequently emerged as the most frequent cause of restraint deaths across many settings (The Joint Commission on Accreditation of Health Care Organizations [JCAHO] 1998, Mohr et al. 2003). However, restraint death can result from many causes. Careful examination of the literature determined death by aspiration, blunt trauma to the chest, malignant cardiac arrhythmias secondary to massive catecholamine rush, thrombosis, rhabdomyolosis, excited delirium with overwhelming metabolic acidosis, and pulmonary embolism to be conditions implicated in deaths proximal to physical restraint use. Potential adverse effects of restraints increase with psychotropic medication use, with children being particularly susceptible to certain drug class effects.

In 1998, a highly publicized asphyxia death of a child who had been restrained in a psychiatric hospital led to an investigative news series in Connecticut's "Hartford Courant" (Megan and Blint 1998). The series sparked a cascade of reactions by professionals, legislators, and consumer/advocacy groups and resulted in sustained change in, and oversight of, the way that R/S is viewed and practiced in the United States. Congressional hearings on the topic occurred in 1999, and the topic of R/S received greater scrutiny in the research literature.

Under pressure from advocacy groups, the U.S. Congress commissioned a review by the United States General Accounting Office (USGAO, 1999). This report supported the Courant's findings and sharply criticized restraint use. JCAHO examined 21 deaths reported under their sentinel event protocol and cited lack of staff training as the single most important factor implicated in these events (JCAHO, 1998). Interestingly, lack of staff trained in the use of physical force, manual restraint, and, particularly, nonviolent intervention of agitated patients has been observed by investigators of the European Convention for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment (Niveau 2004).

The U.S. reports resulted in current legislation governing restraint and seclusion use (see also the Chapter 128).

Subsequent studies indicated that patients attribute aggressive or violent behavior to problematic interactions with "controlling" staff, along with poor communication factors and dehumanizing, restrictive environments. The use of R/S was found to foster distrust between patients and staff and impede recovery (Duxbury 2002). Other studies document that patients recall these events as being confusing and report them as being traumatic to watch, as well as to experience firsthand (Mohr et al. 1998, NETI 2005). When in seclusion, patients described feeling neglected, fearful, isolated, vulnerable, and punished (Martinez et al. 1999).

The scant research on R/S has to do with methodological and ethical difficulties inherent in controlling variables leading to the use of aggression control techniques in live patients, as well as the lack of information that we have in the United States about the use of these procedures. In the United States, data on R/S are not collected except by individual hospitals, and this is done voluntarily. Efforts have been made to collect such data in other countries. In Switzerland and Germany, two independent working groups exist that deal with the prevention of violence and coercion in psychiatry. The German working group "Arbeitskreis zur Prävention von Zwang und Gewalt in der Psychiatrie" (Project of prevention of violence and coercion in psychiatry) consists of hospitals, located primarily in the South of Germany. The Swiss working group "Qualitätszirkel Benchmarking Zwangsmaßnahmen" (Benchmarking coercion in psychiatry) consists of seven hospitals, located in the Northeastern, German-speaking part of Switzerland. Both working groups focus on reducing the frequency and duration of coercive measures, such as R/S in psychiatric settings. They focus cooperatively to coordinate data collection across the countries; efforts such as these are present in Wales as well.

Death data are collected unevenly, even when mandated by state and federal authorities (Levinson 2006). Yet, the problem of restraint death is substantial. Trying to determine the number and causes of child deaths proximal to restraint use, Nunno et al. documented the deaths of 45 children over 10 years by searching the Lexus/Nexus databases in the absence of national data (Nunno et al. 2006).

Patient R/S has provoked international interest as The European Committee for the Prevention of Torture and Inhuman or Degrading Treatment of Punishment (CPT) considers R/S matters of particular concern, given the potential for abuse and ill-treatment (Sailas and Wahlbeck 2005). In addition to publications from clinicians in the UK, Australia, and New Zealand, (Day 2002b) conferences have been organized around the topic. In 2006, an international symposium was organized by faculty at Stirling University in Scotland. Similar conferences were held in Turkey and Germany in 2007. In 2007, The Fifth European Congress on Violence in Psychiatry in Amsterdam devoted significant time to discussing restraint use and reduction.

## The Legal Rights of Psychiatric Patients

A detailed discussion on case law regarding R/S in the United States and other countries, although important and fascinating, is far beyond the scope of this chapter, but several selected examples follow. Patients in the United States are not legally protected, having only civil recourse by way of malpractice lawsuits against injury or death. Even when deaths have occurred, local prosecutors have been loathe to bring criminal action against involved staff members. Logic suggests that incompetently designed behavioral programs and procedures should be subject to analysis under the U.S. Constitution, Eighth Amendment. Some lower courts have so ruled (Converse v. Nelson 1995). However, the U.S. Supreme Court has expressly upheld that the Eighth Amendment standard can be applied only in a *correctional context*, and that the Eighth Amendment is inapplicable in a mental institution setting (Ingraham v Wright, 1977).

Converse v. Nelson, No. 95-16776 (Mass. Superior Ct. July 1995)

Ingraham v. Wright, 430 U.S. 651 (1977)

Sweden has passed legislation entitled the Compulsory Psychiatric Care Act and the Forensic Psychiatric Care Act to secure legal safeguards and reduce violations of patient autonomy, including the use of R/S (Wallsten and Kjellin 2004). And, although R/S are not banned in the Czech Republic, Amnesty International recently reported that the use of the "cage bed" has been banned from use in psychiatric and other institutions.

## The State of Education

The need for clinician education is great and staff training and education is crucial. Presently, staff involved in R/S are the least educated or trained but often are the first responders in conflicts. There are few "best practice" guidelines despite numerous studies in the United States and Canada dating back to 1969 documenting the frequency of patient assaults on physicians. Schwartz and Park (1999) found that of 200 physicians from diverse specialties, 24% reported patient assaults.

The American Psychiatric Association's report on clinical safety, noted that from 30–40% of residents are assaulted during a 4-year residency. It recommended that psychiatric residents should have a 10-hour course in violence management to include: antecedents of violence, evaluation of violent patients, use of verbal, mechanical, and pharmacological interventions, and the psychodynamics of aggression (Schwartz and Park 1999).

Unfortunately, there are no national curricula for professionals providing training in prevention and management of restrictive patient interventions including seclusion, physical, mechanical, or chemical restraint. Such content is poorly, if at all, addressed in clinicians' educations. Psychology students report that their training in the management of potentially violent patients was inadequate (Gately and Stabb 2005). The situation is similar in nursing. Student nurses have less than 1 hour of instruction on this topic, and only 8% know that these procedures can be lethal (Stillwell 1991).

## National and State Reduction Efforts

Since 1998, effective strategies to reduce the use of R/S have emerged (NETI 2005) and best practice models are documented by Substance Abuse and Mental Health Services Administration (SAMHSA) (2003.) The *public health prevention model* has been postulated as an effective theoretical approach to R/S reduction (National Association of State Mental Hospital Program Directors [NASMHPD] 2001). This approach recommends using the public health constructs of *primary, selective, and indicated* prevention intervention guides to frame reduction activities. In this conceptualization, *primary prevention* refers to developing environments that avoid conflict through an analysis and ongoing revisions of operational policies, early individualized assessments of risk, and culture (LeBel et al. 2004). *Selective prevention* activities address employing early interventions to mitigate or defuse conflict when it occurs. *Indicated* or t*ertiary prevention* strategies address most effective ways to minimize damage to individuals experiencing or witnessing R/S, and include problem solving activities in postevent debriefings, including mandatory involvement of patients to identify precipitating antecedents.

Another theoretical rationale supporting R/S reduction strategies use is the *emerging science of trauma-informed care* (Jones and Alexander 2004). The mental health literature contains numerous studies documenting the high prevalence of traumatic life experiences in histories of psychiatric patients and the general public (Saxe et al. 2003). The impact of traumatic life events, together with personal experiences of R/S events and their negative sequelae makes a strong argument for the reduction of R/S (NETI 2005).

Effective R/S reduction strategies that are empirically supported include the following:

1. *Leadership that supports organizational change* is believed to be the most important factor in successful reduction projects (Hardenstine 2001, NETI 2005). This strategy mandates executive leadership that provides staff direction by defining and articulating vision, values, and philosophy; developing a formal reduction plan; and holding people accountable to that plan. This strategy includes the *elevation of oversight* of every R/S event by an executive leader.
2. *Use of data to inform practice* includes using facility data to identify baseline R/S use, subsequent data collection on facility usage, and setting improvement goals and monitoring use and changes over time.
3. *Workforce development strategies* to create a treatment environment whose policies, procedures, and practices are based on the knowledge and principles of recovery and trauma-informed care that aims to reduce conflict and coercion (Jonikas et al. 2004).
4. *Specific prevention tools* to reduce the use of R/S proactively by employing assessments and interventions that are directed by policy and integrated into individual patient's treatment plans (NETI, 2003).
5. *Peer roles in inpatient settings* involve the inclusion of patients, families, and external advocates to assist in R/S reduction strategies (Hardenstine 2001).
6. *Rigorous debriefing techniques* aimed at analyzing each R/S event and using knowledge gained to inform policies, procedures, and practices (Donat 2003). A secondary goal is to reduce adverse and potentially traumatizing effects of R/S for staff, patients, and witnesses to the event.

In sum, R/S reduction and prevention efforts require a multilevel multidisciplinary initiative and sustained methodical implementation. Successful reduction projects demonstrate that no one strategy is effective and that comprehensive interventions have the best chance of long-term reduction.

## Conclusion

Viewing this subject from the perspective of reactive crisis management to violence impairs the development of multidisciplinary approaches to deal with what are often traumatic events for both patients and their health care clinicians. Since physicians are held accountable by law and society for caring for patients, it is essential for them to have a comprehensive understanding of how to prevent these crisis situations.

Frequently, restrictive intervention training is only provided to physicians and nurses by the program in which they work. These approaches vary with patient populations (adult, adolescent, child), the diagnosis (e.g., delirium, posttraumatic disorder flash back, psychotic episode), work sites (e.g., emergency unit, psychiatric hospital, residential treatment center), and philosophy regarding R/S use. This leads to piecemeal, narrowly focused, and ad hoc conceptualizations of global safety issues.

Broad-based multidisciplinary training of health professionals is needed to prevent the use of restrictive, inherently dangerous interventions. When R/S is unavoidable, they should be applied in the least coercive fashion. Additionally, patient participation in decision making is important. Such training might involve teaching by patients who had experienced R/S and could be based on current programs such as those disseminated from the SAMHSA (SAMSHA 2003) and NASMHPD's NETI initiative (2005).

Multidisciplinary health professional education about restrictive interventions, at the time of initial exposure to patient care (i.e., medical and nursing school) would hopefully promote new techniques to enhance patients' physical and psychological safety. For example, the use of pulse oximetry to detect low oxygen saturation during restraints, and development of Snozellen rooms to replace traditional R/S equipment (Masters, in press). Teaching should also provide an impetus to shift the focus of debate from whether R/S are "necessary," to developing and promoting clinical strategies which will make these interventions superfluous.

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CHAPTER

# 118 Psychosomatic Medicine

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## Introduction

Psychosomatic medicine (PM) has had ambiguous connotations in the past, alternatively "psychogenic" or "holistic," but it is the latter meaning that has characterized its emergence as a contemporary scientific and clinical discipline (Lipowski 1984). PM is the newest psychiatric subspecialty approved by the American Board of Medical Specialties. There have been many other names for this specialized field, including consultation–liaison (C-L) psychiatry, medical–surgical psychiatry, psychological medicine, or psychiatric care of the complex medically ill. PM psychiatrists have special expertise in the diagnosis and treatment of psychiatric conditions in complex medically ill patients (Gitlin et al. 2004). Working closely with physicians in primary care and other specialties, its practitioners treat and study four general groups of patients, sometimes referred to as the "complex medically ill": those with comorbid psychiatric and general medical illnesses complicating each other's management; those with psychiatric disorders that are the direct consequence of a primary medical condition or its treatment, such as delirium, dementia or other secondary mental disorders (formerly known as "organic" disorders); those with complex illness behavior such as somatoform and functional disorders; and, patients with acute psychopathology admitted to medical–surgical units, such as after attempted suicide.

PM psychiatrists are trained to deliver services in general medical settings working with the complex medically ill. They may work as hospital-based C-L psychiatrists (Kornfeld 2002), in medical-psychiatric inpatient units (Kishi and Kathol 1999), and in settings in which mental health services are integrated with primary care or medical specialties to provide collaborative care (Unutzer et al. 2002). Thus, the field's name reflects the fact that it exists at the interface of psychiatry and medicine and focuses on the interaction between medical and psychiatric disorders. This chapter begins with the history and current status of PM, and then exemplifies the field by examining psychosomatic aspects of cardiovascular disease, cancer, and endocrine disorders. For fuller coverage of these and other diseases, see Levenson (2005, 2007).

## History

The term "psychosomatic" was introduced by Johann Heinroth in 1818, and "psychosomatic medicine" by Felix Deutsch around 1922 (Lipsitt 2001). Psychoanalysts and psychophysiologists pioneered the study of mind–body interactions from very different perspectives, each contributing to the growth of PM as a clinical and scholarly field. The modern history of the field in the United States (see Table 118–1) perhaps starts with the Rockefeller Foundation's funding of PM units in several U.S. teaching hospitals in 1935. The National Institute of Mental Health (NIMH) made it a priority to foster the growth of C-L psychiatry, the name of the field at the time, through training grants (circa 1975) and a research development program (circa 1985).

**Table 118–1 Key Dates in the Modern History of Psychosomatic Medicine**

| |
|---|
| 1935 Rockefeller Foundation opens first C/L-Psychosomatic Units at Massachusetts General, Duke, and Colorado |
| 1936 American Psychosomatic Society founded |
| 1939 First issue of *Psychosomatic Medicine* |
| 1953 First issue of *Psychosomatics* |
| 1954 Academy of Psychosomatic Medicine founded |
| 1975 NIMH Training Grants for C/L Psychiatry |
| 1985 NIMH Research Development Program for C/L Psychiatry |
| 1991 APM-recognized fellowships number 55 |
| 2001 Subspecialty application for Psychosomatic Medicine |
| 2003 Approval as subspecialty by American Board of Medical Specialties |
| 2005 First subspecialty examination in Psychosomatic Medicine, American Board of Psychiatry and Neurology |

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The integration of C-L psychiatry into the core of psychiatric residency training began in the 1960s at individual institutions. By the 1980s, all psychiatry residency programs were required to provide substantial clinical experience in C-L psychiatry. In the United States, subspecialty fellowship training in C-L psychiatry and PM has been available for over 30 years, with well over 1000 psychiatrists educated in this subspecialty. As of December 2006, there were 35 fellowship programs in the Academy of Psychosomatic Medicine's (APM) directory, with several more under development around the country. In the last national survey of U.S. psychiatrists' practices, more than 2,500 psychiatrists were practicing in this field (Dorwart et al. 1992).

In 2001, The APM applied to the American Board of Psychiatry and Neurology (ABPN) for the recognition of "Psychosomatic Medicine" as a subspecialty of psychiatry, choosing to return to the name for the field imbedded in its history, its journals, and its national organizations (Lyketsos et al. 2001). Formal approval was granted by the American Psychiatric Association, the ABPN, the Residency Review Commission (RRC) of the Accreditation Committee for Graduate Medical Education (ACGME), and the American Board of Medical Specialties (ABMS). The first certifying examination was administered in June 2005 to almost 500 psychiatrists. As of November 2006, the ACGME had accredited 29 fellowship-training programs in PM, with more in the process of accreditation.

An impediment to the field's growth has been the split between general medical and mental health care, with major adverse effects on quality of medical service delivery and patient-oriented care. This split is reflected in disparities and disintegration in the reimbursement of patient care (carve outs, lack of parity in coverage), as well as in research funding mechanisms in silos that do not promote cross-disease studies. PM can help mend the fragmentation in health care, but its growth will depend on correcting the splits in health care financing and research sponsorship.

## International Developments in Psychosomatic Medicine

International developments in PM have recently been reviewed by Smith (2006). A large collaborative study of C-L psychiatry services in Europe in the 1990s by the European Consultation Liaison Workgroup demonstrated significant variation in how C-L services were delivered among countries and played a vital role in the evolution of PM in Europe. In the United Kingdom's national health service, there is integration between primary, specialty, and inpatient care. Many general hospitals have "liaison psychiatry services," but only a minority actually has a dedicated psychiatric consultant. In Germany, psychiatry and neurology did not become separate specialties until 1992. C-L psychiatry services in general hospitals are provided by psychiatrists, while most psychosomatic practitioners are internists who work in outpatient private practice. In Australia, competition for limited resources with psychiatric services for psychosis jeopardized the future of C-L psychiatry, but the most recent national mental health plan does recognize its importance. While insufficient funding has inhibited the development of PM/C-L services in many countries, there nevertheless are enthusiastic growing PM/C-L movements in Japan, the Netherlands, Spain, Mexico, Brazil, Colombia, and elsewhere.

## Psychosomatic Medicine as a Scholarly Discipline

The foundation of PM is a specialized body of scientific knowledge regarding psychiatric aspects of medical illness. This has been articulated in classic (Table 118–2) and contemporary textbooks (Levenson 2005, 2007, Blumenfield and Strain 2006, Lloyd and Guthrie 2007), journals (Table 118–3), and the regular scientific meetings of national (Table 118–4) and international (Table 118–5) societies. A cadre of scholars and researchers has emerged involved in a wide spectrum of investigations looking at the medical illness–psychiatry interface. Important contributions have occurred in the interface between psychiatry and HIV-AIDS, cancer, transplantation, cardiology, neurology, endocrinology, pulmonary, renal and gastrointestinal diseases, obstetrics-gynecology, and geriatric medicine.

The frequent cooccurrence of medical and psychiatric morbidity has repeatedly been documented, especially in the complex medically ill. This comorbidity leads to increased mortality, morbidity, loss of quality of life, and excess health care utilization through several psychosocial and biological mechanisms, including promotion of risk factors,

**Table 118–2 Selected Classic Texts in Psychosomatic Medicine**

| |
|---|
| 1935 Emotions and Body Change (Dunbar) |
| 1943 Psychosomatic Medicine (Weiss and English) |
| 1950 Psychosomatic Medicine (Alexander) |
| 1968 Handbook of Psychiatric Consultation (Schwab) |
| 1978 Organic Psychiatry (Lishman) |
| 1978 MGH Handbook of General Hospital Psychiatry (Hackett and Cassem) |
| 1993 Psychiatric Care of the Medical Patient (Stoudemire and Fogel) |

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**Table 118–3 Selected Journals in Psychosomatic Medicine**

| Journal Name | Date of Initial Publication |
|---|---|
| Psychosomatic Medicine | 1939 |
| Psychosomatics | 1953 |
| Psychotherapy and Psychosomatics | 1953 |
| Psychophysiology | 1954 |
| Journal of Psychosomatic Research | 1956 |
| Advances in Psychosomatic Medicine | 1960 |
| International Journal of Psychiatry in Medicine | 1970 |
| General Hospital Psychiatry | 1979 |
| Journal of Psychosomatic Obstetrics and Gynecology | 1982 |
| Journal of Psychosocial Oncology | 1983 |
| Stress Medicine | 1985 |
| Psycho-Oncology | 1986 |

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| Table 118–4 National Organizations |
|---|
| Academy of Psychosomatic Medicine |
| American Psychosomatic Society |
| American Association for General Hospital Psychiatry |
| Society for Liaison Psychiatry |
| Association for Academic Psychiatry—C/L Section |
| American Neuropsychiatric Association |
| American Psychosocial Oncology Society |
| North American Society for Psychosomatic Obstetrics and Gynecology |
| Association for Medicine and Psychiatry |

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| Table 118–5 International Organizations |
|---|
| European Society for Consultation–Liaison Psychiatry and Psychosomatics |
| International Organization for Consultation–Liaison Psychiatry |
| World Psychiatric Association Section of General Hospital Psychiatry |
| International College of Psychosomatic Medicine |
| International Neuropsychiatric Association |
| International Psychooncology Society |

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amplification of somatic symptoms, noncompliance, adverse effects on the doctor–patient relationship and systems of care, and pathophysiological effects (see also Chapter 83). High prevalence rates of a broad range of psychiatric disorders have been documented in the most common medical illnesses, as well as less common, or newly recognized disease states, as well as in patients with abnormal illness behavior such as unexplained physical complaints and functional disorders. Inpatients in general hospitals have the highest rates of psychiatric disorders but rates are also increased in medical outpatients compared to the general population. Depression, dementia, delirium, and substance abuse are the most common psychiatric disorders in the general hospital, while depression, anxiety disorders, substance abuse, and somatoform disorders are very common in medical outpatient settings.

The impact of psychiatric illness on medical morbidity is substantial. For example, depression has been associated with increased risk of recurrence and mortality from myocardial infarction, increased risk of stroke in hypertensive patients, and worse glycemic control in diabetic patients. Psychiatric morbidity in many medical disorders has been shown to be a potent risk factor for increased medical morbidity and a potent determinant of health-related quality of life. Yet potentially treatable psychiatric disorders in the complex medically ill remain often underdiagnosed and undertreated.

Early empirical efforts to treat psychiatric morbidity in the medically ill have been followed by randomized controlled trials (RCTs) focused on improving medical and psychiatric outcomes in patients with diseases like coronary artery disease and diabetes mellitus. In these studies, the psychiatric condition is treated, while its effects on medical outcomes, compliance with treatment for the medical condition, and quality of life are assessed. Other RCTs have been directed at patients with unexplained somatic symptoms and related "functional" syndromes.

## The Clinical Practice of Psychosomatic Medicine

The major goal of PM is to improve the psychiatric care of medically ill patients. It has long been recognized that nonpsychiatric clinicians provide the great majority of psychiatric care, dubbed as "the de facto mental health care system" (Regier et al. 1978). While there is a higher concentration of patients with psychiatric disorders in inpatient and outpatient medical settings, many do not receive recognition, appropriate diagnosis, initiation of adequate treatment, and/or referral for the follow-up psychiatric care they need. Failure to identify, evaluate, diagnose, treat, or achieve symptom resolution results in preventable adverse outcomes.

One major cause of the failure to identify and treat psychiatric disorders in medical settings is the absence of ready access to psychiatric expertise. Ideally, PM services for patients with psychiatric disorders and complex medical illness are integrated with the care provided by medical/surgical providers in collaborative care, which has great potential for improvement in both psychiatric and medical outcomes. However, most PM psychiatrists are on psychiatric consultation services, rarely found outside teaching hospitals, and their services are mostly acutely focused. Optimal care for patients with complex medical illnesses such as cancer or AIDS, or for those patients being considered for transplant or gastric bypass, calls for collaborative relationships with primary and specialty physicians and other allied health care professionals. Psychiatric liaison, in which psychiatrists are integrated members of a specialized care team, is a more advanced model, with greater ability to provide early detection and prevention. Such liaison services are usually limited to larger teaching and specialty hospitals, and have been difficult to financially support under managed care. Thus, there is an overall shortage of PM psychiatrists in the United States, they are mostly found in tertiary care sites, and they are not evenly distributed geographically.

Both in the United States and in other countries, there is considerable variation among the models of PM service delivery in the provision of psychiatric services in medical settings (Smith 2006). They vary in their focus on medical inpatients versus outpatients, in which disciplines are involved (psychiatry, psychology, psychiatric nursing, social work), and in how integrated they are with nonpsychiatric services and systems. They also differ in their relative devotion to consultation, liaison, education, and continued psychiatric care, and the extent to which they provide emergency psychiatric services.

## Psychiatric Diagnosis in the Medically Ill

Psychiatric disorders are frequently under- and overdiagnosed in the medically ill for a number of reasons. First, psychiatric symptoms are similar to those of medical illness. As a result, it may be problematic to determine whether such symptoms are manifestations of a physical disease or a comorbid psychiatric disorder. For example, a false

positive diagnosis of depression may occur when fatigue, anorexia, and weight loss caused by a medical illness are mistakenly attributed to depression, and a false negative diagnosis when depression's vegetative symptoms are misattributed to the medical illness. A variety of approaches have been proposed to diminish the effect of medical symptoms confounding the diagnosis of depression. In an "exclusive" and "etiologic" approach, symptoms that are judged by the clinician to be etiologically related to a general medical condition are excluded from the diagnostic criteria for Major depressive disorder (MDD). However, how to determine which symptoms are due to a medical illness, and which are due to depression, is unclear. In a "substitutive" approach, symptoms most likely confused with medical illness, such as fatigue and weight loss are substituted with symptoms that are more likely to be affective in origin, such as irritability and social withdrawal. Such substitution eliminates the need to distinguish symptoms of medical illness from those of depression, but it also excludes some somatic symptoms that are core manifestations of depression. Furthermore, valid criteria to determine which symptoms should be substituted have not been established. An "inclusive" approach applies the unmodified diagnostic criteria, which makes it unlikely that depression will be missed, but at the price of more false positives.

A second problem in psychiatric diagnosis in the context of serious medical illness, is that it can be difficult to differentiate a normal psychological reaction from a psychiatric disorder. Normal emotional reactions occur in response to uncertainty about diagnosis or prognosis, loss of body parts or body functions, fear of death, impact of illness on identity and livelihood, dependency, reactions to strangers, and being alone in the hospital, and may include anxiety, sadness, guilt, denial, avoidance, anger, hopelessness, and obsessive control. Normal adaptive emotional and behavioral reactions to illness, maladaptive responses, and psychiatric disorder are on a spectrum, and their differentiation is one of degree, informed by clinical experience. Finally, it must be recognized that a given symptom, e.g., tachycardia or poor concentration, may simultaneously result from a normal reaction, a psychiatric disorder, and the medical disorder itself all in the same patient.

This chapter will next illustrate a PM approach to cardiovascular disease, cancer, and endocrine disorders. For more detailed coverage of these and other topics see Levenson (2005).

## Psychosomatic Aspects of Cardiovascular Disease

The effects of psychological, social, and behavioral factors in cardiovascular disease have received considerable clinical attention and have been a primary focus of epidemiological and PM research for the past 30 years. Patients with severe mental disorders have about twice the prevalence of the classic risk factors for coronary artery disease (CAD) (Birkenaes et al. 2006).

### Depression and Heart Disease

Major depressive disorder is the most common psychiatric disorder in patients with coronary artery disease (CAD), with a prevalence of about 15–20% in those with stable or unstable CAD (i.e., myocardial infarction and unstable angina), which is much higher than in the general population (Glassman and Shapiro 1998). Major depression may be even more common after coronary artery bypass graft (CABG) surgery, approaching 30% in some studies (Blumenthal et al. 2003). Depression is also very common in congestive heart failure with a prevalence of up to 20%. Studies using depression symptom (i.e., not diagnostic) measures report even higher rates in cardiac patients. Despite such extensive studies of depression in heart disease, the diagnosis is still often missed, and only a minority of depressed patients receive treatment, and, fewer yet, adequate treatment.

Depression not only commonly occurs alongside CAD but also negatively affects outcome in CAD. Depression appears to be an independent risk factor for the development of CAD, with the magnitude of risk about 1.5–2.0. The magnitude of the effects of depression on morbidity and mortality in CAD is on a par with the effects of the recognized medical risk factors (Shapiro 2005). In a large epidemiological study, major depression tripled the relative risk of cardiac mortality in those without heart disease and quadrupled it in those who did have cardiac disease (Penninx et al. 2001). Major depression is a significant predictor of mortality after an acute myocardial infarction, with a three- to fourfold increased risk of death, which is equal to the effect of predictors like history of myocardial infarction or indices of cardiac function (Frasure-Smith et al. 1993, Carney et al. 2003b). In patients with CAD undergoing cardiac catheterization, major depression has been found to be a better predictor of cardiac morbidity and mortality than physiological measures such as left ventricular function (Carney et al. 1988). Patients hospitalized for unstable angina who also had depressive symptoms were four times more likely to have myocardial infarction or die the following year than were those without depression (after adjusting for other factors) (Lesperance et al. 2000). In patients who have CABG surgery, perioperative depression predicts an increased risk of subsequent cardiac events and also mortality.

Patients with CAD who are depressed also have poorer health-related quality of life and more functional disability in CAD, and depression has been found to be a stronger determinant of health status than objective measures of heart disease like stenosed coronary arteries, signs of ischemia, and ejection fraction (Ruo et al. 2003). Depression also adversely affects patients with congestive heart failure, worsening symptoms of heart failure, eroding health-related quality of life and functional capacity, as well as increasing the risk of death.

A number of explanations have been considered to account for the effects of depression on CAD (Glassman and Shapiro 1998, Shapiro 2005). Depression is closely associated with nicotine addiction, but depression still adversely affects CAD outcome even after controlling for smoking. Depression may interfere with compliance with recommended lifestyle changes, medication, and cardiac rehabilitation. Depressed patients may have alterations in platelet aggregation mediated by alterations in plasma serotonin. Another potential mechanism is reduced heart rate variability in depression, which may explain the increased risk of ventricular arrhythmias and sudden death in depressed cardiac patients. It is also possible that some of the adverse effects of depression are mediated through the cardiac effects of stress, as described later. Proinflammatory

mediators associated with depression may also be a contributor to CAD (Parissis et al. 2004).

Depression and cardiac disease often share some symptoms in common, which can complicate diagnosis. Insomnia and anorexia occur in both, but sadness and anhedonia occur predominantly in depression. In advanced heart failure, severe anorexia, weight loss, fatigue, poor concentration, and diminished libido all occur. In such patients, the diagnosis of depression should usually be reserved for those who also have psychological symptoms of depression.

## Anxiety, Stress, and Heart Disease

Symptoms of anxiety are also frequent in patients with heart disease, particularly, during acute coronary events and arrhythmias. A variety of presentations are common including panic attacks, generalized anxiety, hypochondriacal anxiety, obsessional rumination, and acute and posttraumatic stress reactions. In younger patients, panic attacks and paroxysmal atrial tachycardia may present with very similar symptoms, be difficult to discriminate between, and also commonly overlap in the same patient. In the past, an association between panic disorder and mitral valve prolapse was described; however, neither is a sensitive or specific marker for the other. The mitral prolapse that has been associated with panic attacks is usually of no hemodynamic significance, and there do not appear to be any important clinical consequences of the association.

Anxiety also adversely affects outcome in CAD. Anxiety after myocardial infarction may lead to more frequent episodes of unstable angina and more recurrent myocardial infarctions, after controlling for confounding factors including depression (Frasure-Smith et al. 1995). Postmyocardial infarction anxiety is one of the strongest predictors of in-hospital complications (Moser and Dracup 1996).

Anxiety's adverse effects on outcome in CAD may be mediated via effects on heart rate variability, QT interval prolongation, or other abnormalities in autonomic nervous system responses (Januzzi et al. 2000). As with depression, some of anxiety's effects may be related to the effects of stress on the heart. In studies of CAD patients under controlled laboratory conditions, acute experimental stress has been associated with increases in heart rate and blood pressure, and with silent (i.e., asymptomatic) myocardial ischemia.

Most patients who receive automatic implantable cardioverter-defibrillators (AICDs) receive them after experiencing life-threatening ventricular arrhythmias, an anxiogenic stressor in itself. A defibrillator discharge is extremely unpleasant physically, as well as reminding patients that they are still prone to potentially lethal arrhythmias. It is, thus, not surprising that in the early days of AICDs, there was a high rate of anxiety and other psychiatric disorders in the recipients. However, as the treatment has become more familiar and more widely used, the frequency and severity of anxious reactions have diminished. A new potential source of anxiety however has been the recent recall of selected AICDs, confronting patients with the difficult choice whether to risk the morbidity associated with replacing the device versus keeping a defibrillator that has a small chance of being defective.

## Type A Behavior

The relation between type A behavior and CAD remains controversial. Type A is a complex construct of multiple elements, including impatience, hostility, intense achievement drive, and time urgency. The findings to date have been divided on whether type A behavior is a risk factor for the development of CAD and a predictor of worse outcome. Overall, there is more support (albeit limited) for type A behavior as a risk factor for developing CAD, than as a cause of increased morbidity or mortality in those who already have CAD. Of the type A traits, hostility has been the most consistently associated with increased coronary events and mortality (Boyle et al. 2004). Anger, which is related to but not identical to the concept of hostility, appears to be an especially potent trigger of ischemia (Ironson et al. 1992). How hostility or other elements of type A behavior might lead to CAD, or worsen its outcome, is unknown but speculated to be due to alterations in the balance between sympathetic and parasympathetic nervous system activity.

## Cognitive Disorders

Postoperative delirium was extremely common in the early days of open-heart surgery but the incidence has declined over time in large part due to improvements in surgical technique and cardiopulmonary bypass technology. Delirium also sometimes occurs in the postoperative period following CABG surgery. More subtle cognitive dysfunction is present in about half of patients after CABG 1 week after surgery, with about a quarter of the patients still significantly cognitively impaired at 6 months (Newman et al. 2001). Persistent cognitive dysfunction in patients with CAD is most often vascular in origin since they frequently also have cerebral atherosclerosis. In severe heart failure, with ejection fraction below 15%, reduced cognitive performance is due to poorer cerebral perfusion.

## Hypertension

Because most hypertension is essential, i.e., idiopathic, psychological factors have been intensively studied as potential contributors to its pathogenesis. The influence of psychological factors in the development of hypertension is less clear than in CAD despite many studies of the potential role of personality, coping style, and blood pressure reactivity in hypertension. In some, but not all, studies, a high level of anxiety has been a strong prospective predictor for the development of hypertension, as has job strain. One prospective study of psychosocial risk factors for hypertension found that two of the components of Type A behavior (time urgency/impatience and hostility) were each associated with double the risk of hypertension at follow-up, but symptoms of anxiety and depression were not predictive (Yan et al. 2003). However, another prospective epidemiologic study found that combined symptoms of depression and anxiety were associated with an increase for hypertension (Jonas et al. 2000). Studies of psychological treatments for hypertension, primarily relaxation techniques and biofeedback, have, sometimes, found modest but clinically significant sustained reductions in blood pressure. However, drug therapy is much more effective than such techniques.

## Psychiatric Drugs in Patients with Heart Disease

Selective serotonin reuptake inhibitors (SSRIs) have almost no reported adverse cardiac effects, although they have rarely caused sinus bradycardia. Sertraline has been studied

in the most depth in the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) study that found no significant adverse effects in patients who had active coronary artery disease (Glassman et al. 2002). Bupropion, mirtazapine, venlafaxine, and duloxetine have occasionally been associated with relatively small increases in blood pressure but appear to be safe for use in patients with cardiac disease. Tricyclic antidepressants (TCAs) can cause orthostatic hypotension and conduction delay (QRS or QT prolongation). An overdose of TCAs may cause fatal ventricular arrhythmias. TCAs have Type 1A antiarrhythmic effects and, therefore, are considered relatively contraindicated after myocardial infarction.

Hypotension, caused by psychiatric drugs, is usually mediated via alpha-adrenergic blockade. It is common with low-potency typical antipsychotics, very common with clozapine, and less common with other atypical antipsychotics. Clozapine is unique among antipsychotics in causing myocarditis, usually presenting as a dilated cardiomyopathy, with an estimated rate between 1/500 and 1/10000. About 85% of the cases occur during the first 2 months of treatment with clozapine.

Antipsychotics all appear capable of prolonging the QT interval but this has primarily been of clinical significance with low-potency phenothiazines, pimozide, and droperidol (droperidol and mesoridazine have been withdrawn in the United States). In patients with other causes of QT-interval prolongation, especially familial long-QT syndrome, or the concurrent use of other QT-prolonging drugs, there is some increased risk of the ventricular arrhythmia, *torsade de pointes.* An electrocardiogram should be obtained for patients who have a history of heart disease, hypokalemia, hypomagnesemia, or a personal or family history of sudden death or syncope.

There has been recent concern regarding an increased risk of death in elderly demented patients who have received antipsychotics, with some of the deaths being cardiovascular. Rather than this absolutely contraindicating the use of antipsychotics in such patients, it is prudent to carefully balance the risks and benefits of treating versus not treating psychotic symptoms in demented patients.

Benzodiazepines have no recognized cardiac adverse effects (except in severe withdrawal) and have been safely used in coronary care units for several decades now. Buspirone is also free of cardiovascular effects.

Although lithium can cause sinus node dysfunction, it has been safely used even in patients with severe heart disease. Lithium levels are difficult to regulate in patients with congestive heart failure who are on salt-restricted diets and receiving varying dosage of diuretics, and it is usually best avoided in such patients. Valproic acid and lamotrigine have no significant cardiovascular effects, while carbamazepine has a similar side effect profile to the tricyclics.

Cholinesterase inhibitors may have vagotonic effects on the heart (e.g., bradycardia). While a number of clinical authorities have reported the safe use of modest doses of stimulants in patients with significant cardiac disease, including congestive heart failure, coronary artery disease, arrhythmias, and hypertension, recent concern has been raised regarding cardiac risk. Here too a careful weighing of potential risks versus benefits is warranted rather than total avoidance.

### Electroconvulsive Therapy (ECT)

Current acute coronary artery disease (myocardial infarction, unstable angina) or recent serious ventricular arrhythmias are relatively strong contraindications to ECT, but ECT has been used safely in a variety of heart diseases including patients with CAD, congestive heart failure, pacemakers, implanted defibrillators, after aneurysm repair, and even after heart transplant. For more detailed review see Rasmussen et al. (2005).

## Psychosomatic Aspects of Cancer

### Psychiatric Disorders in Cancer Patients

An individual's psychological response to cancer is influenced by specific aspects of the particular cancer. Patients' ability to manage a cancer diagnosis and treatment commonly changes over the course of the illness and depends on medical, psychological, and social factors: the disease itself (i.e., site, stage, clinical course, cancer treatments and their complications); prior personality, coping style, and mental health; stage of life; social support; and cultural and religious background.

#### Depression

Cancer is associated with a higher rate of depression than in the general population comparable to other serious medical illnesses (Massie 2004) and may represent a normal reaction, a psychiatric disorder, or a somatic consequence of cancer or its treatment. Cancer types particularly associated with depression include oropharyngeal, pancreatic, breast, and lung. Because cancer may itself cause anorexia, weight loss, fatigue, and other vegetative symptoms, diagnosis of clinical depression relies more heavily on psychological symptoms like social withdrawal, anhedonia, dysphoric mood, feelings of worthlessness or guilt, poor self-esteem, and suicidal thoughts. Thus, there is a risk both of underdiagnosis of depression in cancer patients, misattributing depressive symptoms to the cancer and a "normal reaction," and, overdiagnosis, misattributing cancer-caused symptoms and normal emotional upset to clinical depression. An increased risk of suicide in cancer patients is associated with advanced stage of disease, poor prognosis, delirium, inadequately controlled pain, depression, history of psychiatric illness, substance abuse, previous suicide attempts, social isolation (Massie and Greenberg 2005). Passive suicidal thoughts are far more common than true suicidality in cancer patients, yet may be expressed in some patients' noncompliance with or refusal of treatment.

#### Anxiety

Anxiety leads some patients to deny or ignore cancer symptoms and delay seeking medical attention. Symptoms of anxiety are common after initial diagnosis of cancer, in making treatment decisions, and when worrying about recurrence or progression, but the rate of full anxiety disorders may not be higher than in the general population (Stark et al. 2002). Specific anxiety syndromes can interfere with treatment. Patients with claustrophobia have difficulty tolerating magnetic resonance imaging (MRI) scans, radiation therapy, or isolation because of neutropenia.

Needle phobia may interfere with chemotherapy, and fear of anesthesia gets in the way of surgery. Radiation

phobia makes some patients reluctant to accept radiation treatment (Massie and Greenberg 2005). Chemotherapy can cause conditioned responses of nausea, vomiting, and intense anticipatory anxiety, but this has become less common with improved antiemetic drugs. The traumatic experiences of cancer and its treatment may give rise to posttraumatic stress disorder (PTSD). The differential diagnosis of acute anxiety in cancer patients includes antiemetic-induced akathisia, undertreated pain, pulmonary emboli, and delirium.

### Psychosis and Delirium

Mania in cancer patients is usually due to preexisting bipolar disorder or high-dose corticosteroids, only rarely due to other drugs (e.g., interferon) or brain tumors. Delirium is common in cancer patients as a result of the disease and its treatment, and, particularly, in the terminal stage of illness.

Specific causes include brain tumors (metastatic or primary), antineoplastic drugs (e.g., cytarabine, methotrexate, ifosfamide, asparaginase, procarbazine, fluorouracil), immunotherapeutic agents (e.g., interferon and interleukins), infection (especially in immunosuppressed patients), some antimicrobials (e.g., amphotericin), opioids, hypercalcemia, and the rare paraneoplastic syndrome, limbic encephalopathy.

## Psychiatric Aspects of Specific Cancers

### Breast Cancer

Psychological responses to breast cancer and its treatment vary with women's age, personality, and family and relationship circumstances because of the varying relevance of fertility, body image, side effects of treatment (e.g., alopecia; premature menopause with hot flashes, irritability, and depression), and genetic testing. Family and relationship issues include marital status; the partner's role; family history of cancer; sexual, pregnancy, and breast-feeding history; and desire to have (more) children. Genetic testing can now identify women at risk for the hereditary breast cancer/ovarian cancer syndrome. Women at high risk are confronted with decisions about prophylactic mastectomy or prophylactic oophorectomy, and how and when to inform their mothers, sisters, daughters, and granddaughters. Some women at high risk request prophylactic mastectomy without having had genetic testing, in which case, psychiatric evaluation should be considered.

### Lung Cancer

Almost 90% of lung cancers are attributable to cigarette smoking, and while many smokers with cancer experience guilt, many continue to smoke. Smokers are at higher risk for depression. Some patients and their physicians take a fatalistic attitude and conclude there is no point in trying to stop smoking once the diagnosis of lung cancer has been made. However, continued smoking is associated with decreased survival after diagnosis of lung cancer, so early antismoking intervention is warranted. In terminal lung cancer, if the patient derives pleasure from smoking, there is nothing to be gained from cessation efforts.

Cognitive dysfunction may be the result of brain metastases (very common in lung cancer), leukoencephalopathy caused by chemotherapy and cranial radiation, paraneoplastic syndromes with small-cell lung cancer (e.g., hyperadrenalism, hyponatremia, limbic encephalitis), and pulmonary emboli.

### Head and Neck Cancers

Head and neck cancers are most frequent in patients with a history of alcohol abuse and smoking. Treatment often causes facial deformity, loss of speech, problems with eating because of mucositis, pain, dysphagia, and dry mouth. Feeding tubes and tracheotomies are often necessary.

### Colorectal Cancer

Patients' psychological reactions to colorectal cancer are mainly determined by the extent of surgery, the presence of a stoma and ostomy, and the prognosis. Concerns about body image, leakage, odor, and sexual functioning can lead to social withdrawal. For those with ostomies, self-help groups can provide support, education, and coping skills for patients and their families.

### Pancreatic Cancer

Depression has long been thought to be a common harbinger of pancreatic cancer, before physical signs appear. A recent epidemiological study found that depression preceded pancreatic cancer more often than it did before other gastrointestinal malignancies (odds ratio 4.6:10). In a depressed patient, clues to the diagnosis of pancreatic cancer include abdominal pain and weight loss out of proportion to the degree of psychological symptoms, but the symptoms of pancreatic cancer are typically vague and nonspecific (Carney et al. 2003).

### Prostate Cancer

The serum prostate specific antigen test (PSA) has facilitated early detection of prostate cancer but considerable anxiety can follow because of treatment uncertainties. One uncertainty is when to actively treat because of the difficulty distinguishing between slow-growing prostate tumors with low risk for morbidity and mortality versus more aggressively malignant tumors. In addition, the choice between active treatments is difficult because of uncertainty which treatment (surgery vs. radiation) has the best benefit-to-burden ratio. The choice is often based on the potential consequences of urinary incontinence and impotence. Androgen deprivation therapy via orchiectomy or gonadotropin-releasing hormone agonists may cause hot flashes, diminished libido, fatigue, weakness, and muscle atrophy, and is associated with poorer quality of life (Wei et al. 2002).

## Psychiatric Aspects of Cancer Treatments

### Chemotherapy

The neuropsychiatric side effects of common chemotherapeutic agents are described in detail elsewhere (Massie and Greenberg 2005). The effects of chemotherapy on cognition have not yet been clearly elucidated (Phillips and Bernhard 2003). There are few clinically significant interactions between cancer drugs and most psychotropics, with the exception of procarbazine, which is a weak monoamine oxidase (MAO) inhibitor.

### Radiation

Brain irradiation causes more profound fatigue than radiation treatment of other sites. Late sequelae of brain radiation may include radiation necrosis in focal areas or leukoencephalopathy.

### Bone Marrow Transplantation

Patients undergoing bone marrow transplantation (BMT) have been reported to experience high levels of depressive and anxiety symptoms (Massie and Greenberg 2005). The greatest emotional distress may occur after hospital admission and prior to bone marrow infusion. However, during high-dose chemotherapy and irradiation, while patients are limited in contact with their family (and frequently in isolation) and experience profound nausea, vomiting, and fatigue, psychiatric disorders remain common, especially adjustment disorder with anxiety and depression. As many as half of BMT patients experience delirium during the posttransplantation period (Fann et al. 2002) with severe graft-versus-host disease as one possible cause. While chronic anxiety and depression are the most common psychiatric sequelae, long-term survivors of BMT show no difference in psychological and social functioning than those who receive standard chemotherapy, but mild to moderate cognitive impairment is common (Massie and Greenberg 2005).

## Psychiatric Treatment in Cancer

### Psychotherapy

Psychotherapy can help patients to cope with the diagnosis and treatment of cancer, relieving psychic suffering while supporting patients' morale, search for meaning, and desire for dignity at the end of life (Greenstein and Breitbart 2000, Chochinov 2002). Most studies of group therapy in cancer patients have shown improvement in mood, pain, and quality of life (Goodwin et al. 2001, Spiegel et al. 1989). Relaxation training and cognitive-behavioral therapy also have reduced anxiety and depression in cancer patients. Spiegel et al. (1989) performed a small randomized controlled trial of supportive group therapy with training in self-hypnosis for pain control in women with metastatic breast cancer. The subjects in the psychotherapy treatment group had less mood disturbance, fewer phobic responses, and less pain but were also noted to have increased survival compared with the control group (34.8 vs. 18.9 months). The possibility that a psychological intervention might improve longevity in metastatic breast cancer patients was exciting, supported by some other studies (e.g., Cunningham et al. 1998), but not by the definitive replication study (Goodwin et al. 2001) as well as some others. Thus, the evidence is that psychotherapy in cancer patients results in improvement in indices of quality of life like mood, energy, and pain control. Patients can be told that group therapy contributes to living better, not necessarily longer.

### Psychopharmacology

The SSRIs may cause nausea and weight loss in some cancer patients, particularly, those with cancer-related anorexia–cachexia. Mirtazapine and trazodone may be advantageous in such patients. Fluoxetine's long half life makes it useful for patients intermittently unable to tolerate oral intake (e.g., somatitis from chemotherapy). The SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) reduce hot flashes in abrupt menopause caused by chemotherapy or oopherectomy, and may help with hot flashes caused by treatment in men with prostate cancer. In addition to their psychiatric indications, TCAs and SNRIs are used to treat neuropathic pain syndromes caused by malignancy or its treatment. In addition to their antianxiety effects, benzodiazepines (most often lorazepam) are frequently prescribed to augment antiemetic drugs during chemotherapy. Low doses of neuroleptics are used in the treatment of delirium in cancer patients as in other patients with delirium. Psychostimulants are used for the treatment of depression in terminally ill cancer patients because there is no delay in onset of therapeutic effects, and, more generally, may palliate fatigue and augment opioid analgesia while counteracting sedation.

# Psychosomatic Aspects of Endocrine Disorders

Psychiatric symptoms and syndromes are common in patients with almost all endocrine disorders. Here, we briefly review psychiatric issues in diabetes mellitus, hypoglycemia, thyroid, parathyroid, and adrenal disorders, acromegaly, pheochromocytoma, hyperprolactinemia, polycystic ovary syndrome, and testosterone deficiency. For a more detailed review, see Goebel-Fabbri et al. (2005).

## Diabetes Mellitus

Type I diabetes mellitus (insulin-dependent diabetes) is an autoimmune disorder with additional genetic and environmental influences, affecting 5–10% of U.S. diabetics. Type II diabetes is characterized by insulin resistance, etiologically related to obesity, sedentary lifestyle, and diet, and affects 90–95% of U.S. diabetics. It has been well established that intensive management of both Type I and Type II diabetes reduces diabetic complications and improves long-term health outcomes (Diabetes Control and Complications Trial Research Group 2001, UK Prospective Diabetes Study (UKPDS) Group 1998a, 1998b). Thus, the goal of achieving optimal glucose values requires complex conscientious daily behaviors, which many patients find difficult. In both types of diabetes, psychiatric disorders have been linked to treatment nonadherence, worse glycemic control, and ultimately greater prevalence of micro- and macrovascular complications.

There is conflicting evidence whether stress directly affects the onset of diabetes or its course (Goebel-Fabbri et al. 2005). Stress hormones are involved in the counterregulatory response to insulin, so it is likely that stress plays a role in increasing blood glucose. It is not clear whether stress directly influences metabolic regulation or whether people under stress change their self-care behaviors.

Depression is two to three times more common in diabetics than in the general population, and depression is associated with poorer glycemic control and increased diabetic complications. The demonstration of such associations raises the question, is depression a cause or an effect of poorer diabetic outcomes? There are a number of mechanisms by which depression can increase the risk for or aggravate diabetes. Depression is associated with an increase in the secretion of cortisol and other counterregulatory hormones. Depression is also associated with reduced physical activity, increased

smoking, poor diet, and poor ability to self-monitor. Depression also results in changes in interpersonal functioning that can adversely affect the doctor–patient relationship, which is so central to diabetic management. Depression also increases the risk of a variety of other comorbidities like coronary disease. On the other hand, there are a number of mechanisms by which diabetes can result in or aggravate depression. Diabetes can lead to significant restrictions in lifestyle, demoralizing complications (e.g., renal failure, blindness, gastroparesis, amputations), and chronic pain. Diabetes is also associated with white matter lesions thought to increase risk for "vascular depression."

There have been small randomized controlled trials demonstrating the efficacy of nortriptyline (Lustman et al. 1997) and fluoxetine (Lustman et al. 2000) in the treatment of depression in diabetes, as well as one small randomized controlled trial of cognitive behavioral therapy demonstrating that it improved both depression and glycemic control (Lustman et al. 1998). A large randomized controlled trial of collaborative care, coordinating medical and psychiatric treatment in primary care settings, demonstrated improved depression care and outcome but no improvement in glycemic control (Katon et al. 2004).

Given the high prevalence of depression and its adverse effects in diabetes, and the availability of evidence-based treatments for depression, aggressive identification and treatment of depression are warranted as early as possible in the course of diabetes. Depression should always be suspected in patients who are having difficulty adapting to diabetes and show poor glycemic control.

There is also an increased prevalence of diabetes, mainly Type II, in patients with bipolar disorder. Some of this increase is no doubt due to the increased frequency of obesity in bipolar patients, some of which is iatrogenic since most mood stabilizers may cause weight gain. The increased prevalence of diabetes may also be related to lifestyle factors (diet, sedentary), and other comorbidities. It is not clear whether bipolar disorder might physiologically aggravate diabetes, and there has also been a question of whether diabetes and bipolar disorder may share some degree of genetic risk.

Diabetes is two to four times more common in patients with schizophrenia than in the general population. While some of this increase can be attributed to the proclivity for some antipsychotics, particularly, many of the atypicals, to cause glucose intolerance and obesity, the increased risk of diabetes in schizophrenia preceded the introduction of the atypicals (Goebel-Fabbri et al. 2005). Schizophrenics also tend to have poorer diet and are more likely to be sedentary.

There is also an increased risk of eating disorders in diabetes, with anorexia nervosa and bulimia more frequent in Type I diabetes, and binge eating disorder more frequent in Type II. A downside for many patients of optimally tight control of blood glucose is weight gain. That and the increased attention to dietary intake may aggravate eating disorders. "Caloric purging" refers to the practice of using less insulin than prescribed in order to lose weight, a practice that has been found in up to 40% of Type I diabetics between the ages of 15 and 30 (Polonsky et al. 1994). Those who engage in caloric purging have elevated hemoglobin A1c, more frequent hospitalizations and emergency room visits, and more frequent diabetic complications. This practice can be very difficult to detect if it is the only means of purging used by the patient. Thus, in patients who have both diabetes and anorexia nervosa or bulimia, overly intensive diabetic management can backfire. It is important to remember that metabolic stabilization is the primary goal, and there is a need to avoid excessive zeal in pursuing ideal blood glucose levels in such patients.

While many clinicians would suspect that frequent hypoglycemic episodes from too much insulin would result in permanent cognitive dysfunction in diabetics, the evidence is equivocal. There is more evidence that frequent hyperglycemic episodes result in cognitive dysfunction, probably due to cerebral micro- and macrovascular damage (Goebel-Fabbri et al. 2005).

## Hypoglycemia

"Reactive hypoglycemia" was a popular diagnosis in the past, often offered as an explanation for symptoms of depression, anxiety, inattention, or unexplained fatigue. A 5-hour glucose tolerance test is no longer considered necessary in evaluating such patients. However, significantly symptomatic hypoglycemia is unusual, except when it is due to insulin, usually prescribed, but rarely due to an insulin-secreting tumor (insulinoma) or factitious disorder. True hypoglycemic episodes are distinguishable from panic attacks in that the latter rarely cause acute confusion or loss of consciousness.

## Thyroid Disorders

Hyper- and hypothyroidism are common and easily screened for with a serum thyroid-stimulating hormone (TSH) (except for pituitary or hypothalamic hypothyroidism). Somatic symptoms of hyperthyroidism include sweating, fatigue, heat intolerance, weight loss, weakness, fine tremor, and tachycardia. The psychiatric symptom pattern in hyperthyroidism most often resembles generalized anxiety, but depression, irritability, hypomania, and cognitive dysfunction are all common. In severe hyperthyroidism (thyrotoxicosis, "thyroid storm"), patients may be frankly manic.

The somatic symptoms of hypothyroidism include weakness, fatigue, cold intolerance, weight gain, constipation, and somnolence. The psychiatric presentation of hypothyroidism closely mimics depression, but cognitive dysfunction is not uncommon. Severe hypothyroidism does rarely present with psychosis ("myxedema madness").

"Subclinical hypothyroidism" refers to the clinical condition, in which TSH is elevated but $T_4$ is low or normal, but the patient has few or no symptoms. Subclinical hypothyroidism appears to be a risk factor for depression and is a common cause of rapid cycling in bipolar disorder. Patients with subclinical hypothyroidism often show subtle signs of cognitive dysfunction. Whether and at what point to treat with thyroid replacement in subclinical hypothyroidism remains controversial.

## Parathyroid Disorders

Symptoms in hyperparathyroidism directly reflect serum calcium levels. In mild to moderate hypercalcemia (10–14 mg/dl), depression, apathy, irritability, lack of initiative, and lack of spontaneity are common. In severe hypercalcemia (> than 14 mg/dl), patients are usually delirious with psychosis, catatonia, or lethargy, and may progress to coma.

Symptoms in hypoparathyroidism similarly reflect calcium levels. In mild hypocalcemia, patients have anxiety, paresthesias, irritability, and emotional lability. In severe hypocalcemia, mania, psychosis, tetany, and seizures are common.

### Adrenal Disorders

Hyperadrenalism (Cushing syndrome) most commonly results from exogenous corticosteroids but may also be the result of adrenocorticotropic hormone (ACTH) secretion by a pituitary tumor (Cushing disease), or corticosteroid secretion by an adrenal tumor. In addition to somatic consequences including diabetes, hypertension, muscle weakness, obesity, and osteopenia, psychiatric symptoms are common in hyperadrenalism and may actually appear before physical signs. Depression is most common, but anxiety, hypomania/mania, psychosis, and cognitive dysfunction are all common.

Hypoadrenalism (Addison syndrome) may be primary (a result of adrenal destruction by autoimmune disease, metastatic cancer, tuberculosis, or HIV infection) or secondary through suppression of ACTH secretion by chronic corticosteroid therapy. Common physical symptoms in hypoadrenalism include postural hypotension, anorexia, nausea and vomiting, and weakness. Psychiatric symptoms include apathy, anhedonia, fatigue, and depressed mood. Adrenal insufficiency may, sometimes, be mistakenly diagnosed as major depression. While anorexia is common in both, the presence of nausea and vomiting should suggest the former.

### Acromegaly

Acromegaly is the result of excess growth hormone secretion by a pituitary tumor. Common physical symptoms and signs include headache, disfiguring facial and bodily features, glucose intolerance, and hypertension. Psychiatric symptoms include mood lability, personality change, and depression. Psychosis has also been reported, but this has usually appeared to be due to treatment with dopamine agonists like bromocriptine.

### Pheochromocytoma

Pheochromocytomas are rare catecholamine-secreting tumors. They cause tachycardia, labile hypertension, headache, sweating, and palpitations. They may also cause anxiety symptoms that mimic panic attacks. Pheochromocytomas have occasionally been reported to be unmasked after the prescription of an antidepressant. Screening by testing for urinary catecholamines produces frequent false positives. The best diagnostic test is a plasma metanephrine level, which is more specific. However, these tumors are quite rare and it is not necessary to screen for pheochromocytomas in most anxious patients even if they also have hypertension.

### Hyperprolactimemia

Excessive secretion of prolactin may be caused by pituitary adenoma, pregnancy, antipsychotics (typicals, risperidone), and antidepressants. Hyperprolactimemia in women is manifested by galactorrhea, irregular menses, and infertility. Men usually have no physical symptoms, but both genders may experience reduced libido, depression, and anxiety.

### Polycystic Ovary Syndrome

Polycystic Ovary Syndrome is common, affecting 5–10% of women of childbearing age. Its cause is unknown, but there is increased risk in women receiving valproate. Physical signs include oligo- or amenorrhea, hirsutism, infertility, obesity, hypertension, and insulin resistance. Depression is very common, but it is not clear whether its origin is hormonal or an emotional reaction to the changes in appearance and reproductive function (Goebel-Fabbri et al. 2005).

### Testosterone Deficiency

In men, testosterone deficiency may be the result of aging, or primary or secondary hypogonadism. Physical symptoms in men include reduced libido, sexual dysfunction, low energy, muscle weakness and atrophy, and reduced hair growth. The concept of a male climacteric is controversial. There is evidence of an increase in depression associated with reduction in testosterone levels in men (Shores et al. 2004). However, results have been mixed in randomized controlled trials using testosterone to treat depression in hypogonadal men (Goebel-Fabbri et al. 2005).

In women, testosterone deficiency results in decreased libido, low energy, and depression. However, what level should be considered to constitute deficiency has not been clearly defined, and the indications, risks, and benefits of testosterone replacement therapy in women are even less clear than in men.

## Conclusion

PM has evolved from its beginnings in psychophysiology and psychoanalysis to become a subspecialty of psychiatry devoted to psychiatric care of the medically ill. As illustrated in this chapter for cardiovascular disease, cancer, and endocrine disorders, a PM approach entails a complex understanding of the interrelationships of medical disorders and psychiatric disorders on multiple levels. PM aims to advance the diagnosis and treatment of psychiatric disorders in the medically ill, to improve education and training of both psychiatric and nonpsychiatric medical specialists, and to develop integrated systems of care. To overcome the fragmentation in the existing service delivery system will require changes in health care insurance and financing. This will help overcome the current disintegration and disparities between mental health and general health care.

Formal recognition as a subspecialty has strengthened PM and enhanced its growth and influence. The certification of more psychiatrists with expertise in PM will help address the unmet psychiatric needs of the medically ill, improve the quality of education and training, both in psychiatry and in other areas of medicine, promote integrative research, and improve medical outcomes in complex patients with multiple disorders.

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CHAPTER

# 119 Psychiatric Conditions in Women during Reproductive Transitions

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Growing interest in women's mental health has paralleled the expanding clinical and research focus on women's health issues over the past two decades. Research has shown that prior to puberty, both genders are equally at risk for developing mood disorders; however, with the onset of menstruation, women begin to show an increased risk for unipolar depression compared to men. Although studies have not yet revealed a consistent association between female reproductive hormones and psychiatric illness, there appears to be a subgroup of women at increased risk for psychiatric symptoms during times of hormonal fluctuation, such as premenstruation, during pregnancy, postpartum, and perimenopause. In addition to this biological vulnerability, psychosocial risk factors and intervening life events are key factors in increasing women's risk for psychiatric illness. This chapter will focus on psychiatric conditions during important reproductive transitions in women, including pregnancy, postpartum, and perimenopause, while premenstrual syndrome and premenstrual dysphoric disorder are thoroughly discussed in a separate chapter (see Chapter 68).

## Pregnancy

Pregnancy can be a stressful and high-risk time for mood instability, particularly in women with a past history of mood disorder (Cohen et al. 2006a, Viguera et al. 2000). While there has been increasing research and public health focus on postpartum depression (PPD), a significant number of women with PPD have symptoms that begin in pregnancy (Evan et al. 2001). A systematic review of perinatal depression found that the point prevalence of major and minor depression during pregnancy ranged from 6.5 to 12.9% (Gavin et al. 2005). Far fewer studies have looked at the prevalence and course of bipolar disorder, and anxiety and psychotic disorders during and after pregnancy. Clearly, many pregnant women, particularly those with a history of psychiatric illness, have worsening symptoms during pregnancy, as a result of either psychosocial risk factors', discontinuing or decreasing medications, changes in medication blood levels or other physiologic changes during the course of pregnancy (Altshuler and Hendrick 1996, Wisner et al. 1993). Screening and treatment during pregnancy would not only help symptomatic expectant mothers but also minimize their risk of worsening mood and anxiety after delivery. This section will outline a framework for approaching patients with significant psychiatric symptoms during and after pregnancy.

### Evaluation of Pregnant Women with Psychiatric Symptoms

Depression and anxiety during pregnancy frequently go undetected by providers (Kelly et al. 2001). Timely diagnosis and treatment is often hampered by confusion over whether somatic symptoms, such as fatigue and changes in sleep and appetite, are normal consequences of pregnancy or evolving mood or anxiety disorders. Routine formalized screening for major Axis I diagnoses would assist clinicians in identifying and tracking patients during pregnancy (Spitzer et al. 2000). In addition, screening for the following risk factors would help identify women at risk for depression during and after pregnancy: prior history of depression, young age, limited

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social support, marital strain, and ambivalence about pregnancy (Altshuler et al. 2000).

## Treatment of Pregnant Women with Psychiatric Symptoms

Treatment of psychiatric illness during pregnancy requires a thorough discussion about the risks of untreated illness and the risks and benefits of medication. Many pregnant women overestimate the risk of medication and underestimate the risk of untreated depression or anxiety. It is important for clinicians to put the risks of medication into context. For instance, pregnancy itself carries many risks, including spontaneous abortion and congenital defects. Untreated psychiatric illness can compound these risks by contributing to poor self-care, decreased prenatal compliance, increased nicotine and substance misuse (Hanna et al. 1994, Zhu and Valbo 2002), poor obstetrical outcomes (Chung et al. 2001, Kurki et al. 2000), and increased risk of PPD (Beck 2003). A first step in approaching patients involves reviewing the course of their illness, severity of past depressive episodes, and response to different treatments, including both medications and psychotherapy. Part of this risk–benefit discussion would also include review of the available data, regarding reproductive risks associated with psychotropic medications as well as review of the risks associated with discontinuing medication. For instance, in a recent study, Cohen et al. (2006b) followed 201 women with a history of recurrent major depression and found an increased risk of relapse in those who discontinued antidepressant medication compared to those who continued (68% vs. 26%).

### Major Reproductive Risks Associated with Psychotropic Medications

#### *Congenital Malformations*

Teratogenesis is the malformation of fetal organs, leading to structural or functional anomalies. Drugs ingested in pregnancy are considered teratogenic if they are associated with an increased frequency of congenital malformations above the baseline risk of 3–4%. Most studies of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been reassuring and shown no increased risk of major congenital malformations (Hendrick et al. 2003, Malm et al. 2005). However, there is great disparity in the amount of published information on different antidepressants within these drug classes, and it remains unclear whether all drugs within a class have the same reproductive risk. Recently, GlaxoSmithKline (GSK), the manufacturer of paroxetine, issued a warning that two studies found a possible association between first trimester paroxetine exposure and increased risk for cardiac defects, particularly atrial and ventral septal defects (www.gsk.com/media/paroxetine_pregnancy.htm). In 2005, the Food and Drug Administration (FDA) issued a similar warning that first trimester paroxetine use was associated with an increased risk of major malformations (4% vs. 3%), particularly cardiac malformations (2% vs. 1%). Although the purported association between paroxetine use and cardiac defects contradicts other published studies (Einarson and Einarson 2005, Ericson et al. 1999, Kulin et al. 1998), the manufacturer and the FDA have changed the pregnancy labeling from category C to D, indicating that published studies in pregnant women have demonstrated a risk to the fetus. In addition, the American College of Obstetricians and Gynecologists has recommended avoiding paroxetine use in pregnant women if possible; however, it also encourages an individualized approach to treatment, since in some cases the benefits of paroxetine may outweigh the risks of discontinuing the medication (ACOG Committee on Obstetric Practice 2006).

While there have been fewer reported cases of prenatal exposures to non-SSRI antidepressants, the limited data available have not shown an increased risk of congenital malformations with venlafaxine (Einarson et al. 2001), buproprion (Chun-Fai-Chan et al. 2005), mirtazapine (Djulus et al. 2006), nefazodone, or trazodone (Einarson et al. 2003).

#### *Perinatal Effects Following Late Pregnancy Antidepressant Exposure*

Perinatal toxicity refers to transient symptoms in the neonate following in utero exposure to medication, such as antidepressants, antipsychotics, and benzodiazepines. These symptoms can include irritability, tremulousness, insomnia, poor feeding, temperature dysregulation, increased or decreased muscle tone, and/or respiratory distress. These perinatal syndromes are likely related to medication withdrawal or toxicity and have been described with many serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) (Kallen 2004, Moses-Kolko et al. 2005, Zeskind and Stephens 2004). Using a formal screening tool, one study found that 30% of the newborns exposed to SSRIs in late pregnancy developed neonatal abstinence symptoms (Levinson-Castiel et al. 2006). In general, these neonatal syndromes have been found to be transient and not life threatening. To minimize the risk of perinatal toxicity, antidepressants can be tapered in the last weeks of pregnancy; however, this would not be prudent in patients with significant depression or highly recurrent illness.

Persistent pulmonary hypertension of the newborn (PPHN) is a serious and rare condition, affecting 1–2 out of 1000 live births and leading to death in 10–20%. In 2006, Chambers et al. (2006) published a study in which they found a possible association between PPHN and SSRI exposure after 20 weeks' gestation. Although this study was retrospective in design and involved only a small number of affected infants, its findings are concerning and again highlight the uncertainty that patients and providers must assume in choosing to use antidepressants or any psychotropic medications during pregnancy (see Clinical Vignette 1).

#### *Long-Term Neurobehavioral Effects*

Neurobehavioral teratogenesis refers to the long-term neurologic or behavioral effects of in utero drug exposure. In a study by Nulman et al. (2002), preschool children exposed in utero to TCAs or fluoxetine were found to have no difference in temperament, language, and cognitive development compared to nonexposed children.

#### *Reproductive Risks Associated with Other Psychotropic Medications*

*Lithium* use during the first trimester has been associated with an increased risk of a serious congenital heart defect known as Ebstein's anomaly, which occurs in approximately 1 out of 1000 live births. Lithium has also been associated with perinatal toxicity, including case reports of hypotonia,

cyanosis, neonatal goiter, and diabetes insipidus. For women with severe bipolar illness (i.e., recurrent mania or depression, history of psychosis, etc.), the risk of recurrence during pregnancy may overshadow the relatively small risk of Ebstein's anomaly. For such women, maintenance lithium therapy during pregnancy may be the most appropriate course. On the other hand, for women with significant periods of euthymia and few past mood episodes, slowly tapering off lithium and reintroducing lithium after the first trimester may help reduce the risk of relapse during the postpartum.

*Lamotrigine* is another highly effective mood stabilizer, particularly for bipolar depression. According to the manufacturer-sponsored Lamotrigine Pregnancy Registry and other published studies (Cunnington and Tennis 2005), there appeared to be no increased risk of congenital defects above the baseline risk with lamotrigine monotherapy; however, when combined with valproic acid in pregnancy, the risk estimate was found to be elevated to above 10%. While these initial findings seemed to offer women a relatively safe alternative to other anticonvulsants in pregnancy, the North American Antiepileptic Drug Pregnancy Registry ((888) 233-2334) recently found that infants who are exposed to lamotrigine monotherapy during pregnancy have a much higher risk of oral cleft defects. In this study, 564 children exposed to lamotrigine monotherapy had a prevalence rate of major malformations of 2.7%; however, 5 infants had oral cleft lip and palate, yielding a prevalence rate of 9 out of 1000 births compared to a baseline prevalence of 0.5–2.0 per 1000 in unexposed infants (Holmes et al. 2006). Even if future prospective studies confirm this association between first trimester lamotrigine use and oral cleft lip and palate, the overall risk appears to be low and may be overshadowed by the high risk of recurrent illness in some women with bipolar disorder. Clinicians should encourage all pregnant patients on any anticonvulsant in pregnancy to participate in the North American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334, as this growing database will continue to offer valuable new information.

*Valproic acid* and *carbamazepine* have well-established risks of neural tube defects of 5 and 1%, respectively. Carbamazepine is also a competitive inhibitor of prothrombin precursors and may increase the risk of neonatal hemorrhage. Newer anticonvulsants (e.g., gabapentin, oxcarbazepine, and topiramate) have limited reproductive safety data to guide their use in pregnancy. While they would not be the first choice in pregnancy, they may be indicated for particular pregnant women with refractory bipolar illness and a history of good response to these medications. Providers should encourage pregnant women who elect to continue any mood stabilizer to take high-dose folate (4 mg per day) for the theoretical benefit of reducing the risk of neural tube defects. In addition, pregnant women should undergo a second trimester Level II ultrasound to screen for major congenital anomalies.

*Antipsychotics*, like other psychotropic medications, are often essential during pregnancy to help minimize risks associated with psychosis, such as noncompliance with prenatal care, increased drug and alcohol use, and other high-risk behaviors. High- and midpotency neuroleptics, such as haloperidol and perphenazine, are generally considered to be the antipsychotics of choice during pregnancy since they have not consistently demonstrated teratogenic risk, while low-potency phenothiazines have shown increased risk of congenital malformations and should be avoided. There have been few studies of the reproductive safety of atypical antipsychotics, such as olanzapine, clozapine, risperidone, and quetiapine, and therefore, their risks in pregnancy are unknown.

Studies of *benzodiazepines* use during pregnancy have been contradictory and controversial. Benzodiazepine use during pregnancy has been associated with case reports of perinatal toxicity, including temperature dysregulation, apnea, depressed APGAR scores, hypotonia, and poor feeding. In addition, early studies revealed an elevated risk of oral cleft palate defects compared to the baseline risk in the general population. However, more recent studies have shown that the overall risk of cleft lip and palate with benzodiazepine use in pregnancy is likely quite low (Iqbal et al. 2002, Lin et al. 2004). In considering the risks and benefits of benzodiazepines, clinicians should also consider the risks of untreated insomnia and anxiety in pregnancy, which may lead to physiologic effects as well as diminished self-care, worsening mood, and impaired functioning. Given the consequences of untreated psychiatric symptoms and the limited and controversial risks associated with benzodiazepine use, some women with overwhelming anxiety symptoms or sleep disturbance may find that the benefits outweigh any theoretical risks.

### Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an underutilized treatment during pregnancy despite studies supporting its safety. For high-risk situations, such as psychotic depression or mania, which require prompt relief of psychiatric symptoms to protect both mother and fetus, ECT is the treatment of choice. The safe and effective use of ECT during pregnancy requires coordination of care among the patient's psychiatrist, obstetrician, and anesthesiologist.

### Psychotherapy and Light Therapy

Although concerns about the reproductive safety of medications often prompt women to seek psychiatric consultation during pregnancy, it is important to note that psychotherapy is often a useful alternative (or adjunct) to medication. Establishing a therapeutic alliance, exploring feelings about the pregnancy, and taking inventory of strengths, supports, and stressors can help target interventions, which may include assistance with basic needs for food, shelter, or financial support. Studies have demonstrated that depressed pregnant women can also benefit greatly from interpersonal psychotherapy (IPT), a brief structured therapy focused on certain areas of particular relevance to pregnant women, such as role transitions, grief, and interpersonal disputes (Spinelli and Endicott 2003). Supportive and cognitive–behavioral psychotherapy have also been shown anecdotally to help with depression and anxiety during pregnancy. In addition, for women with a seasonal pattern to their psychiatric symptoms, light therapy can be a helpful and safe treatment during pregnancy (Epperson et al. 2004, Oren et al. 2002).

## Postpartum Psychiatric Illness

Postpartum psychiatric symptoms are extremely common and range in quality and degree of functional impairment. Untreated postpartum psychiatric symptoms can not only

Clinical Vignette 1

Kathy is a 35-year-old attorney with a history of recurrent major depressive disorder. She is happily married and has been stable for 2 years on an antidepressant. She recently learned that she is 7 weeks pregnant and wants to know whether to discontinue her medication. Her psychiatrist reviews with her the available studies regarding her elevated risk of recurrence of depression if she stops the medication, given her past history of two major depressive episodes. In addition, her psychiatrist reviews with her the available data regarding the reproductive safety profile of different antidepressant treatment options. Kathy recalls how much her past depressive episodes cost her emotionally and professionally and is not willing to place her stability at risk by discontinuing her antidepressant. After a thorough risk–benefit discussion, she consents to continuing her selective serotonin reuptake inhibitor (SSRI) and also begins a course of interpersonal psychotherapy to address conflicts with her husband. As she enters her third trimester, she and her psychiatrist again review the risk of perinatal toxicity and pulmonary hypertension of the newborn associated with late trimester SSRI exposure. Kathy feels that the benefit she has gained from her antidepressant far outweighs the relatively slight risk of these adverse outcomes. Kathy also decides that it would be unwise to withdraw medication prior to entering the postpartum period, a time of heightened risk for many women with recurrent depression. She and her psychiatrist therefore decide to maintain her current dose as she heads into the last part of pregnancy.

lead to maternal suffering, but also affect how mothers care for their infants. In a prospective study of 570 postpartum women and their 3-month-old infants, mother–infant dyads with depressed mothers had less vocal and visual communications (Righetti-Veltema et al. 2002). Other studies have shown that maternal depression was associated with impaired mother–infant attachment (Brockington et al. 2001, Moehler et al. 2006) and higher risk of child cognitive and behavioral problems (Brennan et al. 2000, Murray et al. 1996).

Studies examining the pathophysiologic basis of PPD have focused on the dramatic shifts in reproductive hormones during and after pregnancy, as well as the hypothalamic-pituitary-adrenal axis and changes in cortisol, thyroid hormone, prolactin, melatonin, oxytocin, and vasopressin (Hendrick et al. 1998, Kammerer et al. 2006, Parry et al. 2003). While there is no compelling evidence to support most hormonal theories, reproductive hormonal fluctuations appear to contribute to PPD in a subgroup of women at risk for psychiatric symptoms during times of hormonal change (Bloch et al. 2000). This observation is further supported by evidence of the neuromodulatory effects of estrogen and progesterone, which in turn affect mood regulation (Rubinow et al. 1998)

Heightened emotional sensitivity and sleep disturbance are normal experiences during the postpartum transition. In fact, 8 out of 10 new mothers experience the *postpartum blues* (PPB), a self-limited constellation of symptoms that usually begin 2–3 days postpartum and can consist of mood lability, anxiety, insomnia, and appetite disturbance. This is a nonpathologic condition that resolves by 2 weeks postpartum. For some women, however, these symptoms can persist and evolve into *postpartum depression* (PPD), a condition that affects 10–20% of all postpartum women, with higher rates in low-income or disadvantaged populations. The DSM-IV-TR classifies PPD as major depression that occurs within 4 weeks postpartum; however, many new mothers develop PPD more than 2 or 3 months after delivery. Clinical features include all the signs and symptoms of major depression. In addition, *postpartum anxiety* symptoms are extremely common and can include panic attacks, intense anxiety about not getting enough sleep, obsessive worry about the baby's health or safety, and intrusive thoughts or mental images of hurting the baby (Brandes et al. 2004). New mothers with intrusive thoughts are often ashamed of these ego-dystonic images and may develop behaviors to diffuse some of their anxiety and fear, such as avoiding sharp objects or compulsively checking their infants' breathing.

*Postpartum psychosis* (PPP) is a rare condition that occurs in 1–2 of every 1000 postpartum women. PPP can begin acutely within the first 48–72 hours postpartum and may include delirium, memory impairment, irritability, and mood lability. Psychosis can also occur in new mothers with a history of a chronic psychotic disorder or as part of a major depressive or manic episode. Psychotic symptoms in a new mother require immediate intervention in order to protect both mother and infant from harm.

## Evaluation of Postpartum Women with Psychiatric Risk Factors or Symptoms

In assessing any woman with significant mood or anxiety symptoms after delivery, it is important to rule out possible organic causes of low mood, insomnia, and appetite disturbance, such as anemia and thyroid dysfunction. Clinicians should also inquire about the status of patients' physical recovery from delivery, since prolonged pain following a complicated vaginal delivery or cesarean section can certainly contribute to sleep and mood symptoms. In screening for common Axis I diagnoses, such as major depression or anxiety disorders, clinicians should also screen for bipolar disorder, given the heightened risk of postpartum mood episodes in women with bipolar illness (Viguera et al. 2000). In addition, clinicians should ask new mothers about intrusive thoughts regarding their infants' safety or violent images or thoughts about their infants (see Clinical Vignette 2). These intrusive thoughts are common in women with postpartum depression or anxiety, while acting them out is thankfully very rare (Brandes et al. 2004). Nonetheless, specifically asking distressed postpartum mothers about these thoughts and images is extremely important, since psychotic thinking can at times be subtle.

Systematic screening for risk factors as well as current symptoms facilitates prevention, detection, and treatment of postpartum psychiatric syndromes. The Edinburgh Postnatal Depression Scale (EPDS) is a widely recommended, cost-effective means of screening for PPD (Wisner et al. 2002). The EPDS is a 10-item self-rating scale that has been validated in Spanish and English and asks about depressive symptoms in the preceding week, including crying spells, decreased interest and pleasure, increased guilt, anxiety, sleeping problems, and thoughts of self-harm (Cox et al. 1987). To improve prevention interventions, clinicians could also screen for risk factors both during and after pregnancy. These risk factors include a personal history of mood or anxiety disorder, psychiatric symptoms during pregnancy,

limited social support, interpersonal conflicts, and negative life events during and after the pregnancy (O'Hara et al. 1991, Robertson et al. 2004, Stowe and Nemeroff 1995). In addition, a history of extreme premenstrual irritability may be a possible marker for increased vulnerability during times of hormonal fluctuation, such as the dramatic hormonal shifts after delivery (Stewart and Boydell 1993).

## Treatment Considerations in Postpartum Women with Psychiatric Symptoms

### *Support and Psychotherapy*

All women would benefit from education about the normalcy of certain psychiatric symptoms after delivery and review of the differences between the self-limited PPB and more serious conditions such as PPD. Referrals to mothers' groups, childcare resources, or financial assistance agencies can also be extremely therapeutic. In the United Kingdom, postpartum support includes nurses with advanced training, who provide home visits to screen and assist postpartum mothers. Here in the United States, clinicians can refer women to Postpartum Support International (www.postpartum.net), an organization with many local chapters that offers support and resources for women with postpartum psychiatric illness. Other options for surrogate family assistance include the services of a doula, a professional caregiver who can assist not only with childbirth but also during the first postpartum weeks by helping with childcare or household tasks.

Studies of IPT suggest that this time-limited therapy is helpful in treating mild-to-moderate postpartum major depression (O'Hara et al. 2000, Reay et al. 2006). This form of therapy focuses on specific problem areas, such as role transitions or interpersonal disputes. Zlotnick et al. (2001) found that pregnant women receiving group IPT compared to regular care had decreased rates of PPD at 3 months postpartum. A small study comparing *cognitive–behavioral therapy* (CBT) and fluoxetine showed that CBT is also an effective treatment for PPD (Appleby et al. 1997).

### *Antidepressants*

Despite the high prevalence of postpartum psychiatric illness, there are only a limited number of medication treatment studies. In small studies, fluoxetine (Appleby et al. 1997) and venlafaxine (Cohen et al. 2001) have shown efficacy in treating PPD, while sertraline has shown benefit in both preventing and treating PPD (Wisner et al. 2004, 2006). Women at increased risk for PPD should consider initiating prophylactic antidepressants either in late pregnancy or early postpartum. Alternatively, women may elect a wait-and-see approach; however, patients, their loved ones, and psychiatrists should be vigilant for early signs of recurrence in order to institute prompt treatment.

The choice of an antidepressant is largely guided by the patient's depressive symptoms, past history of medication response, and medication side effects. If a patient plans to breastfeed, clinicians must facilitate a careful risk–benefit discussion about taking psychotropic medication during lactation (see below). To temper the tremendous changes in estrogen and progesterone following birth, some studies have looked at hormone therapy (HT). Several studies of estrogen alone or as an adjunct to antidepressants concluded that estrogen improved depressive symptoms; however, these studies were small and have limited generalizability.

### *Breastfeeding*

All psychotropic medications are secreted into breast milk. Mothers on psychotropic medications therefore require a thorough risk–benefit discussion of breastfeeding and taking medication to treat psychiatric symptoms.

1. *Antidepressants*. A recent analysis of the available studies of antidepressants during lactation revealed that sertraline, paroxetine, and nortriptyline are the least likely to lead to accumulation in the infant (Weissman et al. 2004). Other studies of TCAs and SSRIs have been reassuring and shown no consistent association between any particular antidepressant and problems in nursing newborns. There have been isolated case reports of elevated infant levels and toxicity with breastfeeding mothers taking doxepin or fluoxetine. Little is known about the safety of other antidepressants during lactation, such as venlafaxine, buproprion, or mirtazapine.
2. *Mood stabilizers*. For women with bipolar illness, the choice to nurse while on a mood stabilizer is even less clear-cut than with antidepressants. Lithium can quickly accumulate in the nursing infant and lead to levels exceeding 50% of the maternal level. Given this risk of lithium toxicity in the nursing infant, breastfeeding while on lithium is generally not recommended. Although not absolutely contraindicated in nursing mothers, valproate has been associated with infant anemia and thrombocytopenia, and carbamazepine has been associated with transient hepatic dysfunction.

In general, clinicians should advise nursing women on psychotropic medications to monitor infants for behavioral changes, such as excessive sedation, jitteriness, or inconsolable crying. Infants who develop any of these symptoms should be evaluated by their pediatrician for possible drug toxicity. In the meantime, mothers can consider temporarily pumping and storing/discarding their breast milk and using formula to see if their infants' symptoms resolve. In infants who are preterm or have any medical problems, mothers on psychotropic medication could also consider pumping and storing/discarding breast milk and introducing nursing later when the infant is healthy and can presumably metabolize medication more efficiently.

## Menopause

Perimenopause refers to the 5–10-year transition from regular menstrual functioning to menopause. Hormonal changes during this period include significant fluctuations in estrogen and progesterone levels until menstrual cycles cease and reproductive hormones remain stably low. Most women naturally transition to menopause, while other women experience a more abrupt "chemical" or "surgical" menopause as a result of exogenous hormone treatment or following bilateral oophorectomy.

Some women experience significant mood symptoms during the menopausal transition. As with premenstrual syndrome and postpartum psychiatric symptoms,

Clinical Vignette 2

Mary is a 32-year-old married nurse with a history of panic attacks that have been well controlled for years. She presents 3 months postpartum, following a difficult pregnancy complicated by severe hyperemesis gravidarum and dysphoria and resulting in a traumatic delivery with a third-degree perineal tear. Mary now complains of crying spells, decreased appetite, insomnia, and obsessive worry over the baby's health. She feels isolated from her husband, who is overwhelmed by her emotional needs and tends to retreat to work. Her psychiatrist completes a thorough diagnostic assessment and determines that Mary suffers from major depression and generalized anxiety disorder. When she is feeling particularly overwhelmed, she also has violent and intrusive thoughts of throwing her infant against a wall. These thoughts are ego dystonic and very distressing for Mary, who has no evidence of psychosis and no history of violence. She begins a course of cognitive–behavioral therapy to address her anxiety symptoms and negative thinking. She also enlists the support of a babysitter several mornings per week to allow her additional rest, which improves her perineal pain and gives her some much needed time for herself. In addition, she begins a selective serotonin reuptake inhibitor, and within a few weeks, she starts to feel much more composed and connected to her baby.

perimenopausal hormonal fluctuations may increase mood symptoms in a subset of at-risk women. Several studies have found that perimenopausal depressive symptoms are likely associated with reproductive hormonal changes rather than abnormally low levels of estrogen or androgens (Schmidt et al. 2002). Furthermore, several trials have shown that estradiol reduced depressive symptoms in perimenopausal women and that baseline or posttreatment estradiol levels did not predict therapeutic response (Schmidt et al. 2000, Soares et al. 2001). Other theories of perimenopausal depression have highlighted the "domino" effect of somatic symptoms associated with estrogen withdrawal, such as hot flashes, which in turn lead to sleep and mood disturbance. In addition, psychosocial factors have also been shown to increase risk for midlife depression in women, including negative life events, health complaints, and relationship difficulties (Schmidt et al. 2004). The confluence of other developmental midlife transitions, such as having adult children leave home or aging and dying parents, may also play a role in increasing risk for psychological distress; however, studies of this so-called *empty nest* phenomenon have been contradictory (Dennerstein et al. 2002, Greene and Cooke 1980, Schmidt et al. 2004). Although interpreting the available data regarding the link between perimenopause and depression is hampered by the lack of a standard definition for menopausal status in different studies, biological and psychosocial factors seem to play a role. This multifactorial etiology of perimenopausal depression was supported by two recent prospective studies, in which premenopausal women with no history of major depression were found to have increased risk of depression during the menopausal transition (Cohen et al. 2006b, Freeman et al. 2006). A previous depression history, vasomotor symptoms (e.g., hot flashes), negative life events, and variability in estradiol levels were also associated with increased risk for depression. These findings are consistent with the notion that biological as well as psychosocial factors increase risk for depression during the menopausal transition.

## Approach to the Patient with Perimenopausal Mood Symptoms

Perimenopausal depression requires a biopsychosocial assessment and treatment approach (see Clinical Vignette 3). Psychiatric evaluation should include screening for major Axis I diagnoses and a history of psychiatric symptoms during other reproductive events. In addition, clinicians should take inventory of recent stressors, personal coping strengths and liabilities, and the extent of social supports. Screening for alcohol and substance abuse can also help identify possible reasons for worsening psychiatric symptoms. Medical evaluation should include assessment of reproductive endocrine status by taking a menstrual history and screening for perimenopausal vasomotor symptoms, such as hot flashes and vaginal dryness. Hormonal changes in menopause include a decrease in estrogen with subsequent elevations of luteinizing hormone and follicle-stimulating hormone. Clinicians should also rule out possible medical causes of mood symptoms that are common in midlife women, including thyroid and cardiac disease.

## Treatment Considerations in Women with Perimenopausal Mood Symptoms

Studies have clearly shown that HT alleviates vasomotor symptoms, such as hot flashes (Warren 2004). Some studies have also found that estrogen may have antidepressant properties, possibly as a direct neuromodulatory effect as well as a result of the psychological relief depressed women experience as their vasomotor symptoms diminish (Schmidt et al. 2000, Soares et al. 2001). For perimenopausal women with significant vasomotor symptoms, short-term HT may alleviate mild mood symptoms along with insomnia, vaginal dryness, and hot flashes. Prior to recommending HT, however, clinicians should consider the Women's Health Initiative study results, in which HT was associated with an increased risk of breast cancer, coronary heart disease, and thromboembolic events in postmenopausal women (Manson et al. 2003, Rossouw et al. 2002). It remains to be seen whether these risks are generalizable to younger perimenopausal women on HT and whether or not the benefits of short-term HT for depressed perimenopausal women outweigh the risks.

For perimenopausal women who present with major depression, clinicians should consider standard treatment including antidepressant medication and psychotherapy. There is some evidence that menopausal status may affect the efficacy of different classes of antidepressants (Kornstein et al. 2000, Pinto-Meza et al. 2006, Thase et al. 2005). For instance, in one study, premenopausal women with major depression were found to respond better to sertraline than imipramine, while postmenopausal women responded similarly (Kornstein et al. 2000). Some psychotropic medications such as the SSRIs (Gordon et al. 2006, Soares et al. 2006, Stearns et al. 2003), venlafaxine (Evans et al. 2005, Ladd et al. 2005), and gabapentin (Reddy et al. 2006) have also been shown to alleviate hot flashes, although none has an FDA indication for this use. Among the botanical and dietary supplements, St. John's wort and black cohosh appear to be the most beneficial for mood and anxiety changes during

Clinical Vignette 3

Diane is a 50-year-old physician with no psychiatric history until this past year, when she experienced many life changes, including separating from her husband and caring for her ailing parents. In addition, over the last 6 months, her periods have become irregular and she has had recurrent hot flashes that have interrupted her sleep. She presents with symptoms consistent with major depression, including low mood, irritability, decreased interests, poor concentration, sleep and appetite disturbance, and feelings of hopelessness. From Diane's report of vasomotor symptoms and irregular menses, it is clear that she is in the menopausal transition. A trial of an antidepressant improves her depressive symptoms and also alleviates her hot flashes. In addition, a course of psychodynamic psychotherapy helps her begin to understand the connection between her early life experiences and her current anxiety, anger, and sadness as she grieves the end of her marriage and the possible loss of her debilitated parents.

menopause (Geller and Studee 2005). In addition, psychotherapy, both alone and in combination with medication, is also highly beneficial for women coping with the challenges associated with midlife.

## Conclusion

Women have higher rates of major depression compared to men in every age group, with peak rates during the reproductive years. This observation has inspired a field of research examining psychiatric conditions associated with reproductive events, such as menses, pregnancy, and menopause. The transition to motherhood and, later, to menopause can be fraught with challenges as women adapt to shifting roles and other life changes. In addition, the hormonal changes after delivery and during the perimenopausal transition contribute to mood and anxiety problems in a subset of women who are prone to psychiatric symptoms during hormonal shifts. Recent studies questioning the reproductive safety of certain psychotropic medications as well as the thromboembolic and cancer risks associated with postmenopausal HT underscore the fact that reproductive psychiatry is a dynamic and evolving area of research. Whether treating perinatal or perimenopausal patients, clinicians therefore must adopt an individualized treatment approach that addresses biopsychosocial factors as well as incorporates an up-to-date discussion of the risks and benefits of medication and psychotherapy options.

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CHAPTER

# 120 Death and Bereavement

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## Introduction

Death, including dying and bereavement are among life's most difficult experiences. Yet mortality is clearly a natural part of life. Those who understand this are better able to cope with the pain of facing their own death as well as loss of loved ones. CS Lewis provides an eloquent description of death as a natural sequence in a relationship,

> "For all pairs of lovers without exception, bereavement is a universal and integral part of our experience of love. It follows marriage as normally as marriage follows courtship or as autumn follows summer. It is not a truncation of the process but one of its phases; not the interruption of the dance, but the next figure. We are 'taken out of ourselves' by the loved one while she is here. Then comes the tragic figure of the dance in which we must learn to be still taken out of ourselves though the bodily presence is withdrawn, to love the very Her, and not fall back to loving our past, or our memory, or our sorrow, or our relief from sorrow, or our own love." (Lewis 1961, p. 63.)

While Lewis is writing about loss of a spouse, his ideas are applicable to the loss of other loved ones. Yet not everyone arrives at this kind of philosophical acceptance, and those who do, including Lewis, are not spared a prior period of great disruption. As a result, dying patients and their bereaved loved ones often develop mental and/or physical symptoms. Psychiatrists may be called upon to assist in providing support, solace, and clinical interventions to dying patients and their caregivers, and to bereaved people following the death of a loved one. This chapter will provide a discussion of death, including its rates and causes, current thinking about management of terminally ill patients, an overview of the identification and management of suicide risk, and information about bereavement and grief that can inform psychiatric practice.

## Death and Dying

"World Death Rate Holding Steady At 100 Percent" heads a satirical article in the internet journal *The Onion* that draws attention to the American cultural attitude of defiance of death, and the expectation that it is the job of the medical profession to avert death at all costs:

> "World Health Organization officials expressed disappointment Monday at the group's finding that, despite the enormous efforts of doctors, rescue workers and other medical professionals worldwide, the global death rate remains constant at 100 percent. Death, a metabolic affliction causing total shutdown of all life functions, has long been considered humanity's number one health concern. Responsible for 100 percent of all recorded fatalities worldwide, the condition has no cure… Many are suggesting that the high mortality rate represents a massive failure on the part of the planet's health care workers. The inability of doctors and scientists to adequately address this issue of death is nothing less than a scandal," concerned parent Marcia Gretto said." Do you have any idea what a full-blown case of death looks like?…" (Jan. 22, 1997, Issue 13, no.2).

The Onion's 100% lifetime death rate translated into 2,398,343 deaths in the United States during 2004, according to CDC statistics (Minino et al. 2006). This number represents an average age-adjusted rate of 801 per 100,000. Age-adjusted, death rates in 2004 for men were 955/100,000 and for women 680. The leading causes of death in the US were as follows: (1) Diseases of heart; (2) malignant neoplasms; (3) cerebrovascular diseases; (4) chronic lower respiratory diseases; (5) accidents (unintentional injuries); (6) diabetes mellitus; (7) Alzheimer's disease; (8) influenza and pneumonia; (9) nephritis, nephrotic syndrome, and nephrosis; (10) septicemia; (11) intentional self-harm (suicide); (12) chronic liver disease and cirrhosis; (13) essential (primary) hypertension and hypertensive renal disease; (14) Parkinson's disease; and (15) pneumonitis due to solids and liquids. Death rates for men and women, as well as infant death rates, are considerably higher for blacks than whites.

The attitude satirized in the Onion article is still extant among a substantial proportion of the population, and

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especially physicians. Thankfully, there have been important efforts to change this. In spite of medical efforts, death remains an everyday occurrence, and many deaths occur under the care of a physician. For much of the 20th century, medicine was oriented primarily to preventing death whenever possible. To a great degree this effort was successful as the average life span has lengthened considerably. Now, there is now a focus on quality as well as quantity of life, and assistance with dying, provided by hospice and/or palliative care, is a valued activity. The hospice and palliative care movement have a strong foothold and are growing in the United States and elsewhere. Still, a recent survey of hospices in Australia indicates that few function in an optimal manner (Carlson et al. 2007). Moreover, a humane approach to death remains primarily the province of specialty care and has not yet been well infused into the everyday practice of medicine.

Bedell, Cadenhead, and Graboy (Bedell et al. 2001) called attention to the need for physicians to support family members of their deceased patients as their final responsibility to the patient. The authors suggested writing a personal letter of condolence, acknowledging barriers to doing so. They recognize that physicians are very busy and sometimes haven't seen the patient for a while. The physician may hesitate because of not knowing the patient very well, because of feeling a sense of personal failure regarding the death, or simply not knowing what to say. Nevertheless, these authors emphasize the importance of reaching out to the family. They outline a possible approach to such a letter and emphasize how helpful such an approach can be for bereaved family members. It is unclear how widespread this practice has become. Moreover, before death, many physicians are uneasy about maintaining a relationship with a dying patient for whom they have no further healing treatments.

Continuing to provide care to a terminally ill patient is clearly important, even when there are no further curative possibilities. Yet for many physicians, interest in the patient dwindles in parallel with dwindling treatment options. At best, such physicians may refer their patient to a palliative care service. This medical subspecialty is strong and growing. Psychiatrists may be involved in the terminal care of patients, either through their own practice or through work in palliative care. Investigators have begun to document the clinical issues involved in treating terminally ill patients. Reports in the psychiatric literature pertain primarily to the elderly. In fact, due to the tremendous advances in medicine over the last century, 80% of deaths now occur among the elderly. A recent paper outlines the issues relevant to end-of-life care in the elderly (Lyness 2004). The issues raised by this author also have relevance to those relevant for younger people (Table 120–1).

**Table 120–1 End of Life Intervention Targets**

| Patient | Caregiver/Family | System |
|---|---|---|
| Symptoms | Symptoms | Effective recognition and management of symptoms in patient and family |
| Quality of life | Caregiver burden/ quality of life | Address quality of life issues |
| Sense of autonomy | Sense of autonomy | Recognize and promote autonomy in patient and caregiver |
| Sense of connectedness | Sense of connectedness | Recognize and promote connectedness of patient/caregiver and others |
| Participate in decision making | Participate in decision making | Organize effective decision making |
| Optimal medical care | — | Provide optimal medical care |
| Satisfaction with care | Satisfaction with care | — |

## Work with Terminally Ill Patients

A major goal in effective end-of-life care is to bring treatment as closely as possible into alignment with the wishes of patients and their families. Studies to date show that this goal is often not achieved (Butow et al. 2004). Lyness suggests that sensitive discussions about end-of-life care should begin early in the course of a chronic illness, when the clinician can explore lifelong values, including those related to culture and religion, the patient's relationship with her/his family, and her views about life-threatening illness and medical treatment. The physician communicates a commitment to assisting the patient to die with dignity, an attitude of respect for the patient's wishes, and assurance that she will not abandon the patient if and when treatment is no longer effective.

The clinician's tasks change as a terminal disease progresses. At times, there may be bad news to deliver. This should be done with sensitivity to the patient's readiness to hear the news and openness to engage in a discussion about the information. During this and other times, the clinician needs to monitor the patient's symptoms, including pain, anxiety, and depression, as well as changing functional capacities and the status of important relationships. Many dying patients experience cognitive impairments and these must be accurately assessed. Over time, the patient and family will be confronted with choices regarding care options, and they will need to make decisions about these. Clinicians need to provide accurate information about prognosis and treatment options, handle unrealistic hopes and wishes in a sensitive, empathic, and supportive manner and assist in guiding the decision-making process.

The goal of pain management for a dying patient is to eliminate pain, unless the patient states that she/he does not want this. Studies have documented that it is usually possible to achieve this goal without intolerable analgesic side effects. Pain management uses a stepped approach, changing the potency of medication as the pain intensifies. It is important to assess pain, like emotional symptoms, in an ongoing manner and by direct questioning of the patient. Lyness summarizes an approach to pain management in palliative care, beginning with acetaminophen, nonsteroidal anti-inflammatory drugs for mild pain, and progressing to opioids as the treatment of choice for severe pain. Adjunctive doses can be successfully used for breakthrough pain in patients on opioid analgesia. A range of further management strategies have been developed and reviewed in an ongoing series of publications in the Cochrane Library and summarized in the Journal of Pain & Palliative Care Pharmacotherapy. For example, sub-anesthetic doses of

ketamine (Wiffen 2006a, 2006b, 2006c) can reduce analgesia requirements and decrease nausea and vomiting. New approaches target different types of pain such as corticosteroids, biphosphonate, or calcitonin (Chang et al. 2006) to augment opioids for bone pain, or antidepressants or anticonvulsants to augment opioids for neuropathic pain. A number of nonpharmacological approaches to pain management have also been developed and tested. Among these are acupuncture, herbal remedies, and music, all of which have been found to have some beneficial effects as adjunctive treatments in pain management.

Psychiatric symptoms common among dying patients include depression, anxiety, and cognitive impairment. Suicidal ideation is also seen and needs to be carefully evaluated. Although research is scanty in this population, information that exists suggests that major depression occurs, that it responds to standard antidepressant medication and that, untreated depression worsens medical prognosis. Diagnosing depression can be tricky as many symptoms of depression overlap with those of the underlying medical condition. Many researchers use an inclusive approach to diagnosis. However, this can lead to over-diagnosis and is not universally accepted. An alternative approach is symptom management. For example, psychostimulants can be helpful in increasing well-being and reducing anergia, even in the absence of full-blown major depression (Lyness 2004).

A range of anxiety disorders may be seen in dying patients, including generalized anxiety disorder, focused on worries about the future, about the well-being of family members, about disability or loss of resources or a myriad of other daily life difficulties for ill patients. Anxiety may be focused on aspects of the terminal illness including illness progression, pain management, and/or death. PTSD may occur as a reaction to a life-threatening diagnosis and/or painful or frightening medical procedures. Panic attacks may occur and may be more common among patients with respiratory distress. Treatment of anxiety may be achieved with benzodiazepines, though these should be used cautiously in terminal patients as vulnerability to cognitive impairment is increased. Low-dose antipsychotic medication, especially an atypical antipsychotic, can be very helpful in controlling anxiety, including rumination and agitation. Opioid treatment of respiratory distress and pain can be helpful in reducing anxiety related to these problems. Supportive and/or cognitive behavioral psychotherapy can be useful for patients who are alert and able to participate in such a treatment.

Delirium is very common among dying patients. This occurs most commonly as a consequence of progression of the underlying illness, or as a side effect of medication treatment of pain. While reducing medication that is causing a delirium may be useful, this must be balanced against potential loss of pain control. Management of delirium can usually be accomplished with the use of antipsychotic medication, and this may be preferable to treating the underlying problem in a terminally ill patient with anxiety, agitation, and delirium. Stimulus control may also be of some use. Work with family members is often necessary in the management of delirium, as this can be an especially difficult problem for caregivers.

Psychotherapy has a role in the management of terminally ill patients. A supportive therapist can be especially helpful if there is time to develop a strong alliance, and if the therapist has known the patients prior to the onset of the later stages of terminal illness. In such a situation, the therapist can assist the patient in problem solving, goal setting, and interpersonal interactions. Therapists working with terminally ill patients need to include work with the family in order to optimize the supportive resources of the family, assist the family in coping with the illness and impending death of a loved one, and to address interpersonal toxicity, if it occurs. Intervention with distressed family members can be helpful in reducing caregiver burden and may play a role in decreasing the likelihood of bereavement-related problems such as depression or complicated grief. Work with parents of terminally ill children may be especially important as loss of a child is clearly the most difficult stressor a parent can endure. Recent studies by Meert and colleagues have documented the importance of availability and attentiveness of hospital staff to parental needs for information and honest, complete communication (Meert et al. 2005, 2007, Sharman et al. 2005). Physicians may need help in learning to communicate with parents of terminally ill children in a sensitive, respectful, caring, and empathic manner, while not withholding information. Another study documents that parents often want the opportunity to have a conference with the physician after a child dies, and that this occurred in only 13% of deaths in a pediatric ICU. A French group (Lautrette et al. 2007) provided a brochure and a conference to family members of patients dying in ICUs and found evidence that this lowered bereavement-related PTSD and depression.

In summary, physician communication is very important for dying patients and their family members. Psychiatric involvement may facilitate this process. Psychiatrists have a role in providing assessment, pharmacotherapy, and psychotherapy. Effective intervention, including acceptance of death as a normal part of life, honest, empathic, and sensitive communication about terminal illness and its prognosis, is an important part of effective palliative care. However, not everyone dies in a palliative care setting. Among those who do not are people who have taken their own lives.

## Suicide

The American Foundation for Suicide Prevention provides useful information for suicidal individuals, their family members, physicians, and the media. Suicide is frightening and stigmatized, and only recently have we begun to learn about its underlying causes. Treatment studies of suicidal patients are still sparse. Suicide is a surprisingly common cause of death. Among the overall population in the United States, it ranks 11th while among people between the ages of 18 and 65, suicide is the 4th leading cause of death. Rates are estimated as 10–20 per 100,000. An estimated 32,439 people die by suicide each year in the US and 1,000,000 worldwide. Elderly white males have the highest rate of suicidality. Suicide is one of the top three worldwide causes of death among 15–44-year-olds. Women are twice as likely as men to attempt suicide, while men are four times more likely to die from suicide. In 2004, suicide was the 3rd leading cause of death among 15–24-year-olds in the US. While suicide rates among this age group doubled from the 1950s to 1970s, there was a steady decrease since 1990. On the other hand, suicide in younger children increased over this time period. Unfortunately, in recent years, the adolescent suicide rate has again begun to climb.

Psychiatric illness is a critical risk factor for suicide. It is estimated that 90% or more of patients who die by suicide have a diagnosable psychiatric condition. Two-thirds of those who complete suicide have a major depression. Looked at from the other side, an estimated 20–30% of people diagnosed with bipolar disorder die by suicide and up to 50% may make a suicide attempt at some point in the illness. Substance abuse is common among people with bipolar disorder and increases the risk of suicide. Substance abuse alone is also a risk factor. Schizophrenia is a risk factor for suicide with an estimated 40% of people with this diagnosis making a suicide attempt. Approximately 10% of people with schizophrenia die by suicide. Other psychiatric disorders associated with increased risk of suicide include PTSD, panic disorder, social anxiety disorder, generalized anxiety disorder, eating disorders, and personality disorders. In the context of an ongoing psychiatric disorder, often untreated, a suicide attempt is triggered by a specific event such as an important interpersonal loss and/or a marked increase in dysphoric affect. Risk factors for suicide include family history and past history of suicide attempts and impulsivity. Dramatic reporting of high-profile suicides by the media has been found to be associated with increased rates of suicidal behavior among viewers or readers of such reports. Among psychiatric patients, a clear relationship has now been demonstrated between suicide attempts and low CSF serotonin levels. However, it is not clear that serotonin active medication is differentially effective in treating suicidality.

There have been relatively few studies of prevention of suicide or treatment of suicide attempts. It makes sense that treatment of individuals with psychiatric problems comprising high risk for suicidal behavior would be an approach to prevention. However, studies targeting suicide as an outcome have been difficult to undertake, in part because of the very low base rate of completed suicides even among ill populations. Additionally, there has been no uniform, reliable manner of assessing different kinds of suicidal behaviors. Researchers and research ethics committees have faced dilemmas in how to recruit and randomize to experimental treatments of individuals at risk for suicide. Nevertheless, studies are beginning to appear. The most impressive one to date is a study of a 10-session cognitive therapy targeting repeat suicide attempts among a group of people who presented to an emergency room following an attempt (Brown et al. 2005). This group of individuals is estimated to have a 30–40 fold increase in likelihood of future attempts compared to individuals who have never attempted suicide. The approach used targeted thoughts, images, and beliefs that occurred just prior to the suicide attempt as well as assistance in coping with stressors. Additionally, the treatment addressed hopelessness, problems solving difficulties, impulse control, social isolation, and adherence. A relapse prevention task conducted in one of the later treatment sessions activated the specific thoughts, images, and feelings associated with prior suicide attempts in order to test the patient's ability to respond to these effectively. Completion of treatment was based on successful completion of this task and additional sessions were provided until this was accomplished. The result of this intervention was a statistically significant 50% reduction in suicide attempts over the ensuing 18 months. This is clearly a very promising approach for suicidal individuals.

There has been considerable recent controversy regarding the relationship between the use of antidepressant medication and suicide attempts. An FDA meta-analysis of pharmaceutical company studies of serotonin active medications in children suggested that there may be an increased rate of suicide among individuals treated with these drugs. These results led the FDA in 2004 to institute it's most severe "black box" warning related to suicide risk for the use of these medications in children. In 2007 this warning was extended to young adults. However, this ruling has been challenged by experienced investigators. Several major problems with the data sets include the fact that suicidal patients were excluded from studies of the medications in question, so information relates only to people without evidence of serious suicidality at baseline (Posner et al. 2007). Additionally, erratic reporting of suicidal behavior, led in some cases to overestimation of risk. Two large naturalistic studies are in press, one evaluating claims data (Simon and Savarino 2007) and another targeting veterans (Gibbons et al. 2007), each showed more suicide attempts prior to instituting SSRI antidepressants. In an editorial discussing this work, Brent (2007) draws attention to the fact that adolescent suicide rates, on the decline during the past decade, began an alarming rise coincident with publicity related to a possible relationship between antidepressant medication and suicide. Taken together, the emerging information suggests that suicide is more likely when serotonin active medications are withheld than when these medications are provided. Additionally, it is very clear that careful clinical monitoring of suicidal individuals is essential to appropriate clinical management. The use of proven efficacious psychotherapy techniques is highly desirable and clinicians treating suicidal patients should learn to provide this intervention.

Among the problems faced by clinicians working with suicidal patients is the management of bereavement among loved ones if the patient completes suicide. Bereavement is widely recognized as one of the most severe of life stressors, and the ensuing period of grief, variable in intensity and duration, comprises a state of distress and impairment that is equal to some of the most debilitating states of anxiety and/or depression. As pointed out by multiple authors, it is only because of the known cause and the universality of the response that we do not consider grief a pathological condition. We now know that a subgroup of people do develop a pathological form of grief, currently labeled complicated grief. This condition arises when grief is complicated by thoughts, images, beliefs, and behaviors, difficulty with emotion regulation, and/or toxic or deficient social supports that impede integration of the experience of the loss. Circumstances of the death can sometimes trigger these complications. Suicide bereavement is widely believed to be one of the most difficult to cope with because of the stigma surrounding suicide and the tendency for caregivers to blame themselves for not preventing the death. A sensitive, available clinician can be helpful in mitigating these painful aspects of suicide bereavement.

## Bereavement and Grief

> "Loss of a loved person is one of the most intensely painful experiences any human being can suffer. And not only is it painful to experience but

> it is also painful to witness, if only because we are so impotent to help. To the bereaved nothing but the return of the lost person can bring true comfort; should what we provide fall short of that it is felt almost as an insult." Bowlby (1980, pp. 7–8)

Bowlby's comments draw attention to the intensely stressful nature of bereavement, as well as the difficulty in trying to help bereaved people. Because it is a confrontation with death, and because loss of an attachment figure dramatically affects one's sense of safety, it is appropriate to consider bereavement as a trauma (Shear and Shair 2005, Shear et al. 2007) However, unlike other traumatic life events, death of a loved one is an expected and universal occurrence. Among the population bereavement is frequent. Given the yearly US death rate of about 2.4 million people, and using an estimated average of four bereaved people for each death, almost 10 million people lose a close friend or relative in the United States each year. As with other traumatic events, the great majority of people weather the storm of such a death. Some even find themselves stronger, having a greater sense of purpose, renewed faith, or a sense of new meaning of life. While bereavement is considered a risk for a myriad of health problems, in fact only a minority develop such problems. For this clinically important subgroup, bereavement leads to long-lasting negative outcomes. Clinicians may see bereaved individuals who continue to suffer for many years following the death of a loved one. In order to treat such people, it is important to understand the mechanisms by which problematic consequences follow bereavement, and to know as much as possible about what is happening when things go well.

A natural biobehavioral grief process, influenced by cultural input, mediates adjustment to loss of an attachment figure. Rather than an effortful, deliberate psychological process ("grief work") with a goal of detachment from the deceased, it now appears that grief is a more automatic process that is enduring yet fluid, and works to facilitate adjustment. The psychiatric literature pertaining to bereavement and grief sometimes uses terms interchangeably. However, to improve communication and precision of thinking, bereavement researchers have suggested that we define **bereavement** as "the objective condition of having lost someone significant" and **mourning** as "the actions and manner of expressing grief, which often reflect the mourning practices of one's culture" (Stroebe et al. 2001, p. 5). **Grief** is the reaction to bereavement. Different designations have also been used to refer to the clinical syndrome that occurs when the progress of grief is blocked. Currently, the most commonly used designation is complicated grief. From descriptions in the literature, it is clear that this is the same condition as pathological, unresolved, delayed, chronic, or traumatic grief. Since the loss of an attachment figure is the most devastating type of bereavement, we include a brief summary of current thinking about the nature of these relationships.

John Bowlby (1980) introduced the idea that attachment has a biological basis and is important throughout the life span. Subsequently, investigators have demonstrated that an attachment relationship can be identified as a person (1) who is a target of proximity seeking, (2) from whom separation is resisted, (3) to whom a partner turns to for "safe haven" when under stress, and (4) serves as a secure base from which the partner freely interacts in the world, seeking novelty, taking risks, and exploring the unknown (Hazan et al. 1999, Feeney 2004).

Mental representations of attachment relationships enable older children and adults maintain a sense of attachment in the absence of physical proximity to a loved one. Also called "working models," such mental representations devolve from repeated salient experiences with the attachment figure. Information provided by a working model is continuously matched with information derived from experiences pertaining to the relationship it represents. However, once established, the working model does not easily change its configuration (Bretherton 1999). Only in the context of a consistent mismatch, is the working model revised. Given this view of working models, it is clear that these mental representations need to undergo profound change when an attachment figure dies, and also that this change will not occur quickly. This means that bereavement is associated with a temporary impairment in functioning of the attachment system.

Numerous studies have shown that internalized cognitive representations of attachment relationships are activated upon exposure to stress (e.g., Mikulincer et al. 2002, 2003, Pereg and Mikulincer 2004) and that the security of such relationships influence the perception of available social support (Collins and Feeney 2000). Attachment security influences cognition, emotion, and behavior, especially with respect to interpersonal functioning, and may affect other psychological and physiological functions. Individuals with stable secure attachments have been repeatedly shown to be psychologically healthy and resilient. Those with anxious and fearful attachment often have difficulty with affect regulation (Mikulincer et al. 2003) and so experience heightened levels of negative emotions, including sadness, anger, shame, and anxiety as well as lower positive emotions. These people tend to experience low self-esteem and low confidence in the esteem of others, often enter into dependent relationships, and are especially vulnerable to stress.

Attachment security also contributes to motivation for interactions in the world. Thus, the attachment system modulates the activity of the exploratory system (Elliott 2003). The latter, in turn motivates active interest in the environment, needed for learning and overall effective functioning in the world. A physically accessible and emotionally responsive caregiver who provides a sense of security facilitates exploration and learning and minimizes fear. In other words, the biobehavioral systems for attachment, fear, and exploration are linked. Considering that the death of a loved one disrupts attachment functioning, there is associated inhibition of the exploratory system as well as impaired regulation of fear and other emotions.

An important aspect of adult attachment relationships is that caregiving is as important as receiving care (Feeney and Collins 2001, 2003). Among those who lose a loved one, and a child in particular, effects on the caregiving system are likely to be dominant. A very typical though often neglected aspect of grief is the occurrence of self-blame, related to the caregiving function. In summary, the experience of acute grief is characterized by aspects of a trauma relationship, impairment in attachment functioning, inhibition of exploratory functioning, impaired emotion regulation, and a tendency for caregiver self-blame. It is useful to

think of acute grief as having these components. Over time, as the loss integrated, the grief response is also integrated. The trauma is resolved, attachment functioning is re-established, interactions with the world resume, along with effective emotion regulation and resolution of self-blame.

Ideas about grief were outlined by Freud and/or Bowlby. According to Freud and his followers effective adjustment to bereavement requires a period of "grief work" While not explicitly defined, and sometimes misconstrued to mean intense emotional pain, the grief work idea has some merit. The idea is that through a process of "reality testing" in which there is repeated confrontation with unpleasant reminders of the loss, the bereaved person eventually accepts the reality of the loss, and feelings of intense sadness and yearning subside. Unless this is accomplished, the bereaved person remains shackled through an ongoing, unrevised attachment to the deceased. Continued longing and searching for the deceased restricts the freedom of a bereaved person, especially the ability to deeply engage with the living. These people remain preoccupied with thoughts of the deceased loved one, and continually laden with pain and suffering caused by their loss.

Most of these ideas hold true, although often a strong sense of connection to the deceased person remains, even after the loss has been integrated and acute grief subsides. Additionally, there is a new model, supported by some empirical data, that posits coping with bereavement entails coping with a number of different kinds of stressors that can be broadly grouped as restoration-related or loss-related (Stroebe and Schut 1999). Another difference is that the traditional model considers pathological grief to be the consequence of an ambivalent relationship. However, complicated grief appears to occur instead when someone has lost a very special and very positive relationship. Table 120–2 lists some common ideas about grief, and the empirical findings related to these.

Bereavement is widely understood to be a severe stressor. In fact, as Stroebe and Schut (1999) point out, loss of a loved one is not one stressor, but rather a number of simultaneous stressors. Our close friends and family members touch many areas of our lives. When we lose them, our lives are profoundly changed and we must adjust to the changes. Some aspects of bereavement are related to the loss. Loved ones provide us with a sense of purpose. We do things to make them feel proud, to bring them happiness, to keep them close and to help them feel safe. A close relationship is an important source of pleasure and solace. We may attain social status, financial security, and/or self esteem from our relationships with people we love. These are the people who bolster our confidence, help us feel important and proud of ourselves. Our loved ones provide a sense of balance and completeness. They comfort us and humor us when we are feeling vulnerable or hurt. Bereavement entails loss-related stressors such as these. In addition to psychological support, people we live with may regulate our neuroendocrine system, influence our sleep and social rhythms, and provide myriad of small cues that can trigger conditioned emotional responses. Places and things may have special meaning because of associations with a loved one. Activities may be satisfying because they are shared.

Other aspects of adjustment to an important loss are related to how we organize our lives without the person who died. These restoration-related stressors entail taking care of things related to the death, such as disposition of the body and arranging the funeral or memorial service, as well as disposing of personal possessions, managing financial matters and taking on household tasks that were previously done by the deceased person. Social life is reorganized; it may be necessary for someone who was staying at home to become employed. There may be children or other dependents that need to be looked after. Different kinds of plans may need to be changed. Thus, bereavement is not one, but sometimes a virtual encyclopedia of severe stressors.

The stress of bereavement clearly requires active coping. Some information is available about which coping methods are adaptive which are not. Folkman outlines models of coping that she and her colleagues have developed. First, they define coping as "the changing thoughts and acts that an individual uses to manage the external or internal demands of stressful situations." They remind readers that coping and mastery are not the same things. Additionally, coping occurs in an environmental context, that it is a continually unfolding process that may change over time following the stressor. Coping with a specific stressor is usually multidimensional with some problem-focused and some emotion-focused strategies, some approach and some avoidance, and some interpersonal and some intrapersonal.

Bonanno (in Stroebe et al. 2001) employs a social-functional model in considering the emotional response to bereavement. This empirically based model posits an association between negative affect, disrupted social relationships, and later physical and mental health problems across a range of situations. Thus, in contradistinction to traditional ideas about "grief work," a social-functional perspective predicts that internal psychological functioning and adaptive social functioning are impeded by painful negative emotions and enhanced by positive emotions. Studies of bereavement of AIDS caregivers also support the importance of positive mood states in adjustment to

**Table 120–2 Two Forms of Grief**

| Acute Grief (Transient absorbing state; emotionally painful and preoccupying) | Integrated Grief (Permanent background state) |
|---|---|
| Waxing and waning sense of disbelief, difficulty comprehending and/or accepting reality of the death | Comprehension and acceptance of the reality of the death |
| Frequent compelling intrusive memories, thoughts, and images of the deceased; preoccupation with thoughts of the deceased | Memories, thoughts, images accessible, less frequent and compelling; thoughts are not preoccupying |
| Mix of emotions, painful ones usually dominant and intense | Mix of emotions, mostly bittersweet or positive, less intense and frequent |
| Little interest in ongoing life, sense of uneasiness in interacting with others | Reengagement in ongoing life, comfort and confidence in activities and relationships |

bereavement (Moskowitz et al. 2003). With the exception of a few weeks immediately after the death, positive mood states were as prevalent among AIDS caregivers as negative ones during both caregiving and bereavement. Active problem solving and positive reappraisal were important in maintaining positive mood states, and these, in turn helped foster more adaptive coping. This work supports the idea that good grief outcome is as strongly related to the presence of positive mood as to the absence of negative feelings.

Wortman and Silver (1989) wrote a seminal paper challenging traditional concepts of grief, which they described as myths. They concluded that it was not proven that grief work was essential to enable the bereaved to come to terms with their loss. They identified two patterns of normal grieving, one in which a bereaved person moves from high to low emotional distress over time and the other in which people never experience high distress. A third grief trajectory is that of persistent high distress, continuing for years. This is the pattern of complicated grief.

Follow-up studies have continued to find little evidence that low levels of negative emotions and/or absence of a period of preoccupation with the deceased leads to poor adjustment. There is no evidence that early grief intensity is inversely correlated with later pain. Instead, the opposite seems to be true. Stroebe et al. (2002) examined the relationship between self-reported disclosure and emotional distress at 4, 11, 18, and 25 months after the death of a spouse and found that greater distress predicted more disclosure, rather than disclosure predicting lower subsequent grief. In a second study (Stroebe et al. 2005), they compared grief outcome in bereaved widows randomized to keeping a diary about emotions and/or bereavement-related problems to a control group who kept no diary. Intrusion and avoidance symptoms, as well as depression, anxiety, and somatic symptoms, present at baseline decreased over time (1 week and 6 months) in all groups. Frequency of disclosure of emotions, or reported need for disclosure did not moderate these results. These authors conclude that intervention is not needed for bereaved people who do not seek help.

Researchers have also reconsidered the idea of detachment from the deceased. Freud rethought his ideas about bereavement following the death of his daughter, expressing a newer view in a letter to a friend, "Although we know that after such a loss the acute stage of mourning will subside, we also know we shall remain inconsolable and will never find a substitute. No matter what may fill the gap, even it be filled completely, it nevertheless remains something else. Actually, this is how it should be. It is the only way of perpetuating that love which we do not wish to relinquish (1961a, p. 239) (pp. 207–208). In line with this idea, investigators (Richards et al. 1999) studied bereaved male partners of men dying from AIDS more than 3 years after the death and found 70% reported a continuing relationship with the deceased. This sense of inner relationship with the deceased partner did not correlate with distress.

Field and colleagues reported a series of studies of continuing bonds (Field et al. 2003, 2005, Field and Friedrichs 2004, Field 2006a, 2006b). Results suggested that some types of continued connection with the deceased were associated with more prolonged grief. However, grief was not more intense when the connection was related to thoughts about how a deceased spouse made a difference in the life of the bereaved person, or gaining enjoyment from reminiscences about the deceased. These researchers highlight the distinction between behavioral manifestations of continuing bonds, as compared to an internal state of felt-connectedness. The internalized representation seems to allow the deceased to play a sustaining role in the emotional life of the bereaved person that is not inconsistent with the reality of their death. Once integrated in this way, thoughts and memories of the deceased continue to grow and change (Neimeyer et al. 2002).

Sociocultural factors often play a role in grief and mourning. Perhaps more than most stressors, bereavement is a public event that occurs in a larger social context. Most cultures provide rules for the disposition of a deceased body, and some supply procedures for disposing of the belongings of the decease. Cultures frequently contain beliefs about the proper public expression of emotions and private thoughts, and about the need to confront or avoid emotionally provocative situations. Religion has an obvious place in the process of coping. Death rituals and customs are universal components of religious rites. One way cultural/religious practices exert their influence is through directives regarding the expression of emotion after a loss. Formal ceremonies often encourage the bereaved to confront and release emotions. However, the value placed on emotional expression varies in different cultures. For example, in some cultures, emotional expression is thought to be a threat, interfering with good judgment, and affecting others, as well as oneself. In others, open display of emotions is thought to be needed in order to cleanse the soul. In some cultures ancestors, who have the power to do harm to the bereaved, are thought to be offended by excessive show of emotion. In some cultures there is a focus on working through grief in order to distance oneself from a deceased loved one, while in others the emphasis is on maintaining a relationship with the dead ancestor who is treated as a living person, being offered food and other things, and seen as remaining present in the life of the bereaved (Yamamoto 1969).

Religious beliefs help mourners envision a transition of their loved one to a final resting place. This provides an important form of continuity with the person who died. Being able to imaginally locate a deceased person seems to be helpful in the process of coping with the death, especially if this contains an idea that the spirit is at peace. Religious rituals also focus on marking a separation of the dead. In some cultures, a change in residence is prescribed, along with removing all physical reminders of the dead and avoiding mention of the name of the deceased. Some native American tribes have a 4-day accepted length of mourning after which person is expected to return to normal life and neither speak of the deceased nor discuss personal feelings about the loss. These practices are associated with a belief that too much emotion is offensive to the deceased. Interestingly, and in line with findings from naturalistic studies summarized above, it has been reported that members of cultures with such final ceremonies appeared less likely to experience chronic grief. Many religious practices dictate a prescribed period of mourning. For Jews, after a year of mourning there is an unveiling ceremony at the grave site. Clothes that were rent at the time of the death are mended and worn as a sign that life, though scarred, must go on.

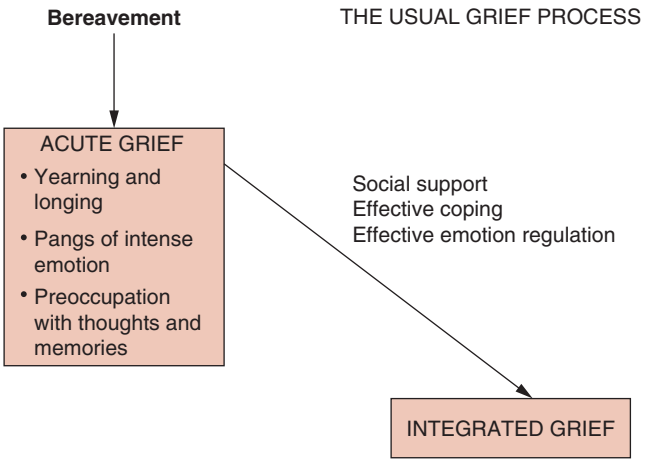



**Figure 120–1** *The trajectory of normal grief.*

In summary, the usual trajectory of grief following loss of someone very close (see Figure 120–1) is for the bereaved person to experience acute grief lasting weeks to months and characterized by symptoms related to (1) trauma (e.g., disbelief, intrusive thoughts and memories, a tendency to avoidance); (2) an activated malfunctioning attachment system (e.g., longing, yearning, searching for the deceased, sense of insecurity or self doubt, intense sadness); (3) emotional and physiological dysregulation; (4) thoughts and feelings of self blame; and (5) inhibition of interest and engagement with ongoing life. In the context of cultural rituals and social support, acute grief usually subsides, transitioning to a state of integrated grief. When loss and grief have been integrated, memories and thoughts are no longer preoccupying. Longing, yearning, and searching lessen. Emotional and physiological regulation is reestablished. Feelings of security and self-confidence are restored, and there is renewed interest and engagement in ongoing life. Metaphorically speaking the deceased loved one has moved from preoccupying the mind of the bereaved person to residing comfortably in her heart. Sometimes, this progression does not occur smoothly and bereavement triggers the onset of a psychiatric disorder, most commonly major depression or PTSD. In addition, for an estimated 10–20% of bereaved people (roughly 1 million people per year) the loss is not integrated and the debilitating chronic condition of complicated grief supervenes.

## Bereavement-Related Depression and Anxiety

Grief resembles depression in the prominence of sadness, loss of interest in ongoing life, and the frequent occurrence of sleep and appetite disturbance and a sense of remorse or guilt. However, grief can also be distinguished from depression. A careful longitudinal survey of spousally bereaved individuals documented an occurrence of major depression of 10–15% over the year following bereavement (Zisook et al. 1994). Rates are higher transiently in the early bereavement period but even then, only 30% met criteria for MDD. A recent study shows that depression in the first 2 months of bereavement can be treated with antidepressant medication (Zisook et al. 2001). Although the DSM currently includes an exclusion for major depression in the first 2 months of bereavement, there is good evidence that bereavement-related depression is not different from depression following any other kind of life stressor and should be diagnosed and treated (Zisook and Kendler 2007, Zisook et al. 2007).

PTSD criteria in DSM-IV-TR include the death of a loved one only if this occurs suddenly and unexpectedly. However, again, studies have documented that PTSD does occur in the wake of bereavement from other causes (Zisook et al. 1998). In fact, in at least one community sample, bereavement was the most common trigger of PTSD (Breslau et al. 1998). As discussed above, loss of an attachment figure is a trauma and typically triggers a response similar to other traumas, that includes a sense of disbelief and a mixture of intrusions, alternating with avoidance. However, grief also differs from other trauma responses in that the prominent emotion is sadness and there is intense yearning and longing not usually seen following a trauma. Individuals with bereavement-related PTSD are sometimes included in treatment studies, and, similar to MDD, do not seem to comprise a clinically meaningful subtype. On the other hand, the trauma-like reaction of complicated grief does differ from PTSD.

## Complicated Grief

Clinicians have long recognized the problem of prolonged intense grief reactions. These have been labeled in various ways, including pathological, unresolved, chronic, delayed, traumatic, or complicated grief. In recent years, researchers have devised reliable ways to assess a syndrome, currently designated as complicated grief, that is believed to be the same condition as these variously named syndromes. The hallmark of complicated grief is persistence of the symptoms of acute grief well beyond the time they would be expected to subside. Grief is prolonged by complicating biological, psychological, and/or social-environmental problems. People with this condition continue to have difficulty comprehending the death, and experience acute grief as though their loved one had died very recently. Additionally, they exhibit negative cognitions related to grief intensity (e.g., fear, embarrassment, or shame regarding their own emotions) and/or catastrophic misinterpretation of the consequences of separation (e.g., ideas that they cannot survive or function without the person who died; thoughts of betrayal or guilt regarding the death) and disruptive behaviors (e.g., impairing avoidance and/or compulsive proximity seeking), ineffective emotion regulation and/or social-environmental toxicity or resource depletion (see Figure 120–2).

Complicated grief is a chronic debilitating syndrome that has been found to be associated with suicidal ideation, serious work and social impairment, long-term health problems (e.g., cardiovascular and neoplastic illness) (Prigerson et al. 1997) and substance abuse. The condition is not currently identified in the DSM-IV-TR but it has been recognized by the psychiatric editor of JAMA as having the features of an illness (Glass 2005). Work is underway to present this condition for inclusion in the DSM V. Complicated grief does not respond to standard treatments for depression (Reynolds et al. 1999). A recently completed study of a targeted treatment resulted in better response than a standard grief-focused psychotherapy (Reynolds et al. 1999). Open trials show some response to antidepressant medication; however, randomized controlled trials have not been done.

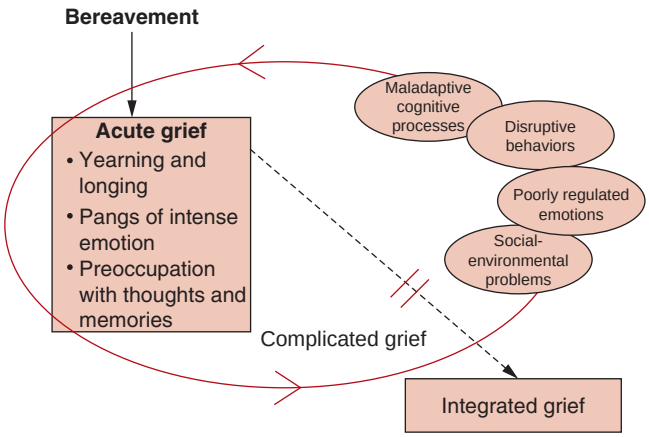



**Figure 120–2** *Complicated grief: A closed loop.*

In summary, psychiatrists encounter death and bereavement in many aspects of their work. Psychiatrists can be helpful in the assessment and treatment of dying patients and their caregivers. Psychiatrists play a central role in the management of suicidality. There are an estimated 10 million bereaved people every year in the United States, and approximately 10–20% of these people will suffer from bereavement-related psychiatric illness. It is important that psychiatrists understand how to diagnose and treat people suffering from mood and anxiety disorders and complicated grief that occur in the wake of bereavement.

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CHAPTER

# 121 Serving People Who Have Mental Illness and Homelessness

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A broad shift in the American economy away from a manufacturing base, combined with related housing shortfalls, ushered into the 1980s a social epidemic of homelessness that continues today (Koegel et al. 1988, U.S. Conference of Mayors 2006). It swept mentally ill persons into particular vulnerability and public attention. This chapter reviews the historical evolution of services for people with mental illness and homelessness and describes a resultant model of care, accentuating psychiatry's role.

## Background: The Evolution of Services

The plight of people with mental illness and homelessness prompted an evolution of specialized services that is understandable in terms of four phases that are demarcated by gradual developments at federal, state, and local levels.

### Phase One: Ad Hoc Service Delivery and Early Epidemiology (1978–1986)

In November 1978, the advocacy group Community for Creative Nonviolence occupied the National Visitor's Center in Washington, DC, USA. This protest was a touchstone moment, bringing into focus a "new" national crisis of homelessness and creating a context for events that quickly unfolded across the country. Although there were already scattered reports of a new generation of mentally ill "street people," by 1981 scholars and social activists around the country were describing an overwhelmed constellation of shelters and soup kitchens that were lodging more and more people with psychiatric disorders (Baxter and Hopper 1981). The appearance of homelessness, juxtaposed with a transition to a service economy that reduced unskilled employment; an emerging low-income housing shortage; and the decline of census in hospitals, led some observers to cite this epidemic among the mentally ill as an unforeseen by-product of deinstitutionalization (Lamb 1984a, 1984b). For example, in 1970, there were 413,066 beds in state and country mental hospitals in the United States. By 1988, these had diminished to 119,033 and by 1998, the decline had continued to 63,526 (Manderscheid et al. 2000).

Population data and funding for needed mental health services were scant or nonexistent and effective methods of service delivery had yet to be developed. Until 1986 there were virtually no federal funds allocated for service delivery. Without adequate information on how to construct a rational service system or federal funding to support services, localities funded programs in an ad hoc manner. While some communities used limited local funds to develop programs, others sought legal remedies to force the homeless off the streets—or out of town. Almost all municipalities had huge service gaps and most had no services at all (Table 121–1).

The patchwork of mental health services that were implemented included a few street outreach programs and mental health services grafted onto preexisting shelters, mission houses, and soup kitchens (Axleroad and Toff 1987). These early programs run by community-based

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**Table 121–1 Factors Contributing to the Growth of the Homeless Population with Serious Mental Illness**

| |
|---|
| Macroeconomic changes |
| Low-income housing shortages |
| Declining state hospital census/de-institutionalization |
| Paucity of mental health professionals working in nontraditional settings, |
| Increasing numbers of patients with untreated/under-treated mental illness and/or substance abuse |
| Limited federal and local funding |

organizations (CBOs) focused on food, clothing, and a place to sleep as a first step toward medical and psychiatric treatment.

There was growing professional attention to the kinds of services, as evidenced by recommendations of the APA Task Force on the Homeless Mentally Ill, for outreach, assertive treatment, rehabilitation, and housing (Lamb and Talbott 1986). Despite this, there were no financial, legal, or other incentives to promote change in medical environments. There were very few psychiatrists working in nontraditional settings, and it was increasingly clear that traditional psychiatric providers, such as community mental health centers and hospitals, had largely failed to adequately engage mentally ill homeless patients (Cohen et al. 1984).

To begin to help address huge service gaps, in 1986 the Robert Wood Johnson/Pew Healthcare for the Homeless initiative was funded (Goldman et al. 1994). This key early initiative began to bring integrated healthcare to many people who were homeless across the country, with a few of its programs providing mental health services.

Simultaneously, state and local resources began to fund studies of homelessness (Morse et al. 1985, Roth et al. 1985, Struening 1986) and enterprising investigators piggybacked such studies onto other efforts. Toward the end of this phase, a series of well-designed research projects (Susser et al. 1993a) contributed the first epidemiological database on the scope of homelessness, the risk factors for it, and potential for preventive strategies (Susser et al. 1987, Belcher 1988, Weitzman et al. 1992). Reliable studies describing psychiatric disorder show reasonably consistent rates ranging between a third and a half of single adult homeless people with severe psychiatric disorders, either major mood disorder (20−30%) or schizophrenia (10−15%) (Roth et al. 1985, Koegel et al. 1988, Breakey et al. 1989, Susser et al. 1989). The phenomenon of co-occurring chemical dependence and mental illness also began to receive attention (Drake et al. 1991).

## Phase Two: Service Development (1987–1992)

The Stuart McKinney Homelessness Assistance Act of 1987 marked Phase Two. Known now through its several amendments as the McKinney-Vento Act, it signified national recognition of the intransigence of homelessness, setting up an interagency governmental council to administer an appropriation in its first year of $350 million (adjusted to year 2000 dollars) to support food, housing, education, shelter, medical care, and mental health services (Foscarinis 1996). By 2000, this had increased to $1.2 billion. Demonstration projects integrating housing, intensive case management, and mental health treatment were established in nine geographically dispersed cities.

The introduction of new funding streams reinforced the development of programs for the mentally ill homeless that had by then begun in many urban areas. The greatest innovation came from staffs of nonprofit CBOs which had both the administrative flexibility and a history of working in nontraditional settings to enable them to transition to service delivery for mentally ill homeless people (Dincin et al. 1995, American Psychiatric Association 1997). Conversely, traditional settings, like hospitals and clinics continued to show limited inclination to meet the service needs of mentally ill homeless people. However, there were exceptions, and a few hospitals experimented with shelter-based services (Caton et al. 1990). New York's Bellevue Hospital created a specialized admission and inpatient service in conjunction with a state hospital and an innovative street outreach team empowered to involuntarily transport people to its emergency room (Katz et al. 1993). So, as Phase Two developed beyond a few well-funded model programs that included psychiatry, only a small number of motivated psychiatrists explored care, largely through their own initiative (Arce et al. 1983, Cohen et al. 1984, Lipton et al. 1983, Susser et al. 1990) and often on a volunteer basis (American Psychiatric Association 1986, American Psychiatric Association 1991a).

Research did continue to develop through this phase. Under McKinney funding, research dollars grew through NIMH and other federal sources and a crucial series of clinical trials were undertaken to test strategies for relief of the homeless among mentally ill individuals. The publication of the findings would appear in the next phase of care.

## Phase Three: Refined and Elaborated Services (1993–2002)

Through the 1990s, the epidemic of homelessness developed to an endemic status. Although on a local level the picture has widely varied, some communities tacitly acknowledged the endemic nature of homelessness by creating bureaucracies for services to homeless people. In 1993, for example, New York City created its Department of Homeless Services to oversee and manage programming in a large municipal shelter system.

During Phase Three, much of the research represented an extension of the epidemiological base already developed. However, five new developments that further underscore the social permanence of homelessness merit noting.

First, research emerged indicating that homelessness is more prevalent than had been understood even by some advocates. Two milestone studies independently estimated that approximately 3% of Americans experienced homelessness in a previous 5-year period (Culhane et al. 1994, Link et al. 1994). Second, the frequency with which families are afflicted by homelessness was brought to greater attention and as of 2001, families represented about one-third of the homeless population, and in many regions were its fastest growing segment (U.S. Conference of Mayors 2001). Third, the emergence of high rates of HIV and tuberculosis (TB) among homeless populations in general, but also specifically among the mentally ill homeless, has been documented, accentuating issues of medical disability. These epidemics have contributed to mortality as well as to the complexity of clinical care.

Fourth, the field began a quest for evidence-based interventions. Assertive community treatment (ACT) (Lehman et al. 1997), supported employment (Bond et al. 2001), and critical time intervention (CTI) (Susser et al. 1997) are examples of services under exploration. The CTI approach focuses on the power of the rehabilitative relationship of case management to assist people as they adapt to new housing and service providers during "critical" transitions. CTI case managers provide extended follow-up, advocate for, and assist their clients as they begin to form new helping relationships through housing programs. Sheltered mentally ill homeless men in CTI have been shown to spend significantly fewer nights than non-CTI cohorts over an 18-month period (30 versus 91 nights).

Without effective rehabilitative intervention, mentally ill homeless people lose housing and often occupy a closed circuit between shelters, hospitals, and incarceration (Hopper et al. 1997). As part of this initiative, and encouraged by epidemiological research, federal and local agencies pursued more systematic approaches to care. In 1994, the US Department of Housing and Urban Development began requiring its housing grantees to provide a "continuum of care" (Barnard Columbia Center for Urban Policy 1996). McKinney funding made possible the multicenter Access to Community Care and Effective Services (ACCESS) program, a major initiative evaluating local models of integrated service (Calloway and Morrissey 1998).

Finally, an influential study by Culhane et al. (2002) explored housing's effect on the costs associated with a person's use of services. Analyzing New York City utilization data concerning 4,679 homeless people placed in supportive housing, and using matched control groups, this investigation documented that 95% of the annual cost of supportive housing in the first two years after placement was offset by cost reductions in shelter, health, and mental health services.

## Phase Four: Outcomes for a Heterogeneous Population (Since 2003)

The Culhane et al. (2002) study heralded deeper understanding by government policymakers that data analysis is practical in service planning. This has influenced a coalescence of policy vision in the first decade of the new century.

Research has also tracked epidemiological shifts. Although there have yet to be a new generation of epidemiological studies of homelessness similar to those carried out in Phase One, there is evidence of an increase in psychopathology. North et al. (2004) analyzed comparable data from 1980, 1990, and 2000 among the adult homeless population of St. Louis, Missouri, USA and discovered that Axis I disorders have increased over the past two decades, notably mood disorders and, dramatically, chemical misuse. In 2000, among 396 homeless single individuals, 84% of men and 58% of women had an alcohol or other chemical misuse disorder, accounting for a majority of overall psychopathology. In a sample of homeless single adults in Grand Rapids, Michigan, USA, Forney et al. (2007) uncovered similar chemical misuse findings (77% of men and 55% of women) and a diagnosis of mental illness in 35%.

Another finding is population heterogeneity among homeless people with psychiatric disorders, leading to programming interventions. For example, during 2006, family units with children were estimated to still comprise between 30% of the American homeless population and therefore represent the single largest bloc of homeless individuals (U.S. Conference of Mayors 2006). Single women usually head homeless families (Smith et al. 2005). Household conflict, violence and sexual trauma, substance use, and individual mental problems fit prominently into the experience of homeless mothers (Banyard and Graham-Bermann 1998, Bassuk et al. 1998, Bogard et al. 1995, Zima et al. 1996, Shinn and Weitzman 1998, Burt et al. 1999). Studies have shown that children and adolescents in shelters with their families appear to have worse health, mental health, behavioral, and educational outcomes than middle class children—and often worse than other poor children (Molnar et al. 1990, Rafferty 1995, Rafferty and Shinn 1991, Shinn and Weitzman 1996).

There has been substantial growth in the development of supportive housing and other programs to assist homeless families as they reestablish residences in the community. Unfortunately, the bulk of research on these programs is evaluative or descriptive in nature with little research on effectiveness (Rog 2004, Nolan et al. 2005). An exception is adaptation of the CTI model to this population which attempts to quickly move families from shelters using intensive short-term case management, focusing on any of the above noted vulnerabilities (Felix and Samuels 2006). The program has shown significant benefits to children engaged in CTI concerning a range of maladaptive behaviors and other psychiatric symptoms, as well as attitudes toward school (Samuels J and Shinn M, unpublished report).

An outgrowth of family distress is the phenomenon of unaccompanied homeless youth. Estimates of the size of this population ranges from 575,000 to 1.6 million per year (Hammer et al. 2002, Thompson et al. 2002). Homeless youth are typically described by the circumstance of their homelessness: runaways, throwaways, and street youth (Green et al. 1995) and adolescents who become homeless upon release from the juvenile justice system and/or age out of the foster care system.

There are over a half a million children in foster care in the U.S. (U.S. Department of Health and Human Services 2005) and approximately 20,000 per year age out of that system (U.S. Department of Health and Human Services 1999). One large follow-up study of aging out youth, the Midwest Evaluation (Courtney et al. 2006), found that at age 19, many leaving foster care are neither employed nor in school and many young women have children who they are unable to care for. Studies of residential instability among youth aging out of foster care consistently show rates of at least one night of homelessness that range from 10-35% (Cook 1991, Casey Family Programs 2003, Mason et al. 2003, Reilly 2003, Courtney et al. 2006). Regardless of their trajectory to homelessness, homeless youth also have a history of academic difficulties and social and behavioral problems (Clark and Robertson 1996). Many have had traumatic experiences such as extreme family conflict, separation from parents and siblings, and a history of residential instability. It is no wonder that they have been found to be at high risk for mood disorders, suicide attempts and post-traumatic stress disorder (PTSD) (Powers et al. 1990, Greenblatt and Robertson 1993, Rotheram-Borus 1993, Clark and Robertson 1996, McCaskill et al. 1998, Fronczak and Toro 2003) and chemical misuse (MacLean et al. 1999, Baer et al. 2003, Thompson et al. 2003, Van Leeuwen et al. 2005). Typically,

services for homeless youth are either outreach services or shelter-based with case management (Toro et al. 2006). Since the most consistent reason for youth homelessness is family conflict (Sanabria 2006), services often include family conflict resolution and reunification. Poignantly, intervention studies for this population have failed to keep pace with comparable initiatives for adult mentally ill homeless populations.

During Phase Four, people released from incarceration have gained increasing prominence among mentally ill homeless populations. First, there is evidence that an arrest history increases the duration of even first-time homelessness (Caton et al. 2005). Second, there is a backdrop of data showing that 24% and 21%, respectively, of individuals in state prison and jail are diagnosed with a psychiatric disorder and that mentally ill inmates are twice as likely to have been homeless in the year before incarceration (James and Glaze 2006). This offers scope to knowledge that homeless ex-offenders face a variety of unmet medical, chemical dependency, and mental health needs (Kushel et al. 2005). Projects have appeared that focus on inmate community re-entry and on diversion from incarceration for people with mental illness, yet there are few programs that specialize in the mentally ill homeless subpopulation. Examples of innovative programs combine housing with teams that resemble an ACT model (Project Renewal 2006).

And if homelessness is endemic and fully eradicated only with broad economic and social policy change, a new national effort to at least end *chronic* homelessness has now emerged. Chronic homelessness arguably presents especially dire consequences, with both personal demoralization and high societal cost. For example, data from New York City's municipal shelter system show that 50% of shelter bednights are occupied by the 16% of homeless adults who have spent at least two of the past four years in shelter (City of New York 2005).

Consistent with the findings of Culhane et al. (2002), resources for shelter could be better used for housing and related supports. This was the basis of two 2003 federal reports (U.S. Department of Health and Human Services 2003, Substance Abuse and Mental Health Services Administration 2003) citing chronic homelessness as particularly pernicious, especially among those with mental illness and chemical misuse. In 2003, the federal government outlined its "blueprint" for ending chronic homelessness among people with mental illness, identifying a need to integrate services, to provide adequate financing, and to use evidence-based and promising practices. It also articulated two relatively novel concepts for the field: adopting the recovery paradigm and measuring programmatic results.

These developments coincide with emerging understanding that people with mental illness experience a process of recovery. Recovery, as such, does not signify "cure," but denotes the personal odyssey of reaching self-defined goals, marked by hope and the development of relationships, work, and for some, spirituality. Recovery's application to mentally ill homeless people lies at the core of reintegration to the mainstream. Services aimed at this population must therefore show concrete outcomes consistent with these values, perhaps the foremost of which is successful housing.

Toward measuring outcome, in 2004, the Federal government resurrected the Federal Interagency Council on Homelessness, first created by McKinney funding in the late 1980's, pooling policy initiatives towards ending chronic homelessness, challenging states and localities to create ten year plans to do so. By 2006, this call to action yielded over two hundred states and localities to create such plans. In New York City, for example, efforts to reduce chronic homelessness by this proportion within five years has led to new initiatives in reorganizing street outreach services, with targets for providers to rapidly house street people (City of New York Departments of Homeless Services and Health and Mental Hygiene 2006).

The need for outreach to rapidly house people continues to be challenged, however, by relentless pressures on low-cost housing and real estate (New York Times 2006). Simultaneously, well-serviced shelter care is viewed as costly. Some localities see economical opportunities in funding "housing-first" models that directly place people into available housing that serve in a transitional or permanent manner, also providing different measures psychosocial support (Chicago Continuum of Care 2003, City and County of San Francisco 2004). These approaches challenge a traditional wisdom developed during Phases Two and Three of a "continuum" model of building services to gradually move a person from street to shelter to transitional, then permanent housing (Federal Task Force on Homelessness and Severe Mental Illness 1992) and have initiated debate concerning the differential application of these models. As discussed below, research has yet to offer clear guidance on housing approaches amply adapted to the heterogeneity of persons with mental illness and homelessness (Table 121–2).

Finally, though full discussion is beyond our chapter's scope, the social and economic underpinnings of homelessness in other developed countries are similar to those in the US, though with national and regional texture. For example, in the European community, immigration has been cited as a particular stress on housing, as well as having a role in creating social exclusion (Edgar 2005). It is generally believed that the magnitude of post-industrial homelessness, especially street homelessness, is not usually as great as in the

**Table 121–2 Historical Phases of Services Development for the Mentally Ill Homeless**

Phase One: Initial Responses to Homeless People with Serious Mental Illness (1978–1986)
- Outreach
- Shelters, mission houses, soup kitchens
- Private grant funding initiatives

Phase Two: Early Organized Service Development (1987–1993)
- Federal funding
- Delivered by non-profit, community based organizations
- Increasing research dollars
- Paucity of organized psychiatric response

Phase Three: A Need for Enhanced Services (1993–2002)
- Mounting numbers of homeless families
- Escalating medical problems (TB/HIV/HepC)
- Limited rehabilitation focus (ACT or supported housing)

Phase Four: A New Focus on Outcomes (Since 2003)
- Ascendance of data analysis in public behavioral health policy
- Homeless population heterogeneity
- The recovery paradigm
- A focus on chronic homelessness
- Alternative service models

United States, but prevalence rates are difficult to evaluate because of differing definitional and methodological approaches (Edgar 2005), thus limiting focused public health intervention. European national policies on solving homelessness have varied from robust, as in the UK's Rough Sleepers Strategy, to nearly invisible (European Federation of National Organizations Working with the Homeless (FEANTSA) 2004, Edgar 2005).

## The Stages of Care

Through these phases of evolving services, a method of engagement and reintegration of mentally ill homeless people has effervesced. It is useful to consider this methodology as an overlapping, stage-wise process from the street (Susser et al. 1992), leading to housing, work, and reestablishing lost social ties. Depicted schematically in Figure 121–1, the current conceptualization of these stages is described in terms of (1) engagement, (2) intensive care, and (3) ongoing rehabilitation. Although these rehabilitative stages might apply to people who are not homeless, they take on a primary application with homeless people, especially considering an often-prolonged engagement and usually very complex treatment process.

Within the stages, there exists a range of services and technologies that are themselves on different levels of development. Furthermore, as we describe below, in most cases care actually begins prior to any contact with mental health professionals, especially psychiatrists (Figure 121–1).

### Engagement

Classically, the first point in the continuum of services is street outreach. Street outreach programs were among the earliest novel interventions in the development of homelessness services, responding to the need to engage a very disaffiliated population of potential clients. Teams of human services workers, many of whom themselves have histories of

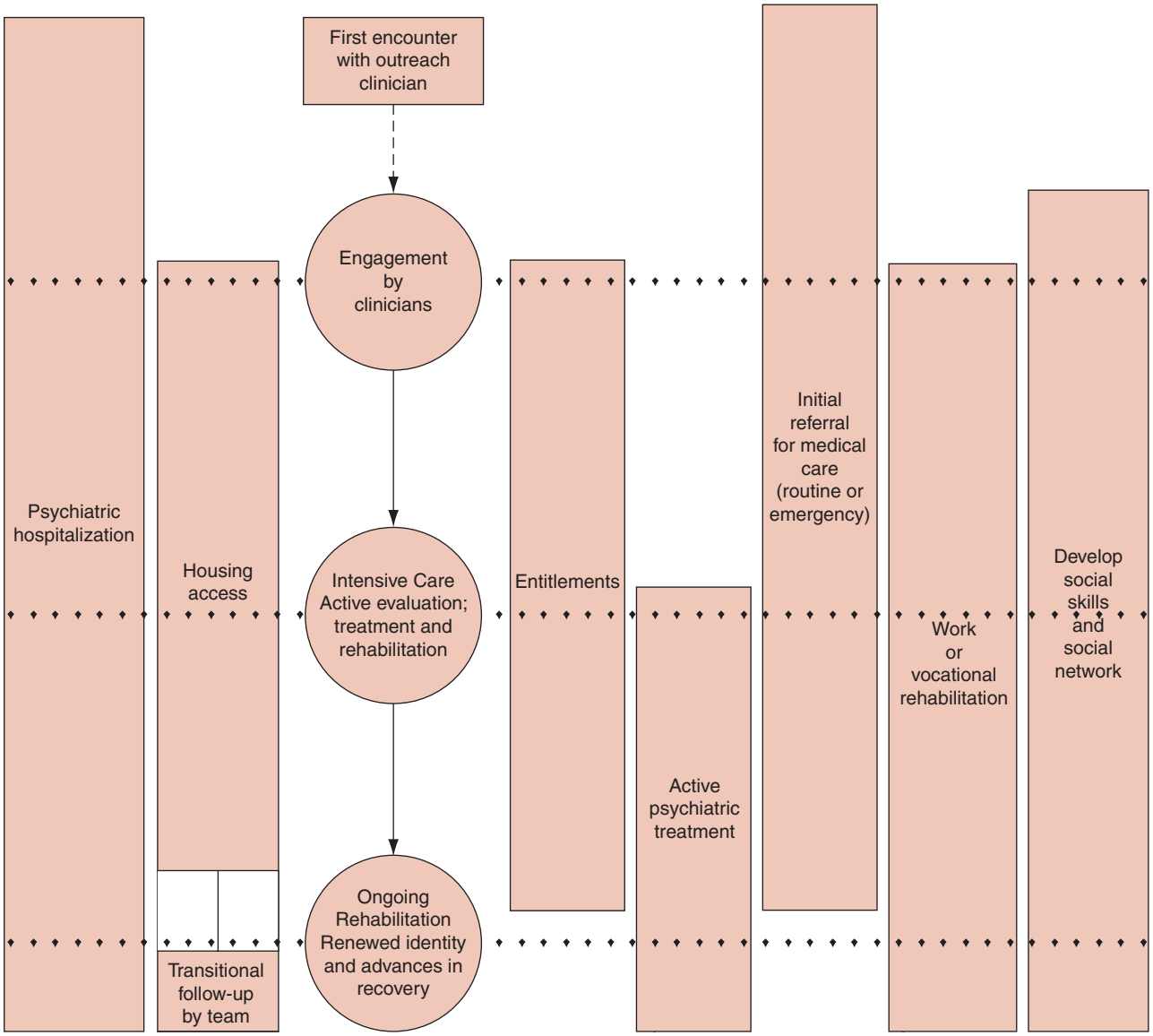



**Figure 121–1** *The stages of rehabilitation in work with mentally ill homeless people. The verticle bars represent possible interventions synchronized with the three stages noted in the circles. (*Source: *Adapted From Gillig PM and McQuistion HL (eds), American Association of Community Psychiatrists' Clinical Guide to the Treatment of Mentally Ill Homeless People. Reproduced by permission of American Psychiatric Publishing, Inc.)*

homelessness, gently but persistently approach and engage homeless people in public spaces, offering incentives like food, clothing, and an open mind for listening (McQuistion et al. 1991). Gradually, they establish sufficient trust such that a homeless individual agrees to take a risk to move into his or her own dwelling with appropriate support or otherwise stay indoors at a shelter or drop-in center where he or she may find meals, showers, and daytime services. This process can take a matter of weeks, but has been known to last much longer, sometimes years. The street population is generally regarded as particularly disabled and alienated and the outreach process is very labor-intensive, requiring many short, usually apparently casual, helping interactions to achieve engagement and to provide service.

Alternatively, some mentally ill homeless people are first encountered in shelter or drop-in settings. Some find their way to shelter after a precipitating personal crisis, while others have been referred to or are accompanied by street outreach teams that are connected with the facility. At the point of arrival at an indoor setting, there is potential opportunity for multidisciplinary intensive care described later, but early interactions indoors also often require outreach while workers concentrate on establishing trust. Relationships are hard-won, and they require patience and flexibility, even tolerating a person's self-destructive behavior that may, for example, include drug or alcohol dependence. At this stage, a harm-reduction approach to chemical misuse, or risky lifestyle (e.g., sex work) is practical (Marlatt 1996). Appropriate techniques include respectfully educating a person about risks, about the "side effects" of using street drugs—like never having money or suffering psychological and other health effects, including trauma from a rough lifestyle. In this manner, a goal during engagement is to move a person from a position of "precontemplation" of drug and alcohol use to contemplating change (Prochaska et al. 1992), illuminating alternatives and beginning to help lift him or her from a condition of demoralization (Frank and Frank 1991).

Simultaneously, a challenge exists of balancing these approaches with being able to respond decisively to a crisis or risk to community safety (Diamond 1996). Mental health professionals, usually psychiatrists who are working in street or shelter settings, must recognize and respond to emergencies that require involuntary transport to an emergency room, and they must have the means for emergency rescue at the service center and in the community. When judiciously employed, this work is humanitarian, potentially lifesaving, and may offer new opportunities for engagement. There is ongoing debate about whether ultimate community reintegration can actually be achieved through such coercive means, yet psychiatry, especially, has a unique responsibility in clinical decisions concerning involuntary treatments.

The combination of homelessness and serious mental illness adds to the complexity of a right to refuse treatment. In the US jurisdictions, the standard for involuntary admission is dangerousness to self or others in the foreseeable future, usually marked by acute suicidality, making threatening statements, or aggressive behavior. However, there are subtler situations where assessment of dangerousness is challenging. Examples include a person who continues to sleep outdoors despite freezing temperatures, who crosses streets without paying attention to traffic, who yells random comments at passersby, or a person who eats out of trash cans without regard for personal health. None of these situations necessarily warrant involuntary intervention. Many people cross streets while engrossed in IPod tunes, free speech is a right, and some choose to camp out in frozen arctic tundra. Yet, in the context of psychosis and impaired judgment, any one of the aforementioned behaviors might indicate dangerousness. The clinician must carefully balance the legal, ethical, and relational risks with exercising unilateral power.

In our view, there is a continuum of clinical negotiation or leverage. It ranges from involuntary hospitalization to subtler forms, for example, when a service provider assumes the role of representative payee of a person's entitlements, or when delays are imposed in making housing referrals for people not addressing chemical misuse. In these cases, the fulcrum of successful leverage is usually the clinical alliance, with the person understanding that there is something advantageous in a continuing relationship. This highlights the critical nature of initial engagement.

Mark's situation, as we now describe, illustrates how involuntary hospitalization, and other uses of leverage, can be carefully constructed to help a chronically homeless person move toward rehabilitation:

Fifty years old and homeless for almost two decades, Mark had not always been destitute. He had excelled in school before entering a prestigious college. In college, though starting to be socially isolated and obsessed with ideas of starting his own religious cult, he did well enough to enter graduate school in engineering, demonstrating exceptional mathematical abilities. During graduate school, he had his first psychotic episode, requiring hospitalization and leave of absence from school. While on leave, he declined continued psychiatric treatment. After several hospitalizations and desperate efforts by his family to stay connected with him, Mark's illness ultimately led him to the streets. After a single day in a municipal shelter, Mark left, fearing he would be killed. He finally found an isolated room in a subway tunnel that became "home" for almost two decades.

During these years, Mark had intermittent contact with an outreach team while he panhandled above ground. Occasionally, he would come to a drop-in center operated by the same outreach team. Though Mark established relationships with a number of case managers and psychiatrists at the center, he never accepted psychiatric medication. But he did become increasingly trusting of program staff, accepting food, clothing, and showers.

Mark's usual problematic behavior included screaming in the street, washing his face in a toilet, eating out of garbage cans, rarely bathing or changing clothes, and pointing at people and saying "The Lord is vengeful." Occasionally, he would push or hit a passerby, necessitating police intervention and transport to an emergency room, where he would always present to clinicians as calm and nonthreatening, culminating in release. During a subsequent period during which Mark was frequently pointing at people and threatening them with divine vengeance, the drop-in center psychiatrist exercised authority under local law to petition an involuntary transport to a hospital.

This was a more studied intervention than a call for less expert (and legally constrained) police to assess a person's acute dangerousness. It was done in close collaboration with the

outreach staff in an attempt to prevent an episode of physical assault. Also, important was work the psychiatrist did with the local psychiatric emergency department to provide history in pursuit of admission, also assuring the hospital staff that the outreach program would work with the hospital to create a satisfactory transition plan, including housing and treatment, once Mark was able to return to the community.

Mark was admitted and accepted medication. While in hospital, he was visited by his outreach case manager and psychiatrist, who also became representative payee for disability benefits, facilitated housing in a closely affiliated transitional supportive residence, and committed to providing ongoing psychiatric treatment.

In this case, a coordinated systems effort effected hospital admission and the necessary inpatient leverage to convince Mark to accept treatment. His desire to be back in the community, combined with a gradually developed trust of his outreach providers, and the added leverage of legal authority to manage his benefits, motivated Mark and put him on a path to psychosocial rehabilitation, even after an involuntary intervention.

## Intensive Care

The long duration of engagement, leading to eventual assertion of services in Mark's circumstances, also illustrates how engagement and intensive care necessarily overlap. This stage usually begins at a point when a person tolerates services rendered indoors. The most successful programs integrate the disciplines of social work, rehabilitation, internal medicine, psychiatry, and peer support, all working collaboratively. They focus on living skills, which include activities of daily living, money management, and planning longer-term goals. In these settings, case managers frequently negotiate complex service systems, creating service linkages with their clients, such as pursuing medical insurance and disability benefits, exploring vocational rehabilitation, and the search for housing. They work hard with their clients while respecting autonomy, fine-tuning interventions as clients are prepared to receive them (Table 121–3).

As previously noted, there is discussion within the field concerning the point at which a person is ready for housing. Some challenge the perspective that a person must not only attain benefits but must be viewed as clinically stable and as having achieved sobriety. These advocates cite the reality of lengthy recovery course and support the rational desire of many homeless people to be rapidly re-housed. Related to this is a phenomenon of "shelterization" or dependence on shelter life, which itself perpetuates homelessness (Gounis and Susser 1990). Some model programs have been devised to address successful transition from shelter to housing. CTI is a prime example of an effective intervention that focuses on using relationships to foster community adaptation (Susser et al. 1997).

**Table 121–3 Focus on Collaboration**

| |
|---|
| Integration of various disciplines |
| Peer support |
| Use of case management for negotiation |
| Respect for consumer autonomy |

Regardless of whether a person is methodically transitioned to a shelter or vigorously supported in housing immediately from the street, treatment of psychiatric disorders, co-occurring chemical dependency problems, and general medical needs also begin to take on an important role during intensive care. Even as intensive care proceeds, approaching these needs requires special skills, primarily using nontraditional techniques (Table 121–4). These techniques are born out of a necessity to treat people who usually do not consider themselves "patients," but rather out of circumstantial necessity, happen to interact with health providers. Psychiatrists in shelters and similar nontraditional settings have to "unlearn" habits while they integrate standard practice and nontraditional techniques (Felix et al. 1996). For example, it is at times acceptable to joke around and laugh with patients, to give gifts, to self-reveal, to play cards or ping-pong, and to be a visible advocate and deliverer of concrete services. Implicit in this is continuing attention to an alliance with the patient, including maintaining unwavering reliability.

**Table 121–4 Techniques in Nontraditional Approaches**

| |
|---|
| Reliable, consistent relationships |
| Alliances vs. hierarchies |
| Realistic expectations |
| Adherence negotiations |
| Focus on harm reduction |

Perhaps in no single area of the relationship between the psychiatrist and the homeless person can alliance be more critical as in the instance of introducing medication. The clinician persistently works with the patient, searching for a shared rationale for prescribing; simultaneously signaling to him or her that the clinician's purpose is in helping him or her meet his or her personal goals. Being a real object communicates this nonverbally.

Choice of medication is tempered by realism. For example, medications that require frequent laboratory monitoring may not be realistic in many nontraditional settings especially if the person cannot predictably appear for phlebotomy. When a medication regimen is established, too, attention to adherence is important. Psychiatrists must be flexible and realistic with dosing schedules, prescribing once a day whenever possible. Many programs have devised ways to track medication adherence through supervision or pill counts. If there is nonadherence, further negotiation is indicated, carefully listening to the person's concerns. Harm-reduction techniques are also appropriate, as in continuing antipsychotic medications when a person is actively using street drugs.

Because intensive care is a time of active psychiatric stabilization, clinicians may continue to be confronted with questions of personal risk to self and others. All basic "intensive care settings" are by necessity least restrictive and particularly in drop-in centers and shelters, staff must be skilled in diffusing potentially explosive interpersonal situations among clients, thereby focusing on preventative environmental techniques to enhance safety, including attending to medication adherence and substance use. People are also at varying stages of recovery and often exit these settings for periods ad libitum. This reality requires staff that tolerates

ambiguous risk. Just as they need to be comfortable with intervening acutely, they must also be ready to take leave of a homeless client, and revise a treatment plan when he or she returns.

During intensive care and especially while exploring housing options, chemical dependency becomes a serious focus. Though it is unlikely that chemical misuse is a primary cause of homelessness (VanGeest and Johnson 2002), the corrosive nature of drug addiction lends support to substance abuse as a cause of chronic homelessness. Mounting data buttresses this (Breakey et al. 2001), and there is emerging consensus on effective techniques addressing co-occurring substance use and psychiatric disorders (Drake et al. 2001). However, gaps remain in understanding differences between homeless and non-homeless dually diagnosed populations. Filling them will offer effective solutions to homelessness. Possible programmatic solutions include housing geared to treating active chemical dependency and integrating substance abuse programming with the psychologically and socially restorative effects of vocational training. The latter offers a pathway out of the demoralization induced by severe poverty, which itself may foster chemical abuse.

Finally, homeless people encounter the same chronic physical illnesses that everyone else does, with the important exception that they have dramatically more difficulty in obtaining care. Compounding this is a higher than usual prevalence of epidemic illness, like HIV and hepatitis C (Susser et al. 1993b, Rosenblum et al. 2001). With the exception of a few innovative mobile programs that visit shelters and drop-in centers or travel on the streets in specially outfitted vehicles (Nuttbrock et al. 2003), homeless people usually get medical care on an emergency basis at a high cost and mortality rate. When they do obtain quality shelter or housing, it may be the first time that they receive ongoing medical services. In these settings, staff is aggressive in addressing often multiple medical problems of clientele. Psychiatrists, especially, have a role in leading the effort to access a mentally ill homeless person to medical care, advocating with human services workers to facilitate Medicaid enrollment and with off-site health care providers to treat homeless patients.

## Ongoing Rehabilitation

The transition from intensive care to an open-ended stage of ongoing rehabilitation is an especially gradual one. Achieving full community integration necessarily involves a new sense of self-identity and recovery, and is composed of several ingredients.

Albeit crucial, housing is merely the first step. Becoming stably domiciled is a formal benchmark and successful transition to housing demands careful clinical attention. A useful approach in determining fit between an individual's needs and housing type involves conceptualizing a spectrum of structure, or treatment intensity, among available housing types. These range from relatively restrictive, usually congregate care "community residence" settings that require on site program attendance and psychiatric care, to less costly "supportive housing." The latter is characterized by more independent apartment living. This may be either a single room occupancy building, often with optional program participation, or in scattered sites, also closely identified with housing-first models. The more structured and intensive the housing environment is, including available mobile services delivery, the more the clinical work continues to resemble intensive care. Furthermore, among the more structured housing environments, accommodations may also be transitional—up to two years. Typically, multidisciplinary outreach teams armed only with experience and clinical skills determine the fit between homeless individuals and housing programs, using program structure as a guidepost.

Services researchers are only beginning to explore reliable approaches to successfully match housing with potential residents based on clusters of personal needs. This includes analyses of housing models and the effects of addressing clinical issues like medication adherence, concurrent treatment of chemical misuse (Susser et al. 1991, Grunebaum et al. 1999), medical comorbidity, and family involvement. As recent reviews have highlighted (Fakhoury et al. 2002, Rog 2004), the challenges have hovered on the realities of performing research in naturalistic settings. This includes problems such as the existence of few controlled studies, relatively low statistical power, inconsistent terminology and methodology, and investigations of housing programs that are themselves incompletely described.

However, formative information does exist. Because of its relatively wide array of housing programs and an overseeing administrative system, New York City has been a frequent study locale. In a retrospective study of 2,937 housing placements in New York, correlation with longer housing tenure in high service intensity settings included the availability of medication management and non-congregate living that contained mixed populations of disabled and nondisabled tenants (Lipton et al. 2000). In low intensity settings, longer tenure was associated with mood disorders. In all settings, it was associated with older age. Not surprisingly, and consistent with other studies, there was an association between co-occurring active substance abuse and short housing stays (Table 121–5). A subsequent quasi-experimental study by Siegel et al. (2006) examined eighteen-month outcomes of 157 New Yorkers placed in either supportive settings (usually low intensity) or community residences (uniformly high-intensity). These authors found that housing tenure was statistically indistinguishable between these settings, though housing satisfaction was rated higher in supportive environments. As other research has noted, for many living in supportive settings—including "housing-first"—there was an associated greater sense of personal isolation. Across both housing paradigms, indices of depression and anxiety yielded poorer community integration and quality of life, indicating that people who experience these issues should be targeted for vigorous mental health intervention. Individuals most likely to lose

**Table 121–5 Factors Related to Stable Housing Tenure**

| |
|---|
| Provide medication management |
| Flexible psychosocial support |
| Older consumers |
| Higher educational level |
| No bipolar diagnosis |
| Lower hospitalization history |
| Sobriety |

housing status were younger; less educated; had a diagnosis of bipolar disorder or polysubstance abuse, and had relatively more frequent psychiatric hospitalization.

Rigorous explorations of housing program structure itself include Goldfinger and colleagues' (1999) in Boston comparing 18 month housing stability among 118 people randomized to an independent apartment program (with case management support) or group homes with on-site psychosocial services. This study found somewhat fewer homeless days among participants in staffed housing. In addition to minority ethnicity and lifetime chemical misuse, participants who had the very highest degree of preference for minimally structured independent living also correlated with housing instability. While respecting consumer preference has also been associated with favorable outcomes (Srebnik et al. 1995), this study highlighted a complex interrelationship of consumer choice and professional judgment, indicating a need to employ active collaboration to find the desired "fit."

As noted above, there is policy interest in understanding who best adapts to housing-first models. Housing-first is often identified with consumers' wish be domiciled quickly and independently, in contradistinction to the continuum model's stepwise method of evaluating housing readiness while accentuating clinical stability and psychosocial support. Partially addressing this from a housing-first stance, Tsemberis et al. (2003) examined the role of psychosocial support in housing stability in independent apartment living. These authors functionally combined ACT services with housing-first opportunities using ACT to aggressively obtain housing placement and flexibly maintain mentally ill clients through recovery. In a six-month follow-up of 99 people randomly assigned to this program, 79% retained housing versus 24% of 156 controls assigned to continuum-model housing. In a 24-month follow-up, the variance in housing stability was maintained (Tsemberis et al. 2004). Housing-first advocates, in fact, argue that the issue of matching program structure and individual characteristics is obviated through the use of flexible ACT-like services.

Once a person has found a satisfying housing environment, the rehabilitative focus transitions from symptomatic stability to emphasis on the development of a set of new roles that render as obsolete the individual's identity as homeless (Table 121–6). Vocational and relational identities are integral at this stage and psychiatrists who work within this phase focus much less on crisis and immediate psychiatric and medical needs, but more on identifying and achieving with their patients long term goals, while also helping them identify stressors: a focus increasingly on illness self-management. This is done by listening carefully to a patient's hopes, translating them into a collaborative reality-based plan, being flexible to tolerate setbacks, and coordinating closely with vocational and social skills programs and other counselors.

**Table 121–6 Consumer-focused Strategies to Enhance Housing Tenure**

| |
|---|
| Clearly identifying long-term goals |
| Illness self-management |
| Educational training: transitional vs. supported employment |
| Meaningful relationships |
| Family ties |
| Other support systems |
| Religious/spiritual affiliations |

Goalsetting around work can often start during the stage of intensive care, with many entering active vocational training at that point. As a person struggles less with day-to-day survival, he or she begins looking for a sense of financial independence and sources of personal pride. Supported employment has enjoyed the highest preference, but many professionals value transitional employment models, like those in clubhouses. These models need further focused research among homeless and formerly homeless populations.

The other important development during ongoing rehabilitation is the formation of more meaningful human relationships, marking dissolution of the alienation engendered by chronic homelessness, especially. This includes the reestablishment of family ties for many who have been separated through the vicissitudes of mental illness and chemical misuse. Psychiatrists and other workers have a role in acting as a conduit to families, providing family psychoeducation and support to their patients. For those people whose families are not accessible, even more incentive exists for professionals to link them to other support systems through clubhouses, redeveloped personal interests, religious and other spiritual affiliations, and work environments. The recovery and reentry of mentally ill homeless people, while often painstaking, is accentuated by their heretofore-severe indigence and disaffiliation. It is therefore ultimately profound.

## Administration, Academics, and Advocacy

Psychiatrists are important in providing both leadership and collaborating in service within all the stages of rehabilitative care of people with homelessness and mental illness. As the evolution of services to this population had progressed over the past two decades, they have found additional roles in administration, academics, and advocacy.

Owing to their location within CBOs, nonmedical professionals lead most programs serving homeless people. Nevertheless, the role of medical director has developed in CBOs (Ranz et al. 2000). The role of the CBO medical director represents both shifts in CBOs toward accepting a meaningful medical contribution and an adaptation of psychiatric administration to include nontraditional models. Medical directors work in partnership with, or under the aegis of, nonmedical program or agency directors, and how they manage this relationship requires flexibility and collaborative skills. For example, in the area of clinical accountability of nonmedical staff, the medical director needs to provide clinical consultation and supervision to nonmedical colleagues, and assert a commitment to quality care, often without direct line authority.

Over the last twenty-five years, there has also been a gradual acceptance of the need to educate psychiatric house staff in meeting the needs of mentally ill homeless people (McQuistion et al. 2004). Academic faculty who came of age during the phases of the homelessness problem lead today's teaching experiences. These teachers understand that working with mentally ill homeless populations affords the trainees opportunity to learn omnibus skills in diagnosis

an management of very complex and distressed patients, including work at the frontiers of epidemics like TB, HIV illness, and hepatitis C.

Training medical students and physicians to work with mentally ill homeless people necessarily involves describing a theoretical framework. In addition to outlining a clinical methodology such as that presented in this chapter, this includes education concerning the social and economic roots of homelessness and how community psychiatry fits within applied public mental health. Trainees are placed in clinical programs that are known to be successful and student-friendly. Supervisors must offer vision, theory, and role modeling, as they also teach cultural competence, work with countertransference, and imbue special techniques.

Finally, advocacy is required to advance recovery and help homeless people with psychiatric disorders to enter the social mainstream. Homelessness is tied to structural economic, social, and political conditions and it will not disappear until poverty is adequately addressed. In our view, the realities of housing shortages, the continual labor shifts within a market economy, and their interplay with race, social class, and a societal value of individual self-sufficiency are at the center of the problem. While constructing a solution for this quintessentially American issue is beyond the purview of the behavioral health sciences, psychiatrists and other mental health professionals nevertheless are uniquely positioned to influence social policymakers and politicians.

On a basic level, the very existence of psychiatrists working with homeless people constitutes advocacy by drawing professional attention. Psychiatrists working with homeless people must also influence the organizations for which they work to identify a corporate function in advocacy, moving beyond service.

Through research, psychiatry can elucidate and then transmit information concerning the public health costs of mental illness and homelessness and inform community intervention strategies that point to technology, such as vocational rehabilitation models, that provide opportunities for impoverished mentally ill people to gain personal and social productivity. Prevention interventions, including models to divert people with psychiatric disorders away from incarceration, are also areas appropriate to psychiatric contribution, as are efforts to inform policymakers about how poor families, and their communities, might be supported to reinforce protective factors against beginning or perpetuating a family cycle of homelessness.

On an activist level, in some localities, litigation has been a critical tool in driving public policy on homelessness. Psychiatry offers special expertise to legal advocacy and exercising this role has a potent effect on facilitating social change. In this manner, psychiatrists have given expert testimony in important class action suits and professional organizations have issued formal statements of support. Organized psychiatry has also combated the stigma of mental illness extending itself to homelessness, too (American Psychiatric Association 1991b, Lamb et al. 1992). These documents provide a recognizable reference point of leadership for psychiatrists to engage in public advocacy as they form alliances with others, including consumers and families, educating policy makers about the needs of this population.

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CHAPTER

# 122 Gender Identity and Sexual Orientation

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In 1973, the American Psychiatric Association's (APA) Board of Trustees, after extensive scientific review and debate, removed homosexuality per se as a mental illness from the *Diagnostic and Statistical Manual of Mental Disorders,* Second Edition (DSM-II). If sexual orientation is not a mental illness, why is there a chapter on this aspect of human sexuality in a psychiatric textbook? Understanding the variations of sexual orientation and the range of adjustments individuals and society in general make to sexual orientation is as important as understanding the influence and importance of culture, ethnicity, race, and gender on the psychological development of a person and the way mental health issues may be shaped or express themselves.

Homosexuality is a normal variation of human sexual and affectional (loving) expression; sexual orientation is a complex phenomenon with many variations along a spectrum of heterosexuality to homosexuality. A nonpathological view of homosexuality as well as homosexual and bisexual men and women removed the stigma of mental illness and opened up vast areas of study, research, hypothesis, and knowledge about sexual orientation itself, the expression of sexual desire, the psychological and social forces that influence the lives of people with homosexual and bisexual sexual orientations, and the life cycles of such men and women, including the nature of bias and prejudice based on intolerance to differences.

## Definitions and Concepts

The term "gay" has a long history of association with homosexual males, but became more of a standard and accepted term replacing "homosexual" since the latter is seen to have a pathological association and is seen as too focused on sex alone, and not on the total complexity of a sexual orientation. In this chapter, males with homosexual sexual orientations will be referred to as "gay men," females with homosexual sexual orientations will be referred to as "lesbians," and men and women with bisexual sexual orientations will be referred to as "bisexuals" or "bisexual men and women."

*Sexual orientation* may be simply defined as the erotic and affectional attraction to another person, including erotic fantasy, erotic activity or behavior, and the need for love and affection. Homosexuality can be seen as part of a continuum of human sexual and affectional expression, ranging from same-sex attraction to opposite sex attraction.

Some people with homosexual or bisexual orientations, as indicated by fantasies, may not engage in homosexual behavior as a result of *internalized homophobia* (the fear of accepting homosexuality or homosexual impulses, discussed below), societal pressures, or personal choice. For some, the fear may lead to denial or repression even at the fantasy level. Many gay men, lesbians, and bisexuals recall feeling different from others—even as early as age 4—and have linked that feeling to a differing sexual orientation (though they may not have acted on their differing sexual feelings until well into adulthood).

*Sexual behavior*, or sexual activity, alone does not define orientation. *Sexual identity* usually refers to one's sense of self as male or female but is also used at times to connote sexual orientation.

*Sex* is the biological distinction between men and women. *Gender* is the concept of maleness and masculinity or femaleness and femininity. *Gender identity* is the sense of self as male or female, with no reference to sexual orientation, gender role, or even biological sex. *Gender role* refers to behaviors and expectations that are viewed as masculine or feminine by a particular culture.

It is common in most Anglo-European/Western cultures to call behavior, styles, or interests shown by a male that are associated with women "effeminate" (boys are often labeled "sissies") and the equivalent by a woman "masculine" or "butch" (girls are often labeled "tomboys"). As will be discussed, much of the confused and prejudicial thinking about homosexuality in the past was due to confounding sexual orientation, sexual behavior, gender identity, and gender roles, overlaid with a generalized sexism that dismissed women and men who were thought to be like women, supporting the mistaken notion that gay men—since they are attracted to men—are in some way like women, and, in turn, lesbians are in some way like men.

*Heterosexism* is defined as an ideological system that denies, ignores, denigrates, or stigmatizes any nonheterosexual form of emotional and affectional expression, sexual

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activity, behavior, relationship, or socially identified community. *Homophobia*, though a popular term, lacks precise meaning: it is used to describe fear and loathing of gay men and lesbians, and also used to describe self-loathing, fear, or resistance to accepting and expressing sexual orientation by gay men, lesbians, and bisexuals. *Antigay bias* and *antihomosexual bias* are better phrases to describe the first concept, and *internalized homophobia* is better for the latter. Internalized homophobia is a key concept in understanding many of the developmental and clinical issues facing gay men, lesbians, and bisexuals.

## History of Homosexuality and Psychiatry

### Early Thinking

Though homosexuality as a specific category was not described in the medical or psychiatric literature until the early 1870s, psychiatry and the fledgling psychoanalytic movement made homosexuality a topic of special interest and focus. Most psychoanalytic approaches tended to seek one cause or explanation for homosexuality, and most of this writing confuses sexual orientation and gender identity, working often from the premise that gay men identify with femininity and lesbians identify with masculinity.

Sexual orientation in and of itself, Freud believed, no way impaired judgment or caused problems in delivering medical or psychiatric care. Freud's (1960) famous "Letter to an American Mother" stated: "Homosexuality is assuredly no advantage, but it is nothing to be ashamed of, no vice, no degradation; it cannot be classified as an illness." He goes on, however, to state: "We consider it to be a variation of the sexual function, produced by a certain arrest of sexual development." Though his thinking on homosexuality itself was not entirely consistent, having described at least four theories of male homosexuality—nor free of pathological associations—he did believe in innate bisexuality and in a biological contribution to sexual orientation (Lewes 1988).

In Europe, Rado (1969) proposed that homosexuality was caused by cultural and familial influences, based on a fear of the opposite sex, and, accordingly, treatable with psychotherapy. Fenichel (1945) further elaborated a fear of castration and developmental arrests and fixations, but described cultural influences on the expression of homosexuality and believed that there was an element of choice in sexual orientation, not just in its expression.

Many American psychiatrists promoted the notion that homosexuality was a mental disorder. Bieber et al. (1962) extended the Freud and Rado theories to propose that family upbringing and childhood influences were entirely responsible for producing homosexuality in male children. He described the "classic" combination of a distant, uninvolved father and an overinvolved mother seeking to meet her needs through her child. (He did not comment on the finding that even more of his heterosexual males had that parental pattern than the matched homosexual males.)

Socarides (1968) described male homosexuality as a preoedipal problem and, therefore, severely psychopathological and developmentally somewhere between borderline and psychotic conditions, seeing family upbringing as the cause of homosexuality. He contended that homosexuality could indeed be "treated" with psychotherapy, especially psychoanalysis, because it resulted from conflictual issues, an attempt to resolve the separation and individuation from mother in the face of a weak or cruel father.

Female homosexuality was not focused on as much as male homosexuality. Freud (1920) was not consistent in his thought about female homosexuality either, seeing it either as severe penis envy with a turning away from heterosexual objects and a regression to earlier fixations on mother, or a narcissistic identification with father, thus seeking other women, and therefore, homosexual objects.

Other psychoanalytic writing also refuted a biological component to female homosexuality, seeing it as caused primarily by early developmental disturbances. Expressing a view that clearly reflected the culture of the times, Deutsch (1932) saw homosexuality as regressive and transitional, with male homosexuals acting out passive or feminine wishes and female homosexuals, failing to learn to sublimate their aggressive energy into acceptable submissive behavior, acting out masculine or active wishes. She believed that the normal progression to adolescent heterosexuality was interrupted in lesbians by a probable masochistic disturbance in the early mother/daughter relationship.

Socarides (1968) also espouses this theory, but further emphasizes the failed separation and individuation at the preoedipal stage. Newer theories suggested that the disturbance between the daughter and mother was due to maternal narcissism, or due to an awareness of societal devaluing of women, and another notes a possible fixation at the genital level and an overidealization or overinvestment in the genitals in a sexual relationship with another woman to make up for poor or limited mothering (reviewed in Magee and Miller 1997).

### Newer Thinking

Kinsey opened the possibility of new perspectives on homosexuality with his surveys of the sexual practices of men and woman (Kinsey et al. 1948, 1954). He proposed a continuum to describe sexual behavior, with a scale from 0 for exclusive heterosexual behavior to 6 for exclusive homosexual behavior. His studies have been criticized for a variety of reasons, including poor sampling, but they certainly made Americans aware of sexuality and sexual behavior previously rarely discussed. Kinsey's data, counting sexual contact resulting in orgasm, found that 37% of the male population had some homosexual experience between the beginning of adolescence and old age. Of unmarried males who are 35 years of age or over, almost 50% had had a homosexual experience since the beginning of adolescence. Kinsey found that 4% of the white male population is exclusively homosexual throughout their lives. Study of the sexual behavior of women showed percentages of women with homosexual encounters to be roughly one-half of the parallel categories for men. Most people fell in a bisexual range from 1 to 5.

The Kinsey Institute did further reviews and surveys including a path analysis of all the data known about homosexuality available to them at the time. It concluded that homosexuality must be biologically based—something one is born with—and not determined by family upbringing (Bell et al. 1981).

Evelyn Hooker can be credited with initiating the acceptance of changes in thinking about homosexuality within the

mental health field. She demonstrated that there were no discernible differences between the psychological profiles of gay men and heterosexuals, effectively beginning the dismantling of the theory that gay men were psychopathological with preoedipal fixations (Hooker 1957).

An era of new thinking from psychoanalysts began in the 1980s. For example, Isay (1989) made the assumption that sexual orientation is probably biologically based and looked at how the oedipal complex may be different for gay men and how some subtle or not so subtle aspects of the gay son may be recognized and responded to by the father, leading the father to withdraw or treat that son differently than a heterosexual son.

Lesbians and female homosexuality have also been studied and reviewed from the nonpathological perspective. The literature on gender and gender roles offers additional ways to look at both male and female homosexuality, and is particularly useful in understanding the issues facing same-sex couples. For example, Gilligan (1982) points out the divergent paths for male and female development: boys are brought up to be not like their mothers, that is different from an important nurturing figure, whereas girls are brought up to be like their mothers, that is closely identifying with the nurturing figure. Such an observation may help to explain the problem of comfort with intimacy within many male couples or the "fusion" or intense intimacy within many lesbian couples as described by many clinicians working with same-sex couples (see below).

Magee and Miller (1997), as noted, completed an extensive review of psychoanalytic thinking on female homosexuality, emphasizing the heterosexist and phallocentric assumptions. They conclude that there are no psychodynamic etiologies to female homosexuality.

## Biology, Genetics, and Cultural Perspectives on Homosexuality and Bisexuality

Data on the true prevalence of homosexuality in America are difficult to obtain, partly because of the difficulty in obtaining honest and complete responses or information in surveys, and partly because of a lack of agreement on terms and definitions of the population to be studied. The popular estimates that 10% of the male population and 5–6% of the female population are exclusively or predominately homosexual are based on an interpretation of the Kinsey data, which only discussed sexual behavior and did not attempt to describe sexual orientation or a self-identified sense of self as gay, lesbian, or bisexual. Michaels (1996) undertook a thorough analysis of the limited data available, differentiating the concepts of sexual behavior, sexual desire (i.e., who the person would prefer to be with sexually), and self-reported identities as gay men, lesbians, or bisexuals. He notes that there is no possibility of giving an overall meaningful prevalence, since the data indicate a wide variety depending on gender, age, marital status, education, religion of upbringing, current religious affiliation, race, and place of residence (ranging from urban to rural). His summary estimates that in America, 9.8% of men and 5.0% of women report same-gender sexual behavior since puberty, 7.7% of men and 7.5% of women report same-gender desire, and 2.8% of men and 1.4% of women report a homosexual or bisexual identity.

### Culture and Cross-Cultural Issues

People who relate to people of the same sex for love, relationships, and sex have been noted throughout history and in almost all countries and cultures. Boswell (1980) documented both the acceptance of and intolerance to homosexuality in Christian Europe, linking the tolerance to economic and political variables: if all was well economically and politically, homosexuality was well tolerated; in periods of political turmoil and economic unrest, gay men and women were scapegoated.

Many studies of the animal kingdom have shown homosexual behavior to occur in other species. There are examples of some animals within a socially organized species, such as some monkeys, who exhibit nearly exclusive homosexual behavior (Denniston 1980).

Cross-cultural studies not only help to put homosexuality into global perspective, but also contribute significantly to the understanding the of clinical issues facing gay men, lesbians, and bisexuals in the United States who are from an ethnic or cultural minority group (Herdt 1996). Most significantly, the understanding of bisexuality benefits from cross-cultural and historical perspectives, since many cultures outside of that in the United States condone homosexual and bisexual behavior, in certain prescribed circumstances.

### Biology

The biological studies, for the most part, seem to grow out of the confusion noted above between sexual orientation and gender identity: most studies have tried to show some physical trait in gay men that must be like that of women, and vice versa for lesbians. Though there have been a multitude of studies and reviews, and critiques of the studies, they have not been consistent in their findings, they have not been replicated, or conclusive, and most have had major flaws in their design (reviewed in Pillard 1998). Animal studies in particular are difficult to correlate with human findings: in some, stereotypic sexual behavior of rats is used to describe a sexual orientation (a male rat who assumes the female lordotic position and allows other male rats to sexually mount him is seen as the "gay" or homosexual rat, where there are no conclusions drawn on the mounting rat).

Some studies of differences in brains between gay men and heterosexual males are based on a hypothesis that the brains of gay men are different and would be similar to those of heterosexual women. LeVay's (1991) study showed a twofold difference in size of the third interstitial nucleus of the anterior hypothalamus (thought to be associated with sexual behavior)—the gay men's being half the size of the straight men's—consistent with the finding that the women's are about half the size of men's. There were several problems with the study—including tissue samples from men who died of AIDS, caused by the neurotropic HIV—and no certainty of the sexual orientation verses the sexual behavior of the deceased; the study has not been replicated.

Hypotheses that gay men must lack testosterone or have high estrogen levels and lesbians have the opposite are based on the same type of thinking noted above, but hormonal differences in gay men and lesbians from heterosexuals have never been demonstrated consistently. There have been some studies looking at hormonal influences on sexual orientation in utero, with the hypothesis that maternal stress may somehow affect the hormonal levels that in turn affect the

development of the fetus, possibly influencing brain development and sexual orientation (Ellis et al. 1988). Other possible correlations between physical traits or developmental events and sexual orientation include the birth order where gay men seemingly are born later in sibling order (Bogaert 2006), left-handedness and homosexuality (Rosenstein and Bigler 1987), and leftward pattern asymmetrical fingerprint patterns and sexual orientation (Hall and Kimura 1994). Other than the birth order review, no studies have been replicated.

Studies of intersexual people, that is, people with sexually ambiguous genitalia or true hermaphrodites, are often conducted, but such studies ultimately illustrate more about gender role expectations; that is, what happens when one is brought up as a male or as a female regardless of biological or genetic sex, than add any additional understanding to homosexuality (Rosario 2006).

### Genetics

The most promising areas of study involve genetics and familial patterns. The genetic and familial patterns studied by Bailey, Pillard, and their colleagues have demonstrated the most consistent and replicated data (Bailey and Pillard 1991, Bailey et al. 1993). Pillard (1996) notes that gay men are much more likely to have other gay or bisexual male siblings than a heterosexual male—based on expectations of the incidence of homosexuality in America—but no more likely to have a lesbian sister; lesbians, in turn, are more likely to have other lesbian siblings, but no more likely to have a gay brother.

Combined with other studies on twins and heritability (Whitam et al. 1993), this body of research helps underline the probable genetic substrate of sexual orientation in all people, with different genetic influences for male homosexuality, male heterosexuality, female homosexuality, female heterosexuality, and, possibly, even for bisexuality. Heritability does not imply a direct gene but does indicate the fraction of the trait studied seen in a given population that is attributable to genetic differences among individuals; certain genes may influence factors that then shape responses that may influence sexual orientation, and thus not be genes for homosexuality itself. Though a complex set of behaviors and feelings such as seen with homosexuality could not be explained by any single factor, the genetic basis may be the foundation on which other biological and familial and societal influences work to shape the development and expression of sexual orientation in adult men and women.

### Bisexuality

Bisexuality has also been known to exist throughout all recorded history. Freud, as noted, believed in innate bisexuality, and that any one individual evolves into having a heterosexual, homosexual, or even bisexual sexual orientation. Though Kinsey demonstrated the frequency of bisexual behavior in America, estimating the prevalence of bisexuality as a sexual orientation is as difficult to determine as is the prevalence of homosexuality. The differences between behavior and self-identification are especially important here. A survey in New York City of the sexual behavior and identity of men reported that 10% of the men who reported to have sex with men called themselves "straight" or heterosexual even if they did not have sex with women (Pathela et al. 2006). Weinberg et al. (1994) have described the theoretical approaches to bisexuality and critically reviewed the research on bisexuality.

## Developmental Issues Facing Most Gay, Lesbian, and Bisexual People

Understanding the developmental issues for most gay men, lesbians, and bisexuals will help in the clinical work with such people, and will further enhance the awareness that many of the clinical issues that are unique for gay and bisexual people are a result of the adjustment to a minority sexual orientation and not due to any psychopathology associated with the orientation itself. There are three major tasks that gay, lesbian, and bisexual people have to undertake that heterosexual people do not need to do: (1) recognize that there is indeed something "different" about them, and that this sense of difference usually precedes an awareness of sexual and affectionate feelings different from the majority; (2) "come out," that is, acknowledge first to themselves and then eventually to others that they have a different sexual orientation from the majority; and (3) process the internalized homophobia and possibly confront both heterosexism and antigay bias in coming out to others and living in the world as openly gay, lesbian, or bisexual.

Learning to live in a society that does not accept difference readily shapes the sexual identity development of many children who will grow up to be gay, lesbian, or bisexual, as they transition from childhood into latency period. De Monteflores (1986) in particular describes how difficult it is growing up different. Whereas a person of color cannot hide skin color, and the difference is obvious to all, a person with a homosexual or bisexual orientation, while aware of being different, may not be recognized as different by anyone else. The sense of difference in these children may be confusing and alienating, leading to social isolation and denial of natural feeling. For those children who are gender discordant in behavior, that is, children who exhibit behaviors or mannerisms associated with the opposite of their biological sex, profound deficits in self-esteem and in other aspects of the personality may result from being shunned, humiliated, and derided by their peers (Hanson and Hartmann 1996).

Most parents are heterosexual and raise their children either assuming that they will be heterosexual, or not thinking about sexual orientation at all. For the pregay or prelesbian child (i.e., the child who will grow up to be gay or lesbian), exposure to such nonconfirming behavior and parental expectations enhances the feelings of being different. As a coping mechanism, pregay or prelesbian children may learn to disconnect and dissociate from their true selves and sexual orientation and adapt to parental expectations by creating and presenting a false self or behaviors that are not genuine reflections of the true self.

Many parents who cannot respond to or give support for what is unfamiliar or uncomfortable for them will either ignore those attributes of the child that suggest difference or try to change them. The process of ignoring may be quite subtle, a process of neglect similar to that described by Swiss psychoanalyst Alice Miller (Miller 1981). Parental reactions help to shape and validate the expression of the needs and longings of their children; since parents more frequently reward what is familiar and acceptable to them and tend to discourage or de-emphasize behavior and needs they do not value or understand.

Dissociation and denial may become major defenses in the personality structures of such children, since they learn early that their feelings and needs are not acceptable and must be hidden or suppressed. In adolescence, their sexual feelings emerge with greater urgency, but there is rarely any context or permission for their expression. Adolescents in particular often reject and isolate those who are different and encourage conformity, which further supports denial and suppression of the emerging homosexual feelings. As a result, the adolescent who is gay or lesbian may even further split off any awareness of affect and behavior related to his or her homosexuality (Martin 1982).

When adolescents begin to recognize the source of their sense of difference—their sexual and affectional attraction to people of the same sex—they may work even harder to suppress these feelings by isolating themselves and avoiding situations that may stir up their longings. Some of these youths may devote extraordinary energy to academic or career success to cover up their underlying shame and sense of being defective; others may become depressed, isolated, guarded, and lonely, expecting to be rejected and ignored if their true feelings are revealed. Often these young people become ashamed not only of their sexual feelings, but also of their bodies, their social interactions, and other aspects of themselves. Because of personal resilience, not all gay men and lesbians have the same degree of difficulty traversing childhood and integrating a sexual identity that is generally stigmatized into a healthy personality structure.

Internalized homophobia and antigay bias combined with heterosexism are the major negative forces that gay men, lesbians, and bisexuals must deal with in our society. Almost all gay people have internalized homophobia, having been brought up in a heterosexist society that tends either to promote prejudicial myths about gay people or to ignore gay and bisexual people in general. The coming out process may be delayed or involve great difficulties depending on the intensity of internalized homophobia (e.g., by holding onto the belief that homosexuality is a sin, an illness, unnatural, evil, or will only lead to sadness, loneliness, and isolation) and may well require the help of psychotherapy.

The process of coming out to family and/or friends may be quite rewarding, but also carries the danger of outright rejection. For many gay and lesbian adolescents, the attempt to get their family to fully accept them by coming out to them has led to physical and verbal abuse, or to being thrown out of the home and running away to live on the streets (Savin-Williams 1994).

Many gay people will create their own "family," that is, a close network of friends that serves the needs often met by traditional families. Becoming part of a couple is also an important step. Even though there are limited legal sanctions for such relationships (varying state by state and country by country), the majority of gay people are in relationships (McWhirter and Mattison 1996). Having or adopting children is yet another step many individual or coupled gay men and lesbians undertake, and there is an ever growing literature on gay or lesbian parents and the children of lesbian or gay parents (discussed below).

## Psychotherapy: Special Considerations

Gay men, lesbians, and bisexuals will seek mental health services for the same reasons anyone might—help with emotional and social problems, treatment for mental illness, treatment for substance abuse, couples therapy, family therapy, and so on—but there are some special considerations in working with this population. Jones and Gabriel (1999) reported that gay men, lesbians, and bisexual utilize psychotherapy more than the general population, though not always satisfied with the therapist.

The higher use may have several explanations. Data suggest that gay, lesbian, and bisexual people are subject to higher rates of affective disorders and anxiety disorders (Gilman et al. 2001, Mills et al. 2004). There are psychosocial stresses related to discrimination (perceived and directly experienced) toward a sexual orientation that differs from that of the majority (Mays and Cochran 2001). And, as discussed below, substance use and abuse seems greater among gay men and lesbians than the general population (Cabaj 1996).

While sexual orientation is usually not the primary issue in most mental health situations, a mental health provider with a clear understanding of the issues facing most gay and bisexual people will be able to provide better and more sensitive care, and will not have to depend on the patient to teach the provider about gay, lesbian, and bisexual issues. A complete and thorough assessment is, of course, necessary to determine the best treatment plan, and all relevant treatment modalities—such as individual short- or long-term therapy, group therapy, psychopharmacology, substance abuse services, medical evaluations, and couples or family work—should be considered in devising the therapeutic intervention.

Most gay and bisexual patients will be quite open about their sexual orientation if asked directly, especially if the therapist sets a nonjudgmental and accepting tone. Ideally, mental health providers will not assume that all patients are heterosexual and will be careful not to use words or phrases that are heterosexist or that imply an assumption of heterosexuality. Clinics and treatment centers should review their forms and documents to eliminate statements or categories that will exclude or alienate gay and bisexual people (e.g., categories limited to "married" or "single" may not allow a gay person in a committed relationship to comfortably provide information).

Even if concerns about being gay are not part of the presenting problem, the therapist's acknowledgment and simple acceptance of the patient's homosexuality can be incredibly powerful and helpful, given the years of hiding and fearing rejection some gay and bisexual people experienced. Asking such people if the adjustment to their sexual orientation was difficult will not imply that the therapist sees homosexuality as pathological or problematic; rather, such inquiry can create an empathetic frame that lets patients know that they are free to talk about their sexual orientation if it is a concern, and implies that the psychotherapist can, if necessary, help provide a corrective experience to past parental avoidance or rejection by parents and others. Being comfortable taking a sexual history is essential for an initial evaluation.

The therapist will need to let patients discuss their own feelings about being gay or bisexual, and not provide quick or immediate assurances that having a different sexual orientation is not a problem; this stance may replicate the rejection of such patients' own feelings and fears, by not allowing a discussion of self-doubts and uncertainties. Allowing an

open presentation and exploration of patients' feelings about their sexual orientation, and how they came to recognize those feelings, will set the stage for an understanding and an acceptance based on the patients' actual experiences.

## Issues Related to Sexual Orientation

The problems that the patient presents may be directly related to sexual orientation, such as in seeking help in coming out, questioning whether one can change one's sexual orientation, attempting to recognize and overcome internalized homophobia, or needing treatment for stress from a verbal or physical attack for being gay. How to accept and be comfortable with a differing sexual orientation will be the focus.

Cohen and Stein (1986) outlined seven major themes that occur frequently in therapy with most gay men and lesbians, including the impact of being different and how coming out as a unique process for each individual gay person has both positive and negative consequences on personal identity development. Successfully negotiating coming out will provide psychological tools useful in other situations. Stein (1988) further elaborated some general issues in therapy with gay men and lesbians, emphasizing how important it is for the therapist to have a solid knowledge base about homosexuality and gay men and lesbians and, in general, to be open minded and nonjudgmental.

Lesbians may have some specific issues that need to be highlighted. Compared to gay men, they are more likely to have lower incomes (as do women in general, compared with men); lesbians are more likely to be parents (about one-third of lesbians are biological parents); lesbians face the prejudices aimed at women as well as those against lesbian; lesbians are more likely to come out later in life (about 28 years of age vs. 18 years of age in men); and lesbians are more likely to have bisexual feelings or experiences (Bell and Weinberg 1978, Bell et al. 1981). According to several surveys, lesbians are somewhat more likely to be in a long-term relationship than gay man and to be parents (Jones and Gabriel 1999), so the psychotherapy with lesbians may require a focus on relationships and parenting and family concerns.

Bisexual people may also have specific concerns—often focused on feeling alienated or not accepted by either gay or straight people. How to express sexual feelings and behaviors may be a focus—single partners, multiple partners, shared complex relationships, for example, may cause the bisexual person confusion or even guilt or acting on wide-ranging sexual feelings. The married or committed bisexual person (as can also be true for a person who thought him- or herself to be heterosexual but then discovered either homosexual or bisexual feeling emerging later in life) may also need help in working with the spouse or partner and acting on sexual feelings for someone of the opposite sex.

## Additional Psychotherapeutic Issues

### Sexual Orientation of the Therapist

Many gay, lesbian, and bisexual patients may wish to see a therapist who is also gay, lesbian, or bisexual, believing that they can avoid the overt effects of antigay bias and more easily develop a sense of trust, safety, openness, and personal comfort with a matched therapist. Many gay, lesbian, or bisexual therapists, in turn, may hold similar beliefs that homophobia can be avoided, that a special rapport can be established quickly, and that a shared base of knowledge and experience exists when gay, lesbian, and bisexual patients and therapists work together. However, not all gay and lesbian therapists will themselves have fully dealt with their own internalized homophobia and care must be taken not to assume that the therapist's and the patient's coming out processes were similar.

In general, conscious awareness of internalized homophobia and parallel heterosexism is an asset for the psychotherapist treating gay, lesbian, and bisexual patients. Gay-sensitive therapy—treatment provided from a perspective that understands and accepts gay, lesbian, and bisexual concerns—and gay-affirmative therapy—treatment provided from the perspective that being gay, lesbian, or bisexual should be affirmed and that openness about sexual orientation should be encouraged—can be provided by heterosexual as well as gay, lesbian, or bisexual clinicians.

### Couples and Family Issues Including Child Rearing

There is extensive literature on what constitutes a gay or lesbian couple and an extended family as well as on couples and family therapy with gay men, lesbians, and bisexuals (Cabaj 1988, Cabaj and Klinger 1996, McWhirter and Mattison 1984). The therapist must understand the impact of internalized homophobia, antigay bias, and the issues involved when two people of the same sex—and similar culturally determined gender role expectations—attempt to meet, bond, and establish relationships.

McWhirter and Mattison (1996) developed a stage model for gay male relationships (the stages may also apply, with some alterations, to lesbian couples, as well as to heterosexual and bisexual relationships). Briefly, the stages can be summarized and characterized as follows. Stage I: blending—marked by merging, romantic love, equalization, and high sexual intensity and activity. Stage II: nesting—marked by homemaking, compatibility, as well as ambivalence and decreased romantic love and sexual activity. Stage III: maintaining—marked by reemergence of the individual, with risk taking, increased conflicts, but establishing traditions. Stage IV: building—marked by collaborating, increasing productivity, independence, but ability to count on partner. Stage V: releasing—marked by trusting, merging of finances and possessions, as well as taking the partner for granted. Stage VI: renewing—marked by security, inward dwelling and remembering, and restoring the partnership.

This author (Cabaj 1988) proposes a four-dimensional assessment to evaluate couples and determine the best treatment intervention: assessment of each individual for those factors that determine stage in the life cycle, maturity, mental health problems, cultural factors; assessment of the gay or lesbian sexual orientation development including openness, coming out, effects of internalized homophobia; staging of the relationship, noting stage discrepancies between the partners; and assessment of other factors such as health, financial issues, children, and influences of families of origin on daily life.

In working with lesbian couples, the concept of merging is often discussed—the intense connection or even fusion of the two individuals in the relationship. Though this

phenomenon is not unique to lesbian couples, the couple's treatment technique known as "intimacy though distancing" was developed to work with such couples (Kaufman et al. 1984).

Since many gay, lesbian, and bisexual people have children, children may also have a role in therapy or may be the concern of the parents in therapy. The children in these families may be adopted or come from previous marriages or through alternative insemination or other biological arrangements. In looking at the sexual orientation of the children of such relationships and families, the children seem to develop sexual orientations that are distributed just like the general population, that is, predominately heterosexual, and they appear to have the same or even better psychological adjustment as other children (reviewed in Patterson 1995). A study (Golombok et al. 2003) indicates that children raised by same-sex couples may actually be better adjusted—more accepting of differences and more tolerant of varying forms or sexual expression—and not experience as much childhood ridicule as was speculated. Further studies are in progress, including looking prospectively and for a long term at the children of lesbian couples (Gartrell et al. 2005).

The issue of same-sex marriage has entered the arena in the last decade. While seen by many people as a religious or civil rights issue, the mental health aspects of marriage and recognized and sanctioned relationships are increasingly being recognized (Pawelski et al. 2006). Evidence shows that people in relationships, especially marriage, have increased mental health and better coping skills with issues that they will face, such as health problems and so on.

## Changing Sexual Orientation

This chapter makes clear that sexual orientation is a very complex phenomenon, with probable genetic, biological, social, familial, and cultural forces in its origins and expression, and psychological and psychodynamic forces that may result from having a particular sexual orientation and the adjustment to and acceptance of it. Sexual orientation, therefore, is not a result of how someone is raised, but sexual behavior, on the other hand, and the adjustment to one's sexual orientation is very much dependent on how and in what setting one is raised.

A limited number of therapists and clergy promote treatments that attempt to change sexual orientation, often from conservative religious sectors as well as a small group of conservative psychoanalysts. These approaches are sometimes called "conversion" or "reparative therapies." Nicolosi (1991) is a strong advocate of such approaches, describing reparative approaches and techniques.

These approaches assume that homosexuality is pathological and the result of deficient parental upbringing. Instead of exploring and understanding internalized homophobia and the consequences of antigay bias in gay and lesbian people who are troubled by their sexual orientation, advocates of such treatments take a "shame-based" approach and usually tell the patient that his or her sexual orientation is, indeed, a major problem and can be changed. Confounding gender role expectation with sexual orientation, these interventions assume that the gay man did not have enough masculine support or modeling with his father and the lesbian did not have enough feminine support or modeling from her mother.

There is very little objective data or clinical material to support such types of treatments (reviewed in Drescher and Zucker 2006). What appears to happen, as a result of such interventions, is that someone temporarily changes sexual behavior but does not change basic sexual orientation (maintaining same-sex sexual fantasies and desires) and usually returning to homosexual behavior over time. Spitzer (2003) reported results of a phone survey of people who wanted to change sexual orientation and a handful who said that they did; Drescher and Zucker (2006) focused on the extremely flawed nature of the survey and Spitzer himself has condemned the use of the study to indicate that true change in sexual orientation is possible.

Gay-, lesbian-, and bisexual-supportive therapists, in fact, report significant emotional and psychological harm from such attempts to change sexual orientation, with resulting depression, shame, anxiety, guilt, and suicidality (Haldeman 1994). Interventions that attempt to treat something that is not an illness, to try and change something that most likely cannot change, and to cause emotional harm in the process seem at best without merit and at worse unethical. All major national organizations related to mental health, including the APA and the American Psychological Association have condemned "reparative" or "conversion" therapy.

If a patient truly is troubled by his or her sexual orientation, exploration of the source of the distress and attempts to relieve the conflicts would be much more beneficial than suggesting the possibility of change. The internalized homophobia or external antigay pressure can usually be addressed in therapy and would help a patient far more than creating a deepened sense of shame and fear of acting on sexual and loving feelings.

## Societal and Domestic Violence

Antigay bias at times takes the form of violent attacks on sexual minorities, or people perceived to be such. The violence may range from verbal abuse to physical assaults violent enough to result in death (Huebner et al. 2004). The attacks are reported as hate crimes in many police surveys: one review reported that up to 28% of urban gay men, lesbians, and bisexuals reported physical assault or abuse, and 50% reported some form of harassment (Otis and Skinner 1996). Survivors of such abuse will need physical and psychological care, often developing posttraumatic stress syndromes with exaggerated internalized homophobia and fears of further antigay bias (Herek et al. 1999).

In addition, people in gay or lesbian relationships are also subject to domestic violence, just as are heterosexuals. Though the topic is not well studied, one survey reported that 25% of lesbians in committed relationships have been abused (Brand and Kidd 1986), and it is estimated that 10–20% of gay men in committed relations have been abused (Island and Letellier 1991); by comparison, battering occurs in 25–33% of heterosexual couples. Domestic abuse may be further fueled by substance abuse, and is often ignored or discounted by medical and mental health providers.

## Substance Abuse

Alcohol and other drugs have a major impact on the lives of many gay men, lesbians, and bisexuals. Most studies or reviews of surveys, and the experiences of clinicians

working with gay men and lesbians, estimate an incidence of substance abuse of all types at approximately 30%, with ranges of 28–35% (in contrasts to a generally accepted incidence of 10–12% for the general population) (Guss and Drescher 2000). While many of the studies are methodologically flawed, it is clear from these studies that gay men and women, on average, drink more than the general population, are likely to abuse certain drugs at different points in their lives (often associated with going to particular social settings), but may not have greater drug or alcohol dependency than the general population.

The increase in substance abuse may have many explanations. Limited types of sanctioned social outlets available to gay men and lesbians make bars, private homes, or clubs where (alcohol and other drugs and prominent) play very important parts of the social fabric for many gay and lesbian people. Often, the role models for many young gay men and lesbians just coming out are gay people using alcohol and other drugs, often met at bars or parties.

For many men and women, this linking of substance use and sexuality persists and may become part of the coming out and social and personal identity developmental processes, many having had their first same-sex sexual experiences while drinking or being drunk to overcome their societally influenced internal fear, denial, anxiety, or even revulsion about gay sex. Many gay people continue to feel self-hatred; the use of mood-altering substances temporarily relieves, but then reinforces this self-loathing in the drug withdrawal period.

For some gay people with high degrees of internalized homophobia, substance use may make "living in the closet," with its built-in need for denial and dissociation possible, or serve as easy relief from guilt or other negative feelings. Alcohol and other drugs can cause dissociation of feelings, anxiety, and behavior, thereby mimicking the emotional state many gay people had to develop in childhood to survive (as described above). Thus, the symptom-relieving aspects of substance use can serve to disinhibit what are experienced as forbidden behaviors, foster social comfort in bars, and, most importantly, provide comfort through the familiar experiences of numbing, dissociation, and isolation of feelings.

Self-acceptance of one's sexual orientation thus appears to be crucial to recovery from substance abuse. Recovery for gay and bisexual people will often depend on participation in 12-step or other self-help programs such as Alcoholic Anonymous (AA) and Narcotics Anonymous (NA), and many AA and NA groups are specifically aimed at gay, lesbian, and bisexual people.

In the last decade or more, the use and abuse of methamphetamine (also known as "speed," "crystal," "tina," "crank," and other names) have emerged as a particular problem for gay men. Though use is not exclusive to gay men (adolescents across the country and urban younger Asian and Latina women are also noted to be high users), the problem has multiple psychological and medical concerns for gay men in particular.

The use of the drug is highly associated with sexual activity and is popular at "circuit parties" where large numbers of gay men gather for partying, dancing, and sexual activity (often accompanied by drugs use) (Mansergh et al. 2001) and with men seeking sexual partners over the internet ("party and play"). Methamphetamine is experienced as heightening sexual feelings and duration of sexual activity, allowing some men to have sex for 12 hours or more. There are risks for increased exposure to HIV with multiple sexual partners and unprotected anal intercourse (sex without condoms) and injecting drug use (IV)—all of which are associated with methamphetamine use (Wainberg et al. 2006).

Many urban areas have started to address the concerns specific to gay men and some specific treatment programs are emerging for methamphetamine abusers. Contingency-management types of behavioral modifications are showing promise as successful interventions, and traditional 12-step programs are increasing with a focus specific to methamphetamine (Rawson et al. 2004).

## Chronic Mental Illness

As noted above, depression of all types and anxiety disorders present more often for gay, lesbian and bisexual people, but gay, lesbian and bisexual people are most likely subject to the same rates of serious mental illness as the general population. Many programs that are specialized for the chronically mentally ill minimize a focus on sexuality and sexual activity and may only rarely address sexual orientation itself. There may be particular benefits to the seriously mentally ill gay, lesbian or bisexual person in addressing sexual orientation—especially when it comes to issues of housing, roommate matching, vocational rehabilitation, and health interventions and education around HIV prevention—and programs that focus on the seriously mentally ill should include a focus on sexual orientation routinely (Hellman and Drescher 2005).

## Aging

As gay, lesbian, and bisexual people age, they will face issues similar to all people moving through the life cycle. There are more studies looking at older gay and lesbian people, some pointing out that the resilience from dealing with antigay bias over the years may make it easier to cope with some of the challenges about getting older. Since many older gay, lesbian and bisexual people have faced losses of close friends in large numbers to AIDS, many such people have developed skill to cope with death and dying and grief as they get older and lose family, friends, and partners (Grossman et al. 2000).

## Suicide

Suicidal thinking, attempts and completed suicides are major concerns for lesbian, gay, bisexual, and transgender (LGBT) people—especially for youths and young adults. All ages have been looked at for LGBT people, but most studies have focused on youth, some noting the incidents of successful suicides as high as three times the national average for that age group, and as many as 30% of gay and bisexual people may have attempted suicide (Cochran and Mays 2000, Paul et al. 2002). The increased rates of suicidality seem tied to the struggles for acceptance in the face of antigay bias and self-esteem damaged by internalized homophobia, but an additional risk factor may be the higher rates of affective disorders among LGBT people noted in studies such as Mills et al. (2004). Studies now look at both the increased incidence as well as the contributing risk factors, and interventions that may help prevent or at least lower the rate of actual suicide if not suicidal ideation itself (Eisenberg and Resnick 2006, Friedman et al. 2006).

### HIV and AIDS

HIV and AIDS affect many gay men, lesbians, and bisexual men and women, either by being infected themselves or by being close to a person with HIV/AIDS. Gay men, who are depressed or suffer from damaged self-esteem and shame due to internalized homophobia, may put themselves at risk for HIV infection, consciously or unconsciously, via risky sexual practices especially under the influence of drugs or alcohol, or sharing needles (Cabaj 1998). Lesbians are also at risk for HIV infection, not only from drug use and shared needles, but from the fact that many lesbians also have sex with men. HIV-prevention efforts are mental health issues for many gay and bisexual people. Therapy with people living with HIV infection and AIDS is beyond the scope of this chapter.

### Minority, Ethnic, and Cultural Issues

There are both cultural and ethnic issues involved for people of color that may make it difficult to come out or adjust comfortably to a gay, lesbian, or bisexual identity (Grov et al. 2006). Many people, especially people of color or people from a culture other than the Anglo/European-Western, who have sex almost exclusively with people of the same sex, may not self-identify as gay or even bisexual (Pathela et al. 2006). The provider may not need to worry about such labels if the patient is allowed to have open and frank discussions with the therapist or provider. Openly gay, lesbian, and bisexual people of color must often deal with bias and prejudice and stigma for racial, cultural, and sexual orientation factors, and thus present with complex social, emotional, and mental health concerns. For example, Cochran and Mays (1994) focused on the specific factors and issues for depression in African-American gay men and lesbians.

### Youth

Awareness of a differing sexual orientation may occur at any point in life, but most often in childhood or adolescence. Recognizing the tremendous social pressures to conform in adolescence, and the extraordinary efforts it takes for a gay male or lesbian to be out with peers and family, will help therapists understand the pressure openly gay, lesbian, or bisexual youth may face. Gay and lesbian youth are also subject to sexual abuse or exploitation by others, often related to insecurity and reduced self-esteem. As noted, some gay, lesbian, and bisexual youth may run away and face the many stresses and risks of living on the streets (Savin-Williams 1994). The youth who stay in school and at home may also face great difficulty from the attitudes of peers, teachers, and parents (D'Augelli 1996).

## Gender Identity and Transgender Issues

Gender identity, as noted above, is an independent variable from sexual orientation. The subject is often included in discussions of sexual orientation since the biases and prejudices against people who have gender identity disorder (GID) or who ultimately identify as transgender (i.e., a person of one biological sex who is contemplating becoming, living like, or undergoing sexual reassignment surgery to the opposite sex) may be similar.

GID is still included in the DSM-IV-TR, though there have been extensive reviews of the justification of such a diagnosis. The diagnosis has been helpful to some people who are undergoing biological treatments (hormone replacement or sexual reassignment surgery) since these treatments may be covered by insurance. Some transgender people and advocates of the study and treatment of gender identity concerns believe that a mental health diagnosis is prejudicial since it is not a mental illness per se but likely a biological or genetic issue. There are insufficient studies to illuminate the origins of gender discordance and identity conflict, but future DSM research agendas may address the issue.

Childhood GID is often a concern both for the youth as well as the family—often a source of confusion, embarrassment, shame when not understood by the family. Gender discordant behavior—that is, behaviors usually associated with the opposite gender of the identified youth—may be a manifestation of childhood GID, but is also demonstrated in youth who grow up to have no conflict between biological and perceived gender. In the past, some therapists urged parents to try and change the behaviors of such children with the belief that if the child could "fit in better" with peers, he or she would be better accepted (and perhaps even change the course of development of either GID and a nonheterosexual orientation similar to the hopes of the reparative therapy literature) (Green 1985). As is true with attempts to change sexual orientation, such interventions with gender discordant children result in psychological harm, shame, frustration, and possible depression and suicidality (Haldeman 1994).

Transgender can be considered a broader concept, including people who live like or become a member of the opposite sex, as well as people who wish to cross-dress or live as a member of the opposite sex, even if there is no perceived difference between biological sex and personal sense of gender. Though often described in terms of gender discordant behavior, a transgender person may look and act just as is societally expected of their biological sex, even if they are quite aware of the difference internally. Many transgender people do begin to dress and live like a member of the other sex, and some eventually seek sexual reassignment surgery. The concept of sexual orientation as independent of sexual identity is demonstrated by this example: a biological male may see himself as a woman or even had sexual reassignment surgery to become a female, and if attracted to women, would be considered to have a female homosexual orientation, and if attracted to men, be considered to have a female heterosexual orientation.

A person with a gender identity discordance may go through several stages of acceptance similar to a person who recognizes a differing sexual orientation. Recognition of the difference, acceptance of it, a decision about how to act on or live with those differences, and deciding who should know are steps all transgender people face.

There is an increasing body of literature on gender identity issues and specific studies of transgender people. Health issues have been a focus—including mental health and substance abuse. These studies indicate that transgender people may experience higher rates of depression, substance abuse, suicidality, may be greater victims of violence, and may have limited access to health care, place themselves at higher risk in sexual situations and therefore have higher rates of HIV infection and AIDS, when compared to the general population (Clements-Nolle et al. 2001, Fitzpatrick et al. 2005).

## Future Efforts and Research

Many issues related to sexual orientation and the understanding of gay men, lesbians, and bisexual men and women require further study and research. A major effort is needed to provide clear, unbiased, and sensitive information about this topic to mental health and medical professionals at all levels of educational efforts. The APA has developed a series of minority curricula for psychiatric residents, and the gay, lesbian, and bisexual curriculum was the first to be published (Stein 1994).

Legal and political forces will continue to shape both the societal attitudes that influence acceptance of gay and bisexual people—and the funding available to study issues related to sexual orientation. Combating antigay bias and its resultant internalized homophobia will be enhanced more by legal protections than by education and attempts at changing social attitudes alone.

Further study and research is clearly needed on topics such as the following: the genetic and biological factors leading to the development of a gay, lesbian, or bisexual identity; bisexuality; transgender issues; substance abuse in the gay, lesbian, and bisexual community; gay, lesbian, bisexual, and transgender youth risk for suicide; people of color with sexual orientations that differ from the majority; attempts to change sexual orientation; what effects legalizing or sanctioning gay and lesbian couples may have; and, the emotional and psychological development of children of gay male and lesbian couples.

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CHAPTER

# 123 Management of the Patient in Geriatric Psychiatry

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## Introduction

The management of the elderly psychiatric patient involves the intersection of a number of important elements. The effects of the aging process itself must be considered, which may include reduced vigor, lessened efficiency of vital organ systems, impairments in vision, hearing, and other senses, loss of mobility, slowed cognition and other changes. Many elders suffer from significant medical morbidity, often involving multiple disease states that may have overlapping or cumulative effects. These medical issues impact mental functioning, while psychiatric illness can also have a significant effect on physical health. Problems such as weight loss, cognitive decline, sleep disturbances, and falling are important in medical geriatrics as well as geriatric psychiatry. The aging process also involves changes in pharmacokinetic and pharmacodynamic processes. Elders frequently take a large number of medications. The effects and interactions of these drugs comprise an important element of geriatric management. Both medical and psychiatric illnesses may present in altered or even atypical fashion in elders, complicating the diagnosis. Older patients and their families must adapt to new roles in the family and community, often involving increased dependence on others. Referral of geriatric patients for psychiatric care is typically made by family, other physicians, or agencies rather than self-referral. Obviously, these sources of referral have a stake in the patient's care often involving an expectation of ongoing involvement. The aging process is markedly heterogeneous, influenced by genetic influences, disease, and other factors. The increasing numbers of elders in many societies will burden health-care systems. Since the number of geriatric specialists is limited, general psychiatrists (and nonpsychiatric physicians) will be called upon to address much of this need. Sophisticated knowledge of geriatric management is particularly important for frail or very elderly patients. This chapter deals with management issues commonly encountered in geriatric psychiatry. Certain syndromes such as dementia and mood disorders are especially important in geriatric psychiatry and will be used to illustrate key elements of geriatric management.

## Approach to the Patient

### Social Setting

Evaluation of an elderly patient involves an understanding of his or her social setting. The patient's role in the family and community is crucial in understanding their behavior. Elders may reside at home alone or with family or other caregivers. They may also live in a variety of other settings. Those who reside in nursing or assisted living homes often face special challenges. Among these challenges are maintaining as much independence as possible while also preserving dignity and privacy. The enormous financial burden of long-term care must often be met by patients and their loved ones. Families are often intimately involved in geriatric care at every level. Families provide much of the caregiving for disabled elders, often at a tremendous physical, emotional, and financial toll. Elderly patients and their families must deal with difficult questions balancing independence with safety, often with limited personal and financial resources. Unfortunately, lack of financial resources often severely limits options for elders. Psychiatrists caring for frail or cognitively impaired elderly patients must forge an alliance with caregivers. Caregivers provide much needed data to the clinician and often carry out the treatment plan. While respecting the patient's autonomy, the psychiatrist must be sensitive to the caregiver's need for support and information.

Certain social situations are common aspects of aging. Retirement involves adjustment to a new schedule and often a change of status, especially for persons whose identity is associated with a profession. Retirement can also lead to social isolation when friendships have been work based. Marital relationships may have to find a new equilibrium. For many, retirement can bring financial hardship as well. Elders must adapt to the "empty nest" as adult children

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move out of the family dwelling and establish their own homes and families, often in a different city. For many elders the role of grandparent can bring great emotional fulfillment. However, an increasing number of elders find themselves having to assume parenting responsibilities for grandchildren or great-grandchildren.

As parents age, their adult children must also learn new roles. They must often assume decision making, caregiving, or financial responsibilities while maintaining their own families and careers. These duties can strain marriages and sometimes provoke conflict among the elder and the adult children or among the children themselves. This problem is compounded when family members reside in different locales, adding distance to the stresses involved. Increasing dependency in an elderly relative evokes powerful emotional reactions in loved ones and can be an especially difficult if the patient or family is in denial. This situation often leads to conflict among relatives over treatment planning decisions, especially when these decisions can reduce the elder's independence.

Many elders are dependent on a web of social programs. In the United States programs such as Social Security, Medicare, or Medicaid can provide income, health insurance, and prescription drug coverage (Hoffman et al. 2005). A basic understanding of these programs and their role in the patient's life is necessary in providing comprehensive care. Although these programs are crucial to the well-being of elders, they do not provide for a seamless system of care. For example, Medicare nursing home coverage provides only for a limited number of skilled care days. Medicaid has much more extensive nursing home coverage, but many elders (even those of limited financial means) do not qualify for Medicaid until their existing financial resources have been exhausted or "spent down." Although Medicare is a federal program and is therefore more or less standardized throughout the United States, Medicaid is a joint federal-state program. Overall Medicaid standards are set by the federal government, but individual states determine eligibility requirements, covered services and provider types, and levels of reimbursement. Medicaid coverage can be quite variable from state to state. Other programs can contribute the well-being of elders, such as Meals on Wheels or adult day programs. Elders residing in rural areas may not have these services available. Government also has a responsibility to investigate, prosecute, and address elder abuse and neglect though adult protective services programs. The cost and accessibility of social services for elders differs dramatically in different countries.

## Functional Assessment

Functional capacity may be affected by aging or illness. An assessment of ability to perform activities of daily living (ADL) is a crucial element of a geriatric evaluation (Resnick 1998). This functional assessment may be informal or may represent a formalized part of the evaluation requiring specialized testing. Such testing can involve referral to other physicians or specialists such as psychologists, physical therapists, audiologists, or occupational therapists. Often, the patient's ability to care for themselves in their own environment becomes as significant as the medical or psychiatric diagnosis. When functional deficits are present, treatment planning must take them into account. Determining the appropriate level of care is largely based on functional level. Basic activities of living such as feeding or dressing one's self are a necessary part of living alone. More advanced activities often involve using tools of some type (such as a telephone). Patients who have impairments of these more advanced functional activities may continue to struggle to maintain independence despite faltering abilities. For instance, a patient who no longer drives may not be able to continue a fully independent life. Inability to negotiate stairs may necessitate a move to a one-story home. On occasion, adaptational methods or devices can be suggested in an effort to maintain as much independence as possible. Function is also greatly influenced by the patient's ability to see and hear. Evaluation and management of deficits in these areas can greatly improve an elder's function and quality of life and sometimes reduce psychiatric morbidity. Impairments of gait and mobility as well as falling are common problems in geropsychiatric patients. These impairments can result from neurological or orthopedic disorders, visual impairments, cognitive loss, or some combination of these factors. A serious fall, especially if injury occurs, often leads to significant psychological effects including loss confidence or even depression. Therefore, treatment planning should involve diagnosis and management of these problems of gait and mobility.

## Cognitive Evaluation and Management

Since cognitive decline is a common problem in geriatric care, the mental status examination should include a thorough cognitive evaluation. Minimally, this evaluation should include an assessment of immediate recall as well as short- and long-term memory. Additionally, orientation, attention, calculation, and visuospatial abilities should be examined. Speech and language functioning should be tested as should reading and writing. Also, executive abilities such as planning and problem solving should be assessed. Cognitive testing will be further discussed later in this chapter.

## Guardianship and Power of Attorney

Cognitively impaired elders who need supervision may require a legally empowered surrogate decision maker (Kane 2001). In the United States and many other countries, this may be accomplished by action of courts through assigning a guardian to oversee and protect the interests of the elder. Such actions typically require a formal, independent evaluation followed by a hearing in which the elder is entitled to legal representation and due process. Usually, substantial cognitive impairment must be demonstrated in order for the court to assign a guardian who will continue to serve unless relieved by the court. Such court-ordered guardianships are therefore involuntary. They are a legal finding that the patient, who is otherwise entitled to a presumption of competency, is now incompetent. A guardianship cannot be established in advance, but only after this determination has been made. The judge delineates the exact limits of the guardian's authority. The power of attorney (POA) is another pathway which can accomplish some of the same goals by a very different mechanism. A POA is a private, voluntary contractual agreement between two or more individuals in which a person is empowered to act on another's behalf.

It is not a court order, but a form of "advance directive." The POA must be created when the patient is sufficiently competent to understand its provisions. Therefore, after a dementia has progressed it may be too late to initiate a POA. A POA designed for health care and dementia is known as a "durable" POA. The POA document typically delineates the precise authority granted, but usually includes health care as well as financial decisions. A durable POA only becomes operative when the patient has become cognitively disabled. Although often useful, POA have limitations. For example, a patient with mild-to-moderate dementia who remains verbal and interactive may not accept a determination that they are disabled, creating doubt about the document's applicability (Table 123–1).

**Table 123–1 Legal Guardianship and Power of Attorney in Dementia**

| Guardianship (Conservatorship) | Power Of Attorney (Durable or Enduring) |
|---|---|
| • Involuntary | • Voluntary |
| • Court mandated | • Private agreement or contract |
| • Process initiated after subject manifests cognitive decline | • Process initiated in advance of substantial cognitive decline |
| • Usually requires formal cognitive evaluation | • Formal cognitive evaluation may not be required |
| • Becomes effective upon court's finding of cognitive incapacity | • Becomes effective contingent on development of substantial cognitive decline |
| • Revocation requires court action | • Subject has right to revoke agreement |

[Reproduced from Arie (1996) with permission of BMJ.]

## Physical Evaluation

Management of geriatric psychiatry patients also involves a careful physical assessment (Finkel and Woodson 1997). While the psychiatrist should participate in this element of care, most patients will also require a medical evaluation by the family physician or other specialists. Ideally, the psychiatrist should communicate with these other physicians in formulating the overall plan of care. Obviously, medical illnesses common in elders such as cancer, heart disease, stroke, diabetes mellitus, COPD, and arthritis have an impact on psychiatric status. Likewise, dementia, depression, or psychosis will have a significant effect on the care of the patient's physical disorders. The choice of medications to treat medical as well as psychiatric disorders should be a matter of discussion among specialists. For example, the anticholinergic drugs commonly used to treat bladder incontinence can have a negative impact on cognition. The drug chosen to treat psychotic symptoms may complicate care of diabetes. Increasingly, psychiatrists are expected to be aware of the intersection between psychiatric and medical management and the medical consequences of psychopharamacologic treatments. Polypharmacy is a common problem among the elderly and can only be dealt with by discussion among the various physicians prescribing for the patient. The entire medication list, including over-the-counter medications must be scrutinized. The psychiatrist should consider the possible psychiatric ramifications of each medication as well as potential drug interactions. In performing this analysis of the medication regimen, the psychiatrist should remember that patients may not take medications as prescribed for a variety of reasons. Patients may forget to take medicines, not be able to afford or obtain their drugs, or stop them because of side effects. Friends or family members may occasionally advise patients not to take prescribed medication. Patients may also save medications from previous episodes of illness, or receive medications from friends or family members. Communication among specialists is also necessary in the evaluation and management of several syndromes that are especially common in elderly patients. For instance, unexplained weight loss can be an indicator of carcinoma, depression, or dementia. Insomnia is also very common in elders and can be related to a host of problems. Psychiatric problems such as depression, dementia, or substance abuse, sleep disorders such as sleep apnea, pain syndromes, or medical problems such nocturia can all contribute to insomnia.

## Multifactorial Approach to Geriatric Assessment and Management

Psychiatrists caring for the elderly must take a multifactorial approach, developing an appreciation for the psychosocial and developmental as well as medical issues in caring for their elderly patients. This approach must be respectful of the special needs of elderly patients yet not be patronizing. The evaluation process involves collecting information not only from the patient but also from other physicians, the medical record, and family members. Frequently, consultation with psychologists, occupational therapists, social workers, physical therapists, and other medical specialists may be required. The psychiatrist plays the role of coordinator of the mental health team. Many geriatric illnesses are chronic and require a strategy of coping and improved quality of life rather than cure. This type of approach requires patience as results unfold over the long run. Some older patients are uncomfortable with psychiatric labels and psychiatrists. These negative attitudes may be a reflection of the societal beliefs of the patient's formative years. Psychiatrists should be sensitive to this self stigmatization and be prepared to educate the patient and family.

In the United States, elders comprise more than 10% of the population. This percentage is expected to grow in the US and many other societies as the "baby boom" generation ages and life expectancy increases. Those over the age of 85 years are the fastest growing segment of the elderly population as well as the group with the greatest medical and psychiatric morbidity. It is unlikely that there will be sufficient geriatric psychiatry specialists to provide care to all these patients. General psychiatrists will need to fill much of this need.

# Management of Dementia

## Evaluation of Dementia

Dementia may be defined as a syndrome of persistent, acquired cognitive deficits sufficient to affect function. Dementia is an increasingly important and prevalent problem as the number of the elderly increases, especially those over the age of 85 years who are at highest risk. Although advancing age is a risk factor, dementia is never

**Table 123–2 Basic Dementia Workup**

- History
- Pysical examination
- Mental status examination including cognitive assessment
- Neuroimaging (head CT or MRI)
- CBC
- Chemistry profile
- Thyroid panel
- $B_{12}$ level

[Reproduced from APA (1997) with permission of American Journal of Psychiatry.]

considered to be merely a part of normal aging. Dementia requires thorough assessment as a prelude to management (Table 123–2). Although fully reversible cases are rare, dementia evaluation requires a careful assessment designed to identify potentially treatable medical problems which may contribute to cognitive impairment. The initial workup includes a complete blood count (CBC), chemistry profile (such as a comprehensive metabolic profile), thyroid profile, and vitamin $B_{12}$. Most clinicians consider neuroimaging with head CT or MRI advisable as part of the initial evaluation. A variety of other tests may be ordered depending on the history and clinical findings such as electroencephalogram, electrocardiogram (ECG), urinalysis, sedimentation rate, or folate level (Table 123–3). Occasionally, screening for heavy metals or inflammatory conditions such as systemic lupus erythematosus may be required. Lumbar puncture may rarely be indicated if meningitis or encephalitis are suspected [American Psychiatric Association (APA) 1997, Spar and La Rue 2006a, 2006b]. PET scanning is not routinely performed today, but may be useful in distinguishing Alzheimer's disease (AD) from frontotemporal dementias such as Pick's disease in certain cases. In the future, PET or MRI may play a greater role in dementia assessment as promising new technologies make it possible to visualize amyloid deposits, which cannot be done with currently available neuroimaging (Petrella et al. 2003).

AD has sometimes been described as a diagnosis of exclusion. By ruling out identifiable medical causes of the syndrome, AD would be left as the likely diagnosis. However, current approaches to diagnosis focus on "ruling in" the disorder by identifying the characteristic clinical presentation and course of AD, which are somewhat distinct from other dementias. Also, since Alzheimer's can coexist with other disease states, identifying other potential causes does not rule out AD. AD usually involves an insidious onset and gradual progression, typically over a period of years. Short-term memory impairment is a hallmark of AD. Diagnosis of AD involves interview and mental status of the patient as well as information from other informants, since AD is also characterized by a lack of awareness of the illness (APA 1997). In some patients, distinguishing the type of dementia is problematic. Individual patients may present atypically or several brain diseases may coexist (for example, AD with vascular lesions or Lewy bodies).

**Table 123–3 Additional Dementia Testing Based on Individual History**

- PET scan of brain
- SPECT scan of brain
- RPR (or other syphilis serology)
- Folate level
- ANA, sedimentation rate
- Heavy metal screen
- Formal neuropsychological testing

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## Cognitive Assessment

Assessment of dementia requires an evaluation of memory including immediate recall, short-term memory, long-term memory, and other memory functions. Speech and language are often impaired in dementia and should be characterized. Dementia evaluations also require an assessment of praxis, visuospatial ability, attention and concentration, and calculation. Executive functions such as planning and problem solving are often impaired in dementia and should also be assessed. ADL are progressively impaired in dementia. Neurovegetative functions such as sleep and appetite are usually affected by dementia as are neuromuscular functions such as gait and balance. These elements also require delineation. Psychiatric and behavioral symptoms are also quite common in dementia and will be discussed separately.

Brief cognitive rating scales are often used for screening purposes and to track the progress of the disease. The best-known scale is the mini-mental state exam (MMSE). The MMSE is a 30-point test of basic cognitive skills that measures orientation, immediate recall, short-term memory, attention, and concentration. It features questions on basic language, reading, writing, and following directions. The patient is also given a figure of two overlapping pentagons to copy (Folstein et al. 1975). Although relatively easy to learn and administer, the MMSE has some limitations. For example, the questions are limited to several cognitive domains and do not address ADL, neurovegetative symptoms, or behavioral aspects of dementia. Patients who receive a similar score may actually have answered individual questions quite differently. Highly intelligent or educated patients may continue to achieve a relatively high score despite having early dementia. The MMSE is difficult to administer and interpret for individuals with limited education, language proficiency, or motivation. Likewise, vision or hearing deficits limit the effectiveness of this test. The MMSE may overestimate cognitive deficits in such patients. For these reasons, the MMSE is neither sensitive nor specific enough to stand alone as a diagnostic instrument. A variety of alternatives to the MMSE have been devised in an effort to find a faster and more reliable measure, but any brief test of cognition involves some limitations. For the clock drawing test (Brodaty and Moore 1997), the patient is usually asked to draw the face of a clock including the numerals and hands to indicate a certain time. Several scoring methods are utilized, but typically the patient receives a point for drawing a closed circle, a point for including all 12 numbers, a point for placing the numbers correctly, and a point for putting the hands in the correct location. Thus, 4 is a perfect score. Any score less than 4 should arouse suspicion while a score of less than 3 is clearly pathological. The Mini-Cog test also involves four possible points. The patient is given a three-item recall task as well as a clock. In this test, one

point is received for each item correctly recalled and one point for a correct clock (Borson et al. 2000).

## Impact on Caregivers

Management of dementia requires an understanding of the impact of the illness on the patient's caregiver and entire family. Caring for the AD patient requires support, advice, and education for the caregiver as well. Helping the family understand and accept the illness is an important role of the psychiatrist. They often require practical advice on topics such as driving, behavior management, ADL, and timing of placement in a nursing home or other facility. Making the diagnosis as early in the disease process as possible is valuable not only for pharmacologic management, but also enables the patient and family to discuss issues such as estate planning, powers of attorney, nursing home placement, and end-of-life care while the patient is cognitively able to participate (McCurry 2006).

## Driving and Dementia

Driving is a significant problem for dementia patients and their families. A few states have enacted laws restricting driving in patients diagnosed with AD or other dementias. However, at present most states have no such legislation. While patients with mild dementia can often continue to drive, moderate-to-severe dementia patients clearly have a higher risk of accidents and should not drive. Some patients may continue to drive if they can observe restrictions such as driving only during the daytime and in good weather, driving only in familiar areas and limited distances, and avoiding expressways. Some communities have evaluation programs designed to test drivers suspected of cognitive impairment. Many dementia patients resist giving up driving. They may fear loss of independence and may also fail to recognize their own illness. In such cases, the physician may have to take action to limit the patient's driving (Spar and La Rue 2006a, 2006b, Wang et al. 2003).

## Pharmacologic Management

Cholinesterase inhibitors (CIs) are widely used in the symptomatic treatment of AD. CI are typically prescribed early in the course of the disease and maintained as long as there are apparent benefits. The decision to stop CI is made on an individual case basis taking into account the degree of benefit, progression of illness, side effects, cost, and goals of treatment. While CI are prescribed primarily for cognitive benefits, they may also help behavioral symptoms, maintain functional abilities, delay nursing home placement, and reduce caregiver burden. However, the effects of CI are generally modest. Goals of treatment with CI include improvement, stabilization, or slower than expected decline.

Establishing the effects of CI may take several months of therapy and be difficult to quantify for an individual patient. While indicated by the Food and Drug Administration (FDA) for AD, CI are also sometimes prescribed for mild cognitive impairment or other forms of dementia. CI are believed to work primarily by blocking acetylcholinesterase in the brain, thereby increasing levels of the neurotransmitter acetylcholine, which is believed to be important for memory function. The three currently utilized CI (donepezil, rivastigmine, and galantamine) vary slightly in exact mechanism but are generally similar in clinical response. CI are not believed to influence amyloid plaques, neurofibrillary tangles, atrophy, or other basic manifestations of the disease. While generally well tolerated, CI may have a variety of side effects that primarily involve, cholinergic functioning. The most common side effects include gastrointestinal effects such as nausea, vomiting, and diarrhea. Less common side effects include muscle weakness, bradycardia, loss of appetite, and sleep or dream disturbance. CI should be used with caution in patients with a history of bleeding peptic ulcers (Takeda et al. 2006).

Memantine is an antagonist of the N-methyl-D-aspartic acid (NMDA) glutamate receptor and is believed to modulate neurotransmission. Clinically, memantine is indicated for moderate-to-severe dementia of the Alzheimer's type (Reisberg et al. 2003) and is occasionally prescribed for other forms of dementia. Although its mechanism is quite distinct, the clinical effects of memantine are roughly similar to those of CI, including modest, symptomatic effects on cognition and behavior rather than curative or true disease-modifying effects. Memantine can be used alone or in combination with a CI. Evidence of a synergistic effect was found in a study of moderate-to-severe AD in which patients being treated with the CI donepezil were also given memantine (Tariot et al. 2004). The side effects of memantine are usually mild and may include constipation. Rarely, patients can experience increased confusion.

A variety of other treatments have been proposed for AD and other dementias. At present, none have been clearly shown to be beneficial. Antioxidants such as vitamin E have been widely discussed. One study of high-dose vitamin E showed benefit in function though not cognition (Sano et al. 1997). However, high doses of vitamin E have also been linked to negative health effects including increased cardiovascular mortality. Early studies of estrogen as well as nonsteroidal anti-inflammatories showed much promise, but subsequent research has not been confirmatory. More recently statins, oral hypoglycemics, lithium, and other medications have been proposed as preventives or treatments in AD but remain investigational. A variety of new medications are in development, including several types of antiamyloid drugs. At present, only the CI and memantine are clinically available. There is no known prevention for AD. Some authors have proposed increased mental or physical activity (Verghese et al. 2003, Larson et al. 2006). Dietary approaches such as red wine, antioxidant-rich diets, the "Mediterranean" diet (rich in fish, olive oil, and whole grains and low in saturated fat) have also been proposed (Scarmeass et al. 2006). Some authors have suggested a link between vascular disease or type II diabetes and AD. According to this viewpoint, managing blood sugar and vascular risk factors such as hypertension and lipids might be helpful in reducing the risk of AD (Haan and Wallace 2004).

## Medical Comorbidity and Dementia

Many dementia patients have comorbid medical problems requiring care. Intensive medical evaluations and aggressive therapies for such conditions usually require a motivated and cooperative patient who can participate in his or her own care. As cognition declines, such an approach becomes quite difficult to apply. In advanced dementia, a palliative-care approach to management of pain and comorbid medical conditions may be appropriate. This approach emphasizes

relief of suffering and psychosocial support for the patient and family rather than intrusive or extensive medical interventions. Palliative care, along with hospice, have gained considerable acceptance in the medical community as well as the community at large. However, these approaches have been utilized primarily for those with terminal medical conditions such as AIDS or cancer. In recent years, some psychiatrists as well as palliative-care specialists have become interested in applying this approach more widely to dementia (Harris 2007). Most dementias can be thought of as terminal diseases, since the patient will continue to decline and will not recover.

## Management of Behavioral Disturbance in Dementia

### Clinical Presentation of Behavioral Disturbance

The great majority of persons with dementia suffer from some form of psychiatric or behavioral disturbance during the course of their disease (Cummings 2005, Lyketsos et al. 2000). Up to 50% are believed to suffer from psychotic symptoms including delusions or hallucinations. Despite these problems, behavioral disturbance in dementia (BDD) has not been a major focus of psychiatric research. Behavioral disturbance contributes greatly to reduced quality of life for the patient, their caregivers, and those around them. Hospitalization and placement of the patient in a long-term care facility is often prompted by BDD. Therefore, BDD drives much of the cost of caring for demented patients. As the problem becomes more prevalent, the most severely disturbed patients move back and forth between the hospital and nursing homes in a new form of "revolving door." In the typical nursing home approximately 50% of patients suffer from dementia. Nursing homes are becoming de facto psychiatric facilities in the management of BDD, a role they are ill suited to play.

Virtually any psychiatric symptom can occur in BDD. Complex combinations of symptoms are common, which evolve over time. These symptoms may or may not resemble typical psychiatric syndromes. In early or mild dementia, anxiety or mood symptoms frequently occur. These symptoms may actually predate the onset of diagnosable memory symptoms of dementia. As dementia progresses through its stages, the earlier symptoms may persist while new symptoms develop.

Moderate dementia is often a challenging period in the management of BDD. Wandering, sleep disturbances, agitation, aggression, and combativeness may begin. Yelling or other vocalization syndromes present significant challenges in management (e.g., chanting, repeatedly asking the same question). Psychosis often begins and usually includes an element of paranoia, often focused on the caregiver or those nearby. When patients no longer recognize loved ones, the paranoia may take the form of delusions of impostors (Capgras syndrome). Hallucinations are less common but may be noted in Lewy Body and other parkinsonian dementias as well as delirium. Hallucinations are predominantly visual. Because of memory disturbance, confabulation, and communication deficits, psychosis can be difficult to diagnose in dementia patients. As dementia progresses, sleep usually becomes more erratic. Patients may not perceive this as a problem, but it is a significant issue for caregivers. Some patients become more agitated or psychotic later in the day or at night, a condition known as "sundowning" (Bachman and Rabins 2006). Disinhibition and inappropriate sexual behaviors may also occur. In late-stage dementia, agitation and aggression may be ongoing problems. Apathy, refusal of care, and eating problems may occur. In addition, behavioral patterns typical of infancy or childhood may reemerge (such a "shadowing" or following the caregiver and becoming distressed if the caregiver is not present).

### Etiology of Behavioral Disturbance

The etiology of BDD is not well understood. It is almost certainly a heterogeneous, multifactorial problem. Preexisting psychiatric illness such as affective disorder, schizophrenia, or substance abuse may be a contributing factor in some cases. Some symptoms, such as anxiety, may be a direct result of cognitive loss. Dementia frequently contributes to stressful life situations such as loss of independence and nursing home placement. Dementia patients often deal with such stressors by acting out behaviorally. Many symptoms undoubtedly follow as a direct result of neurodegeneration. Dementing illnesses lead to changes in neurotransmitter function in key systems that impact thinking and behavior (such as acetylcholine, norepinephrine, dopamine, glutamate, and serotonin). Delirium from comorbid medical conditions or medication frequently contributes to BDD. Pain or physical discomfort can also contribute to problem behaviors, complicated by the patient's difficulty in communication (Desai and Grossberg 2001).

The treatment of BDD must follow from a careful assessment of the patient. This assessment must include screening for medical conditions, which may be a source of delirium or pain. The entire medication list should be scrutinized, including over the counter medications. Polypharmacy is common among elderly patients and is frequently a source of confusion or behavioral disturbance. Dementia patients are particularly prone to negative effects from anticholinergic medications. Benztropine, tricyclic antidepressants (TCA), hydroxizine, and many others have significant anticholinergic effects. In addition, the patient's environment may be an important factor in the development of BDD (Desai and Grossberg 2001).

### Delirium and Dementia

Delirium frequently complicates dementing disorders and can be source of additional confusion, agitation, or psychosis. Such a delirium can be subtle and difficult to recognize against the backdrop of dementia. Even relatively minor medical problems such as a urinary tract infection may provoke a delirium in a dementia patient. Often the delirium occurs in the context of multiple medical problems. Medications, particularly anticholinergic medications, sedatives, or polypharmacy may also be source of delirium. Management of delirium primarily involves treating the underlying disorder or disorders. Prolonged or severe delirium may be a poor prognostic sign, indicating a failing ability of the organism to cope with stress (Casey et al. 1996).

### Nonpharmacologic Management

Nonpharmacologic management of behavioral disturbances should be considered as the initial approach, and should be

**Table 123–4 Nonpharmacologic Management of Behavioral Disturbance in Dementia**

- Predictable daily schedule
- Calm, orderly environment
- Appropriate level of cognitive and social stimulation
- Simple directions
- Distraction rather than confrontation
- Respect for the patient's space\
- Space to safely wander
- Music

continued in the event medications are required (Table 123–4). A variety of interventions can be utilized. After identifying and quantifying the behavior to be addressed, the first step is to identify any environmental or interpersonal triggers that contribute to the behavior. Such triggers might include conflict with a caregiver or roommate, too much or too little stimulation, or variations in the daily schedule. At times, the behavior is reinforced by the responses of others. Dementia patients typically do best with a calm, orderly environment. A predictable schedule helps the patient maintain appropriate behavior. Some patients respond to alterations in the schedule with significant agitation. Since dementia patients cannot comprehend multistep commands, it is necessary to break tasks down into small components. The caregiver should try to "depersonalize" the dementia-related behavior and not respond emotionally. Rather than confrontation, which is rarely productive, dementia patients respond better to reassurance and distraction with alternative activities. A patient approach, respecting the patient's need for time and space, will typically provoke much less agitation than a more forceful tone. Many dementia patients have a need to wander and will be less agitated if a safe wandering space is available (Cohen-Mansfield 2001, Teri et al. 2002).

## Pharmacologic Management of Behavioral Disturbance

Dementia patients suffer from many symptoms, usually in the context of an incurable disease. Treatment will not be able to address many of these symptoms. Therefore, it is important to have a specific goal or goals in mind when initiating treatment. Since the disease provokes strong emotional reactions in caregivers and often precipitates conflict over diagnosis or treatment, it is useful to try to achieve some consensus among key persons in determining the goals and means of treatment. It is often helpful to choose one or more "target symptoms." These should be symptoms that are amenable to pharmacotherapy. In most cases, reducing the intensity of symptoms is a more realistic goal than complete eradication of a behavioral problem. Some means of quantifying the symptom and response is also necessary as the caregivers' impressions may be at odds with one another and greatly influenced by their emotional responses to the patient's illness. Medication therapy is best regarded as an adjunct to nonpharmacologic treatments that focus on modifying the patient's environment (Maher 2004).

The US Food and Drug Administration (FDA) does not currently indicate any medication for BDD. Therefore, pharmacotherapy for BDD is off-label (other than dementia-specific drugs such as CIs and memantine). In such situations, physicians must be aware of the heightened requirements for documentation of the rationale for treatment and monitoring for adverse events. Informed consent is required, usually involving a surrogate rather than solely the patient (Bartels et al. 2002).

The choice of a pharmacologic agent is largely empirical. The clinician attempts to match the drug to the target symptoms to be treated. However, medication effects are often nonspecific and highly variable among patients. The drug should be initiated at the lowest dose and gradually escalated to the dose required to manage the symptoms. Most BDD patients will be managed with low doses of medication, but individual patients may require higher levels. Polypharmacy should be minimized. The clinician must be alert to the possibility of side effects that may be obvious (e.g., sedation, extrapyramidal symptoms, ataxia) or subtle (e.g., apathy, swallowing difficulties). BDD patients are at risk for treatment-induced akithisia or delirium, which may be mistaken for the symptoms of the BDD itself. Patience is required, as the full effects of a new medication may take many weeks to be fully manifest. The overall goal of treatment is improved quality of life for the patient and caregivers rather than "cure" of the disease. Sedation is rarely a goal of treatment and typically reduces quality of life. Instead, reduction of agitation without undue sedation is desirable. Polypharmacy, rapid dose titration, and frequent medication changes can all contribute to poor outcomes (Maher 2004).

Medication management in BDD presents significant ethical challenges. At times, the interests of patients may not be identical to those of caregivers or others. For instance, providing sedation for sleep enables the caregiver to rest even though the patient may not perceive this as a problem. The nature of dementia often prevents the patient from participating in such discussions (Kim et al. 2005).

Pharmacologic management of BDD requires careful, ongoing monitoring. Behavioral symptoms evolve over time, requiring change in medication therapy. Especially close monitoring is required after initiation of a new treatment or dose change. Once patients have been stabilized, patients should be seen at regular intervals. Medications should be reviewed approximately every 3 months. When symptoms abate, consideration should be given to tapering and eventually stopping psychiatric medication.

## Alzheimer's Medications and Behavioral Disturbance

CIs as well as memantine have been shown to affect behavior as well as cognition in patients with AD. These effects have been identified in a wide range of BDD symptoms. Generally, symptoms of BDD are lessened in AD patients taking these medications. Symptoms of BDD may be less likely to emerge in treated patients (treatment emergent effects). However, for patients who already have significant BDD these medications are usually not sufficient. Overall, the effects of these medications on symptoms of BDD are worthwhile but relatively modest. The CIs galantamine and rivastigmine are indicated for mild-to-moderate AD while donepezil is indicated for mild, moderate, or severe disease. Memantine is indicated for moderate-to-severe AD and may be used alone or in combination with a CI (Cummings et al. 2006, Cummings et al. 2006).

## Antipsychotic Medications in Dementia

The "atypical" antipsychotics were introduced beginning in the 1990s and have largely supplanted the older "typical" or conventional antipsychotic medications. These older drugs (such as haloperidol and chlorpromazine) were noted to cause parkinonian side effects such as rigidity and tremor. The designation "atypical" refers to the relative lack of these extrapyramidal side effects (EPS) with these medications. The atypical antipsychotics include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone. Atypical antipsychotics have arguably become the most widely utilized type of medication for BDD (Table 123–5).

**Table 123–5 Recommended Daily Doses of most Commonly Used Atypical Antipsychotics in Dementia**

- Risperidone 0.5–2 mg
- Quetiapine 50—150 mg
- Olanzapine 5−7.5 mg

Alexopolous et al. (2005).

A number of studies have shown modest efficacy with reasonable tolerability for atypical antipsychotics in BDD. Many of these studies were small scale and open label in design. However, a small number of placebo-controlled trials have been published. For example, a 6-week study of olanzapine in dementia revealed efficacy for 5 or 10 mg doses but worsening of behavior at 15 mg per day (Street et al. 1998). A 12-week study of risperidone showed dose-related improvement in psychotic symptoms and agitation, but also revealed greater levels of EPS at higher doses up to 2 mg per day) (Katz et al. 1999). A 52-week open-label study of quetiapine in elderly psychotic patients (with a mixture of diagnoses) revealed overall benefit as well as good tolerability with a mean dose of 138 mg per day (Tariot et al. 2000). Tariot et al. (2004) reviewed the literature and concluded that atypical antipsychotics in general are efficacious for agitation in dementia (with a less clear impact on psychotic symptoms) but have varying tolerability. Sink et al. (2005) reviewed the literature and concluded that treatment with olanzapine or risperidone leads to modest but significant reductions in behavioral symptoms. Sink also concluded that psychiatric medications as a group had limited efficacy, with perhaps the best results for the atypicals. Schneider et al. (2006) performed a meta-analysis of all 16 published placebo-controlled trials of atypical antipsychotics in dementia. They concluded that aripiprazole and risperidone showed efficacy, but not olanzapine. They also found smaller effects for outpatients (who were presumably less ill), those with less severe dementia, and those with psychosis. The overall dropout rate of about a third did not differ between subjects on active treatments and placebo. Adverse events were typically somnolence and urinary tract infection or incontinence across all drugs. EPS and gait disturbances were found with risperidone and olanzapine, but there was not increased injury, falls, or syncope. Cognitive scores were worse in patients on atypicals versus controls. There was an overall increased risk of cerbrovascular adverse events (CVAE), especially with risperidone.

Recently, the CATIE-AD, a large, double-blind, placebo-controlled study showed limited efficacy and generally poor tolerability of atypical antipsychotics in dementia (Schneider et al. 2006). The methodology of CATIE differs from most previous psychopharmacologic trials in using duration of treatment as the primary outcome measure (i.e., how long did the clinician and patient choose to maintain a particular medication). The study included olanzapine, risperidone, and quetiapine as well as placebo. Time to discontinuation for lack of efficacy favored olanzapine and risperidone over quetiapine and placebo. Time to discontinuation due to adverse effects favored placebo. There were no differences among the groups on the CGIC (Clinical Global Impression of Change), a rating scale measure of effectiveness. The authors concluded that "although the atypical antipsychotics were more effective than placebo, adverse effects limited their overall effectiveness, and their use may be restricted to patients who have few or no side effects and for whom benefits can be discerned." Despite these results, it appears clear that individual patients may benefit from atypical antipsychotic therapy. The impact of BDD on quality of life is often so great that these risks are deemed acceptable given the benefits in these cases. Some authors have suggested that patients with risk factors for stroke, early development of side effects, the "old-old" (over the age of 85 years) and the frail are at greatest risk of negative effects from atypical antipsychotics.

In 2003, 2004, and 2005 the FDA issued several "black box" warnings addressing the use of atypical antipsychotics in dementia and suggesting caution in their use (U.S. Food and Drug Administration (2003/2004/2005). These warnings were issued to the medical community and the public in the form of advisories and also mandated labeling changes in the package inserts of the affected medications. The initial warning cited an increased risk of cerebrovascular adverse events such as stroke or transient ischemic attacks in patients treated with risperidone and olanzapine. The magnitude of the increased risk was estimated at roughly two- to three-fold. Later, aripiprazole was added to the warning. This FDA review was prompted in part by an Australian study of risperidone (Brodaty et al. 2003), which showed efficacy but an increased risk of CVAE in dementia patients. An additional warning published in 2005 (U.S. Food and Drug Administration (2003/2004/2005) addressed increased mortality (from all causes) in demented patients treated with atypicals as a class. This warning followed an FDA meta-analysis of all 17 placebo-controlled atypical trials available at that time, involving four different atypicals. This analysis revealed the death rate from all causes (principally cardiovascular diseases and pneumonia) to be 1.6 to 1.7 times higher among patients taking active drug versus placebo. These concerns come amidst other controversies surrounding the atypical antipsychotics, particularly their propensity to cause weight gain and increase the risk of type II diabetes and other metabolic problems. The FDA has also addressed these concerns with changes in labeling that are not specific to dementia patients. The methodologies used in determining these risks have been controversial. Nevertheless, these warnings are part of the FDA labeling of all atypical antipsychotics. These warnings, combined with the lack of an FDA indication, necessitate a special focus on documentation, informed consent, and monitoring for all dementia patients taking atypical antipsychotics. Ironically, the older, the so-called "typical" antipsychotics have not received a similar black box

warning despite abundant evidence that they have greater risks than the atypicals. A 2005 study revealed risks of death for dementia patients treated with conventional (typical) antipsychotics to be at least as great as that for atypicals. The authors advised against returning to the use of the conventional antipsychotics as a replacement for the atypicals (Wang et al. 2005).

### Mood Stabilizers in Dementia

Mood stabilizers such as valproic acid (divalproex) have long been used to treat BDD, especially for agitation, aggression, mood lability, disinhibition, and manic-like symptoms. Studies of valproic acid have revealed a mixed picture. Several studies have shown benefit, but a large placebo-controlled study of nursing home patients failed to do so (Tariot et al. 2005). A meta-analysis of valproic acid in dementia concluded limited efficacy at low doses and problems with adverse effects at higher doses (Lonergan et al. 2004). Another review of the literature on divalproex revealed a conflicting picture of controlled trials with three studies showing some limited benefit while another did not (Porsteinsson 2006). Sink et al. (2005) concluded that the literature did not support the use of valproate. Carbamazepine showed modest but conflicting results in several studies, but concerns persist over its tolerability and side effects. Several reports have suggested some utility in managing sexually aggressive symptoms (Sink et al. 2005). Other anticonvulsant mood stabilizers have been used anecdotally. Lithium has not been well studied in BDD, but has generally been regarded as poorly tolerated in this population.

### Antidepressants and Dementia

Antidepressants have been used to treat depressive symptoms, anxiety, and agitation in dementia. Older studies showed benefit for trazodone, especially for sleep. Several selective serotoinin reuptake inhibitor (SSRI) including sertraline and citalopram have shown benefits in clinical trials. These drugs have shown some efficacy for depressive symptoms, anxiety, and modest evidence of utility in agitation in some studies (Pollock et al. 1997, 2002). Verbal aggression responded to citalopram in several small-scale studies. Other antidepressants including mirtazapine have been widely utilized though not thoroughly studied. Mirtazapine is sometimes used as a sleep or appetite aid (Watson and Steffens 2004). TCA should be avoided, primarily because of their anticholinergic properties.

### Benzodiazepines

Benzodiazepines have been widely utilized in the treatment of BDD despite admonitions against their use. Anxiety, agitation, and sleep disturbances are common reasons for the use of benzodiazepines. They may be given orally or by injection. Recent concerns about atypical antipsychotics may have contributed to renewed interest in this class of medications. Objections to the use of benzodiazepines in elders include sedation, ataxia, falls, cognitive clouding, dependency, and paradoxical excitation. Despite these concerns, the use of benzodiazepines in BDD has not been well studied. Long acting benzodiazepines such as diazepam, chlordiazepoxide, or clonazepam have been shown to be poorly tolerated in elders. Generally, clinicians prefer short-term use of shorter acting drugs with few active metabolites, such as lorazepam or oxazepam. Sleep problems in dementia are common and persistent. Benzodiazepines or other hypnotics such as zolpidem have been used clinically. Benzodiazepines may occasionally prove useful in the treatment of catatonia, which can mimic or complicate dementing disorders (Alisky 2007). Melatonin has been used anecdotally, and melatonin agonist agents may prove useful, but have not been systematically studied in dementia. Buspirone, a nonbenzodiaepine antianxiety agent, has also been used in dementia but seems to have limited utility.

### Summary of Pharamacologic Management of Dementia

Since cure is not possible, the treatment of BDD should focus on maintaining and improving quality of life for the patient as well as the caregivers and those around them (Burke and Morgenlander 1999). Environmental triggers should be identified and nonpharmacologic approaches considered before medication is prescribed. Frequently, these approaches are used alongside pharmacologic approaches. The treatment flows from a careful assessment considering preexisting psychiatric illnesses, current medications, and possible delirium or pain. The spectrum of symptoms needs to be identified and a target or targets for treatment identified. Pharamacotherapy then focuses on managing these targets, using some objective means of outcome measurement wherever possible. The Alzheimer's medications including CIs and memantine can be useful in reducing symptoms. Informed consent (usually from a surrogate) should be obtained, keeping in mind the lack of FDA indication for psychiatric drugs in BDD, the nonspecificity of patient responses, and the concept of risk-benefit analysis. Use of multiple psychiatric medications should be avoided whenever possible. Psychiatric medications require close monitoring and a high index of suspicion for adverse effects, which can negatively impact quality of life. As the dementing illness progresses, the medication requirements evolve over time. Avoidance of anticholinergic medications deserves special emphasis.

The atypical antipsychotics have become a special area of controversy because of their wide use as well as ongoing concerns over limited efficacy, mortality, and side effects. Recent changes in labeling including FDA-mandated black box warnings have heightened these concerns. Although they continue to be prescribed, a clear consensus for how to utilize them is lacking. However, many BDD patients have serious behavior problems that have not responded to other measures and some individual patients have benefited from atypicals. Alternative treatments also have limited efficacy and potential side effect issues. In this setting, it might be prudent to limit antipsychotics to cases who have not responded to other treatments or have significant physical aggression or combativeness. The presence of demonstrable psychotic symptoms would seem to be a logical rationale for the prescription of these medications, although clinical trials have yet to show convincing evidence of their utility.

## Management of Depression in the Elderly

### Clinical Presentation of Depression in the Elderly

Depression is a common disorder among the elderly, especially those with significant medical illness or in long-term

care. Management of depression begins with recognizing the disorder and establishing the diagnosis. However, depression in the elderly is often overlooked in the context of physical symptoms or rationalized as a normal response to loss or aging (Charney et al. 2003, Katz 1996). The diagnosis may be further obscured when the patient presents with multiple diffuse symptoms, weight loss, or preoccupation with bodily functions (e.g., constipation, pain, insomnia, fatigue). Depressed elders may focus on anxiety rather than sadness. Some elders (especially men) may feel stigmatized by a psychiatric diagnosis, and resist being labeled as depressed (Cooper et al. 2003). Loss of function is also an important concern in the assessment of geriatric depression (Koenig and George 1998). Depressed elders may withdraw from activities and even become bedridden. Such patients can exhibit exaggerated helplessness, dependency, and negativism that can reach psychotic proportions. The degree of functional impairment in depressed elders can be similar to that seen in a serious medical illness (Casey 1994, Alexopolous et al. 1996, Unutzer et al. 1997). Diagnosis is also complicated when symptoms such as insomnia, low energy, and loss of appetite or weight could be explained as symptoms of either a comorbid medical disorder or depression. When depression is suspected, geriatricians generally "count" such symptoms toward the diagnosis, even when they may be multiply determined. Although major depression is obviously the most significant issue, elders have a high prevalence of lesser, but still important types of depression. The term "minor" depression has sometimes been used to describe this group. These patients may suffer from adjustment disorders, dysthymia, depression related to medical illness or other conditions that are disabling yet do not meet the full diagnostic criteria for major depression (Beekman et al. 1997, Lavretsky and Kuman 2002).

Loss and grief are virtually universal in the lives of elders and can be triggers for clinical depression. In fact, social isolation and loss are important risk factors for elder depression. Depressive illness must be distinguished from normal grief. Functional impairment in grief usually improves over a period of several months. After the first few weeks, sad mood in grief usually comes in waves. Prolonged, persistent sadness, especially coupled with hopelessness, guilt, or thoughts of death or suicide suggests the advent of an episode of clinical depression (Casey 1994, Serby and Yu 2003).

## Geriatric Depression and Medical Comorbidity

Geriatric depression often occurs in the context of significant medical morbidity such as stroke, cancer, chronic lung disease, arthritis, or Parkinson's disease (Ranga et al. 2002). Depressed elders have a higher overall mortality than their peers (Black and Markides 1999, Schulz et al. 2002). Depressed, medically ill elders present a much greater burden on their caregivers (Sewitch et al. 2004). Geriatric depression is particularly prevalent in primary-care practices (Cronin-Stubbs et al. 2000, Unutzer et al. 2003). Ischemic heart disease has a complex relationship with depression (Ariyo et al. 2000). These illnesses may not only coexist, but also interact in important ways. For example, depression commonly follows myocardial infarction (MI) and can increase post MI mortality. Medications prescribed for medical illnesses can also have effects on mood. Corticosteroids, antineoplastics, anti-parkinsonian drugs, metoclopramide, alpha interferon and others can contribute to depression. Some drugs cause fatigue or loss of appetite that can be confused with clinical depression. Depressed elders are heavy utilizers of general medical care (Katon et al. 2003, Lebowitz et al. 1997). A significant number of their doctor visits are for physical symptoms actually related to depression. Just as physical symptoms may be related to depression, depressive symptoms may be an indication of a physical disorder (Penninx et al. 1998). Assessment of depressive symptoms in an elderly patient requires a thorough medical work-up. Neurological disorders such as multiple sclerosis, AD, and others may present with mood changes or even full blown depression. Endocrine disorders such as hypothyroidism or deficiency states such as lack of vitamin $B_{12}$ can contribute to depressive as well as cognitive symptoms. Failure of basic organ systems including renal failure or congestive hear failure can cause fatigue, loss of appetite and weight, and depressed mood. Cancers, especially pancreatic or small cell lung carcinomas, can present with depressive symptoms even before the patient is aware of the diagnosis (Ell 2006, Evans et al. 1999).

## Depression and Cognitive Impairment

Depression can coexist with cognitive impairment, including dementia. Severe depression may negatively impact cognition. Occasionally, such patients are described as having "pseudodementia." However, when demonstrable, significant cognitive impairment is present, it is more likely that the patient has both depression and dementia (Reifler 1982). Apathy is a common symptom of dementia. This apathy may or may not be a part of a treatable depressive syndrome. Some researchers have suggested that late life depression, especially new onset depression may be an early indicator of AD. New onset depression in late life is often related to medical illness as well as loss or grief. In particular, late life onset depression has been linked to cerebrovascular disease (the "vascular depression" hypothesis) (Watson and Steffens 2004).

## Suicide in the Elderly

Elders have a high rate of suicide. Late onset, unipolar depression seems to be particularly correlated with elder suicide (Table 123–6). Some studies have suggested that the suicide rate is approximately two times that of the general American population. As in other groups, female elders have

**Table 123–6 Characteristics and Risk Factors in Elder Suicide**

- Male gender
- Caucasian
- Medical comorbidity
- Social isolation
- Access to firearm
- Substance Abuse
- Depression
- Previous suicide attempts
- Bereavement

Conwell and Duberstein (1995, 2001), Conwell et al. (2002), and Casey (1991).

a higher prevalence of depression and a higher rate of suicide attempts. However, males (especially white males) predominate in completed elder suicide. These elderly men typically choose highly lethal means of suicide such as gunshot wounds to the head or chest. Many of these patients have not been formally diagnosed or treated for depression. However, many of these patients have visited a physician within weeks of a suicide attempt. Physicians should have a high index of suspicion for suicidal thinking in depressed elders, even those who minimize or deny depressive symptoms. A serious medical illness, especially a terminal or painful illness should be regarded as a risk factor for suicide. Social isolation, the loss of a spouse, substance abuse, or previous suicide attempts should also be considered as risk factors for elder suicide (Casey 1991, Conwell and Duberstein 1995, Juurlink et al. 2004).

## Treatment of Depression in the Elderly

Depression in late life is a very treatable condition. Successful treatment not only improves mood and reduces the chance of suicide, but can also dramatically improve functional deficits and improve quality of life for the patient as well as the caregiver. All treatment modalities for depression can be utilized for elders including pharmacotherapy, psychotherapies, social therapies, and electroconvulsive therapy (ECT).

Studies of pharmacotherapy for geriatric depression have documented the safety and efficacy of antidepressants, particularly the serotonin reuptake inhibitors (Sheikh et al. 2004). The use of older antidepressants, particularly the TCA, should generally be avoided because of concerns over side effects and toxicity. Anticholinergic and cardiovascular effects of TCA can be more problematic for elders than other populations. Approximately 60−80% of elders will respond to pharmacotherapy if carefully managed. However, only about half are likely to respond to the initial medication trial and response time is often longer than in other groups. Up to 8−12 weeks may be needed for maximal response (Thomas et al. 2002, Whyte et al. 2004). Although recent studies have suggested that combinations of antidepressants may be required for good response, geriatricians are generally conservative about such polypharmacy. Since elder depressives may emphasize their symptoms of anxiety, benzodiazepines are often prescribed instead of or in addition to antidepressants. Benzodiazepines are not adequate treatments for depression and are potentially problematic for elders. Careful attention to adherence is required in the management of geriatric depression as rates of noncompliance are high (Salzman 1995). Adherence improves when the patient is seen frequently and counseled about their illness and the need to faithfully take their medication. Despite evidence of their effectiveness, the majority of depressed elders do not receive antidepressant therapy (Dunner 2003, Lyness 2004, Taylor and Doraiswamy 2004).

## Psychotherapy for Elder Depression

At one time, elders were considered to be poor candidates for psychotherapy. However, a number of studies have documented the utility of various psychotherapeutic approaches for geriatric depression, either alone or in combination with medication (Arean and Cook 2002, Gum and Arean 2004). In fact, combination approaches are becoming well accepted in the management of depression in the elderly (Arean et al. 2001). Cognitive therapy is perhaps the best studied psychotherapeutic approach and cognitive therapy manuals for geriatric depression have been prepared (Grant and Casey 1995, Thompson et al. 2001). Interpersonal therapy has also been studied, mostly in combination with medications (Miller et al. 2001). The descriptive literature also delineates psychodynamic and reminiscence approaches to the elderly psychotherapy patient. Reminiscence therapy is designed to allow the patient to review and take stock of their life experience.

## Electroconvulsive Therapy in the Elderly

ECT is a valuable tool in the treatment of depression in the elderly. A substantial proportion of ECT patients are elderly. Several studies have shown the utility and safety of ECT in the elderly. ECT is typically done for treatment-resistant patients who have failed several previous medication trials. However, ECT should not be viewed solely as a treatment of last resort. Patients with catatonic or psychotic symptoms may benefit from ECT early in the course of their illness. Severe psychomotor agitation or retardation, anorexia, or marked suicidal thinking can also be addressed with ECT. Patients who have responded to ECT in the past may be better served by early intervention rather than a new set of pharmacologic trials. Much of ECT for elders is performed on an inpatient basis. Outpatient ECT may be difficult because of severity of medical and psychiatric illness, frailty, lack of social support, or cognitive impairment. Although initial response rates are high, many patients relapse. Maintenance ECT may provide an alternative, especially for patients prone to early relapse. Maintenance ECT may be performed on a scheduled basis (e.g., weekly) or based on early signs of relapse. Maintenance ECT represents a significant effort on the part of the patient as well as their caregivers, particularly for transportation and ongoing supervision. ECT patients receive general anesthesia as well as electrical stimulation. Therefore, a thorough medical evaluation is required prior to treatment. Physical examination, ECG, and basic laboratory evaluation (CBC and electrolytes) are advisable. In the past, neuroimaging and spine films have often been performed prior to ECT. However, these procedures are no longer considered mandatory and are done when an indication exists. Assessment of cardiovascular status is important since elderly ECT patients can be expected to have post-treatment tachycardia and hypertension. ECT is usually avoided in patients with recent MI or stroke as well as cardiovascular instability. However, the decision to perform ECT must always balance the risks against the urgency of the clinical need. Cognitive impairment is an expectable short-term outcome of ECT. Anterograde and retrograde amnesia as well as short-term memory impairment can occur, especially with bilateral ECT. Cognitive impairment can be more persistent with bilateral ECT. Despite these issues, ECT is generally well tolerated in elders (Casey and Davis 1996, Salzman et al. 2002).

Dementia patients who have comorbid depression may be candidates for ECT despite their ongoing cognitive impairment. Dementia patients receiving ECT may become confused. However, these effects are relatively time limited and do not influence the long-term cognitive symptoms

of dementia. Occasionally, severely depressed dementia patients can experience improved cognition following ECT as the depression lifts.

## Conclusion

As the number of elderly patients increases in the US and many other parts of the world, psychiatrists will need to enhance their skills in management of clinical problems common in this age range. Dementia and depression are particularly important syndromes in geriatric psychiatry requiring careful evaluation and management. Care of the geriatric patient requires an appreciation for the effects of the aging process and age-related illnesses on functional abilities. There is considerable overlap between geriatric psychiatry and geriatric medicine, so that psychiatrists much consider the effects of medical illness as well as medications when managing psychiatric illnesses. Psychiatric illnesses also complicate the care of medical conditions. Therefore, open communication among specialists is a necessary component of geriatric management. The role of patients in the family and community evolves as they age. Geriatric management involves an appreciation of the context of care, and cooperation with the patient's caregivers.

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CHAPTER

# 124 Management of Victims of Torture

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## Introduction

### Torture History and Definition

Torture has always been a part of the history of mankind. Numerous accounts tell us how authorities have used torture as a means to deal with defeated enemies, to extract confessions, to show superiority, to humiliate the defeated, or to spread terror among the subordinates. The practice of torture knows no geographical or ideological boundaries, and has been used by all kinds of authorities whether military, clerical, monarchical, or political.

Historically, the French Revolution and the emerging recognition of human dignity and human rights are landmarks in the abolition of torture as an accepted official practice. Subsequently, many countries have taken a firm stand against the use of torture as a legitimate procedure. The awareness of the widespread use of torture and the recognition of the need for international declarations became very prominent following the revelations of the World War II concentration and extermination camps (Eitinger and Weisæth 1998). The adoption of the United Nations (UN) Universal Declaration of Human Rights in 1948 and several other major conventions against human rights violations reflect this. According to the Universal Declaration, "no one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment" (United Nations 1948).

The Geneva Convention (1949) protects those persons who are not taking an active part during war from "violence to life and person, in particular murder of all kinds, mutilation, cruel treatment and torture." This includes soldiers who have "laid down their arms" (International Committee of the Red Cross 1987).

In 1984, the General Assembly of the UN approved the most important international legal instrument against the practice of torture, the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment. Article 2.2 of this states "No exceptional circumstances whatsoever, whether a state of war, internal political instability or any public emergency, may be invoked as a justification for torture." As of December 6, 2006, 144 countries were parties to the Convention, obligating them to accept this principle (www.ohchr.org/english/countries/ratification/9.htm).

Nonetheless, torture has continued and remains a major problem around the world today, and pessimistic voices claim that we will never see an end to torture.

The term "torture" has been defined in various ways depending upon the defining organization and purpose. Among the definitions, two have gained particular importance, the UN's definition from 1984 and the World Medical Association's (WMA) definition, also called the Tokyo Declaration, from 1975.

According to the UN Convention (1984), "For the purposes of this Convention, the term "torture" means any act by which pain or suffering, whether physical or mental, is intentionally inflicted on a person for such purposes as obtaining from him or a third person, information or a confession, punishing him for an act he or a third person has committed or is suspected of having committed, or intimidating or coercing him or a third person for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of or with the consent or acquiescence of a public official or other person acting in an official capacity. It does not include pain or suffering arising only from, inherent in, or incidental to lawful sanctions" (United Nations 1995).

The WMA states, "For the purpose of this Declaration, torture is defined as the deliberate, systematic or wanton infliction of physical or mental suffering by one or more persons acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason" (Amnesty International 1994).

In comparison, the WMA definition is broader as it does not require the perpetrator to be affiliated with any government or to act in any official capacity, and it may also include suffering caused by ritualistic or criminal acts

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(Jaranson 1998). The UN definition, on the other hand, limits torture to acts that are perpetrated by persons in "an official capacity."

From a therapeutic point of view, the two definitions dictate differential approaches. The WMA definition recognizes the severity of the suffering irrespective of who caused it. Since such suffering may lead to mental health consequences, whether or not the torture was officially sanctioned, this definition may favor a broader approach to identification and treatment. The UN definition recognizes the legal and political responsibilities of governments in causing severe suffering. Consequently, this definition may be used as a stepping stone to create therapeutic interventions to alleviate the sequelae due to the suffering. For example, helping a survivor return to political activism may be a component of treatment.

## Prevalence of Torture

Repeated reports by Amnesty International (AI) state that torture is widespread. The AI Report (2006) documents the occurrence of human rights abuses in 150 of the 193 countries around the world (http://web.amnesty.org/report2006/index-eng). As torture is frequently carried out under clandestine circumstances, reliable estimates are very difficult to get, not least due to the political sensitivity of the issue. The AI figures, thus, conservatively estimates the actual situation.

Torture seems particularly common in regions characterized by political unrest, riots, civil war, rebellion, and other social or political conflicts, but is not restricted to those regions (Basoglu et al. 2001). In view of the political nature of torture, certain groups are more likely to be exposed to torture, such as political activists, asylum-seekers, refugees, and persons who have been detained. It is well-known that torture is also used extensively in police custody and in correctional services, including regions that are not afflicted by war. Torture does not exclusively take place in countries with nondemocratic governments.

Democratic governments are also at risk for allowing torture during detention of prisoners. The recent focus on terrorism has been used as a reason to accept the use of "mild" torture in such situations. The long-standing controversy in the United States about which specific interrogation techniques are allowed by the Geneva Convention is one example.

Prevalence rates in non-Western countries range from 8 to 26% in national random samples, 3 to 16% in refugee camps, and an extremely high range of 85 to 100% for detainees remaining in their countries of origin (Quiroga and Jaranson 2005). With nearly 21 million refugees, asylum-seekers, internally displaced persons (IDPs), returnees, and stateless persons reported for 2005 by the United Nations High Commission for Refugees (UNHCR), millions of torture survivors exist worldwide (UNHCR 2006). This, however, includes only those under the responsibility of UNHCR and millions more are not officially recognized, such as those who have sought refuge in the West. In Western settings, prevalence of torture ranges from 7–8% in general primary care clinics and up to 70% in refugee psychiatric clinics (Quiroga and Jaranson 2005). Among a select group of refugees and asylees in the US and Europe, prevalence rates of torture between 6 and 55% (Quiroga and Jaranson 2005) have been reported. Even when using a conservative estimate, we are facing an issue of enormous dimensions from both human rights and therapeutic perspectives, an issue that until recently received limited psychiatric attention.

Estimates of the prevalence of torture vary due to methodological issues, such as the selective delineation of the study populations, restricted access to torture survivors, lack of validated assessment instruments, and reluctance of survivors to reveal their torture experiences. Most studies have been carried out on persons in exile, a selected population, and few studies have used structured procedures in the assessment. Silove et al. (2002) have delineated some of the problems in studies investigating the conditions following severe man-made traumata. These problems include: (1) poor definition of the boundary between torture and other severe trauma; (2) the higher demonstrated prevalence of PTSD in refugee populations although the distinction between torture and other trauma is unclear; (3) small sample sizes; (4) possible selection bias, especially of populations referred to treatment; and (5) lack of precision regarding diagnostic methods. Furthermore, the usual lack of control groups, the absence of follow-up studies, and uncertainty whether the questions may have potential negative impact on the critical legal and psychiatric state of the persons, add to the difficulties. A critical review (Hollifield et al. 2002) of trauma measurements in refugees concluded that the majority of 394 publications about refugee trauma or health in refugees are either descriptive or include quantitative data from instruments that have limited or untested validity and reliability in refugees.

## Methods of Torture

Methods of torture vary over time and across regions. Torture methods are frequently divided into physical and psychological methods, and attempts have been made to develop algorithms in order to facilitate comparative studies of torture experiences (Bøjholm et al. 1992). Perpetrators constantly develop and refine their methods in order to avoid leaving traces. There are, however, commonalities in the use of methods, and several studies report nonsystematic beatings as the most common form of torture, while various kinds of deprivations are also frequent (e.g., Olsen et al., in press). Techniques include beatings to specific parts of the body, such as falanga (to the soles of the feet) or telefono (to both ears); suffocation (such as submarino, or placing the person's head in liquid until near suffocation), suspension in contorted positions or electrical torture to body parts (such as genitalia). Mutilating injuries consist, e.g., of amputation of limbs or other body parts. Sexual torture is reported among a high percentage of torture survivors, not only women.

Torture almost always includes psychological dimensions, alone or simultaneously with the physical torture. Psychological methods, which are generally more difficult to trace, range from general humiliation and threats to mock executions and witnessing the torture of loved ones. Cultural and social differences regarding what is considered shameful or violating are important in psychological torture. As an example, Indian Hindu authorities have used cutting the hair of Sikh men as a method of psychological torture specifically for that group (Wenzel et al., in press).

## Medical Aspects of Torture

### Physical Effects of Torture

The sequelae of torture are both immediate and long term. Therapists in the West rarely encounter the immediate consequences, and it should be remembered that many victims with the most severe immediate health effects may not have survived (Skylv 1992). The survivors who have been encountered in Western health settings may have undergone torture years prior to receiving treatment and represent a selected group.

Ample documentation shows that many torture survivors primarily have somatic complaints but that many subjective physical symptoms are rarely matched with objective signs. Many survivors have been subjected to multiple forms of torture with subsequent overlapping injuries (Basoglu 1992). Thus, it may be difficult to trace signs of a particular form of torture. Among the most prevalent physical sequelae are complaints from the musculo-skeletal system (Rasmussen 1990). Electrical torture will result in characteristic skin changes. Dental torture together with poor dental hygiene during imprisonment may lead to loss of teeth, gingivitis, or dysfunctional temperomandibular joints. Sexual torture is usually revealed late, and leaves not only injuries to the genital organs, sexual dysfunction, and sexually transmitted diseases, but also pain in the lumbar region.

There is an increasing focus on the chronic pain experienced by a large proportion of torture survivors, linking it to the kinds and amount of torture (Olsen et al., in press). Pain is typically localized to the musculo-skeletal system, accompanied by fibrositis and myofascial pain (Amris 2000). Headache is also very common. Falanga may result in pain, primarily in the tibial region and near the joints, damaged heels, and impaired walking (Skylv 1992). Suspension may give rise to joint pain, and trigger points are frequent in the shoulder musculature (Skylv 1992).

Despite presenting physical complaints, psychological problems are frequently revealed later (van Ommeren et al. 2002). The impairment following torture experiences is caused by combinations of both physical and psychological factors, and torture survivors are more than twice as likely as nontorture survivors to have impaired physical and social functioning due to the trauma resulting from the torture (Wenzel et al. 2006).

### Psychological Effects of Torture

Until the first half of the twentieth century, the prevailing thought was that the traumatic life events per se did not result in lasting consequences for the mental health of the individuals affected. In instances where persons nevertheless developed more chronic conditions, they were perceived as having a particular vulnerability. Such vulnerability could be interpreted from two different perspectives, one using a genetic frame of reference, the other psychoanalytic. In the first case, the mental health consequences were seen as a reflection of a premorbid biological weakness; in the latter, consequences were caused by psychological damage in early childhood (Somnier et al. 1992).

Investigations of holocaust survivors (Eitinger 1980) changed this assumption. These investigations described a population that to a great extent had long-lasting psychological sequelae, following the extreme traumatic events in concentration camps. Scandinavian studies of war sailors from World War II (Askevold 1980) revealed similar findings. In both cases, there was no indication that these populations had a high presence of psychopathology prior to the traumatic experiences. Such findings seem to indicate that exposure to continuous extreme stress, if the stressor is sufficiently severe, may induce mental health consequences in individuals with previously normal mental health. Following World War II, similar findings were found in populations exposed to, among other things, the taking of hostages or rape.

Due to such findings, a hypothesis has been proposed that exposure to different forms of stress may result in sequelae that, irrespective of culture or setting, are comparable. Rasmussen (1990), who analyzed the medical aspects of torture in his dissertation, concluded that various stressors seem to overlap with respect to consequences, and that there is good reason to believe that we are dealing with similar mechanisms.

In the 1970s (AI 1977), the Danish Medical Group in AI published some of the first systematic investigations of the immediate consequences following torture. At a very early stage, it was recognized that the psychological consequences were extensive and, in many ways, far more long lasting than the physical consequences.

Studies of some of the first patients seeking treatment at rehabilitation centers for torture victims show similar results (Somnier and Genefke 1986). The psychological problems when compared to the physical complaints showed a higher prevalence among those investigated. The psychological problems were severe and resulted in a significant reduction in the level of functioning. The most frequently reported complaints included anxiety, memory problems, concentration problems, depression, changes in personality, and nightmares (Somnier and Genefke 1986). Fatigue, sexual problems, and headache were also frequently seen. These findings have been confirmed in a number of investigations on torture survivors from all regions of the world (e.g., Allodi et al. 1985) and it seems that, irrespective of cultural background, there are a number of common traits in the symptomatology manifested.

Clinical Vignette 1

A 35-year-old woman, MH, from Bosnia grew up in a well-functioning middle-class family. During the civil war, her father was taken away and presumed killed in a massacre. Her mother died shortly after. MH stayed with her grandmother during the war in Sarajevo, suffering severe deprivation, hunger, and constant bombing. She was raped by soldiers but kept this secret from her grandmother. She fled the country and obtained asylum in the country of exile. MH managed to get a higher education there, learnt the language, got a job, and developed a network. After eight years, she began to have difficulty in concentrating, suffered from flashbacks and nightmares, had attacks of anxiety, and became very sensitive to noise. She could no longer manage her job, and gradually, she became isolated and lost all interests. MH had been under psychiatric treatment for some time, combining pharmacological and psychotherapeutic treatments, and was very grateful, for this treatment relieved some of her anxiety and flashbacks. Her disorder had been assessed as chronic, and she thus received some economic compensation that gave her some rest and removed part of her hopelessness.

In uncontrolled studies, the most prevalent complaints include: (1) psychological symptoms (e.g., anxiety, depression, emotional lability, irritability); (2) cognitive symptoms (e.g., confusion, difficulty with concentration and memory); and (3) neuro-vegetative symptoms (e.g., lack of energy, insomnia, sexual problems) (Goldfeld et al. 1988). Reviews, however, of the psychological effects of torture (Somnier et al. 1992) report significant shortcomings in many of the studies due to their uncontrolled design. Some studies include only refugees, and most consist of treatment populations that show some degree of selection.

A controlled study of Spanish torture survivors showed higher prevalence of depressive symptoms, anxiety, insomnia, concentration, and memory problems than the nontortured controls (Petersen and Jacobsen 1985). Tortured political activists in Turkey were compared with a controlled group of nontortured political activists without political involvement. The torture survivors had significantly more lifetime and current PTSD than the controls (Basoglu et al. 1994a). Among East African refugees in Minnesota, 25% of those exposed to torture met the criteria of suspected PTSD (with a cutoff PCL-C score of 50 or more) compared to 4% of those traumatized in ways other than by torture (Jaranson et al. 2004).

A recent review of surveys of PTSD among traumatized persons documented that PTSD exists across cultures ranging from 9 to 37% (Modvig and Jaranson 2004). Many factors influence the emergence of mental health problems including awaiting asylum, loss of meaningful activities, language inadequacies, and marital conflict (Saraceno et al. 2002).

## Identifying Consequences of Torture and Need for Treatment

### Diagnostic Considerations

Over time, several attempts have been made to delineate phenomenological descriptions of the mental health consequences of severe trauma. The diagnostic considerations of persons exposed to severe trauma may be seen as a continuation of the discussions related to the mental health problems of immigrants and refugees.

In the nineteenth century, an early conceptualization of the reactions to trauma were derived from perspectives of the medical knowledge at that time. Diagnoses such as tunnel disease and railway spine disorder were used. Subsequently, the syndrome was seen as closely related to the context forcing the reaction, e.g., soldier's heart, nervous exhaustion, shell shock, and combat neurosis (Baez and Kastrup 2002).

In the 1930s, Ödegaard (1932) showed that immigrants from Norway had a higher rate of "insanity" than the native Minnesota population. Subsequently, Eitinger (1980) showed a higher incidence of mental illness in World War II refugees compared to their Norwegian counterparts, and found a high proportion of schizophrenia and the so-called "reactive psychoses." Ödegaard and Eitinger made their empiricism based on the local diagnostic criteria and nosology of their time. The question is whether the conditions viewed as psychoses in those days would, in fact, have been diagnosed as PTSD had that diagnostic category existed.

As previously mentioned, the so-called "war sailor syndrome" (Askevold 1980) in the post World War II period showed similarity to the concentration camp syndrome described by Hermann and Thygesen (1954). Common to those descriptions was an initial interest in organic brain symptoms and what, in those days, was called asthenia.

The Vietnam War gave rise to an interest in describing and diagnostically categorizing the consequences of trauma. PTSD first appeared as an independent nosological entity in the American Psychiatric Association's DSM-III in 1980, and may be seen as an attempt to unite various stress response syndromes.

Subsequently, the condition has shown a prevalence ranging from 9% among unselected Vietnamese refugees in Norway to 86% in Cambodian refugees in USA (Andersen 1998). After exposure to a significant trauma, approximately 20–45% of those unprepared will at some time develop PTSD (Andersen 1998). The wide range in these figures can mainly be explained by methodological, conceptual, selective, or investigative difficulties.

Later editions of the DSM classification (DSM-IV-TR) (American Psychiatric Association, 1994) have made certain modifications of the original diagnostic criteria, but the assumption remains that different types of traumatic events have similarities in psychopathological profiles. In the DSM-IV-TR (309.81), the stressor (Criterion A) includes not only those who have experienced torture and other extreme trauma, but those who have witnessed or been confronted with "an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (p. 427). In addition, the person's response must involve "intense fear, helplessness, or horror" (p. 428). Other criteria include the symptom clusters of reexperiencing (Criterion B), avoidance (Criterion C), increased arousal (Criterion D) related to the traumatic event, duration greater than one month (Criterion E), and significant distress or impairment (Criterion F). Duration and onset of symptoms may be specified as acute (less than three months), chronic (lasting three months or more), or delayed (onset at least six months after the trauma). The DSM-IV-TR includes one related diagnosis, acute stress disorder (308.3), which occurs within a month after exposure to an extremely traumatic stressor.

Disorders of extreme stress not otherwise specified (DESNOS) were considered for inclusion in the DSM-IV-TR classification but not accepted.

In the WHO (1992) International Classification of Diseases (ICD-10), the definition of posttraumatic stress (F 43.1) has criteria very similar to those of the DSM-IV-TR. PTSD is a delayed and protracted response to a stressor, which is exceptionally threatening or catastrophic and likely to cause distress in almost anyone. The diagnosis should not be given unless the symptoms occur within six months of the trauma and no alternative disorder is likely. Reexperiencing is required for diagnosis, while avoidance, although common, is not essential. Autonomic and behavioral disturbances or mood disorder contribute to diagnosis, but are also not essential. The ICD-10 also contains broader diagnostic categories, such as dissociative and somatoform disorders under the "neurotic, stress related and somatoform disorders" and recognizes posttraumatic "enduring personality changes after exposure to catastrophic events" (F 62.0). Consequently, ICD-10 includes two diagnostic categories covering consequences of traumatic stress. Chronic traumata may give rise to personality changes

including a tendency for somatization, affect lability, difficulty in social relationships, lack of ability to trust others, and a feeling of having changed. The ICD-10 category F 62.0 better fits these symptoms.

## Torture Syndrome

PTSD was never meant to include the entire range of responses following torture (Jaranson et al. 2001). Rasmussen et al. (1977) proposed the existence of a specific "torture syndrome" in 1977 and a lively debate about whether torture results in a predictable phenomenology ensued during the following years. The concept of "torture syndrome" was subsequently discussed by at least two groups (Allodi and Cowgill 1982, Abildgaard et al. 1984) but both primarily listed symptoms found among torture survivors, and they did not examine whether these symptoms would cluster as a syndrome (Turner and Gorst-Unwowrth 1993). Those in favor of a torture syndrome claimed that the infliction of deliberate violence on one human being by another has a decisive influence on the formation of symptoms (Somnier et al. 1992). It has been suggested that symptoms reflect the method of torture used, and that isolation, blindfolding, impact, or other forms of physical torture may give rise to intrusion symptoms of PTSD, whereas persons exposed to sexual torture more frequently complain about avoidance symptoms (Vesti and Genefke 1998).

Basoglu et al. (2001) pointed out that the existence of a torture syndrome will require evidence of a causal connection between torture experience and symptoms, a meaningful grouping of symptoms, and a comparison of symptoms with established diagnoses, such as PTSD. Turner and Gorst-Unworth (1993) concluded that the attempts to describe an independent torture syndrome have not been very convincing, and Mollica and Caspi-Yavin (1992) also found that it has not been possible to delineate a torture syndrome but that symptoms among severely traumatized refugees were closely associated with the PTSD diagnosis. Investigations have not been able to support the theory of a specific torture syndrome that is different from PTSD (Shresta et al. 1998), and a survey of recent publications carried out by Basoglu et al. (1994b) seems to suggest that we presently do not see a great research interest in this field. Such findings have led to a shift in the focus so that the interest today is less on demonstrating a unique torture syndrome and more on studying the prevalence of PTSD in such populations and describing their psychopathology (Vesti and Genefke 1998).

The diagnosis of complex posttraumatic disorder has been suggested by Herman (1995) and continuous traumatic stress response by Dowdall (1992), taking into consideration more complicated reactions observed in persons who have been subjected to prolonged and repeated forms of violence compared with the single exceptional event in the PTSD criteria.

Increasingly, the classification committees have considered including the diagnosis of DESNOS. DESNOS includes damaged affect regulation, chronic self-destructive behavior, amnesia and dissociation, changes in the relationship to self, distorted relationships to others, and loss of faith (Berliner et al. 2005).

## PTSD Symptomatology and Comorbidity

Frequent misdiagnosis of pathology occurs with refugees. Diagnostically misleading suspiciousness and paranoia are prominent across diagnostic categories within most refugee populations, and psychotic and paranoid symptoms are often misdiagnosed as schizophrenia. Brief, reactive psychoses occur more frequently than schizophrenic disorders. Flashbacks, hallucinations, and dissociative phenomena typical of PTSD may be erroneously interpreted as symptoms of schizophrenia (Baez and Kastrup 2002). Very often, PTSD accompanies a major depressive disorder, a combination suggesting a more serious clinical picture and a less favorable outcome than if either disorder occurs alone.

Evaluation for organic impairment is another area of confusion among practitioners assessing refugees. Head trauma is common during torture, as evidenced by Mollica et al. (1993) finding among Cambodians that most torture involved beatings to the head. A torture survivor who has suffered head trauma might be affected cognitively because of this antecedent. This situation could lead to diverse degrees of confusion, memory impairment, and disorientation, contributing to the stigmatization of refugees or asylum-seekers as malingerers. Since cognitive impairment, especially with memory, can also be found in PTSD and depression, the differential is complicated and difficult.

Clinical Vignette 2

JH is a 53-year-old man from Croatia, who lived a productive life as a migrant with his own firm, family, and friends until the civil war broke out in the former Yugoslavia. JH was referred from neurologists, who had not been able to alleviate his chronic severe headaches and memory problems. He had no previous psychiatric history.

During the war, JH decided to return to his country to fight. There he was involved in several battles, experienced atrocities, and was forced to participate in acts that he is unable to forget. He suffered psychological torture including severe humiliation, mock execution, and witnessing the torture of others. He was beaten on the head and was unconscious for a brief period of time.

Returning to his country of migration, JH found that his firm was bankrupt, and his wife divorced him and left with their children. He lived on welfare and, since he could not tolerate noise, had few social contacts. Despite his chronic PTSD—which improved little with psychopharmacological treatment—cognitive difficulties, and persistent headaches, JH expressed great willingness to work again and hoped that his condition will improve. He was very motivated for and compliant with the treatment.

Substance abuse is frequently comorbid among other populations with PTSD but relatively uncommon among refugee torture survivors. However, this varies considerably by factors such as culture and gender. For example, Farias (1991) has documented alcoholism as relatively common among Central American refugee males, khat has been abused by East Africans, and opiates by Southeast Asians. Substance abuse comorbidity with PTSD is more often seen in men than women (Kastrup and Arcel 2004).

## PTSD Issues

From a clinical perspective, the diagnostic category PTSD is generally seen as meaningful, and an argument emphasizing

the universal aspects of PTSD relates to the research findings on the biological aspects of PTSD (Friedman and Jaranson 1994). Jaranson et al. (2001) mention that the hyperarousal, seen as the startle response, can be interpreted as one of the findings that very strongly support the existence of a universal posttraumatic stress syndrome.

The presence of PTSD is, however, not a necessary consequence of stress and trauma. A large proportion of traumatized or tortured persons develop posttraumatic stress symptoms, whereas others do not. The exact proportion is unknown.

The study of resilience factors is important and still insufficient. However, currently more attention is being paid to understanding the protective aspects in different populations, lessening the focus on the negative impact of trauma. An important area of needed study is identifying factors of resilience that may reduce or modify the development of PTSD, irrespective of the survivors' perceived or experienced traumatic events.

Perceived stress, rather than the objective severity of the stress, has been correlated with the development of PTSD. It is still unknown whether certain types of trauma are more likely to induce PTSD. Many factors, including age, personality, political or ideological inclination, quality of support after exposure to stress, may all influence the development of PTSD (Vesti and Genefke 1998).

### Measurement Issues

In consonance with the increasing emphasis on valid and reliable measurements and evidence-based interventions, the study of torture increasingly recognizes the need to pay more attention to the development of valid and reliable instruments for assessing, e.g., PTSD symptoms, trauma history, and level of social and biological functioning (Marsella 2001).

Particularly pertinent in the study of torture is ensuring the cultural equivalence of the instruments used. In general, Western researchers have developed psychometric tests and structured interviews with little attention to their applicability and acceptability in other cultural settings. Some concepts in a given scale may have differing connotations depending upon the cultural group. Despite shortcomings, quantitative measurements like rating scales and structured interviews may be very useful in the management of torture survivors, but combining them with qualitative measurements may add further insight into the comprehensive situation (Marsella 2001).

All of these factors contribute to the need for culturally informed quantitative instruments that are designed to be linguistically and visually acceptable, universally applicable, and understandable across cultures and settings. There is still a need to encourage studies that combine the intensive narrative approach of the anthropologists with the large-scale surveys of the epidemiologists (Kleinmann 1988).

### Conceptual Models

A number of conceptual models have been developed to explain different aspects of the etiology and course of the human response to traumatic events (Fairbank et al. 2001) (see Table 124–1). Two models dominate: the psychosocial and the neurobiological.

**Table 124–1 Conceptual Models of Response to Traumatic Events**

| Models | Theory | Characteristics |
|---|---|---|
| Psychosocial | Learned helplessness | Apathy, passivity, impossibility of escaping future traumatic events |
| | Information processing | Recall of information linked to traumatic events |
| | Classical conditioning | Increased cardiovascular and sympathetic nervous system activity upon exposure |
| Neurobiological | Overstimulation of stress-response neuromodulators | Overstimulation of memory for the same traumatic event |
| | Hypocampal damage | Explains memory and reexperiencing symptoms |

Among the psychosocial models, Seligman's theory (1975) of learned helplessness explains how exposure to trauma that is impossible to avoid may lead to apathy, passivity, and a conviction that escaping future traumatic events is also impossible. Information processing theory explains how information linked with traumatic events is recalled (Fairbank et al. 2001). Research (Basoglu and Minetka 1997) has shown how preparedness for trauma might alleviate the severity of later symptoms. In classical conditioning theory, exposure to trauma-related stimuli in persons with PTSD may lead to cardiovascular and sympathetic nervous system activity (Fairbank et al. 2001).

Increasing research into the biology of PTSD suggests that persons with PTSD respond to a variety of stressors with heightened catecholamines compared with controls, and that they show abnormal reactivity in response to stressors that resemble the trauma but not to generic stressors (Southwick and Friedman 2001). A possible explanation may be that stressful events result in an overstimulation of the endogenous stress–response neuro-modulators, thereby overstimulating the memory for the same event (Southwick and Friedman 2001).

Modern brain imaging techniques show that PTSD subjects may have alterations of the brain such as a reduced hippocampus, as well as functional alterations, and that the hippocampal damage may explain the memory problems and the reexperiencing symptoms of PTSD (Southwick and Friedman 2001).

## General Therapeutic Considerations

### Approaches to Treatment

The enormous global public health problem of torture in many ways still remains neglected, and many challenges face survivors (see Table 124–2). First, of course, is to survive the immediate consequences of torture. The next steps include escaping the torture setting, successfully settling in a country of exile, finding treatment facilities there, and finally receiving treatment. But remaining as a displaced person in your country of residence may make it difficult to access treatment.

**Table 124–2 General Therapeutic Interventions**

| Models | Theory | Characteristics |
|---|---|---|
| Approaches to treatment | Recognize steps to treatment | • Surviving<br>• Escaping torture setting<br>• Settling in exile<br>• Finding treatment facilities<br>• Getting access to treatment |
| | Face urgent needs | • Shelter, food, school<br>• Medical, psychological, social, legal |
| | General considerations | • Focus on primary needs<br>• Support all needs<br>• Ensure continuity of care |
| Communication with patients | If interpreters necessary | • Caution against nonprofessional interpreters, e.g., family members<br>• Concern regarding confidentiality, sex, and ethnic background of interpreter |
| Therapist–patient relationship | Physical and emotional safety for patient | • Reestablish basic trust<br>• Ensure predictability<br>• Ensure feeling of safety<br>• Recognize losses of patient |
| | Values and stereotypes of therapist and patient | • Respect differences in values<br>• Recreate trust in patient |

The needs of the survivors are frequently multiple, including medical, psychological, social, and legal. But the urgent needs to be met before any therapeutic intervention are, e.g., finding appropriate shelter, food, some kind of income if not employment, as well as access to basic medical care. Furthermore, child care and access to schooling may be needed.

Clinical Vignette 3

A 34-year-old physician, GH, escaped her native, Afghanistan, following jailing and torture at the hands of the Taliban for her treating of both male and female patients. As a result of this brutal violence, which included having her earring ripped from her ear and acid thrown on her, she suffered somatic pain, nightmares, insomnia, hyperarousal, and other symptoms of PTSD. The treatment center provided a psychological and medical affidavit of support for her asylum claim, as well as child care and interpreters for her asylum interview. She was secured primary care and social service assistance for herself and her young daughters, as well as ongoing individual therapy with a Farsi-speaking clinician. After she was granted asylum, GH received postasylum benefits counseling, and received mentoring and information on recertification as a physician directly from the treatment center's Medical Director. Her husband and son were on their way out of hiding to the United States, and GH was looking forward to practicing medicine once again.

Populations entering treatment are characterized by their cultural diversity, necessitating development of culturally competent health care systems. This requires flexibility in approach and problem solving. Ultimately, the aim of the intervention should be to enable the survivor, irrespective of cultural background, to become a productive, or at least participatory, member of society (Quiroga and Jaranson 2005). When dealing with traumatized patients, certain general principles should be taken into consideration (Jaranson et al. 2001). Therapists should above all do no harm, focus on the primary problems when the patient is ready, and support all needs that the patient expresses. One primary care person should offer regular meetings in an atmosphere of trust, providing continuity of care and awareness of cultural differences and religious beliefs. Both pharmacotherapy and other therapies should be considered, as well as the need to maintain a therapeutic relationship over extended periods. Posttraumatic stress symptoms wax and wane over time, often they can be exacerbated by environmental stressors, and can show persistent chronicity.

## Communication with Patients

Working with torture survivors frequently means that therapist and patient have different linguistic backgrounds, thereby challenging the skills of the therapist. The patient rarely masters the language of the therapist fluently, and may have difficulty expressing emotions in detail or lacks terms for crucial concepts. Such cases easily give rise to misunderstandings that can have serious consequences for the therapeutic alliance.

In many settings, the use of interpreters is inevitable. Caution should be expressed regarding the use of nonprofessional interpreters, in particular the family members, who may not be able to keep their distance and get emotionally involved in the session. Working with interpreters requires the therapist to have the special skills of building a relationship with the interpreter as a third party and creating a safe environment. There are many pitfalls working with interpreters, including the reluctance of the patient to accept a given interpreter. Such reluctance may be related to issues like confidentiality or the sex and social background of the interpreter. On the other hand, some patients may express a preference for the presence of a third person of the same cultural background, stating that this provides a sense of security.

## Therapist–Patient Relationship

Serious damage to a person's feeling of safety is central to most traumatic experiences, and reestablishment of basic safety is a prerequisite of any therapeutic intervention (van der Weer and van Waning 2004). The primary need of traumatized persons consists of physical and emotional safety as well as predictability of relationships. The therapist may play a critical role in all of these issues (Kinzie 2001). The insecurity may be particularly common among refugees who experience unpredictability regarding future legal status or economic security, lack of integration into their final resettlement country, or bad news from home.

The patient may look for support to solve the current stress factors and put them in the foreground during therapy. As a therapist, it is essential to recognize and respect this need. (Kastrup and Arcel 2004). Recreating a safe place can be seen as the first step in the therapeutic process and the basis for developing a sustainable therapeutic alliance.

As pointed out by van der Weer and van Waning (2004), safety for a patient means a feeling of not being intimidated or threatened, which implies understanding the nature of the therapeutic intervention, its goals, and the rules guiding it.

Successful communication requires the therapist to have a respectful curiosity and willingness to learn more about the cultural values of the patient, as well as self-awareness of cultural biases, stereotypes, and values. Refugees frequently have a story fraught with betrayal and persecution. The therapist has an important role to recreate a feeling of trust in fellow men and to contain emotions of anger and grief expressed by the patient. The therapist should work to understand the depth and meaning of the patient's losses and the shared powerlessness to undo these losses (van der Weer 1999).

## Treatment Interventions

The applicability of different psychotherapeutic approaches has been widely discussed in the treatment of torture survivors. It is characteristic for the field that most therapeutic approaches are rather pragmatic and do not base themselves on one consistent theory but combine different elements based upon clinical experiences. Over time, several treatment modalities have emerged, and the choice of treatment in a given setting has to a large extent been formed by the professional orientation of the therapists at a given setting (Jaranson et al. 2001).

The severity of torture predicts PTSD, whereas lack of social support relates to depression but not PTSD. As a consequence, measures on social support may have little effect on PTSD (Basoglu et al. 1994b). Most treatment modalities include the telling of the traumatic events, sometimes in the form of imaginal exposure (Jaranson et al. 2001). Despite the communalities in the various treatment approaches, we still have insufficient evidence for the specific effective elements of the interventions (Jaranson et al. 2001). Retelling the traumatic event may cause abreaction, but the risk has not been confirmed in controlled studies (Jaranson et al. 2001) and, if follow-up intervention is not provided, this technique may cause more harm than problem solving (Quiroga and Jaranson 2005).

Clinical Vignette 4

AT is a 60-year-old man from Chile who has lived in the United States for thirty years but not made any contact with the treatment center until this year. He was one of the military officers loyal to Salvador Allende who were imprisoned and tortured in the wake of the coup in 1973. He suffered beatings, electric shocks, and psychological torture during interrogations, and was subsequently sentenced to several years in prison. His wife recalled during an interview with the treatment staff that she did not recognize him when she first saw him again after his arrest because he had lost so much weight. The center helped Mr. AT to document the psychological consequences of his experiences as he and many others were working toward obtaining proper recognition from the Chilean government. Mr. AT desired to become an active volunteer with the center and assist other survivors through his professional experience as a social worker.

### Cognitive–Behavioral Therapy (CBT)

In recent years, interest in the cognitive approach to treatment of traumatized refugees has increased. CBT has already been shown effective in the treatment of depression and anxiety. CBT's premise is that the way one sees and interprets the surrounding world strongly influences one's actions and emotions. The assessment prior to therapy is essential since cognitive therapy presumes that the client is willing and able to participate actively in the treatment (Basoglu 1998) and has basic security (Varvin and Hauff 1998).

In the treatment of torture survivors, it is important to get an overview of the life difficulties, negative thoughts, and assumptions behind these (Berliner et al. 2005). The first step is prioritizing the problems and subsequently facing the negative assumptions lying behind them. The cognitive approach provides the patient with the tools to use in order to change these assumptions and, through assignments, change dysfunctional behavior (Berliner et al. 2005). Berliner et al. (2005) point out that cognitive therapy has certain shortcomings, since it presumes that the thought patterns are dysfunctional and need change, whereas thoughts may be normal reactions without a need to restructure.

### Psychodynamically Oriented Therapy

Psychodynamic psychotherapy has been and is still one of the most frequently used psychotherapeutic approaches in the management of torture survivors, and several overviews of psychotherapeutic interventions have been published (e.g., Vesti and Kastrup 1992, Somnier et al. 1992, Varvin and Hauff 1998, Gurr and Quiroga 2001, Quiroga and Jaranson 2005). Psychoanalytic therapy focuses on the unconscious representation of the traumatic event and its interaction with other life events (Varvin and Hauff 1998). Psychodynamic therapy is characterized by its structured frame, typically a contract between therapist and client. The establishment of a sustainable mutually trusting relationship is key. Torture places a person in a situation of helplessness and destroys a person's internal caring universe that the therapy aims to restore (Varvin and Hauff 1998). The client is encouraged to retell the traumatic experiences. Suitability for psychodynamic intervention includes the patient's motivation for change, ability to introspect, ego strength, and choice of defense mechanisms, frequently dissociation, somatization, and derealization.

Torture survivors frequently suffer from very complex and chronic posttraumatic reactions. As a consequence, there are special concerns to consider before starting a psychotherapeutic intervention. Among such considerations are (Drozdek and Wilson 2004):

- The therapy must start at the right time.
- Decision must be taken as to whether the therapy should be initiated or not.
- Decision must be taken as to whether the therapy should be an individual or a group intervention. Group treatment provides a possibility to identify with others and share experiences, but for many torture survivors, disclosing personal violations, especially of a sexual nature, may be counterproductive.
- A proper therapeutic approach must be chosen. The more supportive therapies aim to help victims cope with

their current situation and modify the effects of the trauma in order to manage their daily life.

In contrast, the "uncovering" insight-oriented approach will face the trauma, and aim to provide the victims a deeper understanding and insight into the experiences they have undergone and their reactions. In general, it is wise to let the person's ego strength be a decisive factor in the choice of therapy: The stronger the ego, the more likely that the person will be able to benefit from an uncovering approach (Varvin and Hauff 1998).

In many settings, a multiphasic model is recommended. One of those is the Five Phase Model described by Drozdek and Wilson (2004). Phase 1 establishes a sustainable therapeutic alliance. Phase 2 focuses on the trauma and the life story of the patient. Then Phase 3 deals with the telling of the trauma story, including the exposure and restructuring. In Phase 4, the focus is on relating the past, present, and future of the patient and, finally, Phase 5 focuses on working with the termination of therapy and future relapse prevention.

## Psychopharmacological Treatment

The previous reluctance in many settings to use pharmacotherapy to avoid undue medicalization of torture is no longer prominent. Increasing evidence supports the use of psychotropic medication to reduce symptoms of PTSD, to help control loss of temper and aggression, to facilitate the psychotherapeutic intervention, or to treat some of the comorbid symptoms of anxiety or depression (Kinzie and Friedman 2004) (see Table 124–3). A combination of psychotherapy and pharmacotherapy is practiced in many settings.

Tricyclic antidepressants (TCAs) in randomized controlled trials have shown a moderate effect in alleviating PTSD symptoms, but today the SSRIs have replaced TCAs as the medication of choice. The SSRIs show a positive effect on the numbing and arousal symptoms of PTSD and on the comorbid symptoms of anxiety and depression (Jaranson et al. 2001).

Antiadrenergic drugs such as beta-blockers have been considered helpful by reducing noradrenaline release and global PTSD symptoms, especially intrusive thoughts, hyperarousal, and nightmares (Kinzie and Friedman 2004).

Antipsychotic medication is not the recommended treatment for PTSD symptoms. For those reporting psychotic symptoms, the atypical antipsychotics may prove useful (Kinzie and Friedman 2004).

Anxiolytics may reduce anxiety that is so prevalent among torture survivors, but due to danger of addiction, these medications are rarely indicated.

Since insomnia is such a frequent symptom among torture survivors, agents to reestablish sleep patterns are often prescribed. Many psychiatrists in the field use nonaddictive but sedating medications, such as antidepressants in small doses (e.g., trazadone) or antiadrenergics (e.g., clonidine), for this problem.

Cultural factors and attitudes toward medication may influence compliance, and attention should be paid to explaining the importance of following the prescription instructions. Many torture survivors may stop their medication as soon as they experience a positive effect on their symptoms or stop because they either cannot wait for an effect or they experience side effects.

## Other Treatment Models

Several other therapeutic approaches have been developed over time (Vesti and Kastrup 1992). The testimony method focuses on the detailed written account of the experiences that the survivor has undergone. Nonverbal techniques such as relaxation therapy have been used, especially when verbal therapies are not possible. Family and group therapy is particularly useful when the acceptance of individual therapy is limited. Recognizing the physical complaints of the torture survivors, physiotherapy has played a role as an integrative part of rehabilitation programs, and physiotherapy may be effective in reducing the distress and the chronic pain that is increasingly seen as a major contributor to suffering.

The narrative method consists of listening to the story of the client, trying not to make a psychological problem out of the story, but instead finding ways to actively change the future (Berliner et al. 2005). This method has little theoretical background and/or demonstrated effectiveness in the treatment of torture survivors.

Eye movement desensitization and reprocessing (EMDR) is increasingly used to relieve the effects of single traumatic events by combining components of exposure and cognitive therapies, but there is little documentation of their effectiveness in torture survivors (Quiroga and Jaranson 2005).

Psychosocial treatment emphasizes psychosocial factors, community activities, and self-help groups. When refugees arrive in a foreign environment, not only their health needs require reevaluation, but also their health promotion, empowerment, and quality of life. Cultural,

**Table 124–3 Psychopharmacological Treatment**

| Medication Category | Effects on PTSD | Other Effects |
|---|---|---|
| Tricyclic antidepressants (TCAs) | Moderate decrease in depressive symptoms | Decrease in symptoms of depression |
| Selective serotonin reuptake inhibitors (SSRIs) | Decrease in numbing and arousal symptoms | Decrease in depression and anxiety symptoms |
| Antiadrenergic agents, e.g., beta blockers | Decrease in intrusive thoughts, hyperarousal, and nightmares | Sedation may decrease insomnia |
| Antipsychotic agents | Not recommended to treat PTSD symptoms | If psychotic symptoms are unrelated to PTSD, consider atypical antipsychotics |
| Anxiolytics | Decrease anxiety-related symptoms | Rarely indicated due to risk of addition, paradoxical reactions |
| Antiinsomnia agents | Reestablishment of sleep patterns | Excessive morning sedation, risk of addiction |

socioeconomic, and sociopolitical factors are important, as migrants undergo severe social changes in the host country (Ekblad and Jaranson 2004). A large proportion of torture survivors are in need of extensive social support, particularly with legal issues, housing, economic support, and access to treatment in countries of resettlement. Adjusting to a different and frequently hostile new environment adds further stress.

In many countries, entire communities have been exposed to organized violence. Here community intervention may be the solution, but limited evidence-based data on the effectiveness exist. According to WHO (2003), it is important to reestablish possibilities for religious, spiritual, and cultural activities, thereby strengthening traditional ways of handling sorrow and loss. Support programs should respect the local culture and preferably integrate local helpers. Individual counseling may not be possible if the person has no social network, but may be combined with community or family support (Madsen 2005). Goals for intervention are to heal the painful experiences, develop skills for coping with the present situation, and rediscover resources within a network (Madsen 2005).

## Organization of Care

### Rehabilitation Models

Since the 1980s, a large number of rehabilitation programs have emerged around the world and are still expanding. In a recent overview (Quiroga and Jaranson 2005), 235 programs or centers were identified by the International Rehabilitation Council for Torture Victims (IRCT).

Some programs may serve multiple needs of the survivors, be they medical, psychological, social, or legal, whereas the other programs specialize. The Global Directory of Centers and Programs (2003–2004) reflects the diversity of services offered by the different institutions, most emphasizing counseling or psychological services and, to some extent, medical services (www.irct.org). The Global Directory also reflects that pathways to care for survivors of torture depend upon the region in which they live. There are a variety of models of care: some are free of charge for those seeking help, and others have to be paid for by the survivors. Economic limitations are a major obstacle to appropriate care, since many torture survivors may be unable to afford any therapeutic intervention. In many regions, availability of appropriate care is limited. This means either that torture survivors do not receive any care, or that the available treatment settings have long waiting lists. Over time, treatment centers have been organized in different ways, recognizing that centers of expertise may be appropriate for some regions. In other areas, where entire populations have been exposed to organized violence, a community-oriented approach may be more appropriate. Mainstreaming the treatment and increasing the competency of mental health professionals may allow the treatment to take place within general mental health services and expand the availability of interventions. Historically, many programs were initiated by nongovernmental organizations (NGOs) in recognition that the official health services did not offer adequate care for this population. Gradually, expertise has been assembled around these programs. Subsequently, in many settings, the expertise has been transferred to and integrated with mainstream services, thereby rendering it possible for the mainstream to offer such treatment.

A bio-psycho-social approach is the philosophy behind many rehabilitation programs for torture survivors. This comprehensive approach to treatment typically provides support on a daily basis aimed at fulfilling many needs, with an awareness of the patient as a client (Berliner et al. 2005).

## Specific Populations and Issues

### Influence of Culture and Sociopolitical Context

Allodi (1991) has described the importance of geographical region from a developmental point of view in the management of care. In the North, i.e., the Western world, where disease classifications have been developed, the approach to treatment and diagnosis is individualistic and based upon a medical model. In the South, i.e., the developing world, this approach frequently meets resistance. For example, PTSD is often viewed as a Western ethnocentric concept that does not take into consideration the socio-political and cultural context.

This discussion has continued, emphasizing that symptom manifestation of PTSD may have different meanings depending upon cultural factors. Torture, however, is a trauma of such horrific dimensions that it essentially overrides the importance of cultural differences. This does not imply that culture has no impact, but rather that cultural differences may appear in the way the traumatized persons express their symptoms and interpret the trauma they have experienced (Jaranson et al. 2001).

The relationship between traumatic experiences and outcome is not clear-cut. Summerfield (1999) finds it problematic when Western researchers believe that PTSD, a Western diagnostic category, captures the essence of response to traumatic events. Applying diagnostic checklists without taking into consideration the cultural and political context may overestimate the need for treatment and render the problem as well as the solution individualistic.

Sommerfield (1999) states that refugee beliefs of causation, such as the supernatural, may override the Western understanding of illness as situated in the individual's body or mind. PTSD symptoms after war or torture fail to explain why many survivors of organized violence have nonetheless been able to think and act appropriately.

According to Kleinman (1988), the cultural dimension is increasingly valued, but that psychiatrists tend to exaggerate what is culturally universal in psychiatric disorder and deemphasize what is culturally particular. Disease entities are meaningful across cultures, and comparative studies across cultures with respect to certain diagnoses are therefore feasible.

Mirdal points out (2001) that there is a tendency to use the term "culture" as an explanation when dealing with "the others" behaving strangely, not when "we ourselves" do it. Culture is used as an explanation when Mustapha behaves aggressively or Fatima complains of respiratory distress, but less likely so if Maria is depressed or John drinks excessively (Mirdal 2001). Culture is a category used as a background factor in dealing with other persons' sufferings but rarely with our own. This also is relevant to the discussion about the mental health aspects of severe trauma.

## Gender Issues

There is a growing concern for the particular problems of female refugees. Research on the role of gender in the experience of torture has focused on individual vulnerability, and studies focusing on gender differences are rare, even though refugee women face multiple difficulties in exile (Kastrup and Arcel 2004). Refugee women risk sexual assaults, and may be forced to provide sexual services to secure survival for themselves and their dependents. Refugee authorities, e.g., UNHCR, recognize that gender aspects are important when considering refugee laws. Women, even as refugees and torture survivors, continue their role as nurturers and providers of emotional support. They have a key role in providing care and frequently have little time to consider their own needs due to their preoccupation with the needs of their immediate families. This may lead to anxious and depressive disorders, particularly in women with young children (Kastrup and Arcel 2004).

When referred to therapy in the country of resettlement, certain issues should be considered in order to provide gender-sensitive treatment. Many women with somatic complaints hope for a rapid improvement and have little knowledge about and confidence in psychotherapeutic interventions. The lack of social independence experienced by many refugee women may imply that their families do not see psychotherapy as an appropriate treatment and even question its legitimacy. Social control is generally stricter among refugee women in the host country, since male relatives may feel threatened by the autonomy and lifestyle of Western women (Kastrup and Arcel 2004). Therapists must consider such issues when establishing a therapeutic alliance. In addition, therapists should respect the values of the refugee women, as well as encourage involvement in decision-making regarding their own lives and survival in a new environment with little support from family. Social networks may be a valuable substitute for the extended family.

Clinical Vignette 5

YC was raped by members of Guatemalan military at the age of 15, forced to witness her mother's rape by those same soldiers, and entrapped for several years in a domestic violence relationship. She came to the treatment center suffering from severe PTSD and depression, with nightmares, headaches, and inability to sleep. The center provided YC with a psychological evaluation for her asylum case, represented by a local legal organization. The center also arranged for YC to begin seeing a primary care physician and begin free English classes, since she could not read or write in any language. Following her granting of asylum, the center secured YC job placement services, cash assistance, and medical insurance. YC reported success in all of these areas, and has referred several friends to treatment at the center.

## Survivor Issues

Those who have been subjected to torture are frequently referred to as "victims." By using this term, there is not only a focus on the human right violations that they have undergone, but also on the severe consequences. The term signals that they have been violated and left in a defeated position. Many have objected to be classified as "victims," and there is an increasing tendency to replace that term with "survivors," focusing on the resilience that the group has manifested, that they have managed to survive in spite of it all.

Several survivors of World War II concentration camps have shared their experiences with the world, and the writings of Primo Levi and Bruno Bettelheim are outstanding examples. Such testimonies provide us with an insight into the universe of those who have lived through atrocities. Other survivors (Ortiz 2001) have emphasized that it is not understandable that mental health professionals provide survivors with diagnoses without thoroughly understanding the ordeals of the survivors. Many object to psychiatric labels, stressing that they are normal persons who have experienced abnormal situations. They do not accept being called "sick" or "in need of treatment" and are concerned with the risk of being "guinea pigs." Therapists have to be aware of this in order to avoid retraumatizing those who seek help.

## Educational Issues

Many mental health professionals who work with severely traumatized persons experience profound reactions. Confrontation with the consequences of torture or strict asylum procedures challenges the neutral therapeutic approach. Some therapists become overinvolved with the patient's situation and lose professional boundaries. Others may intellectualize and avoid the emotional aspects of the traumatic events revealed to them (Kinzie and Engdahl 2001). Bouts of hostility toward the patients and feelings of disillusionment or loss of neutrality may be seen. None of these reactions are healthy and may be related not only to the experience and personal qualities of the therapists, but also to their training.

In order to minimize such reactions, it is essential to provide training and adequate resources to the mental health staff working with such populations. Continuous supervision with discussion of these issues should be part of daily clinical practice. Caring for caregivers has consequently become necessary for the work in all torture rehabilitation centers.

Most centers provide special training for professionals who wish to work with torture survivors. Formal and informal exchanges of personnel within geographical regions of the world, supported by the IRCT, have also provided opportunities for training. On a more global scale, the IRCT, WMA, PHR, and the Human Rights Foundation of Turkey have collaborated to train mental health professionals, as well as doctors and lawyers, in assessment of torture survivors by implementing the Istanbul Protocol mentioned earlier in this chapter. Currently, the project has been piloted in ten countries.

## Ethical Issues

According to the UN Convention Against Torture, countries that have ratified the Convention have also agreed to take steps to redress the consequences of torture. Thus, there is an ethical obligation to create such possibilities for those who have suffered torture.

International law provides the right to be free from torture. From a preventive point of view, it is important to investigate allegations of torture with respect to certain

principles as outlined, e.g., by AI and, in particular, by the Istanbul Protocol (UN 2001). This protocol provides minimum standards for assessing and reporting on examinations of torture survivors based on the accumulated experience worldwide. Subsequently, training manuals have been developed in several languages including a manual developed by the US Physicians for Human Rights, which emphasizes US asylum laws.

## Conclusions

Torture is one of the most traumatic experiences a human being can suffer, often causing long-term physical or psychological consequences. Torture occurs worldwide to an extent that the world has only recently acknowledged, creating a difficult public health situation.

The challenges for psychiatrists and other mental health professionals are enormous, but the reward for rehabilitating survivors can be equally great. Only a small number of survivors overcome the obstacles to receiving treatment. When they do, the assessment, often using interpreters, is complicated by the extreme sensitivity required to elicit a history of torture and the necessity of assuring a sense of safety for the survivor.

Although symptomatology shows many similarities across cultural and gender boundaries, diagnostic questions about the validity of PTSD and the effect of head trauma on cognitive impairment still persist. Many approaches to rehabilitation have been used but evidence-based treatment is minimal. Cognitive therapy has been documented as an effective treatment for anxiety and depression. Pharmacotherapy has been effective in reducing PTSD and other symptoms. A bio-psycho-social approach with a multidisciplinary team of providers may be the best model for addressing the many needs of survivors.

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CHAPTER

# 125 Psychiatric Management of Victims of Physical and Sexual Abuse and Rape

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## Introduction

Physical and sexual abuse and rape are prevalent in all current societies and are often followed by serious physical and psychological disturbances. Women, men, and children may be affected from all walks of life: rich and poor, across ethnicities, from the developed and developing world, and in peace and conflict zones. The common theme throughout is the use of violence as an expression of power, control, and domination.

Throughout the vast literature exploring these issues, there are many definitions of physical and sexual abuse and rape. The World Health Organization WHO (1996) subsumes physical and sexual abuse and rape under the category of interpersonal violence and defines *violence* as:

> "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation."

Physical abuse involves contact intended to cause pain, injury, or other physical suffering. Examples include hitting, punching, pushing, pulling, pinching, kicking, burning, and strangling. Sexual abuse includes unwanted or forced sexual acts and is most often applied as a term in situations where an individual is, or has been, repeatedly victimized. Rape is defined as unwanted or forced sexual (vaginal or anal) intercourse, but sexual assault is a broader term that covers other unwanted sexual acts that do not include penetration. Any of these acts may include use of a weapon either as a coercive mechanism or as physically a part of the abuse or assault. There is overlap between these groups.

It is outside the scope of this chapter to discuss the acute management of child physical and sexual abuse. The objective of this chapter will be to focus on the psychiatric management of interpersonal violence and sexual assault and its sequelae in adults in nonconflict zones.

Victims of interpersonal violence will be divided into: (1) victims of childhood physical and sexual abuse. (2) those experiencing physical and sexual abuse as adults. (3) victims of rape or sexual assault. The first section of the chapter will review the prevalence of these problems and describe who are at risk. In the second part of the chapter, we will outline management issues on initial presentation that include medical stability and safety as well as early psychological intervention. Attention will then be directed to long-term mental health sequelae for victims in all three groups, with a specific focus on posttraumatic stress disorder (PTSD). Although victims of physical and sexual abuse and rape can present with symptoms of almost any mental disorder, symptoms of hyperarousal, reexperiencing of traumatic memories, and avoidance behaviors are very common and fall into the category of PTSD and related disorders. The goal of the last part of the chapter will be to review in detail the management of PTSD and related syndromes in victims of physical and sexual abuse and rape.

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## Epidemiology

### Adult Survivors of Childhood Physical and Sexual Abuse

The US Department of Health and Human Services estimated the rate of child maltreatment in 2001 to be 12.4/1000 or over 903,000 children (US Department of Health and Human Services Administration on Children, Youth and Families 2003). Of these cases, 19% were physically abused and 10% suffered sexual abuse. Gorey and Leslie (1997) calculated the prevalence of child sexual abuse at 16.8% for girls and 7.9% for boys after adjusting for sample variation, response rates, and definition differences in 16 North American community studies. In general, it is estimated that up to 90% of cases of sexual abuse are not reported (Horner 2002).

### Physical and Sexual Abuse of Adults

The most common type of ongoing physical and sexual abuse in adults is intimate partner violence (IPV). This includes acts of physical aggression, psychological abuse, forced intercourse and other forms of sexual coercion, and various controlling behaviors such as isolating a person from family and friends or restricting access to information, finances, and assistance. Elder abuse and maltreatment of persons with intellectual disabilities are also significant problems in which the intimate partner is not necessarily the perpetrator.

#### Intimate Partner Violence

##### *Case #1—Mary*

Mary, age 28 years, is referred by her primary care physician with a history of depression and anxiety for 6 years. She is the mother of two daughters aged 5 and 3 years and has been married for 7 years to a police officer. Her husband, John, comes to the psychiatric consultation and says Mary is too upset to answer questions, so they would like to be seen together. Mary nods her head in agreement. You agree to see them together initially and advise them that you will need to see Mary alone in the latter part of the consultation.

You note that when they are together, John does most of the talking but occasionally says "isn't that so?", and Mary nods her head in agreement. You then ask to see Mary alone and John replies, "can't you see she's not up to answering questions?" You thank him for his helpful information and insist that you need to spend some time with Mary alone. As he reluctantly leaves the room, he stares at Mary and says, "I'll be right outside, don't be long."

Once alone with her, you ask Mary how she feels. She begins to cry and wring her hands. You gently ask if she feels safe and she shakes her head "no." You quietly ask if anyone has threatened her or hurt her physically, and she nods affirmatively and then abruptly says, "I can't talk now." You ask why and she points to the door. You ask if it is safe for her and her children to be at home tonight and she nods yes. You give her the number for the police and an emergency abuse shelter helpline, assure that she has a means of transportation, and arrange for her to return the following day by herself to get further information and decide together on the best plan.

The literature supports the idea that IPV is a prevalent problem with serious consequences. The FBI reports that 30–40% of female murder victims and 4% of male murder victims each year are killed by their partners or ex-partners (Barrier 1998). In the US population-based National Violence against Women (NVAW) survey, IPV was defined as physical or sexual assault and/or rape by an intimate partner (a current or former cohabitant, at least some of the time). In this study, 22% of women and 7% of men reported lifetime IPV (Tjaden and Thoennes 2002). In the WHO multicountry study on violence against women, there were wide variations in prevalence by country and by area within countries (i.e., urban or rural). Women who experienced sexual or physical violence from an intimate partner ranged from a low of 15% in urban Japan to a high of 71% in rural Ethiopia. Generally, rates of IPV were higher in rural than in urban areas of countries (WHO 2005).

It has been well established that most acts of IPV are not reported to police and are underreported in health-care settings. The data reported from epidemiological studies may be a gross underestimate (Cherniak et al. 2005).

##### *Risk Factors*

**Sex** Data from the NVAW survey suggest that women who cohabitate with women incur less IPV than women overall (11% vs. 22%) and that men who live with men incur more IPV than men overall (15% vs. 7%). However, women are more likely to be chronically assaulted with more injurious consequences. For example, in the NVAW survey, women averaged 6.9 assaults by one partner, where men averaged 4.4. During their most recent assault, 41.5% of women were injured, compared to 19.9% of the men (Tjaden and Thoennes 2002).

**Socioeconomic Factors** Many studies have examined risk factors for IPV (For a review, see Acierno et al. 1997). Although there have been differences in rates of IPV in various racial and ethnic populations (usually with ethnic minorities at greater risk), IPV affects all parts of society. Racial and cultural differences are often eliminated when controlling for socioeconomic status where lower income women are at greater risk than higher income women. However, even women from middle and higher socioeconomic families may have no access to cash, credit cards, or bank accounts, as abusive partners often carefully control these by preventing access.

**Relationship-Specific Characteristics** Worldwide, violence is linked to emotionally abusive and controlling behavior in the home. In the NVAW survey, having a verbally abusive partner was associated with the having twice the odds of experiencing IPV. A particularly at-risk time may be directly after one member of the couple has left the cohabitation environment. Unmarried cohabitating female partners (but not males) tend to be at greater risk than married couples. Couples where there is greater financial or educational disparity are at greater risk. For men, being a different race from the other partner is a significant risk factor for abuse. Alcohol and drug abuses are also significant risk factors.

**At-Risk Populations** Individuals who experienced assault as children are more likely to be victimized as adults (Bohn and Holz 1996). Persons with a disability (in particular those with intellectual disability) are at higher risk. It is estimated

that up to 20% of women are beaten during pregnancy, and there are reports that ongoing violence escalates during the pregnancy and postpartum periods (Cherniak et al. 2005). However, it is controversial whether pregnancy itself is a risk factor for IPV. Women are at highest risk of domestic abuse when they are of child-bearing age, and the most consistent finding in the literature is that women who experience IPV during pregnancy have suffered abuse prior to pregnancy (Bowen et al. 2005).

### Elder Abuse

Although the elderly can also experience IPV, they are also at risk of physical and sexual abuse from other sources. Perpetrators include nonpartner family members (often transgenerational) and, if the individual is institutionalized in a nursing home, can include nursing home staff or strangers. In addition to the types of physical abuse commonly seen in adult IPV, in the elderly physical abuse can include force feeding, improper medicating, or improper use of physical restraints (particularly in institutional settings). It is thought to account for about 14% of all elderly trauma. Estimates from the US National Center for Elder Abuse (2005) are that 2–10% of community-dwelling elders are victims of maltreatment (which includes neglect, psychological and financial abuse, as well as physical and sexual abuse). The National Center for Elder Abuse (1996) estimates that physical abuse accounts for 14.6% and sexual abuse for 0.3% of the total. In institutional settings, the prevalence is thought to be much higher. One survey in the USA of nursing home staff found that 10% of nurses' aides reported that they had committed at least one act of physical abuse in the preceding 12 months (Pilemer and Moore 1989). However, elder abuse is thought to be widely underreported, with as many as five in every six cases going unreported (National Center for Elder Abuse 2005). This may be for many of the same reasons as underreporting in IPV, with the additional provision that there is more likely to be physical dependency on a perpetrating caregiver. As well, some elderly victims may feel that their allegations will be dismissed due to ageism or attributed to declining cognitive functions.

#### *Risk Factors (Collins 2006)*

Risk factors for physical and sexual abuse of the elderly include age >75 years, female, social isolation, living with or close to the perpetrator, and being dependent on the perpetrator (physically and financially). Cognitive, physical, and functional impairment; incontinence; and nursing home placement all increase risk of abuse. In addition, a history of physical or sexual abuse in the home increases the risk of recurrence in the elderly (even if the elderly victim was historically a perpetrator).

## Rape and Sexual Assault

In the USA, the estimated prevalence for rape in women is 9–13% and 0.7–5% for men (Spitzberg 1999). The prevalence of sexual assault is even higher, with estimates as high as one in three for women. Data from the National Centre for Victims of Crime and Crime Victims Research and Treatment Centre (1992) reports that 1.3 women are raped every minute in the USA. Rape and sexual assault are epidemic in some countries and may be used as a weapon of war to demoralize large sectors of society. In the WHO multicountry study on violence against women (WHO 2005), rates of rape and sexual assault in women >15 years perpetrated by nonpartners were highest (between 10% and 12%) in rural Peru, Samoa, and Tanzania, with the lowest levels reported in rural Bangladesh and Ethiopia (<1%).

In recent years, there has been the advent of "date rape" drugs, such as the benzodiazepine flunitrazepam (rohypnol) and the GABA-agonist gamma-hydroxybutyrate (GHB). The existence of these drugs obscures prevalence estimates of rape because the drugs leave the victim without memory of the assault.

**Clinical Pearl**
Flunitrazepam can go undetected if added to any drink, has an onset of action within 30 minutes with peak at 2 hours, and can exert its effects for up to 8–12 hours. Along with the well-known effect of associated amnesia, there is somnolence, muscle relaxation, and profound sedation (Kaplan et al. 2001).

### Risk Factors

Young women appear to be most vulnerable to rape. In 1987, Koss et al. conducted a national survey of college women and found that 1 in 4 women had a lifetime history of rape or attempted rape. More than half of all rape and sexual assault victims in the NVAW were women under the age of 18 (Tjaden and Thoennes 2002). Men appear to be most at risk in the prison population where it is estimated that up to 14% of inmates are raped (Dumond 2003).

In general, strangers account for 22% of rapes; partners or dates for 19% and 38% are perpetrated by family members (Tjaden and Thoennes 2002). In the Koss et al. (1987) study of the college students, 84% of women knew their attacker. In older adolescents, date rape appears to be most common, whereas with younger adolescents, perpetrators tend to come from the victim's extended family (Kaplan et al. 2001).

# Management—Acute Presentations of Physical or Sexual Abuse and Rape

Acute presentation of physical and sexual abuse or rape may be to primary care, specialist, or emergency room settings.

## Adult Physical and Sexual Abuse

### Presentation

Any type of injury can be sustained from physical abuse. Risk of injury is associated with threats to harm or kill, use of a weapon, and substance use (Tjaden and Thoennes 2002). Injuries may include contusions, abrasions, lacerations, fractures, or sprains. It is important to consider that head injury can also occur (Dutton et al. 2006). This has been referred to as "shaken adult syndrome" and may be manifested by symptoms such as blurred vision, vomiting, confusion, and headaches. There may be presentation after choking including loss of consciousness and seizure.

Victims may also present with exacerbations of chronic health conditions (e.g., diabetes and cardiac disease) because the abuse has interfered with their ability to manage these conditions. They may present with chronic pain or other somatic symptoms, eating and sleep disturbance, substance

use disorders, mood and anxiety disorders, and suicidality (Cherniak et al. 2005).

## IPV

Clues to the presence of IPV in the clinical setting are outlined in Table 125–1. It should be noted that some of these behavior patterns such as avoidance of eye contact, refusal to completely disrobe, or a male partner refusing to have his female partner seen alone by a male physician may actually be normative in some cultures.

**Table 125–1 Clues That Lead to Suspicion of Intimate Partner Violence**

| Depression | Evasiveness |
|---|---|
| Substance Abuse | Fear |
| Sexual complaints | Frequent crying |
| Injuries inconsistent with explanation of mechanism | One partner refusing to have the other partner seen alone |
| Multiple visits with vague complaints | Refusal to completely disrobe |
| Frequently missed appointments | Avoidance of eye contact |

**Clinical Pearl**
Abusive partners are often overcontrolling and may find many reasons to not allow the patient to be interviewed privately. It is essential to find a way to speak with the patient without the partner, even if it requires obtaining a nonfamily interpreter and moving the patient briefly for "a test" where family is not permitted to enter (remember Mary from Case #1).

## Elder Abuse

Clues to the presence of elder abuse are similar. Injuries in the elderly to areas not commonly affected during daily activities are most worrisome: bruising on inner thighs, pinna of the ear, and patterns that might indicate that physical restraint was used (over abdomen, wrists, or ankles).

### *Case #2—Harry*

Harry, age 75 years, has advancing Alzheimer's disease and has been in a nursing home for 6 months. You are asked to see him because his primary care doctor thinks Harry is also depressed and agitated.

Harry is tearful and looks frightened but is unable to give a coherent history. His daughter reports that he is losing weight and is apathetic and many of his personal items including his radio, wedding ring, and watch are "lost." His daughter also reports that Harry is poorly groomed and his clothes are often soiled with food or urine. During a visit to Harry, his daughter reports that she used her father's washroom and overheard an aide speaking angrily to her father about needing a shower again. On emerging from the washroom a few moments later, the daughter saw her father on the floor being dragged down the hall for a shower by one arm. She is afraid to complain because she is fearful her father will be discharged from the nursing home or treated worse.

You speak with the primary care doctor and together with Harry's daughter you meet with the nursing supervisor in the home and express your concerns. To your surprise, she reports that she has been suspicious of the aide's behavior for some time but has not had grounds to dismiss her.

Harry's daughter later writes you a note to tell you that her father is gaining weight and is much less agitated and depressed since the aide no longer works at the home.

## Case Identification

As noted, victims are often hesitant to disclose. Identified barriers include shame, embarrassment, and fear of retaliation from partners. There may be economic constraints, child custody concerns, or cultural pressure not to disclose abuse. However, disclosure occurs more when questions about abuse or assault are asked.

**Clinical Pearl**
A major barrier to case identification is lack of comfort and knowledge about what to do subsequent to disclosure on the part of clinicians. It is important that frontline clinicians be apprised of resources available to assist victims of physical and sexual abuse and rape in their communities. Physicians need to remember that they do not have to manage every aspect, and referrals to social workers are usually available.

Useful principles to facilitate disclosure include a nonjudgmental, empathic, and respectful clinical environment. "How" the questions are asked (i.e., with sensitivity) matters more than the exact wording of the questions.

- Clinicians must give the message that abuse is a health issue and that they are capable of dealing with "taboo" subjects. This communicates that the problem is not too irrelevant, insignificant, deviant, or shameful to talk about. It may be helpful to normalize the situation (e.g., this is a question that I ask all patients). Good areas to place information about abuse and assault are in waiting rooms and private examination rooms. Restrooms are a great place for posters about abuse, as they are private and the partner is not usually present.
- Show concern. The goal is to communicate that discomfort and reactions are understandable.
- Show an ability to help. This communicates that the situation is not hopeless.
- Show an interest in helping, communicating that the victim is not to blame.
- If a patient initially denies abuse, this could mean that he or she does not yet feel safe to disclose the abuse, does not consider abuse behaviors as abusive, or may not have suffered abuse. It is important to accept this response, provide education around abuse in general, and consider asking again in the future.

There have been studies investigating the utility of universal screening for ongoing physical and sexual abuse; however, there is little evidence that universal screening is effective either at identifying abuse or at reducing it. Therefore, targeted screening is recommended. Some healthcare providers do include screening for violence at annual health examinations, or in the assessment of new patients.

1. Have you been kicked, hit, punched or otherwise hurt by someone within the past year? If so, by whom?

2. Do you feel safe in your current relationship?

3. Is there a partner from a previous relationship who is making you feel unsafe?

1. Within the past year, or since you have become pregnant, have you been hit, slapped, kicked or otherwise physically hurt by someone?

2. Are you in a relationship with a person who threatens or physically hurts you?

3. Has anyone forced you to have sexual activities that made you uncomfortable?

**Figure 125–1** *Partner violence screen (PVS).*

1. Have you ever been emotionally or physically abused by your partner or someone importan to you? A. Yes B. No

2. Within the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone? A. Yes B. No

If yes, by whom? (Circle all that apply)
1. Husband
2. Ex-husband
3. Boyfriend
4. Stranger
5. Others (specify)_____

Number of times _____

3. Since you have been pregnant, have you been hit, slapped, kicked or otherwise physically hurt by someone? A. Yes B. No

If yes, by whom? (Circle all that apply)
1. Husband
2. Ex-husband
3. Boyfriend
4. Stranger
5. Others (specify)_____

Number of times _____
Indicate the area of injury:_____

Score the most severe incident to the following scale:
1. Threats of abuse, including use of a weapon
2. Slapping, pushing; no injuries and/or lasting pain
3. Punching, kicking, bruises, cuts and/or continuing pain
4. Beaten up, severe contusions, burns, broken bones
5. Head, internal, and/or permanent injury
6. Use of weapon, wound from weapon

4. Within the past year, has anyone forced you to have sexual activities? A. Yes B. No

If yes, by whom?
1. Husband
2. Ex-husband
3. Boyfriend
4. Stranger
5. Others (specify)_____

Number of times _____

5. Are you afraid of your partner or anyone you listed above? A. Yes B. No

**Figure 125–2** *(a) Antenatal psychological health assessment. (b) Abuse assessment screen (AAS).*

The American College of Obstetricians and Gynecologists (ACOG 2006) recommends that all pregnant women should be screened for abuse at the first prenatal visit, once per trimester, and at the postpartum visit.

Figures 125–1 and 125–2(a) and (b) offer methods for asking about IPV called the "partner violence screen (PVS)" (Feldhaus et al. 1997), the "antenatal psychological health assessment" (ACOG 2004), and the widely used "abuse assessment screen" (McFarlane et al. 1992). Questions detailing specific behaviors (e.g., slap, hit, and unwanted sexual intercourse) are more sensitive than using the words "abuse" or "assault."

### Initial Management Plan

Once physical or sexual abuse has been disclosed, the first task is to ensure the physical safety of the victim. For example, will emergency accommodation be needed? Is there someone who should or should not be contacted? Are there children involved requiring the assistance of child protective services? Then, it is important to assess the victim's motivation for change in the situation. Many victims are fearful of retaliation or feel bound by financial constraints; children; and familial, cultural, or religious expectations to remain in their current situation. No assumptions should be made about the assistance that the victim wants. Interventions should be targeted to match the victim's readiness for change. For example, if the victim is in a stage where he or she is minimizing the problem, forming an action plan for leaving the relationship would not be appropriate—and would not likely be successful.

Steps in management of physical and sexual abuse:

1. Ensure and explain limits of confidentiality (in most jurisdictions there is no legal responsibility on the part of the health-care professional to report IPV).
2. Document abuse in victim's words, using diagrams or photographs if possible.
3. Physical examination if appropriate (and document when physical examination seems inconsistent with mechanism of injury).
4. Medical stabilization if necessary (e.g., if victim is in your office, does he or she need to go to the emergency department for X-rays, stitches, or investigation of internal injuries?).
5. Validate victim's right to live without abuse.
6. Discuss safety and develop a safety plan (for immediate or later use). This can include planning an escape route from home, strategizing ways to reduce harm done during the abuse or ready important documents and necessities should the victim decide to leave in a rush, before, during, or after an assault.
7. Consider need for child protection (including need for reporting to child welfare authorities if child danger or abuse is suspected).
8. Assess motivation for change and tailor subsequent interventions accordingly.
9. Make referrals to social and legal services as indicated—physicians should realize that they do not need to manage all aspects by themselves.
10. Make referrals to mental health professionals as indicated.
11. Ensure a follow-up appointment.

Management considerations for the long-term mental health consequences will be discussed in detail in subsequent sections.

## Rape

Rape or sexual assault leaves both men and women at risk of physical injury and sexually transmitted infection, with women at risk of (unplanned) pregnancy. Men are more likely to suffer physical harm, as they are more likely to have had multiple assailants and it is more likely that weapons were used. Rape and sexual assault are massively underreported. In particular, adolescents tend to delay seeking care longer than adults and tend to press legal charges less frequently than adults, with males underreporting more than females (Kaplan et al. 2001). Proposed reasons for underreporting include shame, fear of retribution, lack of confidence in police, as well as a desire to forget the event. Many victims of rape or sexual assault may be reluctant to disclose this information and may present instead for STI testing, contraception, or needing treatment for other injuries.

**Clinical Pearl**
Sexual assault or rape may be present in cases of IPV or elder abuse.

### Disclosure

It is well established that case identification improves in settings where clinicians directly ask about the possibility of sexual assault. This happens most often in clinical settings in which clinicians are encouraged to ask, and studies show that most patients do not mind being asked. In order to ensure that the disclosure of information about sexual assault can occur, it is extremely important for the clinician to be explicit about confidentiality and allow for privacy, safety, and adequate time for the victim to tell his or her story. It is important to be nonjudgmental and to acknowledge how difficult it may be for the victim to disclose. It is important to acknowledge that feelings of fear, shame, or guilt are common and to begin to correct any cognitive misattributions such as self-blame.

**Clinical Pearl**
First disclosure is not the time for determining the accuracy of the allegations. The task of investigating the assault will be that of the police, if the victim chooses to pursue this avenue.

### Acute Management of Sexual Assault or Rape

#### *Case #3—Felicia*

An 18-year-old college student named Felicia arrives in the Emergency Room tearful and mute. You are asked to see her for a psychiatric consultation.

You notice that Felicia appears dazed and has a swollen, bleeding lip. You ask her what happened and she shrugs her shoulders and cries. You offer her a tissue that she uses on her eyes and lip and then begins to rock back and forth in her chair. You gently comment that you can see she is very distressed and if she can tell you why, perhaps you can help.

She eventually appears to collect herself and reports that she went out with a friend to celebrate her 17th birthday and drank too much. One of the men in the bar stopped her as she was entering the women's washroom at the end of the long hall in the basement. He punched her in the face and threatened to kill her if she did not cooperate and have sex with him. Following the assault, he told her that if she talked he would "come after her" and anyway he knows she was drinking underage and the police would charge her. She tearfully says, "It's all my fault, anyway. There is nothing anyone can do now."

You tell her that no one deserves to have this happen and that sexual assault is illegal. There is something that can be done. You encourage her to allow the sexual assault team to examine her and make sure that she is physically okay, by testing for sexually transmitted diseases and taking pregnancy precautions if necessary. Her options for reporting to the police can be considered. You inform her about common psychological symptoms after sexual assaults and discuss possible ways of coping. You enquire if she has a safe place to stay with family or friends. You offer her a follow-up appointment for further assessment and management the following day.

Once again, the first task is to ensure the physical safety of the victim. For example, will emergency accommodation be needed? Who should or should not be contacted for support? In some jurisdictions, it will be possible to refer to a sexual assault center where the staff is expert at the medical, forensic, and psychological evaluation of acute sexual assault. For example, in the USA, many facilities have begun to use the Sexual Assault Nurse Examiner (SANE) program, which encompasses the principles discussed below (Ledray 1999). However, there are many places where such a specialized service is unavailable and acute management will be referred to the general emergency department team.

Clear documentation is vital, particularly if the victim decides to report the rape to police. Informed consent for each stage of the management plan is essential.

## History

1. A brief history of the assault is needed.
   (a) What orifices were penetrated?
   (b) Was barrier contraception used?
   (c) Were any weapons used?
   (d) Are there characteristics of the perpetrator known that would help inform risk assessment of STI or HIV status?
   (e) Does the victim suspect that drugs were used unknowingly?
2. Take the victim's medical history (including pregnancy status and date of last menstrual period if applicable), psychiatric history, medications, and allergies.
3. It is helpful to know the victim's initial thoughts about reporting the abuse or assault to the police. This can help direct the clinician in terms of what protocol to follow for DNA and other specimen. However, victims often change their minds with time, so ensure that proper specimens are collected.

## Physical Examination

Physical examination should involve a general examination that includes a screen for external injuries as well as a genital examination for both men and women. When using a proctoscope (anal examination) or speculum (vaginal examination), special care should be taken to explain to the victim exactly what is being done and the reason for it. It can be very important to give feedback about genital damage, as patients may be worried that future partners may be able to see or somehow know that they have been raped. Details for physical examination and documentation are outlined in an American College of Emergency Physicians' Handbook "Evaluation and Management of the Sexually Assaulted or Sexually Abused Patient" (ACEP 1999).

**Clinical Pearl**
Explaining all procedures and getting consent is vital. Warning the patient about the possibility that the examination might trigger a reexperiencing of the event is crucial to ensuring a sense of safety and normalcy.

## Laboratory Investigation

Investigation for pregnancy and sexually transmitted infections should be done according to need. Investigations and proposed follow-up are outlined in Table 125–2.

## Forensic Referral

DNA samples for forensic evidence can be collected up to 10 days after assault (particularly if the samples have been stored in a nondamp environment). It is important to ask victims not to wash themselves or the clothes that they were wearing during the assault prior to forensic investigation. If the victim has changed clothes prior to presenting for treatment, then usually only the undergarments are collected. Local sexual assault response teams will have specific protocols for forensic documentation. Even if the victim is undecided about whether he or she will report the assault,

**Table 125–2 Guidelines for Laboratory Investigation in Acute Sexual Assault of Adolescents and Adults**

| | Test | Site | Timing |
|---|---|---|---|
| Pregnancy | bhcg | Blood | Baseline, 2 weeks |
| *Neisseria gonorrhoea* | Polymerase chain reaction (PCR) or culture and sensitivity (C & S) | Endocervical | Baseline or at 2 weeks |
| *Chlamydia trachomatis* | PCR | Endocervical | Baseline, 2 weeks |
| Trichomonas | C&S | Vaginal | Baseline, 2 weeks |
| Hepatitis B | Surface antibody (anti-HBs) for immunity; hepatitis B surface antigen (HBsAg); core antibody (anti-HBc) | Blood | Baseline, 3 months |
| Syphilis | Rapid plasma regain (RPR) and treponema pallidum hemagglutination assay (TPHA) | Blood | Baseline, 3 months |
| HIV | HIV antibody (ELISA test) | Blood | Baseline, 3–6 months |
| Investigation of unknown ingested substances | Toxicology: alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, GHB, ketamine, marijuana, muscle relaxants, and opiates | Urine | Within 36 hours |

forensic evidence can be collected and stored until such a decision is made.

### Medical Treatment

**Pregnancy Prophylaxis** Postcoital contraception can be used up to 72 hours after rape. There are two main methods: progesterone only (two 750 μg tablet given 12 hours apart) or the Yuzpe method where 2 50 μg estrogen birth control tablets are given 12 hours apart. Progesterone only is the preferred method, as it is just as effective with fewer side effects (Mein et al. 2003).

**STI Prophylaxis** The Centre for Disease Control and Prevention (ACEP 1999) recommends:

1. Prophylaxis for chlamydia, gonorrhea, trichomonas, and bacterial vaginosis.
   (a) ceftriaxone 125 mg IM (intramuscular) once and
   (b) metronidazole 2 g p.o. once and
   (c) azithromycin 1 g p.o. once or doxycycline 100 mg p.o. BID for 7 days.
   Note that some centers will substitute cefixime 400 mg p.o. once for ceftriaxone.
2. Hepatitis B immune globulin (400 IU IM) and hepatitis B vaccination if not immune.

**HIV** Considerations for HIV exposure prophylaxis involve weighing the risk of infection with that of treatment. It is important to consider the time since exposure occurred, the likelihood of transmission, the probability that the perpetrator is infected with HIV, the efficacy and side effects of the proposed regimen, and the expected patient compliance. In Canada, the British Columbia Centre for Excellence in HIV/AIDS recommends that patients who are sexually assaulted receive postexposure antiretroviral therapy. There are no data on postexposure prophylaxis after rape; however, in cases of occupational needlestick injuries or perinatal transmission, postexposure prophylaxis reduces risk of infection by approximately 67% (ACEP 1999). Risk of HIV transmission in various situations is summarized in Table 125–3.

**Table 125–3 Risk of HIV Transmission during Sexual Exposure, with Comparison to Other Types of Exposure (ACEP 1999, Mein et al. 2003)**

| Type of Exposure | Risk of Transmission of HIV Infection per Exposure (%) |
|---|---|
| Receptive vaginal | 0.1–0.2 |
| Receptive anal | 0.1–3 |
| Receptive oral | Has been reported, prevalence unknown |
| Needlestick injury in health-care workers | 0.3–0.9 |
| Shared HIV-contaminated needle | 67% |

### Early Psychological Treatment

Although many victims are in shock and sometimes denial at the outset, initial dissociative and numbing responses have been associated with later mental health difficulties. Therefore, referrals for counseling should be offered at onset. To ensure continuity of care, patients should also be referred back to their primary care physician for ongoing monitoring.

Initial psychological intervention should be individual, supportive, and educational in nature about the effects of trauma and rape. It is important to acknowledge with the patient that any reaction he or she might be having is acceptable and that it is normal to need support. Also, it will be difficult for the patient to process and assimilate general information about rape or specific information about his or her own physical health concerns until there is a sense of psychological safety. Ensure that the patient recognizes that he or she is now in a safe place and that the assault is over. Sometimes dissociative phenomena can be observed in the emergency room. One can assist the patient by providing "grounding strategies" such as touching a table or other object in the examination room. In situations where the victim's symptoms are so overwhelming that they preclude psychotherapeutic support of any kind, pharmacotherapy may be indicated, either with short-term use of benzodiazepines or with the institution of SSRI or SNRI medication to treat the severe anxiety. Any person being started on medication should be closely monitored. Once the patient is feeling safe enough to assimilate information ensure that he or she obtains specific information about health status and educate about the risks of future health problems (victims will often be very concerned about contracting sexually transmitted infections).

**Involvement of Family or Friends** Social support is crucial to help restore effective coping. However, the clinician should gain the patient's involvement in deciding who to contact. There is evidence that negative social support (blame, criticism, etc.) can lead to worse mental health outcomes (American Psychiatric Association 2004). In addition, due to the high prevalence of known assailants, one should take care to ensure that the perpetrator is not mistaken for the intended support system. It can be helpful to discuss the acute and potential longer-term effects of rape with family. Education about sleep disturbance, irritability, hyperarousal, and reexperiencing phenomena can help to ensure a safe and supportive environment, as well as early referral to mental health treatment if symptoms persist. Education of family members about potential misattributions can also help reduce the victim's experience of shame or self-blame.

**Clinical Pearl**
It is important to give written instruction, as patients may not be able to store verbal information in the overwhelmed state subsequent to an assault.

**Clinical Pearl**
Victims' sexual partners should know that unusual responses to sexual advances after rape are universally experienced and do not reflect on the partner him- or herself.

**Debriefing** There is no evidence for "debriefing" groups where the victim is asked to describe his or her experience. There is in fact some concern that this might be detrimental for some

patients, exposing them to triggers of reexperience unnecessarily and possibly causing them to redefine their own rape experience as more horrific in light of hearing others' experiences (American Psychiatric Association 2004).

## Long-Term Mental Health Sequelae of Physical and Sexual Abuse and Rape

### Adult Survivors of Childhood Physical and Sexual Abuse

Abuse in childhood leads to significant biological, psychological, and social consequences. Adult survivors of childhood physical and sexual abuse often have profound mental health sequelae and frequently present for psychiatric treatment. Adult consequences of physical and sexual abuse in women include lower perceptions of overall health, greater physical and emotional disability, more physical health symptoms and a greater number of health-risk behaviors (e.g., physical inactivity, smoking, drug abuse, and prostitution). Risk is at least doubled for psychiatric sequelae of PTSD, major depressive disorder (MDD), anxiety disorders, and somatization (including gastrointestinal, gynecological, and neurological symptoms). Risk is significantly increased for substance abuse, dissociation, aggressive behaviors, and personality disorders.

Although mental health sequelae of childhood sexual abuse in males have been less well studied, there is an increased prevalence of PTSD, depression, anxiety disorders, eating disorders, substance use disorders, personality disorders (borderline and antisocial), poor self-image, future sexually related problems, legal difficulty, and attempted suicide. Men who were abused as children have even greater rates of psychological distress (e.g., up to fourfold increased risk of major depression), substance abuse, and sexually related problems compared to men who were not abused as children than do women who were abused compared to those not abused (Holmes and Slap 1998). For depression, this may reflect the lower baseline prevalence of depression in males. However, it may also reflect the impact of societal beliefs about abuse in males that affects disclosure, feelings of self-blame, and sense of masculinity.

#### Risk Factors for Long-Term Mental Health Sequelae of Childhood Maltreatment

In discussion of risk factors for long-term mental health sequelae of child maltreatment, it is very important to note that child sexual and physical abuses are strongly associated with mental health sequelae regardless. The following factors may mediate or increase risk, but their effect is small relative to the association between abuse and mental health sequelae in general.

##### *Social Factors*

The majority of the research on risk factors for long-term sequelae of abuse has been focused on the characteristics of the abuse. Individuals who suffer multiple types of maltreatment (i.e., physical and sexual abuse as opposed to one or the other), perpetrators and incidents have a higher risk of developing mental health symptoms than those who experience a single type of maltreatment, perpetrator, or incident. The risk of developing psychiatric difficulties is also increased with longer duration of abuse and earlier age of onset. In addition, it has been suggested that "invasiveness" of the abuse (i.e., penetration vs. noncontact) and violence or injury resulting from abuse result in more serious mental health consequences. Studies have shown that having a closer relationship to the perpetrator is also a risk factor, but this is complicated by the fact that a closer relationship (e.g., father–daughter incest) may mean an earlier age of onset, multiple incidents, and longer duration (Lesserman 2005).

Additional traumatic experiences may also be risk factors. In some environments where childhood maltreatment occurs, there is also familial dysfunction and there may be other traumas (e.g., witnessing abuse). Such adverse child experiences, particularly in the absence of protective factors that would help a child develop stable emotional resources, may be mediating factors in the development of long-term mental health sequelae. In addition, for women, at least, there are higher levels of psychiatric symptomatology among those revictimized in adulthood than among those women abused only as adults (Arias 2004).

##### *Psychiatric History and Comorbidity*

Psychological manifestations such as depression or anxiety in childhood at the time of the abuse may increase the risk of future mental health complications. The development of drug and alcohol use disorders is associated with poorer mental health outcomes for abuse survivors. In addition, early childhood abuse may interfere with the establishment of basic trust, an essential ingredient to later stable interpersonal relationships. An important question for the future is whether childhood intervention can prevent the development of long-term mental health sequelae.

##### *Neurobiology*

There is some evidence to suggest that individuals with a history of sexual abuse may actually have measurable hypothalamic–pituitary–adrenocortical (HPA) axis dysregulation and greater autonomic activation (e.g., higher catecholamines) both at baseline and in response to stress. In those with depression, anxiety, or PTSDs as adults, the HPA axis dysregulation and autonomic reactivity are greater. More research needs to be done in this area to determine whether the neurobiology could usefully predict who will develop psychiatric sequelae of childhood trauma (Lesserman 2005).

### Physical and Sexual Abuse of Adults

Over the long term, individuals exposed to IPV report more physical symptoms than those not exposed (Dutton et al. 2006). Common somatic symptoms are headaches, insomnia, choking sensations, hyperventilation, gastrointestinal symptoms, and back, chest, and gynecological pain. Chronic pain syndromes are common in women who report histories of abuse. They also report poorer health status than those not exposed (Campbell and Soeken 1999). In addition, there is a higher risk of engaging in negative health behaviors such as smoking, alcohol and drug use, unsafe sex, and poor eating behaviors. There is a higher risk of HIV or other sexually transmitted infection (Zierler et al. 1996).

At the center of the psychological response to interpersonal trauma is the experience of intense fear, helplessness, or horror. IPV disrupts an individual's sense that the world is a safe place and that others can be trusted. It disrupts an

individual's sense of him- or herself. One of the first conceptualizations of the psychological effects of IPV was the "battered woman syndrome" (Walker 1991). Symptoms included anxiety, depression, posttraumatic stress, helplessness, passivity, and low self-esteem. It was thought that many of these symptoms arose from the chronic, unpredictable nature of the violence. It is more common now to avoid the use of this term in favor of a DSM-IV-TR diagnosis.

Mental health consequences of physical and sexual abuse in adults include PTSD, depression, anxiety, alcohol and drug abuse, attempted suicide, and suicide. In a review by Golding (1999), victims of IPV had a 3–5 × greater likelihood of the above than non-victims. It has been suggested that rates of MDD in physically abused women range from 66% to 80%. It is also important to note that subthreshold symptoms of depression and PTSD are common in this group and can cause significant functional impairment (Hegadoren et al. 2006).

## Sexual Assault and Rape

Similar to the evidence in IPV, the effects of rape can be mediated through health behaviors. In a cross-sectional survey of adolescent girls in Massachusetts (Silverman et al. 2001), physical and/or sexual abuse by a dating partner resulted in increased substance use, unhealthy weight control behaviors, sexual-risk behaviors (including earlier age at first "consensual" intercourse), and pregnancy.

In 1974, Burgess and Holstrom (1974) described the "rape trauma syndrome," which consisted of two phases. First is the acute stage immediately after a rape where symptoms include disorganization, denial, and shock. The reorganization stage occurs weeks to months later. Symptoms of this second stage typically included anxiety (fear and avoidance), depression, emotional and social withdrawal, sleeping and eating disturbances (including nightmares), self-blame, shame, guilt, somatization, and sexual dysfunction. These two stages are most similar to the DSM-IV-TR diagnoses of acute stress disorder (acute stage) and PTSD (reorganization stage). There is evidence that dissociation in the peritraumatic phase characterized by the acute stress reaction may be a risk factor for the subsequent development of PTSD. See Figure 125–3 for DSM-IV-TR diagnostic criteria for acute stress disorder. Note the time period requirements for acute stress disorder, and the symptoms must occur within 4 weeks of the trauma and last for between 2 days and 4 weeks.

The US National Comorbidity Survey (Kessler et al. 1995) found that 49.5% of women and 65% of men who experienced rape met DSM-IV-TR criteria for PTSD. PTSD does not only occur in the acute time after a rape, but many victims continue to suffer for months, if not years subsequent to an assault. Major depression is purported to be higher in rape survivors, although some authors suggest that this is more of a factor in individuals who have experienced repeated sexual trauma. Once again, symptoms that do

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others

(2) the persons response involved intense fear, helplessness, or horror

B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:

(1) a subjective sense of numbing, detachment, or absence of emotional responsiveness
(2) a reduction in awareness of his or her surroundings (e.g.,"being in a daze")
(3) derealization
(4) depersonalization
(5) dissociative amnesia (i.e., inability to recall an important aspect of the trauma)

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience.

G. The disturbance lasts for a *minimum of 2 days and a maximum of 4 weeks* and *occurs within 4 weeks of the traumatic event.*

H. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by Brief Psychotic Disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

**Figure 125–3** *DSM-IV-TR criteria for acute stress disorder (Source: Adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition. Copyright 1994 American Psychiatric Association).*

not meet full criteria for DSM-IV-TR syndromes are common. It is clear that symptoms of anxiety, such as persistent fears, persist in the long term after rape in many individuals. Dissociative reactions including amnesia and depersonalization can be acute and chronic consequences. Suicidality is also of concern, with up to 50% of rape victims reporting suicidal ideation over time. Themes of shame, guilt, and self-blame abound. Sometimes anger is manifest as a symptom.

Although there is less research in men who have been raped, it is important to consider some unique issues for male victims. Long-term psychological themes can include sexual dysfunction and sexual identity confusion, particularly if they ejaculated during the rape. They may not be aware that pressure on the prostate (from anal insertion of a penis) can cause involuntary ejaculation.

## Management Considerations for Long-Term Psychiatric Sequelae of Physical and Sexual Abuse and Rape

As discussed in previous sections, individuals who have been victims of physical and sexual abuse and rape are at increased risk of various psychiatric syndromes, including depression, anxiety, substance abuse, and somatization. In general, the recommended pharmacotherapeutic and psychotherapeutic treatments of these conditions are not different for individuals who have experienced sexual abuse and rape. However, it is essential to recognize the connection between the presenting symptoms and the traumatic experience(s) and to consider the individual's behavior and symptoms in the context of traumatic reenactment. The following are some important factors to consider in the general management of psychiatric illness in individuals with a history of interpersonal trauma:

1. Safety: It is important to consider that sometimes the psychiatric difficulty cannot be resolved if the abuse is ongoing—no matter the treatment.
2. Comorbidity: In many cases, there will be a number of different problems or symptoms that will need to be targets of treatment. As always, a comprehensive assessment is vital and comorbidity needs to be addressed. It will be difficult to ameliorate symptoms in one area without addressing the others.
3. Difficulties with interpersonal relationships and affect regulation: Many victims of abuse and rape have been unable to develop and/or maintain stable emotional resources, resulting in affective instability and difficulty sustaining interpersonal relationships. This will have significant implications for the therapeutic relationship that may challenge therapists in the areas of countertransference and boundary or limit setting. It may also present a clinical dilemma of how to address the trauma history during the treatment of a psychiatric disorder. With significant affective symptoms, particularly if the patient always feels "in crisis," it is vital to equip the patient adequately to address the trauma background. Early on, it is important to help improve daily functioning and relationships while acknowledging that trauma has occurred. Exploration of the trauma itself should only begin after optimal symptom control has been achieved, there is a strong and reliable therapeutic relationship, and there has been some work in the area of expressing and processing emotions in a safe way (i.e., not using substances or self-harm to regulate affect).

While the above points apply to all psychiatric illnesses, there are some considerations specific to individual disorders. This section will review specific considerations for treatment of depression, anxiety, substance use, and somatoform disorders in individuals with a history of interpersonal trauma. The concept of posttraumatic stress is especially relevant for discussion in a chapter on management of victims of physical and sexual abuse and rape. Therefore, the phenomenology and management of PTSD in victims of abuse and rape will be discussed in detail in a subsequent section.

### Depression

There is evidence that abuse influences the expression of mood disorders. There are higher levels of depressive and psychotic symptoms and suicide attempts, as well as more comorbidity with personality disorders, eating disorders, and substance abuse. Individuals with a childhood history of physical and sexual abuse are more likely to present with "atypical" depression as identified by reverse neurovegetative symptoms (e.g., increased appetite and sleep instead of decreased appetite and insomnia) than individuals without interpersonal trauma histories (Levitan et al. 1998). In assessment of a mood disorder in an individual with a trauma history, it is vital to consider symptoms in the context of the history. For example, "body memories" or "voices" may be incorrectly labeled as psychotic phenomenon when in fact they may be more accurately labeled "reexperiencing phenomena".

Furthermore, individuals with "atypical" depression have earlier ages of onset with a more chronic course of depression—more frequent mood episodes and longer duration of episodes (Zlotnick et al. 2001). In tailoring a management plan for these patients, all of the general considerations apply, but there will almost certainly be a need for fairly intensive and multimodal treatment that might not be necessary in the management of an uncomplicated major depressive episode.

### Anxiety

With respect to anxiety disorders, panic disorder and PTSD are the two types most commonly seen in individuals with history of interpersonal trauma. PTSD will be discussed subsequently and panic disorder will be addressed here.

There is evidence that individuals with a history of trauma (particularly as children) may be particularly predisposed to panic disorder, given the high degree of autonomic reactivity that can result in HPA axis dysregulation. From a cognitive perspective, panic disorder is characterized by high levels of fear of anxiety sensations. It is the fear of these anxiety sensations that contributes to the maintenance of panic disorder. In trauma, the original anxiety sensations signaled impending severe trauma, so the connection between the anxiety sensation and the cognitive perception of danger is very strong (Safren et al. 2002).

Therefore, management implications include attention to severe physiological symptoms that will often require pharmacotherapy (i.e., SSRIs). With respect to cognitive-behavior therapy, it will be important to understand the thoughts associated with panic attacks in the context of

the trauma history, addressing cognitive distortions and forming exposure therapy hierarchies with this in mind.

### Substance Abuse and Dependence

In the treatment of substance use disorders in victims of interpersonal trauma, it is important to consider two main points:

1. Memories of the trauma may be triggers for substance use. Use may be a way of coping with the emotional pain of the trauma, although cravings later become associated to drug or alcohol cues as well.
2. As patients start to cut down or become abstinent from substances, feelings and memories may surface about past trauma(s). Therefore, it is essential to continually reassess individuals in treatment for substance use for comorbid depression or posttraumatic stress symptoms that may emerge. If these go unmanaged, the person may not be able to maintain or continue recovery.

Specific therapies for PTSD co-occurring with a substance use disorder have been developed. Techniques are mainly cognitive and behavioral, and the focus is on stabilizing the substance use disorder while developing coping skills to manage symptoms of hyperarousal and reexperiencing of trauma. Pharmacotherapeutic recommendations are the same as for treating these disorders individually, although it may be advisable to avoid the use of benzodiazepines for anxiety symptoms in this population due to the potential for developing dependence.

### Somatization

There is not a large literature on the management of somatic symptoms in individuals with a history of physical and sexual abuse and rape despite the plethora of evidence that somatization is prevalent in this population. The prevailing theory is that exposure to physical and sexual abuse or rape may predispose individuals to respond to stress somatically—perhaps as a result of heightened somatic perception (Stuart and Noyes 1999). Unfortunately, somatization is a maladaptive communication of distress because health-care providers and other potential sources of emotional support may focus only on the physical symptoms and not be responsive to the individual's emotional distress. Particularly when no physiological etiology of the symptoms is found and the level of concern by the health-care provider is lessened, the patient may have feelings of abandonment and despair (leading to a corresponding increase in somatization). Implications for management, therefore, include an empathic and consistent therapeutic environment, whereby, although the health practitioner may set limits on the number of medical investigations that are to be done, he or she remains emotionally available to the patient.

### Posttraumatic Stress

Herman (1992) conceptualized the response to trauma as a spectrum, from an acute stress reaction on one end to "complex PTSD" at the other end, with "simple" PTSD somewhere in the middle. Changes to a person's psychological schema, as well as to his or her neurobiological systems (mediated by the effects of norepinephrine and cortisol), can result in a characteristic response pattern that has been labeled in the DSM-IV-TR as PTSD. Symptoms of PTSD are clustered into three categories—hyperarousal, intrusion, and constriction/numbing. Diagnostic criteria are labeled in Figure 125–4. Hyperarousal refers to the tendency to startle easily, be irritable, and sleep poorly. Intrusion refers to the flashbacks or nightmares or reexperiencing of traumatic memories. Constriction refers to the numbing and avoidance response that is like dissociation from the pain of the trauma. (See Figure 125–4 for DSM-IV-TR diagnostic criteria.)

Complex PTSD or "disorder of extreme stress, not otherwise specified" (DESNOS) (van der Kolk et al. 2005) is thought to arise in individuals who have suffered severe, prolonged, and repeated interpersonal victimization. This includes extended child abuse, chronic spousal abuse, or the effects of forced prostitution or sex trafficking. The repeated nature of the trauma is linked to cognitive, somatic, and dissociative disturbances as well as difficulties in affect regulation, boundary awareness, interpersonal problems, and identity disturbance. Although complex PTSD/DESNOS is not considered a distinct DSM diagnosis, it is widely used by researchers and clinicians who deal with individuals exposed to recurrent trauma, as it may better characterize their symptomatology than any specific DSM-IV-TR diagnosis (see Figure 125–5 for proposed diagnostic criteria).

## Risk Factors for Developing PTSD

Not every victim of physical or sexual abuse or rape develops PTSD, and it is clear that the pathway to the development of PTSD is multifactorial. Greater severity and chronicity of the violence, life threat, use of a weapon, and sexual violence have all been shown to contribute to a higher risk of PTSD. Risk varies with victim-specific factors (e.g., female sex, socioeconomic status, past psychiatric history, less functional coping styles, family psychiatric history, and prior trauma history) as well as the sociocultural environment in which the violence takes place. For example, it has been shown that criticism, blaming responses, or stigmatization strongly predict poor mental health outcome (Briere and Jordan 2004).

## Management

### *Case #3—Felicia (continued)*

Felicia, who you assessed in the emergency room, did not keep her follow-up appointment the day following the assault. You next see her 14 weeks later in the outpatient department. She reports that she tried "to forget the assault by pretending nothing had happened." She has not told anyone about it and returned to classes the next day.

She has recurrent nightmares of the assault, flashbacks, episodes of tearfulness, exaggerated startle reactions, and anxiety. She has avoided all social contacts and has started skipping classes. She feels that she has brought all these events on herself as a result of her bad judgment.

You again affirm that no one "deserves" to be raped. You explain the symptoms and causes of PTSD. You discuss the proposed treatment plan outlined in Figure 125–6 and the following pages.

The American Psychiatric Association (2004) published guidelines for the treatment of PTSD, many principles of which are applicable to treatment of PTSD in the population

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others

(2) the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

(2) recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content.

(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.

(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
(2) efforts to avoid activities, places, or people that arouse recollections of the trauma
(3) inability to recall an important aspect of the trauma
(4) markedly diminished interest or participation in significant activities
(5) feeling of detachment or estrangement from others
(6) restricted range of affect (e.g., unable to have loving feelings)
(7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep
(2) irritability or outbursts of anger
(3) difficulty concentrating
(4) hypervigilance
(5) exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

*Specify* if: **Acute:** if duration of symptoms is less than 3 months
**Chronic:** if duration of symptoms is 3 months or more

*Specify* if: **With Delayed Onset:** if onset of symptoms is at least 6 months after the stressor

**Figure 125–4** *DSM-IV-TR criteria for PTSD (Source: Adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition. Copyright 2000 American Psychiatric Association).*

of victims of physical and sexual abuse and rape. The goal of treatment is to reduce anxiety, fears, and avoidance behaviors, ultimately to return the patient to good functioning and health and prevent relapse. It is important to note that the psychotherapeutic treatment options described below have been studied in samples where the victim is in a safe physical environment. They are not meant to be delivered in an acute setting, prior to the medical stabilization of the individual. Principles of the assessment and treatment can also be applied in the setting of acute stress disorder and in individuals with subsyndromal posttraumatic stress symptoms.

### *Assessment*

First, a full psychiatric interview should be undertaken with exploration into symptoms of posttraumatic stress and their temporal relationship to the trauma(s). Some aspects of the full psychiatric assessment may need to be deferred if the patient is still acutely disturbed from the assault. The general aim is to confirm diagnosis, identify comorbidity, and document baseline functioning and available resources (e.g., stability of housing, social support network, and financial resources). A psychiatric history should be taken with special attention to history of past physical and sexual abuse or rape. There should always be a thorough safety

i) alterations in affect regulation, which in cludes difficulty with modulation of anger and self-destructiveness

ii) alterations in attention and consciousness leading to amnesias and dissociative episodes and depersonalizations

iii) alterations in self-perception, such as a chronic sense of guilt and responsibility, chronically feeling ashamed

iv) alterations in relationship to others, such as not being able to trust, not being able to feel intimate with people

v) somatization–the expression of somatic symptoms on a somatic level for which no medical explanations can be found

vi) alterations in systems of meaning

**Figure 125–5** *Diagnostic criteria of complex PTSD or DESNOS in the DSM-IV-TR.*

Initial Sessions

1. Education about symptoms of PTSD
2. Explain rationale for asking patient to recall traumatic events
3. Do relaxation training
4. Assess patient's ability to tolerate within-session anxiety

Middle Sessions

5. Using reassurance and relaxation training, traumatic event(s) are imagined and/or described during the sessions with focus on negative affects and that the negative affects will subside.
6. Homework assignments are given whereby either patient practices imagining the events OR exposes him or herself to situations that he/she has been avoiding. This must be done in a manner of graded exposure

Later Sessions

7. Later sessions focus on sustaining gains and preventing relapse, including the implementation of relapse plans should there be any recurrence in symptoms.

**Figure 125–6** *Principles of cognitive-behavior therapy for PTSD.*

assessment that includes assessment of suicidality, homicidality, and the safety of the current environment.

### *Rating Scales*

The clinician can combine the clinical interview with rating scales such as the PTSD Checklist (Weathers et al. 1994), the Impact of Event Scale (Horowitz et al. 1979), or the Davidson Trauma Scale (Davidson et al. 1997). This will help to assess the full range of symptoms and functional impairment and provide a baseline for comparison during treatment.

**Choice of Treatment** This may depend on the severity, recency, or ongoing nature of the trauma. For example, it may not be the right time to begin cognitive-behavior therapy for PTSD in the case of a woman who continues to fear for her safety at the hands of an abusive domestic partner. In such a case, supportive intervention and resource mobilization would be more appropriate.

Choice of treatment may also depend on the severity of the symptoms, medical and psychiatric preexisting or comorbid illnesses, or patient preference. Cultural factors should always be considered. For example, cultural norms may contribute to support of a person who has suffered abuse or rape or may contribute negatively through communication that rape is shameful or that interpersonal violence should not be discussed outside the family or community.

**Specific Pharmacotherapy** There is no evidence for *prevention* of PTSD or ASD using pharmacotherapy.

Studies of pharmacotherapy in PTSD have been limited, but there are data to support the use of SSRIs or venlafaxine as first-line treatment. SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) have been shown to reduce symptoms in all three symptom clusters characteristic of PTSD: hyperarousal, reexperiencing, and numbing/avoidance (e.g., Marshall et al. 2001, Connor et al. 1999, Brady et al. 2000). Venlafaxine has been shown to reduce symptoms in all three clusters and induce remission better than placebo in 12-week studies. One recent study of venlafaxine vs. placebo that included follow-up for 6 months revealed continued efficacy of venlafaxine overall, however not for symptoms of hyperarousal (Davidson et al. 2006).

The use of other antidepressants including monoamine oxidase inhibitors is supported by moderate clinical evidence for PTSD, but there are no trials specifically in interpersonal trauma survivors (Baker et al. 1995). Tricyclic antidepressants have been found to be helpful primarily with male combat victims, but not with individuals who have experienced chronic physical and sexual abuse or rape (Kosten et al. 1991, Davidson et al. 1990, Reist et al. 1989).

Benzodiazepines are not recommended as monotherapy due to the possibility of dependence and the withdrawal effects from use. However, they may be useful as temporary adjuncts to treatment, especially in the acute phase.

There are no good clinical trials to support the use of second-generation antipsychotics; however, these medications may be of some use for associated psychotic symptoms. Most anticonvulsants have not been shown to be of benefit for symptoms of PTSD, but there are some preliminary data to suggest that lamotrigine may be helpful in reducing symptoms of "reexperiencing."

Adrenergic inhibitors are theoretical treatments in that alpha-2 adrenergic agonists decrease central adrenergic activity (possibly being effective at reducing symptoms of hyperarousal and anxiety). There are no controlled trials, but there have been open-label studies showing some efficacy for clonidine and prazosin. There is some evidence that propanolol (a beta-adrenergic blocker) may reduce later symptoms of PTSD if administered after acute trauma (Vaiva et al. 2003).

**Psychotherapy** There is good evidence (level I) for the effects of cognitive-behavior therapy. There is some evidence (level II) for the effectiveness of eye-movement desensitization and reprocessing or eye movement desensitization and reprocessing (EMDR). There is also some evidence that stress inoculation, imagery rehearsal, and prolonged exposure-based techniques may be helpful in PTSD symptom reduction. It appears that the common element to these therapies is that they all offer controlled exposure to traumatic memories in a safe environment. Theoretically, this allows for the victim to be reminded of the trauma while in a setting that is not dangerous and therefore allows him or her to learn to discriminate between remembering the trauma and actually being there (i.e., being in danger). In essence, the goal is to break the conditioned association between various stimuli and danger.

### *Cognitive-Behavior Therapy*

The principles of cognitive-behavior therapy for PTSD are described in Figure 125–6. It is important to consider that short-term treatment may be appropriate for those who have experienced a single traumatic event and are suffering from ASD or acute PTSD. However, individuals who are suffering from chronic PTSD or who have history of repeated trauma may require longer-term therapy.

### *Stress inoculation, Imagery Rehearsal, and Prolonged Exposure*

These concepts are closely related to cognitive-behavior therapy. Unfortunately, studies on the efficacy of these treatments have been small and relatively short term. Stress inoculation involves breathing exercises, relaxation, thought stopping, role playing, and cognitive restructuring without any exposure to imagined or real stimuli and has been shown to be effective on its own in reducing overall PTSD symptoms. Prolonged exposure involves imagined or real-life exposure to situations that are being avoided due to association with trauma and has demonstrated effectiveness in reducing symptoms of anxiety and avoidance. Imagery rehearsal is a type of prolonged exposure where only imagined situations are used. There is evidence to support a decrease in overall PTSD symptoms and nightmares with this technique.

### *Eye Movement Desensitization and Reprocessing*

EMDR is a therapy that involves multiple, brief, interrupted exposures to memories and images of trauma combined with rapid lateral eye movements. The eye movements are thought to help with reprocessing of the event, allowing for modification of affective and cognitive responses (Shepherd et al. 2000). There have been several small trials of EMDR that suggest some efficacy in victims of abuse and rape. However, some opponents argue that the eye movements themselves are not necessary for treatment and attribute benefits to the cognitive-behavioral techniques inherent in the therapy (Davidson and Parker 2001).

### *Psychodynamic Psychotherapy*

Although psychodynamic psychotherapy has not been studied systematically in the treatment of PTSD, it may be useful to aid with developmental, interpersonal, or intrapsychic issues that impact on function. Approaches outlined in the literature involve classical, object relations, and self-psychological understandings. Essentially, all approaches are useful in helping patients identify the disruptions in their assumptions about themselves, others, and the world around them that stem from, or were exacerbated by, their trauma experience. From a classical perspective, therapy can help the patient understand his or her defenses and coping abilities in the context of prior psychological conflicts, development, and relationships. From a self-psychological perspective, the focus is on how trauma has affected prior self-object experiences and overwhelmed a person's sense of safety, security, and self-esteem, leading to difficulties with maintaining a cohesive self. Psychodynamic interventions will have to be both supportive and expressive, as indicated by the capacities of the individual at given points of treatment.

### *Supportive Interventions*

Continued supportive interventions, including case management as clinically indicated, have been shown to improve functional outcome and to aid in symptom reduction.

**Nonresponse to Treatment** In the case of nonresponse to treatment, it is important to review the items in the initial assessment and the original goals of the treatment and wonder about barriers to treatment adherence (if this appears to be a factor). Attention should be paid to any difficulties in the therapeutic alliance and the contribution of previous trauma or comorbid psychiatric axis I (e.g., substance abuse) or axis II (personality) disorders.

## Conclusions

Physical and sexual abuse and rape are all common and may be followed by serious physical and psychological disturbances. They are often unreported and should always be considered in assessing individuals for psychiatric disorders or emotional perturbations. A confidential, nonblaming, empathetic line of enquiry is essential for mental health professionals during short- and longer-term management of victims of violence. The treatment, as always, will be determined by the past history, symptoms, coping mechanisms, vulnerabilities, and resilience of the individual patient and the availability of affordable skilled providers.

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CHAPTER

# 126 Correctional Psychiatry

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Deliberate indifference by prison personnel to a prisoner's serious illness or injury constitutes cruel and unusual punishment contravening the Eighth Amendment.

(*Estelle v. Gamble* 1976)

## Epidemiology of Mental Illness in Correctional[1] Populations

According to the Bureau of Justice Statistics (November 2005), by 2004, there were approximately 7 million individuals under the supervision of the local, state, and federal correctional systems of the United States (Table 126–1). This represents a nearly fourfold increase since 1980. Mental health problems are common among correctional populations. While it can be difficult to obtain data regarding the prevalence of mental illness among correctional populations, recent research has improved our understanding of the rates of mental illness within correctional populations, the role of mental illness in leading individuals into the correctional system, and the aspects of the correctional environment that alter the presentation of mental illness within correctional settings.

**Table 126–1** Population of the Criminal Justice System

| Setting | Number of Individuals |
|---|---|
| Probation | 4,100,000 |
| Local jail | 714,000 |
| State and federal prisons | 1,400,000 |
| Parole | 765,000 |
| Total | 6,979,000 |

The United States Department of Justice, Bureau of Justice Statistics (BJS), has conducted two landmark studies examining the prevalence of mental health needs among detainees, prisoners, and offenders on probation in the community. In the first study, BJS identified an estimated 16% of jail and prison inmates and detainees who reported suffering from mental health problems (Ditton 1999). This study identified people as having mental health needs if they responded positively to one or more of the following questions:

1. Do you (or have you been told by a mental health clinician that you) have a mental or emotional condition?
2. Because of a mental or emotional problem, have you ever
   a. taken a medication prescribed by a psychiatrist or other doctor?
   b. been admitted overnight to a mental hospital or treatment program?
   c. received counseling or therapy?
   d. received any other mental health services?

No attempt was made in this initial study to objectively identify inmates', detainees', or probationers' psychiatric conditions; the study relied entirely on the self-report of the study subjects.

To remedy this deficit, BJS conducted a second study (James and Glaze 2006) in which investigators conducted computer-assisted interviews of jail and prison inmates using a modified structured clinical interview for the DSM-IV-TR. Probationers were not included in this second study. Some of the key results of this investigation are summarized in Table 126–2.

**Table 126–2** Prevalence of Serious Mental Illnesses in Jails and Prisons

| | Percent of Inmates in | | |
|---|---|---|---|
| | State Prison (%) | Federal Prison (%) | Local Jail (%) |
| Any mental health problem | 56 | 45 | 64 |
| One or more psychotic symptoms | 15 | 10 | 24 |
| Three or more depressive symptoms | 44 | 35 | 53 |
| Five or more depressive symptoms | 24 | 16 | 30 |
| Four or more mania symptoms | 13 | 9 | 18 |

*Source*: Adapted from James and Glaze (2006).

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Notably, the prevalence rates of serious mental illness are remarkably high in this study: between 9 and 18% of individuals endorsed symptoms consistent with a manic episode, between 16 and 30% endorsed symptoms consistent with a depressive episode, and between 10 and 24% endorsed at least one psychotic symptom. Other important findings from this study are increased rates of many problems for inmates with mental illness than for those without mental illness. For example, inmates with mental illness had higher rates of substance use or dependence (62–63% among those with mental illness compared to 42–49% of those without mental illness), higher rates of homelessness in the year prior to arrest (13–17% vs. 6–9%), increased likelihood of a history of physical or sexual abuse (24–27% vs. 8–10%), an increased likelihood of being charged with rule violations in both prisons (58% vs. 43%) and jails (19% vs. 9%), and an increased likelihood of having been injured in a fight while incarcerated in prisons (20% vs. 10%) and jails (9% vs. 3%). Other data support the findings of BJS. For example, Teplin (1990) and Teplin et al. (1996) found that 6.4% of male jail detainees and 15% of female jail detainees had severe psychiatric disorders.

High rates of mental illness are found in prisons and jails in other countries as well. For example, in England, Gunn et al. (1991) reported that about 37% of male inmates had a mental disorder. A survey of a sample of male detainees in England found that 63% had some type of mental disorder, including 5% with psychosis (Brooke et al. 1996). A more recent study (Brugha et al. 2005) found that there was a greater than tenfold increased prevalence rate of psychosis in English prisons (52 per 1,000) when compared to the community (4.5 per 1,000). Similarly, elevated prevalence rates have been found in France, where between 4 and 6% of surveyed inmates were diagnosed with schizophrenia, and 18–24% were diagnosed with major depression (Falissard et al. 2006).

Data from less developed countries is much more difficult to obtain. International advocacy organizations such as Human Rights Watch (www.hrw.org) and Amnesty International (www.amnesty.org) tend to focus on issues related to detention without due process. While organizations such as Mental Disability Rights International (www.mdri.org) focus specifically on individuals with mental illness, their focus tends to be on individuals who are housed in hospitals or asylums with poor conditions and inadequate or cruel treatments provided. Given attention to the larger issues, little attention has been focused on people with mental illness who are detained in jails and prisons in these countries. Most countries in Latin America "are still struggling to enter into a more dynamic reform of outmoded institutionally-based care. From the point of view of prisons, in those countries where data on prisons are available, no tracking mechanisms exist to determine the number of individuals with psychiatric illness in these institutions" (Arboleda-Flórez, J, personal communication, November 25, 2006. Professor Arboleda-Flórez (http://meds.queensu.ca/medicine/psychiatry/faculty/arboleda.html) is Emeritus Professor and Head, Department of Psychiatry, Queens University, Kingston, Ontario, Canada). This is not meant as a critique of these organizations or these countries, but is included only to note that in most areas of the world, the plight of individuals with mental illness in the criminal justice system does not attract attention.

Jails, defined as locally run detention facilities housing pretrial detainees and individuals serving short sentences, are known to house a disproportionately large percentage of individuals with mental illness. In some places, jails are the housing option of last resort, despite the obvious inadequacy of such a housing "placement" (Roskes and Osher 2006). There are multiple reasons for the overrepresentation of persons with mental illness in local jails, including societal intolerance of unusual behaviors, resistance of persons with mental illness to traditional interventions, and inadequate training of law enforcement officers regarding the ways in which mental illness can lead to unwelcome behaviors.

Because individuals with mental illness may be less able to mount effective defenses, they may be more likely to receive longer sentences, resulting in a high prevalence rate of mental illness in state and Federal prisons. In a study of service utilization, the BJS reported that 13% of inmates in state prisons were receiving mental health therapy or counseling, and that 10% of state inmates were receiving psychiatric medications. In addition, about 1.6% of state inmates (about 10% of those with mental illness) were housed in special housing or psychiatric treatment facilities within the prison system (Beck and Maruschak 2001).

Assuming a flat rate across all parts of the criminal justice system, applying the 16% prevalence rate from the first BJS study to the overall correctional population leads to the fairly conservative conclusion that approximately 1.1 million individuals with mental illness were under some form of criminal justice sanction (incarceration or community supervision) as of 2004. Using the more recent BJS finding that between 45 and 64% of jail and prison inmates and detainees have symptoms of mental illness, the disturbing conclusion is that about 1 million of the 2.1 million currently incarcerated suffer from symptoms of mental illness. The high prevalence of mental illness among correctional populations, when combined with the rapid increase in overall correctional population, means that the overall population of inmates and detainees with mental illness is increasing as well. However, the services infrastructure is not meeting the need. Recently, Manderscheid et al. (2004) demonstrated that "the growth in prison facilities and the growth in prisoner populations are outstripping the more meager growth in mental health services."

Numbers are more difficult to obtain for individuals under any form of community supervision, including parole, probation, or pretrial release. It has long been recognized that individuals with mental illness are less likely to be permitted community release for similar crimes committed by those without mental illness, meaning that it might be expected that these groups will have a lower prevalence rate of mental illness as compared with incarcerated populations. This has become increasingly true over the past two decades, during which legislatures have eroded discretionary release authority of parole boards in favor of guideline-driven sentencing (see Council of State Governments 2002, Chapter 19). However, BJS (Ditton 1999) found a 16% prevalence of mental illness among probationers, very similar to the rate for jail and prison inmates, indicating that judges, at least, continue to permit community release options to individuals with mental illness.

Mental retardation is also overrepresented in the correctional system. Accurate prevalence data are much harder to obtain, but estimates as to the prevalence range from 2 to 10% (Human Rights Watch 2001). While most people with

mental retardation, like most people with mental illness, do not break the law, those who do are more likely to be caught, more likely to confess (even to crimes they did not commit), less likely to be granted parole, and likely to serve more time than nonretarded individuals with similar sentences. In addition, because of difficulties with interpersonal skills management and cognitive limitations, these inmates are more likely to find their way to higher security levels due to an inability to comprehend and follow the complex rules of a correctional institution.

### The Insanity Defense

Most US states have some version of an insanity defense, under which an individual found not to be criminally responsible is diverted from the criminal justice system into mental health care and custody. For example, in Maryland, a defendant found "not criminally responsible" is criminally committed to a state hospital until he is no longer dangerous due to mental disorder or mental retardation (Eligibility for Release n.d.). Because, in general, states may elect to retain people in secure hospitals far longer than they might have served had they been convicted (see *Jones v. US* 1983), the vast majority of defendants who have committed minor crimes may legitimately elect to forego an insanity defense based on their belief that they will not receive long sentences. Under *Frendak v. US* (1979), the Court may not impose an insanity verdict on a competent defendant who elects not to enter an insanity plea.

The insanity defense is a very unusual outcome even in states like Maryland with a fairly liberal two-pronged American Law Institute test for insanity (Test for Criminal Responsibility n.d.). Janofsky et al. (1996) found that in Baltimore City, only about 1 in 10,000 indictments resulted in an outcome of "not criminally responsible," and that in the vast majority of cases, this outcome is not contested by the prosecution.

Thus, for the small minority of defendants who elect to enter an insanity plea, there is a chance for diversion out of the criminal justice system. While this represents a diversion of these few cases from the correctional system, the insanity defense will not dramatically alter the number of individuals with mental illness who become involved in the criminal justice system.

## Criminal Justice/Mental Health Collaborative Interventions

Individuals with mental illness are frequently in contact with law enforcement. For example, Deane et al. (1999) reported that among 174 big city (>100,000 population) police departments, 7% of all police contacts involved persons believed to be mentally ill. Homelessness appears to be a prominent risk factor for criminal justice involvement as well: Martell et al. (1995) reported that the rate of offending behavior was 35 times higher among homeless mentally ill persons than among domiciled mentally ill persons.

Research is beginning to demonstrate directly that individuals in our community mental health systems often have a history of involvement with the criminal justice system. For example, Theriot and Segal (2005) found that 45% of new admissions at community mental health centers and self-help programs in Northern California had a history of at least one contact with the criminal justice system prior to their contact with the program. Thirty-six percent had at least one prior conviction; half of these were for a felony offense. A prospective population-based study (Fisher et al. 2006) demonstrated that, on 10-year follow-up, 28% of individuals who had received publicly funded services in Massachusetts had been arrested at least one time. Arrest rates were higher for individuals who were younger and non-White, as is the case in the general population. Men were arrested at twice the rate for women; this represents an attenuation of the risk for men in the general population, who have a nearly fourfold risk of arrest as compared to women (Federal Bureau of Investigation 2005). The most common causes of arrest were crimes against public order (representing about 58% of all arrests), followed by serious violent personal crimes (49%), nonserious property crimes (38%), serious property crimes (34%), and motor vehicle offenses (29%).[2] Notably, about 10% of the arrests were for assaulting a police officer. These findings lend support to much of the focus on diversion of individuals charged with minor offenses, though the prevalence of serious personal and property crimes highlights a significant public policy blind spot regarding work with serious offenders who are mentally ill. In addition, just as is the case in the general population, a small number of individuals accounted for a disproportionate number of the arrests, indicating a need to attend to highly recidivating individuals.

Police retain substantial discretion regarding the decision to arrest individuals engaging in socially unpleasant behaviors: essentially, they can interpret such behavior as a crime or as a nuisance. Police have been described as "first-line, around-the-clock, emergency responders, mediators, referral agents, counselors, youth mentors, crime prevention actors and much more" (Council of State Governments 2002). When an officer is faced with a situation that does not present an easy, community-based resolution, especially in communities in which urgent or rapidly responsive mental health care is difficult to access or unavailable, the officer may rely on a "quality of life" law to remove the individual with mental illness from the situation. Unfortunately, this response initiates criminal justice procedures rather than a mental health intervention.

Increasingly, police-based interventions are demonstrating effectiveness at reducing this "inflow" of people with mental illness into the criminal justice system. For example, Lamb et al. (1995) reported that of patients referred to a joint police–mental health team, only 2% were arrested at the time of the referral, though after 6 months, 22% had been arrested for subsequent offenses. In a review of three types of police response models, Steadman et al. (2000) found arrest rates ranging from 2 to 13%. The use of specialized police intervention models, which require advanced training of law enforcement officers regarding mental illness, has been demonstrated to reduce the criminalization of individuals with mental illness. Dupont and Cochran (2000) reported that tactical unit ("SWAT team") callouts fell by over 50% after the initiation of the Crisis Intervention Team police intervention model in Memphis, Tennessee. Similar system interventions to assist police in diverting suspects with mental illness into the mental health system have been developed in a variety of jurisdictions in the United Kingdom (Cavadino 1999).

An open question is whether individuals with mental illness involved in criminal justice supervision are at higher risk of violations of the supervision conditions and resultant

reincarceration. Looking only at rearrests (and not specifically at rearrests due to violation of release conditions), Harris and Koepsell (1998) found no differences between those with mental illness and those without. In a sophisticated study, Solomon et al. (1994) found that recidivism among homeless mentally ill individuals leaving jail was related to the receipt of *fewer* mental health services. The highest recidivism rate was found among clients in an assertive community treatment (ACT) program, perhaps implying that "case management… may easily deteriorate into providing monitoring rather than rehabilitative services for forensic clients and thus may facilitate reincarceration." In other words, there is a risk that assertive case management services risk becoming extensions of the criminal justice system rather than agents of positive change for patients. As discussed by several scholars (Roskes et al. 1999, Roskes and Feldman 1999, Skeem et al. 2003), it is important for community providers to avoid the "treater-turned-monitor" phenomenon.

## Legal Considerations

The legal basis for the inmate's right to treatment was established in *Estelle v. Gamble* (1976), as cited at the heading of this chapter. Later cases established that mental illnesses legally are indistinguishable from medical conditions with respect to the inmate's right to treatment while incarcerated (*Bowring v. Godwin* 1977). In *Farmer v. Brennan* (1994), the Supreme Court defined the deliberate indifference standard to mean "something more than negligence, but… something less than acts or omissions for the very purpose of causing harm or with knowledge that harm will result. Thus, it is the equivalent of acting recklessly." In summary, the standard by which a correctional facility can be held accountable is that of deliberate indifference to serious medical need. It is important to note that the original *Estelle* Court in 1976 distinguished between the standard of deliberate indifference (or recklessness) and that of negligence, the basis for medical malpractice claims, stating "medical malpractice does not become a constitutional violation merely because the victim is a prisoner." Minimum standards for an acceptable mental health treatment program within a prison were established in *Ruiz v. Estelle* (1980). The key elements are outlined in Table 126–3.

**Table 126–3** Minimum Standards for Mental Health Services in Prisons

- A systematic program for screening and evaluation
- Treatment that is more than segregation and close supervision
- Treatment that includes the participation of trained mental health professionals available in sufficient numbers for the population
- Accurate, complete, and confidential medical records
- The use of psychiatric medications only with appropriate supervision and periodic reevaluations
- A systematic program for the identification, treatment, and supervision of inmates at risk of suicide

*Source*: *Ruiz v. Estelle* (1980).

Readers interested in more details regarding the legal aspects of correctional mental health care are referred to the seminal work of Cohen (1998, 2003).

## Mental Health Care in the Correctional Setting

### Standards

A number of organizations have adopted the concept of minimum standards by which correctional mental health services would be judged. These organizations include the American Correctional Association (see http://www.aca.org/standards/healthcare), the American Psychiatric Association (2000), the American Psychological Association, the American Public Health Association, and the National Commission on Correctional Health Care (see http://www.ncchc.org). NCCHC also offers accreditation to correctional facilities based on its standards. These standards attend to the following key issues.

#### Screening

Jails and prisons routinely must assess newly arrived detainees and inmates regarding many issues. All of the above-referenced standards setting bodies require a screening process for mental health issues. Typically, this is a brief procedure carried out by a correctional officer who poses a series of yes/no questions to the new arrivals. This process may also consist of a questionnaire to be completed by the inmate. These basic questions usually include historical queries (e.g., "Have you ever had mental problems?" "…taken psychiatric medications?" "…been in a mental hospital?") as well as queries related to current mental status (e.g., "Are you hearing voices?" "…feeling like you want to hurt/kill yourself?"). In the past several years, screening systems have been studied and validated in correctional settings (see, e.g., Steadman et al. 2005).

#### Assessment and Evaluation

Inmates who screen positively for mental illness are to be referred for a more in-depth assessment by a mental health provider. In some cases, this may be a two-step procedure, with a briefer assessment to rapidly rule out false-positives from the screening process, followed by more sophisticated full psychiatric or psychosocial evaluations of those individuals still of concern. In other settings, these two steps may be combined. The decision as to how best to conduct this step is dependant on availability of personnel and other resources (e.g., special housing settings). Often, various providers, including psychiatrists, psychologists, social workers, and nurses, conduct different parts of this assessment. In some instances, the first provider is a nonpsychiatric clinician such as a registered nurse or a physician assistant.

Individuals determined to need rapid psychiatric assessment due to acute presentations should be housed in a special unit designed for safe monitoring and should be prioritized for urgent psychiatric care. Many correctional facilities may not have settings specifically designed for this purpose and may simply house people in a medical clinic setting or in a "segregation" or "lockdown" setting. In addition, small facilities may not have the capacity for urgent psychiatric assessment and may need to rely on local emergency departments or community hospitals, where staff often have very limited understanding of what can and cannot be provided in the correctional setting.

## Treatment and Management

Once the evaluation is complete, individuals who have been determined to require mental health care and treatment should be housed in an appropriate setting for their needs. There are a variety of levels of care and services that may be provided in a correctional system, depending on the size and location of that system (Table 126–4). Large jail and prison systems may include all of these levels of care, while smaller jails may not have any of them and may rely on outside agencies (such as a community mental health center or a state or county hospital) to provide these services (Maier and Miller 1989). Because of their shorter-term mission, jails may not provide all of the services below but may focus instead on identification of individuals with mental illness and may choose to refer them for treatment. Consistent with this mission, many larger jurisdictions are focusing increasingly on options for "diversion" of individuals with mental health problems, partnering with the courts and with the prosecution and defense bars to seek alternatives to incarceration for these individuals, especially those charged with relatively minor offenses.

**Table 126–4** Services and Levels of Care in Correctional Institutions

- "Outpatient" care in general population
- Special housing for individuals with mental health needs
- "Inpatient" psychiatric treatment or residential units
- Medication management
- Psychotherapy
- Release planning

It is important to keep in mind that correctional administrators struggle with finding a balance between their very real budgetary restrictions and the requirement to meet all of the needs of the prison or jail on the one hand, and the requirements of courts vis-à-vis standards for mental health care on the other. What is presented here is to some extent an ideal: many systems struggle to meet this ideal. Further discussion of the economic constraints faced by corrections administrators will be presented below.

### *"Outpatient" Care*

As described above (Beck and Maruschak 2001), 13% of state prison inmates in 2000 were receiving therapy or counseling, and 10% were receiving medication. The majority of these inmates were housed in general population settings (i.e., they did not require specialized housing within the prison). Typically, these inmates are seen periodically by a therapist and/or a psychiatrist. In addition, services may be provided on an as needed basis. This level of care resembles outpatient care provided to individuals in the community who are not hospitalized.

### *Special Housing*

Many large correctional institutions and systems provide special housing units for individuals who are found to have mental illness and who may not be manageable in general population. For example, the Baltimore City Detention Center, with a total male population of around 3,000, includes a 65-bed residential unit for individuals with mental illness. Detainees who are known to have or who are identified as having problems managing jail life in general population due to mental or behavioral disorder, but who are not so ill as to require inpatient care, are housed on this unit. The unit is staffed by a psychologist who conducts rounds every day, and the inmates on this unit have regular access to a psychiatrist. In addition, correctional staff have been assigned to work in this unit and have developed an improved understanding of the mental health needs of the detainees housed there. Other large jail systems have similar models.

### *"Inpatient" Care*

Large institutions and systems may also provide their own inpatient treatment facilities. Some systems (e.g., the Maryland Department of Public Safety and Correctional Services) have created a specialized prison designated as an inpatient facility for seriously mentally ill and behaviorally disturbed inmates. Other systems have established collaborations with health care entities to provide secure inpatient units. For example, the New York City Department of Correction operates units within several City hospitals for the inpatient management of seriously ill inmates and detainees (see http://www.ci.nyc.ny.us/html/doc/html/hospital.html#hospital).

### *Medication Management*

As outlined by the US District Court in *Ruiz v. Estelle* (1980), one of the services to be provided to inmates suffering with mental illness is medication management. At a minimum, this should include rational prescribing following appropriate diagnosis, with adequate monitoring and ongoing reevaluation of ongoing therapy. A significant issue in many correctional systems is the limited formulary, usually imposed due to economic constraints, as discussed further below. Psychiatric medications should never be used simply for sedation or "chemical restraint" in the absence of an appropriate psychiatric diagnosis and treatment plan.

### *Psychotherapy*

Many inmates with mental health problems are appropriate for brief or ongoing psychotherapy, often provided by psychologists and social workers in an individual or group setting. These services may begin upon intake or in response to a crisis during an incarceration. Typical problems include adjustment to incarceration, reactions to family problems outside the prison, as well as psychiatric illnesses that may be responsive or partially responsive to psychotherapies.

Many prison systems provide psychotherapy targeting specific issues. For example, the majority of inmates with mental illness have a co-occurring addictive disorder. Many prison systems offer substance abuse treatment. Typically, however, there are an inadequate number of treatment slots for the population, and mental illness may be used as an official or unofficial exclusion criterion. In addition, some of the treatments offered (e.g., therapeutic communities) may be seen as inappropriate for those with serious mental disorders.

Sexual disorders are increasingly the focus of psychotherapeutic approaches in prison settings. An increasingly common phenomenon is the "diagnosis" of "sexually violent predator." Washington State in 1990 was the first jurisdiction to pass a law regarding such individuals, which requires the civil commitment at expiration of a criminal sentence

of individuals meeting the definition of "sexually violent predator." A "sexually violent predator" is defined under Washington law as "any person who has been convicted of or charged with a crime of sexual violence and who suffers from a mental abnormality or personality disorder which makes the person likely to engage in predatory acts of sexual violence if not confined in a secure facility." Under this law, the person who is found to meet this definition "shall be civilly committed to the custody of the department of social and health services for placement in a secure facility…" either until he no longer meets the definition or until a less restrictive alternative placement is found (Washington State Legislature n.d.). Mental health providers in prisons in states with similar laws may be asked to perform evaluations of inmates based on this or similar definitions. In addition, during an incarceration, inmates may request psychotherapy in an attempt to avoid civil commitment at end of sentence.

### *Release Planning*

Over the past decade, attention has focused on the needs of the inmate with mental illness nearing the end of his/her term of incarceration. Historically, correctional providers have overlooked this important clinical responsibility. However, transition planning increasingly is seen as an important element of the provision of care to incarcerated individuals with mental illness (Council of State Governments 2002, Chapter 20).

A key case in this area is *Brad H., et al. v. City of New York, et al.* (2000). Filed as a class action in 1999, this case was settled in 2003. In the settlement (Stipulation of Settlement 2003), the City agreed to provide eligible individuals with discharge planning services to include referrals to mental health providers (or appointments where a release date was known in advance), medications and prescriptions upon release, applications for medical assistance and public assistance, referrals for supportive housing services, access to shelter placements where necessary, and transportation services. In addition, these individuals would no longer be released in the middle of the night. The case currently is subject to a monitored consent agreement.

A second key case is that of *Wakefield v. Thompson* (1999). In this case, an inmate with a psychotic disorder was provided with a prescription for his antipsychotic to be dispensed on release. The correctional staff failed to provide the inmate with the prescription, and the inmate became psychotic and violent just 11 days after his release. The inmate sued the prison system. In overturning the District Court's dismissal of the case, the Ninth Circuit held

> that the state must provide an outgoing prisoner who is receiving and continues to receive medication with a supply sufficient to ensure that he has medication available during the period of time reasonably necessary to permit him to consult a doctor and obtain a new supply. A state's failure to provide medication sufficient to cover this transitional period amounts to an abdication of its responsibility to provide medical care to those, who by reason of incarceration, are unable to provide for their own medical needs.

The *Wakefield* principle has since been applied to a jail case in which a detainee was released on bond in an effort to evade county responsibility for the detainee's medical bills (*Marsh v. Butler County* 2000) and to a case involving the need for ongoing medical procedures and care upon release from prison (*Lugo v. Senkowski* 2000). The spirit of *Wakefield* is evident in the *Brad H* Stipulation of Settlement as well.

### *Community Treatment of Offenders*

Increasingly, attention has been focused on the treatment needs of individuals under criminal justice or correctional supervision in the community. These individuals may be released pending trial under the jurisdiction of a mental health court, or they may be adjudicated as guilty and given probation in lieu of incarceration. Alternatively, they may have served a partial sentence having been released early under parole supervision. At times, the releasing authority imposes special conditions of treatment, or the supervising agency of its own accord may recommend that the individual seek treatment. Various diversion models have been piloted in jurisdictions across the United States (Council of State Governments 2002). Similarly, in the United Kingdom, efforts have been made toward the diversion of individuals with mental illness from the criminal justice system into appropriate mental health services (Badger et al. 1999, Cavadino 1999). Community providers can effectively work with such individuals in a variety of settings (Roskes et al. 1999, 2005, Roskes and Feldman 1999). In addition, it is important that the providers maintain a clinical focus and avoid becoming an extension of the monitoring entity.

## Special Topics and Challenges in the Correctional Setting

### Refusal of Treatment

In all correctional settings, the inmate or detainee with mental illness who refuses treatment poses a special problem. In addition to the usual balancing of individual rights versus public safety, the correctional environment poses special challenges to providers and correctional managers when faced with a refusing inmate. Clearly, the overarching issue is whether inmates and detainees have the right to provide consent (assuming competence to do so) to recommended treatment. Assuming that the provision of relevant information regarding the treatment proposed is considered a part of standard care, then competent inmates and detainees in theory have as much right to refuse treatment as any other patient.

However, in the correctional setting, such refusal may adversely affect other inmates or detainees. Consider an individual with a psychosis that includes symptoms of paranoia and threats toward other inmates and staff. These potential victims cannot distance themselves voluntarily from the ill person, as they might do in the community. The potential victims have a right to a safe environment, either as inmates (under the Eighth Amendment) or as staff of the institution (under Occupational Safety and Health Administration and similar state codes). Some states have resolved this problem by creating an administrative process that requires a finding that, untreated, the mental illness will cause the inmate to be "gravely disabled or dangerous" (*Washington v. Harper* 1990). While this may superficially resemble civil procedures for forcibly medicating committed inpatients, it differs in

that there is no constitutionally mandated requirement for judicial oversight of the decision. In states without such a statute, the only alternative available is the civil commitment of such inmates to a secure hospital where they might undergo medication over objection proceedings.

## Comorbidity and Mistrust

As a rule, individuals with mental illness in the correctional system usually have multiple co-occurring problems, including substance abuse, medical problems, developmental disorders, and personality disorders. These multiple comorbidities render treatment very complicated. Superseding the complications of treating any person with complex comorbidity is the mistrust that inmates often have in dealing with correctional-based clinicians. Often, inmates and detainees see the provider as part of "the system" and will not accurately report symptoms. A high level of skill is required to make accurate psychiatric diagnoses of patients in this system, some of whom will falsely report symptoms that are not present in order to obtain medications for abuse or sale, others of whom will falsely report lack of symptoms in order to remain unobtrusive and "low profile." Maintaining an appropriate level of suspicion can be difficult (Roskes and Osher 2006).

Offenders who have been released also have some difficulty engaging in community-based treatment. Community psychiatrists and other mental health providers must be aware of this difficulty and work to overcome the added mistrust that individuals with criminal justice histories may have. Specialized training programs have been developed for both providers and patients, in learning to work with each other after an individual has been released (Rotter et al. 2005).

## Seclusion and Restraint

In correctional settings, the use of seclusion and restraint for individuals with psychiatric disorders is confounded by the routine use of nontherapeutic restraints by corrections and law enforcement staff for security reasons. While efforts toward the reduction of seclusion and restraint are proceeding in community settings (see, e.g., SAMHSA 2006–2007), such efforts have not yet made their way into correctional settings. In instances where seclusion or restraint are ordered with therapeutic intent, such decisions should be made by appropriate clinicians, and the inmate subject to such interventions should be monitored closely.

In addition to standard therapeutic types of seclusion and restraints, all corrections agencies have a system of custody levels, ranging from low security (e.g., prerelease or work release), through minimum, medium, and maximum up to "supermax" levels. Inmates are classified based on a variety of factors including the instant offense (the offense leading to the current incarceration), prior criminal record, and institutional adjustment factors. Inmates with persistent difficulty adjusting to the prison setting tend to rise in classification level, ultimately arriving at supermax. Because mental illness and mental retardation may result in difficulty adjusting to prison, it is imperative that administrators have in place a system for the evaluation of inmates for "suitability" for placement in these ultrahigh security settings, which may involve total isolation from other inmates and near-total isolation from staff. Such isolation has been asserted to lead to worsening psychosis in predisposed individuals (see, e.g., Grassian 1983). Ironically, in most correctional institutions in the United States, all forms of psychological and social treatment cease when an inmate is sent to segregated settings due to rule infractions (Toch and Adams 1990). Therefore, inmates for whom difficulty in adjusting is believed to be due to mental illness or retardation should be referred instead for special housing units or treatment/habilitation programs designed to help them accommodate to the prison setting, rather than being placed in higher security levels for punitive purposes. Although this sounds simple in theory, it can be extremely difficult in practice, given the complex diagnostic comorbidities among the correctional population.

## Dual Agency

A frequent dilemma faced by psychiatrists and other mental health professionals working with correctional populations is the problem of dual agency. Familiar to forensic psychiatrists, this issue may present problems for the novice in this area. Providers of services to individuals under correctional supervision have two consumers of their services: the patient and the correctional manager or supervising agent (Packard 1989). These potentially conflicting obligations may arise under varying circumstances. For example, a clinician may be asked to perform a specific forensic evaluation, if a patient under his/her care is accused of a new crime, or if a patient under his/her care is a "sexually violent predator" subject to potential civil commitment at expiration of sentence.

Perhaps a more frequent occurrence is an institutional need: should an inmate under a clinician's care be absolved of responsibility for a rule infraction due to mental illness? If not, should that inmate be placed on segregation (as a punishment) or moved to a higher security level (as a management strategy)? These are examples of common questions posed to the correctional mental health provider that may place the patient's interests at odds with the needs of the institution.

## Economics and Correctional Mental Health Care

Correctional administrators struggle with limited budgets, imposed by the legislature which is ultimately responsible for funding the correctional system. Within their budget, these administrators are responsible for managing all aspects of their institutions—staffing, infrastructure, security, and inmate services. Health care is but one part of the overall set of services provided to inmates, and mental health is but one part of the overall health care service.

Recruitment and retention of mental health providers within correctional settings is a challenge, and often prisons and jails have inadequate numbers of mental health staff. These jobs are perceived as dangerous and unpleasant and hence are not attractive to job seekers. In addition, prisons are often located in rural areas which are underserved by mental health providers in general. Providers working in such settings often feel compelled to play roles in containment and discipline, which may disrupt their ability to establish and maintain a traditional therapeutic alliance.

Correctional providers often outsource the problem of staffing by contracting with private companies who agree to provide health care services in the jail or prison system.

Because these contracts usually operate as a capitated system of care, the contractor is at risk for all costs and therefore may be incentivized to cut costs in a variety of ways. As in the private sector, one of the most common cost saving mechanisms is a restricted formulary. Some jurisdictions have responded to these concerns by establishing independent oversight boards, by offering training to officers, and by seeking accreditation.

## Conclusion

The number of individuals with mental illness or mental retardation in the criminal justice system continues to increase. The US Supreme Court has established a constitutional right to treatment for prisoners, rendering the incarcerated the only group in the United States for whom there is a constitutionally mandated right to health care. However, many correctional systems struggle to meet this requirement due to inadequate resources and staffing, or because of a lack of vision and understanding regarding the importance of providing such care. The situation is similar in other developed countries, while in the developing world, data regarding the prevalence of mental illness in prisons are unavailable. Only when individuals with mental illness are identified can adequate treatments be provided, and prompt provision of appropriate mental health services may lead to improved outcomes. The recent Criminal Justice/Mental Health Consensus Project (Council of State Governments 2002) provides a series of overarching policy recommendations that may be used by jurisdictions interested in improving the services they provide, or by advocates (including psychiatrists) seeking to raise the profile of this important issue in their communities.

## Disclosure

The author serves as a court-appointed compliance monitor in the case *Brad H. et al. v. City of New York, et al.*

## End Notes

1. The term "correctional" in this chapter shall be defined to include those individuals who are serving terms of community supervision (probation or parole) as well as those individuals who are incarcerated.
2. The percentages total more than 100% as individuals may have been arrested more than once, or an individual may have been charged with more than one crime at a given arrest.

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CHAPTER

# 127 Treatment of Violent Behavior

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## Introduction

Violence is a major and growing public health problem globally according to a World Heath Assembly Resolution (WHA49.25) (World Health Organization 2002).

The World Health Organization defines violence as

> The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, mal-development or deprivation. (WHO Global Consultation on Violence and Health, 1996)

This definition implicitly includes all acts of violence, private or public, proactive or reactive, planned (deliberate) or unplanned (impulsive), criminal or noncriminal.

Given an overall age-adjusted rate of 28.8 per 100,000 population, World Health Organization (WHO) data (World Health Organization 2002) on estimates of mortality and nonfatal violence indicate that in 2000, an estimated 1.6 million people died globally from self-inflicted, interpersonal, or collective violence. Underreporting, cultural sanction of violence, poor study design, and inadequate surveillance make accurate estimates of violence difficult. Available estimates rely on surveys and special studies, often examining crime rates or injury rates. Violence also varies with age, gender, between and within regions, and among different racial and ethnic groups.

Most violence is caused by persons without mental illness (Appelbaum 2006). Nevertheless, violence and aggression are frequent reasons why a person may present to a psychiatric emergency service. Psychiatric inpatients may become violent. For example, in a study (Barlow et al. 2000) examining inpatient aggression, 13.7% of patients were recorded as being aggressive over an 18-month period, and most of the aggression occurred within two days of admission. Violence can also be seen among outpatients (Steadman et al. 1998). It is, therefore, incumbent on mental health clinicians to have a sound understanding of the assessment of violence risk among patients. In addition, it is important to know about treatment approaches utilized to help manage violence risk.

Violence is not only multidimensional but also multifactorial. In particular patients, manifest reasons for violence or aggression (such as a dispute with a family member or active manic symptoms) may be apparent, but underlying factors (such as genetics, environment, culture, personality) may also play a contributing role. Therefore, even well-established associations between violence and any mental disorder should not be mistaken for demonstrated causal links. The reverse is also true: failure to conclusively demonstrate a causal link between a specific disorder and a specific type of violence does not mean that none exists or that the knowledge of predictable associations may not be of clinical use, even if the true cause of the relationship is unknown.

In this chapter, we provide an overview of the literature related to violence and its underpinnings. This chapter will review relationships between biological factors and violence and describe pharmacological and nonpharmacological strategies to assess and treat aggression.

## Assessment of Violence Risk in Clinical Settings

As with suicide, a general query as to whether a given patient has ideas of harming or killing anyone is often the mainstay of a brief screening assessment. More open-ended screening questions may yield additional information related to more general violence risk. Examples of areas of exploration in screening questions are listed in Table 127–1.

When screening questions yield a history of violence and/or active violent ideation or intent, or when the facts

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**Table 127–1** Sample Violence Screening Questions*

1. Are you the sort of person who has trouble controlling your temper?
2. Have you found yourself hitting people or damaging things when you are angry?
3. What is the most violent thing you have ever done?
4. How often do you have violent thoughts or images going through your mind? What types of violent thoughts or images go through your mind?
5. Have other people ever been afraid of you? Why?
6. Have you ever responded violently when afraid or ashamed?
7. Is there anyone you hold a grudge against?
8. Is there anyone you think of hurting?
9. Do you have any thoughts of killing anyone? If yes, proceed to gather further details related to plans, intent, feasibility, access to weapons, etc.

*Source:* Adapted in part from Borum (1996).

related to the reasons for presenting for clinical care warrant concern, clinicians should conduct a more thorough violence risk assessment. General risk assessments involve a careful review of the patient's historical, situational, and clinical factors that may contribute to violence risk. Individuals may provide a great deal of important information related to their violence history, with collateral records and conversations with other people who know the patient supplying additional useful information (Steadman et al. 1998). Actuarial and structured clinical risk assessment instruments continue to be developed, though their general applicability in nonforensic settings has not been fully established. For a more thorough review of violence risk assessment, see Borum et al. (1996) and Pinals et al. (in press) for examples.

## Classification of Violence

Attempts have been made to classify violence but none of these has been as comprehensive as the WHO classification (World Health Organization 2002). This classification categorized violence into three broad categories based on the characteristics of the perpetrators of the violent acts (Table 127–2). The categories include:

1. Self-directed violence
2. Interpersonal violence
3. Collective violence

This chapter addresses interpersonal violence, and in particular, interpersonal violence that can become the focus of treatment. Early studies examining the relationship between violence and mental illness have been criticized for the lack of specificity regarding what is meant by violence. One of the first studies to offer a careful distinction between types of violence under study was that of the MacArthur group, whose significant methodologically sound investigation divided violence generally into serious "violence" (defined as battery resulting in injury, weapon use, sexual assault) and "other aggressive acts" (defined as battery without injury) (Steadman et al. 1998). A widely used classification of aggression (Dodge 1991) distinguishes between reactive aggression, which is described as anger motivated and impulsive; and proactive aggression, which is comparatively unemotional and deliberate (for the types of characteristics, see Table 127–3). These types of aggression have also been described as affective and predatory types.

In clinical terms, the words aggression, agitation, and violence are sometimes used interchangeably, though they are not synonymous and doing so can lead to confusion and inaccuracies. For clinical purposes, it is much more useful to describe specific behavior before assigning more general labels. These distinctions help in treatment planning and risk management.

## Link Between Anger and Aggression

Recently "anger" has received increased attention, demonstrated for example, by the widespread establishment of "anger management" groups. Anger is an emotion while aggression is behavior. Anger is an emotion associated with a person's aim to increase the probability of success in the pursuit of ongoing desires and competition for resources (Panksepp 1998). Though not all aggression is caused by anger.

Chronic anger can be debilitating. Research affirms the negative influences of anger on health (Siegman and Smith 1994), work effectiveness (Folger and Baron 1996), and interpersonal relationships (Jacobson and Gottman 1998), and an increase in propensity to aggression and violence (Baumeister et al. 1996).

The *Diagnostic and Statistical Manual of Mental Disorders*, Forth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) lists five diagnoses (Intermittent Explosive Disorder, Posttraumatic Stress Disorder (PTSD), Borderline Personality Disorder, Antisocial Personality Disorder (ASPD) and Paranoid Personality Disorder) that specifically include the symptom of aggressive behavior . In each of these disorders, excessive sudden anger is a possible symptom of the disorder. Sudden anger attacks have also been associated with Panic Disorder and Major Depressive Disorder and aggression is also associated with Sexual Sadism (DSM-IV-TR). Research has shown that mental health practitioners tend to show bias toward assigning personality disorder DSM-IV-TR diagnoses when diagnosing patients with impulsive anger when presented with clinical vignettes related to anger (Lachmund et al. 2005).

The false impression that dysfunctional anger always leads to impulsive type aggression is often perpetuated. Many aggressive acts, however, such as those seen in some school shootings, serial sexual assaults, or stalking cases, may not be related to impulsivity, and they may not be entirely motivated by anger. Furthermore, not all anger-generated aggression (whether impulsive or planned) is related to mental illness.

## Clinical Factors Associated with Violence

Much of the literature dealing with violence and mental health problems derives from samples involving individuals charged or convicted of a crime who for one reason or another were also assessed for psychiatric illness. This pattern makes any firm conclusions about causality difficult since the conclusions may have been biased toward finding associations between mental illness and crime and/or violence. Also, as noted above, violence and aggression are contextual. Violence in a homeless shelter by a paranoid person, in a surgical operating suite, in a barroom knife fight, in a consensual sadomasochistic relationship, or in war, all clearly derive from very different motivations.

**Table 127–2** Classification of Violence

| Characteristics | Types of Violence: Self-Directed Violence | Interpersonal Violence | Collective Violence |
|---|---|---|---|
| Target of violent act | Self | Others (mostly close relationship) | Others (mostly distant or no relationship) |
| Source of violent act | Self | Another individual | Small or large groups (e.g., states, organized political groups, terrorist organizations) |
| Subtypes | (a) Suicidal Behavior (Includes Para suicide, Deliberate self-injury, Completed Suicide) | (a) Family/Partner violence (Usually inside the home e.g., Elderly/Partner/Child) | (a) Social Violence (e.g., terrorist act, mob violence) |
| | (b) Self-abuse (Includes Self-mutilation) | (b) Community violence (Acquintance/Stranger) | (b) Political Violence (e.g., war and related violence conflicts) |
| | | | (c) Economic (e.g., attacks carried out to disrupt economic activity) |
| The Nature of the Acts | | | |
| (a) Physical | + | + | + |
| (b) Sexual | − | + | + |
| (c) Psychological | − | + | + |
| (d) Involving Deprivation or Neglect | + | + | + |

*Source:* Adapted from World Health Organization (2002) World Report on Violence and Health: A Summary. Geneva, Switzerland.

**Table 127–3** Characteristics of Reactive vs. Deliberate Aggression

| Characteristics | Reactive Aggression | Deliberate Aggression |
|---|---|---|
| Anger | Present | Absent |
| Motivation | To harm the victim | To acquire possession of the victim |
| Cognitive Style | Impulsive−No planning | Deliberate−Planning and cost and benefit analysis |
| Arousal | Enhanced | Lowered |
| Anatomical Basis | Orbital frontal cortex, dorsolateral prefrontal cortex, amydgala and cingulate | Amygdala |
| Neural Pathway | Rage pathway | Predatory pathway |

It should be noted that the review below will highlight only a selection of diagnoses and their relationship to violence. For a review of other diagnoses, see individual related chapters in this volume.

## Violence and Mental Illness

Though most persons with mental illness will not become violent, people with untreated mental disorder have a higher incidence of violence and aggression in their lives (Swanson et al. 1990, Coid 1996). This association may be especially significant for those who require psychiatric hospitalization in adolescence (Kjelsberg and Dahl 1998, Soyka 2000).

Of mental disorders, those most commonly associated with nonsexual violence are: substance abuse disorders (including alcohol abuse), schizophrenia, personality disorders and mood disorders. While these disorders are reviewed separately evidence suggests that among those with serious mental illness, risk of violence increases in association with alcohol or other drug abuse combined with medication noncompliance (Swartz et al. 1998, Steadman et al. 1998).

### Schizophrenia and other Psychotic Disorders

Of men convicted of homicide, one literature review found between 5–11% had a previous diagnosis of schizophrenia (Soyka 2000). A study (Wallace et al. 1998) found men with schizophrenia to have a risk of committing murder that is 5–18 times that of the general population. Studies have shown an association between schizophrenia and violence that cannot fully be explained by personality disorders and substance use (Brennan et al. 2000). The risk, however, of violence among people with schizophrenia has also been shown to be strongly associated with substance and alcohol use. For example, in a 26-year follow-up study involving over 11 thousand individuals in an unselected birth cohort, those who were male, and had been diagnosed with schizophrenia and alcoholism were 25.2% more likely to have committed a violent offense than men without schizophrenia or alcoholism (Råsånen et al. 1998). Targets of violence among persons with serious mental disorders such as schizophrenia were most frequently family members (Steadman et al. 1998).

In the Epidemiologic Catchment Area study (ECA) data, 13% of participants diagnosed with schizophrenia (compared to a base rate of 2% for persons with no psychiatric diagnosis) reported having engaged in some form of violent act over the preceding year, a figure much lower than those with substance use disorders (Swanson et al. 1990). Steadman et al. (1998) demonstrated that patients with serious mental illness like schizophrenia were less likely to

be violent during follow-up than those with other mental disorders, such as personality disorders.

Paradoxically, a diagnosis of schizophrenia (regardless of whether or not the individual also abuses alcohol) was found to reduce the risk of violent re-offense by the authors of one actuarial risk assessment instrument; the Violent Risk Appraisal Guide (VRAG) (Quinsey et al. 1998). This finding likely results from the fact that the standardization sample used to create the VRAG included, among others convicted of crimes, men found not criminally responsible for the crime that resulted in them being sent to a maximum secure psychiatric hospital. Within this population, those with schizophrenia would represent a subgroup for whom effective treatment was offered, particularly within the subgroup who were re-released into the community.

A second counterintuitive finding derives from a recent prospective 1-year follow-up study which found that specific paranoid delusions were not predictive of risk of violent re-offense (Monahan et al. 2001). This contradicts earlier opinions that delusions, particularly, types of paranoid delusions represented significant risk factors for subsequent violence (Taylor 1998).

### Mood and Anxiety Disorders

Early ECA data showed that 12% of persons with depression, 11% of persons with a diagnosis of "manic-depression" (bipolar disorder), and 12% of persons with panic disorder reported having engaged in some type of aggressive act during the preceding year in the United States (Swanson et al. 1990). Mania has also been associated with impulsivity and aggression. (Sachs 2006). Clinically significant changes in mood by definition are dysphoric. It would seem likely that disorders that influence mood could also influence predisposition to engage in violence (Davidson et al. 2000). There is an extensive literature linking abnormalities in monoamines (especially serotonin) with mood disorders, impulsivity, and aggression (see for review: Praag et al. 1990).

Though anxiety disorders are less often associated with aggression, some experts have suggested that "anger attacks" may resemble "panic attacks" and may occur in patients with depression (Fava and Rosenbaum 1999).

### Violence and Intellectual Disability

Approximately, 3% of the population in North America meets DSM-IV-TR criteria for mental retardation (hereafter referred to by the preferred designation of "intellectual disability" (American Psychiatric Association 2000). This population, however, is significantly overrepresented in the criminal justice system. A review (Endicott 1991, p. 4) concluded that the percentage of incarcerated inmates with intellectual disabilities is at least twice as high as in the general population with an estimated incidence of between 5 and 10%.

A recurring theme in the literature on aggression is that reduced intelligence is a significant risk factor. Few studies, however, distinguish between intellectual disability per se and intellectual disability in the company of other serious brain disorders. For example, a literature review (Trimble and Elst 1999) of aggression and specific brain lesions concluded that patients with aggression tended to have a combination of lower intelligence combined with increased general psychopathology. The same study's primary reported finding was a failure to find a difference in total amygdala volume though there was an association between aggression and left-sided amygdala atrophy and a history of encephalitis.

### Violence and Personality Disorders

Violence may be seen in persons with personality disorders, particularly paranoid, borderline and ASPDs. ASPD is clearly associated with violence. Impulsivity, irritability, aggressivity, and a history of childhood conduct disorder are among the criteria for this diagnosis. Psychopathy is a personality construct related to but distinct from ASPD. Most persons with psychopathy meet criteria for ASPD, though not all persons with ASPD qualify as psychopathic. Psychopathy includes the social deviant dimensions of ASPD such as antisocial behavior and impulsivity but also includes emotional aspects that include interpersonal manipulation and lack of emotionality. Psychopathy is generally assessed, by those trained in its use, via the Hare Psychopathy Checklist-Revised (PCL-R) (Hare 1991) or the Hare Psychopathy Checklist-Screening Version (PCL-SV) (Hart et al. 1995). Table 127–4 describes an overview of the Screening Version. Though clinicians will more commonly rely on DSM-IV-TR diagnoses of ASPD in clinical settings, consideration of psychopathy as a significant risk factor for violence has been well-established (Hart and Hare 1997, Hart et al. 1994). Still, it is important to remember that not all psychopaths will become violent, and not all violence is related to psychopathy (Babiak and Hare 2006).

**Table 127–4** Selected Aspects of the Hare Psychopathy Checklist-Revised: Screening Version

(1) 12 items; scored 0, 1, or 2
(2) Interpersonal/Affective dimension includes items such as manipulativeness and superficiality/lack of remorse and empathy
(3) Behavioral dimension includes items such as impulsivity, lack of goals, irresponsibility, and antisocial behavior

*Source:* Hart et al. (1995).

## Violence, Physiology, and Biology

The literature on the association of organic disorders and violence and aggression can be broadly subclassified under the headings of substance induced, hormonal, genetic, and brain injured/neurologically based. In addition, specific findings related to neurotransmitter function and violence as well as other neurobiological aspects of aggression have been described. As in previous sections, although these sections are described separately, this is more for heuristic reasons than for clinical accuracy since biologic causes of aggression tend to occur together.

## Substance Induced

### Alcohol

By far the most well documented and researched "aggression inducing" substance is alcohol. Several reviews indicate more than half of all homicides, assaults, and rape occur in the context of alcohol and/or drug consumption by at least one of the parties involved (Roberts et al. 1999). Rates of association are, however, highly variable. For example, one

meta-analysis of studies reporting alcohol use at the time of the commission of murder found rates among homicide offenders to vary from 28% to 86%. These rates were higher than those of sex offenders (13–60%) or sex offense victims (6–40%) but similar to those of homicide victims (14–87%) (Roizen 1997). These findings are not surprising given the widespread use of alcohol; the influence of alcohol on events coming to the attention of authorities; the influence of alcohol in bringing offenders and victims into proximity with each other; and the fact that alcohol and violence appear to have a dose dependent relationship. Other important factors include issues of quantity and pattern of alcohol use. For example, intermittent drinkers are more likely to be involved in violent episodes (either as perpetrators or victims) than are chronic drinkers (Kantor and Straus 1987).

Still, in spite of confounding variables, there is considerable evidence to support the hypothesis that crimes involving violence are more closely associated with alcohol than are nonviolent crimes (Cordilia 1985). Studies aimed at unraveling the direct effects of alcohol on violent behaviors from "expectancy effects" have been reviewed elsewhere with the conclusion that the direct pharmacologic effects of alcohol interact with psychological effects to increase risk of violence (Volavka 1995).

Pharmacologically, alcohol is a sedative associated with behavioral disinhibition and dose dependant decrements in consciousness. Other lines of research (Cloninger 1995, Virkkunen 1979, Virkkunen and Linnoila 1993, 2002) strongly associate alcohol with decreased levels of serotonin, particularly, among a subgroup consisting of early-onset alcoholism and antisocial personality traits. Serotonin is generally viewed as an inhibitory monoamine, so the contradictory and variable effects of alcohol, presumably acting as a systemic inhibitor of an inhibitory neurotransmitter are not unexpected. This will be discussed further below.

While there is good evidence to implicate alcohol in the commission of intentionally aggressive acts, there can be little question that alcohol is even more important as a cause of significant unintended violence in the form of motor vehicle accidents and impulsive aggression.

### Illegal drug use

Compared to alcohol–violence research, the association of illegal drugs with violence is even more difficult to interpret since people using illegal drugs are by definition already involved in criminal activities. For example, although violence is associated with narcotic users, this seems primarily due to the need to engage in criminal activities to pay for narcotics rather than because of a primary effect of the drug. In contrast to emergency rooms where community users of narcotics are encountered, and aside from episodes of aggression associated with delirium, the extensive legitimate use of prescribed narcotic medications in hospitals for pain relief is rarely associated with aggression.

While illegal drug use is frequently cited as a contributor to violent crime, studies directly linking a specific illegal drug with violence independent of other risk factors are rare. A study (Hanlon et al. 1990) found a direct relationship between self reported quantities of opioids used and frequency of crime (including violent crime) at the time of use.

Pharmacologically, opioids including morphine, methadone and heroin, are sedatives that reduce pain and level of consciousness. Ex-abusers given "moderate doses" of heroin have been described as becoming "friendly and mellow" (Volavka et al. 1974). If fact, opioids at one time were considered as a possible treatment for rage and aggression (Berken et al. 1978, Verebey et al. 1978). In contrast, opioid antagonists, such as naloxone have been associated with aggression, especially in emergency room settings in which the effects of opioid drug overdoses are rapidly reversed (Gaddis and Watson 1992).

Similar comments can be made about benzodiazepines, which are generally associated with soporific effects in patients across the life-cycle (Gleser et al. 1965, Yudofsky et al. 1990). However, "paradoxical" disinhibiting effects of benzodiazepines have also been noted Paton 2002).

While cocaine and its derivatives have been associated with violence, a direct pharmacologic effect of cocaine on aggression has been disputed (Resnick 1977). In particular, reports of violence associated with cocaine and free-based cocaine ("crack") consist primarily of reports involving overdoses in which delirium is likely, or in which aggression appears secondary to paranoid thinking either due to the drug itself or to an accurate perception of events resulting from criminal activities involving a valuable illegal commodity (Brody 1990, Manschreck et al. 1988, Inciardi and Pottieger 1994). Multiple drug use, such as combining cocaine and alcohol, may lead to an increased risk of violence (Pennings et al. 2002)

Phencyclidine (PCP) is a drug with a reputed association with uncontrolled violence of almost urban myth proportions. Careful reviews of published clinical reports led a group (Brecher et al. 1988) to conclude, however, that the assumptions about PCP and a direct link to violence may not be as clear as was first thought. The finding of higher self-reported rates of assault in association with PCP use by male jail inmates who also had a history of psychiatric hospitalization led another group to conclude that while violence and PCP use is associated, self-reported behavioral effects of PCP may be (better) associated with personality traits and other background features (McCardie and Fishbein 1989).

As with cocaine and PCP, amphetamines, have also been linked to aggression. In the context of amphetamine-induced delirium, sleeplessness and paranoid thinking can reach delusional proportions (Kalant 1966). There is also evidence that chronic amphetamine use may augment aggression via serotonin depletion in brain areas linked to regulation of aggression: especially the frontal-orbital cortex, anterior cingulate gyrus and temporal cortex (Sekine et al. 2006). Nevertheless, a recent review concluded that acute intoxication may not lead to violence, but may increase the chance of aggression in the context of a provocation (McKetin et al. 2006). However, relative to other factors, methamphetamine appeared to have a small impact on assault rates.

## Hormones and Violence

Virtually, every survey of violence and aggression notes a preponderance of problems in males as compared to females. The two primary hormonal differences between men and women are: (a) higher levels of testosterone in men (b) cyclical variation of estrogen and progesterone in premenopausal women. There have been numerous reports of significant association between testosterone levels and both physical

and verbal aggression (Virkkunen et al. 1994, Brooks and Reddon 1996). A study (Dolan et al. 2001) found that plasma testosterone was positively correlated with aggressive acts in male offenders with personality disorders. In a study of genetics of aggression, hostility, and anger (AHA) syndrome) (Sluyter et al. 2000), found substantial heritable abilities for testosterone and moderate to fair heritable abilities for the other measures of the syndrome.

An open question is the specific relationship of testosterone to sexual aggression. A study (Dabbs et al. 1995) found that male prison inmates with higher testosterone levels were more likely to have committed sexual or violent offenses and more likely to have violated prison rules than individuals with lower testosterone levels.

Using a subsample from the 1995 study, Dabbs et al. (2001) examined characteristics of the index offense in subjects for whom a parole board investigative report was available. Testosterone levels were related to the characteristics of the offense for the "Kill (murder/manslaughter offense) group," but not for the "robbery," "assault rape," or "child molestation" groups.

An independent study (Giotakos et al. 2003) reported significantly higher plasma testosterone in rapists. Luteinizing hormone (LH); the pituitary hormone associated with stimulation of testosterone production, was positively correlated with the experimenter's measures of aggression and impulsivity.

Despite some of these findings, the relationship between testosterone and aggression is less linear than earlier reports may have suggested. In two studies involving groups of forensic patients who had been charged with violent or nonviolent crimes and nonviolent controls, no significant differences were found in terms of testosterone or testosterone metabolites (Bain et al. 1987, 1988). An investigation (Rada et al. 1976) found higher levels of testosterone in rapists who also beat their victims but failed to replicate this finding in a subsequent study (Rada et al. 1983).

## Genetic Factors and Genetic Syndromes

It is generally accepted that genetic factors can predispose people to impulsive and aggressive behaviors. Several genetic conditions have been identified as potentially interesting with regard to their association with violence. The single genetic condition receiving the most attention is the XYY "superman" karyotype. The condition occurs in 1/1,000 males (Allanson and Graham, 2002). For years, XYY was linked to increased risk of violence and several case reports (e.g., Freyne and O'Conner 1992) of crimes committed by men with XYY karyotypes were published . Early reports suggested that men with a history of criminality, arson or sexual offenses should be screened for an XYY karyotype (Hoffman 1977). However, most experts now agree there is no definitive evidence that men with XYY are more prone to criminal violence than other men (Beltz 2005).

Men with an extra X chromosome (Klinefelter's syndrome) have also been identified as being predisposed to aggression (Dervaux and Artiges 2002). Klinefelter's syndrome occurs about twice as frequently as XYY syndrome, and is associated with hypogonadism (low serum testosterone but high serum follicle-stimulating hormone and serum LH levels). Due to delay in closure of the bone epiphisyes, men with Klinefelter's syndrome are of above average height. A large study that examined 4,139 men with height in the top 16 percentile of a Danish cohort, found similar crime rates (including nonviolent crimes) in men with XYY and XXY genetic conditions (Witkin et al. 1976).

Twin and adoption studies have demonstrated that aggressive behaviors are partially heritable (Cadoret et al. 1997). It has been estimated that two-thirds of the measured variations of personality traits can be accounted for by genes (Bouchard 1994). Genetic syndromes cut across numerous etiologic pathways since they not only do involve heredity but also hormones, neurotransmitters, anatomy, and physiology. In a remarkable investigation, 221 pairs of biologically unrelated adopted children were compared to 11 pairs of biologically related children who had been adopted together, as well as a control group consisting of 94 singleton children. In this study, the researchers concluded that 70% of the variance for aggression and 39% of the variance for delinquency was accounted for by genetic (as opposed to familial) factors. Larger variances were also noted for boys on factors involving "externalizing" and "aggressive" behaviors (Ooord et al. 1994). Other genetic studies have further examined the link between monoamine oxidase (MAO) inhibition and violence (see below).

## Brain Lesions/Injuries and Other Neurologically-Based Impairments and Aggression

From the time of Phineas Gage and his infamous frontal lobe injury leading to a wide range of new behaviors, the majority of the literature concerning aggression and brain lesions is derived from observations of individuals with closed head injuries since these are less likely to be lethal than open head injuries. One notable exception is a study (Grafman et al. 1996) involving 279 war veterans who had sustained penetrating head injuries. This study found increased violence and aggression associated with penetrating injuries involving ventromedial brain injuries but the association was neither affected by lesion size nor with presence or absence of seizures.

Researchers have also noted similarities between individuals with ASPD and/or psychopathy and specific brain lesions (especially left frontotemporal hypoperfusion) (Raine et al. 2003). Unfortunately, causal conclusions are problematic because people with ASPDs have a known higher tendency of being the victims of violence themselves (Paanila et al. 1999). Also, with few exceptions, (see e.g., Putkonen 2003), studies include only men. If brain lesions cause violence independent of other mediating variables such as gender, then it would be predicted that girls and women should show the same associations of aggression with brain lesions involving especially the orbitofrontal cortex (Amen et al. 1996), left anterior temporal cortex (Hirono et al. 2000), and amydalo–hippocampal region (Tonkonogy 1991). This theoretical problem has been noted by others who have pointed out that the majority of head injuries result from motor vehicle accidents involving males between the ages of 15 and 24 (McAllister 1992). Head injury is a problem that deserves further attention since depression has also been associated with aggression post head injury (Baguley et al. 2006).

There is an extensive literature concerning the possible relationship between seizure disorders and aggression.

Aggression associated with ictal and immediate post-ictal behavior tends to be disorganized and best understood as resulting from delirium (Treiman 1991). Reports also exist, however, concerning the possibility of an association between aggression and inter-ictal behaviors. Though controversial (Devinsky and Najjar 1999), these findings most often implicate temporal lobe epilepsy (TLE) (Elst et al. 2000). People with TLE and aggression often suffer from other neurological deficits. For example, one case controlled investigation involving Magnetic Resonance Imaging (MRI) studies of 24 patients with TLE and a history of aggression found that aggressive patients had a significant decrease in grey matter, primarily involving the left frontal lobe (Woermann et al. 2000).

### Neurotransmitters and Other Neurobiological Aspects of Dysfunctional Anger and Aggression

Although the pathogenesis of dysfunctional anger and impulsive aggression is largely unknown, low central nervous system (CNS) serotonin (5-hydroxytryptamine, 5-HT) levels are associated with dysfunctional anger, impulsive aggression and violent behavior (Kavoussi et al. 1994). Both human and animal studies have shown an inverse relationship between cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of central 5-HT, and aggression. Furthermore, administration of agents that reduce central serotonin concentration typically are associated with an increase in aggressive behavior. Conversely increased 5-HT levels are associated with decreased aggression. Psychopharmacologic studies have also found that serotonin-enhancing drugs, including selective serotonin reuptake inhibitors (SSRIs) can be effective in reducing anger and impulsive aggression (Salzman et al. 1995). Evidence also points to testosterone having a role in modulation of dysfunctional anger and impulsive aggression at least in part, by decreasing serotonin receptor sensitivity (Zhang et al. 1999). These lines of evidence implicate abnormal serotonergic function in dysfunctional anger and impulsive aggression.

Since a dysfunctional serotonergic neurotransmitter system has been implicated in the etiology of dysfunctional anger and impulsive aggression, genes regulating 5-HT synthesis, release and reuptake, metabolism, or receptor activation are good candidates for studies of genetic disposition to dysfunctional anger and impulsive aggression. Tryptophan hydroxylase (TPH) gene polymorphism may be associated with anger-related traits (Manuck et al. 1999). In a large Dutch kindred, males with a point mutation in the eighth exon of the MAO-A gene were found to show impulsive aggression and sometimes, violent behavior (Brunner et al. 1993). In addition, male MAO-A gene knockout mice were shown to display enhanced aggression (Cases et al. 1995).

Serotonin transporter (5-HTT) plays an important role in regulation of 5-HT transmission, and SSRIs are thought to exert their effect on the treatment of aggression through inhibiting the 5-HTT. The serotonin 2A ($5\text{-HT}_{2A}$) receptor has also been implicated in the pathogenesis of impulsive aggression and suicidal behavior. TPH is a rate-limiting enzyme for serotonin biosynthesis and MAO is a critical enzyme which degrades a variety of biogenic amine, including serotonin. Thus, they are logical candidate genes that may contribute to abnormal serotonin functioning.

Other neurotransmitters have been associated with aggression, in part related to the neurotransmitter function itself, and in part related to the complex network of interactions between neurotransmitter systems. Norepinephrine, for example, known as the "fight or flight" mediator, has also been associated with aggression (Coccaro et al. 2003). Further, beta adrenergic blockade can be effective in decreasing aggression (see below). Other neurotransmitters and compounds implicated in mediating aggression include dopamine, Gamma-Aminobutyric Acid (GABA), glutamate, substance P, cholesterol, acetylcholine, nitrous oxide and endogenous opioids (for a further discussion, see Volavka 1999).

### Other Biological Aspects of Dysfunctional Anger and Aggression

As an example of other biological aspects of aggression, studies have shown a positive association between chronic anger and cardiovascular diseases (CVD). These studies suggest that both extreme inhibition and expression of anger is related to higher CVD risk and associated risk factors (e.g., hypertension). Williams et al. (2000) reported that individuals most prone to anger were 2.7 times more likely to have a heart attack than those with the lowest anger ratings. The two main hypothetical models proposed to explain the mechanisms underlying this association are: (1) An emotional and cardiovascular reactivity model that emphasizes anger inhibition, slow cardiovascular recovery, and low parasympathetic tone (Larkin et al. 1998) and (2) anger inhibition and cardiovascular recovery hypotheses that emphasize anger expression, cardiovascular reactivity and high sympathetic tone (Brosschot and Thayer 1998).

## Treatment of Aggression

As illustrated by the foregoing sections, the etiology of aggression is multi-determined, spanning across many psychiatric syndromes (Fava 1997). Therefore, treatment of the aggressive or violent patient must be multifactorial, and by current standards, should encompass consideration of environmental, psychological, cultural, and biologically-based therapies. It is important to note though that at the time of this writing, no medication has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of aggression. Indeed, evidence based data related to the treatment of aggression is rather limited. Treatment decisions should be made with caution and guided primarily by clinical judgment, and where possible, informed by the results of a comprehensive psychiatric and medical assessment. This is particularly important given that aggressive acts are primarily epiphenomena of other psychiatric, neurological, or other medical disorders (Booth et al. 2006, Fava 1997) or driven by contextual social factors.

### Nonpharmacological Treatment Options

Although pharmacologic treatments may ultimately be required, in the absence of immediate danger, a combination of one or more of the following de-escalation strategies should be initiated when managing acute aggression (Corrigan et al. 1993, Allen et al. 2001). These

can include interventions such as verbal de-escalation by talking to the patient and avoidance of overstimulation. If attempts to de-escalate an acutely aggressive patient fail to yield the desired outcome, displaying a show of force and ultimately the use of mechanical restraint and/or seclusion may become necessary. Cases of death associated with mechanical restraint use and questions of misuse of this technique recently spurned a movement in seclusion and restraint reduction in behavioral healthcare (see e.g., Pinals and Appelbaum 2003). Current United States legislation and US national standards require that behavioral restraint use be an option of last resort after less restrictive alternatives have been tried. Some medications used in an emergency situation to quell aggression, if not part of an existing behavioral treatment plan, can be considered chemical restraints and follow similar restrictions regarding their use.

Chronic management of the violent or aggressive patient can also include a number of nonpharmacological strategies either alone or in combination with psychopharmacological approaches. The specific psychopathology and treatment needs of patients with chronic violence will dictate appropriate interventions. For example, treatment of aggression related to psychosis may require supportive therapy and social skills training as well as psychotropic medications. Potential nonpharmacological interventions are summarized in Table 127–5.

**Table 127–5** Selected Nonpharmacological Interventions for the Treatment of Violence

| |
|---|
| Anger management |
| Dialectical behavioral therapy |
| Victim empathy training |
| Social skills training |
| Behavioral therapy |
| Marital/Family therapy |
| Substance abuse counseling |
| Occupational therapy |

## Pharmacological Treatment

Several medications have been shown to improve aggressive behaviors associated with a number of, and frequently unrelated, disorders. Below is a review of data on the following medication classes and the treatment of aggression: (1) Antipsychotics and benzodiazepines (2) anticonvulsants and lithium, and (3) beta-blockers. In some situations, nonpsychotropic medications may be indicated in the treatment of aggression. When utilized, medications should be selected on the basis of their efficacy in treating the underlying condition. For example, a diabetic patient with hypoglycemia and violence should be treated urgently with glucose either by oral or intravenous routes, whereas psychosis related to violence would be more reasonably treated with an antipsychotic medication.

Although the selective serotonin reuptake inhibitors have shown to decrease impulsive aggressive behavior in carefully selected patients (Coccaro and Kavoussi 1997), their use for the specific treatment of aggression in a broader patient population is limited because of the risk they may cause hypomania, or even increased aggression (Biswas et al. 2001). Data on these and other less established medications or novel medications will not be discussed here (see for review: Coccaro and Kavoussi 1997, Thibaut et al. 1998, Saleh and Guidry 2003).

### Antipsychotics

Typical antipsychotics, given alone or in combination with other medications, have been safely used for decades in the treatment of aggressive behavior (Ladavac et al. 2007). Notwithstanding their seemingly beneficial therapeutic effects, their use is limited by their side effect profiles (Leucht et al. 1999). Extrapyramidal symptoms (e.g., acute dystonic reactions), orthostatic hypotension, akathisia, and anticholinergic effects are concerning and not uncommon occurrences (Yudofsky et al. 1987). Typical antipsychotics have been associated with cardiac conduction abnormalities and a prolongation of the rate-corrected QT interval, resulting in potentially fatal cardiac arrhythmias (McAllister-Williams and Ferrier 2002). The latter side effect has been seen in patients receiving, for example, high dosages of intravenous haloperidol (Salzman and Hoffman 1982). Similarly, droperidol (Inapsine®), a butyrophenone antipsychotic at times used in crisis emergency room circumstances, prescribed both intramuscularly and intravenously, has been associated with a number of cardiac-related side effects, resulting in a "black box" warning by the Federal Drug Administration (FDA) (Federal Drug Administration 2001). In addition, typical antipsychotics have been associated with worsening aggression in some studies (Crowner et al. 1990).

Because of the foregoing concerns, and in light of their seemingly more benign side effect profile, atypical antipsychotics (second generation), such as risperidone, quetiapine, clozapine, aripiprazole, ziprasidone, and olanzapine, have increasingly been prescribed to treat aggressive patients (Hovens et al. 2005). Of note, several atypicals can be given intramuscularly, such as olanzapine, aripiprazole, ziprasidone, and risperidone. Others come in rapidly disintegrating tablets (e.g., risperidone and olanzapine). These alternative forms of medications are useful in the management of acute aggression and with patients presenting with swallowing difficulties or histories of inconsistent medication compliance.

Risperidone, an antipsychotic with both high D2 and 5-HT blocking properties, in combination with a benzodiazepine, has been found to be as effective as haloperidol in the treatment of aggressive patients (Currier et al. 2004). For example, in a prospective, nonrandomized, rater-blinded, double-arm study, Currier and Simpson (2001) reported on a cohort of 60 acutely psychotic and agitated patients who were given either oral risperidone (2 mg) plus oral lorazepam (2 mg) or intramuscular haloperidol (5 mg) plus intramuscular lorazepam (2 mg). Treatment outcome was measured at different time points using the five agitation subscales of the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions (CGI) scale. Both patient groups (30 patients per treatment arm) showed a similar decrease in their level of agitation.

Olanzapine seems effective in the treatment of aggressive behavior (San et al. 2006). In a retrospective, open-label,

naturalistic trial, Janowsky et al. (2003) treated a small cohort of 20 patients, presenting with a history of self-injurious, destructive, and/or assaultive behavior and various degrees of mental retardation, with olanzapine (mean dose: 9.1 mg/day). Most patients received concurrent medications prior to and during the olanzapine trial (e.g., anticonvulsants and lithium, adrenergic agents, serotonergic antidepressants, typical antipsychotics, and benzodiazepines). Psychiatric comorbidity was prevalent among the cohort and consisted of mood, psychotic, and pervasive developmental disorders. Statistically significant improvements in target behaviors were noted. The most common side effect was weight gain (mean weight gain of 3.4 kg) followed by sedation and constipation, in that order. Though this study did not prove that olanzapine by itself is useful in the treatment of aggression, future studies certainly seem warranted.

Among the atypical antipsychotics, clozapine, an antipsychotic with relatively weak dopaminergic activity, has been extensively studied in psychotic and personality disordered patients presenting with various forms of aggression (Chengappa et al. 1999). Of particular interest is a study conducted by Buckley et al. (1995, p. 13) that reported on 30 institutionalized schizophrenic patients treated with clozapine. Eleven patients presented with a history of chronic violent behavior. Treatment response was correlated to both the scores derived from the Brief Psychiatric Rating Scale (BPRS) and the number of hours spent in seclusion/restraint. Psychotic symptoms improved for both study groups after 6 months of treatment with clozapine. In addition, and, according to the authors, seemingly independent of clozapine's effects on psychotic symptoms, the violent cohort showed a significant decrease in the frequency of violent episodes (decreased by approximately 60% at 6 months of treatment), suggesting thus a "distinct anti-aggressive effect…" of clozapine.

Aripiprazole, has also been used in the treatment of aggressive patients. Of interest are results of a double-blind, placebo-controlled study of aripiprazole in the treatment of 52 subjects with DSM-III-R borderline personality disorder (Nickel et al. 2006). Subjects were randomized to receive either 15 mg aripiprazole ($n$ = 26) or placebo ($n$ = 26) for 8 weeks. Treatment outcome was measured using several scales, including the State-Trait Anger Expression Inventory. Subjects receiving active drug treatment showed a significantly greater rate of improvement on all outcome measures than did those receiving placebo. No significant side effects were observed.

The data in support of atypical anti-psychotics has been growing. Nevertheless, some studies have found their side effects can lead to problems in medication adherence. For example, one multicenter, double-blind, placebo-controlled trial, Hsiao et al. (2006) treated a cohort of 421 patients suffering from Alzheimer's disease and psychosis, aggression, or agitation with either olanzapine (mean dose: 5.5 mg/day), quetiapine (mean dose: 56.5 mg/day), risperidone (mean dose: 1.0 mg/day), or placebo, using a flexible dosing schedule. Outcome was measured using the Clinical Global Impression of Change (CGIC) scale at 12 weeks. A substantial number of patients discontinued active treatment as a result of side effects. Improvements on the CGIC scale did not reach statistical significance.

## Benzodiazepines

Benzodiazepines, such as lorazepam, have been used alone or in combination with high-potency antipsychotic medications in the treatment of acute aggression. Although several benzodiazepines have been shown to be effective in the amelioration of aggression (Rund et al. 2006), lorazepam is typically considered the benzodiazepine of first choice in acute settings (Wermeling et al. 2001). For example, in a double-blind, prospective study, Salzman et al. (1991) examined the effects of 2 mg intramuscular lorazepam compared with 5 mg intramuscular haloperidol on aggression in a cohort 60 psychotic patients. Both medications were added, using a fixed-dose schedule, to ongoing neuroleptic therapy. Diagnoses consisted of psychotic spectrum disorders ($n$ = 30), bipolar disorder ($n$ = 11), organic mental disorders ($n$ = 6), and other psychiatric disorders ($n$ = 14). Subjects treated with either medication over a 24-hour period showed a significant decrease in aggressive behaviors, as measured by the Overt Aggression Scale (OAS). The OAS, a frequently used observation-based instrument in aggression-related studies, measures the severity of (1) verbal aggression, (2) aggression directed against objects, (3) self-directed physical aggression, and (4) physical aggression directed towards others (Silver and Yudofsky 1991).

In a second double-blind, prospective, short-term study (Dorevitch et al. 1999), a cohort of 27 acutely aggressive subjects were treated with parenteral haloperidol (5 mg) or the parenteral benzodiazepine flunitrazepam (1 mg) (flunitrazepam is a benzodiazepine that has not been approved by the FDA). In contrast to the aforementioned studies where a benzodiazepine was given as an adjunct to an antipsychotic medication, this study showed that flunitrazepam when given alone was as effective as haloperidol in ameliorating aggressive symptoms. In fact, the use of either medication resulted in a decrease in OAS score. Although the "anti-aggressive" effects lasted for more than 2 hours for both medications, flunitrazepam had an earlier onset of action, achieving maximum "antiaggressive" effects within 30 minutes following its administration. Clinically significant side effects were not reported.

Veser et al. (2006) compared the effects of oral risperidone (2 mg) and haloperidol (5 mg) to oral placebo in patients, presenting in an acute treatment setting, with signs of agitation and/or psychosis. Patients were also given intramuscular lorazepam (2 mg). Interestingly, lorazepam monotherapy was as effective in ameliorating the target symptoms as combination treatment with either risperidone or haloperidol.

Benzodiazepines are usually not used in the treatment of persistent or chronic aggression. In fact, long-term benzodiazepine therapy can result in tolerance, withdrawal, and substance dependence. Similarly, benzodiazepines have been associated with idiosyncratic behavioral disinhibition, especially if used in brain injured patients.

## Lithium and Anticonvulsants

Anticonvulsants, lithium, and several $\beta$-blockers (see below) have been shown to be effective in treating persistently aggressive and irritable patients (Kavoussi and Coccaro 1998). Among the anticonvulsants, carbamazepine has been reported to be effective at therapeutic serum levels (4−12 μg/ml) in aggressive patients presenting with and without

electroencephalogram (EEG) abnormalities (Tariot et al. 1998, Mattes et al. 1984).

Lithium has been used for many decades in the treatment of aggression. Although not recommended as first choice for aggression associated with EEG abnormalities, lithium (with serum levels ranging from 0.6–1.0 mEq/L) has been used with various degrees of success in aggressive patients presenting with PTSD, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, head injuries, and developmental disabilities (Sheard et al. 1976). For example, Craft et al. (1987) assessed the safety and efficacy of lithium, using a double-blind, placebo-controlled design, in a group of 42 aggressive developmentally disabled patients. Frequency of aggressive episodes was tabulated over the course of 4 months. Compared with those receiving placebo, patients taking lithium showed significant decrease in aggressive episodes (73%). Side effects were recorded in 36% of the cohort receiving active treatment. Though not fully conclusive, these findings suggest that lithium may be useful in the treatment of aggressive mentally retarded patients.

Lithium has also been shown to be effective in the treatment of manic episodes and impulsive aggression not associated with mania (Grof and Grof 1990). It is less effective, if not ineffective, in patients suffering from mixed episodes (Swann et al. 1986, Grof and Grof 1990). In these latter cases, anticonvulsants, such as divalproex sodium, seem to be more effective. For example, Ruedrich et al. (1999), studied the effects of divalproex sodium (mean dose: 920 mg/day with mean valproic acid levels of 87.8 μg/ml) on aggressive behavior in 28 developmentally disabled adults, ranging in age between 20 to 63 years, and presenting with various forms of aggressive behaviors, including general aggressiveness (93%) and self-injurious behavior (64%). Other problematic behaviors included sexually inappropriate behavior (36%), rituals (43%), and temper tantrums (43%). Patients were assessed for up to 73 months. Overall, treatment with valproate decreased aggressive episodes in almost all patients. Side effects, including hematological and gastrointestinal, led to discontinued use in some cases.

Other anticonvulsants have been used with various degrees of efficacy in the treatment of aggressive patients. In a placebo-controlled, double-blind, crossover study, Barratt et al. (1997) studied the effects of phenytoin on aggressive acts in 60 prison inmates. Impulsive aggressive acts decreased with active drug treatment by 71% in frequency (35% among nonimpulsive subjects) and by 60% in intensity (29% among nonimpulsive subjects), respectively. Placebo effect on frequency and intensity of aggressive acts was in the lower to mid-20% range for both groups. No significant side effects were reported in either group. In another double-blind, placebo-controlled, parallel group study, Stanford et al. (2005) compared the efficacy of phenytoin (300 mg/day), carbamazepine (450 mg/day), and valproate (750 mg/day) in a cohort of 29 male patients presenting with a history of impulsive aggression. DSM-IV-TR diagnostic criteria for major depression were met by 5 subjects whereas 11 subjects met diagnostic criteria for either alcohol or substance abuse ($n = 11$). Interestingly, twenty-four subjects met diagnostic criteria for a personality disorder, specifically ASPD ($n = 17$). Treatment outcome was measured over the course of 6 weeks using the OAS. Consistent with the findings of previous data, patients in this study receiving active treatment, especially phenytoin and valproate, showed a significant improvement in their average aggression scores compared to placebo.

Published data have also appeared for the use of newer anticonvulsants in the treatment of aggression. Topiramate, a sulfamate-substituted derivative of the monosaccharide d-fructose, is an anticonvulsant used to treat of seizures in patients with epilepsy or Lennox-Gastaut syndrome, mood disorders, and pain disorders. In a recent retrospective, case-controlled, "mirror image" study, Gobbi et al. (2006) studied the effects of topiramate and/or valproic acid on the intensity and frequency of aggressive behavior, using a sample of 45 adult patients afflicted with either schizophrenia, schizoaffective, delusional or bipolar disorder. Patients were treated over a 12-week trial period with either topiramate (mean dose: 250 mg/day), valproate (VPA dose had to be in the therapeutic range), or combination treatment (topiramate and VPA). In addition to the above medications, 98% of patients received concurrent treatment with either a typical or an atypical antipsychotic medication. Episodes of agitation and Overt Aggression scores decreased in the topiramate only cohort. In contrast to patients receiving valproate, patients on topiramate did not show a decrease in their Agitation-Calmness Evaluation scores.

## β-Blockers

Several *β*-Blockers have been found to be useful in treating aggression and/or uncontrollable outbursts of violence associated with brain-injuries, mental retardation, dementia, and chronic schizophrenia (Mansheim 1981, Greendyke et al. 1984, Sorgi et al. 1986, Bond et al. 1989, Brooke et al. 1992). Among the *β*-blockers, propranolol (nonselective and lipid soluble) is the most widely studied (Greendyke et al. 1984). In a recent double-blind, placebo-controlled study, Peskind et al. (2005, p. 24), randomized a group of 31 subjects with probable ($n = 22$) or possible ($n = 9$) diagnosis of Alzheimer disease to receive propranolol ($n = 17$) or placebo ($n = 14$), using a "'augmentation design." Treatment outcome was correlated with a change in scores on the "agitation/aggression," irritability/lability," and/or "aberrant motor activity," items of the Neuropsychiatric Inventory (NPI) and the CGIC. Propranolol was increased, using a flexible dosing schedule, over the course of 9 days to 120 mg/day and maintained at that dose for 6 weeks. Recipients of propranolol showed significant improvements on the "agitation/aggression" and "anxiety" items of the NPI and moderate to marked improvement on the CGIC (1:7). Only one subject receiving placebo was marked as moderately improved. Side effects were primarily cardiovascular in nature. Behavioral improvements though were not maintained over time.

In a double-blind, placebo-controlled study, Ratey et al. (1992) treated 41 chronic psychiatric patients, presenting with at least one aggressive episode per week, with nadolol (more hydrophilic compared to propranolol). Patients were followed for a total of 17 weeks. Treatment outcome was measured using the OAS, BPRS, and the Clinical Global Impressions scale. Subjects given the active drug showed a decrease in target symptoms and an overall improvement in their clinical status.

Although usually used in chronically aggressive patients, Allan et al. (1996) studied the effects of adjunctive nadolol, using a double-blind, placebo-controlled design, on 34 schizophrenic patients presenting with current histories of aggression. Patients were randomized to receive either nadolol (total daily dose of 120 mg) or placebo. Subjects randomized to active treatment showed a statistically significant decrease in their BPRS and Simpson Angus Neurologic Rating Scale scores.

### Summary of Findings Related to Pharmacological Treatment of Aggression

As illustrated in the foregoing paragraphs, much has been written about the use of medications in acutely and chronically aggressive patients. For acute aggression, antipsychotic and/or benzodiazepine use has been a mainstay of treatment. For the treatment of chronic aggression, in clinical settings various classes of medication have been used with good effects. However, it is critical to bear in mind that methodological problems (e.g., heterogeneous study population, concurrent use of different medications, etc.) make it difficult to draw definite conclusions with regard to the "anti-aggressive" efficacy of medications. In order to resolve these issues, well-controlled studies with sophisticated methodologies are needed.

## Conclusions

The assessment and management of violence among psychiatric patients is arguably as important as the assessment and management of suicide. When a patient presents with acute or chronic aggression, it is important to examine the factors that have coalesced to lead to aggressive behaviors. While not all aggression stems from anger, some understanding of anger classification schemes can be helpful. Though most violence is not committed by persons with mental illness, a small but important increased risk of violence is associated with mental illness. Management strategies require a solid understanding of the pathophysiology related to aggression. This understanding requires a careful biopsychosocial assessment to understand the factors that contribute to aggression. Nonpharmacological and pharmacological treatment interventions can provide a useful armamentarium available for prevention, which is the ultimate goal of the treatment of the aggressive and violent patient.

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# *Appendix I*

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CHAPTER

# 128 Research Methodology and Statistics

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## Introduction

The accumulated enduring knowledge in clinical psychiatry has emerged from research studies employing empirical observation in the context of proper study design, reliable and valid measurement, and approaches to data analysis that respect both the assumptions for the use of the techniques and the limits of statistical significance. The centrality of these fundamental and enduring precepts holds even though methods and statistics in psychiatry are like all other arenas of inquiry in that new techniques and approaches are regularly being introduced. Nonetheless, there are a variety of practices in the research literature that have become standard customs in the design and conduct of psychosocial research, of which clinical psychiatry is a subset. These are important to learn about because much information about psychological processes still finds its way into the literature in the form of books and chapters that are not subject to peer review, and because even when material is subject to peer review, the process is not foolproof. Thus, even though studies are published in reputable peer-reviewed journals, this is not an ironclad guarantee that the conclusions are appropriate or that the methods used were sound. Although one may not envision being a practitioner of research, being an informed consumer of research findings is vitally important to the continuing education of psychiatrists. An argument can be made, therefore, that research design and methodology and the statistical techniques that accompany such designs are central to the knowledge of clinicians, since the clinical decisions that will be made should be made on the basis of hard evidence, rather than on the basis of clinical lore or anecdotal case reports. The increasing emphasis on evidence-based treatments is the most recent manifestation of this view.

Even though psychiatry is merely a single specialty in the domain of medical science, it is nonetheless true that the areas of study and the techniques used in research in psychiatry are very broad. These range from basic molecular biology (Malenka 1994) to clinical phenomenology (Ursano et al. 1999) to nationally representative epidemiology of mental disorders (Weiss et al. 1992). Even in the nonbench laboratory areas, a complete account of research methods, measurement issues, and, most of all, statistical techniques would require a whole text. The focus of this chapter will be on basic matters pertaining to the biopsychosocial underpinnings of psychiatry outside the wet laboratory. This covers the kinds of research reports that will have a direct impact on clinical practice (e.g., effectiveness trials such as STAR*D (Rush et al. 2006)) and are more clinical or psychological in nature.

The presentation will begin with a discussion of issues of the design of studies in terms of integrity and statistical power. The next section will examine issues of measurement, explicating the concepts of reliability, validity, interobserver agreement, and the measurement or assessment of change. The chapter continues with a presentation of statistical techniques, starting with some basic parameters, and moves through univariate techniques to multivariate approaches. It also deals with the measurement of change and the proper approach to statistical significance. The final section includes tips on reading research and some practical suggestions for conducting psychiatric research.

## Issues of Design

Psychiatric research spans two broad domains with different implications for design and analysis: (1) experimental investigations (e.g., randomized clinical trials) where the question of interest is controlled or manipulated in some fashion, and (2) field or observational research where questions of explanation and causal inference are drawn from systematic observation and recording of behavior or phenomena but are not subject to experimental intervention. The impact of trauma on subsequent adjustment, the influence of number of prior hospitalizations on risk of relapse, and the effect of early childhood loss on later adult depression are examples of the latter.

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A very thorough, detailed, and thoughtful exposition of these issues is presented by Cook and Campbell (1979). They identify several designs used in research studies, some valid and others not, and the threats to the integrity of the conclusions drawn from data collected with such designs. Although an exhaustive listing of the various designs is beyond the scope of this presentation, many of the basic principles of design are essential to informed conduct or consumption of psychiatric research. These are designs that do not include random assignment of subjects to conditions; as a consequence, they are termed quasiexperimental designs and comprise a surprisingly large number of the psychiatric research studies published in peer-reviewed journals every year.

## Designs and Threats to Validity

Cook and Campbell, and before them Campbell and Stanley (1966), identified common flawed quasiexperimental designs and a variety of threats to the validity of the conclusions drawn from such studies. Although nearly 40 years old, the problems discussed in their presentations still are relevant, since often the psychiatric researcher cannot design the ideal study due to ethical, logistic, or fiscal constraints. The designs appear in Figure 128–1.

The first quasiexperimental design denoted is the *one-group posttest-only* design. This design gathers observations on only one group after treatment has occurred; consequently, virtually nothing can be concluded because no controls exist. Nonetheless, some observational research begins with this activity. The *posttest-only with nonequivalent groups* is a second design that is not likely to yield useful information and has serious threats to internal validity as well. In this design more than one group is observed, but because the groups are not formed randomly, those not receiving treatment may be different in any number of ways having nothing to do with the treatment from those who did receive the treatment. Often there will be an attempt to "statistically equate the groups" or "control for the differences" by using analysis of covariance. This is an inappropriate and invalid use of analysis of covariance (see Miller and Chapman 2001).

A third design is termed the *one-group pretest–posttest*. An obvious improvement on the two prior designs in that subjects are observed prior to treatment so that some baseline can be established; this design, as the others, is nonetheless vulnerable to a variety of alternative interpretations of a change in status at posttest other than the treatment administered. A discussion of the various threats to internal validity will clarify why this is so.

The concept of a threat to the internal validity of a design can be explained as follows. When an experiment is conducted, the goal is to show that manipulation of one variable (e.g., whether the pill is a placebo or is an active pharmacologic compound) has an impact on, has an effect on, or causes a change in another variable (e.g., hyperarousal symptoms of PTSD). A particular study or design possesses good internal validity if there is a strong chance that the conclusion we draw (the medication is or is not effective) is actually due to the variable being manipulated and the output variable being measured. If there are many other plausible or even possible reasons that the output variable might

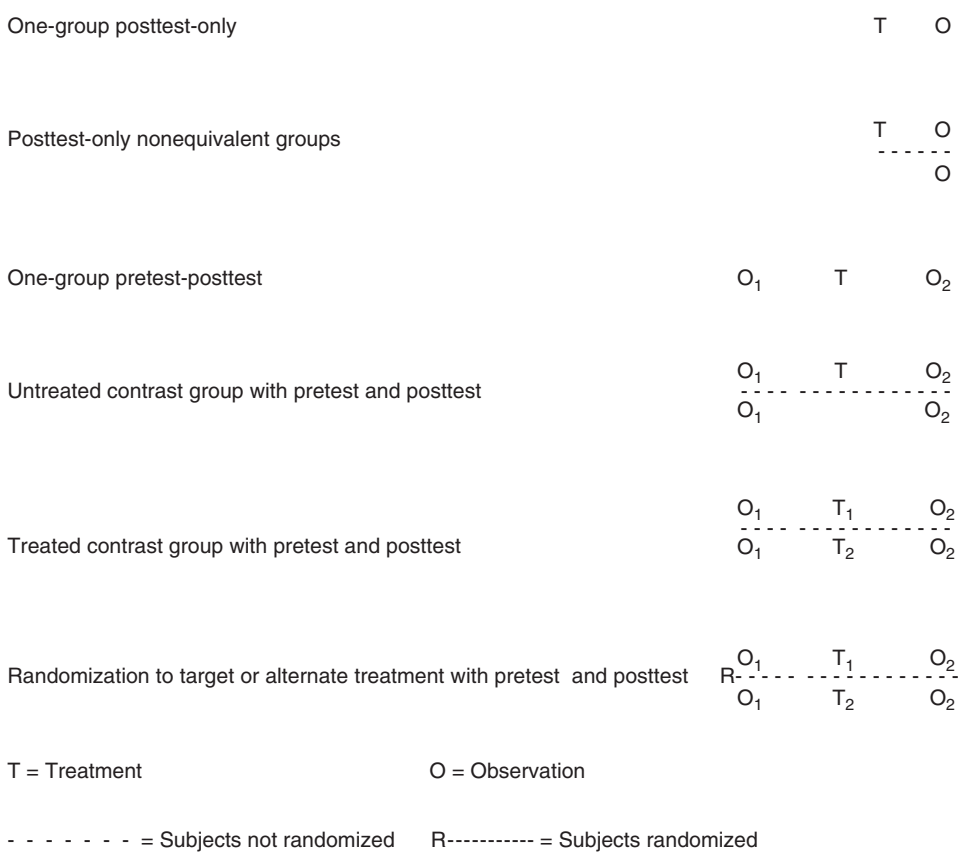



**Figure 128–1** *Schematics of several research designs.*

have changed other than the impact of the experimental or treatment variable, then such a study does not have good internal validity.

Probably the most serious threat to the internal validity of a particular study is what Cook and Campbell term history. By this is meant that an event that takes place between pretest and posttest (e.g., being started on propranolol for management of angina) has an impact on the outcome (a decrease in hyperarousal symptoms). Many studies attempt to deal with this threat to the integrity of the conclusions by carefully isolating the response systems from other influences or, if that is not possible, by carefully tracking such influences. Another strategy for dealing with this problem in design is to choose output variables or dependent variables that will not be changed by outside influences but only the treatment of interest. The latter strategy is usually not practical in the vast majority of psychiatric research, whereas the former strategy may be difficult to implement practically since not all other influences may be readily apparent.

Another threat to internal validity is what Cook and Campbell term maturation. This confound refers to an alternative explanation of status at posttest due not to the treatment provided but rather to natural change during the period between baseline and posttest. Examples of this are gaining more experience, growing stronger, or growing more accustomed to phenomena in a natural way.

Testing itself can also be a threat to internal validity. If cognitively impaired patients are assessed repeatedly with the same measure, their performance may improve simply because the repeated administrations serve as practice for the tasks.

Although considerably more discussion will be devoted to the issue below, the actual measures or instrumentation used in a study may have an effect on the conclusions. If the measure has a floor or ceiling relative to the subjects being measured (e.g., testing individuals with developmental delays with the SAT), or clinical judges become more precise or develop tougher standards in their evaluations over time, changes in scores from pretest to posttest may reflect influences of the instruments and not the impact of the intervention or treatment provided.

Selection is another threat to the internal validity of a number of studies. This threat operates whenever randomization into groups does not occur. Groups that are formed on other bases (first 10 versus second 10 patients presenting to the clinic) carry with them the possibility of differences that influence the posttest that are not due to the treatment but rather due to other factors (e.g., later patients having more serious illness).

The threat to internal validity termed mortality refers to the phenomenon of differential attrition during the course of treatment. That some discontinue the treatment whereas others do not can lead to the groups at posttest comprising people who are substantially different groups of people. An example of this would be those whose symptoms are most severe not tolerating the treatment as well as those whose symptoms are milder. The current state of the art is to analyze data using "an intent to treat" approach, where conclusions are based not on completers but on those who initiate treatment. This is helpful but does not completely compensate for differential attrition.

The final threat to internal validity is termed "statistical regression" or "regression to the mean." This is a somewhat complex concept to describe, but may operate very powerfully, especially in concert with other threats such as selection. Statistical regression refers to the phenomenon of those who obtain extreme scores at pretest tending to obtain less extreme scores at posttest, at both the high and low ends of the measure. The phenomenon is due in part to the reality that virtually all variables are measured with some quantity of error. Because these errors are generally randomly distributed, an individual whose score was unrealistically lowered at pretest by error will show a higher score at posttest, and vice versa, due simply to the error of measurement being distributed differently the next time around. At time 2, other subjects will have unrealistically lower or higher scores due to greater error at that occasion. In circumstances in which the measure being used to index the variable of interest is measured with a great deal of error (is not reliable—see below), statistical regression can potentially exert a greater influence.

Because regression to the mean operates more powerfully at the extremes of distributions of scores, it is easy to see why it is such a potent confounding influence. Many times only a small portion of potential subjects can receive treatment. If the subjects to be studied are selected on the basis of their having obtained the lowest scores, then simply on the basis of regression toward the mean, these same subjects will be likely to obtain higher scores on the posttest assessment. Thus, many treatments that have been claimed to help those who have the worst pretest status are merely demonstrating the influence of unreliability of measurement and statistical regression. It is precisely because of this threat that the three designs described above are so problematic. Even though researchers concerned with carefully delineating the threats to internal validity have shown that regression toward the mean will not inevitably occur (Rogosa 1988), it is a powerful threat when it does. This makes the interpretation of change or improvement a more difficult enterprise than it might at first seem. A more detailed discussion of the measurement of change is presented below.

There are a number of quasiexperimental designs that do not share the same threats to validity of the conclusions. Many are complex and useful only in specialized circumstances for highly precise questions. Of these designs, the most commonly used and relevant is the *untreated contrast group design with pretest and posttest* measures. In this design, two groups of subjects are studied, with observation and assessment occurring at least twice for both groups. The first assessment is prior to the intervention for the group receiving it; the second and any subsequent observations occur after the intervention. In this design, the major threats to the validity of the conclusion that any differences at posttest between the groups not understandable from existing differences at pretest are the threats of selection and maturation. The American Psychological Association's Wilkinson and Task Force on Scientific Inference (1999), in a recent publication, called attention to the need to describe the untreated group in this design a *contrast* group rather than a *control* group—the term that has been typically used. The rationale for this change was the recognition that in such designs it is rarely possible to control, either by selection or by statistical analysis, all the potential variables that could

affect the outcome other than the intervention. This modification in nomenclature emphasizes that our certainty about conclusions in much psychiatric research conducted without the benefit of random assignment is often less than that has previously been thought.

It is one easy step from the untreated contrast group design to a design in which the untreated contrast group receives an alternate treatment with measures at pretest and posttest. This is obviously a better design because it includes an alternate intervention. Nonetheless, even an inert treatment frequently produces effects, sometimes from the mere attention of having been provided a treatment, even if it is a placebo. In fact, in psychopharmacologic trials, placebo response of 20% or even higher may be found. It should be clear, however, that this quasiexperimental design does not rule out alternative interpretations of differences between the groups at posttest other than that the interventions showed an effect.

The fact that there is simply no substitute for the random assignment of subjects to conditions in any study where this is at all feasible cannot be overemphasized. The vast majority of threats to internal validity vanish when subjects are randomly assigned to conditions. Although not all threats are nullified, by far the strongest designs are those that employ random assignment. If a study has assigned subjects to conditions at random, then the robustness of the conclusions are considerably strengthened compared to any other type of design. As a consequence, this should be the goal in study design whenever it is logistically or economically feasible, and this is why evidence-based medicine rests largely on randomized clinical trails (Friedland et al. 1998).

There is another class of threats to validity that the Campbell and Stanley (1966) and Cook and Campbell (1979) approaches enumerate. These are threats to the external validity of the conclusions of the study. Whether the sample of subjects studied in a particular study and the results derived from them can be generalized to other similar and dissimilar groups is a key threat to external validity. This problem can be conceptualized as an answer to the following question: How representative of the population as a whole was the sample that yielded the results of a particular study? Epidemiology and survey research are highly developed disciplines, one of whose key foci is the representativeness of the sample relative to the population from which it was drawn and to which the study's conclusions are to be referred back. Although it may not always be easy to ascertain how representative a sample of subjects is for generalizing the conclusions from that study to other groups, the issue is nonetheless a key one. For example, it might make a great deal of difference if the efficacy of a new antidepressant was initially established on a relatively young sample when a clinician is intending to use it in geriatric settings. Similarly, the mandate by the National Institutes of Health to include research subjects representing both genders and representative ethnicities in federally sponsored research or to provide a rationale why this cannot be done is a dollars and cents statement about the centrality of this concern. Most clinical studies in psychiatry use samples of convenience. Doing so makes the determination of generalizability a more difficult task. Despite the difficulty in ascertaining whether the sample well represents the population of interest, it is an important and frequently overlooked aspect of research and a partial answer for the lack of cumulative findings in clinical psychiatry.

The other threats to external validity are more complex and have to do with the possibility that there will be an interaction between treatment and other factors such as selection or history. The concept of interaction has both a statistical and a conceptual meaning. Leaving aside the former (see below), the latter can be understood as meaning that the impact of the treatment may be different for different subjects depending on their history or selection. For example, if a treatment protocol is time consuming, grueling, and difficult to adhere to, those who are able to complete it may not be representative of those who began it, let alone those to whom it was intended to apply. These threats to external validity are abstruse, but they may operate nonetheless and it is well to attempt to minimize their influence.

A summary of issues of design and threats to validity suggests that many quasiexperimental designs are not worth pursuing, that random assignment and control groups are fundamental requirements for sound designs intended to study the effects of treatments or interventions, and that the representativeness of the sample studied to the population the researcher defines can have important implications for the viability of the findings in other groups of people who are of a different age, gender, ethnicity, or health status. Good research design attempts to minimize both internal and external threats to the validity of the conclusions of the study.

## Power and Statistical Inference

The concept of statistical power in the social and behavioral sciences is now synonymous with the late Jacob Cohen (1962), who alerted the field to the issue of power and whose persistence and high-quality work has produced the standard reference for the field (Cohen 1988), despite other well-done efforts (Kraemer and Thiemann 1987). The revolutionary influence and importance of power analysis on the design and conduct of psychiatric research cannot be understated. Not only have matters of the power of statistical tests become routine considerations in the decision making and funding of extramural grants, but also considerations of power have come to be incorporated in the appraisal of whole bodies of research as well. This is a distinct advance in the conduct of psychiatric research; prior to its recognition much research was conducted, which was, from the perspective of shedding light on theories, a waste of time, resources, and journal space due to the inattention to issues of power.

The power of a statistical test refers to the probability that a given effect (e.g., mean difference in average level of depression between treatment and control group) will be detected using a sample of a specified size, with the probability level of the statistical test being set at a predetermined level. Said more colloquially, power is the chance you have of actually finding what you are looking for in your study, statistically speaking.

Power analysis, or the determination of how many subjects are needed for the study as designed, or the calculation of how likely it was that an effect would be

found (after the research is completed), is a part of null hypothesis significance testing—the currently dominant approach to data analysis in psychiatric research and behavioral sciences in general. This approach is typically credited to the statistician R. A. Fisher (1925) and was used in its early phases for research questions in agronomy—whether there was a difference in yield from corn planted with one versus another fertilizer. The well-known $p < 0.05$ of statistical significance testing (Cohen 1994) is a part of the picture in power analysis. It refers to the probability that the null hypothesis was rejected in error, also referred to as a Type I error. That is, Fisher's system was designed to evaluate whether the mean value obtained on the dependent variable for the sample of observations studied could plausibly have come from the population, as defined by the researcher. Thus, the null hypothesis is generally conceptualized as a difference of exactly zero between an obtained value and a hypothesized one. In this context, the $p < 0.05$ of statistical testing states that a difference as large as the one obtained from the sample studied would occur only five times out of a hundred, if in reality there was no difference in the variable in the population. The 0.05 is referred to as the alpha level.

Power is one of four parameters that are interrelated in such a way so that when three of them are chosen, the fourth is determined from the choices. The four parameters are these: (1) the alpha or probability level of the significance test (typically 0.05 or 0.01); (2) the size of the effect hypothesized or to be detected; (3) the size of the sample being studied; (4) the power of the statistical test. In some ways, it is helpful to think about power as being related to another type of error that is the converse of the Type I error. The power of a statistical test is the quantity 1 minus the probability of making a Type II error, where a Type II error is failing to reject the null hypothesis when in reality in the population the difference is not zero. For completeness, the probability of making a Type II error in any statistical test is termed beta. Power is simply 1 − beta.

If it is not intuitively obvious at this point, and it very well may not be, it should be observed that the design of research studies needs to balance the two types of errors. The first is falsely rejecting the null hypothesis—saying that a new antipsychotic reduces negative symptoms when in reality it does not. The second is failing to reject the null hypothesis—concluding that the new antipsychotic does not reduce negative symptoms when in fact it does. It turns out that the size of the sample has an impact on the probability of making both Type I and Type II errors, for any given effect size (the larger the sample, the better for the hypothesis). It also turns out that much research has failed to reject the null hypothesis and has been taken as evidence against a theory when in fact the study as designed and conducted had such poor power to detect the hypothesized effect that failing to find it should have surprised no one, since the power was well below even as poor a level as only 0.50. Most studies will attempt to have power of at least 0.65, although power of 0.80 is more standard.

Power analysis is so important because it gives the researcher a means to determine how many subjects she or he must include in any particular study to have a fighting chance to show the hypothesized effect. It also gives journal reviewers and grant reviewers a means to determine whether a particular study has been or will be conducted with a sufficient number of subjects ($N$) to make the result and whether it is a rejection of the null hypothesis or a failure to reject it, substantial, meaningful, and worth the expenditure of resources.

One clear byproduct of the increased attention to power in the design of psychiatric research is a concomitant attention to measures of the size of the effect of the study. For example, many thousands of research studies present means and standard deviations for some number of groups being compared, and then an $F$ ratio with either the probability of obtaining that $F$ statistic or the probability of obtaining a number of asterisks indicating the alpha significance level. This type of presentation is not helpful in learning how much of a difference there was, or how many patients improved, or the like. The fact that an effect was statistically significant does not say how big a difference it makes; effect sizes do.

There are a variety of different effect sizes depending on the statistic that is being tested. For example, in a design termed a one-way analysis of variance (ANOVA) (see section on Statistical Techniques), a useful effect size is the percentage of variability in scores on the dependent variable accounted for by knowledge of subjects' group membership. For a two-group comparison, a standardized measure of effect size is the difference between the two means, divided by the average of the standard deviations. This latter effect size, termed $d$, gives a number that is free of the metric of the dependent variable. Cohen (1988) has offered values for this effect size metric of 0.2 for small, 0.5 for medium, and 0.8 for large. For the latter value, this translates into the two groups being separated so that almost half of their distributions do not overlap. Another measure of effect size is simply the square of the Pearson correlation coefficient ($r^2$). This yields the percentage of variability in scores on one variable predictable or knowable from subjects' scores on the other variable.

There is more that can be presented about power analysis, and the interested reader is referred to Cohen (1988) or Kraemer and Thiemann (1987). High-quality research should present measures of effect size in the reports of the results of interventions or other designs to allow meta-analytic research (studies where the raw data are the results of published studies, see Cooper 1998) to be easily conducted. These are far more important than the mere statistical significance of that effect because with enough subjects in a sample, virtually any effect, however minuscule, will obtain statistical significantce. The balance that should be sought is to have enough power to detect the size of the effect hypothesized or deemed important clinically. Thus, thinking about research should be in terms of how many subjects will be needed in a study, in order to detect a difference of some specified magnitude (hopefully that will be clinically meaningful) with a reasonable degree of power. When research design is approached this way, it is then possible to be clear about the trade-offs between power and precision of estimates, costs and logistics, ease, and relevance. Without such an approach, research in any area does not truly become cumulative (Meehl 1978). Recently, Kramer and Kupfer (2006) suggested newer effect sizes, including success rate difference, to highlight clinical significance.

## Issues of Measurement

### Reliability

An essential characteristic of any form of measurement used in psychiatric research is that it be reliable. Reliability is simply the characteristic that measurements of the same phenomenon produce the same result each time the measurement is done, assuming that the characteristic being measured has not changed. For example, if a researcher was interested in measuring the degree of demoralization of a group of patients, his/her measure of demoralization would be reliable if the results for the group of patients were essentially the same every time the measure was administered, given that the actual level of demoralization of each of the patients in the group had not changed. This type of reliability is typically termed test–retest reliability and is usually associated with questionnaires or scales such as the Beck Depression Inventory-II or the Hamilton Anxiety Scale. It is most often indexed with a Pearson correlation coefficient between scores at times 1 and 2. Obviously, reliability of measurement also applies to much "harder" variables in psychiatric research such as serum lithium levels, or hippocampal volume. Reliability is not usually an issue with harder measures, because potential sources of error, such as contaminated laboratory equipment, are so obvious a basis for errors in the result of the measurement that they are controlled and rarely conceptualized as a potential source of unreliability. With imaging data, however, such as from MRI or fMRI, raters are needed to segment images and make other decisions. Consequently, indices of reliability should be part of the research output (e.g., Frisoni et al. 2002).

In the research literature, there is reference to another form of reliability of measures, usually based on questionnaires of some sort. This reliability is termed internal consistency or internal homogeneity reliability. This form of reliability of measurement can be considerably different from the stability of measurement and probably should not be taken as a substitute. Internal consistency refers to the way the set of items or questions that comprise a scale or measure cohere or are interchangeable with each other at that single measurement occasion. That is, a measure is highly internally consistent (and therefore reliable), if the way subjects answer one item tends to predict or correlate with the way they answer the remaining items. The standard indicator of internal homogeneity for scales with a nondichotomous response format is an ANOVA-based coefficient termed alpha ($\alpha$) introduced by Cronbach (1951). Other things being equal, if a measure is presumed to measure a single construct such as neuroticism, a coefficient alpha above 0.75 or 0.80 is desirable. Nonetheless, there are a wide variety of measures that do not have high levels of internal consistency because the construct being measured is broad or complex. Also, the sample used to calculate coefficient alpha can have an impact on the consistency of the set of items. A sample with both depressed and nondepressed subjects may well yield a lower coefficient alpha than a sample with either one or the other group. A little-known but important fact about coefficient alpha is that its magnitude can be increased, and hence the internal consistency reliability of a measure, merely by increasing the number of items in the measure, without changing at all how much on average they go together.

### Validity

Validity has been discussed in the section on research designs. Validity also has a meaning in measurement. Although writers on psychological assessment and psychometrics have delineated a variety of types of validity such as content validity, content validity, predictive validity, convergent validity, and divergent validity, they are all forms or varieties of a more basic type of validity—construct validity (Cronbach and Meehl 1955). Evidence of construct validity answers a deceptively simple question: Does this instrument, test, or scale actually measure what it is claimed to measure? For example, if a new scale for measuring anxiety is offered to the field, the measure will have construct validity if it actually yields higher scores for those who are anxious, if scores on the scale are related to scores on other measures related to anxiety such as neuroticism, and if the theoretical concepts regarding anxiety are born out in what Cronbach and Meehl described as the nomological network of the construct. By this they meant the theory-based predictions that the construct of interest was related (both positively and negatively) to some but not to other constructs. If a theory of anxiety makes no prediction or statement about the relationship between intelligence and anxiety, for example, then the correlation between a well-validated measure of IQ such as the WAIS-III (Wechsler 1997) and this new measure of anxiety should be approximately zero.

The process of accumulating evidence of the construct validity of a measure is actually a daunting task if it is to be done carefully and well. An often overlooked aspect of the validation of tests, scales, or measures is to show that the measure is *not* related to constructs or variables that it should not be related to. That is, variables that are sometimes regarded as nuisance variables such as age, gender, ethnicity, education, or occupation frequently show some degree of relationship with psychological constructs despite the absence of any predicted or theoretically expected relationship. Much more research is conducted to show that a measure does relate to other measures it is theoretically predicted to be related to, than is conducted to show that a measure is not related to other measures of which it is theoretically predicted to be independent. Both forms of evidence are necessary to establish construct validity. Campbell and Fiske (1959) offered an elegant methodology for accruing evidence that a scale or test measures what it claims to measure—the multitrait–multimethod matrix. The fundamental recognition of this work was that this latter divergent validity aspect of the set of relationship among scales or tests was as important as the former convergent evidence. A measure of anxiety should be more strongly related to other measures of anxiety than to measures of depression. It is fair to say that if a measure demonstrates both convergent validity and discriminant or divergent validity in a variety of settings, with a variety of samples under a variety of conditions against criteria that are reliable and valid, then that measure very likely possesses construct validity—it measures what it is claimed to measure.

It should be noted that even though it is relatively simple to describe the concept of validity of instruments or measures, the process of empirically establishing this vital property is quite difficult. Although it might seem intuitively

obvious that patients with a particular disorder, e.g., bipolar disorder, would answer a set of true–false questions in a certain way, empirical studies have repeatedly demonstrated that the only surefire method to construct and determine the scoring of scales is to do so empirically. This is why scale construction is a specialized activity requiring advanced knowledge, training, and experience. Measures such as the Minnesota Multiphasic Personality Inventory-2 (Butcher et al. 1989) demonstrate this truism.

## Interobserver Agreement

There are a number of circumstances in psychiatric research in which the agreement of independent observers is or should be a basic requirement of empirical studies. Among the most basic issues is that of agreement between clinicians about the diagnosis of patients included in studies (Kraemer 1992). As part of the effort to increase interrater reliability in the diagnosis of psychiatric patients, over the last several decades there has been an attempt to construct, validate, and employ structured diagnostic interview protocols such as the Structured Clinical Interview for DSM-IV (SCID-I/P; First et al. 2001) to assist in making the process of arriving at an axis I and axis II diagnosis more homogeneous and uniform. Nonetheless, careful research has shown that diagnosis and diagnostic formulations are difficult decisions about which agreement among seasoned and well-trained clinicians cannot be assumed (DeWitt et al. 1983).

Another important arena in which clinical judgment is necessary, but agreement between or among judges is not always easy to obtain, is in the domain of assessment of outcomes from treatment. Rarely is the outcome or change in clinical status conceptualized simply or in just one dimension. Often the outcome of interest is a complex mix of symptoms, social functioning, and other features such as the Global Assessment of Function, Axis V of the DSM. Similar concerns about whether judgments made by different interviewers or raters of the outcome of psychiatric treatment are interchangeable frequently exist. As a consequence, considerable attention has been paid to methods for assessing the degree of agreement among or between raters.

There are two key statistics for indexing the degree of interchangeability of ratings. The first, kappa (Cohen 1960 (yes, same guy)), is used when the judgments are categorical or measured on a nominal scale of measurement. Here interchangeability between raters is technically described as interrater agreement. Kappa is a statistic that presents the percent agreement between raters on their ratings corrected for the amount of agreement that would be expected by chance, given each judge's distribution of ratings. To illustrate what kappa does, suppose two judges were categorizing nine patients into one of three categories, A, B, or C, and produced the following ratings. Judge 1: A, C, B, A, C, B, A, C, B; Judge 2: A, B, B, B, B, B, B, B, B. An ordinary percent agreement would be four out of nine or 44.4%. But the kappa coefficient for these same data is only 0.167 because chance agreement between the judges based on the marginal distributions is 33%. Even though the ordinary percent agreement is close to 50%, the kappa of 0.167 would be categorized as revealing unacceptably poor agreement. Kappa is the currently accepted standard for any situation where agreement about categorical ratings is at issue. It is remarkable, however, how often only raw % agreement is presented in the literature (Figure 128–2).

| | | Judge 1 A | Judge 1 B | Judge 1 C | |
|---|---|---|---|---|---|
| Judge 2 | A | 1 | 0 | 0 | 1 |
| | B | 2 | 3 | 3 | 8 |
| | C | 0 | 0 | 0 | 0 |
| | | 3 | 3 | 3 | 9 |

**Figure 128–2** *Illustrative data for calculating kappa.*

The second statistic is used in circumstances where the ratings are on an interval scale; the Global Assessment of Functioning is a good example. The decision the rater makes here is not what category into which to place a patient, but rather is to assign a numerical score describing how much or little of the attribute the patient demonstrates or has attained. The appropriate statistic to use in these circumstances is the intraclass correlation coefficient (ICC), the preferred index of interrater reliability. Shrout and Fleiss (1979) provide the best description of the six versions this statistic can take. The ICC is different from the Pearson correlation coefficient in that it takes account of unreliability between judges from two sources. The first is differences between the judges in the relative ordering of subjects; the second is differences between judges in the absolute level of ratings. For example, if two judges rated the same five patients on the GAF, the following scores might be produced: Judge A: 30, 40, 50, 40, 40; Judge B: 40, 50, 60, 50, 50. In these circumstances, the relative ordering is identical, and therefore the Pearson correlation would be +1.00, a coefficient that might, at first glance, indicate perfect interrater reliability. Yet, the two judges agree not at all about the actual rating given. (In fact, kappa is −0.316, showing less than chance agreement if the ratings were analyzed as if they were categorical.) The ICC for these data would be 0.50 for the reliability of a single judge and 0.667 for the reliability of the rating derived from the average of both judges. The vital issue in this example is that the ICC does not indicate perfect reliability even though the Pearson correlation does. This is because the ICC also takes into account the absolute level of ratings assigned, as well as their relative ordering. Using the Pearson correlation instead of the ICC to index interrater reliability is a common error committed in psychiatric research employing ratings made by judges and may well be overlooked in the review process of some journals. ICCs of above 0.65 for single rater estimates and of 0.70 for multiple rater estimates of interrater reliability define the bottom of the range of acceptable coefficients.

## Change

Another key issue in measurement for psychiatric research is how to deal with change in status, functioning, or symptoms, as the result of treatment interventions or otherwise. Since the vast majority of outcome measures in psychiatric research are "soft" (Kraemer and Thiemann 1989) like a rating scale, rather than "hard" like a blood level or weight, the degree of change in rating scales or behavioral

characteristics is often the answer to the question the psychiatric researcher would like to know most. Even the percent of those no longer meeting diagnostic criteria is "soft" and if used should probably have a sense of interrater agreement for the diagnostic decision.

For a variety of different reasons, many of them mathematically complex, there are potential problems with simple change or difference scores (Cronbach and Furby 1970), including potential regression to the mean and unreliability. Another issue is that many times the relationship between the initial score and the change score is much stronger than is desirable. As an alternative, some have proposed the use of residualized gain scores (Bond 1979). These change scores are adjusted for the relationship between pretest and posttest scores. Neither of these solutions, however, has been totally satisfactory. An understandable response to this conundrum has been to examine change from the perspective of percent improvement by designating some arbitrary magnitude (e.g., 50%) as indicating the patient has changed, or the percent no longer meeting the diagnostic criteria of the disorder being studied.

Kraemer (1981) has proposed an alternative strategy to both change scores and statistical techniques that used repeated measures. She has proposed using an intensive design with the slope of the response plotted against time as the outcome measure of change. This technique maximizes sample retention, decreases within-group variation, and maximizes the power of statistical tests using this outcome measure. Added benefits of this technique over residualized gain scores is that the measure is totally individualized and not based on the relationship in the sample between the pretest and final posttest. The principal drawback of this approach is the requirement for intensive measurement. But when this is weighed against the increase in power and the cost efficiency of multiple measurements as against the higher costs of enrolling more subjects, the approach has much to recommend it.

A recently introduced sophisticated set of statistical techniques also targeted at change, but from the perspective of longitudinal data sets (Diggle et al. 1994), is a family of models that have been referred to by a number of different designations. In psychiatric research, the most common terms are random regression models or mixed models. These models provide solutions to the problems of missing data, serial correlation (pre and post scores being correlated), changes in potential confounding variables over time (time-dependent covariates), acquisition of repeated measures at differing time points, and, most recently, nonlinear approaches that do not assume the normality of distributions of the variables, as well as several other highly technical issues. A very instructive presentation of this approach as applied to the data from the National Institute of Mental Health Treatment of Depression Collaborative Research Program served to introduce this approach to many in psychiatric research community (Gibbons et al. 1993).

The measurement of change and improvement is a very important issue, and the use of both the slope method and a categorical approach in combination is likely to yield a better sense of outcome than either method alone. In combination with a differentiated approach to the selection of outcome variables that are reliable, are valid, and measure the facets of clinical phenomena that are central to the research question at hand (Kraemer and Telch 1992), the techniques described here represent a sophisticated and state-of-the-art approach that repeated measures ANOVA, the previous standard in the field, does not possess. Random regression models and intent to treat techniques add depth and breadth to the capacity to analyze data from psychiatric research projects.

## Standard Statistical Techniques

The sheer number of statistical techniques available for the psychiatric researcher can be overwhelming, and when the complexity of some (e.g., random regression models) is added, it might seem that the psychiatrist as a researcher should also have a Ph.D. in Biostatistics. Part of this predicament comes from the wide availability of software capable of carrying out not only the simple and standard statistical analyses but also the complex and sophisticated analyses. The advent of desktop computers and concomitant availability of software packages were initially seen as only positive because it made access easier. Currently, however, there is a fundamental reappraisal regarding the very wide availability and use of desktop-based statistical packages and techniques (Cohen 1990). Simply put, there has come to be an overreliance on statistics, frequently complex statistics with many hard-to-meet assumptions about the data on which they operate, which are completely ignored, with a concomitant decrease in attention to issues of design, fidelity of measurement, and simplicity. Consequently, this section will serve two purposes. First, basic issues in statistics will be addressed; second, comments about the use of various statistical techniques and their liabilities will be presented. Although the personal computer and statistical software packages have brought to the desktop the computing power that just 15 years ago required mainframe computers, it is not evident that the quality of psychiatric research has greatly benefited. This is because there is a growing trend of using statistical techniques without regard for whether the data violate the fundamental assumptions necessary for accurate and valid statistical inference of those techniques. Consequently, many would argue that the easy availability has been more bane than boon (Wilkinson and Task Force on Scientific Interference 1999).

## Basic Statistical Parameters

This section introduces some basic statistical parameters and distributions that are routinely used and frequently comprise most of what is required to get a clear grasp on a set of data in psychiatric research.

### Mean

The mean is defined as the sum of the values of a variable for a set of observations, divided by the number of the observations in the set. It is the average score on the variable and is the most informative measure of central tendency of a distribution when the shape of the distribution is moderately close to the normal distribution or bell-shaped curve.

### Standard Deviation and Variance

The standard deviation is a statistic associated with the mean of a distribution or set of observations on a variable that describes how much variability the set of observations contains. The formula for the standard deviation of the population is based on the deviation of each observation

from the mean of the set. This deviation is squared, this set of squared deviations is summed, and this sum is then divided by the number of observations in the set. For an estimate of the population standard deviation, the divisor is the set of observations minus one; for the sample, it is merely the number of observations. The quantity produced at this step is termed the variance, a fundamental concept and quantity in most statistical approaches. Because the deviations were squared, the variance is expressed in a metric not comparable to the mean. The standard deviation is the square root of the variance, and by taking the square root, the standard deviation returns to the same metric as the mean, the units of the original variable. The standard deviation is the average deviation of scores around the mean of the variable for the set of observations in the sample. It is often designated SD. The standard deviation gives additional valuable information about a set of scores in addition to the information given by the mean. Consider two sets of scores. The first is 1, 3, 5, and 7. The second is 3, 3, 5, and 5. The mean of both distributions is 4. But the standard deviation of the first is 2.58, whereas it is 1.15 for the second. This shows that on average, the first sample distribution has more than twice the spread around its mean than the second; it has more variability, and consequently its standard deviation is larger. The standard deviation can also provide hints about the shape of the distribution of scores on a variable—something that can help assess whether the variable likely meets the assumptions of many common statistical techniques. Unfortunately, many articles omit this crucial datum.

### Correlation

Another basic statistic is the correlation between two variables for a sample of observations, each observation with a score on both variables. There are a number of forms of correlation, but the most common is called the Pearson product moment correlation coefficient. This statistic, designated as $r$, can attain values from +1.0 through 0 to −1.0. The strength of the relationship between the variables is indexed by the correlation, the direction by the sign of the coefficient. A perfect positive relationship yields an $r$ of +1.0 (see the example data set presented in the interrater reliability section). A perfect negative relationship would yield a coefficient of −1.0. In this case, as scores or values on one variable increase, scores on the other variable decrease. In practice, the strength of the relationship between two variables rarely exceeds ±0.60 or 0.65, if the variables are not intended to measure the same construct. Much more common are correlations in the range of ±0.20–0.45 in terms of substantive relationships such as the number of prior hospitalizations on the one hand and the amount of social support on the other.

### Contingency Tables

Another statistical approach used to show the relationship between a pair of variables is the chi-square test (see below) applied to contingency tables. This method is typically used when both variables are categorical or nominal—that is they are not ordered or on a metric. A simple example of such a contingency table is the 2 × 2 table produced by crossing a medical test result that yields a prediction of positive or negative for a disease with an actual independent diagnostic gold standard verdict of positive or negative with respect to disease status. The resulting four cells of this table are true positives, true negatives, false positives, and false negatives. There are a variety of statistics available to test the strength of the relationship between the two variables, but the central idea is that this way of arranging the data of two variables for a set of observations describes whether or not the categorization for one variable is contingent on the categorization of the other variable.

## Univariate Approaches

Some of the central concepts in statistical inference were presented in conjunction with power analysis. This included the concept of rejecting the null hypothesis as the major decision coming from subjecting a set of data gathered from a sample of subjects to statistical analysis. As presented in that section, there is a continuing literature about the inadequacy of null hypothesis testing as a method of supporting theories about human behavior and psychopathology. Nonetheless, this form of statistical analysis continues to be the dominant approach in psychiatric research and will likely be so for many years to come (Wainer 1999). Hence, description of univariate and multivariate techniques using this form of statistical analysis is still a basic tool for the psychiatric researcher. The term univariate analysis refers to situations in which the research study has a single dependent variable to be subjected to statistical analysis. The dependent variable is usually the outcome variable or the variable whose status is thought to depend on the experimental manipulation or treatment intervention. The independent variable is the variable that is free to vary independently across subjects or is the variable whose levels are selected independently by the researcher. The dosage level of a new psychotropic medication would be the independent variable in a study in which carefully diagnosed patients were randomly assigned to one of three conditions of the independent variable—one of three dosage levels of this investigational medication.

### *t*-Tests

When the researcher has two groups to compare—that is, the independent variable has two levels—on a dependent variable using a noncategorical (continuous) metric, the *t*-test comparing two means is typically employed. A significant result ($p < 0.05$) of a *t*-test indicates that the samples that produced the two means being compared were likely drawn from different populations. Put differently, the average score on the dependent variable for the population from which one sample was drawn is likely a different one from which the other was drawn. The effect size for the *t*-test, *d*, is simply the raw difference between the two means, divided by the weighted average of the two standard deviations from each sample. So, in addition to the significance of the result of the *t*-test, the actual size of the difference in standardized terms is relevant and important. Cohen (1988) has defined an effect size of 0.2 as small, 0.5 as medium, and 0.80 and greater as large for *d*.

The *t*-test has associated with it a term called the degrees of freedom, a concept that is too complex to present here. Suffice it to say that the degrees of freedom are related to the total number of data points in an analysis minus one, minus a function of the number of parameters being estimated or

tested. For the typical *t*-test, the degrees of freedom is $n_1 + n_2 - 2$, where $n_1$ and $n_2$ are the sample size of each group.

## Analysis of Variance

The ANOVA is used in situations where the independent variable has more than two levels (there are more than two groups), or there is more than one independent variable of interest being examined simultaneously. An example of the first situation is the three levels of dosage described above. This design would employ what is termed a one-way ANOVA because there is only one independent variable. There are designs, however, where there is interest in the potential joint effect of more than one independent variable on the dependent variable. If there are two independent variables, the analysis would be a two-way ANOVA, for three independent variables a three-way ANOVA, etc. In practice, designs beyond three independent variables are unusual because they are difficult to interpret.

Statistical analysis using ANOVA compares the means of the several groups being studied, like the *t*-test does for two groups. In fact, it can be shown mathematically that the result of a *t*-test is identical to the result of a two-group one-way ANOVA. Thus, in this special case, the ANOVA *F* test and *t*-test are interchangeable ($F = t^2$).

An example of a two-way ANOVA will clarify this method and why it is still a somewhat popular analysis for the underlying design. Suppose that the psychiatric researcher is testing a new medication, but that there is some indication that the dosage might be different for men and women. The researcher might select a design that included gender as one independent variable and dosage level as the other. If there were the same three dosage levels we have been using in our example, then this would yield a two-way ANOVA layout of 2 × 3—two levels of the independent variable gender and three levels of the independent variable dosage. If subjects were randomly assigned to the dosage level within each gender, then the researcher could determine whether gender mattered ignoring dosage level, whether dosage level mattered ignoring gender, or whether the combination of dosage and gender made a unique difference in the dependent variable.

The impacts of gender ignoring dose and dose ignoring gender are termed main effects in an ANOVA. The combination of gender and dosage is termed an *interaction effect*. How is an interaction effect understood? In this example, an interaction effect would occur if the relationship between dose and outcome was different for men and women. Concretely, it might be that symptoms were reduced at all dosages for women with the higher doses producing more symptom reduction, but for men symptom reduction occurred only at the highest dose. In general, however, a significant interaction effect means that the relationship between one independent variable and the dependent variable is contingent on or interacts with the subject's status on another independent variable.

Each main effect and interaction effect in an ANOVA design analysis is tested by the *F* statistic, which is a ratio of two variance estimates. Each *F* ratio has a numerator and a denominator term for degrees of freedom. The total degrees of freedom in an ANOVA are the total sample size minus one ($N - 1$). Typically, each main effect has $k - 1$ degrees of freedom, where $k$ is the number of levels; the degrees of freedom for the interaction term is the product of the degrees of freedom of its constituent effects, and the error term has degrees of freedom equal to the remainder. The *F* ratio is formed by the ratio of an estimate of variability for the effect (main or interaction) divided by an estimate of the variability of the error term, and the test of the *F* statistic requires both numerator and denominator degrees of freedom associated with the terms of the ratio. The ANOVA and *F* have certain assumptions about the data analyzed—these should be verified prior to accepting the results of an ANOVA analysis.

There are a number of measures of effect size for the ANOVA, but probably the most useful one is the percentage of total variability in scores on the dependent variable due to each effect. This can range of course from 0% to 100%; using Cohen's (1988) rules of thumb, a small effect is 1%, a medium effect is approximately 6%, and a large effect is close to 14%.

Although there is a great deal more about ANOVA that is necessary to fully understand research studies that use this data analytic procedure, the basic elements just presented are the core issues needed to start with an understanding of ANOVA approaches.

## Chi-Square

Chi-square (pronounced like "high" with a k, and symbolized $\chi^2$) is a distribution that has many uses in psychiatric research, from the testing of contingency tables (see above) to the testing of complex multivariate hypotheses using advanced multivariate methods. For our purposes here, Pearson's (yes, same guy as correlation) chi-square is used with contingency tables and tests whether there is an association of the dependent and independent variables. The use of chi-square with contingency tables would occur when both the independent and the dependent variables were categorical. If the independent variable were three varieties of SSRI medication and the dependent variable were an outcome designation of worse, no change, or improved, the use of $\chi^2$ would be appropriate.

The degrees of freedom for the chi-square test is defined as the product of one minus the number of categories of the row variable by one minus the number of categories of the column variable, that is $(R - 1)(C - 1)$.

## Multivariate Approaches

In many cases, multivariate statistical approaches are extensions of their univariate forms. When a multivariate analytic technique is referred to, the multivariate characterization refers to the number of either independent or dependent variables, or both, depending on the particular technique.

There are a number of reasons why multivariate analysis might be useful and preferable. Primary among them is the recognition that the statistical hypothesis for univariate analysis is predicated on conducting a single analysis (like a *t*-test) one time. With many dependent variables that may share variability or be correlated with one another, the researcher typically wants to conduct more than a single analysis. Doing so, however, creates a situation in which experimentwise alpha inflation can occur (Cohen 1990). In these analytic situations, the nominal Type I error rate (see section on power) is not 0.05 or 0.01 but can escalate under certain circumstances to near 0.50—meaning that the null

hypothesis could be wrongly rejected not just five times or one time out of 100, but one time out of two. This leads to a distorted interpretation of the actual empirical state of affairs. Another reason that multivariate analysis may be desirable is that theoretical parsimony may be achieved by understanding multiple relationships simultaneously rather than sequentially. Finally, multivariate analysis provides techniques to answer some questions that cannot be answered using univariate approaches.

In the sections that follow, four multivariate approaches will be presented. These are by no means all the multivariate techniques available to the psychiatric researcher or used by those now working in the field. Nonetheless, they are common approaches and ones that address more typical questions in psychiatric research. Among the statistical or data analytic techniques available but not described here are analysis of covariance (ANCOVA), propensity score analysis, discriminant analysis, logistic regression, loglinear models, cluster analysis, random regression models, and life table or survival analysis.

For those desiring more information about the four techniques described below, or several others, an excellent source is the October 1987 special issue of the *Journal of Counseling Psychology*. This whole issue was devoted to review and summary papers describing the quantitative foundations of counseling psychology research. Without exception, each article is relevant for an aspect of psychiatric research, especially the psychosocial and clinical domains. Although somewhat older, the techniques and issues have not changed.

## Multiple Correlation/Regression

Multiple correlation/regression is an extension of bivariate correlation/regression. Simple bivariate regression is just bivariate correlation described above with a couple of differences. In regression, the relationship between the two variables is expressed in terms of the best-fitting straight line that can be plotted through a scatterplot of the two variables, and there is a specific designation of which variable is the independent variable and which is the dependent variable. Regression is employed in developing regression equations that can be used to predict values of $Y$ for new subjects from their scores on $X$ when an equation predicting $Y$ from $X$ has been developed using a previous sample. For the initial or derivation sample, the higher the correlation, the better the prediction, and the closer all the points on the scatterplot fall to the best-fitting line. In the limiting case, a case of perfect correlation, all the points fall on the line, there is no error in prediction, and the scatterplot reduces to a straight line. This description applies to the case of a single independent variable ($X$), for example scores on the Hamilton Rating Scale for Depression completed by the clinician, and the dependent variable ($Y$), for example scores on the Beck Depression Inventory completed by the patient.

In multiple regression, there is still a single dependent variable $Y$, but there are at least two independent or predictor variables, $X_1$, $X_2$, $X_3$, etc. Multiple regression finds the best weighted combination of predictor variables to minimize the errors in predicting the real $Y$ values from those generated from the regression equation. A weighted combination refers to a sign (positive or negative) and a multiplier for each independent variable in the analysis. For example, if the question being addressed by a researcher was to predict the severity of current PTSD symptoms using as the dependent variable the impact of event scale-revised [IES-R] (Weiss 2004), and the predictor variables were a measure of combat exposure [EXP], a measure of current social support [SUP], a measure of peritraumatic dissociation [PTD], and a measure of the severity of substance abuse problems [SAB], the resulting equation might look like this: IES-R = Constant + 1.2*EXP − 0.68*SUP + 2.25*PTD + 0.44*SAB. When each subject's scores for the independent variables were plugged into the equation, a predicted $Y$ would be calculated. The weights of the equation are calculated so as to minimize the deviations between the predicted and actual values of the dependent variable in the derivation sample.

The results of a multiple regression are tested using the $F$ statistic, because the procedure is conceptualized as accounting for variability in the dependent variable. Hence, the measure of effect size is the proportion of variability accounted for, the multiple $R^2$.

There is one additional important aspect of multiple regression, and that is the manner in which independent variables are entered into the equation. This is a problematic issue because quite commonly there is a large set of predictor variables being examined of which only a subset is typically finally included. One method of variable entry is termed the simultaneous solution and includes all variables. A second method is termed stepwise. In this approach, variables are selected for entry into the equation in order of how much variance they account for in the dependent variable. The first variable entered into the equation is always the variable with the largest bivariate correlation with $Y$. The second variable is that one which has the highest adjusted (technically partial correlation) correlation with the dependent variable after the adjustment for the first step. This process is then repeated with each new variable being evaluated; at each step, the effects of the previously entered variables are partialled out. The stepwise procedure terminates when the additional variance accounted for by the next candidate variable is not significantly different from zero.

The third method is termed hierarchical multiple regression. This preferred approach enters variables based not on the sample-specific empirical relationships among the variables being studied, but rather on the basis of theoretical or conceptual considerations. One example of this approach can be found in work examining the prediction of symptomatic distress among emergency services personnel who worked the 1989 Loma Prieta earthquake freeway collapse (Weiss et al. 1995). In this study, the question was this: after accounting for variability in symptomatic distress from variables such as social support, exposure to trauma, work experience, and the like (all entered as a set at step 1), how much additional variance was accounted for by general dissociative tendencies (entered at step 2) and, over and above general dissociation, peritraumatic dissociative experiences during or right after the rescue effort (entered at step 3)? The results showed that peritraumatic dissociation was a significant predictor over and above the variables from the event, and general dissociation. The hierarchical procedure can be used quite effectively to examine very specific hypotheses.

Another use of the hierarchical approach is in examining interactions among predictor variables just as was described for two-way ANOVA. (In fact, although it is too

detailed to describe here, it turns out that ANOVA is just a special case of multiple regression where the predictor variables are categorical—see (Cohen and Cohen 1983).) This is done by entering the main effect variables first and then entering a new variable that is the simply the cross product of the main effect variables in the subsequent step. The partialling in multiple regression makes the cross-product variable contain only that variability not due to the main effects. But if it were entered first, this would not be the case. Most statistical packages use stepwise as the default method to enter independent variables, but this should be verified and the differences in methods should be understood prior to using multiple regression.

The overall multiple regression yields an analogue to the simple Pearson correlation $r$ and the multiple correlation $R$. To derive the effect size for the overall prediction, one simply squares the overall multiple $R$, yielding $R^2$, or the proportion of total variation in the dependent variable accounted for by the set of predictor or independent variables. Multiple regression is frequently used in nonexperimental studies, that is those of psychopathology or clinical phenomena when quasiexplanations or causes are sought. Although it is tempting to infer causality from correlation, this cannot be logically defended. The nonequivalence of correlation and causation applies equally strongly to bivariate correlation as it does to multiple correlation.

## Factor Analysis

Another very common multivariate technique is termed factor analysis. Factor analysis is actually a related family of statistical techniques that have a common goal but approach the solution somewhat differently, depending on underlying assumptions and other technical issues. What factor analysis does is to attempt to identify a much smaller set of underlying or more basic variables from the interrelationships or intercorrelations of a larger set of variables. An example of how factor analysis has been utilized in psychiatric research is for creating only a few variables to measure psychotherapy outcome when many facets of outcome have been measured.

When factor analysis is used, the distinction between independent and dependent variables is not particularly relevant. The starting point of a factor analysis is what is termed a correlation matrix. The elements in the correlation matrix are the simple bivariate correlations of each pair of variables of the set being factor analyzed.

Suppose a psychiatric researcher had nine different measures of anxiety and wanted to know if there were some more basic or underlying dimensions that might be a more simple and parsimonious method for assessing or understanding anxiety. The family of factor analytic techniques is particularly well suited for this problem. In this example, the first step would be to compute the intercorrelation among the nine variables. This would mean calculating the correlation of variable 1 with variable 2, variable 1 with variable 3, variable 1 with variable 4, etc., until the end of the series, that is variable 7 with variable 9, and variable 8 with variable 9. Obviously, the correlation of a variable with itself is +1.0. This square matrix of intercorrelations would contain two identical sets of 36 correlations, one above the main diagonal and one below, and in each cell on the main diagonal would be a value of 1.0, the correlation of the variable with itself.

The mathematics of the extraction of factors involves matrix algebra and is quite complex. Suffice it to say that the family of techniques analyzes the variance in each variable that it shares in common with one or more of the remaining variables in the matrix. It would be convenient if the technique automatically provided an unequivocal solution to the number of underlying factors—hence the name factor analysis—for a set of correlated variables. Unfortunately, there are a number of interpretive decisions that the researcher must make to select the particular approach in the family of factor analytic techniques, including deciding ultimately how many underlying factors to retain.

Tinsley and Tinsley (1987) present several criteria that need to be met in order for a factor analysis to be appropriately conducted for a set of data. First, all subjects must have scores on all variables. Second, the sample size must be sufficiently large. Rules of thumb have been offered that the sample should comprise 10 subjects for every variable, but certainly no fewer than four or five per variable. This rule is applicable up to about 300 subjects. Once more than 300 subjects have been collected, the subjects to variables ratio is less important. Third, a sufficient number of variables for each theoretically expected factor should be included, since variables that are not highly related to any of the others will be swamped in the analysis. This criterion makes it clear that, as in most other areas of psychiatric research employing empirical techniques, brute application of a factor analysis without prior conceptual or theoretical specification does not make optimum use of the power of the quantitative method.

There are four basic decisions to be made about the mode of factor analysis to be used, once it has been determined that the data set is appropriate to factor analyze. First, the researcher must decide what estimate of the common variance to use. There are two common choices: 100% or the squared multiple correlation ($R^2$; SMC) of the variable using as predictors the remaining variables in a simultaneous multiple regression identical to the type discussed in the previous section. If 100% is used, the 1.0 in the main diagonals are retained and the method of factor extraction (the second decision) is automatically selected to be principal components. This technique is not technically a factor analysis because it has an exact mathematical solution and analyzes the total variability of all variables including error variance. Using SMCs as the communality estimate includes only common variance and unique reliable variance in the analysis. Using SMCs is the prevalent practice.

The second decision is the method of factor extraction. There are a variety of methods, each having a slightly different goal and based on slightly different assumptions. The two most prevalent are exploratory descriptive approaches: principal components analysis (using communality estimates of 100%) and principal factors, with the latter being the more appropriate method in most situations where a psychiatric researcher would be conducting a factor analysis in the first place.

The third decision is a fundamental decision and difficult to make: how many factors should be extracted and retained? There have been a number of criteria proposed to make this decision. Sometimes the decision can be made on theoretical grounds because a theory or hypothesis specifies that there should be a certain number of underlying

dimensions. More typically, however, one or several empirical gauges are employed. One such criterion is that the factor has an eigenvalue ≥1.0. Each factor has an eigenvalue, but the technical description of this is beyond the scope of this presentation. Although popular, the eigenvalue ≥1.0 rule has recently been questioned (Cliff 1988). Another empirical criterion is to retain a certain number of factors based on how much of the total common variance they account for. It should be clear from this discussion, however, that the determination of the number of factors underlying a set of variables is not an exact and automatic process and is open to interpretation in any particular analysis. Thus, when used to validate the criteria for a psychiatric diagnosis, a factor analysis result is not self-evident.

The final major decision in factor analysis is the type of rotation method to use with the retained factors. Because there are many factor solutions to any correlation matrix, the choice of rotation method influences the final interpretability of the solution. Factors are interpreted based on the loadings of each variable on the factor. The loading is simply the correlation between that factor and the variable it is associated with. The purpose of the rotation methods is to partition the variability within and across factors to make the final solution clearer. Usually this means trying to achieve a solution, where for all retained factors, only a few variables have high loadings on the factor and the rest have negligible loadings. There are two classes of rotation methods: oblique and orthogonal. The former allows the factors to be correlated; the latter requires that the factors be uncorrelated, also termed orthogonal. An orthogonal rotation method is selected in practice virtually exclusively. The method typically selected is termed varimax. This usually produces the most interpretable structure of loadings.

An increasingly popular factor analytic technique is termed a confirmatory factor analysis. Derived from structural equation modeling (see below), a confirmatory factor analysis begins with more specifications and limitations and is more suitable for actually testing hypotheses about the structure of a set of variables.

The procedures for performing a factor analysis are complex and the decisions involved in an ultimate solution are many. Hence, reporting or reading the results of a factor analysis requires providing complete details and accompanying rationale for all of the decisions made throughout the process. The caveat is that many software packages will make all the decisions with no input from the user at all.

## Multivariate Analysis of Variance

Multivariate analysis of variance (MANOVA) is indeed ANOVA with multiple dependent variables. It has been a procedure that has been gaining in application with advent of statistical packages. The main advantage of MANOVA is that it solves the problem of experimentwise alpha or Type I error inflation (see above), as well as the related Type II error rate when multiple statistical tests are conducted on the same set of data. Also, the approach is able to handle the intercorrelations that typically exist among a set of dependent variables.

MANOVA layouts follow the same structure as ANOVA layouts—one-way, two-way, or multifactorial designs. As in ANOVA, the total variability is partitioned into sources of main effects, interactions, and error, but this time it is the variability in the set of dependent variables. MANOVA employs matrix algebra in its mathematical operations.

Interpreting the results of a MANOVA is more complex than for an ANOVA. ANOVA produces just one test statistic, *F*. MANOVA analyses, however, produce four test statistics, which usually yield slightly different verdicts about the analysis. Some are more commonly used, including Wilks' lambda and Pillai's trace; each is based on the eigenvalues derived and certain degrees of freedom. Nevertheless, all are tests of the null hypothesis.

Once it is shown that the overall multivariate null hypothesis can be rejected, the customary procedure is to examine the univariate *F* tests to determine in which of the dependent variables are the independent variables having their strongest impact.

MANOVA can be an efficient and statistically powerful tool when a research study has multiple dependent variables. On the other hand, it is a complex technique, it has certain distribution assumptions that are rarely examined or verified, and understanding the results cannot be accomplished merely by transcribing the results from the computer printout into a journal article.

## Structural Equation Modeling

The final multivariate approach is termed structural equation modeling and is really a family of statistical approaches. Structural equation modeling, also known as causal modeling or covariance structure analysis, is the newest of the multivariate techniques, gaining real currency in the behavioral sciences only in the late 1970s and early 1980s. It has grown to such a degree that there is now a journal devoted to the technique (*Structural Equation Modeling*). To some (Cliff 1983, Freedman 1987) it is a controversial if not fundamentally flawed approach. Most, however, consider it to be a useful strategy if approached carefully, modestly, and with full awareness that even though it purports to be a method to test causal models, it cannot actually establish causal relationships and that unless competing models are also tested, both more and less plausible, the results carry far less weight (Figure 128–3).

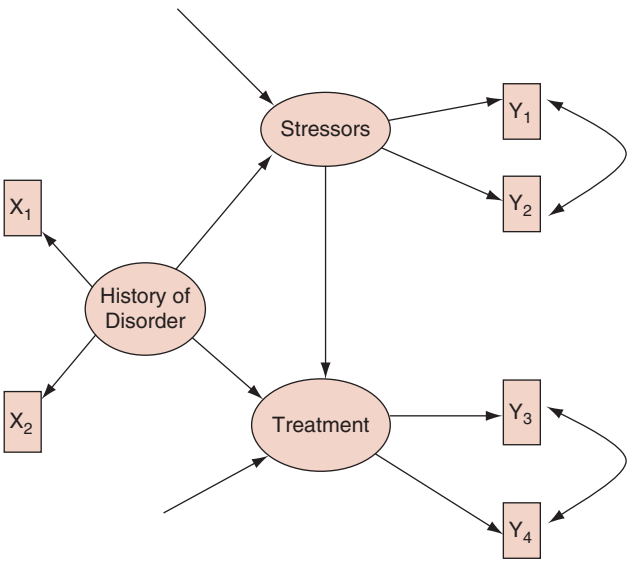



**Figure 128–3** *Simplified structural equation model for outcome.*

Structural equation modeling makes use of what are termed latent variables. These are hypothesized to be truly causal variables that are estimated by or measured by actual empirical measures. An example of this would be a structural equation model with a latent variable of intelligence. The data set collected would need to include several actual measures of intelligence, including perhaps the WAIS-III verbal IQ score, performance IQ score, verbal comprehension, perceptual organization, working memory, processing speed, a score on the Raven progressive matrices, the Miller analogies test, and perhaps the medical college admission test. The approach requires the researcher to specify, in advance of conducting any analyses, the specific causal model of which latent variables explain scores on other latent variables. In our intelligence example, latent explanatory variables might be family income, average intelligence of first-degree relatives, a measure of environmental complexity during the formative years, or a variety of other hypothetical constructs theorized to explain individual differences in intellectual functioning.

A complete structural equation model comprises two parts. The first is the actual structural model that details the hypothesized or theorized causal model including paths and directions of cause or influence among the hypothesized latent variables. The second component is a measurement model that specifies the relationship between the actual empirical variables (sometimes referred to as indicators) and the latent variables that are being used to estimate. The application of structural equation modeling includes an actual path diagram showing arrows of influence, the directionality of the presumed causal effects, and any multiple causal paths that may be postulated.

The analysis employs the covariance matrix among the observed variables. The covariance matrix is of the same form as the correlation matrix except that the existing metric or scale of each variable is used instead of a standardized metric as is used in correlations. The yield from the analysis is an estimate of the relationships among latent variables in a hypothesized population from the actual relationships among variables in a particular sample. Consequently, the statistical question to be tested is: How well do the actual sample data fit the hypothesized structure? This question is assessed with several measures of goodness of fit. The goodness-of-fit indices are derived from one of a number of iterative (repeated many times with small adjustments from the results of the last pass through) procedures. Typical approaches are maximum likelihood estimates or least squares procedures. The typical goodness-of-fit statistic is chi-square, but the derivation of chi-square here is quite different from that discussed for the contingency table.

Structural equation modeling is like factor analysis in that for stable and meaningful results relatively large samples are required. For a model of four to five variables, Bentler (1985) suggests at least a ratio of 10 subjects per variable; others suggest as many as 30 subjects per variable. Clearly, structural equation modeling requires a large sample and many measures taken with that sample and is probably not appropriate for much of clinical psychiatric research.

There are two major difficulties with structural equation modeling. The first is that even if the statistical results suggest that the collected empirical data from the sample are a good fit to the hypothesized latent model, researchers rarely, if ever, construct implausible or impossible causal models and attempt to fit the data to that model. If this were done and presented along with the results of the hypothesized model, then considerably more confidence would accrue to the hypothesized model. Second, the assessment of fit proceeds in the opposite manner from the usual statistical test and can have unforeseen problems (Tomarken and Waller 2003). That is, if the null hypothesis is rejected then the model is rejected; if the null hypothesis is not rejected, then the model is deemed accurate, valid, or supported. But as described in the section on power and Type II errors, failure to reject the null hypothesis may be merely an issue of low power to do so, not strong evidence that the null hypothesis is indeed false. In structural equation modeling, the power of the statistical test is not usually known or even estimable with any accuracy or confidence. Hence, a model may be said to fit the data when it is really not a valid model. On the other hand, if power is very high, which may occur with very large samples, the null hypothesis of the chi-square goodness-of-fit test may be rejected even when the difference between the sample data and the hypothesized population model is quite trivial. All these suggest considerable caution in the use, interpretation, and consumption of research involving causal or structural equation modeling.

The logistics of performing such an analysis are also somewhat intimidating. Specialized computer programs are required, and the specification of the model, its parameters, and a variety of other decisions require considerable investment. There are now a number of widely used statistical programs.

## How to Read Published Research

Even if one is a novice regarding the conduct of psychiatric research, one can be an informed, thoughtful, and careful consumer of the psychiatric literature. As difficult as it might seem to believe, the mere fact of its appearance in a peer-reviewed journal does not automatically and invariably convey upon it integrity of methods, results, or conclusions. The reader should approach empirical psychiatric research with a critical and skeptical stance. The author's job is to present a convincing rationale and method. The reader should be asked to take nothing for granted nor to have to assume certain basics if they are not explicitly presented. With these caveats in mind, the reader can evaluate the adequacy of each major component. Below are a series of questions the reader can ask about each major section of a research study. The paper published by the American Psychological Association Taskforce on Statistical Inference (Wilkinson et al. 1999) can also be a very valuable guide.

## Design

Important questions to ask about the design of a study have to do with the internal and external validity of the study. Are there potential alternate explanations for the results from causal factors that the study is not controlling that the authors address? Are subjects randomly assigned to conditions? How representative of the population of interest is the sample that was studied? Do the methods by which the subjects were recruited promise to avoid introducing bias into the study? Is the design a real

experimental design or is it quasiexperimental? If the latter, are the potential problems with the study made explicit by the author and taken into account when the findings are presented and discussed?

### Sample

Important questions to ask about the sample presented in a research paper are these. How was the sample accumulated or drawn, by convenience or using an explicit sampling strategy from a known population? Was assignment to intervention groups random or was some less desirable method used? Of what population is the sample said to represent? Is the sample adequately characterized in terms of gender, ethnicity, age, or other characteristics that could have an impact on the results of the study? If the final sample studied is a subset of some initially larger group, is it clear why and how those remaining were retained and how and why those who were not retained were excluded? Is there discussion of an analysis of the data showing that the remaining subjects are not different in some important way that could have influenced the final results form those who were excluded? Is enough detail about how subjects were recruited present so that another researcher could replicate the recruitment if he or she wanted to perform the same study? Finally, is there an explicit statement regarding informed consent?

### Measures

Are the measures used clearly identified and are appropriate citations for their origin given in the references? Do the measures possess reliability and validity? If the measures are newly constructed for the study at hand, is there careful attention to the psychometric properties of the measures in the methods section? Is there any mention of missing data for subjects, and, if mentioned, is there a description of how this was dealt with or why it occurred? If missing data are not mentioned, is it plausible that all measures for all subjects for all measurement occasions were actually collected? If ratings have been made, are there indices of interrater reliability or interrater agreement presented for the data in the current study, not just cited from previous work?

### Analysis and Power

In examining power and data analysis, the following questions are relevant. What power was there to detect the effect being studied—that is, were there enough subjects studied so that there was a reasonable chance of detecting the effect of interest? If not, any negative results must be regarded with caution and suspicion. Regarding data analysis, these are apposite questions. Is the method of analysis congruent with the type of variable? Are the basic assumptions about the statistical method met? Does the author present effect sizes along with the significance of the statistical tests? Does the author present the actual values of the variables being compared (e.g., means and standard deviations) in addition to just the test statistic (e.g., *t*-test)? Is there concern with experimentwise alpha inflation and has the author been judicious in his or her use of significance tests? Is there a logical relationship between the analyses conducted and the questions asked—are the analyses appropriate to answer the question?

If the answer to many or most, if not all, of the questions regarding each of the sections of a research report is in the affirmative, then it is likely that the results can be depended on. To the degree that the answers to the questions are negative is the degree to which the results of the study are questionable and might not be considered definitive or even particularly informative.

## Conclusion

Research methodology and statistics are complex areas in which expert consultation is always more helpful prior to starting a research project than it is after the project has begun. This chapter has only scratched the surface of a few of the areas and has left many untouched. Probably the most important advice to give the psychiatric researcher is to consult a professional methodologist, biostatistician, or other experienced person in these arenas before diving into a research project. Although the software and computers are available at relatively small cost, they cannot provide the in-depth knowledge that is required to do things properly and correctly from the start. It is unfortunate, but many research projects have borne no fruit because choices made without prior consultation have rendered the results of the study beyond help even from the most sophisticated and complex statistical rescue strategies. Consequently, many individuals have expended a great deal of effort that did not lead to a desired result. Like all other domains of psychiatry, research method is a specialized area in which training and experience are valuable and for which assistance from a mentor is a prudent investment.

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# Index


'2x2' mood stabilizer definition, 1356, 1359
5-HT *See* Serotonin
12 step recovery programs, 996–997, 1197
16th century, 208–209
17th century, 209–210
18th century, 210–213
19th century, 213–220
20th century, 220–231

AA *See* Alcoholics Anonymous
AADID (American Association definition of intellectual disability), 691
AAI *See* Atlanto-axial instability
AAMR *See* American Association on Mental Retardation
AAS *See* Abuse assessment screen
Abbreviated treatments *See* Brief psychotherapies
Abecarnil, 2231
Ability barriers to compliance, 2452, 2454
Abnormal Involuntary Movement Scale, 533, 534
Abortions
  ethical guidelines, 69
  spontaneous, 2417–2418, 2419
Abreaction to dissociative amnesia therapy, 1562
Abridged somatization disorder *See* Undifferentiated somatoform disorder
Absolute effects *See* Attributable risks
Absorption
  hypnosis, 1984–1985
  pharmacokinetics, 2099–2100
Abstinence
  psychoanalytic psychotherapy, 1856
  therapeutic frame boundaries, 73, 77–78
  vouchers-based incentives, 1052, 1070
Abstraction, schizophrenia patients, 1236
Abstract thought, adolescent development, 169, 171
Abulia, apathy expression, 617
Abuse *See* Child abuse; Physical abuse; Sexual abuse; Substance abuse
Abuse assessment screen (AAS), physical/sexual, 2580
Academic services for mentally ill homeless people, 2534–2535
Academic skills disorders *See* Intellectual disability; Learning and motor skills disorders
Acamprosate, 996, 2396, 2397
Acceleration-sensitive actigraphs, 810
Access to Community Care and Effective Services (ACCESS) program, 2528
Access to mental health services, 1264, 1300
Accreditation of provider organizations, 1844
ACDS *See* Adult Clinician Diagnostic Scale
ACE *See* Angiotensin converting enzyme
Acetaminophen, 1533, 1534
Acetyl-1-carnitine, 2325
*N*-Acetyl aspartate (NAA), 1116
Acetylcholine (ACh)
  Alzheimer's disease, 905, 907
  delirium, 919
  schizophrenia, 309
  sleep, 1630
Achenbach Child Behavior Checklist and Teacher Report Form, 807, 808
Acquired aphasia with epilepsy, 796
Acquired immunodeficiency syndrome *See* HIV/AIDS
Acquired sexual disorders, 1583–1584, 1588–1589, 1590
Acromegaly, 2505
ACT *See* Assertive Community Treatment
Actigraphs, 810
Active therapy, 1899–1900
Activities of daily living (ADL) assessment, 2550, 2552
Activity levels of preschool children, 138
Activity scheduling, behavioral therapies, 1930–1931
Acupuncture
  cocaine use disorders, 1076–1077
  enuresis, 874
Acute depression
  antidepressants, 2131, 2147, 2148
  bipolar disorder, 1336, 1339, 1356, 2210–2214
  interpersonal psychotherapy, 1875, 1877–1878, 1879–1880
  treatment, 1301–1302
Acute extrapyramidal symptoms, 2184–2187
Acute grief, 2521, 2523
Acute intoxication by sedative-hypnotics, 1191
Acute mania *See* Manic episodes
Acute neuroleptic-induced movement disorders
  akathisia, 1779–1780, 1781
  dystonia, 1774–1776, 1781
  Parkinsonism, 1781
Acute phase, schizophrenia treatment, 1245–1246, 2177–2181
Acute stimulant use, attention-deficit hyperactivity disorder, 2284
Acute stress disorder (ASD), 1472, 1485–1490, 1572–1574
  abuse victims, 2585, 2590
  assessment, 1485–1486
  diagnosis, 1476, 1485, 1487, 1489–1490
  differential diagnosis, 1476, 1487
  disaster-related, 2468–2469, 2473
  DSM-IV-TR criteria, 1486, 1489–1490, 1572, 2585
  epidemiology, 1486–1487
  etiology/pathophysiology, 1487
  general features, 320
  hypnosis, 1994–1995
  treatment, 1487–1489
Acute Stress Disorder Interview (ASDI), 1486
Acute Stress Disorder Scale (ASDS), 1486
AD *See* Adjustment disorder; Alzheimer's disease; Asperger's disorder


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ADA *See* Americans with Disabilities Act
Adaptation, post-Freudian psychology, 471–472
Adaptive functioning, 633–646
  autistic disorder, 784
  clinical assessment, 641–642
  domains of functioning, 639–641
  early adulthood problems, 506–508
  elderly adults, 196, 197
  impairments in intellectual disability, 716
  personality styles, 633–639
  problematic behavior patterns, 642–646
  strengths/weaknesses characterization, 560
ADD *See* Attentional-deficit disorder
Add-back hormone strategies *See* Hormone therapy
AD-DBDs *See* Attention deficit-disruptive behavior disorders
Addiction cycle/patterns of substance abuse, 356–358
Addictive disorders
  *See also* Alcohol...; Substance dependence
  kleptomania, 1671
  paraphilia, 1601
  pathological gambling, 1682–1684
  pathophysiology, 354–374
  psychotherapy in correctional settings, 2597
  sexual disorders, 1601, 1603, 1606
Adenosine receptor caffeine action, 1023, 1028, 1032
ADHD *See* Attention-deficit hyperactivity disorder
Adherence
  *See also* Compliance
  use of term, 2447
ADIS *See* Anxiety Disorders Interview Schedule
Adjustment disorder (AD), 1702–1714
  cultural factors, 654
  definition, 1702–1705
  depression, 616, 1289
  diagnosis, 1707–1708
  differential diagnosis, 1475–1476
  DSM classification systems, 676
  DSM-IV-TR criteria, 1703
  epidemiology, 1705–1706
  etiology, 1706–1707
  ICD-10 criteria, 1714
  intellectual disability, 731
  prevalence, 1705
  subtypes, 1708–1709
  treatment, 1710–1713
ADL *See* Activities of daily living
Administration routes, opioids, 1171
Administration of services for mentally ill homeless people, 2534–2535
Adolescents
  adjustment disorders, 1704–1709
  adolescence/puberty relationship, 150
  alcohol use disorders, 982–983, 997–998
  antidepressant suicide risks, 2145–2146
  antipsychotic drugs, 2174
  attention disorder rating scales, 807–809
  avoidant personality disorder, 1741
  behavioral problems, 756, 1805
  biological development, 98, 99, 161, 163–168
  bipolar disorder, 1348, 1366
  body dysmorphic disorder, 1540
  cannabis dependence, 1052, 1053
  clinician-patient relationship, 30, 547–548
  cognitive development, 100, 101, 168–171
  comorbidity patterns, 500
  compliance, 2447, 2448, 2451, 2453
  conversion disorder, 1527
  dementia causes, 918
  depressive disorders, 1290–1291, 1881
  development, 161–178
  developmental phases, 161–162
  disorders, 499–503
  emotional development, 102, 103, 172, 173
  environmental risk factors-genetic factor interaction, 176–177
  families, influence on compliance, 2454–2455
  Freud, 466
  gay men/lesbians, 2546
  gender distribution of disorders, 503
  gender identity disorders, 1595–1596, 1597
  historical attitudes, 172–173, 222, 224
  homeless, 2528–2529
  inhalant-related disorders, 1130, 1131
  initial psychiatric evaluations, 546–554
  interpersonal psychotherapy, 1881
  laboratory assessment, 553
  learning and motor skills disorders, 747–762
  legal issues
    consent/notification of treatment of minors, 84–85
    criminal proceedings, 92
    education rights for disabled, 552–553
  major depression, 1881
  moral development, 103, 104
  neurological/brain development, 168
  neuropsychological tests, 558
  paraphilias, 1600–1601
  pedophilia victims, 1602
  physical development, 98–99, 161, 163–168
  post-traumatic stress disorder, 1474–1475
  psychiatric databases, 40
  psychological factors affecting medical condition, 1756
  psychopathology risk/protective factors, 175–178
  pubertal endocrine/physical changes, 99
  pyromania/fire-setting behavior, 1675
  relational problems, 1799, 1805
  separation anxiety disorder, 879–883
  sleep patterns, 1629
  social development, 102, 104, 172–175
  somatization disorder, 1518, 1521
  substance use disorders, 363–364, 963, 982–983, 997–998, 1052–1053
  suicide risks, 102, 106, 2145–2146
  temperament, 177
  TRAAY aggression treatment recommendations, 825
Adoption studies
  bipolar disorder, 1348–1349
  genetic epidemiology, 259, 261
  mood disorders, 340–341
  schizophrenia, 1212
Adrenal disorders, 2505
Adrenergic agonists *See* Alpha-2 adrenergic receptor agonists
Adrenergic receptor genes, ADHD, 814
ADRs *See* Adverse drug reactions
Adult ADHD Self-Report Scale (ASRS), 810
Adult Clinician Diagnostic Scale (ACDS), 810
Adult development, 181–194
  biological, 98, 99–100, 183–184
  challenges, 182
  cognitive, 100–101
  cohort effects, 184–185
  elderly adults, 196–202
  Eriksonian model, 189–191
  grief, 192
  identity formation, 192–193
  integrated model, 187–188
  longitudinal studies, 97–108
  moral, 103, 105
  resilience, 185–186
  transactional model, 182–183
  transitions/crises, 192
  young adults, 186–187
Adulthood, psychiatric databases, 40
Adults
  abuse, 2577–2578, 2584–2585
  attention-deficit/disruptive behavior disorders, 809–810
  attention disorder rating scales, 807–809
  early adulthood disorders, 503–510, 511
  hippocampus neurogenesis, 349–350
Advanced sleep phase disorders, 1644–1645
Adverse birth outcomes, 2417–2423

Adverse drug reactions (ADRs), 2107, 2108
  antidepressants, 1304–1307, 2123, 2124, 2135–2143
  antipsychotic drugs, 1251–1255, 1773, 2184–2192, 2556
  bipolar disorder medication, 1357–1362
  compliance relationship, 2450, 2455
  ethnic/cultural issues, 2114
  extrapyramidal symptoms, 1251–1252, 1773, 2184–2187, 2556
  first generation antipsychotics, 1251–1253
  insomnia medications, 1637
  intellectual disability medications, 723, 736
  opioid pain medications, 1534
  post-traumatic stress disorder medications, 1481
  St. John's Wort, 2321
  schizophrenia medications, 1247–1249, 1251–1255, 1257
  second generation antipsychotics, 1253–1255
  stimulants, 818–819, 2266, 2276–2284, 2286–2287
  switching antipsychotics, 1257
Adverse effects, brain stimulation therapies, 1316, 2359–2360, 2362–2363, 2364, 2366
Adverse Event Report System (AERS), 2266
Adversity factors
  Conduct Disorder/Oppositional Defiant Disorder, 817
  psychopathology risk, 106
  social psychology, 456–457
Advocacy
  children/adolescents, 554
  conceptual distinctions, 2083–2084
  organizations, 2085–2086, 2088–2090
  Political Advocacy Model, 2085, 2089–2090
  services for mentally ill homeless people, 2534–2535
  State Protection and Advocacy Centers, 2085, 2086
AEDs *See* Antiepileptic drugs
AERPs *See* Auditory evoked response potentials
AERS *See* Adverse Event Report System
Affect
  attunement in infant development, 121–122
  clinical assessment, 608–609
  defence, 472
  expression, 608, 1795, 1798–1799, 1802, 1808
  inappropriate, 603, 604, 948
  Mental Status Examination, 529
Affect dysregulation
  dissociation, 603, 604
  disturbances, 608, 618
  schizophrenia patients, 1234–1235
Affective constructs in animal models, 280–281
Affective disorders
  *See also* Mood disorders
  neuroimage subgrouping, 327–328
  psychiatric disability, 2059–2060
  schizoaffective disorder, 222, 509–510, 1236–1237, 1265–1268, 1278, 2170–2171
  schizophrenia relationship, 1238
  seasonal affective disorder, 728–729, 1289, 1316
  suicide risk, 540
  susceptibility genes, 341–342
Affective dysregulation
  alcohol dependence, 973
  autistic disorder, 782
  pseudobulbar palsy, 948
  schizophrenia, 2176–2177
Affective spectrum model, 1670–1671, 1682
Affect-Related Personality Disorder Criteria, 610
Age, *See also* Elderly adults; Middle adult life; Young adults
Age at onset
  *See also* Early-onset...; Late-onset...
  anxiety disorders, 419, 421, 1415, 1416, 1417, 1497
  lifetime mental disorders, 419–422
  psychopathology across the life span, 489, 490
  social/specific phobias, 1415, 1416
  unusual for condition, 531
Age effects
  alcohol use disorders, 982–983, 984, 985, 997–998
  biological effects, 183–184
  bipolar disorder, 1345, 1347–1348, 1366–1367
  breathing related sleep disturbance, 1642
  cognitive changes, 197–199
  coping resources, 196–197
  depression, 1290–1292
  diagnostic criteria, 182
  effective listening, 5, 6, 15–16
  gay men/lesbians, 2545
  generalized anxiety disorder, 1504–1505
  lifestyle changes, 200–201
  National Comorbidity Survey-Replication, 419–423
  normal sleep/wakefulness changes, 1629
  pharmacokinetics, 2100, 2101, 2104, 2120
  psychopathology, 106, 107, 184, 489–516
  schizoaffective disorder, 1266
  schizophrenia, 1208–1209
  sensory changes, 199–200
  sexual disorders, 1580, 1582, 1586, 1587, 1593
  sexuality, 201–202
  substance use disorders, 360
  suicide risk, 2479
  trichotillomania, 1694
Age of Enlightenment, 210–211
Age of maturity, 172–173
Agency for Health Care Policy and Research (AHCPR), 1354
Agency for Healthcare Research and Quality (AHRQ), 1354–1355
Aggression
  *See also* Intermittent explosive disorder
  alcohol-induced, 2605–2606
  anger link, 2603, 2604
  autistic disorder, 782
  biological factors, 2608
  childhood problems, 497
  differential diagnosis, 1664, 1665
  dual-instinct theory, 470
  efficacy studies in attention-deficit hyperactivity disorder, 2275
  etiology/pathophysiology, 1666
  expression, 617–618
  family relational problems, 1797–1798
  hostility expression, 49, 617–618
  impulsive aggression, 1661, 1665
  infant development, 127
  intellectual disability, 731, 734
  intermittent explosive disorder, 1658, 1661–1668
  monoamine oxidase A genetic effects, 176
  non-pharmacological strategies, 2608–2609
  obsessive-compulsive disorder, 1444, 1447
  paraphilias, 1600
  pharmacological treatment, 2609–2612
  preschool development, 147
  psychiatric interviews, 48–49
  risk assessment, 541–542, 2602–2603
  suicide, 2481
  TRAAY youth treatment recommendations, 825
  treatment, 2608–2612
  types, 2603, 2604
  violent behavior, 2602–2612
Aggression/hostility/anger (AHA) syndrome, 2607
Agitation
  medical conditions, 626–627
  psychiatric interviews, 48–49
  schizophrenia patients, 1234
Agnosia
  dementia, 899
  Klüver-Bucy syndrome, 948–949
  self-experience disorders, 603, 604
Agonist substitution agents, 2390–2391, 2401
  *See also* Substitution therapies
Agoraphobia
  avoidant behavior, 645–646
  childhood separation anxiety disorder relationship, 880
  cognitive and behavioral therapies, 1938, 1939
  definitions, 1393, 1394

Agoraphobia *(Continued)*
differential diagnosis, 1417
general features, 319
generalized anxiety disorder distinction, 1499
history, 1392
panic disorder with agoraphobia definition, 1393, 1394
without panic attacks, 1393
Agranulocytosis, antipsychotic drugs, 2185, 2191
AHA *See* Aggression/hostility/anger
AHCPR *See* Agency for Health Care Policy and Research
AHI *See* Apnea-hypopnea index
AHRQ *See* Agency for healthcare Research and Quality
AIAD *See* Alcohol-induced anxiety disorder
AICDs *See* Automatic implantable cardioverter-defibrillators
AIDS *See* HIV/AIDS
Aim, libido theory, 467
AIMD *See* Alcohol-induced mood disorder
AIPAD *See* Alcohol-induced persisting amnestic disorder
AISD *See* Alcohol-induced sleep disorder
Akathisia
acute neuroleptic-induced, 1779–1780, 1781
antipsychotic drugs, 2184–2187
FGA side effects, 1252
Akinetic mutism, 944
Al-Anon, 992
Alcohol abuse, diagnostic criteria, 975
Alcohol-cocaine abuse, 1060, 1065, 1078, 2410
Alcohol dependence
diagnostic criteria, 974, 975
genetic/environmental factors, 971–973
pharmacotherapy, 2394–2397
subtypes, 972–973
treatment goals, 988–990
Alcoholics Anonymous (AA), 990, 992, 996–997
history, 224
self-help group movement development, 1904, 1916
Alcohol-induced aggression, 2605–2606
Alcohol-induced anxiety disorder (AIAD), 978
Alcohol-induced conditions, Wernicke-Korsakoff's syndrome, 361, 926, 978
Alcohol-induced mood disorder (AIMD), 978
Alcohol-induced persisting amnestic disorder (AIPAD), 977–978
Alcohol-induced persisting dementia, 978
Alcohol-induced psychotic disorder, 978
Alcohol-induced sexual disorder, 979
Alcohol-induced sleep disorder (AISD), 978–979, 1652–1653
Alcohol intoxication, diagnostic criteria, 977
Alcohol sensitizing drugs, 992–993
Alcohol use
adolescents, 173, 174, 175, 501, 502
cultural factors, 649–650
early adulthood, 507
elderly adults, 515
middle adult life, 510, 512
neuropharmacology, 367
patterns, 358–359
Alcohol use disorders, 971–999
addiction patterns, 357
aggression, 2605–2606
alcoholic types, 972–973
caffeine use relationship, 1030–1031, 1032
course/natural history, 988
dementia due to, 915–916
dependence criteria, 355
diagnostic criteria, 974–979
epidemiology, 983–986
etiology/pathophysiology, 971–974
fire-setting behavior, 1676, 1677
general approaches to substance use disorders, 957–970
generalized anxiety disorder comorbidity, 1497
homeless people, 2528, 2531
IED comorbidity, 1664–1665
inhalant-related disorders relationship, 1129, 1140
pathological gambling, 1683
pharmacotherapy, 2391, 2392–2397
psychiatric comorbidity, 986–988, 993–994, 2397
sedative-hypnotics abuse relationship, 1188, 1189, 1191, 1193, 1194, 1197–1198
somatization disorder etiological link, 1521
suicide, 2481
treatment, 988–999
Alcohol use disorders identification test (AUDIT), 979, 980, 989
Alcohol withdrawal
characteristics, 977
diagnostic criteria, 974, 975
management, 990–991
pharmacological detoxification, 2392–2394
Alerting systems
attention, 435
enuresis, 873, 874
Alexander, Franz, 2028
Algorithms *See* Verbal algorithm approach
Alienists/alienation history, 206, 209, 210, 215
Aliphatic phenothiazines, 1242
Alleles *See* Genetic factors
Allergic reactions, 2140
Alliances in structural family therapy, 1950
Allopregnanolone (ALLO), 1382
Alogia, 596–597
Alopecia, 1688, 1690
Alpha-1 receptor blockade, antidepressant side effects, 2136–2137
Alpha-2 adrenergic receptor agonists
alcohol withdrawal, 2393–2394
attention deficit-disruptive behavior disorders, 820–821
cannabis detoxification, 2412
opioid detoxification, 1176–1177, 2398–2399
Alpha-7 nicotinic receptors, schizophrenia, 1259–1260
Alpha adrenergic receptor genes, Attention Deficit/Hyperactivity Disorder, 814
Alpha agonists, intellectual disability treatment, 738–739
Alpha coefficient, measurement method reliability, 2624
Alpha receptor blocking, tetracyclic antidepressants, 1309
Alpha-tocopherol *See* Vitamin E
Alpha waves/bands, 566, 2009, 2327
Alprazolam
generalized anxiety disorder, 2231–2232
panic disorder, 2239
pregnancy, 2423
premenstrual dysphoric disorder, 1386
Alternative medicine *See* Complementary and alternative medicine
Alternatives generation, cognitive and behavioral therapies, 1928
Aluminum, Alzheimer's disease, 905
Alveolar hypoventilation, 1641
Alzheimer, Alois, 902–903
Alzheimer's disease (AD), 393, 394–396, 902–908, 2294–2317
*See also* Dementia
AMPA receptor modulators, 2305
amyloid-based interventions, 2308–2310
anti-excitotoxic therapies, 2311
antioxidants, 2311
antipsychotic drugs, 2172–2173
approved compounds, 2305
behavioral effects, 2305
cholinergic treatment, 2298–2304
cholinesterase inhibitors, 2298–2304, 2312
cognitive enhancers, 2294–2317
cognitive strategies, 2298
combined therapies, 2311–2312
criteria for clinical trials, 2295
cultural factors, 649
depression comorbidity, 1287, 2558
DSM-IV-TR criteria, 903
elderly adults, 513
epidemiology, 903–904
evaluation, 2552
glutamatergic therapies, 2304–2305
history/background, 213, 231, 2294
immunotherapy, 2308

inflammatory processes, 2310–2311
Lewy body dementia relationship, 398
management, 2552–2553
medications, 2555
metabolic enhancement, 2308
neuropathology, 2295
neurotransmitter-based approaches, 2296, 2298–2306
neurotrophic factors, 2306–2308
pathobiology theories, 2295–2296
pathogenic cascade hypothesis, 2296
pathology, 904–906
progression chart, 2297
regulatory issues, 2294–2295
relational problems, 1806
tangle-based therapies, 2310
treatments, 906–908, 2294–2317
vascular dementia differentiation, 909–910
AMA *See* American Medical Association
Amantadine, 1072
Amenorrhea, 1611, 1612
American Association on Mental Retardation (AAMR), 691
American Medical Association (AMA), 68
American Psychiatric Association (APA)
ethical guidelines, 68, 77
history, 218, 224
hypnosis recognition, 1984
practice guidelines, 1845–1846
Americans with Disabilities Act (ADA), 712
γ-Aminobutyric acid *See* GABA
Amino-propylation, 2322–2323
Amisulpride, 2168, 2169, 2178
Amitriptyline, 2126, 2128
Amnesia
characteristics, 585
dissociative amnesia, 1561–1562
dissociative fugue, 1562–1564
electroconvulsive therapy effects, 2359–2360
evaluation, 592
kleptomania-related, 1668
parasomnias, 1649
Amnestic disorders, 897, 924–928
differential diagnosis, 901–902, 926–927
DSM classification systems, 674
DSM-IV-TR criteria, 925
etiology, 925–926
Korsakoff's syndrome, 361, 926, 977–978
treatment, 927–928
Amobarbital, 1529
Amok syndrome, 653, 655, 1665
Amotivational syndrome, 1043
Amphetamine-induced sleep disorder, 1653
Amphetamines
addiction patterns, 357–358
attention deficit-disruptive behavior disorders, 818
cocaine substitution therapy, 1076
disruptive behavior in children, 2264, 2265
narcolepsy, 1639
pharmacotherapy, 366, 2411
violence link, 2606
Amygdala function
animal models, fear/anxiety, 322, 323–324, 325, 326–327
anxiety disorders, 325–332
autism, 386–387
emotional processing/regulation, 325–327
fear/anxiety response neurobiology, 322, 323–324
schizophrenia, 1219
substance use neuropharmacology, 365–366
Amyloid cascade hypothesis of Alzheimer's disease, 2295–2296
Amyloid plaques, 394, 395
Amyloid precursor protein (APP), 395, 396
Anabolic steroid abuse, 969
Anaclitic attachment, 469
Anagnosias, 603, 604
Analgesia, hypnotic, 2000–2003
Analgesics
opioid addiction patterns, 357
opioid doses, 2400
pain disorder treatment, 1533, 1534
Analogies, effective listening, 4–5, 7
Anal phase of childhood sexuality, 466
Analysis of variance (ANOVA), 2272, 2623, 2628, 2631
Anatomical aspects
brain function, 34
neurodegeneration, 393–394
Ancient Greeks, 206, 207
Androgens *See* Sex hormones; Testosterone
Anemia, 843, 844
Anencephaly, 703
Anesthesia
hypnosis, 1982, 2001–2002
inhalant-related disorders, 1127, 1133
post-anesthetic headache, 1026–1027
Anesthesia-assisted heroin detoxification, 2405
Angelman syndrome, 698, 718
Anger
aggression/violence link, 2603, 2604
expression, 617–618
infant development, 119, 122
neurotransmitters, 2608
Angiotensin converting enzyme (ACE) genes, 341
Animal models, 275–286
antidepressant development, 2130
anxiety, 321–326
anxiety disorders, 280–282, 324–325
'a priori' modeling, 284–286
attachment theory, 291
behavioral studies, 1923–1924
conditioning, 323–324
depressive disorders, 280–282, 1297–1298
developmental aspects of anxiety, 330–331
emotions, 605–606
fear responses, 321, 322–324
gene identification, 268–269
mood disorder neuropathology, 344
obsessive-compulsive disorder, 1456–1457
phenotype definition, 277, 278
schizophrenia, 279–280
stimulants, 2268
stress susceptibility/resilience, 324–325
substance dependence, 364–365, 367–368, 373–374
validity, 277–278
Animism, 138
Anomia, 906
Anonymity of therapists, 73, 76–77
Anorexia nervosa, 1609–1618, 1624
adolescents, 502–503
assessment, 1611–1613
body dysmorphic disorder relationship, 1540
cognitive and behavioral therapies, 1939
course, 1614
definition, 1610–1611
DSM-IV-TR criteria, 1611
epidemiology, 1613
etiology/pathophysiology, 1615–1616
feeding disorder of infancy or early childhood, 835
history, 208, 210, 1609–1610
physiological effects, 1611–1613
sleep disturbance, 1650
treatment, 1616–1618
ANOVA *See* Analysis of variance
Antabuse *See* Disulfiram
Antagonism in personality disorders, 1722
Antagonist treatment, substance dependence, 1178–1179, 2391, 2405–2407, 2409
Antenatal, *See also* Fetal...; Pregnancy; Prenatal...
Antenatal psychological health assessment, 2580
Anterior cingulate, 1219
Anterograde amnesia, 585
Anthropology, 55
Antianxiety medication *See* Anxiolytic drugs
Anticholinergic effects of antipsychotic drugs, 2185
Anticholinergic medication
acute neuroleptic-induced dystonia, 1776
enuresis, 873
neuroleptic-induced Parkinsonism, 1778
prophylactic, 1780–1781
schizophrenia, 1258

Anticipatory anxiety, 317–318
Anticonvulsant medication
*See also* Antiepileptic drugs
acute bipolar depression treatment, 2212–2213
acute mania treatment, 2208–2209
aggression treatment, 2610–2611
alcohol withdrawal, 2393–2394
anxiety disorders, 2226
depression treatment, 1303–1304, 1313–1314
generalized anxiety disorder, 2232
insomnia, 2260
intellectual disability treatment, 738
neuroprotection, 1351–1352
obsessive-compulsive disorder, 2246–2247
panic disorder, 2240
post-traumatic stress disorder, 2243
pregnancy, 2509
social anxiety disorder, 2235
Antidepressant medication, 1304–1311, 2123–2157
*See also individual types*
abuse victims, 2590
acute bipolar depression, 2210–2211
acute/response period, 2148
adjustment disorders, 1712
alcohol dependence/depression comorbidity, 2397
Alzheimer's disease treatment, 907
anxiety disorders, 2224–2225
avoidant personality disorder, 1741
bipolar disorder, 1342, 1351–1352, 1355–1356, 1358, 1359–1362
body dysmorphic disorder, 1541
breastfeeding mothers, 2423–2425, 2511
clinical trial methodology, 2439
cocaine dependence, 2410
cognitive and behavioral therapies combination, 1937, 1938
cognitive and behavioral therapies comparison, 1936
combined treatments, 1312–1313, 2434–2435
continuation treatment, 1302–1303, 2148
costs, 2128
cyclic AMP-CREB cascade agents, 347
dementia management, 2554, 2557
depressive personality disorder, 1749
development of new agents, 2130–2131, 2152–2155
discontinuance, 2148–2149
dosage recommendations, 1306
drug-drug interactions, 2141–2143
early/preresponse period, 2147–2148
eating disorders, 1617–1618, 1622, 1624
efficacy determination, 2128–2130
elderly adults, 2559
elderly patients, 1291–1292, 2143
future pharmacotherapies, 2152–2155
history, 2123
hypersomnia, 1641
increased hippocampal neurogenesis, 349–350
indications, 2131–2132
intellectual disability treatment, 737
kleptomania treatment, 1673
lactating mothers, 2424, 2511
latency of effects, 2124
maintenance period, 2149–2150
mechanisms of action, 2123–2124, 2224, 2225
medically ill patients, 2143–2145
mood stabilizer combinations for bipolar disorder, 2210–2211
narcolepsy, 1639
neuroprotection, 1351–1352
neurotrophic factor expression, 348
nicotine dependence, 2408
non-pharmacological, 1342
outcome assessment, 2150
pain/pain disorder treatment, 1533, 1534
patient preparation, 2135–2143
perinatal toxicity, 2508
postpartum women, 2424, 2511
pregnancy, 1366, 2418–2421, 2425–2426
recommendations for use, 2151–2152
S-adenosyl-L-methionine comparison, 2323
schizoaffective disorder treatment, 1268
schizophrenia treatment, 1258–1259
selection, 2132–2134
side effects, 1304–1307, 1342, 1359–1362, 2226
starting doses, 2146–2147
substance use disorder/mood disorder comorbidity treatment, 2391–2392
suicide link, 2519
suicide protection, 2484–2485
switching, 2380–2384
taxonomy, 2124, 2128
treatment formulation, 2131–2143
treatment phases, 2147–2150
treatment-resistant depression, 1312–1315, 2150–2151, 2378–2386
trichotillomania treatment, 1692, 1693–1694
use in other disorders, 2131–2132
vascular dementia treatment, 911
Antiepileptic drugs (AEDs)
attention deficit-disruptive behavior disorders, 821
autistic disorder, 789
bipolar disorder, 2208–2209, 2215–2217
Antihistamine medication
acute neuroleptic-induced dystonia, 1776
insomnia, 1636–1637, 2260
Antimanic medication *See* Mood stabilizing medication
Antioxidants, Alzheimer's disease, 2311
Antiparkinsonian medication, 1778
Antipsychotic drugs (APDs), 2161–2193
*See also* Atypical antipsychotics; First generation antipsychotics; Second generation antipsychotics
adverse effects, 1247–1249, 1251–1255, 1257, 2184–2192
aggression treatment, 2609–2610
Alzheimer's disease treatment, 907
anxiety disorders, 2226, 2228
autistic disorder, 789
bipolar disorder, 2172
borderline personality disorder, 2172
breastfeeding, 2425
brief psychotic disorder, 1269
cardiovascular effects, 2190–2191
childhood schizophrenia, 2173–2174
concomitant psychotropic medications with, 1258–1259
conditions treated, 2170–2174
costs, 2192
delusional disorder, 1274
dementia management, 2556–2557
depolarization inactivation, 2165
depression treatment, 1314–1315, 2171
development history, 2161–2162
diabetes, 2185, 2189
discontinuance, neuroleptic malignant syndrome, 1788
dopamine receptor modulation, 2162–2163
dose, 2179–2181
drug-drug interactions, 2183, 2184
dyslipidemia, 2185, 2189
endocrine effects, 2188
extrapyramidal symptoms, 2184–2187
future directions, 2192–2193
gastrointestinal effects, 2191
gene expression effects, 2165–2166
generalized anxiety disorder, 2232–2233
hematological effects, 2191
hepatic effects, 2185, 2191
history, 1821, 1830–1831
Huntington's disease, 2173
hypotension, 2185, 2190, 2501
intellectual disability treatment, 737–738
intracellular signal transduction, 2165–2166
lactating mothers, 2425
long-acting formulas, 2182
maintenance treatment of schizophrenia, 2181–2182
major depression with psychotic features, 2171
mechanisms of action, 2162–2166
medication-induced tardive dyskinesia treatment, 1785
metabolic syndrome, 2189–2190
neuroleptic malignant syndrome, 1788, 2187–2188
neuroplasticity, 2166

neuroprotective effects, 2166, 2167
neurotransmitter receptor affinities, 2164
*N*-methyl-D-aspartate receptor agonists, 2165
obesity, 2188–2189
obsessive-compulsive disorder, 2247
ocular effects, 2191–2192
panic disorder, 2240
Parkinson's disease, 2173
perinatal toxicity, 2508
pervasive development disorders, 2174
pharmacology, 2166–2170
phencyclidine intoxication, 1097
plasma levels monitoring, 2183
post-traumatic stress disorder, 2243–2244
pregnancy, 2183–2184, 2421–2423, 2508, 2509
psychosis causing, 933
QTc prolongation, 1244
quality of life, 2177
route of administration, 2177–2179
schizoaffective disorder treatment, 1267–1268, 2170–2171
schizophrenia animal models, 279, 280
schizophrenia treatment, 1241, 1244, 1247, 1258–1259, 2170–2171, 2173–2183
sedation, 2185, 2192
seizures, 2185, 2192
selection, 2179
serotonin receptor modulation, 2163, 2165
sexual effects, 2188
side effects, 1247–1249, 1251–1255, 1257, 2184–2192
stereotyped movement disorder, 892
substance-related disorders, 2172
suicidal behavior, 2177, 2485
Tourette's disorder, 2172
treatment resistance, 2182–2183
trichotillomania treatment, 1692–1693
weight gain, 2185, 2188–2189
Antipsychotic-induced movement disorders, 1773–1791
Antireward systems, substance dependence, 370
Antisocial behavior
across the life span, 496, 497
monoamine oxidase A genetic effects, 176
Antisocial personality disorder (ASPD), 1730–1733
aggression/violence link, 2605, 2607
alcohol use disorders comorbidity, 986, 987, 988, 997
cocaine use disorders comorbidity, 1080
comorbidity, 1663–1664, 1722
developmental interlineal decalage, 107
differential diagnosis, 1719, 1730, 1738
DSM-IV-TR criteria, 1730
epidemiology, 1720
etiology/pathophysiology, 1731–1732, 1736
genetics, 1667
hallucinogen intoxication, 1105
impulsivity, 1658
somatization disorder relationship, 1520, 1521
substance use disorder comorbidity, 362, 986, 987, 988, 997, 1080
treatment, 1732–1733
violent behavior, 1661–1662
Anxiety, 609–613
affecting medical conditions, 1757
animal models, 280–281, 285–286, 321–326
anxiety-like symptoms in medical disorders, 627
attentional disruption, 436–437
autism, 381–382
avoidant behavior, 646
bereavement-related, 2523
brief psychotherapies provoking, 1890, 1894, 1899
cancer patients, 2501–2502
depression relationship, 340
etiology, 610–611
evaluation of pregnant women, 2507–2508
expression, 609–613
fecal retention, 876
Freud, 471
general approach to medication use, 2223–2224
generalized anxiety disorder relationships, 1495
heart disease patients, 2500
hyperthyroidism, 932
male erectile disorder, 1587–1588
physical manifestations, 622–624
rumination disorder, 841
selective mutism, 879, 884
sexual pain disorders, 1592–1593
theories, 612
Anxiety/depression/somatoform comorbidity, 651, 652
Anxiety disorders
*See also* Anxiolytic drugs; Generalized anxiety disorder; Panic disorder; Social phobia; Specific phobias
abuse victims, 2586–2587
adolescents, 500–501, 502
alcohol-induced anxiety disorder, 978
alcohol use disorders comorbidity, 986–987, 993–994
amygdala function, 325–332
animal models, 324–325, 326–327, 330–331
antidepressant medication, 2224–2225
Asperger's disorder comorbidity, 793
attention-deficit hyperactivity disorder comorbidity, 2282
caffeine-induced anxiety disorder, 1033–1035
caffeine use disorders comorbidity, 1021–1022
cannabis-induced anxiety disorder, 1047
in childhood, 154, 158, 494–495, 683–684, 879–885
clinical presentation, 611–613
cognitive and behavioral therapies, 1938–1939
cognitive model, 1921–1922, 1923
combined treatments, 2433–2434, 2435–2437
comorbidity patterns, 1398
complementary medicine, 2319, 2326–2327, 2332–2335
cultural factors, 651–652
depression, 1285, 1289
developmental perspectives, 328–329
diagnostic classification, 318, 675, 683–684
differential diagnosis, 1416–1418
DSM classification systems, 318, 675
dying patients, 2518
early adulthood, 505–506
elderly adults, 514
emotional regulation, 326–327
environment/gene interactions, 329–332
general features, 319–320
general medical condition-related, 940–942
genetic epidemiology, 260–261
genetic factors, 320–321, 329–332
heritability, 1421–1422
history, 318–319
hypnosis, 1989, 1993–1994
insomnia, 2261
intellectual disability, 729–730
manic-depressive disorder comorbidity, 1344, 1365
middle adult life, 510
mood disorder comorbidity, 496
motivation and interpretive biases, 446–447
neurobiology, 317–332
neuroimaging, 327–328
obsessive-compulsive disorder comorbidity, 1449
obsessive-compulsive disorder differential diagnosis, 1451, 1745
onset ages, 419, 421, 1415, 1416, 1417, 1497
panic attack types, 613
pathophysiology, 325–328
premenstrual dysphoric disorder differential diagnosis, 1380
psychiatric disability, 2059–2060
psychotherapy efficacy, 292–293
school-age children, 154, 158

Anxiety disorders *(Continued)*
separation anxiety disorder, 879–883
somatoform disorder relationship, 1511, 1520, 1536–1537, 1538, 1540
substance abuse/dependence comorbidity, 361–362
suicide, 2480–2481
traumatic stress disorders, 1472–1493
treatment-resistant depression, 2378
trichotillomania, 1687, 1689
violence link, 2605
vulnerability, 328
Anxiety Disorders Interview Schedule (ADIS), 1413, 1496
Anxiolytic drugs, 2223–2248
*See also* Sedative-hypnotics
abuse, 1186–1198
adjustment disorders, 1712
animal models, 322–323
avoidant personality disorder, 1741
efficacy, 2224
extinction of conditioning blocking, 324
generalized anxiety disorder, 2228–2233
intellectual disability treatment, 739
obsessive-compulsive disorder, 2244–2248
pain treatment, 1533
panic disorder, 2236–2240
pharmacologic properties, 2229–2230
post-traumatic stress disorder, 2240–2244
social anxiety disorder, 2233–2235
trichotillomania treatment, 1692, 1694
Anxiolytic-induced sleep disorder, 1653
APA *See* American Psychiatric Association
Apathy, 617, 2558
APDs *See* Antipsychotic drugs
Aphasia, 396, 596, 597, 796, 898–899
Apnea *See* Sleep apnea
Apnea-hypopnea index (AHI), 1641
Apoptosis, 1222
APP *See* Amyloid precursor protein
Appearance at clinical interview
adaptive functioning assessment, 641–642
Mental Status Examination, 528
schizophrenia patients, 1234
Appearance-reality distinction, 138–139
Appetite suppression, 2277
Appraisal model of emotion, 606–607
Approach-avoidance conflict, 280–281
Apraxia, 899
'A priori' animal modeling, 284–286
Arabic world history, 207–208
Arendt, Hannah, 461
Aripiprazole
bipolar maintenance therapy, 2217, 2218
bipolar mania, 2207, 2210
chemical structure, 2168
dosing parameters, 2178
pharmacology, 2170
rapid cycling bipolar disorder, 2219
schizophrenia, 1245
tic suppression, 858
Army Alpha/Beta Tests, 588
Arousal states
delirium, 919
newborns, 117
panic attacks, 687
post-traumatic stress disorder, 1473
sexual, 1586–1589
Arson, 1674
*See also* Pyromania
Arthritis, 2322
Artificialism, 138
ASD *See* Acute stress disorder; Autism spectrum disorders
ASDI *See* Acute Stress Disorder Interview
ASDS *See* Acute Stress Disorder Scale
Ashwaganda (*Withania somnifera*), 2339
ASPD *See* Antisocial personality disorder
Asperger, Hans, 223, 379
Asperger's disorder (AD), 380, 791–795
autistic disorder differential diagnosis, 787
diagnosis, 791–794
DSM-IV-TR criteria, 791
etiology and pathology, 794
history, 223
treatment, 794–795
Asphyxia
restraint and seclusion, 2492
sexual masochism, 1604
ASRS *See* Adult ADHD Self-Report Scale
Assertive Community Treatment (ACT), 1263–1264, 1268
case management models, 2067–2068, 2070
initial disposition, 544
mentally ill homeless people, 2527
psychiatric rehabilitation, 2062, 2067–2070
Assessment
alcohol use disorders, 974–983
behavioral medicine, 2040
change over time, 560–561
children/adolescents, 546–554
clinical interview, 641–642
clinician-patient relationship, 22
cognitive capacities/deficits, 560
correctional settings, 2596
generalized anxiety disorder, 1496
higher level processes, 595
neuropsychological, 556–567
psychiatric interviews, 33–51
specific/social phobias, 1413–1414
standardized instruments, 548–549
Assessment disorders, 649
Assessment of risk *See* Risk assessment
Associated symptoms
generalized anxiety disorder, 1494–1495
schizophrenia, 1250
Association studies
ADHD, 814
genetic epidemiology, 257, 264–265, 269
schizophrenia, 1212–1215
Associative play, 144
Asthma, 1764, 2004–2005
Asylums *See* Institutions
*Ataque de nevios*, 652, 653, 655
Atlanto-axial instability (AAI), 697
Atomoxetine (ATX), 819–820, 824, 861–862
Atrophy, 348, 904–905, 910, 2124
Attachments
*See also* Reactive attachment disorder; Separation; Separation anxiety disorder
bereavement, 2520–2521
clinician-patient relationship, 22
couples therapy, 1963–1980
falling in love, 1966
feeding disorders, 836
infant development, 110–111, 122–124, 125, 127
infant risk factors, 128–129, 130
insecure attachment in childhood, 628, 836
narcissism, 469
object relations theory, 475
somatization, 628
working models, 2520
Attachment theory, 22, 110–111, 291, 881
Attempted suicide, definition, 2478
Attention
attentional biases, 435–436, 615
attentional capture, 435
attentional filters, 435
brain regions involved, 436
cognitive psychology, 435–440
deficits
automated routines, 249
depression, 251
learning disorders, 750
prefrontal cortex dysfunction, 251
psychiatric disorders, 435–437
schizophrenia, 251
effective listening, 8
executive control, 437–438
hypervigilant states, 583
neural basis, 435
prefrontal cortex role, 250–251
qualitative focus changes in consciousness, 584
schizophrenia, 1232, 1235
Seeking, 841
therapeutic intervention targets, 437
threat responses, 326
top-down control, 437–440
Attentional-deficit disorder (ADD)
anxiety disorders relationship, 326
cognitive enhancement, 2340
Attention deficit-disruptive behavior disorders (AD-DBDs)
assessment, 807–811
comorbidity, 811–812, 823–824
epidemiology, 811

genetic factors, 813–814
psychosocial treatments, 822–823
rating scales, 807–809
somatic treatments, 817–821
stimulants, 2264–2288
Attention-deficit hyperactivity disorder (ADHD), 804–826
autistic disorder comorbidity, 785
cannabis use, 1055
childhood problems, 496–497
cocaine use disorders comorbidity, 1079–1080
cognitive assessment scores, 550
comorbidity, 769, 773, 893
complementary treatments, 2341–2342
definition, 804–805
differential diagnosis, 812–813, 894
effortful control disruption, 157, 158
epidemiology, 811
genetic factors, 814
intellectual disability, 724–725
learning disability comorbidity, 752, 755, 756, 761
manic-depressive disorder comorbidity, 1366
medication compliance, 2456–2457
natural course, 812
neurobiological factors, 814–816
neurochemical basis, 2267
neuropsychological analyses, 562
pathological gambling comorbidity, 1681
psychological factors, 816
smoking, 1152
social/environmental factors, 816–817
tic disorder comorbidity, 849–850, 851, 857, 858–859, 861–862
Attention-deficit hyperactivity disorder Rating Scale (ADHD-RS-IV), 807, 808
Attitudes
effective listening, 8–10
ethnic/cultural issues in psychopharmacology, 2113
of interviewer at clinical interviews, 43
of patient at clinical interview, 642
schemas, cognitive model, 1922–1923
of schizophrenia patients, 1234
to intellectual disability, 709–712
to medication/compliance, 2453
to sexual issues, 1578–1579, 1606
Attributable risks, 406
Attributional style, cognitive model, 1923
Attribution theory, social psychology, 455–456, 461
ATX *See* Atomoxetine
Atypical antipsychotics
*See also* Second generation antipsychotics
acute bipolar depression, 2211–2213
acute mania treatment, 2205–2208
acute neuroleptic-induced akathisia, 1779, 1780
antidepressant treatment augmentation, 2151
attention deficit-disruptive behavior disorders, 821
autistic disorder, 789
bipolar maintenance therapy, 2217–2218
dementia management, 2556–2557
depression treatment, 1314–1315
intellectual disability treatment, 737–738
lactating mothers, 2425
neuroleptic-induced Parkinsonism, 1777
pregnancy, 2420, 2421–2422
rapid cycling bipolar disorder, 2219
tardive dyskinesia risk, 1782
treatment-resistant depression, 2384
Atypical depression
abuse victims, 2586
features, 1289
treatment-resistant, 2378
Atypical eating disorders, 1609, 1620
AUDIT *See* Alcohol use disorders identification test
Auditory evoked response potentials (AERPs), 2010
Auditory perception
age effects, 199–200
central auditory processing disorder, 769
hearing/listening distinction, 5–6
hearing tests in autistic disorder, 784
inhalant-related damage, 1136, 1137
pragmatic social skill difficulties, 757
Augmentation strategies for depression, 1312, 1313–1315, 2151, 2382, 2437–2438
Autism
age-specific vulnerabilities, 106, 107
alternative medicine, 388
behavioral aspects, 380, 387
childhood problems, 494
comorbid features, 381–382
developmental mechanisms, 382–385
diagnosis, 380–381
differential diagnosis, 894
epidemiology, 379–380
genetics, 382–385
history, 222–223
intellectual disability, 714–715, 723–724, 738
interventions, 387–388
language disorders, 380, 770
metabolic genes, 384–385
neuropathology, 385–388
neuroscience, 379–392
preschool development, 136, 139
ritualized behavior, 380
sensory reactions, 380
signal transduction, 383–384
social cognition, 446
treatment delivery, 388
Autism spectrum disorders (ASDs)
*See also* Asperger's disorder; Autistic disorder; Childhood disintegrative disorder; Pervasive developmental disorders; Rett's disorder
disagnostic classification, 380–381
Autistic disorder, 380–381, 779–790
Asperger's disorder differential diagnosis, 793
childhood disintegrative disorder differential diagnosis, 796
diagnosis, 779–788
DSM-IV-TR criteria, 780
etiology and pathology, 788
treatment, 789–790
Autoimmunity
autism, 382
pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, 856, 1450–1451
schizophrenia, 1216
tic disorders, 856, 859
Automatic behavior
breathing related sleep disturbance, 1642
dorsal striatum role, 249–250
sleep-related eating disorders, 1650
Automatic implantable cardioverter-defibrillators (AICDs), 2500
Automatic obedience secondary to a general medical condition, 943
Automatic thoughts, 1921, 1926–1928
Automatism, 91
Autonomic nervous system
fear responses, 321, 322
generalized anxiety disorder, 1500–1501
mood disorders, 2327–2328
Autonomy of patients, 73, 75–76
Autosomal inheritance of intellectual disability, 699–702
Aversive picture attention/reappraisal, 327
Aversive techniques, 841, 1161
Avicenna, 207
Avoidant behavior, 645–646
Avoidant personality disorder (AVPD), 1740–1742
diagnosis, 1418
differential diagnosis, 1726–1727, 1728, 1740
DSM-IV-TR criteria, 1740
Axis I disorders
biogenic spectrum model, 639
comorbidity, 1725
couples therapy, 1972
differential diagnosis, 1733

Axis I disorders *(Continued)*
impulse control, 1689
personality disorders as, 1720, 1722–1723
relational problems, 1803
treatment, 1727, 1735, 1747
Axis II disorders
biogenic spectrum model, 639
relational problems, 1803

BA *See* Behavioral activation
Baclofen, 2410
Bacon, Francis, 210
'Bad historians', versus 'bad listeners', 4, 8, 9
Balanced Budget Act (BBA), 1838
B-amyloid protein, 905
Barbiturates
abuse, 1187, 1188
anxiety therapy, 2223
Barkley Current Symptoms Scale, 810
Barriers to change, strategic therapies, 1897
Basal forebrain, 365–366
BASC-2 *See* Behavioral Assessment Scales for Children
Baseline level of functioning, 34, 37
'Basic rule', free association, 1856
Battie, William, 212
Bazelon Centre for Mental Health Law, 2085, 2086
BBA *See* Balanced Budget Act
BBB *See* Blood-brain barrier
BDD *See* Behavioral disturbance in dementia
BDNF *See* Brain-derived neurotrophic factor
Beaded methylphenidate (B-MPH), 2264, 2281
Beck, Aaron T., 1920–1922, 1923, 1926
Behavior
adaptive functioning, 633–646
assessment, 641–642, 810–811
clinical interviews, 641–642
cyclical changes, 728–729
infant development, 114
Mental Status Examination, 528
prefrontal cortex role, 250–251
preschool development, 137
Behavioral activation (BA), 1924, 1938
Behavioral Assessment Scales for Children (BASC-2), 807, 808
Behavioral disturbance in dementia (BDD), 396, 900, 2172–2173, 2554–2557
Behavioral endophenotypes
animal models, 278–279
intellectual disability, 716–718
Behavioral flexibility, 249, 250–251
Behavioral genetics, 340–341
Behavioral inhibition, 328–330, 1426
Behavioral managed care, 1841–1842
Behavioral marital therapy (BMT), 991, 1804
Behavioral medicine, 2027–2043
AIDS, 2035
beginning, 2029–2030
cancer, 2036–2037
chronic pain, 2035–2036, 2041–2043
definition, 2029–2030
future technology, 2038–2039
historical foundations, 2028–2029
HIV, 2035
lifestyle modifications, 2033
multidisciplinary approaches, 2037–2038
palliative care, 2037–2038
practice of, 2039–2041
preventative measures, 2033
selected health issues, 2032–2039
somatoform disorders, 2034–2035
theoretical foundations, 2030–2032
unexplained medical symptoms, 2034–2035
Behavioral models
cognitive psychology impact, 433
history, 220, 221, 222, 225
new antidepressant development, 2130
post-traumatic stress disorder, 1479
Behavioral momentum, 837
Behavioral naltrexone therapy (BNT), 2406–2407
Behavioral Pediatrics Feeding Assessment Scale, 833–834
Behavioral problems
adolescents, 501–502, 1805
autism, 380, 387
childhood, 496–497
dementia, 396, 900, 2172–2173, 2554–2557
early adulthood, 506–508
intellectual disability, 693, 715–718, 719, 722, 724–725
learning and motor disorder association, 750, 752, 756
maladaptive functioning, 642–646
schizophrenia patients, 1234
substance abuse, 960, 961
treatments for AD, 2305
Behavioral rebound, stimulants, 2278
Behavioral responders, anxiety treatments, 1434
Behavioral rhythms, infant development, 113–115
Behavioral rigidity, 249, 793
Behavioral tests for phobic disorders, 1414–1415
Behavioral therapy
*See also* Cognitive and behavioral therapies; Cognitive-behavioral therapy
attention deficit-disruptive behavior disorders, 822
autistic disorder, 790
brief psychotherapies, 1890, 1896
cognitive-behavioral therapy comparison, 1939
cognitive-behavioral therapy shift, 434
conversion disorder, 1529
dialectical, 293, 1667, 1734–1735, 2485
eating disorders, 1939
efficacy studies, 292
encopresis, 878
encouraging opioid abstinence, 2402, 2406
exposure-based therapies, 1896
feeding disorder of infancy or early childhood, 838
insomnia, 1635–1636
intellectual disability, 740–741
kleptomania, 1674
learning and motor skills disorders, 760
obsessive-compulsive disorder, 1463–1465
opioid detoxification, 1179
pharmacotherapy combination, 2396–2397, 2406–2407
premature ejaculation, 1592
psychosocial rehabilitation, 2063–2064
pyromania, 1677
selective mutism, 884
separation anxiety disorder, 881–882
smoking cessation, 1160–1163
social skills training, 2063–2064
stereotyped movement disorder, 892
substance dependence, 2396–2397, 2402, 2406–2407
tic disorders, 859–860
trichotillomania, 1693
Behavior exchange, 1932
Behavior management training (BMT), 1800
Behavior Rating Inventory of Executive Function (BRIEF), 807, 808
BEIP *See* Bucharest Early Intervention Project
Beliefs
*See also* religious issues
cognitive models, 1922–1923
medication compliance, 2453, 2454
Bender visual-motor gestalt test, 532, 533
Benefit limits of private insurance, 1836–1837
Benzene inhalation, 1139
Benzodiazepine antagonists, 1196
Benzodiazepine receptor agonists (BzRAs), 1636, 1637, 2256–2257
Benzodiazepines (BZs)
abuse, 1186–1198
aggression treatment, 2610
alcohol use disorders with psychiatric comorbidity, 993, 998
alcohol withdrawal, 991, 2392, 2393
animal models of fear responses, 323, 325
anxiety disorders, 325, 2225
behavioral disturbance in dementia, 2557
combination dangers, 1189, 1191
dementia treatment, 917
depression treatment, 1301

detoxification, 1195–1196
diazepam dose equivalents, 2394
direct amygdala injections, animal models of anxiety, 325
extinction of conditioning blocking, 323
GABA receptors, 1187–1188
generalized anxiety disorder, 1501, 2231–2232
history, 1186
HPPD treatment, 1112
insomnia, 1636, 1637, 2257
intellectual disability treatment, 739
lactating mothers, 2424
obsessive-compulsive disorder, 2246
opioid detoxification, 2398, 2400
panic disorder, 2239
perinatal toxicity, 2508
pregnancy, 2423, 2509
receptor sensitivity, 325
schizophrenia treatment, 1246
social anxiety disorder, 2235
tic suppression, 859
violence link, 2606
withdrawal, 1192–1193, 2394, 2333
Bereavement
attachment security, 2520–2521
depression, 613
disaster-related, 2469
grief, 2519–2523
social psychology, 456–457
suicide, 2519
Bergler, Edmund, 1685
Best practice, restraint and seclusion, 2493
Beta-adrenergic blockers (beta-blockers)
aggression treatment, 2611–2612
anxiety disorders, 1427, 1429, 2226
intellectual disability treatment, 739
medication-induced postural tremor, 1789, 1790
obsessive-compulsive disorder, 2246
post-traumatic stress disorder, 2242
PTSD treatment, 1481–1484
social anxiety disorder, 2235
Beta-adrenoreceptors, 2124
Beta bands, 566
Between session relistening/reprocessing, 13
Bezoars, 843
Bias
anti-homosexual, 2539
attention, 435–436
emotionally-based, 41
epidemiological studies, 407, 409–410
ethnic/cultural issues in psychopharmacology, 2113
evidence-based medicine, 1355
forensic psychiatry, 70
sexual issues, 1579
Bibliotherapy, 1590–1591
BICEPS (brevity, immediacy, centrality, expectance, proximity, and simplicity), 1711
Bifeprunox, 2168, 2170
Bilateral electroconvulsive therapy (BL ECT), 2359, 2360
Binet, Alfred, 690
Binge-eating disorder, 503, 1623–1624
Binge-eating with purging, 1611, 1618–1622, 1624–1625
Binging
cocaine, 1060, 1064
eating disorders, 503, 1611, 1618–1625
impulsive behavior, 643, 644
substance use, 357, 1060, 1064
Bioavailability of drugs, 2100
Biofeedback therapy, 878, 2040–2041
Biogenic spectrum model, 639
Bioinformational approach to emotion, 606, 607
Biological development
adolescents, 161, 163–168
adults, 183–184
elderly adults, 197–201
infants, 113–115, 118–119, 121, 124
longitudinal studies, 98–100
preschool, 136–138
school-age children, 151–152, 153
Biological factors
*See also* Neurobiological factors
commonalities in psychiatric disorders, 245–253
drug responses, 2115–2120
historical understanding of mental disorders, 206, 213, 220, 224
homosexuality, 2540–2541
human couples, 1966
psychiatric disorders, 33–37, 245–253
psychotherapy, 295–297
schizophreniform disorder, 1271
sexual function, 1581, 1582, 1587
violence/aggression, 2605–2608
Biological intervention planning, 544
Biological processes, dissociation, 1573
Biological rhythms
*See also* Circadian rhythms
bipolar disorder, 1352, 1353
depressive disorders, 1295–1296
infant development, 113–115
Biomedical assessment of intellectual disability, 706–708
Biopsychosocial models, 1354, 1362, 2030–2031
Bipolar disorder, 1335–1367, 2202–2220
across the life cycle, 1366–1367
acute depression, 1336, 1339, 1356, 2210–2214
acute mania, 1336, 1337, 1339–1340, 1356, 2203–2210
antidepressants, 1359–1361, 2140, 2210–2211
antipsychotic drugs, 2172, 2205–2208
attention deficit-disruptive behavior disorders comorbidity, 811
chronic care models, 1362, 1365, 1367
clinical outcome, 1345–1346, 1354
cognitive and behavioral therapies, 1362, 1363, 1364, 1939–1940
cognitive-behavioral therapy, 1940
comorbidity, 1343–1345, 1365, 1663
complementary medicine, 2319, 2325, 2333
course, 1345–1347
cyclothymic disorder, 1336, 1338
Depression and Bipolar Support Alliance, 2085, 2088–2089
diagnosis, 1336–1341
differential diagnosis, 1347
DSM-IV-TR, 1337, 1338, 1340
early adulthood, 505
ECA study, 416–417
electroconvulsive therapy, 2360, 2361
epidemiology, 1343
euphoria, 617
functional outcomes, 1346–1347, 1354
gene identification, 265–266
genetic epidemiology, 260
genetic factors, 342, 1343, 1348–1350
group psychotherapy, 1916
history of ideas, 215, 221, 225, 1335–1336
ICD-10, 1340
insomnia, 2261
interpersonal psychotherapy, 1882
learning and motor skills disorder comorbidity, 755
lithium compliance, cognitive-behavioral therapy, 1939
maintenance treatment, 2214–2219
manic episodes, 1336, 1337, 1339–1340, 1356, 2203–2210
medical assessment, 1341–1343
medical precipitants of symptoms, 1341–1342, 2140
medication compliance, 2456
mood disorder classification, 339, 340
mood stabilizers, 1355–1359, 2202–2220
pathophysiological hypotheses, 1348
phenomenology, 1338–1340
psychiatric disability, 2059–2060
psychotherapy, 1362
psychotic features, 1238, 1337, 1339, 1340
rapid cycling, 1340–1341, 2218–2219
rating scales, 1342–1343
relational problems, 1806
sleep disturbance relationship, 1634
social/environmental factors, 1353–1354
speech disorders, 596
suicide protection, 2484

Bipolar disorder, *(Continued)*
treatment, 1354–1367
treatment-resistance, 1365, 2375–2376
types I and II, 1336–1338
use of term, 1336
violence link, 2605
Bipolar-type schizoaffective disorder, 1266
Birth
*See also* Low birth weight
adverse birth outcome causes, 2417–2423
complications in schizophrenia, 1216–1217
prematurity effects, 130, 834, 835, 836
season affecting schizophrenia risk, 1210, 1271
Bisexuality, 1979, 2541
Blackouts, 926
Bladder control *See* Enuresis
BL ECT *See* Bilateral electroconvulsive therapy
Bleuler, Eugen, 1202
Blinded trials, 407, 409–410, 2319, 2321
*See also* Clinical trials; Placebo...; Randomized controlled trials
Block design problem solving, 563
Blood-brain barrier (BBB), 2100, 2101
Blood cultures, 535
Blood dyscrasias
anorexia nervosa, 1613
antidepressant drugs, 1306
antipsychotic drugs, 2191
Blood electrolyte imbalance, bulimia nervosa, 1619
Blood flow in brain imaging, 574–576
Blood glucose assessment, 534–535
Blood-injury-injection phobias, 1411, 1412
Blood testing
laboratory assessment, 533–536
medication compliance measurement, 2450
Blunted affect, 603, 604
'Blunts', 1042, 1091
B-MPH *See* Beaded methylphenidate
BMT *See* Behavioral marital therapy; Behavior management training
BNT *See* Behavioral naltrexone therapy
Body dysmorphic disorder, 1538–1542
adolescents, 503
course, 1540
definition/diagnostic features, 1538–1539
differential diagnosis, 1540–1541
DSM-IV-TR criteria, 1539
epidemiology, 1539
obsessive-compulsive disorder differential diagnosis, 1452
obsessive-compulsive spectrum disorders, 1453
physical signs and symptoms, 630
treatment, 1541
Body image
adolescent problems, 502–503
anorexia nervosa, 1611
bulimia nervosa, 1618, 1619
distortions, 602, 604
Body odour, delusions, 1273
Body temperature-sleep relationship, 1628
Body type/psychological relationship, history of ideas, 219, 221, 223
Bone effects in anorexia nervosa, 1613
Bone marrow transplantation, 2503
Borderline, historical use of term, 223
Borderline personality disorder (BPD), 1728, 1733–1735
antipsychotic drugs, 2172
comorbidity, 1663–1664
differential diagnosis, 1733, 1743
dissociative identity disorder comorbidity, 1566
DSM-IV-TR criteria, 1733
epidemiology, 1720, 1733
history of understanding, 223, 224, 225
impulsivity, 1658
psychotherapy efficacy, 292–293
splitting theory, 476
suicide, 2481
treatment, 1734–1735
violent behavior, 1661–1662
Boston approach to evaluation, 562–563
Boston Psychotherapy Study, 294–295
Boston University (BU) approach to psychosocial rehabilitation, 2064–2065
*Boufee delirante*, 1269
Boundaries
couples therapy, 1974
couples within families, 1967
definition issues in adjustment disorders, 1702, 1708, 1709, 1710
group psychotherapy, 1910–1911
structural family therapy, 1950
therapeutic frames, 71–79
violations, 71–73, 79, 87, 1860
Bowel control *See* Encopresis
Bowel disease, 1765–1766
Bowlby, John, 291, 475
BPD *See* Borderline personality disorder
Bradykinesia, 1778
Braid, James, 1982, 1983
Brain, *See also* Central nervous system; Cerebral...
Brain-behavior relationship, 246
Brain circuitry neuroadaptation
multiple psychiatric disorders, 247–253
substance use disorders, 368–371, 2390
Brain damage/injury/lesions
aggression/violence link, 2607–2608
emotional regulation deficits, 607
historical case, 218, 219
learning and motor skills disorders, 755, 757–758
memory deficits, 585
speech disorders, 596, 597
Brain-derived neurotrophic factor (BDNF)
animal maternal behavior effects, 330
antidepressant development, 2154
depression theories, 2124
mood disorder neuropathology, 342, 343, 347–349, 350
Brain development
adolescents, 168, 171
growth, 98, 99
preschool, 136–138
Brain function
anatomical abnormalities, 34
brain stimulation studies, 2358
early views, 206, 208
electrical activity/hypnotizability, 2008–2011
neuropsychological assessment, 556–567
psychiatric disorders, 35–36
Brain imaging, 570–581
anxiety disorders, 1423
attention-deficit hyperactivity disorder, 815, 2267
clinical use, 579–580
dementia, 394
detecting abnormalities, 579
diffuse optical imaging, 579
functional modalities, 573–580
history, 231
hypnotic states, 2011–2012
intermittent explosive disorder, 1667
laboratory assessments, 537–538, 540
magnetoencephalography, 579–580
neurophysiological assessment, 564
psychotherapy studies, 295–297
schizophrenia, 303–304, 311–312, 1217–1224
schizophreniform disorder, 1271
structural modalities, 570–573, 579
treatment-resistant depression, 2386
Brain regions
*See also* Phrenology
Attention Deficit/Hyperactivity Disorder, 815
cognitive psychology, 436, 444, 445
consciousness interactions, 586
intermittent explosive disorder, 1667
separation anxiety disorder, 880
Brain reward system, substance abuse disorders, 1061, 1062, 2390
Brain stem evoked potentials (BSEPs), 566
Brain stimulation, 2354–2368

*See also* Deep brain stimulation; Electroconvulsive therapy; Magnetic seizure therapy; Transcranial direct current polarization; Transcranial electrical stimulation; Transcranial magnetic stimulation; Vagus nerve stimulation
acute versus chronic effects, 2356–2357
adverse effects, 1316, 2359–2360, 2362–2363, 2364, 2366
antidepressant treatment augmentation, 2151
brain function studies, 2358
deep brain stimulation, 909, 2354–2358, 2367–2368
electrical stimulation, 2354–2361, 2365–2368
history, 211, 221, 2354, 2356, 2358–2359, 2361–2362, 2364
magnetic stimulation, 2354, 2355, 2361–2365
mechanisms of action, 2354–2355, 2359, 2362, 2364
neuroplasticity, 2356–2357
pharmacology comparison, 2355–2356
techniques, 2358–2368
Brain structure
anatomical abnormalities/function relationship, 34
Attention Deficit/Hyperactivity Disorder, 815
autism, 385–386
Freud, 290
hemispheres and emotions, 606
historical understanding, 213, 217, 220, 223, 225
schizophrenia, 311
Brain tumors, 2502
Brain waves, 1627, 2009, 2327–2328
Breast cancer, 2502
Breast development (thelarche), 164–166
Breastfeeding
antidepressants, 1293, 2511
methadone, 1182
mood stabilizers, 2511
pharmacotherapy use, 2423–2425
Breathing control
behavioral therapy, 1931–1932
yoga, 2326, 2328–2331, 2332
Breathing related sleep disturbance (BRSD), 510, 1641–1643
DSM-IV-TR criteria, 1642
Breath Water Sound (BWS), 2331
Brenner, Charles, 472–473
Breuer, Joseph, 289, 1559, 2028
Brevity, immediacy, centrality, expectance, proximity, and simplicity (BICEPS), 1711
BRIEF *See* Behavior Rating Inventory of Executive Function
Brief psychotherapies, 1889–1901, 1860, 1869
activity and direction, 1899–1900
change process, 1900
efficacy, 1891–1893
focus, 1889, 1899
group psychotherapy, 1915
history, 1889–1891
interpersonal counseling, 1882, 1883–1884
interpersonal psychotherapy, 1875, 1876, 1877–1878
models, 1893–1898
patient selection, 1890, 1898–1899
short-term anxiety-provoking psychotherapy, 1890
short-term dynamic psychotherapy, 1867
short-term psychoanalytic psychotherapy, 1867, 1868, 1869
Brief psychotic disorder, 1268–1270
diagnosis, 1268–1269
DSM-IV-TR criteria, 1237, 1268, 1278
ICD-10/DSM-IV-TR diagnosis comparison, 1278
treatment, 1269–1270
Bright light therapy
pregnancy, 2509
premenstrual dysphoric disorder, 1387
seasonal affective disorder, 1316
Briquet's syndrome, 1513, 1514
*See also* Somatization disorder
Brofaromine, 2234, 2242
Broker case management model, 2068
Bromocriptine, 1788
Brown Attention-Deficit Disorder scales, 808, 810
BRSD *See* Breathing related sleep disturbance
Bruner, J., 141
BSEPs *See* Brain stem evoked potentials
BU *See* Boston University
Bucharest Early Intervention Project (BEIP), 893–894
Buddha, 205–206
Budgetary advocacy, 2084
Bufotenine, 1101
Bulimia nervosa, 502–503, 1618–1623, 1624–1625
assessment, 1619
course, 1620
definition, 1618–1619
DSM-IV-TR criteria, 1618
etiology/pathophysiology, 1620–1621
history, 207
interpersonal psychotherapy, 1875, 1883
sleep disturbance, 1650
treatment, 1621–1623, 1939
Buprenorphine
benzodiazepine abuse combination, 1189
opioid agonist pharmacotherapy, 1175, 1176, 1177, 1178, 2403–2405
Bupropion, 1310–1311
attention deficit-disruptive behavior disorders, 820, 862
availability, 2128
breastfeeding, 2425
cannabis withdrawal, 1055
cardiovascular patients, 2144
cocaine dependence, 2411
depression, 2381
generalized anxiety disorder, 2231
mechanism of action, 2127
nicotine dependence, 2408
non-nicotine pill, 1151, 1158–1160, 1162
obsessive-compulsive disorder, 2246
panic disorder, 2238–2239
pharmacokinetics, 2133, 2134
post-traumatic stress disorder, 2242
pregnancy, 2420
seizure side effects, 2140
side effects, 2226
social anxiety disorder, 2235
starting doses, 2146
sustained release, 2408
tic disorders, 862
Burton, Richard, 209
Buspirone
alcohol use disorders with psychiatric comorbidity, 993–994
anxiety disorders, 2225–2226
depression treatment, 1314, 2383
generalized anxiety disorder, 2232
obsessive-compulsive disorder, 2246
panic disorder, 2239
social anxiety disorder, 2235
Buss-Perry Aggression scale, 809
Butane-type gas inhalation, 1127, 1128, 1133, 1139
Butyrophenones, 1242, 2421
B-vitamins *See* Vitamin B complex
BWS *See* Breath Water Sound
Bystander effect, 461
BzRAs *See* Benzodiazepine receptor agonists
BZs *See* Benzodiazepines

CAADID *See* Conners Adult ADHD Diagnostic Interview
CACR *See* Computer assisted cognitive remediation
CAD *See* Coronary artery disease
Caffeine
alertness mechanism, 1630
use in sleep deprivation, 1036
use in USA, 1019, 1020
Caffeine-induced sleep disorder, 1653
Caffeine intoxication, DSM-IV-TR criteria, 1019–1020

Caffeine use disorders, 1019–1037
caffeine-induced anxiety disorder, 1021, 1033–1035
caffeine-induced sleep disorder, 1021, 1035–1037
dependence, 1026, 1029–1033
intoxication, 1019–1024
withdrawal, 1024–1028, 1029, 1030, 1032
Caffeine withdrawal, DSM-IV-TR criteria, 1024
CAGE screening test, 979
Calcium, premenstrual dysphoric disorder, 1382, 1386
Calcium channel blockers, Alzheimer's disease, 2311
Calm in disaster situations, 2472, 2473
CAM *See* Complementary and alternative medicine
cAMP *See* Cyclic AMP
Cancer
antidepressants, 2144–2145
behavioral medicine, 2036–2037
female sexual arousal disorder treatment issues, 1586
genetic counseling, 2037
patient adjustment disorders, 1705, 1711
psychological factors affecting, 1760–1761, 2036–2037, 2501–2503
Candidate genes
alcohol dependence, 971–972
attention-deficit hyperactivity disorder, 814
gene identification, 266–267
Cannabis
hashish, 1041
history, 1041–1042
marijuana, 1041, 1043
Marijuana Treatment Project, 1053
MDMA concomitant use, 1116, 1117
methods of use, 1042–1043
neuropharmacology, 367
neuropsychological effects, 1043
PCP-impregnated, 1091, 1095
physiological effects, 1044
psychosocial effects, 1043
Cannabis abstinence syndrome, 2411–2412
*See also* Cannabis withdrawal
Cannabis abuse
DSM-IV-TR criteria, 1044–1045
epidemiology, 1041
Cannabis dependence
addiction patterns, 358
DSM-IV-TR criteria, 1045–1046
epidemiology, 1041
pharmacotherapy, 1054, 1055, 2411–2412
psychotherapy, 1047–1053
Cannabis-induced anxiety disorder, DSM-IV-TR criteria, 1047
Cannabis-induced psychotic disorder, DSM-IV-TR criteria, 1046–1047
Cannabis intoxication
DSM-IV-TR criteria, 1044
treatment, 1053
Cannabis intoxication delirium, DSM-IV-TR criteria, 1046
Cannabis-related disorders, 1041–1057
DSM-IV-TR criteria, 1044–1047
treatment, 1047–1055
Cannabis withdrawal, 355, 1053, 1055, 2411–2412
Cannabis Youth Treatment (CYT) study, 1052–1053
Cannon, Walter, 605–606
CAPA *See* Child and Adolescent Psychiatric Assessment
Capacity–competency distinction, 83
Capacity for treatment, 37
CAPD *See* Central auditory processing disorder
Capgras's syndrome, 1273
Carbamazepine
acute mania treatment, 2209, 2210
alcohol withdrawal, 2393
bipolar disorder, 1357–1361, 1366, 1367, 2217
breastfeeding, 2425
cocaine use disorders, 1075
IED treatment, 1667–1668
pregnancy, 1366, 2422, 2509
side effects, 1360–1362
Carbohydrates, premenstrual dysphoric disorder, 1386–1387
Carbon dioxide challenge, 880
Carbon monoxide (CO), 1139–1140, 1151
Cardiac disorders
arrhythmias, 1642, 1762–1763
breathing related sleep disturbance relationship, 1642, 1643
depression, 2558
myocardial infarction, 1065, 2558
myocarditis, 2185, 2190–2191
psychological factors affecting medical condition, 1761–1763
sexual problems after heart attack, 1980
Cardiac effects
anorexia nervosa, 1613
antipsychotic drugs, 2185, 2190–2191
cocaine use, 1065–1066
inhalant-related disorders, 1139
tricyclic antidepressants, 2140
Cardiorespiratory problems, feeding disorders in infancy, 832
Cardiovascular disease (CVD)
aggression link, 2608
antidepressants, 2144
antipsychotic drugs, 2190–2191
depression comorbidity, 1286
psychosomatic aspects, 2499–2501
psychostimulants, 819
yoga effects, 2329
Caregiving
bereavement effects, 2520–2521
dementia impact, 2553
infant development, 112, 128–129, 130, 131
reactive attachment disorder, 895
reducing burden, 1957–1958
Cartesian dualism, 209, 210
CAS *See* Child Assessment Schedule; Children's Aggression Scale
Case-control studies, 408
*See also* Clinical trials; Randomized controlled trials
Case formulation and treatment planning, 540–543
Case identification *See* Disclosure
Case management models, 1263–1264, 2067–2068, 2070
*See also* Assertive Community Treatment
Castration complex, 467
CAT *See* Cognitive adaptation training
Catalytic antibodies, 1076
Cataplexy, 1638, 1639
Cataracts, 2191–2192
Catatonic disorders
catatonia characteristics, 583–584
catatonic features of depression, 1289
general medical condition-related, 942–944
neuroleptic malignant syndrome comparison, 1786–1787
speech effects, 597
Catatonic-type schizophrenia, DSM-IV-TR criteria, 1205–1206
CATCH 22 syndrome *See* Velocardiofacial syndrome
Catecholamines, 2119–2120
Catechol-O-methyl transferase (COMT)
anxiety disorders, 321
attention-deficit hyperactivity disorder, 814
bipolar disorder susceptibility, 342
schizophrenia, 1214
Categorical models, 423, 635
Cathexis, 468
CATIE *See* Clinical Antipsychotic Trials of Intervention Effectiveness
CBF *See* Cerebral blood flow
CBGD *See* Corticobasal ganglionic degeneration
CBGT *See* Cognitive-behavioral group therapy
CBT *See* Cognitive–behavioral therapy
CCMs *See* Chronic care models
CCRT *See* Core conflictual relationship theme
CD *See* Communication deviance; Conduct disorder
CDD *See* Childhood disintegrative disorder
CDNOS *See* Communication disorder not otherwise specified
C-ECT *See* Continuation ECT
Center for Mental Health Services (CMHS), 2084, 2086, 2090, 2092, 2094

Centers for Medicare and Medicaid Services (CMMS), 734
Central amines, 344
Central auditory processing disorder (CAPD), 769
Central nervous system (CNS)
  alcohol abuse, 915
  communication disorders, 766, 767, 770, 773
  inhalant-related disorders, 1133–1136
  intellectual disability, 692–693, 695, 703
  learning and motor skills disorders, 750, 757–758
  malformation syndromes, 703
Central sleep apnea, 1642
Centration, 138
Cerebral atrophy, 910
Cerebral blood flow (CBF), 2011–2012
Cerebral degenerative disorders, 1651
Cerebral palsy (CP), 693
Cerebral tumors, 934, 945, 946
Cerebral vascular accident (CVA/stroke), 1066, 1287, 1764–1765, 2144
Cerebrolysin, 2307
Cerebrospinal fluid (CSF)
  5-HIAA levels in impulsive control, 644, 1666, 1677, 1690
  evaluation, 536
Cerebrovascular adverse events (CVAE), 2556
  *See also* Cerebral vascular accident
Certification of provider organizations, 1844
CGH *See* Comparative genomic hybridization
CGMP *See* Cyclic GMP
Chamomile, 2319, 2335
Change
  assessment over time, 560–561
  brief psychotherapies, 1900
  study design methodology, 2625–2626
  young adult development, 187
Character *See* Personality
Charcot, Jean-Martin, 216, 1559
Chasteberry, 1386
Checking compulsions, 1443, 1444, 1445, 1447
Chemical inhalant-related disorders, 1127–1142
Chemical restraints, 2609
Chemical structures of antipsychotics, 2168
Chemotherapy, 2502
Cheyne, George, 212
Chief complaint
  psychiatric databases, 38
  psychiatric interview, 526–527
Child abuse, 2576
  adult survivors, 2577, 2584
  aggression/antisocial behavior links, 176
  anxiety disorder neurobiology, 331
  childhood problems, 497
  child protection cases, 732
  communication disorders, 770, 771
  conversion disorder relationship, 1529
  dissociative disorders, 1560, 1565–1566
  factitious disorder by proxy, 1554–1556
  history of understanding, 225–226
  monoamine oxidase A genetic effects, 176
  pedophilia, 1602
  physical, infant development risk factors, 129
  sexual pain disorders, 1592, 1593
  suicide, 2481–2482
Child and Adolescent Psychiatric Assessment (CAPA), 809
Child Assessment Schedule (CAS), 809
Childbearing importance, 56–57
Child–caregiver and family patterns, 681, 682, 688
Childhood disintegrative disorder (CDD), 381, 787, 795–796
  DSM-IV-TR criteria, 795
Childhood disorders, 490–499
  anxiety disorders, 879–885
  attention deficit disorders, 804–826
  attention disorder rating scales, 807–809
  comorbidity patterns, 491–492
  disintegrative disorder, 381, 787, 795–796
  early-onset schizophrenia, 158, 303–304, 2173–2174
  elimination disorders, 498, 868–879
  encopresis, 498, 875–879
  enuresis, 498, 868–875
  feeding disorder of infancy or early childhood, 831–839
  feeding disorders, 830–844
  history, 224
  history of understanding, 214, 222–223
  pervasive developmental disorders, 779–800
  pica, 842–844
  prevalence/gender distribution, 499
  rumination disorder, 839–842
  selective mutism, 495, 883–885
  separation anxiety disorder, 879–883
  tic disorders, 847–854
Childhood experiences
  *See also* Child abuse
  adult psychopathology, 285–286
  anxiety disorders, 329–332
  clinician–patient relationship, 22, 24
  disruptive behavior disorders, 804–826
  paraphilia causes, 1601
  parental influences, 329–332
  personality styles, 634
  psychiatric databases, 39–40
  psychiatric interview, 527
  psychoanalytic psychotherapy, 1853, 1859, 1861
  psychosexual development, 465–467
  psychosocial stressors, bipolar disorder, 1353
  sexual abuse, 1529, 1592, 1593
  trauma, 628, 1560, 1565–1566
Childhood onset schizophrenia (COS), 158, 304, 2173–2174
Child protection cases, 732
Children
  *See also* Families; Parents
  adversity index for psychopathology risk factors, 106
  antipsychotic drugs, 2173–2174
  antisocial personality disorder, 1731
  anxiety, 876, 884
  at-risk of mental illness, 1956–1957, 1958
  avoidant personality disorder, 1741
  behavioral inhibition, 328–330, 611
  biological development, 98, 99, 151–152, 153
  bipolar disorder, 1348, 1366
  caffeine withdrawal, 1025
  childhood problems after abuse, 497
  clinician–patient relationship, 30
  cognitive development, 100, 101, 152–153, 154
  cohabiting parents/carers, 1965
  communication disorders, 767–775
  compliance issues, 2447, 2448
  cultural issues in child-rearing, 112–113
  dementia causes, 918
  dependent personality disorder, 1743
  depression after parental separation, 614
  depressive disorders, 1290–1291
  depressive personality disorder, 1748–1749
  developmental disorders, 130
  developmental influences in anxiety disorders, 328–332
  developmental psychopathology, 157–159
  diagnostic classification, 679–688
  disaster-related stress, 2470
  education rights of disabled, 552–553
  effective listening, 15, 17
  emotional development, 101–102, 103, 153–154, 157
  facial expressions, 605
  factitious disorder by proxy, 1554–1556
  family influence on compliance, 2451, 2454–2455
  family resilience, 1956–1957, 1958
  fear development, 1426
  foster care/homelessness, 2528
  gay/lesbian/bisexual parents/carers, 2543–2544
  gender identity disorders, 1594–1595, 1596

Children *(Continued)*
generalized anxiety disorder, 1504–1505
history of developmental ideas, 221, 223
history of understanding, 221, 222
homeless families, 2528
infant development, 109–131
information from parents, 547
initial psychiatric evaluations, 546–554
insecure attachment, 628, 836
intellectual disability, 689–746
laboratory assessment, 553
learning and motor skills disorders, 747–762
legal issues
consent to treatment of minors, 84–85
criminal proceedings, 92
education rights of disabled, 552–553
longitudinal developmental studies, 97–108
maltreatment, 129
maternal substance abuse, 129–130
meeting psychiatrists, 547–548
mental health service history, 1820, 1830, 1832
moral development, 102–103, 104, 155–157
neuropsychological tests, 558
obsessive–compulsive personality disorder, 1745
paranoid personality disorder, 1725
parasomnias, 1647–1649
phencyclidine intoxication, 1094–1095
post-traumatic stress disorder, 1474–1475, 1483–1484
poverty, 128–129
pregay/prelesbian, 2541–2542
preschool development, 135–149
psychosexual problems, 498
pyromania/fire-setting behavior, 1675, 1677
reactive attachment disorder, 893–895
restraint and seclusion, 2492
schizoid personality disorder, 1727
schizophrenia risk, 260
school-age development (6–12 years), 150–159
severe medical illness in infancy, 130–131
severe punishment effects, 1995, 1996
social development, 102, 104, 154–155, 158
stimulants efficacy, 2269–2276
trichotillomania, 1688–1690, 1694
Children's Aggression Scale (CAS), 809
Children's health belief model, 2448
Chinese Classification of Mental Disorders, 648, 650
Chippers, 1153
ChIs *See* Cholinesterase inhibitors
Chi-square distribution, 2628
Chloral hydrate, 2260
Chlordiazepoxide, 2423
Chlorohydrocarbons inhalation, 1129
Chlorpromazine, 2161
chemical structure, 2168
history, 224
movement disorders, 1773
schizophrenia treatment, 1241
*CHMP2B* gene, 397
Cholinergic enhancing agents, 2337
Cholinergic neurotransmission
alcohol effects, 974
Alzheimer's disease, 905, 907, 2298–2304, 2312
Cholinesterase inhibitors, 2298–2304, 2312, 2553, 2555, 2557
Choline supplements, 2325
Chomsky, N., 140–141
Choose-get-keep model of employment, 2065
*See also* Supported employment
Choreoathetoid dyskinesia, 1783
Chromosomal abnormalities, 267–268, 696–698
Chronically mentally ill patients
effective listening, 15–16
gay men/lesbians, 2545
mental health service history, 1818, 1826
reducing caregiver burden, 1957–1958
Chronic care models (CCMs), bipolar disorder, 1362, 1365, 1367
Chronic depression
cognitive and behavioral therapies, 1936–1937
interpersonal psychotherapy, 1875, 1882
refractoriness to treatment, 2373
Chronic extrapyramidal symptoms, 2187
Chronic homelessness, 2529
Chronic (motor or vocal) tic disorder (CTD), DSM-IV-TR criteria, 848
Chronic pain
behavioral medicine, 2035–2036, 2041–2043
depressive disorders, 629, 1289
relational problems, 1806–1807
Chronic sleep disorders, 1630–1631, 1633–1638
Chronic stimulant effects in ADHD, 2284–2285
Chronic stress in animal models, 686
Chronobiology, 1627–1628
Chronology, 235–240
Chvostek's sign, 623
Cicchetti, D., 135
CIDI *See* Composite International Diagnostic Interview
Cigarettes *See* Nicotine; Smoking
CINAT *See* Critical Incident Needs Assessment Teams
Circadian rhythms
age effects, 1629
depressive disorders, 1295–1296
mood disorder neuropathology, 345
premenstrual dysphoric disorder, 1387
sleep–wake cycle, 1627–1628, 2255
Circadian rhythm sleep disorders, 1643–1646, 1651
Circular interactional pattern, 1798
Circumplex model of emotions, 608
Circumstantiality in speech disorders, 596, 598
CIs *See* Cholinesterase inhibitors
Citalopram
alcohol use disorders, 995
availability, 2128
breastfeeding, 2424
generalized anxiety disorder, 2231
history, 2127
obsessive–compulsive disorder, 1461, 2245
panic disorder, 2237
Citicholine, 2337
Citizen advocacy movements/organizations, 2085–2086
Civil commitment (involuntary hospitalization), 82–83
Civil law issues in clinical practice, 81–88
Civil Rights of Institutionalized Persons Act (CRIPA), 712
Civil rights movement, 1821
Civil unions of homosexual people, 1979–1980
CIWA-Ar *See* Clinical Institute Assessment for Alcohol
CJD *See* Creutzfeldt-Jakob disease
Cl *See* Clearance
C-L *See* Consultation–liaison psychiatry
Clang association, 596, 598
Class A mood stabilizers, 2203
Class A trials of mood stabilizers, 1354–1355, 1356, 1357–1359
Class B mood stabilizers, 2203
Classic texts, 2497
Classification systems, 661–677
*See also Diagnosis and Statistical Manual of Mental Disorders*
approaches, 661–663
categorical vs dimensional, 662–663
conditions requiring clinical attention, 676–677
diagnostic classes, 673–677
diagnostic codes, 667–673
disorders first diagnosed before adulthood, 673–674
disorders not elsewhere classified, 674
DSM-IV, 661–677
etiological vs descriptive, 661–662
goals, 661
history of DSM system, 663–665
levels of consciousness, 582–584
medication-induced movement disorders, 1773–1774
multiaxial system, 666–667
new categories, 677
possible future system, 663

syndrome vs symptom, 662
Clearance (Cl), pharmacokinetics, 2104
Clincial evaluations, clinician–patient relationship, 22
Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), 1831, 1846, 2174–2175, 2176, 2177, 2556
Clinical case management model, SMI, 2068
Clinical epidemiology, 404, 427
Clinical evaluation, 525–545
  behavior/adaptive functioning assessment, 641–642
  behavioral medicine, 2039, 2040
  children/adolescents, 546–554
  correctional psychiatry, 2596
  cultural formulation, 57, 60
  intellectual disability, 722–723
  learning and motor skills disorders, 750–751, 752–755, 762
Clinical factors
  complementary and alternative medicine, 2331–2332, 2342
  compliance, 2455
  opioid use disorders, 1171–1175
  suicide risk/protection, 2480–2482
  treatment-resistant depression, 2373
Clinical Institute Assessment for Alcohol (CIWA-Ar), 2392–2393
Clinical opioid withdrawal scale (COWS), 2400, 2404
Clinical practice, psychosomatic medicine, 2498
Clinical setting, violent behavior, 2602–2603, 2608–2612
Clinical thresholds, diagnostic classification in infants and young children, 682–683
Clinical trials, 407
  *See also* Randomized controlled trials
  antidepressants, 2128–2129
  case-control studies, 408, 2269–2276
  combined treatment/monotherapy comparison, 2436
  design, 2109
  medication/psychotherapy comparison, 2433
  methodological issues, 2438–2439
  stimulant efficacy, 2269–2276
  treatment-resistant depression, 2380, 2387
Clinician–patient relationship, 20–31
  *See also* Countertransference; Therapeutic alliance; Transference
  adolescent's initial evaluations, 547–548
  attachment theory, 22
  bipolar disorder, 1365
  boundaries, 71–79, 87
  changing, 3
  children's initial evaluations, 547–548
  cocaine use disorders, 1071–1072
  combined treatments, 2441–2442
  complementary treatments, 2343
  compliance, 25, 2454, 2458–2459
  confidentiality, 28–29, 72, 73, 76–77, 85
  consent to treatment, 84–85
  cultural issues, 56, 60
  demeanor of psychiatrists, 17
  depressive disorders, 1318
  disability/fitness evaluations, 87–88
  ethical issues, 67–78, 85, 87
  exploitative patients, 78
  factitious disorder, 1553–1554
  financial issues, 76
  fire-setting behavior, 1677
  forensic psychiatry, 81
  formation, 22–26
  gender issues, 56
  intellectual disability, 741
  kleptomania, 1672–1673
  learning and motor skills disorders, 762
  legal issues, 81, 84–88
  listening skills, 3–18
  malpractice, 85–87
  mental status, 26
  modern medicine, 21–22
  obsessive–compulsive disorder, 1466–1467
  panic disorders, 1405
  placebo effects, 20
  post-traumatic stress disorder, 1485
  privilege, 85
  PSD intoxication, 1096
  psychological factors affecting medical condition, 1758
  research, 26–28
  roles and motivations, 21
  schizophrenia, 1240–1241
  sexual disorders, 1578–1579, 1606
  sexual involvement, 71–73, 77–78, 87
  somatization disorder, 1521–1522
  special issues/populations, 28–31
  substance addiction, 967
  torture victims, 2569–2570
  trichotillomania, 1691
Clomipramine
  body dysmorphic disorder, 1541
  combined treatments, 2437
  obsessive–compulsive disorder, 1459–1460, 2246
  premature ejaculation, 1592
  separation anxiety disorder, 882
  trichotillomania treatment, 1692
Clonazepam, 2237, 2239, 2423
Clonidine
  alcohol detoxification, 2393–2394
  cannabis detoxification, 2412
  opioid detoxification, 2398–2399
  opioid withdrawal, 1175
  tic disorders with ADHD, 858–859, 861
Cloninger's alcoholism types, 972–973
Closing phase of psychiatric interviews, 44–45
Clozapine, 1241–1259
  chemical structure, 2168
  dosing parameters, 2178
  history, 2161–2162
  norepinephrine function, 1228
  pharmacology, 2166, 2169
  suicide protection, 2485
  treatment resistance, 1257–1258, 2182
Clubhouse model of psychosocial rehabilitation, 2062–2063
Clumsiness, Asperger's disorder, 792
Cluster analysis of schizophrenia symptoms, 1231
CMHCs *See* Community mental health centers
CMHS *See* Center for Mental Health Services
CMMS *See* Centers for Medicare and Medicaid Services
CMV *See* Cytomegalovirus
CNS *See* Central nervous system
CNVs *See* Copy number repeat variations
CO *See* Carbon monoxide
Coalitions, structural family therapy, 1950
Coalition of self-help groups, 2085
Cocaethylene
  cocaine-alcohol abuse, 1060, 1065, 1078
  cocaine substitution therapy, 1075–1076
  toxicity, 1065
Cocaine
  addiction, 355, 357–358
  features, 1058
  general approaches to substance use disorders, 957–970
  neuropharmacology, 366
  violence link, 2606
Cocaine abuse, DSM-IV-TR, 1062–1063
Cocaine–alcohol abuse, 1060, 1065, 1078
Cocaine dependence, DSM-IV-TR, 1063
Cocaine-induced disorders, 1065
Cocaine-induced sleep disorder, 1653
Cocaine intoxication, DSM-IV-TR, 1064
Cocaine use disorders, 1058–1081
  cocaine abuse, 1062–1063
  cocaine dependence, 1063–1064
  cocaine intoxication, 1064
  cocaine withdrawal, 1060, 1064–1065, 1068
  comorbidity
    other substance use disorders, 1077–1078
    psychiatric disorders, 1059–1060, 1077, 1079–1080, 2411
  course, 1060–1061, 1067–1068
  diagnosis, 1062–1065
  DSM-IV-TR, 1062–1063, 1064

Cocaine use disorders *(Continued)*
management problems, 1077–1079
medical complications, 1065–1066, 1067
other cocaine-induced disorders, 1065
pharmacotherapy, 1072–1077, 2410
psychotherapy, 1069–1072
treatment, 1066–1081
Cocaine withdrawal, DSM-IV-TR, 1064
Codeine, use disorders, 1169–1170
Coding systems, relational problems, 1801–1802
Coefficient alpha, 2624
Coefficient kappa, 2625
Coercive relational processes, 1795, 1797–1798, 1802
Coexisting symptoms *See* Comorbidity
Cognitive adaptation training (CAT), 1262, 2051
Cognitive assessment
adolescents, 170, 549–550
children, 170, 549–550
dementia, 2552–2553
elderly adults, 2550
mental status examination, 41, 529–530, 582–592
monitoring child/adolescent development, 170
neuropsychological tests, 556–563
psychological tests, 532–533
Cognitive-behavioral family therapy, 1952–1953, 1955, 1957, 1960
Cognitive-behavioral group therapy (CBGT), 1430–1432, 1915–1916
Cognitive-behavioral rehearsal, 1928
Cognitive-behavioral theory, 2030, 2031
Cognitive and behavioral therapies, 1920–1941
*See also* Behavioral therapy; Cognitive-behavioral therapy; Cognitive psychology; Exposure-based behavioral therapy
alcohol use disorders, 991
anxiety disorders, 327, 1938–1939
behavioral medicine, 2027–2043
behavioral model, 1923–1924
behavioral techniques, 1930–1933
bipolar disorder, 1362, 1363, 1364, 1939–1940
brief psychotherapies, 1889, 1890–1891, 1895–1896, 1899
case formulation, 1934
cognitive model, 327, 1920–1923
continuation/maintenance phase, 1935–1936
eating disorders, 1939
efficacy, 1936–1940
indications, 1933
mood disorders, 1936–1938
neurobiological basis, 327
outcome assessment, 1935
pharmacotherapy augmentation, 1935, 1937
treatment formulation, 1933–1936
treatment intensity/duration, 1934–1935
treatment phases, 1934
treatment selection, 1933–1934
treatment strategies, 1924–1933
Cognitive-behavioral therapy (CBT)
acute stress disorder, 1488
anorexia nervosa, 1617–1618
attention deficit-disruptive behavior disorders, 822
autistic disorder, 790
behavioral medicine, 2034–2035
binge-eating disorder, 1624
biological/neuroimaging studies, 295–296
body dysmorphic disorder, 1541
bulimia nervosa, 1621–1622
cancer, 2036
cannabis dependence, 1052–1053
chronic pain, 2043
cocaine use disorders, 1069–1070
cognitive psychology, 434
combined treatments, 2431–2438
delusional disorder, 1275
dependent personality disorder, 1744
depressive disorders, 1299, 1317
depressive personality disorder, 1749
efficacy studies, 292–293, 1936–1940
impulse-control disorders, 1667, 1686–1687, 1693
insomnia, 1635–1636
interpersonal psychotherapy comparison, 1875–1876, 1879–1880, 1881, 1883, 1884–1885
key assumptions, 2031
models, 1920–1924
obsessive-compulsive disorder with tic disorders, 862
obsessive-compulsive personality disorder, 1746
pain disorder, 1534
panic disorders, 1402–1406
paraphilia, 1605
PTSD, 1483–1485, 2589, 2590
relational problems, 1803
schizophrenia, 1261
separation anxiety disorder, 882
smoking cessation, 1160–1161
somatization disorder, 1522–1523
specific phobias, 1427–1428, 1430, 1432
suicidal patients, 2485
torture victims, 2570
treatment formulation, 1933–1936
treatment strategies, 1924–1930
use of term, 1921
Cognitive constructs in communication, 1797
Cognitive control, prefrontal cortex role, 250–251
Cognitive decline *See* Cognitive impairment; Dementia
Cognitive development
adults, 183–184
decalage, 106
elderly adults, 197–199, 513
infants, 113, 115, 116–117, 119, 121, 124–125
longitudinal studies, 100–101
preschool, 138–140, 142
schizophrenia, 303, 306
school-age children, 152–153, 154
Cognitive disorders, 897–930
*See also* Cognitive impairment; Dementia
affecting medical conditions, 1757
amnestic disorders, 897, 901–902, 924–928
cultural factors, 649
delirium, 897, 900–901, 917–924
DSM classification systems, 674
heart disease patients, 2500
school-age children, 158
speech/thought/perception/self-experience, 595–604
Cognitive dissonance theory, 460–461
Cognitive endophenotypes in animal models, 278–279
Cognitive enhancers, 2294–2317, 2321, 2335–2344
Cognitive errors in information processing, 1922, 1923
Cognitive flexibility in animal models, 280
Cognitive function
alteration by defence mechanisms, 612
compliance, 2452, 2457
psychiatric interviews, 41
schizophrenia patients, 1236
Cognitive impairment
affecting compliance, 2452, 2457
affecting psychiatric interviews, 41
antipsychotic drug effects, 2176
anxiety disorders, 322
autistic disorder, 782
bipolar disorder, 1353
depression, 2558
disorders of will, 602
elderly adults, 197–199, 513, 2550
intellectual disability, 716
schizophrenia, 1231–1233, 2176
Cognitive management of elderly adults, 2550
Cognitive neuroscience, 250–251, 327, 433, 434
Cognitive phenotypes, animal models, 279–280
Cognitive psychology, 433–447
attention, 435–440
bipolar disorder, 1352
cognitive models, 1920–1923
emotions, 606–607
executive functioning, 439–440

fear development, 1426
health behavior models, 2448–2449
infant development, 110–111
learning and motor skills disorders, 757
memory, 443
modularity/integration, 448
neurobiological basis, 250–251, 327
panic disorders, 1399–1400
post-traumatic stress disorder, 1479
psychiatric disorder effects, 435–437, 443, 446–447
schizophrenia, 1262, 2053–2054
social cognition, 443–448
therapeutic interventions
*See also* Cognitive and behavioral therapies; Cognitive-behavioral therapy
anxiety disorders, 327
attention, 436–437
brief psychotherapies, 1891, 1896
executive functioning, 439–440
memory, 443
social cognition, 447–448
top-down control systems, 437–440
Cognitive remediation therapy (CRT), 1262, 2053
Cognitive response prevention, 1929
Cognitive restructuring technique, 1503, 1994, 1995
Cognitive skills training, 2054
Cognitive Vulnerability to Depression Project (CVD), 455–456
Cohabitation, 1965
Coherent therapeutic frames, 71–79
Cohort effects in adult development studies, 184–185
Cohort studies, 408–409
Cojoint interpersonal psychotherapy for marital disputes (IPT-CM), 1881
Colburn device, 2275
Collaboration of professionals
Assertive Community Treatment, 2069, 2070
behavioral medicine, 2037–2038
children/adolescents, 554
cultural diversity in teams, 62
intellectual disability treatment, 733
legal issues, 87
services for mentally ill homeless people, 2532, 2534
Collaborative empiricism, 1925
Collaborative therapy for bipolar disorder, 1362, 1365
Collateral information, children/adolescents, 546–547
Collective violence, 2603, 2604
Collusion, ethical issues, 73, 76
Colorectal cancer, 2502
Color of medication, ethnic/cultural issues, 2115
Coma
Glasgow Coma Scale, 582–583
phencyclidine intoxication, 1094
sleep comparison, 584
Combined treatments, 2430–2446
*See also* Drug interactions
antidepressants, 2141–2143, 2151
bipolar disorder, 1356, 1359
concomitant psychotropic medication/antipsychotics, 1258–1259
concurrent group/individual psychotherapy, 1914
evidence, 2431–2439
future of, 2439
history, 2430
methodological issues, 2438–2439
panic disorders, 1404–1405
pharmacotherapy/behavioral therapy for alcohol dependence, 2396–2397
schizophrenia, 1264
sequential treatments, 1405, 2440
stimulants/psychotropic medications, 2278–2279
technical considerations, 2439–2444
treatment-resistant depression, 1312–1315, 2382, 2384, 2437–2438
vs. monotherapy, 2434–2437
COMBINE study, 2396–2397
Commonalities in psychiatric disorders, 245–253
Communication
*See also* Language; Speech...
adherence problems, 2114
autistic disorder, 780–782
ethnocultural issues, 57
family therapy, 1953
gender issues, 56
infant development, 113, 117–118, 120, 122
medical competency, 83
relational problems, 1795, 1796–1798, 1801–1802
speech and language pathologists' assessment, 767–768
torture victims, 2569
Communication deviance (CD), 1794, 1798, 1802
Communication disorder not otherwise specified (CDNOS), 765, 774, 776–777
DSM-IV-TR criteria, 776
Communication disorders, 765–778
*See also* Neurodevelopmental disorders of relating and communicating
academic comorbidity, 772–773
childhood problems, 493–494
DSM-III criteria, 765
DSM-IV-TR criteria, 765
etiology/pathophysiology, 770–771, 774, 775–776
expressive language disorder, 765–770
influencing factors, 771
mixed receptive-expressive language disorders, 765–773
treatment, 771–773, 774, 776
Communication therapy, Asperger's disorder, 795
Community intervention
disaster-related, 2469, 2471–2473
torture victims, 2572
Community living
intellectual disability, 713
psychiatric rehabilitation, 2059–2080
Community mental health centers (CMHCs), 1822–1824, 1825, 1826, 1830
Community psychiatry
Assertive Community Treatment, 2067–2070
history, 208, 1819–1820, 1826–1827, 1830
homeless people, 2526, 2527, 2534
treatment of offenders, 2598
Community rating, private insurance, 1836
Community risk factors, 105–106
Community Support Program (CSP), 1826–1827, 2090
Comorbidity
adolescent disorders, 500
alcohol use disorders/psychiatric conditions, 986–988
anxiety and attention-deficit hyperactivity disorder, 2282
anxiety/depression/somatoform cultural syndromes, 651, 652
attention deficit disorders, 811–812
biological commonalities in psychiatric disorders, 245
caffeine use disorders, 1021–1022, 1026, 1030–1031
childhood disorders, 491–492
correctional psychiatry, 2599
couples therapy, 1969–1970
early adulthood disorders, 503–504
ECA study, 416–417
generalized anxiety disorder, 1497–1498
integrated dual disorder treatment, 2075–2077
learning and motor skills disorders, 752, 755–756
mood disorders, 342
National Comorbidity Survey, 417
obsessive-compulsive disorder, 1449
opioid abuse disorders, 1180–1182
panic disorders, 1397–1398
phobic disorders, 1415–1416
psychological factors affecting medical condition, 1755, 1757–1758
schizophrenia, 1250
somatization disorder assessment difficulties, 1520
substance addiction, 964, 968
tic disorders, 849–850, 851–852, 857–859, 861, 863–864

Comparative genomic hybridization (CGH), 699
Comparison cohort studies, 409
COMPEER, 2084
Compensatory model of schizophrenia management, 2051
Competency
  criminal law, 88–89
  minors, 84–85
  to stand trial, 731
  to testify, 731–732
  treatment decisions, 83–84
Complementary and alternative medicine (CAM), 2318–2344
  *See also* Herbal remedies
  acupuncture, 874, 1076–1077
  adjustment disorders, 1712
  autistic disorder, 388, 789–790
  clinical aspects, 2331–2332
  clinician-patient relationships, 2343
  cognitive enhancement, 2335–2344
  contraindications, 2324, 2331–2332
  effects of remedies, 59
  herb-drug interactions, 2108, 2343, 2115, 2119
  homeopathic treatments, 1386, 1712
  hormonal conditions, 2320
  insomnia, 2261
  intellectual disability, 720–721, 739
  mood disorders, 2319, 2321–2326
  post-traumatic stress disorder, 2330–2331
  premenstrual dysphoric disorder, 1386
  quality, 2343–2344
  research review, 2328–2329
  sexual disorders, 2320
  smoking cessation, 1161
Complementary countertransference, 24
Complex carbohydrates, 1386–1387
Complex clinical presentation of tic disorders, 849–850, 852, 863–864
Complex disorders
  animal models, 278–279
  genetic epidemiology, 257
  intellectual disability, 702
Complex patterns of transmission, genetic epidemiology, 261–262
Complex post-traumatic stress disorder (disorder of extreme stress NOS), 2587, 2589
Complex tics, 847, 852
Compliance, 2447–2459
  antidepressants, 2135
  antipsychotic drugs, 2181–2182
  bipolar disorder therapy, 1361
  clinical factors, 2455
  clinician-patient relationship, 25, 2454, 2458–2459
  contextual factors, 2454–2455
  definition, 2447
  demographic factors, 2451
  direct measurement, 2450
  ethnic/cultural issues, 2113–2114
  indirect measurement, 2450–2451
  intervention strategies, 2457–2459
  measurement, 2449, 2450–2451
  naltrexone, 2391, 2407
  patient-related factors, 2451–2454
  pharmacologic therapy, 2107
  provider-related factors, 2454
  psychological factors affecting medical condition, 1756, 1758
  schizophrenia patients, 1259
  specific diagnoses, 2455–2457
  stimulants in ADHD, 2283
  theoretical models, 2448–2449
  treatment concordance, 2458–2459
Complicated grief, 2523–2524
Complication model of depression, 614
Component instincts, 465
Composite International Diagnostic Interview (CIDI), 406–407, 419, 424–426
Comprehensive treatment plan, 544–545
Compulsive behavior
  *See also* Impulse-control disorders; Impulsive behavior
  childhood problems, 495
  definition, 1443
  maladaptive functioning, 643, 644–645
  serotinergic system dysfunction, 645
  sexual, 1601, 1605, 1606
  substance use disorders, 356
  thought disorders, 598, 600
Compulsive-impulsive behavior comparison, 644–645, 1658
Computed tomography (CT), 570–573, 579, 1217–1218, 1219
Computer analogy of human mind, 433–434
Computer assisted cognitive remediation (CACR), 2053–2054
Computerized pharmacy records, 2375
Computer software for schizophrenia rehabilitation, 2053–2054, 2056
COMT *See* Catechol-O-methyl transferase
Concentration-effect relationship, 2105–2106, 2107
Concentration in schizophrenia patients, 1235
Conception, 1387
Conceptualization of mental disorders, 423
Concomitant illness *See* Comorbidity
Concomitant psychotropic medications (CPM), 1258–1259
Concordant countertransference, 24
Concurrent group/individual psychotherapy, 1914
Condensation, dream work, 465
Condensed Hypnotic Approach, 1996–1998
Conditioning
  anxiety disorders, 1424–1426
  behavioral models, 1923–1924
  extinction, 323–324
  fear/danger avoidance, 322, 323
  pain disorder, 1533
  post-traumatic stress disorder, 1479
  safety, 324
Conduct disorder (CD)
  *See also* Antisocial personality disorder
  adolescents, 501–502
  childhood problems, 497
  comorbidity patterns, 811–812
  definition, 804, 806
  developmental interlineal decalage, 107
  differential diagnosis, 812–813
  epidemiology, 811
  learning disability comorbidity, 756
  natural course, 812
  neurochemical basis, 816
  social/environmental factors, 816–817
Confession of feelings, 1996, 1997
Confidentiality
  child/adolescent evaluations, 548, 553–554
  clinician-patient relationship, 28–29, 72, 73, 76–77, 85
  factitious disorders, 1552–1554
  legal issues, 85
  therapeutic frame boundaries, 73, 76
Conflict
  adolescent development, 163, 172
  anxiety/depression animal models, 280–282
  brief psychodynamic therapies, 1894
  defences, adult development, 188–189
  interpersonal psychotherapy, 1875
  parent-child relational problems, 1805
  psychoanalytic psychotherapy, 1853
  resolution, 1795, 1800, 1802, 1805
Conflicts of interest, 70, 73, 74–75
Confounding, 410, 2620–2621
Confrontation of trauma, 1996, 1997
Confusion in psychiatric interviews, 9, 49–50
Congenital abnormalities, 130–131
  antidepressants risks, 2419–2420
  craniofacial anomalies, 834
  feeding disorder of infancy or early childhood, 832
  intellectual disability, 698–699, 702–703
  lamotrigine, 2509
  lithium, 2508–2509
  psychotropic medications, 2508
  stress and mood effects, 2418
Congenital factors in bipolar disorder, 1343, 1348–1349

Congenital infections as intellectual disability causes, 703–704
Congestive heart failure, psychological factors affecting, 1762–1763
Connectedness in disaster situations, 2472, 2473
Connectionist model of information processing, 1573
Conners Adult ADHD Diagnostic Interview (CAADID), 810
Conners Adult ADHD Rating Scale, 807, 808, 809
Conners Parent Rating Scale (CPRS), 2273
Conscientiousness, 1722, 1744, 1746
Consciousness, 582–592
  *See also* Unconscious mind
  brain region interactions, 586
  levels, 582–584, 1786
  mental status examination, 582–584
  neuroleptic malignant syndrome, 1786
  pre-conscious mind, 469, 1853–1854
  psychoanalytic psychotherapy, 1853–1854
  schizophrenia patients, 1235
  topographical theory, 469
Consent *See* Informed consent
Conservation of numbers, 138–139
Conservative attitudes to sexual issues, 1578–1579
Consolation, 1996, 1997
Consolidation, 1900
Constipation/retention encopresis, 875, 876, 877, 878, 879
Constriction, PTSD criteria, 2587
Constructivism, 479–480
Construct validity
  animal models, 277–278
  study design methodology, 2624
Consultant model for combined treatments, 2440–2441, 2444
Consultation between professionals, 87, 554
  *See also* Collaboration
Consultation-liaison (C-L) psychiatry, 2028–2029, 2496–2505
Consumerism
  *See also* Self-help groups
  conceptual distinctions, 2084–2085
  consumer advocacy organizations, 2085, 2088–2090
  consumer movement, 2093–2094
  consumer/survivor operated service programs, 2092
  government roles in consumer empowerment, 2090–2091
  Political Advocacy Model, 2085, 2089–2090
  recovery orientation in mental health care, 2093
  research findings, 2091–2092
  resource centers, 2085
  service development, 2091
  stakeholder organizations, 2085, 2086–2088
Consumer model of recovery, 2049–2050
Consumer Organization and Networking Technical Assistance Center (CONTAC), 2085, 2090
Contamination obsessions, 1444, 1445, 1446
Contextual fear-conditioning, 323
Contextual therapies, 1896–1898
Contingency contracting
  behavioral therapies, 1932
  family therapy, 1953
  smoking cessation, 1161
Contingency management
  attention deficit-disruptive behavior disorders, 822
  opioid detoxification, 1179–1180
Contingency tables, 2627
Continuation ECT (C-ECT), 1315–1316
Continuation treatment for depressive disorders, 1302–1304, 1315–1316, 1880
Continuous Performance Test (CPT), 2273–2274
Continuous positive airway pressure (CPAP), 1643
Contraceptives, 1385
Contrast group/control group comparison, 2621
Control issues
  *See also* Executive functions; Impulse-control disorders
  effective listening, 9
  generalized anxiety disorder, 1501
  locus of control model of social psychology, 455
  obsessive-compulsive disorder, 1466–1467
  top-down processing, 437–440
Controls in studies, 262, 408, 2621
  *See also* Randomized controlled trials
Conversion
  defence mechanism, 25, 1855
  hallucinations, 1520
  history of concept, 212, 1514
  symptoms, 1514, 1517, 1526, 1543
Conversion disorder, 1525–1530
  course, 1527
  definition/diagnostic features, 1525–1527
  differential diagnosis, 1527–1528
  DSM-IV-TR criteria, 1526
  early adulthood, 508
  epidemiology, 1527
  etiology/pathophysiology, 1528–1529
  hypnosis, 1998–1999
  hypnotizability, 1990
  physical signs and symptoms, 628
  treatment, 1529–1530
Conversion therapy, sexual orientation, 2544
Conversion V, Minnesota Multiphasic Personality Inventory, 1532
Convulsions, 1525, 1526
  *See also* Anticonvulsant medication; Electroconvulsive therapy
Co-occuring disorders *See* Comorbidity
Cooperation at clinical interview, 642
Cooperative play, 144
Coordination disorder *See* Developmental coordination disorder
Coping mechanisms
  affecting a general medical condition, 1756, 1759–1760, 1761, 1767–1768
  behavioral medicine, 2031–2032
  cocaine use disorders, 1071
  elderly adults, 196
  self-help groups, 2084
Coprolalia, 847
Copropraxia, 847
Copy number repeat variations (CNVs), 268
Core conflictual relationship theme (CCRT), 1890
Core databases, 38
Coronary artery disease (CAD), 1761–1762, 1767, 2499–2501
Correctional psychiatry, 92, 2529, 2593–2600
Corrective emotional experiences, 1889, 1899
Correlates, National Comorbidity Survey, 417
Correlation, definition, 2627
Cortical atrophy in Alzheimer's disease, 904–905
Cortical-based disorders, 755–756
Cortical circuits in schizophrenia, 282, 283
Cortical-subcortical imbalance, 283
Corticobasal ganglionic degeneration (CBGD), 396, 397
  *See also* Frontal temporal dementia
Corticobulbar tracts, 947–948
Corticotropin releasing factor (CRF), 323, 325, 329, 1295
Cortisol, 343, 345
COS *See* Childhood onset schizophrenia
Cosmetic surgery, 1539, 1540
Costs
  alcohol dependence treatment, 990
  antipsychotic drugs, 2192
  brief psychotherapies, 1891
  insurance benefit limits, 1836–1837
  panic disorders, 1399
  treatment comparison of cost effectiveness, 1831
Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS), 1831, 1846
Cotherapy, 1914
Cotinine, 1151

Counseling *See* Drug counseling; Genetic counseling; Interpersonal counseling
Counterresistance, 1854–1855
Countertransference
bias in psychiatric interviews, 41
clinician-patient relationship, 24–25, 30
cultural issues, 60, 1865
effective listening blocks, 7, 11, 16–17
gender identity disorders, 1600
group psychotherapy, 1916, 1917
history of understanding, 223
object relations theory, 474–475
patient noncompliance, 2454
psychoanalytic psychotherapy, 1854–1855, 1857, 1861
sexual disorders, 1606
social constructivism, 480
Couples
*See also* Marriage; Sexual disorders
affect expression, 1798–1799
behavioral marital therapy, 991, 1804
biological aspects of romantic love, 1966
boundaries in couple development, 1967
cohabitation, 1965
communication, 1796–1797
gay/lesbian/bisexual, 2543–2544
intimate partner violence, 2577–2578, 2579–2581, 2584–2585
partner relational problems, 1795, 1800–1801, 1804
problem solving, 1799–1800
separation, 614, 1965, 1973
structure, 1796
Couples therapy, 1963–1980
Axis I disorders, 1972
biology of couples, 1966
bisexuality/homosexuality, 1979
brief psychotherapies, 1896
concomitant psychiatric illness, 1969–1970
contraindications, 1970–1971
criteria, 1977
definition, 1963–1964
development of couples, 1966
efficacy, 1972–1973
evaluation of couple, 1968–1970
family of origin, 1966–1967
function/dysfunction of couples, 1966–1969
intervention techniques, 1971–1972
sexual disorders, 1585, 1588, 1590, 1592, 1974–1979
Covariance matrices, 2632
COWS *See* Clinical opioid withdrawal scale
CP *See* Cerebral palsy
CPAP *See* Continuous positive airway pressure
CPM *See* Concomitant psychotropic medications
CPRS *See* Conners Parent Rating Scale
CPT *See* Continuous Performance Test
'Crack' cocaine, 1058
Cranial nerve damage, 1136–1137
Cravings
*See also* Impulse-control disorders
animal models, 368
kleptomania, 1671–1672
substance dependence, 357
CREB *See* Cyclic AMP response element binding protein
Creutzfeldt-Jakob disease (CJD), 398–399, 911–912
CRF *See* Corticotropin releasing factor
Crime
adolescent problems, 1805
automatism defence, 91
conviction predictors in children, 877
correctional psychiatry, 92, 2529, 2593–2600
history of understanding, 231
intellectual disability relationship, 731–732
obtaining sedative-hypnotic drugs for abuse, 1188
physical characteristics of criminals, 219
sex offending behaviors, 1601, 1602–1604
violence, 2602, 2604–2605, 2606, 2607
Criminal justice system
competency to stand trial, 89
mental health collaborative interventions, 2595–2596
population, 2593
standards of proof, 86
Criminal law issues in clinical practice, 81, 88–92
Criminal responsibility, 89–91
CRIPA *See* Civil Rights of Institutionalized Persons Act
Crises in adult development, 192
Crisis residences, 544
Critical appraisal of published research, 2632–2633
Critical Incident Needs Assessment Teams (CINAT), 2472
Critical time intervention (CTI), 2527–2528
*Crocus sativa* (saffron), 2324
Cross-dressing, 1595, 1596, 1597–1598, 1604, 1605
Cross-gender identification, 1594–1595, 1596–1597
Cross-sectional factors in antidepressant selection, 2132, 2133
Cross-sectional studies, 408, 1335, 1336
CRT *See* Cognitive remediation therapy
Crystallized intelligence, 198
CSF *See* Cerebrospinal fluid
CSP *See* Community Support Program
CT *See* Computed tomography
CTD *See* Chronic (motor or vocal) tic disorder
CTI *See* Critical time intervention
Cued fear-conditioning, 323
Cultural competence, 60–62, 64–65
Cultural countertransference, 60
Cultural diversity in the USA, 54
Cultural formulation of clinical presentation, 57, 60, 64, 1865
DSM-IV-TR criteria, 648, 656
Cultural issues, 54–65
*See also* Ethnicity issues; Racial issues
adjustment disorders, 654
adult development, 182, 192
alcohol use disorders, 983–984, 998–999
anorexia nervosa, 1615, 1616
anxiety disorders, 651–652, 1418, 1419–1421, 1500
assessment, 60
attention deficit-disruptive behavior disorders, 813
cannabis history, 1041–1042
children with academic difficulties, 754, 755
clinician-patient relationship, 29–30, 50, 60
cognitive disorders, 649
communication disorders, 770, 773–774, 775
couples dynamics, 1967
cultural formulation, 60
definitions, 55
depression/anxiety/somatoform combined disorders, 651, 652
depression presentation, 1293
diagnosis of mental disorders, 648–656
dissociative disorders, 653, 1560, 1570–1571
eating disorders, 654
effective listening, 5, 6, 7, 17
ethnicity relationship, 55
ethnocultural identity, 57–58
factitious disorder, 1552
family therapy, 1953, 1958–1959
gender relationship, 56–57
grief/mourning, 2522
history, 222
histrionic personality disorder, 1736–1737
homosexuality, 2540
illness explanations, 58–59, 61, 64
importance, 54
impulse-control disorders, 1665, 1682, 1690, 1694
infant development, 112–113
information gathering, 61
international differences in alcohol use, 983–984
international family mental health services, 1958–1959
interpersonal counseling, 1884

IQ testing, 550
limitations, 64–65
MDMA use, 1115
mood disorders, 650–651
pain tolerance, 1533
panic disorders, 1399
personality disorders, 654, 1720, 1736–1737
pharmacology, 2112–2115, 2118–2119, 2121
physical signs and symptoms, 621–622
post-traumatic stress disorder, 1476, 2568, 2569, 2572
preschool development, 142–144
professional competence, 60–64
professional cultures, 55–56
psychiatric interviews, 42, 50
psychoanalytic psychotherapy, 1864–1865
psychopharmacology, 2112–2115, 2118–2119, 2121
psychosocial environment, 59–60
race relationship, 55, 60
schizophrenia, 650, 1206–1207
sedative-hypnotics abuse, 1194
sexual disorders, 653–654, 1581, 1582, 1586, 1589, 1590
socioeconomic factors, 649
somatization disorder, 1518, 1521
somatoform disorders, 652–653
stigma of mental illness, 63–64
substance use disorders, 649–650, 962–963
torture victims, 2568, 2569, 2572
working with interpreters/culture-brokers, 62–63
Cultural transference, 60
Culture-bound syndromes, 648, 650, 652, 653, 654–656
Culture-brokers, 62–63
Cumulative incidence rate, 405
CUtLASS *See* Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CVA *See* Cerebral vascular accident
CVAE *See* Cerebrovascular adverse events
CVD *See* Cardiovascular disease; Cognitive Vulnerability to Depression Project
Cyclical behavior changes, 728–729
*See also* Circadian rhythms
Cyclic AMP response element binding protein (CREB), 346–347, 350, 373
Cyclic GMP, 1587, 1589
Cyclic phosphodiesterase genes, 341
Cyclothymic disorder, 505, 1336, 1338
Cyclothymic temperament, 615
Cytochrome P-450 (CYP450) system
antidepressant metabolism, 2134–2135, 2141, 2142
antipsychotic drug interactions, 2183, 2184
expression variation, 2117–2119
genetic polymorphisms, 2116–2117
herbal preparation effects, 2115
inhibitors, 2101–2103
pharmacology, 2100, 2101–2104, 2107
Cytomegalovirus (CMV), 703–704, 1216
CYT study *See* Cannabis Youth Treatment study

$D_2$ receptors *See* Dopamine receptor $D_2$
$D_3$ receptors *See* Dopamine receptor $D_3$
Dalmation sage (*Salvia officianalis*), 2339
DALYs *See* Disability adjusted life years
D Amino Acid Oxidase Activator (DAOA) gene, 1213–1214, 1215
D-amphetamine *See* Dexamphetamine
Danazol, 1385
Dantrolene, 1788
DAOA *See* D Amino Acid Oxidase Activator
Dark/light-potentiated startle, 322–323
Darwin, Charles, 217, 605
DAT *See* Dopamine transporter
Databases, 37–41
Data sharing, 428
'Date rape' drugs, 1189, 1639, 2578
Daycare for preschool children, 144
Day programs, 544
Day residue of dreams, 465
Daytime sleep, 1629
*See also* Excessive daytime sleepiness
DBC *See* Developmental Behavior Checklist
DBH *See* Dopamine beta hydroxide
DBS *See* Deep brain stimulation
DBSA *See* Depression and Bipolar Support Alliance
DBT *See* Dialectical behavior therapy
D-cycloserine, 2244
DDAVP (desmopressin), 872
DDC *See* Dideoxycytidine
Death
*See also* Bereavement; Mortality rates; Suicide
benzodiazepine/drug combinations, 1189, 1191
disasters, 2465–2475
factitious disorder by proxy, 1555
inhalant-related disorders, 1129, 1132–1133
late life coping mechanisms, 196
restraint and seclusion, 2492
terminal care, 24, 30–31, 2516–2524
Death instinct, 470
Death penalty, 732
Death of physician, 29
Debriefing
acute stress disorder, 1488
rape/sexual assault, 2583–2584
restraint and seclusion, 2493
Decalage, 106–107
Deceitful patients, 50–51
Declarative memory, 585, 586, 587
*See also* Episodic memory; Explicit memory
Deep brain stimulation (DBS), 909, 2354–2358, 2367–2368
De-escalation strategies in aggression treatment, 2608–2609
Defence mechanisms
adult development, 188–189
clinician-patient relationship, 25
cognitive appraisal alteration, 612
elderly adults, 196
object relations theory, 473–474, 476
post-Freudian psychology, 471–472
psychoanalytic psychotherapy, 1853, 1855
Dehydroepiandrosterone (DHEA), 2333, 2340
Deinstitutionalization, mentally ill homeless people, 2526
Déjà vu, 584
Delayed help-seeking, 419, 423
Delayed sleep phase disorders, 1644–1645
Deliberate emotional regulation strategies, 251–252
Deliberate self-harm *See* Self-harming; Suicide
Deliberative aggression, 2603, 2604
Delirium, 897, 917–924
assessment, 923–924
brief psychotic disorder, 1269
caffeine intoxication relationship, 1022
cancer patients, 2502
cannabis intoxication, 1046
causes of, 920–922
characteristics, 584
clinical features, 919–920
dementia, 2554
differential diagnosis, 923–924
DSM classification systems, 674
DSM-IV-TR criteria, 918, 919
dying patients, 2518
elderly adults, 513–514
epidemiology, 918–919
historical perspective, 917–918
memory impairment, 901
physical signs, 900
treatment, 924
Delirium tremens (DTs), 977, 2394
Delta waves/bands, 566, 1627
Delusional disorder, 1272–1276
DSM-IV-TR criteria, 1238
epidemiology, 1273–1274
middle adult life, 510
subtypes, 1272–1273, 1275–1276
treatment, 1274–1275

Delusions
body dysmorphic disorder, 1539, 1540
dysmorphophobia, 1273
hypochondriasis, 1535, 1536, 1537
obsessive-compulsive disorder, 1443, 1448, 1451–1452
perceptual disturbances, 601, 602
psychiatric interviews, 47–48
thought disorders, 598–600
violence link, 2605
Demand-withdraw relational patterns, 1796
Demeanor of psychiatrists, 17
Dementia, 897, 898–918
*See also* Alzheimer's disease
alcohol-induced persisting dementia, 978
antipsychotic drugs, 2172–2173
behavioral disturbance, 2554–2557
brain imaging, 579–580
causes, 393–394, 902–914, 918
clinical features, 898–899
cultural factors, 649
definitions, 393, 898
degenerative causes, 902–911
delirium differentiation, 923
depression comorbidity, 1287, 2558
differential diagnosis, 901–902
DSM classification systems, 674
DSM-IV-TR criteria, 898, 917, 918
early understanding, 206, 207
epidemiology, 900–901
evaluation, 2551–2552
frontal temporal dementia, 396–398
general medical conditions, 916–918
infectious causes, 911–914
intellectual disability, 723, 728
late life problems, 513–514
Lewy body dementia, 398
management, 2551–2554
medical comorbidity, 2553–2554
neurodegeneration, 393–399
neurological/physical examinations, 899–900
prion disease, 398–399
sleep disorders, 1651
treatment, 917
Dementia infantilis, 795
*See also* Childhood disintegrative disorder
Dementia with Lewy bodies (DLB), 398
Dementia praecox, 213, 215, 221, 1235, 1239, 1783
Demographic factors
communication disorders, 773
compliance, 2451
nicotine dependence, 1153
obsessive-compulsive disorder, 1448
post-traumatic stress disorder, 1484–1485
schizophrenia, 1208–1211
substance addiction, 968
suicide, 2479–2480
Denial, 1855
*De novo*/familial chromosomal abnormalities, 267
Dental procedure hypnosis, 2000–2001
Dependence
*See also* Alcohol dependence; Substance dependence
Edwards and Gross syndrome, 957, 974
pathological gambling, 1680, 1682–1683
Dependent personality disorder (DPD), 1742–1744
differential diagnosis, 1740, 1743
DSM-IV-TR criteria, 1742
Depersonalization
panic disorder, 1395–1397
self-experience disorders, 602
Depersonalization disorder, 1564–1565
DSM-IV-TR criteria, 1565
Depolarization inactivation of neurons, 2165
Depo-medroxy-progesterone (Provera), 1605
L-Deprenyl, 2339–2340
Depression
*See also* Antidepressant medication; Bipolar disorder; Major depressive disorder
abuse victims, 2586
adjustment disorders, 1704
adolescents, 500, 501
adult development, 185
alcohol dependence comorbidity, 2397
animal models, 280–281, 285–286, 1297–1298
anorexia nervosa relationship, 1614, 1615
antipsychotic drugs, 2171, 2176–2177
Asperger's disorder comorbidity, 793
attentional disruption, 437
behavioral medicine, 2041
bereavement-related, 2523
binge-eating disorder relationship, 1624
body dysmorphic disorder relationship, 1540, 1541
brain stimulation therapies, 2359, 2360, 2363, 2365, 2366–2367, 2368
bulimia nervosa relationship, 1619–1620
cancer patients, 2036, 2037, 2501
childhood problems, 495–496
chronic pain, 629
classification, 339–340
clinical presentation, 615–616
cocaine use disorders comorbidity, 1059, 1079
cognitive and behavioral therapies, 1936–1938
cognitive impairment, 514, 2558
cognitive model, 1920, 1921–1922, 1923
complementary medicine, 2319, 2321–2326
cultural factors, 651, 652
dependency relationship, 1743
diabetes mellitus, 1286–1287, 2503–2504
dissociative identity disorder comorbidity, 1566, 1568–1569
early adulthood, 504–505
elderly adults, 513, 514, 2285–2286, 2557–2560
electroconvulsive therapy, 2359, 2360
emotional expression, 613–615
emotions, 613–615
family psychoeducation, 1957
generalized anxiety disorder distinction, 1498
generalized anxiety disorder relationship, 1495
genetic factors, 176
heart disease patients, 2499–2500
historical murderers, 216
hypochondriasis relationship, 1536–1537, 1538
learned helplessness, 286
learning and motor skills disorder association, 752, 755, 756, 762
maternal effects on children, 836
medically ill patients, 627, 1757, 2143–2145, 2499
medication compliance, 2456
menopause transition, 2512
modafinil, 2287
mood stabilizers, 2210–2214
motivation and interpretive biases, 446–447
multiple biological factors, 246
neurobiological factors, 339–350
opioid dependence comorbidity, 1181, 2407
physical manifestations, 624
prefrontal cortex, 251, 253
pregnancy, 2507–2508
premenstrual dysphoric disorder differential diagnosis, 1380
protection factors for children of depressed parents, 1957, 1958
psychiatric interviews, 49
psychoanalytic psychotherapy, 1869
psychotic features, 339, 1238, 1289, 2151, 2171
relational problems, 1796, 1798–1799, 1806
schizophrenia, 2171, 2176–2177
school-age children, 154
serotonin transporter genetic factors, 176
sleep disturbance relationship, 1630, 1634–1635
social psychology, 455–460
somatization disorder relationship, 1520
steroids, 931
substance use disorder comorbidity, 964, 2391–2392, 2397, 2407

theories, 2123–2124
torture victims, 2565, 2566, 2570
treatment-resistant, 2372–2387
unipolar/bipolar depression classification, 339, 1335
ventral striatum dysregulation, 249
Depression/anxiety/somatoform cultural-based syndrome, 651, 652
Depression and Bipolar Support Alliance (DBSA), 2085, 2088–2089
Depression-induced cognitive impairment (depressive dementia), 514
Depressive disorders, 1283–1330
*See also* Depression; Depressive personality disorder; Dysthymic disorder ; Major depressive disorder
adverse birth outcomes, 2417–2418
alcohol-induced mood disorder, 978
alcohol use disorders comorbidity, 986, 993
animal models, 280–281, 285–286, 1297–1298
assessment, 1284–1285
breastfeeding, 2423–2425
combined treatments, 2431–2433, 2434–2435, 2437–2438
comorbidity patterns, 1285–1288
course, 1288–1290
diagnosis, 1283–1293
differential diagnosis, 1290
epidemiology, 1285
etiology/pathophysiology, 1293–1300
general medical condition-related, 935–938
intellectual disability, 728
interpersonal psychotherapy, 1875–1886
kleptomania, 1671–1672
memory impairment, 901, 902
neurobiological factors, 1293–1298
pregnancy, 2417–2426
psychological factors, 1298–1300
psychosocial treatments, 1316–1318
psychotherapy efficacy, 292–293
PTSD relationship, 1476, 1484
schizophrenia comorbidity, 1251
subgroups, 1288–1290
subsyndromal, 1882–1884
treatment, 1293, 1300–1319
treatment-refractory, 1311–1315, 1319
Depressive episodes
bipolar disorder, 1336, 1339, 1356, 2210–2214
major, 1266, 1283–1330, 1875
Depressive personality disorder (DPPD), 1748–1749
DSM-IV-TR criteria, 1748
Depressive position, Klein, 473, 474
Depressive temperament, 615
Depressive-type schizoaffective disorder, 1266
Derailment, speech disorders, 596
Derealization, 584, 602–603
Dermatology
hypnosis, 2003
psychological factors affecting medical condition, 1766
*Désagrégation*, dissociative disorders, 1558
Descartes, René, 209
Desensitization training, 881–882, 1932
*See also* Eye movement desensitization and reprocessing
Desipramine
ADHD with tic disorders, 862
availability, 2128
cocaine use disorders, 1073
mechanism of action, 2126
Desire, sexual, 1581–1586
Desmopressin (DDAVP), 872
DESNOS *See* Disorder of extreme stress, not otherwise specified
Desperation stage in pathological gambling, 1681
Detachment, 584
Detection of disorders, cultural factors, 649
Detention facilities, 92, 2529, 2593–2600
Detoxification
alcohol, 2392–2394
opioids, 1175–1177, 2398–2401
sedative-hypnotics, 1194–1197
Development
adolescents, 161–178, 499
adult, 181–194
adult psychopathology, 188–189, 192, 285–286
anxiety disorders, 328–332, 1418
attention deficit-disruptive behavior disorders, 813, 819, 825
biological, 98–100, 151–152, 153, 183–184
childhood problems, 492–494
children/adolescent evaluations, 547
cognitive, 100–101, 106, 152–153, 154, 183–184
compliance, 2452, 2457
continence, 868, 875
couples, 1966
elderly adults, 196–202, 512
emotional, 101–102, 103, 106, 153–154, 157
endocrine factors, 99–100
factitious disorder, 1552
gay/lesbian/bisexual people, 2541–2542
genetic factors, 98
growth suppression by stimulants, 819, 2277
infants, 109–131
interlineal decalage, 106–107
learning and motor skills disorders, 747–762
longitudinal studies, 97–108
middle adult life, 510
moral, 102–103, 105, 107, 155–157
neurological factors, 98
normal, 98–104, 105
panic disorders, 1399
personality styles, 633–634
preschool, 135–149
psychopathology, 104–108, 127–131, 147, 157–159, 489–516
school-age children (6–12 years), 150–159
sexual, 1580
sociocultural, 102, 103, 154–155, 158
substance dependence/psychiatric disorder comorbidity, 362
substance use disorders, 363, 962–963
Developmental-based approaches to diagnostic classification in children, 679, 680, 684
Developmental Behavior Checklist (DBC), 722
Developmental communication disorders, 770
Developmental coordination disorder, 748, 749, 751, 760
Developmental crises, 192
Developmental disability, 689, 692, 709
*See also* Intellectual disability
Developmental formulations of adult development, 188–189
Developmental/Individual difference/Relationship-based (DIR) model, 679, 681
Developmentally Reduced Synaptic Connectivity (DRSC) model, 1222
Developmental models, staged versus longitudinal lines, 97
Developmental psychopathology, 127–131, 147, 157–159
Developmental risk factors in infants, 112, 128, 129–130
Developmental stages of drug use, 360
Dexamphetamine (DEX)
attention deficit-disruptive behavior disorders, 818
clinical use, 2280
cocaine substitution therapy, 1076
methylphenidate comparison, 2286
neuroendocrine effects, 2267
pharmacology, 2265
Dexmethylphenidate, 2264, 2265, 2280
Dextramethorphan, 1091
Dextroamphetamine *See* Dexamphetamine
DHEA *See* dehydroepiandrosterone
Diabetes mellitus
antipsychotic drugs, 2185, 2189
depression comorbidity, 1286–1287, 2503–2504
neuroleptic-induced tardive dyskinesia, 1783
psychological factors affecting medical condition, 1756, 1763
psychosomatic medicine, 2503–2504
SGA side effects, 1253, 1254, 1255

Diagnosis
brain circuitry perturbations, 248
commonalities in disorders, 245
cultural factors, 648–656
organic/inorganic distinction, 246
personality trait thresholds, 635
physical signs and symptoms, 621–631
Diagnosis-related group (DRG) payment methodology, 1837–1838
*Diagnosis and Statistical Manual of Mental Disorders* (DSM), 661–677
cultural factors, 57, 648, 650, 654–656
diagnostic codes, 667–673
future directions, DSM-V, 665
history
anxiety disorders, 318
DSM-I, 224, 663–664
DSM-II, 225, 664
DSM-III, 664
DSM-IV, 664–665
DSM-IV-TR, 661, 665
somatoform disorder, 1510–1511, 1518, 1526
multiaxial system, 543, 666–667
Diagnostic educators, 552, 553
Diagnostic Interview for Borderlines-Revised (DIB-R), 1733
Diagnostic Interview Schedule for Children (DISC-IV), 809
Diagnostic interview schedules (DISs), 404, 406–407, 412–414
Diagnostic overshadowing, 714
Dialectical behavior therapy (DBT), 293, 1667, 1734–1735, 2485
Diazepam
alcohol withdrawal, 2393
benzodiazepine equivalents, 2394
pregnancy, 2423
Dibenzoxapines, 1242
DIB-R *See* Diagnostic Interview for Borderlines-Revised
DID *See* Dissociative identity disorder
Dideoxycytidine (DDC), 913
Diet
*See also* Anorexia nervosa; Bulimia nervosa
antidepressant side effects, 2139–2140
attention deficit disorder, 2340–2341
drug metabolizing enzyme expression, 2118, 2119
elderly adults, 200
perimenopausal mood symptoms, 2512
premenstrual dysphoric disorder, 1386–1387
Rett's disorder, 799
Differential patterns in neuropsychological analyses, 562
Differential reinforcement, 837
Differentiation phase in group dynamics, 1907
Differentiation (separation-individuation process), 476
Difficult children, 151, 154
Difficult patients in group psychotherapy, 1913–1914, 1917
Diffuse optical imaging (DOI), 579
Diffusion tensor imaging (DTI), 572, 580, 1217
Diffusion weighted imaging (DWI), 572
Digressive speech, 596
Dihydroindoles, 1242
3,4-Dihydroxymethamphetamine (HHMA), 1116
Dimensional models of personality styles, 635–639
Dimensional view of mental disorders, 423
Dimethyltryptamine (DMT), 1101
Diminished capacity in criminal proceedings, 91–92
Diphenylbutylpiperidines, 1242
DIR (Developmental/Individual difference/Relationship-based) model, 679, 681
Direct conditioning, 1424, 1425
Directiveness in psychiatric interviews, 45–46
Directive therapy, 1899
Directories of mental health groups, 2085
Disabilities
*See also* Intellectual disability; Psychiatric disabilities
child/adolescent education rights, 552–553
definitions, 2060
insurance history, 1826
legal assessment, 87–88
Disability adjusted life years (DALYs), 2060
Disasters, 2465–2475
mental health professionals' activities, 2470–2473
pandemic flu, 2473–2474
rebuilding stage, 2465–2466
response planning, 2471–2472
response types, 2466–2469
types, 2465, 2466
*Disc1* gene, 276, 1214
Disciplinary segregation in correctional psychiatry, 92
DISC-IV *See* Diagnostic Interview Schedule for Children
Disclosure
case identification instruments, 406
family secrets, 1968
intimate partner violence, 2579–2580
rape/sexual assault, 2581
Discontinuation syndromes, 736, 1305–1306
DISCUS acronym, 1899
Disease conviction in hypochondriasis, 1535–1536
Disease phobia, 1535, 1536
Diseases with distinctive features
depressive mood disorder secondary to, 936, 937
mania secondary to, 938, 939
psychosis secondary to, 934
Disgust
fear development, 1425
infant development, 119
Disorder of extreme stress, not otherwise specified (DESNOS), 2567, 2587
DSM-IV-TR criteria, 2589
Disorder of written expression, 749, 750, 758, 759
Disorganized attachment in infant development, 123
Disorganized-type schizophrenia, DSM-IV-TR criteria, 1205
Displacement
defence mechanism, 1855
dream work, 465
Disruptive behavior disorders, 804–826
*See also* Conduct disorder; Oppositional defiant disorder
intellectual disability, 724–725
learning and motor disorder association, 752, 756
stimulants, 2264–2288
Disruptive behavior in preschool children, 147
DISs *See* Diagnostic interview schedules
Dissociation
defence mechanism, 1855
hypnosis, 1984, 1985
models and mechanisms, 1573–1574
qualitative change in consciousness, 584, 592
self-experience disorders, 602–603, 604
Dissociation of feelings, pregay/prelesbian children, 2542
Dissociative amnesia, 1558, 1561–1562
DSM-IV-TR criteria, 1560
Dissociative disorders, 602–603, 1558–1574
conversion disorder relationship, 1526
cultural factors, 653
depersonalization disorder, 1558, 1564–1565
dissociative amnesia, 1558, 1561–1562
dissociative fugue, 1558, 1562–1564
dissociative identity disorder, 1558, 1565–1569
dissociative trance disorder, 653, 1558, 1569–1572
DSM classification systems, 675
DSM-IV-TR criteria, 1560, 1563, 1565, 1569, 1572
early adulthood, 506
epidemiology, 1559–1560
history, 1558–1559
hypnosis, 1995–1996
hypnotizability, 1990
ICD-10 diagnostic criteria, 1574
models, 1573–1574
somatization disorder relationship, 1520

speech disorders, 597
Dissociative fugue, 1558, 1562–1564
DSM-IV-TR criteria, 1563
Dissociative identity disorder (DID), 1558, 1565–1569
comorbidity, 1566–1567
DSM-IV-TR criteria, 1565
hypnotizability, 1989
Dissociative trance disorder, 653, 1569–1572
DSM-IV-TR criteria, 1569
Distortions of body image, 602, 604
*See also* Anorexia nervosa; Body dysmorphic disorder; Gender identity disorder; Somatic type delusional disorder
Distortions of will, 602, 604
Distraction techniques, 1933
Distress
couples therapy, 1973
cultural idiom differences, 58–59, 64
disaster-related, 2467–2468
Distribution, pharmacokinetics, 2100–2101
Disulfiram (Antabuse)
alcohol dependence, 992–993, 2394–2395
cocaine dependence, 1074–1075, 2410
Diurnal enuresis, 868, 869, 874
Divalproex sodium (valproate semisodium)
*See also* Valproic acid
acute bipolar depression treatment, 2212
acute mania treatment, 1359, 2208–2209, 2210
bipolar disorder, 1357–1362, 1366
bipolar maintenance therapy, 2216–2217, 2218
cannabis withdrawal, 1055
children, 1366
pregnancy, 1366
rapid cycling bipolar disorder, 2218–2219
side effects, 1360–1361
Divorce, 1965–1966, 1973
Dix, Dorothea Lynde, 218
DLB *See* Dementia with Lewy bodies
DLPFC *See* Dorsolateral prefrontal cortex
DMT *See* Dimethyltryptamine
DNRI *See* Dopamine noradrenaline-reuptake inhibitors
Doctor-patient relationship *See* Clinician-patient relationship
DOI *See* Diffuse optical imaging
Domains of functioning, 639–641
Domestic violence, 2544
Donepezil, 907, 2300–2304
Dopamine agonist treatment, 1647
Dopamine beta hydroxide (DBH) gene, 247
Dopamine-glutamate theory of schizophrenia, 1228–1229
Dopamine noradrenaline-reuptake inhibitors (DNRI), 1293, 1304, 1305, 1310–1311, 1313
Dopamine receptor $D_2$ (DRD2), 279, 2162–2163, 2164
Dopamine receptor $D_3$ (DRD3), 2107
Dopamine reuptake inhibitors (DRIs), 2127
Dopaminergic agent treatments, 1072–1073
Dopaminergic system
antidepressant side effects, 2138
antipsychotic drugs, 279, 2162–2163
attention-deficit hyperactivity disorder, 814
bipolar disorder, 1350
caffeine effects, 1023, 1032
cannabis effects, 1044
cocaine use disorders, 1061–1062, 1072
depressive disorders, 1294
falling in love, 1966
intoxication/reward, 365, 366, 367
kleptomania, 1671
mood effects, 2123
neuroleptic malignant syndrome, 1786
obsessive-compulsive disorder, 1456
receptor blockade, 1781, 1786
receptor genes, 814
schizophrenia, 301, 306–307, 1225–1226, 1244–1245, 2162–2163, 2164
schizophrenia animal models, 279, 282, 283–284
social phobia, 1423
stereotyped movement disorder, 891
substance use pathophysiology, 365, 366, 367, 368, 369–370
tardive dyskinesia, 1781
tic disorders, 855
Dopamine-serotonin antagonism theory of antipsychotic drugs, 2163
Dopamine transporter (DAT), 815, 1061, 2267
Dorsal striatum, 248, 249–250
Dorsolateral prefrontal cortex (DLPFC)
cognitive functioning, 250–251
emotional regulation strategies, 252
schizophrenia, 1220, 1227
Dosage issues
dose-response relationship, 2105–2106, 2109
intellectual disability treatment, 736
opioid agonist medication, 1177
treatment-resistant depression, 1312, 2375, 2379
Double-hit hypothesis of schizophrenia, 1211
Doubt, obsessive-compulsive disorder, 1445, 1447
Down syndrome
Alzheimer's disease risk, 904
behavioral phenotypes, 718
etiology/pathophysiology, 694, 696–697
solid food aversion, 838
DPD *See* Dependent personality disorder
DPPD *See* Depressive personality disorder
Drawings, child evaluation, 548, 550–551
DRD2 *See* Dopamine receptor $D_2$
DRD3 *See* Dopamine receptor $D_3$
Dreams
day residue, 465
dream censor, 465
dream work, 465
group psychotherapy, 1913, 1918
historical views, 207, 211, 214, 216, 225
interpretation, 1856, 1859
latent content, 465
manifest dream, 465
narcolepsy, 1638
nightmare disorder, 1647
normal sleep, 1627
psychoanalytic theory, 464–465, 1856, 1859
DRG *See* Diagnosis-related group
DRIs *See* Dopamine reuptake inhibitors
Drive/motivation neurocircuit adaptation to substance use, 369–370
Drives *See* Instincts
Drives
aggressive, 469, 470, 473–474
infant development, 110–111
psychoanalytic theories, 467, 469, 470, 472–474, 478–479, 1858
sexual, 467, 469–470, 473–474, 1581, 1582, 1601
Driving
anxiety disorders, 1427
dementia patients, 2553
intoxication effects, 961
MDMA use, 1118
Dronabinol, 2412
Drop-in centers, 2091
Dropout (premature treatment termination), 1068, 1078, 1973
DRSC model *See* Developmentally Reduced Synaptic Connectivity model
Drug counseling, substance use disorders, 1070–1071, 1179, 1180
Drug interactions
antidepressants, 2141–2143
antipsychotic drugs, 2183, 2184
bipolar disorder therapy, 1359
drug metabolizing enzyme expression, 2117
herbal remedies, 2108, 2343, 2115, 2119
lithium, 2204, 2205
St. John's Wort, 2322
stimulants/psychotropic medications, 2278–2279

Drug-receptor concept, 2105
Drug responses
  concomitant herbal medicines, 2115, 2119
  ethnocultural effects, 2118–2119
  genetic polymorphism effects, 2116–2117, 2119–2120
  herbal medicine interactions, 2343, 2115, 2119
  individual variation, 2112–2113, 2119, 2120
  metabolizing enzyme expression variation, 2117–2119
Drugs, *See also* Medication; Pharmacotherapy; Substance abuse; Substance dependence; Substance use disorders
Dry bed technique, enuresis, 873–874
DSM *See Diagnosis and Statistical Manual of Mental Disorders*
DTI *See* Diffusion tensor imaging
DTs *See* Delirium tremens
Dual agency in correctional populations, 2599
Dual diagnosis
  *See also* Integrated dual disorder treatment
  cannabis-related disorders, 1055
  intellectual disability, 719
  prevalence, 2075
Dual-instinct theory, 470
Dualism, 2028
Dual relationships of professionals, 70, 73, 74–75
Duloxetine, 2127, 2128, 2133–2134, 2147
Duration of treatment, treatment-resistant depression, 2375, 2379
Duration of untreated psychosis (DUP), 1239–1240
Duty of care, 85–86
DWI *See* Diffusion weighted imaging
Dyadic theory, 1906
Dying *See* Death
Dynamic viewpoint, psychoanalytic psychotherapy, 1853
Dyscrasias, antipsychotic drugs, 2191
Dysfunctional anger, 2608
  *See also* Aggression
Dyslexia, 2342
Dyslipidemia, 2185, 2189
Dysmorphophobia
  *See also* Body dysmorphic disorder
  delusions, 1273
Dyspareunia, 1592–1593
  DSM-IV-TR, 1593
Dysphoria, premenstrual dysphoric disorder, 1379–1387
Dysthymic disorder
  antidepressant use, 2131
  early adulthood, 505
  interpersonal psychotherapy, 1882
  major depressive disorder combination, 1290
  major depressive disorder distinction, 1498–1499
Dystonias, 1251–1253, 1774–1776, 1781, 2184–2187

Early adulthood *See* Adolescents; Young adults
Early childhood *See* Infants; Preschool children
Early-onset Alzheimer's disease, 394, 396
Early-onset dysthymia, DPPD, 1748
Early-onset schizophrenia, 158, 303–304, 2173–2174
Eating disorders, 1609–1625
  *See also* Anorexia nervosa; Bulimia nervosa; Feeding disorders
  adolescents, 502–503
  binge-eating disorder, 503, 1623–1624
  childhood problems, 497–498
  cognitive and behavioral therapies, 1939
  cultural factors, 654
  definition, 1609
  diabetes patients, 2504
  DSM classification systems, 675–676
  DSM-IV-TR criteria, 1611, 1618
  feeding disorders of early childhood, 830–844
  food-restricting compulsive behavior, 645
  hypnosis, 1990, 1999–2000
  intellectual disability, 726
  obsessive-compulsive spectrum disorders, 1453
  relational problems, 1805
Eating/feeding distinction, 831
Ebstein's anomaly, 2508
ECA study *See* Epidemiological Catchment Area study
ECG *See* Electrocardiography
Echolalia, 847
Echopraxia, 782
Ecological momentary assessment (EMA), 2039
Economic factors
  *See also* Financial issues; Socioeconomic factors
  correctional mental health care, 2599–2600
  homeless people, 2526, 2535
  mental health services, 1834–1841
    history, 1817, 1822–1824, 1826, 1832
Ecstasy (MDMA), 1102–1103, 1113–1119
ECT *See* Electroconvulsive therapy
ED *See* Erectile disorder
EDS *See* Excessive daytime sleepiness
Education
  *See also* Psychoeducation
  autistic disorder, 790
  child/adolescent rights, 747–748, 552–553
  curriculum, 751–752
  drug users, 1068
  intellectual disability, 711–712, 740
  learning/motor skills disorders, 747–762
  restraint and seclusion, 2493, 2494
  schizophrenia, 1261–1262
  somatization disorder, 1522
  tic disorders, 856–857
  young adult development, 186–187
Educational assessment, 748, 749–750, 551–552
The Education for all Handicapped Children law, 747–748
EE *See* Expressed emotion
EEG *See* Electroencephalography
Effect size, study design methodology, 2623
Efficacy
  antidepressants, 2128–2130
  compliance relationship, 2458
  couples therapy, 1972–1973
  patients beliefs in medication, 2453, 2454
  pharmacologic therapy, 2107–2109
  psychotherapy, 292–293
  quality improvement, 1844
  stimulants in attention-deficit hyperactivity disorder, 2269–2276
Efficacy-effectiveness gap, 1355
Efficiency of brief psychotherapies, 1898
Effortful control development, 158
Ego boundaries, 1949
Egocentrism, 139
Ego concept, 470–471
  development, 139, 188
  post-Freudian psychology, 471–473
  psychoanalytic psychotherapy, 1853
Ego-dystonic compromises, 471
Ego ideal, 469–470
Ego-libido, 468
Ego-strengthening techniques, 1992, 1994
Ego-syntonic compromises, 471
ELD *See* Expressive language disorder
Elderly adults, 2549–2562
  abuse, 2578, 2579
  alcohol use disorders, 983, 998
  antidepressants, 2143, 2559
  approach to, 2549–2551
  biological developmental processes, 183–184
  bipolar disorder, 1366–1367
  cognitive changes, 197–199
  coping resources, 196–197
  dementia, 1651, 2551–2557
  depressive disorders, 1291–1292, 1880–1881, 1882–1883, 2143, 2285, 2557–2560
  development, 183–184, 196–202
  effective listening, 15–16

generalized anxiety disorder, 1505
hospitalization, 1882–1883
interpersonal counseling, 1882–1883
interpersonal psychotherapy, 1880–1881
late life disorders, 512–515
lifestyle, 200–201
medical disorder/depression comorbidity, 2558
normal sleep/wakefulness changes, 1629
sensory changes, 199–200
sexuality, 201–202
sleep, 1629, 1651
stimulants use, 2285
suicide, 106, 2558–2559
Elective mutism *See* Selective mutism
Electrical stimulation, 219, 2354–2355
*See also* Deep brain stimulation; Electroconvulsive therapy; Transcranial direct current polarization; Transcranial electrical stimulation; Vagus nerve stimulation
Electrocardiography (ECG), 536–537, 539
Electroconvulsive therapy (ECT), 2354–2361, 2368
antidepressant treatment augmentation, 2151
clinical studies, 2360
coronary artery disease patients, 2501
depression treatment, 1312–1313, 1315–1316
elderly adults, 2559–2560
history, 221, 2354, 2358–2359
indications, 2386
informed consent, 84
mechanisms of action, 2354–2355, 2359
neuroleptic malignant syndrome, 1788
pregnancy, 2421, 2509
side effects, 2359–2360
suicidal patients, 2486
tic disorders, 859
treatment algorithms, 2360–2361
VNS comparison, 2367
Electroencephalography (EEG)
HPPD, 1112, 1113
hypnosis and seizures, 1998
hypnotic process, 2009
impulse-control disorders, 1662
laboratory assessments, 537, 538, 539
neuropsychological assessment, 556, 564, 566
neurotherapy, 2342
patterns, delirium diagnosis, 924
schizophrenia, 1222–1223, 1236
shyness, 1423
SKY breathing, 2330
sleep, 1627, 1632
Electronic monitoring (EM) of medication compliance, 2450–2451
Electrophysiology of schizophrenia, 1222–1223
Electroshock therapy *See* Electroconvulsive therapy
Elements, early understanding of mental disorders, 206, 207
Elimination disorders
children, 498, 868–879
encopresis, 498, 875–879
enuresis, 498, 868–875
Elimination of medications, 2104
EM *See* Electronic monitoring
EMA *See* Ecological momentary assessment
Embarrassment development, 145
EMDR *See* Eye movement desensitization and reprocessing
Emerging adulthood, 186–187
*See also* Adolescents; Young adults
Emotional attachments *See* Attachment
Emotional development
adolescents, 172, 173
decalage, 106
infant development, 113, 116, 117, 119, 121–122, 125
longitudinal studies, 101–102, 103
preschool, 141–142, 143, 145
school-age children, 153–154, 157
Emotional incontinence, 947–948
Emotionally focused therapy, 1964
Emotional neuroadaptation to substance use, 370
Emotional placidity in Klüver-Bucy syndrome, 948–949
Emotional problems
adolescents, 500–501
behavioral medicine, 2042
childhood, 494–496
depression, 253
early adulthood, 504–506
elderly adults, 514
learning and motor disorder association, 747, 750, 755, 756, 762
post-traumatic stress disorder, 252–253
psychiatric interviews, 41
school-age children, 154, 158
Emotional thinking in cognitive model, 1921
Emotions, 605–618
*See also* Anxiety; Depression
amygdala function, 325–326
anger, 119, 122, 617–618, 2603, 2604, 2608
apathy, 617
brain damage, 607
brain functions, 251–253, 325–327
brief psychodynamic therapies, 1894, 1900
circumplex model, 608
cognitive characterization, 606–607
cognitive psychology, 435, 438–439, 442, 446
dimensional models, 607–608
early understanding, 206, 209
emotional regulation, 607, 608, 611
euphoria, 617
memory interactions, cognitive psychology, 438–439, 442
physiological states, history of understanding, 222
positive as cures, 211
prefrontal cortex, 251–253, 326–327
psychiatric interview bias, 41
rage, 617–618
regulation, 251–253, 325–327, 607, 608, 611
Empathy
biological basis, 6, 13
clinician-patient relationship, 23
cognitive psychology, 444–445, 446
effective listening, 4, 7, 8, 17
history of understanding, 231
preschool development, 145
psychiatric interviews, 43
psychoanalytic psychotherapy, 1856–1857, 1863
psychopathy, 446
social interactions, 444–445, 446
Empirically based indications
family/marital treatment, 1804–1806
interpersonal psychotherapy, 1879
social skills training, 2052–2053
Employer-based private insurance, 1834, 1835–1837, 1841
Employment issues
*See also* Supported employment; Unemployment; Vocational rehabilitation
adjustment disorders, 1712
intellectual disability rights, 713
mentally ill homeless people, 2534
psychiatric rehabilitation, 2065, 2077–2078
shift work sleep disorder, 1645
suicide risk, 2480
young adult development, 186–187
Empowerment in recovery-oriented treatment, 2050
Empty nest phenomenon, 2512
Encephalitic psychoses, 933, 934
Encephalitis disseminata, 1288
Encephalopathies, 1133–1135, 1136
Encopresis, 875–879
behavioral therapy, 878
childhood problems, 498
diagnosis, 875, 876
DSM-IV-TR, 875
etiology/pathophysiology, 875–877
ICD-10, 885
pharmacotherapy, 878
psychiatric comorbidity, 877
treatment, 877–879

End of life, 24, 30–31, 2516–2524
Endocannabinoid system, 365, 366, 367, 1043–1044
Endocrine disorders
  *See also* Hormones
  antidepressants, 2145
  complementary treatments, 2320
  delirium, 920
  depression comorbidity, 1286–1287
  psychological factors affecting medical condition, 1763–1764
  psychosomatic medicine, 2503–2505
Endogenous/nonendogenous depression, 339
Endogenous opioids, 2002
Endophenotypes
  anxiety disorders, 321, 328
  complex mental disorder animal models, 278–279
  genetic epidemiology, 263–264, 269
  hippocampal dysfunction, 247–248
  psychiatric disorders, 246
  schizophrenia, 305–306, 1215
Endorphins, 1382, 1966
End stage renal disease (ESRD), 1765
Energy drinks, 1032
Engagement
  brief psychotherapies, 1900
  group dynamics, 1906, 1907
  mentally ill homeless people, 2530–2532
England, history, 209–210, 212, 216–217
Entorhinal cortex, 1219
Enuresis, 868–875
  assessment, 870–871
  childhood problems, 498
  definition, 868
  diagnosis, 868, 870–871
  DSM-IV-TR, 869
  etiology/pathophysiology, 869–870
  ICD-10, 885
  pharmacotherapy, 872–873
  psychosocial treatments, 873
  treatment, 871
Environmental factors
  alcohol use disorders, 971–973
  animal models, 276, 284, 285
  antisocial personality disorder, 1731
  attention-deficit hyperactivity disorder, 816–817
  autistic disorder, 788
  bipolar disorder, 1353–1354
  children with academic difficulties, 754, 755
  communication disorders, 771, 775–776
  delirium, 921
  depressive disorders, 1300
  drug responses, 2113, 2118–2119
  etiological overlap between disorders, 247
  generalized anxiety disorder, 1501–1502
  genetic epidemiology, 263
  histrionic personality disorder, 1736–1737
  illness diagnosis, 34–35
  infant development, 111–112, 128–131
  intellectual disability, 716
  learning and motor skills disorders, 755, 757
  longitudinal developmental studies, 97–98
  MDMA-related disorders, 1119
  nicotine dependence, 1155
  obsessive-compulsive disorder, 1457
  panic disorders, 1402
  post-traumatic stress disorder, 1479
  preschool development, 136–137
  psychiatric disorder, 284, 285
  psychopathology risk factors, 105
  reactive attachment disorder, 894–895
  stereotyped movement disorder, 891
  substance use disorders, 364, 965–966
  tic disorders, 856
Environment-genotype interactions
  anxiety disorders, 328, 329–332
  mood disorders, 342–343
Enzymes, drug metabolizing, 2114–2119
Eosinophilia, 2191
Epicurus, 206
Epidemiological Catchment Area (ECA) program, 406, 411–417, 1207, 2060
Epidemiology, 403–432
Epigenetics, 176–177, 276, 1217
Epilepsy
  *See also* Antiepileptic drugs
  acquired aphasia, 796
  autism, 381
  autistic disorder comorbidity, 785
  depression comorbidity, 1287
  depressive mood disorder secondary to, 936
  psychosis secondary to, 933–934
Epileptiform activity, Rett's disorder, 797
Episodic memory
  characteristics, 585, 587
  dissociative amnesia, 1561–1562, 1573–1574
  preschool development, 139–140
EPS *See* Extrapyramidal symptoms
Equitability, couples therapy, 1974
Erectile disorder (ED), 1587–1589, 1978, 1980
  DSM-IV-TR, 1587
Erikson, Erik H., 135, 196, 476–477
Eriksonian adult development model, 189–191, 196
Erotic preoccupations, 1600–1605
Erotomanic-type delusional disorder, 1272–1273
ERP *See* Exposure and response prevention
ERPs *See* Event-related potentials; Evoked response potentials
Escape extinction, 837, 838
Escitalopram
  availability, 2128
  breastfeeding, 2424
  generalized anxiety disorder, 2228, 2230
  history, 2127
  obsessive-compulsive disorder, 1461
  social anxiety disorder, 2233
Esquirol, Jean-Etienne, 214–215
ESRD *See* End stage renal disease
Estrogens
  Alzheimer's disease, 2307
  female sexual arousal disorder, 1586
  gender identity disorder, 1599
Eszopiclone
  abuse, 1187, 1189, 1190–1191
  insomnia, 1637, 2257, 2262
Ethical issues, 67–78
  *See also* Confidentiality
  conflicts of interest, 70, 73, 74–75
  couples therapy, 1973–1974
  dual relationships, 70, 73, 74–75
  factitious disorders, 1552–1554
  financial issues, 73, 74–75, 76
  forensic psychiatrists, 70–71
  gender reassignment surgery, 1600
  principles/guidelines, 68–70, 77
  sexual relationships, 71–72, 77–78
  suicidal patients, 2486
  therapeutic frame boundaries, 71–79
  therapist anonymity, 76–77
  torture victims, 2573–2574
Ethnicity issues
  *See also* Cultural issues; Racial issues
  adolescent social development, 173
  alcohol use disorders, 984, 985, 998–999
  antidepressants, 2134–2135
  clinician-patient relationship, 29–30, 61
  cognitive and behavioral therapies, 1934
  culture relationship, 55
  depression presentation differences, 1293
  ethical guidelines, 69–70
  ethnocultural allodynia concept, 1865
  ethnocultural identity, 57–58
  factitious disorder, 1552
  matching in institutions, 61
  neuroleptic-induced tardive dyskinesia, 1782
  pharmacotherapy responses, 225
  psychiatric interviews, 42
  psychoanalytic psychotherapy, 1864–1865
  psychopharmacology, 2112–2121
  race/culture relationship, 55
  schizophrenia epidemiology, 1209
  substance use disorders, 360, 361
  USA cultural diversity, 54

Ethnobotanical hallucinogens, 1100–1101
Ethnomedical systems, 56, 58, 59, 61
*See also* Complementary and alternative medicine
Ethology, history, 226
Etiology
biological commonalities, 245–253
changing viewpoints, 245–246
definition, 1217
endophenotypes, 246
Eugenics, history, 209, 217
Euphoria, 617
Europe
alcohol use disorders, 983
history, 207–217, 1818
homelessness, 2529–2530
Euthanasia, 69
Evacuation behavior in disasters, 2468
Evaluation *See* Clinical evaluation
Event characteristics in post-traumatic stress disorder, 1476–1477
Event-related potentials (ERPs)
hypnotic analgesia, 2002
post-traumatic stress disorder, 1478
schizophrenia risk, 1223
Evidence-based medicine, 2108–2109
bipolar disorder, 1354–1359
brief psychotherapies, 1891–1893
cognitive and behavioral therapies, 1927–1928
history, 230
levels of evidence, 1354–1355
psychiatric rehabilitation, 2059, 2062, 2065, 2067–2080
statistical research, 2619–2633
Evidence examination, cognitive and behavioral therapies, 1927–1928
Evoked response potentials (ERPs), 2010
Evolutionary psychiatry, 230–231
Excessive daytime sleepiness (EDS), 1630, 1631, 1638–1641, 1642
Excited catatonia secondary to a general medical condition, 943, 944
Excitement *See* Arousal
Excoriation *See* Skin picking
Excretion
*See also* Elimination disorders
pharmacokinetics, 2100, 2104
Executive functions
adolescent development, 171
attention-deficit hyperactivity disorder, 816
cognitive psychology, 435, 437–438
educational curriculum, 752
impairment, 899
learning disorders, 750–751
neurocircuits, 371
prefrontal cortex role, 250–251
schizophrenia animal models, 280
substance dependence, 371
top-down control, 437–440
Exercise
eating disorders, 1614, 1619
elderly adults, 201
premenstrual dysphoric disorder, 1386, 1387
Exhibitionism, 1600, 1601, 1602
Expanded psychiatric database, 39
Expectations in psychopharmacology, 20, 2114–2115
Experience rating, 1836
Experimental investigations
animal models, 275–286
epidemiological studies, 407–408
hallucinogens, 1102
methodology/statistics, 2619–2633
Expert testimony, 88, 89, 90–91
Explicit memory, 440–442, 1561, 1573–1574
Exploitative patients, 78
Exploratory interactions, bereavement effects, 2520–2521
Exposure-based behavioral therapy, 1932–1933
brief psychotherapies, 1896
generalized anxiety disorder, 1503
neurobiological basis, 324
obsessive-compulsive disorder, 1463–1465
phobias, 324, 1429–1432
post-traumatic stress disorder, 1483, 2590
Exposure and response prevention (ERP), 1463–1465, 2437
Expressed emotion (EE)
epidemiology, 1803
families, 1796, 1799
family psychoeducation, 1955
medical comorbidity, 1806
schizophrenia therapy, 1263
Expression of affect, 608, 1795, 1798–1799, 1802, 1808
Expressive language disorder (ELD), 765–770
assessment, 767–768
comorbidity, 769
diagnosis, 765–767, 770
differential diagnosis, 770
DSM-IV-TR criteria, 765–766, 769, 774
epidemiology, 768
treatment, 772
Expressive-supportive continuum, 1852–1853, 1863
External control, paraphilia, 1605–1606
External threat assessment, 542
External validity threats, 2622
Extinction
escape extinction, 837, 838
fear-conditioning, 323–324, 606–607
Extrapyramidal symptoms (EPS), 1251–1252, 1773, 2184–2187, 2556
Extraversion, 1722, 1736
Eye contact in schizophrenia patients, 1234
Eye movement desensitization and reprocessing (EMDR), 2590
adjustment disorders, 1711
PTSD treatment, 1483
torture victims, 2571
Eye-roll measurement, 1989
Face processing/interpretation of expression, 326, 387, 606
Facial expressions, 605, 781
Factitious disorder
with combined psychological and physical signs and symptoms, 1550
DSM-IV-TR criteria, 1549
historical examples, 209
with predominant physical signs and symptoms, 1549
with predominant psychological signs and symptoms, 1549–1550, 1551
Factitious disorder by proxy, 1549, 1554–1556
Factitious disorders, 1548–1556
comorbidity patterns, 1551, 1555
course, 1552, 1555
delirium differentiation, 923–924
developmental/cultural/gender issues, 1552, 1555
diagnosis, 1549–1551, 1554–1555
dissociation, 603
DSM classification systems, 675, 1549
early adulthood, 508–509
epidemiology, 1551, 1555
etiology/pathophysiology, 1552–1553, 1555
memory impairment, 902, 927
Munchausen's syndrome, 1548, 1550
physical signs and symptoms, 630–631
psychological factors, 1552–1553
social and environment factors, 1553, 1555
somatoform disorders distinction, 1511, 1532
treatment, 1553–1554, 1555–1556
Factor analysis, definition, 2630–2631
Fact-oriented interventions, 47
Fagerström Test for Nicotine Dependence (FTND), 1150
Failure to thrive in infancy, 832
Fainting, phobias, 1412
Fairbairn, W.R.D., 479
False information at psychiatric evaluation, 540
False memories, 1997, 2006
False-negatives/false-positives, diagnostic assessments, 427
False pregnancy (pseudocyesis), 1526, 1543
False selves, 474
Familial/*de novo* chromosomal abnormalities, gene identification, 267
Familial factors, *See also* Genetic factors
Families
*See also* Parents
Alzheimer's disease, 908
clinician-patient relationship, 30
compliance influences, 2448
consumer model of recovery, 2050
couples therapy, 1974
encopresis, 876, 877, 878

Families *(Continued)*
evaluation in children with academic difficulties, 753–755
gender identity disorder, 1595, 1597
group service development, 2091
homeless, 2527, 2528
intellectual disability, 721
interaction assessment in initial child/adolescent evaluation, 551
learning and motor skills disorders, 760
mentally ill homeless people, 2534
patient compliance, 2454–2455
rape/sexual assault victims, 2583
same sex couples, 2543–2544
selective mutism, 884
stakeholder organizations, 2085, 2086–2088
structure changes over time, 182
tic disorders, 856–857
treatment decision making, legal issues, 84
Family advocacy movements, 2085–2086
Family environment
anorexia nervosa, 1616
anxiety disorders, 328, 329–332
infant development, 128, 129, 131
psychopathology, 105
smoking cessation, 1163
suicide risk, 2479–2480
Family history
alcohol use disorders, 982–983, 995, 1030–1031, 1664, 2394–2395
family therapy, 1949–1950
impulse-control disorders, 1666, 1670, 1683
intellectual disabilities, 706, 708
mood disorders, 1285, 1292, 1303
pharmacological considerations, 819
psychiatric interview, 38, 39, 527
schizophrenia, 509, 1197, 1255
substance use disorders, 261, 1171
suicide, 541, 2479–2480, 2483
Family Interaction Coding System, 1802
Family of origin, 39, 1966–1967
Family psychiatry, 1955
Family psychoeducation, 760, 1952–1953, 1955–1956, 1957, 2070–2073
Family relational problems
*See also* Parents
affect expression, 1799
assessment, 1801–1802
communication, 1797–1798
conflict leading to homeless youth, 2528–2529
diagnosis, 1801
learning and motor skills disorders, 747, 750, 761
medical comorbidity, 1807
problem solving, 1800
structure, 1796
treatment, 1804–1806
Family resilience, 1956–1957, 1958
Family secrets in couples therapy, 1967–1968
Family studies
*See also* Adoption studies; Twin studies
bipolar disorder, 1348–1350
genetic epidemiology, 258–259, 261
impulse-control disorders, 1666–1667, 1691
mood disorders, 340–341
schizophrenia, 1212
schizophreniform disorder, 1271
Family support network (FSN), 1053
Family therapy, 1803, 1948–1961
alcohol use disorders, 991
anorexia nervosa, 1617
caregiver burden reduction, 1957–1958
cognitive-behavioral, 1952–1953, 1955, 1957, 1960
history, 1948
impulse-control disorders, 1686
international perspectives, 1958–1959
learning and motor skills disorders, 760–761
mental illness prevention, 1956–1957
postmodern, 1953–1955, 1960–1961
psychodynamic, 1949–1950, 1959
psychoeducation, 760, 1952–1953, 1955–1956, 1957, 2070–2073
schizophrenia, 1263, 1805
shared psychotic disorder, 1277
strategic, 1951–1952, 1960
structural, 1950–1951, 1959–1960
suicidal patients, 2485
tic disorders, 860
Family-to-Family, National Alliance on Mental Illness program, 2087
Fantasies
clinician-patient relationship, 20, 21
Freud, 289–290
gender identity disorders, 1595
paraphilias, 1600–1604
psychiatric evaluations of children, 548
FAS *See* Fetal alcohol syndrome
FASD *See* Fetal alcohol spectrum disorders
Fatalities *See* Death; Mortality
$^{18}$F-deoxyglucose, 1105, 1107
Fear
*See also* Anxiety
animal models, 321, 322–323
anxiety relationship, 321–322, 610, 1409
conditioning, 323–324, 606–607
normal response, 1409
post-traumatic stress disorder, 1479
system activation, 321–322
Fear of disease *See* Disease phobia; Hypochondriasis
Fear-potentiated startle, 322, 323
Fecal retention, 875, 876, 877, 878, 879
Federal Employees Health Benefits (FEHB), 1817, 1837
Federal government
learning disabilities guidelines, 747–748, 749
mental health service history, 1821–1823, 1825–1826, 1831–1832, 1837–1840, 1846
Federation of Families for Children's Mental Health (FFCMH), 2085, 2088
Feedback, psychiatric interviews, 47, 48
Feeding disorders, 830–844
DSM-IV-TR criteria, 831, 839, 842
feeding disorder of infancy or early childhood, 831–839
feeding disorder of mother-infant reciprocity, 832
pica, 842–844
rumination disorder, 839–842
Feeding/eating distinction, 831
Feeding peptides, 2154–2155
Feeling found, 12–13
Feeling-oriented interventions, 47
Fees *See* Financial issues
FEHB *See* Federal Employees Health Benefits
Feighner criteria, 1203
Female gender reassignment, 1599
Female homosexuality *See* Lesbians
Female orgasmic disorder (FOD), 1589–1591
DSM-IV-TR, 1590
Female paraphilias, 1600, 1604
Female sexual arousal disorder (FSAD), 1586–1587
DSM-IV-TR, 1586
Female sexual pain disorders, 1592–1594
Feminine boys, 1594–1595
Feminist family therapy, 1953
Fentanyl, 1169–1170
Feral children, 210, 212
Fertility issues, 1209, 1767
Fetal alcohol spectrum disorders (FASDs), 982
Fetal alcohol syndrome (FAS), 694, 704, 895, 982, 1140
Fetal development, 755, 757, 1217
Fetishism, 1597–1598, 1604, 1605
Fever, 1786
FEWP *See* Free and Easy Wanderer Plus
FFCMH *See* Federation of Families for Children's Mental Health
FGAs *See* First generation antipsychotics
Fibroblast growth factors (FGFs), 343, 347
Fibromyalgia, 1650
Field research, definition, 2619
Figures of speech, 4–5, 7

Financial issues
  clinician-patient relationship, 29
  combined treatments, 2442
  compliance, 2455
  couples therapy, 1974
  effective listening, 7
  ethics, 74–75, 76
  fees in managed care systems, 74–75
  government strategies for cost control, 1837–1839, 1841–1843
  mental health service finance changes, 1822–1824, 1826, 1832, 1833
  non-collusive compensation, 73, 76
  psychoanalytic psychotherapy, 1853
Finding patients, 12–13
Fine motor problems, 750, 751, 759
Fire-setting behavior *See* Pyromania
First aid, psychological, 2472
First episode schizophrenia, 1239–1240, 2170–2171
First generation antidepressants
  drug-drug interactions, 2141–2142
  efficacy determination, 2129
  mechanisms of action, 2124, 2126–2127
  pharmacokinetics, 2133
  starting doses, 2146
  types, 2124, 2126–2127, 2128
First generation antipsychotics (FGAs), 1241–1259
  CPM use with, 1259
  delusional disorder, 1274
  dopamine, 1225–1226
  effective dose, 2180
  history, 2161–2162
  memory effects, 1233
  pharmacology, 2166
  schizoaffective disorder, 1267
  schizophrenia maintenance treatment, 2181
  selection, 2179
  side effects, 1251–1253
  striatum effects, 1221
  treatment resistance, 1256–1258
First-generation psychiatric epidemiology, 410
First-pass effect, pharmacokinetics, 2100
First responders at disasters, 2470
FISH *See* Fluorescence in situ hybridization
Fitness evaluations, legal issues, 87–88
Five-factor model of personality, 636, 1722–1723
Fixation, 466
Flashbacks, 1110–1113
Flexible care
  compliance, 2458
  insurance benefit limits, 1837
Flexible hypothesis-testing approach, 561–563
Flight of ideas, 596
Flooding technique, 1932–1933
Flu *See* Influenza
Fluid intelligence, 198
Flumazenil, 1196
Flunitrazepam (Rohypnol), 1189, 2578
Fluorescence in situ hybridization (FISH), 698–699
Fluorocarbons inhalation, 1128–1129, 1139
Fluoxetine
  acute bipolar depression, 2211, 2213
  alcohol use disorders, 995
  availability, 2128
  body dysmorphic disorder, 1541
  breastfeeding, 2424
  generalized anxiety disorder, 2232
  history, 2127
  hypochondriasis, 1537, 1538
  obsessive-compulsive disorder, 1460, 2244, 2246
  panic disorder, 2236
  pharmacokinetics, 2133, 2134
  post-traumatic stress disorder, 2240
  premenstrual dysphoric disorder, 1383, 1384
  selective mutism, 884
  trichotillomania treatment, 1692, 1694
Fluoxetine-olanzapine combination, 2211, 2213
Fluphenazine, 857–858, 1249, 2243–2244
Fluvoxamine
  availability, 2128
  breastfeeding, 2424
  history, 2127
  obsessive-compulsive disorder, 1460–1461, 2245, 2246
  panic disorder, 2237
  separation anxiety disorder, 882
  social anxiety disorder, 2233
fMRI *See* Functional magnetic resonance imaging
Focal deficits, 37
Focality of brain stimulation techniques, 2357–2358
Focal psychotherapy, 1889–1890
Focus, brief psychotherapies, 1889, 1897–1898, 1899, 1900
FOD *See* Female orgasmic disorder
Folate supplements, 2325, 2335–2336
*Folie a quatre*, 1276, 1277
*Folie simultanee See* Shared psychotic disorder
Food *See* Eating disorders; Feeding disorders
Forensic psychiatry
  competency to stand trial, 89
  criminal responsibility/insanity, 90–91
  ethical principles, 70–71
  history, 231
  hypnosis, 2006–2008
  intellectual disability, 731–732
  legal issues, 81
  rape/sexual assault, 2582–2583
Forgiveness of medication to timing/dose errors, 2449, 2458
Formal thought disorder, 595–596
Formative phase in group dynamics, 1906, 1907
*Forme fruste* somatization disorder *See* Undifferentiated somatoform disorder
Former patients' sexual relationships with therapists, 77–78
Formulations
  antipsychotic drugs, 2177–2179
  pharmacokinetics, 2099–2100
  psychostimulants, 818
ΔFosB, neuroadaptation to substance use, 373
Foster care children, homeless youth, 2528
Foul body odour, delusions of, 1273
Four Ds of medical malpractice, 85–86
Fragile X syndrome
  attention-deficit hyperactivity disorder, 2277
  autistic disorders, 383–384, 785
  intellectual disabilities, 694, 701, 718
France, history, 209, 211–212, 214–216
*F* ratio, 2623, 2628
Free association, 289–290, 1855, 1856
Free and Easy Wanderer Plus (FEWP), 2324
Fregoli's syndrome, 1273
Freighner hysteria criteria, 1514, 1517–1518
Freud, Anna, 135, 222, 471–472
Freud, Sigmund, 214, 220–221, 289–290, 464–471
  children, 135, 150, 151, 465–467
  depression, 470, 1299
  dissociative disorders, 1558, 1559
  dreams, 216, 464–465
  homosexuality, 2539
  impulse-control disorders, 1685
  mood disorders, 339
  psychodynamic theory, 214, 220–221, 289–290, 464–471
  schizophrenia, 221, 1260
  somatic symptoms, 2028
Frontal cortex anatomy, 251
Frontal lobe syndrome, 945
Frontal temporal dementia (FTD), 396–398
Frontal temporal dementia with Parkinsonism (FTDP-17), 397–398
Frotteurism, 1603
  DSM-IV-TR, 1603
FSAD *See* Female sexual arousal disorder
FSIQ *See* Wechsler Full-Scale IQ
FSN *See* Family support network
FTD *See* Frontal temporal dementia
FTDP-17 *See* Frontal temporal dementia with Parkinsonism

FTND *See* Fagerström Test for Nicotine Dependence
Full reciprocal translation, 281–282
Full-Scale IQ *See* Wechsler Full-Scale IQ
Functional assessments
  children, 722
  elderly adults, 2550
Functional domains in personality styles, 639–641
Functional hallucinations, 601–602
Functional imaging, 198–199, 573–580
Functional impairment/incompetence distinction, 83
Functional magnetic resonance imaging (fMRI), 295–296, 576, 580
  attention-deficit hyperactivity disorder, 815
  autism, 386–387
  cognitive age effects, 198–199
  schizophrenia, 311–312
  treatment-resistant depression, 2386
Functional medical complaints, 625
Functional neuropathology, 247–253
Functional/organic distinction, 625, 897

GA *See* Gamblers Anonymous
$GABA_A$/BZ receptor function, 325
GABAergic medications
  alcohol withdrawal, 2393
  cocaine dependence, 2410–2411
  cocaine use disorder treatment, 1073–1074
GABAergic system
  alcohol effects, 974, 996
  animal models, 282, 283–284, 325
  anxiety disorders, 325
  benzodiazepine receptor agonists, 2256
  electroconvulsive therapy, 2359
  genetic factors, 341, 343
  hallucinogen intoxication, 1105, 1106
  mood disorders, 341, 343, 1294, 1350, 1382
  schizophrenia, 282, 283–284, 301, 308–309, 1227, 1229
  sedative-hypnotic effects, 1187–1188
  substance intoxication/reward, 365, 366, 367
Gabapentin
  cocaine dependence, 2411
  panic disorder, 2240
  social anxiety disorder, 2235
GABHS *See* Group A beta-hemolytic streptococcal infections
GAD *See* Generalized anxiety disorder
Gadolinium, 572
Galantamine, 2300, 2302–2304
Galen, 207
Galveston Orientation and Amnesia Test (GOAT), 583
Gamblers Anonymous (GA), 1680, 1685–1686
Gambling *See* Pathological gambling
Gamma-aminobutyric acid *See* GABA
Gamma band activity (GBA), 1224
Gamma hydroxybutyrate (GHB), 1639–1640, 2260
GARF *See* Global Assessment of Relational Functioning Scale
Gasoline inhalation, 1127, 1128, 1135–1136
Gastrointestinal absorption of medications, 2100
Gastrointestinal disorders
  antipsychotic side effects, 2191
  autistic disorder comorbidity, 382, 785–786
  childhood feeding disorders, 830–831, 843
  hypnotherapy, 2003–2004
  psychological factors affecting medical condition, 1765–1766
  sleep disorders, 1650–1651
Gating, schizophrenia, 1223–1224, 1232
Gay
  *See also* Homosexuality
  definition, 2538
Gay-affirmative therapy, 2542, 2543
Gaze patterns in autistic disorder, 781
GBA *See* Gamma band activity
GBD study *See* Global Burden of Disease study
GCBT *See* Group cognitive behavior therapy
GCS *See* Glasgow Coma Scale
Gender, definitions, 2538
Gender identity, 2538–2547
Gender identity disorder not otherwise specified (GIDNOS), 1597–1598
Gender identity disorders (GIDs), 1594–1600
  body dysmorphic disorder relationship, 1540
  childhood, 498, 1594–1595
  diagnosis, 1596–1598
  DSM classification systems, 675
  DSM-IV-TR, 1596
  GIDNOS, 1597–1598
  male erectile disorder link, 1588
  sexual orientation relationship, 2546
  transgender issues, 2546
  treatment, 1598–1600
Gender issues
  adolescent brain development, 168
  adolescent coping skills, 178
  adolescent disorders, 503
  age of puberty, 161
  alcohol use disorders, 971, 981–982, 984, 985, 988, 998
  Alzheimer's disease, 904
  anorexia nervosa, 1613
  antidepressants, 2134
  antisocial personality disorder, 1731
  anxiety disorders, 1418–1419, 1500
  attention deficit-disruptive behavior disorders, 813
  bipolar disorder, 1343, 1348
  brain structure and function, 231
  breathing related sleep disturbance, 1642
  bulimia nervosa, 1620
  child development, 113, 143–144
  childhood disorders, 499
  cocaine use disorders, 1058–1059
  cognitive and behavioral therapies, 1934
  communication disorders, 770, 774, 775
  conversion disorder, 1527
  cultural effects, 56–57
  dependent personality disorder, 1743
  depressive disorders, 615, 1290, 1292–1293
  doctor-patient relationship, 56
  drug responses, 2208
  early adulthood disorders, 511
  effective listening, 6–7, 13
  elderly adults, 515
  encopresis, 875
  enuresis, 869
  factitious disorder, 1552
  generalized anxiety disorder, 1500
  historical attitudes, 206, 209, 212
  histrionic personality disorder, 1736
  impulse-control disorders, 1665, 1682, 1690
  late life disorders, 515
  learning and motor skills disorders, 757
  MDMA use, 1115
  middle adult life disorders, 511
  neuroleptic-induced tardive dyskinesia, 1782
  nicotine dependence, 1153
  obsessive-compulsive disorder, 1453–1454
  panic disorders, 1399
  post-traumatic stress disorder, 1476
  power in relationships, 1964
  preschool development, 143–144
  psychoanalytic psychotherapy, 1864
  schizoaffective disorder, 1266
  schizophrenia, 1209
  social status, 56–57
  somatization disorder, 1518, 1521
  substance use disorders, 360, 962–963
  suicide risk, 2479
  torture victims, 2573
Gender reassignment surgery, 1599–1600
Gene..., *See also* Genetic...
Gene-environment interactions
  adolescents, 176–177

anxiety disorders, 328, 329–332
gene expression, 98
infant development, 111–112
mood disorders, 342–343
Gene expression
animal models, 276, 330–331
antipsychotic drugs, 2165–2166
environmental influences, 98
maternal care effects, 330–331
psychoanalytic psychotherapy influence, 1870
General hospitals, mental health service history, 1823, 1838
Generalized anxiety disorder (GAD), 1494–1506
anticonvulsant medication, 2232
antipsychotic medication, 2232–2233
anxiolytic medication, 2228–2233
assessment, 1495–1497
benzodiazepines, 2231–2232
buspirone, 2232
children, 879, 881, 882
cognitive and behavioral therapies, 1938–1939
comorbidity patterns, 1497–1498
definitions, 1494
DSM-I-DSM to III-R changes, 318, 319
epidemiology, 1497–1500
genetic epidemiology, 261
heritability, 321
hypnosis, 1993
monoamine oxidase inhibitors, 2231
panic disorder distinction, 1393
psychotropic medications efficacy, 2224
PTSD differentiation, 1476
reboxetine, 2231
secondary to a general medical condition, 940–941
selective serotonin reuptake inhibitors, 2228, 2230–2231
serotonin-norepinephrine reuptake inhibitors, 2231
treatment, 1502–1505
tricyclic antidepressants, 2231
Generalized social phobia, 1412
avoidant personality disorder relationship, 1418, 1722–1723, 1740
CBT outcome, 1434, 2434
exposure hierarchy, 1431
genetic factors, 321, 1422
General medical conditions
amnestic disorders due to, 925
antidepressant choice, 2143–2145
anxiety disorder secondary to, 940–942, 1500
anxiety-like symptoms, 612, 627
attention deficit-disruptive behavior disorders comorbidity, 812
behavioral medicine, 2027–2043
biological intervention, 544
bipolar disorder comorbidity, 1344–1345, 1365, 1366–1367
caregiver burden reduction, 1957–1958
catatonic disorder secondary to, 942–944
clinician-patient relationship, 20–22, 30–31
conversion disorder relationship, 1527–1528, 1530
delirium due to, 919
dementia comorbidity, 2553–2554
dementia due to, 916–918
depression comorbidity, 1286–1288, 1881, 1882–1883, 2558
depression-like symptoms, 616, 627, 1341–1342
effective listening, 4, 16, 17
euphoria as presenting symptom, 617
evaluation of physical signs and symptoms, 622
hypnosis applications, 2000–2005
hypochondriasis relationship, 1536
infant development risk factors, 130–131
inhalant-related disorders, 1132–1140
intellectual disability, 721
Klüver-Bucy syndrome secondary to, 947, 948–950
learning and motor skills disorder comparison, 748–749
mania secondary to, 938–940
manic symptoms, 1341–1342
medication psychiatric effects, 528, 530
mood disorder secondary to, 935–940
obsessive-compulsive symptoms secondary to, 941–942
opioid use disorder comorbidity, 1181–1182
pain disorder relationship, 1530, 1532–1533
panic disorder relationship, 1393, 1395
personality change secondary to, 944–946
premenstrual dysphoric disorder differential diagnosis, 1380–1381
pseudobulbar palsy secondary to, 947–948
psychiatric diagnosis in medically ill patients, 2498–2499
psychiatric disorders affecting, 1756, 1759, 1760–1761
psychiatric morbidity, 2498
psychiatric symptoms, 530, 531
psychoanalytic psychotherapy, 1866
psychological factors affecting, 1511, 1754–1768
psychopathological effects, 512, 513, 514, 625, 723, 931–950
psychosis secondary to, 932–935
PTSD comorbidity, 1484
relational problems, 1806–1807
schizophrenia differential diagnosis, 1238–1239
sexual dysfunction, 1581, 1584, 1587, 1592, 1593, 1980
sexual pain disorders, 1592, 1593
sleep disorders, 1633, 1650–1651
somatization disorder relationship, 1518–1520, 1522
somatoform disorder relationship, 1510–1511, 1524
stimulants use in depression, 2285
substance abuse comorbidity, 968
substance use causing, 360–361, 1065–1066, 1067
suicide, 2482
General mental health, therapeutic support group model, 2085
General paresis, 209, 214, 217
General systems approach in group psychotherapy, 1905, 1906
Generating alternatives in cognitive and behavioral therapies, 1928
Generativity, 190–191
Genetic counseling, 860, 2037
Genetic epidemiology, 257–270
adoption studies, 259, 261, 340–341, 1212, 1348–1349
complex patterns of transmission, 262
controls, 262
endophenotypes, 263
environmental factors, 263
family studies, 258–259, 261
future directions, 262, 269–270
gene-gene interactions, 269–270
gene identification, 264–270
impact on science/practice, 263–264
implications for pathophysiology, 270
improving treatments, 270
migration studies, 259
risk estimation, 262–263
sampling strategies, 262
schizophrenia, 258, 260
twin studies, 259
Genetic factors
adolescent development, 176–177
alcohol use disorders, 971–973
Alzheimer's disease, 394, 395, 396, 905–906
animal models, 276, 284–285, 330–331
antidepressant metabolism, 2134–2135, 2141
antipsychotic drugs, 2165–2166
anxiety disorders, 320–321, 328, 329–332, 1421–1422, 1500
attention deficit-disruptive behavior disorders, 813–814
attention-deficit hyperactivity disorder, 814
autistic disorder, 382–385, 788
bipolar disorder, 342, 1343, 1348–1350
caffeine use disorders, 1023, 1027, 1031
cancer, 2037
chromosomal abnormalities, 268, 696–698
circadian rhythm sleep disorders, 1644

Genetic factors *(Continued)*
cocaine use disorders, 1061
communication disorders, 770, 775
conversion disorder, 1529
CYP2D6 enzyme alleles, 2104
depressive disorders, 342, 1296–1297, 2124
drug responses, 2112–2113
enuresis, 869–870
epidemiology, 257–270
frontal temporal dementia, 397
gene association studies, 257, 264–265, 270, 330–331, 814, 1212–1215
gene identification, 264–270
generalized anxiety disorder, 1500
hallucinogen-related disorders, 1105
history of understanding, 221, 222, 224, 225, 231
hypothalamic pituitary adrenal axis role in mood disorders, 345
impulse-control disorders, 1667, 1684
impulsive behavior, 644
infant development, 111–112
intellectual disability, 695–703
learning and motor skills disorders, 757, 760
Lewy body dementia, 398
longitudinal developmental studies, 97–98, 104–105
maternal care effects on gene expression, 330–331
MDMA-related disorders, 1117
molecular genetic factors, 257–270
mood disorders, 340–343, 345, 1296–1297, 2124
narcolepsy, 1639
neuroadaptation to substance use, 373–374
nicotine dependence, 1153–1154, 2408
obsessive-compulsive disorder, 1454
opioid use disorders, 1171
panic disorders, 1402
personality traits, 634, 1422
pharmacodynamic variability, 2106–2107
PLMS/RLS, 1647
post-traumatic stress disorder, 1477
preschool development, 136–138
prion diseases, 399
psychoanalytic psychotherapy, 1853, 1870
reactive attachment disorder, 894
Rett's disorder, 798
schizophrenia, 304–306, 1211–1215
sexual orientation, 2541
sleepwalking disorder, 1649
stereotyped movement disorder, 891
substance use disorders, 363–364, 373–374, 964
tic disorders, 852–853, 860
violence, 2607, 2608
weight-gain/fatness, 1615
Genetic manipulation in animals, 324–325
Genetic polymorphisms
CYP2D6 enzyme alleles, 2104
CYP450 system, 2116–2117
drug responses, 2116–2117, 2119–2120
HTT-linked polymorphic region, 176
MDMA-related disorders, 1117
mood disorder susceptibility, 341, 343
multiple psychiatric disorder association, 247
serotonin transporter system, 342, 343, 1117
single nucleotide polymorphisms, 341
Genital phase of childhood sexuality, 466–467
Genius-insanity link, 219
Genograms, 1949–1950, 1968–1969
Genome-wide association studies, 257, 269
Genomics, 263–264
Geographic Information Systems (GIS), 2039
Geriatric people *See* Elderly adults
German Psychoanalytic Association study, 295
Germany/German speaking countries, history, 209, 211, 213–214, 222
Gestalt techniques, 1746
GFR *See* Glomerular filtration rate
GH *See* Growth hormone
GHB *See* Gamma hydroxybutyrate
GIDNOS *See* Gender identity disorder not otherwise specified
GIDs *See* Gender identity disorders
Gill, M.M., 480
*Ginkgo biloba*, 2311, 2338
Ginseng, 2338
GIS *See* Geographic Information Systems
Glasgow Coma Scale (GCS), 582–583
Global Assessment of Functioning Scale, 533, 535
Global Assessment of Relational Functioning Scale (GARF), 1801
Global Burden of Disease (GBD) study, 404–405
Globalization effects, 55
Glomerular filtration rate (GFR), 2104
Glucocorticoid antagonists, 2307–2308
Glucocorticoid receptor genes, 341–342
Glucose blood tests, 534–535
Glucose metabolism, 573–574
'Glue sniffing' *See* Inhalant-related disorders
Glutamatergic system
alcohol effects, 974, 996
animal models, 283–284
depressive disorders, 1294, 2154
hallucinogen intoxication, 1105, 1106
schizophrenia, 283–284, 301, 308, 1227–1230, 1259
tic disorders, 855–856
Glutamatergic therapies
Alzheimer's disease, 2304–2305
depressive disorders, 1309–1310
treatment-resistant depression, 2384
Glutaminergic system
mood disorders, 343, 1348, 1350
schizophrenia, 312
sleep/wake disorders, 1630
tic disorders, 855
Glycine treatment, 1097
GnRH *See* Gonadotropin-releasing hormone
Goal-directed activities, adolescent development, 171
Goals
psychoanalysis, 1855
psychoanalytic psychotherapy, 1856
recovery approach, 2066–2067
supportive psychoanalytic psychotherapy, 1863
GOAT *See* Galveston Orientation and Amnesia Test
Gonadal steroids *See* Sex hormones
Gonadotropin-releasing hormone (GnRH), 1385
Goodness of fit, 177
Government roles
consumer empowerment, 2090–2091
learning disabilities guidelines, 747–748, 749
mental health service finance, 1837–1840, 1841–1843
G-protein
antidepressant action, 2124, 2125–2126
antipsychotic drugs, 2165–2166
schizophrenia, 1215, 1260
Graded tasks, 1930–1931
Grammar use development, 141
Grandiose-type delusional disorder, 1273
Grandiosity, thought disorders, 599, 600
Grandparents, risk factors and protective factors, 185
Grant applications, 2085
Granulomatous angiitis, 946
Grapefruit juice, 2115, 2118
Graphomotor problems, 750, 759
Graunt, John, 404
Greeks, ancient, 206, 207
Grief
adult development, 192
bereavement, 2519–2523
complicated, 2523–2524
depression, 613
disaster-related, 2469
family therapy, 1949
normal, 2520, 2523
suicide, 2519
Griesinger's single disorder hypothesis, 245

Griesinger, Wilhelm, 213
Gross anatomical changes, 247
Gross motor problems, 751
Group A beta-hemolytic streptococcal infections (GABHS), 850, 856
Group-as-a-whole approaches, 1905
Group cognitive behavior therapy (GCBT), 1937, 2435, 2437
Group cohesion, 1905–1906
Group drug counseling, 1070–1071
Group dynamics/group development, 1906–1908
Group function theory, 223
Group psychotherapy, 1904–1918
  agreements, 1910–1911
  alternative formats, 1914–1917
  avoidant personality disorder, 1741
  cognitive and behavioral therapies, 1937, 2435, 2437
  concurrent individual psychotherapy, 1914
  dependent personality disorder, 1744
  difficult groups/patients, 1913–1914, 1917
  efficacy studies, 292
  female orgasmic disorder, 1590
  gender identity disorders, 1599
  group dynamics/group development, 1906–1908
  history, 221, 1904
  histrionic personality disorder, 1737
  initiation, 1911–1912
  interpersonal psychotherapy, 1876, 1881, 1882, 1883, 1884
  learning and motor skills disorders, 760, 761
  narcissistic personality disorder, 1740
  organization, 1909
  passive-aggressive personality disorder, 1747
  patient selections, 1909–1910
  practice, 1909–1911
  research, 1917–1918
  schizoid personality disorder, 1728
  schizophrenia, 1261
  schizotypal personality disorder, 1730
  self-help group relationship, 1916
  special considerations, 1913–1914
  termination, 1912–1913, 1917
  theories, 1904–1908
  therapeutic factors, 1908–1909
  therapist's role, 1911
  training therapists, 1914, 1918
  treatment course, 1912–1913
  treatment failures, 1917
GROW Inc. (International), 2085, 2089, 2091
Growth
  adolescent development, 167–168
  brain development, 98, 99
  suppression by stimulants, 819, 2277
Growth factors in mood disorders, 343, 346, 347–349, 350
Growth hormone (GH), 167, 1295
Guanfacine, 858–859, 861
Guardianship, 732, 2550–2551
Guided discovery, 1926
Guidelines
  American Psychiatric Association, 68, 77, 1845–1846
  couples evaluation, 1969
  ethical, 68–70, 77
  federal government learning disabilities guidelines, 747–748, 749
  psychotherapy manuals, 226
  quality of care, 1845–1846
Guilt, 145, 533, 537
'Gut-directed hypnotherapy', 2004

Habilitation approaches, 709–713
Habit control hypnosis, 2005–2006
Habit reversal training (HRT), 859–860
Habitual response patterns, dorsal striatum, 249–250
Hair pulling *See* Trichotillomania
Haldol (haloperidol), 2421
Half-life ($T_{1/2}$) of medications, 2104, 2133, 2134
Halitosis delusions, 1273
Hallucinations
  animal models, 280
  conversion disorder, 1526–1527
  delirium, 920
  historical use of term, 214, 215
  hypnotizability, 1990
  narcolepsy, 1638, 1639
  perception disturbances, 601, 602
  stimulants in ADHD, 2278
Hallucinogen abuse, 1107–1108
  DSM-IV-TR criteria, 1107
Hallucinogen intoxication, 1103–1107
  diagnosis, 1103–1105
  DSM-IV-TR criteria, 1103–1104
  etiology/pathophysiology, 1105–1107
  treatment, 1107
Hallucinogen persisting perception disorder (HPPD), 1110–1113
  diagnosis, 1110–1112
  DSM-IV-TR criteria, 1110
  etiology/pathophysiology, 1112
  treatment, 1112–1113
Hallucinogens, 1100–1126
  definition, 1100
  neuropharmacology, 367
Haloperidol
  chemical structure, 2168
  communication disorders, 776
  delirium treatment, 924
  obsessive-compulsive disorder, 2247
  schizophrenia, 1242, 1249
  tic suppression, 857
Halstead-Reitan battery, 563
Hamilton Anxiety Rating Scale (HAM-A) (HARS), 1496, 2228, 2230
Hamilton Rating Scale for Depression (HAM-D) (HRSD), 2109, 2378, 2431–2433
HapMap project, 264
Harm avoidance personality trait, 329
Harm reduction in opioid dependence management, 1182–1183
HARS *See* Hamilton Anxiety Rating Scale
Hatha yoga, 2329
HBM *See* Health belief model
HCFA *See* Health Care Financing Administration
Headaches
  breathing related sleep disturbance, 1642
  caffeine intoxication, 1022
  caffeine withdrawal, 1024, 1025, 1026–1027
  post-anesthetic, 1026–1027
  primary hypersomnia, 1640
  psychological factors affecting medical condition, 1765
Head and neck cancer, 2502
Head trauma
  amnestic disorders, 926
  dementia due to, 914
  depression, 937
Health behavior models, 2448–2449
Health belief model (HBM), 2448, 2454
Health Care Financing Administration (HCFA), 734
Healthcare services for homeless people, 2527, 2533, 2534–2535
Health insurance, 1817, 1834, 1835–1837, 1841
Health maintenance organizations (HMOs), 1840–1841
Health of physician, clinician-patient relationship, 29
Health-related quality of life, 1346–1347
Health-risk behaviors, 2468
Hearing
  *See also* Auditory perception
  listening distinction, 5–6
Heart *See* Cardiac...
Heat stroke, 1787
Heaviness of Smoking Index (HSI), 1150
Height influences, 167–168
Heinroth, Johann, 213
Helplessness
  *See also* Learned helplessness
  PTSD therapy, 1995
Help-seeking
  cultural issues, 58–59
  failure/delay, 419, 423
Hematological drug effects, 2191
Hematopoietic inhalant toxicity, 1139–1140
Hemotypic continuity, 490
Hemp plant, 1041

Hepatic disorders
depression comorbidity, 1287, 2145
mentally ill homeless people, 2535
opioid abusers, 1174
Hepatic function
antidepressant drug effects, 2140, 2145
antipsychotic drug effects, 2185, 2191
atomoxetine effects, 820
blood tests, 535
Kava, 2334
S-adenosyl-L-methionine, 2322, 2323
Hepatitis B, 1174
Hepatitis C, 1174, 2535
Hepatolenticular degeneration *See* Wilson's disease
Herbal remedies
anxiety disorders/insomnia, 2333–2335, 2341–2342
cognitive enhancement, 2337–2339
depression treatment, 1311
drug interactions, 2108, 2343, 2115, 2119
premenstrual dysphoric disorder, 1386
Heritability *See* Genetic factors
Heroin, 355, 357, 1169–1170, 2405
Heterosexism, definition, 2538–2539
Heterotypic continuity, 490
*N*-Hexane inhalation, 1138
HFA *See* High-functioning autism
HHMA (3,4-dihydroxymethamphetamine), 1116
5-HIAA *See* (5-)Hydroxyindoleacetic acid
Hierarchical multiple regression, 2629
Hierarchy in structural family therapy, 1950
High affinity partial agonists, 2391
High-functioning autism (HFA), 793
High-risk developmental periods, 106, 107
Hilgard, E.R., 1559
Hippocampus
Alzheimer's disease, 394, 395
antidepressant effects, 349
biological commonalities between disorders, 247–248
fear responses, 322
memory formation and emotions, 606, 607
neurogenesis in adults, 349–350
neuronal atrophy/cell loss, 348
schizophrenia, 1219
stress effects, 349
volume-PTSD relationship, 328, 330
Hippocrates, 206
Histamines, 2135–2136, 2306
Histopathology, 247
History
agoraphobia, 1392
anxiety disorders, 318–319
attitudes to adolescence, 162–163
behavioral medicine, 2028–2029
bipolar disorder, 1335–1336
brief psychotherapies, 1889–1891
clinician-patient relationship, 20, 21
cognitive psychology, 433–434, 1920
dementia, 393
dissociative disorders, 1558–1559
external validity threat, 2622
family therapy, 1948
homosexuality, 2539
hypnosis, 1982–1984
intellectual disability assessment, 706–707, 719–721
Interdisciplinary Council on Development and Learning Disorders Diagnostic Manual for Infants and young Children, 679–680
marriage, 1964
medication-induced movement disorders, 1773
mental health services, 1818–1834, 1837–1841, 1846
panic disorders, 1392–1393
psychiatric rehabilitation, 2061–2062
psychiatry, 205–241
psychosomatic medicine, 2496–2497
services for mentally ill homeless people, 2526–2530
torture victims, 2565
History of present illness, 4, 8–10, 38–39
Histrionic personality disorder (HPD), 1735–1737
differential diagnosis, 1540, 1736, 1743
DSM-IV-TR criteria, 1736
HIV/AIDS
adolescent behavior, 174
antibody testing, 535–536
behavioral medicine, 2035
bisexuals, 2546
buprenorphine interaction with HIV medications, 1178
caregiver positive mood states, 2521–2522
dementia, 911–914, 1881
depression, 1884
gay men, 2546
intellectual disability causes, 704
interpersonal psychotherapy, 1881, 1884, 2035
lesbians, 2546
mentally ill homeless people, 2527, 2535
neurological/psychiatric manifestations, 532
psychological factors affecting medical condition, 1766
rape/sexual assault, 2583
risk factor assessment, 527, 528
serotonin reuptake inhibitors, 913–914
substance abuse relationship, 361, 1181
treatment, 913–914
HLA *See* Human leukocyte antigens
HMMA (4-hydroxy-3-methoxymethamphetamine), 1116
HMOs *See* Health maintenance organizations
Hoffman, I.Z., 479–480
Holistic approaches, 759, 2050
Holland, history, 211
Holocaust, 461
Holoprosencephaly, 703
Homeless people
administration/academics and advocacy, 2534–2535
correctional system, 2595
epidemiology of mental illness, 2526, 2527, 2528
history, 2526–2530
services, 2526–2535
stages of care, 2530–2534
substance use disorders, 2527, 2528, 2531, 2533
Homeopathic treatments, 1386, 1712
Homeostatic sleep-wake cycle regulation, 1628–1629, 2255
Homocysteine, 2335–2336
Homophobia, definition, 2539
Homosexuality, 2538–2547
couples therapy, 1979–1980
developmental issues, 2541–2542
exhibitionism relationship, 1602
gay-affirmative therapy, 2542, 2543
gender identity relationship, 1594, 1595, 1598
history, 225, 2539, 2540
language use in sexual therapy, 1977
lesbians, 1977, 2539, 2540, 2541–2542
sexual disorders relationship, 1603–1604, 1606
Hopefulness
disaster situations, 2472, 2473
recovery-oriented treatments, 2050, 2067
Hopelessness
model of depression, 455
pathological gambling, 1681
suicidal patients, 2481
Hopi syndromes, 651
Hormones
*See also* Sex hormones
adolescent behavior, 168
anorexia nervosa, 1612
antipsychotic drug effects, 2188
development, 99–100
homosexuality, 2540–2541
premenstrual dysphoric disorder, 1385
puberty, 164, 166, 167
violence link, 2606–2607

Hormone therapy (HT)
anxiety disorders, 2332–2333
depression, 1295, 1313
gender identity disorders, 1599
perimenopausal mood symptoms, 2512
postpartum women, 2511
premenstrual dysphoric disorder, 1385
Hospitalization
*See also* Institutions
anorexia nervosa, 1616–1617
Assertive Community Treatment as alternative, 2068–2069
bipolar disorder, 1339–1340
diagnosis-related group payment method, 1837–1838
initial disposition, 544
inpatient/outpatient transition, 29
insurance benefit limits, 1836, 1837
involuntary, 82–83, 89, 2531, 2532
legal issues, 82–83, 89
mentally ill homeless people, 2527, 2531, 2532
secure inpatient care, 2597
smoking cessation treatment, 1163
subsyndromal disorders, 1882–1884
suicidal patients, 2483
violent patients, 2602
Hostility expression, 49, 617–618
Housing issues
correctional settings, 2597
mentally ill homeless people, 2526, 2529, 2532, 2533–2534
Howe, Samuel Gridley, 710
HPA axis *See* Hypothalamic-pituitary-adrenal axis
HPD *See* Histrionic personality disorder
HPPD *See* Hallucinogen persisting perception disorder
HRSD *See* Hamilton Rating Scale for Depression
HRT *See* Habit reversal training
HSDD *See* Hypoactive sexual desire disorder
HSI *See* Heaviness of Smoking Index
5-HT (5-hydroxytryptamine) *See* Serotonin
HT *See* Hormone therapy
HTT-linked polymorphic region (HTTLPR), 176
Humane treatment of the insane, history, 207, 208, 212–213, 218, 223
Human genome project, 341
Human immunodeficiency virus *See* HIV/AIDS
Human leukocyte antigens (HLA), 1211
Human-made/natural disaster distinction, 2465, 2466
Humoral theories, early understanding of mental disorders, 206, 207, 209
Hunger-satiety cycle, 837
Huntington's disease
animal models, 275, 276
antipsychotic drugs, 2173
dementia due to, 909
Huperzine-A, 2337
Hydrocarbon inhalation, 1127
Hydrocephalus, 916
Hydrocephalus ex vacuo, 906
Hydromorphone use disorders, 1169–1170
4-Hydroxy-3-methoxymethamphetamine (HMMA), 1116
5-Hydroxyindoleacetic acid (5-HIAA), 644, 1666, 1677, 1690
5-Hydroxytryptamine (5-HT) *See* Serotonin
Hyperactive children, 496
*See also* Attention-deficit hyperactivity disorder
Hyperarousal, 2587
Hyperdopaminergia, 1228–1229
Hyperforin, 2322
Hyperglycemia, 1253, 1256
Hypericin, 2322
Hypericum Depression Trial Study Group 2002, 2321
*Hypericum perforatum* (St. John's Wort), 1311, 2319, 2321–2322
Hyperlexia, 782
Hyperlipidemia, 1253, 1254, 1256
Hypermetamorphosis, 948–949
Hyperorality, 948–949
Hyperprolactinemia, 2505
Hypersexuality, 948–949
Hypersomnia, 1638–1641
breathing related sleep disturbance, 1641, 1642, 1643
circadian rhythm sleep disorders, 1643–1644
narcolepsy, 1638–1640
primary, 1640–1641
psychiatric disorder comorbidity, 1634
substance-induced sleep disorder, 1652, 1653
Hypertension
breathing related sleep disturbance, 1642, 1643
heart disease patients, 2500
phencyclidine intoxication, 1094
psychological factors affecting medical condition, 1762–1763
Hyperthymic temperament, 615
Hyperthyroidism, 932, 1342
Hypervigilant states, 583
Hypnagogic/hypnopompic hallucinations, 1638–1639
Hypnosis, 1982–2013
absorption, 1984–1985
analgesia for medical procedures, 2000–2003
applications, 1991–2008
brain electrical activity, 2008–2011
conversion disorder therapy, 1529
definition, 1985–1986
dissociation, 602, 1984, 1985
dissociative disorders, 1559, 1562, 1563–1564, 1567
enhanced hypnotizability, 2013
forensic applications, 2006–2008
general medical applications, 1991, 2000–2005
habit control applications, 1991, 2005–2006
history, 211, 214, 217
neurophysiological correlates, 2008–2012
psychiatric applications, 1991–2000
psychiatric disorder/hypnotizability relationship, 1988–1991
psychiatric evaluation, 540
suggestibility, 1984, 1985
trichotillomania treatment, 1693
Hypnotic Induction Profile, 1987–1988
Hypnotic medication *See* Sedative-hypnotics
Hypnotic restructuring technique, 1992–1993
Hypnotizability, 1984, 1985, 1986–1987, 1988–1991, 2013
Hypoactive sexual desire disorder (HSDD), DSM-IV-TR, 1583
Hypochondriasis, 1535–1538
definition/diagnostic features, 1535–1536
differential diagnosis, 1536–1537
DSM-IV-TR criteria, 1535
early adulthood, 508
epidemiology, 1536
etiology/pathophysiology, 1537
generalized anxiety disorder distinction, 1499–1500
obsessive-compulsive disorder differential diagnosis, 1452
physical signs and symptoms, 629–630
treatment, 1537–1538
Hypofrontality, 1220
Hypoglutamatergia, 1228–1229
Hypoglycaemia, 2504
Hypomanic episodes, bipolar disorder, 1336–1338, 1339–1340, 1356
Hypopneas, 1641
Hypotension, antipsychotic drug effects, 2185, 2190, 2501
Hypothalamic feeding peptides, 2154–2155
Hypothalamic-pituitary-adrenal (HPA) axis
adult abuse, 2584
antidepressant development, 2152
depressive disorders, 1295, 1297
gene discovery, 341–342
mood disorder neuropathology, 341–342, 343, 345
post-traumatic stress disorder, 1477, 1478
psychotherapy studies, 295
stress responses, 247–248
substance dependence, 370

Hypothalamic-pituitary-gonadal axis, 1612, 1619
Hypothalamus, sleep/wakefulness, 1628, 1629, 1630
Hypothesis-testing in neuropsychological assessment, 561–563
Hypoxia, 705
Hysterectomy, 1385
Hysteria
  *See also* Somatization disorder
  historical views, 206, 207, 209, 210, 214
  hypnosis, 1983
  mass hysteria, 1529
  use of term, 1513–1514

Iatrogenic depression, 2145
Iatrogenic substance dependence, 962, 1192, 1193
IBD *See* Inflammatory bowel disease
IBM®, managed health care, 1841
Ibogaine, 1101
IBS *See* Irritable bowel syndrome
ICC *See* Intraclass correlation coefficient
ICCD *See* International Center for Clubhouse Development
ICCM *See* Intensive clinical case management
ICD-9-CN *See* International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10 *See* International Statistical Classification of Diseases and Related Health Problems-Tenth Revision
ICDL-DMIC *See* Interdisciplinary Council on Development and Learning Disorders Diagnostic Manual for Infants and young Children
ICDs *See* Impulse-control disorders
Ictal affective alterations, 618
Id concept, 213, 214, 221, 470, 1853
IDDT *See* Integrated dual disorder treatment
IDEA *See* Individuals with Disabilities Education Act
Idealization, 469–470, 1739
Ideas of reference, 600
Idebenone, 2311
Identifying information, 525–526
Identity
  adolescents, 499
  adult development, 190, 192–193
  dissociative fugue, 1562–1564
  ethnocultural issues, 55, 57–58
  gender issues, 56–57
  psychiatric databases, 40
  self-experience disorders, 602
Idiom of distress, cultural factors, 58–59, 64, 655–656
Idiopathic hypersomnia, 1640–1641
Idiopathic side effects, 2140–2141
IED *See* Intermittent explosive disorder
IEP conferences, 552–553
IGF-1 *See* Insulin like growth factor-1
Illegal immigrants, 60
Illicit Drug Anti-Proliferation Act (2003), 1114
Illicit drugs
  *See also* Substance use disorders
  use patterns, 358–360
Illness awareness *See* Insight
Illness explanations, cultural issues, 58–59, 61, 64
Illness management and recovery (IMR), 2073–2075
Illness of physician, clinician-patient relationship, 29
Illness theories, 33
Illogical thinking, 596, 598
Illusions, 601, 602
  *See also* Hallucinations
Iloperidone, 2168, 2170
IM *See* Intramuscular formulation
Imagery techniques, 1926, 1993, 2001–2002, 2003, 2590
Imaging *See* Brain imaging; *individual imaging techniques*
IMD *See* Institutions for mental diseases
IMI-CM *See* Imipramine plus clinical management
Imipramine
  availability, 2128
  combined treatments, 2431–2432
  history, 2123
  mechanism of action, 2126
  panic disorder, 2238
  S-adenosyl-L-methionine comparison, 2323
  separation anxiety disorder, 882
Imipramine plus clinical management (IMI-CM), 292–293
Immature defences, 188–189
Immediate (short term) memory, 197, 198, 585, 587
Immigration, 60, 1209–1210
Immobility secondary to a general medical condition, 942–943
Immune dysfunction, 382, 856, 859, 1216, 1450–1451
  *See also* HIV/AIDS
Immunotherapy, 2308
Impaired masculinity, 1601
Impaired Response Inhibition and Salience Attribution (I-RISA) syndrome, 357
Implicit emotional regulation strategies, 251–252
Implicit (procedural) memory, 440, 442, 443, 1573–1574
Important persons, clinician-patient relationship, 31
Impotence *See* Male erectile disorder
Impulse-control disorders (ICDs), 1658–1701
  adolescents, 502
  DSM classification systems, 676
  DSM-IV-TR criteria, 1658, 1660, 1695
  early adulthood, 507
  ICD-10 Diagnostic Criteria for Research, 1695
  intermittent explosive disorder, 1658, 1661–1668
  kleptomania, 1658, 1660–1661, 1668–1674
  obsessive-compulsive disorder differential diagnosis, 1452
  onset ages, 422
  pathological gambling, 1658, 1660–1661, 1678–1687
  pyromania, 1658, 1660–1661, 1674–1678
  substance dependence, 356
  trichotillomania, 1658, 1660–1661, 1687–1695
Impulsive aggression, 1661, 1665, 2603, 2604, 2608
  *See also* Intermittent explosive disorder
Impulsive behavior, 1658–1661
  *See also* Compulsive behavior; Impulse-control disorders
  attention-deficit hyperactivity disorder, 2275
  differential diagnosis, 1659, 1665
  maladaptive functioning, 642–644
  suicide, 2481
Impulsive-compulsive shift in substance dependence, 356
IMR *See* Illness management and recovery
Inadequate dosage, treatment-resistant depression, 2375
Inappropriate affect, 603, 604, 948
Inattention, Overactivity with Aggression (IOWA) Conners, 807, 808
Inborn temperament, 633
Incarceration, 92, 2529, 2593–2600
Incentive treatment for drug users, 1052, 1070
Incidence measures, 405–406
Inclusion principle, 711, 713
Incoherence, 597, 598
Incompetence *See* Competency
Indicated prevention, 2493
Indigenous illness syndromes, 648, 650, 652, 653, 654–655
Indigenous treatments, 2115, 2119
Indirect conditioning, 1425
Indirect modulatory pharmacology strategies for substance use disorders, 2391
Individual differences between children, 490–491
Individuality, cultural differences, 1958–1959
Individualized Education Programs, 750
Individualized services, 2050

Individual placement and support (IPS) model, 2079
Individual private insurance, 1835
Individual risk factors for psychopathology, 104–105
Individuals with Disabilities Education Act (IDEA), 712, 747–748, 749
Individual therapy
  concurrent group psychotherapy, 1914
  drug counseling, 1070–1071, 1179
  family therapy relationship, 1955
  gender identity disorders, 1598–1599
  learning and motor skills disorders, 760
  psychoanalytic psychotherapy, 1851–1871
  schizophrenia, 1261
  sexual problems, 1977
  Western versus non-Western cultures, 1958, 1959
Individual variation in drug responses, 2112–2113, 2119, 2120
Indolealkylamines, 1102
Indoleamine hypothesis of mood disorder neuropathology, 344
Inducers in CYP450 system, 2101–2103
Industrialization, 1210
Infanticide, history, 216
Infantile anorexia, 832
Infantile autism, use of term, 780, 783
Infants
  0–2 months, 113–118
  2–3 month transition, 118–120
  7–9 month transition, 121–124
  18–20 month transition, 124–127
  autism, 106, 780
  behavioral inhibition, 328–330
  biological development, 98, 99
  caffeine withdrawal, 1025
  cognitive development, 100, 101
  cultural context of development, 112–113
  development, 98–104, 109–131
  diagnostic classification, 679–688
  emotional development, 101–102, 103
  facial expressions, 605
  feeding disorders, 830–844
  fetal alcohol syndrome, 694, 704, 895, 982, 1140
  moral development, 102–103, 104
  neonatal abstinence syndrome, 2402
  protection factors, 127–128
  reactive attachment disorder, 889, 892–895
  regurgitation, 840
  risk factors, 127–131
  rumination syndrome, 840
  sleep patterns, 1629
  social development, 102, 104
Infectious causes
  delirium, 920
  dementia, 393, 394, 911–914
  intellectual disability, 703–704, 705
  tic disorders, 856, 859
Infectious diseases
  *See also* HIV/AIDS
  depression comorbidity, 1287
  influenza epidemics, 1216, 2473–2474
  psychological factors affecting medical condition, 1766
  sexually transmitted infections, 174, 2583
  substance use relationship, 361
Infertility, 1767
Infestation delusions, 1273
Inflammatory bowel disease (IBD), 1765–1766
Inflammatory disease, dementia, 394
Influenza epidemics, 1216, 2473–2474
Information collection
  *See also* Confidentiality
  bias, 409–410
  children/adolescent evaluations, 546–547
Information processing
  adolescent development, 169–170
  cognitive model, 1921–1923
  dissociation, 1573
  fear development, 1424, 1425
  mind-computer analogy, 433–434
  schizophrenia, 1232, 2050–2051, 2053
Informed consent
  hospitalization, 82
  medication-induced movement disorders, 1774
  minors, 84–85
  neuroleptic treatment, 1774
  treatment, 83, 84
Inhalant-induced disorders, 1131
Inhalant intoxication, DSM-IV-TR, 1132
Inhalant neuropharmacology, 367
Inhalant-related disorders, 1127–1142
  abuse, 1131
  chronic abuse, 1133–1138
  comorbidity, 1132
  dementia due to, 916
  dependence, 1131
  DMS-III-R to DSM-IV-TR changes, 1130–1131
  DSM-IV-TR, 1132
  epidemiology, 1129–1130
  etiology/pathophysiology, 1132–1133
  ICD-10, 1142
  intoxication, 1131–1132
  neurotoxicity, 1133–1138
  non-neurological toxicity, 1132–1133, 1138–1140
  substances, 1127–1129
  treatment, 1140–1141
Inhalation substance classification, 1127
Inhibition constant ($K_i$), 2225
Inhibition reduction, 1671
Inhibition role in top down processing, 438–439
Initial disposition, 544
Initial psychiatric evaluations of children/adolescents, 546–554
Initial treatment plans, 544
Inmates, correctional psychiatry, 92, 2529, 2593–2600
Inner experience, 8, 9
Inner restlessness, 1779–1780
Inositol, 2325
Inpatient care *See* Hospitalization
Inpatient/outpatient transition, 29
Insanity, historical use of term, 205, 210, 217
Insanity defence, 89–91, 2595
Insecure attachment in childhood, 628, 836
  *See also* Reactive attachment disorder
Insight, 603–604
  body dysmorphic disorder, 1539
  early understanding, 206
  evaluation, 592
  hypochondriasis, 1537
  kleptomania, 1674
  obsessive-compulsive disorder, 1443, 1447–1448, 1452
  psychiatric databases, 41
  schizophrenia patients, 1236
  thought disorders, 598
Insight-oriented psychotherapy, 1674, 1857
Insomnia, 1633–1638
  benzodiazepine receptor agonists hypnotics, insomnia, 2256–2257
  breathing related sleep disturbance, 1641, 1642, 1643
  circadian rhythm sleep disorders, 1643–1644
  complementary medicine, 2261, 2326–2327, 2331, 2332, 2333–2335
  early adulthood, 508
  elderly adults, 2551
  FDA-approved medications, 2255–2256
  hypnosis, 2003
  mood disorders, 624
  over-the-counter medications, 2260–2261
  pharmacology, 1636–1638, 2254–2262
  prescription medication off-label use, 2258–2259
  primary, 1633
  psychiatric disorder comorbidity, 1633–1635, 1638, 2261–2262
  sedating antidepressants, 2259
  sedating antipsychotics, 2260
  selective melatonin receptor agonists, 2257–2258
  substance-induced sleep disorder, 1652, 1653
  treatment, 1635–1638
Instincts, 465, 467, 470, 478
  *See also* Drives

Institute of Medicine (IOM) reports, 2108, 2109
Institutions
*See also* Hospitalization
deinstitutionalization movement, 224
epidemiological sampling, 403, 416
history, 208, 210–211, 213, 217, 218, 1819
intellectual disability, 713, 714
reactive attachment disorder, 893–895
reducing availability, 2526
State Care Acts, 1820
Institutions for mental diseases (IMD), mental health service funding history, 1823, 1832, 1838
Instruments
behavior measurement, 722
case identification, 406
future directions, 424
psychometric properties, 406–407
Insulin like growth factor-1 (IGF-1), 347
Insurance, 1817, 1834, 1835–1837, 1841
Integrated brief intervention for cannabis dependence, 1047, 1052
Integrated dual disorder treatment (IDDT), 2075–2077
Integrated grief, 2521, 2523
Integrated models of adult development, 187–188
Integrated pharmacotherapy for intellectual disability, 735
Integrated psychological therapy (IPT), 1262–1263
Integrating mental health in primary care settings, 2038
Integration, cognitive psychology, 448
Integrity development, 191
Intellectual disability, 689–746
assessment, 706–708, 719–722
causation classification, 694–708
childhood, 492–493
comorbidity patterns, 692–694, 735–736
concept of, 689–690
course/natural history, 708–709
definitions, 690–692
diagnostic categories, 717–719
differential diagnosis, 708
DSM-IV-TR criteria, 691–692
etiology/pathophysiology, 694–708
forensic/legal issues, 731–732
mental disorders with, 714–741
perinatal causes, 705
pharmacotherapy, 733–740
postnatal causes, 705–706
prenatal causes, 695–699, 702–704
prevalence, 692
psychosocial problems/interventions, 705–706, 740–741
treatment, 709–713, 732–733
violence link, 2605
Intelligence, 588–591
age effects, 184, 198
children, 490–491, 492–493, 549
Kauffman Brief Intelligence Test, 550
tests history, 220, 223
Intelligence quotient (IQ), 490, 492–493, 588–590, 690, 549
Intensive care of mentally ill homeless people, 2532–2533
Intensive case management model, 2068
Intensive clinical case management (ICCM), 1264
Intent-to-treat random-effects regression, 2272
Interaction effect, analysis of variance, 2628
Interactions *See* Drug interactions
Interaction therapy, parent-child relational problems, 1804–1805
Interactive disorders in infants and young children, 681, 682, 683–684, 686
Interdisciplinary Council on Development and Learning Disorders Diagnostic Manual for Infants and young Children (ICDL-DMIC), 679–688
Interictal depressions, 936
Interictal personality syndrome, 945, 946
Interictal psychosis, 933–934
Interlineal decalage, 106–107
Intermittent explosive disorder (IED), 1658, 1661–1668
assessment, 1662
comorbidity patterns, 1663–1665
diagnosis, 1661–1662
differential diagnosis, 1660, 1665
DSM-IV-TR criteria, 1661, 1662–1663, 1665
epidemiology, 1662–1663
etiology/pathophysiology, 1665–1666
treatment, 1667–1668
Intermittent maintenance medication for schizophrenia, 2171
Internal consistency, study design methodology, 2624
Internalization, object relations theory, 473
Internalized homophobia, 2538, 2539, 2542
International Center for Clubhouse Development (ICCD)
International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 667, 673
*See also* International Statistical Classification of Diseases and Related Health Problems
International comparison, alcohol use disorders, 983–984
International ethical guidelines, 69–70
International family mental health services, 1958–1959
International Statistical Classification of Diseases and Related Health Problems-Tenth Revision (ICD-10)
caffeine dependence, 1029
cocaine use disorders, 1081
cultural factors, 648
dissociative disorders, 1574
elimination disorders, 885
generalized anxiety disorder, 1496–1497
intellectual disability definition, 692
learning and motor skills disorders, 762
obsessive-compulsive disorder, 1448–1449, 1467–1468
panic disorders, 1406
post-traumatic stress disorder, 2566–2567
psychotic disorders diagnosis, 1278
SAD, 885
substance dependence, 354–355
traumatic stress disorders, 1489–1490
Interobserver agreement, study design methodology, 2625
Interpersonal counseling (IPC), 1882–1884
Interpersonal group psychotherapy, 1905–1906
Interpersonal psychoanalysis, 479
Interpersonal psychotherapy for adolescents (IPT-A), 1881
Interpersonal psychotherapy for dysthymic disorder (IPT-D), 1882
Interpersonal psychotherapy for HIV-positive patients (IPT-HIV), 1881
Interpersonal psychotherapy (IPT), 1875–1886
adjustment disorders, 1711
biological/neuroimaging studies, 295–296
bipolar disorder, 1352
brief psychotherapies, 1889, 1894–1895, 1899–1900
cancer, 2036
cocaine use disorders, 1069
cognitive-behavioral therapy comparison, 1875–1876, 1879–1880, 1881, 1883, 1884–1885, 1936
combined treatments, 2431–2437
depressive disorders, 1299, 1317
efficacy studies, 292–293
HIV/AIDS, 1881, 2035
marital disputes, 1881
modifications, 1880–1882
mood disorders, 1875–1883, 1884–1885
nonmood disorders, 1875, 1883
phases, 1877–1878

postpartum women, 2511
pregnancy, 2509
research findings, 1879–1884
training, 1885
Interpersonal relationships
*See also* Clinician-patient relationship
autistic disorder, 781
importance, 20
listening skills, 3
personality styles, 640–641
psychoanalytic theory, 1858
sexual dysfunction, 1581, 1585–1586, 1588
Interpersonal theory, 222, 1352, 1876
Interpersonal violence, 2603, 2604
Interpreters, 62–63, 2569
Interpretive stance, listening skills, 3
Interprofessional communication
*See also* Confidentiality
children/adolescent evaluations, 546–547, 554
Intersex conditions, 1597
Intersubjectivity, 480
Interviews, 33–51, 525–530
*See also* Diagnostic interview schedules
attention-deficit/disruptive behavior disorders, 809, 810
behavioral medicine, 2039
clinical evaluation, 525–530
couples evaluation guidelines, 1969
generalized anxiety disorder, 1496
intellectual disability, 721–722
listening skills, 3
personality disorders, 1719–1720
semistructured, 1413, 1719–1720
specific/social phobias, 1413
technique dimensions, 45–47
Intimate partner violence (IPV), 2577–2578, 2579–2581, 2584–2585
Intimate relationships
*See also* Couples; Marriage; Sexual disorders
adult development, 190
biological aspects of romantic love, 1966
ego boundaries in family therapy, 1949
elderly adults, 201–202
young adult development, 187
Intoxication *See* Substance intoxication
Intracellular signal transduction, 346–347, 2124, 2165–2166
Intraclass correlation coefficient (ICC), 2625
Intracranial pathology
cancer, 2502
delirium, 920
personality change, 945, 946
psychosis, 934
Intramuscular (IM) formulation of medications, 2099–2100
Intrapsychic approaches to group psychotherapy, 1905, 1906
Intravaginal containment times, 1591–1592
Intravenous (IV) administration of medications, 1092, 2099
Introjection, 472, 474
Introversion, 1726, 1741
Intrusion, PTSD criteria, 2587
Invasiveness of brain stimulation techniques, 2357–2358
Investment concepts, 1853
Involuntary hospitalization, 82–83, 89, 2531, 2532
Involuntary movements *See* Movement disorders; Tic disorders
IOM *See* Institute of Medicine
IOWA *See* Inattention, Overactivity with Aggression
IPC *See* Interpersonal counseling
Iproniazid, 2123
IPS *See* Individual placement and support
IPT *See* Integrated psychological therapy; Interpersonal psychotherapy
IPT-A *See* Interpersonal psychotherapy for adolescents
IPT-CM *See* Cojoint interpersonal psychotherapy for marital disputes
IPT-D *See* Interpersonal psychotherapy for dysthymic disorder
IPT-HIV *See* Interpersonal psychotherapy for HIV-positive patients
IPV *See* Intimate partner violence
IQ (intelligence quotient) tests, 490, 492–493, 588–590, 690, 549
Ireland, history, 216–217
I-RISA *See* Impaired Response Inhibition and Salience Attribution
Iron-deficiency anemia, 843, 844
Irrational thinking, 1922
Irritability, 1381
Irritable bowel syndrome (IBS), 1497, 1766, 1767
Ischemia, 705
Isolation, defence mechanism, 1855
Italy, history, 210, 212–213, 219
Itard, Jean-Marc-Gaspard, 210, 212, 690
IV *See* Intravenous administration
Iyengar yoga, 2326, 2329, 2331
Izard's ten basic emotions, 605

Jai-Wei-Xiao-Yao-San, 2324
Jamais vu, 584
James-Lange theory, 605
Janet, Pierre, 1558
Jealous-type delusional disorder, 1272, 1275–1276
Jet lag, 1645–1646, 2333
Jobs *See* Employment issues
Joint attention behaviors, 780, 786
'Joints', 1042
Joy development, 119, 122
Judgement, 41, 592, 1236
Jung, Carl, 1260–1261
Juveniles *See* Adolescents; Children; Minors

Kandel, Eric, 226, 291
Kanner, Leo, 379, 783
Kappa coefficient, 2625
Kasanin, J., 1265
Kauffman Brief Intelligence Test (K-BIT), 550
Kava (*Piper methysticum*), 2333–2334
KD modeling *See* Kinetic-dynamic modeling
Kernberg, Otto, 476
Ketamine, 1091, 1093
7-Keto dehydroepiandrosterone, 2333, 2340
$K_i$ *See* Inhibition constant
Kidney *See* Renal...
Kindling theory of bipolar disorder, 1352, 1353
Kinetic-dynamic (KD) modeling, 2105, 2107
Kinsey reports on sexual behavior, 223, 2539, 2540, 2541
Kira, 2321
Kleine-Levin syndrome, 1640
Klein, Melanie, 221, 473–474
Kleptomania, 1658, 1660–1661, 1668–1674
assessment, 1669
diagnosis, 1668–1669
DSM-IV-TR criteria, 1668, 1669
epidemiology, 1669–1670
etiology/pathophysiology, 1670–1671
impulsive behavior, 643, 644
treatment, 1672–1674
Klinefelter's syndrome, 615, 616, 617, 2607
Klüver-Bucy syndrome, 947, 948–950
Kohut, Heinz, 477, 1299–1300
Korsakoff's syndrome, 361, 926, 977–978
*See also* Wernicke-Korsakoff syndrome; Wernicke's encephalopathy
Kosovo, 1958–1959
Kraepelin, Emil, 213–214
bipolar disease, 1335, 1345
neurosyphilis, 937–938
schizophrenia, 301, 1202, 1239
Kraeplinnean diagnostic framework, 213–214, 245, 662
Kundalini yoga, 2326, 2328–2329

LAAM *See* Levo-alpha acetyl methadol

Laboratory assessment
alcohol use disorders, 980–981
Alzheimer's disease, 906
anorexia nervosa, 1613
attention deficit-disruptive behavior disorders, 810–811
clinical evaluation, 533–538, 539, 540
impulse-control disorders, 1662, 1688
initial child/adolescent evaluation, 553
opioid dependence, 1174
phencyclidine intoxication, 1095–1096
rape/sexual assault, 2582
secondary psychosis, 935
sedative-hypnotics, 1194
substance addiction, 962
Lactation *See* Breastfeeding
LAD *See* Language acquisition device
Lamotrigine
acute bipolar depression treatment, 2212–2213
bipolar disorder, 1358, 1359, 1360–1361
bipolar maintenance therapy, 2215–2216, 2218
post-traumatic stress disorder, 2243
pregnancy, 2422, 2425, 2509
rapid cycling bipolar disorder, 2219
Landau-Kleffner syndrome, 767, 796
Langfeldt, Gabriel, 1270
Language
*See also* Communication
communication disorder assessment, 769
cultural idioms of distress, 58–59, 64
effective listening, 4–5, 6
interpreters, 62–63, 2569
multilingual patients, 57
personality types, 1722
preschool development, 138, 140–141, 142
psychiatric interview, 525
sexual in couples therapy, 1977
torture victims, 2569
Language abnormalities
Asperger's disorder, 792
autism, 380, 781–782, 786, 790
delirium, 920
frontal temporal dementia, 396
Language acquisition device (LAD), 140–141
Language basis, learning and motor skills disorders, 757, 758, 759
Language disorders (LD), 765–774, 776–777
*See also* Communication disorders
childhood problems, 493–494
diagnostic classification in infants and young children, 681, 682, 687
DSM-IV-TR criteria, 769
intellectual disability, 693
treatment, 772
Late life
*See also* Elderly adults
development, 196–202
disorders, 512–515
Latency
childhood sexuality, 466, 467
school-age development, 150–159
sleep, 1627, 1635
Latent dream content, 465
Latent inhibition (LI), 279, 280
Late-onset schizophrenia, 1208–1209
Latin American Guide for Psychiatric Diagnosis, 648
Lavender (*Lavandula angusifolia*), 2324
Law, *See also* Legal issues
Laxatives, 878
Lay interpreters, 63
LBD *See* Lewy body dementia
LBW *See* Low birth weight
LD *See* Language disorders
Leadership
disaster response planning, 2471
group psychotherapy, 1905, 1907, 1908
restraint and seclusion prevention, 2493
Lead pipe rigidity, neuroleptic malignant syndrome, 1786
Lead poisoning
gasoline inhalation-related, 1135–1136
intellectual disability, 705
pica, 843
Learned helplessness, 286, 455, 1923, 1924
Learning
*See also* Cognitive development; Conditioning; Memory
age effects, 197
autistic disorder, 790
psychoanalytical principles, 291
schizophrenia effects, 1232–1233
Learning disabilities
public school system definitions/criteria, 747–748, 749–750
use of term, 689
Learning disorders not otherwise specified, 749
Learning/memory neurocircuits, substance dependence, 371
Learning and motor skills disorders, 747–762
*See also* Intellectual disability
child/adolescent evaluation, 750–751, 752–753, 754
childhood problems, 493
comorbidity, 752, 755–756
complementary treatments, 2342
definitions, 747–750, 762
diagnosis, 748–749, 750–751, 752, 754
doctor-patients relationships, 762
educational curriculum, 751–752
educational interventions, 758–760
environmental/cultural evaluation, 754, 755
epidemiology, 755
family evaluation, 753–755
psychotherapeutic interventions, 760–761
social problems, 747, 750, 756, 760–761
tic disorder comorbidity, 849, 850, 851, 857
treatment, 758–761
Learning tests, 681, 682, 687, 749, 750
Learning theories
anxiety disorders, 1424
obsessive-compulsive disorder, 1457
pain disorder, 1533
somatization disorder, 1521
Learning therapies, 1895–1896
*See also* Cognitive and behavioral therapies
Left-right comparisons, neuropsychological analyses, 562
Legal issues
*See also* Forensic psychiatry
child/adolescent education evaluation, 552–553
civil commitment (involuntary hospitalization), 82–83
civil law issues, 81–88
complementary treatment liability, 2344
compliance, 2448
correctional psychiatry, 2596
disability evaluations, 88
history, 210, 216
intellectual disability, 711–712, 731–732
learning disabilities definitions, 747–748
malpractice litigation, 85–87
medical liability, 2344
medication-induced movement disorders, 1774
mental health law, 81–93
parental competency, 732
psychiatric practice, 81–93
restraint and seclusion, 2493
standards of proof, 86
suicidal patients, 2486
supervision/collaboration/consultation, 87
treatment of minors, 2447
treatment refusal rights, 83–84, 2531
Legislative advocacy, 2083–2084, 2087–2088
Leigh syndrome, 702
Leisure functioning, 641
Leiter International Performance Scale-Revised, 550
Lemon balm (*Melissa officianalis*), 2319, 2334, 2339

LENS *See* Low Frequency Neurotherapy System
Lesbians, 1977, 2539, 2540, 2541–2542
Lesch-Nyhan syndrome, 718, 890, 891
Leteprinim, 2307
Lethal, *See also* Death
Lethal catatonia, 1786–1787
Leucopoiesis disturbance, 1306
Leukopenia, 2191
Levels of analysis, 434
Levels of consciousness, 582–584
Levels of performance, 562
Levetiracetam, 2235, 2240
Levo-alpha acetyl methadol (LAAM), 1177
Lewy bodies in Alzheimer's disease, 396, 398
Lewy body dementia (LBD), 398
Lexical deviance, 597
LI *See* Latent inhibition
Libido (sexual desire), 1581–1586, 1976
Libido theory, 290, 467–469, 474
Licensure of practitioners, 1844
Life instinct, 470
Lifelong sexual disorders, 1583–1584, 1587–1588, 1590, 1593–1594, 1600–1606
Life span psychopathology, 489–516
Lifestyle
  *See also* Alcohol use; Diet; Smoking
  behavioral medicine, 2033
  elderly adults, 200–201
  premenstrual dysphoric disorder, 1386–1387
Life-threatening medical condition risk assessment, 542
Lifetime morbid risk (LMR), schizophrenia, 1208
Lifetime prevalence rate
  ECA study, 412, 413, 415–416
  National Comorbidity Survey, 417–418
  NCS-R, 419–422
  schizophrenia, 1207–1208
  specific fears without specific phobia, 1414
Life transitions, 1875, 1876
Light/dark-potentiated startle, 322–323
Light effects on circadian rhythms, 1628, 1629
Light therapy, 1316, 1387, 2509
Limbic system, 1219
Linear models of infant development, 112
Lines of development, 97–108
Linkage analysis, 264–266, 971–972, 1212–1215
Lisdexamfetamine dimesylate, 2269, 2281
Lisping, 773
Listening, 3–18
  attitudes, 8–10
  blocks, 6–8
  clinical situations, 15–18
  finding patients, 12–13
  increasing skills, 3–4, 16–18
  language, 4–5
  neurobiology, 6, 13
  psychiatric interviews, 43
  self knowledge, 11–12
  self listening, 13–15
  theoretical perspectives, 10–11
'Listening with the third ear', 3
Listing advantages and disadvantages procedure, 1929–1930
Lithium
  adverse effects, 1360–1362, 2204, 2205
  aggression treatment, 2610–2611
  alcohol use disorders with psychiatric comorbidity, 993
  antidepressant treatment augmentation, 2151
  bipolar disorder, 1356
    acute depression treatment, 1358, 1359, 2213
    acute mania treatment, 1357, 1359, 2203–2205, 2210
    maintenance therapy/prophylaxis, 1358, 1359, 2214–2215, 2218
    neuroprotection, 1351–1352
  breastfeeding, 2425
  cannabis-related disorders, 1055
  clinical applications, 2204–2205
  delirium causes, 921
  depression treatment, 1303–1304, 1313
  Ebstein's anomaly, 2508
  history, 223
  intellectual disability treatment, 739
  mechanism of action, 2204
  mood stabilization properties, 2202
  older adults, 1367
  perinatal toxicity, 2508–2509
  pharmacokinetics, 2203–2204
  pregnancy, 1366, 2422, 2508–2509
  rapid cycling bipolar disorder, 2218–2219
  schizoaffective disorder treatment, 1268
  suicide protection, 1356, 2484
  treatment-resistant depression, 2382–2383
Lithium-induced tremor, 1789
Litigation *See* Legal issues
Liver *See* Hepatic...
LMR *See* Lifetime morbid risk
Lobotomy, 223
Locus ceruleus, 965
Locus of control model, 455
Lofexidine, 2398, 2412
Logical reasoning
  adolescent development, 169–170
  speech disorders, 596, 598
Logistical considerations of combined treatments, 2442
Long-acting antipsychotics, 2182
Long-acting stimulants, 2265, 2268, 2280–2281
Longitudinal factors in antidepressant selection, 2132, 2133
Longitudinal lines of development, 97–108
Longitudinal studies, 408–409
  adult development, 182
  bipolar disorder, 1335, 1336, 1339, 1340, 1344, 1345–1346
  future directions, 424, 427
  schizophrenia, 1239–1240
Long-term detoxification, 1175
Long-term memory, 198, 585, 587, 588
Long-term potentiation (LTP), 1224
Long-term psychotherapy, 294–295
Looseness of association, 596
Lorazepam, 1529, 2423
LORETA *See* Low Resolution Electromagnetic Tomography
Losing phase of pathological gambling, 1681
Love
  *See also* Attachment
  biology, 1966
  early understanding, 207, 209
  self-love, 1738, 1740, 1922
Loved ones, 2521
Low birth weight (LBW)
  causes, 2418, 2419
  developmental risks, 130
Low Frequency Neurotherapy System (LENS), 2342
Low-perfusion states, 920
Low Resolution Electromagnetic Tomography (LORETA), 566
LSD (lysergic acid diethylamide), 1101–1102
  HPPD development, 1110–1111, 1112
  intoxication, 1104–1107
  psychotic disorders, 1096, 1108–1110
  scientific publications, 1103
  serotonin effects, 1226
LTP *See* Long-term potentiation
Lumbar puncture, 536, 538
Lung *See* Pulmonary...
Lysergic acid diethylamide *See* LSD
Madonna-whore complex, 1585
Magical thinking, 600
Magnetic brain stimulation, 2354–2358, 2361–2365, 2368
Magnetic resonance imaging (MRI)
  *See also* Functional magnetic resonance imaging
  autism, 385–386
  brain imaging, 571–573, 579–580
  dementia, 2552
  impulse-control disorders, 1662
  inhalant-induced encephalopathy, 1134, 1135
  neurophysiological assessment, 564
  personality change secondary to general medical conditions, 946
  psychotherapy studies, 295–296
  schizophrenia, 311–312, 1217–1218, 1236
  structural MRI studies, 385–386
  stuttering, 770

Magnetic resonance spectroscopy (MRS), 576–577
Magnetic seizure therapy (MST), 2354–2358, 2364–2365, 2368
Magnetoencephalography (MEG), 578–580
Mahler, Margaret, 475–476
Maintenance ECT (M-ECT), 1315–1316
Maintenance treatment
  bipolar disorder, 1358, 1359, 2214–2215, 2218
  depression, 1302–1304, 1315–1316, 1878, 1880, 2149–2150
  opioid dependence, 2401–2407
  schizophrenia, 1246–1251, 2181–2182
Maintenance of wakefulness test (MWT), 1632
Major depressive disorder (MDD), 1283–1330
  abuse victims, 2584, 2585
  biological causal factors, 246, 249, 251, 253
  characteristics, 339–340
  cognitive and behavioral therapies, 1936–1938
  comorbidity patterns, 1285–1288
  differential diagnosis, 1290
  DSM-IV-TR criteria, 1283
  dysthymic disorder combination, 1290
  dysthymic disorder distinction, 1498–1499
  generalized anxiety disorder distinction, 1498
  genetic epidemiology, 260
  interpersonal psychotherapy, 1875, 1879–1882
  obsessive-compulsive disorder comorbidity, 1449
  panic disorder comorbidity, 1398
  premenstrual dysphoric disorder relationship, 1379, 1380, 1382
  psychiatric disability, 2059–2060
  psychiatric rehabilitation, 2069
  with psychotic features, 2171
  PTSD comorbidity, 1475
  relapse/recurrence prevention, 2131
  treatment-resistant, 2372–2387
Major depressive episodes (MDEs), 1266, 1283–1330, 1875
  DSM-IV-TR criteria, 1284
Major mental health organizations, 2085
Maladaptive functioning
  adjustment disorders, 1708
  cognitive model, 1922–1923
  defence patterns, 1894
  health behavior affecting a general medical condition, 1756–1757, 1760
  problematic behaviors, 642–646
Male erectile disorder, 1587–1589
Male gender reassignment, 1599
Male-limited alcoholism, 972
Male orgasmic disorder, 1591–1592
Male sexual pain disorders, 1592, 1593
Malformations *See* Congenital abnormalities
Malingering
  factitious disorders distinction, 1548
  physical signs and symptoms, 630–631
  somatoform disorder distinction, 1511, 1532
Malnutrition
  *See also* Anorexia nervosa
  infant development risk factors, 128, 129
  psychological effects, 1613
Malpractice, legal issues, 85–87
MAM *See* Methylazoxymethanol acetate
Managed health care, 29, 74–75, 1195, 1840–1843
Management in correctional psychiatry, 2597
Mania
  antidepressant side effects, 2140
  childhood problems, 496
  early adulthood, 505
  elderly adults, 514
  historical understanding, 206, 207, 211, 212, 215, 1335–1336
  intellectual disability, 728
  origin of word, 205
  phencyclidine intoxication, 1097
  secondary to a general medical condition, 938–940
Manic-depressive disorder
  *See also* Bipolar disorder
  history, 225, 1335–1336
  use of term, 225, 1336
Manic episodes, bipolar disorder, 1336, 1337, 1339–1340, 1356, 2203–2210
Manifest dream, 465
MANOVA *See* Multivariate analysis of variance
Manuals
  psychotherapy guidelines, 226
  solution-focused brief psychotherapies, 1897–1898
MAO-A *See* Monoamine oxidase-A gene
MAOIs *See* Monoamine oxidase inhibitors
*MAPT* gene, 397, 398
Marijuana *See* Cannabis
Marijuana Treatment Project (MTP), 1053
Marital Satisfaction Inventory, 1802
Marriage
  *See also* Couples; Couples therapy
  alcohol use disorders, 991
  behavioral marital therapy, 991, 1804
  historical context, 1964
  obsessive-compulsive disorder, 1448
  problems, 1795, 1800–1801, 1804
    cognitive and behavioral depression therapies, 1937
    cojoint interpersonal psychotherapy, 1881
    psychological factors affecting medical condition, 1756, 1767
    treatment, 1804–1806
  same-sex, 1979–1980, 2544
  schizophrenia epidemiology, 1209
  separation, 614, 1965, 1973
MAS *See* Mixed salts of amphetamine
Masculine girls, gender identity, 1595
Masked depression, 2041
Masochism, 1600
Massachusetts General Hospital (MGH) staging method, 2372–2373
Mass hysteria, 1529
Mastery-pleasure exercises, 1930–1931
Masturbation
  children/adolescents, 154, 161, 1582
  impulse-control disorders, 1672, 1685
  paraphilia, 1597–1598, 1600–1604
  sexual disorder evaluation, 1587, 1588, 1590
Matchbox sign, 1273
Maternal influences
  *See also* Parental care; Pregnancy
  animal models of anxiety disorders, 330–331
  anxiety disorder, 329–330, 331–332
  behaviorally inhibited children, 329–330
  feeding disorder of infancy or early childhood, 835–836
  infant development risk factors, 128, 129–130
  mother-child feeding interactions, 835–836
  substance abuse effects, 129–130
  supposed cause of disorders, 222–223
Mathematical disorder
  criteria, 748
  educational interventions, 759
  mental activities, 750, 758
Mathematics curriculum, 752
*Matricaria recutita See* Chamomile
MATRICS *See* Measurement and Treatment Research to Improve Cognition in Schizophrenia
Maturation concept, 135
Maturation variable, 2621
Mature defences, 188–189
Mature phase of group dynamics, 1906, 1908
Maudsley method, 1617
MBK *See* Methyl butyl ketone

MBSR *See* Mindfulness Based Stress Reduction
MBT *See* Motivation enhancement plus behavioral coping skills training
MCI *See* Mild cognitive impairment
MDA (3,4-methylenedioxyamphetamine), 1103, 1116
MDD *See* Major depressive disorder
MDEs *See* Major depressive episodes
MDMA (3,4-methylenedioxymethamphetamine; ecstasy), 1102–1103, 1113–1119
Mead, Richard, 212
Mean, statistical definition, 2626
Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), 561, 1259
Measures
  of association, 406
  of behavior, 722
  of disease frequency, 405–406
  psychometric properties, 406–407
  research methodology, 2621, 2624–2632
MEC *See* Minimum effective concentration
Mecamylamine, 2391
Mechanical restraints, 2609
Mechanistic models in drug development, 2130, 2152
*MeCP2* gene, 798
M-ECT *See* Maintenance ECT
Media interaction guidelines, 70
Medial prefrontal cortex (mPFC), 322, 324, 326–327
Medicaid
  Balanced Budget Act, 1838–1839
  diagnosis-related group payment methodology, 1838, 1839
  elderly adults, 2550
  managed mental health care, 1841–1843
  mental health service history, 1822–1823, 1827, 1837
  pharmacotherapy expenses, 1842
Medical conditions *See* General medical conditions
Medical decision making capacity and competence, 83–84
Medical directors of community based organizations, 2534
Medical disability benefits, 88
Medical ethics principles, 68
Medical evaluation of physical signs and symptoms, 622
Medical facilities for disaster response, 2472
Medical history taking, 39, 527–528
Medical malpractice, 85–86
Medical procedures, hypnotic analgesia, 2000–2003
Medical records, 2039
Medical symptoms, unexplained, 2034–2035
Medical trainees, 2535
Medicare
  Balanced Budget Act, 1838–1839
  diagnosis-related group payment methodology, 1837–1838
  elderly adults, 2550
  managed mental health care, 1842
  mental health services, 1837
    history, 1822
  RBRVS system, 1838, 1839
Medicare Prescription Drug, Improvement and Modernization Act (MMA), 1817, 1842
Medication-facilitated interviews (narcoanalysis), 1529, 1563–1564, 1569
Medication holidays, 2450
Medication-induced movement disorders, 1773–1791
Medication management in correctional psychiatry, 2597
Medications *See* Drug interactions; Drug responses; Pharmaco...
Medieval times, 207–208
Meditation, 2328–2329
MEG *See* Magnetoencephalography
Megalomania, 1273
Melancholia
  early understanding of mental disorders, 206, 207, 209–210, 613
  Freud, 470
  mood disorders, 348, 1289
Melatonin
  antidepressants targeting, 1311
  cognitive enhancement, 2340
  insomnia, 2261
  MT receptor agonists for insomnia, 1636, 1637
  sleep, 2319, 2332
*Melissa officianalis* (lemon balm), 2319, 2334, 2339
Memantine, 907, 2304–2305, 2553, 2555, 2557
Memory
  *See also* Amnesia; Amnestic disorders; Dissociative amnesia; Dissociative fugue; Working memory
  age effects, 197–198
  antipsychotic effects, 1233
  attention and executive functioning, 437–438
  binding and retrieval, 441–442
  cognitive psychology, 440–443
  consolidation, 586, 587
  declarative memory, 585, 586, 587
  dissociation, 1573–1574, 1985
  dissociative disorders, 1558–1574
  emotion interactions, 438–439, 442
  encoding, 440–441
  episodic memory, 139–140, 585, 587, 1561–1562, 1573–1574
  evaluation, 591–592
  explicit memory, 440–442, 1561, 1573–1574
  formation, 586, 587, 606, 607
  hippocampus role, 247, 606, 607
  history of understanding, 214, 226
  hypnotic enhancement, 2006
  immediate (short term) memory, 197, 198, 585, 587
  implicit (procedural) memory, 440, 442, 443, 1573–1574
  infant development, 117, 125
  long-term memory, 198, 585, 587, 588
  overview, 584–588
  preschool development, 139–140
  prospective memory, 586, 587
  psychoanalytical principles, 291
  psychoanalytic psychotherapy, 1853–1854, 1870
  recall memory (primary memory), 898
  recent memory (secondary memory), 898
  remote memory (tertiary memory), 587, 898, 926
  representation, 440–443
  retrieval of traumatic events, 1568
  short term (immediate) memory, 197, 198, 585, 587
  substance dependence effects, 371
Memory deficits
  age effects, 197–198, 513–514
  Alzheimer's disease, 901–902, 906
  amnestic disorders, 924–925, 927
  brain injury, 585–586
  delirium, 920
  dementia, 393, 394, 898
  depressive disorders, 901, 902
  elderly adults, 197–198, 513–514
  factitious disorders, 902, 927
  forensic hypnosis, 2007
  hippocampus role, 247
  MDMA use, 1115
  psychiatric disorders, 443
  schizophrenia, 1232–1233, 1235–1236
Men
  *See also* Gender issues; Male...
  alcohol use disorders, 971, 972, 981
Mendelian diseases, 257
Meningomyelocele, 703
Menopausal women
  premenstrual dysphoric disorder, 1381
  psychiatric conditions, 2511–2513
  sexual function, 100, 1586, 1593
Menstrual cycles
  charting, 1379
  eating disorder effects, 1611, 1612, 1619
  menarche, 166
  premenstrual symptoms, 1379–1387

Mental disorders
*See also* Psychiatric disorders
conceptualization of, 423
*Mental Disorders in Urban Areas* study, 410
Mental Health America (MHA), 2085, 2086
Mental health collaborative interventions in criminal justice, 2595–2596
Mental health group directories, 2085
Mental health integration in primary care settings, 2038
Mental health law, 81–93
Mental health services
access to, 1264, 1300
disaster-related activities, 2470–2473
economic factors, 1817, 1822–1824, 1826, 1832, 1834–1843
future directions, 427
government financing, 1837–1840, 1841–1843
history and trends, 1818–1834, 1837–1841, 1846
homeless people, 2526–2535
managed care, 1840–1843
organization, 1817–1846, 2085
private insurance, 1835–1837
quality improvement, 1843–1846
relationship with self-help groups, 2092–2093
use studies, 416, 418, 419, 423
Mental hospitals/institutions *See* Hospitalization; Institutions
Mental hygiene movement, 1820
Mental retardation
*See also* Cognitive impairment; Intellectual disability
attention-deficit hyperactivity disorder, 2276–2277
autistic disorder differential diagnosis, 787
childhood, 492–493
correctional system, 2594–2595
DSM-IV-TR criteria, 691–692
etiology/pathophysiology, 695
IQ scores, 589
pica, 842, 843, 844
use of term, 689
Mental Status Examination, 40–41, 525, 526, 528–530
children/adolescents, 548, 549
consciousness, 582–584
dementia, 899
enuresis, 871
intelligence, 588–591
memory, 591–592
neuropsychological evaluation comparison, 559
orientation, 591
schizophrenia, 1233–1236
Mescaline, 1101, 1102
Mesmer, Franz, 211, 212
Mesocortical pathways, 2163
Mesolimbic dopamine system, 365, 366, 367
Mesolimbic pathways, 2163
MET *See* Motivational enhancement therapy
Meta-analyses of combined treatments, 2433, 2437
Metabolic dysfunction
antipsychotic drugs, 2189–2190
delirium, 920
dementia, 393, 394
feeding disorder of infancy or early childhood, 832
intellectual disability, 700
SGA side effects, 1254
Metabolic syndrome, 2189–2190
Metabolism
MDMA use, 1116–1117
pharmacokinetics, 2100, 2101–2104, 2107
phencyclidine, 1093
S-adenosyl-L-methionine, 2322–2323
Metacognitive capacity development, 169, 170
Metaphors, 4–5, 7
Metapsychology, 290, 1853
Methadone
benzodiazepine abuse combination, 1189, 1191
breastfeeding, 1182
opioid detoxification, 2399–2400
opioid maintenance treatment, 2401–2403
opioid withdrawal, 1175, 1177
use disorders, 1169–1170
Methamphetamines, 366, 2411
Methaqualaone, 1189
5-Methoxy-DMT, 1101
Methylazoxymethanol acetate (MAM), 284
Methyl butyl ketone (MBK), 1138
*N*-methyl-D-aspartate (NMDA) receptor
alcohol intoxication, 974
antipsychotic drugs, 2165
depressive disorders, 1294, 1309–1310, 2154, 2384
learning/memory/conditioning, 324, 2304–2305
phencyclidine intoxication, 1092, 1096, 1097
schizophrenia, 283–284, 301, 308, 1227–1230, 1259
Methylene chloride, 1139
3,4-Methylenedioxyamphetamine (MDA), 1103, 1116
3,4-Methylenedioxymethamphetamine (MDMA; ecstasy), 1102–1103, 1113–1119
Methylphenidate (MPH)
adverse effects, 2279
attention deficit-disruptive behavior disorders, 818
beaded preparations, 2264, 2281
clinical use, 2280
dexamphetamine comparison, 2286
efficacy studies, 2269–2276
history, 224
narcolepsy/hypersomnia, 1639
osmotic-release, 2264, 2268, 2281
pharmacology, 2265, 2267–2268
Mexicans, 649, 651, 1421
Meyer, Adolph, 221, 1260
MFE *See* Multifactored evaluation
MGH *See* Massachusetts General Hospital
MHA *See* Mental Health America
MI *See* Myocardial infarction
Michaelis-Menten equation, 2104
Microcephaly, 703
Microdeletions, 698–699
Midazolam, 1113
Middle adult life disorders, 510–512
Middle childhood *See* School-age
Midtown Manhattan Study, 410–411
Migraine headaches, 1288, 1765
Migration, 59–60, 259
Mild cognitive impairment (MCI), 513, 2294
Miller-Dieker syndrome, 703
Mind, early understanding, 205, 206
Mind-body interactions
behavioral medicine, 2028, 2029, 2030
historical view, 1755
psychological factors affecting medical condition, 1754–1768
Mind-brain relationship, 246
Mind-computer analogy, 433–434
Mindfulness Based Stress Reduction (MBSR), 2326
Mindfulness meditation, 2328–2329
Mindfulness skills, 2039
Mineral deficiency, pica, 844
Mineral supplements, 2341
Mini-Mental Status Examination (MMSE), 530, 649, 2552–2553
Minimum effective concentration (MEC) of medications, 2100, 2105
Minimum essential database, 38–39
Minnesota Multiphasic Personality Inventory, 223, 557, 1532
Minor depressive disorders, 1283–1284, 1317–1318, 2131
Minors
*See also* Adolescents; Children
consent to treatment, 84–85
Miraculous cures, history, 210
Mirror neurons, 454, 480–481
Mirtazapine
availability, 2128
breastfeeding, 2425
comparative trials, 2129
generalized anxiety disorder, 2231
insomnia, 2259
mechanism of action, 2127
obsessive-compulsive disorder, 2246
panic disorder, 2238–2239
post-traumatic stress disorder, 2242
side effects, 2226
social anxiety disorder, 2235
starting doses, 2147

treatment-resistant depression, 2381, 2384
Miscarriage, 2417–2418, 2419
Misidentification syndromes, 603
Mismatch negativity (MMN), 1224
Mistrust in correctional psychiatry, 2599
Mistrust versus trust, 1724–1725
Mitigating factors in criminal proceedings, 91–92
Mitochondrial genetics, 702
Mixed anxiety-depressive disorder, 1707
Mixed episodes, bipolar disorder, 1336, 1337
Mixed receptive-expressive language disorders (MRELD), 765–773
  assessment, 767–768
  comorbidity, 769
  diagnosis, 765–767, 770
  differential diagnosis, 770
  DSM-IV-TR criteria, 766
  epidemiology, 768
  treatment, 772–773
Mixed salts of amphetamine (MAS), 2264, 2265
Mixed serotonin antagonist/reuptake inhibitors, 2127
Mixed sleep apnea, 1641, 1642
Mixed-type delusional disorder, 1273
MK-0677, Alzheimer's disease, 2307
MMA *See* Medicare Prescription Drug, Improvement and Modernization Act
MMN *See* Mismatch negativity
MMSE *See* Mini-Mental Status Examination
MND *See* Motor neuron disease
Moclobemide, 2234
Modafinil
  attention deficit-disruptive behavior disorders, 821
  cocaine substitution therapy, 1076
  depression, 2287
  narcolepsy, 1639
Modern medicine, clinician-patient relationship, 21
Modern structural theory, 472–473
Modularity in cognitive psychology, 448
Molecular aspects
  impulse-control disorders, 1667
  neuroadaptation to substance dependence, 371–374
  neurodegeneration, 394
Molecular brain imaging, 577–578
Molecular genetics, 257–270, 373–374, 1667
Moniz, Egaz, 223
Monoamine hypothesis of mood disorders, 344, 345, 1293–1294, 2123–2124, 2125–2126
Monoamine oxidase-A gene (MAO-A), 176, 342
Monoamine oxidase inhibitors (MAOIs), 1310
  anxiety disorders, 1423, 1427, 1428, 1429
  attention deficit-disruptive behavior disorders, 820
  dietary restrictions, 2139–2140
  dimethyltryptamine, 1101
  drug-drug interactions, 2142
  evidence for depression causes, 344
  generalized anxiety disorder, 2231
  history, 224, 2123
  hypersomnia, 1641
  mechanism of action, 2124, 2225
  obsessive-compulsive disorder, 2246
  panic disorder, 2238
  pharmacokinetics, 2133
  post-traumatic stress disorder, 2241–2242
  pregnancy, 2420
  side effects, 2139, 2226
  social anxiety disorder, 2234
  starting doses, 2146
  treatment-resistant depression, 2382
Monosymptomatic hypochondriacal psychosis *See* Somatic-type delusional disorder
Monotherapy vs. combined treatments, 2434–2437
Mood
  definition, 608
  delirium, 920
  incongruent affect disturbances, 618
  menopause transition, 2511–2513
  Mental Status Examination, 529
  schizophrenia patients, 1234–1235
  spectrum, 615
  states, 609
Mood charts, 2376, 2377
Mood disorders
  *See also* Bipolar disorder; Depression; Depressive disorders; Dysthymic disorder; Major depressive disorder
  adolescents, 500, 501
  alcohol-induced mood disorder, 978
  amygdaloid dysfunction, 327
  binge-eating disorder relationship, 1623–1624
  birth outcome effects of, 2417–2418
  body dysmorphic disorder relationship, 1540
  borderline personality disorder, 1733
  breastfeeding, 2423–2425
  bulimia nervosa relationship, 1619–1620, 1621
  childhood problems, 495–496
  classification, 339–340
  cocaine use disorders comorbidity, 1059, 1079
  cognitive and behavioral therapies, 1936–1938
  complementary medicine, 2319, 2321–2326
  couples therapy, 1969
  cultural factors, 650–651
  depression, 1283–1330
  depressive personality disorder, 1748
  direct effect on birth outcomes, 2417–2418
  DSM classification systems, 675
  early adulthood, 504–505
  elderly adults, 514
  environmental factors, 342–343
  gene expression, 343
  generalized anxiety disorder associations, 1495, 1497
  general medical condition-related, 935–940
  genetic factors, 260, 340–343
  growth factors, 347–349
  hypochondriasis relationship, 1536–1537, 1538
  intellectual disability, 728–729
  interpersonal psychotherapy, 1875–1883, 1884–1885
  intracellular signal transduction pathways, 346–347
  neurobiology, 339–350
  neuroendocrine system hypotheses, 345
  neurogenesis, 349–350
  onset ages, 419, 421
  pathogenic mechanisms, 343–350
  pathological gambling comorbidity, 1680
  physical manifestations, 624–625
  pregnancy, 2417–2426
  premenstrual dysphoric disorder, 1379–1387
  psychotic features, 339, 1238, 1289, 2151, 2171
  relational problems, 1805–1806
  secondary mental symptoms, 625–626
  sleep disturbance relationship, 1634–1635
  somatization disorder relationship, 1520
  somatoform disorder distinction, 1511–1513
  speech disorders, 596
  substance abuse comorbidity, 361–362
  suicide, 2480
  susceptibility genes, 341–342
  transmitter system hypotheses, 343–345
  trichotillomania comorbidity, 1689
  ventral striatum dysregulation, 249
  violence link, 2605
Mood stabilizing medication, 2202–2220
  acute depression, 2210–2214
  acute mania, 2203–2210
  bipolar disorder, 1355–1356, 1357, 2202–2220
  breastfeeding, 2425, 2511
  definitions, 2202–2203, 2219, 2220
  dementia, 2557

Mood stabilizing medication (Continued)
history, 223–224, 225
maintenance therapy, 2214–2219
pregnancy, 2422–2423
rapid cycling bipolar disorder, 2218–2219
schizoaffective disorder treatment, 1268
Moon influences, 210, 212
Moral development
adolescents, 174
decalage, 107
infants, 125–126
longitudinal studies, 102–103, 105
preschool, 144–146
school-age children, 155–157
Moral disengagement, 461
Moral emotions, 145
Moral insanity, historical use of term, 217
Morality of sexual desire, 1582
Moral treatment reforms, 1818, 1819, 1820
Morel, Benedict Augustin, 1202
Mortality rates
anorexia nervosa, 1614
neuroleptic malignant syndrome, 1787
schizophrenia, 1210–1211
suicidal behavior, 2478–2479
'Mortality' variable, threat to internal validity, 2621
Mothers *See* Maternal...; Parent...; Perinatal...; Pregnancy
Motivation
clinician-patient relationship, 21
compliance, 1434, 2452–2453, 2454, 2458
neuroadaptation to substance use, 369–370
patient's, 37
psychoanalytic psychotherapy, 1862
schizophrenia rehabilitation, 2049, 2050, 2054
sexual desire, 1581, 1582
social interactions, 446–447
substance use cessation, 1052–1053, 1070, 1151, 1160
ventral striatum, 248–249
Motivational enhancement therapy (MET), 1052–1053, 1160
Motivational interviewing, 1070, 2041, 2458
Motivation enhancement plus behavioral coping skills training (MBT), 1052
Motor functions
*See also* Developmental coordination disorder; Learning and motor skills disorders; Movement disorders
adaptive functioning assessment, 642
Asperger's disorder, 792
childhood problems, 493, 498, 693
conversion disorder, 1525, 1526
motor skills disorder definitions, 747, 748, 762
preschool development, 138
Rett's disorder, 796, 797
Motor neuron disease (MND), 396, 397
Motor stereotypies, 782
Motor tics, 847, 848
*See also* Tic disorders
Mourning, 2520, 2522
*See also* Grief
Mouthing, pica, 842–843
Movement disorders
*See also* Motor functions
abnormal involuntary movement scale, 533, 534
childhood problems, 498
dementia, 900, 909
dystonias, 1251–1253, 1774–1776, 1781, 2184–2187
intellectual disability comorbidity, 725–726
medication-induced, 1773–1791
neuroleptic-induced tardive, 1781–1785
schizophrenia, 1234, 1252–1253
stereotyped movement disorder, 889–892
tic disorder differential diagnosis, 852
Mowrer's two-stage model, 1424
mPFC *See* Medial prefrontal cortex
MPH *See* Methylphenidate
MRELD *See* Mixed receptive-expressive language disorders
MRI *See* Magnetic resonance imaging
MRS *See* Magnetic resonance spectroscopy
MSLT *See* Multiple sleep latency test
MST *See* Magnetic seizure therapy
MTA *See* Multimodal Treatment Study of Children with ADHD
MTP *See* Marijuana Treatment Project
MT receptor agonists, insomnia, 1636, 1637
Multiaxial classification systems, 666–667, 681–682
Multidisciplinary teams, 62, 2037–2038, 2069, 2070
Multifactored evaluation (MFE), 552
Multifactorial approaches
child/adolescent assessment, 680–681, 688, 552
geriatric management, 2551
Multifactorial intellectual disability, 702
Multifamily group therapy, 1956
Multigenerational transmission of depression, 185
Multimodal Treatment Study of Children with ADHD (MTA), 812
Multiple copy prescription programs, 2279
Multiple correlation/regression, 2629–2630
Multiple etiologies
animal models of psychiatric illness, 276
dementia due to, 916–917, 918
Multiple personalities
*See also* Dissociative identity disorder
history, 218–219, 221
Multiple sclerosis, 1288
Multiple sleep latency test (MSLT), 1632, 1640
'Multi' principle, intellectual disability, 719
Multisystemic therapy, 1805
Multivariate analysis of variance (MANOVA), 2631
Multivariate approach to study design, 2628–2632
Munchausen syndrome, 603, 630, 1548, 1549, 1550, 1552
Mu-opioid partial agonists, 1176
Murder, 173, 215–216, 1603
Muscarinic acetylcholine receptors, 2135, 2136
Muscarinic agonists/antagonists, 2298–2299
Muscles
cataplexy, 1638, 1639
dystonias, 1251–1253, 1774–1776, 1781, 2184–2187
Mushrooms, hallucinogenic, 1101
Mutism, 597, 598
secondary to a general medical condition, 942, 944
selective mutism, 495, 883–885
Mutual-help groups *See* Self-help groups
MWT *See* Maintenance of wakefulness test
Myeloneuropathy, 1137–1138
Myocardial infarction (MI), 1065, 2558
Myocarditis, 2185, 2190–2191
Mythological characteristics of medical complaints, 625

NAA (*N*-acetyl aspartate), 1116
Nail biting, 1689
Naltrexone
alcohol use disorders, 994–995, 2395–2396, 2397
cocaine use disorders, 1074
intellectual disability treatment, 739
kleptomania treatment, 1673
opioid use disorders, 1175, 1176, 1178–1179, 2391, 2399, 2405–2407
NAMI *See* National Alliance on Mental Illness
NAPHS *See* National Association of Psychiatric Health Systems
Narcissism, 469–470, 1736
Narcissistic personality disorder (NPD), 1737–1740, 1745
DSM-IV-TR criteria, 1737
Narcoanalysis, 1529, 1563–1564, 1569
Narcolepsy, 503, 1638–1640

DSM-IV-TR criteria, 1638
NARIs (Noradrenaline-reuptake inhibitors) *See* Norepinephrine reuptake inhibitors
Narratives
listening skills, 3, 5
preschool development, 140, 142, 146
Narrative therapies, 1953–1954, 2571
Nasal complications of substance use, 1066, 1173
NaSSAs *See* Noradrenergic and specific serotonergic antidepressants
National Alliance on Mental Illness (NAMI), 2085, 2086–2088, 2091, 2093, 2094
National Association of Psychiatric Health Systems (NAPHS), 1839
National Comorbidity Survey (NCS), 417–418, 427
National Comorbidity Survey-Replication (NCS-R), 418–423, 427
National Institute of Mental Health (NIMH)
bipolar disorder studies, 1344, 1346
history, 1821, 1822, 1825, 1827
National Mental Health Association *See* Mental Health America
National Mental Health Consumers' Self-help Clearinghouse (NMHCSHC), 2085, 2086, 2090, 2094
National organizations for psychosomatic medicine, 2498
National reduction efforts in restraint and seclusion, 2493–2494
National Violence against Wowen (NVAW) survey, 2577, 2578
Natural disasters, 2465, 2466, 2471–2472
NCS *See* National Comorbidity Survey
NCS-R *See* National Comorbidity Survey-Replication
NDRC *See* Neurodevelopmental disorders of relating and communicating
NDRIs *See* Norepinephrine-dopamine reuptake inhibitors
NE *See* Norepinephrine
NEAR *See* Neuropsychological education approach to remediation
Needle exchange programs, 1182, 1183
Nefazodone
availability, 2128
breastfeeding, 2425
cannabis withdrawal, 1055
generalized anxiety disorder, 2231
liver function side effects, 2140
mechanism of action, 2127
obsessive-compulsive disorder, 2246
panic disorder, 2238–2239
pharmacokinetics, 2133, 2134
post-traumatic stress disorder, 2242
side effects, 2226
social anxiety disorder, 2235
starting doses, 2147
Negative cognitive triad, 1921
Negative life events, 2470
Negative reinforcement in substance dependence, 356, 368
Negative symptoms in schizophrenia, 1230–1231, 1255–1258, 2175–2176
Negative therapeutic reactions, 470
Negativism secondary to a general medical condition, 943
Negativistic personality disorder *See* Passive-aggressive personality disorder
Neglect of infants, 129
Neocorticol regions, 606, 1220–1221
Neodissociation theory, 1559
Neologisms, 597, 598
Neonates
*See also* Perinatal...
caffeine withdrawal, 1025
fetal alcohol syndrome, 694, 704, 895, 982, 1140
infant development, 113–118
inhalant-related disorders, 1140
persistent pulmonary hypertension of the newborn, 2420, 2426, 2508
small for gestational age babies, 2418, 2419
Neoplasias syndrome, 1288
Nerokin-1 receptor agonists, 2152
Nerve growth factor (NGF)
Alzheimer's disease, 2306–2307
CBT treatment, 295
mood disorder neuropathology, 347–349
Nerves, early understanding, 210
Neural pathways *See* Neurocircuits
Neural tube defects, 703
Neurasthenia, 1542–1543
Neuregulin 1 (NRG1), 1213, 1215
Neuritic plaques, 904–905
Neuroadaptations to substance dependence, 368–374, 1062, 1072
Neuroanatomical theories
emotional pathways, 605–606
panic disorders, 1401–1402
schizophrenia, 1217–1224
Neurobehavioral teratogenesis, 2508
Neurobiological factors
anxiety disorders, 317–332, 1422–1423
attention-deficit hyperactivity disorder, 814–816
autistic disorder, 788
bipolar disorder, 1350–1352
bulimia nervosa, 1621
cocaine use, 1061–1062
cognitive and behavioral therapies relationship, 1921, 1922
cognitive psychology, 433, 434, 435
depressive disorders, 1286
endophenotypes, 246
factitious disorder, 1552
generalized anxiety disorder, 1500–1501
historical understanding, 223, 224
listening, 6, 13
mood disorders, 339–350
obsessive-compulsive disorder, 1454–1457
panic disorders, 1400–1402
post-traumatic stress, 2568
psychotherapy, 1869–1870, 1871
separation anxiety disorder, 880–881
substance addiction, 965
tic disorders, 853–856
violence link, 2605
Neurocircuits
cognitive fear model, 1922
schizophrenia, 1221–1222
substance dependence, 368–371
substance intoxication/reward, 365–367
Neurocognitive phenotypes, animal models, 279–280
Neurodegenerative processes
dementia, 393–399, 902–911
depressive mood disorder secondary to, 936–937
Klüver-Bucy syndrome secondary to, 949
mania secondary to, 938–939
personality change secondary to, 945, 946
pseudobulbar palsy secondary to, 947, 948
schizophrenia, 1229–1230
Neurodevelopment, 98, 99
adolescents, 168, 171
preschool children, 136–137
schizophrenia, 284, 302, 1229–1230
Neurodevelopmental disorders of relating and communicating (NDRC), 681, 682, 685–686
Neuroendocrine systems
*See also* Hypothalamic-pituitary-gonadal axis
bipolar disorder, 1351
depression, 1295–1296
mood disorders, 345
post-traumatic stress disorder, 1478
Neurofibrillary tangles, 394, 395, 904–905, 2296, 2310
Neurogenesis in adult hippocampus, 349–350
Neuroimaging
affective disorder subgrouping, 327–328
anxiety disorder studies, 326, 327
brain stimulation combination, 2358
generalized anxiety disorder, 1501
mood disorder neuropathology, 345
psychotherapy, 295–297

Neurokinin (NK) receptors, 1294–1295
Neuroleptic..., *See also* Antipsychotic drugs
Neuroleptic-induced movement disorders, 1773–1791
  *See also* Tardive dyskinesia
  acute akathisia, 1779–1780
  acute dystonia, 1774–1776
  DSM-IV-TR criteria, 1775, 1777, 1779, 1782
  Parkinsonism, 1776–1779
Neuroleptic-induced psychosis, 933
Neuroleptic malignant syndrome (NMS), 1252, 1775, 1785, 2185, 2187–2188
  DSM-IV-TR criteria, 1785
Neuroleptization, 2180
Neurological assessment, 532
Neurological disorders
  aggression/violence link, 2607–2608
  depression comorbidity, 1286, 1287–1288
  feeding disorder of infancy or early childhood, 834
  IED differentiation, 1662, 1665
  learning and motor skills disorder relationship, 755–756
  psychological factors affecting medical condition, 1764–1765
Neurological symptoms in conversion disorder, 1525–1527
Neurology, historical understanding, 210, 220
Neuromodulation, brain stimulation techniques, 2354–2368
Neuronal atrophy/cell loss, mood disorder neuropathology, 348, 2124
Neuropathology
  addiction, 354–374
  alcohol use disorders, 973–974
  Alzheimer's disease, 904–906
  animal model phenotypes, 281, 282
  anorexia nervosa effects, 1612
  definition, 1217
  genetic epidemiology, 270
  historical views, 213
  neurotoxic effects of substance use, 361, 1133–1138
  role in psychiatric disorders, 246, 247–253
Neurophysiology
  brain stimulation combination, 2358
  evaluation, 564–567, 757–758
  hypnosis correlates, 2008–2012
Neuroplasticity
  age effects, 198–199
  antipsychotic drugs, 2166
  brain stimulation, 2356–2357
  mood disorders, 2327–2328
Neuroprotection
  antipsychotic drugs, 2166, 2167
  bipolar disorder treatments, 1351–1352
  *Ginkgo biloba*, 2338
  schizophrenia, 1229–1230
  vinpocetine, 2338
Neuropsychological assessment, 532–533, 556–567, 810
Neuropsychological education approach to remediation (NEAR), 2053
Neuroreceptors
  *See also individual neurotransmitters/receptors*; Receptor systems
  characterization by molecular imaging, 577–578
Neuroses
  historical use of term, 216
  symptom formation, 471
Neurosyphilis, 914, 934, 937–938
Neurotensin levels, 1227–1228
Neurotherapy, EEG feedback, 2342
Neurotic anxiety definition, 610
Neurotic defences, 188–189
Neuroticism, 1500, 1722, 1732, 1736, 1741, 1748
Neurotic triad, Minnesota Multiphasic Personality Inventory, 1532
Neurotoxic effects of substance use, 361, 1133–1138
Neurotransduction factors, 371–373
Neurotransmitters
  *See also individual neurotransmitters*
  aggression/violence link, 2608
  alcohol effects, 973–974
  bipolar disorder, 1350
  cocaine use, 1061–1062
  emotions, 606
  generalized anxiety disorder, 1501
  genetic polymorphism/ethnic origin effects, 2119
  hypnotizability, 2008
  monoamine neurotransmitter life cycle, 2125–2126
  mood disorder neuropathology, 343–345
  multiple psychiatric disorder association, 247
  neuroleptic malignant syndrome, 1786
  panic disorders, 1400–1401
  pathological gambling, 1683–1684
  schizophrenia, 306–309, 1225–1229
  sleep, 1629–1630
  stimulant action and ADHD, 2267
  substance intoxication/reward, 365–366
  tardive dyskinesia, 1781
  tic disorders, 855–856
Neurotrophic factors in mood disorder neuropathology, 347–349, 1297
Neuterdom, 1597
Neutopenia, 2191
Neutrality, therapeutic frame boundaries, 73, 75–76
Newborns *See* Neonates
Newsgiving in end-of-life care, 2517
New York Teacher Rating Scale, 807, 809
NGF *See* Nerve growth factor
Nicotine
  fading, 1161
  gum, 1157–1159, 1162
  inhaler, 1158–1159, 1162
  lozenge, 1158
  patches, 1158–1159, 1162
  receptor antagonists, 2391, 2409
Nicotine Anonymous, 1162
Nicotine dependence, 1149–1168
  addiction patterns, 357
  antagonist treatment, 2391, 2409
  antidepressants, 2408
  assessment, 1150–1151
  behavioral medicine, 2033
  caffeine use relationship, 1030–1031, 1032
  combination treatments, 1159–1160, 1162
  comorbidity patterns, 1152–1153
  co-occurring mental illness, 1163–1164
  course, 1153
  definition/diagnosis, 1149–1150, 1153
  demographic/gender differences, 1153
  DSM-IV-TR criteria, 1150
  epidemiology, 1151–1152
  genetic factors, 1153–1154
  management problems, 1162–1163
  medical history, 1151
  motivation for smoking cessation, 1151, 1160
  neurobiology, 366–367, 1154–1155
  other substance abuse, 1151
  pharmacotherapy, 1151, 1157–1159, 1162, 2407–2410
  physician's advice, 1160–1162
  psychiatric disorder comorbidity, 2409
  psychiatric history, 1151
  psychological dependence, 1155
  psychosocial treatments, 1160–1163
  self help, 1161–1162
  social/environmental factors, 1155
  treatment, 1155–1164, 2391, 2407–2408, 2409
Nicotine-induced sleep disorder, 1653
Nicotine replacement therapy (NRT), 1151, 1157, 1159–1163, 2407–2408
Nicotinic agonists in Alzheimer's disease, 2299
Night alarms, enuresis, 873, 874
Nightmare disorder, 1647–1648
  DSM-IV-TR criteria, 1648
NIMH *See* National Institute of Mental Health
Nitrite abuse, 969–970, 1127, 1140
Nitrous oxide, 1127, 1129, 1133, 1137–1138
NK receptors *See* Neurokinin receptors
NLD *See* Nonverbal learning disability
NMDA *See* (*N*-)methyl-D-aspartate
NMDA receptor *See* (*N*-)methyl-D-aspartate receptor

NMHCSHC *See* National Mental Health Consumers' Self-help Clearinghouse
NMS *See* Neuroleptic malignant syndrome
'No-abuse' contracts in couples therapy, 1970
Nocturnal enuresis, 868–875
'No-harm'/'no-suicide' contracts, 86, 2483, 2485–2486
Nonadherence *See* Compliance
Nonassociative fear pathway, 1426
Nonbenzodiazepine hypnotics
  abuse, 1187, 1189–1191
  insomnia, 1637, 2257, 2262
Nonbizarre delusions, 1272
Non-collusive compensation, 73, 76
Noncompliance
  *See also* Compliance
  measurement, 2449, 2450
  patterns, 2449–2450
  prevalence, 2449
  problems, 2447
  reasons, 2447, 2451–2455
  risk factors, 2451, 2452
Noncontingent positive regard, 4, 8
Nondeclarative memory, 585, 586
Nonexperimental studies, 408–409
Nongeneralized social phobia, 1412, 1434
Nonlinear recovery-oriented treatment, 2050
Nonnutritive substances, pica, 842–844
Nonparkinsonian tremor, 1778
Non-rapid eye movement (NREM) sleep, 1627, 1629–1630
Nonresponse to treatment *See* Treatment-refractory patients
Nonrestraint movement, history, 217
Nonshared environmental influences, 111–112
Non-steroidal anti-inflammatory drugs (NSAIDs), 1533, 1534
Non-traditional approaches
  *See also* Complementary and alternative medicine
  services for mentally ill homeless people, 2527, 2532
Nonverbal communication
  group psychotherapy, 1913
  listening skills, 4, 5–6
  pragmatic social skill difficulties, 756–757
  psychiatric interviews, 42
Nonverbal learning disability (NLD), 792
Non-Western cultures
  *See also* Cultural issues
  combined anxiety/depression/somatoform complaints, 651, 652
  individual versus family therapies, 1958–1959
Nootropics, 2308, 2339–2340, 2341
Noradrenaline *See* Norepinephrine (NE)
Noradrenaline-reuptake inhibitors (NARIs) *See* Norepinephrine reuptake inhibitors
Noradrenergic and specific serotonergic antidepressants (NaSSAs), 1309, 2127
Norepinephrine-dopamine reuptake inhibitors (NDRIs), 2127
Norepinephrine (NE)
  acute neuroleptic-induced akathisia, 1779
  antidepressant side effects, 2136, 2137
  cocaine use, 1061
  genes in attention-deficit hyperactivity disorder, 814
  mood disorder neuropathology, 343, 344, 345, 1293–1294, 2123
  premenstrual dysphoric disorder, 1382
  schizophrenia, 1228
  tic disorders, 855
Norepinephrine reuptake inhibitors (NRIs), 819–820, 1309, 2126, 2127
Normalization principle, 713
Normal-pressure hydrocephalus, 916
Norms in group psychotherapy, 1906
Nortriptyline
  ADHD with tic disorders, 862
  availability, 2128
  mechanism of action, 2126
  nicotine dependence, 2408
'No-suicide'/'no-harm' contracts, 86, 2483, 2485–2486
Nova Scotia Stirling Country research, 410–411
Novel treatments for refractory depression, 2372–2387
Novelty, anxiety responses, 322, 328–330
NPD *See* Narcissistic personality disorder
NREM *See* Non-rapid eye movement
NRG1 *See* Neuregulin, 1
NRIs *See* Norepinephrine reuptake inhibitors
NRT *See* Nicotine replacement therapy
NSAIDs (non-steroidal anti-inflammatory drugs), 1533, 1534
Nucleus accumbens, 965
Nuisance variables, study design validity, 2624
Null hypothesis, 2623
Numbing, 2587
Nursing homes, 1823, 1824, 1825
Nutritional deficiencies
  *See also* Anorexia nervosa
  alcohol withdrawal, 2392
  feeding disorder of infancy or early childhood, 837–838
  intellectual disability, 739–740
  mood effects, 2325–2326
  pica, 843
NVAW survey *See* National Violence against Wowen survey
Nystagmus, 1094, 1095
OAS *See* Overt Aggression Scale
OAS-M *See* Overt Aggression Scale-Modified
Obesity
  antipsychotic drugs, 1253–1254, 1255, 2188–2189
  behavioral medicine, 2033
  eating disorder relationship, 1609, 1623
Object constancy, 142
Objective measurement of hypnotizability, 1986–1987
Objective opioid withdrawal scale (OOWS), 2404
Object libido, 468
Object relations theory, 473–477, 1858
Objects
  libido theory, 467–468
  self-psychology, 477–478
OBOT *See* Office-based opioid treatment
Observation
  feeding disorder of infancy or early childhood, 834
  initial child/adolescent evaluation, 548, 551
  psychiatric interviews, 43
Observation bias, 409–410
Obsessions
  definition, 1443
  thought disorders, 598, 599, 600
Obsessive–compulsive anxiety disorder (OCAD), 1745
Obsessive–compulsive disorder (OCD), 1443–1468
  *See also* Compulsive behavior
  adolescents, 500–501, 502, 503
  anorexia nervosa relationship, 1613, 1614
  anticonvulsants, 2246–2247
  antipsychotics, 2247
  anxiolytic drugs, 2244–2248
  Asperger's disorder comorbidity, 793
  behavioral therapy, 1463–1465
  benzodiazepines, 2246
  beta-blocker medication, 2246
  biological/neuroimaging studies, 296
  body dysmorphic disorder relationship, 1540–1541
  cognitive and behavioral therapies, 1938
  combined treatments, 2433–2434, 2436–2437
  comorbidity, 1449
  diagnosis, 1443–1449
  differential diagnosis, 1451–1453, 1665
  dorsal striatum dysregulation, 250
  DSM-I to DSM-III changes, 318
  effortful control disruption, 158
  epidemiology, 1448–1449
  etiology/pathophysiology, 1454–1457
  general features, 319–320

Obsessive–compulsive disorder (Continued)
generalized anxiety disorder distinction, 1499
genetic epidemiology, 261
history of understanding, 212, 225
hypochondriasis relationship, 1537
ICD-10 criteria, 1448–1449
impulsive/compulsive behavior, 645
intellectual disability, 726, 730
kleptomania etiology, 1670–1671
monoamine oxidase inhibitors, 2246
paraphilia relationship, 1601, 1605
pathological gambling, 1680, 1683
pharmacotherapy, 1458–1463
psychotropic medications efficacy, 2224
PTSD differentiation, 1476
selective serotonin reuptake inhibitors, 2244–2246
serotonin-norepinephrine reuptake inhibitors, 2246
tic disorder comorbidity, 850, 851–852, 857
treatment, 859, 862, 863
treatment, 1457–1467
trichotillomania, 1690–1691, 1692, 1694
tricyclic antidepressants, 2246
Obsessive-compulsive personality disorder (OCPD), 1450, 1744–1746
DSM-IV-TR criteria, 1745
OCD differential diagnosis, 1452–1453
psychotherapy, 1465
Obsessive-compulsive spectrum disorders, 1453, 1537, 1544
Obsessive-compulsive symptoms secondary to a general medical condition, 941–942
Obstetric conditions
*See also* Pregnancy
psychological factors affecting medical condition, 1767
schizophrenia complications, 302
Obstructive interventions, 46
Obstructive sleep apnea, 1641–1642
OCAD *See* Obsessive-compulsive anxiety disorder
Occupational functioning, 641, 1712
OCD *See* Obsessive-compulsive disorder
OCPD *See* Obsessive-compulsive personality disorder
Ocular effects of antipsychotic drugs, 2191–2192
ODD *See* Oppositional Defiant Disorder
Oedipus complex
child development, 142, 146, 150, 151
psychoanalytic theory, 290, 467
sexual desire disorder, 1585
OFC *See* Olanzapine-fluoxetine combination
Offenders, correctional psychiatry, 92, 2529, 2593–2600
Office-based opioid treatment (OBOT), 1177
Off-label medication use
insomnia, 2258–2259
treatment-resistant depression, 2379
Ohio state mental health policy and funding, 1827–1830, 1832, 1833, 1839
Olanzapine
acute bipolar depression, 2211, 2213
bipolar maintenance therapy, 2217, 2218
bipolar mania, 2206, 2210
chemical structure, 2168
dosing parameters, 2178
generalized anxiety disorder, 2232
obsessive-compulsive disorder, 2247
pharmacology, 2169
post-traumatic stress disorder, 2243–2244
pregnancy, 2422
schizoaffective disorder treatment, 1267
schizophrenia, 1243–1244
suicide protection, 2485
tic suppression, 858
treatment resistance, 1257–1258
Olanzapine-fluoxetine combination (OFC), 2211, 2213
Older people *See* Elderly adults
Oldham and Morris personality style-personality disorder continuum, 635–636
Olfactory decline with age, 200
Olfactory reference syndrome, 1273
Omega-3-fatty acids, 1311, 2319, 2325–2326, 2336
Oncology *See* Cancer
Ondansetron, 996
*One-group posttest only* design, 2620
*One-group pretest-posttest* design, 2620
One-month prevalence rate, ECA study, 412, 414–415
One practitioner model, 2440–2443
Ongoing rehabilitation for mentally ill homeless people, 2533–2534
Onset *See* Age at onset; Season of onset
Oophorectomy, 1385
OOWS *See* Objective opioid withdrawal scale
Opening phase of psychiatric interviews, 44
Open systems theory, 1906
Operant conditioning, 1534, 1953
Operant paradigm, 1533
Opioid abuse, DSM-IV-TR criteria, 1173
Opioid agonists, 1177–1178
Opioid antagonists, 994–995, 2391, 2405–2407
Opioid dependence, DSM-IV-TR criteria, 1173
Opioid-induced disorders, 1169–1170
Opioid-induced sleep disorder, 1653
Opioid intoxication, DSM-IV-TR criteria, 1171
Opioid receptors, 371, 373, 1169
Opioids
neuropharmacology, 367
pain/pain disorder treatment, 1533, 1534
tic disorders, 856
Opioid system
alcohol effects, 973
kleptomania, 1671–1672
stereotyped movement disorder, 891, 892
substance intoxication/reward, 365, 366, 367
Opioid use disorders, 957–970, 1169–1183
addiction patterns, 357
anesthesia-assisted detoxification, 2405
antagonist treatment, 994–995, 2391, 2405–2407
benzodiazepine abuse combinations, 1188, 1189, 1191, 1193
buprenorphine, 2403–2405
clinical aspects, 1171–1175
detoxification, 1175–1177, 2398–2401, 2405
epidemiology, 1170
etiology, 1170–1171
heroin, 355, 357, 1169–1170, 2405
infections, 2398
maintenance treatment, 2401–2405
medical conditions, 2398
methadone, 2401–2403
pharmacotherapy, 2397–2407
signs/symptoms, 1171–1172
violence link, 2606
Opioid withdrawal, DSM-IV-TR criteria, 1172
Oppositional behavior, childhood problems, 496
Oppositional Defiant Disorder (ODD), 804, 805–806, 811, 812–813, 1747
Oral administration of medications, 2100
Oral cleft defects, 2509
Oral cocaine substitution therapy, 1075
Oral contraceptives, 1385
Oral phase of childhood sexuality, 466
Oral smokeless tobacco, 2410
Organic factors *See* Neurobiological factors
Organic/inorganic distinction, 246
Organicity construct, 557
Organic nitrite inhalation, 1127, 1140
Organic solvents inhalation, 1127–1142
Organization of families, 1950

Organization problems, 750–751
Organization skills educational, 752
Organ systems, anxiety effects, 623
Organ transplantation, 69
Orgasmic disorders
female, 1589–1591
male, 1591–1592
Orientation
*See also* Sexual orientation
attention, 435
delirium, 920
evaluation, 591
phase of group dynamics, 1907
schizophrenia, 1235
Orthostatic hypotension, 2185, 2190
Osmotic-release methylphenidate (OROS-MPH), 2264, 2268, 2281
OTC *See* Over-the-counter
Other/unspecified psychological factors affecting a general medical condition, 1757
Ototoxicity, 1136, 1137
Outcomes assessment, study design methodology, 2625
Out-of-pocket payment, 1835
Outpatient care
alcohol use disorders, 990
cocaine use disorders, 1067
correctional psychiatry, 2597
hospital transition, 29
initial disposition, 544
insurance benefit limits, 1836
mental health service history, 1824
RBRVS payment system, 1838
violent patients, 2602
Outreach services for mentally ill homeless people, 2526–2535
Overall relationship functioning, 1801–1802
Overextension in language development, 141
Overinvolvement in relational problems, 1795, 1796, 1801
Overt Aggression Scale-Modified (OAS-M), 807, 809
Overt Aggression Scale (OAS), 807, 809
Over-the-counter (OTC) remedies, 2108, 2260–2261
Overvalued ideas, 599, 600
Ovulation suppression treatments, 1385
Oxazepam, 2393
Oxycodone abuse, 1169–1170
Oxytocin, 1966

P&As *See* State Protection and Advocacy Centers
*P2RX7* gene, 342
P3 potential, 566
Package inserts (PIs), 2107
Pagoclone, 2240
Pain
chronic pain, 629, 1289, 1806–1807, 2035–2036, 2041–2043
definition, 1533
depression relationship, 340, 629, 1289
elderly adults, 515
etiology/pathophysiology, 1533
physical/psychological, 629
relational problems, 1806–1807
sexual, 1592–1594, 1976
Pain disorder, 1530–1535
course, 1532
definition/diagnostic features, 1530–1531
differential diagnosis, 1532–1533
DSM-IV-TR criteria, 1531
epidemiology, 1531–1532
etiology/pathophysiology, 1533
panic disorder comorbidity, 1398
treatment, 1533–1534
Pain management
behavioral medicine, 2035–2036, 2041–2043
end-of-life care, 2517
hypnotic analgesia, 2000–2003
NSAIDs, 1533, 1534
opioid dependence, 1174
patients on methadone maintenance treatment, 2402
Palilalia, 847
Paliperidone, 1245, 2168, 2170, 2178
Paliroden, 2307
Palliative care, 2037–2038, 2554, 2517
Pancreatic cancer, 2502
PANDAS *See* Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
Pandemic flu, 2473–2474
Panic attacks
assessment decision tree, 1396
avoidant behavior, 646
definition, 1393
hallucinogen intoxication, 1104
hypnosis, 1993
presentation, 611–613
records/diaries, 1395, 1397
secondary to a general medical condition, 940–941
specific phobia types, 1411, 1412
Panic disorder with agoraphobia, 1393, 1394
Panic disorder (PD)
abuse victims, 2586–2587
adolescents, 500
animal models, 325
anticonvulsants, 2240
antipsychotic medication, 2240
anxiolytic drugs, 2236–2240
benzodiazepines, 2239
buspirone, 2239
childhood separation anxiety disorder relationship, 880
clinician-patient relationship, 1405
cognitive and behavioral therapies, 1938, 1939
cognitive model, 1399–1400, 1922
comorbidity patterns, 1397–1398
costs, 1399
definitions, 1393–1395
diagnostic assessment, 1395–1397
diagnostic criteria, 1393–1395, 1406
differential diagnosis, 1396, 1399, 1417
DSM-I to DSM-III changes, 318
epidemiology, 1397
etiology and pathophysiology, 1399–1400
general features, 319
generalized anxiety disorder distinction, 1499
genetic epidemiology, 260–261
genetic factors, 1402
history, 1392–1393
impacts, 1399
interpersonal psychotherapy, 1883
middle adult life, 510
monoamine oxidase inhibitors, 2238
panic attack types, 613
pharmacological treatments, 1404–1406
physical signs and symptoms, 622–623
psychodynamic models, 1400
psychosocial treatments, 1402–1406
psychotropic medications efficacy, 2224
PTSD differentiation, 1476
selective serotonin reuptake inhibitors, 2236–2237
serotonin-norepinephrine reuptake inhibitors, 2237–2238
social and environmental factors, 1402
suicide, 2480–2481
treatment, 1402–1406
tricyclic antidepressants, 2238
violence link, 2605
Panic disorder without agoraphobia, 1394–1395
PAPD *See* Passive-aggressive personality disorder
Paragrammatisms, 597, 598
Paralanguage, 757
Parallel distributed processing model, 1573
Parallel play, 144
Paralysis, 1638, 1639
Paraneoplastic syndrome, 1288
Paranoia
definitions, 1272
history, 220
thought disorders, 598
Paranoid personality disorder (PPD), 1724–1726
DSM-IV-TR criteria, 1724
Paranoid-schizoid position, 473–474
Paranoid-type schizophrenia, DSM-IV-TR criteria, 1205
Paraphasias, 597
Paraphilias, 1600–1606
characteristics, 1600–1601
criminal, 1601, 1602–1603
early adulthood, 509
gender identity disorder relationship, 1597–1598, 1604

Paraphilias *(Continued)*
impulsive behavior, 643, 644
male erectile disorder link, 1588, 1603–1604
non-criminal, 1604
pharmacotherapy, 1605
psychopathology, 1601–1602
sexual obsessions in OCD, 1444, 1445, 1447
treatment, 1604–1606
Paraphrenia, 515
Parasitic infestations
delusions, 1273
pica, 843
Parasomnias, 1647–1650
childhood problems, 498, 503
substance-induced sleep disorder, 1652, 1653
Parasympathetic nervous system (PNS), 2327
Parathyroid disorders, 2504–2505
Parental care
*See also* Family relational problems
adolescent social development, 174
animal models, 330–331
anxiety disorder relationship, 329–330, 331–332
emotional reactivity in children, 331
feeding disorder of infancy or early childhood, 835–836, 839
influence on behaviorally inhibited children, 329–330
parent-child relational problems, 1795–1797, 1799, 1801, 1804–1805
preschool development, 136, 142–143, 145
selective mutism, 884
separation anxiety disorder, 880, 881
Parental competency in child protection cases, 732
Parental consent/notification of treatment of minors, 84–85
Parental separation, 614
Parent-child interaction therapy (PCIT), 1804–1805
Parenting in adults, 185, 191
Parents role in initial child/adolescent evaluations, 547, 549, 551, 554
Parent Training, 1804
Parkinsonism, medication-induced, 1776–1779, 1781, 2184–2187
Parkinson's disease with dementia (PDD), 398, 908–909
Parkinson's disease (PD)
adult developmental effects, 184
antipsychotic drugs, 2173
depression comorbidity, 1287–1288
psychological factors affecting medical condition, 1765
sleep disorders, 1651
Paroxetine
availability, 2128
breastfeeding, 2424
congenital malformations, 2508
generalized anxiety disorder, 2228
history, 2127
obsessive-compulsive disorder, 1461, 2244
panic disorder, 2236–2237
post-traumatic stress disorder, 2241
premenstrual dysphoric disorder, 1383–1384
Partial chromosomal anomalies, 697–698
Partial mood stabilizers, use of term, 2219, 2220
Partner relations *See* Couples; Marriage
Partner violence screen (PVS), 2580
'Passing the test', psychoanalytic psychotherapists, 1861
Passionflower (*Passiflora incarnata*), 2319, 2334–2335
Passive-aggressive personality disorder (PAPD), 1746–1747
DSM-IV-TR criteria, 1747
Passive-dependent personality trait disturbance, 1742
Paternal eating habits, 836
Pathognomonic signs, 562
Pathological doubt, 1447, 1466
Pathological Gambling Modification of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), 1679
Pathological gambling (PG), 643, 1658, 1660–1661, 1678–1687
adolescents, 502
assessment, 1679
comorbidity patterns, 1680–1681
diagnosis, 1678–1679
differential diagnosis, 1682
DSM-IV-TR criteria, 1678, 1679, 1683
epidemiology, 1679–1680
etiology/pathophysiology, 1682–1685
treatment, 1685–1687
Pathological personality traits, 635, 642–646
Pathoplasty model, 490, 614
Patient guides for interpersonal psychotherapy, 1884
Patient matching in alcohol dependence treatment, 990
Patient Outcome Research Team (PORT), 1845–1846
Patient-related factors, compliance, 2451–2452
Patients
*See also* Compliance; Consumer..
combined treatment preferences, 2441–2442
heterogeneity in schizophrenia, 2048–2049
legal rights, 82–85
medication self-regulation, 2458
panic disorder treatment preference, 1406
preparation for therapy, 1909–1910, 1934
satisfaction with quality of care, 1845
schizophrenia role, 2049–2050
sleep disorder management in psychiatric patients, 1638, 2261–2262
therapeutic frame boundaries, 71–73, 75–76, 77–78
violent, 2602
Patient selection
brief psychotherapies, 1890, 1898–1899
group psychotherapy, 1909–1910
PATS *See* Preschool ADHD Treatment Study
Pavlovian conditioning, 323–324
Pavlov, Ivan Petrovich, 220
Payment for care, types, 1834–1836
PCIT *See* Parent-child interaction therapy
PCL-R *See* Psychopathy Checklist-Revised
PCOS *See* Polycystic ovary syndrome
PCP *See* Phencyclidine
PD *See* Panic disorder; Parkinson's disease; Pharmacodynamics; Phonological disorder
PDCA *See* Plan-Do-Check-Act
PDD *See* Parkinson's disease with dementia; Pervasive developmental disorders
PDD-NOS *See* Pervasive developmental disorder - not otherwise specified
PDE-5i *See* Phosphodiesterase type 5 inhibitors
PDNOS *See* Personality disorder not otherwise specified
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), 850, 856, 859, 1450–1451
Pediatric OCD Treatment Study (POTS), 2436–2437
Pedophilia, 1600, 1601, 1602
Peer counselors, 2091
Peer interactions
adolescent social development, 174–175
learning and motor skills disorders relationship, 756–757
preschool development, 143–144
Peer review of research methodology, 2632–2633
Peer support, 2050, 2065, 2085, 2091
Peer-to Peer, National Alliance on Mental Illness program, 2087
Pemoline (PEM), 2264, 2265, 2282
Penetrance, variable genetic influence, 98
Penrose, Lionel, 690–691
Peptic ulcer disease (PUD), 1766
Peptides, schizophrenia, 1227–1228
Perception
disturbances, 279, 601–602, 919–920, 1235
lack of control, 1501
mental status examination, 41, 529

necessity of medication, 2453–2454
Perfectionism, 1426
Performance anxiety, 1423, 1588
Performance Intellectual Functioning (PIQ), 589, 590
Pergolide, 859
Perimenopausal women
premenstrual dysphoric disorder, 1381
psychiatric conditions, 2511–2513
sexual function, 100, 1586, 1593
Perinatal depression, 2417–2426, 2507
Perinatal history, 39
Perinatal medication complications
antidepressants, 2420–2421, 2508
antipsychotics, 2422–2423
benzodiazepines, 2423
lithium, 2422, 2508–2509
Perinatal pathology
intellectual disability, 705
learning and motor skills disorders, 757
Perinatal stress, 286
Periodic limb movements in sleep (PLMS), 1631, 1632, 1646–1647
Period prevalence rate, 405
Peripartum depression, 1881–1882
Peripheral neuropathy, 1138
Permanent Product Measure of Performance (PERM-P), 810
Perospirone, 2168, 2169–2170
Perphenazine, 2168
Persecutory-type delusional disorder, 1272
Perseveration, 596, 598
Persistence of psychopathology across the life span, 489–490
Persistent pulmonary hypertension of the newborn (PPHN), 2420, 2426, 2508
Personal history, 39, 527
Personal illness management and recovery, 2073–2075
Personality
*See also* Personality styles
changes in dementia, 395, 396
changes secondary to a general medical condition, 944–947
character neuroses, 471
functioning model, 1722–1723
history of understanding, 222
role in depression, 614
seven-factor character model, 636–639
Personality disorder not otherwise specified (PDNOS), 1718–1719, 1746–1749
Personality disorders, 1718–1753
*See also* Antisocial personality disorder; Borderline personality disorder
alcohol dependence, 973
antisocial personality disorder, 1730–1733
assessment, 1719–1720
avoidant personality disorder, 1740–1742
Axis I disorders biogenic spectrum, 639
borderline personality disorder, 1733–1735
categorical versus dimensional models, 635
cognitive model, 1922
comorbidity, 1663–1664, 1681, 1721–1722
course, 1722–1723
cultural factors, 654
definition, 1718–1719
dependent personality disorder, 1742–1744
depression comorbidity, 1286
depressive personality disorder, 1748–1749
differential diagnosis, 1719
DSM classification systems, 676
DSM-IV-TR criteria, 1718, 1719–1720, 1721, 1723–1724
early adulthood, 507–508
eating disorder relationship, 503
epidemiology, 1720–1721
etiology/pathophysiology, 1723
history of understanding, 226, 230
histrionic personality disorder, 1735–1737
hypnotizability, 1990
impulsivity, 1658
intellectual disability, 730
maladaptive functioning behaviors, 642–646
narcissistic personality disorder, 1737–1740
obsessive-compulsive disorder comorbidity, 1450
obsessive-compulsive personality disorder, 1744–1746
panic disorder comorbidity, 1398
paranoid personality disorder, 1724–1726
passive-aggressive personality disorder, 1746–1747
personality change distinction, 946
personality style continuum models, 635–636
premenstrual dysphoric disorder differential diagnosis, 1380
psychiatric disability, 2059–2060
schizoid personality disorder, 1726–1728
schizotypal personality disorder, 1728–1730
somatoform disorder relationship, 1520, 1521, 1529, 1540
treatment, 1723–1724
treatment-resistant depression, 2376
violence link, 2605
Personality styles
adaptive functioning/behavior, 633–639
affecting a general medical condition, 1756, 1759–1760, 1761, 1767–1768
anorexia nervosa, 1615–1616
categorical versus dimensional models, 635
fear development, 1426
functional domains, 639–641
heritability, 1422
personality disorder continuum models, 635–636
Personality theory, 10–11
Personal strengths case management model, 2068
Person-centered services, 2050
Perspective taking, 445
Pervasive developmental disorder - not otherwise specified (PDD-NOS), 380–381, 787, 793–794, 799
Pervasive developmental disorders (PDDs), 765, 767, 779–800
*See also* Autism
antipsychotic drugs, 2174
Asperger's disorder, 380, 787, 791–795
autistic disorder, 380–381, 779–790
childhood disintegrative disorder, 381, 787, 795–796
childhood problems, 494
differential diagnosis, 787, 890, 893, 894
feeding disorder of infancy or early childhood, 833
intellectual disability, 723–724
pica, 842, 843, 844
Rett's disorder, 796–799
rumination disorder, 839
stimulants, 2277
Perversions *See* Paraphilias; Sexual perversion
PET *See* Positron emission tomography
Peyote, 1101
PFA *See* Psychological first aid
PFAMC *See* Psychological factors affecting medical condition
PFC *See* Prefrontal cortex
PG *See* Pathological gambling
P-glycoprotein medications, 2100, 2101
*PGRN* gene, 397–398
PG-YBOCS *See* Pathological Gambling Modification of the Yale-Brown Obsessive-Compulsive Scale
Phallic/phallic-oedipal phase of childhood sexuality, 466–467
Phantom pregnancy (pseudocyesis), 1526, 1543
Pharmacodynamics (PD), 2105–2107, 2116, 2117
Pharmacogenetics, 2386
Pharmacogenic depression, 1286
Pharmacokinetics (PK), 2099–2105, 2107
antidepressant drug-drug interactions, 2141
antidepressants, 2133–2134
compliance, 2458
genetic effects, 2116, 2117
MDMA use, 1116–1117
phencyclidine, 1092–1093
psychotropic medications, 2227–2228
Pharmacological phenotypes, 281

Pharmacological vulnerability, 973
Pharmacology
  antipsychotic drugs, 2166–2170
  caffeine, 1023, 1027–1028, 1032
  stimulants, 2266–2269
  substance intoxication/reward, 364–367
Pharmacotherapy
  *See also* Antidepressant medication; Antipsychotic drugs; Drug interactions; Drug responses; *individual drugs*
  ADHD with tic disorders, 861–862
  adjustment disorders, 1712
  alcohol use disorders, 992–996
  anxiety disorders, 1422–1423, 1427–1429, 1432
  behavioral disturbance in dementia, 2555
  biodiversity effects, 2115–2120
  bipolar disorder, 1355–1362
  cancer patients, 2503
  cannabis-related disorders, 1053–1055
  cocaine use disorders, 1072–1077
  cognitive and behavioral therapies combination, 1935, 1937, 1938
  cognitive and behavioral therapies comparison, 1936, 1938–1939
  combined with psychotherapy, 2430–2446
  compliance, 1939, 2447–2459
  cultural issues, 2112–2115
  dementia, 395, 397, 398, 2553, 2555, 2557
  drug metabolizing enzymes, 2116–2119
  efficacy, 2107–2109
  ethnic issues, 2112–2121
  financial issues, 1842
  forgiveness of medication, 2449, 2458
  general principles, 2099–2111
  group psychotherapy combinations, 1914
  heart disease patients, 2500–2501
  history, 223–224, 225, 226
  informed consent, 84
  intellectual disability, 733–735, 736–740
  intellectual disability, 720, 723, 733–740
  interpersonal psychotherapy combination, 1877
  interpersonal psychotherapy comparisons, 1879–1882
  learning and motor skills disorders, 761
  lithium toxicity, 2205
  manic/depressive symptoms, 1341–1342
  medical condition therapy psychiatric effects, 528, 530
  medication development, 1076–1077, 2130–2131, 2152–2155
  medication error types, 2449–2450
  medication holidays, 2450
  medication-induced movement disorders, 1773–1791
  mental health service history, 1821, 1830–1831
  mentally ill homeless people, 2532
  neuroprotection, 1351–1352, 2166, 2167, 2338
  nicotine dependence, 1157–1159
  obsessive-compulsive disorder, 862, 1458–1463
  opioid agonists, 1177–1178
  opioid detoxification, 1175
  pain relief, 629
  panic disorders, 1393, 1404–1406
  patient attitudes, 2449, 2453
  perimenopausal mood symptoms, 2512
  post-traumatic stress disorder, 1480–1483
  pregnant women, 2417–2426, 2508–2509
  prescribing principles, 2108, 2383
  psychoanalysis influences, 290–291
  recovery orientation, 2067
  safety, 532, 2107–2109
  schizophrenia, 1241–1260, 1264
  sexual dysfunction, 1975
  societal influences, 2449
  stimulants for disruptive behavior disorders, 2264–2288
  substance abuse disorders, 967, 2390–2412
  suicidal patients, 2484–2485
  tic disorders, 857–859, 864
  tolerance assessment, 530
  torture victims, 2571
  treatment planning, 544, 545
  treatment-refractory depression, 1312–1315, 2378–2386
  vs. psychotherapy, 2431–2434
  withdrawal, 1937
Pharmacotherapy/behavioral therapy combination for alcohol dependence, 2396–2397
Pharmacy records, 2375, 2450
Phase-response curves, 1628
Phencyclidine (PCP)
  street names, 1091
  use disorders, 1090–1099
    assessment, 1095–1096
    diagnosis, 1093–1095, 1096
    differential diagnosis, 1104, 1108
    DSM-IV-TR criteria, 1094
    epidemiology, 1090–1092
    etiology/pathophysiology, 1092–1093
    schizophrenia relationship, 1227
    treatment, 1096–1097
    violence link, 2606
Phenelzine, 2241
Phenethylamines, 1102
Phenobarbital, 1195–1196
Phenothiazines, 1242
Phenotypes
  *See also* Endophenotypes
  animal models, 277–284
Phenylketonuria (PKU), 694, 700–701
Phenytoin, 2393
Pheochromocytoma, 2505
Phobias
  *See also* Social phobia; Specific phobias
  anxiety presentation, 612–613
  avoidant behavior, 646
  disease phobia/hypochondriasis distinction, 1535, 1536
  genetic epidemiology, 261
  hypnotizability, 1989
  social/specific, 1409–1436
  thought disorders, 598
  vaginismus, 1594
  weight-gain/fatness, anorexia nervosa, 1610, 1615
Phonological (phonation) disorder (PD), 765, 769, 773–774
  DSM-IV-TR criteria, 773
Phosphatidylinositol phosphatase (PTEN), 383
Phosphatidyl serine, 2340
Phosphodiesterase type 5 inhibitors (PDE-5i), 1579, 1582, 1587, 1589
Phototherapy, 1316, 1387, 2509
Phrenology, 214, 215, 2028
Phylogenetic model of obsessive-compulsive disorder, 1457
Physical abnormalities in infants *See* Congenital abnormalities
Physical abuse, 2576–2592
  acute presentations, 2578–2584
  adults, 2577–2579, 2584–2585
  disclosure in couples, 1968
  elders, 2578, 2579
  epidemiology, 2577–2578
  infant development risk factors, 129
  long-term mental health sequelae, 2584–2591
  management considerations, 2578–2584, 2586–2591
Physical disorders *See* General medical conditions
Physical effects
  alcohol use disorders, 977, 982, 989
  anorexia nervosa, 1611–1613
Physical examinations
  alcohol use disorders, 980–981
  clinical assessment, 530–532
  dementia, 899–900
  elderly adults, 2551
  impulse-control disorders, 1662
  intellectual disability, 707–708
  opioid use disorders, 1173–1174
  phencyclidine intoxication, 1095–1096
  rape/sexual assault, 2582
  schizophrenia, 1236
  substance addiction, 962
  trichotillomania, 1688
Physical functioning
  adolescent problems, 502–503
  childhood problems, 497–498
  early adulthood problems, 508–509
  late life problems, 515
Physical-psychiatric continuum, 621–631

Physical relaxation, 1993–1994, 2002
Physical restraints
aggression treatment, 2609
correctional psychiatry, 2599
definition, 2491
restraint and seclusion, 2609, 2599, 2491–2495
Physical signs and symptoms, 621–631
anxiety, 622–624
cultural issues, 58–59
factitious, 630–631
malingering, 630–631
mood disorders, 624–625
schizophrenia, 303
somatizing distress, 59
somatoform disorders, 1510–1544
unknown etiology, 627–631
Physical substance dependence, 355–356, 368–374, 1187, 1191, 1194
Physicians
*See also* Clinician-patient relationship
buprenorphine prescription qualification, 2403
child/adolescent information sharing, 546, 554
education in complementary treatments, 2344
as patients, 31
terminal care, 2517, 2518
Physiognomy, history, 209, 211, 219
Physiological responders, anxiety treatments, 1434
Physiological systems, bipolar disorder, 1352
Physiological theories of depression, 615
Physiology, consciousness alterations, 584
Piaget, Jean
adolescent development, 169
adult development, 188
history, 223
preschool development, 135, 138–139
school-age development, 150, 152–153
Pica, 726, 842–844
DSM-IV-TR criteria, 842
Picamilon, 2336–2337
Pick's disease, 396, 908
Pill burden, 2035
Pill counting, medication compliance measurement, 2450
Pimozide, 858
Pindolol
depression treatment, 1314, 2383–2384
obsessive-compulsive disorder, 2246
social anxiety disorder, 2235
Pinel, Philippe, 210, 212, 690, 710, 1201–1202, 1241
Piperazine phenothiazines, 1242
Piperidine phenothiazines, 1242
*Piper methysticum* (Kava), 2333–2334
PIQ *See* Performance Intellectual Functioning
PIs *See* Package inserts
PK *See* Pharmacokinetics
PKU *See* Phenylketonuria
Placebo effects
antidepressant trials, 2129
clinician-patient relationship, 20
ethnic/cultural issues, 2114–2115
Placebo pill plus clinical management (PLA-CM), 292–293
Placebo treatment, clinical trials, 407, 410, 2109, 2438–2439
Placental insufficiency, 704
PLA-CM *See* Placebo pill plus clinical management
Plan-Do-Check-Act (PDCA), 1843
Planning
acts of aggression/violence, 2603, 2604
disaster responses, 2471–2472, 2474–2475
release from correctional institutions, 2598
safety plans for suicidal patients, 2483
theory of planned behavior, 2448
treatment, 525–545, 560
Plant products
drug interactions, 2108, 2343, 2115, 2119
drug metabolizing enzyme expression, 2117–2118
Plasticity, 198–199
Plastic surgery, 1539, 1540
Play
autistic disorder, 782
observation of children, 548, 551
preschool development, 144
Pleasure, kleptomania as, 1671–1672
Pleasure exercises in behavioral therapies, 1930–1931
Pleasure principle, 467, 473
PLMS *See* Periodic limb movements in sleep
PM *See* Psychosomatic medicine
PMDD *See* Premenstrual dysphoric disorder
PMS *See* Premenstrual syndrome
PMT *See* Protection motivated theory
PNS *See* Parasympathetic nervous system
POA *See* Power of attorney
Point prevalence rate, 405
Poisonous substances *See* Toxic insults
Police, 2595
Political Advocacy Model, 2085, 2089–2090
Political issues, 1821, 2572
*See also* Government
Polycystic ovary syndrome (PCOS), 2505
Polygenic disease animal models, 276
Polymorphisms *See* Genetic polymorphisms
Polypharmacy, 2551
Polysomnography (PSG), 1632, 1640
Polysubstance abuse, 957–970, 1188–1189, 1191, 1193
Polyunsaturated fatty acids (PUFA), 2325
Population-based surveys, 403
Population pharmacokinetics, 2099, 2105
Population studies of homosexuality, 2540
PORT *See* Patient Outcome Research Team
Positive attention, 841
Positive illusions, 456–457
Positive reinforcement in substance abuse, 356, 364–367, 368
Positive symptoms in schizophrenia, 1230–1231, 2174–2175
Positron emission tomography (PET), 573–575
blood flow tracers, 574–575
clinical use, 579–580
dementia, 2552
$^{18}$F-deoxyglucose, 1105, 1107
FDG-PET scans, 573–574, 580
hypnotic states imaging, 2011–2012
MDMA-related disorders, 1116
molecular imaging, 577–578
neurophysiological assessment, 564
psychotherapy studies, 295–296
schizophrenia, 312
SPECT vs PET, 576
stimulants and brain glucose metabolism, 2267
treatment-resistant depression, 2386
Possession by demons, history, 206, 207
Possession trance, 653, 1570
Post-anesthetic headache, 1026–1027
Postcoital dyspareunia, 1592, 1593
Postconceptual congenital factors, 1349–1350
Post-Freudian ego psychology, 471–473
Post-LSD psychoses, 1096, 1108–1110
Postmodern family therapy, 1953–1955, 1960–1961
Postnatal brain damage, 705–706, 757
Postoperative delirium, 920–921
Postpartum anxiety, 2510
Postpartum blues (PPB), 2510
Postpartum depression (PPD), 624, 1293, 1882, 2510
Postpartum psychiatric evaluation/treatment, 2509–2511
Postpartum psychosis (PPS), 2510
Post-termination sexual relationships with patients, 77–78
*Posttest-only nonequivalent groups* design, 2620
Post-traumatic amnesia (PTA), 585–586
Post-traumatic family-centered therapies, 1958–1959

Post-traumatic self-experience disorders, 602
Post-traumatic stress disorder (PTSD), 1472–1485
abuse victims, 2576, 2584–2587, 2589–2590
animal models, 325
anticonvulsant medication, 2243
antipsychotic medication, 2243–2244
anxiolytic medication, 2240–2244
ASD relationship, 1487, 1489
assessment, 1474–1475
bereavement-related, 2523
beta-blockers, 2242
childhood problems, 495
comorbidity, 893, 1475, 1484, 2567
complementary medicine, 2330–2331, 2333
diagnosis, 1472–1474, 1475–1476, 1489, 2566–2567
differential diagnosis, 1475–1476
disaster-related, 2468–2470, 2473
dissociative disorders, 1558, 1566–1567, 1568, 1572–1573
DSM-I to DSM-III changes, 318
DSM-IV-TR criteria, 1473, 2585, 2588–2589
early adulthood, 506
emotional regulation systems, 326
epidemiology, 1475
etiology/pathophysiology, 1476–1479
general features, 320
hypnosis, 1994–1995
insomnia, 2261
intellectual disability, 730
interpersonal psychotherapy, 1883
monoamine oxidase inhibitors, 2241–2242
neurobiological factors, 328, 1477–1478
novel treatments, 2244
post-traumatic stress disorder, 2243
prefrontal cortex, emotional dysregulation, 252–253
psychotropic medications efficacy, 2224
selective serotonin reuptake inhibitors, 2240–2241
serotonin-norepinephrine reuptake inhibitors, 2241
social psychology, 456–457
suicide, 2481
torture victims, 2566–2568, 2570, 2571, 2572, 2574
treatment, 1479–1485, 2224, 2240–2244, 2570–2572
tricyclic antidepressants, 2241–2242
vulnerability, 328
Postural tremor
DSM-IV-TR criteria, 1789
medication-induced, 1788–1790
Posturing secondary to a general medical condition, 943
POTS *See* Pediatric OCD Treatment Study
Pouching, 838
Poverty, 128–129, 130, 173, 182
Poverty of speech, 596–597, 598
Power, *See also* Control issues
Power analysis, study design methodology, 2622–2623, 2633
Power of attorney (POA), 2550–2551
Power phase of group dynamics, 1906, 1907
Power sharing, 9
Power struggles in relationships, 1796
PPA *See* Primary progressive aphasia
PPB *See* Postpartum blues
PPD *See* Paranoid personality disorder; Postpartum depression
PPHN *See* Persistent pulmonary hypertension of the newborn
PPI *See* Prepulse inhibition
PPS *See* Postpartum psychosis
Practice guidelines
attention deficit-disruptive behavior disorders treatment, 825–826
couples evaluation, 1969
psychotherapy manuals, 226
quality of care, 1845–1846
Prader-Willi syndrome, 698, 718, 890
Pragmatic barriers to compliance, 2451–2452, 2454
Pragmatic language, 767
Pragmatic social skill difficulties, 756–757
Prazosin, 2244
Preattentional deficits, 279
Precipitating stressors
adjustment disorders, 1711
brief psychotic disorder, 1269
depressive mood disorder, 935, 936
Klüver-Bucy syndrome, 949
mania, 938–939
mental disorders, 933–934
personality change, 945, 946
Pre-conscious mind, 469, 1853–1854
Predictive validity of animal models, 278
Preferred provider organizations, 1840
Prefrontal cortex (PFC)
*See also* Medial prefrontal cortex
attention-deficit hyperactivity disorder, 815
attention role, 250–251
emotions, 251–253, 606–607
intermittent explosive disorder, 1666
schizophrenia, 282, 283, 284, 1220–1221, 1227
Pregabalin, 2232, 2235
Pregnancy
adolescent behavior, 174
adverse birth outcomes, 2417–2418
alcohol use disorders, 979, 982, 998
animal models of risk factors, 285
antenatal psychological health assessment, 2580
antidepressant medication, 1366, 2418–2421, 2425–2426
antipartum depression, 1882
antipsychotic drugs, 2183–2184, 2421–2423
bipolar disorder, 1366
cocaine use disorders, 1059
depression treatment, 1293
electroconvulsive therapy, 2509
evaluation, 2507–2508
fetal alcohol syndrome, 694, 704, 895, 982, 1140
fetal development, 755, 757, 1217
infections, 285, 703–704
inhalant-related disorders, 1134, 1139, 1140
interpersonal psychotherapy, 1880, 1881–1882
light therapy, 2509
maternal nutrition, 128
MDMA use, 1119
methadone maintenance treatment, 2401, 2402
miscarriage, 2417–2418, 2419
mood disorders, 2417–2426
pharmacotherapy, 2418–2423, 2425–2426, 2508–2510
placental insufficiency, 704
postpartum psychiatric illness, 624, 1293, 1882, 2509–2511
prenatal brain damage, 695–699, 702–704, 755, 757
prenatal diagnosis of intellectual disability, 708
pseudocyesis, 1526, 1543
psychiatric treatment planning, 536
psychological factors affecting medical condition, 1767
psychotherapy, 2509
schizophrenia etiology, 285, 1216–1217
stress and mood effects on adverse birth outcomes, 2417–2418
substance use consequences, 129–130, 361
termination ethics, 69
tic disorder etiology, 856
in utero medication exposure, 2420–2421, 2422–2423, 2508–2510
Pregnancy prophylaxis after rape/sexual assault, 2583
Pregnancy testing, 536
Premack principle, 837, 838
Premature birth, 130, 834, 835, 836, 2418, 2419
Premature ejaculation, 1591–1592
DSM-IV-TR, 1591
Premature treatment termination (dropout), 1068, 1078, 1973
Premenstrual dysphoric disorder (PMDD), 1379–1387
DSM-IV-TR criteria, 1380
Premenstrual syndrome (PMS), 1379–1387
Premonitory sensations/urges in tic disorders, 848, 860
Prenatal brain damage, 695–699, 702–704, 755, 757
Prenatal diagnosis of intellectual disability, 708
Prenatal history in psychiatric databases, 39
Prenatal influences *See* Pregnancy
Preoccupation with substance dependence, 357

Preoperational stage of reasoning, 138–139
Preparedness theory, 1424, 1426
Prepotent responses, 438
Prepulse inhibition (PPI), 279, 280, 1223–1224
Preschool ADHD Treatment Study (PATS), 2272–2273
Preschool children
  *See also* Infants
  development, 124–127, 135–149
  diagnostic classification, 679–688
  historic considerations, 135–136
  initial psychiatric evaluations, 548, 551
  language, 138, 140–141, 142
  risk/protective factors, 146–147
  sociocultural influences, 142–144
Prescribing principles, 2108, 2383
Prescription medication
  agitation, 626–627
  off-label use for insomnia, 2258–2259
  opioid resale, 1174
  sedative-hypnotic drug abuse, 1186–1198
  violence link, 2606
Presenilin mutations, 396
Present state examination (PSE), 1203
Pressure, libido theory, 467
Pressured speech, 598
Presynaptic group secretory function (PSYN) gene group, 1215
Preterm delivery (PTD), 130, 834, 835, 836, 2418, 2419
Prevalence rates, 405–406, 412–418, 419–423, 424–426
Prevention factors in mental illness, 1956–1957, 1958
Preventive interventions
  *See also* Prophylaxis
  adult development perspective, 193
  behavioral medicine, 2033
  intellectual disability, 713–714
  postpartum depression, 1882
  public mental health, 1832
  restraint and seclusion, 2493–2494
  suicidal patients, 2519
Pride, 145
Primary care settings
  children/adolescent referrals, 546, 554
  interpersonal therapies, 1881, 1882–1884
  major depression, 1881
  mental health integration, 2038
  psychotherapy, 1318
  subsyndromal disorders, 1882–1884
Primary encopresis, 876, 877
Primary hypersomnia, DSM-IV-TR, 1640
Primary insomnia, DSM-IV-TR, 1633
Primary memory, 898
Primary narcissism, 469
Primary process thinking, 465
Primary progressive aphasia (PPA), 396
Priming memory effects, 442, 1561
Primitive defences, 474, 476
Prion diseases, 398–399, 911–912
Prisons, 92, 2529, 2593–2600
Privacy, 1554, 1967
  *See also* Confidentiality
Private health insurance, 1817, 1834, 1835–1837, 1841
Private hospitals, 1838–1839
Privilege, legal issues, 85
Problem solving, 1795, 1799–1800
  adolescent development, 169–170, 177–178
  assessment, 1802
  block designs, 563
  families, 1807, 1953
  parent-child relational problems, 1804
  training, 1953
Problem-solving communication training (PSCT), 1800
Problem-Solving Therapy for Primary Care (PST-PC), 1318
Procedural (implicit) memory, 440, 442, 443, 1573–1574
Process communication, 1861
Processing speed, 197, 198
Prodromal stages of schizophrenia, 2171
Professionals *See* Clinician-patient relationship; Ethical issues; Legal issues; Mental health services
Progesterones, 1385–1386, 1605
Programmatic approach to intellectual disability, 740
Progranulin, 397–398
Progression of psychopathology across the life span, 489–490
Progressive supranuclear palsy (PSP), 396, 397
  *See also* Frontal temporal dementia
Projection, 465, 472, 474, 1855
Projective identification, 474, 476, 1949, 1855
Prolactin, 1255, 2185, 2188
Prolonged exposure treatment, 1483, 2590
Propellant inhalation, 1127
Propentofylline, 2311
Prophylaxis
  anticholinergic medication, 1780–1781
  bipolar disorder, 2214–2217
  depressive episodes, 1303
Propranolol, 1667–1668, 1790, 2242
Proprioceptive sensory processing disorder, 751
Prosocial actions in preschool development, 146
Prospective memory, 586, 587
Prospective studies, 408–409, 1346
Prostate cancer, 2502
Protection and advocacy organizations, 2085, 2086
Protection motivated theory (PMT), 2449
Protective factors
  *See also* Resilience
  adolescents, 177–178
  adult development, 185–186, 188
  infant development, 127–128
  longitudinal developmental studies, 104–107
  preschool development, 146–147
  psychopathology across the life span, 104–107, 490
  school-age children, 157
  suicide, 2479–2482
Protracted benzodiazepine withdrawal syndrome, 1193
Provera (depo-medroxy-progesterone), 1605
Provider organization certification and accreditation, 1844
Provider-related factors in compliance, 2454
PSCT *See* Problem-solving communication training
PSE *See* Present state examination
Pseudobulbar palsy, 618, 947–948
Pseudocyesis, 1526, 1543
Pseudodementia, 514
Pseudohallucinations, 1527
Pseudologia phantasica, 603
Pseudoneurotic schizophrenia, 224
Pseudoseizures, 1998
PSG *See* Polysomnography
Psilocybin, 1101, 1105, 1107
PSP *See* Progressive supranuclear palsy
PST-PC *See* Problem-Solving Therapy for Primary Care
Psychiatric databases, 37–41
Psychiatric disabilities
  definitions, 2059–2060
  prevalence, 2060–2061
  rehabilitation for community living, 2059–2080
Psychiatric disorders
  conceptualization of mental disorders, 423
  diagnosis in medically ill patients, 2498–2499
  gay men/lesbians, 2545
  stigma, 63–64, 621, 623, 1264, 2453
  violence link, 2603–2605
Psychiatric epidemiology, 403–432
Psychiatric evaluations
  *See also* Clinical evaluation
  competency to stand trial, 89
  criminal responsibility/insanity, 90–91
  disability/fitness evaluation, 88
  special assessment techniques, 538, 540
Psychiatric interviews *See* Interviews
Psychiatric patients *See* Patients
Psychiatric rehabilitation, 2059–2080
  Assertive Community Treatment, 2062, 2067–2070
  Boston University approach, 2064–2065
  case management models, 2067–2068, 2070
  clubhouse model, 2062–2063
  definitions, 2061
  evidence-based practices, 2059, 2062, 2065, 2067–2080
  family psychoeducation, 2070–2073
  illness management recovery, 2073–2075

Psychiatric rehabilitation *(Continued)*
integrated dual disorder treatment, 2075–2077
peer support approach, 2065
recovery orientation, 2065–2067
serious mental illness, 2059–2080
social skills training, 2063–2064
supported employment, 2065, 2077–2080
Psychiatric symptoms in somatization disorder, 1519, 1520
Psychiatric training in behavioral medicine, 2041
Psychiatrists
*See also* Clinician-patient relationship
demeanor, 17
developmental understanding, 107–108
mentally ill homeless people, 2527, 2532, 2534–2535
self-awareness, 11–12, 14–15, 18
Psychiatry, historical use of term, 213
Psychoactive medication *See* Pharmacotherapy
Psychoactive substances *See* Substance use disorders
Psychoanalysis
*See also* Psychoanalytic theories
brief psychotherapies, 1889
characteristics, 1855
cognitive and behavioral therapies comparison, 1920
definition, 464
history, 214, 221–224, 230, 1858
principles, 289–290
psychoanalytic psychotherapy distinction, 1851, 1855–1856, 1860
Psychoanalytic psychotherapy, 1851–1871
basic technique, 1855–1857
contraindications, 1858, 1862–1863
effectiveness, 1866–1869
expressive-supportive continuum, 1852–1853, 1863
indications, 1858, 1862
phases, 1861
principles, 1851–1853
process, 1857–1859
supportive techniques, 1860, 1862, 1863
techniques, 1855–1857
theory, 1853–1855
therapist's tasks, 1860–1862
Psychoanalytic theories, 464–485
anxiety disorders, 1423–1424
bipolar disorder, 1352–1353
development, 464–473
infant development, 110–111
interpersonal psychoanalysis, 479
intersubjectivity, 480
object relations theory, 473–477
obsessive-compulsive disorder, 1457
psychoanalytic psychotherapy, 1851
relational perspective, 478–479
self-psychology, 477–478
social constructivism, 479–480
Psychobiological model of bipolar disorder, 1353
Psychobiological model of self-regulation, 2031
Psychodynamic theory
conversion symptoms, 1514
depression, 1299–1300
group psychotherapy, 1904–1905
panic disorders, 1400
pathological gambling, 1685
psychiatric disorders, 33–36
Psychodynamic therapy, 292, 294
anorexia nervosa, 1617
brief psychotherapies, 1889, 1891–1893, 1894, 1898, 1867
depressive disorders, 1317
family therapy, 1949–1950, 1959
PTSD treatment, 1484, 1485, 2590
schizophrenia, 1260–1261
torture victims, 2570–2571
trichotillomania treatment, 1693
Psychoeducation
bipolar disorder, 1362, 1363, 1364
cognitive and behavioral therapies, 1925–1926
depression, 1876, 1877
family therapy, 1952–1953, 1955–1956, 1957
generalized anxiety disorder, 1503
learning and motor skills disorders, 758–760
relational problems, 1803
schizophrenia, 1261–1262
Psychogenic pain disorder *See* Pain disorder
Psychological conflict, conversion symptoms, 1526, 1528
Psychological construct validity in animal models, 277–278
Psychological factors
anxiety disorders, 1423–1427, 1501
attention-deficit hyperactivity disorder, 816
autistic disorder, 788
bipolar disorder, 1352–1353
obsessive-compulsive disorder, 1457
pain perception, 2001
psychiatric disorders, 37
sexual disorders, 1581, 1582, 1587–1589, 1592–1593
substance addiction, 965, 1155
Psychological factors affecting medical condition (PFAMC), 1754–1768
*See also* General medical conditions; *individual disorders*
DSM-IV-TR, 1755
somatization disorder relationship, 1511
Psychological factors affecting physical condition, DSM-III-R criteria, 1754
Psychological first aid (PFA), 2472
Psychological investment in psychoanalytic psychotherapy, 1853
Psychological parameters of endophenotypes, 246
Psychological processing in learning disorders, 748, 757–759
Psychological testing, 532–533, 1567
*See also* Mental status examination
Psychology, historical use of term, 209, 210, 211
Psychometric properties, 406–407
Psychooncology, 2036–2037
*See also* Cancer
Psychopathic hospitals, history, 1820
Psychopathological domains of schizophrenia, 302
Psychopathology across the life span, 489–516
Psychopathology risks/protective factors, 104–107
Psychopathy
*See also* Antisocial personality disorder
history of understanding, 215–216, 224, 231
use of term, 1730, 1738
violence link, 2605
Psychopathy Checklist-Revised (PCL-R), 1730
Psychopharmacoepidemiology, 404
Psychopharmacologic bridge hypothesis of mood disorders, 344
Psychopharmacology *See* Pharmacotherapy
Psychosexual development, 110–111, 465–466, 477
Psychosexual problems, 498, 509
*See also* Sexual disorders
Psychosis
*See also* Psychotic disorders
historical use of term, 213
Psychosocial development, 110–111, 477
Psychosocial model of post-traumatic stress, 2568, 2571–2572
Psychosocial rehabilitation, 1260, 2047–2056, 2062–2063
Psychosomatic illness, 1755
history, 222
somatoform disorder distinction, 1511
Psychosomatic medicine (PM), 2496–2505
behavioral medicine historical foundations, 2028–2029
cancer, 2501–2503
cardiovascular disease, 2499–2501
clinical practice, 2498
endocrine disorders, 2503–2505
Psychostimulants *See* Stimulants
Psychotherapy
adjustment disorders, 1710–1712
antidepressant treatment augmentation, 2151
behavioral medicine, 2041
biological/neuroimaging studies, 295–297
bipolar disorder, 1362
brief psychotherapies, 1889–1901
brief psychotic disorder, 1269
cancer patients, 2503
cannabis-related disorders, 1047–1053

clinician-patient relationship research, 27
cocaine use disorders, 1069–1072
combined with medication, 2430–2446
communication disorders, 772
community living, 2059
correctional settings, 2597–2598
definitions, 1851
depression, 1316–1318, 2421, 2559
disaster-related, 2473
dissociative disorders, 1562, 1567–1568
drug dependence treatment, 1197
efficacy studies, 292–293
elderly adults, 2559
evidence-based practices, 2059, 2062, 2065, 2067–2080
family-based treatment, 1948–1961
gender identity disorders, 1598–1599
impulse-control disorders, 1674, 1686–1687, 1693
individual psychoanalytic psychotherapy, 1851–1871
informed consent, 84
insurance benefit limits, 1836
intellectual disability, 740
interpersonal psychotherapy, 1875–1886
learning and motor skills disorders, 760–761
mechanisms of, 293–294
obsessive-compulsive disorder, 1465
paraphilia, 1605
postpartum women, 2511
post-traumatic stress disorder, 2590
pregnancy, 2421, 2509
schizophrenia, 1261
scientific basis, 289–300
sexual orientation issues, 2542–2543
terminal care, 2518
tic disorders, 860
types, 1852
vs. medication, 2431–2434
Psychotic disorders, 1201–1282
*See also* Schizophrenia
alcohol-induced psychotic disorder, 978
bipolar disorder with psychotic features, 1238, 1337, 1339, 1340
brief psychotic disorder, 1237, 1268–1270, 1278
cancer patients, 2502
cannabis-induced, 1046–1047
cocaine use disorders comorbidity, 1080
cultural factors, 650
delirium differentiation, 923–924
delusional disorder, 1238, 1272–1276
depression with psychotic features, 339, 1238, 1289, 2151, 2171
DSM classification systems, 674–675
early adulthood, 509–510
elderly adults, 515
general medical condition-related, 932–935
historical overview, 1201–1202
hypnotizability, 1990
intellectual disability, 726–728
LSD-related, 1096, 1108–1110
middle adult life, 510
obsessive-compulsive disorder relationship, 1449–1450, 1451–1452
PCP-related, 1094, 1096–1097
postpartum psychosis, 2510
schizoaffective disorder, 1236–1237, 1265–1268, 1278
schizophreniform disorder, 1237–1238, 1270–1272, 1278
shared psychotic disorder, 1276–1278
somatoform disorder relationship, 1513, 1520, 1527, 1537, 1540
speech disorders, 596
stimulants in attention-deficit hyperactivity disorder, 2278
treatment-resistant depression relationship, 2376, 2378, 2379–2380
violence link, 2604–2605
Psychotomimetics, 1092, 1102
Psychotropic medications *See* Pharmacotherapy
PSYN *See* Presynaptic group secretory function
PTA *See* Post-traumatic amnesia
PTD *See* Preterm delivery
PTEN *See* Phosphatidylinositol phosphatase
PTSD *See* Post-traumatic stress disorder
Puberty
adolescence comparison, 150
biological development, 183, 184
endocrine factors, 99
physical changes, 161, 163–168
social transitions, 161, 163
Pubic hair development (pubarche), 164–166
Public health, 1832, 2493
Public school system
*See also* Education...
learning disabilities, 747–748, 749–750
Published research, critical appraisal, 2632–2633
PUD *See* Peptic ulcer disease
PUFA *See* Polyunsaturated fatty acids
Pulmonary disease
inhalant-related toxicity, 1139
lung cancer, 2502
psychological factors affecting medical condition, 1764
Punishment of children, 1995, 1996
Purging
early treatment for mental disorders, 209, 211
eating disorders, 1611, 1618–1622
Purkinje cells, 386
PVS *See* Partner violence screen
Pyromania, 1658, 1660–1661, 1674–1678
assessment, 1675
comorbidity patterns, 1676
diagnosis, 1674–1675, 1676
DSM-IV-TR criteria, 1675
etiology/pathophysiology, 1676–1677
impulsive behavior, 643, 644
treatment, 1677–1678
Pyrrolidones, 2339

qEEG *See* Quantitative electroencephalography
Qigong, 2329
*Qi* therapy, 1386
QOL *See* Quality of life
QTc interval of antipsychotic drugs, 1244, 2185, 2190, 2501
QTL model *See* Quantitative trait loci
Qualitative changes in consciousness, 584
Quality of care, 1843–1846, 2343–2344
Quality of life (QOL)
antipsychotic drugs, 2177
bipolar disorder, 1346–1347
intellectual disability, 733
schizophrenia, 2177
Quantitative electroencephalography (qEEG), 566
Quantitative trait loci (QTL), 267, 770
Quasi-experimental studies, 407–408
Quasi-therapeutic abuse of prescription drugs, 1188, 1189, 1193
Questioning, Socratic, 1926
Questionnaires
feeding disorder of infancy or early childhood, 834
initial child/adolescent evaluation, 549, 551
panic disorders, 1395
Quetiapine
bipolar depression, 2212, 2213
bipolar mania, 2207, 2210
chemical structure, 2168
dosing parameters, 2178
obsessive-compulsive disorder, 2247
pharmacology, 2169
rapid cycling bipolar disorder, 2219
schizophrenia, 1244
tic suppression, 858

Rachman's pathways to fear development, 1424–1426
Racial issues
*See also* Cultural issues; Ethnicity issues
antidepressants, 2134–2135
anxiety disorders, 1419–1421
effective listening, 5, 6, 7, 17
panic disorders, 1399
psychiatric interviews, 42
race/culture relationship, 55
racial discrimination/prejudice/racism, 55, 60, 69–70, 2113
schizophrenia epidemiology, 1209
Racing thoughts, 597, 600
RAD *See* Reactive attachment disorder
Radiation therapy, 2503
Radiological investigation, 906
Rado theories of homosexuality, 2539
Rage expression, 617–618
*See also* Aggression; Anger

Ramelteon, 1637, 2257–2258
Random assignment, internal validity importance, 2622
*Randomization to target or alternate treatment with pretest and posttest* design, 2620
Randomized controlled trials (RCTs), 407
  cannabis dependence, 1052
  combined treatments, 2431
  evidence-based medicine, 1355
  long-term psychotherapy, 294
  St. John's Wort, 2319, 2321
  stimulants, 2264, 2272
  treatment efficacy studies, 292–293
Range of affect, definition, 609
Rape
  *See also* Sexual abuse
  acute management, 2581–2584
  epidemiology, 2578
  long-term mental health sequelae, 2585–2591
  management considerations, 2581–2584, 2586–2591
  paraphilia relationship, 1600, 1601, 1602
Rapid cycling bipolar disorder (RCBD), 1340–1341, 2218–2219
Rapid detoxification opioids, 1176
Rapid eye movement *See* REM
Rapid neuroleptization, 2180
Rapport in clinician-patient relationship, 23
Rapprochement in separation-individuation process, 476
Rating scales
  attention deficit-disruptive behavior disorders, 807–809
  Post-traumatic stress disorder, 2589–2590
  psychological testing, 533, 534, 535, 536, 537
  stimulants use in attention-deficit hyperactivity disorder, 2283
Ratings interchangeability, kappa coefficient, 2625
Rationalization, defence mechanism, 1855
Raynaud's phenomena, 1640
RBD *See* REM behavior disorder
RBRVS (resource-based relative value scale), 1838, 1839
RCBD *See* Rapid cycling bipolar disorder
RCTs *See* Randomized controlled trials
RD *See* Rett's disorder
RDC *See* Research diagnostic criteria
RDI *See* Respiratory disturbance index
Reaction formation, defence mechanism, 1855
Reactive aggression, 2603, 2604
Reactive anxiety, 317–318
Reactive attachment disorder (RAD), 889, 890, 892–895
  DSM-IV-TR criteria, 892, 894
Reactive phase in group dynamics, 1906, 1907
Reading disorder, 748, 750, 757–758
Reading educational curriculum, 751
Reality-based elements in clinician-patient relationship, 20, 21, 23–24
Reality principle, 467
Reality testing problems, 509–510, 515
Real-life crossgender experience test, 1599
Reappraisal treatment, 1488
Reason/imagination division of mind, 210
Reassurance in somatization disorder, 1522
Rebound phenomenon, 2278
Reboxetine
  generalized anxiety disorder, 2231
  obsessive-compulsive disorder, 2246
  panic disorder, 2238
  post-traumatic stress disorder, 2241
  side effects, 2226
  social anxiety disorder, 2234
Recall memory (primary memory), 898
Recent memory (secondary memory), 898
Receptive language disorders *See* Mixed receptive-expressive language disorders
Receptor antagonists *See* Antagonist treatment; *individual receptor antagonists*
Receptor systems
  antidepressant action, 2124
  antidepressant side effects, 2135–2137, 2138–2139
  antipsychotic affinities, 2164
  molecular genetics of addiction, 373–374
  neuroadaptations to substance use, 368, 369–370, 371–373
  neuroreceptor characterization by molecular imaging, 577–666
  substance intoxication/reward, 366
Rechewing food, 839–842
Record keeping
  panic attacks, 1395, 1397
  pharmacy records, 2375, 2450
  thought recording, 1926–1927
Recovered memories, 84
Recovery
  consumer model, 2049–2050
  definitions, 2066
  depression treatment goals, 1300–1304
  illness management and recovery, 2073–2075
  mental health care orientation, 2093
  personal management, 2073–2075
  psychopharmacology, 2067
  rehabilitation comparison, 2065–2066
  serious mental illness, 2065–2067
Recreational abuse of prescription drugs, 1188, 1193
Recurrent brief depression, 1290
Recurrent hypersomnia, 1640
Recursive thinking, 170–171
'Reeducation/reassurance/suggestion' approach, 1521–1522
Reelin, 1221
Referential thinking, 600
Referrals
  children and adolescents, 546, 554
  complementary and alternative medicine, 2331–2332
  intellectual disability, 720
  neuropsychological questions, 559
Reflex changes with dementia, 900
Refractory treatment response *See* Treatment-refractory patients
Refugees
  disaster-related stress, 2470
  family-centered therapies, 1958
  post-traumatic stress disorder, 2567–2568, 2573
  psychosocial effects, 59–60
Refusing treatment *See* Treatment refusal
Regression
  autistic disorder, 786, 796
  childhood sexuality, 466
  defence mechanism, 1855
Regression to the mean, 2621
Regulator of G-protein signaling 4 (RGS4), 1215
Regulatory-sensory processing disorders (RSPD), 681, 682, 683, 684–685, 686, 687
Regurgitation (vomiting), 839–842, 1619
Rehabilitation, 2059–2080
  *See also* Cognitive; Vocational
  case management model, 2068
  definition, 2048
  mentally ill homeless people, 2530–2534
  recovery orientation, 2093
  schizophrenia, 1260, 2047–2056
  torture victims, 2572
Rehabilitation Services Administration, 2060
Reil, Johann, 213
Reinforcement
  solid food aversion, 837, 838
  substance use, 369, 1031
Relapse
  alcohol dependence treatment, 990
  anorexia nervosa, 1618
  anxiety disorders, 1435, 1939
  bipolar disorders, 1940
  cocaine use disorders, 1060–1061, 1067, 1068–1070, 1077
  cognitive and behavioral therapies, 1937, 1939, 1940
  depression, 1937
  methadone maintenance treatment, 2402
  opioid detoxification, 2401
  smoking, 1160–1163
  substance dependence pathophysiology, 354
Relapse prevention therapy (RPT), 1069–1070
Relational disorders
  assessment, 1801–1802
  definition, 1795
  diagnosis, 1800–1801

epidemiology, 1802–1803
Relational perspective, 478–479
Relational problems, 1794–1814
constructs/manifestations, 1795
definition, 1794–1795
depressive personality disorder, 1748
medical comorbidity, 1806–1807
not otherwise specified, 1795
obsessive-compulsive personality disorder, 1745
schizoid personality disorder, 1727
treatment, 1803–1806, 1808
Relational risk factors, definition, 1795
Relational therapies
*See also* Interpersonal psychotherapy; Psychodynamic therapy
brief psychotherapies, 1893–1895
Relationships *See* Clinician-patient relationship; Couples; Couples therapy; Interpersonal relationships; Intimate relationships; Marriage; Neurodevelopmental disorders of relating and communicating
Relationship-specific intimate partner violence, 2577
Relative risks, 406
Relatives
*See also* Families
clinician treating own relatives, 31
Relaxation techniques
behavioral therapies, 1932
generalized anxiety disorder, 1503–1504
hypnosis, 1993–1994, 2002
pain treatment, 1533, 1534
vaginismus, 1594
Reliability of instruments, 407, 563, 2624
Religious issues
adolescents, 162
dissociative disorders relationship, 653
effective listening, 5, 6, 17
ethnobotanical hallucinogens, 1101
ethnocultural identity, 57–58
grief/mourning, 2522
historical understanding of mental disorders, 205–206, 207, 208, 212, 215
illness explanations, 58
suicide risk, 2479
Relistening and reprocessing between sessions, 13
REM behavior disorder (RBD), 1650, 2332
Reminiscence, 197
Remission
definition, 2432–2433
depression, 1300–1304, 1937–1938
Remote memory (tertiary memory), 587, 898, 926
REM sleep
behavior disorder, 1650, 2332
latency, 1627, 1629, 1630, 1634–1635
mood disorders, 1634–1635
narcolepsy, 1638–1639
normal organization, 1627, 1629–1630
Renal disease
antidepressant effects, 2145
cocaine effects, 1066
depression comorbidity, 1287
inhalant-related toxicity, 1138–1139
psychological factors affecting medical condition, 1765
Renal function blood tests, 535
Reparative therapy, 2544
Repetition
autistic disorder, 780
compulsion, 470
psychoanalytic psychotherapy, 1860
Representation in cognitive psychology, 440–443
Repression, 25, 1559, 1560
Reprocessing and relistening between sessions, 13
Reproductive transitions, 2507–2513
Resale of prescription opioids, 1174
Research
clinician-patient relationship, 26–28
complementary medicine, 2328–2329
consumer self-help, 2091–2092
group psychotherapy, 1917–1918
interpersonal psychotherapy, 1879–1883
methodology, 2619–2633
psychoanalytic psychotherapy, 1866–1869
Research Committee of the International Psychoanalytic Association, 295
Research diagnostic criteria (RDC), 406, 1203
Reserpine, 344, 2130
Residential treatment for alcohol use disorders, 990
Residualized gain scores, 2626
Residual-type schizophrenia, DSM-IV-TR criteria, 1206
Resilience
adolescents, 177–178
adult development, 185–186
animal stress models, 324–325
children and family, 1956–1957, 1958
post-disaster trait, 2467
post-traumatic stress, 2568
psychopathology across the life span, 490
psychopathology risk factors, 106
Resistance
obsessive-compulsive disorder, 1447–1448, 1463
psychoanalytic psychotherapy, 1853, 1854–1855
relational perspective, 478
Resource-based relative value scale (RBRVS), 1838, 1839
Respect, 2050
Respiratory conditions, 1139, 1776, 2004–2005
Respiratory disturbance index (RDI), 1641
Responder categories in anxiety treatments, 1434
Response-oriented theories, 610
Response time trials, 2129
'Response to Intervention' model, 749–750
Responsibility, 2050
Restless legs syndrome (RLS), 1646–1647
Restraint and seclusion (R/S), 2609, 2599, 2491–2495
Restrictive/repetitive behaviors, 780
Retentive encopresis, 875, 876, 877, 878, 879
Retrograde amnesia, 585
Retrolental fibroplasis, 705
Retrospective cohort studies, 408
Rett's disorder (RD), 702, 796–799
animal models, 275, 276
autism relationship, 381, 384, 787
childhood disintegrative disorder relationship, 796
differential diagnosis, 787, 796
DSM-IV-TR criteria, 797
'Reverse funnel effect', 1519
Reverse symptom identification technique, 1999
Reversible inhibitors of monoamine oxidase (RIMA), 1428–1429
Reward mechanisms
animal models of substance use, 364–365
kleptomania, 1671
substance use pathophysiology, 364–367, 368–369
ventral striatum, 248–249
Reynolds, John Russell, 1230
Rey-Osterrieth Complex, 565
RGS4 *See* Regulator of G-protein signaling, 4
Rhabdomyolysis, 1094, 1096
Rheumatological disorders, 1650, 1764
*Rhodiola rosea*, 2319, 2324, 2337–2338
Rhythms *See* Biological rhythms; Circadian rhythms; Social rhythm theory
Right hemispheric dominance theory, 2009
Rights *See* Legal issues
Right unilateral electroconvulsive therapy (RUL ECT), 2359, 2360
Rigidity, 793
RIMA *See* Reversible inhibitors of monoamine oxidase
Rimonabant, 1053, 2412
Ring chromosomes, 697–698
Risk assessment
adult abuse, 2577–2578
attributable risks, 406
rating scales, 533, 537
suicide, 86, 533, 537, 540–541
treatment planning, 540–541
violent behavior, 2602–2603

Risk-benefit balance, 1774, 2508
Risk factors
  adult abuse, 2577–2578, 2584
  adult development, 185–186, 188
  children, 146–147, 157, 1956–1957, 1958
  depression recurrence, 1303
  disaster-related psychiatric problems, 2469–2470
  elder abuse, 2578
  family resilience, 1956–1957, 1958
  FGA medications, 1251–1253
  genetic epidemiology, 262–263
  identification, 407, 427
  infant development, 112, 127–131
  intellectual disability, 715–716
  longitudinal developmental studies, 104–107
  National Comorbidity Survey, 417
  neuroleptic-induced Parkinsonism, 1777
  neuroleptic-induced tardive dyskinesia, 1782–1783
  neuroleptic malignant syndrome, 1786
  postpartum women, 2510–2511
  preschool development, 146–147
  PTSD in abuse victims, 2587
  rape, 2578
  schizophrenia, 302–303
  school-age children, 157
  suicide, 2479–2482, 2519
Risperidone
  bipolar mania, 2206–2207, 2210
  chemical structure, 2168
  communication disorders, 776
  dosing parameters, 2178
  generalized anxiety disorder, 2232–2233
  maintenance treatment, 1249
  obsessive-compulsive disorder, 2247
  pharmacology, 2169
  post-traumatic stress disorder, 2243
  pregnancy, 2422
  schizoaffective disorder treatment, 1267–1268
  schizophrenia, 1243, 1245
  tic suppression, 858
  treatment resistance, 1257–1258
Ritalin *See* Methylphenidate
Rivastigmine, 2300, 2302–2304
RLS *See* Restless legs syndrome
Rohypnol (flunitrazepam), 1189, 2578
Role-playing, 1749, 1926
Roles
  clinician-patient relationship, 21
  group psychotherapy, 1907, 1908
Romans, 207
Romanticism, 213
Romantic love, 207, 209, 1966
ROP disorder, 705
Rotation methods in factor analysis, 2631
Route of administration of antipsychotic drugs, 2177–2179
RPT *See* Relapse prevention therapy
R/S *See* Restraint and seclusion
RSPD *See* Regulatory-sensory processing disorders
Rubella, 703
Rubinstein-Taybi syndrome, 698
RUL ECT *See* Right unilateral electroconvulsive therapy
Rule of thirds, psychotherapy sessions, 1568
Rumination disorder, 839–842
  DSM-IV-TR criteria, 839
Ruminations, thought disorders, 598
Rush, Benjamin, 217

SA *See* Sedative/anxiolytics
SAD *See* Seasonal affective disorder; Separation anxiety disorder; Sexual aversion disorder; Social anxiety disorder
S-adenosyl-L-methionine (SAMe)
  cognitive enhancement, 2336
  contraindications, 2324
  mood disorders, 2319, 2322–2324
Sadism, 1600, 1602–1603
Sadness
  *See also* Grief
  infant development, 119
Sadomasochism, 1603, 1604
SADS *See* Schedule for Affective Disorders and Schizophrenia; Schedule for affective disorders and schizophrenia
Safe environment in psychoanalytic psychotherapy, 1860
Safety
  anxiety models, 324
  Condensed Hypnotic Approach, 1997–1998
  disaster situations, 2472–2473
  hypnosis, 1986
  melatonin, 2333
  pharmacologic therapy, 2107–2109
  stimulants, 2286–2287
Safety conditioning in animal models, 324
Safety nets in public mental health services, 1834
Safety plans for suicidal patients, 2483
Saffron (*Crocus sativa*), 2324
Sage (*Salvia lavandulaefolia*/*Salvia officianalis*), 2339
Sain-Denys, Hervé, 216
St. John's Wort (SJW)(*Hypericum perforatum*), 1311, 2319, 2321–2322
*Salvia lavandulaefolia*/*Salvia officianalis* (Spanish/Dalmation sage), 2339
Salvinorin-A, 1101
SAMe *See* S-adenosyl-L-methionine
Same-sex marriage, 1979–1980, 2544
SAMHSA *See* Substance Abuse and Mental Health Services Administration
Sampling procedures, 403, 427
SBS *See* Stereotyped Behavior Scale
Scapegoating in group psychotherapy, 1906, 1907, 1913
Schafer, R., 480
Schedule for Affective Disorders and Schizophrenia (SADS), 406, 1203
Schemas, cognitive model, 1921, 1922–1923, 1928–1930
Schizoaffective disorder, 1236–1237, 1265–1268
  antipsychotic drugs, 2170–2171
  bipolar disorder relationship, 1336
  course/prognosis, 1266–1267
  diagnosis, 1265–1266, 1278
  DSM-IV-TR criteria, 1237, 1265, 1278
  early adulthood, 509–510
  history, 222
  ICD-10, 1278
  treatment, 1267–1268
Schizoid personality disorder (SZPD), 794, 1726–1728
  DSM-IV-TR criteria, 1726
Schizophrenia, 1201–1282
  *See also* Antipsychotic drugs
  acute phase treatment, 2177–2181
  adult developmental effects, 184
  affective symptoms, 2176–2177
  alcohol use disorders comorbidity, 987
  animal models, 279–280
  autistic disorder differential diagnosis, 787
  bipolar disorder distinction, 1335–1336
  body dysmorphic disorder relationship, 1540
  brain imaging, 303–304, 311–312
  caregiver burden reduction, 1958
  childhood onset, 158, 304, 2173–2174
  clinical manifestations, 1230–1233
  cocaine use disorders comorbidity, 1080
  cognitive aspects, 303, 306, 2176
  cognitive-behavioral therapy, 1940
  comorbidity, 1211
  cortical/subcortical circuit abnormalities, 282
  couples therapy, 1972
  course of illness, 1239–1240
  cultural factors, 650
  diabetes patients, 2504
  diagnosis, 1203–1207, 1278
  differential diagnosis, 1233–1239
  *Disc1* gene, 276
  DSM classification systems, 674–675
  DSM-IV-TR criteria, 1204–1206, 1278
  early adulthood, 509–510
  early onset, 158, 303–304, 2173–2174
  eating problems, 1614
  elderly adults, 515
  electroconvulsive therapy, 2360, 2361
  electrophysiological abnormalities, 311–312
  endophenotypes, 305–306
  epidemiology, 1207–1211
  etiology, 1211–1217
  family influences, 1955–1957
  first-episode treatment, 2170–2171
  gene identification, 265, 267

genetic epidemiology, 258, 260, 270
genetics expressed through development, 304–306
group psychotherapy, 1916
hallucinations, 601
history of understanding, 210, 217, 220–226
hypochondriasis distinction, 1537
ICD-10/DSM-IV-TR diagnosis comparison, 1278
intellectual disability, 726–728
intermittent maintenance medication, 2171
maintenance treatment, 2181–2182
Measurement and Treatment Research to Improve Cognition in Schizophrenia, 561, 1259
medication compliance, 2456
modern concept of, 1202–1203
negative symptoms, 2175–2176
neural circuits, 310–311
neurobiology, 301–316
neurochemical abnormalities, 306–309
neurodevelopment model, 302
neuropsychological analyses, 564, 565
nicotine dependence comorbidity, 362
obsessive-compulsive disorder comorbidity, 1449–1450
pathophysiology, 1217–1230
perception disturbances, 601
personality disorder diagnosis, 1724
pharmacotherapy history, 1831
phencyclidine intoxication, 1092, 1093–1094, 1096, 1097
phenomenology, 1230–1233
plasma membrane, 309–310
positive symptoms, 2174–2175
post-traumatic stress disorder differential diagnosis, 2567
prefrontal cortex dysfunction, 251
in pregnancy, 2421
premenstrual dysphoric disorder differential diagnosis, 1380
premorbid risk, 302–303
pre/perinatal risk, 302
prodromal stages treatment, 2171
psychopathological domains, 302
psychosocial interventions, 2047–2056
quality of life, 2177
rehabilitation, 2047–2056, 2066–2067, 2071, 2074, 2079
relational problems, 1795, 1796, 1798, 1799, 1805
schizotypal personality disorder relationship, 1728, 1729
self-experience disorders, 603
skeletal/muscle/motor abnormalities, 303
social psychology, 303, 446, 454
somatization disorder relationship, 1520
speech disorders, 596–597
structural brain changes, 311
subtypes, 1205–1206
suicide, 2177, 2480, 2485
toxin exposure causation, 285
treatment, 1240–1265, 2177–2183
treatment resistance, 2182–2183
ventral striatum dysregulation, 249
violence link, 2604–2605
Schizophrenia spectrum disorder, 2059–2060, 2066–2067, 2071, 2074, 2079
Schizophreniform disorder, 509, 1237–1238, 1270–1272
DSM-IV-TR criteria, 1238, 1278
Schizotypal personality disorder (STPD), 1726–1730
DSM-IV-TR criteria, 1728
Schneider, Kurt, 1202–1203
School-age children, 150–159, 546–554
School refusal, 881, 882–883
Schools, 175, 552–554
*See also* Education
SCID *See* Structured Clinical Interview for DSM-IV
Science history, 206, 208
SCM *See* Standard case management
SCN *See* Suprachiasmatic nucleus
Scotland, history, 212, 216–217
Screening
alcohol use disorders, 979, 982
bipolar disorder, 1340
correctional psychiatry, 2596
violent behavior risks, 2602–2603
Screen technique for dissociative amnesia, 1562–1563
SE *See* Supported employment; Supportive-expressive
Seasonal affective disorder (SAD), 728–729, 1289, 1316, 2378
Season of onset of schizophrenia, 1210
Seclusion and restraint, 2609, 2599, 2491–2495
Secondary amines, 2126
Secondary causes
anxiety disorder, 940–942
catatonic disorder, 942–944
Klüver-Bucy syndrome, 947, 948–950
mania, 938–940
mood disorder, 935–940
obsessive-compulsive symptoms, 941–942
personality change, 944–946
pseudobulbar palsy, 947–948
psychosis, 932–935
Secondary depression in medically ill patients, 2144
Secondary elaboration of dreams, 465
Secondary encopresis, 876, 877
Secondary memory, 898
Secondary narcissism, 469
Second generation antidepressants
drug-drug interactions, 2142–2143
efficacy determination, 2129
mechanisms of action, 2127
pharmacokinetics, 2133
starting doses, 2146
Second generation antipsychotics (SGAs), 1241–1259
*See also* Atypical antipsychotics
CPM use with, 1259
delusional disorder, 1274
dopamine, 1225
dose, 2178, 2180–2181
history, 2161–2162
maintenance treatment, 2181
memory effects, 1233
names and manufacturers, 2162
norepinephrine, 1228
pharmacology, 2166–2170
schizoaffective disorder, 1267
selection, 2179
serotonin, 1226–1227
side effects, 1253–1255
treatment resistance, 1256, 1258, 2182
Second-generation psychiatric epidemiology, 410–411
Second-messenger systems, 1350–1351, 2124, 2126
Secrets in couples therapy, 1967–1968
Sedation effects
antidepressants, 2259
antipsychotics, 2185, 2192, 2260
Sedative/anxiolytics (SA), 1258
Sedative/hypnotic/anxiolytic intoxication, DSM-IV-TR, 1191
Sedative-hypnotics
*See also* Narcoanalysis
abuse, 1186–1198
diagnosis, 1191, 1192, 1194
DSM-IV-TR definitions, 1187
potential of drugs, 1188
psychosocial treatment, 1196–1197
acute intoxication, 1191
benzodiazepine receptor agonists hypnotics, 2256–2257
detoxification, 1194–1197
high-dose withdrawal, 1192, 1195–1196
iatrogenic dependence, 1191, 1193
ICD-10/DSM-IV-TR comparison, 1198
insomnia in psychiatric patients, 2261–2262
laboratory tests, 1194
low-dose withdrawal, 1192–1193, 1195, 1196
physical effects, 1191, 1194
withdrawal, 1191, 1192–1193, 1195–1196
Sedatives
history, 224
insomnia, 1636, 1637, 1653–1654, 2258–2259, 2260
pain treatment, 1533
psychiatric evaluation, 540
substance-induced sleep disorder, 1653–1654
Sedentary behavior, 2033
Seductive patients, 50
Segregation in correctional psychiatry, 92
Seguin, Edouard, 690, 710
Seizures
aggression/violence link, 2607–2608
antidepressant side effects, 2140
antipsychotic drugs, 2185, 2192
autism, 381
brain imaging, 579–580
cocaine use, 1066

Seizures *(Continued)*
conversion disorder, 1525, 1526
dissociative identity disorder comorbidity, 1567, 1569
hypnosis, 1998
intellectual disability, 693–694
Selection threats to validity, 409, 2621, 2622
Selective eating, 833
Selective melatonin receptor agonists, 2257–2258
Selective mutism, 495, 883–885
DSM-IV-TR, 883
Selective norepinephrine reuptake inhibitors, 819–820, 1309, 2126, 2127
Selective serotonin-noradrenaline reuptake inhibitors *See* Serotonin-norepinephrine reuptake inhibitors
Selective serotonin reuptake inhibitors (SSRIs)
abuse victims, 2590
aggression treatment, 2609
AIDS-related dementia, 913–914
alcohol use disorders, 993, 995
attention deficit-disruptive behavior disorders, 821
autistic disorder, 789
body dysmorphic disorder, 1541
breastfeeding, 2424
cardiovascular patients, 2144
cocaine use disorder treatment, 1073
comparative trials, 2129
congenital malformation association, 2419–2420, 2508
drug-drug interactions, 2142–2143
efficacy, 1307–1308
generalized anxiety disorder, 2228, 2230–2231
history, 1830–1831, 2127
hypersomnia, 1641
hypochondriasis, 1537, 1538
intellectual disability treatment, 737
kleptomania treatment, 1673
mechanisms of action, 2124
narcolepsy, 1639
obsessive-compulsive disorder, 862, 1455, 1458–1463, 1537, 2244–2246
panic disorders, 1404–1405, 2236–2237
paraphilia, 1605
pathological gambling, 1684, 1686
perinatal complications, 2420–2421, 2508
persistent pulmonary hypertension of the newborn, 2508
pharmacokinetics, 2133
post-traumatic stress disorder, 2240–2241
pregnancy, 2419–2421, 2426
premature ejaculation, 1592
premenstrual dysphoric disorder, 1382, 1383–1385, 1387
PTSD treatment, 1480–1481
safety/tolerability, 1308
St. John's Wort comparison, 2321
selective mutism, 884
separation anxiety disorder, 882
sexual dysfunction effects, 2138, 2140–2141
side effects, 1304–1305, 2138, 2140–2141, 2226
social anxiety disorder, 2233–2234
social phobia treatment, 1422, 1427, 1428, 1429
starting doses, 2146
stereotyped movement disorder, 891–892
suicide link, 2519
suicide protection, 2484
switching strategies, 2380
trichotillomania, 1692
use of term, 2124
Selegiline, 2234, 2306
The Self, 458–461
character factors, 636, 639
cognitive approaches, 459–461
multidimensionality, 459
narcissistic personality disorder, 1738, 1740
schemas, 460–461
self-efficacy, 2472, 2473
self-esteem/self-worth, 1738, 1740, 1922
self-evaluation maintenance theory, 459
self-experience disorders, 602–604
self-image in adolescence, 502–503
self-objects, 477–478
self-verification theory, 459–460
sense of self in infant development, 110–111, 125, 476
social psychology, 458–461
true selves, 474
Self-awareness of psychiatrists, 11–12, 14–15, 18
Self-directed treatment, 1264, 2050
Self-evaluation maintenance theory, 459
Self-harming
*See also* Suicide
adolescents, 1704
children, 498
dissociative states, 1990
impulsive behavior, 643, 644
intellectual disability, 693, 725–726, 738
stereotyped movement disorder, 889–892
suicidal intent relationship, 2478
violence categorization, 2603, 2604
Self-help
paraphilia, 1605
smoking cessation, 1161–1162
Self-help groups
adjustment disorders, 1711
Alcoholics Anonymous, 224, 990, 992, 996–997, 1904, 1916
coalition of self-help groups, 2085
cocaine use disorders, 1070
collaborative partnerships with professionals, 2084
conceptual distinctions, 2084
development, 1904, 1916–1917
diagnosis-specific, 2085
Gamblers Anonymous, 1680, 1685–1686
Nicotine Anonymous, 1162
pharmacotherapy attitudes, 1197
professionals relationship, 2092–2093
psychosocial rehabilitation centre movement/clubhouse model, 2062–2063
research findings, 2085, 2091
trichotillomania, 1693
Self-hypnosis
Condensed Hypnotic Approach, 1997
dissociative disorders, 1564–1565
hypnosis definition, 1986, 1993
Self-injurious behavior (SIB) *See* Self-harming
Self-medication/abuse relationship, 358, 362
Self-monitoring in generalized anxiety disorder, 1502–1503
Self-mothering technique, 1992
Self-mutilation *See* Self-harming
Self-protection by therapists, 78
Self-psychology, 477–478, 1299–1300
Self-referential thinking, 598–599, 600
Self-regulation, 358, 2031
Self-reporting
behavioral medicine, 2040
medication compliance, 2450
personality disorders, 1720
symptoms, 43–44
Self-report measures
generalized anxiety disorder, 1495–1496
specific/social phobias, 1413–1414
Self-respect, therapist role model, 78
Self-selection bias, 409
Self-soothing behavior, 841, 842
Self-verification theory, 459–460
Self-worth/self-esteem, 1738, 1740, 1922
Semantic memory *See* Implicit (procedural) memory
Semistructured interviews, 1413, 1719–1720
Senile dementia, 393, 394
*See also* Alzheimer's disease; Dementia
Sensate focus techniques, 1588, 1594, 1977–1978
Sensitivity of instruments, 406
Sensorimotor gating, 279, 1223–1224
Sensorineural system (SNS), 2327, 2329–2330
Sensory deficits
*See also* Auditory perception
intellectual disability, 694
learning and motor skills disorder comparison, 748–749
presenting problems, 751
Sensory functions
age effects, 199–200
conversion disorder, 1525, 1526
delirium, 921
memory formation, 587

regulatory-sensory processing disorders, 681, 682, 683, 684–685, 686, 687
Sensory gating, 1223–1224
Sensory-motor development, 152, 153
Sensory stimulation in autistic disorder, 782
Separateness from family, 1949, 1958–1959
Separation anxiety disorder (SAD), 879–883
DSM-IV-TR, 880
Separation of couples, 614, 1965, 1973
Separation-individuation process in infants, 110–111, 476
Sequenced Treatment Alternatives to Relieve Depression (STAR*D), 1937, 2373–2374, 2381–2384, 2438
Sequencing of change in brief psychotherapies, 1900
Sequential treatments, 1405, 2440
Serial relationships in couples therapy, 1964
Serious mental illness (SMI)
mental health service history, 1825–1826, 1829–1830
NCS-R definition, 419
prevalence, 2060
psychiatric disability, 2059–2060
psychiatric rehabilitation, 2059–2080
approaches, 2062–2065
Assertive Community Treatment, 2062, 2067–2070
case management models, 2067–2068, 2070
family psychoeducation, 2070–2073
illness management recovery, 2073–2075
integrated dual disorder treatment, 2075–2077
supported employment, 2065, 2077–2080
psychotherapeutic evidence-based practices, 2059, 2062, 2065, 2067–2080
public mental health service provision, 1834, 1843
recovery, 2065–2067
substance use disorder co-occurrence, 2075–2077
Serological evaluations, 533–536
Serotonergic system
*See also* Selective serotonin reuptake inhibitors; Serotonin; Serotonin transporter genes
alcohol abuse medication, 995–996
alcohol effects, 974
antidepressant action, 2123–2124, 2126
antidepressant side effects, 2137–2138
antipsychotic drug effects, 1226–1227, 2163, 2164, 2165
attention-deficit hyperactivity disorder, 814
cocaine use disorder, 1073
compulsive behavior, 645
Conduct Disorder, 816
conflict behavior in animal models, 282
impulsive behavior, 644, 1660
MDMA use, 1116, 1117
obsessive-compulsive disorder, 1455–1456, 1458–1463
premenstrual dysphoric disorder, 1382
Serotonin (5-HT)
alcohol use disorders, 974, 995–996
antidepressant modulation, 1310
autism, 384
bipolar disorder, 1350
CNS reduction, aggression link, 2608
cocaine use, 1061, 1062
CSF 5-HIAA levels in impulsive control, 644, 1666, 1677, 1690
depression, 1293–1294
kleptomania, 1671
mood disorder neuropathology, 343, 344, 345
mood effects, 2123
schizophrenia, 301, 307–308, 1226–1227
stimulants, 2267
syndrome, 1787, 2142
tic disorders, 855
Serotonin 5-$HT_{2A}$ receptors, hallucinogen intoxication, 1105, 1106
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
adverse effects, 1308–1309, 2226
breastfeeding, 2424–2425
efficacy, 1308
generalized anxiety disorder, 2231
mechanism of action, 2127
obsessive-compulsive disorder, 2246
panic disorder, 2237–2238
perinatal toxicity, 2508
post-traumatic stress disorder, 1480, 2241
social anxiety disorder, 2234
Serotonin reuptake inhibitors (SRIs) *See* Selective serotonin reuptake inhibitors
Serotonin reuptake transporter (SERT) gene, 247
Serotonin syndrome, 1787, 2142
Serotonin transporter (5-HTT) genes
anxiety disorders, 321, 329
bipolar disorder susceptibility, 342
life stress interaction, 176
MDMA-related disorders, 1117
mood disorder neuropathology, 176, 341, 342, 343, 345
Serotonin transporter linked promoter region (5-HTTLPR) polymorphism, 342, 343
SERPs *See* Somatosensory event-related potentials
SERT *See* Serotonin reuptake transporter
Sertindole, 2168, 2169
Sertraline
availability, 2128
breastfeeding, 2424
generalized anxiety disorder, 2230–2231
history, 2127
obsessive-compulsive disorder, 1461, 2245–2246
panic disorder, 2236
post-traumatic stress disorder, 2240–2241
premenstrual dysphoric disorder, 1383, 1384
social anxiety disorder, 2233–2234
Settings for clinical evaluation/treatment, 42, 525, 526
Seven-factor model of personality styles, 636
Severely mentally disabled (SMD), 1829–1830
Severe mental illness *See* Serious mental illness
Sex
*See also* Gender
definition, 2538
meaning to couples, 1975–1976
Sex hormones
Alzheimer's disease, 2307
arousal, 1586
depressive disorders, 1295
estrogens, 1586, 1599, 2307
gender identity disorders, 1599
premenstrual symptoms, 1382
progesterones, 1385–1386, 1605
psychosomatic medicine, 2505
puberty, 164, 166, 167
sexual arousal disorders, 1586
sexual drive, 1582
testosterone, 1582, 2505, 2606–2607
tic disorders, 856
violence link, 2606–2607
Sex offenders, 1601, 1602–1603, 1605–1606, 2597–2598
Sex therapy, 1977
Sexual abuse, 2576–2592
acute presentations, 2578–2584
adults, 2577–2579, 2584–2585
comorbid with opioid dependence, 1181
elders, 2578, 2579
epidemiology, 2577–2578
hypnotherapy, 2007
long-term mental health sequelae, 2584–2591
management considerations, 2578–2584, 2586–2591
sexual pain disorders, 1592, 1593
SKY breathing, 2331
suicide, 2482
Sexual addiction, 1601, 1603, 1606
*See also* Paraphilias
Sexual arousal, 1586–1589
Sexual assault
*See also* Rape
acute management, 2581–2584
epidemiology, 2578
long-term mental health sequelae, 2585–2586
Sexual aversion disorder (SAD), 1582–1584
DSM-IV-TR, 1583

Sexual avoidance, 1588, 1593–1595
Sexual behavior, definition, 2538
Sexual compulsivity, 645, 1601, 1605, 1606, 1978
*See also* Paraphilias
Sexual desire disorders, 1581–1586, 1976
Sexual development, 99–100, 163–164, 174, 465–467
*See also* Puberty
Sexual disorder not otherwise specified, 1606
Sexual disorders, 1578–1607
affecting fertility, 1767
alcohol-induced sexual disorder, 979
antidepressant side effects, 2138, 2140–2141
antipsychotic side effects, 2188
arousal disorders, 1581, 1586–1589
complementary treatments, 2320
couples therapy, 1974–1979
cultural factors, 653–654
desire disorders, 1581, 1583–1586
DSM classification systems, 675
DSM-IV-TR criteria, 1580, 1583–1587, 1590, 1591, 1593, 1594, 1596, 1602–1605
dysfunction evaluation, 1976–1977
dysfunctions, 1580–1594, 1601, 1974–1979, 2138, 2140–2141
epidemiology, 1580–1581
gender identity disorders, 1594–1600
ICD-10/DSM-IV-TR comparison, 1606–1607
orgasmic disorders, 1581, 1589–1592
pain disorders, 1581, 1592–1594
paraphilias, 1600–1606
psychotherapy in correctional settings, 2597–2598
Sexual drive
biological aspects, 1581–1582
kleptomania, 1672
MDMA use, 1118
paraphilia, 1601
psychoanalytic theory, 467, 469–470, 473–474
Sexual equilibrium of a couple, 1581, 1591–1592
Sexual function components, 1579–1580
Sexual history in psychiatric databases, 40
Sexual identity, 1579–1580, 1600, 1601
*See also* Gender identity disorders; Homosexuality; Sexual orientation
Sexuality
*See also* Homosexuality
bisexuality, 1979, 2541
clinical attitudes, 1578–1579, 1606
components, 1579–1580
early understanding of mental disorders, 206, 207
elderly adults, 201–202
falling in love, 1966
history of ideas, 220, 223, 226
psychoanalytic theory, 465–468
through the life cycle, 1580
Sexually transmitted infections (STIs), 174, 2583
*See also* Syphilis
Sexually violent predators, 2597–2598
Sexual masochism
DSM-IV-TR, 1605
paraphilia, 1604
Sexual obsessions, 1444, 1445, 1447
*See also* Paraphilias
Sexual orientation, 2538–2547
*See also* Homosexuality
changing, 2544
definition, 2538
distress, 1603–1604, 1606
gender identity relationship, 1594, 1595, 1598
psychotherapy, 2542–2543
therapist's, 2543
Sexual pain disorders, 1592–1594
couples therapy, 1976
DSM-IV-TR, 1593, 1594
Sexual perversion, 465, 643, 644, 645
*See also* Paraphilias
Sexual relationships
*See also* Couples; Intimate relationships; Marriage
therapist-patient, 71–73, 77–78
Sexual sadism, 1600, 1602–1603
DSM-IV-TR, 1603
Sexual violence, 2607
SFBT *See* Solution-focused brief psychotherapies
SGA *See* Small for gestational age
SGAs *See* Second generation antipsychotics
Shame development, 145
Shared decision making, 2458–2459
Shared psychotic disorder, 1276–1278
ICD-10/DSM-IV-TR diagnosis comparison, 1278
Shedler-Westen Assessment Procedure-200 (SWAP-200), 1720
Sheldon, W.H, 223
Shelter-based services for mentally ill homeless people, 2526, 2528, 2531, 2532
Shift work sleep disorder, 1645
Shock therapy *See* Brain stimulation; Electroconvulsive therapy
Short-acting stimulants, 2265, 2268
Short-term anxiety-provoking psychotherapy, 1890
Short-term dynamic psychotherapy (STDP), 1867
Short term (immediate) memory, 197, 198, 585, 587
Short-term opioid detoxification, 1176
Short-term psychoanalytic psychotherapy (STPP), 1867, 1868, 1869
Short-term therapies, *See also* Brief psychotherapies
Shprinzen syndrome *See* Velocardiofacial syndrome
Shyness
anxiety disorders, 328–329, 357
avoidant personality disorder, 1740, 1741
selective mutism, 884
social phobia, 1409, 1410, 1413, 1418, 1421, 1426
Siblings, 143, 1795
SIB (self-injurious behavior) *See* Self-harming
Sick role
depression, 1876
factitious disorders, 1548–1549, 1552
Side effects *See* Adverse drug reactions; Adverse effects
Signal anxiety, 471
Signal transduction mechanisms, 371–373, 2120
*See also* Neurotransmitters
Sildenafil (PDE-5i), 1579, 1582, 1587, 1589, 1603–1604
Similes, 4–5, 7
Simon, Theodore, 690
Simple phobias, 1938
Simple tic phenomenology, 847
Simultaneous treatments, *See also* Combined treatments
Simultaneous versus sequential treatments, 2440
Single nucleotide polymorphisms (SNPs), 341
Single photon emission computed tomography (SPECT), 575–577, 580
attention-deficit hyperactivity disorder, 2267
hallucinogen-related disorders, 1105
MDMA-related disorders, 1116
Sinsemilla, 1041, 1043
Situational exposure in generalized anxiety disorder, 1503
Situational factors in psychiatric interviews, 41–42
SJW *See* St. John's Wort
Skills acquisition *See* Cognitive skills training; Social skills training; Vocational training
Skin picking, 1689
SKY *See* Sudarshan Kriya Yoga
Sleep, 1626–1656
*See also* Circadian rhythms; REM sleep
age effects, 184, 1629
autistic disorder, 782
delirium effects, 920
depressive disorder effects, 1295–1296
hygiene, 1636, 1651, 2386
hypnosis comparison, 1986
laboratory studies, 1631–1633
neurophysiology/neurobiology, 1629–1630
non-rapid eye movement sleep, 1627, 1629–1630
phenomenology, 1627–1630
physiological regulation, 584, 1627–1629, 2254–2255
sleep-wake cycle regulation, 2254–2255
Sleep apnea, 1630, 1631, 1641–1642
Sleep deprivation, 1036, 1316, 1387
Sleep disorders, 1626, 1630–1656
adolescents, 503

alcohol-induced sleep disorder, 978–979
breathing related sleep disturbance, 1641–1643
caffeine-induced sleep disorder, 1021, 1035–1037
childhood problems, 498
circadian rhythm sleep disorders, 1643–1646
complementary medicine, 2319
DSM classification systems, 676
due to depressive disorders, 1295–1296
early adulthood, 508
elderly adults, 515
evaluation, 1630–1633
hypersomnia, 1638–1641
ICD-10, 1656
insomnia, 1633–1638, 2254–2262
middle adult life, 510
parasomnias, 1647–1650
periodic limb movements in sleep, 1631, 1632, 1646–1647
pharmacologic treatment, 1636–1638, 2254–2262
post-traumatic stress disorder, 1478–1479
societies/associations, 1653
Sleep disorders due to general medical conditions, 1650–1651
Sleep hygiene, 1636, 1651, 2386
Sleepiness
*See also* Hypersomnia; Narcolepsy
assessment, 1633
Sleeping pills *See* Nonbenzodiazepine hypnotics; Sedative-hypnotics; Sedatives
Sleep onset REM period (SOREMP), 1639, 1640
Sleep paralysis, 1638, 1639
Sleep-related eating disorders, 1650
Sleep restriction therapy, 1636
Sleep terror disorder, 1648–1649
DSM-IV-TR criteria, 1649
Sleep-wake schedule disorders *See* Circadian rhythm sleep disorders
Sleepwalking disorder, 1649, 1650
DSM-IV-TR criteria, 1649
Slow wave sleep (SWS), 1627, 1629
SLPs *See* Speech and language pathologists
Small for gestational age (SGA) babies, 2418, 2419
SMC *See* Squared multiple correlation
SMD *See* Severely mentally disabled
Smell *See* Olfactory...
SMHAs *See* State mental health agencies
SMI *See* Serious mental illness
Smoking
*See also* Nicotine...
behavioral medicine, 2033
caffeine use relationship, 1032
cessation therapies, 1151, 1158–1159, 1160–1163
drug metabolizing enzyme expression, 2117
Heaviness of Smoking Index, 1150
hypnotherapy, 2005
MDMA comorbidity, 1114
tobacco-caused diseases, 1151–1152
Smoking cannabis, 1042
SNAP *See* Swanson, Nolan, and Pelham
Snoring, 1642
Snow, John, 404
SNPs *See* Single nucleotide polymorphisms
SNRIs *See* Serotonin-norepinephrine reuptake inhibitors
SNS *See* Sensorineural system
Social Adjustment Scale, 640, 641
Social anxiety disorder (SAD)
*See also* Social phobia
anticonvulsants, 2235
anxiolytic drugs, 2233–2235
benzodiazepines, 2235
beta-blocker medication, 2235
general features, 320
monoamine oxidase inhibitors, 2234
pathophysiology, 326
psychotropic medications efficacy, 2224
selective serotonin reuptake inhibitors, 2233–2234
serotonin-norepinephrine reuptake inhibitors, 2234
tricyclic antidepressants, 2234
Social class *See* Socioeconomic factors
*Social Class and Mental Illness* study, 411
Social cognition
*See also* Social psychology
brain regions, 444, 445
cognitive psychology, 443–448
empathy, 444–445, 446
health behavior models, 2448–2449
motivation, 446–447
perspective taking, 445
psychiatric disorders, 446
schizophrenia, 1233
therapeutic interventions, cognitive psychology, 447–448
uniqueness, 444
Social constructivism, 479–480
Social control strategies for ASD, 1488
Social development
adolescents, 172–175
infant development, 113, 116, 118, 120, 122–124, 126–127
longitudinal studies, 102, 104
psychosocial development, 477
schizophrenia, 303
Social drugs *See* Alcohol; Nicotine; Substance use
Social environment
communication disorders, 771, 775–776
depressive disorders, 1300
elderly adults, 2549–2550
intellectual disability, 716
interpersonal psychotherapy, 1875, 1876
MDMA-related disorders, 1119
mentally ill homeless people, 2534
post-traumatic stress disorder, 1479
reactive attachment disorder, 894–895
stereotyped movement disorder, 891
Social factors
adult abuse, 2584
anorexia nervosa, 1616
attention-deficit hyperactivity disorder, 816–817
autistic disorder, 788
bipolar disorder, 1353–1354
depression theories, 615, 1299
generalized anxiety disorder, 1501–1502
homelessness, 2535
nicotine dependence, 1155
panic disorders, 1402
psychological factors affecting medical condition, 1755
substance addiction, 965–966
suicide risk/protection, 2479
tic disorders, 856
Social impairment
autistic disorder, 780–782, 784
learning and motor skills disorder, 747, 750, 756–757, 760–761, 762
Social interactions
Asperger's disorder, 791–792
autistic disorder, 786
cognitive processes, 444–445
personality styles, 640–641
Social phobia
*See also* Social anxiety disorder
adolescents, 500–501
assessment, 1413–1414
body dysmorphic disorder relationship, 1540
characteristics, 1416–1418
childhood problems, 495
children, 879, 881, 882
cognitive and behavioral therapies, 1938
diagnosis, 1416–1418
diagnostic decision tree, 1419
differential diagnosis, 1740
DSM-III to DSM-III-R changes, 318–319
DSM-IV-TR criteria, 1409–1410
interpersonal psychotherapy, 1883
psychosocial treatments, 1430–1432
selective mutism relationship, 884
subtypes/phenomenology, 1412–1413
treatments, 1427–1429, 1433
Social psychology, 454–463
attribution theory, 455–456, 461
benefits/growth through adversity, 456–457
depression, 455–460
diffusion of responsibility, 461
obedience to authority, 461
the self, 458–461
Social referencing
autistic disorder, 780
emotional development, 141
infant development, 122
Social rhythm theory of depression, 1299

Social Security Administration, 88, 2060
Social skills training (SST)
attention deficit-disruptive behavior disorders, 822–823
behavioral therapies, 1933
learning and motor skills disorders, 757, 761
psychosocial rehabilitation, 2063–2064
schizophrenia, 1262, 2051–2053
social phobia, 1430
Social stress theories of depression, 615
Social support
cultural issues, 59
mentally ill homeless people, 2534
resilience, 185, 186
self-help groups, 2084
Society, view of adolescents, 172–173
Sociocultural factors
diagnosis, 648–656
drug responses, 2113
grief/mourning, 2522
histrionic personality disorder, 1736–1737
preschool development, 142–144
school-age development, 154–155, 158
Socioeconomic factors
adult abuse, 2577
bipolar disorder, 1343
cognitive disorders, 649
communication disorders, 773
culture relationship, 55
diagnostic bias, 1343
effective listening, 5, 6
schizophrenia epidemiology, 1209
*Social Class and Mental Illness* study, 411
Sociopolitical issues, 2572
Socratic questioning, 1926
Sodium oxybate (Xyrem), 1639–1640
*See also* Gamma hydroxybutyrate
SOGS *See* South Oaks Gambling Screen
Solid food aversion, 837, 838
Solitary confinement, 92
Solitary play, 144
Solution-focused brief psychotherapies (SFBT), 1897–1898, 1900
Solvents inhalation, 1127–1142
Somatic obsessions, 1444, 1445, 1447
Somatic-type delusional disorder, 1273, 1275
Somatization
abuse victims, 2587
distress symptoms, 59
signs/symptoms, 627–631, 651
theories, 1511
Somatization disorder
Briquet's syndrome, 1513, 1514
comorbidity, 1520
course, 1518
definition/diagnostic features, 1513–1514, 1517–1518
differential diagnosis, 1518–1521
DSM-IV-TR criteria, 1517
early adulthood, 508
epidemiology, 1518
etiology/pathophysiology, 1521
evolution of definition, 1517–1518
history, 1513–1514
pharmacotherapy, 1523
treatment/management, 1521–1523
Somatoform disorder not otherwise specified, 1542–1543
DSM-IV-TR criteria, 1542
Somatoform disorders, 1510–1544
anxiety/ depression comorbidity, cultural factors, 651, 652
behavioral medicine, 2034–2035
body dysmorphic disorder, 1538–1542
conversion disorder, 1525–1530
cultural factors, 652–653
differential diagnosis, 1511–1513, 1515, 1524
DSM classification systems, 675
DSM-IV-TR criteria, 1517, 1523, 1526, 1531, 1535, 1539
epidemiology, 1513, 1514
factitious disorders distinction, 1548
hypochondriasis, 1535–1538
ICD-10, 1511, 1518, 1526, 1539, 1544
natural history, 1514
pain disorder, 1530–1535
panic disorder comorbidity, 1398
physical signs and symptoms, 628
somatization disorder, 1513–1514, 1517–1523
treatment, 1513, 1516–1517
undifferentiated somatoform disorder, 1523–1525
unusual symptoms in non-western cultures, 652
Somatosensory event-related potentials (SERPs), 2010–2011
Somatostatin, 2306
Soothing behavior, 841, 842
SOREMP *See* Sleep onset REM period
Soul in explanations of madness, 206, 208
South Oaks Gambling Screen (SOGS), 1679
Spanish sage (*Salvia lavandulaefolia*), 2339
Spatial memory, 198
Special assessment techniques, 538, 540
Special education services, 750, 552–553
Special housing units, 2597
Specific developmental disorder of motor function, 762
*See also* Developmental coordination disorder
Specific disorder of arithmetic skills, 762
*See also* Mathematical disorder
Specific phobias
assessment, 1413–1414
characteristics, 1410, 1411
comorbidity patterns, 1415–1416
diagnostic decision trees, 1420
differential diagnosis, 1416–1418
DSM-IV-TR criteria, 1411
exposure therapy, neurobiological basis, 324
general features, 320
neurobiological basis of therapy, 324
psychosocial treatments, 1429–1430
somatic treatments, 1427–1428
subtypes, 1411–1412
treatment decision tree, 1433
Specific reading disorder, 762
*See also* Reading disorder
Specific spelling disorder, 762
SPECT *See* Single photon emission computed tomography
Spectrum model of depression, 614
Speech
*See also* Communication; Expressive language disorder; Language
Asperger's disorder, 792
assessing communication, 767–768
assessing higher level processes, 595
autistic disorder, 781, 786
Mental Status Examination, 528–529
psychiatric interviews, 42
relational problems, 1796–1797
schizophrenia patients, 1234
Speech disorders, 595–598
*See also* Communication disorders; Expressive language disorder; Mutism
Speech and language pathologists (SLPs), 767–768, 771, 776
Spelling disorders, 759, 762
Spermarche, 166
Spina bifida, 703
Spirituality, 57–58
Spitz, Rene, 475
Splitting as defence mechanism, 474, 476, 1855
Split treatment model of combined treatments, 2440–2442, 2443–2444
Spongiform encephalopathies, 398–399, 911–912
Spontaneous abortion, 2417–2418, 2419
Spontaneous hypnotic states, 1985
Squared multiple correlation (SMC), 2630
SRIs (serotonin reuptake inhibitors) *See* Selective serotonin reuptake inhibitors
SSP *See* Strange situation procedure
SSRIs *See* Selective serotonin reuptake inhibitors
SST *See* Social skills training
Stability of therapeutic frame boundaries, 73, 74
Stage model of gay male relationships, 2543
Stages of change theory, 2448–2449
Stages of development, 97, 110–111
Stahl, Georg, 211
Stakeholder (family and consumer) organizations, 2085, 2086–2088
Stalking, 1603
Stammering *See* Stuttering
Standard case management (SCM), 1263–1264
Standard deviation, 2626–2627
Standardized assessment instruments, 1845, 548–549

Standards in correctional settings, 2596–2598
Standards of proof, 86
Stanford-Binet Intelligence Scale-Fourth Edition, 550
Stanford Hypnotic Clinical Scale, 1984
Stanford Hypnotic Susceptibility Scale, 1986–1987
STAR*D *See* Sequenced Treatment Alternatives to Relieve Depression
Startle responses, 322
Starvation, 1613
State anxiety, 317–318, 324
State Care Acts, 1819–1820
State hospitals, mental health service history, 1820, 1821, 1822–1823, 1824–1825, 1827, 1828, 1833
State mental health agencies (SMHAs), 1822, 1823, 1825, 1826–1828
State Protection and Advocacy Centers (P&As), 2085, 2086
Statins, 2310
Statistics in research methodology, 2619–2633
STDP *See* Short-term dynamic psychotherapy
Stepwise multiple regression, 2629
Stereochemistry of stimulants, 2268
Stereotyped behavior in autistic disorder, 781, 782
Stereotyped Behavior Scale (SBS), 890
Stereotyped movement disorder, 498, 725–726, 889–892
  DSM-IV-TR criteria, 889, 890
Stereotyped speech, 781
STG *See* Superior temporal gyrus
Stigma, definition, 63
Stigma of mental illness, 63–64, 621, 623, 1264, 2453
Stimulant-related toxic psychosis, 2278
Stimulants
  acceleration of response, 2286
  antidepressant treatment augmentation, 2151
  attention deficit-disruptive behavior disorders, 817–819
  attention-deficit hyperactivity disorder, 815, 2269–2276
  clinical use, 2279–2284
  cocaine dependence, 2411
  commercial forms, 2266
  disruptive behavior disorders, 2264–2288
  efficacy, 2269–2276
  enuresis, 873
  intellectual disability, 737
  neuropharmacology, 366
  sedative-hypnotic abuse combination, 1188
  side effects, 2276–2284, 2286–2287
  substance use disorder pharmacotherapy, 2410–2411
Stimulation control therapy, 1636
Stimulation need in rumination disorder, 841, 842
Stimulus control strategies in smoking cessation, 1161
Stimulus-oriented theories in anxiety, 610
Stimulus-response assessment, 582, 583
STIs *See* Sexually transmitted infections
Stockholm Outcome of Psychotherapy and Psychoanalysis Project, 295
STPD *See* Schizotypal personality disorder
STPP *See* Short-term psychoanalytic psychotherapy
Strange situation procedure (SSP), 123
Strategic brief psychotherapies, 1891, 1897, 1900
Strategic family therapy, 1951–1952, 1960
Strategic psychotherapy, 292
Strategic-systemic approaches to relational problems, 1803
Strengths-based approach, recovery-oriented treatment, 2050
Strengths case management model, 2068
Streptococcal infections
  group A beta-hemolytic streptococcal infections, 850, 856
  obsessive-compulsive disorder, 1450–1451
  pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, 850, 856, 859, 1450–1451
Stress
  *See also* Acute stress disorder; Post-traumatic stress disorder
  adjustment disorders, 1702–1714
  adverse birth outcomes, 2417–2418
  animal models, 324–325
  behavioral medicine, 2031–2032
  bereavement, 2521
  brief psychotic disorder, 1269
  decreased hippocampal neurogenesis, 349–350
  depressive disorders, 1297–1298, 1300
  disaster psychiatry, 2467–2469
  dissociative amnesia, 1560, 1561
  early adulthood, 196, 197, 506
  encopresis, 876
  genetic factor interactions, 176
  heart disease patients, 2500
  ICDL-DMIC, 681, 682, 688
  physiological response affecting a general medical condition, 1756, 1757, 1760, 1763
  premenstrual syndrome, 1382–1383
  rumination disorder, 841
  substance dependence, 356
  trichotillomania, 1691–1692
Stress-diathesis, 490, 1922
Stress inoculation, 2590
Stress neurocircuits in substance dependence, 370
Stressor analysis, 1711
Striatum, 1221
Stroke (cerebral vascular accident/cerebrovascular adverse event), 1066, 1287, 1764–1765, 2144, 2556
Stroop tasks, 438
Structural abnormalities *See* Congenital abnormalities
Structural Analysis of Social Behavior model, 640–641
Structural equation modeling, 2631–2632
Structural family therapy, 1950–1951, 1959–1960
Structural imaging modalities, 570–573
Structural lesions in dementia, 393, 394
Structural theory, 469, 470–471
  post-Freudian, 472–473
  psychoanalytic psychotherapy, 1853
  relational problems, 1795–1796, 1801, 1803
  Winnicott, 474
Structured clinical instruments
  diagnostic assessments, 411
  psychological testing, 533, 534, 535, 536, 537
  risk assessment, 533, 537, 540–542
  stimulants use in attention-deficit hyperactivity disorder, 2283
Structured Clinical Interview for DSM-IV (SCID), 1231
Structured interviews, 1413, 1496
Study design methodology, 2619–2633
Study disciplines in psychosomatic medicine, 2497–2498
Stuporous catatonia, 942, 943, 944
Stuttering, 597, 765, 770, 772, 774–776
  DSM-IV-TR criteria, 774, 775
Subacute sclerosing panencephalitis, 911
Subcortical circuits, 282, 283
Sublimation defence mechanism, 1855
Submicroscopic chromosome rearrangements, 699
Substance abuse
  adolescents, 174, 501, 502
  aggression, 541–542, 2605–2606
  caffeine link with drugs/alcohol/nicotine, 1030–1031, 1032
  correctional psychiatry, 2594
  couples therapy, 1969
  'date rape' drugs, 1189, 1639, 2578
  depression, 936
  depression comorbidity, 1285
  diagnostic criteria, 354, 355, 356
  DSM-IV-TR, 1062–1063
  gay men/lesbians, 2544–2545
  generalized anxiety disorder comorbidity, 1497
  historical view, 224
  impulsive behavior, 643, 644
  interpersonal psychotherapy, 1883
  maternal, infant development risk factors, 129–130
  mentally ill homeless people, 2533
  opioids, 1172, 1173
  pathological gambling comorbidity, 1680
  personal history, 528
  pharmacologic therapy, 2108
  physical examination, 531
  prescription drugs, definitions, 1187, 1188

Substance abuse *(Continued)*
recreational/quasi-therapeutic abuse of prescription drugs, 1188, 1193
relational problems, 1805
social drugs as pharmacologic therapy, 2108
somatoform disorder relationship, 1510–1511
treatment-resistant depression, 2376
violence risk, 541–542, 2605–2606
Substance Abuse and Mental Health Services Administration (SAMHSA), 2050, 2060, 2065, 2066, 2079
Substance addiction *See* Substance dependence
Substance dependence, 957–970
addiction cycle, 356–357
addiction development, 358
addiction patterns, 357–358
alcohol, 971–973, 974, 975, 988–990, 2394–2397
animal models, 364–365, 367–368, 373–374
Antisocial personality disorder, 1730
caffeine, 1029–1033
definitions, 355–356
diagnostic criteria, 354–355
dorsal striatum dysregulation, 250
DSM-IV-TR criteria, 961, 1029, 1063, 1683
fear of psychiatric medication dependency, 2453
opioids, 1172, 1173
pathophysiology, 354–374
phencyclidine, 1093
prescribed medications, 515
ventral striatum dysregulation, 249
withdrawal delirium criteria, 922
withdrawal syndrome criteria, 959
Substance-induced anxiety disorder, DSM-IV-TR criteria, 1034
Substance-induced persisting amnestic disorder, DSM-IV-TR criteria, 925
Substance-induced persisting dementia, 915–916
DSM-IV-TR criteria, 915
Substance-induced psychotic disorder, DSM-IV-TR criteria, 1108
Substance-induced sexual dysfunction, 1581
Substance-induced sleep disorder, 1651–1654
caffeine, 1035
DSM-IV-TR criteria, 1035, 1652
Substance intoxication
alcohol effects, 977
anxiety/agitation, 687
caffeine use disorders, 1019–1024
criminal proceedings, 91–92
differential diagnosis, 963
DSM-IV-TR criteria, 958–959
hallucinogens, 1103–1107
opioids, 1171
pathophysiology, 357, 364–367
sedative-hypnotics, 1191
Substance intoxication delirium, 921–922
DSM-IV-TR criteria, 921
Substance P, 1294–1295, 2152
Substance use disorders
abuse victims, 2587
across the life cycle, 512
addiction cycle, 356–357
addiction development, 358
addiction patterns, 357–358
adolescents, 501, 502
age/gender/race/ethnicity issues, 360, 361
alcohol use disorder, 971–999
anorexia nervosa relationship, 1613
antipsychotic drugs, 2172
brain circuit neuroadaptations, 368–371
caffeine use disorders, 1019–1037
cannabis-related disorders, 1041–1057
cocaine use disorders, 1058–1081
cognitive-behavioral therapy, 1940
comorbidity patterns, 361–362, 1077–1078
criminal proceedings, 91–92
cultural factors, 649–650
definitions, 356
developmental versus cohort effects, 184, 185
drug counseling, 1070–1071, 1179, 1180
drug use/alcohol use comorbidity, 986
DSM classification systems, 674
early adulthood, 507
ECA study, 416–417
elderly adults, 514–515
general approaches, 957–970
genetic epidemiology, 261
hallucinogen-related disorders, 1100–1126
homeless people, 2527, 2528, 2531, 2533
impacts, 360–362
inhalant-related disorders, 1127–1142
intermittent explosive disorder comorbidity, 1664–1665
manic-depressive disorder comorbidity, 1343–1344, 1365
manic/depressive symptoms, 1341, 1342
medical consequences, 360–361
medication compliance, 2456–2457
middle adult life, 510, 512
molecular neuroadaptations, 371–374
neuroadaptations, 368–374
nicotine dependence, 1149–1168
onset ages, 422
opioid use disorders, 1169–1183
panic disorder comorbidity, 1398
pharmacotherapy, 2108, 2390–2412
phencyclidine intoxication, 1090–1099
physical examination, 531
prevalence, 358–360, 361
psychiatric comorbidity, 2391–2392
schizophrenia differentiation, 1238
sedative-hypnotics, 1186–1198
SMI co-occurrence, 2075–2077
stimulants, 2279, 2287
suicide, 2481
violence/aggression link, 2604, 2605–2606
vulnerability factors, 363–364
Substance use patterns, 358–360
Substance withdrawal delirium, DSM-IV-TR criteria, 922
Substance withdrawal syndrome, criteria, 959
Substantia nigra, neuroleptic-induced Parkinson's disease, 1776
Substitution therapies
cocaine use disorders, 1075–1076
nicotine replacement therapy, 1151, 1157, 1159–1163, 2407–2408
opiate use disorders, 2401
substance use disorders, 2390–2391
Subsyndromal depression, 1882–1884
Subsyndromal somatization disorder *See* Undifferentiated somatoform disorder
Subthreshold adjustment disorders, 1702
Subthreshold mixed anxiety-depressive disorder, 1707
Sudarshan Kriya Yoga (SKY), 2326, 2330
Suggestibility, 1984, 1985, 1998
Suggestion in conversion disorder therapy, 1529
Suicidal behavior, 2478–2490
acute neuroleptic-induced akathisia, 1780
adjustment disorders in adolescents, 1704, 1705, 1708, 1710
adolescents, 102, 106, 2145–2146
adoption studies, 261
age-specific vulnerabilities, 102, 106, 107, 514, 2558–2559, 2479
antidepressant links, 1306–1307, 2145–2146, 2519
antipsychotic drug effects, 2177
assessment, 2482–2483
atomoxetine, 820
bereavement, 2519
body dysmorphic disorder, 1540
borderline personality disorder, 1734
caffeine intoxication relationship, 1022
definitions, 2478
depression, 1288–1289, 1291, 2379
elderly adults, 514, 2558–2559
ethnic factors, 173
family history, 541, 2479–2480, 2483
gay men/lesbians, 2545
history, 212, 224
impulsive behavior, 643, 644
lithium effects, 1356
malpractice lawsuits, 86–87
management, 2478–2490
neurobiology, 344, 2482
'no-suicide' contracts, 86, 2483, 2485–2486
pathological gambling, 1680, 1681
post-traumatic stress disorder, 1484
prevalence, 2518–2519
protective factors, 1356, 2479–2482, 2484

risk assessment, 86, 533, 537, 540–541
schizophrenia, 2177, 2480, 2485
scope of problem, 2478–2479
selective serotonin reuptake inhibitors, 1306–1307, 2519
somatization disorder, 1518
treatment, 2483–2486
as type of violence, 2604
Suicidal ideation
assessment, 2483
definition, 2478
depression, 1288–1289, 1291, 2379
psychiatric evaluations of children/adolescents, 548
risk/protective factors, 2480
Suicide attempts, definition, 2478
Suicide protection, 1356, 2479–2482, 2484
Sullivan, Harry Stack, 222, 479, 1261
Sulpiride, 858, 2168
Superego concept, 470–471, 1853
Superior temporal gyrus (STG), 1219–1220
'Superman' (XYY) syndrome, 2607
Supervised housing, 544
Supervised medication taking, 2450
Supervision of therapists, 87
Supported employment (SE), 2055, 2065, 2077–2080, 2527
Support groups *See* Self-help groups
Supportive-expressive (SE) therapy, 1069, 1890
Supportive interventions, 46–47
abuse victims, 2591
cognitive and behavioral therapies comparison, 1936
delusional disorder, 1275
effective listening, 8–9
efficacy studies, 292, 293
group therapy, 2036
neuroleptic malignant syndrome, 1788
psychoanalytic psychotherapy, 1852–1853, 1860, 1862, 1863
somatization disorder, 1521
Suppression of homosexual feelings, 2542
Suprachiasmatic nucleus (SCN), 1628
Surgery
body dysmorphic disorder, 1539, 1540
brain structures and emotional effects, 605–606
breathing related sleep disturbance, 1643
enuresis, 872
gender identity disorders, 1599–1600
hypnotic analgesia, 2000–2003
obsessive-compulsive disorder, 1465–1466
patients on methadone maintenance treatment, 2402
post-anesthetic headache, 1026–1027
postoperative delirium, 920–921
premenstrual dysphoric disorder, 1385
Survivor operated service programs, 2092
Survivor/victim distinction, 2573
Suspiciousness, 599, 600
Sustained-release medication, 2408, 2268
Swanson, Nolan, and Pelham (SNAP) Parent and Teaching Rating Scales, 807, 808
SWAP-200 *See* Shedler-Westen Assessment Procedure-200
Switching medications, 1257, 2380–2384
Switzerland, history, 211, 223
SWS *See* Slow wave sleep
Symbolic incest, 1585
Symbolism, 1526, 1528
Symbolization, 142, 465
Symbols, 4–5, 6
Symmetry obsessions, 1444, 1445, 1446
Sympathetic arousal, 1500–1501
Sympathetic nervous system, 1478
Symptomatic listening, 5
Symptom cluster analysis, 1231
Symptom complexes, 2033–2037
Symptom formation, 471
Symptom neuroses, 471
Symptoms, *See also* Physical signs and symptoms
Symptoms dependent on culture and gender, 58–59
DSM-IV-TR criteria, 648
Synaptic apoptosis, 1222
Synthetic hallucinogens, 1102
Synthetic tetrahydrocannabinol, 2411–2412
Syphilis
historical understanding, 209, 214, 217, 221
neurosyphilis, 914, 934, 937–938
tests, 535, 914
Systematic cue exposure, 1071
Systemic psychotherapy, 292
SZPD *See* Schizoid personality disorder

$T_{1/2}$ *See* Half-life
T-ACE screening test, 982
Tacrine, 2300–2304
Tactile sensory processing disorder, 751
TADS *See* Treatment for Adolescents with Depression Study
Tai Chi Chuan, 2329
Tailoring medication regimens, 2458
Tandospirone, 1314
Tangentiality, 596, 598
Tangles *See* Neurofibrillary tangles
Tardive dyskinesia (TD), 1252–1253
acute dystonia distinction, 1776
acute neuroleptic-induced akathisia, 1780
antipsychotic drugs, 1243, 1252–1253, 1781–1785, 2185, 2187
history, 1773
Task mastery in adult development, 189–191
Taste, 200
Tau protein, 395, 396, 397, 2296
Tax Equity and Fiscal Responsibility Act (TEFRA), 1838
TB *See* Tuberculosis
TBI *See* Traumatic brain injury
TCAs *See* Tricyclic antidepressants
TCE *See* Trichloroethylene
TCs *See* Therapeutic communities
TD *See* Tardive dyskinesia; Tourette's disorder
TDCRP *See* Treatment of Depression Collaborative Research Program
tDCS *See* Transcranial direct current polarization
TDM *See* Therapeutic drug monitoring
Teacher evaluations, 549
Technology in behavioral medicine, 2038–2039
TEFRA *See* Tax Equity and Fiscal Responsibility Act
Telephone therapy, 1884
Telepsychiatry, 51
Temperament
*See also* Personality styles
adolescents, 177
behavioral medicine, 2028
cross-gender children, 1595
inborn, 633
individual differences in children, 491
seven-factor model, 636–639
spectrum, 615
Temperature metaphors, 2001–2002
Temperature-sleep relationship, 1628
Temporal lobe, 1219–1220
Temporal relationships
medication-induced movement disorders, 1774
psychological factors affecting medical condition, 1754, 1755, 1756
Temptation, 146
Teratogenesis, 2508
Terminal care, 24, 30–31, 2516–2524
Termination of group psychotherapy, 1912–1913, 1917
Termination phase in group dynamics, 1906, 1908
'Terrible two's', 127
Terrorist disasters, 2465, 2466
Tertiary amines, 2126
Tertiary (remote) memory, 587, 898, 926
TES *See* Transcranial electrical stimulation
Testosterone, 1582, 2505, 2606–2607
Test-retest reliability, 2624
Test of Variables of Attention, 2274
Tetracyclic antidepressants, 1309, 2127
Δ-9-Tetrahydrocannabinol (THC), 367, 1041, 1042–1043
*See also* Cannabis...
Texas Medication Algorithm Project (TMAP), 824, 2384–2385
TFP *See* Transference-focused psychotherapy
Thalamus, 1221
Thase and Rush 5-stage model, 2372
THC *See* Tetrahydrocannabinol

Thelarche (breast development), 164–166
Theory of mind (ToM), 139, 146, 289–290, 1233
Theory neutral diagnosis, 245
Theory of planned behavior (TPB), 2448
Theory of reasoned action (TRA), 2448
Therapeutic alliance, 23–24, 294, 295
  *See also* Clinician-patient relationship
  brief psychotherapies, 1895, 1898
  compliance, 2454
  cultural issues, 63, 1865
  effective listening, 3, 8
  psychoanalytic psychotherapy, 1857, 1858, 1859, 1861, 1863, 1865
  research, 27–28
  somatization disorder, 1522
  threats, 1861
Therapeutic boundaries, 71–79
Therapeutic communities (TCs), 1180
Therapeutic drug monitoring (TDM), 1301–1302, 1314, 2106, 2147
Therapeutic frames, ethical boundaries, 71–79
Therapeutic neutrality in psychoanalytic psychotherapy, 1856
Therapeutic privilege, 84
Therapeutic support group model, 2085, 2089
'Therapeutic use' hypothesis, 2491–2492
Therapist authenticity, 4
Therapist factors in psychotherapy, 294
Therapist-patient relationship *See* Clinician-patient relationship
Therapists' attitudes to sexual issues, 1578–1579, 1606
Therapists' role group psychotherapy, 1911
Therapists' sexual orientation, 2543
Theta waves/bands, 566, 2327
Thiamine, 2392
Thioxanthines, 1242
Third generation antidepressants
  drug-drug interactions, 2143
  efficacy determination, 2129
  mechanisms of action, 2127
  pharmacokinetics, 2133–2134
  starting doses, 2146–2147
  types, 2127, 2128
Third-generation psychiatric epidemiology, 411–418
Thought blocking, 597, 598
Thought broadcasting, 599, 600
Thought control, 599, 600
Thought disorders, 598–600
Thought processes
  Mental Status Examination, 529
  schizophrenia patients, 1235
  speech disorders, 595–596, 597, 598, 599, 600
Thought recording, 1926–1927, 1953
Thought stopping techniques, 1933
Threat-fear responses, 321–322
Thyroid disorders
  anxiety/depression, 626
  psychological factors affecting medical condition, 1763–1764
  psychosomatic medicine, 2504
Thyroid hormones
  antidepressant treatment augmentation, 2151
  attention deficit-disruptive behavior disorders, 810
  bipolar disorder, 1341, 1351
  blood tests, 535
  depression treatment, 1313
  treatment-resistant depression, 2383
Tiagabine
  cocaine use disorders, 1073–1074
  generalized anxiety disorder, 2232
  panic disorder, 2240
  post-traumatic stress disorder, 2243
Tianeptine, 1309–1310
Tiapride, 858
Tic disorder not otherwise specified, diagnostic criteria, 848
Tic disorders
  ADHD comorbidity, 849–850, 851, 857
  childhood problems, 498
  comorbid conditions, 849–850, 851–852, 857, 863
    treatment, 858–859, 861–862, 863–864
  complex clinical presentations, 849–850, 852, 863–864
  course, 850
  diagnosis, 847–850
  differential diagnosis, 849–850, 852
  epidemiology, 850
  etiology/pathophysiology, 852–856
  learning and motor skills disorder comorbidity, 755
  medication-induced tardive dyskinesia, 1784
  nonpharmacological therapy, 859–860
  obsessive-compulsive disorder comorbidity, 850, 851–852, 857, 1443, 1446, 1449
  obsessive-compulsive disorder differential diagnosis, 1452
  pharmacotherapy, 857–859
  stimulants in attention-deficit hyperactivity disorder, 2276
  treatment, 856–864
  treatment-refractory conditions, 862–863
Tics
  phenomenology, 847–848
  severity ratings, 849
Time *See* Temporal factors
Time-effectiveness in brief psychotherapies, 1898
Time limitation, effective listening, 7
Time-limited therapies
  *See also* Brief psychotherapies
  group psychotherapy, 1915
  interpersonal counseling, 1882, 1883–1884
  interpersonal psychotherapy, 1875, 1876, 1877–1878
  Mann's Time Limited Psychotherapy, 1890
Timeline, 232–235
Timing
  *See also* Temporal relationships
  couples therapy, 1970
  schizophrenia treatment, 2048
  stress, 1707
TM *See* Transcendental Meditation ™
TMAP *See* Texas Medication Algorithm Project
TMS *See* Transcranial magnetic stimulation
Tobacco *See* Nicotine...; Smoking
Toddlers *See* Preschool children
Tolerance
  alcohol, 972, 973, 974, 975
  caffeine, 1023, 1031
  cocaine, 1061, 1063
  opioids, 2400
  phencyclidine, 1093
  substance dependence criteria, 354, 355
Toluene inhalation, 1128, 1131, 1133–1136, 1138, 1139
ToM *See* Theory of mind
Tomboys, 1595
Top-down control of attention/executive functions, 437–440
Topiramate, 2243, 2410–2411
Topographical theory, 468–469
Tort law, 85–87, 88
  *See also* Civil law issues
Torture, 2563–2574
  definitions, 2563–2564
  ethical guidelines, 69
  methods, 2564, 2567
  physical effects, 2565
  prevalence, 2564
  psychological effects, 2565–2566
  psychosocial effects, 59–60
  treatment for victims, 2568–2574
Torture syndrome, 2567
Touch sense, 200
Tourette's disorder (TD)
  antipsychotic drugs, 2172
  Asperger's disorder comorbidity, 793
  autoimmunity, 856
  comorbid disorders, 849–850, 851–852, 857, 863
    treatment, 858–859, 861–862, 863–864
  DSM-IV-TR criteria, 848
  effortful control disruption, 158
  epidemiology, 850
  genetic factors, 852–853
  history, 847
  neurobiology, 853–856
  obsessive-compulsive disorder differential diagnosis, 1452
  PANDAS, 850, 856, 859
  social/environmental factors, 856
  stimulants in attention-deficit hyperactivity disorder, 2276
  treatment, 856–864, 1693
Toxemia in pregnancy, intellectual disability, 704
Toxic insults
  dementia, 394
  inhalant-related disorders, 1132–1133, 1138–1140

intellectual disability causes, 704, 705
laboratory assessment, 533, 538
learning and motor skills disorders, 755, 757
neurotoxic effects of substance use, 361, 1133–1138
parental exposure, 285
pica, 843
Toxic psychosis hypothesis, 2171
Toxoplasmosis, 704, 913
TPB *See* Theory of planned behavior
TRA *See* Theory of reasoned action
TRAAY *See* Treatment recommendations for the use of antipsychotics for aggressive youth
Traditional medicine, 56, 58, 59, 61
*See also* Complementary and alternative medicine
Training
*See also* Cognitive skills training; Education; Social skills training; Vocational training
schizophrenia rehabilitation, 2051–2053
Training professionals
brief psychotherapies, 1900–1901
ethnocultural issues, 61, 65
group psychotherapy, 1918
interpersonal psychotherapists, 1885–1886
psychiatric in behavioral medicine, 2041
restraint and seclusion prevention, 2494
torture victims, 2573
Trait anxiety, 317–318, 324
Trait-state dichotomy, 610
Trance logic, 1984
Trance states
dissociative disorders, 653, 1569–1572
hypnosis, 1982–2013
possession trance, 653, 1570
Tranquilizers
*See also* Sedative-hypnotics
history, 224
Transactional development models, 112, 136, 182–183
Trans-aminopropylation, 2322–2323
Transcendental Meditation ™ (TM), 2328, 2329
Transcranial direct current polarization (tDCS), 2354, 2355, 2356, 2357, 2365–2366
Transcranial electrical stimulation (TES), 2354
Transcranial magnetic stimulation (TMS), 2354–2358, 2361–2364, 2368
Transcription factors, 373
Transdermal methylphenidate patches, 2281
Transdermal nicotine patches, 1158–1159, 1162
Transference, 293–294
bias, 41
childhood abuse victims, 1568
clinician-patient relationship, 21, 24
cultural issues, 60
effective listening, 11, 16–17
Freud, 290
implicit memory, 442
object relations theory, 474–475
preschool development, 140
psychoanalytic psychotherapy, 1854–1855, 1857
relational perspective, 478
social constructivism, 480
Transference-focused psychotherapy (TFP), 1866
Transfer processing, 170
Transgender issues *See* Gender identity disorder
Transgenic animals, 325
Transient situational disturbance, definition, 1703
Transient situational personality disorder, definition, 1703
Transient tic disorder (TTD), DSM-IV-TR criteria, 848
Transinstitutionalization, 1823–1824
Transitional objects, 475
Transitions in development, 113, 118–127, 192
Translation of language, 57, 62–63, 525, 2569
Trans-methylation, 2322–2323
Trans-sulfuration, 2322–2323
Transtheoretical model (TTM) of behavior change, 2032
Transvestic fetishism, 1597–1598, 1604
DSM-IV-TR, 1605
Transvestism, 1595, 1596, 1597–1598, 1604, 1605
Trauma-informed care, 2493
Traumatic brain injury (TBI), 218, 219, 579–580, 585–586
Traumatic events
childhood problems, 495, 686
disaster responses, 2466–2469
dissociative disorders, 1558, 1560, 1561, 1568, 1571–1572
early adulthood, 506
personality styles, 634
Traumatic stress disorders *See* Acute stress disorder; Post-traumatic stress disorder
Traumatic stressors definition, 1489
Traumatic transference, 1997
Trazodone
availability, 2128
drug-drug interactions, 2142
generalized anxiety disorder, 2231
insomnia, 2259
obsessive-compulsive disorder, 2246
panic disorder, 2238–2239
pharmacokinetics, 2133, 2134
post-traumatic stress disorder, 2242
side effects, 2141
social anxiety disorder, 2235
starting doses, 2146
TRD *See* Treatment-resistant depression
*Treated contrast group with pretest and posttest* design, 2620
Treatment adequacy for 12-month disorders, 423, 425–426
Treatment adherence *See* Compliance
Treatment for Adolescents with Depression Study (TADS), 2435, 2438
Treatment of Depression Collaborative Research Program (TDCRP), 1936, 2431–2432
Treatment-emergent side effects *See* Adverse drug reactions; Adverse effects
Treatment interference, psychological factors affecting medical condition, 1756
Treatment planning, 525–545, 560
Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY), 825
Treatment-refractory patients
abuse victims, 2591
adjustment disorders, 1713
anorexia nervosa, 1618
antidepressants, 2151, 2152
anxiety disorders, 1432, 1434
augmentation strategies, 2437–2438
bipolar disorder, 1365
cocaine use disorders, 1078–1079
communication disorders, 772
depression, 1311–1315, 1319, 2372–2387
eating disorders, 1622
generalized anxiety disorder, 1505
HPPD, 1113
kleptomania, 1674
panic disorders, 1405–1406
post-traumatic stress disorder, 1484–1485
substance addiction, 968–969
tic disorders, 862–863
trichotillomania, 1694
Treatment refusal
*See also* Compliance; Noncompliance
correctional psychiatry, 2598–2599
cultural issues, 64
legal issues, 83–84, 2531
mentally ill homeless people, 2531
types, 2448
Treatment-resistant depression (TRD), 2150–2151, 2372–2387
Treatment-resistant medical disease, 1756
Treatment-resistant schizophrenia, 1255–1258, 2182–2183
Treatment settings, 28–29
Treatment termination (premature), 1068, 1078, 1973
Tremor, 1777, 1778, 1783, 1788–1790
*See also* Parkinson's disease
Trephination, 1201, 1202
Triage, 33–37
Triamine, 2139–2140
Triangle of conflict, 1890
Triangle of person, 1890
Triangles of insight, 1890, 1899
Trichloroethylene (TCE), 1136, 1137

Trichotillomania, 1658, 1660–1661, 1687–1695
adolescents, 502
assessment, 1688
comorbidity, 1689
course, 1689–1690
diagnosis, 1687–1688, 1690
DSM-IV-TR criteria, 1687
epidemiology, 1688–1689
etiology/pathophysiology, 1690–1691
impulsive behavior, 643
stereotyped movement disorder distinction, 890
treatment, 1691–1695
Tricyclic antidepressants (TCAs), 1304, 1309
alcohol use disorders with psychiatric comorbidity, 993
attention deficit-disruptive behavior disorders, 820
breastfeeding, 2424
cardiovascular patients, 2144
cognitive and behavioral therapies combination, 1937
cognitive and behavioral therapies comparison, 1936
congenital malformations, 2508
dementia management, 2554
drug-drug interactions, 2141–2142
elderly adults, 2559
enuresis, 872–873
evidence for depression causes, 344
generalized anxiety disorder, 2231
heart disease patients, 2501
history, 224, 2123
insomnia, 2259
mechanisms of action, 2124, 2126–2127, 2225
norepinephrine reuptake inhibition, 2126
obsessive-compulsive disorder, 2246
panic disorder, 2238
pharmacokinetics, 2133
post-traumatic stress disorder, 2241–2242
pregnancy, 2419
serotonin reuptake inhibition, 2124, 2126
side effects, 2226
social anxiety disorder, 2234
starting doses, 2146
treatment-resistant depression, 2381–2382
Trigeminal neuropathy, 1137
Tripartite model of anxiety and depression, 1495
Trotter, Thomas, 217–218
True selves, 474
Trust versus mistrust, 1724–1725
TSC *See* Tuberous sclerosis complex
TTD *See* Transient tic disorder
*T*-tests, definition, 2627–2628
TTM *See* Transtheoretical model
Tube feeding, 835
Tuberculosis (TB), 1182, 2527, 2535
Tuberous sclerosis complex (TSC), 383, 694, 699–700, 785
Turner syndrome, 697
TWEAK test, 979
Twelve-month prevalence rate, 417–418, 419, 423, 424–426
Twelve step recovery programs, 996–997, 1197
*See also* Alcoholics Anonymous; Self-help groups
Twin studies
anxiety disorders, 320–321, 1422
bipolar disorder, 1348–1349
genetic epidemiology, 259
history, 222, 225
impulse-control disorders, 1666–1667
mood disorders, 340
post-traumatic stress disorder, 1477
schizophrenia, 1212
Type A behavior pattern-coronary artery disease relationship, 1761, 2500
Type I/II error, study design methodology, 2623

Ubiquitin inclusions, 396, 397–398
Ujjayi (Victorious Breath), 2329–2330, 2332
Ultra-rapid detoxification, 1176
Ultrasonic bladder volume alarm, 874
Unawareness of illness, 603–604
Uncertainty, 9
Unconscious mind, 290
*See also* Consciousness
biological/neuroimaging studies, 297
fear responses, 322
history of ideas, 209, 213, 214
psychoanalytic psychotherapy, 1853–1854, 1858
topographical theory, 469
Underextension in language development, 141
Understanding in legal competency, 83, 89–90
Undifferentiated somatoform disorder, 1523–1525
DSM-IV-TR criteria, 1523
Undifferentiated-type schizophrenia, DSM-IV-TR criteria, 1206
Unemployment, 2077, 2480
Unexplained medical symptoms, 2034–2035
Unipolar/bipolar depression classification, 339, 1335
United States history, 217–219
Univariate approaches, 2627–2628
University of Michigan national survey, 410
Unpredictable events in adolescent development, 163
Unresolved grief, 1949
Unselective monoaminoreuptake-inhibitors, 1309
Unspecified-type delusional disorder, 1273
*Untreated contrast group with pretest and posttest* design, 2620–2622
Unusual eroticism *See* Paraphilias
Urine testing, 536, 538, 962, 1174
User-friendly medication, 2458

Vaccination as cocaine use prevention, 1076
Vagal efferents, 2327
Vaginal lubrication, 1586
Vaginismus, 1593–1594
DSM-IV-TR, 1594
Vagus nerve stimulation (VNS), 2354–2358, 2366–2367, 2368
Valerian, 2319, 2334
Validity
animal models, 277–278
experimental research designs, 2620–2622, 2624–2625
instruments, 407
neuropsychological analyses, 563
threats in epidemiological studies, 409–410
Valproate semisodium *See* Divalproex sodium
Valproic acid
*See also* Divalproex sodium
bipolar disorder, 1358–1362, 1367
breastfeeding, 2425
panic disorder, 2240
pregnancy, 2422, 2509
Vanderbilt ADHD Parent and Teacher Rating Scales, 807, 808
Vapors, early views of mental state, 206
Varenicline, 1151, 1158–1159, 1162, 2409
Variance, definition, 2626–2627
Vascular dementia, 909–911
DSM-IV-TR criteria, 910
Vascular disorders, 947, 948
*See also* Cardiovascular disease; Cerebral vascular accident; Cerebrovascular adverse events
Vascular endothelial growth factor (VEGF), 347, 350
VCFS *See* Velocardiofacial syndrome
$V_D$ *See* Volume of distribution
VDRL *See* Venereal Disease Research Laboratory
Vegetative symptoms of depression, 616, 624
VEGF *See* Vascular endothelial growth factor
Veins, opioid use, 1173
Velocardiofacial syndrome (VCFS), 699, 718, 934–935, 1214–1215
Venereal Disease Research Laboratory (VDRL) test, 914
Venereal diseases *See* Sexually transmitted infections; Syphilis
Venlafaxine
attention deficit-disruptive behavior disorders, 820
availability, 2128
comparative trials, 2129
generalized anxiety disorder, 2231
mechanism of action, 2127

mirtazapine combination treatment, 2384
obsessive-compulsive disorder, 2246
'off label' use, 2379
panic disorder, 2237
pharmacokinetics, 2133, 2134
post-traumatic stress disorder, 2241
side effects, 2226
social anxiety disorder, 2234
starting doses, 2146
Ventral striatum, 248–249
Ventral tegmental area (VTA), 248
Ventricles, 1218–1219
Ventrolateral preoptic nucleus (VLPO), 2254–2255
Verbal algorithm approach, 795
Verbal communication *See* Communication; Language; Speech
Verbal Intellectual Functioning (VIQ), 589, 590
Verbal memory, 198
VERPs *See* Visual evoked response potentials
Very important people (VIPs), clinician-patient relationship, 31
Vestibular sensory processing disorder, 751
Vicarious acquisition of fear, 1424, 1425
Victims, use of term, 2573
Victorious Breath (Ujjayi), 2329–2330, 2332
Vigilance in schizophrenia, 1232
Vineland Adaptive Behavior Scales, 550
Vinpocetine, 2338–2339
Violence, 2602–2612
*See also* Aggression; Physical abuse
aggression treatment, 2608–2612
antigay, 2544
biological factors, 2605–2608
classification, 2603, 2604
definition, 2602, 2576
disclosure in couples, 1968
genetic factors, 2607
hormones, 2606–2607
impulse-control disorders, 1661–1662
mental illness links, 2603–2605
murder, 173, 215–216, 1603
neurological factors, 2607–2608
non-pharmacological strategies, 2608–2609
pharmacological treatment, 2609–2612
psychiatric interviews, 48–49
risk assessment, 541–542, 2602–2603
substance induced, 2605–2606
VIPs *See* Very important people
VIQ *See* Verbal Intellectual Functioning
Viral hypotheses of schizophrenia, 1216
Virtual reality exposure for phobias, 1431
Viscosity, interictal personality syndrome, 945
Vision, 199, 200, 756–757
Visual evoked response potentials (VERPs), 2010
Visual memory, 198
Visuospatial capacities, ICDL-DMIC, 681, 682, 688
Vitamin B complex
$B_1$ (thiamine), 2392
$B_6$, 1386, 2335–2336
$B_{12}$, 934, 946, 2319, 2335–2336
cognitive enhancement, 2335–2336
folate, 2325
mood disorders, 2319, 2325
Vitamin E, 1386, 1785, 2311
Vitamin supplements
alcohol withdrawal, 2392
Alzheimer's disease, 2311
cognitive enhancement, 2325–2326, 2335–2336, 2341
mood symptoms, 1386, 2319, 2325, 2512
tardive dyskinesia, 1785
*Vitex agnus castus*, 1386
Vives, Juan Luis, 208–209
VLPO *See* Ventrolateral preoptic nucleus
VNS *See* Vagus nerve stimulation
Vocal tics
chronic tic disorder, DSM-IV-TR criteria, 848
phenomenology, 847
Vocational rehabilitation, 2054–2055, 2065, 2077–2078
Vocational training, 2055
Volatile substance inhalation disorders, 1127–1142
Volume of distribution ($V_D$), 2101, 2104
Volunteerism, 2084
Vomiting, 839–841, 1619
Voucher-based incentive treatment for substance use disorders, 1052, 1070
Voyeurism, 1600, 1602
DSM-IV-TR, 1602
VTA *See* Ventral tegmental area
Vulnerability
anxiety disorders, 328
depression, 614
psychopathology across the life span, 490
substance use disorders, 363–364

WAIS *See* Wechsler Adult Intelligence Scale
WAIS-III *See* Wechsler Adult Intelligence Scale-Third Edition
Waivers, informed consent, 84
Wakefulness, 1627–1629
*See also* Insomnia
Wake time after sleep onset (WASO), 1627
Waking, enuresis management, 872
War, 410, 1393, 1820–1821, 1958–1959, 2563–2566, 2573
WASO *See* Wake time after sleep onset
WBC testing *See* White blood cell testing
WCST *See* Wisconsin Card Sorting Test
Weak-mindedness, 1986
Weather-related disasters, 2465, 2466
Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), 589–590
Wechsler Adult Intelligence Scale (WAIS), 557, 810
Wechsler Full-Scale IQ (FSIQ), 588, 589, 590
Wechsler Individual Achievement Test (WIAT), 810
Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), 810, 549–550
Wechsler Intelligence Scale for Children-Third Edition (WISC-III), 550
Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III), 550
Weight control, hypnotherapy, 2005–2006
Weight gain
antipsychotic drugs, 2185, 2188–2189
SGA side effects, 1253–1254, 1255–1256
smoking cessation, 1163
Weight loss
anorexia nervosa, 1610, 1611
feeding disorder of infancy or early childhood, 831
psychiatric/medical causes, 1614
Weight phobia, 1611, 1615
Wender-Reimherr Adult Attention Deficit Disorder Scale, 808, 809
Wernicke-Korsakoff syndrome, 361, 898, 915, 917, 926, 978
Wernicke's aphasia, 899
Wernicke's encephalopathy, 361, 926, 978, 2392
Western culture, 1042, 1963, 1964
Weyer, Johann, 209
White blood cell (WBC) testing, 1242–1243
White matter lesions, 910–911
WHO *See* World Health Organization
WHO-CIDI *See* World Health Organization Composite International Diagnostic Interview
WIAT *See* Wechsler Individual Achievement Test
Will disorders, 602
Williams syndrome, 699, 718, 894, 895
Willis-Thomas, 210
Wilson's disease, 916
Winnicott, Donald W., 474–475
Winning phase of pathological gambling, 1681, 1682
WISC-III *See* Wechsler Intelligence Scale for Children-Third Edition
WISC-IV *See* Wechsler Intelligence Scale for Children-Fourth Edition

Wisconsin Card Sorting Test (WCST), 280, 1232
Witches/witchcraft, history, 208, 209
*Withania somnifera* (Ashwaganda), 2339
Withdrawal
  *See also* Demand-withdraw relational patterns
  addiction patterns, 357–358
  alcohol
    characteristics, 977
    disorder diagnosis, 974, 975, 977
    management, 990–991, 2392–2394
  animal models, 368
  benzodiazepines, 2394
  caffeine, 1024–1028, 1029, 1030, 1032
  cannabis, 1053, 1055
  cocaine, 1060, 1064–1065, 1068
  DSM-IV-TR criteria, 959
  neuroadaptation to substance use, 370
  opioids, 1172, 2398–2401, 2404
  sedative-hypnotics, 1188, 1189, 1191, 1192–1193
  substance dependence criteria, 354, 355–356
Witness statements under hypnosis, 2006, 2007
Wolff, Christian, 211
Women
  *See also* Female...; Gender issues
  alcohol use disorders, 981–982, 998
  reproductive transitions, 2507–2513
  role in relationships, 1964
Word salad, 597, 598
Work *See* Employment issues
Workers compensation for disability, 88
Working alliance *See* Therapeutic alliance
Working memory
  age effects, 197–198
  characteristics, 587, 588
  endophenotypes, 246
  executive control, 437–438
  prefrontal cortex role, 251
  schizophrenia, 1233
Working Memory Index, 590
Working models of attachment relationships, 2520
Working phase of group dynamics, 1906, 1908
'Working through' concept, 1857
World Health Organization Composite International Diagnostic Interview (WHO-CIDI), 1496
World Health Organization (WHO)
  generalized anxiety disorder, 1496–1497
  psychiatric disability, 2060
  schizophrenia studies, 1207
  violence, 2603, 2604
World Psychiatric Association (WPA), 69–70
World War I, 1820
World War II, 410, 1820–1821, 2563, 2565, 2566, 2573
Worry
  GAD/OCD distinction, 1499
  generalized anxiety disorder, 1494–1506
  nonpathological, 1498
  pathological, 1501
WPA *See* World Psychiatric Association
WPPSI-III *See* Wechsler Preschool and Primary Scale of Intelligence-III
Writing, educational curriculum, 751–752
Writing disorders, 749, 750, 758, 759

Xaliproden, 2307
X-linked intellectual disability, 694, 701–702, 718
X-ray imaging, CT, 570
Xyrem (sodium oxybate/gamma hydroxybutyrate), 1639–1640
XYY syndrome, 2607
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), 1443–1444, 1459, 1679
Yale Family Study of Stuttering (YFSS), 775
Yoga breathing, 2326, 2328–2331, 2332
Yohimbine test, 2130
Young adults
  *See also* Adolescents
  body dysmorphic disorder, 1540
  conversion disorder, 1527
  development, 186–187
  early adulthood disorders, 503–510, 511
  gender identity disorders, 1596, 1597
  homeless, 2528–2529
  somatization disorder, 1518, 1521
Young children *See* Infants; Preschool children

Zaleplon, 1187, 1189, 1190, 1637, 2257
Zeitgebers, 1628, 1629
'Z' hypnotics (eszopiclone; zaleplon; zolpidem; zopiclone), 1187, 1189–1191, 1637, 2257, 2262
Ziprasidone, 1244
  bipolar mania, 2207, 2210
  chemical structure, 2168
  dosing parameters, 2178
  pharmacology, 2169
  schizoaffective disorder treatment, 1267
  tic suppression, 858
Zolpidem, 1187, 1189, 1190, 1637, 2257
Zopiclone, 1187, 1189, 1190, 2257
Zotepine, 2168, 2170, 2178